Nitrenes. Part III.[1,2] The Reaction of 4-(2-Nitrophenyl)pyridine Derivatives with Triethyl Phosphite

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Reductive cyclisation of 4-(2-nitrophenyl)pyridine derivatives by triethyl phosphite afforded β-carboline and benzo[*c*][2,7]naphthyridine derivatives, the structures of which were elucidated by spectroscopic methods.

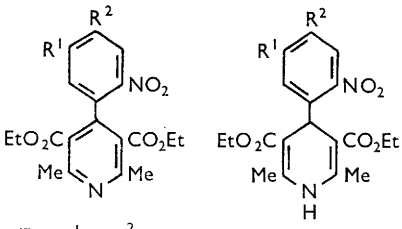
REDUCTIVE cyclisation of aromatic compounds has been carried out by a number of investigators[1,3-8] with triethyl phosphite and it has been postulated that the nitrene intermediates are involved in these reactions. We have previously[6] reported modified syntheses of β-carboline derivatives through nitrene intermediates and now report the reaction of 4-(2-nitrophenyl)pyridine derivatives (I) and (II) with triethyl phosphite to give the expected β-carboline derivatives (III) and (IV) and the benzo[*c*][2,7]naphthyridine derivatives (V) and (VI). These results suggest the possibility of the participation of nitrene.

When the pyridine derivatives (I) and (II) (1 mole) [obtained from 3,4-dimethoxy-6-nitrobenzaldehyde and 3,4-methylenedioxy-6-nitrobenzaldehyde by a modified Hantzsch method[9] by way of the 1,4-dihydropyridine derivatives (Ia) and (IIa)] were heated with triethyl phosphite (5 moles) at 160—170° for 20 hr. in a current of nitrogen, the β-carboline derivatives (III) (24·7%), m.p. 99—101° and (IV) (17%), m.p. 121—123°, and the benzo[*c*][2,7]naphthyridine derivatives (V) (19·4%), m.p. 116—119° and (VI) (23·5%), m.p. 168—170°, were formed.

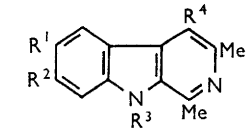
The compounds (III) and (IV), formed by removal of two oxygen atoms from the starting materials, showed the corresponding molecular ion peaks in their mass spectra. Their n.m.r. spectra each showed two methyl and two ethoxy-groups, and two aromatic protons. Hydrolysis of (III) and (IV) with ethanolic potassium hydroxide gave the expected de-ethoxycarbonylation products (VII) and (VIII), the mass spectra of which showed the corresponding molecular ion peaks, and the i.r. spectra of which showed NH-stretching absorptions.

The compounds (V) and (VI), formed by removal of three oxygen atoms from the starting materials, showed the corresponding molecular ion peaks in the mass spectrum. Their n.m.r. spectra showed the same substituents as compounds (III) and (IV), but the chemical shift values were different. The compounds were stable to alkaline hydrolysis, but easily hydrolysed with concentrated hydrochloric acid to give the corresponding de-ethylated compounds (IX) and (X).

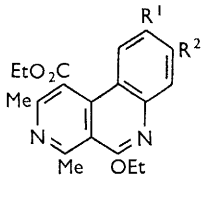
The formation of these compounds is explicable in terms of nitrene intermediates. The β-carboline derivatives (III) and (IV) are presumably formed by the characteristic insertion reaction of nitrenes;[10,11] this is the first example of this type of reaction in which



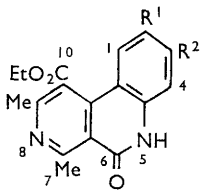
(I) $R^1 = R^2 = OMe$ (Ia)
(II) $R^1 = R^2 = O{\cdot}CH_2{\cdot}O$ (IIa)



(III) $R^1 = R^2 = OMe$, $R^3 = R^4 = CO_2Et$
(IV) $R^1 = R^2 = O{\cdot}CH_2{\cdot}O$, $R^3 = R^4 = CO_2Et$
(VII) $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = CO_2Et$
(VIII) $R^1 = R^2 = O{\cdot}CH_2{\cdot}O$, $R^3 = H$, $R^4 = CO_2H$



(V) $R^1 = R^2 = OMe$
(VI) $R^1 = R^2 = O{\cdot}CH_2{\cdot}O$



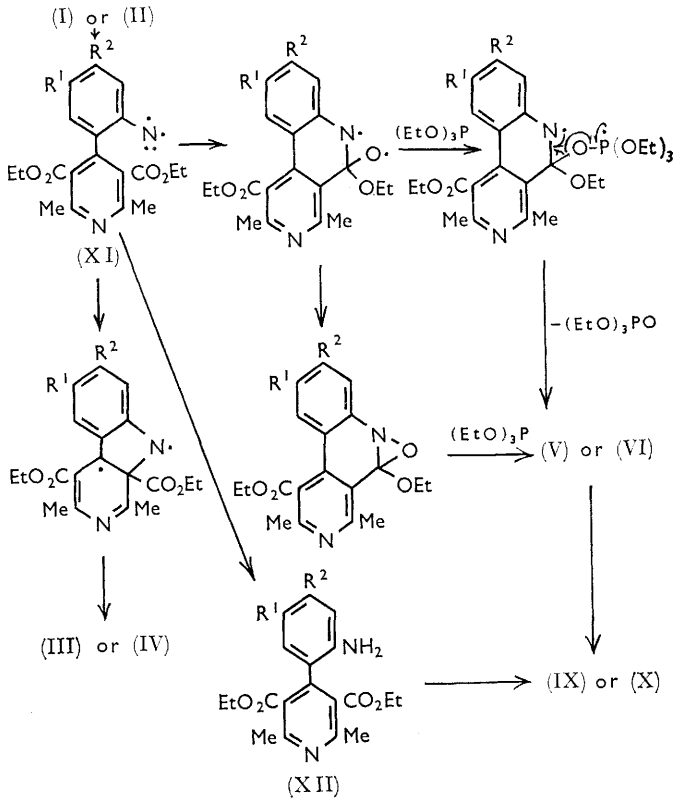
(IX) $R^1 = R^2 = OMe$
(X) $R^1 = R^2 = O{\cdot}CH_2{\cdot}O$

insertion of the nitrene into an aromatic carbon–carbon bond α to a carbonyl group has taken place. Compounds (V) and (VI) could be formed by attack of the nitrene on the ester carbonyl carbon, followed by deoxygenation with an excess of triethyl phosphite.

Compounds (IX) and (X) were separated as by-products after the reactions of (I) and (II) with triethyl phosphite; this could indicate the formation of (V) and (VI) by ethylation of the intermediates (IX) and (X) with an excess of triethyl phosphite. However, when (IX) and (X) were heated with an excess of triethyl phosphite, only the starting materials were recovered. The formation of (IX) and (X) could result from an abstraction reaction of nitrene (XI) to give the amino-derivative (XII); amide formation could then

[1] Preliminary communication, T. Kametani, T. Yamanaka, and K. Ogasawara, *Chem. Comm.*, 1968, 786.
[2] Part II, T. Kametani, T. Yamanaka, and K. Ogasawara, *J. Org. Chem.*, in the press.
[3] J. I. G. Cadogan, N. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, *J. Chem. Soc.*, 1965, 4831.
[4] J. I. G. Cadogan, R. K. Mackie, and M. J. Todd, *Chem. Comm.*, 1966, 491.
[5] R. J. Sundberg, *J. Org. Chem.*, 1965, **30**, 3604.
[6] R. J. Sundberg and T. Yamazaki, *J. Org. Chem.*, 1967, **32**, 299.
[7] A. W. Murray and K. Vaughan, *Chem. Comm.*, 1967, 1282.
[8] T. Kametani, K. Ogasawara, and T. Yamanaka, *J. Chem. Soc.* (*C*), 1968, 1006.
[9] T. Kametani, K. Ogasawara, and A. Kozuka, *J. Pharm. Soc. Japan*, 1966, **86**, 815.
[10] G. Smolinsky and B. I. Feuer, *J. Org. Chem.*, 1966, **31**, 3882.
[11] J. I. G. Cadogan and M. J. Todd, *Chem. Comm.*, 1967, 178.

occur to give the compounds (IX) and (X). The mechanism shown in the Scheme appears the most likely explanation of our observations.



SCHEME

Thus, in case of compounds whose cyclisation position is occupied by a substituent, ring-closure resulting from nitrene formation should still be possible. Furthermore, our results substantiate the presence of nitrene intermediates as shown by Smolinsky and Feuer [10] and Cadogan and Todd.[11]

EXPERIMENTAL

Infrared spectra were measured with a Hitachi EPI-3 recording spectrophotometer, and n.m.r. spectra with Hitachi H-60 spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded with a Hitachi RMU-6D spectrometer.

3,5-Diethoxycarbonyl-1,4-dihydro-2,6-dimethyl-4-(4,5-dimethoxy-2-nitrophenyl)pyridine (Ia).—A mixture of 3,4-dimethoxy-6-nitrobenzaldehyde (42 g.), ethyl acetoacetate (26 g.), ethyl β-aminocrotonate (26 g.), and a few drops of piperidine was heated on a water-bath overnight; yellow crystals were precipitated. After trituration with ethanol, the solid was filtered off to give the *dihydropyridine derivative* (Ia) (52 g.) as yellow prisms, m.p. 238—239° (from chloroform–ethanol) (Found: C, 58·15; H, 6·1; N, 6·55. $C_{21}H_{26}N_2O_8$ requires C, 58·05; H, 6·05; N, 6·45%).

3,5-Diethoxycarbonyl-2,6-dimethyl-4-(4,5-dimethoxy-2-nitrophenyl)pyridine (I).—To a suspension of compound (Ia) (28 g.) in acetic acid (80 ml.) was added a saturated solution of chromic anhydride (6 g.) in water, and the mixture was heated on a water-bath for 2 hr. It was then cooled and poured into cold water (500 ml.), and the crystals were filtered off to give the *pyridine derivative* (I) (22·5 g.) as colourless prisms, m.p. 154—155° (from ethanol) (Found: C, 58·3; H, 5·7; N, 6·45. $C_{21}H_{24}N_2O_8$ requires C, 58·35; H, 5·6; N, 6·5%).

3,5-Diethoxycarbonyl-1,4-dihydro-2,6-dimethyl-4-(4,5-methylenedioxy-2-nitrophenyl)pyridine (IIa).—A mixture of 3,4-methylenedioxy-6-nitrobenzaldehyde (19·5 g.), ethyl acetoacetate (13 g.), ethyl β-aminocrotonate (12·9 g.), and a few drops of piperidine was treated as in the preparation of (Ia) to give the *1,4-dihydropyridine* (IIa) (20 g.) as yellow prisms, m.p. 98° (from ethanol) (Found: C, 57·4; H, 5·75; N, 6·55. $C_{20}H_{22}N_2O_8$ requires C, 57·4; H, 5·3; N, 6·7%).

3,5-Diethoxycarbonyl-2,6-dimethyl-4-(4,5-methylenedioxy-2-nitrophenyl)pyridine (II).—A suspension of (IIa) (28 g.) in acetic acid (100 ml.) was oxidised with saturated aqueous chromic anhydride (6 g.) as described for the preparation of (I) to give the *pyridine derivative* (II) (25 g.) as pale yellow prisms, m.p. 134—135° (from ethanol) (Found: C, 57·8; H, 4·95; N, 6·6. $C_{20}H_{20}N_2O_8$ requires C, 57·7; H, 4·85; N, 6·75%).

Reaction of the Pyridine Derivative (I) *with Triethyl Phosphite*.—A solution of compound (I) (5 g.) in triethyl phosphite (9·6 g.) was heated under reflux at 160—170° for 20 hr. under a current of nitrogen, and the mixture was distilled at 100°/3 mm. to remove a lower-boiling substance. The residue was dissolved in a little benzene and the crystals which separated from the cooled solution were filtered off to give *ethyl 5,6-dihydro-2,3-dimethoxy-7,9-dimethyl-6-oxobenzo*[c][2,7]*naphthyridine-10-carboxylate* (IX) (50 mg.) as colourless leaflets, m.p. 268—270° (from chloroform–ethanol) (Found: C, 63·6; H, 5·8; N, 7·4. $C_{19}H_{20}N_2O_5$ requires C, 64·05; H, 5·65; N, 7·85%), $\nu_{max.}$ (KBr) 1725 (ester C=O) and 1678 (amide C=O) cm.$^{-1}$, δ (CF_3CO_2H) 1·40 (3H, *J* 6·6 c./sec., O·CH_2·CH_3), 2·77 (3H, s, CMe), 3·26 (3H, s, CMe), 3·90 (3H, s, OMe), 4·07 (3H, s, OMe), 4·55 (2H, q, *J* 6·6 c./sec., O·CH_2·CH_3), and 6·81 and 7·41 (each 1H, s, aromatic) p.p.m., *m/e* 356 (M^+, 100%) and 281 (40).

The filtrate from the recrystallisation of compound (IX) was chromatographed on silica gel and eluted with benzene. The benzene was removed from the eluate to leave *ethyl 6-ethoxy-2,3-dimethoxy-7,9-dimethylbenzo*[c][2,7]*naphthyridine-10-carboxylate* (V) (0·9 g., 19·4%) as colourless needles, m.p. 116—119° (from hexane) (Found: C, 66·0; H, 6·35; N, 7·05. $C_{21}H_{24}N_2O_5$ requires C, 65·6; H, 6·3; N, 7·3%), $\nu_{max.}$ (KBr) 1720 cm.$^{-1}$ (ester C=O), δ ($CDCl_3$) 1·38 (3H, t, *J* 6·5 c./sec., O·CH_2·CH_3), 1·51 (3H, t, *J* 6·5 c./sec., O·CH_2·CH_3), 2·62 and 3·07 (each 3H, s, CMe), 3·91 and 3·99 (each 3H, s, OMe), 4·49 (2H, q, *J* 6·5 c./sec., O·CH_2·CH_3), 4·58 (2H, q, *J* 6·5 c./sec., O·CH_2·CH_3), and 7·19 and 7·49 (each 1H, s, aromatic) p.p.m., *m/e* 384 (M^+, 100%), 369 (75), 356 (33), 340 (16), and 281 (30).

Elution with chloroform gave *diethyl 1,3-dimethyl-6,7-dimethoxy-β-carboline-4,9-dicarboxylate* (III) (1·1 g., 24·7%) as colourless needles, m.p. 99—101° (from hexane) (Found: C, 62·8; H, 6·05; N, 6·85. $C_{21}H_{24}N_2O_6$ requires C, 63·0; H, 6·05; N, 7·0%), $\nu_{max.}$ (KBr) 1735 and 1715 cm.$^{-1}$ (ester C=O), δ ($CDCl_3$) 1·47 (6H, t, *J* 6·5 c./sec., 2O·CH_2·CH_3), 2·67 and 2·70 (each 3H, s, CMe), 3·91 and 3·99 (each 3H, s, OMe), 4·50 (2H, q, *J* 6·5 c./sec., O·CH_2CH_3), 4·55 (2H, q, *J* 6·5 c./sec., O·CH_2·CH_3), and 7·41 and 7·77 (each 1H, s, aromatic) p.p.m., *m/e* 400 (M^+, 100%) and 327 (57).

Reaction of the Pyridine Derivative (II) *with Triethyl Phosphite*.—A mixture of compound (II) (5 g.) and triethyl phosphite (9·5 g.) was treated as described for compound (I) to give *ethyl* 5,6-*dihydro*-7,9-*dimethyl*-2,3-*methylenedioxy*-6-*oxobenzo*[c][2,7]*naphthyridine*-10-*carboxylate* (X) (100 mg.) as colourless leaflets, m.p. >280° (from chloroform–ethanol) (Found: C, 63·4; H, 4·9; N, 8·05. $C_{18}H_{16}N_2O_5$ requires C, 63·5; H, 4·75; N, 8·25%), $\nu_{max.}$ (KBr) 1725 (ester C=O) and 1675 (amide C=O) cm.$^{-1}$, δ (CF_3CO_2H) 1·44 (3H, t, *J* 6·2 c./sec., O·CH_2·CH_3), 2·77 and 3·27 (each 3H, s, CMe), 4·61 (2H, q, *J* 6·2 c./sec., O·CH_2·CH_3), 6·22 (2H, s, O·CH_2·O), and 6·90 and 7·34 (each 1H, s, aromatic) p.p.m., *m/e* 340 (M^+, 100%), 312 (20), 295 (25), and 265 (17); *ethyl* 6-*ethoxy*-7,9-*dimethyl*-2,3-*methylenedioxybenzo*-[c][2,7]*naphthyridine*-10-*carboxylate* (VI) (1·75 g., 17·1%) as yellow needles, m.p. 168—170° (from benzene–hexane) (Found: C, 65·5; H, 5·55; N, 7·45. $C_{20}H_{20}N_2O_5$ requires C, 65·2; H, 5·45; N, 7·6%) $\nu_{max.}$ (KBr) 1720 cm.$^{-1}$ (ester C=O), δ ($CDCl_3$) 1·41 (3H, t, *J* 6·5 c./sec., O·CH_2·CH_3), 1·49 (3H, t, *J* 6·5 c./sec., O·CH_2·CH_3), 2·61 and 3·06 (each 3H, s, CMe), 4·48 (2H, q, *J* 6·5 c./sec., O·CH_2·CH_3), 4·56 (2H, q, *J* 6·5 c./sec., O·CH_2·CH_3), 6·04 (2H, s, O·CH_2·O), and 7·14 and 7·41 (each 1H, s, aromatic) p.p.m., *m/e* 368 (M^+, 100%), 353 (73), 339 (65), 323 (19), 311 (19), 294 (13·6), and 264 (15); and *diethyl* 1,3-*dimethyl*-6,7-*methylenedioxy*-β-*carboline*-4,9-*dicarboxylate* (IV) (1·1 g., 23·5%) as colourless prisms, m.p. 131—133° (from benzene–hexane) (Found: C, 62·75; H, 5·45; N, 7·35. $C_{20}H_{20}N_2O_6$ requires C, 62·5; H, 5·25; N, 7·3%), $\nu_{max.}$ (KBr) 1735 and 1715 cm.$^{-1}$ (ester C=O), δ ($CDCl_3$) 1·48 (6H, t, *J* 6·5 c./sec., 2O·CH_2·CH_3), 2·66 and 2·69 (each 3H, s, CMe), 4·35—4·75 (4H, m, 2O·CH_2·CH_3), 6·05 (2H, s, O·CH_2·O), and 7·29 and 7·65 (each 1H, s, aromatic) p.p.m., *m/e* 384 (M^+, 100%), 339 (16), 311 (72), 283 (32), 261 (16), and 253 (16).

Acidic Hydrolysis of the Benzonaphthyridine (V).—A mixture of (V) (150 mg.), ethanol (5 ml.), and concentrated hydrochloric acid (0·5 ml.) was heated under reflux on a water-bath overnight. The ethanol was then distilled off and the residue gave the *hydrochloride* of (IX) (120 mg.) as yellow needles, m.p. >280° (from ethanol) (Found: C, 58·05; H, 5·8; N, 7·0 $C_{19}H_{20}N_2O_5$,HCl requires C, 58·05; H, 5·4; N, 7·15%), δ (CF_3CO_2H) 1·38 (3H, t, *J* 6·6 c./sec., O·CH_2·CH_3), 2·88 and 3·34 (each 3H, s, CMe), 3·89 and 4·04 (each 3H, s, OMe), 4·53 (2H, q, *J* 6·6 c./sec., O·CH_2·CH_3), and 6·86 and 7·40 (each 1H, s, aromatic), which gave a positive Beilstein test. Treatment of this hydrochloride with 10% ammonium hydroxide gave the free base (IX), m.p., mixed m.p., and i.r. and n.m.r. spectra identical with those of the authentic sample.

Acidic Hydrolysis of the Benzonaphthyridine (VI).—A mixture of compound (VI) (100 mg.), ethanol (5 ml.), and concentrated hydrochloric acid (0·5 ml.) was heated on a water-bath for 1 hr., then cooled. The crystals which separated gave the *hydrochloride* (100 mg.) of (X) as yellow needles, m.p. >280° (from dimethylformamide–ethanol) (Found: C, 57·6; H, 4·75; N, 7·65. $C_{18}H_{16}N_2O_5$,HCl requires C, 57·35; H, 4·55; N, 7·45%), δ (CF_3CO_2H) 1·50 (3H, *J* 6·2 c./sec., O·CH_2·CH_3), 2·83 and 3·33 (each 3H, s, CMe), 4·72 (2H, q, *J* 6·2 c./sec., O·CH_2·CH_3), 6·20 (2H, s, O·CH_2·O), and 6·97 and 7·47 (each 1H, s, aromatic), which gave a positive Beilstein test. The i.r. and n.m.r. spectra of the free base were identical with those of the authentic sample.

Basic Hydrolysis of the β-*Carboline* (III).—A mixture of (III) (0·2 g.), ethanol (20 ml.), and potassium hydroxide (30 mg.) was heated under reflux for 3 hr. After removal of ethanol, the residue was acidified with hydrochloric acid to give yellow crystals, which gave the *hydrochloride of ethyl* 1,3-*dimethyl*-6,7-*dimethoxy*-β-*carboline*-4-*carboxylate* (VII) (90 mg.) as hygroscopic yellow leaflets, m.p. 246—247° (from chloroform–hexane) (Found: C, 55·9; H, 6·7; N, 7·1. $C_{18}H_{20}N_2O_5$,HCl,$2H_2O$ requires C, 55·45; H, 6·45; N, 7·15%), $\nu_{max.}$ (KBr) 3400 (NH) and 1720 (ester C=O) cm.$^{-1}$, δ ($CDCl_3$) 1·50 (3H, t, *J* 6·5 c./sec., O·CH_2CH_3), 2·91 and 3·00 (each 3H, s, CMe), 3·91 and 4·00 (each 3H, s, 2OMe), 4·52 (2H, q, *J* 6·5 c./sec., O·CH_2·CH_3), and 7·26 and 7·48 (each 1H, s, aromatic) p.p.m., *m/e* 328 (M^+, 100%) and 313 (50), which gave a positive Beilstein test.

Basic Hydrolysis of the β-*Carboline* (IV).—A mixture of (IV) (50 mg.), ethanol (5 ml.), and potassium hydroxide (50 mg.) was heated under reflux on a water-bath for 3 hr. After removal of ethanol, the residue was extracted with chloroform to give starting material (30 mg.). The residue was acidified with 10% hydrochloric acid to give yellow crystals, which gave 3-*dimethyl*-6,7-*methylenedioxy*-β-*carboline*-4-*carboxylic acid* (VIII) (15 mg.) as hygroscopic yellow prisms, m.p. >280° (from dimethylformamide–ethanol) (Found: C, 57·55; H, 5·1. $C_{15}H_{12}N_2O_4$,$1·5H_2O$ * requires C, 57·85; H, 4·85%), δ (CF_3CO_2H) 2·96 and 3·03 (each 3H, s, CMe), 6·13 (2H, s, O·CH_2·O), and 7·08 and 7·63 (each 1H, s, aromatic) p.p.m., *m/e* 284 (M^+, 100%), 240 (13), and 239 (12).

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* When this sample was dried (P_2O_5) at 100°/3 mm. for 5 days, its analysis showed N, 9·75 ($C_{15}H_{12}N_2O_4$ requires N, 9·85%).