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Studies on Orchidaceae Alkaloids

XXXVIII.* Asymmetric Synthesis of 2-Isobutylmalic Acid and 2-(Cyclohexylmethyl)malic Acid

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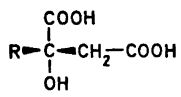
In order to determine the absolute configurations of 2-isobutylmalic acid (I) and 2-benzylmalic acid (II), the (+)-dimethylesters of the former acid and of 2-(cyclohexylmethyl)malic acid (IX) were prepared by asymmetric syntheses. Results from studies of these synthetic materials and from CD studies of the molybdate complexes of the natural and synthetic acids and of (*S*)-(+)-citramalic acid (III), indicate that the natural acids I and II both have the *R*-configuration.

The Orchidaceae alkaloids cornucervine [1] and phalaenopsine La [2] are esters of 2-isobutylmalic acid (I) and 2-benzylmalic acid (II), respectively. Several 2-alkylmalic acids occur naturally, but for only one of these, 2-methylmalic acid (citramalic acid), does the absolute configuration seem to be known. Thus, (+)-citramalic acid (III) possesses the *S*-configuration.[3,4]

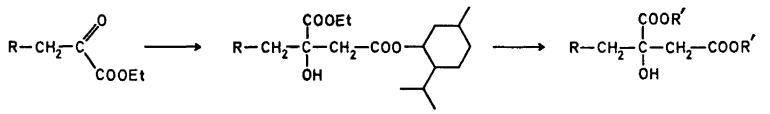


III: R=CH_3
X: R=H

We recently reported an asymmetric synthesis of (+)-diethyl citramalate.[5] Ethyl pyruvate was added to a solution of the lithium enolate formed from (−)-menthyl acetate and lithium diisopropylamide at −70°, and the resulting mixed ester was transferred into the diethyl ester. *(S)*-(+)-Diethyl citramalate was obtained in 26 % optical yield.

* For No. XXXVII in this series, see Ref. 10.

Repetition of this synthesis using ethyl 4-methyl-2-oxo-pentanoate (IV), gave (+)-dimethyl 2-isobutylmalate (V). From the optical rotation, assuming that the natural (−)-ester is the pure enantiomer, the optical yield was found to be approximately 20 %. A corresponding synthesis of dimethyl 2-(cyclohexylmethyl)malate (VII) was carried out, starting from VIII, and the (+)-form was obtained in excess. This synthesis was considered more favourable than that of dimethyl 2-benzylmalate (VI) as ethyl cyclohexylpyruvate (VIII) should give less enolisation than ethyl phenylpyruvate on reaction with the lithium enolate of (−)-menthyl acetate. The dimethyl ester VII was also prepared by catalytic hydrogenation of VI having a natural origin. Due to the small amount available, the optical rotation of the sample of VII thus formed was not determined.



IV: R = i-Pr
VIII: R = c-hexyl

V: R = i-Pr, R′ = Me
VI: R = phenyl, R′ = Me
VII: R = c-hexyl, R′ = Me
I: R = i-Pr, R′ = H
II: R = phenyl, R′ = H
IX: R = c-hexyl, R′ = H

It is reasonable to assume that the asymmetric syntheses of the esters of 2-methyl-, 2-isobutyl-, and 2-(cyclohexylmethyl)malic acid (IX) all follow the same steric course, and that these esters should consequently all have the *S*-configuration. The dimethyl ester of the natural 2-isobutylmalic acid has the opposite optical rotation and should therefore have the *R*-configuration.

CD spectra of α-hydroxyacids, as their molybdate complexes, give valuable information for the determination of their absolute configurations.[6] The molybdate complexes of (*S*)-(+)-malic acid [6] (X) and (*S*)-(+)-citramalic

Table 1. Molecular ellipticities obtained in the CD spectra of molybdate complexes of some 2-alkylmalic acids (nm, $[\theta] \times 10^{-4}$).

Acid	pH	Lowest wavelength measured	Third extremum		Second extremum		First extremum	
Natural I	3.5	225, +20	237, −20	243, 0	251, +29	259, 0	272, −25	
Natural II	3,4	220, +27	236, −27	247, 0	250, +3.2	253, 0	267, −27	
IX (derived from natural II)	3.6	224, +17	239, −8.5	247, 0	250, +1.3	253, 0	268, −11	
II	4.2	210, −28	237, +13	250, 0	250, 0	250, 0	270, +11	
Synthetic I	3.8	225, −8.0	237, +3.6	243, 0	250, −7.2	259, 0	272, +5.6	
Synthetic II	3.5	233, +1.0	237, +2.9	242, 0	251, −7.9	259, 0	272, +6.2	

acid (III) show similar CD spectra. The spectra of the acids themselves, however, show bands at 212 nm with $[\theta]$ $+0.26\times10^4$ and $[\theta]$ -1.6×10^4 degree mol^{-1} cm^2, respectively.

The above synthetic esters were transformed into the acids, and the CD spectra of their molybdate complexes were recorded. The results are summarised in Table 1. The acids III, I, and IX all gave similar CD spectra, indicating that they have the same absolute configuration, for III known to be *S*. The molybdate complexes of the natural acids I and II, and of IX, the latter prepared from VI with natural origin, show the opposite Cotton effects and should consequently have the *R*-configuration. From the magnitudes of the Cotton effects the optical yields of I and IX could be estimated as 22 and 63 %, respectively, provided that the natural acids and IX, prepared from one of them, are optically pure.

The CD spectra of the molybdate complexes are considerably influenced by the pH value,[6] as exemplified in Fig. 1 for 2-benzylmalic acid. Small variations in the pH value were found when determining the other spectra, and this explains minor differences in shape between spectra given by enantiomers.

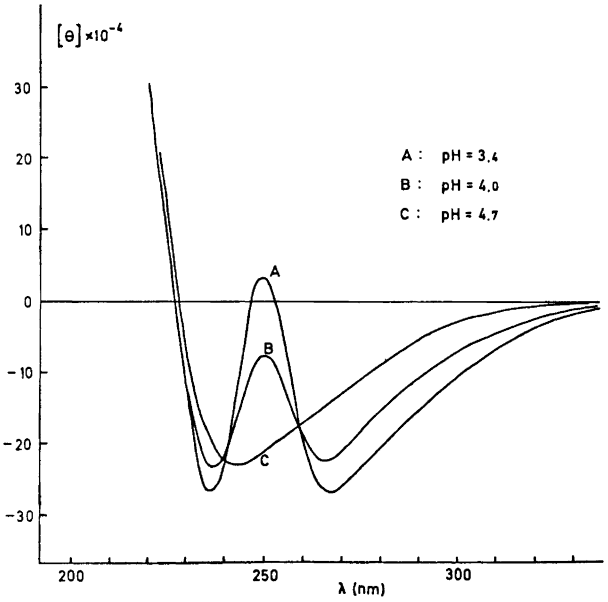


Fig. 1. Molybdate complex of natural II at different pH values.

EXPERIMENTAL

GLC was performed as described previously.[5] Optical rotations were measured on a Perkin-Elmer 141 polarimeter. A Nester-Faust NFT-51 spinning band column was used in the distillations. A Cary 60 spectropolarimeter was used for the measurements of CD spectra (cell length 0.1 cm) and a Beckman pH meter (accuracy 0.1 units) was used for the pH determinations. The CD spectra were measured in dilute hydrochloric acid solu-

tions, containing 2.3 – 2.5 mol of sodium molybdate per mol hydroxyacid. Molecular ellipticities are given in degree mol^{-1} cm^2.

(S)-(+)-Citramalic acid [7] in hydrochloric acid (pH 0.8) gave the following CD spectrum (0.043 M solution): $[\theta]_{240}$ -0.07×10^4, $[\theta]_{230}$ -0.42×10^4, $[\theta]_{220}$ -1.18×10^4, $[\theta]_{212}$ -1.56×10^4 (min), $[\theta]_{203}$ -1.30×10^4 (!).

Ethyl 4-methyl-2-oxo-pentanoate (IV) was obtained from isobutylmagnesium bromide, diethyl oxalate and water according to Akimova.[8] The product was distilled (b.p. 70 – 72°, 10 mm) giving an 80/20 mixture of keto and enol forms (NMR). The enol content increased on storage.

2-Isobutylmalic acid (I). Ethyl (–)menthyl 2-isobutylmalate was synthesised (the yield according to GLC was approximately 70 %) as described previously for ethyl (–)menthyl citramalate,[5] using lithium diisopropylamide as base. The crude reaction product was stirred under vacuum (1 mm, 100°) to remove volatile impurities, and was then hydrolysed with 2 M potassium hydroxide in ethanol (reflux overnight). Part of the ethanol was evaporated, water was added, and the aqueous layer was washed several times with ether. After acidification and concentration of the aqueous layer, methanol was added, and the mixture was refluxed for three days. Part of the methanol was evaporated and the residue was partitioned between water and chloroform. The chloroform layer was dried (Na_2SO_4) and concentrated and pure *dimethyl ester V* was obtained by preparative GLC, $[\alpha]_{578}$ +0.17°, $[\alpha]_{436}$ −0.05°, $[\alpha]_{365}$ −0.68° (*c* 9.8, ethanol). The same compound obtained by methanolysis of cornucervine showed $[\alpha]_{578}$ −0.64°, $[\alpha]_{436}$ +0.16°, $[\alpha]_{365}$ +3.9° (*c*1,9, ethanol).[1] The acid I was obtained by hydrolysis of the dimethyl ester with 4 M hydrochloric acid (115°, 2 days) followed by evaporation (15 mm, 40°). The molybdate solution was prepared using the acid thus formed.

Synthesis of ketoester VIII. A solution of sodium dihydro-bis(2-methoxyethoxy)-aluminate (333 g, 1.3 mol) in benzene and tetrahydrofuran (300 ml) was added in portions to a stirred solution of cyclohexylmethanoic acid (78 g, 0.61 mol) in tetrahydrofuran (700 ml) during 1 h, and the mixture was then stirred overnight. Dilute hydrochloric acid and ether were added, and the organic layer was dried (Na_2SO_4) and concentrated. The residue was distilled giving cyclohexylmethanol (57 g, 82 %). The corresponding bromide was obtained in 60 % yield by reaction with phosphorus tribromide.[9] The ketoester VIII was synthesised analogously to IV. After distillation somewhat impure VIII (6.6 g, b.p. 94 – 98°, 7 mm) was obtained from 24 g of the bromide. The enol content was less than 3 % (NMR). Preparative GLC gave an analytical sample. (Found: C 65.8; H 9.05. Calc. for $C_{11}H_{18}O_3$: C 66.6; H 9.15.) MS (*m/e*, relative intensity): $M^+ = 198(3)$, 125(96), 97(100). Impure VIII was used in the reaction with (–)-menthyl acetate.

2-(Cyclohexylmethyl)malic acid (IX). Ethyl (–)-menthyl 2-(cyclohexylmethyl)malate was synthesised (the yield according to GLC was approximately 80 %) analogously to ethyl (–)-menthyl 2-isobutylmalate, and was converted into the dimethyl ester VII which was purified by preparative GLC, $[\alpha]_{578}^{23}$ +3.3° (*c* 2,5, ethanol). MS: $M^+ = 258$ lacking, 199(75), 125(100), 97(56). Hydrolysis of this purified dimethyl ester with 4 M hydrochloric acid (115°, 3 days) and evaporation (15 mm, 40°) yielded the acid IX.

Acid IX, derived from phalaenopsine La. The dimethyl ester VI,[2] obtained by methanolysis of the alkaloid, was hydrogenated (5 atm, 3 h) in acetic acid using PtO_2. Ether was added and the mixture was extracted repeatedly with sodium hydrogen carbonate solution, and finally with water. The ether layer was dried (Na_2SO_4). The solution gave a single peak on GLC (3 % JXR) with the same retention time as the starting material VI. The intensity of the mass spectra peaks, *e.g.* those at *m/e* 91 and 97, clearly showed, however, that very little of the starting material was left. The ester VII was hydrolysed to IX as described above.

2-Benzylmalic acid (II) was prepared by hydrolysis as above. No dehydrated material could be detected in the product (NMR).

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REFERENCES

1. Brandänge, S., Lüning, B., Moberg, C. and Sjöstrand, E. *Acta Chem. Scand.* **25** (1971) 349.
2. Brandänge, S. and Lüning, B. *Acta Chem. Scand.* **23** (1969) 1151.
3. vonder Mühll, P. A., Settimj, G., Weber, H. and Arigoni, D. *Chimia* **19** (1965) 595.
4. Weber, H. *Dissertation*, Eidgenössische Technische Hochschule, Zürich 1965.
5. Brandänge, S., Josephson, S. and Vallén, S. *Acta Chem. Scand.* **27** (1973) 1084.
6. Voelter, W., Bayer, E., Barth, G., Bunnenberg, E. and Djerassi, C. *Chem. Ber.* **102** (1969) 2003.
7. Barker, H. A. *Biochem. Prep.* **9** (1962) 25.
8. Akimova, L. N. *Vestn. Mosk. Univ. Khim.* **24** (1969) 124; *Chem. Abstr.* **72** (1970) 21255.
9. Hiers, G. S. and Adams, R. *J. Am. Chem. Soc.* **48** (1926) 2385.
10. Blomqvist, L., Brandänge, S., Gawell, L., Leander, K. and Lüning, B. *Acta Chem. Scand.* **27** (1973) 1439.

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