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THE STEREOCHEMISTRY OF DESOSAMINE, AN NMR ANALYSIS

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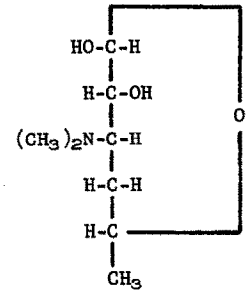
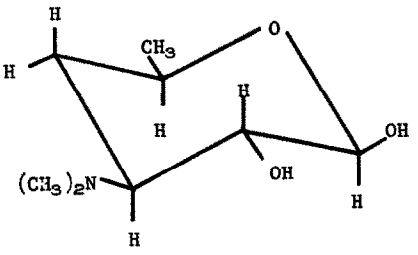
DESOSAMINE, a 3,4,6-trideoxy-3-dimethylaminohexose[1] obtained from a number of antibiotics (erythromycins A, B and C, methymycin, neomethymycin, narbomycin, oleandomycin and picromycin), was recently shown to belong to the D family,[2] but its complete configuration has not been reported. An NMR study has now provided data (cf. Table 1) which indicate that in desosamine (m.p. 86-87°), desosamine hydrochloride (m.p. 188-190°) and diacetyldesosamine hydrochloride (m.p. 197-198°) the hydrogens at C-1, C-2, C-3 and C-5 are all axial. Thus, based on the established configuration at C-5, desosamine may be sterically represented as I and II.



I



II

[1] R.K. Clark, Jr., Antibiotics & Chemotherapy 3, 663 (1953); H. Brockmann, H.B. König and R. Oster, Chem. Ber. 87, 856 (1954).

[2] C.H. Bolton, A.B. Foster, M. Stacey and J.M. Webber, J. Chem. Soc. 4831 (1961).

TABLE 1

Coupling Constants of Desosamine and Derivatives[a]

	Desosamine (cps)	Diacetyldesosamine hydrochloride (cps)	Desosamine hydrochloride (cps)
$J_{1a,2a}$	7.8	7.6	-
$J_{2a,3a}$	10.2	10.4	-
$J_{3a,4e}$	3.9 (4.2)[b]	4.2 (4.5)[b]	(4.2) or (2.3)
$J_{3a,4a}$	12.0 (11.7)[b]	12.5 (12.2)[b]	(12.0) or (10.5)
$J_{4a,4e}$	13.1	12.7	13.0
$J_{4a,5a}$	11.1 (10.7)[b]	11.1 (10.7)[b]	(10.5) or (12.0)
$J_{4e,5a}$	1.8 (2.2)[b]	1.9 (2.3)[b]	(2.3) or (4.2)
$J_{5a,6}$	6.3	6.1	6.2
$J_{1e,2a}$	4.0[c]	none	3.0[c]
$J_{2a,3a}$	10.9[c]	none	-

[a] All spectra were determined with a Varian A-60 instrument using deuterium oxide as solvent.

[b] Measured values, from which J values were estimated as described in ref. 6.

[c] Values for the minor anomer.

The NMR spectrum of desosamine (cf. Fig. 1) immediately after solution in deuterium oxide shows that the C-1 hydrogen doublet centered at 4.97 p.p.m. is coupled to the hydrogen at C-2 with $J_{1,2}$ = 7.8 cps, a magnitude indicative of a diaxial orientation of these two hydrogens.[3,4] Diacetyl-

[3] From NMR studies of acetylated pyranose, cyclohexane and related ring systems, R.U. Lemieux, R.K. Kulling, H.J. Bernstein and W.G. Schneider [J. Amer. Chem. Soc. 80, 6098 (1958)] reported these data: (a) for hydrogens on adjacent carbons, $J_{a,a}$ = 5-8 cps, $J_{a,e}$ or $J_{e,e}$ = 2-3.5 cps (cf. ref. 4); (b) in β-D-xylopyranose tetraacetate, $J_{5a,5e}$ = 12 cps, $\delta_{5e} > \delta_{5a}$ (cf. ref. 5); (c) for a number of acetylated pyranoses, δ_{1e} = 5.66-6.11 p.p.m., δ_{1a} = 5.37-5.75 p.p.m. (cf. Ref. 5).

[4] J.I. Musher [J. Chem. Phys. 34, 594 (1961)] shows that $J_{a,a}$ = 12.35 cps $J_{a,e}$ = 4.25 cps in 1,1,4,4-tetramethylcyclohexyl-cis-2,6-diacetate.

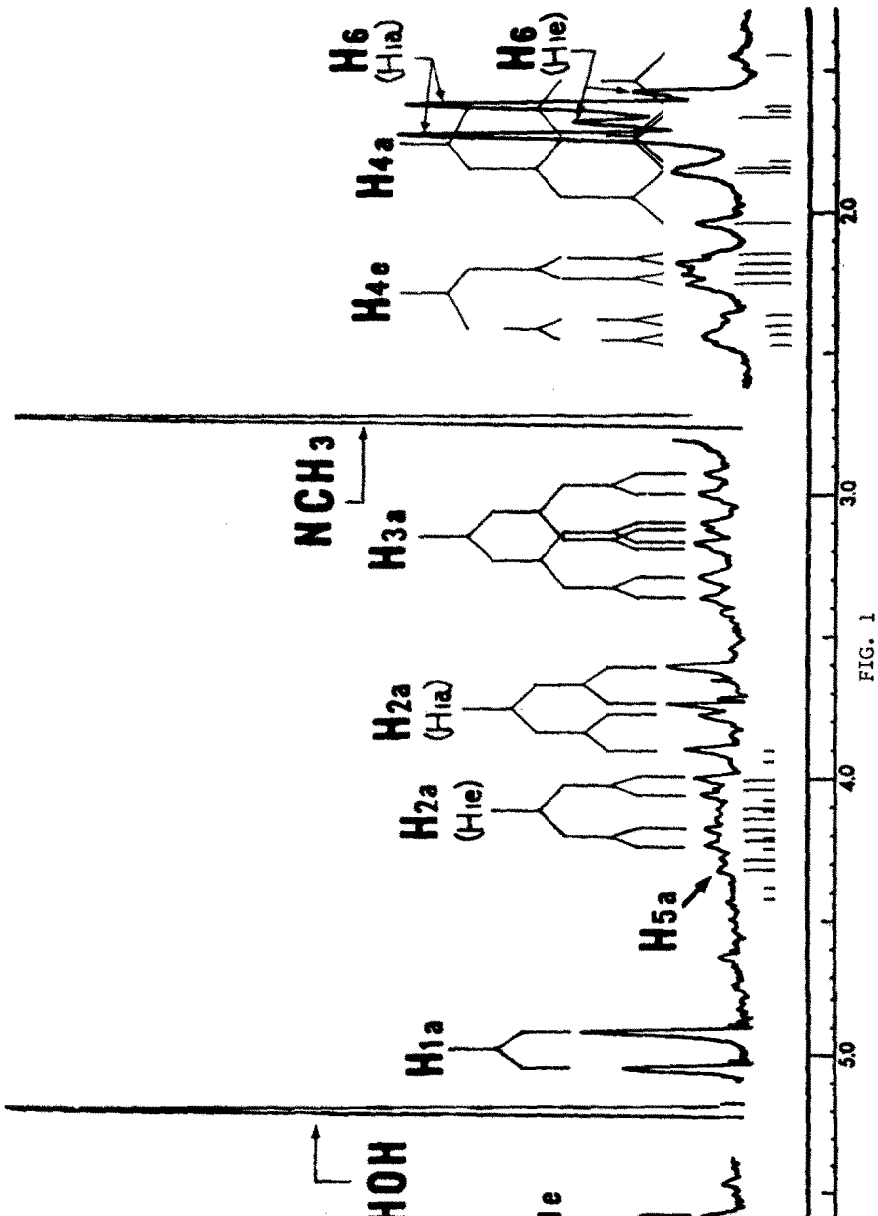


FIG. 1

NMR spectrum of desosamine in deuterium oxide at 60 mc with chemical shifts given in p.p.m. from tetramethylsilane as zero.

desosamine hydrochloride, not complicated by anomerization, shows this same diaxial orientation at C-1 and C-2; its spectrum shows the C-1 hydrogen doublet down field centered at 6.20 p.p.m. and the C-2 hydrogen quartet down field centered at 5.65 p.p.m., both exhibiting axial-axial splitting of 7.6 cps.[3,4] The two groups of doublets in the desosamine spectrum centered at 3.75 p.p.m. are assigned to the C-2 hydrogen, and the splitting pattern shows $J_{2a,3}$ = 10.2 cps, a magnitude which indicates that the C-3 hydrogen is axial.[3,4] The axial C-3 hydrogen signals at 3.14 p.p.m. confirm this value of $J_{2a,3a}$ and further give indication that $J_{3a,4e}$ is 3.9 and $J_{3a,4a}$, 12.0 cps, approximately.

The two groups of quartets for the equatorial hydrogen at C-4 at 2.14 to 2.47 p.p.m. show coupling with the axial C-4 hydrogen at higher field with $J_{4a,4e}$ = 13.1 cps,[3,5] and with the neighboring hydrogens at C-3 and C-5 with J values of approximately 3.9 and 1.8 cps,[6] respectively. The splitting pattern of the axial C-4 hydrogen (partly hidden by the C-methyl doublet centered at 1.66 p.p.m.), having a total width of 35.5 cps, indicates that it is coupled to the two hydrogens at C-3 and C-5 with J values of approximately 12.0 and 11.1 cps.[6] These large values confirm the axial nature of the C-3 hydrogen deduced previously and establish the axial orientation of the C-5 hydrogen.[3,4] The axial C-4 hydrogen signals in diacetyldesosamine hydrochloride are all visible and fit the theoretical

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[5] J.N. Shoolery and M.T. Rogers [J. Amer. Chem. Soc. 80, 5121 (1958)] give other examples showing that the equatorial proton absorbs at a larger δ value than its axial counterpart.

[6] The hydrogens are treated as an ABX system [J.A. Pople, W.G. Schneider and H.J. Bernstein, High Resolution Nuclear Magnetic Resonance p. 132. McGraw-Hill, New York (1959)] with each line further coupled to Y which is non-interacting with X. The H_{4a} splitting in Fig. 1 was obtained by first treating H_{4a}, H_{4e} and H_{3a} as an ABX system, then, as an approximation, splitting each line symmetrically with respect to chemical shift and intensity by H_{5a} as Y. With this approximation the J values were estimated from the observed splittings given in parentheses in Table 1. Similarly by treating H_{5a} as X and H_{3a} as Y an estimate of $J_{4a,5a}$ was obtained.

splitting pattern estimated from the appropriate J values in Table 1.[6]

Anomerization of desosamine in deuterium oxide gave after five minutes significant amounts of the minor anomer in which the equatorial C-1 hydrogen doublet appeared down field at 5.62 p.p.m., $J_{1e,2a}$ = 4.0 cps,[3,5] and the C-2 hydrogen quartet, down field centered at 4.12 p.p.m., $J_{2a,3a}$ = 10.9 cps. These data show that desosamine (m.p. 86-87°) exists primarily as the anomer with relative configuration II.

Similar consideration leads to the conclusion that desosamine hydrochloride (m.p. 197-198°) also possesses the all-trans configuration (cf. Table 1[7]). Its spectra in deuterium oxide show the occurrence of anomerization and exhibit the typical signal patterns which indicate that the C-3 and C-5 hydrogens are axial.

It is of biogenetic interest that desosamine and the methyl glycoside of chalcose,[8] a 3,4,6-trideoxy-3-methoxyhexose found in the antibiotic chalcomycin, are identical in configuration.

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[7] In the desosamine hydrochloride spectra the C-3 hydrogen signals, due to a down field shift similar to that shown also by the N-methyl singlet (0.68 p.p.m. from that in Fig. 1), overlap the C-2 hydrogen signals and thus produce a highly complex pattern [Pople et al., loc. cit. (ref. 6), pp. 96-98] from which it is difficult to obtain the values of $J_{3a,4a}$ and $J_{3a,4e}$ and thus to distinguish them from $J_{4a,5a}$ and $J_{4e,5a}$.

[8] P.W.K. Woo, H.W. Dion and L.F. Johnson, J. Amer. Chem. Soc. 84, 1066 (1962).