

STEREOCHEMISTRY OF PARTHEMOLLIN AND RELATED XANTHANOLIDES¹

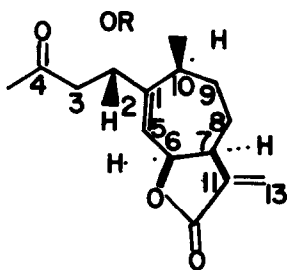
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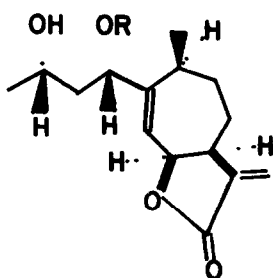
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(Received in USA 18 June 1973, received in UK for publication 10 August 1973)

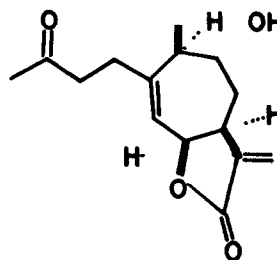
Although absolute configuration of the naturally-occurring xanthanolides parthemollin (1a, exclusive of stereochemistry at C-6 and C-7),² acetylparthemollin (1b)^{2,3} apachin (2b)³ and ivambrin (2a)³ at C-2, C-4 and C-10 is known, the stereochemistry of the lactone ring has remained uncertain. Application² of an empirical rule⁴ relating the sign of the lactone Cotton effect to the nature of the lactone ring closure indicated trans-fusion of the lactone ring (H-6 β , H-7 α). On the other hand, application of the modified Hudson-Klyne rule⁵ suggested² that parthemollin and the compounds correlated with it should be cis-lactones (H-6 α , H-7 α), a conclusion which is supported by another rule which depends on the magnitude of $J_{7,13}$ ($J \leq 3$ Hz).⁶



1a. R=H
b. R=Ac



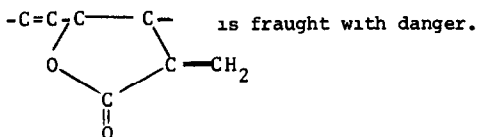
2a. R=H
b. R=Ac



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To test the validity of the various rules and to settle the stereochemical ambiguity, the crystal structure of parthemollin was determined by direct methods.* The results show that the lactone ring fusion is cis. Since the absolute configuration at

several centers is known,² the complete stereochemistry of parthemollin and its relatives is as depicted in the formulas. Consequently, as has been pointed out previously,^{7,8} indiscriminate application of the Stöcklin-Waddell-Geissman rule to lactones of the type



A single crystal of parthemollin obtained by recrystallization from ethyl acetate-hexane was examined on a Hilger-Watts Y 290 automatic diffractometer using molybdenum K α radiation. The crystal for which absorption was negligible was shown to belong to the space group P2₁ from the Weissenberg photographs and the intensities of the 0k0 reflection where k = 2n + 1. Unit cell dimensions obtained by least-squares fit of observed angles were: a = 10.48 (2), b = 6.581 (2), c = 10.792 Å (2), β = 111.79°, which for two molecules per unit cell gave a crystallographic density of 1.27 g/cm³. This compared favorably with the density of 1.28 g/cm³ determined by flotation in carbon tetrachloride - heptane.

Of the 4321 measurements made, 1907 were independent and had a positive non-zero intensity. Structure factors were obtained for the independent reflections after the standard corrections had been applied.

The structure was solved by direct methods using the XRAY-72 system of programs devised by Stewart.⁹ Normalized structure factors were calculated using a linear isotropic temperature correction. All reflections having positive non-zero intensities were included as "observed" reflections for the calculation and for all steps in the phase determination. A total of 11751 triplets were found for the 434 reflections having an E value of 1.2 or greater.

Three origin-defining reflections (104, E = 3.09; 811, E = 2.43; 501, E = 2.10) were selected^{10a,b} and assigned phases of 180°, 0° and 180°, respectively. In addition, two other reflections (871, E = 2.68; 147, E = 2.32) were assigned¹¹ phases of 90° and 255°. Reiterative application of the tangent refinement formula^{10a} led to the determination of 264 phases with an agreement factor of 0.15.

*A number of attempts to prepare suitable heavy atom derivatives failed.

Use of these phases gave an E map which revealed the positions of the 19 carbon and oxygen atoms of the molecular structure. A structure factor calculation for carbon atoms at these positions gave an R factor of 0.395. Two cycles of full matrix least-squares refinement using individual isotropic temperature factors and unit weights led to an R factor of 0.235. Replacement of carbon atoms with oxygens at the appropriate positions reduced the R factor to 0.197.

At this point "observed reflections were redefined as those for which the intensity was greater than three times the standard deviation of the measurement. Least-squares minimisation of the function $\sum \omega (|F_o| - |F_c|)^2$, with anisotropic temperature factors for all 19 atoms resulted in an R-factor of 0.132 over 1765 observed reflections. The weighting scheme used in the last cycle of refinement was $\omega = X.Y$ where $X = 1$ if $|F_o| < 8$ and $X = 8/|F_o|$ otherwise and $Y = 1$ for $\sin \theta > .35$, $Y = \sin \theta / .35$ otherwise. At this point, all bond angles and lengths were as expected with standard deviations around 1° and 0.02 \AA respectively. Refinement is continuing and full details of the analysis, the first of a xanthanolide, will be published elsewhere.

Although parthemollin has not been correlated with ivalbatin, another closely related xanthanolide,¹² nmr and CD evidence presented previously¹² indicated that the fusion of the lactone ring in 1a and ivalbatin was the same. Hence ivalbatin can be represented as 3.

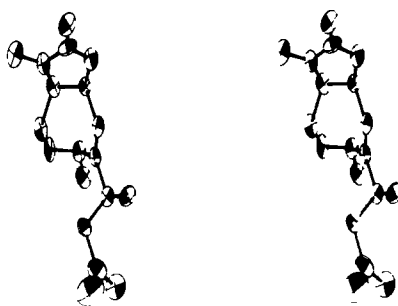


Figure 1.-Stereoscopic diagrams of the structure of parthemollin.

Acknowledgment

This work was supported in part by U.S. Public Health Service Research Grant CA-13121 from the National Cancer Institute.

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