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.

Acknowledgment.—We are indebted to Mrs. K. S. Warren of this laboratory for many of the spectral observations recorded here.

(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).

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

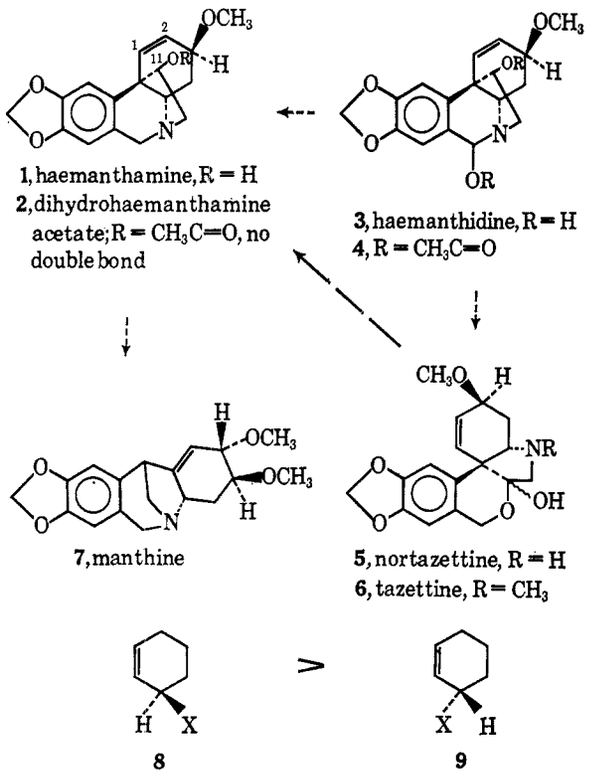
(3) T. Kitagawa, S. Uyeo, and N. Yokayama, *ibid.*, 3749 (1959).

(4) Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960).

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

(6) H. M. Fales and W. C. Wildman, *ibid.*, **82**, 197 and 3368 (1960).

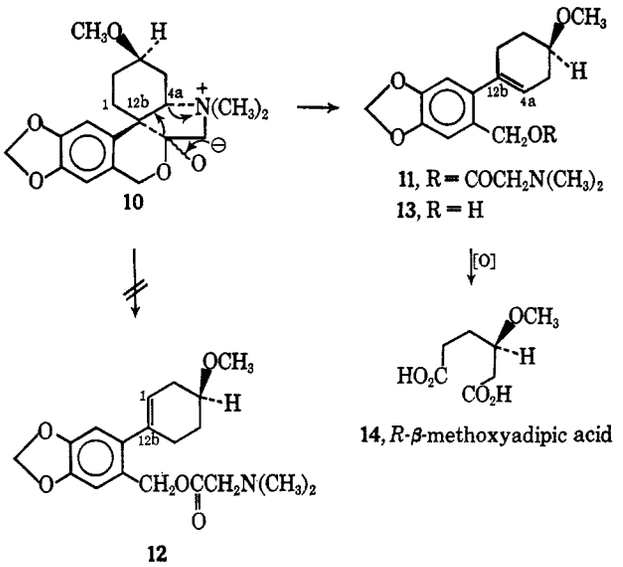
(7) T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 4749 (1956).



than its epimer, **9**.[8] Early in the work on tazettine it was observed that the rotations of four epimeric pairs of derivatives of tazettine allowed a consistent application of this rule. Tazettine was therefore assigned the configuration of **6**, with the reservation that applying the rule to these alkaloids was uncertain, for it had been derived from studies on steroids.[7] Work to 1960 provided a total of seven pairs, including crinine derivatives, with rotations consistent with the previous assignment.[9] The continuing proliferation of alkaloids and derivatives within the group has now provided at least 17 pairs of epimers, listed in Table I. The series includes a variety of structural types, and the fact that there are no anomalies in rotation strongly suggests that Mills' rule is indeed applicable here. However, there has been no unequivocal evidence on the point, and a recent extensive survey of the optical rotatory dispersion and circular dichroism of structurally related alkaloids has suggested that the assignment must be reversed in the series.[10]

Recently, it has been demonstrated that the product of Hofmann reaction of dihydrotazettine possesses the structure **11**,[11] which retains only one of the asymmetric centers of the parent alkaloid. It appeared likely that this material would provide a basis for relating the series to material of known configuration through its oxidation to β-methoxyadipic acid, the absolute configuration of which has been determined by degradation of calciferol[12] and by synthesis from malic acid.[13] Although the sterically hindered double bond is rather unreactive, exhaustive ozonization and peroxide treatment[14] of recrystallized dihydrotazettine methine alcohol produced a mixture of acids which contained the desired acid in good yield. Preparative gas chromatography of the methyl esters provided a convenient means of isolating this product in sufficient quantity to determine that it was the methyl ester of (+)-(*R*)-β-methoxyadipic acid.

It is now essential to consider the course of the Hofmann decomposition of dihydrotazettine methohydroxide. It has been pointed out[11] that decomposition must occur on the intact hemiacetal, for the ether linkage of the alkaloid appears as the ester linkage of the methine and, furthermore, since the course of the decomposition of O,N-dimethyltazettine proceeds in quite a different manner,[7] that the decomposition in question must involve the hydroxyl group. The course of the reaction is most credibly represented as in process **10** by which the double bond of the methine **11** appears at the atoms C-4a and C-12b of the original alkaloid. However, were the reaction to take an unexpected course with the double bond appearing at the atoms C-12b and C-1 of the parent alkaloid, the product would be the mirror image, **12**. Thus proof of the absolute



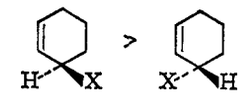
configuration of the alkaloid requires that the position of the double bond of dihydrotazettine methine be known in relation to the parent alkaloid. This was shown by running the Hofmann reaction on dideuteriotazettine.

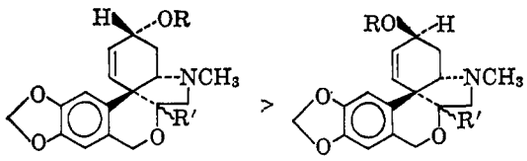
Although catalytic deuteration has been shown to produce extensive isotope exchange at saturated centers in some cases,[15a] the deuteration of tazettine proceeded substantially without exchange. The mass spectrum of the product showed a parent peak at the required *m/e* of 335, with a somewhat enhanced peak at 336. Hofmann decomposition of the methohydroxide and hydrolysis of the methine provided the crystalline alcohol. The vinyl proton appears at δ 5.55 ppm in full strength, and the mass spectrum shows a molecular ion at *m/e* 264, 2 higher than the undeuterated compound, with a negligible peak at 263. If the new double bond were to occur between C-12b and C-1, the product must

(8) J. A. Mills, *J. Chem. Soc.*, 4976 (1952).
(9) P. W. Jeffs, F. L. Warren, and W. G. Wright, *ibid.*, 1090 (1960).
(10) G. G. DeAngelis, Ph.D. Thesis, Iowa State University, Ames, Iowa, 1966.
(11) R. J. Highet, J. C. N. Ma, and P. F. Highet, *J. Org. Chem.*, **33**, 3096 (1968).
(12) S. Bergstrom, A. Lardon, and T. Reichstein, *Helv. Chim. Acta*, **32**, 1617 (1949).
(13) M. Viscontini and P. Miglioretto, *ibid.*, **38**, 930 (1954).
(14) H. Corrodi and E. Hardegger, *ibid.*, **39**, 889 (1956).
(15) K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962: (a) pp 227, 241; (b) p 102.

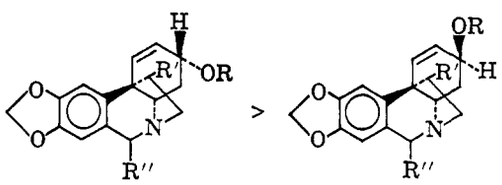
TABLE I

OPTICAL ACTIVITY OF EPIMERIC PAIRS RELATED TO CRININE

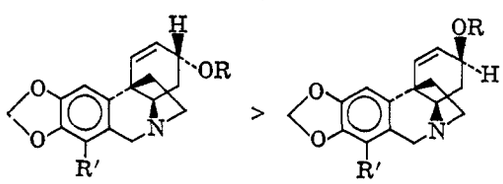




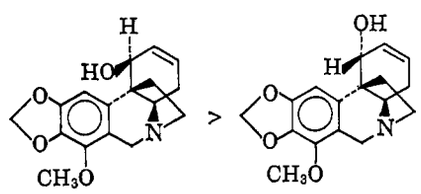
R	R′	R″		MD, deg	Ref		MD	Ref
H	OH		Isotazettinol	+831	*a*	Tazettinol	+377	*a*
H	H		Deoxyisotazettinol	+988	*a*	Deoxytazettinol	+632	*a*
$CH_3C{=}O$	H		Acetyldeoxyisotazettinol	+680	*a*	Acetyldeoxytazettinol	+185	*a*
CH_3	OCH_3		O-Methylisotazettine methiodide	+696	*a*	O-Methyltazettine methiodide	+330	*a*
CH_3	OH		Criwelline	+728	*b*	Tazettine	+536	*c*



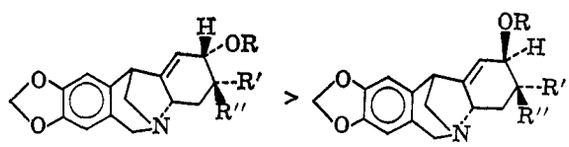
CH_3	OH	H, OH	6-Hydroxycrinamine	+146	*d, e*	Haemanthidine	−130	*f,e*
CH_3	OH	O	6-Oxocrinamine	+91	*g*	Oxohaemanthidine	−130	*h*
CH_3	OH	H_2	Crinamine	+471	*i*	Haemanthamine	+59	*j*
H	H	H_2	(+)-Epicrinine	+368	*k*	Vittatine	+103	*l*



H	H		Crinine	−30	*i*	(−)-Epicrinine	−384	*m*
H	OCH_3		Powelline	0	*n*	Epipowelline	−310	*m*
CH_3	H		Buphanisine	−74	*o*	(−)-Epibuphanisine	−396	*p*



			Epibuphanamine	+69	*q*	Buphanamine	−617	*r*

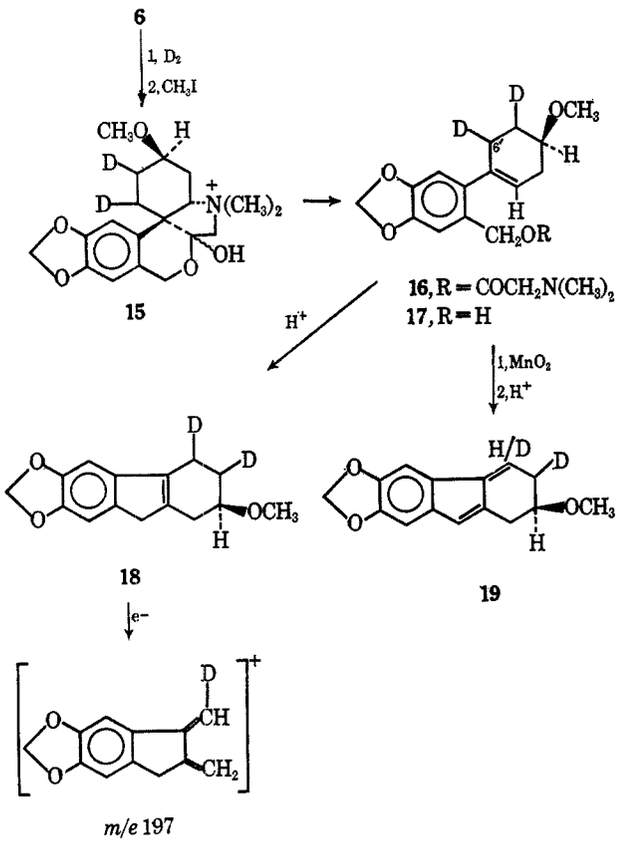


CH_3	H	OH	Montanine	−294	*j*	Coccinine	−569	*j*
			Montanine methiodide	+44.3	*s*	Coccinine methiodide	−268	*j*
H	H	OCH_3	Isohaemanthamine	−219	*s*	Epiisohaemanthamine	−372	*s*
CH_3	H	OCH_3	Manthine	−250	*s*	O-Methylcoccinine	−412	*s*
H	OCH_3	H	β-Isocrinamine	−313	*s*	α-Isocrinamine	−583	*s*

[a] T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 4749 (1956). [b] H.-G. Boit and H. Ehmke, *Chem. Ber.*, **89**, 2093 (1956). [c] W. C. Wildman and C. J. Kaufman, *J. Amer. Chem. Soc.*, **76**, 5815 (1954). [d] H. M. Fales, D. H. S. Horn, and W. C. Wildman, *Chem. Ind.* (London), 1415 (1959). [e] It has recently been shown that 6-hydroxycrinamine and haemanthidine exist in solution as mixtures of the C-6 epimers. R. W. King, C. F. Murphy, and W. C. Wildman, *J. Amer. Chem. Soc.*, **87**, 4912 (1965). [f] H.-G. Boit, *Chem. Ber.*, **87**, 1339 (1954). [g] J. Goosen, P. W. Jeffs, J. Graham, F. L. Warren, and W. G. Wright, *J. Chem. Soc.*, 1088 (1960). [h] S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Amer. Chem. Soc.*, **89**, 2590 (1958). [i] L. H. Mason, E. R. Puschett, and W. C. Wildman, *ibid.*, **77**, 1253 (1955). [j] W. C. Wildman and C. J. Kaufman, *ibid.*, **77**, 1248 (1955). [k] R. E. Lyle, E. A. Kielar, J. R. Crowder, and W. C. Wildman, *ibid.*, **82**, 2620 (1960). [l] H.-G. Boit, *Chem. Ber.*, **89**, 1129 (1956). [m] W. C. Wildman, *J. Amer. Chem. Soc.*, **80**, 2567 (1958). [n] H.-G. Boit and H. Ehmke, *Chem. Ber.*, **88**, 1590 (1955). [o] H. M. Fales and W. C. Wildman, *J. Amer. Chem. Soc.*, **82**, 3368 (1960). [p] H. Hauth and D. Stauffacher, *Helv. Chim. Acta*, **45**, 1307 (1962). [q] H. M. Fales and W. C. Wildman, *J. Org. Chem.*, **26**, 881 (1961). [r] J. Renz, D. Stauffacher, and E. Seebeck, *Helv. Chim. Acta*, **38**, 1209 (1955). [s] Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960).

either possess a vinyl deuterium atom or must have lost a deuterium in the course of decomposition; or, in the likely event that either the reduction or decomposition occur without stereospecificity, some combination of these two states must exist.

The location assigned these deuterium atoms was further established by study of known derivatives of the methine. Acid treatment of the methine, **16**, provided the dideuteriodihydrofluorene **18**, with the anticipated nmr spectrum. The mass spectrum of this material is characterized by a base peak resulting from the familiar "reverse Diels–Alder" process;[15b] in this case the methyl vinyl ether fragment lost from the dideuterated parent (*m/e* 246) contained a single deuterium atom. As a result, the base peak at *m/e* 197 is one more than that of undeuterated material and is consistent with the assigned position. Oxidation of the alcohol **17** by manganese dioxide provided the aldehyde, which was



converted by acid treatment into the isofluorene derivative **19**. This cyclization involved the loss of a proton or deuterium from C-6′ of the aldehyde, producing a mixture of dideuterio and monodeuterio material, characterized by a vinyl proton of half strength in the nmr and a mass spectrum with parent peaks of 243 and 244 of equal height.

Thus the study of the derivatives of dideuteriotazettine confirms that the double bond of the methine is situated at C-4a and C-12b of the original alkaloid. The stereochemical relation of the alkaloid, the methine, and the methoxyadipic acid are as depicted in **10**, **11**, and **14**, and the isolation of a dextrorotatory sample of the last compound substantiates the earlier assignment of the absolute configuration.

Experimental Section[16]

Degradation of Dihydrotazettine Methine Alcohol to β-Methoxyadipic Acid.[14]—Ozone was bubbled through a solution of 122 mg of dihydrotazettine methine alcohol[11] in 10 ml of 10:1 chloroform–ethanol for 5 hr, the solvent being replenished as necessary. The solution was allowed to stand overnight, then concentrated to dryness under reduced pressure. The residue was refluxed for 1 hr in a mixture of 2 ml each of formic acid and hydrogen peroxide, again concentrated to dryness under reduced pressure to yield 125 mg of material which was estimated by glpc to contain 49 mg of β-methoxyadipic acid, contaminated with materials of lower molecular weight. The sample was methylated with diazomethane and purified by glpc, using a 12 ft × 4 mm glass column, packed with 100–120 mesh Gas-Chrom P coated with 20% Reoplex 400, at 165°, with argon carrier gas at a pressure of 15 psi. Fractions were collected by condensing the carrier gas with liquid nitrogen. Center cuts of the appropriate peak produced 12 mg of dimethyl β-methoxyadipate, identical with authentic dimethyl *dl*-β-methoxyadipate in ir and mass spectrum and glpc on three columns: retention times on a 12-ft column of 20% Reoplex 400 on 100–120 mesh Gas-Chrom P at 180°, 15 psi, 5.2 min; on a 6-ft column of 1% SE-33 on 80–100 mesh Gas-Chrom P at 120°, 20 psi, 3.5 min; on a 6-ft column of 3% OV-17 on 60–80 mesh Gas-Chrom Q at 120°, 15 psi, 3.9 min; $[\alpha]^{25}_{589}$ +8.50°, $[\alpha]_{436}$ +16.9, $[\alpha]_{350}$ +30.0, $[\alpha]_{300}$ +48.2, $[\alpha]_{260}$ +72.8 (*c* 0.103, $CHCl_3$); ir ($CHCl_3$) 1723 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 204 (0.1), 189 (1), 174 (5), 173 (15), 157 (4), 141 (22), 131 (57), 118 (6), 117 (31), 113 (15), 109 (7), 101 (9), 99 (19), 89 (11), 85 (10), 81 (5), 75 (100), 74 (6), 72 (8), 71 (84), 59 (28), 58 (7), 55 (11), 53 (6), 47 (6), 45 (8), 43 (11), 41 (16).

Synthetic (−)-(*S*)-β-Methoxyadipic Acid and Dimethyl Ester.—Authentic *dl*-β-methoxyadipic acid was prepared by the method of Viscontini and Kohler[17] and resolved by converting material of mp 84.5–87° (lit. mp 85–86°) into the strychnine salt and recrystallizing from water until regenerated portions of the acid showed no further change of rotation. The acid was regenerated by chromatography on Dowex 50 and recrystallized from ether–petroleum ether: mp 71–74.5° (lit.[18] mp 74–75°); $[\alpha]^{25}_{589}$ −14.0°, $[\alpha]_{436}$ −28.2°, $[\alpha]_{350}$ −49.7° (*c* 4.97, $CHCl_3$) (lit.[18] $[\alpha]^{18}_{D}$ −14.5 ± 1.5°, $CHCl_3$).

A 51-mg sample of the (−)-(*S*) acid was treated with diazomethane to provide 61 mg of the methyl ester, which was distilled at 50° (3 μ) to produce material of $[\alpha]^{25}_{589}$ −10.3°, $[\alpha]_{436}$ −20.9, $[\alpha]_{350}$ −35.7, $[\alpha]_{300}$ −56.2, $[\alpha]_{260}$ −85.2 (*c* 0.130, $CHCl_3$).

Dideuteriotazettine was prepared by stirring a solution of 386 mg of tazettine in ethanol-*d* under deuterium in the presence of 167 mg of 10% palladium on charcoal. The product was purified as usual by chromatography on alumina and crystallization from benzene–hexane to yield 251 mg of material of mp 164–167° and 33 mg of less pure material of mp 161–165°. The infrared spectrum differed from that of dihydrotazettine primarily by having a small peak at 2175 cm^{-1}. The nmr differed only in the integrated strength of the broad peaks at *ca.* 2 ppm.

The other deuterated compounds were prepared from this material by previously described methods.[11]

The Hofmann reaction was run on 124 mg and yielded 130 mg (101%) of methine. A 100-mg sample of this was hydrolyzed to 75 mg of the alcohol, which was chromatographed and recrystallized from ether–pentane to give 56 mg (74%) of material of mp 63–64°.

Acid cyclization of 15 mg of the alcohol produced 10 mg (71%) of material, which was crystallized three times from methanol to give 4 mg (29%) of mp 90–92°.

Oxidation of 29 mg of the alcohol with manganese dioxide gave 26 mg of the aldehyde, recrystallized from methanol to 17 mg (59%) of mp 65–68°.

(16) Melting points were observed on a Kofler microscope hot stage and are corrected. Rotations were measured with a Rudolph photoelectric spectropolarimeter using a 2-dm tube or with a Cary 60 recording spectropolarimeter in 1-cm cells. Infrared spectra were recorded on a Perkin-Elmer Model 21. Nmr measurements were obtained on a Varian A-60 spectrometer in deuteriochloroform solution, using tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were determined with a single-focusing LKB mass spectrometer equipped with a gas chromatographic inlet.

(17) M. Viscontini and H. Köhler, *Helv. Chim. Acta*, **37**, 41 (1954).

(18) A. Lardon and T. Reichstein, *ibid.*, **32**, 1613 (1949).

A 19-mg sample of the aldehyde was cyclized with acid and the product crystallized twice from methanol to yield 9 mg (53%) of yellow crystals, mp 131.5–137.5°. Further recrystallization (four times) produced material of mp 138–142°.

Registry No.—Tazettine, 507-79-9; dihydrotazettine methine alcohol, 16831-67-7; (−)-(*S*)-β-methoxyadipic acid dimethyl ester, 16859-76-0; dieuteriotazettine, 16831-30-4.

The Perchloric Acid Catalyzed Acetic Anhydride Enol Acetylation of Steroidal Δ4-3 Ketones

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The perchloric acid catalyzed acetic anhydride acylation of 17β-hydroxyandrost-4-en-3-one gave complex mixtures of products in which both O and C acylation occurred. The major constituents of the reaction were 3,17β-diacetoxy-2-acetylandrosta-2,4-diene (6) and 3,17β-diacetoxy-6-acetylandrosta-3,5-diene (3).

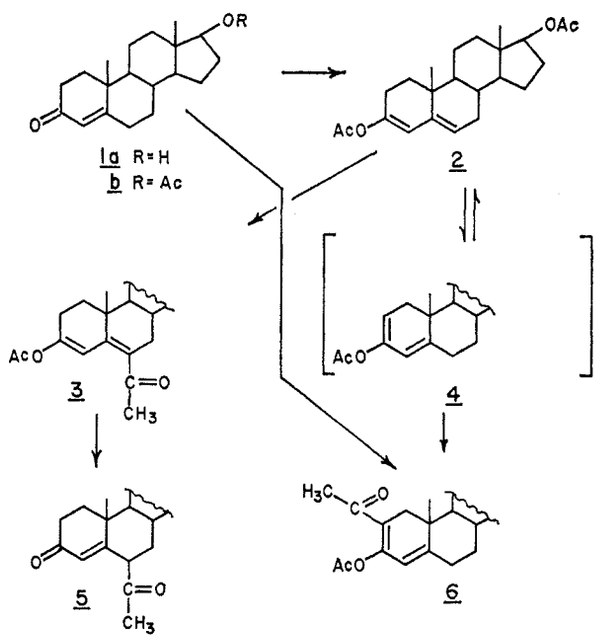
It was previously demonstrated that the C-11β-hydroxyl group of steroids has a pronounced influence on the enolization properties of 3-oxo-5β steroids as measured by the thermodynamically controlled enol acetylation reaction which employs acetic anhydride–perchloric acid mixtures.[2] In order to measure this effect in the biologically active steroids, it became necessary to investigate the perchloric acid–acetic anhydride enol acetylation of Δ4-3 ketones. There are reports[3–6] that this mixture is capable of carrying out O acylations on unsaturated compounds; however, the reagent has not been carefully studied with Δ4-3 ketones.

17β-Hydroxyandrost-4-en-3-one (**1a**) was treated with a solution of perchloric acid in acetic anhydride and the reaction was quenched in 40 min. Gas chromatographic analysis (glpc) of the crude reaction mixture indicated the product to be essentially pure 3,17β-diacetoxyandrosta-3,5-diene (**2**). The compound was isolated in 72% yield and identified by comparison with an authentic sample prepared from the isopropenyl acetate enol acetylation of **1a**.[7,8]

When the reaction time of the perchloric acid catalyzed enol acetylation was extended to 4 hr, eight compounds were detected by glpc in the reaction mixture; five were isolated (Scheme I). The first one eluted by preparative glpc was 3,17β-diacetoxyandrosta-3,5-diene (**2**), identified by comparison with authentic material.[7] A second substance, isolated by preparative glpc, was shown to be 17β-acetoxyandrost-4-en-3-one (**1b**) by comparison with known material. Further attempts to isolate the remaining products by preparative glpc were not successful owing to thermal decomposition of the products during chromatography.

Preparative tlc was used to isolate the remainder of the products. From a band at R_f 0.60 there was obtained pure 3,17β-diacetoxy-6-acetylandrosta-3,5-diene which was assigned structure **3** on the basis of its spectral properties. The infrared spectrum demonstrated enol acetate, ester, and conjugated carbonyl bands. The ultraviolet spectrum exhibited absorptions at λ_{max} 281 mμ (ε 7900) and 220 (8800). The predicted absorption maximum by the Scott modification of the Woodward rules[9a] is at 296 mμ. The observed maximum at 281 mμ and the relatively low intensity of the band suggests an extended chromophore with incomplete conjugation due to the *peri* effect from the C-4 vinylic proton.[10,11] The nmr spectrum of 3,17β-diacetoxy-6-acetylandrosta-3,5-diene (**3**) is recorded in Table I and is consistent with the assigned structure. The locations of the angular methyl group signals in the

SCHEME I



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(2) A. J. Liston and M. Howarth, *J. Org. Chem.*, **32**, 1034 (1967).

(3) The use of perchloric acid–acetic anhydride acetylating conditions[4] leads to enol–acetate mixtures which reflect the enolization properties of the cyclic ketone.[5] The enol–acetate ratio has been related to the theoretically calculated stability between isomeric enolic forms.[6]

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(7) The Δ3,5-dienol acetate was conveniently prepared by the isopropenyl acetate method[8] and compared with known material; *cf.* U. Westphal, *Chem. Ber.*, **70**, 2128 (1937).

(8) W. G. Dauben, R. A. Micheli, and J. F. Eastham, *J. Amer. Chem. Soc.*, **74**, 3852 (1952).

(9) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964: (a) p 50; (b) p 67.

(10) A similar ultraviolet spectrum for 6-acetylcholesta-3,5-diene with uv absorptions at λ_{max} 281 mμ (ε 6150), 221 (9400), was recorded by Elmes, Hartshorn, and Kirk.[11] In both instances the compounds were strongly levorotatory, the 3,17β-diacetoxy-6-acetylandrosta-3,5-diene (**3**) exhibiting an $[\alpha]^{28}D$ −167.8° and 6-acetylcholesta-3,5-diene having $[\alpha]D$ −159°.

(11) B. C. Elmes, M. P. Hartshorn, and D. N. Kirk, *J. Chem. Soc.*, 2285 (1964).