It is unlikely that the aluminum end of the aluminum–vanadium complex is the catalytically active site since this portion is structurally identical to one end of an alkyl aluminum halide dimer, and these compounds are not low pressure polymerization catalysts. The polymer molecule is believed to grow from the vanadium center by a two-step process[4,5] of coördination of the ethylene with a vacant orbital of the vanadium species followed by a rearrangement to give net addition of the V–R bond across the ethylene double bond. The function of the aluminum alkyl is to reduce the vanadium to the divalent state and alkylate it to form the active species (RVX). By formation of a complex, the aluminum bromide (or $RAlX_2$) dissolves the active species, stabilizes it, and prevents further reduction of the vanadium.

(4) D. B. Ludlum, A. W. Anderson and C. E. Ashby, THIS JOURNAL, **80**, 1380 (1958).

(5) W. L. Carrick, W. T. Reichle, R. W. Kluiber, E. F. Bonner, and J. J. Smith, Paper No. 47, Polymer Division, 133rd Meeting of the American Chemical Society, San Francisco, California.

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RECEIVED AUGUST 28, 1958

## EFFECTS OF DIAMINES ON THE PROTOPLAST-INFECTING AGENT DERIVED FROM T2 BACTERIOPHAGE

*Sir:*

Hershey[1] has reported the presence in T2 bacteriophage of two low molecular weight, ninhydrin-positive components derived biosynthetically from arginine, and associated with the deoxyribonucleic acid (DNA) of the virus in the process of infection of cells of *Escherichia coli*. Ames, *et al.*,[2] have identified these two components as putrescine (tetramethylenediamine) and spermidine ($H_2N$-$(CH_2)_4NH(CH_2)_3NH_2$). We now wish to report that the probable function of these amines is the preservation of the bacteriophage DNA in an infective conformation. The basis for this hypothesis is found in experiments with the protoplast-infecting agent ($\pi$)[3] (Table I): (1) heating at 72.5° destroys $\pi$ very rapidly; (2) certain preparations of $\pi$ show marked inactivation with dilution in 0.10 or 0.15 *M* NaCl; (3) repeated freezing and thawing of $\pi$ renders it much more labile to subsequent heat inactivation.

TABLE I

PROTECTIVE EFFECTS OF CADAVERINE

| Retention, % of infectivity after treatment | Treatment: Dilution 64-fold | Heat Treatment 72.5°/5 min. | Heat Treatment 67.5°/1.5 min. | Heat treatment 67.5°/1.5 min. after 10 × freezing-thawing In saline | Heat treatment 67.5°/1.5 min. after 10 × freezing-thawing In 0.01 *M* cadaverine |
|---|---|---|---|---|---|
| In 0.15 *M* saline | <2.0 | <0.04 | 6.0 | 0.19 | 1.6 |
| Same plus 0.01 *M* cadaverine | 100 | 88 | 85 | 12 | 56 |

(1) A. D. Hershey, *Virology*, **4**, 237 (1957).

(2) B. Ames, D. T. Dubin and S. M. Rosenthal, *Science*, **127**, 814 (1958).

(3) D. Fraser, H. R. Mahler, A. L. Shug and C. A. Thomas, *Proc. Natl. Acad. Sci.*, **43**, 939 (1957).

Certain polymethylene diamines of the general structure $H_2N$-$(CH_2)n$-$NH_2$ as well as spermidine protect $\pi$ against all of these effects to a remarkable degree; maximum protective action is exerted by cadaverine ($n$ = 5). A reasonable model for the cadaverine dihydrochloride molecule (the species present at *p*H 5.5) leads to an N–N distance of 7.30 Å. The distance between phosphate oxygens in the revised DNA structure proposed by Wilkins[4] is 7.65 Å.

All experiments performed at the temperature indicated, in 0.15 *M* NaCl (plus cadaverine where indicated) at a *p*H of 5.5. The $\pi$ preparation was diluted 1:20 into the incubation tube and samples were withdrawn at 30-second intervals, and diluted 1:20 into chilled 0.15 *M* NaCl kept at 0°. They were then assayed for infectivity in our standard system.[3]

(4) *Cf.* drawing by J. C. Kendrew, and M. F. Perutz, in *Ann. Rev., Biochem.*, **26**, 340 (1957); also R. Langridge, W. E. Seeds, H. R. Wilson, C. W. Hooper, M. H. F. Wilkins and L. D. Hamilton, *J. Biophys. Biochem. Cytol.*, **3**, 767 (1957).

(5) Supported by Grant No. E-1854 from the Institute of Microbiology and Immunology of the National Institutes of Health.

(6) Contribution No. 867.

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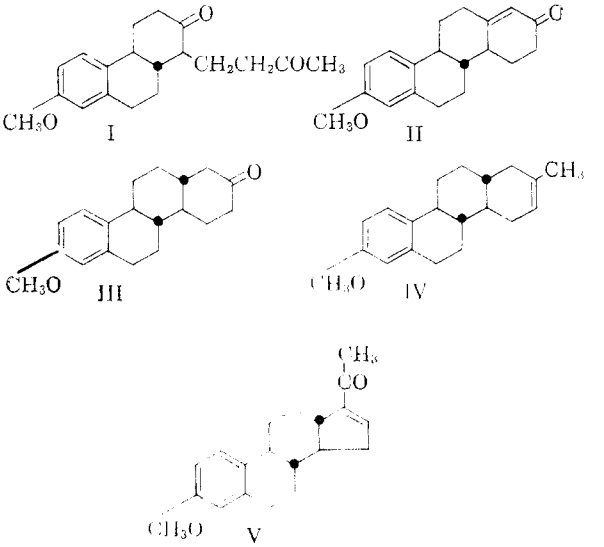
RECEIVED OCT. 22, 1958

## SYNTHESIS OF 18,19-DINOR STEROIDS

*Sir:*

A practicable route from natural steroids to 18,19-dinor steroids, including the estrone, testosterone, progesterone, and desoxycorticosterone analogs, has been achieved and is reported here.

Boric acid-catalyzed rearrangement of estradiol 3-methyl ether[1] followed by ozonolysis of the resulting olefin produced the diketone I, m.p. 119–120°; $[\alpha]_D$ +98°; (*Anal.* Found: C, 76.14; H,




(1) Personal communication from Dr. D. A. Tyner of these laboratories.

7.81).[2] Treatment with base effected cyclization[3] to 8-methoxy-2,3,4,4a$\alpha$,4b$\beta$,5,6,10b$\alpha$,11,12-decahydrochrysen-2-one (II), m.p. 145–146°; $[\alpha]_D$ +85°; $\lambda_{max}$ 233 m$\mu$ ($\epsilon$ 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 - 1,4,4a$\alpha$,4b$\beta$,5,6,10b$\alpha$,11,12,-12a$\beta$-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°; $\lambda_{max}$ 231 m$\mu$ ($\epsilon$ 13,900), 278 m$\mu$ (2010), 287 m$\mu$ (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°; $\lambda_{max}$ 240 m$\mu$ ($\epsilon$ 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-13$\alpha$-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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RECEIVED OCTOBER, 14, 1958

(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.

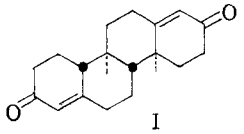
(8) C. Djerassi and C. T. Lenk, THIS JOURNAL, **76**, 1722 (1954).

## SYNTHESIS OF 17,18-BISNORSTEROIDS

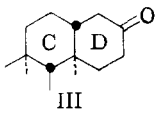
*Sir:*

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

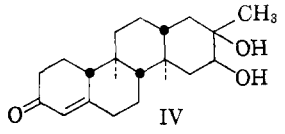
We have transformed I into its ethylene glycol monoketal[2] II, m.p. 150–151° (Found: C, 76.40; H, 8.45); reduction of II with lithium and ammonia gave III, m.p. 145–147° (Found: C, 76.02; H, 8.87); semicarbazone m.p. 202–203° (Found: C, 67.55; H, 8.33). Reaction of III with methylmagnesium iodide, dehydration 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 $\beta$-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 m$\mu$, $\epsilon$ 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).