3-keto-Δ^4-steroids,[1,2] in particular their reaction with Grignard reagents.

11β-Hydroxy-4-androstene-3,17-dione (I)[1,3] was converted to 3-(N-pyrrolidinyl)-11β-hydroxy-3,5-androstadien-17-one (II) in essentially quantitative yield by the reaction of pyrrolidine with I as previously described,[2] m.p. 190° (dec.), $[\alpha]_D$ −81° ($CHCl_3$); *Anal.* Calcd. for $C_{23}H_{33}NO_2$: C, 77.69; H, 9.36; N, 3.94. Found: C, 78.09; H, 9.55; N, 4.03. The reaction of II with a large excess of methylmagnesium bromide, followed by alkaline hydrolysis gave in 56% yield, 11β,17β-dihydroxy-17-methyl-4-androsten-3-one (III), m.p. 205–209°, $[\alpha]_D$ +125° ($CHCl_3$), $\lambda_{max.}^{alc.}$ 243 (ϵ 15,575); *Anal.* Calcd. for $C_{20}H_{30}O_3$: C, 75.44; H, 9.49. Found: C, 75.61; H, 9.27. Compound III was also prepared from 17β-hydroxy-17-methyl-4-androstene-3,11-dione (IV).[4] Reaction of IV with pyrrolidine gave 3-(N-pyrrolidinyl)-17β-hydroxy-17-methyl-3,5-androstadien-11-one (V), m.p. 175–185° (dec.), $[\alpha]_D$ −90° ($CHCl_3$); *Anal.* Calcd. for $C_{24}H_{35}NO_2$: C, 78.01; H, 9.52; N, 3.79. Found: C, 77.87; H, 9.51; N, 3.83. Reduction of V with lithium aluminum hydride and hydrolysis gave III, identical by melting point and infrared comparison with the product prepared as described above.

17β-Hydroxy-17-methyl-4,9(11)-androstadiene-3-one (VI), m.p. 170–172°, $[\alpha]_D$ +57° ($CHCl_3$); *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.59; H, 9.08, was prepared from 11α,17β-dihydroxy-17-methyl-4-androsten-3-one[4] by the action of base[5] on its 11-tosyl derivative (VII), m.p. 141–144° (dec.), $[\alpha]_D$ +41° ($CHCl_3$); *Anal.* Calcd. for $C_{27}H_{36}O_5S$: C, 68.61; H, 7.68; S, 6.78. Found: C, 68.86; H, 7.86; S, 6.89, as well as by the action of a large excess of methylmagnesium bromide on 3-(N-pyrrolidinyl)-3,5,9(11)-androstatrien-17-one (VIII)[6] with subsequent alkaline hydrolysis.

Compound VI was converted to 11β,17β-dihydroxy-9α-fluoro-17-methyl-4-androsten-3-one (XI) by a sequence of reactions essentially the same as that described by Fried and Sabo[7] for the preparation of 9α-fluorohydrocortisone from 17α,21-dihydroxy-4,9(11)-pregnadiene-3,20-dione 21-acetate. The reaction of VI with N-bromoacetamide in aqueous acid and acetone at 15° produced 9α-bromo-11β,17β-dihydroxy-17-methyl-4-androsten-3-one (IX), m.p. 150–154° (dec.), $[\alpha]_D$ +112° ($CHCl_3$); *Anal.* Calcd. for $C_{20}H_{29}BrO_3$: Br, 20.11. Found: Br, 18.75. Compound IX in methanol, upon titration with 1 equivalent of 0.1*N* sodium hydroxide afforded 17β-hydroxy-9β,11β-epoxy-17-methyl-4-androsten-3-one (X), m.p. 183–185°, $[\alpha]_D$ −40° ($CHCl_3$); *Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.92; H, 8.92. Found: C, 75.60; H, 8.96. The epoxide (X) in methylene chloride was treated with 48% hydrofluoric acid to give XI, m.p. 270° (dec.), $[\alpha]_D$ +109° (EtOH), $\lambda_{max.}^{alc.}$ 240 mμ (ϵ 16,700); *Anal.* Calcd. for $C_{20}H_{29}FO_3$: C, 71.40; H, 8.69; F, 5.65. Found: C, 71.71; H, 8.66; F, 5.75. Oxidation of XI with chromium trioxide in acetic acid yielded 17β-hydroxy-9α-fluoro-17-methyl-4-androstene-3,11-dione (XII), m.p. 213–220° (dec.), $[\alpha]_D$ +144° ($CHCl_3$); *Anal.* Calcd. for $C_{20}H_{27}FO_3$: C, 71.83; H, 8.14; F, 5.68. Found: C, 72.13; H, 8.30; F, 5.83.

TABLE I

ORAL ANABOLIC-ANDROGENIC ACTIVITY

Compound	Anabolic	Androgenic
17-Methyltestosterone	1.0	1.0
11β,17β-Dihydroxy-17-methyl-4-androsten-3-one (III)	2.9	0.9
11β,17β-Dihydroxy-9α-fluoro-17-methyl-4-androsten-3-one (XI)	20.0	9.5
17β-Hydroxy-9α-fluoro-17-methyl-4-androstene-3,11-dione (XII)	22.0	8.5

We are indebted to S. C. Lyster, G. H. Lund and and R. O. Stafford[8] of the Department of Endocrinology, The Upjohn Research Division, for the data in Table I, which records the oral anabolic and androgenic potency[9] of several of these substances in terms of 17-methyltestosterone as a standard.

The authors are indebted to J. L. Johnson, Mrs. G. S. Fonken and J. E. Stafford for spectral data, and to W. A. Struck and associates for microanalyses.

(8) S. C. Lyster, G. H. Lund and R. O. Stafford, *Endocrinology*, in press.

(9) Measured by weight increase in levator ani muscle and seminal vesicles in castrate immature rats.

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(2) F. W. Heyl and M. E. Herr, THIS JOURNAL, **75**, 1918 (1953).

(3) C. J. W. Brook and J. K. Norymberski, *Biochem. J.*, **55**, 374 (1953), have described a preparative method for obtaining this compound from cortisol by sodium bismuthate oxidation.

(4) S. H. Eppstein, P. D. Meister, H. Marian Leigh, D. H. Peterson, H. C. Murray, L. M. Reineke and A. Weintraub, THIS JOURNAL, **76**, 3174 (1954).

(5) S. Bernstein, R. H. Lenhard and J. H. Williams, *J. Org. Chem.*, **19**, 41 (1954).

(6) F. W. Heyl and M. E. Herr, THIS JOURNAL, **77**, 488 (1955).

(7) J. Fried and E. F. Sabo, *ibid.*, **75**, 2273 (1953); **76**, 1455 (1954).

A TOTAL SYNTHESIS OF 11-OXYGENATED STEROIDS[1]

Sir:

Three total synthetic routes to 11-oxygenated steroids have been described[2,3,4] but it still seemed to us that there was a need for a short yet flexible synthesis capable of leading to substances of type I where R_1, R_2 and R_3 may be any desired groups. The precursor of I that we chose to synthesize is II, and this communication reports the total synthesis of II, $R_1 = R_2 = CH_3$, $R_3 = H$.

6-Methoxy-α-tetralone[5] was converted *via* the hydroxymethylene ketone to the 2-methyl deriva-

(1) This work was supported, in part, by a research grant (G-3974) from the National Institutes of Health.

(2) (a) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, THIS JOURNAL, **74**, 4223 (1952); (b) L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *ibid.*, **76**, 5014 (1954).

(3) L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns and J. M. Constantin, *ibid.*, **74**, 4974 (1952), and subsequent papers.

(4) W. S. Johnson, R. Pappo and A. D. Kemp, *ibid.*, **76**, 3353 (1954).

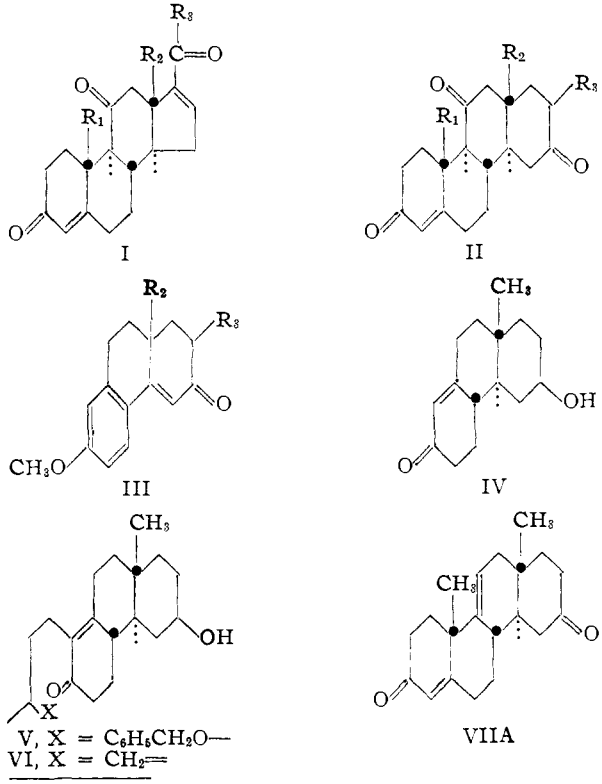
(5) G. Stork, *ibid.*, **69**, 576 (1947).

tive which was condensed with 4-diethylamino-2-butanone methiodide in the presence of potassium *t*-butoxide to produce 1,9,10,10a-tetrahydro-7-methoxy-3(2H)-phenanthrone III, $R_2 = CH_3$, $R_3 = H$ (m.p. 87–87.5°), λ_{max}^{EtOH} 328 mμ, ε 22,000. Found: C, 79.35; H, 7.38). Reduction of III with sodium borohydride gave the corresponding alcohol (m.p. 105–106°. Found: C, 78.61; H, 8.15) which was reduced catalytically over palladium on strontium carbonate to a single saturated alcohol (m.p. 117–119°. Found: C, 77.97; H, 8.92). Reduction of the anisole ring with lithium and liquid ammonia, followed by cleavage of the resulting enol ether with concentrated hydrochloric acid, yielded the α,β-unsaturated ketone IV as a single isomer (m.p. 137–138°. Found: C, 77.17; H, 9.48. Semicarbazone, m.p. 231–233°, dec. Found: C, 66.00; H, 8.57). 3-Benzyloxybutyl iodide was synthesized by addition of benzyl alcohol to ethyl crotonate, followed by reduction to 3-benzyloxy-1-butanol (b.p. 98–107° (1 mm.); Found: C, 73.29; H, 8.72) which was transformed with phosphorus tribromide into the corresponding bromide (b.p. 83–86° (0.5 mm.); Found: C, 54.36; H, 6.47; Br, 32.77). The benzoate of IV (m.p. 143–144°; Found: C, 77.96; H, 7.62) was transformed into its potassium enolate by removal of the *t*-butyl alcohol from its solution in benzene containing one equivalent of potassium *t*-butoxide. This was alkylated with 3-benzyloxybutyl bromide or iodide to give mainly monoalkylated product[6] V which was alkylated again with methyl iodide by the same procedure. Transformation to tetracyclic ketones VIIA and VIIB was carried out, without isolation of intermediates, by ketalization with ethylene glycol-*p*-toluenesulfonic acid, removal of the benzyl group with sodium in liquid ammonia, oxidation with chromic acid-pyridine, acid-hydrolysis of the cyclic ketal and, finally, base cyclization. Fractional crystallization of the tetracyclic ketone mixture from ethyl acetate–cyclohexane gave roughly equal amounts of VIIA (m.p. 206°; Found: C, 80.65; H, 8.90) and its C_{10} epimer, VIIB (m.p. 148°; Found: C, 80.51; H, 8.57).

Reduction of VIIA with sodium borohydride in ethanol and reoxidation with manganese dioxide in chloroform gave $\Delta^{4,9(11)}$-D-homoandrostadien-16-ol-3-one (m.p. 186–188°; Found: C, 79.96; H, 9.59). Transformation into the tosylate (m.p. 173–174°, dec.), followed by refluxing with collidine gave $\Delta^{4,9(11),16}$-D-homoandrostatrien-3-one, m.p. 150.8–151.8°, identical with a sample kindly supplied by Dr. W. S. Knowles.[2b] The stereochemistry of VIIA is thus confirmed. Introduction of an 11-keto group was easily accomplished by conversion to the 9,11-bromohydrin, oxidation to the 9-bromo-11-keto compound and reduction with chromous chloride[7] to the desired Δ^4-3,11,16-D-homoandrostenetrione, II ($R_1 = R_2 = CH_3$, $R_3 = H$; m.p. 206.5–208°. Found: C, 76.72; H, 8.54).

Alternatively, IV as its acetate (m.p. 137–138°; Found: C, 73.86; H, 8.89) was ozonized in ethyl acetate and the enol lactone of the resulting keto acid was treated at −30° in ether with the grignard reagent from 5-chloro-2-methyl-1-pentene[8] (b.p. 127–129.5°. Found: C, 60.85; H, 9.72; Cl, 29.60). Cyclization of the resulting product with base yielded VI, isolated as its *p*-bromobenzoate (m.p. 105–107.5°; 129°. Found: C, 66.83; H, 6.87; Br, 16.26). The latter was alkylated with methyl iodide as in the benzyloxybutyl series, and the resulting C_{10} epimers were separated as *p*-nitrobenzoates yielding *p*-nitrobenzoate A (m.p. 157–158°. Found: C, 72.28; H, 7.79; N, 2.88) and *p*-nitrobenzoate B (m.p. 148°. Found: C, 72.21; H, 7.70; N, 2.94). The *p*-nitrobenzoate A was the predominant isomer (2:1) and its stereochemistry at C_{10} was the desired one since on ozonolysis, followed by base cyclization, it produced the same $\Delta^{4,9(11)}$-D-homoandrostadien-16-ol-3-one that has been described above.

Experiments are in progress with III, $R_2 = R_3 = CH_3$; and $R_2 = CO_2R$, $R_3 = CH_3$.



(6) For related monoalkylations of enones, see J. M. Conia, *Bull. soc. chim.*, 690, 943 (1954).

(7) *Cf.* J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953).

(8) Synthesized by boron fluoride-etherate catalyzed addition of ketene to 5-chloro-2-petanone and thermal decomposition of the resulting β-lactone.

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THE CRYSTAL STRUCTURE OF AMMONIA-BORANE, H_3NBH_3

Sir:

Recently Shore and Parry[1] described a new compound, H_3NBH_3, and as evidence of crystallinity they outlined its X-ray diffraction powder pattern.

(1) S. G. Shore and R. W. Parry, THIS JOURNAL, **77**, 6084 (1955).