[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Cis-Trans Isomers of 6-Methyl-3-cyclohexene-1-carboxylic Acid and Their *sec*-Butyl Esters

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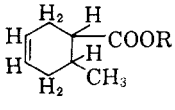
Commercially produced *sec*-butyl 6-methyl-3-cyclohexene-1-carboxylate was less effective as a Mediterranean fruit fly lure than the laboratory-prepared compound. The difference in activity was traced to their *cis-trans* isomer content, the *trans* ester being much superior to the *cis* analog. In the laboratory the intermediate acid, which is prepared by a Diels-Alder condensation and is known to be the *trans* isomer, is converted to the ester *via* the acid chloride route. The *cis* acid was prepared and isolated in pure form for the first time by means of a partition chromatographic procedure, which also proved useful for determining the isomer content of acid mixtures. An isomer analysis of the *sec*-butyl ester depended on infrared spectroscopy. With the aid of the two analytical methods conditions affecting epimerization of the acid, acid chloride, and ester isomers were studied. Thus the acid was not epimerized by refluxing with 6*N* sulfuric acid or 1*N* alkali but epimerization did take place when the acid chloride was heated at 150° or when the ester was saponified. Epimerized solutions contained 50–62% of the *trans* isomer at equilibrium.

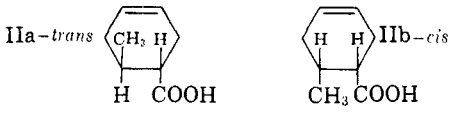
The recent successful eradication of the Mediterranean fruit fly [*Ceratitis capitata* (Wied.)] from Florida depended on traps baited with an attractant to delineate the infested areas. Angelica seed oil,[1] first used as the attractant, was replaced by a synthetic lure, the *sec*-butyl ester of 6-methyl-3-cyclohexene-1-carboxylic acid (Ia),[2] now known as siglure.



Ia. R = $-CH(CH_3)CH_2CH_3$
Ib. R = H

Commercially produced lots of the ester were consistently less attractive than those synthesized in the laboratory. The investigation of this problem shed much light on the chemistry of 6-methyl-3-cyclohexene-1-carboxylic acid (Ib) and its *sec*-butyl ester (Ia). *Cis-trans* isomerism was found to affect the attractiveness of the ester.

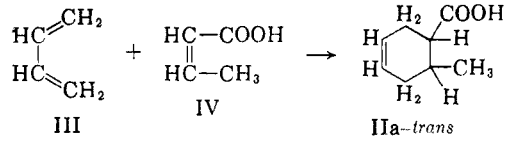
Previous work. Perkin[3] first prepared the free acid (Ib) from 4-hydroxy-*o*-toluic acid by a long, tedious procedure involving fractional esterification and hydrolysis. His final product was a liquid, and he made no attempt to separate the *cis* (IIb) and *trans* (IIa) isomers.



IIa-*trans* IIb-*cis*

Only the *cis* configuration of the double bond is possible in a six-membered ring; the *trans* configuration would give rise to too much strain.[4] This point was confirmed by the absence of a *trans* double-bond peak in the 10.3-μ region of the infrared spectra of the esters and acids of this study. A cyclohexene ring, which is not made rigid by ring fusion, can readily exist in two conformations which closely resemble the boat and chair (or "half-chair") forms.[5] X-ray data indicate that the half-chair form is the favored one and Barton, *et al.*[6] state that this conformation may exist in two interconvertible forms. In view of these investigations it is reasonable to assume that the compounds of this study exist mainly, if not entirely, as the half-chair conformation.

The Diels-Alder reaction provided a far simpler means of preparing the *trans* acid (IIa): Butadiene (III) is heated in a bomb with excess crotonic acid (IV) for 3 hours at 150–170°.[7]



III IV IIa-*trans*

According to the Alder rules,[8] the relative position of the substituents in the dienophile are retained in the adduct. Therefore, the product IIa of the foregoing reaction is *trans* because crotonic acid in *trans*. This fact was confirmed by hydrogenating the acid to the *trans*-2-methylcyclohexanecarboxylic acid, identified by its melting point and that of its amide.[7]

Present Work. Although the *trans* acid has been known for some time, we could find no report on the preparation or isolation of the *cis* isomer (IIb). We were able to isolate this acid by a partition-chromatographic method, which was also useful for the quantitative determination of the isomers.

(1) L. F. Steiner, D. H. Miyashita, and L. D. Christenson, *J. Econ. Entomol.*, **50**, 505 (1957).
(2) S. I. Gertler, L. F. Steiner, W. C. Mitchell, and W. F. Barthel, *J. Agr. Food Chem.*, **6**, 592 (1958).
(3) W. H. Perkin, Jr., *J. Chem. Soc.*, **99**, 741 (1911).
(4) F. Ebel, *Freudenberg's Stereochemie*, Franz Deuticke, Leipzig and Vienna, 1933, p. 650.
(5) M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley & Sons, New York, 1956, p. 38.
(6) D. H. R. Barton, R. C. Cookson, W. Klyne, and C. W. Shopee, *Chem. & Ind. (London)*, 21, (1954), and references therein.
(7) O. Diels and K. Alder, *Ann.*, **470**, 88 (1929).
(8) M. C. Kloetzel, *Org. Reactions*, **4**, 10 (1948).

With slight modifications this method may be generally useful for the separation and determination of other *cis* and *trans* acids.

The pure *cis* acid is a liquid. Its identity was established by hydrogenation of the double bond to the known *cis*-2-methylcyclohexanecarboxylic acid. The melting point (151–153°) of the amide of this saturated acid agreed with that reported in the literature.

In laboratory preparations of the ester the *trans* acid (IIa) was treated with thionyl chloride to give the acid chloride, which was reacted with the alcohol to give the ester. Acid catalytic esterification of the *trans* acid gave low yields of product, probably due to dehydration of the alcohol. At first the acid chloride was prepared under reflux and was reacted with the alcohol without an acid acceptor. By the partition chromatographic method we were able to demonstrate that the *trans* acid was being changed partially to *cis* by this treatment. Thus, hydrolysis of the acid chloride, prepared from the *trans* acid under reflux, gave a product containing only 70% of the *trans* isomer. It was postulated that the acid may isomerize as a result of the hydrogen chloride being liberated in the formation of the acid chloride. Refluxing of the *trans* acid with 6*N* hydrochloric acid gave some substitution of hydrogen chloride onto the double bond of the ring, so that the results were not clear-cut. However, attempts to add dry hydrogen chloride to the *trans* acid directly or in a nonaqueous medium were unsuccessful, and it was noted that hydrogen chloride did not add appreciably to the double bond in the course of the thionyl chloride treatment. The fact that refluxing of the *trans* acid with 6*N* sulfuric acid caused no isomerization shows that heating with acidic reagents *per se* does not account for the conversion.

Additional experiments showed that epimerization of *trans*- and *cis*-rich acid chlorides could be effected thermally; isomerization took place after several hours of heating at 150° and 200° but not at 100°. When the acid chloride was prepared at room temperature, there was no epimerization.[9] In subsequent laboratory preparations of the ester the acid chloride was formed at room temperature and pyridine was included as an acid acceptor. Under these mild conditions little, if any, *cis-trans* isomerization took place.

We attempted to adapt the chromatographic procedure for determining the *cis* and *trans* contents of commercial lots of the ester, but saponification yielded isomerized acids. The free *trans* acid, oddly enough, did not isomerize even after prolonged heating with alkali. The method of Redemann and Lucas,[10] known to saponify refractory esters (*ca.* 125°), was ineffective in the saponification of the ester. Higher temperatures (obtained by refluxing with potassium hydroxide–diethylene glycol) were necessary to effect the conversion.

Other unsuccessful attempts to determine the isomer content of the ester included fractional distillation and gas chromatography.

The difficulty was finally overcome by employing infrared spectroscopy. In carbon disulfide solution the ester gives a *trans* peak at 14.26 μ; the absorbance at 8.79 μ, an isosbestic point, can be subtracted from that at 8.27 μ to give a measure of the *cis* content. Several acid mixtures of known *cis-trans* contents were esterified under mild conditions with *sec*-butyl alcohol and their spectra determined. By setting up calibration curves it was possible to get independent estimates of the two isomers, which generally were in good agreement.

These procedures enabled us to establish the relationship between *cis-trans* content and attractiveness to the Medfly. The all-*trans* product consistently outperformed products of lower *trans* content.[11] Commercial preparations were shown to contain only about 70% of the *trans* isomer, and thus their lesser activity was accounted for.

EXPERIMENTAL

trans-6-Methyl-3-cyclohexene-1-carboxylic acid (IIa). The acid was prepared according to Diels and Alder.[7] It distilled at 132–142°/16 mm. and solidified in colorless crystals. After 3 crystallizations from aqueous methanol, it melted at 64–65° (lit. b.p. 144–145° *in vacuo*, m.p. 68°,[6] b.p. 240°[12]).

The previously unreported amide of IIa was prepared by allowing the acid to stand at room temperature overnight with a slight excess of thionyl chloride in benzene solution and then pouring the product into ice cold ammonia. It melted at 154.5–155.5° after crystallization from benzene-hexane.

Anal. Calcd. for $C_8H_{13}NO$: N, 10.06. Found: N, 9.69.

The p-chlorophenacyl ester of IIa was prepared in the usual manner.[13] It crystallized from ethanol as needles melting at 88–89°.

Anal. Calcd. for $C_{16}H_{17}ClO_3$: C, 65.64; H, 5.81. Found: C, 65.76; H, 6.00.

The p-phenylphenacyl ester of IIa was prepared in the usual manner,[13] m.p. 124–125° after recrystallization from ethanol.

Anal. Calcd. for $C_{22}H_{23}O_3$: C, 79.04; H, 6.59. Found: C, 78.75; H, 6.80.

cis-6-Methyl-3-cyclohexene-1-carboxylic acid (IIb). A commercial semiliquid acid (70% *trans*, 30% *cis*) was used for this preparation. The liquid portion was kept at −15° for several hours and filtered cold. The solid portion was mainly the *trans* isomer; it could be purified by several

(9) This experience parallels that reported by A. K. Macbeth, J. A. Mills, and D. H. Simmonds, *J. Chem. Soc.*, 1011 (1949), in their preparation of the anilide of *cis*-2-methylcyclohexane-1-carboxylic acid. They found that the acid was partially epimerized by refluxing with thionyl chloride but not by the cold reagent.

(10) C. E. Redemann and H. J. Lucas, *Ind. Eng. Chem., Anal. Ed.*, 9, 521 (1937).

(11) L. F. Steiner, W. C. Mitchell, Nathan Green, and M. Beroza, *J. Econ. Entomol.*, 51, 921 (1958).

(12) N. A. Chayanov and P. I. Grishin, *Colloid J. (U.S.S.R.)*, 3, 461 (1937).

(13) R. L. Shriner and R. C. Fuson, *Systematic Identification of Organic Compounds*, 2nd ed., John Wiley and Sons, New York, 1940, p. 132.

crystallizations from petroleum ether. The liquid portion, which was found to contain 69% of the *cis* isomer, deposited no additional crystals even when solvents such as petroleum ether were added.

About 0.7 g. of the *cis*-rich fraction was chromatographed exactly as described later except that a 200-g. column was used. Yield of the *cis* isomer was about 0.5 g. Final purification was effected by distillation; b.p. 104–105°/0.6 mm.; n_D^{25} = 1.4780. The compound would not crystallize even at Dry Ice temperatures.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.92; H, 8.79.

Hydrogenation. Five g. (0.036 mole) of the crude *cis* acid absorbed 744 ml. (0.033 mole) of hydrogen to form *cis*-2-methylcyclohexanecarboxylic acid, also a liquid. Its amide, prepared as described in the next paragraph, deposited from aqueous methanol crystals melting at 151–152.5° (lit. 151–153°).[14] A mixed melting point using equal amounts of the *cis* and *trans* saturated amides was not depressed but fell between the two melting points.

The amide of IIb was prepared in the same manner as the amide of IIa; m.p. 122–124° after recrystallization from benzene-hexane.

Anal. Calcd. for $C_8H_{13}NO$: N, 10.06. Found: N, 9.66.

The p-chlorophenacyl ester of IIb was prepared in the usual manner,[13] m.p. 53.5–54° (ethanol).

Anal. Calcd. for $C_{16}H_{17}ClO_3$: C, 65.64; H, 5.81. Found: C, 65.34; H, 6.11.

The p-phenylphenacyl ester of IIb was prepared in the usual manner,[13] m.p. 90–91° (ethanol).

Anal. Calcd. for $C_{22}H_{23}O_3$: C, 79.04; H, 6.59. Found: C, 78.52; H, 6.50.

Treatment of trans acid (IIa) *with acidic reagents.* Fourteen g. of IIa was refluxed with 10 ml. of thionyl chloride for 2 hr.; water was cautiously added to the cooled mixture. Extraction of the acids with ether in the usual manner yielded a partially solid product which was shown by chromatography to contain 36% of the *cis* isomer.

Refluxing of the *trans* acid with 6*N* sulfuric acid failed to isomerize it. However, refluxing it with 6*N* hydrochloric acid for 4 hr. resulted in partial addition of hydrogen chloride to the double bond to give some 4- (or 5-)chloro-2-methylcyclohexanecarboxylic acid. The impure product distilled at 106–111°/0.4 mm. and melted at 50–65°.

Treatment of trans acid (IIa) *and ester with alkali.* Ten g. of the *trans* acid was refluxed with 100 ml. of an 8% solution of potassium hydroxide in diethylene glycol for 7 hr. After dilution with 10 volumes of water, the mixture was extracted several times with ether. The aqueous layer was acidified with 6*N* hydrochloric acid while the mixture was kept cool. Ether was added, and the organic layer was washed with water and saturated brine and then filtered through dry cotton. Evaporation of the ether and distillation of the residue (86°/0.7 mm.) gave a product which solidified immediately. The melting point, 62–64°, was undepressed in admixture with a sample of the untreated acid; practically no isomerization had occurred.

In another experiment 2.0 g. of the all-*trans* ester was saponified by refluxing for 2 hr. with 20 ml. of 1*N* potassium hydroxide in diethylene glycol. The mixture was worked up as outlined immediately above; the acid product distilled at 140°/4 mm. The isomer analysis (by partition chromatography) was 41% *cis* and 59% *trans*. A similar saponification of a 69% *cis*–31% *trans* ester gave an acid containing 55% *cis* and 45% *trans* isomers. In both cases epimerization had occurred upon saponification.

Thermal isomerization of acid chlorides. Although the isomers of 6-methyl-3-cyclohexene-1-carboxylic acid appear to be resistant to isomerization, their acid chlorides were readily epimerized by heating at 150–200°. Acid chlorides were prepared under mild conditions that avoid isomerization as described in the next section from acids of known *cis-trans* content, the excess thionyl chloride and benzene being evaporated as indicated. The undistilled acid chlorides were then heated with no solvent, as shown below, and the converted to their *sec*-butyl esters in order to analyze them for isomer content by the infrared method.

Temperature, °C.	Duration of Heating, Hr.	Isomer Content, % Untreated Acid Chloride *cis*	Untreated Acid Chloride *trans*	Treated Acid Chloride *cis*	Treated Acid Chloride *trans*
200	2.5	0	100	50	50
150	0.5	0	100	32	68
	1	0	100	36	64
	2	0	100	38	62
	0.5	66	34	47	53
	1	66	34	38	62
	2	66	34	38	62
100	1	0	100	0	100
	2	0	100	1	99

A sample of all-*trans* acid chloride that was refluxed for 2 hr. with 2 volumes of benzene was not isomerized.

Preparation of esters to avoid isomerization. The following procedure was sufficiently mild so that isomerization was avoided. To a solution of 420 mg. of *cis* acid (IIb) in 4 ml. of benzene was added 725 mg. (100% excess) of thionyl chloride, the temperature being kept below 28°. After the mixture had stood overnight at room temperature, the excess thionyl chloride and solvent were evaporated off below 50° at reduced pressure. To the cold product 500 mg. of pyridine mixed with an excess of *sec*-butyl alcohol was slowly added without allowing the temperature to rise above 30°. After the mixture had stood for 16 hr., it was taken up in ether, washed successively with water, dilute hydrochloric acid, sodium bicarbonate, and brine, and dried over sodium sulfate. After the solvent was removed, the product distilled at 112°/16 mm.; n_D^{25} 1.4518.[15]

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.45; H, 9.85.

Partition chromatography of cis and trans acids. The immobile solvent was a solution of 1.5 g. of ethylenediamine and 50 mg. of bromthymol blue in 100 ml. of anhydrous methanol. The mobile solvent was prepared by equilibrating 1 l. of petroleum ether (b.p. 60–70°) with 25 ml. of 95% methanol. After the lower layer was rejected, the solvent was filtered through a cotton plug.

The column was prepared by mixing in a mortar 10 g. of silicic acid (Mallinckrodt's 100-mesh partition chromatographic grade dried overnight at 110°) with 11.5 ml. of immobile solvent to form a uniform free-flowing slurry; the latter was introduced into a glass column (400 mm. long, 21 mm. i.d.) fitted with a fritted disk at the bottom; the adsorbent was settled by tapping and applying gentle air pressure on the solvent in the usual manner. From 40 to 50 mg. of the acid sample was introduced in 1 ml. of the mobile solvent and washed into the adsorbent with three 1-ml. portions of solvent. The tube was then filled with solvent using a 250-ml. separatory funnel as a reservoir. The acids were visible on the column as yellow zones on a blue background. Twenty-five-ml. fractions were titrated with standardized 0.03*N* sodium ethoxide solution in ethanol. Titrations were conducted at the boiling point of the liquid after addition of 5 ml. of neutralized isopropanol containing a few drops of bromothymol blue solution in methanol. The *cis* acid is eluted between 150 and 290 ml. and the *trans* analog between 290 and 750 ml.

The foregoing procedure was set up for the quantitative determination of the acid isomers. For preparative purposes larger columns were employed.

(14) N. Zelinsky, *Ber.*, 41, 2676 (1908).

(15) Constants of the corresponding *trans* ester have been reported by Gertler *et al.*[2] to be 113–114°/15 mm., n_D^{25} = 1.4482.

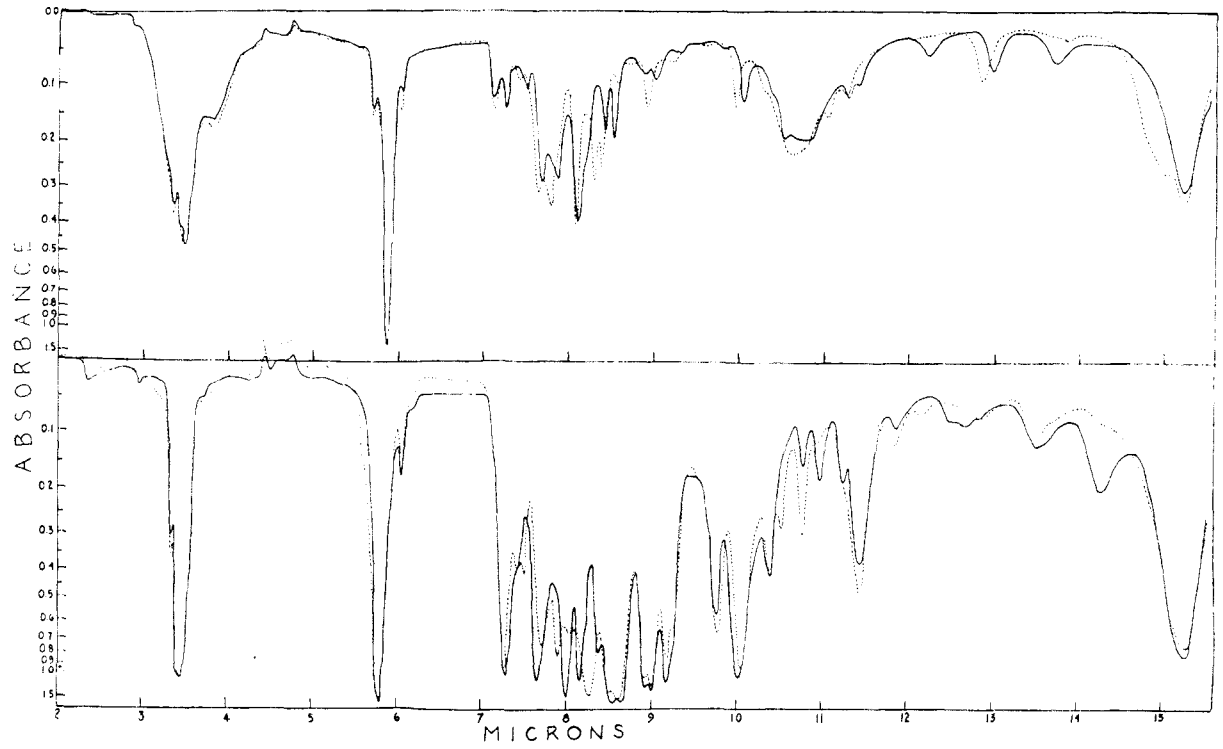


Fig. 1. Infrared spectra of 6-methyl-3-cyclohexene-1-carboxylic acid isomers (upper spectra) 10 mg./ml., and their *sec*-butyl esters (lower spectra) 50 mg./ml. in carbon disulfide. *Trans* isomers solid line, *cis* isomers broken line

Determination of cis-trans content of the sec-butyl esters by infrared spectroscopy. The infrared spectra of the acids and their *sec*-butyl esters are shown in Fig. 1. Two regions of the ester spectra exhibited absorbance differences that were adapted for analytical purposes. A *trans* peak appearing at 14.27 μ was measured by subtracting a background correction at 14.0 and 14.6 μ. A measure of *cis* absorption was obtained by subtracting the absorbance at 8.79 μ (an isosbestic point) from that at 8.27 μ. Several ester mixtures of known isomer content were prepared by careful esterification of known mixtures of the acid isomers and their spectra determined in the 2 regions. Although the absorbances did not follow Beer's law, this ideal was approached. Calibration curves made it possible to estimate isomer content, and in general the results obtained by the foregoing 2 procedures, which gave independent measures of *cis* and *trans* content, agreed within a few per cent.

Acknowledgment. The suggestion that *cis-trans* isomerism may affect the attractive properties of the ester was made by H. L. Haller, Agricultural Research Service, U. S. Department of Agriculture. We also acknowledge the assistance received from S. A. Hall, S. I. Gertler, W. F. Barthel, and B. H. Alexander of the Entomology Research Division during various phases of this problem. David Henley, student trainee, performed most of the chromatographic analyses reported here.

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Derivatives of Piperazine. XXXIV. Some Reactions of Trimethylene Chlorobromide with 1-Arylpiperazines

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The variety of pharmacological activities shown by piperazine derivatives led to the syntheses of 38 new compounds by the reactions of trimethylene chlorobromide with various 1-arylpiperazines and other amines. The 1-arylpiperazines required for these syntheses were prepared by the method of Pollard *et al.*[1,2]

The compounds in Table I were prepared by the reaction of equimolar quantities of trimethylene

(1) C. B. Pollard and L. G. MacDowell, *J. Am. Chem. Soc.*, **56**, 2199 (1934).

(2) C. B. Pollard and T. H. Wicker, Jr., *J. Am. Chem. Soc.*, **76**, 1853 (1954).