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A TOTAL SYNTHESIS OF MYCOPHENOLIC ACID

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Mycophenolic acid (14) whose recent linear total synthesis is due to Birch[1], has been obtained by us by a convergent synthesis starting from intermediates (1) and (11).

Synthesis of the bromoester (1) was accomplished as related in the accompanying paper.

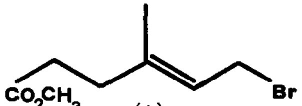
For the synthesis of the intermediate (11) condensation between sodiumdiethylmalonate and 3-methylpent-3-en-2-one in ethanol afforded (2), which was aromatised to (3), $C_{11}H_{14}O_4$, m.p. 115-116°, either by conversion into the bromoderivative (4) with bromine in acetic acid and subsequent hydrogenolysis with palladium on charcoal or by direct treatment with ferric chloride in refluxing acetic acid. Compound (3) was transformed into (5), $C_{13}H_{18}O_4$, m.p. 62-63°, by treatment with CH_2N_2 or with CH_3I and K_2CO_3 in acetone; the hydrolysis of (5) furnished the acid (6), $C_{11}H_{14}O_4$, m.p. 208-210°, which was converted into the amide (7), m.p. 225-229°, by reaction with ammonia of the acid chloride (8).

Treatment of the amide (7) with t-butylhypochlorite in CH_2Cl_2 yielded the corresponding N-chloroamide (9) which was photolysed[2] to the intermediate iminolactone immediately hydrolysed to (10). The phthalide (10) with hydriodic acid in acetic acid in the presence of red phosphorous at reflux yielded the intermediate (11)[4].

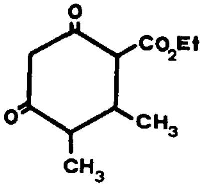
Condensation of (1) and (11) with silver oxide in dioxane at room temperature yielded (12) (36% yield), and an O-alkylderivative which were separated by accurate chromatography. At last, monomethylation with diazomethane, in benzene solution, yielded (13)[5] which was hydrolysed with aqueous sodium hydroxide to mycophenolic acid (14), identical with the natural substance (I.R. Mass Spectra and mixed m.p.).

On the contrary, the condensation of (1) and (15)[4] in the same conditions yielded only an O-alkylation product; also in the biosynthesis[4] of mycophenolic acid the introduction of the side chain at C_6 needs the presence of the free hydroxyl group at C_5.

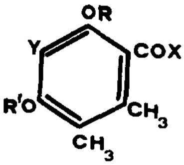
Satisfactory elemental analyses have been obtained for all new compounds.



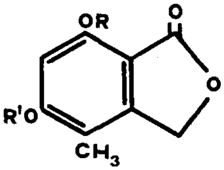
(1)



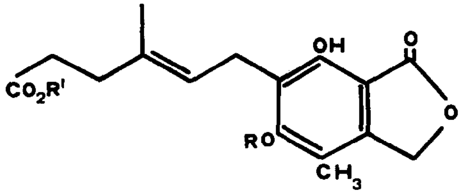
(2)



(3) R=R'=H	X=OEt	Y=H
(4) R=R'=H	X=OEt	Y=Br
(5) R=R'=CH_3	X=OEt	Y=H
(6) R=R'=CH_3	X=OH	Y=H
(7) R=R'=CH_3	X=NH_2	Y=H
(8) R=R'=CH_3	X=Cl	Y=H
(9) R=R'=CH_3	X=NHCl	Y=H



(10) R=R'=CH_3
(11) R=R'=H
(15) R=H R'=CH_3



(12) R=H R'=CH_3
(13) R=R'=CH_3
(14) R=CH_3 R'=H

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