Nitrenes. Part IV.[1] Synthesis of Oxazolo[5,4-*b*]quinoline through a Nitrene Intermediate [2]

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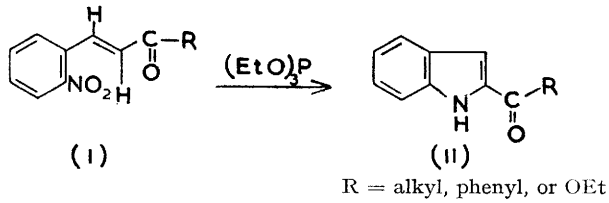
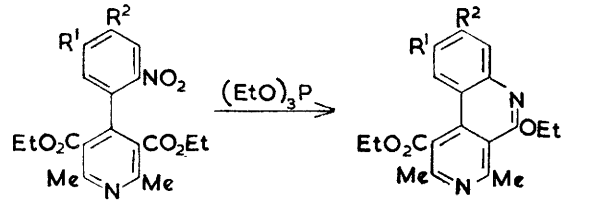
Treatment of 2-phenyl- (VII and IX) and 2-methyl-4-(4,5-dialkoxy-2-nitrobenzylidene)oxazol-5-ones (VIII and X) with triethyl phosphite afforded the corresponding 2-phenyl- (XI and XIII) and 6,7-dialkoxy-2-methyloxazolo-[5,4-*b*]quinolines (XII and XIV), respectively, the former of which were hydrolysed to give the 3-benzamido-quinolin-2-ones (XV and XVI).

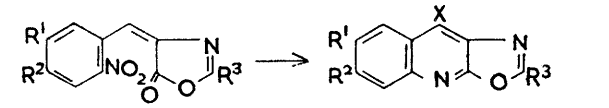
REDUCTIVE cyclisation of aromatic compounds has been carried out with triethyl phosphite by a number of investigators [1,3-12] and it has been postulated that nitrene intermediates were involved in these reactions. We have previously reported modified syntheses of β-carboline [8] and benz[*a*]carbazole [11] derivatives by way of nitrene intermediates, and a novel reaction of 4-(2-nitrophenyl)pyridine derivatives with triethyl phosphite.[1] In general, the reactions of 2-nitrostyryl alkyl (or phenyl) ketone and of 2-nitrocinnamic ester (I) with triethyl phosphite gave the five-membered ring compounds (II), which were obtained in poor yield with the carbonyl group intact.[12] We have recently reported a novel reaction between a nitrene and a carbonyl group:[1,10] treatment of 4-(2-nitrophenyl)pyridines (III) and (IV) with triethyl phosphite gave the corresponding benzo[*c*]naphthyridines (V) and (VI), respectively. In view of this, we performed the reaction of 2-phenyl- (VII and IX) and 2-methyl-4-(4,5-dialkoxy-2-nitrobenzylidene)oxazol-5-ones (VIII and X) with triethyl phosphate and obtained the expected product: (XI—XIV).

The oxazolones (VII) and (VIII) afforded 2-phenyl- and 2-methyl-6,7-methylenedioxyoxazolo[5,4-*b*]quinoline (XI) and (XII), respectively. Similar treatment of oxazolones (IX) and (X) afforded the cyclisation products (XIII) and (XIV).

Acidic hydrolysis of the compounds (XI) and (XIII) afforded the corresponding 3-acylaminoquinolin-2-ones (XV) and (XVI), respectively; basic hydrolysis of (XI)







(VII) $R^1 = R^2 = O{\cdot}CH_2{\cdot}O$, R^3 = Ph
(VIII) $R^1 = R^2 = O{\cdot}CH_2{\cdot}O$, R^3 = Me
(IX) $R^1 = R^2$ = OMe, R^3 = Ph
(X) $R^1 = R^2$ = OMe, R^3 = Me

(XI) $R^1 = R^2 = O{\cdot}CH_2{\cdot}O$, R^3 = Ph, X = H
(XII) $R^1 = R^2 = O{\cdot}CH_2{\cdot}O$, R^3 = Me, X = H
(XIII) $R^1 = R^2$ = OMe, R^3 = Ph, X = H
(XIV) $R^1 = R^2$ = OMe, R^3 = Me, X = H
(XVII) R^1 = Cl, R^2 = H, R^3 = Me, X = Ph

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[2] This forms Part CCLXXI of 'Studies on the Syntheses of Heterocyclic Compounds,' by T. Kametani.
[3] J. I. G. Cadogan, M. 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.
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[7] A. W. Murray and K. Vaughan, *Chem. Comm.*, 1967, 1282.
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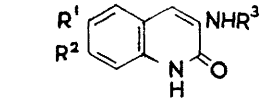
[10] T. Kametani, T. Yamanaka, and K. Ogasawara, *Chem. Comm.*, 1968, 996.
[11] T. Kametani, T. Yamanaka, and K. Ogasawara, *J. Org. Chem.*, in press.
[12] J. I. G. Cadogan, *Quart. Rev.*, 1968, **22**, 222.

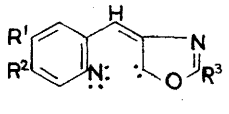
with ethanolic sodium hydroxide also gave the amide (XV). These reactions agree with the oxazoloquinoline structures of (XI) and (XIII). The only previous synthesis of an oxazolo[5,4-*b*]quinoline involved treatment of a benzodiazepine derivative with acetic anhydride to give the oxazoloquinoline (XVII) (20%).[13]

In the cinnamoyl derivatives (I), the phenyl and carbonyl groups are *trans*, whereas in the pyridine derivatives (III) and (IV) the phenyl and ethoxycarbonyl groups are *cis*. It thus appears that steric factors control whether the double bond or the carbonyl group reacts preferentially with the nitrene. Several investigations[14] have shown the phenyl and carbonyl groups in the oxazolone derivatives to be *cis*; thus the observed cyclisations agree with the above argument.

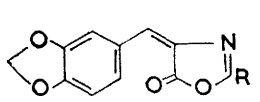
It could be argued that the oxazolo[5,4-*b*]quinolines are formed by the reaction between nitrene and carbene as shown in (XVIII). However, treatment of 2-phenyl- (XIX)[15] or 2-methyl-4-(4,5-methylenedioxybenzylidene)-oxazolone[16] (XX) with triethyl phosphite under the conditions as above resulted in quantitative recovery of starting material and gave no dimerisation product



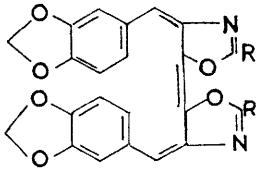
(XV) $R^1 = R^2 = O{\cdot}CH_2{\cdot}O$, $R^3 = Bz$
(XVI) $R^1 = R^2 = OMe$, $R^3 = Bz$



(XVIII)



(XIX) R = Ph
(XX) R = Me



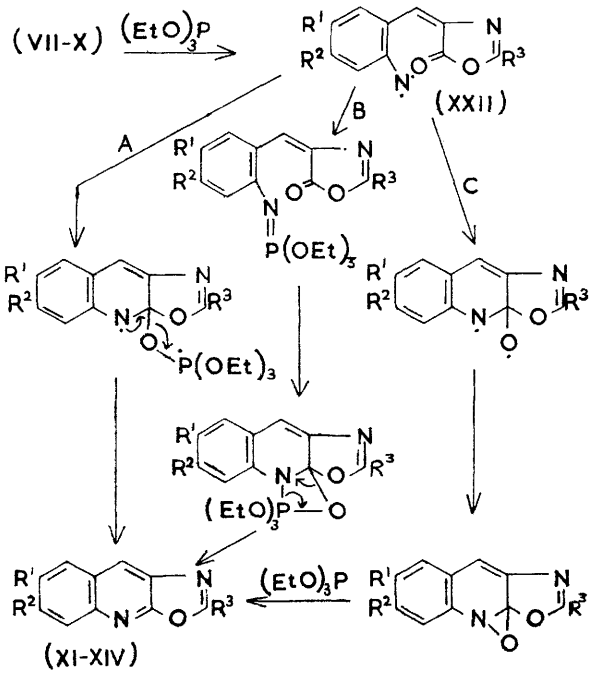
(XXI)

(XXI); this is evidence against the formation of carbene. Perhaps the simplest mechanism to explain the formation of oxazolo[5,4-*b*]quinolines (XI—XIV) involves initial reduction of the nitro-group and formation of the nitrene (XXII), followed by one or more of the routes A, B, and C (see Scheme).

EXPERIMENTAL

I.r. spectra were measured with a Hitachi EPI-3 recording spectrophotometer, n.m.r. spectra with a Hitachi H-60 spectrometer, with tetramethylsilane as internal standard, and mass spectra with on a Hitachi RMU-6D mass spectrometer.

4-(4,5-*Methylenedioxy*-2-*nitrobenzylidene*)-2-*phenyloxazol*-5-*one* (VII).—A mixture of 4,5-methylenedioxy-2-nitrobenzaldehyde (24 g.), *N*-benzoylglycine (11 g.), potassium hydrogen carbonate (6·25 g.), and acetic anhydride (20 ml.) was stirred; heat was evolved and the temperature finally reached *ca.* 100°. Stirring was continued to give a paste which was set aside overnight. The mixture was then decomposed with hot water and the crystals were filtered off and yielded *oxazolone* (VII) (30 g.) as yellow leaflets,



SCHEME

m.p. 198—199° (from acetone) (Found: C, 60·8; H, 3·1; N, 8·35. $C_{17}H_{10}N_2O_6$ requires C, 60·35; H, 3·0; N, 8·3%).

2-*Methyl*-4-(4,5-*methylenedioxy*-2-*nitrobenzylidene*)*oxazol*-5-*one* (VIII).—A mixture of 4,5-methylenedioxy-2-nitrobenzaldehyde (10 g.), *N*-acetylglycine (6 g.), potassium hydrogen carbonate (6 g.), and acetic anhydride (16 ml.) was heated on a water-bath for 5 hr.; the solid dissolved with gas evolution. After 1 hr., crystals began to separate and the mixture was set aside overnight. It was then treated with hot water, and the crystals were filtered off and washed with water to give the *oxazolone* (VIII) (12 g.) as pale brown needles, m.p. 156—158° (from acetone) (Found: C, 52·6; H, 3·0; N, 9·7. $C_{12}H_8N_2O_6$ requires C, 52·2; H, 2·9; N, 10·15%).

4-(4,5-*Dimethoxy*-2-*nitrobenzylidene*)-2-*phenyloxazol*-5-*one* (IX).—A mixture of 4,5-dimethoxy-2-nitrobenzaldehyde (24 g.), *N*-benzoylglycine (10·5 g.), potassium hydrogen carbonate (6·2 g.), and acetic anhydride (20 ml.) was treated as before, and the resultant solid gave the *azlactone* (IX) as yellow leaflets (28·5 g.), m.p. 223—225° (from chloroform–ethanol) (Found: C, 61·2; H, 4·0; N, 7·95. $C_{18}H_{19}N_2O_6$ requires C, 61·0; H, 4·0; N, 7·9%).

4-(4,5-*Dimethoxy*-2-*nitrobenzylidene*)-2-*methyloxazol*-5-*one* (X).—4,5-Dimethoxy-2-nitrobenzaldehyde (10 g.), *N*-acetylglycine (7 g.), acetic anhydride (20 ml.), and triethylamine (5 ml.), were mixed thoroughly and the mixture was set aside at 37° for 2 days, then at 50° for 4 days in the dark. Hot water was added and the solid was filtered off and

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[14] R. Filler, *Adv. Heterocyclic Chem.*, 1965, **4**, 95.
[15] W. Kropp and H. Decker, *Ber.*, 1909, **42**, 1188.
[16] S. Sugasawa and T. Tsuda, *J. Pharm. Soc. Japan*, 1935, **55**, 1050.

washed with water to give the *azlactone* (X) as yellow leaflets (7·5 g.), m.p. 218° (decomp.) (from acetone) (Found: C, 53·8; H, 4·2; N, 9·35. $C_{13}H_{12}N_2O_6$ requires C, 53·45; H, 4·15; N, 9·6%).

6,7-*Methylenedioxy*-2-*phenyloxazolo*[5,4-b]*quinoline* (XI).—A mixture of 4-(4,5-methylenedioxy-2-nitrobenzylidene)-2-phenyloxazol-5-one (VII) (6·5 g., 0·015 mole) and triethyl phosphite (12·5 g., 0·075 mole) was heated under reflux at 165—170° for 20 hr. in a current of nitrogen, then cooled. Crystals were filtered off and gave the oxazoloquinoline (XI) (3·3 g., 57%) as *needles*, m.p. 270·5° (from benzene) (Found: C, 70·0; H, 3·85; N, 9·7. $C_{17}H_{10}N_2O_3$ requires C, 70·35; H, 3·45; N, 9·65%), *m/e* 290 (M^+), $\nu_{max.}$ (KBr) 1635 cm.$^{-1}$, δ (CF_3CO_2H) 6·38 (2H, s, $-O{\cdot}CH_2{\cdot}O-$), 7·64 (2H, s, aromatic), 7·81br (3H, s, aromatic), 8·35 (2H, m, aromatic), and 9·20 [1H, s, C(4)-proton] p.p.m.

2-*Methyl*-6,7-*methylenedioxyoxazolo*[5,4-b]*quinoline* (XII).—A mixture of 2-methyl-4-(4,5-methylenedioxy-2-nitrophenyl)oxazolone (VIII) (3 g.) and triethyl phosphite (10 g.) was heated under reflux at 165—170° for 20 hr. in a current of nitrogen. After unchanged reagent and triethyl phosphate were distilled off (100°/3 mm.) and the residue was chromatographed on silicic acid. Evaporation of the benzene eluate gave the *oxazoloquinoline* (XII) (1·2 g., 45%) as needles, m.p. 200—202° (from ethanol) (Found: C, 63·45; H, 3·6; N, 12·3. $C_{12}H_8N_2O_3$ requires C, 63·15; H, 3·55; N, 12·3%), *m/e* 228 (M^+), $\nu_{max.}$ ($CHCl_3$) 1635 cm.$^{-1}$, δ (in CF_3CO_2H) 2·91 (3H, s, CMe), 6·32 (2H, s, $O{\cdot}CH_2{\cdot}O$), 7·55 (2H, singlet, aromatic protons), and 9·08 p.p.m. [1H, s, quinoline C(4)-proton] p.p.m.

6,7-*Dimethoxy*-2-*phenyloxazolo*[5,4-b]*quinoline* (XIII).—A solution of the oxazolone (IX) (5 g.) in triethyl phosphite (11·7 g.) was heated under reflux at 165—170° for 20 hr. in a current of nitrogen, then cooled. The crystals were filtered off and gave the *oxazoloquinoline* (XIII) (2·1 g., 48·4%) as leaflets, m.p. 240—241° (from benzene) (Found: C, 71·05; H, 4·7; N, 9·05. $C_{18}H_{14}N_2O_3$ requires C, 70·6; H, 4·6; N, 9·15%), $\nu_{max.}$ (KBr) 1627 cm.$^{-1}$, δ ($CDCl_3$) 4·00 and 4·02 (each 3H, s, OMe) 7·17 and 7·40 (each 1H, s, aromatic), 7·55 (3H, m, aromatic), 8·23 [1H, s, C(4)-proton], and 8·34 (2H, aromatic) p.p.m.

6,7-*Dimethoxy*-2-*methyloxazolo*[5,4-b]*quinoline* (XIV).—A mixture of the oxazolone (X) (3·5 g.) and triethyl phosphite (11 g.) was heated under reflux at 165—170° for 20 hr. in a current of nitrogen, then cooled. The crystals were filtered off and the filtrate was evaporated to remove unchanged triethyl phosphite and triethyl phosphate. A little benzene was added to the residue and the crystals were collected. The two crops of crystals were combined and gave the *oxazoloquinoline* (XIV) (1·1 g., 37·5%) as pale brown cubes, m.p. 227—229° (from benzene–hexane) (Found: C, 64·1; H, 5·1; N, 11·55. $C_{13}H_{12}N_2O_3$ requires C, 63·9; H, 4·95; N, 11·45%), $\nu_{max.}$ (KBr) 1635 cm.$^{-1}$, δ ($CDCl_3$) 2·67 (3H, s, CMe), 4·00 and 4·02 (each 3H, s, OMe), 7·18 and 7·41 (each 1H, s, aromatic), and 8·17 [1H, s, C(4)-proton] p.p.m.

3-*Benzoylamino*-6,7-*methylenedioxyquinolin*-2(1H)-*one* (XV).—(*a*) A mixture of the oxazoloquinoline (XI) (0·5 g.), methanol (25 ml.) and sodium hydroxide (2·5 g.) was heated under reflux on a water-bath for 4 hr. then acidified with dilute hydrochloric acid. The crystals which separated gave the *quinolone* (XV) (0·4 g., 75·5%) as leaflets, m.p. >290° (from ethanol–dimethylformamide) (Found: C, 65·85; H, 3·6; N, 9·45. $C_{17}H_{12}N_2O_4$ requires C, 66·25; H, 3·9; N, 9·1%), $\nu_{max.}$ (KBr) 3290 and 1655 cm.$^{-1}$, δ [$(CD_3)_2SO$] 6·06 (2H, s, $O{\cdot}CH_2{\cdot}O$), 6·85 and 7·20 (each 1H, s, aromatic), 7·50—7·70 (3H, m, aromatic), 7·85—8·05 (2H, m, aromatic), 8·66 [1H, s, C(4)-proton], and 9·28 and 12·25 (each 1H, broad s, NH) p.p.m.

(*b*) A suspension of compound (XI) (0·5 g.) in concentrated hydrochloric acid (5 ml.) was heated on a water-bath for 5 hr., then cooled. The crystals were collected, washed with water, and gave the same quinolone (XV) (0·45 g., 85%), m.p. >290°.

3-*Benzoylamino*-6,7-*dimethoxyquinolin*-2(1H)-*one* (XVI).—A suspension of the oxazoloquinoline (XIII) (0·4 g.) in concentrated hydrochloric acid (8 ml.) was heated on a water-bath for 4 hr. and cooled. The crystals were collected and washed to give the *quinolone* (XVI) (0·35 g., 82·6%) as leaflets, m.p. >280° (from dimethylformamide–ethanol) (Found: C, 66·6; H, 5·0; N, 8·85. $C_{18}H_{16}N_2O_4$ requires C, 66·65; H, 4·95; N, 8·65%), $\nu_{max.}$ (KBr) 3350 and 1645 cm.$^{-1}$, δ [$(CD_3)_2SO$] 3·80 (6H, s, 2OMe), 6·88 and 7·23 (each 1H, s, aromatic), 7·83—8·08 (2H, m, aromatic), 8·67 [1H, s, C(4)-proton], and 9·30 and 12·15 (each 1H, s, NH) p.p.m.

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