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

Senecio Alkaloids: α-Longilobine; Structure of α-Longinecic Acid

BY ROGER ADAMS, T. R. GOVINDACHARI, J. H. LOOKER AND J. D. EDWARDS, JR.

α-Longinecic acid is dibasic, contains two carbon–carbon double bonds as determined by hydrogenation and a hydroxyl group as shown by the infrared spectrum. The yellow color with ferric chloride indicates the presence of an α-hydroxy acid. When treated with lead tetraacetate, it is converted to an optically inactive methyl ketone with loss of carbon dioxide. Ozonization gives acetaldehyde but no formaldehyde. Tetrahydro-α-longinecic acid is converted with lead tetraacetate to a methyl ketone which by the action of sodium hypobromite is degraded to a dibasic acid. This acid was characterized as α-methyl-α′-ethylglutaric acid by conversion to its imide. Infrared and ultraviolet absorption data confirm the deductions concerning the relative positions of the two carbon–carbon double bonds. The structure of α-longinecic acid may be designated as 2-hydroxy-3-methylhepta-3,5-diene-2,5-dicarboxylic acid.

By the alkaline hydrolysis of the alkaloid α-longilobine, retronecine and an acid of formula $C_{10}H_{14}O_5$ were obtained.[1] The structure of this acid, designated as α-longinecic acid, is the subject of this report. The acid was shown to be dibasic by direct titration. It readily formed a dimethyl ester with diazomethane. The character of the fifth oxygen atom was difficult to establish by chemical means. Neither α-longinecic acid nor its dimethyl ester gave positive tests for a keto carbonyl or hydroxyl group. On the other hand, both the acid and ester showed strong absorption in the infrared at 3452 and 3497 cm.$^{-1}$, respectively, which are characteristic of a hydroxyl group. Because of its chemical non-reactivity, the hydroxyl was assumed to be tertiary. The distinct yellow coloration of α-longinecic acid with ferric chloride is evidence that it is an α-hydroxy acid.

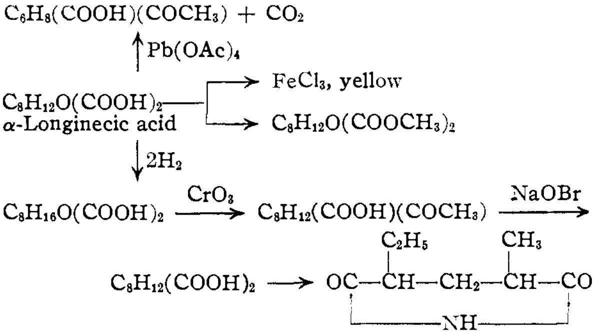
On reduction with hydrogen in the presence of platinum oxide, one mole of hydrogen was absorbed rapidly and the second mole of hydrogen at a considerably lower rate. The sirupy tetrahydro-α-longinecic acid so formed was characterized by preparation of the crystalline bis-*p*-bromophenacyl ester. The presence of two carbon–carbon double bonds was thus established.

The infrared absorption spectrum of dimethyl α-longinecate showed two absorptions in the carbonyl region at 1736 and 1717 cm.$^{-1}$ corresponding to a normal and a conjugated ester function respectively. This would rule out the possibility of both carboxyls being in conjugation with one of the carbon–carbon double bonds.

α-Longinecic acid reacted with a mole of lead tetraacetate yielding an oily carbonyl compound which gave negative reactions for an aldehyde function and was, therefore, presumed to be a ketone. The ketone was characterized by preparation of the crystalline 2,4-dinitrophenylhydrazone and thiosemicarbazone. It was significant that the pure thiosemicarbazone did not show any optical activity in contrast to the acid from which it was derived. From the analysis of the derivatives, it was evident that the α-longinecic acid had reacted with lead tetraacetate with loss of one carbon atom as carbon dioxide forming a ketone of the formula $C_9H_{12}O_3$, a behavior characteristic of a tertiary α-hydroxy acid. The carbonyl compound $C_9H_{12}O_3$ gave a positive iodoform reaction, indicating that it was a methyl ketone. On treating the carbonyl compound with a large excess of sodium hypobromite, there was an immediate separation of carbon tetrabromide and some bromoform. The other product of the reaction was an oily acid which should be dibasic with the formula $C_8H_{10}O_4$. All attempts to obtain it in a crystalline condition were unsuccessful. Moreover, efforts to prepare crystalline derivatives with a variety of reagents failed.

On oxidation of tetrahydro-α-longinecic acid with chromic acid, a keto acid, with the formula $C_9H_{16}O_3$, was formed and characterized through the 2,4-dinitrophenylhydrazone of its methyl ester. The keto acid on treatment with excess sodium hypobromite formed a mixture of carbon tetrabromide and bromoform and a solid acid, difficult to purify, which was presumably a dibasic acid of formula $C_8H_{14}O_4$. Conversion of the dibasic acid to the anhydride was accomplished by heating with acetyl chloride. The anhydride when fused with urea yielded α-methyl-α′-ethylglutarimide as shown by comparison with an authentic sample. α-Methyl-α′-ethylglutarimide was synthesized by Rydon[2] who separated the sodium bicarbonate insoluble stereoisomer for which he reported a melting point of 116°. Repeated crystallization of a sample of imide prepared in like manner melted at 149.5–151.5° and indications were that the true melting point of pure product might be even higher. The melting points of samples from the natural product melting at 118–120° and 125.5–126.5° admixed with imide of the same melting points showed no depression. A mixture of the imide from the natural source, m.p. 118–120°, and the synthetic imide, m.p. 149.5–151.5° melted at 139–142°. In spite of the fact that all of these samples must contain at least traces of stereoisomeric impurities, the infrared absorption spectra of variously melting samples of the synthetic imide

CHART I



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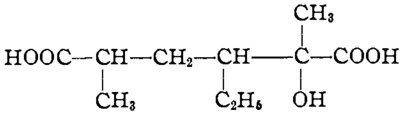
[1] R. Adams and T. R. Govindachari, THIS JOURNAL, **71**, 1180 (1949).

[2] H. N. Rydon, *J. Chem. Soc.*, 1444 (1936). See also P. L. Pickard and H. L. Lochte, THIS JOURNAL, **69**, 14 (1947).

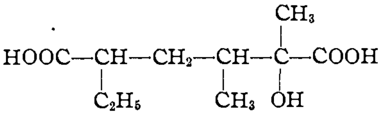
were essentially identical with each other and the same as that of the imide obtained from the alkaloid.

The above degradations are summarized in Chart I.

From these data tetrahydro-α-longinecic acid appears to have one of two structures, of which the second is the more likely because it coincides with possible formation from two isoprene units.

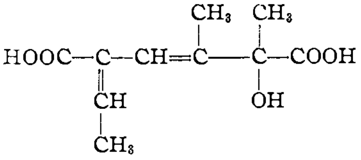


$$\mathrm{HOOC{-}\underset{CH_3}{CH}{-}CH_2{-}\underset{C_2H_5}{CH}{-}\overset{CH_3}{\underset{OH}{C}}{-}COOH}$$



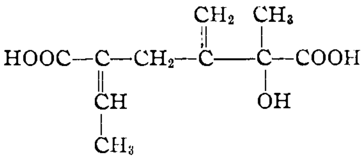
$$\mathrm{HOOC{-}\underset{C_2H_5}{CH}{-}CH_2{-}\underset{CH_3}{CH}{-}\overset{CH_3}{\underset{OH}{C}}{-}COOH}$$

α-Longinecic acid was subjected to treatment with ozone; the ozonide was decomposed with water and zinc dust and the resulting mixture was steam distilled. From the distillate a 32% yield of the theoretical amount of the dimedone derivative of acetaldehyde was isolated. Acetaldehyde was also isolated as its 2,4-dinitrophenylhydrazone. With this information and with knowledge that the tetrahydro-α-longinecic acid is degraded to α-methyl-α′-ethylglutarimide, two double bonds may be introduced into formulas I and II in only four ways (III–VI).



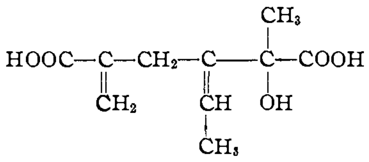
$$\mathrm{HOOC{-}\underset{\underset{CH_3}{|}}{\underset{CH}{\overset{\|}{C}}}{-}CH{=}\overset{CH_3}{C}{-}\overset{CH_3}{\underset{OH}{C}}{-}COOH}$$

III



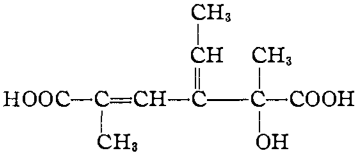
$$\mathrm{HOOC{-}\underset{\underset{CH_3}{|}}{\underset{CH}{\overset{\|}{C}}}{-}CH_2{-}\overset{CH_2}{\overset{\|}{C}}{-}\overset{CH_3}{\underset{OH}{C}}{-}COOH}$$

IV



$$\mathrm{HOOC{-}\underset{CH_2}{\underset{\|}{C}}{-}CH_2{-}\underset{\underset{CH_3}{|}}{\underset{CH}{\underset{\|}{C}}}{-}\overset{CH_3}{\underset{OH}{C}}{-}COOH}$$

V



$$\mathrm{HOOC{-}\underset{CH_3}{C}{=}CH{-}\overset{\overset{CH_3}{|}}{\overset{CH}{\overset{\|}{C}}}{-}\overset{CH_3}{\underset{OH}{C}}{-}COOH}$$

VI

In several repetitions of the ozonization experiments under different conditions, only traces of the dimedone derivative of formaldehyde could be isolated and these were considered of no significance.[3] When, under similar conditions, mixtures of acetaldehyde and formaldehyde in quantities equal to those expected in the degradation reactions were studied, no difficulty was encountered in obtaining and separating the dimedone derivative of formaldehyde. It was concluded, therefore, that a terminal methylene group was not present which excludes formulas IV and V. Moreover, only III and VI would explain the presence of more than two C–CH_3 groups (found 2.2). An attempt to demonstrate the presence of the diene conjugated system in III and VI by reaction of the dimethyl ester of α-longinecic acid with maleic anhydride was unsuccessful but, since many instances are known in which polysubstituted dienes do not undergo the Diels–Alder additions, this experiment failed to give information. Neither was it possible to obtain by ozonization fragments which would aid in the constitution studies.

Absorption spectra strongly supported the conclusion that no terminal methylene groups were present and that structure III represents the proper orientation of the carbon–carbon double bonds. Infrared analysis of α-longinecic acid showed no intense band at or near 890 cm.$^{-1}$ which is usually found in compounds containing the group $RR'C{=}CH_2$ and which is due to the out-of-plane bending vibration of the ethylenic hydrogens. The spectra of compounds containing the structure $RR'C{=}CHR$ do not show a strong band due to the vibration and generally have a broad, relatively weak band in the neighborhood of 835 cm.$^{-1}$. The spectrum of α-longinecic acid shows two bands in this region, at 824 and 849 cm.$^{-1}$.

The ultraviolet absorption spectrum of α-longinecic acid (solvent, 95% ethanol) with $\lambda_{\max}$ 214 mμ and $\epsilon_{\max}$, 8130 is characteristic of an α,β-unsaturated acid. The position of the maximum excludes the presence of a 1,3-diene system in complete conjugation with a carboxyl group as in sorbic acid, since it was shown that in going from crotonic to sorbic acid a shift of the maximum from approximately 210 to 260 mμ occurs.[4,5] This would eliminate structure VI and leave structure III as that which explains all the facts most satisfactorily.

The carbon skeleton of α-longinecic acid thus corresponds to that found in senecic and isatinecic (β-longinecic) acids.[6] The prediction that these three acids and riddellic acid, all of which are present as esters of retronecine in *Senecio* longilobus, would have the same carbon skeleton[7] is thus strongly indicated. The study of the structure of riddellic acid is not yet completed.

The authors are indebted to Miss Elizabeth Petersen of this Laboratory and to Drs. R. E. Kitson and C. F. Hammer of the Polychemicals Division of

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[3] C. R. Clemo and J. M. Macdonald, *J. Chem. Soc.*, 1294 (1935).

[4] E. A. Braude, *Ann. Repts. on Progress Chem.* (*Chem. Soc. London*), **42**, 114 (1945).

[5] Braude[4] cites references which report that the ultraviolet absorption spectrum of crotonic acid (solvent, water) has a maximum at 200 mμ and sorbic acid (solvent, *n*-hexane) at 261 mμ. For purposes of comparison, the spectra were all determined in 95% ethanol as solvent; crotonic acid exhibited a maximum at 211–213 mμ, sorbic acid at 256–257 mμ and α-longinecic acid at 214 mμ. The maximum of crotonic acid shifted from 1–3 mm. depending on the concentration. Similar results have been observed in certain crotonic acid derivatives [H. E. Ungnade and I. Ortega, THIS JOURNAL, **73**, 1564 (1951)].

[6] S. M. H. Christie, M. Kropman, L. Novelle and F. L. Warren, *J. Chem. Soc.*, 1703 (1949); M. Kropman and F. L. Warren, *ibid.*, 2852 (1949); F. L. Warren, M. Kropman, R. Adams, T. R. Govindachari and J. H. Looker, THIS JOURNAL, **72**, 1421 (1950).

[7] R. Adams and T. R. Govindachari, *ibid.*, **71**, 1956 (1949).

the E. I. du Pont de Nemours and Company for determination and interpretation of the infrared spectra and to Miss Emily Davis for the microanalytical work.

Experimental

Dimethyl α-Longinecate.—This was prepared by the addition of an ethereal solution of diazomethane to an ethereal solution of α-longinecic acid. The product was purified by distillation *in vacuo* and boiled at 110° (0.75 mm.); n^{20}D 1.4785.

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 59.49; H, 7.49. Found: C, 59.66; H, 7.76.

Tetrahydro-α-longinecic Acid.—A suspension of 50 mg. of platinum oxide catalyst in 5 ml. of ethanol was shaken with hydrogen until the absorption was complete. A solution of 300 mg. of α-longinecic acid in 10 ml. of ethanol was then added and the shaking with hydrogen continued. The first mole of hydrogen was absorbed in less than five minutes after which the shaking had to be continued for a further two hours for the complete absorption of the second mole of hydrogen. No more hydrogen was absorbed. The catalyst was filtered off and the solvent was removed *in vacuo*. The yield of tetrahydro-α-longinecic acid which was a colorless gum was 300 mg.

The bis-*p*-bromophenacyl ester was prepared by the customary procedure and purified by two recrystallizations from ethanol, m.p. 127°.

Anal. Calcd. for $C_{26}H_{28}Br_2O_7$: C, 51.00; H, 4.61. Found: C, 50.96; H, 4.64.

Action of Lead Tetraacetate on α-Longinecic Acid. Formation of the Ketonic Acid, $C_9H_{12}O_3$.—A solution of 500 mg. of α-longinecic acid in 75 ml. of anhydrous benzene at the boiling temperature was allowed to cool to 40° and treated with 1.15 g. of pure lead tetraacetate in two portions. The mixture was vigorously shaken and the flocculent white precipitate which first separated shrank to a small bulk. The mixture was then warmed at 50° for one hour and the slight excess of lead tetraacetate was destroyed by the addition of a few drops of ethylene glycol. The benzene was then removed by distillation *in vacuo* at 45–50° and the residue was taken up in 30 ml. of warm water. The filtered aqueous solution was treated with sufficient 5% sulfuric acid to precipitate the lead as sulfate which was then removed by centrifugation. The clear aqueous solution was saturated with sodium sulfate and extracted continuously with ether for 15 hours. The ether extract was dried over anhydrous sodium sulfate, filtered and the ether removed. The yield of the product, which was a light brown oil, was 350 mg.

2,4-Dinitrophenylhydrazone of the Ketonic Acid, $C_9H_{12}O_3$.—This was prepared in methanol solution with the addition of a few drops of concentrated hydrochloric acid. The 2,4-dinitrophenylhydrazone was purified by recrystallization from methanol and consisted of yellow crystals with a slight orange cast, m.p. 184° (cor.).

Anal. Calcd. for $C_{15}H_{16}N_4O_6$: C, 51.72; H, 4.63; N, 16.09. Found: C, 51.85; H, 4.82; N, 15.79.

Thiosemicarbazone of the Ketonic Acid, $C_9H_{12}O_3$.—A solution of 150 mg. of the ketonic acid in 2 ml. of ethanol was treated with 80 mg. of thiosemicarbazide in 1 ml. of hot water and refluxed for two hours. The solution was then concentrated to 1 ml. and cooled. An oil separated which solidified on rubbing. The product was filtered, washed with a small volume of water and purified by two recrystallizations from 10% ethanol; colorless crystals, m.p. 163–164° (cor.). This compound showed no optical rotation.

Anal. Calcd. for $C_{10}H_{15}N_3O_2S$: C, 49.77; H, 6.27; N, 17.42. Found: C, 49.71; H, 6.31; N, 17.10.

Action of Sodium Hypobromite on the Ketonic Acid, $C_9H_{12}O_3$.—A solution of 500 mg. of the oily ketonic acid in 15 ml. of 10% aqueous sodium hydroxide was treated with a solution of sodium hypobromite prepared by the addition of 1 ml. of bromine to a solution of 3 g. of sodium hydroxide in 30 ml. of water at −5°. The mixture was vigorously stirred for four hours during which it was allowed to warm to room temperature and the reaction was completed by warming at 50° for 10 minutes. The carbon tetrabromide which had separated was filtered off (m.p. 94°) and the filtrate was repeatedly extracted with ether. The aqueous solution was saturated with sulfur dioxide, then saturated with sodium sulfate and continuously extracted with ether for 24 hours. The ether extract was dried over anhydrous sodium sulfate, filtered and the ether removed. The residual oil after drying to constant weight weighed approximately 300 mg. It was not obtained in a solid state. Attempts to obtain crystalline derivatives of the product, such as the benzyl isothiuronium salt, the amide, the *p*-toluidide, the phenyl hydrazide, were all unsuccessful.

Oxidation of Tetrahydro-α-longinecic Acid with Chromic Oxide.—A solution of 300 mg. of tetrahydro-α-longinecic acid in 5 ml. of sulfuric acid was treated with a solution of 100 mg. of chromic anhydride in 4 ml. of 5% sulfuric acid, in 1-ml. portions, shaking and warming gently on a water-bath. After the addition was complete, the solution was heated for a further hour at 70–80°, cooled and repeatedly extracted with ether. The ether extract was dried over anhydrous sodium sulfate, filtered and the ether removed. The product was a light brown oil weighing 230 mg.

A solution of 75 mg. of this oil in 1 ml. of methanol was treated with a clear solution of 70 mg. of 2,4-dinitrophenylhydrazine in 15 ml. of methanol, one drop of concentrated hydrochloric acid was added and the mixture refluxed for three hours. The solution was then allowed to evaporate spontaneously in an open beaker. When most of the methanol had evaporated yellow crystals separated. The liquid was removed by decantation and the residue washed with a few ml. of methanol. The residue was first recrystallized from methanol and then from ligroin. Even then, the crystals did not melt sharply and had to be purified by passage through an alumina column in benzene solution. The material eluted from the column was purified by two further crystallizations from petroleum ether (b.p. 80–110°) and melted at 108°. The product is the 2,4-dinitrophenylhydrazone of the methyl ester of the ketonic acid, $C_9H_{16}O_3$. Esterification and hydrazone formation took place simultaneously.

Anal. Calcd. for $C_{16}H_{22}N_4O_6$: C, 52.45; H, 6.05; N, 15.29. Found: C, 52.35; H, 6.09; N, 15.36.

Action of Sodium Hypobromite on the Ketonic Acid, $C_9H_{16}O_3$.—A solution of 185 mg. of the ketonic acid in 4 ml. of water and 0.4 g. of sodium hydroxide was treated with 15 ml. of a solution of sodium hypobromite. This was prepared by adding 0.8 ml. of bromine to a solution of 3.2 g. of sodium hydroxide in 30 ml. of water at −5°. The mixture was vigorously shaken for two hours, warmed briefly to 50°, cooled and extracted with ether. The clear aqueous solution was saturated with sulfur dioxide, then with sodium sulfate and extracted continuously with ether for 15 hours. The ether extract was dried over anhydrous sodium sulfate, filtered and the ether removed. The yield of crude material which was a slightly sticky crystalline solid was 160 mg. About 0.5 g. of crude dibasic acid was treated with acetyl chloride and then with urea (preferably with an air condenser) in the same manner as described by Rydon.[2] After obtaining the imide, it was treated with sodium bicarbonate and the mixture extracted with ether. The crystalline product obtained from the ether was crystallized four times from petroleum ether (b.p. 80–110°), m.p. 125.5–126.5°. A melting point of the mixture with the synthetic imide, m.p. 126–127°, showed no depression. Infrared absorption spectra of these products were identical.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44. Found: C, 61.96; H, 8.52.

α-Methyl-α′-ethylglutarimide.—Ethyl α-bromoisobutyrate was condensed with diethyl ethylmalonate as described by Rydon.[2] On fusing α-methyl-α′-ethylglutaric acid with urea at 160° it was found that unless an air condenser was attached, the major portion of the α-methyl-α′-ethylglutarimide was lost by sublimation. From 19 g. of glutaric acid, 6.5 g. of sodium bicarbonate insoluble material was obtained, which after one recrystallization from petroleum ether (b.p. 80–100°), melted at 116–118°. Extraction of the sodium bicarbonate solution afforded 6 g. more of the glutarimide. After 24 recrystallizations of the sodium bicarbonate insoluble imide from petroleum ether (b.p. 80–100°) the material melted at 149.5–151.5° with shrinkage at 142°. Conversion of the glutaric acid to the imide by the procedure of Pickard and Lochte[2] gave only a 40% yield. Infrared absorption spectra of six different samples in the m.p. range 116–150° showed very minor differences, generally only in intensity of absorption. The absorption was identical with that observed for the imide obtained from the alkaloid.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.90; H, 8.41; N, 9.09.

Ozonolysis of α-Longinecic Acid.—A current of ozone was passed into a cooled solution of 500 mg. of α-longinecic acid in 20 ml. of pure dry ethyl acetate at the rate of 0.00028 mole per minute for 20 minutes. The solvent was then removed completely *in vacuo* at 25°. A mixture of zinc dust and water was added and subjected to steam distillation. The distillate was worked up in the manner described by Vorländer and Yoe.[8] A 32% yield of the acetaldehyde derivative of dimedone and a 2–3% yield of formaldehyde dimedone resulted. Both were identified by melting point determinations when mixed with authentic samples. Several experiments gave similar results.

By treatment of the distillate with 2,4-dinitrophenylhydrazine in hydrochloric acid and water, the acetaldehyde 2,4-dinitrophenylhydrazine was obtained in its two forms, both purified from ethanol, m.p. 160 and 150°.

Dimethyl α-longinecate did not react with maleic anhydride when refluxed in benzene or without solvent.

In an ozonization of the methyl ketone derived from the treatment of α-longinecic acid with lead tetraacetate, no biacetyl could be isolated as the *o*-phenylenediamine derivative.

URBANA, ILLINOIS

RECEIVED JUNE 4, 1951

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[8] D. Vorländer, C. Ihle and H. Volkholz, *Z. anal. Chem.*, **77**, 321 (1929); J. H. Yoe and L. C. Reid, *Ind. Eng. Chem. Anal. Ed.*, **13**, 238 (1941).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND COMPANY]

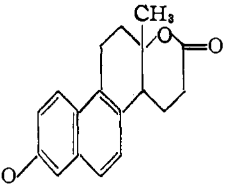
The Oxidation of Isoequilenin Acetate with Peracetic Acid[1]

BY GEORGE M. PICHA

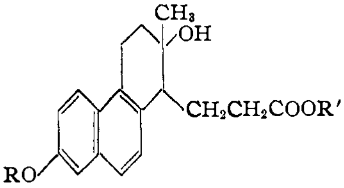
The peracetic acid oxidation product of isoequilenin acetate has been prepared and characterized, along with the parent phenol, the propionate, the methyl ether and certain other derivatives. The oxidation product has been formulated as a lactone stereoisomeric with bisdehydroestrololactone acetate. Some comparisons have been made between the compounds described in this paper and those similarly obtained from natural equilenin.

The peroxide oxidations of a number of 17-ketosteroids, including estrone,[2] estrone acetate,[3] equilenin acetate[4] and the acetates of androsterone, epiandrosterone and dehydroepiandrosterone dibromide,[5] have been reported by various groups. These oxidations have been shown to proceed with the conversion of ring D into a six-membered lactone ring.[6] Other ring D lactones, prepared by methods of partial synthesis, have previously been described.[7]

An investigation has now been made of the peracetic acid oxidation of isoequilenin acetate, which differs from the naturally-occurring 17-ketosteroids in having a *cis* juncture between rings C and D. The initial oxidation product (I)[8] was converted by saponification and relactonization into isobisdehydroestrololactone (II).[9] Like other steroidal hydroxy lactones of analogous structure, this compound is characterized by its relatively high melting point and its slight solubility in most organic solvents. The 3-hydroxyl group can be readily converted into esters and ethers by customary procedures.



I, R = CH_3CO-
II, R = H–
III, R = CH_3CH_2CO-
IV, R = CH_3-



V, R = H–, R′ = H–
VI, R = CH_3-, R′ = Na–
VII, R = CH_3-, R′ = Ag–
VIII, R = CH_3-, R′ = CH_3-

In the case of compounds I–IV formulation as lactones, rather than as unsaturated acids of identical elemental composition, is based in part on analogy with other 17-ketosteroids, as well as on the fact that I, III and IV dissolve in dilute sodium hydroxide only after a heating period of several hours, and are similarly resistant to solution in aqueous ammonia. In a test for unsaturation, compound I did not decolorize neutral permanganate.

In basic solution the lactone ring is opened with the formation of a salt of the resulting carboxylic acid, isobisdehydroestrolic acid (V). While the free acid correspondingly related to natural equilenin is sufficiently stable to be isolated and re-

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[1] Presented before the Division of Organic Chemistry at the 119th Meeting of the American Chemical Society, Cleveland, Ohio, April, 1951.

[2] W. W. Westerfeld, *J. Biol. Chem.*, **143**, 177 (1942).

[3] R. P. Jacobsen, *ibid.*, **171**, 61 (1947).

[4] R. P. Jacobsen, G. M. Picha and H. Levy, *ibid.*, **171**, 81 (1947).

[5] H. Levy and R. P. Jacobsen, *ibid.*, **171**, 71 (1947).

[6] For a more generalized consideration of the reactions of ketones with peracids, see W. von E. Doering and L. Speers, THIS JOURNAL, **72**, 5515 (1950).

[7] These include (a) E. B. Hershberg, E. Schwenk and E. Stahl, *Arch. Biochem.*, **19**, 300 (1948); (b) M. N. Huffman, M. H. Lott and J. Ashmore, THIS JOURNAL, **70**, 4268 (1948); (c) C. von Seemann and G. A. Grant, *ibid.*, **72**, 4073 (1950).

[8] The compounds described in this paper are represented as the products of oxidative attack on the 13–17 bond, in accordance with what the author considers to be the preponderance of evidence accumulated from various sources. It is recognized that an opposing school of thought holds that the lactones formed by peroxide oxidation of 17-ketosteroids result from attack on the 16–17 bond, with the (potential) carboxyl group then being attached to C-13. See, for example, M. Keller and J. Weiss, *J. Chem. Soc.*, 1247 (1951). The infrared absorption spectra studies of R. N. Jones, P. Humphries and K. Dobriner, THIS JOURNAL, **72**, 956 (1950), might be regarded as lending support to this view, but the concurring formulation given by L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Third Edition, Reinhold Publishing Corp., New York, N. Y., 1949, p. 354, is believed to be a misprint.

Evidence for the 13–17 attack may be found in: (1) The analogies and theoretical considerations discussed by Doering and Speers, reference 6. (2) The lack of identity of either of the lactones of von Seemann and Grant, reference 7, with the dehydroisoandrololactone of Levy and Jacobsen, reference 5. (3) The lack of identity of the methyl ether triols prepared by lithium aluminum hydride reductions of marrianolic acid methyl ether and estrololactone methyl ether, J. Jacques, A. Horeau and R. Courrier, *Compt. rend.*, **229**, 321 (1949). This argument and the preceding one require the reasonable assumption that the configurations remain intact. It is understood that there exists additional, unpublished information supporting the 13–17 attack.

[9] System of nomenclature of Jacobsen and co-workers.