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Steroid Acids and Their Transformation Products. V. 24-Phenyl-5,23-choladien-3β-ol and Derivatives

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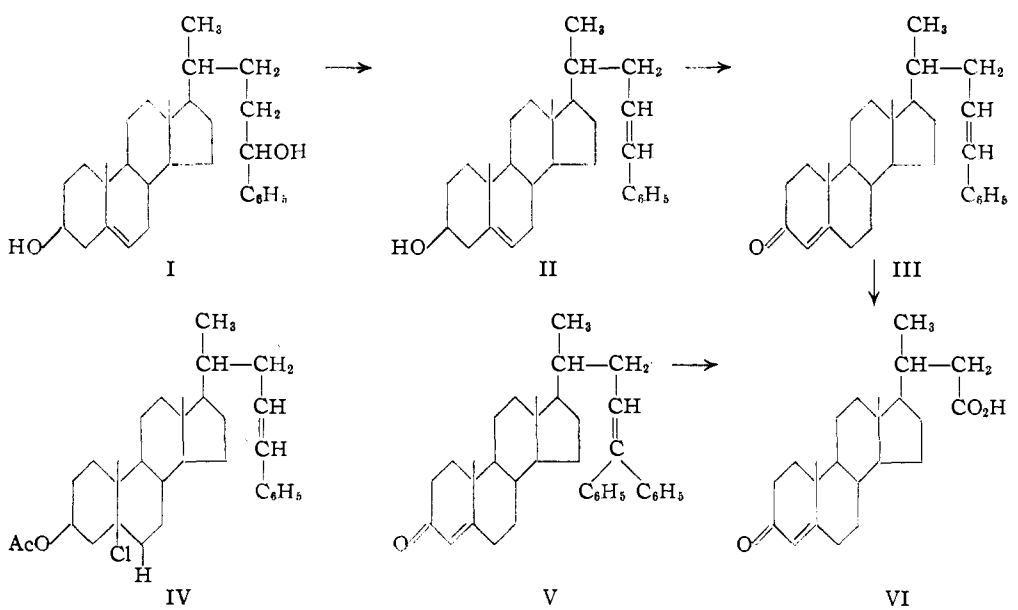
The preparation of two 24-phenyl-5-cholen-3β,24-diols (I), epimeric at C-24, has been reported recently.[1] When the mixture of epimeric diols, or either pure isomer, was treated with anhydrous oxalic acid in refluxing Dowtherm A[2] selective dehydration occurred, giving a choladiene in 60–75% yield. The dehydration product (II) was precipitable with digitonin and readily formed a monoacetate which, on treatment with excess bromine in carbon tetrachloride, gave a tetrabromide. The acetate of II exhibited an ultraviolet absorption curve having a principal peak at 251 mμ and two smaller maxima at 285 mμ and 293 mμ, respectively. This is in good agreement with published data for substituted phenylethylene,[3] indicating that the dehydration product is 24-phenyl-5,23-choladien-3β-ol (II). If dehydration had occurred at C-3 the product would have been a derivative of 2,4-cholestadiene, or 3,5-cholestadiene, having absorption maxima in the region 267–275 mμ and 234–240 mμ, respectively.[4]



An Oppenauer oxidation of 24-phenyl-5,23-choladien-3β-ol (II) with aluminum isopropoxide and cyclohexanone gave 24-phenyl-4,23-choladien-3-one (III), whose absorption curve exhibited maxima at 247, 285 and 293 mμ. The same ketone (III) was obtained by oxidizing the tetrabromide of II with chromic acid in acetic acid, debrominating with zinc, and isomerizing the 5,6 double bond with alkali. To complete the structure proof of these compounds, the ketone (III) was oxidized with chromic acid to give 3-keto-nor-4-cholenic acid (VI) in 50% yield. This keto acid, which has not been recorded previously in the literature, was also obtained, in 25% yield, by a similar oxidation of the corresponding diphenylethylene (V).

The acetate of the dehydration product (II) was treated at 0° with a saturated solution of hydrogen chloride in chloroform and acetic acid (1:1). The product of this reaction was characterized as 5-chloro-24-phenyl-23-cholene-3β-ol acetate (IV) on the basis of analysis and the fact that its ultraviolet absorption spectrum is identical with that of compound (II). When the acetate of 24-phenyl-5,23-choladien-3β-ol (II) was treated with hydrogen chloride in acetic acid–ether (1:16) at 0°, a mixture of mono- and dihydrohalogenated products was formed, as indicated by analysis and ultraviolet absorption data. Attempts to separate the components by fractional crystallization were not successful.

When cholesterol was treated with anhydrous oxalic acid in refluxing Dowtherm A for a period four times as long as the optimum time for the dehydration of the diol (I), better than 70% of the cholesterol was recovered unchanged. The selectivity of the dehydrating action of the oxalic

(1) Paper IV of this series, Levin, Spero, McIntosh and Rayman, THIS JOURNAL, **70**, 2958 (1948).

(2) Dowtherm A is a mixture consisting of 90% diphenyl ether and 10% biphenyl.

(3) Campbell, Linden, Godshalk and Young, THIS JOURNAL, **69**, 880 (1947); see also Campbell and Young, *ibid.*, **71**, 296 (1949).

(4) Dimroth, *Angew. Chem.*, **52**, 545 (1939).

acid on these secondary alcohols may be due to the influence of activating groups adjacent to the hydroxyl. Experiments designed to study and extend this reaction are now under way.

Acknowledgment.—We wish to express our appreciation to Dr. George Pish for the ultraviolet absorption data reported in this paper.

Experimental[5]

24-Phenyl-5,23-choladien-3β-ol Acetate (II).—Eight grams (0.018 mole) of a mixture of the two epimers of 24-phenyl-5-cholen-3β,24-diol (I)[1] was allowed to reflux for ninety minutes with 16 g. of anhydrous oxalic acid[6] and 160 ml. of Dowtherm A. Most of the Dowtherm A was then removed by distillation *in vacuo*. During the distillation the oxalic acid sublimed out of the reaction mixture. The residue was cooled, dissolved in 200 ml. of ether and washed with 2% sodium bicarbonate solution and water. The ether solution was dried over anhydrous sodium sulfate and the solvent removed. The residue was dissolved in 200 ml. of hexane and passed over 230 g. of alumina[7] in a column 5 cm. in diameter. Elution with 700 ml. of hexane–benzene (1:1) removed the Dowtherm A, and the product (II) was obtained by the use of 800 ml. of benzene–methanol (92:8). The benzene–methanol eluate was taken to dryness and the residue crystallized from ether, giving 5.28 g. (69%) of 24-phenyl-5,23-choladien-3β-ol, m.p. 105–118°. This material could not be crystallized to a sharper melting point because of its tendency to solvate. It was heated for three hours on the steam-bath with acetic anhydride and pyridine, giving 4.88 g. (87%) of the acetate, m.p. 172–176°. Recrystallization from methanol–ether gave pure material, m.p. 176.5–177.5°; $[\alpha]^{24}D$ −31.4° (62.1 mg. in 10 ml. of chloroform; 2-dm. tube: α_D −0.39°). Absorption spectrum: maxima at 251 mμ (log *E*, 4.29), 285 mμ (log *E*, 3.25), 293 mμ (log *E*, 2.97), taken in 95% alcohol (*c*, 2.210 mg. in 100 ml.).

Anal. Calcd. for $C_{32}H_{44}O_2$: C, 83.43; H, 9.63; CH_3CO, 9.3. Found: C, 83.10; H, 9.60; CH_3CO, 9.5.

The tetrabromide was formed by treating 60 mg. of the acetate in 2 ml. of carbon tetrachloride with an excess of bromine in the same solvent. After standing at room temperature the solution was evaporated to dryness and the residue crystallized from methanol–ether, m.p. 168–175°. Recrystallization gave the tetrabromide of 24-phenyl-5,23-choladien-3β-ol acetate, m.p. 171–175°.

Anal. Calcd. for $C_{32}H_{44}O_2Br_4$: Br, 40.96. Found: Br, 40.56, 40.88.

Saponification of 3.94 g. of the acetate in 225 ml. of methanol with 3.9 g. of potassium hydroxide in 9 ml. of water gave 3.12 g. (84%) of recrystallized hydroxy compound (II), m.p. 107–113°. Numerous recrystallizations from ether, benzene, alcohol, acetone and other solvents failed to give sharper melting material. Analysis indicated varying degrees of solvation.

24-Phenyl-4,23-choladien-3-one (III). **A. By Oppenauer Oxidation.**—Three grams (0.007 mole) of 24-phenyl-5,23-choladien-3β-ol was dissolved in 90 ml. of toluene and 60 ml. of cyclohexanone. Ten ml. of the solution was distilled to remove traces of moisture and 3 g. of aluminum isoproxide was added. The mixture was heated under reflux for two and one-half hours, cooled, and diluted with a mixture of 200 ml. of 5% hydrochloric acid and 100 ml. of ether. The aqueous phase was separated and extracted with 100 ml. of fresh ether. The combined ether solution was washed with 5% hydrochloric acid and water, then dried and concentrated *in vacuo*. The residue was crystallized from methanol giving 2.6 g. (86%) of the keto diene (III), m.p. 130–154°. Recrystallization from ether–methanol gave 76% of pure material, m.p. 159–160.5°; $[\alpha]^{25}D$ +99.8° (52.6 mg. in 5 ml. of chloroform; 2-dm. tube; α_D +2.10°. Absorption spectrum: maxima at 244 mμ (log *E*, 4.50), 285 mμ (log *E*, 3.24), 293 mμ (log *E*, 2.98) taken in 95% alcohol (*c*, 2.192 mg. in 100 ml.).

Anal. Calcd. for $C_{30}H_{40}O$: C, 86.47; H, 9.68. Found: C, 86.51; H, 9.43.

B. By Chromic Acid Oxidation of the Tetrabromide of II.—The tetrabromide prepared from 270 mg. of 24-phenyl-5,23-choladien-3β-ol was oxidized with chromic anhydride in acetic acid, debrominated with zinc dust and acetic acid in ether, and isomerized with alkali to give 55 mg. (32%) of crystals melting at 159–163°. The 3-keto compounds (III) prepared by the two methods gave the same melting point on admixture.

5-Chloro-24-phenyl-23-cholen-3β-ol Acetate (IV).—A solution of 2.25 g. (0.005 mole) of 24-phenyl-5,23-choladien-3β-ol acetate in 9 ml. of chloroform and 4.5 ml. of glacial acetic acid was cooled to 0° and saturated with dry hydrogen chloride. After standing at 0° for twelve days, the solution was evaporated to dryness *in vacuo*. The residue was crystallized from ether, giving 0.8 g. (33%) of the 5-chloro compound (IV), m.p. 160–188°. Several recrystallizations from acetone gave a small recovery of pure material, m.p. 194–198° (dec.). Absorption spectrum: maxima at 251 mμ (log *E*, 4.30), 285 mμ (log *E*, 3.27), 295 mμ (log *E*, 2.99), taken in 95% alcohol (*C*, 2.171 mg. in 100 ml.); $[\alpha]^{25}D$ +21.4° (163.8 mg. in 10 ml. of chloroform; α_D +0.35°).

Anal. Calcd. for $C_{32}H_{45}O_2Cl$: C, 77.31; H, 9.12; Cl, 7.13. Found: C, 77.30; H, 9.05; Cl, 6.99.

When 4.7 g. of 24-phenyl-5,23-choladien-3β-ol acetate was dissolved in 800 ml. of ether and 50 ml. of acetic acid and similarly treated with dry hydrogen chloride, 4.3 g. of material, m.p. 178–186°, was obtained. Repeated crystallizations gave material with a constant m.p. of 185–187°. Analyses indicated it was essentially the dichloro compound, contaminated with some of the monochloro derivative. On refluxing this mixture with quinoline pure 24-phenyl-5,23-choladien-3β-ol acetate, m.p. and mixed m.p. 175–176.5°, was recovered in poor yield. Similar treatment with pyridine and dimethylaniline gave intractable mixtures.

3-Keto-nor-4-cholenic Acid (VI).—A solution of 700 mg. of chromic anhydride in 0.7 ml. of water and 7 ml. of acetic acid was added over a period of an hour to 400 mg. (0.0009 mole) of 24-phenyl-4,23-choladien-3-one (III) dissolved in 15 ml. of acetic acid at room temperature. The mixture was allowed to stand one hour, then the excess chromic acid was decomposed with 3 ml. of methanol. The solution was poured into 4 volumes of water, extracted with ether, and the ether solution washed with dilute hydrochloric acid and with water. On extraction of the ether solution with 5% aqueous sodium carbonate an insoluble sodium salt was formed. The aqueous suspension was separated and acidified with 3 *N* hydrochloric acid, giving 187.5 mg. (54%) of the keto acid (VI), m.p. 190–200°. Several crystallizations from acetone–water (1:1) brought the melting point to 208–211°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.29; H, 9.64.

The methyl ester of 3-keto-nor-4-cholenic acid was prepared with diazomethane and was crystallized from alcohol–water, m.p. 140–142°; $[\alpha]^{25}D$ +96.2° (15.6 mg. in 2 ml. chloroform; α_D +0.75°). Absorption spectrum: maximum at 241 mμ (log *E*, 4.20 in absolute alcohol).

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.58; H, 9.58.

Oxidation of 350 mg. of 24,24-diphenyl-4,23-choladien-3-one (V)[8] with 500 mg. of chromic anhydride under similar conditions over a period of three hours gave a

(5) All m. p.'s are corrected. Analyses and rotations by the Upjohn microanalytical and physics group. Ultraviolet absorption spectra taken on a Beckman Quartz Spectrophotometer, Model DU.

(6) "Org. Syntheses," Coll. Vol. I, 421, 2nd ed., 1941.

(7) Fisher Adsorption Alumina; obtained from the Fisher Scientific Co. and used without further treatment.

(8) Meystre, Wettstein and Miescher, *Helv. Chim. Acta*, **30**, 1022 (1947).

gummy acid fraction, which on crystallization from acetone–water yielded 66.6 mg. of 3-keto-nor-4-cholenic acid, m.p. 200–207°; methyl ester, m.p. 139–142°. A mixture of the methyl esters obtained from the monophenylethylene (III), and the diphenylethylene (V) gave no depression of the melting point.

Treatment of Cholesterol with Oxalic Acid.—A mixture of 1.0 g. of cholesterol, 4.0 g. of anhydrous oxalic acid, and 30 ml. of Dowtherm A was heated under reflux for five hours in an atmosphere of nitrogen. The Dowtherm was removed by steam distillation, and the water insoluble residue was adsorbed on 116 g. of chromatographic alumina from petroleum ether solution. Elution with petroleum ether–benzene (3:2) gave 90 mg. of material which was not further investigated. Elution with benzene–methanol (96:4) gave 727 mg. of cholesterol which after one recrystallization from 95% alcohol melted at 148–149°.

Summary

24-Phenyl-5-cholen-3β,24 diols, epimeric at C-24, have been dehydrated by anhydrous oxalic acid to give 24-phenyl-5,23-choladien-3β-ol.

24-Phenyl-4,23-choladien-3-one has been prepared and oxidized to 3-keto-nor-4-cholenic acid.

The addition of hydrogen chloride to 24-phenyl-5,23-choladien-3β-ol acetate has been studied.

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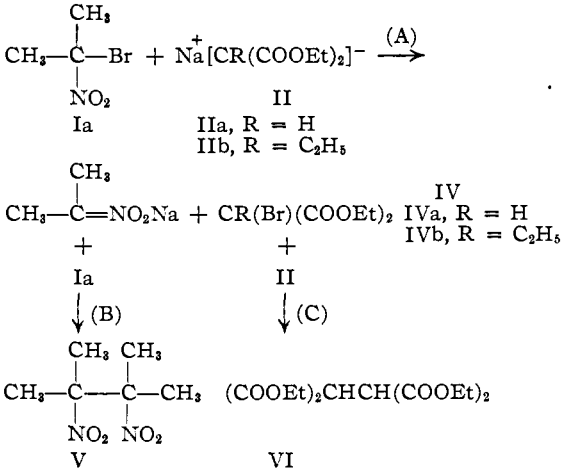
The Malonic Ester Reaction with 1-Halo-nitroparaffins

BY EUGENE E. VAN TAMELEN[1] AND GERRIT VAN ZYL

In view of the present availability of the nitroparaffins, the reaction of the readily prepared 1-halo-nitroparaffins with malonic ester was undertaken with the purpose of determining the effect, if any, of the highly electronegative nitro group upon the course of the reaction. In only one instance was a normal alkylation accomplished which resulted in a 1-nitroalkyl malonic ester.

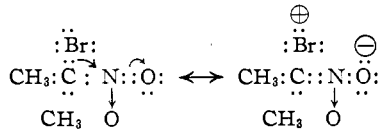
2-Bromo-2-nitropropane, Ia, was selected as a model for the bromo series, since there is no acidic hydrogen present to complicate the reaction. Upon carrying out the reaction of Ia with sodium malonic ester, IIa, under the usual conditions, two organic products were isolated: 2,3-dinitro-2,3-dimethylbutane, V, and ethane tetracarboxylic ester, VI. Since bromomalonic ester, IVa, is known to react rapidly with IIa to yield VI, IVa was postulated as an intermediate.



According to this series, one-half mole of Ia should be sufficient to convert IIa completely to VI, provided the known reaction (B) is slow.[2] It was found that the rapid addition of one-half mole of Ia to IIa gave 73% VI, with no detectable amount of V.

Since the reaction of alkyl bromomalonic esters with sodium alkyl malonic esters is not nearly as rapid as that of IVa and IIa,[3] it seemed likely that an intermediate, IVb, could be isolated if sodium ethyl malonic ester, IIb, were employed instead of IIa. Indeed, a 69% yield of IVb was obtained in this way. No matter how rapidly Ia was added to IIb, however, the formation of V could not be completely avoided—a reflection of the less rapid reaction rate of alkyl malonic esters. Increased time of addition of Ia and prolonged stirring may result in as high a yield as 30% of V.

Reaction (A) may probably be best interpreted in terms of a positively charged bromine ion. Similar reactions have been recorded in which one of the reactants possesses a halogen atom attached to the same carbon atom as one or more highly negative groups.[3] The displacement of halogen as a positive ion may be attributed to two causes: (1) the higher attraction of electrons by the nitro group as illustrated in the resonance forms



and (2) the stabilization of the resulting nitro carbanion through resonance.

The mixture of sodium salts which precipitated from the alcoholic medium during the course of the reaction was shown to consist of sodium 2-nitropropane, III, sodium bromide and sodium nitrite VII. The presence of VII along with III was unexpected, but is paralleled by the observations of Meyer[4] and Nygaard, *et al.*[5]

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(2) L. W. Seigle and H. B. Hass, *J. Org. Chem.*, **5**, 100 (1940).

(3) C. L. Jackson and F. C. Whitmore, THIS JOURNAL, **37**, 1919 (1915).

(4) V. Meyer, *Ann.*, **175**, 88–93 (1875).

(5) E. M. Nygaard, J. H. McCracken and T. T. Noland, U. S. Patent 2,370,185.