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Published on 01 January 1969 on http://pubs.rsc.org | doi:10.1039/C29690000788
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A Total Synthesis of Mycophenolic Acid

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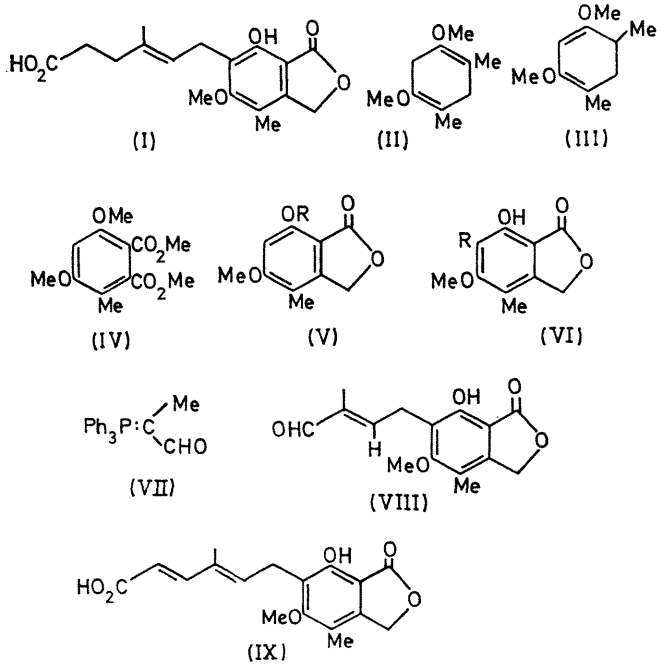
Summary Mycophenolic acid has been synthesised by a method adaptable to analogues and to biogenetic intermediates.

MYCOPHENOLIC ACID (I), from *Penicillium brevi-compactum*[1] is of interest because of its complex biosynthesis,[2] and



because it shows anti-viral and anti-tumour activities.[3] We have synthesised it by a route which can be modified to provide analogues and possible biosynthetic intermediates.

The diene (II) was readily produced by metal–ammonia reduction of the corresponding aromatic compound and it was converted by potassium t-butoxide in dimethyl sulphoxide[4] into the conjugated diene (III). Reaction of this with dimethyl acetylenedicarboxylate gave the phthalic ester (IV) with elimination of the bridge.[5] This product was selectively monodemethylated with boron trichloride[6] to the *o*-hydroxyphthalic ester, which was converted into the corresponding anhydride. Reduction of the anhydride with Zn–HCl–AcOH gave the *o*-hydroxy-lactone (V; R = H), m.p. 216—218°, ν_{max} ($CHCl_3$) 3450 and 1735 cm.$^{-1}$; *m/e* 194. The situation of the OH was further supported by production of a purple colour with ferric ion.

The hydroxyphthalide (V; R = H) was converted by allyl bromide and potassium carbonate into the ether (V; R = CH_2·CH : CH_2) which underwent thermal rearrangement into (VI; R = CH_2·CH : CH_2). Ozonolysis of this phenol gave the aldehyde (VI; R = CH_2·CHO) the acetate of which was identical with the aldehyde obtained by selective ozonolysis of acetylmycophenolic acid. The aldehyde was converted by (VII)[7] into the aldehyde (VIII), m.p. 110—111°; ν_{max} ($CHCl_3$) 3450, 1735, and 1690 cm.$^{-1}$; τ ($CDCl_3$) 0·62 (1H, s, CHO); 3·5 (1H, triplet of quartets, *J* 7, *J* 1Hz., olefinic proton). Comparison with the published n.m.r. data on similar systems[8] confirms that the olefinic proton is *cis* to the formyl group. Further treatment with the carbanion of triethylphosphonoacetate gives the ester of the crystalline acid (IX). Catalytic hydrogenation of (IX) could not be controlled selectively under a variety of conditions, but complete hydrogenation of the side-chain gave dihydromycophenolic acid (m.p. 139—140°), identical in properties with an authentic specimen. Reduction of (IX) with di-imide[9] gave mycophenolic acid (I)

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(m.p. 140—141°) fully identical with the natural substance (i.r., mass spectra, and mixed m.p.).

In addition to confirming the gross structure of mycophenolic acid, the configuration of the side-chain double-bond has been established for the first time.

Satisfactory data were obtained to support all of the assigned structures and yields in various steps varied from 50—95%.

(*Received, April 28th*, 1969; *Com.* 585.)

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