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SYNTHESIS AND TRANSFORMATIONS IN THE PHOSPHONOMYCIN SERIES

N. N. Girotra and N. L. Wendler

Merck Sharp & Dohme Research Laboratories
Merck & Co., Inc., Rahway, N. J.

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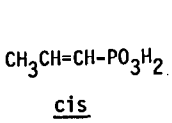
The structure and a synthesis of the promising new antibiotic phosphonomycin (3) were reported recently (1). An alternative synthesis of this substance together with the interconversion of its optical antipodes and related chemical transformations are now presented.

Treatment of cis-1-propenylphosphonic acid 1 (1,2) in aqueous solution with t-butyl- or sodium hypochlorite afforded threo-1-chloro-2-hydroxypropylphosphonic acid (2) (85%) mp 152-154° (calcd for $C_3H_8PO_4Cl$: C, 20.64; H, 4.62; Cl, 20.31. Found: C, 20.76; H, 4.67; Cl, 20.10). Resolution of 2 with (-)α-phenylethyl amine yielded (+) chlorohydrin (80%) mp 107.5-108.5° $[\alpha]_{405}$ + 19.03° (C 3.415, H_2O) converted to (-) phosphonomycin (3) (85-90%) in 10 N aqueous sodium hydroxide. The antibiotic thus prepared was isolated as its monobenzylammonium salt and found to be identical in all respects with material derived from natural sources (cf. also ref. 1).

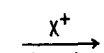
Reaction of phosphonomycin dimethyl ester 3a [prepared from 3 with diazomethane bp 55-56°/2 mm, $[\alpha]_{578}$ + 6.11 (C 4.335, CH_3OH); calcd for $C_5H_{11}PO_4$: C, 36.15; H, 6.67. Found: C, 36.32; H, 6.61] with 48% aqueous HBr-chloroform yielded threo bromohydrin 6 [bp 123-125°/0.2 mm, $[\alpha]_{578}$ -30.12° (C 4.35, $CHCl_3$); calcd for $C_5H_{12}PO_4Br$: C, 24.31; H, 4.89. Found: C, 24.22; H, 5.16] reconverted to 3a with 1 N sodium hydroxide in methanol. Hydrogenolytic debromination of 6 (Pd/$CaCO_3$-90% CH_3OH) gave dimethyl 1-hydroxypropylphosphonate (8) [bp 89-90°/0.075 mm, $[\alpha]_{578}$ -18.3 (C 4.58; CH_3OH); calcd for $C_5H_{13}PO_4$: C, 35.71; H, 7.79. Found: C, 35.74; H, 7.95] shown to have the R-configuration as deduced by the Horeau method (3). The latter permits the 1R:2S configurational assignment 3 to phosphonomycin, further confirmed by chromic acid oxidation of 6 to R (+)-α-bromopropionic acid (3a $\xrightarrow{C2}$ 6) (4).

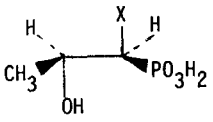
Whereas the α-halohydrins 2 and 2a [1 + N-bromosuccinimide: mp 135-137°; calcd for $C_3H_8PO_4Br$: C, 16.45; H, 3.68; Br, 36.49. Found: C, 16.53; H, 3.71; Br, 36.56] are converted by base to oxide 3, the corresponding β-halohydrins 6a [± 3 (R = Na) + HBr/ether: mp 150-152°;



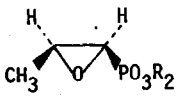
cis

1

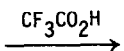


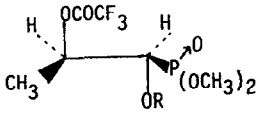


2, X = Cl
2a, X = Br

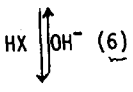


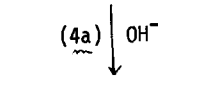
3, R = H
3a, R = CH_3

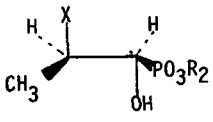




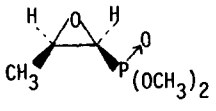
4, R = H
4a, R = $-SO_2CH_3$







6, R = CH_3; X = Br
6a, R = H; X = Br
6b, R = H, X = Cl



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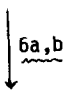

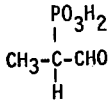

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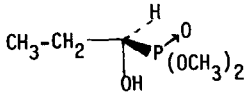

8

found: C, 16.47; H, 3.74; Br, 36.44] and 6b [± 3 (R = Na) HCl/ether; mp 157-160°; calcd for $C_3H_8PO_4Cl$: C, 20.64; H, 4.62; Cl, 20.31; found: C, 20.62; H, 4.81; Cl, 19.99] rearranged instantaneously in the presence of aqueous sodium bicarbonate and slowly in water alone to yield α-formylethylphosphonic acid (7) (5) nmr: ($NaHCO_3$-H_2O) δ1.21 (q, JP-H = 14.5 cps, JH-H, 7 cps, CH_3-), ca 3.10 (m -CH-) and 9.73 (broad doublet, J = 2.5 cps, -CHO). The signals at δ1.21 and 9.73 collapsed to a doublet (δ1.20, d, JP-H = 14.5 cps) and a singlet (δ9.72) respectively when D_2O was substituted for H_2O, whereas the multiplet at δ3.10 disappeared as a result of exchange of α-hydrogen by deuterium; dinitrophenylhydrazone (90%) mp 198-200° calcd for $C_9H_{11}PN_4O_7$: C, 33.97; H, 3.48; N, 17.61. Found: C, 34.03; H, 3.63; N, 17.89. This consequence is in marked contrast with the usual fragmentation pattern of β-halophosphonic acids to olefin and phosphate under alkaline conditions (6). The structure of 7 was confirmed by successive reduction ($NaBH_4$), esterification (CH_2N_2) and dehydration ($TSCl$-Py/Na_2CO_3) to known dimethyl-2-propenylphosphonate (7).

Interconversion of the optical antipodes of phosphonomycin, via successive inversion at each chiral center, could be effected smoothly by conversion of the dimethylester 3a $[\alpha]_{578}$ +6.1 with trifluoracetic acid to the threo glycol monoester 4 [orthoester derivative formed with diazomethane bp 71-72°/0.1 mm; calcd for $C_8H_{14}PO_6F_3$: C, 32.66; H, 4.79; F, 19.37. Found: C, 32.88; H, 4.96; F, 19.66] followed by mesylation (CH_3SO_2Cl/pyridine) to 4a and concluding ring closure (KOH-methanol) to 5 $[\alpha]_{578}$ -6.0 (c 2.75, CH_3OH). The ir and nmr spectra of 3a and 5 were identical.

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2. This acid in our hands was obtained crystalline (hygr.) mp 54-56°: Anal calcd for $C_3H_7PO_3$: C, 29.52; H, 5.78. Found: C, 29.28; H, 5.97.

3. A. Horeau and H. B. Kagan, Tetrahedron, 20, 2431 (1964). Recovered α-phenylbutyric acid from esterification of 8 with (±) α-phenylbutyric anhydride in pyridine had a rotation $[\alpha]_{578}$ -14.2 (C 4.80, C_6H_6). 8 is a unique instance of a carbinol in which the asymmetric center bears a substituent of higher atomic number than oxygen whereby the usual rotation-configuration relationship characteristic of R_1R_2CHOH systems in general is reversed.

4. B. G. Christensen, et al. (ref. 1) independently arrived at the same absolute configurational assignment.

5. The esters of these halohydrins on the other hand do not rearrange but undergo oxide formation.

6. J. A. Maynard and J. M. Swan, Aust. J. Chem., 16, 596 (1963); G. L. Kenyon and F. H. Westheimer, J. Am. Chem. Soc., 88, 3561 (1966). Less than 5% of propionaldehyde isolated as DNPH mp 149-151° was formed from 6a as a scission product. Recently oxidophosphonates have been reported to rearrange to aldehydic phosphonates with boron trifluoride [R. H. Churi and C. E. Griffin, J. Am. Chem. Soc., 88, 1824 (1966); M. Sprecher and D. Kost, Tetrahedron Letters, 703, (1969)]. Under these conditions the dimethylester 3a gave no discrete product.

7. L. A. Hamilton, Chem. Abst., 39, 4619 (1945); U.S. 2365, 466 (1944).