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# Structures of Montanine, Coccinine, and Manthine[1]

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Montanine, coccinine, and manthine are shown to be Amaryllidaceae alkaloids derived from a new ring system, 5,11-methanomorphanthridine. Degradative and synthetic evidence establishes montanine, coccinine, and manthine as XI, XV, and X, respectively. Evidence for the inclusion of manthidine, $C_{17}H_{19}NO_4$, and brunsvigine in this new group of alkaloids is presented.

Two early papers of this series[4,5] described the isolation and characterization of Amaryllidaceae alkaloids from bulbs of various *Haemanthus* species. This genus is native to South Africa. Subsequent isolation studies, largely in our laboratory and that of Prof. H.-G. Boit, have shown that many of the *Haemanthus* alkaloids occur abundantly in other genera of the family which are quite accessible in the Northern Hemisphere. Four exceptions to these findings are the alkaloids montanine, coccinine, manthine, and manthidine which had been isolated only from *Haemanthus coccineus*, *H. amarylloides*, and *H. montanus*.[4] The present paper reports their isolation from *H. tigrinus* and presents structures for the first three of these bases.

Preliminary characterization[4] indicated that montanine and coccinine are isomeric and possess the expanded molecular formula $C_{15}H_{13}N(O_2CH_2)(OCH_3)(OH)$. Spectral and chemical evidence showed that the methoxyl and hydroxyl groups are attached to aliphatic carbon atoms rather than to the benzene ring. This has now been verified by oxidation of the alkaloids to *N*-ethyl hydrastimide. Manthine possessed no hydroxyl group, and from spectral and rotational similarities to montanine, it was tentatively considered to be the *O*-methyl ether of montanine. Catalytic hydrogenation of either montanine or coccinine was reported to occur with the uptake of one equivalent of hydrogen, and the presence of one double bond was established in this manner. The ultraviolet spectra of the alkaloids indicated that the unsaturation is not conjugated with the aromatic ring. No evidence was found for an *N*-methyl group in any of the three alkaloids, although acetylation experiments suggested that the nitrogen atom is tertiary. At this point a number of qualitative tests were applied to montanine and coccinine to determine whether they might be analogs of known Amaryllidaceae alkaloids. From empirical comparisons in the infrared, it seemed unlikely that these alkaloids were elaborated on the 5,10b-ethanophenanthridine (crinane)[6] nucleus. It was determined that neither montanine nor coccinine formed two methiodides, a property that is characteristic of the lycorine group.[7,8] The lycorane nucleus appeared even less likely when it was found that neither alkaloid was oxidized by selenium dioxide in ethanol at 80°.[9,10] Neither montanine nor coccinine was affected by manganese dioxide in chloroform, and it was concluded that probably the alkaloids are neither allylic nor benzylic alcohols. The failure of the compounds to be oxidized and the absence of secondary amino or *N*-methyl groups precluded the possibility that montanine and coccinine are hemiacetals of the lycorenine type.[11] Finally, the galanthamine[12] and tazettine[13] nuclei could be excluded since all oxygen functions are accounted for. Neither base contains a sufficient number of carbon atoms to give a tertiary amine derived from the tazettine skeleton.

A degradative pathway of considerable importance was found in the Oppenauer oxidation of either montanine or coccinine. Under these conditions each alkaloid afforded the same substance, $C_{17}H_{17}NO_4$, which was named dehydrococcinine. Analytical and spectral data showed that the same oxygen-containing functional groups (methylene-

(1) Paper XVII in a series on alkaloids of the Amaryllidaceae; previous paper, H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 3368 (1960). A recent review of the alkaloids of this family has been reported by W. C. Wildman, *The Alkaloids*, Vol. 6, R. H. F. Manske, ed., Academic Press, Inc., New York, 1960, p. 289.

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(4) W. C. Wildman and C. J. Kaufman, *J. Am. Chem. Soc.*, **77**, 1248 (1955).

(5) C. K. Briggs, P. F. Highet, R. J. Highet, and W. C. Wildman, *J. Am. Chem. Soc.*, **78**, 2899 (1956).

(6) W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2567 (1958).

(7) L. E. Humber, H. Kondo, K. Kotera, S. Takagi, K. Takeda, W. I. Taylor, B. R. Thomas, Y. Tsuda, K. Tsukamoto, S. Uyeo, H. Yajima, and N. Yanaihara, *J. Chem. Soc.*, 4622 (1954).

(8) E. W. Warnhoff and W. C. Wildman, *J. Am. Chem. Soc.*, **79**, 2192 (1957).

(9) H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Am. Chem. Soc.*, **77**, 5885 (1955).

(10) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 4395 (1958).

(11) R. J. Highet and W. C. Wildman, *J. Am. Chem. Soc.*, **77**, 4399 (1955).

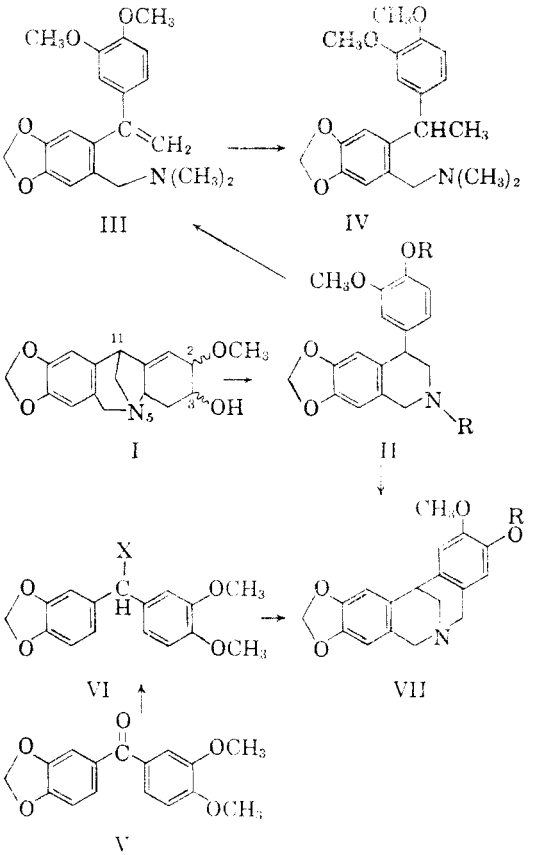
(12) S. Uyeo, Congress Handbook, *Intern. Congr. Pure and Appl. Chem.*, XVIth Congr., Paris, 1957, p. 209.

(13) T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 4749 (1956).

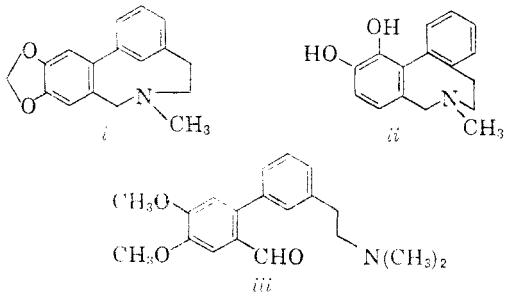
dioxy, methoxyl, and hydroxyl) are present in dehydrococcinine and in the parent base. Dehydrococcinine was soluble in both acid and base and formed an *O,N*-diacetate in the presence of acetic anhydride and pyridine. From the infrared absorption of the *O,N*-diacetate at 1761 and 1639 cm.$^{-1}$ and the characteristic shift of the ultraviolet spectrum of dehydrococcinine in alkali, it was established that this oxidation product contained a new aromatic ring and was a secondary aminophenol. Aromatization of a hydroaromatic ring under relatively mild conditions is characteristic of many of the Amaryllidaceae alkaloids, but this reaction usually is accompanied by loss of optical activity.[14] However, it was found that dehydrococcinine is optically active and stable to heat.

A second observation provided more evidence that these alkaloids are not members of any of the known ring systems of the Amaryllidaceae. Without exception, the cyclohexene ring of all previously known alkaloids of this family which may become aromatic is situated in such a manner that this aromatization forms a derivative of biphenyl. In the case of dehydrococcinine, the ultraviolet spectrum represents the sum of two isolated benzenoid chromophores [$\lambda_{inf}^{C_2H_5OH}$ 232 mμ (ε 11,800) and $\lambda_{max}^{C_2H_5OH}$ 290 mμ (ε 7000)], and no evidence for biphenyl conjugation exists. *O,N*-Dimethyldehydrococcinine, formed by the methylation of dehydrococcinine with diazomethane, showed an ultraviolet absorption spectrum [$\lambda_{max}^{C_2H_5OH}$ 288 mμ (ε 6600)] identical with that obtained from equimolar amounts of veratrole and piperonyl alcohol. From this observation, it was established that the two aryl groups of the oxidation product either are separated by at least one carbon atom or deviate considerably from coplanarity.[19] Hofmann degradation of *O,N*-dimethyldehydrococcinine gave an optically inactive methine, $C_{20}H_{23}NO_4$, which showed infrared and ultraviolet absorption characteristic of a 1,1-diarylethylene [3090 and 895 cm.$^{-1}$; $\lambda_{max}^{C_2H_5OH}$ 265 mμ (ε 12,000)].[20] Catalytic reduction of the methine gave a dihydro derivative, the ultraviolet spectrum of which was identical with that of *O,N*-dimethyldehydrococcinine.

We propose that structures II (R = $CH_3$), III, and IV represent *O,N*-dimethyldehydrococcinine, *O,N*-dimethyldehydrococcinine methine, and its dihydro derivative, respectively. Chemical proof for these structures was provided by an alternative methylation of dehydrococcinine. When II (R = H) was treated with formaldehyde and formic acid, a tertiary aminophenol was obtained. Methylation




(14) Caranine anhydromethine (*i*), as isolated from the Hofmann degradation of caranine,[8] is optically inactive; however, it is capable of optical activity and has been resolved. The extreme ease of racemization of *i* at 80° provides a satisfactory explanation for the isolation of a racemic product from the Hofmann degradation which is carried out at 120°. Tazettine affords 6-phenylpiperonal under a variety of conditions;[13] galanthamine is rearranged by acid to apogalanthamine (*ii*);[15,16] and Hofmann degradation of lycorenine methohydroxide affords *iii*.[17,18]




(15) N. F. Proskurnina and A. P. Yakovleva, *Zhur. Obshcheĭ Khim.*, **25**, 1035 (1955).

(16) S. Kobayashi and S. Uyeo, *J. Chem. Soc.*, 638 (1957).

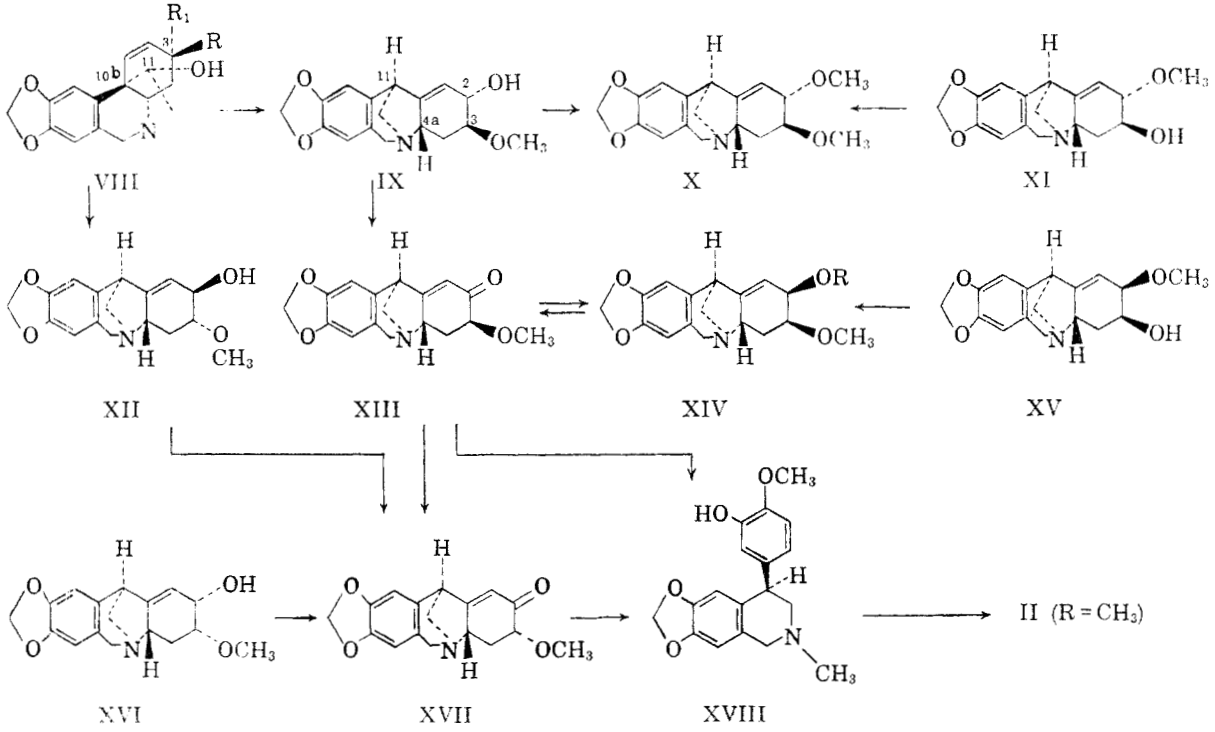
(17) H. Kondo and T. Ikeda, *Ber.*, **73**, 867 (1940).

(18) T. Kitigawa, W. I. Taylor, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 1066 (1955).

(19) The optical activity of *i* is derived from the noncoplanarity of the two aromatic rings. Its ultraviolet absorption [$\lambda_{max}^{C_2H_5OH}$ 255 (ε 8460) and 302 mμ (ε 7080)] differs from that observed for 6-phenylpiperonyl alcohol [$\lambda_{max}^{C_2H_5OH}$ 257 (ε 7220) and 293 mμ (ε 5330)], *N*-(6-phenylpiperonyl)-glycine [$\lambda_{max}^{C_2H_5OH}$ 252 (ε 7020) and 293 mμ (ε 5130)], and *N*-methyl-*N*-(6-phenylpiperonyl)glycine [$\lambda_{max}^{C_2H_5OH}$ 252 (ε 5440) and 293 mμ (ε 4350)] primarily in the wave length found for the maximum near 300 mμ.

(20) Both *cis* and *trans* stilbene isomers would be expected to show more intense absorption at a longer wave length; *e.g.*, *cis*-2,3,3′,4′-tetramethoxystilbene, $\lambda_{max}^{C_2H_5OH}$ 305 mμ (ε 10,700); *trans*-2,3,3′,4′-tetramethoxystilbene, $\lambda_{max}^{C_2H_5OH}$ 325 mμ (ε 28,200), personal communication from Professor R. A. Barnes, Rutgers University.

**Chart 1**




of this product with diazomethane afforded an *O*-methyl ether which was not identical with II (R = $CH_3$). Analysis indicated that the new product contained two hydrogen atoms less than *O,N*-dimethyldehydrococcinine, and it was apparent that the reaction with formaldehyde had produced a new ring by Pictet-Spengler cyclization. This was supported both by the observation that the same product was obtained when formaldehyde and hydrochloric acid were used and by the synthesis of the methyl ether of the deduced structure (VII, R = $CH_3$).

Condensation of piperonyl chloride and veratrole in the presence of aluminum chloride gave the expected ketone (V) which was reduced smoothly to the alcohol (VI, X = OH) with sodium borohydride. Successive treatment of the benzhydrol with thionyl chloride and cuprous cyanide gave a nitrile (VI, X = CN) which was reduced by lithium aluminum hydride to VI (X = $CH_2NH_2$). Cyclization of this amine with formaldehyde and hydrochloric acid gave racemic VII (R = $CH_3$) which was resolved *via* the dibenzoyl tartrate salt. Regeneration of the free base gave a product that was identical in all respects with that obtained from dehydrococcinine.

This proof of structure II (R = $CH_3$) for *O,N*-dimethyldehydrococcinine does not lead directly to structure II (R = H) for dehydrococcinine since no evidence has been presented that the methoxyl and hydroxyl groups of ring C might not be reversed. However, an inspection of the course of the Oppenauer oxidation leads to the conclusion that these groups are placed correctly. If montanine and coccinine are considered stereoisomers of I, the formation of dehydrococcinine results from oxidation of the $C_3$ hydroxyl to a ketone, followed by $\beta$-elimination of the amino group and enolization. A reversal of the substituents on $C_2$ and $C_3$ would provide no reason for the easy aromatization of ring D and would make the lack of oxidation by manganese dioxide anomalous. The double bond is placed as in I since neither alkaloid behaves as an enol or an enol ether. Basicity measurements show that montanine and coccinine are relatively strong bases. Unsaturation at $C_{4a}$–$C_{11a}$ or $C_4$–$C_{4a}$ would be expected to result in a very weak base because of the proximity of such a double bond to the basic nitrogen and its inability to migrate to the nitrogen in acid solution.[21] As located in I, the double bond provides two allylic positions, $C_2$ and $C_{4a}$, which are substituted by methoxyl and amino groups, respectively. This activation provides an explanation for the uptake of considerably more than one equivalent of hydrogen when either alkaloid is reduced catalytically. In contrast with our earlier results,[4] it now was impossible to isolate a pure dihydro derivative from either coccinine or montanine. It is apparent that hydrogenolysis is occurring simultaneously with hydrogenation since the crude reduction product contains at least one secondary amine as shown by paper chromatography.

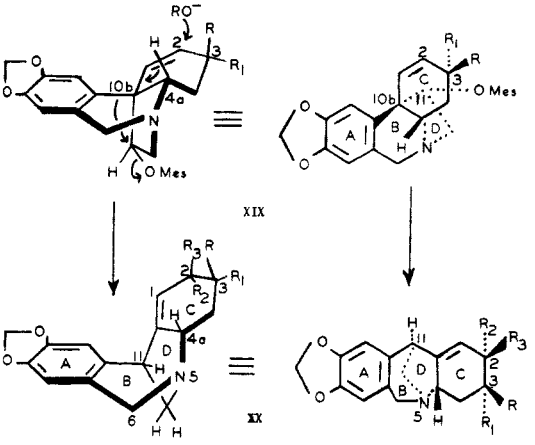
From these degradative and synthetic studies, we feel that montanine and coccinine are firmly

(21) *Cf.*, strychnine, $pK_a$ 7.37; neostrychnine, $pK_a$ 3.8. V. Prelog and O. Häfliger, *Helv. Chim. Acta*, 32, 1851 (1949).

established as stereoisomers of I. This nucleus has not been reported in the chemical literature up to the present time and may be considered a partially hydrogenated derivative of 5,11-methanomorphanthridine.[22]

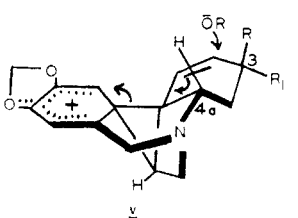
The complete structures and absolute configurations of these alkaloids and that of manthine came from an unexpected source. In the course of studies on the structures and absolute configurations of haemanthamine (VIII, R = $OCH_3$, $R_1$ = H) and crinamine (VIII, R = H, $R_1$ = $OCH_3$),[1,23] it was hoped that some method might be found to replace the $C_{11}$ hydroxyl by hydrogen. When haemanthamine was allowed to stand overnight in the presence of pyridine and mesyl chloride, then hydrolyzed with aqueous alkali, a sulfur-free isomer of haemanthamine was obtained. From empirical correlations in the infrared spectrum it appeared that the ring system of VIII had undergone a profound rearrangement to give a material isomeric with but not identical with montanine and coccinine. From the evidence discussed below, this isomer is established as IX. Whereas haemanthamine is stable to manganese dioxide, isohaemanthamine (IX) was oxidized to oxoisohaemanthamine (XIII) which showed infrared (1681 cm.$^{-1}$) and ultraviolet [$\lambda_{max}^{C_2H_5OH}$ 234 m$\mu$ ($\epsilon$ 18,500)] absorption characteristic of an $\alpha,\beta$-unsaturated ketone. In alkali, the methiodide of XIII was converted to an aminophenol (XVIII) which was not identical with II (R = H). Methylation with diazomethane gave a product which was identical with *O,N*-dimethyldehydrococcinine (II, R = $CH_3$). When crinamine was treated with mesyl chloride and pyridine under the same conditions, two rearranged products (XII and XVI) were isolated; they differed only in the configuration of the hydroxyl group since manganese dioxide oxidation of each gave the same methoxy ketone (XVII). The methiodide of XVII also gave II (R = $CH_3$) when treated with alkali and then diazomethane. Since it has been established that haemanthamine and crinamine differ only in the configuration of the $C_3$ methoxyl,[23] it was expected that the configuration of the methoxyl group of XIII and XVII was responsible for their non-identity. This was confirmed by the observation that either alkali or prolonged treatment with manganese dioxide converted XIII to XVII.

The configurations of IX, XII, XIII, XVI, and XVII are derived from the proposed mechanism of the rearrangement. Since haemanthamine and crinamine form normal *O*-acetyl derivatives in the presence of pyridine and acetic anhydride,[4,24] it would appear that the mesylate group, which is readily displaced, is essential for the reaction. Although the yields were superior when the reaction was carried out in pyridine solution, pyridine is not essential because isohaemanthamine was obtained in 11% yield when the potassium salt of haemanthamine was treated with mesyl chloride in benzene. The rearrangement fails both with dihydrohaemanthamine and epihaemanthamine, indicating that the presence of a double bond and a specific configuration of the hydroxyl group are required for the rearrangement. If we assume that the first step of the rearrangement is the formation of a normal mesylate, the aryl group in XIX is situated ideally for nucleophilic displacement of the mesylate. Such a migration requires a relatively rich source of electrons at a stereochemical position which is *trans* antiparallel to the departing group.



The rearrangement is completed by attack of base at $C_2$ and migration of the double bond.[25] The nature of the $C_2$-substituent in the rearranged product depends upon the method of hydrolysis. When aqueous sodium bicarbonate is used, the $C_2$ group is hydroxyl. If the reaction mixture is poured into methanol containing sodium methoxide, the corresponding methyl ether is obtained.

The net effect of the rearrangement of XIX to XX is the migration of the methylenedioxyphenyl



(22) An alternative name for morphanthridine is 11H-dibenz[b,e]azepine; A. M. Patterson, L. T. Capell, and D. F. Walker, *The Ring Index*, American Chemical Society, Washington, D. C., 1960, p. 480.

(23) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 197 (1960); *Chemistry & Industry (London)*, 561 (1958).

(24) L. H. Mason, E. R. Puschett, and W. C. Wildman, *J. Am. Chem. Soc.*, **77**, 1253 (1955).

(25) Alternatively, this rearrangement may be considered to proceed through $Ar_1$-3 participation.[26] By such a process, solvolysis of XIX would lead to an intermediate carbonium ion (*v*). Anionic approach to $C_2$ would lead to XX also.

(26) R. Heck and S. Winstein, *J. Am. Chem. Soc.*, **79**, 3105 (1957) and references cited therein.

group from $C_{10b}$ to $C_{11}$ with concomitant inversion of the hydrogen at $C_{11}$ and loss of asymmetry at $C_{10b}$. In XIX, with regard to ring D, the $C_{11}$ hydrogen was *cis* with respect to the hydrogen at $C_{4a}$; in XX, they are *trans*. By the mechanism that we have proposed, the configurations of substituents at $C_3$ and $C_{4a}$ in XIX are retained in XX. With ring C of XIX in the half-chair form, the methoxyl group at $C_3$ is *quasi* axial. By the mechanism cited above, such a substituent becomes axial in XX providing ring C of XX is in the half-chair form and the substituent at $C_3$ is not epimerized. Proof of this is found both in the isolation of different products from the rearrangement and allylic oxidation of haemanthamine and crinamine and in the isomerization of XIII to XVII by alkali.[27] The configurations of the methoxyls at $C_3$ in XIII and XVII provide the necessary reference points to complete the structure of the rearrangement products.

The configurations of the hydroxyl groups at $C_2$ in the rearranged products were determined by spectral means. It has been shown that a hydrogen bonded hydroxyl absorbs at lower frequencies and shows a broader, more intense band than an unbonded hydroxyl.[28,29] This manifests itself in increased B values[30] for the hydrogen-bonded members of the series of Chart 1. The infrared absorption spectrum of isohaemanthamine (IX) in a dilute solution of carbon tetrachloride showed no evidence of hydrogen bonding of the hydroxyl group at $C_2$ with the $C_3$-methoxyl. ($\nu$ 3623 cm.$^{-1}$, B 0.26). Since it has been shown that the methoxyl at $C_3$ is axial in IX, the $C_2$-hydroxyl is assigned a *trans quasi* axial configuration and isohaemanthamine may be described completely as XX (R = $OCH_3$, $R_1$ = H, $R_2$ = OH, $R_3$ = H). The $C_2$ epimer, epiisohaemanthamine (XIV, R = H), prepared by the sodium borohydride reduction of XIII, showed a completely hydrogen-bonded hydroxyl ($\nu$ 3567 cm.$^{-1}$, B 0.50). No epimerization of the methoxyl group occurred in the preparation of XIV (R = H) since it was reoxidized by manganese dioxide to XIII. Therefore, epiisohaemanthamine may be described as XX (R = $OCH_3$, $R_1$ = H, $R_2$ = H, $R_3$ = OH). The assignment of hydroxyl configurations in $\alpha$- and $\beta$-isocrinamine, which possess an equatorial methoxyl at $C_3$ was more equivocal because bonding might be expected in both epimers.[31,32] As determined both by the frequencies and intensities of the absorption, this was found to be the case. $\beta$-Isocrinamine was completely bonded ($\nu$ 3570 cm.$^{-1}$, B 0.62) and these values are in good agreement with those found for XIV (R = H). Consequently, $\beta$-isocrinamine is assigned the *cis* configuration and is represented by XVI or, more completely, XX (R = H, $R_1$ = $OCH_3$, $R_2$ = OH, $R_3$ = H). $\alpha$-Isocrinamine shows a single band at 3607 cm.$^{-1}$ (B 0.50). The apparent integrated absorption intensity (B) was in agreement with the values found for other bonded members of this series (B = 0.50 to 0.68) and nearly twice that found for the unbonded cases (B = 0.24 to 0.29). The frequency of absorption (3607 cm.$^{-1}$) is half way between the frequencies assigned to free and bonded hydroxyl groups. This frequency is in good agreement with that found for the intramolecular hydrogen bond of *trans* 1,2-cyclohexanediol ($\nu^{CCl_4}$ 3602 cm.$^{-1}$)[29] existing in the *trans* diequatorial conformation. These data are reflected in the assignment of a *trans quasi* equatorial configuration at $C_2$ and $C_3$, respectively, in $\alpha$-isocrinamine. In terms of structure XX for $\alpha$-isocrinamine, R = H, $R_1$ = $OCH_3$, $R_2$ = H, $R_3$ = OH.

From infrared spectra in dilute solution it was established that the hydroxyl group of coccinine showed intramolecular hydrogen bonding to the adjacent methoxyl ($\nu^{CCl_4}$ 3566 cm.$^{-1}$, B 0.68) and there was no evidence for a free hydroxyl group. No strong intramolecular hydrogen bonding existed in montanine.[33] From these observations it was expected that coccinine is a 2,3-*cis* isomer, while montanine is 2,3-*trans*. Chromatographic behavior of the alkaloids supported these assignments in that coccinine was eluted from a column of alumina before montanine. To determine which of the two possible 2,3-*cis* isomers represents coccinine and which of the two possible 2,3-*trans* isomers represents montanine, it was necessary to convert the isohaemanthamines (IX and XIV) and the isocrinamines (XII and XVI), as well as montanine and coccinine, to common derivatives. The methyl ethers were chosen for this purpose. In a previous paper a process for the *O*-methylation of hydroxyl-containing alkaloids without concurrent *N*-methylation was described.[1] Methylation of isohaemanthamine gave a dimethoxy product (X) which was identical in melting point, infrared spectrum (potassium bromide), and optical rotation with the alkaloid manthine. Manthine also was obtained when a mixture of

(27) Closely analogous to this epimerization is the conversion of oxo-$\alpha$-dihydroundulatine (axial $OCH_3$) to epioxo-$\alpha$-dihydroundulatine (equatorial $OCH_3$) by alkali. E. W. Warnhoff and W. C. Wildman, *Chemistry & Industry (London)*, 1293 (1958), *J. Am. Chem. Soc.*, **82**, 1472 (1960).

(28) C. A. Coulson, *Research*, **10**, 153 (1957).

(29) N. D. Coggeshall, *J. Chem. Phys.*, **18**, 981 (1950).

(30) The apparent integrated absorption intensity (B) has the units mole$^{-1}$ l. cm.$^{-2}$ $\times$ $10^4$. B may be considered approximately equal to the true integrated absorption intensity (A) since halving the slit width produced negligible change in band shape; *cf.* D. A. Ramsay, *J. Am. Chem. Soc.*, **74**, 72 (1952).

(31) L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952).

(32) A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, 4391 (1956).

(33) The main hydroxyl absorption band of montanine is at 3624 cm.$^{-1}$ (B 0.29). A small shoulder is present at 3598 cm.$^{-1}$ which may represent either a slight amount of intramolecular hydrogen bonding to the double bond or changes in the rotational conformation of the hydroxyl group. *Cf.*, R. Piccolini and S. Winstein, *Tetr. Letters* [13] 4 (1959).

haemanthamine, pyridine, and mesyl chloride was decomposed with methanolic sodium methoxide. *O*-Methylation of montanine afforded manthine also, and thus our earlier suggestion concerning the relationship between montanine and manthine was verified. *O*-Methylation of $\alpha$- and $\beta$-isocrinamines provided two methyl ethers (XVI and XII, $OCH_3$ instead of OH) neither of which was identical with the *O*-methylation product of coccinine. However, *O*-methylation of epiisohaemanthamine provided XIV (R = $CH_3$) which was identical with the *O*-methylation product of coccinine. With the established structures of IX and XIV (R = H) and previous knowledge that the *O*-methylation proceeds with retention of configuration,[1] it is possible to assign structures X, XI, and XV to manthine, montanine, and coccinine, respectively. The absolute configurations represented by these structures follow from those determined previously[1,23] for haemanthamine and crinamine.

At this point it seems pertinent to add some further comments on two alkaloids which, in all likelihood, also are members of this new ring system. Manthidine has been isolated along with coccinine and montanine from *H. coccineus* L. and from two unidentified *Haemanthus* species which contained manthine, montanine, and coccinine.[4] Manthidine was reported to possess the expanded molecular formula $C_{16}H_{15}N(O_2CH_2)(OCH_3)(OH)$. This is anomalous in that all Amaryllidaceae alkaloids isolated to date appear to be based on a $C_{15}$ nucleus. When manthidine was reanalyzed, it became apparent that the molecular formula should be revised to $C_{15}H_{13}N(O_2CH_2)(OCH_3)(OH)$. From the ultraviolet absorption of manthidine [$\lambda_{max}^{C_2H_5OH}$ 240 ($\epsilon$ 4250) and 294 m$\mu$ ($\epsilon$ 5400)] and lack of infrared absorption at 1620 cm.$^{-1}$, it can be stated that the aromatic ring is substituted by the methylenedioxy group alone and that the methoxyl is aliphatic.[34] The infrared spectrum of manthidine, particularly in the distinctive region from 1250 to 1450 cm.$^{-1}$, was virtually identical with that shown by all the compounds related to the 5,11-methanomorphanthridine nucleus reported here. The molecular formula and the spectral correlations make it quite likely that manthidine is a stereoisomer of montanine and coccinine. The intramolecularly bonded hydroxyl of manthidine ($\nu^{CCl_4}$ 3567 cm.$^{-1}$, B 0.39) suggests that the methoxyl and hydroxyl groups are vicinal and *cis*.[35] Since manthidine is not identical with XIV (R = H), XV, or XVI, the structure for further consideration is XVI (OH and $OCH_3$ reversed). Unfortunately, the quantity of manthidine at our disposal did not permit *O*-methylation. Such a methylation should afford *O*-methyl-$\beta$-isocrinamine if these speculations are correct.

Another probable alkaloid of the 5,11-methanomorphanthridine group is brunsvigine whose isolation from *Brunsvigia cooperi* Baker and preliminary characterization have been reported recently.[36] Several years ago we isolated the same alkaloid, together with crinamine and crinine, from *Brunsvigia radulosa* Herb. A mixture melting point determination, kindly performed by Professor Warren in 1954, confirmed the identity of the two materials. The South African workers reported that brunsvigine, $C_{16}H_{17}NO_4$, is isomeric with lycorine and contains the methylenedioxyphenyl group, one trisubstituted double bond, and two vicinal hydroxyl groups which probably are *trans*. It was noted by these workers that brunsvigine differed from the lycorine-type alkaloids because the former resisted dehydration and dihydrobrunsvigine underwent Hofmann degradation with ease.[37] These observations are compatible with the formulation of brunsvigine as XI (OH instead of $OCH_3$), the 2,3-dihydroxy analog of montanine. This is supported by the close correlation between the infrared spectra of brunsvigine and the title compounds in the 1250–1450 cm.$^{-1}$ region.

## EXPERIMENTAL[41]

*Isolation and preliminary characterization of the alkaloids.* Montanine, coccinine, manthidine, and manthine were isolated from *Haemanthus amarylloides* by the procedure reported in an earlier paper.[4] Montanine, coccinine, and manthine were obtained by this method from *H. tigrinus* in 0.10, 0.01, and 0.02% yields, respectively. Each alkaloid was recrystallized to give material of the same melting point, rotation, and infrared spectrum as that reported earlier.

(34) W. C. Wildman and C. J. Kaufman, *J. Am. Chem. Soc.*, **77**, 4807 (1955).

(35) Manthidine also exhibits a very small unassociated band at 3618 cm.$^{-1}$ (B 0.08). This is the only case where both possible forms, bonded and unbonded, were observed.

(36) L. J. Dry, M. Poynton, M. E. Thompson, and F. L. Warren, *J. Chem. Soc.*, 4701 (1958).

(37) Lycorine and its analogs, methylpseudolycorine and galanthine, are readily dehydrated by heat and a trace of alkali to give products containing a new aromatic ring.[38-40] In contrast, dihydrolycorine methiodide is not affected by forcing Hofmann degradation conditions.

(38) J. W. Cook, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.*, 4176 (1954).

(39) H. M. Fales, L. D. Guiffrida, and W. C. Wildman, *J. Am. Chem. Soc.*, **78**, 4145 (1956).

(40) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **78**, 4151 (1956).

(41) All melting points were observed on a Kofler microscope hotstage and are corrected. The boiling points are uncorrected. Unless otherwise noted, rotations were measured by a Rudolph photoelectric spectropolarimeter, model 200 S-80, in chloroform solution using a 2-dm. tube. Ultraviolet spectra were obtained in absolute ethanol solution with a Cary model 11MS spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer model 21 double-beam spectrophotometer in chloroform solution. Hydrogen bonding studies were performed in carbon tetrachloride solution at high dilution using a Beckman Model IR-7 prism-grating spectrophotometer equipped with a scale expansion. Frequency measurements in this region are believed to be accurate to $\pm 2$ wave numbers. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J.

Coccinine (15 mg.) in 3 ml. of 10% hydrochloric acid was recovered in 80% yield after refluxing for 1.5 hr. Ethanolic solutions of either coccinine or montanine containing an excess of selenium dioxide gave no yellow color or precipitate when heated for 45 min. at 80°.

*Montanine methiodide.* A mixture of 67 mg. of montanine-acetone complex and 2 ml. of benzene was treated with 2 ml. of redistilled methyl iodide. A white precipitate formed immediately. The reaction mixture was allowed to stand at room temperature for 15 min. and then was washed twice by decantation with benzene. The dried methiodide weighed 96 mg. (106%), $[\alpha]_D^{25}$ +7.3° (*c* 0.45, water). The crude methiodide melted from 160–165°; upon seeding the melt at 170° with authentic montanine methiodide, m.p. 269–272° dec., $[\alpha]_D^{23}$ +10° (*c* 0.3, water),[42] the melt solidified and finally remelted at 260–263° dec. Recrystallization of the crude methiodide from water afforded 64 mg., m.p. 270–272° dec., $[\alpha]_D^{23}$ +10° (*c* 0.47, water). A sample of crude methiodide prepared in 1956, m.p. 160–165°, was found now to melt at 270–272° dec.

*Coccinine methiodide.* By the method used for the preparation of montanine methiodide 71 mg. of coccinine afforded 110 mg. (105%) of crude methiodide, m.p. 162–170°, $[\alpha]_D^{23}$ −57° (*c* 0.66, water). One recrystallization from water afforded prisms, m.p. 223–224°; reported[4] m.p. 219–220°, $[\alpha]_D^{26}$ −60.5° (*c* 1.41, water).

*Manthidine.* The alkaloid was purified by sublimation at 200° (2 μ) for analysis, m.p. 269–272°; reported[4] m.p. 269–270°.

*Anal.* Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; $OCH_3$, 10.30. Found: C, 67.48; H, 6.06; $OCH_3$, 10.11.

The bulbs (2.36 kg.) of *Brunsvigia radulosa* Herb. were ground and extracted by the process described in a previous paper.[24] The crude alkaloid fraction, 13.76 g. (0.58%), was divided into smaller portions each of which was treated in the following manner. A 2.29-g. portion of the extract was extracted with hot benzene in a Soxhlet apparatus for 14 hr. The residue in the porous cup (0.105 g.) on trituration with ethanol gave 20 mg. of crude lycorine, m.p. 252–257° dec. Upon cooling, the benzene solution deposited 1.2 g. of crude brunsvigine, m.p. 235–244°, which was recrystallized from ethyl acetate, m.p. 242–244°; $[\alpha]_{589}^{24}$ −106.5° (*c* 0.37, chloroform); reported[36] m.p. 243°, $[\alpha]_{589}^{20}$ −76.6° (ethanol).

*Anal.* Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88; mol. wt., 287. Found: C, 67.09; H, 6.04; N, 4.76; mol. wt. (Rast), 290.

*Brunsvigine picrate.* Prepared in ethanol and recrystallized from water, the picrate formed yellow needles, m.p. 195–196° dec.; reported[36] m.p. 190° or 219°.

*Anal.* Calcd. for $C_{16}H_{17}NO_4 \cdot C_6H_3N_3O_7$: C, 51.16; H, 3.90; N, 10.85. Found: C, 51.12; H, 4.09; N, 10.85.

The benzene solution from which the brunsvigine originally precipitated was concentrated and chromatographed on alumina. Elution with 20% (by volume) ethyl acetate in benzene gave 0.62 g. of oil which crystallized upon trituration with ethyl acetate to yield 0.412 g. (0.017%) of crude crinamine, m.p. 193–195°. Continued elution with the same solvents gave 0.254 g. of crude crinine which crystallized on trituration with ethyl acetate, 0.150 g. (0.006%), m.p. 209–210°. Identification of crinamine and crinine was achieved by comparison of infrared spectra and mixture melting point determinations.[43]

(42) The melting point of montanine methiodide is quite dependent on the rate of heating. It has been observed to melt from 252–254° dec.[4] upon slow heating. With more rapid heating the melting point was found to be 269–272° dec. The rotation reported[4] for montanine methiodide is erroneous and should have read +18.4° (*c* 2.01, water) for the determination made at that time. A reexamination of the specific rotation of montanine methiodide with more accurate equipment gave the results cited above and $[\alpha]_D^{23}$ +13° (*c* 1.9, water).

(43) This isolation was performed by Dr. L. H. Mason.

*Permanganate oxidation of montanine and coccinine.* Coccinine (169 mg.) recovered from an Oppenauer oxidation and crude montanine (671 mg.) were combined and dissolved in 40 ml. of dilute hydrochloric acid (*ca.* 1%). The solution was just barely made basic with 10% sodium hydroxide solution. This solution was stirred with a Vibromischer while a solution of 4.5 g. of potassium permanganate in 200 ml. of water was added dropwise over a period of 20 min. The permanganate was not completely reduced at the end of the addition period and the reaction was allowed to stand overnight at room temperature. No permanganate remained at this point. The manganese dioxide was taken into solution by the addition of sulfur dioxide. The clear yellow solution was acidified with a few milliliters of dilute sulfuric acid and extracted with three portions of ethyl acetate. The ethyl acetate solutions were washed once with a small amount of saturated salt solution, dried over magnesium sulfate, filtered and evaporated to leave 134 mg. of yellow oil.

The original aqueous solution from the oxidation was continuously extracted with ether for 18 hr. The ether extract was dried over magnesium sulfate, filtered, and evaporated to leave 53 mg. of yellow oil. The two extracts were combined (188 mg.) and partitioned between dilute sodium bicarbonate solution and ethyl acetate. The bicarbonate extract was washed once with ether, acidified with dilute sulfuric acid, and the solution extracted continuously with ether for 5 hr. The slightly yellow ether extract was dried over magnesium sulfate, filtered, and evaporated to leave 85 mg. of acidic material which was sublimed at 150° (0.4 mm.). The crystals were separated from the oily material to give 26 mg., m.p. 159–176°, of crude hydrastic anhydride.

The crude hydrastic anhydride was triturated with several drops of aqueous ethylamine solution in a sublimation tube. The excess ethylamine and water were driven off at reduced pressure and the residue sublimed at 150° (0.3 mm.). A second sublimation at 130° (0.4 mm.) was carried out to remove traces of brown color, m.p. 156–167°, 18 mg. (3%). One recrystallization from ethanol (95%) gave 15 mg., m.p. 169–170°; a second recrystallization gave 14 mg. of colorless blades, m.p. 169–170°. The mixture melting point with authentic *N*-ethyl hydrastimide (m.p. 169–170°) was 168–169°.

*Dehydrococcinine* (II, R = H). (a) *From coccinine.* A solution of 0.34 g. of potassium metal in anhydrous *t*-butyl alcohol was evaporated to dryness at the aspirator on the steam bath. To the dry, solid *t*-butoxide was added 450 mg. of coccinine (m.p. 162–163°), 800 mg. of fluorenone, and 35 ml. of sodium-dried benzene. A magnetic stirring bar was added and the reaction was put under nitrogen. A dark brown color developed immediately. The reaction mixture was stirred at room temperature for 1.5 hr. At the end of this time the *t*-butoxide was destroyed by addition of water. The color lightened to a yellow. The organic layer was diluted with ether and extracted several times with dilute (*ca.* 3%) potassium hydroxide solution. These combined basic, aqueous solutions were washed twice with ether and acidified to *p*H 7. A precipitate formed and was extracted with ethyl acetate. Evaporation of the dried extract left 159 mg. (35%) of phenolic material which after three recrystallizations from ethyl acetate–cyclohexane and after prolonged drying at 80° (0.05 mm.) to remove occluded ethyl acetate gave white felted needles, m.p. 191–193°; $[\alpha]_{589}$ +40° (*c* 0.60); $\lambda_{max}$ 290 mμ (ε 7050), $\lambda_{inf}$ 232 mμ (ε 11,900); $\lambda_{max}^{Nujol}$ 3257 (NH), 2469 (hydrogen-bonded phenol OH), 1592, 1034, and 927 cm.$^{-1}$.

*Anal.* Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; 1 $OCH_3$, 10.36. Found: C, 68.18; H, 5.99; $OCH_3$, 10.22.

From the organic layer was extracted unchanged coccinine by means of dilute hydrochloric acid. In this way 167 mg. (37%) of crude coccinine was recovered.

(b) *From montanine.* Under conditions identical with those described in (a), 625 mg. of montanine-acetone complex[4]

gave a 60% yield of crude dehydrococcinine, m.p. 180–190°. Four recrystallizations from ethyl acetate–hexane gave felted white needles, m.p. 190.5–192.5°, $[\alpha]_{589}^{22}$ +41° (*c* 0.73); $\lambda_{max}$ 290 mμ (ε 7000), $\lambda_{inf}$ 232 mμ (ε 11,800). In 0.1*N* potassium hydroxide in ethanol the ultraviolet spectrum showed maxima at 248 mμ (ε 13,100) and 297 mμ (ε 8950). The material was identical with that obtained from coccinine, and the mixture melting point was undepressed.

*Anal.* Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68; $OCH_3$, 10.36; (2) active H, 0.67. Found: C, 68.03; H, 5.69; N, 4.65; $OCH_3$, 10.78; active H, 0.67.

A solution of 26 mg. of dehydrococcinine in 20 ml. of xylene was refluxed under nitrogen for 27 hr. The xylene was evaporated under reduced pressure and the residue was recrystallized from ethyl acetate to give 20 mg., m.p. 184–186.5°, $[\alpha]_{589}^{22}$ +47° (*c* 0.77). Therefore, no racemization occurred.

There was no change in the ultraviolet spectrum of dehydrococcinine in 0.1*N* alcoholic hydrochloric acid or after refluxing for 1 hr. with dilute hydrochloric acid (*ca.* 1%).

A solution of 110 mg. of dehydrococcinine in 4 ml. of glacial acetic acid containing 1 drop of 70% perchloric acid was added to 60 mg. of 10% palladium-on-carbon catalyst in 3 ml. of glacial acetic acid which had previously been equilibrated with hydrogen. After 3.5 hr. no hydrogen had been absorbed. The catalyst was not poisoned since the addition of cyclohexene resulted in rapid uptake of hydrogen.

*O,N-Diacetyldehydrococcinine* (II, R = $COCH_3$). Oxococcinine (98 mg.) was dissolved in a few milliliters of dry pyridine to which several drops of acetic anhydride were added. The solution was heated on the steam bath for 30 min., cooled, diluted with 10% potassium carbonate solution, and extracted with chloroform. The dried chloroform extracts were evaporated to leave 107 mg. of an amber-colored glass, $\nu_{max}$ 1761 cm.$^{-1}$ (phenol acetate) and 1639 cm.$^{-1}$ (dialkyl substituted acetamide). The material did not crystallize, decomposed on attempted evaporative distillation at 170° (0.05 mm.), and was insoluble in dilute hydrochloric acid.

*O,N-Dimethyldehydrococcinine* (II, R = $CH_3$). To a solution of 675 mg. of II (R = H) in 10 ml. of methanol was added an excess of distilled ethereal diazomethane. After the mixture had been allowed to stand 2 days, the solvents were removed by evaporation. The residue was dissolved in 2% sulfuric acid and the aqueous solution was washed twice with benzene. The acidic solution was made basic with sodium hydroxide and extracted with chloroform. The extracts were dried over potassium carbonate and evaporated to yield 513 mg. of yellow oil. This material was chromatographed over alumina. Elution with 20% ethyl acetate in benzene afforded 41 mg. of colorless oil which was evaporatively distilled at 100° (7 μ), $[\alpha]_{589}^{24}$ +27° (*c* 0.94); $\lambda_{max}^{C_2H_5OH}$ 288 mμ (ε 6600).

*Anal.* Calcd. for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.59; H, 6.27; N, 4.33.

Elution with 50% ethanol–ethyl acetate gave 281 mg. of more strongly adsorbed materials, probably partially methylated intermediates. Yields of *O,N*-dimethyldehydrococcinine ranged from 14–45%. Purest material was obtained when the non-phenolic product from methylation with diazomethane was reductively methylated with formalin and palladium-on-charcoal catalyst. Under these conditions 350 mg. of dehydrococcinine gave 55 mg. of crystalline *O,N*-dimethyldehydrococcinine, m.p. 100–101°, from ether–hexane, $[\alpha]_{589}^{24}$ +26°, $[\alpha]_{436}^{24}$ +83° (*c* 1.35). The infrared spectrum (potassium bromide) was identical with that found for *O,N*-dimethyldehydrococcinine prepared from oxoisohaemanthamine. A mixture melting point was not depressed.

*O,N-Dimethyldehydrococcinine methine* (III). A solution of 174 mg. of *O,N*-dimethyldehydrococcinine in 5 ml. of acetone was treated with an excess of methyl iodide and heated briefly. The acetone and excess methyl iodide were removed by evaporation, leaving 180 mg. of yellow oil which resisted all attempts at crystallization. This methiodide was converted to its methohydroxide with freshly prepared silver oxide, concentrated to a viscous oil, and then heated at 100° (1 mm.) for 30 min. The reaction products were extracted with benzene. The benzene extract was washed with water and shaken three times with 2% hydrochloric acid. The acidic solution was made basic with sodium hydroxide solution and extracted three times with chloroform. The extracts were combined, dried over potassium carbonate, and concentrated to 130 mg. of colorless oil which was chromatographed on 10 g. of Merck aluminum oxide. Elution with benzene afforded 85 mg. of methine base (III) which was distilled at 145–155° (5 μ), $[\alpha]_{589}^{25}$ −380° (*c* 0.71, ethanol). The ultraviolet spectrum showed maxima at 265 mμ (ε 12,000) and 293 mμ (ε 10,500).

*Anal.* Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.50; H, 6.90; N, 4.08.

*Dihydro-O,N-dimethyldehydrococcinine methine* (IV). A solution of 22 mg. of III in 5 ml. of ethanol was hydrogenated at atmospheric pressure and room temperature in the presence of 20 mg. of 10% palladium-on-charcoal. The reaction stopped in 20 min. when the sample had absorbed 106% of the theoretical amount of hydrogen. The filtered solution was concentrated to a yellow oil. The oil was dissolved in 2% hydrochloric acid and washed twice with ether. Treatment of the aqueous solution with sodium hydroxide and extraction with benzene gave 19 mg. of colorless oil. For analysis, a sample was distilled at 150–160° (7 μ). The ultraviolet spectrum showed a maximum at 287 mμ (ε 6900) and a shoulder at 233 mμ (ε 13,000).

*Anal.* Calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33; N, 4.08. Found: C, 70.08; H, 7.60; N, 4.08.

*3-Hydroxy-6,12-methano-2-methoxy-9,10-methylenedioxy-5,6,12,13-tetrahydro[7H]dibenz[c,f]azocine* (VII, R = H). To a solution of 80 mg. of dehydrococcinine (II) in 3 ml. of 2*N* hydrochloric acid was added 0.2 ml. of 38% formaldehyde solution. The mixture was heated for 30 min. on the steam bath. At the end of this time, the hydrochloride of the product appeared as fine crystals. The hydrochloride was collected by filtration, and several recrystallizations from ethanol gave fine prisms which darkened from 245° and finally decomposed at 255–260°.

*Anal.* Calcd. for $C_{18}H_{17}NO_4 \cdot HCl$: C, 62.15; H, 5.21; N, 4.02; Cl, 10.19. Found: C, 61.99; H, 5.11; N, 4.05; Cl, 10.15.

The aqueous solution of hydrochloride was combined with the original filtrate, made basic with sodium bicarbonate and extracted with chloroform. The chloroform extracts were dried over anhydrous sodium sulfate. Evaporation of the solvents left 70 mg. of amorphous powder which could not be crystallized.

*2,3-Dimethoxy-6,12-methano-9,10-methylenedioxy-5,6,12,13-tetrahydro[7H]dibenz[c,f]azocine* (VII, R = $CH_3$). To a solution of 70 mg. of VII (R = H) in 5 ml. of methanol was added an ethereal solution of diazomethane. The reaction mixture was allowed to stand overnight. The solvents were evaporated, and the slightly yellow residue was dissolved in 10 ml. of 3% hydrochloric acid. The acidic solution was washed twice with ether, made basic with sodium hydroxide solution, and extracted with chloroform. The extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent left 55 mg. of oil which crystallized upon trituration with ether. This was combined with 50 mg. from a similar run and chromatographed on Merck aluminum oxide. Elution with 20% ethyl acetate in benzene yielded 73 mg. of product. Three recrystallizations from ether gave colorless plates. After drying at 60° for 3 hr. under reduced pressure, the material melted at 126–131°. Further recrystallization from ether did not improve the melting point, $[\alpha]_{589}^{23}$ +41°, $[\alpha]_{436}^{23}$ + 119° (*c* 0.89). The ultraviolet spectrum showed at maxima 285 mμ (ε 6900) and 297 mμ (ε 7600). The differences between this spectrum and those of all other diphenylmethane derivatives (*e.g.*, II, R = $CH_3$) may be attributed to π-bond overlap between the two aromatic

rings which are forced into close proximity by the rigid ring fusion.

*Anal.* Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31; $OCH_3$, 19.07. Found: C, 70.07; H, 5.85; N, 4.24; $OCH_3$, 19.82.

*3,4-Dimethoxy-3',4'-methylenedioxybenzophenone* (V). To a solution of 18 g. of piperonyl chloride and 13 g. of veratrole in 50 ml. of carbon disulfide, 20 g. of finely powdered aluminum chloride was added gradually. The reaction mixture was refluxed on the steam bath for 2 hr. The slightly yellow carbon disulfide was decanted. After ice and hydrochloric acid had been added to the residue, the product was extracted with benzene. The benzene extracts were washed several times with 3% sodium hydroxide solution and water and then dried over anhydrous potassium carbonate. Evaporation of the solvents left 16 g. (58%) of a yellow crystalline mass which was purified by chromatography on acid-washed alumina and recrystallized from benzene to give 5.3 g. of colorless prisms, m.p. 164–165°. The ultraviolet spectrum showed maxima at 235 mμ (ε 22,400), 281 mμ (ε 9300), and 317 mμ (ε 15,000). For analysis, a sample was sublimed at 160–165° (5 μ).

*Anal.* Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93; $OCH_3$, 21.66. Found: C, 67.25; H, 4.95; $OCH_3$, 21.97.

*3,4-Dimethoxy-3',4'-methylenedioxybenzhydrol* (VI, X = OH). To a stirred suspension of 2 g. of 3,4-dimethoxy-3',4'-methylenedioxybenzophenone in 50 ml. of methanol was added 0.4 g. of sodium borohydride in small portions. After 1 hr., a colorless, clear solution was obtained. The excess of sodium borohydride was destroyed with 3% hydrochloric acid, and the reaction mixture was concentrated to a colorless oil by evaporation. The oily residue was extracted with chloroform, and the extracts were washed with water, dried over sodium sulfate, and concentrated to 2.0 g. of oil which crystallized on trituration with methanol. Recrystallization from methanol gave fine needles, m.p. 105°, $\lambda_{max}^{C_2H_5OH}$ 232 (ε 11,700) and 286 mμ (ε 6800).

*Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.67; H, 5.68.

*3,4-Dimethoxyphenyl-3',4'-methylenedioxyphenylacetonitrile* (VI, X = CN). To a solution of 2.0 g. of benzhydrol (VI, X = OH) in 15 ml. of dry benzene was added dropwise 6 ml. of thionyl chloride. The reaction mixture was heated on the steam bath for 2 hr. The benzene and excess thionyl chloride were removed by evaporation. The residue, 2.0 g. of slightly orange oil, was mixed with 0.6 g. of cuprous cyanide (dried at 110°, 1 mm.) and immersed in an oil bath preheated to 180°. After 1 hr., the flask was removed and cooled. The product was dissolved in chloroform, and the solution was filtered. The filtrate was concentrated to an oil which was redissolved in benzene and chromatographed over acid-washed alumina. Elution with benzene afforded 1.07 g. of colorless oil. For analysis, a sample was distilled at 160–170° (7 μ).

*Anal.* Calcd. for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71; $OCH_3$, 20.87. Found: C, 68.79; H, 5.13; N, 4.74; $OCH_3$, 21.12.

*2-(3,4-Dimethoxyphenyl)-2-(3',4'-methylenedioxyphenyl)-ethylamine* (VI, X = $CH_2NH_2$). A solution of 2.0 g. of VI (X = CN) in 10 ml. of tetrahydrofuran was added to a solution of 2.0 g. of lithium aluminum hydride in 30 ml. of tetrahydrofuran. The mixture was stirred vigorously and refluxed on the steam bath for 24 hr. Decomposition of excess hydride was effected by the addition of ethyl acetate and sodium hydroxide solution. The precipitate that had formed was separated by filtration and washed with tetrahydrofuran. After evaporation of the tetrahydrofuran, the residue was dissolved in 3% hydrochloric acid. The aqueous solutions were washed once with benzene and once with ether, then made basic with sodium hydroxide solution and extracted with chloroform. After drying over sodium sulfate, the solvents were evaporated to give 1.0 g. of yellow oil which could not be crystallized. The *3,5-dinitrobenzoate* of this amine formed yellow prisms from methanol-benzene, m.p. 193–194°.

*Anal.* Calcd. for $C_{24}H_{21}N_3O_9$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.41; H, 4.37; N, 8.32.

(±)-*2,3-Dimethoxy-6,12-methano-9,10-methylenedioxy-5,6-12,13-tetrahydro[7H]dibenz[c,f]azocine* (VII, R = $CH_3$). (a) To a solution of 0.5 g. of VI (X = $CH_2NH_2$) and 0.2 g. of sodium carbonate in aqueous ethanol was added dropwise 1 ml. of 38% formaldehyde solution. The clear solution deposited an oil, and the reaction was completed by heating the mixture for 30 min. on the steam bath. The oil was extracted with benzene, and the extracts were washed several times with water. Evaporation of the solvents left 0.5 g. of a yellow oil which was dissolved in 5 ml. of 6*N* hydrochloric acid and heated for 1.5 hr. The acidic solution was washed with ether, made basic, and extracted with chloroform. The extracts were dried over sodium sulfate. Evaporation of the solvent yielded 0.4 g. of an oil which when triturated with ether solidified and was recrystallized from ether to give colorless prisms, m.p. 142–145°. Several recrystallizations did not improve the melting point. The ultraviolet absorption spectrum showed maxima at 285 mμ (ε 6900) and 297 mμ (ε 7400); $pK_a$ 7.04. The infrared spectra (both in chloroform and potassium bromide) were identical with those of the corresponding product obtained from montanine.

*Anal.* Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31; $OCH_3$, 19.07. Found: C, 70.24; H, 5.83; N, 4.37; $OCH_3$, 19.40.

The *hydrochloride* was prepared by the addition of ethanolic hydrochloric acid to a solution of the free base in ethanol, and the solid was recrystallized from ethanol to yield fine prisms which darkened from 225–235° and finally decomposed at 254°.

*Anal.* Calcd. for $C_{19}H_{19}NO_4 \cdot HCl$: C, 63.07; H, 5.57; N, 3.87; Cl, 9.79. Found: C, 62.90; H, 5.79; N, 3.77; Cl, 9.40.

(b) A solution of 70 mg. of VI (X = $CH_2NH_2$) in 3 ml. of 2*N* hydrochloric acid was treated with 0.2 ml. of 38% formaldehyde solution and heated for 50 min. on the steam bath. The reaction mixture was diluted with water, made basic with sodium hydroxide solution, and extracted with chloroform. The extracts were dried over sodium sulfate and evaporated to yield 65 mg. of an oil which solidified upon trituration with ether. Recrystallization from ether gave colorless prisms, m.p. 142–145°. The infrared spectrum of this sample was identical with that of the specimen obtained in (a) and the mixture melting point was not depressed.

(+) *and* (−)-*2,3-Dimethoxy-6,12-methano-9,10-methylenedioxy-5,6,12,13-tetrahydro [7H]dibenz[c,f]azocine.* To a solution of 120 mg. (0.33 mmole) of dibenzoyl-*d*-tartaric acid in 10 ml. of ether was added a solution of 108 mg. (0.33 mmole) of racemic V (R = $CH_3$) in 20 ml. of ether. The mixture was warmed for a few minutes. The precipitate was collected by filtration and washed thoroughly with three 20-ml. portions of ether. The crystalline precipitate was recrystallized six times from ethanol. Finally, the dibenzoyl-*d*-tartrate of the (+)-base was obtained as prisms, m.p. 145–146° dec. An aqueous solution of this salt was made basic with sodium hydroxide solution and extracted with chloroform. The extracts were dried over anhydrous sodium sulfate and evaporated to a sirup which crystallized upon trituration with ether. Two recrystallizations gave 26 mg. of colorless plates, m.p. 127–132°; $[\alpha]_{589}^{23}$ +40°, $[\alpha]_{436}^{23}$ +115° (*c* 0.870). A mixture melting point with VII (R = $CH_3$) obtained from dehydrococcinine was not depressed.

The dibenzoyl-*d*-tartrate of the (−)-base was obtained from the first mother liquor from recrystallizations of the racemic salt. The filtrate was concentrated to a sirup which crystallized upon trituration with a small amount of acetone. Two recrystallizations from acetone gave fine needles, m.p. 145–146° dec. The aqueous solution of this salt was made basic with sodium hydroxide solution, extracted with chloroform, dried over anhydrous sodium sulfate and evaporated

to a sirup which crystallized from ether. Two recrystallizations from ether yielded 28 mg. of the (−)-base as plates, m.p. 127–132°; $[\alpha]_{589}^{23}$ −39°, $[\alpha]_{436}^{23}$ −114° (*c* 0.910).

*Isohaemanthamine* (IX). (a) A chilled solution of 600 mg. of haemanthamine in 10 ml. of dry pyridine was treated with 0.5 ml. of methanesulfonyl chloride and allowed to stand at 0° overnight. The mixture was poured into 50 ml. of water containing 6 g. of sodium bicarbonate. The solution was again allowed to stand overnight and then extracted with chloroform. The extracts were dried over magnesium sulfate. Evaporation of the solvent and crystallization of the residue from ethyl acetate furnished 540 mg. (90%) of isohaemanthamine, m.p. 248–256°. One recrystallization from ethanol raised the melting point to 258–260°; $[\alpha]_{589}^{24}$ −72.8°, $[\alpha]_{436}^{24}$ −211° (*c* 0.79).

*Anal.* Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; $OCH_3$, 10.31. Found: C, 67.70; H, 6.31; $OCH_3$, 10.71.

(b) Isohaemanthamine also was obtained in low yield without the use of pyridine. A solution of 600 mg. of haemanthamine was added to a finely dispersed suspension of 200 mg. of potassium in benzene and stirred for 15 min.; 0.20 ml. of methanesulfonyl chloride was added at 0°, and the mixture was stirred for 1 hr. The excess potassium was destroyed with wet ether, and the organic layer was washed with water and dried. The residue (400 mg.) obtained on evaporation was passed twice over alumina to yield 274 mg. (46%) of recovered haemanthamine and 65 mg. (11%) of isohaemanthamine which was identical with that obtained above.

Neither ethanesulfonyl chloride nor *p*-toluenesulfonyl chloride was effective in the conversion of haemanthamine to IX.

Isohaemanthamine was unaffected by lithium aluminum hydride in tetrahydrofuran. Isohaemanthamine, treated with methanesulfonyl chloride under the above conditions, was recovered in 20% yield and was the only basic product obtained.

Dihydrohaemanthamine was recovered unchanged in 78% yield from methanesulfonyl chloride and pyridine under the above conditions.

*Dihydroisohaemanthamine.* A solution of 132 mg. of isohaemanthamine in 50 ml. of 5% methanol in ethyl acetate was added to 50 mg. of prereduced platinum oxide catalyst and stirred in the presence of hydrogen overnight. The theoretical amount of hydrogen was absorbed. The solution was filtered and evaporated to dryness. The residue was acidified with dilute sulfuric acid and extracted with benzene. The aqueous raffinate was made basic with sodium hydroxide, extracted with chloroform, and the extracts dried and evaporated. The residue (135 mg.) was crystallized and recrystallized from ethyl acetate to give colorless prisms which melted at 175–176° and immediately recrystallized as fine needles, m.p. 184–185°; $[\alpha]_{589}^{24}$ +26.1°, $[\alpha]_{436}^{24}$ +38.7° (*c* 0.36).

*Anal.* Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; $OCH_3$, 10.23. Found: C, 67.34; H, 6.92; $OCH_3$, 10.26.

Dihydroisohaemanthamine failed to react with activated manganese dioxide in chloroform when stirred overnight.

*Oxoisohaemanthamine* (XIII). A solution of 300 mg. of isohaemanthamine in 50 ml. of chloroform was treated with 2 g. of activated manganese dioxide and stirred for 5 hr. The manganese dioxide was removed by filtration. Evaporation of the chloroform left an oil which was chromatographed on ethyl acetate–washed alumina. Elution with ethyl acetate gave 234 mg. (78%) of a clear glass which showed no absorption from 5000–3100 $cm.^{-1}$ but a strong band at 1681 $cm.^{-1}$ in the infrared. A negative Zimmerman test was obtained with this ketone.

The *hydroperchlorate* of XIII was prepared in aqueous perchloric acid and recrystallized from dilute acid, forming hydrated plates which evolved gas at 170° and finally melted at 196–198°.

*Anal.* Calcd. for $C_{17}H_{17}NO_4 \cdot HClO_4 \cdot H_2O$: C, 48.87; H, 4.80; neut. equiv., 418. Found: C, 49.33; H, 5.29; neut. equiv., 419.

Because of the unsatisfactory nature of this analysis, the sample was dried thoroughly at 130° (vac.), and an anhydrous sample was obtained.

*Anal.* Calcd. for $C_{17}H_{17}NO_4 \cdot HClO_4$: C, 51.07; H, 4.54. Found: C, 50.93; H, 4.92.

The free base, which was recovered from the perchlorate by treatment with aqueous bicarbonate, remained noncrystalline but showed an infrared spectrum identical with that of starting material. This was distilled at 120° (1 $\mu$) for analysis and characterization, $[\alpha]_{589}^{258}$ −167°, $[\alpha]_{436}^{25}$ −177° (*c* 0.91); $\lambda_{max}^{C_2H_5OH}$ 234 m$\mu$ ($\epsilon$ 18,500), 298 m$\mu$ ($\epsilon$ 6390). A differential ultraviolet spectrum (the spectrum of XIII less that of IX) showed $\lambda_{max}^{C_2H_5OH}$ 230 m$\mu$ ($\epsilon$ 16,450), 309 m$\mu$ ($\epsilon$ 2970).

*Anal.* Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; neut. equiv., 299. Found: C, 68.06; H, 5.83; neut. equiv. 296.

A *2,4-dinitrophenylhydrazone* of XIII was obtained by combining 65 mg. of base with 50 mg. of 2,4-dinitrophenylhydrazine in 8 ml. of ethanol with 5 drops of 12*N* hydrochloric acid. A precipitate formed after the solution was refluxed for 5 min. This was washed with water and finally neutralized with ammonia, collected, and dried. After recrystallization from chloroform-ethanol, red-orange prisms were obtained, m.p. 232–234°, $\lambda_{max}^{C_2H_5OH}$ 253 m$\mu$ ($\epsilon$ 17,100), 293 m$\mu$ ($\epsilon$ 11,700), 380 m$\mu$ ($\epsilon$ 31,200).

*Anal.* Calcd. for $C_{23}H_{21}N_5O_7$: C, 57.62; H, 4.42; $OCH_3$, 6.47. Found: C, 57.48; H, 4.65; $OCH_3$, 6.47.

This compound depressed the melting point of the corresponding derivative of oxoisocrinamine.

*O,N-Dimethyldehydrococcinine* (II, R = $CH_3$). A solution of 210 mg. of XIII in acetone was allowed to stand overnight with an excess of methyl iodide. The solvents were evaporated, and the amorphous residue was dissolved in water and washed with chloroform to remove any unchanged base. The aqueous solution (75 ml.) was treated with 15 ml. of 50% sodium hydroxide and heated on the steam bath for 1 hr. Addition of Dry Ice to the solution caused the free aminophenol to precipitate. The precipitate was removed by filtration, and the solution was extracted with chloroform. The chloroform extracts were combined with the first precipitate. The chloroform solution was dried and evaporated to yield 128 mg. of a clear, amorphous product (XVIII) which gave an intense red color with diazotized sulfanilic acid, $[\alpha]_{589}^{25}$ +61° (*c* 1.25). The same aminophenol (as determined by infrared spectrum) was obtained when oxoisocrinamine (XVII) was substituted for oxoisohaemanthamine under the above conditions.

A methanolic solution of XVIII was treated with several portions of distilled ethereal diazomethane (from a total of 6 g. of *N*-methyl-*N*-nitroso-*N'*-nitroguanidine) over a 2-day period. The ether was evaporated and the residue was taken up in chloroform, washed with alkali, and dried over magnesium sulfate. Upon evaporation and trituration with hexane-ether, 85 mg. (38% overall) of crystalline product was obtained, m.p. 95–101°. Recrystallization from hexane and sublimation at 95° (1 $\mu$) produced irregular prisms, m.p. 100–101°, $[\alpha]_{589}^{25}$ +26°, $[\alpha]_{436}^{25}$ +76° (*c* 0.90).

*Anal.* Calcd. for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; $OCH_3$, 18.99; $NCH_3$, 4.59; neut. equiv., 327. Found: C, 69.43; H, 6.49; $OCH_3$, 19.83; $NCH_3$, 5.01; neut. equiv., 321.

This compound showed infrared (potassium bromide) and ultraviolet spectra identical with those of *O,N*-dimethyldehydrococcinine (II, R = $CH_3$) obtained from montanine and coccinine. The optical rotatory dispersion curves of the two specimens were superimposable. A mixture melting point of the two was not depressed.

*Epiisohaemanthamine* (XIV, R = H). A solution of 572 mg. of oxoisohaemanthamine (XIII) in 25 ml. of methanol was treated portionwise with 500 mg. of sodium borohydride at 0°. The solution was allowed to stand at room temperature for 1 hr., decomposed with acetic acid, and made strongly basic. Extraction with chloroform and evaporation

of the extracts left 570 mg. of an oil which was chromatographed over basic alumina with 2% methanol in chloroform. A total of 535 mg. (94%) of epiisohaemanthamine was obtained as a viscous oil which resisted crystallization. A sample was distilled at 120° (5 $\mu$), but the resulting oil proved to be hygroscopic, and an analysis corresponding to a hemihydrate was obtained, $[\alpha]_{589}^{25}$ −120°, $[\alpha]_{436}^{25}$ −318° (*c* 0.96).

*Anal.* Calcd. for $C_{17}H_{19}NO_4 \cdot 1/2\ H_2O$: C, 65.85; H, 6.50. Found: C, 65.54; H, 6.45.

The distilled oil showed a strongly bonded intramolecular hydroxyl stretching band at 3566 cm.$^{-1}$ at high dilution in carbon tetrachloride. It was very soluble in this solvent, in contrast to isohaemanthamine.

The *picrate* was precipitated quantitatively from ethanol as very insoluble orange tablets which were recrystallized from dimethylformamide-water, m.p. 270–275° dec.

*Anal.* Calcd. for $C_{17}H_{19}NO_4 \cdot C_6H_3N_3O_7$: C, 52.08; H, 4.18; N, 10.56. Found: C, 52.29; H, 4.36; N, 10.81.

A solution of 30 mg. of XIV was stirred with 1.5 g. of activated manganese dioxide in chloroform overnight. The residue on evaporation was rendered acidic and extracted with benzene. The aqueous solution was made basic with ammonia, extracted with chloroform, and the solvent was evaporated, leaving 20 mg. of an oil which was identical in infrared spectrum with oxoisohaemanthamine and contained no oxoisocrinamine by the same criterion.

*α- and β-Isocrinamine.* Under the same conditions that were used in the conversion of haemanthamine to isohaemanthamine, 300 mg. of crinamine furnished 234 mg. of an oil. Chromatography on ethyl acetate–deactivated alumina with 10% benzene in ethyl acetate and then 3% ethanol in ethyl acetate produced 106 mg. (35%) of α-isocrinamine (XII), followed by 96 mg. (32%) of β-isocrinamine (XVI).

The α-isocrinamine formed ill-defined, hydrated crystals, m.p. 95–105°, which resisted efficient recrystallization but were evaporatively distilled at 150° (5 $\mu$) for analysis.

*Anal.* Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; neut. equiv., 301. Found: C, 67.80; H, 6.27; neut. equiv., 303.

Proof of the purity of this product was obtained by the formation of a picrate, m.p. 198–200°, $[\alpha]_{589}^{24}$ −75°, $[\alpha]_{500}^{24}$ −124° (*c* 0.25, 50% aqueous dimethylformamide).

*Anal.* Calcd. for $C_{17}H_{19}NO_4 \cdot C_6H_3N_3O_7$: C, 52.08; H, 4.18; N, 10.56. Found: C, 51.87; H, 4.41; N, 10.45.

A sample of the free base, which was recovered from the picrate by passage over alumina in 2% methanol in chloroform, showed an infrared spectrum identical with starting material. The free base showed $[\alpha]^{24}589$ −194°, $[\alpha]_{436}^{24}$ −461° (*c* 1.1).

The β-isocrinamine was easily recrystallized from ethyl acetate as tablets, m.p. 201–202°, $[\alpha]_{589}^{24}$ −104°, $[\alpha]_{436}^{24}$ −282° (*c* 0.3).

*Anal.* Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; neut. equiv., 301. Found: C, 67.96; H, 6.29; neut. equiv., 297.

The α-isomer exhibited a free hydroxyl stretching band at 3607 cm.$^{-1}$ in carbon tetrachloride at high dilution, while the β-isomer possessed only an intramolecular bonded band at 3570 cm.$^{-1}$.

Dihydrocrinamine was recovered unchanged in 47% yield from methanesulfonyl chloride and pyridine under the above conditions.

*Oxoisocrinamine* (XVII). (a) A solution of 25 mg. of either α- or β-isocrinamine was combined with 300 mg. of manganese dioxide and stirred for 5 hr. Infrared spectra indicated that both alcohols had been converted to the same α,β-unsaturated ketone, $\nu_{max}^{CHCl_3}$ 1667 cm.$^{-1}$. Both samples were chromatographed over ethyl acetate–deactivated alumina with 50% benzene in ethyl acetate and crystallized from ethyl acetate as birefringent prisms, m.p. 165–170°, $[\alpha]_{589}^{25}$ −150°, $[\alpha]_{436}^{25}$ −183° (*c* 0.72); $\lambda_{max}^{C_2H_5OH}$ 228 mμ (ε 19,900), 298 mμ (ε 1660). A differential ultraviolet spectrum between XVII and isocrinamine exhibited $\lambda_{max}^{C_2H_5OH}$ 229 mμ (ε 16,100), 309 mμ (ε 2930).

*Anal.* Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; neut. equiv., 299. Found: C, 68.29; H, 5.77; neut. equiv., 299.

(b) Oxoisocrinamine also was obtained when 510 mg. of oxoisohaemanthamine (XIII) was stirred in benzene with potassium *t*-butoxide (prepared from 300 mg. of potassium which had been dissolved in *t*-butyl alcohol and aspirated to dryness). After 1 hr. the solution was treated with water, and the free base was extracted with additional benzene. Evaporation of the solvent left 310 mg. of ketone, m.p. 165–170°, identical with authentic oxoisocrinamine.

A similar epimerization occurred, in one case, when a solution of isohaemanthamine was allowed to stir for 48 hr. at *ca.* 40° with manganese dioxide.

A *2,4-dinitrophenylhydrazone* of oxoisocrinamine was prepared by the same technique as that used for oxoisohaemanthamine. The compound formed bright orange needles from aqueous dimethylformamide, m.p. 275–277°, $\lambda_{max}^{C_2H_5OH}$ 254 mμ (ε 18,000), 294 mμ (ε 13,600), 385 mμ (ε 32,600).

*Anal.* Calcd. for $C_{23}H_{21}N_5O_7$: C, 57.62; H, 4.42; $OCH_3$, 6.47. Found: C, 57.46; H, 4.46; $OCH_3$, 6.65.

*Manthine* (X). (a) *From haemanthamine:* A solution of 400 mg. of haemanthamine in pyridine was treated at 0° with 0.4 ml. of methanesulfonyl chloride in 6 ml. of pyridine and kept at 0° overnight. After standing at 25° for 1 hr., the solution was added to an ice-cold solution of sodium methoxide prepared from the addition of 3 g. of sodium hydride to 40 ml. of methanol. After remaining at 0° for 10 min., the solution was warmed momentarily on the steam bath, poured into 500 ml. of water, and extracted with chloroform. The extracts were dried and evaporated to give 208 mg. of an oil which was chromatographed over ethyl acetate–washed alumina. Elution with 10% ethyl acetate in benzene yielded 143 mg. (34%) of crystalline product, m.p. 115–116° alone or when mixed with authentic manthine. The infrared spectra (potassium bromide) of the product and authentic manthine were identical, $[\alpha]_{589}^{24}$ −80°, $[\alpha]_{436}^{24}$ −230° (*c* 0.51); reported[4] $[\alpha]_{589}^{24}$ −78°, $[\alpha]_{43}^{24}$ −214° (*c* 0.53).

(b) *From isohaemanthamine:* A solution of 305 mg. of isohaemanthamine was added to a fine suspension of 275 mg. of potassium in benzene and stirred for 15 min. A solution of 190 mg. of methyl *p*-toluenesulfonate was added and the mixture was stirred for 3 hr. at room temperature. The mixture was decomposed with ethanol and dilute hydrochloric acid, and the neutral compounds were extracted into benzene. The aqueous layer was made basic with sodium hydroxide, extracted with benzene, and the extracts were evaporated, leaving 197 mg. of an oil. Chromatography over ethyl acetate–deactivated alumina as above yielded 78 mg. (24%) of manthine, m.p. 114–116°, which was identical with that obtained above. Further elution with 10% methanol in ethyl acetate produced 42 mg. (14%) of recovered isohaemanthamine.

(c) *From montanine:* By the procedure described for the conversion of isohaemanthamine to manthine, 300 mg. of montanine was treated with 275 mg. of potassium and 190 mg. of methyl *p*-toluenesulfonate. The reaction product was chromatographed on 15 g. of Merck aluminum oxide. Elution with 30% ethyl acetate in benzene afforded 55 mg. of colorless oil which crystallized on trituration with ether. Two recrystallizations from hexane gave 36 mg. of pure manthine, m.p. 114–116°; $[\alpha]_{589}^{25}$ −80°, $[\alpha]_{436}^{25}$ −218° (*c* 0.58). A mixture melting point with authentic manthine was undepressed. The infrared spectra (potassium bromide) of the product and manthine were identical.

*Anal.* Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; 2 $OCH_3$, 19.68. Found: C, 68.68; H, 6.60; $OCH_3$, 19.18.

*O-Methylcoccinine.* (a) *From coccinine:* Treatment of 300 mg. of coccinine with 275 mg. of potassium, followed by 190 mg. of methyl *p*-toluenesulfonate provided 130 mg. of crude product which was chromatographed on 15 g. of Merck aluminum oxide. Elution with 30% ethyl acetate in benzene afforded 23 mg. of colorless oil which crystallized on trituration with ether. Sublimation and recrystallization

from ether gave pure *O*-methylcoccinine, m.p. 122–126°; $[\alpha]^{25}_{589}$ − 131°, $[\alpha]^{25}_{436}$ −342° (*c* 0.36).

*Anal.* Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.45; H, 6.81; N, 4.45.

(b) *From epiisohaemanthamine:* A solution of 200 mg. of epiisohaemanthamine (XIV, R = H) in benzene was added to a dispersion of 250 mg. of potassium and finally was treated with 150 mg. of methyl *p*-toluenesulfonate, as in the *O*-methylation of isohaemanthamine. A 150-mg. yield of crude product was chromatographed on alumina with ethyl acetate, producing 75 mg. of crystalline *O*-methylcoccinine which was sublimed at 150° (5 μ) and recrystallized from a small amount of ether, m.p. 122–123° alone or on admixture with *O*-methylcoccinine derived from the *O*-methylation of coccinine. The infrared spectra (potassium bromide) of the two compounds also were identical. Subsequent elution with 20% methanol in ethyl acetate produced a trace of recovered epiisohaemanthamine.

*O-Methyl-α-isocrinamine* (XII, $OCH_3$ instead of OH). (a) *From crinamine:* A solution of 120 mg. of crinamine in 10 ml. of pyridine was treated with 0.20 ml. of methanesulfonyl chloride and finally with sodium methoxide in methanol under the conditions used in the conversion of haemanthamine to manthine. Chromatography of the crude reaction product on alumina with ethyl acetate produced 13 mg. (11%) of crystals, m.p. 171–172° (unchanged on crystallization from ethyl acetate). A mixture melting point with authentic *O*-methyl-α-isocrinamine prepared below was not depressed, and the infrared spectra (potassium bromide) were identical.

*Anal.* Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; $OCH_3$, 19.68. Found: C, 68.61; H, 6.43; $OCH_3$, 19.55.

(b) *From α-isocrinamine:* A benzene solution of 150 mg. of α-isocrinamine was combined with 180 mg. of potassium dispersed in benzene and 110 mg. of methyl *p*-toluenesulfonate under the conditions employed in the conversion of isohaemanthamine to manthine. A yield of 57 mg. of crude product possessing the correct infrared spectrum was obtained, but after chromatography on alumina this was reduced to 28 mg. (18%) of crystalline product, m.p. 171–172° alone or on admixture with that obtained above.

*O-Methyl-β-isocrinamine* (XVI, $OCH_3$ instead of OH). Methylation of 115 mg. of β-isocrinamine (XVI) by the method described previously gave 58 mg. of crude product. Chromatography on aluminum oxide and elution with 50% ethyl acetate in benzene gave 20 mg. of the methyl ether which was crystallized from ether, 15 mg., m.p. 155–156°; $[\alpha]^{24}_{589}$ −70°, $[\alpha]^{24}_{436}$ −203° (*c* 0.26).

*Anal.* Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; 2 $OCH_3$, 19.68. Found: C, 68.67; H, 6.91; $OCH_3$, 19.83.

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

# Naturally Occurring Oxygen Heterocyclics. VII.[1] The Structure of Mammein.[2,3]

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Degradation experiments are reported which demonstrate that mammein, an insecticidal principle of *Mammea americana* L., is 4-*n*-propyl-5,7-dihydroxy-6-isopentenyl-8-isovalerylcoumarin (I).

In an earlier paper[5] there was reported the characterization of some of the functional groups of mammein, a crystalline insecticidal principle which had been isolated earlier from *Mammea americana* L. by Morris and Pagan.[6] Its empirical formula was established[5] as $C_{22}H_{28}O_5$ and of the five oxygen atoms, two were shown to be present as phenolic hydroxyl groups, two form part of a lactone system (possibly in a coumarin) and the remaining one was assumed to exist as a carbonyl function on the basis of infrared evidence. Furthermore, the presence of an isopentenyl system, $(CH_3)_2C{=}CHC$, was demonstrated by ozonization and hydrogenation experiments.

The initial characterization studies[5] indicated that mammein was very sensitive towards alkali. Under mild conditions, mammein was isomerized irreversibly to isomammein, while more severe conditions resulted in rupture of the molecule. The present paper is concerned with a detailed examination of the behavior of mammein and some of its transformation products towards alkaline reagents and this has led to the complete elucidation of the structure of mammein. For the sake of simplicity, the subsequent discussion will be presented in terms of the expression I for mammein.

Hydrogenation[5] of mammein (I) results in the facile uptake of one equivalent of hydrogen with the formation of dihydromammein (II), whose ultraviolet absorption spectrum was very similar to that of the parent (I), thus showing that the double bond was not conjugated with the main chromophoric system. When dihydromammein (II) was heated with 5% aqueous alkali and the steam volatile constituents collected, there was isolated up to 88% of methyl *n*-propyl ketone (IV) and 93% of volatile acid. Esterification and

(1) Paper VI. R. A. Finnegan and C. Djerassi, *Tetrahedron Letters*, **No. 13**, 11 (1959).

(2) For preliminary communication see C. Djerassi, E. J. Eisenbraun, R. A. Finnegan, and B. Gilbert, *Tetrahedron Letters*, **No. 1**, 10 (1959).

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(5) C. Djerassi, E. J. Eisenbraun, B. Gilbert, A. J. Lemin, S. P. Marfey, and M. P. Morris, *J. Am. Chem. Soc.*, **80**, 3686 (1958).

(6) M. P. Morris and C. Pagan, *J. Am. Chem. Soc.*, **75**, 1489 (1953).