X-RAY CRYSTAL STRUCTURE OF THE *tert*-OCTYLAMINE SALT (RMS-431) OF PRAVASTATIN

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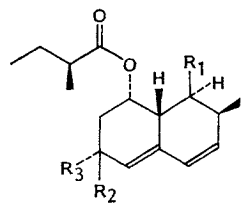
In the course of studies to detect specific inhibitors of cholesterol synthesis from microbial products, several compounds were isolated from the culture broth of *Penicillium citrinum*.[1] One compound, sodium (+)-(3*R*,5*R*)-3,5-dihydroxy-7-[(1*S*,2*S*,6*S*,8*S*,8a*R*)-6-hydroxy-2-methyl-8-[(*S*)-2-methylbutyryloxy]-1,2,6,7,8,8a-hexahydro-1-naphthyl]heptanoate (CS-514) (**Ia**, pravastatin sodium) found as a minor urinary metabolite of ML-236B (**Ib**) in dogs was especially significant on account potency, tissue selectivity and low toxicity.[2] **Ia** was also obtained by microbiral transformation of ML-236B.[3] The structures of **Ib** (ML-236B),† **Ic** (monakolin K),[4] and **Id** (RMS-414)[5] have already been studied by X-ray analyses. Similar results for **Ib** and **Ic**, designated as compactin and mevinolin, were also reproted by BROWN *et al.*,[6] and ALBERTS *et al.*,[7] respectively. The aim of the present investigation was to establish the stereochemical configuration of CS-514, especially of the asymmetric carbon at the 5 position. Despite many attempts at crystallization of CS-514 as the sodium salt, a single crystal suitable for X-ray analysis could not be obtained. Thus, we decided to use for the analysis the *tert*-octylamine salt (RMS-431) of CS-514, in which the sodium has been replaced by the organic amine cation.

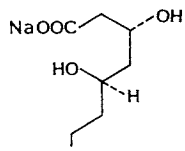
RMS-431 was prepared by means of the following procedure:

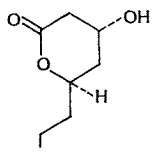
$$\text{CS-514} \xrightarrow[\text{add HCl (pH 4), separation from water}]{\text{EtOAc containing water}} \text{Free acid} \xrightarrow[\text{evaporation, precipitation}]{\text{add } \textit{tert}\text{-octylamine}} \text{RMS-431}$$

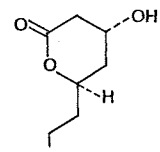
After many attempts, a usable single crystal was obtained from CH_3CN - H_2O (5 : 1). The crystal used in the analysis had $0.6\times0.2\times0.1$ mm. Lattice constants were determined by a least-squares fit to the angular settings of 20 reflections within the range $15<\theta<25°$. Intensity data were obtained on a Rigaku AFC-5R appa-

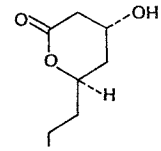
Scheme 1.



Ia R_1 =  R_2 = OH R_3 = H

Ib R_1 =  R_2 = H R_3 = H

Ic R_1 =  R_2 = H R_3 = CH_3

Id R_1 =  R_2 = OH R_3 = H

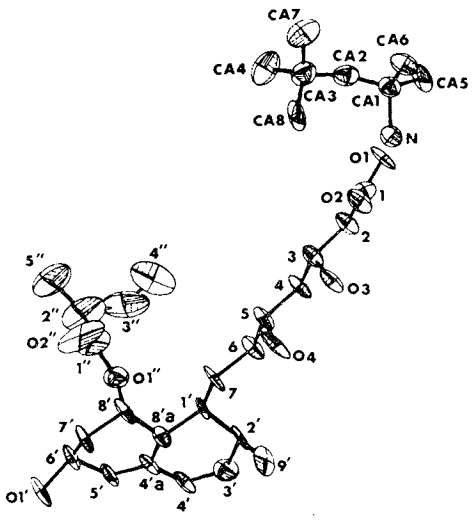
† C. TAMURA; unpublished data, 1974.

ratus equipped with graphite monochromatized CuKα radiation and using the $\theta \sim 2\theta$ scan technique ($2\theta < 128°$). During data collections, three standards, measured before every 200 reflections, showed no significant variation. Of 2973 independent reflections measured, only 2188 were considered as observed on the basis of the criterion $F_0 > 2\sigma(F_0)$. All intensities were corrected for Lorentz and polarization effects but not for absorption. Crystal data are as follows: $C_{23}H_{35}O_7 \cdot C_8H_{20}N$, MW=553.8, monoclinic, space group $P2_1$, a=16.850(3), b=5.801(1), c=17.290(3) Å, β=108.04(1)°, U=1610.9 Å^3, Z=2, D_{calc}=1.15 gcm^{-3}, μ(CuKα)=6.4 cm^{-1}, T=297K. The structure was solved by direct methods using the MULTAN 84[8] series of programs, with RANTAN being used to obtain the phases. The positions of the hydrogen atoms were estimated from standard geometrical criteria except for those of the three hydroxyl groups which could not be located. The final refinements using block-diagonal least-squares methods with anisotropic temperature factors for the nonhydrogen atoms and isotropic temperature factors for the hydrogen atoms lowered the R value to 0.093 (wR=0.104, $w=1/\sigma^2(F_0)$). The goodness of fit was 1.4. The peaks in the final difference Fourier synthesis were within the range ± 0.5 eÅ^{-3}. In the final cycle of refinement, the shifts in the parameters were all less than the corresponding standard deviations.

The molecular structure† is shown in Fig. 1, which also shows the atom labels used. As the absolute configuration of the C2″ atom at the methylbutanoate moiety had been determined previously to be *S* (OGISO, A. and A. TERAHARA; unpublished data, 1977), it follows that the configurations at the other asymmetric carbon atoms are C1′(*S*), C2′(*S*), C6′(*S*), C8′(*S*), C8′a(*R*), C3(*R*), and C5(*R*), respectively. All the configurations at the chiral centers are the same as those in the lacton form, RMS-414.[5] The conformations of the carbon chain from the C1′ atom to the carboxyl group are all *trans* in

† The atomic coordinates, bond lengths and angles involving the nonhydrogen atoms are deposited with the Crystallographic Data Centre, Cambridge, England. The atomic thermal parameters, observed and calculated structure factors are available from one of the authors (S. SATO) upon request.

Fig. 1. ORTEP drawing of the molecular structure with atomic numbering scheme.



the heptanoic acid side group. The O2 atom of the carboxylate group and the O3 and O4 hydroxyl oxygen atoms point in the same direction and form intramolecular hydrogen bonds O3(H)···O2 and O4(H)···O3 with distances of 2.679(9) and 2.716(10) Å, respectively. In the carboxylate group, the C1-O1 and C1-O2 bonds are 1.249(11) and 1.261(11) Å, respectively and the bond angle is 122.2(8)°. These values agree with those found in the zwitterion structures in amino acids. The present compound is therefore a salt with the carboxylic acid proton having migrated to the *tert*-octylamine. In the crystal, the *tert*-octylamine group is placed between the two main units along of the *b*-axis. Hydrogen bonds are formed between the carboxylate group and the *tert*-octylamine; O1···N(x, y, z) has a length of 2.745(10) Å, and O2···N($x, 1+y, z$) is 2.891(10) Å. These hydrogen bonds may contribute to the stability of the crystal structures. Other weak hydrogen bonds are also observed between O3···N($-x, \frac{1}{2}+y, 1-z$) with a value of 3.050(10) Å, and O1′···O1′($1-x, -\frac{1}{2}+y, -z$) with a value of 3.044(20) Å.

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