Anal. Calcd. for $C_{30}H_{20}O_9$: C, 68.7; H, 3.85. Found: C, 68.8; H, 3.99.

Action of Acetic Anhydride and Sulfuric Acid on Ellagorubin.—Two drops of concentrated sulfuric acid were added to a solution of ellagorubin (0.1 g.) in acetic anhydride (3.0 ml.) cooled in an ice-bath. Colorless crystals began to separate at once. After ten minutes, excess of water was added and the crystals were collected and recrystallized from dioxane–methanol. Colorless needles, m.p. 307–308°, undepressed on admixture with 5,5′-di-C-benzylellagic acid tetraacetate, were obtained.

The Benzylation of 5,5′-Di-C-benzylellagic Acid.—A mixture of 5,5′-di-C-benzylellagic acid (50 mg.), benzyl chloride (1.0 ml.), potassium iodide (0.1 g.), anhydrous potassium carbonate (3.0 g.) and dry acetone (25 ml.) was heated under reflux for 6 hours. The filtered solution was diluted with an equal volume of methanol and concentrated until crystallization began (yield 12 mg.). The solid from the reaction flask was suspended in water to dissolve the potassium carbonate and the undissolved colorless crystalline solid was collected (53 mg.) and combined with the product from the acetone filtrate. Recrystallization from dioxane–methanol caused the colorless benzylation product to separate in needles, m.p. and mixed m.p. 235–236°.

Benzoylation of Ellagic Acid. (a) **In Pyridine.**—Ellagic acid (0.2 g.) was dissolved in hot pyridine (6.0 ml.). Benzoyl chloride (1.0 ml.) was added and the hot solution was allowed to cool and stand for 20 hours. The red solution was then poured into excess of water. The gummy precipitated benzoate was washed with ether and filtered, leaving the benzoate as a white crystalline solid. On recrystallization from dioxane–methanol ellagic acid tetrabenzoate separated in colorless thick rods, m.p. 329–330°.

Anal. Calcd. for $C_{42}H_{22}O_{12}$: C, 70.2; H, 3.09. Found: C, 69.9; H, 3.20.

(b) **In Aqueous Sodium Hydroxide.**—Ellagic acid (0.2 g.) was dissolved in 20 ml. of 5% aqueous sodium hydroxide by heating to the boiling point for about 10 seconds. The solution was cooled quickly in an ice-bath and benzoyl chloride (1.0 ml.) was added with shaking. After 5 minutes a further 10 ml. of 10% sodium hydroxide and 1.0 ml. of benzoyl chloride were added with shaking. The solid benzoate was collected, washed free of excess benzoyl chloride with hot methanol (20 ml.) and recrystallized from dioxane–methanol. Ellagic acid tetrabenzoate separated in colorless rods, m.p. 329°.

Acknowledgments.—The author wishes to thank L. Rolle for his helpful assistance in the preparation of ellagic acid and L. M. White for performing the elementary analyses.

PASADENA, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KANSAS]

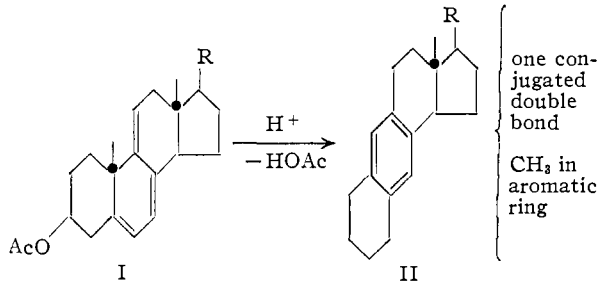
A Contribution to the Anthrasteroid Problem. The Location of the Aromatic C-Methyl Group and the Position of the Conjugated Double Bond

BY ALBERT W. BURGSTAHLER

RECEIVED JULY 3, 1957

As a proof of structure, an oxidative opening of the unsaturated ring followed by a reverse Michael reaction of the resulting keto-aldehyde has been employed to convert the anthrasteroid rearrangement product IIb derived from 5,7,9(11)-cholestatrien-3β-ol acetate (Ib) to 4-keto-3,9-dimethyl-*s*-octahydroanthracene (VII) which has been degraded further to 3,9-dimethylanthracene (IX).

The typical conversion, by acid catalysis, of a steroid containing the nuclear triene system of dehydroergosterol acetate (Ia) to an unsaturated derivative of *s*-octahydroanthracene (IIa) has been investigated extensively in recent years, especially by Nes and Mosettig and their co-workers, and has been designated by them as the "anthrasteroid rearrangement."[1] Numerous lines of evidence have



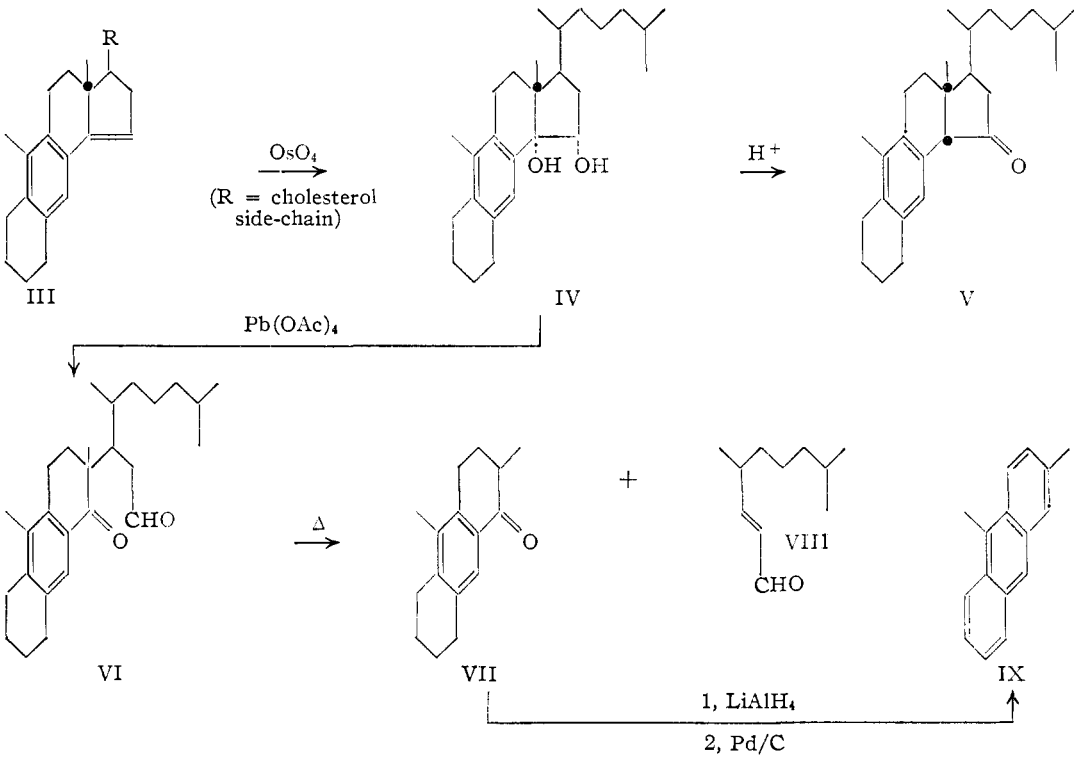
I II

Ia, R = ergosterol side-chain
Ib, R = cholesterol side-chain
IIa, R = ergosterol side-chain
IIb, R = cholesterol side-chain

been accumulated, largely by the skillful experiments of these authors, to establish and to verify the anthrasteroid structure (II) as the correct formula of the rearrangement products derived from such steroidal trienes. Thus, the ultraviolet absorption spectrum of IIa reveals the presence of a highly alkylated benzene ring conjugated to an olefinic bond,[1a,c] and further evidence, including precise ultraviolet spectral comparisons of the corresponding double bond-reduced product with *s*-octahydroanthracene and *s*-octahydrophenanthrene,[1b] an oxidative degradation to 1-methyl-2,3,5,6-tetracarboxybenzene[1b] and dehydrogenation to hydrocarbon derivatives of anthracene,[1b,d,e] has served to demonstrate the general structure II for the rearrangement products, without, however, distinguishing between the two possible locations of the aromatic C-methyl group or determining the position of the conjugated double bond.

In consideration of the probable mechanism for the rearrangement, as outlined at the end of this discussion, it appeared to the present author that formula II could be reasonably expanded to III, and, as a means to establish these further details indicated by structure III, it was proposed to submit a typical rearrangement product to the degradation sequence indicated below. For this purpose, in order to avoid possible complications arising from unsaturation present in the side-chain in the ergosterol series (IIa), it was decided to employ the rearrangement product (IIb) derived from 5,7,9(11)-cholestatrien-3β-ol acetate (Ib) in the degradation scheme.

(1) (a) W. R. Nes and E. Mosettig, THIS JOURNAL, **75**, 2787 (1953); (b) **76**, 3182, 3186 (1954); (c) W. R. Nes, *ibid.*, **78**, 193 (1956); (d) W. R. Nes, R. B. Kostic and E. Mosettig, *ibid.*, **78**, 436 (1956); (e) *cf.* K. Tsuda and R. Hayatsu, *ibid.*, **77**, 3089 (1955).



Initially, the oxidation of the conjugated olefinic bond in IIb was attempted using ozone, but this did not lead to satisfactory results, apparently because of side-reactions occurring in the reductive hydrolysis of the ozonide. Hydroxylation of the double bond by the agency of osmium tetroxide proceeded smoothly, however, and, by adopting the hydrogen sulfide isolation technique introduced recently by Barton and Elad,[2] the corresponding *cis*-glycol IV, m.p. 149–150°, $[\alpha]D$ +68°, was obtained in 76% yield.[3] Attempted oxidative cleavage of IV with periodic acid in dilute aqueous acetone appeared to lead to extensive pinacol rearrangement, giving, at least in part, the saturated ketone V (single carbonyl absorption peak at 1735 $cm.^{-1}$; simple benzene spectrum in the ultraviolet), characterized as its light yellow 2,4-dinitrophenylhydrazone, m.p. 161–162°, λ_{max} 367 mμ (log ε 4.4).

Because of its insolubility in aqueous systems, IV could not be induced to react with sodium periodate in solution or as a suspension. With lead tetraacetate, however, successful cleavage of the sensitive glycol function occurred, producing the non-crystalline keto-aldehyde VI, which exhibited intense absorption peaks at 1730 and 1680 $cm.^{-1}$ in the infrared and at 265 and 305 mμ (log ε 4.3 and 3.5, respectively) in the ultraviolet, as would be anticipated for this structure.[4,5] Heated gradually from 180 to 260° over a period of 1 hr., under reduced pressure, VI underwent a reverse Michael reaction, typical of the behavior of 1,5-dicarbonyl systems of this type,[6] to furnish the crystalline tricyclic ketone VII (4-keto-3,9-dimethyl-*s*-octahydroanthracene), m.p. 87–89° (infrared 1680 $cm.^{-1}$, intense ultraviolet maxima at 265 and 305 mμ),[4,5] along with the more volatile unsaturated aldehyde (VIII) which, for lack of material, was not characterized. Reduction of VII with lithium aluminum hydride, followed by dehydrogenation of the product with palladium–charcoal at 330°, readily afforded 3,9-dimethylanthracene (IX), m.p. 84.5–85°, undepressed with an authentic sample prepared essentially by the method of Barnett and Goodway.[7,8] The picrate, m.p. 127.5–128°, likewise gave no depression with an authentic sample.

By virtue of this degradation of IIb to an anthracene derivative of known structure, these results thus serve to establish unequivocally the location of the aromatic C-methyl group in relation to the remaining angular methyl group and also the position of the conjugated double bond as shown in III in the anthrasteroid rearrangement product. Considered in the light of the extensive experi-

(2) D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 2085 (1956).

(3) In analogy with the catalytic hydrogenation of Δ^{14}-cholestene to cholestane (L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publ. Co., New York, N. Y., 1949, p. 249) the α-configuration has been assigned to the hydroxyl groups in IV. Like IV, the dihydro derivative of IIb, prepared by catalytic hydrogenation (*cf.* ref. 1d), is dextrorotatory ($[\alpha]D$ +30°) whereas IIb has $[\alpha]D$ −34° (ref. 1d).

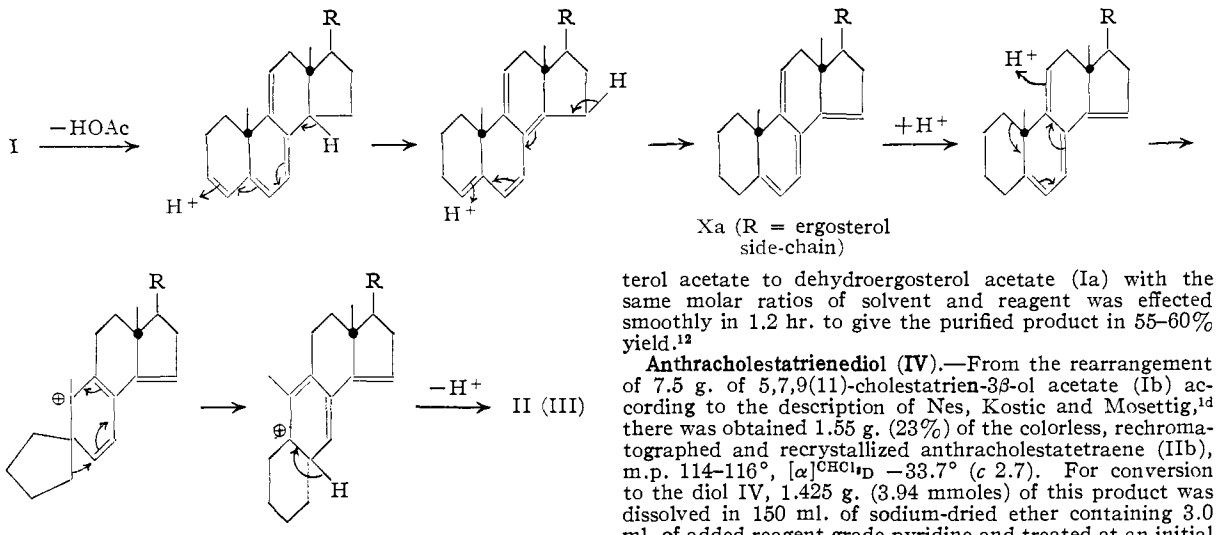
(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1956, Ch. 9, pp. 114–120.

(5) *Cf.* the nearly identical ultraviolet spectrum of 1-keto-*s*-octahydroanthracene (R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, spectrum No. 61).

(6) For the closely related degradation of Δ^{14}-ergostenol acetate to the corresponding tricyclic ketone, *cf.* T. Auchtermann, *Z. physiol. Chem.*, **226**, 141 (1934), and F. Laucht, *ibid.*, **237**, 236 (1935). For a recent review and a modern interpretation of the reverse Michael reaction, *cf.* S. A. Julia, A. Eschenmoser, H. Heusser and N. Tarköy, *Helv. Chim. Acta*, **36**, 1885 (1953).

(7) E. DeB. Barnett and N. F. Goodway, *J. Chem. Soc.*, 1754 (1929).

(8) The alternative position of the methyl group in IIb would have given rise to 2,9-dimethylanthracene in the dehydrogenation. An authentic sample of this substance, m.p. 82–83° (prepared by the modification of D. D. Phillips and J. Cason, THIS JOURNAL, **74**, 2934 (1952); *cf.* reference 7 above), produced a depressed mixed melting point of 61–73° with the dehydrogenation product.



mental findings of Nes, *et al.*,[1] they likewise provide strong evidence that the structure of the acid-catalyzed rearrangement product derived from $\Delta^{5,7,9,(11)}$-steroidal trienes in general is of the same type. A reasonable mechanism which will account for this behavior and which is in accord with other experimental results of Nes, *et al.*, concerning the pathway of the reaction,[1b,c] involves a dienone-phenol type of rearrangement which may be written as follows. (In the case of Ia → IIa, the intermediate Xa has been isolated under mild conditions and has been found to undergo conversion to IIa in high yield.[1c] This result was also confirmed during the course of the present work.)

Experimental[9]

5,7,9(11)-Cholestatrien-3β-ol Acetate (Ib).—The preparation of this substance by the action of mercuric acetate on 7-dehydrocholesterol acetate[10] was conducted by a modification of the procedure described by Nes, Kostic and Mosettig,[1d] with a considerable improvement in yield. To a magnetically stirred, refluxing solution of 5.0 g. of 7-dehydrocholesterol acetate, m.p. 129–130°, in 80 ml. of carbon tetrachloride and 125 ml. of absolute ethanol was added a hot solution of 11.5 g. of mercuric acetate in 80 ml. of absolute ethanol containing 4.0 ml. of glacial acetic acid. The mixture was refluxed, with stirring, for exactly 2.2 hr., cooled to room temperature over a 15-minute period, filtered and the product recovered by dilution with water and several extractions with carbon tetrachloride, followed by washing with water and sodium bicarbonate solution, drying over magnesium sulfate, removal of the solvent under reduced pressure on the steambath and crystallization of the residue from 20 ml. of a mixture of acetone–methanol (3:1) at −20°. A single recrystallization from acetone–ethyl acetate–methanol afforded 1.8 to 2.0 g. (35–40%) of colorless plates, m.p. 88–90°, as reported.[11] Any decrease in this period of reflux led to the recovery of considerable amounts of starting material which contaminated the product, while more extended reaction periods served to diminish the yield significantly. By contrast, the conversion of ergosterol acetate to dehydroergosterol acetate (Ia) with the same molar ratios of solvent and reagent was effected smoothly in 1.2 hr. to give the purified product in 55–60% yield.[12]

Anthracholestatrienediol (IV).—From the rearrangement of 7.5 g. of 5,7,9(11)-cholestatrien-3β-ol acetate (Ib) according to the description of Nes, Kostic and Mosettig,[1d] there was obtained 1.55 g. (23%) of the colorless, rechromatographed and recrystallized anthracholestatetraene (IIb), m.p. 114–116°, $[\alpha]^{CHCl_3}D$ −33.7° (*c* 2.7). For conversion to the diol IV, 1.425 g. (3.94 mmoles) of this product was dissolved in 150 ml. of sodium-dried ether containing 3.0 ml. of added reagent grade pyridine and treated at an initial temperature of −20° with 1.00 g. (3.94 mmoles) of osmium tetroxide dissolved in 50 ml. of dry ether. After warming to room temperature the reaction mixture was allowed to stand for four days at 22–25° in the dark. At the end of this period the precipitated osmate ester–pyridine complex was dissolved by the addition of 50 ml. of 95% ethanol to give a clear, dark brown solution. An excess of gaseous hydrogen sulfide was passed slowly into this solution,[2] and the black precipitate of osmium disulfide was removed by filtration through Filter-cel. Concentration of the nearly colorless filtrate under reduced pressure on the steam-bath, followed by crystallization of the residue from ethyl acetate–petroleum ether (30–40°) furnished the hydroxylation product IV as colorless matted needle clusters, m.p. 145–149°, yield 1.19 g. (76%). Recrystallized for analysis, the material melted at 149–150°, $[\alpha]^{CHCl_3}D$ +68° (*c* 1.98).

Anal. Calcd. for $C_{27}H_{42}O_2$ (398.61): C, 81.35; H, 10.62. Found: C, 81.41; H, 10.60.

On standing in aqueous acetone containing a twofold excess of periodic acid, this substance was converted to an oily product which appeared to contain, at least in part, a significant amount of the corresponding pinacol rearrangement product V, as shown by the infrared spectrum (single carbonyl peak at 1735 cm.$^{-1}$) and by the absence of a conjugated chromophore absorption in the ultraviolet. The 2,4-dinitrophenylhydrazone crystallized from a mixture of ethanol–ethyl acetate as fine yellow needles, m.p. 161–162°, $\lambda_{max}^{CHCl_3}$ 367 mμ (log ε 4.4).

Anal. Calcd. for $C_{33}H_{44}N_4O_4$ (560.71): C, 70.68; H, 7.91. Found: C, 70.91; H, 8.04.

Glycol Cleavage and Pyrolysis of VI to 4-Keto-3,9-dimethyl-*s*-octahydroanthracene (VII).—To a well-stirred solution of 1.0 g. of lead tetraacetate in 40 ml. of acetic acid, 330 mg. of the above diol IV which had been dissolved in 10 ml. of acetone–acetic acid (1:1) was added over a 5-minute period at room temperature. After stirring for an additional 45 minutes, a few drops of glycerol were added to destroy the excess oxidizing agent and the oily product recovered by thorough ether extraction after dilution with water. This material, which weighed 290 mg., could not be induced to crystallize[13] but displayed intense carbonyl peaks at 1730 and 1680 cm.$^{-1}$ in the infrared. The ultraviolet spectrum had λ_{max} at 265 and 305 mμ (log ε 4.3 and 3.4, respectively). No further efforts were made to characterize this material. For pyrolysis, the product was heated slowly over a period of 30 minutes from 180° to 210° (bath) under a pressure of 20 mm. Considerable darkening occurred, and a few droplets of a fragrant, nearly colorless distillate were collected which gave an orange precipitate with 2,4-dinitrophenylhydrazine reagent but which was not examined further. Upon raising the temperature to

(9) Melting points are corrected. Infrared spectra were determined in carbon tetrachloride solution with a Perkin–Elmer, model 21, double beam recording spectrophotometer. Except where noted, ultraviolet spectra were taken in ethanol on a Beckman DK-1 recording spectrophotometer. Analyses were performed by Mr. R. K. Kulkarni of this Department and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(10) 7-Dehydrocholesterol was purchased from Vitamins, Inc., Chicago, Ill., and was acetylated with acetic anhydride in pyridine at room temperature in 80% yield (*cf.* ref. 11 below).

(11) R. Antonucci, S. Bernstein, D. Giancola and K. J. Sax, *J. Org. Chem.*, **16**, 1159 (1951); *cf.* ref. 1d.

(12) R. Antonucci, *et al.* (ref. 11), report a yield of 54% for this reaction.

(13) The closely related keto-aldehyde formed by the ozonolysis of β-ergostenol acetate (Δ^{14}-ergostenol acetate) is likewise reported to be non-crystalline (*cf.* T. Auchtermann and F. Laucht, ref. 6).

250–260°, at still lower pressure (2 mm.), distillation of the remaining material occurred, giving 180 mg. of a viscous yellow oil which displayed but a single carbonyl band in the infrared at 1680 cm.$^{-1}$. Chromatography on a 0.8 × 10 cm. column of activated alumina furnished a major fraction of *ca.* 85 mg. with benzene–petroleum ether (4:1) which partially crystallized on standing to yield clusters from methanol, m.p. 87–89°, $[\alpha]^{CHCl_3}D$ 0°, λ_{max} 265 mμ (log ε 4.2) and 305 mμ (log ε 3.4).[5] Further characterization of this substance (VII) was deferred in order to retain sufficient material to complete the degradation scheme.

Conversion of VII to 3,9-Dimethylanthracene (IX).—To a stirred solution of 0.3 g. of lithium aluminum hydride in 20 ml. of anhydrous ether, the above crude ketone VII was added rapidly in ether solution. After stirring for an additional ten minutes the excess reagent was destroyed with ethyl acetate in ether, the mixture treated with cold dilute hydrochloric acid and the product recovered by ether extraction. This material was then transferred to a long Pyrex tube (300 × 10 mm., partially constricted at the lower end), 50 mg. of 10% palladium–charcoal was introduced and the contents heated carefully at 310–330° (bath) for 30 minutes. At the end of this period gas evolution appeared to be complete, and the product was taken up in petroleum ether (30–40°) and purified by elution from a 1.2 × 10 cm. column of strongly activated alumina. A nearly colorless fraction which exhibited a strong blue fluorescence in ultraviolet light was eluted slowly with petroleum ether and crystallized readily from ethanol as light cream colored needle clusters, weighing 23 mg. and melting at 81–84°. Recrystallized from ethyl acetate–methanol these had a melting point of 84.5–85° which was undepressed on admixture with an authentic sample of 3,9-dimethylanthracene prepared essentially by the method of Barnett and Goodway[7] but improved in yield by employing methyllithium in the addition step to 3-methyl-9-anthrone, as suggested by Phillips and Cason.[8,14] The picrate crystallized from ethanol as dark maroon needles, m.p. 127.5–128°, also undepressed with an authentic sample.

Anal. Calcd. for $C_{22}H_{17}O_7N_3$ (435.38): C, 60.69; H, 3.94. Found: C, 60.89; H, 4.02.

When it was mixed with a sample of 2,9-dimethylanthracene, m.p. 82–83°,[8,14] the melting point of the dehydrogenation product was depressed to 61–73°. The ultraviolet spectrum of 3,9-dimethylanthracene was found to be very similar to that of 2,9-dimethylanthracene, reported by Phillips and Cason,[8] and showed λ_{max} (log ε) values of 260 mμ (5.4), 334 mμ (3.5) (shoulder), 348 mμ (3.7), 368 mμ (3.8) and 387 mμ (3.75).

(14) The author gratefully acknowledges the assistance of Mr. Delbert Meyer in the preparation of this authentic sample of 3,9-dimethylanthracene and also that of 2,9-dimethylanthracene.

LAWRENCE, KANSAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Formation of Five- and Six-membered Rings by the Acyloin Condensation. VI. Cyclization of the Cholesterol *a* Ring *via* a 2,3-Secodiester

BY JOHN C. SHEEHAN AND WILLIAM F. ERMAN

RECEIVED MARCH 27, 1957

Cyclization of 2,3-secocholestane-2,3-dioic acid dimethyl ester (I) by an acyloin condensation in homogeneous medium afforded a mixture, from which an acyloin assigned the structure 3β-hydroxycholestane-2-one (II) was isolated in 82% yield. Minor products of the reaction were an isomeric 2-hydroxycholestane-3-one, cholestane-2α,3β-diol, and 2,3-secocholestane-2,3-dioic acid. Reduction of the acetate derivative of II with sodium borohydride and with sodium led to the new epimeric cholestane-2β,3β-diol and a diol of unassigned structure, respectively. By formation of the tosylate derivative, subsequent reduction with sodium borohydride and treatment with collidine, the ketol II was converted to cholestane-2-one in excellent yield.

Previous communications in this series have reported the formation of steroid C and D rings in high yield by the acyloin reaction in homogeneous solution. In each instance only one of the four possible isomeric acyloins was isolated. These cases do not favor a Dieckmann-type of condensation, and no such side product was detected. However, it seemed worthwhile to extend the scope of the acyloin reaction to include a steroid diester in which the α-carbon atoms are unsubstituted and which could yield a five-membered ring by a Dieckmann condensation. The 2,3-secocholestane series was chosen as a representative model for the condensation, due both to structural features and to the intrinsic interest in oxygenated cholestane derivatives.

Essentially the method of Sheehan, Coderre and Cruickshank[1] for the acyloin condensation of dimethyl marrianolate methyl ether was followed for the cyclization of the diester I. A ratio of exactly 4 moles of sodium per mole of diester dissolved in a medium containing 60% liquid ammonia and 40% anhydrous ether was employed. Chromatography of the crude reaction mixture afforded 3β-hydroxycholestane-2-one(II) in 82% yield, an isomeric 2-hydroxycholestanone (III) in 5% yield and cholestane-2α,3β-diol (IV) in 2% yield. The basic extracts from the crude reaction mixture afforded 2,3-secocholestane-2,3-dioic acid (V) in 1% yield.

From physical and chemical evidence the structure 3β-hydroxycholestane-2-one was assigned for the acyloin II. The infrared spectrum of this material showed all the characteristic absorption bands associated with an acyloin: a rather weak hydroxyl band at 3515 cm.$^{-1}$ (2.82 μ) and a strong carbonyl band at 1715 cm.$^{-1}$ (5.85 μ) characteristic of a six-membered ring carbonyl.[2]

The crude acyloin mixture VI was oxidized to 2,3-secocholestane-2,3-dioic acid (IV) with chromic acid and converted by means of cupric acetate to the dione VII, which was isolated as the quinoxaline derivative VIII in 89% over-all yield. The quinoxaline VIII gave no depression of melting point upon admixture with a sample of cholestane-2,3-dione quinoxaline prepared by an unambiguous route. This method involved formation of 2-isonitrosocholestane-3-one, conversion to cholestane-2,3-dione with pyruvic acid and treat-

(1) J. C. Sheehan, R. A. Coderre and P. A. Cruickshank, THIS JOURNAL, **75**, 6231 (1953).

(2) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 128.