# SELECTIVE DEMETHYLATION OF PAPAVERINOL

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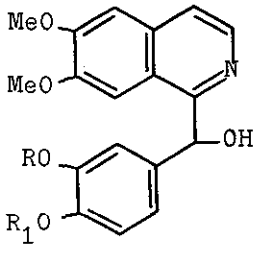
Compound (II), obtained from synthesis, was found to be identical with the product from the reaction of papaverinol with 90% sulphuric acid. 89% Orthophosphoric acid was found to be the acid of choice for the selective demethylation of papaverinol.

Structure (I) was assigned to a monodemethylation product obtained from the reaction of papaverinol with 90% sulphuric acid[1]. We have recently synthesized various 1-isoquinolyl-phenylcarbinol derivatives[2], and from this synthetic study, the structure of the monodemethylation product should be revised to its isomeric structure[3] (II).

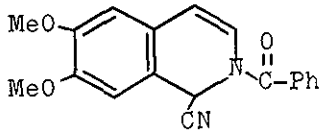



I R = H, $R_1$ = Me

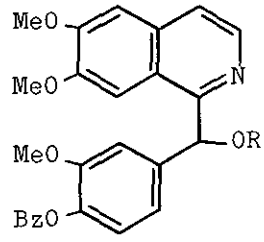
II R = Me, $R_1$ = H

Papaverinol R = $R_1$ = Me

Reissert compound (III) was synthesized by the new procedure[4]. Reaction of 6,7-dimethoxyisoquinoline with trimethylsilyl cyanide, benzoyl chloride in methylene chloride and a catalytic amount of aluminium chloride gave the Reissert compound (III) in 75% isolated yield, mp 159-160°. The carbanion was generated from compound (III) by the action of 50% sodium hydroxide and benzyltrimethylammonium chloride. Reaction of the derived carbanion with O-benzylvanillin gave first compound (IV) which was not isolated but hydrolysed further with ethanolic sodium hydroxide to give compound (V) in 63% yield. Compound (V) has the following physical data: mp 143.5-144°; ir 3275 $cm^{-1}$; nmr ($CDCl_3$) δ 3.78 (s, 2xOC$\underline{H}_3$), 4.00 (s, OC$\underline{H}_3$) 5.13 (s, -C$\underline{H}_2$O), 6.18 (s, $\underline{H}$C-OH), 6.88 (s, C-2', C-5', C-6' Ar$\underline{H}$), 7.13, 7.16 (2s, C-5, C-8 Ar$\underline{H}$), 7.38 (s, $C_6\underline{H}_5$), 7.57 (d, J = 6Hz, C-4 $\underline{H}$C=), 8.30 (d, J = 6Hz, C-3 C$\underline{H}$-N). Debenzylation of compound (V) with 89% orthophosphoric acid (vide infra) gave compound (II) which was shown to be identical (mp, ir, nmr, and tlc) with the product obtained from the reaction of papaverinol with 90% sulphuric acid.




III




IV R = -C-Ph (O)

V R = H

We have investigated the reaction of various acids with papaverinol and found that selective demethylation was best achieved with 89% orthophosphoric acid. When a solution of papaverinol in 89% orthophosphoric acid was heated at 37-40° (oil bath temperature) for 48 hr., compound (II) was isolated in 67% yield together with some unreacted papaverinol. Compound (V) could be debenzylated with 89% orthophosphoric acid at room temperature (48 hr.) in 61% yield.

## References and Footnotes

1 S. Ruchirawat, N. Tongpenyai, N. Prasitpan, and P. Prempree, Heterocycles, 1976, 4, 1893.

2 Modified procedure was employed, cf. M. D. Rozwadowska, Can. J. Chem., 1977, 55, 164.

3 Professor L. Castedo et al. have independently reached the same conclusion and we are grateful for his preprint, L. Castedo, J. M. Saa, R. Suau, and C. Villaverde, Heterocycles, 1978, 9, 659.

4 S. Ruchirawat, N. Phadungkul, M. Chuankamnerdkarn, and C. Thebtaranonth, Heterocycles, 1977, 6, 43.

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