aldehyde nitrogen mustard IV and *o*-tolualdehyde nitrogen mustard V were obtained commercially.[7] All melting points are corrected.

N,N′-Bis(2,4-dichlorobenzylidene)-1,3-diaminopropane (VIc).—A 44.9-g. (0.606 mole) portion of 1,3-diaminopropane was added to a refluxing solution of 216.0 g. (1.23 moles) of 2,4-dichlorobenzaldehyde in 400 ml. of absolute ethanol. The addition took 20 min. and a white oil separated from the solution during this period. The mixture was refluxed for 1 additional hr., then 150 ml. of absolute ethanol was added to dissolve the oil and the solution was poured into a beaker. As the mixture cooled, a white oil again separated. However, this crystallized as the solution approached room temperature. There was obtained 208.5 g. (89.1%) of white solid, m.p. 103–104.5°. This material was recrystallized from absolute ethanol to give 206.0 g. (87.6%) of crystals, m.p. 104.0–104.5°.

Anal. Calcd. for $C_{17}H_{14}Cl_4N_2$: N, 7.22. Found: N, 7.40.

N,N′-Bis(3,4-dichlorobenzylidene)-1,3-diaminopropane (VId).—This di-Schiff base was prepared in a manner similar to VIc from 25.2 g. (0.34 mole) of 1,3-diaminopropane and 125.0 g. (0.715 mole) of 3,4-dichlorobenzaldehyde. This furnished 110.5 g. (83.7%) of crude material, m.p. 74.5–76.5°. It was recrystallized 3 times from absolute ethanol to yield 94.0 g. (71.2%) of white solid, m.p. 76.5–77.5°.

Anal. Calcd. for $C_{17}H_{14}Cl_4N_2$: N, 7.22. Found: N, 7.45.

N,N′-Bis(2,4-dichlorobenzyl)-1,3-diaminopropane (IIIc).—A mixture of 79.0 g. (0.203 mole) of N,N′-bis(2,4-dichlorobenzylidene)-1,3-diaminopropane (VIc) and 1 l. of methanol was cooled in an ice–water bath. The di-Schiff base was relatively insoluble in the cold methanol. The mixture was stirred and 23.0 g. (0.61 mole) of solid sodium borohydride were added in small portions over a 10-min. period. The mixture was warmed until there was an evolution of gas. The external heating was discontinued, although stirring was continued until 1 hr. after all of the solids had dissolved. One-half of the solvent was distilled at atmospheric pressure and when the solution had cooled to room temperature, 1 l. of a 1.2 *M* solution of sodium hydroxide was added. The mixture was shaken briefly and then divided into two approximately equal parts, each part was extracted 3 times with 75-ml. portions of diethyl ether. The ether extracts were combined and dried over sodium hydroxide pellets. The solution was filtered into a round-bottomed flask and the ether was removed with a rotary evaporator. There was obtained 70.0 g. (78.7%) of a clear, colorless oil.

Anal. Calcd. for $C_{17}H_{18}Cl_4N_2$: N, 7.15. Found: N, 7.29.

A small portion of this oil was dissolved in acetonitrile and cooled overnight. A white solid separated and was recrystallized from acetonitrile to give material which melted at 46.0–47.0°.

N,N′-Bis(3,4-dichlorobenzyl)-1,3-diaminopropane (IIId) was prepared by a procedure like that used to prepare IIIc. A 78.0-g. (0.201 mole) sample of VId was reduced using 50.0 g. (1.32 moles) of sodium borohydride. The product was 61.2 g. (77.7%) of a clear, colorless oil, $n^{25}D$ 1.5880. An analytical sample was obtained by short-path distillation at 170° (0.1 mm.).

Anal. Calcd. for $C_{17}H_{18}Cl_4N_2$: N, 7.15. Found: N, 7.32.

2-[4-(N,N-Bis(2-chloroethyl)amino)aryl]-1,3-bis(aralkyl)-hexahydropyrimidines (Table I).—The synthesis of 2-[4-(N,N-bis(2-chloroethyl)amino)-*o*-tolyl]-1,3-bis(*p*-chlorobenzyl)-hexahydropyrimidine (XII) was typical of these compounds. A 5.20-g. (0.02 mole) sample of *o*-tolualdehyde nitrogen mustard (V) was dissolved in 25 ml. of warm absolute ethanol. To this solution was added 6.47 g. (0.02 mole) of N,N′-bis(*p*-chlorobenzyl)-1,3-diaminopropane, also in 25 ml. of absolute ethanol. The mixture was refluxed for 15 min., then 10 ml. of solvent was allowed to distil at atmospheric pressure over another 15-min. period. The solution was allowed to cool slowly to room temperature and then stored overnight in a refrigerator. This effected the separation of a light yellow solid. There was 5.3 g. of this material, m.p. 103–130°. This was recrystallized from 7.5 ml. of acetonitrile to furnish 4.05 g., m.p. 123–131°. The filtrate from the reaction mixture was reduced to approximately 1/3 of the original volume. Subsequent cooling of this solution yielded an additional 2.62 g. of white solid which melted at 129–131°. This was combined with the 4.05 g. of solid obtained from the initial crop of product and recrystallized twice from acetonitrile. This gave 4.73 g. (41.8%) of crystals, m.p. 130.0–131.5°.

Anal. Calcd. for $C_{29}H_{33}Cl_4N_3$: N, 7.43. Found: N, 7.56.

(7) Frinton Laboratories, South Vineland, N. J.

Acknowledgment is due Drs. H. W. Bond, R. B. Ross, and J. Leiter of the Cancer Chemotherapy National Service Center for their cooperation in obtaining the screening data. We wish to thank the Union Carbide Chemicals Company for the 1,3-diaminopropane which they supplied.

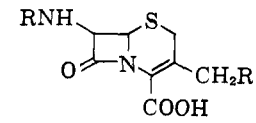
7-Aminodesacetoxycephalosporanic Acid and Its Derivatives

R. J. STEDMAN, K. SWERED, AND J. R. E. HOOVER

Smith Kline and French Laboratories, Philadelphia, Pennsylvania

Received September 24, 1963

Catalytic hydrogenation of the antibiotic cephalosporin C (Ia)[1] gave a product which we have identified as the desacetoxy derivative IIa.[2] This new antibiotic material was not isolated, but its structure was established by hydrolysis to 7-aminodesacetoxycephalosporanic acid (IIb). Although IIb had no appreciable antibacterial action, three derivatives (IId, IIe, and IIf) prepared from it showed modest activities. Since the completion of this work, Morin, *et al.*,[3] have reported briefly the hydrogenation of a cephalosporin derivative; the structure given for their product is in accord with our findings.



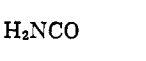
I R′ = CH_3COO
II R′ = H

a, R = $H_2NCH(CH_2)_3CO$ (COOH)

b, R = H

c, R = $C_6H_3(NO_2)_2NHCH(CH_2)_3CO$ (COOH)

d, R = $C_6H_5CH_2CO$

e, R = 

f, R = H_2NCO

The hydrogenation of Ia was carried out at low pressure using a large quantity of palladium catalyst. Paper electrophoresis showed that in addition to unchanged starting material there was present a new antibacterial substance (IIa) which gave a purple color with ninhydrin and had a strong ultraviolet absorption. The reaction mixture was treated with 2,4-dinitrofluorobenzene to give a mixture of Ic and IIc, and the latter, after partial purification, was hydrolyzed with acid to afford a small yield of IIb, isolated by ion-exchange chromatography. The dinitrophenyl group did not influence the hydrolytic cleavage of the side chain, but its introduction facilitated the manipulation of the intermediates and the isolation of the product.[4]

(1) E. P. Abraham and G. G. F. Newton, *Biochem. J.*, **79**, 377 (1961).

(2) (a) E. P. Abraham and G. G. F. Newton, *ibid.*, **62**, 658 (1956), reported that cephalosporin C absorbed hydrogen in the presence of a catalyst, but they did not characterize the product; (b) according to the nomenclature recommended in ref. 5, the hydrogenation product is a derivative of 7-amino-3-methyl-Δ^3-cephem-4-carboxylic acid (IIb).

(3) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, **85**, 1896 (1963).

(4) The hydrolysis and isolation procedures were similar to those described for the preparation of Ib in Belgian Patent 593,777 (1959).

Hydrogenation of 7-aminocephalosporanic acid (Ib), which has recently become available in quantity,[5] provided a convenient route for the preparation of larger quantities of IIb.

The strong ultraviolet absorption of IIb [$\lambda_{max}^{water\ pH\ 6}$ 263 mμ (ε 7800) with a shoulder at 242 mμ (ε 6000)] indicated that the unsaturation of the dihydrothiazine ring had survived the hydrogenation.[6] The infrared spectrum had the stretching band of the β-lactam carbonyl (λ_{max}^{Nujol} 5.58 μ), but lacked the prominent peaks attributable to the acetoxy group shown by Ib.[7] The n.m.r. spectrum of IId, the phenylacetyl derivative of IIb, showed, in addition to the aromatic[8] and benzylic (6.34 τ) hydrogens, a three-proton singlet (8.11 τ) assigned to the allylic methyl group, two one-proton peaks (6.74 and 6.57 τ) assigned to the methylene group[9] in the dihydrothiazine ring, and two one-proton doublets (4.98 and 4.47 τ, J = 4 c.p.s.) attributed to the hydrogens of the β-lactam ring. The pK_a values of the ammonium and carboxylic acid groups of IIb were found to be 4.79 and 2.38, respectively; the acid group of IId had a pK_a of 2.74.[10]

Table I compares the antibacterial activities of the phenylacetyl (IId), 2-thienylacetyl (IIe), and carbamoyl (IIf) derivatives of IIb with those of 7-phenylacetamidocephalosporanic acid (Id)[10c] and penicillin G. The three desacetoxy compounds were less effective *in vitro* than Id against all the organisms in the test and less effective than penicillin G against all except the penicillinase-producing staphylococci. Compound IIe displayed better activity than IId or IIf against the Gram-negative organisms; it was reported[10c] that in a series of 7-aminocephalosporanic acid derivatives the corresponding compound (Ie, cephalothin) had outstanding Gram-negative activity.

TABLE I

ANTIBACTERIAL ACTIVITIES OF 7-AMINODESACETOXYCEPHALOSPORANIC ACID DERIVATIVES

Organism	Minimal inhibitory concentrations[a] (μg./ml.) IId	IIe	IIf	Id	Penicillin G
Streptococcus pyogenes C203	2.5	1.2	31	0.055	0.012
S. aureus[b]	5	5	125	0.22	0.049
S. aureus[c]	20	20	250	1.8	>1000
S. typhimurium	250	62	500	31	12
E. coli	250	62	500	31	31
Proteus vulgaris	250	62	>1000	16	7.8
K. pneumoniae	250	31	500	16	7.8

[a] Measured in broth by serial twofold dilutions. End points were determined by macroscopic readings after incubation for 18 hr. at 37°. Inoculum, 10^6 organisms per ml. [b] Coagulase positive, not phage typable. [c] Finland 400, phage type 54 (penicillinase-producer).

Experimental

Corrected capillary melting points (Thomas–Hoover apparatus) are reported; melting points with decomposition were dependent on the rate of heating and were often preceded by darkening of the solid. Air-equilibration of samples was carried out by exposing them to the atmosphere (*ca.* 25° and 40% relative humidity) for several days. Recrystallizations and evaporations (aspirator vacuum) were performed without heating. Infrared spectra were determined with a Perkin–Elmer Infracord, ultraviolet spectra with a Cary Model 14 recording spectrophotometer, and n.m.r. spectra with a Varian Model A-60 spectrometer. The pH values reported for aqueous or methanolic solutions refer to readings given by a Beckman Zeromatic pH meter with glass and silver chloride electrodes.

Electrophoreses were run on paper strips (Whatman 3MM) in a Durrum-type cell (Beckman Spinco Model R) with a potential gradient of 17 v./cm. for 3 hr. The solvents used were 10% (v./v.) acetic acid (pH 2.2) and 1% (v./v.) 2,4,6-trimethylpyridine adjusted to pH 7 with acetic acid.[11] Colorless materials were detected on the strips by (a) examination under a 254-mμ lamp, (b) dipping in ethereal ninhydrin containing 5% of pyridine and allowing the colors to develop at room temperature, (c) bioautograph on agar plates seeded with *Bacillus subtilis*.

Hydrogenation of Cephalosporin C.—Hydrogenation of 63 mg. of cephalosporin C sodium salt dihydrate in 5 ml. of water at atmospheric pressure over 200 mg. of pre-reduced 10% palladium on carbon resulted in the uptake of 70% of a molar equivalent of hydrogen in 45 min. Electrophoresis at pH 2.2 showed major components (ultraviolet, bioautograph, purple with ninhydrin) which moved 1.2 and 3.4 cm. toward the cathode (Ia and IIa, respectively); at pH 7 both components moved 4.1 cm. toward the anode. Larger quantities of cephalosporin C were hydrogenated at 4 kg./cm.^{2}, with the same ratio of catalyst to substrate as above. The product was strongly adsorbed on the catalyst. It was eluted by adding 4 volumes of methanol to the reaction mixture and stirring for 30 min. while the pH was kept at 8 by adding sodium hydroxide.[12] The extraction was repeated with fresh 80% methanol, and the combined extracts were brought to pH 6 with hydrochloric acid and evaporated to remove most of the methanol. The residual aqueous solution, containing Ia and IIa, was used for the degradation described below.

7-Aminodesacetoxycephalosporanic Acid (IIb). A.—The product from the hydrogenation of 50 g. of cephalosporin C was treated with 40 ml. of 2,4-dinitrofluorobenzene in aqueous ethanol in the presence of sodium bicarbonate. Acidification gave 19.9 g. of a yellow gum[13] which was dissolved in equal volumes of *N* hydrochloric acid and acetonitrile, incubated overnight at 37°, and then partitioned between ethyl acetate and water at pH 4.5. Acidification of the aqueous phase gave 7.5 g. of a yellow gum, shown by electrophoresis to be almost pure IIc. This material was dissolved in equal volumes of acetonitrile and *N* hydrochloric acid and kept at 37° for 10 days to take off the side chain. IIb

(5) R. B. Morin, B. G. Jackson, E. H. Flynn, and R. W. Roeske, *J. Am. Chem. Soc.*, **84**, 3400 (1962).

(6) (a) In N-acyl derivatives of IIb the peak was at 261 mμ and the shoulder was absent; (b) A. G. Long and A. F. Turner, *Tetrahedron Letters*, 421 (1963), offer some interesting thoughts on the origin of the ultraviolet absorption of the cephalosporins.

(7) Bands at 5.75, 8.1, and 9.7 μ in the spectrum of Ib may be assigned to the acetoxy group. See L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, Second Edition, pp. 179 and 189.

(8) The n.m.r. spectrum was determined for a solution of the potassium salt of IId in deuterium oxide. In the absence of a satisfactory internal standard, peak locations were calculated by assigning the value 2.67 τ to the aromatic protons; this is their position in a $CDCl_3$ solution of phenylacetamide.

(9) The two signals observed were assumed to be the dominant peaks of the four expected from the ring methylene AB system. See L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p. 89.

(10) (a) Measurements were made at 25° in water. A spectrophotometric method was used to determine the values for the carboxyl groups. (b) Ib had pK_a 4.63 (ammonium) and 1.75 (carboxyl) and was thus a substantially stronger acid than IIb. In the phenylacetyl derivatives, the relative mobilities of Id and IId on paper electrophoresis at pH 2.2 indicated that the former was the more highly ionized. (c) R. R. Chauvette, E. H. Flynn, B. G. Jackson, E. R. Lavagnino, R. B. Morin, R. A. Mueller, R. P. Pioch, R. W. Roeske, C. W. Ryan, J. L. Spencer, and E. Van Heyningen, *J. Am. Chem. Soc.*, **84**, 3401 (1962), reported the pK_a of Id as 4.8. The apparent disagreement with our results might be due to the use of a different solvent system by these authors.

(11) J. D'A. Jeffery, E. P. Abraham, and G. G. F. Newton, *Biochem. J.*, **75**, 216 (1960).

(12) A similar procedure was used to elute penicillin N (synnematin B) from carbon (R. K. Clark, H. H. Fricke, and B. Lanius, in "Antibiotics Annual 1956-1957," H. Welch and F. Marti-Ibañez, Ed., Medical Encyclopedia, Inc., New York, N. Y., 1957, p. 749).

(13) Electrophoresis at pH 2.2 showed yellow zones moving 1.7 and 3.3 cm. toward the anode (IIc and Ic, respectively). Subsequent steps were designed to purify IIc before hydrolyzing it to IIb. Overnight incubation with acid did not affect IIc, but cleaved the acetyl group from Ic and converted the resulting γ-hydroxy acid to its lactone, which, lacking the strong cephalosporin nuclear carboxyl group, could be extracted into ethyl acetate at pH 4.5.

was isolated from the hydrolysate by absorption from solution at pH 6–7 onto a column of Dowex 1-X8 (acetate form) and elution with N acetic acid. The fractions showing strong absorption at 260 mμ deposited crystals which were dissolved in water by bringing to pH 8 with sodium hydroxide and reprecipitated by adding hydrochloric acid to pH 3.7. The yield of colorless product was 26 mg., m.p. 241–242° dec.

Anal. Calcd. for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08. Found: C, 44.64; H, 4.94; N, 12.98.

B.—7-Aminocephalosporanic acid (6.81 g., 0.025 mole) dissolved in 100 ml. of water containing 4.20 g. (0.05 mole) of sodium bicarbonate was hydrogenated for 1.5 hr. at 4 kg./cm.^{2} over 27 g. of 5% palladium on barium sulfate.[14] The catalyst was removed and washed with dilute sodium bicarbonate. To the dark solution were added 60 ml. of 6 N hydrochloric acid and 9 g. of charcoal. Filtration gave a clear yellow solution which was cooled in ice and brought to pH 3.7 with 2 N sodium hydroxide to precipitate 3.32 g. (62%) of light tan crystals, sufficiently pure for the preparation of derivatives. A colorless product was obtained by dissolving in 0.5 N hydrochloric acid and reprecipitating by adding sodium hydroxide to pH 3.7. An analytical sample (reprecipitated as in method A) was indistinguishable by m.p., infrared spectrum and electrophoretic mobility from material prepared by method A.

Anal. Calcd. for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08. Found: C, 44.63; H, 4.75; N, 13.03.

7-Phenylacetamidodesacetoxycephalosporanic Acid (IId).—A solution of 4.29 g. (0.02 mole) of IIb in 200 ml. of water containing 5.04 g. (0.06 mole) of sodium bicarbonate was mixed with 300 ml. of acetone and stirred at −20° while 3.71 g. (0.024 mole) of phenylacetyl chloride was added. The reaction mixture was kept at −20° for 30 min. and then at 3° for 2 hr. Two washings with ether removed the acetone. The aqueous residue was acidified with 30 ml. of 6 N hydrochloric acid and extracted twice with ethyl acetate. The extracts were washed with a little 0.5 N hydrochloric acid and evaporated to dryness. The residual foam was triturated with ether to give 5.51 g. of white solid (IId as free acid). This was dissolved in 300 ml. of 1-propanol containing 5% of water and treated with 12 ml. of 1.65 N potassium 2-ethylhexanoate[15] in 2-propanol to precipitate 5.14 g. (65%) of the colorless **potassium salt** of the product. A sample recrystallized from water–1-propanol and air-equilibrated[16] had m.p. 212–213° dec.; lactam carbonyl stretching at 5.75 μ (Nujol).

Anal. Calcd. for $C_{16}H_{15}KN_2O_4S\cdot1.5H_2O$: C, 48.35; H, 4.56; N, 7.05. Found: C, 48.18; H, 4.43; N, 7.14.

7-(2-Thienylacetamido)desacetoxycephalosporanic Acid (IIe).—A procedure similar to that described in the foregoing experiment was used to acylate 1.07 g. (0.005 mole) of IIb with 2-thienylacetyl chloride[17] and to isolate the product as the free acid (1.25 g. of white solid). This was dissolved in 80 ml. of 2-propanol containing 5% of water and 2.7 ml. of 1.8 M sodium 2-ethylhexanoate[18] in 2-propanol was added to precipitate 1.17 g. (63%) of the colorless **sodium salt**. A sample recrystallized from water–2-propanol and air-equilibrated had m.p. 231–232° dec.; lactam carbonyl stretching at 5.75 μ (Nujol).

Anal. Calcd. for $C_{14}H_{13}N_2NaO_4S_2\cdot0.5H_2O$: C, 45.52; H, 3.82; N, 7.58. Found: C, 45.50; H, 3.66; N, 7.57.

7-Ureidodesacetoxycephalosporanic Acid (IIf).—A suspension of 2.14 g. (0.01 mole) of IIb in 20 ml. of water containing 0.811 g. (0.01 mole) of potassium cyanate was stirred for 7 hr. at room temperature. Acidification of the resulting clear solution to pH 0.5 with hydrochloric acid gave 1.95 g. of white solid (IIf as free acid). This was suspended in 70 ml. of methanol and stirred at 5° while cyclohexylamine was added to pH 7.3. The solid dissolved and the solution was evaporated to a foam which was crystallized from water–*tert*-butyl alcohol to give 1.74 g. (45%) of the colorless **cyclohexylammonium salt** of the product, m.p. 173–174° dec. after air-equilibration; lactam carbonyl stretching at 5.71 μ (Nujol).

Anal. Calcd. for $C_9H_{11}N_3O_4S\cdot C_6H_{13}N\cdot H_2O$: C, 48.11; H, 7.00; N, 14.96. Found: C, 48.17; H, 6.89; N, 14.68.

Acknowledgments.—The authors are indebted to Mrs. D. A. Rolston and her staff for the microanalyses reported herein, to Dr. W. E. Thompson for valuable discussions of the interpretation of n.m.r. spectra, and to Dr. C. A. Simpson for the determination of pK_a values. They also wish to thank Miss M. Dolan and her staff for carrying out the microbiological work.

(14) From Engelhard Industries, Inc., Newark, N. J. The catalyst was a brown powder. A gray-colored palladium on barium sulfate produced by the same company gave less satisfactory results, as did palladium on carbon.

(15) German Patent 965,703 (1957).

(16) Several weeks were required for equilibration. A shorter period gave material with propanol of crystallization.

(17) 2-Thienylacetic acid (J. H. Ford, G. C. Prescott, and D. R. Colingsworth, *J. Am. Chem. Soc.*, **72**, 2109 (1950)) was converted to the acid chloride (b.p. 52° at 0.2 mm.) by refluxing with thionyl chloride in benzene.

(18) A. Gourevitch, C. T. Holdrege, G. A. Hunt, W. F. Minor, C. C. Falnigan, L. C. Cheney, and J. Lein, *Antibiot. Chemotherapy*, **12**, 318 (1962).

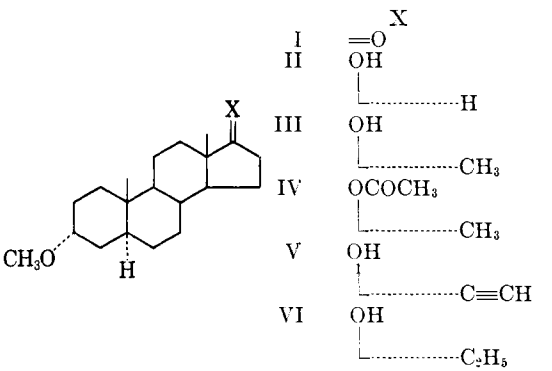
Hypocholesterolemic Agents. IV.[1] 3α-Methoxy-5α-androstane Derivatives

R. E. COUNSELL AND P. D. KLIMSTRA

Division of Chemical Research of G. D. Searle and Co., Chicago 80, Illinois

Received October 10, 1963

In 1959 Hellman and associates[2] demonstrated that the serum cholesterol levels of hypercholesterolemic patients could be reduced by the parenteral administration of androsterone (3α-hydroxy-5α-androstan-17-one). Later studies by Cohen, *et al.*,[3,4] however, showed that this hypocholesterolemic effect was not achieved when the steroid was given orally. As a consequence of these findings, a program was initiated in our Laboratories aimed at preparing an orally active androsterone analog having a good separation of hypocholesterolemic and androgenic properties. Since it had been previously shown[4,5] that orally administered androsterone is rapidly conjugated in the liver and excreted predominantly as the 3-glucuronide, it was felt that etherification of the 3α-hydroxyl group would inhibit this conjugation and lead to orally effective compounds. As a result, a series of 3α-methoxy-5α-androstane derivatives was synthesized and biologically evaluated.



The methyl ether of androsterone (I)[6] was readily prepared (74% yield) from epiandrosterone (3β-hy-

(1) Paper III: R. E. Counsell, P. D. Klimstra, and R. E. Ranney, *J. Med. Pharm. Chem.*, **5**, 1224 (1962).

(2) L. Hellman, H. L. Bradlow, B. Zumoff, D. K. Fukushima, and T. F. Gallagher, *J. Clin. Endocrinol. Metab.*, **19**, 936 (1959).

(3) W. D. Cohen, N. Higano, and R. W. Robinson, *Circulation*, **22**, 659 (1960).

(4) W. D. Cohen, N. Higano, R. W. Robinson, and R. J. LeBeau, *J. Clin. Endocrinol. Metab.*, **21**, 1208 (1961).

(5) O. Crépy, M. F. Jayle, and F. Meslin, *Compt. rend. soc. biol.*, **151**, 234 (1957).

(6) Since completion of this work, this compound has been prepared in essentially the same manner by R. Gardi, R. Vitalli, and A. Ercoli, *Gazz. Chim. Ital.*, **92**, 632 (1962).