7.81).[2] Treatment with base effected cyclization[3] to 8-methoxy-2,3,4,4aα,4bβ,5,6,10bα,11,12-decahydrochrysen-2-one (II), m.p. 145–146°; $[\alpha]_D$ +85°; λ_{max} 233 mμ (ϵ 20,900); (*Anal.* Found: C, 80.57; H, 7.82). Birch reduction followed by oxidation with chromium trioxide produced the *trans*[4] dihydro ketone III, m.p. 188–190°; $[\alpha]_D$ +31°; (*Anal.* Found: C, 79.99; H, 8.65). Catalytic reduction of II gave the *cis* ketone, m.p. 127–129°; $[\alpha]_D$ +40°; (*Anal.* Found: C, 80.52; H, 8.82).

The ketone III was treated with methylmagnesium iodide. Subsequent dehydration gave 2-methyl - 8 - methoxy - 1,4,4aα,4bβ,5,6,10bα,11,12,-12aβ-decahydrochrysene (IV), m.p. 124–125°; $[\alpha]_D$ −36°; (*Anal.* Found: C, 84.84; H, 9.27). Ozonolysis followed by base-catalyzed cyclization of the resulting keto aldehyde (m.p. 143.0–143.5°; *Anal.* Found: C, 76.61; H, 8.27) gave 3-methoxy-18,19-dinorpregna-1,3,5(10),16-tetraen-20-one (V), m.p. 168–169°; $[\alpha]_D$ +112°; λ_{max} 231 mμ (ϵ 13,900), 278 mμ (2010), 287 mμ (1990); (*Anal.* Found: C, 81.08; H, 8.31). Successive Birch reduction, acid hydrolysis and chromium trioxide oxidation of V provided *d*-dinorprogesterone, m.p. 137–139°; $[\alpha]_D$ +87°; λ_{max} 240 mμ (ϵ 17,900); (*Anal.* Found: C, 79.58; H, 9.12).[5]

Rearrangement of the oxime of ketone V produced 18-norestrone methyl ether, m.p. 161–163°; $[\alpha]_D$ +188°; (*Anal.* Found: C, 79.87; H, 8.36). Base-catalyzed isomerization gave an equilibrium mixture, $[\alpha]_D$ +12°, consisting of approximately 30% starting material and 70% 18-nor-13α-estrone 3-methyl ether,[6,7] m.p. 121–122°; $[\alpha]_D$ −66°; (*Anal.* Found: C, 80.14; H, 8.25).

Hydride reduction of 18-norestrone methyl ether afforded 18-norestradiol methyl ether, m.p. 157–159°; $[\alpha]_D$ +76°; (*Anal.* Found: C, 79.41; H, 9.12). Birch reduction followed by acid hydrolysis gave 18,19-dinortestosterone, m.p. 197–199°; (*Anal.* Found: C, 78.16; H, 9.48).

The enol acetate of V on treatment with N-iodosuccinimide and potassium acetate[8] yielded 3-methoxy - 21 - acetoxy - 18,19 - dinorpregna-1,3,5(10),16-tetraen-20-one, m.p. 157–158°; $[\alpha]_D$ +65°; (*Anal.* Found: C, 73.72; H, 7.12). Hydrogenation afforded the dihydro compound, m.p. 114–115°; (*Anal.* Found: C, 74.03; H, 7.62). The corresponding C-20 dioxolane was reduced with lithium in ammonia. Acid hydrolysis gave 18,19-dinordesoxycorticosterone, m.p. 164–167°; (*Anal.* Found: C, 75.39; H, 8.31).

The principal physiological activity of the 18-nor compounds was generally no greater than 10% of their methylated prototypes.

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(2) All rotations are in chloroform; ultraviolet spectra in methanol.

(3) *Cf.* K. Miescher and H. Kagi, *Helv. Chim. Acta*, **32**, 761 (1949).

(4) The configuration is inferred from the work of D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(5) N. A. Nelson and R. B. Garland, THIS JOURNAL, **79**, 6313 (1957), prepared *dl*-dinorprogesterone. Structural identity of the two series was proved by solution infrared spectra of *dl*- and *d*-16,17-dihydro V (*d*-: m.p. 125–126°; *Anal.* Found: C, 80.47; H, 8.81).

(6) Since the completion of this work an announcement of the synthesis of *dl*-18-norestrone methyl ether and its C-13 epimer has appeared from W. S. Johnson, *et al.*, *Biochim. et Biophys. Acta*, **28**, 214 (1958). Infrared comparison of these compounds with the epimers reported here showed the structural identity of the two pairs.

(7) W. S. Johnson and W. L. Meyer, private communication, by means of optical rotary dispersion studies have independently arrived at a similar value for the equilibrium position.

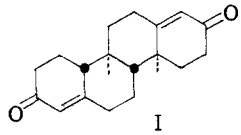
(8) C. Djerassi and C. T. Lenk, THIS JOURNAL, **76**, 1722 (1954).

SYNTHESIS OF 17,18-BISNORSTEROIDS

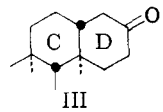
Sir:

The synthetic dione I[1] is interesting in connection with possible syntheses of 18,19-bisnorsteroids.

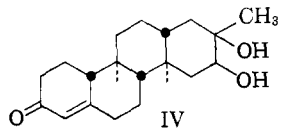
We have transformed I into its ethylene glycol monoketal[2] II, m.p. 150–151° (Found: C, 76.40; H, 8.45); reduction of II with lithium and ammonia gave III, m.p. 145–147° (Found: C, 76.02; H, 8.87); semicarbazone m.p. 202–203° (Found: C, 67.55; H, 8.33). Reaction of III with methylmagnesium iodide, dehydration with phosphorus oxychloride, deketalization and hydroxylation with osmium tetroxide gave the dihydroxyenone IV, m.p. 174–176° (Found: C, 75.29; H, 9.36).



I



III



IV

That the lithium–ammonia reduction of systems such as II gives the required C/D *trans* stereochemistry of III had to be established. The *optically active* enone V can be prepared from the tosylate of β-estradiol-3-methyl ether: Solvolysis with acetic acid–potassium acetate led to a mixture of VIa, m.p. 108–110° (Found: C, 85.14; H, 9.17) and (mainly) VI, obtained as an oil. Osmium tetroxide transformed VI into a glycol m.p. 176–177° (Found: C, 75.35; H, 8.45), but cleavage was more efficiently performed with a solution of ozone in ethyl acetate. The resulting diketone VII, m.p. 115–116.5° (Found: C, 75.91; H, 8.22) was cyclized to the required unsaturated ketone V, m.p. 144.5–145.5° (Found: C, 80.77; H, 7.82) $\lambda_{max}^{C_2H_5OH}$ 238 mμ, ϵ 13,000. Lithium ammonia reduction of V gave the saturated ketone VIII (*cf.* III), m.p. 188–189° (Found: C, 80.47; H, 8.84). This was rigorously shown to have acquired the necessary *trans* C/D stereochemistry by its rotatory dispersion curve which was antipodal to that of cholestanone.[3]

The feasibility of converting D-homoketones such as III or VIII into 18,19-bisnorsteroids was demonstrated by the synthesis of *d*-18,19-bisnorprogesterone from VIII: reaction of VIII with methylmagnesium iodide and dehydration with phosphorus oxychloride–pyridine formed the olefin IX, m.p. 112–114° (Found: C, 85.14; H, 9.12). Ozonolysis of IX in methylene chloride-methanol and base cyclization of the resulting ketoaldehyde,

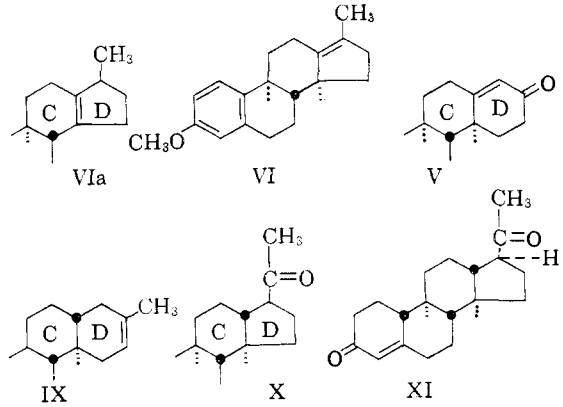
(1) A. J. Birch and H. Smith, *J. Chem. Soc.*, 1882 (1951).

(2) First prepared by Dr. J. Szmuszkovicz in this laboratory.

(3) *Cf.* C. Djerassi, *Bull. soc. chim.*, 741 (1957).

followed by hydrogenation over palladium on strontium carbonate produced X, m.p. 162–164° (Found: C, 80.36; H, 8.74).

Conversion of X to the Δ^4-3-ketone *via* Birch reduction followed by reoxidation at C_{20} with chromic acid–sulfuric acid in acetone gave *d*-18,19-bisnorprogesterone XI, m.p. 136–140°, $\lambda_{max}^{C_2H_5OH}$ 240 mμ, ε 17,000, $\lambda_{max}^{CHCl_3}$ 5.89, 6.02, after purification by paper chromatography and recrystallization from aqueous methanol. The rotatory dispersion was closely similar to that of Δ^4-3-cholestenone.[4] It may be of some interest that



bisnorprogesterone shows no progestational activity at twice the effective dose of progesterone.[5]

(4) Showing the essentially symmetric environment around C_{18} caused by removal of the methyl group at C_{18}.

(5) A total synthesis of a *dl*-18,19-bisnorprogesterone, also essentially inactive, has been reported by N. A. Nelson and R. B. Garland, THIS JOURNAL, **79**, 6133 (1957).

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STUDIES ON POLYPEPTIDES. XII THE SYNTHESIS OF A PHYSIOLOGICALLY ACTIVE BLOCKED TRIDECAPEPTIDE AMIDE POSSESSING THE AMINO ACID SEQUENCE OF α-MSH[1]

Sir:

The corticotropins[2] and the melanocyte expanding principle α-MSH[3] embody within their structures the amino acid sequence ser.tyr.ser.met.glu.his.phe.arg.try.gly.lys.pro.val.... In the corticotropins the amino group of the terminal serine is free, whereas in α-MSH it is acylated, presumably by an acetyl group. We wish to record at this time a synthesis and the physiological activity of the blocked tridecapeptideamide carbobenzoxyseryltyrosylserylmethionylglutaminylhistidylphenylalanylarginyltryptophylglycyl - ε - tosyllysylprolylvalineamide which contains the entire amino acid sequence of α-MSH.

(1) Supported by grants from the U. S. Public Health Service, The National Science Foundation, The American Cancer Society, Armour and Company and Eli Lilly and Company.

(2) (a) P. H. Bell, THIS JOURNAL, **76**, 5565 (1954); (b) W. F. White and W. A. Landmann, *ibid.*, **77**, 1711 (1955); (c) C. H. Li, I. I. Geschwind, R. D. Cole, I. D. Raake, J. I. Harris and J. S. Dixon, *Nature*, **176**, 687 (1955); (d) R. G. Shepherd, S. D. Willson, K. S. Howard, P. H. Bell, D. S. Davies, S. B. Davis, E. A. Eigner and N. E. Shakespeare, THIS JOURNAL, **78**, 5067 (1956); (e) C. H. Li, J. S. Dixon and D. Chung, *ibid.*, **80**, 2587 (1958).

(3) J. I. Harris and A. B. Lerner, *Nature*, **179**, 1346 (1957).

Carbobenzoxyserylmethionylglutamine[4] was decarbobenzoxylated to give serylmethionylglutamine, dec. 228°, $[\alpha]^{27}D$ −13.3° (in water), R_f = 0.39 (Partridge), migrates faster than his in the 2-butanol–ammonia system. *Anal.* Calcd. for $C_{13}H_{24}C_6N_4S\cdot H_2O$: C, 40.8; H, 6.9; N, 14.6; S, 8.4. Found: C, 40.6; H, 7.2; N, 14.9; S, 7.8. Completely digestible by leucine aminopeptidase (LAP), amino acid ratios in digest ser_1met_1.[5] The interaction of this tripeptide with the azide of carbobenzoxyseryltyrosine[6] afforded carbobenzoxyseryltyrosylserylmethionylglutamine, m.p. 167–171°, $[\alpha]^{27}D$ −15.5° (in glacial acetic acid). *Anal.* Calcd. for $C_{33}H_{44}O_{12}N_6S.H_2O$: C, 51.7; H, 6.0; N, 11.0. Found: C, 51.4; H, 5.9; N, 11.5. The acylated pentapeptide was converted into its azide (subunit A) *via* the methyl ester and hydrazide.[7] Carbobenzoxyhistidylphenylalanylnitroarginyltryptophylglycine benzyl ester[8] was saponified and the ensuing acylated pentapeptide coupled with ε-tosyllysylprolylvalineamide[9] to give carbobenzoxyhistidylphenylalanylnitroarginyltryptophylglycyl-ε-tosyllysylprolylvalineamide.

The presence of the C-terminal glycine residue precluded racemization in this N,N′-dicyclohexylcarbodiimide[10] induced reaction. Hydrogenation of the acylated octapeptide afforded histidylphenylalanylarginyltryptophylglycyl - ε - tosyllysylprolylvaline amide (subunit B) which was purified by countercurrent distribution,[11] and isolated as the diacetate dihydrate, $[\alpha]^{25}D$ −40.0° (in 0.1*N* HCl), homogeneous on paper in the Partridge system, R_f = 0.72. *Anal.* Calcd. for $C_{61}H_{90}O_{16}N_{16}S$: C, 54.9; H, 6.8; N, 16.8. Found: C, 55.2; H, 7.0; N, 16.2. Completely digestible by LAP, amino acid comp. of digest: $his_1phe_1arg_1try_1gly_1$-ε-$toslys_1val_1$. Proline present but not determined. Tryptophan, calcd. 15.3; found: 15.1.[12]

The interaction of subunits A and B in dimethylformamide and triethylamine at *p*H 8 afforded carbobenzoxyseryltyrosylserylmethionylglutaminylhistidylphenylalanylarginyltryptophylglycyl ε-tosyllysylprolylvalineamide. After countercurrent distribution single spot on paper, R_f = 0.90 (Partridge), ninhydrin negative, positive color with the Pauly, Ehrlich, Sakaguchi and methionine reagents. Composition of acid hydrolysate $ser_{2.1}$-

(4) K. Hofmann, T. A. Thompson and E. T. Schwartz, THIS JOURNAL, **79**, 6087 (1957).

(5) Because of pyrrolidonecarboxylic acid formation glutamine cannot be determined by the ninhydrin technique.

(6) K. Hofmann, A. Jöhl, A. E. Furlenmeier and H. Kappeler, THIS JOURNAL, **79**, 1636 (1957).

(7) Decarbobenzoxylation of the acylated pentapeptide gave seryltyrosylserylmethionylglutamine $[\alpha]^{26}D$ −19.4° (in 2*N* HCl), R_f = 0.48 (Partridge). Completely digestible by LAP, amino acid ratios in digest $ser_{2.4}tyr_{1.0}met_{1.1}$.[5] *Anal.* Calcd. for $C_{28}H_{38}O_{12}N_6S.1.5H_2O$: C, 46.8; H, 6.4; N, 13.1. Found: C, 46.8; H, 6.3; N, 13.8.

(8) K. Hofmann, M. E. Woolner, G. Spühler and E. T. Schwartz, THIS JOURNAL, **80**, 1486 (1958).

(9) Prepared from α-carbobenzoxy-ε-tosyllysine and prolylvalineamide followed by decarbobenzoxylation: hydrochloride $[\alpha]^{24}D$ −52.5° (in water), R_f = 0.77 (Partridge), migrates faster than ε-tosyls in the 2-butanol-ammonia system; completely digestible by LAP, molar amino acid ratios in digest ε-$tosyls_1val_1$. Anal. Calcd. for $C_{28}H_{38}O_8N_6SCl$: N, 13.2; Cl, 6.6; S, 6.0. Found: N, 13.0; Cl, 6.3; S, 5.9.

(10) J. C. Sheehan and G. P. Hess, THIS JOURNAL, **77**, 1067 (1955).

(11) Solvent system 1-butanol–10% acetic acid.

(12) T. W. Goodwin and R. A. Morton, *Biochem. J.*, **40**, 628 (1946).