[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The *dl*-3-Methylcyclopentane-1,2-dicarboxylic Acids and the Configurations of the Nepetic Acids

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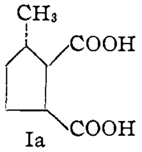
RECEIVED JANUARY 25, 1958

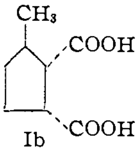
The four *dl*-3-methylcyclopentane-1,2-dicarboxylic acids (I) have been prepared and their configurations determined. A comparison of the infrared spectra of derivatives of these acids with the corresponding derivatives of the nepetic acids showed that the *cis-trans* configuration previously assigned to *cis*-nepetic acid is correct, but that *trans*-nepetic acid has the *trans-trans* rather than the *trans-cis* arrangement of the ring substituents. A synthesis of I, previously reported by Fargher and Perkin, was found to yield the isomeric acyclic unsaturated acid, 3-carboxy-5-heptenoic acid (II), instead of I. A recent synthesis of I by Blomquist and collaborators using a variation of the Fargher and Perkin procedure produced a mixture of the two racemates with *trans*-carboxyl groups.

Two optically active 3-methylcyclopentane-1,2-dicarboxylic (nepetic) acids have been obtained as degradation products of nepetalactone.[3] One of these nepetic acids, m.p. 118°, $[\alpha]^{23}\text{D}$ $-35.4°$, was assigned the *trans-cis*[4] configuration Ic and the other acid, m.p. 132°, $[\alpha]^{25}\text{D}$ $+69.1°$, obtained from the acid, m.p. 118°, *via* the anhydride, was assigned the *cis-trans* structure Ia. These assignments were connected with other stereochemical deductions in regard to the configurations of the various asymmetric centers of nepetalactone and related compounds.[3]

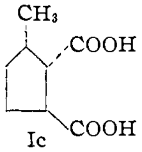
Certain evidence, which has been obtained subsequently and will be discussed elsewhere, indicated that the configurations assigned to nepetalactone and some of its degradation products might be open to question. It seemed, therefore, desirable to prepare and characterize the four *dl*-3-methylcyclopentane-1,2-dicarboxylic acids so that the nepetic acids could be related to them. These synthetic acids are represented by the enantiomers Ia–d in which the ring carbon carrying the methyl group has the same absolute configuration as that established[5] for the degradation products of nepetalactone.



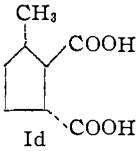
Ia



Ib

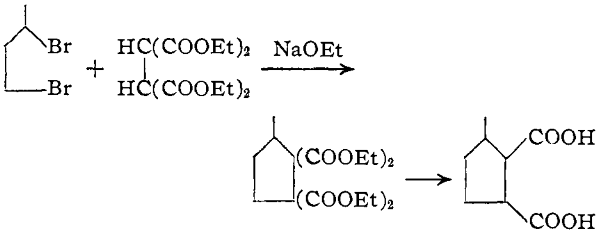


Ic

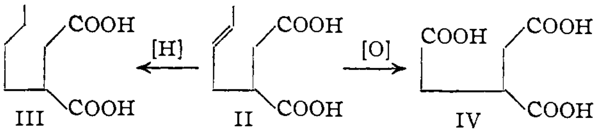


Id

At the time this work was undertaken there was only one report of a synthesis of a 3-methylcyclopentane-1,2-dicarboxylic acid. Fargher and Perkin[6] reported that the following sequence of reactions starting with 1,3-dibromobutane and 1,1,2,2-tetracarbethoxyethane yielded an acid, m.p. 100–104°.



When this reaction sequence was repeated in this Laboratory, the only crystalline product obtained was an acid, m.p. 113–115°, whose elemental analyses and neutral equivalent were satisfactory for the desired methylcyclopentanedicarboxylic acid. This acid, however, was unsaturated. It absorbed one equivalent of hydrogen to yield *n*-butylsuccinic acid (III) and gave tricarballylic acid (IV) on oxidation. These derivatives indicate that the reaction product was one of the 3-carboxy-5-heptenoic acids (II). The infrared spectrum of the acid shows a maximum at 10.37 μ, indicating the *trans* configuration.[7] Alder and co-workers[8] reported this acid, synthesized in a different manner, to melt at 114–115° and converted it to the same derivatives, III and IV. Clearly the reactants in the Fargher and Perkin sequence yield the isomeric acyclic unsaturated acid II instead of a methylcyclopentanedicarboxylic acid.



After the Fargher and Perkin procedure was found unsuitable, the preparation of the desired 3-methylcyclopentane-1,2-dicarboxylic acids from 5-methyl-2-carbethoxycyclopentanone[9] (IV) was undertaken. This ketoester was converted *via* the cyanohydrin VI to a mixture of cyanoesters, VIIa and b, which yielded on hydrolysis two methylcyclopentenedicarboxylic acids. This mixture of acids was separated readily by their marked difference in ether solubility; VIIIa, m.p. 109–111°, is quite soluble in ether and was obtained in 60–

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[3] S. M. McElvain and E. J. Eisenbraun, THIS JOURNAL, **77**, 1599 (1955).

[4] In this and all other designations of configurations in this paper the relationship of the functional substituents is given first and that of the methyl group and the adjacent functional substituent second.

[5] E. J. Eisenbraun and S. M. McElvain, THIS JOURNAL, **77**, 3383 (1955).

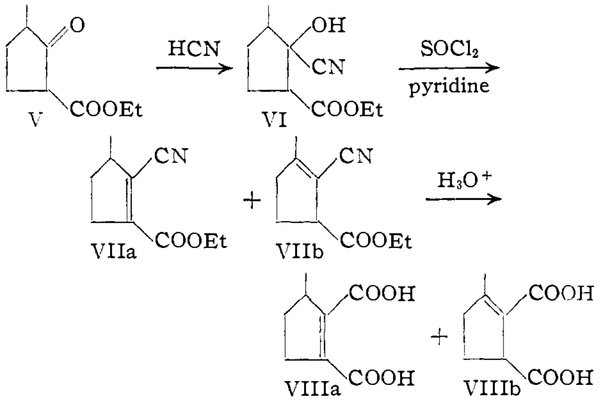
[6] R. G. Fargher and W. H. Perkin, Jr., *J. Chem. Soc.*, **105**, 1365 (1914).

[7] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 40.

[8] K. Alder, F. Pascher and A. Schmitz, *Ber.*, **76**, 28 (1943).

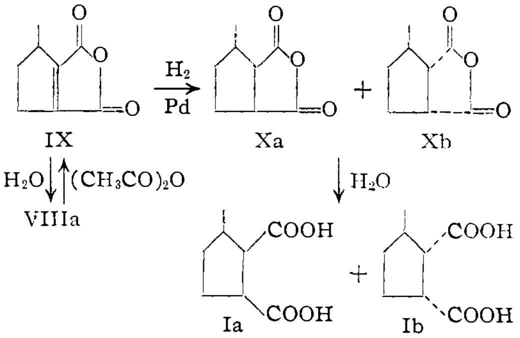
[9] W. Dieckmann, *Ann.*, **317**, 51 (1901).

80% yields, while VIIIb, m.p. 198–200°, which is quite insoluble in this solvent, was obtained in 2–9% yields. The structure of VIIIa was shown by its ozonolysis and subsequent oxidation to *dl*-α-methylglutaric acid. No characterizable product could be obtained from the ozonolysis of VIIIb. However, the structure of this acid is indicated by the fact that the nuclear magnetic resonance spectrum of its dimethyl ester shows no vinyl hydrogen absorption[10]; also, the ultraviolet maximum for VIIIb is 10 mμ greater than that of 1-methyl-2-cyclopentene-1,2-dicarboxylic acid, whose λ_{max} is 216 mμ (log ε 3.85).



Direct hydrogenation of VIIIa and VIIIb in acetic acid with platinum and palladium catalysts was attempted in the hope of obtaining only the two 3-methylcyclopentane-1,2-dicarboxylic acids resulting from *cis* addition of hydrogen in each case. The results were erratic; hydrogen uptake usually was considerably less than one mole and starting material was recovered in varying amounts. However, from one of the more complete hydrogenations of VIIIb two crystalline saturated acids were obtained: one, m.p. 130–132°, in 63% yield and the other, m.p. 135–136°, in 3% yield. As these acids were separated by virtue of the insoluble barium salt of the former, it appears that this acid has *cis*-carboxyl groups and that the acid, m.p. 135–136°, whose barium salt is soluble, has *trans*-carboxyl groups.[3] Furthermore, on the assumption of *cis* addition of hydrogen to the double bond of VIIIb, the acid melting at 130–132° is the *cis-cis*[4] isomer, one enantiomer of which is Ib, and the acid, m.p. 135–136° in the *trans-cis* isomer Ic. Confirmation of the *cis* relationship of the carboxyl groups in Ib was obtained by converting it in excellent yield to an anhydride, which gave only Ib on hydrolysis. The predominance of this *cis-cis*-acid would be expected from the addition of hydrogens to the less hindered side of the molecule of VIIIb.

The most satisfactory conversion of the unsaturated acid VIIIa to 3-methylcyclopentane-1,2-dicarboxylic acids involved the hydrogenation of its anhydride IX over a palladium catalyst with or without benzene as a solvent. Under these conditions the reduction was essentially complete. The resulting mixture of saturated anhydrides yielded on hydrolysis a mixture of saturated acids, which was separated by fractional crystallization from ether–petroleum ether into the *cis-cis* isomer, m.p. 130–132°, in 48% yield and a new isomer, m.p. 118–119°, in 13% yield. This new isomer gave a water-insoluble barium salt and could be regenerated from its anhydride IXa in excellent yield; therefore, it was assigned the *cis-trans* configuration, one enantiomer of which is Ia.



From a comparison of the infrared spectra of the pure anhydrides (Xa and b), prepared from the separated *cis*-acids Ia and Ib with the spectrum of the mixture of saturated anhydrides from the hydrogenation of the unsaturated anhydride IX, it was estimated that this mixture contained 42% of Xa and 58% of Xb. This ratio of hydrogenation products gives some substantiation to the assigned structures for Ia and Ib as the hydrogens would be expected to add more readily to the less hindered side of the essentially flat molecule of IX to give a preponderance of the *cis-cis*-anhydride Xb.

The methyl esters of Ia, Ib and the *trans-cis* isomer Ic, obtained from the hydrogenation of VIIIb, were separately treated with sodium methoxide in refluxing absolute methanol for 24 hours and in each case the resulting mixtures of esters hydrolyzed to the acids. From these acid mixtures *trans-trans*-3-methylcyclopentane-1,2-dicarboxylic acid, m.p. 117–118°, one enantiomer of which is Id, was isolated in yields of 56, 31 and 41% from the methyl esters of Ia, Ib and Ic, respectively. The structure of the isomer Id follows from its difference in properties from the other isomers and from the fact that its dimethyl ester was formed in substantial amounts from the treatment of the esters of Ia, Ib and Ic with base.

When the dimethyl esters of Ia, Ib, Ic and Id were separately treated with sodium methoxide in refluxing absolute methanol for 48 hours, the same (refractive index, infrared spectrum) equilibrated diester mixture was obtained in each case. The only pure acid that could be isolated after hydrolysis of this mixture was the *trans-trans*-acid Id (33% yield). The equilibrated ester had none of the peaks characteristic of the *cis*-esters in its infrared spectrum and the dibasic acids obtained from its hydrolysis gave no precipitate with barium hydroxide. Hence, this equilibrium mixture contained little if any of the *cis*-esters. Although there is little difference between the infrared spectra of the two *trans*-esters, there is a significant difference in their refractive indexes, and from the values for the pure esters and that of the equilibrium mixture it was calculated that the mixture contained 28% of the ester of Ic and 72% of the

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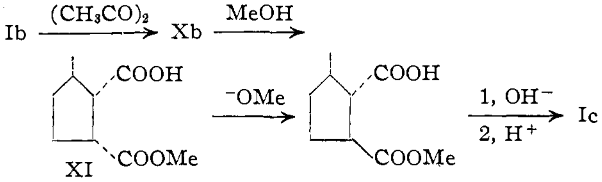
(10) The authors are indebted to Professor John D. Roberts of the California Institute of Technology for this information.

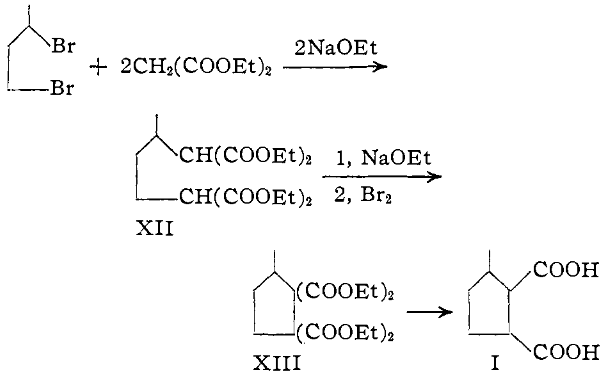
ester of Id. Thus the dimethyl ester of Id is clearly the most stable stereoisomer.

Since there was as yet no convenient way of preparing the *trans-cis*-acid Ic in quantities comparable to those for the other three stereoisomers, the following method was developed. The anhydride (Xb) of the relatively abundant *cis-cis*-acid was treated with dry methanol in the hope that the predominant product would be the half-ester XI.[11] Epimerization of the resulting acid ester for two hours with sodium methoxide in refluxing methanol, and then hydrolysis, gave the desired acid Ic, m.p. 132–133°, in 54% over-all yield from Ib.



In view of the conversion of *trans*-nepetic acid to *cis*-nepetic acid,[3] it was of interest to test the behavior of one of the racemic acids with *trans*-carboxyl group[5] toward acetic anhydride. It was found by infrared analysis that the racemic *trans-trans*-acid Id gave an anhydride mixture containing 63% of the *cis-trans*-anhydride Xa and 37% of the *cis-cis*-anhydride Xb. However, because the yield of the anhydride mixture was low, the yield of pure *cis-trans*-acid Ia that was isolated amounted to only 4% of the theoretical from Id.

Recently another synthesis of I by a variation of the procedure of Fargher and Perkin[6] was reported by Blomquist and collaborators.[12] In this synthesis 1,3-dibromobutane was condensed with two equivalents of malonic ester and the resulting acyclic ester XII converted to the cyclic tetraester XIII with sodium ethoxide and bromine. Hydrolysis and decarboxylation of XIII yielded acids I, which the authors believe to be a mixture of the four racemates. A sample of this crude acid was recrystallized and sublimed to give a product, m.p. 115–117°, which was thought to consist of only the two racemates with *trans*-carboxyl groups.



In this Laboratory a sample of I, m.p. 111–114°, kindly furnished by Dr. J. Wolinsky, was found to give no precipitate with barium hydroxide solution indicating the absence of either of the racemates with *cis*-carboxyl groups. After seven recrystallizations from acetonitrile a 2% yield of the *trans-cis* isomer Ic was obtained. The dimethyl ester mixture prepared from these *trans*-acids appeared from the refractive index to contain 47% of Ic and 53% of Id. Equilibration of this ester mixture with sodium methoxide gave the same (refractive index, infrared spectrum) mixture of esters as had been obtained from the equilibration of each of the esters of Ia–d.

The above sequence of reactions leading to the tetraester XIII proved successful, in contrast to the Fargher and Perkin procedure, because the by-products resulting from the elimination reaction were much lower boiling than the acyclic tetraester XII. The Fargher and Perkin procedure gave tetraesters by both elimination and displacement reactions, *i.e.*, the precursor of II and possibly some of XIII, which could not be separated readily from each other or from the starting tetraester, tetracarbethoxyethane.

Comparison of the infrared spectra of the two optically active nepetic acids obtained from the degradation of nepetalactone with those of the four synthetic *dl*-3-methylcyclopentane-1,2-dicarboxylic acids were made. Since all of these acids have rather similar spectra in chloroform solution, the dimethyl esters (Figs. 1 and 2) and the anhydrides of the *cis*-acids (Fig. 1), all of which were run as pure liquids, were used.

From these spectra it is apparent that *cis*-nepetic acid had been correctly assigned the *cis-trans* structure Ia (Fig. 1), but that the configuration previously assigned to *trans*-nepetic acid is incorrect. This acid, as may be seen from the spectra of the *trans*-esters in Fig. 2, has the *trans-trans* configuration Id rather than the *trans-cis* configuration Ic. The effect of this revision of the structure of *trans*-nepetic acid on the stereochemistry of the intermediates leading to it from nepetalactone will be discussed in the following paper.

Experimental

Condensation of 1,3-Dibromobutane and 1,1,2,2-Tetracarbethoxyethane.—It made little difference in the refractive indexes and boiling points of the products whether this reaction was carried out in a sealed vessel as described in the literature,[6] or by adding the dibromide to a mixture of the other components in refluxing ethanol. The latter procedure was employed for convenience in a large-scale run.

A solution of sodium ethoxide in ethanol was prepared under nitrogen from 25 g. of sodium and 500 ml. of ethanol in a three-necked, 2-l. round-bottom flask protected by a calcium chloride drying tube. To this solution 159 g. of tetracarbethoxyethane,[13] m.p. 71–74°, was added. The mixture was stirred and heated to reflux, after which 135 g. of 1,3-dibromobutane,[6] b.p. 77–79° (45 mm.), was added dropwise over a period of 1.5 hours. After refluxing and stirring for 24 hours, the flask was chilled in ice and 300 ml. of water added. The organic material was extracted with ether, the ethereal solution dried over magnesium sulfate, filtered, and the ether distilled. The residual oil was fractionated three times through a 15-inch Podbielniak column. The yield of tetraester boiling at 149–153° (0.6 mm.) was 84 g. (45%), and the recovery of crystalline tetracarbethoxyethane from the lower boiling fractions amounted to 50 g. (32%).

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[11] It has been shown (J. Cason, *J. Org. Chem.*, **13**, 227 (1948)) that α,α-dimethylglutaric anhydride with methanol gives a quantitative yield of $MeOOCCH_2CH_2C(CH_3)_2COOH$.

[12] A. T. Blomquist, J. Wolinsky, Y. C. Meinwald and D. T. Longone, THIS JOURNAL, **78**, 6057 (1956).

[13] M. Conrad and C. A. Bischoff, *Ann.*, **214**, 68 (1882).

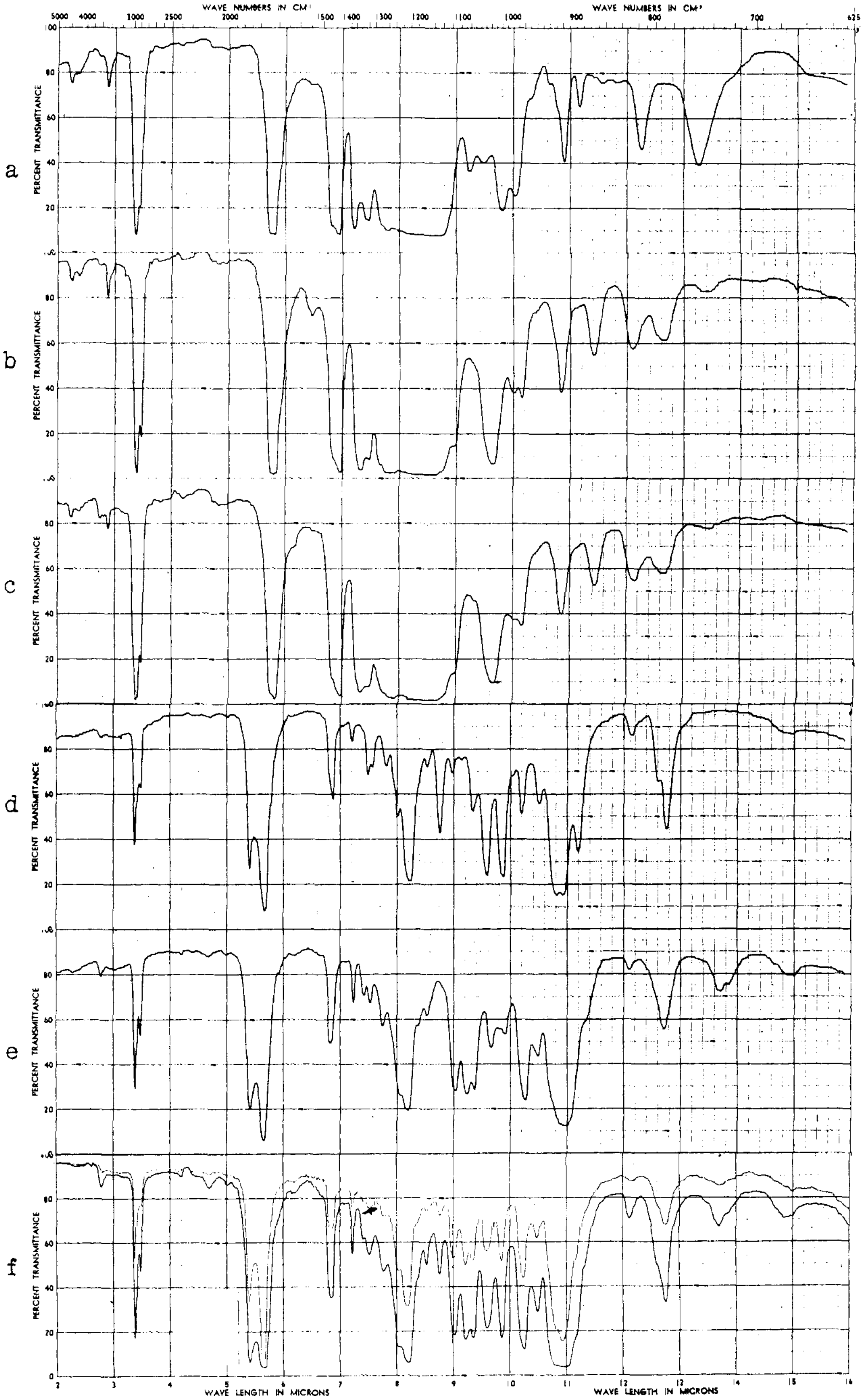

Fig. 1.—Dimethyl esters and anhydrides of *cis*-acids: a, *dl-cis-cis*-dimethyl 3-methylcyclopentane-1,2-dicarboxylate, liquid film, 0.029-mm. cell; b, *dl-cis-trans*-dimethyl 3-methylcyclopentane-1,2-dicarboxylate, liquid film, 0.029-mm. cell; c, *cis*-dimethyl nepetate, liquid film, 0.029-mm. cell; d, *dl-cis-cis*-3-methylcyclopentane-1,2-dicarboxylic anhydride (Xb), liquid film; e, *dl-cis-trans*-3-methylcyclopentane-1,2-dicarboxylic anhydride (Xa), liquid film; f, *cis*-nepetic anhydride, liquid film, two thicknesses.

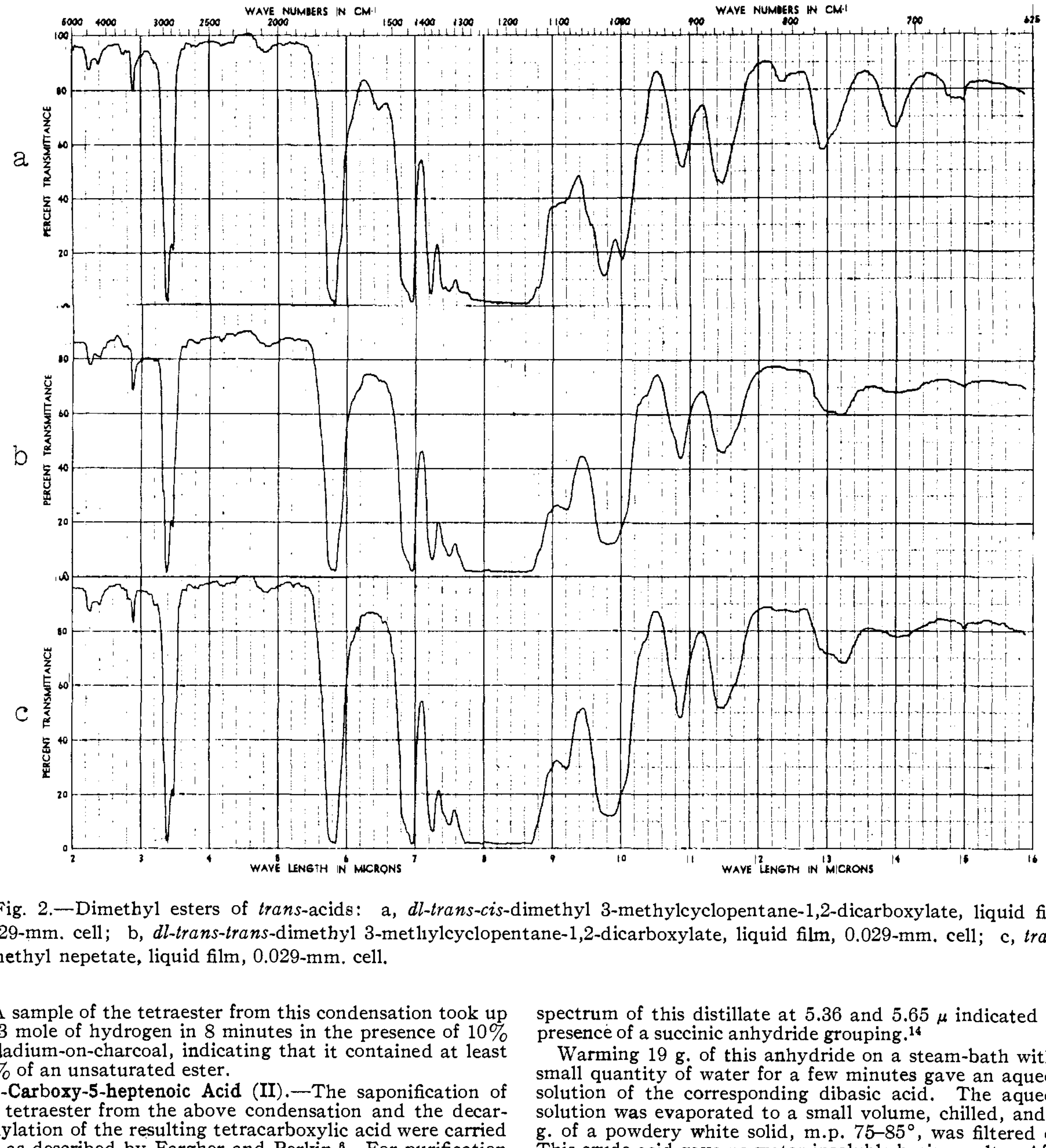

Fig. 2.—Dimethyl esters of *trans*-acids: a, *dl-trans-cis*-dimethyl 3-methylcyclopentane-1,2-dicarboxylate, liquid film, 0.029-mm. cell; b, *dl-trans-trans*-dimethyl 3-methylcyclopentane-1,2-dicarboxylate, liquid film, 0.029-mm. cell; c, *trans*-dimethyl nepetate, liquid film, 0.029-mm. cell.

A sample of the tetraester from this condensation took up 0.83 mole of hydrogen in 8 minutes in the presence of 10% palladium-on-charcoal, indicating that it contained at least 83% of an unsaturated ester.

3-Carboxy-5-heptenoic Acid (II).—The saponification of the tetraester from the above condensation and the decarboxylation of the resulting tetracarboxylic acid were carried out as described by Fargher and Perkin.[6] For purification purposes the yellow oil resulting from the decarboxylation was esterified with azeotropic removal of water. The yield of diester boiling at 146–155° (30 mm.) or 254–260° (745 mm.) averaged 70% based on tetraester.

Saponification of this diester was effected by boiling with 10% sodium hydroxide solution for an hour. After acidification, the dibasic acid was continuously extracted with ether for 24 hours. A quantitative yield of an acidic brownish solid with oily impurity remained after evaporation of the ether solution. A saturated solution of barium hydroxide was added to this crude solid until the solution was basic to litmus, but no insoluble barium salt formed, indicating that the crude acid contained little if any of 3-methylcyclopentane-1,2-dicarboxylic acid (I) with *cis*-carboxyl groups.

In an attempt to repeat Fargher and Perkin's preparation of a *cis*-acid, the crude acid from the previous saponification was converted to an anhydride by refluxing for 7 hours with freshly distilled acetic anhydride. The yield of anhydride, b.p. 159–126° (30 mm.) or 80–83° (0.1 mm.), $n^{25}D$ 1.674–1.700, was 70%; considerable tarry residue remained from the distillation. The presence of bands in the infrared spectrum of this distillate at 5.36 and 5.65 μ indicated the presence of a succinic anhydride grouping.[14]

Warming 19 g. of this anhydride on a steam-bath with a small quantity of water for a few minutes gave an aqueous solution of the corresponding dibasic acid. The aqueous solution was evaporated to a small volume, chilled, and 10 g. of a powdery white solid, m.p. 75–85°, was filtered off. This crude acid gave no water-insoluble barium salt. After a recrystallization from water and 7 recrystallizations from ether–petroleum ether, 1.0 g. of 3-carboxy-5-heptenoic acid[8] (II) melting at 110–112° remained. Working up the mother liquors gave an additional 0.8 g. of acid with this melting point, bringing the yield of II based on anhydride to 8%. A better yield of II resulted when the initial water solution of acid was evaporated to dryness and the waxy residue freed from some oily impurity (one third of its weight) by contact with porous procelain overnight. The white solid remaining melted at 89–104°; after three recrystallizations from ether–petroleum ether the yield of II melting at 110–112° was 15%.

The infrared spectrum of II showed a maximum at 10.37 μ, interpreted as due to a *trans* double bond.[7] The compound did not decolorize bromine in carbon tetrachloride solution; however, it gave an immediate precipitate of manganese dioxide when a few crystals were added to a 2% aqueous potassium permanganate solution. This acid contained 55.64% C, 6.99% H, and gave a neutral equivalent of 86 (calcd. for II: 55.81, 7.03 and 86, resp.) It was found that

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[14] G. Stork and R. Breslow, THIS JOURNAL, **75**, 3291 (1953).

by recrystallization of this material from acetonitrile the melting point could be raised to 113–115° (reported[8] for II 114–115°).

A sample of the acid, m.p. 110–112°, was converted to the anhydride in the usual way. The product (88% yield, n^{25}D 1.4708) was evaporatively distilled at 70° (0.1 mm.). This anhydride was converted in quantitative yield to the original acid, m.p. 109–112°, on hydrolysis.

A solution of 100 mg. of II in 5 ml. of water was stirred under an atmosphere of hydrogen with 10 mg. of 10% palladium-on-charcoal. In 14 minutes 0.98 mole of hydrogen had been taken up; no more was absorbed in an additional hour. After filtering off the catalyst, washing well with water, and evaporating to dryness, 99 mg. of colorless oil remained which crystallized on scratching to a solid, m.p. 71–76°. The first crop of this acid from an ether–petroleum ether recrystallization melted alone or mixed with authentic *n*-butylsuccinic acid[15] (III) at 82–84°.

A solution of 200 mg. of II in 50 ml. of ethyl acetate was chilled to −70° and a slow stream of ozone passed in through a fritted glass bubbling tube. The blue color indicating the presence of excess ozone appeared in 5 minutes. The ethyl acetate solution was added to a stirred solution of 20 ml. of 30% hydrogen peroxide and 20 ml. of 10% sodium hydroxide, and the resulting mixture stirred overnight. After evaporation on a steam-bath until the organic layer had disappeared, the basic solution was evaporated repeatedly with water to remove ethanol, then acidified with 6 *N* hydrochloric acid and continuously extracted with ether for 24 hours. The ether solution was evaporated and the residue kept under diminished pressure for several hours to remove acetic acid. The residue was taken up in ether, filtered, and evaporated, leaving 86 mg. of a white solid melting at 135–150°. Four recrystallizations from ether–petroleum ether gave 21.7 mg. of tricarballylic acid[16] (IV), m.p. 158–159°. It contained 40.98% C, 4.67% H, and had a neutral equivalent of 58 (calcd. 40.91, 4.58, 59, resp.). A mixed melting point with a known sample of IV (m.p. 160–161°) was 159.5–160.5°.

3-Methyl-1-cyclopentene-1,2-dicarboxylic Acid (VIIIa) and 3-Methyl-2-cyclopentene-1,2-dicarboxylic Acid (VIIIb).—A mixture of 30 ml. of liquid hydrogen cyanide and 34.0 g. of 5-methyl-2-carbethoxycyclopentanone[9] (V), b.p. 90–93° at 0.8 mm., n^{25}D 1.4464, was chilled to 10°, flushed with nitrogen, and one drop of 50% potassium hydroxide solution added. After 20 hr. of stirring at this temperature, 3 drops of 85% phosphoric acid was added and the excess hydrogen cyanide was removed under reduced pressure at room temperature. The residual cyanohydrin VI was obtained as a pale yellow oil weighing slightly more than the theoretical amount. It was taken up in 20 ml. of benzene and dried over magnesium sulfate overnight.

The mixture was filtered into a 500-ml. three-necked round-bottom flask and the drying agent rinsed with 20 ml. of benzene. After the addition of 100 ml. of pyridine, the system was flushed with nitrogen, cooled to 10°, and 20 ml. of purified thionyl chloride added; a small amount of light brown precipitate appeared. After stirring overnight at 10°, water was added and the layers were separated. The aqueous layer was acidified with dilute hydrochloric acid, extracted with ether, and the combined organic layers were washed successively with dilute hydrochloric acid, sodium bicarbonate solution, and dilute hydrochloric acid. After drying overnight over magnesium sulfate and filtering, the solvent was removed from the orange solution and the residual oil was distilled to give a 65–85% yield (based on V) of a mixture of ethyl 3-methyl-2-cyano-1-cyclopentenecarboxylate (VIIa) and ethyl 3-methyl-2-cyano-2-cyclopentenecarboxylate (VIIb), b.p. 95–102° (0.8 mm.), n^{25}D 1.4758–1.4763, $\lambda_{\max}^{\mathrm{EtOH}}$ 231 mμ, log ε 3.92.

After refluxing 20 g. of this unsaturated cyanoester mixture with 200 ml. of concentrated hydrochloric acid for half an hour, a homogeneous solution was obtained; the refluxing was continued for 12 hours. In some runs a small amount of black scum was removed from the surface of the solution at this point. The solution was evaporated to dryness and ether added to the brownish residual solid to dissolve the organic material. In one run the ammonium chloride was filtered to determine the yield of this inorganic product of the hydrolysis (96%); normally magnesium sulfate was added before filtering. After washing the cake of ammonium chloride and magnesium sulfate with ether, the ether solutions were evaporated to dryness, leaving a brown solid, m.p. 93–106°. This solid was boiled with 60 ml. of ether, the mixture allowed to stand in a refrigerator for several hours, after which crystals of the acid VIIIb were filtered off. This crude VIIIb was recrystallized from ethyl acetate–petroleum ether to m.p. 198–200°; the yield varied from 2–9%. For analysis a sample was sublimed at 160° (0.1 mm.) and then recrystallized once. The ultraviolet spectrum of VIIIb showed $\lambda_{\max}^{\mathrm{EtOH}}$ 226 mμ, log ε 3.90.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92; neut. equiv., 85. Found: C, 56.59; H, 6.02; neut. equiv., 85.

Dimethyl 3-methyl-2-cyclopentene-1,2-dicarboxylate was prepared from VIIIb in quantitative yield with diazomethane. It was evaporatively distilled at 75° (0.1 mm.), n^{25}D 1.4764. The nuclear magnetic resonance spectrum[10] of this ester showed no vinyl hydrogen absorption in accordance with the assigned structure.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.37; H, 6.91.

The ether solution from which the acid VIIIb had been removed was evaporated to dryness and the residual brown solid was recrystallized by dissolving it in a small volume of water and adding an equal volume of concentrated hydrochloric acid. The yield of VIIIa, m.p. 106–109°, was 60–80%. An analytical sample of VIIIa, m.p. 109–111°, $\lambda_{\max}^{\mathrm{EtOH}}$ 236 mμ, log ε 3.96, was prepared by sublimation at 145° (0.1 mm., with some anhydride formation) and then recrystallization from ether–cyclohexane.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92; neut. equiv., 85. Found: C, 56.65; H, 6.08; neut. equiv., 86.

The acid VIIIa (235 mg.) was ozonized by a previously described[17] procedure to *dl*-α-methylglutaric acid (68%), m.p. 75–77°, which was not depressed on admixture with authentic material.

Hydrogenation of VIIIb to *cis-cis*-3-Methylcyclopentane-1,2-dicarboxylic Acid (Ib) and *trans-cis*-3-Methylcyclopentane-1,2-dicarboxylic Acid (Ic).—A mixture of 1.00 g. of sublimed VIIIb, 20 ml. of acetic acid and 100 mg. of Adams catalyst was stirred under a hydrogen atmosphere. After 8 hours the uptake of hydrogen stopped at 1.00 mole. The catalyst was filtered off, rinsed with water, and the aqueous solution evaporated to dryness under diminished pressure at room temperature. Concentrated barium hydroxide solution was added dropwise to the crystalline residue until the mixture was basic to phenolphthalein. The mixture was chilled overnight and then filtered.

The precipitated barium salt was acidified to *p*H 1 by adding 6 *N* hydrochloric acid dropwise, and the resulting solution was extracted with ether. The ether solution was dried over magnesium sulfate, filtered, and evaporated to dryness, leaving 715 mg. of a crystalline acid. One recrystallization from ether–petroleum ether gave 608 mg. of Ib as stout prisms, m.p. 130–132°, pK_1 6.60, pK_2 9.37.[18] A second crop brought the yield of this isomer to 632 mg. (63%).

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.03; neut. equiv., 86. Found: C, 56.07; H, 6.86; neut. equiv., 86.

An ether solution of diazomethane converted Ib to **dimethyl *cis-cis*-3-methylcyclopentane-1,2-dicarboxylate.** This ester was evaporatively distilled at 60° (0.1 mm.), n^{25}D 1.4493; the infrared spectrum is shown in Fig. 1.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 59.83; H, 8.09.

A 500-mg. sample of the acid Ib was refluxed with five times its weight of acetic anhydride for 6 hours. The acetic acid and excess acetic anhydride were removed under reduced pressure, and the residue was evaporatively distilled at 75° (0.2 mm.), giving 358 mg. (88%) of ***cis-cis*-3-methylcyclopentane-1,2-dicarboxylic anhydride** (Xb), n^{25}D 1.4770; the infrared spectrum is shown in Fig. 1. A sample was evaporatively distilled a second time for analysis.

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[15] H. Scheibler and F. Rettig, *Ber.*, **59**, 1195 (1926).

[16] H. Gilman, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 523.

[17] E. J. Eisenbraun and S. M. McElvain, THIS JOURNAL, **77**, 3383 (1955).

[18] These and the other *pK* values given in this paper were kindly determined by Professor V. Prelog, Eidg. Technische Hochschule, Zürich.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.65; H, 6.63.

A sample of the anhydride Xb was stirred with a few drops of water until a homogeneous solution resulted. The excess water was removed under reduced pressure, leaving a quantitative yield of a solid, m.p. 126–128°, mixed m.p. with Ib, 128–130°.

The filtrate containing water-soluble barium salts was similarly acidified with hydrochloric acid, extracted with ether, and the ether solution dried and evaporated, yielding 260 mg. of acid, m.p. 100–113°. Twenty-one recrystallizations from ether–petroleum ether gave 32 mg. (3%) of Ic, m.p. 132–133°, pK_1 6.32, pK_2 9.06.

Anal. Calcd. for $C_8H_{10}O_4$: C, 55.81; H, 7.03; neut. equiv., 86. Found: C, 55.88; H, 7.00; neut. equiv., 87.

It was later found that acetonitrile was a better recrystallization solvent for Ic; by using this solvent the melting point of this acid was raised to 135–136°.

A sample of Ic, m.p. 132–134°, was converted in the usual way into **dimethyl *trans-cis*-3-methylcyclopentane-1,2-dicarboxylate**, which was evaporatively distilled at 70° (0.2 mm.), $n^{25}D$ 1.4485, infrared spectrum shown in Fig. 2.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 59.58; H, 8.16.

Conversion of VIIIa to Ib and *cis-trans*-3-Methylcyclopentane-1,2-dicarboxylic Acid (Ia).—A 15.4-g. sample of the unsublimed acid VIIIa, m.p. 107–110°, was refluxed with 80 ml. of freshly distilled acetic anhydride for 6 hours. The acetic acid and excess acetic anhydride were distilled off at reduced pressure and the residual **3-methyl-1-cyclopentene-1,2-dicarboxylic anhydride (IX)** distilled. The yield of IX, b.p. 81–82° (0.1 mm.), $n^{25}D$ 1.4926, was 13.35 g. (97%).

Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.52; H, 5.10.

By warming a sample of IX with water on a steam-bath for an hour and then evaporating to dryness under diminished pressure, it was reconverted quantitatively to VIIIa, m.p. 106–110°.

A 13.35-g. sample of the anhydride IX in 5 ml. of benzene was stirred with 1.0 g. of 10% palladium-on-charcoal under a hydrogen atmosphere. The uptake of hydrogen was very slow under these conditions (69% of theoretical in 7 days). The catalyst was filtered off, rinsed with benzene, the benzene removed by distillation, and the residue distilled. This partially saturated anhydride was then shaken in a bomb with 1.0 g. of 10% palladium-on-charcoal and 5 ml. of benzene at 150 p.s.i. of hydrogen. No more hydrogen was taken up after 2 hours. The resulting mixture of the 3-methylcyclopentane-1,2-dicarboxylic anhydrides Xa (see below) and Xb was distilled at 81–83° (0.15 mm.), $n^{25}D$ 1.4763. From a quantitative infrared analysis, this mixture was found to contain 42% of Xa and 58% of Xb. This anhydride mixture was stirred with two volumes of water on a steam-bath for 3 hours and the resulting solution evaporated to dryness. The residual oil crystallized very slowly on standing. Fractional crystallization from ether–petroleum ether (seeding with Ib) gave stout prisms of Ib, m.p. 130–132° (48%), and, from the mother liquors after removal of Ib, needles of a new isomer, Ia, m.p. 118–119° (13%), pK_1 6.54, pK_2 9.34.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.03; neut. equiv., 86. Found: C, 55.82; H, 7.03; neut. equiv., 87.

In the usual way the acid Ia was converted to **dimethyl *cis-trans*-3-methylcyclopentane-1,2-dicarboxylate**, which was evaporatively distilled at 60° (0.1 mm.), $n^{25}D$ 1.4482; the infrared spectrum is shown in Fig. 1.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 60.40; H, 8.21.

A sample of *cis*-nepetic acid[3] (m.p. 130–132°) that had been obtained from the degradation of nepetalactone was converted into dimethyl *cis*-nepetate, which was evaporatively distilled at 60° (0.1 mm.), $n^{25}D$ 1.4476. The infrared spectrum of this optically dimethyl ester (Fig. 1) is indistinguishable from the ester of *dl*-Ia, and unlike the spectrum of any of the isomeric racemic dimethyl esters in Figs. 1 and 2.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 59.82; H, 8.01.

In the usual way Ia was converted to **_cis-trans_-3-methylcyclopentane-1,2-dicarboxylic anhydride (Xa)**, which was evaporatively distilled at 90° (0.2 mm.), $n^{25}D$ 1.4748. Hydrolysis of Xa gave the acid Ia, m.p. 117–118°, without recrystallization.

Anal. Calcd. for $C_3H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.16; H, 6.45.

The infrared spectrum of nepetic anhydride[3] (Fig. 1) is nearly identical with the spectrum of this racemic anhydride Xa (Fig. 1), and very different from the spectrum of the other racemic anhydride Xb (Fig. 1). The nepetic anhydride spectrum has a peak at 8.75 μ which Xa does not show; Xb has a sharp peak at this wave length, and thus it appears that the nepetic anhydride, while containing mainly *cis-trans*-anhydride, is contaminated with some of the *cis-cis*-anhydride.

***trans-trans*-3-Methylcyclopentane-1,2-dicarboxylic Acid (Id).**—Each of the dimethyl esters of the acids Ia–c was subjected to the following treatment: About 100 mg. of ester was refluxed with a solution prepared from 50 mg. of sodium and 2 ml. of anhydrous methanol. After 16 hours, 1 ml. of water was added and refluxing was continued for 0.5 hour. The methanol was allowed to distil away, another ml. of water was added, and the evaporation repeated. The cooled basic solution was washed with ether and then acidified with 6 *N* hydrochloric acid. After continuous extraction with ether overnight, the ether solution was evaporated and the crystalline residue recrystallized from ether–petroleum ether. From each of the esters the same (mixed m.p.) new acid Id, melting in the range 114.5–117°, was obtained after about 5 recrystallizations. The yields of Id from Ia, Ib and Ic, respectively, were 54, 31 and 41%. By further recrystallization from water the melting point of Id was raised to 117–118°, pK_1 5.89, pK_2 9.01.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.04; neut. equiv., 86. Found: C, 55.67; H, 6.87; neut. equiv., 86.

Dimethyl *trans-trans*-3-methylcyclopentane-1,2-dicarboxylate was prepared from Id. This ester was evaporatively distilled for analysis at 60° (0.3 mm.), $n^{25}D$ 1.4453.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 59.83; H, 7.92.

***trans*-Dimethyl nepetate** was prepared by treatment of an ether solution of nepetic acid, m.p. 117–118°, with diazomethane. The ester is a colorless oil, b.p. 54° (0.1 mm.), $n^{25}D$ 1.4453. It is seen from Fig. 2 that the infrared spectrum of this ester is identical with that of the dimethyl ester of Id.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 59.90; H, 8.14.

Each of the four esters of the acids Ia–d was converted to the same equilibrated ester mixture by the following procedure. A 100-mg. sample of the ester was refluxed for 48 hours with a solution prepared from 50 mg. of sodium and 1 ml. of anhydrous methanol. After cooling, 5 ml. of petroleum ether was added, followed by 10 ml. of 5% sodium bicarbonate solution. The layers were separated and the aqueous layer washed once with petroleum ether. The combined organic solutions were dried over magnesium sulfate, filtered, and the solvent evaporated. The residual equilibrated ester was evaporatively distilled at 60° (0.1 mm.), and had $n^{25}D$ 1.4462–1.4463.

A 4.2-g. sample of equilibrated ester, b.p. 70–71° (0.3 mm.), was saponified by boiling for 3 hours with 25 ml. of 10% sodium hydroxide. Recrystallization of the acidic product from ether–petroleum ether and water gave 1.2 g. (33%) of Id, m.p. 117–118°

Ic from Ib.—A 1.00-g. sample of *cis-cis*-acid Ib was converted to the anhydride Xb as described above. The product was evaporatively distilled once, and the distillate rinsed into a sublimation tube with 5 ml. of anhydrous methanol. After refluxing this methanol solution for 2 hours, a solution prepared from 0.5 g. of sodium and 10 ml. of methanol was added and refluxing was continued for half an hour. Water (5 ml.) was added and the reaction mixture refluxed for another half-hour to saponify the half-ester. The methanol was then allowed to distil away and the solution was evaporated repeatedly with water. After cooling and washing with ether, the aqueous solution was acidified with 6 *N* hydrochloric acid and continuously extracted with ether overnight. Evaporation of the ether and five recrystallizations from ether–petroleum ether gave

366 mg. of Ic, m.p. 132–133°. Reworking of the mother liquors increased the yield of Ic to 536 mg. (54%).

Ia from Id.—A mixture of 202 mg. of the *trans-trans*-acid Id, 7 ml. of acetic anhydride and 1 mg. of sodium acetate was refluxed for 16 hours. Then the mixture was slowly fractionated through a 15-inch Podbielniak column until the boiling point rose to 138° (1 hour). The remainder of the acetic anhydride was removed below 70° (10 mm.). The residual oil was transferred to a centrifuge tube, made basic with a saturated solution of barium hydroxide, chilled centrifuged, and decanted. The precipitated barium salt was washed with ether to remove any soluble organic material and then the acid was isolated from the salt in the usual way. The resulting acid crystallized slowly. In one run it was recrystallized from ether–petroleum ether, giving a 4% yield of *cis-trans*-acid Ia, m.p. 110–112°, mixed m.p. with a pure sample of Ia, 111–115°. In another run the crude acid from the precipitated barium salt was converted to its anhydride and the anhydride mixture evaporatively distilled. From a quantitative infrared analysis this anhydride mixture was calculated to contain 63% of the *cis-trans*-anhydride Xa and 37% of the *cis-cis*-anhydride Xb.

3-Methylcyclopentane-1,2-dicarboxylic Acid (I) Prepared by the Procedure of Blomquist, *et al*.—A sample of this sublimed and recrystallized acid (I),[12] m.p. 111–114°, gave no precipitate with barium hydroxide. A second sample was recrystallized seven times from acetonitrile, giving a 2% yield of Ic, m.p. 133–134°, m.p. undepressed by admixture with an authentic sample of Ic. Attempts to isolate Id from the mother liquors were without success.

A third sample was converted to the dimethyl esters, $n^{25}\mathrm{D}$ 1.4468 after two evaporative distillations. Assuming this ester mixture to contain only the esters of Ic and Id, it was calculated from this refractive index to consist of 47% of the former and 53% of the latter ester. By the previously described treatment with sodium methoxide, this ester mixture was converted to the same (refractive index, infrared spectrum) equilibrated ester mixture as had been obtained from the esters of the acids Ia–d.

MADISON 6, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

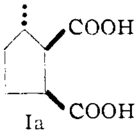
The Configurations of the Nepetalactones and Related Compounds

BY ROBERT B. BATES,[1] E. J. EISENBRAUN[2] AND S. M. McELVAIN

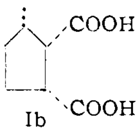
RECEIVED JANUARY 25, 1958

The nepetalactone fraction as obtained from oil of catnip is shown to consist of two stereoisomeric lactones. The predominant one has the *cis-trans* configuration IXa and the one present in lesser amounts has the *trans-cis* configuration IXc. The lactone with the *cis-trans* configuration is shown to be the precursor of the *trans-trans*-nepetonic acid (IId) which yields the *trans-trans*-nepetic acid (Id) on oxidation. From the *trans-cis*-nepetalactone, *trans-cis*-nepetonic acid (IIc) and *trans-cis*-nepetic acid (Ic) have been obtained. These results require revision of the previously assigned configurations of the nepetalinic acids to those shown in Xa–d and of the ant lactones, iridomyrmecin and isoiridomyrmecin, to XIIa and b.

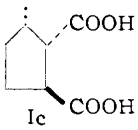
In the previous paper[3] it was shown that the *trans*-nepetic acid obtained from the degradation of nepetalactone *via* nepetalic and nepetonic acids has the *trans-trans* configuration Id rather than the previously assigned[4] *trans-cis* configuration Ic, and that the *cis*-nepetic acid had been correctly assigned[4] the *cis-trans* structure Ia. Although the anhydrides obtained[3] from both *trans*-nepetic acid and *dl-trans-trans*-3-methylcyclopentane-1,2-dicarboxylic acid (Id) were mixtures (infrared spectra) of the anhydrides of the two *cis*-acids, represented as the enantiomers Ia and Ib, only the *cis-trans*-acid Ia could be isolated from these anhydride mixtures.



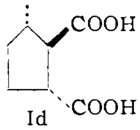
Ia



Ib

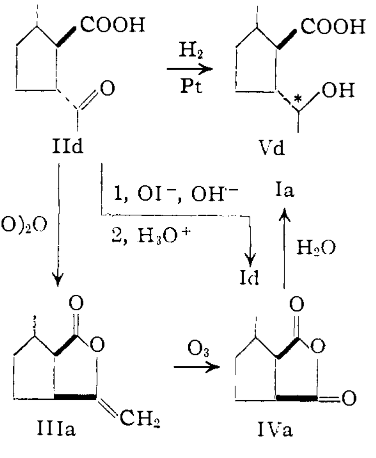


Ic



Id

It appears that nepetonic acid, the immediate precursor of Id, must also have the *trans-trans* configuration IId, instead of the previously assigned[4] *trans-cis*[5] configuration, because it yields Id *via* the haloform reaction and is converted by hydrogenation to a nepetolic acid Vd, m.p. 105°, whose failure to lactonize indicates the *trans* relationship between the functional substituents. Also, the transformation of nepetonic acid to nepetonolactone IIIa, the configuration of which has been established by its conversion *via* the anhydride IVa to *cis*-nepetic acid (Ia), is better explained by the *trans-trans* configuration IId because epimerization at the α-position to the carbonyl function should be more facile than epimerization at the α-position to the carboxyl group, which would be required if nepetonic acid had the *trans-cis* configuration. Consequently, nepetonic acid (IId) and the various compounds that have been prepared from it now are assigned the configurations:



With these configurations established for nepetonic acid and its derivatives, it is apparent that

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[3] R. B. Bates, E. J. Eisenbraun and S. M. McElvain, THIS JOURNAL, **80**, 3413 (1958).

[4] S. M. McElvain and E. J. Eisenbraun, *ibid.*, **77**, 1599 (1955).

[5] In this and all other designations of configurations in this paper the relationship of the functional substituents is given first and that of the methyl group and the adjacent functional substituent second.