[CONTRIBUTION OF THE RESEARCH LABORATORIES, THE UPJOHN CO.]

A Synthesis of 4-Androsten-3,17-dione from 22-(1-Piperidyl)-bisnor-4,20(22)-choladien-3-one via a β-Bromo Ternary Iminium Bromide

BY R. L. PEDERSON, J. L. JOHNSON, R. P. HOLYSZ AND A. C. OTT

RECEIVED SEPTEMBER 11, 1956

Bromine was found to add selectively to the enamine group in 22-(1-piperidyl)-bisnor-4,20(22)-choladien-3-one. The infrared absorption spectrum showed the bromine addition product to be a β-bromo ternary iminium salt. Hydrolysis of the latter gave 3-keto-20-bromobisnor-4-cholen-22-al which on dehydrohalogenation gave 3-ketobisnor-4,17(20)-choladien-22-al. The aldehyde was converted to a monocyanohydrin which on ozonolysis produced 4-androsten-3,17-dione. All these reactions gave high yields.

Bromine was found to react selectively with the enamine group in 22-(1-piperidyl)-bisnor-4,20(22)-choladien-3-one (I).[1] The resulting unstable dibromo compounds had solubility properties suggestive of a salt-like structure. Previous reports[2,3] on other enamines have described the addition of bromine to form dibromides of the general formula RRCBrCHBrNHR. The structures of our dibromo compounds were elucidated by a study of their absorption spectra.

The ultraviolet and infrared absorption spectra of I were complicated in the regions 200–250 mμ and 1600–1700 cm.$^{-1}$ due to the absorptions by the conjugated ketone in ring A. The ultraviolet and infrared spectra of 3α-acetoxy-22-(1-piperidyl)-bisnor-20(22)-cholene (VII) appeared more suitable and were used for this study. The parent enamine VII had an ultraviolet absorption maximum at 235 mμ in ether (log E 3.80); this absorption was eliminated on bromination. The infrared spectrum of the bromination product, however, established the β-bromo ternary iminium structure VIII. It showed a double bond absorption at 1626 cm.$^{-1}$ which was more intense than the analogous absorption (1646 cm.$^{-1}$) of the parent enamine. The decrease in the band frequency must be ascribed to the adjacent bromine since a simple ternary iminium bromide XI showed an increase in frequency to 1666 cm.$^{-1}$, analogous to that observed in earlier work[4] on tetrahydropyridine derivatives. By analogy, structure II was assigned to the bromination product of I.

The β-bromo ternary iminium bromides II and VIII hydrolyzed with water[3] to form α-bromoaldehydes III and IX. The α-bromoaldehyde III on treatment with pyridine gave 3-ketobisnor-4,17-(20)-choladien-22-al (IV). Ozonolysis of IV using one equivalent of ozone yielded 4-androsten-3,17-dione (VI) and pyruvaldehyde.

Attempts were made to alter the course of elimination of hydrogen bromide from the α-bromoaldehyde IX. Various reagents were tried and the structures of the products were determined with the aid of ultraviolet absorption spectra. In all the experiments elimination followed primarily the course indicated by the Saytzeff rule, *i.e.*, the more branched olefin resulted.

As mentioned above ozonolysis of 3-ketobisnor-4,17(20)-choladien-22-al (IV) gave androstendione, but the yield was low. This could be a result of random attack on two similar conjugated double bonds. The side chain double bond was removed from conjugation by converting the aldehyde group to the monocyanohydrin V. The non-conjugated side chain double bond of V underwent ozonolysis to give a high yield of 4-androsten-3,17-dione (VI).[5,6]

Acknowledgments.—The authors are grateful to W. A. Struck and associates for analyses; to J. E. Stafford and A. E. Fonken for spectral data.

Experimental

The infrared spectra were obtained from a Perkin–Elmer model 21 spectrophotometer equipped with a sodium chloride prism. The ultraviolet spectra were obtained from a Cary model 11 spectrophotometer.

Preparation of a Ternary Iminium Bromide XI.—A solution containing 300 mg. of 3α-acetoxy-22-(1-piperidyl)-bisnor-20(22)-cholene (VII) in 45 ml. of absolute ether was cooled in an ice-bath. Anhydrous hydrogen bromide was added to give a solid precipitate. The mixture was filtered, the precipitate was washed with fresh ether to yield 290 mg. of the hydrobromide, m.p. 224–227°.

Anal. Calcd. for $C_{29}H_{48}BrNO_2$: Br, 15.29; N, 2.68. Found: Br, 15.64, 15.61; N, 3.00.

The infrared absorption spectrum on a chloroform solution showed a peak at 1666 cm.$^{-1}$ characteristic of —C=N$^+$<[4] and no peak at 1646 cm.$^{-1}$ (C=C) as in the parent enamine VII.

Preparation of a β-Bromo Ternary Iminium Bromide VIII.—A solution containing 239 mg. of 3α-acetoxy-22-(1-piperidyl)-bisnor-20(22)-cholene (VII) in 3 ml. of chloroform was brominated using 0.8 ml. of a 0.38 M solution in chloroform. (When more bromine was added a bromine color persisted.) After diluting to 5.0 ml. with chloroform an infrared absorption spectrum was obtained which showed a new —C=N$^+$< absorption at 1626 cm.$^{-1}$. The disappearance of C=C absorption at 1646 cm.$^{-1}$ was noted also.

Isolation of the β-Bromo Ternary Iminium Bromide II.—A suspension of 11.87 g. of enamine I in 300 ml. of petroleum ether was cooled to −78°. A solution of 4.80 g. of bromine in 50 ml. of methylene chloride was added dropwise in 30 minutes while stirring the reaction mixture. After addition of all the bromine the mixture was concentrated to dryness

(1) The preparation and some reactions of this enamine were reported by (a) M. E. Herr and F. W. Heyl, THIS JOURNAL, **74**, 3627 (1952); (b) D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, Jr., J. E. Stafford, R. L. Pederson and A. C. Ott, *ibid.*, **77**, 1212 (1955).

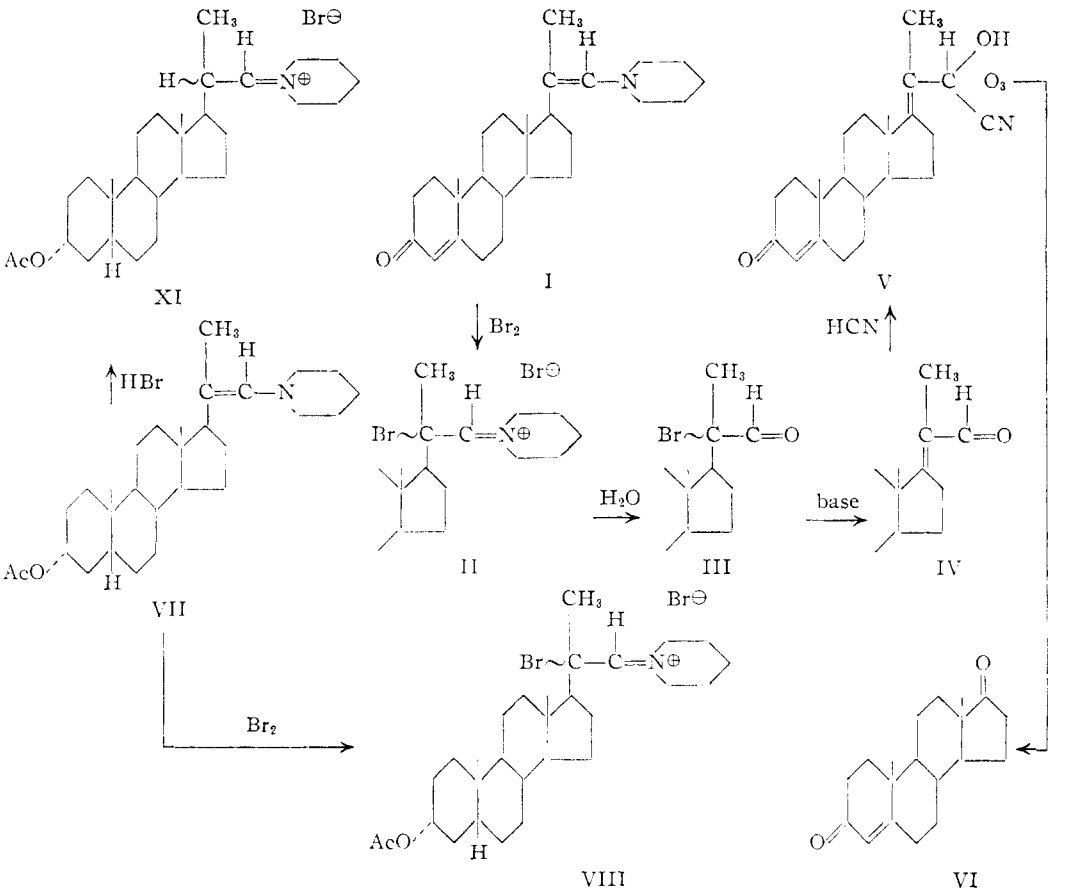
(2) M. A. Berg, *Bull. soc. chim.*, **37**, 637 (1925); *cf. C. A.*, **19**, 2645 (1925).

(3) J. Turcan, *ibid.*, **51**, 486 (1932); *cf. C. A.*, **26**, 4588 (1932).

(4) N. J. Leonard and V. W. Gash, THIS JOURNAL, **76**, 2781 (1954).

(5) The metabolism of 4-androsten-3,17-dione in man was reported by R. I. Dorfman, *J. Clin. Endocrinology and Metabolism*, **14**, 318 (1954).

(6) The following are examples of the importance of 4-androsten-3,17-dione as an intermediate in the synthesis of: (a) testosterone by F. W. Heyl and M. E. Herr, THIS JOURNAL, **75**, 1918 (1953); (b) 17-methyl- and 17-ethynyltestosterone by K. Miescher, U. S. Patent 2,435,013; (c) estrone and estradiol by C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki, THIS JOURNAL, **72**, 4534 (1950).



in vacuo, leaving 16.40 g. (98.5%) of granular β-bromo ternary iminium bromide II, m.p. <50° dec. The compound darkened on standing.

Anal. Calcd. for $C_{27}H_{41}Br_2NO$: Br, 28.78. Found: Br, 29.23.

3-Keto-20-bromobisnor-4-cholen-22-al (III). A. By Bromination of Enamine.—A solution containing 39.6 g. (0.10 *M*) of 22-(1-piperidyl)-bisnor-4,20(22)-choladien-3-one (I) in 1200 ml. of methylene chloride was cooled to about −25°. Bromine (16.0 g. or 0.10 *M*, in 100 ml. of methylene chloride) was added to the cold solution over a period of 20 minutes while stirring. The reaction mixture was warmed to −5°, 300 ml. of cold water was added, and the mixture was stirred vigorously for 1.5 hours. The organic layer was separated, washed twice with water, dried over sodium sulfate, filtered and concentrated at reduced pressure. The residue weighed 41.8 g. (theory 40.7), and darkened on drying overnight in a vacuum oven. Repetition of the hydrolysis and concentration yielded a stable bromoaldehyde weighing 40.1 g., m.p. 95–100° dec. The combined water layers titrated 0.110 g. atom of Br^-.

Anal. Calcd. for $C_{22}H_{31}BrO_2$: Br, 19.62. Found: Br, 16.48.

Recrystallization from Skellysolve B gave 3-keto-20-bromobisnor-4-cholen-22-al, m.p. 124–126° dec., $[\alpha]D$ +33° (*c* 1.11 in $CHCl_3$). *Anal.*: Br, 19.70. As in preparation of IX piperidine hydrobromide was isolated.

B. From Enamine Hydrochloride and N-Bromoacetamide.—Enamine I (11.87 g., 30 mmoles) was dissolved in a mixture of 70 ml. of *t*-butyl alcohol and 30 ml. of 10% hydrochloric acid at room temperature. A solution of 4.55 g. (33 mmoles) of N-bromoacetamide in 30 ml. of *t*-butyl alcohol was added in 10 minutes. A precipitate began to form when about half of the N-bromoacetamide solution had been added. The mixture was stirred for 30 minutes, then 200 ml. of water containing 5 g. of sodium bisulfite was added. The mixture was cooled for 10 minutes with an ice-bath, then filtered. The white solid was washed with water and dried in a desiccator; yield 10.25 g. (83.7%), m.p. 123–126° dec. Recrystallization from ether–methylene chloride afforded material, m.p. 124–126° dec.

Anal. Calcd. for $C_{22}H_{31}BrO_2$: Br, 19.62. Found: Br, 20.30.

3-Ketobisnor-4,17(20)-choladien-22-al (IV).—A solution containing 16.75 g. (40 mmoles) of 22-(1-piperidyl)-bisnor-4,20(22)-choladien-3-one (I) in 800 ml. of methylene chloride was cooled to −55° using a Dry Ice–acetone-bath. To this was added a solution containing 6.74 g. (42 mmoles) of bromine in 80 ml. of methylene chloride; the solution was stirred throughout the addition and the temperature was kept at about −55°. The reaction mixture was warmed to about 0°, 100 ml. of water was added and the reaction mixture was stirred vigorously for a period of 2 hours. The layers were separated, and the organic layer was washed twice with 100-ml. portions of water. After drying the organic layer, 20 ml. of pyridine was added and then the methylene chloride was distilled at reduced pressure. An additional 80 ml. of pyridine was added; the solution was then warmed to 70° for 1 hour, and on the steam-bath for 0.5 hour. Distillation at reduced pressure left a sirupy residue containing a trace of pyridine. This residue was dissolved in 200 ml. of methylene chloride, and washed twice with 10% hydrochloric acid, once with 5% sodium carbonate and water. Evaporation of the methylene chloride yielded 12.46 g., m.p. 132–137°, λ_{max}^{alc} 248 mμ, log *E* 4.44.

A portion (10 g.) of the above residue was dissolved in benzene and chromatographed on 430 g. of Florisil. Elution was done with 15 fractions (1 l. each) of each of the solvents: 1, 2.5 and 4% acetone in petroleum ether. Fractions 33–37 were combined and recrystallized from acetone to give 3-ketobisnor-4,17(20)-choladien-22-al, m.p. 139–141°, λ_{max}^{alc} 248.5 mμ, log *E* 4.44, $[\alpha]D$ +113° (*c* 1.186 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 81.01, 80.87; H, 8.98, 9.23.

Ozonolysis of 3-Ketobisnor-4,17(20)-choladien-22-al. Isolation of 4-Androsten-3,17-dione VI and Pyruvaldehyde.—A solution containing 1.42 g. (4.36 mmoles) of 3-ketobis-

nor-4,17(20)-choladien-22-al (IV), 100 ml. of ethyl acetate, 100 ml. of methylene chloride and 2 ml. of pyridine was placed in a tubular ozonization flask equipped with bubbler and cooled to 0°. An ozone stream containing 0.22 mmole of ozone per minute was used; the ozonization time was 22 minutes (4.8 mmoles). The ozonization mixture was placed under a Dry Ice–acetone condenser, 20 ml. of water was added and the mixture was warmed to reflux for a period of 1.5 hours. After cooling, the layers were separated and the organic layer was washed 3 times with water; the combined water layers were treated as described in the next paragraph. The organic layer was washed with dilute acid, dilute bicarbonate, and water; evaporation of the solvent yielded 0.75 g. of gelatinous residue. The residue was dissolved in benzene and chromatographed on 75 g. of Florisil. Elution was done with ten fractions (200 ml. each) of each of the solvents: 0.5, 1.0, 1.5, 2.0% acetone in petroleum ether. Fractions 33–40 were combined (wt. 0.28 g.) and crystallized from acetone to give 0.16 g. of 4-androsten-3,17-dione, m.p. 171–172°, m.m.p. 171–172°.

Treatment of the combined water washes with 0.200 g. of dimedon together with a drop of pyridine for two weeks yielded 0.038 g. of pyruvaldehyde dimethone, m.p. 163–166° (lit. m.p. 164°), m.m.p. 163–166°.

Anal. Calcd. for $C_{19}H_{26}O_6$: C, 68.24; H, 7.84. Found: C, 67.99, 68.89; H, 7.76, 7.64.

The isolation of 4-androstene-3,17-dione and pyruvaldehyde establishes the structure for 3-ketobisnor-4,17(20)-choladien-22-al.

Cyanohydrin of 3-Ketobisnor-4,17(20)-choladien-22-al (V).—A slurry of 3-ketobisnor-4,17(20)-choladien-22-al (IV) (m.p. 124–133°, λ_{max}^{alc} 248 mμ, log E 4.44) was prepared by adding 8.16 g. (25 mmoles) of the aldehyde to a solution of 12.3 g. (250 mmoles) of sodium cyanide in 75 ml. of anhydrous methanol which was cooled to −20°. While stirring rapidly, 11.5 ml. (200 mmoles) of glacial acetic acid was added dropwise over a period of 1 hour. The mixture became very thick. Stirring was continued until the internal temperature reached 0°. This required about 2 hours. The mixture was placed in the refrigerator and kept at 0–5° for 48 hours. The thick paste was shaken with 300 ml. of ice-cold methylene chloride. The resulting mixture was washed with one 150-ml. portion, then with four 50-ml. portions of ice-water. The methylene chloride solution was dried with 10 g. of anhydrous sodium sulfate for 18 hours at 0–5°. The mixture was filtered and concentrated to 250 ml. at 20–25° at partially reduced pressures. This solution was ready for the next step, ozonolysis.

Evaporation to dryness of such a solution yielded an amorphous solid. Recrystallization from absolute ether gave a 25% yield of fine white crystals of the cyanohydrin V, m.p. 178–183° dec.

Anal. Calcd. for $C_{23}H_{31}NO_2$: C, 78.14; H, 8.84; N, 3.96. Found: C, 78.20; H, 9.30; N, 4.15; λ_{max}^{ether} 232.5 mμ, log E 4.23; λ_{max}^{Nujol} 3360 cm.$^{-1}$ (OH), 1660 cm.$^{-1}$ (conj. C=O), 2230 cm.$^{-1}$ (C≡N).

The sirupy residue (75% yield) was also the desired cyanohydrin as indicated by its infrared spectrum.

Ozonolysis of the Cyanohydrin V to 4-Androstene-3,17-dione (VI).—The 250 ml. of methylene chloride solution containing theoretically 25 mmoles of the monocyanohydrin was cooled to −70°, 2.4 ml. (30 mmoles) of anhydrous pyridine was added and the solution was ozonized for 75 minutes with an ozone–oxygen stream (300 ml. per minute at a pressure head of 11.2 cm.) producing 0.405 mmole of ozone per minute. During the last three minutes ozone passed into the overflow trap. The absorption of ozone was 29.4 mmoles or 1.18 moles per mole of steroid. The cold ozonized solution was transferred quickly to a flask equipped with a stirrer, and 50 ml. of acetic acid was added in one portion, followed immediately by 5 g. of zinc dust. The mixture was stirred rapidly for 2 hours, during which time it reached room temperature. The mixture was filtered and diluted with 250 ml. of Skellysolve A. It was washed with 100 ml. of water, two 50-ml. portions of water, two 50-ml. portions of 10% sodium hydroxide solution, 50 ml. of water, 50 ml. of 10% hydrochloric acid solution and two 50-ml. portions of water. After drying overnight at 0–5° with sodium sulfate the mixture was filtered and concentrated to dryness *in vacuo*. The last traces of solvent were removed at 60° at 20–30 mm. pressure, leaving 6.55 g. (91.4% yield) of 4-androsten-3,17-dione, m.p. 155–160°, after softening at 142–143°, $[\alpha]_D$ +166° (c 0.52 in $CHCl_3$).

3α-Acetoxy-20-Bromobisnorcholan-22-al (IX). A. From Isolated Enamine.—A solution containing 3.14 g. (7.1 mmoles) of 3α-acetoxy-22-(1-piperidyl)-bisnor-20(22)-cholene (VII) in 210 ml. of ethyl acetate was cooled to about 8°. Bromine (0.5 M) in carbon tetrachloride was added slowly until the bromine color persisted for 1 minute; the amount of bromine solution added was 12.7 ml. (6.4 mmoles). The products were characterized as follows: (1) **Isolation of Piperidine Hydrobromide.**—A precipitate had formed which was isolated by filtration. The precipitate weighed 0.92 g., m.p. 200–240°. A water solution of this material gave a precipitate with silver ion.

Anal. Calcd. for piperidine hydrobromide, $C_5H_{12}BrN$: Br, 48.2. Found: Br, 48.5.

(2) Isolation of 3α-Acetoxy-20-bromobisnorcholan-22-al (IX).—The filtrate described above was washed with water and dried over sodium sulfate. Evaporation of the solvent at reduced pressure yielded 3.07 g., m.p. 118–122°. Two recrystallizations from acetone yielded 1.28 g., m.p. 131–132°.

Anal. Calcd. for $C_{24}H_{37}BrO_3$: C, 63.56; H, 8.22; Br, 17.62. Found: C, 63.65; H, 8.13; Br, 16.97; infrared spectrum had carbonyl band at 1720 cm.$^{-1}$ and acetate C–O at 1245 cm.$^{-1}$.

Elimination Studies. A. Dehydrobromination with Pyridine and Isolation of 3α-Acetoxybisnor-17(20)-cholen-22-al (X).—A solution of 4.53 g. (10 mmoles) of the above-described 3α-acetoxy-20-bromobisnorcholan-22-al (IX) in 25 ml. of pyridine was heated for 2 hours on a steam-bath. The pressure was reduced and the mixture was concentrated to dryness. The solid residue was dissolved in a mixture of 100 ml. of ether and 50 ml. of water. After separation of the layers the ether solution was washed with 25 ml. of water, 25 ml. of 10% hydrochloric acid solution, and two 25-ml. portions of water. The solution was dried with sodium sulfate, filtered and concentrated to *ca.* 5 ml. It was diluted with an equal volume of Skellysolve A and refrigerated. The first crop of crystals was 2.58 g. (69.3%), m.p. 124–132°, λ_{max}^{alc} 255 mμ. Evaporation of the mother liquor gave 0.85 g. of impure $\Delta^{17,20}$-aldehyde.

Recrystallization of $\Delta^{17(20)}$-aldehyde (λ_{max}^{alc} 253.5 mμ, log E 4.18) from ether–Skellysolve A afforded analytical material, m.p. 151–154°, $[\alpha]_D$ +43° (c 0.938 in $CHCl_3$), λ_{max}^{alc} 253 mμ, log E 4.20.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.52, 77.38; H, 9.52, 9.21.

B. Dehydrobromination with Lithium Chloride in Dimethylformamide.[7]—A solution of 4.53 g. (10 mmoles) of 3α-acetoxy-20-bromobisnorcholan-22-al and 1.27 g. (30 mmole) of anhydrous lithium chloride in 12.5 ml. of dimethylformamide was heated 2 hours (N_2 atm.) on a steam-bath. The solution was diluted with 125 ml. of water, and the gummy solid which precipitated was triturated with several portions of water. It was dissolved in 100 ml. of ether; the solution was washed with four 25-ml. portions of water, dried with 5 g. of sodium sulfate, and concentrated to *ca.* 5 ml. The solution was diluted with 5 ml. of Skellysolve A and refrigerated. The first crop of crystals was 2.43 g. (65.2%) of 3α-acetoxybisnor-17(20)-cholen-22-al, m.p. 115–123°, λ_{max}^{alc} 255.5 mμ. Evaporation of the mother liquor gave 1.00 g. of impure $\Delta^{17(20)}$-aldehyde.

C. Dehydrobromination *via* the Semicarbazone.—A solution of 2.23 g. (20 mmoles) of semicarbazide hydrochloride and 1.64 g. (20 mmoles) of anhydrous sodium acetate in 10 ml. of water was added to 4.53 g. (10 mmoles) of 3α-acetoxy-20-bromobisnorcholan-22-al in 50 ml. of dioxane (N_2 atm.). The mixture was stirred and heated at 45° for 20 minutes. The originally yellow solution became colorless and 5 g. (57 mmoles) of pyruvic acid was added. The mixture was heated at 65° for 2 hours. The pressure was reduced and the dark solution was concentrated to 10 ml. The sirup was shaken with 100 ml. of water and the mixture was extracted with three 50-ml. portions of ether. The extract was washed with 25 ml. of water, two 25-ml. portions of ice-cold 10% sodium hydroxide solution, 25 ml. of 10% hydrochloric acid solution, and two 25-ml. portions of water. The yellow ether solution was dried with 5 g. of sodium sulfate, filtered and concentrated to 5 ml. Dilution with 5 ml. of Skellysolve A and refrigeration yielded 0.45

(7) R. P. Holysz, THIS JOURNAL, **75**, 4432 (1953).

g. (12.1%) of 3α-acetoxybisnor-17(20)-cholen-22-al, m.p. 140–148°, λ_{max}^{alc} 254 mμ; λ_{max}^{Nujol} 1735 (acetate), 1655 (conj. ald.), 1620 cm.$^{-1}$ (conj. C=C). The resinous residue (3.06 g.) was a mixture containing much 3-hydroxy compound, probably resulting from hydrolysis of the 3-acetate, λ_{max}^{alc} 256 mμ.

D. Dehydrobromination with γ-Collidine.—A solution of 2.27 g. (5 mmoles) of 3α-acetoxy-20-bromobisnorcholan-22-al in 5 ml. of γ-collidine was heated 2 hours (N_2 atm.) on a steam-bath. The mixture was diluted with 25 ml. of ether and filtered. The yield of collidine hydrobromide was 0.82 g. (82%). The filtrate was diluted with 75 ml. of ether and was washed with two 25-ml. portions of ice-cold 10% hydrochloric acid, and two 25-ml. portions of water. The solution was dried, concentrated to 5 ml., diluted with 5 ml. of Skellysolve A, and refrigerated. The first crop of crystals (0.29 g.) was 3α-acetoxybisnor-17(20)-cholen-22-al, m.p. 130–137°, λ_{max}^{alc} 253.5 mμ. The gummy residue (1.35 g.) was a mixture of the desired $\Delta^{17(20)}$-aldehyde and a large amount of the saturated aldehyde, probably from reductive removal of bromine.

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[CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA DE LA UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO]

The Favorskii Rearrangement in the Pregnane Series. *cis–trans* Isomerism in Some 17,20-Dehydro Derivatives

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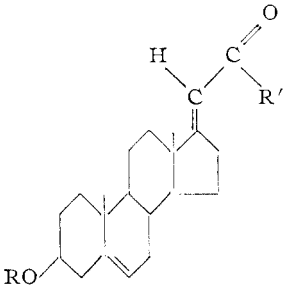
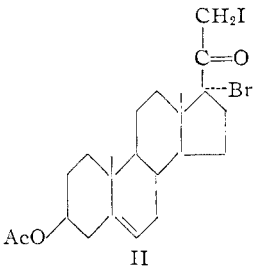
RECEIVED SEPTEMBER 5, 1956

Treatment of 17α-bromo-21-iodo-Δ^5-pregnen-3β-ol-20-one acetate (II) with methanolic potassium hydroxide under the conditions of the Favorskii rearrangement yielded two isomeric acids, *cis*-$\Delta^{5,17(20)}$-pregnadien-3β-ol-21-oic acid (IIIa) and *trans*-$\Delta^{5,17(20)}$-pregnadien-3β-ol-21-oic acid (Ia), as well as the corresponding methyl esters IIIc and Ib. 20-Bromo-$\Delta^{5,17(20)}$-pregnadien-3β-ol-21-oic acid (Xa) was obtained from the 17α,21,21-tribromo-Δ^5-pregnen-3β-ol-20-one acetate which accompanies the iodinated ketone II as an impurity. The structure of Xa was proved definitely by zinc debromination. Various experiments with lithium aluminum hydride are described which afforded derivatives of the *cis* series. The *trans* configuration is assigned to various homologs of the pregnane series that were prepared by a new method.

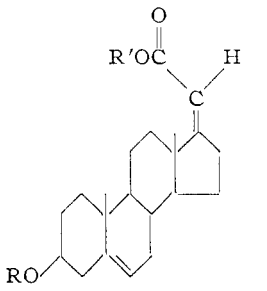
Marker, *et al.*,[1] carried out a Favorskii rearrangement on the crude product obtained by treatment of 5,6,17α,21-tetrabromo-pregnan-3β-ol-20-one acetate with sodium iodide and obtained $\Delta^{5,17(20)}$-pregnadien-3β-ol-21-oic acid (Ia). Julian and Karpel[2] reported a quantitative yield of this acid using pure 17α-bromo-21-iodo-Δ^5-pregnen-3β-ol-20-one acetate (II) but gave no experimental data. Sondheimer, *et al.*,[3] also carried out the reaction with the halogenated derivative II and these authors obtained an 85% yield of crude acid with m.p. 215–222°. By repeated crystallization the m.p. rose to a constant value of 252–254°, and these authors[3] assumed that the low m.p. of the crude acid was due to the presence of the β,γ-unsaturated acid.





II

Ia, R = H, R′ = OH
b, R = H, R′ = OCH_3
c, R = Ac, R′ = OCH_3
d, R = H, R′ = CH_3
e, R = Ac, R′ = CH_3



IIIa, R = H, R′ = H
b, R = H, R′ = CH_3
c, R = Ac, R′ = CH_3

When we carried out the Favorskii reaction with the iodinated derivative II (m.p. 153–157° dec.) in methanolic potassium hydroxide, we obtained approximately 70% yield of an acidic fraction with m.p. 211–218°, which gave a positive Beilstein test and about 20% yield of a partially crystalline neutral fraction. By fractional crystallization of the crude acid we could isolate three acids: A, B and C. The acid A (m.p. 253–255°, λ_{max} 222 mμ, log ε 4.22) is identical with the one obtained previously,[1,3] Ia. The methyl ester prepared by treatment with diazomethane and the methyl ester acetate have physical constants in good agreement with those reported by Plattner and Schreck[4] for Ib and Ic.

These authors prepared the acid (Ia) (m.p. 249–250°) by Reformatzky reaction between bromo acetic ester and Δ^5-androstene-3β-ol-17-one acetate followed by dehydration.

The acid B ($C_{21}H_{30}O_3$, m.p. 265–267°, λ_{max} 224 mμ, log ε 4.10) is isomeric with A, since partial hydrogenation of its methyl ester acetate afforded the same unconjugated methyl ester IVa that Plattner and Schreck[4] obtained by selective hydrogenation of the methyl ester Ic.

As both acids have the ultraviolet absorption for α,β-unsaturated carboxylic acids, they must be *cis–trans* isomers.[5]

Examination of models[6] of the two isomers show very clearly that in the acid with the carboxyl

(1) R. E. Marker, H. M. Crooks, E. M. Jones and A. C. Shabica, THIS JOURNAL, **64**, 1276 (1942).

(2) P. L. Julian and W. J. Karpel, *ibid.*, **72**, 362 (1950).

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(5) The term *trans* is given to the isomer with the carboxyl group opposite to the angular methyl group, and the *cis* isomer has then the reverse configuration.

(6) Molecular models, made by Catalin Products, Ltd., Waltham Abbey, Essex, England.