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# FREMY'S SALT OXIDATION OF SOME ISOQUINOLINE ALKALOIDS. BIOGENETIC CONSIDERATIONS

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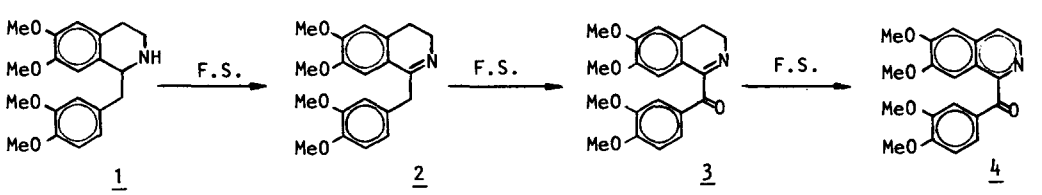
Summary:Fremy's salt oxidation of benzylisoquinoline and aporphine alkaloids to isoquinolones and oxoaporphines is described. Aminium radicals are suggested to account for the observed results Their possible involvement in alkaloid biosynthesis is considered.

C-C bond formation during the biosynthesis of isoquinoline alkaloids is now a well established process[1]. However some intriguing problems are still controversial, and therefore a matter of current interest. One of them is the dehydrogenation of the nitrogen-containing ring to the fully aromatic state present in such structures as papaverine, oxoaporphines, berberines and aromatic benzophenanthridines.

Several possibilities have been considered to account for the formation of the aromatic benzylisoquinolines such as papaverine. Common to all of them is the assumed necessity of phenolic precursors to explain the aromatization steps[1]. Contrary to these speculations is the fact that, at least in the opium poppy, tetrahydropapaverine is the immediate precursor of papaverine[2]. On the other hand, no serious proposals, to our knowledge, have been made on the mechanism of the oxidation of aporphines to oxoaporphines and dioxoaporphines.

A recent report[3] made clear that some non-phenolic tetrahydro-norisoquinolines suffer stepwise oxidation by Fremy's salt[4]. This observation can be interpreted as assuming the formation of an aminium radical followed by proton loss from an α or δ position[5]. An interesting alternative to phenolic oxidation is then amenable to explain the aromatization of isoquinoline alkaloids; i.e., dehydrogenation of ring B could take place through oxidation on the nitrogen atom. The present report might shed some light on this subject.

We first reasoned that the mechanistic rationale behind the reported[3] result 1 ⟶ 2 ⟶ 3 (Fig. 1), called for still another oxidation to 4 since an electron pair on N[6] was still available. Our expectation turned out right, and dihydropapaverine 2 was converted into papaveraldine 4 in 30% yield when the Fremy's salt oxidation was carried out for seven days.




1 2 3 4

Fig.1

We then turned our attention to the oxidation of N-methyl tetrahydroisoquinolines with Fremy's salt. Laudanosine (5a) should now give the alkaloid N-methylxanthaline(7)[7] in an analogous process. However, treatment of 5a in EtOH/$H_2O$ with a solution of Fremy's salt in 4% aqueous carbonate, gave after 72 hr (disappearance of starting material was complete after 24 hr) a 67% yield of the isoquinolone (8a)[8] and 28% of 3,4-dimethoxybenzaldehyde[9]. This result can be rationalized as shown in Fig. 2.

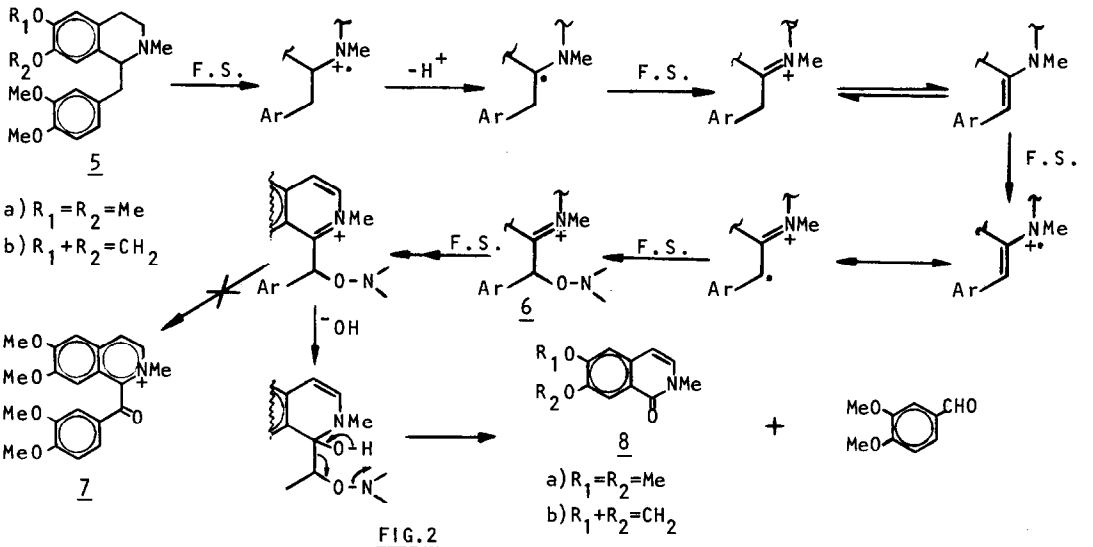



FIG.2

In agreement with this mechanistic interpretation[10], quenching of the reaction mixture with sodium borohydride after 24 hr gave laudanosine (5a) as the major component as well as a mixture of minor amounts of 8a and 9. The formation of 9 should result from a cleavage of the intermediate 6 as shown in Fig.3. Similar oxidation of 5b in Py/4% aqueous $CO_3Na_2$ yielded the alkaloid doryanine (8b)[11] in 59%.

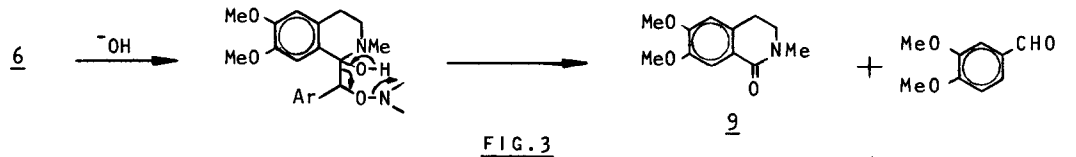
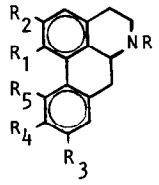



FIG.3

The above results may be taken as a supporting evidence in favour of the assumed biogenetic pathway of monomeric isoquinolones, as well as mixed isoquinolones such as baluchistanamine[12]. Furthermore, this oxidative C-C cleavage of benciliso-quinolines may turn out to be an useful alternative to the ones already known[13].

At this point it seemed reasonable that Fremy's oxidation of aporphines and noraporphines should give quaternary oxoaporphines and oxoaporphines, respectively. As expected, oxidation of norglaucine (10a) produced O-methylatheroline (11a) in 84% in only 24 hr. Fremy's salt oxidation of the corresponding nonphenolic apor-

phines proceeded at much slower rate and produced also the oxoaporphines in fair to good yields as shown in Table 1. The extra N-demethylation step observed here takes place by nucleophilic displacement on an intermediate stage. The reason for this assumption lies on the fact that quaternary oxoaporphines having a methoxy substituent at C-1 give on treatment with 4% aqueous carbonate (with or without Fremy's salt) a 1/1 mixture of oxoaporphine and corunnine-like oxoaporphine. Therefore, the oxidation of aporphines by Fremy's salt provides new methodology to prepare oxoaporphines.[14]



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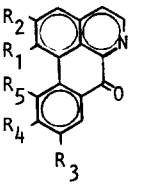
a) $R_1=R_2=R_3=R_4=OMe; R_5=R=H$
b) $R_1+R_2=OCH_2O; R_3=R_4=OMe; R_5=H; R=Me$
c) $R_1=R_2=R_4=R_5=OMe; R_3=H; R=Me$
d) $R_1=R_2=OMe; R_3=R_4=R_5=H; R=Me$
e) $R_1+R_2=OCH_2O; R_3=R_4=R_5=H; R=Me$
f) $R_1=R_2=R_3=R_4=OMe; R_5=H; R=Me$



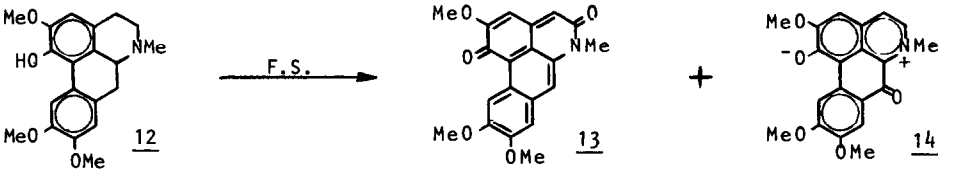
11

a) $R_1=R_2=R_3=R_4=OMe; R_5=H$
b) $R_1+R_2=OCH_2O; R_3=R_4=OMe; R_5=H$
c) $R_1=R_2=R_4=R_5=OMe; R_3=H$
d) $R_1=R_2=OMe; R_3=R_4=R_5=H$
e) $R_1+R_2=OCH_2O; R_3=R_4=R_5=H$

Table 1

| Aporphine | Time (days) | Solvent | Yield | Oxoaporphine |
|---|---|---|---|---|
| Norglaucine (10a) | 1 | EtOH/$CO_3Na_2$ 4% in $H_2O$ | 84% | O-methylatheroline (11a) |
| Dicentrine (10b) | 3 | " " " " | 60" | Dicentrinone (11b) |
| 1,2,10,11-tetramethoxy aporphine (10c) | 3 | " " " " | 50" | 1,2,10,11- tetramethoxy oxoaporphine (11c) |
| Nuciferine (10d) | 8 | " " " " | 10" | Lysicamine (11d) |
| Nuciferine (10d) | 3 | Py/$CO_3Na_2$ 2% in $H_2O$ | 60" | Lysicamine (11d) |
| Roemerine (10e) | 8 | ETOH/$CO_3Na_2$ 4% in $H_2O$ | 27" | Lirioderine (11e) |
| Roemerine (10e) | 3 | Py/$CO_3Na_2$ 2% in $H_2O$ | 61" | Lirioderine (11e) |
| Glaucine (10f) | 3 | EtOH/$CO_3Na_2$ 4% in $H_2O$ | 71" | O-methylatheroline (11a) |

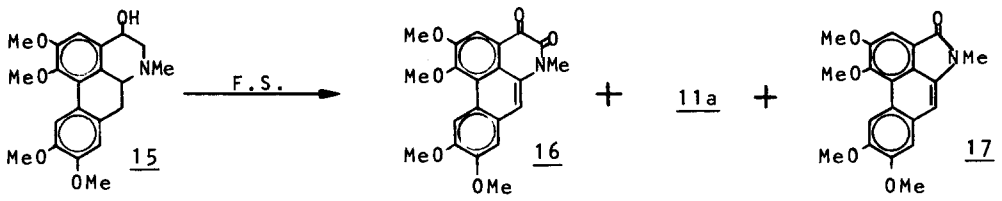
Curiously, oxidation of the phenolic thalicmidine (12) was a very fast process yielding 15% of the non-natural quinone (13)[15] and 10% of corunnine (14)[16] after half an hour. Yields were lower when reaction time was longer.




12 13 14

On the other hand, no biogenetic studies have been done to determine the actual pathway for the formation of 4,5-dioxoaporphines and 4-substitued oxoaporphines. It seems to us that 4-hydroxyaporphines could be the actual precursors if oxidation of ring B occurs with no dehydration. We have met with partial success

on this subject. Thus, oxidation of cataline (15) yields pontevedrine (16) (40%), O-methyl-atheroline (11a) (28%) and cepharanone (17) (6%) as the major compounds.




These results cannot be taken as a real demostration of the actual dehydrogenation and oxidation steps during biogenesis of isoquinoline alkaloids. However, they clearly show that secondary and tertiary amines are oxidized to different levels through the intermediacy of the aminium radicals, therefore suggesting its possible involvement in alkaloid biosynthesis. Aminium radicals are the proposed intermediates during amine oxidation by MAO[17].

The full scope and synthetic importance of the oxidation of amines by Fremy's salt is under study.

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