Syntheses of Labelled Methyl Malvalate

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Summary Practical syntheses of homogeneous methyl malvalate, adaptable for inserting radiocarbon at positions 1, 9, 10, and ring CH_2, are described.

ALTHOUGH some evidence is available consistent with the idea that sterculic acid (9,10-methyleneoctadec-9-enoic acid) is metabolically degraded to the nor-compound, malvalic acid (8,9-methyleneheptadec-8-enoic acid),[1] very little is known about the fate of malvalic acid. The difficulty in isolating homogeneous malvalate from natural sources[2] and, even more so, the unavailability of specifically labelled compounds have severely handicapped research in this area. We now report syntheses that lead to pure methyl malvalate, and that offer the opportunity of inserting labels at various positions.

Methyl [1-^{14}C]malvalate has been synthesized from dec-1-yne, which as its lithium derivative,[3] couples with 1,6-dichlorohexane to give 1-chlorohexadec-7-yne (65%). Heating this acetylene with diazoacetic ester in the presence of copper-bronze inserts the ethoxycarbonylmethylene grouping into the triple bond[4] and, after saponification, produces a cyclopropenecarboxylic acid (63%).† When the corresponding acid chloride is allowed to react with zinc chloride,[5] carbon monoxide is lost; and when the resulting intermediate is reduced with lithium aluminium hydride,[5,6] 1-chloro-7,8-methylenehexadec-7-ene is obtained (50%). Displacing the chloro-group with ^{14}CN gives [1-^{14}C]malvalonitrile (99%), which on alkaline hydrolysis followed by diazomethane esterification furnishes methyl [1-^{14}C]malvalate (78%).

For the preparation of the ester labelled in the cyclopropene methylene carbon, methyl heptadec-8-ynoate can be derived from 1-chlorohexadec-7-yne *via* 1-cyanohexadec-7-yne in three steps (87%). Now, by utilizing ethyl [2-^{14}C]diazoacetate‡ and following essentially the same six-step procedure as in the conversion of methyl octadec-9-ynoate into methyl sterculate,[5] the methyl heptadec-8-ynoate can be converted in 23% overall yield into methyl [*methylene*-^{14}C]malvalate.

The ester labelled in the 10-position has been obtained by starting with [1-^{14}C]octanoic acid, prepared by treating 1-bromoheptane with sodium [^{14}C]cyanide and hydrolysing (71%). Lithium aluminium hydride reduction of the acid[7] gives the corresponding alcohol (87%), which is converted into [1-^{14}C]-1-bromo-octane with hydrobromic acid (91%), and then into [3-^{14}C]dec-1-yne with sodium acetylide in dimethyl sulphoxide[8] (77%). Application of the sequence described above has furnished methyl [10-^{14}C]malvalate in 17% yield calculated from the radioactive decyne.

Although methyl [9-^{14}C]malvalate has not been prepared, the pathway for its synthesis has been well defined. The starting point is 1-cyano-octane obtained from 1-bromo-octane and sodium cyanide (94%). After direct esterification to ethyl nonanoate with ethanol and sulphuric acid, the ester is first reduced to nonan-1-ol and then converted into 1-bromononane (66% from the cyano-compound). The ylide from the derived triphenylphosphonium salt is condensed with methyl 7-formylheptanoate[9] to form methyl heptadec-8-enoate (25%), obtained presumably as a mixture of *cis*- and *trans*-forms. Bromination, dehydrobromination,[10] and methylation lead to methyl heptadec-8-ynoate (*ca.* 70%), which could be converted into methyl malvalate as already described. If radioactive sodium cyanide were used with the 1-bromo-octane, the product here would be methyl [9-^{14}C]malvalate.

In the preliminary work on these syntheses, nonradioactive methyl malvalate was produced, homogeneous according to t.l.c., and showing the expected cyclopropene i.r. absorption peaks at 1870 and 1008 cm^{-1}. The n.m.r. spectrum had the cyclopropene CH_2 signal at δ0·72, but was entirely clear in the low-field olefinic proton region. The methanethiol adduct,[11] formed in quantitative yield and homogeneous by g.l.c., confirmed the homogeneity of the methyl malvalate.

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† All new compounds have been analysed and well characterized.

‡ Obtained from [2-^{14}C]glycine essentially according to the method of F. B. LaForge, W. A. Gersdorff, N. Green, and M. S. Schechter, *J. Org. Chem.*, 1952, **17**, 381. We are indebted to John L. Langone for preparing the radioactive diazoacetic ester.

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