INDOLES XI.[1] SYNTHESES AND STEREOCHEMISTRY OF 5,6,7,8,13,13b-HEXAHYDROBENZ[*a*]INDOLO[2,3-*h*]QUINOLIZINES AND OF 5,6,7,8,13,13b-HEXAHYDRO-14*H*-BIS-INDOLO[3,2-*a*][2,3-*h*]-QUINOLIZINE

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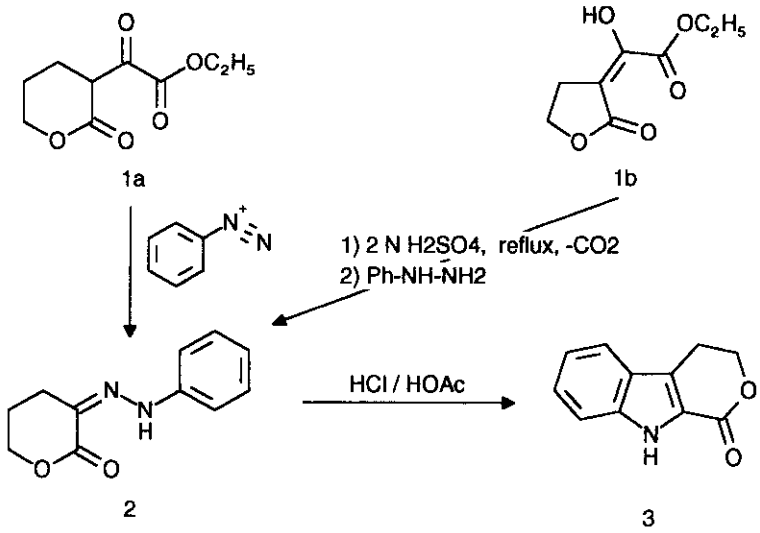
Abstract - A new and efficient synthesis of substituted 5,6,7,8,13,13b-hexahydrobenz[*a*]indolo[2,3-*h*]quinolizines (**5b,d**) *via* lactamisation of dihydropyrano[3,4-*b*]indol-1-one (**3**), cyclisation with phosphorus oxychloride and reduction with sodium borohydride is described. The unsubstituted 5,6,7,8,13,13b-hexahydrobenz[*a*]indolo[2,3-*h*]quinolizine (**5**) is prepared by analogy starting with the lactamisation of isochromanone with tryptamine. The unsubstituted 5,6,7,8,13,13b-hexahydro-14*H*-bisindolo[3,2-*a*][2,3-*h*]quinolizine (**9**) is synthesized by lactamisation of **3** with tryptamine, cyclisation and again reduction of the intermediate immonium salt. The stereochemistry of the unsubstituted quinolizine derivatives is investigated by ^{1}H-; ^{13}C-nmr-, NOE spectroscopy and by X-ray analysis.

The preparation of the hexahydro-2,3-dimethoxybenz[*a*]indolo[2,3-*h*]quinolizine (**5d**) was described by Sugasawa and Deguchi[2] in 1960, their synthesis comprising twelve steps. We now succeeded in reducing the required reaction steps by half and in introducing a more general method. Several authors reported on the syntheses of the unsubstituted hexahydrobenz[*a*]indolo[2,3-*h*]quinolizine (**5**),[3-5] but except for elementary analyses and uv spectra most of these accounts lack analytical details elucidating conformational facts. Only

van Binst quotes some ^{13}C-shifts and states a *cis*[1]-conformation for **5**.[15] The hexahydrobisindolo[3,2-*a*][2,3-*h*]-quinolizine skeleton (**9**) is still unknown.

SYNTHESES

The lactamisation of the pyranoindolone (**3**) is the crucial step in the formation of the required β-carboline derivates. There are two different ways to synthesize **3** and its substituted derivatives (Scheme 1). The starting compound of the first method is the δ-lactone (**1a**) which gives 3-phenylhydrazonotetrahydro-2*H*-pyran-2-one (**2**) with phenyldiazonium chloride and finally **3** *via* the Fischer synthesis [6,7] Method two differs in the generation of **2**.[8] Treatment of the γ-lactone (**1b**) with hot, dilute sulphuric acid induces ring cleavage and decarboxylation yielding a mixture of compounds with 2-hydroxytetrahydrofuran-2-carboxylic acid as a main product. Adding phenylhydrazine to that mixture also gives **2**.

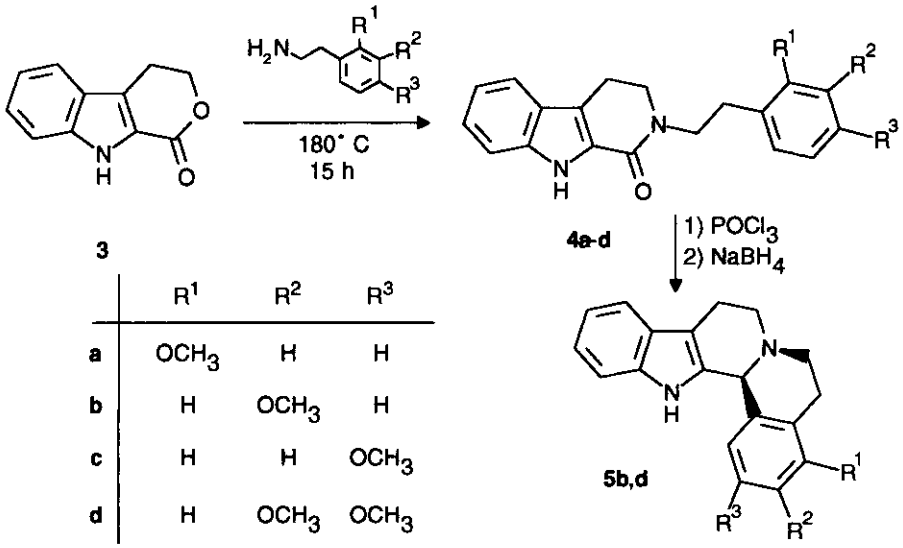


Scheme 1 Preparation of pyranoindolone (**3**)

The lactone (**3**) can either be converted to 2-unsubstituted β-carbolines[6-8] or to the required lactams (**4**) using various arylethylamines Cyclisation of **4** by Bischler-Napieralski reaction in the presence of phosphorus oxychloride results in the formation of quinolizinium salts. These are reduced by sodium borohydride to yield the hexahydroquinolizines (**5b,d**) (Scheme 2). Accordingly, we managed the cyclisation and reduction of 3-methoxy- and 3,4-dimethoxyphenylethyl lactams, whereas the 2-methoxy- and 4-methoxyphenylethyl analogues

as well as the unsubstituted derivatives of **4** proved inert even after refluxing them in phosphorus oxychloride for 7 days

Similar cyclisations are described for the preparation of hexahydrodibenzo[a,*h*]quinolizines,[9] but they differ in reaction conditions and working up methods.



3

	R^1	R^2	R^3
a	OCH_3	H	H
b	H	OCH_3	H
c	H	H	OCH_3
d	H	OCH_3	OCH_3

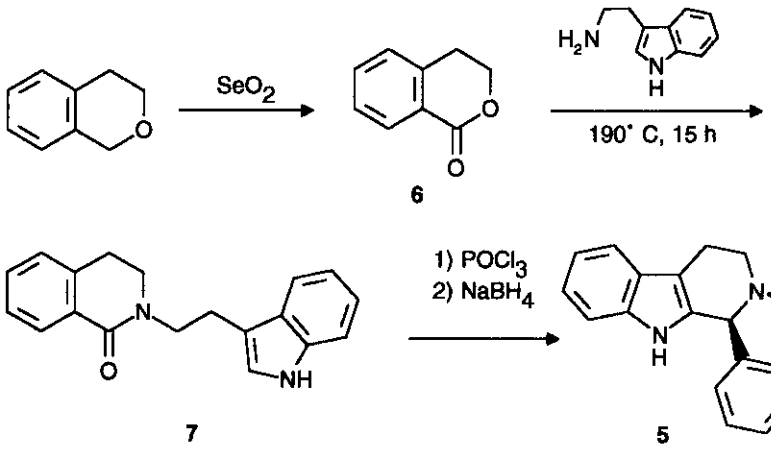
Scheme 2: Preparation of substituted benzindoloquinolizines (**5**)

The fact that only 3-methoxylated and 3,4-dimetoxylated, that is to say in position 6 of the phenylethyl moiety activated, derivatives of **4** can be transformed to quinolizines by the route mentioned above (this being valid for h0exahydrodibenzo[a,*h*]quinolizines, too[9]), led us to look for a more suitable strategy for preparing unsubstituted **5**

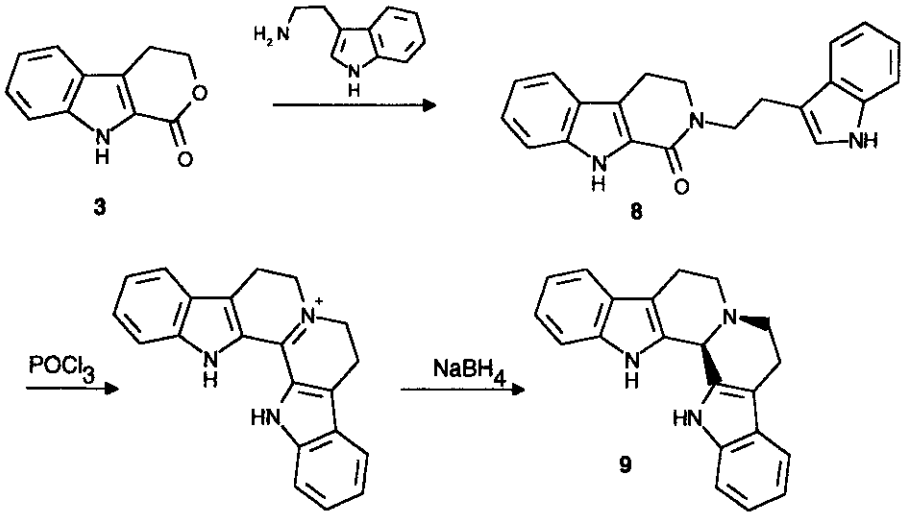
The lactamisation is carried out using isochromanone (**6**) and tryptamine. After treatment of **7** with phosphorus oxychloride and reduction of the intermediate with sodium borohydride **5** is obtained (Scheme 3). Recrystallisation from methanol leads to the formation of colourless thick needles, which were taken for X-ray analysis

The 1-isochromanone itself results from the oxidation of isochroman with selenium dioxide.[10,11]

The bisindoloquinolizine (**9**) is synthesized in a similar way by reacting **3** with tryptamine followed by cyclisation and reduction of the intermediate (Scheme 4).



Scheme 3: Preparation of 5,6,7,8,13,13b-hexahydrobenz[*a*]indolo[2,3-*h*]quinolizine



Scheme 4: Preparation of 5,6,7,8,13,13b-hexahydro-14*H*-bis-indolo[3,2-*a*][2,3-*h*]quinolizine

STEREOCHEMISTRY

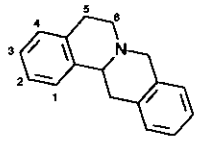
It is an intriguing question of stereochemistry whether quinolizine rings in quinolizine derivates are *trans*- or *cis*-connected. Many authors dealt with this question before.[12-19]

In principle, quinolizine systems can exist in three different conformations. The *trans*-conformation can change into a *cis*[1]-conformation by nitrogen-inversion, the latter can change into another *cis*[2]-conformation by ring-inversion.[17,20] A first hint to the conformation can be drown from the ir spectra as *trans*-connected systems

exhibit Bohlmann bands (2550 - 2850 cm^{-1}) in contrast to *cis*-connected ones.[21] Conformational information is also deducible from ^{13}C-nmr data in dibenzo[a,*h*]quinolizidines and in benzo[*a*]quinolizidines, especially from the ^{13}C-shifts of the alicyclic carbon atoms C^5 and C^6. In *cis*-connected rings there is a distinct up field shift for these atoms.[19]

$C^5_{trans} \approx 30$ ppm $\quad C^6_{trans} > 50$ ppm

$C^5_{cis} \approx 28$ ppm $\quad C^6_{cis} < 50$ ppm



Generally speaking, the ^{13}C-shifts for the above mentioned carbon atoms in the *trans* series are larger than those in the *cis*-series, the difference ranging from 2 ppm to 11 ppm.[18] In addition in *cis*-connected systems the C-H coupling of the methine-carbon (in **5** and **9** C^{13b}) is larger (>132 Hz) than in *trans*-connected ones (<122 Hz).[19] Based on ^{13}C-nmr studies, a *trans*-conformation is generally deduced for the yohimboid ring-system.[12,20,22] For dibenzoquinolizines a rapid equilibrium between two *cis*-conformations is stated.[14,15,18] For benzoindolo-quinolizines one *cis*-conformation without equilibrium is declared,[15] although one should be careful in drawing conclusions by comparing model values with nmr shifts. In one case the *cis*-conformation was proved by a low temperature nmr spectrum. It was shown, that the ^{13}C-shifts at room temperature are the observed averaged ^{13}C-shifts of a low temperature nmr spectrum.[14]

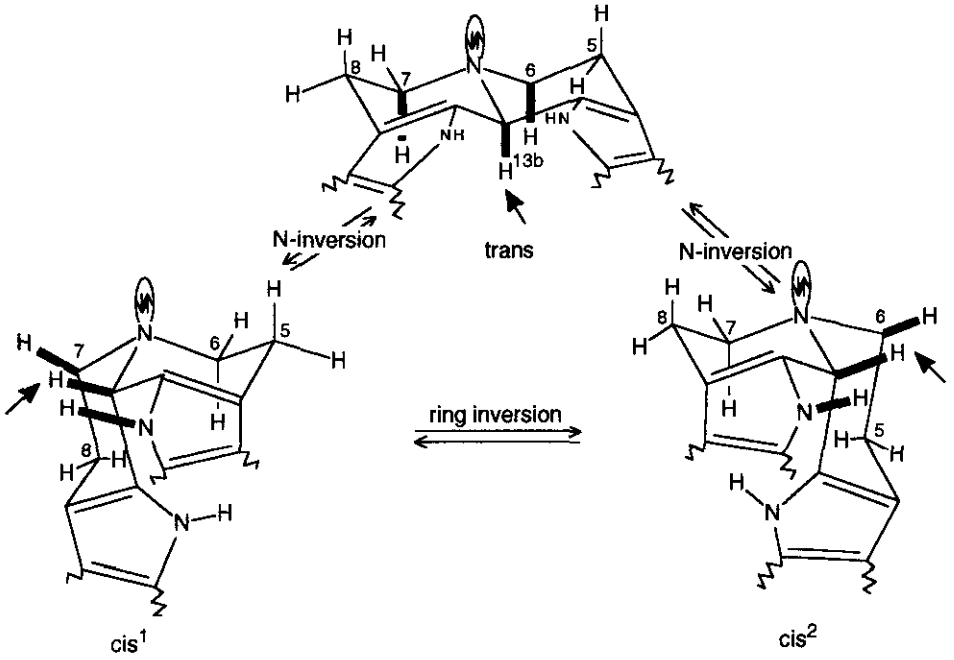
An attempt to elucidate the conformation of the quinolizine rings by INEPT ^{15}N-nmr spectroscopy failed because of the similarity of the coupling constants between N-H^{13b} and between N-H^{5-8} entailing their mutual extinction due to interference.

A direct way to get an information about the conformation of quinolizines is an X-ray analysis, although this information is only valid for the solid state and is not comparable with the conclusions drawn from an nmr-spectrum (solution).

Results: The ir spectra of the penta- and hexacyclic compounds (**5**), (**5b,d**) and (**9**) synthesized do not show any Bohlmann bands which is an indication for *cis*-connected quinolizine rings. The ^{13}C-shifts of the prepared sub-stances suggest a *cis*-conformation too (Table 1). Furthermore the CH-coupling of the 13b-position (158 Hz) in the hexacycle (**9**) indicates a *cis*-conformation. The X-ray analysis of 5,6,7,8,13,13b-hexahydrobenz[*a*]-indolo[3,2-b]quinolizine (**5**) and hexahydrobisindolo[3,2-*a*][2,3-*h*]quinolizine (**9**) proves that both systems are *cis*-connected (Figures 2 and 4). This does not necessarily mean, that the corresponding nmr spectrum is that of one *cis*-conformation. The nmr spectrum of the symmetric molecule (**9**) shows only four signals for the eight aliphatic methylene protons. This might be considered an indication for *trans*-connected rings, because in the

trans-conformation the protons H^5 and H^8, $H^{5'}$ and $H^{8'}$, H^6 and H^7 as well as the protons $H^{6'}$ and $H^{7'}$ are chemical and above all magnetically equivalent. But let us remember that the measured ^{13}C-shifts suggest a *cis*-conformation By combining these results it becomes clear that in dimethyl sulfoxide solution there must be an equilibrium between the two *cis*-conformations, perhaps including the *trans*-conformation formed by nitrogen inversion as well. The question, whether the equilibrium is only between the two *cis*-conformations or between the *cis*-conformations and the *trans*-conformation can unambigiously be answered by NOE experiments.

While emitting the frequency of the H^{13b}-proton in the hexacycle (**9**), we notice a distinct NOE effect on the proton H^6_{ax} in the *cis*^{2}-conformation and H^7_{ax} in the *cis*^{1}-conformation (that means on the protons, which are directed to the lone pair of the N^{6a}-Atom) and the two NH-protons. The *trans*-conformation or an equilibrium between the *trans*- and the two *cis*-conformations would reveal themselves giving only one NOE effect on the protons H^6_{ax} in the *cis*^{2}-conformation and H^7_{ax} in the *cis*^{1}-conformation or an enhanced NOE effect on these protons respectively. So there is no doubt that the equilibrium is only between the two *cis*-conformations (Scheme 5). There is no nitrogen inversion. These thoughts apply for the pentacyclus as well: The NOE experiments entailed the same results (NOE effect on the protons H^6_{ax} and NH, respectively H^1 and H^7_{ax}) meaning an equilibrium between the two *cis*-conformations only.

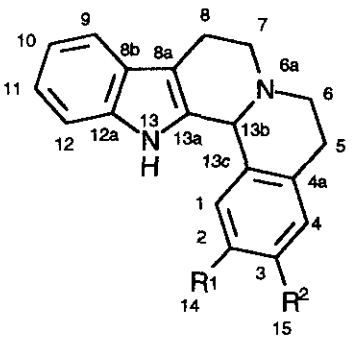


Scheme 5: Conformations of bis-indoloquinolizine (**9**)

Interestingly van Binst[15] states only one *cis*-conformation (no equilibrium) for the benzindoloquinolizine (**5**), (measured in deuterochloroform) based on the ^{13}C-shifts of atoms C^5-C^8. If this were the case there would be only one NOE effect either on the proton H^1 or on the NH-proton H^{13}.

To give a short summary of our results: Based on NOE experiments we could exclude the presence of the *trans*-conformation of **5** and **9** in solution, X-ray analyses exclude *trans*-conformations in solid state as well. For the hexacyclus ^1H-nmr data suggest a rapid equilibrium of the two possible *cis*-conformations. The equilibrium between the two *cis*-conformations of the pentacyclus can be proved by a single NOE experiment.

NMR-DATA and X-RAY-DATA



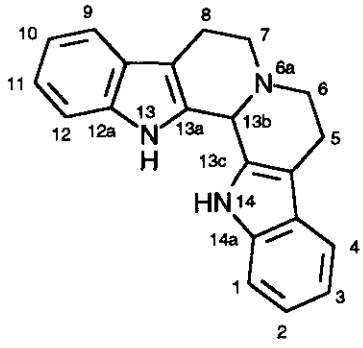


Table 1: ^1H-Nmr shifts of prepared quinolizines (shifts in ppm, couplings (in brackets) in Hz)

	(5)	(5b)	(5d)	(9)
1-H	7.55 dd (7.5; 1.5)	7.46 d (8 4)	7.04 s	7.41 dd (8.0; 1.0)
2-H	7.26 ddd (7.5; 7.5 ;1.5)	6.84 dd (8.4; 1 7)	-	6.99 ddd (8.0; 7.0; 1.0)
3-H	7.20 ddd (7.5; 7.5; 1.5)	-	-	7.08 ddd (8.0; 7.0; 1.0)
4-H	7.13 dd (7.5; 1.5)	6.71 d (1.7)	6.71 s	7.42 dd (8.0; 1.0)
5-H - 7-H	2.50-3 05. 6 protons 3.13. 2 protons	2 55-3.05: 6 protons 3.15: 2 protons	2.55-3 05: 6 protons 3 18: 2 protons	2.67-3.19 (see Table 2)
9-H	7 41 dd (6 5; 1.5)*	7 38 dd (7.2; 1.5)	7.38 dd (7 5; 1.5)	see 4-H
10-H	7.05 ddd (7.0; 6.5; 1.5)	7 04 ddd (7.2, 7 2; 1.5)	7.03 ddd (7.5; 7.5; 1.5)	see 3-H
11-H	6.95 ddd (7.0; 6.5; 1.5)	6.96 ddd (7.2; 7.2; 1 5)	6.94 ddd (7.5; 7.5; 1.5)	see 2-H
12-H	7.36 dd (6.5; 1.5)*	7.38 dd (7.2; 1.5)	7.38 dd (7.5; 1.5)	see 1-H
13-H	10.35 s	10.37 s	10.28 s	10.62 s
13b-H	5.25 s	5.18 s	5.18 s	5.35 t (1.3)
14-H	-	-	3.87 s	see 13-H
15-H	-	3.72 s	3.72 s	-

*= interchangeable

Table 2: ^{1}H-Nmr shifts of aliphatic protons in **9** from NOE experiments

5-Hax1, 8-Heq1 and 5-Heq2, 8-Hax2	2.67 dddd (17.5; 6.5; 6.5; 1.3)
5-Heq1, 8-Hax1 and 5-Hax2, 8-Heq2	2.81 dddd (17.5; 6.5; 5.5; 1.3)
6-Heq1, 7-Hax1 and 6-Hax2, 7-Heq2	3.09 ddd (12.0; 6.5; 5 5)
6-Hax1, 7-Heq1 and 6-Heq2, 7-Hax2	3.19 ddd (12.0; 6 5; 6.5)
13b-H	5.35 t (1.3)

H_{ax1} means. axial in the *cis*[1]-conformation
H_{eq2} means: equatorial in the *cis*[2]-conformation

Table 3· ^{13}C-Nmr shifts of prepared quinolizines (shifts in ppm)

	(5)	**(5b)**	**(5d)**	**(9)**
C-1	126.24*	128.93	112.09	111.13
C-2	128.68*1	112.29	147.01*	118.44
C-3	127.56*1	157.83	146.92*	120.70
C-4	125.58*	113.39	111.53	117.68
C-4a	133.99	136 02	125.95	126.59
C-4b	-	-	-	106.49
C-5	26.96	27.48	26 82	19.26
C-6	45.09	44.98	44.72	47.78
C-7	48.65	48 85	48.97	as C-6: 47.78
C-8	18.28	18.33	18.10	as C-5: 19.26
C-8a	105.45	105.44	105.25	as C-4b: 106.49
C-8b	126.61	126.92	126.83*1	as C-4a: 126.59
C-9	117 30	117.63	117.09	as C-4: 117.68
C-10	120.27	120.54	120.51	as C-3: 120.70
C-11	118.14	118.43	118.41	as C-2: 118 44
C-12	111.14	111.43	111 37	as C-1: 111.13
C-12a	135.72	135.66	135 92	135.92
C-13a	133.56	127 46	126.95*1	132.57
C-13b	56.38	56.03	56.22	52.90
C-13c	134.98	134.28	134.31	as C-13a: 132.57
C-14	-	-	55 50*2	-
C-14a	-	-	-	as C12a: 135.92
C-15	-	54.97	55.43*2	-

*= interchangeable

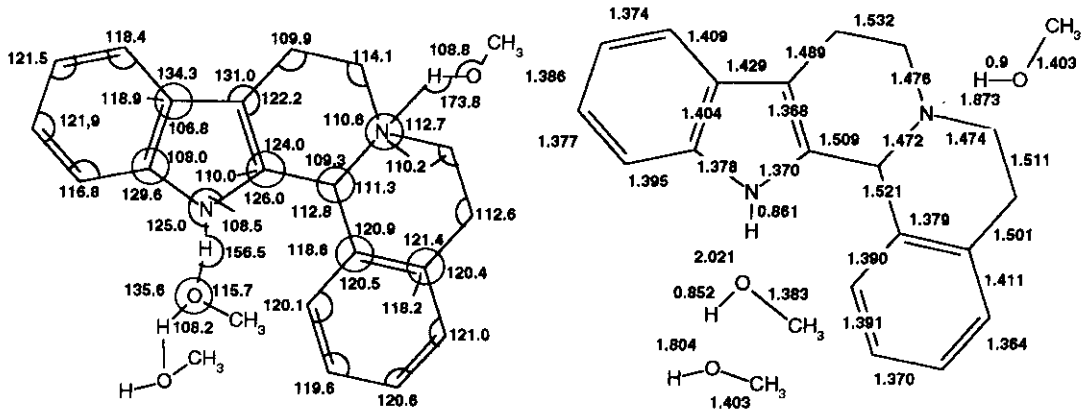


Figure 1 Data of the X-ray analysis: a) binding angles [°] b) bond lengths [Å]) of 5,6,7.8,13,13b-hexahydro-benz[*a*]indolo[2,3-*h*]quinolizine (**5**)

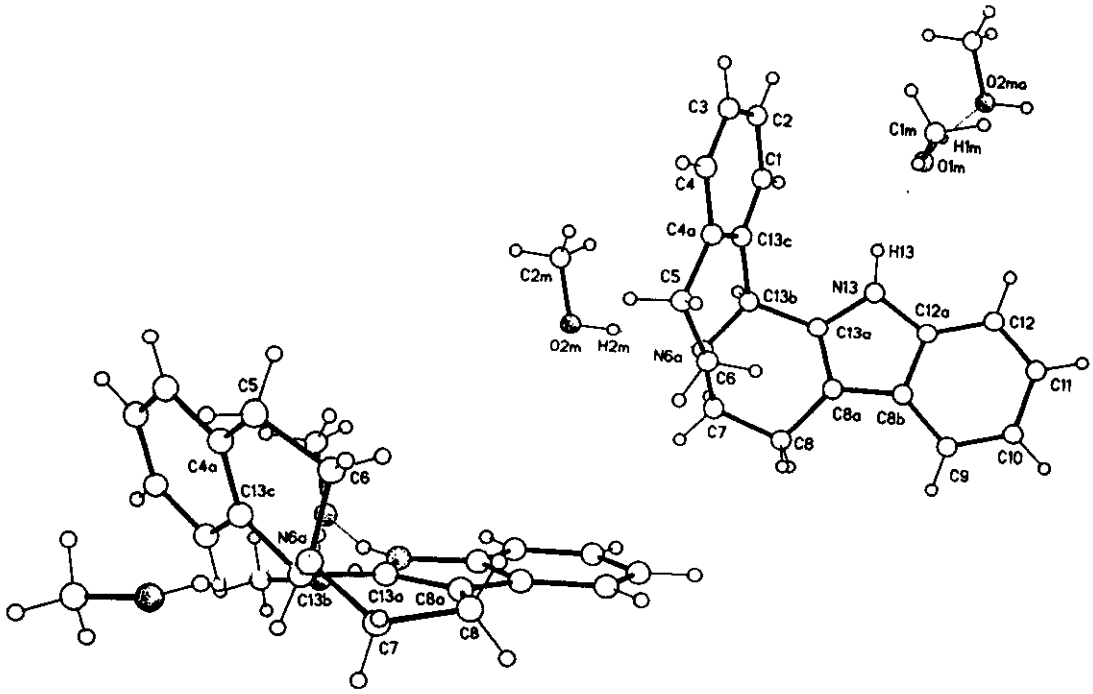


Figure 2: The structure of **5** resulting from X-ray analysis

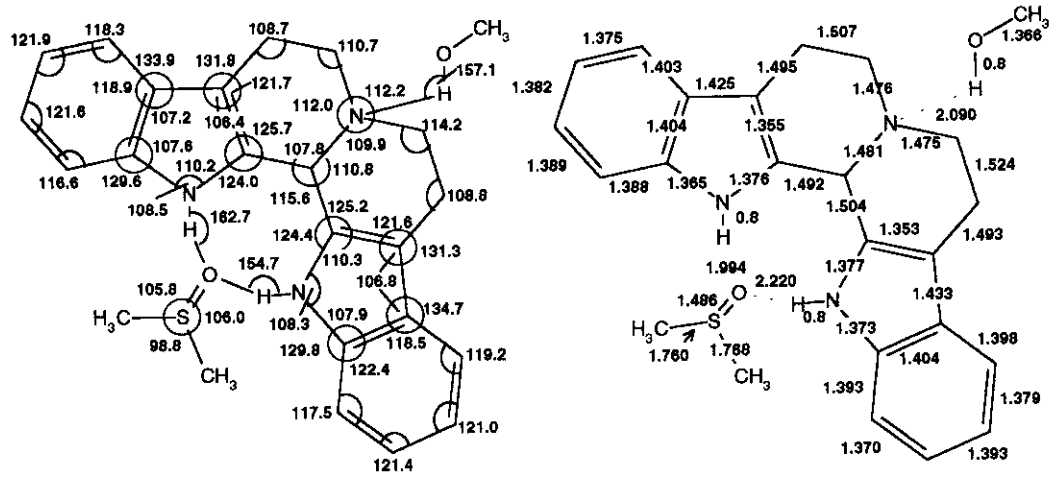


Figure 3: Data of the X-ray analysis: a) binding angles [°] b) bond lengths [Å]) of 5,6,7,8,13,13b-hexahydro-14*H*-bisindolo[3,2-*a*][2,3-*h*]quinolizine (**9**)

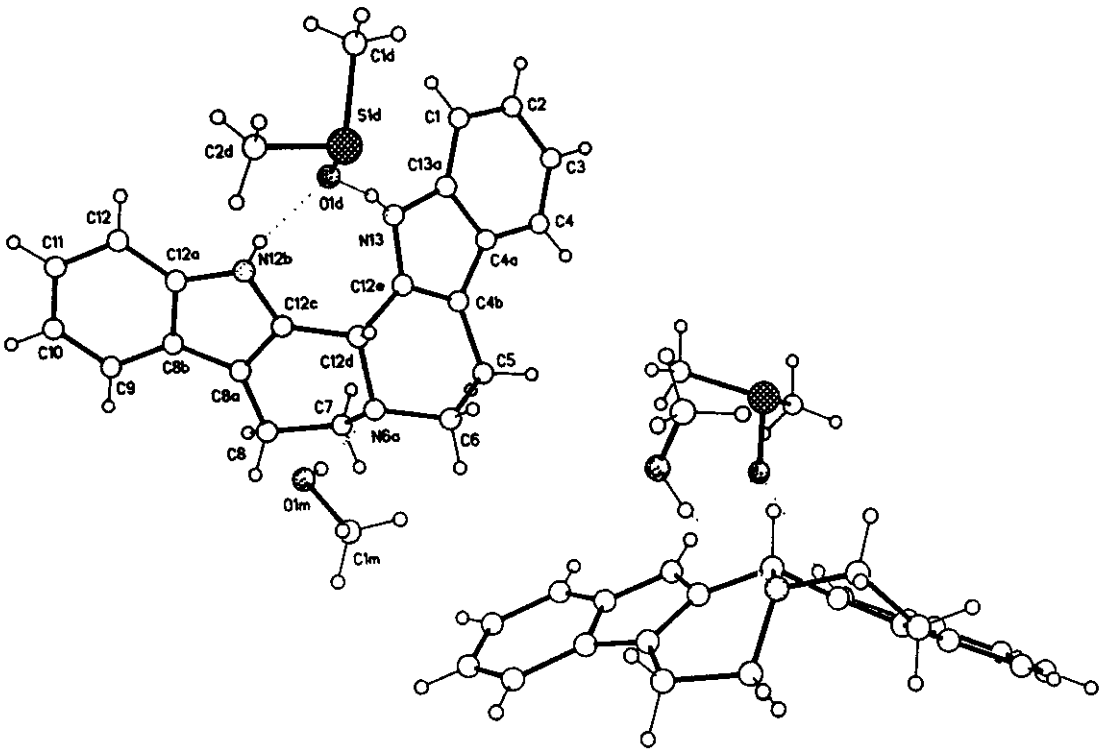


Figure 4: The structure of **9** resulting from X-ray analysis

EXPERIMENTAL

Melting points are uncorrected and are measured in open capillary tubes, using a Gallenkamp melting point apparatus. Spectral data are obtained on the following instruments: ir: Perkin-Elmer 1420; ^{1}H-nmr: Varian XL300 (300 MHz) and Bruker AC 200 (200 MHz); ^{13}C-nmr: Varian XL300 (75.43 MHz) and Bruker AC 200 (50.32 MHz); Mass spectroscopy: MS-30 and MS-50 of A.E.I., Manchester, England. The ionisation energy was 70 eV and the source-temperature was 180°C.

General procedure for preparing substituted 5,6,7,8,13,13b-hexahydrobenz[*a*]indolo[2,3-*h*]quinolizines

a) Lactamisation

20 Mmol of the lactone (**3**)[6,8] and 35 mmol of phenylethylamine are stirred at 190°C for 22 h. The water formed during the reaction is absorbed in a dropping funnel filled with molecular sieve. The mixture is cooled to 100°C and 10 ml of ethanol are added. At room temperature the tarry remainder is diluted with as much ethanol as necessary to generate a dispersion which can be stirred easily. After one night in the refrigerator the solid is filtered and washed with ethanol.

2-[2-(2-Methoxyphenyl)ethyl]-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-1-one (**4a**)

Yield: 4.0 g (62.5 %); sand coloured powder; mp: 195.5° - 198°C; ir (KBr): 3210 cm^{-1} (NH), 1630cm^{-1} (CO), ^{1}H-nmr: 11.5 (NH), 6.6-7.6 (m, 8H), 3.8 (s, 3H), 3.68 (t, 2H, J = 7 Hz), 3.57 (t, 2H, J = 7 Hz), 2.85 (t, 4H, J = 7 Hz); ms: 321 (10%), 320 (45%), 100 (100%), exact mass: 320.1517 (calcd for $C_{20}H_{20}N_2O_2$: 320.1525)

2-[2-(3-Methoxyphenyl)ethyl]-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-1-one (**4b**)

Yield: 4 54 g (71 %); sand coloured powder; mp: 167° -168.5°C; ir (KBr): 3250 cm^{-1} (NH), 1630cm^{-1} (CO); ^{1}H-nmr: 11.55(NH), 6.7-7.6 (m, 8H), 3.72 (s, 3H), 3.70 (t, 2H, J = 8 Hz); 3.65 (t, 2H, J = 7 Hz), 2.9 (t, 2H, J = 7 Hz), 2.85 (t, 2H, J = 8 Hz); ms: 320 (24%), 200 (16%), 199 (100%), exact mass: 320.1517 (calcd for $C_{20}H_{20}N_2O_2$: 320.1525)

2-[2-(4-Methoxyphenyl)ethyl]-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-1-one (**4c**)

Yield: 3.3 g (51%) sand coloured powder; mp: 208° - 211°C; ir (KBr): 3220 cm^{-1} (NH), 1630cm^{-1} (CO); ^{1}H-nmr: 11.5 (NH), 6.7-7.6 (m, 8H), 3.7 (s, 3H), 3.6 (t, 4H, J = 7 Hz), 2.87 (t, 2H, J = 7 Hz), 2.82 (t, 2H, J = 7 Hz); ms: 320 (33%), 200 (25%), 199 (100%), 186 (55%), exact mass: 320 1516 (calcd for $C_{20}H_{20}N_2O_2$: 320.1525)

2-[2-(3,4-Dimethoxyphenyl)ethyl]-2,3,4,9-tetrahydropyrido[3,4-*b*]indol-1-one (**4d**)

Yield. 4 33 g (61 %); sand coloured; mp: 199.5° - 201°C; ir (KBr): 3200 cm^{-1} (NH), 1630cm^{-1} (CO); ^{1}H-nmr: 11.5 (NH), 6.6-7.6 (m, 7H), 3.70 (s, 6 H), 3.60 (t, 4H, J = 7 Hz), 2.87 (t, 2H, J = 7 Hz), 2.82 (t, 2H, J = 7 Hz); ms. 350 (33%), 336 (9%), 199 (100%), 186 (60%), 164 (75%), exact mass: 350.1629 (calcd for $C_{21}H_{22}N_2O_3$: 350.1630)

b) Cyclisation and reduction to substituted 5,6,7,8,13,13b-hexahydrobenz[*a*]indolo[2,3-*h*]quinolizines (**5b**, **5d**)

5,6,7,8,13,13b-Hexahydro-3-methoxybenz[*a*]indolo[2,3-*h*]quinolizine (**5b**)

5 Mmol of lactam (**4b**) (1.6 g) in 15 ml of phosphorus oxychloride (0.16 mol) are stirred at 100°C for one day. The further preparation is performed analogous to the cyclisation and reduction of **5.** Yield· 0 69 g (45%); colourless rhombic crystals, mp: 130°C (decomp.); ir (KBr): 3320 cm^{-1} (NH), 1610 cm^{-1} (aromatic); ^{1}H-nmr· see Table 1; ^{13}C-nmr. see Table 3, ms: 305.16 (8.2%), 304.16 (70.5%), 303.15 (100%), exact mass: 304.1575 (calcd for $C_{20}H_{20}N_2O$: 304.1576).

5,6,7,8,13,13b-Hexahydro-2,3-dimethoxybenz[*a*]indolo[2,3-*h*]quinolizine (**5d**)

7.8 Mmol of lactam (**4d**) (2.75 g) in 30 ml of phosphorus oxychloride (0.32 mol) are stirred at 115°C for 1 h. The flask is cooled in an ice water bath and 100 ml of a 10% sodium hydroxide solution are very slowly added through a dropping funnel. The resulting solution is stirred overnight and filtered The dried residue is dissolved in 40 ml of methanol. At 0°C 2 g of sodium borohydride (53 mmol) are added during a period of half an hour. The solvent is evaporated in vacuo below 40°C. The residue is dissolved in 60 ml of water and worked up as usual (see cycl. of **5**). Yield: 0.67 g (37%), sand coloured powder; mp: 225-227°C (decomp.); ir (KBr): 3360 cm^{-1} (NH), 1610 cm^{-1} (aromatic); ^{1}H-nmr: see Table 1; ^{13}C-nmr: see Table 3, ms: 334.16 (87%), 333.16 (100%), exact mass: 334.1671 (calcd for $C_{21}H_{22}N_2O_2$. 334.1681).

Procedure for preparing 5,6,7,8,13,13b-hexahydrobenz[*a*]indolo[2,3-*h*]quinolizine (5)

a) Oxidation of isochroman to isochromanone (**6**)[10,11]

260 Mmol of isochroman (35.44 g) and 260 mmol of selenium dioxide (28.86 g) in 160 ml of xylene are refluxed overnight. After cooling the solid is filtered off. Again 260 mmol of selenium dioxide (28.86 g) are added to the filtrate and the mixture is refluxed for another 12 h After cooling the solid is filtered off and the solvent is evaporated in vacuo. The residue is purified by distillation (bp 117°C at 0.07 Torr; lit.,[10] 165° / 14 Torr C) to yield 22.3 g (76 %) of a bright yellow liquid. Ir (KBr): 1725 cm^{-1}, 1710 cm^{-1}, ^{1}H-nmr: 7.92 (dd, H^8, 7 Hz, J = 2 Hz), 7.8-7.4 (3H), 4.5 (t, $2H^3$, J = 6 Hz), 3.4 (t, $2H^2$, J = 6 Hz).

b) Lactamisation to 2-[2-(3-indolyl)ethyl]-3,4-dihydroisochinolin-2*H*(1)-one (**7**)

30 Mmol of isochromanone (4.44 g) and 75 mmol of tryptamine (12.02 g) are heated to 195°C overnight During this period the reaction water is absorbed in a dropping funnel filled with molecular sieve. Consequently the mixture is cooled to 90°C and 5 ml of methanol are added. At room temperature another 13 ml of methanol are added. After standing for a few hours the solid is filtered off. Yield: 5.2 g (65 %), white grey powder, mp: 156.5 °C; ir (KBr): 3360 cm^{-1} (NH), 1630 cm^{-1} (CO); ^{1}H-nmr: 7 92 (dd, H^8, J = 7 Hz, J = 2 Hz), 7.8-6.9 (8H), 3.8 (t, 2H, J = 7 Hz), 3.5 (t, 2H, J = 7 Hz), 2.97 (t, 2H, J = 7 Hz), 2.92 (t, 2H, J = 7 Hz) ; ms: 290 (27%), 160 (45%), 143 (100%), 130 (51%), exact mass: 290 1429 (calcd for $C_{19}H_{18}N_2O$· 290.1419).

c) Cyclisation and reduction to 5,6,7,8,13,13b-hexahydrobenz[*a*]indolo[3,2-b]quinolizine (**5**)

20 Mmol of lactam (7) (5.8 g) in 60 ml of phosphorus oxychloride (0.64 mol) are stirred at 45°C for 29 h. The flask is cooled in an ice water bath and 280 ml of a 10% sodium hydroxide solution are very slowly added through a dropping funnel. The resulting solution is stirred overnight and filtered. The dried residue is dissolved in 100 ml of methanol. At 0°C 10 g of sodium borohydride (265 mmol) are added during a period of half an hour. After stirring for 15 min the solvent is evaporated in vacuo. The residue is dissolved in 160 ml of water and thereafter extracted exhaustively with ether. The combined organic layers are washed with little water, dried with magnesium sulfate and evaporated in vacuo. The residue is crystallised from methanol to give 3.05 g (56 %) of colourless crystals, which change to bright yellow when exposed to daylight; mp: 167°-168°C; ir (KBr): 3440 cm^{-1}(NH), 1575, 1610 cm^{-1}(aromatic); ^{1}H-nmr: see Table 1; ^{13}C-nmr: see Table 3; ms: 275.15 (10.09%), 274 14 (85.04%), 273.14 (100%), exact mass 274.1463 (calcd for $C_{19}H_{18}N_2$: 274.1470)

Procedure for preparing 5,6,7,8,13,13b-hexahydrobisindolo[3,2-*a*][2,3-*h*]quinolizine (9)

a) Lactamisation

20 Mmol of pyranoindolone (**3**) (3.74 g) and 50 mmol of tryptamine (8.00 g) are heated overnight at 220°C in the analogous manner to the preparation of 7. The flask is allowed to cool entirely before 4 ml of ethanol are added. The resulting sticky solid is heated to 100°C and ethanol was added to complete solution (about 2 ml). After cooling to room temperature, further 6 ml of ethanol are added, the flask is shaken for a short time and filtered. The residue is washed with ethanol. 3.75 g (57%) of greyish white powder, which turns to light yellow on exposure to daylight; mp: 189-190°C; ir (KBr): 3380 cm^{-1} (NH), 3220 cm^{-1} (NH), 1630 cm^{-1} (CO); ^{1}H-nmr: 11.6 (s, indolylethyl-NH, D_2O exchangeable), 10.8 (s, NH), 7.8-6.8 (9H), 3.7 (t, 2H, J = 7 Hz), 3.6 (t, 2H, J =

7 Hz), 3.0 (t, 2H, J = 7Hz), 4.85 (t, 2H, J = 7 Hz); ms: 329 (61%), 199 (72 %), 143 (100%), 130 (45%), exact mass: 329 1522 (calcd for $C_{21}H_{19}N_3O$: 329 1528).

b) Cyclisation and reduction to 5,6,7,8,13,13b-hexahydro-14*H*-bisindolo[3,2-*a*][2,3-*h*]quinolizine (9)

20 Mmol of lactam (**8**) (6.6 g) and 60 ml of phosphorus oxychloride (0.64 mol) are refluxed for 1h. While cooling the flask on an ice bath 160 ml of water are very slowly added through a dropping funnel, which entails the formation of hydrogen chloride. The solid is filtered and the residue is dried. The crude product is solved in 100 ml of methanol and cooled on an ice bath. 10 g of sodium borohydride (265 mmol) are added during a period of half an hour. The resulting dispersion is refluxed for 1 h. The solvent is then evaporated and the residue is dissolved in 160 ml of water followed by extraction with ether. After usual working up, the solvent is removed in vacuo and the residue is recrystallised from methanol to give white needles, which are stable in the refrigerator. Yield· 2.28 g (37%), mp: 170°C (decomp.), mp (hydrochloride): 270-271°C. For X-ray analyses crystals were formed in dimethyl sulfoxide over a saturated methanolic atmosphere (exsiccator). Ir (KBr): 3520 cm^{-1}; ^{1}H-nmr. see Table 1 and Table 2; ^{13}C-nmr: see Table 3; ms: 313 16 (100%), 312.15 (98%); exact mass: 313.1577 (calcd for $C_{21}H_{19}N_3$: 313.1579).

X-ray analysis of 5

Diffraction data were collected on a Enraf Nonius CAD4 - diffractometer at 293 K with graphite monochromated CuKα radiation (λ = 1.54178 Å). The crystals (coloreless blocks, 0.35 × 0.40 × 0.50 mm^3) are triclinic, space group $P\bar{1}$ with 2 formula units $C_{19}H_{19}N_2$-2 CH_3OH in the unit cell: a = 9.945 (1) Å, b= 10.021 (1) Å, c= 10.18 (1) Å, α = 97.74 (1)°, β = 107 87 (1)°, γ = 106.50 (1)°, V= 945.4 (1) $Å^3$, ρ (calcd) = 1 19 g / cm^3, μ (CuKα) 0.60 mm^{-1}, F(000) = 364 There were 6341 reflections (2θ / ω-scan, scan range (0.42+0.22 tan θ)°, $2\theta_{max}$ = 140°) collected with 3587 independent (R_{int} = 0.024) and 3031 observed reflections (F > 4.0 σ (F)). The structure was solved with SHELXTL PLUS by direct methods and refined with full matrix-least squares refinement on F (236 parameters to R = 0.053 (R_W =0.068, $W^{-1} = \sigma^2 (F) + 0.0005 F^2$) The non-hydrogen atoms were refined anisotopically, H-atoms by using a riding model. The H (N) were refined free. An extinction correction was applied.

Table 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement coefficients ($Å^2 \times 10^3$) of **5** U(eq) is defined as one third of the trace of orthoganlized U_{ij} tensor

	x	y	z	U(eq)
C(1)	4315(2)	1469(2)	7029(2)	64(1)
C(2)	4497(3)	2040(3)	5954(2)	81(1)
C(3)	4118(3)	3226(3)	5751(2)	87(1)
C(4)	3569(2)	3854(2)	6597(2)	76(1)
C(4A)	3380(2)	3302(2)	7700(2)	58(1)
C(5)	2689(2)	3951(2)	8572(2)	72(1)
C(6)	2879(2)	3439(2)	9858(2)	65(1)
N(6A)	2506(2)	1870(1)	9559(1)	57(1)
C(7)	2404(2)	1274(2)	10727	67(1)
C(8)	3855(2)	1884(2)	11980	71(1)
C(8A)	5182(2)	2020(2)	11574	59(1)
C(8B)	6742(2)	2400(2)	12367	62(1)
C(9)	7579(3)	2753(2)	13764	80(1)
C(10)	9115(3)	3108(3)	14183	97(1)
C(11)	9842(3)	3142(3)	13266(3)	99(1)
C(12)	9066(2)	2792(2)	11892(3)	80(1)
C(12A)	7507(2)	2438(2)	11461(2)	61(1)
N(13)	6459(2)	2084(1)	10170(2)	56(1)
C(13A)	5065(2)	1844(2)	10251(2)	51(1)
C(13B)	3604(2)	1466(2)	9076(2)	50(1)
C(13C)	3774(2)	2113(2)	7905(2)	52(1)
O(1M)	7986(2)	2292(2)	8327(2)	118(1)
C(1M)	8389(3)	3619(3)	8036(3)	107(1)
O(2M)	-425(2)	753(2)	7739(2)	83(1)
C(2M)	-517(3)	314(3)	6406(3)	100(1)

Table 5: H-Atom coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^3$) of **5**.

	x	y	z	U(eq)
H(1)	4542	618	7164	75
H(2)	4903	1606	5372	95
H(3)	4242	3628	5012	104
H(4)	3289	4675	6442	89
H(5A)	1636	3722	8072	84
H(5B)	3158	4975	8801	84
H(6A)	2229	3694	10274	77
H(6B)	3899	3895	10480	77
H(7A)	2143	252	10473	77
H(7B)	1609	1468	10961	77
H(8A)	3840	1276	12599	84

H(8B)	3940	2815	12434	84
H(9)	7087	2744	12408	95
H(10)	9712	3375	15130	114
H(11)	10913	3363	13594	116
H(12)	9573	2819	11259	94
H(13)	6662(22)	2036(19)	9443(16)	66
H(13B)	3219	442	8741	58
H(1M)	8461(36)	1809(33)	8048(33)	141
H(1MA)	7954	4212	8441	127
H(1MB)	9464	4073	8379	127
H(1MC)	8004	3489	7073	127
H(2M)	542(19)	1129(25)	8276(22)	98
H(2MA)	-1551	-107	5811	120
H(2MB)	-22	1125	6126	120
H(2MC)	-28	-382	6375	120

X-ray analysis of 9

Diffraction data were collected on a Nicolet R3m-diffractometer at 293 K with graphite monochromated CuKα radiation (λ = 0.71073 Å). The crystals (0.90 × 0.70 × 0.40 mm^3) are orthorhombic, space group $Pna2_1$ with 4 formula units $C_{21}H_{19}N_3$- DMSO - CH_3OH in the unit cell: a = 21.365 (6) Å, b = 11.494 (2) Å, c = 9.030 (2) Å, V= 2218 (1) $Å^3$, ρ (calcd) = 1.27 g / cm^3, μ (CuKα) 0.17 mm^{-1}, F(000) = 904. There were 4025 reflections (ω-scan, scan range 1.20° + 2 θ_{max}= 50°) collected with 3883 independent (R_{int} = 0.039) reflections. The structure was solved with SHELXTL PLUS (VMS) by direct methods and refined with full matrix-least squares (281 parameters, 3 restraints) refinement on F^2 (SHELXL-93) to wR^2 = 0.111 ($w^{-1}= \sigma^2 (F_O)^2 + (0.0758P)^2$ with P = $(F_O^2 + 2 F_C^2) / 3$;R_1 = 0.040 for I > 2σ (I)). The non-hydogen atoms were refined anisotopically, H-atoms by using a riding model. The absolute structure was determined by refining the Flack parameter (X = -0.09 (8)). The H (N) were refined free.

Table 6: Atomic coordinates (× 10^4) and equivalent isotropic displacement coefficients ($Å^2$ × 10^3) of **9**. U(eq) is defined as one third of the trace of orthoganlized U_{ij} tensor

	x	y	z	U(eq)
C(1)	4914(1)	883(2)	-7(3)	43(1)
C(2)	4376(1)	291(2)	348(3)	51(1)
C(3)	3883(1)	211(2)	654(3)	51(1)
C(4)	3915(1)	739(2)	2023(3)	48(1)
C(4A)	4452(1)	1371(2)	2399(3)	39(1)
C(4B)	4651(1)	2005(2)	3682(2)	38(1)

C(5)	4359(1)	2148(3)	5172(3)	50(1)
C(6)	4866(1)	2480(2)	6281(3)	48(1)
N(6A)	5281(1)	3426(2)	5776(2)	40(1)
C(7)	4935(1)	4512(2)	5479(3)	47(1)
C(8)	5378(1)	5523(2)	5324(3)	49(1)
C(8A)	5890(1)	5188(2)	4277(2)	39(1)
C(8B)	6351(1)	5862(2)	3526(3)	40(1)
C(9)	6516(1)	7044(2)	3545(3)	52(1)
C(10)	7021(1)	7395(2)	2714(4)	66(1)
C(11)	7356(2)	6625(3)	1846(4)	65(1)
C(12)	7202(1)	5452(3)	1780(3)	55(1)
C(12A)	6703(1)	5092(2)	2649(3)	41(1)
N(12B)	6473(1)	3998(2)	2879(2)	39(1)
C(12C)	5985(1)	4068(2)	3871(2)	35(1)
C(12D)	5646(1)	3037(2)	4473(2)	34(1)
C(12E)	5234(1)	2404(2)	3389(2)	34(1)
N(13)	5416(1)	2074(2)	1988(2)	36(1)
C(13A)	4945(1)	1422(2)	1373(2)	36(1)
S(1D)	7270(1)	803(1)	2435(1)	52(1)
O(1D)	6782(1)	1707(2)	2214(4)	91(1)
C(1D)	7367(2)	123(3)	693(3)	64(1)
C(2D)	7988(2)	1550(3)	2522(5)	78(1)
O(1M)	6382(1)	3801(3)	7519(3)	89(1)
C(1M)	6344(2)	3220(4)	8835(4)	94(1)

Table 7: Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) of **9**.

	x	y	z	U(eq)
H(1)	5245(1)	924(2)	-672(3)	52
H(2)	4340(1)	-65(2)	-1269(3)	61
H(3)	3525(1)	-204(2)	397(3)	62
H(4)	3585(1)	676(2)	2689(3)	58
H(5A)	4160(1)	1426(3)	5473(3)	59
H(5B)	4041(1)	2750(3)	5136(3)	59
H(6A)	4668(1)	2717(2)	7199(3)	57
H(6B)	5118(1)	1799(2)	6490(3)	57
H(7A)	4645(1)	4662(2)	6284(3)	56
H(7B)	4694(1)	4427(2)	4575(3)	56
H(8A)	5156(1)	6197(2)	4947(3)	59
H(8B)	5554(1)	5721(2)	6282(3)	59
H(9)	6289(1)	7576(2)	4105(3)	63
H(10)	7140(1)	8173(2)	2736(4)	79
H(11)	7692(2)	6899(3)	1293(4)	78
H(12)	7423(1)	4935(3)	1185(3)	65
H(12B)	6633(12)	3389(21)	2621(33)	47

H(12D)	5961(1)	2483(2)	4825(2)	41
H(13)	5776(11)	2042(23)	1776(30)	43
H(1D1)	7706(7)	-423(15)	745(8)	96
H(1D2)	7458(11)	702(3)	-43(6)	96
H(1D3)	6989(4)	-278(17)	430(12)	96
H(2D1)	8324(2)	999(3)	2594(35)	117
H(2D2)	7991(6)	2049(21)	3375(20)	117
H(2D3)	8040(7)	2011(21)	1643(17)	117
H(1M)	6032(3)	3857(30)	7154(22)	134
H(1M1)	6035(11)	2616(19)	8760(12)	141
H(1M2)	6226(15)	3753(7)	9605(7)	141
H(1M3)	6743(5)	2882(25)	9066(18)	141

We would like to dedicate this paper to Prof. Dr.H.J. Roth, Tübingen, on the occasion of his 65th birthday.

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Received, 27th July, 1993