165–167°. A second recrystallization from heptane raised the m.p. to 168–169°.

Anal. Calcd. for $C_{13}H_{19}Cl_2N_5$: C, 49.40; H, 6.02. Found: C, 49.45; H, 6.47.

8-Chloro-2-ethoxy-6-di-*n*-butylaminopurine (V).—One gram of 2,8-dichloro-6-di-*n*-butylaminopurine (I) was dissolved in an alcoholic solution of sodium ethoxide, prepared by dissolving 1.0 g. of sodium in 10 ml. of absolute ethanol. This solution was placed in a sealed glass tube and heated in an oven (temperature 130°) for 3.5 hours. The contents of the tube were diluted with 10 ml. of water and then acidified with acetic acid. The white solid was collected, washed with a little cold water, and recrystallized from an ethanol–water mixture yielding 0.8 g., m.p. 162–164°. A small amount was recrystallized from 95% ethanol for analytical purposes, m.p. 164–165°. A mixed m.p. of this product and the starting material (V) was 125°.

Anal. Calcd. for $C_{15}H_{24}N_5ClO$: C, 55.4; H, 7.40. Found: C, 55.4; H, 7.56.

6-Di-*n*-butylamino-2-purinone (IV, R = *n*-C_4H_9). Method (2).—To 10 ml. of hydroiodic acid (sp. gr. 1.5, preserved with hypophosphorous acid) was added 0.6 g. of 8-chloro-2-ethoxy-6-di-*n*-butylaminopurine (V). The solution was boiled gently for five minutes, and then vigorously boiled for an additional ten minutes. The cooled reaction mixture was then diluted with 5 ml. of cold water and made slightly alkaline with concd. ammonium hydroxide. The white precipitate thus obtained was washed several times with cold water and then recrystallized from methanol, yield 0.3 g. of product, m.p. 275–277° (m.p. taken with a copper block). A second recrystallization from methanol raised the m.p. 278.5–279.5°. A mixed m.p. of this product and 6-di-*n*-butylamino-2-purinone (IV, R = *n*-C_4H_9) prepared by method (1) was 278.5–280°.

2(6)-Chloro-6(2)-diethylaminopurine.—Into a 500-ml. flask was placed 15.0 g. of xanthine, 200 ml. of phosphorus oxychloride and 10 ml. of triethylamine. The solution was refluxed; every 20 minutes 10 ml. of additional triethylamine was added until a total of 65 ml. had been used. The solution was then refluxed 12 hours more and the reaction mixture processed in the usual manner. The crude product, 6.5 g. of brown gum, was extracted with heptane using a soxhlet extractor. Upon cooling the heptane solution 0.4 g. of crude material separated from the more heptane-soluble 2,6-bis-(diethylamino)-purine (III, R = C_2H_5). The crude product was dissolved in a propanol-2–water mixture, decolorized with charcoal and allowed to crystallize. A second recrystallization from the same solvent gave a white product of m.p. 224–226°. A final recrystallization from heptane gave fine needles, m.p. 225–227°.

Anal. Calcd. for $C_9H_{12}ClN_5$: C, 47.89; H, 5.34. Found: C, 47.62, 47.58; H, 5.44, 5.39.

The isolation of this product from subsequent similar runs could not be consistently repeated. None of this material could be isolated when the preparation of 2,6-bis-(diethylamino)-purine (III, R = C_2H_5) was carried out in the usual manner.

CORVALLIS, OREGON

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

"Enamine" Derivatives of Steroidal Carbonyl Compounds. I

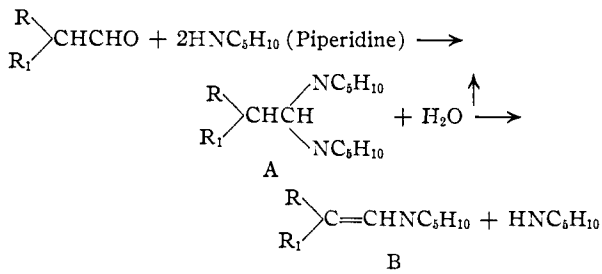
BY M. E. HERR AND F. W. HEYL

RECEIVED JANUARY 25, 1952

Representative steroidal aldehydes have been treated with secondary amines under conditions chosen to facilitate the formation of α,β-unsaturated amines—"enamines." This reaction affords an improved method of degrading the side chain of bisnorcholenaldehydes to 20-ketopregnenes. Isomers of 3-ketobisnor-4-cholenaldehyde and 3-ketobisnor-4-cholenic acid have been prepared and characterized.

It has recently been shown that enol acetates, readily prepared from bisnorcholenaldehydes, in which a double bond is introduced at C-20(22) in the side chain, are converted upon ozonolysis into the corresponding C_{20}-ketones.[1] 3-Ketobisnor-4-cholenaldehyde was readily prepared in good yield by the selective ozonization of stigmastadienone. When, however, this ketoaldehyde was enolized with acetic anhydride and sodium acetate, the resulting mixture of enol acetates proved to be an oil.

A new type of steroidal carbonyl derivative is now reported. It is prepared by a reaction described by Mannich and Davidsen[2] in which a secondary amine, preferably piperidine, reacts with an aldehyde in the presence of potassium carbonate, splitting out a molecule of water to produce in the first phase a dipiperidyl derivative (A). The subsequent loss of one molecule of piperidine in the second phase leads to an α,β-unsaturated amine (B), designated as an "enamine." The aldehydes used by Mannich and Davidsen were liquids and the enamines were isolated from the reaction mixture by fractional distillation at various pressures, which were selected in order to facilitate the splitting out of one mole of the secondary amine.



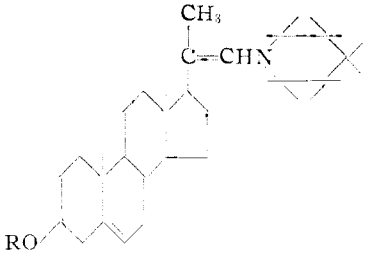
Since the steroidal carbonyl compounds were crystalline solids, modification of the conditions employed by Mannich and Davidsen[2] was necessary. 3β-Acetoxybisnor-5-cholenaldehyde[3] gave 22-(N-piperidyl)-bisnor-5,20(22)-choladien-3β-ol acetate (I) in 84% yield, when the aldehyde and a small excess of piperidine in benzene were heated under reflux, using a Bidwell–Sterling moisture trap to collect the water of reaction. Under similar conditions 3β-hydroxybisnor-5-cholenaldehyde gave 22-(N-piperidyl)-bisnor-5,20(22)-choladien-3β-ol (II); 3-ketobisnor-4-cholenaldehyde[1] gave 22-(N-piperidyl)-bisnor-4,20(22)-choladien-3-

(1) F. W. Heyl and M. E. Herr, THIS JOURNAL, **72**, 2617 (1950).

(2) C. Mannich and H. Davidsen, *Ber.*, **69B**, 2106 (1936). In a recent paper, P. L. deBenneville and J. H. Macartney, THIS JOURNAL, **72**, 3073 (1950), a wide range of yields has been reported for a number of examples of this reaction.

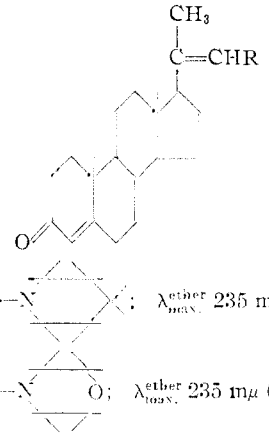
(3) A. P. Centolella, F. W. Heyl and M. E. Herr, *ibid.*, **70**, 2953 (1948).

one (III) when heated with piperidine and the corresponding 22-(N-morpholinyl) compound (IV) with morpholine. Under these conditions evidence of the formation of corresponding dipiperidyl compounds of the type A was absent. In fact, this reaction appeared to be a condensation involving one mole of carbonyl compound and one mole of secondary amine with the elimination of water. Other reaction media than refluxing benzene could be employed, *e.g.*, Skellysolve C, a petroleum fraction, b.p. 93°. As expected, selective ozonolysis of I yielded pregnenolone acetate; likewise, progesterone was obtained *via* the selective ozonolysis of III.



I, R = Ac; $\lambda_{max.}^{ether}$ 235 mμ (ε 7,355)

II, R = H; $\lambda_{max.}^{ether}$ 236 mμ (ε 6,695)



III, R = —N⟨ ⟩CH₂; $\lambda_{max.}^{ether}$ 235 mμ (ε 24,795)

IV, R = —N⟨ ⟩O; $\lambda_{max.}^{ether}$ 235 mμ (ε 24,305)

Mannich and Davidsen[2] found that some ketones such as phenylacetone and cyclohexanone could be converted to enamines. We have found that piperidine reacted readily with 3-ketobisnor-4-cholenaldehyde forming the 3-keto-22-(N-piperidyl)-enamine (III) in high yield. This was a nicely crystalline compound which lent itself readily to the oxidative cleavage step, resulting in a high overall yield of progesterone. As this work progressed certain other advantages of this process over the "enol acetate" method[1] of preparing progesterone from stigmasterol became apparent.

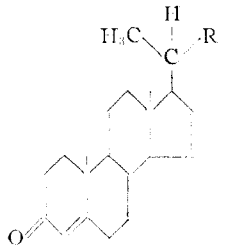
The ultraviolet absorption of the piperidyl enamines (I and II) is in agreement with data reported by Bowden, *et al.*[4,5]

Also of interest was the observation that the replacement of the aldehyde group in 3-ketobisnor-4-cholenaldehyde, λ_{max}^{alc} 241 mμ (ε 16,500), by the ultraviolet chromophoric enamine groups of compounds III and IV caused an increment in the molecular extinction coefficients of these compounds over that of the parent ketoaldehyde. This increment was approximately equivalent to the molecular extinction coefficients of the enamines I and II where no chromophoric 3-keto-Δ^4-system existed.

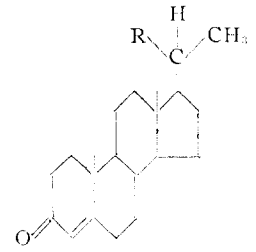
Further studies on the preparation and reactions of steroidal enamines will be reported in detail at a later date.

During the course of this work an interesting isomerism, apparently at C_{20},[6] was studied. When the hydrochloride of 22-(N-piperidyl)-bisnor-4,20-(22)-choladien-3-one (III) was dissolved in water, crystals began to deposit almost immediately and after standing 16 hours a quantitative yield of an isomeric "α"-ketoaldehyde (VI) was recovered by filtration. Recrystallization gave long prisms, m.p. 140–142°, and repeated recrystallization did not raise the melting point, which is 20° lower than that of the normal "β"-3-ketobisnor-4-cholenaldehyde (V).[1] Also this "α" compound gave a 23° higher specific rotation, [α]D +106° (chloroform), on the dextro side than the "β"-ketoaldehyde, [α]D +83° ($CHCl_3$). The "β"-ketoaldehyde was also directly converted to this same isomer (VI) by heating at reflux with methanolic sulfuric acid containing water. The "α"-ketoaldehyde (VI) was oxidized with chromic acid to a mixture of the new "α"-3-ketobisnor-4-cholenic acid (VIII) and the "β"-3-ketobisnor-4-cholenic acid (VII) already known.[1,7] A similar oxidation of the normal "β"-aldehyde gave only the "β"-ketoacid. The methyl esters (IX and X) of both the "β"- and "α"-acids were prepared and the rotations and melting points are reported for comparison with existing data on similar isomerism.

The same epimerization at C_{20} is known for bisnorcholanic acid[8] in which the normal acid melts at 214°, [α]D −7.5° while the iso-acid melts at 242° and [α]D +23.3°.



V, R = CHO
VII, R = CO_2H
IX, R = CO_2CH_3



VI, R = CHO
VIII, R = CO_2H
X, R = CO_2CH_3

Acknowledgments.—The authors are indebted to Dr. J. L. Johnson of our Physics Department for his assistance in the interpretation of the absorption

(4) K. Bowden, E. A. Braude, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 45 (1946); these authors point out that the conjugation of a single ethylenic bond with an amino group results in light absorption equivalent to that exhibited by classical conjugated systems such as butadiene; thus for $C_2H_5CH{=}CH{\cdot}NC_5H_{10}$ (piperidyl) they report λ_{max}^{hexane} 228 mμ.

(5) After noting that the molecular extinction coefficient of most enamines decreased rapidly on standing in alcoholic solution and also the "sparingly soluble in alcohol and hexane" properties of these compounds, we decided in favor of ether solutions for the ultraviolet absorption determinations

(6) See L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948), for a discussion of epimerization and nomenclature at C_{20}.

(7) A. Butenandt and L. Mamoli, *Ber.*, **68B**, 1857 (1935).

(8) H. Wieland, P. Schlichting and R. Jacobie, *Z. physiol. Chem.*, **161**, 100 (1926); see also M. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **27**, 1631 (1944); *ibid.*, **28**, 875 (1945).

spectra, and to Mr. Wm. A. Struck and staff of our Microanalytical Laboratory for the analytical data.

Experimental[9]

3β-Hydroxybisnor-5-cholenaldehyde.—Two and seven-hundredths grams of 3β-acetoxybisnor-5-cholenaldehyde[3] was dissolved in 120 ml. of methanol, and 0.9 g. of potassium carbonate dissolved in 5 ml. of water was added. The solution was refluxed for 25 minutes and concentrated *in vacuo*. The organic residue was dissolved in ether and the washed and dried solution upon concentration gave 3β-hydroxybisnor-5-cholenaldehyde melting at 145°. It was recrystallized from methanol to give needles melting at 150–152°; $[\alpha]^{25}D$ −59.3°.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.94; H, 10.37. Found: C, 79.87; H, 10.28.

The semicarbazone, which crystallized from alcohol in prisms, melted at 250° (dec.).

Anal. Calcd. for $C_{23}H_{37}N_3O_2$: N, 10.84. Found: N, 10.92.

22-(N-Piperidyl)-bisnor-5,20(22)-choladien-3β-ol (II).—To a solution of 4.1 g. of 3β-hydroxybisnor-5-cholenaldehyde in 60 ml. of benzene was added 1.47 ml. (1.2 equivalents) of piperidine and the mixture heated at brisk reflux under nitrogen using a Bidwell–Sterling moisture trap to collect the water of reaction. After 3 hours the calculated amount of water had collected in the trap; the reaction mixture was taken to dryness *in vacuo* on a hot water-bath and the residue placed in a desiccator under reduced pressure over P_2O_5 for 72 hours. The product weighed 4.9 g., m.p. 92–95° (dec.). It was crystallized from acetone in hexagonal plates, m.p. 97–100° (dec.); $[\alpha]^{23}D$ −65°.

Anal. Calcd. for $C_{27}H_{43}NO$: C, 81.56; H, 10.71; N, 3.52. Found: C, 81.36; H, 10.91; N, 3.39.

When a methanolic solution of this compound was heated with semicarbazide acetate, the semicarbazone of 3β-hydroxybisnor-5-cholenaldehyde melting at 252° (dec.) was recovered.

22-(N-Piperidyl)-bisnor-5,20(22)-choladien-3β-ol Acetate (I) (A).—A solution of 2.12 g. of 3β-acetoxybisnor-5-cholenaldehyde in 35 ml. of benzene was heated at reflux with piperidine (10% excess) under the conditions of the previous experiment. The reaction was complete in 2 hours and upon removal of solvent *in vacuo* the white crystalline residue weighed 2.50 g. When recrystallized from acetone this enamine separated in large plates, m.p. 132–138° (dec.), yield 84%, $[\alpha]^{24}D$ −62°.

Anal. Calcd. for $C_{29}H_{45}NO_2$: C, 79.21; H, 10.32; N, 3.19. Found: C, 79.35; H, 10.31; N, 3.37.

(B).—An alternative method of preparing this compound is similar to that of Mannich and Davidsen.[2] A mixture of 1.3 g. of acetoxyaldehyde, 6 ml. of piperidine and 0.4 g. of anhydrous potassium carbonate was stirred for 3 hours at 50–52° in an atmosphere of nitrogen. After dilution with ether the mixture was filtered from the potassium carbonate and the filtrate concentrated on a hot water-bath, finally heating the residue at 70–80° *in vacuo* for 30 minutes. The solid product was triturated with 10 ml. of methanol and the insoluble material, recovered by filtration, amounted to 59% of theory. When crystallized from acetone the product melted and analyzed as in (A).

5-Pregnene-3β-ol-20-one Acetate by Ozonolysis of 22-(N-Piperidyl)-bisnor-5,20(22)-choladien-3β-ol Acetate.—One gram of the acetoxyenamine (I) was dissolved in 75 ml. of anhydrous ether and the solution cooled to −35°. A mixture of ozone and oxygen was passed through the solution for 16 minutes during which time 140% of the ozone theoretically required for one double bond was introduced. The mixture was allowed to warm to room temperature, 25 ml. of acetic acid added and the ozonide decomposed by mixing and warming with zinc dust. Upon processing for the neutral fraction and, in turn, treating this with semicarbazide acetate reagent there was obtained 0.51 g. (54%) of pregnenolone acetate semicarbazone, m.p. 240–242° (dec.).

Anal. Calcd. for $C_{24}H_{37}N_3O_3$: N, 10.11. Found: N, 9.98.

Acid hydrolysis of the semicarbazone gave 5-pregnene-3β-ol-20-one, m.p. 185–187°.

22-(N-Piperidyl)-bisnor-4,20(22)-choladien-3-one (III).—This enamine was prepared by the azeotropic removal of water exactly as described above using a 20% excess of piperidine in refluxing benzene. An alternative method was to add a water-binding agent, *e.g.*, barium oxide or potassium carbonate, in place of the Bidwell–Sterling water trap. In either method the clear solution of the reaction product was evaporated to dryness *in vacuo*. The white crystalline residue was triturated with absolute methanol, cooled at 4°, and the product recovered by filtration and washed with cold methanol. The yield was 86%, m.p. 128–133° (dec.); $[\alpha]^{25}D$ +90°.

Anal. Calcd. for $C_{27}H_{41}NO$: C, 81.98; H, 10.45; N, 3.54. Found: C, 81.92; H, 10.45; N, 3.52.

This compound may be recrystallized by dissolving in hot methanol, acetone or ether to give needles, m.p. 133–136°. However, manipulation in hot solvents tends to cause decomposition with corresponding loss of product.

Progesterone by Ozonolysis of 22-(N-Piperidyl)-bisnor-4,20(22)-choladien-3-one.—A solution of 0.83 g. of ketoenamine (III), m.p. 130–133°, $[\alpha]D$ 88° ($CHCl_3$), in 75 ml. of anhydrous ether was cooled and ozonized at −30°. A stream of ozone–oxygen was passed through the solution for 16 minutes during which time 150% of the theoretical amount of ozone for one double bond was introduced. The ether solution was warmed to room temperature, diluted with 25 ml. of acetic acid, mixed and warmed with 2 g. of zinc dust for 15 minutes and processed as usual for the neutral fraction. This crystalline residue upon treatment with 10 ml. of 50% methanol yielded, after cooling, 0.51 g. (76%) of crude progesterone, m.p. 120–122°. When recrystallized from dilute methanol the product melted at 127–129° and did not depress the m.p. of an authentic sample of progesterone.

22-(N-Morpholinyl)-bisnor-4,20(22)-choladien-3-one (IV).—This compound was prepared from 3-ketobisnor-4-cholenaldehyde and 10% excess morpholine in refluxing toluene using the moisture trap for the azeotropic removal of water as described above. The reaction was complete in 3.5 hours and upon crystallizing the product from acetone there was obtained an 84% yield of the morpholinylenamine, m.p. 160–161° (dec.), $[\alpha]^{24}D$ +87°.

Anal. Calcd. for $C_{26}H_{39}NO_2$: C, 78.72; H, 9.89; N, 3.52. Found: C, 78.98; H, 9.70; N, 3.58.

"α"-3-Ketobisnor-4-cholenaldehyde (VI) from the Enamine Hydrochloride.—Eleven grams of 22-(N-piperidyl)-bisnor-4,20(22)-choladien-3-one (III) dissolved in 50 ml. of benzene was poured into a stirred solution of 350 ml. of anhydrous ether containing excess dry hydrogen chloride. The white crystalline precipitate was filtered and washed with ether and dried in a desiccator over sodium hydroxide; yield 12.04 g. of hygroscopic enamine hydrochloride, m.p. 126–130° (dec.). This enamine hydrochloride (1.95 g.) dissolved readily in water. Within a few minutes the solution began to deposit a crystalline solid and after 16 hours the crystals were recovered, washed with water, and dried to give 1.50 g., m.p. 138–142°. Recrystallization from dilute acetone, ether–methylene chloride or benzene–Skellysolve C, disclosed that this compound is much more soluble than the "β"-ketoaldehyde (V); m.p. of the long prisms after several recrystallizations was 140–142°, $[\alpha]^{24}D$ +106°.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.43; H, 9.82. Found: C, 80.41; H, 9.75.

The infrared spectrum in nujol of this compound is similar to that of "β"-3-ketobisnor-4-cholenaldehyde showing absorption for the following functional groups: aldehyde CH—CHO, 2703 $cm.^{-1}$; aldehyde C=O, 1724 $cm.^{-1}$; conj. ketone C=O, 1667 $cm.^{-1}$; conj. ethylene C=C, 1615 $cm.^{-1}$. Only a few low $cm.^{-1}$ changes were observed, the most pronounced being a shift of the 874 $cm.^{-1}$ to 867 $cm.^{-1}$.

"α"-3-Ketobisnor-4-cholenaldehyde (VI) by Treatment of the "β"-Ketoaldehyde (V) with Acid.—Ten grams of the normal ketoaldehyde (V) was heated at reflux under nitrogen for 10 minutes in 500 ml. of ethanol, 50 ml. of concentrated sulfuric acid and 50 ml. of water. The mixture was poured onto ice, diluted with water and extracted with ether. The washed and dried ether solution was evaporated and the residue recrystallized from benzene–Skellysolve C to give 6.5 g. of aldehyde, m.p. 140–142°, $[\alpha]^{24}D$ ($CHCl_3$) +105°.

(9) Melting points are as read on a Fisher–Johns block which checked the melting point of standard compounds within ±1° over a range from 70° to 237°. All rotations were determined in chloroform.

"β"-3-Ketobisnor-4-cholenic Acid (VII) from the Oxidation of the "β"-Ketoaldehyde (V).—A solution of 1.09 g. of the "β"-ketoaldehyde in 20 ml. of benzene and 20 ml. of glacial acetic acid was cooled to 0–4° and, while stirring, a solution of 0.25 g. of chromic acid anhydride in 1 ml. of water and 20 ml. of glacial acetic acid was added dropwise during 10 minutes. The oxidation was allowed to proceed for 1 hour while cooling in an ice-bath and 10 ml. of methanol was added. The mixture was diluted with water, extracted with ether, washed with water and 10% sodium hydroxide to the point of removal of the insoluble sodium salt of the acid. This sodium salt was recovered by centrifugation, washed well with ether, and the free acid recovered by treatment with 20% sulfuric acid. The "β"-ketoacid (0.77 g.) melted at 260–265° (dec.) and after recrystallizing from methylene chloride–methanol melted at 268–270° (dec.) and did not depress the decomposition point of the known acid[1,7]; $[\alpha]^{24}D$ ($CHCl_3$) +60°.

From the neutral ether solution after the removal of the acid fraction there was obtained 0.20 g. of recovered "β"-ketoaldehyde.

"β"-3-Ketobisnor-4-cholenic Acid Methyl Ester (IX).—The "β"-ketoacid (0.92 g.) (prepared as described above) in 10 ml. of methylene chloride and 2 ml. of methanol was added to a cold solution of methylene chloride containing an excess of diazomethane. After standing 2 hours in an ice-bath the solvent was evaporated and the residue dissolved in ether, washed with water, and dried over sodium sulfate. The solvent was evaporated and the crystalline residue upon recrystallizing from acetone gave long prisms, m.p. 178°, $[\alpha]^{24}D$ +72°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.43; H, 9.85.

"α"-3-Ketobisnor-4-cholenic Acid (VIII) from the Oxidation of the "α"-Ketoaldehyde.—The "α"-ketoaldehyde (VI) (3.28 g.) was oxidized with chromic acid as described above. The alkali solution containing the soluble salts, upon making acid with 20% sulfuric acid, gave an acid fraction weighing 1.40 g. and melting at 210–215°. From methanol a first crop of "β"-ketoacid was obtained, m.p. 260–265°. The filtrate upon concentration and dilution with water gave the "α"-ketoacid which after three further crystallizations from benzene–Skellysolve C formed needles melting at 220–222°, $[\alpha]^{24}D$ +109°.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.68; H, 9.34. Found: C, 76.21; H, 9.01.

"α"-3-Ketobisnor-4-cholenic acid methyl ester (X) was prepared in the same manner as the "β"-ketoacid methyl ester. From dilute acetone it crystallized in needles, m.p. 119–121°, $[\alpha]^{22}D$ +98°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.15; H, 9.36.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

The Synthesis of 11-Hydroxylated Cortical Steroids. 17-Hydroxycorticosterone[1]

BY N. L. WENDLER, R. P. GRABER, R. E. JONES AND M. TISHLER

RECEIVED JANUARY 11, 1952

The synthesis of 17-hydroxycorticosterone (Compound F) from 20-cyano-17-pregnene-21-ol-3,11-dione is described.

17-Hydroxycorticosterone[2] was first isolated from adrenal cortex in 1937 by Reichstein[3] and shortly thereafter by Mason, Hoehn and Kendall.[4] Recent studies[5] have indicated that this substance possesses therapeutic activity similar to Cortisone; consequently the need for a practical synthesis of this compound was suggested.

The biosynthesis of 17-hydroxycorticosterone from Reichstein's Substance S has been demonstrated using techniques of perfusion in the isolated beef adrenal gland[6] and incubation with adrenal homogenates.[7,8] This same transformation has also been effected by employing the enzyme system associated with the insoluble cellular constituents of the adrenal cells.[9]

We have synthesized 17-hydroxycorticosterone starting with 20-cyano-17-pregnene-21-ol-3,11-dione (Ia), prepared previously in connection with the synthesis of Cortisone from the bile acids.[10] This cyanopregnene as its 21-acetate (I) was converted with methyl or ethyl orthoformate to the corresponding 3-dialkyl ketal (II) and (IIa), respectively. The dimethyl ketal was found to possess superior crystallizing properties and could be isolated in a direct yield of 80–85%.

Hydrolysis of II with bicarbonate afforded the 21-hydroxy ketal (III) nearly quantitatively. The latter was reduced with lithium borohydride at 25° or preferably with sodium borohydride at 65–70° to produce IV, which was acid-hydrolyzed without isolation to give crystalline 20-cyano-17-pregnene-11(β),21-diol-3-one (V) in 80% yield based on the 21-acetoxy ketal (II).

Attempts to convert 20-cyano-17-pregnene-21-ol-3,11-dione (Ia) directly to the 3-dimethyl ketal (III) were without substantial success. Similar efforts aimed at the direct employment of II in the hydride reduction were equally unrewarding. The failure of Ia, in an early phase of this work, to give a crystalline ketal derivative suggested masking the 3-carbonyl group as the semicarbazone (IX). Reduction of IX with lithium borohydride and removal of the semicarbazone grouping afforded the desired 20-cyano-17-pregnene-11,21-diol-3-one (V) in substantial yield.[11]

Hydroxylation of Va with osmium tetroxide yielded 4,5-dihydro-17-hydroxycorticosterone-21-acetate (VI). Bromination of the latter followed by dehydrobromination with semicarbazide ace-

(1) A preliminary announcement of this work was reported in a Communication to the Editor, THIS JOURNAL, **72**, 5793 (1950).

(2) This substance has been variously designated Reichstein's "Substance M" and Kendall's "Compound F." "Hydrocortisone" was suggested as a generic name for 17-hydroxycorticosterone by Dr. E. C. Kendall in a paper presented before the American Academy of Orthopaedic Surgeons at Chicago, Illinois, in January, 1951.

(3) Reichstein, *Helv. Chim. Acta*, **20**, 953 (1937).

(4) Mason, Hoehn and Kendall, *J. Biol. Chem.*, **124**, 459 (1938).

(5) Hench, Kendall, Slocumb and Polley, *Arch. Int. Med.*, **85**, 545 (1950).

(6) Hechter, Jacobsen, Jeanloz, Levy, Marshall, Pincus and Schenker, *Arch. Biochem.*, **25**, 457 (1950).

(7) McGinty, Smith, Wilson and Worrel, *Science*, **112**, 506 (1950).

(8) Kahnt and Wettstein, *Helv. Chim. Acta*, **34**, 1700 (1951).

(9) Sweat, THIS JOURNAL, **73**, 4056 (1951).

(10) Sarett, *ibid.*, **70**, 1454 (1948).

(11) Reference to this work has already been cited. *Cf.* Wendler, Huang-Minlon and Tishler, *ibid.*, **73**, 3818 (1951).