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Dehalogenative Decarboxylation and other Elimination Reactions of 2,3-Dibromo-2-methylsuccinic Acid. The Preparation of *cis*- and *trans*-3-Bromomethacrylic Acid

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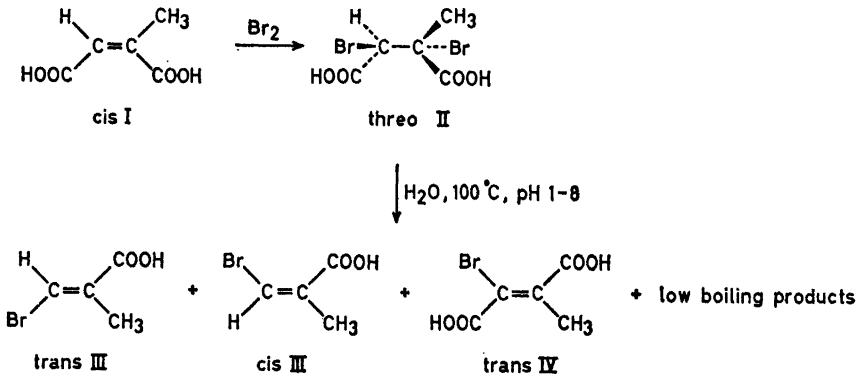
The elimination of DL-*threo*- and DL-*erythro*-2,3-dibromo-2-methylsuccinic acid (*threo* and *erythro* II) has been studied. It is shown that the dibasic acids IV and the monobasic acids III are formed in competetive reactions. The dibasic acids IV are formed in an E2 reaction. A dehalogenative decarboxylation (E1) is working in the formation of both *cis* and *trans* III from *erythro* II, and *trans* III together with small amounts of *cis* III from *threo* II.

The elimination reactions of DL-*threo*- and DL-*erythro*-2,3-dibromo-2-methylsuccinic acid (*threo* and *erythro* II) have been studied in a series of papers.[1–5] Several products have been isolated, *cis*- and *trans*-3-bromomethacrylic acid (*cis* and *trans* III), bromomesaconic acid (*trans* IV), bromocitraconic acid anhydride (V), propionic aldehyde and other low boiling products. However, in all these papers the mechanism of the elimination reactions has not been discussed, not even do the authors discuss if the various products are formed in competetive or consecutive reactions. These questions are studied in the present paper, and our interest has been focused on the formation of the two isomeric 3-bromomethacrylic acids (*cis* and *trans* III).

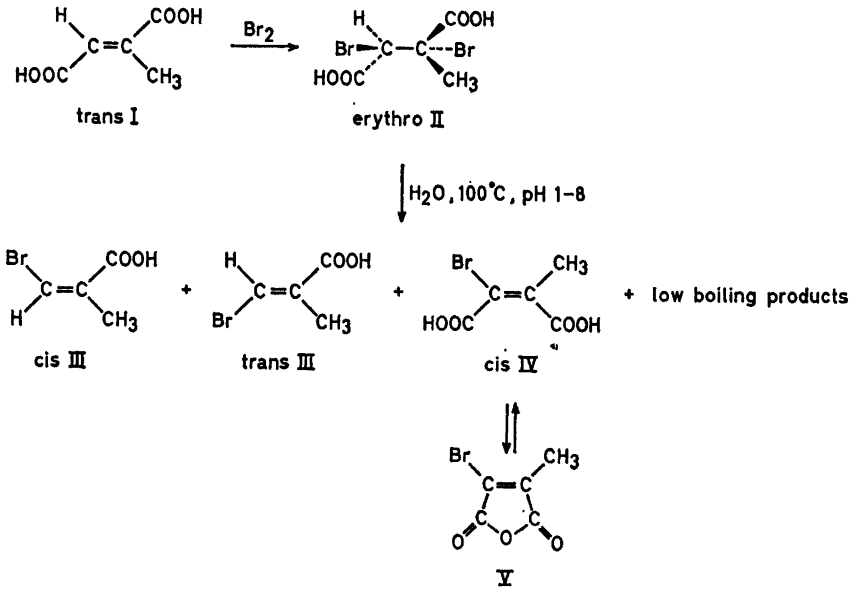
RESULTS

The DL-*threo*- and DL-*erythro*-2,3-dibromo-2-methylsuccinic acid (*threo* and *erythro* II) were prepared by addition of bromine to citraconic acid (*cis* I) and mesaconic acid (*trans* I), respectively, see Schemes 1 and 2. The *threo* II and *erythro* II used were pure (NMR), but the *erythro* acid can be contaminated with small amounts of the *threo* isomer, due to halogen-catalyzed isomerization of *cis* I to *trans* I during the halogen addition.

When *threo* II was treated with boiling water for 1 h, low boiling products were distilled off, especially in the beginning of the reaction. An NMR-spectrum of the distillate showed a variety of products. From the reaction pure



Scheme 1



Scheme 2

trans-3-bromomethacrylic acid (*trans* III) could be isolated in 30 % yield. An NMR-spectrum showed that about 80—90 % of the crude evaporated extract consisted of this acid. When an aqueous solution of *erythro* II was boiled for 3 h, a 15 % yield of bromocitraconic acid could be isolated as its anhydride (V). In this reaction a variety of low boiling products were also

formed. The pH of the reaction mixtures decreased from pH 1.2 at the beginning to pH 0.3 at the end of the reactions.

The behaviour of the dibromo acids II changed when the pH of the solvent was changed. In one set of experiments the pH was maintained at pH 6—7 during the whole reaction by titration with sodium carbonate (hydrogen bromide was formed during the reaction) using bromothymol blue as indicator, or at pH 8—9 using phenolphthalein as indicator.

An aqueous solution of *threo* II kept at pH 6—9 at 100°C for 15 min was found to have reacted completely. The solution was extracted, acidified and reextracted. NMR-analyses of the evaporated acidic extract showed that the two main products formed were *trans* III and *trans* IV. The ratio of these two acids was estimated as 3.5—4.0/1.0. The acid *cis* III could also be detected among the products but only in small amounts, about 5—10 % of the *trans*-isomer.

The *erythro* acid II gave after 30 min at pH 6—7 at 100°C an acidic crude product, which consisted of both isomers of III with a ratio *cis*/*trans* = 2.2/1.0. From this mixture both isomers could be isolated, the *cis*-isomer in 12 % yield and the *trans*-isomer in 16 % yield.

The rate of the reaction and the ratio of products formed was the same in the experiments performed at pH 6—7, as in those performed at pH 8—9, which indicates that an E1 mechanism is operating. It is found that at both pH's the *threo* and *erythro* II are in the form of a dibasic salt.

As reported in the literature the melting points of the *cis-trans* pair are very close.[5] We found the *cis*-isomer to have m.p. 65.5—66.0°C, the *trans*-isomer 64.0—64.5°C. A mixture of both acids gave a considerable melting point depression (30°C). The IR-spectra are very alike, see Figs. 1 and 2, but they provide a possibility for separation. The best identification was

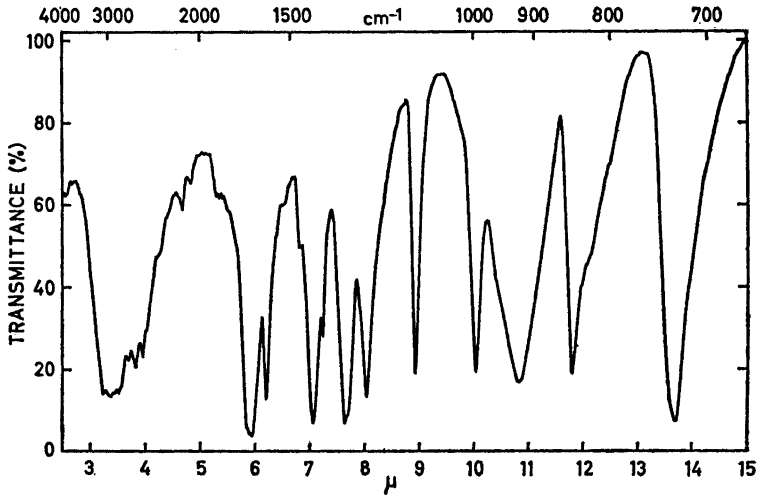


Fig. 1. IR-spectrum of *trans*-3-bromomethacrylic acid (*trans* III, KBr).

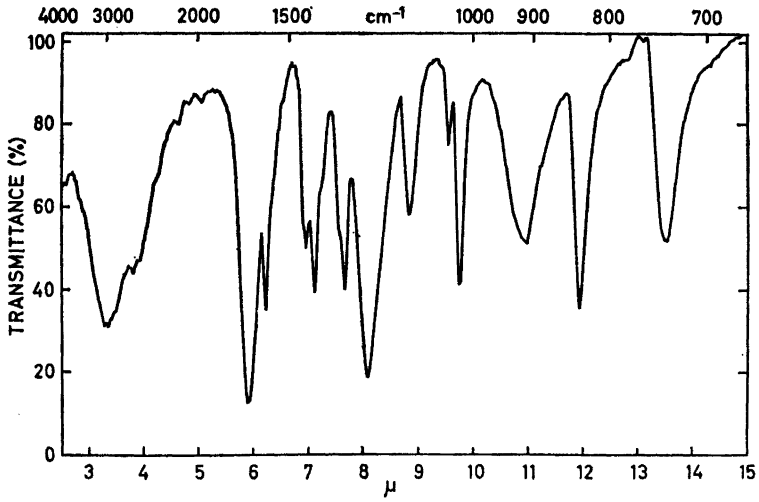


Fig. 2. IR-spectrum of *cis*-3-bromomethacrylic acid (*cis* III, KBr).

accomplished by the NMR-spectra. These contained a doublet (J = 1.4—1.5, *trans* III, and 1.6 cps, *cis* III) and a quartet with the ratio 3:1 for both acids. The chemical shifts of the ethylenic protons were different, the *cis* acid III (a *trans*-proton) gave a value δ = 6.73 ppm, the *trans* isomer (a *cis*-proton) δ = 7.70 ppm. The methyl doublet was at δ = 2.0 ppm for both isomers.

It is reported that *cis* III can be isomerized to the *trans* isomer by boiling an aqueous solution.[5] However, when treated in this way, no isomerisation could be detected as long as direct sunlight was omitted. When exposed to direct sunlight and a trace of bromine present, the isomerisation of a solution in carbon tetrachloride was completed at room temperature within 5 min.

Bromocitraconic acid (*cis* IV) can only be isolated as its anhydride (V). An aqueous solution of the anhydride was extracted with ether, and the undried ether extract analyzed by NMR. It contained two singlets (δ = 2.13 and δ = 2.16) while the carefully dried extract had only one singlet (δ = 2.16). This can be interpreted as in an aqueous solution there is an equilibrium between *cis* IV and V.

DISCUSSION OF POSSIBLE REACTION MECHANISMS

One important question is if *cis*- and *trans*-3-bromomethacrylic acids (III) are formed directly from *erythro* and *threo* II or if they are formed by a decarboxylation of *cis* and *trans* IV, *i.e.* if III and IV are formed in consecutive or competetive reactions. In general it is found that at higher pH's the ratio III/IV decreased, *cf.* Lossen and Gerlach,[4] who found that in aqueous hydroxides the *trans* isomer of IV is the only product. This is a clue of competetive reactions. A proof for this hypothesis is the observation that both *cis* and *trans* IV at the actual conditions do not give *cis* and *trans* III. The forma-

tion of *cis* and *trans* IV from *erythro* and *threo* II, respectively, are good examples of a *trans* E2 elimination.

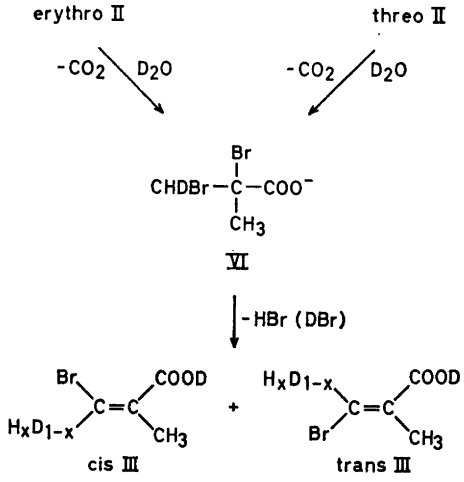
Discussing the formation of *cis* and *trans* III it is of interest to know whether the ratio *cis*/*trans* = 2.2/1.0 is a real measure of the formation rates of the two isomers or if it is a measure of the equilibrium between the two isomers. In one experiment using *erythro* II, samples were taken during the reaction and the products analyzed by NMR. In all these samples the ratio *cis*/*trans* was 2.2/1.0. In another two experiments 0.10 g and 0.20 g, respectively, of *trans* III was added to the starting 5.0 g of *erythro* II. The ratio *cis*/*trans* for the products in these experiments was 1.7/1.0 and 1.2/1.0, in fact the value with 0.10 g of *trans* III added is a mean value of the other two. These experiments show that the ratio 2.2/1.0 is a good measure of the rates of formation.

Using these values with added *trans* III it can be calculated that the yield in the primary reaction of *cis* III is 19 % and of *trans* III is 8 %. Lossen *et al.* gave the yields *cis* III = 10 % and *trans* III = 18 %.[5] The fact that we isolated a larger yield of the *trans* isomer is due to secondary isomerization (light-catalyzed) during the isolation process.

At least three possible mechanisms can be discussed for the formation of *cis* and *trans* III from *erythro* and *threo* II.

1. A stepwise reaction, elimination of hydrogen bromide followed by decarboxylation.
2. A stepwise reaction, decarboxylation followed by elimination of hydrogen bromide.
3. A dehalogenative decarboxylation.

Mechanism 1 means that *cis* and *trans* IV are intermediates in the reaction (consecutive reactions). As it was shown that the two isomers of IV do not give *cis* and *trans* III under the conditions used, this possibility can be excluded.



Scheme 3

In mechanism 2 both *erythro* and *threo* II would give the same intermediate, 2,3-dibromoisobutyric acid (VI), see Scheme 3. Since the *cis*/*trans* ratio is quite different for the *erythro* and *threo* isomer, this mechanism seems less plausible. In fact *trans* III was found to be the only product from an elimination of VI. Further evidence for this view are experiments performed in deuterium oxide. If mechanism 2 was operating, up to one equivalent of deuterium would have been incorporated, see Scheme 3, giving a ratio of $CH_3/CH \gg 3$. An NMR-investigation of the product from reaction in D_2O gave a ratio $CH_3/CH = 3.0/1.0$.

The elimination of DL-*erythro*- and DL-*threo*-2,3-dibromo-3-phenylpropionic acid (*trans*- and *cis*-cinnamic acid dibromide) have been studied as examples of dehalogenative decarboxylation.[6,7] In this reaction, as in the present one, an E2 reaction yielding *trans*-eliminated products is observed to compete with an E1 dehalogenative decarboxylation yielding both *cis* and *trans* bromostyrene. The stereospecificity of the dehalogenative decarboxylation is much discussed.[8–10] The overall result is a nonstereospecific reaction, but it is considered that the main reaction is a stereospecific *trans* dehalogenative decarboxylation. This reaction operates together with a third reaction, a carbonium ion mechanism yielding *cis*- and *trans*-elimination. Vaughan and Milton discuss a stereospecific *cis* elimination.[8] Changes in the solvent or introduction of substituents are considered to favour one or the other of the possible mechanisms in predicted ways.[6–10]

The steric situation in the present case is the same. *Trans*-elimination dominates in the dehalogenative decarboxylation, but a substantial amount of *cis*-elimination is also present. Recently it was proposed by Ingold[11] that E1 reactions have no pronounced stereospecificity, *trans*-elimination dominates but *cis*-eliminations are often observed. For additional examples, see Ref. 12.

The behaviour of the dehalogenative decarboxylation for *threo* and *erythro* II in the present paper as well as for *cis*- and *trans*-cinnamic acid dibromide reported previously are in good accordance with this general view of the steric course of E1 eliminations.

EXPERIMENTAL

The NMR-spectra were recorded on a Varian A-60 spectrometer. The micro analyses were performed by the Analytical Department, Chemical Institute, University of Uppsala.

2,3-Dibromoisobutyric acid (VI) was prepared according to Ref. 13, m.p. 47.0—48.0°C (carbon disulfide). The NMR-spectra (carbon tetrachloride, TMS) showed two singlets at $\delta = 2.12$ and 12.36 ppm, respectively, and a AB quartet at $\delta = 4.08$ ppm ($J = 10$ cps): the peak ratio was 3:1:2.

DL-threo-*2,3-Dibromo-2-methylsuccinic acid* (*threo* II) was prepared according to Ref. 14, m.p. 152.0—153.0°C. Vaughan gave the m.p. 153—153.5°C. The NMR-spectrum (ether, TMS) showed two singlets in addition to the OH-band, and they were at $\delta = 2.19$ ppm (CH_3) and $\delta = 4.98$ ppm (CH), with the peak ratio 3:1.

DL-erythro-*2,3-Dibromo-2-methylsuccinic acid* (*erythro* II) was prepared according to Ref. 14 with some modifications. 130 g (1.0 mole) of mesaconic acid was dissolved in 150 ml of water, heated to boiling, and 176 g (1.1 mole) of bromine added over 1 h. The water was then removed on a steam-bath under reduced pressure. The residue was allowed to cool and was left over night. The crystalline solid was slurried with benzene (2 × 100 ml) and washed with 25 ml of nitromethane. After drying, 115 g (40 %) of white crystals were collected, m.p. 192—194°C (decomp.). Recrystallization from boiling nitromethane

raised the m.p. to 196.0—197.0°C (decomp.) on slow heating. In addition to the OH-peak the NMR-spectrum showed two singlets (δ_{CH_3} = 2.22 ppm and δ_{CH} = 5.03 ppm) with the ratio 3:1. Evaporation of the benzene extract yielded 41 g (25 %) of 2-bromocitraconic acid anhydride, m.p. 93—96°C.

Methyl-DL-threo-*2,3-dibromo-2-methylsuccinate* was prepared according to Ref. 14, starting from 50.0 g (0.17 mole) of *trans* II. The product was distilled twice under nitrogen and yielded 45.5 g (83 %) of the ester, b.p. 92.0—93.0°C (0.50 mm), n_D^{22} = 1.4972. Vaughan reported the b.p. 94.9°C (1.8 mm) and n_D^{25} = 1.4959. The NMR-spectrum (carbon tetrachloride, TMS) contained two singlets at δ = 2.17 ppm and δ = 5.00 ppm, respectively, and a doublet at δ = 3.74 ppm, with the peak ratio 3:1:6. (Found: C 26.42; H 3.16; Br 49.95. Calc. for $C_7H_{10}Br_2O_4$: C 26.44; H 3.17; Br 50.27).

Methyl-DL-erythro-*2,3-dibromo-2-methylsuccinate* was prepared in an analogous way, starting from 36 g (0.13 mole) of the *erythro* acid. The product was distilled twice under nitrogen and 32 g (79 %) of the ester could be collected, b.p. 112.0—113.0°C (0.70 mm), n_D^{21} = 1.5005. (Found: C 26.58; H 3.16; Br 50.00. Calc. for $C_7H_{10}Br_2O_4$: C 26.44; H 3.17; Br 50.27). The NMR-spectrum showed two singlets at δ = 2.21 ppm and δ = 5.11 ppm, respectively, and a doublet at δ = 3.82 ppm, with the ratio 3:1:6. The *erythro* ester was found to react with pyridine about 10 times as fast as the *threo* ester at 25°C.

2-Bromomesaconic acid (*trans* IV) was prepared according to Ref. 14, starting from 10.0 g (0.031 mole) of methyl-DL-*threo*-2,3-dibromo-2-methylsuccinate. The intermediate product, methyl-2-bromomesaconate was not isolated, the hydrolysis afforded 4.3 g of white crystals, which were recrystallized from 40 ml of boiling nitromethane. From this procedure 2.6 g (40 %) of white crystals were collected, m.p. 222.0—223.0°C. Vaughan gave the m.p. 222.5—223.0°C.[14] The NMR-spectrum (D_2O) showed two singlets with the ratio 3:2.

When an aqueous solution of the bromomesaconic acid (1.0 g in 3 ml of water) was refluxed for 4 h, nothing but the starting material could be collected; as indicated by NMR- and IR-spectra, 0.6 g of the acid was recovered.

Methyl-2-bromocitraconate was prepared by treating 10.0 g (0.031 mole) of methyl-DL-*erythro*-2,3-dibromo-2-methylsuccinate with 6.0 g of pyridine at room temperature for 24 h. White crystals separated after 20 min. The crystalline mass was washed with ether, acidified with diluted hydrochloric acid and extracted with ether. The ethereal solution was washed with water, dried, and evaporated. The residue was distilled under nitrogen, 5.5 g (61 %) was collected, b.p. 85.0°C (0.50 mm), n_D^{22} = 1.4897. (Found: C 35.20; H 3.82; Br 34.01. Calc. for $C_7H_9BrO_4$: C 35.46; H 3.83; Br 33.71). The NMR-spectrum (carbon tetrachloride, TMS) contained a singlet at δ = 2.10 ppm and a doublet at δ = 3.75 ppm, with the ratio 1:2. The IR-spectrum had a band at 1620 cm^{-1}.

2-Bromocitraconic acid and its anhydride (*cis* IV + V) was prepared in an analogous way as 2-bromomesaconic acid.[14] 1.0 g (0.004 mole) of methyl-2-bromocitraconate was refluxed with 0.50 g (0.012 mole) of sodium hydroxide in 3.5 ml of water for 10 min, until the solution became homogeneous. After cooling, the solution was washed with ether, acidified and reextracted with ether. The ethereal solution was dried over $MgSO_4$. Upon evaporation, the ether left 0.8 g of white crystals, which were recrystallized from 5 ml of carbon tetrachloride, yielding 0.30 g (38 %) of 2-bromocitraconic acid anhydride, m.p. 99.5—101.0°C. Vaughan reported the m.p. 100—101°C.[14] By NMR-technique it was possible to observe the equilibrium of the acid and its anhydride in water solutions. The NMR-spectrum (ether, TMS) of the anhydride gave one singlet at δ = 2.16 ppm: if dissolved in water and the water solution extracted with ether, NMR-studies of the ethereal solution showed two singlets at δ = 2.13 and δ = 2.16, respectively. If this ether solution was dried over $MgSO_4$ for half an hour, only one singlet persisted (δ = 2.16 ppm). The IR-spectrum contained a band at 1650 cm^{-1}. Acidimetric titration gave the equivalent weight 95.1. Calc. for $C_5H_3BrO_3$: 95.5.

A solution of 5.0 g (0.017 mole) of DL-*erythro*-2,3-dibromo-2-methylsuccinic acid in 15 ml of water was refluxed for 3 h. The cooled solution was extracted with ether, the ethereal solution dried and evaporated. 0.6 g (18 %) of 2-bromocitraconic acid anhydride was collected.

2.5 g of the anhydride was recovered after boiling 3.0 g of this compound in aqueous solution for 2.5 h with continuous titration with sodium carbonate (20 % by weight) to keep the pH at 6—7 (bromothymol blue). In the NMR-spectrum of the crude extract, nothing but the bromocitraconic acid and its anhydride could be detected.

trans-*3-Bromomethacrylic acid* (*trans* III) was obtained in two different ways.

A. This is a description a little changed from that in Ref. 13. A solution of 12.3 g (0.05 mole) of 2,3-dibromoisobutyric acid and 6.5 g (0.16 mole) of sodium hydroxide in 25 ml of water was placed into a water bath at 55°C for 20 min. (The reaction time was estimated from cursory kinetics). When cooled, the reaction mixture was acidified with concentrated hydrochloric acid. A voluminous precipitate separated. The mixture was extracted with ether (2 × 50 ml), the ethereal extract dried and evaporated. The solid residue (8.3 g) was recrystallized from 200 ml of water (55°C), and 6.3 g (77 %) of white needles, m.p. 64.0—64.5°C were collected. The NMR-spectrum (carbon tetrachloride, TMS, chloroform) showed a doublet at $\delta = 2.00$ ppm ($J = 1.4-1.5$ cps), a quartet (the ethylenic proton, $\delta = 7.70$ ppm), and a singlet (OH-peak) with the peak ratio 3:1:1.

B. This description is according to Ref. 5. A solution of 14.5 g (0.05 mole) of DL-*threo*-2,3-dibromo-2-methylsuccinic acid in 45 ml of water was refluxed for 1 h. (Lossen *et al.*[5] refluxed for 4 h, but cursory kinetics using NMR-technique showed that all starting material had disappeared within 1 h. Refluxing for additional 3 h decreased the yield somewhat). When cooled a voluminous precipitate separated. The collected crystals were recrystallized from hot water and yielded 2.5 g (30 %) of *trans*-3-bromomethacrylic acid.

In the same way 5.0 g of *threo* II was refluxed in 12 ml of D_2O for 1 h. A crude ether extract was analyzed by NMR and gave the ratio $CH_3/CH = 3.0/1.0$. After recrystallization 0.8 g (28 %) of *trans* III was collected, which gave the same ratio CH_3/CH.

cis-*3-Bromomethacrylic acid* (*cis* III) was prepared according to Ref. 5. 50 g (0.172 mole) of DL-*erythro*-2,3-dibromo-2-methylsuccinic acid was slurried with 50 ml of water. Bromothymol blue was added and the solution titrated with aqueous sodium carbonate (20 % by weight) till the blue colour of the indicator persisted (pH 6—7). The flask was immersed into boiling water, and was rapidly titrated with the sodium carbonate solution from a dropping funnel to maintain the blue colour of the indicator. Low boiling products were distilled off during the reaction. After 30 min, the flask was cooled by immersing into ice-water. The blue solution was washed with ether, which removed most of the indicator and basic impurities. After acidifying with concentrated hydrochloric acid, the solution was extracted with light petrol (3 × 50 ml), which removed the *trans* III acid and most of the residual indicator. The aqueous solution was then extracted with ether (5 × 50 ml), the ethereal extract washed with water, dried over $CaCl_2$ and evaporated. The ether left 3.5 g of *cis* III as a crystalline mass, which was recrystallized from 5 ml of nitromethane (40°C), yielding 2.5 g of *cis* III (9 %), white crystals, m.p. 65.5—66.0°C. The NMR-spectrum (carbon tetrachloride, TMS, chloroform) showed a doublet at $\delta = 2.03$ ppm ($J = 1.6$), a quartet at $\delta = 6.73$ ppm and the OH-peak, ratio 3:1:1.

By exposing a solution of the *cis* III acid in carbon tetrachloride (a drop of bromine in carbon tetrachloride added) to direct sunlight, isomerisation to the *trans* III acid occurred within 5 min.

The light petrol extract yielded upon evaporation and recrystallization 16 % *trans*-3-bromomethacrylic acid (*trans* III).

A synthesis was performed in the same way using D_2O as solvent. After completed reaction the solution was acidified with deuterochloric acid, and extracted with ether. The crude ether extract was analyzed by NMR giving *cis*/*trans* = 2.2/1.0 and CH_3/CH (*cis* + *trans*) = 3.0/1.0.

Cursory kinetics. Syntheses were performed with DL-*threo*- and DL-*erythro*-2,3-dibromo-2-methylsuccinic acid without isolation of products.

General. The solutions used had the same concentrations as described above. Samples were taken out during the reaction or after completed reaction. The acids in the sample solutions were extracted with ether, the ethereal extract washed with water, and dried over $CaCl_2$. After evaporation in part, TMS was added and the ether phase analyzed by NMR.

In this way the optimal conditions could be estimated for the formation of *cis* and *trans* III. Furthermore, it was observed that *erythro* II at pH> 6 yielded *cis* and *trans* III with the ratio *cis*/*trans* = (2.2 ± 0.1)/1.0. Five syntheses performed at different occasions, and a series of samples taken during a reaction (6—30 min) established the ratio.

To 5.0 g *erythro* II was added 0.10 g and 0.20 g, respectively, of *trans* III. After completed reaction at pH 6—7, the acidic ether concentrates showed *cis/trans* in a ratio 1.7/1.0 and 1.2/1.0, respectively. A blank solution without added *trans* III afforded the ratio 2.2/1.0.

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