[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

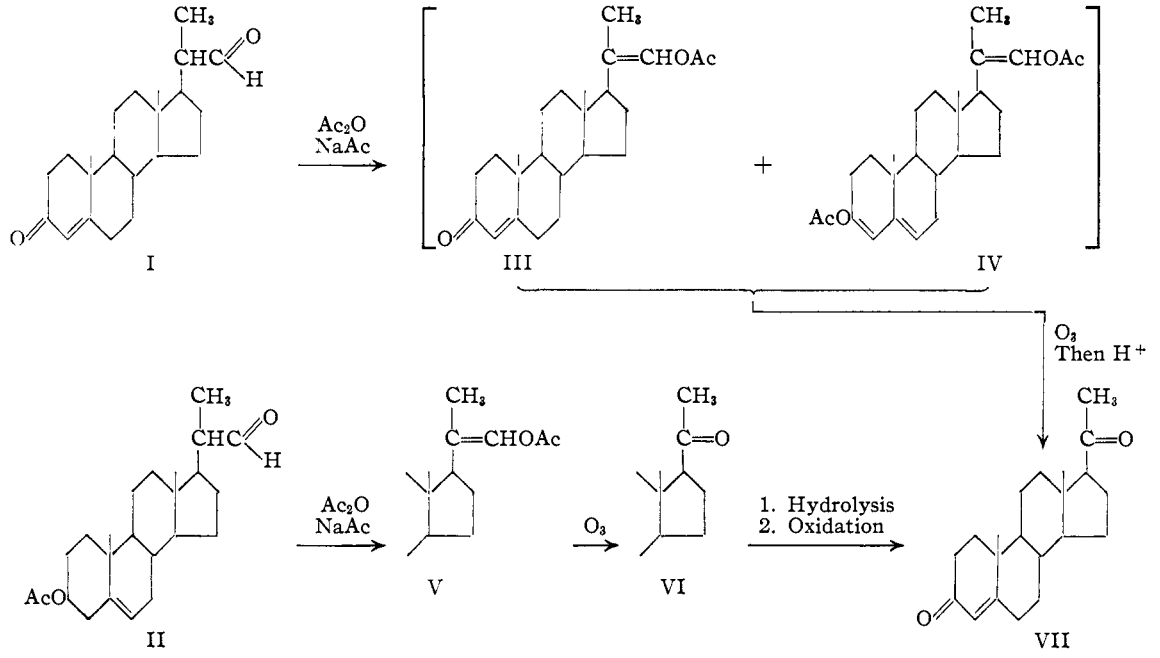
Progesterone from 3-Acetoxybisnor-5-cholenaldehyde and 3-Ketobisnor-4-cholenaldehyde

BY F. W. HEYL AND M. E. HERR

The preparation of derivatives of bisnor-5-cholenaldehyde by the ozonization of the corresponding stigmasterol derivatives[1] has been extended to the ozonization of stigmastadienone,[2] from which a yield of not less than 60% of 3-ketobisnor-4-cholenaldehyde (I) was readily obtained. The amount of ozone used in this reaction was carefully controlled to obtain a maximum yield of aldehyde and a minimum yield of 3-ketobisnor-4-cholenic acid[3] along with some easily recoverable starting material.

This new aldehyde (I) and 3β-acetoxybisnor-5-cholenaldehyde[1] (II) have now been successfully degraded to progesterone by a method first used by Semmler[4] who showed that aldehydes, including eksantalol, phenylacetaldehyde, citronellal, citral and others, which possess one or two labile hydrogen atoms on the carbon adjacent to the aldehyde group, may be converted upon heating under reflux with acetic anhydride and sodium acetate into an unsaturated ester designated as an enol acetate. In the case of eksantalol he described a method of degrading the side chain; by ozonization of the enol acetate a new aldehyde or ketone which is one carbon poorer results.

We have found that when 3β-acetoxybisnor-5-cholenaldehyde (II) was heated under reflux with acetic anhydride and sodium acetate for periods varying from six to twenty-four hours, the nicely crystalline unsaturated enol acetate (V) could be isolated in yields of 70%. This enol acetate (V), as such or as the C-5,6 dibromide, was readily ozonized to give 5-pregnene-3β-ol-20-one acetate (VI) which, upon saponification and oxidation, is readily convertible into progesterone (VII). Somewhat better over-all yields of pregnenolone acetate from the aldehyde were obtained when the enol acetate (V) was not isolated and the double bond in the nucleus was left unprotected by bromine during the ozonolysis.



When 3-ketobisnor-4-cholenaldehyde (I) was heated under reflux with acetic anhydride and sodium acetate the pure intermediate enol acetate was not obtained. This product is very likely a mixture of di- and mono-enol acetates (III and IV). It was found, however, that this crude mixture could be very conveniently ozonized directly to progesterone (VII) in 60% over-all yield from the keto-aldehyde (I).

(1) Heyl, Centolella and Herr, THIS JOURNAL, **69**, 1957 (1947); **70**, 2953 (1948).

(2) Stigmastadienone was prepared by the Oppenauer oxidation of stigmasterol; Fernholz and Stavely, *ibid.*, **61**, 2956 (1939).

(3) This keto-acid has previously been prepared by chromic acid oxidation of 3-hydroxybisnor-5-cholenic acid dibromide; Butenandt and Mamoli, *Ber.*, **68B**, 1857 (1935).

(4) Semmler, *ibid.*, **42**, 584, 962, 1161, 2014 (1909); Semmler and Schossberger, *ibid.*, **44**, 991 (1911); Bedoukian, THIS JOURNAL, **66**, 1325 (1944); *ibid.*, **67**, 1430 (1945); see also Bergmann and Stevens, *J. Org. Chem.*, **13**, 10 (1948).

Experimental[5]

Enol Acetate (V) of 3β-Acetoxybisnor-5-cholenaldehyde.—A mixture of 1.57 g. of 3β-acetoxybisnor-5-cholenaldehyde (II), 50 ml. of acetic anhydride and 1.0 g. of freshly fused sodium acetate was heated under nitrogen for six hours at reflux. After removing the excess acetic anhydride *in vacuo* below 100°, the residue was taken up in acetone and the insoluble sodium acetate removed by filtration. From the concentrated acetone solution there separated a top crop of enol acetate (V) weighing 0.63 g. and melting at 153–154°. The filtrate to which a small amount of water was added gave, upon concentration and standing in the refrigerator, a further crop of 0.61 g., m. p. 143–146°. The total yield was 1.24 g., equivalent to 72%.

A mixture of 1.62 g. of the aldehyde (II), 75 ml. of acetic anhydride and 1.5 g. of freshly fused sodium acetate was heated for twelve hours under the conditions described above. Upon standing overnight at 4°, most of the enol acetate (V) had crystallized. The crystalline material was filtered and dried in a vacuum desiccator. The accompanying sodium acetate was dissolved from the dried material with water and the enol acetate again dried. This crude product weighed 0.94 g., m. p. 147–153°; on working up the acetic anhydride filtrate there was obtained a second crop weighing 0.33 g., m. p. 144–152°; The total yield of crude enol acetate was 1.27 g. or 70%.

A third experiment, in which the aldehyde (II) was heated under reflux for twenty-four hours gave 70% yield of enol acetate. The yield, when the time of refluxing was reduced to three hours, was about 54%.

The enol acetate separated in needles when crystallized from ethyl alcohol or from concentrated ether solution, m. p. 156–157°.

Anal. Calcd. for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 75.51; H, 9.01; $[\alpha]^{25}D$ −60.4° (0.0508 g. made up to 10 ml. with chloroform, $\alpha^{25}D$ −0.307°, *l*, 1 dm.).

5-Pregnene-3β-ol-20-one Acetate (VI) from the Enol Acetate (V) of 3β-Acetoxybisnor-5-cholenaldehyde.—(a) Sixty-three hundredths gram of the enol acetate (V) (152–153°) was dissolved in 30 ml. of chloroform and 0.243 g. of bromine in 7.6 ml. of chloroform was added dropwise while stirring at 0°. The solution was ozonized for sixteen minutes using 140 mg. of ozone (190%). The resulting ozonide was reduced in the usual manner using zinc dust and acetic acid and the neutral fraction consisting of pregnenolone acetate, when triturated with dilute acetone, melted at 125–130°. To more accurately determine the yield the entire fraction was converted into the corresponding semicarbazone which melted at 240–242° and weighed 0.37 g. or 57%.

Anal. Calcd. for $C_{24}H_{37}O_3N_3$: N, 10.11. Found: N, 10.18.

(b) The aldehyde (II) (3.39 g.) was heated at reflux for eight hours under nitrogen with 125 ml. of acetic anhydride and 2.0 g. of fused sodium acetate. The reaction mixture was evaporated to dryness under reduced pressure and the steroid residue redissolved in chloroform. The insoluble sodium acetate was removed by filtration and the filtrate, having a volume of 50 ml., was cooled in an ice-bath and ozonized for twenty-two minutes (20.4 mg. ozone per minute). After removing the chloroform *in vacuo* the ozonide was decomposed with zinc dust (3 g.) and glacial acetic acid in the presence of ether. The alkali-washed ether solution of the neutral ketonic product was dried, the solvent removed and the residue redissolved in 50 ml. of methanol and 10 ml. of water. Upon refluxing with 3 g. of semicarbazide hydrochloride and 3 g. of sodium acetate the semicarbazone crystallized from the mixture. Filtered and dried, the derivative weighed 2.17 g. and melted at 235° (dec.). The yield of pregnenolone acetate calculated from the aldehyde is 57%.

3-Ketobisnor-4-cholenaldehyde (I).—An ice-cooled solution of 4.11 g. (0.01 mole) of stigmastadienone,[2] m. p. 124–125°, in 250 ml. of chloroform and 5 ml. of pyridine was ozonized for thirty-eight minutes by passing through a stream of ozone–oxygen (25 mg. of ozone per minute). The solvent was removed under nitrogen *in vacuo* and the colorless sirupy residue taken up in 25 ml. of glacial acetic acid and 50 ml. of ether. Four grams of zinc dust was added while shaking over a period of ten minutes, the mixture diluted with 300 ml. of ether and filtered. The filtrate was washed twice with water followed by cold 10% sodium hydroxide (at which point an insoluble sodium salt separated) and finally with water. The ether solution after drying over sodium sulfate was evaporated and the residue crystallized from isopropyl ether. The keto-aldehyde which separated in needles was collected on a Buchner funnel and washed with a little cold isopropyl ether; yield 1.95 g. (60%), m. p. 148–151°. A sample for analyses was crystallized from ether to constant m. p. 160–161°.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.43; H, 9.82. Found: C, 80.69; H, 10.02; $[\alpha]^{24}D$ +82.5 (0.1252 g. made up to 10 ml. with chloroform, $\alpha^{24}D$ +1.032, *l*, 1 dm.).

The residue from the isopropyl ether filtrate, upon crystallization from dilute acetone, gave 0.73 g. of starting material, m. p. 121–123°. If this recovered material is taken into account the yield of aldehyde is 72%.

3-Ketobisnor-4-cholenic Acid.—The insoluble sodium salt obtained in the above reaction was stirred with 20% sulfuric acid and extracted with chloroform. After washing with water, drying over sodium sulfate, and removing the solvent there was obtained 0.27 g. of nicely crystalline acid. Recrystallized from methanol–chloroform the m. p. (268° dec.) agreed with that obtained by Butenandt and Mamoli[3] for 3-ketobisnor-4-cholenic acid.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.68; H, 9.34. Found: C, 76.52; H, 9.34.

3-Ketobisnor-4-cholenaldehyde Cyanohydrin.—In an ozonization conducted exactly as described above, the neutral ether solution obtained after the zinc dust reduction and alkali wash was concentrated to 30 ml., diluted with 25 ml. of methanol and shaken vigorously with 50 ml. of 40% sodium bisulfite solution. The mixture formed a thick gel which was extracted with three 200-ml. portions of ether. The gel was treated with ice-water and centrifuged to obtain the bisulfite addition complex which was further purified by washing with ether and ice-water on a Buchner funnel; yield 2.86 g.

One gram of the bisulfite complex was suspended in 40 ml. of water and 10 ml. of a solution containing 0.5 g. of potassium cyanide was added with stirring. After one hour of continued stirring at room temperature the product was extracted with ether. Upon concentration of the washed and dried ether extract a crop of fine needles, m. p. 190–195° (dec.), separated. Recrystallized from acetone, the melting point of the cyanohydrin was raised to 200–202° (dec.).

Anal. Calcd. for $C_{23}H_{33}O_2N$: C, 77.69; H, 9.36; N, 3.94. Found: C, 77.69; H, 9.27; N, 4.08.

Progesterone (VII) from 3-Ketobisnor-4-cholenaldehyde Enol Acetates (III and IV).—The 3-keto-aldehyde (I), 3.29 g., was heated at reflux under nitrogen for six hours in a mixture of 100 ml. of acetic anhydride and 1.7 g. of freshly fused sodium acetate. The solvent was removed *in vacuo* on the hot water-bath and the slightly yellow residue was dissolved in 50 ml. of chloroform. The insoluble sodium acetate was filtered off and washed with chloroform and the filtrate and washing made up to a volume of 300 ml. with chloroform. This solution, cooled in an ice-bath, was ozonized for twenty-two minutes (21.5 mg. ozone per minute). After removing the solvent *in vacuo*, the residue was taken up in 30 ml. of acetic acid and 50 ml. of ether and mixed with 4 g. of zinc dust for ten minutes. The mixture was diluted with 400 ml. of ether, filtered, the ether solution washed with 10% sodium hydroxide solution, water and dried. The ether was evaporated and the residue refluxed with a mixture of 90 ml. of methanol and 50 ml. of 5 *N* sulfuric acid for forty-

(5) Melting points are corrected. Analyses and rotations were carried out by personnel of the Upjohn Microanalytical Laboratory.

five minutes in order to hydrolyze any C-3 enol ester.[6] The solution was concentrated *in vacuo* to half volume and extracted with ether. The ether solution was washed with 10% sodium hydroxide solution, water and dried over sodium sulfate. After taking to dryness the residue was taken up in 10 ml. of anhydrous ether by warming. On standing, prisms of progesterone separated and after cooling for forty-eight hours there was obtained 1.90 g. (60%), m. p. 118–122°. Recrystallization from a small volume of acetone raised the m. p. to 125–128° (prisms). Mixed with authentic progesterone there was no m. p. depression.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.20; H, 9.62. Found: C, 80.09; H, 9.69.

(6) Westphal, *Ber.*, **70**, 2128 (1937).

Summary

1. Utilizing stigmasterol as a starting material a simplified procedure for the partial synthesis of progesterone is described. The number of steps has been reduced in comparison with present published methods and the yields for the types of reaction involved are excellent.

2. The enol acetates of 3-acetoxybisnor-5-cholenaldehyde and of 3-ketobisnor-4-cholenaldehyde have been prepared as new intermediates in the above synthesis.

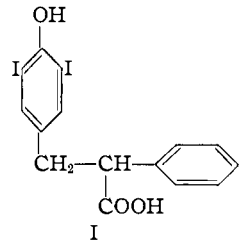
KALAMAZOO, MICHIGAN RECEIVED OCTOBER 10, 1949

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

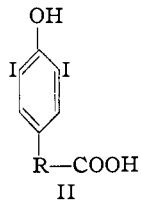
X-Ray Diagnostics. II. Cholecystographic Agents[1]

BY DOMENICK PAPA, ERWIN SCHWENK, HILDA BREIGER AND VIRGINIA PETERSON

Shortly after the discovery by Dohrn and Diedrich that α-phenyl-β-(3,5-diiodo-4-hydroxyphenyl)-propionic acid[2] (I) was clinically efficacious as an oral cholecystographic agent,[3] we undertook an extended study on the correlation of chemical structure and cholecystographic property of several series of iodinated compounds.[4] This paper describes the synthesis and pharmacological data for a series of 3,5-diiodo-4-hydroxyphenyl aliphatic and alicyclic acids of general formula II, wherein R is a saturated or unsaturated straight or branched alkyl radical having 1 to 9 carbon atoms or an alkyl-alicyclic radical, the alicyclic group having 5 to 6 carbon atoms in the ring.

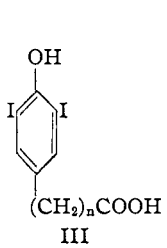


I

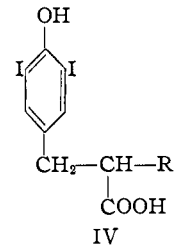


II

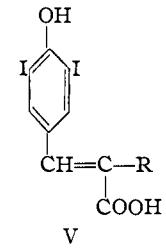
Three series of compounds[5] within the scope of formula II were synthesized for pharmacological investigation and may be represented by formulas III, IV and V, wherein n is an integer from 1 to 9 and R is an alicyclic group or a straight chain alkyl group having 1 to 8 carbon atoms.



III



IV



V

The diiodo compounds of formula III were secured from the known ω-(*p*-hydroxyphenyl) aliphatic acids[6] by iodination with potassium triiodide in alkaline solution. The iodinated acids IV and V, wherein R is aliphatic, were obtained as outlined in the equations.

The syntheses of a number of acids of formulas III and IV have been outlined by Natelson, *et al.*[5a]; but in no instance are yields indicated or any physical constants reported for either the intermediates or final products. Furthermore, the initial step in the synthesis of the acids IV as described by Natelson involves the condensation of *p*-methoxybenzaldehyde with the anhydrous alkali metal salt of the appropriate aliphatic acid at 100° for four hours. Under these conditions, we have not been able to secure any of the Perkin condensation products.[7] However, with the more reactive *p*-hydroxybenzaldehyde at 135–140° for thirty to forty

(1) Presented in abstract before the Division of Medicinal Chemistry, American Chemical Society Meeting, Atlantic City, September 21, 1949.

(2) (a) Dohrn and Diedrich, *Deutsche Med. Wchnschr.*, **66**, 1133 (1940); (b) Grunke and Finger, *Klin. Wchnschr.*, **19**, 1187 (1940); (c) Junkmann, *ibid.*, **20**, 125 (1941); (d) Dohrn and Diedrich, U. S. Patent 2,345,384, March 28, 1944.

(3) This compound, Priodax, has been extensively used clinically as a gall bladder contrast agent: (a) Einsel and Einsel, *Am. J. Digest. Dis.*, **10**, 206 (1943); (b) Vaughan and Eichwald, *Radiology*, **43**, 578 (1948); (c) Dannenberg, *Am. J. Roent.*, **51**, 328 (1944).

(4) For previous investigations on cholecystographic agents reported from this Laboratory, see (a) Schwenk and Papa, U. S. Patent 2,436,270, Feb. 17, 1948; (b) Papa, *Arch. Biochem.*, **23**, 163 (1949); (c) Papa, Schwenk and Klingsberg, THIS JOURNAL, **72**, 2623 (1950); (d) Papa, *ibid.*, in press.

(5) Other investigators have reported on the synthesis and pharmacology of compounds within the scope of formula II: (a) Natelson, Kramer and Tekel, U. S. Patent 2,400,433, May 14, 1946; (b) Epstein, Natelson and Kramer, *Am. J. Roent.*, **56**, 201 (1946); (c) Grayzel and Natelson, *J. Lab. and Clin. Med.*, **32**, 292 (1947); (d) Pratt, Hoppe and Archer, *J. Org. Chem.*, **13**, 576 (1948).

(6) Papa, Schwenk and Hankin, THIS JOURNAL, **69**, 3018 (1947).

(7) Compare, "Organic Reactions," "The Perkin Reaction," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 224, 251.