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THE MOLECULAR AND CRYSTAL STRUCTURE OF 1,2-DIAZEPINES AND THEIR CONFORMATIONAL MOBILITY IN SOLUTION[1]

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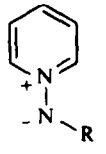
Abstract—X-ray diagrams of 1,2-diazepines showed them to be boat-shaped molecules with a localized imine double-bond. Variable temperature NMR and variable temperature CD of the optically active 1,2-diazepine (**15**) indicated the existence of a fast equilibrium between the two boat shaped diastereoisomeric conformations. In the iron-tricarbonyl complex (**6**) of the 1-isopropoxycarbonyl 1,2-diazepine (4) the seven-membered ring is bent by 40° along the C(4)—C(7) line.

INTRODUCTION

[1-H]-1,2-DIAZEPINES (**3**) WERE SYNTHESIZED for the first time in 1968 by means of a photoinduced rearrangement of 1-iminopyridinium ylides (**1**).[2] The structure of the seven-membered ring in these compounds (**3**) could be proven unambiguously by spectral analysis (NMR, UV and IR), as well as by a chemical correlation.[2–5] However, since 1,2-diazepines formally bear 8 π electrons in the ring, it was of interest to further investigate the structural and conformational features.

In order to gain information about the overall conformation of the [1-H]-1,2-diazepine ring and about the localized character of the imine double bond, several 1,2-diazepine derivatives were examined by X-ray diffraction. Low temperature NMR and variable temperature circular dichroism (CD) were applied to two optically active 1,2-diazepines in order to demonstrate their conformational mobility.



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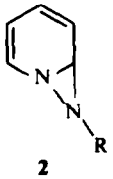

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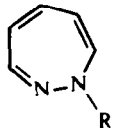

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The molecular and crystal structure of 1-*tosyl* 1,2-*diazepine* (**5**). (*R. Allmann*)

The first compound to be examined was 1-isopropoxycarbonyl 1,2-diazepine (**4**) (**1** in Table 1). Unfortunately, it decomposed during X-ray irradiation (CuK_α) within 8 to 12 hr. Therefore the more stable iron-tricarbonyl complex (**6**) (compound **2** in

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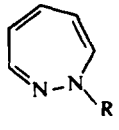
Table 2) was chosen for further studies. The structure of the complex could be refined to an R-index of 4·5% and the diazepine ring was found to be linked to the iron atom through its butadiene moiety —C(4)=C(5)—C(6)=C(7)— in a Diels–Alder like cycloaddition. The complex diazepine ring is bent along the C(4)—C(7) line by 40° and the isopropoxycarbonyl part of the molecule is nearly in plane with the [C(7)—N(1)—N(2)—C(3)—C(4)] moiety. This results in a nearly planar surrounding to N(1) and indicates that N(1) is in an sp^2 hybridization. N(1) lies only 0·065 Å out of the plane —N(2)—C(7)—C(8)— formed by its three neighbours.

The same molecular structure was previously found for the analogue iron-tricarbonyl complexes of 1-methoxycarbonyl-azepine[7,8] and 1-H-azepine.[9] In contrast

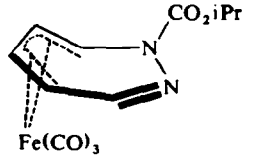
TABLE 1. CRYSTAL DATA OF EXAMINED 1,2-DIAZEPINES $C_5H_5N_2$—R

R	1 —$CO_2 \cdot C_3H_7$	2 —$CO_2 \cdot C_3H_7 \cdot Fe(CO)_3$	3 —$SO_2 \cdot C_6H_4 \cdot CH_3$	4 —$SO_2 \cdot C_6H_4 \cdot CH_3$
a(Å)	8·29	12·277 ± 3	12·179 ± 4	9·96
b(Å)	19·22	17·241 ± 5	16·547 ± 5	17·54
c(Å)	6·05	6·639 ± 2	5·914 ± 2	8·03
β(deg)	90	101·60 ± 5	90	113
V(Å^3)	999·1	1376·6	1191·8	1291
Space group	$P2_12_12_1$	$P2_1/n$	$P2_12_12_1$	$P2_1$?
M(amu)	180·2	320·1	248·3	248·3 + x
Z(mol·/cell)	4	4	4	4
mp(deg)	56–57	104–105	166	(166?)
D_m(g·cm^{-3})	1·19 ± 2	1·53 ± 2	1·38 ± 1	?
D_x(g·cm^{-3})	1·20	1·545	1·384	1·28?
colour	orange	yellow	yellow	yellow
shape	needles ‖ c	laths ‖ c	plates ‖ (100)	plates

the free 1-(*p*-Br-benzensulfonyl)-azepine was found to exist in a "boat" conformation with definitely localized double bonds at C(2)—C(3), C(4)—C(5) and C(6)—C(7), N(1) deviating by 0·22 Å from the plane defined by C(2), C(7) and S. This rather small deviation from planarity implies substancial sp^2 character admixed to the sp^3-state of the nitrogen atom in the azepine ring.[7,8]



4 R = CO_2iPr
5 R = Ts



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To see whether the same holds true for the 1,2-diazepine ring, crystals of uncomplexed 1-tosyl-1,2-diazepine (**5**) were studied. The first crystal, out of a batch of material recrystallized from diethylether, turned out to be monoclinic (**4**, Table 1), whereas most of the other crystals were orthorhombic (**3**, Table 1). The monoclinic cell is about 100 Å^3 greater than the orthorhombic one (both Z = 4) and it seems to contain some additional small molecule the nature and the amount of which are not known. Furthermore, the monoclinic cell contains two diazepine molecules per

TABLE 2. FINAL ATOMIC PARAMETERS OF 1-TOSYL-1,2-DIAZEPINE

The standard deviations for x,y,z refer to the last given digits. $\bar{\sigma}$(xyz) is the absolute average s.d. for x,y and z. The βik-values of the expression $(h^2 \cdot \beta_{11} + \ldots + 2hk \cdot \beta_{12} + \ldots)$ are converted into Bik-values (in Å^2, Bik = βik·4/($a_i^* \cdot a_k^*$)). The 6 Bik-values have nearly equal standard deviations, which are averaged as $\bar{\sigma}$(B)

Atom	x	y	z	$\bar{\sigma}$(xyz) (10^{-3} Å)	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}	$\bar{\sigma}$(B) (Å^2)
N(1)	0·35150 (18)	0·36216 (14)	0·28913 (39)	2	3·00	2·82	3·00	0·02	0·18	−0·32	0·09
N(2)	0·29850 (21)	0·43298 (14)	0·38215 (49)	3	3·73	3·45	4·53	0·11	0·30	−1·03	0·10
C(3)	0·19823 (27)	0·42146 (20)	0·41905 (64)	4	3·72	4·27	5·10	0·41	0·35	−1·12	0·14
C(4)	0·12994 (25)	0·35172 (19)	0·36353 (61)	4	3·22	4·50	4·73	0·06	0·42	0·27	0·14
C(5)	0·13899 (26)	0·31036 (19)	0·17237 (64)	4	3·33	4·18	5·00	−0·27	−0·75	−0·02	0·14
C(6)	0·22371 (29)	0·32166 (20)	0·00647 (59)	4	4·91	4·71	3·47	0·33	−0·43	−0·22	0·15
C(7)	0·32415 (24)	0·34787 (18)	0·05782 (51)	3	3·75	3·78	2·69	0·03	−0·49	−0·00	0·11
S	0·48285 (5)	0·36067 (4)	0·35674 (12)	1	2·79	2·80	2·59	0·05	0·12	0·18	0·02
O(1)	0·48742 (19)	0·36473 (14)	0·59630 (37)	2	4·64	5·50	3·46	−0·50	−0·09	0·65	0·09
O(2)	0·52558 (17)	0·29139 (12)	0·24100 (40)	2	3·92	3·14	4·97	0·60	0·36	0·27	0·09
C(11)	0·54504 (22)	0·44794 (16)	0·24536 (49)	3	2·60	2·64	2·69	−0·13	−0·16	−0·00	0·10
C(12)	0·53826 (24)	0·52059 (17)	0·36379 (56)	3	3·72	3·61	3·28	0·21	0·04	−0·65	0·12
C(13)	0·58667 (25)	0·58871 (18)	0·27245 (62)	3	3·49	3·27	4·54	0·18	0·03	−0·95	0·12
C(14)	0·64046 (23)	0·58599 (16)	0·06803 (57)	3	2·83	2·87	4·45	−0·10	−0·17	0·14	0·11
C(15)	0·64594 (23)	0·51300 (18)	−0·04761 (55)	3	3·05	3·58	3·38	−0·15	0·31	−0·11	0·11
C(16)	0·59803 (22)	0·44389 (16)	0·04041 (51)	3	3·02	2·87	2·76	−0·25	−0·05	−0·56	0·10
C(17)	0·69185 (32)	0·66085 (20)	−0·03125 (79)	4	5·29	3·79	7·11	−0·70	1·12	0·21	0·17
H(3)	0·1565 (33)	0·4625 (23)	0·5040 (87)	43	6·90	7·26	9·90	0·49	−1·63	−4·34	2·53
H(4)	0·0689 (35)	0·3423 (25)	0·4682 (73)	42	8·20	8·13	6·64	1·60	0·76	3·70	2·52
H(5)	0·0897 (29)	0·2747 (26)	0·1343 (71)	40	5·68	8·62	6·91	0·30	3·26	−0·53	2·33
H(6)	0·2123 (33)	0·3196 (23)	−0·1397 (71)	40	7·06	8·71	7·93	−2·73	3·66	2·42	2·51
H(7)	0·3785 (27)	0·3584 (21)	−0·0380 (64)	35	3·75	6·14	6·00	0·84	1·61	−0·33	1·84
H(12)	0·5068 (28)	0·5232 (20)	0·5199 (68)	36	5·51	4·39	6·70	−1·49	−1·57	1·80	1·88
H(13)	0·5792 (27)	0·6391 (21)	0·3682 (64)	35	5·05	5·95	5·88	0·78	2·34	1·18	1·97
H(15)	0·6799 (26)	0·5121 (18)	−0·1936 (56)	32	5·77	3·70	3·90	0·11	0·22	−0·49	1·71
H(16)	0·5984 (22)	0·3973 (18)	−0·0442 (54)	30	3·08	4·51	3·40	−1·45	−0·19	1·71	1·56
H(17)	0·6981 (43)	0·6633 (25)	−0·1874 (84)	48	11·67	8·78	8·79	−2·19	−0·14	0·01	2·95
H(18)	0·6505 (35)	0·7024 (30)	−0·0337 (90)	49	9·33	9·86	11·36	1·53	6·18	1·65	3·01
H(19)	0·7512 (34)	0·6734 (24)	0·0757 (79)	43	7·36	8·37	10·38	−1·52	−4·11	3·20	2·69

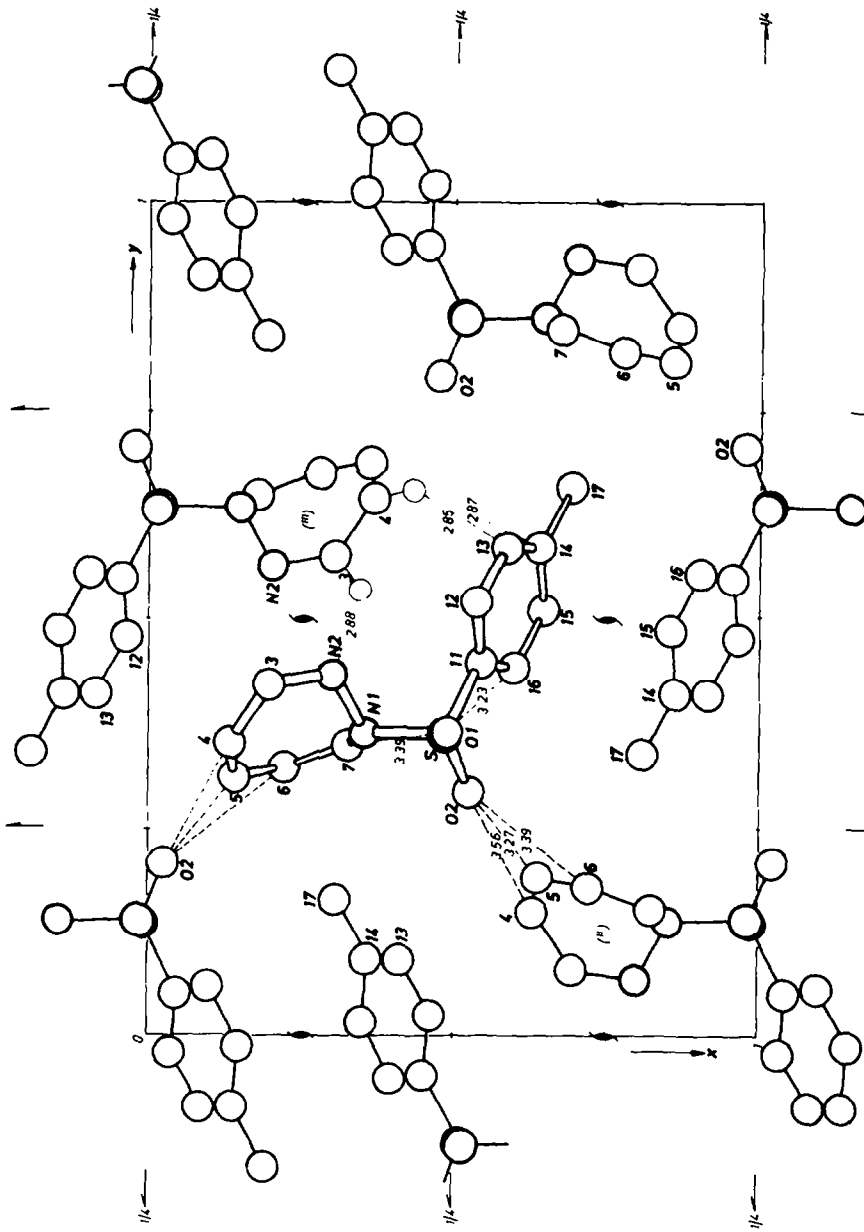
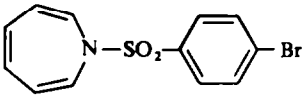


FIG 1. 1-Tosyl-1,2-diazepine **5**. View of the molecular packing along the c-axis. Most of the hydrogen atoms are omitted. The numbering of the atoms is the same as in Table 2. (For "and" see text)

asymmetric unit, assuming $P2_1$ to be the correct space group. Therefore the monoclinic phase was not further examined. The results for the orthorhombic phase of 1-tosyl-1,2-diazepine is discussed and compared with similar compounds below.

Two crystals of the orthorhombic modification of 1-tosyl-1,2-diazepine (3 in Table 1) were used for intensity measurements on an automatic two-circle diffractometer and for Weissenberg films. The prominent crystal faces were {100}, {101} and {120}. One crystal was set along [001] (dimensions about 0·21-0·38-0·65 mm^3 parallel to a, b, c), the other along [100] (0·20–0·61–0·60 mm^3). 1127 independent reflections could be measured with Ni-filtered CuK_α-radiation in the range until $\theta = 60°$: 227 more reflections in the range 60–70° were visually estimated from Weissenberg-films hk0–hk5 and 0kl–11kl. Out of these 1354 independent reflections, 101 were below the limit of observation. After LP-correction, the F^2- values were



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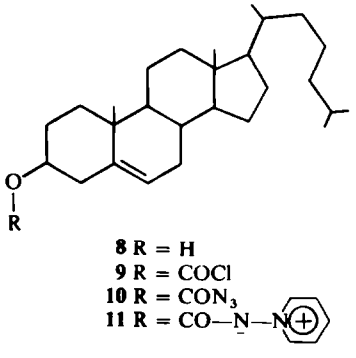
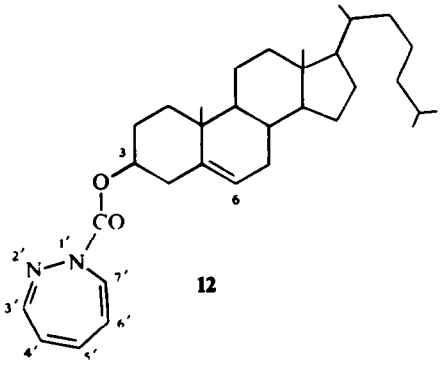
scaled to a common scale and averaged. No absorption correction has been applied ($\mu = 23{\cdot}0\ cm^{-1}$).

A Patterson map, somewhat sharpened with $\exp(3 \cdot \sin^2\theta/\lambda^2)$, showed clearly all S–S Harker-peaks and most S–X peaks well resolved (X=C, N, O). So the coordinates of all non-hydrogen atoms could be taken from this Patterson map, resulting in a starting R-index of 25%. Only the chemical nature of N(2) and C(7) could not be



8 R = H
9 R = COCl
10 R = CON_3
11 R = CO—N—N⊕



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fixed. In the beginning both were handled as C-atoms, but soon a low temperature factor indicated N(2) to be the second nitrogen atom of the diazepine ring. In 3 full matrix isotropic refinements the conventional R value could be reduced to 7·7% for the observed reflections neglecting the hydrogen atoms. The following standard deviations for the F_o-values were used: $\sigma(Fo) = 0{\cdot}7$ for $Fo \leq 14{\cdot}0$, else $\sigma(Fo) = 0{\cdot}05\ Fo$. The 101 unobserved reflections were considered as follows taking $\sigma(F_{no}) = 2{\cdot}4 = F_{min}$:

$$\text{if } |Fc| < 2{\cdot}4\,|Fo| - |Fc| \text{ was set equal 0 (85 cases in final cycle)}$$

$$\text{if } |Fc| \geq 2{\cdot}4\,|Fo| - |Fc| \text{ was set } = \frac{F_{min}}{\sqrt{2}} - |Fc| \text{ (16 cases).}$$

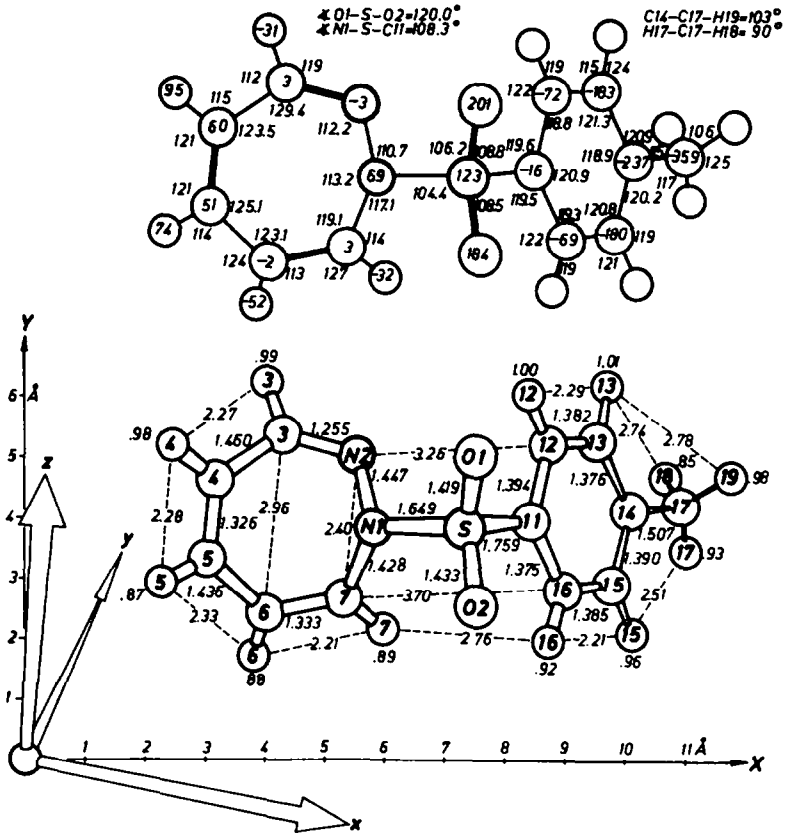


FIG 2. Bond lengths (in Å, lower part) and bond angles (upper part) in 1-tosyl-1,2-diazepine (uncorrected for thermal vibration). The molecule is projected onto the best plane through N(2), C(3), C(6) and C(7) of the diazepine ring. x, y, z indicate the positions of the cell axes and of the origin. The numbers within the circles of the lower part correspond to the numbering of the atoms in Table 2, those in the upper part give the deviation from the projection plane in 10^{-2} Å. The standard deviations of the bond lengths are about 0·005 Å (0·04 Å if hydrogen atoms are involved, compare Table 3), and those of the bond angles are about 0·3° (2·5° involving H)

At R = 7·7% a difference Fourier map revealed the hydrogen positions. Only the hydrogens of the Me group were difficult to detect because of rather high anisotropy effects particularly around C(7), O(1) and O(2).

By including all 12 hydrogen atoms in an isotropic refinement R dropped to 6·6%. Then refinement was continued using a diagonal approximation of the matrix. Within 7 anisotropic refinement cycles R decreased to 3·7% for the observed reflections and to 3·8% including the unobserved ones (only the unobserved with $|Fc| \geqslant F_{min}$ contribute to R. R_w in both cases = 4·5%). In the last cycle no parameter change was greater than $0{\cdot}5\sigma$, the average being about $0{\cdot}1\sigma$ for x, y, z and $0{\cdot}2\sigma$ for the B_{ik}. The final parameters are given in Table 2. A table of the Fo and Fc values may be obtained from R. A.

Discussion of the molecular structure of 1-tosyl 1,2-diazepine (R. Allmann).

The structure found for 1-tosyl-1,2-diazepine turned out to be isomorphic with that of 1-(*p*-Br-benzenesulfonyl)-azepine (7),[7] which crystallized in the same space group (lattice constants 12·32, 16·53 and 5·96 Å as compared with 3, Table 1). Therefore, differences in bond lengths and angles are mainly due to structural differences in the diazepine and azepine molecules and are not caused by packing effects, which are nearly identical for both molecules (Fig 1).

Fig 2 shows the resulting bond lengths and angles not corrected for anisotropic vibration effects. After applying a thermal vibration correction (riding model), the following five bond lengths are increased by more than 2σ: S–O(1), S–O(2), N(1)–N(2), C(11)–C(12), and C(14)–C(17) (Table 3). The average of the S–O bond lengths did increase from 1·42 to 1·44 Å and the difference between the two S–O bonds did decrease.

Like the azepine ring,[7] the 1,2-diazepine ring exists in a boat conformation. The deviations from the best plane through the atoms N(2), C(3), C(6), and C(7) are for N(1) 0·69 Å, for C(4) 0·60 Å and for C(5) 0·51 Å (Fig 2). The dihedral angle between the best planes through atoms 2–3–6–7 and through atoms 3–4–5–6 is 152·4°, that

TABLE 3. 1-TOSYL-1,2-DIAZEPINE 5. BOND LENGTHS CORRECTED FOR THERMAL VIBRATION (RIDING MODEL[10]). THE GIVEN STANDARD DEVIATIONS ARE ONLY DUE TO THOSE OF THE COORDINATES (TABLE 1)

N(1)–N(2)	1·458(4)	S–C(11)	1·759(3)
N(2)–C(3)	1·262(5)	C(11)–C(12)	1·405(4)
C(3)–C(4)	1·463(6)	C(12)–C(13)	1·385(4)
C(4)–C(5)	1·326(6)	C(13)–C(14)	1·381(4)
C(5)–C(6)	1·439(6)	C(14)–C(15)	1·391(4)
C(6)–C(7)	1·343(5)	C(15)–C(16)	1·395(4)
C(7)–N(1)	1·434(4)	C(16)–C(11)	1·378(4)
N(1)–S	1·651(3)	C(14)–C(17)	1·530(5)
S–O(1)	1·440(2)	C(12)–H(12)	1·01(4)
S–O(2)	1·447(2)	C(13)–H(13)	1·02(4)
		C(15)–H(15)	0·97(3)
C(3)–H(3)	1·04(4)	C(16)–H(16)	0·93(3)
C(4)–H(4)	1·03(4)	C(17)–H(17)	1·00(5)
C(5)–H(5)	0·90(4)	C(17)–H(18)	0·93(5)
C(6)–H(6)	0·91(4)	C(17)–H(19)	1·06(4)
C(7)–H(7)	0·92(4)		

between the planes through 2–3–6–7 and through 7–1–2 is 118·2°; thereby the two planes 3–4–5–6 and 7–1–2 are nearly perpendicular to each other ($\measuredangle$ = 90·6°).

The double bonds are clearly localized at N(2)–C(3) = 1·255 Å, C(4)–C(5) = 1·326 Å and C(6)–C(7) = 1·333 Å. The imine bond is quite isolated (C(3)–C(4) = 1·460 Å, dihedral angle of this bond = 38·8°), whereas some resonance is present in the butadiene-like part –C(4) = C(5)–C(6) = C(7)–. The single bond C(5)–C(6) = 1·436 Å is shorter than C(3)–C(4) by 0·024 Å ($\sim 4\sigma$) and the dihedral angle (28·9°) is smaller by 9·9° (see Table 4). (For comparison: in the butadiene molecule the bond lengths are 1·35° and 1·48 Å, the dihedral angle is about 0°.) The five hydrogen

TABLE 4. TORSION ANGLES (DEG) IN THE 1,2-DIAZEPINE AND AZEPINE RING IN THE FREE STATE AND WHEN COMPLEXED WITH IRON TRICARBONYL

atoms	free state		complexed with $Fe(CO)_3$	
	diazepine[a]	azepine[b]	diazepine[c]	azepine[d]
7–1–2–3	74·0	64	9·1	–1
1–2–3–4	–6·0	–3	1·0	5
2–3–4–5	–38·8	–34	35·9	40
3–4–5–6	7·5	1	–45·4	–50
4–5–6–7	28·9	35	–2·1	–4
5–6–7–1	2·9	–2	58·9	60
6–7–1–2	–71·8	–61	–57·4	–49

[a] 1-tosyl-1,2-diazepine **5** (this paper)
[b] 1-(*p*-Br-benzenesulfonyl)-azepine **7**[7]
[c] 1-isopropoxycarbonyl-1,2-diazepine **4** (unpublished)[6]
[d] 1-methoxycarbonyl-azepine[8]

atoms are all nearly in plane with their three neighbouring ring atoms, H(4) having the greatest deviation of 0·14 Å ($=3{\cdot}5\sigma$), the average being 0·07 Å.

When the diazepine is complexed with iron tricarbonyl, the iron atom is bound to the butadien moiety [C(4) to C(7)],[6] the same holding for the 1-H-azepine,[9] and the 1-methoxycarbonyl-azepine[8] complexes (bond lengths see Table 5). In the complexed molecules the N(1) atom adopts a planar sp^2—configuration and the 7-membered ring consists of two planar parts bent along the C(4)...C(7) line by 40°[6], 37°[9] and by 43°[8] respectively. The internuclear distances most affected by complexation are those of the butadiene moiety and N(1)—N(2) or C(2), the latter decreasing by 0·05 to 0·08 Å in the complexed state.

TABLE 5. BOND LENGTHS (UNCORRECTED, IN Å) IN THE 1,2-DIAZEPINE AND AZEPINE RING IN THE FREE STATE AND WHEN COMPLEXED WITH IRON TRICARBONYL

	free state		complexed with $Fe(CO)_3$		
	diazepine[a]	azepine[b]	diazepine[c]	azepine[d]	1-H-azepine[9]
C(7)—N(1)	1·428	1·45	1·42	1·436	1·402
N(1)—N(2) (C(2))	1·447	1·43	1·37	1·382	1·352
N(2) (C(2))—C(3)	1·255	1·38	1·28	1·334	1·322
C(3)—C(4)	1·460	1·44	1·47	1·439	1·451
C(4)—C(5)	1·326	1·34	1·41	1·398	1·414
C(5)—C(6)	1·436	1·46	1·38	1·409	1·406
C(6)—C(7)	1·333	1·37	1·43	1·440	1·409
⟨Fe—C(4), C(7)⟩	–	–	2·10	2·118	2·190
⟨Fe—(5), C(6)⟩	–	—	2·04	2·050	2·036
standard deviation	0·005	0·02	0·01	0·01–0·015	0·01

[a] 1-tosyl-1,2-diazepine **5** (this paper)
[b] 1-(*p*-Br-benzenesulfonyl)-azepine **7**[7]
[c] 1-isopropoxycarbonyl-1,2-diazepine **4**[6]
[d] 1-methoxycarbonyl-azepine[8]
The values for 1-H-azepine are the averages for two independent molecules

The dimensions of the sulfonyl group in **5** are similar to those found in other sulfonyl compounds. The angle O(1)—S—O(2) is increased to 120·0°, whereas the other five angles around S range from 104·4 to 108·8° (for comparison in 4,4'-dichlordiphenyl-sulfonyl (11): ∢ O—S—O = 120·4°, ∢ C—S—O = 104·8°, S—C = 1·765 A and S—O = 1·432 Å, dihedral angle between a Ph ring and the plane C—S—C = 84·4°, or in **7**: ∢ O—S—O = 119·7°, other angles around S = 106·1—109·6°, S—C = 1·750, S—N = 1·606, S—O = 1·41 Å (personal communication I. C. Paul)).

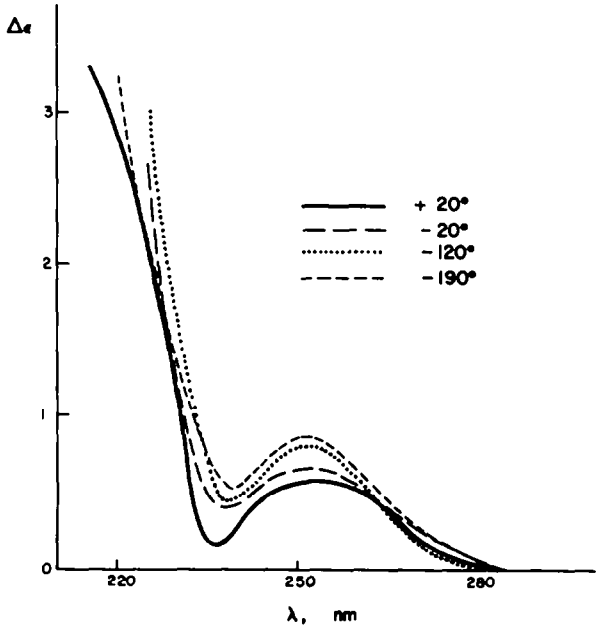


FIG 3. Variable temperature Circular Dichroism of cholesteryl-diazepine (**12**) measured in EPA (ether–isopentane–EtOH)[15]

The Ph ring shows an average C—C distance of 1·384 (±7) Å (1·388 Å when corrected for thermal vibration), a value which is, as would have been expected, somewhat too short (the Raman spectrum for gaseous benzene[12] yields 1·397 Å). The ring is planar within the limits of error. The deviations from the best plane through C(11) to C(16), $10{\cdot}406x - 3{\cdot}631y + 2{\cdot}785z - 4{\cdot}726 = 0$, are less than 0·003 Å for C(11) to C(16), 0·013 Å for C(17) and 0·018 Å for S. H(12) to H(16) deviate less than 0·10 Å, H(17) −0·39, H(18) −0·60, and H(19) +0·86 Å from this plane. The dihedral angle between this Ph plane and the plane through the atoms 2–3–6–7 of the diazepine ring is 126·9° (134·5° in 1-(*p*-Br-benzenesolfonyl)-azepine **7**).

In 1,2-diazepine (**5**), the N(2) atom needs less space than the C(7)H group, whereas in the azepine ring **7** (C2) and C(7) are chemically equivalent. Because of the possible closer approach of N(2) to C(12) as compared with that of C(7) to C(16), the ideal values of 90° for the dihedral angles between the plane N(1)—S—C(11) and the plane of the Ph ring or the diazepine ring (plane 2–3–6–7) are lowered to 83·3° and 86·4°

respectively (87·8° and 87·1° in 7). The distances N(2) . . . C(12) and C(7) . . . C(16) are 3·26 and 3·70 Å (C(2) . . . C(12) = 3·51 and C(7) . . . C(16) = 3·71 Å in 7). Thereby the stress at the nitrogen atom N(1) is released in comparison to 1-(*p*-Br-benzene-sulfonyl)-azepine, allowing the sp^3-character of N(1) to develop more clearly. In the diazepine **5** N(1) deviates from the plane through N(2)—C(7)—S by 0·38 Å and the average angle X—N(1)—X is 113·7°, whereas the corresponding values for the azepine **7** are 0·22 Å and 118° (7).

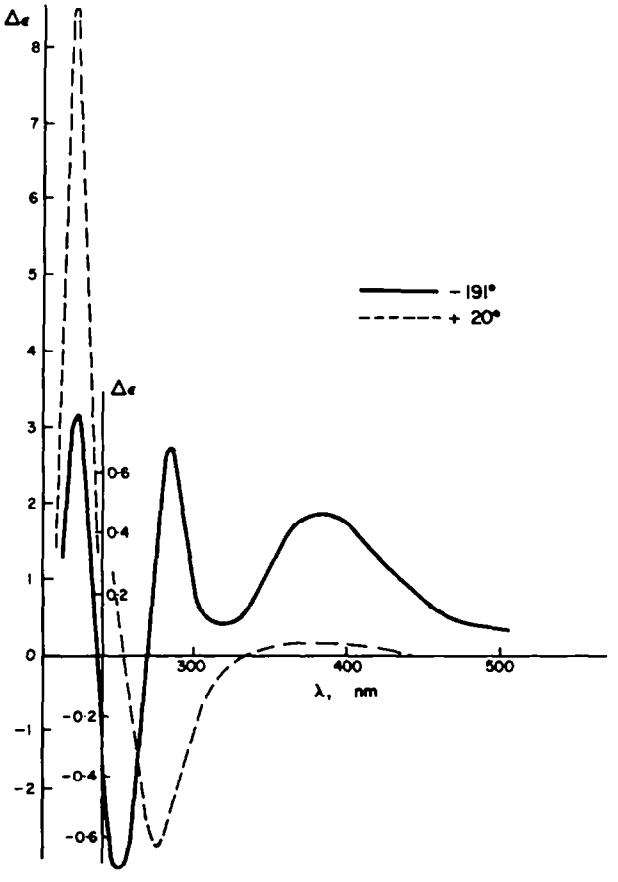
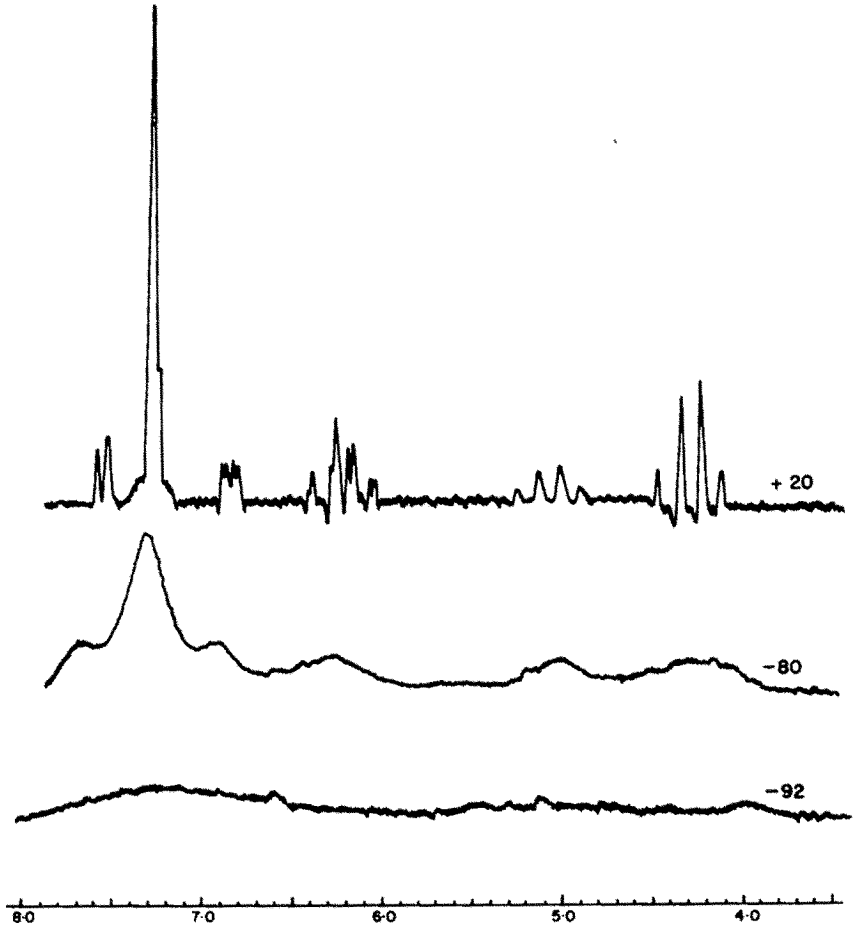


FIG 4. Variable temperature Circular Dichroism of diazepine **15** measured in EPA

The packing of the molecule (Fig 1) allows all intermolecular distances between non-hydrogen atoms to be greater than 3·6 Å except for five O—C distances, namely O(1) . . . C(7′) = 3·99 and O(1) . . . C(16′) = 3·23 Å to the molecule in x, y, 1 + z, O(2) . . . C(4″) = 3·56, O(2) . . . C(5″) = 3·27 and O(2) . . . C(6″) = 3·39 Å to the molecule in 1/2 + x, 1/2 − y, −z. All H . . . H distances are longer than 2·4 Å. The following X . . . H distances are shorter than 3·0 Å: N(2) . . . H(3‴) = 2·88, O(1) . . . H(7′) = 2·54, O(1) . . . H(16′) = 2·58, O(2) . . . H(4″) = 2·85, O(2) . . . H(5″) = 2·59, O(2) . . . H(6″) = 2·98, C(13) . . . H(4‴) = 2·85, and C(14) . . . H(4‴) = 2·87 Å [‴ = molecule in 1/2 − x, 1 − y, z − 1/2].

The conformational flexibility of 1,2-*diazepines* (*A. Frankowski and J. Streith*)

Since 1-substituted 1,2-diazepines (3) are boat-shaped molecules in the solid state (*vide supra*), they are totally asymmetric. From Dreiding molecular models it can be seen that these molecules may undergo a conformational inversion, which is therefore an equilibrium between equal concentrations of the two enantiomers. It was thought that the low temperature NMR spectrum of any given diazepine would enable one



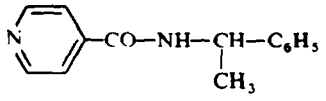
F G 5. Variable temperature NMR measurements of the optically active diazepine **15** in deuteriomethanol

to obtain direct evidence for the conformational flexibility of **3**. Unfortunately 1-substituted 1,2-diazepines proved to be insoluble in the usual NMR solvents at temperatures below − 80°; no coalescence could be observed above this temperature.

Therefore, we turned our attention to a different approach. As stated above, the conformational flexibility—provided that it occurs— is an equilibrium between opposite enantiomers. Attaching an optically active substituent to the diazepine should lead to an *equilibrium between diasteroisomeric conformations*. Such an equilibrium should be temperature dependent. Therefore the circular dichroic curves

of optically active diazepines were expected to exhibit a change of shape as a function of temperature.

Optically active 1,2-diazepines can be built up in different ways. Two syntheses were performed, the first one by attaching an optically active handle at N-1, the second one by attaching a chiral center to the C-5 atom. The CD curves of the optically active cholesteryl diazepine (**12**), the synthesis of which is described below, did not exhibit any significant change when measurements were performed at temperatures ranging from + 20° to − 192° in the EPA solvent[13] (Fig. 3). We assume therefore that one of the diastereoisomers of diazepine **12** exists in a conformation which is thermodynamically highly favoured, whatever the temperature. Quite to the contrary, the CD curves (several Cotton effects) of the optically active diazepine **15**, which was



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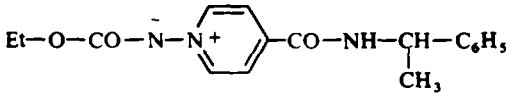

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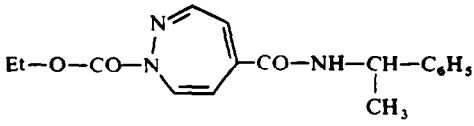

15

synthesized starting from (+) α-phenyl ethyl amine (*vide infra*), underwent a dramatic change when measurements were performed in the same temperature range as indicated above (Fig. 4). On the other hand the variable temperature NMR spectrum of diazepine **15**, measured in deuteriomethanol, shows the coalescence of all proton resonance peaks (Fig. 5). At the coalescence temperature of − 92° the product precipitates; therefore no spectrum could be measured below the coalescence temperature range.

Both CD and NMR spectra of compound **15**, as measured at various temperatures, point to its existing in a fast equilibrium between different conformations. We suggest naming such a dynamic property *conformational diastereoisomerism*. Should the diazepine boat conformation, which occurs in the solid state, be retained in solution, then the molecule **15** would oscillate between boat-like conformations.

Diazepine **12** was synthesized as follows: cholesterol (**8**) reacted with phosgene to give the corresponding 3-chloroformate (**9**); reaction of **9** with NaN_3 in acetone led to the 3-azidoformate derivative (**10**) which was heated up to 100° in pyridine solution to give the expected 1-iminopyridinium ylide (**11**) m.p. 232–234° in 43% yield. UV irradiation of **11** in C_6H_6 gave the orange diazepine (**12**) m.p. 180–183° in 58% yield. The synthesis of the optically active diazepine (**15**) was performed starting from ethyl isoniconinate which reacted with (+) α phenyl ethyl amine to yield the

corresponding isonicotinic amide (**13**), m.p. 108–109. The amide (**13**) was eventually transformed in two steps, according to the Sasaki procedure,[4] into the 1-iminopyridinium ylide (**14**) m.p. 165–168°. UV irradiation of ylide **14** in C_6H_6 led to the formation of diazepine **15** m.p. 38–40° in 42% yield.

CONCLUSION

The three physical methods employed in the previously described experiments, namely X-ray diffraction, variable temperature NMR and variable temperature CD, permit one to establish unambiguously the non planar conformation of 1,2-diazepines and their undergoing a fast conformational equilibrium in solution. Both stereochemical properties, the static one in the solid state and the dynamic property in solution, were expected to occur by comparison with known properties of azepines.[7,8] In addition, the non-conjugated character of the imine double bond was ascertained by X-ray diffraction.

EXPERIMENTAL

(A. Frankowski and J. Streith). Microanalyses were performed by the Service Central de Microanalyse of the CNRS, divisions of Strasbourg and of Lyon. M.ps were measured on a Leitz apparatus and are uncorrected. IR spectra were determined with a Beckman IR-20-A spectrophotometer in KBr discs. UV spectra were measured on a Beckman DB spectrophotometer. NMR spectra were obtained with a Varian A-60-A spectrometer in $CDCl_3$ solution, unless otherwise stated, using TMS as an internal standard [chemical shifts are given in τ values]. CD spectra were measured on a Roussel-Jouan Dichrograph in the EPA solvent mixture (ether–isopentane–EtOH).[13] Column chromatographies, thin and thick layer chromatographies were carried out with silicic acid (Merck, Darmstatt). Solvents were reagent grade and distilled before use. Photochemical reactions were carried out in Pyrex glass, the reactor being of the Hanovia cooling finger type.

Diazepines **4** *and* **5** *and iron-tricarbonyl complex* **6** have been synthesized previously.[1c]

Synthesis of 3-cholesteryl azidoformate **10**. To a stirred solution of 4 g phosgene in 50 ml ether was added dropwise a solution of 11·6 g cholesterol (0·03 mole) in 100 ml ether at normal temperature. After four hr the solvent was evaporated *in vacuo*. The crude 3-cholesteryl chloroformate (**9**) so obtained was dissolved in 300 ml acetone and a solution of 4 g NaN_3 in 40 ml water added dropwise at normal temperature. After continuous stirring at 40° for 10 hr, the mixture was poured into 600 ml water. A crop of 8·7 g 3-cholesteryl azidoformate (**10**) (colourless crystals) precipitated and was separated (yield: 64%).

Synthesis of (−) 3-cholesteryl-1-iminopyridinium ylide **11**. A solution of 8·7 g azidoformate (**10**) (0·19 mole) in 100 g pyridine was heated and maintained at 100° until the cessation of N_2 evolution (about 85 hr). Excess pyridine was removed *in vacuo* and the dark residue treated several times with charcoal in MeOH until complete decoloration of the solutions. MeOH was evaporated *in vacuo* and the solid material was recrystallized from DMSO and washed with diethyl ether to yield 4·15 g of pyridinium ylide (**11**) (yield: 43%), m.p. 232–234° (MeOH): $[\alpha]_D^{20°}$ (EtOH) −17·9°. IR ν(C—H) arom. and olef. 3110, 3080, 3040 cm^{-1}: ν(C—H) aliph. 2940, 2860 cm^{-1}: ν(C=O) 1646 cm^{-1}: ν(C=C) 1610, 1480 cm^{-1}: ν(C—O) 1300, 1700 cm^{-1}. UV (C_6H_6) λ_{max} 342 nm (ε 10,500). NMR: pyridinium moiety: τ 1·2 (2H: m) and τ 2·45 (3H: m): cholesteryl moiety: τ 4·68 (1H: m) and between τ 7·5 and 9·22 (44H). (Calc. for $C_{33}H_{50}N_2O_2$: C, 78·21: H, 9·94: N, 5·53. Found: C, 78·0: H, 9·8: N, 5·4%).

Photochemical synthesis of (−) 3-cholesteryl diazepine **12**. A solution of 1·65 g pyridinium ylide (**11**) in 1·2 liter thiophene free C_6H_6 was irradiated under N_2 for 8 hr a with a Philips HPK mercury high pressure lamp through a Pyrex filter at room temperature. After evaporation of the solvent *in vacuo*, the orange residue was chromatographed over 200 g silicic acid (elution with cyclohexane/EtOAc 7/3). Diazepine **12** was obtained in 57% yield as orange crystals, m.p. 180–183° (acetone). $[\alpha]_D^{20°}$ ($CHCl_3$) −12·3°. UV (MeOH) λ_{max} 346 nm (ε 350) and 245 nm (ε 4400). IR ν(C—H) olef. 3030 cm^{-1}: ν(C—H) aliph. 2970, 2900 cm^{-1}: ν(C=O) 1725 cm^{-1}: ν(C=C) 1640, 1625, 1585 cm^{-1}: ν(C—O) 1350, 1100 cm^{-1}. CD (EPA): see theoretical section. NMR diazepine moiety: τ 2·7 (1H: m: J = 3·5): τ 3·5 (1H: J = 11 Hz): τ 3·78 (1H: m): τ 3·94 (1H: m): τ 4·35 (1H: m): cholesteryl moiety: τ 4·69 (1H: m); and between τ 7·6 and 9·32 (44H). (Calc. for $C_{33}H_{50}N_2O_2$: C, 78·21: H, 9·94: N, 5·53. Found: C, 78·1; H, 9·9; N, 5·5%).

Synthesis of (+) α *phenyl ethyl isonicotinamide* **13**. Ethyl isonicotinic ester (15·1 g; 0·1 mole) was reacted with 25 g of (+) α phenyl ethyl amine (0·2 mole) at 150 to 170° during 6 hr, EtOH being continuously distilled. The solid material obtained was washed several times with petrol ether and was recrystallized from EtOAc/petrol ether to yield 2·34 g of solid. The filtrate was evaporated to dryness and the solid residue recrystallized from EtOAc/ether to yield 10·74 g α phenyl ethyl isonicotinamide as colourless crystals m.p. 108–109°. $[\alpha]_D^{20°}$ ($CHCl_3$) +40·5°. IR ν(N—H) 3320, 3090 cm^{-1}; ν(C—H) 2980, 2920 cm^{-1}; ν(C=O) 1645; 1540 cm^{-1}; ν(C=C) 1600, 1500 cm^{-1}. NMR τ 8·43 (3H; d; J = 7 Hz); τ 4·76 (1H; m; J = 7 Hz) τ 2·73 (5H; s); τ 2·48 (2H; q; J = 6 Hz and J = 2 Hz); τ 1·48 (2H; q; J = 6 Hz and J = 2 Hz). (Calc. for $C_{14}H_{14}ON_2$: C, 74·31; H, 6·24; N, 12·38. Found: C, 74·4; H, 6·4; N, 12·7%).

Synthesis of 1-*iminopyridinium ylide* **14**. To a stirred solution of 4·52 g hydroxylamine-O-sulfonic acid (0·04 mole) in 30 ml water was added dropwise a solution of 2·244 g KOH in 20 ml water, the temperature being kept below 5°. A suspension of 10·18 g (+) α phenyl ethyl isonicotinamide in 50 ml water was poured into the solution and the resulting mixture stirred for an hr at 60–65°. K_2CO_3 (2·75 g in 20 ml water) was added and the resulting solution kept at 60–65° for two hr. The oily supernatant was extracted with C_6H_6 and $CHCl_3$ and the water solution concentrated *in vacuo* to about 50 ml. After addition of 150 ml EtOH, K_2SO_4 precipitated and was removed by filtration. After evaporation to dryness of the filtrate the residue was dissolved in 100 ml EtOH along with 4·3 g ethyl chloroformate (0·04 mole) and 8 g K_2CO_3. The solution was stirred at normal temperature overnight. After filtration the solution was evaporated to dryness *in vacuo*: the resulting solid material was treated with charcoal in MeOH and recrystallized from C_6H_6/cyclohexane to yield 1·21 g 1-iminopyridinium ylide (**14**) m.p. 165–168° (hygroscopic crystals) $[\alpha]_D^{20°}$ ($CHCl_3$ +62·9°. UV (C_6H_6) λ_{max} 370 nm (ε 15,500). IR ν(N—H) 3320, 3060 cm^{-1}; ν(C—H) arom. 3020 cm^{-1}; ν(C—H) aliph. 2990, 2940 cm^{-1}; ν(C=O) 1720, 1660, 1640, 1540 cm^{-1}; ν(C=C) arom. 1600, 1500 cm^{-1}; ν(C—O) 1320, 1120 cm^{-1}. NMR ($CDCl_3$) τ 8·66 (3H; t; J = 7 Hz); τ 8·4 (3H; d; J = 7 Hz); τ 5·88 (2H; q; J = 7 Hz); τ 4·8 (1H; m; J = 7 Hz); τ 2·68 (5H; s); τ 2·20 (2H; d; J = 7·5 Hz); τ 1·68 (2H; d; J = 7·5 Hz). (Calc. for $C_{17}H_{19}N_3O_3$: C, 65·16; H, 6·11; N, 13·41. Found: C, 64·6; H, 6·1; N, 13·5%). Compound **14** is hygroscopic and did not give a satisfactory analysis. Mass spectrum: *m/e* 313 (parent ion).

Photochemical synthesis of the optically active diazepine **15**. A solution of 1·14 g 1-iminopyridinium ylide (**14**) in 900 ml thiophene-free C_6H_6 was irradiated under N_2 with a Philips HPK 125 mercury high pressure lamp through a Pyrex filter. After total consumption of the starting material, as monitored by UV spectroscopy (duration of the reaction: 50 hr), the solvent was removed in vacuo. The remaining solid material was purified by thick layer chromatography over silicic acid (eluant: EtOAc, cyclohexane 3/7) to yield 0·48 g diazepine **15**, m.p. 38–40° (red crystals). $[\alpha]_D^{20°}$ ($CHCl_3$) +17·5°. UV (C_6H_6) λ_{max} 366 nm (ε 310) and 256 nm (ε 7000). IR ν(N—H) 3320 cm^{-1}; ν(C—H) arom. 3040 cm^{-1}; ν(C—H) 2990, 2940 cm^{-1}; δ(C—H) arom. 1740 cm^{-1}; ν(C=O) 1660, 1550 cm^{-1}; ν(C=O) 1650 cm^{-1}; ν(C=C) 1500 cm^{-1}; ν(C—O) 1320, 1090 cm^{-1}. NMR ($CDCl_3$) τ 8·72 (3H; d; J = 7 Hz); τ 8·56 (3H; t; J = 7 Hz); τ 5·7 (2H; q; J = 7 Hz); τ 4·88 (1H; m; J = 7 Hz); τ 4·06 (1H; q; J = 7·5 Hz, J = 1·5 Hz); τ = 3·72 (1H; q; J = 7·5 Hz, J = 1·5 Hz); τ 3·19 (1H; m; one of the coupling constants is about equal to J = 3·5 Hz; resolution not sufficient for further assignments); τ 2·71 (5H; s) ; τ 2·56 (1H; d; J = 3·5). CD (EPA) see theoretical section. (Calc. for $C_{17}H_{19}N_3O_3$: C, 65·16; H, 6·11; N, 13·41. Found: C, 65·0; H, 6·2; N, 13·4%). Mass spectrum: *m/e* 313 (parent ion).

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REFERENCES

[1] [a] Part VI in the series: Photochemical synthesis of 1,2-diazepines;
[b] Part V, R. Gleiter, D. Schmidt and J. Streith, *Helv. Chim. Acta* in press;
[c] Part IV, J. P. Luttringer, M. Nastasi and J. Streith, *J. Org. Chem.* in press

[2] J. Streith and J. M. Cassal, *Angew. Chem.* **80**, 117 (1968). *Angew. Chem. Intern. Edit. Engl.* 7, 129 (1968); *Tetrahedron Letters* **43**, 4541 (1968); *Bull. Soc. Chim. France* 2175 (1969)

[3] J. Streith, A. Blind, J. M. Cassal and C. Sigwalt, *Bull. Soc. Chim. France* 948 (1969)

[4] T. Sasaki, K. Kanematsu and A. Kakehi, *Chem. Comm.* 432 (1969): T. Sasaki, K. Kanematsu, A. Kakehi, I. Ichikawa and K. Hayakawa, *J. Org. Chem.* **35**, 426 (1970)
[5] V. Snieckus, *Chem. Comm.* 831 (1969); A. Balasubramanian, J. M. McIntosch and V. Snieckus, *J. Org. Chem.* **35**, 433 (1970)
[6] R. Allmann, *Angew. Chem.* **82**, 982 (1970): *Angew. Chem. Intern. Edit. Engl.* **9**, 958 (1970)
[7] I. C. Paul, S. M. Johnson, L. A. Paquette, J. H. Berrett and R. J. Haluska, *J. Am. Chem. Soc.* **90**, 5023 (1968)
[8] S. M. Johnson and I. C. Paul, *J. Chem. Soc.* (*B*), 1783 (1970)
[9] W. Hoppe, *Pure and Appl. Chem.* **18**, 465 (1969)
[10] W. R. Busing and H. A. Levy, *Acta Cryst.* **17**, 142 (1964)
[11] J. G. Sime and S. C. Abrahams, *Ibid.* **13**, 1 (1960)
[12] B. P. Stoicheff, *Can. J. Phys.* **32**, 339 (1954)
[13] A. Moscowitz, K. M. Wellmann and C. Djerassi, *J. Am. Chem. Soc.* **85**, 3515 (1963); K. M. Wellmann, R. Records, B. Bunnenberg and C. Djerassi, *Ibid.* **86**, 492 (1964)