The Mycolic Acids from Human and Avian Tubercle Bacilli

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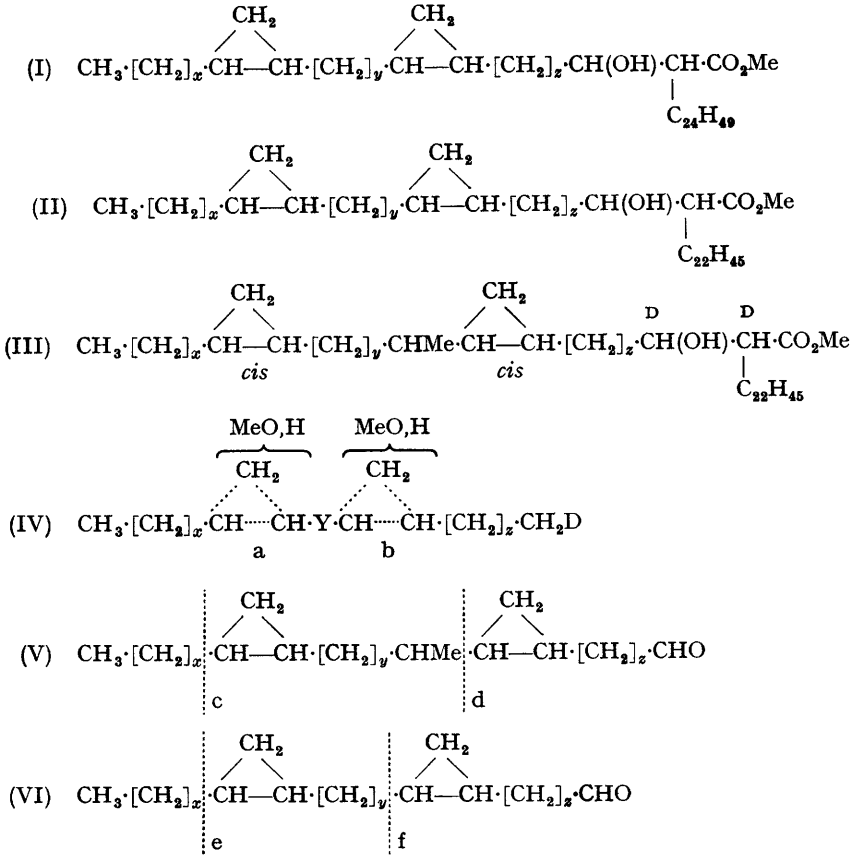
ETÉMADI and his co-workers have claimed recently that the methyl esters of certain mycolic acids isolated from human and avian strains of tubercle bacilli have the analogous structures (I; $y = 14$, $z = 13$)[1] and (II; $x = 17$, $y = 14$, $z = 17$),[2] respectively (the figures refer to the main homologue). We have carried out a parallel investigation of these compounds and we find that the structure of the human mycolic ester (methyl hominomycolate) is (I; $x = 19$, $y = 14$, $z = 13$), but that (III; $x = 17$, $y = 12$, $z = 17$) represents the probable structure of the avian mycolic ester.

Methyl avimycolate-I, $[\alpha]_D$ +3·05° and a new sample of methyl hominomycolate-I, $[\alpha]_D$ +3·7°, were obtained from *M. avium* (strains Dn., 485 and 7169)[3] and *M. tuberculosis* var. *hominis* (strains D.T., P.N., and C.)[3] as described previously[4] for methyl hominomycolates. Pyrolysis of the two esters gave the corresponding meroaldehydes which were reduced to the alcohols with $LiAlH_4$. Conversion of the meroalcohols into the methanesulphonates followed by reduction with $LiAlD_4$ gave the corresponding 1-deuteromeromycolanes. These hydrocarbons were treated with boron trifluoride–methanol,[5] and the methoxylated products separated and their mass spectra studied.

The spectrum of the avian dimethoxy-derivative (IV) shows peaks at *m/e* 727, 755, *783*, 811, 839, 867 ($M-2$MeOH) (the most abundant peak in any series is in italics). Cleavage at centres a and b gives ions of *m/e* 297, 311, 325, and 298, 312, 326, respectively, which lead to the values $x = 17$ and $z = 17$ for the main component (*m/e* 783); it follows that the portion Y has the composition $C_{14}H_{28}$. Similar calculations based on the ions observed in the spectrum of the human dimethoxy-derivative lead to the structure (I; $x = 19$, $y = 14$, $z = 13$) for the main component of this sample of methyl hominomycolate-I [the figures in the structure suggested earlier[5] for another sample of this ester were miscalculated and should have been (I; $x = 19$, $y = 14$, $z = 11$)].

The n.m.r. spectra ($CDCl_3$) of hominomeromycolic alcohol-I and its methanesulphonate show the



presence of a single terminal methyl group (τ 9·06), but the spectra of the corresponding avian compounds contain, downfield from the expected terminal methyl group signal, a doublet (τ 9·01) which may be attributed to a single methyl branch.

The optical rotations of hominomeromycolic alcohol-I, its methanesulphonate, and 1-deuteromeromycolane-I are, as expected, very small ($[\alpha]_D$ −0·13°, −0·14°, −0·12°, respectively); the values for the corresponding avian compounds are significantly larger ($[\alpha]_D$ −1·33°, −0·75°, −0·51°, respectively).

The mass spectrum of avimeromycolal-I (V) shows molecular ions of *m/e* 740, 768, *796*, 824, 852, 880, and intense oxygen-containing fragments of *m/e* 515, *543*, 571, 599, and *307*, attributable to cleavage at positions c and d, respectively. The spectrum of hominomeromycolal-I (VI), however, while showing fragments at *m/e* 459, *487*, 515, 543 due to cleavage at position e, does not show single intense peaks due to cleavage at position f; it hows groups of peaks of only medium intensity. In the light of the comparatively ready cleavage of avimeromycolal-I it seems probable that the position of the methyl branch is as indicated in the structure (V).

The n.m.r. spectrum of methyl avimycolate-I shows the presence of two *cis*-cyclopropane groups (τ 10·3 and 9·4), and the stereochemistry at C-2 and C-3 was found to be the same as for the human mycolic esters.[6] The structure (III; $x = 17$, $y = 12$, $z = 17$) may, therefore, be put forward for the main component of methyl avimycolate-I. It is notable that, assuming the presence of only one methyl branch, this structure would contain an odd number of carbon atoms in the main chain; the n.m.r. spectrum does not seem to admit the presence of a second methyl branch.

The structure (II) has also been suggested by Etémadi and his co-workers for the methyl esters of α-kansamycolic acid[2] and a mycolic acid from *M. phlei*.[7] The mass spectra of the meroaldehydes corresponding to these esters have not been reported, but if in fact they contain an intense peak in

the mass spectrum at *m/e* 307 as claimed, then these esters may well have structures analogous to the structure (III) suggested above for methyl avimycolate-I. The bicyclopropane compound from *M. phlei* is the only mycolic acid of this type which at present is known[7] to occur in the presence of possible unsaturated precursors. A detailed investigation of these mycolic acids should throw light on the mode of biosynthesis of the above compounds.

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[1] A. H. Etémadi, *Compt. rend.*, 1966, **263**, *C*, 1257.
[2] A. H. Etémadi, F. Pinte, and J. Markovits, *Bull. Soc. chim. France*, 1967, 195.
[3] H. H. Green, *Veterinary J.*, 1946, **102**, 267.
[4] D. E. Minnikin and N. Polgar, *Tetrahedron Letters*, 1966, 2643.
[5] D. E. Minnikin and N. Polgar, *Chem. Comm.*, 1967, 312.
[6] D. E. Minnikin and N. Polgar, *Chem. Comm.*, 1966, 648.
[7] G. Lamonica and A. H. Etémadi, *Compt. rend.*, 1967, **264**, *C*, 1711.