Nitrene. Part XIII.[1] Novel Conversion of 2-Nitrophenyl Substituted Butyrolactones into Indoles with Triethyl Phosphite

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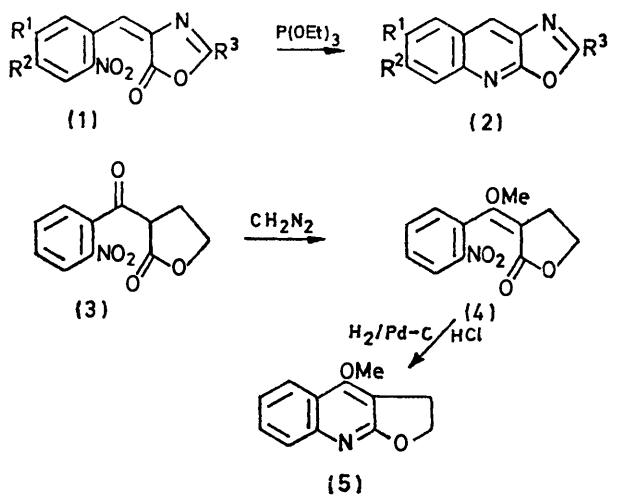
Reductive cyclization of α-(2-hydroxyethyl)-β-methoxy-*o*-nitrocinnamic acid γ-lactone (4) with triethyl phosphite produced 3,4-dihydro-5-methoxy[1,3]oxazino[3,4-*a*]indol-1-one (6), a new heterocyclic ring system. Reduction of 2-*o*-nitrobenzoyl-γ-butyrolactone (3) yielded 4,5-dihydro-1'H-spiro[furan-3,2'-indole]-2,3'-dione (8) as the major product, in addition to a trace amount of the 5-ethoxy-analogue of (6). Lactone (8) was hydrolysed and decarboxylated to give 1,2-dihydro-2-(2-hydroxyethyl)indol-3-one (9). These results provide a route to novel reactive heterocyclic lactones.

THE reduction of aromatic nitro-compounds by triethyl phosphite has been employed to prepare a wide variety of nitrogen-containing heterocyclic systems.[2,3] Although many types of nitrobenzylidene, and a limited number of nitrobenzoyl compounds have been reduced, nitro-derivatives of α-alkoxybenzylidene- and benzoyl-butyrolactones have not been investigated. Reduction of these types of compounds was of interest as an alternative route to furo[2,3-*b*]quinolines. Previously, we have described an analogous synthesis of oxazolo[5,4-*b*]-quinolines (2) from nitrobenzylideneoxazolones (1).[4]



(1) (2) (3) (4) (5)

SCHEME 1

Kuwayama[5] reported the preparation of the furo-quinoline, dihydrodictamnine (5) by catalytic reduction of α-(2-hydroxyethyl)-β-methoxy-*o*-nitrocinnamic acid γ-lactone (4), which was obtained by methylation of the corresponding benzoyl-butyrolactone (3). We now report the reduction of these lactones by use of triethyl phosphite.

Reduction of lactone (4) with triethyl phosphite at 160—170° for 17 h produced, after chromatography, a neutral white crystalline compound. The i.r. spectrum showed the absence of NO_2 and NH absorption and the presence of CO absorption at 1730 cm^{-1}, which eliminated furoquinoline (5) as a possible structure. Mass spectrometry (M^+ 217) and microanalysis established the molecular formula as $C_{12}H_{11}NO_3$ and indicated the loss of two oxygen atoms. The n.m.r. spectrum showed signals at δ 3·19 and 4·48 (each 2H, t, *J* 6·5 Hz, CH_2CH_2O), 3·95 (s, OCH_3), and 7·38 (3H) and 8·20 (1H) (both m, Ar). These data, in addition to the u.v. spectrum, which is typical of an *N*-acylindole,[6] supported assignment of the 1*H*-[1,3]oxazino[3,4-*a*]indole structure (6). The fragmentation pattern in the mass spectrum is also consistent with this structure. Ions at *m/e* 202, 173, 158, 130, and 104 account for the loss of CO_2, CH_3, CH_2CH_2, and CN radicals. This represents the first reported example of the 1*H*-[1,3]oxazino[3,4-*a*]indole ring system.

In general, the reduction of nitro-compounds is effected in an excess of triethyl phosphite at reflux temperature over six or more hours. In contrast, reduction of the nitrobenzoyl-lactone (3) proceeded very rapidly and exothermically at *ca.* 140° and was complete after 2 h at 160—165°. The composition of the reaction mixture did not change when the reduction was carried out at 160—170° for 23 h.

Chromatography on silica gel separated three products. The first component consisted of a trace quantity of unidentified crystals. The second product, obtained in 0·68% yield, was the 5-ethoxyoxazinoindole (7). Spectral data were qualitatively identical with those of the methoxy-derivative (6).

The major component was a yellow crystalline non-basic compound which exhibited strong i.r. bands at 1610, 1700, and 1770 and a medium band at 3400 cm^{-1}. Absence of NO_2 absorption and retention of γ-lactone (1770) and ketone (1700 cm^{-1}) bands could only be accounted for by the formation of a spiro-indolinone (8). This assignment was confirmed by microanalysis and by the mass spectrum (M^+ 203), which showed a fragmentation pattern similar to (6). The n.m.r. spectrum showed a complex ABX_2 pattern accounting for the ethylene and

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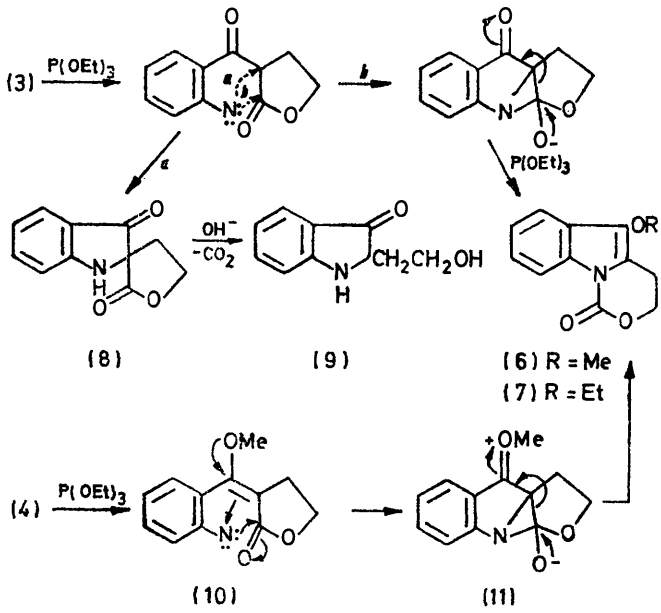
NH (exchangeable with deuterium oxide) protons at δ 2·69, 4·36—4·68, and 4·71—5·17, and aromatic multiplets at δ 7·0 (2H) and 7·63 (2H). The u.v. spectrum, typical of a 3-indolinone,[6] brilliant blue fluorescence, and i.r. bands at 1610 and 1700 cm^{-1} correspond to that of known 2,2-disubstituted 3-indolinones.[7,8] To further confirm this structural assignment, (8) was hydrolysed with alkali. The spectral properties of the resulting alcohol, 2-(2-hydroxyethyl)indolin-3-one (9) fully support the structural assignment. The indolinone (9) did not autoxidize to the 2,2′-bi-indoxyl as did the 2-methyl- and 2-phenyl-indolin-3-ones,[9] based on mass spectral analysis (M^+, 177).

Unlike the benzylideneoxazolones (1), the reductive cyclization of lactones (3) and (4) further exemplifies the strong tendency towards the formation of the indole ring rather than deoxygenation of the lactone and quinoline formation. Possible mechanisms, involving nitrene intermediates, to account for the products are shown in Scheme 2. Formation of the oxazinoindole (6) by lactone ring expansion to the indole nitrogen could involve a nitrene addition (10; see arrows) to the lactone carbonyl with the formation of the aziridine intermediate (11) followed by rearrangement. By a similar mechanism (*b*) coupled with *O*-ethylation, the analogous ethoxy-derivative (7) is formed from the benzoyl-lactone (3). Direct nitrene insertion (*a*) into the α-position of the lactone would lead to the spiro-indolinone (8).



SCHEME 2

EXPERIMENTAL

M.p.s were measured with a Yanagimoto micro-melting point apparatus (MP-S2). I.r. spectra were measured with a Hitachi 215 grating spectrophotometer, n.m.r. spectra with Hitachi H-60 and JEOL JNM-PS-100 spectrometers with tetramethylsilane as internal standard, mass spectra with a Hitachi RMU-7 spectrometer, and u.v. spectra with a Hitachi 124 spectrometer.

Reaction of α-(2-Hydroxyethyl)-β-methoxy-o-nitrocinnamic Acid γ-Lactone (4) *with Triethyl Phosphite.*—A mixture of the lactone (4) (0·3 g, 1·2 mmol) and triethyl phosphite (1 g) was heated at 160—170° for 17 h under nitrogen. Triethyl phosphite and triethyl phosphate were distilled off at 2 mmHg, and the dark residue was chromatographed on silica gel with benzene–chloroform (1 : 1) as eluant to give crystalline 3,4-*dihydro*-5-*methoxy*[1,3]*oxazino*[3,4-a]*indol*-1-*one* (6) (116 mg, 45%). Rechromatography afforded prisms, m.p. 65·5—66·5° (from propan-2-ol) (Found: C, 65·5; H, 5·0; N, 6·3. $C_{12}H_{11}NO_3$,0·25H_2O requires C, 65·0; H, 5·0; N, 6·3%); $\lambda_{max.}$ (MeOH) 270 and 232 nm; $\nu_{max.}$ ($CHCl_3$) 1730 cm^{-1} (C=O); δ ($CDCl_3$) 3·19 (2H, t, *J* 6·5 Hz, CH_2·CH_2·O), 3·95 (3H, s, ArOMe), 4·48 (2H, t, *J* 6·5 Hz, CH_2·CH_2·O), 7·13—7·64 (3H, m, ArH), and 8·09—8·30 (1H, m, 9-H); *m/e* 217 (M^+), 202 (M − CH_3), 173 (M − CO_2), 158 (202 − CO_2 or 173 − CH_3), 130 (158 − CH_2CH_2), and 104 (130 − CN).

Reaction of 2-o-*Nitrobenzoyl-γ-butyrolactone* (3) *with Triethyl Phosphite.*—A mixture of the lactone (3) (3 g, 12·8 mmol) and triethyl phosphite (10 g) was heated under nitrogen. At a bath temperature of 140°, a vigorous exothermic reaction occurred with refluxing of the triethyl phosphite. After the initial reaction had subsided, the bath temperature was raised to 160—165° and maintained at this level for 2 h, and then the mixture was allowed to cool overnight. Triethyl phosphite and triethyl phosphate were removed by distillation at 3 mmHg. The dark viscous residue was dissolved in chloroform and the solution washed with water, dried (Na_2SO_4), and evaporated. The residual dark red oil was chromatographed on silica gel with benzene–chloroform (1 : 1) as eluant.

The first fraction after extraction with hexane and evaporation yielded pale yellow needles (30 mg), m.p. 67—68° (solidifies and remelts at 75—77°), violet fluorescence ($CHCl_3$); $\lambda_{max.}$ (MeOH) 280, 240sh, 232, and 228sh nm; $\nu_{max.}$ ($CHCl_3$) 3500, 3385, 1715, 1680, and 1640 cm^{-1}; δ ($CDCl_3$) 1·4 (3H, t, *J* 7 Hz), 3·2 (2H, t, *J* 9 Hz), 4·51 (2H, q, *J* 7 Hz), 4·77 (2H, t, *J* 9 Hz), and 7·1—7·8 (4H, m, ArH); *m/e* 215 (M^+), 200, 187, 186, 171, and 130.

The second fraction yielded 5-*ethoxy*-3,4-*dihydro*[1,3]-*oxazino*[3,4-a]*indol*-1-*one* (7) as an oil (20 mg, 0·68%) (Found: N, 4·8. $C_{13}H_{13}NO_3$,2H_2O requires N, 5·2%); $\lambda_{max.}$ (MeOH) 270 and 232 nm; $\nu_{max.}$ ($CHCl_3$) 1730 cm^{-1} (C=O); δ ($CDCl_3$) 1·38 (3H, t, *J* 7 Hz, CH_3CH_2·O), 3·17 (2H, t, *J* 6·5 Hz, CH_2·CH_2·O), 4·16 (2H, q, *J* 7 Hz, CH_3CH_2·O), 4·48 (2H, t, *J* 6·5 Hz, CH_2CH_2·O), 7·15—7·65 (3H, m, ArH), and 8·10—8·31 (1H, m, 9-H); *m/e* 231 (M^+), 202 (M − CH_2CH_3), 187 (M − CO_2), 158 (202 − CO_2 or 187 − CH_2CH_3), 130 (158 − CH_2CH_2), and 104 (130 − CN).

The last and major fraction was a yellow oil which crystallized with ether to give 4,5-*dihydro*-1′H-*spiro*[*furan*-3,2′-*indole*]-2,3′-*dione* (8) as yellow prisms (325 mg, 12·5%), m.p. 141—142° (from propan-2-ol) (Found: C, 64·8; H, 4·5; N, 6·9. $C_{11}H_9NO_3$ requires C, 65·0; H, 4·5; N, 6·9%); blue fluorescence ($CHCl_3$, Et_2O, and Me_2CO); $\lambda_{max.}$ (MeOH) 390, 257sh, and 232 nm; $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1770 (lactone C=O), 1700 (C=O), and 1610 cm^{-1} (Ar–N(–)–CR^1R^2);[7,10] δ ($CDCl_3$) 2·69 (2H, dd, *J* 8 and 3 Hz, X_2 part of ABX_2,

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CH_2CH_2·O), 4·36—4·68 (1H, m, A part of ABX_2, CH_2CH_2·O), 4·71—5·17 (2H, m, B part of ABX_2, CH_2CH_2·O and NH exchangeable with D_2O), 6·84—7·16 (2H, m, ArH), and 7·43—7·84 (2H, m, ArH); *m/e* 203 (M^+), 159 ($M - CO_2$), 130 (159 − CH_2CH_2 − H), and 104 (130 − CN).

Hydrolysis of the γ-Lactone (8).—The lactone (8) (100 mg, 0·5 mmol) in 10% sodium hydroxide (1·5 ml) was heated at 70—75°. After 10 min, the orange solution, which started to turn green, was cooled and then acidified with acetic acid to cause the liberation of carbon dioxide. Yellow crystals separated on cooling and were filtered off and washed with water and acetone. More solid was obtained from the filtrate upon neutralization of the excess of acetic acid with dilute sodium hydrogen carbonate and evaporation. The combined yield of 1,2-*dihydro*-2-(2-*hydroxyethyl*)-*indol*-3-*one* (9) was 37 mg (42%), m.p. 164° (decomp.) (from dimethyl sulphoxide–water) (Found: C, 67·35; H, 5·85; N, 7·8. $C_{10}H_{11}NO_2$ requires C, 67·8; H, 6·25; N, 7·9%); $\lambda_{max.}$ (MeOH) 395, 260sh, and 237 nm; $\nu_{max.}$ (KBr) 3400 (OH), 3300 (NH), 1660 (C=O), and 1610 cm^{-1} (Ar·N·CR^1R^2); [7,10] δ [$(CD_3)_2SO$] 6·55—7·05 (2H, m, ArH), 7·15—7·65 (2H, m, ArH), other protons not discernible; *m/e* 177 (M^+) and 146 ($M - CH_2OH$).

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