The Absolute Configuration of (+)-2-Methyl-2-isopropylglutaric and (+)-2-Methyl-2-isopropylsuccinic Acid

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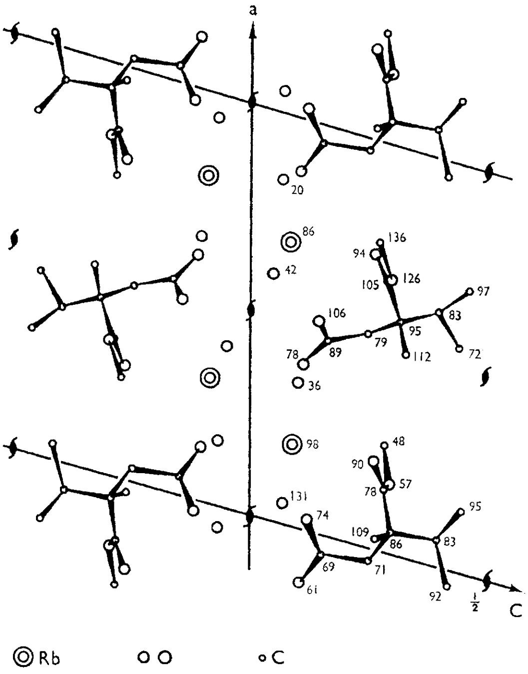
IN an investigation of the methylation of (+)-pulegone, Djerassi *et al*,[1] employed the quasi-racemate technique to deduce that (+)-2-isopropyl-2-methylglutaric acid had the absolute configuration (I). However, in an independent investigation concerning the absolute stereochemistry of various terpenes, Norin[2] concluded on the basis of chemical correlations that this acid, and hence (+)-2-isopropyl-2-methylsuccinic acid which occupies a key position in the definition of the absolute configuration of numerous terpenes including (+)-camphor,[3] had the opposite configuration (II). This contradiction has now been resolved in favour of (II) by an *X*-ray arbitration.



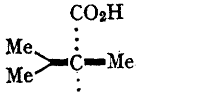
The b-*axis projection of the crystal structure of the rubidium salt of* 3-*isopropyl*-3-*methoxycarbonyl*-3-*methylpropionic acid. The heights* (*as a percentage of* b) *are indicated.* b *is directed upwards from the paper. The principal difference between the conformations of the two independent molecules is that the methoxycarbonyl group has been rotated about* 180°. *Six water molecules seem to be distributed fairly evenly over the eight sites shown.*

Thus, resolution of (±)-3-isopropyl-3-methoxycarbonyl-3-methylpropionic acid with dehydroabietylamine gave the (+)-ester (III; R = CO_2Me), which furnished the corresponding (+)-acid (III; R = CO_2H) upon hydrolysis. The rubidium salt of (+)-3-isopropyl-3-methoxycarbonyl-3-methylpropionic acid has been shown by an *X*-ray study to have the absolute configuration (III; R = CO_2Rb).

Crystals grown from wet methanol–ether are monoclinic needles, space group $P2_1$, with a = 13·75, b = 6·15, c = 16·53 Å, β = 105·6°, D_m = 1·48 g.cm.$^{-3}$, D_c = 1·49 g.cm^{-3} for a total cell contents of $4[\mathrm{Rb(C_9H_{15}O_4)}]6H_2O$. The crystals deteriorate on exposure to *X*-radiation (especially Mo–K_α radiation) in air, but could be preserved long enough for photography if enclosed in a capillary tube. Some 1961 independent reflections were recorded with Cu–K_α radiation and estimated visually. Analysis by Patterson's functions revealed that the two crystallographically independent molecules have different conformations, though of course identical relative configurations. (Figure.) *R* is now 0·139. The absolute configuration was determined from 13 pairs of Bijvoet anomalies[4] excited by Cu–K_α radiation: 10 indicated the configuration shown in the figure and (III), 2 were noncommittal, and one weak pair was contrary.

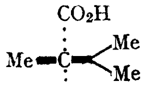
This result is in agreement with the production of (−)-2-isopropyl-2-methylsuccinic acid from (−)-camphoronic acid[3] and the unequivocal definition[5] of the absolute configuration of (+)-3-bromocamphor.

Conversion of the (+)-ester (III; R = CO_2H) into the corresponding (+)-2-isopropyl-2-methylglutaric acid, by way of the stages (III; R = COCl), (III; R = $CO{\cdot}CHN_2$), and (III; R = $CH_2{\cdot}CONH_2$) unequivocally establishes the absolute configuration of this acid as (II), in agreement with the work of Norin,[2] but at variance with the conclusions of Djerassi *et al.*[1] It follows that the absolute configurations assigned[2] to (+)-sabinene, (−)-umbellulone, the thujanes and their congeners are confirmed but that the absolute configuration assigned to (−)-methylisopulegone[1] must now be represented by (V) (*cf.*, Melera *et al.*[6]) and not by (IV).[1] A further consequence of our findings is that the absolute configurations of numerous derivatives of (−)-methylisopulegone and (−)-menthone (*cf.* refs. 1 and 7) must be revised to conform to (II).



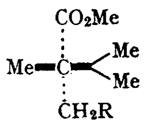
$$\begin{array}{c}\mathrm{CO_2H}\\ \vdots\\ {}^{\mathrm{Me}}_{\mathrm{Me}}\!>\!\mathrm{C{-}Me}\\ \vdots\\ \mathrm{CH_2{\cdot}CH_2{\cdot}CO_2H}\end{array}$$

(I)



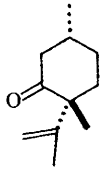
$$\begin{array}{c}\mathrm{CO_2H}\\ \vdots\\ \mathrm{Me{-}C}\!<\!{}^{\mathrm{Me}}_{\mathrm{Me}}\\ \vdots\\ \mathrm{CH_2{\cdot}CH_2{\cdot}CO_2H}\end{array}$$

(II)

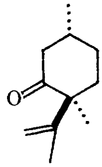


$$\begin{array}{c}\mathrm{CO_2Me}\\ \vdots\\ \mathrm{Me{-}C}\!<\!{}^{\mathrm{Me}}_{\mathrm{Me}}\\ \vdots\\ \mathrm{CH_2R}\end{array}$$

(III)



(IV)



(V)

The mechanistic problem[1] inherent in the formulation of (−)-methylisopulegone as (IV) now has no substance.

The establishment of (+)-2-isopropyl-2-methylsuccinic acid and (+)-2-isopropyl-2-methylglutaric acid as absolute standards confirms the presently accepted configurations of (+)-2-isopropylsuccinic and (+)-2-isopropylglutaric acids and consolidates the absolute stereochemical relationships within a wide area of associated compounds. Thus, the absolute configuration of (−)-methylsuccinic acid has been unequivocally defined[8] whilst two independent routes[9] have confirmed the absolute configuration of (+)-2-ethyl-2-succinic acid, which has been related[10] to (+)-2-isopropyl-2-methylsuccinic acid by the quasi-racemate technique. Since this acid, (+)-methyl-, (+)-ethyl-, and (+)-n-propyl-succinic acid have been interrelated[10,11] (by the quasi-racemate method) it follows that the absolute stereochemical relationships between numerous lower alkylsuccinic acids and (+)-pulegone have been established by two independent and mutually confirmatory routes.

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