Conversion of Tetrahydro-γ-carbolines into Hexahydro[1,2]diazepino[5,4-*b*]indoles *via* Ylide Intermediates. *X*-Ray Crystal Structure Determination of 9-Bromo-2,3-dimethyl-1,2,3,4,5,6-hexahydro[1,2]diazepino[5,4-*b*]indole

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N-Amination of 2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles with *N*-alkyl-*O*-tosylhydroxylamines followed by base treatment gave 1,2,3,4,5,6-hexahydro-2,3-dialkyl[1,2]diazepino[5,4-*b*]indoles, the structure of one of which was determined by spectroscopic evidence and an *X*-ray structure analysis.

In connection with our interests in the ring transformations of heterocycles through ylide intermediates,[1] we describe a novel ring expansion reaction of the *N*-imides derived from 2-alkyltetrahydro-γ-carbolines (2-alkyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles) (1) to give 1,2,3,4,5,6-hexahydro[1,2]diazepino[5,4-*b*]indoles (3).[2]

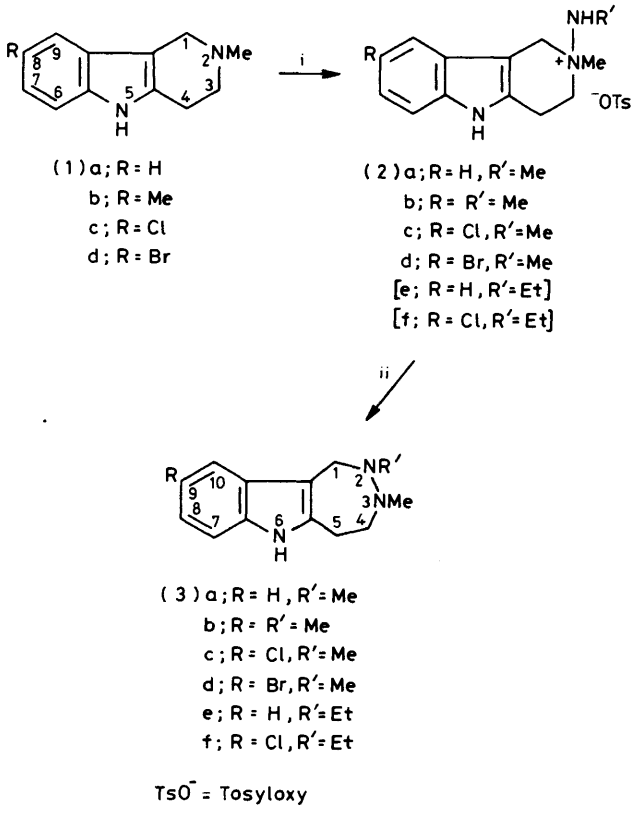
Treatment of compound (1a) with *N*-methyl-*O*-tosylhydroxylamine [3] in methylene dichloride at room temperature for 2 h gave the *N*-methylamine salt (2a) in *ca.* quantitative yield. Refluxing the salt (2a) in ethanol in the presence of potassium carbonate for 2 h gave the hexahydro[1,2]diazepino[5,4-*b*]indole (3a) in quantitative yield. Similarly, compounds (1b—d) were converted into the corresponding *N*-methylamine salts (2b—d) which, upon treatment with base, afforded compounds (3b—d) in good yield (Scheme 1).

The structures of the diazepinoindoles (3a—d) were determined on the basis of their spectroscopic data. For example, compound (3a) showed a strong indolic NH absorption at 3 500 cm^{-1} in the i.r. spectrum and a similar u.v. spectrum to those of (1a) [4,5] and related compounds.[6] The n.m.r. spectrum ($CDCl_3$) revealed two *N*-methyl singlets at δ 2.44 and 2.57, a multiplet between δ 2.8—3.3 (4 H, 4- and 5-H_2), a singlet at δ 4.12 (2 H, 1-H_2), a multiplet (4 H) in the aromatic region, and a broad singlet at δ 7.8 (1 H, NH). Final confirmation of the assigned structure (3) was obtained by an *X*-ray analysis of the 9-bromo derivative (3d) (see later).

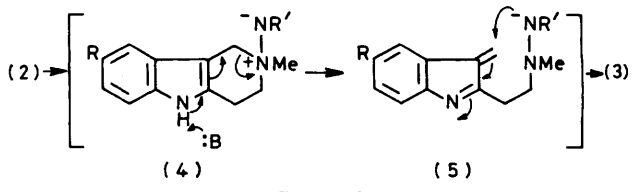
By using *N*-ethyl-*O*-tosylhydroxylamine,[3] the carbolines (1a) and (1c) were transformed into the diazepinoindoles (3e and f) *via* the salts (2e and f). The structures of compounds (3e and f) are based on spectroscopic data and mechanistic considerations.

This base-promoted ring-expansion reaction may proceed *via* intermediates (5) formed by cleavage of the weak C–N bond of the initially formed *N*-imides (4) (Scheme 2). This reaction closely resembles that proposed for the displacement reaction of gramine methiodide by nucleophiles.[4,7] Intramolecular Michael-type cyclization of the intermediates (5) leads to the diazepinoindoles (3). However, an attempt to trap the intermediate (5) by cyanide ion was unsuccessful: probably the intramolecular cyclization is much faster than the intermolecular reaction.

We have also prepared the *N*-amine mesitylenesulphonate (2g) (2; R = R′ = H, $^-$OMs instead of $^-$OTs) † by reaction of the carboline (1a) with *O*-mesitylsulphonylhydroxylamine.[8] Treatment of compound (2g) with base (*e.g.*, potassium carbonate in refluxing ethanol, sodium ethoxide in refluxing ethanol, or potassium t-butoxide in refluxing t-butyl alcohol), however, gave only an intractable oily mixture.



Scheme 1. *Reagents:* i, R′NHOTs; ii, K_2CO_3



Scheme 2.

† Ms = mesitylsulphonyl, Ts = tosyl.

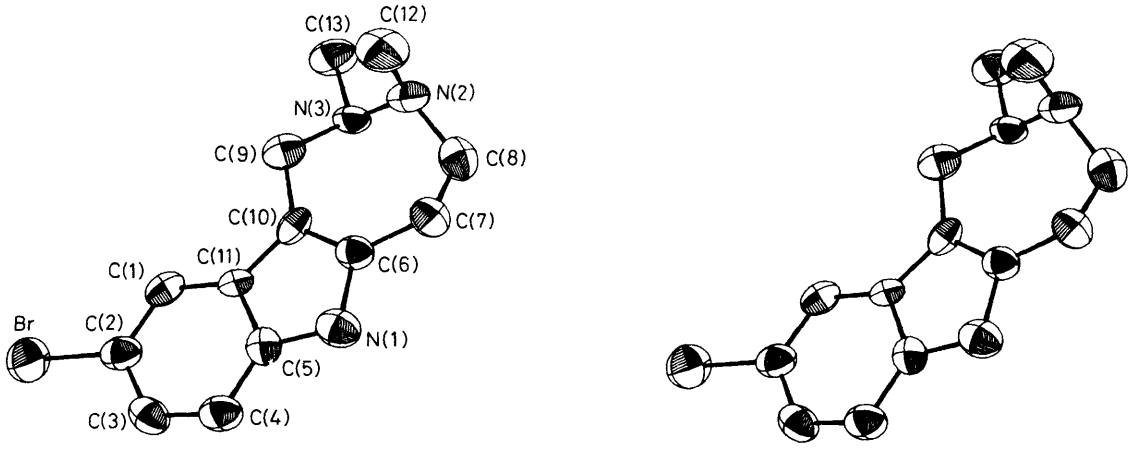


Figure. A stereoview of the molecular structure of compound (3d)

Crystal Structure of Compound (3d).—The molecular structure of compound (3d) is illustrated in the Figure.* The seven-membered heterocyclic ring has a chair-like conformation; the deviations of atoms N(3), N(2), and C(8) from the best plane through C(7)–C(6)–C(10)–C(9) were 0.77, 0.26, and 0.69 Å, respectively. It is of interest to note that the N(2)-methyl group occupies an axial and the N(3)-methyl group an equatorial position.

Experimental

^{1}H N.m.r. spectra were determined with a Hitachi R-22 spectrometer (tetramethylsilane as internal standard). I.r. spectra were recorded with a JASCO IRA spectrophotometer and u.v. spectra with a Hitachi 124 spectrophotometer.

Starting Materials.—2-Methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (1a), and its 8-methyl (1b), 8-chloro (1c), and 8-bromo (1d) derivatives were prepared according to the reported procedure.[5]

General Procedure for the Preparation of 2-Methyl-2-methylamino-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]*indol-2-ium Toluene-p-sulphonates* (2a—d).—A solution of a carboline (1) (1 mmol) and *N*-methyl-*O*-tosylhydroxylamine (1.1 mmol) in methylene dichloride (5 ml) was stirred at room temperature for 2 h. Diethyl ether was added to the reaction mixture and the precipitated crystals were collected and recrystallised from ethanol. Thus were prepared *2-methyl-2-methylamino-2,3,4,5-tetrahydro-1H-pyrido*[4,3-b]*indol-2-ium toluene-p-sulphonate* (2a) (89%), m.p. 170—171 °C (Found: C, 62.0; H, 6.5; N, 10.9. $C_{20}H_{25}N_3O_3S$ requires C, 62.0; H, 6.5; N, 10.8%); the *8-methyl derivative* (2b) (94%), m.p. 171—172 °C (Found: C, 62.6; H, 6.85; N, 10.3. $C_{21}H_{27}N_3O_3S$ requires C, 62.8; H, 6.8; N, 10.5%); the *8-chloro derivative* (2c) (74%), m.p. 174—176 °C (Found: C, 56.9; H, 5.7; N, 9.9. $C_{20}H_{24}ClN_3O_3S$ requires C, 56.9; H, 5.7; N, 10.0%); the *8-bromo derivative* (2d) (63%), m.p. 175—176 °C (Found: C, 51.5; H, 5.2; N, 8.95. $C_{20}H_{24}BrN_3O_3S$ requires C, 51.5; H, 5.2; N, 9.0%).

General Procedure for the Preparation of 2-Ethylamino-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]*indol-2-ium Toluene-p-sulphonates* (2e and f).—A solution of a carboline (1) (1 mmol) and *N*-ethyl-*O*-tosylhydroxylamine (1.1 mmol) in methylene dichloride (5 ml) was stirred at room temperature for 2 h. The solvent was removed under reduced pressure to give a crude oily product which was used for the next step without purification.

General Procedure for the Preparation of 1,2,3,4,5,6-Hexahydro[1,2]*diazepino*[5,4-b]*indoles* (3a—f).—A mixture of a toluenesulphonate (2) (1 mmol) and potassium carbonate (276 mg, 2 mmol) in ethanol (10 ml) was refluxed for 2 h. The reaction mixture was concentrated under reduced pressure and methylene dichloride (10 ml) was added. The methylene dichloride solution was washed with water, dried ($MgSO_4$), and concentrated. The residual solid was recrystallised. Thus were prepared *2,3-dimethyl-1,2,3,4,5,6-hexahydro*[1,2]*diazepino*[5,4-b]*indole* (3a) (88%), m.p. 174—175 °C (from diethyl ether) (Found: C, 72.7; H, 8.0; N, 19.4. $C_{13}H_{17}N_3$ requires C, 72.5; H, 8.0; N, 19.5%); $\nu_{max.}$ ($CHCl_3$) 3 500 cm^{-1}; $\lambda_{max.}$ (EtOH) 226, 275sh, 284, and 292 nm (log ε 4.24, 3.55, 3.60, and 3.56); δ ($CDCl_3$) 2.44 and 2.57 (each 3 H, s, NCH_3), 2.8—3.3 (4 H, m, 4- and 5-H_2), 4.12 (2 H, s, 1-H_2), 6.9—7.4 (4 H, m, ArH), and 7.8 (1 H, br s, NH); the *9-methyl derivative* (3b) (72%), m.p. 159—161 °C (from benzene) (Found: C, 73.7; H, 8.4; N, 17.8. $C_{14}H_{19}N_3$ requires C, 73.3; H, 8.35; N, 18.3%); $\nu_{max.}$ ($CHCl_3$) 3 500 cm^{-1}; $\lambda_{max.}$ (EtOH) 229, 281sh, 288, and 299 nm (log ε 4.19, 3.61, 3.62, and 3.55); δ ($CDCl_3$) 2.40 (6 H, s, 9-CH_3 and NCH_3), 2.52 (3 H, s, NCH_3), 2.7—3.3 (4 H, m, 4- and 5-H_2), 4.09 (2 H, s, 1-H_2), 6.75—7.3 (3 H, m, ArH), and 7.75 (1 H, br, NH); the *9-chloro derivative* (3c) (67%), m.p. 177—179 °C (from benzene) (Found: C, 62.8; H, 6.4; N, 16.7. $C_{13}H_{16}ClN_3$ requires C, 62.5; H, 6.5; N, 16.8%); $\nu_{max.}$ ($CHCl_3$) 3 500 cm^{-1}; $\lambda_{max.}$ (EtOH) 233, 285sh, 293, and 302 nm (log ε 4.26, 3.55, 3.59, and 3.55); δ ($CDCl_3$) 2.38 and 2.51 (each 3 H, s, NCH_3), 2.7—3.3 (4 H, m, 4- and 5-H_2), 4.04 (2 H, s, 1-H_2), 7.0 (2 H, m, 7- and 8-H), 7.27 (1 H, br, 10-H), and 7.8 (1 H, br s, NH); the *9-bromo derivative* (3d) (70%), m.p. 166—167 °C (from benzene) (Found: C, 53.2; H, 5.5; N, 14.1. $C_{13}H_{16}BrN_3$ requires C, 53.1; H, 5.5; N, 14.3%); $\nu_{max.}$ ($CHCl_3$) 3 500 cm^{-1}; $\lambda_{max.}$ (EtOH) 233, 286sh, 294, and 303 nm (log ε 4.04, 3.31, 3.36, and 3.30); δ ($CDCl_3$) 2.40 and 2.53 (each 3 H, s, NCH_3), 2.7—3.3 (4 H, m, 4- and 5-H_2), 4.05 (2 H, s, 1-H_2), 7.08 (2 H, br, 7- and 8-H), 7.45 (1 H, br, 10-H), and 7.8 (1 H, br s, NH); *2-ethyl-3-methyl-1,2,3,4,5,6-hexahydro*[1,2]*diazepino*[5,4-b]*indole* (3e) [76% overall yield from (1a)], m.p. 129—131 °C (from benzene–n-hexane) (Found: C, 72.7; H, 8.2; N, 17.6. $C_{14}H_{19}N_3 \cdot 1/5H_2O$ requires C, 72.2; H, 8.4; N, 18.0%); $\nu_{max.}$ ($CHCl_3$) 3 500 cm^{-1}; $\lambda_{max.}$ (EtOH) 226, 278sh, 285, and 293 nm (log ε 4.22, 3.59,

* *Note:* The crystallographic numbering used differs from the systematic numbering used in the compound name.

Table 1. Bond lengths (Å) for compound (3d) with estimated standard deviations in parentheses [a]

Br–C(2)	1.859(7)	C(2)–C(3)	1.411(9)
N(1)–C(5)	1.398(8)	C(3)–C(4)	1.361(10)
N(1)–C(6)	1.421(8)	C(4)–C(5)	1.376(9)
N(2)–N(3)	1.447(7)	C(5)–C(11)	1.421(8)
N(2)–C(8)	1.467(9)	C(6)–C(7)	1.497(9)
N(2)–C(12)	1.480(9)	C(6)–C(10)	1.362(9)
N(3)–C(9)	1.470(8)	C(7)–C(8)	1.527(9)
N(3)–C(13)	1.491(8)	C(9)–C(10)	1.510(9)
C(1)–C(2)	1.373(9)	C(10)–C(11)	1.442(9)
C(1)–C(11)	1.374(9)		

[a] Crystallographic numbering scheme used for Tables 1—3.

Table 2. Bond angles (°) for compound (3d) with estimated standard deviations in parentheses

C(5)–N(1)–C(6)	107.1(5)	N(1)–C(5)–C(11)	109.0(5)
N(3)–N(2)–C(8)	112.7(5)	C(4)–C(5)–C(11)	121.7(6)
N(3)–N(2)–C(12)	115.5(5)	N(1)–C(6)–C(7)	116.5(5)
C(8)–N(2)–C(12)	112.4(5)	N(1)–C(6)–C(10)	109.5(5)
N(2)–N(3)–C(9)	116.4(5)	C(7)–C(6)–C(10)	133.7(6)
N(2)–N(3)–C(13)	108.4(5)	C(6)–C(7)–C(8)	113.7(5)
C(9)–N(3)–C(13)	109.9(5)	N(2)–C(8)–C(7)	118.6(6)
C(2)–C(1)–C(11)	122.1(6)	N(3)–C(9)–C(10)	114.7(5)
Br–C(2)–C(1)	122.2(5)	C(6)–C(10)–C(9)	128.8(6)
Br–C(2)–C(3)	119.3(5)	C(6)–C(10)–C(11)	108.5(5)
C(1)–C(2)–C(3)	118.4(6)	C(9)–C(10)–C(11)	122.6(5)
C(2)–C(3)–C(4)	121.5(6)	C(1)–C(11)–C(5)	117.5(6)
C(3)–C(4)–C(5)	118.7(6)	C(1)–C(11)–C(10)	136.5(6)
N(1)–C(5)–C(4)	129.4(6)	C(5)–C(11)–C(10)	106.0(5)

3.61, and 3.56); δ ($CDCl_3$) 1.09 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.46 (3 H, s, NCH_3), 2.61 (2 H, q, *J* 7 Hz, NCH_2CH_3), 2.6—3.3 (4 H, m, 4- and 5-H_2), 4.07 (2 H, s, 1-H_2), 6.8—7.5 (4 H, m, ArH), and 7.95 (1 H, br s, NH); the 9-*chloro derivative* (3f) [30% overall yield from (1c)], m.p. 122—123 °C (from benzene–n-hexane) (Found: C, 63.8; H, 6.9; N, 15.75. $C_{14}H_{18}ClN_3$ requires C, 63.75; H, 6.9; N, 15.9%); $\nu_{max.}$ ($CHCl_3$) 3 500 cm^{-1}; $\lambda_{max.}$ (EtOH) 235, 286sh, 293, and 303 nm (log ε 4.23, 3.57, 3.65, and 3.55); δ ($CDCl_3$) 1.09 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.46 (3 H, s, NCH_3), 2.60 (2 H, q, *J* 7 Hz, NCH_2CH_3), 2.65—3.3 (4 H, m, 4- and 5-H_2), 4.00 (2 H, s, 1-H_2), 6.95 (2 H, br, 7- and 8-H), 7.25 (1 H, br, 10-H), and 8.1 (1 H, br s, NH).

X-Ray Analysis of Compound (3d).—The structure of compound (3d) was established by *X*-ray analysis. The crystal data and intensity data were derived from measurements on a Syntex R3 four-circle diffractometer with graphite-monochromated Mo-K_α radiation.

Crystal data: $C_{13}H_{16}BrN_3$, monoclinic, space group $P2_1/n$, $a = 8.575(5)$, $b = 8.871(6)$, $c = 17.788(9)$ Å, $\beta = 94.33(5)°$, $D_x = 1.45$ g cm^{-3}, $Z = 4$, and μ(Mo-K_α) = 32.1 cm^{-1}. Intensity data for 1 260 reflections [$I > 1.96\sigma(I)$] were collected using an ω-scan mode with $2\theta < 45°$. Lorentz and polarization corrections were applied, but no absorption corrections were made. The structure was solved by direct methods using MULTAN [9] on a Syntex XTL program. All the hydrogen atoms except the one bonded to the indole nitrogen atom were found on a difference Fourier map. The refinement of atomic parameters was carried out by block-diagonal least-squares calculations. The final *R*-value was 0.065 assuming anisotropic thermal motions for non-hydrogen atoms and isotropic ones for hydrogen atoms. A stereoview of the molecular structure of compound (3d) is illustrated in the Figure. Bond lengths and bond angles are listed in Tables 1 and 2. Atomic co-ordinates for non-hydrogen atoms are given in Table 3. Observed and calculated structure factors, additional atomic co-ordinates, thermal parameters, and additional bond lengths and angles are listed in Supplementary Publication No. SUP 23637 (12 pp.).*

Table 3. Atomic co-ordinates (× 10^4) for non-hydrogen atoms of compound (3d) with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
Br	37(1)	1 270(1)	1 542(1)
N(1)	6 514(6)	−1 288(6)	2 013(3)
N(2)	8 352(7)	469(6)	4 283(3)
N(3)	7 198(6)	1 593(6)	4 041(3)
C(1)	3 026(8)	765(7)	2 297(4)
C(2)	2 059(8)	505(7)	1 659(4)
C(3)	2 593(8)	−449(7)	1 098(4)
C(4)	4 059(8)	−1 049(7)	1 162(4)
C(5)	5 004(7)	−767(7)	1 807(4)
C(6)	6 971(8)	−663(7)	2 732(4)
C(7)	8 505(7)	−1 182(8)	3 099(4)
C(8)	9 259(8)	−57(7)	3 666(4)
C(9)	5 694(8)	1 024(7)	3 704(4)
C(10)	5 787(7)	204(7)	2 965(4)
C(11)	4 511(7)	179(7)	2 388(3)
C(12)	7 773(9)	−791(8)	4 731(4)
C(13)	6 930(9)	2 582(8)	4 697(4)

References

1 Y. Tamura, J. Minamikawa, Y. Kita, J. H. Kim, and M. Ikeda, *Tetrahedron*, 1973, **29**, 1063; Y. Tamura, S. M. M. Bayomi, M. Ikeda, and M. Kise, *Chem. Pharm. Bull.*, 1980, **28**, 1597; Y. Tamura, S. M. M. Bayomi, C. Mukai, M. Ikeda, and M. Kise, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2830; Y. Tamura, Y. Takebe, S. M. M. Bayomi, C. Mukai, M. Ikeda, M. Murase, and M. Kise, *ibid.*, 1981, 1037; Y. Tamura, Y. Takebe, C. Mukai, and M. Ikeda, *ibid.*, p. 2978; Y. Tamura, M. Tsunekawa, H. Ikeda, and M. Ikeda, *Heterocycles*, 1982, **19**, 1598.

2 Preliminary communication, Y. Tamura, I. Morita, H. Tsubouchi, H. Ikeda, and M. Ikeda, *Heterocycles*, 1982, **17**, 163.

3 Y. Tamura, I. Morita, H. Ikeda, H. Tsubouchi, and M. Ikeda, *Chem. Pharm. Bull.*, 1982, **30**, 1221.

4 A. N. Kost, M. A. Yurovskaya, A. G. Belikov, and P. B. Terent'ev, *Khim. Geterotsikl. Soedin*, 1973, 1050.

5 C. J. Cattanach, A. Cohen, and B. Heath-Brown, *J. Chem. Soc. C*, 1968, 1235.

6 J. B. Hester, A. H. Tang, H. H. Keasling, and W. Veldkamp, *J. Med. Chem.*, 1968, **11**, 101.

7 M. A. Yurovskaya and I. L. Rodionov, *Khim. Geterotsikl. Soedin.*, 1981, 1072.

8 Y. Tamura, J. Minamikawa, and M. Ikeda, *Synthesis*, 1977, 1.

9 G. Mermain, P. Main, and M. Woolfson, *Acta Crystallogr.*, 1971, **A27**, 368.

* For details of the Supplementary Publications Scheme, see Instructions for Authors (1983) in *J. Chem. Soc., Perkin Trans. 1*, 1983, Issue 1, p. xvii.

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