(iv).—A tenth mole of α-oximinopropiophenone in 100 ml. of 3 *N* absolute ethanolic HCl in the presence of 2 g. of Pd–Rh catalyst took up 0.272 mole of hydrogen in 40 minutes, and 0.0729 mole of purified amino alcohol was isolated. When this catalyst was used a second time, 0.200 mole of hydrogen was taken up in about 2 hours; and from the product was isolated 0.069 mole of the hydrochloride of α-aminopropiophenone. Other reductions with fresh Pd–Rh catalyst did not give such good yields of amino alcohol. For example, in one experiment 0.200 mole of hydrogen was absorbed in 90 minutes, and it was possible to isolate 0.080 mole of amino ketone hydrochloride. However, in none of these reductions was oximino alcohol isolated.

(v).—A solution of 16.3 g. (0.1 mole) of α-oximinopropiophenone in 100 ml. of 5% ethanolic NaOH was hydrogenated in the presence of 2 g. of Pd "acetate" catalyst; 0.265 mole of hydrogen was taken up in about 75 minutes. The catalyst was removed and washed; filtrate and washings were made neutral to congo red by the addition of HCl and evaporated to dryness. The residue was taken up in 150 ml. of water and filtered to remove insoluble material and then the solution was made strongly alkaline with 20% NaOH and extracted with ether. The residue after removal of the ether weighed 12.3 g. (80%); crystallization from 100 ml. of benzene gave 10.1 g. (66.9%) of pure norephedrine.

Reduction of 1,3-Diphenyl-2-oximino-1-propanone[12] (i).—Twelve grams of the oximino ketone (0.05 mole) in 100 ml. of 1.5 *N* absolute ethanolic HCl was hydrogenated with 2 g. of Pd catalyst. After 45 minutes reduction ceased, when 0.082 mole of hydrogen had been absorbed. In the reaction mixture considerable crystallization had taken place. All the solid was collected on a buchner funnel, and the crystals were removed from the charcoal by extracting with 100 ml. of boiling water. The filtrate and washing were combined and evaporated to dryness on a water-bath and under reduced pressure. The residue was dissolved in 200 ml. of boiling water; on cooling an oil separated out, which later crystallized, forming a greenish mass weighing 7.5 g. Recrystallized from alcohol, it formed a colorless product, m.p. 114–116°, which contained neither halogen or nitrogen; it formed a semicarbazone, m.p. 188–189°. The product was identified as 1,3-diphenylpropan-1-ol-2-one, previously prepared by Stoermer and Tier[13] who report the keto alcohol m.p. 116–117°, and its semicarbazone m.p. 189–190°. The precursor of this compound is presumably the oxime, which is hydrolyzed either during the hydrogenation reaction or the isolation process. Addition of 15 ml. of concd. NH_3 to the aqueous solution liberated a base, which was extracted with ether; yield 2.5 g., m.p., 117–118°; calcd. for $C_{15}H_{17}ON$: N, 6.16; found: N, 6.28, 6.35. Hydrochloride is colorless silky crystals, m.p. 185–186°; calcd. for $C_{15}H_{17}ON\cdot HCl\cdot H_2O$: N, 4.97; found: N, 4.90, 5.08.

(ii).—From a similar experiment in which 0.05 mole of oximino ketone was hydrogenated with Pd–Pt catalyst, 0.10 mole of hydrogen taken up in 45 minutes, there was isolated 3.5 g. of amino alcohol and 5.8 g. of keto alcohol.

(iii).—Twelve grams of the oximino ketone (0.05 mole) in 100 ml. of 1.5 *N* absolute ethanolic HCl hydrogenated with 2 g. of Pd–Rh catalyst took up 0.087 mole of hydrogen in about 2 hours. The product consisted of 3.3 g. of crystalline 1,3-diphenylpropan-1-ol-2-one and 7.4 g. of the hydrochloride of 1,3-diphenyl-2-amino-1-propanone, m.p. after three crystallizations from alcohol, 225–226° (dec.). Amino ketone hydrochloride: calcd. for $C_{15}H_{15}ON\cdot HCl$: N, 5.38; found, N, 5.48 and 5.26. Further reduction of the amino ketone hydrochloride in aqueous solution with Pd catalyst formed the amino alcohol.

(iv).—Twelve grams of the oximino ketone dissolved in 100 ml. of 2.5% ethanolic NaOH hydrogenated with Pd catalyst absorbed 0.154 mole of hydrogen. The catalyst was removed, the filtrate and washings were diluted with 50 ml. of water and the solution made acid to congo red and evaporated to dryness; the residue was taken up in water, filtered and basified, thus liberating a quantitative yield of amino alcohol which, recrystallized from benzene, gave 8.8 g. (77.5%) of 1,3-diphenyl-2-amino-1-propanol, m.p. 118°.

(12) This oximino ketone prepared by the regular nitrosation[4] of 1,3-diphenylpropanone, recrystallized from benzene, formed white crystals, m.p. 126–127°. It is known from the work of W. Schneidewind, *Ber*, **21**, 1326 (1888).

(13) R. Stoermer and C. Tier, *ibid.*, **58**, 2613 (1925).

CHAPEL HILL, NORTH CAROLINA

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

Hydrogenation of $\Delta^{5,7}$-Sterol Derivatives

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A smooth, generally applicable method for the hydrogenation of $\Delta^{5,7}$-steroids to Δ^{7}-allosteroids with Raney nickel in benzene is described. By this procedure the isomerization of Δ^{7}-allosteroids to $\Delta^{8(14)}$-allosteroids encountered with the use of platinum and palladium catalysts is avoided and pure Δ^{7}-allosteroids are obtained in 80–90% yields.

During the course of an investigation which led to the utilization of plant steroids for the synthesis of cortisone,[1] we studied the hydrogenation of a number of steroid derivatives. As some of the procedures described in the literature were frequently inadequate with respect to reproducibility or to optimum yields, at least in our hands, we wish to report our experience in this field.

Following the procedures of earlier investigators we were unable to bring about the satisfactory hydrogenation of ergosterol acetate[2] or methyl $\Delta^{5,7}$-3β-acetoxybisnorcholadienate[3] to $\Delta^{7,22}$-ergostadiene-3β-ol acetate and methyl Δ^{7}-3β-acetoxyallobisnorcholenate, respectively.[4] In practically every experiment in which platinum catalysis was used in accordance with previously described directions, the absorption of hydrogen was erratic and pure products were difficult to obtain. In the case of ergosterol acetate even when one mole of hydrogen was absorbed, a practically inseparable mixture was obtained in which considerable $\Delta^{5,7}$-diene was still present as judged from the ultraviolet absorption spectrum. Hydrogenation of methyl $\Delta^{5,7}$-3β-acetoxybisnorcholadienate with one mole of hydrogen with the aid of platinum in ethyl acetate evidently afforded the same methyl Δ^{7}-3β-acetoxyallo-

(1) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, THIS JOURNAL, **73**, 2396 (1951); J. M. Chemerda, E. M. Chamberlin, E. Wilson and M. Tishler, *ibid.*, **73**, 4052 (1951).

(2) I. M. Heilbron and W. A. Sexton, *J. Chem. Soc.*, 921 (1929); H. Wieland and W. Benend, *Ann.*, **554**, 1 (1943).

(3) W. Bergmann and P. G. Stevens, *J. Org. Chem.*, **13**, 10 (1948).

(4) Since the completion of our work, three reports have appeared on the hydrogenation of ergosterol and its derivatives; R. C. Anderson, R. Budizarek, G. T. Newbold, R. Stevenson and F. S. Spring; *Chemistry and Industry*, 1635 (1951); H. Heusser, K. Eichenberger, P. Kurath, H. R. Dallenbach and O. Jeger, *Helv. Chim. Acta*, **34**, 2123 (1951); G. D. Laubach and K. J. Brunings, THIS JOURNAL, **74**, 705 (1952).

bisnorcholenate preparation previously described.[3] However, this preparation proved to be impure and was probably a mixture of the desired Δ^7-derivative and the closely related $\Delta^{8(14)}$-derivative. In the case of methyl $\Delta^{5,7}$-3β-hydroxybisnorcholadienate, similar difficulties were likewise experienced but in this instance, the platinum-catalyzed reduction product could be separated into the pure Δ^7- and $\Delta^{8(14)}$-derivatives by a tedious fractional crystallization process.

Raney nickel[5] was observed to be satisfactory for the partial hydrogenation of a number of $\Delta^{5,7}$-steroids at the Δ^5-double bond to the allo-Δ^7-steroids. With this catalyst, hydrogenation proceeded smoothly at one to three atmospheres pressure and pure Δ^7-derivatives were isolated in 80–90% yield. Under these conditions, successful hydrogenations were carried out upon $\Delta^{5,7}$-pregnadiene-3β-ol-20-one-acetate, methyl $\Delta^{5,7}$-3β-acetoxybisnorcholadienate, $\Delta^{5,7}$-isospirostadiene-3β-ol acetate (7-dehydrodiosgenin acetate) and ergosterol acetate at the Δ^5 double bond.

Benzene, proved to be an excellent solvent for the hydrogenation of these ester derivatives. Peroxide-free dioxane likewise proved useful in this respect. Ergosterol acetate in benzene smoothly absorbed one mole of hydrogen in one to two hours at one to three atmospheres of hydrogen pressure. Ultraviolet absorption spectroscopy of the entire product at this point indicated that less than 1–3% of the $\Delta^{5,7}$-moiety was still present. Further hydrogenation of the $\Delta^{7,22}$-ergostadiene-3β-ol acetate did not occur readily with our Raney nickel preparations. However, recently it has been reported[6] that ergosterol acetate is hydrogenated to Δ^7-ergostene-3β-ol acetate by the action of Raney nickel in ethyl acetate for 20 hours. In a few cases, hydrogen absorption continued at a very slow rate after the initial fast absorption of one mole of hydrogen but examination of the reaction mixture indicated that benzene was being hydrogenated in preference to the $\Delta^{7,22}$-ergostadiene-3β-ol acetate. The factors responsible for the hydrogenation of benzene in these instances have defied elucidation. $\Delta^{5,7}$-Pregnadiene-3β-ol-20-one acetate in benzene solution was likewise smoothly hydrogenated to Δ^7-allopregnene-3β-ol-20-one acetate with little or no reduction of the 20-carbonyl group.

Raney nickel does not appear to catalyze the isomerization of the Δ^7-derivatives to the $\Delta^{8(14)}$-derivatives which is often encountered with the use of platinum or palladium catalysts. The detection of the $\Delta^{8(14)}$-derivatives is often somewhat difficult but mixtures of Δ^7- and $\Delta^{8(14)}$-derivatives usually possess lower melting points than the corresponding pure individuals. Judging from the ease with which pure $\Delta^{7,22}$-ergostadiene-3β-ol acetate and the other Δ^7-allosteroids described were isolated in good yields from these Raney nickel hydrogenations, the amount of $\Delta^{8(14)}$-derivative formed must have been negligible.[7] In connection with the use of platinum catalyst, we have also observed that isomerization of certain Δ^7-steroids to the corresponding $\Delta^{8(14)}$-derivatives was repressed if suitable conditions of hydrogenation were employed. Thus, pure Δ^7-ergostene-3β-ol was obtained when the $\Delta^{7,22}$-derivative was hydrogenated in ethyl acetate with a trace of acetic acid in the presence of a large proportion of platinum catalyst. Under these conditions, the absorption of hydrogen was exceedingly rapid. Separation of the steroid from the catalyst immediately after the required amount of hydrogen had been absorbed was also necessary. This technique was successfully applied to the hydrogenation of $\Delta^{7,9(11),22}$-ergostatriene-3β-ol acetate to Δ^7-ergostene-3β-ol acetate but was unsuccessful for the hydrogenation of methyl $\Delta^{5,7}$-3β-hydroxybisnorcholadienate and its derivatives to the Δ^7-compounds.

The $\Delta^{5,7}$-steroids used in this investigation (with the exception of ergosterol acetate) were prepared by the action of N-bromosuccinimide on the Δ^5-steroids followed by dehydrobromination of the 7-bromo derivatives. The preparation of $\Delta^{5,7}$-pregnadiene-3β-ol-20-one benzoate[8] and $\Delta^{5,7}$-isospirostadiene-3β-ol acetate[9] were recently described after the completion of our research. Our results are in general accord with the results already presented except for the values of the molar extinction coefficients of the $\Delta^{5,7}$-dienes as noted in the Experimental section.

During the study of the dehydrobromination of Δ^5-7-bromopregnene-3β-ol-20-one benzoate (III) with dimethylaniline, we made some observations worthy of mention. On heating a solution of III in xylene and dimethylaniline under reflux, there was obtained benzoic acid, a conjugated triene, and a $\Delta^{5,7}$-diene, which exhibited the expected ultraviolet absorption $\lambda_{max.}$ 228, 272, 282 and 294 mμ. Further examination of the $\Delta^{5,7}$-diene indicated that its optical rotation was different from the $\Delta^{5,7}$-pregnadiene-3β-ol-20-one benzoate produced by the action of collidine. In the latter case practically no benzoic acid or conjugated triene were formed. Since the optical rotation of the product obtained by dehydrobromination with collidine was normal insofar as could be determined by comparison of the molecular rotation differences of the known Δ^7-derivative and the related $\Delta^{5,7}$-derivatives, it was concluded that partial inversion about C-17 was responsible for the anomalous rotation of the product obtained by dehydrobromination of III with dimethylaniline. This conclusion was strengthened by studies with Δ^5-pregnene-3β-ol-20-one benzoate where the related iso-derivatives are known. Thus dimethylanilinium bromide in boiling xylene equilibrated Δ^5-pregnene-3β-ol-20-one benzoate to a mixture of the 17-normal and 17-iso forms although collidine, dimethylaniline and collidine-collidinium bromide were ineffective. The isomerization of Δ^5-pregnene-3β-ol-20-one and its derivatives to the iso-form has been accomplished previously by the action of strong alkali.[10] In this case, the dimethylanilinium ion which is a stronger

(5) Prepared according to R. Mozingo, *Org. Syntheses*, **20**, 15 (1951).

(6) P. Bladon, J. M. Fabian, H. B. Henbest, H. R. Koch and G. W. Wood, *J. Chem. Soc.*, 2407 (1951).

(7) Additional justification for this belief is provided by the experience of P. Bladon, *et al.*,[7] who obtained pure Δ^7-ergostene-3β-ol acetate after prolonged action of Raney nickel on ergosterol acetate.

(8) C. Djerassi, J. Romo and G. Rosenkranz, *J. Org. Chem.*, **16**, 754 (1951).

(9) G. Rosenkranz, J. Romo and J. Berlin, *ibid.*, **16**, 290 (1951).

(10) A. Butenandt and G. Fleischer, *Ber.*, **70**, 96 (1937).

acid than the collidinium ion, promotes the enolization of the 20-carbonyl through the formation of the conjugate acid involving the 20-carbonyl group.[11] Likewise the acid strength of the dimethylanilinium ion appears sufficient to catalyze the decomposition of $\Delta^{4,6}$-pregnadiene-3β-ol benzoate to the conjugated triene.

Methyl $\Delta^{5,7}$-3β-hydroxybisnorcholadienate has previously been prepared from ergosterol *via* degradation of the maleic anhydride adduct and the regeneration of the $\Delta^{5,7}$-diene by pyrolysis of the maleic anhydride adduct.[3] It was found more convenient to prepare $\Delta^{5,7}$-bisnorcholadienate derivatives from the 7-bromo derivatives obtained by the action of N-bromosuccinimide on either the benzoate or the acetate of methyl Δ^{5}-3β-hydroxybisnorcholenate. From the standpoint of purification of both the 7-bromo derivatives and the dehydrobromination products, the use of the benzoate proved more desirable. Hydrolysis of the benzoate with alcoholic alkali yielded methyl $\Delta^{5,7}$-3β-hydroxybisnorcholadienate which was previously described.[3]

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Experimental

All m.ps. are corrected; rotations are determined on 1% solutions.

Hydrogenation of Ergosterol Acetate.—A solution of 439 g. (1.0 mole) of ergosterol acetate in 4.1 liters of thiophene-free benzene was placed in a 5-liter stainless steel hydrogenation vessel together with two tablespoons of Raney nickel catalyst.[12] Hydrogenation proceeded rapidly at an initial pressure of 40 p.s.i. and 1.1 moles of hydrogen was absorbed in three hours at which time hydrogen absorption ceased. The catalyst was filtered, the benzene filtrate concentrated *in vacuo* and the residue was crystallized from 2.2 liters of ethyl acetate. Practically pure **$\Delta^{7,22}$-ergostadiene-3β-ol acetate** was obtained in 90% yield, m.p. 182.5–186.8°, $[\alpha]^{22}D$ −17.4° ($CHCl_3$), less than 0.5–1% of ergosterol as determined by ultraviolet absorption spectrophotometry. A recrystallization of the product from ethyl acetate did not materially affect the properties of the preparation, m.p. 184–186.8°, $[\alpha]^{22}D$ −19.2° ($CHCl_3$), phase purity 98.6 ± 0.5%.

Methyl Δ^{5}-3β-Benzoxy-7-bromobisnorcholenate.—A solution of 50.9 g. of methyl-Δ^{5}-3β-benzoxybisnorcholenate in 650 ml. of carbon tetrachloride was distilled until 100 ml. of solvent had been removed. Under nitrogen atmosphere, 21.4 g. of N-bromosuccinimide was added to the solution and the mixture was illuminated under reflux with two photoflood lamps (No. RFL-2, General Electric Co.) for 15 minutes. After cooling the reaction mixture to 0–5°, the succinimide was removed by filtration and the solvent was removed *in vacuo*. The residue was digested with acetone, and 43.5 g. of crude 7-bromo compound was obtained, m.p. 140–141°. One recrystallization from acetone yielded pure **methyl Δ^{5}-3β-benzoxy-7-bromobisnorcholenate**, m.p. 144–145° (dec.), $[\alpha]^{24}D$ −166° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{39}O_4Br$: C, 66.29; H, 7.23; Br, 14.70. Found: C, 66.27; H, 7.15; Br, 14.27.

Methyl $\Delta^{5,7}$-3β-Benzoxybisnorcholadienate.—A mixture of 22.9 g. of methyl Δ^{5}-3β-benzoxy-7-bromobisnorcholenate, 300 ml. of xylene and 23 ml. of γ-collidine was heated under reflux in a nitrogen atmosphere for 20 minutes. The cooled mixture was washed successively with 250 ml. of ice-water, 250 ml. of cold 1 *N* hydrochloric acid and 100 ml. of cold aqueous sodium bicarbonate solution. The xylene layer was dried, and the solvent removed *in vacuo*. The residual material, upon digestion with acetone, yielded 11.4 g. of material which contained 85% of the desired $\Delta^{5,7}$-diene by ultraviolet absorption analysis. After recrystallization from acetone and from methanol, pure **methyl $\Delta^{5,7}$-3-benzoxybisnorcholadienate** was obtained, m.p. 189–192°, $[\alpha]^{24}D$ −66.6° ($CHCl_3$), λ_{max}^{EtOH} 231 mμ (E_M 14,100), 271 mμ (E_M 13,750), 281 mμ (E_M 14,350), 293 mμ (E_M 7,260).

Anal. Calcd. for $C_{30}H_{38}O_4$: C, 77.85; H, 8.28. Found: C, 78.02; H, 8.25.

Methyl $\Delta^{5,7}$-3β-Hydroxybisnorcholadienate.—The 3-benzoate was saponified with methanolic potassium hydroxide as described by Bergmann and Stevens[3] to give the 3-hydroxy compound which appeared identical with the preparation previously reported, m.p. 167–169°, $[\alpha]^{24}D$ −130° ($CHCl_3$), λ_{max}^{EtOH} 271 mμ (E_M 10,900), 281 mμ (E_M 11,700), 293 mμ (E_M 6,400).

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.20; H, 9.33.

Acetylation of the $\Delta^{5,7}$-hydroxy diene by the use of pyridine and acetic anhydride at room temperature yielded **methyl-$\Delta^{5,7}$-3β-acetoxybisnorcholadienate**, m.p. 145–150°, $[\alpha]^{24}D$ −88° ($CHCl_3$), λ_{max}^{EtOH} 270 mμ (E_M 11,200), 281 mμ (11,700), 293 mμ (E_M 6,690).

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.90; H, 9.37.

Methyl Δ^{5}-3β-Acetoxy-7-bromobisnorcholenate.—Methyl Δ^{5}-3β-acetoxybisnorcholenate, 12.75 g., was dissolved in 300 ml. of purified Skellysolve B, and the solution was distilled until 50 ml. of solvent had been removed. Six and two-tenths grams of N-bromosuccinimide was added, and the mixture was illuminated at reflux temperature with a photoflood lamp for 15 minutes. The reaction mixture was cooled and filtered, and the filtrate concentrated to a small volume. After cooling in a Dry Ice–acetone-bath, the crude bromo compound crystallized, and the mixture was filtered and washed with cold Skellysolve B; yield 8.97 g., m.p. 114–120°. After one recrystallization from Skellysolve B, pure **methyl Δ^{5}-3β-acetoxy-7-bromobisnorcholenate** was obtained, m.p. 119–120°, $[\alpha]^{24}D$ −219° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{37}O_4Br$: C, 62.36; H, 7.75; Br, 16.60. Found: C, 62.37; H, 7.56; Br, 16.68.

Methyl $\Delta^{5,7}$-3β-Acetoxybisnorcholadienate.—A solution of 8.97 g. of methyl Δ^{5}-7-bromobisnorcholenate in 80 ml. of xylene and 10 ml. of collidine was refluxed for 15 minutes. After the usual work-up, the crude product was triturated with methanol to obtain 4.46 g. of crystalline material, m.p. 115–130°. Upon recrystallization from methanol, 2.22 g. of material was obtained, m.p. 125–140°. This material was a mixture containing 44% of the $\Delta^{4,6}$-isomer, and 56% of the $\Delta^{5,7}$-isomer on the basis of ultraviolet absorption analysis. Since this mixture could not be separated by recrystallization, 0.75 g. of the mixture was chromatographed over 50 g. of acid-washed alumina. No material was eluted with 600 ml. of petroleum ether. Elution with 500 ml. of 1:10 ether, petroleum ether mixture yielded a substance which melted at 133–136° after recrystallization from methanol, λ_{max}^{EtOH} 239 mμ (E_M 27,600). A satisfactory analysis was not obtained with this material, which is evidently impure **methyl $\Delta^{4,6}$-3β-acetoxybisnorcholadienate**. Elution of the column with 1500 ml. more of 1:10 ether–petroleum ether mixture yielded first a low-melting fraction, evidently a mixture, and then pure **methyl $\Delta^{5,7}$-3β-acetoxybisnorcholadienate**, m.p. 145–150°, identical in all respects with the sample prepared by acetylation of methyl-$\Delta^{5,7}$-3β-hydroxybisnorcholadienate.

Methyl Δ^{7}-3β-Acetoxybisnorallocholenate.—A solution of 5.0 g. of methyl $\Delta^{5,7}$-3β-acetoxybisnorcholadienate in 100 ml. of benzene was hydrogenated with 1.5 g. of Raney nickel at 3 atmospheres until 1.2 moles had been absorbed, the catalyst was filtered off, and the benzene-free crystalline residue was triturated with methanol; yield 4.35 g., m.p. 150–155°. After two recrystallizations from methanol pure **methyl Δ^{7}-3β-acetoxybisnorallocholenate** was obtained, m.p. 156–157°, $[\alpha]^{24}D$ −5.5° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.71; H, 9.45.

Saponification of the acetate by Bergmann and Stevens'

(11) E. R. Alexander, "Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 120.

(12) For best results it is advisable to flush the Raney nickel catalyst consecutively with absolute alcohol and benzene prior to use.

procedure[3] yielded **methyl Δ^7-3β-hydroxybisnorallocholenate**, m.p. 179–181°, $[\alpha]^{24}D$ −6.5° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.33; H, 10.19.

Benzoylation of the 3-hydroxy compound with pyridine and benzoyl chloride gave the **3-benzoxy derivative**, m.p. 169–170° after crystallization from acetone, $[\alpha]^{24}D$ −2° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{40}O_4$: C, 77.55; H, 8.68. Found: C, 77.90; H, 8.85.

Hydrogenation of Methyl $\Delta^{5,7}$-3β-Hydroxybisnorcholadienate with Platinum.—A solution of 1.96 g. of methyl $\Delta^{5,7}$-3β-hydroxybisnorcholadienate in 50 ml. of ethyl acetate containing 0.5 ml. of glacial acetic acid, was hydrogenated at slightly more than one atmosphere pressure with 100 mg. of prereduced platinum oxide catalyst. In 15 minutes, 1 mole of hydrogen was absorbed, and after ten minutes more the mixture was filtered and concentrated to dryness *in vacuo*. By recrystallization of the mixture (free of $\Delta^{5,7}$-diene as indicated by its absorption spectrum) from ethanol, two crops were obtained; 0.75 g., m.p. 142–165°, and 1.04 g., m.p. 135–142°. After a tedious process of triangular fractional crystallization from ethanol, Skellysolve B or ethyl acetate, two pure components were isolated from the above mixtures; the more insoluble component being **methyl Δ^7-β-hydroxybisnorallocholenate**, m.p. 179–181°, $[\alpha]^{24}D$ −6.1° ($CHCl_3$), identical in all respects with the product obtained from Raney nickel reduction of the diene, and the other component, m.p. 158–160°, being **methyl $\Delta^{8(14)}$-3β-hydroxybisnorallocholenate**, $[\alpha]^{24}D$ +9.1° ($CHCl_3$), which was identical with the substance prepared by rearrangement of the Δ^7-derivative as described below.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.67; H, 10.06. Found: C, 76.33; H, 10.19.

Similar results were obtained with methyl $\Delta^{5,7}$-3β-acetoxybisnorcholadienate. Upon hydrogenation in neutral ethyl acetate, only 75% of the required amount of hydrogen was absorbed, at which point the uptake of hydrogen ceased abruptly. Examination of the product indicated that considerable $\Delta^{5,7}$-derivative remained.

Hydrogenation of the 3-acetate as described above for the 3-hydroxy derivative using ethyl acetate and a trace of acetic acid led to the absorption of the required amount of hydrogen in eight minutes. Upon work-up of the reaction mixture in the usual manner (immediately after the absorption of the required amount of hydrogen) and crystallization of the hydrogenation product from methanol, the product melted at 132–136°, $[\alpha]^{24}D$ −6.3° ($CHCl_3$), yield 85%. Ultraviolet absorption indicated complete absence of $\Delta^{5,7}$-diene. The preparation was evidently a mixture of Δ^7- and $\Delta^{8(14)}$-isomers judging from the melting point. Reaction of the preparation with mercuric acetate[13] confirmed this conclusion since the $\Delta^{7,9(11)}$-derivative was obtained in poor yield, in contrast to our experience with preparations obtained with Raney nickel catalyst.

Methyl $\Delta^{8(14)}$-3β-Acetoxybisnorallocholenate.—One gram of methyl $\Delta^{5,7}$-3β-acetoxybisnorcholadienate in a mixture of 12.5 ml. of glacial acetic acid and 25 ml. of ethyl acetate was hydrogenated in the presence of 100 mg. of platinum oxide catalyst at slightly more than one atmosphere pressure. One molar proportion of hydrogen was absorbed in three minutes and shaking was continued for 30 minutes more during which time no more hydrogen absorption occurred. The product, methyl $\Delta^{8(14)}$-3β-acetoxybisnorallocholenate, was isolated in the usual manner and melted at 140–142.5° after recrystallization from methanol, $[\alpha]^{22}D$ −6.7, yield 80%. Hydrolysis of the acetate by brief reflux with 1 *N* sodium hydroxide in methanol yielded **methyl $\Delta^{8(14)}$-3β-hydroxybisnorallocholenate** in 70% yield, m.p. 157–159.5°, $[\alpha]^{22}D$ +9.5° ($CHCl_3$), which proved to be identical with the product isolated as a by-product in the hydrogenation of the $\Delta^{5,7}$-diene with platinum in ethyl acetate.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.38; H, 9.51.

Dehydrobromination of Δ^5 7-Bromopregnene-3β-ol-20-one Benzoate. (a) **Collidine.**—A solution of 25 ml. of collidine and 300 ml. of xylene was heated to boiling and 23.3 g. of Δ^5-7-bromopregnene-3β-ol-20-one benzoate was added in small portions, and the resulting mixture was refluxed for an additional 25 minutes. Upon cooling the reaction mixture to 0–5° and washing with 500 ml. of ice-water, the crude $\Delta^{5,7}$-diene precipitated and was filtered off. After recrystallization from chloroform–acetone, 4.5 g. of **$\Delta^{5,7}$-pregnadiene-3β-ol-20-one benzoate** was obtained, m.p. 217–222°. Analytically pure material was obtained after an additional recrystallization from acetone; m.p. 220–223°, $[\alpha]^{24}D$ −7.3° ($CHCl_3$), λ_{max}^{EtOH} 228 mμ (E_M 14,500), 272 mμ (E_M 12,700), 282 mμ (E_M 13,000), 294 mμ (E_M 7,200).[14]

Anal. Calcd. for $C_{28}H_{34}O_3$: C, 80.34; H, 8.19. Found: C, 80.57; H, 7.94.

(b) **Dimethylaniline.**—A solution of 35.7 g. of the Δ^5-7-bromo derivative in 600 ml. of xylene and 18 g. of dimethylaniline was refluxed for 20 minutes in a nitrogen atmosphere. The cooled reaction liquor was separated from dimethylaniline hydrobromide by decantation and the decantate was washed successively with 2 *N* sulfuric acid, sodium bicarbonate solution and finally water. By acidification of the bicarbonate extract, 2.94 g. of benzoic acid was obtained. After concentrating *in vacuo*, the residual steroid was crystallized by trituration with ice-cold methanol and a crude $\Delta^{5,7}$-diene preparation was obtained; yield 6.6 g., m.p. 176–178°. Further crystallization from acetone yielded a $\Delta^{5,7}$-pregnadiene-3β-ol benzoate preparation which was evidently a mixture of the 17-normal derivative (obtained exclusively in the case of collidine) and the 17-iso-derivative, m.p. 188–189°, $[\alpha]^{22}D$ −22°, λ_{max}^{EtOH} 228 mμ (E_M 15,620), 272 mμ (E_M 14,100), 282 mμ (E_M 14,400), 294 mμ (E_M 8,100) and was not investigated further.

Homogeneous products could not be separated from methanolic mother liquor. Examination of this material by ultraviolet absorption spectroscopy indicated the presence of considerable triene, probably $\Delta^{2,4,6}$-pregnatriene-20-one, in view of the fairly intense absorption peaks at 295, 305 and 320 mμ.

Epimerization of Δ^5-Pregnene-3β-ol-20-one Benzoate with Dimethylanilinium Bromide.—Δ^5-Pregnene-3β-ol-20-one benzoate was recovered unchanged after treatment with collidine, dimethylaniline or collidine–collidinium bromide in refluxing xylene under the conditions used for dehydrobromination. However, when 1.0 g. of Δ^5-pregnene-3β-ol-20-one benzoate was refluxed with 281 mg. of dimethylaniline and 479 mg. of dimethylanilinium bromide in 28 cc. of xylene for 20 minutes only 51% of the Δ^5-pregnene-3β-ol-20-one benzoate was recovered, m.p. 180–183.6°, $[\alpha]^{24}D$ +32° ($CHCl_3$) (pure, m.p. 195–197°, $[\alpha]^{24}D$ +36° ($CHCl_3$)). The residual material, m.p. 168–186, $[\alpha]^{22}D$ −0.5° ($CHCl_3$), contained an even greater proportion of the iso-derivative. In the case of a parallel experiment with collidine–collidinium bromide, 95% of the starting product was recovered in two crops, m.p. 189–193°, m.p. 187–192°, $[\alpha]D$ +33° ($CHCl_3$), indicating that epimerization was insignificant in the latter case. Similar results were obtained in experiments with either free collidine or dimethylaniline.

Δ^7-Allopregnene-3β-ol-20-one Acetate.—A solution of 7.8 g. of $\Delta^{5,7}$-pregnadiene-3β-ol-20-one acetate in 200 ml. of benzene was hydrogenated at three atmospheres pressure in the presence of 3 g. of Raney nickel catalyst. After working up the product in the usual manner, and recrystallizing from methanol, 6.61 g. of product was obtained, m.p. 170–175°. One more recrystallization from methanol afforded pure **Δ^7-allopregnene-3β-ol-20-one acetate**, m.p. 172–175.5°, $[\alpha]^{24}D$ +82° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.15; H, 9.30.

Δ^7-Isoallospirostene-3β-ol Acetate.—A solution of 2.87 g. of $\Delta^{5,7}$-spirostadiene-3β-ol acetate[15] in 125 ml. of dioxane was hydrogenated under three atmospheres pressure with 1.5 g.

(13) The reaction of Δ^7-derivatives with mercuric acetate is described in a subsequent paper, THIS JOURNAL, in press.

(14) C. Djerassi, J. Romo and G. Rosenkranz (ref. 8) reported m.p. 226–229°, $[\alpha]^{20}D$ +0, $\lambda_{max}^{95\%\ EtOH}$ 240 mμ (E_M 16,600), 272 mμ (E_M 14,100), 282 mμ (E_M 15,900), 294 mμ (E_M 9150).

(15) After the completion of our research, the preparation of this diene was described by G. Rosenkranz, J. Romo and S. Berlin (ref. 9). For pure $\Delta^{5,7}$-spirostadiene-3β-ol acetate we obtained m.p. 202–206°, $[\alpha]^{24}D$ −134° ($CHCl_3$) λ_{max}^{EtOH} 271 mμ (E_M 11,500), 282 mμ (E_M 12,000), 293 mμ (E_M 6,900) whereas Rosenkranz, *et al.*, obtained m.p. 202–205°, $[\alpha]^{20}D$ −127° ($CHCl_3$) and $\lambda_{max}^{95\%\ EtOH}$ 272 mμ (E_M 15,500), 282 mμ (E_M 15,800) and 293 mμ (E_M 9800).

of Raney nickel catalyst. One molar proportion of hydrogen was absorbed in 40 minutes and crystalline Δ^7-compound separated from solution. The mixture was warmed to dissolve the precipitated steroid, filtered and the filtrate concentrated *in vacuo* to dryness. Trituration of the residue with methanol yielded 2.78 g. of practically pure Δ^7-derivative, m.p. 234–237°. After recrystallization from methanol pure Δ^7-isoallospirostene-3β-ol acetate was obtained, m.p. 236–238°, $[\alpha]^{24}D$ −76° ($CHCl_3$).[16]

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.26; H, 9.57.

Saponification of the acetate yielded Δ^7-spirostene-3β-ol, m.p. 201–204°.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.44; H, 10.20.

Preparation of Δ^7-Ergostene-3β-ol.—Two hundred milligrams of Adams catalyst was reduced in 75 cc. of purified ethyl acetate[17] containing 0.1 cc. of glacial acetic acid. Seven hundred ninety-six milligrams of $\Delta^{7,22}$-ergostadiene-3β-ol was added and shaken with hydrogen at 27°. Hydrogen absorption ceased after 50.1 cc. was taken up (theory for 1 mole, 49.5 cc.). After filtration of the mixture and evaporation of the solvent, recrystallization of the residue from methanol yielded 440 mg. of Δ^7-ergostene-3β-ol, m.p. 145–146°, $[\alpha]^{24}D$ +0.44° ($CHCl_3$).[18]

Hydrogenation of $\Delta^{7,9(11)22}$-Ergostatriene-3β-ol Acetate.—A suspension of 200 milligrams of Adams catalyst was reduced in 75 cc. of purified ethyl acetate[17] containing 0.1 cc. of glacial acetic acid. One gram of $\Delta^{7,9(11)22}$-ergostatriene-3β-ol acetate was added and shaken with hydrogen at 27°; hydrogen uptake 98.8 cc. (theory for 2 moles, 97.0 cc.). The solvent was evaporated after removal of the catalyst and the residue recrystallized from methanol–chloroform. The product, Δ^7-ergostene-3β-ol acetate crystallized in plates, m.p. 159–162°, $[\alpha]^{24}D$ −3.1° ($CHCl_3$),[19] end absorption in the ultraviolet region above 220 mμ.

(16) G. Rosenkranz, J. Romo, E. Batres and C. Djerassi, *J. Org. Chem.*, **16**, 298 (1951), reported m.p. 222–223°, $[\alpha]^{20}D$ −66.5° ($CHCl_3$) for Δ^7-isoallospirostene-3β-ol acetate prepared by hydrogenation of the $\Delta^{5,7}$-derivative with platinum in ethyl acetate.

(17) Louis F. Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., Boston, Mass., 1941, p. 364.

(18) A. Windaus and R. Langer report m.p. 145–146°, $[\alpha]D$ +0° ($CHCl_3$).

(19) Previously reported by A. Windaus and R. Langer (ref. 19), m.p. 157° $[\alpha]D$ −5.3° ($CHCl_3$).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Microbiological Transformations of Steroids.[1] I. Introduction of Oxygen at Carbon-11 of Progesterone

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A microbiological method is described for the oxygenation of steroids at carbon-11 by fungi of the genus *Rhizopus* (order *Mucorales*); yields are high and the oxygenation is accomplished in one simple step. Progesterone yields 11α-hydroxyprogesterone and a dihydroxyprogesterone when oxygenated by *Rhizopus arrhizus* Fischer (A.T.C.C. 11145) or *Rhizopus nigricans* Ehrb. (A.T.C.C. 6227b). The latter species in particular produces excellent yields of 11α-hydroxyprogesterone and in addition, 11α-hydroxyallopregnane-3,20-dione. A simple direct isolation method and characterization of the transformation products are reported.

Discussion

Following the observation[2] that cortisone is effective in the treatment of rheumatoid diseases, a major effort has been devoted to developing an improved synthesis of this hormone. That effort has been necessitated by demand for the drug and by the need to reduce the high cost of producing it.

In the production of cortisone much of the expense is due to the many steps[3–6] which are required to introduce the necessary oxygen atom at carbon-11. Thus a better method of oxygenating at carbon-11 became imperative.

Our objective was to oxygenate readily available steroids directly to the adrenal cortical hormones or to intermediates which could be easily converted to these substances. Accordingly, we were led to investigate the microbiological approach to the oxygenation of steroids because of the manifold and complex reactions which are performed by various microörganisms.

Among the transformations of steroids by microorganisms reported in the literature are the oxidation of a hydroxy group, the reduction of a ketone group, and the reduction of a ring double bond.[7] A conversion of cholesterol to 7-hydroxycholesterol by *Proactinomyces roseus*, was reported by Krámli and Horváth.[8] However, until the publication of our preliminary communication[9] the microbiological oxygenation of steroids at other positions had not been reported. In that article, we outlined a method for the introduction of oxygen into the strategic C-11 position of the steroid nucleus.

In the microbiological transformation of progesterone, as herein described more completely, 11α-hydroxyprogesterone is the main product formed. In addition, small amounts of a dihydroxyproges-

(1) A preliminary report of this work was published as a communication, THIS JOURNAL, **74**, 1871 (1952). See also U. S. Patent 2,602,769 issued July 8, 1952; originally filed Aug. 19, 1950.

(2) P. S. Hench, C. H. Slocumb, A. R. Barnes, H. L. Smith, H. F. Polley and E. C. Kendall, *Proc. Staff Meetings Mayo Clinic*, **24**, 181 (1949); **24**, 277 (1949).

(3) B. F. McKenzie, V. R. Mattox, L. L. Engel and E. C. Kendall, *J. Biol. Chem.*, **173**, 271 (1948).

(4) E. M. Chamberlain, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and Max Tishler, THIS JOURNAL, **73**, 2396 (1951).

(5) Louis F. Fieser, Josef E. Herz and Wei-Yuan Huang, *ibid.*, **73**, 2397 (1951).

(6) Gilbert Stork, J. Romo, G. Rosenkranz and Carl Djerassi, *ibid.*, **73**, 3546 (1951).

(7) This subject has been reviewed by M. Welsch and G. Heusghem, *Compt. rend. soc. biol.*, **142**, 1074 (1948).

(8) A. Krámli and J. Horváth, *Nature*, **162**, 619 (1948).

(9) Since our preliminary report,[1] Perlman, Titus, and Fried, THIS JOURNAL, **74**, 2126 (1952), have reported the introduction of oxygen at the C-16 position using an unknown Actinomycetes. Colingsworth, Brunner, and Haines, *ibid.*, **74**, 2381 (1952), have also presented evidence for 11-oxygenation of steroids using *Streptomyces fradeae*.