THE DEMETHYLATION OF PAPAVERINOL WITH SULFURIC ACID[1]

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Structure 3 is definitively established instead of the reported 2 for the monodemethylated compound obtained by treatment of papaverinol (1) with 90% sulfuric acid as shown by C-13 nmr spectroscopy.A tentative mechanism is proposed for the reaction.

It has recently been reported[2] that the treatment of papaverinol (1) with 90% sulfuric acid yields mainly a monodemethylated compound (2), its structure being assigned largely by comparing the pmr spectrum with that of its corresponding diacetate derivative. We reasoned mechanistically that structure 3 instead of 2 could be the most probable one. We have now obtained evidence that enables us to establish definitively the structure 3 for the above monodemethylated compound.

Thus, when finely powdered papaverinol (1) was added to 90% sulfuric acid, a deep purple color developed immediately ($\lambda_{max.}^{90\% H_2SO_4}$: 555 nm). The reaction was kept at room temperature overnight, quenched with water and then neutralized. After usual work up, a single product (20- 30 % yield) was isolated from the phenolic fraction that showed

Table 1

Carbon-13 chemical shifts of 5, 4, 3 (ring C) and their corresponding phenoxide ions[a,b,c]

	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
5	134.84	115.50	146.01	147.80	113.19	120.36
5 anion	135.41	118.75	158.04	151.38	113.08	112.89
	+ 0.57	+ 3.25	+12.03	+ 3.58	- 0.11	- 7.47
4	133.89	112.83	148.22	145.26	116.25	121.49
4 anion	125.24	112.20	151.38	158.34	118.50	122.26
	- 8.65	- 0.63	+ 3.16	+13.08	+ 2.25	+ 0.77
3 (ring C)	135.86	111.84	148.57	146.11	116.33	120.99
3 anion	127.53	111.70	151.66	159.84	118.90	121.93
	- 8.33	- 0.14	+ 3.09	+13.73	+ 2.57	+ 0.94

[a] All spectra have been recorded in a CFT-20 apparatus at 20 MHz.For the phenols DMSO:D_2O (1:1) was used as solvent and dioxane as internal reference.δ_C ppm from TMS. Data converted using $\delta_C^{dioxane} = 67.46$ ppm. To these samples solid NaOH was added until pH 14 was reached, to ensure the generation of the phenoxide ions.

[b] The assignement of the chemical shifts is based on proton noise and off-resonance decoupling and the application of general chemical shift theory. They are in agreement with the data reported for vanillactic acid and isovanillactic acid[6].

[c] Since the signals corresponding to the isoquinoline moiety of 3 did not show any significant change on going from the phenol to the phenoxide ion, they are omitted for simplicity's sake.

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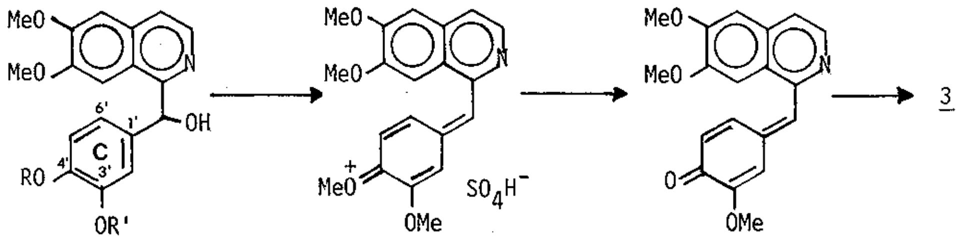
the same physical data (mp, ir and pmr) as those described for the above monodemethylated papaverinol (2)[2]. However, we observed that it *failed to give the Gibb's test*[3] *which indicates the lack of a free* position *para* to the phenolic group in the isolated monophenolic papaverinol[4]. This suggests that the monodemethylation of papaverinol (1) occurred at the 4' instead of the 3' position to give compound 3. Further support for the new structure was obtained by comparing the C-13 nmr spectrum with that of its corresponding phenoxide ion. It

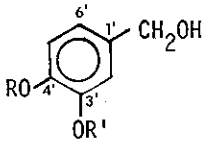


1 R=R'= Me
2 R=Me, R'=H
3 R=H, R'=Me
7 $R=CH_2C_6H_5$, R'=Me

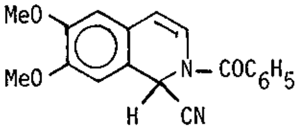
8

9

Scheme 1



4 R=H, R'=Me
5 R=Me, R'=H



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has been found that conversion of a phenolic group into its anion, results in an upfield shift by ∿6 ppm of the *para* carbon to the phenolic group[5]. To check the validity of this we obtained the C-13 nmr spectra of vanillyl alcohol (4), isovanillyl alcohol (5), monodemethylated papaverinol (3) and their corresponding phenoxide ions. Table 1 contains assignements of the C-13 nmr chemical shifts observed for the aryl carbons of model compounds 4 and 5 and ring C of 3 in neutral and basic solutions. As expected, the off resonance spectrum of 5 as the phenoxide ion showed an upfield shift for the C-6' doublet of -7.47 ppm, while for 4 a *para* shielding effect of -8.65 ppm was observed for the C-1' singlet. Compound 3 behaved similarly to 4 showing a *para* shielding effect of -8.33 ppm for the C-1' singlet.

Total synthesis of compound 3 confirmed this structure for the isolated monophenolic compound. Condensation of the Reissert compound (6)[7] with O-benzylvanillin under phase-transfer conditions[8] yielded the compound 7 which under mild acidic conditions was converted into the compound 3.

A tentative mechanism for the monodemethylation of papaverinol (1) with sulfuric acid is proposed as is shown in Scheme 1. According to this mechanism, papaverinol (1) should be dehydrated to give the quinone methide intermediate (8). Subsequently 8 should be demethylated to the intermediate (9) and then react with water to give the compound 3. Concerning this type of mechanism, structure 2 must also be discarded for the isolated monodemethylated compound.

ACKNOWLEDGMENT: To the Comisión Asesora de Investigación Científica y Técnica (Spain) for its financial support.

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Received, 24th January, 1978