[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

The Structure of Flavothebaone[1]

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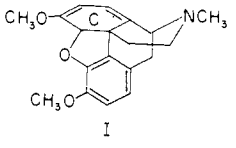
RECEIVED JANUARY 8, 1957

Structure V is deduced for flavothebaone, a rearranged derivative of the alkaloid thebaine, on the basis of a probable mechanism for its formation from thebainehydroquinone (IIIa). This structure differs from part-structure IV originally proposed by Schöpf, in 1938, and from VI and VII put forward, in 1954, by Bentley. New experimental evidence provides strong support for this formulation. Thus, the discovery that dihydrothebainehydroquinone (VIII) undergoes a parallel transformation proves that the C_7–C_8 unsaturation is not essential for the flavothebaone rearrangement. Spectral as well as chemical evidence corroborates the presence of an *isolated* α,β-unsaturated carbonyl system. This new feature is reconciled with the red color developed by flavothebaone in base. The ultraviolet spectrum of flavothebaone, not directly predictable from V, is discussed briefly.

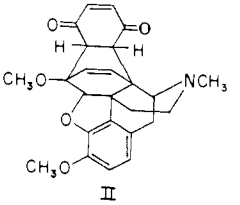
Introduction and Theoretical Discussion

The reaction of *p*-benzoquinone with the alkaloid thebaine (I), described for the first time by Sandermann[3] and by Schöpf,[4] in 1938, gives the expected Diels–Alder adduct thebainequinone (II). This adduct may be regarded as the diketo form of a hydroquinone, and in accord with the generally observed behavior of this type of compound it may be doubly enolized under a variety of conditions to thebainehydroquinone (IIIa). IIIa suffers a deep-seated change on strong acid treatment, losing one methylene group and giving rise to the rearrangement product flavothebaone, $C_{24}H_{23}O_5N$.

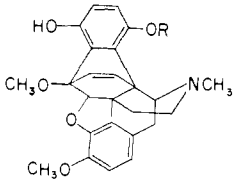
Extensive studies by Schöpf revealed that flavothebaone contained one new phenolic hydroxyl group, an intact tertiary nitrogen, and an α,β-unsaturated ketone system.[4] When flavothebaone is dissolved in base, a striking red coloration develops. This phenomenon led Schöpf to the conclusion that the unsaturated ketonic chromophore *must be conjugated with the hydroquinone ring*. Since methylation of the hydroquinone hydroxyls *or* saturation of the double bond produced derivatives which were not red in base, this relationship seemed entirely reasonable. On the basis of these early studies, Schöpf tentatively advanced part structure IV for flavothebaone, but was unable to arrive at a complete structure.



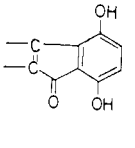
I



II



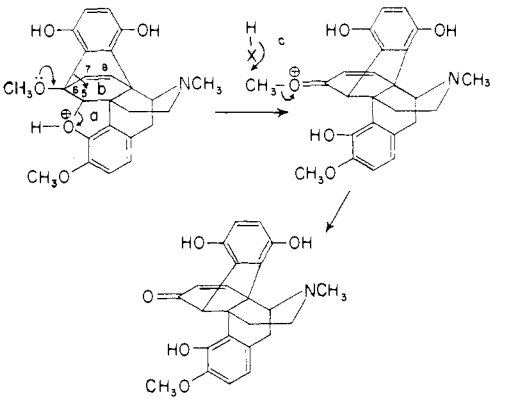
IIIa, R = H
IIIb, R = CH_3



IV

The work of Schöpf incorporated a large number of carefully performed transformations, including a successful Hofmann degradation and Beckmann rearrangement. Oxidative degradations were less fruitful. In view of the complexity of the flavothebaone molecule, it seemed that little progress could be hoped for until a plausible structure could be derived which would serve as a sound working hypothesis. Toward this end, it was of interest to speculate on what acid-catalyzed reactions IIIa might be expected to undergo.

Of the many rearrangement pathways open to the substrate IIIa, one reaction sequence appeared to be so compelling as to eliminate from detailed consideration all other possibilities until the favored scheme could be tested. The postulated sequence, as shown in equation 1, is initiated by protonation of the cyclic ethereal oxygen, and proceeds *via* (a) cleavage of the C_5–O bond, (b) migration of the hydroquinone moiety from C_6 to C_5, and finally (c) attack of the resultant hybrid by any nucleophilic species to give V. This simple mechanism



(1)

V

seemed particularly attractive in view of the high yield and lack of side products obtained in the reaction. It involves only a single 1,2-shift of an electronically excellent migrating group which furthermore is almost exactly *trans* to the vanishing C_5–O bond. Since the easily derived structure V possesses a new phenolic hydroxyl group, an intact tertiary nitrogen and an α,β-unsaturated ketone system, this formula was tentatively assigned to flavothebaone.

That the application of theoretical considerations to the evidence discussed above does not necessarily lead to this conclusion was dramatically demonstrated by the publication of a highly imagi-

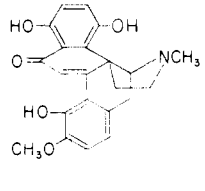
(1) A preliminary Communication of some of the results reported in this paper has appeared in *Chemistry & Industry*, 957 (1956).

(2) Opportunity Fellow, John Hay Whitney Foundation, 1955–1956; Allied Chemical and Dye Corp. Fellow, 1956–1957.

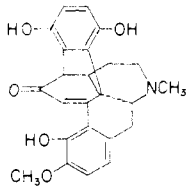
(3) W. Sandermann, *Ber.*, **71**, 648 (1938).

(4) C. Schöpf, K. von Gottberg and W. Petri, *Ann.*, **536**, 216 (1938).

native discussion of the flavothebaone problem by Bentley in 1954.[5] This discussion appeared well after work aimed at testing the validity of structure V had begun in these laboratories, and served to stimulate interest in this research by offering alternate flavothebaone structures. A complete review of this significant discussion is beyond the scope of the present paper, but the key points may be readily summarized. Rather complex mechanistic considerations led to structures VI ($C_{22}H_{21}O_5N$) *or* VII for flavothebaone. Bentley was able to exclude VI by confirming Schöpf's molecular formula and by an analysis of ultraviolet data. With some reservations he was thus led to VII as the correct flavothebaone structure. Brief



VI



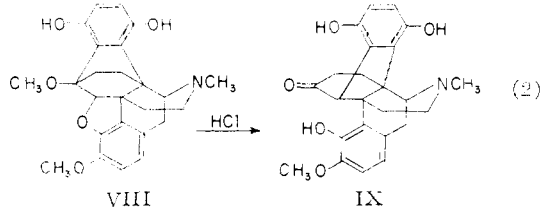
VII

consideration was also given to V, but this possibility was quickly dismissed, largely because of its failure to incorporate extended conjugation.[6]

After a preliminary account of the results of our flavothebaone researches had appeared,[1] Bentley and co-workers published a brief note in which "flavothebaone is allotted structure V."[7] Although they did not present the reason(s) for abandoning their earlier assignment or the evidence supporting V, it is apparent that these workers have deduced structure V independently.

Discussion of Results

One key experiment serves to exclude both VI and VII as suitable expressions for flavothebaone. The mechanisms leading to either of these require the C_7–C_8 unsaturation for their operation.[5] On the other hand, the route from IIIa to V makes no special use of this double bond, and it might therefore be predicted that dihydrothebainehydroquinone (VIII) should be capable of rearranging to dihydroflavothebaone (IX), as shown in equation 2. This transformation has been realized in good yield (in contrast to a previous report that it could not be brought about[5]). It is thus established that the C_7–C_8 double bond is not essential for the flavothebaone rearrangement.



VIII IX (2)

Three types of evidence indicate the presence of an *isolated* α,β-unsaturated ketone system in flavothebaone. The first of these is outlined on Chart 1, and provides information on the point of attachment of the carbonyl group. Lithium aluminum hydride reduction of flavothebaone trimethyl ether (X) gives rise to flavothebaol trimethyl ether (XI). XI is readily reoxidized to X by manganese dioxide, indicating its allyl or benzyl nature.[8] In sharp contrast, dihydroflavothebaol trimethyl ether (XIII), prepared by lithium aluminum hydride reduction of dihydroflavothebaone trimethyl ether (XII) or by catalytic reduction of XI, is resistant to manganese dioxide oxidation even under more drastic conditions. These observations indicate that the carbonyl group of flavothebaone must be insulated from both aromatic rings.

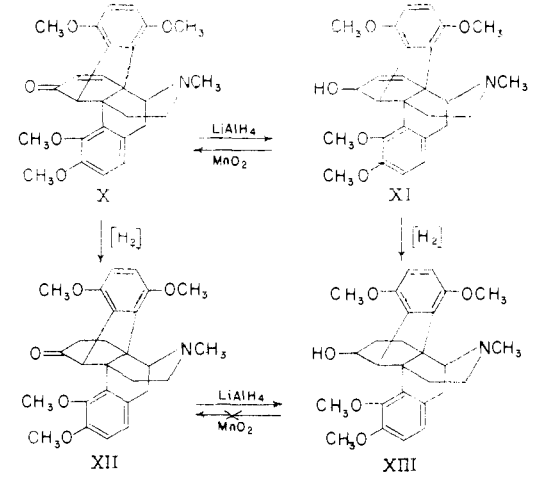
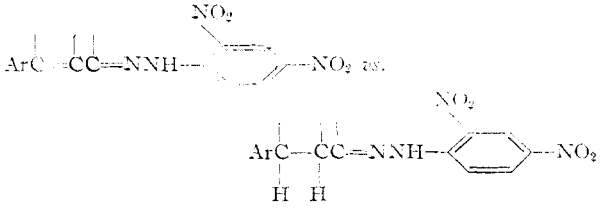


CHART 1

Infrared data support this conclusion. XII shows a single carbonyl absorption band at 5.82 μ (in $CHCl_3$ solution), as would be expected for an isolated carbonyl chromophore. X, on the other hand, shows carbonyl absorption at 5.97 μ (in $CHCl_3$ solution), in accord with expectation.

Ultraviolet data provide insight into the environment of the other end of the α,β-unsaturated carbonyl system. Thus, the long wave length ultraviolet maxima of the 2,4-dinitrophenylhydrazones of X and XII were found to *differ* in position by only 17 mμ. This is in good agreement for a $\Delta\lambda$ value to be expected for a pair of compounds differing by one conjugated double bond,[9] but is much too small to be compatible with a difference of the type shown below.



(5) K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Clarendon Press, Oxford, 1954, pp. 293–301.

(6) It should be pointed out that VII has the conjugation extending to the catechol rather than to the hydroquinone ring. As a result of this, it becomes impossible to use VII to rationalize Schöpf's findings with respect to the color reaction as discussed above.

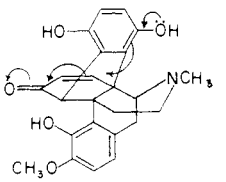
(7) K. W. Beutley, J. Dominguez and J. P. Ringe, *Chemistry & Industry*, 1353 (1956).

(8) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(9) A typical $\Delta\lambda$ value of 20 mμ is given by A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold Ltd., London, 1954, p. 107.

All these observations support V to the exclusion of all other structures so far considered. There are two objections that must be overcome, however, before this formulation can be accepted without reservation. The first of these is the necessity of rationalizing the red color of flavothebaone in base. Re-examination of this phenomenon reveals that the coloration is not due to the development of an intense, long wave length absorption maximum, as had been generally assumed, but rather to the appearance of a long, low-intensity tail in the visible. In fact, the actual spectral change accompanying anion formation is to *shorter* wave lengths (from λ_{max} 280 mμ (3.50), 345 mμ (3.55) to λ_{max} 257 (4.04), 298 mμ (3.84)). Furthermore, the reversibility of this color formation never has been demonstrated. When this point was investigated, it was found that although on a preparative scale flavothebaone can be recovered from basic solutions, *in very dilute solutions* (such as those used for determining ultraviolet spectra) *the reaction is not reversible.* This result takes on increased significance when compared with the behavior of flavothebaone monomethyl ether (XIV). This derivative undergoes a spectral shift to longer wave lengths in base (from λ_{max} 280 mμ (3.49), 344 mμ (3.53) to λ_{max} 293 mμ (3.78) and 404 mμ (3.32)) and the change is reversed by addition of acid, even in very dilute solutions. Finally it should be mentioned that even dihydroflavothebaone (IX), in which no extended conjugated system can exist, develops a brownish color irreversibly in base. From all this it seems clear that the appearance of a color in base is associated with a *reaction* of the unprotected hydroquinone ring which is more complex than simple anion formation.[10] One objection to structure V for flavothebaone is thus overcome.

The remaining difficulty is the unexpected 345 mμ maximum in the flavothebaone spectrum, which could not have been predicted on the basis of structure V. In view of the weight of the evidence presented thus far, it seems best to regard this spectrum as a problem *per se.* It is nevertheless a problem that must be resolved before V can be accepted unconditionally. A number of "abnormal" ultraviolet spectra have come to light recently,[11]



and it is tempting to ascribe this long wave length absorption to "homoconjugation" interaction, perhaps of the sort shown in formula XV. In the absence of any direct analogy for this particular system, however, it is necessary to put this speculation on firm ground by examination of a suitable model system. A synthesis of an appropriate model is now underway. The results of this study as well as of some confirmatory degradations which are now in progress will be presented in a subsequent publication.

Acknowledgments.—This problem was first brought to the attention of one of the authors by Dr. Bernhard Witkop in 1948. We are indebted to Professor Gilbert Stork for valuable discussions and encouragement, and to Dr. Max Tishler, Merck and Co., for a generous supply of thebaine.

Experimental[12]

Dihydrothebainehydroquinone (VIII).—Thebainehydroquinone (IIIa) was hydrogenated in glacial acetic acid over PtO_2 according to the procedure of Schöpf.[4] The H_2 uptake was 1.12 moles and a crude product was obtained in 94% yield. After recrystallization from absolute methanol the m.p. was 281–282° (lit.[4] 273°); infrared spectrum (KBr): 2.98, 3.78 and 3.99 μ (diffuse); ultraviolet spectrum: λ_{max}^{EtOH} 299 mμ (3.79).

Flavothebaone (V).—Compound V was prepared according to the method of Schöpf.[4] Best yields were obtained (in excess of 90%) when thebainehydroquinone (IIIa) was heated at 100° with concentrated HCl for 6 rather than 3 hours. The phenolic base was isolated most conveniently as the bright yellow acid hydrochloride trihydrate ($C_{24}H_{23}O_5N\cdot 2HCl\cdot 3H_2O$). Recrystallization from water gave the hydrochloride trihydrate ($C_{24}H_{23}O_5N\cdot HCl\cdot 3H_2O$). Further drying in a vacuum desiccator gave pale yellow needles of a hydrochloride monohydrate ($C_{24}H_{23}O_5N\cdot HCl\cdot H_2O$)[4]; infrared spectrum (KBr): 2.99, 3.17, 3.72, 5.98, 6.18, 6.32 μ; ultraviolet spectra (taken on $C_{24}H_{23}O_5N\cdot HCl\cdot 3H_2O$): λ_{max}^{EtOH} (0.1 N H^+) 279 mμ (3.51) and 346 mμ (3.56); λ_{max}^{EtOH} (0.1 N OH^-) 257 mμ (4.04) and 298 mμ (3.84).

Anal. Calcd. for $C_{24}H_{23}O_5N\cdot HCl\cdot H_2O$: C, 62.65; H, 5.65. Found: C, 62.82; H, 5.80.

An additional amount of V, as the free base, could be precipitated from the aqueous recrystallization liquors with saturated $NaHCO_3$ solution. In our hands this material was difficult to recrystallize and further purification was not achieved.

Flavothebaone dissolves in sodium hydroxide solution to give a deep red solution. Acidification of this solution reprecipitates flavothebaone (identified by ultraviolet and infrared spectra).

Dihydroflavothebaone (IX).—The hydrogenation was carried out on flavothebaone hydrochloride trihydrate using 10% Pd:$BaSO_4$ catalyst as described by Schöpf.[4] The H_2 uptake was 1.16 moles. Recrystallization from methanol–water yielded a colorless crystalline hydrochloride (presumably dihydrate); infrared spectrum (KBr): broad 2.98–3.25, 3.74(w), 5.85, 6.20, 6.32 μ; ultraviolet spectra (intensities calculated on the basis of $C_{23}H_{25}O_5N\cdot HCl\cdot 2H_2O$): λ_{max}^{EtOH} (0.1 N H^+) 291 mμ (3.73) and 309 mμ (3.70); λ_{max}^{EtOH} (0.1 N OH^-) 259 mμ (3.89) and 303 mμ (3.84); 2,4-dinitrophenylhydrazone: infrared spectrum: 2.94, 5.84(w), 6.17, 6.28 μ.

Anal. Calcd. for $C_{30}H_{29}O_8\cdot HCl\cdot H_2O$: C, 56.10; H, 5.02; N, 10.90. Found: C, 56.33; H, 4.97; N, 10.55.

Rearrangement of Dihydrothebainehydroquinone (VIII) **to Dihydroflavothebaone** (IX).—Dihydrothebainehydroquinone (4.70 g.) was dissolved in 25 ml. of glacial acetic acid. This solution was added to a concentrated HCl solution held at 95–100° on a water-bath. White crystals soon began to appear. After 9 hours the solution was cooled and the crystals filtered, washed and dried (2.77 g.). Additional material was obtained by diluting the filtrate with water and cooling to 5° (1.84 g.). The total yield was 86% (based on the dihydrate formulation). Recrystallization from water yielded colorless crystalline hydrochloride. The infrared spectrum (KBr) was indistinguishable from that of the authentic sample of IX; ultraviolet spectra (in-

(10) A very careful attempt to make the formation of an anion from flavothebaone reversible in dilute solution by operating under an atmosphere of nitrogen is described in the Experimental section.

(11) Some early cases are cited by J. Meinwald, S. L. Emerman, N. C. Yang and G. Büchi, THIS JOURNAL, **77**, 4401 (1955). Two excellent recent papers dealing with this general problem have been published by R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 2302 (1956), and by E. R. H. Jones, G. H. Mansfield and M. C. Whiting, *ibid.*, 4073 (1956).

(12) All melting points were taken on a calibrated Fisher–Johns hot-stage. Ultraviolet spectra were recorded using a Beckman ultraviolet spectrophotometer, model DK.

tensities calculated on the basis of $C_{23}H_{25}O_5N\cdot HCl\cdot 2H_2O$): λ_{max}^{EtOH} (0.1 N H^+) 291.5 mμ (3.70) and 309 mμ (3.71); λ_{max}^{EtOH} (0.1 N OH^-) 257 mμ (3.99) and 302 mμ (3.78).

A 2,4-dinitrophenylhydrazone was prepared and found to have an infrared spectrum (KBr) indistinguishable from that of authentic dihydroflavothebaone 2,4-dinitrophenylhydrazone.

Flavothebaone Trimethyl Ether (X).—Methylation of flavothebaone was carried out as prescribed by Schöpf employing sodium ethoxide and phenyltrimethylammonium chloride.[4,13] The free base was obtained in 72% yield and gave a m.p. of 252.5–253.0° with sintering below 240° (lit.[4] 253°) after recrystallization from absolute methanol; infrared spectrum ($CHCl_3$ soln.): 5.97, 6.25, 6.34 μ; ultraviolet spectrum: λ_{max}^{EtOH} 266–290 mμ (3.43) and 337 mμ (3.49); 2,4-dinitrophenylhydrazone: m.p. 298–299° (browns after melting) ultraviolet spectrum: λ_{EtOH}^{max} 3.94 mμ (4.35).

Anal. Calcd. for $C_{33}H_{33}O_8N_5$: C, 63.15; H, 5.30. Found: C, 63.29; H, 5.40.

Flavothebaol Trimethyl Ether (XI).—To an agitated suspension of flavothebaone trimethyl ether (5.0 g.) in 250 ml. of absolute ether which had previously been cooled to 0–5°, was added a 2-fold amount of ethereal $LiAlH_4$ solution over a 2-hour period. After stirring 24 hr. at 0–5°, saturated Na_2SO_4 solution and then solid anhydrous Na_2SO_4 were added. After several hours the mixture was filtered and the solid washed thoroughly with ether. The ether was evaporated to leave a white solid (4.57 g., 91%). Several recrystallizations from absolute ethanol gave white feathery crystals, m.p. 267.5–268°, with browning after melting; infrared spectrum ($CHCl_3$ solution): 2.91, 6.23, 6.36 μ; ultraviolet spectrum: λ_{max}^{EtOH} 291 mμ (3.70), shoulder around 300 mμ.

Anal. Calcd. for $C_{27}H_{31}O_5N$: C, 72.14; H, 6.95; N, 3.12. Found: C, 72.17; H, 7.10; N, 3.39.

MnO_2 Oxidation of Flavothebaol Trimethyl Ether (XI).—Active MnO_2 (500 mg.), prepared after the method of Attenburrow, *et al.*,[8] was ground to a fine powder and suspended in 150 ml. of absolute benzene. Flavothebaol trimethyl ether (50 mg.) was added and the mixture agitated for 4 hours. After filtration and evaporation of the benzene a yellowish residue was left which had an ultraviolet spectrum identical with that of flavothebaone trimethyl ether. After recrystallization from absolute methanol its melting point was 252.5–254° and not depressed when mixed with an authentic specimen.

Dihydroflavothebaone Trimethyl Ether (XII).—Flavothebaone trimethyl ether was hydrogenated over PtO_2 in glacial acetic acid as described by Schöpf.[4] Colorless needles were obtained on recrystallization from absolute methanol, m.p. 242–244° with browning after melting (lit.[4] 219–20°, clear at 238°); infrared spectrum ($CHCl_3$ solution): 5.82, 6.21, 6.31 μ; ultraviolet spectrum: λ_{max}^{EtOH} 291–300 mμ (3.66); 2,4-dinitrophenylhydrazone: m.p. 251–252°. ultraviolet spectrum: λ_{max}^{EtOH} 377 mμ (4.4).

Anal. Calcd. for $C_{33}H_{35}O_8N_5$: C, 62.94; H, 5.60; N, 11.12. Found: C, 62.82; H, 5.64; N, 11.18.

Dihydroflavothebaol Trimethyl Ether (XIII). A. From Flavothebaol Trimethyl Ether (XI).—Flavothebaol trimethyl ether (250 mg.) was hydrogenated over PtO_2 in 40 ml. of glacial acetic acid. After 70 minutes H_2 uptake had stopped at 0.91 mole. After filtration and evaporation of most of the acetic acid, the free base was precipitated with aqueous ammonia. Recrystallization from absolute ethanol gave colorless clusters of needles, m.p. 193–194°.

B. **From Dihydroflavothebaone Trimethyl Ether (XII).**—Dihydroflavothebaone trimethyl ether (500 mg.) was slurried in 50 ml. of absolute ether and reduced with $LiAlH_4$. The product was worked up in the usual way and after several recrystallizations from absolute ethanol, gave colorless needle clusters, m.p. 193–194°, with no depression on mixing with a specimen prepared by method A; infrared spectrum (KBr): 2.80, 6.25, 6.37 μ; ultraviolet spectrum: λ_{max}^{EtOH} 288.5 mμ (3.74), shoulder *ca.* 300 mμ.

Anal. Calcd. for $C_{27}H_{33}O_5N$: C, 71.81; H, 7.37; N, 3.10. Found: C, 71.62; H, 7.11; N, 3.37.

Treatment of Dihydroflavothebaol Trimethyl Ether (XIII) with MnO_2.—Agitation of dihydroflavothebaol trimethyl ether with active MnO_2 in absolute benzene for 24 hr. gave back only unchanged starting material, identified by m.p., mixture m.p. and ultraviolet spectrum.

Thebainehydroquinone Monomethyl Ether[14] (IIIb).—IIIb was prepared from thebainehydroquinone (IIIa) as described by Schöpf, by heating with methyl *p*-toluenesulfonate in the absence of base.[4] After recrystallization from absolute methanol, off-white rectangular plates were obtained, m.p. 238–240° (lit.[4] 238°); infrared spectrum (KBr): 3.01, 6.13, 6.25 μ; ultraviolet spectra: λ_{max}^{EtOH} (0.1 N H^+) 310 mμ (3.83) and shoulder *ca.* 290 mμ; λ_{max}^{EtOH} (0.1 N OH^-) 320 mμ (3.63) and shoulder *ca.* 294 mμ.

Flavothebaone Monomethyl Ether (XIV).—XIV was prepared by rearrangement of thebainehydroquinone monomethyl ether (IIIb) as described by Schöpf.[4] Isolated as the hydrochloride and crystallized from water, it formed light yellow cubes (presumably a dihydrate); infrared spectrum (KBr): 2.94, 3.13, 3.27, 3.69(w), 5.85, 5.95, 6.20, 6.30 μ; ultraviolet spectra (intensities calculated on basis of the dihydrate formula): λ_{max}^{EtOH} (0.1 N H^+) 280 mμ (3.49), 344 mμ (3.53) and shoulder *ca.* 320 mμ; λ_{max}^{EtOH} (0.1 N OH^-) *ca.* 240 mμ shoulder on intense end-absorption, 293 mμ (3.78) and 404 mμ (3.32).

Ultraviolet Spectral Studies.—The spectra presented in Table I were taken as described below.

TABLE I

Compound and medium	λ_{max}^{EtOH} mμ (log ε)	Color of solution
Flavothebaone		
Acidic	279(3.51), 346(3.56)	Yellow
Basic	257(4.04), 298(3.84)	Red-brown
Reverse (acidic)[a]	285(3.54), 315sh.	.....
Reverse after 20 hr.[a]	283(3.62), 315sh.	.....
Double reverse (basic)[a]	257(3.46), 298(3.50)	.....
Dihydroflavothebaone		
Acidic	291(3.73), 309(3.70)	Colorless
Basic	259(3.89), 303(3.84)	Pale pink
Reverse (acidic)[b]	285(3.71), 310(3.33)	.....
Flavothebaone monomethyl ether		
Acidic	280(3.49), 344(3.53), 320sh.	Yellow
Basic	293(3.78), 404(3.32)	Bright yell.
Reverse (acidic)[b]	280(3.52), 344(3.54), 320sh.	Yellow

[a] It appears that the KCl precipitate adsorbs some of the alkaloid. Note that the double reverse has lower intensities than the original spectrum in alkaline solution. [b] These reverses were done with ethanolic H_2SO_4 in place of HCl. It appears from the intensities of flavothebaone monomethyl ether after reverse that the $KHSO_4$ does not adsorb appreciable quantities of alkaloid.

A. **Acidic.**—Ten-ml. aliquots of ethanolic solution of alkaloid were acidified with 2.5 ml. of 1.0 N ethanolic HCl and diluted to 25.0 ml. with ethanol. These solutions were run against a similarly prepared solvent blank.

B. **Basic.**—Ten-ml. aliquots were prepared and run as A substituting 1.0 N ethanolic KOH for the HCl.

C. **Reverse.**—These experiments were run by taking 10.0-ml. aliquots of alkaloid stock solutions and adding

(13) Poor results were obtained when this reagent was contaminated with the iodide from which it is prepared. A good grade of this reagent is readily prepared by agitating a solution of phenyltrimethylammonium iodide with excess AgCl for 48 hr. After filtering and stripping the water, a crude product is obtained which gives a negative test for I^- (no iodine color in organic layer on shaking a sample with "Clorox" and CCl_4). It is conveniently crystallized from acetone–ether.

(14) The position of the new methyl group in IIIb had originally been assigned as shown by Schöpf. A series of experiments, involving chiefly a spectral study of IIIb and many related compounds, has tended to confirm this structure. A full discussion of this point would be out of place here, however, and should appear in a separate publication.

2.5 ml. of 1.0 *N* ethanolic KOH solution. After brief shaking 5.0-ml. portions of 1.0 *N* ethanolic HCl were added and the solutions diluted to 25.0 ml. Portions of the solutions were centrifuged and the spectra run against similarly prepared blanks.

D.—The double reverse was achieved by treating a 5.0-ml. aliquot of the reverse (acidic) solution with 5.0 ml. of 1.0 *N* ethanolic KOH, diluting to 25.0 ml., centrifuging and running against a similarly prepared blank.

Anaerobic Attempt to Recover Flavothebaone from Dilute Base.—A stock solution of flavothebaone was de-oxygenated with N_2 for 0.5 hour as was an ethanolic KOH solution. Some of the stock solution was pipetted into the KOH solution while continuing to sweep with N_2. The solution turned orange-yellow but became light yellow after a few minutes. An evacuated gas cell was attached to the system and a portion of the solution was thereby withdrawn. The ultraviolet spectrum of this yellow sample was the same as those of the red-brown solutions obtained without the above precautions. A portion of the alkaline solution was poured into ethanolic H_2SO_4, centrifuged and the spectrum taken. It was the same as the spectrum given by flavothebaone after acidification of the basic solution as listed in Table I.

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[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

7-Azaindole. IV. The Hydrogenation of 7-Azaindole and Related Compounds[1,2]

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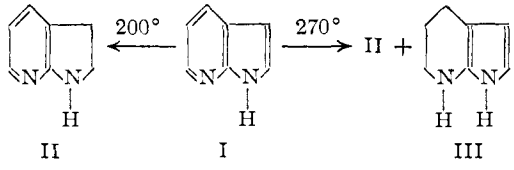
RECEIVED DECEMBER 12, 1956

High-pressure hydrogenation of 7-azaindole (I) in neutral medium at 200° produces 2,3-dihydro-7-azaindole (II), while at higher temperatures the pyrroline ring is cleaved to yield 2-amino-3-ethylpyridine (IV). In acid medium, however, the ring is hydrogenated at atmospheric temperature and pressure to form 2,3,3a,4,5,6-hexahydro-1H-pyrrolo[2,3-b]pyridine (VI). The structure of this product was demonstrated by comparison with the corresponding hexahydro compounds obtained from the reductions of 1-methyl-7-azaindole (VII) and 7-methyl-7H-pyrrolo[2,3-b]pyridine (IX). 1,7-Dimethyl-1H-pyrrolo[2,3-b]pyridinium iodide (XV), on the other hand, reacts with five moles of hydrogen under similar conditions and 1-methyl-3-(2-methylaminoethyl)-piperidine hydroiodide (XVI) is formed. Miscellaneous derivatives of 7-azaindole including a number resulting from ring closure across the 1- and 7-positions are also described.

In 1943, Kruber[3] attempted to cleave the pyrrole ring of 7-azaindole (I) by high-pressure hydrogenolysis with a nickel catalyst in decalin solution. He reported that the pyrrolopyridine, unlike indole which can be cleaved to form *o*-ethylaniline,[4] reacts with one mole of hydrogen at 200° to form 2,3-dihydro-7-azaindole (II), and that at 250–270° a tetrahydroazaindole is produced as well. On the basis of its formation of a dibenzoyl derivative, Kruber proposed the structure 4,5,6,7-tetrahydro-7-azaindole (III) for the latter, but no conclusive evidence was offered for the structure of either hydrogenation product. An interest in "7-azaindoline" as an intermediate for the preparation of 7-



II I III

azaindoles substituted in the pyridine ring led us to reinvestigate the course of these hydrogenations and to extend the investigation to related reductions.

Hydrogenation of 7-azaindole at the prescribed[3] temperature and pressure with an aged W-4 Raney nickel catalyst[5] afforded a dihydro compound apparently identical with that described by Kruber. Evidence in support of the azaindoline structure was obtained from the ultraviolet spectrum of the compound (Fig. 1). The absorption maxima in the

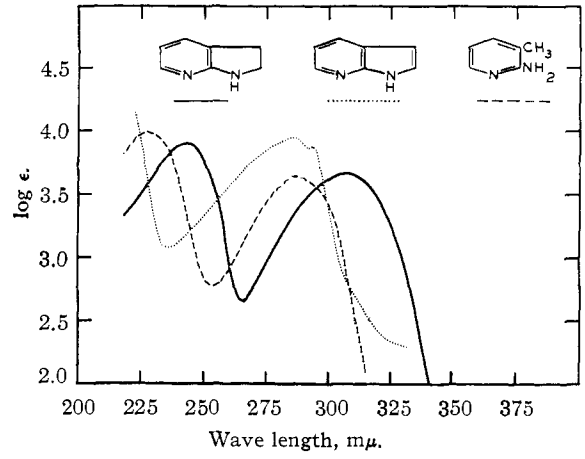


Fig. 1.

spectrum of the dihydro derivative show a bathochromic shift relative to the 7-azaindole absorption and the spectrum of II is more comparable to that of 2-amino-3-picoline, although the peaks in the latter spectrum also occur at a shorter wave length. Similar relationships are noted between the spectra of 2-methylindole,[6] 2-methylindoline[6] and *o*-toluidine[7] and between those of indene and hydrindene.[8] Although such a comparison does not provide conclusive evidence for the 2,3-dihydro structure, it does lend strong support to such a formulation. Attempts at substitution reactions in the pyridine ring of the dihydro compound are anticipated and these, if successful, will serve to confirm the structure.

In this Laboratory it was found that hydrogena-

(1) This investigation was supported by a research grant, number C-2574, from the National Cancer Institute of the National Institutes of Health, Public Health Service.

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