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MASS SPECTROMETRY OF SOME *N*-ACYLDAUNOSAMINE DERIVATIVES

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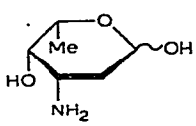
ABSTRACT

The principal modes of fragmentation subsequent to electron impact of some *N*-acyl derivatives of daunosamine, the glycoside moiety of the antitumour antibiotics daunomycin and adriamycin, have been studied by using specifically deuterated derivatives and high-resolution measurements. In particular, the elimination of MeOH from methyl β-daunosaminides is shown to occur extensively and stereospecifically, and involves HO-4. The splitting of the moieties C-1–C-2 and C-5–O-5 affords the fragments D_2, D'_2, and D''_2, which are among the most abundant.

INTRODUCTION

Daunosamine, 3-amino-2,3,6-trideoxy-L-*lyxo*-hexose (**1**), is an amino sugar found in Nature as the glycoside moiety of the antibiotics daunomycin[1] and adriamycin[2], which show interesting antitumour properties[3].



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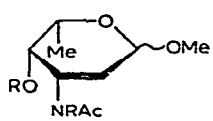

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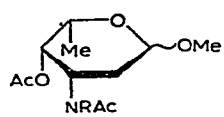
2a R = D



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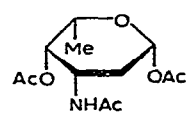

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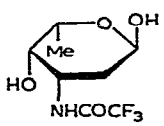

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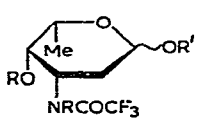
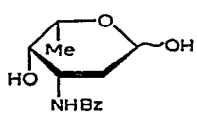


6 R = H, R' = Me
6a R = D, R' = Me
6b R = H, R' = CD_3



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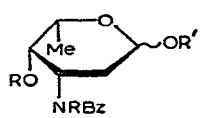


8 R = H, R' = Me
8a R = D, R' = Me
8b R = H, R' = CD_3

A study of the mass spectra of some *N*-acyldaunosamine derivatives has been undertaken in order to provide basic information on this series of substances. The

following compounds have been examined: methyl *N*-acetyl-α-daunosaminide[1] (**2**), methyl *N*-acetyl-*N*-deuterio-4-*O*-deuteriodaunosaminide (**2a**), methyl *N*-acetyl-*O*-acetyl-α-daunosaminide[1] (**3**), methyl *N*-acetyl-4-*O*-acetyl-*N*-deuteriodaunosaminide (**3a**), triacetyl-β-daunosamine[1] (**4**), *N*-trifluoroacetyl-α-daunosamine (**5**), methyl *N*-trifluoroacetyldaunosaminide (**6**), methyl *N*-deuterio-4-*O*-deuterio-*N*-trifluoroacetyldaunosaminide (**6a**), trideuteriomethyl *N*-trifluoroacetyldaunosaminide (**6b**), *N*-benzoyldaunosamine[1] (**7**), methyl *N*-benzoyl-α-daunosaminide (**8**) (the D enantiomer of compound **8** has been synthesized by Richardson[4]), methyl *N*-benzoyl-*N*-deuterio-4-*O*-deuteriodaunosaminide (**8a**), and trideuteriomethyl *N*-benzoyldaunosaminide (**8b**). The compounds for which configuration at C-1 is not specified have been examined as anomeric mixtures. The structure of the fragments and the main features of the fragmentation patterns have been established by comparison of the spectra of the compounds with those of their deuterium-labelled derivatives. High-resolution measurements have been carried out in order to confirm the composition of a number of fragments. All the relevant data are collected in Tables I–III.

TABLE I

m/e VALUES AND RELATIVE INTENSITIES (GIVEN IN PARENTHESES) OF THE FRAGMENTS IN THE MASS SPECTRA OF THE *N*-ACETYL DERIVATIVES

Fragments	*Compounds*				
	2	*2a*	*3*	*3a*	*4*
$[M]^+$	203 (—)	205 (0.2)	245 (0.5)	246 (0.4)	273 (—)
A_1	171 (8)	173 (10)	213 (1)	214 (1)	213 (0.3)
A_2	153 (5)	154 (8)	153 (14)	154 (15)	153 (8)
A_3	138 (1)	139 (2)	138 (5)	139 (6)	138 (6)
B_1	185 (4)	186 (10)	185 (15)	186 (12)	213 (0.3)
B_2	142 (4)	143 (6)	142 (23)	143 (22)	170 (0.4)
C_1	172 (11)	174 (18)	214 (12)	215 (14)	214 (1)
C_2	113 (18)	114 (17)	155 (4)	155 (6)	155 (0.6)
C_3	95 (8)	95 (10)	95 (29)	95 (33)	95 (2)
D_1	159 (5)	161 (8)	201 (4)	202 (5)	229 (—)
D_2	101 (68)	103 (74)	143[a] (27)	144 (35)	143 (3)
D_2'	59 (100)	61 (100)	101[a] (69)	102 (76)	101 (15)
D_2''	—	—	59[a] (22)	60 (22)	59 (11)
E_1	145 (0.5)	147 (0.6)	187 (0.6)	188 (—)	187 (2)
E_2	58 (28)	58 (27)	58[a] (16)	58 (15)	86 (20)
F_1	129 (10)	130 (13)	129 (3)	130 (3)	157 (0.5)
F_1'	114 (7)	115 (9)	114 (5)	115 (5)	—
F_2	128 (4)	129 (6)	128[a] (23)	129 (24)	156 (4)
H_1	86 (26)	87 (21)	86[a] (36)	87 (40)	86 (20)
H_2	72 (19)	73 (21)	72[a] (13)	73 (11)	72 (33)
L	86 (26)	88 (12)	—	—	—
$[M-33]$	—	172 (15)	—	—	—
$[CH_3CO]^+$	43 (57)	43 (71)	43 (100)	43 (100)	43 (100)

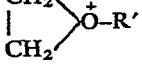
[a]The composition has been confirmed by high-resolution measurements (accuracy ±0.003 mass unit).

RESULTS AND DISCUSSION

The fragmentation patterns shown in Scheme 1, due to the elimination of neutral molecules or radicals, do not break the daunosamine ring and, for the *A* and *C* processes, lead to substituted pyrylium ions. Metastable peaks corresponding to transitions $C_1 \rightarrow C_2$ and $C_2 \rightarrow C_3$ were observed. These patterns have been observed in the mass spectra of amino sugar derivatives[5]. The elimination of R'OH from the pure α-anomer can occur through 1:3 or 1:4 processes[6], in addition to the 1:2 process shown in Scheme 1. It may be pointed out that, whereas for compounds **2**, **6**, and **8** elimination of MeOH from the molecular ion is observed (A_1, M−32), in the corresponding deuterium-labelled derivatives **2a**, **6a**, and **8a**, in addition to the M−32 peak, a more-abundant M−33 fragment appears. As the last fragmentation is an elimination of MeOD, C-4-OD must be involved, probably in the stereospecific way shown in Scheme 2. Only the compounds having the β configuration at C-1

TABLE II

m/e VALUES AND RELATIVE INTENSITIES (GIVEN IN PARENTHESES) OF THE FRAGMENTS IN THE MASS SPECTRA OF THE *N*-TRIFLUOROACETYL DERIVATIVES

Fragments	*Compounds*			
	5	*6*	*6a*	*6b*
$[M]^+$	243 (—)	257 (—)	259 (—)	260 (—)
A_1	225 (0.5)	225 (4)	227 (3)	225 (2)
A_2	207 (1)	207 (0.6)	208 (1)	207 (1)
A_3	192 (1)	192 (1)	193 (1)	192 (3)
B_1	225 (0.5)	239 (—)	240 (—)	242 (—)
B_2	128 (0.6)	142 (—)	143 (7)	145 (0.4)
C_1	226 (1)	226 (9)	228 (5)	226 (7)
C_2	113 (6)	113 (23)	114 (12)	113 (19)
C_3	95 (2)	95 (4)	95 (5)	95 (5)
D_1	199 (3)	213 (6)	215 (3)	216 (2)
D_2	155 (40)	155[a] (48)	157 (59)	155 (48)
$D_2^{\bullet}$	86 (100)	86[a] (23)	88 (43)	86 (31)
$D_2^{\bullet\bullet}$	58 (23)	58 (43)	60 (100)	58 (22)
E_1	199 (3)	199[a] (5)	201 (4)	199 (3)
E_2	44 (12)	58 (43)	58 (63)	61 (31)
F_1	169 (18)	183[a] (4)	184 (6)	186 (4)
$F_1^{\bullet}$	—	168[a] (4)	169 (6)	168 (11)
F_2	168 (5)	182 (2)	183 (3)	185 (2)
H_1	140 (33)	140[a] (13)	141 (17)	140 (16)
H_2	126 (4)	126 (1)	127 (2)	126 (2)
L	140 (33)	140[a] (13)	142 (14)	140 (16)
[M−33]	—	—	226 (7)	—
$[CF_3]^+$	69 (21)	69 (11)	69 (19)	69 (17)
	45 (28)	59[a] (100)	59 (55)	62 (100)

[a]The composition has been confirmed by high-resolution measurements (accuracy ±0.003 mass unit).

TABLE III

m/e VALUES AND RELATIVE INTENSITIES (GIVEN IN PARENTHESES) OF THE FRAGMENTS IN THE MASS SPECTRA OF THE *N*-BENZOYL DERIVATIVES

Fragments	*Compounds*			
	7	*8*	*8a*	*8b*
$[M]^+$	251 (0.2)	265 (—)	267 (0.1)	268 (0.2)
A_1	233 (4)	233 (9)	235 (4)	233 (9)
A_2	215 (2)	215 (3)	216 (2)	215 (3)
A_3	200 (1)	200 (0.7)	201 (1)	200 (4)
B_1	233 (4)	247 (3)	248 (4)	250 (3)
B_2	128 (4)	142 (6)	143 (6)	145 (5)
C_1	234 (1)	234 (5)	236 (4)	234 (4)
C_2	113 (—)	113 (6)	114 (4)	113 (3)
C_3	95 (0.4)	95 (2)	95 (2)	95 (2)
D_1	207 (2)	221 (1)	223 (1)	224 (1)
D_2	163 (4)	163[a] (19)	165 (16)	163 (14)
E_1	207 (2)	207 (—)	209 (0.3)	207 (0.3)
E_2	44 (2)	58 (7)	58 (4)	61 (0.9)
F_1	177 (7)	191[a] (7)	192 (6)	194 (7)
F_1'	—	176[a] (3)	177 (2)	176 (6)
F_2	176 (5)	190[a] (3)	191 (3)	193 (2)
H_1	148 (6)	148[a] (3)	149 (1)	148 (3)
H_2	134 (—)	134 (—)	135 (—)	134 (0.4)
L	148 (6)	148[a] (3)	150 (2)	148 (3)
[M−33]	—	—	234 (9)	—
$[C_6H_5]^+$	77 (21)	77 (24)	77 (26)	77 (28)
$[C_6H_5CO]^+$	105 (100)	105 (100)	105 (100)	105 (100)
$[C_6H_5CONH_3]^+$	122 (30)	122[a] (17)	124 (16)	122 (12)

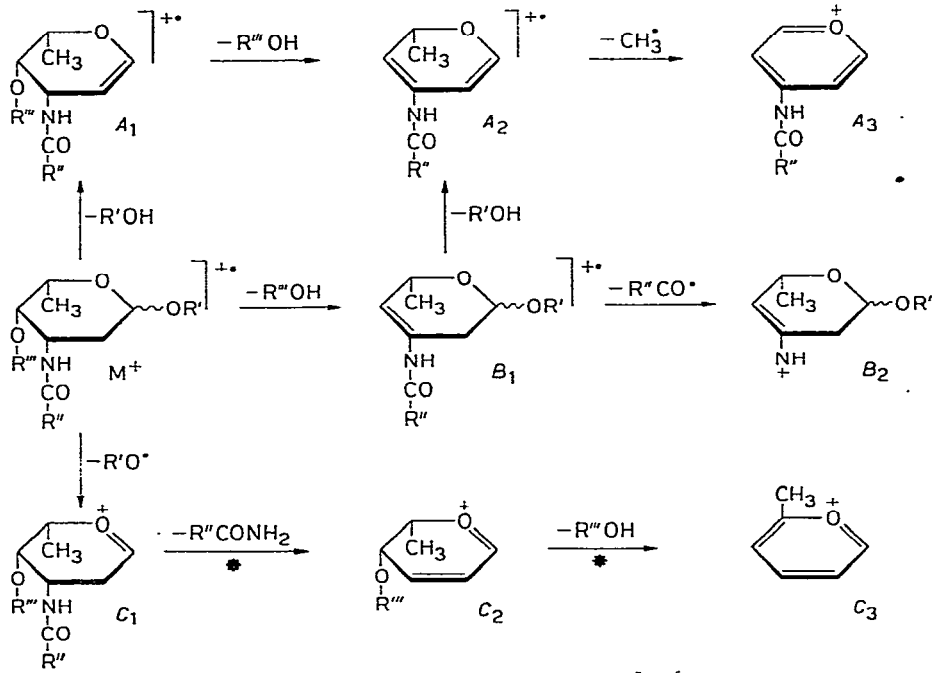
[a]The composition has been confirmed by high-resolution mass measurements (accuracy ±0.003 mass unit).

undergo MeOD elimination. For compounds **2a** and **8a**, obtained from the α anomers **2** and **8**, respectively, by exchange with heavy water (see Experimental), anomerisation occurs during deuteration [the p.m.r. spectra ($CDCl_3$) of **2** and **8** show splitting of the main peaks after treatment with D_2O] allowing elimination of MeOD from the resulting β anomer. A similar, stereospecific elimination has been described for cyclohexane-*cis*-1,4-diol[7], whereas, to our knowledge, the only example mentioned in the carbohydrate field is the elimination of MeOD observed for methyl 5-deoxy-β-D-xylofuranoside[8] after exchange with D_2O.

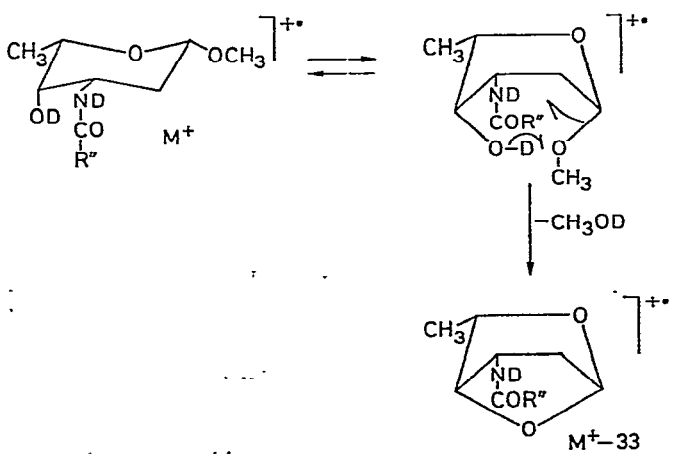
For pathway *B*, it may be mentioned that the ions B_1 and B_2 are of low abundance in the spectra of the *N*-trifluoroacetyl derivatives **5** and **6**.

In Scheme 3, the fragmentation processes arising from the initial cleavage of the O–C-1 bond are shown. Pathway *D* is generally observed in the amino sugar derivatives[5]. The first step is elimination of acetaldehyde to give the radical-ion D_1, which loses the C-1–C-2 moiety as a neutral molecule giving the ion D_2, one of the most abundant in the spectra of *N*-acyldaunosamines. Subsequent fragmentations of

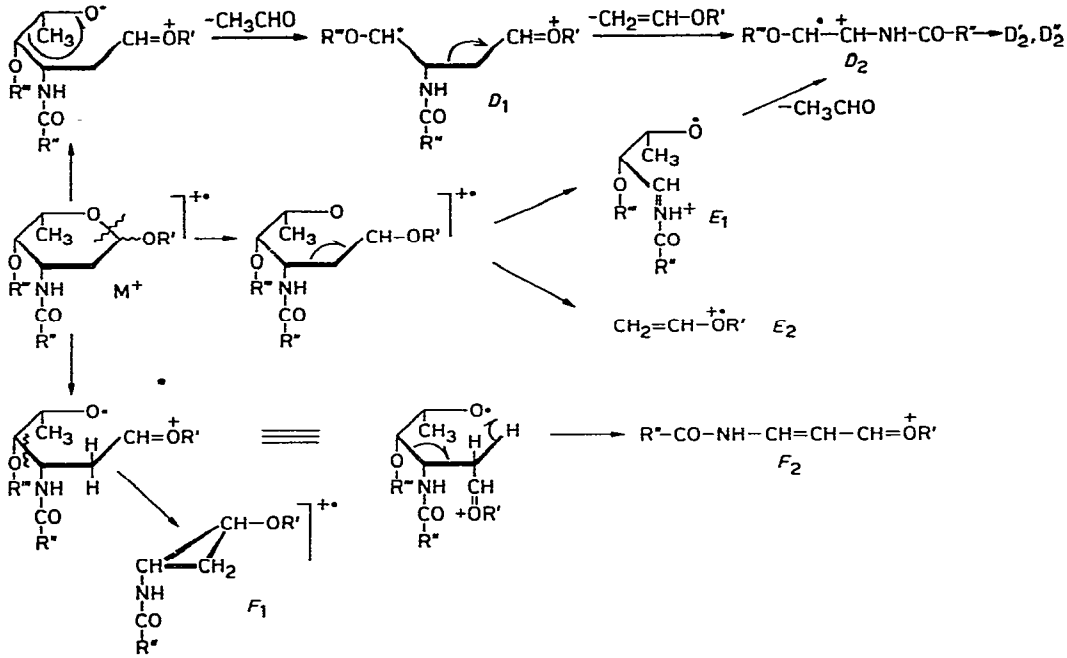
D_2 depend on its substituents. The D_2 ions of **3** and **4** (*m/e* 143) undergo successive loss of two ketene molecules, affording the ions D_2' and D_2'' (*m/e* 101 and 59, respectively); for D_2'', the structure $(HO{-}CH{=}CH{-}NH_2)^{+\cdot}$ (or one of its isomers) is proposed. On the other hand, for compound **2**, the ion D_2 (*m/e* 101) can undergo loss



Scheme 1



Scheme 2



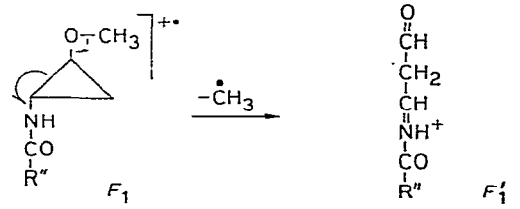
Scheme 3

of only one ketene molecule to give D_2' (*m/e* 59). A somewhat different fragmentation pattern is observed for the *N*-trifluoroacetyl derivatives **5** and **6**, for which the D_2 ion (*m/e* 155) loses a trifluoromethyl radical, giving the ion with *m/e* 86 (D_2') [metastable at *m/e* 47.5 (calc. 47.7)]. The abundance of the D_2' ion is strongly affected by the ion-source temperature; for **6** at 180°, the peak at *m/e* 86 is the base peak, whereas at 140°, its relative abundance is 23%. The D_2 ion also loses a trifluoroacetyl radical, giving the ion with *m/e* 58 (D_2'', $HO{-}CH{=}CH{-}\overset{+}{N}H$) [metastable at *m/e* 21.7 (calc. 21.7)]. For the *N*-benzoyl derivatives **7** and **8**, the D_2 ion (*m/e* 163) does not fragment according to the above-mentioned pattern.

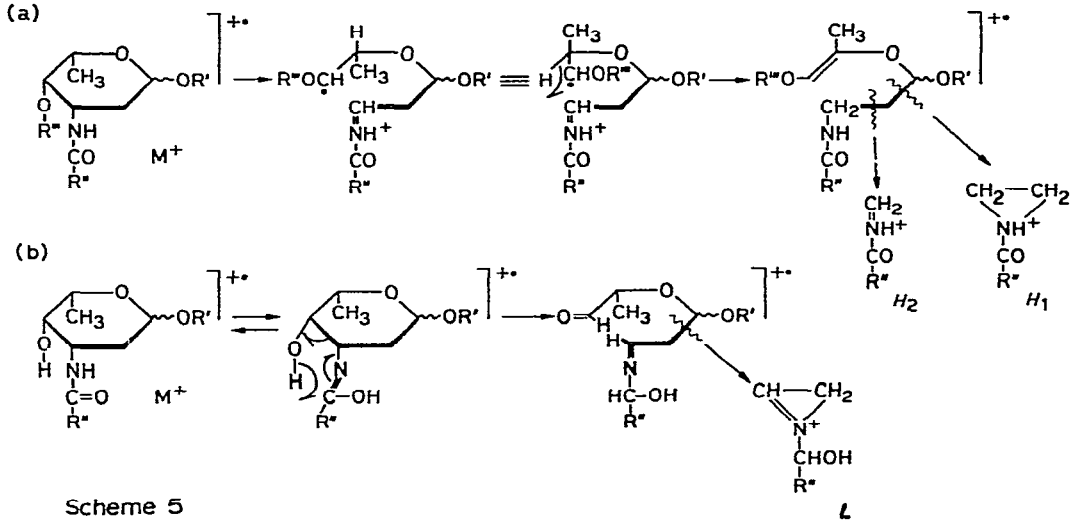
In the *E* process, either E_1 or E_2 ions are obtained, depending on charge localization at the ring oxygen or at C-1. The presence of an ion with a structure corresponding to E_2 has been observed in the spectra of tetrahydropyranyl ethers[9]. For the *N*-benzoyl derivatives, E_1 and E_2 ions are practically absent and, for the *N*-acetyl derivatives (with the exception of **4**), the E_1 ion is very weak. In the mass spectrum of **6**, the E_2 and D_2'' ions are isobaric. However, for the deuterated derivative **6a**, the two ions are differentiated because D_2'' shifts to *m/e* 60, whereas E_2 stays at *m/e* 58. Moreover, the appearance of a metastable peak at *m/e* 120.8 (calc. 120.7) in the spectrum of **6** shows that the E_1 ion loses the O–C-5 moiety as acetaldehyde, giving D_2.

In the *F* process, after the initial cleavage of the O–C-1 bond, fragmentation can proceed according to two different paths. By one path, F_1 is formed as aconse quence

of the cleavage of the C-3–C-4 bond. Alternatively, rearrangement of one of the methylene hydrogens is assumed to take place before the cleavage of the C-3–C-4 bond, with subsequent formation of the F_2 ion. Since a prominent peak analogous to F_2 is present in the mass spectra of the derivatives of vancosamine (3-*C*-methyldaunosamine[10] and of the derivatives of some analogues of daunosamine[11], this fragment is considered typical of the derivatives of 3-amino-2,3-dideoxy-*lyxo*-hexoses. The ion F_1 is more abundant than F_2, except for the 4-*O*-acetyl derivatives, for which the intensity ratio is reversed. In the spectra of the *N*-benzoyl derivatives, the F_1 and F_2 ions are of similar intensity. The F_1 ion derived from the fragmentation of methyl daunosaminides is probably responsible for the formation of the F_1' ion (F_1-15), according to Scheme 4.



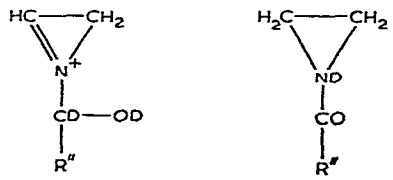
Scheme 4



Scheme 5

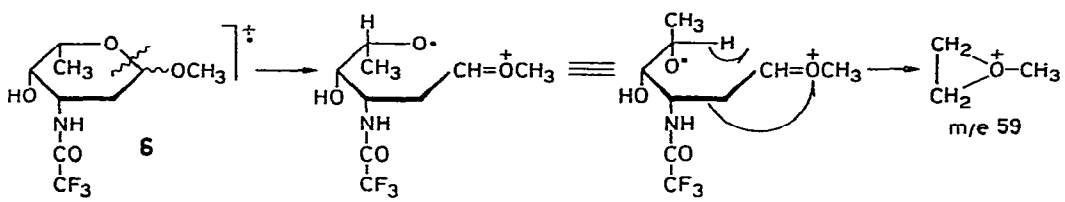
In Scheme 5, the fragmentation patterns arising from the cleavage of the C-3–C-4 bonds are collected; in Scheme 5a, the rearrangement of the C-5 hydrogen is proposed in order to give an ion that can undergo cleavage of the C-1–C-2 or C-2–C-3 bonds. The fragmentation giving the H_2 ion has been described for *cis*-2-aminocyclohexanols[12]. For the *N*- acetyl derivatives, H_1 (*m/e* 86) undergoes loss of ketene,

affording the ion with *m/e* 44 [metastable at *m/e* 22.5 (calc. 22.50)]. In the spectra of the *N*-benzoyl derivatives **7** and **8**, peaks for the H_2 ion are absent. In Scheme 5b, the cleavage of the C-3–C-4 bond is due to a McLafferty rearrangement involving the double bond of the tautomeric imino-form of the amide. As the hydrogen atom in HO-4 is involved, the rearrangement cannot occur for compounds **3** and **4**. After the rearrangement, the C-1–C-2 bond breaks, forming the ion *L*. The ions H_1 and *L* have the same elemental composition. However, for compounds **2a**, **6a**, and **8a**, which contain –ND- and DO-4 groups, H_1 and *L* appear at different *m/e* values because of their different origin. In fact, the *L* ion (**9**) contains the hydrogen atom coming from HO-4 and its *m/e* value increases by two mass units, whereas the value of H_1 (**10**) increases by only one unit.



9 (*L*) 10 (H_1)

The ions at *m/e* 59 (compound **6**) and at *m/e* 122 (*N*-benzoyl derivatives **7** and **8**) merit comment. As the ion at *m/e* 59 shifts to *m/e* 62 in the trideuteriomethyl derivative **6b**, it must contain the C-1–OMe group. It is probably analogous to the E_2 ion, but its formation (Scheme 6) is preceded by the rearrangement of the hydrogen at C-5. In the spectrum of compound **5**, an ion at *m/e* 45 ($CH_2{=}\overset{+}{O}H$), of lower abundance, is observable.



Scheme 6

The ion at *m/e* 122, to which the structure $C_6H_5{-}CO{-}\overset{+}{N}H_3$ is attributed, probably derives from a double hydrogen rearrangement, as described for cycloalkyl amides[13]. One of the hydrogen atoms involved is derived from HO-4, because the peak shifts to *m/e* 124 in the deuterated compound **8a**. For the *N*-acetyl derivative **2**, the corresponding fragment (*m/e* 60) is observable, whereas, of the *N*-trifluoroacetyl derivatives, only **5** shows an abundant peak at *m/e* 114 ($CF_3{-}CO{-}\overset{+}{N}H_3$).

It may be noted that, in the spectrum of triacetyldaunosamine (**4**), the ions B_2 and F_2 undergo a loss of ketene giving fragments with *m/e* 128 (8%) and 114 (15%), respectively.

As far as the comparison of the abundances of the ions of the different types of derivatives is concerned, the Tables show that there are no significant differences between the spectra of the *N*-acetyl and *N*-trifluoroacetyl derivatives, whereas the relative intensity of most fragments in the spectra of the *N*-benzoyl derivatives is smaller, indicating that they are less suitable for mass spectrometry. Triacetyl-β-daunosamine constitutes an exception to this trend because its behaviour is similar to that of the *N*-benzoyl derivatives. Inspection of the Tables shows also that the spectra of the methyl glycosides are not substantially different from those of the compounds containing a C-1–OH group.

EXPERIMENTAL

General methods. — Mass spectra were recorded with a Perkin–Elmer 270 spectrometer at an ionizing voltage of 70 eV. The direct-insertion technique was used with a probe temperature of 50–80°. Measurements of exact mass were made with a Varian Mat CH-5 spectrometer at a resolution of 10,000, using the peak-matching technique with perfluorokerosene as reference compound. P.m.r. spectra were recorded with a Varian A60-A spectrometer for 5% solutions with Me_4Si as the internal reference. M.p.s. (uncorrected) were determined with a Kofler hot-stage. Optical rotations were measured at 20 ±3° with a Perkin–Elmer 141 polarimeter.

Deuteration of OH and NH groups was performed by dissolving the sugars in D_2O and pumping off the liquid phase. The process was repeated three times in order to accomplish a complete isotopic exchange. The trideuteriomethyl daunosaminides **6b** and **8b** were prepared from compounds **5** and **7**, respectively, by dissolution in MeOD containing a trace of HCl and pumping off the liquid phase after an interval of 1 h. The process was twice repeated without adding further HCl.

N-*Trifluoroacetyl-α-daunosamine* (**5**). — A solution of methyl *N*-trifluoroacetyl-daunosaminide (**6**, 0.2 g) in methanol (5 ml) and 0.2M hydrochloric acid (5 ml) was kept for 2 h at 90°. The methanol was then evaporated, the residual solution was adjusted to pH 6 with 0.5M sodium hydroxide, and extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. Recrystallization of the residue from ethyl ether gave **5** (120 mg, 63%), m.p. 149–150°, $[\alpha]_D$ −137° (*c* 0.4, *p*-dioxane). N.m.r. data (*p*-dioxane-d_8): δ 1.11 (*d*, C-5-Me), 4.73 (*q*, αC-1–OH), 5.20 (broad, βC-1–H).

Anal. Calc. for $C_8H_{12}F_3NO_4$: C, 39.51; H, 4.97; N, 5.76. Found: C, 39.90; H, 5.04; N, 5.94.

Methyl N-*trifluoroacetyldaunosaminide* (**6**). — To a suspension of daunosamine hydrochloride[1] (1.1 g) in dichloromethane (20 ml), anhydrous pyridine (2.2 ml) and trifluoroacetic anhydride (2.75 ml) were added. The mixture was maintained at 0° for 1 h with stirring, a mixture of water and ice (15 ml) was then added, and stirring was

continued for 1 h. The aqueous phase was separated and extracted with dichloromethane (30 ml). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give a solid residue, the p.m.r. spectrum of which was consistent with a mixture of *N*- and *O*-trifluoroacetyl derivatives. A solution of the mixture in methanol (50 ml) was refluxed for 2 h and then concentrated, and the residue was eluted from silica gel with chloroform–acetone (9:1) to give **6** (300 mg, 20%), m.p. 125° (from ether–light petroleum), $[\alpha]_D$ −54° (*c* 0.4, chloroform). The p.m.r. spectrum ($CDCl_3$) was consistent with a 1:1 mixture of α and β anomers (C-1–OMe signals of equal intensity at δ 3.38 and 3.53).

Anal. Calc. for $C_9H_{14}F_3NO_4$: C, 42.03; H, 5.49; N, 5.44. Found: C, 42.54; H, 5.52; N, 5.57.

Methyl N-*benzoyl-α-daunosaminide* (**8**). — To a cooled (0°) solution of methyl α-daunosaminide hydrochloride[1] (50 mg) in water (2 ml), potassium hydrogen carbonate (0.25 g) and a solution of benzoyl chloride (0.1 ml) in acetone (1 ml) were separately added. After stirring for 2 h at 0° and for 1 h at room temperature, the acetone was evaporated and the pH of the residual solution was adjusted to 3.5 with 0.1M hydrochloric acid. Benzoic acid was extracted with ether. The pH was then adjusted to 6 with 0.1M sodium hydroxide and the solution was continuously extracted overnight with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated *in vacuo*. Crystallization of the residue from ethanol–ethyl acetate gave **8** (30 mg, 45%), m.p. 155–156°, $[\alpha]_D$ −167° (*c* 0.4, methanol).

Anal. Calc. for $C_{14}H_{19}NO_4$: C, 63.37; H, 7.23; N, 5.28. Found: C, 63.31; H, 7.10; N, 5.35.

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