Tetrahedron Letters No.60, pp. 6301-6304, 1968. Pergamon Press. Printed in Great Britain.

THE CRYSTAL AND MOLECULAR STRUCTURE OF PEDERIN DI-*p*-BROMOBENZOATE

Akio Furusaki and Tokunosuké Watanabé

Faculty of Science, Kwansei Gakuin University, Nishinomiya, Japan

and

Takeshi Matsumoto and Mitsutoshi Yanagiya

Department of Chemistry, Faculty of Science, Hokkaido University,

Sapporo, Japan

(Received in Japan 19 September 1968; received in UK for publication 19 November 1968)

Pederin, $C_{25}H_{45}O_9N$, is a toxic principle isolated from *Paederus fuscipes*.[1,2] The partial structure of this material was reported by A. Quilico *et al.*[3] and T. Matsumoto *et al.*[4], and recently the whole structural formula was proposed as is shown in Fig. 1.[5]

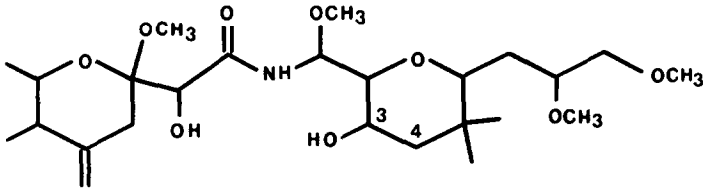

Fig. 1

From the NMR spectrum, T. Matsumoto suggested that a free hydroxyl group in one of two tetrahydropyran rings should be attached in the position 4 to the oxygen atom of the ring rather than in the position 3 as shown in Fig. 1.[6] In order to confirm the chemical structural formula proposed by C. Cardani *et al.* and elucidate the stereochemistry of pederin, including the absolute configuration, an X-ray crystal analysis of a di-*p*-bromobenzoate derivative has been carried out.

Single crystals of pederin di-*p*-bromobenzoate, $C_{39}H_{51}O_{11}NBr_2$, grown from a methanol-ether solution, were colorless and of the shape of plates or prisms. As a result of the present study, the crystals were found to contain one molecule

of methanol per molecule of the derivative as alcohol of crystallization. This is supported also by the result of the elementary analysis. The crystal data were derived from oscillation and Weissenberg photographs taken around the *b* and *c* axes with Cu *K*α radiation. The crystal is monoclinic with two units of $C_{39}H_{51}O_{11}NBr_2 \cdot CH_3OH$ in a unit cell of the dimensions a = 17.37, b = 12.93, c = 9.935 A and $\beta = 95.6^\circ$. The corresponding space group is uniquely determined as $P2_1$ from the systematic absences of reflections.

The intensity data were obtained from equi-inclination integrating Weissenberg photographs taken with Cu *K*α radiation from the zeroth to the ninth layer around the *b* axis and from the zeroth to the fourth layer around the *c*. The intensities were measured visually using a calibrated scale, and after the Lorentz and polarization correction, were converted into an absolute scale by Wilson's method, the average temperature factor obtained being 6.1 A^2. Thus, the structure factors of 3212 independent reflections were derived.

The crystal structure was elucidated by means of the Fourier method using only the contribution of heavy atoms to phases of structure factors. From the first Fourier map, fifty-one peaks corresponding to carbon, nitrogen and oxygen atoms of a pederin di-*p*-bromobenzoate molecule could be picked out. The second Fourier map calculated using these atomic positions and those of bromine atoms showed the presence of a methanol molecule per asymmetric unit in the crystal. Then, in order to refine the parameters of the fifty-four atoms except the methanol carbon whose position was doubtful at this stage, the least squares method was carried out assuming anisotropic thermal motions for bromine atoms and isotropic vibrations for all the other atoms. After three cycles of the refinement, the *R* factor reached a value of 13.2 %. Since, from the difference map calculated at this stage, the position of the methanol carbon could be found out, three additional cycles of the refinement including this atom were carried out, the final *R* factor being 12.7 %. The absolute configuration of the molecule was determined using the anomalous dispersion of bromine. The observations were obtained from the Weissenberg photographs around the *c* axis, already mentioned.

The bond lengths and angles calculated from the atomic parameters thus obtained are all reasonable considering their average standard deviations (0.003

A for Br and 0.02-0.03 A for C, N and O atoms). The molecular framework of pederin di-*p*-bromobenzoate in the crystal and the corresponding chemical structural formula are shown in Figs. 2 and 3 respectively.

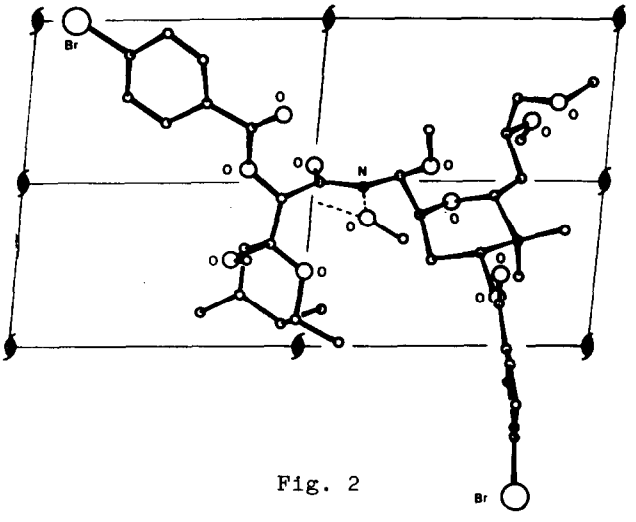

Fig. 2

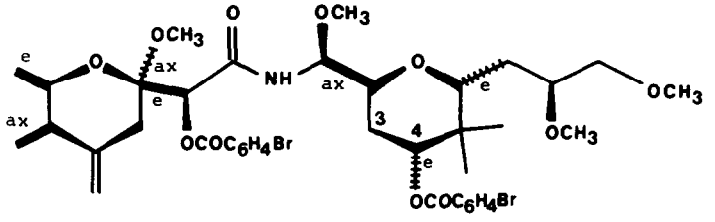

Fig. 3

Thus, it is found that, as T. Matsumoto suggested, the hydroxyl group in the tetrahydropyran ring of a pederin molecule is in the position 4 to the ring oxygen atom.

Both of the two rings take a stable chair-like form. In one of these rings, containing an exocyclic double bond, two methyl groups are present; of these, one attached to the carbon atom adjoining to the ring oxygen takes the equatorial orientation and the other, the axial orientation. These configurations are just in agreement with the conclusions of the study on the basis of the NMR spectrum.[6] On the other hand, the methoxyl group is axial in the opposite sense to the axial methyl group mentioned above. In the other tetrahydropyran ring, having the benzoylated hydroxyl group, five groups are present. Of these, the hydroxyl

group is equatorial, and the two methyl groups are necessarily axial and equatorial respectively since these two are attached to the same carbon atom. The large side chain containing an amide group is joined to the ring in the axial orientation antiparallel to the axial methyl group. It is of interest to notice the fact that the methoxyl oxygen atom in this side chain projects over the ring in spite of its close approach to the ring carbon atoms. The only remaining side chain containing two methoxyl groups takes the equatorial configuration.

The methanol molecule present in the crystal as alcohol of crystallization forms two hydrogen bonds; one is formed with the nitrogen atom of an amide group and the other with the oxygen of another amide group. In other words, the methanol molecules connect molecules of pederin di-*p*-bromobenzoate around a two-fold screw axis, forming a one-dimensional hydrogen-bonded chain.

References

1) A. Ueta, *Kyushu Igaku Zasshi (Journal of Kurume Medical College, Kyushu)*, **1939**, 249.

2) M. Pavan and G. Bo, *Phys. Com. et Oecol.*, **3**, 307 (1953).

3) A. Quilico, C. Cardani, D. Ghiringhelli and M. Pavan, *La Chim. e l'Ind.*, **43**, 1434 (1961); C. Cardani, D. Ghiringhelli and A. Quilico, Abstracts of papers, International Symposium on the Chemistry of Natural Products, Kyoto (1964), p. 139.

4) T. Matsumoto, S. Tsutsui, M. Yanagiya, S. Yasuda, S. Maeno, J. Kawashima, A. Ueta and M. Murakami, *Bull. Chem. Soc. Japan*, **37**, 1892 (1964).

5) C. Cardani, D. Ghiringhelli, R. Mondelli and A. Quilico, *Tetrahedron Letters*, **1956**, 2537.

6) T. Matsumoto, Abstract of 9th Symposium on the Organic Chemistry of Natural Products, Osaka, Japan (1965), p. 67.