NEW CONTRIBUTIONS TO PROTOPINE CHEMISTRY

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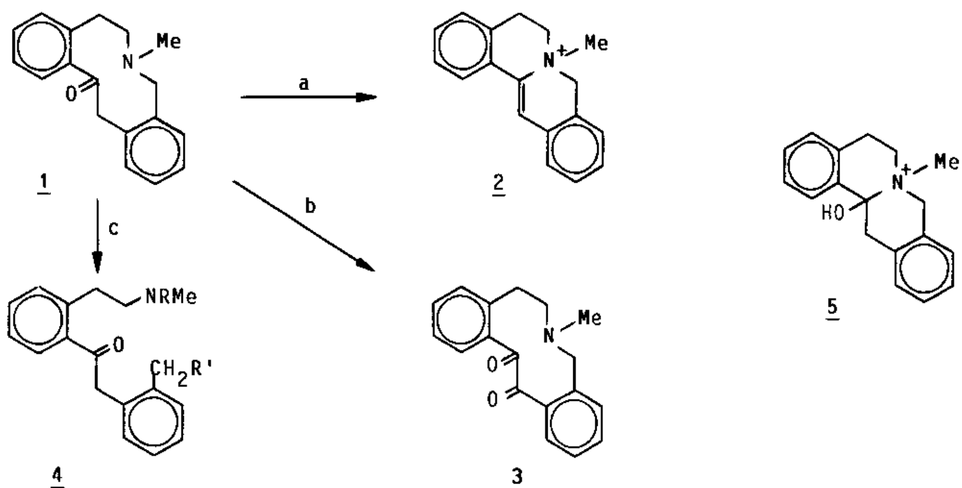
Abstract- Protopine undergoes electrophilic aromatic substitution at C-12 by reaction with Br_2/HOAc and HNO_3/HOAc. Simpler alternative methods for the obtention of dihydrocoptisine and 13-oxycoptisine from protopine are also described.

Protopines[3] are a group of alkaloids found in large quantities in most species of Papaveraceae. Their reactivity however, has been little studied. In fact, only three kinds of reactions of these compounds have been reported:

a) Intramolecular cyclization to obtain compounds with a protoberberine skeleton 2[3].
b) Oxidation alpha to the carbonyl group to give 13-oxoprotopines 3[4].
c) Cleavage of the N-7 to C-8 bond and formation of the corresponding deoxybenzoins 4[5].

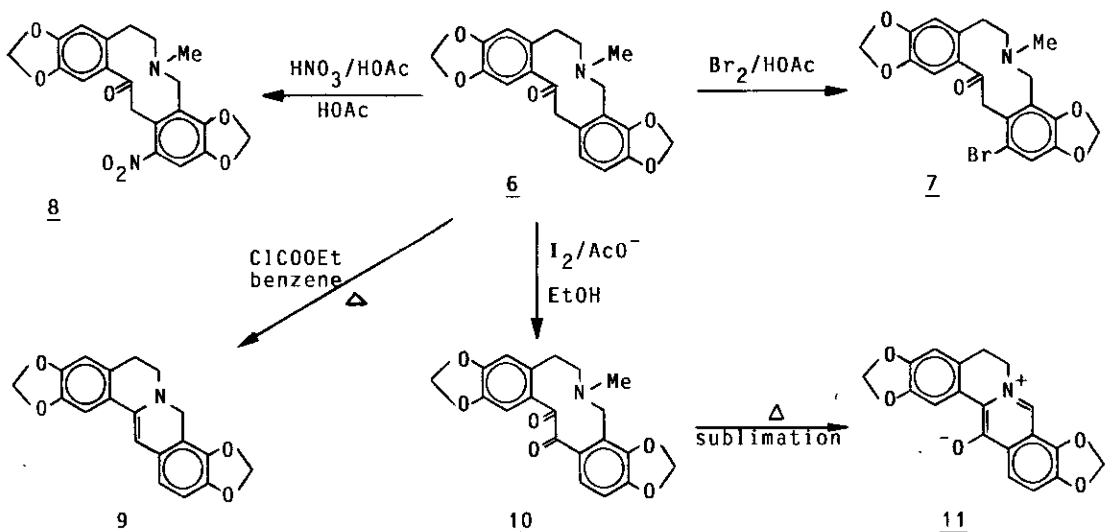


The reactivity of protopines is probably determined by the transannular interaction between the electron pair of the nitrogen and the carbonyl group[6], which is enhanced in acidic media to give the cyclic structure 5[7]. It is therefore of interest to perform new reactions to increase knowledge of the behaviour of these alkaloids.

Protopine reacts very specifically under electrophilic aromatic substitution conditions, For instance, its reaction with Br_2/HOAc (room temperature, argon atmosphere, 40 min) gave a product (92% yield) which crystallized from EtOH (mp 187°C) and was identified as 12-bromoprotopine 7 on the basis of its spectroscopic data[8]. Comparison of its NMR spectrum with that of protopine 6 shows a downfield shift of the C-13 methylene signal from 3.78 to 3.98 ppm and the disappearance of a proton from C-12.

An analogous result was obtained when protopine 6 was treated for 20 min with HNO_3/HOAc (3:2 v/v) in HOAc. This reaction produced in 85 % yield 12-nitroprotopine 8 (mp 180°C, MeOH), identified by its spectral data[8]. Its NMR spectrum was very similar to that of 12-bromoprotopine 7.

Surprisingly, when protopine 6 reacted with ClCOOEt (1:2) in benzene (reflux, argon atmosphere) the product obtained was dihydrocoptisine 9 (95% yield). This is a very interesting result because it constitutes the first one-step synthesis of dihydrocoptisine 9. Until now, at least two steps have been necessary to accomplish this transformation, and with lower yields[3a].



When protopine was refluxed in EtOH containing I_2, crystalline 13-oxoprotopine 10 was obtained in 86% yield as its corresponding hydroiodide, whose sublimation led to the formation of 13-oxycoptisine 11[3a] in 80% yield. The same product was obtained in similar yield when a solution of 13-oxoprotopine 10 in dioxane with a few drops of aqueous HI solution was refluxed for 12 h. This approach constitutes a simpler alternative method for the synthesis of 13-oxyberberines.

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REFERENCES AND NOTES

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8. All new compounds gave satisfactory elemental analysis:

   12-bromoprotopine 7: white prisms, mp 187°C (EtOH); λ_{max}^{EtOH} : 246 and 294; ν_{max}(KBr): 1030, 1240, 1455, 1480 and 1650 cm^{-1}; $\delta(CDCl_3)$: 7.04(s, 1H, H-11), 6.98(s, 1H, H-1), 6.63(s, 1H, H-4), 5.93(s, 4H, $2xOCH_2O$), 3.98(s, 2H, H-13), 3.58(s, 2H, H-8), 3.05-2.75(m, 2H, H-6), 2.68-2.45(m, 2H, H-5) and 1.89(s, 3H, N-Me) ppm; m/e(%): 433(M^+, 4), 431(M^+, 4), 418(2), 416(2), 352(2), 228(100), 226(100), 163(59), 148(11), 147(16) and 134(34).

   12-nitroprotopine 8: yellow needles, mp 180°C (MeOH); λ_{max}^{EtOH}: 246, 292 and 342; ν_{max}(KBr): 1037, 1233, 1464, 1515, 1616 and 1655 cm^{-1}; $\delta(CDCl_3)$: 7.40(s, 1H, H-11), 7.00(s, 1H, H-1), 6.67(s, 1H, H-4), 6.09 and 5.98(2s, 4H, $2xOCH_2O$), 4.22(s, 2H, H-13), 3.66(s, 2H, H-8), 3.10-2.75(m, 2H, H-6), 2.75-2.45(m, 2H, H-5) and 1.89(s, 3H, N-Me) ppm; m/e(%): 398(M^+, 8), 381(6), 309(6), 235(6), 219(8), 205(25), 193(100), 176(38), 163(66) and 134(43).

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