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THE CRYSTAL STRUCTURE OF 13-ACETYL-8-p-BROMOBENZOYL SERRATININE: THE REVISED CONFIGURATION OF C_4-N BOND OF SERRATININE

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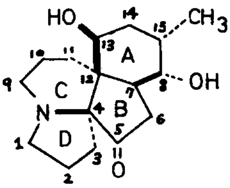
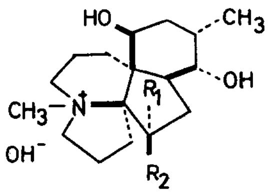
Serratinine has been reported to have the absolute stereostructure (I) on the basis of chemical and spectroscopic studies.[1a,b] In these studies, the assignment of the β configuration to the C_4-N bond mainly depended on the results from Hofmann degradation reactions of two dihydroserratinine methohydroxides (IIa and IIb).[1b] However, there still leaves some ambiguity on this assignment, since it has been recently suggested that the stereochemistry of Hofmann elimination in small and medium ring compounds is more complex than earlier workers have suggested.[2] To make this obscurity clear and to confirm the rest of the structure, an X-ray crystal-structure analysis of 13-acetyl-8-p-bromobenzoyl serratinine* was undertaken. The present result led us to the conclusion that the configuration of the bond concerned should be revised to the α configuration as shown in the formula (III).

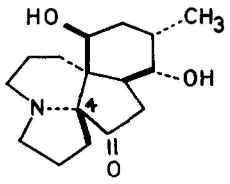


(I)



(IIa) R_1=H, R_2=OH

(IIb) R_1=OH, R_2=H

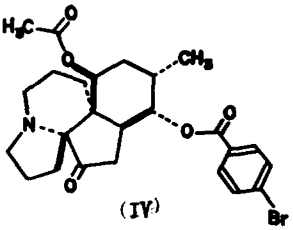


(III)

The crystal structure was solved by the heavy atom method with partial three dimensional data and its absolute structure (IV) was determined by the anomalous dispersion method. The crystal was a colourless monoclinic needle elongated along the b-axis. The crystal density value of 1.38 g/cc determined by the flotation method in calcium chloride aqueous solution indicated that this crystal contained four molecules in the unit cell. The linear absorption coefficient for Cu-Kα radiation was 27.9 cm^{-1}. The cell dimension and space group determined from oscillation, Weissenberg and precession photographs were: a=12.47, b=11.44, c=17.52 A, β=104°15', and C2 which was judged from the number of molecules per unit cell (Z=4) and the absent spectra (hkl when h+k is odd, h00 when h is odd, 0k0 when k is odd). Although other space groups, Cm and C2/m, also satisfy these conditions, they should be excluded because the derivative of natural product must not contain the racemic compound and these two space groups have the mirror plane and center of symmetry, respectively.

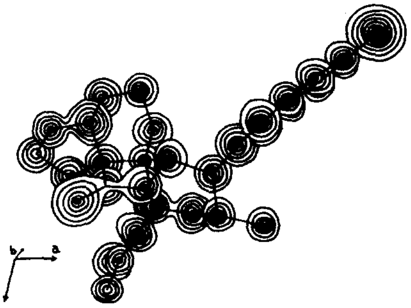
Intensity data of 968 independent reflections were collected on equi-inclination Weissenberg photographs about the b-axis (k=0-8) taken with Cu-Kα radiation. Intensities were estimated by visual comparison with a standard scale, and were corrected with the appropriate Lorentz and polarization factors, but no absorption or extinction correction was made. A Wilson plot was then made to estimate an approximate scale factor and overall temperature factor (B=5.4 A^2). The coordinates of the bromine atom were determined as x=0.225, z=0.005 by locating the Br-Br peak on the Patterson Harker sections at V=0 and V=1/2, whereas the y coordinate was arbitrarily chosen as y=0.100 because there is no restriction for y coordinate in this space group. The phase calculated from the bromine position was used for the first Fourier synthesis, and the benzene ring extending from bromine atom could be identified. The whole structure (Fig. 1) was determined by successive Fourier synthesis with the chemical and structural considerations, and the reliability factor, R, was 0.38. At this stage, however, no significant spurious peaks were observed in this electron density map. Further refinement of the structure was carried out by the block diagonal least-squares program 'HBLS IV' on the HITAC 5020E Computer. After three cycles refinement with isotropic temperature factors, the layer ratio of b-axis data was adjusted to that of calculated value. Following five cycles refinement with individual anisotropic temperature factors for all atoms, dropped R value to 0.10.

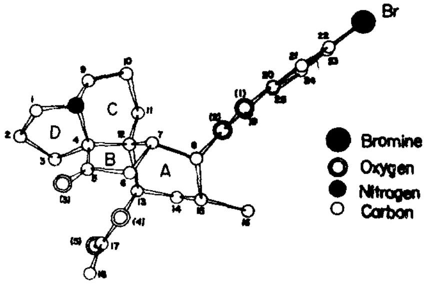
Determination of the absolute configuration was carried out using the anomalous dispersion effect of the bromine ($\Delta f'=-0.9$ and $\Delta f''=1.5$) for Cu-Kα radiation. Structure factors were calculated for the Friedel's pairs, (hkl) and $(h\bar{k}l)$, where $(h\bar{k}l)$ is equal to $(\bar{h}\bar{k}\bar{l})$ in the space group C2. The order of index h,k,l was referred to the left-handed coordinate system. The oscillation photographs setting the b-axis were actually taken with Cu-Kα radiation in order to compare $F^2(hkl)$ with $F^2(h\bar{k}l)$. A comparison between observed and calculated intensities of 48 out of 61 pairs indicated that the assumed configuration was the true structure. Thus, the absolute configuration of 13-acetyl-8-p-bromobenzoyl serratinine has been now established as the formula (IV).



(IV)

The absolute stereostructure (III) thus established for serratinine is only different from the chemically proposed structure (I) in the stereochemistry around C_4: the spatial relation between the C_4-N bond and the C_{12}-C_{13} bond in the former is trans with respect to the B ring, whereas the relation in the latter is cis as shown in the formula (I).

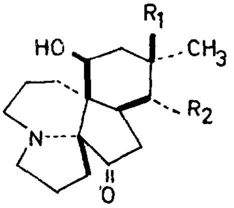




The intramolecular hydrogen bonding observed in serratinine, which was suggested to be due to the nitrogen atom and the C_{13} hydroxyl group in the previous paper$^{1)}$, would be ascribable to the ketone and the C_{13} hydroxyl group because the interatomic distance between the nitrogen atom and the C_{13}

oxygen atom is 4.15 A, and moreover, these two atoms occupy the opposite site about the B ring, i.e. the C_4–N bond is the α configuration and the C_{13}–O bond is β axial. The obtained bond lengths and bond angles are all acceptable values at the stage of the refinement, and the molecules are surrounded each other with Van der Waals contacts.

Since the structures of 8-deoxyserratinine(3), serratine(4), and serratanidine(5) have been proposed by the chemical correlations with serratinine, respectively, in which the C_4–N bond of serratinine is intact, their structures, therefore, should be revised as (V), (VI) and (VII), respectively.



(V) $R_1 = R_2 = H$

(VI) $R_1 = OH$, $R_2 = H$

(VII) $R_1 = R_2 = OH$

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* Hydrolysis of this compound with 10% sodium hydroxide solution in 50% aqueous methanol regenerated serratinine.