Seven-Membered Ring Mesomeric Betaines.

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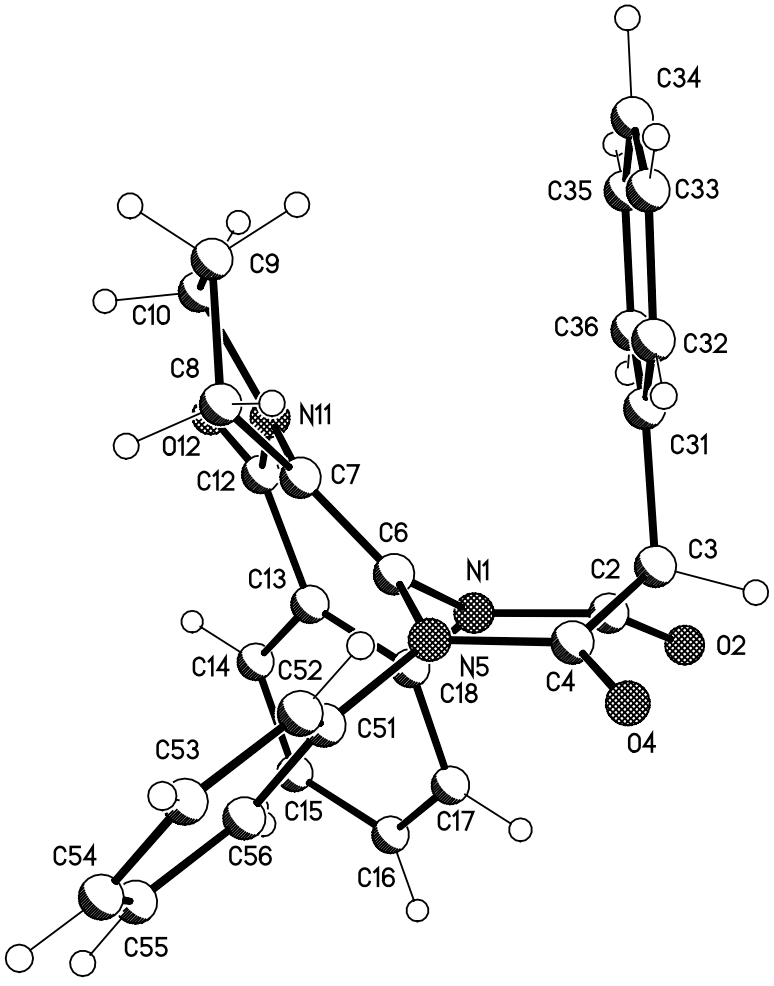

Dissertation

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Seven-Membered Ring Mesomeric Betaines. From Anti-Hückel Aromatics to Model Compounds of the Pyrrolobenzodiazepine Alkaloids Circumdatin A and B.

(Siebengliedrige Ringe in Mesomeren Betainen. Von Anti-Hückel-Aromaten zu Modellverbindungen der Pyrrolobenzodiazepin-Alkaloide Circumdatin A und B.)

DISSERTATION

zur Erlangung des Grades eines

Doktors der Naturwissenschaften

vorgelegt von

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Dekan:	Prof. Dr. Wolfgang Schade
Referent:	PD Dr. Andreas Schmidt
Korreferent:	Prof. Dr. Ernst Schaumann

Mein besonderer Dank gilt Herrn PD Dr. A. Schmidt, dass er mich nach Clausthal gebracht und mir den Arbeitsbeginn ermöglicht hat und für die Überlassung des Themas.
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Contents

List of Abbreviations

abs.	Absolute
Bn	benzyl
d	day(s)
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
DMSO	dimethysulfoxide
DNA	desoxyribonucleic acid
EA	ethyl acetate
EI	electron impact
ESI	electron spray ionisation
Et	ethyl
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
h	hour(s)
HSQC	heteronuclear single quantum correlation
HMBC	heteronuclear multiple bond correlation
HR-MS	high resolution mass
IR	infrared
J	coupling constant [Hz]
Lit.	literature
M	molar
M^+	molecular ion
Me	methyl
min	minute(s)
mp	melting point
MS	mass spectrometry
N	normal
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser effect spectroscopy
PBD	pyrrolobenzodiazepine
Ph	phenyl
Pr	propyl

Py	pyridine
R_f	retention factor
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TLC	thin layer chromatography
TMS	tetramethylsilyl
UV	ultra-violet

1. Introduction

1.1. General aspects of heterocyclic mesomeric betaines

Natural products which belong to the class of heterocyclic mesomeric betaines form a relatively small group of compounds with interesting biological properties as primary and secondary metabolites.[1] In contrast to zwitterions which can be formulated by at least one uncharged covalent structure, heterocyclic mesomeric betaines (MB) are defined as neutral conjugated molecules which can be represented exclusively by dipolar structures in which an even number of positive and negative charges are delocalised within the π-electron system. Conjugated tripoles which possess an odd number of charges within a common π-electron system form a distinct class of compounds.[1,2,3] A comprehensive classification of 5- and 6-membered mesomeric betaines including the well-known class of mesoions (sydnones, münchnones, and derivatives) was proposed in 1985.[4] All types of mesomeric betaines, including mesoions, ylides, and N-oxides, as well as betainic alkaloids and nucleobases, can be comprehensively divided by their type of conjugation into four major classes, conjugated (CMB), cross-conjugated (CCMB), pseudo-cross-conjugated mesomeric betaines (PCCMB), and heterocyclic N-ylides (Figure 1).

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[1] Schmidt, A., *Adv. Heterocycl. Chem*. **2003**, *85*, 67.
[2] Schmidt A., Kindermann, M. K., *J. Org. Chem*. **1998**, *63*, 4636.
[3] (a) Schmidt, A., Nieger, M., *Heterocycles* **1999**, *51*, 2119. (b) Schmidt, A., Nieger, M., *Heterocycles* **2001**, *55*, 827. (c) Schmidt, A., Mordhorst, T., Habeck, T., *Org. Lett*. **2002**, *4*, 1375. (d) Schmidt, A., *J. Heterocycl. Chem*. **2002**, *39*, 949.
[4] Ollis W. D., Stanforth S. P., *Tetrahedron* **1985**, *41*, 2239.

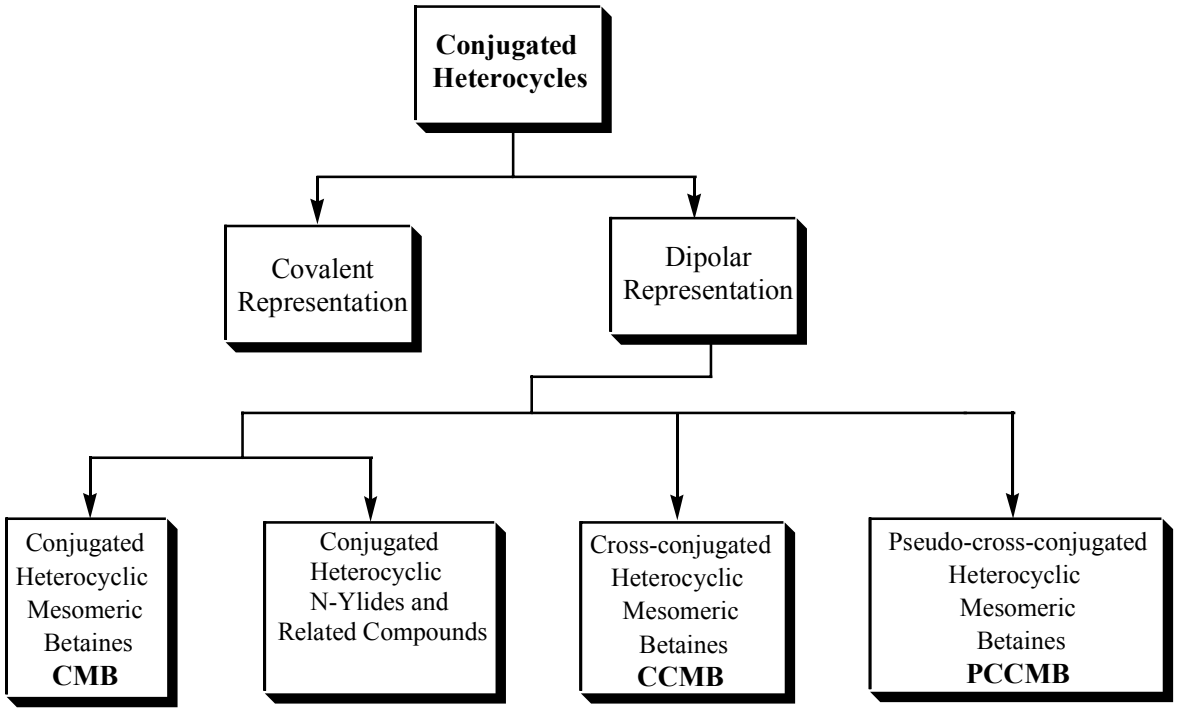


Figure 1: Classification of heterocyclic mesomeric betaines according to ref.4.

On the basis of their isoconjugate equivalents to hydrocarbons, these four major classes can be subdivided into four subclasses, respectively. The term isoconjugate, originally introduced by R. S. Muliken, describes two molecules that have the same number of atoms and π-orbitals in the conjugated system.[5] Conjugated hydrocarbons are either alternant (**I**, **II**, **III**) or nonalternant systems (**IV**, **V**, **VI**) which possess either an even (**I**, **II**, **IV**, **V**) or an odd number of carbon atoms (**III**, **VI**) participating in the conjugated systems (Figure 2). Even alternant hydrocarbons are either Kekulé structures such as benzene (**I**) or *o*-quinodimethane, or non-Kekulé structures such as *m*-quinodimethane (**II**), which must be a diradical. Odd alternant hydrocarbons must also be radicals; the benzyl radical (**III**) is given as an example. Conjugated even nonalternant hydrocarbons are either Kekulé structures such as fulvene (**IV**) or non-Kekulé structures for which the 3,4-dimethylene fulvene is presented (**V**). As shown, the latter mentioned species (**V**) must be a diradical. Odd nonalternant hydrocarbons such as 3-methylene fulvene (**VI**) are radicals as well.

[5] Platt, J. R., *J. Chem. Phys.* **1951**, *19*, 101.

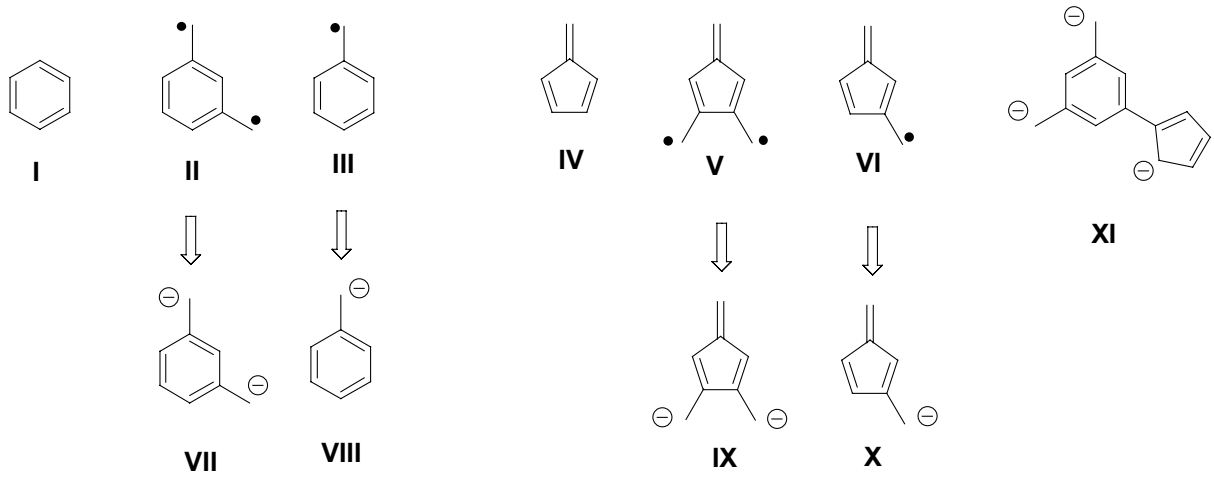


Figure 2

Heterocyclic mesomeric betaines are isoconjugate to dianions such as **VII** and **IX** or anions such as **VIII** or **X,** which derive by formal addition of two electrons or one electron to the corresponding radical species, respectively. Thus, the isoconjugate relationships of the four major classes CMB, CCMB, PCCMB, and *N*-ylides to even and odd, alternant and nonalternant hydrocarbon anions and dianions such as **VII**–**X** lead to four subclasses, respectively, *i.e.* to at least 16 distinct classes of heterocyclic mesomeric betaines (Figure 3). Some of these classes (No.1, 4, 5, 7, 8, 11) are well-known and numerous representatives have been described, whereas other classes (No. 3, 6, 15, 16) are very sparsely populated or seemingly still remain theoretically predicted. Few examples, however, are known to date, which are isoconjugate with trianionic hydrocarbons such as **XI**.[6]

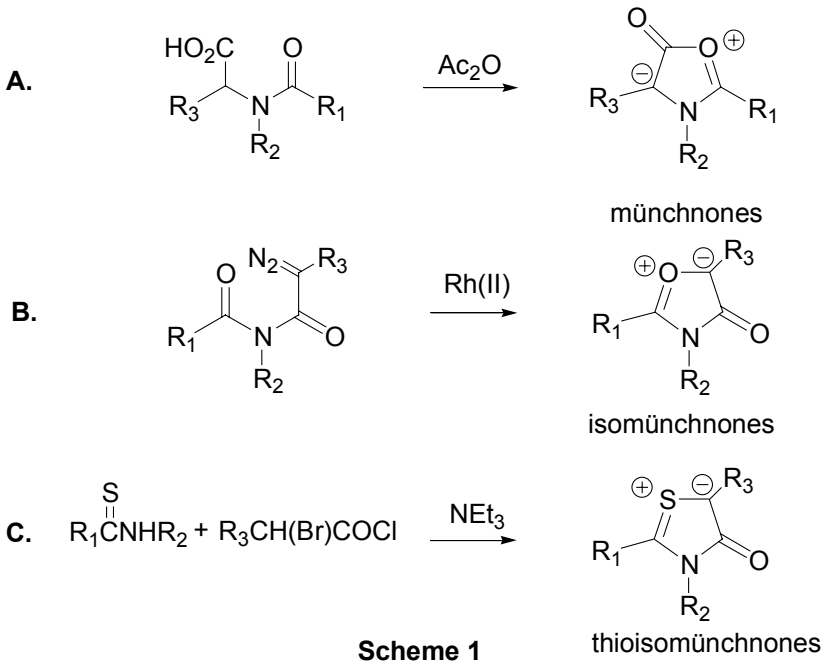
Isoconjugate equivalents	Odd alternant hydrocarbon anions	Odd non-alternant hydrocarbon anions	Even alternant hydrocarbon dianions	Even non-alternant hydrocarbon dianions
CMB	1. many	2. few	3. two	4. many
N-Ylides	5. many	6. two	7. many	8. many
CCMB	9. ten	10. none	11. many	12. few
PCCMB	13. ten	14. four	15. none	16. three

Figure 3: Subdivision of isoconjugate equivalents to hydrocarbons in 1985.

[6] Schmidt. A., *Curr. Org. Chem.* **2004**, *8*, 653.

1.2. Mesoionic thioisomünchnones and pyrimidinum betaines

The term mesoionic is generally restricted to five-membered heterocyclic mesomeric betaines including sydnones, münchnones, and derivatives (iso- and thioisomünchnones). Mesoionic compounds have been known for many years and have been extensively utilized as substrates for 1,3-dipolar cycloaddition chemistry. The peculiar structure and reactivity of such heterocycles continue to receive considerable attention, especially since these mesoionic compounds have been utilized as effective synthones in natural product synthesis.[7] In addition, these compounds have been shown to be good synthons for the synthesis of various fused heterocyclic systems.[8] Perhaps the two most extensively studied mesoionic heterocycles are the münchnones and isomünchnones (Scheme 1). These masked 1,3-dipoles readily react with a wide variety of double and triple-bond dipolarophiles.



Scheme 1

Thioisomünchnones which are easily prepared by reaction of N-monosubstituted thioamides with α-haloacyl halides in the presence of NEt_3, contain a thiocarbonyl ylide dipole within their backbone. Interest in the thioisomünchnone class of mesoions may be attributed to (a)

---

[7] Osterhout, M. H., Nadler, W. R., Padwa, A., *Synthesis* **1994**, 123.

[8] (a) Potts, K. T., Rochanapurk, T., Coats, S. J., Hadjiarapoglou, L., Padwa, A., *J. Org. Chem.* **1993**, *58*, 5040. (b) Sainsbury, M., Strange R. H., Woodward, P. R., Barsanti, P. A., *Tetrahedron* **1993**, *49*, 2065. (c) Padwa, A., Austin, D. J., Price, A., Weingarten, M. D., *Tetrahedron* **1996**, *52*, 3247.

their ease of preparation from simple thioamides, (b) the interesting physical properties they possess, (c) the propensity for its thiocarbonyl ylide dipole to undergo 1,3-dipolar cycloaddition with a wide range of dipolarophiles to produce complex heterocyclic ring systems.[9] Potts and co-workers have extensively studied the biomolecular cycloaddition behaviour of thioisomünchnone.[10]

On the other hand, during the last decades the synthesis of six-membered heterocyclic pyrimidinium betaines has been extensively studied which are regarded as being good cycloadducts for 1,4-type cycloaddition reactions with electron-poor or electron-rich multiple bond systems.[11] In recent years, much attention has been focused on the biological and pharmacological activities[12] of bicyclic six-membered betaines, which are still unexplored. These betainic heterocycles have wide industrial applications e.g. as a nonaqueous electrolyte battery[13] and pressure transfer photothermographic copying materials;[14] some show even marked hair-growth stimulation.[15]

In general, reaction of *N*,*N*′-disubstituted amidines with bis(2,4,6-trichlorophenyl) malonates results in the formation of pyridinium-4-olates. Mechanistically, one possible explanation for the syntheses of these compounds is the ring closure by loss of two molecules of trichlorophenol through a ketene intermediate (Scheme 2). 3-Unsubstituted pyrimidinium betaines (R = H) could be easily synthesized in excellent yield by condensation of *N*,*N*′-disubstituted amidines with carbon suboxide.

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[9] Hertzog, D. L., Nadler, W. R., Zhang, Z. J., Padwa, A., *Tetrahedron Lett.* **1992**, *33*, 5877.

[10] (a) Potts, K. T., Houghton, E., Singh, U. P., *J. Org. Chem.* **1974**, *39*, 3627. (b) Potts, K. T., Chen, S. J., Kane, J., Marshall, J. L., *J. Org. Chem.* **1977**, *42*, 1633. (c) Potts, K. T., Baum, J., Datta, S. K., Houghton, E., *J. Org. Chem.* **1976**, *41*, 813. (d) Potts, K. T., Baum, J., Houghton, E., *J. Org. Chem.* **1976**, *41*, 818.

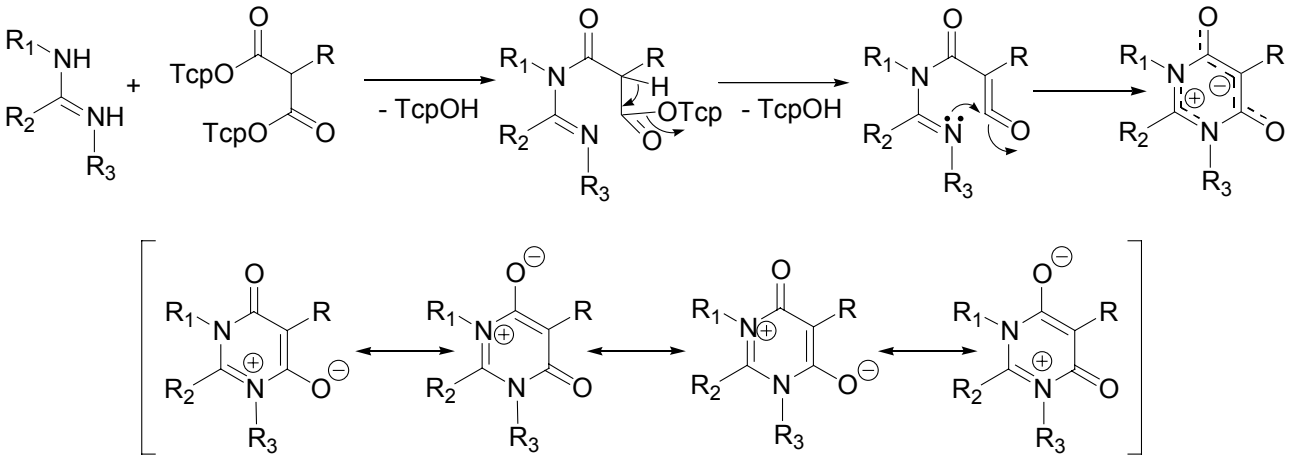
[11] (a) Potts, K. T., Sorm, M., *J. Org. Chem.* **1972**, *37*, 1422. (b) Kappe, T., Lube, W., *Mh. Chem.* **1971**, *102*, 781. (c) Kappe T., Lube, W., *Angew. Chem.* **1971**, *83*, 967. (d) Gotthardt, H., Schenk, K. H., *Chem. Ber.* **1985**, *118*, 4567.

[12] (a) Kappe, C. O., Kappe, T., *Arch. Pharm.* **1991**, *324*, 863. (b) Satyanarayana K., Rao, M. A., *Indian J. Pharm. Sci.* **1995**, *57*, 243.

[13] Kurisu, N., Chiba, N., Sasaki, Y., H., JP 054246, Feb 1993; *Chem. Abstr.* **1993**, *119*, 52892.

[14] Yabuki, Y., Kojima, T., Hiroyuki, H., JP 05313362, Nov 1993; *Chem. Abstr.* **1994**, *121*, 191433.

[15] Yokomori, S., Takeki, T., Oota, T., Hasegawa, M., Harayama, K. JP 05139936, Jun 1993; *Chem. Abstr.* **1993**, *119*, 146349.

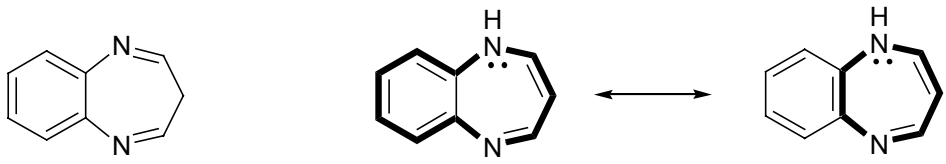


Tcp = 2,4,6-Trichlorophenyl

Scheme 2

1.3. 1,5-Benzodiazepines

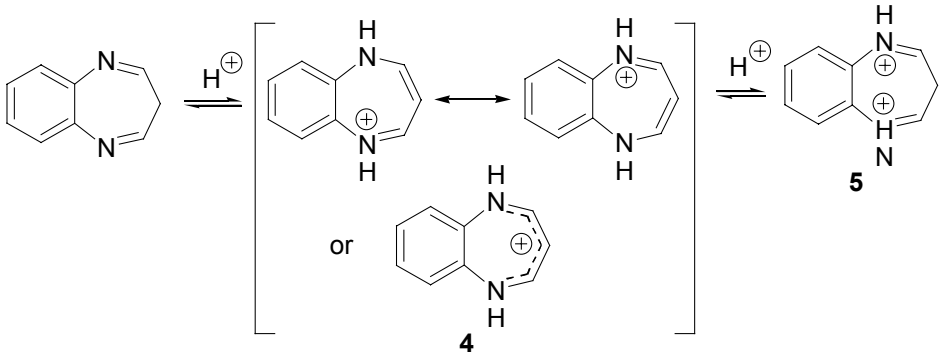
Benzodiazepines usually occur in the diimine form **1** rather than in the conjugated vinamidine forms depicted in formulas **2** and **3**. In the diimine form **1**, some extra stabilization arises from the conjugation of the imine groups with the benzene ring. Cyclic conjugation as in **2** and **3** may indeed lead to destabilization of the molecules because it involves interaction of 12 π-electrons around the periphery of the molecule as implied in **2** or of 8 π-electrons around the 7-membered ring as in **3**; either of these are destabilizing 4n π-electron systems.[16]



1 **2** **3**

Protonation of benzodiazepines leads to the successive formation of monocations **4** and dicationes **5** (Scheme 3).

[16] Lloyd, D., McNab, H., *Adv. Heterocycl. Chem.* **1998**, *71*, 1.



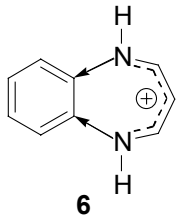
Scheme 3

The conjugated form, which would have eight π-electrons associated with the 7-membered ring, is electronically an analog of benzocyclooctatetraene. Annular conjugation around either the diazepine ring or the overall periphery makes no positive contribution to the stability of the system, whereas electronic interaction between the benzene ring and the two imino groups in the imino form does.

With a few exceptions the bases are colorless or pale yellow, as are the dications, which must exist as bisiminium salts. In contrast, the monocations are intensely colored, commonly purple or blue. Formation of the monocation involves setting up a stable 6 π-electron vinamidinium system; such systems have stabilization energies of the order of 20 Kcal/mol.[17] There is energetic advantage in generating the stabilized vinamidinium system, but there is disadvantage if it interacts appreciably with the 6 π-electron system of the benzene ring. To minimize such interactions, the bonds linking the nitrogen atoms to the benzene ring are long for aryl C–N bonds. More recently a number of X-ray structure determinations have been carried out.[18] As evidenced by calculations and X-ray single crystal structural analyses, the positive segment of the molecule are separated from the benzene ring by long C–N bonds to decrease the possibility of *4n* circuit of π-electrons. Thus the benzene ring and the vinamidinium moiety in known molecules are more or less isolated systems as exemplified by **6**.

[17] Lloyd, D., Marshall, D. R., *Chem. Ind. (London),* **1972**, 335.

[18] (a) Speakman, J. C., Wilson, F. B., *Acta Crystallogr., Sect. B,* **1976**, B*32*, 622. (b) Blake, A. J., Schröder, M., Sorbie, R. J., *Z. Kristallogr.,* **1991**, *194*, 148. (c) Svensson, C., Timby, L., *Cryst. Struct. Commun.,* **1981**, *10*, 429.



6

1,5-Benzodiazepines have been rather overshadowed by the isomeric 1,4-benzodiazepines, which have been of enormous pharmacological interest, largely because of their very wide use as tranquillizers. Some 1,5-benzodiazepines also have physiological effects, *inter alia*, some 2-amino-4-phenyl derivatives as tranquillizers[19] and some 2-*p*-fluorophenyl-4-phenyl-8-chloro derivatives as antidepressant agents (in mice).[20]

Some 2-amino-methylthio derivatives act as depressants of the central nervous system and anticonvulsants, whereas 2,4-diamino analogs act as stimulants of the central nervous system convulsants.[21] Certain benzodiazepines, in particular 2-thioderivatives, show antibacterial activity,[22,23,24] whereas some 2,4-dimethyl derivatives are said to inhibit the growth of certain sarcomas in rats.[25] Post emergence herbicidal activity has been shown by certain benzodiazepines.[26]

1.4. DNA and its interactions with bioactive molecules

Deoxyribonucleic acid (DNA) is the genetic material of all cellular organisms and provides the chemical basis for inheritable characteristics to be passed on to the next generation of cells. The structure of DNA was established as a double-stranded helix in 1953 in seminal scientific studies from James Watson and Francis Crick.

The individual bases in DNA are flat and categorized by monocyclic or bicyclic structures, which are referred to as pyrimidines (cytosine and thymine) or purines (guanine and adenine) respectively. The naturally occurring DNA usually consists of two twisted backbone chains of alternating units of phosphoric acid and deoxyribose, linked by cross-pieces of the purine and

[19] Tajana, A., Pennini, R., Nardi, D., *Farmaco, Ed. Sci.* **1980**, *35*, 181.
[20] Joshi, K. C., Pathak, V. N., Arya, P., Chand, P., *Pharmazie* **1979**, *34*, 718.
[21] Roma, G., Vigevano, E., Balbi A., Ermili, A., *Farmaco, Ed. Sci.* **1979**, *34*, 718.
[22] Nardi, D., Massarani, E., Tajana, A., Cappelletti, R., Veronese, M., *Farmaco, Ed. Sci.*, **1975**, *30*, 727.
[23] Giodano, F., Greco, C., Silipo, C., Vittoria, A., *Boll. Sco. Ital. Biol. Sper.* **1975**, *51*, 1069.
[24] Greco, C., Silipo C., Vittoria, A., *Farmaco, Ed. Sci.* **1977**, *32*, 909.
[25] Kravchenco, A. I., *Farmakol. Toksikol. (Moscow)* **1974**, *37*, 474.
[26] Clifford, D. P., Jackson, D., Edwards, R. V., Jeffrey, P., *Pestic. Sci.* **1976**, *7*, 453.

pyrimidine bases. It is the sequence of bases in DNA that encodes the genetic information of the molecule (Figure 4).

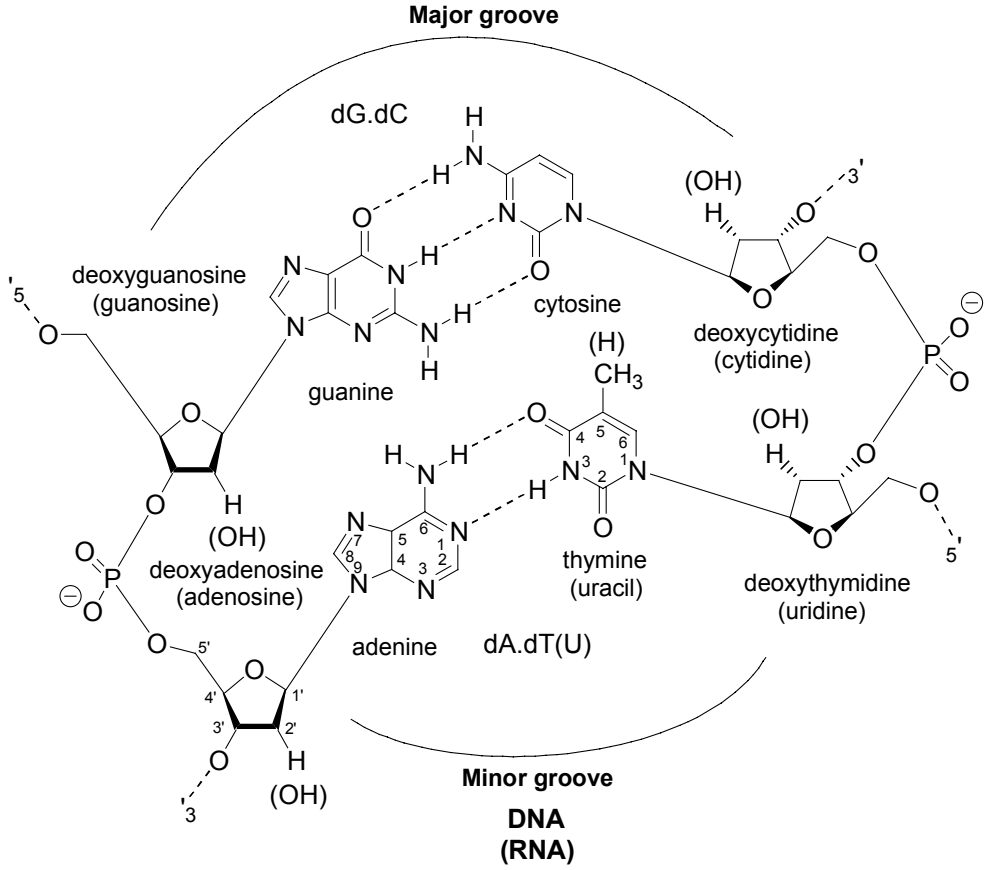


Figure 4

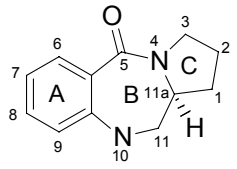
There are three helical forms of DNA (A, B and Z) that differ with respect to various parameters that describe their three-dimensional structure. B-form DNA is the most biologically relevant as it persists under physiological conditions.

As a consequence of base pair stacking, the gap between sugars forms continuous grooves in the surface, which are parallel to the sugar-phosphodiester backbone. The asymmetry present in base pairs leads to the formation of two types of groove, referred to as major and minor. The B-form helix has a wide major groove and a narrow minor groove, which are established by the edge of the base pair presented. Depending on the size of molecules this has advantages for drugs which bind. Big molecules, like proteins bind in the major groove. Flat molecules comprising of fused aromatic rings, like polycyclic aromatic hydrocarbons (PAHs) slot in between the bases and are known as *intercalators*. Some small molecules bind in the minor groove, mainly because they are the same shape as it. Binding can be reversible, *e.g.* non-covalent groove binders netropsin and distamycin, or irreversible, *e.g.* covalent groove binders CC-1065, mustards and pyrrolobenzodiazepines (PBDs). Some ligands interact with

specific bases, *e.g.* PBDs interact with guanine (G). This is important because they can be used in areas where there are known to be lots of guanine bases. If these bases, known as the genetic information, are damaged, the DNA may replicate in an uncontrollable manner and cancer may occur.

1.5. Pyrrolo[2,1-c][1,4]benzodiazepines and their natural occurrence

Alkaloids belong to an important class of natural products which are known as nitrogenous compounds occurring in plants, toads and animals including mammalian and fungi. Most of them are optically active, and nearly all of them are of basic nature. Among the most known naturally occurring alkaloids, benzodiazepines form a class of biologically active compounds from which widely prescribed psychoactive drugs have been developed.[27] In the area of molecular recognition there is growing interest in ring systems such as the pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) that can recognize and bind to specific sequences of DNA. Such compounds have potential as regulators of gene expression with possible application as therapeutic agents in the treatment of certain genetic disorders including some cancers.[28] They also have potential as highly selective anti-infective agents and as tools such as affinity-cleavage reagents for use in molecular biology.[27,29] The PBD ring system **7** (Scheme 4) is found in a group of naturally-occurring DNA-interactive antitumor antibiotics known as the "anthramycins".



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Scheme 4

[27] Medina, H. J., Paladini, A. C., Izqierdo, I., *Behav. Brain. Res.* **1993**, *58*, 1.
[28] (a) Hurley, L. H., Boyed, F. L., *TIPS* **1988**, *9*, 402. (b) Hurley, L. H., *J. Med. Chem.* **1989**, *32*, 2027. (c) Thurston, D. E., Thompson, A. S., *Chem. Br.* **1990**, *26*, 767.
[29] Dervan, P. B., *Science* **1986**, *232*, 464.

To date, 13 members are produced by various *Streptomyces* species; well-known members include anthramycin[30] **8**, and tomaymycine[31] **12** (Scheme 5). Other antibiotics in the series include abbeymycin[32] **18**, chicamycin A[33] **17**, DC-81[34] **16**, mazethramycin[35] **9**, the neothramycins A and B[36] **15**, prothracarcin[37] **13**, sibanomicin (DC-102)[38] **14**, sibiromycin[39] **11**, and porothramycin B[40] **10**. The biosynthesis of number of PBDs has been studied by Hurley.[41]

[30] (a) Leimgruber, W., Stefanovic, V., Schenker, F., Karr, A., Berger, J., *J. Am. Chem. Soc.* **1965**, *87*, 5791. (b) Leimgruber, W., Batcho, A. D., Schenker, F., *J. Am. Chem. Soc.* **1965**, *87*, 5793. (c) Arora, S. K., *Acta Crystallogr.* **1979**, B*35*, 2945.

[31] (a) Arima, K., Kohsaka, M., Tamura, J., Imanaka, H., Sakai, H., *J. Antibiot.* **1972**, *25*, 437. (b) Nishioka, Y., Beppu, T., Kohsaka, M., Arima, K., *J. Antibiot.* **1972**, *25*, 660. (c) Tazuka, Z., Takaya, T., *J. Antibiot.* **1983**, *36*, 142.

[32] Hochlowski, J. E., Andres, W. W., Theriault, R. J., Jackson, M., McAlpine J. B., *J. Antibiot.* **1987**, *40*, 145.

[33] Konishi, M., Ohkuma, H., Naruse, N., Kawaguchi, H., *J. Antibiot.* **1984**, *37*, 200.

[34] Kyowa Hakko Kogyo Co. Ltd., Jpn Kokai Tokyo Koho JP 58180487, 21 Oct 1983; *Chem. Abstr.* **1984**, *100*, 173150.

[35] Kunimoto, S., Masuda, T., Kanbayashi, N., Hamada, M., Naganawa, H., Miamota, M., Takeuchi, T., Umezawa, H., *J. Antibiot.* **1980**, *33*, 665.

[36] (a) Takeuchi, T., Miamota, M., Ishizuka, M., Naganawa, H., Kondo, S., Hamada, M., Umezawa, H., *J. Antibiot.* **1976**, *29*, 93. (b) Miyamoto, M., Kondo, S., Naganawa, H., Maeda, K., Ohno, M., Umezawa, H., *J. Antibiot.* **1977**, *30*, 340.

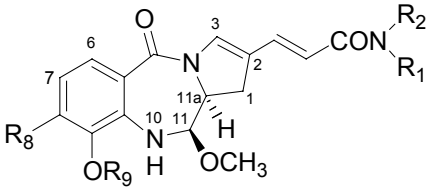
[37] Shimizu, K.–I., Kawamoto, I., Tomita, F., Morimoto, M., Fujimoto, K., *J. Antibiot.* **1982**, *35*, 972.

[38] (a) Hara, M., Tamaoki, T., Yoshida, M., Morimoto, M., Nakano, H., *J. Antibiot.* **1988**, *51*, 702. (b) Itoh, J., Watabe, H.–O., Ishii, S., Gomi, S., Nagasawa, M., Yamamoto, H., Shomura, T., Sezaki, M., Kondo, S., *J. Antibiot.* **1988**, *41*, 1281.

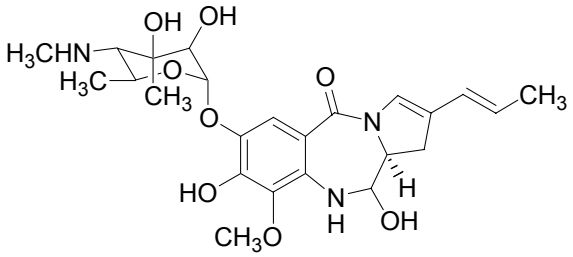
[39] Leber, J. D., Hoover, J. R. E., Holden, K. G., Johnson, R. K., Hecht, S. M., *J. Am. Chem. Soc.* **1988**, *110*, 2992.

[40] Tsunkawa, M., Kamei, H., Konishi, M., Miyaki, T., Oki, T., Kawakuchi, H., *J. Antibiot.* **1988**, *41*, 1366.

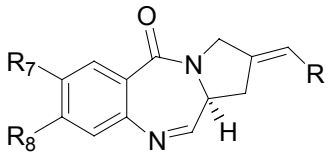
[41] (a) Hurley, A. H., *Acc. Chem. Res*. **1980**, *13*, 263. (b) Hurley, A. H., Speedie, M. K. In *Antibiotics IV. Biosythesis*; Corcoran, J. W., Ed.; Springer-Verlag: Berlin, Heidelberg, **1981**; pp 261-294.



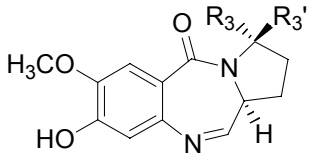
8 Anthramycin (R_8=CH_3, R_9=R_1=R_2=H)
9 Mazethramycin (R_8=R_1=CH_3, R_9=R_2=H)
10 Porothramycin (R_8=H, R_9=R_1=R_2=CH_3)



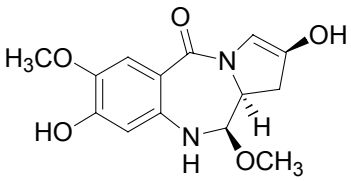
11 Sibiromycin



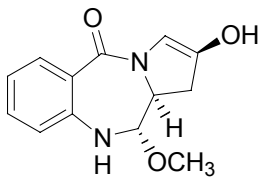
12 Tomaymycin (R_7=CH_3O, R_8=OH, R=CH_3)
13 Prothracarcin (R_7=R_8=H, R=CH_3)
14 Sibanomicin (R_7=sibirosamine pyranoside as in **11,** R8=H, R=Et)



15a Neothramycin A (R_3=H, R_3'=OH)
15b Neothramycin B (R_3=OH, R_3'=H)
16 DC-81 (R_3=R_3'=H)



17 Chicamycin A

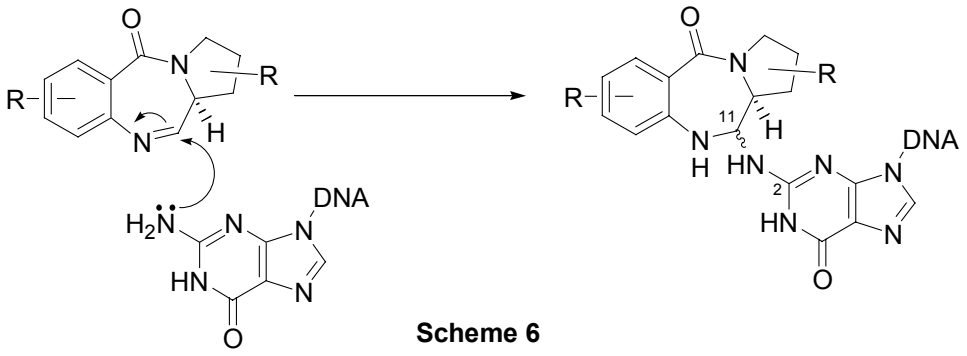


18 Abbeymycin

Scheme 5

The PBDs differ in the number, type, and position of substituents in both the aromatic A rings and pyrrolo C rings and in the nature of the C ring which is either fully saturated or unsaturated at either C(2)–C(3) (endocyclic) or at C(2) (exocyclic). In the B-ring there is either an imine (N=C), a carbinolamine (NH–CH(OH)) or a carbinolamine methyl ether (NH–CH(OMe)) at the N(10)–C(11) position which is the electrophilic center responsible for alkylating DNA. All naturally-occurring compounds possess the (S)-configuration at the chiral C11a which provides the molecules with a right-handed twist when viewed from the C ring toward the A ring. This provides the appropriate three-dimensional shape for snug fit within the minor groove of B-form double-stranded DNA spanning three base pairs, and consequently, the ability to form an adduct in the minor groove enables them to interfere with DNA processing, hence their use as antitumor agents. For instance, the structure of anthramycin methyl ether **8** based on X-ray crystallography data[29c] demonstrates the twist of the molecule that provides *isohelicity* with the minor groove of DNA. Racemization at C11a

can significantly reduce biological activity, and there is one example of a synthetic PBD with the (R)-configuration at C11a that is devoid of antitumor activity and DNA-binding affinity.[42] The mechanism of action of PBDs derives from their ability to bind covalently within the minor groove, thus interfering with DNA function.[43] After insertion in the minor groove, an aminal bond is formed through nucleophilic attack of the exocyclic N^2 of a guanine at the electrophilic C11-position (Scheme 6).



Scheme 6

Recently, the structure of the anthramycin-DNA adduct was studied by NMR, fluorescence spectroscopy, and molecular modelling techniques. Structure-activity relationship (SAR) predictions based upon CPK models have also been proposed by Thurston and Hurley.[42,44] DNA footprinting studies have demonstrated that, in general, PBDs bind to DNA in a sequence-selective manner with a preference for 5′-Pu-G-Pu motifs and indeed, the adducts span three base-pairs with a rank order of 5′-Pu-G-Pu > 5′-Pu-G-Py or 5′-Py-G-Pu > 5′-Py-G-Py sequences (where Pu = purine base, Py = pyrimidine base and G = guanine). Although recent high-field NMR and molecular modelling studies have provided detailed information about the precise three-dimensional structure of some PBD-adducts, including orientation of the molecule in the groove and stereochemistry at C-11 position, however, there is little understanding of the relationship between DNA-binding affinity, sequence-selectivity, and either *in vitro* cytotoxicity, or *in vivo* antitumor activity. More recently, PBDs have been joined through their C-8 positions to form potent irreversible DNA cross-linking agents with remarkable cross-linking efficiency and cytotoxicity.[45] NMR and modelling studies have

[42] Hurley, A. H., Reck, T., Thurston, D. E., Langley, D. R., Holden, K. G., Hertzberg, R. P., Hoover, J. R. E., Gallagher, G. Jr., Faucette, L. F., Mong, S.-M, Johnson, R. K., *Chem. Res. Toxicol.* **1988**, *1*, 258.

[43] Thurston, D. E., Advances in the study of pyrrolo[2,1-c][1,4]benzodiazepine (PBD) Antitumour Antibiotics. In *Molecular Aspects of Anticancer Drug-DNA Interactions*; Neider, S., Waring, M. J., Eds.; Macmillan Press Ltd.: U.K. **1993**; Vol. 1, pp 54-88.

[44] (a) Thurston, D. E., Hurley, L. H., *Drugs Future* **1983**, *8*, 957. (b) Hurley, L. H., Thurston, D. E., *Pharm. Res.* **1984**, *2*, 52.

[45] Kaneko, T.; Wong, H.; Doyle, T. W.; Rose, W. C; Bradner. W. T., *J. Med Chem.* **1985**, *28*, 388.

shown that these PBD dimers span six or seven base pairs compared to three for the parent PBD units.

In contrast to the anthramycin family, pyrrolo[2,1-c][1,4]benzodiazepine-5,11-diones are a class of compounds that bind to DNA by non-covalent interactions such as hydrophobic, *van-der-Waals* interactions and hydrogen bonding between ring substituents and DNA, and are also responsible for influencing sequence selectivity. Some dilactams such as (7-methoxy-2-methylcarbonyloxy-5,11-dioxo-(2S)-2,3,5,10,11,11a-hexahydro-1-*H*-pyrrolo[2,1-c][1,4]-benzodiazepine-5,11-dione-8-yl acetate is reported to possess significant *in vivo* anti-tumor activity in the P388 rat model.[44]

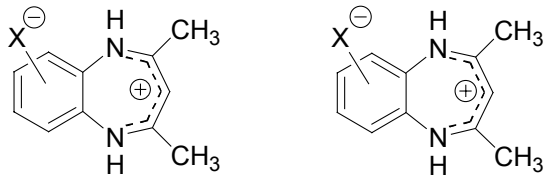
1.6. Purposes of the work

1.6.1. Anti-Hückel mesomeric betaines

In continuation of our research group activities on heterocyclic mesomeric betaines and highly charged heteroarenium compounds we developed our interest in synthesizing and studying new types of anti-Hückel mesomeric betaines. To the best of our knowledge, however, the synthetic efforts have been described always resulted in mesomeric betaines whose cationic segments contained (4n + 2) π-electrons and all of which were aromatic. In contrast, our interest was in synthesizing cationic segments containing (4n) π-electrons, i.e., anti-aromatic system, to ascertain their overall influence on the stability of the mesomeric betaines.

Whereas the first comprehensive classification of mesomeric betaines by Ollis, Stanforth, and Ramsden in 1985 resulted in a better understanding of 5- and 6-membered ring heterocyclic compounds, however, it is apparent that until now only a little information is available on 7-membered heterocyclic mesomeric betaines. Most of them rapidly decomposed after formation, or attempts made to synthesize them were failed. Obviously, the reason for these instabilities is the number of (4n) π-electrons in the cationic part, which contradicts the Hückel rule of aromaticity. We became interested in 1,5-benzodiazepine derivatives, which would result from an intramolecular proton shift and the formation of betainic structures. An additional impetus was the interesting game with the number of π-electrons delocalised in

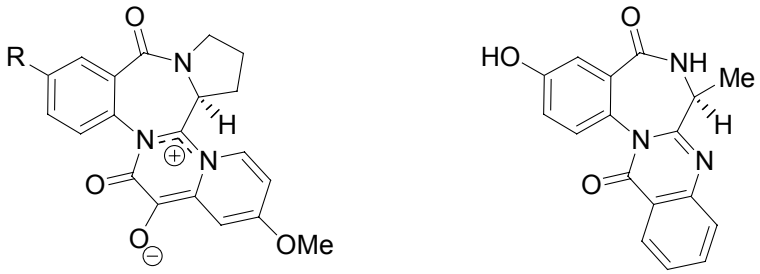
such systems. We intended to investigate here the syntheses and properties of 2,4-dimethyl-monosubstituted-6,7-benzo-1,5-diazepinium salts as hydrogensulfate, trifluoroacetate, and picrate which on deprotonation of the susceptible acidic group on benzene ring would lead to the corresponding stable 7-membered ring mesomeric betaines (Scheme 7). Moreover, in order to gain additional insights into these 4n π-electron systems, in particular on long distance C–N bond length as an effective force to overcome the anti-aromaticity of the system, we like to present typically the X-ray single crystal analysis of resulted 1,5-benzodiazepinium mesomeric betaines.



Scheme 7

1.6.2. On Circumdatins as mesomeric natural product betaines

According to a recent publication[46] three new benzodiazepine alkaloids, named Circumdatin A (**18**), B (**19**), and C (**20**), were isolated from the fungus *Aspergillus ochraceus* (Scheme 8 and Figure 5).



18: R = OMe
19: R = H

20

Scheme 8

[46] Rahbaek, L., Breinhold, J., Frisvad, J. C., Christophersen C., *J. Org. Chem*. **1999**, *64*, 1689.

Figure 5: *Aspergillus ochraceus*, found in grains, soil, and salted food.

The structures **18** and **19** consisted of a seven-membered benzodiazepine ring as part of a cyclic dipeptide, which involved anthranilic acid and L-proline and represent the first naturally occurring zwitterionic benzodiazepines. The fungus *Aspergillus ochraceus* is cultivated in Petri dishes with Czapek yeast extract agar after incubation at 25 °C for 22 days. The culture and media are extracted with EtOAc, giving a crude extract which is subjected to purification by liquid chromatography to afford eight fractions. A second fraction is further purified on a HPLC column to yield Circumdatin B as a pure red-orange solid with $[\alpha]^{22}_{D}$ – 163° (c 0.040, EtOH). Assuming the inability of HMBC technique to discriminate between two-, three, and in some cases, four-bound correlations, recourse has been taken to recently developed ^{1}H-detected INEPT2-INADEQUATE NMR (allows detection of coupling between pairs of carbon atoms of which at least one is protonated) and HMBC-INADEQUATE NMR (allows to correlate pairs of *J*-coupled carbon atoms of which at least one exhibits long-range coupling to a proton) experiments (Figure 6).

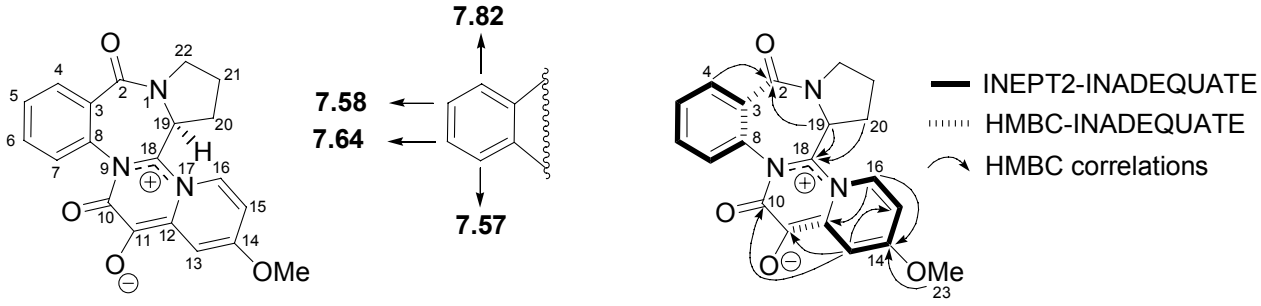


Figure 6

Supplementary, the proposed structural fragment C(10)–N(9)–C(18)–N(17) is reported to be in accordance with several naturally occurring benzodiazepines[47] and biosynthetic experiments with labelled ^{13}C-anthranilic acid are warranted in order to determine if anthranilic acid is a precursor for the pyridine skeleton in **19**.

In addition, the hydrolysis products of **19** in 6 *N* HCl were analysed by ^{1}H NMR and ESIMS identified major degradation products as anthranilic acid, proline, and anthranilic acid coupled with proline. The absolute configuration of the L-proline moiety was determined by reaction of the hydrolysis products with Marfey's reagent.

Taking the aforementioned structure elucidation of Circumdatin B into consideration, some doubts, however remain regarding to the betainic structure of this alkaloid which could be summarized as follows:

- First, the parent pyrido[1,2-c]pyrimidinium-3,4-diolate moiety is - to the best of our knowledge - without precedent in the chemistry of heterocyclic mesomeric betaines.
- Second, a considerable acidity of the α-hydrogen atom of the pyrrolidine moiety is to be expected due to the adjacent delocalised positive charge.
- Third, the resonance frequencies of the anthranilic acid partial structure are not in accordance with a cationic substituent at the benzene ring as they appear between δ = 7.57 and 7.82 ppm (Figure 6).
- Fourth, no stabilization of the negative charge can be expected with a methoxy group in the γ-position of the enolate moiety and it is not in accordance with Kröhnke's rule.

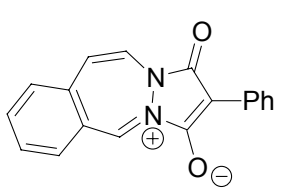
In order to ascertain the unambiguous structure elucidation of Circumdatin B we became interested at least in preparation of model compounds and relatively close structures for stereochemically and spectroscopic comparison.

[47] Sun, H. H., Barrow, C. J., Sedlock, D. M., Gillum, A. M., Cooper, I., *J. Antibiot.* **1994**, *47*, 515.

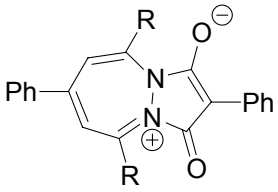
2. Anti-Hückel 7-Membered Ring Mesomeric Betaines

2.1. General introduction to 1,5-benzodiazepines

Since the first preparation of a mesomeric betaine (MB) by *Emil Fischer*[48] and the recognition that certain representatives play important biological roles as modified nucleobases or alkaloids, this class of compounds were found of considerable interest as valuable starting materials for the synthesis of heterocycles and natural product analogs, drugs, or indicators. However, the existence of 7-membered ring mesomeric betaines was rarely reported. The structures **21** and **22** are mentioned in the literature.[49] The betaine **21**, which was only identified by mass spectrometry, rapidly decomposed in solution. The syntheses of **22a** and **22b** failed. These observations are due to the number of 4n π-electrons (n = 3 or 2) in the cationic part, which contrasts with the Hückel rule.



21



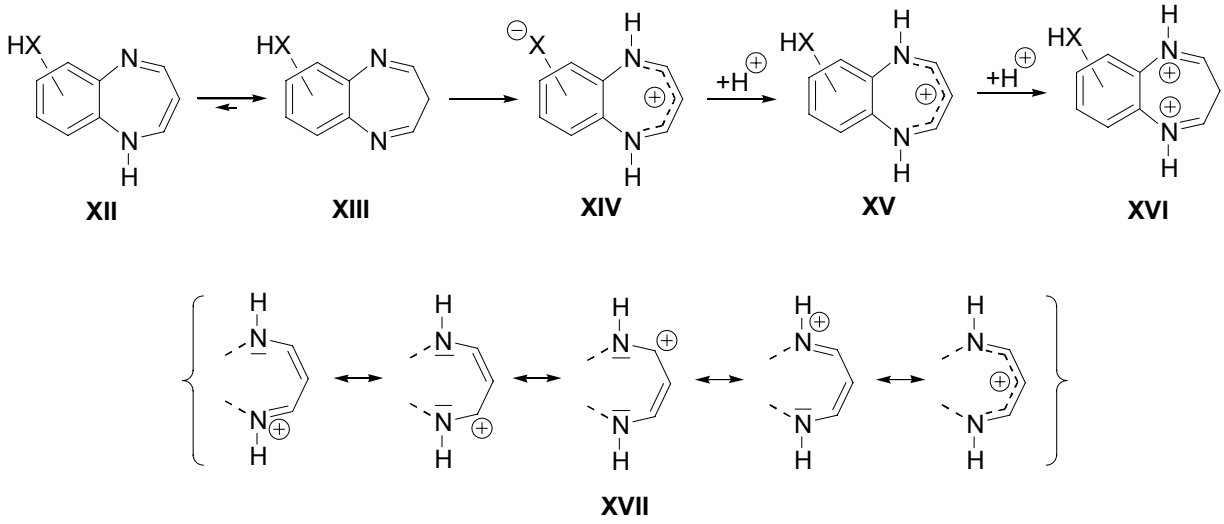
22a: R = Ph
22b: R = 4-C_6H_4OMe

Scheme 9

For the case of the benzo[b][1,4]diazepinium (1,5-benzodiazepinium) ring system, we intended to take advantage of the destabilizing number of electrons to force a charge-separation to a mesomeric betaine as shown in Scheme 10. It is known that the diimine form **XIII** of this ring system, from which numerous examples have been described, is more stable than the conjugated form **XII**. The latter would have 4n π-electrons associated with the 7-membered ring, which is electronically an analog of benzocyclooctatetraene. There is no positive contribution to the stability of the system by annular conjugation around either the diazepine ring or the overall periphery. Obviously, electronic interaction between the benzene ring and the two imino groups in the diimino form **XIII** and formation of the 3*H* tautomer, however, causes a considerable stabilization. To the best of our knowledge, the conversion into the mesomeric betaine **XIV**, which would have 4n π-electrons, has never been observed

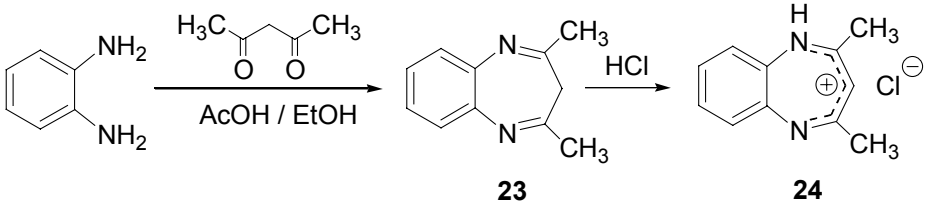
[48] Fischer, E., Besthorn, E., *Ann.* **1882**, *212*, 316.
[49] Potts, K. T., Murphy, P. M., Kuehnling, W. R., *J. Org. Chem*. **1988**, *53*, 2889.

to date. Betaine **XIV** contained a stabilizing, intensely colored vinamidinium chromophor **XVII** which is known to overcome the destabilizing influence of the number of 4n π-electrons in 1,5-benzodiazepinium salts like **XV**. In strongly acidic media, almost colorless bisiminium salts such as **XVI** have been observed.[16,50]



Scheme 10

The first example of 1,5-benzodiazepines, the 2,4-dimethyl derivative **23**, was prepared in 1907 by Thiele and Steimmig,[51] by condensation of *o*-phenylenediamine with acetylacetone in ethanol-acetic acid. Addition of hydrochloric acid precipitated the purple hydrochloride **24** (Scheme 11). Both base and salt are stable in moist air and in moderately strong acidic or basic solutions at ordinary temperature. To date, the most common method for the preparation of 1,5-benzodiazepines indeed remains the reaction of *o*-phenylenediamine with 1,3-dicarbonyl compounds.[52]



Scheme 11

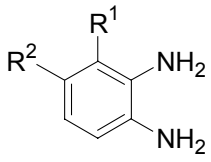
[50] (a) Boyd, G. V. in *Houben-Weyl:* '*Six-membered and Larger Hetero-Rings with Maximum Unsaturation*', Schaumann, E. (Ed.), Thieme Verlag, Stuttgart, New York, **1998**, Vol. E9d, p. 299. (b) Chimirri, A., Gitto, R., Grasso, S., Monforte, A. M., Omeo, G., Zappalà, M., *Heterocycles* **1993**, *36*, 865. (c) Fryer R. I., Walser, A., *Chem. Heterocycl. Compd*. **1991**, *50*, 209. (d) Lloyd, D., Cleghorn, H. P., *Adv. Heterocycl. Chem*. **1974**, *17*, 27.

[51] Thiele, J., Steimmig G., *Ber.* **1907**, *40*, 955.

[52] Linand, A. L., Hoch, J. M., *Arzneim.-Forsch.* **1984**, *34*, 640.

2.2. Synthesis of 1,2-diaminobenzene derivatives

We chose 2,3-diaminophenol **25**, 3,4-diaminophenol **26**, 3,4-diaminobenzenethiol **28**, 2,3-diaminobenzoic acid **29**, and 3,4-diaminobenzoic acid **30** as starting materials for the synthesis of betainic benzo[b][1,4]diazepines and as potentially negatively charged building elements of the target mesomeric betaines which would result from the formation of the olate, thiolate, and carboxylate group, respectively (Scheme 12). For spectroscopic comparison we used 4-methoxy-1,2-diaminobenzene **27** which cannot be deprotonated.

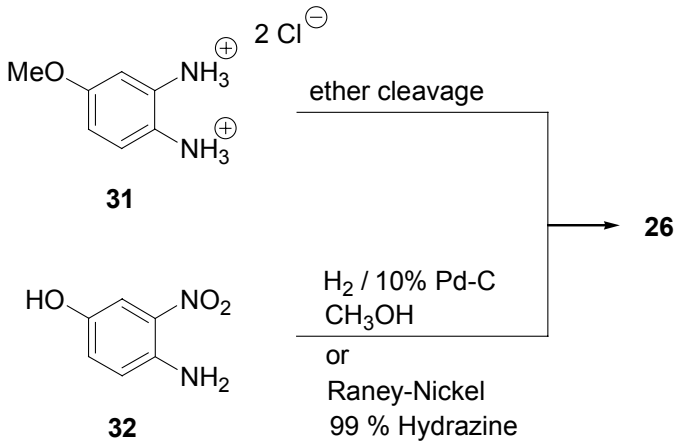


	R^1	R^2
25	OH	H
26	H	OH
27	H	OMe
28	H	SH
29	COOH	H
30	H	COOH

Scheme 12

The aromatics **26** and **28** were unknown, and the benzoic acid **29** was prepared by a modification of a patented procedure as described below. As ether cleavage of 4-methoxy-1,2-diaminobenzene dihydrochloride **31**, readily available by catalytic hydrogenation of 4-methoxy-2-nitroaniline in the presence of palladium/charcoal,[53] with HI, 48% HBr / tetra-*n*-butylphosphonium bromide and thiophenolate, respectively, proved to give only unsatisfactory yields of the starting material **26**, we chose an alternative approach. Thus, we found that hydrogenation of the readily available 4-amino-3-nitrophenol **32** in the presence of catalytic amounts of 10% Pd-C resulted in the formation of 3,4-diaminophenol **26** in good yield (Scheme 13). Moreover, the diamine **26** was elegantly prepared by reduction of starting material **32** with Raney-nickel in the presence of 98% hydrazine hydrate in quantitative yield.

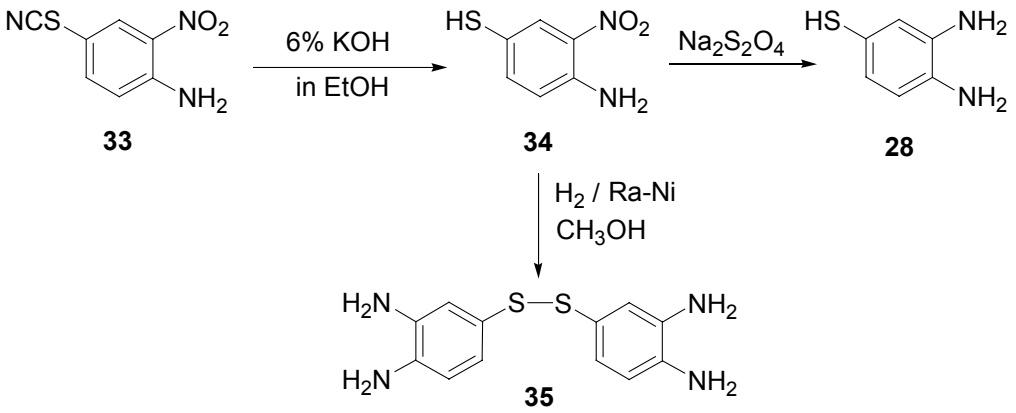
[53] Kim, J. S., Sun, Q., Yu, C., Liu, A., Liu, L. F., LaVoie, E. J., *Bioorg. Med. Chem.* **1998**, *6*, 163.



Scheme 13

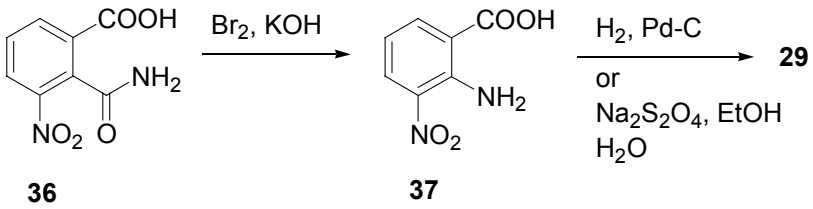
3,4-Diaminobenzenethiol **28** was synthesized in a three-step procedure. Sequential treatment of 2-nitroaniline with sodium thiocyanate and bromine in glacial acetic acid afforded 2-nitro-4-thiocyanatoaniline **33** in good yield.[54] We treated **33** with potassium hydroxide in ethanol to obtain 4-amino-3-nitrobenzenethiol **34** in 68% yield. The existence of the mercapto function was proved by a singlet at δ = 3.42 ppm in ^{1}H NMR spectroscopy which corresponds to one proton. Catalytical hydrogenation of **34** in the presence of Raney-nickel immediately yielded the symmetric disulfide **35** *via* the monomeric form on exposure to air in 54% yield (Scheme 14). This dimerization with atmospheric air in alkaline media has also been observed with other aromatic thiols[55] and can be monitored by the spontaneous formation of a nonpolar spot on the TLC. Correspondingly, the molecular peak is found at *m/z* = 279.1 amu (M + H$^+$) in ESI mass spectrometry. We found that performing the reduction of **34** with sodium dithionite in aqueous ethanol resulted in the formation of the desired starting material **28** in excellent yield. The thiol group gives a resonance frequency at δ = 3.36 ppm in ^{1}H NMR spectroscopy.

[54] Dalton, S. E., Gingell, W. G., Jenkins, D. C., King, L. G., Lee, G. E., Thompson, G. M., US Patent, Jan. 31, 1978, 4.071.528; *Chem. Abstr.* **1978**, *87*, 84983.
[55] Hirano, M., Yakabe, S., Chikamori, H., Clark, J. H., Morimoto, T., *J. Chem. Res. (S)* **1998**, 310.



Scheme 14

2,3-Diaminobenzoic acid **29** was prepared starting from 2-nitrophthalic acid anhydride[56], which was treated with ammonia to yield 3-nitrophthalamic acid **36**. Hofmann rearrangement with potassium hydroxide and bromine afforded 2-amino-3-nitrobenzoic acid **37** which was finally reduced with hydrogen in the presence of palladium/charcoal or sodium dithionite in 50% aqueous ethanol to 2,3-diaminobenzoic acid **29** which we obtained as brown needles after recrystallization (Scheme 15).



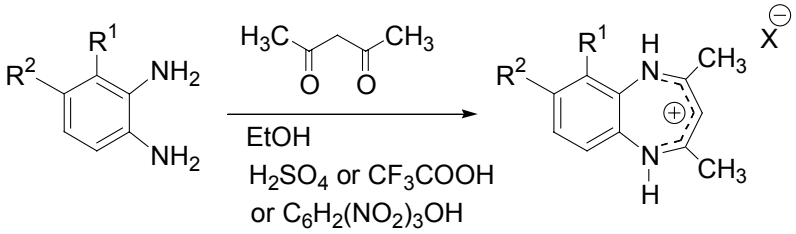
Scheme 15

2.3. Synthesis of benzodiazepinium salts

The diamines were reacted with stoichiometric amounts of 2,4-pentanedione in ethanol at room temperature in the presence of sulfuric acid or trifluoroacetic acid to give the corresponding 1,5-benzodiazepinium salts **38a,b**–**43a,b** in high yields as intensely violet solids, respectively (Scheme 16).[57] It proved to be advantageous to conduct the condensation of the less reactive α-carboxy derivative **30** to **43a** in hydrochloric acid. Anion exchange to hydrogensulfate was then accomplished with excess sulfuric acid.

[56] Griffin, R. J., Calvert, A. H., Curtin, N. J., Newell, D. R., Golding, B. T., US Patent, Oct. 30. 2001, 6.310.082; *Chem. Abstr.* **2001**, *126*, 212151.

[57] The diazepinium **43** was already described as perchlorate: Lloyd, D., McDougall, R. H., and Marshall, D. R., *J. Chem. Soc.* **1965**, 3785.



25 - 30

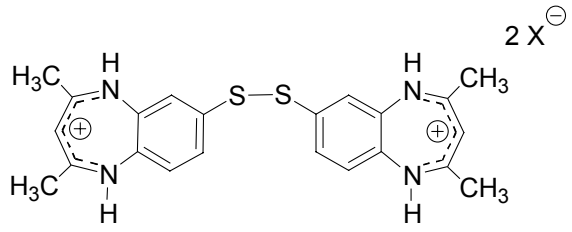
38a - 43a: X = HSO_4
38b - 43b: X = CF_3COO
38c - 40c: X = picrate

	R^1	R^2
25, 38	OH	H
26, 39	H	OH
27, 40	H	OMe
28, 41	H	SH
29, 42	COOH	H
30, 43	H	COOH

Scheme 16

Moreover, reaction of the 1,2-diaminobenzenes **25**–**27** with acetylacetone in ethanol in the presence of picric acid gave the 1,5-benzodiazepinium picrates **38c**–**40c** as intensely violet crystals. The presence of picric acid proved to be advantageous in comparison with other acids because the resulting salts readily precipitate from the reaction mixture and are analytically pure after washing with diethyl ether (Scheme 16). Not unexpected, the products are protonated due to the strong acidity of picric acid (pK_a 0.25).

The bisulfide **35** yielded the bis(benzodiazepinium) salts **44** (Scheme 17).



44a: X = HSO_4
44b: X = CF_3COO

Scheme 17

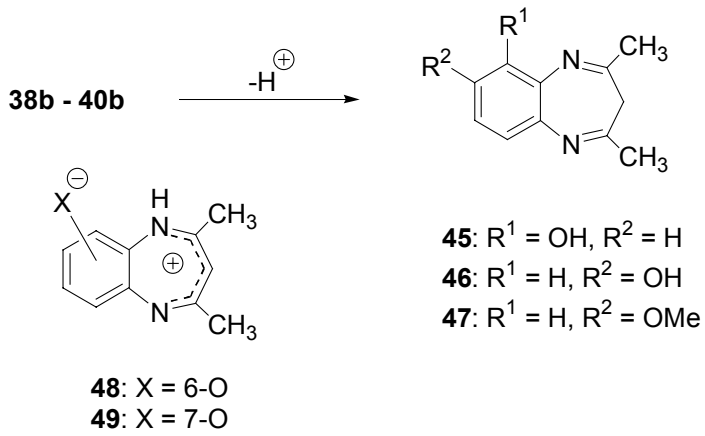
Depending on the substitution pattern the benzo[b][1,4]diazepinium hydrogensulfates **38a**–**44a,** trifluoroacetates **38b**–**44b**, and the picrates display characteristic UV-VIS absorption maxima between $\lambda_{max}(H_2O)$ = 482 nm and 536 nm which is due to the stabilizing vinamidinium chromophor. Correspondingly, C(3) of the salts **38**–**44** give signals between δ =

94 ppm and 99 ppm in ^{13}C NMR spectroscopy, and the NH groups of the chromophor are detectable at δ = 9.82–10.75 ppm and 9.68–9.82 ppm in DMSO-d_6, respectively. All attempts to methylate the salts at the vinamidinium chromophor with methyl iodide in DMF in the presence of potassium carbonate, or dimethylsulfate, methyltrifluoromethylsulfonate, and Meerwein's reagent failed.

2.4. Betaine Formation

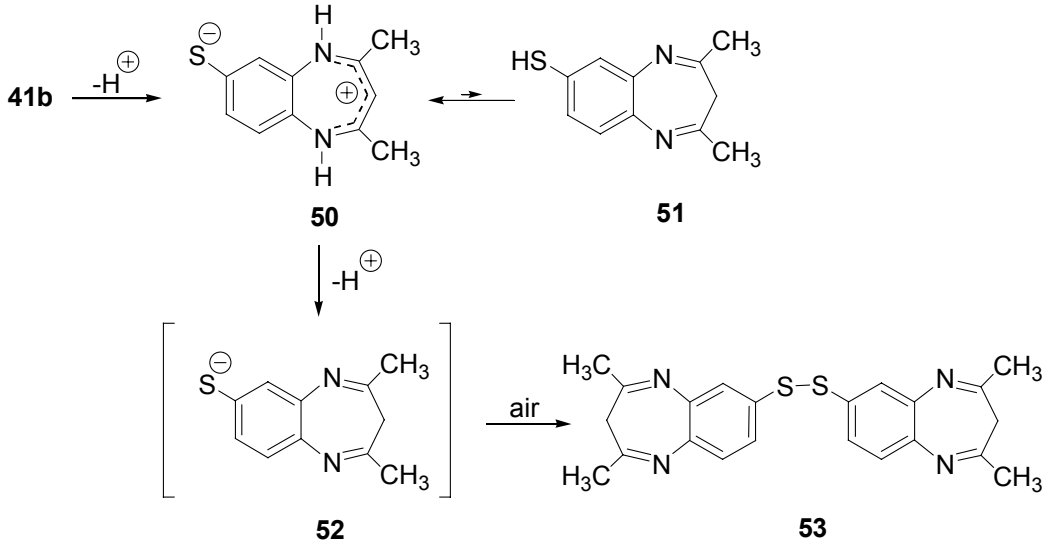
The trifluoroacetates were used for titrations in order to prevent protonation/deprotonation equilibria between hydrogensulfate and sulfate. The pK_a values for the monocation **XV**/base **XIII** equilibria of benzo[b][1,4]benzodiazepines, which is a combination of the equilibria of the species **XII**, **XIII**, and **XV** depicted in Scheme 10, were determined to be approximately 5.[58] The pK_a for the monocation **XV**/dication **XVI** equilibrium was found to be approximately –1.[59] Titration of 6-hydroxy-benzo[b][1,4]diazepine **38b** with 0.1 *N* NaOH gives a typical titration curve of a weak acid with a strong base. The release of a proton from one of the NH groups (pK_a 7.8 in H_2O at 25 °C) results in the immediate formation of the diimine form **45**. An analogous behaviour was observed on titration of the 7-hydroxy and the 7-methoxy derivatives, the pK_a values of which were determined to be 8.9 and 6.8 in water at 25 °C, respectively. These deprotonations can easily be observed by a decolorization of the initially deeply violet solutions to pale yellow and can be monitored by UV-VIS spectroscopy. On deprotonation, the aromatic protons 7-H, 8-H, and 9-H of *e.g.* **38b** shift from δ = 6.54, 6.79, and 5.99 ppm, respectively, to δ = 7.02, 6.72, and 6.65 ppm. In the diimine form, the OH protons of **38b** and **39b** are still detectable at δ = 8.69 and δ = 9.12 ppm, respectively. A comparison with the methoxy derivatives **40b** and **47** reveals that mesomeric betaines such as **48** and **49** do not form (Scheme 18).

[58] (a) Schwarzenbach, G., Lütz, K., *Helv. Chim. Acta* **1940**, *23*, 1147. (b) Halford, J. O., Fitch, R. M., *J. Am. Chem. Soc*. **1963**, *85*, 3354. (c) El-Rabbat, N. A., Youssef, A. F., Omar, N. M., *Analyst (London)* **1980**, 165.
[59] Schwarzenbach, G., Lütz, K., *Helv. Chim. Acta* **1940**, *23*, 1162.



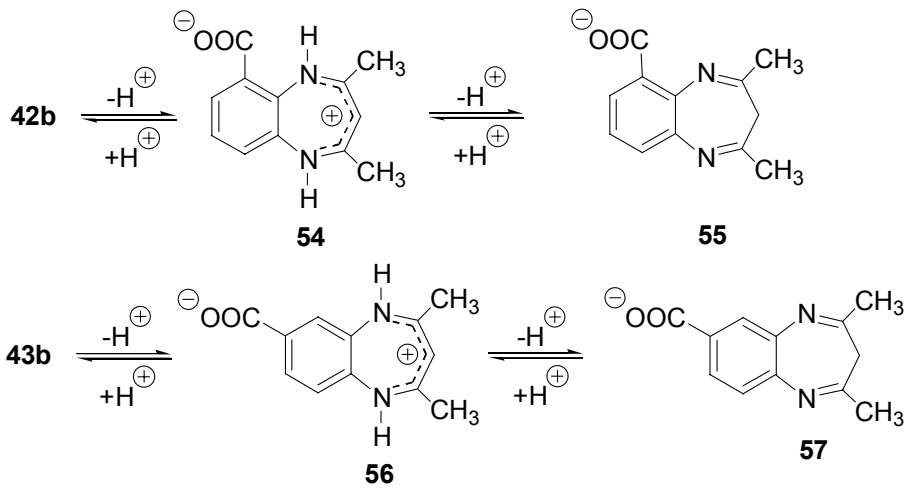
Scheme 18

By contrast, the thiol **41b** readily forms a mesomeric betaine **50** as violet solid on increasing the *p*H of the solution. Two pK_a values at 3.3 and 7.1 were determined on titration of **41b** with 0.1 *N* NaOH in water at 25 °C. Unambiguously, the mesomeric betaine and not the tautomeric diimine **51** forms at pK_a = 3.3, because the characteristic UV-VIS absorption maximum at λ_{max} = 536 nm remains unchanged. Thus, the vinamidinium chromophor still is intact. The second release of a proton obviously forms the instable anionic species **52**, which immediately dimerizes on air to the pale yellow colored disulfide **53** (Scheme 19). Correspondingly, no anionic species were detected in the electrospray ionisation mass spectra (ESIMS) measured in the negative ion detection mode. Instead, in accordance to structure **53** the base peak of the spectrum is detected at *m/z* = 429.0 amu ($M + Na^+$) in the positive ion detection mode spraying from methanol.



Scheme 19

Next, we turned our attention to the benzoic acid derivatives **42** and **43**. In agreement with the spontaneous formation of mesomeric betaines in water, aqueous solutions of the salts are acidic while UV-VIS absorption maxima of the vinamidinium chromophor were found at λ_{max} (H_2O) = 498 nm and 520 nm, respectively. On titration of **42b** with 0.1 *N* NaOH in water at 25 °C the mesomeric betaine **54** precipitates as a slightly violet solid at *p*H values above 2.6, and at *p*H above 8.8 the mixture becomes colorless. However, we were not able to isolate the anionic species **55** which decomposed according to an NMR spectrum taken in D_2O/NaOD. The titration of the carboxy derivative **43b** with 0.1 *N* NaOH (Figure 7) clearly proves the release of two protons on increasing the *p*H. The pK_a values were determined to be 4.8 and 9.8, and can unambiguously be attributed to the deprotonation of the carboxylic acid which causes the formation of the mesomeric betaine **56**, followed by deprotonation of the vinamidinium chromophor, forming the diimine **57** as sodium salt (Scheme 20).



Scheme 20

The cation-betaine transition can unambiguously be proved by UV-VIS spectroscopy. Thus, the vinamidinium group remains intact after the first deprotonation, as absorption maximum at λ_{max} = 526 nm is detectable in the range between *p*H 2.2 (pure substance in H_2O) and 7.0 (Figure 8).

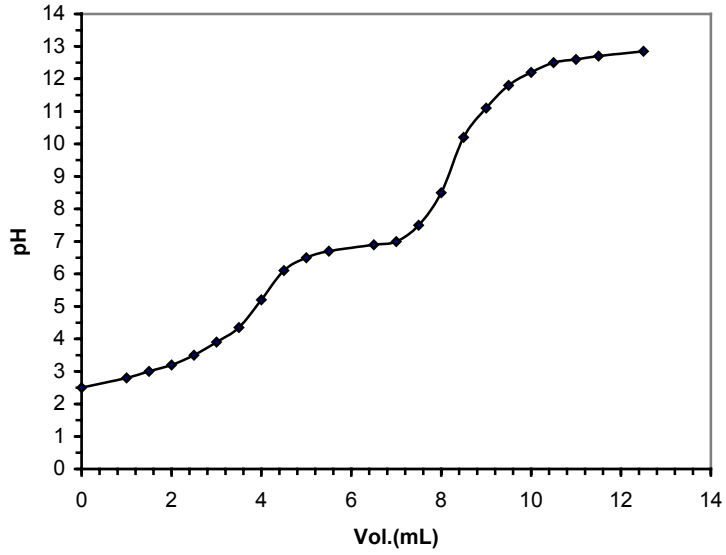


Figure 7: Titration curve of **43b** (NaOH, 0.1 *N*).

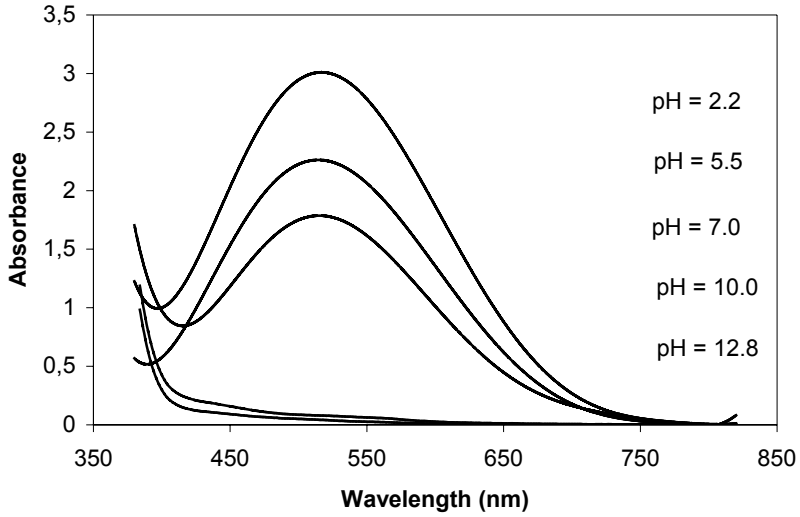


Figure 8: Absorbance *vs.* wavelength (nm) of **43b** in various *p*H in H_2O (0.25% w/v)

The formation of the mesomeric betaine **56** is accompanied by broadening of the ^{1}H NMR signals, which shift slightly to lower (6-H) and higher field (9-H), respectively. ^{1}H NMR measurements of **43b** in D_2O at various *p*D values adjusted by 0.1 *N* NaOD in D_2O were performed in order to confirm the structure, and to exclude decompositions, ring contractions to benzimidazoles, or ring cleavages from consideration. We focused our attention on the benzene ring protons, because these protons are more stable toward exchange with deuterium (Figure 9). In accordance with the results of the NMR titration and the UV-VIS measurements, the ^{1}H NMR taken in D_2O at *p*D 5.1 display the pure betaine **56**, whereas the spectra between *p*D 5.70 and 7.20 show a mixture of the mesomeric betaine and the diimine **57**. The anionic diimine **57** gives resonance frequencies at δ = 7.79 (6-H), 7.71 (8-H), 7.14 (9-

H), and 2.82 ppm (CH_2) in DMSO-d_6, and the imine carbon atoms appear at δ = 158.31 and 157.91 ppm in ^{13}C NMR spectroscopy. The electrospray ionization mass spectrometric measurements of the pure compound clearly prove the existence of sodium salt. Thus, the intense peak of the anion $C_{12}H_{11}N_2O_2^-$ of **57** is detected at *m/z* = 215.1 amu (100%) in the negative ion detection mode, spraying a sample from methanol at 0 V fragmentor voltage. An additional peak is found at *m/z* = 454.1 amu which corresponds to a dimerised anionic species plus one sodium.

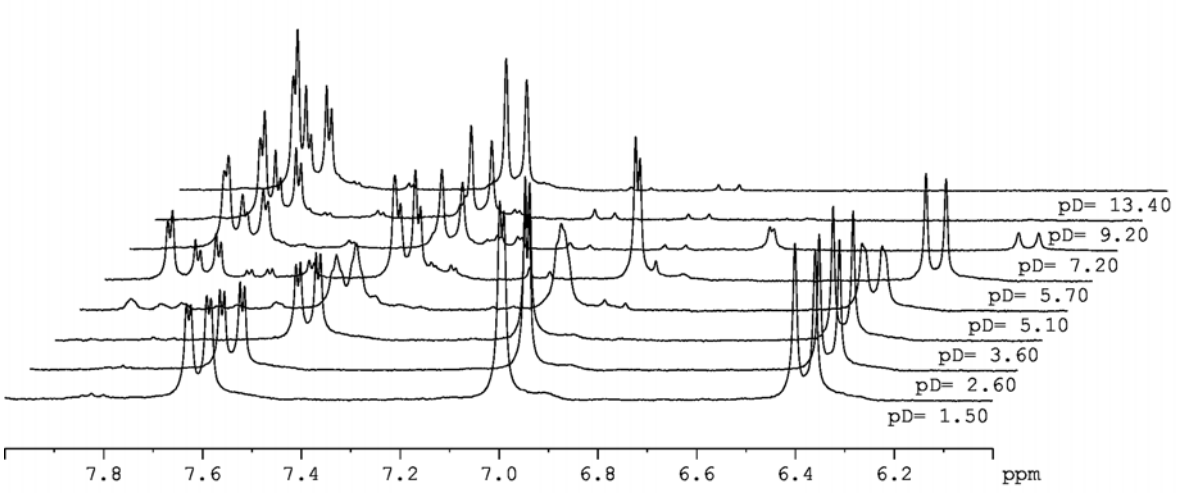


Figure 9: ^1H NMR spectra of **22b** at various pD values at 25°C.

2.5. X-Ray structural analysis

In order to gain additional insights into the structure we tried to obtain single crystals for an X-ray analysis. We were finally successful in that by slow evaporation of a concentrated solution of a 1:1 mixture of 7-carboxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepinium **43** and picric acid in methanol. As a consequence of the strong acidity of picric acid (pK_a 0.25), the substance crystallized as a salt. The elemental cell contains three molecules, the benzodiazepinium cation, the picrate anion, and one molecule of methanol. The crystallographic numbering of the molecule is shown in Figure 10.

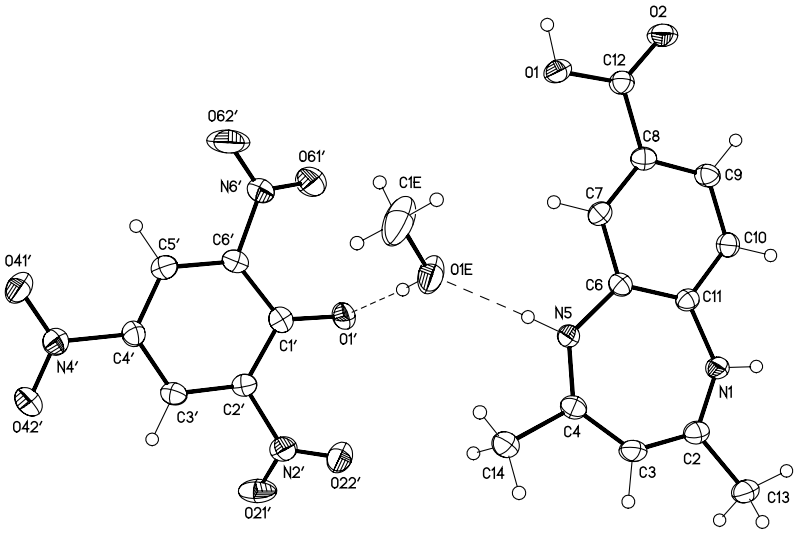


Figure 10: ORTEP plot of **43** as picrate.

As a confirmation of the ^{1}H NMR spectrum and titration curve, the ORTEP drawing shows the presence of a COOH group which is slightly twisted out of the plane of the benzene ring and which is hydrogen bonded to the COOH group of another molecule. The corresponding dihedral angle C(7)–C(8)–C(12)–O(2) is 175.74(17)°. In addition, the nitrogen atoms are slightly twisted out of the plane of the benzene ring [N(5)–C(6)–C(11)–C(10) = 177.16(16)°], and the 7-membered ring is slightly twisted as well [C(3)–C(4)–N(5)–C(6) = – 6.4(3)°; C(11)–N(1)–C(2)–C(3) = 4.6(3)°].

By contrast, X-ray analyses of 2,4-dimethylbenzodiazepinium chloride[60] and hexafluorophosphate[61] as well as of the hydrochloride of 2,4-dimethylnaphthodiazepine showed nearly planar structures. The vinamidinium chromophor has bond distances characteristic of a fully delocalised 6π push-pull electron system. Thus, the bond lengths N(1)–C(2) and C(4)–N(5) are 133.4(2) and 132.3(2) pm, respectively. The bond distances between C(2) and C(3), and between C(3) and C(4) were determined to be 138.4(3) and 139.4(3) pm, respectively, and are longer than corresponding bond lengths in reported molecules.[55,56] As the bond distances between the vinamidinium chromophor and the benzene ring are very large [N(1)–C(11) = 141.9(2) pm; N(5)–C(6) = 142.6(2) pm] for C(sp^2)–N–bonds, there obviously is no considerable electronic interaction between these two parts of the molecule. This result strongly confirms, that the (4n π)-mesomeric betaines described here

[60] Speakman, J. C., Wilson, F. B., *Acta Crystallogr*., *Sect. B* **1976**, B*32*, 622.
[61] Rodier, N., Agafonev, A., Dubois, P., Mariand, M., Levillain, P., and Sense, J. M., *Acta Crystallogr., Sect. C* **1993**, C*49*, 156.

contain isolated cationic and anionic segments as in **XVII** (Scheme 10), and that the charges are exclusively restricted to separate parts of the conjugated system. In the crystal the benzodiazepinium molecules form several hydrogen bonds. The N(1)H (crystallographic numbering) forms a hydrogen bond to the olate group of the picrate, and N(5)H to the oxygen atom of crystallisation methanol. Two molecules form stacks at a distance of 343 pm which is slightly more than the two-fold *van-der-Waals* radii of carbon atoms (r_{vdW} = 165–170 pm). Two benzodiazepinium molecules are head-to-tail orientated. The stacked molecules are additionally connected by two sets of three N(5)–H…(Me)O–H…$OC_6H_2(NO_2)_3$…N(1)´–H hydrogen bonds.

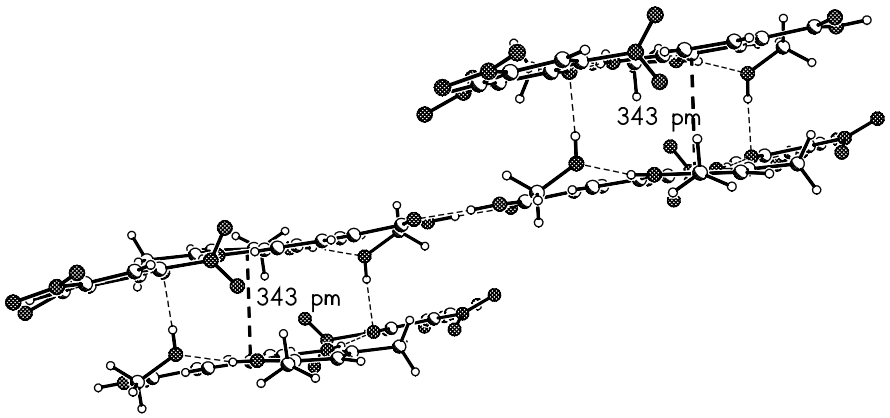


Figure 10: ORTEP-drawing of the hydrogen-bonded tetrameric interactions of compound **43** as picrate.

Complementary information was evolved from an X-Ray analysis of single crystals of 1,5-diazepinium picrate **38c**, which was obtained by slow evaporation of a concentrated solution in acetone. The compound crystallized triclinic with one molecule of acetone of crystallisation (Figure 11).

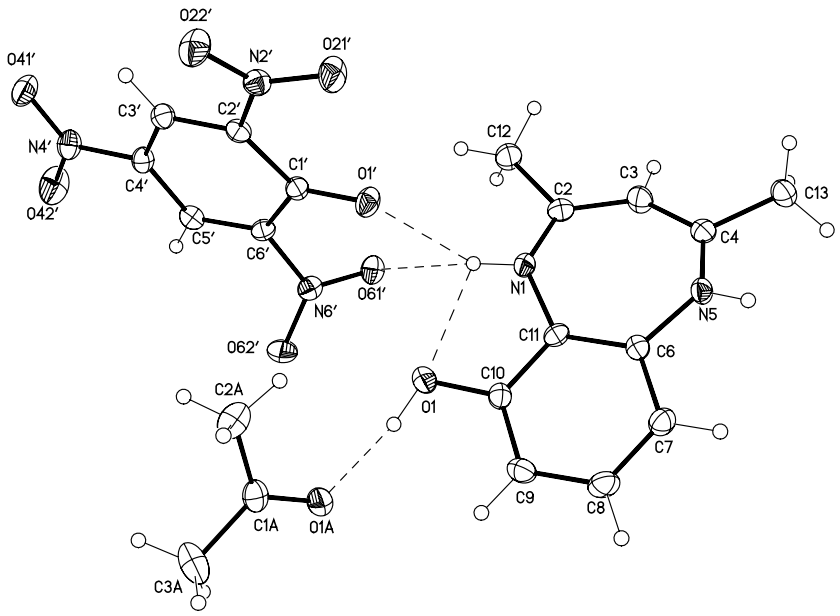


Figure 11: ORTEP plot of **38c**.

The dihedral angles C(3)–C(4)–N(5)–C(6) = 13(2)° and C(11)–N(1)–C(2)–C(3) = – 10.3(2)° confirm the slightly helical structure of the diazepinium moiety which was also found in 2,3-dihydro-1,4-diazepines[62] and mixed crystals consisting of 2,4-dimethylbenzodiazepinium and benzene-1,2-diammonium cations and chloride anions.[63] As expected, the bond distances in the vinamidinium chromophor N(1)–C(2)–C(3)–C(4)–N(5) are in agreement with the extensive delocalisation of 6 π-electrons, but they are slightly longer than reported in other systems. By contrast, the bond lengths N(1)–C(11) and N(5)–C(6) are 142.48(18) pm and 142.38(18) pm, respectively, and thus separate the benzene moiety from the 7-membered ring. And so, the molecule avoids a conjugation of 4n π-electrons around the periphery of the rings by isolation of the two parts of the molecule. The bond angles in the 7-membered ring are larger than the 120° expected for sp^2-hybridized carbon atoms.

Several hydrogen bonds are formed between the three molecules. One intramolecular hydrogen bond is detected between N(1)–H and the oxygen atom of the 6-hydroxy group (Figure 11). The hydrogen atom of this group forms a hydrogen bond to the carbonyl oxygen atom of the acetone molecule of crystallisation. The hydrogen bonds between the acidic N(1)–H group of the diazepinium moiety and the olate group of the picrate anion on one hand, and between N(1)–H and one of the oxygen atom of one of the *ortho*-nitro groups of the picrate on the other stabilize the layers of 1,5-benzodiazepines (Figure 12). The individual molecules

[62] Brisander, M., Harris, S. G., Lloyd, D., McNab, H., Parsons, S., *J. Chem. Res. (S)* **1998**, 72.
[63] Svensson, C., Timby, L., *Cryst. Struct. Commun*. **1981**, *10*, 429.

are in the layers head-to-tail orientated in such a way, that the 7-membered rings are overlapped (Figure 13). The olate group and two oxygen atoms of the *ortho*-nitro groups of the picrate combine two stacked 1,5-benzodiazepine molecules by hydrogen bonds through N(1)–H and N(5)–H.

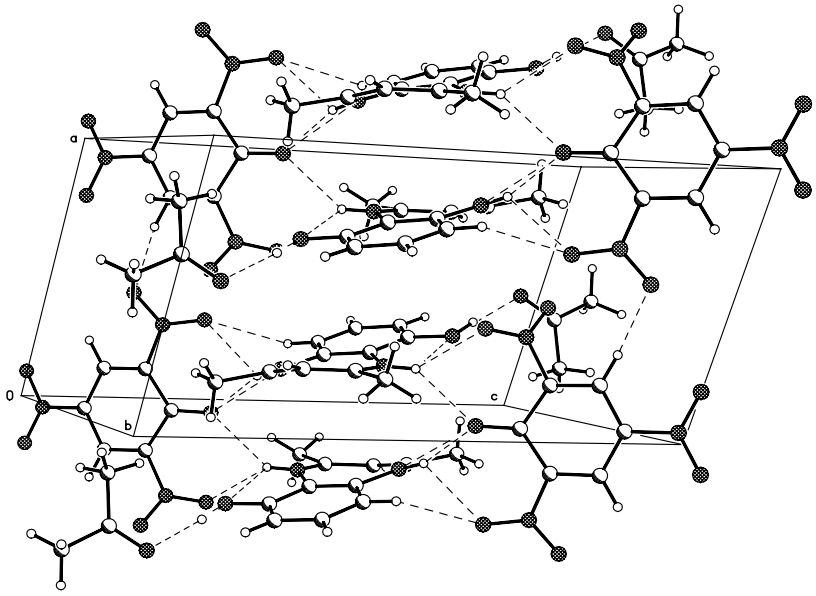


Figure 12

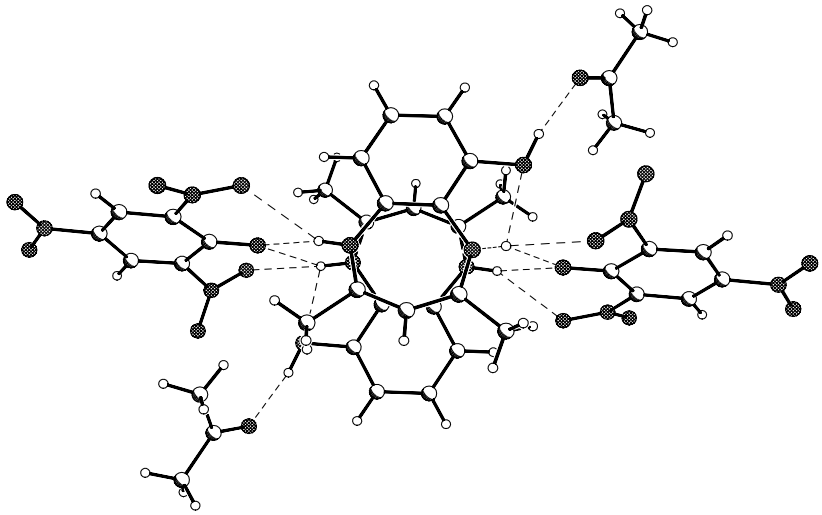


Figure 13

The distance between two molecules of 1,5-benzodiazepinium in two layers is 368 pm which is larger than the two-fold *van-der-Waals* radii of carbon [r_{vdW} = 165–170 pm] and nitrogen [r_{vdW} = 155 pm], respectively (Figure 14).

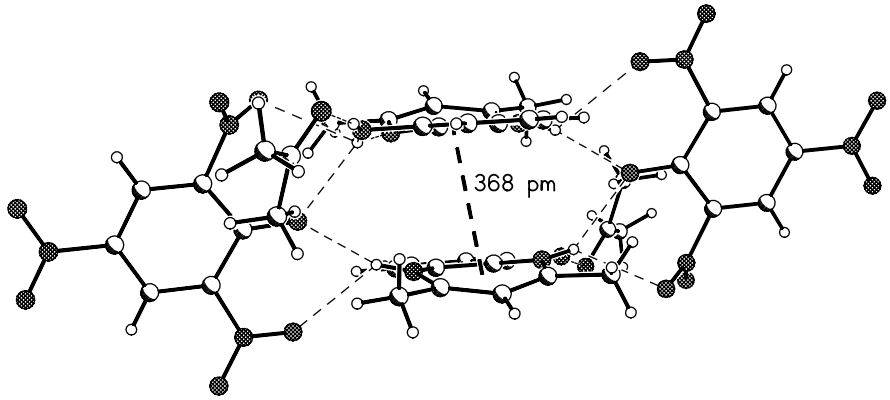


Figure 14

2.6. Classification of the 4n π-electron mesomeric betaines

Structures of the mercaptobetaine **50** can be drawn with the negative charge delocalized in the benzene ring as well as in the 7-membered ring. Formally, common atoms for the delocalization of the positive as well as of the negative charges exist, and this fact is characteristic for conjugated mesomeric betaines (CMB). As the X-ray analysis of **43** revealed, however, obviously there is *no conjugation* between the positive and the negative part of the molecule, because this would result in the conjugation of 4n π-electrons. Thus, the classification of **50** as conjugated mesomeric betaine seems not to be unambiguous. In contrast, due to the long C–N bonds, the negative charges in the mesomeric betaines **54** and **56** are *exclusively* restricted to separated parts of the molecule which is characteristic for cross-conjugated mesomeric betaines (CCMB). In conclusion, in completion of the former MB classification we were able to establish the first representatives of stable 7-membered ring mesomeric betaines.

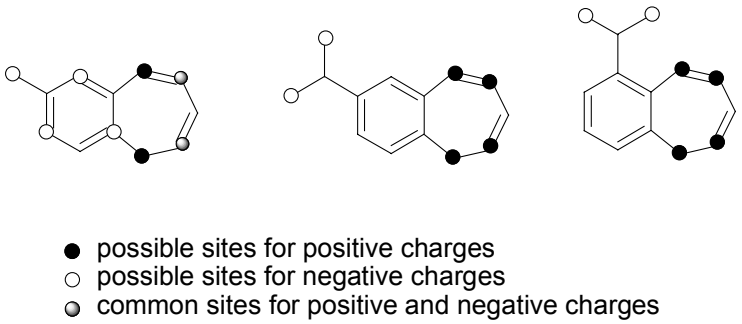


Figure 15: Charge distribution according to the canonical formulae of benzodiazepinium-olates and -thiolates (left), and -carboxylates (middle and right).

3. Annulated Pyrrolobenzodiazepine Model Compounds

3.1. General introduction to annulated pyrrolo[2,1-c][1,4]benzodiazepine derivatives

In continuation of our growing interest in alkaloids, nucleobase betaines and ionic heteroaromatics we became interested in this class of compounds, because some alkaloids, Circumdatin A–G, were isolated from the fungus *Aspergillus ochraceus* and were suggested to be suitable chemotaxonomic markers for this species. Total syntheses of Circumdatin C and F,[64] and a building block approach to a diverse multi-arrayed library of the Circumdatin family using an aza-Wittig reaction[65] were published recently. We focussed our attention on compounds related to the proposed structures **18** and **19** for Circumdatin A and B in order to study stereochemical and spectroscopic effects of possible tautomerisations, in particular in view of the biological relevance of the twisted conformation of the pyrrolobenzodiazepine ring system. In this chapter, the investigations concerning syntheses and surprising spectroscopic properties of structures related to these natural products, including 11-aminosubstituted and dioxopyrimidine annulated pyrrolobenzodiazepines were reported, which are first representatives of a new ring system. In addition the syntheses and properties of thiazolidinone annulated pyrrolobenzodiazepines which - to the best of our knowledge - are the first representatives of a new ring system have been investigated. We focussed our attention on the potential tautomerism of the thiazole moiety, which is known to be complex[66] and strongly influenced by the nature and location of the substituents, solvents and architecture of the molecule.[67] Thus, three forms, thiazolidin-4-one, thiazol-4-ols as well as mesoionic partial structures had to be taken into consideration. The latter mentioned aromatic thioisomünchnone caused an intact (*S*)-configurated pyrrolidine moiety of this biologically highly important ring system. The aromaticity indices, I_A indicates that the mesoionic forms have comparable aromaticities to the parent hydroxy thiazoles.[68] Finally we wish here to report the syntheses and characterizations of 1,3-imidazol-4-one- and 1,3-pyrimidin-4-one-

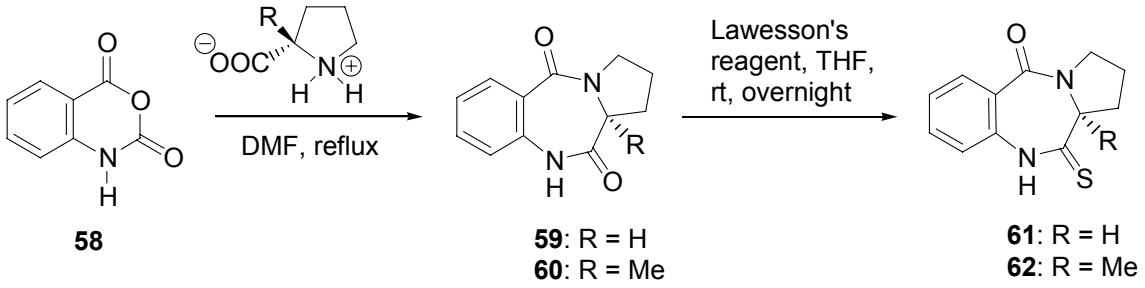
[64] Witt, A., Bergman, J., *J. Org. Chem*. **2001**, *66*, 2784.
[65] Grieder, A., Thomas, A. W., *Synthesis* **2003**, 1707.
[66] Elguero, J., Marzin, C., Katritzky, A. R., and Linda, P., in '*The Tautomerism of Heterocycles*,' Academic Press, New York, **1976**, p. 363.
[67] Kikelj, D., Urleb, U., in '*Science of Synthesis*,' Vol. 11, ed. by E. Schaumann, Chapter 11.17, Thieme Verlag, Stuttgart, **2002**, p. 627.
[68] Bird, C. W., *Heterocycles* **1994**, *37*, 249.

annulated pyrrolobenzodiazepines species, which are important structure elements of the proposed structures, and investigations of the synthetic approaches and spectroscopic properties.

3.2. 11-Aminosubstituted pyrrolobenzodiazepines

3.2.1. Synthesis of cyclic amidines

We started our investigation from the pyrrolo[2,1-*c*][1,4]benzodiazepine natural product **59** (from *Isatis indigotica*[69]) which is readily available by refluxing isatoic anhydride **58** with (*S*)-proline in DMF by literature procedures.[70,71] Its methylated derivative **60** was obtained analogously starting from (*S*)-methyl proline. Thionation in THF at room temperature with 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent)[72] resulted in the formation of the monothiolactams **61** and **62** in good yields.



58 **59**: R = H, **60**: R = Me **61**: R = H, **62**: R = Me

Scheme 21

The monothiolactams **61** and **62** react with amines such as ammonia, methylamine, aniline, and piperidine in the presence of mercury(II)chloride to the cyclic amidines **63**–**67** in high yields (Scheme 22). Alternatively, amidation could be catalysed in the presence of bismuth compounds such as $BiCl_3$ or $Bi(NO_3)_3.5H_2O$ salts, which are commercially available, inexpensive and easy to handle. This method deals as a substitute for the toxic $HgCl_2$ methodology.[73]

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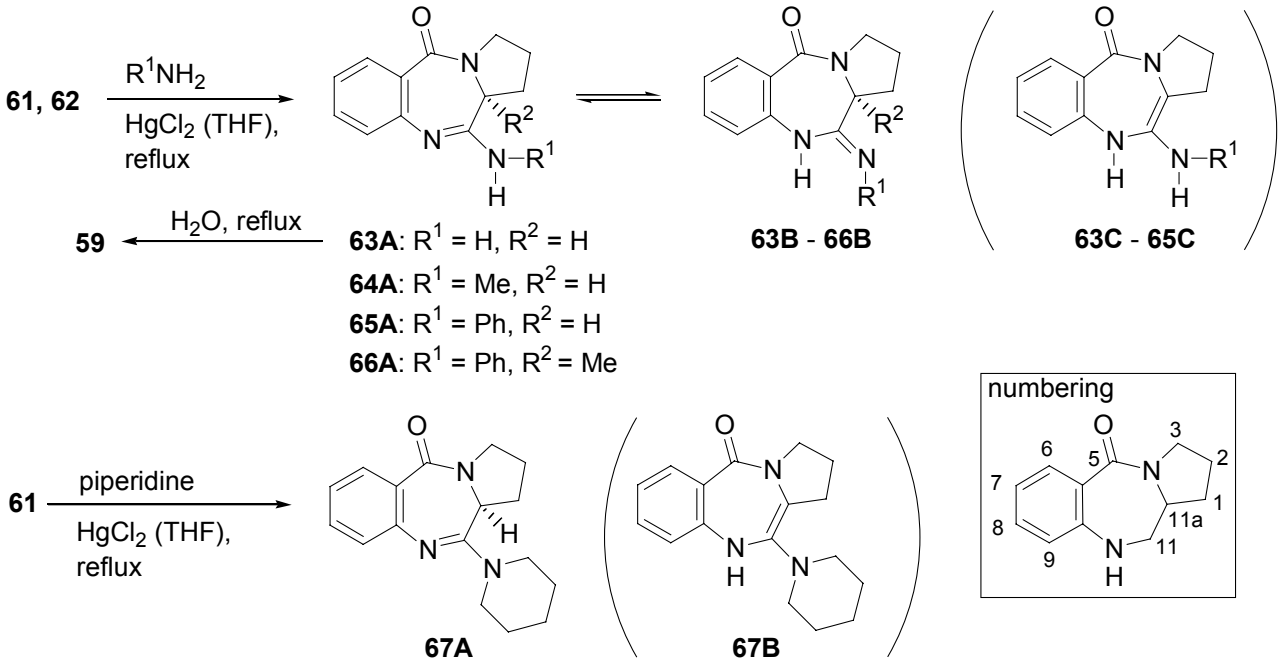
[69] Wu, X., Y. Liu, W. Sheng, J. Sun, G. Qin, *Planta Med*. **1997**, *63*, 55.
[70] Kamal, A., *J. Org. Chem*. **1991**, *56*, 2237.
[71] Wright, Jr., W. B., Brabander, H. J., Greenblatt, E. N., Day, I. P., Hardy, Jr., R. A., *J. Med. Chem*. **1978**, *21*, 1087.
[72] Kamal, A., Howard, P. W., Reddy, B. S. N., Reddy, B. S. P., Thurston, D. E., *Tetrahedron* **1997**, *53*, 3223.
[73] Cunha, S., Lima, B. R., Souza, A. R., *Tetrahedron Lett.* **2002**, *43*, 49.



Scheme 22

We observed that the neat reaction of **61** and the amines (aniline and piperidine) gave better yields than reactions conducted in THF. The *N*-unsubstituted amidine **63** reacts quantitatively to the starting material **59** on heating in water or dilute aqueous sodium hydroxide. We obtained **63**, **64** and **66** as optically active compounds, whereas **65** racemized under these conditions. In the ^{1}H NMR spectra of **64**–**66** in $CDCl_3$ at 20 °C only one set of signals is present. In DMSO-d_6 at 20 °C, however, two distinct tautomeric forms of **64**–**66** are detectable. In contrast to **64**–**66**, only one tautomer of the amidine **63** in DMSO-d_6 and MeOD is observable. One broad H/D-exchangeable signal of two protons with a center of gravity at δ = 7.49 ppm in DMSO-d_6 provides strong evidence for the formation of the tautomer **63A** under these conditions. Unambiguous peak assignments by a combination of HSQC and HMBC NMR experiments proved the coupling of the more deshielded NH-group with the two *ortho*-protons of the aniline moiety and C(11a)–H of **65**, and couplings of the more shielded NH–group with C(9)–H and C(11a)–H, respectively. Thus, at 20 °C the ratios of **64A** : **64B**, **65A** : **65B**, and **66A** : **66B** in DMSO-d_6 were determined to be 10 : 11, 10 : 6, and 10 : 12, respectively. These ratios are changing with temperature. As an example, the ratio **65A** : **65B** changes to 10 : 11 at 100 °C in DMSO-d_6 (Figure 16).

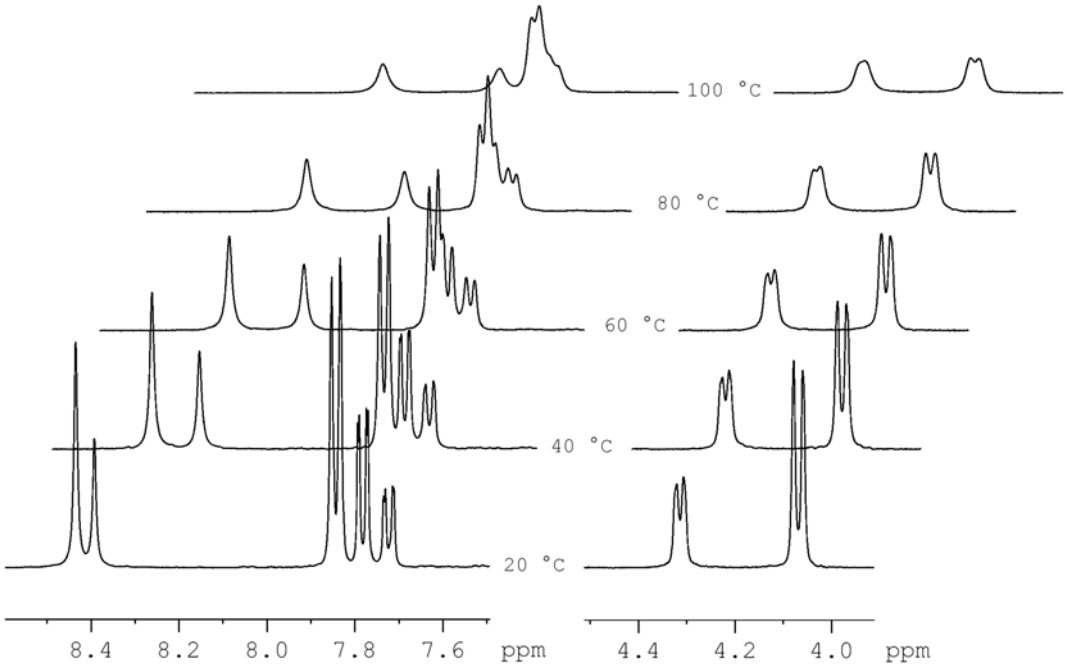
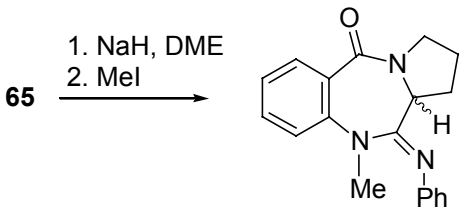


Figure 16: Stacked VT-^{1}H NMR experiment of **65** in DMSO-d_6.

The tautomeric forms **63C**, **64C** and **65C**, which are assumed to be responsible for racemization of the pyrrolidine moiety, were not detected spectroscopically. A control experiment with the piperidino derivative **67** confirmed these observations. No traces of **67B** were found in the ^{1}H NMR spectra in DMSO-d_6; only one set of signals was observable regardless of the solvent used.

Methylation of racemic **65** with sodium hydride and methyl iodide gives only one product **68**, as evidenced by couplings of the methyl group to C(9a) and C(11) in HMBC-NMR experiments.



68

Scheme 23

3.2.2. X-Ray structural analysis of amidines

In the solid state, compound **65** forms the exocyclic imine **65B** in the *Z*-configuration as evidenced by a single crystal X-ray analysis (Figure 17). The phenylimino group is strongly twisted out of the plane defined by the phenyl ring of the benzodiazepine moiety. The bond length of the C=N bond [crystallographic numbering: C(2)–N(2)] was determined to be 128.03(13) pm, whereas the distance between N(10)–C(11) [N(1)–C(2)] is 138.07(13) pm. The bond length between C-11 and C-11a [C(2)–C(2A)] is 151.61(13) pm.

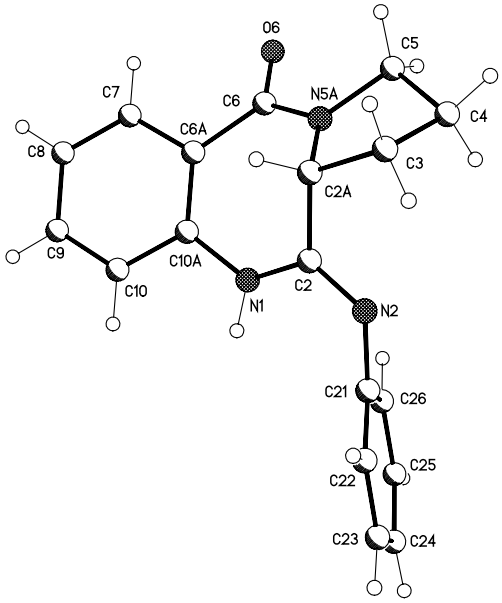


Figure 17: Molecular structure of **65** according to a single crystal X-ray analysis.

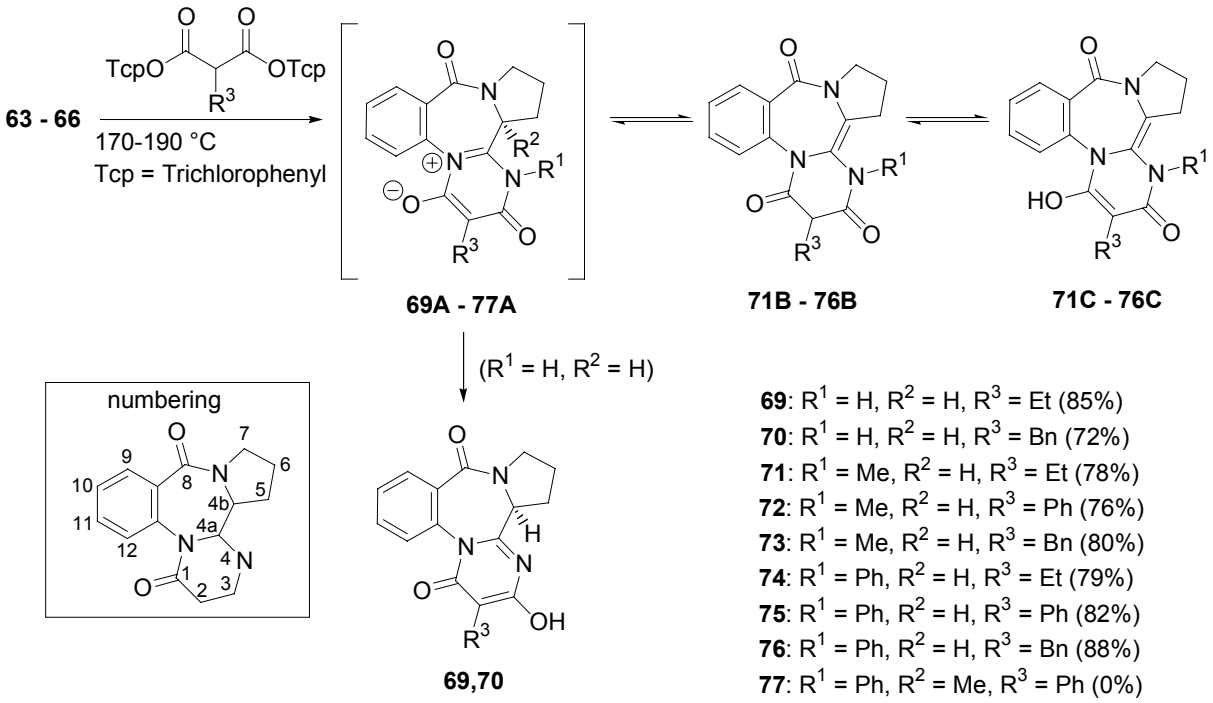
3.3. Pyrimidine annulated pyrrolo[2,1-c][1,4]benzodiazepines

3.3.1. Synthesis of oxopyrimidines

Neat reaction of the amidines **63**–**66** with bis(2,4,6-trichlorophenyl)-2-phenylmalonates in a *Zincke* apparatus resulted in the formation of the pyrimidine-annulated pyrrolo-

benzodiazepines **69**–**77** and the leaving group 2,4,6-trichlorophenol which can be distilled off during the reaction. Dependent on the substitution pattern **69**–**77** form different tautomers in solution as well as in the solid state. Thus, only the 4,7a,12b-triaza-dibenzo[*e,g*]azulenes **69** and **70** resulting from the N^{11}-unsubstituted pyrrolobenzodiazepine **63** were isolated as optically active compounds. These two new compounds form only one tautomer in DMSO-d_6, MeOD, and $CDCl_3$ at room temperature, respectively, as evidenced by ^{1}H NMR spectroscopy. A combination of HMBC and HSQC NMR unambiguously proved the existence of enolic partial structures in **69** and **70** under these conditions, as couplings between 4b-*H* and C-5, C-6, and C-4a were detected. The latest mentioned carbon atom C-4a appears at δ = 157.4 ppm (**69**) and 158.0 ppm (**70**). The carbon atom C-2 is sp^2 hybridized and appears at δ = 103.5 ppm (**11**) and 101.6 ppm (**70**). The hydroxy group causes one broad, H/D-exchangeable signal at δ = 11.45 ppm in DMSO-d_6 and at δ = 6.34 ppm in $CDCl_3$ in the ^{1}H NMR spectra. NOESY experiments of **69**, which possesses the *N*-(3-oxopropenyl)formamidine chromophor, provide evidence for close proximities between the hydroxy group at C-3 and the ethyl group as well as C-5 of the pyrrolidine ring.

In contrast to this, the pyrrolobenzodiazepines derived from the N^{11}-substituted pyrrolobenzodiazepines **64** and **65** form the tautomers **71**–**76** in good yields on recrystallization of the residue as faintly yellow solids, whereas no isolable compounds were obtained starting from the methylated species **66** (Scheme 23). All NMR spectra taken in $CDCl_3$ are in agreement with tautomers **71B**–**76B** which resulted from deprotonation of the α-hydrogen atoms of the pyrrolidine ring. The NMR spectrum in $CDCl_3$ clearly indicates the existence of only three CH_2-groups, and one CH-group which is joined to ethyl, phenyl and benzyl respectively. The latter carbon atom C-2, which appears between δ = 53.6 ppm and 55.8 ppm, unambiguously is in sp^3 hybridized. HMBC and HSQC NMR measurements displayed couplings of C-2 with the ethyl, phenyl and benzyl groups, respectively. These results prove the formation of a 3*H*-2,4-dioxopyrimidine ring and a sp^2 hybridized C-11a in tautomers **71B**–**76B** instead of the cross-conjugated mesomeric betaines **71A**–**76A** in $CDCl_3$ solution which would resemble to the proposed structures of Circumdatin A and B. Moreover, these findings explain the failure of the reaction of **66** to **77**, which would be compelled to adopt a betainic structure **77A** which obviously is not stable.



Scheme 24

A striking feature of 2-phenylpyrimidines **(72** and **75)**, however, is a doubling of the ^{1}H NMR and ^{13}C NMR resonance frequencies in DMSO-d_6, C_6D_6, DMF-d_7, and MeOD (Figures 17 and 18). Whereas traces of acids and bases, respectively, do not cause any changes of the spectra taken in $CDCl_3$, on addition of DMSO-d_6 into this solution a splitting of the signals is observable, the chemical shift difference of which depends on the relative concentration of these two solvents.

As evidenced by HSQC, HMBC, NOESY experiments and ^{13}C NMR, either form of **75** possesses the C(=O)–CHPh–C(=O) partial structure, so that the formation of tautomers such as the mesomeric betaine **75A** and enols such as **75C** in the solvents mentioned above were excluded from consideration. NOESY-experiments, however, detected closely spaced protons of the pyrrolidine and of the phenyl ring at C-2 (15-*H*↔5-*H*, 15-*H*↔6-*H* 15-*H*↔7-*H*, 16-*H*↔5-*H*, 16-*H*↔6-*H*) in one of the two conformers, which is observable in the spectra. This finding provides evidence for a conformation of **75** in which these partial structures are in close proximity and which cause the more shielded resonance frequencies. A boat conformation of the dioxopyrimidine moiety with an axial phenyl ring at C-2 could explain the proximity of these partial structures, and this assumption was supported by the chemical shift difference of 2-*H* which is in agreement to axial and equatorial positions. Interconversion of the ring system obviously is fast in $CDCl_3$. As $CDCl_3$-solutions solidified

to glassy materials on cooling, however, we were prevented from taking NMR spectra at low temperatures.

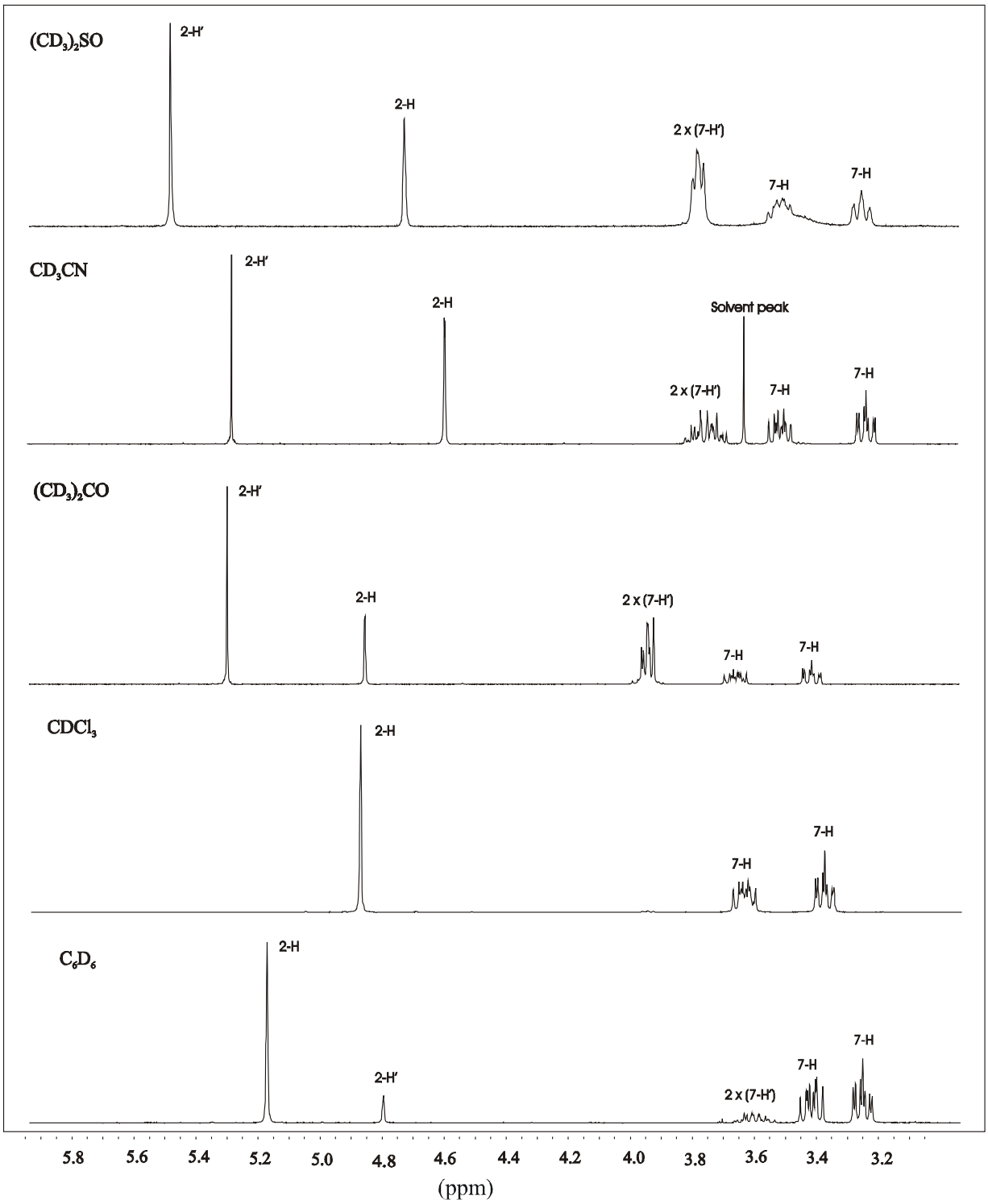


Figure 17: ^{1}H NMR-spectra of **75** in various solvents.

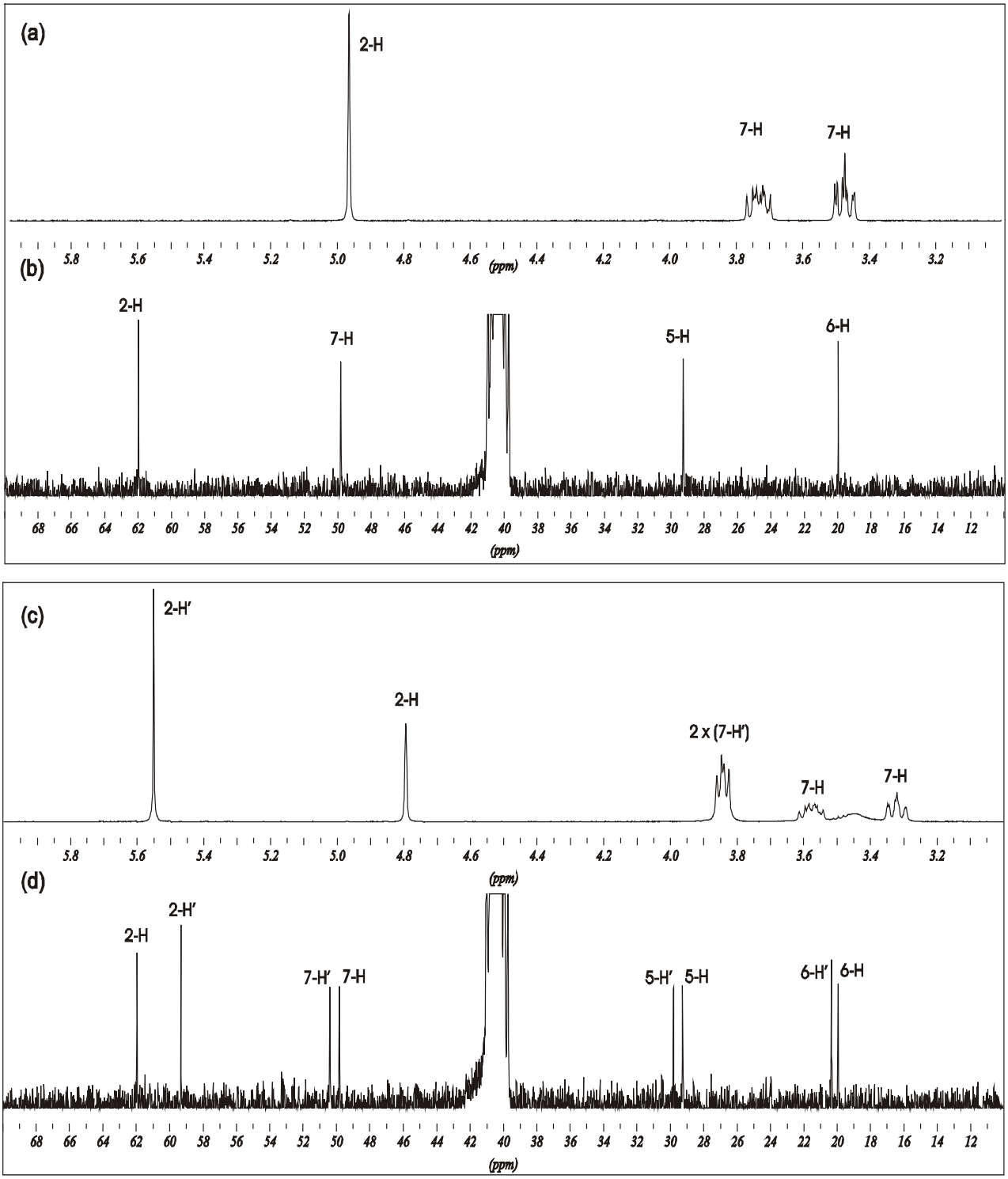


Figure 18: ^{1}H and ^{13}C NMR of 2,4-dioxopyrimidine **75** in $CDCl_3$ (a, b) and DMSO-d_6 (c, d).

We were able to unambiguously assign the resonance frequencies to the two forms from the spectra and our results are presented in Table 1.

Table 1: Chemical Shifts of **75** in $CDCl_3$ and DMSO-d_6.

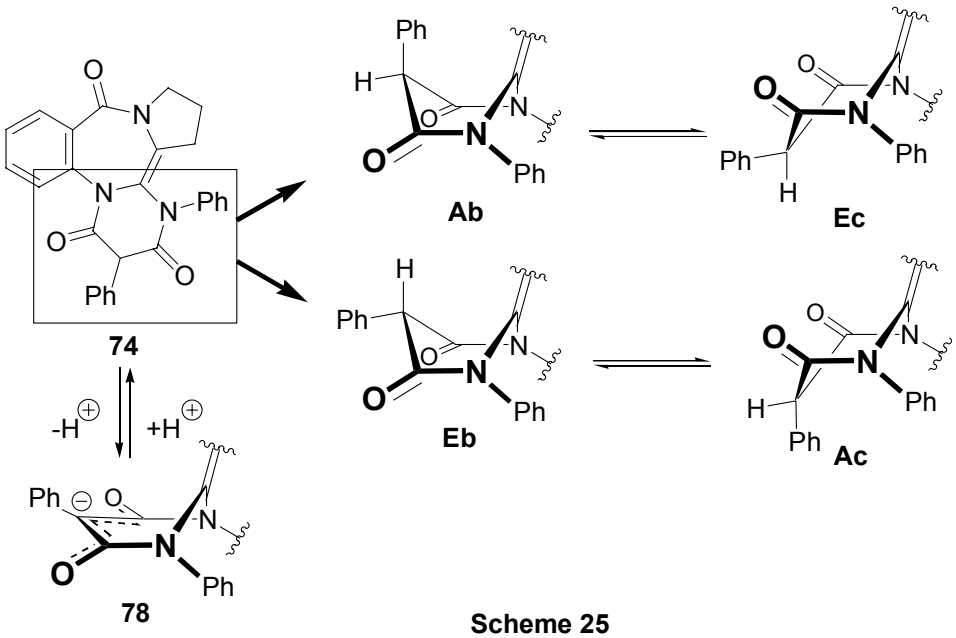
position	$CDCl_3$		DMSO-d_6	
	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR
1		166.7		166.2 / 166.7
2	4.94 (s)	62.3	4.79 (s) / 5.54 (s)	59.3 / 62.0
3		166.7		166.5 / 166.8
4a[a]		128.6		128.9
4b		119.3		118.7 / 118.1
5	1.61 – 1.65 (m)	29.3	1.63 – 1.68 (m) / 1.87 – 2.01 (m)	29.3 / 29.8
	1.73 – 1.80 (m)		1.79 – 1.84 (m) / 1.87 – 2.01 (m)	
6	0.88 – 1.00 (m)	19.8	0.83 – 0.94 (m) / 1.77 – 1.85 (m)	19.9 / 20.3
	1.54 – 1.60 (m)		1.58 – 1.62 (m) / 1.77 – 1.85 (m)	
7	3.41 – 3.47 (m)	49.5	3.29 – 3.35 (m) / 3.82 – 3.86 (m)	49.8 / 50.4
	3.66 – 3.73 (m)		3.55 – 3.62 (m) / 3.82 – 3.86 (m)	
8		165.2		164.8 / 165.3
8a		139.5		139.9
9	8.08 (dd)	132.9	7.92 (dd) / 7.93 – 7.96 (m)	132.5
10	7.70 (ddd)	134.1	7.76 – 7.77 (m) / 7.72 – 7.74 (m)	134.2 / 134.4
11	7.48 (ddd)	128.4	7.51 – 7.55 (m) / 7.48 – 7.52 (m)	128.7
12	7.53 (dd)	126.2	7.75 (d) / 7.71 – 7.72 (m)	127.3 / 127.4
12a		139.5		140.4
13[a]		133.2		133.4
14	7.40 – 7.44 (m)	126.3	7.45 – 7.48 (m)	126.5
15	7.37 – 7.40 (m)	129.5	7.37 – 7.39 (m)	129.9
16	7.35 – 7.37 (m)	132.1	7.41 – 7.42 (m)	128.9
17		139.0		139.5
18	7.18 – 7.20 (m)	124.2	7.18 – 7.21 (m)	124.9 / 125.1
19	7.29 – 7.33 (m)	129.7	7.33 – 7.35 (m)	130.1
20	7.15 – 7.18 (m)	126.8	7.22 – 7.23 (m)	127.1

a : peak assignments exchangeable

In order to confirm these assumptions, we performed *ab-initio* calculations on boat and chair conformations of the dioxopyrimidine ring of **75** with equatorial (**Ec**, **Eb**) and axial (**Ab**, **Ac**) substituents at C-2, respectively (Scheme 25). All calculations were carried out with the projector-augmented wave method as implemented in the PAW programme.[74,75] The calculations show that the boat conformation with axial phenyl ring (**Ab**) has indeed the lowest total energy. The difference to the boat conformation with equatorial phenyl ring (**Eb**) is ΔE = 8.9 KJ/mol. Both, axial (**Ac**) and equatorial phenyl rings (**Ec**) in chair conformation have a higher energy of ΔE = 78.0 KJ/mol and ΔE = 58.2 KJ/mol, respectively. In addition, the calculations show twisted conformations of the pyrrolobenzodiazepine partial structure.

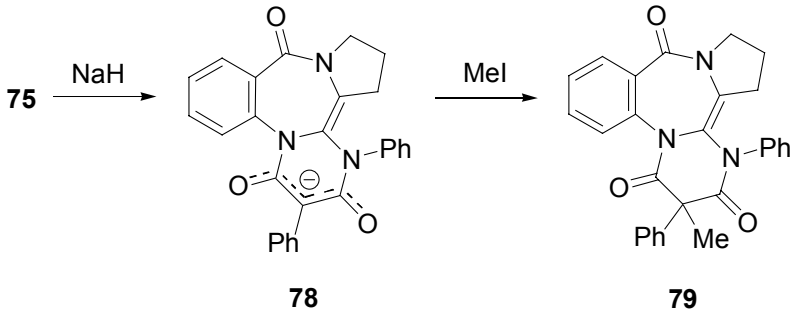
[74] Blöchl, P. E., *Phys. Rev. B.* **1994**, *50*, 17953.

[75] The wavefunctions were expanded into augmented plane waves up to a cutoff energy of 30 Ry (408 eV), the densitiy up to 60 Ry (816 eV). The number of projector functions of (s,p,d) type were as follows: H: (1,0,0); C, N, O: (1,1,0). The frozen-core approximation was employed for the corresponding next-lower noble-gas shell, that is, a [He] core for C, N and O. Periodic boundary conditions were used, with an fcc unit cell spanned by the lattice vectors [0.0 12.5 12.5], [12.5 0.0 12.5], [12.5 12.5 0.0] (in Å). To prevent electrostatic interactions between the periodic images, the charge decoupling scheme due to Blöchl was used. The calculations were done within the local-density approximation as parameterized by Perdew and Wang with gradient corrections for exchange and correlation due to Perdew, Becke and Ernzerhof.



Scheme 25

Conversion of the configuration at C-2 of **75** must proceed *via* an anionic species **78** as represented in Scheme 25. On isomerisation, the phenyl ring changes from an axial into an equatorial position, which must be accompanied, by a considerable change of the NMR signals. In order to confirm these assumptions, we deprotonated **75** with NaH in dimethoxyethane and indeed obtained the anionic molecule **78** which is a stable yellow solid. The anion displays a single set of signals in the ^{1}H NMR spectra, regardless of the solvent used. In electrospray ionization mass spectrometry in methanol in the negative ion detection mode, the molecular peaks appear at *m/z* = 434.0 u as base peak. Methylation of the salt **78** with methyl iodide gave **79** in good yield.



Scheme 26

3.3.2. X-Ray structural analysis of oxopyrimidines

The *ab-initio* calculation results are in qualitative agreement with an X-ray single crystal analysis of **75** which shows tautomer **75B** in the solid state (Figure 19): The 6:7:5 pyrrolobenzodiazepine ring system adopts a twisted conformation. The C(6)–C(7) bond distance is 132.71(16) pm (calcd.: 135.2 pm) which corresponds to a $C(sp^2)=C(sp^2)$ double bond. This C=C–bond is twisted due to the helicity of the 6:7:5 ring system, so that the dihedral angles N(1)–C(6)–C(7)–N(11) and N(5)–C(6)–C(7)–C(8) are 4.77(18)° and 6.37(19)°, respectively [calcd. 4.9° and 4.7°, resp.]. In the elemental cell, the 3*H*-2,4-dioxopyrimidine ring adopts a boat-like conformation with C(6) and C(3) above the plane formed by N(1), N(5), C(4), and C(2), and the phenyl ring at C(3) in axial position (Figure 20). The phenyl ring is twisted by – 30.16(12)° [C(4)–C(3)–C(31)–C(32), calcd. – 34.2°].

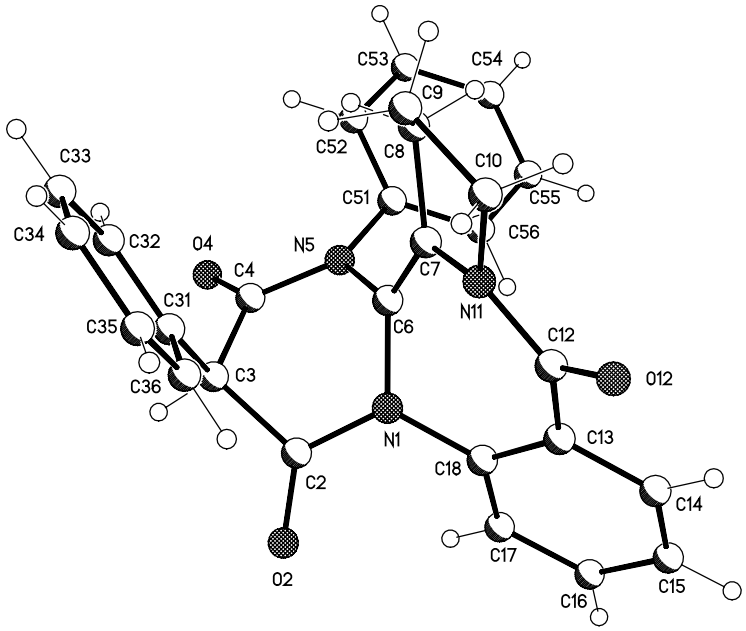


Figure 19: Results of an X-ray analysis of **75**. The drawing shows the helicity of the benzopyrrolodiazepine moiety of **75**.

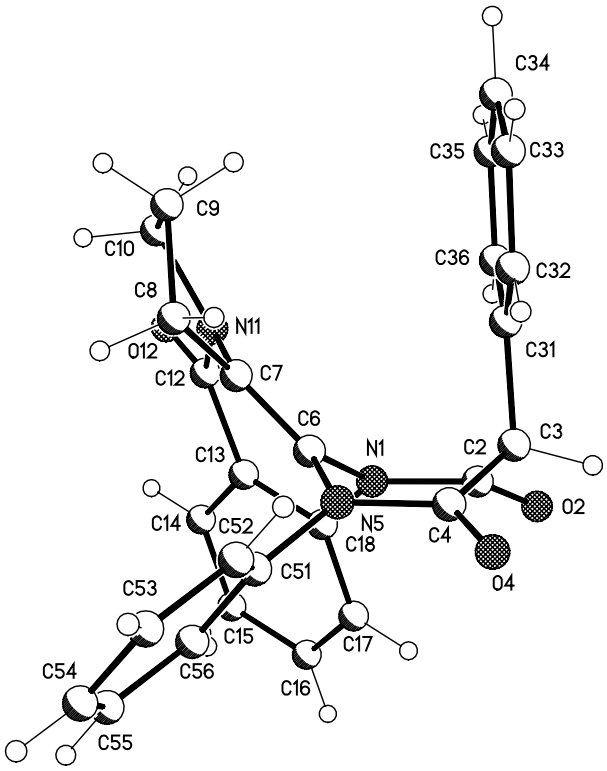


Figure 20: X-ray analysis of **75**. In the single crystal, the dioxopyrimidine fragment of **75** adopts a boat-like conformation with the phenyl ring at C(3) in axial position.

The *ab-initio* calculations lead to a bond length of 135.3 pm between C-4a and C-4b [crystallographic numbering: C(6)–C(7)] in conformer **Ab** (Scheme 25) in which the phenyl ring is in axial position of the boat conformation of the dioxopyrimidine moiety. Again, this double bond is twisted by – 3.5° [C(6)–N(1)–C(2)–C(3)].

In order to compare the structure of a non-splitting derivative in solid state, we performed an X-ray single crystal structure analysis of the benzyl derivative **76**. Single crystals were obtained by slow evaporation of a concentrated solution in 2-butanol. The molecular structure and the crystallographic numbering are shown in Figure 21. The molecule crystallized with one molecule of 2-butanol in the elemental cell which forms a hydrogen bond to the C(12)=O(12) carbonyl group [crystallographic numbering]. The carbon atom [C(3)] of the 1,3-diketo moiety is sp^3 hybridized, as its bond angles are 107.89(8)° [C(2)–C(3)–C(4)], 113.80(9)° [C(31)–C(3)–C(4)], and 112.05(9)° [C(31)–C(3)–C(2)], respectively. The bond length C(6)–C(7) was determined to be 132.93(15) pm and corresponds to a $C(sp^2)=C(sp^2)$ double bond. The bond angles N(1)–C(6)–N(5), C(6)–C(7)–N(11), and C(7)–C(6)–N(5) are

114.82(9)°, 124.74(10)°, and 123.30(10)°, respectively. The dioxopyrimidine moiety N(1)–C(2)–C(3)–C(4)–N(5)–C(6) adopts a boat conformation with the benzyl substituent in equatorial position.

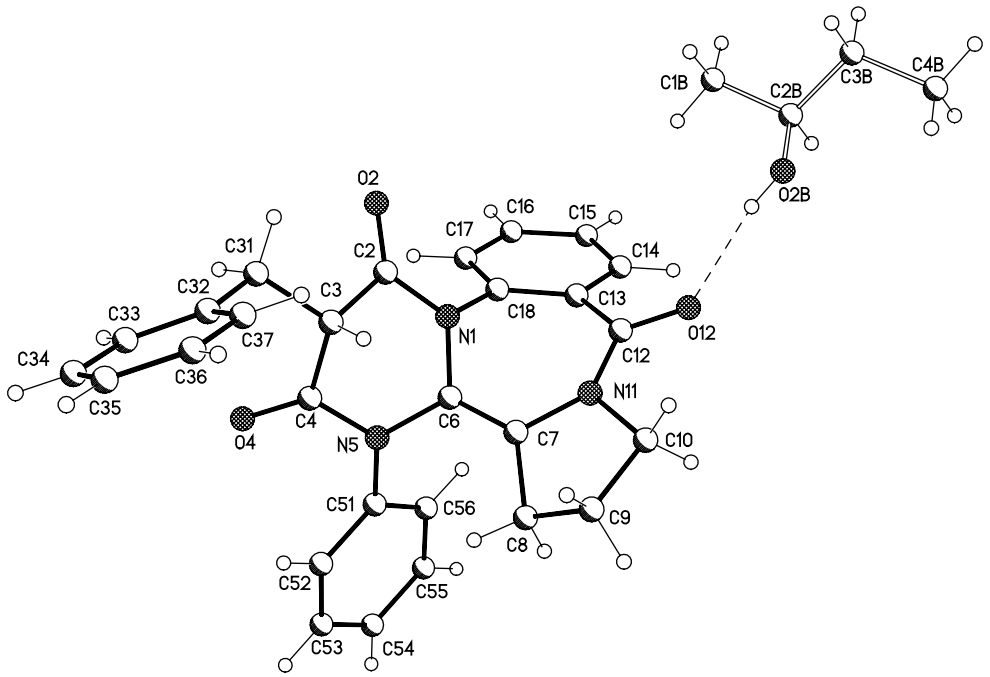


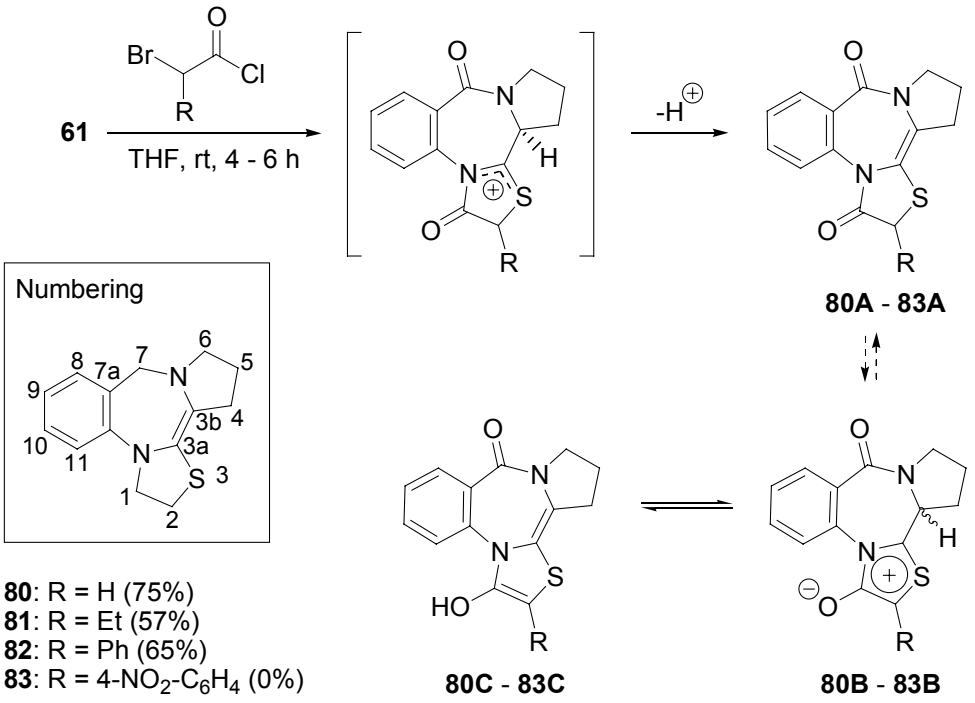
Figure 21: Molecular drawing of 4,7a,12b-triaza-dibenzo[*e,g*]azulene-1,3,8-trione (**76**).

3.4. Thiazolidine annulated pyrrolo[2,1-c][1,4]benzodiazepines

3.4.1. Synthesis of thiazolidines

2-Bromoacetyl chloride and its 2-ethyl- and 2-phenyl-substituted derivatives converted the monothiolactam **61** at room temperature in THF into the 5,6-dihydro-4*H*-3-thia-6a,11b-diazabenzo[g]cyclopenta[e]-azulene-1,7-diones **80**–**83**. This reaction typically proceeds via intermediary iminium salts which can sometimes be trapped and used for heterocyclic synthesis. The treatment of the thiolactam **80** with 2-(4-nitrophenyl)-2-bromoacetyl chloride, however, resulted in the formation of a complex mixture of compounds from which no nitro

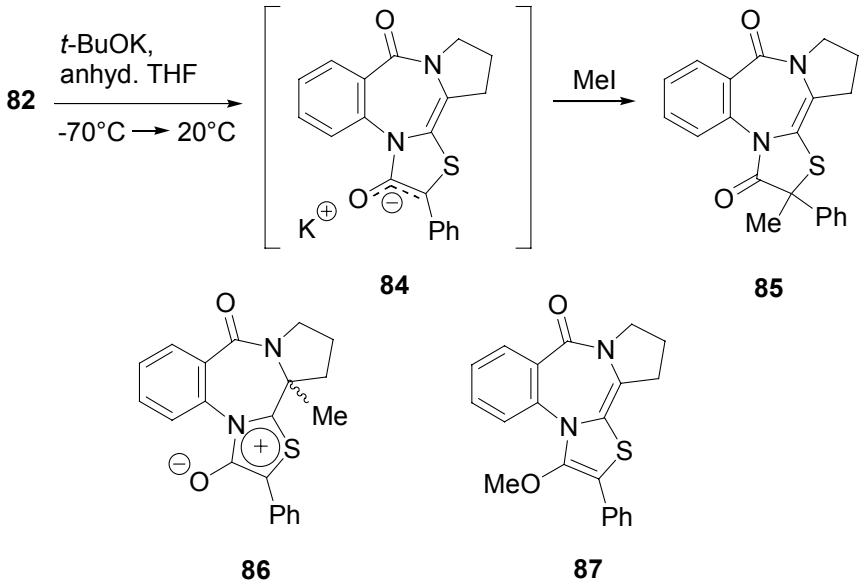
derivative **83** could be isolated (Scheme 27). The formations of the thiazolidinones **80A**–**82A** in $CDCl_3$ and DMSO-d_6, respectively, were unambiguously proved by the existence of only three CH_2-groups (4-H, 5-H, 6-H) of the pyrrolidine ring, and one additional sp^3-hybridized carbon atom which couples with the ethyl (**81A**) and phenyl (**82A**) group, respectively. In the 2-unsubstituted compound (**80A**), this CH_2-group forms a singlet at δ = 3.83 ppm in $CDCl_3$. In contrast to thiazol-4(5H)-ones, neither the tautomeric thioisomünchnones **80B**–**82B**, nor hydroxy isomers **80C**–**82C** were detectable by NMR spectroscopy, regardless of the solvent used. The C(2)-H protons are acidic and can be exchanged by deuterium on addition of D_2O to the solutions, respectively.



Scheme 27

It is known that aromatizations of thiazolidines can be accomplished by addition to exocyclic double bonds.[67] We therefore studied the behaviour of the new ring system towards acids, bases, and alkylating agents. The non-nucleophilic base 1,8-dimethylaminonaphthalene (proton sponge®) induced an immediate decomposition of **82** in THF to a complex mixture, whereas 4-dimethylaminopyridine (DMAP) and triethylamine, respectively, were not able to deprotonate this compound. On addition of NaOD/D_2O to a DMSO-d_6-solution of **82**, the resoncance frequencies shift considerably upfield due to the formation of the enolate **84**. Thus, the proton in the para-position of the phenyl ring, which is overlapped in DMSO-d_6 by other signals at approximately δ = 7.39 ppm, shifts to δ = 6.53 ppm on addition of the base.

The signal of C(2)–H at δ = 5.59 ppm disappears in parallel with a shifting of the resonance frequency of C(2) at δ = 52.6 ppm to δ = 72.6 ppm in the ^{13}C NMR spectra on addition of the base (for numbering, cf. Scheme 27). Potassium tert-butoxide proved to be the most suited base to deprotonate the phenyl derivative **82** at C(2) in THF at – 70 °C to the corresponding enolate on a preparative scale. The enolate could be trapped by methyl iodide to form the 2-methyl-2-phenyl-substituted pyrrolobenzodiazepine **85** in 82% yield. HMBC-NMR spectroscopic experiments proved the couplings of the methyl protons with C(2), C(1)=O, and the phenyl group. Neither mesoion **86**, which - in contrast to **85** - contained two aromatic rings, nor the *O*-methylated enol **87** were detected. Accordingly, no changes were moreover observable in the NMR spectra on addition of DCl, so that a protonation of the C(3a)=C(3b)–double bond could be excluded from consideration under these conditions.



Scheme 28

3.4.2. X-Ray structural analysis of thiazolidines

As remarkable differences in the tautomerisations of thiazols and its reduced derivatives exist in the solid state and in solution,[66] we performed an X-Ray analysis. Suitable single crystals of the 2-phenyl derivative **82** were obtained by slow evaporation of a concentrated solution in 2-propanol. The compound crystallized monoclinic. The molecular structure and the crystallographic numbering are shown in Figure 22. The 6:7:5 pyrrolobenzodiazepine ring

system adopts a twisted conformation. The C(6)–C(7) bond distance (crystallographic numbering) is 132.21(17) pm which corresponds to a $C(sp^2)=C(sp^2)$ double bond. This C=C–bond is twisted due to the helicity of the 6:7:5 ring system, so that the dihedral angles C(5)–C(6)–C(7)–N(11) and N(2)–C(6)–C(7)–S(8) are – 173.40(12)° and 172.06(9)°, respectively. The thiazolidine ring adopts an envelope conformation. The sulfur atom is located above a plane defined by C(9)–C(10)–N(11)–C(7), the dihedral angle of which is 1.44(15)°. The dihedral angles N(11)–C(7)–S(8)–C(9) and S(8)–C(9)–C(10)–N(11) were determined to be 31.81(9)° and 21.43(12°), respectively. The phenyl ring is twisted by approximately 51° around the C(9)–C(91)–bond. Thus, **82** displays a different behaviour than thiazol-4-ones, the 4-hydroxy isomers of which predominate in the solid state. One hydrogen bonding is found between the CH-acidic C(9)–H and the C(1)=O carbonyl group of a neighbouring molecule.

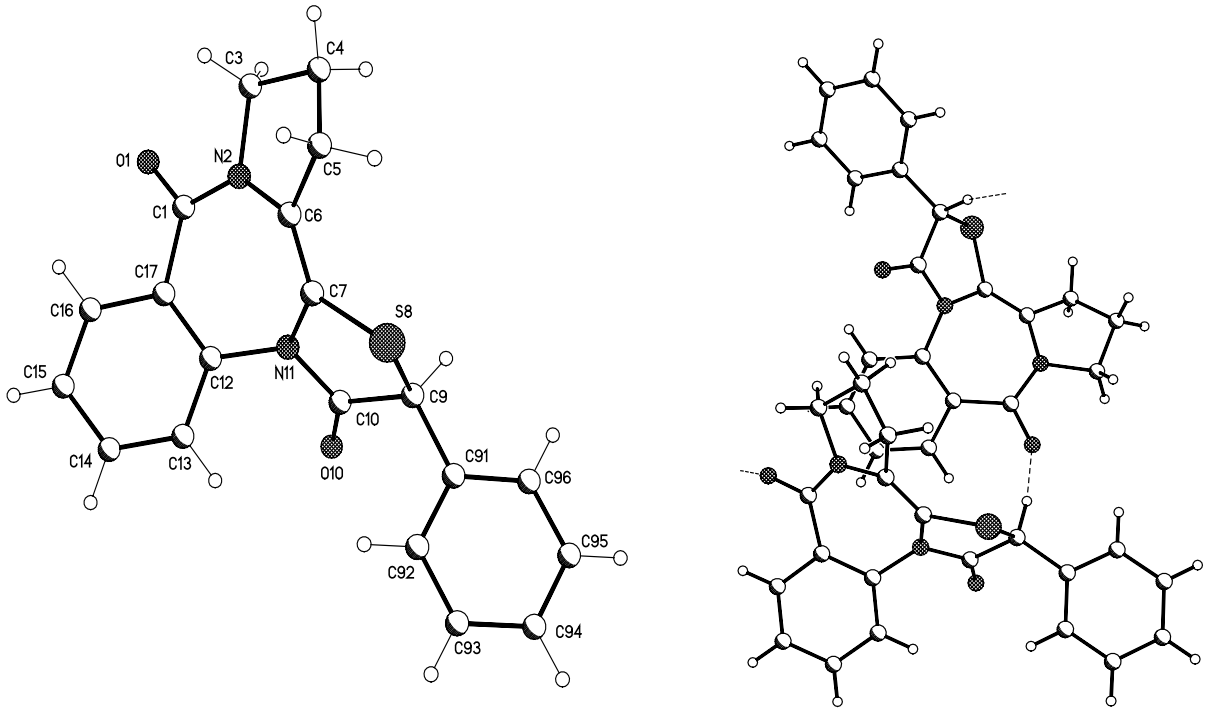
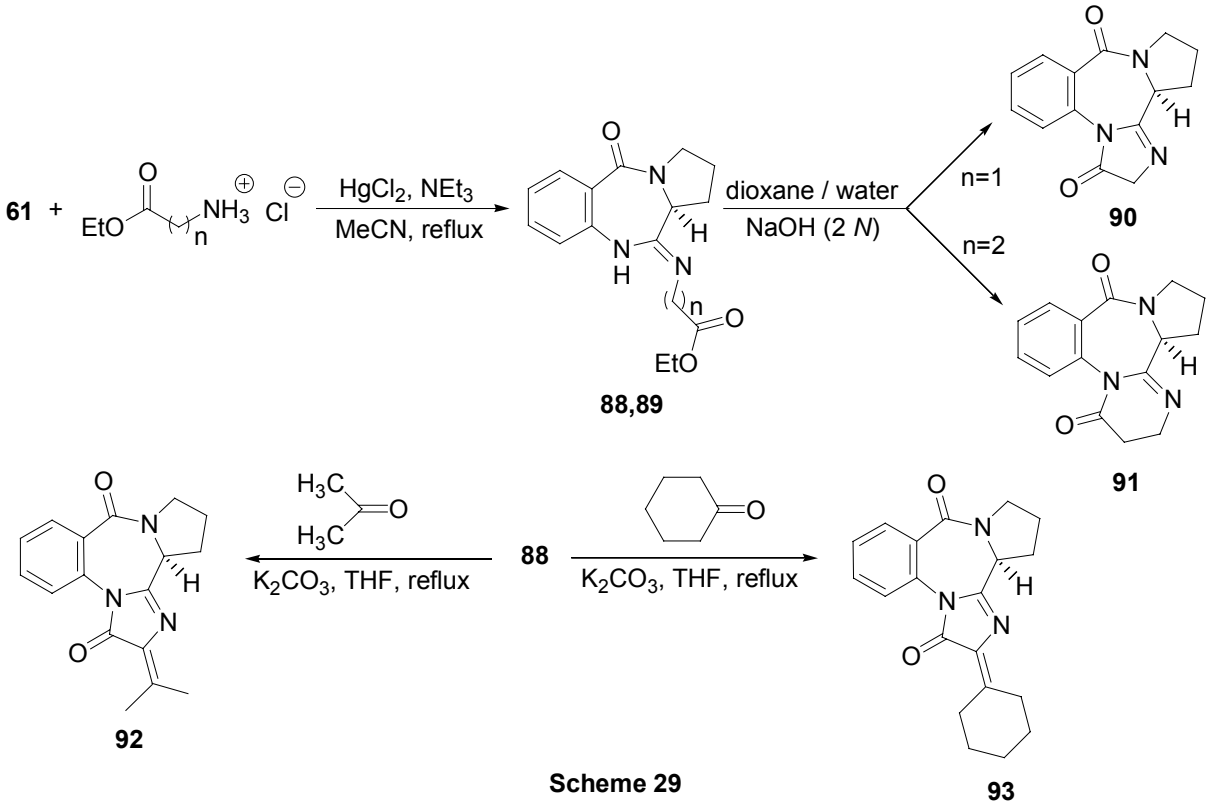


Figure 22: Molecular drawing of **82A** (left); hydrogen bonding between two molecules (right)

3.5. Imidazol- and pyrimidin-4-one annulated pyrrolo[2,1-c][1,4]benzodiazepines

3.5.1. Syntheses of 1,3-imidazol-4-one and 1,3-pyrimidin-4-ones

We treated thiolactam **61** and amino acid ethylesters as hydrochlorides in the presence of $HgCl_2$ and triethylamine in acetonitrile to give the iminoesters in high yields. Using glycine and β-alanine ethyl ester hydrochlorides furnished the optically active products **88** and **89**, respectively (Scheme 29).



Scheme 29

The ^{1}H NMR spectrum showed characteristic signals for the new products, including a methylene multiplet at δ 4.10–4.27 ppm for **88** and two multiplet signals at δ 2.64–2.71 and 3.57–3.74 ppm for compound **89**, respectively. Broad signals were observed at δ 5.46 and 5.74 ppm, suggesting secondary amine protons. In comparison with starting material **61**, addition of one carbon signal at δ 43.7 ppm for **88** and two carbon resonance peaks at δ 33.0 and 36.7 ppm for **89**, as well as creating of a new carbonyl signal blong to ethylester group, clearly indicated the formation of target molecules. The H,H-COSY experiment showed a correlation between NH group and CH_2 indicating the enamine group as N(10)=C(11)–NH partially structure.

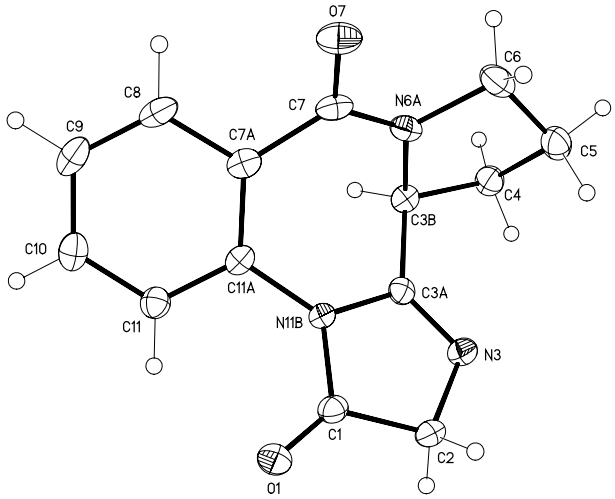
After many attempts using several bases and different solvents, finally we elegantly succeeded to close the ring in the presence of 2 *N* NaOH solution in a mixture of dioxane/water (2:1) at room temperature to yield the corresponding 5- and 6-membered imidazole **90** and pyrimidine **91** derivatives as optically active compounds. In contrast to the glycine ester, the β-alanine ester formed the amidine in the presence of sodium hydride in anhydrous DMF at room temperature. In the ^{1}H NMR spectrum, the ethyl signals were exchanged to methylene resonance frequencies, which strongly shifted downfield. They are observed as multiplets at δ 4.32–4.35 ppm for **90** and two methylene signals as a multiplet at 2.36–2.48 ppm and a triplet at δ 3.43 ppm. In addition, the chemical shift at 59.0 ppm for **90** and 35.1 and 38.5 ppm for **91** correspond to the formation of the new ring in ^{13}C NMR, respectively.

Surprisingly, during attempts to involve the compound **88** in an amidation ring closure reaction in acetone in the presence of K_2CO_3 at reflux temperature we observed the condensation to the olefinic imidazoles in good yields. We optimized this reaction in THF and used acetone and cyclohexanone as typical ketones to afford the corresponding 2-isopropylidene and 2-cyclohexylidene-imidazole products, respectinely (**92**,**93**). In the ^{13}C NMR spectra, the observation of two new quaternary olefinic sp^2 carbon signals at δ 153.4 and 156.4 ppm for **92** and δ 156.4 and 161.3 ppm for **93** supported the new tetracyclic structure. Moreover, ^{1}H NMR experiment clearly shows the two new methyl singlet signals at δ 2.32 and 2.46 ppm for **92** and five new methylene resonance frequencies for **93.**

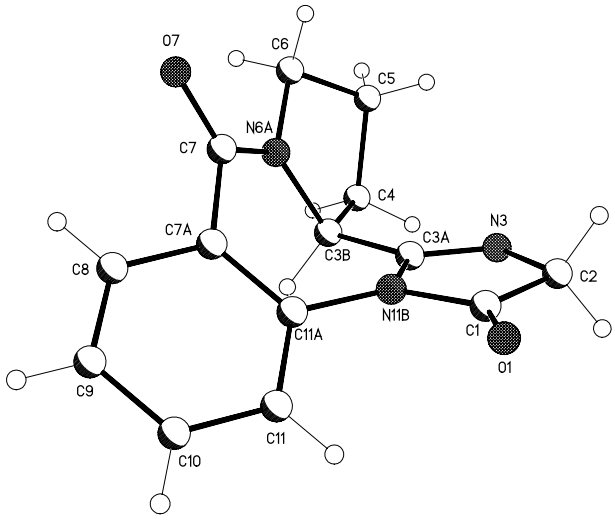
3.5.2. X-Ray structural analysis of 1,3-imidazol-4-one derivative

The single crystals were obtained by slow evaporation of a saturated solution of compound **90** in acetone with a monoclinic unit cell. The molecular construction and the crystallographic numbering are shown in Figure 23. In accordance with former derivatives, PBD ring involves in a twisted conformation while the 7-membered ring adopts a boat arrangement. This finding is in agreement with the dihedral angles of N(11B)–C(3A)–C(3B)–N(6A) (crystallographic numbering) and C(11A)–C(7A)–C(7)–N(6A) which were determined to be 63.22(14)° and 42.37(19)°, respectively. Moreover, torsion angles of C(7A)–C(7)–N(6A)–C(3B) with – 2.24(19)° and C(7)–C(7A)–C(11A)–N(11B) with – 177.28(12)° further supply this observation. The bond distance of C(3A)–N(3) is 127.39(17) pm which corresponds to imino C(sp^2)=N(sp^2) double bond. The presence of distinct C(3A)–C(3B) single bond with

149.96(19) pm unambiguously excludes any involving of 3b-H hydrogen in tautomerization to form an optically inactive tautomer. In the crystal the imidazole-annulated pyrrolobenzodiazepine molecules are lined in chains through C(11)…H…O(7) hydrogen bonds between neighbouring molecules. Figure 24 shows the elemental cell of compound **90**.



(**a**)



(**b**)

Figure 23: ORTEP drawings of compound **90** in two perspectives (a, b).

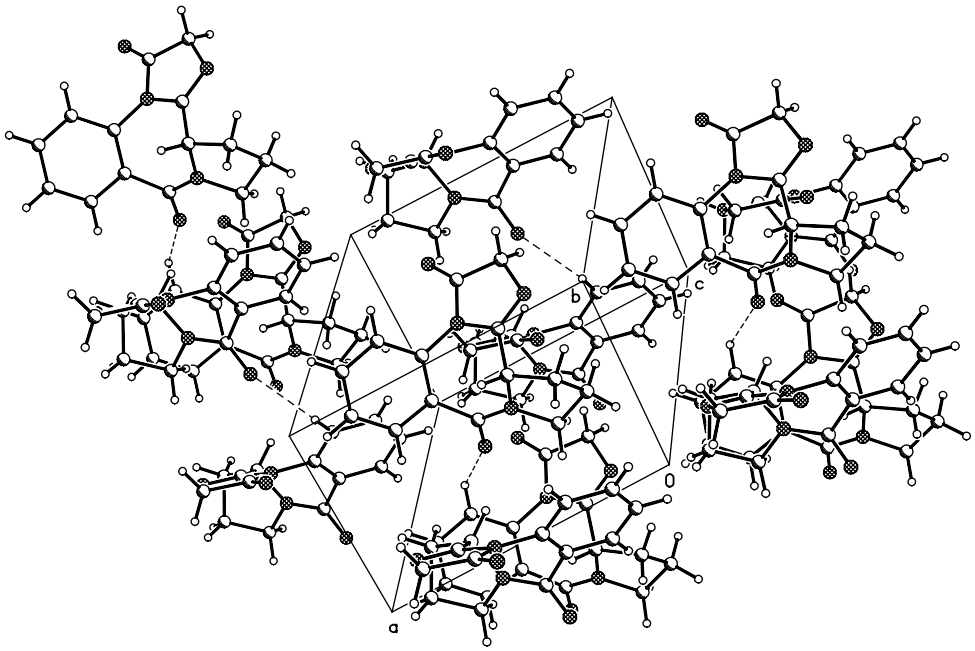


Figure 24: Element cell of compound **90**.

4. Experimental Section

General methods: The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE 400 and AVANCE DPX-200 spectrometers and were taken in DMSO-d_6 and $CDCl_3$ at 200 and 400 MHz. The chemical shifts are reported in ppm relative to internal tetramethylsilane ($\delta = 0.00$). Multiplicities are described by using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. FT-IR spectra were obtained on a Bruker Vektor 22 in the range of 400 to 4000 cm^{-1} (2.5 % pellets in KBr). The GC-MS spectra (EI) were recorded either on a GC Hewlett Packard 5980, Series II / MS Hewlett Packard 5989 B, or on a Varian GC3900 with SAT2100T. The ESI mass spectra were measured with an Agilent LCMSD Series HP1100 with APIES. Samples were sprayed from methanol at 0V fragmentor voltage unless otherwise noted. All reactions were monitored by analytical thin layer chromatography using silica gel 60 F^{254} precoated plates and spots were detected either by UV-absorption or iodine. All commercially available chemicals were purchased from Fluka and Lancaster Chemical Co. and used as received without further purification.

4.1. Experiments to chapter 2.2.

*3,4-Diaminophenol (**26**)*

Method A:

Activated palladium on carbon catalyst (10% Pd, 200 mg) was added cautiously as a slurry in methanol (10 mL) to a solution of 4-amino-3-nitrophenol **32** (2.0 g, 13 mmol) in methanol (100 mL), and the mixture was stirred under a hydrogen atmosphere for 6 hours until the absorption of gas ceased. The catalyst was removed by filtration through Celite, and the filtrate was evaporated to dryness under reduced pressure to afford **26** as a brown solid.

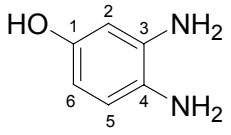
Yield: 1.50 g (93 %).

Method B:

To a suspension of activated Raney nickel (200 mg) and hydrazine hydrate (98%, 2 mL) in ethanol (40 mL) was cautiously added a solution of 4-amino-3-nitrophenol **32** (1.54 g, 10 mmol) in ethanol (10 mL) and the mixture was stirred for 30 min at room temperature. The

catalyst was then removed by filtration through Celite and the solvent was distilled off under reduced pressure to give 3,4-diaminophenol **26** as a brown pure solid.

Yield: 1.19 g (96 %).



m.p.: 155 °C.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 4.21 (br s, 4H, 2 × NH_2), 5.81 (dd, *J* = 8.1, 2.6 Hz, 1H, 6-H), 6.03 (d, *J* = 2.6 Hz, 1H, 2-H), 6.31 (d, *J* = 8.1 Hz, 1H, 5-H), 8.12 (br s, 1H, OH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 102.2, 103.2, 115.8 (C-2), 126.8 (C-4), 136.7 (C-3), 149.7 (CO).

UV λ_{max}(MeOH): 343 nm.

IR (KBr): $\tilde{\nu}$ = 3398, 3353, 3272, 3024, 2931, 1621, 1606, 1510, 1486, 1382.

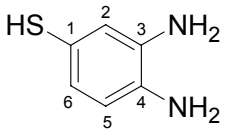
GC-MS (70 eV) *m/z* (%): 124 (100) [M^+], 96 (28), 68 (11), 52 (12).

Anal. calcd. for $C_6H_8N_2O$ (124.14): C, 58.0; H, 6.5; N, 22.6; found: C, 57.7; H, 6.3; N, 22.5.

*3,4-Diaminobenzenethiol (**28**)*

4-Amino-3-nitrobenzenethiol **34** (3.40 g, 20 mmol) was dissolved in 50% aqueous ethanol (300 mL) and then sodium dithionite (13.93 g, 80 mmol) was added portionwise over a period of 20 min. The stirred solution was first refluxed for 1 hour and then extracted with chloroform after cooling to room temperature. The aqueous layer was evaporated *in vacuo* and the resulting solids were extracted with methanol. Evaporation of the solvent gave a crude solid which was subjected to column chromatography on silica gel using MeOH/EtOAc (1:5) to give a fine dark yellow powder.

Yield: 2.07 g (74 %).



m.p.: 147–150 °C.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 3.36 (s, 1H, SH), 4.18 (br s, 4H, 2 × NH_2), 6.42 (d, 1H, *J* = 8.1 Hz, 5-H), 6.49 (dd, *J* = 8.1, 1.9 Hz, 1H, 6-H), 6.68 (d, 1H, *J* = 1.9 Hz, 2-H).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 114.0, 117.5, 121.6 (C-2), 122.6, 135.3 (C-4), 136.2 (C-3).

UV λ_{max}(MeOH): 236, 318 nm.

IR (KBr): $\tilde{\nu}$ = 3411, 3398, 3320, 1619, 1578, 1502, 1282.

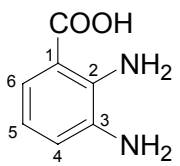
GC-MS (70 eV) *m/z* (%): 140 (100) [M^+], 107 (39), 95 (16), 80 (16), 52 (13).

Anal. calcd. for $C_6H_8N_2S$ (140.21): C, 51.4; H, 5.7; N, 20.0; found: C, 51.5; H, 5.4; N, 20.3.

*2,3-Diaminobenzoic acid (**29**)*

Sodium dithionite (1.39 g, 8 mmol) was added portionwise over a period of 10 min to a solution of 4-amino-3-nitrobenzoic acid (0.364 g, 2 mmol) in 50% aqueous ethanol (50 mL) at room temperature. The reaction mixture was heated under reflux for 1 hour and extracted with ethyl acetate (3 × 30 mL) after cooling. The combined extracts were dried over magnesium sulfate and evaporated to dryness. The resulting solid was purified by recrystallization from water to give **29** as pale brown needles.

Yield: 0.225 g (74 %).



m.p.: 198–200 °C.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 6.36 (t, *J* = 7.8, 1H, 5-H), 6.69 (dd, *J* = 7.8, 1.5 Hz, 1H, 4-H), 6.86 (br s, 4H, 2 × NH_2), 7.10 (dd, *J* = 7.8, 1.5 Hz, 1H, 6-H).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 109.7 (C-1), 115.0, 117.2, 119.4, 135.6 (C-2), 139.7 (C-3), 170.3 (CO).

UV λ_{max}(MeOH): 232, 344 nm.

IR (KBr): $\tilde{\nu}$ = 3420, 3361, 3331, 1635, 1559, 1467, 1375.

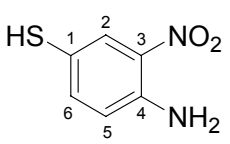
GC-MS (70 eV) *m/z* (%): 152 (100) [M^+], 134 (67), 106 (100), 79 (52), 52 (41).

Anal. calcd. for $C_7H_8N_2O_2$ (152.15): C, 55.2; H, 5.3; N, 18.4; found: C, 55.0; H, 5.4; N, 18.4.

*4-Amino-3-nitro-benzenethiol (**34**)*

2-Nitro-4-thiocyanatoaniline **33** (3.51 g, 18 mmol) was added portionwise to a stirred solution of potassium hydroxide (6 g) in ethanol (100 mL) at 10 °C and the stirring was continued for further 30 min at room temperature. A solution of sulfuric acid in ethanol (5%) was cautiously added whereupon the color of the mixture changed from dark violet to orange. The mixture was then poured into water (400 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, and evaporated to give **34** as a red solid.

Yield: 2.08 g (68 %).



m.p.: 99–100 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.42 (s, 1H, SH), 5.85 (br s, 2H, NH_2), 6.78 (d, 1H, *J* = 8.7 Hz, 5-H), 7.33 (dd, *J* = 8.7, 2.1 Hz, 1H, 6-H), 8.14 (d, 1H, *J* = 2.1 Hz, 2-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 116.3 (C-3), 119.6, 128.3, 139.0, 143.4 (C-6) (one signal not detectable).

UV λ_{max}(MeOH): 343 nm.

IR (KBr): $\tilde{\nu}$ = 3463, 3344, 2555, 1634, 1554, 1502.

GC-MS (70 eV) *m/z* (%): 170 (100) [M^+], 124 (69), 97 (23), 80 (30), 52 (19).

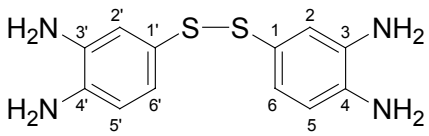
Anal. calcd. for $C_6H_6N_2O_2S$ (170.19): C, 42.3; H, 3.5; N, 16.5; found: C, 42.2; H, 3.5; N, 16.4.

*Bis(3,4-diaminophenyl)disulfide (**35**)*

A 50% suspension of activated Raney-nickel catalyst (100 mg) in water was washed several times with water and methanol, respectively. A solution of **34** (0.34 g, 2.0 mmol) in methanol (50 mL) was added cautiously to the suspension of the catalyst in methanol (5 mL), and the mixture was stirred under hydrogen atmosphere for 5 hours at room temperature until the absorption of gas ceased. The catalyst was removed by filtration through Celite, and the filtrate was evaporated *in vacuo* to give crude **35**. The product was purified by column chromatography on silica gel using CH_2Cl_2/EtOAc (4:1). Recrystallization from water afforded a fine dark yellow powder.

Yield: 0.54 g (54 %).

m.p.: 155 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 4.62 (s, 4H, 2 × NH_2), 4.78 (s, 4H, 2 × NH_2), 6.40–6.51 (m, 4H, 5,5′,6,6′-H), 6.68 (d, 2H, *J* = 1.8 Hz, 2,2′-H).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 114.0, 117.5, 121.6, 122.6, 135.3, 136.2.

UV λ_{max}(MeOH): 230, 318 nm.

IR (KBr): $\tilde{\nu}$ = 3414, 3365, 1619, 1578, 1498, 1420, 1283.

GC-MS (70 eV) *m/z* (%): 278 (84) [M^+], 140 (100), 122 (9), 112 (12), 95 (25).

Anal. calcd. for $C_{12}H_{14}N_4S_2$ (278.40): C, 51.7; H, 5.1; N, 20.1; found: C, 51.3; H, 5.3; N, 20.1.

4.2. Experiments to chapter 2.3.

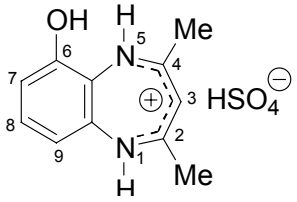
*General procedure for the preparation of the 2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium hydrogensulfates, trifluoroacetates and picrates **(38–43)***

Solutions of the diaminobenzene derivatives **25–30** (1.0 mmol) in ethanol (20 mL) were treated with pentane-2,4-dione (0.1 mL, 1.0 mmol) and a few drops of concentrated sulfuric acid or trifluoroacetic acid or 0.5 g of picric acid (50% water). The reactions started immediately whereupon the color changed to dark violet. The mixtures were stirred for 30 min at room temperature. After concentrating the ethanolic solutions to 20% of its original volume, addition of diethyl ether precipitated solids which were filtered off and washed with diethyl ether to give intensely violet solids, respectively.

*6-Hydroxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium hydrogensulfate **(38a)***

2,3-Diaminophenol **25** (0.124 g, 1 mmol) was used.

Yield: 0.24 g (92 %).



m.p.: 195–197 °C.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.80 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 4.32 (s, 1H, 3-H), 5.99 (d, *J* = 8.2 Hz, 1H, 9-H), 6.54 (d, *J* = 8.2 Hz, 1H, 7-H) , 6.79 (t, *J* = 8.2 Hz, 1H, 8-H), 9.12 (s, 1H, NH), 9.62 (s, 1H, NH), 10.75 (s, 1H, OH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 24.1 (CH_3), 24.2 (CH_3), 95.8 (C-3), 113.7, 116.3 , 120.3, 129.8, 136.2, 149.9, 175.2, 176.6.

UV λ_{max}(H_2O): 362, 492 nm; λ_{max}(MeOH): 368, 496 nm; λ_{max}(MeCN): 366, 520 nm.

IR (KBr): $\tilde{\nu}$ = 3283, 3050, 1623, 1605, 1519, 1448.

GC-MS (70 eV) *m/z* (%): 188 (80) [M^+ – 1], 173 (28), 148 (49), 64 (100).

HRMS (ESI-Tof): calcd. for $C_{11}H_{13}N_2O$: 189.1028; found: 189.1027.

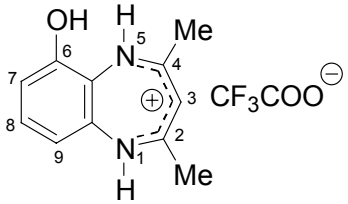
Anal. calcd. for $C_{11}H_{14}N_2O_5S$ (286.31): C, 46.1; H, 4.9; N, 9.8; found: C, 45.7; H, 4.9; N, 9.6.

*6-Hydroxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium trifluoroacetate (**38b**)*

2,3-Diaminophenol **25** (0.41 g, 3.3 mmol) was used.

Yield: 0.82 g (82 %).

m.p.: 190–193 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.80 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 4.31 (s, 1H, 3-H), 6.00 (dd, *J* = 8.1, 1.1 Hz, 1H, 9-H), 6.56 (dd, *J* = 8.1, 1.1 Hz, 1H, 7-H) , 6.79 (t, *J* = 8.1, 1H, 8-H), 9.10 (br s, 1H, NH), 9.74 (br s, 1H, NH), 11.06 (s, 1H, OH).

^{13}C-NMR (50 MHz, DMSO-d_6)[i]: δ = 24.0 (CH_3), 24.2 (CH_3), 95.7 (C-3), 113.7, 116.3 , 120.3, 129.8, 136.2, 150.1, 175.1, 176.4.

UV λ_{max}(H_2O): 492 nm; λ_{max}(MeOH): 370, 496 nm; λ_{max}(EtOH): 256, 372, 484 nm.

IR (KBr): $\tilde{\nu}$ = 3241, 3073, 3005, 1663, 1633, 1607, 1590, 1460, 1391.

GC-MS (70 eV) *m/z* (%): 188 (100) [M^+ – 1], 173 (44), 148 (46), 107 (15), 79 (11).

HRMS (ESI-Tof): calcd. for $C_{11}H_{13}N_2O$: 189.1028; found: 189.1029.

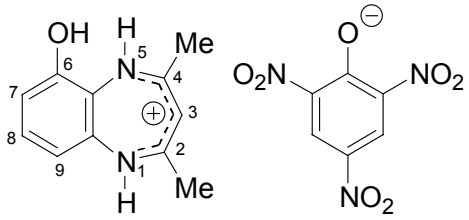
Anal. calcd. for $C_{13}H_{13}F_3N_2O_3$ (302.25): C, 51.7; H, 4.3; N, 9.3; found: C, 51.6; H, 4.3; N, 9.2.

*6-Hydroxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium picrate (**38c**)*

2,3-Diaminophenol **25** (0.372 g, 3.0 mmol) was used.

Yield: 0.75 g (61 %).

m.p.: 198–200 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.80 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 4.30 (s, 1H, 3-H), 5.96 (dd, *J* = 8.1, 1.2 Hz, 1H, 9-H), 6.51 (dd, *J* = 8.1, 1.2 Hz, 1H, 7-H) , 6.78 (t, *J* = 8.1, 1H, 8-H), 8.60 (s, 2H, Ph-pic), 9.07 (s, 1H, NH), 9.55 (s, 1H, NH), 10.70 (s, 1H, OH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 24.1 (CH_3), 24.2 (CH_3), 95.7 (C-3), 113.8, 116.2 , 120.2, 124.1, 125.2, 129.8, 136.1, 141.8, 149.9, 160.8, 175.1, 176.5.

[i] After prolonged measuring time the trifluoroacetate anions are detectable at δ = 118 (q, $^1J_{CF}$ = 299 Hz). The coupling constant and the long dipolar relaxation time of the CF_3 carbon atom cause a very small intensity of these signals.

UV $\lambda_{max}(H_2O)$: 218, 256, 358 nm; λ_{max}(MeOH): 356, 590 nm; λ_{max}(EtOH): 258, 360 nm.

IR (KBr): $\tilde{\nu}$ = 3313, 3083, 1609, 1566, 1542, 1429.

GC-MS (70 eV) *m/z* (%): 188 (100) [M^+ – 1], 173(33), 148(29), 91(46), 77(29), 62(85), 52(64).

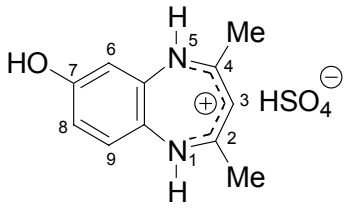
Anal. calcd. for $C_{17}H_{15}N_5O_8$ (417.33): C, 48.9; H, 3.6; N, 16.8; found: C, 49.0; H, 3.5; N, 16.9.

*7-Hydroxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium hydrogensulfate (**39a**)*

3,4-Diaminophenol **26** (0.248 g, 2.0 mmol) was used.

Yield: 0.37 g (64 %).

m.p.: 225–227 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.71 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 4.08 (s, 1H, 3-H), 5.94 (d, *J* = 2.5 Hz, 1H, 6-H), 6.20 (dd, *J* = 8.6, 2.5 Hz, 1H, 8-H) , 6.33 (d, *J* = 8.6 Hz, 1H, 9-H), 9.13 (s, 1H, NH), 9.82 (br s, 1H, NH), 9.99 (s, 1H, OH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 23.7 (CH_3), 23.8 (CH_3), 94.3 (C-3), 110.7, 113.0 , 123.5, 125.2, 135.3, 158.3, 172.7, 173.7.

UV $\lambda_{max}(H_2O)$: 482 nm; λ_{max}(MeOH): 342, 464 nm; λ_{max}(EtOH): 262, 346, 450 nm.

IR (KBr): $\tilde{\nu}$ = 3214, 3051, 2981, 1643, 1613, 1524, 1481, 1383.

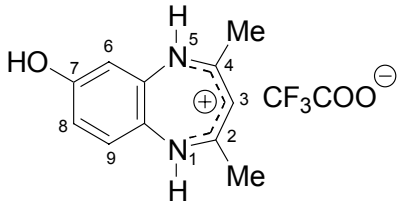
GC-MS (70 eV) *m/z* (%): 188 (80) [M^+ – 1], 173 (20), 148 (26), 118 (16), 106 (13), 51 (35).

HRMS (ESI-Tof): calcd. for $C_{11}H_{13}N_2O$: 189.1028; found: 189.1025.

*7-Hydroxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium trifluoroacetate (**39b**)*

3,4-Diaminophenol **26** (0.248 g, 2.0 mmol) was used.

Yield: 0.526 g (87 %).



m.p.: 181–183 °C.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.71 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 4.06 (s, 1H, 3-H), 5.96 (d, *J* = 2.5 Hz, 1H, 6-H), 6.20 (dd, *J* = 8.6, 2.5 Hz, 1H, 8-H) , 6.34 (d, *J* = 8.6 Hz, 1H, 9-H), 9.27 (s, 1H, NH), 10.01 (br s, 1H, NH), 10.17 (s, 1H, OH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 23.6 (CH_3), 23.7 (CH_3), 94.2 (C-3), 110.8, 113.0 , 123.5, 125.1, 135.3, 158.4, 172.6, 173.6.

UV λ_{max}(H_2O): 266, 330, 480 nm; λ_{max}(MeOH): 266, 344, 460 nm; λ_{max}(EtOH): 268, 284, 346, 472 nm.

IR (KBr): $\tilde{\nu}$ = 3443, 3311, 3086, 2998, 1659, 1604, 1538, 1484, 1438, 1397, 1208.

GC-MS (70 eV) *m/z* (%): 188 (100) [M^+ – 1], 172 (34), 146 (28), 118 (7), 6 (15), 51 (10).

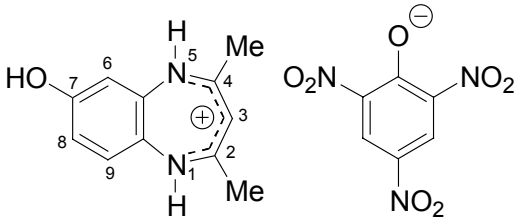
HRMS (ESI-Tof): calcd. for $C_{11}H_{13}N_2O$: 189.1028; found: 189.1022.

*7-Hydroxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium picrate (**39c**)*

3,4-Diaminophenol **26** (0.248 g, 2.0 mmol) was used.

Yield: 0.59 g (71 %).

m.p.: 228–230 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.70 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 4.06 (s, 1H, 3-H), 5.92 (d, *J* = 2.4 Hz, 1H, 6-H), 6.18 (dd, *J* = 8.6, 2.4 Hz, 1H, 8-H) , 6.29 (d, *J* = 8.6 Hz, 1H, 9-H), 8.60 (s, 2H, Ph-pic), 9.09 (s, 1H, NH), 9.78 (s, 1H, NH), 9.97 (s, 1H, OH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 23.7 (CH_3), 23.8 (CH_3), 94.2 (C-3), 110.7, 113.0, 123.5, 124.1, 125.2, 135.2, 141.8, 158.3, 160.7, 172.6, 173.6.

UV λ_{max}(H_2O): 204, 262, 352 nm; λ_{max}(MeOH): 284, 348 nm; λ_{max}(EtOH): 268, 286, 354 nm.

IR (KBr): $\tilde{\nu}$ = 3424, 3306, 3080, 1612, 1541, 1480, 1432.

GC-MS (70 eV) *m/z* (%): 188 (100) [M^+ – 1], 173 (10), 146 (23), 106 (7), 77 (88), 5 (11).

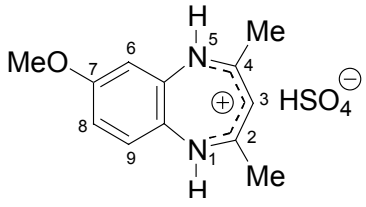
Anal. calcd. for $C_{17}H_{15}N_5O_8$ (417.33): C, 48.9; H, 3.6; N, 16.8; found: C, 48.7; H, 3.8; N, 16.8.

*7-Methoxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium hydrogensulfate (**40a**)*

4-Methoxy-*o*-phenylenediamine dihydrochloride **27** (0.422 g, 2 mmol) was used.

Yield: 0.505 g (91 %).

m.p.: 210–212 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.74 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 4.05 (s, 1H, 3-H), 6.18–6.27 (m, 1H, 9-H), 6.37–6.43 (m, 1H, 6-H) , 6.53–6.62 (m, 1H, 8-H), 9.52 (s, 1H, NH), 10.19 (s, 1H, NH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 23.8 (CH_3), 23.9 (CH_3), 55.8 (OCH_3), 94.7 (C-3), 110.7, 111.1, 125.4, 125.9, 135.9, 159.9, 173.0, 174.1.

UV λ_{max}(H_2O): 330, 500 nm; λ_{max}(MeOH): 344, 506 nm; λ_{max}(MeCN): 332, 520 nm.

IR (KBr): $\tilde{\nu}$ = 3407, 3308, 3070, 3005, 1642, 1608, 1528, 1482.

GC-MS (70 eV) *m/z* (%): 202 (100) [M^+ – 1], 187 (77), 147 (24), 119 (10), 80 (11).

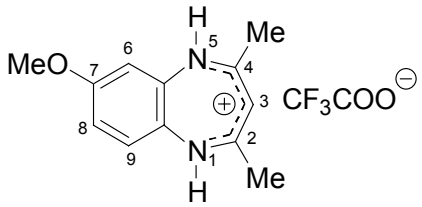
HRMS (ESI-Tof): calcd. for $C_{12}H_{15}N_2O$: 203.1184; found: 203.1180.

*7-Methoxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium trifluoroacetate (**40b**)*

4-Methoxy-*o*-phenylenediamine dihydrochloride **27** (1.05 g, 5 mmol) was used.

Yield: 1.16 g (73 %).

m.p.: 208–210 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.76 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 3.63 (s, 3H, OCH_3), 4.02 (s, 1H, 3-H), 6.33–6.41 (m, 2H, 6,9-H), 6.68 (d, *J* = 8.5 Hz, 1H, 8-H), 9.82 (s, 1H, NH), 10.53 (s, 1H, NH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 23.4 (CH_3), 23.5 (CH_3), 55.4 (OCH_3), 94.3 (C-3), 110.3, 110.7, 125.0, 125.5, 135.5, 159.5, 172.6, 173.7.

UV $\lambda_{max}(H_2O)$: 520 nm; λ_{max}(MeOH): 334, 522 nm; λ_{max}(EtOH): 334, 522 nm.

IR (KBr): $\tilde{\nu}$ = 3045, 2903, 1637, 1602, 1572, 1473, 1385.

GC-MS (70 eV) *m/z* (%): 202 (100) [M^+ – 1], 187 (77), 147 (16), 118 (7).

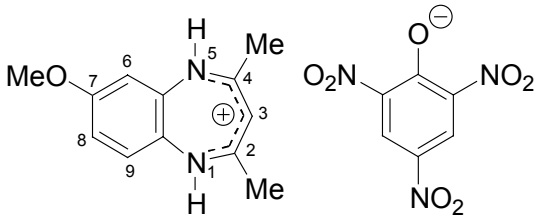
HRMS (ESI-Tof): calcd. for $C_{12}H_{15}N_2O$: 203.1184; found: 203.1182.

*7-Methoxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium picrate (**40c**)*

4-Methoxy-1,2-diaminobenzene dihydrochloride **27** (1.056 g, 5.0 mmol) was used.

Yield: 1.83 g (86 %).

m.p.: 210–212 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.71 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 4.09 (s, 1H, 3-H), 6.00–6.04 (m, 1H, 6-H), 6.39 (d, *J* = 1.3 Hz, 2H, 8,9-H), 8.61 (s, 2H, Ph-pic), 9.20 (s, 1H, NH), 9.83 (s, 1H, NH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 24.5 (CH_3), 24.6 (CH_3), 56.2 (OCH_3), 95.3 (C-3), 110.8, 111.6 , 124.9, 125.7, 125.9, 126.0, 136.0, 142.5, 160.4, 161.5, 173.6, 174.7.

UV $\lambda_{max}(H_2O)$: 214, 264, 350 nm; λ_{max}(MeOH): 350, 524 nm; λ_{max}(EtOH): 266, 284, 358 nm.

IR (KBr): $\tilde{\nu}$ = 3321, 1630, 1609, 1559, 1521, 1481, 1365.

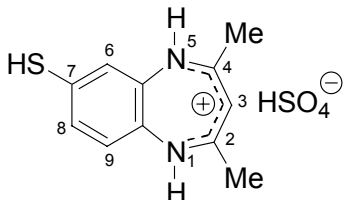
GC-MS (70 eV) *m/z* (%): 202 (100) [M^+ – 1], 187(54), 159(10), 147(18), 118(11), 91(13), 77(7), 62(7).

Anal. calcd. for $C_{18}H_{17}N_5O_8$ (431.36): C, 50.1; H, 4.0; N, 16.2; found: C, 50.2; H, 3.9; N, 16.0.

*7-Mercapto-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium hydrogensulfate (**41a**)*

3,4-Diaminobenzenethiol **28** (0.14 g, 1 mmol) was used (oily product).

Yield: 0.256 g (85 %).



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.78 (s, 6H, 2 × CH_3), 3.37 (s, 1H, SH), 4.23 (s, 1H, 3-H), 6.50 (d, *J* = 8.3 Hz, 1H, 9-H), 6.63 (d, *J* = 1.8 Hz, 1H, 6-H), 6.99 (dd, *J* = 8.3, 1.8 Hz, 1H, 8-H), 9.69 (s, 1H, NH), 9.89 (s, 1H, NH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 24.0 (2 × CH_3), 95.9 (C-3), 121.4, 124.3 , 127.3, 133.2, 135.1, 135.9, 175.9, 176.0.

UV λ_{max}(H_2O): 264, 520 nm; λ_{max}(MeOH): 270, 526 nm; λ_{max}(EtOH): 268, 524 nm.

IR (KBr): $\tilde{\nu}$ = 2977, 1636, 1590, 1508, 1474, 1374, 1283, 1175.

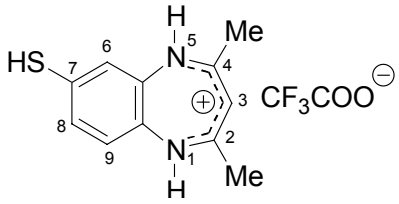
GC-MS (70 eV) *m/z* (%): 204 (18) [M^+ – 1], 164 (84), 131 (20), 96 (16), 64 (100).

HRMS (ESI-Tof): calcd. for $C_{11}H_{13}N_2S$: 205.0799; found: 205.0735.

*7-Mercapto-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium trifluoroacetate (**41b**)*

3,4-Diaminobenzenethiol **28** (0.14 g, 1 mmol) was used.

Yield: 0.30 g (94 %).



m.p.: 130–132 °C.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.77 (s, 6H, 2 × CH_3), 3.40 (s, 1H, SH), 4.21 (s, 1H, 3-H), 6.50 (d, *J* = 8.3 Hz, 1H, 9-H), 6.63 (d, *J* = 2.0 Hz, 1H, 6-H), 6.98 (dd, *J* = 8.3, 2.0 Hz, 1H, 8-H), 9.90 (s, 1H, NH), 10.08 (s, 1H, NH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 23.9 (CH_3), 24.0 (CH_3), 95.9 (C-3), 121.4, 124.2 , 127.2, 133.4, 135.3, 135.9, 175.7, 175.8.

UV λ_{max}(H_2O): 270, 516 nm; λ_{max}(MeOH): 272, 526 nm; λ_{max}(EtOH): 272, 528 nm.

IR (KBr): $\tilde{\nu}$ = 3303, 3138, 3065, 1673, 1645, 1596, 1507, 1478, 1373.

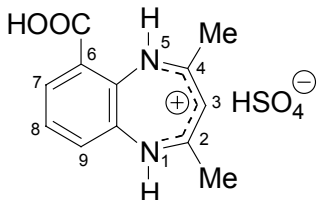
GC-MS (70 eV) *m/z* (%): 204 (100) [M^+ – 1], 163 (25), 122 (16), 95 (11), 69 (54), 51 (26).

HRMS (ESI-Tof): calcd. for $C_{11}H_{13}N_2S$: 205.0799; found: 205.0791.

*6-Carboxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium hydrogensulfate (**42a**)*

2,3-Diaminobenzoic acid **29** (0.188 g, 1.24 mmol) and concentrated HCl as a catalyst were used. Addition of H_2SO_4 in excess gave the corresponding hydrogensulfate.

Yield: 0.32 g (80 %).



m.p.: 182–185 °C.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.89 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 4.68 (s, 1H, 3-H), 6.82 (dd, *J* = 7.9, 1.4 Hz, 1H, 9-H), 7.08 (t, *J* = 7.9 Hz, 1H, 8-H) , 7.56 (dd, *J* = 7.9, 1.4 Hz, 1H, 7-H), 10.47 (s, 2H, 2 × NH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 24.4 (CH_3), 25.1 (CH_3), 98.7 (C-3), 121.9, 127.9, 128.0, 130.8, 135.4, 138.3, 167.8, 177.5, 180.7.

UV λ_{max}(H_2O): 498 nm; λ_{max}(MeOH): 344, 498 nm; λ_{max}(EtOH): 244, 274, 338 nm.

IR (KBr): $\tilde{\nu}$ = 2956, 2823, 1689, 1639, 1594, 1543, 1481, 1378.

GC-MS (70 eV) *m/z* (%): 216 (10) [M^+ – 1], 172 (100), 130 (87), 103 (24), 89 (13), 77 (21), 63 (34), 51 (24).

HRMS (ESI-Tof): calcd. for $C_{12}H_{13}N_2O_2$: 217.0970; found: 217.0973.

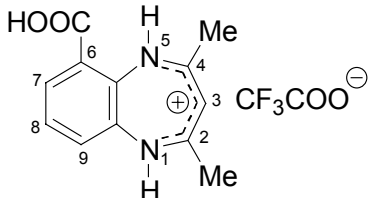
Anal. calcd. for $C_{12}H_{14}N_2O_6S$·1/2 H_2O (314.32): C, 44.6; H, 4.7; N, 8.7; found: C, 44.9; H, 4.4; N, 8.7.

*6-Carboxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium trifluoroacetate (**42b**)*

2,3-Diaminobenzoic acid **29** (0.10 g, 0.66 mmol) was used.

Yield: 0.18 g (83 %).

m.p.: 177–179 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.88 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 4.62 (s, 1H, 3-H), 6.77 (dd, *J* = 7.9, 1.4 Hz, 1H, 9-H), 7.06 (t, *J* = 7.9 Hz, 1H, 8-H) , 7.55 (dd, *J* = 7.9, 1.4 Hz, 1H, 7-H), 10.75 (br s, 2H, 2 × NH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 12.4 (2 × CH_3), 114.9, 118.8, 124.9 , 126.8, 130.1, 132.4, 142.9, 153.6, 158.6, 165.6.

UV λ_{max}(H_2O): 278, 318, 496 nm; λ_{max}(MeOH): 276, 328, 526 nm; λ_{max}(EtOH): 278, 328, 532 nm.

IR (KBr): $\tilde{\nu}$ = 2969, 1688, 1646, 1600, 1547, 1481, 1377, 1274, 1194.

GC-MS (70 eV) *m/z* (%): 216 (20) [M^+ – 1], 172 (100), 132 (36), 103 (7), 77 (7).

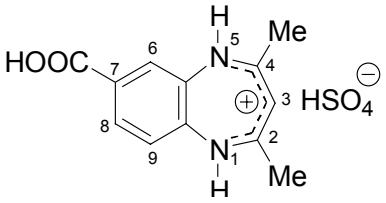
HRMS (ESI-Tof): calcd. for $C_{12}H_{13}N_2O_2$: 217.0970; found: 217.0977.

*7-Carboxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium hydrogensulfate (**43a**)*

3,4-Diaminobenzoic acid **30** (1.52 g, 10 mmol) was used.

Yield: 2.85 g (90 %).

m.p.: 175–178 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.76 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 4.24 (s, 1H, 3-H), 6.52 (d, *J* = 8.2 Hz, 1H, 9-H), 7.01 (d, *J* = 1.8 Hz, 1H, 6-H) , 7.41 (dd, *J* = 8.2, 1.8 Hz, 1H, 8-H), 9.71 (s, 1H, NH), 9.90 (s, 1H, NH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 24.0 (CH_3), 24.1 (CH_3), 96.2 (C-3), 123.2, 124.0, 130.5, 130.6, 133.6, 138.3, 165.2, 175.5, 176.7.

UV λ_{max}(H_2O): 520 nm; λ_{max}(MeOH): 524 nm; λ_{max}(MeCN): 262, 520 nm.

IR (KBr): $\tilde{\nu}$ = 3433, 3303, 3069, 3006, 1704, 1640, 1602, 1478.

GC-MS (70 eV) *m/z* (%): 216 (100) [M^+ – 1], 199 (11), 176 (13), 159 (15), 130 (13), 80 (18).

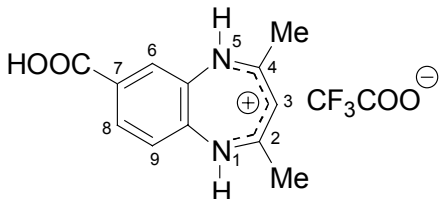
HRMS (ESI-Tof): calcd. for $C_{12}H_{13}N_2O_2$: 217.0970; found: 217.0976.

*7-Carboxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium trifluoroacetate (**43b**)*

3,4-Diaminobenzoic acid **30** (0.76 g, 5 mmol) was used.

Yield: 0.82 g (50 %).

m.p.: 185–187 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.76 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 4.24 (s, 1H, 3-H), 6.52 (d, *J* = 8.2 Hz, 1H, 9-H), 7.02 (d, *J* = 1.8 Hz, 1H, 6-H) , 7.42 (dd, *J* = 8.2, 1.8 Hz, 1H, 8-H), 9.84 (br s, 2H, 2 × NH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 23.9 (CH_3), 24.0 (CH_3), 96.2 (C-3), 123.2, 124.0 , 130.6, 130.7, 133.7, 138.3, 165.1, 175.5, 176.7.

UV λ_{max}(H_2O): 520 nm; λ_{max}(MeOH): 328, 524 nm; λ_{max}(EtOH): 330, 524 nm.

IR (KBr): $\tilde{\nu}$ = 3302, 3019, 1646, 1601, 1477, 1363.

GC-MS (70 eV) *m/z* (%): 216 (100) [M^+ – 1], 199 (11), 171 (12), 159 (12), 130 (16), 69 (21), 51 (20).

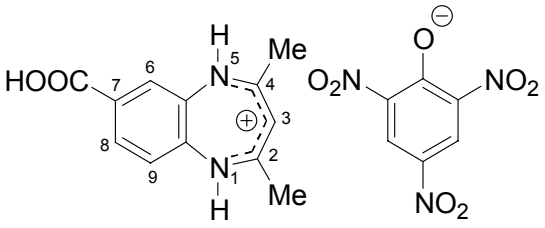
HRMS (ESI-Tof): calcd. for $C_{12}H_{13}N_2O_2$: 217.0970; found: 217.0979.

*7-Carboxy-2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium picrate (**43c**)*

3,4-Diaminobenzoic acid **30** (1.52 g, 10.0 mmol) was used.

Yield: 3.87 g (88 %).

m.p.: 205–207 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.75 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 4.23 (s, 1H, 3-H), 6.48 (d, *J* = 8.1 Hz, 1H, 9-H), 6.99 (s, 1H, 6-H) , 7.40 (d, *J* = 8.1 Hz, 1H, 8-H), 8.60 (s, 1H, Ph-pic), 8.61 (s, 1H, Ph-pic), 9.63 (s, 1H, NH), 9.85 (s, 1H, NH), 13.15 (br s, 1H, COOH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 24.1 (2 × CH_3), 96.1(C-3), 123.1, 124.0, 124.1, 125.2, 130.6, 133.5, 133.5, 138.2, 141.8, 165.1, 175.3, 176.5.

UV λ_{max}(H_2O): 268, 354 nm; λ_{max}(MeOH): 352, 524 nm; λ_{max}(EtOH): 242, 270, 360 nm.

IR (KBr): $\tilde{\nu}$ = 3310, 3071, 3003, 1692, 1631, 1600, 1568, 1554, 1520, 1435.

GC-MS (70 eV) *m/z* (%): 216 (100) [M^+ – 1], 199(16), 171(21), 159(13), 130(29), 103(13), 91(31), 77(28), 63(52), 53(29).

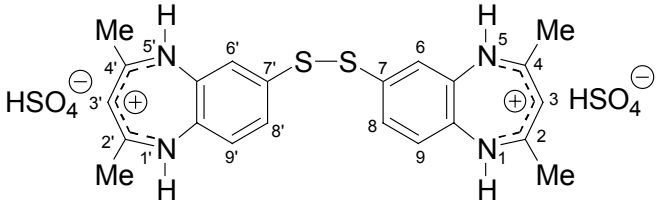
Anal. calcd. for $C_{18}H_{15}N_5O_9$ (445.34): C, 48.5; H, 3.4; N, 15.7; found: C, 48.6; H, 3.4; N, 15.4.

*7,7′-Dithiobis(2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium hydrogensulfate) (**44a**)*

Bis(3,4-diaminophenyl)disulfide **35** (0.208 g, 0.75 mmol) was used.

Yield: 0.361 g (87 %).

m.p.: 170–172 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.78 (s, 12H, 4 × CH_3), 4.23 (s, 2H, 3,3′-H), 6.49 (d, *J* = 8.3 Hz, 2H, 9,9′-H), 6.61 (d, *J* = 1.9 Hz, 2H, 6,6′-H), 6.99 (dd, *J* = 8.3, 1.9 Hz, 2H, 8,8′-H), 9.68 (br s, 2H, 2 × NH), 9.86 (br s, 2H, 2 × NH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 24.0 (2 × CH_3), 24.1 (2 × CH_3), 95.9 (C-3,3′), 121.4, 124.3, 127.3, 133.2, 135.2, 135.9, 175.8, 175.9.

UV λ_{max}(H_2O): 536 nm; λ_{max}(MeOH): 270, 528 nm; λ_{max}(EtOH): 220, 270 nm.

IR (KBr): $\tilde{\nu}$ = 3421, 3208, 3049, 2982, 1636, 1592, 1507, 1474, 1374.

GC-MS (70 eV) *m/z* (%): 204 (7) [M^{2+}/2], 64 (100), 58 (11).

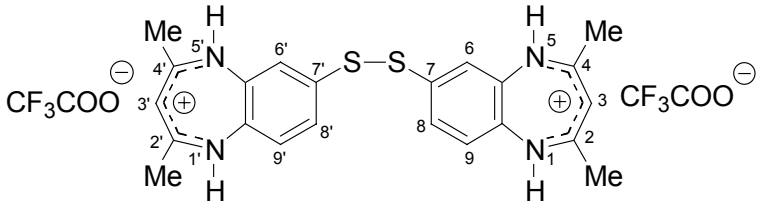
HRMS (ESI-Tof): calcd. for $C_{22}H_{23}N_4S_2$: 407.1372; found: 407.1368.

*7,7′-Dithiobis(2,4-dimethyl-5*H*-benzo[b][1,4]diazepin-1-ium trifluoroacetate) (**44b**)*

Bis-(3,4-diaminophenyl)disulfide **35** (0.062 g, 0.223 mmol) was used.

Yield: 0.092 g (65 %).

m.p.: 138–142 °C.



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.77 (s, 12H, 4 × CH_3), 4.21 (s, 2H, 3,3´-H), 6.48 (d, *J* = 7.7 Hz, 2H, 9,9´-H), 6.61 (s, 2H, 6,6´-H), 6.98 (d, *J* = 7.7 Hz, 2H, 8,8´-H), 9.96 (br s, 4H, 4 × NH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 23.9 (2 × CH_3), 24.0 (2 × CH_3), 95.9 (C-3,3´), 121.4, 124.2, 127.2, 133.3, 135.3, 135.9, 175.7, 175.9.

UV λ_{max}(H_2O): 268, 518 nm; λ_{max}(MeOH): 272, 528 nm; λ_{max}(EtOH): 270, 526 nm.

IR (KBr): $\tilde{\nu}$ = 3418, 3301, 3058, 2559, 1672, 1597, 1506, 1480, 1377, 1202, 1132.

GC-MS (70 eV) *m/z* (%): 204 (59) [M^{2+}/2], 189 (11), 164 (100), 140 (38), 122 (21), 96 (23), 69 (25), 51 (16).

HRMS (ESI-Tof): calcd. for $C_{22}H_{23}N_4S_2$: 407.1372; found: 407.1364.

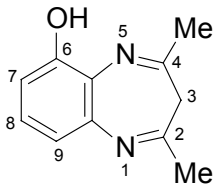
*General procedure for the preparation of the 2,4-dimethyl-5*H*-benzo[b][1,4]diazepine derivatives (**45, 46, 47, 53** and **57**)*

A solution of **38b**–**43b** (1 mmol) in water (20 mL) was neutralized with 0.1 *N* NaOH until the color of the solution changed to light yellow. The diimines were extracted with ethylacetate (2 × 30 mL). The combined organic phases were dried over $MgSO_4$ and evaporated *in vacuo* to afford the diimines. Purification of derivative **57** was accomplished by evaporation of the aqueous solution and extraction of the solids with methanol.

*6-Hydroxy-2,4-dimethyl-3*H*-benzo[b][1,4]diazepine (**45**)*

Salt **38b** (0.302 g, 1.0 mmol) was used.

Yield: 0.412 g (74 %).



m.p.: 195–197 °C.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.82 (s, 2H, 3-H), 6.66 (dd, *J* = 8.0, 1.4 Hz, 1H, 9-H), 6.73 (dd, *J* = 8.0, 1.4 Hz, 1H, 7-H) , 7.03 (t, *J* = 8.0 Hz, 1H, 8-H), 8.69 (s, 1H, OH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 27.0 (CH_3), 27.1 (CH_3), 43.3 (C-3), 109.4, 117.4, 124.8, 128.6, 140.6, 152.1, 157.6, 157.7.

IR (KBr): $\tilde{\nu}$ = 3159, 2997, 1633, 1560, 1464, 1446.

GC-MS (70 eV) *m/z* (%): 188 (100) [M^+], 173 (41), 148 (39), 107 (16).

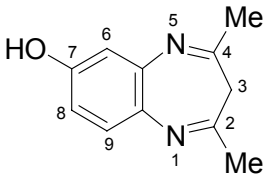
HRMS (ESI-Tof): calcd. for $C_{11}H_{12}N_2O$: 189.1028; found: 189.1029.

Anal. calcd. for $C_{11}H_{12}N_2O \cdot 1/2\ H_2O$ (188.23): C, 66.9; H, 6.6; N, 14.2; found: C, 66.5; H, 6.3; N, 13.7.

*7-Hydroxy-2,4-dimethyl-3*H*-benzo[b][1,4]diazepine (**46**)*

Salt **39b** (0.302 g, 1.0 mmol) was used.

Yield: 0.165 g (88 %).



m.p.: 155–157 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.31 (s, 6H, 2 × CH_3), 2.83 (s, 2H, 3-H), 6.72–6.78 (m, 2H, 6,9-H), 7.14–7.19 (m, 1H, 8-H), 9.12 (br s, 1H, OH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 32.1 (CH_3), 32.2 (CH_3), 47.8 (C-3), 116.6, 118.9, 133.3, 138.2, 146.1, 158.9, 159.9, 162.0.

IR (KBr): $\tilde{\nu}$ = 3039, 2783, 1628, 1607, 1555, 1456, 1379.

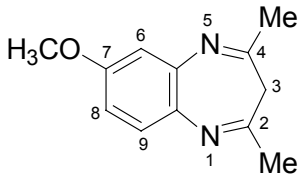
GC-MS (70 eV) *m/z* (%): 189 (100) [M^+ + 1], 171 (5), 145 (21).

HRMS (ESI-Tof): calcd. for $C_{11}H_{12}N_2O$: 189.1028; found: 189.1020.

*7-Methoxy-2,4-dimethyl-3*H-*benzo[b][1,4]diazepine (**47**)*

Salt **40b** (0.316 g, 1.0 mmol) was used (oily product).

Yield: 0.16 g (78 %).



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.33 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.83 (s, 2H, 3-H), 3.83 (s, 3H, OCH_3), 6.82–6.88 (m, 2H, 6,9-H), 7.26–7.31 (m, 1H, 8-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 27.5 (CH_3), 27.6 (CH_3), 43.7 (C-3), 55.4 (OCH_3), 109.1, 114.0, 128.8, 134.3, 141.1, 155.3, 156.4, 157.2.

IR (KBr): $\tilde{\nu}$ = 3380, 2994, 2940, 2907, 1630, 1602, 1549, 1478, 1438.

GC-MS (70 eV) *m/z* (%): 202 (100) [M^+], 187 (69), 147 (20), 119 (8).

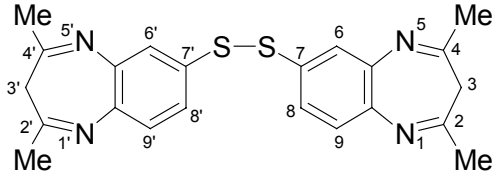
HRMS (ESI-Tof): calcd. for $C_{12}H_{14}N_2O$: 203.1184; found: 203.1182.

*7,7′-Dithiobis(2,4-dimethyl-3*H*-benzo[b][1,4]diazepine) (**53**)*

Salt **41b** (0.32 g, 1.0 mmol) was used.

Yield: 0.20 g (88 %).

m.p.: 104–106 °C.



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 6H, 2 × CH_3), 2.33 (s, 6H, 2 × CH_3), 2.82 (s, 4H, 3-H), 7.26–7.34 (m, 4H, 8,9-H), 7.51–7.53 (m, 2H, 6-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 27.7 (4 × CH_3), 43.5 (C-3,3′), 124.2, 126.1, 128.4, 133.1, 139.4, 140.5, 158.0, 158.5.

IR (KBr): $\tilde{\nu}$ = 3385, 1633, 1585, 1458, 1427, 1288, 1253.

GC-MS (70 eV) *m/z* (%): 406 (38) [M^+], 204 (100), 163 (35), 122 (23), 77 (11), 63 (10).

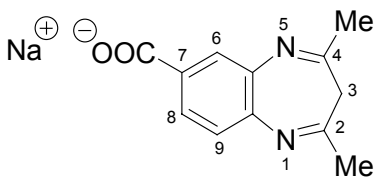
HRMS (ESI-Tof): calcd. for $C_{22}H_{23}N_4S_2$: 407.1364; found: 407.1359.

*Sodium, 2,4-dimethyl-3*H*-benzo[b][1,4]diazepine -7-carboxylate (**57**)*

Salt **43b** (0.314 g, 1.0 mmol) was used.

Yield: 0.15 g (63 %).

m.p.: > 250 °C (dec.).



^{1}H-NMR (200 MHz, DMSO-d_6): δ = 2.28 (s, 6H, 2 × CH_3), 2.32 (s, 2H, 3-H), 7.14 (d, 1H, *J* = 8.2 Hz, 9-H), 7.71 (dd, 1H, *J* = 8.2, 1.7 Hz, 8-H), 7.79 (d, 1H, *J* = 1.7 Hz, 6-H).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 27.1 (2 × CH_3), 42.8 (C-3), 125.3, 125.7, 128.0, 136.5, 139.0, 140.4, 157.9, 158.3, 169.6.

IR (KBr): $\tilde{\nu}$ = 3382, 1634, 1582, 1536, 1384.

ESI-MS (anion detection mode): *m/z* (amu): 454.1 [2M + Na], 215.1 [M].

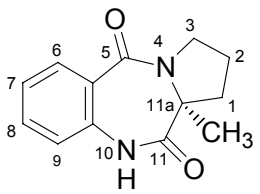
HRMS (ESI-Tof, cation detection mode): calcd. for $C_{12}H_{12}N_2O_2$: 217.0977; found: 217.0977.

4.3. Experiments to chapter 3.2.1.

*11a-Methyl-1,2,3,11a-tetrahydro-10*H*-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11-dione (**60**)*

Isatoic anhydride (1.84 g, 11.3 mmol) and 2-methyl-proline (1.47 g, 11.3 mmol) were dissolved in DMF (10 mL) and were then heated under reflux for 3 h. After cooling, the solvent was removed under reduced pressure to yield an oily residue. Purification by flash column chromatography on silica gel using petroleum ether/EtOAc (5:1) afforded **60** as a colorless solid.

Yield: 0.20 g (77 %).



m.p.: 203–204 °C.

$[\alpha]_D^{20}$ = + 385.9 (*c* = 1.0 in $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.23 (s, 3H, CH_3), 1.74–1.96 (m, 3H, 1,2-H), 3.06–3.22 (m, 1H, 1-H), 3.64–3.78 (m, 1H, 3-H), 3.92–4.02 (m, 1H, 3-H), 6.99 (dd, *J* = 8.0, 1.0 Hz, 1H, 9-H), 7.20-7.28 (m, 1H, 8-H), 7.43–7.51 (m, 1H, 7-H), 8.02 (dd, *J* = 8.0, 1.6 Hz, 1H, 6-H), 8.66 (br s, 1H, NH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 21.7 (C-2), 22.1 (CH_3), 38.7 (C-1), 49.8 (C-3), 66.28 (C-11a), 119.7, 124.6, 126.0, 131.4, 132.6, 135.3, 165.1 (CO), 173.3 (CO).

IR (KBr): $\tilde{\nu}$ = 3227 (N–H), 3069, 2997, 1677 (C=O), 1630 (C=O), 1483, 1435, 1404, 1361, 1256, 1180.

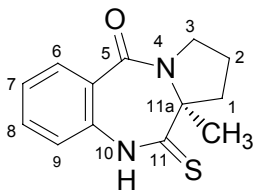
GC-MS (70 eV) *m/z* (%): 230 (99) [M^+], 187 (100), 119 (16), 84 (54), 63 (17).

Anal. calcd. for $C_{13}H_{14}N_2O_2$ (230.26): C, 67.8; H, 6.1; N, 12.2; found: C, 67.5; H, 6.1; N, 12.1.

11a-Methyl-11-thioxo-1,2,3,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one ***(62)***

A mixture of dilactam **60** (2.30 g, 10.0 mmol) and Lawesson's ragent (2.02 g, 5.0 mmol) in THF (40 mL) was stirred over night at room temperature. Evaporation of solvent in vacuo gave a solid residue, which was purified by flash chromatography on silica using CH_2Cl_2/acetone (100:1) to give pure monothiolactam **62** as a yellow solid.
colorless solid.

Yield: 1.77 g (72 %).



m.p.: 258–260 °C.

$[\alpha]_D^{20}$ = + 113.1 (*c* = 0.2 in $CHCl_3$).

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.14 (s, 3H, CH_3), 1.71–1.86 (m, 2H, 2-H), 1.90–2.09 (m, 1H, 1-H), 3.40–3.61 (m, 2H, 1,3-H), 3.71–3.81 (m, 1H, 3-H), 7.29–7.37 (m, 2H, 8,9-H), 7.53–7.62 (m, 1H, 7-H), 7.83 (dd, *J* = 8.1, 1.6 Hz, 1H, 6-H), 12.47 (br s, 1H, NH).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 20.6 (C-2), 22.2 (CH_3), 42.4 (C-1), 49.4 (C-3), 66.3 (C-11a), 120.7, 125.4, 126.4, 130.4, 132.4, 136.6, 163.6 (CO), 205.0 (CS).

IR (KBr): $\tilde{\nu}$ = 3178 (N–H), 2968, 1605 (C=O), 1582, 1519, 1479, 1419, 1352, 1270, 1146, 1108, 1076.

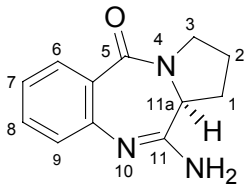
GC-MS (70 eV) *m/z* (%): 247 (24) [M^+ + 1], 162 (8), 84 (100).

Anal. calcd. for $C_{13}H_{14}N_2O_2$ (230.26): C, 63.4; H, 5.7; N, 11.4; found: C, 63.2; H, 5.6; N, 11.3.

*11-Amino-1,2,3,11a-tetrahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one (**63**)*

To a solution of thiolactam **61** (1.16 g, 5.0 mmol) in anhydrous THF (50 mL) was added $HgCl_2$ (1.63 g, 6.0 mmol) and pure anhydrous ammonia was bubbled through the mixture for 1 h at 60 °C. After cooling, the resulting suspension was filtered off through a pad of Celite and eluted with methanol. The organic solution was evaporated under reduced pressure at room temperature. Addition of an acetone/ether mixture afforded a white solid which was washed with ether and recrystallized from anisole/methanol.

Yield: 0.925 g (86 %).



m.p.: > 240 °C (dec.).

$[\alpha]_D^{20}$ = + 510.5 (*c* = 1.0 in DMSO).

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.91–2.00 (m, 2H, 2-H), 2.08–2.18 (m, 1H, 1-H), 2.43–2.59 (m, 1H, 1-H), 3.35–3.42 (m, 1H, 3-H), 3.63–3.69 (m, 1H, 3-H), 4.22 (d, *J* = 7.8 Hz, 1H,

11a-H), 7.15 (d, *J* = 7.5 Hz, 1H, 9-H), 7.22 (t, *J* = 7.5 Hz, 1H, 8-H), 7.28–7.70 (br s, 2H, NH_2), 7.49–7.54 (m, 1H, 7-H), 7.79 (dd, *J* = 7.8, 1.5 Hz, 1H, 6-H).

^{13}C-NMR (50 MHz, DMSO-d_6): δ = 24.0 (C-2), 26.7 (C-1), 47.4 (C-3), 55.1 (C-11a), 124.6, 125.1, 127.7, 131.0, 132.8, 141.3, 164.3, 165.4 (CO).

IR (KBr): $\tilde{\nu}$ = 3125 (N–H), 1614 (C=O), 1578, 1456, 1239.

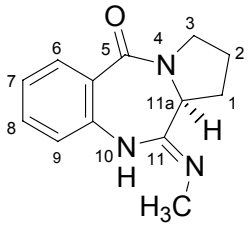
GC-MS (70 eV) *m/z* (%): 215 (39) [M^+], 70 (100).

Anal. calcd. for $C_{12}H_{13}N_3O$ (215.25): C, 66.9; H, 6.1; N, 19.5; found: C, 66.7; H, 6.3; N, 19.6.

*11-Methylamino-1,2,3,11a-tetrahydro-benzo[e]pyrrolo[1,2-a]diazepin-5-one (**64**)*

To a suspension of monothiolactam **61** (2.32 g, 10 mmol) and $HgCl_2$ (3.26 g, 12 mmol) in THF (100 mL) was added a 2 *M* solution of monomethylamine in THF (20 mL, 40 mmol) at room temperature and stirred for 30 min at the same temperature. The mixture was heated at reflux for 15 min. After cooling, the mixture was filtered off through a plug of Celite and dried over $MgSO_4$. Evaporatin of solvent in vacuo gave a white solid residue, which was recrystallized from acetonitril to afford **64** as colorless crystals.

Yield: 1.90 g (83 %).



m.p.: 204–206 °C.

$[\alpha]_D^{20}$ = + 1190.4 (*c* = 1.0 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.99–2.14 (m, 2H, 2-H), 2.18–2.27 (m, 2H, 1-H), 3.00 (s, 3H, CH_3), 3.56–3.63 (m, 1H, 3-H), 3.85–3.91 (m, 1H, 3-H), 4.03 (dd, *J* = 7.7, 2.0 Hz, 1H, 11a-H), 5.18 (br s, 1H, NH), 7.08–7.12 (m, 1H, 8-H), 7.14 (d, *J* = 8.1 Hz, 1H, 9-H), 7.40 (ddd, *J* = 8.0, 7.1, 1.7 Hz, 1H, 7-H), 7.96 (dd, *J* = 8.0, 1.3 Hz, 1H, 6-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.2 (C-2), 27.1 (C-1), 29.0 (CH_3), 46.9 (C-3), 54.8 (C-11a), 122.6, 126.9 (C-11), 127.3, 130.4, 132.1, 147.9, 157.6, 167.1 (CO).

IR (KBr): $\tilde{\nu}$ = 3304 (N-H), 3061, 2887, 1620 (C=O), 1603 (C=N), 1536, 1453, 1406, 1226, 1149.

GC-MS (70 eV) *m/z* (%): 230 (100) [M^+ + 1].

Anal. calcd. for $C_{13}H_{15}N_3O$ (229.28): C, 68.1; H, 6.6; N, 18.3; found: C, 68.2; H, 6.7; N, 18.4.

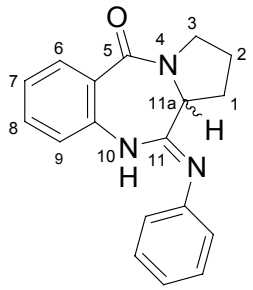
*General procedure for preparation of the 11-substituted pyrrolobenzo[1,4]diazepin-5-ones (**65**–**67**)*

To a stirred suspension of the monothiolactam **61** and **62** (1.16 g and 1.23 g , 5.0 mmol) and the corresponding amine (5.0 mL) was added $HgCl_2$ (1.75 g, 6.5 mmol) at 80–90 °C, and the mixture was stirred for further 30 min at this temperature. After cooling to room temperature, chloroform (100 mL) was added and the mixture was filtered through a plug of Celite. The filtrate was then dried over $MgSO_4$, filtered, and the solvent and excess amine were evaporated under reduced pressure. The resultant solid was purified by recrystallization in an appropriate solvent to afford pure colorless crystals in very good yield.

*11-Phenylamino-1,2,3,11a-tetrahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one (**65**)*

Using starting materials **61** and aniline afforded a crude product which was purified by crystallization from 2-propanol to yield **65** as colorless crystals.

Yield: 1.32 g (91 %).



m.p.: 150–152 °C.

$[\alpha]_D^{20}$ = 0 (*c* = 1.0 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.05–2.24 (m, 3H, 1,2-H), 3.03–3.05 (m, 1H, 1-H), 3.67–3.74 (m, 1H, 3-H), 3.86–3.92 (m, 1H, 3-H), 4.32 (d, *J* = 7.0 Hz, 1H, 11a-H), 6.63 (s, 1H, NH), 6.66 (d, *J* = 8.0 Hz, 1H, 9-H), 6.91 (d, *J* = 7.5 Hz, 2H, Ph), 7.10–7.17 (m, 2H, Ph), 7.32–7.41 (m, 3H, Ph), 7.95 (dd, *J* = 7.9, 1.5 Hz, 1H, 6-H).

^{1}H-NMR (400 MHz, DMSO-d_6) of **8A**: δ = 1.90–2.22 (m, 3H, 1,2-H), 2.80–2.84 (m, 1H, 1-H), 3.50–3.57 (m, 1H, 3-H), 3.63–3.72 (m, 1H, 3-H), 4.31 (d, *J* = 5.6 Hz, 1H, 11a-H), 6.75 (d, *J* = 7.3 Hz, 2H, Ph), 7.01–7.13 (m, 3H, Ph), 7.29–7.34 (m, 2H, Ph), 7.36–7.40 (m, 1H, 7-H), 7.73 (dd, *J* = 8.0, 1.5 Hz, 1H, 6-H), 7.84 (d, *J* = 7.6 Hz, 2H, Ph), 8.36 (s, 1H, NH).

^{1}H-NMR (400 MHz, DMSO-d_6) of **8B**: δ = 1.90–2.22 (m, 3H, 1,2-H), 2.80–2.84 (m, 1H, 1-H), 3.33–3.44 (m, 1H, 3-H), 3.63–3.72 (m, 1H, 3-H), 4.07 (d, *J* = 7.2 Hz, 1H, 11a-H), 7.01–7.13 (m, 3H, Ph), 7.29–7.34 (m, 2H, Ph), 7.40–7.41 (m, 1H, 7-H), 7.78 (dd, *J* = 7.9, 1.7 Hz, 1H, 6-H), 7.84 (d, *J* = 7.6 Hz, 2H, Ph), 8.42 (s, 1H, NH).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 23.8 (C-2), 27.2 (C-1), 47.8 (C-3), 57.1 (C-11a), 120.7, 121.6, 124.2, 124.3, 126.9 (C-11), 130.4, 131.6, 132.6, 137.1, 148.1, 154.0, 166.4 (CO).

^{13}C-NMR (100 MHz, DMSO-d_6) of **8A**: δ = 23.8 (C-2), 27.4 (C-1), 47.6 (C-3), 57.3 (C-11a), 122.1, 122.7, 123.5, 123.7, 127.4 (C-11), 130.2, 130.9, 132.5, 138.7, 149.2, 153.7, 165.8 (CO).

^{13}C-NMR (100 MHz, DMSO-d_6) of **8B**: δ = 24.50 (C-2), 26.8 (C-1), 47.1 (C-3), 55.9 (C-11a), 122.3, 122.9, 123.4, 124.1, 127.3 (C-11), 129.1, 130.4, 132.1, 140.5, 147.6, 155.8, 166.0 (CO).

IR (KBr): $\tilde{\nu}$ = 3273 (N–H), 3246, 2945, 2876, 1649 (C=O), 1624, 1593, 1475, 1416, 1377, 1264, 1223.

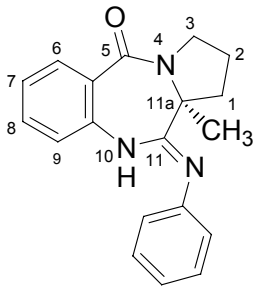
GC-MS (70 eV) *m/z* (%): 291 (100) [M^+], 251 (6), 221 (37), 187 (14), 160 (18), 119 (28), 92 (25), 77 (40), 51 (28).

Anal. calcd. for $C_{18}H_{17}N_3$ (291.35): C, 74.2; H, 5.9; N, 14.4; found: C, 74.2; H, 5.9; N, 14.3.

*11a-Methyl-11-phenylamino-1,2,3,11a-tetrahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one (**66**)*

Using starting materials **62** and aniline gave **66** as colorless crystals after crystallization from nitromethane.

Yield: 1.31 g (86 %).



m.p.: 182–184 °C.

$[\alpha]_D^{20}$ = + 530.5 (*c* = 1.0 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 3H, CH_3), 1.89–2.01 (m, 3H, 1,2-H), 3.40–3.46 (m, 1H, 1-H), 3.74–3.81 (m, 1H, 3-H), 4.00–4.06 (m, 1H, 3-H), 6.57 (d, *J* = 7.9 Hz, 1H, ph), 6.60 (br s, 1H, NH), 6.89 (d, *J* = 7.5 Hz, 2H, Ph), 7.09–7.14 (m, 2H, 8,9-H), 7.30–7.34 (m, 1H, 7-H), 7.48–7.42 (m, 2H, Ph), 7.96 (dd, *J* = 7.8, 1.6 Hz, 1H, 6-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.9 (C-2), 24.4 (CH_3), 39.8 (C-1), 50.4 (C-3), 63.7 (C-11a), 119.3, 121.5, 123.8, 124.2, 125.7 (C-11), 130.5, 131.9, 132.7, 137.4, 148.2, 156.3, 166.0 (CO).

IR (KBr): $\tilde{\nu}$ = 3376 (N–H), 3218, 3055, 2968, 1651 (C=O), 1616 (C=N), 1597, 1536, 1437, 1354, 1222, 759, 699.

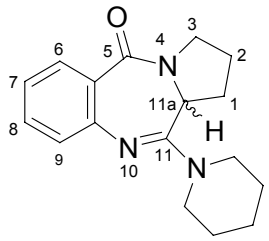
GC-MS (70 eV) *m/z* (%): 306 (100) [M^+ + 1].

Anal. calcd. for $C_{19}H_{19}N_3O$ (305.37): C, 74.7; H, 6.3; N, 13.8; found: C, 74.4; H, 6.2; N, 13.7.

*11-(Piperidin-1-yl)-1,2,3,11a-tetrahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one (**67**)*

Using starting materials **61** and piperidine afforded a crude product which was purified by crystallization from diethylether to give **67** as colorless crystals.

Yield: 1.26 g (89 %).



m.p.: 105–107 °C.

$[\alpha]_D^{20} = 0$ (c = 1.0 in $CHCl_3$).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.64 (s, 6H, 3 × CH_2), 1.80–1.89 (m, 1H, 2-H), 1.98–2.07 (m, 1H, 2-H), 2.22–2.43 (m, 2H, 1-H), 3.03–3.08 (m, 2H, CH_2), 3.26–3.35 (m, 3H, CH_2, 3-H), 3.83–3.89 (m, 1H, 3-H), 3.95 (dd, J = 7.7, 6.2 Hz, 1H, 11a-H), 7.05 (dd, J = 8.1, 1.3 Hz, 1H, 9-H), 7.10–7.14 (m, 1H, 8-H), 7.45 (ddd, J = 8.0, 7.2, J = 1.3 Hz, 1H, 7-H), 7.76 (dd, J = 8.0, 1.5 Hz, 1H, 6-H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 24.4 (C-2), 24.8 (CH_2), 26.1 (C-1), 29.2 (2 × CH_2), 47.2 (C-3), 50.6 (2 × CH_2), 56.7 (C-11a), 123.6, 126.2 (C-11), 127.0, 130.2, 132.1, 147.2, 164.5, 166.1 (CO).

IR (KBr): $\tilde{\nu}$ = 3141, 2935, 2857, 2833, 1629 (C=O), 1605, 1593, 1452, 1405, 1375, 1240.

GC-MS (70 eV) *m/z* (%): 283 (100) [M^+].

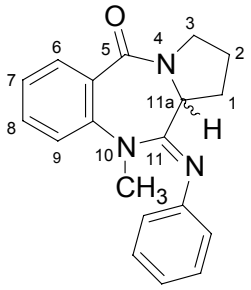
Anal. calcd. for $C_{17}H_{21}N_3O$ (283.37): C, 72.1; H, 7.5; N, 14.8; found: C, 72.0; H, 7.5; N, 14.9.

*11-(N-Phenyl)imino-10-methyl-1,2,3,11a-tetrahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one (**68**)*

To a suspension of NaH (60% in mineral oil) (20 mg, 0.5 mmol), which had been washed with n-hexane (2 × 10 mL), in anhydrous dimethoxyethane (20 mL) was added cycloamidine **65** (146 mg, 0.5 mmol) portionwise at room temperature under nitrogen. A reaction occurred whereupon the color changed to yellow. To the resulting solution was added CH_3I (0.5 mL)

and the mixture was then stirred for further 30 min at room temperature. Evaporation of the solvent and excess CH_3I yielded *N*-methylated cycloamidine **68** as a colorless solid.

Yield: 0.15 g (98 %).



m.p.: 65–68 °C.

$[\alpha]_D^{20}$ = 0 (*c* = 1.0 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.88–1.96 (m, 2H, 2-H), 2.10–2.20 (m, 1H, 1-H), 2.77–2.83 (m, 1H, 1-H), 2.93 (s, 3H, CH_3), 3.60–3.67 (m, 1H, 3-H), 3.80–3.85 (m, 1H, 3-H), 4.28 (d, *J* = 6.7 Hz, 1H, 11a-H), 6.82 (d, *J* = 7.6 Hz, 2H, Ph), 6.95 (t, *J* = 7.3 Hz, 1H, 8-H), 7.13 (d, *J* = 8.2 Hz, 1H, 9-H), 7.23–7.27 (m, 4H, Ph), 7.48 (t, *J* = 7.8 Hz, 1H, 7-H), 7.86 (d, *J* = 7.8 Hz, 1H, 6-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.0 (C-2), 28.3 (C-1), 42.4 (CH_3), 46.9 (C-3), 60.2 (C-11a), 120.8, 122.0, 123.5, 125.7, 129.0, 130.0, 131.5 (C-11), 132.4, 144.4, 149.9, 153.3, 166.5 (CO).

IR (KBr): $\tilde{\nu}$ = 3347, 2968, 2875, 1637 (C=O), 1591, 1457, 1412, 1359.

GC-MS (70 eV) *m/z* (%): 306 (100) [M^++1].

Anal. calcd. for $C_{19}H_{19}N_3O$ (305.37): C, 74.7; H, 6.3; N, 13.8; found: C, 74.4; H, 6.2; N, 13.6.

4.4. Experiments to chapter 3.3.1.

*General procedure for preparation of the 2-hydroxy-4-oxopyrimidines and 2,4-dioxo-pyrimidines (**69**–**76**)*

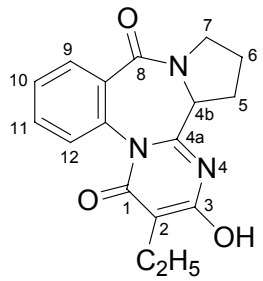
A mixture of the cycloamidines **63**–**65**, respectively, (1.0 eq.) and 2-phenyl bis-2,4,6-trichlorophenyl malonate (1.0 eq.) was heated at 170–180 °C for 10 min in a *Zincke* apparatus

under high vacuum. The residue was treated with diethyl ether (20 mL) to give a precipitate which was collected by filtration and washed with diethylether. The crude solids were purified by crystallization in an appropriate solvent.

*2-Ethyl-3-hydroxy-4b,5,6,7-tetrahydro-4,7a,12b-triaza-dibenzo[e,g]azulene-1,8-dione (**69**)*

Cycloamidine **63** (0.430 g, 2.0 mmol) and 2-ethyl bis(2,4,6-trichlorophenyl)malonate (0.982 g, 2.0 mmol) were used, to give colorless crystals after crystallization from nitromethane.

Yield: 0.529 g (85 %).



m.p.: > 250 °C.

$[\alpha]_D^{20}$ = - 6.1 (*c* = 0.5 in DMSO).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.00 (t, *J* = 7.4 Hz, 3H, CH_3), 1.92–1.98 (m, 1H, 6-H), 2.01–2.12 (m, 2H, 5,6-H), 2.35 (q, *J* = 7.4 Hz, 2H, CH_2), 2.74–2.81 (m, 1H, 5-H), 3.38–3.45 (m, 1H, 7-H), 3.61–3.66 (m, 1H, 7-H), 4.48–4.50 (m, 1H, 4b-H), 7.49–7.51 (m, 1H, 12-H), 7.51–7.55 (m, 1H, 11-H), 7.61 (td, *J* = 7.6, 1.7 Hz, 1H, 10-H), 7.79 (dd, *J* = 7.6, 1.7 Hz, 1H, 9-H), 11.46 (s, 1H, OH).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 13.3 (CH_3), 17.3 (CH_2), 24.2 (C-6), 27.0 (C-5), 47.0 (C-7), 58.9 (C-4b), 103.5 (C-2), 129.2, 129.7, 129.8, 131.1, 132.7, 133.8, 157.4 (C-4a), 163.6, 163.9, 164.3.

IR (KBr): $\tilde{\nu}$ = 1650, 1554, 1458.

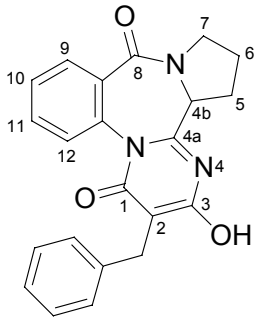
GC-MS (70 eV) *m/z* (%): 311 (100) [M^+].

Anal. calcd. for $C_{17}H_{17}N_3O_3 \cdot 0.5\ (H_2O)$ (311.34): C, 63.7; H, 5.7; N, 13.1; found: C, 63.5; H, 5.5; N, 13.3.

*2-Benzyl-3-hydroxy-4b,5,6,7-tetrahydro-4,7a,12b-triaza-dibenzo[e,g]azulene-1,8-dione (**70**)*

Cycloamidine **63** (0.430 g, 2.0 mmol) and 2-benzyl bis(2,4,6-trichlorophenyl)malonate (1.106 g, 2.0 mmol) were used to afford colorless crystals after crystallization from methanol.

Yield: 0.537 g (72 %).



m.p.: > 250 °C.

$[\alpha]_D^{20}$ = - 29.6 (*c* = 0.5 in DMSO).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.92–1.97 (m, 1H, 6-H), 2.01–2.14 (m, 2H, 5,6-H), 2.75–2.77 (m, 1H, 5-H), 3.17 (s, 2H, CH_2), 3.37–3.44 (m, 1H, 7-H), 3.58–3.69 (m, 1H, 7-H), 4.50 (d, *J* = 6.3 Hz, 1H, 4b-H), 7.12–7.15 (m, 1H, Ph), 7.21–7.27 (m, 4H, Ph), 7.48 (d, *J* = 8.0 Hz, 1H, 12-H), 7.52–7.55 (m, 1H, 11-H), 7.59–7.64 (m, 1H, 10-H), 7.80 (dd, *J* = 7. 5, 1.1 Hz, 1H, 9-H), 11.71 (s, 1H, OH).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 24.1 (C-6), 27.0 (C-5), 29.6 (CH_2), 47.0 (C-7), 58.9 (C-4b), 101.6 (C-2), 126.6, 129.0, 129.2, 129.3, 129.7, 129.8, 131.1, 132.6, 133.8, 141.4, 158.0 (C-4a), 163.8, 164.2, 164.5.

IR (KBr): $\tilde{\nu}$ = 1667, 1626, 1604, 1558, 1458.

GC-MS (70 eV) *m/z* (%): 373 (100) [M^+].

Anal. calcd. for $C_{22}H_{19}N_3O_3 \cdot 0.5\ (H_2O)$ (373.40): C, 69.1; H, 5.3; N, 11.0; found: C, 68.9; H, 5.3; N, 10.8.

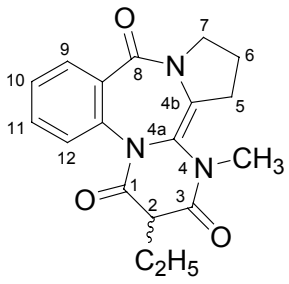
*2-Ethyl-4-methyl-4,5,6,7-tetrahydro-4,7a,12b-triaza-dibenzo[e,g]azulene-1,3,8-trione (**71**)*

Cycloamidine **64** (0.458 g, 2.0 mmol) and 2-benzyl bis(2,4,6-trichlorophenyl)malonate (0.982 g, 2.0 mmol) were used. The crude product was recrystallized from xylene to afford a pale yellow crystals.

Yield: 0.507 g (78 %).

m.p.: 185–187 °C.

$[\alpha]_D^{20} = 0$ (c = 1.0 in $CHCl_3$).



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.04–2.16 (m, 1H, 6-H), 2.09 (dd, J = 7.4, 6.3 Hz, 2H, CH_2CH_3), 2.20–2.28 (m, 1H, 6-H), 2.72–2.77 (m, 2H, 5-H), 3.22 (s, 3H, NCH_3), 3.25–3.28 (m, 1H, 2-H), 4.00–4.06 (m, 2H, 7-H), 7.35 (dd, J = 8.2, 0.8 Hz, 1H, 12-H), 7.38–7.42 (m, 1H, 11-H), 7.59 (ddd, J = 8.1, 7.4, 1.6 Hz, 1H, 10-H), 8.05 (dd, J = 8.1, 1.6 Hz, 1H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.9 (CH_3), 17.2 (CH_2), 20.9 (C-6), 29.7 (C-5), 29.7 (NCH_3), 49.7 (C-7), 53.6 (C-2), 120.6, 125.8, 127.7, 129.0, 129.7, 132.6, 133.6, 140.5, 165.6 (CO), 167.1 (CO), 168.4 (CO).

IR (KBr): $\tilde{\nu}$ = 1681, 1632, 1574, 1489, 1452.

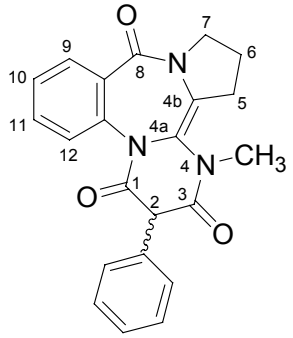
GC-MS (70 eV) *m/z* (%): 325 (100) [M^+].

Anal. calcd. for $C_{18}H_{19}N_3O_3$ (325.36): C, 66.5; H, 5.9; N, 12.9; found: C, 66.4; H, 5.9; N, 12.9.

*4-Methyl-2-phenyl-4,5,6,7-tetrahydro-4,7a,12b-triaza-dibenzo[e,g]azulene-1,3,8-trione (**72**)*

Starting materials cycloamidine **64** and 2-phenyl-bis(2,4,6-trichlorophenyl) malonic acid ester (2.695 g, 5.0 mmol) were used. The crude product was purified by crystallization from 2-propanol to give **72** as faintly yellow crystals.

Yield: 1.417 g (76 %).



m.p.: 225–227 °C.

$[\alpha]_D^{20}$ = 0 (*c* = 1.0 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.94–1.07 (m, 1H, 6-H), 1.67–1.85 (m, 1H, 6-H), 2.04–2.10 (m, 1H, 5-H), 2.35–2.44 (m, 1H, 5-H), 3.20 (s, 3H, NCH_3), 3.54–3.60 (m, 1H, 7-H), 3.69–3.75 (m, 1H, 7-H), 4.82 (s, 1H, 2-H), 7.27–7.33 (m, 5H, Ph), 7.38–7.45 (m, 2H, 11,12-H), 7.62 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H, 10-H), 8.03 (dd, *J* = 8.0, 1.3 Hz, 1H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.3 (C-6), 29.3 (C-5), 35.6 (CH_3), 49.3 (C-7), 61.5 (C-2), 120.6 (C-4b), 126.0, 126.4, 128.1, 128.5, 129.0 (C-4a), 129.3, 131.0, 132.2, 132.7, 133.8, 140.1, 165.3 (CO), 166.7 (CO), 168.4 (CO).

IR (KBr): $\tilde{\nu}$ = 3082, 2972, 1724 (C=O), 1697 (C=O), 1682 (C=O), 1632, 1493, 1452, 1380, 1354, 1258, 1155.

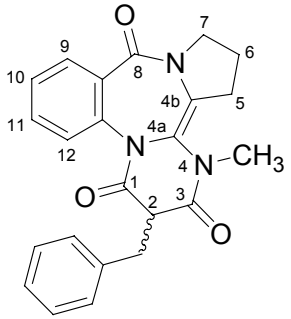
GC-MS (70 eV) *m/z* (%): 373 (100) [M^+], 344 (27), 305 (7), 256 (8), 187 (22), 118 (18), 89 (17), 63 (12).

Anal. calcd. for $C_{22}H_{19}N_3O_3$ (373.40): C, 70.8; H, 5.1; N, 11.2; found: C, 70.5; H, 5.2; N, 11.0.

*2-Benzyl-4-methyl-4,5,6,7-tetrahydro-4,7a,12b-triaza-dibenzo[e,g]azulene-1,3,8-trione (**73**)*

Cycloamidine **64** (0.458 g, 2.0 mmol) and 2-benzyl bis(2,4,6-trichlorophenyl)malonate (0.982 g, 2.0 mmol) were used. The crude product was purified by crystallization from xylene to yield pale yellow crystals.

Yield: 0.619 g (80 %).



m.p.: 185–187 °C.

$[\alpha]_D^{20}$ = 0 (*c* = 1.0 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.95–2.06 (m, 1H, 6-H), 2.14–2.19 (m, 1H, 6-H), 2.62–2.72 (m, 2H, 5-H), 3.19 (s, 3H, NCH_3), 3.42 (d, *J* = 5.7 Hz, 2H, C*H*$_2$Ph), 3.57–3.60 (m, 1H, 2-H), 3.91–4.01 (m, 2H, 7-H), 7.21–7.42 (m, 7H, Ph), 7.55–7.59 (m, 1H, 10-H), 8.01 (dd, *J* = 7.7, 1.1 Hz, 1H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.7 (C-6), 29.3 (C-5), 29.7 (*C*H_2Ph), 35.7 (NCH_3), 49.7 (C-7), 54.9 (C-2), 120.2, 125.7, 126.8, 127.8, 128.8, 129.0, 129.2, 130.1, 132.7, 133.7, 140.4, 140.6, 165.5 (CO), 166.7 (CO), 168.0 (CO).

IR (KBr): $\tilde{\nu}$ = 1721, 1682, 1644, 1597, 1487, 1450.

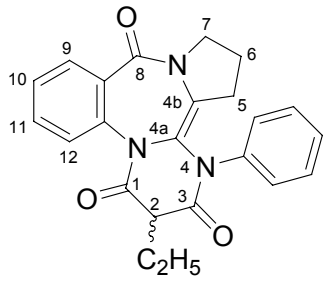
GC-MS (70 eV) *m/z* (%): 387 (100) [M^+].

Anal. calcd. for $C_{23}H_{21}N_3O_3$ (387.16): C, 71.3; H, 5.5; N, 10.8; found: C, 71.4; H, 5.5; N, 11.6.

*2-Ethyl-4-phenyl-4,5,6,7-tetrahydro-4,7a,12b-triaza-dibenzo[e,g]azulene-1,3,8-trione (**74**)*

Cycloamidine **65** (0.582 g, 2.0 mmol) and 2-benzyl bis(2,4,6-trichlorophenyl)malonate (0.982 g, 2.0 mmol) were used. Resulting crude product was purified by crystallization from n-butanol to afford pale yellow crystals.

Yield: 0.612 g (79 %).



m.p.: 201–202 °C.

$[\alpha]_D^{20}$ = 0 (*c* = 1.0 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.19 (td, *J* = 7.5, 0.8 Hz, 3H, CH_2CH_3), 1.82–2.02 (m, 3H, 5,6-H), 2.08–2.15 (m, 2H, CH_2CH_3), 2.44–2.50 (m, 1H, 6-H), 3.47 (td, *J* = 6.2, 0.8 Hz, 1H, 2-H), 3.94–3.98 (m, 2H, 7-H), 7.08–7.20 (m, 3H, Ph), 7.27–7.34 (m, 2H, Ph), 7.41–7.46 (m, 2H, Ph), 7.61–7.66 (m, 1H, 10-H), 8.07–8.09 (m, 1H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.9 (CH_3), 17.3 (CH_2), 20.4 (C-6), 29.8 (C-5), 50.0 (C-7), 54.5 (C-2), 119.1, 124.5, 124.8, 126.7, 128.0, 129.2, 129.6, 131.7, 132.9, 133.9, 139.1, 139.9, 165.6 (CO), 166.9 (CO), 167.0 (CO).

IR (KBr): $\tilde{\nu}$ = 1724, 1684, 1635, 1600, 1490, 1453.

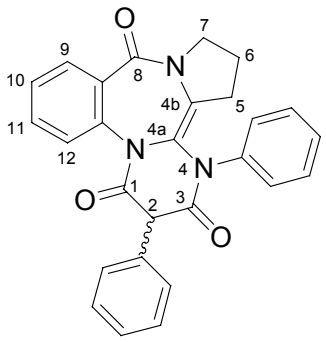
GC-MS (70 eV) *m/z* (%): 387 (100) [M^+].

Anal. calcd. for $C_{23}H_{21}N_3O_3$ (387.43): C, 71.3; H, 5.5; N, 10.8; found: C, 71.0; H, 5.6; N, 10.7.

*2,4-Diphenyl-4,5,6,7-tetrahydro-4,7a,12b-triaza-dibenzo[e,g]azulene-1,3,8-trione (**75**)*

The starting materials cycloamidine **65** and 2-phenyl-bis(2,4,6-trichlorophenyl) malonic acid ester (2.695 g, 5.0 mmol) gave **75** as pale yellow crystals after recrystallization from 2-butanol.

Yield: 1.78 g (82 %).



m.p.: 207–208 °C.

$[\alpha]_D^{20}$ = 0 (*c* = 1.0 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90–0.98 (m, 1H, 6-H), 1.56–1.65 (m, 2H, 5,6-H), 1.73–1.80 (m, 1H, 5-H), 3.41–3.47 (m, 1H, 7-H), 3.67–3.74 (m, 1H, 7-H), 4.94 (s, 1H, 2-H), 7.13–7.20 (m, 3H, Ph), 7.28–7.43 (m, 7H, Ph), 7.47–7.51 (m, 1H, 11-H), 7.53 (dd, *J* = 8.1, 1.2 Hz, 1H, 12-H), 7.70 (ddd, *J* = 8.0, 7.3, 1.2 Hz, 1H, 10-H), 8.08 (dd, *J* = 8.0, 1.5 Hz, 1H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 19.8 (C-6), 29.2 (C-5), 49.5 (C-7), 62.3 (C-2), 119.3 (C-4b), 124.2, 126.2, 126.3, 126.9, 128.3, 128.6, 129.3 (C-4a), 129.5, 129.7, 132.1, 132.9, 133.1, 134.1, 138.9, 139.5, 165.2 (CO), 166.6 (CO), 166.7(CO).

IR (KBr): $\tilde{\nu}$ = 3057, 2967, 1732 (C=O), 1709 (C=O), 1694 (C=O), 1632, 1597, 1495, 1454, 1256.

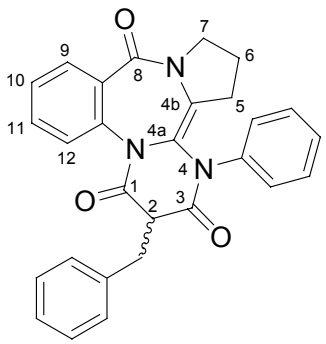
GC-MS (70 eV) *m/z* (%): 435 (100) [M^+], 407 (6), 317 (10), 260 (6), 172 (7), 90 (14).

Anal. calcd. for $C_{27}H_{21}N_3O_3$ (435.47): C, 74.5; H, 4.9; N, 9.6; found: C, 74.4; H, 4.8; N, 9.4.

*2-Benzyl-4-phenyl-4,5,6,7-tetrahydro-4,7a,12b-triaza-dibenzo[e,g]azulene-1,3,8-trione (**76**)*

Cycloamidine **65** (0.582 g, 2.0 mmol) and 2-benzyl bis(2,4,6-trichlorophenyl)malonate (0.982 g, 2.0 mmol) were used to afford pale yellow crystals after crystallization from 2-propanol.

Yield: 0.790 g (88 %).



m.p.: 187–188 °C.

$[\alpha]_D^{20}$ = 0 (*c* = 1.0 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.82–1.97 (m, 3H, 5,6-H), 2.39–2.45 (m, 1H, 5-H), 3.47 (d, *J* = 6.0 Hz, 2H, C*H*$_2$Ph), 3.81 (t, *J* = 6.0 Hz, 1H, 2-H), 3.87–3.98 (m, 2H, 7-H), 7.06–7.09 (m, 2H, Ph), 7.15–7.19 (m, 1H, Ph), 7.22–7.35 (m, 5H, Ph), 7.42–7.48 (m, 4H, Ph), 7.63–7.67 (m, 1H, 10-H), 8.06–8.08 (m, 1H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.2 (C-6), 29.3 (C-5), 29.8 (*C*H$_2$Ph), 50.0 (C-7), 55.8 (C-2), 118.7, 124.5, 125.8, 126.8, 128.1, 128.9, 129.2, 129.4, 129.7, 130.2, 132.1, 132.9, 134.0, 139.1, 139.8, 140.6, 165.5 (CO), 166.4 (CO), 166.6 (CO).

IR (KBr): $\tilde{\nu}$ = 1735, 1695, 1633, 1619, 1574, 1496, 1454.

GC-MS (70 eV) *m/z* (%): 449 (100) [M^+].

Anal. calcd. for $C_{28}H_{23}N_3O_3 \cdot 0.5$ (2-propanol) (449.50): C, 73.9; H, 5.7; N, 8.8; found: C, 73.7; H, 5.7; N, 8.7.

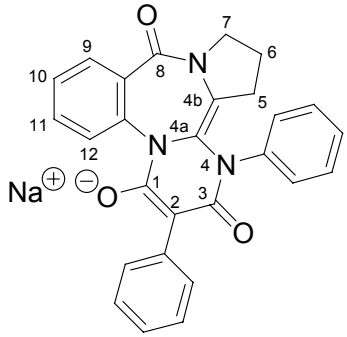
*Sodium 3,8-dioxo-2,4-diphenyl-4,5,6,7-tetrahydro-3*H,*8*H-*4,7a,12b-triaza-dibenzo[e,g]-azulen-1-olate (**78**)*

To a solution of dioxopyrimidine **75** (0.435 g, 1.0 mmol) in anhydrous dimethoxyethane (20 mL) was added NaH (60% in mineral oil) (20 mg, 0.5 mmol), which had been washed with n-hexane (2 × 10 mL), and the mixture was stirred at room temperature for further 30 min. The solvent was then removed under reduced pressure to afford the product **78** as a yellow solid.

Yield: 0.444 g (97 %).

m.p.: > 250 °C (dec).

$[\alpha]_D^{20}$ = 0 (*c* = 0.5 in CH_3OH).



^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.46–1.54 (m, 1H, 6-H), 1.69–1.79 (m, 2H, 5,6-H, 2.10–2.16 (m, 1H, 5-H), 3.57–3.63 (m, 1H, 7-H), 3.67–3.77 (m, 1H, 7-H), 6.76–6.80 (m, 1H, Ph), 6.91–6.95 (m, 1H, Ph), 7.03–7.07 (m, 2H, Ph), 7.11–7.22 (m, 6H, Ph), 7.47–7.51 (m, 1H, 10-H), 7.75 (dd, *J* = 7.8, 1.5 Hz, 1H, 9-H), 7.85–7.87 (m, 2H, Ph).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 20.6 (C-6), 28.3 (C-5), 48.8 (C-7), 87.9 (C-2), 121.6, 122.4 (C-4b), 123.6, 124.7, 125.8, 126.4, 126.5 (C-4a), 126.8, 128.7, 130.2, 130.5, 131.7, 132.9, 141.7, 143.9, 147.2, 164.7 (CO), 166.4 (2 × CO).

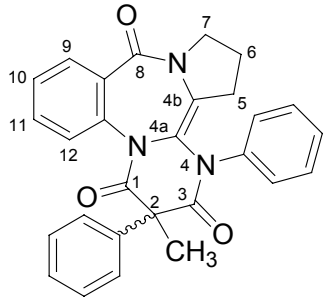
IR (KBr): $\tilde{\nu}$ = 3057, 2934, 1634 (C=O), 1575, 1550, 1488, 1404, 1068.

GC-MS (70 eV) *m/z* (%): 435 (4) [M^+], 390 (12), 185 (100), 119 (9), 93 (34), 66 (13).

Anal. calcd. for $C_{27}H_{20}N_3NaO_3$ (457.46): C, 70.9; H, 4.4; N, 9.2; found: C, 70.5; H, 4.7; N, 9.4.

*2-Methyl-2,4-diphenyl-4,5,6,7-tetrahydro-4,7a,12b-triaza-dibenzo[e,g]azulene-1,3,8-trione (**79**)*

A suspension of pyrimidine-olate **78** (0.457 g, 1.0 mmol) in anhydrous dimethoxyethane (20 mL) was treated with CH_3I (1.0 mL) at room temperature and the mixture was then heated at 60 °C for 3 h. Evaporation of the solvent and excess CH_3I under reduced pressure gave a residue which was purified by flash column chromatography on silica gel using EtOAc/petroleum ether (2:1) to afford the dioxopyrimidine **79** as a colorless solid.



Yield: 0.40 g (89 %).

m.p.: 112–114 °C.

$[\alpha]_D^{20}$ = 0 (*c* = 1.0 in $CHCl_3$).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 0.58–0.66 (m, 1H, 6-H), 0.79–0.89 (m, 1H, 6-H), 1.49–1.62 (m, 2H, 5-H), 1.56 (s, 3H, CH_3), 3.06–3.12 (m, 1H, 7-H), 3.48–3.55 (m, 1H, 7-H), 7.16–7.22 (m, 3H, Ph), 7.26–7.29 (m, 2H, Ph), 7.35–7.44 (m, 5H, Ph), 7.52 (ddd, *J* = 8.0, 7.1, 1.3 Hz, 1H, 11-H), 7.70 (dd, *J* = 8.0, 1.1 Hz, 1H, 12-H), 7.73–7.77 (m, 1H, 10-H), 7.89 (dd, *J* = 7.9, 1.3 Hz, 1H, 9-H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 19.6 (C-6), 23.4 (CH_3), 28.9 (C-5), 49.6 (C-7), 61.5 (C-2), 118.8 (C-4b), 125.1, 125.2, 127.0, 127.4, 128.5, 128.6, 129.6 (C-4a), 129.9, 130.0, 132.4, 132.8, 134.3, 139.6, 140.0, 140.7, 164.8 (CO), 168.9 (CO), 169.0 (CO).

IR (KBr): $\tilde{\nu}$ = 3069, 2989, 1720 (C=O), 1685 (C=O), 1640 (C=O), 1598, 1490, 1454, 1356, 1259.

GC-MS (70 eV) *m/z* (%): 450 (100) [M^+ + 1], 289 (6), 261 (8), 172 (16), 132 (20), 104 (15), 77 (14).

Anal. calcd. for $C_{28}H_{23}N_3O_3$ (449.50): C, 74.8; H, 5.2; N, 9.3; found: C, 74.6; H, 5.2; N, 9.1.

4.5. Experiments to chapter 3.4.1.

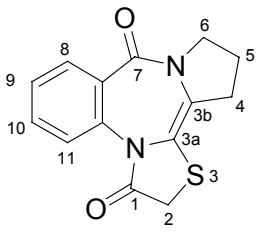
*General procedure for the preparation of the benzocyclopentaazulene-1,7-diones (**80**–**82**)*

To a solution of monothiolactam **61** (0.232 g, 1.0 mmol) in anhydrous THF (30 mL) was added the corresponding freshly distilled bromoacetyl chloride (1.2 mmol). The mixture was stirred for 4–6 hours at room temperature under nitrogen and then quenched by addition of saturated solution of $NaHCO_3$ (20 mL). After extraction with chloroform (2 × 20 mL), the combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel column chromatography using EtOAc/petroleum ether (1:4) as eluent to give yellow solids.

*5,6-Dihydro-4*H*-3-thia-6a,11b-diazabenzo[g]cyclopenta[e]azulene-1,7-dione (**80**)*

α-Bromoacetyl chloride (0.19 g, 1.2 mmol) was used. Crystallization from ethanol afforded yellow crystals.

Yield: 0.20 g (75 %).



m.p.: 165–167 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.98–2.05 (m, 2H, 5-H), 2.67 (t, *J* = 8.0 Hz, 2H, 4-H), 3.83 (s, 2H, 2-H), 3.90–3.94 (m, 2H, 6-H), 7.28–7.32 (m, 1H, 10-H), 7.44 (dd, *J* = 8.2, 1.0 Hz, 1H, 11-H), 7.51–7.55 (m, 1H, 9-H), 8.00 (dd, *J* = 8.0, 1.6 Hz, 1H, 8-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.8 (C-5), 31.1 (C-4), 35.8 (C-2), 50.1 (C-6), 115.5, 124.3, 124.9, 127.2, 128.5, 133.3, 133.6, 138.9, 165.4 (CO), 172.7 (CO).

IR (KBr): $\tilde{\nu}$ = 3074, 2983, 2934, 1721, 1700, 1625, 1528, 1489, 1451, 1393, 1325, 1242, 1209.

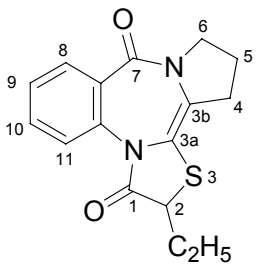
GC-MS (70 eV) *m/z* (%): 272 (100) [M^+], 230 (9), 201 (11), 76 (12), 50 (13).

Anal. calcd. for $C_{14}H_{12}N_2O_2S$ (272.32): C, 61.7; H, 4.4; N, 10.3; found: C, 61.4; H, 4.4; N, 10.2.

*2-Ethyl-5,6-dihydro-4*H*-3-thia-6a,11b-diazabenzo[g]cyclopenta[e]azulene-1,7-dione (**81**)*

α-Bromoethylacetyl chloride (0.22 g, 1.2 mmol) was used to afford yellow crystals after crystalization from ethanol.

Yield: 0.17 g (57 %).



m.p.: 131–132 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): 1.10 (t, *J* = 7.3 Hz, 3H, CH_3), 1.86–2.08 (m, 3H, CH_2,5-H), 2.11–2.32 (m, 1H, 5-H), 2.64–2.72 (m, 2H, 4-H), 3.88–3.95 (m, 2H, 6-H), 4.03 (dd, *J* = 8.7, 4.3 Hz, 1H, 2-H), 7.24–7.32 (m, 1H, 10-H), 7.40 (dd, *J* = 8.2, 1.1 Hz, 1H, 11-H), 7.47–7.56 (m, 1H, 9-H), 7.99 (dd, *J* = 7.9, 1.6 Hz, 1H, 8-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 11.6 (CH_3), 20.5 (C-5), 25.8 (CH_2), 30.8 (C-4), 49.7 (C-6), 52.1 (C-2), 114.3, 123.9, 124.3, 126.6, 128.0, 132.8, 133.0, 138.6, 165.0 (CO), 174.4 (CO).

IR (KBr): $\tilde{\nu}$ = 2966, 2874, 1724, 1703, 1628, 1451, 1393, 1319, 1199.

GC-MS (70 eV) *m/z* (%): 300 (100) [M^+], 195 (10).

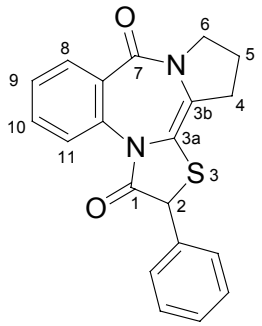
Anal. calcd. for $C_{16}H_{16}N_2O_2S$ (300.38): C, 64.0; H, 5.4; N, 9.3; found: C, 63.8; H, 5.3; N, 9.4.

*2-Phenyl-5,6-dihydro-4*H*-3-thia-6a,11b-diazabenzo[g]cyclopenta[e]azulene-1,7-dione (**82**)*

α-Bromophenylacetyl chloride (0.28 g, 1.2 mmol) was used. Crystallization from 2-propanol gave yellow crystals.

Yield: 0.26 g (65 %).

m.p.: 193–195 °C.



^{1}H-NMR (400 MHz, $CDCl_3$): 1.96–2.07 (m, 2H, 5-H), 2.65–2.77 (m, 2H, 4-H), 3.90–4.00 (m, 2H, 6-H), 5.15 (s, 1H, 2-H), 7.29–7.33 (m, 1H, Ph), 7.36–7.48 (m, 6H, Ph), 7.51–7.56 (m, 1H, 9-H), 8.02 (dd, *J* = 8.0, 1.5 Hz, 1H, 8-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.0 (C-5), 31.3 (C-4), 50.2 (C-6), 54.3 (C-2), 114.3, 124.4, 125.6, 127.2, 128.5, 128.8, 129.1, 129.5, 133.3, 133.6, 136.6, 139.1, 165.5 (CO), 173.3 (CO).

IR (KBr): $\tilde{\nu}$ = 3057, 2896, 1719, 1699, 1625, 1574, 1489, 1451, 1394, 1328, 1242, 1201.

GC-MS (70 eV) *m/z* (%): 348 (100) [M^+], 320 (6), 199 (7), 90 (8).

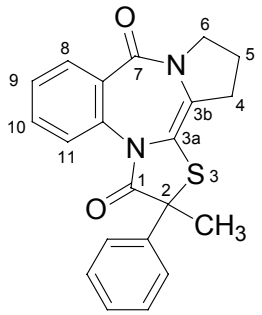
Anal. calcd. for $C_{20}H_{16}N_2O_2S$ (348.42): C, 68.9; H, 4.6; N, 8.0; found: C, 69.1; H, 4.7; N, 7.8.

*2-Methyl-2-phenyl-5,6-dihydro-4*H*-3-thia-6a,11b-diazabenzo[g]cyclopenta[e]azulene-1,7-dione (**85**)*

To a solution of phenylthiazolidinone **82** (0.174 g, 0.50 mmol) in anhydrous THF (10 mL) was added of potassium *tert*-butoxide (0.068 g, 0.6 mmol) portionwise at – 70 °C under nitrogen. The resulting mixture was stirred for additional 10 min at the same temperature. Methyl iodide (0.3 mL) was then added at – 70 ° C, and the mixture was warmed to rt over a period of 10 min. Stirring was then continued for additional 30 min at rt. Then, the reaction was cautiously quenched with saturated NH_4Cl solution (10 mL) and extracted with of chloroform (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, and concentrated in *vacuo*. Purification by flash chromatography using EtOAc/petroleum ether (1:3) as eluent and crystallization from acetonitrile gave product **85** as colorless crystals.

Yield: 0.148 g (82 %).

m.p.: 230–232 °C.



^{1}H-NMR (400 MHz, $CDCl_3$): 1.74–1.99 (m, 2H, 5-H), 2.03 (s, 3H, CH_3), 2.52–2.78 (m, 2H, 4-H), 3.83–3.90 (m, 2H, 6-H), 7.28–7.42 (m, 4H, Ph), 7.50–7.60 (m, 4H, Ph), 7.97–8.02 (m, 1H, 8-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 20.6 (C-5), 26.4 (CH_3), 31.1 (C-4), 49.7 (C-6), 60.4, 123.9, 126.1, 126.7, 127.9, 128.0, 128.6, 132.7, 133.1, 138.7, 140.5, 165.2 (CO), 175.4 (CO).

IR (KBr): $\tilde{\nu}$ = 3070, 2965, 1715, 1690, 1630, 1489, 1454, 1389, 1328, 1197.

GC-MS (70 eV) *m/z* (%): 363 (100) [M^+ + 1], 333 (25), 301 (18), 226 (37), 195 (29), 159 (14), 104 (20), 79 (8).

Anal. calcd. for $C_{21}H_{18}N_2O_2S$ (362.45): C, 69.6; H, 5.0; N, 7.7; found: C, 69.4; H, 5.0; N, 7.8.

4.6. Experiments to chapter 3.5.1.

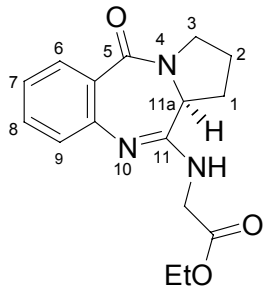
*General procedure for preparation of 11-imino-ethylester pyrrolobenzo[1,4]diazepin-5-ones (**88** and **89**)*

To a suspension of thiolactam **61** (0.232 g, 1.0 mmol) and $HgCl_2$ (0.272 g, 1.0 mmol) in acetonitril (30 mL) was added glycine ethyl ester hydrochloride and β-alanine ethyl ester hydrochloride (0.21 g and 0.23 g, 1.5 mmol), and then Et_3N (1.0 mL) at room temperature. Refluxing for 2–3 h, whereupon the color changed to intense black, and subsquent cooling, results in a mixture, which was filtered through a plug of Celite and washed with chloroform. The filtrate was washed with saturated $NaHCO_3$ solution (20 mL) and a solution of $Na_2S_2O_3$ (20 mL). The solvents were removed under reduced pressure to give the corresponding crude products which were purified by recrystallization from appropriate solvents.

*(5-Oxo-1,2,3,5,10,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-11-ylideneamino)-acetic acid ethyl ester (**88**)*

Glycine ethyl ester hydrochloride gave an oily crude product. By addition of diethyl ether (15 mL) and stirring for 10 min at room temperature, the crude product precipitated as a pale yellow solid which was filtered off and washed with diethyl ether. Recrystallization from EtOAc/petroleum ether afforded faintly yellow crystal.

Yield: 0.25 g (83 %).



m.p.: 89–91 °C.

$[\alpha]_D^{20}$ = + 717.2 (*c* = 1.0 in $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 2.04–2.18 (m, 2H, 2-H), 2.22–2.38 (m, 2H, 1-H), 3.54–3.61 (m, 1H, 3-H), 3.86–3.92 (m, 1H, 3-H), 4.06 (dd, *J* = 7.8, 1.9 Hz, 1H, 11a-H), 4.10–4.27 (m, 2H, $NHCH_2$), 4.27 (qd, *J* = 7.1, 0.7 Hz, 2H, CH_2CH_3), 5.46 (br s, 1H, NH), 7.08–7.12 (m, 2H, 8,9-H), 7.38–7.42 (m, 1H, 7-H), 7.96 (dd, *J* = 8.3, 1.7 Hz, 1H, 6-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_2CH_3), 24.2 (C-2), 27.2 (C-1), 43.7 ($NHCH_2$), 46.9 (C-3), 54.5 (C-11a), 62.1 (CH_2CH_3), 123.1, 127.0, 127.2, 130.5, 132.0, 147.0, 156.2 (C-11), 166.9 (CO), 171.0 (CO_2).

IR (KBr): $\tilde{\nu}$ = 3312 (NH), 3055, 2976, 1784, 1620, 1593, 1541, 1461, 1277, 1199.

GC-MS (70 eV) *m/z* (%): 301 (100) [M^+], 255 (42), 226 (10), 186 (13), 158 (25), 131 (14), 102 (16), 70 (17).

Anal. calcd. for $C_{16}H_{19}N_3O_3$ (301.34): C, 63.8; H, 6.4; N, 13.9; found: C, 63.8; H, 6.1; N, 13.5.

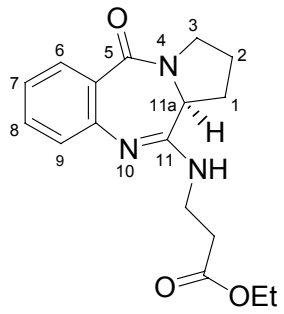
*3-(5-Oxo-1,2,3,5,10,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-11-ylideneamino)-propionic acid ethyl ester (**89**)*

β-Alanine ethyl ester hydrochloride afforded a solid crude product which was purified by crystallization from benzene to yield **89** as colorless crystal.

Yield: 0.222 g (70 %).

m.p.: 122–124 °C.

$[\alpha]_D^{20}$ = + 878.5 (*c* = 1.0 in $CHCl_3$).



^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.93–2.35 (m, 4H, 1,2-H), 2.64–2.71 (m, 2H, $COCH_2$), 3.48–3.62 (m, 1H, 3-H), 3.57–3.74 (m, 2H, $NHCH_2$), 3.81–3.92 (m, 1H, 3-H), 4.00–4.05 (m, 1H, 11a-H), 4.27 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 5.74 (br s, 1H, NH), 7.04–7.12 (m, 2H, 8,9-H), 7.36–7.44 (m, 1H, 7-H), 7.40 (ddd, *J* = 8.1, 7.2, 1.6 Hz, 1H, 6-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 14.2 (CH_2CH_3), 23.6 (C-2), 26.6 (C-1), 33.0 ($COCH_2$), 36.7 ($NHCH_2$), 46.4 (C-3), 54.4 (C-11a), 60.9 (CH_2CH_3), 122.4, 126.5, 126.6, 130.1, 131.6, 146.7, 156.2 (C-11), 166.9 (CO), 171.0 (CO_2).

IR (KBr): $\tilde{\nu}$ = 3283 (NH), 3059, 2973, 2870, 1728, 1603, 1524, 1465, 1342, 1174, 1032.

GC-MS (70 eV) *m/z* (%): 315 (100) [M^+], 270 (19), 242 (52), 215 (14), 200 (19), 172 (28), 146 (34), 118 (15), 70 (31).

Anal. calcd. for $C_{17}H_{21}N_3O_3$ (315.37): C, 64.7; H, 6.7; N, 13.3; found: C, 64.6; H, 6.5; N, 13.3.

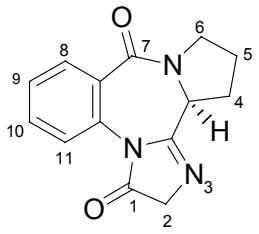
*General procedure for preparation of 1,3-imidazol- and 1,3-pyrimidine-4-one-pyrrolobenzo[1,4]diazepin-5-ones (**90** and **91**)*

To a solution of cycloamidine ethyl esters **88** and **89** (1.505 g and 1.575 g, 5.0 mmol) in a mixture of dioxane/water (2:1) (50 mL) was added a solution of NaOH (2 *N*) (3.0 mL) at 0 °C (ice-bath). The reaction mixture was stirred for 30 min at room temperature, and then acidified to p*H* = 3 with HCl (0.5 *N*) at 0 °C. Compound **90** was purified by extraction with chloroform (2 × 50 mL), drying of the combined organic layers over Na_2SO_4 and evaporation of the solvent under reduced pressure to afford the crude solid residue. The mixture containing compound **91** was extracted with dichloromethane (50 mL) to remove impurities. The aqueous phase was evaporated in vacuum to leave a solid residue. Extraction with methanol and evaporation of solvent gave **91** as colorless solids.

*3b,4,5,6-Tetrahydro-2*H*-3,6a,11b-triaza-benzo[g]cyclopenta[e]azulene-1,7-dione (**90**)*

Ethyl ester **88** afforded a solid crude product which was purified by crystallization from acetone to yield **90** as faintly yellow crystals.

Yield: 1.084 g (85 %).



m.p.: 199–201 °C.

$[\alpha]_D^{20}$ = + 130.5 (*c* = 1.0 in $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.98–2.31 (m, 3H, 4,5-H), 2.84–2.98 (m, 1H, 4-H), 3.60–3.68 (m, 1H, 6-H), 3.82–3.93 (m, 1H, 6-H), 4.32–4.35 (m, 2H, 2-H), 4.41–4.45 (m, 1H, 3b-H), 7.41 (ddd, *J* = 7.9, 7.4, 1.4 Hz, 1H, 10-H), 7.54–7.63 (m, 1H, 9-H), 7.69 (dd, *J* = 7.9, 1.1 Hz, 1H, 11-H), 7.99 (dd, *J* = 7.8, 1.4 Hz, 1H, 8-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 23.3 (C-5), 26.0 (C-4), 47.3 (C-6), 53.9 (C-3b), 59.0 (C-2), 122.3, 126.4, 127.8, 129.5, 130.4, 131.1, 162.8 (C-3a), 164.0 (CO), 177.4 (CO).

IR (KBr): $\tilde{\nu}$ = 2959, 2876, 1749, 1624, 1465, 1340, 1220, 1170, 1026.

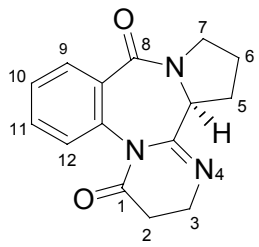
GC-MS (70 eV) *m/z* (%): 255 (100) [M^+], 226 (25), 198 (14), 184 (16), 172 (16), 158 (34), 130 (36), 103 (31), 69 (23).

Anal. calcd. for $C_{14}H_{13}N_3O_2$ (255.27): C, 65.9; H, 5.1; N, 16.5; found: C, 65.4; H, 5.1; N, 16.1.

*2,3,4b,5,6,7-Hexahydro-4,7a,12b-triaza-dibenzo[e,g]azulene-1,8-dione (**91**)*

Ethyl ester **89** gave a solid crude product which was purified by crystallization from EtOH/2-propanol to yield **91** as colorless crystals.

Yield: 1.049 g (78 %).



m.p.: 194–196 °C.

$[\alpha]_D^{20}$ = + 485.2 (*c* = 1.0 in CH_3OH).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.87–2.12 (m, 3H, 5,6-H), 2.36–2.48 (m, 3H, 3,5-H), 3.33–3.38 (m, 1H, 7-H), 3.43 (t, *J* = 6.9 Hz, 2H, 2-H), 3.57–3.64 (m, 1H, 7-H), 3.91 (d, *J* = 7.6 Hz, 1H, 4b-H), 6.96–7.00 (m, 2H, 11,12-H), 7.36 (td, *J* = 7.7, 1.1 Hz, 1H, 10-H), 7.70 (dd, *J* = 7.7, 1.3 Hz, 1H, 9-H).

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 24.1 (C-6), 26.7 (C-5), 35.1 (C-3), 38.5 (C-2), 47.1 (C-7), 55.1 (C-4b), 121.7, 127.2, 127.5, 130.4, 132.0, 148.6, 158.1 (C-4a), 166.2 (CO), 175.4 (CO).

IR (KBr): $\tilde{\nu}$ = 2967, 2873, 1693, 1630, 1455, 1394, 1257, 1202.

GC-MS (70 eV) *m/z* (%): 270 (100) [M^+ + 1], 240 (8), 216 (26), 201 (13), 172 (17), 146 (9), 103 (8), 63 (11).

Anal. calcd. for $C_{15}H_{15}N_3O_2$ (269.30): C, 66.9; H, 5.6; N, 15.6; found: C, 66.6; H, 5.7; N, 15.2.

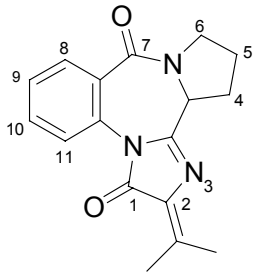
*General procedure for preparation of 2-imidazolidenone derivatives of PBD (**92** and **93**)*

To a solution of cycloamidine ethyl esters **88** and **89** (0.301 g and 0.315 g, 1.0 mmol) in THF (20 mL) was added K_2CO_3 (0.5 g) and the appropriate ketone (1.0 mL) at room temperature. The mixture was heated at reflux for 4-6 h. After cooling, the the exess K_2CO_3 was filtered off and the filtrate was evaporated in vacuum to give a solid residue. The crude product was subjected to a flash column chromatography on silica gel using EtOAc/petroleum ether (1:1) to afford the corresponding pure products **92** and **93**.

*2-Isopropylidene-3b,4,5,6-tetrahydro-2*H*-3,6a,11b-triaza-benzo[g]cyclopenta[e]azulene-1,7-dione (**92**)*

Ethyl ester **88** and acetone afforded compound **92** as faintly yellow solids.

Yield: 0.23 g (78 %).



m.p.: 214–217 °C.

$[\alpha]_D^{20}$ = – 4.8 (*c* = 0.5 in $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.96–2.27 (m, 3H, 4,5-H), 2.32 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.95–3.08 (m, 1H, 4-H), 3.62–3.89 (m, 2H, 6-H), 4.46–4.50 (m, 1H, 3b-H), 7.38 (ddd, *J* = 7.9, 7.4, 1.4 Hz, 1H, 10-H), 7.57 (ddd, *J* = 8.0, 7.4, 1.3 Hz, 1H, 9-H), 7.69 (dd, *J* = 7.9, 1.3 Hz, 1H, 11-H), 7.99 (dd, *J* = 8.0, 1.4 Hz, 1H, 8-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 19.8 (CH_3), 22.7 (CH_3), 23.4 (C-5), 26.0 (C-4), 47.2 (C-6), 53.6 (C-3b), 123.5, 126.9, 128.9, 131.2, 131.3, 131.9, 136.0, 153.4, 156.4 (C-3a), 165.1 (CO), 166.2 (CO).

IR (KBr): $\tilde{\nu}$ = 2942, 2869, 1709, 1641, 1459, 1395, 1334, 1234, 1155, 1064.

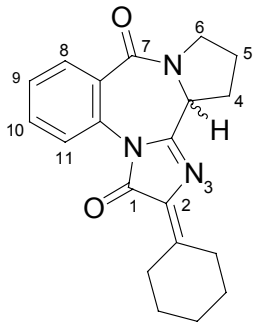
GC-MS (70 eV) *m/z* (%): 295 (100) [M^+], 280 (31), 227 (14), 199 (17), 130 (30), 102 (34).

Anal. calcd. for $C_{17}H_{17}N_3O_2$ (295.34): C, 69.1; H, 5.8; N, 14.2; found: C, 68.8; H, 5.6; N, 14.0.

*2-Cyclohexylidene-3b,4,5,6-tetrahydro-2*H*-3,6a,11b-triaza-benzo[g]cyclopenta[e]azulene-1,7-dione (**93**)*

Ethyl ester **89** and cyclohexanone gave compound **93** as pale yellow solids.

Yield: 0.24 g (71 %).



m.p.: 161–164 °C.

$[\alpha]_D^{20}$ = 0 (*c* = 0.5 in $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.65–1.82 (m, 6H, 3 × CH_2), 1.95–2.31 (m, 3H, 4,5-H), 2.79–2.85 (m, 2H, CH_2), 2.94–3.05 (m, 1H, 4-H), 3.07–3.15 (m, 2H, CH_2), 3.62–3.89 (m, 2H, 6-H), 4.44–4.50 (m, 1H, 3b-H), 7.38 (ddd, *J* = 7.9, 7.5, 1.4 Hz, 1H, 10-H), 7.57 (ddd, *J* = 8.0, 7.5, 1.3 Hz, 1H, 9-H), 7.69 (dd, *J* = 7.9, 1.3 Hz, 1H, 11-H), 7.98 (dd, *J* = 8.0, 1.4 Hz, 1H, 8-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 23.4 (C-5), 26.0 (C-4), 26.1 (CH_2), 28.2 (2 × CH_2), 28.7 (CH_2), 31.7 (CH_2), 47.2 (C-6), 53.6 (C-3b), 123.5, 126.9, 128.9, 131.2, 131.3, 131.8, 133.4, 156.4, 161.3 (C-3a), 165.2 (CO), 166.7 (CO).

IR (KBr): $\tilde{\nu}$ = 2934, 2853, 1715, 1651, 1459, 1396, 1284, 1173.

GC-MS (70 eV) *m/z* (%): 335 (100) [M^+], 307 (7), 227 (14), 281 (27), 255 (13), 199 (11), 130 (15), 102 (20).

Anal. calcd. for $C_{20}H_{21}N_3O_2$ (335.40): C, 71.6; H, 6.3; N, 12.5; found: C, 71.3; H, 6.2; N, 12.1.

5. **X-Ray Data Section**

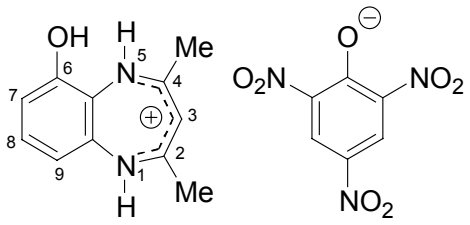


Table 2: Crystal data and structure refinement for **38c**.

Empirical formula:	$C_{20}\ H_{21}\ N_5\ O_9$
	$(C_{11}\ H_{13}\ N_2\ O)+\ (C_6\ H_2\ N_3\ O_7)-$ aectone
Formula weight:	475.42
Temperature:	123(2) K
Wavelength:	0.71073 Å (MoKα)
Crystal system:	Triclinic
Space group:	P-1 (No.2)
Unit cell dimensions:	a = 8.0073(2) Å, α = 81.282(2)°
	b =9.6532(3) Å, β = 82.257(2)°
	c = 14.6882(5) Å, γ = 71.068(2)°
Volume:	1057.06(6) $Å^3$
Z:	2
Calculated density:	1.494 Mg/m^3
Absorption coefficient :	0.120 mm^{-1}
F(000):	496
Crystal size:	0.50 x 0.40 x 0.25 mm
Θ-Range for data collection:	2.78 to 27.47°
Limiting indices:	-10<=h<=10, -12<=k<=12, -18<=l<=18
Reflections collected:	10292
Unique	4708 [R_{int} = 0.0306]
Absorption correction :	None
Refinement method:	Full-matrix least-squares on F^2
Data / restraints / parameters:	4708 / 3 / 320
Goodness-of-fit on F^2:	1.039
Final R indices [I > 2σ(I)]:	R1 = 0.0393, wR2 = 0.0992
R indices (all data):	R1 = 0.0580, wR2 = 0.1058
Largest diff. peak and hole:	0.270 and -0.318 $eÅ^{-3}$

Table 3: Bond lengths [Å] and angles [°] for **38c**.

N(1)-C(2)	1.3307(18)	N(5)-C(4)-C(13)	115.17(13)
N(1)-C(11)	1.4248(18)	C(3)-C(4)-C(13)	117.62(13)
N(1)-H(1N)	0.872(12)	C(4)-N(5)-C(6)	130.07(12)
C(2)-C(3)	1.385(2)	C(4)-N(5)-H(5N)	115.1(11)
C(2)-C(12)	1.498(2)	C(6)-N(5)-H(5N)	114.7(11)

C(3)-C(4)	1.388(2)
C(4)-N(5)	1.3258(18)
C(4)-C(13)	1.500(2)
N(5)-C(6)	1.4238(18)
N(5)-H(5N)	0.861(13)
C(6)-C(7)	1.386(2)
C(6)-C(11)	1.3946(19)
C(7)-C(8)	1.390(2)
C(8)-C(9)	1.377(2)
C(9)-C(10)	1.394(2)
C(10)-O(1)	1.3538(17)
C(10)-C(11)	1.397(2)
O(1)-H(1O)	0.902(14)
C(1')-O(1')	1.2538(16)
C(1')-C(2')	1.449(2)
C(1')-C(6')	1.4529(19)
C(2')-C(3')	1.3822(19)
C(2')-N(2')	1.4496(17)
C(3')-C(4')	1.3825(19)
C(4')-C(5')	1.392(2)
C(4')-N(4')	1.4471(18)
C(5')-C(6')	1.3615(19)
C(6')-N(6')	1.4633(18)
N(2')-O(21')	1.2297(15)
N(2')-O(22')	1.2361(14)
N(4')-O(42')	1.2339(15)
N(4')-O(41')	1.2351(16)
N(6')-O(61')	1.2289(14)
N(6')-O(62')	1.2290(15)
O(1A)-C(1A)	1.2223(17)
C(1A)-C(3A)	1.492(2)
C(1A)-C(2A)	1.494(2)
C(2)-N(1)-C(11)	129.86(13)
C(2)-N(1)-H(1N)	115.8(10)
C(11)-N(1)-H(1N)	113.9(10)
N(1)-C(2)-C(3)	126.42(14)
N(1)-C(2)-C(12)	114.91(13)
C(3)-C(2)-C(12)	118.66(13)
C(2)-C(3)-C(4)	129.37(14)

C(7)-C(6)-C(11)	119.72(13)
C(7)-C(6)-N(5)	115.19(13)
C(11)-C(6)-N(5)	125.10(13)
C(6)-C(7)-C(8)	120.93(14)
C(9)-C(8)-C(7)	120.00(14)
C(8)-C(9)-C(10)	119.35(14)
O(1)-C(10)-C(9)	122.33(13)
O(1)-C(10)-C(11)	116.49(13)
C(9)-C(10)-C(11)	121.16(13)
C(10)-O(1)-H(1O)	110.6(11)
C(6)-C(11)-C(10)	118.83(13)
C(6)-C(11)-N(1)	126.26(13)
C(10)-C(11)-N(1)	114.87(13)
O(1')-C(1')-C(2')	126.16(12)
O(1')-C(1')-C(6')	122.68(13)
C(2')-C(1')-C(6')	111.12(12)
C(3')-C(2')-C(1')	124.24(12)
C(3')-C(2')-N(2')	115.56(12)
C(1')-C(2')-N(2')	120.18(12)
C(2')-C(3')-C(4')	119.15(13)
C(3')-C(4')-C(5')	121.15(13)
C(3')-C(4')-N(4')	119.60(12)
C(5')-C(4')-N(4')	119.22(12)
C(6')-C(5')-C(4')	118.60(12)
C(5')-C(6')-C(1')	125.48(13)
C(5')-C(6')-N(6')	116.73(12)
C(1')-C(6')-N(6')	117.79(12)
O(21')-N(2')-O(22')	122.26(11)
O(21')-N(2')-C(2')	120.14(11)
O(22')-N(2')-C(2')	117.60(11)
O(42')-N(4')-O(41')	123.15(12)
O(42')-N(4')-C(4')	118.10(12)
O(41')-N(4')-C(4')	118.74(11)
O(61')-N(6')-O(62')	124.04(12)
O(61')-N(6')-C(6')	118.11(12)
O(62')-N(6')-C(6')	117.83(11)
O(1A)-C(1A)-C(3A)	120.38(15)
O(1A)-C(1A)-C(2A)	121.79(14)
C(3A)-C(1A)-C(2A)	117.83(14)

Table 4: Torsion angles [°] for **38c**.

C(11)-N(1)-C(2)-C(3)	-10.3(2)
C(11)-N(1)-C(2)-C(12)	170.71(13)
N(1)-C(2)-C(3)-C(4)	-13.6(3)
C(12)-C(2)-C(3)-C(4)	165.30(15)
C(2)-C(3)-C(4)-N(5)	11.6(3)
C(2)-C(3)-C(4)-C(13)	-164.33(15)
C(3)-C(4)-N(5)-C(6)	13.0(2)
C(13)-C(4)-N(5)-C(6)	-170.95(13)
C(4)-N(5)-C(6)-C(7)	160.18(14)
C(4)-N(5)-C(6)-C(11)	-19.7(2)
C(11)-C(6)-C(7)-C(8)	-0.1(2)
N(5)-C(6)-C(7)-C(8)	-179.97(12)
C(6)-C(7)-C(8)-C(9)	-0.1(2)
C(7)-C(8)-C(9)-C(10)	0.8(2)
C(8)-C(9)-C(10)-O(1)	-179.64(12)
C(8)-C(9)-C(10)-C(11)	-1.4(2)

C(6')-C(1')-C(2')-C(3')	-4.80(19)
O(1')-C(1')-C(2')-N(2')	-4.0(2)
C(6')-C(1')-C(2')-N(2')	173.53(12)
C(1')-C(2')-C(3')-C(4')	2.1(2)
N(2')-C(2')-C(3')-C(4')	-176.30(12)
C(2')-C(3')-C(4')-C(5')	2.9(2)
C(2')-C(3')-C(4')-N(4')	-179.13(12)
C(3')-C(4')-C(5')-C(6')	-4.5(2)
N(4')-C(4')-C(5')-C(6')	177.52(12)
C(4')-C(5')-C(6')-C(1')	1.3(2)
C(4')-C(5')-C(6')-N(6')	-179.19(12)
O(1')-C(1')-C(6')-C(5')	-179.31(13)
C(2')-C(1')-C(6')-C(5')	3.1(2)
O(1')-C(1')-C(6')-N(6')	1.1(2)
C(2')-C(1')-C(6')-N(6')	-176.44(11)
C(3')-C(2')-N(2')-O(21')	-161.98(13)

C(7)-C(6)-C(11)-C(10)	-0.41(19)
N(5)-C(6)-C(11)-C(10)	179.41(12)
C(7)-C(6)-C(11)-N(1)	177.40(13)
N(5)-C(6)-C(11)-N(1)	-2.8(2)
O(1)-C(10)-C(11)-C(6)	179.51(12)
C(9)-C(10)-C(11)-C(6)	1.2(2)
O(1)-C(10)-C(11)-N(1)	1.47(17)
C(9)-C(10)-C(11)-N(1)	-176.87(12)
C(2)-N(1)-C(11)-C(6)	22.0(2)
C(2)-N(1)-C(11)-C(10)	-160.12(14)
O(1')-C(1')-C(2')-C(3')	177.72(13)

C(1')-C(2')-N(2')-O(21')	19.5(2)
C(3')-C(2')-N(2')-O(22')	17.77(18)
C(1')-C(2')-N(2')-O(22')	-160.70(13)
C(3')-C(4')-N(4')-O(42')	-175.30(13)
C(5')-C(4')-N(4')-O(42')	2.7(2)
C(3')-C(4')-N(4')-O(41')	3.94(19)
C(5')-C(4')-N(4')-O(41')	-178.04(13)
C(5')-C(6')-N(6')-O(61')	125.92(13)
C(1')-C(6')-N(6')-O(61')	-54.50(17)
C(5')-C(6')-N(6')-O(62')	-52.95(17)
C(1')-C(6')-N(6')-O(62')	126.63(13)

Table 5: Hydrogen bonds for **38c** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1')	0.872(12)	2.242(14)	2.9671(16)	140.5(13)
N(1)-H(1N)...O(61')	0.872(12)	2.439(14)	3.1548(16)	139.7(12)
N(1)-H(1N)...O(1)	0.872(12)	2.174(16)	2.6012(16)	109.7(13)
N(5)-H(5N)...O(1')#1	0.861(13)	2.050(13)	2.8773(15)	160.9(14)
N(5)-H(5N)...O(21')#1	0.861(13)	2.534(15)	3.1361(17)	127.7(13)
O(1)-H(1O)...O(1A)	0.902(14)	1.802(14)	2.6937(15)	169.7(17)

Symmetry transformations used to generate equivalent atoms:
#1 -x+2,-y+1,-z+1

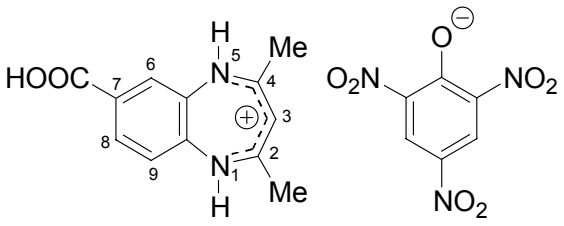


Table 6: Crystal data and structure refinement for **43** as picrate.

Empirical formula	$C_{19}\ H_{19}\ N_5\ O_{10}$ $(C_{12}\ H_{13}\ N_2\ O_2)+ (C_6\ H_2\ N_3\ O_7)-$ methanol
Formula weight	477.39
Temperature	123(2) K
Wavelength	0.71073 Å (MoKα)
Crystal system	Triclinic
Space group	P-1 (No.2)
Unit cell dimensions	a = 8.8117(2) Å, α = 79.339(1)° b =11.0726(2) Å, β = 73.059(1)° c = 11.2477(3) Å, γ = 86.946(1)°
Volume	1031.68(4) $Å^3$
Z	2
Calculated density	1.537 Mg/m^3
Absorption coefficient	0.127 mm^{-1}
F(000)	496
Crystal size	0.50 x 0.40 x 0.10 mm
Θ-Range for data collection	2.91 to 25.00°
Limiting indices	-10<=h<=10, -13<=k<=13, -13<=l<=13
Reflections collected	17842
Unique	3648 [R_{int} = 0.0368]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3648 / 4 / 322
Goodness-of-fit on F^2	1.074
Final R indices [I > 2σ(I)]	R1 = 0.0431, wR2 = 0.1165
R indices (all data)	R1 = 0.0519, wR2 = 0.1218
Largest diff. peak and hole	0.673 and -0.413 $eÅ^{-3}$

Table 7: Bond lengths [Å] and angles [°] for **43** as picrate.

N(1)-C(2)	1.334(2)
N(1)-C(11)	1.419(2)
N(1)-H(1N)	0.861(15)
C(2)-C(3)	1.384(3)
C(2)-C(13)	1.493(2)
C(3)-C(4)	1.394(3)
C(4)-N(5)	1.323(2)
C(4)-C(14)	1.503(2)
N(5)-C(6)	1.426(2)
N(5)-H(5N)	0.851(15)
C(6)-C(7)	1.384(2)
C(6)-C(11)	1.409(2)

N(5)-C(4)-C(14)	115.10(15)
C(3)-C(4)-C(14)	117.89(16)
C(4)-N(5)-C(6)	131.11(15)
C(4)-N(5)-H(5N)	115.7(14)
C(6)-N(5)-H(5N)	113.0(14)
C(7)-C(6)-C(11)	118.61(16)
C(7)-C(6)-N(5)	115.16(15)
C(11)-C(6)-N(5)	126.23(16)
C(6)-C(7)-C(8)	122.13(16)
C(9)-C(8)-C(7)	119.08(16)
C(9)-C(8)-C(12)	120.00(16)
C(7)-C(8)-C(12)	120.92(16)

C(7)-C(8)	1.395(3)
C(8)-C(9)	1.386(2)
C(8)-C(12)	1.488(2)
C(9)-C(10)	1.386(3)
C(10)-C(11)	1.385(3)
C(12)-O(2)	1.235(2)
C(12)-O(1)	1.301(2)
O(1)-H(1O)	0.878(16)
C(1')-O(1')	1.264(2)
C(1')-C(2')	1.443(3)
C(1')-C(6')	1.447(3)
C(2')-C(3')	1.368(3)
C(2')-N(2')	1.459(2)
C(3')-C(4')	1.387(3)
C(4')-C(5')	1.374(3)
C(4')-N(4')	1.448(2)
C(5')-C(6')	1.380(3)
C(6')-N(6')	1.453(2)
N(2')-O(22')	1.227(2)
N(2')-O(21')	1.233(2)
N(4')-O(41')	1.230(2)
N(4')-O(42')	1.232(2)
N(6')-O(62')	1.219(2)
N(6')-O(61')	1.221(2)
O(1E)-C(1E)	1.384(3)
O(1E)-H(1E)	0.836(17)
C(2)-N(1)-C(11)	131.11(15)
C(2)-N(1)-H(1N)	115.8(14)
C(11)-N(1)-H(1N)	113.0(14)
N(1)-C(2)-C(3)	127.28(16)
N(1)-C(2)-C(13)	114.70(16)
C(3)-C(2)-C(13)	118.00(16)
C(2)-C(3)-C(4)	130.23(17)

C(8)-C(9)-C(10)	119.04(17)
C(11)-C(10)-C(9)	122.38(16)
C(10)-C(11)-C(6)	118.70(16)
C(10)-C(11)-N(1)	115.28(15)
C(6)-C(11)-N(1)	126.02(16)
O(2)-C(12)-O(1)	124.43(16)
O(2)-C(12)-C(8)	120.29(15)
O(1)-C(12)-C(8)	115.27(15)
C(12)-O(1)-H(1O)	111.1(16)
O(1')-C(1')-C(2')	122.89(17)
O(1')-C(1')-C(6')	125.84(17)
C(2')-C(1')-C(6')	111.27(16)
C(3')-C(2')-C(1')	125.72(16)
C(3')-C(2')-N(2')	115.64(16)
C(1')-C(2')-N(2')	118.63(15)
C(2')-C(3')-C(4')	118.18(17)
C(5')-C(4')-C(3')	121.22(17)
C(5')-C(4')-N(4')	120.08(16)
C(3')-C(4')-N(4')	118.68(16)
C(4')-C(5')-C(6')	119.72(17)
C(5')-C(6')-C(1')	123.75(17)
C(5')-C(6')-N(6')	115.42(16)
C(1')-C(6')-N(6')	120.83(16)
O(22')-N(2')-O(21')	123.99(17)
O(22')-N(2')-C(2')	118.45(17)
O(21')-N(2')-C(2')	117.53(16)
O(41')-N(4')-O(42')	123.61(16)
O(41')-N(4')-C(4')	118.57(16)
O(42')-N(4')-C(4')	117.80(16)
O(62')-N(6')-O(61')	121.99(17)
O(62')-N(6')-C(6')	118.79(16)
O(61')-N(6')-C(6')	119.18(16)
C(1E)-O(1E)-H(1E)	113(2)

Table 8: Torsion angles [°] for **43** as picrate.

C(11)-N(1)-C(2)-C(3)	4.6(3)
C(11)-N(1)-C(2)-C(13)	-177.08(18)
N(1)-C(2)-C(3)-C(4)	4.3(3)
C(13)-C(2)-C(3)-C(4)	-173.96(19)
C(2)-C(3)-C(4)-N(5)	-4.1(3)
C(2)-C(3)-C(4)-C(14)	174.98(19)
C(3)-C(4)-N(5)-C(6)	-6.4(3)
C(14)-C(4)-N(5)-C(6)	174.49(17)
C(4)-N(5)-C(6)-C(7)	-169.23(18)
C(4)-N(5)-C(6)-C(11)	11.3(3)
C(11)-C(6)-C(7)-C(8)	0.6(3)
N(5)-C(6)-C(7)-C(8)	-178.91(16)
C(6)-C(7)-C(8)-C(9)	1.8(3)
C(6)-C(7)-C(8)-C(12)	-177.33(16)
C(7)-C(8)-C(9)-C(10)	-2.4(3)
C(12)-C(8)-C(9)-C(10)	176.71(16)
C(8)-C(9)-C(10)-C(11)	0.7(3)
C(9)-C(10)-C(11)-C(6)	1.7(3)
C(9)-C(10)-C(11)-N(1)	-178.07(16)
C(7)-C(6)-C(11)-C(10)	-2.3(2)
N(5)-C(6)-C(11)-C(10)	177.16(16)
C(7)-C(6)-C(11)-N(1)	177.43(16)

O(1')-C(1')-C(2')-C(3')	-178.75(18)
C(6')-C(1')-C(2')-C(3')	1.6(3)
O(1')-C(1')-C(2')-N(2')	2.7(3)
C(6')-C(1')-C(2')-N(2')	-176.98(15)
C(1')-C(2')-C(3')-C(4')	-3.7(3)
N(2')-C(2')-C(3')-C(4')	174.97(16)
C(2')-C(3')-C(4')-C(5')	2.0(3)
C(2')-C(3')-C(4')-N(4')	-179.45(16)
C(3')-C(4')-C(5')-C(6')	1.4(3)
N(4')-C(4')-C(5')-C(6')	-177.08(17)
C(4')-C(5')-C(6')-C(1')	-3.6(3)
C(4')-C(5')-C(6')-N(6')	176.92(16)
O(1')-C(1')-C(6')-C(5')	-177.54(18)
C(2')-C(1')-C(6')-C(5')	2.1(3)
O(1')-C(1')-C(6')-N(6')	1.9(3)
C(2')-C(1')-C(6')-N(6')	-178.46(16)
C(3')-C(2')-N(2')-O(22')	-130.71(18)
C(1')-C(2')-N(2')-O(22')	48.0(2)
C(3')-C(2')-N(2')-O(21')	47.2(2)
C(1')-C(2')-N(2')-O(21')	-134.05(17)
C(5')-C(4')-N(4')-O(41')	-8.1(3)
C(3')-C(4')-N(4')-O(41')	173.34(17)

N(5)-C(6)-C(11)-N(1)	-3.1(3)
C(2)-N(1)-C(11)-C(10)	173.30(18)
C(2)-N(1)-C(11)-C(6)	-6.5(3)
C(9)-C(8)-C(12)-O(2)	-3.4(3)
C(7)-C(8)-C(12)-O(2)	175.74(17)
C(9)-C(8)-C(12)-O(1)	177.44(16)

C(5')-C(4')-N(4')-O(42')	170.17(19)
C(3')-C(4')-N(4')-O(42')	-8.4(3)
C(5')-C(6')-N(6')-O(62')	19.9(3)
C(1')-C(6')-N(6')-O(62')	-159.6(2)
C(5')-C(6')-N(6')-O(61')	-157.92(19)
C(1')-C(6')-N(6')-O(61')	22.6(3)

Table 9: Hydrogen bonds for **43** as picrate [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1')#1	0.861(15)	2.202(16)	3.0626(19)	176.9(19)
N(5)-H(5N)...O(1E)	0.851(15)	1.950(16)	2.793(2)	170(2)
O(1)-H(1O)...O(2)#2	0.878(16)	1.758(17)	2.6354(18)	178(3)
O(1E)-H(1E)...O(1')	0.836(17)	1.894(18)	2.728(2)	176(3)

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,-y+1,-z+2 #2 -x+2,-y,-z+2

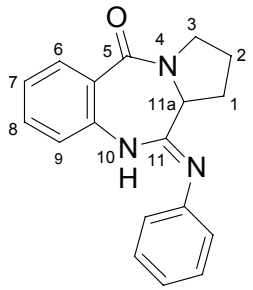


Table 10: Crystal data and structure refinement for Schmidt **65**.

Empirical formula	$C_{18}\ H_{17}\ N_3\ O$
Formula weight	291.35
Temperature	123(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, Pna2(1) (No.33)
Unit cell dimensions	a = 14.17263(2) A α = 90 °
	b = 10.2387(1) A β = 90 °
	c = 9.7927(1) A γ = 90 °
Volume	1421.01(3) A^3
Z, Calculated density	4, 1.362 Mg/m^3
Absorption coefficient	0.087 mm^{-1}
F(000)	616
Crystal size	0.50 × 0.50 × 0.50 mm
Diffractometer	Nonius KappaCCD
Θ-Range for data collection	3.22 to 27.48 °
Limiting indices	-18<=h<=18, -13<=k<=13, -12<=l<=12
Reflections collected / unique	27829 / 3253 [R(int) = 0.0300]
Completeness to theta = 25.00	99.5 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3253 / 2 / 202
Goodness-of-fit on F^2	1.038
Final R indices [I^2sigma(I)]	R1 = 0.0259, wR2 = 0.0673
R indices (all data)	R1 = 0.0263, wR2 = 0.0675
Largest diff. peak and hole	0.176 and -0.172 $e.A^{-3}$

Table 11: Bond lengths [Å] and angles [°] for compound **65**.

N(1)-C(2)	1.3807(13)	N(1)-C(2)-C(2A)	115.75(8)
N(1)-C(10A)	1.4079(12)	C(2)-N(2)-C(21)	121.84(8)
N(1)-H(1)	0.880(12)	C(26)-C(21)-C(22)	118.86(10)
C(2)-N(2)	1.2803(13)	C(26)-C(21)-N(2)	122.22(9)
C(2)-C(2A)	1.5161(13)	C(22)-C(21)-N(2)	118.54(9)
N(2)-C(21)	1.4181(13)	C(23)-C(22)-C(21)	120.17(11)
C(21)-C(26)	1.3951(15)	C(24)-C(23)-C(22)	120.77(11)
C(21)-C(22)	1.4003(14)	C(25)-C(24)-C(23)	119.26(10)
C(22)-C(23)	1.3900(15)	C(24)-C(25)-C(26)	120.37(11)
C(23)-C(24)	1.3889(19)	C(25)-C(26)-C(21)	120.50(10)
C(24)-C(25)	1.3883(18)	N(5A)-C(2A)-C(2)	110.32(7)
C(25)-C(26)	1.3947(16)	N(5A)-C(2A)-C(3)	103.39(7)
C(2A)-N(5A)	1.4749(11)	C(2)-C(2A)-C(3)	113.92(8)

C(2A)-C(3)	1.5339(13)
C(3)-C(4)	1.5310(15)
C(4)-C(5)	1.5229(14)
C(5)-N(5A)	1.4697(12)
N(5A)-C(6)	1.3426(12)
C(6)-O(6)	1.2380(12)
C(6)-C(6A)	1.4978(13)
C(6A)-C(7)	1.4036(14)
C(6A)-C(10A)	1.4066(13)
C(7)-C(8)	1.3822(14)
C(8)-C(9)	1.3933(14)
C(9)-C(10)	1.3841(15)
C(10)-C(10A)	1.4072(14)
C(2)-N(1)-C(10A)	127.47(8)
C(2)-N(1)-H(1)	112.8(9)
C(10A)-N(1)-H(1)	114.6(9)
N(2)-C(2)-N(1)	124.50(9)
N(2)-C(2)-C(2A)	119.69(8)

C(4)-C(3)-C(2A)	103.89(8)
C(5)-C(4)-C(3)	103.01(9)
N(5A)-C(5)-C(4)	102.32(7)
C(6)-N(5A)-C(5)	120.98(8)
C(6)-N(5A)-C(2A)	124.99(8)
C(5)-N(5A)-C(2A)	112.21(7)
O(6)-C(6)-N(5A)	121.33(9)
O(6)-C(6)-C(6A)	120.48(9)
N(5A)-C(6)-C(6A)	118.19(8)
C(7)-C(6A)-C(10A)	118.64(9)
C(7)-C(6A)-C(6)	114.76(8)
C(10A)-C(6A)-C(6)	126.54(9)
C(8)-C(7)-C(6A)	122.10(9)
C(7)-C(8)-C(9)	118.98(10)
C(10)-C(9)-C(8)	120.18(10)
C(9)-C(10)-C(10A)	121.18(9)
C(6A)-C(10A)-C(10)	118.86(9)
C(6A)-C(10A)-N(1)	125.63(9)

Table 12: Torsion angles [°] for compound **65.**

C(10A)-N(1)-C(2)-N(2)	176.41(10)
C(10A)-N(1)-C(2)-C(2A)	0.71(14)
N(1)-C(2)-N(2)-C(21)	5.57(15)
C(2A)-C(2)-N(2)-C(21)	-177.41(9)
C(2)-N(2)-C(21)-C(26)	65.70(14)
C(2)-N(2)-C(21)-C(22)	-121.40(11)
C(26)-C(21)-C(22)-C(23)	0.93(16)
N(2)-C(21)-C(22)-C(23)	-172.22(9)
C(21)-C(22)-C(23)-C(24)	1.28(17)
C(22)-C(23)-C(24)-C(25)	-2.72(17)
C(23)-C(24)-C(25)-C(26)	1.96(16)
C(24)-C(25)-C(26)-C(21)	0.24(16)
C(22)-C(21)-C(26)-C(25)	-1.68(15)
N(2)-C(21)-C(26)-C(25)	171.20(9)
N(2)-C(2)-C(2A)-N(5A)	118.30(10)
N(1)-C(2)-C(2A)-N(5A)	-64.43(11)
N(2)-C(2)-C(2A)-C(3)	2.56(13)
N(1)-C(2)-C(2A)-C(3)	179.83(8)
N(5A)-C(2A)-C(3)-C(4)	-25.05(10)
C(2)-C(2A)-C(3)-C(4)	94.69(10)
C(2A)-C(3)-C(4)-C(5)	38.24(10)
C(3)-C(4)-C(5)-N(5A)	-35.94(10)
C(4)-C(5)-N(5A)-C(6)	-173.38(9)
C(4)-C(5)-N(5A)-C(2A)	21.23(11)

C(2)-C(2A)-N(5A)-C(6)	75.52(11)
C(3)-C(2A)-N(5A)-C(6)	-162.30(9)
C(2)-C(2A)-N(5A)-C(5)	-119.79(8)
C(3)-C(2A)-N(5A)-C(5)	2.38(10)
C(5)-N(5A)-C(6)-O(6)	3.18(14)
C(2A)-N(5A)-C(6)-O(6)	166.61(9)
C(5)-N(5A)-C(6)-C(6A)	-176.77(8)
C(2A)-N(5A)-C(6)-C(6A)	-13.34(14)
O(6)-C(6)-C(6A)-C(7)	-27.33(13)
N(5A)-C(6)-C(6A)-C(7)	152.61(9)
O(6)-C(6)-C(6A)-C(10A)	149.58(10)
N(5A)-C(6)-C(6A)-C(10A)	-30.47(14)
C(10A)-C(6A)-C(7)-C(8)	-1.03(15)
C(6)-C(6A)-C(7)-C(8)	176.15(9)
C(6A)-C(7)-C(8)-C(9)	-1.27(16)
C(7)-C(8)-C(9)-C(10)	1.97(16)
C(8)-C(9)-C(10)-C(10A)	-0.39(16)
C(7)-C(6A)-C(10A)-C(10)	2.58(14)
C(6)-C(6A)-C(10A)-C(10)	-174.23(9)
C(7)-C(6A)-C(10A)-N(1)	177.88(9)
C(6)-C(6A)-C(10A)-N(1)	1.08(16)
C(9)-C(10)-C(10A)-C(6A)	-1.92(15)
C(9)-C(10)-C(10A)-N(1)	-177.69(9)
C(2)-N(1)-C(10A)-C(6A)	36.84(15)

Table 13: Hydrogen bonds for compound **65** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(6)#1	0.880(12)	2.5272(13)	2.9882(11)	138.5(11)
C(10)-H(10)...O(6)#1	0.95	2.50	3.2384(12)	134.7

Symmetry transformations used to generate equivalent atoms:
#1 x+1/2,-y+1/2,z

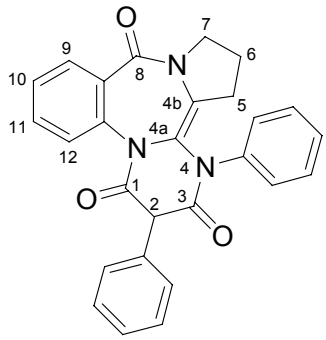


Table 14: Crystal data and structure refinement for compound **75**.

Empirical formula	$C_{27}\ H_{21}\ N_3\ O_3$
Formula weight	435.47
Temperature	123(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n (No.14)
Unit cell dimensions	a = 11.4423(1) A α = 90 °
	b = 12.8594(2) A β = 105.130(1) °
	c = 15.0055(2) A γ = 90 °
Volume	2131.39(5) A^3
Z, Calculated density	4, 1.357 Mg/m^3
Absorption coefficient	0.090 mm^{-1}
F(000)	912
Crystal size	0.60 × 0.40 × 0.30 mm
Diffractometer	Nonius KappaCCD
Θ-Range for data collection	3.23 to 25.02 °
Limiting indices	-13<=h<=13, -15<=k<=15, -17<=l<=17
Reflections collected / unique	37476 / 3763 [R(int) = 0.0358]
Completeness to theta = 25.02	99.8 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3763 / 0 / 298
Goodness-of-fit on F^2	1.072
Final R indices [I^2sigma(I)]	R1 = 0.0320, wR2 = 0.0832
R indices (all data)	R1 = 0.0387, wR2 = 0.0867
Largest diff. peak and hole	0.159 and -0.233 $e.A^{-3}$

Table 15: Bond lengths [Å] and angles [°] for compound **75**.

N(1)-C(2)	1.3736(15)
N(1)-C(6)	1.4275(14)
N(1)-C(18)	1.4318(14)
C(2)-O(2)	1.2146(14)
C(2)-C(3)	1.5308(16)
C(3)-C(4)	1.5299(16)
C(3)-C(31)	1.5327(16)
C(31)-C(36)	1.3886(17)
C(31)-C(32)	1.3903(16)
C(32)-C(33)	1.3881(18)
C(33)-C(34)	1.3819(18)
C(34)-C(35)	1.3809(18)
C(35)-C(36)	1.3849(18)

C(36)-C(31)-C(32)	118.91(11)
C(36)-C(31)-C(3)	121.29(10)
C(32)-C(31)-C(3)	119.77(10)
C(33)-C(32)-C(31)	120.27(11)
C(34)-C(33)-C(32)	120.30(11)
C(35)-C(34)-C(33)	119.73(12)
C(34)-C(35)-C(36)	120.13(12)
C(35)-C(36)-C(31)	120.66(11)
O(4)-C(4)-N(5)	124.31(11)
O(4)-C(4)-C(3)	123.58(10)
N(5)-C(4)-C(3)	112.10(9)
C(4)-N(5)-C(6)	116.32(9)
C(4)-N(5)-C(51)	122.68(9)

C(4)-O(4)	1.2154(13)
C(4)-N(5)	1.3767(15)
N(5)-C(6)	1.4240(14)
N(5)-C(51)	1.4390(15)
C(51)-C(52)	1.3820(16)
C(51)-C(56)	1.3860(16)
C(52)-C(53)	1.3896(18)
C(53)-C(54)	1.3800(18)
C(54)-C(55)	1.3813(18)
C(55)-C(56)	1.3840(18)
C(6)-C(7)	1.3271(16)
C(7)-N(11)	1.4052(14)
C(7)-C(8)	1.4979(15)
C(8)-C(9)	1.5335(18)
C(9)-C(10)	1.5218(16)
C(10)-N(11)	1.4808(15)
N(11)-C(12)	1.3691(14)
C(12)-O(12)	1.2306(14)
C(12)-C(13)	1.4994(17)
C(13)-C(18)	1.4001(17)
C(13)-C(14)	1.4010(16)
C(14)-C(15)	1.3803(18)
C(15)-C(16)	1.3852(19)
C(16)-C(17)	1.3829(17)
C(17)-C(18)	1.3916(17)
C(2)-N(1)-C(6)	116.00(9)
C(2)-N(1)-C(18)	124.51(9)
C(6)-N(1)-C(18)	118.45(9)
O(2)-C(2)-N(1)	124.70(10)
O(2)-C(2)-C(3)	122.84(11)
N(1)-C(2)-C(3)	112.46(10)
C(4)-C(3)-C(2)	110.63(9)
C(4)-C(3)-C(31)	110.89(9)
C(2)-C(3)-C(31)	111.95(9)

C(6)-N(5)-C(51)	119.92(9)
C(52)-C(51)-C(56)	120.50(11)
C(52)-C(51)-N(5)	120.70(10)
C(56)-C(51)-N(5)	118.79(10)
C(51)-C(52)-C(53)	119.14(11)
C(54)-C(53)-C(52)	120.66(11)
C(53)-C(54)-C(55)	119.74(12)
C(54)-C(55)-C(56)	120.21(12)
C(55)-C(56)-C(51)	119.73(11)
C(7)-C(6)-N(5)	122.73(10)
C(7)-C(6)-N(1)	122.29(10)
N(5)-C(6)-N(1)	114.76(9)
C(6)-C(7)-N(11)	124.13(10)
C(6)-C(7)-C(8)	127.14(10)
N(11)-C(7)-C(8)	108.42(9)
C(7)-C(8)-C(9)	100.99(9)
C(10)-C(9)-C(8)	103.55(9)
N(11)-C(10)-C(9)	103.57(9)
C(12)-N(11)-C(7)	128.70(10)
C(12)-N(11)-C(10)	117.82(9)
C(7)-N(11)-C(10)	109.89(9)
O(12)-C(12)-N(11)	118.93(11)
O(12)-C(12)-C(13)	119.70(10)
N(11)-C(12)-C(13)	121.37(10)
C(18)-C(13)-C(14)	117.83(11)
C(18)-C(13)-C(12)	126.66(10)
C(14)-C(13)-C(12)	115.43(10)
C(15)-C(14)-C(13)	121.41(12)
C(14)-C(15)-C(16)	119.74(11)
C(17)-C(16)-C(15)	120.33(12)
C(16)-C(17)-C(18)	119.82(12)
C(17)-C(18)-C(13)	120.87(11)
C(17)-C(18)-N(1)	119.05(10)
C(13)-C(18)-N(1)	120.05(10)

Table 16: Torsion angles [°] for compound **75**.

C(6)-N(1)-C(2)-O(2)	178.11(11)
C(18)-N(1)-C(2)-O(2)	10.02(18)
C(6)-N(1)-C(2)-C(3)	-1.41(14)
C(18)-N(1)-C(2)-C(3)	-169.49(10)
O(2)-C(2)-C(3)-C(4)	-131.82(12)
N(1)-C(2)-C(3)-C(4)	47.71(13)
O(2)-C(2)-C(3)-C(31)	103.96(13)
N(1)-C(2)-C(3)-C(31)	-76.52(12)
C(4)-C(3)-C(31)-C(36)	-140.88(11)
C(2)-C(3)-C(31)-C(36)	-16.80(16)
C(4)-C(3)-C(31)-C(32)	41.22(14)
C(2)-C(3)-C(31)-C(32)	165.30(10)
C(36)-C(31)-C(32)-C(33)	-0.03(18)
C(3)-C(31)-C(32)-C(33)	177.92(11)
C(31)-C(32)-C(33)-C(34)	0.9(2)
C(32)-C(33)-C(34)-C(35)	-0.9(2)
C(33)-C(34)-C(35)-C(36)	0.1(2)
C(34)-C(35)-C(36)-C(31)	0.8(2)
C(32)-C(31)-C(36)-C(35)	-0.83(19)
C(3)-C(31)-C(36)-C(35)	-178.75(11)
C(2)-C(3)-C(4)-O(4)	131.21(11)

C(51)-N(5)-C(6)-N(1)	-121.50(11)
C(2)-N(1)-C(6)-C(7)	127.60(12)
C(18)-N(1)-C(6)-C(7)	-63.57(15)
C(2)-N(1)-C(6)-N(5)	-47.22(13)
C(18)-N(1)-C(6)-N(5)	121.62(11)
N(5)-C(6)-C(7)-N(11)	179.17(10)
N(1)-C(6)-C(7)-N(11)	4.77(18)
N(5)-C(6)-C(7)-C(8)	6.37(19)
N(1)-C(6)-C(7)-C(8)	-168.03(11)
C(6)-C(7)-C(8)-C(9)	143.57(12)
N(11)-C(7)-C(8)-C(9)	-30.16(12)
C(7)-C(8)-C(9)-C(10)	36.40(12)
C(8)-C(9)-C(10)-N(11)	-30.14(12)
C(6)-C(7)-N(11)-C(12)	40.17(18)
C(8)-C(7)-N(11)-C(12)	-145.88(11)
C(6)-C(7)-N(11)-C(10)	-162.06(11)
C(8)-C(7)-N(11)-C(10)	11.90(12)
C(9)-C(10)-N(11)-C(12)	172.40(10)
C(9)-C(10)-N(11)-C(7)	11.90(13)
C(7)-N(11)-C(12)-O(12)	164.80(11)
C(10)-N(11)-C(12)-O(12)	8.51(16)

C(31)-C(3)-C(4)-O(4)	-103.96(13)
C(2)-C(3)-C(4)-N(5)	-47.95(13)
C(31)-C(3)-C(4)-N(5)	76.89(11)
O(4)-C(4)-N(5)-C(6)	-177.16(10)
C(3)-C(4)-N(5)-C(6)	1.99(13)
O(4)-C(4)-N(5)-C(51)	-9.07(17)
C(3)-C(4)-N(5)-C(51)	170.07(10)
C(4)-N(5)-C(51)-C(52)	58.45(15)
C(6)-N(5)-C(51)-C(52)	-133.88(11)
C(4)-N(5)-C(51)-C(56)	-122.15(12)
C(6)-N(5)-C(51)-C(56)	45.52(15)
C(56)-C(51)-C(52)-C(53)	-1.20(18)
N(5)-C(51)-C(52)-C(53)	178.20(11)
C(51)-C(52)-C(53)-C(54)	0.16(19)
C(52)-C(53)-C(54)-C(55)	0.79(19)
C(53)-C(54)-C(55)-C(56)	-0.7(2)
C(54)-C(55)-C(56)-C(51)	-0.3(2)
C(52)-C(51)-C(56)-C(55)	1.28(18)
N(5)-C(51)-C(56)-C(55)	-178.13(11)
C(4)-N(5)-C(6)-C(7)	-127.86(12)
C(51)-N(5)-C(6)-C(7)	63.70(15)

C(7)-N(11)-C(12)-C(13)	-14.28(18)
C(10)-N(11)-C(12)-C(13)	-170.57(10)
O(12)-C(12)-C(13)-C(18)	153.82(12)
N(11)-C(12)-C(13)-C(18)	-27.11(18)
O(12)-C(12)-C(13)-C(14)	-22.63(16)
N(11)-C(12)-C(13)-C(14)	156.44(11)
C(18)-C(13)-C(14)-C(15)	0.33(18)
C(12)-C(13)-C(14)-C(15)	177.10(11)
C(13)-C(14)-C(15)-C(16)	-0.71(19)
C(14)-C(15)-C(16)-C(17)	0.7(2)
C(15)-C(16)-C(17)-C(18)	-0.3(2)
C(16)-C(17)-C(18)-C(13)	-0.04(19)
C(16)-C(17)-C(18)-N(1)	177.93(11)
C(14)-C(13)-C(18)-C(17)	0.05(17)
C(12)-C(13)-C(18)-C(17)	-176.32(11)
C(14)-C(13)-C(18)-N(1)	-177.90(10)
C(12)-C(13)-C(18)-N(1)	5.73(18)
C(2)-N(1)-C(18)-C(17)	43.10(16)
C(6)-N(1)-C(18)-C(17)	-124.71(12)
C(2)-N(1)-C(18)-C(13)	-138.91(12)
C(6)-N(1)-C(18)-C(13)	53.27(15)

Table 17: Hydrogen bonds for compound **75** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(8)-H(8B)...O(2)#1	0.99	2.52	3.1458(14)	121.2
C(54)-H(54)...O(12)#1	0.95	2.50	3.2056(15)	131.2

Symmetry transformations used to generate equivalent atoms:
#1 -x+1/2,y-1/2,-z+1/2

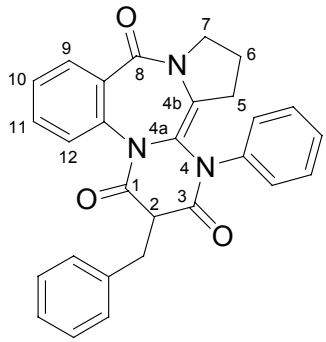


Table 18: Crystal data and structure refinement for compound **76**.

Empirical formula	C_{30} H_{28} N_3 $O_{3.5}$ C_{28} H_{23} N_3 O_3 – 0.5 2-butanol
Formula weight	486.55
Temperature	123(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-2 (No.2)
Unit cell dimensions	a = 10.9276(1) A α = 106.467(1) ° b = 11.6818(1) A β = 115.771(1) ° c = 11.6878(1) A γ = 99.841(1) °
Volume	1211.439(18) A^3
Z, Calculated density	2, 1.334 Mg/m^3
Absorption coefficient	0.088 mm^{-1}
F(000)	514
Crystal size	0.50 × 0.30 × 0.20 mm
Diffractometer	Nonius KappaCCD
Θ-Range for data collection	2.95 to 27.47 °
Limiting indices	-14<=h<=14, -15<=k<=15, -15<=l<=15
Reflections collected / unique	23952 / 5427 [R(int) = 0.0292]
Completeness to theta = 25.02	97.8 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5427 / 16 / 330
Goodness-of-fit on F^2	1.074
Final R indices [I^2sigma(I)]	R1 = 0.0387, wR2 = 0.0982
R indices (all data)	R1 = 0.0431, wR2 = 0.1008
Largest diff. peak and hole	0.387 and -0.360 $e.A^{-3}$

Table 19: Bond lengths [Å] and angles [°] for compound **76**.

N(1)-C(2)	1.3763(14)
N(1)-C(6)	1.4224(13)
N(1)-C(18)	1.4316(13)
C(2)-O(2)	1.2134(13)
C(2)-C(3)	1.5322(14)
C(3)-C(31)	1.5240(15)
C(3)-C(4)	1.5341(15)
C(31)-C(32)	1.5155(16)
C(32)-C(33)	1.3858(18)
C(32)-C(37)	1.3935(18)

C(32)-C(31)-C(3)	114.67(9)
C(33)-C(32)-C(37)	118.49(12)
C(33)-C(32)-C(31)	120.22(11)
C(37)-C(32)-C(31)	121.25(11)
C(34)-C(33)-C(32)	121.05(14)
C(35)-C(34)-C(33)	120.40(14)
C(34)-C(35)-C(36)	119.74(13)
C(35)-C(36)-C(37)	119.89(15)
C(32)-C(37)-C(36)	120.42(13)
O(4)-C(4)-N(5)	124.32(10)

C(33)-C(34)	1.380(2)
C(34)-C(35)	1.375(3)
C(35)-C(36)	1.386(3)
C(36)-C(37)	1.394(2)
C(4)-O(4)	1.2151(13)
C(4)-N(5)	1.3852(13)
N(5)-C(6)	1.4236(13)
N(5)-C(51)	1.4318(14)
C(51)-C(52)	1.3915(15)
C(51)-C(56)	1.3932(15)
C(52)-C(53)	1.3905(17)
C(53)-C(54)	1.3857(18)
C(54)-C(55)	1.3866(17)
C(55)-C(56)	1.3864(16)
C(6)-C(7)	1.3293(15)
C(7)-N(11)	1.4105(14)
C(7)-C(8)	1.5015(15)
C(8)-C(9)	1.5367(17)
C(9)-C(10)	1.5224(18)
C(10)-N(11)	1.4819(14)
N(11)-C(12)	1.3680(15)
C(12)-O(12)	1.2316(14)
C(12)-C(13)	1.4942(16)
C(13)-C(18)	1.3972(15)
C(13)-C(14)	1.4035(16)
C(14)-C(15)	1.3799(18)
C(15)-C(16)	1.3894(18)
C(16)-C(17)	1.3870(16)
C(17)-C(18)	1.3927(15)
C(1B)-C(2B)	1.501(5)
C(2B)-O(2B)	1.439(4)
C(2B)-C(3B)	1.512(4)
O(2B)-H(2BO)	0.849(18)
C(3B)-C(4B)	1.529(5)
C(2)-N(1)-C(6)	116.95(9)
C(2)-N(1)-C(18)	122.89(9)
C(6)-N(1)-C(18)	119.16(9)
O(2)-C(2)-N(1)	123.71(10)
O(2)-C(2)-C(3)	125.38(10)
N(1)-C(2)-C(3)	110.87(9)
C(31)-C(3)-C(2)	112.05(9)
C(31)-C(3)-C(4)	113.80(9)
C(2)-C(3)-C(4)	107.89(8)

O(4)-C(4)-C(3)	124.23(10)
N(5)-C(4)-C(3)	111.44(9)
C(4)-N(5)-C(6)	115.51(9)
C(4)-N(5)-C(51)	123.74(9)
C(6)-N(5)-C(51)	119.55(8)
C(52)-C(51)-C(56)	120.13(10)
C(52)-C(51)-N(5)	120.92(10)
C(56)-C(51)-N(5)	118.95(9)
C(53)-C(52)-C(51)	119.07(11)
C(54)-C(53)-C(52)	121.20(11)
C(53)-C(54)-C(55)	119.20(11)
C(56)-C(55)-C(54)	120.51(11)
C(55)-C(56)-C(51)	119.88(10)
C(7)-C(6)-N(1)	121.85(10)
C(7)-C(6)-N(5)	123.30(10)
N(1)-C(6)-N(5)	114.82(9)
C(6)-C(7)-N(11)	124.74(10)
C(6)-C(7)-C(8)	127.12(10)
N(11)-C(7)-C(8)	107.94(9)
C(7)-C(8)-C(9)	101.21(9)
C(10)-C(9)-C(8)	104.42(10)
N(11)-C(10)-C(9)	103.90(9)
C(12)-N(11)-C(7)	131.28(9)
C(12)-N(11)-C(10)	117.80(9)
C(7)-N(11)-C(10)	110.29(9)
O(12)-C(12)-N(11)	118.71(10)
O(12)-C(12)-C(13)	120.31(10)
N(11)-C(12)-C(13)	120.84(10)
C(18)-C(13)-C(14)	118.31(10)
C(18)-C(13)-C(12)	125.44(10)
C(14)-C(13)-C(12)	116.24(10)
C(15)-C(14)-C(13)	120.77(11)
C(14)-C(15)-C(16)	120.04(11)
C(17)-C(16)-C(15)	120.45(11)
C(16)-C(17)-C(18)	119.28(11)
C(17)-C(18)-C(13)	121.12(10)
C(17)-C(18)-N(1)	119.24(9)
C(13)-C(18)-N(1)	119.64(9)
O(2B)-C(2B)-C(1B)	111.2(3)
O(2B)-C(2B)-C(3B)	105.3(2)
C(1B)-C(2B)-C(3B)	112.4(2)
C(2B)-O(2B)-H(2BO)	103(2)
C(2B)-C(3B)-C(4B)	113.2(2)

Table 20: Torsion angles [°] for compound **76**.

C(6)-N(1)-C(2)-O(2)	-179.17(10)
C(18)-N(1)-C(2)-O(2)	-10.68(16)
C(6)-N(1)-C(2)-C(3)	3.03(12)
C(18)-N(1)-C(2)-C(3)	171.52(9)
O(2)-C(2)-C(3)-C(31)	3.96(15)
N(1)-C(2)-C(3)-C(31)	-178.28(9)
O(2)-C(2)-C(3)-C(4)	129.99(11)
N(1)-C(2)-C(3)-C(4)	-52.26(11)
C(2)-C(3)-C(31)-C(32)	-162.90(9)
C(4)-C(3)-C(31)-C(32)	74.36(12)
C(3)-C(31)-C(32)-C(33)	-115.08(12)
C(3)-C(31)-C(32)-C(37)	67.25(15)
C(37)-C(32)-C(33)-C(34)	0.8(2)

C(4)-N(5)-C(6)-C(7)	135.43(11)
C(51)-N(5)-C(6)-C(7)	-56.58(14)
C(4)-N(5)-C(6)-N(1)	-42.62(12)
C(51)-N(5)-C(6)-N(1)	125.38(10)
N(1)-C(6)-C(7)-N(11)	-0.74(17)
N(5)-C(6)-C(7)-N(11)	-178.65(9)
N(1)-C(6)-C(7)-C(8)	173.45(10)
N(5)-C(6)-C(7)-C(8)	-4.46(18)
C(6)-C(7)-C(8)-C(9)	-144.00(12)
N(11)-C(7)-C(8)-C(9)	30.98(11)
C(7)-C(8)-C(9)-C(10)	-34.42(12)
C(8)-C(9)-C(10)-N(11)	25.97(13)
C(6)-C(7)-N(11)-C(12)	-30.00(19)

C(31)-C(32)-C(33)-C(34)	-176.98(12)
C(32)-C(33)-C(34)-C(35)	-0.6(2)
C(33)-C(34)-C(35)-C(36)	-0.1(2)
C(34)-C(35)-C(36)-C(37)	0.7(2)
C(33)-C(32)-C(37)-C(36)	-0.12(19)
C(31)-C(32)-C(37)-C(36)	177.59(12)
C(35)-C(36)-C(37)-C(32)	-0.6(2)
C(31)-C(3)-C(4)-O(4)	1.84(15)
C(2)-C(3)-C(4)-O(4)	-123.15(11)
C(31)-C(3)-C(4)-N(5)	-179.01(9)
C(2)-C(3)-C(4)-N(5)	56.00(11)
O(4)-C(4)-N(5)-C(6)	169.74(10)
C(3)-C(4)-N(5)-C(6)	-9.41(12)
O(4)-C(4)-N(5)-C(51)	2.31(16)
C(3)-C(4)-N(5)-C(51)	-176.84(9)
C(4)-N(5)-C(51)-C(52)	-42.59(15)
C(6)-N(5)-C(51)-C(52)	150.45(10)
C(4)-N(5)-C(51)-C(56)	138.01(10)
C(6)-N(5)-C(51)-C(56)	-28.94(14)
C(56)-C(51)-C(52)-C(53)	-0.92(17)
N(5)-C(51)-C(52)-C(53)	179.69(10)
C(51)-C(52)-C(53)-C(54)	-0.02(18)
C(52)-C(53)-C(54)-C(55)	0.66(19)
C(53)-C(54)-C(55)-C(56)	-0.36(18)
C(54)-C(55)-C(56)-C(51)	-0.57(17)
C(52)-C(51)-C(56)-C(55)	1.22(16)
N(5)-C(51)-C(56)-C(55)	-179.39(10)
C(2)-N(1)-C(6)-C(7)	-131.32(11)
C(18)-N(1)-C(6)-C(7)	59.74(14)
C(2)-N(1)-C(6)-N(5)	46.76(12)

C(8)-C(7)-N(11)-C(12)	154.87(12)
C(6)-C(7)-N(11)-C(10)	159.49(11)
C(8)-C(7)-N(11)-C(10)	-15.64(12)
C(9)-C(10)-N(11)-C(12)	-178.88(10)
C(9)-C(10)-N(11)-C(7)	-6.93(13)
C(7)-N(11)-C(12)-O(12)	-178.65(11)
C(10)-N(11)-C(12)-O(12)	-8.71(16)
C(7)-N(11)-C(12)-C(13)	-3.04(18)
C(10)-N(11)-C(12)-C(13)	166.89(10)
O(12)-C(12)-C(13)-C(18)	-151.56(12)
N(11)-C(12)-C(13)-C(18)	32.90(17)
O(12)-C(12)-C(13)-C(14)	27.45(16)
N(11)-C(12)-C(13)-C(14)	-148.09(11)
C(18)-C(13)-C(14)-C(15)	0.08(18)
C(12)-C(13)-C(14)-C(15)	-179.00(11)
C(13)-C(14)-C(15)-C(16)	-1.03(19)
C(14)-C(15)-C(16)-C(17)	0.59(19)
C(15)-C(16)-C(17)-C(18)	0.80(18)
C(16)-C(17)-C(18)-C(13)	-1.78(17)
C(16)-C(17)-C(18)-N(1)	177.26(10)
C(14)-C(13)-C(18)-C(17)	1.33(16)
C(12)-C(13)-C(18)-C(17)	-179.68(11)
C(14)-C(13)-C(18)-N(1)	-177.70(10)
C(12)-C(13)-C(18)-N(1)	1.29(17)
C(2)-N(1)-C(18)-C(17)	-47.93(14)
C(6)-N(1)-C(18)-C(17)	120.32(11)
C(2)-N(1)-C(18)-C(13)	131.12(11)
C(6)-N(1)-C(18)-C(13)	-60.62(13)
O(2B)-C(2B)-C(3B)-C(4B)	59.5(3)
C(1B)-C(2B)-C(3B)-C(4B)	-179.3(4)

Table 21: Hydrogen bonds for compound **76** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2B)-H(2BO)...O(12)	0.849(18)	2.01(2)	2.825(2)	160(3)
C(54)-H(54)...O(2)#1	0.95	2.33	3.2552(14)	164.6
C(17)-H(17)...O(4)#2	0.95	2.59	3.4312(14)	147.7
C(1B)-H(1B2)...O(4)#3	0.98	2.47	3.435(4)	168.2
C(4B)-H(4B3)...O(4)#4	0.98	2.57	3.524(4)	163.3
C(3)-H(3)...O(12)#4	1.00	2.62	3.5897(14)	162.5
C(3)-H(3)...O(2B)#4	1.00	2.50	3.242(2)	130.6

Symmetry transformations used to generate equivalent atoms:
#1 x-1,y,z #2 -x+1,-y+1,-z+1 #3 x+1,y,z+1 #4 -x+2,-y+2,-z+2

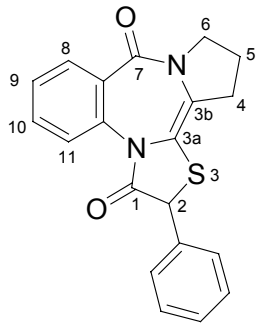


Table 22: Crystal data and structure refinement for compound **82**.

Empirical formula	$C_{20}\,H_{16}\,N_2\,O_2\,S$
Formula weight	348.41
Temperature	123(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n (No.14)
Unit cell dimensions	a = 13.4178(3) A α = 90 °
	b = 9.1816(2) A β = 100.101(1) °
	c = 13.4360(4) A γ = 90 °
Volume	1629.61(7) A^3
Z, Calculated density	4, 1.420 Mg/m^3
Absorption coefficient	0.215 mm^{-1}
F(000)	728
Crystal size	0.50 × 0.30 × 0.15 mm
Diffractometer	Nonius KappaCCD
Θ-Range for data collection	2.97 to 27.48 °
Limiting indices	-17<=h<=17, -11<=k<=11, -17<=l<=17
Reflections collected / unique	15182 / 3629 [R(int) = 0.0347]
Completeness to theta = 25.02	99.8 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3629 / 0 / 226
Goodness-of-fit on F^2	1.081
Final R indices [I^2sigma(I)]	R1 = 0.0329, wR2 = 0.0850
R indices (all data)	R1 = 0.04511, wR2 = 0.0890
Largest diff. peak and hole	0.260 and -0.303 $e.A^{-3}$

Table 23: Bond lengths [Å] and angles [°] for compound **82**.

O(1)-C(1)	1.2341(16)	C(3)-C(4)-C(5)	104.33(11)
C(1)-N(2)	1.3607(17)	C(6)-C(5)-C(4)	101.98(11)
C(1)-C(17)	1.4977(18)	C(7)-C(6)-N(2)	125.22(12)
N(2)-C(6)	1.4188(16)	C(7)-C(6)-C(5)	127.64(12)
N(2)-C(3)	1.4844(17)	N(2)-C(6)-C(5)	106.83(11)
C(3)-C(4)	1.515(2)	C(6)-C(7)-N(11)	124.81(12)
C(4)-C(5)	1.530(2)	C(6)-C(7)-S(8)	125.50(10)
C(5)-C(6)	1.4980(18)	N(11)-C(7)-S(8)	109.37(9)
C(6)-C(7)	1.3221(17)	C(7)-S(8)-C(9)	88.49(6)
C(7)-N(11)	1.4254(15)	C(91)-C(9)-C(10)	114.53(10)
C(7)-S(8)	1.7626(13)	C(91)-C(9)-S(8)	112.53(9)
S(8)-C(9)	1.8366(14)	C(10)-C(9)-S(8)	105.02(8)
C(9)-C(91)	1.5025(18)	C(96)-C(91)-C(92)	118.74(12)

C(9)-C(10)	1.5315(17)
C(91)-C(96)	1.3907(17)
C(91)-C(92)	1.3936(18)
C(92)-C(93)	1.3819(18)
C(93)-C(94)	1.385(2)
C(94)-C(95)	1.379(2)
C(95)-C(96)	1.3881(19)
C(10)-O(10)	1.2102(15)
C(10)-N(11)	1.3816(16)
N(11)-C(12)	1.4374(15)
C(12)-C(13)	1.3921(18)
C(12)-C(17)	1.3956(18)
C(13)-C(14)	1.3818(19)
C(14)-C(15)	1.382(2)
C(15)-C(16)	1.383(2)
C(16)-C(17)	1.4002(17)
O(1)-C(1)-N(2)	119.10(12)
O(1)-C(1)-C(17)	119.84(12)
N(2)-C(1)-C(17)	120.88(11)
C(1)-N(2)-C(6)	131.21(11)
C(1)-N(2)-C(3)	118.21(11)
C(6)-N(2)-C(3)	110.27(10)
N(2)-C(3)-C(4)	104.11(11)

C(96)-C(91)-C(9)	119.64(11)
C(92)-C(91)-C(9)	121.62(11)
C(93)-C(92)-C(91)	120.55(12)
C(92)-C(93)-C(94)	120.18(12)
C(95)-C(94)-C(93)	119.84(13)
C(94)-C(95)-C(96)	120.10(13)
C(95)-C(96)-C(91)	120.56(13)
O(10)-C(10)-N(11)	124.87(12)
O(10)-C(10)-C(9)	124.17(11)
N(11)-C(10)-C(9)	110.93(11)
C(10)-N(11)-C(7)	113.99(10)
C(10)-N(11)-C(12)	122.39(10)
C(7)-N(11)-C(12)	120.05(10)
C(13)-C(12)-C(17)	120.36(12)
C(13)-C(12)-N(11)	117.97(12)
C(17)-C(12)-N(11)	121.58(11)
C(14)-C(13)-C(12)	120.32(13)
C(13)-C(14)-C(15)	120.20(13)
C(14)-C(15)-C(16)	119.55(13)
C(15)-C(16)-C(17)	121.46(13)
C(12)-C(17)-C(16)	118.09(12)
C(12)-C(17)-C(1)	127.05(12)
C(16)-C(17)-C(1)	114.85(12)

Table 24: Torsion angles [°] for compound **82**.

O(1)-C(1)-N(2)-C(6)	175.70(12)
C(17)-C(1)-N(2)-C(6)	0.6(2)
O(1)-C(1)-N(2)-C(3)	2.73(18)
C(17)-C(1)-N(2)-C(3)	-172.40(11)
C(1)-N(2)-C(3)-C(4)	179.60(11)
C(6)-N(2)-C(3)-C(4)	5.23(14)
N(2)-C(3)-C(4)-C(5)	-24.96(14)
C(3)-C(4)-C(5)-C(6)	34.73(14)
C(1)-N(2)-C(6)-C(7)	29.9(2)
C(3)-N(2)-C(6)-C(7)	-156.68(12)
C(1)-N(2)-C(6)-C(5)	-156.14(13)
C(3)-N(2)-C(6)-C(5)	17.26(14)
C(4)-C(5)-C(6)-C(7)	141.69(13)
C(4)-C(5)-C(6)-N(2)	-32.06(14)
N(2)-C(6)-C(7)-N(11)	-0.7(2)
C(5)-C(6)-C(7)-N(11)	-173.40(12)
N(2)-C(6)-C(7)-S(8)	172.06(9)
C(5)-C(6)-C(7)-S(8)	-0.6(2)
C(6)-C(7)-S(8)-C(9)	-141.92(12)
N(11)-C(7)-S(8)-C(9)	31.81(9)
C(7)-S(8)-C(9)-C(91)	-154.78(9)
C(7)-S(8)-C(9)-C(10)	-29.57(9)
C(10)-C(9)-C(91)-C(96)	129.54(13)
S(8)-C(9)-C(91)-C(96)	-110.61(12)
C(10)-C(9)-C(91)-C(92)	-50.98(16)
S(8)-C(9)-C(91)-C(92)	68.86(14)
C(96)-C(91)-C(92)-C(93)	-0.70(19)
C(9)-C(91)-C(92)-C(93)	179.82(12)
C(91)-C(92)-C(93)-C(94)	1.6(2)
C(92)-C(93)-C(94)-C(95)	-1.3(2)
C(93)-C(94)-C(95)-C(96)	0.0(2)
C(94)-C(95)-C(96)-C(91)	0.9(2)

C(9)-C(91)-C(96)-C(95)	178.95(12)
C(91)-C(9)-C(10)-O(10)	-36.58(17)
S(8)-C(9)-C(10)-O(10)	-160.53(11)
C(91)-C(9)-C(10)-N(11)	145.38(11)
S(8)-C(9)-C(10)-N(11)	21.43(12)
O(10)-C(10)-N(11)-C(7)	-176.59(11)
C(9)-C(10)-N(11)-C(7)	1.44(15)
O(10)-C(10)-N(11)-C(12)	24.75(19)
C(9)-C(10)-N(11)-C(12)	-157.23(11)
C(6)-C(7)-N(11)-C(10)	148.52(12)
S(8)-C(7)-N(11)-C(10)	-25.26(13)
C(6)-C(7)-N(11)-C(12)	-52.27(17)
S(8)-C(7)-N(11)-C(12)	133.95(10)
C(10)-N(11)-C(12)-C(13)	33.23(17)
C(7)-N(11)-C(12)-C(13)	-124.19(13)
C(10)-N(11)-C(12)-C(17)	-150.38(12)
C(7)-N(11)-C(12)-C(17)	52.21(16)
C(17)-C(12)-C(13)-C(14)	0.40(19)
N(11)-C(12)-C(13)-C(14)	176.84(11)
C(12)-C(13)-C(14)-C(15)	0.80(19)
C(13)-C(14)-C(15)-C(16)	-0.7(2)
C(14)-C(15)-C(16)-C(17)	-0.5(2)
C(13)-C(12)-C(17)-C(16)	-1.60(18)
N(11)-C(12)-C(17)-C(16)	-177.91(11)
C(13)-C(12)-C(17)-C(1)	176.88(12)
N(11)-C(12)-C(17)-C(1)	0.6(2)
C(15)-C(16)-C(17)-C(12)	1.67(19)
C(15)-C(16)-C(17)-C(1)	-176.99(12)
O(1)-C(1)-C(17)-C(12)	154.77(13)
N(2)-C(1)-C(17)-C(12)	-30.14(19)
O(1)-C(1)-C(17)-C(16)	-26.71(17)
N(2)-C(1)-C(17)-C(16)	148.38(13)

Table 25: Hydrogen bonds for compound **82** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(9)-H(9)...O(1)#1	1.00	2.21	3.1308(16)	153.0

Symmetry transformations used to generate equivalent atoms:
#1 -x+3/2,y+1/2,-z+1/2

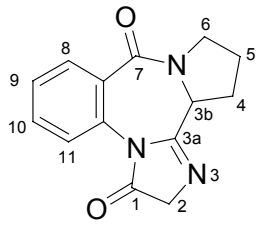


Table 26: Crystal data and structure refinement for compound **90**.

Empirical formula	$C_{14}\ H_{13}\ N_3\ O_2$
Formula weight	255.27
Temperature	123(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1) (No.14)
Unit cell dimensions	a = 9.3330(2) A α = 90 °
	b = 7.0934(2) A β = 114.714(1) °
	c = 9.4243(3) A γ = 90 °
Volume	596.86(3) A^3
Z, Calculated density	2, 1.420 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F(000)	268
Crystal size	0.40 × 0.30 × 0.20 mm
Diffractometer	Nonius KappaCCD
Θ-Range for data collection	3.65 to 27.48 °
Limiting indices	-12<=h<=12, -9<=k<=7, -11<=l<=12
Reflections collected / unique	5713 / 2197 [R(int) = 0.0233]
Completeness to theta = 27.48	98.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3629 / 0 / 226
Goodness-of-fit on F^2	1.081
Final R indices [I^2sigma(I)]	R1 = 0.0282, wR2 = 0.0677
R indices (all data)	R1 = 0.0304, wR2 = 0.0686
Absolute structure parameter	-0.1(10), cannot be determined reliable
Largest diff. peak and hole	0.129 and -0.215 $e.A^{-3}$

Table 27: Bond lengths [Å] and angles [°] for compound **90**.

O(1)-C(1)	1.2134(16)
C(1)-N(11B)	1.3913(17)
C(1)-C(2)	1.5117(17)
C(2)-N(3)	1.4660(19)
N(3)-C(3A)	1.2739(17)
C(3A)-N(11B)	1.4085(16)
C(3A)-C(3B)	1.4996(19)
C(3B)-N(6A)	1.4769(18)
C(3B)-C(4)	1.5309(17)
C(4)-C(5)	1.530(2)
C(5)-C(6)	1.523(2)
C(6)-N(6A)	1.4739(18)
N(6A)-C(7)	1.3439(17)
C(7)-O(7)	1.2402(17)

N(3)-C(3A)-N(11B)	115.43(12)
N(3)-C(3A)-C(3B)	127.26(11)
N(11B)-C(3A)-C(3B)	117.27(10)
N(6A)-C(3B)-C(3A)	108.63(11)
N(6A)-C(3B)-C(4)	102.78(11)
C(3A)-C(3B)-C(4)	113.29(11)
C(5)-C(4)-C(3B)	103.92(11)
C(6)-C(5)-C(4)	103.39(11)
N(6A)-C(6)-C(5)	103.46(12)
C(7)-N(6A)-C(6)	121.29(12)
C(7)-N(6A)-C(3B)	126.19(11)
C(6)-N(6A)-C(3B)	112.33(10)
O(7)-C(7)-N(6A)	121.46(13)
O(7)-C(7)-C(7A)	120.22(12)

C(7)-C(7A)	1.504(2)	N(6A)-C(7)-C(7A)	118.30(12)
C(7A)-C(8)	1.3992(17)	C(8)-C(7A)-C(11A)	118.09(13)
C(7A)-C(11A)	1.4001(19)	C(8)-C(7A)-C(7)	116.68(12)
C(8)-C(9)	1.382(2)	C(11A)-C(7A)-C(7)	125.21(11)
C(9)-C(10)	1.385(2)	C(9)-C(8)-C(7A)	121.52(14)
C(10)-C(11)	1.3867(17)	C(8)-C(9)-C(10)	119.36(12)
C(11)-C(11A)	1.3891(18)	C(9)-C(10)-C(11)	120.52(14)
C(11A)-N(11B)	1.4277(16)	C(10)-C(11)-C(11A)	119.87(14)
O(1)-C(1)-N(11B)	126.73(12)	C(11)-C(11A)-C(7A)	120.62(11)
O(1)-C(1)-C(2)	129.47(13)	C(11)-C(11A)-N(11B)	118.25(13)
N(11B)-C(1)-C(2)	103.73(11)	C(7A)-C(11A)-N(11B)	121.10(12)
N(3)-C(2)-C(1)	106.87(11)	C(1)-N(11B)-C(3A)	108.00(10)
C(3A)-N(3)-C(2)	105.88(10)	C(1)-N(11B)-C(11A)	125.86(11)

Table 28: Torsion angles [°] for compound **90**.

O(1)-C(1)-C(2)-N(3)	-179.79(14)	O(7)-C(7)-C(7A)-C(11A)	-139.68(15)
N(11B)-C(1)-C(2)-N(3)	-2.68(14)	N(6A)-C(7)-C(7A)-C(11A)	42.37(19)
C(1)-C(2)-N(3)-C(3A)	2.87(15)	C(11A)-C(7A)-C(8)-C(9)	-1.1(2)
C(2)-N(3)-C(3A)-N(11B)	-2.02(16)	C(7)-C(7A)-C(8)-C(9)	-179.47(14)
C(2)-N(3)-C(3A)-C(3B)	175.64(13)	C(7A)-C(8)-C(9)-C(10)	0.5(2)
N(3)-C(3A)-C(3B)-N(6A)	-114.40(15)	C(8)-C(9)-C(10)-C(11)	0.4(2)
N(11B)-C(3A)-C(3B)-N(6A)	63.22(14)	C(9)-C(10)-C(11)-C(11A)	-0.6(2)
N(3)-C(3A)-C(3B)-C(4)	-0.9(2)	C(10)-C(11)-C(11A)-C(7A)	0.0(2)
N(11B)-C(3A)-C(3B)-C(4)	176.75(12)	C(10)-C(11)-C(11A)-N(11B)	178.14(13)
N(6A)-C(3B)-C(4)-C(5)	30.26(13)	C(8)-C(7A)-C(11A)-C(11)	0.82(19)
C(3A)-C(3B)-C(4)-C(5)	-86.76(14)	C(7)-C(7A)-C(11A)-C(11)	179.09(13)
C(3B)-C(4)-C(5)-C(6)	-38.14(14)	C(8)-C(7A)-C(11A)-N(11B)	-177.28(12)
C(4)-C(5)-C(6)-N(6A)	30.49(14)	C(7)-C(7A)-C(11A)-N(11B)	1.0(2)
C(5)-C(6)-N(6A)-C(7)	163.27(12)	O(1)-C(1)-N(11B)-C(3A)	178.78(14)
C(5)-C(6)-N(6A)-C(3B)	-11.99(15)	C(2)-C(1)-N(11B)-C(3A)	1.56(14)
C(3A)-C(3B)-N(6A)-C(7)	-66.18(15)	O(1)-C(1)-N(11B)-C(11A)	-5.1(2)
C(4)-C(3B)-N(6A)-C(7)	173.53(12)	C(2)-C(1)-N(11B)-C(11A)	177.70(12)
C(3A)-C(3B)-N(6A)-C(6)	108.80(12)	N(3)-C(3A)-N(11B)-C(1)	0.26(16)
C(4)-C(3B)-N(6A)-C(6)	-11.49(14)	C(3B)-C(3A)-N(11B)-C(1)	-177.64(11)
C(6)-N(6A)-C(7)-O(7)	5.3(2)	N(3)-C(3A)-N(11B)-C(11A)	-175.87(13)
C(3B)-N(6A)-C(7)-O(7)	179.83(13)	C(3B)-C(3A)-N(11B)-C(11A)	6.23(19)
C(6)-N(6A)-C(7)-C(7A)	-176.80(13)	C(11)-C(11A)-N(11B)-C(1)	-40.27(19)
C(3B)-N(6A)-C(7)-C(7A)	-2.24(19)	C(7A)-C(11A)-N(11B)-C(1)	137.88(14)
O(7)-C(7)-C(7A)-C(8)	38.6(2)	C(11)-C(11A)-N(11B)-C(3A)	135.19(13)
N(6A)-C(7)-C(7A)-C(8)	-139.35(13)	C(7A)-C(11A)-N(11B)-C(3A)	-46.67(19)

Table 29: Hydrogen bonds for compound **90** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(11)-H(11)...O(7)#1	0.95	2.45	3.1389(17)	129.3

Symmetry transformations used to generate equivalent atoms:
#1 x,y+1,z

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Poster Presentations:

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On Betaine Pyrrolobenzodiazepines as Derivatives of Circumdatins

8. **Summary**

Mesomeric betaines have attracted considerable interest in the chemistry of heterocyclic compounds during the last decades. In contrast to 5- and 6-membered representatives which have been extensively reported in the literature, information about 7-membered mesomeric betaines is rare. This fact stimulated our interest in syntheses and characterisations of betainic benzo[*b*][1,4]diazepiniums which possesses 4n π-electrons (anti-Hückel heteroaromatics). 2,3-Diaminophenol, 3,4-diaminophenol, 4-methoxy-1,2-diaminobenzene, 3,4-diamino-benzenethiol, 2,3-diaminobenzoic acid and 3,4-diaminobenzoic acid were the starting materials for reactions with 2,4-pentanedione in the presence of sulfuric acid, trifluoroacetic acid and picric acid, respectively, for the synthesis of benzo[b][1,4]diazepinium salts. Among these, the hydroxy-benzo[b][1,4]diazepinium salts do not form mesomeric betaines (MB) on deprotonation. Instead, they are converted into diimines. By contrast, the 7-mercapto-benzo[b][1,4]diazepinium salt yields the corresponding thiolate on increasing the *p*H of the solution. This MB, which possesses 4n π-electrons, does not fit into the classification system of heterocyclic mesomeric betaines accepted today. The carboxy derivatives readily form cross-conjugated mesomeric betaines. X-Ray structural analysis of 7-carboxy and 6-hydroxy-benzo[b][1,4]diazepinium picrates unambiguously demonstrate the unique construction of the 7-membered ring with respect to C–N bond distances which are unusually longer than conjugated bonds. This observation is clearly in contrast to the formation of Anti-Hückel 4n π-electron systems, as conjugation is interrupted in order to avoid anti-aromaticity. In the single crystal, the benzodiazepinium molecules form layers with overlapped 7-membered rings in head-to-tail arrangement.

Next, we turned our attention to the proposed structures of Circumdatin A and B which have been recently reported as new pyrrolobenzodiazepine alkaloids with an annulated pyrimidinium olate cross-conjugated betainic structure. They were isolated from the fungus *Aspergillus ochraceus* by Christophersen *et al*. As the proposed structures are without precedent in heterocyclic as well as natural product chemistry, we prepared first representatives of this class of heterocyclic mesomeric betaines as model compounds or closely related structures for stereochemical and spectroscopic comparisons.

First, a pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione was converted into the corresponding C-11-monothiolactam and subsequently treated with amines to cyclic amidines which form tautomers (NMR, X-ray analysis) under basic conditions. Depending on the substitution

pattern as well as the reaction conditions, these amidines racemize and loose their isohelicity to the minor groove of DNA which cause the considerable biological activity of this class of compounds. We then reacted *N*-substituted cycloamidines with bis(trichlorophenyl)malonic esters. Formation of neutral tautomers of 1,3,8-triones instead of corresponding betainic structures resulted in twisted molecules with helical as well as chiral structure elements (NMR, X-ray analysis). These stereochemical features cause a splitting of the NMR signals of this new ring system into two sets. X-Ray single crystal analyses and *ab-initio* calculations confirm the boat conformation of the dioxopyrimidine moiety with the phenyl ring in axial position. The stereochemical outcome of this reaction strongly depends on substituent effects. Thus, reaction of *N*-unsubstituted cycloamidine with malonic esters resulted in the formation of the 3-hydroxy-4b,5,6,7-tetrahydro-4,7a,12b-triaza-dibenzo[*e,g*]azulene-1,8-diones as optically active compounds.

After we were able to show that a cross-conjugated charge-separation in model compounds of the proposed structures of Circumdatin A and B is not stable, we next focused our interest on thioisomünchnones of pyrrolobenzodiazepines which possess a *formal* charge separation. First representatives of the new ring system of the 3-thia-6a,11b-diazabenzo[g]cyclopenta[e]-azulene-1,7-diones were synthesized starting from a thiolactam and 2-bromoacetyl chlorides. Tautomerisations including the biologically important C-11a position in solution as well as in the solid state were examined by spectroscopic investigations and an X-ray analysis.

Consequently, the reaction of the thiolactam and amino acid esters and subsequent ring closure afforded 1,3-imidazol-4-one- and 1,3-pyrimidin-4-one-annulated pyrrolobenzo-diazepines. They are important structure elements of the proposed structures. We investigated the synthetic approaches and spectroscopic properties.

In conclusion, we present first representatives of new tetracyclic ring systems, 5,6-dihydro-4*H*-3-thia-6a,11b-diazabenzo[g]cyclopenta[e]azulene and 4,5,6,7-tetrahydro-4,7a,12b-triaza-dibenzo[*e,g*]azulene and its precursors, which are related to biologically interesting natural products, and which display *a priori* unexpected spectroscopic features. Interestingly these findings prove that neither pyrimidine nor thiazolidine derivatives are able to form iminium partially structures ($[N{=}C{-}N]^{+}$) in proximity of the acidic hydrogen in the pyrrolidine moieties. Instead, they adopt the more stable neutral tautomers. Thus, spectroscopic comparisons of our annulated new compounds with the originally proposed structures of Circumdatin A and B gain knowledges about possible constitution of these natural products.

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