

[CONTRIBUTION FROM THE ARTHRITIS RESEARCH LABORATORY, DEPTS. OF MEDICINE AND BIOCHEMISTRY, UNIVERSITY OF ALABAMA MEDICAL CENTER, BIRMINGHAM, ALA.]

Glycosides of 2-Acetamido-2-deoxy-D-glucosamine and Benzylidene Derivatives

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The methylation of 2-acetamido-2-deoxy-4,6-*O*-benzylidene-D-glucopyranose is a convenient method for the preparation of pure methyl α - and β -glycosides of D-glucosamine. The anomeric configuration of the glycosides depends on the solvent. New physical constants are given for 2-acetamido-2-deoxy-4,6-*O*-benzylidene-D-glucopyranose, methyl 2-acetamido-2-deoxy-4,6-*O*-benzylidene- β -D-glucopyranoside, methyl 2-acetamido-2-deoxy-3-*O*-methyl-4,6-*O*-benzylidene- β -D-glucopyranoside, methyl 2-acetamido-2-deoxy-4,6-*O*-benzylidene- α -D-glucopyranoside. The following new compounds are described: methyl 2-acetamido-2-deoxy-5,6-*O*-benzylidene- β -D-glucopyranoside, methyl 2-acetamido-2-deoxy-3-*O*-methyl-5,6-*O*-benzylidene- β -D-glucopyranoside and methyl 2-acetamido-2-deoxy-3-*O*-methyl- β -D-glucopyranoside.

Masamune and associates¹ recently have described the preparation of 2-acetamido-2-deoxy-4,6-*O*-benzylidene-D-glucose by treatment of N-acetyl-D-glucosamine with benzaldehyde and zinc chloride. The benzylidene compound was successively methylated with dimethyl sulfate in methanol to form mono- and dimethyl derivatives which were identified as methyl 2-acetamido-2-deoxy-4,6-*O*-benzylidene- β -D-glucopyranoside (IX) and methyl 2-acetamido-2-deoxy-3-*O*-methyl-4,6-*O*-benzylidene- β -D-glucopyranoside (XI).

We had studied the same reactions independently, using several solvents for the methylation reaction. The products which we obtained showed some marked differences in properties from those reported in the literature as shown in Table I. These discrepancies and the finding of previously undescribed furanose isomers necessitated a re-consideration of the structure of the compounds.

TABLE I

PHYSICAL CONSTANTS FOR SOME GLUCOSAMINE DERIVATIVES

Compound	Melting point, °C.	Optical rotation	Ref.
II	214-215 d.	+10.0° (pyridine)	1
	247-248 d.	+38.2 (pyridine)	New
IV	225	+19 (CHCl ₃)	3
	261-262	+39.5 (CHCl ₃)	New
IX	252-253 d.	-40 (CHCl ₃)	1
	278-279 d.	-63.8 ((CH ₃) ₂ SO)	New
XI	208-209 d.	-76 (CHCl ₃)	1
	310-315	-64.7 ((CH ₃) ₂ SO)	New
NIII	164-165	-58.4 (H ₂ O)	1
	229	-45.9 (H ₂ O)	New

2-Acetamido-2-deoxy-D-glucopyranose (I) was found to react with benzaldehyde to give a 4,6-benzylidene derivative (II) as described by Masamune, *et al.* On recrystallization from water, however, the crude II was separated from a contaminating isomer (III) and was transformed from a mixture of anomers to the pure β -anomer which showed a dextrorotation in pyridine.

The methylation of the benzylidene compounds II and III with dimethyl sulfate and aqueous alkali proceeded with the successive formation of mono- and dimethyl compounds. With an equimolar ratio of dimethyl sulfate to II or to III, only the anomeric OH-group was methylated.

When the reaction was carried out in dimethyl sulfoxide, the known methyl α -glycoside (IV) was

formed, independently of the α,β -configuration of the starting material II. Evidence for the structure of IV was obtained by removing the benzylidene group by the action of 60% acetic acid. The melting point and the optical rotation of the resulting methyl 2-acetamido-2-deoxy- α -D-glucopyranoside (V) agreed with corresponding data reported by Kuhn, *et al.*² A mixed melting point with this material did not show any depression. Further evidence for the structure of IV was given by its methylation with dimethyl sulfate in dioxane. The resulting compound VI could also be prepared directly from II by methylation with an excess of dimethyl sulfate in dimethyl sulfoxide.

The structure of compound VI was established by removal of the benzylidene group and comparison of the resulting compound VII with the product described by Neuberger.³ Further hydrolysis of VII with 2.5 *N* hydrochloric acid at 100° gave a substance which could be identified as the well known 3-*O*-methyl-glucosamine hydrochloride (VIII).³

Compound IV was previously described by Neuberger³ but his data reported for melting point and optical rotation were significantly different from those found in the present work. When Neuberger's procedures were repeated, the product, described as the methyl 2-acetamido-2-deoxy-4,6-*O*-benzylidene- α -D-glucopyranoside (IV), was found to be mixed with the β -glycoside IX. By fractional recrystallization, the mixture was separated and the pure α -anomer was obtained which had the same properties as when prepared from II by the procedure described above.

When the methylation of 2-acetamido-2-deoxy-4,6-*O*-benzylidene-D-glucose (II) was carried out in water solution with dimethyl sulfate and alkali, the β -glycoside IX was formed. The formation of β -glycosides under aqueous conditions has been often reported, as by Schlubach⁴ and Isbell.⁵ The structure of the methyl β -glycoside (IX) was established by removal of the benzylidene group. The resulting compound X was identical with the methyl 2-acetamido-2-deoxy- β -D-glucopyranoside described by Neuberger and Pitt-Rivers.⁶ Hydrolysis of IX with 2.5 *N* hydrochloric acid gave glucosamine hydrochloride (XII). Methylation of IX with dimethyl sulfate in dioxane yielded com-

(2) R. Kuhn, F. Zilliken and A. Gauhe, *Chem. Ber.*, **86**, 466 (1953).

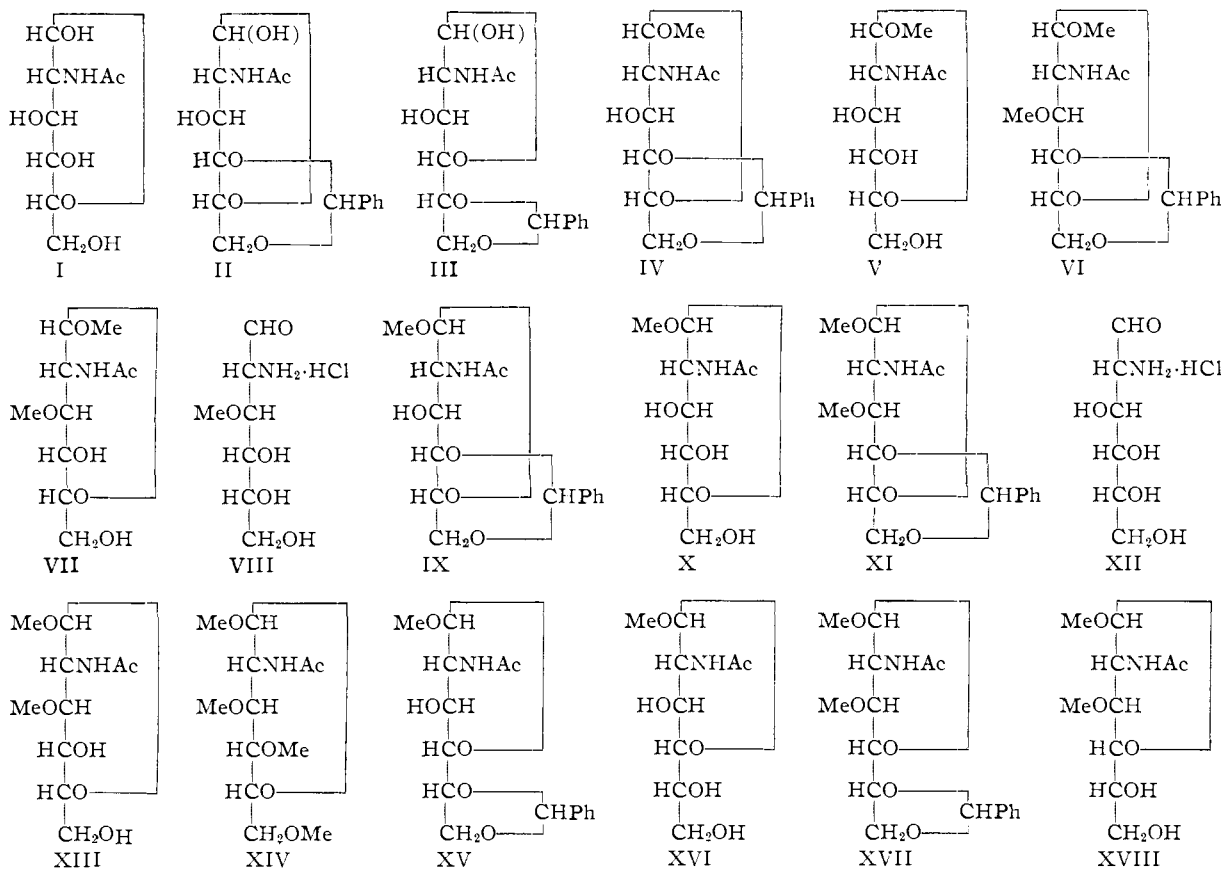
(3) A. Neuberger, *J. Chem. Soc.*, 50 (1941).

(4) H. Schlubach and K. Maurer, *Ber.*, **57**, 1686 (1924).

(5) H. S. Isbell and H. L. Frush, *J. Research Natl. Bur. Standards*, **24**, 125 (1940).

(6) A. Neuberger and R. V. Pitt-Rivers, *J. Chem. Soc.*, 122 (1939).

(1) H. Masamune, T. Okugama and H. Sinohara, *Tohoku J. Exp. Med.*, **68**, 181 (1958).



compound XI. The structure of XI was established by drastic acid hydrolysis, which produced 3-*O*-methyl-glucosamine hydrochloride (VIII). The pyranose ring for compound IX was thus established because of the relation to compounds XI, XIII and XIV; the benzylidene group of XI was removed and the resulting compound XIII was treated with an excess of dimethyl sulfate. The formed compound XIV was identical in melting point and optical rotation with known methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-methyl- β -D-glucopyranoside.⁷

The preparation of compound IX from II was accompanied by the formation of the α -isomer IV up to 10% of the total yield. This anomer could be separated by repeated recrystallizations and isolated from the mother liquors.

If the crude benzylidene compound II was used for the preparation of IX another isomer was formed in an amount of nearly 10%. It was established as the previously unknown methyl 2-acetamido-2-deoxy-5,6-*O*-benzylidene- β -D-glucopyranoside (XV) by removal of the benzylidene group with acetic acid and comparison of the resulting product XVI with the compound described by Whitehouse and Kent⁸ as methyl 2-acetamido-2-deoxy- β -D-glucopyranoside. Further evidence for its structure was given by methylation of XV with dimethyl sulfate in dioxane yielding compound XVII. The benzylidene group of XVII could be removed with acetic acid, and the resulting compound XVIII was hy-

drolyzed with hydrochloric acid yielding VIII. This result showed the presence of a free OH-group in the 3-position of XV, which by direct acid hydrolysis yielded glucosamine hydrochloride (XII).

Acknowledgment.—We are indebted to Chas. Pfizer and Co., Inc., for their gift of glucosamine and to the U. S. Public Health Service, National Institute of Arthritis and Metabolic Diseases, who supported this work (Grants A-1225, A-3555).

Experimental

2-Acetamido-2-deoxy-4,6-*O*-benzylidene- β -D-glucopyranoside (II).—N-Acetyl-D-glucosamine (8 g.) and finely powdered zinc chloride (5 g.) were suspended in 20 ml. of freshly distilled benzaldehyde and shaken for 12 hr. at room temperature. The semi-crystalline reaction mixture was agitated 3 times in 100 ml. of petroleum ether and 2 times in 100 ml. of water. The residue was then recrystallized from water (5 l.); yield 92%, m.p. 247–248° dec., $[\alpha]_D^{20} = -29.4^\circ$ (*c* 1 in $(\text{CH}_3)_2\text{SO}$ with no mutarotation in 12 hr.), -16.2° (initial, extrapolated) $\rightarrow +38.2^\circ$ (*c* 1 in pyridine, final, 24 hr.). Masamune, *et al.*,¹ reported: m.p. 214–215° dec., $[\alpha]_D^{16} + 10.0^\circ$ (*c* 1.0, pyridine, final), insoluble in water.

Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{O}_6\text{N}$: C, 58.24; H, 6.20; N, 4.53. Found: C, 57.97; H, 6.29; N, 4.60.

Methyl 2-Acetamido-2-deoxy-4,6-*O*-benzylidene- α -D-glucopyranoside (IV).—A solution of 9.27 g. (30 mmoles) of II in 50 ml. of dimethyl sulfoxide was prepared and 3.78 g. (30 mmoles) of dimethyl sulfate and 2.40 g. (60 mmoles) of sodium hydroxide dissolved in 5 ml. of water were added simultaneously over 5 min., keeping the temperature at 0°. The reaction mixture was stirred then for 30 min. at room temperature and subsequently poured in a large volume of ice-water. The precipitate was filtered off, washed with water, and recrystallized 3 times from methanol; yield 86%, m.p. 261–262°, $[\alpha]_D^{20} + 39.5^\circ$ (*c* 0.5 in chloroform). Neuberger³ reported: m.p. 225°, $[\alpha]_D + 19^\circ$ (*c* 0.5 chloroform).

(7) W. Cutler, W. Haworth and S. Peat, *J. Chem. Soc.*, 1979 (1937).

(8) M. W. Whitehouse and P. W. Kent, *Tetrahedron*, **4**, 425 (1958).

Anal. Calcd. for $C_{16}H_{21}O_6N$: C, 59.42; H, 6.56; N, 4.33. Found: C, 59.27; H, 6.51; N, 4.21.

Methyl 2-Acetamido-2-deoxy- α -D-glucopyranoside (V).—Compound IV was treated with 60% acetic acid and worked up as described for the preparation of XIII. The resulting material, recrystallized from 1-propanol, showed $[\alpha]^{20}_D + 130.1^\circ$ (c 1 in water), m.p. 189–190°. The product was pure according to paper chromatographic analysis.²

Methyl 2-Acetamido-2-deoxy-3-O-methyl-4,6-O-benzylidene- α -D-glucopyranoside (VI). (A).—To a solution of 9.27 g. (30 mmoles) of II in 50 ml. of dimethyl sulfoxide was added simultaneously 10 ml. of dimethyl sulfate and 9 g. of sodium hydroxide dissolved in 10 ml. of water. The reaction mixture was stirred for 1 hr. at 60° and then poured into 1 l. of water. The precipitate was filtered off, washed with water and recrystallized twice from alcohol; yield 96%, m.p. 280°, $[\alpha]^{20}_D + 50.4^\circ$ (c 0.5 in chloroform). Neuberger³ reported: m.p. 277–279°, $[\alpha]_D + 39^\circ$ (c 0.52 in chloroform).

Anal. Calcd. for $C_{17}H_{23}O_6N$: C, 60.51; H, 6.88; N, 4.15. Found: C, 60.82; H, 6.75; N, 4.28.

(B).—A solution of 3.2 g. (10 mmoles) of IV in 100 ml. of dioxane was treated 5 times with 3 ml. of dimethyl sulfate and 6 ml. of 30% aqueous sodium hydroxide solution at 10-min. intervals at 50° and kept at this temperature for 1 hr. The reaction mixture was then poured into a large volume of water; the precipitate was filtered off and twice recrystallized from alcohol; yield 80%, physical data like described for method A.

Methyl 2-Acetamido-2-deoxy-3-O-methyl- α -D-glucopyranoside (VII).—Compound VI was hydrolyzed with 60% acetic acid and worked up as described for the preparation of XIII; yield 60%, m.p. 213°, $[\alpha]^{20}_D + 118^\circ$ (c 1 in water).

2-Amino-2-deoxy-3-O-methyl-D-glucose Hydrochloride (VIII). (A).—A suspension of 300 mg. of XVIII in 10 ml. of 2.5 *N* hydrochloric acid was heated under reflux for 4 hr., then evaporated *in vacuo* to dryness, dissolved in water, treated with charcoal and evaporated again. The residue was dissolved in hot methanol and precipitated with acetone; yield 100 mg., $[\alpha]^{20}_D + 113^\circ$ (7 min.) $\rightarrow + 91.0^\circ$ (c 1 in water, final 18 hr.), m.p. 210–215° dec.

(B).—Substance XI was treated as described under A, yielding a compound with $[\alpha]^{20}_D + 93^\circ$ (c 2 in water, final).

Anal. Calcd. for $C_7H_{16}O_5ClN$: N, 6.10. Found: N, 6.01.

(C).—Substance VII was hydrolyzed as described under A, to give a product with $[\alpha]^{20}_D + 94^\circ$ (c 2 in water, final).

Anal. Calcd. for $C_7H_{16}O_5ClN$: N, 6.10. Found: N, 6.25.

Methyl 2-Acetamido-2-deoxy-4,6-O-benzylidene- β -D-glucopyranoside (IX).—With mild warming 9.27 g. (30 mmoles) of II was dissolved in a solution of 3.7 g. (30 mmoles) of sodium hydroxide in 50 ml. of water. Then 3.78 g. (30 mmoles) of dimethyl sulfate was added with vigorous stirring. This was continued for 1 hr. while a substance precipitated, which was filtered off, washed with water and recrystallized 3 times from methanol; yield 70%, m.p. 278–279°, $[\alpha]^{20}_D - 63.8^\circ$ (c 0.5 in $(CH_3)_2SO$). Masamune, *et al.*,¹ reported: m.p. 252–253° dec., $[\alpha]^{15}_D - 40^\circ$ (c 1 in chloroform). With our compound it was not possible to prepare a chloroform solution in a concentration of that order.

Anal. Calcd. for $C_{16}H_{21}O_6N$: C, 59.42; H, 6.56; N, 4.33. Found: C, 59.73; H, 6.42; N, 4.59.

The combined mother liquors were evaporated and the residue fractionally recrystallized from methanol. The last fractions were once more recrystallized from methanol yielding 600 mg. of the α -isomer IV, $[\alpha]^{20}_D + 38^\circ$ (c 0.5 in chloroform), m.p. 260°, showing no depression when mixed with substance IV.

Methyl 2-Acetamido-2-deoxy- β -D-glucopyranoside (X).—A suspension of 2 g. of IX in 10 ml. of 60% acetic acid was heated on a steam-bath for 30 min. and further treated as described for XIII; $[\alpha]^{20}_D - 42^\circ$ (c 2 in water), m.p. 190–191°, paper chromatographic analysis² indicated a pure substance.

Anal. Calcd. for $C_6H_{17}O_6N$: N, 5.95. Found: N, 6.04.

Methyl 2-Acetamido-2-deoxy-3-O-methyl-4,6-O-benzylidene- β -D-glucopyranoside (XI).—A solution of 1.3 g. of IX in 50 ml. of dioxane was prepared with warming and then 0.5 g. of sodium hydroxide dissolved in 3 ml. of water and 0.6 ml. of dimethyl sulfate were added. The reaction mixture was

stirred for 1 hr. at 80–90°, then evaporated *in vacuo*, the residue extracted with alcohol, again evaporated and finally twice recrystallized from methanol; yield 75%, m.p. 310–315°, $[\alpha]^{20}_D - 64.7^\circ$ (c 0.5 in $(CH_3)_2SO$).

Anal. Calcd. for $C_{17}H_{23}O_6N$: C, 60.51; H, 6.88; N, 4.15. Found: C, 60.43; H, 7.00; N, 4.18.

Masamune, *et al.*,¹ reported: m.p. 208–209° dec., $[\alpha]^{15}_D - 76.0^\circ$ (c 1 in chloroform).

2-Amino-2-deoxy-D-glucose Hydrochloride (XII). (A).—A suspension of 2 g. of IX in 20 ml. of 2.5 *N* hydrochloric acid was heated under reflux for 4 hr., treated with activated carbon, evaporated *in vacuo*, dissolved in hot methanol and precipitated by addition of acetone; $[\alpha]^{20}_D + 93^\circ \rightarrow + 72^\circ$ (c 2 in water).

Anal. Calcd. for $C_6H_{14}O_5ClN$: N, 6.50. Found: N, 6.34.

(B).—Compound XV was hydrolyzed as described under A, yielding a salt with $[\alpha]^{20}_D + 95^\circ \rightarrow + 74^\circ$ (c 2 in water).

Anal. Calcd. for $C_6H_{14}O_5ClN$: N, 6.50. Found: N, 6.27.

Methyl 2-Acetamido-2-deoxy-3-O-methyl- β -D-glucopyranoside (XIII).—A suspension of 3 g. of XI in 20 ml. of 60% acetic acid was heated on a steam-bath for 30 min. The solution, which soon became clear, was then evaporated *in vacuo*, dissolved in water, treated with activated carbon, evaporated again under reduced pressure, and recrystallized finally from alcohol; yield 60%, m.p. 229°, $[\alpha]^{20}_D - 45.9^\circ$ (c 2 in water). Masamune, *et al.*,¹ reported: m.p. 164–165°, $[\alpha]^{15}_D - 58.4^\circ$ (c 1.4 in water).

Anal. Calcd. for $C_{16}H_{21}O_6N$: C, 48.17; H, 7.70; N, 5.62. Found: C, 47.75; H, 7.60; N, 5.56.

Methyl 2-Acetamido-2-deoxy-3,4,6-tri-O-methyl- β -D-glucopyranoside (XIV).—A solution of 2.5 g. of XIII in 20 ml. of water was heated to 50°, and 5 g. of dimethyl sulfate was added simultaneously with 10 ml. of 30% aqueous sodium hydroxide solution during the course of 15 min. With continuous stirring, the reaction mixture was kept at this temperature for 1 hr., then heated at 100° for 30 min. and extracted three times with chloroform. The combined extracts, were dried, evaporated and the residues recrystallized from ethyl acetate; yield 50%, m.p. 192–193°, $[\alpha]^{20}_D + 20.3^\circ$ (c 0.3 in chloroform).

Anal. Calcd. for $C_{12}H_{23}O_6N$: N, 5.05. Found: N, 5.23.

Methyl 2-Acetamido-2-deoxy-5,6-O-benzylidene- β -D-glucopyranoside (XV).—The mother liquor of IX prepared from crude compound II (not recrystallized from water) was concentrated to a gel which was dissolved in hot 1-propanol. The crystals which precipitated by cooling were fractionated by recrystallization from methanol. The first fractions, yielding 8% based on compound II, showed a m.p. 296°, $[\alpha]^{20}_D - 71.3^\circ$ (c 0.5 in $(CH_3)_2SO$).

Anal. Calcd. for $C_{16}H_{21}O_6N$: C, 59.42; H, 6.56; N, 4.33. Found: C, 59.50; H, 6.47; N, 4.49.

Methyl 2-Acetamido-2-deoxy- β -D-glucopyranoside (XVI).—Compound XV was treated with acetic acid and worked up as described for XVIII. The resulting sirup was dissolved in hot isopropyl alcohol, forming white crystals when cooled; m.p. 198–199°, $[\alpha]^{20}_D - 27.4^\circ$ (c 2 in water). Whitehouse and Kent³ reported: m.p. 193°, $[\alpha]^{22}_D - 25^\circ$, -20° (c 0.8 in water).

Anal. Calcd. for $C_6H_{17}O_6N$: C, 45.94; H, 7.30; N, 5.95. Found: C, 46.07; H, 7.30; N, 6.10.

Methyl 2-Acetamido-2-deoxy-3-O-methyl-5,6-O-benzylidene- β -D-glucopyranoside (XVII).—A solution of 1.6 g. of XV in 50 ml. of dioxane was prepared and 0.6 g. of sodium hydroxide, dissolved in 5 ml. of water, and 0.7 ml. of dimethyl sulfate were added with stirring. After heating for 1 hr. at 60° the reaction mixture was concentrated *in vacuo* and the residue recrystallized twice from methanol (300 ml.); yield 60%, m.p. 273°, $[\alpha]^{20}_D - 66.4^\circ$ (c 1 in $(CH_3)_2SO$).

Anal. Calcd. for $C_{17}H_{23}O_6N$: C, 60.51; H, 6.88; N, 4.15. Found: C, 60.12; H, 6.79; N, 4.09.

Methyl 2-Acetamido-2-deoxy-3-O-methyl- β -D-glucopyranoside (XVIII).—In 10 ml. of 60% acetic acid 500 mg. of XVII was suspended and heated on a steam-bath until the solution became clear (10 min.). Then the solution was evaporated *in vacuo* to dryness, dissolved in 10 ml. of water, treated with

charcoal, and evaporated again under reduced pressure; yield 300 mg., m.p. 182–184°, $[\alpha]_D^{20}$ -31° (*c* 1 in water).

Anal. Calcd. for C₁₉H₁₉O₆N: C, 48.17; H, 7.70; N, 5.62. Found: C, 48.01; H, 7.61; N, 5.52.

[CONTRIBUTION FROM THE RESEARCH DIVISION OF THE SCHERING CORP.]

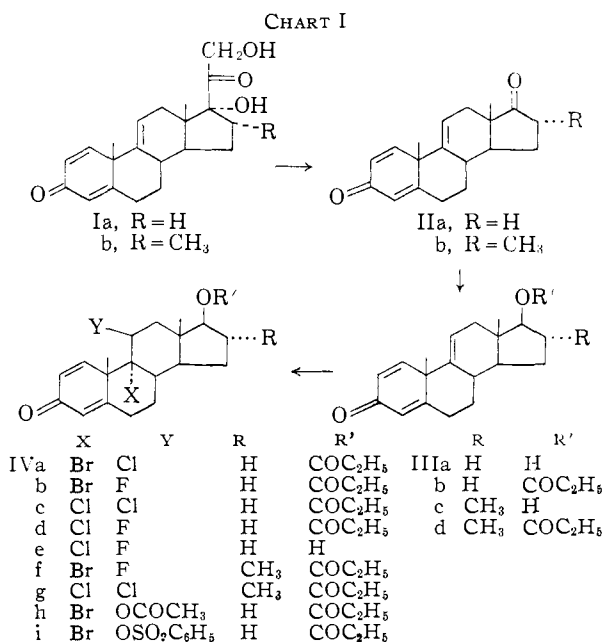
New Anabolic Agents: 9 α ,11 β -Dihalogenoandrostande Derivatives

BY C. H. ROBINSON, L. E. FINCKENOR, R. TIBERI, M. EISLER, R. NERI, A. WATNICK, P. L. PERLMAN, P. HOLROYD, W. CHARNEY AND EUGENE P. OLIVETO¹

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A number of 9 α ,11 β -dihalogeno derivatives of testosterone, 1-dehydrotestosterone, methyltestosterone and 1-dehydro-methyltestosterone have been synthesized. Some of these compounds possess favorable anabolic-androgenic ratios.

The synthesis of 19-nortestosterone² in 1950 (and the subsequently recognized fact³ that this compound showed a favorable anabolic-androgenic ratio relative to testosterone) marked the beginning of an intensive search⁴ for anabolic agents in both the androstane and estrane series.



In view of the physiological activity manifested by 9,11-dihalogencorticoids⁵ and progestins,⁶ the preparation and biological evaluation of the corresponding androstane analogs were undertaken in these laboratories. As will be shown in the sequel, this new class of hormone analogs provides yet an-

(1) C. H. Robinson, L. E. Finckenor, R. Tiberi and Eugene P. Oliveto (Natural Products Research Dept.); M. Eisler, R. Neri, A. Watnick and P. L. Perlman (Biochemistry Dept.); P. Holroyd and W. Charney (Industrial Microbiology Dept.).

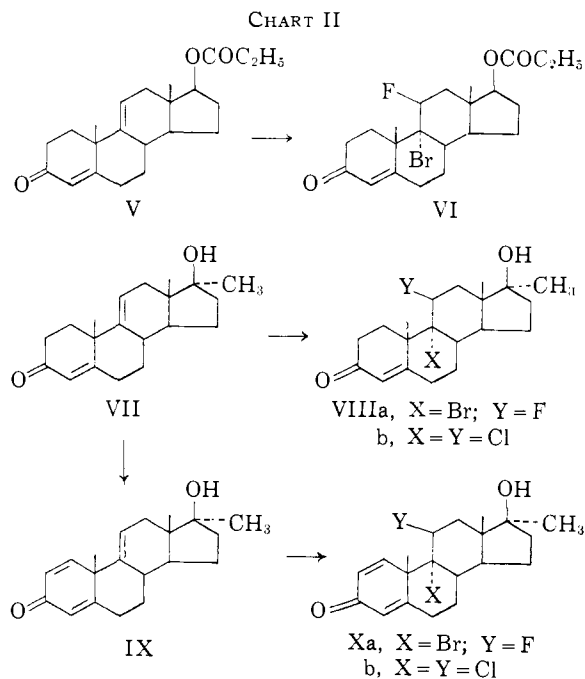
(2) A. J. Birch, *J. Chem. Soc.*, 367 (1950).

(3) (a) L. G. Hershberger, E. G. Shipley and R. K. Meyer, *Proc. Soc. Exper. Med.*, **83**, 175 (1953); (b) R. S. Stafford, B. J. Bowman and K. J. Olsen, *ibid.*, **86**, 322 (1954); (c) F. J. Saunders and V. A. Drüll, *Endocrinol.*, **58**, 567 (1956).

(4) (a) For pertinent references see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publ. Corp., New York, N. Y., 1959, p. 592 *et seq.* (b) See also R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts and A. Arnold, *THIS JOURNAL*, **81**, 1513 (1959).

(5) C. H. Robinson, L. Finckenor, E. P. Oliveto and D. H. Goodd, *ibid.*, **81**, 2191 (1959).

(6) H. Reimann, E. P. Oliveto, R. Neri, M. Eisler and P. Perlman, *ibid.*, **82**, 2308 (1960).



other example of physiologically active 9 α ,11 β -dihalogeno steroids.

The androstatrienediones IIa and IIb served as starting materials for the key intermediates IIIb and IIIc, which led to a series of 9,11-disubstituted derivatives of 1-dehydrotestosterone propionate.

Thus, enzymic reduction^{7,8} at C-17 of 1,4,9(11)-androstatriene-3,17-dione⁹ proceeded uneventfully in 55% yield, to give 1,4,9(11)-androstatriene-17 β -ol-3-one (IIIa) which was converted to the 17 β -propionate IIIb.

The preparation of 16 α -methyl-1,4,9(11)-androstatriene-3,17-dione (IIb) from 16 α -methyl-1,4,9(11)-pregnatriene-17 α ,21-diol-3,20-dione-21-acetate¹⁰ followed conventional procedures (*i.e.*, hydrolysis to the 21-alcohol followed by sodium bismuthate degradation), and reduction by yeast then afforded the desired 17 β -ol IIIc and thence the 17 β -propionate IIIb.

(7) L. Mamoli and A. Vercellone, *Ber.*, **70**, 470 (1937).

(8) H. L. Herzog, M. A. Jevnik, P. L. Perlman, A. Nobile and E. B. Hershberg, *THIS JOURNAL*, **75**, 266 (1953).

(9) B. J. Magerlein and J. A. Hogg, *ibid.*, **80**, 2220 (1958).

(10) E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **81**, 4431 (1959).