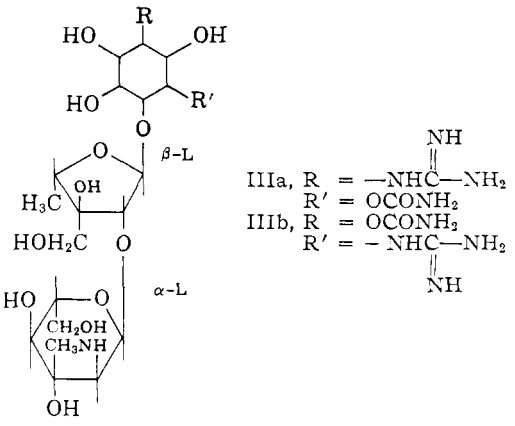
only the impure amorphous free methyl dihydrostreptobiosaminide has been described, no further comparison of data could be made.

An authentic sample of methyl dihydrostreptobiosaminide was now obtained crystalline from the methanolysis of dihydrostreptomycin trihydrochloride, and shown to be indistinguishable from I [m.p. and mixed m.p. 108–111°, $[\alpha]^{25}D$ −147° (*c*, 1, water)]. Acetylation gave α-methyl pentaacetyldihydrostreptobiosaminide,[5] identical with II [m.p. and mixed m.p., 197–198.5°, $[\alpha]^{25}D$ −120° (*c*, 1, chloroform)].

Degradation of I with concentrated hydrochloric acid gave an aminosugar which afforded (acetic anhydride–pyridine) a crystalline pentaacetate, m.p. 161–162°, $[\alpha]^{25}D$ −101° (*c*, 1, chloroform), identical with an authentic sample of pentaacetyl N-methyl-α-L-glucosamine.[6a]

Final confirmation of the structure of I was obtained by the mercaptolysis of bluensomycin dihydrochloride in ethyl mercaptan. Separation of bluensidine carbonate from the ethyl thioglycoside was achieved by carbon chromatography, and the amorphous product gave a crystalline pentaacetate, m.p. 115.5–116.5°, $[\alpha]^{25}D$ −170°, (*c*, 1, chloroform). Authentic ethyl pentacetylthiodihydrostreptobiosaminide[7] was obtained by the corresponding mercaptolysis of methyl dihydrostreptobiosaminide and acetylation, and the two samples proved to be identical in all respects.

Data presented in this and the previous communication point to a structure for bluensomycin in which bluensidine is linked glycosidically to dihydrostreptobiosamine by condensation of one of the four hydroxyl groups present in bluensidine with the hemi-acetal hydroxyl group present in dihydrostreptobiosamine. Comparative periodate oxidation of bluensomycin and dihydrostreptomycin hydrochlorides, which are identical in the disaccharide portion of their respective molecules, showed that both antibiotics consumed the same amount of periodate with identical rates and with production of the same amount of acid. This indicates that one glycol grouping is present in the bluensidine part of bluensomycin as it is in the streptidine part of dihydrostreptomycin. When dihydrostreptomycin and bluensomycin hydrochlorides were hydrolyzed with *N* aqueous hydrochloric acid at room temperature, the specific rotations of the solutions decreased from initial values of −93 and −92° to constant values of −73 and −71°, respectively, obtained after 52 hr. Under the conditions of hydrolysis, these antibiotics are cleaved to dihydrostreptobiosamine and to streptidine (optically inactive) and bluensidine ($[\alpha]^{25}D$ + 0.5 to 1.5°), respectively. This indicates that the glycosidic bond between bluensidine and dihydrostreptobiosamine in bluensomycin has the same configuration[8] as that between streptidine and dihydrostreptobiosamine in dihydrostreptomycin, limiting the possible structures for bluensomycin to IIIa and IIIb. It is of considerable interest that bluensomycin is the first member of the streptomycin family in which it has been found that the streptidine moiety has been replaced by



a different, though biogenetically-related, guanidine-containing base.

Acknowledgments.—The authors are grateful to Dr. R. W. Rinehart and associates for analyses and to Mr. K. T. Geipel for technical assistance.

RESEARCH LABORATORIES
THE UPJOHN COMPANY B. BANNISTER
KALAMAZOO, MICHIGAN A. D. ARGOUDELIS

RECEIVED NOVEMBER 30, 1962

ABNORMAL DIRECTION OF RING-OPENING OF A 2,3-ANHYDROFURANOSIDE[1a]

Sir:

The 2,3-anhydrofuranose sugars are some of the most useful intermediates for the preparation of unusual nucleosides and sugars. As examples the synthesis of 2′-deoxyadenosine,[2] of 9-(β-D-arabinofuranosyl)-adenine,[3] and of puromycin[4] all utilized a 2,3-anhydrofuranoside derivative as a key intermediate. In all cases studied to date, the opening of such a sugar or nucleoside epoxide by a nucleophile has occurred very predominantly at C.3[5] so that this has been accepted as the essentially invariable result of 2,3-anhydrofuranoside-opening: a rationalization of this reaction course has been presented.[6] This manuscript reports the first exception to this rule of very predominant C.3 opening of a 2,3-anhydrofuranoside.

The reaction of sodium benzyl mercaptide with methyl 2,3-anhydro-β-D-lyxofuranoside (III)[7] gave an essentially quantitative yield of a sirup that was treated with *p*-nitrobenzoyl chloride in pyridine. Fractional crystallization of the acylated mixture afforded two crystalline esters,[8] m.p. 91–92°, $[\alpha]^{25}D$ −114° (2% in chloroform) and m.p. 139–140°, $[\alpha]^{25}D$ +11° (2% in chloroform). The assignment of structures I and IV, respectively, to these two compounds was based on the comparison of their n.m.r. spectra with those of the corresponding diols (II and V) obtained by saponification, and of the corresponding diacetates.

(1) (a) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. (b) Istituto di Chimica Farmaceutica e Tossicologica, Università di Roma (Italy); holder of a NATO fellowship during 1962.

(2) C. D. Anderson, L. Goodman and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 3967 (1959).

(3) W. W. Lee, A. Benitez, L. Goodman and B. R. Baker, *ibid.*, **82**, 2648 (1960).

(4) B. R. Baker, R. E. Schaub, J. J. Joseph and J. H. Williams, *ibid.*, **76**, 4044 (1954).

(5) See C. D. Anderson, L. Goodman and B. R. Baker, *ibid.*, **81**, 898 (1959), for a discussion of this point.

(6) R. E. Schaub and M. J. Weiss, *ibid.*, **80**, 4683 (1958).

(7) B. R. Baker, R. E. Schaub and J. H. Williams, *ibid.*, **77**, 7 (1955).

(8) Satisfactory analytical data were obtained for all the compounds reported herein.

(3) I. R. Hooper, L. H. Klemm, W. J. Polglase and M. L. Wolfrom, *J. Am. Chem. Soc.*, **68**, 2163 (1946); **69**, 1052 (1947).

(4) Q. R. Bartz, J. Controulis, H. M. Crooks, Jr., and M. C. Rebstock, *ibid.*, **68**, 2163 (1946).

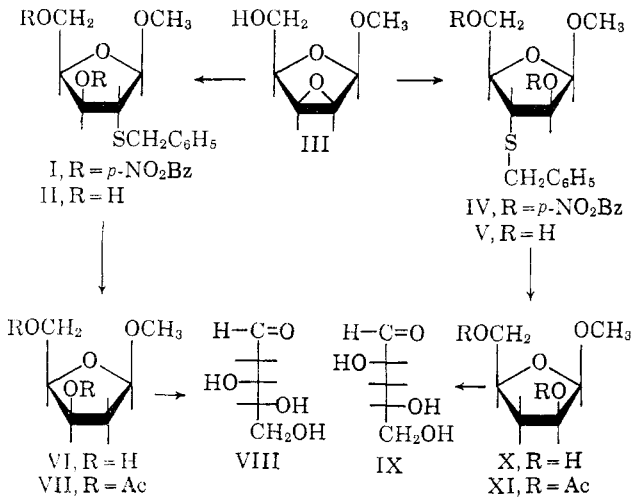
(5) N. G. Brink, F. A. Kuehl, Jr., E. H. Flynn and K. Folkers, *ibid.*, **68**, 2557 (1946).

(6) J. Fried and O. Wintersteiner, *ibid.*, **69**, 79 (1947).

(6a) Prepared from N-methyl-L-glucosamine, kindly provided by Dr. H. E. Renis of The Upjohn Company.

(7) R. V. Lemieux, W. J. Polglase, C. W. DeWalt and M. L. Wolfrom, *J. Am. Chem. Soc.*, **68**, 2747 (1946).

(8) M. L. Wolfrom, M. J. Cron, C. W. DeWalt and R. M. Husband, *ibid.*, **76**, 3675 (1954).



The optical rotation of the mixture of *p*-nitrobenzoates derived from the reaction of sodium benzyl mercaptide and the epoxide (III) indicated that approximately a 60:40 mixture of II and V, respectively, was formed in the ring-opening of III, *as the result of predominant attack at C.2.*

In order to provide chemical proof of structure, the diols (II and IV) were desulfurized with Raney nickel, affording, after acetylation, the acetates VII, isolated as a liquid by preparative gas chromatography,[9] and XI as a solid, m.p. 63–64°. The n.m.r. spectra of the desulfurized compounds were in complete agreement with their assignments as 2-deoxy- and 3-deoxyglycosides, respectively. Thus the C.1 proton signal of the 2-deoxy acetate (VII) appeared as a pair of doublets while that of the 3-deoxyacetate (XI) was found as a well-resolved doublet. These acetates were deacetylated to the deoxyfuranosides (VI and X), and hydrolyzed to the free sugars (VIII and IX). The α-benzylphenylhydrazone of 2-deoxy-D-*threo*-pentose (VIII) agreed in properties with the derivative reported in the literature[10] and the α-benzylphenylhydrazone of 3-deoxy-D-*threo*-pentose (IX), a new sugar, was a crystalline solid, m.p. 86–87°.

Clearly the assumption of invariable predominant opening of a 2,3-anhydrofuranoside at C.3 can lead to an incorrect structure assignment.

Studies are in progress to determine whether the disulfonate esters of II and V will provide a common episulfonium ion intermediate for further transformations.

(9) The desulfurization of II, but not of V, led to appreciable amounts of furfuryl acetate.

(10) F. Weygand and H. Wolz, *Ber.*, **85**, 256 (1952); G. Rembarz, *ibid.*, **95**, 1565 (1962).

LIFE SCIENCES RESEARCH GIOVANNI CASINI[1b]
STANFORD RESEARCH INSTITUTE
MENLO PARK, CALIFORNIA LEON GOODMAN

RECEIVED NOVEMBER 1, 1962

16-METHYLATED STEROIDS. IV. 6,16α-DIMETHYL-Δ⁶-HYDROCORTISONE AND RELATED COMPOUNDS

Sir:

The unrelenting search for an antiinflammatory steroid with superior therapeutic properties had led to intense synthetic effort during the last decade. It has been shown that a number of substituents on the hydrocortisone molecule, including methyls at C-2,[1] 6[2] and 16,[3,4,5] fluorine at C-6[6], 9[7] and 16[8] and a double bond at C-1[9] have increased the antiinflammatory potency of the parent compound.

We wish to report a number of compounds having a methyl group at C-16 in combination with a Δ⁶-6-methyl group showing pronounced activity, which is retained to a substantial degree by the corresponding 21-desoxy derivatives. Particularly interesting are the [3,2-c]-2′-phenylpyrazole[10] X of 6,16α-dimethyl-Δ⁶-hydrocortisone and the corresponding 21-deoxy derivative XVI which show anti-inflammatory activities in rats of 550 and 350 times hydrocortisone, respectively. Furthermore the [3,2-c]-2′-phenylpyrazole XII of 9α-fluoro-6,16α-dimethyl-Δ⁶-hydrocortisone is by far the most potent corticoid ever reported. This compound is 2000 × hydrocortisone in the rat systemic granuloma assay.

Although the introduction of a double bond between C-6 and C-7 causes a reduction of the glucocorticoid activity of hydrocortisone by a factor of two,[11] this is not observed with 16α-methylated steroids.[12] For example the antiinflammatory activity of 9α-fluoro-16α-methyl-1,4,6-pregnatriene-11β,17α,21-triol-3,20-dione 21-acetate (Δ⁶-dexamethasone), I, m.p. 204–209°; $\alpha^{23}D$ +55° ($CHCl_3$): ultraviolet λ_{max}^{MeOH} 219, 248, 298 mμ, ε 13,000, 9,850, 11.500; (*Anal.* Found: C, 66.21; H, 6.73), prepared in low yield from dexamethasone[13]) II by chloranil dehydrogenation[14] was approximately equal to the parent compound. A similar result was obtained with 9α-fluoro-16α-methyl-4,6-pregnadiene-11β,-17α,21-triol-3,20-dione 21-acetate III, m.p. 235–241°: $\alpha^{25}D$ +112° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 281 mμ, ε 27,100; (*Anal.* Found: C, 66.56; H, 7.33), prepared from 16α-methylhydrocortisone *via* chloranil dehydrogenation[14] at C-6 followed by dehydration at C-11[13] and elaboration of the C-ring fluorohydrin system.[7,15]

Combination of the Δ⁶-function with a C-6 methyl group afforded a number of surprisingly active antiinflammatory agents.

Reaction of 6α,16α-dimethyl-17α,20,20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one[16] with chloranil[14] afforded the C-6 unsaturated derivative IV, m.p. (dec.) 294–295°; $\alpha^{25}D$ +35° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 290 mμ, ε 22,900; (*Anal.* Found: C, 69.95; H, 8.03), which after reaction with 60% formic acid[17] and acetylation at C-21 afforded 6,16α-dimethyl-4,6-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate, V, m.p. 208–210°; $\alpha^{26}D$ +180° ($CHCl_3$); ultraviolet λ_{max}^{MeOH}

(1) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955).

(2) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *ibid.*, **78**, 6213 (1956).

(3) G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff and L. H. Sarett, *ibid.*, **80**, 3160 (1958).

(4) D. Taub, R. D. Hoffsommer, H. L. Slates and N. L. Wendler, *ibid.*, **80**, 4435 (1958).

(5) E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **80**, 4428 (1958).

(6) A. Bowers and H. J. Ringold, *ibid.*, **80**, 4423 (1958).

(7) J. Fried and E. F. Sabo, *ibid.*, **76**, 1455 (1954); **79**, 1130 (1957).

(8) B. J. Magerlein, R. D. Birkenmeyer and F. Kagan, *ibid.*, **82**, 1252 (1960).

(9) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955).

(10) R. Hirschmann, N. G. Steinberg, P. Buchschacher, J. H. Fried, G. J. Kent and M. Tishler, *J. Am. Chem. Soc.*, **85**, 120 (1963); *cf.* R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts and A. Arnold, *ibid.*, **81**, 1513 (1959).

(11) S. Tolksdorf, M. L. Battin, J. W. Cassidy, R. M. MacLeod, F. H. Warren and P. L. Perlman, *Proc. Soc. Exptl. Biol. Med.*, **92**, 207 (1956).

(12) This was first established with 16α-methyl-4,6-pregnadiene-11β,17α,-21-triol-3,20-dione acetate. Unpublished results of J. Korntved, D. R. Hoff and G. E. Arth of these laboratories.

(13) G. E. Arth, J. H. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958).

(14) E. J. Agnello and G. D. Laubach, *ibid.*, **79**, 1257 (1957).

(15) R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, *ibid.*, **78**, 4956 (1956).

(16) M. Sletzinger and W. Gaines, to be published.

(17) R. E. Beyler, R. M. Moriarty, Frances Hoffman and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).