at 200°, extensive rearrangement, isomerization, and fragmentation occurs. A 2:1 mixture of XII, disemicarbazone, m.p. 222°, and XI, semicarbazone, m.p. 213°, was obtained in 75% yield after heating X for 10 hr. The diastereoisomer IX is slower to react, giving 43% rearrangement to a similar mixture in the same period. An independent preparation of XI and XII by ozonolysis of a mixture of 4-methylisopulegone diastereoisomers[22] completed the proof of structure and enabled us to assign configurations to these isomers. Appropriate experiments have established that this unusual thermal rearrangement[23] is not catalyzed by acids or radical initiators and is insensitive to increases in surface area.

(22) C. Djerassi, J. Osiecki, and E. J. Eisenbraum, *J. Am. Chem. Soc.*, **83**, 4433 (1961). In our hands the methylation of pulegone yielded a mixture of 76% (−)-4-methylisopulegone and 24% of the dextrorotatory diastereomer, identified by semicarbazone derivatives.

(23) Epoxyketones I and III do not exhibit similar thermal reactions, but are transformed instead by a high temperature, free-radical decomposition initiated by oxirane hydrogen abstraction: W. Reusch and C. K. Johnson, *J. Am. Chem. Soc.*, **84**, 1759 (1962).

(24) Holder of a National Science Foundation Cooperative Graduate Fellowship, 1962–1963.

(25) National Science Foundation Undergraduate Research Participant.

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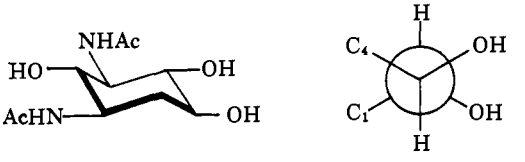
The Absolute Configuration of Streptidine in Streptomycin

Sir:

The gross structural features of the potent antibiotic substance streptomycin were derived[1] many years ago. The component fragments are N-methyl-L-glucosamine, the elusive L-streptose (which has been assigned the structure 5-deoxy-3-C-formyl-L-lyxose),[2] and streptidine. The configuration of the glycosidic linkage between N-methyl-L-glucosamine and streptose has been shown to be α,[3] that between streptose and streptidine has been shown to be β.[3] Streptidine was shown to be a *meso* form of 1,3-diguanido-2,4,5,6-tetrahydroxycyclohexane[4] and, furthermore, by synthesis[5] and degradation[6] to possess the all *trans* configuration. The streptobiosamine moiety of streptomycin has been shown to be attached to position 4[7] of streptidine in *either* the R or S[9] absolute configuration by the degradation of streptomycin of optically active ($[\alpha]_D$ −4° (*c* 1.1, 50% acetic acid)) N,N′-dibenzoyl-4-deoxystreptamine (I).[10] Although streptidine is a *meso* form, the asymmetric attachment of streptobiosamine to it causes each of the ring carbons of streptidine in streptomycin to be asymmetric. We wish to report the determination of the absolute configuration of N,N′-diacetyl-4-deoxystreptamine, derived from N,N′-dibenzoyl-4-deoxystreptamine and, hence, the complete configurational assignment of streptomycin and other members of the streptomycin antibiotic group.

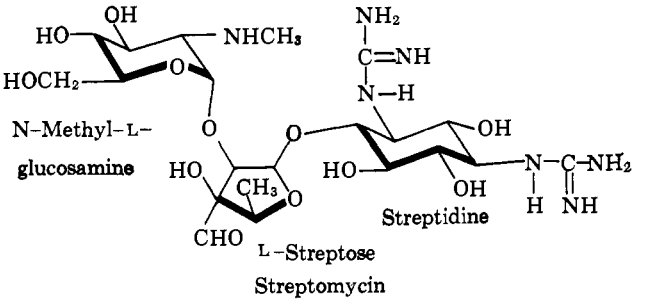
Acid hydrolysis of N,N′-dibenzoyl-4-deoxystreptamine (I), m.p. 284–286° dec. (lit.[10] m.p. 287–289°), furnished 4-deoxystreptamine, which on acetylation gave pentaacetyl-4-deoxystreptamine (II), m.p. 319–320° (*Anal.* Calcd. for $C_{16}H_{24}O_8N_2$: C, 51.60; H, 6.50; N, 7.52. Found: C, 51.39; H, 6.47; N, 7.48). The polyacetate II, on treatment with methanolic ammonia, gave N,N′-diacetyl-4-deoxystreptamine (III), m.p. 291–292°, $[\alpha]^{29}_D$ +5° (*c* 0.97, water) (*Anal.* Calcd. for $C_{10}H_{18}O_5N_2$: C, 48.77; H, 7.36; N, 11.37. Found: C, 48.50; H, 7.29; N, 11.15).

The absolute configuration of III was determined by the application of Reeves' cuprammonium method.[11] Compound III showed $[\alpha]^{29}_{436}$ +5° (*c* 0.97, water) and $[\alpha]^{29}_{436}$ −970° (*c* 0.88, Cupra B); this gives the result $\Delta[M]_{\text{Cupra B}}$ −2400°.[12] The strong negative increment is similar to that obtained for the 2,3-glycol complex of D-glucosides ($\Delta[M]_{\text{Cupra B}} \sim -2075°$) but opposed to that obtained for the 3,4-glycol complex of D-glucosides ($\Delta[M]_{\text{Cupra B}} \sim +2150°$).[11] Interferences from a potential *trans* 1,3-glycol complex are not observed,[11] and interference from acetamido groups does not occur.[13] Thus, the dihedral angle of the 5,6-glycol grouping (formed from the planes of HO–C_5–C_6 and C_5–C_6–OH) of N,N′-diacetyl-4-deoxystreptamine (III) is *clockwise*[11] 60° and III has the absolute configuration shown *rather* than its mirror image.[14]



III

Using this configurational assignment, the structure of streptomycin in complete stereochemical detail may be written as indicated.[15] This stereochemical result also establishes the complete structure



(1) R. U. Lemieux and M. L. Wolfrom, *Advan. Carbohydrate Chem.*, **3**, 337 (1948), and references cited therein.

(2) F. A. Kuehl, Jr., R. L. Clark, M. N. Bishop, E. H. Flynn, and K. Folkers, *J. Am. Chem. Soc.*, **71**, 1445 (1949).

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

(4) H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, P. S. Skell, and W. A. Strong, *Science*, **103**, 540 (1946).

(5) M. L. Wolfrom, S. M. Olin, and W. J. Polglase, *J. Am. Chem. Soc.*, **72**, 1724 (1950).

(6) O. Wintersteiner and A. Klingsberg, *ibid.*, **73**, 2917 (1951).

(7) The numbering system used here is that suggested by Rinehart, *et al.*,[8] for the 2-deoxystreptamine moiety of the neomycin antibiotic group. For streptomycin, this attaches the streptobiosamine fragment at C-4 of streptidine.

(8) K. L. Rinehart, Jr., M. Hichens, A. D. Argoudelis, W. S. Chilton, H. E. Carter, M. P. Georgiadis, C. P. Schaffner, and R. T. Schillings, *J. Am. Chem. Soc.*, **84**, 3218 (1962).

(9) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(10) F. A. Kuehl, Jr., R. L. Peck, C. E. Hoffhine, Jr., and K. Folkers, *J. Am. Chem. Soc.*, **70**, 2325 (1948). The hydroxyl group of streptidine that is replaced by hydrogen in this degradation sequence is that to which streptobiosamine is glycosidically attached in streptomycin.

(11) R. E. Reeves, *Advan. Carbohydrate Chem.*, **6**, 107 (1951), and references cited therein.

(12) $\Delta[M]_{\text{Cupra}} = ([\alpha]_{436}$ Cupra − $[\alpha]_{436}$ water) × (mol. wt./100).

(13) M. Hichens and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **85**, 1547 (1963).

(14) Using the R, S[9] convention, the absolute configuration of III may be written 1(R),3(R)-diacetamido-2(S),5(S),6(S)-trihydroxycyclohexane.

(15) The asymmetry of the streptidine ring in streptomycin is thus 1(R),-2(R),3(S),4(R),5(R),6(S). This assignment is in agreement with the suggestion of Tatsuoka,[16] which was based on the fact that N,N′-diacetyl-2,5,6-tri-O-methylstreptamine, derived from dihydrostreptomycin, has the same sign (positive) of rotation as N,N′-diacetyl-5,6-di-O-methyl-2-deoxystreptamine, derived from pseudoneamine. We thank Dr. K. L. Rinehart, Jr., for bringing this suggestion to our attention.

(16) S. Tatsuoka and S. Horii, *Proc. Japan Acad.*, **39**, 314 (1963).

determination of dihydrostreptomycin,[10,17] hydroxystreptomycin,[18] and mannosidostreptomycin.[19]

The configurational determination of the asymmetry of the streptidine ring in streptomycin yields the same result (*i.e.*, R at C-4) as that recently determined chemically[16] and by the cuprammonium method[13] for the 2-deoxystreptamine ring of the neomycins,[13,16] paromomycins,[13] and kanamycins.[13] Thus these two vital components of a number of powerful antibiotics may have stereochemically similar biogenetic precursors.

Acknowledgment.—This investigation was supported in part by research grant No. G-6041 from the National Science Foundation.

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(19) J. Fried and H. E. Stavely, *ibid.*, **74**, 5461 (1952).

(20) National Science Foundation Cooperative Graduate Fellow, 1960–1962.

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Reactions of Organolithium Compounds and Diphenylacetylene

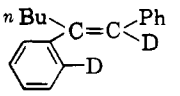
Sir:

The literature contains little information concerning the reaction between organolithium compounds and noncarbonyl, conjugated acetylenes. In contrast Grignard reagents are generally unreactive toward simple nonterminal alkynes[1] even under forcing conditions.

We find that diphenylacetylene and organolithium compounds react to form addition and/or metalation products or a dimer depending upon the choice of organolithium compound and conditions.

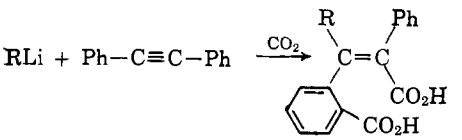
n-Butyllithium and diphenylacetylene do not react in pentane solution over a period of several hours, whereas the same compounds react in ethyl ether (24 hr., 30°) to give after hydrolysis, in addition to recovered starting material, a 40% yield of *trans*-α-*n*-butylstilbene, b.p. 143–144° (0.4 mm.) $\lambda\lambda_{max}$ 225 mμ (ε 5200), 268 mμ (ε 16,200). *Anal.* Calcd. for $C_{18}H_{20}$: C, 91.47; H, 8.53; mol. wt., 236. Found: C, 91.27; H, 8.63; mol. wt., 232. The *trans* nature of the product (single peak from v.p.c.) was demonstrated by photoisomerization using a Hanovia mercury arc lamp and isolating by means of preparative scale v.p.c. the new component which appears to the extent of approximately 24% after 72 hr. of illumination. The new component *cis*-α-*n*-butylstilbene had $\lambda\lambda_{max}$ 222 mμ (ε 13,000), 257 mμ (ε 10,900). In addition to having the expected shorter wave length maximum in the ultraviolet, the new compound (*cis*) displays olefinic proton resonance at 3.62 τ in contrast to the unisomerized compound (*trans*) in which olefinic proton resonance occurs at 3.36 τ. That the higher-field olefinic proton resonance is characteristic of the *cis* isomer in this sort of compound has been pointed out by Curtin, Gruen, and Shoulders.[2]

In order to demonstrate the existence of an olefinic organolithium intermediate, the *n*-butyllithium–diphenylacetylene reaction mixture was treated with deuterium oxide. The deuterated product showed no proton resonance in the 3.3 to 3.6 τ region, but, in addition, the deuterium content indicated that two protons had been exchanged, and the integrated n.m.r. spectrum revealed that one of the exchanged protons was from an aromatic ring. Based on the results of carbonation experiments (see below) the structure of the dideuterated adduct is I.



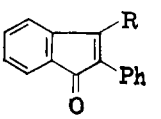
I

If diphenylacetylene in ethyl ether is treated with either ethyllithium or *n*-butyllithium, one obtains (after carbonation) in about 15% yield each a neutral (orange or red) ketone (II) and a dicarboxylic acid (III) besides recovered starting material.



IIIa,b

a, R = *n*-C_4H_9
b, R = C_2H_5



IIa,b

The structures of the 2-phenyl-3-alkylindones were confirmed by comparison with authentic samples synthesized according to published procedures.[3] The dicarboxylic acid structures III [IIIa, m.p. 176–177°. *Anal.* Calcd. for $C_{18}H_{18}(COOH)_2$: C, 74.05; H, 6.21; neut. equiv., 162. Found: C, 74.35; H, 6.45; neut. equiv., 166. IIIb, m.p. 191–192°: *Anal.* Calcd. for $C_{16}H_{14}(COOH)_2$: C, 72.96; H, 5.44; neut. equiv., 148. Found: C, 73.13; H, 5.48; neut. equiv., 148] are in accord with what one would expect on the basis of the indone products. Further structural elucidation was provided by converting IIIa to its dimethyl ester (IV), b.p. 162° (0.2 mm.) [*Anal.* Calcd. for $C_{18}H_{18}(COOCH_3)_2$: C, 74.98; H, 6.86; mol. wt., 352. Found: C, 75.20; H, 6.90; mol. wt., 349], using diazomethane. The n.m.r. spectrum of the ester shows two methyl singlets at 6.17 and 6.78 τ. The n.m.r. spectra of both the acid IIIa (in dioxane) and the dimethyl ester IV indicate eight aromatic protons in the region 2.6 to 2.7 τ and another single aromatic proton at a lower field in the 2.0 τ region, the latter being split into a doublet having coupling constants of 7–10 c.p.s. Both the chemical shift and the coupling constant are of the correct magnitude for an aromatic proton *ortho* to a —COO— group.[4] Because the integrated intensity of this low-field proton indicates only one hydrogen *ortho* to the —COO— group, the —COO— group must in turn be *ortho* to the olefinic bond.

The formation of the acids (III) and the indones (II) is most readily explained in terms of an intermediate (V) arising from metalation of the aromatic ring and ad-

(1) (a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice Hall, New York, N. Y., 1954; (b) for a recent exception see the unusual trimerization and tetramerization reactions of diphenylacetylene and phenylmagnesium bromide: M. Tsutsui, *Chem. Ind.* (London), 780 (1962).

(2) D. Y. Curtin, H. Gruen, and B. A. Shoulders, *Chem. Ind.* (London), 1205 (1958).

(3) R. L. Frank, H. Eklund, J. W. Reiliter, C. R. Vanneman, and A. N. Wennerberg, *J. Am. Chem. Soc.*, **66**, 1 (1944). 2-Phenyl-3-*n*-butylindone (IIa) is not reported in the literature. We have obtained this compound as a slightly impure high boiling red liquid. The 2,4-dinitrophenylhydrazone of this compound, m.p. 176–178°, correct anal., was identical with the 2,4-dinitrophenylhydrazone obtained from the red liquid indone prepared in a similar manner to the general method described in this reference.

(4) P. L. Corio and B. P. Dailey, *ibid.*, **78**, 3043 (1956). See also L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 85.