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TRANSFORMATIONS OF 13-OXOPROTOBERBERINIUM METHO SALTS II: CONVERSIONS TO PROTOPINE ANALOGUES

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The 13-oxoberberinium salt 1, previously converted[1] to the spirobenzylisoquinoline 2 is also an attractive intermediate for the elaboration of other benzylisoquinoline alkaloid systems. We now report the preparation and properties of some interesting protopine alkaloid[2] analogues from 1.

Compound 1 upon stirring with zinc and 30% aqueous acetic acid at room temperature suffered reductive ring scission to the tricyclic ketone 3 in a process analogous to the Schöpf-Schweikert proposal[3]. [3; yield = 64%; m.p. = 179°; ν_{max}^{nujol} 1685 cm^{-1}; λ_{max}^{EtOH} 237(sh) and 287 nm, log ε_{max} 4.08 and 3.94 resp.; $\delta(CDCl_3)^4$ 1.82 (s, 3H, N-Me), 3.80 and 3.86(s,2x3H), 2 x OMe),5.90(s,2H, $O\text{-}CH_2\text{-}O$), 6.62 and 6.82(s,2 x 1H, H_1 and H_4), 6.83 and 7.07(q, 2H, J_{AB} = 8.5 Hz, H_{11} and H_{12}); M^+ = 369]. Compound 3 is the first member of a new group of 13-oxo analogues of the protopine alkaloids, and poses interesting questions concerning the existence of transannular interaction between the nitrogen atom and carbonyl group in its ten-membered ring. The existence of such interaction in the protopine alkaloids has been amply documented[5]. However, extensive studies[6] had indicated that in the azacyclodecanones 4 and 5 the extent of transannular interaction was greater in 4 (creating effectively, two six-membered rings) than 5 (five and seven-membered rings). Specifically, it was observed that while the carbonyl absorption in the free bases differed little (1694 and 1700 cm^{-1} resp.), the perchlorate of 4 was transparent in the 1700 cm^{-1} region of its infra-red spectrum but the perchlorate of 5 possessed carbonyl absorption at 1698 cm^{-1}.

The availability of 3 now made possible the verification of these conclusions in actual alkaloidal molecules. The dimethoxyacetophenone type of carbonyl chromophore of 3 is best compared with the carbonyl absorption of cryptopine, 6 (1675 cm^{-1}, 1686 cm^{-1} in cryptopine methiodide[5a]). The 10 cm^{-1} difference as well as the close correspondence between carbonyl absorption in 3 and the methiodide of 6, accords well with the conclusions of the earlier studies. However, the perchlorate of 3 is transparent in the 1700 cm^{-1} region and possesses hydroxyl absorption at 3500 cm^{-1} in its i.r. spectrum. The u.v. spectrum of 3 is also changed upon addition of acid, and the minimum at 268 nm was observed to shift to 258 nm and deepen as reported[5c] earlier for the protopine alkaloid coulteropine, 7. The p.m.r. spectrum of 3 in pure TFA was generally similar, in the absorptions of the methylene ring protons, to the pure TFA spectrum of coulteropine[5d] but the N-methyl group is now found at δ3.3 (in 3) rather than at δ2.98 (in 7) probably reflecting the different ring fusions in the two salts. The spectrum of 3 in $CDCl_3$ containing 6% TFA was different from the spectrum in pure TFA suggesting the existence of an N-protonated uncyclised form but no equilibration between the two species was observed. The spectrum in pure TFA showed no change after six hours. Thus it seems clear that, contrary to the conclusions of the model studies[6] with 4 and 5, transannular bond formation leading to a 'five-seven' ring fusion does take place in the salts of 3.

The reduction of the carbonyl group of 3 could not be effected with sodium borohydride under the usual conditions. Lithium aluminium hydride, or more conveniently zinc and acetic acid (on a steam bath for two hours) provided the alcohol 8 [m.p. 193°; ν_{max}^{nujol} 3500 cm^{-1}; λ_{max}^{EtoH} 285 nm, log ϵ_{max} 3.71; δ($CDCl_3$) 2.15 (s,3H, N-Me), 2.70-3.00(br.s, 4H,-CH_2-CH_2-), 3.00-3.40 (br. m,2H), 3.83 and 3.91 (s, 2 x 3H, 2 x OMe), 3.95-4.07(br. s, 2H, C_8-H) 4.80-5.30 (br.m, 1H, C_{14}-H), 5.95(s, 2H, OCH_2O) and δ(C_2D_6CO) 6.73 and 7.05 (s, 2 x 1H, C_1-H and C_4-H), 6.93, 7.51 (q. 2H, J_{AB} = 8 Hz,C_{11}-H and C_{12}-H); M^+=371.] The stability of the ketone to borohydride is probably another manifestation of transannular interaction. Similar modification of ketonic properties in the protopine alkaloids is well known[5a,5b], and we have found that protopine itself is stable to borohydride.

When the berberinium salt 1, was treated with sodium hydride in dimethoxyethane with exposure to air and in the presence of potassium iodide it was smoothly converted into 13-oxo-allocryptopine 9 [59% yield; m.p. 208° (lit.[7] 207-9°); $\nu_{max}^{CHCl_3}$ 1660-1680cm^{-1}; δ ($CDCl_3$) 1.82

(s,3H,N-Me) 2.50-3.00(br. s, 4H,$-CH_2-CH_2-$), 3.85 and 3.95 (s, 2 x 3H, 2 x OMe); 3.9-4.1 (2H, C_8-H), 6.03 (s,2H,$O-CH_2-O$), 6.57 and 7.35(s, 2 x 1H, C_4-H and C_1-H resp.), 7.00 and 7.73 (q, 2H, J_{AB} = 8.5 Hz, C_{11}-H, C_{12}-H); M^+ = 383]. The structure of 9 was confirmed by its synthesis from allocryptopine 10 by mercuric acetate oxidation[8]. This transformation constitutes a total synthesis of oxoallocryptopine and is also a simple one step conversion of a protoberberine to a protopine. It probably involves the intermediacy of the hydroperoxide 11 which is reduced by iodide ion to the product.[9,10]

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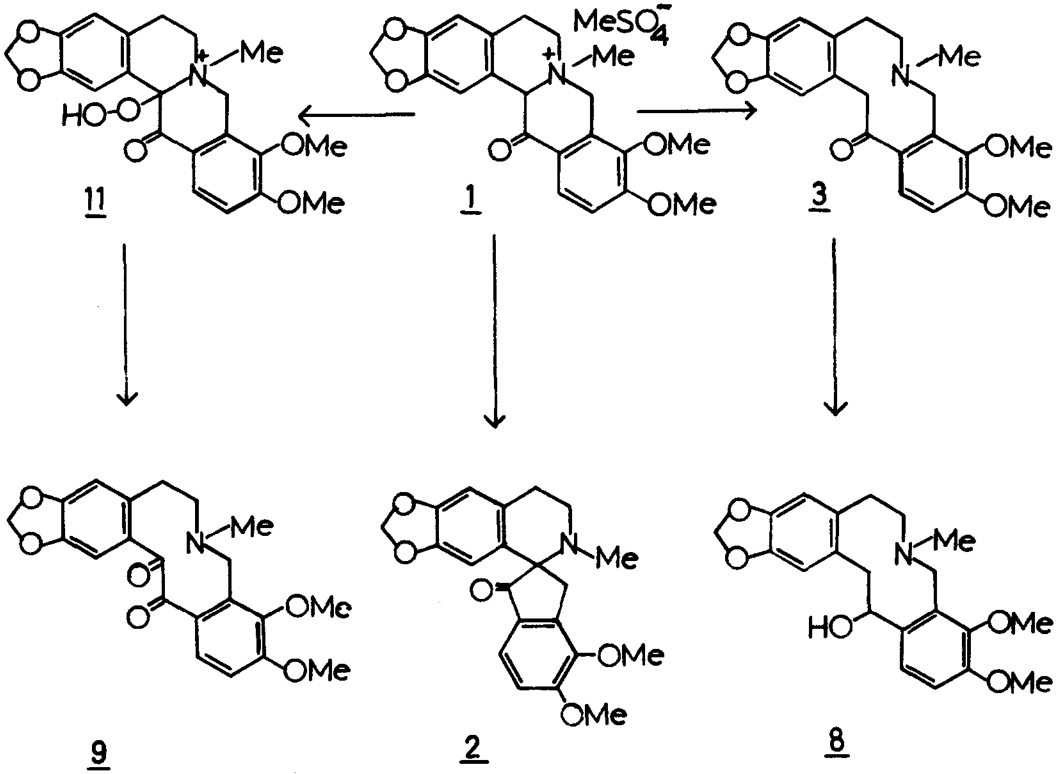

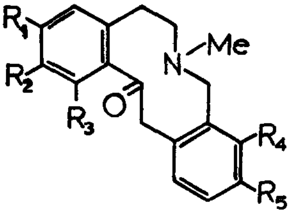

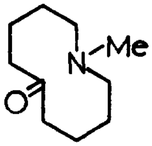

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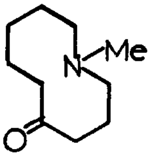

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6 $(R_1{=}R_2{=}OMe, R_3{=}H, R_4{+}R_5{=}OCH_2O)$

7 $(R_1{+}R_2{=}R_4{+}R_5 = OCH_2O,\ R_3{=}OMe)$

10 $(R_1{+}R_2{=}OCH_2O,\ R_3{=}H,\ R_4{=}R_5 = OMe)$