Chiral 1,4-Benzodiazepines. XII (1). Conformation in a Solution of 7-Chloro-5-phenyl-3(*S*)methyl-1,3-dihydro-2*H*-1,4-benzodiazepine

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Deuterium labeled congeners of 7-chloro-5-phenyl-3(*S*)-methyl-1,3-dihydro-2*H*-1,4-benzodiazepine (**8**), *i.e.*, compounds **9** and **16-18** were prepared and their lis-nmr spectra run. For computational studies compounds **9** and **16** were chosen. The results of lis measurements revealed that **16** is present in more than 97% in the boat-like conformation I (Scheme 3).

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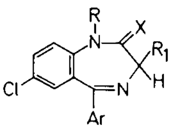
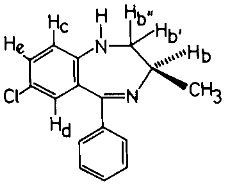
Introduction.

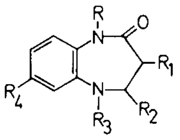
The lis-nmr in H^1-nmr spectroscopy has been used for determination of conformation in solution of one chiral 1,4-benzodiazepin-2-one (**1**) in the enantiomerically pure form (3), as well as for a series of achiral 2-oxo-derivatives **2-5** (4). Recently Aversa and others (5) have studied a group of 1,3,4,5,-tetrahydro-2*H*-1,5-benzodiazepines (**6-6G**), and have found that 2,4-dioxo compound **6** retains the boat conformation in solution, its 4-deoxo congeners **6A-6G** however, change their stable conformation into the chair conformation (6).



	R	R1	Ar	X
1	H	CH_3	Ph-d_5	O
2	H	H	Ph	O
3	CH_3	H	Ph	O
4	$CH_2C{\equiv}CH$	H	Ph	O
5	$(CH_2)_2N(CH_2CH_3)_2$	H	o-F-Ph	O
6	CH_3	H	Ph	2H



8



	R	R1	R2	R3	R4
6A	H	H	H	Ph	Cl
6B	Me	H	Me	Me	H
6C	H	H	Me	H	H
6D	H	H	Me	Me	H
6E	H	Me	H	Me	H
6F	H	H	H	H	H
6G	H	H	H	Me	H

Representatives of the above listed compounds possess high activity on the central nervous system (CNS), some of them are in current use as valuable psychotherapeutic agents (7,8). Therefore a study of the solution conformation of their "pharmacophoric" unit (9) might offer some new insight into their structure-activity relationships.

Proceeding our research on the C(3)-chiral 1,4-benzodiazepines we have undertaken a lis-nmr study of the 2-deoxy congener of **7**, *i.e.*, compound **8**, as the pure *S*-enantiomer. We were interested to find if there is the same absolute boat conformation present in the solution of both *S*-**7** and *S*-**8**, and if there is any significant contribution of some other possible conformations. These data are expected to contribute to the interpretation of our recent *in vitro* biological studies on enantioselectivity of binding on human serum albumine (HSA) of both enantiomers of **7** and **8**. While *S*-**7** exhibits much higher binding affinity then *R*-**7** (10, 11), for *S*-**8** and *R*-**8** very limited difference of binding parameters was found (12).

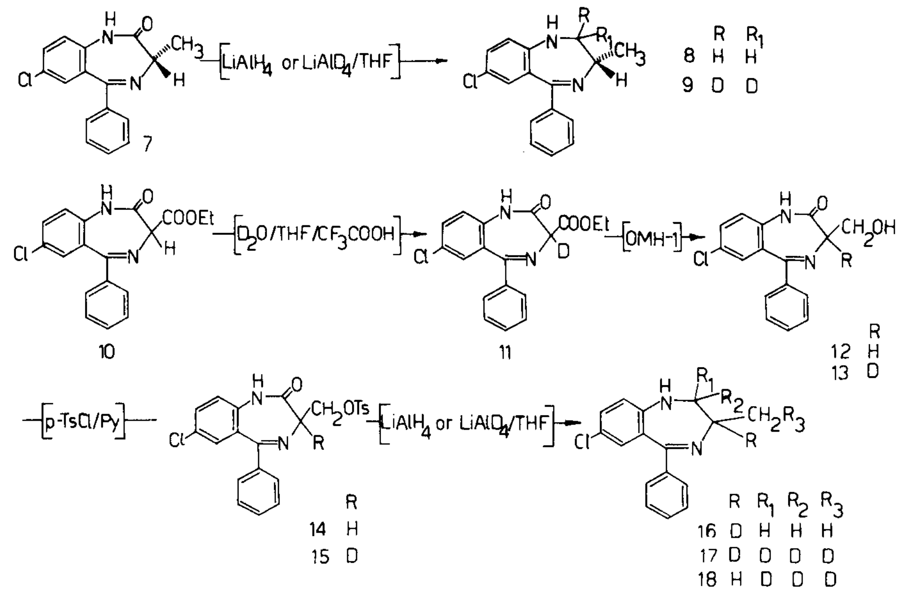
Results and Dicussion.

Since the seven membered ring protons of **8** present a rather complicated ^{1}H-nmr spectrum at 60 MHz, we prepared specifically deuterated congeners of this compound in order to use the lis-nmr method. Thereby it was anticipated that a conformational isotope effect is negligible, in view of the recent CD-studies, revealing that the energies which control the conformer distribution vary from 2-7 cal/mole/for β, and γ-deuterated cyclohexanones and cyclopentanones (13), to 10 ± 2 cal/mole (50.43% equatorial: 49.57% axial!) in α-deuterated cyclopentanone (14). It has also been observed (15) that the substitution of protons for deuterium atoms has a minor effect upon the value of the lanthanide induced shifts, since differences only up to 3% were generally noticed.

Synthetic Part.

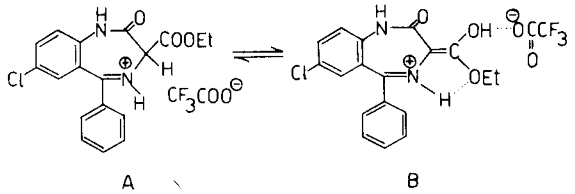
2-Oxo-1,4-benzodiazepines **7** and **10** have been used as the starting materials. Reduction of **7** with lithium aluminum hydride or deuteride afforded the compounds **8** and **9**, respectively. Compound **10**, however, has been utilized along two pathways, *i.e.*, either before or after

SCHEME 1



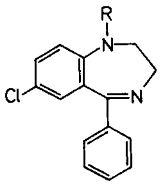
C(3)-H/D exchange into **11** (Scheme 1). On the basis of our earlier observation (16) of C(3)-H/D exchange in **10**, we optimized the reaction conditions for quantitative deuteration to **11**. Acid catalysis with trifluoroacetic acid-d$_1$ has been found particularly effective. We assume that the *N*(4)-protonated form of **10** undergoes very fast prototropic equilibrium $A \rightleftharpoons B$, according to Scheme 2.

SCHEME 2

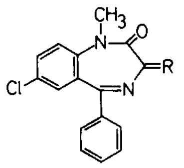


The uv spectra of the compound **10** in chloroform, however, did not reveal any change on addition of trifluoroacetic acid, or in DMSO as the solvent in comparison to those of the compounds **21** and **2** (Table I).

The spectra of compounds **10** and **2**, differing only in the small bathochromic shift of the long wave bands in relation to those of **21**, excluded the presence of the enolic forms of **10** or **11** in the solution. The equilibrium concentration of the tautomer *B*, which is presumably the reactive species for H/D exchange, should be very low.



	R
19	H
20	CH_3



	R
21	$=CH_2$

It is interesting to note that base catalysed double deuteration at C(3) in some 2-amino-3*H*-1,4-benzodiazepines has been recently described (17). However deuterium exchange in these compounds occurred *via* an amidine-enamine equilibrium.

To incorporate other deuterium atoms into **11** according to Scheme 1, carbinols **12** and **13** prepared by a modified procedure (18) were used as the starting

Table 1

Characteristic UV Maxima (nm) of the Compounds **2**, **10** and **21**.

Compound	DMSO		DMSO + trifluoroacetic acid (a)		chloroform		chloroform + trifluoroacetic hydrochloric acid	
2	258	318	258	317	242	312	—	—
10	258	318	258	318	241	315	241	314
21	260	312 (sh)	260	310 (sh)	242	308 (sh)	242	309 (sh)

(a) A few drops added to 10.0 ml of the 0.4 × 10^{-4} *M* solutions.

materials. Compound **13** was subsequently tosylated to **15**, while deuteration with concomitant deuterolysis of the tosyl group, using lithium aluminium deuteride, afforded **17**, in 69% overall yield. Reduction of **15** with lithium aluminium hydride afforded **16**, while **18** was obtained *via* the sequence **10** → **12** → **14**. Compound **21** has been isolated as the minor product along with **22**, when hydroxymethylation of **3** was preformed according to the procedure described (19).

Spectroscopic Part.

In the first step qualitative lis-nmr spectra were run for the compounds **9** and **16-18**. The lis spectra of the compounds **17** and **18** did not afford any obscure information about there position of the methyl group based on the shifts of the signals of its diastereotopic protons within the CH_2D moiety. Therefore, subsequent efforts were concentrated on the computation of the lis-spectra of the compounds **9** and **16**. The experiments were carried out by the incremental dilution method, using $Pr(fod)_3$-d_{27} as the shift reagent. The bound shifts were determined as already reported (3,20,21) and their values are given in the Table 2.

Table 2

Experimental Bound Shifts for Compounds **9** and **16** (a).

Proton or group of protons	**16**	**9**
H_a	1.00 (b)	1.00 (b)
CH_3	1.00	1.10
H_b	–	2.55
H_b'	1.15	–
H_b''	1.15	–
H_c	0.60	0.48
H_e	0.38	0.39

(a) Correlation coefficients are within the required limits. (b) All bound shifts are scaled with respect to H_a bound shift.

The experimental bound shifts were compared with those calculated from the McConnell-Robertson equation (22) $(3\cos^2\theta-1)/r^3)$ and the acceptability of the results was discussed in terms of the agreement factor (23) where unit-

Equation 1

$$R = [\Sigma_i\omega_i(obs_i-calc_i)^2/\Sigma_i\omega_i(obs_i)^2]$$

ary weights ($\omega i = 1$) were actually used. The binding of substrate of LSR was considered to be the 1:1 type, whereas 2:1 binding was excluded because of the bulkiness of the substrate, as already done for the conformation determination of **1** (3). The principal magnetic axis was taken along the direction of the lanthanide-donor atom bond. The methyl group shift (△H) was calculated as the mean of the contributions from twelve different positions of the methyl protons, using the formula (24):

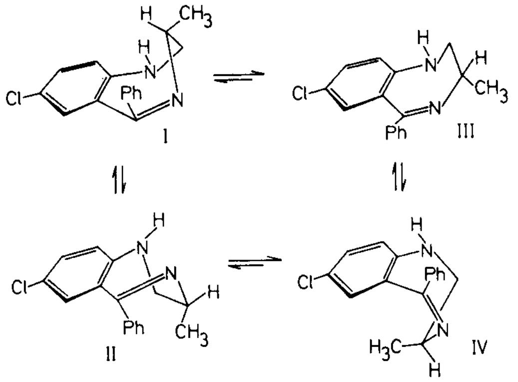
Equation 2

$$\triangle H = \sum_{i=1}^{12}(3\cos^2\theta_i-1/r_i^3)$$

The starting geometry of **8** was detemined from X-ray structural data for medazepam **20** (25). Standard bond lengths and bond angles (26) and dihedral angles were estimated from Dreiding models. (26).

In the first step of the calculations we tried to discriminate between two possible binding sites, *i.e.*, between N(1) and N(4). At this stage, calculations were carried out only for the two boat conformations of **16** (I and IV in the Scheme 3), since more data were available for it.

SCHEME 3



The R factor was minimized with respect to the parameters which definite the lanthanoid atom position, *i.e.*, ϱ,θ and ψ (Table 3).

Table 3

R (a) Factors for Compound **16**.

Conformation (b)	Binding site N(1)	N(4)
I	44.7	7.3
IV	30.1	26.8

(a) Values given in percentage. (b) According to the Scheme 3.

The only acceptable R value was obtained for conformation I, and for N(4) as binding site, rendering 95% probability for the presence of this conformation in the LSR-substrate complex (27). At this step we argued that, if at all, only a small ratio of the conformation IV can be expected in equilibrium, owing to the sterical hindrance of the methyl group in the pseudo axial position. Since the best agreement factor for I appeared to be considerably high, the possibility of equilibrium between I and IV was analysed. Furthermore from the inspection of the

Dreiding models it can be seen that the two "planar" conformations II and III are reached from conformations I and IV, respectively, by rotation about the N(1)-C(2) bond.

In the next step two other series of calculations for **16** were preformed. In the first, the bound shift (△H) of the protons in the seven membered ring was calculated as weighted means of the shifts of the conformers I and IV according to the formula:

$$\triangle H = n_I \triangle H_I + n_{IV} \triangle H_{IV}$$

wherein n_I and n_{IV} are the molar fractions of I and IV and where varied with increment of 0.05 between 0 and 1,ϱ,ψ and θ were employed as variable parameters in the minimization of R. Two minima were found, one for $n_I = 1.0$, $n_{IV} = 0.0$ (R = 7.3%), and another (R = 6.4%) for $n_I = n_{IV} = 0.5$. The second one was discarded as it required physically nonacceptable lanthanide-donor atom bond distance (4Å). Subsequently we optimized the starting geometry of the molecule by minimizing the R factor with respect to the dihedral angles within the seven membered ring, and those relative to the methyl group and the protons in the propylenic subunit. Their values (changed at maximum 5°), allowed an improvement of the R factor up to 3.6%. Starting from this geometry, a second series of calculations for **16** was carried out by keeping constant the percentage of conformations II and IV (1% each) while the percentage of I and III was varied stepwise between 98% and 0%, with increments of 5%, except in the range 98%-94% for I and 0%-4% for III where increments of 1% were employed. The agreement factor fell down to 3.3 for 97% of I and 1% of III; furthermore we found that its value did not change sensitively either if we eliminated conformations II and IV or if we included small percentage of them. It can be therefore concluded that conformations II, III and IV, if present, contribute in very small quantity. This result is in full agreement with unpublished results of Aversa *et al.*, who found that racemic **8** is present as only one conformer at room temperature, (28).

The same type of calculations for **9** confirmed those results, since satisfactory agreement factors were afforded as can be seen in Table 4.

As a final step we added H_b' and H_b'' bound shifts of **16** to those of **9** and with these seven data we minimized the R factor with respect to the dihedral angles of the seven membered ring and then with respect to ϱ,ψ and θ. As can be seen in Table 4 satisfactory R's were still obtained; a comparison between calculated and experimental bound

Table 4

R Factors and Differences Between Experimental and Calculated Bound Shifts for **9**, **16** and Overlapping of **9** and **16**.

Percentage conformers			**9**	**16**	**9** + $\triangle H_b'$, $\triangle H_b''$	**16** + $\triangle H_b$
I	100	(a) CH_3	0.03	0.10	0.02	0.03
II	0	δH_b	0.12	—	0.04	0.07
III	0	$\delta H_b'$	—	0.10	0.08	0.08
IV	0	$\delta H_b''$	—	0.12	0.01	0.00
		δH_c	0.04	0.01	0.09	0.02
		δH_e	0.02	0.07	0.04	0.05
		R (b)	4.5	3.5	4.6	4.6
I	99	δCH_3	0.02	0.01	0.01	0.00
II	0	δH_b	0.09	—	0.02	0.04
III	1	$\delta H_b'$	—	0.01	0.05	0.05
IV	0	$\delta H_b''$	—	0.02	0.01	0.00
		δH_c	0.03	0.08	0.09	0.03
		δH_e	0.02	0.03	0.04	0.04
		R	3.5	3.2	3.8	3.6

(a) $\delta = (\triangle H\text{exp} - \triangle H \text{ calcd})$; $\delta H_a = 0$, since $\triangle H_a$ is taken as reference. (b) Agreement factor in percentage.

Table 5

A Survey of H/D Exchange Experiments (**10** → **11**).

Run No.	Solvent	Deuterating agent	Mol ratio **10**/deuterium oxide	Temp./°C	Time/hours	Yield % on **11**	% D
1.	CF_3COOD	CF_3COOD	1:11	100	3	6	—
2.	CF_3COOD	D_2O	1:18	rt	24	(b)	26
3.	CF_3COOD	CF_3COOD	1:21	rt	22	—	26
4.	CF_3COOD	CF_3COOD	1:22	100	2	—	62
5.	DMSO	D_2O	1:18	rt	24	—	30
6.	DMSO	D_2O	1:18	60	3-6	—	46-47
7.	DMSO	D_2O	1:11	60	4	—	53
8.	DMSO	D_2O	1:18	60	4	56	70-80
9.	DMSO	D_2O	1:18	60	4	(b)	100
10.	DMSO	D_2O	1:18	60	4	82	100
11.	Acetone	D_2O	1:18	80	22	(b)	30
12.	THF	D_2O	1:18	85-90	5	—	63
13.	THF	D_2O	1:18	85-90	21	95	90-100
14.	THF	D_2O	1:18	85-90	22	97	100
15.	THF	D_2O	1:18	85-90	24	100	100

(a) In the runs 7,8,10-15 catalytic quantities (2-3 drops) of CF_3COOD were added. (b) Not isolated, incorporation of deuterium monitored by the nmr.

shifts shows that $\triangle H_b''$ fits well to the data of **9**, with discrepancy of 0.01. Instead $\triangle H_b''$ gives a worse fitting ($\triangle H_{esp}$- $\triangle H_{calc}$ = 0.08 or 0.05 see (Table 4). A certain discrepance appears of $\triangle H_c$.

The same overlap of data was performed for compound **16** by adding $\triangle H_b$ of **9**, and the R factor obtained was still satisfactory with an acceptable deviation between the experimental and calculated values of $\triangle H_b$ (0.07 or 0.04). Therefore, although the R factors are slightly enhanced when overlapping the data of **9** and **16**, the conformation provided is that afforded by calculations for **9** and **16** separately, thus confirming the proposed conformation for **8**.

In conclusion it could be stated that chiral compound **8** is present in solution largely in the conformation I (Scheme 2). Since we already found (3) that its 2-oxo analogue possesses the same absolute conformation in solution, it is worth noticing that the reduction of the amide carbonyl group does not perturb substantially the 7-membered ring conformation.

It remains to be determined experimentally *e.g.*, by dynamic-nmr which group of C(3)-chiral compounds has the higher ring-inversion barrier and how much higher. Similar CNS activity profile of 2-oxo and 2-deoxo-benzodiazepines (7,8) and their dissimilar binding properties for HSA (10,12) obviously cannot by explained only by conformational considerations.

EXPERIMENTAL

Melting points were determined on a Kofler microheating stage (Boetius) and are not corrected. Infrared spectra (potassium bromide discs) were obtained with a Perkin Elmer M297 spectrophotometer. The nmr spectra were run, and lis measurements preformed on a Perkin Elmer R 12 instrument, equipped with internal lock facilities. Shifts are given in ppm values downfield from TMS. Tlc was performed on aluminum plates precoated with Merck's silica gel 60F_{254}. Column chromatography was run over granular silica gel (0.05-0.2 mm) from Merck. Organic extracts were regularly dried over sodium sulfate and evaporated *in vacuo*.

The lis-nmr measurements have been preformed with $Pr(fod)_3d_{27}$, from Aldrich (Uvasol grade), which was purified prior to use by sublimation at 0.1 mmHg. All measurements were performed for the range of substrate concentration between 0.2 *M* and 0.08 *M*, while the concentration of $Pr(fod)_3$ was kept constant (0.008 M). All manipulations with this reagent solvents and deuterated compounds were carried out in a glove-box, which was continuously flushed with dry nitrogen. Other experimental calculation conditions are recently described (3,20). Compound **1** has been prepared and purified as described in reference (29), compounds **10** and **12** as described in references (13).

7-Chloro-5-phenyl-3(*S*)-methyl-1,3-dihydro-2*H*-1,4-benzodiazepine (**8**).

To the suspension of lithium aluminium hydride (2.0 g, 52.7 mmoles) in dried tetrahydrofuran (200 ml), a solution of the compound **7** (7.0 g, 24.0 mmoles) in tetrahydrofuran (100 ml) was added dropwise maintaining a reflux of the solvent. Thereafter the reaction mixture was heated under reflux for 20 minutes and then 2 ml of water was added under ice cooling. The inorganic precipitate was filtered off, washed with tetrahydrofurane (2 × 20 ml), then with methylene chloride (10 ml) and the filtrate evaporated to dryness. After chromatography of 150 g silica gel column using ether as eluent, 5.2 g (80%) of the product **8** was obtained, which on recrystallization from diisopropyl ether afforded pure **8**, mp 128-129° $[\alpha]_d^{22} = +362°$ (c = 1.0 in chloroform): ir 3350, 2950, 2900, 1605, 1570, 1480, 1440 cm^{-1}; nmr (deuteriochloroform): 1.5 (d, 3H, CH_3), 3.4-4.2 (m, 3H), 6.4-7.9 (m, 8H, ArH).

Anal. Calcd. for $C_{16}H_{15}ClN_2$ (270.753): C, 70.97; H, 5.58; N, 10.35. Found: C, 70.96; H, 5.70; n, 10.55.

7-Chloro-5-phenyl-3(*S*)-methyl-1,3-dihydro-2,2-dideuterio-1,4-benzodiazepine (**9**).

Using the same conditions as described for **8**, compound **1** has been reduced with lithium aluminium deuteride into **9** in 84% yield, mp 125-126°; ir: 3370, 2970, 1612, 1575, 1470, 1448, 1370, 1305, 1290, 1240, 1090, 820, 700 cm^{-1}; nmr (deuteriochloroform): 1.48 (d, 3H, CH_3), 3.80 (q, 1H), 6.4-7.8 (m, 8H, ArH).

Anal. Calcd. for $C_{16}H_{17}ClN_2$ (272.769): C, 70.45; H, 6.28; N, 10.27. Found: C, 70.32; H, 5.98; N, 10.44.

7-Chloro-5-phenyl-3-carboxyethyl-3-deuterio-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**11**).

To the solution of **10** (5.0 g, 14.5 mmoles) in absolute tetrahydrofurane (50 ml) deuterium oxide (10 ml) and trifluoroacetic acid-d$_1$ (10-15 drops) was added. The slightly yellow solution was heated under reflux for 24 hours. After evaporation of the solvent the solid obtained was dried *in vacuo* (0.02 mm Hg, over phosphorus pentoxide) for 24 hours, affording **11** (5.01 g, quantitative), mp 219-220°. On recrystallization from acetonitrile (70 ml) which contained 2% deuterium oxide, white crystals of pure **11** (3.4 g, 70%) were obtained, mp 229-231°; ir: 3330, 1750, 1600, 1475, 1440, 1310, 1295, 1265, 1095, 835, 700 cm^{-1}; nmr (pyridine-d$_5$): 1.25 (t, 3H, CH_2CH_3), 4.45 (q, 2H, CH_2CH_3), 7.25-7.95 (m, 8H, ArH), 12.45 (s, 1H, NH), no observable signal at 5.05 ppm for C(3)H.

Anal. Calcd. for $C_{18}H_{16}ClN_2O_3$ (343.78): C, 62.88; H, 4.69; N, 8.15. Found: C, 62.84; H, 4.43; N, 8.04.

Some experiments which illustrate the effect of reaction conditions on the rate and degree of H/D exchange are summed up into Table 5.

Table 5

7-Chloro-5-phenyl-3-hydroxymethyl-3-deuterio-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**13**).

25% solution of sodium diethyldihydroaluminate (OMH-1, from Aldrich) in toluene (15 ml) was diluted with absolute tetrahydrofuran (30 ml) under continuous nitrogen flow at -5° to 0°. Then compound **11** (2.74 g, 8.0 mmoles) dissolved in tetrahydrofuran (50 ml) was added dropwise during 1 hour. The reaction was complete after 30 minutes at room temperature. The solution was then poured into 200 ml of ice-water. Organic solvent was evaporated *in vacuo* at 30°, the aqueous phase was extracted with ethyl acetate (3 × 50 ml), the organic extracts were dried and evaporated to dryness. Crude material was crystallized from acetone to afford 2.04 g (85%) of pure **13**, mp 200-201°; ir: 3340, 1680, 1603, 1595, 1470, 1325, 1035, 830, 690 cm^{-1}; nmr (pyridine-d$_5$): 4.77 (d, 2H), 5.11 (d, 1H, OH), 7.0-7.9 (m, 8H, ArH), 11.9 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{14}ClN_2O_2$ (301.74): C, 63.68; H, 4.68; N, 9.28. Found: C, 63.82; H, 4.58; N, 9.42.

7-Chloro-5-phenyl-3-(*p*-toluenesulfonyl)methyl-2*H*-1,3-dihydro-1,4-benzodiazepin-2-one (**14**).

Compound **12** (1.89 g, 6.3 mmoles) was dissolved in dry pyridine (25 ml) and to the resulting solution tosyl chloride (1.33 g, 17 mmoles) was added at room temperature. The reaction was followed by tlc using the solvent system methylene chloride-ethyl acetate (2:1) and was found to be completed after 2 hours. The reaction mixture was poured into ice-water (200 ml) which contained 4.5 ml of concentrated sulfuric acid. After chilling on ice for 1 hour separated crystals were collected on a filter and washed with water until neutral. On drying *in vacuo* 2.50 g (88%) of crude **14** was obtained which on recrystallization from dioxane had mp 183-185°; ir: 3200, 1680, 1355, 1180, 985 cm^{-1}; nmr (DMSO-d$_6$): 2.45 (s, 3H, $ArCH_3$), 4.1-4.5 (braod s, 1H), 7.2-8.1 (m, 12 H, ArH), 10.9 (s, 1H, NH).

Anal. Calcd. for $C_{22}H_{19}ClN_2O_4$ (442.90): C, 58.07; H, 4.31; N, 6.32. Found: C, 57.87; H, 4.15; N, 6.06.

C(3)-Deuterio-compound **15** has been prepared from **13** as described for **14**, mp 183-185°, nmr (DMSO-d$_6$): no signal at 4.1-4.5 ppm for C(3)H.

Anal. Calcd. for $C_{22}H_{20}ClN_2O_4S$ (443.91): C, 59.51; H, 4.54; N, 6.32. Found: C, 59.40; H, 4.71; N, 6.17.

7-Chloro-5-phenyl-3-methyl-2,2,3,3,'-tetradeuterio-1,3-dihydro-2*H*-1,4-benzodiazepine (**17**).

Compound **15** (2.28 g, 5.0 mmoles) was slurried in absolute tetrahydrofuran (50 ml) and lithium aluminium deuteride (1.16 g, 27.6 mmoles) was added portionwise using a Schlenk-tube under inert atmosphere of nitrogen and cooling the reaction mixture with ice-water. With ether as eluent the formation of 2,2-dideuterio intermediate (yellow spot, $R_f \sim 0.9$) could be indicated on tlc, then slow formation of the product **11** (yellow spot, $R_f \sim 0.45$) begain. After 16 hours stirring at room temperature the starting **15** disappeared (fluorescence spot, $R_f \sim 0.7$), as well as the intermediate compound at $R_f \sim 0.9$. Water. (2.2 ml) was added dropwise at 0° and the crystalline precipitate formed. It was suctioned off, washed with tetrahydrofuran (2 × 10 ml) and methylenechloride (10 ml). The filtrate was evaporated to dryness and purified on a column (45 g silica gel) with ether as the eluent. It was collected and 0.95 g (69%) of pure **17** was obtained which was crystallized from diisopropyl ether, mp 126-127°; ir: 3315, 3240, 2185, 2090, 1610, 1568, 1475, 1315, 1305, 1262, 1235, 812, 745, 695 cm^{-1}; nmr (deuteriochloroform): 1.41 (s, 2H, CH_2D), 3.8 (broad s, 1H, NH), 6.5-7.8 (m, 8H, ArH).

Anal. Calcd. for $C_{16}H_{19}ClN_2$ (274.78): C, 69.93; H, 6.97; N, 10.19. Found: C, 69.88; H, 6.71; N, 10.25.

7-Chloro-5-phenyl-3-methyl-3-deutero-1,3-dihydro-2*H*-1,4-benzodiazepine (**16**).

Compound **16** has been prepared from **15** as described for **17**, using lithium aluminium hydride, however. The same isolation procedure afforded **16** in 76% yield, mp 128-129° (on recrystallization from diisopropyl ether); ir: 3320, 3240, 3060, 2860, 1605, 1565, 1482, 1370, 1285, 1235, 810, 765, 738, 695 cm^{-1}; nmr (deuteriochloroform): 1.42 (s, 3H, CH_3), 3.35-4.1 (m, 2H and NH), 6.5-7.8 (m, 8H, ArH).

Anal. Calcd. for $C_{16}H_{16}ClN_2$ (271.76): C, 70.71; H, 5.92; N, 10.30. Found: C, 70.56; H, 6.11; N, 10.08.

7-Chloro-5-phenyl-3-methyl-2,2,3'-trideuterio-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**18**).

This compound has been prepared from **14** as described for the preparation of **17** from **15**, yield 86%, mp 126-127°; nmr (deuteriochloroform): 1.42 (d, 2H, CH_2D), 3.82 (broad s, 1H and NH), 6.6-7.75 (m, 8H, ArH).

Anal. Calcd. for $C_{16}H_{18}ClN_2$ (273.777): C, 70.19; H, 6.63; N, 10.23. Found: C, 70.08; H, 6.60; N, 10.10.

7-Chloro-5-phenyl-3-methylene-1-methyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**21**).

Compound **3** (2.0 g, 7.03 mmoles), paraformaldehyde (4.0 g) and 40% sodium hydroxide (0.2 ml) were dissolved in 40 ml of 96% ethanol and the reaction mixture heated under reflux for 16 hours. Then solvent was evaporated to dryness, the residue slurried in water (50 ml) and extracted with chloroform (3 × 50 ml). The dried extracts were evaporated and the residue chromatographed on 150 g of silica gel with methylene chloride-acetone (9:1) as the eluent. In the fractions 38-53 (10 ml per fraction) 245 mg of the pure **21** (12%) was obtained on recrystallization from ethanol, mp 138-139°; ir: 1660, 1625, 1610, 1475, 1395, 1315, 1210, 1115, 972, 900, 835, 820, 695 cm^{-1}; nmr (deuteriochloroform): 3.42 (s, 3H, NCH_3), 4.98-5.24 (d, J = 14 Hz, 2H), 7.2-7.9 (m, 8H, ArH).

Anal. Calcd. for $C_{17}H_{13}ClN_2O$ (296.75): C, 68.80; H, 4.41; N, 9.43. Found: C, 68.71; H, 4.16; N, 9.70.

From the fractions 70-110, 3-hydroxymethyl derivative **22** was isolated (1.22 g, 55%) which on recrystallization from ethanol had mp 230-233° [literature (19) mp 229-231°, obtained on hydrogenation of the 3-hydroxymethylene congener].

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