(III) which was cyclized by base to dihydroconessine (IV) (80% yield from II), m.p. 101.5–102.5°, $[\alpha]^{26}$ +53.5°, infrared spectrum identical with that of authentic dihydroconessine, mixture m.p. undepressed.

The above synthesis of dihydroconessine confirms the previously assigned structure[6] and stereochemistry.[7]

The introduction of other functional groups at C_{18} *via* intermediates such as III is an obvious possibility which is presently under investigation in these laboratories. In addition, the application of these methods to the functionalization of methyl groups in other systems is under study.[8]

(6) R. D. Haworth, J. McKenna, R. G. Powell and G. H. Whitfield, *Chem. and Ind.*, 215 (1952).

(7) V. Cerny, L. Labler and F. Sorm, *Coll. Czech. Chem. Comm.*, **22**, 76 (1957).

(8) Drs. O. Jeger, D. Arigoni and co-workers have also been concerned with this problem and our results are published simultaneously with theirs by friendly agreement.

(9) Predoctoral Research Fellow (AF-7544, 1957–58) of the National Institute of Arthritis and Metabolic Diseases; Alfred P. Sloan Foundation Fellow (1956, 1957).

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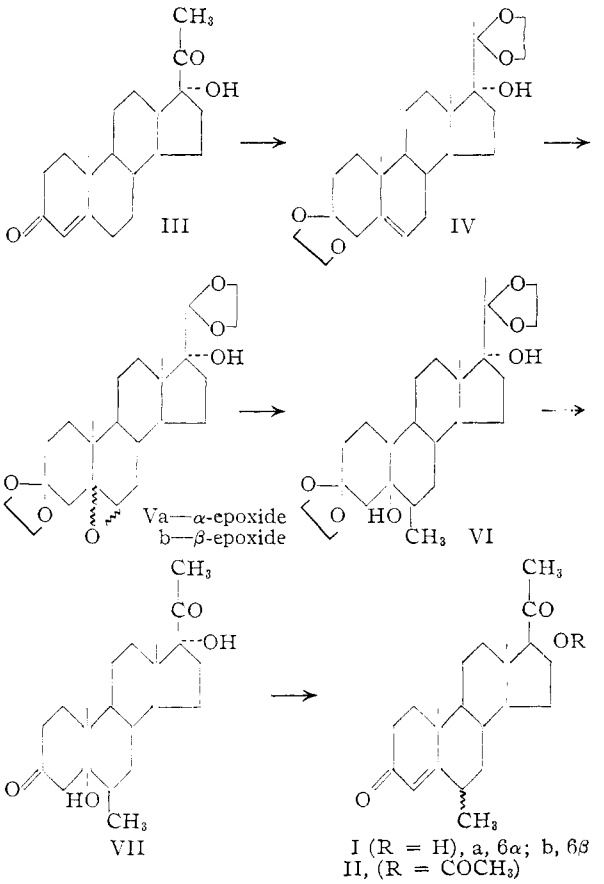
6α-METHYL-17α-HYDROXYPROGESTERONE 17-ACYLATES; A NEW CLASS OF POTENT PROGESTINS[1]

Sir:

Recent communications from These Laboratories[2,3] and others[4] have described the preparation of a number of 6-methyl steroids. We now wish to report the synthesis of 6α-methyl-17α-hydroxyprogesterone (Ia), the acetate (II) of which is believed to be the most active progestational agent yet known.

The bisethylene acetal (IV) of 17α-hydroxyprogesterone (III)[5] was treated with peracetic acid to give a mixture of 5α,6α-epoxy-17α-hydroxypregnane-3,20-dione bisethylene acetal (Va), m.p. 216–218.5°, $[\alpha]_D$ −70°, and the corresponding 5β,6β-epoxide (Vb), m.p. 170–172.5°, $[\alpha]_D$ −14°, which could be separated by crystallization from acetone. The α-epoxide (Va) when refluxed with methylmagnesium bromide in tetrahydrofuran, afforded the bisethylene acetal of 5α,17α-dihydroxy-6β-methylpregnane-3,20-dione (VI), m.p. 160-163°, $[\alpha]_D$ −38°. Upon hydrolysis in acidic acetone, 5α,17α-dihydroxy-6β-methylpregnane-3,20-dione (VII), m.p. 274–279°, $[\alpha]_D$ −6°, was produced. Dehydration of VI by very dilute sodium hydroxide in pyridine afforded 6β-methyl-17α-hydroxyprogesterone (Ib), m.p. 232-240°, $[\alpha]_D$ +34°, λ_{max} 242 mμ (a_M 16,500), which was epimerized in chloroform[6] saturated with gaseous hydrogen chloride to 6α-methyl-17α-hydroxyprogesterone (Ia), m.p. 220–223.5°, $[\alpha]_D$ +75°, λ_{max} 241 mμ (16,150). Alternatively, dehydration and epimerization of VII to Ia could be effected directly with chloroform–hydrogen chloride.



Acylation of Ia with acetic anhydride–acetic acid–*p*-toluenesulfonic acid[7] produced the 17-acetate II, m.p. 205–209°, $[\alpha]_D$ +56°, λ_{max} 240 mμ (a_M 15,950). With cyclopentylpropionic acid and trifluoroacetic anhydride[8] there was obtained the 17-(β-cyclopentylpropionate), m.p. 135–137°, $[\alpha]_D$ +44°, λ_{max} 240.5 mμ (a_M 15,775). Similarly, the propionate (m.p. 155–157°, $[\alpha]_D$ +45° (EtOH), λ_{max} 240 mμ (a_M 16,075)), caproate (m.p. 105–107°, $[\alpha]_D$ +46°, λ_{max} 240 mμ (a_M 15,300)), phenylacetate (m.p. 164–166°, $[\alpha]_D$ +62° (EtOH), λ_{max} 240 mμ (a_M 16,125)) and related esters were prepared.

In the McPhail modification of the Clauberg assay[9] 6α-methyl-17α-hydroxy-progesterone 17-acetate (II, Provera[10]) was 50-60 times more active than progesterone on subcutaneous administration and 100-300 times more active than ethisterone

(1) Rotations were in chloroform unless otherwise specified; ultraviolet maxima were determined in 95% alcohol.

(2) G. B. Spero, J. L. Thompson, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, THIS JOURNAL, **78**, 6213 (1956).

(3) J. A. Campbell, J. C. Babcock and J. A. Hogg, *ibid.*, in press.

(4) (a) O. S. Madaeva, M. I. Ushakov, N. F. Kosheleva, *J. Gen. Chem.* (USSR), **10**, 213 (1940); *C. A.*, **34**, 7292 (1944); (b) M. Ehrenstein, *J. Org. Chem.*, **8**, 83 (1943); (c) G. Cooley, B. Ellis, D. N. Kirk, and V. Petrow, *J. Chem. Soc.*, 4412 (1957), and preceding papers; (d) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(5) S. Bernstein, M. Heller and S. M. Stolar, THIS JOURNAL, **76**, 5674 (1954).

(6) Commercial chloroform (containing 0.7% alcohol) was used.

(7) (a) Huang-Minlon, E. Wilson, N. L. Wendler, and M. Tishler, THIS JOURNAL, **74**, 5394 (1952); (b) R. B. Turner, *ibid.*, **75**, 3489 (1953).

(8) E. J. Bourne, M. Stacey, J. C. Tatlow and J. M. Tedder, *J. Chem. Soc.*, 2976 (1949).

(9) M. K. McPhail, *J. Physiol.*, **83**, 145 (1934).

(10) Registered Trademark, The Upjohn Company.

(17α-ethinyltestosterone) on oral administration.[11] As an ovulation inhibitor in the rabbit, II was 10-20 times more active parenterally than progesterone. When administered parenterally to pregnant rats castrated on the 8th day of pregnancy, II was 25-100 times progesterone in maintaining pregnancy to term. These results, which indicate 6α-methyl-17α-hydroxyprogesterone 17-acetate to be a progestational agent of exceptional potency, will be described in greater detail shortly.[12]

(11) In the same assays, the corresponding non-methylated steroid, 17α-hydroxyprogesterone 17-acetate,[7b] was *ca.* 6 times progesterone (parenterally) and 2–4 times ethisterone (orally).

(12) The chemical portion of this work will be submitted to THIS JOURNAL (Babcock, Gutsell, Herr and Hogg); the endocrine studies will be reported elsewhere (Stucki, Barnes and Dulin).

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DIRECT INTRODUCTION OF A NITROGEN FUNCTION AT C-18 IN A STEROID[1]

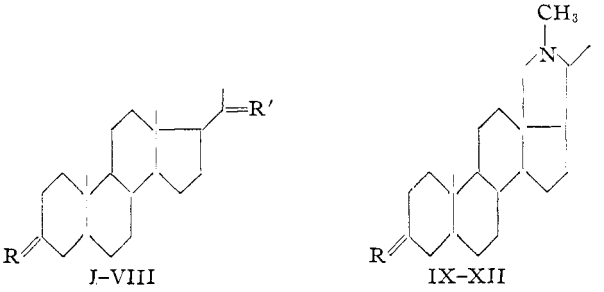
Sir:

Current interest in aldosterone,[1a] has prompted several investigations on the synthesis of C-18 oxygenated steroids, total[2] as well as partial synthesis using steroids lacking substitution at C-18 as starting material.[3] In the latter case opening of ring D has been used for modification of C-18.

We have developed a third way of approaching the problem, the direct introduction of a substituent into the *intact* tetracyclic steroid molecule by the Loeffler-Freytag reaction.[4,5]

3β-Acetoxy-20-keto-5α-pregnane (I)[6] was converted via the oxime (II) (m.p. 198°, $[\alpha]^{20}D$ +17° ($CHCl_3$), *Anal.* found: C, 73.49: H, 9.94) to 3β-acetoxy-20α-amino-5α-pregnane (III)[7] (m.p. 171°; pK^*[8] 9.30) (Pt–H_2), thence with ethyl formate to the N-formyl derivative (IV) (m.p. 185–186°, $[\alpha]^{19}D$ −3° ($CHCl_3$), *Anal.* found: C, 74.01; H, 10.13; N, 3.52) and further with $LiAlH_4$ to 3β-hydroxy-20α-N-methylamino-5α-pregnane (V) (m.p. 211°, $[\alpha]^{20}D$ +27° ($CHCl_3$), pK^* 9.17, *Anal.* found: C, 79.20; H, 11.79; N, 4.16). Oxidation of (V) (CrO_3–HOAc) gave the 3-keto-derivative (VI) (pK^* 9.20; N-acetate: m.p. 216-217°, $[\alpha]^{19}D$ +15° ($CHCl_3$), *Anal.* found: C, 77.06; H, 10.69) which was reduced by the Huang-Minlon procedure to 20α-N-methylamino-5α-pregnane (VII) (m.p. 96°, $[\alpha]^{20}D$ +32° ($CHCl_3$), pK^* 9.32, *Anal.* found: C, 83.22; H, 12.33; N, 4.31). The N-chloro derivative (VIII), made from (VII) according to the procedure of Ruschig, *et al.*,[9] furnished by treatment with a mixture of concd. sulfuric and acetic acid[10] a tertiary base, m.p. 107°, formulated as the hitherto unknown conanine (IX),[11,12] $[\alpha]^{19}D$ +61° ($CHCl_3$), (pK^* 8.28 *Anal.* found: C, 83.66; H, 12.08; N, 4.43).

The constitution of (IX) was proved as follows: dihydro-isoconessimine (X)[13] was converted via the N-chloro derivative (XI) to 3-keto-conanine (XII) (m.p. 146°, $[\alpha]^{20}D$ +80° ($CHCl_3$), pK^* 8.26, *Anal.* found: C, 80.15; H, 10.64; N, 4.13 ($NaOCH_3$ followed by H_3O^+). Removal of the 3-keto group in the latter afforded conanine (IX) (m.p. 107°, $[\alpha]^{20}D$ +63° ($CHCl_3$), pK^* 8.28, *Anal.* found: C, 83.85; H, 11.79, N, 4.39), identical in all respects with the tertiary base from the cyclization reaction. Assuming that C-20 is not involved in the latter reaction the precursors of (IX) must therefore be formulated as 20α-compounds.[12]



I–VIII IX–XII

I	R = —H, —OAc	R′ = O
II	R = same	R′ = NOH
III	R = same	R′ = —H, —NH_2
IV	R = same	R′ = —H, —NHCHO
V	R = —H, —OH	R′ = —H, —$NHCH_3$
VI	R = O	R′ = same
VII	R = H_2	R′ = same
VIII	R = same	R′ = —H, —$NClCH_3$
IX	R = H_2	
X	R = —H, —$NHCH_3$	
XI	R = —H, —$NClCH_3$	
XII	R = O	

(1) This paper is part of a joint effort of CIBA AG,[2a] Basle, Organische Anstalt der Universitat,[2b] Basel, N.V. Organon,[2c] Oss, and organisch-chemisches Laboratorium der Eidg. Technischen Hochschule, Zurich, on synthesis of C-18 oxygenated steroids.

(1a) S. Å. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. von Euw, O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **37**, 1163, 1200 (1954).

(2) (a) P. Wieland, K. Heusler, H. Ueberwasser and A. Wettstein, *Helv. Chim. Acta*, **41**, 416 (1958) and earlier papers; (b) A. Lardon, O. Schindler and T. Reichstein, *ibid.*, **40**, 666, 1034 (1957); (c) W. J. van der Burg, D. A. van Dorp, O. Schindler, C. M. Siegmann and S. A. Szpilfogel, *Rev. Trav. Chim.*, **77**, 171 (1958), and previous papers.

(3) D. H. R. Barton, A. da S. Campos-Neves and A. I. Scott, *J. Chem. Soc.*, 2698 (1957).

(4) (a) A. W. Hofmann, *Ber.*, **18**, 5, 109 (1885); (b) K. Loeffler and C. Freytag, *Ber.*, **42**, 3427 (1909); K. Loeffler, *ibid.*, **43**, 2035 (1910).

(5) For references *cf.* R. Lukes and M. Ferles, *Coll. Czech.*, **20**, 1227 (1955).

(6) A. Butenandt, U. Westphal and W. Hohlweg, *Z. physiol. Chem.*, **227**, 84 (1934).

(7) The stereochemistry of C-20 in III and related compounds is discussed below.

(8) Measured in methylcellosolve according to W. Simon, E. Kovats, L. H. Chopard-dit-Jean and E. Heilbronner, *Helv. Chim. Acta*, **37**, 1872 (1954).

(9) H. Ruschig, W. Fritsch, J. Schmidt-Thome and W. Haede, *Ber.*, **88**, 883 (1955).

(10) According to a private communication of Prof. E. J. Corey the cyclization reaction of aliphatic N-chloro-amines is promoted by traces of ferrous sulfate. We thank Prof. Corey for this information. A similar effect we have now noted in the cyclization of compound (VIII).

(11) Nomenclature as proposed by R. D. Haworth and M. Michael, *J. Chem. Soc.*, 4973 (1957).

(12) For the proof of configuration of C-20 *cf.* V. Cerny, L. Labler and F. Sorm, *Coll. Czech.*, **22**, 76 (1957).

(13) R. D. Haworth, J. McKenna and G. H. Whitfield, *J. Chem. Soc.*, 1102 (1953).