Synthesis of 5*S*-5-[$^{3}\text{H}_{1}$]Mevalonic Acid[1]

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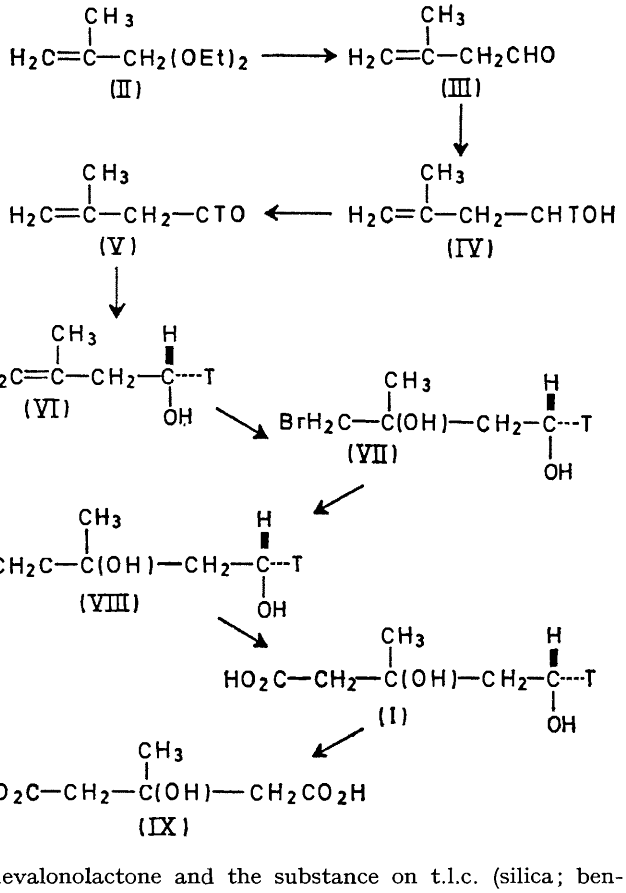
Summary The three methylene groups of mevalonic acid permit six modes of stereospecific labelling by introduction of an isotopic hydrogen atom; five of these are already known, and synthesis of the sixth, 5*S*-5-[$^{3}\text{H}_{1}$]-mevalonic acid, is now reported.

1,1-DIETHOXY-3-METHYLBUT-3-ENE (II), obtainable from methallylmagnesium chloride and ethyl orthoformate,[2,3] was hydrolysed by cold aqueous oxalic acid to 3-methylbut-3-enal (III), b.p. 92—94°; semicarbazone, thick needles from ethanol–water, m.p. 128—130°. The i.r. and n.m.r. spectra were in agreement with the structures assigned. Earlier claims to have prepared this aldehyde[4,5] and derivatives[2,5] appear to be in error, and may refer to preparations of the conjugated 3-methylbut-2-enal and its derivatives. Reduction of the aldehyde by adding it to a tetrahydrofuran solution of lithium borohydride previously treated with an equimolar amount of tritiated water[6] gave 1-[^{3}H]3-methylbut-3-enol (IV) which was oxidized to 1-[^{3}H]3-methylbut-3-enal (V) by dimethyl sulphoxide–dicyclohexylcarbodi-imide–phosphoric acid.[7] The aldehyde (V) proved to be a good substrate for liver alcohol dehydrogenase and was reduced thereon almost quantitatively at pH 7·3 by a threefold excess of reduced nicotinamide-adenine dinucleotide to *S*-1-[$^{3}\text{H}_{1}$]3-methylbut-3-enol (VI). The stereospecificity of aldehyde reduction on liver alcohol dehydrogenase has previously been demonstrated both for geranial and for acetaldehyde.[8]



The isopentenol (VI) after dilution with non-radioactive material was treated with *N*-bromosuccinimide in water to give a bromohydrin (VII) which reacted with potassium cyanide in boiling methanol to afford a nitrile (VIII) hydrolysed by hot 2N-aqueous sodium hydroxide to the mevalonic acid (I), isolated as the lactone in 65% overall yield without purification of intermediates. The i.r. spectrum of the lactone was identical with that of authentic mevalonolactone and the substance on t.l.c. (silica; benzene: methanol 2 : 1) showed only one radioactive spot (R_F 0·46). The specific radioactivity of the first preparation was 0·018 μCi/μmole. That the radioactivity was confined to position 5 was shown by oxidation with zinc permanganate; the resulting 3-hydroxy-3-methylglutaric acid (IX) had $< 0{\cdot}5\%$ of the radioactivity of the mevalonate.

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[1] For the syntheses of the other five $^3H_1$-labelled mevalonic acids, see G. Popják and J. W. Cornforth, *Biochem. J.*, 1966, **101**, 553 (review).

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