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THE STRUCTURES OF COULTEROPINE AND OTHER PROTOPINE-TYPE ALKALOID ACID SALTS[1]

F.R. Stermitz and R.M. Coomes

Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521

D. R. Harris

Department of Applied Statistics and Computer Science, Utah State University

Logan, Utah 84321

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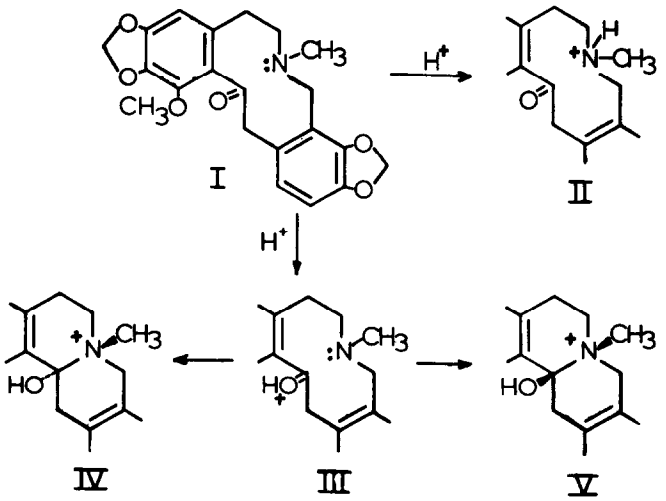
Infrared evidence[2] has made it clear that acid salts of protopine-type alkaloids cannot be represented by a simple N-protonated structure, but that closure of the central 10-membered ring must have occurred. The recently isolated[3] coulteropine (I), would be expected to behave similarly. Thus, coulteropine hydrobromide would not be II, but rather IV or V. Infared studies[2] did not distinguish between the two possible structures IV and V for the acid salts of protopine and



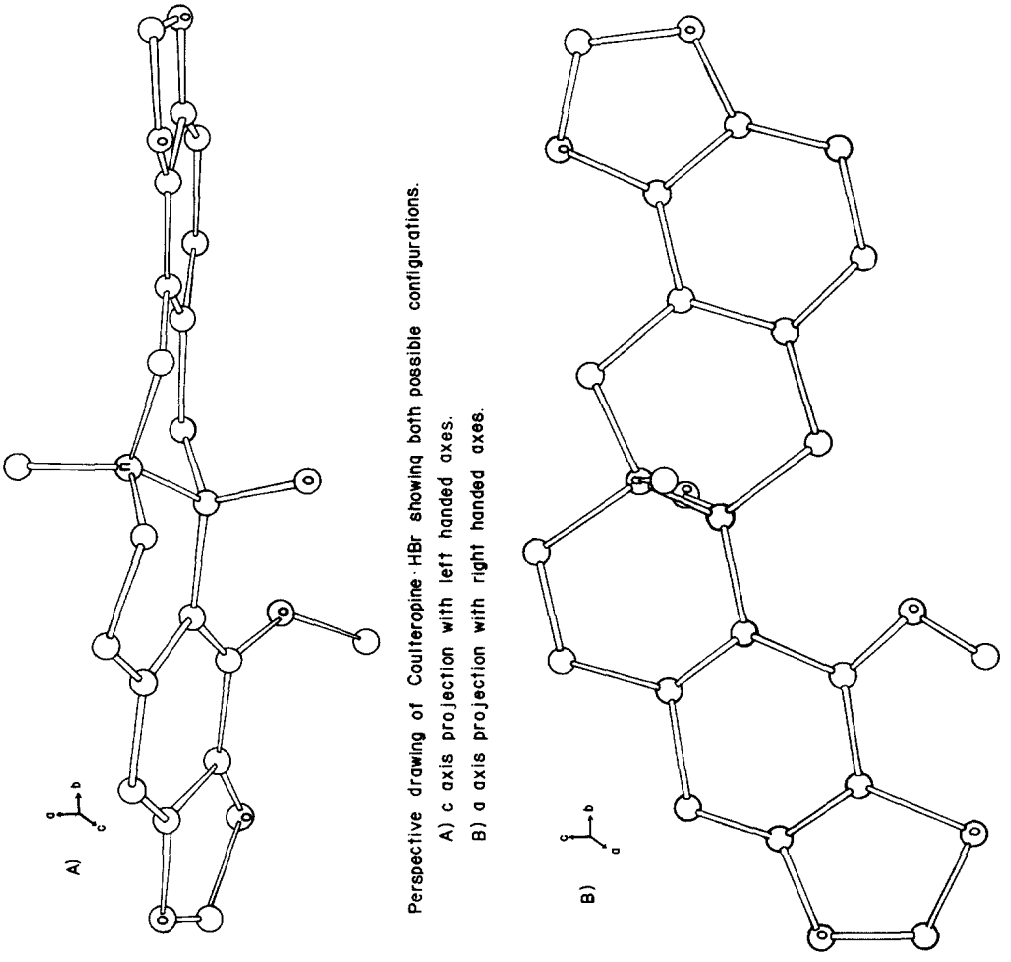


Fig. 1. X-Ray Diffraction Structure Determination of Coulteropine Hydrobromide

cryptopine. The present communication describes X-ray and nmr studies bearing on this problem and on Perkin's attempted resolution of cryptopine.

X-Ray Diffraction Studies. Anhydrous HBr was bubbled through a solution of coulteropine (I) in benzene and the amorphous solid which precipitated was recrystallized from methanol-benzene to yield the hydrobromide salt, mp 231-232°. The crystal morphology consisted of colorless, elongated rhombohedral prisms. A suitable crystal was mounted on a GE XRD-5 diffractometer with SCO. The following cell data were obtained:

Space Group: $P\,2_1 2_1 2_1$ (orthorhombic) $\lambda_{CuK\alpha} = 1.5418$ Å

$a = 15.19$ Å; $b = 17.82$; $c = 7.20$. $Z = 4$. $\rho_c = 1.571$ g/cc.

X-Ray intensities were collected, using the stationary-crystal, stationary-counter method. Of 2222 reflections accessible to the instrument, 2144 had intensities different from background. No absorption correction was applied nor was the anomalous scattering effect measured. The bromide ion was located using Patterson methods and the phase determination proceeded smoothly using alternate cycles of structure factor and electron density calculations. Refinement was by least squares. A final difference map showed no peaks significantly different from background. The final R-factor was .118.

The X-ray structure confirmed that suggested from chemical data[3] and confirmed ring closure as suggested by infrared studies[2] on cryptopine and protopine perchlorates. Figure 1 shows a view of the molecule for either possible hand. It is of interest to note that the trans compound (e.g. IV) has been obtained. Bond distances and angles showed no unusual features with the exception of a slight distortion of the right hand aromatic ring (Fig. 1) and an unusually long C-N bond (1.58 + .02 Å) where ring closure had occurred. This suggests some crowding in the area of ring closure, particularly as a result of the aromatic methoxyl group. Packing is controlled by hydrogen bonding through the bromide and by van der Walls' contacts.

Nuclear Magnetic Resonance Studies. An interesting series of changes were observed when the nmr spectrum of coulteropine was taken in varying concentrations of trifluoroacetic acid (TFA) in $CDCl_3$. Three of the spectra obtained are reproduced in Fig. 2

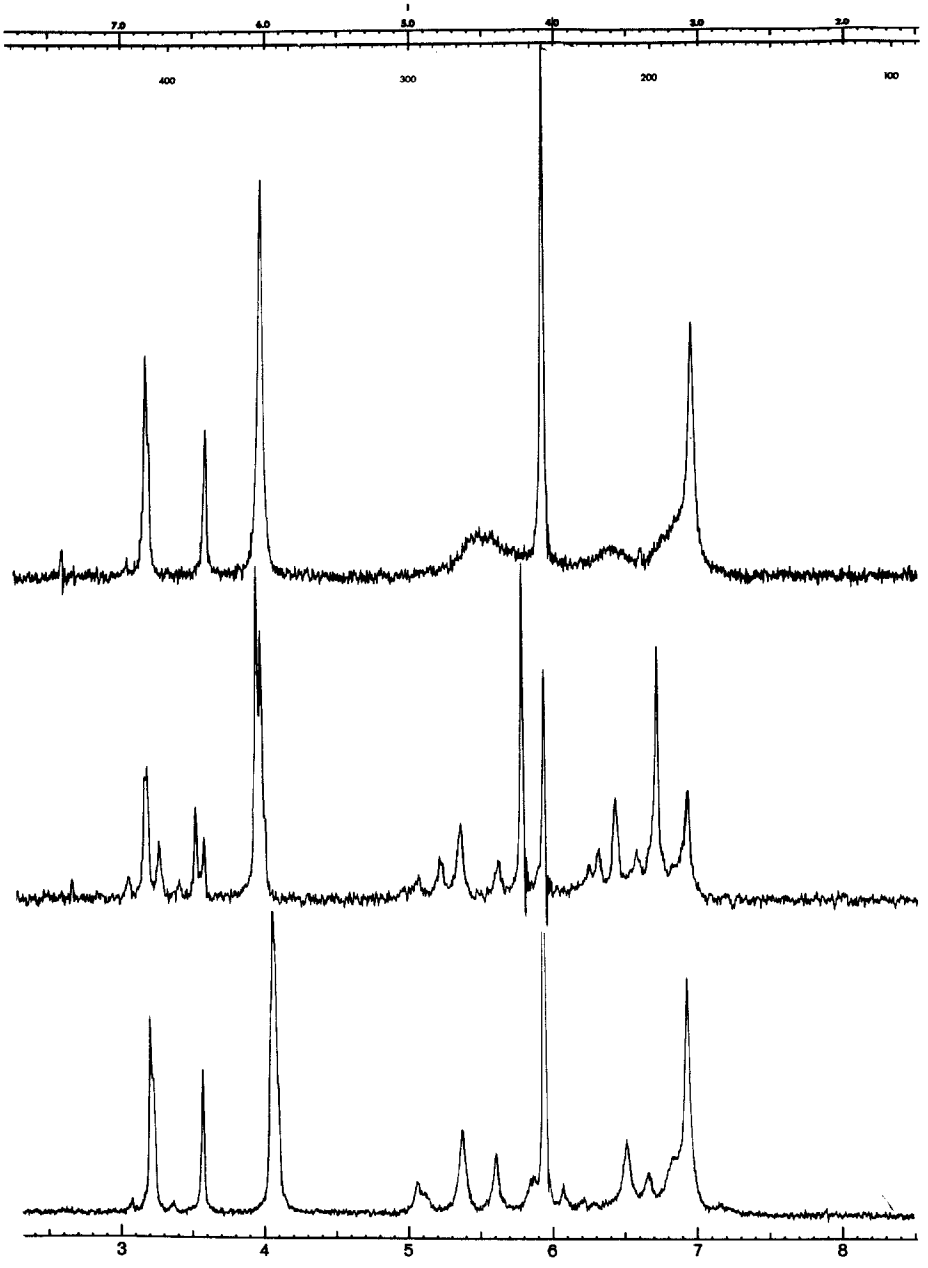


Fig. 2a (Top). Coulteropine nmr in 5% TFA-$CDCl_3$
2b (Center). " " in 9% TFA-$CDCl_3$ or pure TFA after standing.
2c (Bottom). " " in pure TFA taken immediately.

Addition of 5% TFA to I in $CDCl_3$ resulted in spectrum 2a, which can be assigned to structure II. Characteristic was the shift of the N-methyl singlet (7.95 tau in the free base[3]) to 7.02 tau. The methylene ring protons of the central 10-membered ring appear in 2a even broader than in the free base.[3] Anet and Brown have shown[5] a temperature dependence for the resonances of these protons in the case of protopine and their interpretation of broadening as a result of relatively slow ring inversion seems likely. Spectrum 2a suggests that, under proper conditions, a coulteropine acid salt which has not ring closed could be isolated.

Addition of 9% TFA and delay of several minutes resulted in the nmr spectrum in Fig. 2b, which is manifestly a mixture of two substances. The ratio of concentrations of the two substances changes with time and changes considerably more rapidly at the temperature of the A60-A nmr cavity (37°) than at room temperature. The meaning of these data will be discussed after description of spectrum 2c.

Spectrum 2c results if coulteropine or coulteropine hydrobromide (see X-ray results above) is dissolved in pure TFA and the spectrum is taken immediately. The same spectrum is obtained if coulteropine hydrobromide is dissolved in 9% TFA-$CDCl_3$ and the spectrum is recorded immediately. Since the structure of coulteropine hydrobromide as prepared above was established as IV by X-ray determination, nmr spectrum 2c can be assigned to IV. However, spectrum 2c is time dependent under either of the solvent conditions and changes to that of 2b after several hours at room temperature. We can thus assign a portion of the peaks in 2b (e.g. N-methyl at 7.02 and O-methyl at 6.02) to structure IV. With increasing time, these two peaks decrease in intensity and the corresponding peaks at 6.80 and 5.88 increase. Other peaks in the spectrum show similar changes. No irreversible changes have occurred since the free base I can be reisolated unchanged after basification at any time. Preliminary attempts at isolation of the second component (which we think may be V) from the mixture (spectrum 2b) have not been successful, but are continuing as is a more detailed analysis of the nmr spectra.

In general, protopine, cryptopine, and allocryptopine exhibit acid-dependent nmr spectra somewhat similar to those of Fig. 2. However, no exact correlations with the coulteropine spectra could be made and it is hazardous at this time to attempt exact structure assignment of the acid salts of these alkaloids prior to detailed analysis. All show the existence, in 5% TFA, of only II, while mixtures are apparent in 9% TFA.

Perkin's Cryptopine "Resolution." Anet and Brown commented[5] on Perkin's attempted[4] resolution

of cryptopine and suggested that this failure was due to too rapid ring inversion in the central 10-membered ring. Perkin prepared[4] a bromocamphorsulfonic acid salt of cryptopine, which salt had an initial rotation of +37.8° and, after five recrystallizations, showed a rotation of +40.8°. It is interesting that the calculated rotation of a mixture of equal parts of inactive cryptopine and active bromocamphorsulfonic acid ($[\alpha]_D$ = +84.5°) is + 39.8°. It is thus possible (although not conclusive) that Perkin was dealing with a double salt which had not been resolved at all. Further, it is apparent that acid salts prepared in the usual manner will have structure IV or V and hence the problem of whether or not I can maintain a specific configuration is complicated by a necessary ring opening after IV or V has been resolved. Our nmr studies suggest that a better approach may be through a controlled preparation and resolution of diastereomeric II salts at low temperatures.

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