our observation that N,N-diacetyl (F) also takes up this oxidant only slowly[7] indicates that this conclusion is not justified.

In view of the close similarity of streptolin–streptothricin and certain *streptomyces* antibiotics such as roseothricin, geomycin and others, we suggest that the general expression I[8] may be applicable to these other members of this ubiquitous group.

Acknowledgment.—Structural investigations on streptolin, streptothricin and degradation products were supported by Research Grant G-4118 and E-618 (University of Illinois) and E-585 (University of Wisconsin) from the Institute of Allergy and Infectious Diseases of the National Institutes of Health, Public Health Service; and Contract (Nonr1202(10) (University of Wisconsin) with the Office of Naval Research.

(7) Considered to be a conformational effect, caused by the presence of diaxial hydroxyl groups.

(8) The structure I established herein differs in several important respects from the proposal for roseothricin-A by Goto, *et al.* (footnote 6), and the more recent structural suggestion for the closely related racemomycin-O (S. Takemura, *Chem. and Pharm. Bull.*, **8**, 578 (1960).

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STREPTOTHRICIN AND STREPTOLIN: THE STRUCTURE OF STREPTOLIDINE (ROSEONINE)

Sir:

On acid hydrolysis, the *streptomyces* antibiotics streptothricin[1] and streptolin[2] yield carbon dioxide, ammonia, L-β-lysine,[3,4] 2-amino-2-deoxy-α-D-gulose,[5] and a basic amino acid, streptolidine[6] (I) the structure of which now has been elucidated.[10]

(1) H. E. Carter, R. K. Clark, Jr., P. Kohn, J. W. Rothrock, W. R. Taylor, C. A. West, G. B. Whitfield, and W. G. Jackson, *J. Am. Chem. Soc.*, **76**, 566 (1954).

(2) E. E. Smissman, R. W. Sharpe, B. F. Aycock, E. E. van Tamelen, and W. H. Peterson, *ibid.*, **75**, 2029 (1953).

(3) H. E. Carter, W. R. Hearn, E. M. Lansford, Jr., A. C. Page, Jr., N. P. Salzman, D. Shapiro, and W. R. Taylor, *ibid.*, **74**, 3704 (1952).

(4) E. E. van Tamelen and E. E. Smissman, *ibid.*, **74**, 3713 (1952).

(5) E. E. van Tamelen, J. R. Dyer, H. E. Carter, J. V. Pierce, and E. E. Daniels, *ibid.*, **78**, 4817 (1956).

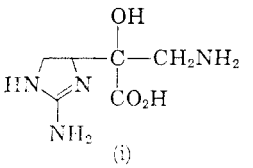
(6) Streptolidine is the trivial name assigned to a basic amino acid present in the acid hydrolysate of streptolin.[3,7] Streptolidine has been shown to be identical with a basic amino acid present in the acid hydrolysate of streptothricin,[1,8] originally termed compound B.[9]

(7) Glenn Brewer, Ph.D. Thesis, University of Wisconsin, 1953.

(8) Charles C. Sweeley, Ph.D. Thesis, University of Illinois, 1955.

(9) Charles A. West, Ph.D. Thesis, University of Illinois, 1952.

(10) By direct comparison, streptolidine has been shown to be identical with roseonine, derived from roseothricin,[11-13] geamine, derived from geomycin,[14-16] and a basic amino acid derived from racemomycin[17] and mycothricin.[18] A structural formula (i) has been proposed[11,12] for roseonine based primarily on oxidation, which gave glycine and guanidine; degradation using silver nitrite followed by phosphorus and hydriodic acid, which gave 2-amino-4-ethyl-imidazole; periodate oxidation data; and pK_a values.



(i)

Cellulose and charcoal chromatography of streptothricin and streptolin hydrolysates yielded I as a crystalline hydrochloride, m.p. 173–190° dec., $[\alpha]^{22}D$ +56.8° (*c* 2.35, water). (Found: C, 27.97; H, 5.20; N, 21.55; Cl, 27.03). Streptolidine showed pK_a values of 2.5, 8.72, and 11.3 (water) and 3.95, 9.10, and 12.65 (66% dimethylformamide)[19]; it gave positive Weber and ninhydrin tests and negative Sakaguchi, Ehrlich, Benedict, Schiff, Elson–Morgan, and biuret tests. Van Slyke analysis indicated one primary amino function; C-methyl, O-methyl, N-methyl, and α-amino acid groups were shown to be absent. Streptolidine consumed one mole of periodate rapidly, giving in addition to formaldehyde and ammonia, an unstable *aldehyde* (II) $[\alpha]D$ +108° (*c* 1.0, water) (positive Benedict, Tollens, and Schiff tests).[20] Treatment of I with excess periodate for an extended period of time gave glycocyamidine. The N-2,4-dinitrophenyl derivative of I, m.p. 202–208° (Found: C, 40.53; H, 3.94; N, 23.43) did not consume lead tetraacetate[21]; thus I is not an α-hydroxyacid.[20] That the aliphatic amino group is terminal was suggested most directly by the earlier observation that glycine was produced on oxidation of streptolidine,[11] and this view is now supported by the formation of terminal methyl product (Found: C—CH_3, 2.67) on reductive deamination[22] of chromatographically pure but non-crystalline mono-(N-benzenesulfonyl)-streptolidine (Found: C, 43.21; H, 4.72; C–CH_3, 0.0). Thus streptolidine is a 2-aminoimidazoline having the substituent groups —CO_2H and —CHOH—CH_2NH_2.

Sodium borohydride reduction of the aldehyde II furnished the crystalline hydroxyacid III, m.p. 250° dec., $[\alpha]D$ +93.2° (*c* 3.10, water) (Found: C, 37.70; H, 5.86; N, 26.21). Treatment of III with methanolic hydrogen chloride gave an ester[23] (λ_{max} 5.75 μ), hydrogenation of which produced the *diol* IV, $[\alpha]D$ +40° (*c* 1.18, water), flavianate, m.p. 234–235° (Found: C, 39.24; H, 3.64; N, 15.69), which did not reduce periodate.[20] Hence III is *trans*-2-amino-5-hydroxymethylimidazoline-4-carboxylic acid. DL-*trans*-2-Amino-5-hydroxymethylimidazoline-4-carboxylic acid (V) was secured as follows. Alkaline hydrolysis and epimerization of 3,4-(1′,3′-dibenzyl-2′-ketoimidaz-

(11) K. Nakanishi, T. Ito, M. Ohashi, I. Morimoto, and Y. Hirata, *Bull. Chem. Soc. Japan*, **27**, 539 (1954).

(12) K. Nakanishi and M. Ohashi, *ibid.*, **30**, 725 (1957).

(13) T. Goto, Y. Hirata, S. Hosoya, and N. Komatsu, *ibid.*, **30**, 729 (1957).

(14) H. Brockmann and H. Musso, *Naturwissenschaften*, **41**, 451 (1954).

(15) H. Brockmann and H. Musso, *Angew. Chem.*, **67**, 167 (1955).

(16) H. Brockmann and H. Musso, *Ber.*, **88**, 648 (1955).

(17) H. Taniyama and S. Takemura, *Yakugaku Zasshi*, **77**, 1215 (1957) (*C.A.*, **52**, 3886*i* (1958)).

(18) G. Rangaswami, C. P. Schaffner, and S. A. Waksman, *Antibiotics and Chemotherapy*, **6**, 675 (1956).

(19) We are grateful to Dr. Harold Boaz, Eli Lilly and Co., for determining the pK_a values.

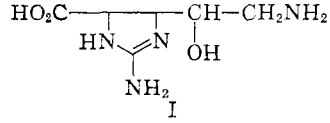
(20) This experimental finding is inconsistent with structure (i) (ref. 10).

(21) Observed by Dr. C. R. Narayanan, University of Wisconsin.

(22) A. Nickon and A. Sinz, *J. Am. Chem. Soc.*, **82**, 753 (1960).

(23) Similar treatment of *cis*-2-amino-5-hydroxymethylimidazoline-4-carboxylic acid, m.p. 144–146°, derived from reaction of *erythro*-2,3-diamino-4-hydroxybutyric acid with cyanogen bromide, furnished a lactone (λ_{max} 5.67 μ).

olido)-2-keto-5-acetoxytetrahydrofuran,[24] then sodium borohydride reduction, gave *trans*-1,3-dibenzyl - 5 - hydroxymethylimidazolid - 2 - one-4-carboxylic acid, m.p. 160–161.5° (found: C, 66.46; H, 6.42; N, 8.14). Treatment of the latter with sodium in liquid ammonia, then with hot mineral acid, led to formation of *threo*-2,3-diamino-4-hydroxybutyric acid, which was converted into V, m.p. 237–240° (found: C, 37.32; H, 5.54), by treatment with cyanogen bromide. III and V could not be differentiated by paper chromatography in three different systems. The structure of streptolidine (I) is thus 4-(1-hydroxy-2-aminoethyl)-2-aminoimidazoline-5-carboxylic acid.



I

(24) A gift from Hoffmann-La Roche, Inc.

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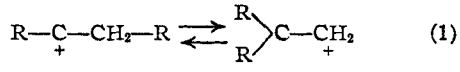
BIMOLECULAR REACTIONS IN CARBONIUM ION REARRANGEMENTS

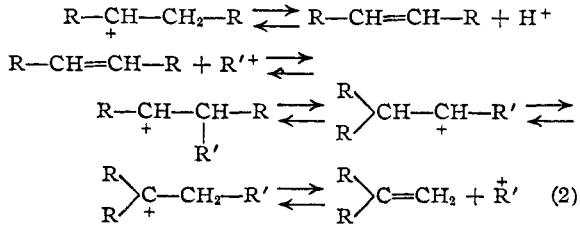
Sir:

Primary carbonium ions, arising from intramolecular rearrangements of secondary and tertiary ones, frequently are postulated as intermediates in *liquid phase* isomerizations of paraffins and related compounds. Calculations[1] indicate that at



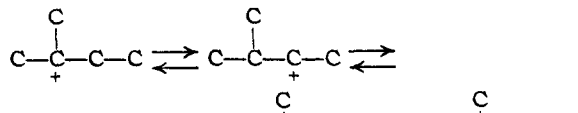
(1)

least 22 kcal./mole of activation energy are needed for rearrangements of secondary to primary carbonium ions, and 33 kcal./mole for rearrangements of tertiary to primary. We considered such energies large enough to warrant examination of alternate mechanistic paths, not involving primary carbonium ions. Specifically, rearrangements via *bimolecular* reactions (2) appeared attractive.

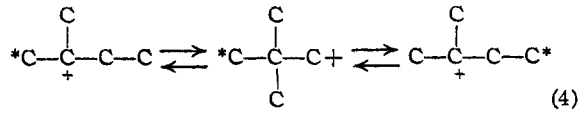


(2)

It was demonstrated[2] that isotopic scrambling of C-2 ⇄ C-3 of 2-methyl-2-chlorobutane-2-C^{14} with aluminum chloride does not proceed twice as fast as the scrambling of C-1 ⇄ C-4 of 2-methyl-2-chlorobutane-1-C^{14} as anticipated if (3) was the only path of isotopic equilibration. Instead, the rate of scrambling of C-2 ⇄ C-3 *versus* C-1 ⇄ C-4 was 1.55. The data necessitated the interpretation that 87% of the rearrangement occurs *via* (3) and 13% *via* (4), since (4) effects C-1 ⇄ C-4 equilibration, but not C-2 ⇄ C-3.

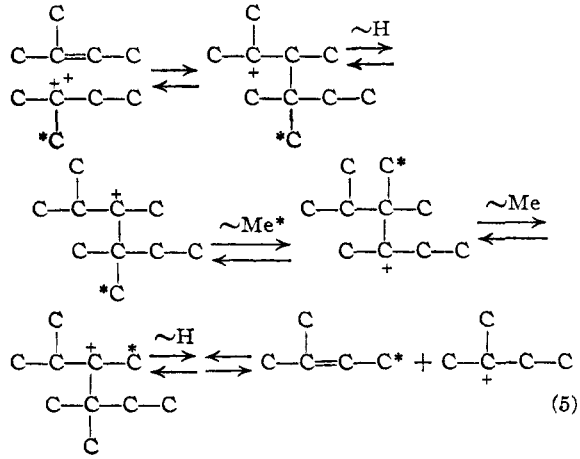


(3)



(4)

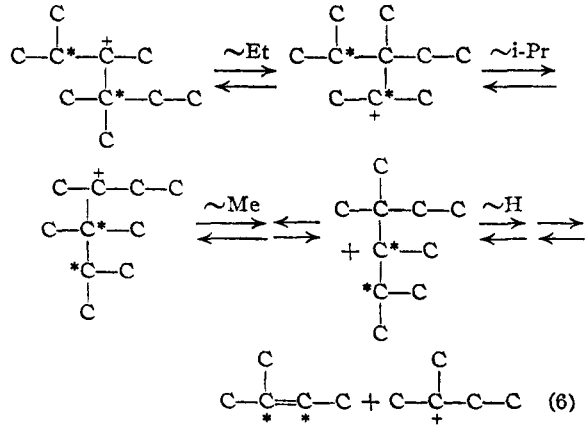
However, the data are also explicable on the basis of bimolecular reactions, without intervention of primary carbonium ions (neopentyl)



(5)

Reaction (5), as far as its effect on isotopic equilibration is concerned, is identical with (4). Differentiation between (5) and (4) becomes obvious upon consideration of the implication of (5). If both the cation and the olefin are labeled the recovered *t*-amyl chloride should contain dilabeled species.

Another source of rearrangement and dilabeled species besides (5) is (6).



(6)

Reaction (6), unlike (5), leads to dilabeled species from either the C-1 or C-2 labeled chloride (shown

(1) A. G. Evans, "The Reactions of Organic Halides in Solution," The Manchester University Press, Manchester, England, 1946, p. 15.

(2) J. D. Roberts, R. E. McMahon and J. H. Hine, *J. Am. Chem. Soc.*, **72**, 4237 (1950).