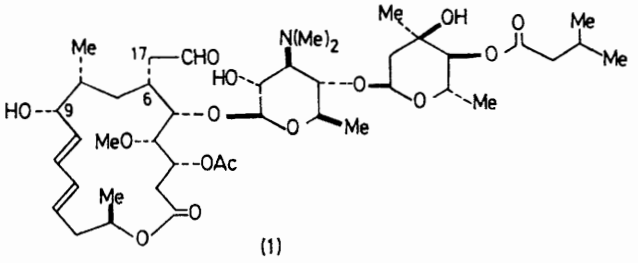
Crystal and Molecular Structure of Diacetyl-3,6-bicyclo-leuconolide A_3

By ARNAUD DUCRUIX, CLAUDINE PASCARD,* AKIRA NAKAGAWA, and SATOSHI ŌMURA†

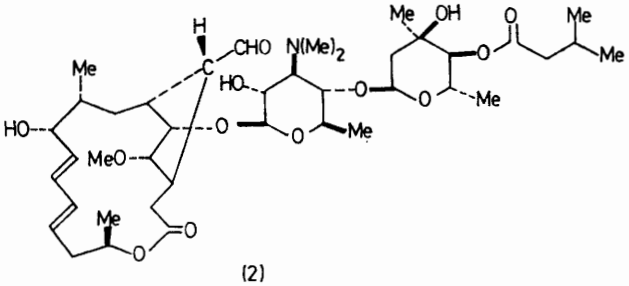
(*Institut de Chimie des Substances Naturelles du C.N.R.S., 91190, Gif-sur-Yvette, France,* and †Kitasato University and The Kitasato Institute, Shirokane, Minato-ku, Tokyo* 108, *Japan*)

Summary *X*-Ray crystal structure analysis of diacetyl-3,6-bicyclo-leuconolide A_3 (**3**), obtained from 3,6-bicyclo-leucomycin A_3 (**2**), has led to the assignment of the stereochemistry at C–3, C–9, and C–17 in the latter.

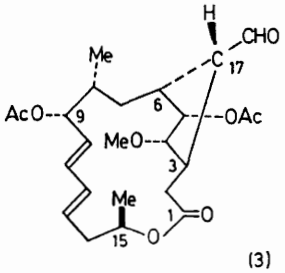
WE have proposed a bicyclic structure with a C–C bond between C–17 and C–3 in the aglycone ring[1] for the compound obtained by treatment of leucomycin A_3 (**1**) with lithium hydroxide in ethanol, whereas Osono *et al.*[2] assumed that the same product from josamycin (leucomycin A_3) was an epimer with respect to the carbon atom to which the aldehyde group was attached. This point was cited as evidence for their tentative assignment that josamycin contains a 17-membered lactone ring. The absolute configuration of the asymmetric carbon atoms of the



(1)



(2)



(3)

lactone ring of (**1**), except for C–9, has been established by an *X*-ray crystallographic study of the hydrochloride of the acid degradation product, demycarosyl iso-leucomycin A_3.[3] The absolute configuration at C–9 was assigned as (*S*) on the basis of the benzoate or Mill's rule for (**1**) and its derivatives.[4] The absolute configuration at C–9 was later assigned as (*R*), on the basis of i.r. and n.m.r. spectroscopic data for (**1**) and 9-epi-leucomycin A_3.[5]

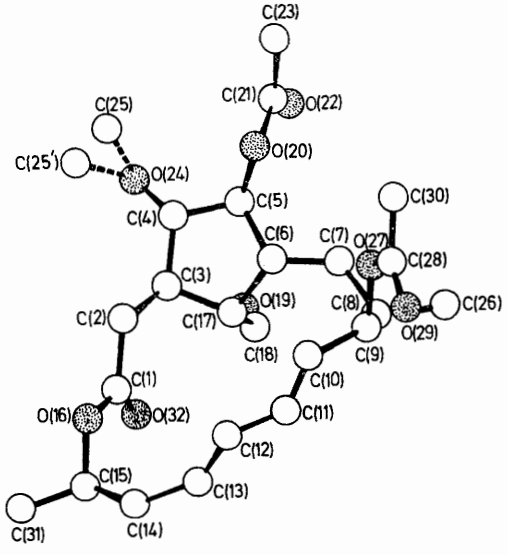


FIGURE. Structure of diacetyl-3,6-bicyclo-leuconolide A_3 (**3**).

In order to resolve these differences and to determine the configuration at C–3 as well as that at C–9 and C–17 of 3,6-bicyclo-leucomycin A_3 (**2**), an *X*-ray crystallographic analysis of diacetyl-3,6-bicyclo-leuconolide A_3 (**3**), obtained from (**2**),[1,6] was performed.

The material crystallizes in the monoclinic space group $P2_1$, with cell dimensions $a = 11{\cdot}206$, $b = 8{\cdot}248$, $c = 14{\cdot}272$ Å, $\beta = 107°\ 66'$ and $Z = 2$. 2464 reflections were collected on a Philips automatic diffractometer, and the structure was solved by direct methods.[7] Refinement led to a final R value of 5·1%.

The structure is shown in the Figure. There was some disorder for C(25) which adopts the two positions shown in the Figure. The geometry of the five-membered ring can be described as follows: $\Delta = 8°$ and $\phi = 47°5'$ (twisted half-chair).[8] The planes defined by C–9, C–10, C–11, and C–12 and that containing C–12, C–13, and C–14 form an angle of 12°. Thus the general shape of the macrolide is very similar to that of demycarosyl-leucomycin A_3 hydrobromide.[3]

From the known absolute configuration of the last compound[3] and the relative stereochemistry of (**3**), established by this work, the absolute configurations of leucomycin A_3 (josamycin), 3,6-bicyclo-leucomycin A_3, and diacetyl-3,6-bicyclo-leuconolide A_3 are as shown in (**1**), (**2**), and (**3**) respectively. The configuration at C–9 is (*R*).

(*Received, 20th August* 1976; *Com.* 963.)

[1] S. Ōmura, A. Nakagawa, K. Suzuki, and T. Hata, *J. Antibiotics*, 1974, **27**, 370.
[2] T. Osono, K. Moriyama, and M. Murakami, *J. Antibiotics*, 1974, **27**, 366.
[3] M. Hiramatsu, A. Furusaki, T. Noda, K. Nawa, Y. Tomiie, I. Nitta, T. Watanabe, T. Take, J. Abe, S. Ōmura, and T. Hata, *Bull. Chem. Soc. Japan*, 1970, **43**, 1966.
[4] S. Ōmura, M. Katagiri, T. Hata, M. Hiramatsu, T. Kimura, and K. Naya, *Chem. and Pharm. Bull.* (*Japan*), 1968, **16**, 1402; S. Ōmura, A. Nakagawa, M. Katagiri, T. Hata, M. Hiramatsu, T. Kimura, and K. Naya, *ibid.*, 1970, **18**, 1501.
[5] L. A. Freiberg, R. S. Egan, and W. H. Washburn, *J. Org. Chem.*, 1974, **39**, 2474.
[6] S. Ōmura, A. Nakagawa, K. Suzuki, T. Hata, A. Jakubowski, and M. Tishler, *J. Antibiotics*, 1974, **27**, 147.
[7] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst*, 1971, A**27**, 368.
[8] C. Altona, H. J. Geise, and C. Romers, *Tetrahedron*, 1968, **24**, 13.