Nitrene. Part VI.[1] Reaction of 6′-Nitropapaverine and its Analogue with Triethyl Phosphite [2]

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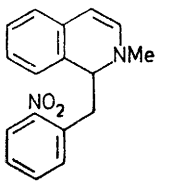
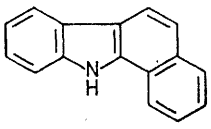
The reaction of 6′-nitropapaverine (IX) and its analogue (X) with triethyl phosphite afforded two unexpected pairs of indolo[2,3-*a*][3]benzazepine derivatives, (XI) and (XIII), and (XII) and (XIV), respectively, the structures of which were assigned on the basis of spectroscopic evidence.

We have previously [1,3-8] investigated novel synthetic procedures for nitrogen-containing heterocyclic compounds by the reaction of various nitro-compounds with triethyl phosphite. An interesting result [4,6] was the production of the benzo[*a*]carbazole (II) (37%) and 5,6-dihydro-2,3,9,10-tetramethoxybenzo[*a*]carbazole (IV) (38·5%), on treatment of 1,2-dihydro-2-methyl-1-(2-nitrobenzyl)isoquinoline (I) and 6′-nitrolaudanosine (III), respectively, with triethyl phosphite. Similar treatment of the methiodide (V) of (III), however, gave no benzo[*a*]carbazole; 6′-aminolaudanosine methiodide (VI) was obtained instead.[6] We have now studied the reaction of 6′-nitropapaverine (IX) with triethyl phosphite, which gives, unexpectedly, two indolobenzazepine derivatives.



(I)



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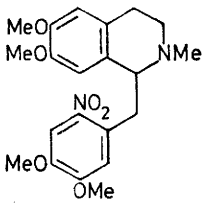

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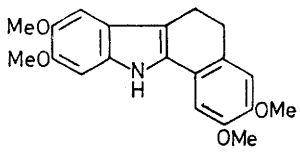

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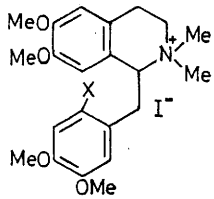
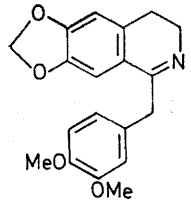
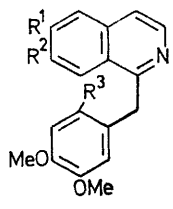


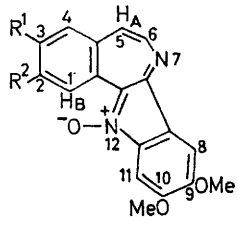
(V) X = NO_2
(VI) X = NH_2



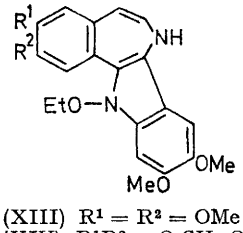
(VII)



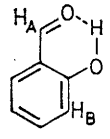
(VIII) R^1R^2 = O·CH_2·O, R^3 = H
(IX) R^1 = R^2 = OMe, R^3 = NO_2
(X) R^1R^2 = O·CH_2·O, R^3 = NO_2



(XI) R^1 = R^2 = OMe
(XII) R^1R^2 = O·CH_2·O



(XIII) R^1 = R^2 = OMe
(XIV) R^1R^2 = O·CH·O



(XV)

The structures of these compounds, (XI) and (XIII), were assigned on the basis of spectroscopic evidence. Microanalysis and the mass spectrum of compound (XI) verified its composition as $C_{20}H_{18}N_2O_5$. The mass spectrum showed only the characteristic peaks (*M* −15 and −43) at *m/e* 351 and 323, with a strong molecular ion peak at 366. The i.r. spectrum showed strong absorptions at 1220 and 1258 cm.$^{-1}$ (C–O and/or N–O) and those of the aromatic ring system. The n.m.r. spectrum showed signals for four methoxy-groups [δ 4·00 (6H), 4·04 (3H), and 4·15 (3H)] and four aromatic protons (6·99, 7·08, 7·73, and 10·35 p.p.m.) as singlets; the resonance at 10·35 p.p.m. was shifted to a lower field owing to the paramagnetic anisotopy of the *N*-oxide oxygen. An AB quartet attributable to the 5- and 6-protons was also observed, at δ 7·48 and 8·37 (*J* 7 c./sec.). On decoupling a further long-range coupling (*J* *ca.* 0·7 c./sec.) between the C-5 proton (H_A) and the C-1 proton (H_B) was revealed. This type of coupling has been recognised in the case of the compound (XV) [9,10] and

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[2] This forms Part CCCXL of 'Studies on the Syntheses of Heterocyclic Compounds,' by T. Kametani.
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supports the partial structure of (XI) (relationship between H_A and H_B). The signals showed no change on addition of deuterium oxide.

Compound (XIII) had the composition $C_{22}H_{24}N_2O_5$ (microanalysis and mass spectrum). The i.r. (KBr) spectrum showed an NH group (3450 cm.$^{-1}$) and the n.m.r. spectrum showed signals for four methoxy-groups as [δ 4·00 (12H, s)], an ethoxy-group [δ 1·55 (t) and 4·42 (q) (*J* 6·6 c./sec.)], and four aromatic protons [6·87, 7·27, 7·50, and 7·63 p.p.m.]. The resonances of the 5- and 6-protons were observed as an AB system (*J* 8·3 c./sec.) and a one-proton signal at 4·26 p.p.m. was removed on addition of deuterium oxide.

Similar treatment of the nitroisoquinoline derivative (X) with triethyl phosphite afforded two compounds, (XII) and (XIV), shown to correspond to the compounds (XI) and (XIII), respectively, by spectroscopic evidence. In this case, even if an excess of triethyl phosphite was used, the N–O linkage was preserved (*cf.* ref. 11).

EXPERIMENTAL

I.r. spectra were measured with a Hitachi EPI-3 recording spectrophotometer, n.m.r. spectra with a Hitachi H-60 spectrometer and a JNM-4H-100 spectrometer (with tetramethylsilane as internal standard), and mass spectra with a Hitachi RMU-7 spectrometer.

Reaction of 6′-Nitropapaverine with Triethyl Phosphite.—A solution of 6′-nitropapaverine (IX) (5 g.) in triethyl phosphite (11·2 g.) was heated under reflux at 160—170° for 20 hr. in a current of nitrogen; the excess of triethyl phosphite and the triethyl phosphate formed were distilled off *in vacuo* to give a syrup, which crystallised when triturated with ethanol. Filtration and recrystallisation from chloroform gave 2,3,9,10-*tetramethoxyindolo*[2,3-a][3]-*benzazepine* 12-*oxide* (XI) (0·2 g., 4·2%) as yellow powder, m.p. 277—278° (Found: C, 65·1; H, 5·0; N, 7·7. $C_{20}H_{18}N_2O_5$ requires C, 65·55; H, 4·95; N, 7·65%), $\nu_{max.}$ (KBr) 1220 and 1258 cm.$^{-1}$, *m/e* 366 (M^+ 100%), 351 ($M-15$), and 323 ($M-43$), δ ($CDCl_3$) 4·00 (6H, s, 2 × OMe), 4·04 and 4·51 (each 3H, s, OMe), 6·99 and 7·07 (each 1H, s, aromatic), 7·48 (1H, d, *J* 7 c./sec., 5-H), 7·73 (1H, s, aromatic), 8·37 (1H, d, 6-H), and 10·35 (1H, s, aromatic) p.p.m.

The filtrate was chromatographed on silica gel with benzene as eluant to give 12-*ethoxy*-5,6,7,12-*tetrahydro*-2,3,9,10-*tetramethoxyindolo*[2,3-a][3]*benzazepine* (XIII) (0·3 g., 6·1%) as colourless leaflets, m.p. 181—182° (from benzene) [Found (sample dried *in vacuo* at 60° over P_2O_5 for 2 days): C, 65·55; H, 5·85; N, 6·85. $C_{22}H_{24}N_2O_5,0{\cdot}5H_2O$ requires C, 65·25; H, 6·2; N, 6·9%], *m/e* 396 (M^+, 2%), 395 ($M-1$, 4%), 366 ($M-30$, 6%), 351 ($M-45$, 6%), 339 ($M-57$, 31%), and 338 ($M-58$, 100%), $\nu_{max.}$ (KBr) 3450 (NH) and 1620 cm.$^{-1}$, δ ($CDCl_3$) 1·55 (3H, t, *J* 6·6 c./sec., $CH_2{\cdot}CH_3$), 4·00 (12H, s, 4 × OMe), 4·26 (1H, s, NH, exchangeable), 4·42 (2H, q, *J* 6·6 c./sec., $CH_2{\cdot}CH_3$), 3·87 and 7·27 (each 1H, s, aromatic), 7·41 (1H, d, *J* 8·3 c./sec., 5- or 6-H), 7·50 and 7·63 (each 1H, s, aromatic), and 7·58 (1H, d, *J* 8·3 c./sec., 5- or 6-H) p.p.m.

1-(3,4-*Dimethoxybenzyl*)-6,7-*methylenedioxyisoquinoline* (VIII).—A mixture of 3,4-dihydro-1-(3,4-dimethoxybenzyl)-6,7-methylenedioxyisoquinoline[12] (VII) (5 g.), benzene (5 ml.), decalin (20 ml.), and 5% palladium–charcoal (0·3 g.) was heated under reflux at 140° in an oil-bath for 10 hr. in a current of nitrogen. The mixture was filtered while warm and the filtrate, when set aside at room temperature, deposited the *isoquinoline derivative* (VIII) as colourless needles (2·7 g.), m.p. 125—127° (from benzene–hexane) (Found: C, 70·2; H, 5·4; N, 4·65. $C_{19}H_{17}NO_4$ requires C, 70·55; H, 5·3; N, 4·35%), δ ($CDCl_3$) 3·78 (6H, s, 2 × OMe), 4·43 (2H, s, benzylic CH_2), 6·00 (2H, s, $O{\cdot}CH_2{\cdot}O$), 6·73br (3H, s, aromatic), 6·99 (1H, aromatic), 7·31 (1H, d, *J* 7 c./sec., 4-H), 7·34 (2H, s, aromatic), and 8·33 (1H, d, *J* 7 c./sec., 3-H) p.p.m.

1-(4,5-*Dimethoxy*-2-*nitrobenzyl*)-6,7-*methylenedioxyisoquinoline* (X).—To nitric acid (*d* 1·42; 40 ml.) was added in portions the isoquinoline (VIII) (5 g.) at 0—5° during 3 hr. with stirring. The mixture was then poured into ice–water (300 ml.); the product was basified with saturated potassium carbonate solution and extracted with benzene. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the *nitroisoquinoline derivative* (X) as orange needles (3·1 g.), m.p. 208—210° (from benzene–hexane) (Found: C, 62·1; H, 4·5; N, 7·85. $C_{19}H_{16}N_2O_6$ requires C, 61·95; H, 4·4; N, 7·6%), $\nu_{max.}$ (KBr) 1520 and 1320 cm.$^{-1}$ (NO_2), δ ($CDCl_3$) 3·89 and 3·95 (each 3H, s, OMe), 4·92 (2H, s, benzylic CH_2), 6·11 (2H, s, $O{\cdot}CH_2{\cdot}O$), 6·68, 7·10, 7·42, and 7·75 (each 1H, s, aromatic), and 7·37 and 8·29 (each 1H, d, *J* 7 c./sec., 4- and 3-H) p.p.m.

Reaction of (X) *with Triethyl Phosphite.*—A mixture of the nitroisoquinoline (X) (2·5 g.) and triethyl phosphite (25 ml.) was refluxed at 170° in an oil-bath for 20 hr. under nitrogen. It was then set aside at room temperature; the crystals deposited gave the 9,10-*dimethoxy*-2,3-*methylenedioxyindolo*[2,3-a][3]*benzazepine* 12-*oxide* (XII) (35 mg., 1·6%) as a yellow powder, m.p. 288—290° (from chloroform–ethanol) (Found: C, 65·6; H, 4·35. $C_{19}H_{14}N_2O_5$ requires C, 65·15; H, 4·05%), δ ($CDCl_3$) 3·98 and 4·03 (each 3H, s, OMe), 6·12 (2H, s, $O{\cdot}CH_2{\cdot}O$), 6·90, 7·15, 7·51, and 10·03 (each 1H, s, aromatic), and 7·45 and 7·80 (each 1H, d, *J* 7 c./sec., 5- and 6-H) p.p.m.

Evaporation of the filtrate gave a syrup, which was chromatographed on silica gel with benzene as eluant to give 12-*ethoxy*-5,6,7,12-*tetrahydro*-9,10-*dimethoxy*-2,3-*methylenedioxyindolo*[2,3-a][3]*benzazepine* (XIV) (42 mg., 1·8%) as pale green needles, m.p. 184—186° (from benzene–hexane) [Found (sample dried at 60° *in vacuo* over P_2O_5 for 2 days): C, 64·9; H, 5·88. $C_{21}H_{20}N_2O_5,0{\cdot}33H_2O$ requires C, 65·35; H, 5·4%], $\nu_{max.}$ ($CHCl_3$) 3400 cm.$^{-1}$ (NH and H_2O), δ ($CDCl_3$), 1·61 (3H, t, *J* 6·6 c./sec., $CH_2{\cdot}CH_3$), 3·93 and 3·95 (each 3H, s, OMe), 4·18 (2H, q, *J* 6·6 c./sec., $CH_2{\cdot}CH_3$), 4·37br (1H, s, NH), 6·08 (2H, s, $O{\cdot}CH_2{\cdot}O$), 6·78, 6·99, 7·28, and 7·54 (each 1H, s, aromatic), and 7·05 and 7·30 (each 1H, d, *J* 8 c./sec., 5- and 6-H) p.p.m.

We thank Miss R. Hasebe, Miss A. Kawakami, Miss Y. Tadano, Miss T. Yoshida, Miss K. Shima, and Miss R. Kato, Pharmaceutical Institute, Tohoku University, for microanalyses and n.m.r. determinations.

[9/555 *Received, March 31st,* 1969]

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