Dihydrotazettine Methine, an Unusual Noncoplanar Phenylcyclohexene

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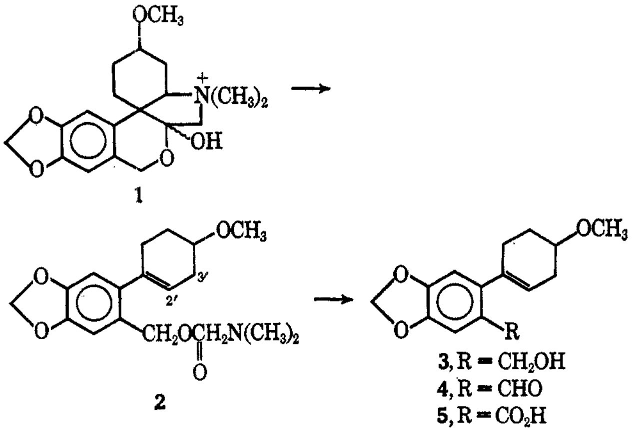
The structure of dihydrotazettine methine must be corrected to **2**, in which steric crowding prevents a planar conformation and conjugation. The derivative alcohol **3** displays a strong hydrogen bond forming a ten-membered ring. Acid treatment converts **2** into the tetrahydrofluorene **11**, and the aldehyde **4** into the dihydroisofluorene **12**. Performic acid converts the acid **5** into the lactones **15** and **16**. In the mass spectra of these compounds, some fragmentation routes apparently correspond to these cyclizations.

During the brief period in which the chemistry of dihydrotazettine methine was critical to the structural studies on tazettine, attention centered upon the position of the double bond.[1,2] This paper describes an investigation which unexpectedly revealed that the position generally accepted for this double bond (2′,3′ in 2) is erroneous.



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2

3, R = CH_2OH
4, R = CHO
5, R = CO_2H

In the context of the chemistry of tazettine, the main features of the product of the Hofmann decomposition of the methiodide of dihydrotazettine (1) are quite clear. The 6-(4′-methoxycyclohexenyl)piperonyl system is present and has been demonstrated by reduction of the methine to a derivative of haemanthamine.[3] The presence of the ester function is inferred from the infrared absorption and analogy to the formation of an ester in the Hofmann decomposition of tazettine.[4] These characteristics have been further substantiated by the observations recorded below. Evidence on the position of the double bond was limited to the ultraviolet spectrum (Figure 1), which resembles that of safrole, rather than that of the styrene system of isosafrole, and the nonconjugated position (2′,3′) has been generally accepted.[1,2,5]

In the course of the earlier work it was observed that acid treatment converts the methine into a neutral material. To allow further investigation of this product, a fresh quantity of the methine was prepared, which was now examined by nmr spectrometry. This spectrum displays the characteristics anticipated of a compound known to possess the gross features enumerated above, but, surprisingly, shows a peak corresponding to a single olefinic hydrogen atom and requires that the double bond be in the 1′,2′ position (2). Although the alicyclic protons could not be well resolved in deuteriochloroform, in perdeuterioacetic acid[6] the spectrum showed resonance at δ 2.0 (m, ~2, C-5′), at 2.2 (m, ~4, C-3′ and C-6′), and a broad peak centered at 3.6 ppm (1, C-4′). Were the double bond in the 2′,3′ position, the spectrum should show a peak near 2.0 ppm (4, C-5′, 6′), peaks for *two* olefinic protons, and peaks for the C-1′ proton substantially downfield from those observed at 2.2 ppm.

Basic hydrolysis of the methine proceeded smoothly to provide a neutral alcohol, 3. The nmr spectrum resembles that of the relevant portion of 2, again with a single olefinic proton; the ultraviolet spectrum again resembles that of safrole. Stirring a chloroform solution of this material with manganese dioxide for 10 hr provided the aldehyde 4, again showing a single olefinic proton in the nmr, and with an ultraviolet absorption resembling that of piperonal. Alkaline hydrogen peroxide converted the aldehyde into an acid 5, with similar spectral features.

Although evidence cited to this point comprises two conflicting sets of spectral observations, the more circumstantial nature of the nmr spectra greatly favors the formally conjugated structure 2. Oxidation to β-methoxyadipic acid, discussed elsewhere in connection with the absolute configuration of the parent alkaloid,[7] settled the conflict unambiguously. The studies described below provide further evidence in support of this conclusion.

Although it is somewhat surprising that the ultraviolet spectra of these compounds fail to show the double bond conjugated with the aromatic system, evidently the bulk of the group *ortho* to the cyclohexenyl system in each is sufficient to force the double bond out of a position coplanar with the aromatic group. Reference to the spectra of the tolyl cyclohexenes removes all doubt: 1-*p*-tolylcyclohexene shows a styrene chromophore [λ_{max} 249 mμ (ϵ 12,800)], while 1-*o*-tolylcyclohexene does not [λ_{max} 271 (ϵ 350)].[8]

Reassigning the position of the double bond in dihydrotazettine methine requires that the mechanism of the Hofmann decomposition be reconsidered. It is quite clear that the hydroxyl group of the hemiacetal is involved, for the Hofmann decomposition of O,N-

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[1] R. J. Highet and W. C. Wildman, *Chem. Ind.* (London), 1159 (1955).

[2] T. Ikeda, W. I. Taylor, Y. Sude, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 4749 (1956).

[3] H. M. Fales and W. C. Wildman, *J. Amer. Chem. Soc.*, **82**, 197 (1960).

[4] W. I. Taylor, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 2962 (1955).

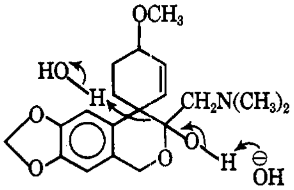
[5] *Cf.* W. C. Wildman in "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, p 289; H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Academie-Verlag, Berlin, 1961, p 410.

[6] *Cf.* J. C. N. Ma and E. W. Warnhoff, *Can. J. Chem.*, **43**, 1849 (1965).

[7] R. J. Highet and P. F. Highet, *J. Org. Chem.*, **33**, 3105 (1968).

[8] *o*-Tolylcyclohexene shows a rising end absorption which, however, has ϵ 1700 at 249 mμ. The nmr spectra of these compounds similarly reflect these effects: 1-*o*-tolylcyclohexene, δ 7.13 (4 H, aromatic), 5.57 (1 H olefinic); 1-*p*-tolylcyclohexene, 7.30, 7.08 (2 H each, aromatic), 6.05 ppm (1 H, olefinic). On the basis of these chemical shifts, the dihedral angle of the olefinic bond and the aromatic ring of *o*-tolylcyclohexene has been estimated as 69 or 100°; *cf.* E. W. Garbisch, *J. Amer. Chem. Soc.*, **85**, 927 (1963).

dimethyltazettine takes quite a different course.[2] The fact that the dimethylaminomethylene moiety is retained requires that the benzylic ether bond remain in the product ester and that the decomposition occur on the intact hemiacetal. The earlier belief that the double bond occupies the nonconjugated position required that the formation of the methine be rationalized by a mechanism involving a normal Hofmann decomposition to 6, followed by the cleavage indicated. This mechanism is clearly precluded by the conjugated position of the double bond, and a concerted mechanism 7 is now more attractive.[1,9,10]



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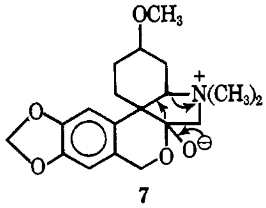

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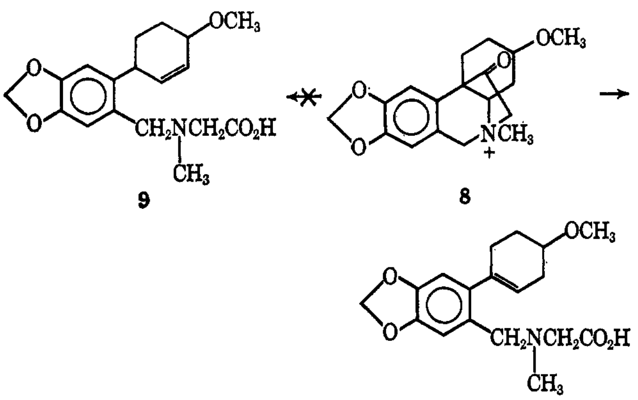
The formation of a product similar to dihydrotazettine methine has been reported from the Hofmann degradation of dihydrooxohaemanthamine methiodide, **8**.[3] Assigning the position of the double bond again depended on the ultraviolet absorption which favored the 2′,3′ position **9**. Through the courtesy of Dr. H. M. Fales, of this laboratory, it has been possible to examine the nmr spectrum of this methine which reveals a single olefinic proton (δ 5.55 ppm, m). It is evident that **10** is the correct structure and that the ultraviolet absorption is also misleading in this case.



Because the double bond of the methine is crowded by the hydroxymethyl, it was anticipated that the alcohol might show hydrogen bonding to it. The infrared spectrum of the alcohol reveals intramolecular hydrogen bonding by two peaks in the OH-stretching region, at 3620 and 3500 cm^{-1}, the latter with a width at half-intensity of 80 cm^{-1}, unchanged on dilution to 0.004 M in carbon tetrachloride.[11] However, it is unlikely that the absorption at 3500 cm^{-1} results from interaction of the hydroxyl with the double bond, for hydroxyl groups so bonded seldom absorb below 3550 cm^{-1}.[12] Dreiding models of the molecule reveal the probable nature of this bond, for the hydroxyl can approach within 1.6 Å of the methoxyl oxygen, with a linear conformation and O···O distance of 2.6 Å.

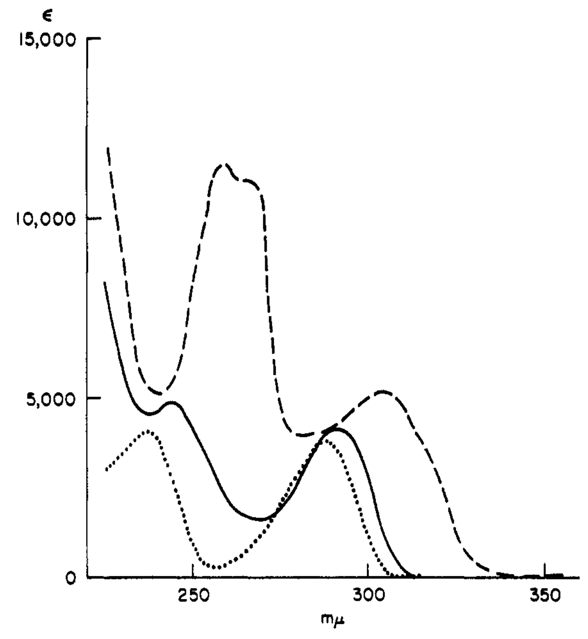
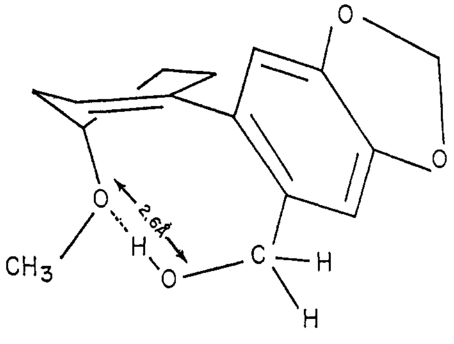


Figure 1.—Ultraviolet spectra: ———, dihydrotazettine methine; – – – –, isosafrole; · · · ·, safrole.



dihydrotazettine methine alcohol

This unusual hydrogen bond adds rigidity to the molecular conformation, which is revealed in the nmr spectrum of the benzylic methylene group. This appears as an AB quartet, which coalesces to a singlet at approximately 68° (see Figure 2). Because the outer limbs of the quartet are sometimes lost in the instrumental noise, the signal sometimes appears as a doublet, such as might result from coupling of the methylene protons with the hydroxyl proton. However, the hydroxyl signal is a singlet, and exchanging the proton for a deuterium atom does not alter the absorption of the benzylic methylene group.

It is clear that the nonequivalence of the methylene protons results from the hydrogen bond, for the parent ester **2** does not show this phenomenon, and addition of a polar material [here $(CD_3)_2SO$] to a dilute carbon

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(9) K. Wiesner and Z. Valenta, *Chem. Ind.* (London), R36 (1956).

(10) It is ironic to note that such a four-center elimination was first suggested to lead to the methine when it was supposed to have a nonconjugated double bond and led to an erroneous structure for tazettine.[1] Had the conjugated nature of the methine been recognized, this mechanism would have led to the correct structure for tazettine.

(11) A preliminary description of the phenomena associated with this hydrogen bond has appeared; *cf.* R. J. Highet, J. C. N. Ma, and P. F. Highet, *Tetrahedron Lett.*, 1049 (1966).

(12) *Cf.* (a) H. M. Fales and W. C. Wildman, *J. Amer. Chem. Soc.*, **85**, 784 (1963); (b) P. von R. Schleyer, D. S. Trifan, and R. Backsai, *ibid.*, **80**, 6691 (1958); (c) P. von R. Schleyer, C. Wintner, D. S. Trifan, and R. Backsai, *Tetrahedron Lett.*, 1 (1959). (d) It is further unlikely that the olefin is involved in the hydrogen bond because 2-hydroxymethylbiphenyls fail to show bonding of the hydroxyl to the adjacent aromatic ring; *cf.* W. F. Baitinger, P. von R. Schleyer, and K. Mislow, *J. Amer. Chem. Soc.*, **87**, 3168 (1965).

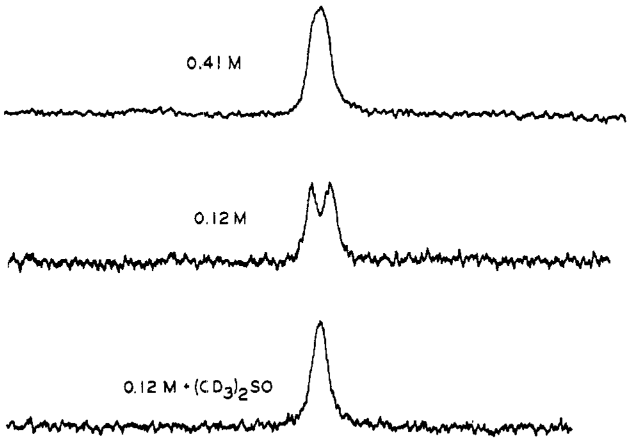


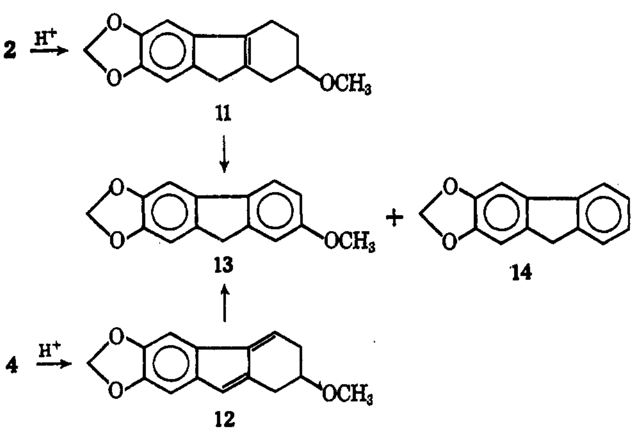
Figure 2.—Nmr spectra of dihydrotazettine methine alcohol in carbon tetrachloride solution at δ 4.7 ppm.

tetrachloride solution of the alcohol disrupts the bond, converting the quartet into a singlet.

The cage structure resulting from this hydrogen bond places the aromatic system in an asymmetric environment, which can be detected in the optical rotatory properties of the molecule. The ORD curve (Figure 3) of a dilute hexane solution of the alcohol shows a Cotton effect which is not present in the parent ester. A methanolic solution of the alcohol reveals only a plain curve to 250 mμ.

Such a hydrogen bond made possible across many atoms by an unusual conformation is not unique to this molecule, but such bonds are unusual in simple systems.[13] Although the methoxyl group must occupy the energetically less favored axial position, the energy difference of the axial and equatorial conformations is evidently comparable with that of the hydrogen bond.

Acid Transformation Products.—The methine 2 turns cloudy on warming in acid, producing a neutral material of the composition $C_{15}H_{16}O_3$. The ultraviolet spectrum of this product showed a double bond conjugated with the aromatic system, while the infrared and nmr spectra showed the environment of the aromatic system, the alicyclic protons and the methoxyl group to be otherwise unchanged; there were no olefinic peaks, and one broad singlet of two protons remained unassigned, δ 3.08 ppm. As the nmr spectrum and empirical formula show the benzylic substituent to have been eliminated, the product may be supposed to be that of cyclization, **11**.[14] The chemical shift of the unassigned peak corresponds reasonably to that of indene, 3.33.[15]



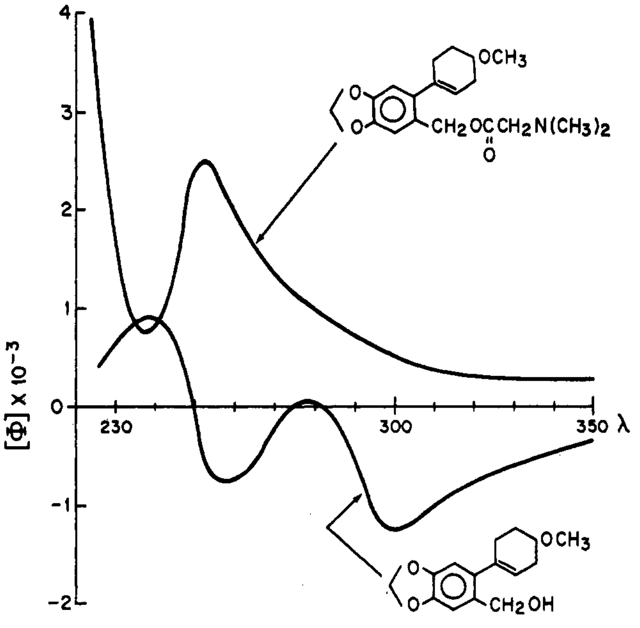


Figure 3.—ORD of dihydrotazettine methine and its alcohol in hexane solution.

The aldehyde 4 also proved to be sensitive to acid, brief warming forming a handsome golden precipitate with the composition $C_{15}H_{14}O_3$. The nmr spectrum of this product shows two olefinic protons, one as a singlet broadened only by allylic coupling, and the other as a triplet corresponding to coupling with an adjacent methylene group. These may reasonably be assigned to C-9 and C-4 of **12**. Although the spectra of **12** do not eliminate the C-1 position for the methoxyl, dehydrogenation produces a mixture of the methylenedioxyfluorene **14** and its methoxy derivative **13**, with the characteristic nmr spectrum of a 1,2,4-substituted aromatic ring. The same materials are produced by dehydrogenation of the tetrahydrofluorene **11**.

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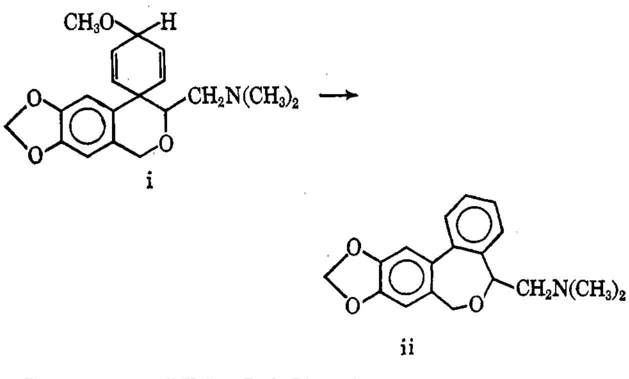
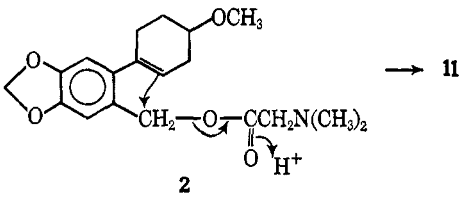
[13] A remarkable case is that of dehydropristimerin II: K. Nakanishi, Y. Takahashi, and H. Budzikiewicz, *J. Org. Chem.*, **30**, 1729 (1965).

[14] The sensitivity of the methine to acid parallels that of deoxytazettine methine (i), which is converted under similar conditions into the optically active neomethine ii and piperonyl alcohol. (*Cf.* E. W. Warnhoff in "Molecular Rearrangements," Vol. 2, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 851. As this material has been previously reported optically inactive[2] and experimental details supporting the optical activity have not been reported elsewhere, these have kindly been supplied by Dr. Warnhoff and are included in the Experimental Section.)

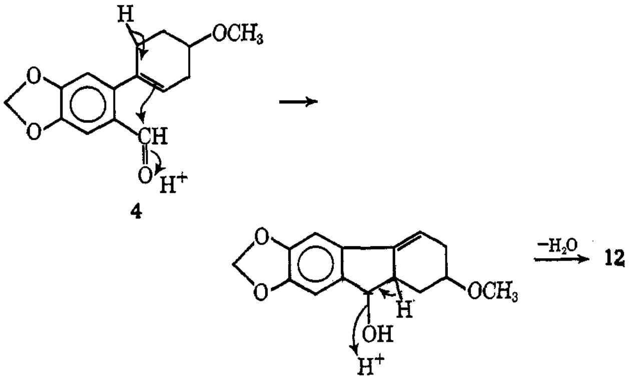


[15] N. B. Bhacca, L. F. Johnson, and J. N. Shoolery, "Nmr Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, No. 227.

The cyclization of the methine **2** may be represented by the path



The reaction cannot proceed by a mechanism initiated by protonation of the double bond to form a benzylic carbonium ion, for a symmetrical intermediate would be formed, and the product could not possess the optical activity observed. As anticipated from this mechanism, the same product is obtained from acid treatment of the alcohol **3**, but only under prolonged heating. A similar route is proposed for the formation of **12**. Not only is the product optically active, but when the cyclization is performed on the dideuterioaldehyde (**4**, D at 5′ and 6′) one-quarter of the deuterium content is lost in the formation of **12**.[7]



The double bond of the alcohol **3** is quite resistant to oxidation. The acetate of **3**, formed by the action of acetic anhydride in pyridine, was not attacked by treatment with potassium permanganate solution for 2 hr. However, peroxide oxidation of the aldehyde **4** provided the acid **5**, which, with performic acid,[16] produced a series of neutral materials which could be separated by tlc. The two major components, A, mp 182–185°, and B, mp 178–181°, were shown by mass spectrometry to possess the composition $C_{15}H_{16}O_6$. Infrared spectra of these materials show carbonyl peaks near 1750 cm^{-1}, corresponding to five-membered lactones (*cf.* methyl piperonylate, 1719 cm^{-1}). The hydroxyl-stretching frequencies reveal the stereochemistry of the compounds. In dilute carbon tetrachloride solution, A shows a free hydroxyl group, 3632 cm^{-1}, while B shows a hydroxyl group with a strong hydrogen bond, 3490 cm^{-1}. Neither of these corresponds to a *cis*-cyclohexanediol nor a *trans*-equatorial cyclohexanediol derivative, either of which should produce a weakly bonded hydroxyl of *ca.* 3550 cm^{-1}.[17] The two materials are therefore to be represented by **15**, A, with the free hydroxyl and **16**, B, with the hydroxyl strongly bonded to the *cis*-methoxyl in a 1,3-diaxial relation.

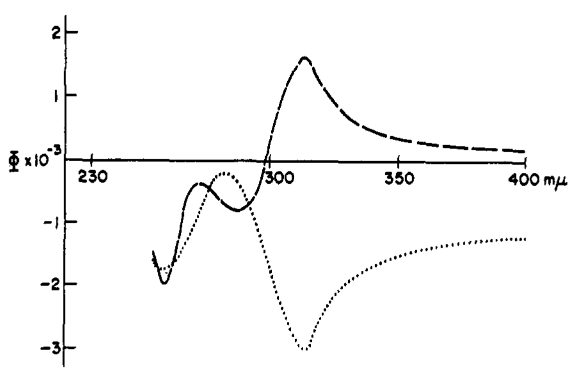
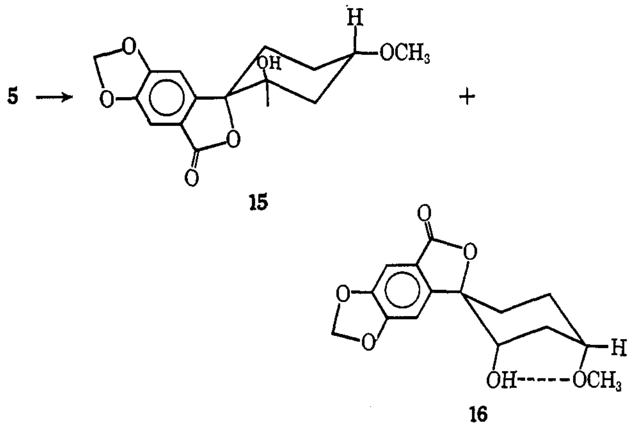


Figure 4.—ORD of lactones A (— — — —) and B (......) in ethanol.



The properties conform quite well to the products anticipated from the reaction, for the cyclohexenyl ring of the acid **5**, with the methoxyl in the equatorial conformation, should be equally hindered on either side; the two intermediate epoxides are evidently formed in similar amounts and suffer *trans*-diaxial opening to the lactones observed.[16]

Although the two lactones have one asymmetric center in common, that bearing the methoxyl group, the two asymmetric centers nearest the chromophoric group possess opposite absolute configurations. The optical rotatory dispersion curves reflect this fact and show Cotton effects of opposite character, centered at 305 mμ (see Figure 4).

Mass Spectral Observations.—The mass spectra of the compounds discussed here (Experimental Section and Figure 5) comprise ions evidently formed largely by the elimination of small and simple moieties, as summarized in Table I. The processes postulated conform to the composition of the ions determined by accurate mass measurement (Table II) and to the corresponding peaks of the deuterated materials available from the study of the absolute configuration of alkaloids related to tazettine.[7] They are perhaps best discussed in order of the increasing complexity of the compounds.

(Table III lists the mass spectra of **11–16**.)

The sequential elimination of the elements of formaldehyde and carbon monoxide from the methylenedioxyaromatic system form the dominant ions of the dehydrogenation products **13** and **14**, and the terminating sequences of the fragmentations of the more complex molecules of the series. The elimination of the elements of methanol from the dihydroisofluorene **12**

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[16] G. Berti, F. Bottari, B. Macchia, and F. Macchia, *Tetrahedron*, **21**, 3277 (1965).

[17] E. Galantay, *ibid.*, **19**, 319 (1963); E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 110.

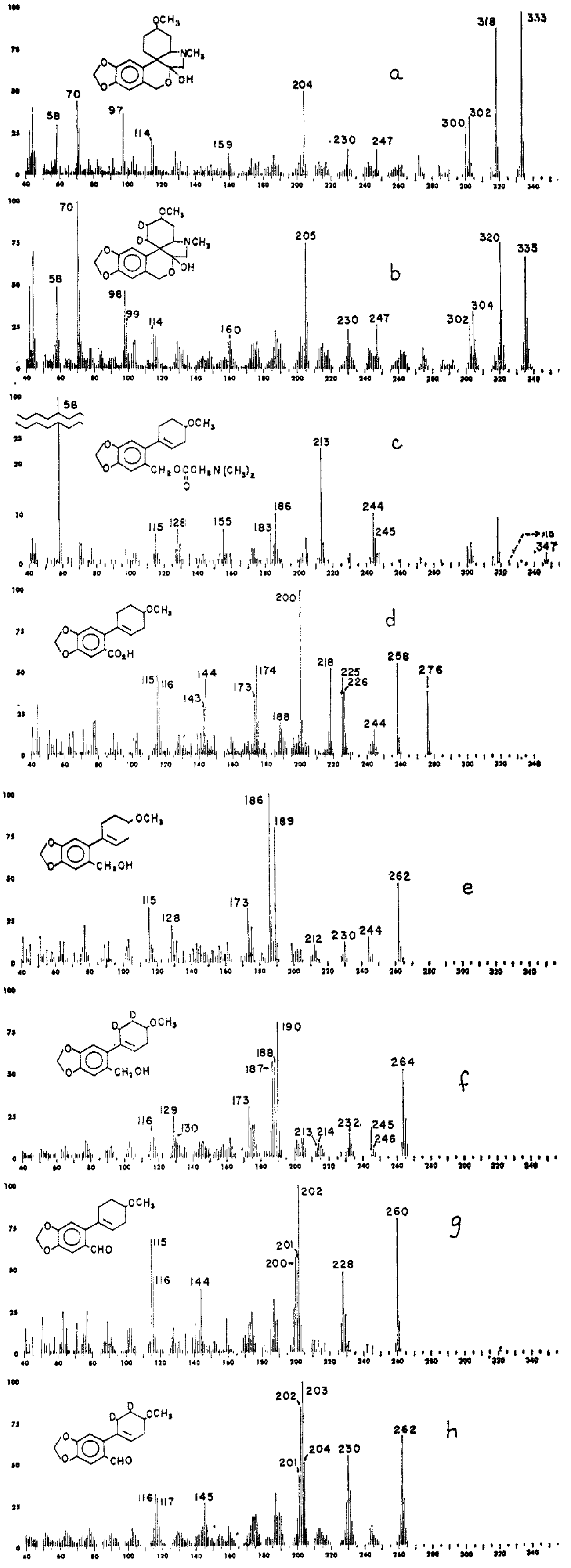


Figure 5.—Mass spectra of dihydrotazettine methine and derivatives. Registry no.: a, 16831-29-1; b, 16831-30-4; f, 16831-31-5; h, 16831-32-6.

Table I

Fragmentation under Electron Bombardment[a]

Compd

$$\begin{tikzcd} \mathbf{14} & 210 \arrow[r, "a*"] & 180 \arrow[r, "b*"] & 152 \end{tikzcd}$$

$$\begin{tikzcd} \mathbf{13} & 240 \arrow[r, "c*"] \arrow[dr, "a*"] & 225 \arrow[r, "b*"] & 197 \arrow[dr, "a"] & & \\ & & 210 \arrow[r, "b*"] & 182 \arrow[r, "c"] & 167 \arrow[r, "b*"] & 139 \end{tikzcd}$$

$$\begin{tikzcd} \mathbf{12} & 242 \arrow[r, "d*"] \arrow[dr, "c"] & 210 \arrow[r, "a*"] & 180 \arrow[r, "b*"] & 152 & & \\ & & 227 \arrow[r, "a"] & 197 \arrow[r, "b"] & 169 \arrow[r, "e"] & 167 \arrow[r, "b"] & 139 \end{tikzcd}$$

$$\begin{tikzcd} \mathbf{11} & 244 \arrow[r, "d"] \arrow[dr, "f"] & 212 & & \\ & & 186 \arrow[r, "a"] & 156 \arrow[r, "b"] & 128 \end{tikzcd}$$

$$\begin{tikzcd} \mathbf{4} & 260 \arrow[r, "d*"] \arrow[dr, "f*"] & 228 \arrow[r, "b"] & 200\ (C_{13}H_{12}O_2) \arrow[r, "g"] & 199\ (C_{13}H_{11}O_2) & & \\ & & 202 \arrow[r, "g*"] \arrow[dr, "b*"] & 201 \arrow[r, "g"] & 200\ (C_{12}H_8O_3) \arrow[r, "g"] & 199\ (C_{12}H_7O_3) & \\ & & & 174\ (C_{11}H_{10}O_2) \arrow[r, "a*"] & 144 \arrow[r, "b*"] & 116 \arrow[r, "g"] & 115 \end{tikzcd}$$

$$\begin{tikzcd} \mathbf{3} & 262 \arrow[r, "h*"] \arrow[ddr, "d*"] \arrow[dddr, "i"] & 244 \arrow[r, "d"] \arrow[dr, "f*"] & 212 & & & \\ & & & 186 \arrow[r, "a"] & 156 \arrow[r, "b"] & 128 & \\ & & 230 \arrow[r, "j"] & 213 \arrow[r, "k"] & 173 \arrow[r, "a"] & 143 \arrow[r, "b"] & 115 \\ & & 189 & & & & \end{tikzcd}$$

$$\begin{tikzcd} \mathbf{2} & 347 \arrow[r, "i"] \arrow[dr, "i"] & 58\ [(CH_3)_2\overset{+}{N}CH_2] & & & & \\ & & 245 \arrow[r, "d*"] \arrow[ddr, "g"] & 213 \arrow[r, "k"] \arrow[dr, "a*"] & 173 \arrow[r, "a"] & 143 \arrow[r, "b"] & 115 \\ & & & & 183 \arrow[r, "b*"] & 155 & \\ & & & 244 \arrow[r, "f"] & 186 \arrow[r, "a*"] & 156 \arrow[r, "b*"] & 128 \end{tikzcd}$$

$$\begin{tikzcd} \mathbf{1} & 333 \arrow[r, "c*"] \arrow[dr, "l"] \arrow[dddddr, "i"] & 318 \arrow[r, "h*"] & 300 & \\ & & 302 \arrow[r, "h*"] \arrow[dr, "i"] \arrow[ddr, "i"] \arrow[dddr, "i"] & 284 & \\ & & & 247 \arrow[r, "j"] & 230 \\ & & & 204 \arrow[r, "m, g"] & 159 \\ & & & 97 & \\ & & 70 & & \end{tikzcd}$$

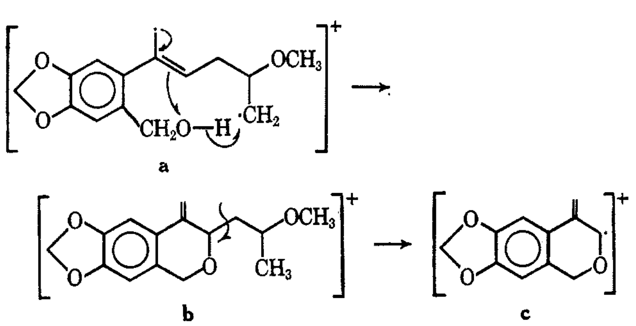
$$\begin{tikzcd} \mathbf{5} & 276 \arrow[r, "h"] \arrow[dr, "d"] \arrow[ddr, "f"] & 258 \arrow[r, "f*"] & 200 & & & \\ & & 244 \arrow[r, "h*"] & 226 \arrow[r, "g*"] & 225 & & \\ & & 218 \arrow[r, "m*"] \arrow[dr, "a"] & 174 \arrow[r, "g*"] \arrow[ddr, "a"] & 173 \arrow[r, "a"] & 143 \arrow[r, "b"] & 115 \\ & & & 188 & & & \\ & & & & 144 \arrow[r, "b"] & 116 & \end{tikzcd}$$

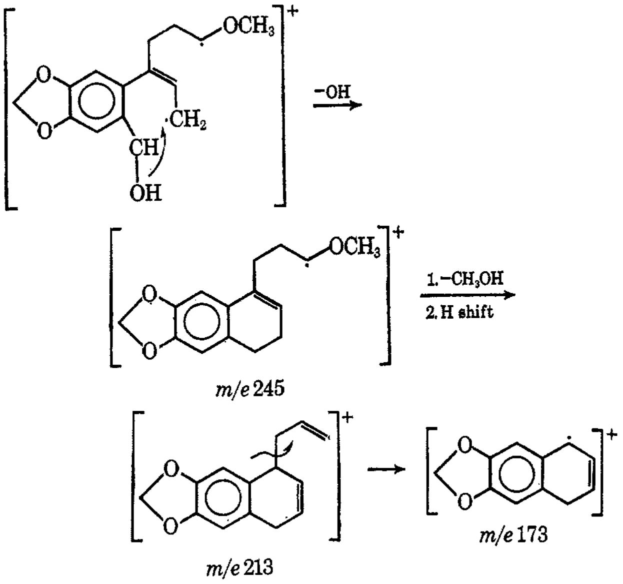
[a] An asterisk indicates that spectra show metastable ions corresponding to these transitions: a, CH_2O; b, CO; c, CH_3; d, CH_3OH; e, H_2; f, $CH_3OCH{=}CH_2$; g, H; h, H_2O; i, see text; j, OH; k, C_3H_4; l, CH_3O; m, CO_2.

evidently produces an ion very similar to the parent ion of **14**, for the characteristic ions from the fragmentation of that parent appear, along with those of the competing sequence originated by the elimination of methyl from the methoxyl group.

The spectrum of the tetrahydrofluorene **11** is dominated by the reverse Diels–Alder elimination, the process which also produces the base peak of the aldehyde **4** (Figure 5g and h) and of the acid **5** (Figure 5d). However, in the fragmentation of these latter compounds, alternative routes compete to produce spectra of greater complexity.

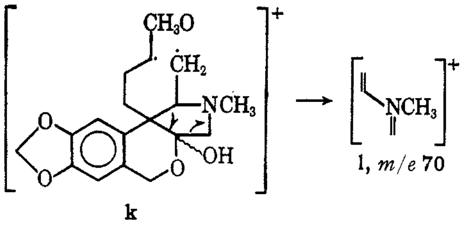
The striking feature of the spectrum of **3** (Figure 5e and f) is that the reverse Diels–Alder process forming the base peak does not occur from the parent ion, but from the product of dehydration, *m/e* 244, which can evidently be assigned the structure of the tetrahydrofluorene **11**, for the characteristic peaks of this latter compound can be seen at lower masses. The dehydration process evidently is preceded by an isomerization of the double bond, for the dideuterated material shows dehydration products as mono- and dideuterated doublets (244 shifts to 245 and 246; 186 to 187 and 188). The appearance of a strong peak at *m/e* 189 (190 in the deuterated compound) is rationalized as cleavage of an allylic bond to form **a**, cyclization and proton transfer in one or two steps to form **b**, which cleaves to the observed ion of *m/e* 189, **c**. The sequence leading to the ion of *m/e* 173, unchanged in the spectrum of the deuterated material, is represented as the product of the alternative allylic cleavage and cyclization.



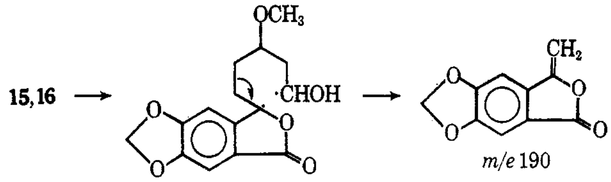


The mass spectrum of the methine **2** is dominated by the facile departure of the dimethylaminomethylene moiety, *m/e* 58, which provides the base peak. The same cleavage forms the ion of *m/e* 245, which fragments by processes common to the alcohol and tetrahydrofluorene described above. The ions of *m/e* 333, 318, 302, 300, 204, 97, 71, and 70 evidently arise from dihydrotazettine contaminating the difficultly purified methine.

The stability of the polycyclic system of dihydrotazettine **1** is reflected in the appearance of the parent ion as the base peak. The familiar losses of methyl, hydroxyl, and methoxyl are observed, the last leading to the intermediate **d**, *m/e* 302 (Chart I), regarded as the starting point for fragmentations of the alicyclic ring. Elimination of C-1 to C-4 *via* the process **e** produces the ion of *m/e* 247, **f**, and, with loss of hydroxyl, *m/e* 230, both of which incorporate no deuterium. Cleavage next to the hemiketal position with hydrogen transfer allows the elimination of C-2 to C-4 (**g**), and the formation of **h**, *m/e* 204. A similar cleavage without hydrogen transfer, **i**, produces a charge-bearing moiety of small weight, **j**, *m/e* 97. Cleavage of the parent ion at the methoxyl site to produce **k** allows the elimination of the ion of *m/e* 70, **l**. The peaks of *m/e* 114, 71, and 58 can evidently be similarly explained.



The base peaks of the very simple spectra of the lactones **15** and **16** evidently arise from elimination following the facile glycol cleavage.



Experimental Section[18]

Dihydrotazettine Methine (2).[1,2]—A solution of 440 mg of dihydrotazettine in 10 ml of acetone was treated with 5 ml of methyl iodide at room temperature for 30 min and then evaporated to dryness. The residue was dissolved in 5 ml of methanol and stirred 2 hr with silver oxide, freshly prepared from 280 mg of silver nitrate and dilute sodium hydroxide. The suspension was filtered, the filtrate was evaporated to dryness, and the residue was heated at 130° under reduced pressure for 30 min. The residue was dissolved in ether, and the solution was washed with brine and evaporated to dryness, providing 404 mg of the methine as an oil which was unstable to distillation, but could be shown by tlc and glpc to be essentially one material, $[\alpha]^{25}_{589}$ +29.5°. The methine formed a picrate which crystallized from ethanol, mp 136.5–137.5° (lit.[1] mp 136–137°).

Anal. Calcd for $C_{25}H_{28}N_4O_{12}$: C, 52.08; H, 4.89; N, 9.72. Found: C, 52.35; H, 4.89; N, 9.57.

Regeneration of the free base provided material with the following spectral properties: λ_{max} 243 mμ (ϵ 4900) and 290 (4100) [safrole shows λ_{max} 237 (4120) and 287 (3900); isosafrole shows 259 (11,650), 266.5 (11,150), and 305 (5180)]; ν_{max} 1740, 1040, and 935 cm^{-1}.

Anal. Calcd for $C_{19}H_{25}NO_5$: *m/e*, 347.173. Found: *m/e*, 347.174.

6-(4′-Methoxycyclohexenyl)piperonyl Alcohol (3).—A solution of 90 mg of the above ester in 4 ml of ethanol was treated with 2 ml of 1 *M* sodium carbonate and refluxed 1 hr. The solution was diluted with water and extracted with ether, and the ethereal layer was washed with brine, filtered, and evaporated to dryness to provide 70 mg of an oil. Crystalline material was obtained after sublimation (75°, 0.001 mm) or preparative tlc (ether-chloroform, 1:1): mp 63–64°; $[\alpha]_{589}$ −3.2° (*c* 0.34); λ_{max} 240 mμ (ϵ 5100), and 290 (3900); ν_{max} (dil CCl_4) 3630 and 3500 cm^{-1}; nmr 6.93 (C-2, s, 1), 6.64 (C-5, s, 1), 5.95 (OCH_2O, s,

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[18] Melting points were observed on a Kofler microscope hot stage and are corrected. Rotations were measured in chloroform with a Rudolph photoelectric spectropolarimeter using 2-dm tubes; the optical rotatory dispersions of Figures 3 and 4 were determined on a Cary 60 recording spectropolarimeter in 1-cm cells; ultraviolet spectra were obtained in absolute ethanol solution on a Cary Model 11 MS recording spectrophotometer; infrared spectra were recorded on either a Perkin-Elmer Model 21 or a Beckman IR-7 double-beam spectrophotometer in chloroform solution; nmr measurements were obtained on a Varian A-60 spectrometer in deuteriochloroform solution, using tetramethylsilane (δ 0.0) as an internal standard. Exceptions to the specified solvents are noted in the text. Mass spectra were determined with an Associated Electrical Industries MS-9 double-focusing mass spectrometer at 70 eV; accurate mass measurements were obtained by comparing the weights of unknown ions with those of ions of heptacosafluorotributylamine of slightly lower weight. Tlc was performed on silicic acid plates.

Table II

Accurate Masses of Ions

Compd	Obsd	Formula	Required
14	210.067	$C_{14}H_{10}O_2$	210.068
	180.056	$C_{13}H_8O$	180.058
	152.062	$C_{12}H_8$	152.063
13	240.077	$C_{15}H_{12}O_3$	240.079
	225.054	$C_{14}H_9O_3$	225.055
	210.065	$C_{14}H_{10}O_2$	210.068
	197.058	$C_{13}H_9O_2$	197.060
	182.070	$C_{13}H_{10}O$	182.073
	167.050	$C_{12}H_7O$	167.050
	139.056	$C_{11}H_7$	139.055
12	242.093	$C_{15}H_{14}O_3$	242.094
	227.072	$C_{14}H_{11}O_3$	227.071
	210.070	$C_{14}H_{10}O_2$	210.068
	197.060	$C_{13}H_9O_2$	197.060
	180.058	$C_{13}H_8O$	180.056
	169.065	$C_{12}H_9O$	169.065
	167.051	$C_{12}H_7O$	167.050
	152.063	$C_{12}H_8$	152.063
	139.057	$C_{11}H_7$	139.055
11	244.108	$C_{15}H_{16}O_3$	244.110
	212.083	$C_{14}H_{12}O_2$	212.084
	186.063	$C_{12}H_{10}O_2$	186.068
	156.055	$C_{11}H_8O$	156.058
	128.062	$C_{10}H_8$	128.063
4	260.101	$C_{15}H_{16}O_4$	260.105
	244.111	$C_{15}H_{16}O_3$	244.110
	242.097	$C_{15}H_{14}O_3$	242.094
	228.078	$C_{14}H_{12}O_3$	228.079
	202.060	$C_{12}H_{10}O_3$	202.063
	201.052	$C_{12}H_9O_3$	201.055
	200.082	$C_{13}H_{12}O_2$	200.084
	200.045	$C_{12}H_8O_3$	200.048
	199.074	$C_{13}H_{11}O_2$	199.076
	199.038	$C_{12}H_7O_3$	199.040
	187.073	$C_{12}H_{11}O_2$	187.076
	174.068	$C_{11}H_{10}O_2$	174.068
	174.034	$C_{10}H_6O_3$	174.032
	159.044	$C_{10}H_7O_2$	159.045
	144.056	$C_{10}H_8O$	144.058
	116.064	C_9H_8	116.063
	115.054	C_9H_7	115.055
3	262.118	$C_{15}H_{18}O_4$	262.121
	244.111	$C_{15}H_{16}O_3$	244.110
	230.094	$C_{14}H_{14}O_3$	230.094
	213.090	$C_{14}H_{13}O_2$	213.092
	212.081	$C_{14}H_{12}O_2$	212.083
	199.076	$C_{13}H_{11}O_2$	199.076
	189.054	$C_{11}H_9O_3$	189.055
	186.066	$C_{12}H_{10}O_2$	186.068
	175.074	$C_{11}H_{11}O_2$	175.076
	175.040	$C_{10}H_7O_3$	175.039
	173.064	$C_{11}H_9O_2$	173.061
	156.057	$C_{11}H_8O$	156.058
	143.047	$C_{10}H_7O$	143.050
	128.062	$C_{10}H_8$	128.063
	115.056	C_9H_7	115.055
2	347.172	$C_{19}H_{25}NO_5$	347.173
	245.115	$C_{15}H_{17}O_3$	245.118
	244.112	$C_{15}H_{16}O_3$	244.110
	230.088	$C_{14}H_{14}O_3$	230.094
	213.091	$C_{14}H_{13}O_2$	213.095
	186.067	$C_{12}H_{10}O_2$	186.068
	183.081	$C_{13}H_{11}O$	183.081
	155.084	$C_{12}H_{11}$	155.086
	155.050	$C_{11}H_7O$	155.050
	155.016	$C_{10}H_3O_2$	155.013
	143.048	$C_{10}H_7O$	143.050
	128.063	$C_{10}H_8$	128.063
	115.055	C_9H_7	115.055
	586.048	C_8H_8N	58.0657
1	333.157	$C_{18}H_{23}NO_5$	333.158
	318.131	$C_{17}H_{20}NO_5$	318.134
	302.138	$C_{17}H_{20}NO_4$	302.139
	300.124	$C_{17}H_{18}NO_4$	300.124
	290.116	$C_{17}H_{18}O_5$	290.115
	284.129	$C_{17}H_{18}NO_3$	284.129
	272.127	$C_{16}H_{18}NO_3$	272.129
	272.105	$C_{16}H_{16}O_4$	272.105
	247.084	$C_{13}H_{13}NO_4$	247.084
	230.082	$C_{13}H_{12}NO_3$	230.082
	204.040	$C_{11}H_8O_4$	204.042
	186.065	$C_{12}H_{10}O_2$	186.068
	173.120	$C_9H_{17}O_3$	173.118
	173.060	$C_{11}H_9O_2$	173.060
	159.043	$C_{10}H_7O_2$	159.045
	128.062	$C_{10}H_8$	128.063
	115.055	C_9H_7	115.055
	114.092	$C_6H_{12}NO$	114.092
	97.088	$C_6H_{11}N$	97.089
	71.0726	C_4H_9N	71.0735
	71.0492	C_4H_7O	71.0497
	70.067	C_4H_8N	70.066
	58.067	C_3H_8N	58.066
15	292.094	$C_{15}H_{16}O_6$	292.095
	190.026	$C_{10}H_6O_4$	190.026
16	292.094	$C_{15}H_{16}O_6$	292.095
	190.026	$C_{10}H_6O_4$	190.026
5	276.101	$C_{15}H_{16}O_5$	276.100
	258.089	$C_{15}H_{14}O_4$	258.089
	244.073	$C_{14}H_{12}O_4$	244.074
	226.061	$C_{14}H_{10}O_3$	226.063
	225.056	$C_{14}H_9O_3$	225.055
	218.057	$C_{12}H_{10}O_4$	218.058
	200.047	$C_{12}H_8O_3$	200.047
	188.046	$C_{11}H_8O_3$	188.047
	174.065	$C_{11}H_{10}O_2$	174.068
	173.058	$C_{11}H_9O_2$	173.060
	144.057	$C_{10}H_8O$	144.058
	143.048	$C_{10}H_7O$	143.050
	116.062	C_9H_8	116.063
	115.055	C_9H_7	115.055

2), 4.56 (α-C, s or q, 2), 5.50 (C-2′, br, 1) 3.42 (OCH_3, s, 3), *ca.* 3.7 (C-4′, m, 1), *ca.* 2.3 (C-3′, C-6′, and OH, demonstrated by exchange with D_2O,[19] br, 5), *ca.* 1.93 (C-5′, m, 2).

Anal. Calcd for $C_{15}H_{18}O_4$: *m/e*, 262.120. Found: *m/e*, 262.123.

6-(4′-Methoxycyclohexenyl)piperonyl Acetate.—The alcohol **3**, 40 mg, in 1 ml of pyridine was mixed with 0.2 ml of acetic anhydride. After standing overnight at 5°, the solution was evaporated to dryness under reduced pressure. The residue was dissolved in ether, washed with water, and dried with sodium sulfate to give 42 mg of 90% purity as shown by glpc: $[\alpha]_{589}$ +10.4° (*c* 0.23); ν_{max} 1725 cm^{-1}; nmr 6.87 (C-2, s, 1), 6.64 (C-5, s, 1), 5.94 (OCH_2O, s, 2), 5.46 (C-2′, br, 1), 5.01 (α-C, s,

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[19] H. M. Fales and A. V. Robertson, *Tetrahedron Lett.*, No. 3, 111 (1962).

CHART I

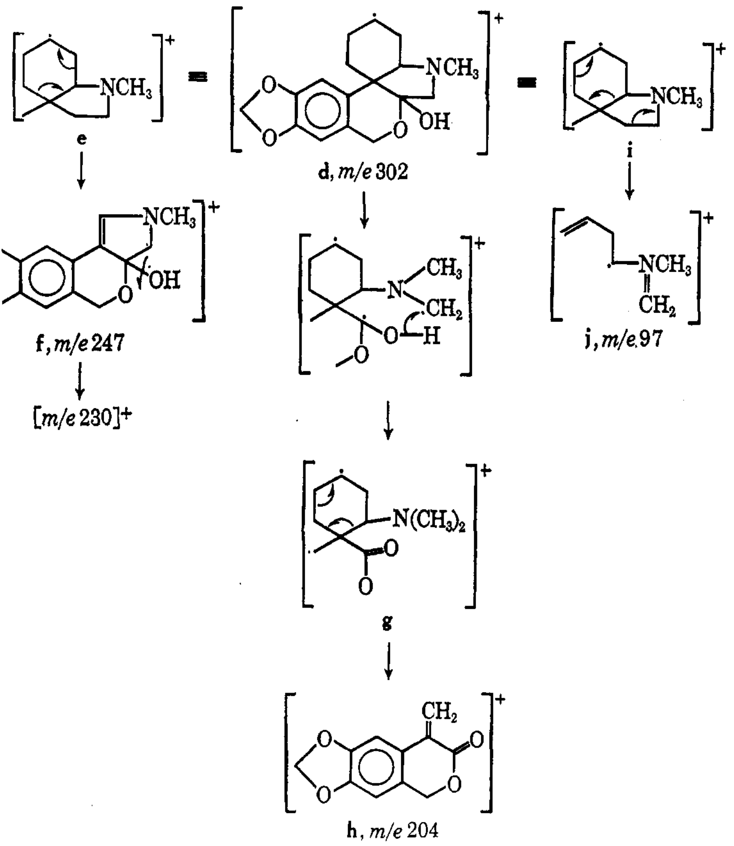

TABLE III

MASS SPECTRA OF FLUORENE DERIVATIVES AND LACTONES

Compd	*m/e* (relative intensity)
11	245 (9), 244 (26), 213 (5), 212 (17), 210 (5), 187 (23), 186 (100), 185 (15), 156 (8), 152 (5), 128 (25), 115 (7), 77 (5), 76 (8), 71 (7), 63 (5), 55 (5), 45 (6), 44 (8), 43 (6), 41 (5)
11, 1,2-d_2	247 (12), 246 (29), 245 (9), 214 (11), 188 (22), 187 (100), 186 (38), 185 (7), 157 (8), 156 (5), 154 (5), 130 (6), 129 (19), 128 (10), 116 (6), 77 (5), 44 (12)
12	243 (21), 242 (100), 227 (7), 212 (8), 211 (19), 210 (41), 209 (6), 199 (6), 198 (9), 197 (34), 181 (13), 180 (19), 169 (10), 168 (5), 167 (7), 153 (15), 152 (29), 151 (8), 141 (10), 140 (9), 139 (23), 128 (5), 126 (5), 115 (9), 76 (9), 69 (5), 44 (5)
12, 2-*d* and 12, 1,2-d_2	246 (14), 245 (44), 244 (100), 243 (96), 242 (13), 229 (8), 228 (8), 214 (13), 213 (35), 212 (62), 211 (48), 210 (15), 200 (19), 199 (39), 198 (38), 183 (23), 182 (40), 181 (28), 171 (14), 170 (17), 169 (14), 155 (29), 154 (52), 153 (48), 152 (22), 143 (18), 142 (25), 141 (40), 140 (34), 139 (11), 116 (14), 77 (15), 76.5 (11), 44 (28)
13	241 (16), 240 (100), 226 (9), 225 (50), 210 (4), 197 (2), 182 (4), 167 (6), 139 (20), 120 (11)
14	211 (18), 210 (100), 209 (9), 181 (10), 180 (46), 153 (19), 152 (90), 151 (28), 150 (16), 126 (7), 105 (6), 104 (6), 76 (28), 75.5 (5), 75 (10), 74 (6), 63 (10), 51 (6), 44 (29)
15	292 (11), 204 (5), 192 (5), 191 (19), 190 (100), 189 (5), 149 (9), 148 (6), 134 (8), 120 (6), 89 (10), 71 (21), 59 (6), 44 (7), 41 (5)
16	292 (15), 216 (5), 204 (7), 191 (18), 190 (100), 189 (7), 188 (6), 149 (10), 148 (8), 134 (9), 120 (10), 119 (5), 89 (10), 77 (5), 71 (22), 65 (7), 63 (7), 62 (7), 59 (5), 57 (5), 55 (6), 51 (5), 44 (6), 43 (6), 41 (12)

2), 3.40 (OCH_3, s, 3), *ca.* 3.5 (C-4′, m, 1), *ca.* 2.3 (C-3′ and C-6′. m, 4), *ca.* 2.0 (C-5′, m, 2).

Anal. Calcd for $C_{17}H_{20}O_5$: *m/e,* 304.131. Found: *m/e,* 304.126.

6-(4′-Methoxycyclohexenyl)piperonal (4).—A solution of 300 mg of the above alcohol in 30 ml of chloroform was stirred for 6 hr at room temperature with 3 g of manganese dioxide;[20] the suspension was filtered and the filtrate concentrated to dryness under reduced pressure to leave a residue of 292 mg, mp 70°. Recrystallization from methanol provided rectangular plates of mp 73–74°; $[\alpha]_{589}$ +28.7° (*c* 0.54); λ_{max} 238 mμ (ε 22,100), 278 (6800), and 321 (6800) [*cf.* piperonal: λ_{max} 275 mμ (6300) and 315 (10,000)]; ν_{max} 1667, 1610, 1036, and 935 cm^{-1}; nmr 10.07 (α-C, s, 1), 7.38 (C-2, s, 1), 6.75 (C-5, s, 1), 6.04 (OCH_2O, s, 2), 5.55 (C-2′, m, 1), 3.65 (C-4′, br, 1), 3.41 (OCH_3, s, 3), *ca.* 2.4 (C-3′ and C-6′, br), *ca.* 1.95 (C-5′, br).

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20; *m/e,* 260.105. Found: C, 68.98; H, 6.31; *m/e,* 260.108.

2-Methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydrofluorene (**11**) (**7-Methoxy-5,6,7,8-tetrahydro[9H]fluoreno[2,3-*d*]-1,3-dioxole**).—A 150-mg sample of dihydrotazettine methine was dissolved in 4 ml of 1 *N* hydrochloric acid and heated on a steam bath 30 min. The suspension was diluted with brine and extracted with ether; the ethereal solution was washed with water and dried over sodium sulfate. The suspension was filtered and concentrated to dryness under reduced pressure to provide 102 mg of the tetrahydrofluorene; examination of the crude material by glpc and tlc (15% ether in benzene) showed it to be essentially pure. Crystallization from methanol provided material with mp 96–98°; $[\alpha]_{436}$ +91.6°, $[\alpha]_{589}$ +42.9° (*c* 1.01); λ_{max} 278 mμ (ε 6700), 307.5 (5800), and 320 sh (4350); ν_{max} 1635, 1605, 1035, 938 cm^{-1}; nmr 6.88 (C-8, s, 1), 6.67 (C-5, s, 1), 5.90 (OCH_2O, s, 2), *ca.* 3.6 (C-2, m, 1), 3.40 (OCH_3, s, 3), *ca.* 3.1 (C-9, br, 2), *ca.* 2.4 (C-1 and C-4, m, 4), *ca.* 2.0 (C-3, m, 2).

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; *m/e,* 244.110. Found: C, 73.60; H, 6.59; *m/e,* 244.109.

2-Methoxy-6,7-methylenedioxy-1,2-dihydro[3H]isofluorene (**12**) (**7-Methoxy-7,8-dihydro[6H]fluoreno[2,3-*d*]-1,3-dioxole**).—A suspension of 42 mg of the aldehyde **4** in 5 ml of 1 *N* hydrochloric acid was heated on a steam bath for 1 hr; yellow crystals formed

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

promptly during the heating. The suspension was distilled to dryness under reduced pressure; the residue was dissolved in ether; the ethereal solution was washed with sodium bicarbonate solution and brine and dried over sodium sulfate. Distillation of the ether left a residue of 40 mg which was shown by gas chromatography to be essentially pure. In an alternative preparation, 75 mg of the aldehyde was dissolved in 1 ml of 6 *N* hydrochloric acid. The solution was warmed on a steam bath for 10 min, then allowed to cool. The yellow precipitate was separated by centrifugation, washed with water and ethanol, and dried under reduced pressure, yielding 41 mg of material, mp 140°. Recrystallization from methanol provided golden prisms: mp 142–143°; $[\alpha]_{589}$ +38.4° (*c* 0.08); λ_{max} 272 mμ (ε 19,800), 277 (18,800), 282 (19,100), 320 (6300), and 389 (400); ν_{max} (CS_2) 1037, 940, 855, and 811 cm^{-1}; nmr 7.00 (C-8, s, 1), 6.72 (C-5, s, 1), 6.66 (C-4, t, br, 1), 6.34 (C-9, s, br, 1), 5.93 (OCH_2O, s, 2), *ca.* 3.65 (C-2, m, 1), 3.40 (OCH_3, s, 3), *ca.* 2.8 (C-1 and C-3, br, 4).

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83; *m/e*, 242.094. Found: C, 74.36; H, 5.93; *m/e*, 242.096.

Dehydrogenation Experiments.—A 25-mg sample of the tetrahydrofluorene **11** was mixed with 100 mg of palladized charcoal (5%) and heated under nitrogen for 20 min in an oil bath maintained at 200°. The residue was dissolved in chloroform, the suspension was filtered through Celite, and the filtrate was evaporated to dryness to provide 15 mg of a mixture which was shown by glpc (190°) to be approximately 17% the fluorene **14** (retention time, 3.7 min) and 83% the methoxyfluorene **13** (8.5 min). Separation by preparative tlc (benzene–petroleum ether, 3:2) provided small samples of 2,3-methylenedioxyfluorene **14**, R_f 0.41, mp 111.5–113° after being sublimed at 80°, 0.001 mm and recrystallized from methanol, and 7-methoxy-2,3-methylenedioxyfluorene **13**, R_f 0.22, mp 158–159.5° after being sublimed and recrystallized from ethyl acetate.

The fluorene **14** showed these spectral properties: λ_{max} 270 mμ sh (ε 9000), 275 (10,000), 291 (6000), 315 sh (9500), 322 (11,000), and 327 (10,500); ν_{max} (CS_2) 1036, 941, 840, 761, and 724 cm^{-1}; nmr *ca.* 7.2 (aromatic, br, 6), 5.92 (OCH_2O, s, 2), 3.67 (C-9, s, 2).

Anal. Calcd for $C_{14}H_{10}O_2$: *m/e*, 210.068. Found: *m/e*, 210.071.

The 7-methoxy-2,3-methylenedioxyfluorene **13** showed the following spectral properties: λ_{max} 235 mμ (ε 9000), 280 (13,000), 298 (9000), 323 sh (9000), and 333 (10,000); ν_{max} (CS_2) 1033, 941, 840, 833, 816, 803, 754, and 740 cm^{-1}; nmr *ca.* 7.2 (aromatic, br, 5), 5.97 (OCH_2O, s, 2), 3.85 (OCH_3, s, 3), 3.72 (C-9, br, 2).

Anal. Calcd for $C_{15}H_{12}O_3$: *m/e*, 240.079. Found: *m/e*, 240.077.

In a similar manner, a 23-mg sample of 2-methoxy-6,7-methylenedioxy-1,2-dihydro[3H]isofluorene (**12**) was heated under nitrogen with 100 mg of 5% palladized charcoal at 200° to provide 10 mg of a similar mixture, which was again separated by preparative thin layer chromatography to give 2,3-methylenedioxyfluorene and 7-methoxy-2,3-methylenedioxyfluorene. The two products were identical in all respects with the fluorene **14** and the methoxyfluorene **13**.

***6-(4′-Methoxycyclohexenyl)piperonylic Acid* (5).**—A solution of 590 mg of the aldehyde in 6 ml of 50% sodium hydroxide and 15 ml of ethanol diluted to 30 ml with water was heated on a steam bath and treated with approximately 30 ml of 30% hydrogen peroxide in 1-ml portions. Addition and heating were at rates sufficient to maintain foaming; total addition time was 90 min. Most of the ethanol was then boiled off, and the mixture was diluted with water and extracted three times with chloroform. The chloroform was washed with water and brine and evaporated under reduced pressure to give 29 mg of neutral material.

The aqueous solution was acidified with hydrochloric acid and extracted repeatedly with chloroform and 4:1 chloroform–ethanol; the organic layers, when washed with water and brine and concentrated under reduced pressure, provided 477 mg of material of mp 145–175° after trituration with acetone. This was recrystallized twice from acetone to yield 186 mg of colorless needles: mp 170–173°; $[\alpha]_{589}$ +40°, $[\alpha]_{436}$ +84°, $[\alpha]_{380}$ +125.5° (*c* 1.20); λ_{max} 252 mμ (ε 7850) and 294 (5060); ν_{max} 2620 (OH, br), 1685 (C=O), 1612 (aromatic), 1035, 932 (OCH_2O); nmr, *ca.* 10.1 (COOH, br, 1), 7.43 (C-2, s, 1), 6.63 (C-5, s, 1), 6.00 (OCH_2O, s, 2), *ca.* 5.42 (C-2′, br, 1), *ca.* 3.6 (C-4′, br, 1), 3.40 (OCH_3, s, 3), 2.5–2.1 (C-3′ and C-6′, br, *ca.* 4), 2.1–1.8 (C-5, br, *ca.* 2).

Anal. Calcd for $C_{15}H_{16}O_5$: *m/e*, 276.100. Found: *m/e*, 276.101.

Performic Acid Treatment of 6-(4′-Methoxycyclohexenyl)-piperonylic Acid.—A solution of 150 mg of the acid **5**, mp 170–173°, in 20 ml of ether was stirred with 210 mg of sodium acetate trihydrate, 1.5 ml of 88% formic acid, and 2 ml of 30% hydrogen peroxide for 18 hr at room temperature. The mixture was diluted with water, made basic with potassium bicarbonate, and extracted three times with ether, which was then washed twice with water and twice with brine, and concentrated to dryness under reduced pressure to provide 169 mg of a crystalline residue. Tlc (benzene–dioxane–acetic acid, 90:25:4) showed three products: a minor component with blue fluorescence under λ 254 mμ, R_f 0.42, imperfectly separated from A; A, R_f 0.45; and B, R_f 0.64. Glpc showed 10% the minor component, 30% A, and 60% B. Fractional crystallization from ethyl acetate provided 65 mg of slightly impure B and, on concentration, 34 mg of A. Chromatography on silicic acid (above solvents) and repeated recrystallization provided analytical samples of A and B.

A, mp 182–185°, was recrystallized from benzene: $[\alpha]_{589}$ +32°, $[\alpha]_{436}$ +76°, $[\alpha]_{350}$ +199° (*c* 0.438); ν_{max} (dil CCl_4) 3632 cm^{-1}; ν_{max} ($CHCl_3$) 1752 (C=O), 1612 (aromatic), 1035, and 935 cm^{-1} (OCH_2O); λ_{max} 223 mμ (ε 27,600), 258 (5600), 301 (7160), unchanged by base; nmr 7.15 (C-2?, s, 1), 7.02 (C-5?, s, 1), 6.00 (OCH_2O, s, 2), 3.83 (C-2′ and C-4′, br, 2), 3.38 (OCH_3, s, 3), 2.53 (OH, eliminated by exchange with D_2O,[19] br, 1), 2.2–1.0 (br).

Anal. Calcd for $C_{15}H_{16}O_6$: *m/e*, 292.095. Found: *m/e*, 292.094.

B, mp 178–181°, was recrystallized from ethyl acetate: $[\alpha]_{589}$ −87°, $[\alpha]_{436}$ −183°, $[\alpha]_{350}$ −399° (*c* 0.519); ν_{max} (dil CCl_4) 3490 cm^{-1}; ν_{max} ($CHCl_3$) 1748 (C=O), 1612 (aromatic), 940 (OCH_2O); λ_{max} 223 mμ (ε 27,300), 258 (5340), 301 (700), unchanged with base; nmr 7.12 (C-2, C-5, s, 2), 6.08 (OCH_2O, s, 2), 4.33 (OH, eliminated by exchange with D_2O, d, $J = 10$, 1), 3.75 (C-2′, t, br, 1), 3.55 (C-4′, br, 1), 2.5–1.3 (br); mmp 148–171° with A.

Anal. Calcd for $C_{15}H_{16}O_6$: *m/e*, 292.095. Found: *m/e*, 292.093.

Attempted Oxidation of the Acetate.—To a solution of 30 mg (0.1 mmol) of the acetate of **3** in 2 ml of purified acetone was added 0.0158 g (0.1 mmol) of potassium permanganate in 0.5 ml of water. No change in color was seen after 20 min. The precipitate which formed after 2 hr of stirring was removed by filtration. The filtrate was evaporated to dryness, washed with sodium thiosulfate solution, and extracted with chloroform to give almost complete recovery of unreacted acetate as shown in the nmr spectrum.

Oxodihydrohaemanthamine Methine (10).—The low solubility of the perchlorate in D_2O made it impossible to determine the chemical shifts of broadened peaks accurately. The singlets observed were at 7.03 (C-5), 6.70 (C-2), 6.02 (OCH_2O), 4.38 (α), 3.93 (α′), 3.43 (OCH_3), and 2.85 ($N\text{-}CH_3$). The salt was more soluble in NaOD solution: nmr 7.05 (C-5, s, 1), 6.45 (C-2, s, 1), 5.90 (OCH_2O, s, 2), 5.30 (C-2′, m, 1), 3.50 (α and C-4′, br, 3), 3.40 (OCH_3, s, 3), 3.04 (α′, s, 2), 2.16 ($N\text{-}CH_3$, s, 3); the remaining alicyclic protons formed a broad peak between 1.6 and 2.5.

Tazettadiol.[14]—A solution of 1.535 g (4.61 mmol) of tazettine in 50 ml of dry tetrahydrofuran was heated to reflux whereupon 0.6 g of lithium aluminum hydride was added in small portions. After a 43-hr reflux period the reaction was worked up as usual to yield 1.502 g (97.5%) of a colorless glass that crystallized on trituration with ether–water–ethanol. Recrystallization from ethanol–ether containing a few drops of water gave the hydrate in two crops which were dried at 80° (0.01 mm) to give 1.123 g (73%) of anhydrous tazettadiol.[2]

Deoxytazettine.[14]—To 1.075 g of anhydrous tazettadiol was added 15 ml of 3% aqueous sulfuric acid. A slight cloudiness developed. The solution was heated on a steam bath for 1.5 hr, then diluted with water, washed once with ether, basified with concentrated sodium hydroxide solution, and finally extracted with three portions of ether. The dried combined ethereal solutions were evaporated to leave 919 mg of partially crystalline glass. Recrystallization from ether gave 629 mg (62%) of large colorless prisms, mp 133–138°. A second recrystallization raised the melting point to 136–138° (lit.[2] mp 135–136°).

Deoxytazettine Methiodide.[14]—A solution of 513 mg of deoxytazettine, 7 ml of absolute methanol, and 4 ml of redistilled methyl iodide was refluxed for 3 hr. The clear solution was evaporated to dryness, and the resulting oil was recrystallized from acetone–methanol to give 632 mg (85%) of stout yellowish prisms in two crops, mp 236–237.5° dec when put on the hot stage at 200° (lit.[2] mp 231–233°).

Deoxytazettine Methine.[14]—A mixture of 250 mg of deoxytazettine methiodide and 8 ml of water was stirred until the methiodide was in solution. Then the freshly prepared silver oxide (neutral) from 0.3 g of silver nitrate was added and the mixture stirred for 15 min more when a test portion showed no iodide ion to be present. The insoluble silver salts were removed by filtration through a layer of Filter-Cel. The colorless clear filtrate was evaporated to dryness *in vacuo*, and the residue was heated at 100° for 30 min under aspirator vacuum. The reaction product was dissolved in benzene and separated from some insoluble material. Evaporation of the benzene left 177 mg (98%) of colorless methine which was chromatographed on 5 g of activity I Merck alumina. Benzene and benzene–ether combinations eluted a total of 145 mg (80%) of methine. A middle fraction had $[\alpha]^{27}_{589}$ −73° (*c* 2.45 in 95% ethanol) (lit.[2] $[\alpha]^{17}_{589}$ −64.2°). The material was a colorless glass that did not crystallize.

Deoxytazettine Neomethine.[14]—Chromatographed deoxytazettine methine (96 mg) was dissolved in 10 ml of 5% hydrochloric acid at room temperature. The solution became cloudy within a few seconds and then deposited crystals. After 1 hr the reaction mixture was washed with two portions of ether. The aqueous layer was basified with concentrated sodium hydroxide solution and extracted with three portions of ether. The ethereal solutions were dried and evaporated to leave 54 mg (62%) of colorless glass, $[\alpha]^{27}_{589}$ −40° (*c* 2.65 in 95% ethanol).

Deoxytazettine Neomethine Methiodide.[14]—(The solution used for the optical rotation was recovered and used.) Deoxytazettine neomethine (52 mg) was dissolved in a mixture of redistilled methyl iodide and acetone (several milliliters) and allowed to stand at room temperature for 20 hr. The acetone and methyl iodide were evaporated to leave 77 mg (99%) of glass which crystallized on trituration with 1 drop of methanol. One recrystallization from acetone–methanol gave 63 mg: mp 254–255.5° dec, $[\alpha]^{27}_{589}$ −5.4° (*c* 1.65, 95% ethanol). A second recrystallization from acetone–methanol raised the melting point to 257–258° dec, $[\alpha]^{27}_{589}$ −5.4° (*c* 1.38, 95% ethanol) {lit. mp 251° dec, $[\alpha]^{18}_{589}$ ±0° (*c* 0.51, ethanol)[2]}.

Registry No.—**1**,[21] 16831-68-8; **2**, 16831-69-9; picrate of **2**, 16831-70-2; **3**, 7111-88-8; acetate of **3**, 16831-72-4; **4**, 16831-73-5; **5**, 16831-74-6; **10**, 16831-75-7; **11**, 16831-76-8; **11**, 1,2-d_2, 16831-21-3; **12**, 16831-22-4; **12**, 2-*d*, 16831-23-5; **12**, 1,2-d_2, 16831-24-6; **13**, 16831-25-7; **14**, 242-90-0; **15**, 16831-27-9; **16**, 16831-28-0.

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[21] Methiodide.

The Absolute Configuration of Alkaloids Related to Crinine, Tazettine, and Manthine

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Oxidation of dihydrotazettine methine alcohol to (+)-(*R*)-2-methoxyadipic acid establishes unequivocally the stereochemistry of C-3 of tazettine and, hence, of related alkaloids, previously assigned on the basis of Mills' rule. Studies on dideuteriotazettine demonstrate the course of the Hofmann reaction leading to the critical derivative. Compilation of 17 pairs of interrelated epimers shows that Mills' rule may be applied with consistency throughout the group.

One of the results of the extensive investigations of the alkaloids of the *Amaryllidaceae* has been to establish a sizable group, to date comprising some 30 natural materials,[1] of interrelated compounds with the fundamental ring systems of tazettine, crinine, or manthine. The structures and stereochemistry of the three groups have been securely interrelated by studies on two key members, haemanthamine (**1**) and haemanthidine (**3**). Thus hydrogenolysis of diacetyl haemanthidine (**4**) provides dihydrohaemanthamine acetate (**2**) while treatment of haemanthidine with base provides nortazettine (**5**).[2] The interrelation is confirmed by the conversion of tazettine (**6**) by successive treatment with lithium aluminum hydride and with thionyl chloride and pyridine to the methiodide of the C-11 epimer of haemanthamine.[3] Treatment of haemanthamine (**1**) by methanesulfonyl chloride in pyridine and then by methanolic sodium methoxide converts the alkaloid into manthine (**7**).[4] Exhaustive chemical and spectral studies have established the structural and stereochemical relations of the various hydroxyl- and methoxyl-bearing analogs within the groups and the stereochemistry of the ring junctions.[5,6]

The absolute configuration of this series of alkaloids has been assigned on the basis of Mills' rule,[7] which states that a 2-cyclohexenyl derivative of the configuration of **8** will possess a more positive rotation

[1] Review articles list the following related alkaloids: crinine (crinidine), vittatine, (+)-epicrinine, powelline, buphanidrine, buphanisine, undulatine, crinamidine, flexinine, nerbowdine, buphanamine, haemanthamine, haemanthidine, 6-hydroxycrinamine, criwelline, isotazettine, and haemultine. *Cf.* W. C. Wildman in "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, p 289; H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Academie-Verlag, Berlin, 1961, p 410. Later work has assigned the following alkaloids to this group: (a) montanine, coccinine, and manthine: Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960); (b) crinamine: H. M. Fales and W. C. Wildman, *J. Amer. Chem. Soc.*, **82**, 197 (1960); (c) epihaemanthidine: J. Goosens, P. W. Jeffs, J. Graham, F. L. Warren, and W. G. Wright, *J. Chem. Soc.*, 1088 (1960); (d) epibuphanisine: H. Hauth and D. Stauffacher, *Helv. Chim. Acta*, **45**, 1307 (1962); (e) ambelline: P. Naegeli, E. W. Warnhoff, H. M. Fales, R. E. Lyle, and W. C. Wildman, *J. Org. Chem.*, **28**, 206 (1963); (f) acetylnerbowdine: H. Hauth and D. Stauffacher, *Helv. Chim. Acta*, **46**, 810 (1963); (g) cripaline: W. Doepke, *Arch. Pharm.* (Weinheim), **295**, 868 (1962); (h) squamigerine: S. H. Hung and K. E. Ma, *Yao Hseuh Hsueh Pao*, **11**, 1 (1964); *Chem. Abstr.*, **61**, 3154 (1964); (i) amaryllisine: A. L. Burlingame, H. M. Fales, and R. J. Highet, *J. Amer. Chem. Soc.*, **86**, 4976 (1964); (j) macronine: C. F. Murphy and W. C. Wildman, *Tetrahedron Lett.*, 3857 (1964); (k) tubispacine: W. Doepke, *Arch. Pharm.* (Weinheim), **298**, 704 (1965); (l) pretazettine: W. C. Wildman and D. T. Bailey, *J. Amer. Chem. Soc.*, **89**, 5515 (1967).

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