Continued elution with the same solvent mixture gave 1.48 g. (29.8%) of crude N-(α-mesitoylthioacetyl)-morpholine (VI). Recrystallization, first from hexane and then from aqueous methanol, yielded 1.21 g., m.p. 128.8–130.4°.

Anal. Calcd. for $C_{16}H_{21}O_2NS$: C, 65.94; H, 7.26; N, 4.81; S, 11.01. Found: C, 66.06; H, 7.17; N, 4.97; S, 10.79.

The material from another experiment has a m.p. 121.0–123.6° after recrystallization from hexane. The two different melting forms are dimorphic crystals since their infrared spectra in $CHCl_3$ were identical. The compound gave an intense red color with aqueous methanolic $FeCl_3$ and was soluble in 5% aqueous sodium hydroxide and recovered upon acidification.

Acid Hydrolysis of N-(α-Mesitoylthioacetyl)-morpholine (VI).—A mixture of 185 mg. (0.64 mmole) of N-(α-mesitoylthioacetyl)-morpholine, 5 ml. of 6 *N* hydrochloric acid and 5 ml. of acetic acid was heated under reflux for 6 hr., during which time hydrogen sulfide was evolved. The reaction mixture was cooled, diluted with water and extracted with ether. The extract was washed with 5% sodium hydroxide (acidification of which yielded no material), saturated NaCl solution and dried over $MgSO_4$. The ether was removed on a steam-bath and the residue was an oil. This material was nitrated at 0° with fuming HNO_3.[18] The reaction mixture was swirled in the ice-bath for 30 seconds and then diluted with ice-water. The white precipitate was filtered and recrystallized from aqueous ethanol to yield 72 mg. (45%) of material, m.p. 136.5–138.5°. A mixed m.p. with an authentic sample of *dinitroacetylmesitylene* (m.p. 138.5–140.2°) was 137.5–138.8°. The infrared spectra of the two solid derivatives in $CHCl_3$ solution were identical.

Willgerodt Reaction with *n*-Butyrylmesitylene.—A mixture of 2.0 g. (10.5 mmoles, b.p. 145–147° (20 mm.), $n^{25}D$ 1.5049) of *n*-butyrylmesitylene,[17] 0.67 g. (21 mmoles) of sulfur and 1.80 g. (20.7 mmoles) of morpholine was heated under reflux for 7 hr. The reaction mixture was diluted with benzene, washed twice with water and then with saturated NaCl solution. The benzene was removed on the steam-bath and the residual oil dissolved in a mixture of 75–25 hexane–benzene and chromatographed on 25 g. of alumina. Elution with 50–50 hexane–benzene first yielded 1.13 g. of starting ketone and then 700 mg. of material which solidified on standing. The crude N-(β-mesitoylthiopropionyl)-morpholine was recrystallized three times from benzene–hexane, yield 285 mg. (8.8%), m.p. 99.7–100.4°.

Anal. Calcd. for $C_{17}H_{23}O_2NS$: C, 66.86; H, 7.59; N, 4.59; S, 10.50. Found: C, 66.78; H, 7.32; N, 4.87; S, 10.41.

The low recovery yield from the recrystallizations was due to the extreme difficulty in obtaining colorless rather than slightly discolored crystals.

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(18) R. C. Fuson and J. T. Walker, THIS JOURNAL, **52**, 3269 (1930).

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE]

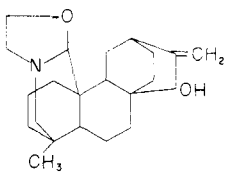
The Aconite Alkaloids. XXX.[1] Products from the Mild Permanganate Oxidation of Atisine[1,2]

BY S. WILLIAM PELLETIER AND WALTER A. JACOBS

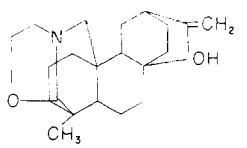
RECEIVED FEBRUARY 3, 1956

The structures assigned earlier to atisine (I) and isoatisine (II) are given additional support by further oxidation studies. Thus mild permanganate oxidation of atisine gave the γ-lactam, α-oxoatisine (VIIa), the δ-lactam, β-oxoatisine (VIIIa), and an unsaturated base (XI) in which the oxyethyl group of atisine is lacking. Catalytic reduction of β-oxatisine in 70% acetic acid gave the known dihydroöxoisoatisine (IX), thus relating oxidation products from the atisine and isoatisine series. Selective oxidation of α- and β-oxoatisine with a periodic acid–permanganate mixture afforded the corresponding dicarboxylic acids X and VI. A mixture of these acids was also isolated from the acidic fraction obtained from the mild permanganate oxidation of atisine. Vigorous permanganate oxidation of atisine in the presence of pyridine and sodium hydroxide gave a mixture from which only the δ-lactam dicarboxylic acid (VI) could be isolated. The transformations described interrelate the various degradation products of atisine and place the structures assigned to atisine and isoatisine on a firmer basis.

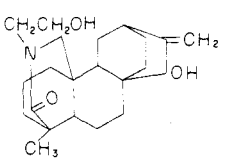
In recent communications on the Aconite Alkaloids, it has been shown that the various reactions of atisine[3] and isoatisine may be accounted for on the basis of structures I and II, respectively.[1,4,5] Mild permanganate oxidation of isoatisine in acetone and acetic acid furnishes a good yield of oxoisoatisine, $C_{22}H_{33}NO_3$,[6] III (*vide infra*), while more vigorous conditions give rise to an oxoisoatisinedicarboxylic acid[7] and an oxoisoatisine-



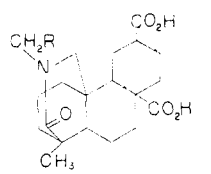
I



II



III



IV, R = CH_2OH
V, R = CO_2H

tricarboxylic acid[8] which will be shown to have structures IV and V, respectively. Although oxidation of atisine under vigorous conditions has given an analogous oxoatisinedicarboxylic acid

(1) For paper XXIX in this series, see S. W. Pelletier and W. A. Jacobs, *Chem. and Ind.*, 1385 (1955).

(2) Presented in part at the Gordon Research Conference on Steroids and Related Natural Products, New Hampton, N. H., August 21, 1955.

(3) E. S. Stern, The Aconitum and Delphinium Alkaloids in "The Alkaloids, Chemistry and Physiology," edited by R. H. F. Manske and H. L. Holmes, Vol. IV, Academic Press, Inc., New York, N. Y., 1954, p. 280.

(4) K. Wiesner, R. Armstrong, M. F. Bartlett and J. A. Edwards, *Chemistry and Industry*, 132 (1954); K. Wiesner and J. A. Edwards, *Experientia*, **11**, 255 (1955). These workers were the first to propose the presently accepted carbon skeleton for the atisine alkaloids.

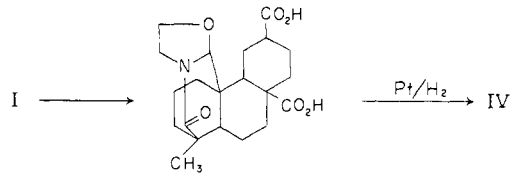
(5) S. W. Pelletier and W. A. Jacobs, THIS JOURNAL, **76**, 1496 (1954).

(6) C. F. Huebner and W. A. Jacobs, *J. Biol. Chem.*, **170**, 515 (1947).

(7) W. A. Jacobs, *J. Org. Chem.*, **16**, 1593 (1951).

(8) C. F. Huebner and W. A. Jacobs, *J. Biol. Chem.*, **174**, 1001 (1948).

(VI)[7,8] (*vide infra*) which can be reduced to IV,[7]

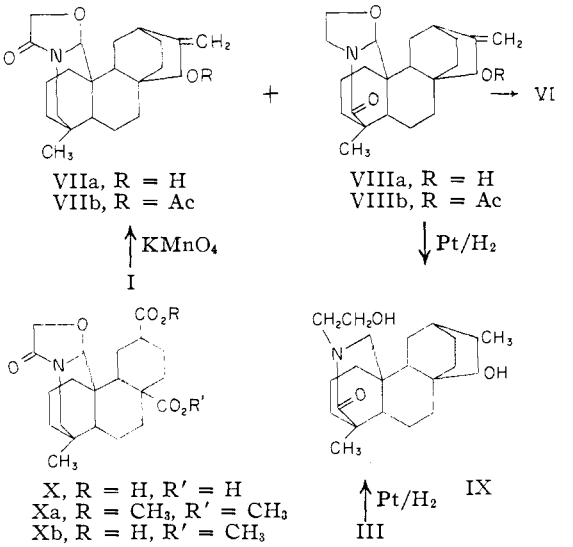


VI

no simple lactam derivative of atisine has ever been described. This behavior appeared inconsistent with the parallelism which has been observed between the Atisine and Garrya alkaloids. Thus, while permanganate oxidation of garryine[9] furnishes an oxogarryine analogous to oxoisoatisine, veatchine furnishes isomeric lactams of five- and six-membered rings.[10,11] In an effort to resolve the apparent anomalous behavior of atisine and to accumulate more evidence concerning the environment about the nitrogen atom, we have studied the oxidation of atisine under mild and carefully controlled conditions.

Treatment of atisine with permanganate in dry acetone at 5° gave a complex mixture which was separated in chloroform with dilute hydrochloric acid and sodium hydroxide into basic, acid and "neutral" fractions. This "neutral" fraction was later shown to contain the hydrochloride of a base (XI) because of its appreciable solubility in chloroform. Chromatography of the "neutral" fraction over alumina gave two principal components.[12] The first was a lactam, $C_{22}H_{31}NO_3$, designated α-oxoatisine, which was eluted with benzene and crystallized from methanol–acetone as beautiful rhomboids, m.p. 244–246°, $[\alpha]D$ −69° (chf.). The infrared spectrum in KBr showed absorption bands at 3096, 1656 and 890 cm.$^{-1}$ characteristic of a terminal methylene group, a band at 1375 cm.$^{-1}$ typical of a C–CH_3 group, and a strong band at 1697 cm.$^{-1}$ which may be attributed to a γ-lactam. A tabulation of C=O stretching frequencies of γ- and δ-lactams in the atisine and isoatisine series appears in Table I. Acetylation of α-oxoatisine with acetic anhydride in pyridine gave a monoacetate (VIIb), m.p. 184.5–186.5°, $[\alpha]D$ −107° (chf.), which showed the absence of hydroxyl absorption in the infrared. Mild saponification regenerated the parent alcohol.

Elution of the chromatogram with benzene–ether gave another lactam, **β-oxoatisine,** which crystallized from benzene as flat needles containing one mole of benzene, m.p. 95–105°, $[\alpha]D$ −52° (chf.). The infrared spectrum in KBr showed the bands characteristic of a terminal methylene group and also a strong, broad band at 1629 cm.$^{-1}$ which may be attributed to a δ-lactam.[13] Acetylation gave a monoacetate VIIIb, m.p. 202–205°, $[\alpha]D$ −102°, with the expected absorption in the infrared. When reduced catalytically in 70% acetic acid, β-oxoatisine absorbed two moles of hydrogen to give the known dihydroöxoisoatisine[6] (infrared spectrum in KBr, 1618 cm.$^{-1}$)[14] (identical m.p. and infrared spectra). The formation from atisine of both five- and six-membered lactams by the loss of two hydrogen atoms is consistent with oxidation at the methylene groups adjacent to the nitrogen atom. It follows that α-oxoatisine and β-oxoatisine have structures VIIa and VIIIa, respectively. Since oxoisoatisine is a six-membered lactam (infrared spectrum in KBr, 1616 cm.$^{-1}$)[14] which is formed from isoatisine without the loss of hydrogen and which furnishes a dihydro derivative identical with the reduction product of β-oxoatisine (VIIIa), it is evident that oxoisoatisine has structure III, and its dihydro derivative has structure IX. The derived oxoisoatisinedi- and tri-carboxylic acids would then have structures IV and V, respectively.



It was desirable at this point to convert α-oxoatisine and β-oxoatisine into the dicarboxylic acids VI and X which are derived by opening the ring bearing the secondary hydroxyl group, with accompanying loss of the exocyclic methylene group. A new reagent which might be expected to smoothly effect this type of transformation has recently been described by Lemieux and Rudloff.[15] It involves the use of an aqueous solution of periodate containing small amounts of permanganate and has been shown to cleave terminal methylene groups. Oxidative cleavage of this group from either α- or β-oxoatisine would be expected to produce an acyloin which would be susceptible to further oxidation by periodate to give the corresponding dicarboxylic acid. Treatment of β-oxoatisine in aqueous pyridine with the Lemieux reagent did indeed give a good yield of a δ-lactam acid (infrared spectrum in

(9) The structures of atisine and isoatisine are analogous to those of veatchine and garryine [K. Wiesner, *et al.*, THIS JOURNAL, **76**, 6068 (1954)], except that the hydroxyl-bearing ring terminates at C-6 rather than at C-7.

(10) K. Wiesner, S. K. Figdor, M. F. Bartlett and D. Henderson, *Can. J. Chem.*, **30**, 608 (1952).

(11) M. F. Bartlett, W. I. Taylor and K. Wiesner, *Chemistry and Industry*, 173 (1953).

(12) A third neutral component which was obtained by elution with ether-methanol had the formulation $C_{22}H_{31}NO_4$ and melted at 246–250°. It appears to be derived from something other than atisine (possibly a hydroxy atisine) since it was not found in a subsequent experiment in which purified atisine was oxidized.

(13) In Nujol the lactam carbonyl absorbed at 1631 cm.$^{-1}$ which is closer to the usual position at 1640 cm.$^{-1}$.

(14) Hydrogen bonding to the carbonyl group of the lactam is probably responsible for this somewhat low frequency.

(15) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710 (1955); E. von Rudloff, *ibid.*, **33**, 1714 (1955).

Nujol, 1658 cm.$^{-1}$), **β-oxoatisine dicarboxylic acid (VI)**, m.p. 315–320°, which proved to be identical in every respect (m.p., spectrum in Nujol) with that isolated by Jacobs[7,8] from the vigorous permanganate oxidation of atisine. A similar oxidation of α-oxoatisine furnished a new acid, **α-oxoatisine dicarboxylic acid (X)**, m.p. 305–310°, containing a γ-lactam (infrared spectrum in Nujol, 1694 cm.$^{-1}$). In agreement with structure X the acid gave with diazomethane a dimethyl ester Xa, m.p. 216–217.5°, which by alkaline saponification gave a monomethyl ester Xb, m.p. 265–267°, which was resistant to further hydrolysis. This parallels the behavior of acid VI toward esterification and saponification. The formation of these two dicarboxylic acids from atisine *via* the respective lactams suggested that direct oxidation of atisine itself should give rise to both dicarboxylic acids. With this in mind the acid fraction from the mild oxidation of atisine was investigated. On long standing in acetone this fraction deposited an acid which melted at 295–310° and proved to have the formulation $C_{21}H_{21}NO_6$. The infrared spectrum of this material showed that it consisted of a mixture of both the γ- and δ-lactam dicarboxylic acids X and VI. Repeated recrystallization of this mixture from aqueous acetone did not appear to alter its character. Since in earlier work[7,8] with the vigorous permanganate oxidation of atisine, only β-oxoatisinedicarboxylic acid (VI, infrared spectrum 1659 cm.$^{-1}$) was isolated, the crystalline fractions from its mother liquors were recently examined for the presence of any of the γ-lactam isomer. The infrared spectra of these crystalline fractions showed the presence of only the δ-lactam acid VI. Repetition of the vigorous permanganate oxidation of atisine has confirmed the fact that only the δ-lactam dicarboxylic acid VI is formed, whereas mild oxidation in acetone leads to a mixture of the γ- and δ-lactam dicarboxylic acids. To explain this rather unusual behavior, one must assume that under conditions of vigorous oxidation atisine is either selectively oxidized to the δ-lactam dicarboxylic acid or that both products are initially formed but that the γ-lactam dicarboxylic acid is preferentially degraded. An improved procedure for the preparation of the δ-lactam dicarboxylic acid is described in the Experimental section.

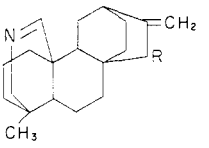
TABLE I

INFRARED ABSORPTION ASSOCIATED WITH LACTAM CARBONYL GROUP

Substance	Max., cm.$^{-1}$ KBr	Nujol
γ-Lactams		
α-Oxoatisine (VIIa)	1697	1686
α-Oxoatisine acetate (VIIb)	1699[a]	1723
α-Oxatisinedicarboxylic acid (X)		1694
X-Dimethyl ester (Xa)		1696
X-Monomethyl ester (Xb)		1681
δ-Lactams		
β-Oxoatisine (VIIIa)	1629	1631
β-Oxoatisine acetate (VIIIb)		1654
β-Oxoatisinedicarboxylic acid (VI)		1658
VI-Dimethyl ester	1642[a]	1658
VI-Monomethyl ester		1617
Oxoisoatisine (III)[6]	1616	1611
Dihydroöxoisoatisine (IX)[6]	1618	1616
Oxoisoatisinedicarboxylic acid (IV)[7]		1608
IV-Dimethyl ester[7]		1622 (film)

[a] In chloroform

An interesting degradation product was obtained by rechromatography of the mother liquors from α-oxoatisine. It crystallized from acetone as white leaflets, m.p. 178.5–180.5°, $[\alpha]D$ −17° (chf.). Analysis and titration with perchloric acid in acetic acid showed this substance to be a base with an empirical formula of $C_{20}H_{29}NO$. The solubility of its hydrochloride in chloroform accounts for its presence in the "neutral" fraction. In subsequent experiments sulfuric acid was used for the separation of the basic fraction. The liberated basic material was then re-converted to the hydrochloride and its aqueous solution continuously extracted with chloroform. The extract gave a good yield of the hydrochloride of the above base. The infrared spectrum of the base in KBr showed bands at 3096 and 888 cm.$^{-1}$ characteristic of a terminal methylene group and a strong band at 1654 cm.$^{-1}$ which may be attributed to an azomethine band (>C=N<).[16] The spectrum of the hydrochloride in chloroform showed immonium bands ($-\overset{+}{N}=$) at 2169, 2068 and 1970 cm.$^{-1}$; a protonated azomethine band ($H\overset{+}{N}=C<$) at 1685 cm.$^{-1}$ and terminal methylene bands (KBr) at 3086, 1655 and 901 cm.$^{-1}$. Oxidation of this unsaturated base with chromium trioxide in pyridine gave a ketone, m.p. 129–133°, with the empirical formula of $C_{20}H_{27}NO$. The infrared spectrum in Nujol showed bands assignable to a conjugated ketone in a six-membered ring (1708 cm.$^{-1}$),[17] a double bond conjugated with a carbonyl group (1636 s. cm.$^{-1}$) and an azomethine band at 1650 cm.$^{-1}$. The spectrum showed the absence of hydroxyl absorption. These data are consonant with structures XI and XII for the unsaturated base and its derived ketone. It appears that XI has its source in the oxidative cleavage of the oxyethyl



XI, R = OH
XII, R = O

group from atisine and is analogous to a base obtained from the low temperature selenium pyrolysis of veatchine by Wiesner, *et al.*[18]

The transformations described interrelate the various degradation products of atisine and make

(16) The unusual intensity of this band undoubtedly is due to the contribution from the terminal methylene group reinforcing that of the azomethine group.

(17) This value is somewhat high since α,β-unsaturated six-membered ring ketones usually absorb from 1674–1684 cm.$^{-1}$ [R. N. Jones, P. H. Humphries and K. Dobriner, THIS JOURNAL, **72**, 956 (1950)]. However, Wiesner has reported that in the veatchine series only a very small shift is observed in going from an unconjugated to a conjugated ketone [K. Wiesner, *et al.*, *ibid.*, **76**, 6068 (1954)]. The α,β-unsaturated ketones corresponding to atisine and isoatisine also show carbonyl absorption in this same range, 1702 and 1710 cm.$^{-1}$, respectively.[6]

(18) M. F. Bartlett, J. Edwards, W. I. Taylor and K. Wiesner, *J. Chem. Soc.*, 323 (1953).

more certain the structures assigned to atisine and isoatisine.

Experimental[19]

Mild Permanganate Oxidation of Atisine.—To a solution of 6.3 g. of atisine in 50 ml. of acetone was added 7 g. of potassium permanganate in 600 ml. of acetone. After 15 minutes the mixture was cooled to 5° and left at this temperature for 20 hours. A solution of hydrazine was added to remove a slight excess of permanganate and the mixture was filtered. The filtrate yielded a residue which was taken up in chloroform and extracted twice with 5% hydrochloric acid. The acid extracts were in turn extracted four times with chloroform and the aqueous fraction was reserved for later study. The combined chloroform solutions were designated fraction AN. A suspension of manganese dioxide in ice-water was reduced with sulfur dioxide and the colorless solution was extracted five times with chloroform. These chloroform extracts were added to fraction AN and the whole extracted twice with 0.1 *N* sodium hydroxide to remove acidic components. This alkaline solution (fraction A) was reserved. The chloroform solution containing the "neutral" products was evaporated to dryness *in vacuo* to give 1.90 g. of resin (N).

Chromatography of the "Neutral" Fraction (N).—The 1.90 g. of resin in 10 ml. of benzene was chromatographed over 30 g. of Merck alumina. Fractions 1–10 of 50 ml. each were collected using benzene as the eluent. Fractions 11–15 of 50 ml. each were collected using benzene–ether (1:4). Fractions 16, 17 of 85 ml. each were collected using ether. Fractions 19–24 of 50 ml. each were collected using ether–methanol (2:1). Fraction 25 of 200 ml. was eluted with methanol. The fractions were evaporated to dryness and processed as described.

α-Oxoatisine.—Treatment of fractions 1–10 (0.93 g.) with acetone gave crystalline fractions with melting points ranging from 212–244°. These were combined and recrystallized three times from methanol–acetone and once from methanol, to give 192 mg. of hexagonal prisms, m.p. 244–246°, $[\alpha]^{29}D$ −69° (*c* 1.4 in chf.); infrared spectrum ν^{KBr} (>C=CH_2) 3096, 1656 and 890 cm.$^{-1}$; (>C=O in γ-lactam) 1697 s. cm.$^{-1}$; (C–CH_3) 1375 cm.$^{-1}$; (OH) 3407 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.76. Found: C, 74.29, 74.22; H, 8.58, 8.60.

α-Oxoatisine Acetate.—A solution of 100 mg. of α-oxoatisine in a mixture of 3 ml. of dry pyridine and 3 ml. of acetic anhydride was allowed to stand 16 hours at room temperature. After evaporation to dryness *in vacuo*, the residue crystallized from petroleum ether, m.p. 180–188°. After two recrystallizations from ether, the acetate formed hexagonal prisms, m.p. 184.5–186.5°, $[\alpha]^{27}D$ −107° (*c* 1.5 in chf.); infrared spectrum, no hydroxyl band; ν^{CHCl_3} (OAc) 1724 sh., 1244, 1235 cm.$^{-1}$; (>C=O in γ-lactam) 1699 cm.$^{-1}$; ν^{Nujol} (>C=CH_2) 1656, 898 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; OAc, 10.77. Found: C, 72.24, 72.20; H, 8.29, 8.41; OAc, 11.56, 12.10.

Saponification of α-Oxoatisine Acetate.—A solution of 50 mg. of α-oxoatisine acetate in 5 ml. of methanol containing 200 mg. of potassium hydroxide was allowed to stand for a half-hour. The solution was evaporated to dryness *in vacuo*, and the residue taken up in chloroform and washed. The chloroform yielded a resin which crystallized from acetone to give 32 mg. of hexagonal prisms of α-oxoatisine, m.p. 244.5–245.5°, $[\alpha]^{27}D$ −65° (*c* 1.15 in chf.).

Fractions 11–13.—This material crystallized from acetone to give a mixture of heavy rhombs (α-oxoatisine) and fine needles (unsaturated base, XI) melting at 212–218°.

β-Oxoatisine.—Fractions 14–17 (134 mg.) crystallized readily from benzene to give flat needles, m.p. 95–110°. All the mother liquors from fractions 1–13 when combined, evaporated to dryness, and taken up in 5 ml. of hot benzene yielded flat blades (349 mg.) of m.p. 98–105°. The combined mother liquors containing 450 mg. were chromatographed in benzene over alumina. Three benzene fractions of 50 ml. each were collected, followed by four ether fractions of 50 ml. each. The first three fractions (B) were found to contain a base and were reserved for further processing. The last three ether fractions crystallized from benzene to give more of the 100° material. The various fractions of 100° material (600 mg.) were combined in benzene and extracted with 5% sulfuric acid to remove any basic contaminant, washed, and then evaporated to dryness *in vacuo*. Two recrystallizations from benzene gave clusters of flat needles, containing one mole of benzene, m.p., 95–105°, $[\alpha]^{29}D$ −52° (*c* 1.6 in chf.); infrared spectrum ν^{KBr} (>C=CH_2) 3096, 1656 sh., 895 cm.$^{-1}$; (>C=O in δ-lactam) in 1629 cm.$^{-1}$; (C–CH_3) 1378 cm.$^{-1}$; (OH) 3442 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{31}NO_3C_6H_6$: C, 77.20; H, 8.56. Found (dried at 60°): C, 77.62; H, 8.58. Calcd. for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.76. Found (dried at 120°): C, 74.20; H, 8.67.

β-Oxoatisine Acetate.—A solution of 102 mg. of β-oxoatisine in 3 ml. of pyridine and 3 ml. of acetic anhydride was allowed to react at room temperature for 24 hours. After concentration to dryness with benzene *in vacuo*, the residue was dissolved in chloroform and washed successively with 5% sulfuric acid, bicarbonate and water. Evaporation gave a residue which crystallized from petroleum ether as prisms, 80 mg., m.p. 200–205°. Two more recrystallizations from ether gave 59 mg. of diamond-shaped platelets or rhombs, m.p. 202–205°; $[\alpha]D$ −102° (*c* 1.44 in chf.); infrared spectrum, no hydroxyl bond; ν^{Nujol} (OAc) 1744, 1239 cm.$^{-1}$; (>C=O in δ-lactam) 1654 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; OAc, 10.77. Found: C, 72.43, 72.35; H, 8.37, 8.25; OAc, 10.98.

Saponification of β-Oxoatisine Acetate.—A solution of 33 mg. of β-oxoatisine in 5 ml. of methanol containing 200 mg. of potassium hydroxide was allowed to stand a half-hour. Processing in the usual way afforded material which crystallized from benzene as thin leaflets of β-oxoatisine, m.p. 95–100°, $[\alpha]^{28}D$ −54° (*c* 1.6 in chf.).

Reduction of β-Oxoatisine to Dihydroöxoisoatisine (IX).—β-Oxoatisine (55 mg.) in 5 ml. of 70% acetic acid was shaken with 107 mg. of platinum oxide and hydrogen for 24 hours. The filtrate from the catalyst was evaporated *in vacuo* with benzene to remove acetic acid. The residue was made basic with aqueous sodium hydroxide and extracted six times with chloroform. When the material from the extracts was dissolved in a small volume of ethyl acetate, small prisms separated, 34 mg., m.p. 212–216°. Recrystallization from ethyl acetate gave 24 mg. melting at 211–213°, undepressed when mixed with an authentic sample.[6] The infrared spectrum (Nujol) of IX was identical with that of dihydroöxoisoatisine throughout the fingerprint region, though the presence of a small amount of impurity was evidenced by a small peak at 1740 cm.$^{-1}$ ν^{Nujol} (OHs) 3442, 3242 cm.$^{-1}$; (>C=O in δ-lactam) 1616 cm.$^{-1}$.

The Unsaturated Base XI.—The first three fractions (B) eluted from the chromatogram of the mother liquors of fractions 1–13 (see β-oxoatisine above) crystallized from acetone as flat plates, 120 mg., m.p. 179–181°, and titrated as a base. Recrystallization from acetone gave 64 mg. of thin leaflets which sublimed to curved blades above 150° and then melted at 178.0–179.0°, $[\alpha]^{29}$ −21° (*c* 1.4 in chf.). ν^{KBr} (>C=CH_2) 3096, 888 cm.$^{-1}$; (>C=N) 1654 s. cm.$^{-1}$; (OH) 3362 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68; mol. wt., 299.4. Found: C, 80.27, 80.44; H, 9.60, 9.65; N, 4.74; mol. wt., 298.3.

A larger quantity of this base was obtained in a subsequent experiment involving the oxidation of 20 g. of atisine in the following manner. The filtrate from the reaction mixture yielded a residue which was dissolved in chloroform and extracted three times with 5% sulfuric acid. The acid extract was made strongly basic with sodium hydroxide, extracted with three portions of chloroform, and the extract taken to dryness. The basic residue was dissolved in 200 ml. of 5% hydrochloric acid and continuously extracted with chloroform. The chloroform extract containing the hydrochloride of base XI was concentrated to dryness *in vacuo*, the salt dissolved in water and then treated with an excess of sodium hydroxide. The extracted base crystallized from acetone to give 718 mg. of needles. Recrystallization from acetone afforded 656 mg. of thin leaflets and

(19) Melting points are corrected. They were taken on a hot-stage under a microscope equipped with a polarizer. Samples were placed on the stage about 15° below the melting point and the temperature raised rapidly to within 5° of the melting point. The temperature was then raised 2° per minute.

flat pointed needles of m.p. 178.5-180.5°, $[\alpha]^{32}D$ −17° (*c* 1.5 in chf.).

Hydrochloride of XI.—This was prepared from XI in acetone with an excess of hydrochloric acid. Evaporation *in vacuo* gave a residue which crystallized from acetone–ether as heavy prisms which melted at 160° then changed to needles and remelted at 210–219°. The infrared spectrum in chloroform showed immonium bands ($-\overset{+}{N}H=$) at 2169, 2068 and 1970 cm.$^{-1}$ and a protonated azomethine band ($H\overset{+}{N}=C<$) at 1685 cm.$^{-1}$. Terminal methylene bands were evident at 3086, 1655 and 890 cm.$^{-1}$ (KBr disk).

Anal. Calcd. for $C_{20}H_{29}NO\cdot HCl$: C, 71.51; H, 9.00. Found: C, 71.35; H, 9.06.

Oxidation of Base XI to Ketone XII.—To a suspension of 50 mg. of chromium trioxide in 0.5 ml. of dry pyridine was added 60 mg. of XI. After six hours at room temperature and then overnight at 0°, the mixture was diluted, made basic with sodium hydroxide and extracted six times with benzene. The extracts when washed and evaporated to dryness *in vacuo* yielded 50 mg. of a resin. This was chromatographed in petroleum ether–benzene (1:1) on 2.0 g. of Merck alumina. The eluate (36 mg.) crystallized from ether, m.p. 129–133°, ν^{Nujol} (>C=O) conjugated in a 6-membered ring[16] 1708 cm.$^{-1}$; (>C=N) 1650 cm.$^{-1}$; (conjugated C=C) 1636 s. cm.$^{-1}$. No hydroxyl band was evident.

Anal. Calcd. for $C_{20}H_{27}NO$: C, 80.76; H, 9.15. Found: C, 80.59; H, 9.20.

The lactam, $C_{22}H_{31}NO_4$, fractions 18–22 crystallized from acetone to give 30 mg. of fine needles, m.p. 232–241°. Recrystallization from methanol–acetone afforded fibrous needles, 24 mg., m.p. 246–250°. This substance did not titrate against perchloric acid in acetic acid; infrared spectrum ν^{Nujol} (>C=CH_2) 3086, 1662, 892, 901 cm.$^{-1}$; (>C=O in δ-lactam) 1713 cm.$^{-1}$; (OH) 3373 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.71, 70.80; H, 8.21, 8.57; N, 3.89.

Oxidation of β-Oxoatisine to β-Oxoatisinedicarboxylic Acid (VI).—To 72 mg. of β-oxoatisine in a mixture of 4 ml. of pyridine and 16 ml. of water was added 5 ml. of 0.2 *M* sodium metaperiodate and 5 ml. of 0.004 *M* potassium permanganate. After two hours the mixture was taken to dryness *in vacuo*. The residue in water was treated with hydrazine hydrate to destroy excess permanganate, made alkaline and extracted three times with chloroform. The aqueous layer was acidified to congo red with sulfuric acid and extracted ten times with chloroform. Evaporation of the chloroform extracts gave a resin which crystallized from acetone to give 38 mg. of small rectangular prisms, m.p. 315–318°. Recrystallization from aqueous acetone afforded material melting at 315-320°. The infrared spectrum in Nujol was identical in every respect with that of the dicarboxylic acid obtained by the vigorous permanganate oxidation of atisine; infrared spectrum ν^{Nujol} (−CO_2H) 1701 cm.$^{-1}$; (>C=O in δ-lactam) 1658 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; neut. equiv., 195.7. Found: C, 64.41; H, 7.59; neut. equiv., 193.8.

Oxidation of α-Oxoatisine to α-Oxoatisinedicarboxylic Acid (X).—A solution of 74 mg. of α-oxoatisine in a mixture of 30 ml. of water and 10 ml. of pyridine was treated with 20 ml. of 0.2 *M* sodium metaperiodate and 20 ml. of 0.004 *M* potassium permanganate. After one hour the orange colored solution was taken to dryness *in vacuo*, the residue was made basic and then freed of neutral products by extraction with chloroform. Acidification of the aqueous solution and extraction with chloroform gave a resin (66 mg.) which crystallized from acetone as pointed blades, m.p. 302–305°, $[\alpha]^{25}D$ −30° (*c* 1.6 in EtOH); ν^{Nujol} (−CO_2H) 1720 cm.$^{-1}$; (>C=O in γ-lactam) 1694 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; neut. equiv., 195.7. Found: C, 64.68; H, 7.40; neut. equiv., 194.6.

The Dimethyl Ester Xa.—The dibasic acid (36 mg.) was esterified in acetone with diazomethane. After filtering and concentrating to a small volume, the diester (26 mg.) crystallized as tiny needles, m.p. 216–217.5°; infrared spectrum, ν^{Nujol} (CO_2Me) 1734, 1709 cm.$^{-1}$; (>C=O in γ-lactam) 1696 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93. Found: C, 65.86; H, 7.93.

The Monomethyl Ester Xb.—The dimethyl ester (2.15 mg.) in methanol was heated under reflux for 2 hours at 100° with an excess of 0.1 *N* sodium hydroxide. Back titration showed 0.056 ml. of 0.1 *N* alkali was consumed. The theoretical for one ester group is 0.0513 ml. When the experiment was carried out on a larger scale (14 mg.) and worked up in the usual way, a resin was obtained which crystallized from acetone as needles, m.p. 265–267°; infrared spectrum, ν^{Nujol} (>CO_2Me) 1723; (>C=O in γ-lactam) 1681 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{31}NO_6$: C, 65.16; H, 7.71. Found: C, 65.40; H, 7.64.

Processing of Fraction A.—The alkaline solution containing the acidic products from the mild permanganate oxidation of atisine was concentrated *in vacuo* to 200 ml. and acidified to *p*H 1 with 50% sulfuric acid. After the solution was extracted twenty times with 50-ml. portions of chloroform, the extracts were washed and evaporated to dryness to give 2.7 g. of resin. After standing two days in 25 ml. of acetone, a fine crystalline powder separated. This was recrystallized from methanol–acetone to give 291 mg. of a dicarboxylic acid, m.p. 300–308°, $[\alpha]^{26}D$ −29° (*c* 1.5 in EtOH). Further recrystallization did not alter the melting point. The infrared spectrum revealed this substance to be a mixture of α- and β-oxoatisinedicarboxylic acids; ν^{Nujol} (−CO_2H) 1701 sh, 1724 cm.$^{-1}$; (>C=O in δ- and γ-lactams) 1657, 1695 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47. Found: C, 64.43; H, 7.39.

Vigorous Permanganate Oxidation of Atisine to β-Oxoatisinedicarboxylic Acid (VI).—To a cooled solution (5°) of 5.0 g. of atisine hydrochloride in 150 ml. of aqueous pyridine (1:1) was added 56 ml. of 10% sodium hydroxide. Twelve grams of powdered potassium permanganate was added in small portions over a period of 90 minutes, maintaining the temperature at 5-10°. After a half-hour the mixture was filtered and the manganese dioxide washed with 250 ml. of hot water. Extraction of the faint brown filtrate with seven 100-ml. portions of benzene gave 573 mg. of basic and neutral components. The aqueous solution was treated with 3 g. of Celite filter-aid and filtered. The pale yellow filtrate with 100 ml. of washings was acidified with 25 ml. of 50% sulfuric acid and extracted with 100-ml. portions of chloroform (8×, fraction A_1) and ethyl acetate (10×, fraction A_2). Fraction A_1 was canary yellow and yielded 1.80 g. of resin which crystallized from acetone to give the following fractions: 770 mg., m.p. 308–317°; 98 mg., m.p. 303–315°; 39 mg., m.p. 299–304°. These fractions had identical infrared spectra which showed the absence of any α-oxoatisinedicarboxylic acid (X); ν^{Nujol} (−CO_2H) 1701 cm.$^{-1}$; (>C=O in δ-lactam) 1659 cm.$^{-1}$. Seeding the mother liquors with X did not afford any α-oxoatisinedicarboxylic acid.

The dark brown ethyl acetate extract (A_2) yielded 873 mg. which did not crystallize from acetone.

Dimethyl Ester of VI.—The dicarboxylic acid (56 mg.) was esterified in acetone with diazomethane. Removal of the solvent and crystallization of the residue from ether gave 35 mg. of rosettes of the dimethyl ester, m.p. 188–191°.

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

When saponified with excess 0.1 *N* sodium hydroxide, 3.29 mg. of the diester consumed 0.0803 ml. of 0.1 *N* alkali. The theoretical amount for one equivalent is 0.0785 ml.

The manganese dioxide obtained from the oxidation of 10 g. of atisine hydrochloride was decomposed in water with sulfur dioxide. Repeated extraction of the solution with chloroform gave an acidic and neutral fraction of only 27 mg. Separation gave 18 mg. of acidic material from which only a trace of crystalline material was obtained.

Acknowledgment.—All analytical data have been obtained by Mr. D. Rigakos of this Laboratory. The technical assistance of Miss Vera Bohan is also gratefully acknowledged.

NEW YORK 21, N. Y.