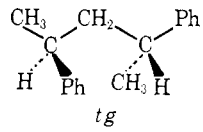
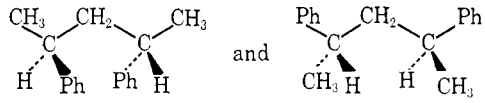
rium mixture, a result which agrees with the analysis by gas chromatography within the combined experimental errors. Gas chromatographic analysis is believed to be the more reliable method.

The only conformers of the *meso* isomer not precluded by severe steric overlaps are the *trans,gauche* (*tg*), *i.e.*



tg

and its analog (*gt*) of opposite screw sense. The eligible conformations of the racemic isomer are *tt* and *gg*, *i.e.*,



tt *gg*

Let η denote the statistical weight for a conformation in which phenyl is *gauche* with respect to a CH group separated from it by three skeletal bonds. This statistical weight is to be assigned relative to a statistical weight of unity for a CH_3 group similarly situated with respect to CH. On this basis the combined statistical weight for the two equivalent *meso* conformers is 2η; the statistical weights for the *tt* and *gg* conformers of the racemic form are η^2 and 1, respectively. Hence, the fraction of *meso* at equilibrium[1] is $f_{meso} = 2\eta/(1 + \eta)^2$. Taking $f_{meso} = 0.48$ as a weighted mean of the experiments here reported, $\eta = 1.5$ at 25°.[14] The *tt* conformer of the racemic isomer is predicted to be favored over the *gg* by the factor $\eta^2 = 2.25$. At the same temperature the ratio of these two conformers deduced from nmr spectra interpreted in terms of coupling constants is *ca.* 3.0 according to Bovey[8] and Doskočilová[15] and their co-workers, in satisfactory agreement with our deductions.

At least one additional parameter is required for the interpretation of the stereochemical equilibrium and the distribution among conformers for any higher homolog.[1] Analysis of the epimerization equilibrium for the next homolog, namely, 2,4,6-triphenylheptane, should yield this parameter and also test the validity of the scheme presented elsewhere.[1] Experiments directed to this end are in progress, along with investigation of the epimerization of polystyrene. These results and their implications concerning the conformations of vinyl chain molecules will be subjects of future publications.

Acknowledgment. This work was supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research Contract No. AF49(638)1341.

(14) The other root, $\eta = 0.667$, of the quadratic equation for f_{meso} has been dismissed on the grounds that it is irreconcilable with the preference for the *tt* conformer of the racemic isomer.

(15) D. Doskočilová, S. Sýkora, H. Pivcová, B. Obereigner, and D. Lím, *J. Polymer Sci.*, in press.

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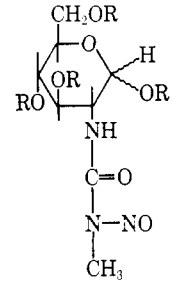
The Structure of Streptozotocin

Sir:

Streptozotocin,[1-4] an antibiotic produced by *Streptomyces achromogenes*, is a broad spectrum antibacterial agent and also has antitumor activity in both *in vitro* and *in vivo* systems. We wish to present evidence supporting the assignment of structure I to streptozotocin.



I, R = H
II, R = $COCH_3$

Streptozotocin has the molecular formula[5,6] $C_8H_{15}N_3O_7$ and decomposes with evolution of gas at *ca.* 115°. The molecular weight determined by isothermal distillation in water is 269 (calcd, 265). Potentiometric titration showed the absence of any titratable groups. The nmr spectrum[7] of streptozotocin could not be completely interpreted; however, it showed the presence of an N-CH_3 group (singlet, 3 H, at δ 3.15) and the absence of any C-CH_3 groups.

Acetylation of streptozotocin with acetic anhydride and pyridine afforded crystalline tetraacetate II, $C_8H_{11}N_3O_7(COCH_3)_4$, $[\alpha]^{25}D$ +41° (*c* 0.78, 95% ethanol), mp 111–114° dec. The nmr spectrum of II showed the presence of four O-acetyl groups (12 H, δ 1.97–2.08) and the N-CH_3 group which is also present in streptozotocin.

Treatment of the antibiotic with alkali (2 *N* aqueous NaOH) at 0° resulted in the evolution of diazomethane,[8] and carbon chromatography of the neutralized reaction mixture resulted in the isolation of III as an amorphous colorless solid, $C_7H_{11}NO_6$, $[\alpha]^{25}D$ −40° (*c* 1, water). III exhibited infrared absorption at 1725 cm^{-1} and yielded carbon dioxide and D-glucosamine hydrochloride, $C_6H_{13}NO_5 \cdot HCl$, by treatment with 2 *N* aqueous HCl. Treatment of the alkali degradation reaction mixture with acetic anhydride and pyridine afforded IV, a crystalline colorless solid, $C_7H_7NO_6(COCH_3)_4$, mp 178–180° (uncor), $[\alpha]^{25}D$ −46° (*c* 0.7, 95% ethanol). Acid hydrolysis of IV (2 *N* HCl, reflux) again yielded D-glucosamine hydrochloride and carbon dioxide. The infrared spectrum (carbonyl absorption at 1790 and 1745 cm^{-1}) and the nmr spectrum (3 H, singlet, at δ

(1) J. J. Vavra, C. DeBoer, A. Dietz, L. J. Hanka, and W. T. Sokolski, *Antibiot. Ann.*, **1959–1960**, 230 (1960).

(2) W. T. Sokolski, J. J. Vavra, and L. J. Hanka, *ibid.*, **1959–1960**, 241 (1960).

(3) C. Lewis and A. R. Barbiers, *ibid.*, **1959–1960**, 247 (1960).

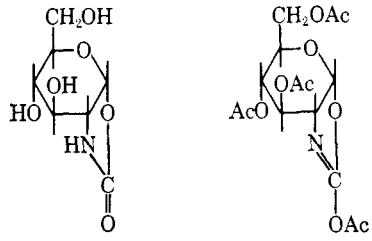
(4) R. R. Herr, T. E. Eble, M. E. Bergy, and H. K. Jahnke, *ibid.*, **1959–1960**, 236 (1960).

(5) Analytical values for all the compounds described in this paper are consistent with the indicated formulas.

(6) The molecular formula was previously reported as $C_{11}H_{27}N_5O_{12}$,[4] based on early molecular weight determinations.

(7) Nmr spectra were observed in dimethylformamide-d_7 on a Varian A-60 spectrometer using internal tetramethylsilane as a reference.

(8) Diazomethane was collected in ether and this solution was mixed with an ether solution of *p*-nitrobenzoic acid. Crystalline methyl *p*-nitrobenzoate isolated was identical with an authentic sample.



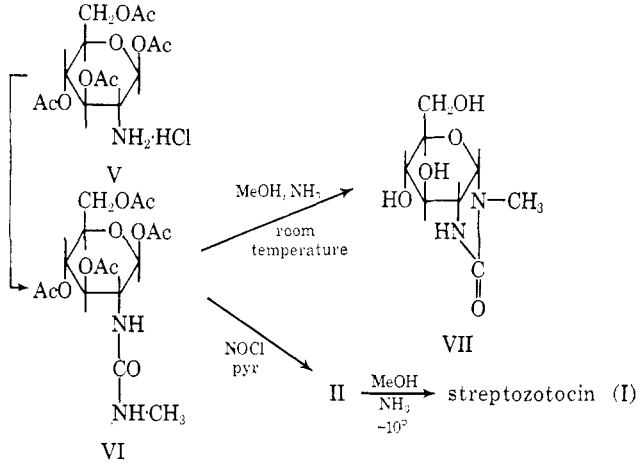
III IV, Ac = $COCH_3$

2.48; three singlets, 3 H each, at δ 1.97, 2.03, and 2.07) of the tetraacetate IV are consistent with the postulation of the presence of an enol acetate grouping in IV.

The formation of diazomethane and a positive Liebermann nitroso test[9] suggested the presence of an N-nitrosomethylamide group in streptozotocin. The absence of a free amino group in streptozotocin, together with the isolation of carbon dioxide and D-glucosamine from acid hydrolysis of III or IV, indicate the nitrosoamide to be present as a urea derivative involving the nitrogen of the glucosamine. This conclusion is consistent with both the ultraviolet [λ_{max} 228 mμ (ε 6360)][10] and the infrared spectra (carbonyl absorption at 1700 cm^{-1},[11,12] –NN=O at 1530 cm^{-1} [13]) of streptozotocin. These data establish the structure of streptozotocin as I.

Various lots of crystalline streptozotocin as isolated, identical in all other respects, have shown wide variations in optical rotation ([α]^{25}D +15 to 68°). However, aqueous solutions of these samples rapidly undergo mutarotation to an equilibrium value of [α]^{25}D 39°. This indicates that streptozotocin is a mixture of α and β anomers with the C_1-hydroxyl unsubstituted.

The structure of streptozotocin was confirmed by its synthesis. Tetra-O-acetylglucosamine hydrochloride[14] (V) treated with methyl isocyanate[15] gave VI, $C_{16}H_{24}N_2O_{10}$, mp 142–144°, [α]^{25}D +18° (*c* 0.9, 95% ethanol). Attempts to deacetylate VI prior to nitrosation, using



ammonia in methanol (room temperature), afforded only the cyclic product VII, $C_8H_{14}N_2O_5$,[16] mp 177–178°, [α]^{25}D −21° (*c* 0.77, water). VII, which shows no reducing properties, has also been obtained from streptozotocin by treatment with 0.1 *N* aqueous sulfamic acid; 1 mole of N_2/mole of I is evolved during this reaction. Treatment of VI with nitrosyl chloride in pyridine[17] afforded tetraacetylstreptozotocin (II) identical with an authentic sample. Ammonolysis of II in methanol (−10°) afforded streptozotocin identical in all respects with that obtained from fermentations.

In addition to streptozotocin, *S. achromogenes* produces enteromycin[18,19] and U-15,774,[19] both compounds containing unusual nitrogen functions.

Acknowledgments. The authors are grateful to members of the Physical and Analytical Chemistry Department for microanalytical and spectral data.

(9) W. J. Hickinbottom, "Reactions of Organic Compounds," 2nd ed, Longmans, Green and Co., Ltd., London, 1948, p 358.

(10) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The MacMillan Co., New York, N. Y., 1964, p 41.

(11) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 2nd ed, 1958, p 223.

(12) The reported value for amide carbonyl absorption in substituted ureas is 1660 cm^{-1}.[11] However, the presence of the electronegative N-nitroso group is expected to reduce the contribution of the ionic form of the amide and as a result the carbonyl frequency is raised. A similar effect may account for the high frequencies of N-nitrosoamides which absorb near 1740 cm^{-1} in solution.[13]

(13) E. H. White, *J. Am. Chem. Soc.*, **77**, 6008 (1955).

(14) M. Bergmann and L. Zervas, *Ber.*, **64B**, 975 (1931).

(15) F. Micheel and W. Lengsfeld, *ibid.*, **89**, 1246 (1956).

(16) This cyclization of the methyl ureido compound is contrary to the results reported by C. J. Morel, *Helv. Chim. Acta*, **44**, 403 (1961), who did not obtain the cyclic product during ammonolysis of several other alkyl derivatives, but is analogous to the results reported by both Morel and Micheel[15] with aryl derivatives.

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Metal Ion Facilitation of Atom-Transfer Oxidation–Reduction Reactions[1]

Sir:

Reactions of transition metal compounds can often be classified in analogous patterns, from which new reactions can be deduced. The efficacy of this approach is illustrated by the oxidative addition reactions of d^8 [2,3] and d^{10} [4] systems. Herein we propose another class of transition metal reactions: metal ion promoted atom-transfer oxidation–reduction reactions.

Consider a molecule or ion X–Y reacting with a molecule or ion Z to form products X–Z and Y such that atom (or group) transfer takes place, X–Y being reduced and Z being oxidized (eq 1).

$$X\text{–}Y + Z \longrightarrow X\text{–}Z + Y \qquad (1)$$

A partial list of potential oxidizing agents X–Y includes RN_3, N_3^-, $RCHN_2$, RNCNR, RNO_2, NO_2, NO_2^-, NO, NO^+, ArN_2^+, N_2O, SeO_2, O_3, O_2, H_2O_2, ROOR, and ROOH.[5] Reducing agents Z might include H^-, R^-, $RC{\equiv}C:^-$, RC≡CR, RCH=CHR, R_3P, CO, RNC, CN^-, N_3^-, SO_2, and $SnCl_2$.[6] Most of the possible permutations afford thermodynamically allowed reactions; however, many combinations lack a low-energy

(1) This research was supported by the National Science Foundation and the Advanced Research Projects Agency, Contract SD 100.

(2) (a) L. Vaska and S. S. Bath, *J. Am. Chem. Soc.*, **88**, 1333 (1966); (b) P. B. Chock and J. Halpern, *ibid.*, **88**, 3511 (1966).

(3) J. P. Collman and W. R. Roper, *ibid.*, **87**, 4008 (1965); **88**, 3504 (1966).

(4) C. D. Cook and G. S. Jauhal, *Can. J. Chem.*, **45**, 301 (1967).

(5) In a few instances atom transfer takes place from the reducing agent to the oxidizing agent rather than the converse which is shown in eq 1.

(6) Ligands are written in their uncoordinated state.