Tetrahedron Vol. 41, No 14, pp. 2891 to 2897, 1985
Printed in Great Britain

0040-4020/85 $3.00 + .00
© 1985 Pergamon Press Ltd

SEDUM ALKALOIDS—VII

STRUCTURE AND SYNTHESIS OF (+)-4-HYDROXYSEDAMINE AND (+)-4-HYDROXYALLOSEDAMINE

F. HALIN, P. SLOSSE and C. HOOTELÉ†*
Service de Chimie Organique, Faculté des Sciences, Université Libre de Bruxelles, B-1050 Bruxelles, Belgique

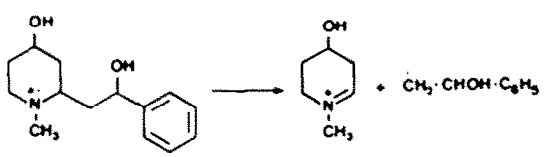
(*Received in UK 6 August* 1984)

Abstract The structures of (+)-4-hydroxysedamine **1** and (+)-4-hydroxyallosedamine **2**, two new minor alkaloids from *Sedum acre*, are reported. **1** and **2** were synthesized, and their absolute configuration established, via the optically pure tetrahydro 1,3-oxazines **17** and **18**.

Sedum acre contains a variety of piperidine alkaloids. In our continuing investigation of Sedum alkaloids we reported recently the isolation of sedacrine, the major alkaloid, and a number of related bases.[1] Extensive fractionation, by countercurrent distribution and preparative chromatography, of a mixture of more polar alkaloids from this species has now led to the isolation of some new minor bases bearing an hydroxyl group on the piperidine ring. The structures and the synthesis of two of them, (+)-4-hydroxysedamine **1** and (+)-4-hydroxyallosedamine **2** are reported in the present communication.

Structure of (+)-*4-hydroxysedamine* **1** *and* (+)-*4-hydroxyallosedamine* **2**

The mass spectra of **1** and **2** are virtually identical and establish that the alkaloids are isomeric $C_{14}H_{21}NO_2$ hydroxyderivatives of sedamine **5** and/or allosedamine **6**.‡ The molecular ion appeared at *m/z* 235 and a prominent peak (a) at *m/z* 114 resulting from α-cleavage with loss of the CH_2—CHOH—C_6H_5 side chain implied the location of the supplementary hydroxyl group on the N-methylpiperidine ring.



m/z 235 a: *m/z* 114

Treatment of **1** and **2** by acetic anhydride in pyridine yielded the corresponding diacetyl derivatives **3** and **4** ($M^{+\cdot}$ at *m/z* 319). The proton NMR spectra of **3** and **4** supported the presence in both compounds of a N—CH_3 group and a CH_2—CHOAc—C_6H_5 side chain and showed that the second acetoxy function was located on a methine flanked by two methylene groups: the proton geminal to this acetoxy group appeared as a triple triplet with typical equatorial–equatorial and equatorial–axial coupling constants at 4.99 ppm in **3** (J = 3.4 and 5.3 Hz) and at 4.97 ppm in **4** (J = 3.5 and 4.8 Hz). As shown in Table 1, the ^{13}C-NMR spectra of **3** and **4** are very similar. Comparison of these spectra with those of acetylsedamine **7** and acetylallosedamine **8** led to the conclusion that the extra acetyl group in **3** and **4** is located at C4 and is axial (i.e. *trans* with respect to the equatorial bulky side chain); shielding of 5–6 ppm (γ-effect) at C2,6 and deshielding of 2–3 ppm (β-effect) at C3,5 were observed in **3** and **4** compared with **7** and **8**. Other assignments (or structural attribution) led to inconsistencies. The new hydroxy-derivatives have therefore the same *trans* C2–C4 relative configuration and differ by their relative C2–C8 configuration. Definite evidence for structures **1** and **2** rests on the correlation of the two alkaloids with the synthetic tetrahydro 1,3-oxazines **21** and **22** whose relative and absolute configurations were established unambiguously (*v. infra*). $LiAlH_4$ reduction of the dextrorotatory tetrahydro 1,3-oxazines **21** and **22** in THF yielded respectively (+)-4-hydroxysedamine **1** ($[\alpha]_D^{22}$ +58° (*c* = 1.6, MeOH); picrate m.p. 130–131°) and (+)-4-hydroxyallosedamine **2** (m.p. 91–92°, $[\alpha]_D^{22}$ +20.6° (*c* = 1.3, MeOH)) identical in all respects with the natural compounds. Structures **1** (2*R*,4*R*,8*R*) and **2** (2*R*,4*R*,8*S*) therefore represent the absolute configurations of the two new bases. It is worthy of note that **1** and **2** are hydroxy-derivatives of (+)-sedamine ent-**5** and (+)-allosedamine ent-**6** whereas sedamine exists in *S. acre* as a mixture of (−)-sedamine **5** and (±)-sedamine rac-**5**[4] and allosedamine as (−)-allosedamine **6**.[5]

First-order partial analysis of the 250 MHz spectra with double irradiation of **1** and **2** (Table 2) allowed us to establish the preferred solution conformations ($CDCl_3$) of these two bases. Although **1** and **2** differ only by their configuration at C8, the C4 hydroxyl group is equatorially oriented in **1** and axially oriented in **2**. The phenyl group is equatorial in both compounds on the pseudo-cycle resulting from the H-bond between the N atom and the C8 hydroxyl group. Compounds **1** and **2** therefore adopt predominently the conformations **1a** and **2a**. These conformations are identical with those of sedamine **5** and allosedamine **6** respectively.[5] The agreement of the experimental ^{13}C chemical shifts of **1** and **2** with the values calculated[6] for the introduction of an equatorial hydroxyl group at C4 on **5** and of an axial hydroxyl group at C4 on **6** (Table 3) support the above conclusions.

Synthesis of the tetrahydro 1,3-*oxazines* **21** *and* **22**

A simple and reproducible synthesis of the 2,4-disubstituted piperidine **12** was achieved from the

† Research Associate of the National Fund for Scientific Research.

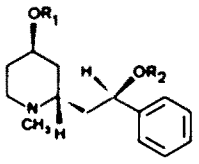
‡ The presence of "hydroxysedamine" in *Sedum acre* has been inferred previously from mass spectrometry.[2,3]

Table 1. ^{13}C chemical shifts ($CDCl_3$) of diacetyl-4-hydroxysedamine **3**, diacetyl-4-hydroxyallosedamine **4**, acetylsedamine **7** and acetylallosedamine **8**

Carbon	C2	C3	C4	C5	C6	C7	C8	NCH_3
3	55.3	34.0	68.0	29.0	50.3	38.3	73.4	42.1
4	55.7	34.6	68.2	29.2	50.4	38.0	74.3	42.2
7	60.1	30.8	23.8	25.4	56.4	39.5	73.6	42.8
8	60.4	31.3	23.6	25.3	56.1	38.7	74.7	42.8

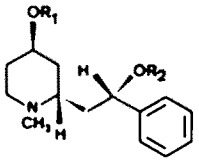
Table 2. First-order parameters of 4-hydroxysedamine **1** and 4-hydroxyallosedamine **2** in $CDCl_3$ at 250 MHz

	4-Hydroxysedamine **1**			4-Hydroxyallosedamine **2**		
Proton		mult.	J Hz (coupled proton)		mult.	J Hz (coupled proton)
H8	4.86	dd	2.5(H7e), 10.6 (H7a)	5.07	dd	3.7 (H7e), 9.3 (H7a)
H4	3.82	trtr	9.2 (H3a, H5a), 4.3 (H3e, H5e)	4.12	trtr	3.2 (H3e, H5e), 5.0 (H3a, H5a)
H2	3.20	ddtr	10.6 (H7a), 3.6 (H7e), *ca* 4 (H3e, H3a)	2.75	ddtr	*ca* 9.5 (H3a), *ca* 5 (H7e), *ca* 4 (H3e, H7a)
H6a	3.06	ddd	14.2 (H6e), 10.3 (H5a), 3.7 (H5e)	2.56	ddd	12.6 (H6e), 10.6 (H5a), 3.3 (H5e)
H6e	2.78	dtr	14.2 (H6a), 4.5 (H5a, H5e)	2.82	dtr	12.6 (H6a), 4.7 (H5e, H5a)
NCH_3	2.51	s		2.45	s	
H7a	1.98	dtr	14.4 (H7e), 10.6 (H8), 10.6 (H2)	2.07	ddd	15 (H7e), 9.3 (H8), 3.7 (H2)
H7e	1.47	ddd	14.4 (H7a), 3.6 (H2), 2.5 (H8)	1.72	m	



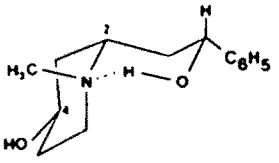
1 $R_1 = R_2 = H$

3 $R_1 = R_2 = Ac$

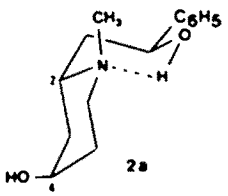


2 $R_1 = R_2 = H$

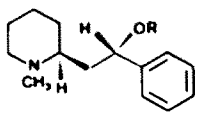
4 $R_1 = R_2 = Ac$



1a

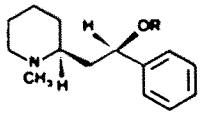


2a



5 R = H

7 R = Ac



6 R = H

8 R = Ac

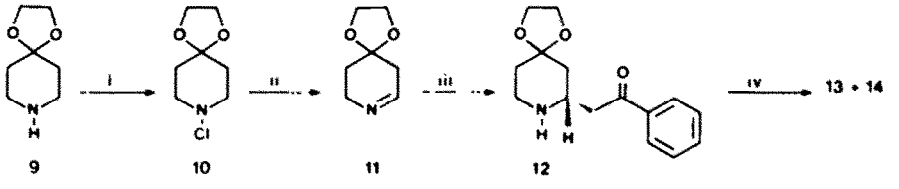
commercially available amine **9** via condensation of the piperideine **11** with benzoylacetic acid. The condensations of Δ^1-piperideine with β-ketoacids are known to proceed with good yields[7] but the synthesis of Δ^1-piperideine itself is unsatisfactory.[8] In order to avoid the isolation of the presumably unstable piperideine **11**, we prepared this intermediate in solution and added it directly to benzoylacetic acid; a similar procedure was found recently to be efficient for the synthesis of the alkaloid pelletierine from piperidine and acetoacetic acid.[8]

The N-chloroamine **10** was prepared by treatment of

Table 3. Experimental ($CDCl_3$) and calculated ^{13}C chemical shifts of 4-hydroxysedamine 1 and 4-hydroxyallosedamine 2

Carbon	C2	C3	C4	C5	C6	C7	C8	NCH_3
1 (exp)	59.9	33.8	65.4	28.9	46.8	39.9	75.2	40.7
1 (calc)	59	34	64	30.5	49	40	75	40
2 (exp)	56.5	35.5	64.6	31.5	49.4	38.6	72.1	43.0
2 (calc)	56	34	63	30.5	50	39.5	72	44

9 with N-chlorosuccinimide in ether solution and converted into 11 by potassium superoxide in the presence of 18-crown-6 ether.[9] The piperideine 11 was extracted from ether with aqueous hydrochloric acid and the condensation (with decarboxylation) was performed by addition of this solution to an aqueous solution of benzoylacetic acid at pH 5. By this procedure, the phenacylpiperidine rac-12, isolated in the pure form as its crystalline perchlorate in 45% overall yield from 9, was obtained in three steps without the isolation of any intermediates. The condensation product yielded spectroscopic data consistent with the formula rac-12.



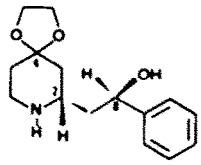
i N-chlorosuccinimide; ii KO_2/18-crown-6 ether; iii $C_6H_5COCH_2CO_2H$; iv $NaBH_4$

Reduction of the ketone rac-12 with $NaBH_4$ in methanol yielded quantitatively a 1:1 mixture of the diastereoisomeric alcohols rac-13 and rac-14 which were separated by fractional crystallization and fully characterized. The stereochemical attributions for rac-13 and rac-14 rest on their transformation into rac-17 and rac-18 respectively. Deketalization of rac-13 and rac-14 in 2N aqueous hydrochloric acid at 50° yielded the β-amino-ketones rac-15 and rac-16, which were cyclized into the corresponding tetrahydro 1,3-oxazines rac-17 and rac-18 respectively by treatment with formaldehyde in methanol. Both steps occurred without appreciable epimerization at C2: rac-17 and rac-18 were obtained in 85–90% overall yield from rac-13 and rac-14.

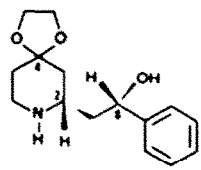
The tetrahydro 1,3-oxazines rac-19 and rac-20 are known to exist predominantly in a *trans*-fused ring conformation[10] as shown by the presence of Bohlmann bands[11] in their IR spectra and by the value of the geminal coupling constant (−8 Hz) for the C2 protons in their NMR spectra. Compounds rac-17 and rac-18 also exhibited Bohlmann bands and J_{gem} of −8.5 Hz for the C2 protons and must therefore also exist predominantly in *trans*-fused ring conformation and chair conformation for the tetrahydro 1,3-oxazine ring. The chemical shifts of the C4 proton and the vicinal coupling constants of the C4 proton with the C5 protons in each compound allow to establish their configuration at C4. The C4 proton of rac-17 appeared at 4.07 ppm (in C_6D_6) and showed axial–axial (J = 11.2 Hz) and axial–equatorial (J = 1.6 Hz) coupling constants while the C4 proton of rac-18 appeared at 4.82 ppm with equatorial–equatorial and equatorial–axial coupling constants (J = 4.3 and 4.3 Hz); rac-17 is accordingly the epimer with an equatorial phenyl group and rac-18 the epimer with an axial phenyl group. Additional evidence for these assignments is that the chemical shift difference ($CDCl_3$) between the two C2 protons in each compound (rac-17: 0.66 ppm; rac-18: 0.34 ppm) is similar to that observed (CCl_4) for the model compounds rac-19 (0.63 ppm) and rac-20 (0.26 ppm).[10] The ^{13}C chemical shifts of rac-17 and rac-18 are shown in Table 4 and support the above conclusions: in rac-18 C2, C4, C5 and C6 are shielded (6.7, 6.6, 6.1 and 4.3 ppm respectively) from their positions in rac-17 as expected for the substitution of an equatorial by an axial phenyl group on a *trans*-fused

Table 4. ^{13}C chemical shifts ($CDCl_3$) of compounds 17–24

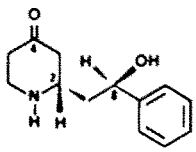
Carbon	C2	C4	C5	C6	C7	C8	C9	C10
17	85.9	79.0	39.0	59.3	47.0	207.2	41.0	47.9
18	79.2	72.4	32.9	55.0	46.2	207.6	40.5	48.3
19	86.9	79.9	39.5	60.2	31.9	23.5	25.2	48.6
20	80.3	72.9	32.8	55.4	31.6	23.7	24.8	48.8
21	86.6	80.1	38.7	54.7	39.1	64.4	32.9	43.1
22	80.0	73.1	32.4*	49.9	38.8	64.5	32.0*	43.1
23	86.5	79.6	40.2	58.9	41.2	68.3	34.4	47.2
24	79.9	72.7	33.8	54.0	40.3	68.6	33.8	47.5



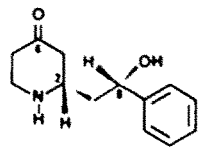
13



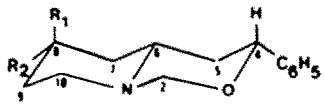
14



15



16

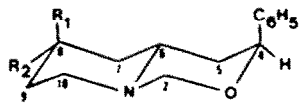


17 $R_1, R_2 = O$

19 $R_1 = R_2 = H$

21 $R_1 = OH, R_2 = H$

23 $R_1 = H, R_2 = OH$



18 $R_1, R_2 = O$

20 $R_1 = R_2 = H$

22 $R_1 = OH, R_2 = H$

24 $R_1 = H, R_2 = OH$

ring system. The relative configurations of the alcohols rac-**13** and rac-**15** (the precursors of rac-**17**) and rac-**14** and rac-**16** (the precursors of rac-**18**) are therefore also fixed.

The two tetrahydro 1,3-oxazines **17** and **18** were then prepared in optically pure forms whose absolute configurations were established. The aminoketone rac-**17** was converted into the diastereoisomeric camphorsulfonic salts in acetone. Several crystallizations (cyclohexane) of the free base liberated from the less soluble salt yielded the optically pure dextrorotatory (chloroform) tetrahydro 1,3-oxazine **17**. On the other hand, the ketal rac-**14** was resolved with tartaric acid in methanol. With (+)-tartaric acid, the salt of the laevorotatory ketal separated first and was purified by repeated crystallizations. The optically pure laevorotatory (MeOH) ketal **14** isolated after liberation from its salt was hydrolyzed and the resulting ketone cyclized with formaldehyde to give the crystalline optically pure dextrorotatory (methanol) tetrahydro 1,3-oxazine **18**. The two dextrorotatory tetrahydro 1,3-oxazines **17** and **18** exhibited positive Cotton effects in cyclohexane; their absolute configurations are therefore established as depicted in **17** and **18** (**17**: 4*S*, 6*R*; **18**: 4*S*,6*S*) and the laevorotatory ketal **14** has the 8*S* configuration. This last attribution was confirmed independently by application of Horeau's method[12] to the N-methyl derivative of **14**.

Reduction of the ketone **17** with potassium trisiamylborohydride in THF at −78° yielded a 9:1 mixture of the diastereoisomeric alcohols **21** and **23** which were separated by column chromatography. Comparison of their proton NMR spectra clearly established that the major compound is the expected axial alcohol **21**: the C8 proton shows equatorial-equatorial and equatorial-axial coupling constants and comes 0.4 ppm to lower field than the C8 proton of the minor isomer **23** which exhibits axial-axial and axial-equatorial J_{vic}. On the other hand, the equatorial alcohol **23** was obtained as the major isomer (more than 90%) when the reduction of **17** was performed with $NaBH_4$ in methanol. Similarly, reduction of the ketone **18** with potassium trisiamylborohydride in THF at −78° yielded predominantly (*ca* 90%) the axial alcohol **22**, while the reduction with $NaBH_4$ in methanol gave the equatorial alcohol **24** as the major isomer.

The ^{13}C chemical shifts of the tetrahydro 1,3-oxazines **17**-**24** are shown in Table 4. The assignments were assisted by off-resonance decoupling and in the case of **17**, **21** and **23** by comparison with the spectra of the tetradeuteriated (at C7 and C9) analogues. For the *trans*-4,6-H-derivatives (**18**, **20**, **22** and **24**) C2, C4 and C5 are shielded by 6–7 ppm relative to the corresponding carbon atoms of the *cis*-4,6-H-derivatives (**17**, **19**, **21** and **23**). Similarly, upfield shifts of 4–5 ppm are observed for C6 in the two series, while the chemical shifts of C7, C8, C9 and C10 remain virtually identical. This implies that the phenyl group is axially oriented in the *trans*-4,6-H-derivatives and that the *trans*-fused ring conformation is preserved in the alcohols **22** and **24**. The chemical shifts and the vicinal coupling constants of the C4 proton with the C5 protons in the proton NMR spectra of **18**, **20**, **22** and **24** verify this conclusion. It must be pointed out however that no "W" coupling[13] is observed between the two equatorial C2 and C4 protons in the spectra of **18**, **20**, **22** and **24**. It is likely therefore that the tetrahydro 1,3-oxazine ring exists as a slightly flattened chair in these compounds.

EXPERIMENTAL

M.ps were determined on a Kofler microscope and are uncorrected. IR spectra were determined on a Perkin Elmer 237 spectrometer. Mass spectral data were obtained on a Micromass 7070 spectrometer and optical rotations measured on a Perkin–Elmer 141 polarimeter. Unless otherwise stated, NMR were recorded in $CDCl_3$ with TMS as internal standard (Jeol JNM-MH-100 and Bruker WM 250). The countercurrent distributions were analyzed by measuring the optical density (420 nm) of the $CHCl_3$ phase of each tube after basification (NaOH aq), drying and addition of a $CHCl_3$ soln of picric acid.

Isolation of (+)-4-hydroxysedamine **1** *and (+)-4-hydroxyallosedamine* **2**

The crude alkaloids obtained by the procedure described earlier[1] from fresh whole plants of *Sedum acre* (*ca* 20 kg) were subjected to two successive countercurrent distributions ($CHCl_3$/Borax-HCl buffer pH 8.7; 50 transfers). Fractionation of the alkaloids from tubes 10-42 by preparative TLC on alumina plates developed in $CHCl_3$ sat with NH_4OH yielded a mixture (150 mg) which contained mostly isomeric $C_{14}H_{21}NO_2$ (by MS) compounds. This mixture was acetylated with acetic anhydride–pyridine. Fractionation by column chromatography on aluminum oxide (benzene-EtOAc as eluent) yielded diacetyl-5-hydroxysedamine[5] (35 mg), a mixture of diacetyl-4-hydroxysedamine and diacetyl-4-hydroxyallosedamine (102 mg), and O,N-diacetyl-4-hydroxynorsedaminone[5] (30 mg). 60 mg of the mixture of diacetyl-4-hydroxysedamine and diacetyl-4-hydroxyallosedamine were allowed to react with lithium aluminum hydride (45 mg) in refluxing THF (10 ml) for 4 hr, then cooled and the excess of hydride was decomposed by addition of water. After filtration through celite and evaporation of the solvent, the residue was subjected to a countercurrent distribution ($CHCl_3$/Borax-HCl buffer pH 8.7; 37 transfers). Tubes 12–19 yielded a fraction (17 mg) containing mostly (+)-4-hydroxyallosedamine. Purification by preparative TLC on alumina developed in $CHCl_3$ NH_4OH CH_3OH yielded homogeneous (+)-4-hydroxyallosedamine **2** (12 mg); $[\alpha]_D^{22}$ +20° (*c* = 1.2, CH_3OH); MS: 235 (M^+, 4%), 114 (100), 96 (5); PMR: see Table 2; CMR: see Table 3. Tubes 20–30 yielded a mixture (25 mg) of (+)-4-hydroxyallosedamine and (+)-4-hydroxysedamine from which a small sample (3 mg) of homogeneous (+)-4-hydroxysedamine **1** could be isolated by preparative TLC on alumina developed in $CHCl_3$–NH_4OH CH_3OH; $[\alpha]_D^{22}$ +55° (*c* = 0.3, CH_3OH); MS: 235 (M^+, 4%), 114 (100), 96 (11); PMR: see Table 2; CMR: see Table 3.

Diacetyl-4-hydroxysedamine **3** *and diacetyl-4-hydroxyallosedamine* **4**

Ac_2O–pyridine acetylation of natural **1** and **2** provided **3** and **4** respectively.

Compound **3**: MS: 319 (M^+, 14%), 276 (12), 200 (10), 156 (100); PMR: δ 5.84 (dd, J = 4.9 and 9 Hz, C8-H), 4.99 (trtr, J = 3.4 and 5.3 Hz, C4-H), 2.3 (s), 2.06 (s), 2.01 (s); CMR: see Table 1.

Compound **4**: MS: 319 (M^+, 12%), 276 (10), 200 (9), 156 (100); PMR: δ 5.81 (tr, J = 7.1 Hz, C8-H), 4.97 (trtr, J = 3.5 and 4.8 Hz, C4-H), 2.28 (s), 2.03 (s), 1.97 (s). CMR: see Table 1.

*Preparation of the ketone rac-***12**

Compound **9** (14.32 g) was added dropwise to a vigorously stirred slurry of N-chlorosuccinimide (14.88 g) in ether (200 ml). After 18 hr, the mixture was filtered and concentrated *in vacuo*; ether (200 ml) was added and the soln was filtered again. 18-Crown-6 ether (264 mg) and potassium superoxide (14.22 g) were added and the suspension was stirred for 24 hr. After filtration, the soln containing **11** was extracted twice with 0.5 N HCl (500 ml). An aqueous soln of benzoylacetic acid was prepared by dissolving 57.7 g of ethyl benzoylacetate in 1 N NaOH (500 ml). After standing overnight at room temp the soln was acidified with 12 N HCl to pH 5. To this soln was added dropwise the aqueous soln of **11**; pH was maintained between 4.8 and 5.2 with 10 N NaOH. After standing 48 hr the soln was basified with NH_4OH and extracted twice with $CHCl_3$ (1 l); the combined organic layers were concentrated to about 100 ml. The soln was extracted with three 100-ml portions of 1 N HCl. The combined aqueous layers were basified with NH_4OH and extracted twice with $CHCl_3$ (250 ml). The combined $CHCl_3$ layers were evaporated to dryness. The residue was dissolved in acetone (100 ml) and perchloric acid was added dropwise until neutralization. The insoluble crystalline material was filtered off and recrystallized twice from acetone. Sixteen g of the perchlorate of rac-**12** m.p. 223–225° (dec) were obtained (yield 44%). MS: 261 (M^+, 7%), 216 (4), 142 (19), 120 (36), 105 (100), 87 (36), 86 (26), 77 (78); PMR of the free base: δ 7.9 (2H, m, phenyl), 7.5 (3H, m, phenyl), 3.9 (4H, s, dioxolane), 3.3 (2H, m), 3.0 (3H, m), 2.3 (1H, NH), 1.6 (4H, m).

*Preparation of the diastereomeric alcohols rac-***13** *and rac-***14**

The ketone rac-**12** (3.65 g) was dissolved in MeOH (120 ml) and $NaBH_4$ (910 mg) was added. The mixture was stirred for 2 hr, after which the MeOH was evaporated *in vacuo* and $CHCl_3$ (200 ml) was added. The soln was washed, dried and evaporated to dryness. Fractional crystallization from $CHCl_3$ pentane yielded virtually homogeneous (TLC) rac-**14** m.p. 142–144° (1.71 g; 46% yield) and rac-**13** m.p. 96–98° (1.77 g; 48% yield).

The alcohol rac-**14** was recrystallized to a m.p. of 145–146° from $CHCl_3$ pentane; MS: 263 (M^+, 12%), 142 (100), 87 (97); PMR: δ 4.99 (1H, dd, J = 6.8 and 4.5 Hz, C8-H).

The alcohol rac-**13** was recrystallized to a m.p. of 99–100° from ether pentane; MS: 263 (M^+, 10%), 142 (100), 87 (92); PMR: δ 4.95 (1H, dd, J = 10.5 and 2.4 Hz, C8-H).

*Deketalization of rac-***13** *to rac-***15** *and preparation of the tetrahydrooxazine rac-***17**

The ketal rac-**13** (1.05 g) was dissolved in 2 N HCl (25 ml) and the mixture was heated for 22 hr at 50°. The soln was basified with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ soln was washed, dried and evaporated to dryness. The crude ketone rac-**15** (M^+ at *m/z* 219) was dissolved in MeOH (25 ml) and 37% aqueous formaldehyde (0.7 ml) was added. After 5 hr the mixture was evaporated to dryness *in vacuo*. The residue was purified by countercurrent distribution ($CHCl_3$/McIlvaine buffer pH 2.4; 23 transfers); 778 mg of pure rac-**17** were obtained from tubes 4–18 (84% yield from rac-**13**). MS: 231 (M^+, 27%), 127 (16), 126 (26), 104 (100); PMR ($CDCl_3$): δ 4.08 and 4.74 (2d, J = 8.5 Hz, C2-H_2), 4.49 (dd, X part of an ABX system, C4-H); PMR (C_6D_6): δ 3.59 and 4.38 (2 d, J = 8.4 Hz, C2-H_2), 4.07 (dd, J = 1.6 and 11.2 Hz, C4-H); CMR: see Table 4; IR (CCl_4): 2780 (sh), 2760, 2720 and 1725 cm^{-1}.

*Resolution of the tetrahydrooxazine rac-***17**

The tetrahydrooxazine rac-**17** (778 mg) and camphor-10-sulfonic acid (785 mg) were dissolved in hot acetone (25 ml) and the soln was allowed to stand overnight. The crystalline salt was collected by filtration and dissolved in water; basification with ammonia and extraction with $CHCl_3$ yielded 447 mg of base $[\alpha]_D^{22}$ +43° (*c* = 4, $CHCl_3$). The free base (329 mg) liberated from the camphorsulfonic salt of the mother liquors had $[\alpha]_D^{22}$ −58° (*c* = 3, $CHCl_3$). Five successive crystallizations from cyclohexane of the dextrorotatory free base yielded 205 mg (53% yield) of **17**, m.p. 118–119°, $[\alpha]_D^{22}$ +81° (*c* = 1, $CHCl_3$); $[\alpha]_{578}^{22}$ +97°, $[\alpha]_{546}$ +113°, $[\alpha]_{436}$ +219°, $[\alpha]_{408}$ +281°, $[\alpha]_{366}$ +460°, $[\alpha]_{334}$ +983°, $[\alpha]_{313}$ +1645°, $[\alpha]_{312}$ +1670°, $[\alpha]_{302}$ +713°, $[\alpha]_{297}$ −41°, $[\alpha]_{289}$ −680°, $[\alpha]_{280}$ −1310° (*c* = 2, cyclohexane).

Preparation of the diastereomeric alcohols **21** *and* **23** *by reduction of* **17**

(a) *Reduction of* **17** *with potassium trisiamylborohydride*. The ketone **17** (230 mg) in THF (25 ml) was reduced at −78° with potassium trisiamylborohydride (8 ml of 0.5 M soln in THF). After 2 hr at −78° the mixture was allowed to equilibrate to

room temp and evaporated to dryness after addition of water. The residue was dissolved in 2 N HCl (30 ml) and extracted with $CHCl_3$ (30 ml). After basification the aqueous phase was extracted again with $CHCl_3$ (60 ml). Evaporation of the solvent gave a mixture of **21** and **23** (9:1 by PMR). Fractionation by chromatography on alumina (eluent: EtOAc) afforded 177 mg of the pure **21** (yield 76%) and 26 mg of the pure **23** (yield 11%).

Compound **21**: $[\alpha]_D^{22}$ + 54° (*c* = 3, $CHCl_3$); MS: 233 (M^+, 59%), 232 (27), 129 (85), 128 (100), 104 (99), 100 (35), 99 (60); PMR (C_6D_6): δ 7.1 (5H, m), 4.5 and 3.9 (2H, 2d, J = 8.5 Hz, C2-H_2), 4.3 (1H, dd, J = 11.3 and 3.3 Hz, C4-H), 3.8 (1H, m, C<u>H</u>OH); PMR ($CDCl_3$): δ 4.60 and 4.07 (2H, 2d, J = 8.5 Hz, C2-H_2), 4.51 (1H, dd, J = 10.4 and 3.6 Hz, C4-H), 4.10 (1H, quint, J = 4 Hz, C<u>H</u>OH).

Compound **23**: *v. infra.*

(b) *Reduction of* **17** *with sodium borohydride.* The ketone **17** (41 mg) was dissolved in MeOH (5 ml); $NaBH_4$ (60 mg) was added and the mixture was stirred for 2 hr. After workup in the usual manner, 40 mg of a mixture of **21** and **23** (containing more than 90% **23** by PMR) were obtained; crystallization from cyclohexane afforded 25 mg of pure **23**, m.p. 184–185°; $[\alpha]_{579}^{22}$ + 47° (*c* = 0.5, $CHCl_3$); 233 (M^+, 76%), 129 (93), 128 (100), 104 (88), 100 (33), 97 (71); PMR: δ 4.62 and 3.82 (2d, J = 8 Hz, C2-H_2), 4.44 (dd, J = 10.5 and 3.5 Hz, C4-H), 3.68 (trtr, J = 4.5 and 11 Hz, C<u>H</u>OH).

(+)-4-Hydroxysedamine **1** *by reduction of* **21**

The alcohol **21** (143 mg) was dissolved in THF (25 ml) and $LiAlH_4$ (200 mg) was added. The mixture was then heated under reflux overnight. EtOAc, then water were added and the mixture was filtered through celite and evaporated to dryness yielding 140 mg of crude **1**. The picrate was crystallized from isopropanol to a m.p. 130–131°; $[\alpha]_D^{22}$ + 23° (*c* = 0.8, MeOH); the free amorphous base had $[\alpha]_D^{22}$ + 58° (*c* = 1.6, MeOH). The synthetic compound was identical with the natural base by TLC, PMR, CMR.

Diacetyl-4-hydroxysedamine **3**

28 mg of (+)-4-hydroxysedamine **1** were treated at room temp during 24 hr with a mixture (2 ml) pyridine/Ac_2O (1:1). After evaporation of the solvent, filtration of the residue through a short column of alumina yielded 38 mg of **3**, $[\alpha]_D^{22}$ + 86° (*c* = 3.4, CH_3OH).

*Resolution of the ketal rac-***14**

The ketal rac-**14** (2.06 g) and (+)-tartaric acid (0.588 g) were dissolved in hot MeOH (60 ml) and the soln was allowed to stand overnight. The crystalline salt was collected and crystallized three times from MeOH. Dissolution in water, basification with ammonia and extraction with $CHCl_3$ yielded 537 mg (52% yield) of base **14**, $[\alpha]_D^{22}$ − 22.1° (*c* = 1.8, CH_3OH), m.p. 117–118°. Crystallization of **14** from chloroform–pentane (1:3) did not improve the specific rotation.

Deketalization of **14** *to* **16** *and preparation of the tetrahydrooxazine* **18**

The ketal **14** (537 mg) was dissolved in 2 N HCl (15 ml) and the mixture was heated for 20 hr at 50°. The soln was basified with NH_4OH and extracted with $CHCl_3$. After evaporation of the solvent, the crude **16** was dissolved in MeOH (15 ml) and 37% aqueous formaldehyde (0.18 ml) was added. After 20 hr, the mixture was evaporated to dryness *in vacuo* and the homogeneous **18** (425 mg; 90% yield from **14**) was obtained; m.p. 87–90° (cyclohexane), $[\alpha]_D^{22}$ + 120° (*c* = 1.2, CH_3OH); $[\alpha]_D^{22}$ + 154°, $[\alpha]_{579}$ + 164, $[\alpha]_{546}$ + 190°, $[\alpha]_{436}$ + 339°, $[\alpha]_{404}$ + 392°, $[\alpha]_{366}$ + 597°, $[\alpha]_{334}$ + 953°, $[\alpha]_{312}$ + 1372°, $[\alpha]_{302}$ + 1013°, $[\alpha]_{289}$ + 520°, $[\alpha]_{280}$ + 391° (*c* = 0.2, cyclohexane); MS: 231 (M^+, 43%), 127 (24), 126 (30), 104 (100); PMR ($CDCl_3$): δ 4.04 and 4.40 (2d, J = 8.5 Hz, C2-H_2), 5.12 (dd, J = 3.5 and 5 Hz, C4-H); PMR (C_6D_6): δ 3.80 and 4.05 (2d, J = 8.5 Hz, C2-H_2), 4.82 (tr, J = 4.3 Hz, C4-H); CMR: see Table 4; IR (CCl_4): 2780, 2740 (w), 1725 cm^{-1}.

Preparation of the diastereomeric alcohols **22** *and* **24** *by reduction of* **18**

(a) *Reduction of* **18** *with potassium trisiamylborohydride.* The ketone **18** (415 mg) in THF (37 ml) was reduced at − 78° with potassium trisiamylborohydride (8.5 ml of 1 M soln in THF). After 2 hr at − 78° and 20 hr at room temp water was added and the mixture was evaporated to dryness. The residue was dissolved in 2 N HCl (40 ml); the soln was extracted with $CHCl_3$ (80 ml) and the organic phase was discarded. The aqueous phase was basified and extracted again with $CHCl_3$. Evaporation of the $CHCl_3$ gave a mixture (415 mg) of **22** and **24** (9:1 by PMR). Fractionation by chromatography on alumina (eluent: EtOAc) afforded 295 mg of the pure **22** (yield 70%) and 25 mg of the pure **24** (yield 6%).

Compound **22**: $[\alpha]_D^{22}$ + 125° (*c* = 0.5, CH_3OH); MS: 233 (M^+, 58%), 232 (15), 129 (87), 128 (100), 114 (35), 104 (97), 100 (36), 99 (70); PMR ($CDCl_3$): δ 5.16 (tr, J = 3.5 Hz, C4-H), 4.17 and 3.97 (2d, J = 8.5 Hz, C2-H_2), 4.11 (quint, J = 3.8 Hz, C<u>H</u>OH); PMR (C_6D_6): 5.05 (br d, J = 5.5 Hz, C4-H), 4.10 and 4.0 (2d, J = 8.5 Hz, C2-H_2), 3.69 (quint, J = 4 Hz, C<u>H</u>OH); CMR: see Table 4.

Compound **24**: MS: 233 (M^+, 28%), 232 (12), 129 (88), 128 (100), 114 (35), 104 (97), 100 (42), 99 (70); PMR: δ 5.09 (dd, J = 2.6 and 5.2 Hz, C4-H), 4.24 and 3.79 (2d, J = 8 Hz, C2-H_2), 3.60 (trtr, J = 4.5 and 10.9 Hz, C<u>H</u>OH); CMR: see Table 4.

(b) *Reduction of* **18** *with potassium borohydride.* Reduction of **18** with KBH_4 at 0° in MeOH yielded a mixture of the alcohols **22** and **24** (more than 90% by PMR).

(+)-4-Hydroxyallosedamine **2** *by reduction of* **22**

The alcohol **22** (253 mg) was dissolved in THF (25 ml) and $LiAlH_4$ (350 mg) was added. The mixture was then heated under reflux overnight. EtOAc then water were added and the mixture was filtered through celite and evaporated to dryness to yield after one crystallization from ether 196 mg of **2** (77% yield) m.p. 86–91°. Compound **2** was recrystallized from ether to a m.p. of 91 92°, $[\alpha]_D^{22}$ + 20.6° (*c* = 1.3, CH_3OH). The synthetic compound was identical with the natural base by TLC, PMR, CMR.

Diacetyl-4-hydroxyallosedamine **4**

30.5 mg of **2** were treated at room temp during 22 hr with a mixture (2 ml) pyridine/Ac_2O (1:1). After evaporation of the solvent, filtration of the residue through a short column of alumina yielded 43 mg of **4**, $[\alpha]_D^{22}$ − 3.5° (*c* = 3.4, CH_3OH).

N-Methylation of **14**

212 mg of **14** were dissolved in MeOH (15 ml) containing aqueous formaldehyde (0.072 ml). After 5 hr the mixture was evaporated to dryness. Treatment of the crude tetrahydrooxazine with $LiAlH_4$ (300 mg) in THF (20 ml) for one night under reflux yielded after the usual workup a virtually quantitative yield of the N-methyl derivative of **14**; perchlorate (from 2-butanone): m.p. 180–182°, $[\alpha]_D^{22}$ − 35° (*c* = 0.8, CH_3OH). PMR of the free base: δ 5.08 (dd, J = 3.3 and 10.5 Hz, C8-H), 3.95 (m, dioxolane), 2.45 (s, N-CH_3).

The base (21 mg) was allowed to react with α-phenylbutyric anhydride (46 mg) in pyridine (1 ml) for 20 hr at room temp. Some drops of water were added and the mixture was neutralized with 0.1 N NaOH and extracted with $CHCl_3$. The basic aqueous phase was acidified with 0.1 N HCl acid and extracted with $CHCl_3$. Evaporation of the solvent yielded laevorotatory α-phenylbutyric acid; optical yield 17%.

REFERENCES

[1] B. Colau and C. Hootelé, *Can. J. Chem.* **61**, 470 (1983) and refs cited.

[2] J. H. Kooy, *Planta Medica* **30**, 295 (1976).

[3] L. P. S. Francis and G. W. Francis, *Planta Medica* **32**, 268 (1977).

[4] B. Franck, *Chem. Ber.* **91**, 2803 (1958).

[5] C. Hootelé, F. Halin, S. Thomas and D. Tourwé, to be published.

[6] F. W. Wehrli and T. Wirthlin, *Interpretation of Carbon-13 NMR Spectra*. Heyden, London (1976).
[7] J. Van Noordwijk, J. J. Mellink, B. J. Visser and J. H. Wisse, *Rec. Trav. Chim.* **82**, 763 (1963).
[8a] J. Quick and R. Oterson, *Synthesis* 745 (1976); [8b] J. Quick and C. Meltz, *J. Org. Chem.* **44**, 573 (1979).
[9] F. E. Scully, *J. Org. Chem.* **45**, 1515 (1980).
[10] T. A. Crabb and R. F. Newton, *Tetrahderon* **24**, 4423 (1968).
[11] F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958).
[12] A. Horeau, *Stereochemistry, Fundamentals and Methods* (Edited by H. B. Kagan), Vol. 3. Georg Thieme, Stuttgart (1977).
[13] S. Sternhell, *Q. Rev.* **23**, 236 (1969).