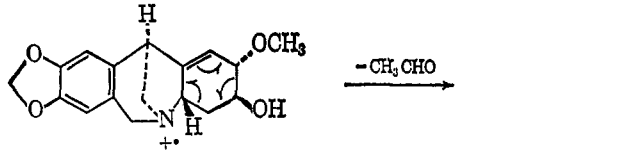
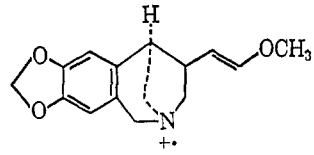
m/e 257 arose from such a single stage decomposition of the molecular ion of montanine.



XVa



xxx, *m/e* 257

Experimental Section[17]

Criwelline-N-d_3. A solution of 200 mg. of 6-hydroxycrinamine and 1.5 ml. of methyl iodide-d_3[18] in 10 ml. of methanol–acetone (1:5) was allowed to stand at room temperature for 30 min. The excess methyl iodide-d_3 and solvents were removed by distillation and collected in a liquid nitrogen trap. The residue was dried at room temperature under reduced pressure, dissolved in water, and made basic (pH 10) with 10% sodium hydroxide. The basic solution was extracted three times with chloroform and the chloroform was removed under reduced pressure to give 202 mg. of criwelline-N-d_3, m.p. 201–202° (from acetone–chloroform). The deuterium incorporation was greater than 98% as determined by mass spectrometry and by the complete absence of the N-methyl peak in the n.m.r. spectrum of criwelline-N-d_3.

Tazettine-N-d_3. The methyl iodide-d_3 solution recovered in the synthesis of criwelline-N-d_3 was added to 50 mg. of haemanthidine (VIII). The solution was allowed to stand at room temperature for 30 min. The solvents were removed by distillation and collected in a liquid nitrogen trap. The residue was dried under reduced pressure, dissolved in water, and made basic (pH 10) with 10% sodium hydroxide. The aqueous solution was extracted three times with chloroform and the chloroform was removed under reduced pressure to give 42 mg. of tazettine-N-d_3 which was recrystallized twice from acetone and sublimed at 200° (0.001 mm.), m.p. 211–213°.

(17) All low resolution mass spectra were determined with an Atlas CH-4 mass spectrometer using the TO-4 ion source (70 e.v.). High resolution mass spectra, unless designated otherwise, were determined using an A.E.I. MS-9 double focussing mass spectrometer, with an apparent resolution of 12,000.

(18) F. A. Cotton, J. A. Fassnacht, W. D. Horrocks, and N. A. Nelson, *J. Chem. Soc.*, 4138 (1959).

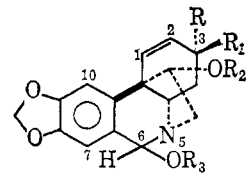
6-Hydroxycrinamine and Haemanthidine

R. W. King, C. F. Murphy,[1] and W. C. Wildman

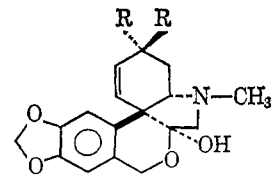
Contribution from the Department of Chemistry, Iowa State University of Science and Technology, Ames, Iowa 50010. *Received July 20, 1965*

On the basis of chemical and spectroscopic studies, it is suggested that haemanthidine, 6-hydroxycrinamine, and all derivatives of these alkaloids having a 6-hydroxyl group exist in solution as a mixture of C-6 epimers.

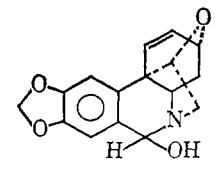
6-Hydroxycrinamine (Ia) and haemanthidine (Ib) are unique among the numerous alkaloids of the Amaryllidaceae derived from the 5,10b-ethanophenanthridine nucleus because these two bases alone possess an hydroxyl substituent at C-6. The structures assigned to these alkaloids are based both on reductive transformations to known 6-deoxy derivatives[2] and on the facile conversion of Ia and Ib to criwelline (IIa) and tazettine (IIb), respectively, by methylation and treatment with dilute base.[3-5] The structures of IIa and IIb have been firmly established by degradative and synthetic methods.[4,6]



Ia, R_1, R_2, R_3 = H; R = OCH_3 (6-hydroxycrinamine)
b, R, R_2, R_3 = H; R_1 = OCH_3 (haemanthidine)
c, R_1, R_2, R_3 = H; R = OCH_3; no double bond at C-1–C-2 (dihydro-6-hydroxycrinamine)
d, R_1, R_3, = H; R = OCH_3; R_2 = CH_3CO (11-acetyl-6-hydroxycrinamine)
e, R_1, R_3 = H; R = OCH_3; R_2 = CH_3CO; no double bond at C-1–C-2 (11-acetyldihydro-6-hydroxycrinamine)
f, R_1 = H; R = OCH_3; R_2, R_3 = CH_3CO; no double bond at C-1–C-2 (diacetyldihydro-6-hydroxycrinamine)
g, R = H; R_1 = OCH_3; R_2, R_3 = CH_3CO (diacetylhaemanthidine)
h, R = H; R_1 = OCH_3; R_2, R_3 = CH_3CO; no double bond at C-1–C-2 (diacetyldihydrohaemanthidine)



IIa, R = OCH_3; R_1 = H
b, R = H; R_1 = OCH_3



III
apohaemanthidine

In a recent communication[5] on the mechanism of the conversion of Ia to IIa, we reported that the n.m.r.

(1) NASA Fellow, 1964-1965.

(2) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 197 (1960).

(3) H.-G. Boit and W. Stender, *Chem. Ber.*, **89**, 161 (1956).

(4) H. M. Fales, D. H. S. Horn, and W. C. Wildman, *Chem. Ind.* (London), 1415 (1959).

(5) C. F. Murphy and W. C. Wildman, *Tetrahedron Letters*, 3863 (1964).

(6) S. Uyeo and co-workers have thoroughly studied the chemistry and stereochemistry of tazettine. See S. Uyeo, H. Irie, U. Kitayama, T. Hirose, and A. Yoshitake, *Chem. Pharm. Bull.* (Tokyo), **12**, 489 (1964), and references cited therein.

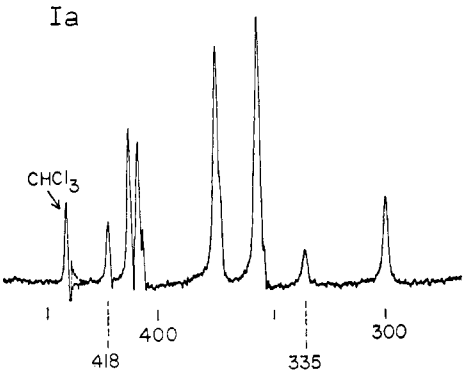


Figure 1. Partial n.m.r. spectrum of 6-hydroxycrinamine (Ia).

spectrum of Ia (Figure 1) was unusual because the protons at C-6 and C-7 each showed two chemical shifts. A recent paper[7] described detailed n.m.r. studies on 6-hydroxycrinamine and several other Amaryllidaceae alkaloids. It is curious that the authors made no comment about the dual chemical shifts of the C-6 and C-7 protons; each was described as a singlet appearing at only one resonance.

This paper extends our n.m.r. studies to compounds Ia–h as well as III in several solvents. As shown in Table I, anomalies are found in the low-field region (>280 c.p.s.)[8] for every compound listed. Partial

Table I. Chemical Shifts of C-6 and C-7 Protons

Compd.	Solvent	C_6H, c.p.s. Major component	C_6H, c.p.s. Minor component	C_7H (minor component), c.p.s.
Ia	$CDCl_3$	300	335	418
Ia	DMSO	287	320	411[a]
Ia	CF_3COOH	441	465	412
Ib	$CDCl_3$	299	336	417
Ic	DMSO	286	319	405
Id	$CDCl_3$	302	337	418
Ie	$CDCl_3$	300	335	416
If	$CDCl_3$	366	393	397[a]
Ig	$CDCl_3$	~363[b]	393	398[a]
Ih	$CDCl_3$	364	391	396[a]
III	$CDCl_3$	308	340	420

[a] Same chemical shift as C_7H major component. [b] Obscured because of olefinic proton resonance. Integration showed ~2.7 protons present.

n.m.r. spectra of haemanthidine (Ib) and diacetyldihydro-6-hydroxycrinamine (If) are given in Figure 2. The spectra of Ia and Ib show only very minor differences in the region below 280 c.p.s. However, the ratio of the areas of the peaks at 300 and 335 c.p.s. is about 1:1 in Ib and 2:1 in Ia. This difference is reflected in a larger peak at 417 c.p.s. in Ib. This phenomenon is associated with the presence of an hydroxyl group at C-6, since analogous compounds with a methylene or carbonyl group at C-6 possess completely normal n.m.r. spectra.

One possible explanation for the multiple peaks would be to dismiss the minor peaks as impurities.

(7) R. D. Haugwitz, P. W. Jeffs, and E. Wenkert, *J. Chem. Soc.*, 2001 (1965).

(8) Chemical shifts are expressed in cycles per second downfield from an internal tetramethylsilane standard.

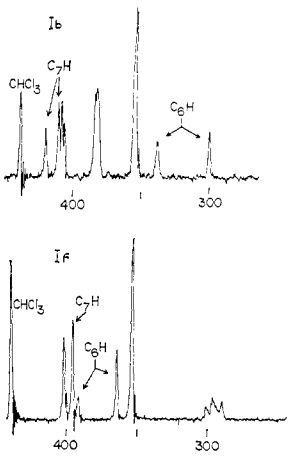


Figure 2. Partial n.m.r. spectra of haemanthidine (Ib) and diacetyldihydro-6-hydroxycrinamine (If).

However, the areas of these peaks must be included in every case if the correct three-proton integration is to be obtained for the benzylic and aromatic hydrogens. In a chemical sense, the compounds listed in Table I appear to be pure, and we have been unable to find any chemical evidence for the presence of two compounds. With the exceptions of Ib (m.p. 190–193°) and If, which is not crystalline, the compounds listed melt sharply. In all cases these compounds are homogeneous by thin layer and column chomatographic criteria. All compounds have satisfactory analyses. Simple transformations such as acetylation, reduction, oxidation, and hydrolysis, as well as the conversions of I to II, proceed to give homogeneous products in high yield. On the basis of the above evidence and the spectral and chemical data cited below, we propose that all 6-hydroxy alkaloids cited in Table I exist in solution as an equilibrating mixture of C-6 epimers.

The protons at C-1, C-2, C-3, C-4, C-6, C-7, C-10, C-11, methylenedioxy, and methoxyl of 6-hydroxycrinamine have been assigned previously to respective peaks in the n.m.r. spectrum.[7] Our work agrees with that reported except for the peaks assigned to protons at C-6, C-7, and C-10. In the spectra reported in this paper, the methylenedioxy protons appear near 350, the olefinic protons at 370–390, and the aromatic protons at 390–425 c.p.s. Since the aromatic protons in the spectra of these compounds were not readily assignable, field sweep spin decoupling experiments were performed on Ia, Ib, If, and III. The operating procedure was to scan the aromatic region while irradiating each component of the C-6 proton resonance in turn. The C-6 and C-7 protons are expected to exhibit small coupling, whereas the C-6 and C-10 protons are not.[9]

Irradiation with a radiofrequency field of 0.38 mgauss of the peak at 335 c.p.s. in the spectrum of haemanthidine (Ib) produced a marked sharpening of the small singlet peak at 418 c.p.s.; no other change in the spectrum was noted. Irradiation (0.25 mgauss) of the peak at 300 c.p.s. caused only the peak at 408 c.p.s. to sharpen. These data led to the assignments made in Figure 2. Similar spin decoupling experiments were carried out with Ia which led to the assignments made in Figure 6.

(9) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

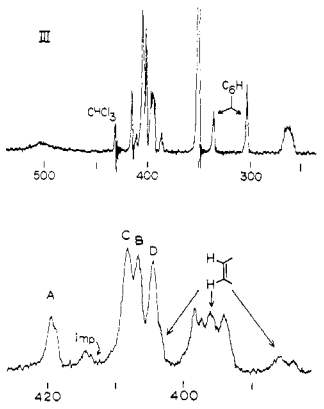


Figure 3. Partial n.m.r. spectrum of apohaemanthidine. Lower curve expands the 380–430 c.p.s. region of upper curve. Peak labeled imp. was unaffected in all decoupling experiments.

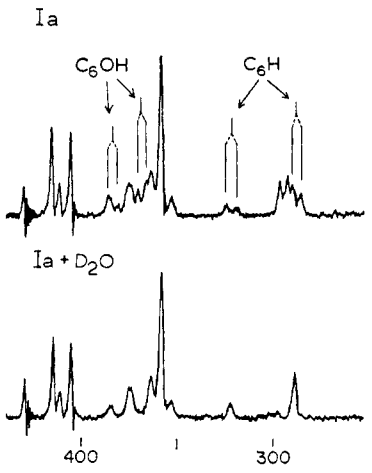


Figure 4. Partial n.m.r. spectrum of 6-hydroxycrinamine in dimethyl sulfoxide.

The olefinic proton resonances of III formed the AB part of an ABX system which partially overlapped the aromatic proton resonances (Figure 3). Irradiation (2.2 mgauss) of the C-3 proton caused the olefinic region to collapse to the expected AB pattern. Peak D (lower Figure 3) was almost unaffected, indicating that it was largely an aromatic proton resonance. When the peak at 308 c.p.s. was irradiated (1.1 mgauss), peak B sharpened, whereas irradiation (1.1 mgauss) of the peak at 340 c.p.s. sharpened peak A. Peaks C and D were unaffected by irradiation of the C-6 proton. This establishes peaks A and B as the C-7 proton resonances, and by difference C and D are the C-10 proton resonances.

Spin decoupling studies with If showed that both peaks due to the benzylic proton (366 and 393 c.p.s.) are coupled to the aromatic C-7 proton (397 c.p.s.) as shown in Figure 2.

Additional support for the assignment of the C-6 proton as the source of the two peaks at 335 and 300 c.p.s. was obtained by examining the n.m.r. spectra of 6-hydroxycrinamine in different solvents. In dimethyl sulfoxide both C-6 proton peaks appear as doublets resulting from coupling to the C-6 hydroxy proton(s) (Figure 4). In the upper spectrum given in Figure 4, the highest field multiplet consists of two

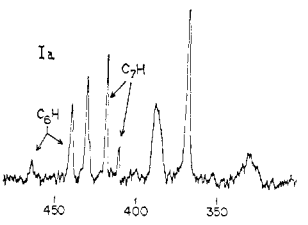


Figure 5. Partial n.m.r. spectrum of Ia in trifluoroacetic acid.

doublets, the C-6 proton major component and the C-11 hydroxyl. The C-6 hydroxyl is superimposed upon the olefinic proton resonances, but by deuteration and by studying the spectrum of 11-acetyldihydro-6-hydroxycrinamine in dimethyl sulfoxide, the assignment of the C-6 hydroxyl as two doublets was made as shown. The splitting of the C-6 proton disappears upon exchange with deuterium oxide. This establishes with certainty that both C-6 epimers are secondary benzylic alcohols.[10]

6-Hydroxycrinamine was found to be stable in trifluoroacetic acid. A partial spectrum is shown in Figure 5. Both C-6 proton peaks were shifted considerably downfield as expected, since a fully positive charge resides on the adjacent nitrogen and the C-6 hydroxyl probably is esterified by the solvent. Spin decoupling experiments with Ia in this solvent led to the assignment of the C-7 proton peaks given in Figure 5. 6-Hydroxycrinamine-6-*d* produced a similar spectrum except the two lowest field peaks were absent. No hydrogen–deuterium exchange occurred in this solvent at 25° during a 24-hr. period.

The n.m.r. spectrum of Ia recorded at various temperatures provides strong proof that the dual chemical shifts of the C-6 and C-7 protons are caused by C-6 proton epimerization. No spectral change, other than a sharpening of the hydroxyl resonances, was observed at −30°. At 40° (Figure 6), the n.m.r. spectrum of Ia is essentially that found at room temperature. At 60, 80, and 100°, the two peaks assigned to the C-6 proton broaden, the two peaks assigned to the C-7 proton coalesce, and the peak assigned to the C-10 proton sharpens to a singlet. This suggests that at room temperature the rate of interconversion of epimers is slow (certainly less than 1 $sec.^{-1}$), but sufficiently fast to preclude isolation of a single epimer.

Chemical evidence supporting this conclusion was obtained in the conversion of Ia to IV. 6-Hydroxycrinamine (Ia) was dissolved in chloroform and stirred with activated manganese dioxide. At given intervals, aliquots of the mixture were taken, the manganese dioxide was removed by filtration, and an n.m.r. spectrum was obtained. An examination of the integrals of the benzylic proton region showed that the ratio of the areas of the two peaks remained constant during oxidation. If two components were present which were not interconvertible, a differential rate of oxidation should be observed. If the components could interconvert rapidly, no differential rate of oxidation would be observed. Reduction of the lactam (IV) with sodium borohydride or lithium aluminum hydride gave Ia as the only product. The n.m.r. spectra of the crude product and a purified crystalline

(10) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, 86, 1256 (1964).

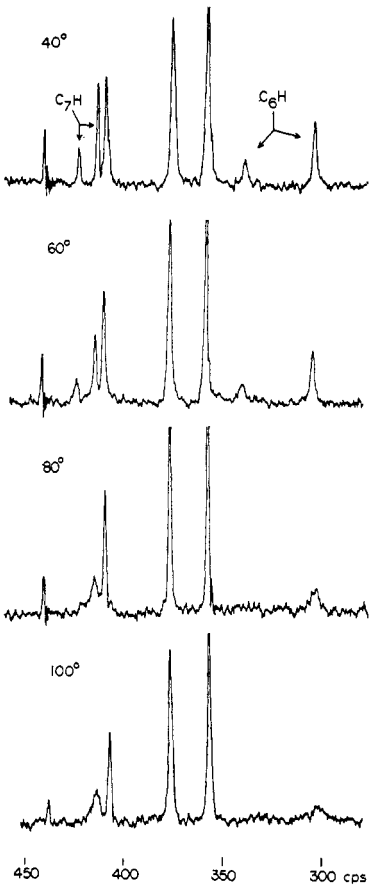
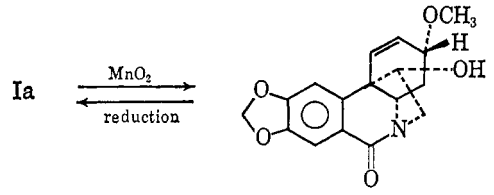


Figure 6. Partial n.m.r. spectra of Ia at 40, 60, 80, and 100°.

sample were identical with that of the natural alkaloid.

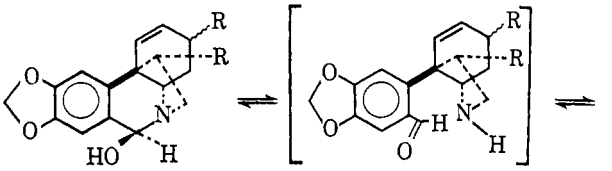


IV

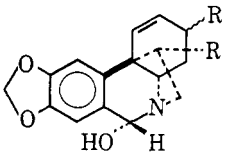
Discussion

The dual chemical shift of the benzylic proton in the n.m.r. spectra of 6-hydroxycrinamine, haemanthidine, and other derivatives with a free hydroxyl group in the C-6 position appears to be a general phenomenon for this class of alkaloids. Either conformational or configurational changes at C-6 could provide a different environment for the benzylic proton resulting in the observed n.m.r. spectra. It is difficult to rationalize this effect on conformational grounds. Alkaloids derived from 5,10b-ethanophenanthridine have been cited as semirigid.[11] Rings A, B, and D are inflexible because of the aromatic and bicyclic nature of the system. Atoms C-6, C-6a, C-10a, C-10b, and N-5 of ring B are coplanar with the aromatic ring, and substituents at C-6 are bisected by this plane. Only ring C has conformational mobility, and this is limited to the half-chair to half-boat interconversion. In apohaemanthidine (III) even this flexibility is removed, yet III shows two chemical shifts for the benzylic proton. Furthermore, if conformational factors are responsible for the effect, it might be expected that the n.m.r. spectrum of diacetyldihydro-6-hydroxycrinamine (If) would vary with temperature. However, the spectrum was found to be unchanged from 25 to 125°.

We feel that the phenomenon is best explained by the existence of two C-6 epimers (Va and Vc) which are interconvertible in solution *via* the aminoaldehyde Vb. Our estimate of this rate of epimerization from variable-



Va Vb



Vc

temperature n.m.r. data was cited earlier. The concentration of free aldehyde is so low that it cannot be detected by n.m.r., infrared, or ultraviolet spectroscopy. Chemical reactions of the aldehyde group with external reagents are limited both by steric hindrance of Vb and by the presence of sterically favorable and reactive functional groups within the molecule itself, *e.g.*, a C-11 hydroxyl or the secondary >N–H. Thus, 6-hydroxy alkaloids and their derivatives are stable to Schiff's and Tollen's reagents, lithium aluminum hydride and sodium borohydride, and hydroxylamine. Somewhat enhanced carbonyl activity is found in certain N-methyl quaternary salts. N-Methylapohaemanthidine salts will form carbonyl derivatives,[12] and the role of the aldehyde in the rearrangements of 6-hydroxycrinamine and haemanthidine to criwelline and tazettine has been reported earlier.[5]

The epimerization process appears to occur over a large pH range. The dual chemical shifts of Ia in deuteriochloroform solution persisted upon addition of small quantities of trifluoroacetic acid or triethylamine. The conversion of haemanthidine to N-demethyltazettine[13] using sodium methoxide can be envisioned to proceed by an intramolecular hydride transfer of the type proven for haemanthidine and 6-hydroxycrinamine metho salts. Less is known about the chemical behavior of 6-hydroxy compounds in acidic media, because the reaction mixtures often must be made basic for the isolation of the product, and such a medium permits secondary base-catalyzed reactions to occur. A good example is the conversion of haemanthidine to tazettine with formaldehyde and formic acid.[14] We consider this reaction to proceed by N-methylation of the aminoaldehyde (Vb), followed

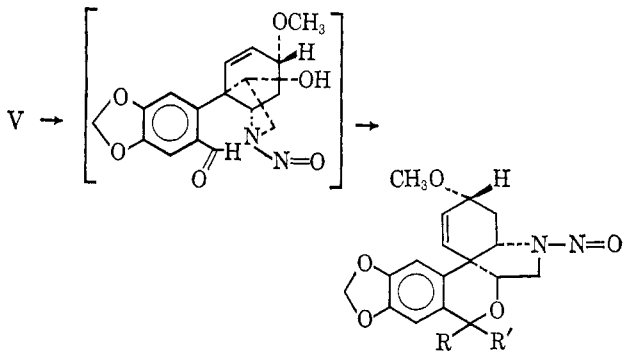
(11) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **85**, 784 (1963).

(12) H. M. Fales, R. J. Highet, and W. C. Wildman, unpublished data.

(13) H. Irie, Y. Tsuda, and S. Uyeo, *J. Chem. Soc.*, 1446 (1959).

(14) W. C. Wildman, *Chem. Ind.* (London), 123 (1956).

by hydride transfer from C-11 to the aldehyde group when the reaction mixture is basified in the isolation procedure. Base-catalyzed rearrangements can be avoided if the reaction product is neutral. Addition of sodium nitrite to a dilute acetic acid solution of Ia gave a high yield of VI (R = H; R′ = OH) which possessed spectral properties compatible with the assigned structure and was oxidized readily by manganese dioxide to the N-nitrosolactone (VI; R, R′ = O).



VI

If the dual chemical shifts of the benzylic and C-7 protons in this series of 6-hydroxy-5,10b-ethanophenanthridine alkaloids is the result of epimerization *via* Vb, an explanation must be found for the occurrence of the same phenomenon in all 6-acetyl derivatives. Facile epimerization with a C-6 acetoxy group present is difficult to explain mechanistically. In the case of If, the n.m.r. spectrum was unchanged up to 100°. Although column and two-dimensional thin layer chromatography provided no evidence that the acetylation products were mixtures, the n.m.r. spectra of If, Ig, and Ih show significant side peaks about 5 c.p.s. on the low-field side of the major acetyl methyl resonances. These resonances are absent in the 11-acetyl-6-hydroxy compounds. Additional evidence for the presence of a C-6 acetoxy mixture has been obtained by acetylation of dihydro-6-hydroxycrinamine at room temperature and at 110°. The n.m.r. spectra of the acetates obtained at these two temperatures show significant differences in the acetyl side peak ratio and in the ratio of the two benzylic proton resonances.

Finally, an explanation must be advanced for the large difference in chemical shift observed for the two epimers. It seems rather unlikely that the magnetic anisotropy of the aromatic ring plays a role because its plane bisects the angle of the hydrogen and hydroxyl bonds at C-6. It is more probable that the difference is associated with the magnetic anisotropy of the electron pair of the nitrogen atom and the asymmetric environment of the nitrogen in the 1-azabicyclo[3.2.1]-octane system.

Experimental Section[15]

The isolation or preparation of 6-hydroxycrinamine,[4] haemanthidine,[16,17] dihydro-6-hydroxycrinamine,[4] dihydrohaemanthidine,[16,18] diacetylhaemanthidine,[17] and apohaemanthidine[16] has been reported.

11-Acetyl-6-hydroxycrinamine (*Id*). A solution of 0.600 g. of 6-hydroxycrinamine in 5 ml. of pyridine was treated with 5 ml. of acetic anhydride and allowed to stand at room temperature for 28 hr. The excess pyridine and acetic anhydride were removed under reduced pressure. The residue was dissolved in benzene and chromatographed on 40 g. of basic alumina. Elution with 1% ethyl acetate in benzene gave 120 mg. of 6,11-diacetyl-6-hydroxycrinamine. Elution with chloroform gave 320 mg. of Id which was purified by recrystallization from ethyl acetate: m.p. 134–135°; $[\alpha]^{25}_{589}$ +49°, $[\alpha]^{25}_{436}$ +139° (*c* 0.42); λ_{max}^{KBr} 5.76 μ; λ_{max}^{EtOH} 240 mμ (ϵ 3600) and 290 mμ (ϵ 4500).

Anal. Calcd. for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.42; H, 6.15; N, 3.89.

6,11-Diacetyl-6-hydroxycrinamine. The diacetyl-6-hydroxycrinamine obtained above was sublimed (0.001 mm., 120°) to give a solid: m.p. 95–97°; $[\alpha]^{25}_{589}$ +21°, $[\alpha]^{25}_{436}$ +67° (*c* 0.54); λ_{max}^{KBr} 5.76 μ; λ_{max}^{EtOH} 241 mμ (ϵ 4200) and 291 mμ (ϵ 4800).

Anal. Calcd. for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.78; N, 3.49. Found: C, 62.76; H, 5.77; N, 3.63.

11-Acetyldihydro-6-hydroxycrinamine (*Ie*). A solution of 0.350 g. of diacetyl-6-hydroxycrinamine in 10 ml. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure with 0.100 g. of platinum oxide. The reduction stopped after the uptake of 1 equiv. of hydrogen. The catalyst was removed by filtration, and the solvent was evaporated under reduced pressure. The residue (0.348 g.) was chromatographed on 20 g. of basic alumina. Elution with solvents ranging from 10% ethyl acetate in benzene through 10% methanol in chloroform gave 190 mg. of Ie which was recrystallized from acetone–ether and sublimed for analysis: m.p. 217–218°; $[\alpha]^{25}_{589}$ +168°, $[\alpha]^{25}_{436}$ +316° (*c* 0.11); λ_{max}^{KBr} 5.74 μ; λ_{max}^{EtOH} 237 mμ (ϵ 4400) and 288 mμ (ϵ 5300).

Anal. Calcd. for $C_{19}H_{23}NO_6$: C, 63.14; H, 6.42; N, 3.88. Found: C, 63.06; H, 6.18; N, 3.88.

6,11-Diacetyldihydro-6-hydroxycrinamine (*If*). A solution of 0.400 g. of dihydro-6-hydroxycrinamine in 10 ml. of acetylating reagent[19] was allowed to stand at room temperature for 30 min. The solution was cooled in an ice bath and made basic (pH 9) with 20% sodium hydroxide solution. The solution was diluted with 50 ml. of water and extracted twice with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the ethyl acetate was removed under reduced pressure. The gum (0.450 g.) was chromatographed on 25 g. of Florisil. Elution with 1% ethyl acetate in benzene gave 410 mg. of diacetyldihydro-6-hydroxycrinamine (If) which resisted all attempts at crystallization. The sublimed glass showed $[\alpha]^{25}_{589}$ +73°, $[\alpha]^{25}_{436}$ +204° (*c* 0.66); λ_{max}^{KBr} 5.75 μ; λ_{max}^{EtOH} 239 mμ (ϵ 5300) and 290 mμ (ϵ 5700).

(15) Melting points were taken on a Köfler microscope hot stage and are corrected. Optical rotations were observed in 95% ethanol with a Jasco recording spectropolarimeter. All ultraviolet spectra were determined in 95% ethanol. N.m.r. spectra were determined in the solvents specified with either a Varian A-60 or HR-60 spectrometer operating at 60 Mc.p.s. Spin decoupling experiments were performed by a modification of the method of Johnson (L. F. Johnson, "Proton-proton Spin Decoupling Using the Varian V-3521 Integrator," Varian Associates, Palo Alto, Calif., 1962).

(16) S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2590 (1958).

(17) H.-G. Boit, *Chem. Ber.*, **87**, 1339 (1954).

(18) H.-G. Boit and W. Döpke, *Naturwiss.*, **47**, 470 (1960).

(19) J. S. Fritz and G. A. Schenk, *Anal. Chem.*, **31**, 1808 (1959).

Anal. Calcd. for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.48; H, 6.26; N, 3.40.

6,11-Diacetyldihydrohaemanthidine (Ih). By the procedure cited for the preparation of If, 0.245 g. of dihydrohaemanthidine was converted to 0.200 g. of crude diacetate. The product was recrystallized from acetone–ether: m.p. 246–248°; $[\alpha]^{25}_{589}$ +39°, $[\alpha]^{25}_{436}$ +76° (*c* 0.51); λ_{max}^{KBr} 5.74 μ; λ_{max}^{EtOH} 238 mμ (ϵ 3900) and 289 mμ (ϵ 4100).

Anal. Calcd. for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.35; H, 6.23; N, 3.42.

Reaction of 6-Hydroxycrinamine with Nitrous Acid. To a solution of 0.300 g. of 6-hydroxycrinamine in 100 ml. of 1.5% aqueous acetic acid was added 0.300 g. of sodium nitrite. The reaction mixture was allowed to stand at room temperature for 4 hr. At this time, a negative alkaloid test was obtained with silicotungstic acid. The aqueous solution was extracted three times with chloroform, and the chloroform solution was washed with 5% sodium bicarbonate solution. Evaporation of the chloroform solution under reduced pressure gave 0.310 g. of crystalline residue which was recrystallized from ethanol–acetone: m.p. 207–208°; $[\alpha]^{25}_{589}$ +345°, $[\alpha]^{25}_{436}$ +875° (*c* 0.24); λ_{max}^{Nujol} 2.69 μ; λ_{max}^{EtOH} 239 mμ (ϵ 14,000) and 290 mμ (ϵ 4800). The n.m.r. spectrum in dimethyl sulfoxide showed one proton doublet at 423 c.p.s. that was removed upon treatment of the sample with deuterium oxide. This is consistent with the hemiacetal formation.

Anal. Calcd. for $C_{17}H_{18}N_2O_6$: C, 58.95; H, 5.24; N, 8.09. Found: C, 59.31; H, 5.41; N, 8.00.

N-Nitrosolactone (VI; R, R′ = O). A solution of 0.310 g. of VI (R = H, R′ = OH) in 80 ml. of chloroform was stirred for 6 hr. with 1.50 g. of manganese dioxide at room temperature. The manganese dioxide was removed by filtration, and the solvent was concentrated to dryness under reduced pressure to give 0.285 g. of residue which crystallized upon trituration with ether. Recrystallization from acetone–methanol–chloroform gave white prisms: m.p. 251–252°; $[\alpha]^{25}_{589}$ +360°, $[\alpha]^{25}_{436}$ +880° (*c* 0.15, pyridine); λ_{max}^{KBr} 5.80 and 6.19 μ; λ_{max}^{EtOH} 231 mμ (ϵ 35,000), 266 mμ (ϵ 6800), and 308 mμ (ϵ 7200). The n.m.r. spectrum (saturated in dimethyl sulfoxide) showed no benzylic protons.

Anal. Calcd. for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.12; H, 4.66; N, 7.91.

6-Hydroxycrinamine-6-d. A solution of 0.200 g. of 6-oxocrinamine (IV)[4] in 20 ml. of dry tetrahydrofuran was treated with 0.100 g. of lithium aluminum deuteride for 2 hr. at 0°. The excess deuteride was destroyed by water, and the inorganic salts were removed by filtration. The filtrate was concentrated under reduced pressure to provide 0.205 g. of amorphous material which crystallized upon seeding with 6-hydroxycrinamine and was recrystallized from chloroform–acetone: m.p. 209–210°; $[\alpha]^{25}_{589}$ +62°, $[\alpha]^{25}_{436}$ +167° (*c* 0.455). The deuterium incorporation was greater than 95% as determined by n.m.r. spectroscopy. The n.m.r. spectrum was identical with that of 6-hydroxycrinamine except for the lack of peaks at 300 and 335 c.p.s.

Acknowledgment. We are grateful to the National Science Foundation for providing funds both to support this research (NSF-GP253) and to purchase the Beckman DK-2 ultraviolet spectrophotometer (G-14916). We wish to thank Dr. Lloyd Jackman for stimulating discussions.

Fluorine-19 Magnetic Resonance Study of Secondary Deuterium Isotope Effects of the Methyl Group[1]

Daniel D. Traficante and Gary E. Maciel

Contribution from the Frank J. Seiler Research Laboratory, Office of Aerospace Research, U. S. Air Force Academy, Colorado, and the University of California, Davis, California. *Received June 4, 1965*

The F^{19} chemical shifts of m- and p-fluorotoluene-α,α,α-d_3 and their nondeuterated analogs were determined. No appreciable isotope effect was detected for the meta isomer; however, the chemical shift of p-fluorotoluene-α,α,α-d_3 was found to be about 0.7 c.p.s. less than that of p-fluorotoluene. In terms of Taft's correltions of F^{19} shifts for meta- and para-substituted fluorobenzenes with σ_I and σ_R^0, these results imply negligible or zero inductive isotope effects of the methyl group, but a small resonance isotope effect in the direction expected from recent results on secondary deuterium isotope effects in kinetic and equilibrium studies.

(1) Reproduction in whole or in part is permitted for any purpose of the U. S. Government.

Introduction

The subject of secondary deuterium isotope effects has been of considerable interest in the past few years, both from the point of view of understanding their origin and for their application to mechanism studies.[2,3] Such effects have been observed in proton and fluorine magnetic resonance spectra[4-9] and in kinetic studies[2a] and equilibrium data.[2,3]

(2) (a) E. A. Halevi, *Progr. Phys. Org. Chem.*, **1** (1963); (b) E. A. Halevi, M. Nussin, and A. Ron, *J. Chem. Soc.*, 866 (1963).
(3) E. A. Halevi and M. Nussin, *ibid.*, 876 (1963).
(4) M. Saunders, J. Plostnieks, P. S. Wharton, and H. H. Wasserman, *J. Chem. Phys.*, **32**, 317 (1960).
(5) E. B. Whipple, W. E. Stewart, G. S. Reddy, and J. A. Goldstein, *ibid.*, **34**, 2136 (1961).