

## 62. The Crystal Structure of the $\text{NH}_4\text{NCS}$ Complex of Nonactin

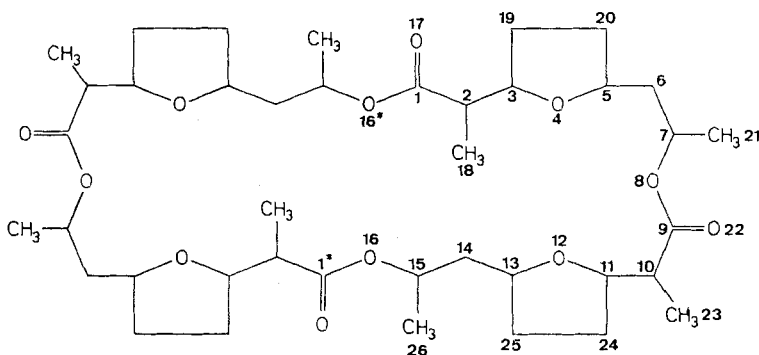
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*Summary.* The  $\text{NH}_4\text{NCS}$  complex of the macrotetrolide antibiotic nonactin crystallizes in the space group  $\text{P}\bar{1}$ ,  $a = 12.565$ ,  $b = 13.115$ ,  $c = 14.999 \text{ \AA}$ ,  $\alpha = 91.22$ ,  $\beta = 90.10$ ,  $\gamma = 104.97^\circ$ . The X-ray crystal structure analysis shows that the  $\text{NH}_4^+$  ion is coordinated by hydrogen bonds to the four ether oxygen atoms ( $\text{NH} \dots \text{O}$ ,  $2.86 \text{ \AA}$ ). These four atoms and the four carbonyl oxygen atoms ( $\text{N} \dots \text{O}$ ,  $3.08 \text{ \AA}$ ) enclose the  $\text{NH}_4^+$  ion in a somewhat distorted cube.

Crystal structure determinations of nonactin (1) [1], its  $\text{KNCS}$  complex [2] and its  $\text{NaNCS}$  complex [3] have provided a structural basis for understanding the complexing behaviour and ion-selectivity of this macrotetrolide antibiotic. The structure determination of the  $\text{NH}_4^+$  complex has been undertaken to study the effect of a nonspherical ion on the ligand conformation. Ammonium ions are strongly bound by the actins but to a lesser extent by valinomycin [4]. This has been attributed to the more favourable interaction of  $\text{NH}_4^+$  with four tetrahedrally arranged oxygen atoms in the actins *vs.* six octahedrally arranged ones in valinomycin.



The present analysis shows that the  $\text{NH}_4^+$  complex of nonactin has the same overall  $S_4$  conformation of the ligand as the  $\text{K}^+$  and  $\text{Na}^+$  complexes. The cubic coordination is, however, distorted in such a way that the four ether oxygen atoms are appreciably closer ( $2.83$ – $2.89 \text{ \AA}$ ) to the nitrogen atom than the four carbonyl oxygen atoms ( $3.01$ – $3.16 \text{ \AA}$ ). The four hydrogen atoms of the ammonium ion form almost linear hydrogen bonds ( $\text{N-H} \dots \text{O}$ ,  $161.1$ – $170.9^\circ$ ) with the ether oxygen atoms.

**Crystallographic Data.** - Ammonium thiocyanate complex of nonactin,  $\text{C}_{40}\text{O}_{12}\text{H}_{64} \cdot \text{NH}_4\text{NCS}$ , Mol. Wt. 813. Triclinic,  $a = 12.565$ ,  $b = 13.115$ ,  $c = 14.999 \text{ \AA}$ ,  $\alpha = 91.22$ ,  $\beta = 90.10$ ,  $\gamma = 104.97^\circ$ ,  $U = 2387 \text{ \AA}^3$ ,  $Z = 2$ . Space group  $\text{P}\bar{1}(\text{C}_i^1)$ ,  $D_m = 1.14$ ,  $D_x = 1.13$ . Cell constants were obtained from  $30^\circ$  precession photographs ( $\text{CuK}\alpha$  radiation) and diffractometer measurements ( $\text{MoK}\alpha$  radiation). They are accurate to about 0.15%.

**Data Collection.** – Intensities from a crystal with dimensions  $0.3 \times 0.3 \times 0.5$  mm were measured with a computer-controlled diffractometer (*Nonius* CAD4), using graphite-mono-chromatized  $\text{MoK}\alpha$  radiation. In the range  $\theta < 20^\circ$  all reflections were measured, in the range  $20^\circ < \theta < 24^\circ$  only those judged by a preliminary scan to be significantly above background. The 7460 intensity measurements obtained were processed in the usual way, yielding 3186 unique reflections with  $F_0 > 3 \sigma(F_0)$ . Absorption corrections were not applied ( $\mu_{\text{Mo}} = 1.4 \text{ cm}^{-1}$ ).

**Structure Analysis.** – An attempt to solve the crystal structure with *Mulltan* 74 [5] was not successful. Manual sign determination using the symbolic addition procedure was then used. It was necessary to introduce nine symbolic signs, in addition to the three origin-defining reflections, in order to derive symbolic indications for the 398 reflections with  $|E| > 1.90$ . Strong indications of this kind enabled four symbols to be eliminated with some confidence. The remaining 32 sign combinations were then used as input to *Mulltan*, and the one with the best 'figure of merit' yielded an E-map in which 41 of the major peaks could plausibly be ascribed to atoms in the molecule. Two subsequent  $F_0$ -Fourier maps calculated with signs based on these 41 atoms revealed all remaining non-hydrogen atoms of the nonactin complex, but only two unresolved peaks were found for the NCS anion, indicating disorder of the anion as in the analogous KNCS [2] and NaNCS [3] complexes. Refinement of the structure was carried out by block-diagonal least-squares analysis. Three cycles with isotropic temperature factors and three cycles with anisotropic temperature factors (except  $\text{NCS}^-$ ) were followed by a difference Fourier map. This showed clear indications of the hydrogen atoms of the ammonium ion, but not for many of the other hydrogen atoms. In the subsequent refinement cycles, the 64 hydrogen atoms of the ligand were included at calculated positions (assumptions: C–H, equal angles with the three attached bonds, H–C–H, local  $C_{2v}$  symmetry, bond angle  $109^\circ$ , H–C distance  $1.1 \text{ \AA}$ , methyl groups staggered). The atoms of the NCS anion were held at reasonable positions (S; 0.37, 0.67, 0.25, N; 0.37, 0.45, 0.25, C; 0.37, 0.54, 0.25), assigned extremely large temperature factors, and not further refined. The analysis was terminated by four cycles of block-diagonal least-squares analysis using anisotropic temperature factors for all non-hydrogen atoms (except the NCS anion) and isotropic temperature factors for the hydrogen atoms of the  $\text{NH}_4^+$  ion. The final R factor, based on the 3186 reflections with  $F_0 > 3 \sigma(F_0)$  and  $F_0 > 4.0$  was 0.108. The rather high R factor is probably due to the disorder of the NCS anions.

**Results.** – The results are summarized in the following Tables. Fractional coordinates, vibrational parameters and calculated hydrogen atom positions are given in Tables 1, 2 and 3. Standard deviations were estimated by inversion of the least-squares normal equations. Bond lengths and angles and torsion angles relevant to the ligand conformation are given in Tables 4 and 5. The corresponding standard deviations for C–C and C–O bonds are between 0.01 and  $0.02 \text{ \AA}$ , for the bond angles between  $0.8$  and  $1.2^\circ$ . The standard deviations for the  $\text{NH}_4^+ \dots \text{O}$  distances are  $0.01 \text{ \AA}$ .<sup>1)</sup>

**Discussion.** – The structure of the  $\text{NH}_4^+$  complex is depicted in Fig.1. In the previously reported crystal structures of uncomplexed nonactin [1], its  $\text{K}^+$  complex [2] and its  $\text{Na}^+$  complex [3] the ligand molecule was characterized by a crystallographic twofold rotation axis and noncrystallographic  $S_4$  symmetry. The  $\text{NH}_4^+$  complex crystallizes in a triclinic space group and therefore has no crystallographic symmetry. The conformation is nevertheless very similar to those of the  $\text{K}^+$  and  $\text{Na}^+$  complexes. The deviations of individual atoms from an idealized molecule with an exact twofold axis (as calculated by least-squares) lie, with one exception, in the range  $0.016$ – $0.156 \text{ \AA}$  (mean  $0.057 \text{ \AA}$ ). Only the pair of atoms C(26), C(26\*) deviates by more ( $0.269 \text{ \AA}$ ). The molecule also approximates quite well to  $S_4$  symmetry, the deviations in related atom positions being in the range  $0.1$ – $0.2 \text{ \AA}$ . The structural

<sup>1)</sup> A table of observed structure amplitudes is available on request.



Table 2. *Anisotropic vibrational parameters*. The corresponding temperature factors have the form  $\exp(-2\pi^2(U_{11a}a^2 + U_{22b}b^2 + U_{33c}c^2 + U_{23a}ab + U_{13a}ac + U_{12ab}bc))$

N	U11	U22	U33	U12	U13	U23	U11	U22	U33	U12	U13	U23
C(1)	.046	.065	.059	.016	.005	-.004	.088	.077	.051	.010	.006	-.013
C(2)	.072	.091	.075	.009	-.023	-.009	.092	.069	.067	.018	-.001	-.022
C(3)	.054	.112	.087	.013	-.006	-.016	.073	.076	.079	.026	-.003	-.010
C(4)	.060	.096	.082	.022	.007	-.007	.078	.066	.058	.018	.011	.005
C(5)	.065	.085	.068	.023	.018	0.000	.088	.059	.056	.008	.004	.003
C(6)	.067	.106	.073	.021	.013	-.008	.095	.058	.058	.008	.003	.011
C(7)	.066	.093	.082	-.005	.014	.008	.093	.071	.044	.001	.011	-.003
C(8)	.075	.097	.072	.017	.012	.011	.103	.062	.057	.017	.013	.010
C(9)	.073	.058	.083	.006	.016	.008	.054	.071	.077	.017	.012	.013
C(10)	.080	.077	.083	.015	.005	.018	.075	.056	.091	.016	.026	.003
C(11)	.071	.100	.085	.026	-.005	.023	.084	.055	.104	.015	.026	-.004
C(12)	.065	.074	.086	.008	-.019	.001	.064	.071	.085	.011	.010	-.025
C(13)	.084	.078	.090	-.005	-.015	.012	.078	.077	.122	-.004	.014	-.046
C(14)	.086	.089	.077	-.006	-.027	.010	.066	.136	.090	-.012	.005	-.038
C(15)	.109	.077	.064	-.020	-.012	.002	.068	.139	.085	.007	-.011	-.014
C(16)	.099	.074	.074	-.013	-.018	.000	.060	.122	.087	-.005	-.007	-.028
C(17)	.103	.109	.093	-.018	-.000	-.026	.084	.088	.096	-.008	-.012	-.005
C(18)	.084	.254	.146	.058	-.021	.042	.197	.108	.104	.057	.035	-.019
C(19)	.074	.137	.124	.038	.025	-.019	.109	.081	.110	.040	-.020	-.001
C(20)	.119	.121	.097	.037	.042	-.001	.112	.094	.089	.028	-.011	.025
C(21)	.127	.093	.144	.005	-.025	-.008	.088	.115	.080	.014	-.006	-.015
C(22)	.093	.137	.074	.001	.013	.020	.165	.080	.079	.018	-.011	.025
C(23)	.114	.103	.182	.030	-.003	.057	.090	.091	.180	.033	.050	.005
C(24)	.085	.132	.127	.044	-.014	.024	.127	.074	.175	.026	.047	-.024
C(25)	.071	.148	.110	.010	-.016	.019	.116	.091	.186	-.018	.033	-.053
C(26)	.172	.118	.069	-.016	.011	.002	.110	.258	.101	.035	-.008	.030

Table 3. *Calculated hydrogen atom fractional coordinates*

	x	y	z		x	y	z
H(2)	1.150	.320	.340	H(2*)	.682	-.106	.121
H(3)	1.031	.170	.207	H(3*)	.863	-.003	.237
H(5)	.956	.341	.089	H(5*)	.711	.039	.399
H(6)	1.143	.496	.159	H(6*)	.541	-.132	.329
H(6)	1.081	.505	.065	H(6*)	.550	-.087	.432
H(7)	.982	.510	.236	H(7*)	.506	.028	.282
H(10)	.724	.464	.042	H(10*)	.571	.245	.506
H(11)	.592	.376	.193	H(11*)	.645	.396	.368
H(13)	.553	.135	.118	H(13*)	.905	.415	.412
H(14)	.528	.099	-.035	H(14*)	.953	.392	.563
H(14)	.591	.222	-.056	H(14*)	.827	.324	.582
H(15)	.757	.193	-.004	H(15*)	.854	.190	.484
H(18)	1.205	.172	.402	H(18*)	.820	-.132	.020
H(18)	1.142	.097	.320	H(18*)	.917	-.076	.092
H(18)	1.250	.194	.300	H(18*)	.829	-.188	.115
H(19)	1.228	.334	.179	H(19*)	.699	-.201	.262
H(19)	1.198	.212	.140	H(19*)	.832	-.177	.281
H(20)	1.068	.241	.044	H(20*)	.823	-.072	.403
H(20)	1.161	.353	.039	H(20*)	.708	-.163	.412
H(21)	1.116	.672	.207	H(21*)	.349	-.107	.318
H(21)	1.052	.679	.113	H(21*)	.359	-.061	.421
H(21)	.993	.692	.207	H(21*)	.325	.006	.341
H(23)	.637	.577	.182	H(23*)	.438	.350	.403
H(23)	.718	.635	.103	H(23*)	.390	.259	.476
H(23)	.594	.564	.079	H(23*)	.468	.373	.509
H(24)	.455	.394	.098	H(24*)	.649	.510	.486
H(24)	.524	.375	.009	H(24*)	.671	.426	.558
H(25)	.409	.206	.029	H(25*)	.848	.528	.538
H(25)	.419	.218	.137	H(25*)	.826	.545	.432
H(26)	.660	.038	-.136	H(26*)	1.020	.240	.617
H(26)	.722	.160	-.158	H(26*)	.894	.172	.633
H(26)	.792	.080	-.124	H(26*)	.975	.123	.573

parameters of the four chemically equivalent subunits show good agreement, with standard deviations in corresponding bond lengths of 0.004–0.018 Å, in bond angles of 0.3–1.4° and in the torsion angles of 0.3–4.2°. In Fig. 2 the  $\text{NH}_4^+$  complex is shown projected down the approximate twofold rotation axis.

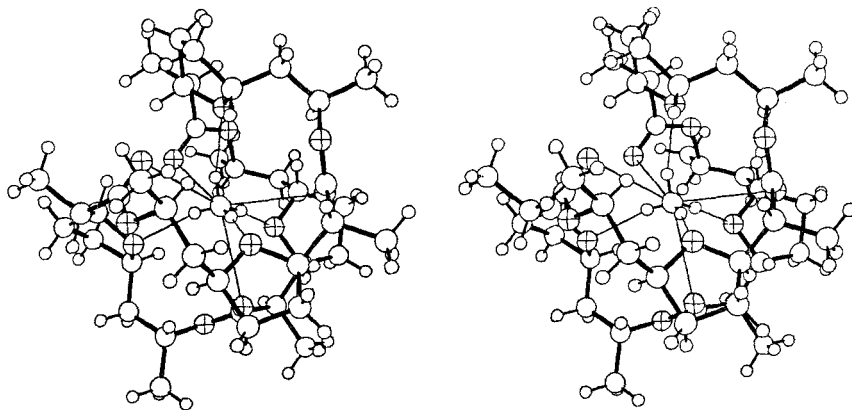


Fig. 1. *Stereoscopic view of the  $\text{NH}_4^+$  complex of nonactin*

Table 4. Bond lengths (in Å) and angles (in degrees). Values related by the non-crystallographic twofold rotation axis are grouped together

C(2)	-C(1)	1.307	113.8	C(2*)	-C(1*)	1.329	114.3
C(16*)	-C(1)	1.190	121.9	C(16)	-C(1*)	1.198	123.5
C(2)	-C(1)	1.190	121.9	C(2*)	-C(1*)	1.198	123.5
C(1)	-C(2)	1.524	109.5	C(1*)	-C(2*)	1.503	111.1
C(3)	-C(2)	1.543	107.1	C(3*)	-C(2*)	1.528	107.0
C(1)	-C(3)	1.438	108.7	C(1*)	-C(3*)	1.450	107.7
C(2)	-C(3)	1.523	116.9	C(2*)	-C(3*)	1.526	116.3
C(4)	-C(3)	1.467	110.0	C(4*)	-C(3*)	1.461	109.9
C(3)	-C(4)	1.509	110.1	C(3*)	-C(4*)	1.495	109.4
C(4)	-C(5)	1.531	113.7	C(4*)	-C(5*)	1.530	112.8
C(6)	-C(5)	1.507	115.0	C(6*)	-C(5*)	1.520	115.9
C(5)	-C(6)	1.467	106.1	C(5*)	-C(6*)	1.479	106.5
C(6)	-C(7)	1.510	112.4	C(6*)	-C(7*)	1.494	113.9
C(7)	-C(7)	1.328	116.9	C(7*)	-C(7*)	1.321	118.5
C(8)	-C(7)	1.491	112.9	C(8*)	-C(7*)	1.523	111.4
C(7)	-C(8)	1.207	121.7	C(7*)	-C(8*)	1.188	123.3
C(8)	-C(9)	1.528	110.0	C(8*)	-C(9*)	1.517	109.5
C(9)	-C(9)	1.545	107.5	C(9*)	-C(9*)	1.533	108.8
C(10)	-C(9)	1.439	107.5	C(10*)	-C(9*)	1.432	108.0
C(11)	-C(10)	1.517	114.9	C(11*)	-C(10*)	1.526	114.4
C(10)	-C(11)	1.456	109.2	C(10*)	-C(11*)	1.454	109.5
C(12)	-C(11)	1.527	109.4	C(12*)	-C(11*)	1.535	107.7
C(11)	-C(12)	1.514	106.4	C(11*)	-C(12*)	1.507	105.9
C(12)	-C(13)	1.482	115.6	C(12*)	-C(13*)	1.489	115.7
C(13)	-C(13)	1.484	108.0	C(13*)	-C(14*)	1.489	114.9
C(14)	-C(13)	1.514	106.4	C(14*)	-C(15*)	1.471	106.5
C(13)	-C(14)	1.482	115.6	C(13*)	-C(16*)	1.489	114.3
C(14)	-C(15)	1.484	108.0	C(14*)	-C(17*)	1.489	108.6
C(15)	-C(15)	1.514	115.0	C(15*)	-C(18*)	1.497	101.8
C(16)	-C(15)	1.493	101.6	C(16*)	-C(19*)	1.497	101.8
C(1*)	-C(16)	1.522	101.7	C(1*)	-C(20*)	1.515	101.2
C(3)	-C(19)	1.522	101.7	C(3*)	-C(21*)	1.515	101.2
C(5)	-C(20)	1.522	101.7	C(5*)	-C(22*)	1.515	101.2
C(11)	-C(24)	1.522	101.7	C(11*)	-C(23*)	1.515	101.2
C(13)	-C(25)	1.522	102.3	C(13*)	-C(24*)	1.515	101.2
				C(13*)	-C(25*)	1.515	103.9

Table 5. *Torsion angles (in degrees) for the 32-membered ring and for the 4 tetrahydrofuran rings*

C(15*)-O(16*)-C(1)	-C(2)	-177.1	C(19*)-C(3*)-O(4*)	-C(5*)	25.0				
O(16*)-C(1)	-C(2)	-C(3)	-133.8	C(3*)-O(4*)	-C(5*)	-C(20*)	-1.5		
C(1)	-C(2)	-C(3)	-O(4)	64.3	O(4*)	-C(5*)	-C(20*)	-C(19*)	-23.2
C(2)	-C(3)	-O(4)	-C(5)	148.6	C(5*)	-C(20*)	-C(19*)	-C(3*)	37.7
C(3)	-O(4)	-C(5)	-C(6)	-121.9	C(20*)	-C(19*)	-C(3*)	-O(4*)	-38.6
O(4)	-C(5)	-C(6)	-C(7)	-59.6					
C(5)	-C(6)	-C(7)	-O(8)	-62.0	C(24*)	-C(11*)	-O(12*)	-C(13*)	-18.2
C(6)	-C(7)	-O(8)	-C(9)	132.5	C(11*)	-O(12*)	-C(13*)	-C(25*)	-4.8
C(7)	-O(8)	-C(9)	-C(10)	174.3	O(12*)	-C(13*)	-C(25*)	-C(24*)	26.0
O(8)	-C(9)	-C(10)	-C(11)	139.5	C(13*)	-C(25*)	-C(24*)	-C(11*)	-35.7
C(9)	-C(10)	-C(11)	-O(12)	-64.7	C(25*)	-C(24*)	-C(11*)	-O(12*)	33.4
C(10)	-C(11)	-O(12)	-C(13)	-144.9					
C(11)	-O(12)	-C(13)	-C(14)	119.9	C(19)	-C(3)	-O(4)	-C(5)	23.2
O(12)	-C(13)	-C(14)	-C(15)	55.5	C(3)	-O(4)	-C(5)	-C(20)	.3
C(13)	-C(14)	-C(15)	-O(16)	62.2	O(4)	-C(5)	-C(20)	-C(19)	-24.2
C(14)	-C(15)	-O(16)	-C(1*)	-133.6	C(5)	-C(20)	-C(19)	-C(3)	37.4
C(15)	-O(16)	-C(1*)	-C(2*)	-174.4	C(20)	-C(19)	-C(3)	-O(4)	-37.4
O(16)	-C(1*)	-C(2*)	-C(3*)	-132.7					
C(1*)	-C(2*)	-C(3*)	-O(4*)	60.7	C(24)	-C(11)	-O(12)	-C(13)	-22.3
C(2*)	-C(3*)	-O(4*)	-C(5*)	148.7	C(11)	-O(12)	-C(13)	-C(25)	-2.2
C(3*)	-O(4*)	-C(5*)	-C(6*)	-122.6	O(12)	-C(13)	-C(25)	-C(24)	25.5
O(4*)	-C(5*)	-C(6*)	-C(7*)	-58.1	C(13)	-C(25)	-C(24)	-C(11)	-38.0
C(5*)	-C(6*)	-C(7*)	-O(8*)	-61.9	C(25)	-C(24)	-C(11)	-O(12)	37.5
C(6*)	-C(7*)	-O(8*)	-C(9*)	137.4					
C(7*)	-O(8*)	-C(9*)	-C(10*)	173.9					
O(8*)	-C(9*)	-C(10*)	-C(11*)	129.3					
C(9*)	-C(10*)	-C(11*)	-O(12*)	-61.6					
O(10*)	-C(11*)	-O(12*)	-C(13*)	-141.2					
C(11*)	-O(12*)	-C(13*)	-C(14*)	119.6					
O(12*)	-C(13*)	-C(14*)	-C(15*)	59.4					
C(13*)	-C(14*)	-C(15*)	-O(16*)	61.4					
C(14*)	-C(15*)	-O(16*)	-C(1)	-137.7					

Table 6. *Coordination of NH<sub>4</sub><sup>+</sup> by oxygen atoms. The N-H distances are subject to large experimental error and are systematically too short*

N...O(4)	2.890 Å	N-H(1)	0.872 Å	H(1)...O(4*)	2.012 Å
N...O(12)	2.832	N-H(2)	0.802	H(2)...O(4)	2.102
N...O(4*)	2.861	N-H(3)	0.715	H(3)...O(12*)	2.161
N...O(12*)	2.847	N-H(4)	0.968	H(4)...O(12)	1.872
N...O(17)	3.126				
N...O(22)	3.012				
N...O(17*)	3.020				
N...O(22*)	3.157				
N-H(1)...O(4*)	164.2°	H(1)-N-H(2)	96.2°		
N-H(2)...O(4)	167.4	H(1)-N-H(3)	116.8		
N-H(3)...O(12*)	161.1	H(1)-N-H(4)	107.9		
N-H(4)...O(12)	170.9	H(2)-N-H(3)	120.4		
		H(2)-N-H(4)	116.1		
		H(3)-N-H(4)	99.8		

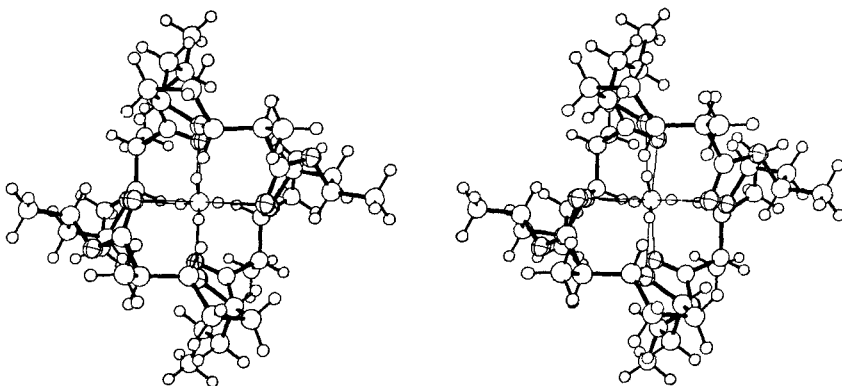


Fig. 2. Projection of the structure of the  $\text{NH}_4^+$  complex of nonactin along the non-crystallographic twofold rotation axis. This axis is a least-squares line through the mid-points of related atoms (Cl, Cl\*, etc.). Its equation in crystal space is:  $x = 0.7797 - 0.0506 t$ ;  $y = 0.2313 + 0.0469 t$ ;  $z = 0.2518 + 0.0089 t$

The coordination of the  $\text{NH}_4^+$  ion is shown in Fig. 3. It forms four hydrogen bonds with the ether oxygen atoms ( $\text{NH}\dots\text{O}$ , 2.832–2.890 Å; mean 2.858 Å,  $\text{N-H}\dots\text{O}$  angles, 161.1–170.9°). The  $\text{N}\dots\text{O}$  (carbonyl) distances are 3.012–3.157 Å (mean 3.079 Å). With four  $\text{N}\dots\text{O}$  distances of 2.86 Å and four of 3.08 Å, both sets arranged tetrahedrally, the cube of oxygens has maximally  $T_d$  symmetry with twelve equal

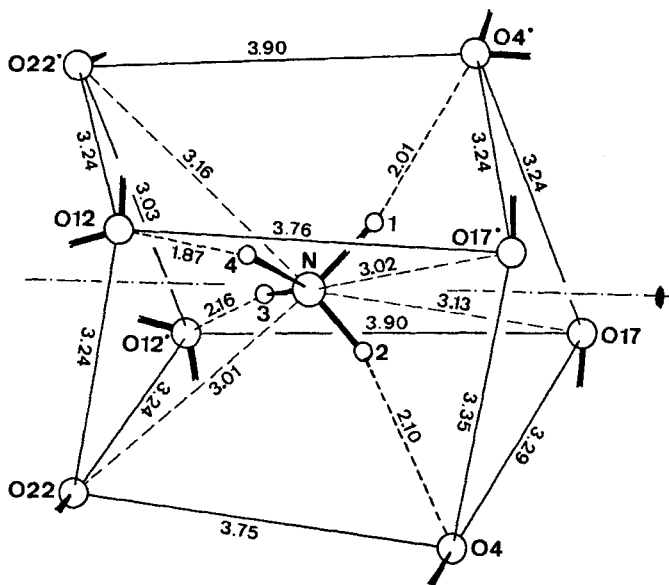


Fig. 3. Coordination of  $\text{NH}_4^+$  by ligand oxygen atoms. The non-crystallographic twofold rotation axis is indicated



O...O edges of 3.43 Å. The observed cube is more distorted. Four edges are 3.75–3.90 Å whereas the other eight are 3.03–3.35 Å. This elongation of the coordinating cube is reflected in the H–N–H bond angles. Those that span the two square faces, H(1)–N–H(2) (96.2°) and H(3)–N–H(4) (99.8°) are somewhat smaller than the other four.

Whereas the conformational change from free nonactin to its complexes is quite drastic, involving a change from outward to inward pointing carbonyl and tetrahydrofuran oxygen atoms, the changes within the series of Na<sup>+</sup>, K<sup>+</sup> and NH<sub>4</sub><sup>+</sup> complexes are quite smooth. In the Na<sup>+</sup> complex, the carbonyl oxygen atoms are closer to the centre of the molecule than the ether oxygen atoms (2.42 Å vs. 2.77 Å). In the K<sup>+</sup> complex, the two sets of oxygen atoms are almost equidistant (2.80 Å), and in the NH<sub>4</sub><sup>+</sup> complex, the carbonyl oxygen atoms are further from the centre (3.08 Å vs. 2.86 Å). The overall expansion of the cube is associated mainly with an outward displacement of the carbonyl oxygen atoms, which is effected by a gradual rotation of the plane of the ester groups, involving changes of 20–30° in the torsion angles around C(7)–O(8), C(9)–C(10) and symmetry equivalent bonds (Fig. 4). The changes in the remaining 24 torsion angles around the ring do not amount to more than a few degrees. The conformations of the tetrahydrofuran rings remain virtually the same in all three complexes so far studied; an envelope conformation with C(19) (C(24)) out of the plane of the four other ring atoms.

Similar results to those discussed here have recently been reported for a NH<sub>4</sub><sup>+</sup> complex of tetranactin [6]. The N...O (ether) distances are 2.86–2.93 Å, the N...O (carbonyl) distances 2.97–3.05 Å and the N–H...O angles are 168–176°.

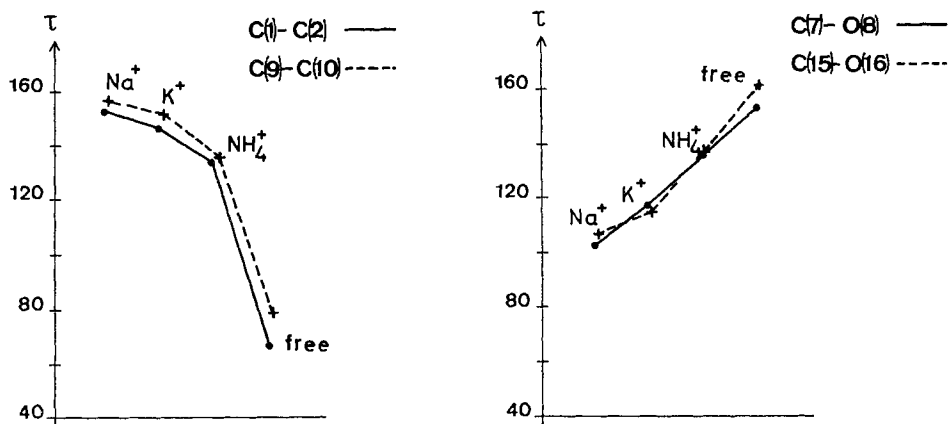


Fig. 4. Torsion angles around C(7)–O(8), C(9)–C(10) and symmetry equivalent bonds of Na<sup>+</sup>, K<sup>+</sup>, NH<sub>4</sub><sup>+</sup> and free nonactin. The values for the NH<sub>4</sub><sup>+</sup> complex are the mean of the two units related by non-crystallographic twofold rotation symmetry

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**63. 1-Aralkylated Tetrahydro-2-benzazepines<sup>1)</sup>.****Part II: Synthesis from 3-(3,4-Dimethoxyphenyl)-propylamine**by **Daniel Berney** and **Theodor Jauner**Research Institute *Wander* Ltd., a *Sandoz* Research Unit, Berne, Switzerland.

(7. I. 76)

*Summary.* 3-(3,4-Dimethoxyphenyl)-propylamine was N-acylated with aralkanecarboxylic acid chlorides. The resulting amides were subjected to *Bischler-Napieralski* ring closure to give the corresponding 1-aralkyl-dihydro-2-benzazepines. These were reduced to the title compounds.

**Introduction.** – In Part I of this study, the synthesis of some 1-aralkyl-tetrahydro-2-benzazepines from methoxylated phenylpropionamides was described [1]. The method reported in the previous paper was found to be unsuccessful for the preparation of 2-benzazepines where the 1-aralkyl group had methoxy- or chloro-substituents in the aromatic nucleus. The difficulties encountered in the synthesis of these compounds were avoided by the use of the route here described, which involves a *Bischler-Napieralski* ring closure.

**Results.** – 3-(3,4-Dimethoxyphenyl)-propylamine **1** was allowed to react with the phenylacetyl chlorides **2a**, **b** and **c**, giving the amides **3a**, **b** and **c**. These amides did not cyclize when heated with POCl<sub>3</sub> alone; one mol of anhydrous AlCl<sub>3</sub> had to be added for each mol of amide to effect ring closure. The imines **4a**, **b** and **c** were used as crude oils in the reduction with NaBH<sub>4</sub>, giving the corresponding amines **5a**, **b** and **c**. Compound **5a** was identical with the product obtained by the route previously described [1]. The amine **5b** was treated with formaldehyde, and the adduct was reduced with NaBH<sub>4</sub>, giving the methylated compound **6b**. The amine **5c** was methylated by the *Clarke-Eschweiler* method to give **6c**. The 'homoxypine' **7** was obtained by treating **5b** with formaldehyde and HCl.

Similarly the phenylpropylamine **1** was allowed to react with the phenylpropionyl chlorides **2d** and **2e** to give the amides **3d** and **3e**, respectively. These amides were cyclized to **4d** and **4e** which were then reduced to **5d** and **5e**. Product **5d** was identical with the benzazepine previously reported [1]. The amines **5d** and **5e** were methylated to **6d** and **6e** by the *Clarke-Eschweiler* method.

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<sup>1)</sup> 19th Communication on seven-membered heterocycles; 18th Communication: [1].