was identical with that observed for the imide obtained from the alkaloid.

Anal. Calcd. for $C_8H_{13}NO_3$: 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.

(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).

URBANA, ILLINOIS RECEIVED JUNE 4, 1951

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

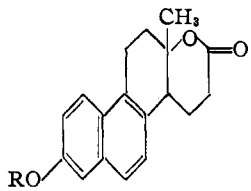
The Oxidation of Isoequilenin Acetate with Peracetic Acid[1]

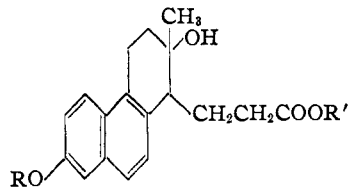
BY GEORGE M. PICHA

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-

(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.

crystallized,[4] attempts to prepare a free carboxylic acid in this series gave only lactones. A referee has kindly pointed out that the greater ease of lactonization in the iso as compared with the natural stereochemical series is in conformity with the speed of ring D lactam formation observed by W. E. Bachmann and F. Ramirez, THIS JOURNAL, 72, 2527 (1950), in a series of cyclization experiments carried out on aminoesters related to desoxyequilenin and desoxyisoequilenin.

Although strictly quantitative comparisons are lacking, studies of the rate of oxidative attack on isoequilenin acetate indicate that the unnatural *cis* configuration at the C/D juncture decreases the susceptibility to oxidation. Thus, using a large excess of peracetic acid and reaction conditions approximately equivalent (100 hours, 10°) to those which cause almost complete oxidation of estrone acetate[3] and equilenin acetate,[4] an appreciable amount of unreacted isoequilenin can be recovered by taking advantage of the difference in acidity between a phenol and a carboxylic acid. By means of a sufficiently long reaction time, however, the yield of lactonic oxidation product is equivalent to that obtainable with the *trans* isomer.

The results of several oxidations of isoequilenin acetate are presented in Table I. The reactions on which this table is based varied widely in size and in some details of isolation procedure, but within the limits thus imposed they illustrate the effect of reaction time on yields. In each case the products, isolated as free phenols, are calculated as acetates, and all values are recalculated to the basis of 1.0 g. of starting material. The maximum yield of lactone is approached at a reaction time of about 200 hours; the ratio of lactone to recovered isoequilenin continues to increase with longer reaction time.

TABLE I

Reaction time, hours at 10°	Recovered isoequilenin acetate, grams(A)	Acetoxy-lactone, grams(B)	Ratio B/A
65	0.52	0.33	0.63
120	.43	.48	1.1
185	.12	.65	5.4
264	.09	.60	6.7
305	.07	.66	9.4

When isoequilenin methyl ether was oxidized with an excess of peracetic acid for 90 hours at 10°, the results were less satisfactory, and the products consisted chiefly of water-soluble materials. These are assumed to result from extensive attack on ring A.

The stereochemical course of peracid oxidations of certain ketones has recently been elucidated. Turner[10] has demonstrated that *cis*- and *trans*-1-acetyl-2-methylcyclohexane and *cis*- and *trans*-1-acetyl-2-methylcyclopentane are converted by perbenzoic acid oxidation into the corresponding cycloalkanyl acetates with retention of configuration. Similarly Gallagher and Kritchevsky[11] have shown that perbenzoic acid oxidations of 20-keto-pregnanes yield 17-acetoxyetiocholane derivatives in which the acetoxy group retains the configuration of the original C-17 side-chain.

These results appear to warrant the conclusion that the peracid oxidations of estrone acetate and equilenin acetate proceed with retention of the natural *trans* configuration between rings C and D, and that oxidation of a synthetic 17-ketosteroid with C/D *cis* produces a lactone ring which retains the *cis* configuration to ring C.

Acknowledgments.—The author is indebted to Dr. Gregory Pincus and Dr. Robert P. Jacobsen for advice, and to Dr. William S. Johnson for a generous gift of chemicals.

Experimental

All melting points were taken with a totally-immersed thermometer or were corrected for the exposed stem. Analyses, carried out by Dr. Robert T. Dillon and staff, are recorded as the average of multiple determinations. Isoequilenin acetate was prepared by standard procedures from isoequilenin methyl ether, obtained as a gift from the Research Committee of the Graduate School of the University of Wisconsin.

Oxidation of Isoequilenin Acetate with Peracetic Acid in Glacial Acetic Acid.—A number of oxidations were carried out in which the reaction time was varied from 65 to 305 hours. The procedure for the largest run is given. A solution was prepared from 10.05 g. of *dl*-isoequilenin acetate,[12] 50 ml. of glacial acetic acid, 160 ml. of a solution of peracetic acid in glacial acetic acid (containing 0.0011 mole of peracetic acid per ml.) and 0.2 g. of *p*-toluenesulfonic acid monohydrate. This reaction mixture was refrigerated at 8–10° for 185 hours, and then diluted with water until precipitation of the product was complete. This initial product was saponified with 400 ml. of 2% sodium hydroxide, and the cooled solution was diluted to 800 ml. and saturated with carbon dioxide. The precipitate (1.01 g., m.p. 201–203°) was recovered isoequilenin. The filtrate was heated to 80°, acidified with excess hydrochloric acid, allowed to cool slowly, and refrigerated. The product (5.7 g., m.p. 230–233°) was the crude hydroxy lactone.

Isobisdehydroestrololactone Acetate (I).—Six and four-tenths grams of the crude hydroxy lactone was acetylated by warming it on the steam-bath for 2 hours with 40 ml. of pyridine and 30 ml. of acetic anhydride. The cooled solution was gradually diluted with water. Crystallization (ethanol) of the gummy precipitate gave 5.0 g. of dark, crystalline material, m.p. 182–185°. For removal of color it was dissolved in benzene, passed through a short alumina column, and eluted with further quantities of benzene. Repeated recrystallization from ethanol, ethanol–acetone, and benzene gave dense, almost white crystals of the acetate, m.p. 187–188°.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 73.86; H, 6.13.

Isobisdehydroestrololactone (II).—The pure acetoxy lactone (1.15 g.) was saponified with 50 ml. of 2% sodium hydroxide. The hot solution was acidified with excess hydrochloric acid and allowed to cool slowly. The product (0.98 g., m.p. 244–249°) was recrystallized twice from redistilled ethylene glycol monoethyl ether to give the pure hydroxy lactone, m.p. 258–260°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.57; H, 6.68.

Isobisdehydroestrololactone Propionate (III).—This derivative was prepared from the hydroxy lactone, pyridine and propionic anhydride, with a procedure similar to that used for the acetate. After crystallization from ethanol, the propionate melted at 118–119°.

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.53; H, 6.55. Found: C, 74.59; H, 6.57.

(10) R. B. Turner, THIS JOURNAL, **72**, 878 (1950).

(11) T. F. Gallagher and T. H. Kritchevsky, *ibid.*, **72**, 882 (1950).

(12) All compounds described in this paper were prepared from *dl*-isoequilenin acetate, although similar results were obtained in a micro oxidation of *d*-isoequilenin acetate, prepared from equilin by the procedure of H. Hirschmann and O. Wintersteiner, *J. Biol. Chem.*, **126**, 737 (1938).

The identity of this ester was confirmed by saponifying a small sample to the parent hydroxy lactone.

Isobisdehydroestrololactone Methyl Ether (IV).—The acetoxy lactone (193 mg.) was saponified with 10 ml. of 2% sodium hydroxide, and this solution at 50° was treated by the alternate, portionwise addition of dimethyl sulfate and sodium hydroxide solution. The warm mixture (containing some solid material) was acidified with excess hydrochloric acid, and the precipitate was collected, resaponified and again precipitated from hot solution with hydrochloric acid. The 140 mg. of product thus obtained melted at 183–185°. After recrystallization from ethanol, it melted at 189–191°.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.06; H, 6.71.

A mixture of the methoxy lactone of m.p. 189–191° and the acetoxy lactone of m.p. 187–188° melted at 160–180°.

Derivatives of Isobisdehydroestrolic Acid (V).—All aqueous media in this section were prepared from distilled water. The acetoxy lactone (173 mg.) was saponified and methylated, and the initially-precipitated methoxy lactone was resaponified with 10 ml. of 2% sodium hydroxide. When this solution was concentrated to 5 ml. and cooled, the white, crystalline **sodium salt (VI)** separated. This could not be washed ion-free, as it dissolved almost immediately in water, methanol and ethanol, and no satisfactory solvent was found for recrystallization. It was collected on a filter, and repeatedly resuspended in and washed with portions of a solution prepared from 50 g. of sodium nitrate and 100 ml. of water, until the contaminating hydroxide ion was quantitatively replaced by nitrate ion. The organic sodium salt (with the adhering sodium nitrate) was dissolved in 15 ml. of warm water, and this solution was treated with dilute silver nitrate until precipitation was complete. The pale grey **silver salt (VII)** weighed 162 mg. and melted with decomposition at 176°. It is insoluble in water, organic solvents and sodium hydroxide solution, but it dissolves readily in aqueous ammonia. Analytical values indicate that it has the composition of a dihydrate.

Anal. Calcd. for $C_{19}H_{21}O_4Ag \cdot 2H_2O$: Ag, 23.59; CH_3O–, 6.79. Found: Ag, 23.68; CH_3O-, 6.73.

The silver salt (90 mg.) was covered with 10 ml. of methyl iodide and allowed to stand at 25°, with occasional shaking, for 20 hours. When the mixture was boiled gently to dryness and the residue was extracted with several portions of warm methanol, a fraction of about 48 mg. remained undissolved (calculated for silver iodide = 46.2 mg., assuming the organic silver salt to be a dihydrate). The methanol soluble fraction, after two recrystallizations from very small amounts of methanol, gave 6 mg. of a material, m.p. 107–108°, tentatively formulated as the **methyl ester (VIII)**, along with a larger amount of less pure material. This compound is soluble in ethyl acetate, moderately soluble in methanol, slightly soluble in benzene, and almost insoluble in aliphatic hydrocarbon solvents and water. Although the material melted sharply and was thought to be the pure ester, a single carbon–hydrogen determination failed to substantiate the proposed formula. Confirmation of the identity of this compound must therefore be held in abeyance.

CHICAGO 80, ILLINOIS RECEIVED JULY 19, 1951

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

Corticosteroid Intermediates. A Selective Hydrogenation of Steroid Polyenes

BY G. D. LAUBACH AND K. J. BRUNINGS

Hydrogenation of several polyunsaturated sterols in the presence of Raney nickel catalyst at room temperature and atmospheric pressure has been shown to proceed selectively without bond isomerization or saturation of non-conjugated side-chain double bonds. The important intermediate 5-dihydroergosterol has been prepared by this technique in quantitative yield from ergosterol. The method has been applied to four of the isomers of ergosterol, and in the course of this work $\Delta^{8(14),22}$-ergostadien-3β-ol acetate has been prepared and characterized.

Discussion

The $\Delta^{7,9(11)}$-sterol dienes[1,2] have long been considered attractive intermediates for the synthesis of 11-oxygenated steroids. A key step in the preparation of dienes of this type from readily available starting materials involves the selective hydrogenation of $\Delta^{5,7}$-sterol dienes to Δ^{7}-monounsaturated ("5-dihydro") derivatives. A typical example is the preparation of the important intermediate ergosterol-D-acetate ($\Delta^{7,9(11),22}$-ergostatrien-3β-ol acetate,[3] which involves selective hydrogenation of ergosterol (I) to 5-dihydroergosterol ($\Delta^{7,22}$-ergostadien-3β-ol) (III)[4] followed by dehydrogenation at the 9,11-position. In all sterols possessing a synthetically useful side-chain double bond, selective hydrogenation of ethylenic linkages within the sterol nucleus is rendered difficult by the reactivity of the side-chain function. Furthermore, the 7,8-double bond generated in the reduction is extremely labile and susceptible to migration to the 8,14-position under certain catalytic hydrogenation conditions.[5] Despite the extensive study devoted to the selective hydrogenation of ergosterol,[4] no method satisfactory for large-scale operation has been described. The best yields thus far reported have been of the order 30 to 35%[4a] and purification of the product (by fractional recrystallization) has been described as capricious and difficult.[4]

A series of attempts to repeat in this Laboratory the hydrogenation of ergosterol acetate over platinum in chloroform,[4a] which appeared to be the most straightforward of the published procedures, did not give consistent results, the product generally containing varying proportions of the monounsaturated rearranged sterol, $\Delta^{8(14)}$-ergosten-3β-ol acetate. This product could in fact be obtained in excellent yields by allowing the hydrogenation to proceed to completion. Incorporation of solid calcium carbonate in an attempt to maintain the neutral conditions essential for non-migration of steroid

(1) W. Bergmann and J. Klacsman, *J. Org. Chem.*, **13**, 21 (1948).

(2) Subsequent to the completion of this work M. Tishler and co-workers, THIS JOURNAL, **73**, 2396 (1951), and Fieser and co-workers, *ibid.*, **73**, 2397 (1951), reported the first successful conversion of $\Delta^{7,9(11)}$-sterol dienes to 11-oxygenated corticosteroid intermediates. A second route was later announced by G. Stork, *et al.*, *ibid.*, **73**, 3546 (1951).

(3) A. Windaus and E. Auhagen, *Ann.*, **472**, 185 (1929); I. Heilbron, F. Johnstone and F. Spring, *J. Chem. Soc.*, 2248 (1929). (a) D. R. H. Barton and J. Cox, *ibid.*, 219 (1949).

(4) A. Windaus and J. Brunken, *Ann.*, **460**, 225 (1927); I. Heilbron and W. Sexton, *J. Chem. Soc.*, 921 (1929); H. Wieland and W. Benend, *Ann.*, **554** 1 (1943). (a) D. R. H. Barton and J. Cox, *J. Chem. Soc.*, 1354 (1948).

(5) A survey of bond migration on hydrogenation of steroids is given by L. F. and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Edition, Reinhold Publishing Corp., New York, N. Y., 1949, p. 240. See also Wieland and Benend, ref. 4.