# Stereochemical Studies on the Mycolic Acids

By D. E. MINNIKIN and N. POLGAR
(*Dyson Perrins Laboratory, Oxford University*)

IN a previous communication[1] derivatives of three mycolic acids (-I, -II, and -III) from human tubercle bacilli were described and the structures (I), (II), and (III) advanced for the main components, the structure (I) corresponding to that proposed earlier[2] for methyl α-mycolate (Test). The esters (I) and (II) as well as the parent hydroxy-ester of (III) contain asymmetric centres (at C-2 and C-3) bearing a long alkyl chain and a hydroxyl group, respectively, and the present studies concern their stereochemistry in respect of these centres.

(I) $CH_3\cdot[CH_2]_{n1}$–CH(*cis*)–CH–$[CH_2]_{n2}$–CH(*cis*)–CH–$[CH_2]_{n3}\cdot$CH(OH)·CH($C_{24}H_{49}$)·$CO_2$Me

(II) $CH_3\cdot[CH_2]_{17}\cdot$CHMe·CH(OMe)–CH(*cis*)–CH–$[CH_2]_{33}\cdot$CH(OH)·CH($C_{24}H_{49}$)·$CO_2$Me

(III) $CH_3\cdot[CH_2]_{17}\cdot$CHMe·CO–CH(*trans*)–CH–$[CH_2]_{36}\cdot$CH(OAc)·CH($C_{24}H_{49}$)·$CO_2$Me

Recently, Asselineau and Asselineau[3] have established that corynomycolic acid has 3(D)-configuration and they suggested that the centre at C-2 probably also has (D)-configuration. These authors were unable to distinguish, by their infrared spectra, α-branched β-hydroxy-esters having, respectively, *erythro*- and *threo*-configurations with respect to C-2 and C-3. We have been able, however, to detect very significant differences in the high-resolution infrared spectra (Perkin–Elmer 21 instrument, *ca.* 0·005M-solutions in carbon tetrachloride) of methyl mycolate-I and methyl 2-epimycolate-I,[1] m.p. 56—57°, $[\alpha]_{589}^{20}$ −0·6°. In the case of the epimer the ratio (0·99) of the intensity of the free hydroxyl band (3626 cm.$^{-1}$) to that of the bonded hydroxyl band (3534 cm.$^{-1}$) was greater than the corresponding ratio in the spectrum of methyl mycolate-I (0·56). Accordingly, the ratios of the free (1736 cm.$^{-1}$) to bonded (1719 cm.$^{-1}$) ester carbonyl absorptions were 1·02 and 0·39, respectively. The corresponding 1,3-diols (2-epimycolic alcohol-I and mycolic alcohol-I) gave similar results (ratios of free to bonded hydroxyl, 0·66 and 0·55, respectively). This comparison shows that the six-membered intramolecularly hydrogen-bonded ring (presumably chair form) is destabilised in the case of methyl 2-epimycolate-I and the corresponding

1,3-diol due to an axial arrangement of one of the substituents, *i.e.*, the α-branch and the β-hydroxyl group are *threo* to one another (Fischer projection formula). Methyl mycolate-I, therefore, has *erythro*-configuration in respect of these centres.

The n.m.r. spectrum of the ethylidene acetal of mycolic alcohol-I showed a quartet at $\tau$ 5·38 due to the ethylidene proton, and the $-CH_2-O-$ ring protons showed a complex pattern analogous to that in the spectrum of the ethylidene acetal of 2-hexadecylpropane-1,3-diol prepared for comparison. The spectrum of the acetal derived from the epimer showed a similar quartet at $\tau$ 5·29, indicating deshielding by the presence of an axial substituent on the same side of the six-membered ring.[4] The pattern of the $-CH_2-O-$ protons was disturbed, suggesting that the conformation of the ring has been destabilised by an axial substituent. These results support the assignment of the *erythro*-configuration in respect of C-2 and C-3 in methyl mycolate-I; similar results have been obtained for mycolic esters-II and -III.

It should be noted that the above configurational assignments conflict with the views expressed earlier[5] (see also ref. 3).

Determination of the absolute configuration at C-3 by preferential esterification of one of the antipodes of racemic α-phenylbutyric acid according to the method of Horeau[6] indicated (D)-configuration, *i.e.* the same configuration as that established[3] for corynomycolic acid. Accordingly, the above mycolic esters are regarded as having 2(D),3(D)-configurations.

(*Received, August* 23*rd*, 1966; *Com.* 622.)

[1] D. E. Minnikin and N. Polgar, *Tetrahedron Letters*, 1966, 2643.
[2] A. H. Etemadi and E. Lederer, *Bull. Soc. chim. France*, 1965, 2640.
[3] C. Asselineau and J. Asselineau, *Bull. Soc. chim. France*, 1966, 1992.
[4] N. Baggett, K. W. Buck, A. B. Foster, M. H. Randall, and J. M. Webber, *J. Chem. Soc.*, 1965, 3394.
[5] J. Asselineau and E. Lederer, "CIBA Foundation Symposium on Experimental Tuberculosis", Churchill, London, 1955, p. 14.
[6] A. Horeau, *Tetrahedron Letters*, 1961, 506; 1962, 965; A. Horeau and H. B. Kagan, *Tetrahedron*, 1964, **20**, 2431.