Halogenated Analogues of Mycophenolic Acid

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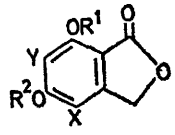
Summary Halogenated analogues of mycophenolic acid (I) were produced by cultures of *Penicillium brevi-compactum* fed respectively with 4-bromo-5,7- dihydroxyphthalide (V) and 4-chloro-5,7-dihydroxyphthalide (VI).

THE biological properties of mycophenolic acid[1] (I) prompted studies to provide analogues. The use of mycophenolic acid as a preparative starting material permitted only a few modifications,[2] but our studies[3] on the biosynthesis of mycophenolic acid indicated that *P. brevi-compactum* is able to transform non-natural precursors such as 5,7-dihydroxyphthalide (II) into (III) and 6-geranyl-5,7-dihydroxy-4-methylphthalide (IV) into (I), and showed that the biosynthesis of the aromatic part is slower than the biosynthesis of the terpenoid portion of the molecule.

These data suggested that analogues of mycophenolic acid could be prepared by feeding aromatic modified precursors to the culture of the mould at the beginning of the fermentation, in order to provide molecules with modified or enhanced activity and also to examine how far the natural precursors of the metabolites can be modified before being rejected by the enzyme systems of the *P. brevi-compactum*.

We describe here the synthesis of 4-bromo- (V) and 4-chloro-5,7-dihydroxyphthalide (VI) and their transformation into the corresponding analogues of mycophenolic acid (VII) and (VIII), respectively.

Hydrolysis of 4-bromo-5,7-dimethoxyphthalide (IX)[4] with boron tribromide gave (V). Treatment of 5,7-dimethoxyphthalide (X)[5] with trichloroisocyanuric acid[6] and then with BBr_3 afforded (VI).



(I) $R^1=H; R^2=Me;$ X=Me; $Y=HO_2C[CH_2]_2C(Me)=CHCH_2-$
(II) $R^1=R^2=H;$ X=Y=H
(III) $R^1=R^2=H;$ X=H; $Y=HO_2C[CH_2]_2C(Me)=CHCH_2-$
(IV) $R^1=R^2=H;$ X=Me; Y=geranyl
(V) $R^1=R^2=H;$ X=Br; Y=H
(VI) $R^1=R^2=H;$ X=Cl; Y=H
(VII) $R^1=H; R^2=Me:$ X=Br; $Y=HO_2C[CH_2]_2C(Me)=CHCH_2-$
(VIII) $R^1=H; R^2=Me;$ X=Cl; $Y=HO_2C[CH_2]_2C(Me)=CHCH_2-$
(IX) $R^1=R^2=Me;$ X=Br; Y=H
(X) $R^1=R^2=Me;$ X=Y=H

Compounds (V) and (VI) were added to the culture of *P. brevi-compactum* (250 mg/l); their transformation into analogues of (I) was slower than that of the natural precursors of (I) (4-methyl-5,7-dihydroxyphthalide). The acidic metabolites were isolated from the fermentation broth in the usual way[3] and were chromatographed on silica gel.

In this way it was possible to separate the chloro-derivative (VIII) (transformation yield 52%), $C_{16}H_{17}ClO_4$, m.p. 147—150° (AcOEt–hexane) from mycophenolic acid. In the addition of the bromophthalide (V) to the culture, after the usual work-up and silica-gel chromatography, a crystalline fraction was obtained which was shown to consist of a 1 : 1 mixture of (I) and its bromo-analogue (VII). Preparative t.l.c. [development (× 3) in AcOH–$CHCl_3$–AcOEt 1 : 50 : 50] separated (VII), $C_{16}H_{17}BrO_4$, m.p. 165—166°, as the faster running band (transformation yield 40%).

The structures of compounds (VII) and (VIII) were determined from i.r., n.m.r., and m.s. evidence. All new compounds gave satisfactory spectral and analytical data.

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