was refluxed for 2 hours. At the end of this period the pyridine was removed *in vacuo* and the residue extracted with ether. The ether solution was washed successively with dilute aqueous hydrochloric acid, water, and potassium bicarbonate solution. Evaporation of the dried ether solution and crystallization of the product from acetone–hexane ether afforded 3α-acetoxy-16-deuterio-Δ[16]-pregnene-11,20-dione (XI), m.p. 167–169°. An n.m.r. spectrum of this material revealed 15–20% of —C=C—H (Δ[16]-protonium) contamination.

*Anal.* Calcd. for $C_{23}H_{31}O_4D$: C, 73.99; H(D), 8.85; D, 1 atom/molecule. Found: C, 74.20; H(D), 8.65; D, 1.03 atoms/molecule.

**(B) By Lithium Chloride in Dimethylformamide.**—A solution of 500 mg. of bromoketone X and 0.13 g. of lithium chloride in 5 cc. of dimethylformamide was heated on the steam-bath for 6 hours. The product was watered out, extracted with ether and the residue obtained after evaporation of the ether was crystallized from acetone–hexane to give XI, m.p. 165–168°. This product was identical by mixed m.p. and infrared comparison with XI obtained in part A. Again an n.m.r. spectrum of this material showed the presence of 15–20% of —C=C—H.

*Anal.* Calcd. for $C_{23}H_{31}O_4D$: C. 73.99, H(D), 8.85; D, 1 atom/molecule. Found: C, 73.80; H(D), 8.78; D, 0.98 atom/molecule.

**3α-Hydroxy-16α,17α-oxido-16β-deuteriopregnane-11,20-dione (XII).**—To a cold stirred solution of 2.00 g. of the 16-deuterio-Δ[16]-pregnene XI in 60 ml. of methanol at 10° was added 3 cc. of cold 4 *N* aqueous sodium hydroxide and 6 cc. of cold 30% hydrogen peroxide (procedure of Julian, *et al.*[17]). After 40 hours at 5° and 1 hour at 25° the Δ[16]-20-keto ultraviolet absorption band was no longer present. The solution was concentrated to 30 cc., water was added and the mixture extracted with chloroform. The chloroform extract was washed with saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated to dryness. Crystallization of the residue from methanol led to the 16α,17α-oxido-16β-deuteriopregnane XII as plates, m.p. 219–223°.

*Anal.* Calcd. for $C_{21}H_{29}O_4D$: C, 72.61; H(D), 9.00; D, 1.00. Found: C, 72.63; H(D), 8.71; D, 0.93.

An additional 0.37 g. of XII, m.p. 215–220° (total yield 86%), was obtained on concentration of the filtrate. Paper chromatography of the crystalline fractions as well as the crystalline residue (benzene–formamide system) showed each fraction to consist of a single component with the same mobility as an authentic sample of undeuterated oxide IV.

**Alkaline Rearrangement of 3α,16β-Diacetoxy-17α-hydroxy-16α-deuteriopregnane-11,20-dione (XIV, R = Ac) to 3α,16α-Diacetoxy-17α-hydroxy-17β-methyl-16β-deuterio-D-homo-5β-androstane-11,17a-dione (XVI).**—A 1-g. sample of the deuterated oxide XII was acetolyzed as previously described in 30 cc. of acetic acid containing 2 cc. of concentrated sulfuric acid. The product XIV (R = Ac) was dissolved in 64 cc. of dioxane, treated with 600 mg. of potassium hydroxide in 32 cc. of water and allowed to stand at room temperature for 18 hours. At the end of this period the reaction mixture was acidified, the dioxane removed *in vacuo* and the residue extracted with ethyl acetate. Evaporation of the ethyl acetate and crystallization of the residue from acetone–ether gave XVI in copious crystalline form, m.p. 212–215°, not depressed on mixed m.p. with authentic XVI. The infrared spectra of the two samples were identical.

*Anal.* Calcd. for $C_{25}H_{35}O_7D$: D, 1 atom/molecule; corrected for $C_{16}$–H contamination (n.m.r.) D, 0.8–0.85. Found: D, 0.85 atom/molecule.

In a like manner 3α-acetoxy-16α,17α-dihydroxypregnane-11,20-dione (XIII) under the same conditions of alkaline rearrangement gave XVI.

**Acknowledgment.**—The authors are grateful to Dr. N. Trenner and Mr. B. Arison for n.m.r. evaluations.

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[CONTRIBUTION FROM THE MERCK, SHARPE AND DOHME RESEARCH LABORATORIES, A DIVISION OF MERCK AND CO., INC., RAHWAY, N. J.]

# Alkylated Adrenal Hormones. The Synthesis of 5α-Methylated Androstanes

BY JOHN H. FRIED, ANTHONY N. NUTILE AND GLEN E. ARTH

RECEIVED MAY 5, 1960

The synthesis of 5α-methyl-androstane-17β-ol-3-one *via* angular methylation of a suitable 6-ketone, IV, is described.

It is a well known fact that the double bond between carbons four and five in testosterone is not a necessary prerequisite for biological activity. For instance an A/B-*trans* saturated analog of testosterone, 5α-androstane-3α-ol-17-one, is a potent androgen.[1] On the other hand, the corresponding C-5 epimer, 5β-androstane-3α-ol-17-one, is inactive in this regard, but exhibits a pyrogenic[2] effect in humans. The introduction of α-methyl groups at positions 2[3a] and 6[3b] into C-19 steroids has the effect of increasing the ratio of anabolic to androgenic activity. One of these compounds, 2α-methyl-androstane-17β-ol-3-one has also found utility in the treatment of some cases of metastatic breast cancer.[4]

In order to study the effect of substitution, at the ring juncture of an A/B-*trans* steroid, on androgenic and anabolic activity, it was of interest to prepare a C-5α-methylated androstane derivative. This paper describes the synthesis of 5α-methyl-androstane-17β-ol-3-one (VII) from testosterone acetate.

No 5α-methylated derivative of the biologically active steroid hormones has been reported.[5] Modification of a recent synthesis[6] of 5β-methylated pregnanes by alkylation of 17α,20,20,21-bismethylenedioxy-3-ethylenedioxy-allopregnane-6,11-dione (A) offered a possible approach to the desired compound.

Examination of the factors responsible for the stereospecific introduction of methyl on the β-

(1) R. I. Dorfman and R. A. Shipley, "The Androgens," John Wiley and Sons, Inc., New York, N. Y., 1956.

(2) A. Kappas, L. Hellman, D. K. Fukushima and T. F. Gallagher, *J. Clin. Endocrinol. Metabolism*, **17**, 451 (1957).

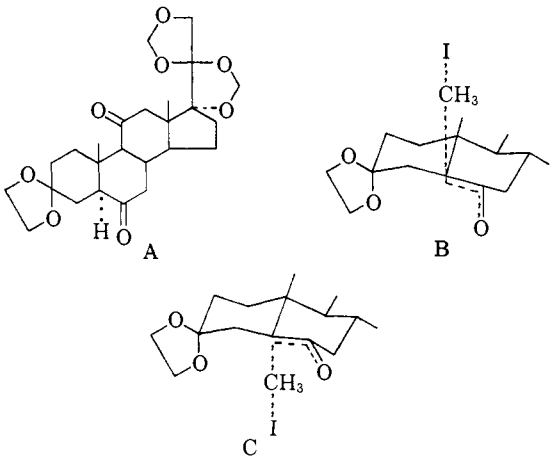
(3) (a) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956); H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, THIS JOURNAL, **81**, 427 (1959); (b) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.*, 4099 (1957).

(4) C. M. Blackburn and D. S. Childs, *Proc. Staff Meet., Mayo Clinic*, **34**, 113 (1959).

(5) 5α-Methyl-cholestane-3β,6β-diol is the only reported example of a 5α-methylated steroid; M. Chuman, *J. Chem. Soc., Japan, Pure Chem. Section*, **70**, 253 (1949); see, however, ref. 6.

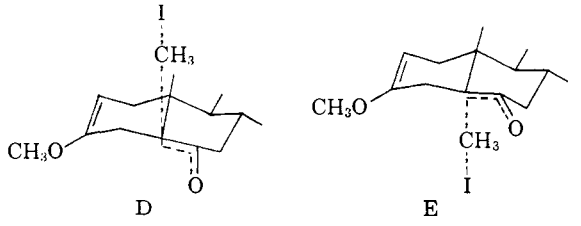
(6) J. H. Fried, G. E. Arth and L. H. Sarett, THIS JOURNAL, **82**, 1684 (1960).

face of the molecule suggested that useful predictions could be made on the basis of two transition states,[6] B resembling the anion of the enol form of the starting material, and C resembling the anion of the keto form of the starting material.[7]




Qualitative comparison[6] of the energetics of these transition states suggested that B was favored relative to C by a steric factor consisting of one 1:3 $CH_3$:O interaction and at least one 1:3 $CH_3$:H interaction. However, a greater degree of electron delocalization and maximum bonding is possible with C relative to B. The results[6] of the methylation indicate that the steric effect was clearly dominant.

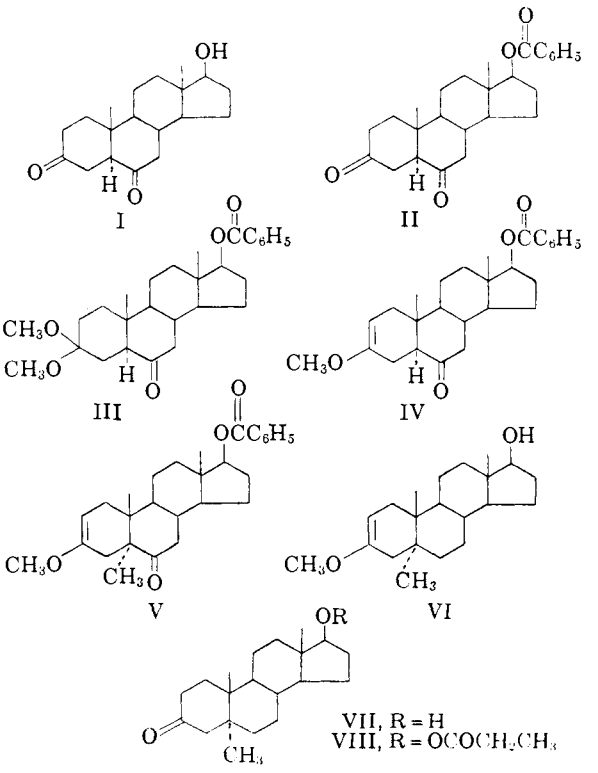
However, it appeared reasonable to suppose that the electronic effect would control the stereochemistry of the methylation[8]; if steric factors were more nearly balanced. It was apparent that the important 1:3 $CH_3$:O interaction present in B could be eliminated by replacing the dioxolane function in I by an enol ether as for example in compound IV.[9] Transition states D and E corresponding to B and C would then be more closely related in energy content with E still favored electronically and D favored now by a reduced steric factor, consisting of about one to two 1:3 $CH_3$:H interactions.




Testosterone acetate was converted into androstane-17β-ol-3,6-dione by bromination with N-bromosuccinimide followed by acid hydrolysis.[10a,b] Benzoylation of I followed by ketalization of the 3-oxo function with methanol and selenium dioxide[11] afforded 3,3-dimethoxy-androstane-17β-ol-6-one benzoate (III). Pyrolysis[11] of III yielded the enol ether IV.

Methylation of IV with sodium hydride and methyl iodide in refluxing xylene[6] afforded 5α-methyl-androstane-17β-ol-3-one (V) in about 35% yield. The structure assigned to V is consistent with analytical and physical data. The n.m.r. spectrum[12] of VI was particularly significant in that a signal indicative of one additional quaternary C-methyl group was clearly evident. The stereochemistry of the newly introduced methyl was shown to be alpha by rotational dispersion studies[13] carried out with compound VII. In addition to V and recovered starting material, a small amount of 5-methyl-3,17β-dimethoxy-2-androstene-6-one was isolated. The stereochemistry of this compound was not determined but is presumably A/B *trans* by analogy with the major product. No other pure components could be isolated. However, paper strip evidence indicated the presence of trace amounts of a component slightly less polar than V, possibly the corresponding 5β-isomer, in the mother liquors from the methylation.

The formation of a predominantly 5α-methylation product is best interpreted on the basis of transition state E. Since E is destabilized relative to D by about 0.9–1.8 kcal.,[14] the electronic factor due to greater electron delocalization must stabi-




(7) Subtle electronic and conformational effects arising from the presence or absence of the 11-ketone have been neglected in the following discussion.

(8) *Cf.* E. J. Corey, THIS JOURNAL, **76**, 175 (1954); E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956).

(9) *Cf.* W. S. Johnson and D. S. Allen, Jr., *ibid.*, **79**, 1261 (1957).

(10) (a) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki, *ibid.*, **72**, 4534 (1950); (b) F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, *ibid.*, **75**, 4712 (1953).

(11) E. P. Oliveto, C. Gerald and E. B. Hershberg, *ibid.*, **76**, 6113 (1954).

(12) We wish to thank Dr. N. R. Trenner and B. Arison for the determination and interpretation of the n.m.r. spectrum.

(13) We wish to thank Dr. D. Williams of these Laboratories for carrying out the rotational dispersion measurement.

(14) A value of 0.9 kcal. has been assigned to a single 1:3 diaxial $CH_3$:H interaction; C. W. Beckett, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 977, 2488 (1947).

lize E relative to D by at least as great an amount. An upper limit can be placed on the value of the electronic factor by considering the methylation of A. In this case the imposition of a further 1:3 diaxial methyl:oxygen interaction over that present in E destabilizes C sufficiently to afford only a 5β-methylation product *via* transition state B.

Wolff–Kishner reduction[15] of V led to 3-methoxy-2-androstene-17β-ol-3-one which on treatment with *p*-toluenesulfonic acid in acetone afforded 5α-methyl-androstane-17β-ol-3-one (VII).

The rotational dispersion curve[13] of compound VII exhibited a positive Cotton effect characteristic of A/B *trans*-steroids.[16] The α-configuration was therefore assigned to the new methyl group at C-5 since it has been shown that the sign of the Cotton effect of a 3-keto steroid is not affected by replacement of hydrogen with methyl at this position.[6]

Compound VIII was evaluated for androgenic and anabolic activities in the Merck Institute for Therapeutic Research, and found to be inactive.[17,18]

## Experimental[19]

**Androstane-17β-ol-3,6-dione (I).**—Testosterone acetate (19.2 g.) was converted into 6β-bromotestosterone acetate by bromination with N-bromosuccinimide in carbon tetrachloride.[10a] Illumination from a 300 w. General Electric reflector spot lamp and *ca.* 10 mg. of benzoyl peroxide were used to catalyze the reaction.

The crude bromination product was refluxed with 16 ml. of concentrated hydrochloric acid in 400 ml. of methanol[10b] for 3 hr. and allowed to stand at room temperature overnight. The reaction mixture was treated with 20 g. of sodium acetate and concentrated *in vacuo* to a small volume. The concentrate was diluted with water and extracted with chloroform. The chloroform layer was washed with aq. sodium bicarbonate solution, dried and concentrated *in vacuo*. Crystallization from an ether–petroleum ether mixture afforded 2.0 g. of androstane-17β-ol-3,6-dione, m.p. 222–227°. Treatment of the mother liquors with 200 mg. of *p*-toluenesulfonic acid in 200 ml. of acetone at room temperature overnight afforded an additional 5.9 g. of I, m.p. 226–233°; infrared: $\lambda_{max}^{Nujol}$ 2.74, 5.88 μ.

**Androstane-17β-ol-3,6-dione Benzoate (II).**—An ice-cold solution consisting of 6.0 g. of I in 40 ml. of anhydrous pyridine was treated with 2.54 ml. of benzoyl chloride and allowed to stand at room temperature overnight. The reaction mixture was diluted with chloroform–ether (2:3) and washed sequentially with ice-cold 10% aq. sodium carbonate solution, cold dilute acetic acid, water and cold 5% aqueous sodium bicarbonate solution. The organic layer was dried and concentrated *in vacuo*. Crystallization from ethyl acetate afforded 6.2 g. (78%) of androstane-17β-ol-3,6-dione benzoate, m.p. 230–234°. The sample for analysis was recrystallized from ethyl acetate, m.p. 232–235°, $\alpha^{24}D$ + 30° (*c* 0.9, $CHCl_3$); infrared: $\lambda_{max}^{CHCl_3}$ sh. 5.78. 5.85, 6.20, 6.26, 6.85 μ. *Anal.* Calcd. for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90. Found: C, 76.37; H, 7.79.

**3,3-Dimethoxyandrostane-17β-ol-6-one Benzoate (III).**—A suspension consisting of 7.0 g. of II and 20 g. of selenium dioxide[11] in 500 ml. of methanol was heated at 50–55° for 2 hr. during which time the steroid went into solution. The solution was allowed to stand at room temperature for 1 hr. and cooled in ice. An ice-cold solution of 20 g. of potassium hydroxide in 100 ml. of water was added and the resulting mixture poured into 3 l. of water. The product was filtered and chromatographed on 140 g. of basic alumina (Merck). Material eluted with benzene to ether–petroleum ether (7:3) was combined and crystallized from methanol to yield 6.7 g. (85%) of 3,3-dimethoxy-androstane-17β-ol-6-one benzoate, m.p. 157–161°. The sample for analysis was recrystallized from methanol, m.p. 158–161°, $\alpha^{25}D$ +19° (*c* 0.8, $CHCl_3$); infrared: $\lambda_{max}^{CHCl_3}$ 5.84, 6.20, 6.26, 6.85 μ. *Anal.* Calcd. for $C_{28}H_{38}O_6$: C, 73.98; H, 8.43. Found: C, 74.41; H, 8.53.

**3-Methoxy-2-androstane-17β-ol-6-one Benzoate (IV).**—A 15-ml. centrifuge tube containing 270 mg. of III and 0.20 g. of powdered Pyrex glass was capped with a glass wool plug and heated in a Wood metal-bath at 215 ± 3° for 35 min.[11] The cooled melt was dissolved in chloroform, filtered and concentrated. Chromatography on 15 g. of basic alumina (Merck) and elution with ether–petroleum ether (5:5–7:3) afforded 147 mg. (58%) of 3-methoxy-2-androstene-17β-ol-6-one benzoate, m.p. 217–228°. The sample for analysis was crystallized from ethyl acetate, m.p. 228–235°, $\alpha^{25}D$ + 46° (*c* 0.9, $CHCl_3$); infrared: $\lambda_{max}^{Nujol}$ 5.86, sh. 5.95, 6.25, 6.33 μ. *Anal.* Calcd. for $C_{27}H_{34}O_4$: C, 76.74; H, 8.11. Found: C, 77.02; H, 7.80.

**5-Methyl-3-methoxy-2-androstene-17β-ol-6-one Benzoate (V).**—A solution consisting of 3.33 g. of IV in 70 ml. of xylene was dried by azeotropic distillation. The solution was cooled and 450 mg. of a 53% dispersion of sodium hydride in mineral oil and 1 drop of *t*-butyl alcohol was added, and the reaction mixture refluxed under nitrogen for 50 minutes. The yellow suspension was cooled, 20 ml. of methyl iodide, dried by passing through a tube filled with calcium chloride, was added and the suspension refluxed overnight. The cooled solution was poured into water, separated, and the aq. layer extracted with benzene. The combined organic phase was washed with water, dried and concentrated *in vacuo*. Chromatography on 320 g. of basic alumina (Merck) and elution with ether–petroleum ether (4:6) afforded 90 mg. of a fraction, m.p. 155–165°, presumably 5-methyl-3,17β-dimethoxy-2-androstene-6-one. Crystallization from ether yielded a sample for analysis, m.p. 164–170°, $\alpha^{22}D$ −12° (*c* 0.5, $CHCl_3$); infrared: $\lambda_{max}^{Nujol}$ 5.85, 5.98 μ; nuclear magnetic resonance spectrum: the presence of two methoxy groups and three quaternary C-methyl groups is indicated. *Anal.* Calcd. for $C_{28}H_{34}O_4$: C, 76.26; H, 9.89. Found: C, 76.64; H, 9.84.

Further elution with ether–petroleum ether (5:5) afforded a second fraction consisting of 1.32 g. of material. Crystallization of this fraction from ether yielded 0.32 g. of 5-methyl-3-methoxy-2-androstene-17β-ol-6-one benzoate (V), m.p. 159–167°. Rechromatography and crystallization of mother liquors yielded an additional 0.52 g. of V, a total of 0.84 g. Paper strip analysis[20] of the remaining mother liquors using 2-phenoxyethanol–ether (1:1) as the stationary phase and *n*-heptane saturated with phenoxyethanol as the mobile phase indicated only traces of a faster moving component than V. The sample for analysis was crystallized from ether–petroleum ether, m.p. 164–167°, $\alpha^{22}D$ + 18° (*c* 0.6, $CHCl_3$); infrared: $\lambda_{max}^{Nujol}$ 5.84, 5.96, 6.22, 6.32 μ; nuclear magnetic resonance spectrum: the presence of one methoxy group and three quaternary C-methyl groups is indicated. *Anal.* Calcd. for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 77.27; H, 8.15. A sample, m.p. 167–172°, was obtained by recrystallization from ethyl acetate. Elution with ether afforded *ca.* 1.0 g. of starting material. Taking this material into consideration, the yield of VI is 35%.

**5α-Methyl-androstane-17β-ol-3-one (VI).**—A solution consisting of 0.44 g. of V, 5 ml. of 85% hydrazine hydrate and 3.5 g. of potassium hydroxide in 50 ml. of diethylene glycol was heated under an atmosphere of nitrogen at 152–168° for 1.75 hr. The temperature was then raised by removing an aqueous fraction by distillation and maintained at 225° for 4 hr.[15] The solution was cooled, allowed to stand at room temperature overnight, and extracted with ether. The ether phase was washed with water, dried and concentrated. The crude 5α-methyl-3-methoxy-2-androstane-17β-ol (VI) was percolated through 15 g. of basic alumina (Merck) with a solution consisting of chloroform–ether (2:8). The product was not crystallized but hydrolyzed directly with 45 mg. of *p*-toluenesulfonic acid in 30 ml. of acetone at room temperature overnight. The acetone

(15) Huang-Minlon, *ibid.*, **71**, 3301 (1949).

(16) C. Djerassi and W. Closson, *ibid.*, **78**, 3761 (1956).

(17) Modification of the method of L. G. Hershberger, E. G. Shipley and R. K. Meyer, *Proc. Soc. Exp. Biol. and Med.*, **83**, 175 (1953).

(18) We are indebted to Dr. S. L. Steelman for carrying out these determinations.

(19) Melting points were determined on a Kofler micro hot-stage and are corrected. We wish to thank R. Boos and his associates for microanalyses and R. Walker and N. Allen for some of the infrared spectra here reported.

(20) *Cf.* R. Neher, "Chromatographie von Sterinen, Steroiden und Verwandten Verbindungen," Elsevier Publishing Co., Amsterdam, 1958.

solution was diluted with aqueous sodium bicarbonate solution and extracted with chloroform. The crude product was isolated from the chloroform layer after washing with water, drying and concentrating. Two crystallizations from methanol afforded 88 mg. of 5α-methyl-androstane-17β-ol-3-one (VII), m.p. 196–201°, $\alpha^{25}D$ + 40° (*c* 0.7, $CHCl_3$); infrared: $\lambda_{max}^{Nujol}$ 2.92, 5.83 μ; nuclear magnetic resonance spectrum: the presence of three quaternary C-methyl groups is indicated. *Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.73; H, 10.79.

A sample of VII, m.p. 201–202°, was obtained by recrystallization from methanol; $[\alpha]D$ + 43°, $[\alpha]_{400}$ +141°, $[\alpha]_{350}$ +302°, $[\alpha]_{325}$ +832°, $[\alpha]_{315}$ +1110°, $[\alpha]_{300}$ +369°, $[\alpha]_{286}$ −351° [*c* 0.18, dioxane]. Chromatography of the mother liquors on 20 g. of basic alumina and elution with ether–petroleum ether (2:8) followed by crystallization from methanol afforded 50 mg. of a fraction, m.p. 203–204°, presumably 5α-methyl-androstane-17β-ol. A sample for analysis was recrystallized from methanol, m.p. 204–207°; infrared: $\lambda_{max}^{Nujol}$ 2.95–3.05 μ. *Anal.* Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.54; H, 11.53. Further elution with ether–petroleum ether (8:2 and 9:1) and crystallization from methanol yielded an additional 95 mg. of VII, m.p. 196–200°, a total of 183 mg. (60% yield).

**5α-Methyl-androstane-17β-ol-3-one Propionate (IX).**—Acylation of VIII with propionic anhydride in pyridine at room temperature overnight afforded 5α-methylandrostane-17β-ol-3-one propionate (IX). A sample for analysis was crystallized from methanol, m.p. 157–160°, $\alpha^{26}D$ +32° (*c* 0.8, $CHCl_3$); infrared: $\lambda_{max}^{KBr}$ 5.77, 5.84 μ. *Anal.* Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.25; H, 10.11.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, TRINITY COLLEGE, HARTFORD 6, CONN.]

# Parallel Amide Groups[1]

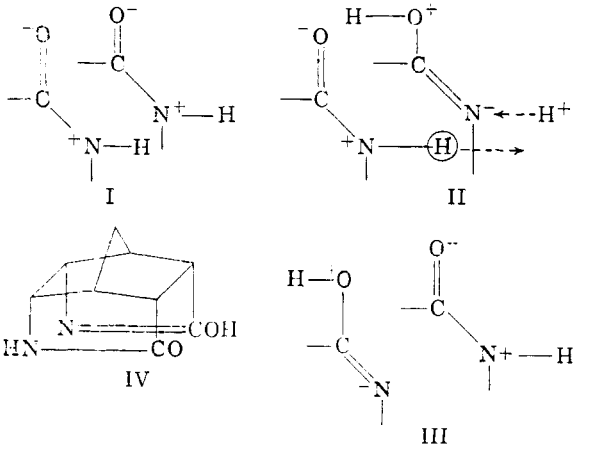
BY W. SCOTT WORRALL

RECEIVED APRIL 1, 1960

The synthesis of the dilactam of *endo-cis*-2,3-dicarboxy-*endo-cis*-5,6-diaminonorbornane, which contains two amide groups held rigidly side by side in space, is described. This work is the beginning of a search for possible changes in the normal properties of functional groups due to intramolecular action of neighboring amide groups.

Functional groups, which participate in reactions catalyzed by proteolytic enzymes, during the reaction are probably in the more or less immediate neighborhood of amide groups, *i.e.*, peptide linkages. The phrase, functional groups, is intended to include both groups in the substrate molecules and groups in the protein enzyme. Therefore it is of interest to attempt to synthesize molecules in which various functional groups are held in well defined orientations with respect to one or more amide groups. A search can then be made for possible changes in the normal properties, *e.g.*, nucleophilicity, of the functional groups. As the beginning of such a project a novel arrangement of two amide groups is speculatively presented in this paper and the synthesis is reported of a molecule containing this arrangement of amide groups.

It is possible to imagine two planar[2] amide groups held rigidly side by side in space, *i.e.*, parallel amide groups, with the oxygen opposite the oxygen, and the nitrogen opposite the nitrogen, etc. (I). However, in this configuration the large dipoles associated with each amide group[3] would oppose each other and, therefore, it is reasonable to assume that one of the amide groups would exist in the enolic form (II). In this way the two dipoles would complement each other and conceivably would interact to form four regions of intense localized charge. Speculation in this area leads to the concept of a chemical reaction in which parallel amide groups participate by simultaneously giving and accepting a proton and, at the same time, the parallel amide groups are converted to their mirror image, *i.e.*, II→III. In this process the original quadrupole disappears in the transition state and then reappears in the reverse orientation. This intense reciprocating quadrupole hypothetically present in parallel amide groups is novel, and, therefore, the properties of parallel amide groups are of interest both with respect to the isolated structure and also with respect to any possible relationship with neighboring functional groups. It is conceivable that such an arrangement, *i.e.*, parallel, of amide groups occurs in protein molecules. The dilactam of *endo-cis*-2,3-dicarboxy-*endo-cis*-5,6-diaminonorbornane (IV) contains parallel amide groups and the synthesis of this molecule is described in this paper.



I II IV III

The carbon framework of norbornane was used as a rigid framework to which the paired amide groups were fastened. Treatment of *endo-cis*-2,3-dicarboxy-*exo-cis*-5,6-dibromonorbornane anhydride[4] (V) with concentrated aqueous ammonia

(1) This work was presented at the 136th Meeting of the American Chemical Society, September, 1959, and was supported by a research grant, G-1951, from the National Science Foundation.

(2) L. Pauling, R. B. Corey and H. R. Branson, *Proc. Natl. Acad. Sci. (U. S.)*, **37**, 205 (1951); L. Pauling and R. B. Corey, *ibid.*, **37**, 272 (1951).

(3) W. W. Bates and M. E. Hobbs, THIS JOURNAL, **73**, 2151 (1951).

(4) J. A. Berson and R. Swidler, *ibid.*, **76**, 4060 (1954).