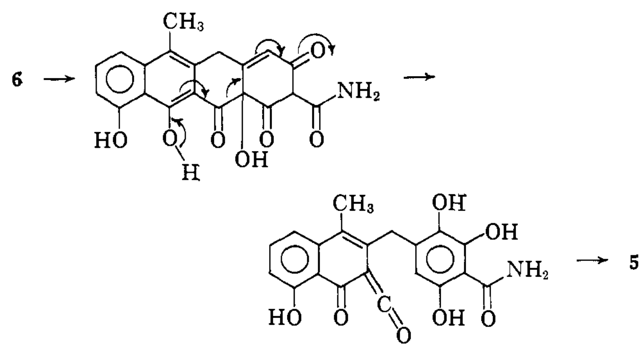
H, 4.5; N, 3.75; Cl, 8.8) 7-chloro-4a,12a-anhydro-4-dedimethylamino-4-hydroxytetracycline, **8**; $\lambda_{max}^{0.1N HCl}$ 250 and 362 mμ (log ϵ 4.32 and 4.01). *Anal.* Found for $C_{20}H_{16}NO_8Cl$: C, 55.5; H, 4.2; N, 3.19; Cl, 8.8. Reaction of **8** with 30% hydrogen bromide in acetic acid yielded 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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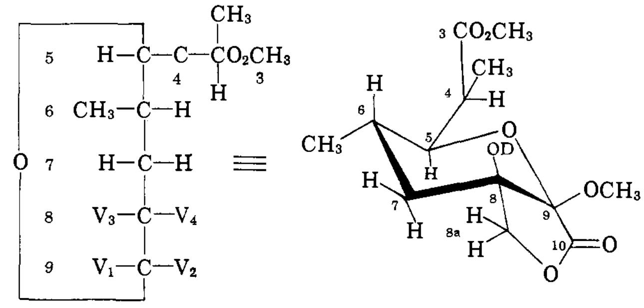
Received February 2, 1965

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] 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]



"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

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.

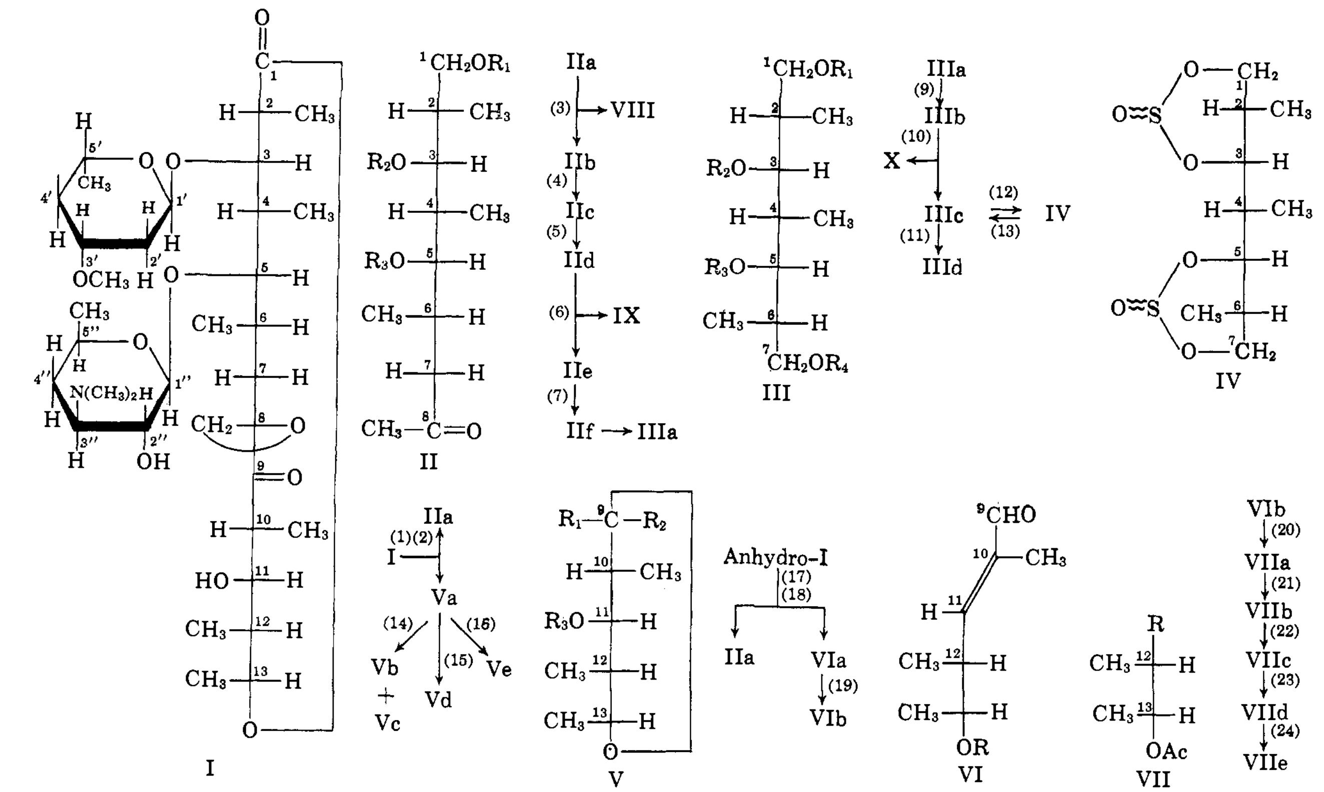
(12) B. L. Shapiro, "A Summary of Proton Magnetic Resonance Studies on Compounds Related to Oleandomycin," Mellon Institute, Pittsburgh, Pa., April 27, 1960, example No. 20 (a privately circulated report). Excerpts from this reference (60 and 40 Mc., Me_2CO-d_6 data and conclusions summarized in a chair 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).

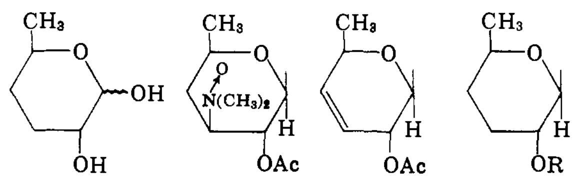
(14) R. E. Reeves, *Advan. Carbohydrate Chem.* **6**, 107 (1951).

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

Chart I[a,b]



[a] Steps: (1) $LiAlH_4$, (2) HIO_4, (3) dil. HCl, (4) Ac_2O–pyridine, (5) AcOOH, (6) Cope elimin., (7) H_2–Pd/C, (8) Baeyer–Villiger, (9) MeOH–NaOH, (10) dil. H_2SO_4, (11) *cf.* 4, (12) $SOCl_2$–pyridine, (13) *cf.* 1, (14) MeOH–HCl, (15) *cf.* 4, (16) Br_2–H_2O, (17) *cf.* 1, (18) *cf.* 2, (19) *cf.* 4, (20) Lemieux oxidn., (21) $(COCl)_2$, (22) NaN_3, (23) Curtius rearr., (24) AcOH. Physical properties of these compounds are given in Table I. [b] IIa: R_1 = H; R_2, R_3 = *cf.* I; IIb: R_1, R_2 = H; R_3 = *cf.* I; IIc: R_1, R_2 = Ac; R_3 = *cf.* Ac-I; IId: R_1, R_2 = Ac, R_3 = *cf.* XI; IIe: R_1, R_2 = Ac; R_3 = *cf.* XII; IIf: R_1, R_2 = Ac; R_3 = *cf.* XIIIa; IIIa: R_1, R_2, R_4 = Ac; R_3 = *cf.* XIIIa; IIIb: R_1, R_2, R_4 = H; R_3 = *cf.* XIIIb; IIIc: R_1, R_2, R_3, R_4 = H; IIId: R_1, R_2, R_3, R_4 = Ac; Va: R_1 = OH; R_2, R_3 = H; Vb: R_1, R_3 = H; R_2 = OCH_3; Vc: R_1 = OCH_3; R_2, R_3 = H; Vd: R_1 = OAc; R_2 = H; R_3 = Ac; Ve: R_1, R_2 = carbonyl; R_3 = H; VIa: R = H; VIb: R = Ac; VIIa: R = CO_2H; VIIb: R = COCl; VIIc: R = CON_3; VIId: R = N=C=O; VIIe: R = NHAc; VIII: L-oleandrose; IX: $(CH_3)_2NOH$.



X XI XII XIIIa, R = Ac
b, R = H

groups in various environments[16] leads to the inescapable conclusion that the observed[12] τ 6.31 and 6.37 values can arise from only one remaining possibility (β-D-*R*), hence 8*R* in I.[17]

Table I

Properties[a]	IIa	IIb	IIe	IIf	IIIa	IIIb	IIIc	IIId	
M.p., °C.	104.5	108	95	79	53	118	*b*	*b*	
$[\alpha]^{25}D$ (MeOH)	−64.5°	−8.0°	−68°	−32°	−48°	−65°	+4.2°	−6.9°	
	IV	Va	Vb	Vd	Ve	VIa	VIb	VIIa	VIIe
M.p., °C.	*c*	152	115	50	58	*d*	*e*	*f*	63–64
$[\alpha]^{25}D$ (MeOH)	(+)	+93°	+218°	+46°	+89°	+30°		−6.1°	−33.4°

[a] Properties are given for analytically pure compounds. [b] Distilled sirup. [c] Sublimed four co-crystalline $(-O)_2S{=}O$ epimers, ν^{KBr} 1180 and 1235 cm.$^{-1}$ [d] $n^{25}D$ 1.4830. [e] $n^{25}D$ 1.4602. [f] $n^{25}D$ 1.4300.

Coupling of (2R:3S:4S) with (5S:6S) in III. The structure of the constitutionally symmetrical, optically active C_{10} tetraol[2b,c] (IIIc) (*cf.* Chart I) follows from the method of preparation, confirmed by indifference toward periodate together with formation of diagnostic tetraacetate (IIId) and crystalline bistrimethylene sulfite (IV) derivatives. Configurational information up to this point[18] leaves only two possible configurations for the C_{10} tetraol which, when viewed as a 2,4,6-tri-deoxy-2,4,6-tri-C-methylheptitol,[19] are L-*glycero*-L-*ido* (P-1) and L-*glycero*-L-*gluco* (P-2). Choice of P-1 over P-2 is concluded on two counts: (1) n.m.r. considerations consistent with observed[20] relative shielding of C-methyl groups in IIId and those in model compounds and (2) optical rotatory properties[21] of both IIIc and IIId which place them in a distinctive LD-ABA

(16) H. Conroy, *Advan. Org. Chem.*, 2, 308 (1960).

(17) This conclusion was reached earlier by another line of correlations; *cf.* ref. 2b,c and 1b.

(18) The known fixed nature of C-5 and C-6 (now equated with 5-L and 6-L) eliminates half of the 16 possible configurations for the C_{10} tetraol. Observed molecular dissymmetry rejects remaining *meso*-forms, leaving six candidates. The *xylo* configuration concluded earlier for C-2,3,4 dismisses four, leaving only two possibilities for further consideration. It is noted that the P-2 possibility, discussed above, was favored by analogy to older 2*S*:4*R* specifications in erythromycin which have been subsequently revised (*cf.* ref. 1b and 2b,c) and now correspond to 2*R*:3*S*:4*S*, *i.e.*, P-1.

type of dissymmetric system. Hence 2*R*:3*S*:4*S*:5*S*:6*S* applies to I.

(10R:11S:12R:13R) Coupled with Known (2S:3R) VIIe. N.m.r. analyses on Va and its variants[22] (*cf.* Chart I) disclosed the relative configuration ascribed to segment C-9, 10, 11, 12. Rotational properties in the V-series were consistent with a D-center at C-13, which provided the over-all D-*galacto* absolute configuration, as depicted.[23] This was confirmed *via* the alternate degradation route (Chart I), leading to known[24] (2*S*:3*R*)-2-acetamido-3-acetoxybutane (VIIe). Accordingly, specifications (10*R*:11*S*:12*R*:13*R*) are established in oleandomycin, completing the definition of all centers shown in I.[25]

(19) R. L. Lohmar, "The Carbohydrates," W. Pigman, Ed., Academic Press, Inc., New York, N.Y., 1957, pp. 241–267.

(20) N.m.r. (IIId in $CDCl_3$): C-3 H, C-5 H, complex splitting at τ 5.11; C-1, C-6 methylene, apparent doubled doublet at τ 6.08; OAc (4), τ 7.94 ± 0.01; C-6 Me, τ 9.01; C-2 Me, τ 9.06; C-4 Me, τ 9.10. The shielding relationship of the specific C-methyl groups are compatible with the configuration of P-1 but not P-2. All non-*meso* configurations at C-2,3,4 were also eliminated in these considerations (*cf.* ref. 1a).

(21) P-1 and P-2 represent known ABA types (*cf.* p. 28 and Chapters 5 and 14 in ref. 15) possessing predictable rotation and rotational shift following acetylation. The observed (+) for IIIc and (−) for IIId, and the (−) shift, are in accord with P-1; the opposite is expected for P-2.

(22) N.m.r. (Vd in $CHCl_3$): C-9 H, τ 4.58 (J (9a,10a) = 9 c.p.s.); C-11 H, τ 5.26 (J (11a, 10a/11a, 12e): 11/5 c.p.s.); C-13 H, τ 6.17 (J (13, 12/13, Me) = 2.5/7 c.p.s.); C-9 OAc, C-11 OAc, τ 7.87, 7.89; C-13 Me, C-10 Me, C-12 Me, τ 8.79, 9.04, 9.11 (all J = 7 c.p.s.); C-10 H and C-12 H, complex splitting pattern.

(23) J. A. Mills and W. Klyne, *Progr. Stereochem.*, **1**, 177 (1959).

(24) F. H. Dickey, W. Fickett, and H. J. Lucas, *J. Am. Chem. Soc.*, **74**, 944 (1952).

(25) Thanks are expressed to Dr. I. A. Solomons and to many research colleagues for their interest and stimulating discussions and to Dr. R. L. Wagner and his Physical Measurements Staff for analyses. Special gratitude is extended to Mr. M. Jefferson and Mr. C. Zervos for their technical assistance.

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Received February 24, 1965

Macrolide Stereochemistry. II. Configurational Assignments at Certain Centers in Various Macrolide Antibiotics[1]

Sir:

This report reveals additional support for a thesis of predictable configurational uniformity among macrolide antibiotics. Occurrence of the same absolute configuration at anomeric centers, *i.e.*, α-L:β-D (*cf.* Klyne's rule[2,3]), in various macrolide glycosides and revision of controversial specifications, *i.e.*, (β-L),[4] (2*S*:4*R*),[5] (3*R*),[6] in erythromycin are noted.

(1) (a) Part I: *J. Am. Chem. Soc.*, **87**, 1797 (1965); (b) part III: *ibid.*, **87**, 1801 (1965); (c) footnote 2c in ref. 1a.

(2) W. Klyne, *Biochem. J.*, **47**, xli (1950).

(3) (a) T. Reichstein and E. Weiss, *Advan. Carbohydrate Chem.*, **17**, 65 (1962). (b) Klyne's rule (*cf.* pp. 98, 99 in ref. 3a), originally applied to steroid glycosides, is now regarded with an explicit 6-deoxypyranoside proviso to circumvent understandable exceptions involving D-glucosides (*cf.* ref. 3c,d). While the rule notably holds for oleandrose found in both macrolide and steroid glycosides (*cf.* Table I), it need not apply outside these fields. (c) R. Okazaki, T. Okazaki, J. L. Strominger, and A. M. Michelson, *J. Biol. Chem.*, **237**, 3025 (1962); S. Matsuhashi, *Federation Proc.*, **23**, 170 (1964). (d) Nucleotide-bound 4-keto-6-deoxy-α-D-glucose apparently serves as a common intermediate for both D- and L-6-deoxypyranosides in bacterial cell wall biosynthesis.[3c] It follows that while still nucleotide-bound the "completed" sugars possess the same anomeric configuration, *i.e.*, α-D- and β-L-; by invoking a *common* transferase mechanism involving *net inversion*, the resulting glycosides must occur as β-D- and α-L-, as observed and as empirically predicted by Klyne's rule.

The α-L:β-D Nature of Anomeric Centers. Table I covers cited and new assignments to anomeric centers in various macrolide[1c,7–19] and pertinent[3b] steroid[3a,20,21] glycosides involving pyranosides of known[7] 6-deoxyhexoses.

Either n.m.r.[22] or molecular rotational difference[2] (m.r.d.) or both of these methods were employed for analyses. Reference data stem from evident or predictable properties in keeping with known (hexose)[7] configuration[23] and preferred conformation[24] of the corresponding pyranoside in each case. The observed conformity suggests a biogenetic basis for Klyne's rule consistent with known ramifications of 6-deoxy sugar biosynthesis.[1c,3c,d]

Coupling of New Specifications (2R:3S:4S:9S) in Dihydroerythromycin with Established (8R:10R)[5,10] and (xylo-C-2,3,4)[6,25] in Erythromycin.[26] Confrontation in erythromycin of predictable (2*R*:3*S*:4*S*)[1b] and circumstantially derived (2*S*:3*R*:4*R*)[5,6] specifications prompted the following re-examination of established data. In recalling the isomeric pairs (A:B) of C_7 compounds (lactones, hydrazides, triols, *cf.* Chart I) derived from the nucleus of dihydroerythromycin by Gerzon, *et al.*,[10] one need only consider I and II for A as well as III and IV for B, *i.e.*, four sets of absolute configurational possibilities. However, it is now pointed out that a simple arithmetical process,[27,28]

(4) W. Hofheinz and H. Grisebach, *Ber.*, **96**, 2867 (1963).

(5) C. Djerassi, O. Halpern, D. I. Wilkinson, and E. J. Eisenbraun, *Tetrahedron*, **4**, 369 (1958).

(6) S. G. Batrakov and L. L. Bergelison, *Izv. Akad. Nauk, SSSR, Ser. Khim.*, **9**, 1640 (1964).

(7) For reviews see: (a) M. Berry, *Quart. Rev.* (London), **17**, 343 (1963); (b) H. Grisebach and W. Hofheinz, *J. Roy. Inst. Chem.*, 332 (1964).

(8) 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.

(9) (a) P. P. Regna, F. A. Hochstein, R. L. Wagner, Jr., and R. B. Woodward, *J. Am. Chem. Soc.* **75**, 4625 (1953); (b) R. L. Wagner, F. A. Hochstein, K. Murai, N. Messina, and P. P. Regna, *ibid.*, **75**, 4684 (1953); (c) R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957).

(10) K. Gerzon, E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley, R. Monohan, and U. C. Quarck, *J. Am. Chem. Soc.*, **78**, 6396 (1956).

(11) P. F. Wiley, M. V. Sigal, Jr., O. Weaver, R. Monohan, and K. Gerzon, *ibid.*, **79**, 6070 (1957).

(12) P. F. Wiley, R. Gale, C. W. Pettinga, and K. Gerzon, *ibid.*, **79**, 6074 (1957).

(13) R. L. Hamill, M. E. Haney, Jr., M. Stamper, and P. F. Wiley, *Antibiot. Chemotherapy*, **11**, 328 (1961).

(14) R. B. Morin and M. Gorman, *Tetrahedron Letters*, 2339 (1964).

(15) (a) W. Keller-Schierlein and G. Roncari, *Helv. Chim. Acta*, **45**, 138 (1962); (b) *ibid.*, **47**, 78 (1964).

(16) J. D. Dutcher, D. R. Walters, and O. Wintersteiner, *J. Org. Chem.*, **28**, 995 (1963).

(17) O. Ceder, J. M. Waisvisz, M. G. Van der Hoeven, and R. Ryhage, *Acta Chem. Scand.*, **18**, 111 (1964).

(18) P. W. K. Woo, H. W. Dion, and Q. R. Bartz, *J. Am. Chem. Soc.*, **86**, 2724 (1964).

(19) (a) K. Murai, B. A. Sobin, W. D. Celmer, and F. W. Tanner, *Antibiot. Chemotherapy*, **9**, 485 (1959); (b) W. D. Celmer, unpublished studies regarding the isolation of D-desosamine from PA-133-A,B.

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

(21) C. W. Shoppee, R. E. Lack, and A. V. Robertson, *J. Chem. Soc.*, 3610 (1962).

(22) H. Conroy, *Advan. Org. Chem.*, **2**, 308 (1960).

(23) (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).

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

(25) In these laboratories, the n.m.r. spectrum ($CDCl_3$) of the known O-acetylanhydride of the *meso*-1,5-diacid corresponding to lactone-A (*cf.* ref. 10 and Chart I) showed J 10/10 c.p.s. at τ 4.93, *i.e.*, J 3a,2a/3a,4a (*xylo*); *cf.* chemical proof in ref. 6.

(26) *Cf.* ref. 5, 6, 10, 11, 27 for the over-all development of constitutional and configurational relationships.