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NITRENES–XV[1]

1-HYDROXYMETHYL-4,5-DIMETHOXY-7H-AZIRINO[1,2-a]-INDOLE-7a-CARBOXYLIC ACID γ-LACTONE, A NITRENE ADDITION COMPOUND

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Abstract—Triethyl phosphite deoxygenation of α-(6-nitroveratrylidene)-γ-butyrolactone **1** under moderate conditions affords a mixture of 3-(6-nitroveratryl)-2(5*H*)-furanone **5**, α-(6-ethylaminoveratrylidene)-γ-butyrolactone **6** and 1-hydroxymethyl-4,5-dimethoxy-7*H*-azirino[1,2-a]indole-7a-carboxylic acid γ-lactone **7**, in addition to 3,4-dihydro-7,8-dimethoxy[1,3-a]oxazino[3,4-a]indol-1-one **2**, ethyl 5,6-dimethoxyindole-2-carboxylate **3**, and 2,3-dihydro-6,7-dimethoxyfuro[2,3-b]quinoline **4**, obtained under more drastic reaction conditions.

The isolation of lactones **5** and **7** provides strong evidence for the intermediacy of nitrenes in this reaction which appears to provide the first example of intramolecular aziridine formation from a nitro-aromatic compound and triethyl phosphite.

In the previous paper,[1] we reported the triethyl phosphite deoxygenation of α-(6-nitroveratrylidene)-γ-butyrolactone **1**, and proposed nitrene and aziridine intermediates to account for the products. Since the product yields after 20 h at 160–165° were very low, we have now re-examined this reaction under less severe conditions.

Heating lactone **1** in an excess of triethyl phosphite at 140–150° for 5 h produced a dark red solution, as was obtained in the previous study. After distillation of the excess triethyl phosphite and triethyl phosphate, chromatography of the residue on silica gel with benzene-chloroform (1:1) afforded several fractions containing mixtures of at least seven compounds. Although not completely separated by the solvent system, four compounds could be readily identified by IR spectral analysis: unreacted nitro-lactone **1**, and the three cyclic compounds obtained in the earlier work,[1] 3,4 - dihydro - 7,8 - dimethoxy[1,3-a]oxazino[3,4-a]indol - 1 - one **2**, ethyl 5,6 - dimethoxyindole - 2 - carboxylate **3** and 2,3 - dihydro - 6,7 - dimethoxyfuro[2,3-b]quinoline **4**.

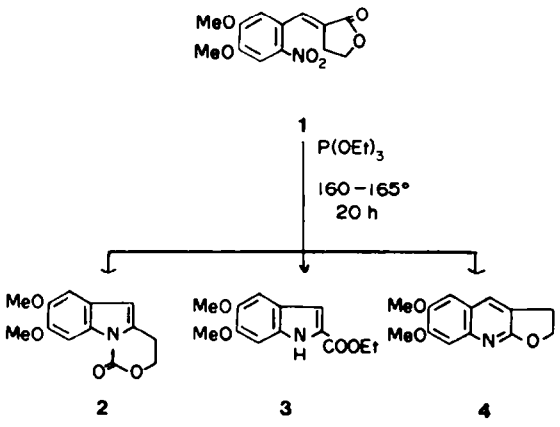

Chart 1.

In order to effect a better separation of the products, the first fractions, which contained predominantly 1730 and 1750 cm^{-1} absorbing compounds, **2** and **1** respectively, and traces of **3**, were rechromatographed on silica gel with benzene-chloroform (2:1). Likewise, the later fractions, containing **4** and a compound showing IR absorption at 1775 cm^{-1}, were rechromatographed with a 3:2 benzene-chloroform mixture.

Oxazinoindole **2** was obtained in 3·7% yield,[3] compared with 4·5% at the higher temperature and longer reaction time. The 1750 cm^{-1} fractions were further resolved into a trace of **1** and a pale yellow isomer (7% yield) having an IR spectrum almost identical with that of **1**. However, the UV spectrum was typical of a 6-nitroveratryl derivative.[1] The NMR spectrum showed one olefinic proton as a triplet at 7·18 ppm coupled (J = 1·5 Hz) with the γ-methylene protons of a 5-membered lactone, which appear as a doublet at 4·75 ppm instead of a triplet as in the saturated lactone **1**. Two benzylic and six methoxy protons appear as two singlets at 3·93 and 3·98 ppm, and two aromatic protons are at 7·02 and 7·63 ppm. Therefore, the isomer of **1** is 3-(6-nitroveratryl)-2(5*H*)-furanone **5**.

In addition to **2**, a trace quantity of a second compound exhibiting carbonyl absorption at 1730 cm^{-1} in the IR was isolated. The UV and IR spectra were very similar to those of the 6-amino derivative[1] of **1**, and the NMR spectrum revealed one exchangeable proton and an N-ethyl group. Therefore, reductive alkylation of **1** had occurred to give α-(6-ethylaminoveratrylidene)-γ-butyrolactone **6**. A trans-configuration of carbonyl and phenyl groups in **6** is indicated from the chemical shift (7·44 ppm) of the benzylidene proton in the NMR spectrum.[1]

On rechromatography, furoquinoline **4** was separated from a colorless solid which showed saturated γ-lactone absorption at 1775 cm^{-1} and the absence of NO_2, NH and OH bands in the IR spectrum. The NMR spectrum was most informative in showing the presence of two pairs of geminal protons with large coupling constants. A pair of doublets integrating for two protons appear at 3·33 and 3·63 ppm (J = 18 Hz), and another pair (2H) is centered at

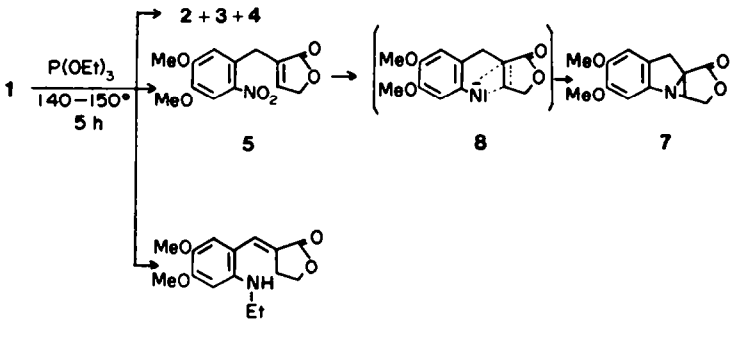

Chart 2.

4·45 ppm (J = 10 Hz). The higher field doublet (4·27 ppm) of the latter pair is further coupled (J = 3 Hz) with a methine proton at 2·82 ppm. Two aromatic (each 1H) and two methoxyl (6H) proton signals completed the spectra and led to the assignment of the 1-hydroxymethyl-4,5-dimethoxy-7*H*-azirino[1,2-a]indole-7a-carboxylic acid γ-lactone **7** structure to the product. Since this compound was obtained as a minor product, chemical investigation could not be accomplished.

Microanalysis and the mass spectrum supported the structural assignment. The fragmentation pattern in the mass spectrum of **7** showed a close resemblance to that of the isomeric [1,3]oxazino[3,4-a]indole **2**. The molecular ion (*m/e* 247) is also the base peak, and other peaks appear at *m/e* 232, 203, 188 and 160. These data, therefore, suggest the fragmentation mechanism shown in Chart 3, whereby the molecular ion undergoes cleavage of the aziridine ring and isomerization to the [1,4]oxazino[4,3-a]indole **9**. The structural similarity of **2** and **9** is obvious and would account for the similar fragmentation pattern.

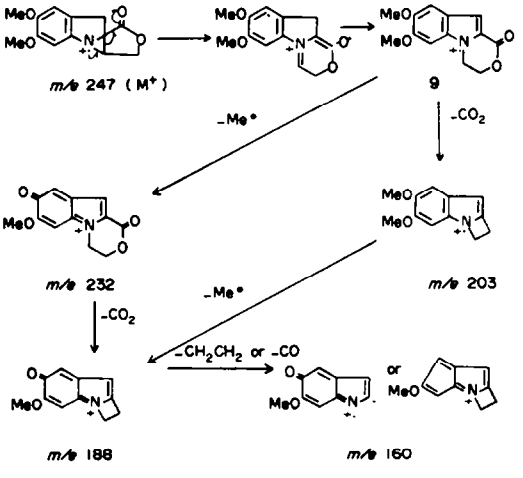

Chart 3.

The UV spectrum (λ_{max} 290 and 235 nm), which is typical of the indoline chromophore,[4] shifts irreversibly to λ_{max} 308 and 242 nm in methanolic hydrochloric acid possibly due to opening of the 3-membered aziridine ring.

Rearrangement of the exocyclic α,β-unsaturated lactone **1** to the endocyclic α,β-unsaturated lactone **5** would presumably lead to the formation of the azirino-indole **7** via nitrene addition to the olefinic bond of **8** as shown in Chart 2.

Although aziridines have been suggested as intermediates in the triethyl phosphite deoxygenation process,[1,5] there appear to be no other examples of their isolation. These results, therefore, are of great interest as the intermediacy of nitrenes and aziridines in this reaction.

EXPERIMENTAL

All m.ps are uncorrected and were measured with a Yanagimoto micro melting point apparatus (MP-22). IR spectra were measured with a Hitachi 215 grating spectrophotometer, NMR with Hitachi H-60 and JEOL JNM spectrophotometers with Me_4Si as an internal standard, mass spectra with a Hitachi RMU-7 spectrometer, and UV spectra with a Hitachi 124 spectrometer.

Reaction of α-(6-nitroveratrylidene)-γ-butyrolactone **1** *with triethyl phosphite.* A mixture of 4 g (14·4 mmol) of **1** and 12 g of triethyl phosphite was heated at 140–150° for 5 h under N_2. Excess triethyl phosphite and triethyl phosphate were distilled at 2 mm Hg, and a benzene solution of the residue was washed with water, dried over Na_2SO_4 and evaporated. Chromatography of the dark red residue on silica gel with benzene-$CHCl_3$ (1:1) separated two main fractions. The first fraction, containing **1**, **2**, **3** (trace), **5** and **6**, was rechromatographed on silica gel with benzene-$CHCl_3$ (2:1). The first eluate gave 130 mg (3·7%) of **2**. The second eluate gave 285 mg (7·1%) of the nitrobenzyl-lactone **5** as pale yellow needles, m.p. 122°, 134°[dec] (from MeOH) (Found: C, 55·88; H, 4·87; N, 4·66. $C_{13}H_{13}O_6N$ requires C, 55·91; H, 4·70; N, 5·02%), ν_{max} ($CHCl_3$) 1750 (C=O), 1580, 1500 and 1325 cm^{-1} (NO_2), λ_{max} (MeOH) 340, 300[sh], 243 nm, δ ($CDCl_3$), 3·93 and 3·98 (8H, s, 2×OCH_3 and $ArCH_2$), 4·75 (2H, distorted d, J = 1·5 Hz, OCH_2CH), 7·02 (1H, s, Ar 2–H), 7·18 (1H, distorted t, J = 1·5 Hz, OCH_2CH), 7·63 (1H, s, Ar 5–H), *m/e* 279 (M^+), 262 (M^+–OH), 233 (M^+–NO_2). The third eluate gave 10 mg of a mixture of **1** and **5**. The fourth eluate gave 20 mg of solid which was triturated with ether to give **6** as yellow needles, m.p. 131–134° (Found: C, 64·75; H, 6·82; N, 5·11. $C_{15}H_{19}O_4N$ requires: C, 64·96; H, 6·91; N, 5·05%), ν_{max} ($CHCl_3$) 3435 (NH), 1730 (C=O), 1605 cm^{-1} (Ar-NHEt), λ_{max} (MeOH) 405, 305, 270, 240 nm; λ_{max} (MeOH–HCl) 320, 295, 235 nm, δ ($CDCl_3$) 1·28 (3H, t, J = 8 Hz, CH_2CH_3), 2·05 (1H, br NH exchangeable with D_2O), 3·16 (2H, q, J = 8 Hz, $NHCH_2CH_3$), 3·18 (2H, dt, J = 3 and 8 Hz, OCH_2CH_2), 3·74 and 3·83 (each 3H, s, 2×OCH_3), 4·35 (2H, t, J = 8 Hz, OCH_2CH_2), 6·15 (1H, s, Ar 5–H), 6·76 (1H, s, Ar 2–H), 7·44 (1H, t, J = 3 Hz, ArCH), *m/e* 277 (M^+), 262 (M^+–Me), 260 (M^+–OH), 141.

The second main fraction was rechromatographed on silica gel with benzene-$CHCl_3$ (3:2). After elution of traces of **2** and **5**, the next eluate contained 125 mg (3·5%) of solid which was recrystallized from MeOH to give **7** as colorless needles, m.p. 179–180° (Found: C, 63·06; H, 5·43; N, 5·47. $C_{13}H_{13}O_4N$ requires: C, 63·15; H, 5·30; N, 5·67%), ν_{max} ($CHCl_3$) 1775 cm^{-1} (C=O), λ_{max} (MeOH) 290, 235 nm, δ ($CDCl_3$) 2·82 (1H, d, J = 3 Hz, $NCHCH_2$), 3·33 and 3·63 (each 1H, pair of d, J = 18 Hz, $ArCH_2$), 3·78 (6H, s, 2×OCH_3), 4·27 (1H, dd, J = 10 and 3 Hz, OCH_2CH), 4·45 (1H, d, J = 10 Hz, OCH_2CH), 6·66 and 6·73 (each 1H, s, ArH), *m/e* 247 (M^+), 232 (M–Me), 203 (M–CO_2), 188 (203–Me or 232–CO_2), 160 (188–CH_2CH_2 or –CO). The last eluate gave 25 mg of **4**.

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[2]On leave from Norwich Pharmacal Co., Div. of Morton-Norwich Products, Inc., Norwich, N.Y.

[3]Because of the complex mixture and multiplet chromatographic separations, actual yields may be higher.

[4]A. I. Scott, *Interpretation of the Ultraviolet Spectra of Natural Products*, Pergamon, Oxford (1964), pp. 172, 198.

[5]J. I. G. Cadogan, *Quart. Revs.* **22**, 222 (1968).

[6]Melts at 122°, resolidifies and remelts at 134°.