Benzylbromomalononitrile (II).—A sodium hypobromite solution was prepared by adding 1.8 ml. (5.1 g., 0.032 mole) of bromine dropwise to a stirred, cold sodium hydroxide solution prepared from 3.85 g. (0.096 mole) of sodium hydroxide and 45 ml. of water. The nitrile solution was prepared by adding 5.00 g. (0.032 mole) of benzylmalononitrile (I) to a cold solution prepared from 5.0 g. (0.13 mole) of sodium hydroxide and 50 ml. of water. The mixture was stirred and warmed in a hot water-bath until compound I was dissolved. The nitrile solution was poured rapidly into the stirred, cold hypobromite solution. The precipitated yellow solid was filtered with suction, washed with cold water and dried to constant weight in air at room temperature to give 4.57 g. (60.8%) of yellow II of m.p. 115–119°. One recrystallization from benzene–hexane gave 3.29 g. (43.8%) of nearly colorless II of m.p. 119.5–120.5°.

Hydrolysis of II.—A mixture of 2.00 g. (8.5 millimoles) of II, 4.0 ml. (73.5 millimoles) of concentrated sulfuric acid, 20 ml. of glacial acetic acid and 10 ml. of water was refluxed for 16 hours. The solution was poured into 150 ml. of water and the mixture was extracted four times with benzene. The benzene extract was washed once with water and then extracted twice with a saturated aqueous sodium bicarbonate solution. After washing the combined bicarbonate extract once with ether, it was acidified with hydrochloric acid and the insoluble liquid, III, was taken up in ether and the aqueous layer extracted once with ether. After drying with magnesium sulfate, the combined ether solution was freed of ether to leave 1.81 g. (92.8%) of crude III.

***dl*-Phenylalanine (IV).**[7]—Crude III, 1.81 g. (*ca.* 7.9 millimoles) and 25 ml. (0.37 mole) of 28% aqueous ammonia were stored in a closed flask at room temperature for one week. The light yellow solution was evaporated *in vacuo* at 50° until solid began to separate. The *p*H was adjusted to between 6 and 7 with dilute hydrochloric acid and the mixture was cooled in ice. The solid was filtered with suction and dried to give 0.76 g. (58%) of crude IV. The crude IV was recrystallized from ethanol–water to give colorless plates.[4] After filtering, washing with ethanol and drying, the solid weighed 0.57 g. (43.5%) and had a decomposition temperature of 275°. Authentic *dl*-phenylalanine decomposed at 275° under the same conditions.

Benzoylation of recrystallized IV was carried out by shaking 0.50 g. (3.0 millimoles) of IV, 25.4 ml. of water, 0.254 g. (6.35 millimoles) of sodium hydroxide and 0.35 ml. (0.43 g., 3.06 millimoles) of benzoyl chloride until the odor of benzoyl chloride disappeared. Acidification of the solution gave crude V of m.p. 182.5–185° which was purified by one recrystallization from water–ethanol to give crystals of m.p. 186.5–187.5°; reported m.p. 188°.[8] The m.p. of a mixture of V and authentic N-benzoyl-*dl*-phenylalanine was not depressed.

Alkaline Degradation of II.—A suspension of II in aqueous base was prepared from 1.56 g. (10.0 millimoles) of I, 1.2 g. (30 millimoles) of sodium hydroxide, 0.55 ml. (1.60 g., 10 millimoles) of bromine and 15 ml. of water as given for the preparation of II. The resulting suspension of II in aqueous base was steam distilled until insoluble liquid no longer distilled. The steam distillate was made weakly acid and was extracted twice with ether. After drying with magnesium sulfate, the magnesium sulfate was filtered and the ether was removed to leave 0.17 g. (16% from I) of crude benzaldehyde. When a solution of the crude benzaldehyde (*ca.* 1.6 millimoles) in 5 ml. of ethanol was added to an aqueous solution prepared from 0.46 g. (3.2 millimoles) of phenylhydrazine hydrochloride, 0.26 g. (3.2 millimoles) of sodium acetate and 5 ml. of water, a precipitate of the phenylhydrazone separated immediately. After heating to boiling, the mixture was cooled in ice and filtered. The crude derivative had m.p. 150–154°. After two recrystallizations from ethanol–water the m.p. was 154–155°. The reported m.p. of benzaldehyde phenylhydrazone is 156.[9] The identity of the benzaldehyde was confirmed by dividing the ethanol solution from a similar degradation into two parts and preparing the semicarbazone (m.p. 214.5–215.5°, reported m.p. 214°[9]) and 2,4-dinitrophenylhydrazone (m.p. 235–235.8°, reported m.p. 237°[9]).

A similar experiment starting with *p*-methoxybenzylmalononitrile gave anisaldehyde (15.4% crude). The 2,4-dinitrophenylhydrazone had m.p. 257–259°. The reported m.p. of anisaldehyde 2,4-dinitrophenylhydrazone is 254°.[9]

3-Bromocyclohexene.—A mixture of 0.73 g. (3.1 millimoles) of II, 1.6 ml. (1.3 g., 16 millimoles) of cyclohexene of b.p. 80.5–81° (730.7 mm.) and $n^{23.5}$D 1.4450, 34.4 mg. (0.14 millimole) of benzoyl peroxide and 7 ml. of carbon tetrachloride was refluxed for 12 hours and 45 minutes. The carbon tetrachloride, excess cyclohexene and 3-bromocyclohexene were removed from the reaction mixture at 0.05 mm. and 50°. The carbon tetrachloride and cyclohexene were separated from the 3-bromocyclohexene by distilling at 130 mm. and a final pot temperature of 50°. The residue of crude 3-bromocyclohexene was evaporatively distilled at 0.05 mm. to give 0.11 g. of colorless liquid. Quantitative measurements of the infrared absorption spectrum of this liquid and of the spectrum of pure 3-bromocyclohexene, prepared by the method of Ziegler, *et al.*,[10] permitted the 3-bromocyclohexene content of the liquid to be calculated. Based on measurements of the peak at 19.4 μ (KBr prism) the liquid contained 54.6 ± 2% of 3-bromocyclohexene or a 12 ± 2% yield of pure 3-bromocyclohexene based on II.

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α-Reduction of a Steroidal Δ[16]-20-Ketone with Lithium Aluminum Hydride

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It has generally been observed that reduction of steroidal 20-ketones by means of catalytic hydrogenation, or lithium aluminum hydride, proceeds to give 20β-hydroxy compounds as the major products.[1] Indeed when there is substitution at C-17, the formation of the β-hydroxyl configuration generally proceeds almost quantitatively.[2] Heretofore, 20α-hydroxypregnanes have been obtained as the major product only in procedures such as that of Ercoli, who used zinc and acetic acid to obtain a 20α- and 20β-mixture of 5,16-pregnadiene-3β,20-diols from 5,16-pregnadien-3β-ol-20-one acetate.[3] Reduction to the 20β-configuration has been observed so generally that Romo, *et al.*, assumed that the treatment of 7,16-allopregnadien-3β-ol-20-one acetate with lithium aluminum hydride led to the corresponding 20β-hydroxy compound.[4] Our results, using a Δ[16]-20-ketopregnene, however, show that it is also possible to obtain 20α-hydroxyl groups by reduction with this reagent.

When we treated 5,16-pregnadien-3β-ol-20-one

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acetate with lithium aluminum hydride in tetrahydrofuran, the principal product was found to be 5,16-pregnadiene-3β,20α-diol, the same compound as was obtained by Ercoli using zinc and acetic acid.[3] The structure of the product which we obtained was proved by purification through the known diacetate,[3] and saponification which led to the recovery of the dienediol. That there was no reduction of the conjugated double bond at C-16 was shown by Oppenauer oxidation of the reaction product to the known 16-dehydroprogesterone. In addition, catalytic hydrogenation of the diol gave the known allopregnane-3β,20α-diol, which was acetylated to give the known allopregnane-3β,-20α-diol diacetate.

While it is not possible to label C_{20}-hydroxyl groups according to their conformation on a cyclohexane ring, the known reductions of C_{20}-ketones fit into a pattern indicating that the sterically restricted rotation of the 17β side chain inherent in the molecule tends to cause the 20β-hydroxyl group to be more hindered than the 20α. Thus reductions of 20-ketopregnanes by methods which give equatorial or unhindered hydroxyl groups, *e.g.*, sodium and alcohol[5] or hydrogen and nickel in basic solution[5] lead largely to 20α-OH compounds. Conversely, methods such as hydrogenation with platinum in acetic acid[5,6] or Meerwein–Ponndorf reduction,[7] which form axial or hindered hydroxyl groups,[8] lead to 20β-hydroxy steroids.

Reductions with lithium aluminum hydride should in the case of the relatively hindered 17β-acetyl group, give the more hindered hydroxyl group,[8] and the observed 20β-hydroxyl formation[1,2] agrees. On the other hand, lithium aluminum hydride reductions of relatively unhindered carbonyls in general lead to the less hindered hydroxyl groups.[8] The apparent anomaly of the α-reduction in the case at hand may be resolved by examination of molecular models which confirms that the carbonyl group of an acetyl side chain in Δ^{16}-steroids is significantly less hindered than that of pregnan-20-ones.

Experimental[9]

Lithium Aluminum Hydride Reduction of 5,16-Pregnadien-3β-ol-20-one Acetate.—A solution of 200 ml. of dry tetrahydrofuran containing 20.0 g. (0.56 mole) of 5,16-pregnadien-3β-ol-20-one acetate was added to a stirred solution of 12.0 g. of lithium aluminum hydride suspended in 200 ml. of dry tetrahydrofuran. Addition was complete in 15 minutes. Stirring was continued for 30 minutes and then the solution was refluxed with stirring for 5 hours.

After the reaction had cooled, 90 ml. of acetone was added followed by 200 ml. of a saturated solution of Rochelle salts. The supernatant liquid was decanted and the diluted salt solution was extracted with three 150-ml. portions of methylene chloride. The organic extracts were combined and evaporated to a gelatinous solid. Crystallization from benzene gave 15 g. of needles, m.p., softens 165°, melts 172–175°. From the mother liquor was isolated 1.1 g. (theory, 17.7 g.), m.p., softens 163°, melts 172–174°.

Although it was possible by several crystallizations from methanol to separate 5,16-pregnadiene-3β,20α-diol from contaminants, it was found that the pure product could be obtained easily in about 50% yield by acetylation, followed by saponification.

5,16-Pregnadiene-3β,20α-diol Diacetate.—To 1.0 g. of the crude dienediol was added 6.0 ml. of dry pyridine and 2.0 g. of acetic anhydride. The solution was allowed to remain at room temperature for approximately 20 hours, then poured into 200 ml. of water. The precipitate was filtered off and crystallized twice from methanol to yield 0.62 g., m.p. 138–140°, $[\alpha]^{25}D$ −59.98° ($CHCl_3$) (reported[3] 137–138°, $[\alpha]^{16}D$ −57° ($CHCl_3$)).

5,16-Pregnadiene-3β,20α-diol.—To 0.5 g. of the diacetate obtained above was added 20 ml. of methanol and 0.3 g. of 86% KOH in 3 ml. of water. The solution was refluxed for 3 hours and evaporated to dryness. The residue was triturated with 10 ml. of water, and the solid collected and dried *in vacuo* at 70° and 30 mm. to yield 0.36 g. (91.4%), m.p. 178–180°. Crystallization from methanol gave 5,16-pregnadiene-3β,20α-diol, m.p. 174–176°, $[\alpha]^{25}D$ −74.6° ($CHCl_3$) (reported[3] 180–181°, $[\alpha]^{17}D$ −72° ($CHCl_3$)).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.20. Found: C, 79.50; H, 10.02.

16-Dehydroprogesterone.—A sample of 150 mg. of 5,16-pregnadiene-3β,20α-diol was dissolved in 7.5 ml. of toluene and 3.0 ml. of cyclohexanone. After traces of water were removed by boiling, 0.15 g. of aluminum isopropoxide was added in 2.0 ml. of toluene. The reaction mixture was refluxed 1 hour, and 0.15 ml. of water was added. The water was distilled off, the solution filtered, and the filtrate steam distilled. The solid was extracted with benzene and the residue obtained on evaporation was crystallized from benzene–hexane to give 50 mg. of needles, m.p. 184–188°, which showed no depressed m.p. when mixed with authentic 16-dehydroprogesterone,[10] m.p. 184–188°, log ϵ 4.39 (at 239 mμ in ethanol).

Allopregnane-3β,20α-diol.—A sample of 200 mg. of the crude dienediol was reduced according to Marker[6] with platinum oxide in a Parr shaker under 3 atmospheres of hydrogen. After crystallization from acetone 100 mg. of allopregnane-3β,20α-diol was obtained, m.p. 214–216° (reported 216[11] and 217–218°[3]).

Allopregnane-3β,20α-diol Diacetate.—Treatment of this allopregnanediol with acetic anhydride in pyridine followed by crystallization from aqueous ethanol gave allopregnane-3β,20α-diol diacetate, m.p. 165–168°, $[\alpha]^{25}D$ −2.2° ($CHCl_3$) (reported 165–167°, $[\alpha]D \pm 0°$ ($CHCl_3$)[1c]; 164–165°, $[\alpha]^{19}D$ +0.8° ($CHCl_3$)[3]).

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