time can detect the presence of less than 1%. Some of the L-form will then subsequently crystallize, the remainder on concentration. The melting point and optical rotation of this material are not absolute criteria of optical purity, since other impurities may be present. This may account for the lack of detection of racemization in the synthesis of the same peptide by Sheehan and Hess.

Following the conditions of Sheehan and Hess[1] as closely as possible, we treated 0.010 molar quantities of carbobenzoxyglycyl-L-phenylalanine (carefully recrystallized from water; m.p. 127.5° (sharp), $[\alpha]^{24}D$ +38.8° ± 0.5° (*c*, 5; ethanol))[4] and ethyl glycinate (freshly distilled) in the presence of 0.011 mole of N,N'-dicyclohexylcarbodiimide[5] in 50 ml. of dry tetrahydrofuran at room temperature. The temperature of the mixture spontaneously rose to 37°, then fell. After four hours, acetic acid was added to decompose excess reagent. Dicyclohexylurea was removed here and after concentrating the filtrate *in vacuo* to about 10 ml. (89.4% yield). Addition of 50 ml. of water and chilling precipitated the tripeptide; it was washed with 2 × 10 ml. of water, 10 ml. of 5% potassium bicarbonate solution, then 2 × 10 ml. of water. The crude dry yield was quantitative, and the m.p. 106–109°. A 2% solution of the product in absolute alcohol gave crystallization on refrigeration (0°). During several hours, fractions of the DL-tripeptide, m.p. in the 129–133° range (the pure compound melts at 132–133°) amounting to 6.6% were collected. After a fraction of a few mg. in the 120–130° range, the L-form began to appear; concentration of the filtrates gave a total of 76% yield, m.p. 116.5–119.5°, $[\alpha]^{25}D$ −11.5°, (*c*, 2, ethanol).[6,7] Two repetitions of the synthesis gave yields of 7.6% DL, 74% L and 8.2% DL, 69% L. For comparison, the reaction was performed in 7 ml. of tetrahydrofuran with tetraethyl pyrophosphite as the reagent, and at reflux temperature for 30 minutes, giving 4.39 g. of crude product, m.p. 118.5–119.5°. Crystallization from 2% solution in ethanol gave no DL form, and 4.24 g. (96% yield) of L-, m.p. 120–120.5°, $[\alpha]^{25}D$ −13.2° (*c*, 2, ethanol).

An experiment with dicyclohexylcarbodiimide at −5° for 48 hours gave 0.5% DL and 75% L of the tripeptide, and another in methylene chloride at room temperature gave 12% DL and 75% L. Thus, temperature and solvent are factors in racemization.

(4) K. Hofmann and M. Bergmann, *J. Biol. Chem.*, **134**, 225 (1940), give m.p. 125–126°, $[\alpha]^{24}D$ +38.5° (*c*, 5, EtOH).

(5) Purchased from Aldrich Chemical Co.

(6) Rotations reported here were obtained by W. Fulmor and staff. The statistical deviation for the tripeptide is ±1°.

(7) Ref. (1) gives m.p. 118–119°, $[\alpha]^{27}D$ −13.5° [ethanol].

ORGANIC CHEMICAL RESEARCH DEPARTMENT
RESEARCH DIVISION GEORGE W. ANDERSON
AMERICAN CYANAMID COMPANY FRANCIS M. CALLAHAN
PEARL RIVER, NEW YORK

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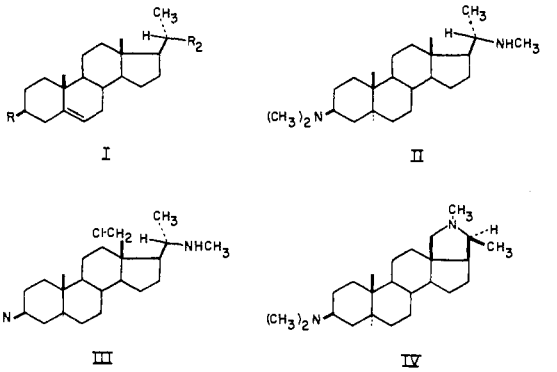
THE SYNTHESIS OF DIHYDROCONESSINE. A METHOD FOR FUNCTIONALIZING STEROIDS AT C_{18}

Sir:

The selective introduction of a functional group in place of hydrogen at a carbon atom not directly joined to labilizing centers such as C=O, C=C, *etc.*, poses an interesting challenge in synthetic chemistry, which is magnified by the rife occurrence of such transformations in Nature under the influence of enzymes. In the field of steroids the problem assumess pecial trenchency with regard to the C_{18} (C/D fusion) angular methyl group because functionality at this position is a special feature of the important hormone, aldosterone, and of the *Holarrhena* alkaloids.[1] This communication describes an efficient and selective method for functionalizing C_{18}, the free radical chain decomposition of an N-chloro-20-aminosteroid in acid solution, and the illustrative synthesis of dihydroconessine (IV).

3β-Acetoxy-20α-aminopregnene-5 acetate[2] (I, R = AcO, R_2 = NH_2·HOAc) was formylated to give 3β-acetoxy-20α-formamidopregnene-5 (I, R = AcO, R_2 = NHCHO), m.p. 191–193°, $[\alpha]^{16}D$ −66°, found: C, 74.32; H, 9.87, which was hydrolyzed to 3β-hydroxy-20α-formamidopregnene-5, m.p. 229–230° (dec.), $[\alpha]^{24}D$ −70.4°, found: C, 76.31; H, 10.08; N, 4.32. Treatment of the hydroxyformamide with *p*-toluenesulfonyl chloride–pyridine yielded crude 3β-tosyloxy-20α-isocyanopregnene-5,[3] which readily was hydrated to 3β-tosyloxy-20α-formamidopregnene-5 (I, R = OTs, R_2 = NHCHO), m.p. 132–133°, $[\alpha]^{27}D$ −47.4°, found: C, 69.92; H, 8.32. 3β-Dimethylamino-20α-formamidopregnene-5, m.p. 226–230° (dec.), $[\alpha]^{27}D$



−52°, found: C, 77.31; H, 10.90; N, 7.23, obtained from the tosylate and dimethylamine, was reduced ($LiAlH_4$) to 3β-dimethylamino-20α-methylaminopregnene-5, m.p. 123–124.5°, $[\alpha]^{27}D$ −37°, found: C, 80.23; H, 11.84; N, 7.78, which on hydrogenation gave 3β-dimethylamino-20α-methylaminoallopregnane (II), m.p. 103.5–104.5°, $[\alpha]^{27}D$ +27.5°, found: C, 79.23; H, 12.06; N, 7.80. 20-N-Chloro-II, prepared using N-chlorosuccinimide in ether,[4] upon irradiation (in 90% H_2SO_4) with ultraviolet light was converted to 3β-dimethylamino-18-chloro-20α-methylaminoallo-pregnane[5]

(1) See R. Tschesche and A. C. Roy, *Ber.*, **89**, 1288 (1956).

(2) P. L. Julian, E. W. Meyer and H. C. Printy, THIS JOURNAL, **70**, 887 (1948).

(3) See W. R. Hertler and E. J. Corey, *J. Org. Chem.*, in press, for other formamide → isocyanide conversions.

(4) H. Ruschig and J. Schmidt-Thomé, U. S. Patent 2,697,107 (1954).

(5) The general intermediacy of δ-chloro-secondary amines in the N-chloroamine → pyrrolidine process has been demonstrated by experiments which will be published separately. *Cf.* W. R. Hertler, Ph.D. Thesis, University of Illinois, 1958, and S. Wawzonek, M. F. Nelson, Jr., and P. J. Thelen, THIS JOURNAL, **73**, 2806 (1951).

(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).

DEPARTMENT OF CHEMISTRY AND
CHEMICAL ENGINEERING
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

E. J. COREY
W. R. HERTLER[9]

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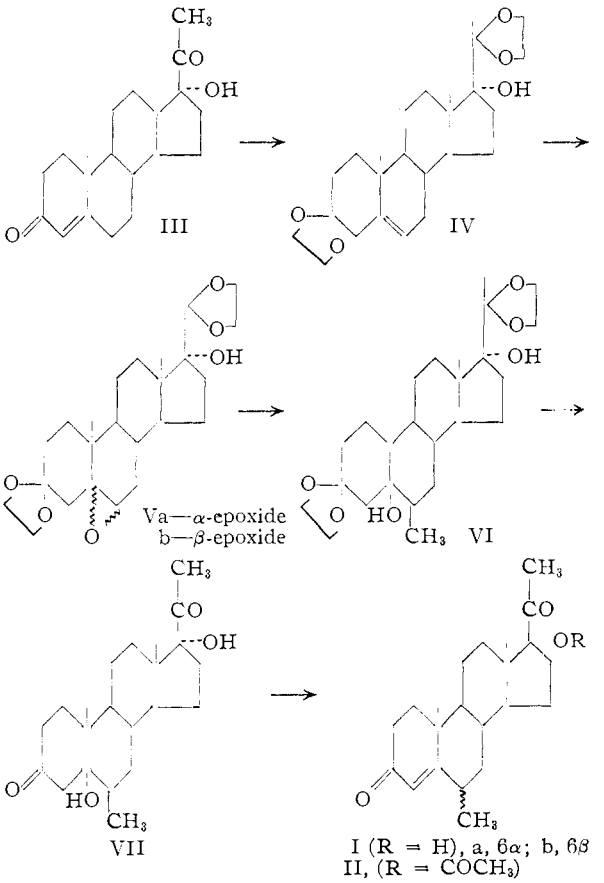
6α-METHYL-17α-HYDROXYPROGESTERONE 17-ACYLATES; A NEW CLASS OF POTENT PROGESTINS[1]

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).

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