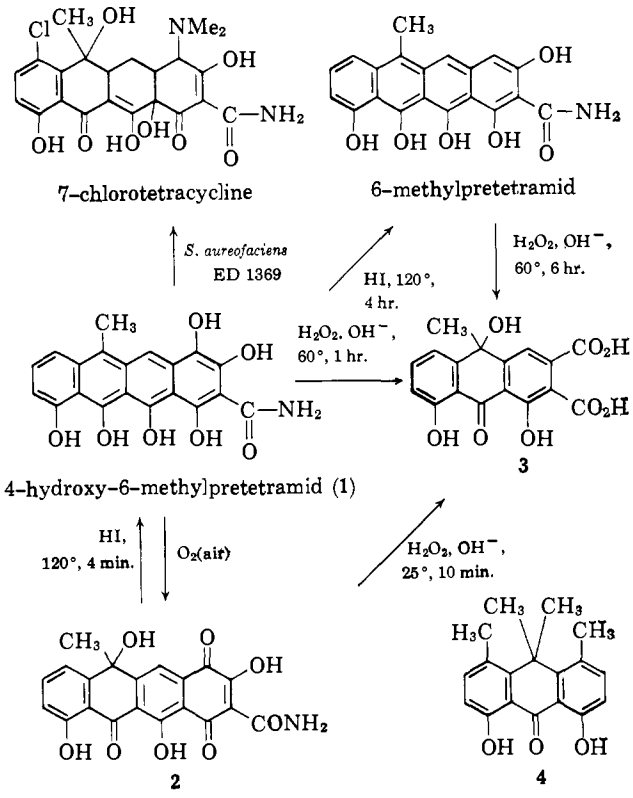
tion spectrum of the solution at this point showed λ_{max} (ϵ) 283 (6260) and 540 mμ (10,400). Dilution of the solution with 0.1 *N* aqueous hydrochloric acid yielded crystalline 1,4,6,11-tetrahydro-3,6,10,12-tetrahydroxy-6-methyl-1,4,11-trioxonaphthacene-2-carboxamide (**2**). *Anal.* Found for $C_{20}H_{13}NO_8$: C, 60.9; H, 3.44; N, 3.29; C-methyl, 2.6. The dark red, very finely crystalline product did not melt, but decomposed over the range 200–300°. The structure of **2** was elucidated by its ready reduction back to **1** and by the easy further oxidation with alkaline hydrogen peroxide to racemic 1,8,10-trihydroxy-10-methylanthrone-2,3-dicarboxylic acid (**3**); yellow needles (acetone solvate) from acetone–benzene; m.p. 140° dec. ($-H_2O$). *Anal.* Found for $C_{17}H_{12}O_8 \cdot 0.5C_3H_6O$: C, 59.6; H, 4.43; acetone, 0.47 mole (as iodoform). This product, **3**, was also prepared by the slower oxidation in alkaline hydrogen peroxide of 6-methylpretetramid itself. Spectra of specimens of **3** from each starting material were identical, λ_{max} (ϵ) (0.1 *N* hydrochloric acid in methanol): 255 (shoulder, 6340), 265 (7500), 274 (7680), 304 (9300), and 376 mμ (9300); infrared maximum (KBr disk): 1710 cm.$^{-1}$ (carboxyl C=O) and 1600 cm.$^{-1}$ (hydrogen bonded aryl C=O). The structure of **3** was confirmed by the detailed similarity of its ultraviolet absorption spectrum to that of 1,8-dihydroxy-4,5,10,10-tetramethylanthrone (**4**) [λ_{max} (ϵ) (0.1 *N* hydrochloric acid–methanol): 252 (shoulder, 6350), 260 (8890), 268 (9340), 300 (13,500), and 371 mμ (10,100)], which had been prepared earlier in these laboratories as a model compound for spectral comparisons.[5]

Scheme I. Reactions of 4-Hydroxy-6-methylpretetramid



(5) J. R. D. McCormick and W. E. Gardner, unpublished work. 1,8-Dihydroxyanthrone was allowed to react with methyl iodide in aqueous alkaline solution to yield a complex mixture of C-methylated products from which the cryptophenolic 4,5,10,10-tetramethyl derivative was isolated by exhaustive recrystallization from methanol and acetic acid, giving yellow platelets, m.p. 173–175°; infrared maximum at 1600 cm.$^{-1}$ (hydrogen bonded aryl C=O); n.m.r. (60 Mc., in $CDCl_3$ *vs.* TMS): six-proton singlet at 98 c.p.s. (alkyl methyls), six-proton singlet at 136 c.p.s. (aryl methyls), four protons in a characteristic pair of doublets centered at 421 and 444 c.p.s. (vicinal pairs of aryl protons), and a two-proton singlet at 780 c.p.s. (phenolic OH). *Anal.* Found for $C_{18}H_{18}O_3$: C, 77.1; H, 6.6; C-methyl, 13.2; O-methyl, 0.00.

Upon mild reduction (hydriodic acid in phenol, 120°, 4 min.), the quinone **2** was reduced back to **1**, which in turn, under more vigorous conditions (HI, phenol, 120°, 4 hr.), was further reduced to 6-methylpretetramid. (We have previously observed that terrarubein, 4-dimethylamino-6-methylpretetramid, is similarly reductively cleaved to 6-methylpretetramid under these vigorous conditions.[6])

The analyses, spectral relations, and transformations summarized in Scheme I identify **I** as 1,3,4,10,11,12-hexahydroxy-6-methylnaphthacene-2-carboxamide, that is, 4-hydroxy-6-methylpretetramid.[7]

(6) J. R. D. McCormick and J. Reichenthal, unpublished work.

(7) This compound has now been prepared by degradation of tetracycline: J. Hlavka, P. Bitha, and J. Boothe, *J. Am. Chem. Soc.*, 87, 1795 (1965).

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Pearl River, New York

Received February 18, 1965

4-Hydroxy-6-methylpretetramid.[1] Synthesis *via* Quaternary Tetracyclines

Sir:

The isolation and identification of 4-hydroxy-6-methylpretetramid (**5**), a precursor in the biosynthesis of tetracycline, has recently been described.[2] We wish to report on three synthetic approaches to this important biosynthetic intermediate. We have found that refluxing tetracycline methyl betaine[3] (**1**) in acetonitrile yields a new dedimethylamino derivative to which we have assigned the structure **2**, 4a,12a-anhydro-4-dedimethylamino-4-hydroxytetracycline; $\lambda_{max}^{0.1NHCl}$ 370 and 485 mμ (log ϵ 3.75 and 4.17); n.m.r.[4] showed nine nonexchangeable protons. *Anal.* Found for $C_{20}H_{17}NO_8$: C, 59.9; H, 4.6; N, 3.5.

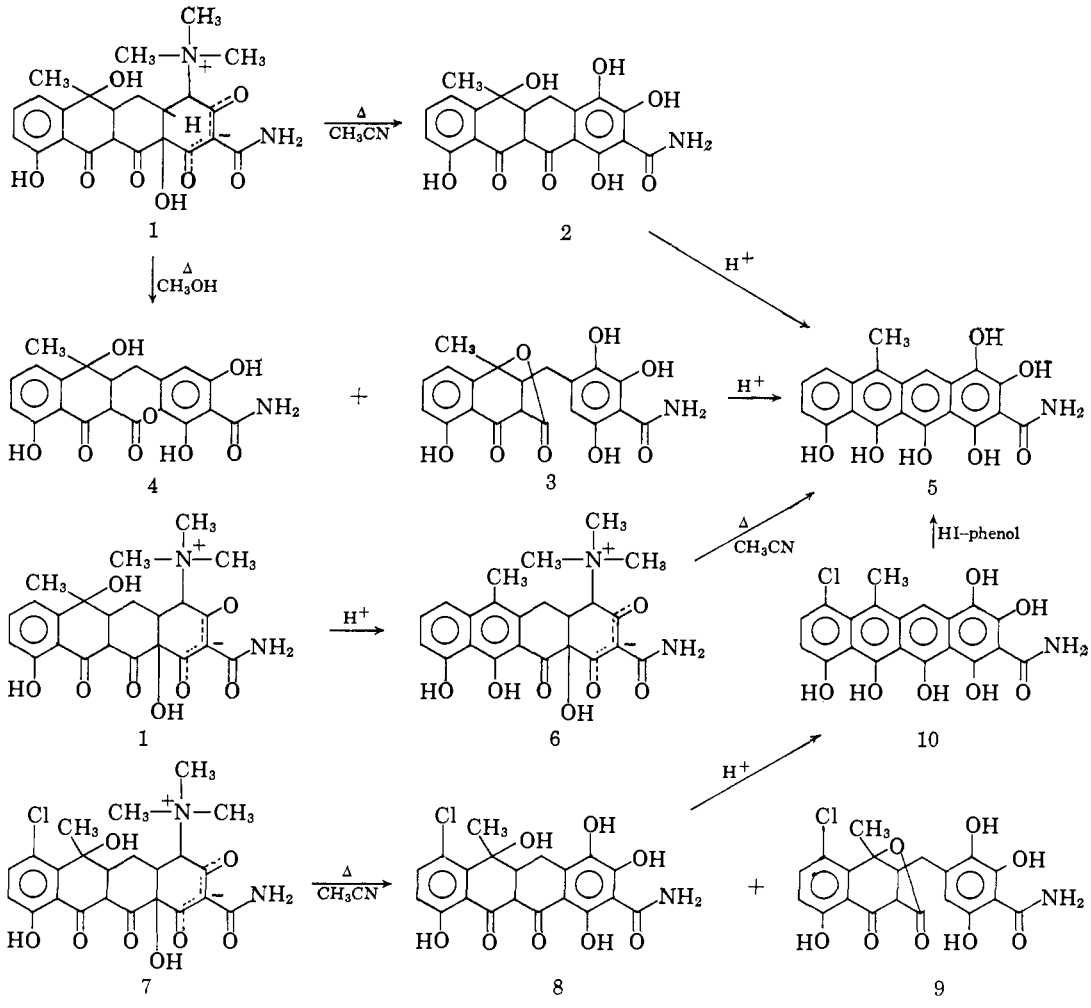
On the other hand, when the betaine **1** was refluxed in methanol we obtained as the major products both the γ-lactone **3** and the ϵ-lactone **4**. The structure of **3** was based on composition and spectral properties; $\lambda_{max}^{0.1NHCl}$ 260 and 335 mμ (log ϵ 4.14 and 3.79); λ_{max}^{KBr} 5.61 μ. *Anal.* Found for $C_{20}H_{17}NO_8$: C, 60.4; H, 5.0; N, 3.5. The n.m.r. spectrum of this material **3** exhibited a singlet at τ 3.8 due to the lone proton[5] on

(1) The name "pretetramid" has been suggested for 1,3,10,11,12-pentahydroxynaphthacene-2-carboxamide: J. R. McCormick, S. Johnson, and N. Sjolander, *J. Am. Chem. Soc.*, **85**, 1694 (1963).

(2) J. R. McCormick, Congress on Antibiotics, Prague, Czechoslovakia, June 1964; *J. Am. Chem. Soc.*, 87, 1793 (1965).

(3) J. Boothe, G. Bonvicino, C. Waller, J. Petisi, R. Wilkinson, and R. Broschard, *ibid.*, 80, 1654 (1958).

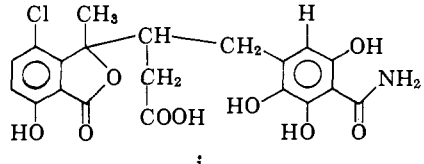
(4) All n.m.r. spectra were measured in deuterated dimethyl sulfoxide with tetramethylsilane as the internal standard using a Varian Model A60 spectrometer.



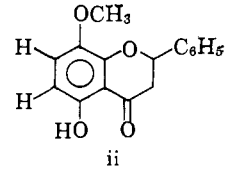
the aromatic ring bearing the three hydroxyl and one carboxamido groups. In a similar manner, the identity of **4** was based on analysis and spectral properties; $\lambda_{max}^{0.1NHCl}$ 261 and 335 mμ (log ε 4.12 and 3.79); λ_{max}^{KBr} 5.75 μ; aromatic singlet[5] at τ 3.8 found in the n.m.r. *Anal.* Found for $C_{20}H_{17}NO_8$: C, 59.5; H, 5.1.

Reaction of either **2** or **3** with strong acid affords 4-hydroxy-6-methylpretetramid (**5**). In both cases (**1** → **2** → **5** or **1** → **3** → **5**), this sequence of reactions represents an over-all shift[6,7] of the 12a-hydroxyl group[8] to the 4-position.

(5) The following model compounds were studied to verify the position of this aromatic proton



i



ii

The chemistry of i is described: C. Waller, B. Hutchings, A. Goldman, C. Wolf, R. Broschard, and J. Williams, *J. Am. Chem. Soc.*, **74**, 4979 (1952). ii is described: G. Lindstedt, *Acta Chem. Scand.*, **4**, 444 (1950).

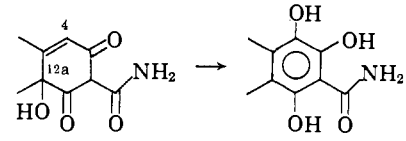
The isolation of **2** suggested that the pretetramid **5** could be obtained directly from anhydrotetracycline methyl betaine (**6**); $\lambda_{max}^{0.1NHCl}$ 272 and 432 mμ (log ε 4.70 and 3.54). *Anal.* Found for $C_{23}H_{24}O_7N_2 \cdot H_2O$: C, 60.78; H, 5.76; N, 5.85. Refluxing **6** in acetonitrile resulted in a facile elimination of trimethylamine with the formation[8] of the completely aromatic system **5**.

When 7-chlorotetracycline methyl betaine (**7**) was refluxed in acetonitrile, we isolated in addition to the chloro lactone **9** ($\lambda_{max}^{0.1NHCl}$ 260 and 352 mμ (log ε 4.09 and 3.68); λ_{max}^{KBr} 5.61 μ; n.m.r. showed a singlet[5] at τ 3.8. *Anal.* Found for $C_{20}H_{16}NO_8Cl$: C, 55.8;

(6) It is assumed that a Hofmann elimination of the trimethylamino group is the first step in formation of **2**, **3**, or **4**. Although the requirement [A. C. Cope and E. Acton, *J. Am. Chem. Soc.*, **80**, 355 (1958)] that the hydrogen at C-4a and the nitrogen at C-4 be in the *trans* conformation is at first not satisfied, it has been shown [A. Doerschuk, B. Bitler, and J. R. McCormick, *ibid.*, 77, 4687 (1955)] that epimerization at the 4-position readily occurs in various organic solvents.

(7) L. H. Conover, Symposium on Antibiotics and Mould Metabolites, The Chemical Society, London, 1956. At this symposium Dr. Conover described an investigation, carried out by Professors R. B. Woodward and H. Zimmerman at Harvard University, of the elimination of the dimethylamino group of 5-hydroxytetracycline resulting in the breaking of both the 4a–5 and 12–12a bonds.

(8) Two possibilities for the mechanism of this rearrangement of the 12a-hydroxyl group to the 4-position are given: (a) an allylic type rearrangement involving an intermediate Hofmann product:

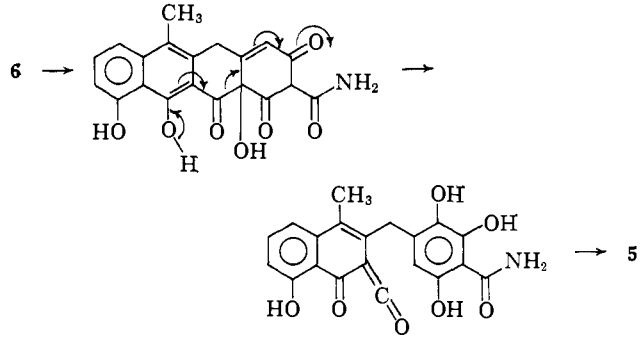


(b) A more attractive possibility is a ring-opening mechanism similar

H, 4.5; N, 3.75; Cl, 8.8) 7-chloro-4a,12a-anhydro-4-dedimethylamino-4-hydroxytetracycline, **8**; $\lambda_{max}^{0.1NHCl}$ 250 and 362 mμ (log ε 4.32 and 4.01). *Anal.* Found for $C_{20}H_{16}NO_8Cl$: C, 55.5; H, 4.2; N, 3.19; Cl, 8.8. Reaction of **8** with 30% hydrogen bromide in acetic acid yielded 7-chloro-4-hydroxy-6-methylpretetramid, **10**; $\lambda_{max}^{conc\ H_2SO_4-1\%\ Na_2B_4O_7}$ 272, 313, 487, and 514 mμ (log ε 4.24, 4.30, 3.98, and 3.98). Refluxing this material **10** for a few minutes in a phenol–hydrogen iodide mixture yielded the deschloro compound **5**; further heating (3 hr.) afforded 6-methylpretetramid.[1,2]

Acknowledgment. We wish to thank Professor H. Zimmerman, University of Wisconsin, and Dr. A. Kende for many stimulating discussions, Mr. L. Brancone and staff for analytical data, and Mr. G. Morton for n.m.r. interpretations.

to that formulated by D. H. R. Barton and I. Scott (*J. Chem. Soc.*, 1767



(1958)) for the racemization of geodin and by G. Stork (*Chem. Ind.* (London), 915 (1955)) for the racemization of usnic acid.

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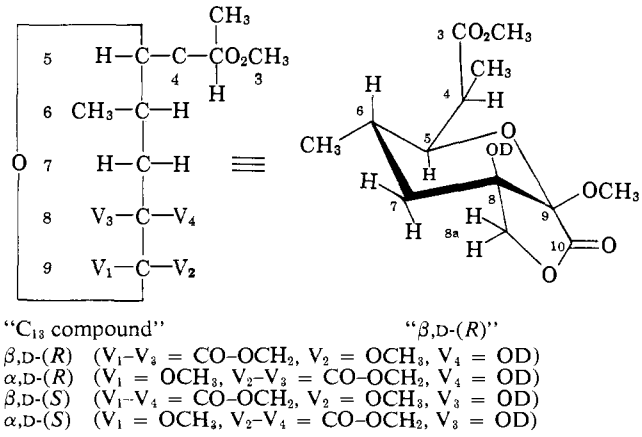
Received February 2, 1965

Macrolide Stereochemistry.[1] I. The Total Absolute Configuration of Oleandomycin[2]

Sir:

This report announces the total absolute configuration of oleandomycin[3,4] as I (*cf.* Chart I), a consequence of arriving at specifications[4b] for all 18 asymmetric centers, *i.e.* 2*R*:3*S*:4*S*:5*S*:6*S*:8*R*:10*R*:11*S*:12*R*:13*R*:1′*R*:3′*S*:4′*R*:5′*S*:1″*S*:2″*R*:3″*S*:5″*R*.

Earlier Configurational Data Applicable to Oleandomycin: (1′R:3′S:4′R:5′S:1″S:2″R:3″S:5″R:6S and xylo-C-2,3,4. These specifications follow from L-*arabino*-oleandrose[3d,5,6] and D-*xylo*-desosamine,[2d,7,8]



"C_{13} compound" "β,D-(*R*)"

β,D-(*R*) (V_1–V_3 = CO–OCH_2, V_2 = OCH_3, V_4 = OD)
α,D-(*R*) (V_1 = OCH_3, V_2–V_3 = CO–OCH_2, V_4 = OD)
β,D-(*S*) (V_1–V_4 = CO–OCH_2, V_2 = OCH_3, V_3 = OD)
α,D-(*S*) (V_1 = OCH_3, V_2–V_4 = CO–OCH_2, V_3 = OD)

Figure 1

occurring as α-L- and β-D-pyranoside substituents in I[9] and from the isolation of certain segments of I as known L-(−)-methylsuccinic acid,[3e] *i.e.*, 6*S*, and as *xylo*-2,4-dimethyl-3-hydroxyglutaric acid.[1a,3e,10,11]

Extension of Previous Studies: (5S:8R Coupled with 6S). Unpublished details[12] of previously mentioned n.m.r. data on a pertinent $C_{13}H_{20}O_7$ compound[3e] establish the relative configuration of C-5:C-6 as *erythro*.[13] Accordingly, 5*S* must follow fixed 6*S* which, in turn, allows the C_{13} compound to be viewed generally as a 5-D-ketopyranoside (*cf.* Figure 1 where numbering reflects ultimate origin in I and theoretically possible structures are indicated according to remaining epimeric (C-8) and anomeric (C-9) variables.) Since observed[12] *J* (5a,6a) dictates a Cl conformation,[14] one candidate (β-D-*S*) is automatically dismissed as an impossible, diaxially fused, 6–5 ring system.[15] Further study on base lines for chemical shifts of methoxyl

(1) (a) Part II: *J. Am. Chem. Soc.*, **87**, 1799 (1965); (b) part III: *ibid.*, **87**, 1801 (1965).

(2) For preliminary accounts, see W. D. Celmer, Congress on Antibiotics, Prague, Czechoslovakia, June 15–19, 1964: (a) Abstracts of Papers, p. 171; (b) Proceedings, Paper No. B2-262 (in press); (c) Proceedings of Panel Discussion on Basic Antibiotic Research (B-6, in press). See also Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964, p. 8P.

(3) (a) B. A. Sobin, A. R. English, and W. D. Celmer, *Antibiotics Annual*, 827 (1955); (b) W. D. Celmer, H. Els, and K. Murai, *ibid.*, 476 (1958); (c) W. D. Celmer, *ibid.*, 277 (1959); (d) H. Els, W. D. Celmer, and K. Murai, *J. Am. Chem. Soc.*, **80**, 3777 (1958); (e) F. A. Hochstein, H. Els, W. D. Celmer, B. L. Shapiro, and R. B. Woodward, *ibid.*, **82**, 3225 (1960).

(4) (a) The triacetate ester of I (generic name, triacetyloleandomycin, *cf.* ref. 3b–d) is a certified antibiotic product known also as Tao, a registered trademark of J. B. Roerig and Co., a Division of Chas. Pfizer & Co., Inc. (b) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(5) W. Neumann, *Ber.*, 70, 1547 (1937).

(6) F. Blindenbacher and T. Reichstein, *Helv. Chim. Acta*, **31**, 2061 (1948).

(7) R. K. Clark, *Antibiot. Chemotherapy*, **3**, 663 (1953).

(8) (a) C. H. Bolton, A. B. Foster, M. Stacey, and J. M. Webber, *Chem. Ind.* (London), 1945 (1962); (b) W. Hofheinz and H. Grisebach, *Tetrahedron Letters*, 377 (1962); (c) P. W. K. Woo, H. W. Dion, L. Durham, and H. S. Mosher, *ibid.*, 735 (1962); (d) F. Korte, A. Bilow, and R. Heinz, *Tetrahedron*, **18**, 657 (1962); (e) A. C. Richardson, *Proc. Chem. Soc.*, 131 (1963); this reference outlines a stereospecific synthesis of D-desosamine.

(9) W. D. Celmer and D. C. Hobbs, Congress on Antibiotics, Prague, Czechoslovakia, June 15–19, 1964: (a) Abstract of Papers, p. 179; (b) Proceedings, Paper No. B2-262b (in press); (c) forthcoming complete manuscript.

(10) (a) K. Gerzon, E. H. Flynn, M. V. Sigal, P. F. Wiley, R. Monohan, and U. C. Quarck, *J. Am. Chem. Soc.*, **78**, 6396 (1956); (b) P. F. Wiley, M. V. Sigal, Jr., O. Weaver, R. Monohan, and K. Gerzon, *ibid.*, **79**, 6070 (1957).

(11) S. G. Batrakova and L. L. Bergelison, *Izv. Akad. Nauk, SSSR, Ser. Khim.*, **9**, 1640 (1964). These authors conclude a 3*R* specification for erythromycin which is no longer tenable. *Cf.* ref. 1a.

(12) B. L. Shapiro, "A Summary of Proton Magnetic Resonance Studies on Compounds Related to Oleandomycin," Mellon Institute, Pittsburgh, Pa., April 27, 1960, example No. 20 (a privately circulated report). Excerpts from this reference (60 and 40 Mc., Me_2CO-d_6 data and conclusions summarized in a chair conformation complete except for the nature of the ring junction) are adapted to numbering in Chart I as follows: C-5 H, a doubled doublet centering at τ 6.07, *J* (5, 4 gauche/5a, 6a) = 3/10 c.p.s.; C-3 OMe, C-9 OMe as singlets at τ 6.31 and 6.37; *cf.* CH_3COOCH_3, τ 6.35. The author expresses appreciation to Dr. Shapiro for permission to reveal this information.

(13) (a) Nomenclature Committee, Division of Carbohydrate Chemistry of the American Chemical Society, *J. Org. Chem.*, **28**, 281 (1963); (b) S. Furberg and B. Pedersen, *Acta Chem. Scand.*, **17**, 1160 (1963).

(14) R. E. Reeves, *Advan. Carbohydrate Chem.* **6**, 107 (1951).

(15) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 112–114.