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The Meisenheimer Rearrangement in Heterocyclic Synthesis. I Synthesis of Some Tetrahydro-2,3-benzoxazepines

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Abstract

Melt pyrolysis of the *cis*-6,7-dimethoxy-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline *N*-oxide (2b) afforded the Meisenheimer rearrangement product, 7,8-dimethoxy-3-methyl-1-phenyl-1,3,4,5-tetrahydro-2,3-benzoxazepine (5b), in good yield, as did pyrolysis of the corresponding *trans*-*N*-oxide (3b) (in a melt) or a mixture of (2b) and (3b) (melt or in solution). The synthesis of the 1-deuterated analogue, (5c), of (5b) is described, together with products derived from (5b) by cleavage of the N–O bond which were used to confirm its structure. Meisenheimer rearrangement of the *N*-oxides (10) and (11) of 6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline and 2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline gave the analogous 2,3-benzoxazepine derivatives (12) and (13), respectively.

Introduction

The thermal rearrangement of tertiary amine *N*-oxides to trisubstituted hydroxylamines was first described[1] by Jakob Meisenheimer in 1919. Since then many investigations have been carried out on the mechanism and scope of this rearrangement,[2,3] with an emphasis on the former.[3–5] Of particular interest synthetically is the fact that, when the *N*-oxide moiety is incorporated in an appropriately substituted ring, the Meisenheimer rearrangement provides an entry into a variety of 1,2-oxaza heterocyclic systems; six-,[6,7] seven-,[8,9] and eight-membered[9] rings have been made in this way. However, there seems to be little in the literature on the preparation of fused oxaza-heterocyclic derivatives by this ring expansion. Johnstone *et al.* discussed[10] the mass spectrum of a 7,8-dihydro-5*H*-dibenz[*d*,*f*][1,2]oxazocine, presumably made

[1] Meisenheimer, J., *Ber. Dtsch. Chem. Ges.*, 1919, **52**, 1667.
[2] Kleinschmidt, R. F., and Cope, A. C., *J. Am. Chem. Soc.*, 1944, **66**, 1929.
[3] Johnstone, R. A. W., 'Mechanisms of Molecular Migrations' (Ed. B. S. Thyagarajan) Vol. 2, pp. 249–66 (Interscience: New York 1969).
[4] Castagnoli, N., Jr, Cymerman Craig, J., Melikian, A. P., and Roy, S. K., *Tetrahedron*, 1970, **26**, 4319.
[5] Lorand, J. P., Grant, R. W., Samuel, P. A., O'Connell, E. M., Zaro, J., Pilotte, J., and Wallace, R. W., *J. Org. Chem.*, 1973, **38**, 1813.
[6] Rayburn, C. H., Harlan, W. R., and Hanmer, H. R., *J. Am. Chem. Soc.*, 1950, **72**, 1721.
[7] Quin, L. D., and Roof, G. L., *J. Org. Chem.*, 1962, **27**, 4451.
[8] Quin, L. D., and Shelburne, F. A., *J. Org. Chem.*, 1965, **30**, 3135.
[9] Carruthers, W., and Johnstone, R. A. W., *J. Chem. Soc.*, 1965, 1653.
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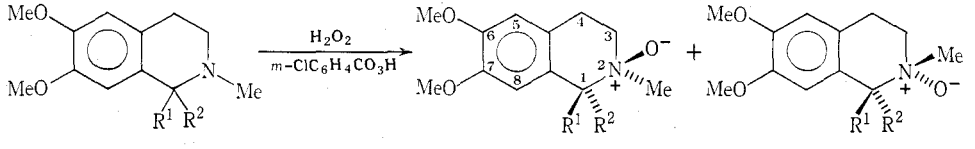
by thermal rearrangement of the corresponding dibenzazepine *N*-oxide derivative, although no details could be found in the references given. Thermolysis of the phthalideisoquinoline derivative, α-narcotine *N*-oxide, did give[11] a fused heterocyclic product, but this was shown to be a 3,4-benzoxazocine derivative rather than the 2,3-benzoxazepine to be expected[12] from a normal Meisenheimer rearrangement.

During work[12] on the thermolysis of *cis*-(±)-laudanosine *N*-oxide (2a) (see Scheme 1), a substituted 1,3,4,5-tetrahydro-2,3-benzoxazepine (5a) (see Scheme 2), the product of a Meisenheimer rearrangement, was isolated in low yield; the other products resulted from a Cope elimination [probably after conversion of the *cis*- into the *trans*-*N*-oxide (3a)] and subsequent reactions. It was thought that, if the Cope elimination could be suppressed by replacement of the C 1 benzylic substituent with, for example, an aryl group at this position, the rearrangement might then proceed smoothly to give 2,3-benzoxazepine derivatives. The other known representatives of this ring system, which are of some pharmacological[13] as well as chemical interest, have been made[13,14] by a condensation procedure and subsequent functional group manipulation.

Results and Discussion

Reaction of the 1-phenyltetrahydroisoquinoline (1b) with aqueous hydrogen peroxide or with *m*-chloroperbenzoic acid produced a mixture of the *cis*- and *trans*-*N*-oxides (2b) and (3b) (Scheme 1), the former being the major isomer; these isomers could be separated by careful p.l.c. with the multiple development technique. The structures of (2b) and (3b) were assigned primarily on the basis of their n.m.r. spectra, the chemical shift difference of the C 1 proton [(2b), δ 5·45; (3b), δ 5·32] being diagnostic [cf.[12] *cis*- and *trans*-(±)-laudanosine *N*-oxide]; the assignment of this proton was confirmed in turn by comparison with the n.m.r. spectrum of the C 1 deuterated analogue (2c) from (1c).



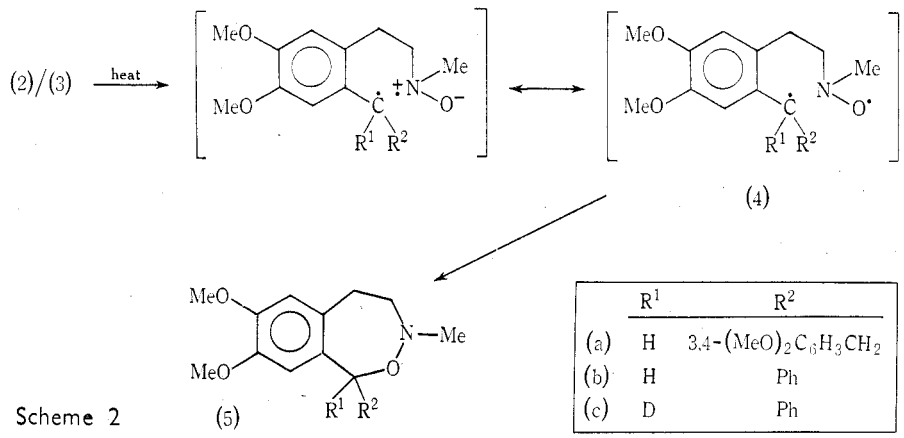
	R^1	R^2
(a)	H	3,4-$(MeO)_2C_6H_3CH_2$
(b)	H	Ph
(c)	D	Ph

Scheme 1

Direct pyrolysis (melt; 120°) of the *cis*-*N*-oxide (2b) gave the tetrahydro-2,3-benzoxazepine (5b) (Scheme 2) in good yield, as did a mixture of the *cis*- and *trans*-*N*-oxides (2b)/(3b) (melt, 120°; or in ethanenitrile or pyridine solutions at reflux). In the same

[11] Klötzer, W., and Oberhänsli, W. E., *Helv. Chim. Acta*, 1973, **56**, 2107.
[12] Bremner, J. B., and Thuc, L. v., *Aust. J. Chem.*, 1980, **33**, 379.
[13] Pifferi, G., Omodei-Salè, A., and Consonni, P., Ger. Offen. 2,212,692 (Cl. C 07*d*.), 21 Sept. 1972 (*Chem. Abstr.*, 1972, **77**, 164781w); see also *Chem. Abstr.*, 1975, **83**, 58900y.
[14] Pifferi, G., Consonni, P., Monguzzi, R., and Omodei-Salè, A., *J. Heterocycl. Chem.*, 1971, **8**, 911.

way (melt, 140°), the C 1 deuterated benzoxazepine (5c) was obtained from the *N*-oxide [essentially (2c)]. Melt pyrolysis (*c.* 160°) of the *trans*-*N*-oxide (3b) alone also gave (5b), although in somewhat lower yield, possibly due to some decomposition of the product at the higher temperature used.



	R^1	R^2
(a)	H	3,4-$(MeO)_2C_6H_3CH_2$
(b)	H	Ph
(c)	D	Ph

Scheme 2

On the basis of mechanistic studies[3–5] on the Meisenheimer rearrangement in other systems, it seems reasonable to assume that (5b) and (5c) arise by homolytic cleavage of the C 1–N bond giving a diradical intermediate (4) followed by C–O bond formation (Scheme 2). The initial cleavage would also be assisted[3,15] by the fact that the C 1 position is doubly benzylic in these cases.

The assignment of structure (5b) is supported by analytical, spectroscopic, and chemical data. In particular, in the n.m.r. spectrum, H 1 appeared as a sharp singlet well downfield at δ 6·05; this signal was missing in the n.m.r. spectrum of (5c). The position of the *N*-methyl signal in (5b) (δ 2·75) was consistent[11] with this group being part of a 1,2-oxaza moiety.

In confirmation of the structural assignment, reductive cleavage of the N–O bond in (5b) on treatment with zinc in acetic acid[6,9] gave the secondary amino alcohol (7), which was then *N*-methylated to give the more stable tertiary amino alcohol (9) (Scheme 3). Both (7) and (9) were also made by alternative routes involving photosolvolysis[16] of the hydrochloride and methiodide salts, respectively, of the base (1b). The key amino alcohol (9) could also be inter-related with (5b) by reductive cleavage of the methiodide salt (6) or through the amino ketone (8), the product of a Hofmann-like elimination;[7,17] the latter ketone could in turn be reformed from (9) by oxidation with Jones reagent (Scheme 3).

In an extension of this work, the tetrahydroisoquinoline *N*-oxides (10) and (11) were prepared from the corresponding tertiary bases. No attempt was made to separate the *cis* and *trans* isomers in these cases, and, on pyrolysis, the Meisenheimer rearrangement products (12) and (13) (Scheme 4) were obtained in yields of 83% and 35% respectively. Comment on the substituent effects is difficult without quanti-

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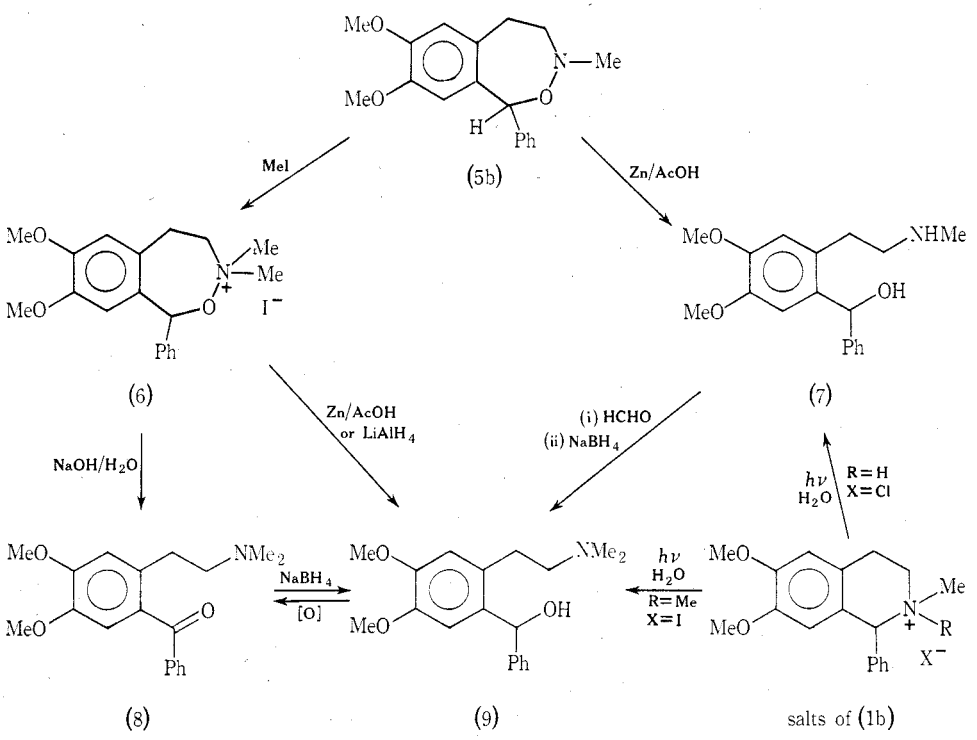
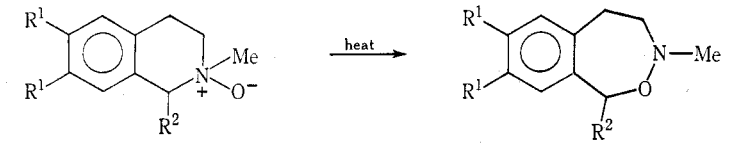
[16] Bremner, J. B., and Thuc, L. v., *Chem. Ind.* (*London*), 1976, 453.
[17] Rautenstrauch, V., *Helv. Chim. Acta*, 1973, **56**, 2492.

tative data and further studies are planned in this particular area. It is clear, however, that thermal ring-expansion of the readily accessible 1-aryl-1,2,3,4-tetrahydroisoquinoline *N*-oxides does provide a facile route to the substituted tetrahydro-2,3-benzoxazepine system.



Scheme 3



	R^1	R^2		R^1	R^2
(10)	OMe	3,4-$(MeO)_2C_6H_3$	(12)	OMe	3,4-$(MeO)_2C_6H_3$
(11)	H	Ph	(13)	H	Ph

Scheme 4

The use of the Meisenheimer rearrangement in the synthesis of other fused-ring heterocycles will be described in later papers.

Experimental

Melting points were determined on a Yanagimoto Seisakusho micro-melting point apparatus, and are uncorrected. Preparative t.l.c. (p.l.c.) was performed on Merck silica gel GF_{254} or Camag

silica gel DSF-5; in some cases, as specified, the silica gel slurry was made up with 0·5 M potassium hydroxide solution rather than water. Ultraviolet spectra were determined in methanol on a Carl Zeiss PMQ-II spectrophotometer, and infrared spectra as mulls on a Beckman IR-33 spectrometer. N.m.r. spectra were performed at 100 MHz with a Jeol JNM-4H-100 spectrometer, tetramethylsilane being used as internal standard. High-resolution mass spectra were determined on a VG MM 7070F mass spectrometer, and low-resolution spectra on an EAI Quad 300 spectrometer. Photolyses were carried out at 25° under argon in a water-cooled immersion-type photochemical reactor, a Hanovia 450 W mercury arc lamp and a Corex glass filter sleeve being used.

Analyses were performed by the Australian Microanalytical Service, Melbourne. Aliphatic or alicyclic-type *N*-oxides are frequently too thermally labile and too hygroscopic for combustion analysis (cf.[18]) (and hence are often used *in situ* for further reactions[19]); our oxides proved no exception. Moreover, their mass spectra (EAI Quad MS) were effectively identical with those of the ring-expanded products; this indicated that the Meisenheimer rearrangement had taken place during the heating of compounds prior to volatilization. High-resolution mass spectra, in this situation, would not afford proof of the identity of the compound; hence characterization was limited to the interpretation of n.m.r. spectra and the determination of the usual criteria of purity.

6,7-Dimethoxy-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (1b)

The isoquinoline (1b) was prepared from *N*-[2-(3,4-dimethoxyphenyl)ethyl]benzamide by a Bischler–Napieralski reaction followed by methylation and reduction (cf.[20]). M.p. 82°–83° from hexane (lit.[21] 81–82°).

N-*Oxidation of (1b)*

(A) *With hydrogen peroxide (general procedure).*—A solution of 30% aqueous hydrogen peroxide (10 ml) was added to the isoquinoline (1b) (283 mg), and the mixture was stirred at 20° until it was homogeneous (40 h). Water (20 ml) was added and the excess hydrogen peroxide destroyed by stirring with platinum foil for 6 h. The aqueous solution was filtered and the filtrate extracted with chloroform (3 × 50 ml). The extracts were dried (sodium sulfate) and the solvent was removed in vacuum. The residual foam was subjected to p.l.c. (chloroform/10% methanol, v/v).

Fraction 1, R_F 0·8, was unchanged (1b) (104 mg, 37%).

Fraction 2, R_F 0·3, was isolated as a foam (147 mg, 47%), which was recrystallized from ethyl acetate to give *6,7-dimethoxy-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline* N-*oxide*, m.p. 115–118°. N.m.r. δ ($CDCl_3$) 3·02, s, 3·23, s (3 : 1), NCH_3; 2·8–4·3, m, CH_2CH_2; 3·67, s, OCH_3; 3·91, s, OCH_3; 5·36, s, 5·50, s (1 : 3), H1; 6·15, s, 6·28, s (1 : 3), H8; 6·77, s, H5; 7·25–7·55, m, 5ArH. The n.m.r. showed the *N*-oxide consisted of two isomers in a ratio of approximately 3 : 1, which was confirmed by p.l.c. (chloroform/10% methanol). The isomers were separated by multiple development (four times) to give the *cis-N*-oxide (239 mg), R_F 0·5, and the *trans-N*-oxide (81 mg), R_F 0·4.

The *cis* isomer (2b) was recrystallized from ethyl acetate to give crystals, m.p. 120–122°. Mass spectrum: *m/e* 299 (M) ($C_{18}H_{21}NO_3$ requires 299). N.m.r. δ ($CDCl_3$) 3·00, s, NCH_3; 2·8–4·2, m, CH_2CH_2; 3·66, s, OCH_3; 3·89, s, OCH_3; 5·45, s, H1; 6·27, s, H8; 6·75, s, H5; 7·2–7·5, m, 5ArH.

The *trans* isomer (3b) was recrystallized from ethyl acetate to give crystals, m.p. 166–167°. Mass spectrum: *m/e* 299 (M). N.m.r. δ ($CDCl_3$) 3·20, s, NCH_3; 2·7–4·3, m, CH_2CH_2; 3·62, s, OCH_3; 3·90, s, OCH_3; 5·32, s, H1; 6·17, s, H8; 6·75, s, H5; 7·3–7·55, m, ArH.

(B) *With* m-*chloroperbenzoic acid (general procedure).*—A solution of *m*-chloroperbenzoic acid (610 mg) in chloroform (20 ml) was added dropwise with stirring to a solution of the base (1b) (500 mg) in chloroform (20 ml) at 0–5°. Stirring was continued for 40 h as the temperature rose to 20°. The solution was then washed with 5% aqueous sodium carbonate (20 ml). The aqueous layer was evaporated to dryness in vacuum and the residue extracted with chloroform (2 × 20 ml). The combined chloroform solutions were dried (sodium sulfate) and evaporated to an oil, which

[18] Culvenor, C. C. J., *Rev. Pure Appl. Chem.*, 1953, **3**, 83.
[19] Yardley, J. P., *Synthesis*, 1973, 543.
[20] Leander, K., Lüning, B., and Ruusa, E., *Acta Chem. Scand.*, 1969, **23**, 244.
[21] Kametani, T., Shiro, M., and Fukomoto, K., *Yakugaku Zasshi*, 1965, **85**, 960.

was subjected to p.l.c. (chloroform/10% methanol). After recrystallization from methanol/diethyl ether, the *N*-oxides (2b)/(3b), R_F 0·2, were isolated as prisms (399 mg, 76%), m.p. 115–118°.

7,8-Dimethoxy-3-methyl-1-phenyl-1,3,4,5-tetrahydro-2,3-benzoxazepine (5b)

(A) *By direct pyrolysis.*—The *N*-oxides [(2b) and (3b)], as initially isolated (186 mg), were placed in a flask which was immersed in an oil bath. The flask was heated under vacuum (< 1 mmHg) to 120° during 0·5 h, and the crude reaction mixture was then subjected to p.l.c. (chloroform/2% methanol). The fraction, R_F 0·75, was recrystallized from diethyl ether/light petroleum (b.p. 40–60°) to give the *benzoxazepine* (5b) (140 mg, 77%), m.p. 78–79° (Found: C, 72·2; H, 7·3; N, 4·7. $C_{18}H_{21}NO_3$ requires C, 72·2; H, 7·1; N, 4·7%). Mass spectrum: Found: 299·1531. Calc. for $C_{18}H_{21}NO_3$: 299·1521. λ_{max} (log ε) 285 (3·50), 239 (3·88) nm. N.m.r. δ ($CDCl_3$) 2·75, s, NCH_3; 2·6–3·1, m, CH_2; 3·1–3·7, m, CH_2; 3·69, s, OCH_3; 3·88, s, OCH_3; 6·05, s, H1; 6·38, s, H9; 6·71, s, H6; 7·33, m, 5ArH.

The *cis*-*N*-oxide (2b) (50 mg) similarly gave the benzoxazepine (5b) (41 mg, 82%), and the *trans*-*N*-oxide (3b) (22 mg), heated to *c.* 160°, gave (5b) (10 mg, 45%). Separation of the *N*-oxides was thus not necessary for preparation of the ring-expanded product.

(B) *Pyrolysis in solution.*—(i) A solution of the *N*-oxide (2b)/(3b) (50·5 mg) in dry ethanenitrile (3·6 ml) was refluxed for 40 min. The solvent was removed in vacuum and the residue worked up as described before to give the benzoxazepine (5b) (35 mg, 84%), and unchanged *N*-oxide (9 mg).

(ii) The *N*-oxide (2b)/(3b) (56·5 mg) was refluxed in dry pyridine (3·5 ml) for 25 min. The solvent was removed and the residue worked up as above to give the benzoxazepine (5b) (43 mg, 76%), and the deoxygenated base (1b) (10 mg, 18%).

6,7-Dimethoxy-2-methyl-1-phenyl-1,2,3,4-[1-D]tetrahydroisoquinoline (1c)

6,7-Dimethoxy-2-methyl-1-phenyl-3,4-dihydroisoquinolinium iodide (447 mg) in methan[D]ol (10 ml) and deuterium oxide (0·2 ml) was stirred at 20° for 12 h in the presence of sodium tetradeuteroborate (100 mg). After removal of the solvent in vacuum, water (100 ml) was added and the mixture extracted with chloroform (3 × 10 ml). The extracts were dried (sodium sulfate), the solvent was removed and the residue subjected to p.l.c. (chloroform/4% methanol). The *deuterated isoquinoline* (1c), R_F 0·5, was recrystallized from light petroleum (b.p. 60–80°) as crystals, m.p. 79–81° (238 mg, 77%). Mass spectrum: Found: 284·1634. Calc. for $C_{18}H_{20}DNO_2$: 284·1630. N.m.r. δ ($CDCl_3$) 2·25, s, NCH_3; 2·5–2·9, m, CH_2; 3·0–3·3, m, CH_2; 3·57, s, OCH_3; 3·85, s, OCH_3; 6·12, s, H8; 6·63, s, H5; 7·29, m, 5ArH.

N-*Oxidation of (1c)*

The deuterated isoquinoline (1c) (187 mg) was oxidized with 30% aqueous hydrogen peroxide, as described for (1b), to yield the 1-deuterated *N*-oxide (2c)/(3c) (115 mg, 59%), which recrystallized from ethyl acetate as prisms, m.p. 117–118°. N.m.r. δ ($CDCl_3$) 3·03, s, NCH_3; 2·7–3·9, m, CH_2CH_2; 3·68, s, OCH_3; 3·91, s, OCH_3; 6·28, s, H8; 6·77, s, H5; 7·25–7·5, m, 5ArH. After recrystallization the product consisted essentially of the *cis* isomer (2c).

7,8-Dimethoxy-3-methyl-1-phenyl-1,3,4,5-[1-D]tetrahydro-2,3-benzoxazepine (5c)

The 1-deuterated *N*-oxide (111 mg) was pyrolysed as described for (2b)/(3b) (method A) to give the *[1-D]benzoxazepine* (5c) (52 mg, 47%), m.p. 76–77°. Mass spectrum: Found: 300·1583. Calc. for $C_{18}H_{20}DNO_3$: 300·1583. N.m.r. δ ($CDCl_3$) 2·76, s, NCH_3; 2·5–3·8, m, CH_2CH_2; 3·70, s, OCH_3; 3·90, s, OCH_3; 6·41, s, H9; 6·72, s, H6; 7·33, m, 5ArH.

[4,5-Dimethoxy-2-{2-(dimethylamino)ethyl}phenyl]phenylmethanol (9) by Photosolvolysis

A solution of 6,7-dimethoxy-2,2-dimethyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium iodide (415 mg) in water (250 ml), acidified with 10% aqueous sulfuric acid to pH 1–2, was irradiated for 1 h. The solution was washed with diethyl ether (3 × 30 ml), basified to pH 10–11 with concentrated aqueous ammonia, and extracted with chloroform (3 × 100 ml). The extracts were dried (sodium sulfate) and the solvent was removed in vacuum. The residue was recrystallized twice from methanol/light petroleum (b.p. 60–80°) to yield (9) (124 mg). P.l.c. (KOH–silica plate developed with chloroform/5% methanol) on the mother liquors gave more of the tertiary *amino alcohol* (9), R_F 0·35

(119 mg, total yield 79%), which recrystallized from methanol/light petroleum (b.p. 60–80°) as needles, m.p. 117–118° (Found: C, 72·6; H, 7·9. $C_{19}H_{25}NO_3$ requires C, 72·4; H, 8·0%). ν_{max} 3380 (br) cm^{-1} (OH). N.m.r. δ ($CDCl_3$) 2·21, s, $N(CH_3)_2$; 2·4–3·0, m, CH_2CH_2; 3·68, s, OCH_3; 3·88, s, OCH_3; 5·25, br s, OH; 5·93, s, CHPh; 6·55, s, ArH; 6·68, s, ArH; 7·2–7·5, m, 5ArH. The product was identical with (9) prepared by other routes described.

Reduction of the 2,3-Benzoxazepine (5b) with Zinc and Acetic Acid

A solution of the 2,3-benzoxazepine (5b) (167 mg) in acetic acid (10 ml), and zinc dust (200 mg), was stirred at 20° for 1 h. Aqueous sodium hydroxide (2 M) was added to pH 5, and 5% aqueous sodium carbonate to pH 8. The solution was extracted with chloroform (3 × 20 ml), the extracts were dried (sodium sulfate) and the solvent was removed. The residue was subjected to p.l.c. (KOH–silica plate developed with chloroform/5% methanol).

Fraction 1, R_F 0·7, was unchanged (5b) (47 mg).

Fraction 2, R_F 0·15, was obtained as an oil identified as *[4,5-dimethoxy-2-{2-(methylamino)-ethyl}phenyl]phenylmethanol* (7) (104 mg). Mass spectrum: Found: 301·1626. Calc. for $C_{18}H_{23}NO_3$: 301·1678. ν_{max} 3300 (br) cm^{-1} (OH). N.m.r. δ ($CDCl_3$) 2·32, s, NCH_3; 2·5–3·0, m, CH_2CH_2; 3·68, s, OCH_3; 3·85, s, OCH_3; 3·7–4·2, br s, NH/OH; 5·95, s, CHPh; 6·60, s, ArH; 6·67, s, ArH; 7·2–7·5, m, 5ArH.

Photosolvolysis of 6,7-Dimethoxy-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolium Chloride

A solution of this hydrochloride salt [derived from 250 mg of the free base (1b)] in water (250 ml) and 10% aqueous sulfuric acid (3 ml) was irradiated for 3 h. The solution was basified to pH 10–11 with concentrated aqueous ammonia, and extracted with chloroform (3 × 100 ml). The extracts were dried (sodium sulfate) and the solvent was removed in vacuum.

The residue was subjected to p.l.c. (KOH–silica plate, developed with chloroform/5% methanol) to give the secondary amino alcohol (7), R_F 0·15 (170 mg), shown by n.m.r. to be identical with that prepared by the reduction of (5b) with zinc and acetic acid.

This secondary amino alcohol (7) (170 mg) in methanol (20 ml) was stirred with 37% formalin (12 ml) at 20° for 0·5 h. Sodium tetrahydroborate (240 mg) was added and the solution stirred for a further 0·5 h. After removal of the solvent in vacuum the residue was basified with 5% aqueous hydroxide, and then extracted with diethyl ether (2 × 50 ml). The extracts were washed with water (10 ml), dried (sodium sulfate) and the solvent was removed. Treatment of the residue by p.l.c. (KOH–silica plate developed with chloroform/10% methanol) gave *[4,5-dimethoxy-2-{2-(dimethylamino)ethyl}phenyl]phenylmethanol* (9). Mass spectrum: *m/e* 315 (M) ($C_{19}H_{25}NO_3$ requires 315). N.m.r. δ ($CDCl_3$) 2·22, s, $N(CH_3)_2$; 2·4–3·0, m, CH_2CH_2; 3·68, s, OCH_3; 3·87, s, OCH_3; 5·8, br s, OH; 5·95, s, CHPh; 6·62, s, ArH; 6·70, s, ArH; 7·2–7·5, m, 5ArH.

7,8-Dimethoxy-3,3-dimethyl-1-phenyl-1,3,4,5-tetrahydro-2,3-benzoxazepinium Iodide (6)

A solution of the 2,3-benzoxazepine (5b) (342 mg) in dry methanol (5 ml) and iodomethane (2 ml) was kept at 20° in the dark for 50 h. The solvent was removed in vacuum, and the residue washed with dry diethyl ether. Recrystallization from methanol gave the *methiodide* (6) (242 mg) (48%) as needles, m.p. 123–124° (Found: C, 51·7; H, 5·7. $C_{19}H_{24}INO_3$ requires C, 51·9; H, 5·5%). N.m.r. δ ($CDCl_3$) 3·45, s, NCH_3; 3·3–3·7, m, CH_2; 3·78, s, 3H; 3·85, s, 3H, OCH_3 and NCH_3; 4·18, s, OCH_3; 4·4–5·2, m, CH_2; 5·97, s, H1; 6·92, s, H9; 7·3–7·7, m, 6ArH.

Reduction of (6) with Zinc and Acetic Acid

A solution of the methiodide (6) (50 mg) in acetic acid (10 ml) was stirred with zinc dust (200 mg) at 20° for 1 h, and the residue was then worked up as described earlier. The crude product was subjected to p.l.c. (chloroform/5% methanol) with multiple development (twice) to give two fractions.

Fraction 1 (< 10 mg) was essentially the ketone (8), ν_{max} 1655 cm^{-1} (C=O).

Fraction 2 (34 mg) was shown by n.m.r. to consist of about 85% of the tertiary amino alcohol (9).

Reduction of (6) with Lithium Tetrahydroaluminate

A solution of the methiodide (6) (100 mg) and lithium tetrahydroaluminate (200 mg) in dry tetrahydrofuran (50 ml) was stirred at 20° for 12 h. Ethyl ethanoate (2 ml) was added, and the solu-

tion evaporated to dryness. The residue was partitioned between chloroform (50 ml) and 5% aqueous hydrochloric acid (50 ml), and the solutions were filtered. The filtrate was neutralized with 10% aqueous ammonia, and the chloroform layer was separated, washed with water (10 ml) and dried (sodium sulfate). Removal of the solvent left a solid which was subjected to p.l.c. (chloroform/10% methanol) to yield the tertiary *amino alcohol* (9) (27 mg), shown by n.m.r. to be identical with that prepared by previous methods.

Conversion of (6) into the Amino Ketone (8)

A solution of the methiodide (6) (87 mg) and sodium hydroxide (200 mg) in water (2 ml) was refluxed for 5 min. Water (10 ml) was added, the aqueous solution extracted with chloroform (2 × 30 ml), and the extracts were dried (sodium sulfate). The residue, after removal of the solvent, was subjected to p.l.c. (KOH–silica plate, developed twice with chloroform/5% methanol) and gave as the major fraction [*4,5-dimethoxy-2-{2-(dimethylamino)ethyl}phenyl]phenylmethanone* (8) (38 mg). Mass spectrum: Found: 313·1669. Calc. for $C_{19}H_{23}NO_3$: 313·1678. ν_{max} 1655 cm^{-1} (C=O). N.m.r. δ ($CDCl_3$) 2·21, s, $N(CH_3)_2$; 2·4–2·65, m, CH_2; 2·7–2·95, m, CH_2; 3·82, s, OCH_3; 3·98, s, OCH_3; 6·88, s, 2ArH; 7·4–7·7, m, 3ArH; 7·75–7·9, m, 2ArH.

Reduction of the Ketone (8) with Sodium Tetrahydroborate

To a solution of ketone (8) (18 mg) in ethanol (5 ml) was added sodium tetrahydroborate (50 mg), and the mixture was stirred at 20° for 1 h. The solvent was removed, water (10 ml) was added, and the mixture extracted with chloroform (2 × 10 ml). The extract was dried (sodium sulfate), and the solvent removed to yield the tertiary amino alcohol (9) (15 mg).

Oxidation of the Alcohol (9)

The tertiary amino alcohol (9) (74 mg) in acetone (10 ml), and Jones reagent[22] (1 ml) was stirred at 20° for 3 h. Excess sodium bisulfite was added, and stirring continued for a further 10 min. The solution was neutralized and extracted with chloroform (2 × 10 ml), dried (sodium sulfate), and the solvent removed to give the amino ketone (8) (15 mg), identical with the previous preparation.

6,7-Dimethoxy-1-(3,4-dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline N-*Oxide (10)*

6,7-Dimethoxy-1-(3,4-dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline[20] (1·312 g) and 30% aqueous hydrogen peroxide (10 ml) were stirred at 20° until the mixture became homogeneous (58 h). Water (50 ml) was added, and the solution was extracted with chloroform (2 × 100 ml) after destruction of the excess hydrogen peroxide with platinum foil. The extracts were dried (sodium sulfate), the solvent removed in vacuum, and the residue subjected to p.l.c. (chloroform/12% methanol). The *isoquinoline* N-*oxide* (10), R_F 0·25, was isolated as an oil (545 mg, 70%) which crystallized from light petroleum (b.p. 60–80°) as prisms, m.p. 105–108°. Mass spectrum: *m/e* 359 (M) ($C_{20}H_{25}NO_5$ requires 359). N.m.r. δ $CDCl_3$ 3·00, s, 3·18, s (3 : 1), NCH_3; 2·8–4·2, m, CH_2CH_2; 3·68, s, OCH_3; 3·74, s, OCH_3; 3·90, s, 2 × OCH_3; 5·30, s, 5·43, s (1 : 3), H1; 6·18, s, 6·31, s (1 : 3), H8; 6·72, s, H5; 6·7–6·95, m, 3ArH. The n.m.r. indicated a mixture of isomers.

7,8-Dimethoxy-1-(3,4-dimethoxyphenyl)-3-methyl-1,3,4,5-tetrahydro-2,3-benzoxazepine (12)

The isoquinoline *N*-oxide (10) (200 mg) was placed in a 10-ml flask which was immersed in an oil bath. The flask was heated under vacuum (< 1 mmHg) to 106° during 0·5 h to give an oil. The crude product was subjected to p.l.c. (chloroform/2% methanol) to yield the *benzoxazepine* (12) (166 mg, 83%), R_F 0·5, which recrystallized from dry diethyl ether as needles, m.p. 91–93° (Found: C, 66·5; H, 7·0. $C_{20}H_{25}NO_5$ requires C, 66·8; H, 7·0%). Mass spectrum: Found: 359·1792. Calc. for $C_{20}H_{25}NO_5$: 359·1733. λ_{max} (log ε): 284sh (3·58), 281 (3·59), 235 (3·96) nm. N.m.r. δ ($CDCl_3$) 2·74, s, NCH_3; 2·1–3·3, m, CH_2; 3·3–4·2, m, CH_2; 3·72, s, OCH_3; 3·86, s, 2 × OCH_3; 3·90, s, OCH_3; 6·03, s, H1; 6·42, s, H9; 6·72, s, H6; 6·7–6·9, m, 3ArH.

[22] Fieser, L. F., and Fieser, M., 'Reagents for Organic Synthesis' p. 142 (John Wiley: New York 1967).

2-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline N-*Oxide* (*11*)

2-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline was prepared by a Bischler–Napieralski cyclization of *N*-(2-phenylethyl)benzamide with phosphorus oxychloride, followed by formation of the methiodide salt[23] and reduction with sodium tetrahydroborate (cf.[20]). The product was recrystallized from light petroleum (b.p. 60–80°) to give crystals, m.p. 69–71° (lit.[24] 72°).

This base was oxidized with *m*-chloroperbenzoic acid, as previously described, and the product was subjected to p.l.c. (chloroform/12% methanol), R_F 0·15, to give the N-*oxide* (11) (62%) as prisms, m.p. 141–142°. N.m.r. δ ($CDCl_3$) 3·02, s, 3·17, s (3 : 1), NCH_3; 3·2–4·2, m, CH_2CH_2; 5·45, s, 5·67, s (1 : 3), H1; 6·78, s, 6·85, s (1 : 3), H8; 7·0–7·5, m, 8ArH. The n.m.r. indicated a mixture of isomers.

3-Methyl-1-phenyl-1,3,4,5-tetrahydro-2,3-benzoxazepine (*13*)

The *N*-oxide (11) (143 mg) was pyrolysed at 140–150° (melt; < 1 mmHg; 0·5 h), and the crude product subjected to p.l.c. (chloroform) to give the *2,3-benzoxazepine* (13), R_F 0·3 (50 mg, 35%), as needles from hexane, m.p. 67–68° (Found: C, 80·3; H, 7·5. $C_{16}H_{17}NO$ requires C, 80·3; H, 7·2%). Mass spectrum: Found: 239·1357. Calc. for $C_{16}H_{17}NO$: 239·1310. λ_{max} (log ε): 272sh (2·62), 267sh (2·86), 263sh (2·81), 259 (2·85), 252sh (2·83) nm. N.m.r. δ ($CDCl_3$) 2·74, s, NCH_3; 2·6–3·8, m, CH_2CH_2; 6·12, s, H1; 6·8–7·0, m, ArH; 7·0–7·25, m, 3ArH; 7·25–7·4, m, 5ArH.

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[23] Cannon, J. G., and Webster, G. L., *J. Am. Pharm. Assoc., Sci. Ed.*, 1958, **47**, 353 (*Chem. Abstr.*, 1958, **52**, 17273a).
[24] Brook, P. R., and Karrer, P., *Helv. Chim. Acta*, 1957, **40**, 260.