[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CLARK UNIVERSITY AND FROM THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

A Preparation of 3β-Hydroxypregn-5-en-20-one-4-C^{14}

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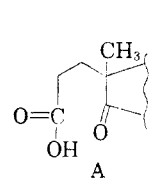
Methyl 3-ketoetiochol-4-enate-4-C^{14} was transformed *via* two different routes to bisnorchol-5-ene-3β,20,21-triol-4-C^{14} which was in turn oxidized with sodium bismuthate to the desired pregnenolone-4-C^{14}.

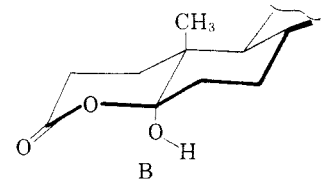
Radio-pregnenolone was required for metabolism studies. The following investigation was undertaken to improve the yield of the transformation of the methyl 3-ketoetiochol-4-enate-4-C^{14} (V) to the 3β-hydroxypregn-5-en-20-one-4-C^{14} (IV).

The alternate two syntheses, shown in flow sheet I are closely patterned after two papers from Reichstein's group.[1,2] Both ways required the preparation of a 20,21-dihydroxybisnorcholane derivative (III), which could, without any further protection, readily be cleaved to the methyl ketone (IV) by the action of sodium bismuthate.

The first synthesis uses as starting material methyl 3-ketoetiochol-4-enate-4-C^{14} (V), the synthesis of which has already been described in detail by Thompson *et al.*[3] Following this procedure the ozonolysis of nonradioactive V gave varying amounts of acidic material. Therefore the crude ozonolysis product of methyl 3-ketoetiochol-4-enate was separated into a neutral and an acidic fraction. The latter has already been obtained by Reichstein and Fuchs,[4] and represents the true keto acid A, in full agreement with its infrared absorption spectrum: 2820 (—OH); 1737, 1245 (—$COOCH_3$);1705, 950 (—COOH) cm.$^{-1}$.[5] The neutral fraction, which could not be crystallized, gave



A



B

the same elemental analysis as the keto acid obtained from the acidic fraction. The infrared spectrum had bands at 3450 (—OH), shifting upon dilution to 3600; 1735, 1700 (>C=O); 1140 (—C—O—C—) cm.$^{-1}$ Inspection of molecular models suggests that the pseudo acid B with its 5α-hydroxyl would be available for intramolecular hydrogen bonding; the infrared data, therefore, support the assignment of structure. The pseudo acid is transformed to the desired enol lactone (IX) upon refluxing its acetic anhydride solution containing anhydrous sodium acetate, suggesting that the pseudo acid may very well be an intermediate in the transformation of the keto acid A to its lactone. Base, such as anhydrous sodium acetate in acetic anhydride, will bring about *trans* elimination of one molecule of water from the pseudo acid.

Methyl 3-ketoetiochol-4-enate-4-C^{14} (V) was converted to its enol acetate, the enol acetate reduced with sodium borohydride, and the reduced product finally hydrolyzed with alkali to give 3β-hydroxyetiochol-5-enoic acid-4-C^{14} in 47% yield.

Acetylation to (Ia) and subsequent elaboration of the side chain to 3β,21-diacetoxypregn-5-en-20-one-4-C^{14} (II) by modifications of known procedures[6,7] was accomplished in a yield of 75%. The diacetate (II) was then treated with 10 moles of methylmagnesium bromide and the resulting mixture of 20-isomeric flisnorchol-5-en-3β,20,21-triols-4-C^{14} (III), obtained in a yield of 90%, was oxidized with sodium bismuthate to 3β-hydroxypregn-5-en-20-one-4-C^{14} (IV). The over-all yield of 3β-hydroxypregn-5-en-20-one-4-C^{14} from (II) was 85%, while the yield from methyl 3-ketoetiochol-4-enate-4-C^{14} amounted to 25%. The reaction of a ketol ester with methylmagnesium bromide, followed by oxidation with sodium bis-

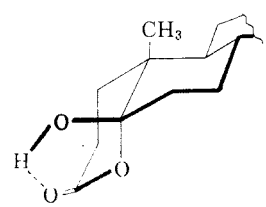
(1) P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **24**, 828 (1941).

(2) B. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944).

(3) L. M. Thompson, C. H. Yates, and A. D. Odell, *J. Am. Chem. Soc.*, **76**, 1194 (1954).

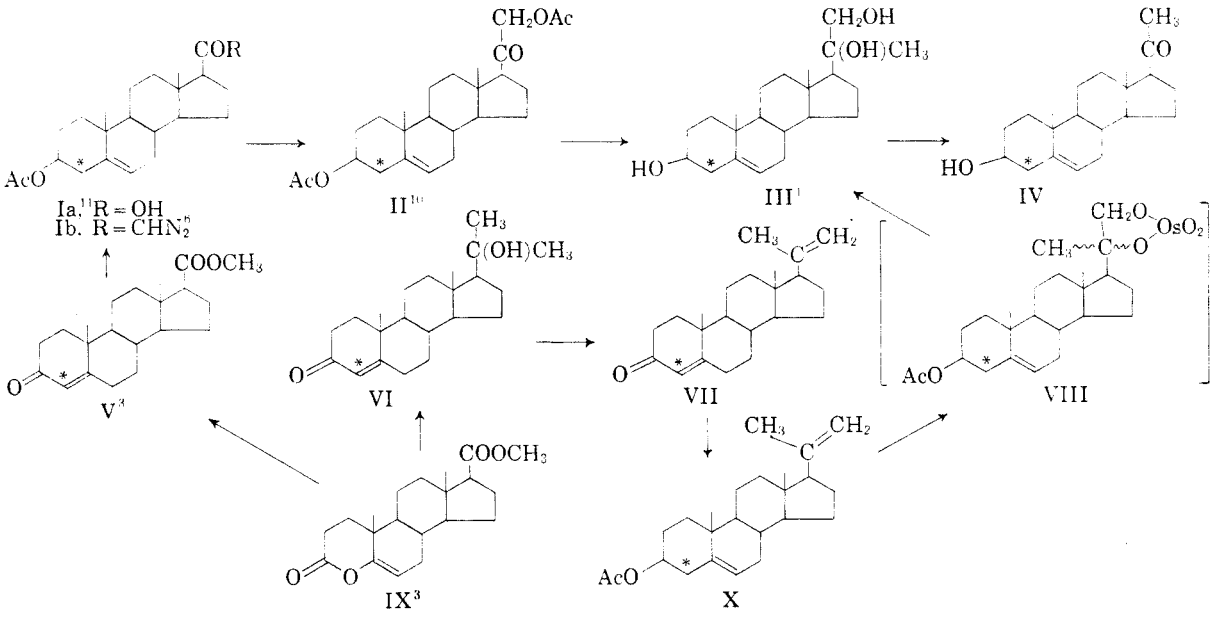
(4) T. Reichstein and H. G. Fuchs, *Helv. Chim. Acta*, **23**, 676 (1940).

(5) The "keto acid" of progesterone,[4] m.p. 173–175°, $[\alpha]_D$ −108 (acetone) is exclusively in the 5β-pseudo acid form as can be judged from its infrared spectrum in chloroform: 3200 (—OH), intramolecular (6-ring) hydrogen bonding, not disappearing upon dilution; 1737, 1675 (>C=O); 1185 (—C—O—C—); 1695 (20- >CO) cm.$^{-1}$ Inspection of a model indicates strong hinderance of the free rotation of the 5-hydroxyl group; and it is pushed into a preferred position for intramolecular hydrogen bonding only when we assume the hydroxyl to be in the 5β position.



(6) M. Staiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937).

(7) A. L. Wilds and C. H. Shunk, *J. Am. Chem. Soc.*, **70**, 2427 (1948).



muthate is a useful method for the conversion of a ketol side chain to the corresponding methyl ketone.

The alternate synthesis involves the reaction of one mole of methylmagnesium iodide-4-C^{14} on the enol lactone (IX), followed by the addition of two more moles of non-radioactive Grignard compound.[8] After hydrolysis and cyclization with alkali the 20-hydroxybisnorchol-4-en-3-one-4-C^{14} (VI)[9] was obtained, which had identical physical constants with the Oppenauer oxidation product of bisnorchol-5-ene-3,20-diol (XI). VI was treated with a saturated solution of dry hydrochloric acid in benzene; then the benzene was evaporated and the resulting semicrystalline 20-chloro derivative was shaken with a 5% methanolic potassium hydroxide solution. The elimination gave in quantitative yield the bisnorchola-4,20-dien-3-one-4-C^{14} (VII). The dienone VII was converted to its enol acetate which was reduced with sodium borohydride. The reacetylation of the crude product followed by chromatographic separation gave the bisnorchola-5,20-dien-3β-ol acetate-4-C^{14} (X), which had identical physical constants than the compound (XIX) obtained from bisnorchol-5-ene-3β,20-diol (XIa),[10] shown on Flowsheet II: (XIa→XIb→XV→XIX). The methylene derivative (X) was oxidized with osmium tetroxide and the osmate esters hydrolyzed to the triol which had an identical infrared spectrum but a slightly higher melting point than the mixture of the 20-isomeric triols (III), obtained from the first synthesis. Since the product had also a different melting point from either individual 20-isomeric triols, it must be a mixture also; its oxidation gave IV. This shows that the osmium tetroxide oxidation of the 20-double bond was not stereospecific. The over-all yield of (III) from methyl iodide-4-C^{14} was for both syntheses approximately 15%.

The 20-isomeric mixture of bisnorchol-5-en-3β,20,21-triols (XIII), obtained from non-radioactive 3β,21-diacetoxypregn-5-en-20-one gave the acetonide (XIV) when reacted with dry acetone and *p*-toluenesulfonic acid. A minor by-product, which was however not an acetonide, was not further identified. The Oppenauer oxidation of XIV, followed by hydrolysis of the isopropylidene group, gave 20,21-dihydroxybisnorchol-4-en-3-one (XVIII). Since the identical product was obtained *via* the osmium tetroxide oxidation of bisnorchola-4,20-dien-3-one (XVI), a non-stereospecific reaction, the 20,21-diol (XVIII) must be a 20-isomeric mixture also; it follows that XIV is an isomeric mixture in spite of its apparent homogenous behavior. The diol (XVIII) was oxidized with sodium bismuthate to progesterone (XX).

Bioassay. Compound XIa was found to give statistically significant antiandrogenic activity in the chick assay. Details of bioassays of this and other intermediates will be published elsewhere.

EXPERIMENTAL

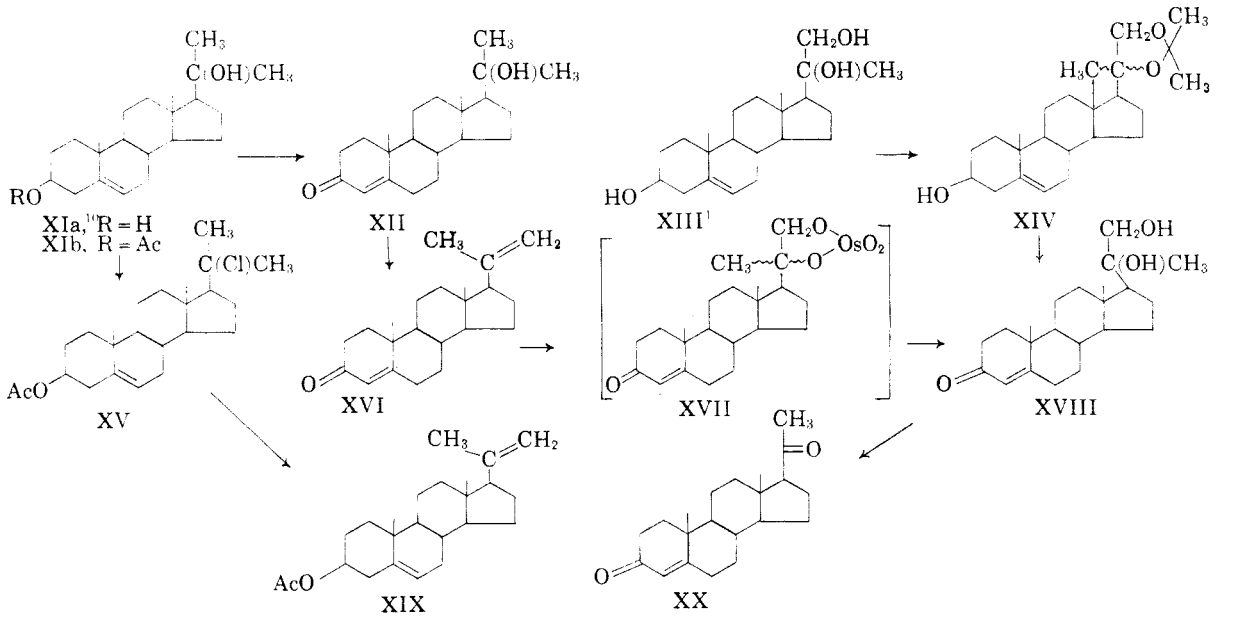
Melting points were determined on a Fisher-Johns hot stage and are uncorrected. Analyses were performed by

(8) For the synthesis of 21-labeled compounds the order of addition, in respect to radioactivity, could also be reversed: reacting the lactone IX first with one mole of non-radioactive methylmagnesium iodide, followed by the addition of two moles of radioactive Grignard would give the carbinol VI labeled at the carbons 21 and 22. In spite of the subsequent loss of 50% of the introduced activity this scheme could be attractive, since it circumvents the synthesis of radioactive diazomethane which is ordinarily used for the labelling of carbon 21.

(9) The same compound was also obtained by the Oppenauer oxidation of XIa.

(10) R. E. Marker, H. M. Crooks, Jr., E. M. Jones, and A. C. Shabica, *J. Am. Chem. Soc.*, **64**, 1276 (1942).

(11) M. Staiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 1040 (1937).



Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. Ultraviolet absorption spectra were determined in methanol with a Cary model 11 MS spectrophotometer. Optical rotations were determined in a 1-dm. semimicro tube. The infrared spectra were taken from a pressed potassium bromide prism on a Perkin-Elmer Model 12C spectrometer. All chromatographic separations were made on Davison silica gel mesh 100–200.

Methyl-3-ketoetiochol-4-enate-4-C^{14} (V) was made exactly as described by L. M. Thompson *et al.*[3]

3β-Acetoxyetiochol-5-en-oic acid-4-C^{14} (Ia). To 1.7 gm. of methyl 3-keto-etiochol-4-enate-4-C^{14} (V) were added 20 ml. acetic anhydride and 10 ml. acetyl chloride and the mixture refluxed under a stream of nitrogen for 3 hr. Then the solution was evaporated to dryness *in vacuo* and the residue dried for 2 days in a vacuum desiccator over solid sodium hydroxide.

A solution of the crude enol acetate in 25 ml. methanol was added to a freshly prepared suspension of one gram of sodium borohydride in 30 ml. methanol and allowed to stand with occasional shaking at room temperature for one day. One more gram of sodium borohydride was added in portions while the reaction mixture stood for an additional day. Then the mixture was evaporated to dryness, the residue taken up in methylene chloride, the methylene extract washed successively with 2*N* hydrochloric acid, water, 2*N* sodium carbonate solution and again with water. The residue which remained after evaporation of the methylene chloride was dissolved in 45 ml. of 95% ethanol, 1 ml. of concentrated hydrochloric acid was added, and the resulting solution refluxed under nitrogen for 2 hr. This solution was again evaporated to dryness *in vacuo*, extracted with methylene chloride, the methylene chloride extract washed with water, 2*N* sodium carbonate solution and water. After drying and evaporation, the residue was chromatographed. From the benzene–ethyl acetate fraction 850 mg. crude methyl 3β-hydroxyetiochol-5-enate-4-C^{14}, m.p. 176–181° were obtained.

The conversion of this methyl ester to (Ia) was carried out following the directions given in the FIAT FINAL REPORT NO. 996; yield 839 mgs. of Ia.

3β,21-Diacetoxypregn-5-en-20-one-4-C^{14} (II). A solution of 839 mg. of 3β-acetoxyetiochol-5-en-oic acid 4-C^{14} (Ia) in 50 ml. anhydrous ether was cooled to 5°, 185 mg. of pyridine added, and then 278 mg. of thionyl chloride in 20 ml. of anhydrous ether added dropwise within 5 min.[13] The mixture was stirred for 0.5 hr. at −5° and for an additional 2 hr. at 25°. The precipitated pyridine hydrochloride was filtered off (nitrogen flushing for moisture protection) and washed with anhydrous ether. The filtrate, after evacuation *in vacuo*, gave the crystalline acid chloride as a fine powder in quantitative yield.

An analytical sample was crystallized from hexane and melted from 152–152.5°. On further heating the substance suffers decomposition (effervescence) at 165° and finally resolidifies; $[\alpha]_D^{25}$ −34° (c, 1.01 in CH_2Cl_2); infrared; ν_{max} 1798, 1730, 1440, 1239, 838, 771 cm.$^{-1}$

The ethereal solution of the chloride was added to a threefold excess of diazomethane in dry ether at 0°, and after standing overnight, the excess diazomethane was destroyed by passing the ether solution through a column of aluminum oxide. Evaporation in vacuum left as semicrystalline residue the diazoketone (Ib), which was refluxed for 2 hr. with the solution of anhydrous potassium acetate in acetic acid. After cooling, the solution was poured into water, the mixture extracted with ether, and the organic phase washed with 2*N* sodium carbonate solution and water; it was finally dried over sodium sulfate and evaporated. On chromatography, the fractions obtained with 2% and 5% ethyl acetate in benzene gave 725 mg. 3β,21-diacetoxypregn-5-en-20-one-4-C^{14}, m.p. 162–164°.

Bisnorchol-5-ene-3β,20,21-triol (20-isomeric mixture)-4-C^{14} (III) *from* II. The solution of 725 mg. of II in 10 ml. anhydrous benzene was added dropwise with stirring at 0° to the ether solution of Grignard reagent, prepared from 2.133 gm. of magnesium and 12.40 gm. of methyl iodide. The reaction mixture was heated under reflux for 4 hr., cooled with ice water, and hydrolyzed with cold saturated aqueous ammonium chloride solution. The solids were filtered off, the ether layer separated and evaporated. The residue from the evaporation and the solids were combined, dried and recrystallized from methanol giving 610 mg. III, m.p. 224–224.5°; infrared: ν_{max} 3540, 1065, 1050, 812 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{36}O_3$ (348.51): C, 75.81; H, 10.41. Found: C, 75.93; H, 10.18.

3β-Hydroxy-pregn-5-en-20-one-4-C^{14} (IV) *from* III. A solution of 600 mgs. of III in 600 ml. 65% aqueous acetic acid was shaken overnight with 30 gm. sodium bismuthate. The excess reagent was reduced with 20 ml. of a 10% aque-

(12) T. Reichstein and C. Montigel, *Helv. Chim. Acta*, **22**, 1218 (1939).

(13) P. Carré and D. Libermann, *Comt. rend.*, **199**, 1422 (1934).

ous potassium pyrosulfite solution and, after adding 150 ml. 2*N* sodium hydroxide solution, the mixture was extracted with ether, the extract washed with 2*N* sodium hydroxide solution and water, dried over sodium sulfate and evaporated to dryness. The crystalline residue, recrystallized from acetone, gave 518 mg. pure 3β-hydroxy-pregn-5-en-20-one-4-C^{14} (IV), m.p. 185–187°, not depressed on admixture to authentic material.

20-Hydroxy-bisnorchol-4-en-3-one-4-C^{14} (VI) *from* IX. Under careful exclusion of all moisture, the solution of 1.333 gm. (4 mmoles) of IX in 85 ml. of benzene-ether (2:1), was added dropwise at −25° to a solution of 4 mmoles of methyl magnesium iodide-4-C^{14} in 25 ml. of ether. After the addition was completed the mixture was stirred until it reached room temperature, let stand for one more hour, and then four moles of non-radioactive methyl magnesium iodide in 50 ml. of ether were added over a period of 1 hr. The thick suspension was stirred at 35° for an additional 2 hr. Then the mixture was poured into 100 ml. of cold ammonium chloride solution and shaken for 0.5 hr. The aqueous phase was thoroughly extracted with methylene chloride and the combined extracts washed with water. Removal of the solvent left an amorphous residue which was rearranged by stirring at room temperature for 2 hr. in 50 ml. of methanol containing 3 ml. of 6*N* aqueous sodium hydroxide solution. The solution was concentrated until most of the methanol was removed, saturated saline added to the residue, and the aqueous layer repeatedly extracted with methylene chloride. The combined extracts were brought to dryness and the brown syrup chromatographed on neutral aluminum oxide, activity grade I. The benzene-ether 9:1 fractions gave 528 mgs. of VI, m.p. 220–222°; $[\alpha]_D^{23}$ + 83° (c, 0.966 in chloroform); infrared: ν_{max} 3600, 1675, 1615 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{34}O_3$ (330.49): C, 79.95; H, 10.27. Found: C, 79.78; H, 10.60.

20-Hydroxybisnorchol-4-en-3-one (XII) from XIa. Water was removed by azeotropic distillation from the solution of 200 mg. of bisnorchol-5-en-3β,20-diol (XIa), prepared by the method of Marker,[10] in 10 ml. toluene and 2 ml. cyclohexanone. A solution of 100 mg. aluminum isopropoxide in anhydrous toluene was then added, and the mixture refluxed for 30 min. Finally, the aluminum complex was hydrolyzed with a solution of acetic acid in toluene. The organic solvents were distilled off with steam and 2 gm. of Celite added to the residue which was filtered, dried, and extracted in a Soxhlet with ethyl acetate. The ethyl acetate solution was brought to dryness and the crystalline residue recrystallized from methanol, m.p. 220–222°; infrared: ν_{max} 3600 (hydroxyl), 1675, 1615 (conjugated ketone) cm.$^{-1}$

Bisnorchola-4,20-dien-3-one-4-C^{14} (VII) from VI. To 100 ml. of benzene, saturated with dry hydrochloric acid, were added 520 mg. VI and the mixture shaken for 2 hr. After removal of the benzene *in vacuo*, the remaining semicrystalline residue was dissolved in 50 ml. 5% methanolic potassium hydroxide solution and shaken for 4 hr. Then the mixture was poured into a large volume of water. The aqueous phase was extracted with ether and the organic layer washed with water to neutrality, then dried and finally the solvent removed by distillation. The residue was chromatographed and the suitable combined ethyl acetate-benzene (1:99) fractions were recrystallized from methanol yielding 445 mg. X, m.p. 155–157°; $[\alpha]_D^{24}$ +106 (c, 0.85 in chloroform); infrared: ν_{max} 1667, 1610, 885, 870, 780 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{32}O$ (312.48): C, 84.56; H, 10.32. Found: C, 84.39; H, 10.23.

The same dehydration, though with inferior yields, could also be carried out by refluxing VI with anhydrous sodium acetate in acetic anhydride for 2 hr.

Bisnorchola-5,20-dien-3β-ol acetate-4-C^{14} (X) *from* VII. The solution of 400 mgs. of bisnorchola-4,20-dien-3-one-4-C^{14} in 10 ml. acetic anhydride and 5 ml. acetyl chloride was refluxed for 3 hr., then brought to dryness and the residue dried over sodium hydroxide in a vacuum desiccator for three days. The crude enol acetate was dissolved in 50 ml. of methanol, containing 500 mg. of sodium borohydride and the mixture magnetically stirred overnight. Then most of the methanol was evaporated off, the residue extracted with ethyl acetate, the extract washed with 2*N* hydrochloric acid and water, dried, and evaporated. This residue was dissolved in 95% ethanol containing 2% concentrated hydrochloric acid and refluxed for 2 hr. After evaporating the solvent at room temperature, the residue was chromatographed and the fractions obtained with benzene containing 2% ether gave 380 mg. of an oily product, the infrared absorption (3550, 885, and 810 cm.$^{-1}$) of which agreed with the desired alcohol. Acetylation with acetic anhydride and pyridine gave a crystalline product which was chromatographed. The benzene-hexane (1:4) eluates were recrystallized from methanol yielding 213 mg. of the desired X, m.p. 124–126°, identical with the substance obtained from XV by dehydrochlorination.

20-Chloro-bisnorchol-5-en-3β-ol acetate (XV) *from* XIb. The bisnorchol-5-ene-3β,20-diol 3β-monoacetate (XIb) was obtained by acetylation of the known XIa[10] with acetic anhydride and pyridine. The acetate was recrystallized from methanol, m.p. 151–152°; $[\alpha]_D^{21}$ −76.8° (c, 0.716 in chloroform).

Benzene, saturated with dry hydrochloric acid, was added to 1 gm. of XIb and shaken for 1.5 hr. Then the solvent was evaporated to dryness and the crystalline residue recrystallized from acetone, yielding 1.0 gm. of XV, m.p. 161–162°; $[\alpha]_D^{21}$ −67.7° (c, 1.108 in chloroform); infrared: ν_{max} 1735, 1445, 1245, 803, 760 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{37}O_2Cl$ (393.00): C, 73.34; H, 9.49; Cl, 9.02. Found: C, 73.32; H, 9.90; Cl, 8.87.

Bisnorchola-5,20-dien-3β-ol-acetate (XIX) *from* XV. The solution of 1 gm. of XIV in 100 ml. 5% methanolic potassium hydroxide solution was shaken for 4 hr. Then the mixture was poured in a large volume of water, the aqueous layer extracted with ether, the ether washed with water to neutrality, dried, and evaporated. The residue, upon chromatography, gave with the ether-benzene (2:98) eluates an oily product which was reacetylated with acetic anhydride acid and pyridine. After the usual workup the product was chromatographed and the benzene-hexane (1:3) mixture furnished 820 mg XIX, m.p. 124–126° (from methanol). $[\alpha]_D^{22}$ −69.3° (c, = 0.902 in chloroform); infrared: ν_{max} 1737, 1373, 1250, 1040, 903, 885, 810 cm.$^{-1}$

Bisnorchol-5-ene-3β,20,21-triol (20-isomeric mixture)-4-C^{41} (III) *from* X. To the solution of 903 mg. of X in 25 ml. of anhydrous ether were added 750 mg. of osmium tetroxide (1.15 moles) and let stand for two days in the dark at room temperature. After most of the ether was evaporated off, a solution of 6 gm. of sodium sulfite in 70 ml. of water and 30 ml. of alcohol was added and the mixture refluxed for 5 hr. The suspension was filtered off, washed thoroughly with water, water-alcohol, and finally with alcohol. The solution was concentrated to a small volume and the precipitate filtered off. After recrystallization from methanol-acetone 633 mg. of III, m.p. 224–227°, was obtained, possessing an infrared absorption identical with III obtained from II.

Bisnorchol-5-ene-3β,20,21-triol 20,21-isopropylidene (20-isomeric mixture) (XIV) *from* XIII. To a solution of 100 mg. of bisnorchol-5-en-3β,20,21-triol in 20 ml. anhydrous acetone were added 10 mg. of *p*-toluenesulfonic acid and the mixture refluxed for 18 hr. After distilling off the acetone the residue was taken up in ether, the ether solution washed with 1*N*. sodium hydroxide solution and water, dried over sodium sulfate and evaporated. The residue was chromatographed and 85 mg. XIV, m.p. 177–181°, was eluted with the benzene-ether (1:1) fractions $[\alpha]_D^{22}$ −61° (c, 0.70 in chloroform).

Anal. Calcd. for $C_{25}H_{40}O_3$ (388.57): C, 77.27; H, 10.38. Found: C, 76.97; H, 10.36.

With the same solvent pair another substance was obtained in very small amounts, m.p. 230° (under decomposition). The infrared absorption excludes an isopropylidene derivative and excludes also the starting material.

20,21-Dihydroxybisnorchol-4-en-3-one (20-isomeric mixture) (XVIII) *from* XIV. The isopropylidene derivative XIV was oxidized by Oppenauer oxidation in the usual manner and the oxidation product chromatographed. The ether-benzene (1:20) eluates gave, after recrystallization from ether, XVIII in 75% yield, m.p. 168–169°; $[\alpha]_D^{23}$ +55° (c, 0.55 in chloroform); infrared: ν_{max}. 3600, 1675, 1620 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{34}O_3$ (346.49): C, 76.26; H, 9.89. Found: C, 76.43; H, 9.67.

20,21-Dihydroxy-bisnorchol-4-en-3-one (20-isomeric mixture) (XVIII) *from* XVI. The oxydation of XVI to XVII followed by the hydrolysis to XVIII was carried out as described for the conversion of X to III. From 100 mg. of XVI there was obtained 77 mg. XVIII, m.p. 167–169°, having an infrared absorption identical with that of XVIII obtained from XIV.

Progesterone (XX) *from XVII.* A solution of 100 mg. of XVIII in 100 ml. 80% acetic acid was shaken overnight with 5 gm. of sodium bismuthate. The mixture was worked up exactly as described for IV from III. The crude product was chromatographed and the fractions, obtained with ethyl acetate–benzene (1:10) gave, after recrystallization from ethyl acetate–hexane, progesterone, m.p. 125–128°, in quantitative yield.

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WORCESTER, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, SCHOOL OF MEDICINE, YALE UNIVERSITY]

Synthesis of Some 5-Alkyl-6-azauracils[1]

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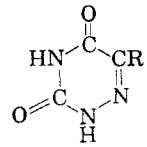
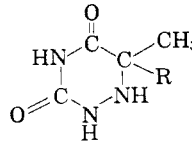
A number of 5-alkyl-6-azauracils (6-alkyl-*asym*-triazine-3,5-diones) have been synthesized by ring closure of the appropriate α-keto acid semicarbazones in non-aqueous media in the presence of sodium ethoxide. As compared to 6-azauracil, these compounds show increased narcotic activity in mice, and were designed to aid in studies dissociating the narcotic from the anti-tumor activities of 6-azauracil. Their acid dissociation constants, ultraviolet spectra, and infrared spectra were measured.

Recent work on the anti-tumor activity of 6-azauracil (*asym*-triazine-3,5-dione, I)[2–4] disclosed that this compound also possesses narcotic activity in mice[5] and induces a variety of disturbances of the central nervous system in man.[6] The 5-methyl homolog of 6-azauracil, 6-azathymine (6-methyl-*asym*-triazine-3,5-dione, II) exhibits even greater narcotic activity in mice than does 6-azauracil.[5,7] On the other hand, 5,6-dihydro-6-azathymine (6-methyl-1,6-dihydro-*asym*-triazine-3,5-dione, IX)[8] and 5,5 - dimethyl - 5,6 - dihydro - 6 - azauracil (6,6-dimethyl-1,6-dihydro-*asym*-triazine-3,5-dione, X)[9] failed to show any narcotic activity in mice.[10] These observations indicate that the 6-alkyl substitution on the *asym*-triazine ring may be closely related to the increase in narcotic potency and that unsaturation of the triazine structure is essential for this activity. In order to clarify and substantiate the above correlation and thus possibly to contribute to studies of the relation of the narcotic and the anti-tumor activities of 6-azauracil, as well as to search for a new structural type of hypnotics related to the barbiturates, several higher homologs of the 6-alkylated *asym*-triazine-3,5-diones have been synthesized.[11]



I, R = H
II, R = CH_3
III, R = C_2H_5
IV, R = n-C_3H_7



V, R = $CH(CH_3)_2$
VI, R = n-C_5H_{11}
VII, R = n-C_7H_{15}
VIII, R = $CH_2C_6H_5$
IX, R = H
X, R = CH_3

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(2) For a discussion of the nomenclature of this compound see P. K. Chang and T. L. V. Ulbricht, *J. Am. Chem. Soc.*, **80**, 976 (1958).

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(11) A number of 6-arylalkyl-*asym*-triazine-3,5-diones and 6-*t*-butyl-*asym*-triazine-3,5-dione were synthesized by Bougault (*J. pharm. chim.*, **11**, 5 (1915), and ref. 12), but most of them did not fit in the testing scheme in which a regular lengthening of the 6-alkyl chain was desired.