Structure of the Four Isomers of the Insect Attractant Trimedlure[1]

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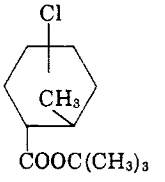
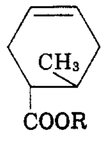
Received November 11, 1965

Trimedlure, *t*-butyl 4- (or 5-) chloro-2-methylcyclohexanecarboxylate, a powerful attractant for the Mediterranean fruit fly [*Ceratitis capitata* (Wiedemann)], is used to detect incipient infestations of this injurious insect. Commercial trimedlure consists mainly of four isomers in which the methyl group is *trans* to the ester group. The four isomers were separated by crystallization and preparative gas chromatography and their structures determined by chemical and spectral analyses. One of the isomers is practically unattractive to the Mediterranean fruit fly; the others are attractive with one being highly active and long lasting.

Chemical insect attractants are playing an increasingly important role in the detection, control, and eradication of economically important insect species.[2a-d] One such attractant in current use is trimedlure, *t*-butyl 2-methyl-4- (or 5-) chlorocyclohexanecarboxylate (I), a powerful lure for the Mediterranean fruit fly [*C. capitata* (Wiedemann)] or medfly. The attractant is synthesized by adding hydrogen chloride to the double bond of *trans*-6-methyl-3-cyclohexenecarboxylic acid (IIa) and condensing the product with isobutylene to form the *t*-butyl ester of the acid.[3] Although eight isomers are possible, the commercial product consists mainly of the four isomers that have the methyl and ester substituents on the ring in a *trans* configuration. These four "*trans*" isomers of trimedlure have been separated by gas-liquid partition chromatography[4] (glpc).


I


IIa, R = H
b, R = $CH(CH_3)CH_2CH_3$

The *trans* isomer of siglure IIb, which was used as an attractant for the medfly prior to the discovery of trimedlure, is more active than its *cis* counterpart.[5] As in many biological systems certain stereochemical configurations are superior to others in activity. Accordingly, the relationship between the four *trans* trimedlure isomers and attractiveness to the medfly was investigated. The investigation was further spurred by the finding that one of the trimedlure isomers is almost completely unattractive.[6] Keeping the amount of the unattractive isomer at a minimum is, therefore, of practical interest.

Separation of Isomers.—The first stage of the investigation required separation of the isomers, which were designated A, B_1, B_2, and C, according to their order of elution from the gas chromatographic column. At room temperature A and B_1 are liquids; B_2 and C, solids. The solids were separated in pure form from the commercial mixture by cooling and repeated crystallization, the liquids by preparative gas chromatography. An approximate analysis of a typical trimedlure mixture is 35% A, 15% B_1 and B_2, and 50% C. Isomer B_1, comprising about 5% of the mixture, was the most difficult to obtain in sufficient amount. By rechromatographing a center cut of the B_1 fraction several times, it was obtained in 90–95% purity, but in extremely poor yield. Subsequently an improved procedure was devised, based on the finding that isomers A and C could be removed completely from the original mixture by chemical means. Isomer B_2, the major contaminant, was then partly removed by crystallization from the cooled residual mixture, and a sufficient amount of pure B_1 was obtained by gas chromatographing the product.

Structural Analysis.—Chart I summarizes the reaction scheme proposed for locating the position of the chlorine atom. The isomers were to be dehydrohalogenated with alkali to cyclohexene acids or esters, and the corresponding unsaturated acids oxidized to known di- or tricarboxylic acids. An important consideration in the reactivity of the isomers is the axial or equatorial configuration of the substituents on the cyclohexane ring of the molecule.

For an ionic E2 elimination reaction to occur the four centers involved should be in a planar *trans* state.[7] In a cyclohexane derivative this state can only be found when the substituents are situated in a *trans*-diaxial configuration. This criterion would be met by all four isomers if the normal interconversion of the chair form of the cyclohexane ring were allowed. Thus, a chlorine atom located preferentially in an equatorial position unfavorable for E2 elimination could, by ring interconversion, assume the axial position favorable for such elimination. In the trimedlure isomers, which are trisubstituted cyclohexanes, the bulky *t*-butyl ester and methyl groups, being *trans* and vicinal to each other,[3] can be expected to occupy the lower energy diequatorial position.[8,9] With this conformation two isomers have an equatorial and two an axial chlorine atom. Ring interconversion of a trimedlure isomer with an equatorial chlorine atom would require the flipping of all three equatorial substituents to the axial conformation,

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(1) Presented in part at the 150th National Meeting of the American Chemical Society, Abstracts, Atlantic City, N. J., Sept 1965, p 18x.

(2) (a) S. A. Hall, N. Green, and M. Beroza, *J. Agr. Food Chem.*, **5**, 663 (1957); (b) M. Beroza, *Soap Chem. Specialties*, **36**, 74 (1960); (c) W. L. Popham and D. G. Hall, *Ann. Rev. Entomol.*, **3**, 335 (1958); (d) L. F. Steiner, *J. Econ. Entomol.*, **50**, 508 (1957).

(3) M. Beroza, N. Green, S. I. Gertler, L. F. Steiner, and D. H. Miyashita, *J. Agr. Food Chem.*, **9**, 361 (1961).

(4) M. Beroza and R. Sarmiento, *J. Assoc. Offic. Agr. Chemists*, **47**, 838 (1964).

(5) N. Green and M. Beroza, *J. Org. Chem.*, **24**, 761 (1959).

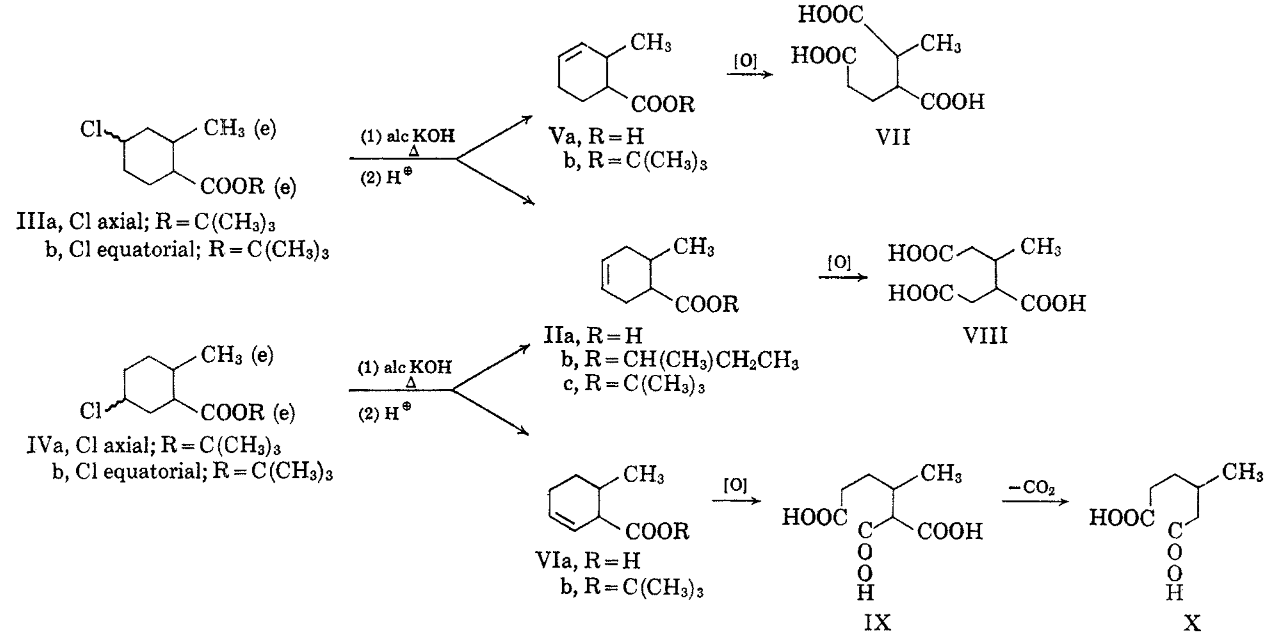
(6) L. F. Steiner, private communication.

(7) (a) E. D. Hughes, C. K. Ingold, and J. B. Rose, *J. Chem. Soc.*, 3839 (1953); (b) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 484.

(8) (a) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956); (b) W. Klyne, "Progress in Stereochemistry," Vol. 1, W. Klyne, Ed., Academic Press Inc., New York, N. Y., 1954, p 36.

(9) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 204.

CHART I



which would be sterically very unfavorable.[8,10] This ring interconversion should occur only with difficulty because the energy barrier will be high. It follows then that the two isomers with an axial chlorine will eliminate hydrogen chloride much more readily than the two with an equatorial chlorine. When the four trimedlure isomers (IIIa, b and IVa, b) were refluxed (*ca.* 80°) with alcoholic potassium hydroxide, isomers A and C eliminated hydrogen chloride readily; B_1 and B_2 did not. These results, in agreement with the foregoing reasoning, indicate that the energy barrier for interconversion is high and that under normal conditions isomers B_1 and B_2 exist as conformationally pure isomers. Only by treatment with alkali at much higher temperatures (140–150°) could isomers B_1 and B_2 be induced to eliminate hydrogen chloride. This higher temperature may facilitate ring interconversion or elimination may occur via another mechanism.

Nuclear magnetic resonance and infrared spectral analyses provided additional support for the proposed configuration of the chlorine atom (Table I). The proton α to the chlorine atom in isomers B_1 and B_2 exhibited a multiplet in the nmr spectra at higher frequencies than that observed for A and C. This relationship of chemical shifts is characteristic of absorptions due to an axial and an equatorial proton.[11]

TABLE I

NMR AND INFRARED ABSORPTIONS

Isomer	H–C–Cl, δ (ppm)[a]	Indicated proton configuration	–C–Cl, cm^{-1}	Indicated chlorine configuration
A	4.45	H equatorial	692	Cl axial
B_1	3.73	H axial	748	Cl equatorial
B_2	3.80	H axial	741	Cl equatorial
C	4.40	H equatorial	684	Cl axial

[a] Multiplets equivalent to one proton.

These chemical shifts also agree very closely with those reported for an axial and equatorial proton α to the chlorine atom in chlorocyclohexane.[12] The equatorial proton absorbs at 4.44 ppm; the axial proton absorbs at 3.79 ppm. Isomers B_1 and B_2 have a C–Cl stretching band in the infrared at higher frequencies than do isomers A and C, which is characteristic of an equatorial chlorine. An equatorial C–Cl absorption is reported to occur in the 742-cm^{-1} region, and an axial C–Cl absorption in the 688-cm^{-1} region.[13]

Inasmuch as the three parameters—chemical elimination, nmr, and the infrared spectra of the isomers—agree as to the axial and equatorial configuration of the chlorine atom, the assignment of complete or almost complete conformational rigidity to the trimedlure isomers at room temperature appeared to be justified. The question as to the position (4 or 5) of the chlorine atom in each isomer remained to be determined.

Each of the four isomers, when subjected to the dehydrohalogenation reaction, yielded four esters, which were separated by preparative gas chromatography. The glpc retention times of the four *t*-butyl esters obtained from isomer A were identical with those obtained from isomer B_1; the retention times of the four esters obtained from isomer B_2 corresponded with those obtained from isomer C (Table II). The esters with the same retention times that were obtained from different isomers were shown to be identical by comparing their infrared spectra. A and B_1 can be paired as isomers with the chlorine on one of the carbon atoms; B_2 and C can be similarly paired with the chlorine on the other carbon atom.

All four isomers yielded two esters in common. Esters 2 and 6 (Table II) were identified as *trans* IIc and esters 3 and 7 as *cis* IIc (Chart I). The infrared

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[10] (a) O. Hassel, *Quart. Rev.* (London), **7**, 221 (1953); (b) W. G. Dauben and K. S. Pitzer, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 13.

[11] (a) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p 116; (b) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 390.

[12] L. W. Reeves and K. O. Strømme, *Can. J. Chem.*, **38**, 1241 (1960).

[13] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p 331.

TABLE II

DEHYDROHALOGENATION REACTION PRODUCTS FROM TRIMEDLURE ISOMERS

Ester products	Structure	% of the total ester yielded from trimedlure isomers at °C indicated[a] A 80	A 150	B$_1$ 150	B$_2$ 150	C 80	C 150	n^{25}_D	Typical glpc retention times, min
1	XIIb	4	40	3	0	0	0	1.4498	21
2 or 6	*trans* IIc	68	30	40	23	55	32	1.4444	29
3 or 7	*cis* IIc	11	16	15	10	13	33	1.4512	32
4	XIb	17	14	42	0	0	0	1.4629	45.5
5	*trans* Vb	0	0	0	57	28	28	1.4432	26
8	*cis* Vb	0	0	0	10	4	7	1.4562	35.5

[a] Percent calculated from the peak height of the reesterified reaction product on glpc.

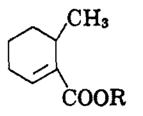
spectra and glpc retention times of these esters are identical with those of *cis* and *trans* IIc prepared by an alternate method. The index of refraction of esters 2 and 3 follows the von Auwers-Skita or "conformational rule,"[14] which states that among alicyclic epimers not differing appreciably in dipole moment the isomer of highest enthalpy has the higher density and index of refraction.[15] The *cis*-1,2-disubstituted isomer is considered the epimer of highest enthalpy. The *cis*- and *trans*-1,2-disubstituted cyclohexanes (ea and ee conformations) have, to a first approximation, the same angles between substituents and should not differ in dipole moment.[14] Comparison of models of the 1,2-disubstituted cyclohexenes described here also showed little change in angle between the *cis-trans* isomers. Additional confirmatory evidence was obtained by oxidizing ester 6 to VIII.

Some epimerization occurred during the elimination reaction, which is to be expected since saponification also occurs. This finding is consistent with a previous one[5] in which siglure epimerized when it was treated with alkali. To demonstrate that epimerization does occur, pure *trans* IIc was treated with alkali under the two conditions used for elimination; in each case the compound produced a 45:55 *cis-trans* mixture of IIc. With epimerization occurring, each trimedlure isomer should yield four unsaturated esters.

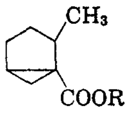
Esters 5 and 8 were shown to be *cis-trans* isomers by isomerizing ester 5 to a 90:10 mixture of esters 5 and 8. Ester 5, with absorption of two olefinic protons in its nmr spectrum, could be *cis* or *trans* Vb or VIb. It was concluded that the ester was the *trans* isomer by observations that were analogous with those from the known *cis-trans* IIc. The index of refraction of ester 5 is lower than that of ester 8, a characteristic of a *trans*-1,2-disubstituted cyclohexane;[14] ester 5 formed a much larger percentage of the elimination product and was also epimerized in low yield to ester 8. That ester 5 is *trans* Vb was determined by oxidizing its acid to the tricarboxylic acid VII. Accordingly, ester 8 is its *cis* analog.

Esters 1 and 4, obtained from the dehydrohalogenation of isomers A and B$_1$, did not appear to be simple *cis-trans* isomers of the expected structure VIb. The glpc retention times were markedly different, and the spectral data did not support structure VIb.

Ester 4 was identified as XIb. The infrared, nmr, and ultraviolet spectra were consistent with the presence of an α,β-unsaturated carbonyl group. Nmr showed only one proton on the double bond. The only absorption in the ultraviolet region of the acid of ester 4 appeared at 214 mμ.[16] Additional evidence was obtained by oxidizing the acid to α-methyladipic acid, which was identified as its methyl ester.

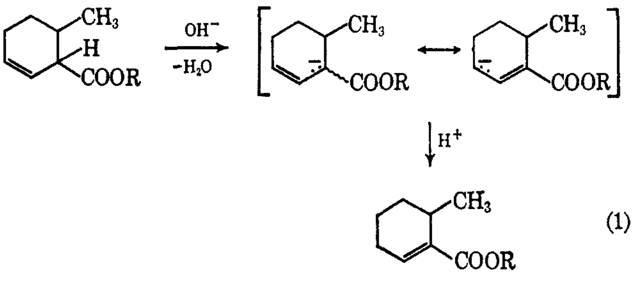


XIa, R = H
XIb, R = C(CH$_3$)$_3$



XIIa, R = H
XIIb, R = C(CH$_3$)$_3$

Double-bond rearrangement in an alkaline medium has been observed several times. The process, described as a base-catalyzed prototropic rearrangement,[17] is initiated by a nucleophilic attack and removal of an allylic proton. The isomer is obtained through resonance and proton recovery, as illustrated in eq 1.



(1)

XIb, R = C(CH$_3$)$_3$

Double-bond migration into α,β-conjugation from positions further removed than β,γ is possible, but conditions more drastic than those used in this study are usually required, *e.g.*, alkali fusion or higher temperatures.[17] To show that the double bond of esters II and V (Chart I) does not rearrange under the reaction conditions employed, each ester was refluxed in alcoholic potassium hydroxide. No double-bond rearrangement took place. Only the *cis-trans* epimerized mixture was recovered.

Our evidence, especially the spectra data, indicates that ester 1 is XIIb, which could be formed by an intramolecular anionic displacement[18] as shown in eq 2.

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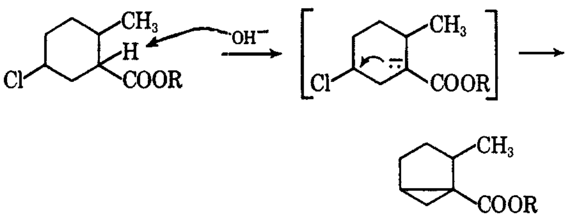
[14] N. L. Allinger, *J. Am. Chem. Soc.*, **79**, 3443 (1957).

[15] E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 216.

[16] H. H. Jaffé and M. Orchin, "Theory and Application of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p 212.

[17] (a) T. L. Jacobs and S. Singer, *J. Org. Chem.*, **17**, 475 (1952); T. L. Jacobs, R. Akawie, and R. G. Cooper, *J. Am. Chem. Soc.*, **73**, 1273 (1951); (b) J. W. Cornforth and G. Popják, *Biochem. J.*, **58**, 403 (1954).

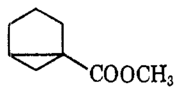
[18] (a) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 1786 (1952); (b) R. H. Eastman and A. Oken, *J. Am. Chem. Soc.*, **75**, 1029 (1953); (c) L. E. Smith and R. M. Scribner, *ibid.*, **78**, 3412 (1956); (d) N. A. Nelson and G. A. Mortimer, *J. Org. Chem.*, **22**, 1146 (1957).



(2)

XIIb, R = C(CH$_3$)

The nmr spectrum contains a multiplet centered at δ 0.70, characteristic of the cyclopropyl protons of a bicyclic structure.[19] Absorption associated with olefinic protons is missing. The methyl group absorption is split into a doublet (δ 1.04) eliminating the possibility of a double bond being positioned between the methyl and ester groups. The carbonyl absorption frequency in the infrared, compared with that of IIc and Vb, is shifted to a lower frequency by 10 cm^{-1} and is, therefore, in agreement with the α,β-conjugated character of such a system. A comparison of the infrared and nmr spectra of XIIb and a closely related known compound, methyl bicyclo[3.1.0]hexane-1-carboxylate (XIII), prepared as described by Nelson and Mortimer,[18d] provided additional support for structure XIIb. Infrared absorption bands characteristic of the cyclopropyl group are at 3080, 3030, 3000, and 1030 cm^{-1}.[19,20] All of these bands were found in the infrared spectra of XIIb and XIII, and each was present in roughly the same intensity. The nmr spectrum of XIII contained a complex multiplet at δ 0.75 with an absorption envelope of the same shape as the multiplet at δ 0.70 in the spectrum of XIIb.



XIII

These data are consistent with the assignment of the chlorine atom to the 5 position of isomer A (IVa) and B$_1$ (IVb).

On the basis of the foregoing studies we concluded that the isomers have the structures given in Table III and shown in Figure 1. Isomers B$_1$ and B$_2$ are believed to be "fixed" molecules in the conformation indicated; isomers A and C are thought to exist predominantly, if not exclusively, in their indicated conformation.

Table III

Trimedlure Isomer Structures

Isomer	Substituents	Relation COOR-CH$_3$	Relation COOR-Cl	Structure
A	1,2,5	1,2 *trans* (e,e)	1,5 *trans* (e,a)	IVa
B$_1$	1,2,5	1,2 *trans* (e,e)	1,5 *cis* (e,e)	IVb
B$_2$	1,2,4	1,2 *trans* (e,e)	1,4 *trans* (e,e)	IIIb
C	1,2,4	1,2 *trans* (e,e)	1,4 *cis* (e,a)	IIIa

It is interesting to correlate the assigned structures with attractiveness to the medfly.[6] In each case the isomer with the equatorial chlorine was less active than its axial congener. Isomer B$_2$ was essentially inactive; isomer C was highly active. Isomer A was 1.5 times as active as B$_1$. The biological data will be reported elsewhere.

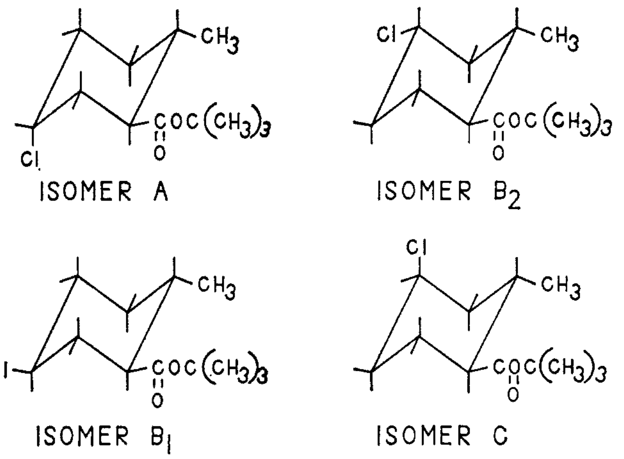


Figure 1.—Isomers of trimedlure.

Experimental Section

Melting points were determined on a calibrated Thomas–Hoover capillary melting point apparatus. Infrared data were obtained either on a Perkin-Elmer Model 21 or a Model 521 grating spectrophotometer. The ultraviolet data were obtained on a Beckman DU Spectrophotometer. Nmr spectra were obtained on a Varian A-60 instrument with tetramethylsilane as an internal reference. Glpc data were obtained on an F and M Scientific Corp. Model 609 flame ionization gas chromatograph, and separations were made using Aerograph Autoprep Model A-700, Wilkins Instrument Co. Analyses were made on a 15 ft × 3/16 in. column containing 7% RC Polymeric BGA (Polyadipate, mol wt *ca.* 2500, Rubber Corp. of America, Hicksville, N. Y.) on 60–80 mesh Gas Chrom P (Applied Science Lab., State College, Pa.) with nitrogen as the carrier gas. Preparative separations were made on a 15 ft × 5/16 in. column containing 15% RC Polymeric BGA on 60–80 mesh Gas Chrom P with helium as the carrier gas. Elemental analyses were made by Galbraith Laboratories, Inc., Knoxville, Tenn.

Typical Elimination Reaction at 80°.—A mixture of 500 mg of isomer A and 2.6 ml of 25% methanolic potassium hydroxide was heated under reflux for 17 hr. The precipitated potassium chloride was filtered off from the cooled solution, and the filter cake was washed with warm methanol. Most of the methanol from the combined washings and filtrate was removed *in vacuo*. Water was added to the residue, and the solution was extracted with two 25-ml portions of ether; the ether contained a small amount of ester and was discarded. The alkaline layer was strongly acidified with dilute sulfuric acid and then extracted with three 25-ml portions of ether. The ether layer was dried (magnesium sulfate) and the product obtained on evaporation of the solvent.

Typical Elimination Reaction at 150°.—Reaction and work-up were the same as described for the 80° elimination except that the reactants were heated in a sealed pressure bottle placed in a sand bath at 150°.

Esterification.—The *t*-butyl esters from the acid products of the foregoing hydrogen chloride eliminations and of other acids in this study were made according to the general directions of Rabjohn[21] by reacting isobutylene with the free acid. A 5:1 excess of isobutylene over acid afforded an 80–85% yield of ester.

***t*-Butyl 2-Methyl-4-chlorocyclohexanecarboxylate (IIIa).**—Isomer C, IIIa, was obtained in pure form from both the preparative gas chromatography and from the commercial trimedlure mixture by freezing and seeding the mixture with pure isomer. Crystallization from ethanol produced colorless rods that melted at 57–58°. The infrared spectrum (potassium bromide pellet) contained absorption bands at 1720 (C=O), 1150 (C–O), and 684 (axial C–Cl) cm^{-1}; nmr spectrum: a doublet equivalent to the three protons of the ring methyl group (δ 0.90), a singlet equivalent to the nine protons of the *t*-butyl group (δ 1.43), and a multiplet equivalent to one proton (δ 4.40); the remaining eight

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[19] P. K. Freeman, M. F. Grostic, and F. A. Raymond, *J. Org. Chem.*, **30**, 771 (1965).

[20] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, Chap 2.

[21] N. Rabjohn, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 261.

cyclohexyl protons formed a complex pattern (δ 1.55–2.60). The nmr spectrum was consistent with structure IIIa.

Anal. Calcd for $C_{12}H_{21}ClO_2$: C, 61.92; H, 9.10; Cl, 15.24. Found: C, 61.74; H, 91.5; Cl, 15.04.

_t_-Butyl 2-Methyl-4-chlorocyclohexanecarboxylate (IIIb).—Isomer B_2, IIIb, was obtained in pure form as described for IIIa and was crystallized from ethanol as colorless needles that melted at 71–72°. Its infrared spectrum (potassium bromide pellet) contained absorption bands at 1718 (C=O), 1150 (C-O), and 741 (equatorial C-Cl) cm^{-1}; nmr spectrum: a doublet equivalent to the three protons of the ring methyl group (δ 0.93), a singlet equivalent to the nine protons of the *t*-butyl group (δ 1.42), and a multiplet equivalent to one proton (δ 3.80); the remaining eight cyclohexyl protons formed a complex pattern (δ 1.50–2.50). The nmr spectrum was consistent with structure IIIb.

Anal. Calcd for $C_{12}H_{21}ClO_2$: C, 61.92; H, 9.10; Cl, 15.24. Found: C, 61.76; H, 9.01; Cl, 15.17.

_t_-Butyl 2-Methyl-5-chlorocyclohexanecarboxylate (IVa).—Isomer A, IVa, was obtained in pure form by preparative gas chromatography. The infrared spectrum (neat) contained absorption bands at 1720 (C=O), 1142 (C-O), and 693 (axial C-Cl) cm^{-1}; nmr spectrum: a doublet equivalent to the three protons of the ring methyl group (δ 0.95), a singlet equivalent to the nine protons of the *t*-butyl group (δ 1.43), and a multiplet equivalent to one proton (δ 4.45); the remaining eight cyclohexyl protons formed a complex pattern (δ 1.50–2.50). The nmr spectrum was consistent with structure IVa. The refractive index of IVa was $n^{25}D$ 1.4579.

Anal. Calcd for $C_{12}H_{21}ClO_2$: C, 61.92; H, 9.10; Cl, 15.24. Found: C, 62.21; H, 9.03; Cl, 15.24.

_t_-Butyl 2-Methyl-5-chlorocyclohexanecarboxylate (IVb).—The commercial trimedlure mixture was subjected to the dehydrohalogenation reaction at 80° and the free acid esterified (isobutylene).[21] After distilling off the lower boiling dehydrohalogenated esters, the remaining mixture of IIIb and IVb was dissolved in a small amount of pentane and cooled to −40°; if IIIb did not crystallize out, the solution was seeded with the isomer. Filtration of the cold solution removed a large portion of IIIb. Evaporation of the solvent from the filtrate gave a product from which IVb was isolated in pure form by gas chromatography. The infrared spectrum (neat) contained absorption bands at 1720 (C=O), 1143 (C-O), and 749 (equatorial C-Cl) cm^{-1}; nmr spectrum: a doublet equivalent to the three protons of the ring methyl group (δ 0.88), a singlet equivalent to the nine protons of the *t*-butyl group (δ 1.43), and a multiplet equivalent to one proton (δ 3.73); the remaining eight cyclohexyl protons formed a complex pattern (δ 1.50–2.60). The nmr spectrum was consistent with structure IVb. The refractive index of IVb was $n^{25}D$ 1.4576.

Anal. Calcd for $C_{12}H_{21}ClO_2$: C, 61.92; H, 9.10; Cl, 15.24. Found: C, 61.99; H, 9.07; Cl, 15.25.

_t_-Butyl _trans_-6-Methyl-3-cyclohexenecarboxylate (_trans_ IIc).—Esters 2 and 6 were shown to be identical with each other and with an independently prepared sample of *t*-butyl *trans*-6-methyl-3-cyclohexenecarboxylate[22] by comparing their infrared spectra. The spectra contained absorption bands at 1719 (C=O), 1650 w (C=C), 1140 (C-O), and 660 (H-C=C-H) cm^{-1}; nmr spectrum: two olefinic protons (δ 5.61), a multiplet due to the three protons of the ring methyl group (δ 0.97), and a singlet equivalent to the nine protons of the *t*-butyl group (δ 1.44); the six remaining cyclohexyl protons formed a complex pattern (δ 1.70–2.50). Additional confirmatory evidence was obtained by saponifying the ester and oxidizing the free acid (*trans*-IIa) to VIII. The refractive index of *trans* IIc was $n^{25}D$ 1.4444 (lit.[22] 1.4445).

_t_-Butyl _cis_-6-Methyl-3-cyclohexenecarboxylate (_cis_ IIc).—The infrared spectra of esters 3 and 7 were identical with each other as well as with the spectrum of *t*-butyl *cis*-6-methyl-3-cyclohexenecarboxylate synthesized by the author as will be described. The infrared spectra (neat) contained absorption bands at 1720 (C=O), 1650 vw (C=C), 1144 (C-O), and 654 (HC=CH) cm^{-1}; nmr spectrum: two olefinic protons (δ 5.56), a doublet equivalent to the three protons of the ring methyl group (δ 0.88), and a singlet equivalent to the nine protons of the *t*-butyl group (δ 1.42); the six remaining cyclohexyl protons formed a complex pattern (δ 1.60–2.60). The refractive index of *cis* IIc was $n^{25}D$ 1.4512. Pure *trans* IIc was epimerized to a 45:55 *cis–trans* IIc mixture.

Synthesis of _t_-Butyl _cis_-6-Methyl-3-cyclohexenecarboxylate.—*cis* IIc was prepared by a separate procedure for comparison with the ester obtained *via* the dehydrohalogenation reaction. A 66:34 *cis–trans* mixture of 6-methyl-3-cyclohexenecarboxylic acid (10.5 g) (prepared in an earlier study)[5] was esterified in the usual manner (isobutylene).[21] The fraction that boiled at 100–101° (18 mm) was collected (11.8 g). The product consisted of a 64:36 *cis–trans* ester mixture (glpc analysis: flow rate, 30 ml/min, temperature 132°, helium carrier gas). The *cis* ester was obtained in pure form by preparative gas chromatography. The refractive index was $n^{25}D$ 1.4513. The infrared and nmr spectra were identical with those described for *cis* IIc.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.42; H, 10.27. Found: C, 73.31; H, 10.15.

Epimerization of _trans_ IIc.—A 1-g sample of pure *trans* IIc was heated with 10 g of 25% methanolic potassium hydroxide in a sealed pressure bottle for 16 hr at 150°. The work-up and esterification were the same as those described for the 150° dehydrohalogenation reaction. The over-all yield was 60%. glpc analysis showed the ester product was a 45:55 *cis–trans* IIc mixture. No evidence of double bond migration was found. The reaction was repeated at reflux temperature (*ca.* 80°) and the recovered acid was esterified as described previously. Again a 45:55 *cis–trans* IIc epimerization mixture was obtained.

2-Methylbutane-1,3,4-tricarboxylic Acid (VIII).—From 300 mg of *trans* IIa oxidized by the method of von Rudloff,[23] 253 mg of crude oxidation product was obtained. Trituration with chloroform gave an amorphous solid that melted at 99–101° with gassing. Similar results were obtained with other polar solvents. Recrystallization of these acid–solvent complexes with acetic acid gave a crystalline solid that melted at 110°. Heating to 110–115° drove off the occluded solvent and yielded an amorphous white powder that melted at 153–154° (lit.[24] 153–154°). Average molecular weight of three micro neutralization equivalent determinations was 203; required for $C_8H_{12}O_6$, 204. Glpc analysis of the methyl ester gave a single peak.

Anal. Calcd for $C_8H_{12}O_6$: C, 47.06; H, 5.93. Found: C, 47.68; H, 6.08.

_t_-Butyl _trans_-2-Methyl-3-cyclohexenecarboxylate (_trans_ Vb).—Ester 5 was obtained from isomer C by dehydrohalogenation at 80° and from isomer B_2 by dehydrohalogenation at 150°. Identical retention times from glpc as well as identical infrared spectra proved that the same ester was obtained from each isomer. The infrared spectrum (neat) contained absorption bands at 1720 (C=O), 1650 vw (C=C), 1140 (C-O), and 675 (H-C=C-H) cm^{-1}; nmr spectrum: two olefinic protons (δ 5.50), a doublet equivalent to the three protons of the ring methyl group (δ 0.98), and a singlet equivalent to the nine protons of the *t*-butyl group (δ 1.43); the six remaining cyclohexyl protons formed a broad complex multiplet (δ 1.60–2.50). Additional confirmation of structure was obtained by saponifying *trans* Vb and oxidizing *trans* Va to the tricarboxylic acid VII. The refractive index of *trans* Vb was $n^{25}D$ 1.4432.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.42; H, 10.27. Found: C, 73.45; H, 10.39.

_t_-Butyl _cis_-2-Methyl-3-cyclohexenecarboxylate (_cis_ Vb).—The infrared spectrum of ester 8 contained absorption bands at 1720 (C=O), 1650 vw (C=C), 1143 (C-O), and 660 (HC=CH) cm^{-1}; nmr spectrum: two olefinic protons (δ 5.57), a doublet equivalent to the three protons of the ring methyl group (δ 0.90), and a singlet equivalent to the nine protons of the *t*-butyl group (δ 1.44); the remaining six protons formed a complex multiplet (δ 1.60–2.60). The refractive index of *cis* Vb was $n^{25}D$ 1.4562.

Epimerization of _trans_ Vb.—Ester 5 (100 mg) was subjected to the conditions for dehydrohalogenation at 150°, and the *t*-butyl esters of the crude acids (53 mg) were prepared. Gas chromatographic analysis showed the product to be a 90:10 mixture of esters 5 and 8 with no indication of double-bond migration.

Pentane-1,3,4-tricarboxylic Acid (VII).—*trans* Va (12 mg) was oxidized by the method of von Rudloff[23] with sodium periodate and potassium permanganate. From the reaction mixture 17 mg of an oily semisolid was recovered. Digesting the residue with water and evaporating the water layer to dryness yielded 10 mg of a white solid. Recrystallization from acetic acid gave a white powder that melted at 174–175.5° (lit.[25] 175–176°).

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***t*-Butyl 6-Methyl-1-cyclohexenecarboxylate (XIb).**—The ester was obtained pure by preparative gas chromatography. The infrared spectrum of ester 4 (neat) contained absorption bands at 1700 (C=C–C=O), 1640 w-m (C=C), 1160 (C–O), and 750 (H–C=C–COOR) cm^{-1}; nmr spectrum: one olefinic proton (δ 6.73), a doublet equivalent to the three protons of the ring methyl group (δ 1.04), and a singlet equivalent to the nine protons of the *t*-butyl group (δ 1.46); the remaining seven cyclohexyl protons formed a complex multiplet (δ 1.20–2.80). The refractive index of XIb was n^{25}D 1.4629.

6-Methyl-1-cyclohexenecarboxylic Acid (XIa) and Its Periodate Oxidation.—The acid was obtained in pure form both by saponification of XIb and by crystallization from a mixture of the acids from the dehydrohalogenation reaction. In the latter case the liquid acids were decanted from the solid which was washed with cold pentane. Recrystallization from aqueous ethanol yielded a white crystalline product that melted at 104–105° (lit.[26] 105.5°). The infrared spectrum (potassium bromide pellet) contained absorption bands at 1680 (C=C–C=O), 1640 (C=C), 1220 (C–O), and 930 broad (OH deformation) cm^{-1}; ultraviolet absorption data: $\lambda_{\max}^{\text{EtOH}}$ 214 mμ (ϵ 6600);[16] nmr spectrum: one olefinic proton (δ 7.04), a multiplet equivalent to one proton (δ 2.70), a multiplet equivalent to two protons (δ 2.23), a multiplet equivalent to four protons (δ 1.65), and a doublet equivalent to the three protons of the ring methyl group (δ 1.12).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.57. Found: C, 68.78; H, 8.46.

XIa was oxidized by the method of von Rudloff[23] to α-methyladipic acid (52% yield). Its methyl ester was identical with that of a known sample by infrared spectrum and gas chromatographic retention time.

***t*-Butyl 2-Methylbicyclo[3.1.0]hexane-1-carboxylate (XIIb).**—Ester 1 (XIb) was obtained pure by preparative gas chromatography. Its infrared spectrum (neat) contained absorption bands at 3080, 3040, 3000, 1025 (cyclopropyl group),[18d,19] 1709 (C=O), and 1140 (C–O) cm^{-1}. There was no C=C absorption band; nmr spectrum: a multiplet equivalent to one proton (δ 2.55), a multiplet equivalent to four protons (δ 1.72), a singlet equivalent to nine protons of the *t*-butyl group (δ 1.43), a doublet equivalent to three protons of the ring methyl group superimposed on a multiplet for one proton (δ 1.03), and a multiplet equivalent to two protons (δ 0.70). The spectrum did not contain absorption associated with olefinic protons. The refractive index of XIIb was n^{25}D 1.4498.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.42; H, 10.72. Found: C, 73.67; H, 10.11.

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Hydroxymonoenoic Acids of *Lesquerella densipila* Seed Oil

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Received December 3, 1965

Two hydroxy fatty acids of *Lesquerella densipila* seed oil are characterized as (+)-12D-hydroxy-*cis*-9-octadecenoic (ricinoleic) acid and as the previously unknown (+)-12-hydroxy-*cis*-9-hexadecenoic acid. The fatty acid composition of the oil is given.

Most seed oils of examined[2] *Lesquerella* species contain large percentages of hydroxyeicosenoic acid, but *L. densipila* and *L. lescurii* seed oils instead contain C-18 hydroxy acids. Smith and co-workers characterized the hydroxyeicosenoic acid as (+)-14-hydroxy-*cis*-11-eicosenoic acid[3] and the major hydroxy acid of *L. densipila* as 12-hydroxy-*cis*-9-*cis*-15-octadecadienoic acid.[4] Recent work[5] shows that these acids have the D configuration. Smaller amounts of a C-18 hydroxy acid, presumed[4] to be ricinoleic acid, and of an apparently monoenoic C-16 hydroxy acid were also found[2,4] in *L. densipila* oil. The present paper describes the characterization of these minor hydroxy acids.

After methyl esters were prepared by sodium methoxide-catalyzed methanolysis of *L. densipila* seed oil, distillation provided a C-18 hydroxy ester fraction. The monoenoic ester was separated from methyl densipolate (12-hydroxy-*cis*-9-*cis*-15-octadecadienoate) on a silver ion macroreticular ion-exchange resin.[6] Chromatography on silicic acid then gave a liquid ester that showed no impurity by gas–liquid partition chromatography (glpc) or thin layer chromatography (tlc).

The nuclear magnetic resonance (nmr) spectrum of this ester indicated a methyl ester of a straight chain monounsaturated fatty acid with a secondary hydroxyl group and the double bond not β to the terminal methyl group (*cf.* methyl densipolate). Mass spectral analysis of the hydrogenated derivative located the hydroxyl group at C-12.[7] To locate the double bond, the parent ester was cleaved by a modification of von Rudloff's[8] permanganate–periodate oxidation procedure. Methyl esters of the fragments were identified as dimethyl azelate and methyl 3-hydroxynonanoate by mass spectrometry, so the double bond is in the 9,10 position. The infrared, nmr, and mass spectra of the parent ester are indistinguishable from the corresponding spectra of methyl ricinoleate [(+)-12D-hydroxy-*cis*-9-octadecenoate]. That the compound is in fact methyl ricinoleate is shown by the coincidence of the optical rotatory dispersion (ORD) curves of the ester and its hydrogenated derivative with the curves of methyl ricinoleate and hydrogenated methyl ricinoleate.

The compound tentatively identified as a monoenoic C16 hydroxy ester was concentrated from *L. densipila* methyl esters and finally purified by repeated chromatography on silicic acid.

Features of the pure C-16 methyl ester shown by the nmr spectrum included an unbranched chain containing one ethylenic bond not β to the terminal methyl group and a secondary hydroxyl group. As there is no absorption in the infrared spectrum at 10.3 μ, the

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