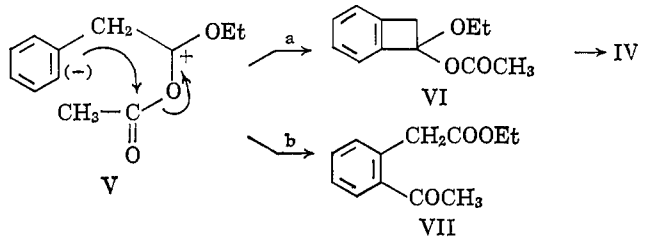
cyclobutenone (IV).[8] Comparison with an authentic sample prepared by the oxidation of benzocyclobutenol[8] confirmed the identity. The ketone undoubtedly arises from breakdown of the intermediate ethoxyacetoxybenzocyclobutene (VI). The main component of the reaction, m.p. 65.5–66° (25%), was identified as the ethyl ester of *o*-acetylphenylacetic acid (VII) by comparison with an authentic sample prepared by esterification of the known acid.[9] *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 70.05; H, 6.82.



In the above reactions with electron-rich olefinic systems, benzyne appears to behave as an electrophilic agent, forming an intermediate such as V. Collapse of V to the four-membered ring (path a) or intramolecular acylation (path b, arrows) represent alternate reaction paths. Further studies on this aspect of benzyne chemistry are in progress.

(8) M. P. Cava, D. Mangold, and K. Muth, *J. Org. Chem.*, **29**, 2947 (1964).
(9) J. O. Halford and B. Weissmann, *ibid.*, **18**, 30 (1953).
(10) National Science Foundation Cooperative Fellow, 1962–1965.

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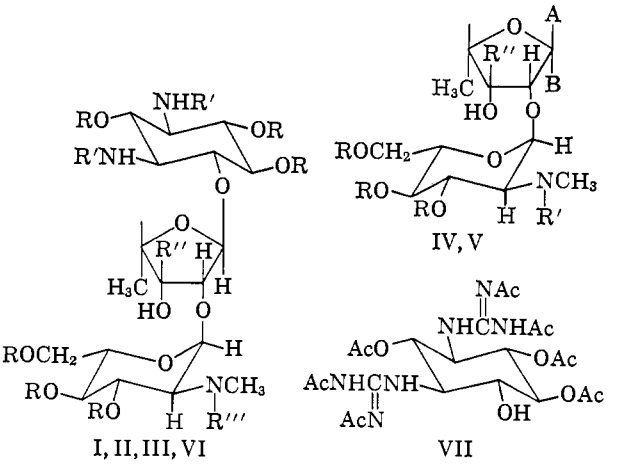
The Anomeric Linkage of Streptose in Streptomycin and Bluensomycin

Sir:

With the assignment of absolute stereochemistry to the substituted streptidine fragment of streptomycin[1a,2] and confirmation of the previously assigned[3] stereochemistry of the streptose fragment by its synthesis,[4] the structure of this medicinally important antibiotic appeared to be complete[1a,b] except for the anomeric configuration of streptose in its attachment to streptidine. The usually quoted[1a,b] assignment is β-L-,[5] made in 1954[6] from rotational arguments on polybenzoyl derivatives, though the 1947 assignment of α-L- configuration,[7] based on rotations of polyacetyl derivatives, appears now to have greater validity. We present nuclear magnetic resonance evidence here which assigns as α-L- the anomeric configuration of streptose in its attachment to streptidine in streptomycin (reversing the 1954 assignment[6] but agreeing with the 1947 assignment)[7] and related evidence which confirms as α-L- the earlier[6,7] stereochemical assignment of the anomeric configuration of N-methyl-L-glucosamine in its attachment to streptose.

The nuclear magnetic resonance spectra[8] of dihydrostreptomycin (I), of dihydrostreptomycin sulfate, of streptomycin (II) sulfate, and of tri-N-acetyldideguanyldihydrostreptomycin (III) contain two signals in the anomeric proton region (Table I). The signal for the anomeric proton of the N-methyl-L-glucosamine fragment is, predictably, shifted downfield in the sulfate and, less predictably, shifted upfield in the N-acetylated compounds. Its coupling constant ($J \sim 3.0$ c.p.s.) corresponds clearly to an axial–equatorial (but not axial–axial) H-1–H-2 relationship and thus to the α-L- configuration for N-methyl-L-glucosamine, in agreement with that previously assigned from rotational arguments.[6,7] Of greater interest, the anomeric proton of streptose, found near τ 4.70 in all compounds, occurs as a broad singlet ($J \leq 1$ c.p.s.). In accordance with the previously enunciated rule,[9] this can only be the case when the C-1 and C-2 protons of a furanoside are *trans* to one another. Since streptose has been established[3,4] to have the L-*lyxo* configuration, a C-1 proton *trans* to the C-2 proton corresponds to the α-L- configuration for streptose, and the complete stereochemical formula for dihydrostreptomycin (I) (and for streptomycin, II, which can be reduced to dihydrostreptomycin) is that shown.[10]



I, R = R‴ = H; R′ = C(=NH)NH$_2$; R″ = CH_2OH
II, R = R‴ = H; R′ = C(=NH)NH$_2$; R″ = CHO
III, R = H; R′ = R‴ = Ac; R″ = CH_2OH
IV, R = H; R′ = Ac; R″ = CH_2OH
a, A = OCH_3; B = H; b, A = H; B = OCH_3
V, R = R′ = Ac; R″ = CH_2OAc
a, A = OCH_3; B = H; b, A = H; B = OCH_3
VI, R = R‴ = Ac; R = C(=NAc)NHAc; R″ = CH_2OAc

Application of Hudson's rules[5,11] to compound III allows the same conclusion (that streptose has the

(1) (a) J. R. Dyer and A. W. Todd, *J. Am. Chem. Soc.*, **85**, 3896 (1963). This reference provides a concise review of earlier streptomycin chemistry. (b) Other recent reviews of streptomycin chemistry: H. Umezawai, "Recent Advances in Chemistry and Biochemistry of Antibiotics," Microbial Chemistry Research Foundation, Tokyo, 1964, p. 67; J. D. Dutcher, *Advan. Carbohydrate Chem.*, **18**, 360 (1963).
(2) S. Tatsuoka, S. Horii, K. L. Rinehart, Jr., and T. Nakabayashi, *J. Antibiotics* (Tokyo), **A17**, 88 (1964).
(3) F. A. Kuehl, Jr., M. N. Bishop, E. H. Flynn, and K. Folkers, *J. Am. Chem. Soc.*, **70**, 2613 (1948).
(4) J. R. Dyer, W. E. McGonigal, and K. C. Rice, *ibid.*, **87**, 654 (1965).
(5) The terms "α-L-" and "β-L-" are employed in accordance with the Hudson nomenclature convention [C. S. Hudson, *ibid.*, **31**, 66 (1909)].
(6) M. L. Wolfrom, M. J. Cron, C. W. DeWalt, and R. M. Husband, *ibid.*, **76**, 3675 (1954).
(7) (a) R. U. Lemieux, C. W. DeWalt, and M. L. Wolfrom, *ibid.*, **69**, 1838 (1947); (b) R. U. Lemieux and M. L. Wolfrom, *Advan. Carbohydrate Chem.*, **3**, 337 (1948).
(8) N.m.r. spectra were determined on deuterium oxide solutions at 20°, employing the methyl signal of 3-trimethylsilyl-1-propanesulfonic acid as standard.
(9) K. L. Rinehart, Jr., W. S. Chilton, M. Hichens, and W. von Phillipsborn, *J. Am. Chem. Soc.*, **84**, 3216 (1962).
(10) The proton of the streptose C-3 formyl group of II (see Table I), in the hemiacetal or hydrate form, appears as a sharp singlet at τ 4.93.
(11) C. S. Hudson, *J. Am. Chem. Soc.*, **38**, 1566 (1916); **46**, 483 (1924).

Table I. Chemical Shifts and Coupling Constants

Compd.	N-Methyl-L-glucosamine H-1 τ	N-Methyl-L-glucosamine H-1 J, c.p.s.	Streptose H-1 τ	Streptose H-1 J, c.p.s.	Streptose 3-Formyl τ	Streptose 3-Formyl J, c.p.s
I	4.80	3.0	4.73	Singlet		
I sulfate	4.46	3.0	4.68	Singlet		
II sulfate	4.43	3.5	4.69	Singlet	4.93	Singlet
III	4.99	3.0	4.73	Singlet		
IVa	4.96	2.6	5.01	1.5		
IVb	4.99	3.0	5.06	4.7		

α-L- configuration in streptomycin) to be reached on rotational grounds. Compound III was prepared by the following reaction sequence. Deguanylation[12] of dihydrostreptomycin sulfate gave dideguanyldihydrostreptomycin bicarbonate, m.p. 157°, $[\alpha]^{26}D$ −119° (*c* 2.0, water),[13,14] which was polyacetylated,[12,14] then de-O-acetylated by barium methoxide in dry methanol during 20 hr. at room temperature. Repeated recrystallization of the product from ethanol gave microcrystalline tri-N-acetyldideguanyldihydrostreptomycin (III)[15] hemiethanolate, m.p. 196–198°, $[\alpha]^{26}D$ −100° (*c* 2.0, water), R_{Gm} 0.5[16] [*Anal.* Calcd. for $C_{24}H_{43}N_3O_{15}\cdot 0.5C_2H_5OH$: C, 47.27; H, 7.28; N, 6.59. Found: C, 47.51; H, 7.31; N, 6.55], whose infrared spectrum (KBr pellet) showed amide (but no ester) carbonyl absorption at 1640 cm.$^{-1}$.

The requisite methyl N-acetyldihydrostreptobiosaminide anomers (IVa and IVb) were obtained by the following sequence. Dihydrostreptomycin sulfate was methanolyzed[17] and the mixture of methyl dihydrostreptobiosaminide anomers was acetylated and separated[18] into the ether-insoluble methyl pentaacetyl-α-L-dihydrostreptobiosaminide (Va), m.p. 197°, $[\alpha]^{25}D$ −120° (*c* 2.0, $CHCl_3$), and the ether-soluble methyl pentaacetyl-β-L-dihydrostreptobiosaminide (Vb), m.p. 155°, $[\alpha]^{25}D$ −37° (*c* 2.0, $CHCl_3$).[13,18] Treatment of the pentaacetyl methyl α-glycoside with barium methoxide at room temperature for 48 hr. gave methyl N-acetyl-α-L-dihydrostreptobiosaminide (IVa) hemihydrate, $[\alpha]^{27}D$ −160° (*c* 2.0, water), R_f 0.495 (*n*-BEW 415), R_{Gm} 3.5[16] [*Anal.* Found: C, 47.70; H, 7.47; N, 3.35], while treatment of the pentaacetyl methyl β-glycoside with ammonia-saturated anhydrous methanol for 48 hr. at room temperature gave methyl N-acetyl-β-L-dihydrostreptobiosaminide hemihydrate (IVb), $[\alpha]^{27}D$ −32° (*c* 2.0, water), R_f 0.432 (*n*-BEW 415), R_{Gm} 3.3[16] [*Anal.* Found: C, 47.82; H, 7.26; N, 2.89].[19]

(12) W. J. Polglase, *J. Org. Chem.*, 27, 1923 (1962).
(13) These physical properties are in excellent agreement with values in the cited reference.
(14) M. L. Wolfrom and W. L. Polglase, *J. Am. Chem. Soc.*, 70, 2835 (1948).
(15) This compound (III) was prepared earlier by direct N-acetylation of dideguanyldihydrostreptomycin [S. Tatsuoka and S. Horii, *Proc. Japan. Acad.*, 39, 314 (1963)] and reported (without crystallization, melting point, or microanalyses) to have $[\alpha]^{21}D$ −87.5° (*c* 1.0, water). N.m.r. values reported by Tatsuoka and Horii for chemical shifts of the methyl groups generally agree with those found for the present sample.
(16) The value R_{Gm} here refers to the mobility of a compound relative to glucosamine hydrochloride on silica gel thin layer chromatography. The solvent system employed (*n*-BEW 415) was the organic phase of the system *n*-butyl alcohol–ethyl alcohol–water, 4:1:5.
(17) J. Fried and D. Wintersteiner, *J. Am. Chem. Soc.*, 69, 79 (1947).
(18) N. G. Brink, F. A. Kuehl, Jr., E. H. Flynn, and K. Folkers, *ibid.*, 68, 2557 (1946).
(19) The anomeric configurations assigned the two glycosides from their rotational properties[16] are in agreement with those derived from their n.m.r. spectra (see Table I).

Employing Hudson's rules of isorotation for compounds IVa and IVb, one calculates the molecular rotational contribution of the N-acetyldihydrostreptobiosamino unit as $[M]_B = -38{,}800$, that of the anomeric glycosidic center as $[M]_A = \pm 25{,}900$ (− for the α-L-anomer). It follows then that the molecular rotation of III is constituted $[M]_{III} = [M]_S + [M]_A + [M]_B$, where $[M]_S$, the contribution of an asymmetrically substituted N-diacetylstreptamine, may be estimated from the rotation of N,N′-diacetyl-2,6-di-O-methylstreptamine,[2] $[\alpha]^{26}D$ +6.3° (*c* 3.5, water), which is of the opposite absolute configuration, since the streptamine portion of III is substituted at C-4 instead of C-6. Thus, $-64{,}600 = -1800 + [M]_A - 38{,}800$, and $[M]_A = -24{,}000$, clearly indicating the α-L- configuration for streptose.[20]

Similar conclusions regarding glycosidic bond stereochemistry can be reached for the closely related antibiotic bluensomycin,[22] which has the same structure as dihydrostreptomycin except that one of the guanidine groups is replaced by a carbamate group. In the n.m.r. spectrum of bluensomycin sulfate the values for the anomeric protons corresponding to the respective columns of Table I are: N-methyl-L-glucosamine H-1, τ 4.44, J = 3.0 c.p.s.; dihydrostreptose H-1, τ 4.66, singlet. These values are clearly in accord with an α-L-configurational assignment for both sugars.

Acknowledgments. We thank the Department of Scientific and Industrial Research (London) for a N.A.T.O. Postdoctoral Fellowship (to I. J. McG.). This investigation was supported in part by Public Health Service Research Grant No. AI-01278 from the National Institute of Allergy and Infectious Diseases.

(20) The same conclusion can be reached by still another route, essentially that of Lemieux, DeWalt, and Wolfrom.[7a] Thus, dodecaacetyldihydrostreptomycin (VI) has $[\alpha]^{22}D$ −67°,[7a] its hydrolysis product N-tetraacetyl-2,5,6-O-triacetylstreptidine (VII) dihydrobromide monohydrate has $[\alpha]^{19}D$ −5.4°,[21] methyl pentaacetyl-α-L-dihydrostreptobiosaminide (Va) has $[\alpha]^{25}D$ −117°,[18] and methyl pentaacetyl-β-L-dihydrostreptobiosaminide (Vb) has $[\alpha]^{25}D$ −34°,[18] from which $[M]_{VI} = [M]_{VII} + [M]_A + [M]_B$, and $[M]_A = -32{,}700$, indicating again the α-L-configuration.
(21) A. H. Comrie, H. C. Mital, and J. B. Stenlake, *J. Med. Pharm. Chem.*, 2, 153 (1960).
(22) B. Bannister and A. D. Argoudelis, *J. Am. Chem. Soc.*, 85, 234 (1963).

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Photoisomerization of Tri-*t*-butylbenzenes. Prismane and Benzvalene Isomers[1]

Sir:

The photoisomerization[2–4] of polyalkylbenzenes has been shown[4] to result from transposition of ring carbon atoms and has been explained[3,4] in terms of nonbenzenoid intermediates. We have now established

(1) Based on work performed under the auspices of the U. S. Atomic Energy Commission.
(2) K. E. Wilzbach and L. Kaplan, *J. Am. Chem. Soc.*, 86, 2307 (1964).
(3) A. W. Burgstahler and P. L. Chien, *ibid.*, 86, 2940, 5281 (1964). *Cf.* also E. M. Arnett and J. M. Bollinger, *Tetrahedron Letters*, 3803 (1964).
(4) L. Kaplan, K. E. Wilzbach, W. G. Brown, and S. S. Yang, *J. Am. Chem. Soc.*, 87, 675 (1965).