Tetrahedron Letters No.40, pp. 4909-4914, 1966. Pergamon Press Ltd.
Printed in Great Britain.

THE REACTION OF MELICOPINE WITH BROMINE

R.H. Prager and H.M. Thredgold

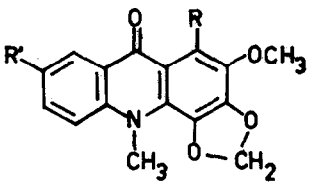
Organic Chemistry Department, The University of Adelaide,

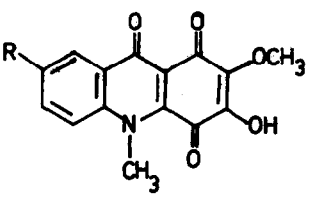
Adelaide, South Australia.

(Received 1 August 1966)

In connection with some other work, a method was required for obtaining 7-bromomelicopine, I, from melicopine (1).

The first method attempted was the bromination of melicopine, II, in acetic acid. By analogy with the work of Acheson (2) on N-methylacridone, which readily formed 2,7-dibromo-N-methylacridone in acetic acid, bromination was expected to proceed smoothly. The products isolated from this reaction mixture, however, were 7-bromonormelicopine (III; 18%), normelicopine (IV; 6%) and the quinones V (10%) and VI (5%).





I R=OCH_3; R'=Br

II R=OCH_3; R'=H

III R=OH; R'=Br

IV R=OH; R'=H

XI R=R'=H

V R=H

VI R=Br

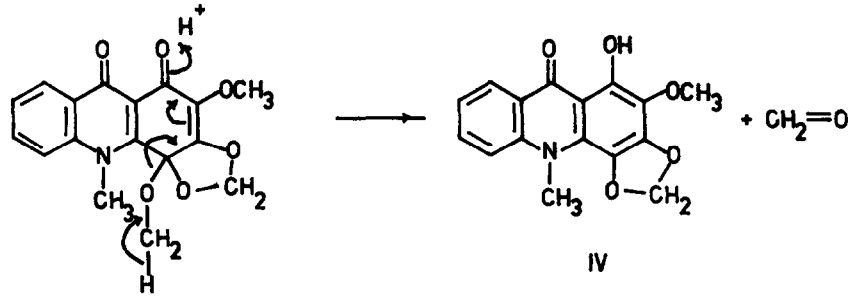
Addition of bromine in chloroform to melicopine yielded a red complex, which decomposed in dilute aqueous sodium hydroxide to melicopine. On standing in air for several weeks a gas was slowly evolved, and normelicopine and the quinone, V, were formed. The red complex melted at 95° with the evolution of a gas, but rapidly resolidified. Treatment of the residue with dilute aqueous sodium hydroxide gave 7-bromonormelicopine (49%).

Bromination of melicopine in methanol gave a rapid precipitation of an orange compound, $C_{17}H_{17}O_6NBr_2$, m.p. 127-130° (d) (94%), which acted as a brominating agent; acetone was rapidly converted to bromoacetone on warming and normelicopine (82%) was obtained. Addition of bromine in methanol to normelicopine yielded the same compound, to which structure VII was ascribed. The infrared spectrum showed a band of medium strength at 1680 cm^{-1}, ascribable to a double bond with two oxygenated substituents (3), and a strongly bonded OH (ν_{max} 3200-3400 cm^{-1}). Hydrogenation of VII gave an almost quantitative yield of normelicopine.

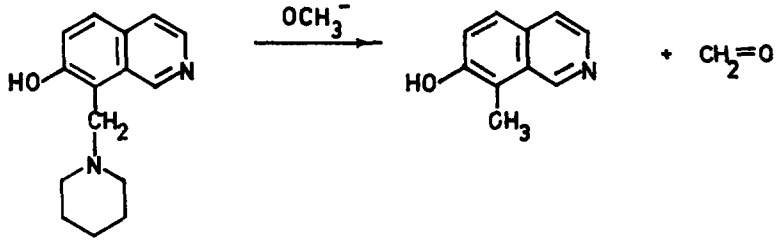
Compound VII on treatment with dilute alkali at room temperature gave a compound $C_{17}H_{15}O_6N$, VIII, (72%) the infrared spectrum of which showed a strong band at 1720 cm^{-1} due to the oxygenated double bond. The methylenedioxy protons were non-equivalent, and formed singlets at τ 4.24 and 4.31; the methoxyl groups absorbed at τ 6.73 and 6.05. Bromine in ethanol formed an analogous compound to VII with similar spectral properties, which yielded a compound $C_{18}H_{17}NO_6$, m.p. 145-7°, on treatment with dilute alkali. The N.M.R. of this compound showed that the singlet at τ 6.73 was replaced by a triplet at τ 8.86 (J = 8) and a quartet at τ 6.59 ($O-CH_2-CH_3$).

Hydrogenation of VIII gave X, $C_{17}H_{17}O_6N$, m.p. 167-8° (66%). This gave a positive ferric chloride test, and the N.M.R. spectrum confirmed the presence of a strongly hydrogen-bonded OH (τ -5.00) and the single hydrogen attached at C-3 (τ 5.00). The infrared spectrum showed a strong peak at 1685 cm^{-1}. Treatment of X for a few minutes with sulphuric acid at room temperature formed normelicopine in high yield.

Compound VIII was refluxed with 15% aqueous hydrochloric acid, the product being mainly V. In methanolic hydrochloric acid normelicopine, IV, (8%) was also formed. The formation of normelicopine involves an oxidation-reduction, which we formulate as below, and is somewhat analogous to the reduction of certain Mannich bases by methoxide ion (4).



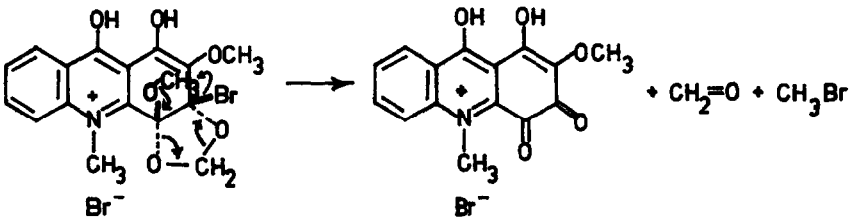
IV



Reduction of compound VIII with sodium borohydride yielded an extremely complex mixture of products at room temperature, but at 0° for 5 minutes the main product (88%) was X. By preparative thick-layer chromatography on silica gel it was possible to isolate from the reaction at room temperature 15% of another compound, XI, $C_{16}H_{13}O_4N$, m.p. 203–4°, in addition to X.

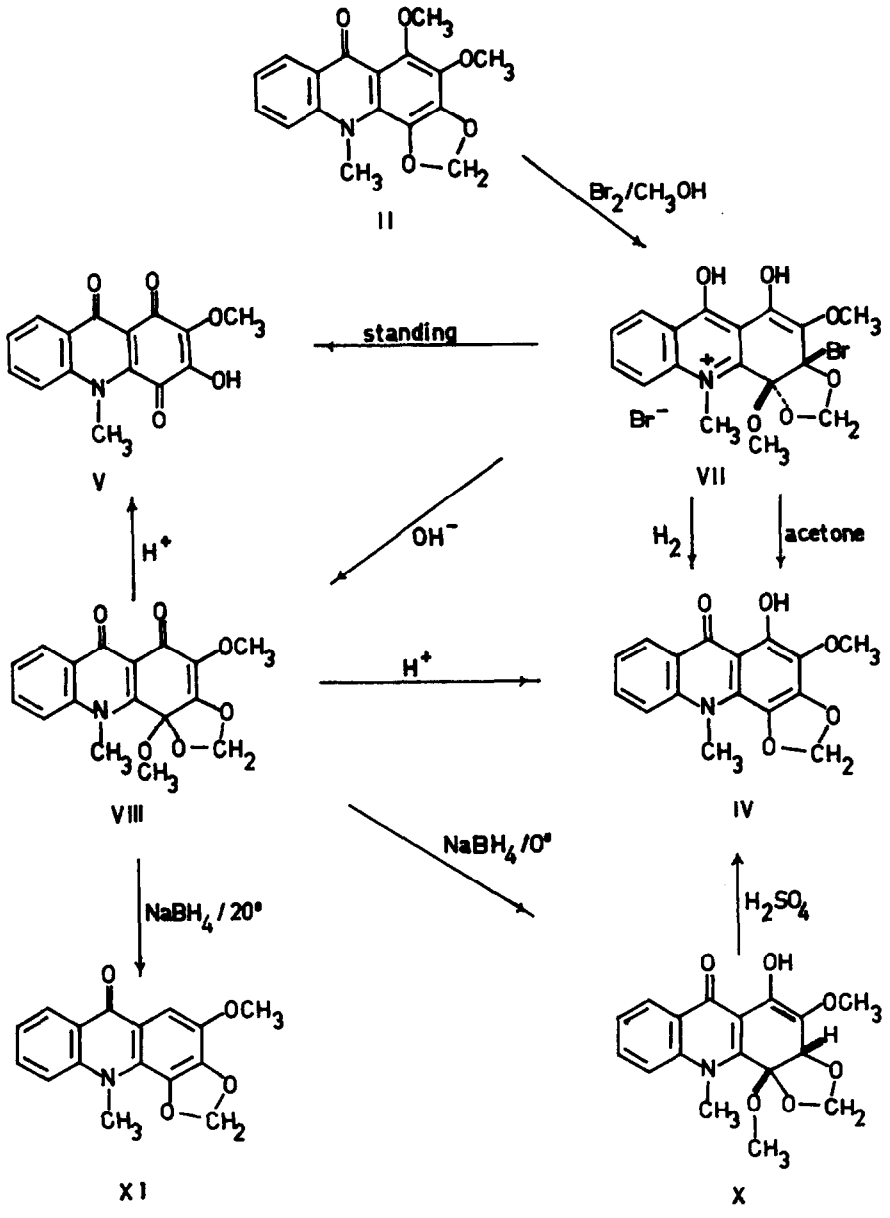
The U.V. spectrum of XI was very similar to that of melicopine, as was its fluorescence. In addition the N.M.R. spectrum was identical with that of melicopine with the exception of the loss of the methoxyl group at τ 6.16 and the replacement of it by a 1-proton singlet at τ 2.35.

If VII was allowed to stand, either in the dark or light for over a week, it was converted to a deep red-purple compound, which contained only one bromine by analysis. On treatment with dilute alkali V was formed immediately. The compound was probably the hydrobromide of V, and the following mechanism is suggested for its formation.



In an attempt to speed up this reaction, VII was gently heated to its melting point. The melt evolved a gas and almost immediately resolidified, and after the addition of dilute alkali, 7-bromonormelicopine, III, (65%) was obtained. This is obviously a thermally induced self bromination.

Further work is proceeding on the mechanism of the oxidative demethylation, and on the bromination of other acridones.


II
Br2/CH3OH
standing
V
VII
OH-
H+
H2
acetone
VIII
IV
H+
NaBH4/0°
NaBH4/20°
H2SO4
XI
X

REFERENCES

1. J.R. Price, Aust.J.Sci.Res. 2A, 249 (1949).

2. R.M. Acheson and M.J.T. Robinson, J.Chem.Soc. 1953, 232.

3. J.B. Miller, J.Org.Chem. 25, 1279 (1960).

4. R.B. Woodward and W.E. Doering, J.Amer.Chem.Soc. 67, 860 (1945).