THE DEMETHYLATION OF APORPHINES WITH SULFURIC ACID[1]

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Abstract - Sulfuric acid at room temperature has been found a useful reagent for interconverting aporphine alkaloids by selective O-demethylation. This was controlled by electronic or steric effects.

Regioselective O-demethylation of aryl methyl ethers offers a useful synthetic opportunity of interconverting alkaloids in the aporphine series. No systematic work on the demethylation of aporphine alkaloids has been carried out with the exception of Cava et al.[2] They have found by the use of benzylselenolate in hot dimethylformamide that those methoxyl groups which lie out of the plane of the aporphine skeleton are selectively demethylated since they are more accesible to attack by the nucleophile. Similar steric type of control explains the regioselective O-demethylation of nuciferine with HI [3].

On the other hand, we have recently reported [4] that papaverinol can be regioselectively demethylated with sulfuric acid via a resonance stabilised intermediate, which is consistent with a process controlled by electronic effects. Therefore we were attracted by the possibility of carrying out selective demethylations of aporphine alkaloids controlled by electronic and/or steric factors.

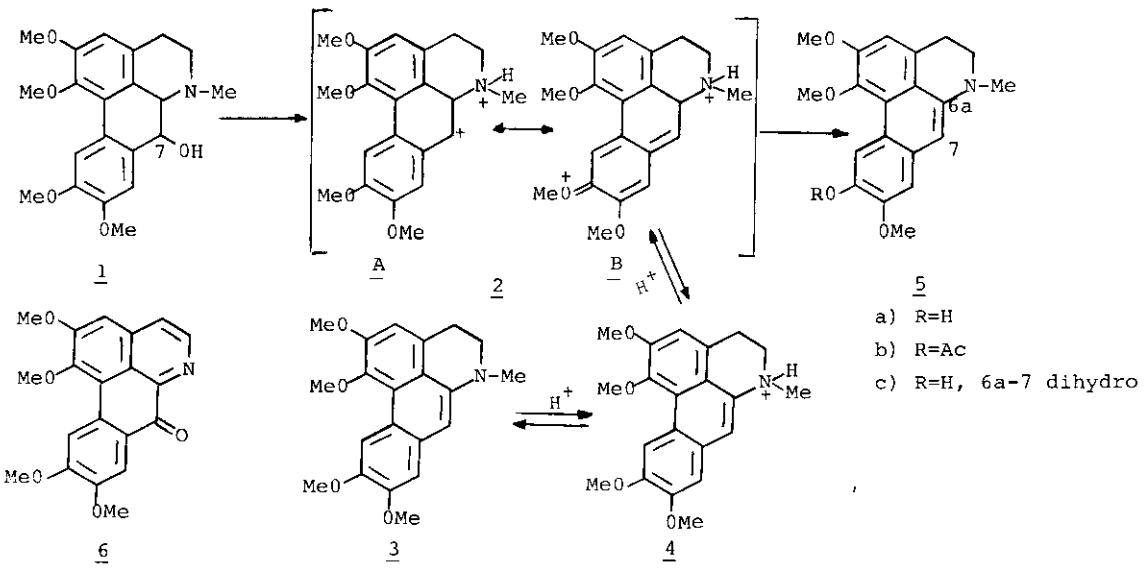
It seemed to us that 7-hydroxyglaucine (1) [5] was a good model to outweigh both factors, since demethylation of methoxyl C-1 would be controlled by steric factors and of methoxyl C-10 by electronic effects.

Treatment of 1 with 98% sulfuric acid (RT, 16 h) gave the non-phenolic compounds dehydroglaucine (3) and oxoglaucine (6), and a single phenolic one, namely the unstable dehydrolirioferine (5a), mp 140-42ºC (dec.) (EtOAc) in 10% yield [6]. This, upon acetylation, afforded its acetate (5b) as yellow needles (EtOH), {mp 210-12ºC; λ_{max}(EtOH)(log ε) 262(4.50), and 333(3.87); pmr($CDCl_3$) δ 9.07(1H, s, H-11), 7.04(1H, s, H-8), 6.92(1H, s, H-3), 6.52(1H, s, H-7), 3.96, 3.91 and 3.83 (3H each, s, 3xOMe), 3.28(4H, bs, H-4 and H-5), 3.05(3H, s, NMe), and 2.35(3H, s, OCOMe); m/e(%) 381(78,M^+), 339(100)}. Zn/HCl reduction of 5a gave lirioferine (5c) identical with authentic material by direct comparison.

The obtention of 5a suggested that 7-hydroxyglaucine (1) in sulfuric acid should be dehydrated and protonated to the doubly charged and resonance stabilized intermediate (2, A⟷B)(scheme 1) and this then demethylated at C-10. In a similar manner, selective demethylation of dehydroglaucine (3) should take place also on the C-10 methoxyl since it has been found that dehydroaporphines are kinetically protonated on nitrogen [7]. It seemed reasonable that the resulting

ammonium salt (4) might then be protonated at the 6a-7 double bond to give the same intermediate (2) as 7-hydroxyglaucine (1) (Scheme 1).
Thus, when dehydroglaucine (3) was treated with 98% sulfuric acid and a small amount of formic acid at RT for 5 days a 40% yield of dehydrolirioferine(5a) was obtained together with a 20% yield of oxoglaucine(6) and 5% of starting material. This demethylation provides a simple means of preparing lirioferine(5c) from the readily available dehydroglaucine (3).

SCHEME 1

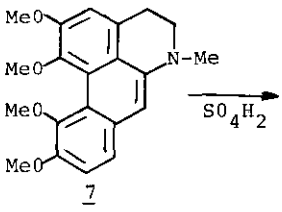


The demethylation of dehydro-O,O'-dimethylcorytuberine (7) under similar conditions (90% SO_4H_2-HCO_2H,RT, 15 h) took a different course. We have now isolated dehydrocorydine (8) [8] in 50% yield and the quinonoid compound (9) (25% yield) as violet crystals (mp, 209-10ºC; λ_{max}(EtOH) (log ε) 225 (4.43), 281(4.17), 327(4.32), 566 (3.57) nm; ν_{max}(KBr) 1580, 1620, 1650 cm^{-1};pmr($CDCl_3$) δ 6.93, 6.91 and 5.88 (1H each, s), 3.96, 3.93 and 3.87(3H each,s,3xOMe), 3.18(3H,s,NMe); m/e (%)353(100,M^+)).
Synthesis of compound (9) confirmed its structure.Thus, stirring of isocorydine (10a) in the presence of an excess of Fremy's salt [9] afforded a quantitative yield of the p-quinone compound (9). The obtention of dehydrocorydine(8)suggested that, at least in this case, the electronic effects are overwhelmed by the steric ones.
In order to ascertain the general validity of the demethylation, dehydrodicentrine (11) was treated under similar conditions. The pmr analysis of the reaction mixture showed that the methylendioxy group had disappeared. Clearly this acid sensitive group is incompatible with the reagent used. The methylendioxy function of dicentrine (12a) did not survive also the reaction (entry 1, Table I).
We have also investigated the reaction of sulfuric acid with a variety of simple aporphines (Table I). In this case the observed preferential demethylation of C-1 methoxyl (see entries 2,3 and 4) was controlled by steric factors as expected. A serious drawback of the reaction was found whenever phenolic aporphines(entries 5,

TABLE I: Reaction of aporphines with sulfuric acid

Entry	Aporphines	Reaction products (%yield)	Reaction time
1	Dicentrine, 12a	----------	
2	Glaucine, 12b	Thalicmidine, 12c (73)	13 days
		Bracteoline, 12d (5)	
3	Norglaucine, 12e	Wilsonirine, 12f (45)	27 "
4	O,O'-dimethyl-corytuberine, 10b	Corydine, 10c (17)	3 "
5	Lirioferine, 5c	Bracteoline, 12d (traces)	27 "
6	N-methyllauro-tetanine, 12g	Isoboldine, 12h (15)	18 "
7	Predicentrine, 12i	----------	14 "
8	Thalicmidine, 12c	Isoboldine, 12h (traces)	16 "
		Bracteoline, 12d (traces) and 14	

All reactions were carried out by dissolving the alkaloid in 90% sulfuric acid, with stirring at RT, for the period of time necessary to allow a high conversion. Identification of reaction products has been done by spectrosopic analysis and comparison with authentic samples.



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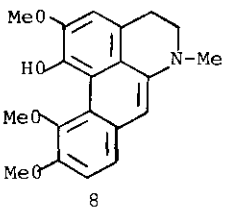

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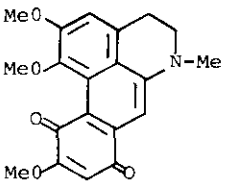

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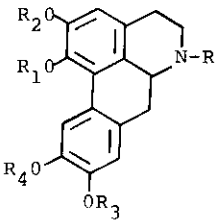

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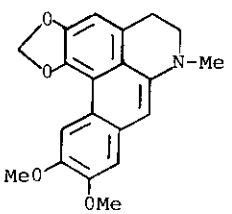
a) $R_1+R_2=CH_2$, $R=R_3=R_4=Me$
b) $R=R_1=R_2=R_3=R_4=Me$
c) $R=R_2=R_3=R_4=Me$, $R_1=H$
d) $R=R_2=R_3=Me$, $R_1=R_4=H$
e) $R_1=R_2=R_3=R_4=Me$, $R=H$
f) $R_2=R_3=R_4=Me$, $R=R_1=H$
g) $R=R_1=R_2=R_4=Me$, $R_3=H$
h) $R=R_2=R_4=Me$, $R_1=R_3=H$
i) $R=R_1=R_3=R_4=Me$, $R_2=H$



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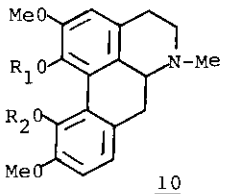

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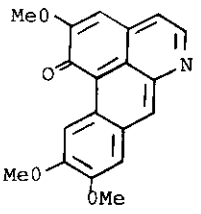
a) $R_1=Me$, $R_2=H$
b) $R_1=Me$, $R_2=Me$
c) $R_1=H$, $R_2=Me$



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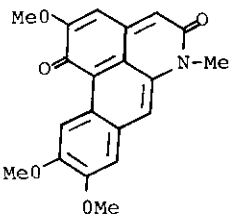

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6,7 and 8)having free ortho or para positions were present in the reaction medium; then large quantities of sulfonated compounds were obtained (IR studies and analytical data support this conclusion).

A low yield of a red compound, mp294-6ºC(dec) has been isolated from the reaction of thalicmidine(12c) and 7-hydroxythalicmidine with sulfuric acid,to which we have assigned structure (14) on the basis of the following data{λ_{max}(EtOH) (log ε) 246 (4.98), 294 (4.11), 304 (3.94), 3.82(4.06) and 486(4.00) nm; ν_{max} (KBr) 1650 cm^{-1}; pmr($CDCl_3$) δ 9.36(1H,s,H-11), 7.87, 7.15, 6.90 and 6.51(1H each,s, H-3, H-4, H-7 and H-8), 4.08, 4.05 and 3.97 (3H each, s,3xOMe), and 3.85(3H, s, NMe); m/e(%) 351 (100, M^+)}.

Since the proposed structure (14) has a novel oxidation arrangement on the aporphine nucleus, a synthesis of 14 seemed necessary. Oxoaporphine (13)[10] was treated with MeI to give the corresponding methiodide which on oxidation($Fe(CN)_6K_3$,OH^-) afforded 14 in 60% overall yield.

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