Summary

3(β)-Acetoxy-22-hydroxy-bisnor-5-cholene and the 3(β)-hydroxy-3(β)-acetoxy- and 3(β)-benzoxy-24-hydroxy-5-cholenes have been produced by the reductive desulfurization of the corresponding ethyl thiol esters with Raney nickel catalyst.

Derivatives of these alcohols have been prepared by acylation and hydrolysis.

3(β)-Acetoxy-5-cholen-24-al and 3(β)-acetoxy-bisnor-5-cholen-22-al have been obtained from the ethyl and benzyl thiol esters of the corresponding acids by treatment with a deactivated Raney nickel catalyst.

The 2,4-dinitrophenylhydrazones of 3(β)-hydroxy- and 3(β)-formoxy-5-cholen-24-al have been prepared from crude aldehydes obtained by desulfurization of the corresponding thiol esters with a deactivated Raney nickel catalyst.

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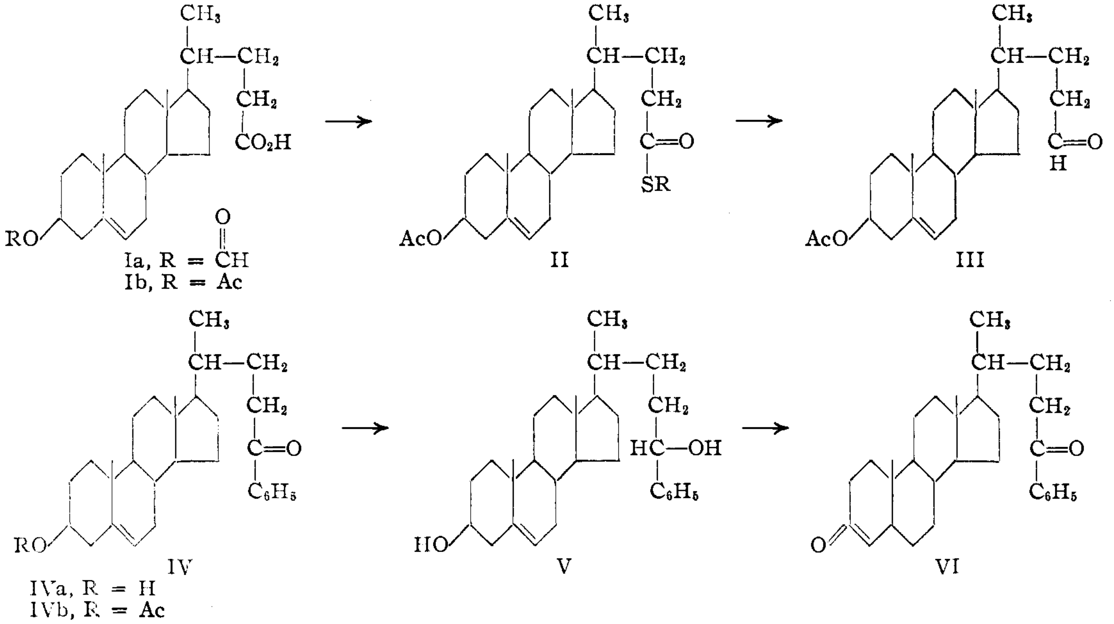
[Contribution from the Research Division, The Upjohn Company]

Steroid Acids and their Transformation Products. IV. Epimeric 24-Phenyl-5-cholen-3(β),24-diols and Related Compounds

By Robert H. Levin, George B. Spero, A. Vern McIntosh, Jr., and Douglas E. Rayman

The preparation of 3(β)-acetoxy-5-cholenic aldehyde (III) from 3(β)-acetoxy-5-thiolcholenates (II)[1] by the use of deactivated W-1 Raney nickel has recently been reported.[2] The aldehyde (III) has now been treated with phenylmagnesium bromide to form the 24-phenyl-5-cholene-3(β),24-diols, epimeric at C-24, in yields of 70–80%. The same diols (V) also have been obtained by the reduction of the corresponding phenyl ketone (IVb), previously prepared from 3(β)-formoxy-5-cholenic acid (I).[3] The reduction of the phenyl ketone (IVb) with aluminum isopropoxide in isopropanol gave a reaction mixture difficult to work up, and the diols (V) were obtained in total yields averaging 40%, although in one experiment the yield was 80%. With lithium aluminum hydride[4] the reaction proceeded rapidly and smoothly in ether at room temperature giving the same mixture of diols (V) in 80–90% yields.



Ia, R = $\overset{O}{\overset{\|}{CH}}$
Ib, R = Ac

II

III

IV
IVa, R = H
IVb, R = Ac

V

VI

It was found possible to separate the epimeric diols (V) by solubility differences in benzene or ether and the acetates and benzoates of both isomers were prepared. The diols and their derivatives are listed in Table I.

Table I

Epimeric 24-Phenyl-5-cholen-3(β),24-diols

	A		B	
Compound	M. p., °C.	$[\alpha]^{25}D$	M. p., °C.	$[\alpha]^{25}D$
Diol	214–217	− 7.0	184–186	−38.2
Diacetate	92–94	−22.3	164–165	−60.4
Dibenzoate	160–161	−27.2	175–177	−10

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[1] Levin, McIntosh, Spero, Rayman and Meinzer, This Journal, **70**, 511 (1948).

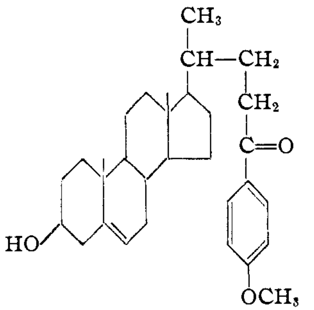
[2] McIntosh, Meinzer and Levin, *ibid.*, **70**, 2955 (1948).

[3] Hoehn and Moffett, *ibid.*, **67**, 740 (1945).

[4] Finholt, Bond and Schlesinger, *ibid.*, **69**, 1199 (1947). Ott and Murray, Abstracts 113th American Chemical Society Meeting, Medicinal Section, Chicago, Ill., April, 1948.

Oxidation of each isomer gave the same diketone (VI), identical with that obtained directly by oxidation of 3(β)-hydroxy-24-keto-24-phenyl-5-cholene (IVa). The ultraviolet spectrum of this compound is given in Fig. 1.

In preparing the phenyl ketone from 3(β)-formoxy-5-cholenic acid chloride, it was found desirable to modify the diphenylcadmium method of Hoehn and Moffett[3] by adding the cadmium chloride to the Grignard solution, and by using a lower reaction temperature. The diphenylcadmium procedure[3] was also compared with the amide-Grignard method[5] which has not been previously reported in the steroid literature. It was found that both methods gave essentially the same yields, but the diarylcadmium method required greater experimental proficiency. However, when the corresponding anisyl ketone (VII) was prepared, the amide route gave yields of 40%, whereas the diarylcadmium procedure gave yields of 20%.[6] The new compound, 3(β)-hydroxy-24-keto-24-anisyl-5-cholene (VII), has a m.p. of 154–157°, and forms an oxime, m.p. 177–179°.



VII

Experimental[7]

24-Phenyl-5-cholen-3(β),24-diols (V). (a) From 3(β)-Acetoxy-5-cholenic Aldehyde (III).—To a Grignard solution prepared from 0.6 g. of magnesium and 5.5 g. of bromobenzene in 250 ml. of anhydrous ether was added 2 g. (0.005 mole) of 3(β)-acetoxy-5-cholen-24-al in 75 ml. of benzene over a period of one hour. During addition and for an additional hour the solution was kept at reflux temperature. On cooling and decomposing with 3 *N* hydrochloric acid, a white precipitate resulted and was separated by filtration. This material (0.72 g., m. p. 195–230°) was recrystallized twice from 125 ml. of benzene and yielded 0.35 g. of epimer A, m. p. 214–217°. The ether-benzene phase of the filtrate was separated, washed with water and steam distilled. The resulting solid residue (0.93 g., m. p. 186–190°) was recrystallized from benzene and yielded 0.71 g. of epimer B, m. p. 184–186°. The total yield was 1.65 g. (76.5%).

Anal. Calcd. for $C_{30}H_{44}O_2$: C, 82.51; H, 10.15. Found (epimer A): C, 82.34; H, 9.87. Found (epimer B): C, 82.19; H, 10.12. $[\alpha]^{25}\text{D}$ (epimer A) −7.0° (35.9 mg. in 10 ml. $CHCl_3$; 2 dm. tube; α −0.02°). $[\alpha]^{25}\text{D}$ (epimer B) −38.2° (107.4 mg. in 10 ml. $CHCl_3$; 1 dm. tube; α −0.41°).

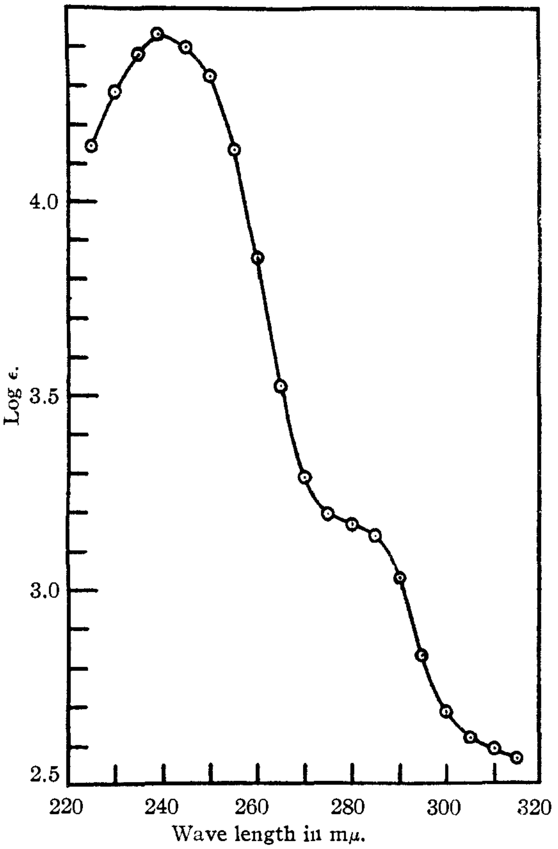


Fig. 1.—Ultraviolet absorption spectrum of 3,24-diketo-24-phenyl-4-cholene in abs. alcohol taken on a Beckman quartz spectrophotometer, model DU.

(b) From 3(β)-Acetoxy-24-keto-24-phenyl-5-cholene (IVb) by Reduction with Aluminum Isopropoxide and Isopropyl Alcohol.—Thirty grams (0.06 mole) of IVb was refluxed for three and one-half hours with 500 ml. of toluene and 120 g. of aluminum isopropoxide. The mixture was cooled and 600 ml. of dry isopropyl alcohol was added. After refluxing for an additional hour, the reflux condenser was replaced by a Vigreux column fitted with a condenser for downward distillation. Distillation was then started and adjusted to a rate of 4 drops per minute. After four hours (the distillate gave a negative acetone test with 2,4-dinitrophenylhydrazine) the reaction was stopped and the reaction mixture was cooled, poured into 2 l. of 1% hydrochloric acid, and extracted with 2 liters of chloroform. The chloroform was washed well with water, dried and concentrated to 500 ml. On cooling, 22.2 g. (80.7%), m. p. 194–198°, of the mixture of the diols crystallized. This was digested with 400 ml. of benzene and filtered. The insoluble fraction (6.5 g., m. p. 210–212°) was recrystallized from chloroform and yielded 5.64 g. of epimer A, m. p. 214–217°. The soluble fraction was crystallized from benzene and recrystallized from alcohol; yield, 9.27 g. of epimer B, m. p. 184–186°.

(c) From 3(β)-Acetoxy-24-keto-24-phenyl-5-cholene (IVb) by Reduction with Lithium Aluminum Hydride.—In an atmosphere of nitrogen, a solution of 15 g. (0.03 mole) of IVb in 1600 ml. of anhydrous ether was added dropwise over a period of forty-five minutes to a solution of 6.66 g. of lithium aluminum hydride[4] in 300 ml. of anhydrous ether. The mixture was stirred for an additional thirty minutes and water was then cautiously added until no more reaction was evident: 300 g. of ice and 400 ml. of 10% hydrochloric acid were added and the mixture was stirred for ten minutes. The ether layer was separated

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[5] Jenkins, THIS JOURNAL, **55**, 703 (1933).

[6] It is possible that the diarylcadmium procedure as improved by Cason, *ibid.*, **68**, 2078 (1946), would give better yields than obtained here. Our experiments were completed before the publication of the modified procedure. We are indebted to the referee for calling our attention to Dr. Cason's work.

[7] All m. p.'s are corrected. Analyses by the Upjohn microanalytical group.

and the water layer was extracted with 1000 ml. of chloroform. After washing with water and drying, the chloroform and ether were combined and concentrated to 300 ml. On cooling, 5.14 g. of crystalline material, m. p. 195–202°, was obtained. By further concentrating and diluting the mother liquor with hexane two more crops of product were obtained: 3.41 g., m. p. 180–187° and 3.54 g., m. p. 171–182°. The total yield of epimeric diols was 12.09 g. (88%).

Acetylation of Diols (V).—One-half gram of each epimer was acetylated by refluxing for four and one-half hours with 5 ml. of acetic anhydride and 15 ml. of pyridine. Epimer A gave 0.26 g. of the diacetate, m. p. 90–92°, which was recrystallized from alcohol and melted at 93–94°. Epimer B gave 0.45 g. of diacetate, m. p. 135–148°, which on recrystallization from alcohol melted at 164–165°.

Anal. Calcd. for $C_{44}H_{48}O_4$: C, 78.42; H, 9.29; CH_3CO, 16.59. Found (epimer A): C, 78.45; H, 9.17; CH_3CO, 17.4. Found (epimer B): C, 78.30; H, 9.11; CH_3CO, 17.6. $[\alpha]^{25}D$ (epimer A) −22.3° (71.8 mg. in 10 ml. $CHCl_3$; 1 dm. tube; α −0.16°. $[\alpha]^{25}D$ (epimer B) −60.4° (129.1 mg. in 10 ml. $CHCl_3$; 1 dm. tube; α −0.78°).

Benzoylation of Diols (V).—One gram of each epimer was allowed to stand with 1.5 ml. of benzoyl chloride and 4 ml. of pyridine for sixteen hours at room temperature. After working up, epimer A gave 1.44 g. of crude dibenzoate, m. p. 150–155°. Several recrystallizations from benzene and hexane raised the m. p. to 160–161°. Epimer B gave 1.12 g. of crude dibenzoate, m. p. 153–157°. Several recrystallizations from benzene yielded a pure product melting at 175–177°.

Anal. Calcd. for $C_{44}H_{52}O_4$: C, 82.25; H, 8.16. Found (epimer A): C, 82.23; H, 8.24. Found (epimer B): C, 81.70; H, 8.15. $[\alpha]^{25}D$ (epimer A) −27.2° (119.6 mg. in 10 ml. $CHCl_3$; 2 dm. tube; α −0.65°). $[\alpha]^{27}D$ (epimer B) −10.1° (4.96 mg. in 10 ml. $CHCl_3$; 1 dm. tube; α −0.05°).

Oxidation of Diols (V).—One-half gram of each of the epimers was dissolved in 15 ml. of toluene, 5 ml. of cyclohexanone and 0.5 g. of aluminum isopropoxide were added, and the mixture was refluxed for four hours. The reaction mixture was cooled, poured into 50 ml. of 5% hydrochloric acid and extracted with 50 ml. of ether. The ether was washed, dried, and concentrated till crystallization took place. The yield from epimer A was 0.2 g. of 3,24-diketo-24-phenyl-4-cholene (VI), m. p. 168–170°. Recrystallization from acetone gave a pure product, m. p. 169–171°. Epimer B gave 0.4 g. which on recrystallization from acetone melted at 171–173°. Admixture of the two products showed no depression in melting point.

Similarly, 3(β)-hydroxy-24-keto-24-phenyl-5-cholene (IVa) was oxidized to the same 3,24-diketo-24-phenyl-4-cholene, m. p. 169.5–171.5°; $[\alpha]^{25}D$ +78.1° (83.2 mg. in 10 ml. $CHCl_3$; 1 dm. tube, α +0.65°).

Anal. Calcd. for $C_{30}H_{40}O_2$: C, 83.27; H, 9.32. Found: C, 83.33; H, 9.23.

3(β)-Hydroxy-24-keto-24-phenyl-5-cholene IVa. (a) **Amide Method.**—Four grams (0.01 mole) of 3(β)-formoxy-5-cholenylamide,[8] m. p. 170–172°, was added in powder form, over a period of thirty minutes, to a Grignard solution prepared from 1.7 g. of magnesium, 11 g. of bromobenzene and 50 ml. of anhydrous ether. The mixture was allowed to stir and reflux for fifty hours and was then decomposed by pouring into 60 ml. of 10% sulfuric acid and ice. A precipitate resulted and was collected. The ether phase was separated and the water was extracted with ether. The ether portions were combined, washed, dried and evaporated to dryness. The residue was added to the precipitate and the whole was digested with 300 ml. of acetone. A small amount of insoluble material was discarded. On concentrating the acetone solution, 2.4 g. (52%) of product, m. p. 110–145°, was obtained. Without further purification a portion was converted to the acetate by refluxing with acetic anhydride and acetic acid. The acetate after recrystallization from acetone melted at 158–159.5°. A second portion was converted to the formate by heating at 55–60° for four hours with formic acid. Recrystallization from formic acid and from acetone resulted in pure material, m. p. 150–153°.

(b) **Diphenylcadmium Method.**—A Grignard solution, prepared from 15 g. of magnesium, 77 ml. of bromobenzene and 700 ml. of ether, was cooled with an ice–salt-bath and 78 g. of cadmium chloride was added over a period of five minutes. The mixture was refluxed for one hour and cooled to −20°. A solution of 3(β)-formoxy-5-cholenic acid chloride in 250 ml. of benzene was then added dropwise over a period of twenty minutes (the acid chloride was prepared from 30 g. of 3(β)-formoxy-5-cholenic acid and 120 ml. of thionyl chloride and was not crystallized). Efficient stirring is necessary to avoid formation of a gummy precipitate which becomes semi-solid. The reaction mixture was then allowed to reflux for one hour, cooled, and poured into iced hydrochloric acid. The product was extracted with ether, washed with dilute sodium hydroxide and water, dried and evaporated to dryness. The resulting residue was refluxed for one hour with 750 ml. of alcohol, and 5 g. of potassium hydroxide dissolved in 5 ml. of water. On cooling, the product crystallized and was collected; yield, 24 g. (69%), m. p. 113–120°. This was treated with acetic anhydride and pyridine without further purification. The yield of acetate was 23 g., m. p. 155–157°.

3(β)-Hydroxy-24-keto-24-*p*-anisyl-5-cholene (VII).—Essentially the same procedure was followed as that described above for the phenyl ketone. Ten grams (0.025 mole) of 3(β)-formoxy-5-cholenylamide was treated with a Grignard solution prepared from 4.85 g. of magnesium, 25.8 ml. of *p*-bromoanisole and 100 ml. of anhydrous ether. The yield of anisyl ketone was 4.2 g. (37.1%), m. p. 152–156°. With the dianisylcadmium method, 8 g. (0.02 mole) of 3(β)-formoxy-5-cholenic acid was converted to the acid chloride and was allowed to react with a solution of di-*p*-anisylcadmium prepared from 2.4 g. of magnesium, 13 ml. of *p*-bromoanisole, 9.17 g. of cadmium chloride and 50 ml. of anhydrous ether. The yield was 1.7 g. (18.5%), m. p. 153–156°. Recrystallization from acetone raised the melting point to 154–157°.

Anal. Calcd. for $C_{31}H_{44}O_3$: C, 80.13; H, 9.55. Found: C, 79.88; H, 9.06.

To 0.5 g. of the ketone dissolved in 75 ml. of alcohol was added a solution of 1.25 g. of hydroxylamine hydrochloride in 3.5 ml. of water. The **oxime** crystallized after heating on the steam-bath for thirty minutes, diluting with 25 ml. of water and cooling. After several recrystallizations from alcohol and water and from acetone, pure material was obtained that melted at 177–179°.

Anal. Calcd. for $C_{31}H_{45}O_3N$: C, 77.62; H, 9.64; N, 2.93. Found: C, 77.57; H, 9.21; N, 2.94.

Acknowledgment.—We wish to express our appreciation to Dr. George Pish of the Physics Department for the ultraviolet absorption data, and to Mr. Norman Drake for determining the optical rotations reported in this paper.

Summary

24-Phenyl-5-cholen-3(β),24-diols, epimeric at C-24, have been prepared by (a) reaction of 3(β)-acetoxy-5-cholen-24-al with phenylmagnesium bromide; and (b) reduction of the corresponding phenyl ketone.

The epimeric diols have been separated and characterized.

3(β)-Hydroxy-24-keto-24-anisyl-5-cholene has been prepared.

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[8] Prepared according to the method of Cortese and Bauman for desoxycholylamide, *J. Biol. Chem.*, **113**, 779 (1936).