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SYNTHESIS OF SOME RACEMIC ISOMERS OF VALIDOXYLAMINE A[1)]

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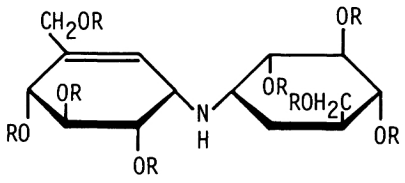
Two racemic isomers of validoxylamine A were synthesized by the condensation reaction of the blocked DL-validamine and the allyl bromide, the precursor of the unsaturated branched-chain cyclitol moiety.

Validoxylamine A, [(1S)-(1,4,6/5)-3-hydroxymethyl-4,5,6-trihydroxycyclohex-2-enyl][(1S)-(1,2,4/3,5)-2,3,4-trihydroxy-5-hydroxymethylcyclohexyl]-amine (1), was first isolated from the hydrolysate of antibiotic validamycin A with 1M sulfuric acid,[2)] and was later found to be present in the fermentation broth of Streptomyces hygroscopicus var. limoneus.[3)] It showed a very low activity, compared to the parent validamycin A, by the "dendorid test method", but exhibited considerable activity by the green house test.[3)]

In the present communication, we wish to report the first synthesis of some isomers of validoxylamine A in order to study the structure-activity relationship of this type of pseudo-disaccharides.

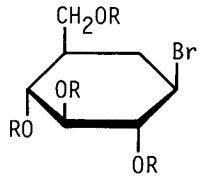
We have chosen the reaction of the blocked DL-validamine and the allyl bromide, the precursor of the unsaturated branched-chain cyclitol moiety, for synthesis of the validoxylamine A analogs.

Di-O-isopropylidene derivative (7) of DL-validamine was prepared by the following reaction sequence. Hydrolysis of DL-tetra-O-acetyl-(1,3/2,4,6)-4-bromo-6-hydroxymethyl-1,2,3-cyclohexanetriol (3)[4)] with 2M hydrochloric acid (EtOH, 80°C, 3 h) gave the hydroxy compound (4, mp 155.5–156°C, 90%), which was converted into the di-O-isopropylidene derivative (5, mp 148–149°C, 86%) by treatment with 2,2-dimethoxypropane in N,N-dimethylformamide (DMF) (TsOH, 60°C, 3 h). Compound 5

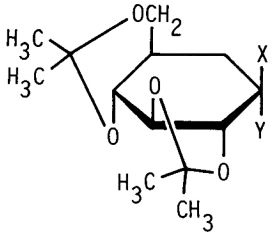


1 R = H
Validoxylamine A

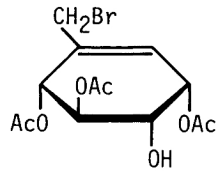
2 R = Ac
Octa-O-acetate

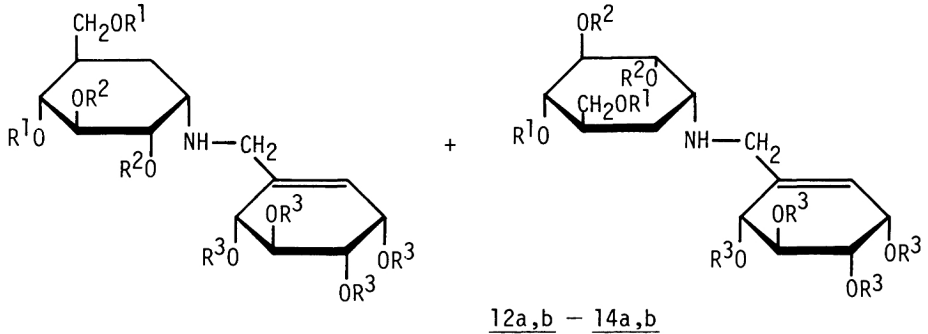


3 R = Ac
4 R = H

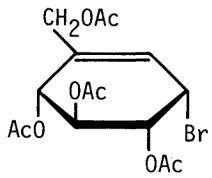


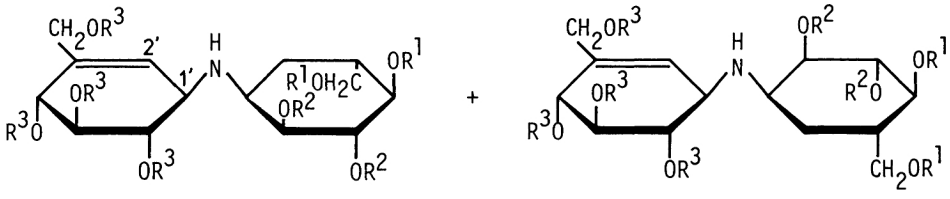
	X	Y
5	Br	H
6	H	N_3
7	H	NH_2
8	H	NHAc
9	H	NHTs
10	H	$NHCOCF_3$

7 +  → 11



12a,b – 14a,b

7 +  → 15



16a,b – 18a,b

	R^1	R^2	R^3
12, 16	$-C(CH_3)_2$	$-C(CH_3)_2$	Ac
13, 17	Ac	Ac	Ac
14, 18	H	H	H

was subjected to the azidolysis (sodium azide, dimethyl sulfoxide, 110°C, 15 h) to give via S_N2 reaction the sole azido compound (6, mp 109.5–110.5°C, 78%), which was reduced catalytically with Raney nickel T-4[5] in ethanol to give 7 (mp 153–154°C, 76%). This compound was also less satisfactorily prepared from DL-tetra-O-acetyl-(1,3,4/2,6)-4-azido-6-hydroxymethyl-1,2,3-cyclohexanetriol,[4] confirming the assigned structure. Compound 7 was further characterized as the N-acetyl (8, mp 231–232°C), the N-(p-tolylsulfonyl) (9, mp 190–191°C), and the N-(trifluoroacetyl) derivatives (10, amorphous solid).

The condensation of 7 and DL-tri-O-acetyl-(1,2,4/3)-5-bromomethyl-5-cyclohexene-1,2,3,4-tetrol (11)[6] in chloroform (2 molar equivalent of diisopropylethylamine, reflux, 3 d), followed by treatment with acetic anhydride in pyridine, gave a mixture of the condensates (12a and 12b, 80%), which was fractionated on a silica gel column with 1:3 2-butanone–toluene as an eluent to give two racemic isomers 12a (mp 176–177°C, 19%) and 12b (syrup, 27%). The analytical and ^{1}H NMR spectral data are consistent with the proposed structures: ^{1}H NMR for 12a, δ 1.43 (9H, s) and 1.50 (3H, s) (isopropylidene), 1.99 (3H, s), 2.02 (3H, s), 2.07 (3H, s), and 2.10 (3H, s) (OAc), 5.96 (1H, br d, J = 7 Hz, olefinic), and for 12b, δ 1.46 (9H, s) and 1.49 (3H, s) (isopropylidene), 2.00 (3H, s), 2.02 (3H, s), 2.07 (3H, s), and 2.10 (3H, s) (OAc), 5.85 (1H, br d, J = 6 Hz, olefinic). Treatment of 12a and 12b with 70% aqueous acetic acid (room temperature, overnight) and successive acetylation gave the corresponding octa-O-acetyl derivatives (13a) and (13b), respectively: ^{1}H NMR for 13a, δ 1.93 (3H, s), 1.97 (6H, s), 1.98 (3H, s), 2.00 (3H, s), 2.05 (6H, s), and 2.07 (3H, s) (OAc), 5.81 (1H, br d, J = 6 Hz, olefinic), and for 13b, δ 1.94 (3H, s), 1.97 (6H, s), 2.00 (6H, s), 2.04 (6H, s), and 2.06 (3H, s) (OAc), 5.74 (1H, br d, J = 5 Hz, olefinic). De-O-acetylation was effected by treatment with methanolic sodium methoxide in methanol (room temperature, overnight) to give the racemic "reversed" isomers (14a and 14b) of validoxylamine A, which showed a single spot at Rf 0.11 on TLC in 4:1:1 1-propanol–acetic acid–water (1,[7] : Rf 0.33).

Next, the synthesis of the racemic epivalidoxylamine A (18a and 18b) was carried out by the condensation of 7 and DL-tetra-O-acetyl-(1,3,6/2)-6-bromo-4-hydroxymethyl-4-cyclohexene-1,2,3-triol (15).[6,8] The reaction proceeded very slowly in dry DMF (3.2 molar equivalent of diisopropylethylamine, room temperature), and, after 20 days, when 7 was almost consumed, a mixture of the products was separated by silica gel column chromatography. A 40% yield of the desired condensates (16a and 16b) was obtained as a homogeneous syrup, along with several side-products: 8 and some acetyl derivatives of DL-(1,2,4/3)-5-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol.[9] Both 16a and 16b had similar mobilities on TLC in several solvent systems. De-O-isopropylidenation (EtOH, TsOH, room temperature, 1 d) followed by the conventional acetylation gave the racemic isomers (17a and 17b) of the octa-O-acetyl epivalidoxylamine A, which were successfully separated by chromatography on silica gel with 1:2 ethyl acetate–toluene giving 17a (23%) and 17b (41%) as a homogeneous syrup. The analytical and ^{1}H NMR spectral data supported the assigned structures: ^{1}H NMR for 17a, δ 1.89–2.06 (24H, m, OAc), 3.83 (1H, dd, J = 4.2 and 11.5 Hz) and 4.03 (1H, dd, J = 4.7 and 11.5 Hz) (CH_2OAc), 4.24 (1H, br d) and 4.60 (1H, br d) (J = 12.5 Hz, C=CCH_2OAc), and for 17b, δ 1.90–

2.07 (24H, m, OAc), 3.79 (1H, dd, J = 3.2 and 11.5 Hz) and 4.01 (1H, dd, J = 4.5 and 11.5 Hz) (CH_2OAc), 4.26 (1H, br d) and 4.52 (1H, br d) (J = 13.5 Hz, C=CCH_2OAc). Compounds 17a and 17b showed a single spot at Rf 0.40 and 0.35, respectively, on TLC in 1:1 ethyl acetate–toluene, while, an authentic sample of octa-O-acetyl validoxylamine (2)[10] at Rf 0.32. In the ^{1}H NMR spectra of 17a and 17b, the observed small coupling constants between the C-2' olefinic proton and the C-1' proton indicated that the imino groups oriented in the pseudo-equatorial positions.[11] It is interesting to note that, in the spectrum of 17b, the chemical shifts and the splitting pattern of the signals due to the ring protons of the validamine portion as well as two acetoxymethyl protons resemble those of 2, suggesting that 17b adopts more similar conformation to that of 2 in chloroform than 17a does. Deblocking of a mixture (16a and 16b) by treatment with TsOH in ethanol followed by de-O-acetylation with sodium methoxide in methanol gave 18a and 18b as a homogeneous mixture showing Rf 0.28 on TLC in 4:1:1 1-propanol–acetic acid–water (2: Rf 0.31).

Biochemical and biological studies on the isomers of validoxylamine A obtained in this work are on the way.

References and Notes

1) Presented in part at the 43rd National Meeting of the Chemical Society of Japan, Tokyo, April 1981, Abstr. No. 4F39. All the compounds described in this paper are racemic. For convenience, the formulas depict only one of the respective enantiomers. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Varian EM-390 (90 MHz) spectrometer in chloroform-d with reference to tetramethylsilane as an internal standard. TLC was performed on precoated silica gel 60 F-254 plaques (Merck, Darmstadt). All the new compounds gave satisfactory analytical data.

2) S. Horii, T. Iwasa, and Y. Kameda, J. Antibiot., 24, 57 (1971).

3) S. Horii, Y. Kameda, and K. Kawahara, J. Antibiot., 25, 48 (1972).

4) S. Ogawa, K. Nakamoto, M. Takahara, Y. Tanno, N. Chida, and T. Suami, Bull. Chem. Soc. Jpn., 52, 1174 (1979).

5) S. Nishimura, Bull. Chem. Soc. Jpn., 32, 61 (1959).

6) S. Ogawa, T. Toyokuni, and T. Suami, Chem. Lett., 1980, 713.

7) The authentic sample was kindly supplied by Dr. Satoshi Horii.

8) Compound 15 (α-bromide) crystallized out, by addition of ethanol, from the mixture of α- and β-bromides: mp 66–67.5°C (recrystallized from ethanol). ^{1}H NMR, δ 6.07 (1H, br d, J = 4.7 Hz, olefinic) [cf. β-bromide, δ 5.99 (1H, br s, olefinic)].

9) When the condensation reaction of 7 and 15 was conducted at elevated temperature, the formation of these side-products became preferable.

10) Prepared from 1 by the conventional acetylation.

11) The olefinic protons of 17a and 17b appeared as a broad singlets at δ 5.70 and 5.65, respectively, while, that of 2 as a doublet (J = 5.3 Hz) at δ 5.95.

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