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REACTIONS OF PAPAVERINOL WITH ACIDS

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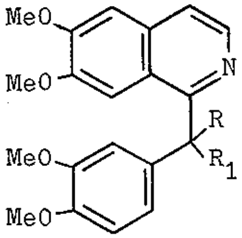
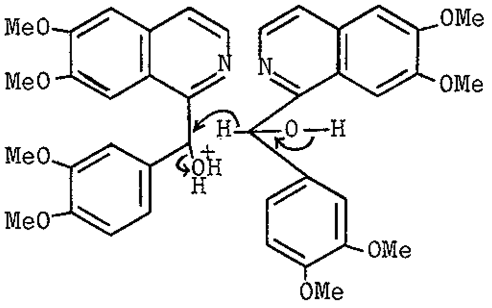
Reaction of papaverinol (I) with glacial acetic acid gave papaverine (II) and papaveraldine (III). However, reaction of papaverinol with 90% sulphuric acid gave a demethylation product (IVa) and another product (V) resulting from carbon-carbon bond cleavage.

In connection with other studies, we were interested in the generation and reactivity of the carbonium ion at the benzylic position of the benzylisoquinoline. We wish to report some interesting reactions discovered during this investigation.

By treatment of papaverinol[1] (I) with glacial acetic acid under reflux for 14 hr, two compounds were formed and separated by plc (a mixture of methanol:chloroform (5:95) was used as developing solvents). Their identities were proved to be papaverine (II, 32.1 % yield) and papaveraldine (III, 32.7 % yield). The mechanism of disproportionation is shown in scheme I.

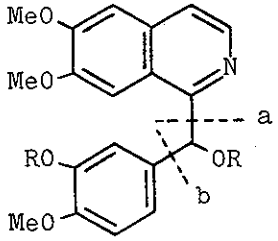


I R = H, R_1 = OH
II R = R_1 = H
III $R+R_1$ = O

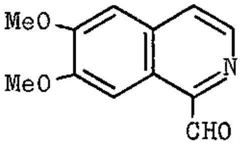


Scheme I

To suppress a 'hydride transfer' reaction, the reaction of papaverinol with stronger acid was investigated. Papaverinol was treated with 90% sulphuric acid at room temperature for 15 hr and the reaction mixture was then adjusted with conc. sodium hydroxide to ca. pH 6, followed by treatment with sodium bicarbonate solution. After the usual work up, compounds (IVa) and (V) were separated by plc in 45% and 6% yields respectively. It was found from various experiments that the ratio of compounds (IVa) and (V) diminished when the reaction was carried out at higher temperature and/or more concentrated acid was employed. For example, treatment of papaverinol with 90% sulphuric acid at 60-70°C (oil-bath temperature) followed by the usual work up, compounds (IVa) and (V) were formed in 10% and 15% yields respectively.



(IV) a) R = H
b) R = Ac



(V)

Compounds (IVa) and (V) had the following physical data, compound (IVa); mp 186-187°C; ir: 3350, 3460 cm^{-1} (2xO$\underline{H}$); nmr: (δ in $CDCl_3$) 3.73, 3.80, 3.98 (3s, 3xOC$\underline{H}_3$), 6.16 (s, -C$\underline{H}$-OH), 6.80 (d, J=1Hz, C-2$'$ Ar$\underline{H}$), 6.90 (br s, C-5$'$ & C-6$'$ 2xAr$\underline{H}$), 7.09 (s, C-8 Ar$\underline{H}$), 7.18 (s, C-5 Ar$\underline{H}$), 7.53 (d, J=6Hz, C-4 $\underline{H}$C=), 8.45 (d, J=6Hz, C-3 C$\underline{H}$-N), m/e 341 (M^+). Compound (V); mp 172-173°C (Lit.[2], 176°C); ir: 1702 cm^{-1}(CHO); nmr: (δ in $CDCl_3$) 4.05, 4.09 (2s, 2xOC$\underline{H}_3$) 7.15 (s, C-5 Ar$\underline{H}$), 7.43 (d, J=6Hz, $\underline{H}$C=), 8.78 (d, J=6Hz, C-3 C$\underline{H}$-N), 8.90 (s, C-8 Ar$\underline{H}$), 10.50 (s, C$\underline{H}$O); m/e 217 (M^+).

The monodemethylation was clearly supported from three methoxyl groups in the nmr spectrum of compound (IVa) and the appearance of phenolic hydroxyl group in the ir spectrum. The combinations of peaks, in the mass spectrum, at m/e 189, 151 and 218, 123 firmly established that the methyl group in ring C was lost in the reaction. These peaks could be rationalised to arise from cleavage at bonds a and b as shown in structure (IV). To differentiate which methyl group in ring C was lost, comparison of the nmr spectra of compounds (IVa) and its corresponding diacetate was made. It has been found[3] that acetylation of a phenolic hydroxyl group results in a downfield shift of the chemical shifts of protons, the ortho and para protons are most shifted and meta proton is least shifted. The downfield shift (0.49) of signals due to C-2$'$ aromatic proton supported the assigned structure. The diacetate[4] (IVb) was prepared in quantitative yield by acetylation of papaverinol with acetic anhydride in pyridine.

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References and Footnote

1) K. W. Bentley and A. W. Murray, J. Chem. Soc., 1963, 2487.

2) C. K. Bradsher and N. L. Dutta, J. Org. Chem., 1961, **26**, 2231.

3) R. J. Highet and P. F. Highet, J. Org. Chem., 1965, **30**, 902.

4) The diacetate (IVb) had the following physical data; mp 120°C; ir: 1705, 1732 (2xAc); nmr: 2.28 (s, 2xAc), 3.82, 3.97, 4.00 (3xs 3xOC$\underline{H}_3$), 7.19 (br s, 3$\underline{H}$, C$\underline{H}$-OAc, C-5', C-6', 2xAr$\underline{H}$), 7.29 (d, J= 1.5Hz C-2' Ar$\underline{H}$), other aromatic protons appeared as a group of peaks centred at 7.60; m/e 425 (M^+, calcd for $C_{23}H_{23}NO_7$ 425.147 found 425.146)

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