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NITRENES—XIV[1]

TRIETHYL PHOSPHITE DEOXYGENATION OF α-(6-NITROVERATRYLIDENE)-γ-BUTYROLACTONE

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Abstract—Triethyl phosphite reduction of α - (6 - nitroveratrylidene) - γ - butyrolactone (**6**) produced a mixture of 3,4 - dihydro - 7,8 - dimethoxy[1.3]oxazino[3.4-a]indol - 1 - one (**8**), ethyl 5,6 - dimethoxyindole - 2 - carboxylate (**9**) and 2,3 - dihydro - 6,7 - dimethoxyfuro[2.3-b]quinoline (**10**). Photolysis of the corresponding 6-aminoveratrylidene derivative **11** also produced **10**. Probable mechanisms and spectral evidence for the *trans*-configuration of **6** and **11** are presented.

Nitration of α - veratrylidene - γ - butyrolactone (**5**) afforded not only the mononitro compound **6** but also a low yield of α - (α - nitrato - 6 - nitroveratryl) - α - nitro - γ - butyrolactone (**7**).

Although many cyclization procedures have been utilized in the synthesis of the naturally occurring furo[2.3-b]quinoline ring system, the triethyl phosphite reductive process has not been applied successfully. Previously we reported the first attempts to convert nitrophenyl compounds to furo[2.3-b]quinolines with triethyl phosphite. Reduction of α-*o*-nitrobenzoyl-(**1**) and α-(α-methoxy-*o*-nitrobenzylidene)-(**3**) γ-butyrolactones, however, afforded to remove the spiro[furan-3.2'-indole]dione **2** and the [1.3]oxazino[3.4-a]indolone **4**, respectively.[1]

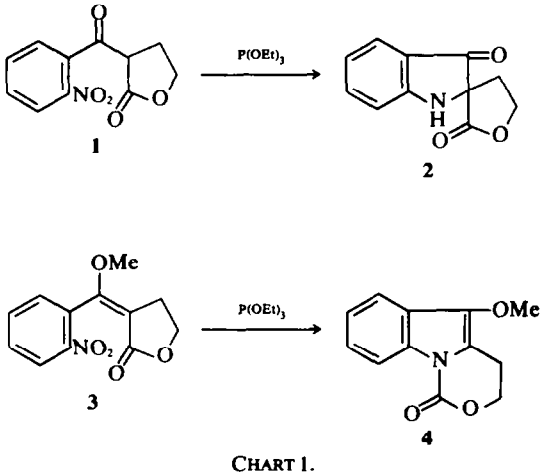


CHART 1.

We now wish to report an extension of these studies to the triethyl phosphite reduction of α - (6 - nitroveratrylidene) - γ - butyrolactone (**6**). Deoxygenation of **6** and cyclization *via* a nitrene intermediate could lead to a furoquinoline.

Veratraldehyde was condensed with γ-butyrolactone by a modification of literature methods[3] which resulted in an improved yield of α - veratrylidene - γ - butyrolactone (**5**). Nitration of **5** with concentrated nitric acid (*d* 1·42) at the recommended[4] temperature of − 10° resulted in almost complete recovery of **5**. At 0°, however, nitration proceeded to give a good yield of **6**, in addition to an ether soluble compound in low yield.

The IR spectrum of the nitration by-product exhibited strong CO absorption at 1790 cm^{-1}, indicative of a saturated γ-lactone, characteristic nitro bands, and a very intense band at 1660 cm^{-1}, suggesting a nitrate group. Microanalysis and mass spectral analysis (M^+ 387) confirmed the presence of a benzylic nitrate and two nitro groups, and led to the assignment of structure **7** to the nitration product. The NMR spectrum revealed three low field singlets (δ 7·26, 7·68 and 7·85, each 1H) which were assigned to the benzylic and para aromatic hydrogens. Multiplets at δ 2·46–3·05 (2H) and 4·16–4·50 (2H), accounting for the β and γ butyrolactone hydrogens, respectively, established the α-position for the second nitro group. The similarity of the UV spectra of **7** (λ max 247, 305 and 340 nm) and (4,5-dimethoxy-2-nitrophenyl) acetic acid[5] (λ max 243, 300 and 340 nm) in methanol also supported the structure of **7**. Further treatment of pure **6** with nitric acid under the same conditions used to form **6** did not produce more **7**. Therefore, **7** is most likely formed by addition of nitric acid to the benzylidene double bond of **5** followed by esterification and nitration. Van Der Lee isolated similar nitric acid addition products from *meta*- and *para*- nitrocinnamate esters and "absolute" nitric acid, but was unable to obtain the corresponding *o*-nitro isomer.[6]

Reduction of recrystallized nitro-lactone **6** with triethyl phosphite at 160–165° for 20 hr, and

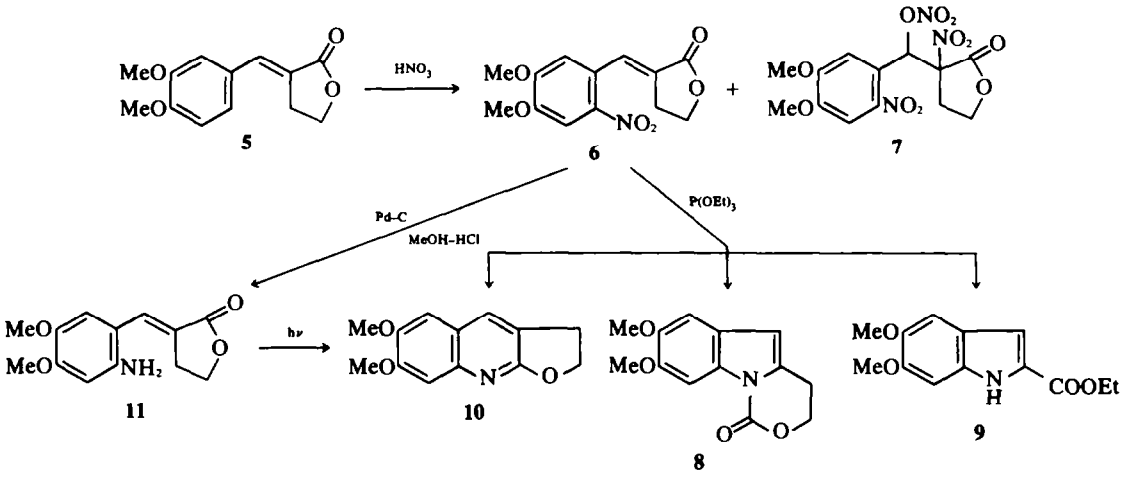


CHART 2.

chromatography of the residue, after distillation, separated two crystalline components. The first to be eluted was further separated into two solids by differential solubility in ether. The more insoluble fraction (yield, 4·5%) showed CO absorption at 1730 cm^{-1} in the IR, similar to **4**, and on comparison of other spectral data, was readily assigned the 3,4 - dihydro - 7,8 - dimethoxy[1.3]oxazino[3.4-a]indol - 1 - one (**8**) structure.

The ether soluble fraction consisted of a trace quantity of pale yellow crystals which exhibited a strong band at 1690 cm^{-1} (C=O) and a medium band at 3470 cm^{-1} (NH) in the IR ($CHCl_3$). The mass spectrum revealed the molecular ion (*m/e* 249) as the base peak which loses ethanol to give the next most intense ion at *m/e* 203. Other fragment ions at *m/e* 234 (M^+–Me), 204 (M^+–OEt), 188 (234–EtOH), 175 (203–CO) and 149 (175–CN) also support a 2-ethoxycarbonylindole structure. Powers[7] reported a similar fragmentation pattern for ethyl indole-2-carboxylate, which also showed CO absorption in the IR at 1695 cm^{-1} (KBr).[8] Also, the UV spectrum was similar to that of 5,6-dimethoxyindole-2-carboxylic acid,[9] having maxima at 212 and 322 nm. Finally, the NMR spectrum with signals at δ 1·38 and 4·36 (CH_3CH_2O, J = 7 Hz); 3·88 ($2 \times OCH_3$); 6·81, 6·99 and 7·08 (each 1H, olefinic); and 8·77 (NH exchangeable with deuterium oxide) confirmed the ethyl 5,6-dimethoxyindole-2-carboxylate (**9**)[10] structure.

The second component eluted from the column was identified as the anticipated furoquinoline, 2,3 - dihydro - 6,7 - dimethoxyfuro[2.3-b]quinoline (**10**) (yield, 3%), by a comparison of m.p. and IR data with those reported for **10**, which was previously prepared by polyphosphoric acid cyclization of the corresponding 3-(2-hydroxyethyl)carbostyril.[11] Thus, the first synthesis of a furo[2,3-6]quinoline *via* the triethyl phosphite reductive process has been achieved.

Additional evidence for structure **10** was derived from an independent synthesis. Although catalytic reduction of **3**[12] and the 4,5-methylenedioxy[13,14] and 4,5-dimethoxy[13] derivatives of **3** with palladium on carbon in methanolic hydrochloric acid effected reductive cyclization to the corresponding 4-methoxyfuro[2.3-b]-quinolines, reduction of **6** under the same conditions afforded only the amino-benzylidene lactone **11** in 73% yield. Previously **11** was prepared in an undisclosed yield by reduction of **6** with stannous chloride and concentrated hydrochloric acid.[4] Zimmer[14] reported, without supporting data, that substituted α-benzylidene-γ-butyrolactones similar to **3**, **6** and **11** are in the *trans*-configuration due to the sterical hindrance between the substituent in the 2-position of the aromatic nucleus and the lactone-carbonyl group, and that radiation or acid treatment is necessary for rearrangement (isomerization). However, acid treatment of **6** and **11** (Pd/C–HCl or $SnCl_2$–HCl) did not cause isomerization and cyclization. The ready isomerization and cyclization of α-methoxybenzylidene-lactones (*e.g.*, **3**) in acid, in contrast to the unsubstituted benzylidene-lactones (*e.g.*, **6** and **11**) may be explained by considering the following protonated forms which lead to the *cis*-configuration and cyclization.

A comparison of the NMR spectra of the α-benzylidene-γ-butyrolactones **5**, **6** and **11** revealed that the benzylidene protons are at δ 7·44, 7·91 and 7·58, respectively. Valente and Wolfhagen[15] compared the NMR spectra of several α-substituted cinnamates and found the signal due to the β-proton at δ 7·4–7·5 when it is *cis* to the ester group, and at 6·4–6·7 when it is *trans*. Thus, these data provide additional evidence for the *trans*-configuration of CO and phenyl groups in **5**, **6** and **11**.

Irradiation of amine **11** in ethanol produced a 15% yield of furoquinoline **10**, which was identical

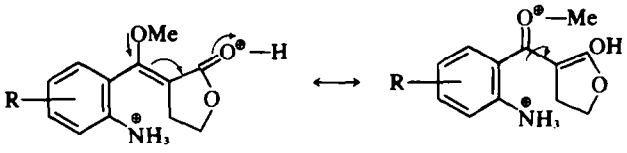


CHART 3.

to **10** prepared by triethyl phosphite reduction. In the NMR spectrum of furoquinoline **10**, the signals for the α- and β-furan protons are at δ 4·62 and 3·29, respectively, with $J = 8$, in agreement with the spectrum of a related furoquinoline, dihydrodictamnine.[16]

Previously, irradiation of α - (*o* - aminobenzylidene) - and α - (6 - aminopiperonylidene) - γ - butyrolactones afforded the corresponding 3-(2-hydroxyethyl) carbostyrils (yield, 35% in the case of the former lactone) and an undisclosed yield of the dihydrofuro[2.3-b]quinolines.[17] We were unable to isolate the corresponding carbostyril from the photolysis of **11**.

Isomerization (*trans* → *cis*) in the triethyl phosphite reaction could take place by addition of phosphite to the olefinic group thus permitting free rotation of the lactone (**12** → **13** → **14**). Nitrene addition to the double bond and to the carbonyl through intermediate **15** would lead to oxazinoindole **8** (Path a). Similarly, further deoxygenation (Path b) would afford furoquinoline **10**. Logical mechanisms for the formation of ethyl 5,6-dimethoxyindole-2-carboxylate (**9**) are more difficult to propose. Addition of a nitrene to the double bond with subsequent reductive cleavage of a C–C bond is one possibility.

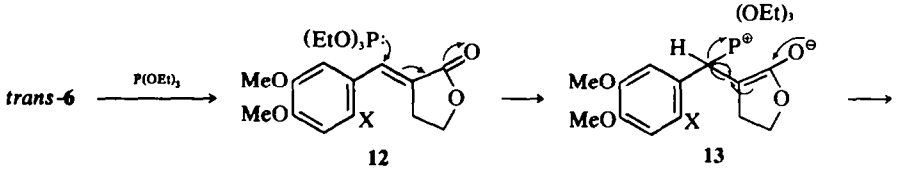
It is interesting to note that 2,3-disubstituted indoles, which form on deoxygenation of β,β-disubstituted *o*-nitrostyrenes with triethyl phosphite,[18] were not isolated from the reductions of *o*-nitrobenzylidene-butyrolactones.

EXPERIMENTAL

M.ps were measured with a Yanagimoto micro m.p. apparatus (MP-S2). IR spectra were measured with a Hitachi 215 grating spectrophotometer, NMR spectra with Hitachi H-60 and JEOL JNM-100 spectrometers with tetramethylsilane as an internal standard, mass spectra with a Hitachi RMU-7 spectrometer, and UV spectra with a Hitachi 124 spectrometer.

α-Veratrylidene-γ-butyrolactone (**5**). Na (4 g; 0·174 mol) was added in portions to 35 ml of MeOH. After heating under reflux to complete the reaction, excess of MeOH was distilled *in vacuo* and then dry benzene was added and the distillation repeated. The residue was suspended in 100 ml dry benzene and γ-butyrolactone (20 g; 0·232 mol) was added with stirring over 20 min at 5°. After 30 min at 5°, veratraldehyde (17·2 g; 0·104 mol) in 120 ml benzene was added over 15 min at 4–7°. The temp. was increased to 50° over 20 min, and then the mixture was stirred at 25° for 80 min. After adding 75 ml of 10% HCl and stirring for 1 hr, the benzene layer was washed with 5% $NaHCO_3$ and water, and evaporated. The residue was washed with ether to give 18·8 g (78%) of **5**, m.p. 119–120° (lit.[3a] m.p. 116–116·5°); UV (MeOH) 220, 238, 300, 323 nm; IR ($CHCl_3$) 1735 (C=O), 1645 cm^{-1}; NMR ($CDCl_3$) δ 3·20 (2H, dt, J = 7·5 and 3 Hz, OCH_2CH_2), 3·89 (6H, s, 2 × OCH_3), 4·42 (2H, t, J = 7·5, OCH_2CH_2), 6·86 (1H, d, J = 7 Hz, aromatic 5-H), 6·97 (1H, d, J = 1·5 Hz, aromatic 2-H), 7·10 (1H, dd, J = 7 and 1·5 Hz aromatic 6-H), 7·44 (1H, t, J = 3 Hz, aromatic CH).

Nitration of **5**. **5** (9 g; 0·0385 mol) was added to 50 ml conc HNO_3 (*d* 1·42) gradually at 0–3°. After standing for 4 hr at 0°, the soln was poured into 200 ml water. The yellow solid was washed with water, air dried and then washed with ether to give **6** (9·43 g; 88%), m.p. 155–165°.



X = NO_2 or N:

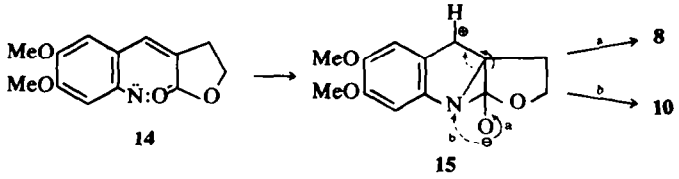


CHART 4.

Recrystallization of **6** (5·4 g) from 500 ml MeOH gave 4·4 g yellow needles, m.p. 171–172° (lit.[4] m.p. 165°); UV (CH_3OH) 273, 347 nm; IR ($CHCl_3$) 1750 (C=O), 1500 and 1325 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 3·09 (2H, dt, J = 7 and 3 Hz, OCH_2CH_2), 4·00 (6H, s, 2 × OCH_3), 4·44 (2H, t, J = 7 Hz, OCH_2CH_2), 6·92 (1H, s, aromatic 2-H), 7·71 (1H, s, aromatic 5-H), 7·91 (1H, t, J = 3 Hz, aromatic CH).

The ethereal filtrate was evaporated and the residue triturated with a minimum of MeOH to give 0·9 g of solid, m.p. 114–121°. The recrystallization filtrate on evaporation and extraction of the residue with ether gave 0·3 g of a solid, m.p. 103–110°. The combined yield of **7** was 9·5%. Several recrystallization from MeOH and then EtOH produced pale yellow prisms, m.p. 123–125°; UV (CH_3OH) 247, 305^{sh}, 340 nm; IR ($CHCl_3$) 1790 (C=O), 1660 (ONO_2), 1570, 1510 and 1330 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 2·46–3·05 (2H, m, OCH_2CH_2), 3·97 (6H, s, 2 × OCH_3), 4·16–4·50 (2H, m, OCH_2CH_2), 7·26, 7·68 and 7·85 (each 1H, s, 2 × ArH and $ArCH$); MS *m/e* 387 (M^+), 340 (M^+–HNO_2), 325 (M^+–ONO_2), 211, 210, 182, 181, 136. (Found: C, 40·50; H, 3·63; N, 10·96. $C_{13}H_{13}N_3O_{11}$ (387·26) requires: C, 40·32; H, 3·38; N, 10·85%).

Reaction of **6** *with triethyl phosphite.* A mixture of **6** (4 g; 14·4 mmol) and triethyl phosphite (12 g) was heated at 160–165° for 20 hr under N_2. Triethyl phosphite and triethyl phosphate were distilled off at 2 mmHg. The residue was dissolved in benzene and the soln was washed with water, dried (Na_2SO_4) and evaporated. Chromatography of the dark red residue on silica gel with benzene-chloroform (1 : 1) as the eluant gave a pale yellow solid in the first fraction which was further separated into two solids with ether. The ether insoluble solid (160 mg, 4·5%) was recrystallized from MeOH and then benzene to give **8** as colorless needles, m.p. 162·5–163·5°; UV (MeOH) 246, 254^{sh}, 270, 295 nm; IR ($CHCl_3$) 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3·16 (2H, dt, J = 6 and 1·5 Hz, OCH_2CH_2), 3·90 and 3·95 (each 3H, s, 2 × OCH_3), 4·52 (2H, t, J = 6 Hz, OCH_2CH_2), 6·27 (1H, br, 5-H), 6·94 (1H, s, 6-H), 7·81 (1H, s, 9-H); MS *m/e* 247 (M^+), 232 (M^+–Me), 188 (232-CO_2), 160 (188-CH_2CH_2), 145 (160-Me), 117 (145-CO). (Found: C, 63·19; H, 5·28; N, 5·69. $C_{13}H_{13}NO_4$ (247·24) requires: C, 63·15; H, 5·30; N, 5·67%).

Evaporation of the ether and treatment of the residue with a minimum of ether yielded **9** (5 mg) as pale yellow crystals, m.p. 155–175° (lit.[10a] m.p. 172°; lit.[10b] softened at 155°, m.p. 160°); UV (MeOH) 212, 322 nm; IR ($CHCl_3$) 3470 (NH), 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1·38 (3H, t, J = 7 Hz, CH_2CH_3), 3·88 (6H, s, 2 × OCH_3), 4·36 (2H, q, J = 7 Hz, CH_2CH_3), 6·81 (1H, s, 7-H), 6·99 (1H, s, 4-H), 7·08 (1H, distorted d, J = 2 Hz, 3-H), 8·77 (1H, br, NH exchangeable with D_2O); MS *m/e* 249 (M^+), 234 (M^+–Me), 204 (M^+–OEt), 203 (M^+–EtOH), 188 (234-EtOH), 175 (203-CO), 160 (188-CO or 175-Me), 149 (175-CN).

The second fraction, which was eluted with benzene-chloroform (1 : 1 and 1 : 3), gave **10** (95 mg; 3%) as almost colorless needles after washing with ether, which was recrystallized from 2-propanol to give colorless needles, m.p. 195–196° (subl) (lit.[11] m.p. 192–193°); UV (MeOH) 222, 240^{sh}, 328, 343 nm; IR ($CHCl_3$) 1630 cm^{-1} (lit.[11] 1639 cm^{-1}); NMR ($CDCl_3$) δ 3·29 (2H, dt, J = 8 and 1·5 HZ, OCH_2CH_2), 3·93 and 3·96 (each 3H, s, 2 × OCH_3), 4·62 (2H, t, J = 8 Hz, OCH_2CH_2), 6·91 (1H, s, 5-H), 7·19 (1H, s, 8-H), 7·65 (1H, br, 4-H).

Catalytic reduction of **6**. To a suspension of **6** (1 g 3·6 mmol) in 50 ml MeOH 1N HCl (3·6 ml; 3·6 mmol) was added, and the mixture was hydrogenated over 0·3 g of 5% Pd-C at atmospheric pressure. H_2 absorption ceased at 3 mol. The soln was filtered and evaporated, and the residue treated with 10 ml of 10% NH_4OH to give an orange solid which was washed with water. The hydrated solid (0·65 g, 73%, m.p. 156–161°) was recrystallized from 12 ml of EtOH to give **11** as yellow crystals, m.p. 159–163° (lit.[4] m.p. 162°); UV (CH_3OH) 235, 265, 302 nm; IR ($CHCl_3$) 3500 and 3400 (NH_2), 1735 (C=O), 1615 cm^{-1} (NH_2); NMR ($CDCl_3$) δ 3·18 (2H, dt, J = 7·5 and 3 Hz, OCH_2CH_2), 3·67 (2H, br, NH_2 exchangeable with D_2O), 3·81 and 3·85 (each 3H, s, 2 × OCH_3), 4·42 (2H, t, J = 7·5 Hz, OCH_2CH_2), 6·30 (1H, s, aromatic 5-H), 6·83 (1H, s, aromatic 2-H), 7·58 (1H, t, J = 3 Hz, aromatic CH).

Photolysis of amine **11**. A soln of **11** (200 mg; 0·8 mmol) in EtOH (1 l.) was irradiated for 4·5 hr at 20–30° under N_2 with a Riko 400 W mercury lamp fitted with a Pyrex filter. After evaporation of the EtOH, the red oil was chromatographed on silica gel with chroroform as the eluant to give 28 mg (15%) of (**10**), m.p. 195–196° (subl), whose UV and IR spectra were identical with those of **10** prepared from **6**.

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