The Diterpene Alkaloids. Further Studies of Atisine Chemistry[1]

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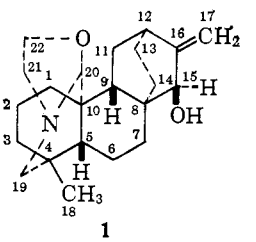
A functional group analysis of atisine (**1**), *isoatisine* (**4**), *and dihydroatisine* (**2**) *by infrared spectroscopy, Kuhn–Roth oxidation, and ozonolysis indicates the presence of hydroxyl, CCH_3, and exocyclic methylene groups in each compound. The existence of an oxazolidine ring in atisine is demonstrated by oxidation to a lactam dicarboxylic acid* (**6**) *whose dimethyl ester* (**7**) *shows no hydroxyl absorption in the infrared. Oxidation of atisine and isoatisine with chromium trioxide–pyridine gave enones* **10** *and* **11**, *respectively, which showed the absence of hydroxyl absorption in the infrared. By-products obtained in this oxidation were compounds to which structures* **13** *and* **20** *were assigned. Treatment of isoatisine with HCl in ethanol gave a mixture of methyl ketones* **24a** *and* **24b**, *which were separated by crystallization. Wolff–Kishner reduction of* **24** *gave deoxytetrahydroatisine* (**25**). *Selenium dehydrogenation of* **25** *gave 1-methyl-6-isopropylphenanthrene* (**26**), *an unknown $C_{18}H_{18}$ hydrocarbon, imines* **27** *and* **29**, *and a lactam* (**31**). *Reduction of the lactam and acetylation afforded an N-acetate* (**30**) *which was related to imine* **29**. *The formation of* **26** *is evidence for the disposition of the allylic alcohol grouping on the bicyclo[2.2.2]octane system as in* **23**, *rather than* **22**. *The chemistry of the ternary imimum salts* (**33** *and* **36**) *of atisine and isoatisine is discussed. Treatment of atisinium chloride diacetate* (**33**, *X = Cl*) *with cold 0.1 N sodium hydroxide gives atisine monoacetate* (**39**). *Methanolysis of the latter furnished atisine* (**1**). *Reduction of the imino alcohol* (**42**) *with zinc dust–acetic anhydride gave an N-acetate* (**43a**) *and a small yield of a bimolecular reduction product* (**44a**). *Refluxing* **42** *in acetic anhydride for extended periods gave what appeared to be an aziridine* (**48**). *Catalytic reduction of atisine gives a mixture of α- and β-tetrahydroatisines as well as the methyl ketones* (**53**). *High-resolution infrared studies allow assignment of the configuration to the secondary methyl group in α-* (**51**) *and β-tetrahydroatisine* (**52**). *Methyl ketones* **24a** *and* **24b** *were related to α- and β-tetrahydroatisine, respectively. The relative stereochemistry of atisine is assigned by conformational analysis of certain derivatives and by the fact that the ketone group in* **65** *can be shown to be relatively unhindered. Reduction of* **65** *with sodium borohydride gave epimers* **64a** *and* **64b** *each of which readily formed an acetate. The N-ethyl derivatives* (**67a** *and* **69a**) *and their corresponding acetates* (**67b** *and* **69b**) *have pK_a' values which also confirm the unhindered character of the carbonyl group in* **65**. *These results limit the stereochemistry of atisine to* **60** *or* **63**. *Since ajaconine chemistry requires anticoupling of rings A and C, the complete relative chemistry of atisine is expressed by* **60**.

In the course of our continuing studies on atisine, the major diterpene alkaloid[3] of *Aconitum heterophyllum* Wall (*Ranunculaceae*), we have found it expedient from time to time to present our work describing the elucidation of certain structural features of atisine in the form of preliminary communications.[4-13] Now that this work and that from other laboratories[14-18] have culminated in the assignment of the complete structure and stereochemistry to this compound, we wish to disclose the details of our work and to discuss certain interesting chemical features of the atisine molecule. This chemistry will be discussed in terms of structure **1** which has recently been confirmed by two independent total syntheses.[19,20]



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(1) This investigation was supported in part by Grants RG5807 and GM 10921 from the National Institutes of Health, U. S. Public Health Service.

(2) The Department of Chemistry, University of Georgia, Athens, Ga.

(3) Recent review articles on the diterpene alkaloids are: (a) S. W. Pelletier, *Experientia*, 20, 1 (1964); (b) S. W. Pelletier, *Tetrahedron*, **14**, 76 (1961); (c) H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Academie-Verlag, Berlin, 1961, pp. 851–905, 1009–1011; (d) E. S. Stern in "The Alkaloids," Vol. VII, R. H. F. Manske, Ed., Academic Press, Inc., New York, N. Y., 1960, pp. 473–503; (e) K. Wiesner and Z. Valenta, "Progress in the Chemistry of Organic Natural Products," Vol. XVI, Springer-Verlag, Vienna, 1958, pp. 26–63.

(4) S. W. Pelletier and W. A. Jacobs, *J. Am. Chem. Soc.*, **76**, 4496 (1954).

(5) S. W. Pelletier and W. A. Jacobs, *Chem. Ind.* (London), 1385 (1955).

(6) S. W. Pelletier, *ibid.*, 1670 (1957).

(7) D. M. Locke and S. W. Pelletier, *J. Am. Chem. Soc.*, **80**, 2588 (1958).

(8) S. W. Pelletier, *Chem. Ind.* (London), 1116 (1958).

(9) S. W. Pelletier, *J. Am. Chem. Soc.*, **82**, 2398 (1960).

(10) A. J. Solo and S. W. Pelletier, *Chem. Ind.* (London), 1108 (1960).

(11) A. J. Solo and S. W. Pelletier, *Proc. Chem. Soc.*, 14 (1961).

(12) S. W. Pelletier and P. C. Parthasarathy, *Tetrahedron Letters*, **No. 4**, 205 (1963).

(13) S. W. Pelletier and K. Kawazu, *Chem. Ind.* (London), 1879 (1963).

(14) K. Wiesner and J. A. Edwards, *Experientia*, 11, 255 (1955).

(15) D. Dvornik and O. E. Edwards, *Can. J. Chem.*, **35**, 860 (1957).

(16) J. W. ApSimon, O. E. Edwards, and R. Howe, *ibid.*, **40**, 630 (1962).

(17) H. Vorbrueggen and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 2990 (1962).

(18) J. W. ApSimon and O. E. Edwards, *Can. J. Chem.*, **40**, 896 (1962).

(19) W. Nagata, T. Sugasawa, M. Narisuda, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, **85**, 2342 (1963).

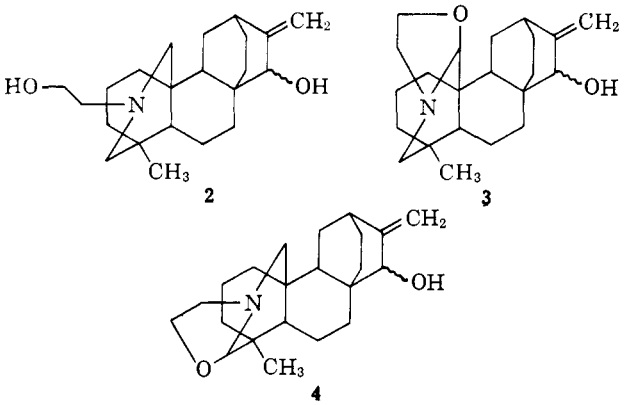
(20) S. Masamune, *ibid.*, **86**, 291 (1964).

Table I

	Atisine	Isoatisine	Dihydroatisine	Tetrahydroatisines
Infrared data, cm.$^{-1}$	3390[a,b] (OH) 3067[a] 1647[a] (>C=CH$_2$) 894[b] 1370[b] (C—CH$_3$)	3456[c] (OH) 3012[c] 1656[c] (>C=CH$_2$) 893[c] 1385[c] (C—CH$_3$)	3425,[d] 3356 sh (OH) 3058[d] 1650[d] >C=CH$_2$ 889[d] 1370[e] (C—CH$_3$)	α-3515,[f] 3639[f] (OH) β-3515,[f] 3628[f] (OH) 1370[e] (C—CH$_3$)
Ozonization, % CH$_2$O as dimedon deriv.	42	45	57	...
Kuhn-Roth (C—CH$_3$), mole fraction of acetic acid	0.6	0.5	0.6	1.0

[a] Nujol, CaF_2 prism. [b] Film, NaCl prism. [c] KBr, NaCl prism. [d] Nujol, NaCl prism. [e] Solution in $CHCl_3$. [f] Solution in CCl_4.

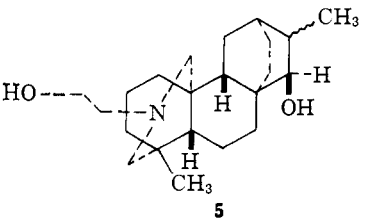
At the time the studies described in this paper were initiated, Jacobs and his collaborators had defined the relationship of the functional groups of atisine, demonstrated its diterpene nature, carried out exhaustive degradative studies, and postulated a structure consonant with the then known facts.[21-27] In subsequent work on the alkaloids of *Garrya veatchii* Kellogg, Wiesner paralleled Jacobs' early studies on atisine and showed the striking similarity in the chemistry of the two groups of alkaloids.[28,29] When the structure of veatchine was clarified, on the basis of analogy he suggested structure **2** for dihydroatisine and by implication structures **3** and **4** for atisine and isoatisine.[30] Rigorous proof for the atisine skeleton, the location of functional groups, and the presence of the oxazolidine ring was lacking, and the stereochemistry was entirely



2 **3** **4**

unknown. At the time our own studies afforded clear support for structures **3** and **4** for atisine and isoatisine, respectively.[4] The details of these and subsequent studies will now be presented.

The results of a functional group analysis of atisine, isoatisine, dihydroatisine, and the epimeric tetrahydroatisines (**5**) are shown in Table I and indicate the presence in all four compounds of a hydroxyl group and a CCH_3 group. The presence of an exocyclic methylene group is suggested in atisine, isoatisine, and dihydroatisine, but is entirely missing in the spectrum of the



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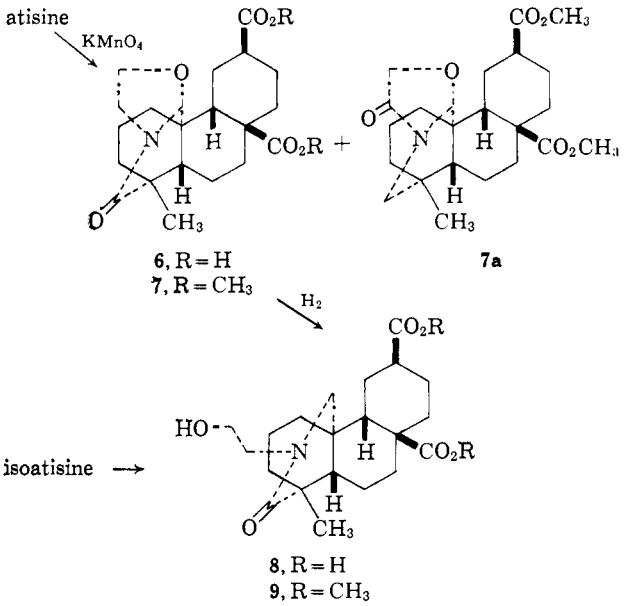
tetrahydroatisines. These results are confirmed by the ozonization and Kuhn-Roth oxidation data presented in Table I. Clearly, transformation of atisine, isoatisine, or dihydroatisine to tetrahydroatisines[21,22] proceeds by reduction of the exocyclic methylene group to a new CCH_3 group. N-Alkyl determinations indicated the presence of an N-ethyl group or suitable precursor in atisine and isoatisine.[25]

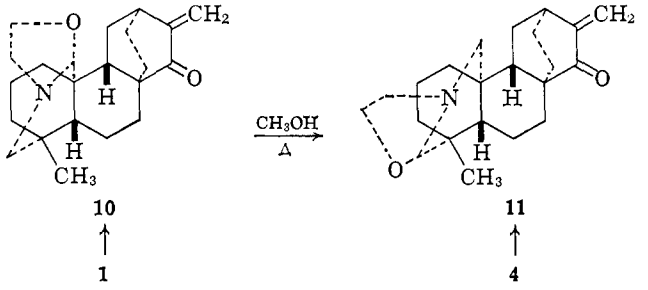
Oxazolidine Ring System. Direct proof for the existence of an oxazolidine ring in atisine and isoatisine was provided by two lines of evidence.[4] (1) Oxidation of atisine with potassium permanganate in acetone gives a lactam dicarboxylic acid (**6**).[25-27,31] Examination of the infrared spectrum of the dimethyl ester (**7**) reveals bands at 1731 (broad, —CO_2CH_3) and 1642 cm.$^{-1}$ (δ-lactam), *but no band indicative of a hydroxyl group.* The Tschugaeff–Zerewitinoff determination was negative on the diester **7** but showed one active hydrogen for atisine (**1**). The γ-lactam, α-oxoatisine dicarboxylic ester (**7a**),[31] also showed the absence of



6, R = H
7, R = CH_3
7a
8, R = H
9, R = CH_3

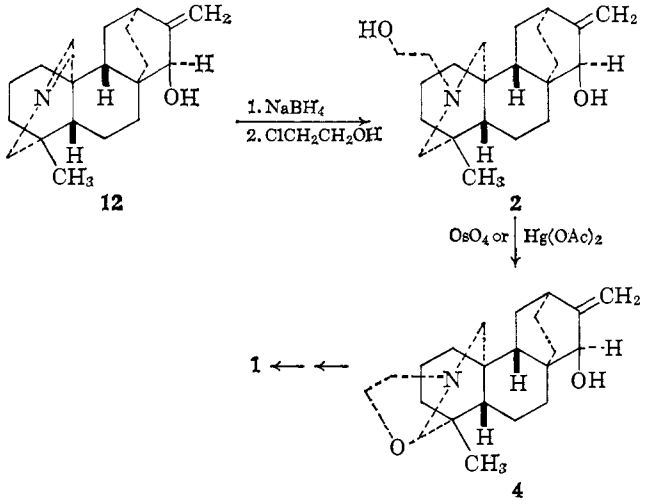
(21) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, 143, 589 (1942).
(22) W. A. Jacobs and L. C. Craig, *ibid.*, 147, 567 (1943).
(23) L. C. Craig and W. A. Jacobs, *ibid.*, **152**, 651 (1944).
(24) C. F. Huebner and W. A. Jacobs, *ibid.*, 170, 203 (1947).
(25) C. F. Huebner and W. A. Jacobs, *ibid.*, 170, 515 (1947).
(26) C. F. Huebner and W. A. Jacobs, *ibid.*, **174**, 1001 (1948).
(27) W. A. Jacobs, *J. Org. Chem.*, **16**, 1593 (1951).
(28) K. Wiesner, S. K. Figdor, M. F. Bartlett, and D. R. Henderson, *Can. J. Chem.*, 30, 608 (1952).
(29) K. Wiesner, W. I. Taylor, S. F. Figdor, M. F. Bartlett, J. R. Armstrong, and J. A. Edwards, *Ber.*, **86**, 800 (1953).
(30) K. Wiesner, R. Armstrong, M. F. Bartlett, and J. A. Edwards, *Chem. Ind.* (London), 132 (1954).
(31) S. W. Pelletier and W. A. Jacobs, *J. Am. Chem. Soc.*, 78, 4139 (1956)

hydroxyl absorption in the infrared. A similar controlled oxidation of isoatisine furnished oxoisoatisinedicarboxylic acid (**8**).[25-27] The infrared spectrum of its dimethyl ester **9** displays a band attributable to hydroxyl group at 3378 cm.$^{-1}$, as well as bands at 1730 (—CO_2CH_3) and 1622 cm.$^{-1}$ (δ-lactam). Hydrogenation of oxoatisinedicarboxylic acid (**6**) over Adams catalyst furnished a product identical with oxoisoatisinedicarboxylic acid (**8**) as shown by melting point, rotation, and infrared spectra. (2) The second line of evidence for the oxazolidine ring is the oxidation of both atisine and isoatisine to conjugated enones which *show no hydroxyl absorption in the infrared.*[4] Thus treatment of atisine (**1**) with chromium trioxide–pyridine complex at 15° furnished in 60% yield the enone, atisone (**10**), m.p. 100–102°, λ_{max}^{EtOH} 229 mμ (ϵ 9500), $\nu_{max}^{CCl_4}$ 1704 and 1642 cm.$^{-1}$ (strong, conjugated enone). Similar oxidation of isoatisine (**4**) gave the



10 ↑ **1** **11** ↑ **4**

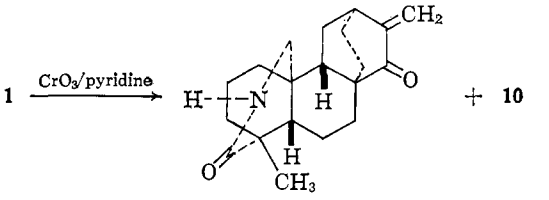
enone, isoatisone (**11**), m.p. 161.5–162.5° then 285–295° dec., λ_{max}^{EtOH} 227.5 mμ (ϵ 8074), ν_{max}^{Nujol} 1706 and 1642 cm.$^{-1}$ (strong, conjugated enone). Refluxing atisone (**10**) in methanol or ethanol effected a smooth isomerization to isoatisone (**11**), a reaction which parallels the facile atisine → isoatisine isomerization.[3a,11,22] The Tschugaeff–Zerewitinoff active hydrogen determination was negative for both enones (**10** and **11**). Final confirmation of the presence of an oxazolidine moiety in atisine and isoatisine was provided by reconstitution of these compounds from the imino alcohol (**12**) by the scheme outlined below.[32] Reduction of **12**



12 **2** **4** → **1**

with sodium borohydride and alkylation of the resulting secondary amine gave dihydroatisine (**2**) in good yield. Cyclization of the β-hydroxyethyl group to give isoatisine (**4**) was effected with either 1 equiv. of osmium tetroxide[29] in ether (60–70%) or 1 equiv. of mercuric acetate in aqueous acetic acid (30%). We have already described the conversion of isoatisine (**4**) to atisine (**1**) by two different routes.[13,32]

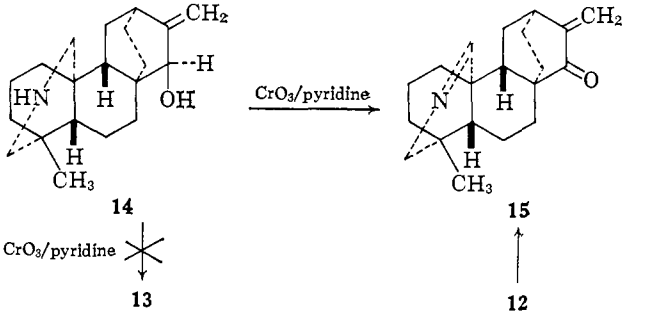
The Sarett oxidation of atisine and isoatisine described above also gave rise to neutral by-products of interest. From atisine was obtained in about 1.5% yield a neutral product, m.p. 181.5–182.5°, with an analysis corresponding to $C_{20}H_{27}NO_2$ and to which structure **13** was assigned. The infrared spectrum in Nujol showed bands at 3289, 3195, and 3077 (—NH), 1704 and 1629 (strong, cisoid enone), and 1658 cm.$^{-1}$



1 → **13** + **10**

(secondary lactam). The ultraviolet spectrum also supported the presence of a conjugated chromophore in the molecule (λ sh 228.5 mμ (7800)). In the p.m.r. spectrum a tertiary methyl group, deshielded by an adjacent lactam carbonyl, appears as a singlet at τ 9.05. The two protons of the exocyclic methylene appear as a pair of doublets at τ 4.12 and 4.84 (J = 2 c.p.s.). The proton on the lactam nitrogen (—N*H*-CO—) appears as a diffuse multiplet around τ 3.95.[33]

It was anticipated that compound **13** might be prepared by oxidation of **14** with chromium trioxide–pyridine complex. However, **14** afforded enone **15**



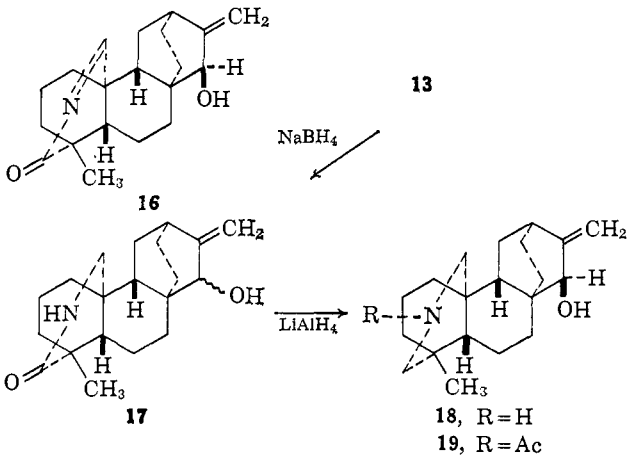
14 → **15** → **12**; **14** → **13**

as the only product. Compound **15** had previously been prepared by oxidation of **12** with chromium trioxide–pyridine complex.[31] Oxidation of **14** with potassium permanganate in dry acetone at 5° afforded a neutral product, m.p. 217–218°, in small yield, with most of the starting material being recovered. This product was tentatively assigned structure **16** on the basis of its molecular formula, $C_{20}H_{27}NO_2$, and infrared spectrum: ν_{max}^{Nujol} 3436 (OH), (>C=CH_2), 1653 (strong, >C=N), and 1631 cm.$^{-1}$ (δ-lactam). Attempts to reduce the imine linkage of **16** under various conditions with sodium borohydride failed.

The structure of **13** was established by the following sequence. Reduction of **13** with sodium borohydride gave a mixture of the epimeric lactam alcohols **17** which was in turn reduced with lithium aluminum hydride in refluxing tetrahydrofuran. The basic product was

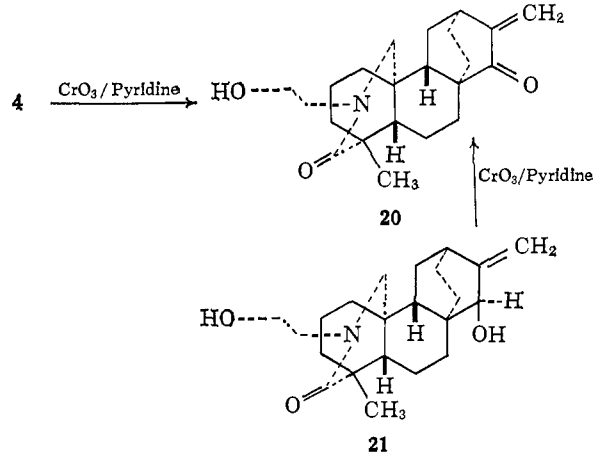
(32) S. W. Pelletier and W. A. Jacobs, *J. Am. Chem. Soc.*, 78, 4144 (1956).

(33) It is pertinent to note that the proton on the nitrogen of N-acetyl-β-phenylethylamine absorbs at τ 3.50: N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectral Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., Spectrum No. 265.



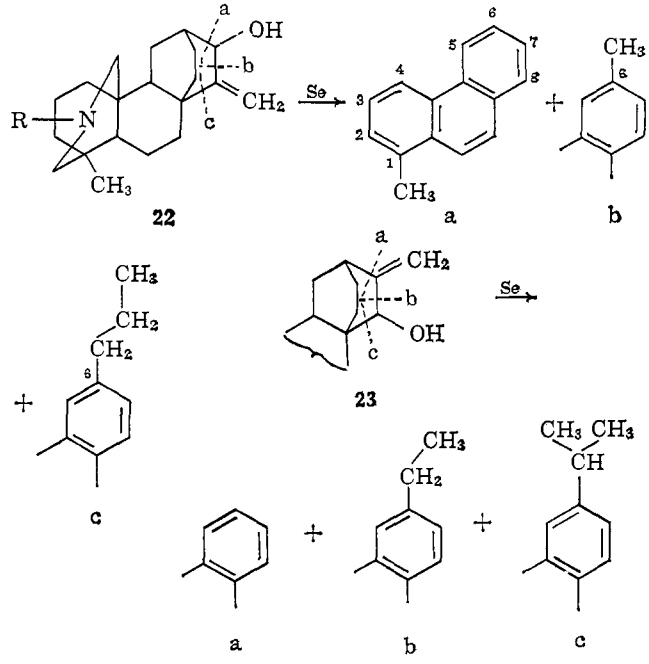
chromatographed to give the known compound **18**, isolated as the N-acetate **19**.[9,34] Obviously **18** could also have arisen by reduction of a compound with the lactam carbonyl at position 20. However, since the oxidation of the extremely hindered C-20 methylene to a carbonyl group has not been possible,[35] the neutral product derived from the Sarett oxidation of atisine is best represented by structure **13**.

The neutral fraction produced during the Sarett oxidation of isoatisine was chromatographed to give a 10% yield of a lactam, $C_{22}H_{31}NO_3$, m.p. 216–219°. This compound was assigned structure **20** on the basis of the following data. The infrared spectrum showed well-defined peaks corresponding to hydroxyl (3390 cm.$^{-1}$), exocyclic methylene (3086 and 901 cm.$^{-1}$), δ-lactam (1616 cm.$^{-1}$), and conjugated enone (1701 cm.$^{-1}$) groups. The ultraviolet spectrum, λ sh (EtOH) 227 mμ (ε 8500), was also in accord with the presence of a conjugated enone. In the p.m.r. spectrum a tertiary methyl group, deshielded by an adjacent lactam carbonyl, appears as a singlet at τ 8.83 and the two protons of the exocyclic methylene appear as a pair of doublets at τ 3.98 and 4.70 (J = 2 c.p.s.). Compound **20**, like oxoisoatisine (**21**),[25] was recovered unchanged



on treatment with benzoic anhydride in pyridine, a behavior suggestive of a hindered or intramolecular hydrogen-bonded hydroxyl. Oxidation of oxoisoatisine (**21**) with chromium trioxide–pyridine complex gave a product identical in all respects with **20**. It is interesting to note that reoxidation of enone **11** with chromium trioxide in pyridine gave a small yield of lactam **20**.

Skeleton of Atisine. Important evidence bearing on the atisine skeleton is the structure of the products obtained by dehydrogenation.[21] The three key products have been identified as 1-methylphenanthrene,[21] 1-methyl-6-ethylphenanthrene,[24] and 1-methyl-6-ethyl-3-azaphenanthrene.[7,36] Barring rearrangements, these products account for 19 of the 22 carbon atoms of atisine and are easily derivable from structure **1**. Clearly, however, the isolation of these dehydrogenation products does not provide positive evidence for the relative position of the secondary hydroxyl and exocyclic methylene group. Thus, for example, a compound of structure **22** might give rise to some of the same dehydrogenation products as **23**. Cleavage at points a, b, and c, would be expected to lead to 1-methyl-, 1,6-dimethyl-, and 1-methyl-6-*n*-propylphenanthrenes from structure **22** and to 1-methyl-, 1-methyl-



6-ethyl-, and 1-methyl-6-isopropylphenanthrenes from structure **23**. Since the actual compounds isolated from the dehydrogenation of atisine[21] and tetrahydroatisine[27] bear either a hydrogen or an ethyl group at the 6-position of the phenanthrene nucleus, it seemed unlikely that the secondary hydroxyl and exocyclic methylene are arranged as in **22**. However, more certainty on this point was desirable. We anticipated that dehydrogenation of a derivative lacking the secondary hydroxyl might proceed with less fragmentation to give either a 6-isopropyl or a 6-*n*-propylphenanthrene derivative depending on whether atisine possessed the arrangement as in **22** or **23**, respectively. We thus proceeded to investigate a means for removing the allylic alcoholic group of a suitable atisine derivative. The use of lithium aluminum hydride and aluminum chloride in ether, a reagent with which Birch successfully removed the allylic hydroxyl of 3,4-methylenedioxy-

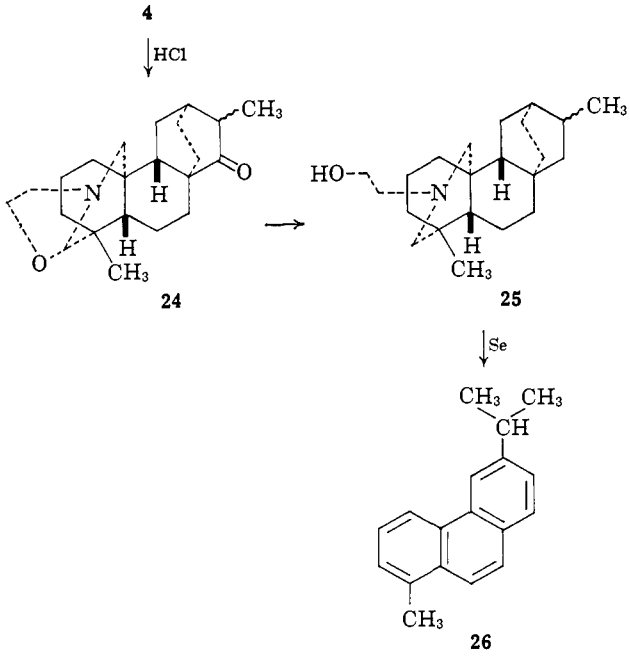
(34) S. W. Pelletier and D. M. Locke, *J. Am. Chem. Soc.*, 87, 761 (1965).

(35) Except in the case of ajaconine chemistry, where the 7-carbonyl participates in a transannular hydride shift to give a lactam carbonyl at C-20: D. Dvornik and O. E. Edwards, *Tetrahedron*, 14, 54 (1961).

(36) D. M. Locke and S. W. Pelletier, *J. Am. Chem. Soc.*, 81, 2246 (1959).

cinnamyl alcohol,[37] effected reduction of only the oxazolidine ring of isoatisine to give a good yield of dihydroatisine (**2**). Reduction of the enone, isoatisone (**11**), with $LiAlH_4$–$AlCl_3$, again failed to remove the allylic oxygen function,[38] but gave what appeared to be a mixture of dihydroatisines epimeric at the secondary hydroxyl. Likewise unsuccessful was the Wolff–Kishner reduction of atisone (**10**) or the Clemmensen reduction of isoatisone (**11**). A successful method of removing the oxygen function involved isomerization of the allylic alcohol to a methyl ketone[39] followed by Wolff–Kishner reduction of the ketone as detailed below.

Treatment of isoatisine under reflux conditions with 8% hydrogen chloride in ethanol gave a complex mixture from which a crystalline product could be isolated in 40–50% yield. It proved to be a mixure of the epimeric 16-methyl ketones (**24**). The mixture could be separated by extensive crystallization to give



isomer A as heavy prisms: m.p. 150–153°; $[\alpha]^{27}D$ −4.6°; $\nu_{max}^{CS_2}$ 1715 (>C=O) and 1368 cm.$^{-1}$ (CCH_3), no hydroxyl absorption; τ 8.93 and 9.09 (v weak, CCH_3), 8.93 and 8.82 (3H doublet, $CHCH_3$); and isomer B as needles: m.p. 132.5–134.5°; $[\alpha]^{26}D$ −8.3°; $\nu_{max}^{CS_2}$ 1712 (>C=O) and 1366 cm.$^{-1}$ (CCH_3), no hydroxyl absorption; p.m.r. spectrum τ 8.93 and 9.09 (v weak, CCH_3) and 8.93 and 8.80 (3H doublet, $CHCH_3$). Treatment of either ketone with methanolic potassium carbonate under reflux conditions effected epimerization to give the same mixture of epimeric ketones. That a skeletal rearrangement had not occurred during isomerization to **24** was demonstrated by sodium borohydride reduction of isomer A (146–153°). Separation of the product by triangular crystallization, monitored by thin layer chromatography, afforded as the major product the known α-tetrahydroatisine,[21] m.p. 177–179°, and a small amount of a new isomer, *α-tetrahydro-15-epiatisine*, m.p. 165.5–166.5°. The configuration of the ring-D methyl group of the ketones (**24**) and the derived tetrahydro derivatives will be discussed in another section of this paper.

Attempts to remove the 15-carbonyl group of **24** by either the Clemmensen reduction or the ordinary Huang-Minlon procedure failed. The use of anhydrous hydrazine with sodium in diethylene glycol gave a good yield of a mixture of desoxytetrahydroatisine epimers (**25**) which was purified as the hydrochloride, m.p. 200–204°, $[\alpha]^{27}D$ −33.2°. The infrared spectrum showed no carbonyl absorption. The opening of the oxazolidine ring during the Wolff–Kishner reduction is to be expected since both atisine and isoatisine are reduced to dihydroatisine when heated with ethanolic sodium hydroxide in a sealed tube at 100°.[22] The mixture of epimeric bases (13.6 g.) was dehydrogenated by heating with excess selenium for 8 hr. at 335–340°. The neutral fraction consisting of 5.1 g. was separated by chromatography into a hydrocarbon (3.4 g.) and a lactam fraction (1.5 g.). Repeated chromatography of the hydrocarbon fraction[43] and fractional crystallization of derivatives afforded two pure aromatic hydrocarbons: (1) an unknown $C_{18}H_{18}$ phenanthrene, m.p. 69–71°, and (2) 1-methyl-6-isopropylphenanthrene (**26**) m.p. 47–50°. The latter was identified by direct comparison (melting point, infrared[44] in KBr) with an authentic sample kindly placed at our disposal by Professor S. N. Slater.[45] The picrate and *sym*-TNB derivatives were also identical. The formation of **26** provides additional evidence for locating the allylic alcohol function of atisine as in formula **23**. This same conclusion has been independently demonstrated in another laboratory by a different sequence of reactions.[46]

We turn now to a consideration of the other products of the dehydrogenation of **25** by selenium. The basic fraction is extremely nonpolar and as a matter of fact was almost overlooked in the "neutral" fraction. In the work-up of the first dehydrogenation run, it was assumed that extraction of a benzene solution of the dehydrogenation mixture with dilute hydrochloric acid had removed the basic fraction. Subsequently when a crystalline base (**27**), to be described later, appeared during chromatography of the so-called neutral fraction, it was apparent that this base was not readily extractable with dilute acid. In the particular run described in the Experimental, a benzene solution of the dehydrogenation mixture required extraction with forty 50-ml. portions of 3% sulfuric acid to remove all the basic fraction.

(37) A. J. Birch and M. Slayton, *Chem. Ind.* (London), 1524 (1956).

(38) Contrast the experience of J. Broome and R. B. Brown, *ibid.*, 1307 (1956), who were able to convert cholestenone to cholestene-4 with this reagent.

(39) Several examples of the acid-induced allyl alcohol → methyl ketone isomerization are known in the diterpenes.[8,40,41] A simple example involving the transformation of 2-methylenecyclohexanol to 2-methylcyclohexanone has also been described.[42]

(40) C. Djerassi, C. R. Smith, A. E. Lipman, S. K. Figdor, and J. Herran, *J. Am. Chem. Soc.*, 77, 4801 (1955).

(41) E. Mosettig and W. R. Nes, *J. Org. Chem.*, 20, 884 (1955).

(42) A. Dierding and J. A. Hartman, *J. Am. Chem. Soc.*, 78, 1216 (1956).

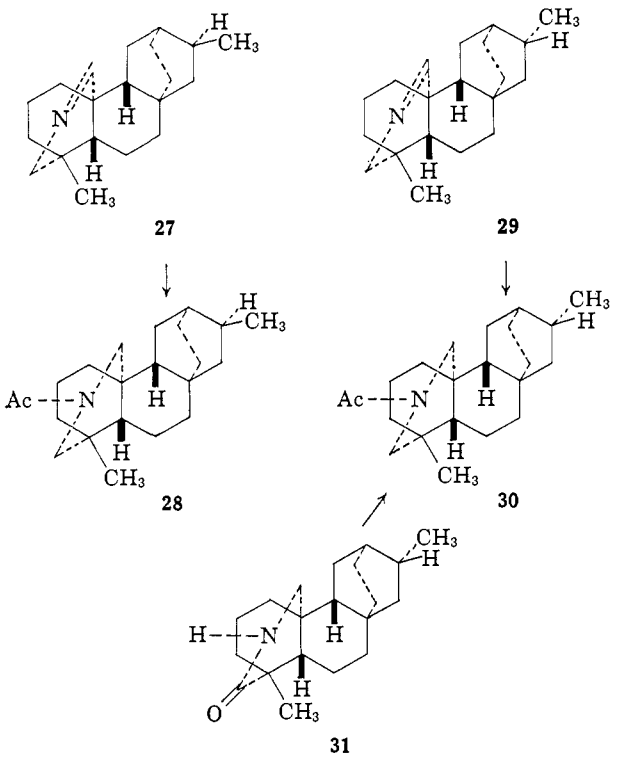
(43) Gas phase chromatography (A. J. Solo and S. W. Pelletier, *Anal. Chem.*, **35**, 1584 (1963)) of the hydrocarbon fraction showed that the bulk of this fraction consists of partially dehydrogenated materials. Of the phenanthrene fraction, the major component is 1-methyl-6-isopropylphenanthrene.[44] We thank Dr. Alan J. Solo for running this analysis.

(44) It is interesting to note that the KBr pellet of 1-methyl-6-isopropylphenanthrene after standing for several months gave a spectrum which differed markedly in the fingerprint region from that of the original spectrum of the pellet.

(45) S. N. Slater, *J. Chem. Soc.*, 68 (1941).

(46) D. Dvornik and O. E. Edwards, *Chem. Ind.* (London), 623 (1958).

Chromatography of the basic fraction (6.15 g.) afforded a mixture of two imines, A and B. Only imine A could be isolated in pure condition. It crystallized as heavy prisms, m.p. 122–124°, and had an analysis corresponding to $C_{20}H_{31}N$. The infrared spectrum showed a strong —C=N— band at 1642 cm.$^{-1}$. The p.m.r. spectrum disclosed the presence of >C—CH_3 (τ 9.18, 3H singlet), CHCH_3 (τ 8.98, 3H doublet, J = 6.5 c.p.s.), CH_2N=C (τ 6.60, 2H doublet, J = 2.5 c.p.s.), and NCH (τ 2.15, 1 H broad signal with half-band width of 7 c.p.s.) groups.[47,48] Reduction with sodium borohydride and acetylation of the product gave a crystalline N-acetate, m.p. 166.5–167.5°, ν_{max}^{Nujol} 1645 and 1631 cm.$^{-1}$. The p.m.r. spectrum showed the presence of CCH_3 (τ 9.15), CHCH_3 (τ 9.10, doublet J = 7 c.p.s.), and NCOCH_3 (τ 7.90 and 7.93) groups. Based on these data imine A is assigned structure **27** and the N-acetate structure **28**,[49] with the



configuration shown for the $CHCH_3$ group arbitrary. An attempt to isolate imine B (**29**) from the mother liquors by chromatography of the bases or fractional crystallization of the hydrochlorides failed. However, conversion of the mixture to the N-acetates and fractional crystallization by the triangle scheme gave a pure N-acetate (**30**), m.p. 147.5–149.5°, ν_{max}^{Nujol} 1645 and 1631 cm.$^{-1}$ (NAc), derived from imine B (**29**). The p.m.r. spectrum showed the presence of CCH_3 (τ 9.17, 3H singlet), CHCH_3 (τ 9.10, doublet, J = 6.5 c.p.s.), and NCOCH_3 (τ 7.90 and 7.93) groups.

One final product isolated from the earlier mentioned lactam fraction from the deydrogenation mixture deserves mention. This compound, m.p. 235–236°, $[\alpha]D$ −47.4°, showed bands in the infrared characteristic of a secondary lactam, ν_{max}^{Nujol} 3215, 1650, and 1631 cm.$^{-1}$. In the p.m.r. spectrum bands characteristic of a CHCH_3 group (τ 8.98, 3H doublet, J = 7 c.p.s.), and a secondary lactam, —NHCO— (τ 3.70),[33] were observed. The frequency of the tertiary CCH_3 group appears at τ 8.88. This is unusually low compared to that for other derivatives in this series and suggests that the amide carbonyl is located near this C-methyl. The structure assigned to this lactam is **31** since reduction with lithium aluminum hydride and acetylation furnished an N-acetate (**30**) identical with that derived from imine B (**29**).[49]

Ternary Iminium Salts. We turn now to a consideration of the chemistry of the salts of atisine and isoatisine. Work from several laboratories has established that the salts of atisine and isoatisine have ternary iminium structures **33** and **36**, respectively.[5,14,15,50] The position of the >C=N$^+$< bond is fixed in each compound under ordinary conditions since on treatment with base each salt regenerates the corresponding base. However, we have shown recently that refluxing solutions of the isotype salts (**36**) in a variety of solvents (DMF, DMSO, DEF, and Cellosolve) affords the normal salt (**33**) in high yield.[13] Thus, for example, atisinium chloride (**33**, X = Cl) was obtained in 85% yield by refluxing isoatisinium chloride (**36**, X = Cl) for 30 min. in DMSO. Similar treatment of garryinium chloride afforded veatchinium chloride. Since the normal-type ternary iminium salts can be smoothly converted to the corresponding bases by treatment with cold aqueous sodium hydroxide, the present work provides a convenient method of reversing the facile normal → isobase isomerization.

The infrared spectra of the hydrochlorides of atisine and isoatisine show bands at 1680 and 1692 cm.$^{-1}$, respectively, which are absent in the parent bases and which may be attributed to the >C=N$^+$< group. It has been claimed that solutions of the hydrochlorides show more intense absorption in the ultraviolet above 220 mμ than the free bases.[50,51] This behavior is reported to be characteristic of aliphatic bases whose salts bear the >C=N$^+$< chromophore.[52,53] However, careful studies have shown that freshly prepared solutions of quinolizidine perchlorate in ethanol are transparent down to the wave length limit of the instrument.[54] After brief aging, however, the solutions showed strong absorption above 220 mμ. Determinations of several other ternary iminium salts have likewise shown transparency above 220 mμ.[54] It is therefore likely that any absorption above 220 mμ in the atisine or isoatisine salts is not due to the >C=N$^+$< group, but to some chemical change occurring in solution before the spectrum is determined.

(47) The p.m.r. spectrum of the imino alcohol **12** showed the presence of CCH_3 (τ 9.18, 3H, singlet), CH_2—N=C (τ 6.60, 2H, doublet, J = 2.5 c.p.s.), and —N=CH— (τ 2.13, 1H, broad signal, half-band width, 7 c.p.s.) groups. The corresponding signals for the imine lacking the exocyclic methylene and secondary hydroxyl groups are reported as CCH_3 (τ 9.17), —CH_2—N=C— (τ 7.5, J = 2.4 c.p.s.), and —N=CH— (τ 2.3, half-band width, 7.4 c.p.s.) (ref. cited in footnote 35).

(48) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," The Macmillan Co., New York, N. Y., 1959, pp. 50–65.

(49) We thank Dr. P. Ragagopalan for preliminary experiments concerned with the separation of acetates **28** and **30** and the reduction of lactam **31**.

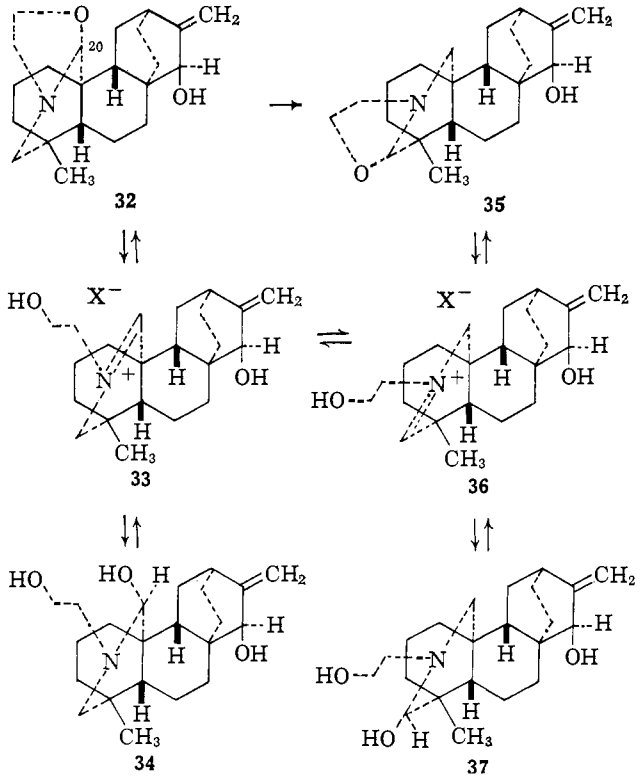
(50) O. E. Edwards and T. Singh, *Can. J. Chem.*, **32**, 465 (1954).

(51) L. C. Craig, L. Michaelis, S. Granick, and W. A. Jacobs, *J. Biol. Chem.*, **154**, 293 (1944).

(52) O. E. Edwards and L. Marion, *Can. J. Chem.*, **30**, 627 (1952).

(53) O. E. Edwards, F. H. Clarke, and B. Douglas, *ibid.*, **32**, 235 (1954).

(54) Private communication, Professor N. J. Leonard, Dec. 1, 1955.

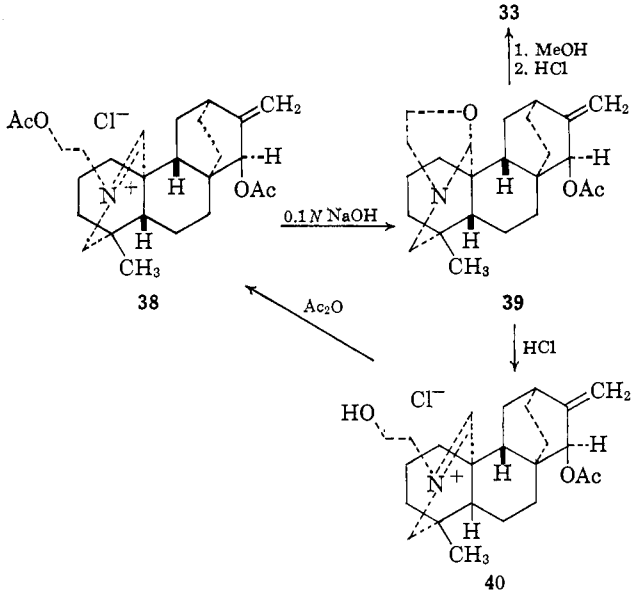


The pK_a' values in 50% methanol for atisine and isoatisine are 12.8 and 10.35, respectively.[5] Parallel titrations of atisine and sodium hydroxide show that atisine is almost as strong a base as sodium hydroxide. Thus, for example, a 0.0098 *N* solution of atisine at the half-neutral point showed a pH of 12.8. Sodium hydroxide at the same concentration gave a pH of 12.9. The reasons for the large difference in basic strengths between atisine and isoatisine is that in atisine a higher proportion of the ternary aminium hydroxide (**33**, X = OH^-) is present in an equilibrium between the oxazolidine (**32**), ternary iminium (**33**), and pseudo-base (**34**) forms whereas in the case of isoatisine a higher proportion of the oxazolidine (**35**) or pseudo-base (**37**) forms is present. The reason for the preponderance of the ternary iminium hydroxide in the atisine equilibrium has been recognized as the steric interference with substituents on the tetrahedral C-20 in the oxazolidine form and has been discussed in detail elsewhere.[3a,b,e,5,14,40]

Early work on atisine reported the formation of a "diacetate hydrochloride"[21] which was at one time formulated as a triacetate hydrochloride.[55] More recent studies have shown that this material is actually atisinium chloride diacetate (**38**).[5,14] Brief treatment of atisinium chloride with refluxing acetic anhydride or acetylation of atisine in acetic anhydride–pyridine followed by treatment with hydrochloric acid affords **38** in almost quantitative yields, m.p. 242.5–245°, $[\alpha]D$ −17° (EtOH). The infrared spectrum in KBr (1667 $cm.^{-1}$) and Nujol (1678 $cm.^{-1}$) shows the presence of the >C=N⁺< chromophore and in chloroform the absence of hydroxyl bands. The presence of two acetate groups (1739 $cm.^{-1}$) was shown by hydrolysis with 25% *p*-toluenesulfonic acid.

Treatment of **38** with saturated sodium bicarbonate solution failed to liberate the free base. However,

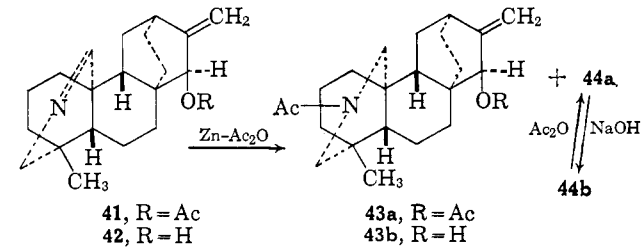
(55) O. E. Edwards and T. Singh, *Can. J. Chem.*, 33, 448 (1955).



treatment with ice-cold 0.1 *N* sodium hydroxide gave an amorphous base which proved to be atisine monoacetate (**39**),[5] ν_{max}^{film} 3026, 1650, and 895 (>C=CH_2), 1738 and 1235 (OAc), and 1370 $cm.^{-1}$ (CCH_3). The lack of hydroxyl absorption in the infrared shows that **39** contains an oxazolidine ring. Methanolysis of **39** in 50% methanol furnished atisine (**1**). Treatment of an ether solution of the monoacetate with dry HCl gave a new ternary iminium salt, atisinium chloride monoacetate (**40**), m.p. 238–241°, ν_{max}^{KBr} 1673 $cm.^{-1}$ (strong). Treatment of **40** with boiling acetic anhydride regenerated **38**.

It is interesting to note that if the product from the acetylation of atisine with acetic anhydride–pyridine was not converted to the chloride salt but was washed with dilute base and chromatographed, a small yield of the imine acetate (**41**), m.p. 144–148°, was obtained. This material can be obtained in up to 70% yield by the treatment of the diacetate chloride (**38**) with strong base under nonhydrolytic conditions.[15]

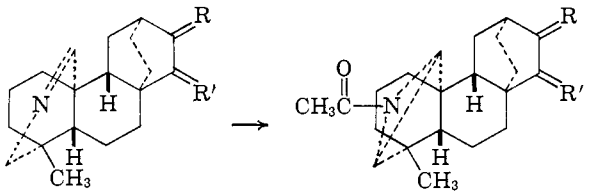
Reactions of the Imine Linkage. Reduction of the imino alcohol (**42**) with zinc dust in acetic anhydride afforded as a major product the O,N-diacetate **43a**[32] and a neutral acetate **44a**, m.p. 231°, in a yield of 6%. The latter on saponification gave an alcohol (**44b**), m.p. 289–291°, which on acetylation regenerated **44a**. In the infrared, compound **44a** has bands corresponding to OAc (1742 $cm.^{-1}$), exocyclic methylene (3067 and



889 $cm.^{-1}$), and amide carbonyl (1642 and 1629 $cm.^{-1}$), while **44b** has bands corresponding to hydroxyl (3472 and 3356 $cm.^{-1}$), amide (1629 $cm.^{-1}$), and exocyclic methylene (891 $cm.^{-1}$) groups.

Since the formation of an aziridine (**47**) on prolonged refluxing of imine **45** in acetic anhydride has been re-

ported,[56] it appeared possible that compound **44a** was the analogous aziridine **48**. Refluxing imine **42** with acetic anhydride for 30 hr. gave a neutral product (**48**), m.p. 191–192.5°, with an analysis corresponding to $C_{24}H_{33}NO_3$. In the infrared were well-defined bands for OAc (1730 cm.$^{-1}$), amide carbonyl (1642 and 1637 cm.$^{-1}$), and exocyclic methylene (907 cm.$^{-1}$) groups. Mild saponification of **48** afforded the aziridine alcohol **49**, m.p. 191–192°, which in the infrared showed bands for the hydroxyl (3448 cm.$^{-1}$), amide (1642 and 1637 cm.$^{-1}$), and exocyclic methylene (897 cm.$^{-1}$) groups. Treatment of **49** with acetic anhydride–pyridine regenerated **48**. That the allylic alcohol grouping in **42**



45, R = R′ = H_2
42, R = CH_2; R′ = OH,H
46, R = CH_2; R′ = OAc,H

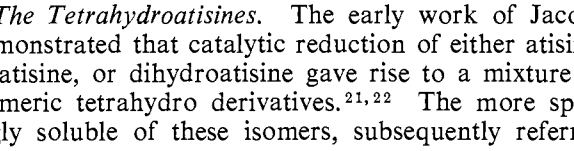
47, R = R′ = H_2
48, R = CH_2; R′ = OAc,H
49, R = CH_2; R′ = OH,H

did not participate in the reaction leading to **48** was shown by the fact that the imino acetate **46** also afforded **48** on prolonged treatment with acetic anhydride. A comparison of the aziridines **48** and **49** with by-products **44a** and **44b**, respectively, showed nonidentity. Since aziridine **48** was recovered unchanged under conditions for the formation of **44a** from **42**, it is not likely that **44a** is formed from **48** by cleavage of the aziridine ring.

The structure assigned to the by-product **44a** is that of a bimolecular reduction product.[57] The Rast molecular weight determination indicated a value in the order of 700–800 and the analysis agreed with the formula $C_{48}H_{68}N_2O_6$. The hydrolysis product **44b** on oxidation with chromium trioxide–pyridine afforded a conjugated enone (**50**), m.p. 210° and 250–255°, ν_{max} 1701 and 1639 (conjugated enone), and 1634 cm.$^{-1}$, strong (NAc); λ sh 228 mμ (ε 16,430). The linkage between the two halves of the compound is believed to be at C-19, because of the severely hindered environment about C-20.

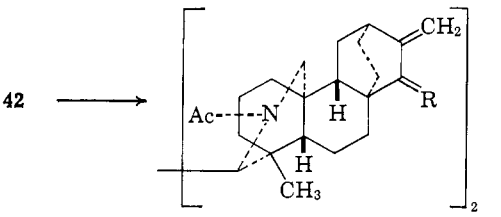
The Tetrahydroatisines. The early work of Jacobs demonstrated that catalytic reduction of either atisine, isoatisine, or dihydroatisine gave rise to a mixture of isomeric tetrahydro derivatives.[21,22] The more sparingly soluble of these isomers, subsequently referred

(56) O. E. Edwards, *Chem. Can.*, 13, 40 (1961).
(57) A similar bimolecular reduction of i to ii has been effected with aluminum amalgam in moist ether.[58] The bimolecular reduction of pyridines to tetrahydrobipridyls with zinc in acetic anhydride is well known.[59–62]



i ii

(58) B. B. Dey and T. R. Govindachari, *Proc. Natl. Inst. Sci. India*, 6, 219 (1940); *Chem. Abstr.*, 36, 5178 (1942).
(59) O. Dimroth and R. Heene, *Ber.*, 54, 3934 (1921).
(60) O. Dimroth and F. Frister, *ibid.*, 55, 3693 (1922).
(61) J. P. Wibaut and J. F. Arens, *Rec. trav. chim.*, 60, 119 (1941); *ibid.*, 61, 452 (1942).
(62) J. F. Arens and J. P. Wibaut, *ibid.*, 61, 452 (1942).



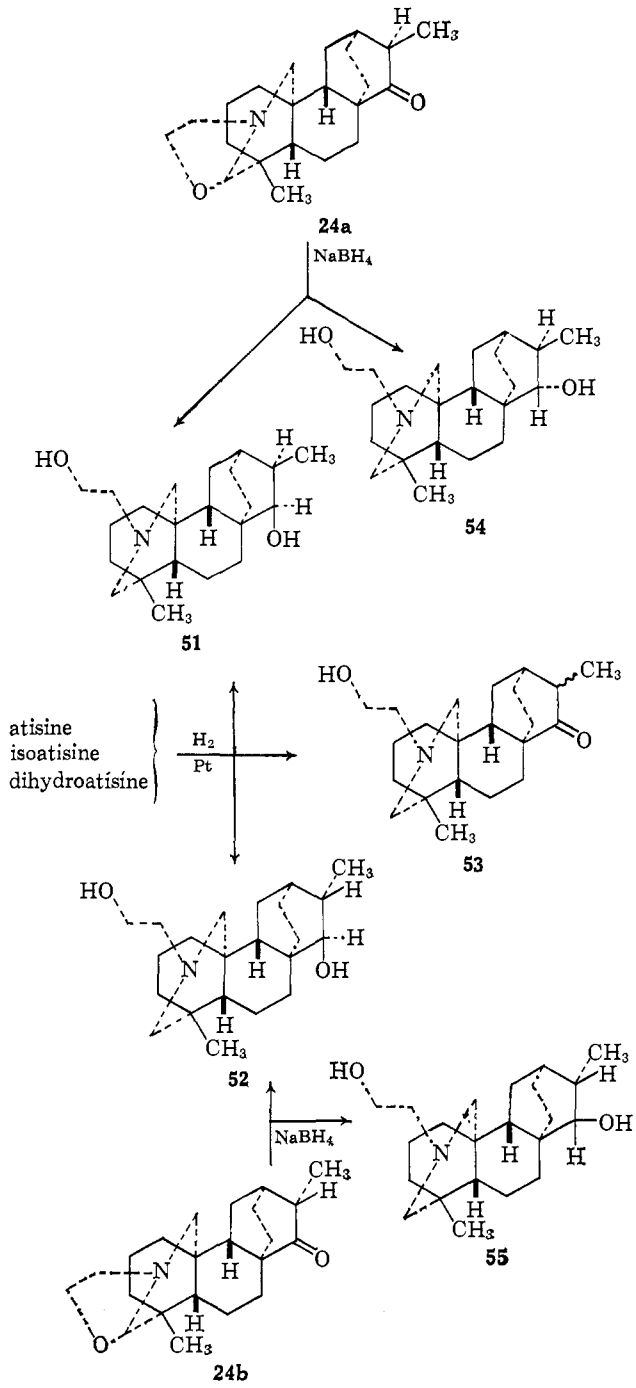
44a, R = OAc,H
44b, R = OH,H
50, R = O

to as α-tetrahydroatisine,[8] showed m.p. 171–174°, $[\alpha]^{25}D$ −23°. From the mother liquors Jacobs isolated another isomer (impure) of m.p. 155–168°, $[\alpha]^{25}D$ −57° (toluene). Repetition of this work on a large scale, using column and thin layer chromatography for separation, has revealed that the reduction mixture contains at least three compounds. Repeated crystallization of the sparingly soluble α-tetrahydroatisine (**51**) gave material with m.p. 178–178.5°, $[\alpha]D$ −21.4°; *hydrochloride*, m.p. 268–279° dec.; *monobenzoate*, m.p. 111–112.5°, $[\alpha]D$ −27.6°; *monobenzoate hydrochloride*, m.p. 226–230°. The β-isomer obtained by fractional crystallization, constant m.p. 171–173°, $[\alpha]^{23}D$ 60°, was shown by t.l.c. to be contaminated with small amounts of α-tetrahydroatisine and a ketone. Careful chromatography of the 171–173° material gave pure *β-tetrahydroatisine* (**52**), m.p. 185.5–186°, $[\alpha]^{18}D$ −72.4°; *hydrochloride*, m.p. 283.5–295.5° dec. The ketonic contaminent was not isolated but undoubtedly consists of one or both of the epimeric methyl ketones (**53**). The appearance of a ketone among the noble metal catalysed hydrogenation products of an exocyclic methylene group is typical of the behavior of the alkaloids hypognavine,[63] ignavine,[64] kobusine,[65] and songorine[66] and involves rearrangement of an allyl alcohol system to a methyl ketone.[39]

A study of the hydroxyl region of high-resolution infrared spectra of α- and β-tetrahydroatisine[67] allows the assignment of configuration of the secondary methyl to be made with reasonable certainty. Both isomers show absorption for the primary hydroxyl at 3515 cm.$^{-1}$ (bonded to N). In α-tetrahydroatisine, absorption of the secondary hydroxyl is at 3639 cm.$^{-1}$ while in the β-isomer the absorption is at 3628 cm.$^{-1}$. Absorption at 3628 cm.$^{-1}$ is normal for a nonbonded secondary alcohol, but 3639 cm.$^{-1}$ is rather high. Steric crowding which is present in the isomer with the methyl and secondary hydroxyl *cis* would be expected to raise the frequency. Thus α-tetrahydroatisine has the *cis*-Me/OH (**51**) and β-tetrahydroatisine has *trans*-Me/OH (**52**).[68]

Two other tetrahydro derivatives have been prepared by reduction of the isomeric methyl ketones (**24**) resulting from the acid-catalysed rearrangement of isoatisine. The high-melting isomer (**24a**) on reduction

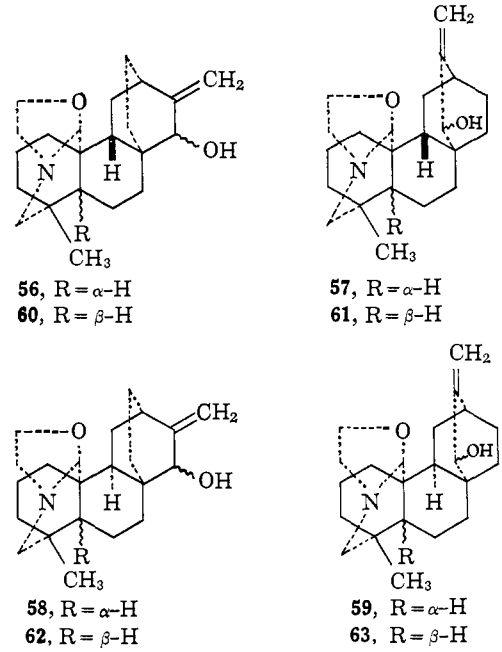
(63) S. Sakai, *J. Pharm. Sci. Japan*, 76, 1436 (1956).
(64) E. Ochiai and T. Okamoto, *Chem. Pharm. Bull.* (Tokyo), 7, 550 (1959).
(65) T. Okamoto, *ibid.*, 7, 44 (1959).
(66) T. Sugasawa, *ibid.*, 9, 897 (1961).
(67) We thank Dr. A. Robertson for these infrared spectra which were taken on a Beckman IR-7 spectrometer.
(68) Unfortunately the choice of nomenclature made several years ago (ref. 8, footnote 14) was such that the α-isomer now turns out to have the secondary methyl in the β-configuration and *vice versa*. To avoid the possible confusion which would accompany a name change, the old designation is retained.



with sodium borohydride gave a mixture which was separated by chromatography and fractional crystallization into α-tetrahydroatisine (**51**) and *α-tetrahydro-15-epiatisine* (**54**), m.p. 165.5–166.5°. The low-melting methyl ketone (**24b**) on reduction with sodium borohydride afforded *β-tetrahydro-15-epiatisine* (**55**), m.p. 146–148°, and a small amount of β-tetrahydroatisine (**52**). The former isomer is probably identical with the "tetrahydroatisine," m.p. 145°, prepared by Wiesner by treatment of an atisine pyrolysis product with lithium aluminum hydride followed by reaction with ethylene chlorohydrin.[69] The configuration of the secondary methyl groups in **24a** and **24b** follows from the configuration of the methyl in α-tetrahydroatisine (**51**) and β-tetrahydroatisine (**52**), respectively.

(69) M. F. Bartlett, J. Edwards, W. I. Taylor, and K. Wiesner, *Chem. Ind.* (London), 323 (1953). Unfortunately a sample of this isomer was not available for comparison.

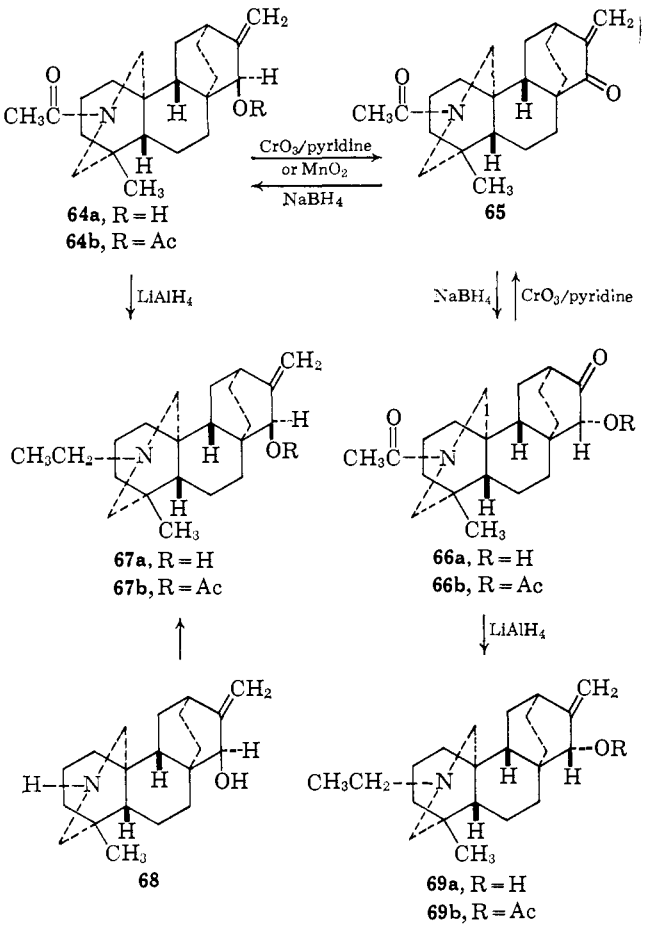
Stereochemistry of Atisine. At the time when the selenium dehydrogenation results discussed above were available it was assumed that the atisine-type alkaloids possessed the *trans-anti* skeleton which is common to most diterpenes. Until recently little evidence supporting this assumption was available. The eight theoretically possible *dl*-isomers of atisine are shown in formulas **56–63**. Four are A/B-*cis* isomers (**56–59**) and four are A/B-*trans* isomers (**60–63**). We recently utilized the work of Dvornik and Edwards[70] on ajaco-



nine to show that the A/B-*trans* stereochemistry is present in atisine.[10] The choice is therefore narrowed to a consideration of isomers **60–63**. Differentiation between isomers **60** and **61**, in which the *trans-anti* backbone is present, or between isomers **62** and **63** with a *trans-syn* backbone, involves the choice of locating the allyl alcohol group on the front or back side of the bicyclo[2.2.2]octane system. The chemical reactions[71] which allow assignment of the relative stereochemistry shown in **60** will be presented *in toto* and the stereochemical implications of these reactions will be discussed subsequently.

Oxidation of the N-acetyl derivative **64a** to the conjugated enone **65**, m.p. 153–156°, then 162–164°, $[\alpha]_D$ 5.8°, ν_{max}^{Nujol} 1701 and 1631 cm.$^{-1}$, λ sh 228 mμ (ε 9150), was effected using either chromium trioxide–pyridine or manganese dioxide in refluxing chloroform. Reduction of enone (**65**) with sodium borohydride gave a mixture which could be cleanly separated by chromatography on alumina to give N-acetyldes(N-β-hydroxyethyl)dihydroatisine (**64a**),[82,84] m.p. 228–230.5°, $[\alpha]$ −20.1°, and the epimer with the unnatural configuration, N-acetyldes(N-β-hydroxyethyl)dihydro-15-epiatisine (**66a**),[8] 176–177°, $[\alpha]_D$ −34.7°. Oxidation of **66a** with chromium trioxide–pyridine regenerated the enone **65**. Epimer **66a** provided an amorphous O-acetate (**66b**). Reduction of the O,N-diacetate **64b** with lithium aluminum hydride gave N-ethyldes-(N-β-hydroxyethyl)dihydroatisine (**67a**), isolated as the hydrochloride, m.p. 246–250°, $[\alpha]_D$ −27°. The same

(70) D. Dvornik and O. E. Edwards, *Proc. Chem. Soc.*, 305 (1958).
(71) The reactions are presented in terms of the subsequently derived correct relative stereochemistry.



compound was obtained by treatment of the secondary amine (**68**),[82] derived from atisine, with ethyl iodide and sodium carbonate. The free base (**67a**) was amorphous, but the *O*-abetate **67b** was crystalline, m.p. 78.5–80°, ν_{max}^{Nujol} 1739 and 1235 (OAc), and 1656 and 912 cm.$^{-1}$ (>C=CH$_2$). Saponification of the acetate (**67b**) regenerated the alcohol (**67a**).

Reduction of epimer **66a** with lithium aluminum hydride furnished N-ethyldes(N-β-hydroxyethyl)dihydro-15-epiatisine (**69a**) isolated as the hydrochloride, m.p. 268–271°. The O-acetate **69b** was amorphous but the acetate hydrochloride was crystalline, m.p. 204.5–214°. The pK_a' values for the two N-ethyl epimers and their acetates are as follows: **67a**, 9.25; **69a**, 9.13; **67b**, 8.30; and **69b**, 8.11.

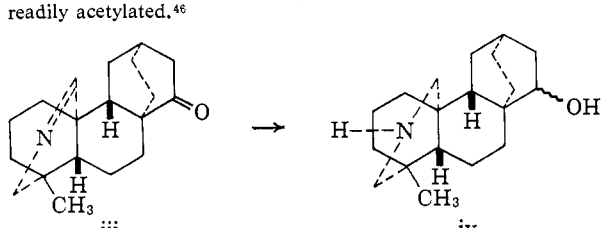
The stereochemical implications of the above data can be most readily appreciated by a comparison of conformational drawings of isomers **60** with **61** and **62** with **63**. Reduction of ketone **65** to a mixture of about equal parts of epimeric alcohols (**64a** and **66a**), each of which forms an acetate, indicates the relatively unhindered character of the hydroxyls.[72] But in structure **61**, a ketone group at C-14 is extremely hindered and would not be expected to give substantial amounts of each epimer upon reduction. Moreover, the N-ethyl derivatives **67a** and **69a** and their acetates **67b** and **69b** confirm the unhindered nature of the hydroxyls. The pK_a' values for both sets of compounds also rule out structure **61** as a possibility. Clearly if the allylic alcohol system is on the C-13–C-14 bridge in **61** there will be more interaction between a hydroxyl (or acetoxyl) and the nitrogen atom in one epimer than the other. However, in structure **60** the interaction, if any, should be small for either epimer. The pK_a' for **67a** (9.25) is almost the same as for **69a** (9.13), and acetate **67b** (8.30) has nearly the same value as **69b** (8.11). Though there appears to be a small amount of interaction, the fact that the magnitude of the drop in pK_a' in going from hydroxyl derivative to acetate is the same for each epimer supports location of the allylic alcohol system on an unhindered bridge such as C-15–C-16 in **60** but not on the C-13–C-14 bridge as in **61**.[72]

In isomers **62** and **63**, rings ABC constitute *trans–syn–trans*-perhydrophenanthrene systems with ring B in the form of a boat. Since C-14 and the hydrogen on C-5 occupy the bowsprit positions of a boat, serious eclipsing occurs between C-5–H and the adjacent substituent on C-14. But both epimers from the reduction of ketone **65** have already been shown to be unhindered—a condition satisfied in the *trans–syn* series if the hydroxyl is on C-15 as in **63**, but not if it is at C-14 as in **62**. These arguments rigorously limit the stereochemistry of atisine to either isomer **60** or **63**. Since anticoupling of rings A and C is demanded by the known chemistry of ajaconine,[10,73] the complete relative stereochemistry of atisine is expressed by **60**.

Since the Garrya alkaloid, veatchine, has been correlated with atisine,[9,34] it has the same stereochemistry of the ring fusions and may be represented by structure **70**. Recently the absolute configuration of atisine has been demonstrated by an elegant series of experiments by Vorbrueggen and Djerassi.[17] Edwards[18] has also provided independent evidence for the absolute configuration by a synthesis of the antipode of the phenol **71** originally obtained by degradation of atisine. Thus the Atisine and the Garrya alkaloids join the ranks of terpenes with antipodal stereochemistry of the A/B ring fusion as compared with that of the steroids.[74]

The assignment of configuration of the secondary hydroxyl in atisine is made difficult by the high degree of symmetry of the bicyclo[2.2.2]octane system. However, a tentative assignment of the β-configuration as in **1** has been made on the basis of the difference in the absorption of the epimeric alcohols (**64a** and **66a**) on alumina.[3b] In isomer **66a** the hydroxyl and N-acetate groups are so oriented that they can be adsorbed simultaneously on the alumina surface. In isomer **64a** these groups are on opposite sides of the molecule and therefore cannot be adsorbed by the alumina surface at the same time. Thus the more strongly adsorbed epimer (the one with the unnatural configuration)

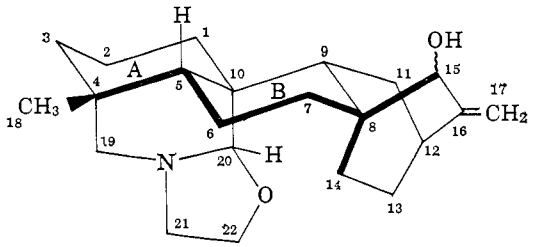
(72) Edwards has established the same point by reducing ketone iii with sodium borohydride to the epimeric alcohols (iv), each of which is readily acetylated.[46]



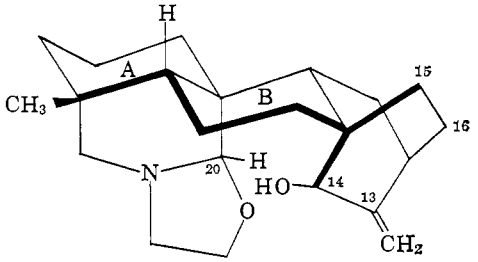
iii iv

(73) D. Dvornik and O. E. Edwards, *Tetrahedron*, 14, 54 (1961).

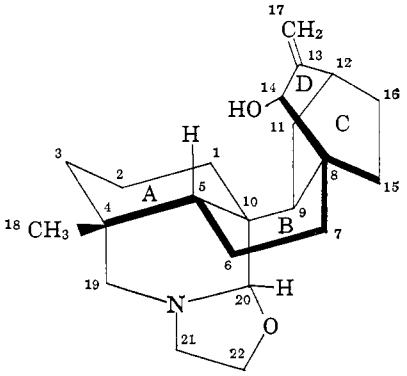
(74) Other terpenes possessing antipodal stereochemistry of the A/B ring fusion compared with the steroids are aconitine, andrographolide, cafestol, copalic acid, daniellic acid, darutigenol, delphinine, eperuic acid, farnesiferol-A, iresin, (−)-kaurene, polyalthic acid, and steviol.



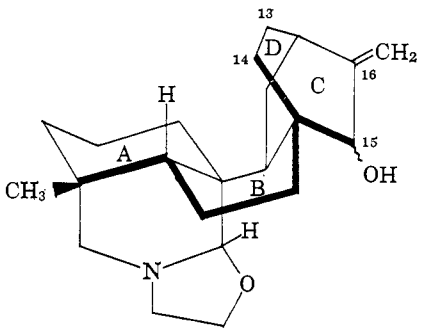
60, A/B-*trans-anti*



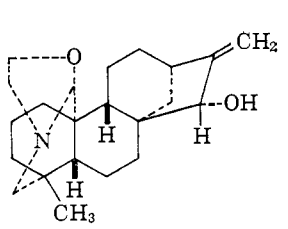
61, A/B-*trans-anti*



62, ABC-*trans-syn-trans*



63, ABC-*trans-syn-trans*



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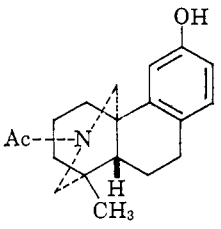

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must be **66a** in which the hydroxyl and N-acetyl absorption reinforce each other. Atisine must therefore be represented by the configuration in **64a**. Since atidine and ajaconine have been correlated with dihydroatisine,[6] the secondary hydroxyl group in these compounds would also have the β-configuration as in **64a**.

Experimental

General Experimental Procedures. Melting points are corrected and were taken on a hot stage equipped with a microscope and polarizer. Finely powdered samples were placed on the stage 15° below the melting point and the temperature was raised at a rate of about 4°/min. Rotations were taken in chloroform unless otherwise noted. Ultraviolet spectra were determined in 95% ethanol on a Beckman Model DU or a Perkin-Elmer Model 203 spectrophotometer and infrared spectra on Perkin-Elmer Model 21 and Infracord spectrophotometers. Proton magnetic resonance (p.m.r.) spectra were taken on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Petroleum ether refers to a light petroleum fraction of b.p. 30–70°. Ligroin refers to a light petroleum fraction of b.p. 30–70°. The removal of solvents *in vacuo* was accomplished with a Craig-type rotating flash evaporator at 15–20 mm. and with the water bath usually at 35–50°.

Thin Layer Chromatography. Thin layer plates were prepared with Brinkman equipment using alumina. Solvent mixtures utilized are indicated in each experiment. Visualization of spots was effected by exposing the developed plate to iodine vapor until spots became visible, removal of the plate from the iodine chamber, and exposing the surface of the plate briefly to a steam jet. The plate was then re-exposed to iodine vapor. The steam treatment and re-exposure to iodine vapor gave much more intense spots than a single exposure to iodine.

Ozonolysis of Dihydroatisine. A solution of 250 mg. of dihydroatisine in 15 ml. of chloroform was treated with ozone for 2 hr. at 0°. After standing for another 0.5 hr., the solution was taken to dryness *in vacuo* and the residue was treated with 150 ml. of 5% sulfuric acid. The solution was distilled and then more water was added and distilled again. Treatment of the first 240 ml. of distillate with 6 ml. of 5% dimedon in ethanol and a drop of piperidine gave 121 mg. (57%) of formaldehyde dimedon derivative, m.p. 191–192°, undepressed by an authentic sample.

Ozonolysis of Atisine. A solution of 248 mg. of atisine in 15 ml. of chloroform was ozonized for 2 hr. at 0°. After work-up as described for dihydroatisine, there was obtained 88 mg. (42%) of the formaldehyde dimedon derivative, m.p. 191–192°, undepressed by an authentic sample.

Ozonolysis of Isoatisine. A solution of 500 mg. of isoatisine in 25 ml. of chloroform was ozonized for 3 hr. at 0°. After work-up as described for dihydroatisine, there was obtained 191 mg. (45%) of the formaldehyde dimedon derivative, m.p. 191.5–192.5°, undepressed by an authentic sample.

Ozonolysis of α-Tetrahydroatisine. A solution of 78 mg. of α-tetrahydroatisine, m.p. 171–173°, in 10 ml. of ethanol-free chloroform was ozonized for 2 hr. at 0°. After work-up as described for dihydroatisine, there was obtained only 2.5 mg. (3.8%) of the formaldehyde dimedon derivative. Ozonization of chloro-

form and work-up also gave a small amount of dimedon derivative.

β-Oxoatisine Dicarboxylic Acid Dimethyl Ester (**7**). A solution of 56 mg. of the lactam dicarboxylic acid (**6**)[31] from atisine in acetone was esterified with diazomethane. Evaporation *in vacuo* and crystallization of the residue from ether gave 35 mg. of rosettes of the dimethyl ester (**7**): m.p. 188–191°; ν_{max}^{Nujol} 1731 (—CO_2CH_3) and 1658 cm.$^{-1}$ (strong, δ-lactam); no hydroxyl absorption; $\nu_{max}^{CHCl_3}$ 1731 and 1642 cm.$^{-1}$. The Tschugaeff–Zerewitinoff determination at both 25 and 90° was negative on this compound.

Anal.[75] Calcd. for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93. Found: C, 65.65; H, 7.91.

α-Oxoatisine Dicarboxylic Acid Dimethyl Ester (**7a**).[31] In Nujol this compound showed bands for the ester groups at 1734 cm.$^{-1}$ and the γ-lactam at 1709 cm.$^{-1}$ No hydroxyl band was present.

Oxoisoatisine Dicarboxylic Acid Dimethyl Ester (**9**).[25–27] The infrared spectrum of a film from chloroform showed bands at 3378 (associated $^{-}$OH), 1730 (—CO_2Me), and 1622 cm.$^{-1}$ (δ-lactam).

Oxidation of Atisine with CrO_3–Pyridine Complex. A solution of 3.6 g. of atisine in 36 ml. of anhydrous pyridine was added dropwise to a complex prepared from 3.1 g. of chromium trioxide in 31 ml. of pyridine at 15°. The reaction mixture was stirred gently at 10° for 8 hr. and then left in the refrigerator overnight. Next morning, the contents were allowed to warm to room temperature and stirred for 3 hr. After evaporating to dryness *in vacuo*, the dark brown residue was extracted several times with hot acetone. The residue was reserved. The combined acetone extracts, on evaporating to dryness, afforded 1.08 g. of a light brown resin which was dissolved in benzene (100 ml.) and extracted thoroughly with ice-cold 20-ml. portions of 5% sulfuric acid to separate the basic and the neutral products of the reaction.

Basic Fraction. The brown residue remaining from the acetone extraction was suspended in 100 ml. of water and basified with cold 1 *N* sodium hydroxide. After continuous extraction with ether, the organic layer was washed with water and dried and the solvent was evaporated to yield 2.5 g. of a light-brown basic material. This was crystallized twice from ether to give 2.25 g. of the crystalline enone, atisone (**10**), m.p. 100–102°, $[\alpha]^{31}D$ −27° (*c* 2.3); λ_{max}^{EtOH} 229 mμ (ε 9500), $\nu_{max}^{CCl_4}$ 1704 (>C=O), and 1642 and 900 cm.$^{-1}$ (>C=CH_2); p.m.r., τ 9.17 and 9.22 (CCH_3) and 4.83, 4.10 (>C=CH_2).

Anal. Calcd. for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15. Found: C, 77.25; H, 8.97.

The 5% sulfuric acid extract referred to earlier was chilled to 10°, basified with 1 *N* sodium hydroxide, and extracted with chloroform. The residue (620 mg.) was chromatographed over neutral Woelm alumina to give 120 mg. of atisone, m.p. 95–102°. Recrystallization afforded 90 mg. of material melting at 97–99°.

Neutral Fraction. The Secondary Lactam Enone (**13**). The benzene layer afforded 120 mg. of a colored material which was purified by passing through a column of 25 g. of neutral Woelm alumina in benzene. Elution of the column gave 60 mg. of a crystalline material, m.p. 178–180°, which when crystallized twice from acetone melted at 181.5–182.5°; ν_{max}^{Nujol} 3289, 3195, and 3077 (NH of the lactam), 1704 and 1629 (conjugated enone), and 1658 cm.$^{-1}$ (δ-lactam); λ sh (EtOH) 228.5 mμ (ε 7800).

Anal. Calcd. for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68. Found: C, 76.53; H, 8.58.

The p.m.r. spectrum of the crystalline neutral compound disclosed the presence of a tertiary methyl group, deshielded by the adjacent lactam carbonyl (singlet at τ 9.05). The presence of an enone double bond was also revealed in the p.m.r. spectrum by the appearance of the two β-protons as a pair of doublets at τ 4.12 and 4.84 (J = 2 c.p.s.). The proton on the lactam nitrogen (—N*H*CO—) appears as a diffuse multiplet centered around τ 3.95.[33]

Oxidation of Des(N-β-hydroxyethyl)dihydroatisine (**14**) *to Enone* **15**. A solution of 200 mg. of the secondary amine **14**[32] in 2 ml. of dry pyridine was slowly added to the complex prepared from 450 mg. of chromium trioxide in 4.5 ml. of dry pyridine at 15°. The reaction mixture was stirred at room temperature for 0.5 hr. and then left overnight in the refrigerator. The reaction mixture was evaporated to dryness *in vacuo* and the dark brown residue, suspended in water (50 ml.), was made alkaline with 1 *N* sodium hydroxide. After extraction with benzene, the organic layer was washed with water and extracted four times with ice-cold 10-ml. portions of 5% sulfuric acid to separate the basic and the neutral products. The acid extract was cooled, basified with 1 *N* sodium hydroxide, and extracted with chloroform. Evaporation *in vacuo* afforded 158 mg. of a colorless gum which was chromatographed over neutral Woelm alumina (15 g.) using a mixture of ether and petroleum ether (1:1) as the eluent. The first 60-ml. fraction of the eluate, on evaporation of the solvent, afforded 75 mg. of a crystalline material, m.p. 127–130°, raised to 129–131° on recrystallization (ether–petroleum ether, 1:1) and undepressed on admixture with an authentic sample of enone, **15**[31]; ν_{max} 1706 (conjugated >C=O), and 1645 and 1631 cm.$^{-1}$ (azomethine and enone double bond). No neutral material was obtained from the oxidation reaction.

Oxidation of **14** *with Potassium Permanganate to Lactam* **16**. A solution of 120 mg. of **14** dissolved in 5 ml. of acetone (refluxed over potassium permanganate and distilled) was treated at room temperature with finely powdered potassium permanganate (150 mg.) in dry acetone (20 ml.). After 1 hr. the reaction mixture was allowed to stand in the refrigerator overnight. A few drops of hydrazine (95%) was added and the dark brown residue was filtered. The residue was washed with hot acetone and filtered. The colorless filtrate on evaporation gave a gummy residue (135 mg.) which was dissolved in benzene and extracted with ice-cold 5% sulfuric acid to separate the basic and the nonbasic materials. The basic fraction (80 mg.) was found to be starting material.

The neutral material (15 mg.) was chromatographed over neutral Woelm alumina (5 g.) using acetone as the eluent. The first 60 ml., on removal of the solvent *in vacuo* and crystallization, furnished 9 mg. of a nicely crystalline compound (**16**), m.p. 217–218°. On recrystallization it melted at 217–218°; ν_{max}^{Nujol} 3436

(75) Analyses are by Mr. James Rigakos of the Rockefeller Institute and the Midwest Microlab, Indianapolis, Ind.

(—OH), 1653 (azomethine), and 1631 cm.$^{-1}$ (lactam carbonyl); λ_{max} (EtOH) 205 mμ (ϵ 6400).

Anal. Calcd. for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68. Found: C, 76.73; H, 8.66.

The neutral compound was recovered unchanged on refluxing with sodium borohydride in 80% methanol.

Conversion of Lactam Enone (**13**) *to N-Acetyldes-(β-hydroxyethyl)dihydroatisine* (**19**). A solution of 85 mg. of **13** in methanol (10 ml.) containing water (5 drops) was treated with $NaBH_4$ (60 mg.). After the reaction had subsided, the reaction mixture was allowed to stand at room temperature overnight. Methanol was removed *in vacuo* and the residue was extracted several times with chloroform. The organic layer, after drying, was evaporated to dryness to yield 72 mg. of a crude product (**17**) insoluble in dilute acid. The product was almost insoluble in tetrahydrofuran.

A solution of 175 mg. of lithium aluminium hydride in 40 ml. of anhydrous tetrahydrofuran (distilled over lithium aluminium hydride) was added carefully, with vigorous stirring, to a suspension of 72 mg. of the foregoing neutral compound in 80 ml. of anhydrous tetrahydrofuran and the resulting mixture was refluxed (protected from moisture) for 60 hr. It was then cooled and the excess lithium aluminium hydride and the complex were decomposed carefully by dropwise addition of moist ether. After decomposition, the tetrahydrofuran–ether layer was decanted from the sludge, which was then extracted thoroughly with ether. The combined ether extracts were washed thrice with 2% dilute sulfuric acid using 2 ml. each time. The benzene solution furnished, on evaporation, a small quantity (10 mg.) of unchanged starting material. The combined acid washings were made strongly alkaline with 20% sodium hydroxide and extracted with chloroform. The combined chloroform extracts, on evaporation *in vacuo*, furnished 40 mg. of a highly viscous oil which without purification was treated with 0.3 ml. of pyridine and 0.3 ml. of acetic anhydride and left overnight. After evaporating to dryness, the light brown residue was left at room temperature with 2 ml. of 5% methanolic sodium hydroxide for 6 hr. After working up as usual, the gummy residue was chromatographed over alumina using benzene as the eluent. One of the fractions crystallized on trituration with ether. Recrystallization from acetone gave colorless needles of **19** (8 mg.), m.p. 230–232°, identical in all respects with an authentic sample.[32,34]

Oxidation of Isoatisine with Chromium Trioxide–Pyridine Complex. A solution of 2.3 g. of the title compound in 25 ml. of dry pyridine was slowly added to the complex prepared from 2.5 g. of chromium trioxide in 25 ml. of dry pyridine at 15°. The reaction mixture was stirred gently at 20° for 4 hr. and then left overnight in the refrigerator. After evaporating to dryness *in vacuo*, the residue was extracted several times with hot acetone. On concentrating to dryness, the extracts (350 ml.) afforded 2.1 g. of a brown resin which was dissolved in benzene (100 ml.) and extracted thrice with ice-cold, 20-ml. portions of 5% sulfuric acid to separate the basic and the neutral products. The neutral fraction amounted to 380 mg.

Basic Fraction, Isoatisone (**11**). The acidic extract was chilled to 5°, basified with 1 *N* sodium hydroxide, and extracted with chloroform. After the extract was washed, dried, and evaporated the residue (1.05 g.) was crystallized from acetone to give 590 mg. of isoatisone (**11**), m.p. 159–162°; occasionally samples showed a melting point of 285–295°. The infrared spectra of the 160 and 295° material were identical. An analytical sample melted at 161.5–162.5°; $[\alpha]^{29}D$ −9.3° (*c* 1.9); λ_{max}^{EtOH} 227.5 mμ (ϵ 8074); ν_{max}^{Nujol} 1706 and 1642 (strong, conjugated enone) and 3086 and 887 cm.$^{-1}$ (>C=CH$_2$); $\nu_{max}^{CHCl_3}$ 3077, 1709, 1631, and 883 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15. Found: C, 77.28, 77.49; H, 8.87, 9.17.

In another experiment 2.4 g. of isoatisine was oxidized with 2.5 g. of chromium trioxide in 25 ml. of pyridine under the conditions described above. The reaction mixture was decomposed by treatment with sodium hydroxide and extracted with benzene to give 2.05 g. of crystalline material. Separation into basic and neutral fractions afforded 1.45 g. of base and 0.45 g. of neutral material. Crystallization of the basic fraction from acetone afforded 980 mg. of heavy prisms of isoatisone (**11**), m.p. 158–161°.

Neutral Fraction, Lactam–Enone (**20**) The 380 mg. of neutral fraction was chromatographed in benzene over 15 g. of neutral alumina. Elution of the column with 1% methanol in benzene furnished 210 mg. of crystals, m.p. 211–214°. An analytical sample, crystallized twice from methanol, melted at 216–219°; λ sh (EtOH) 227 mμ (ϵ 8500); ν_{max}^{Nujol} 3390 (—OH), 1701 (conjugated >C=O), and 1616 cm.$^{-1}$; (δ-lactam) 3086 and 901 cm.$^{-1}$ (>C=CH$_2$). This product was also obtained by oxidation of oxoisoatisine (**21**) with chromium trioxide–pyridine (*vide infra*).

Anal. Calcd. for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74. Found: C, 73.82; H, 8.72.

Oxidation of Oxoisoatisine (**21**) *with Chromium Trioxide–Pyridine to Give* **20**. A solution of 95 mg. of oxoisoatisine (**21**) in 1 ml. of dry pyridine was added to the complex prepared from 81 mg. of chromium trioxide in 0.5 ml. of dry pyridine at 15°. After standing overnight in the ice chest, the reaction mixture was worked up as described above. Evaporation of the benzene extract gave a light brown residue (70 mg.) which on crystallization from methanol melted at 210–213°. Recrystallization furnished colorless cubes melting at 215–217°, undepressed with a sample of the neutral compound (**20**) described above. The infrared and the p.m.r. spectra of the two samples were also identical.

Anal. Calcd. for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74. Found: C, 74.13; H, 8.77.

The p.m.r. spectrum of the compound showed, as expected, a methyl singlet at τ 8.83 while dihydroatisine exhibited the methyl signal at τ 9.25. In addition, the p.m.r. spectrum also disclosed the presence of an enone double bound, the two β-protons appearing as a pair of doublets at τ 4.0 and 4.72 (J = 2 c.p.s.).

The Isomerization of Atisone (**10**) *to Isoatisone* (**11**). *A.* A solution of 200 mg. of atisone in 10 ml. of methanol was refluxed on a steam bath for 1.5 hr. Methanol was then removed *in vacuo*, and the colorless gummy residue was dissolved in ether (30 ml.), concentrated to 2 ml., and allowed to stand overnight in the refrigerator. Isoatisone (**11**, 40 mg.) crystallized as prisms, m.p. 166–168° dec., identical in all respects

(melting point and infrared) with an authentic sample of isoatisone.

B. A solution of 100 mg. of atisone in 5 ml. of ethanol was refluxed gently on a steam bath for 6 hr. and then allowed to stand overnight at room temperature. The reaction mixture was worked up as before to give 77 mg. of isoatisone, m.p. 166–167 and 295° dec., undepressed with an authentic sample.

Mercuric Acetate Cyclization of Dihydroatisine (**2**) *to Isoatisine* (**4**). To a solution of 3.69 g. of mercuric acetate in 5 ml. of 5% acetic acid at 60° was added a solution of 1.0 g. of dihydroatisine in 10 ml. of 5% acetic acid. The temperature after mixing was 31°. Mercurous acetate began to precipitate after a few minutes. After 24 hr. the mixture was filtered. The precipitated mercurous acetate weighed 1.656 g. (theoretical, 1.50 g.). The filtrate was treated with H_2S and filtered through a bed of Celite-505. The filtrate was basified with sodium carbonate and the solution was extracted eight times with benzene. Evaporation of the benzene extract gave 1.00 g. of resin. This was dissolved in 2% sulfuric acid and extracted several times with benzene. The aqueous phase was basified with sodium hydroxide solution and extracted with benzene to give 950 mg. of pale yellow resin. This was chromatographed in benzene over 40 g. of Woelm neutral alumina (activity 3). The first 500 ml. of solvent eluted 794 mg. which crystallized from acetone to give 206 mg. of isoatisine, m.p. 145–149°. Concentration of the mother liquors afforded a fraction which on recrystallization gave another 114 mg. of isoatisine. The isoatisine fractions were homogeneous by thin layer chromatography on alumina using benzene–2% methanol. T.l.c. of the mother liquors indicated the presence of at least two other components.

Reduction of Isoatisine with $LiAlH_4$ and $AlCl_3$. To a well-stirred suspension of 2.0 g. of $LiAlH_4$ and 2.0 g. of $AlCl_3$ in 200 ml. of ether was added 2.0 g. of isoatisine in 100 ml. of ether. The mixture was boiled under reflux for 24 hr. and excess hydride was decomposed by the dropwise addition of water. After filtration and evaporation of the ether, 1.48 g. of dihydroatisine separated, m.p. 159–160°. Processing the mother liquors yielded another 238 mg. of dihydroatisine. The infrared in Nujol was identical with that of an authentic sample of dihydroatisine.

Anal. Calcd. for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21. Found: C, 76.66; H, 10.05.

Reduction of Isoatisone (**4**) *with $LiAlH_4$–$AlCl_3$.* A solution of 700 mg. of isoatisone in 100 ml. of dry ether was added to a refluxing solution of 2 g. of $AlCl_3$ and 2 g. of $LiAlH_4$ in 200 ml. of ether. After refluxing for 24 hr., water was added carefully to decompose excess hydride, then sodium hydroxide solution. Extraction with benzene gave 234 mg. of resin. Crystallization and chromatography over neutral Woelm alumina gave fractions melting over the range 133–139° which appeared to be mixtures of dihydroatisines. The infrared spectrum was similar to that of dihydroatisine, but showed a substantial amount of ketonic contaminant at 1709 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21. Found: C, 76.12; H, 10.14.

Acid-Catalyzed Isomerization of Isoatisine to Methyl Ketones A and B (**24**). A solution of 23.2 g. of isoatisine in 400 ml. of 95% ethanol was treated with 80 ml. of concentrated hydrochloric acid and boiled under reflux for 9.5 hr. The mixture was concentrated under reduced pressure, diluted with 600 ml. of water, and extracted once with benzene. The benzene extract was discarded. Basification of the aqueous phase with dilute sodium hydroxide and extraction with benzene yielded 23 g. of resin. After standing in acetone over a weekend, the resin deposited 11 g. of a mixture of the epimeric methyl ketones, m.p. 120–135°. Crystallization by the triangle scheme gave 5.56 g. of heavy prisms, m.p. 142–146°. Three more crystallizations from acetone gave ketone A (**24a**) of constant melting point, 150–153°, $[\alpha]^{27}D$ −4.6° (*c* 1.2). This material gave one spot by thin layer chromatography on alumina in the systems benzene–methanol (75:1) and benzene–pyridine–methyl ethyl ketone (20:1:3). However, material melting at 157–160° was obtained after fractionation through the hydrochloride (*vide infra*), though the infrared spectrum was unchanged. The infrared spectra in Nujol and carbon disulfide showed the absence of hydroxyl absorption: ν_{max}^{Nujol} 1712 cm.$^{-1}$ (>C=O); $\nu_{max}^{CS_2}$ 1715 (>C=O) and 1368 cm.$^{-1}$ (CCH_3); τ 8.93 and 9.09 (v. weak,[76] CCH_3) and τ 8.93 and 8.82 (3H, doublet, $CHCH_3$).

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 76.87, 77.02; H, 9.73, 9.63; N, 4.15.

Hydrochloride of Ketone A. A solution of 350 mg. of ketone A in acetone was treated at 5° with dry HCl. Evaporation *in vacuo* gave a crystalline residue which was recrystallized several times from methanol–acetone to give needles of the hydrochloride, 160 mg., m.p. 283–286.5°; ν_{max}^{Nujol} 3175 (associated —OH), 1709 (>C=O), and 1678 cm.$^{-1}$ (>C=N$^+$<).

Anal. Calcd. for $C_{22}H_{33}NO_2 \cdot HCl$: C, 69.52; H, 9.02. Found: C, 69.60; H, 8.87.

The hydrochloride (153 mg.) in water was treated with cold, dilute sodium carbonate and extracted to give a resin (122 mg.) which crystallized from acetone as prisms, 77 mg., m.p. 157–160°. The infrared spectrum in Nujol was identical with the 150–153° material described above.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 76.92; H, 9.54.

Isomer B Ketone (**24b**). This isomer was obtained by careful crystallization of the low-melting fraction from early mother liquors of isomer A. Initial recrystallization of this fraction from ether–petroleum ether gave needles, 700 mg., m.p. 116–122°. Three more recrystallizations gave delicate fibrous needles, m.p. 132.5–134.5°, $[\alpha]^{26}D$ −8.3° (*c* 1.3). The infrared spectra in Nujol and carbon disulfide showed the absence of hydroxyl absorption. The fingerprint region of the Nujol spectrum of this epimer differed somewhat from that of ketone A. In CS_2, small differences were apparent in the 8–9 μ region: ν_{max}^{Nujol} 1712 cm.$^{-1}$ (>C=O), $\nu_{max}^{SC_2}$ 1712 (>C=O) and 1366 cm.$^{-1}$ (CCH_3); τ 8.93, 9.09 (v. weak).[76]

Anal. Found: C, 76.96, 76.76; H, 9.36, 9.69.

Hydrochloride of Ketone B. A solution of 32 mg. of ketone B in acetone was treated with dry HCl at

(76) The weak signal at τ 9.09 in isomers A and B is probably due to a certain population of molecules with a conformation of the heterocyclic ring different from that giving rise to the signal at τ 8.93. In atisine the two peaks are of about equal intensity.

5°. Evaporation *in vacuo* gave a product which crystallized from acetone as thin needles or platelets. When placed on the hot stage at 200°, it melted at 214.5–217.5°, crystallized, and then remelted at 269–281°. It appeared that the 214–217° hydrochloride may slowly isomerize during heating to the hydrochloride of ketone A.

A 13.25-g. sample of the mother liquor from ketone A was chromatographed in benzene over 300 g. of Merck acid-washed alumina (H_2SO_4). Elution with methanol gave 4.5 g. of yellow resin which on trituration with ether yielded 3.12 g. of an insoluble powder. The latter crystallized from chloroform–acetone as stout rods, m.p. 342–349°. This material proved to be the acid sulfate salt of the mixed methyl ketones described above.[77]

Anal. Calcd. for $C_{22}H_{33}NO_2 \cdot H_2SO_4$: C, 59.84; H, 7.99; S, 7.26. Found: C, 60.12; H, 7.81; S, 7.40.

A 1.2-g. sample of the sulfate salt in water was basified with dilute sodium hydroxide and extracted with chloroform. Evaporation gave 1.01 g. of resin which crystallized from acetone to give prisms, m.p. 136–146°. The infrared spectrum was identical with that of the mixture of epimeric ketones A and B.

Isomerization of Ketone A to Mixture of Epimeric Ketones. A solution of 105 mg. of ketone A in 15 ml. of methanol was treated with 300 mg. of potassium carbonate in 2.3 ml. of water and boiled under reflux for 5 hr. Work-up gave 100 mg. of resin. The infrared spectrum in CS_2 showed the product consisted of a mixture of ketone A and ketone B. The resin crystallized from acetone as prisms, m.p. 127–138°.

Isomerization of Ketone B to Mixture of Epimeric Ketones. A solution of 30 mg. of ketone B, m.p. 132.5–134.5°, in 6 ml. of methanol was treated with 120 mg. of potassium carbonate in 1 ml. of water. After refluxing for 90 min., work-up gave 28 mg. of material which crystallized from acetone as prisms of the mixed ketones, m.p. 137–143.5°. Repeated crystallization from acetone and petroleum ether gave a sample of ketone A, m.p. 158–161°.

Modified Wolff–Kishner Reduction of Mixture of Methyl Ketones A and B to **25**. Several trials indicated that the standard Huang-Minlon procedure is ineffective in removing the carbonyl function in this case. Recourse to anhydrous hydrazine and sodium in diethylene glycol was effective, however. From a mixture of 46 ml. of diethylene glycol and 10 ml. of anhydous hydrazine in a 200-ml., round-bottom flask, a small amount was distilled to ensure dryness (b.p. 170°) and then 6.25 g. of a mixture of ketones A and B (**24**), m.p. 136–146°, was added. The contents, which was protected by a drying tube, was boiled under reflux at 165–170° for 23 hr. A solution made from 1.0 g. of clean sodium dissolved in 10 ml. of diethylene glycol was then added and the reaction temperature was raised over a period of 30 min. to 205° by boiling off hydrazine. After refluxing at 205–210° for 23.5 hr., the mixture was cooled and poured into 800 ml. of water. Extraction of the aqueous solution with benzene gave 5.88 g. of a colorless resin. This material was chromatographed in benzene over 140 g. of basic alumina. The fractions were examined for the absence of infrared absorption in the 5.8-μ region. After rejection of the first 100 ml. of eluate containing 45 mg., the next three 100-ml. fractions were combined to give 5.13 g. of colorless resin showing strong absorption in the 3350-cm.$^{-1}$ region (OH), but only a trace of absorption at 5.83 μ (film from benzene).

Anal. Calcd. for $C_{22}H_{33}NO$: C, 79.70; H, 11.25. Found: C, 79.81, 80.15; H, 11.02, 11.11.

The material was further purified by conversion to the hydrochloride. Material from several reductions was combined (14.7 g.) in 500 ml. of acetone and treated with an excess of dry HCl at 0°. There was collected 9.97 g. of m.p. 199–207°. Concentration of the mother liquors to dryness to remove excess HCl and crystallization of the residue from acetone afforded an additional 3.88 g., m.p. 197.5–208°. Combination of these two fractions and recrystallization from acetone gave 11.26 g. of needles, m.p. 200–204°, $[\alpha]^{27}D$ −33.2° (*c* 1.48), and 1.95 g. of m.p. 197–203.5°. The melting point is very dependent on the rate of heating.

Anal. Calcd. for $C_{22}H_{33}NO \cdot HCl$: C, 71.80; H, 10.65. Found: C, 72.02, 72.06; H, 10.60, 10.50.

A solution of 13.3 g. of the hydrochloride in 500 ml. of water was basified with dilute sodium hydroxide and extracted with benzene. After washing and drying, the benzene extracted yielded 12.0 g. of a mixture of deoxytetrahydroatisine epimers (**25**), which showed no absorption in the 5.8-μ region (film from benzene), $[\alpha]^{27}D$ −52.9° (*c* 2.2).

Anal. Calcd. for $C_{22}H_{37}NO$: C, 79.70; H, 11.25; N, 4.23. Found: C, 79.71; H, 11.13; N, 4.16.

Selenium Dehydrogenation of Deoxytetrahydroatisine Epimers (**25**). In a 250-ml. distillation flask fitted with a side arm sealed 6 in. above the bulb was placed 13.6 g. of the title compound (**25**) and 34 g. of powdered gray selenium. The flask was inserted into a metal bath at 180° and the temperature was raised over a period of 30 min. to 290°, while a very slow stream of nitrogen was passed through the apparatus. The contents was boiled vigorously and water distilled. Over the course of the next 30 min., the bath temperature was raised to 335–340° where it was held for 8 hr. After cooling the contents consisted of a dark sirup covering the hard selenium cake. The sirup which was washed from the flask and delivery tube with benzene amounted to 11.5 g. Continuous extraction of the ground selenium cake with ether yielded only 14 mg. The two fractions were combined and processed together.

A solution of the 11.5 g. in 700 ml. of benzene was extracted with 3% sulfuric acid until basic material was no longer present in the aqueous extract.[78] The acid extracts were combined, made basic with sodium hydroxide, and extracted with benzene. A basic fraction (B) of 6.146 g. resulted.

The benzene solution containing the neutral fraction was washed with dilute sodium hydroxide to remove any possible phenols, shaken with mercury to remove selenium, and filtered through Filter-cel. Evaporation of the filtrate gave 5.10 g. of neutral fraction (N).

(77) This experiment was performed by Dr. P. Ragagopalon.

(78) The basic imines, which are products of the dehydrogenation, are extremely nonpolar and are removed from benzene slowly even by sulfuric acid. Forty extractions with 50-ml. portions of 3% sulfuric acid were necessary to remove all the bases.

Basic Fraction (B) Imines **27** *and* **29**. This material (6.146 g.) containing imine A and B was chromatographed in benzene over 100 g. of Woelm neutral alumina. The first ten fractions of 100 ml. were combined and evaporated to give 4.9 g. of semicrystalline material. After treatment with Norit in petroleum ether, crystallization at −60° gave three fractions: 531 mg., m.p. 113–118.5°; 438 mg., m.p. 100.5–111.5°; and 30 mg., m.p. 98–108°. These fractions were combined and recrystallized repeatedly from petroleum ether to give 538 mg. of heavy prisms of imine A (**27**): m.p. 122–124°, ν_{max}^{Nujol} 1642 cm.$^{-1}$ s. (—N=C); τ 9.15 (3H singlet, CCH_3), 9.10 (3H doublet, J = 7 c.p.s., CHCH_3), and 7.90 and 7.93 (3H, —NCOCH_3—, presumably two conformations of ring E). This material gave a single spot in t.l.c. in the system benzene–methanol–carbon tetrachloride (25:1:1).

Anal. Calcd. for $C_{20}H_{31}N$: C, 84.14; H, 10.95; N, 4.91. Found: C, 84.21; H, 11.06; N, 4.96.

Hydrochloride. The compound, crystallized from ethyl acetate, had m.p. 167–177°; ν_{max}^{Nujol} 3484, 3413, and 2532 (broad) (N^+H); 2130, 1934, and 1874 (=N^+H); and 1691 cm.$^{-1}$ (>C=N^+<).

Anal. Calcd. for $C_{20}H_{31}N\cdot HCl\cdot 0.5H_2O$: C, 72.58; H, 10.05. Found: C, 72.56; H, 10.00.

The mother liquors were combined and 2.67 g. was converted to the hydrochloride in acetone. Since repeated crystallization of the hydrochloride by the triangle scheme failed to effect a separation of epimeric imines, the material was reconverted to the base. By careful crystallization from cold ethyl acetate, a small additional quantity of imine A, m.p. 120–123, was obtained. Careful chromatography of 295 mg. of the mother liquors over 21 g. of neutral Woelm alumina (activity 2) failed to effect any separation whatever. Likewise ineffective was thin layer chromatography on silica gel in several solvent systems. The mother liquor consisting mostly of imine B was converted to an N-acetate as described below.

Conversion of Imine B (**29**) *to N-Acetate* (**30**). A solution of 260 mg. of crude imine B in 11 ml. of 85% methanol was treated with 0.32 g. of sodium borohydride and allowed to stand at room temperature for 4 hr. The mixture was evaporated *in vacuo*, taken up in water, and extracted with ether. The product (231 mg.) was acetylated by treatment with 0.5 ml. of acetic anhydride in 0.5 ml. of dry pyridine overnight. Work-up in the usual manner gave 270 mg. of residue. Crystallization from acetone by the triangle scheme gave what appeared to be a pure fraction of the N-acetate of imine B (**30**): 92 mg.; m.p. 147.5–149.5°; ν_{max}^{Nujol} 1645 and 1631 cm.$^{-1}$ (NAc); τ 9.17 (3H singlet, CCH_3), 9.10 (3H doublet, J = 6.5 c.p.s., —CHCH_3), and 7.90 and 7.93 (3H, —NCOCH_3 presumably two conformations of ring E).

Anal. Calcd. for $C_{22}H_{35}NO$: C, 80.19; H, 10.71. Found: C, 80.18, 80.37; H, 10.58, 10.59.

Conversion of Imine A (**27**) *to N-Acetate* (**28**). A solution of 100 mg. of imine A (**27**) in 5 ml. of 85% methanol was reduced with sodium borohydride and acetylated in acetic anhydride–pyridine as described for imine B. The product (112 mg.) was crystallized twice from acetone to give 77 mg. of prisms: m.p. 166.5–167.5°; ν_{max}^{Nujol} 1645 and 1631 cm.$^{-1}$ (NAc); p.m.r. τ 9.15 (3H singlet, CCH_3), 9.1 (3H doublet, J = 7 c.p.s., CHCH_3), and 7.93 and 7.90 (3H, NCOCH_3, presumably indicates two conformations of ring E).

Anal. Calcd. for $C_{22}H_{35}NO$: C, 80.19; H, 10.71. Found: C, 80.01, 80.14; H, 10.60, 10.72.

Conversion of Lactam (**31**) *to N-Acetate* (**30**). To a suspension of 125 mg. of lithium aluminum hydride in 15 ml. of dry tetrahydrofuran was added dropwise a solution of 53.7 mg. of lactam (**31**) in 15 ml. of tetrahydrofuran. After stirring and refluxing for 48 hr., moist ether was added to decompose the complex and the excess hydride. After the usual work-up, a colorless gum was obtained which was dissolved in ether and extracted three times with 2-ml. portions of 2% sulfuric acid. On basification of the acidic extract with 2 *N* sodium hydroxide, a colorless, oily substance separated. This was extracted with ether and the ether layer was washed and dried. Evaporation of the solvent, followed by acetylation of the residue (28 mg.) with acetic anhydride (0.1 ml.) and dry pyridine (5 drops) at 50° for 4 hr. and then at room temperature overnight, afforded a semicrystalline residue (20 mg.) which on repeated crystallization gave the N-acetate (8 mg.), m.p. 144–145.5°, identical with the N-acetate (**30**) described above.

Neutral Fraction (*N*). The 5.1 g. of neutral material was chromatographed in benzene over 75 g. of Woelm neutral alumina. The first 300 ml. of eluent consisted of 3.46 g. of dark brown oil. Ether and benzene–methanol (20:1) elution gave 1.15 g. of crystalline lactam material. These fractions were processed separately.

1-Methyl-6-isopropylphenanthrene (**26**) *and an Unknown* $C_{18}H_{18}$ *Phenanthrene.* A 1.8-g. sample of neutral dark brown oil from the early fractions of the above chromatogram was chromatographed in benzene over 57 g. of alumina. The first two fractions of 110 ml. of benzene eluted 1.07 g. of oil and the next five fractions of 460 ml. eluted 0.48 g. of oil. The 1.07-g. fraction was converted to a picrate and recrystallized three times from methanol to give material melting at 153–157°. A benzene solution of the picrate was passed over a short column of alumina to liberate the hydrocarbon, 109 mg. This was crystallized from petroleum ether at 5° to give crystals of m.p. 50–67°. Three more crystallizations gave material of constant melting point, 67.5–70.5°.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.18; H, 7.66.

The 0.48-g. sample of oily hydrocarbon mixture was converted to a picrate and crystallized five times from methanol to give crystals, m.p. 156–159°. The hydrocarbon which was liberated by passing over a short column of alumina consisted of oily crystals, m.p. 50–62°. This sample was recrystallized twice from cold petroleum ether to give material of constant melting point, 67.5–70.5°. This fraction was combined with the previously obtained one of the same melting point and sublimed *in vacuo* to give three fractions: (a) 9.7 mg., m.p. 68.5–70.5°; (b) 14.7 mg., m.p. 68.5–70.5°; and (c) 2.9 mg., 64.5–68.5°. Samples a and b were combined and crystallized from cold petroleum ether to give the pure alkylphenanthrene, m.p. 69–71°, ν_{max}^{KBr} 881, 804, and 750 cm.$^{-1}$ (strong).

Anal. Calcd. for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.35; H, 7.69.

Table II

Solvent	Fraction	Ml.	Wt., mg.	Picrate m.p., °C.
Petroleum ether	1, 2	20	102.7	No picrate
	3	10	62.6	132–140
	4	10	32.9	140–144
	5	10	20.2	135–140
	6	25	27.2	130.5–135
	7	25	14.9	130–143
	8	50	13.6	154–157.5
Petroleum ether–benzene (3:1)	9, 10	50	52.5	146–151

The mother liquors from all the above picrate fractions were combined and reconverted to hydrocarbon to give 365 mg. This was chromatographed in petroleum ether over 10 g. of alumina (see Table II). Fractions 3 and 4 were combined, converted to a picrate, and crystallized twice to give material melting at 140–147°. This was converted to the hydrocarbon and crystallized in petroleum ether at −60° to give crystals, m.p. 38–46°. Conversion back to the picrate and fractional crystallization from methanol gave 29 mg. of orange needles, m.p. 143.5–145°, undepressed on admixture with an authentic sample of the picrate prepared from Professor Slater's 1-methyl-6-isopropylphenanthrene.[45]

The liberated hydrocarbon (13 mg.) was crystallized three times from methanol, to give leaflets, m.p. 47–50°, undepressed on admixture with an authentic sample of 1-methyl-6-isopropylphenanthrene (**26**) of m.p. 46.5–48°. The infrared spectrum in KBr was identical with that of Slater's 1-methyl-6-isopropylphenanthrene[45]: ν_{max}^{KBr} 839, 800, and 759 cm.$^{-1}$ (strong).

The trinitrobenzene (TNB) derivative melted at 155–156°, undepressed by an authentic sample prepared from Slater's hydrocarbon (*vide infra*).

1-Methyl-6-isopropylphenanthrene Picrate. A solution of 8 mg. of Slater's 1-methyl-6-isopropylphenanthrene[45] in 1.0 ml. of methanol was treated with 0.1 ml. of a saturated solution of picric acid in methanol. The yellow-orange needles which separated (9 mg.) melted at 142.5–144° (lit.[45] 143°).

1-Methyl-6-isopropylphenanthrene–TNB Adduct. A solution of 10 mg. of Slater's hydrocarbon[45] in 2 ml. of hot methanol was treated with 12 mg. of TNB in 1 ml. of methanol. The lemon yellow needles which separated, m.p. 152–155.5°, were recrystallized from methanol to give 15 mg., m.p. 155–157°.

Lactam (**31**) *from Neutral Fraction of Dehydrogenation Mixture.* The 1.15-g. crystalline fraction previously obtained by chromatography of the neutral fraction was dissolved in methanol, treated with Norit, and the solution was filtered and concentrated. A lactam, m.p. 233–237°, separated as fuzzy needles. Recrystallization from methanol–acetone gave 516 mg. of lactam **31**, m.p. 235.5–236.5°. An analytical sample melted at 235–236°; $[\alpha]^{30}D$ −47.4° (*c* 1.23); ν_{max} 3215 (NH), 1650, and 1631 cm.$^{-1}$ (—NH—CO); p.m.r. τ 8.88 (3H singlet, CCH_3), 8.98 (3H doublet, J = 7 c.p.s., $CHCH_3$), and 3.70 (1H broad, N*H*CO—).

Anal. Calcd. for $C_{20}H_{31}NO$: C, 79.67; H, 10.37; N, 4.65. Found: C, 79.74, 79.94; H, 10.37, 10.38; N, 4.80, 4.44.

Atisinium Chloride Diacetate (**38**). (*A*). A suspension of 50.0 g. of atisinium chloride (**33**, X = Cl) in 200 ml. of acetic anhydride and 30 ml. of acetic acid was boiled under reflux for 15 min. after all the crystals had dissolved (10 min.). The mixture was cooled, evaporated *in vacuo* to a small volume, and then repeatedly flashed *in vacuo* at 50° with methanol–benzene until free of acetic acid. The sirup was dissolved in 125 ml. of methanol and then diluted slowly with 1 l. of ether. The diacetate salt (**38**) separated as fine needles, 63.9 g., m.p. 234–238°. Reprocessing the mother liquors afforded an additional 1.2 g. of material of the same melting point.

Recrystallization of the crude diacetate chloride from methanol–acetone or methanol–ethyl acetate gave material of m.p. 242.5–245° which retained solvent even at 100°: $[\alpha]^{25}D$ −17° (*c* 1.27, EtOH); ν_{max}^{KBr} 1739 and 1235 (OAc), 1667 (>C=N$^+$<), 3040, 1658 sh, 902 (>C=CH$_2$), and 1372 cm.$^{-1}$ (CCH_3); ν_{max}^{Nujol} 1733, 1678, 1645, and 1250 cm.$^{-1}$ The spectrum in chloroform showed the absence of absorption in the hydroxyl region.

Anal. Calcd. for $C_{26}H_{37}NO_4 \cdot HCl \cdot H_2O$: C, 64.78; H, 8.36; OAc, 17.86. Found: C, 64.61, 64.97, 64.75; H, 8.35, 8.48, 8.22; Ac,[79] 18.45, 19.0.

After drying for several hours at 135° *in vacuo*, the sample was free of solvent.

Anal. Calcd. for $C_{26}H_{37}NO_4 \cdot HCl$: C, 67.29; H, 8.25; Ac, 18.55. Found: C, 67.34, 67.02; H, 8.20, 8.25; Ac,[79] 18.4, 17.8.

Recrystallization of a sample of the anhydrous diacetate chloride from methanol–ether again gave material retaining solvent: C, 63.02; H, 7.99.

B. A solution of 180 mg. of atisine in 4 ml. of acetic anhydride and 2 ml. of pyridine was allowed to stand at room temperature for 64 hr. The solution was diluted with water, evaporated to dryness *in vacuo*, and the residue was taken up in chloroform and shaken with 10% hydrochloric acid. Evaporation of the chloroform afforded the crystalline diacetate chloride. Crystallization from ethanol gave needles, m.p. 242–245°.

Anal. Found (dried at 100°): C, 64.61; H, 8.35. Found (dried at 130°): C, 66.97; H, 8.19.

Conversion of Atisinium Chloride Diacetate (**38**) *to Atisine Monoacetate* (**39**). Saturated sodium bicarbonate failed to liberate the free base from the salt. A solution of 265 mg. of the diacetate chloride in 25 ml. of ice–water was treated with a slight excess of ice-cold 0.15 *N* sodium hydroxide solution. As the solution slowly became turbid, it was quickly extracted with cold ether. Evaporation *in vacuo* gave 182 mg. of the monoacetate (**39**) as a white resin. The infrared spectrum (film from ether) showed no hydroxyl absorption; ν_{max} 3026, 1650, and 895 (>C=CH$_2$); 1738 and 1235 (OAc); and 1370 cm.$^{-1}$ (CCH_3).

Anal. Calcd. for $C_{24}H_{35}NO_3$: C, 74.76; H, 9.15; Ac, 11.16. Found: C, 74.71; H, 9.22; Ac, 11.35.

Chromatography of a 105-mg. sample of the resin in benzene over Woelm neutral alumina gave 75 mg. of unchanged monoacetate.

Anal. Found: C, 74.85; H, 8.94; Ac, 12.5.

(79) Acetyl determinations were conducted in the usual way by hydrolysis in 25% *p*-toluenesulfonic acid except that silver sulfate was added to retain HCl liberated from the chloride salt.

Atisinium Chloride Monoacetate (**40**). Treatment of atisine monoacetate (**39**) in ether with dry hydrogen chloride gave atisinium chloride monoacetate (**40**), which crystallized from aqueous acetone with solvent, m.p. 238–241°. The infrared spectrum (KBr) indicated the compound exists as a ternary iminium salt; ν_{max} 1736 and 1248 (OAc), 1673 (>C=N⁺<), 1656 sh and 904 (>C=CH₂), and 1374 cm.⁻¹ (CCH₃).

Anal. Calcd. for $C_{24}H_{35}NO_3 \cdot HCl \cdot 0.5H_2O$: C, 66.87; H, 8.65; Ac, 9.99. Found: C, 66.50, 67.12, 66.75; H, 8.77, 8.75, 8.82; Ac, 10.12.

Methanolysis of Atisine Monoacetate (**39**). The solution remaining from the pK_a' determination on 161 mg. of the monoacetate in 50% methanol was treated with excess hydrochloric acid and evaporated to dryness *in vacuo*. Crystallization from acetone and methanol–ether gave atisinium chloride (**33**, X = Cl), m.p. 310–312° dec., with an infrared spectrum in KBr identical with that of an authentic specimen.

Conversion of Atisinium Chloride Monoacetate (**40**) *to Atisinium Chloride Diacetate* (**38**). A suspension of 30 mg. of the monoacetate hydrochloride in 3 ml. of acetic anhydride was boiled under reflux for 5 min. The faintly yellow solution was evaporated to dryness *in vacuo* and flashed several times with methanol–benzene to remove acetic acid. The residue was crystallized from methanol–ether, m.p. 240.5–242°, undepressed by an authentic sample of atisinium chloride diacetate. The infrared spectrum in Nujol was identical with that of an authentic specimen.

Formation of Azomethine Acetate (**41**) *by Acetylation of Atisine* (**1**). A sample of atisine prepared from 1.0 g. of atisinium chloride was acetylated in acetic anhydride and pyridine in the usual manner. After dilution with water and evaporation *in vacuo*, the sirup was dissolved in chloroform and washed with sodium carbonate solution, sodium hydroxide, and water. Evaporation of the chloroform gave a resin which slowly crystallized from acetone to give 96 mg. of crystals, m.p. 122–132°. Chromatography over Woelm neutral alumina and crystallization from petroleum ether gave needles of m.p. 144–148°. This material was identical with that prepared by the Edwards' procedure.[15]

Anal. Calcd. for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15. Found: C, 77.54, 77.56; H, 9.20, 9.18.

Zinc Dust–Acetic Anhydride Reduction of Atisine Imino Alcohol (**42**) *to O,N-Diacetate* (**43**) *and* **44a**. The imino alcohol (**42**, 500 mg.) in freshly distilled acetic anhydride (5 ml.) was allowed to boil for a couple of minutes in an oil bath maintained at 160°. Zinc dust (3 g.) was added in three portions. The reaction mixture was heated under reflux for 15 min., cooled, diluted with dry ether (50 ml.), filtered, and the residual zinc was washed several times with ether. The combined filtrate and washings were evaporated and the gummy residue was flashed several times with benzene *in vacuo* to remove all traces of acetic anhydride. After treatment with water (20 ml.), the residue was dissolved in ether, washed twice with 2% sulfuric acid, and then with water. After drying and evaporation of the solvent, the crude material (407 mg.) was crystallized from ether to give a mixture of compounds melting over a range 140–180°. Chromatography over alumina and triangular crystallization of the mixture from ether gave two sharp-melting crystalline compounds; one (107 mg.) was identical with N-acetyldes(N-β-hydroxyethyl)atisine acetate (**43a**), m.p. 169.5–170.5°, and the other (**44a**, 49 mg.), after repeated crystallization from ether containing 1% methanol, melted at 230.5–231° (rosettes of needles); ν_{max}^{Nujol} 1742 (OAc), 1642 and 1629 (amide), and 3067 and 889 cm.⁻¹ (>C=CH₂).

Anal. Calcd. for $C_{48}H_{68}N_2O_6$: C, 74.96; H, 8.91; mol. wt., 768. Found: C, 74.63; H, 9.04; mol. wt. (Rast), 699, 806.

In a subsequent experiment, the crude material (620 mg.) obtained from 500 mg. of imino alcohol (**42**) was treated with potassium hydroxide (2.5 g.) dissolved in a mixture of water (6 ml.) and methanol (30 ml.). After refluxing for 15 min., methanol was removed *in vacuo* and the residue was treated with water. The white solid (400 mg.) that separated was filtered and dried. Triangular crystallization from acetone containing 5% methanol gave 260 mg. of N-acetyldes-(N-β-hydroxyethyl)atisine (**43b**), m.p. and m.m.p. 228–231°, and 80 mg. of the bimolecular alcohol (**44b**), m.p. 289–291°, identical with the compound described below.

Saponification of the Bimolecular Acetate (**44a**). The title compound (10 mg.) dissolved in methanol (0.5 ml.) was treated with a solution of 50 mg. of potassium hydroxide in 0.5 ml. of water and 2 ml. of methanol. After boiling for 15 min., methanol was removed *in vacuo*, and the crystalline solid that separated was collected, washed with water, and dried under vacuum. Crystallization from acetone containing 1% chloroform gave colorless needles of **44b** (4 mg.), m.p. 289–290°. The infrared spectrum (Nujol) had bands at 3484 and 3378 (—OH) and 1603 cm.⁻¹ (amide carbonyl).

Anal. Calcd. for $C_{44}H_{64}N_2O_4$: C, 77.15; H, 9.42. Found: C, 77.42; H, 9.20.

On acetylation of **44b** with acetic anhydride–pyridine, the acetate **44a** was regenerated.

Oxidation of Bimolecular Alcohol (**44b**) *to Conjugated Enone* (**50**). A solution of the title compound (32 mg.) in dry pyridine (1 ml.) was slowly added to the complex prepared below 15° from chromium trioxide (25 mg.) in pyridine (0.5 ml.). The reaction mixture was shaken and left at room temperature for 4 hr., and then in the refrigerator overnight. After the usual work-up, a white solid (12 mg.), melting over the range 190–210°, was obtained. On crystallization from methanol, it melted at 210–213° and 250–255°; ν_{max}^{Nujol} 1701 and 1639 (conjugated enone), and 1634 cm.⁻¹ (amide); λ sh 228 mμ (ε 16,430).

Anal. Calcd. for $C_{44}H_{60}N_2O_4$: C, 77.60; H, 8.88. Found: C, 77.09; H, 9.31.

Conversion of Imino Alcohol (**42**) *to Aziridine* (**48**). The imino alcohol (**42**) (100 mg.) dissolved in acetic anhydride (5 ml.) containing acetic acid (2 ml.) was refluxed for 30 hr. in an oil bath maintained at 160°. After this period, acetic anhydride and acetic acid were evaporated *in vacuo*, and the gum was suspended in 10 ml. of water and allowed to stand at room temperature for 3 hr. The partly solidified material was extracted with benzene and the benzene layer was washed twice with 2% sulfuric acid, then with aqueous sodium bicarbonate, and finally with water. Evaporation of

the solvent afforded a nicely crystalline solid (78 mg.), m.p. 190–191°. An analytical sample was prepared by crystallization from acetone: m.p. 191–192.5°; ν_{max}^{Nujol} 1730 (acetate carbonyl), 1639 and 1642 (amide carbonyl), and 907 cm.$^{-1}$ (>C=CH$_2$); τ 9.13 (singlet, tertiary C-methyl).

Anal. Calcd. for $C_{24}H_{33}NO_3$: C, 75.16; H, 8.67. Found: C, 74.94; H, 8.58.

The foregoing compound was recovered unchanged on treatment with zinc dust and boiling acetic anhydride.

Conversion of Atisine Azomethine Acetate (**46**) *to Aziridine* (**48**). A solution of 332 mg. of the title compound in acetic anhydride (4 ml.) and acetic acid (1 ml.) was refluxed for 55 hr. At the end of this period, acetic anhydride and acetic acid were removed *in vacuo* and the gummy residue was warmed to 40° in water (5 ml.). After decomposing the last traces of acetic anhydride, the solid that separated was extracted with ether, washed with 2% sulfuric acid, then with aqueous sodium bicarbonate, and finally with water. After drying over anhydrous sodium sulfate, ether was evaporated to leave a solid (300 mg.). On crystallization from acetone, the aziridine acetate (**48**) was obtained as needles, m.p. 192–193.5°, identical in melting point and mixture melting point with the acetate described earlier. The infrared spectra of the two samples were also identical.

Mild Hydrolysis of the Aziridine Acetate (**48**). The title compound (15 mg.) dissolved in methanol (2 ml.) was refluxed with 50 mg. of potassium hydroxide in water (0.5 ml.). After allowing to stand for 10 min., methanol was removed *in vacuo*, and the white solid that separated was dissolved in benzene and washed with 2% sulfuric acid and then with water. Evaporation of the solvent *in vacuo* furnished a nicely crystalline compound (**49**, 8 mg.), which on crystallization from acetone melted at 191–192°; ν_{max}^{Nujol} 3448 (—OH), 1637 and 1642 (amide carbonyl), and 897 cm.$^{-1}$ (>C=CH$_2$).

Anal. Calcd. for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15. Found: C, 77.55; H, 9.17.

On acetylation with acetic anhydride–pyridine, the acetate (**48**) was regenerated.

α- and β-Tetrahydroatisines (**51** *and* **52**). A solution of 12.1 g. of atisinium chloride (**33**, X = Cl) in 175 ml. of methanol was hydrogenated in the presence of 317 mg. of Adams catalyst. After 2.5 hr., another 200 mg. of catalyst was added and the hydrogenation was continued until no more uptake of hydrogen was observed. The solution was filtered, evaporated under reduced pressure, and the residue dissolved in water and basified with dilute sodium hydroxide solution. Extraction with chloroform gave 10.7 g. of the mixed tetrahydroatisines. Crystallization from methanol gave 4.4 g. of the crude α-tetrahydro isomer, m.p. 169–173°. Recrystallization from methanol gave relatively pure *α-tetrahydroatisine* (**51**): 2.90 g., m.p. 176–177.5°, $[\alpha]^{28}D$ −22.8° (*c* 1.86). Two more recrystallizations from methanol gave the analytical sample, m.p. 178–178.5°, $[\alpha]^{26}D$ −21.4° (*c* 1.42). The infrared spectrum (Nujol) indicated the absence of an exocyclic methylene group: ν_{max} 3333–3226 cm.$^{-1}$ (OH). A high-resolution spectrum (Beckman IR-7, 1 mg./1 ml. in CCl_4, 1-cm. cell) showed ν_{max} 3639 (nonbonded secondary OH) and 3515 cm.$^{-1}$ (primary OH bonded to N).[67]

Anal. Calcd. for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73; N, 4.03. Found: C, 75.96, 76.30; H, 10.70, 10.80; N, 4.09.

Concentration of the first mother liquors afforded prisms rich in the β-isomer. Fractional crystallization by the triangle scheme afforded prisms melting constant at 171–173°, $[\alpha]^{23}D$ −60° (*c* 1.32). However, in later work, this substance showed the presence of three components by thin layer chromatography (benzene–methanol, 75:1), and the infrared spectrum indicated weak carbonyl absorption at 1701 cm.$^{-1}$.

A 3.7-g. sample of material from the mother liquors was chromatographed in benzene over 400 g. of Woelm neutral alumina (activity grade 3) and the column was monitored by t.l.c. (benzene–methanol, 75:1). The first four fractions totaling 1.90 g. consisted of a mixture of three compounds. The next four fractions containing 1.48 g. consisted mainly of one component. These fractions were combined and recrystallized three times from methanol to give 597 mg. of pure *β-tetrahydroatisine* (**52**), m.p. 185.5–186.0°, $[\alpha]^{18}D$ −71.9 (*c* 0.9). The infrared spectrum in Nujol showed no absorption in the carbonyl region; ν_{max} 3472 cm.$^{-1}$ (OH). A high-resolution spectrum in CCl_4 showed ν_{max} 3628 (nonbonded secondary OH) and 3515 cm.$^{-1}$ (primary OH bonded to N).[67]

Anal. Calcd. for $C_{22}H_{37}NO_3$: C, 76.03; H, 10.73; N, 4.03. Found: C, 75.96; H, 10.59; N, 4.17.

Material from the mother liquors of the 597-mg. sample was chromatographed to eliminate contaminants and crystallized from methanol to give an additional 556 mg. of β-tetrahydroatisine, m.p. 186–186.5°, $[\alpha]^{21}D$ −70° (*c* 0.6).

Anal. Found: C, 76.05, 75.95; H, 10.69, 10.74.

α-Tetrahydroatisine Hydrochloride. α-Tetrahydroatisine (51 mg.) in 10 ml. of dry acetone was treated with a slight excess of concentrated hydrochloric acid. Evaporation gave a crystalline product which was recrystallized from methanol–acetone to give feathery needles, 49 mg., m.p. 268–279° dec.

Anal. Calcd. for $C_{22}H_{37}NO_2 \cdot HCl$: C, 68.81; H, 9.97. Found: C, 68.87; H, 9.79.

α-Tetrahydroatisine Monobenzoate. A. A solution of 689 mg. of α-tetrahydroatisine, m.p. 176–177.5°, in 8 ml. of pyridine was treated with 0.23 ml. of freshly distilled benzoyl chloride and allowed to stand overnight. In the morning the crystals which had separated from solution were collected (731 mg.). Recrystallization from methanol gave 627 mg. of the *benzoate hydrochloride*, m.p. 226–230°.

Anal. Calcd. for $C_{29}H_{41}NO_3 \cdot HCl$: C, 71.23; H, 8.66. Found: C, 71.36; H, 8.74.

A suspension of 86 mg. of the sparingly soluble benzoate hydrochloride in warm water was treated with dilute ammonium hydroxide and extracted repeatedly with benzene. Evaporation of the washed benzene extract gave 70 mg. of resin which crystallized from methanol as needles of the benzoate, m.p. 111.5–113°.

Anal. Calcd. for $C_{29}H_{41}NO_3$: C, 77.12; H, 9.15. Found: C, 77.19; H, 9.12.

B. The preparation of the monobenzoate is more easily accomplished using benzoic anhydride. A solution of 169 mg. of α-tetrahydroatisine, m.p. 176–177.5°, in 2.0 ml. of pyridine was treated with 130 mg.

of benzoic anhydride (1 equiv. = 113 mg.) and allowed to stand 24 hr. The mixture was evaporated to dryness *in vacuo* and the residue was taken up in 75 ml. of hexane–benzene (5:1) and extracted ten times with 5% sulfuric acid. The sulfate salt precipitated out on the walls of the funnel but gradually dissolved in the acid phase.[80] The sulfuric acid phase was neutralized with dilute sodium carbonate solution at ice bath temperature and the mixture was extracted with chloroform to give 198 mg. of resin. The resin crystallized from methanol to give 187 mg. of needles, m.p. 109.5–112°. Two crystallizations from methanol gave 114 mg. of the pure benzoate: m.p. 111–112.5°; $[\alpha]^{32}D$ −27.6° (*c* 1.2); ν_{max}^{Nujol} 3509 (OH), and 1718, 1277, and 1122 cm.$^{-1}$ ($OCOC_6H_5$).

Anal. Calcd. for $C_{29}H_{41}NO_3$: C, 77.12; H, 9.15; N, 3.10. Found: C, 77.06, 77.14; H, 9.26, 9.21; N, 3.25.

Saponification of α-Tetrahydroatisine Benzoate. A solution of 45 ml. of the benzoate in 10 ml. of methanol was treated with two pellets of potassium hydroxide and boiled under reflux for 5 min. Evaporation *in vacuo* gave a residue which was taken up in water and extracted with benzene. Evaporation gave 33 mg. of needles which were recrystallized twice from methanol to give 21.8 mg. of α-tetrahydroatisine, m.p. 176–177.5°. The infrared spectrum in Nujol was identical with an authentic sample.

β-Tetrahydroatisine Hydrochloride. β-Tetrahydroatisine (130 mg.) in 25 ml. of acetone was treated with an excess of dry HCl and concentrated *in vacuo*. The hydrochloride crystallized as needles, 135 mg., m.p. 277.5–290.5° dec. Recrystallization from methanol–acetone gave fine needles, 124 mg., m.p. 283.5–295.5° dec.; ν_{max}^{Nujol} 3356 and 3155 cm.$^{-1}$ (OH).

Anal. Calcd. for $C_{22}H_{37}NO_2 \cdot HCl$: C, 68.81; H, 9.97. Found: C, 68.80, 69.04; H, 9.96, 9.93.

Reduction of Ketone A (**24a**) *to α-Tetrahydroatisine* (**51**) *and α-Tetrahydro-15-epiatisine* (**54**). A solution of 480 mg. of ketone A, m.p. 146–153°, $[\alpha]D$ −6.8°, in 50 ml. of methanol was treated with 800 mg. of sodium borohydride and allowed to stand over the weekend. Work-up in the usual manner gave material which crystallized from benzene as needles, m.p. 166–171.5°. Careful fractional crystallization from methanol or acetone by the triangle scheme afforded fractions of α-tetrahydroatisine (**51**) totaling 332 mg., m.p. 177.5–179°. The infrared spectrum in Nujol was identical with that of an authentic sample of α-tetrahydroatisine. The more soluble fractions from the mother liquors showed the presence of at least three components by thin layer chromatography. These were combined (103 mg.) and chromatographed over 5.0 g. of Woelm neutral alumina (activity grade 3), the column being monitored by thin layer chromatography. The first two fractions to emerge contained four components, A, B, C, and D, of which B was identical with α-tetrahydroatisine. Fractions 3–7, amounting to 18 mg., contained one component, D. Rechromatography of fractions 1 and 2 gave an additional 35 mg. of D. Two crystallizations of 53 mg. of D from acetone gave 29 mg. of *α-tetrahydro-15-epiatisine* (**54**), m.p. 165.5–166.5°. The infrared spectrum in Nujol showed hydroxyl absorption at 3344 cm.$^{-1}$, but no carbonyl absorption.

Anal. Calcd. for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73. Found: C, 75.94; H, 10.60.

Reduction of Ketone B (**24b**) *to Give β-Tetrahydro-15-epiatisine* (**55**). A solution of 247 mg. of ketone B, m.p. 129–131°, in 5 ml. of 90% methanol was treated with 500 mg. of sodium borohydride and let stand 18 hr. Evaporation and work-up gave 196 mg. which crystallized from acetone as heavy prisms which were strongly birefringent, m.p. 141–144°. Repeated crystallization raised the melting point to 146–148°.

Anal. Calcd. for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73. Found: C, 76.04; H, 10.59.

T.l.c. of the mother liquors showed the presence of material which had the same mobility in the systems benzene–methanol (75:1) and benzene–pyridine–methyl ethyl ketone (20:1:3) as β-tetrahydroatisine.

The Oxidation of N-Acetyldes(N-β-hydroxyethyl)-dihydroatisine (**64a**). *A. With Chromium Trioxide–Pyridine Complex.* A solution of 4.12 g. of the title compound in 60 ml. of dry pyridine was added at 10° to a suspension of the complex prepared from 6.0 g. of chromium trioxide in 60 ml. of pyridine. After standing at room temperature for 5 hr. and overnight in the refrigerator, the mixture was treated with 50 ml. of methanol and allowed to stand for 1 hr. After evaporation *in vacuo*, the resulting residue was extracted five times with 200-ml. portions of hot acetone. When concentrated to dryness the extracts yielded 3.43 g. of a brown resin which was dissolved in benzene and was extracted twice with dilute sodium carbonate solution. The faintly colored benzene solution on evaporation gave 3.33 g. of a resin. Crystallization from acetone gave 2.83 g. of heavy prisms of the enone (**65**), m.p. 143–153°. Concentration of the mother liquor gave an additional 125 mg. of product melting at 139–146°. Recrystallization of the 2.83 g. from acetone afforded 2.14 g. of prisms, m.p. 145–156°.

Repeated crystallization of the product from acetone, ether, methanol, or ethyl acetate gave material with a melting point very dependent on the rate of heating. Occasionally samples melted at 143–150°, partially solidified, and then remelted at 160–164°. This double melting point effect was noticed most often with samples which had been recrystallized from ether. Chromatography of a sample in benzene over Woelm neutral alumina gave material which crystallized from ether: m.p. 153–156°, then 162–164°; $[\alpha]^{25}D$ +5.8° (*c* 1.9); ν_{max}^{Nujol} 1701 (conjugated >C=O) and 1631 cm.$^{-1}$ (NAc); λ sh 228 mμ (ε 9150).

Anal. Calcd. for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15. Found: C, 77.21; H, 9.24.

B. With Manganese Dioxide. A solution of 280 mg. of the title compound in 30 ml. of chloroform was stirred with 2.5 g. of active manganese dioxide[81] for 18 hr. Since work-up showed only half of the material had been oxidized, the mixture was treated with another 2.5 g. of manganese dioxide and boiled under reflux for 2.5 hr. Evaporation of the filtrate gave 240 mg. which crystallized from ether, m.p. 138–

(80) The monobenzoate salts are rather insoluble in aqueous solution but quite soluble in benzene. The hexane was added to benzene to decrease the solubility in the organic phase and thereby promote extraction into the sulfuric acid phase.

(81) O. Mancera, G. Rosenkranz, and F. Sondhejmer, *J. Chem. Soc.*, 2189 (1953).

143°. Chromatography in benzene gave prisms, 147 mg., m.p. 145–148°, with an infrared spectrum in Nujol identical with that of a sample prepared by oxidation with chromium trioxide–pyridine.

Reduction of N-Acetyl Enone (**65**) *with Sodium Borohydride.* A solution of 2.0 g. of the title compound in 150 ml. of methanol was treated with 3.0 g. of sodium borohydride and allowed to stand for 5 hr. After evaporation, the residue was taken up in water and extracted with benzene. Removal of the benzene gave 1.92 g. of resin which was separated into the epimeric alcohols by chromatography in benzene over 50 g. of Merck alumina (activity 3). Fractions 1 and 2 (200 ml.) gave 165 mg. of material, m.p. 169–189.5°; fractions 3–6 gave 736 mg. of m.p. 194.5–224.5°; and fractions 7–12 gave 1.00 g. of m.p. 168–181°.

Rechromatography of material in fraction 3–6 gave 559 mg., m.p. 211–226°. Repeated crystallization from acetone gave pure *N-acetyldes(N-β-hydroxyethyl)dihydroatisine* (**64a**): 295 mg., m.p. 228–230.5°, $[\alpha]^{29}D$ −20.1 (*c* 1.79). The infrared spectrum in Nujol was identical with that of an authentic sample of N-acetyldes(N-β-hydroxyethyl)dihydroatisine.[32,34]

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 76.95, 77.16, 76.87; H, 9.61, 9.57, 9.52.

Repeated crystallization of material from fractions 7–12 from acetone gave 608 mg. of *N-acetyldes-(N-β-hydroxyethyl)dihydro-15-epiatisine* (**66a**),[8] m.p. 172–175°, $[\alpha]^{27}D$ −34.5 (*c* 1.56). Crystallization from ether gave material melting at 176–177°, $[\alpha]^{27}D$ −34.7 (*c* 1.89).

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 76.78, 76.87, 77.05; H, 9.68, 9.75, 9.87.

Acetylation of N-Acetyldes(N-β-hydroxyethyl)dihydro-15-epiatisine (**66a**) *to Give* **66b**. A solution of 51 mg. of **66a** in 1.5 ml. of acetic anhydride and 1.0 ml. of dry pyridine was allowed to stand overnight. Work-up in the usual manner gave 48 mg. of amorphous O,N-diacetate (**66b**) which did not crystallize from the usual solvents.

Anal. Calcd. for $C_{24}H_{35}NO_3$: C, 74.76; H, 9.15; Ac, 11.16. Found: C, 74.58; H, 9.24; Ac, 11.23.

Oxidation of N-Acetyldes(N-β-hydroxyethyl)dihydro-15-epiatisine (**66a**) *to Enone* **65**. A solution of 25 mg. of the title compound in 0.3 ml. of dry pyridine was added to the complex prepared at 10° from 25 mg. of chromium trioxide in 0.3 ml. of pyridine. The mixture stood at room temperature for 3 hr. and overnight in the refrigerator. Evaporation *in vacuo* gave a residue which was extracted several times with hot acetone. The acetone extract was concentrated to dryness, the residue was dissolved in benzene, and the solution washed twice with dilute sodium carbonate solution. Removal of the benzene *in vacuo* gave 25 mg. of a yellow resin which was chromatographed in benzene over 500 mg. of Woelm neutral alumina (activity 3). The first 20 ml. of eluate gave 15.9 mg. of colorless resin which crystallized from ether to give 13 mg. of prisms, m.p. 141–144°. Two more recrystallizations from ether gave 9.7 mg., m.p. 142–145°, with an infrared spectrum in Nujol identical with that of an authentic sample of the N-acetyl enone (**65**).

N-Ethyldes(β-hydroxyethyl)dihydroatisine (**67a**). *A. By Reduction of N-Acetyldes(β-hydroxyethyl)dihydroatisine Acetate* (**64b**). A solution of 11.83 g. of **64b** in 300 ml. of ether was added dropwise to a well-stirred suspension of 8.0 g. of lithium aluminum hydride in 800 ml. of ether. After refluxing for 4 hr. the mixture stood overnight. The excess hydride was decomposed with a mixture of 35 ml. of ethyl acetate and 50 ml. of ether and then 50 ml. of water was added dropwise to decompose the complex. The mixture was filtered and the granular precipitate was washed well with ether. The filtrate was dried over sodium sulfate, evaporated under reduced pressure, and the residue was converted to the hydrochloride in cold acetone with a slight excess of concentrated hydrochloric acid. The solution was evaporated to dryness *in vacuo* and flashed repeatedly with methanol–benzene to remove water and excess hydrochloric acid. The residue was dissolved in a minimum of hot methanol and diluted with 10 volumes of acetone. After standing overnight, 7.5 g. of the hydrochloride was collected: m.p. 246–250°, $[\alpha]^{26}D$ −27.0° (*c* 1.7), −26.2° (*c* 1.9, EtOH). Concentration of the mother liquors afforded an additional 1.17 g., m.p. 242–246°. The infrared spectrum of the 246–250° material in Nujol was identical in every respect with the hydrochloride prepared by the ethylation procedure described below; ν_{max} 3300 (OH), and 1650 and 904 cm.$^{-1}$ (>C=CH$_2$).

Anal. Calcd. for $C_{22}H_{35}NO\cdot HCl$: C, 72.20; H, 9.92. Found: C, 71.73, 71.68; H, 9.87, 9.97.

B. By Ethylation of Des(N-β-hydroxyethyl)dihydroatisine (**68**). A solution of 100 mg. of the secondary base (**68**) in 15 ml. of dry methanol was treated with 300 mg. of anhydrous sodium carbonate and 5 ml. of ethyl iodide and boiled under reflux for 22 hr. The mixture was evaporated to dryness *in vacuo*, taken up in dilute sodium thiosulfate solution, and extracted with chloroform. Evaporation of the chloroform solution gave 96 mg. of a resin which was treated with concentrated hydrochloric acid in acetone. The hydrochloride separated as needles, 85 mg., m.p. 244–249°. Crystallization from methanol–acetone gave 62 mg. of long, rectangular prisms, m.p. 246–249°. This material was identical with material prepared by procedure A.

Anal. Calcd. for $C_{22}H_{35}NO\cdot HCl$: C, 72.20; H, 9.92. Found: C, 72.22; H, 9.96.

N-Ethyldes(N-β-hydroxyethyl)dihydroatisine (**67a**). A solution of 1.0 g. of the hydrochloride in 50 ml. of water was treated with dilute sodium carbonate solution and the mixture was extracted with chloroform. Evaporation under reduced pressure gave the base as a colorless varnish which did not crystallize from the usual solvents. The infrared spectrum of a thick film showed a small amount of ketonic contaminant (1709 cm.$^{-1}$), perhaps due to some rearrangement of the allylic alcohol to the methyl ketone during formation of the hydrochloride; ν_{max} (film from ether) 3333 (OH), and 1650 and 897 cm.$^{-1}$ (>C=CH$_2$).

Anal. Calcd. for $C_{22}H_{35}NO$: C, 80.19; H, 10.71; N, 4.25. Found: C, 77.99; H, 10.82; N, 4.29.

N-Ethyldes(N-β-hydroxyethyl)dihydroatisine Acetate (**67b**). A solution of 900 mg. of N-ethyl derivative (**67a**) in 5 ml. of acetic anhydride and 5 ml. of dry pyridine was allowed to stand 24 hr. The mixture was evaporated under reduced pressure and flashed with benzene to remove excess acetic anhydride. The residue was taken up in ice–water and treated with cold sodium

bicarbonate solution. Extraction with chloroform yielded 935 mg. of partially crystalline material. The crude product was recrystallized by solution in hot methanol, cooling to 35°, and addition of enough methanol to prevent oiling out. The acetate (**67b**) crystallized as long prismatic needles, 641 mg., m.p. 77–79°. Careful recrystallization by the same procedure gave material melting at 78.5–80°; $[\alpha]^{27}D$ −89° (*c* 1.97); ν_{max}^{Nujol} 1739 and 1235 (OAc), and 1656 and 912 cm.$^{-1}$ (>C=CH_2).

Anal. Calcd. for $C_{24}H_{37}NO_2$: C, 77.58; H, 10.04; N, 3.77; Ac, 11.58. Found: C, 77.62, 77.35; H, 10.13, 10.15; N, 3.94; Ac, 11.47, 11.45.

Saponification of N-Ethyldes(N-β-hydroxyethyl)dihydroatisine Acetate (**67b**). A solution of 100 mg. of **67b** in 25 ml. of methanol and 1 ml. of water was treated with 600 mg. of potassium hydroxide and boiled under reflux for 3 hr. The solution was diluted with water and extracted with chloroform. The extracts were washed, dried, and evaporated to dryness *in vacuo* to give 88 mg. of **67a** as a colorless resin. The infrared spectrum of a film from ether was essentially identical with that of the same compound before acetylation.

Lithium Aluminum Hydride Reduction of N-Acetyldes(N-β-hydroxylethyl)dihydro-15-epiatisine (**66a**) *to the N-Ethyl Derivative* (**69a**). To a suspension of 1.0 g. of lithium aluminum hydride in 100 ml. of refluxing ether was added dropwise a solution of 350 mg. of N-acetyl derivative (**66a**) in 125 ml. of ether. After refluxing for 6 hr., ethyl acetate was added slowly to decompose excess hydride. Then 5 ml. of water was added and the mixture was stirred for 30 min. The mixture was filtered through sintered glass and the precipitate was washed well with ether. Evaporation of the filtrate gave 350 mg. of the amorphous N-ethyl derivative (**69a**). The base was converted in acetone to the hydrochloride with dry HCl. Recrystallization twice from methanol–acetone gave 114 mg. of the N-ethyl hydrochloride: m.p. 263–269°, ν_{max}^{Nujol} 3333 cm.$^{-1}$ (OH), no $NCOCH_3$ absorption. An analytical sample melted at 268–271° and contained acetone of crystallization (ν_{max} 1718 cm.$^{-1}$).

Anal. Calcd. for $C_{22}H_{35}NO \cdot HCl \cdot C_3H_6O$: C, 70.80; H, 9.99. Found: C, 70.89, 70.80; H, 10.06, 10.08.

N-Ethyldes(N-β-hydroxyethyl)dihydro-15-epiatisine Acetate (**69b**). A solution of 583 mg. of the amorphous N-ethyl derivative (**69a**) in 4.0 ml. of acetic anhydride and 4.0 ml. of dry pyridine was allowed to stand at room temperature for 72 hr. The mixture was evaporated to dryness *in vacuo*, taken up in benzene, and washed successively with aqueous sodium bicarbonate and 3% sulfuric acid. The acidic extract was basified with cold bicarbonate solution and extracted with benzene. Evaporation of the benzene extract gave 580 mg. of a resin which was chromatographed in benzene over 15 g. of neutral Woelm alumina (activity 2). The first fraction of 25 ml. eluted 494 mg. of amorphous N-ethyl acetate derivative (**69b**), ν_{max} (film from benzene) 1739 and 1242 cm.$^{-1}$ (OAc), no hydroxyl absorption.

Anal. Calcd. for $C_{24}H_{37}NO_2$: C, 72.58; H, 10.04; N, 3.77; Ac, 11.58. Found: C, 77.72; H, 10.14; N, 3.79; Ac, 11.30.

Acetate Hydrochloride. Treatment of 190 mg. of the acetate (**69b**) in acetone with dry HCl gave fine, silky needles of the hydrochloride, 184 mg., m.p. 198.5–209°. Two recrystallizations from acetone gave 132 mg., sinters 185–195°, m.p. 204.5–214°.

Anal. Calcd. for $C_{24}H_{37}NO_2 \cdot HCl$: C, 70.65; H, 9.39. Found: C, 70.15; H, 9.48.

pK_a' Determinations. Samples of the free bases (about 35–40 mg.) in 25–50 ml. of solvent were titrated with 0.568 *N* HCl. The titrations were followed using a glass electrode and a Beckman Model G pH meter. The reference electrode was a saturated KCl–calomel electrode. The system was standardized frequently against freshly prepared buffer solutions. The half-neutralization points were determined graphically. The values given are the average of at least two determinations which agreed within 0.05 pH unit (see Table III).

Table III

Compd.	pK_a' 50% MeOH[a]	pK_a' 80% Methyl Cellosolve	pK_a' 80% EtOH[a]
67a	9.25	7.28	7.57
69a	9.13	7.05[b]	...
67b	8.30	7.01	7.25
69b	8.11	7.12[b]	...
Atisine (**1**)	12.8[b]		
Isoatisine (**4**)	10.35		
Dihydroatisine (**5**)	8.31		
α-Tetrahydroatisine (**51**)	8.14[b]		

[a] By volume. [b] Single determination.