Carboxylate Ion Participation in the Alkaline Hydrolysis of an Epoxide. Revision of the Absolute Configuration of a Methylcitric Acid

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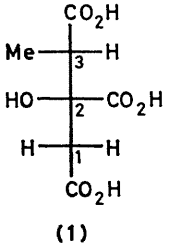
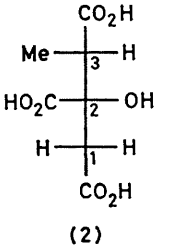
Summary The hydrolytic opening of the epoxide ring of (**5b**) under alkaline conditions proceeds *via* a β-lactone according to Scheme 2; one of the methylcitric acids obtained in the citrate synthase reaction possesses the stereostructure (**3**) and not, as previously published, structure (**2**).

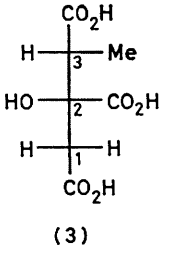
Two diastereomeric methylcitric acids are formed in the *si*-citrate synthase (EC 4.1.3.7) mediated reaction of propionyl-CoA with oxaloacetate, and the stereostructures (**1**) (2*S*,3*S*) and (**2**) (2*R*,3*S*) have been ascribed to these acids.[1,2] The trimethyl esters of the acids show $[\alpha]_D$ + 12·0° and − 21·9°, respectively.[1]



(1)



(2)

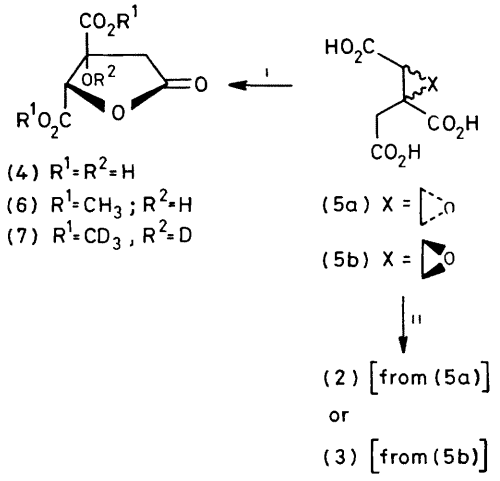


(3)

Treatment of the enantiomer of the latter trimethyl ester, $[\alpha]_D$ + 21·5°, with sodium methoxide in methanol has now been found to give a 50/50 mixture (^{1}H n.m.r. spectroscopy, g.l.c.) of stereoisomeric esters which showed $[\alpha]_D$ + 3·5°. One of the components was the starting ester and the other showed (slightly contaminated) $[\alpha]_D$ −9·7°. It is most probable that an epimerisation at the methyl-bearing carbon (C-3) takes place under these conditions; the two methylcitric acids thus being epimeric at C-3. Consequently, one of the stereostructures which have previously been ascribed to the acids must be wrong.

There are biosynthetic reasons for believing that the stereostructure (**2**) is incorrect and should be replaced by the enantiomeric structure (**3**). Structure (**2**) was inferred from a correlation with hibiscus acid (**4**) *via* an optically active epoxy acid (**5**) (Scheme 1†).[1] It was assumed that the alkaline hydrolysis of the epoxide ring of (**5**) (0·1 M NaOH, 100 °C, 72 h) proceeded by attack of hydroxide ion at the least substituted three-ring carbon and therefore the epoxy acid possessed the stereostructure (**5a**) (Scheme 1). The basis for this assumption were the numerous results showing this regioselectivity to be valid for various kinds of nucleophiles under conditions excluding acidic catalysis.[3] If instead the epoxide ring was opened by nucleophilic attack at the *most* substituted three-ring carbon, the epoxy acid must have had the enantiomeric structure (**5b**).

† Support for the inversion of configuration at carbon in the reaction of (**5b**) with lithium dimethylcuprate was provided in the previous work (ref. 1). Reaction of dimethyl *trans*-2,3-epoxybutanedioate with the cuprate reagent gave dimethyl *erythro*-3-methylmalate. Further, in agreement with Cram's rule (ref. 5), the lithium ester enolate obtained from (−)-menthyl acetate reacted with diethyl 3-methyl-2-oxo-butanedioate to give a great preponderance (> 95 : 5) of the (2*RS*, 3*SR*) isomers of methylcitric acid over the (2*RS*, 3*RS*) isomers.

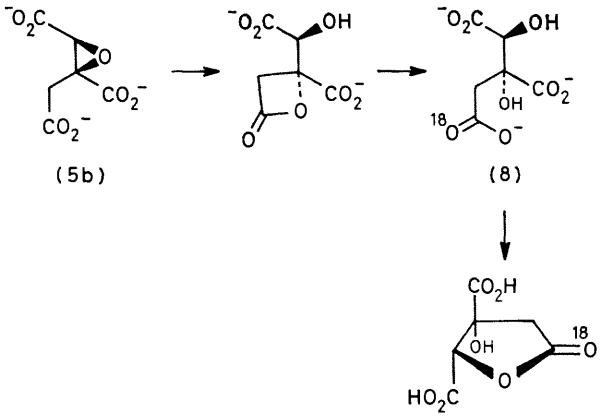


SCHEME 1 Correlation of a methylcitric acid with hibiscus acid (**4**) (ref 1) The epoxy acid was assumed (ref 1) to be (**5a**) but has now been shown to be (**5b**) *Reagents*, i, OH^- then H^+ ii, CH_2N_2, $LiMe_2Cu$, OH^- then H^+

The optical purity of (**4**) shows that the hydrolysis exhibits a virtually full regioselectivity

By performing the alkaline hydrolysis of (**5**) in H_2O–$H_2{}^{18}O$ and locating the ^{18}O in compound (**6**), we have been able to show that the ring-opening reaction displays the unexpected regioselectivity, *i e*, nucleophilic attack at the most substituted carbon To locate ^{18}O, a ^{13}C n m r spectrum of the ^{18}O-labelled (**6**) was recorded (25 and 50 MHz) This method is based on the observation by Risley and Van Etten that the signal from C-2 in 2-methyl-2-propanol shifts 0 035 p p m upfield in going to the ^{18}O-analogue [4] Only one signal (172 74 p p m) in our spectrum [$(CD_3)_2SO$, internal Me_4Si] showed a splitting (0 037 p p m) attributable to the ^{18}O labelling (44% ^{18}O) This signal is assigned to the ring carbonyl carbon atom in (**6**) on grounds of the multiplicity (triplet) seen in the proton-coupled spectrum of compound (**7**), unlabelled with ^{18}O, the other two carbonyl carbons (170 92 and 166 22 p p m) showed the expected singlet and doublet multiplicities, respectively These clear-cut multiplicities were not observed (25 MHz) for the protio analogue of (**7**), probably owing to interfering long-range couplings over three or more bonds The possibility that ^{18}O occupied the position of the ring-oxygen was excluded by a glycol cleavage of the trimethyl ester of (**8**) with chromium(VI) oxide and examination of the two cleavage products with respect to ^{18}O content

The above results indicate a hydrolysis mechanism in which the epoxide ring is opened intramolecularly with the simultaneous formation of a β-lactone, subsequent acyl–oxygen cleavage of the β-lactone leading to the hydroxycitric acid (Scheme 2)



SCHEME 2 Steric course in the alkaline hydrolysis of (**5b**) (0 1 M NaOH in H_2O–$H_2{}^{18}O$, 100 °C, 27 h) The β-lactone is opened by acyl–oxygen cleavage

As a result, one of the methylcitric acids should be ascribed the stereostructure (**3**) and not, as previously published,[1,2] structure (**2**)

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[2] S Brandange, S Josephson, A Måhlen L Morch, L Sweetman and S Vallen *Acta Chem Scand*, 1977 **B31**, 628
[3] A H Haines in '*Comprehensive Organic Chemistry*,' ed J F Stoddart, Series eds D Barton and W D Ollis, Pergamon Press, Oxford, 1979, vol 1, p 866, and references given therein
[4] J M Risley and R L Van Etten, *J Am Chem Soc*, 1979, **101**, 252
[5] D J Cram and F A Abd Elhafez, *J Am Chem Soc*, 1952, **74**, 5828