from rats have been described.[14] An aqueous solution of the radioactive drug was administered by intraperitoneal injection to rats at a dose level of 10 mg./kg. of body weight. The dog experiments were performed on a female chihuahua weighing two kilograms. The collection of urine and respiratory carbon dioxide was done through the use of a specially designed all glass metabolic cage. The dose employed for the dog study was 5.0 mg./dog (i.p.).

Urine samples were hydrolyzed by refluxing 1 hr. after adding 10% by volume of concentrated hydrochloric acid. In the case of the rat urine hydrolysis by incubation with β-glucuronidase was also employed.[14] The hydrolyzed urine samples were first extracted at *p*H 2, and then a second extract was made at *p*H 8. Ether was used as the extraction solvent. The *p*H 8 extracts from the dog urine contained 55–65% of the urinary radioactivity. The figure was 75–85% in the case of the rat. The amount of radioactive material in the acid extracts was negligible and was not investigated further.

The material which was extractable at *p*H 8 was examined by chromatographic separation on Whatman No. 1 paper, which had been buffered by treatment with 0.1 *M* phosphate buffer (*p*H 6.1). The papergrams were developed with *t*-amyl alcohol–*n*–butyl ether–water (80:7:13).[15] The radioactive spots were located in an automatic scanner equipped with a windowless gas flow counter. Phenols were located by spraying with diazotized sulfanilamide.[5]

(14) R. E. McMahon, THIS JOURNAL, **80**, 411 (1958).

(15) A. Brossi, O. Haflinger and O. Schnider, *Arzneim. Forsch.*, **5**, 62 (1955).

Isolation of the Metabolite III from Urine.—Two dogs were given a total of 320 mg. of II by i.p. injection, and the urine was collected for 36 hr. The urine was made 1 *N* with hydrochloric acid and refluxed for 1 hr. An extract of the acidic solution was made and discarded, and the urine was then adjusted to *p*H 8 and extracted with methylene chloride.

The alkaline extract was a dark oil which was acetylated by dissolving in a mixture of 3 ml. of pyridine and 0.5 ml. of acetic anhydride. The diacetate so obtained was heated to boiling with 1 *N* alcoholic NaOH to hydrolyze the ester grouping. The crude N-acetyl derivative of the metabolite was then purified by chromatography on silica gel (Davidson) using benzene–ether mixture for elution. The peak radioactive fractions were combined to give 10 mg. of radioactive metabolite which had an infrared spectrum quite consistent with the proposed structure, *i.e.*, the N-acetyl derivative of III. Other properties of this material are discussed in the text.

The same material was also isolated from the urine of rats which had received a total of 50 mg. of II by intraperitoneal injection. The physical properties (infrared, ultraviolet and paper chromatographic behavior) were identical to those of the material isolated from dogs.

Acknowledgments.—Thanks are due both Dr. Jack Mills and Dr. E. C. Kornfeld for invaluable advice, to Mr. Warren Miller for technical assistance and to Mr. Lee Howard and D. O. Woolf for interpretation of physical data.

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN, AND THE C.S.I.R.O. CHEMICAL RESEARCH LABORATORIES, ORGANIC CHEMISTRY DEPARTMENT, UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA]

The Alkaloids of *Senecio jacobaea L.* IV. The Structures of Jacobine, Jaconine, Jacoline and their Constituent Acids

BY R. B. BRADBURY AND SATORU MASAMUNE

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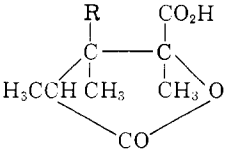
Degradation of jaconecic acid with lead tetraacetate at 100° yielded carbon dioxide, acetaldehyde, β-methyllevulinic acid and β-methyl-γ-carboxy-γ-valerolactone. Under the same conditions *iso*jaconecic acid gave a ketonic acid $C_9H_{14}O_4$. The lithium aluminum hydride reduction product of dimethyl jaconecate is almost inert to periodic acid, whereas that from dimethyl *iso*jaconecate consumes more than one mole, and liberates formaldehyde. These results, together with the ferric chloride test and active hydrogen determinations establish that *iso*jaconecic acid is an α-hydroxy acid whereas jaconecic acid is not. The dimethyl ester from the acid $C_9H_{14}O_6$ obtained by nitric acid oxidation of jaconecic acid, on reduction with lithium aluminum hydride, consumes two moles of periodic acid and liberated formaldehyde. These, together with previous results, have been reinterpreted in terms of new formula, which are supported by nuclear magnetic resonance data.

A number of different structures have been proposed for jaconecic acid (Ia),[1] (Ib),[2] (II),[3] *iso*jaconecic acid (III)[1b] and the chlorodilactone (IV),[1b] (V).[3,4] These formulas were based on the assumption that, in the chlorodilactone, the presence of an infrared carbonyl band at 1781 cm.$^{-1}$ and the absence of a band between 1750 and 1735 cm.$^{-1}$[5] indicated the presence of two five-membered lactone rings. Relevant data are collected in Table I. However, it is possible for spiro-type δ-lactones to show absorption in the region 1793–1786 cm.$^{-1}$,[7] and this shift can occur where there is ring strain.[5] In addition, since it has hitherto been necessary to postulate methyl group migration[2] to explain the conversion of Ib to β-methyl-γ-carboxy-γ-valerolactone, and since the formulas proposed by Adams[3,4,8] cannot be satisfactorily explained in terms of the experimental data, the

TABLE I

INFRARED CARBONYL FREQUENCIES, CM.$^{-1}$ (CHLOROFORM)		
Chlorodilactone		1781
Jacolinecic dilactone acetate		1780, (1742)
p-Bromophenacyl derivative of β-methyl-γ-carboxy-γ-valerolactone		1779, (1751, 1702)
Monocrotalic acid[6]		
	[α]	
	acid, 5.6°, R = H	1774
	acid, −60.0°	1782
	acid, −5.0°, R = OH	1780

(1) (a) R. B. Bradbury, *Chemistry & Industry*, 1021 (1954); (b) R. B. Bradbury and J. B. Willis, *Aust. J. Chem.*, **9**, 258 (1956).

(2) R. B. Bradbury, *Tetrahedron*, **2**, 363 (1958).

(3) R. Adams, M. Gianturco and B. L. van Duuren, THIS JOURNAL, **78**, 3513 (1956).

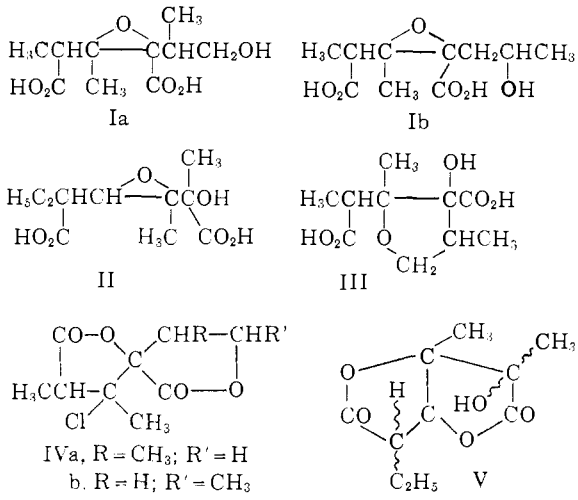
(4) R. Adams and M. Gianturco, "Festschrift Prof. Arthur Stoll," Druck von Birkhauser Ag., Basel, Switzerland, 1957, p. 77.

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., Methuen and Co., Ltd., London, 1958, pp. 179, 185, 186.

(6) R. Adams, P. R. Shafer and B. H. Braun, THIS JOURNAL, **74**, 5612 (1952).

(7) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

(8) R. Adams and M. Gianturco, *Angew. Chem.*, **69**, 1252 (1954).



assumption that the chlorodilactone contains two five-membered lactone rings has now been discarded. It is the purpose of this paper to present new results which, together with those previously obtained, can be interpreted in terms of new formulas.

*iso*Jaconecic acid, together with jaconecic acid, has been obtained from the alkaline hydrolysis of jacobine, jaconine and the chlorodilactone ($C_{10}H_{13}O_4Cl$) and is undoubtedly also formed under the same conditions from tomentosine[3] and othosenine,[9] but has apparently been overlooked by the American and Russian workers. It is produced in approximately equimolecular proportions to jaconecic acid, and was first detected by its higher rotation and different R_f value. Although jaconecic acid can be obtained pure by recrystallization of the mixed acids from ethyl acetate, a clear separation of *iso*jaconecic acid can only be achieved by partition chromatography on silica gel or, better, anion exchange chromatography. It is possible that some specimens of jaconecic acid previously obtained were contaminated with *iso*jaconecic acid since they gave a faint color with ferric chloride. It has now been found that pure jaconecic acid does not give a reaction with ferric chloride whereas *iso*jaconecic acid does. When the test is performed on neutral solutions of the acids prepared by addition of a slight excess of ammonia and boiling, both give brown solutions, but *iso*jaconecic acid gives a brown precipitate which gradually dissolves on standing. Jaconecic acid gives a positive iodoform reaction. The difference in reactivity of jaconecic and *iso*jaconecic acids with oxidizing agents is notable. While jaconecic acid is readily oxidized by dilute nitric acid to oxalic acid, α,β-dimethylmalic acid and two other dibasic acids ($C_9H_{14}O_6$ and $C_9H_{12}O_7$),[10] *iso*jaconecic acid is largely recovered unchanged. With lead tetraacetate in aqueous acetic acid at 100° jaconecic acid reacts vigorously liberating carbon dioxide and acetaldehyde. This contrasts with its inertness to periodic acid at room temperature which was taken to indicate the absence of a glycol grouping.[1b] Extraction of the non-steam volatile products from the lead tetraacetate reaction mixture gave two liquid acids which were detected by paper chromatography and separated by partition chromatography on silica gel. The first, which analyzed for the formula $C_6H_{10}O_3$, was an optically active, monobasic acid containing a carbonyl group and two carbon methyl groups. It did not give a Schiff's test, nor was it oxidized by dilute alkaline permanganate at 0°, but gave a positive iodoform test, and therefore was a methyl ketone. It was isolated as a hygroscopic oil, which could be distilled without decomposition, and therefore was not a β-keto acid. The infrared spectrum of the oily ketonic acid showed carbonyl absorption at 1716 cm.$^{-1}$. Its *p*-bromophenacyl derivative showed bands at 1698 and 1745 cm.$^{-1}$ due to phenacyl carbonyl and ester groupings, respectively. This compound was thought to be α-methyllevulinic acid, and a synthetic specimen of this acid was prepared by the condensation of ethyl α-bromopropionate and ethyl acetoacetate, followed by hydrolysis and decarboxylation.[11] The synthetic and natural acids showed only one spot on paper at the same R_f value. Their semicarbazones, although melting at the same temperature, showed depression when admixed, and the dinitrophenylhydrazones were different. Resolution was achieved using cinchonidine, to give on recovery the pure dextrorotatory α-methyllevulinic acid, but its specific rotation was much lower than that of the natural acid, and its semicarbazone and *p*-bromophenacyl derivatives were different. The only other likely alternative, β-methyllevulinic acid, was prepared in a similar manner from ethyl bromoacetate and ethyl methylacetoacetate,[11] followed by hydrolysis and decarboxylation. The semicarbazone and dinitrophenylhydrazone showed no depression when admixed with the derivatives from the natural keto-acid obtained from the action of lead tetraacetate on jaconecic acid.

The second product from the action of lead tetraacetate on jaconecic acid was also a hygroscopic, optically active oil, which gave a positive iodoform test, but a negative Schiff's test. Analysis of the *p*-bromophenacyl derivative indicated the formula $C_7H_{10}O_4$, and it contained two carbon methyl groups, but did not yield carbonyl derivatives. It behaved as a monobasic acid on titration with alkali at room temperature, but required a second equivalent of alkali at 100°, indicating a lactone structure. The *p*-bromophenacyl derivative was evidently dimorphous since when first prepared it had m.p. 82–83°, but on standing changed to 109°. The infrared spectrum of this derivative showed carbonyl absorption at 1702, 1751 and 1779 cm.$^{-1}$ due to phenacyl carbonyl, ester and a γ-lactone, respectively. The band at 1751 cm.$^{-1}$ is somewhat higher than the frequency for a normal ester (*vide infra*), and corresponds with that of an ester with an oxygen containing substituent on the α-carbon atom.[1b,12] There is no band in the hydroxyl

(9) E. S. Zhdanovich and G. P. Menshikov, *J. Gen. Chem., U.S.S.R.*, **11**, 835 (1941).

(10) R. B. Bradbury, *Aust. J. Chem.*, **9**, 521 (1956).

(11) E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 3313 (1953).

(12) The *p*-bromophenacyl ester of the stereoisomer, $[\alpha]_D$ −60.0°, of dihydroanhydromonocrotalic acid (R. Adams and F. B. Hauserman, THIS JOURNAL, **74**, 694 (1952)) shows a band in the infrared at approximately the same frequency.

region. This compound was thought to be β-methyl-γ-carboxy-γ-valerolactone, and a specimen was prepared in small yield by treatment of β-methyllevulinic acid with liquid hydrogen cyanide followed by hydrolysis and lactonization. The crude product showed three spots by paper chromatography at R_f 0.86 due to unchanged β-methyllevulinic acid, one at R_f 0.66 corresponding to the compound $C_7H_{10}O_4$ obtained from jaconecic acid, and an unidentified spot at R_f 0.71. The compound of R_f 0.66 was separated from unchanged β-methyllevulinic acid by partition chromatography on silica gel, and resolved by means of the cinchonidine salt to give a dextrorotatory oil having approximately the same specific rotation as that of the carboxylactone obtained from the lead tetraacetate oxidation of jaconecic acid. Its *p*-bromophenacyl derivative melted at 105–106°, and showed no depression with the derivative of the natural product, and the infrared spectra in Nujol were virtually identical, only small differences in resolution of bands being evident, which could be attributed to admixture of the natural sample with the lower melting dimorphic form.

The oxidation of *iso*jaconecic acid with lead tetraacetate under the same conditions gave carbon dioxide, a small amount of acetaldehyde, and from the non-steam volatile residue a relatively large yield of an oil which showed two spots by paper chromatography, one corresponding to unchanged *iso*jaconecic acid and the other to a new compound. Separation of these on silica gel as before yielded a new optically active, monobasic acid of the formula $C_9H_{14}O_4$. The infrared spectrum of the *p*-bromophenacyl derivative of this acid, showed three bands in the carbonyl region at 1702, 1726 and 1743 cm.$^{-1}$, which correspond to the phenacyl carbonyl, ketone and ester groupings, respectively, and no band in the hydroxyl region. An attempt to prepare a dinitrophenylhydrazone resulted in the formation of a compound having the probable formula $C_{21}H_{22}O_{11}N_8$.[13] It contained a free carboxyl group.

Jaconecic and *iso*jaconecic acids also differ in the reactivity of their hydroxyl groups. Whereas jaconecic acid yields a monoacetate[1b] with acetyl chloride, a crystalline derivative could not be obtained from *iso*jaconecic acid. Active hydrogen determinations carried out on dimethyl *iso*jaconecate and bis-*p*-toluene sulfonyl derivative of its lithium aluminum hydride reduction product gave approximately one-third of one mole of methane. Normal values corresponding to one mole of methane were obtained with these derivatives of jaconecic acid. However, although only bis-*p*-toluenesulfonyl derivatives of the lithium aluminum hydride reduction products of both dimethyl jaconecate and dimethyl *iso*jaconecate were obtained, triacetates of both resulted on reaction with acetyl chloride. These results suggest the presence of a secondary hydroxyl group in jaconecic acid and probably a tertiary hydroxyl in *iso*jaconecic acid. Analyses of the derivatives confirm the formula $C_{10}H_{20}O_4$[1b] for the reduction products, and since an oxygen atom is unaccounted for in the formation of derivatives and in active hydrogen determinations it must be present in an oxygen containing ring which is resistant to lithium aluminum hydride. The reduction products of jaconecic and *iso*jaconecic acids consume 0.2 and 1.3–1.8 mole of periodic acid per mole of substance, respectively, and the latter yields formaldehyde, which definitely establishes the presence of an α-hydroxy acid group in *iso*jaconecic acid. Extraction of the steam distilled solution from the reaction between periodic acid and the reduction product of dimethyl *iso*jaconecate gave an oil from which a solid, m.p. 232° (probable formula $C_{18}H_{32}O_7$), was obtained. This substance showed no carbonyl absorption in its infrared spectrum, but strong hydroxyl absorption at 3436 cm.$^{-1}$. It has not been studied further. The residual oil after the removal of this solid gave a bis-2,4-dinitrophenylhydrazone, $C_{21}H_{24}O_{10}N_8$, which indicates a formula $C_9H_{16}O_4$ for the oxidation product.

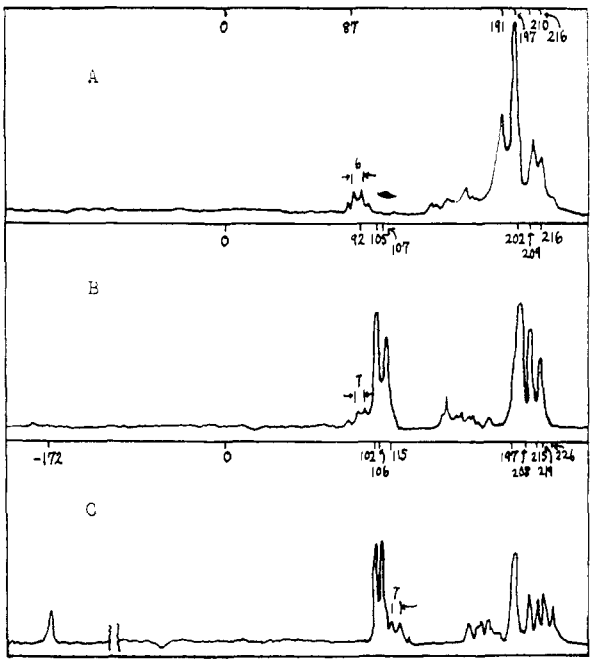


Fig. 1.—Nuclear magnetic resonance spectra in $CDCl_3$ solution: A, chlorodilactone; B, dimethyljaconecate; C. dimethyl *iso*jaconecate.

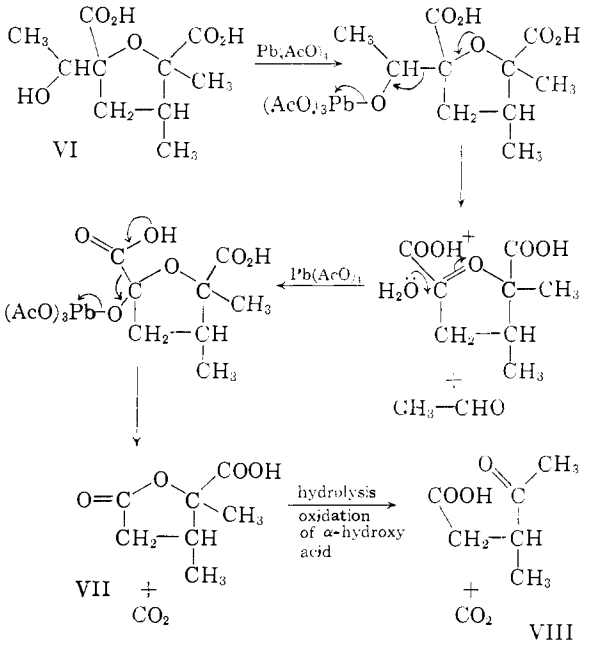
The relationship between jacobine and jaconine has previously been established[1b] as that of an epoxide and a chlorohydrin, respectively, and the suggestion then made that jacoline was the corresponding glycol[1b] has now been confirmed.[14] Jacobine can be hydrolyzed with 25% sulfuric acid to jacoline, with the concomitant formation of a neutral compound which on acetylation gives acetyl jacolinecic dilactone. Periodic acid oxidation of jacoline has also been found to yield acetaldehyde.

By a consideration of the products obtained from the reaction of jaconecic acid with lead tetraacetate,

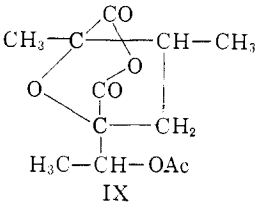
(13) This compound was at first thought to have the formula $C_{11}H_{12}O_6N_4$,[2] and was considered to be a derivative of methylacetoacetic acid. However, in attempts to prepare an authentic specimen only the pyrazolone resulted. The nitrogen values are about 1% too low for the formula $C_{21}H_{22}O_{11}N_8$, but this may have been due to the formation of a difficultly combustible nitrogenous tar in the micro-Dumas nitrogen determination.

(14) Information kindly supplied by Dr. T. A. Geissman.

namely, carbon dioxide, acetaldehyde, β-methyllevulinic acid (VIII) and β-methyl-γ-carboxy-γ-valerolactone (VII), it is possible to arrive at a formula VI for jaconecic acid. The decomposition can be represented



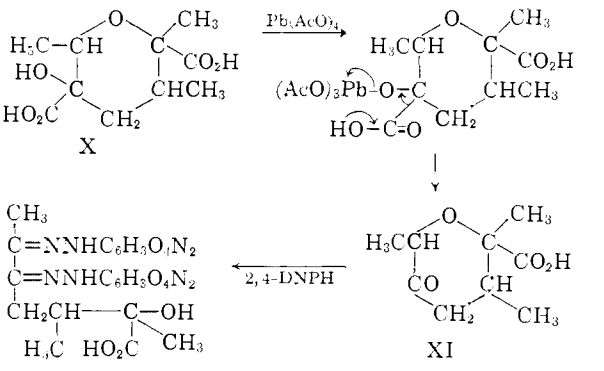
This formula can explain most of the properties of jaconecic acid: positive iodoform test, negative ferric chloride test, formation of a monoacetate with acetyl chloride and an anhydride (IX) with acetic anhydride and reduction of its dimethyl



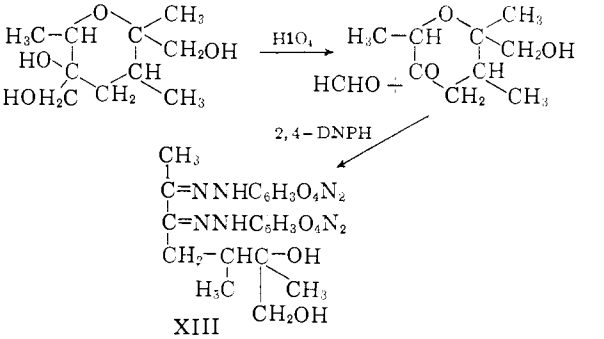
ester with lithium aluminum hydride to yield a triol which is almost inert to periodic acid. The lithium aluminum hydride reduction product of the dimethyl ester of the dibasic acid $C_9H_{14}O_6$, obtained from nitric acid oxidation of jaconecic acid,[10] consumed two moles of periodic acid and liberated formaldehyde. The infrared spectrum of the bis-*p*-bromophenacyl derivative of the dibasic acid $C_9H_{12}O_7$[10] showed bands at 1770, 1748 and 1702 cm.$^{-1}$. However, until further results are obtained, structures cannot with certainty be proposed for these compounds.

*Iso*jaconecic (X) is an α-hydroxy acid, and when oxidized with lead tetraacetate it gives carbon dioxide, a small amount of acetaldehyde[15] and a keto-acid $C_9H_{14}O_4$ (XI), according to the scheme X–XII. When treated with 2,4-dinitrophenylhydrazine in acid solution ring opening and oxidation occurs to give a bis-dinitrophenylhydrazone (XII).[13]

(15) A small amount of acetaldehyde can be explained in a similar manner to that used for jaconecic acid.

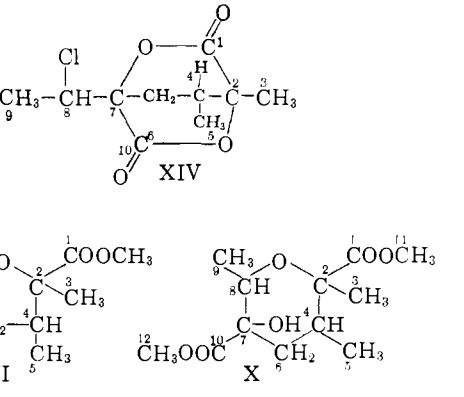


The lithium aluminum hydride reduction product of dimethyl *iso*jaconecate consumed more than one mole of periodic acid with the liberation of formaldehyde, and the non-steam-volatile product formed gave a bis-dinitrophenylhydrazone (XIII), corresponding in composition with that



above (XII). *Iso*jaconecic acid is not appreciably oxidized by nitric acid in contrast to jaconecic acid.[16] Advantage can be taken of this fact to obtain pure *iso*jaconecic acid.

The proton magnetic resonance spectrum[17] (curve A) of the chlorodilactone XIV (*vide infra*)



(16) This is remarkable because of the ease with which cineolic acid is oxidized by nitric acid (O. Wallach and E. Gildemeister, *Ann.*, **246**,

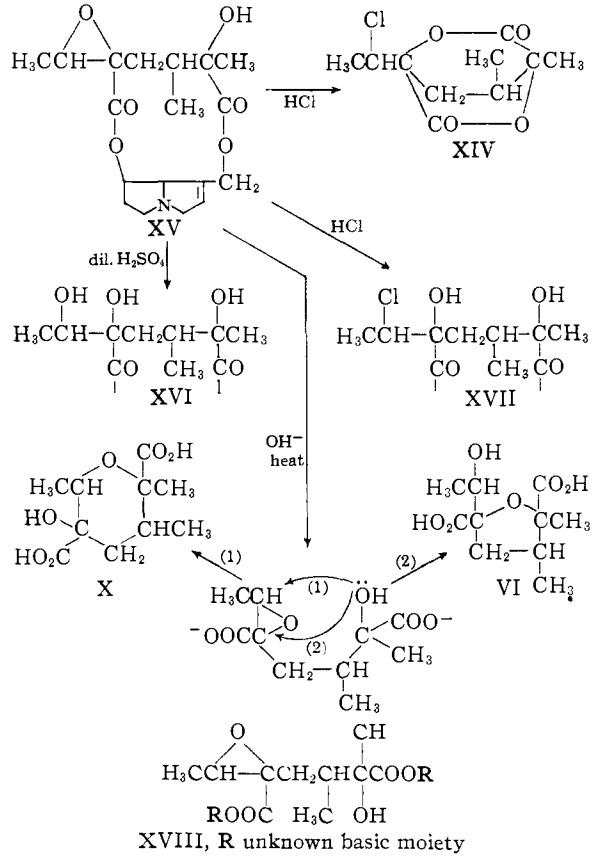
265 (1888)), and the resistance shown by tetrahydrofuran-2,5-dicarboxylic acid under the same conditions (W. W. Haworth, W. G. M. Jones and L. F. Wiggins, *J. Chem. Soc.*, 1 (1945)).

(17) All spectra of the compound (in deuterated chloroform) were obtained at 40 megacycles per second in a magnetic field of approximately 9400 gauss, employing benzene as a reference.

showed a peak at 87 c.p.s. (area ≅ 1 proton, quadruplet), demonstrating that one hydrogen is attached to a carbon (C-8) carrying a methyl group (C-9) and chlorine atom. In the C-methyl region, a doublet (area ≅ 3 protons) at 210 and 216 c.p.s. can be ascribed to the C-5 methyl group. Peaks at 191 and 197 c.p.s. (area ≅ 6 protons) comprise a doublet, assigned to the C-9 methyl group, and a singlet, assigned to the C-3 methyl group. The spin–spin coupling constant, J, between the C-9 and C-8 methine group is 6 c.p.s.

In the case of dimethyl *iso*jaconecate (curve C), singlets at 102 (area ≅ 3 protons), 106 (area ≅ 3 protons), 197 (area ≅ 3 protons) and a doublet at 219 and 226 c.p.s. (area ≅ 3 protons) are assigned to C-11 (or C-12), C-12 (or C-11), C-3 and C-5 methyl groups, respectively. Peaks at 115 c.p.s. (area ≅ 1 proton, quadruplet), 208 and 215 c.p.s. support the presence of the C-8 and C-9 system (the coupling constant, 7 c.p.s.). The appearance of the proton resonance of the hydroxyl group at an unusually low field can be rationalized by strong hydrogen bonding of the α-hydroxy ester.

The overlapping of peaks in the spectrum of dimethyl jaconecate VI (curve B) presents some difficulty in interpretation, with the exception of the methyl ester peaks at 105 and 107 c.p.s.



Careful measurement of each area and comparison with the spectrum of dimethyl *iso*jaconecate, however, leads to quite reasonable assignments. The area at 202, 209 and 216 c.p.s. corresponds to 1.5, 1 and 0.5 protons. This suggests the presence of (1) one singlet at 202 c.p.s., (2) one doublet at 202 and 209 c.p.s., and (3) one doublet at 209 and 216 c.p.s. In a similar manner to that used for dimethyl *iso*jaconecate, these peaks are assigned, C-3, C-9 and C-5 methyl groups, the second one being coupled with the C-8 proton, which appeared at 92 c.p.s. (quadruplet).

Jacobine, jacoline and jaconine can be represented as XV, XVI, and XVII, respectively, the chlorodilactone as XIV and mechanisms of hydrolysis to jaconecic and *iso*jaconecic acids as shown. Tomentosine[3] must now be written as XVIII.

Further confirmation of the structure of jacobine has been obtained by its reaction with lead tetraacetate in which acetaldehyde and β-methyllevulinic acid are formed. With periodic acid a solid compound of the formula $C_{18}H_{27}O_6NI_4$ (see Experimental) is formed. A compound analogous to jaconine hydrochloride of the composition $C_{18}H_{27}O_6NBr_2$ can be isolated by treating jacobine with two moles of hydrobromic acid,[1b] and this confirms the presence of an epoxide group in this compound.

Acknowledgment.—Thanks are due to Mr. S. Mosbauer for capable technical assistance, and to Dr. J. B. Willis and Mr. A. Moritz for measuring the infrared spectra.

Experimental[18]

Reaction of Jacobine with Hydrobromic Acid.[19]—When jacobine was treated with exactly two moles of aqueous hydrobromic acid as described previously[1b] colorless prisms from alcohol, m.p. 254°, were obtained.

Anal. Calcd. for $C_{18}H_{27}O_6NBr_2$: C, 42.12; H, 5.30; N, 2.73; Br, 31.14. Found: C, 42.3; H, 5.4; N, 2.5; Br, 30.9.

Reaction of Jacobine with Periodic Acid.—Jacobine (0.179 g.) was treated with aqueous periodic acid following the procedure of Jackson[20] and allowed to stand at room temperature for 64 hr. It dissolved slowly in the solution and at the end of 64 hr. was found on titration to have consumed only 0.4 mole of periodic acid per mole substance. Toward the end of the titration with iodine brown crystals separated, and more could be obtained by addition of excess of iodine (total 0.37 g.). Recrystallization from alcohol gave glistening purplish-brown needles, m.p. 209–210°.

Anal. Calcd. for $C_{18}H_{27}O_6NI_4$: C, 25.10; H, 3.16; O, 11.15; N, 1.63; I, 58.95. Found: C, 25.5; H, 3.1; O, 11.7; N, 1.5; I, 58.7.

Reaction of Jacobine with Lead Tetraacetate.—Jacobine (3.5 g.) in glacial acetic acid (90 ml.) and water (20 ml.) was heated to 100° and lead tetraacetate (3.5 g.) added portionwise. Gas was evolved. The solution was steam distilled and the distillate collected in 2,4-dinitro-phenylhydrazine (0.5 g.) in 2 *N* HCl (100 ml.). A yellow precipitate was obtained which when recrystallized from alcohol gave colorless plates, m.p. 165–166°, undepressed when admixed with acetaldehyde dinitrophenylhydrazone. The steam-distilled solution was treated with dilute sulfuric acid (5 ml. concd. to 50 ml. water) and the lead sulfate filtered and washed with water. The filtrate was continuously extracted with ether for 16 hr. The ether was distilled and left a viscous residue which when chromatographed on silica gel gave a fraction from which a *p*-bromophenacyl derivative, m.p. 91° (*Anal.* Calcd. for $C_{14}H_{15}O_4Br$: C, 51.4; H, 4.6. Found: C, 51.2; H, 4.8), was obtained

(18) All melting points are corrected. Microanalyses were carried out in the C.S.I.R.O. Microanalytical Laboratory at the Melbourne University. The spectrophotometer employed for the nuclear magnetic resonance spectra was a Varian Associates high resolution n.m.r. spectrophotometer with superstabilizer.

(19) This experiment was performed by S. Mosbauer.

(20) E. L. Jackson, "Organic Reactions," ed. R. Adams, Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 361.

which was identical with the *p*-bromophenacyl derivative of β-methyllevulinic acid described later.

Reaction of Jacoline with Periodic Acid.—Two experiments using the procedure of Jackson[20] showed that jacoline consumed one mole of periodic acid per mole substance after a period of one hour and twenty minutes. When the steam distillate was collected in an aqueous solution of dimedone, colorless needles, m.p. 142–143°, undepressed on admixture with the authentic derivative of acetaldehyde, were obtained.

Reaction of Acid Moiety from Jacoline with Periodic Acid.—Jacoline (1.34 g.) was hydrolyzed with sodium hydroxide (0.5 g.) and water (25 ml.) at 100° for 2 hr. The solution was acidified with hydrochloric acid and on continuous extraction with ether gave a yellow oil (0.58 g.). This required 38.93 ml. of 0.0872 *N* sodium hydroxide on titration. The neutral solution was evaporated to dryness and treated with periodic acid in the usual way.[20] After standing for 16 hr. at room temperature 1.13 moles of periodic acid was consumed. Steam distillation of the solution and collection of the distillate in dimedone (0.5 g.) in water (100 ml.) yielded a solid, m.p. 140–141°, identical with an authentic derivative of acetaldehyde.

Separation of Jaconecic and Isojaconecic Acids on an Anion Exchange Resin.—Two chromatographic columns of dimensions 3 × 46 cm. and 1.8 × 32 cm. were packed with −40 + 50 B.S.S. and −80 + 100 B.S.S. Deacidite FF resin, respectively, and connected together. The columns were washed several times with carbon dioxide free 0.1 *N* hydrochloric acid and 0.1 *N* sodium hydroxide interspersed with carbon dioxide-free water. After regeneration of the columns with sodium hydroxide a mixture of jaconecic and *iso*jaconecic acids (16.8 g.) in water was run through followed by 0.1 *N* hydrochloric acid. When the first eluate emerged, fractions of 50 ml. were collected using an automatic fraction collector.[21] These were tested for homogeneity using paper chromatography[1b] and imilar fractions were combined as shown in Table II.

TABLE II

ANION EXCHANGE SEPARATION OF JACONECIC AND *iso*-JACONECIC ACIDS

Fraction	R_f value	Wt., g.	Designation
1–7	0.86, 0.70, 0.43	3.1	Probably mixt. of monolactonic monocarboxylic acids
8–13	0.76	6.7	*iso*Jaconecic acid
14–19	0.76, 0.52	2.3	Mixt. of *iso*jaconecic and jaconecic acids
20–98	0.52	1.22	Jaconecic acid

***iso*Jaconecic Acid.**—A purer sample than that previously obtained[1b] was recovered unchanged after reaction with lead tetraacetate (see below). When recrystallized from ethyl acetate–light petroleum it gave colorless needles radiating from a center, m.p. 119–120°, $[\alpha]^{16}D$ +116.5° (water, *c* 0.94).

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.7; H, 6.9; 3 CH_3C, 19.4; neut. equiv., 116. Found: C, 52.1; H, 6.9; CH_3C, 18.9; neut. equiv., 115.

It appeared to be very hygroscopic. Re-examination of the ferric chloride reaction showed that pure *iso*jaconecic acid gave a positive, jaconecic acid a negative test. Samples were also tested according to the procedure given by Mann and Saunders.[22] Samples of jaconecic and *iso*jaconecic acids were made slightly alkaline with dilute ammonia, and the solution boiled until free of ammonia, then two drops of ferric chloride solution added. *iso*Jaconecic acid gave a brown color and a precipitate which redissolved on standing. Jaconecic acid gave a brown color but no precipitate.

Anhydride of jaconecic acid was prepared by refluxing jaconecic acid (1.0 g.) with acetic anhydride (10 ml.) for two hours, removal of the excess acetic anhydride and distillation of the residue. A colorless oil, b.p. 134–135° at 0.5 mm., was obtained.

Anal. Calcd. for $C_{12}H_{16}O_6$: C, 56.2; H, 6.3; CH_3CO, 16.8. Found: C, 56.6; H, 6.4; CH_3CO, 16.6.

It was insoluble in water, and could be neutralized on warming with alkali. Acidification and extraction of the solution with ether gave a residue which when recrystallized from ethyl acetate yielded monoacetyljaconecic acid, m.p. 195°, undepressed on admixture with an authentic specimen.

Attempted Reaction of Jaconecic Acid with Hydrochloric Acid in the Presence of Retronecine Hydrochloride.—Jaconecic acid (0.5 g.), retronecine hydrochloride (0.5 g.) and aqueous (1:1) hydrochloric acid (10 ml.) were refluxed for 24 hours. No crystals of the chlorodilactone ($C_{10}H_{13}O_4Cl$) separated on cooling, so the solution was diluted somewhat with water, and continuously extracted with ether for 96 hours. The residue (0.5 g.) showed only one spot by paper chromatography at the same R_f value as that of authentic jaconecic acid, and when recrystallized from ethyl acetate gave colorless needles, m.p. 182–183°, undepressed on admixture with an authentic specimen. Jaconecic acid gave a positive iodoform test.

Dimethyl *Iso*Jaconecate.—*iso*Jaconecic acid (9.1 g.) in ether was treated with diazomethane in ether from nitrosomethylurea (21 g.), and allowed to stand for 16 hours. After removal of the excess diazomethane and ether the liquid was distilled. The middle fraction (5.0 g.) had b.p. 130–131° at 1.2 mm., m.p. 51–52°, $[\alpha]^{16}D$ +98° (ethanol, *c* 1.51), $n^{18}D$ 1.4681 d^{18}_{18} 1.171.

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 55.4; H, 7.7; 2 CH_3O, 23.8; 3 CH_3C, 17.3; 1 act. H, 0.39; sapon. equiv., 130. Found: C, 55.6; H, 7.7; CH_3O, 22.3; CH_3C, 15.8; act. H, 0.11; sapon. equiv., 129.

The infrared spectrum showed bands in the hydroxyl region at 3492 and 3570 cm.$^{-1}$, at 1722 and 1739 cm.$^{-1}$ in the carbonyl region and at 1195, 1158, 1145, 1128 and 1081 cm.$^{-1}$.

Reduction of Dimethyl *iso*Jaconecate with Lithium Aluminum Hydride.—Dimethyl *iso*jaconecate (7.6 g.) in dry ether (150 ml.) was added dropwise to powdered lithium aluminum hydride (20 g.) in dry ether (150 ml.) with shaking. After standing for 16 hours at room temperature and refluxing for 1 hour, 10% aqueous sulfuric acid (200 ml.) was added cautiously to the cooled solution. The mixture on continuous extraction with ether for 8 hours gave an oil (5.4 g.) which after drying *in vacuo* over solid sodium hydroxide had $[\alpha]^{19}D$ +58.6° (ethanol, *c* 1.60).

Preparation of a Bis-*p*-toluenesulfonyl Derivative.—The above oil (0.40 g.), *p*-toluenesulfonyl chloride (2.2 g.) and pyridine (5 ml.) were heated on a boiling water-bath for 0.5 hour. After pouring into ice-cold water (10 ml.), the oily material was extracted with ether, and the ether solution dried over sodium sulfate. Evaporation of the ether left an oil which gradually solidified. When recrystallized from benzene–light petroleum it formed colorless prisms, m.p. 116–117°.

Anal. Calcd. for $C_{24}H_{32}O_8S_2$: C, 56.2; H, 6.3; S, 12.5; 1 act. H, 0.196; mol. wt., 513. Found: C, 55.9; H, 6.2; S, 12.2; act. H, 0.08; mol. wt. (Rast), 540.

Triacetate of Reduced Dimethyl *iso*Jaconecate.—The above oil (0.39 g.) was refluxed with acetyl chloride (10 ml.) for 1.25 hours. The excess acetyl chloride was removed and the residue distilled. The middle fraction had b.p. 148° at 0.6 mm., $[\alpha]^{21}D$ +47.8° (ethanol, *c* 1.80), $n^{20}D$ 1.4590.

Anal. Calcd. for $C_{16}H_{26}O_7$: C, 58.2; H, 7.9; O, 33.9; 3 CH_3O, 39.1. Found: C, 58.2; H, 7.8; O, 33.3; CH_3CO, 37.9.

Oxidation with Periodic Acid.—Using the procedure of Jackson[20] the reduction product of dimethyl *iso*jaconecate consumed 1.3–1.8 moles of periodic acid per mole substance over periods of 17–90 hours. Steam distillation of the oxidation solution and collection of the distillate in an aqueous solution of dimedone gave colorless needles, m.p. 189°, undepressed when admixed with the authentic dimedone derivative of formaldehyde.

Continuous extraction of the steam distilled solution with ether gave an oil, $[\alpha]^{18}D$ +8.0° (50% ethanol, *c* 0.996). From 0.63 g. of the lithium aluminum reduction product 0.5 g. of the oil was obtained. When this was treated with a small amount of alcohol a solid separated, which when recrystallized from acetone–benzene gave colorless needles, m.p. 232°.

(21) G. F. H. Box and R. B. Bradbury, *J. Sci. Instr.*, **34**, 183 (1957).

(22) F. G. Mann and B. C. Saunders, "Practical Organic Chemistry," 2nd edition, Longmans, Green and Co. Ltd., 1952, p. 215.

Anal. Calcd. for $C_{18}H_{32}O_7$: C, 60.0; H, 8.9; 4 act. H, 1.12. Found: C, 60.0, H, 8.9; act. H, 1.05.

This compound showed no carbonyl absorption in its infrared spectrum, but strong absorption at 3436 cm.$^{-1}$ due to hydroxyl groups.

The residual oil remaining after removal of the above compound (0.11 g.) was treated with a solution of 2,4-dinitrophenylhydrazine (0.26 g.) in 2 *N* hydrochloric acid (50 ml.). After heating on a boiling water-bath a derivative separated which gave red granules from alcohol, m.p. 192–193°, depressed on admixture with 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_{21}H_{24}O_{10}N_8$: C, 46.0; H, 4.4; N, 20.4. Found: C, 45.8; H, 4.5; N, 20.1.

The oil (0.134 g.), platinum oxide (0.1 g.) and ethanol (20 ml.) were shaken with hydrogen for 6 days when almost two moles of hydrogen was absorbed. The oily product consumed approximately 0.5 mole of periodic acid per mole substance.

Reduction of Dimethyl Jaconecate with Lithium Aluminum Hydride.—This experiment had been carried out previously[1b] using a less pure sample of dimethyl jaconecate. Dimethyl jaconecate (6.4 g.) in dry ether (100 ml.) was added dropwise to powdered lithium aluminum hydride (20 g.) in dry ether (100 ml.) and the solution was refluxed for 16 hours. To the well cooled mixture cold 5% aqueous sulfuric acid (200 ml.) was added dropwise, and then the mixture continuously extracted with ether. Removal of the ether gave an oil (4.2 g.), $[\alpha]^{18}D$ +25.4° (ethanol, *c* 2.28). Reaction with periodic acid showed that it consumed only 0.23 mole per mole substance after 48 hours.

Preparation of a Bis-*p*-toluenesulfonyl Derivative.—The reduction product of dimethyl jaconecate (0.43 g.) in pyridine (6 ml.) was treated with *p*-toluenesulfonyl chloride (2.2 g.) and heated on a boiling water-bath for 0.5 hr. The solution cooled to 0° was poured into ice-cold water (20 ml.) and extracted with ether (6 × 20 ml.). The ether extract after drying over sodium sulfate and removal of the ether left an oil (1.09 g.). Attempts to recrystallize it from benzene–light petroleum were unsuccessful. Chromatography on alumina using benzene–ether mixtures for elution gave a fraction (0.68 g.) which on recrystallization from benzene–light petroleum yielded colorless prisms, m.p. 109–110°, depressed to 97–99° on admixture with the tosyl derivative from reduced dimethyl *iso*jaconecate.

Anal. Calcd. for $C_{24}H_{32}O_8S_2$: C, 56.2: H, 6.3; S, 12.5; 1 act. H, 0.196. Found: C, 56.3; H, 6.4; S, 13.0; act. H, 0.23.

The **triacetate** was obtained as before, b.p. 151–152° at 0.5 mm., $[\alpha]^{21}D$ +12.2° (ethanol, *c* 2.29).

Anal. Calcd. for $C_{16}H_{26}O_7$: C, 58.2; H, 7.9; O, 33.9; CH_3CO, 39.1. Found: C, 58.3; H, 8.1; O, 33.2; CH_3CO, 37.8.

Reduction of the Dimethyl Ester of the Compound $C_9H_{14}O_6$[10] Obtained from the Nitric Acid Oxidation of Jaconecic Acid with Lithium Aluminum Hydride.—The dimethyl ester $C_{11}H_{18}O_6$[23] (1.65 g.) in dry ether (50 ml.) was added dropwise to powdered lithium aluminum hydride (6 g.) in dry ether (50 ml.) with shaking. The mixture was refluxed for 2 hr., allowed to stand at room temperature for 16 hr., and cautiously treated with dilute aqueous 10% sulfuric acid (100 ml.) with cooling. The mixture was continuously extracted with ether for 6 hr. to give an oil (0.92 g.). Quantitative tests[20] showed that this oil consumed 2.1 and 2.2 (two tests) moles of periodic acid per mole substance over a period of 20 hr. Steam distillation of the titration solution and collection of the distillate in an aqueous solution of dimedone gave colorless needles, m.p. 190°, undepressed on admixture with the dimedone derivative of formaldehyde. In another experiment the dinitrophenylhydrazone of formaldehyde was obtained.

Oxidation of *iso*Jaconecic Acid with Lead Tetraacetate.—*iso*Jaconecic acid (5.7 g.) dissolved in glacial acetic acid (50 ml.) and water (10 ml.) was heated on a boiling water-bath and lead tetraacetate (10 g.) added portionwise. When evolution of carbon dioxide had ceased, the solution was steam distilled and the distillate collected in a solution of 2,4-dinitrophenylhydrazine (1 g.) in 2 *N* hydrochloric acid (200 ml.). The precipitate (0.47 g.) when recrystallized from alcohol gave orange-yellow needles, m.p. 147–148°.

Anal. Calcd. for $C_8H_8O_4N_4$: C, 42.8; H, 3.6; N, 25.0. Found: C, 43.0; H, 3.7; N, 24.4.

This was evidently one of the dimorphic forms of acetaldehyde 2,4-dinitrophenylhydrazone.[24] The steam distilled solution was treated with *N* sulfuric acid (50 ml.), the lead sulfate filtered, and the filtrate continuously extracted with ether for 4 hr. A yellow viscous oil (4.17 g.) was obtained which showed two spots on paper at R_f 0.88 and 0.73. Chromatography on silica gel (500 g.) containing 0.5 *N* sulfuric acid (50 ml.) using chloroform–acetone mixtures for elution gave the fractions.

Fraction	R_f value	Wt., g.	Designation
1–28	..	0.15	Discarded
29–43	0.88	2.10	Pure oily fraction
44–69	..	Nil	.....
70–81	0.73	1.14	Pure *iso*jaconecic acid

Fraction 29–43 was a yellow oil having $[\alpha]^{17}D$ +48.2° (water c 1.20). It gave a positive iodoform test.

Preparation of a *p*-Bromophenacyl Derivative.—Fraction 29–43 (0.23 g.) on titration with 0.1843 N sodium hydroxide required 7.5 ml. This solution was evaporated to dryness, *p*-bromophenyl bromide (0.38 g.) added, and alcohol to effect solution, and the solution refluxed for 1 hr. It was taken to dryness, extracted with boiling acetone, filtered hot and the filtrate evaporated to dryness (0.27 g.). Recrystallization from alcohol gave small colorless needles radiating from a center, m.p. 107–108°.

Anal. Calcd. for $C_{17}H_{19}O_5Br$: C, 53.3; H, 5.0; Br, 20.8; 3 CH_3C, 11.8; mol. wt., 383. Found: C, 53.5; H, 5.1; Br, 21.2; CH_3C, 10.7; mol. wt. (Rast), 318.

The infrared spectrum of this compound shows carbonyl absorption at 1702, 1726 and 1743 cm.$^{-1}$ due to phenacyl carbonyl, unconjugated carbonyl and ester carbonyl groups, respectively.

Preparation of a 2,4-Dinitrophenylhydrazone.—Fraction 29–43 (0.18 g.) was treated with 2,4-dinitrophenylhydrazine (0.5 g.) in 2 *N* hydrochloric acid (100 ml.). An orange colored solid separated which when recrystallized from alcohol had m.p. 240°.

Anal. Calcd. for $C_{21}H_{22}O_{11}N_8$[13]: C, 44.8; H 3.9; N, 19.9. Found: C, 44.9, 45.0; H, 4.3, 4.4; N, 18.5, 18.8.

The **semicarbazone** of this compound was prepared from the oily material (0.155 g.), semicarbazide hydrochloride (0.093 g.), hydrated sodium acetate (0.113 g.) and 50% alcohol (1 ml.). The derivative when recrystallized from acetone–benzene gave colorless prisms, m.p. 165–166°.

Anal. Calcd. for $C_{10}H_{17}O_4N_3$: C, 49.4; H, 7.0; N, 17.3. Found: C, 49.8; H, 6.9; N, 16.7.

Oxidation of Jaconecic Acid with Lead Tetraacetate.—Jaconecic acid (5.0 g.) in glacial acetic acid (50 ml.) and water (10 ml.) was heated on a boiling water-bath and lead tetraacetate (10 g.) added portionwise, allowing the carbon dioxide evolution to abate before the next addition. The steam distillate was collected in a solution of 2,4-dinitrophenylhydrazine (1.0 g.) in 2 *N* hydrochloric acid (200 ml.). The yellow precipitate after drying (0.82 g.) was chromatographed on alumina (150 g.) using benzene–ether mixtures for elution. The main fraction (0.80 g.) when recrystallized from alcohol gave orange-yellow plates, m.p. 168°, undepressed when admixed with the dinitrophenylhydrazone of acetaldehyde.

Anal. Calcd. for $C_8H_8O_4N_4$: C, 42.8; H. 3.6; N, 25.0. Found: C, 43.0; H, 38; N, 24.5.

The steam-distilled residue was treated with *N* sulfuric acid (50 ml.) and the lead sulfate filtered. The filtrate on continuous extraction with ether gave a slightly yellow oil (1.45 g.) which showed by paper chromatography the presence of three spots at R_f 0.83, 0.70 and 0.49. The oily mixture from two experiments (2.8 g.) was chromatographed on a column of silica gel (280 g.) containing 0.5 *N* sulfuric acid (28 ml.) using chloroform–acetone mixtures for elution. The fractions as tabulated were obtained.

Compound $C_6H_{10}O_3$.—Fractions 23–27 on distillation gave a middle cut at 0.7 mm. as a colorless mobile liquid, b.p. 112–113° $[\alpha]^{17}D$ +43° (water, *c* 1.56).

(23) This compound itself is unreactive to periodic acid.

(24) Southwick, *et al.*, THIS JOURNAL, **78**, 10 (1956).

Fraction	R_f value	Wt., g.	Designation
1–22	....	0.14	Discarded
23–27	0.84	.83	Pure oily fraction
28–32	0.86, 0.70	.56	Mixture
33–42	0.68	.23	Pure oily fraction
43–111	0.49	.14	Unchanged jaconecic acid

Anal. Calcd. for $C_6H_{10}O_3 \cdot 0.5\ H_2O$: C, 51.8; H, 8.0; O, 40.2; CH_3C, 21.6; neut. equiv., 139. Found: C, 51.4; H, 7.8; O, 40.2; CH_3C, 20.1; neut. equiv., 138.

It gave a negative reaction with Schiff reagent, was not oxidized by alkaline permanganate at 0° for 64 hr., but gave a positive iodoform test. The infrared spectrum of this compound showed carbonyl absorption at 1716 cm.$^{-1}$.

Preparation of a *p*-Bromophenacyl Derivative.—The above oil (0.19 g.) required 7.75 ml. of 0.1843 *N* sodium hydroxide to the phenolphthalein end-point, and the solution was evaporated to dryness *in vacuo*. *p*-Bromophenacyl bromide (0.39 g.) and alcohol (5 ml.) was added and the solution was refluxed for 1 hr. The alcohol was distilled and the residue taken to dryness *in vacuo*. The residue was refluxed with acetone, filtered hot, and the filtrate concentrated to dryness to give a slightly yellow solid (0.18 g.) which on recrystallization from alcohol gave colorless needles, m.p. 90°.

Anal. Calcd. for $C_{14}H_{15}O_4Br$: C, 51.4; H, 4.6; Br, 24.4; 2 CH_3C, 9.2. Found: C, 51.7; H, 4.7; Br, 24.8; CH_3C, 9.9.

The infrared spectrum of this compound showed carbonyl absorption at 1698 and 1745 cm.$^{-1}$ due to phenacyl carbonyl and ester carbonyl groups, respectively.

The *p*-phenylphenacyl derivative was prepared in a similar manner and when recrystallized from acetone–light petroleum gave colorless plates, m.p. 59°.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.0; H, 6.2; mol. wt., 324. Found: C, 74.0; H, 6.2; mol. wt. (Rast), 354.

The semicarbazone was prepared from the oil (0.15 g.), semicarbazide hydrochloride (0.18 g.), hydrated sodium acetate (0.22 g.) and water (2 ml.). The crystals separated after about 0.5 hr. standing, and when recrystallized from alcohol gave colorless granules, m.p. 186–187°, $[\alpha]^{21}D$ +62° (ethanol, *c* 0.45).

Anal. Calcd. for $C_7H_{13}O_3N_3$: C, 44.9; H, 7.0; N, 22.5. Found: C, 45.2; H, 6.7; N, 22.0.

The 2,4-dinitrophenylhydrazone prepared from the oil (0.13 g.) and 2 *N* hydrochloric acid (26 ml.) was obtained as orange-yellow prisms from benzene, m.p. 152°.

Anal. Calcd. for $C_{12}H_{14}O_6N_4$: C, 46.4; H, 4.5. Found: C, 46.6; H, 4.5.

Compounds $C_7H_{10}O_4$.—Fractions 33–42 were an almost colorless oil, $[\alpha]^{18}D$ +13.0° (water, *c* 1.38).

Anal. Calcd. for $C_7H_{10}O_4 \cdot 5H_2O$: C, 50.3; H, 6.6; 2 CH_3C, 18.0. Found: C, 49.0; H, 7.0; CH_3C, 17.7.

It gave a negative Schiff test, but a positive iodoform test.

Preparation of a *p*-Bromophenacyl Derivative.—This derivative was prepared in a similar manner to that previously described, and was obtained as colorless plates from alcohol, m.p. 83–84°, which changed on standing to 108°.

Anal. Calcd. for $C_{15}H_{15}O_5Br$: C, 50.7; H, 4.3; Br, 22.5; 2 CH_3C, 8.5; mol. wt., 355. Found: C, 51.0; H, 4.3; Br, 22.9; CH_3C, 9.2; mol. wt. (Rast), 328.

Its infrared spectrum showed carbonyl absorption at 1702, 1751 and 1779 cm.$^{-1}$ due to phenacyl, ester and γ-lactone carbonyl, respectively.

α-Methyllevulinic Acid.—The method of Baker and Laufer[25] was used. To a cooled solution of sodium ethylate prepared from sodium (12.7 g.) and ethyl alcohol (200 ml.), ethylacetoacetate (71.8 g.) was added, and then gradually ethyl α-bromopropionate (100 g.). The solution was refluxed for 2 hr., filtered, the ethyl alcohol removed, and the residue distilled. Diethyl 1-acetyl-2-methylsuccinate (48 g.), b.p. 147° at 22 mm., was obtained. This compound (25 g.) was hydrolyzed and decarboxylated by refluxing with concentrated hydrochloric acid (100 ml.) for 2 hr. Continuous extraction of the solution with ether gave a mixed product (17.4 g.) showing two spots by paper chromatography, one at the same R_f value as the compound $C_6H_{10}O_3$ obtained from jaconecic acid. This was chromatographed on silica gel in the usual way and cleanly separated into 3-carboxy-2,4-dimethylbuten-3-olide (5.6 g.), m.p. 180°, and α-methyllevulinic (6.7 g.) which on distillation gave a colorless liquid, b.p. 117–118° at 1.4 mm. Its semicarbazone was obtained as colorless prisms from alcohol, m. p. 184–185°, depressed on admixture with the semicarbazone of the compound $C_6H_{10}O_3$ obtained from the reaction of jaconecic acid with lead tetraacetate.

Anal. Calcd. for $C_7H_{13}O_3N_3$: C, 44.9; H, 7.0; N, 22.4; Found: C, 45.0; H, 7.1; N, 21.8.

Its **2,4-dinitrophenylhydrazone** was obtained as yellow prisms from alcohol, m.p. 195°.

Anal. Calcd. for $C_{12}H_{14}O_6N_4$: C, 46.4; H, 4.5; N, 18.1. Found: C, 46.8; H, 4.6; N, 17.7.

The infrared spectrum of α-methyllevulinic acid showed a rather broad band in the carbonyl region at 1704 cm.$^{-1}$.

Resolution of α-Methyllevulinic Acid.—α-Methyllevulinic acid (1.11 g.), cinchonidine (2.52 g.) and water (15 ml.) were heated until a solution was obtained, the water was then completely removed under vacuum, and the residue recrystallized from acetone. Colorless needles radiating from a center were obtained (2.0 g.), m.p. 146–147°, $[\alpha]^{21.5}D$ −88° (ethanol, *c* 1.40). Another recrystallization from acetone did not change the rotation.

Anal. Calcd. for $C_{22}H_{32}O_4N_2$: C, 70.7; H, 7.6; N, 6.6. Found: C, 71.1; H, 7.6; N, 6.6.

The α-methyllevulinic acid (0.33 g.) was recovered by treatment with dilute 1:1 hydrochloric acid (20 ml.) and continuous extraction with ether. It had $[\alpha]^{12}D$ +22.6° (water, *c* 151). **The semicarbazone** of this optically active methyllevulinic acid had m.p. 178°, $[\alpha]^{21}D$ + 66.3° (ethanol, *c* 0.935). Recrystallization did not raise the melting point, and it was depressed when admixed with the semicarbazone from the natural product. **The *p*-bromophenacyl** derivative prepared in the usual way was obtained as colorless needles from alcohol, m.p. 74–75°.

Anal. Calcd. for $C_{14}H_{15}O_4Br$: C, 51.4; H, 4.6; Br, 24.4. Found: C, 51.4; H, 4.6; Br, 24.4.

β-Methyllevulinic Acid.—To sodium ethylate prepared from sodium (7.6 g.) and ethanol (130 ml.) and ethyl methylacetoacetate (47.4 g.), was added ethyl bromoacetate (55 g.) with shaking and cooling. After refluxing for 2 hr. the sodium bromide was filtered and the ethanol removed. The product on distillation gave diethyl 1-acetyl-1-methylsuccinate, b.p. 112–117° at 2 mm. (37.3 g.). This compound (20 g.) and concd. hydrochloric acid (70 ml.) were refluxed for 3 hr. and continuously extracted with ether. A yellow oil (12.3 g.) which on distillation had b.p. 120–123° at 2 mm. was obtained. It gave a spot by paper chromatography at the same R_f value as that obtained with the natural compound. **Its semicarbazone** gave colorless granules from alcohol, m.p. 182–183°, undepressed on admixture with the semicarbazone of the natural product.

Anal. Calcd. for $C_7H_{13}O_3N_3$: C, 44.9; H, 7.0; N, 22.4. Found: C, 44.9; H, 6.8; N, 22.3.

The 2,4-dinitrophenylhydrazone crystallized from alcohol as orange-yellow prisms, m.p. 148–149°, undepressed when admixed with the same derivative of the natural product.

Anal. Calcd. for $C_{12}H_{14}O_6N_4$: C, 46.4; H, 5.5; O, 29.9. Found: C, 46.2; H, 4.6; O, 29.7.

Preparation of β-Methyl-γ-carboxy-γ-valerolactone.—β-Methyllevulinic acid (4.05 g.) was treated with liquid hydrogen cyanide (3.9 g.) and a few crystals of sodium cyanide, and allowed to stand at room temperature for 70 hr. The colorless solution was then heated on a boiling water-bath under vacuum to remove the excess hydrogen cyanide. The residue (4.15 g.) was refluxed with concd. hydrochloric acid (25 ml.) for 4 hr., cooled and continuously extracted with ether for 8 hr. A mobile oil (4.0 g.) was obtained which by paper chromatography showed three spots at R_f 0.86, 0.73 and 0.66, corresponding to β-methyllevulinic acid, an unknown compound and the sought carboxylactone, respectively. These were separated on silica gel in the usual manner to give unchanged β-methyllevulinic acid (2.1 g.), a mixture of β-methyllevulinic acid, the new compound and the carboxylactone, and the pure carboxylactone (0.34 g.).

Resolution of β-Methyl-γ-carboxy-γ-valerolactone.—The oily product from the last experiment (0.34 g.), and cinchonidine (0.55 g.) was dissolved in acetone (10 ml.) at the boiling point. On cooling, colorless needles (0.33 g.), m.p. 201°, were obtained.

(25) J. W. Baker and A. S. Laufer, *J. Chem. Soc.*, 1342 (1937).

Anal. Calcd. for $C_{26}H_{34}O_6N_2 \cdot 0.5H_2O$: C, 67.6; H, 7.2; N, 6.1. Found: C, 67.5; H, 7.7; N, 5.9.

This salt was dissolved in dilute (1:4) hydrochloric acid (20 ml.) and continuously extracted with ether for 8 hr. Removal of the ether gave a colorless oil (0.096 g.) which was dried over solid sodium hydroxide *in vacuo* for 16 hr., $[\alpha]^{16.5}D$ +14.5° (water, *c* 1.93).

Anal. Calcd. for $C_7H_{10}O_4$: equiv., 158. Found: neut. equiv., 162.

The *p*-bromophenacyl derivative prepared in the usual way after recrystallization once from benzene-light petroleum and twice from alcohol gave colorless needles radiating from a center, m.p. 105–106°, undepressed when admixed with the derivative from the natural carboxylactone.

Anal. Calcd. for $C_{15}H_{15}O_5Br$: C, 50.7; H, 4.3; Br, 22.5. Found: C, 50.7; H, 4.4; Br, 22.8.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Dihydroconessine[1]

BY E. J. COREY[2a] AND W. R. HERTLER[2b]

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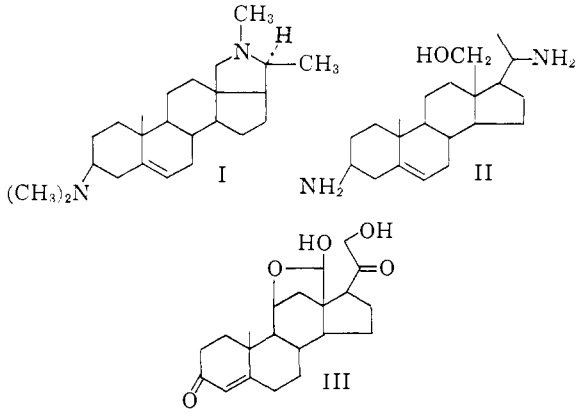
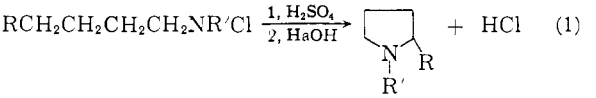
Dihydroconessine has been synthesized from 3β-acetoxybisnorcholenic acid. Introduction of the amino function at C_{18} was effected by the free radical chain decomposition of 3β-dimethylamino-20α-methylchloroaminoallopregnane (Hofmann–Löffler–Freytag reaction), which offers a general method for the selective functionalization of the C_{18} angular methyl group of steroids.

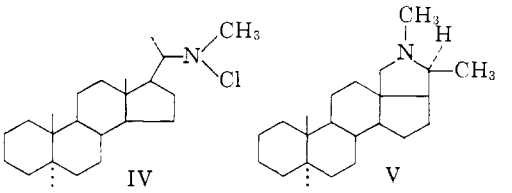
The structural feature which imparts special interest to the *Holarrhena* steroid-alkaloid conessine (I) is the presence of functionality at the C_{18} angular methyl group, a feature shared with the related alkaloid holarrhimine[3] (II) and the important steroid hormone aldosterone (III). The synthesis of such structures poses a unique problem, functionalization of an angular methyl group which cannot be activated by standard procedures, for which the extensive steroid literature provides little assistance.



Attempts to synthesize aldosterone from steroid precursors lacking substitution at C_{18} by cleavage and reclosure of ring D[4] have led to products lacking the appropriate stereochemistry, and previous to this work the preparation of C_{18}-substituted steroids with normal configurations has been limited to arduous total synthesis as exemplified by the recent work on aldosterone.[5] A different approach to the problem appeared to be the use of reactions capable of transforming unactivated angular methyl groups selectively because of favorable proximity, and in this connection the free-radical chain decomposition of a C_{20}-N-chloroamine (Hofmann–Löffler–Freytag reaction)[6] seemed especially attractive. This reaction, which generally results in the transformation of an aliphatic chloroamine to a pyrrolidine[7] as shown in equation 1, should in the case of a steroidal N-chloro-20-amine result in the formation of a C_{18}–C_{20} imine bridge as is found in conessine. This paper describes the synthesis of dihydroconessine (XVII) using the Hofmann–Löffler–Freytag reaction as the key step.



Jeger, Arigoni and co-workers[8] in a preliminary communication have described a similar synthesis of the previously unknown conanine (V) from 20α-methylchloroaminoallopregnane (IV). Jeger[9] also



(1) Described in a preliminary communication, THIS JOURNAL, **80**, 2903 (1958).

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(3) See L. Labler, V. Cerny and F. Sorm, *Coll. Czech. Chem. Comm.*, **20**, 1484 (1955), for the elegant interrelation of conessine and holarrhimine.

(4) D. H. R. Barton, A. Da S. Campos-Neves and A. I. Scott, *J. Chem. Soc.*, 2698 (1957).

(5) (a) J. Schmidlin, G. Anner, J. R. Billeter and A. Wettstein, *Experientia*, **11**, 365 (1955); (b) E. Vischer, J. Schmidlin and A. Wettstein, *ibid.*, **12**, 50 (1956); W. S. Johnson, J. C. Collins, R. Pappo and M. B. Rubin, THIS JOURNAL, **80**, 2585 (1958).

(6) (a) A. W. Hofmann, *Ber.*, **16**, 558 (1883); (b) K. Löffler and C. Freytag, *ibid.*, **42**, 3427 (1909).

(7) See, however, S. Wawzonek and P. J. Thelen, THIS JOURNAL, **72**, 2118 (1950), and S. Wawzonek, M. F. Nelson and P. J. Thelen, *ibid.*, **73**, 2806 (1951).

(8) P. Buchschacher, J. Kalvoda, D. Arigoni and O. Jeger, *ibid.*, **80**, 2905 (1958).

(9) F. Greuter, J. Kalvoda and O. Jeger, *Proc. Chem. Soc.*, 349 (1958).