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Mass Spectrometry of Tautomeric Compounds. I. Absence of Keto-Enol Tautomerism in Fragment Ions

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In order to examine a possibility of keto-enol tautomerism in molecular and fragment ions, diethyl di-*n*-butylmalonate (Ia), methyl 2-*n*-butylhexanoate (IIa), and 2,2-di-*n*-propyl-5,5-dimethyl-1,3-cyclohexanedione (IIIa) were synthesized and their mass spectra were compared with those of respective mono-alkyl derivatives, Ib, IIb, and IIIb. The first step of the fragmentation of each dialkyl compounds is the cleavage of one of the alkyl side chains by McLafferty rearrangement to give an enol fragment ion (E). Comparisons of the behavior of this enol fragment ion with that of the corresponding molecular ion (K) of mono-alkyl derivatives indicate that the keto and enol forms of these compounds exhibited entirely different fragmentation patterns. Thus, the enol fragment ion of *m/e* 216 from Ia loses $C_3H_7\cdot$ through the allylic cleavage of an enol double bond to give an abundant *m/e* 173 peak, while the keto ion of *m/e* 216 from Ib loses C_4H_8 to afford a strong *m/e* 160 peak. In a similar manner, the enol fragment ion of *m/e* 130 from IIa gives an intense peak at *m/e* 87, and the keto ion of *m/e* 130 from IIb yields an ion at *m/e* 74. In the spectrum of IIIa, a peak at *m/e* 140 that is observed in the IIIb spectrum did not appear. These results clearly suggest that no keto-enol tautomerism takes place in these ions in a mass spectrometer.

During the course of an investigation of mass spectrometry of barbituric acid derivatives[1] we have found that the keto and enol forms of ethylbarbituric acid showed different fragmentation patterns, and therefore, a suggestion has been made[1] that no keto-enol tautomerism of this compound occurred in a mass spectrometer. We now extended the work to other tautomeric systems to clarify the correlation between mass spectrometry and prototropic rearrangement.

It is possible to produce unstable enol intermediates in a mass spectrometer by utilizing the well-

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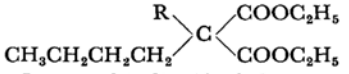
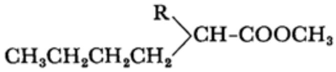
[1] H. Nakata, A. Tatematsu, H. Tsuyama and H. Doi, *Shitsuryo Bunseki (Mass Spectroscopy)*, **5**, 112 (1967).

defined McLafferty rearrangement[2-4] of suitably chosen compounds. We have synthesized diethyl di-*n*-butylmalonate (Ia), methyl 2-*n*-butylhexanoate (methyl di-*n*-butylacetate) (IIa), and 2, 2-di-*n*-propyl-5,5-dimethyl-1,3-cyclohexanedione (IIIa), and their corresponding mono-alkyl derivatives (Ib, IIb, and IIIb). The mass spectra of these compounds are shown in Figs. 1—6.

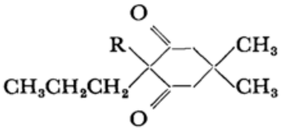
The first step of the fragmentation of these dialkyl compounds is the cleavage of one of the alkyl side chains by the McLafferty rearrangement to give an enol fragment ion, *e.g.*, E. The corresponding ion of the keto form, *e.g.*, K, is identical with the molecular ion of mono-alkyl derivatives. Therefore, if we compare the mass spectral behavior of these enol fragment ions with that of respective mono-alkyl derivatives, it can be seen whether or not the keto-enol tautomerism, E⇄K, takes place in a mass spectrometer.



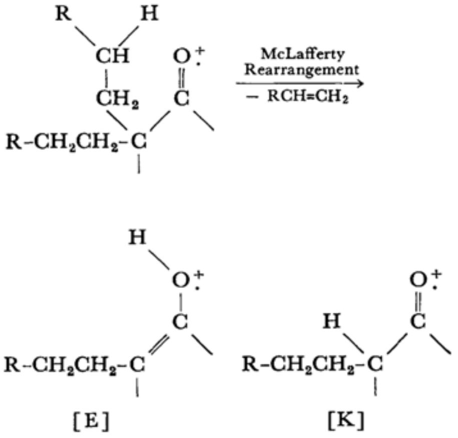
Ia $R=CH_2CH_2CH_2CH_3$
Ib $R=H$



IIa $R=CH_2CH_2CH_2CH_3$
IIb $R=H$



IIIa $R=CH_2CH_2CH_3$
IIIb $R=H$



From spectra shown in Figs. 1 and 2, it is clear that the keto and enol forms of mono-*n*-butylmalo-

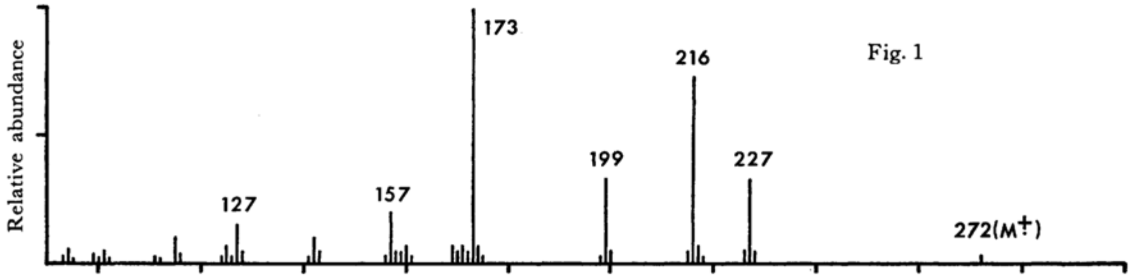


Fig. 1

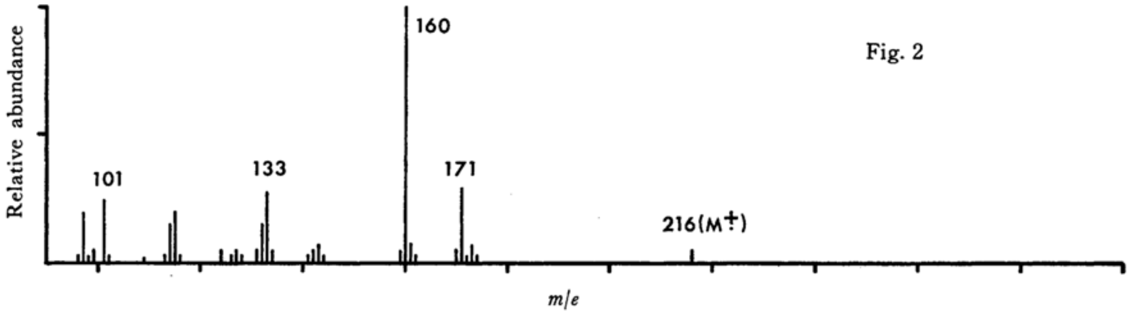


Fig. 2

Fig. 1. Mass spectrum of diethyl di-*n*-butylmalonate (Ia).
Fig. 2. Mass spectrum of diethyl *n*-butylmalonate (Ib).

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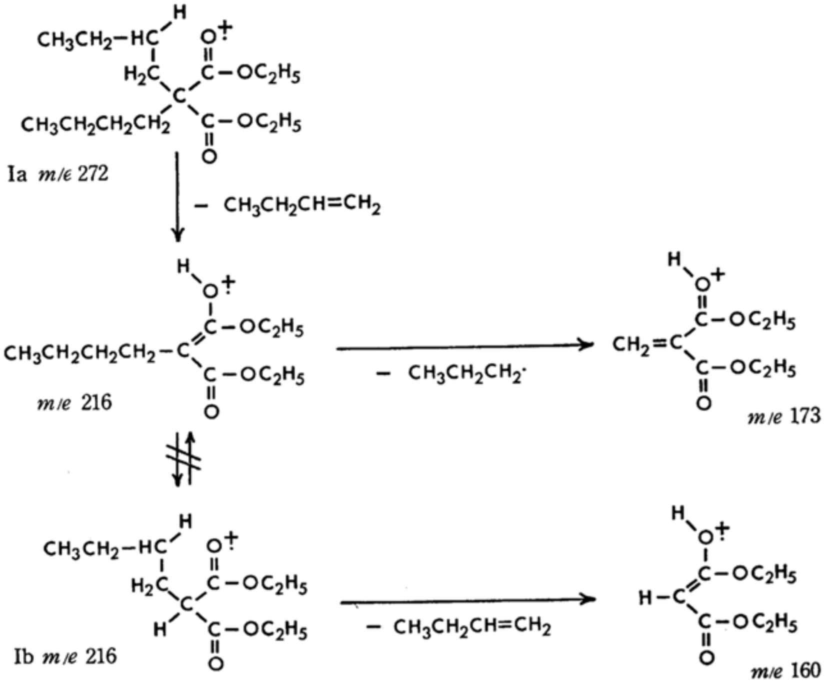
2) F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).

3) S. Meyerson and J. D. McCollum, "Advances in Analytical Chemistry and Instrumentation," ed. by C. N. Reilley, Vol. II, Interscience, New York (1963), p. 184.

4) H. Budzikiewicz, C. Djerassi and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco (1967), p. 155.



Scheme I

nate exhibited entirely different fragmentation patterns. Thus, the enol fragment ion of *m/e* 216 from di-*n*-butylmalonate (Ia) loses $C_3H_7\cdot$ through the allylic cleavage of an enol double bond to give an abundant *m/e* 173 peak (observed metastable ion peak at *m/e* 138.6), while the keto ion of *m/e* 216 from mono-*n*-butylmalonate (Ib) loses C_4H_8 by the McLafferty rearrangement to afford a strong *m/e* 160 peak. These fragmentations are summarized in Scheme I. Because no common peak of appreciable intensity was observed in these two spectra, it is concluded that the keto-enol tautomerism in these *m/e* 216 ions did not occur in a mass spectrometer.

Moreover, the *m/e* 160 ion from mono-*n*-butylmalonate (Ib) (Scheme I) corresponds to the enol form of diethyl malonate itself. It has already been known that the latter compound shows a very strong peak at *m/e* 115.[5] In Fig. 2, however, no intense peak at *m/e* 115 appeared, and this is consistent with the conclusion for the absence of the keto-enol tautomerism in this case also.

Essentially the same results were obtained with other two pairs of compounds. In the spectrum of methyl 2-*n*-butylhexanoate (IIa) (Fig. 3), the McLafferty rearrangement of the molecular ion gives an enol fragment ion at *m/e* 130, which then affords an intense peak at *m/e* 87 with elimination of $C_3H_7\cdot$ through the allylic cleavage. On the other hand, methyl hexanoate (IIb) (keto form) yields a strong *m/e* 74 peak (Scheme II). A moderately intense peak at *m/e* 87 in IIb probably arises from a fragmentation that is often encountered in long-chain methyl esters,[6] and not from the allylic cleavage of an enol double bond of the ester. From the bond energy considerations[7] the enol form of the ester is very unstable and should rearrange very rapidly to the ordinary ester (keto form), if other factors are not operative. The absence of the *m/e* 74 peak in the IIa spectrum (Fig. 3), therefore, showed that apparently very facile enol→keto tautomerism did not take place at all in fragment ions.

The general features of fragmentation of 2-*n*-propyl-5,5-dimethyl-1,3-cyclohexanedione (IIIb) are in good agreement with those observed for the corresponding 2-ethyl derivative, the fragmentation of which has been discussed in detail on the basis of double focusing technique[8] and deuterium labeling experiments.[9] The only difference in the IIIb spectrum is the appearance of an intense peak at *m/e* 140 (Fig. 6). This peak corresponds to M−42 and should originate from the McLafferty rearrangement of the molecular ion. The 2,2-di-*n*-propyl deriva-

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[5] J. H. Bowie, D. H. Williams, S.-O. Lawesson and G. Schroll, *J. Org. Chem.*, **31**, 1792 (1966).

[6] Ref. 4, p. 179.

[7] G. W. Wheland, "Advanced Organic Chemistry," 3rd Ed., John Wiley, New York (1960), p. 695.

[8] T. Goto, A, Tatematsu, Y. Nakajima and H. Tsuyama, *Tetrahedron Letters*, **1965**, 757.

[9] A. Maquestiau and P. Lejeune, *Bull. Soc. Chim. Belges*, **76**, 133 (1967).

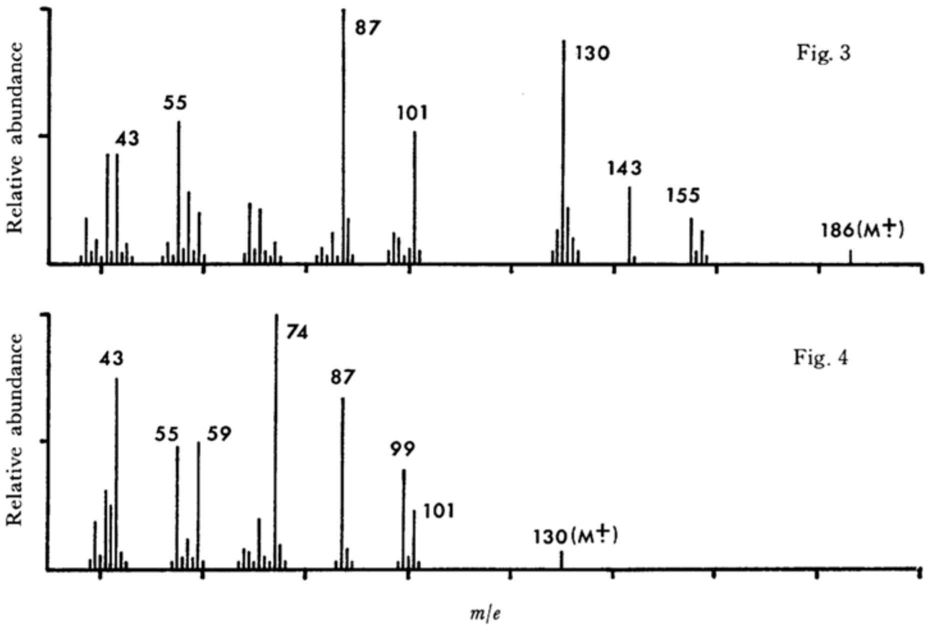
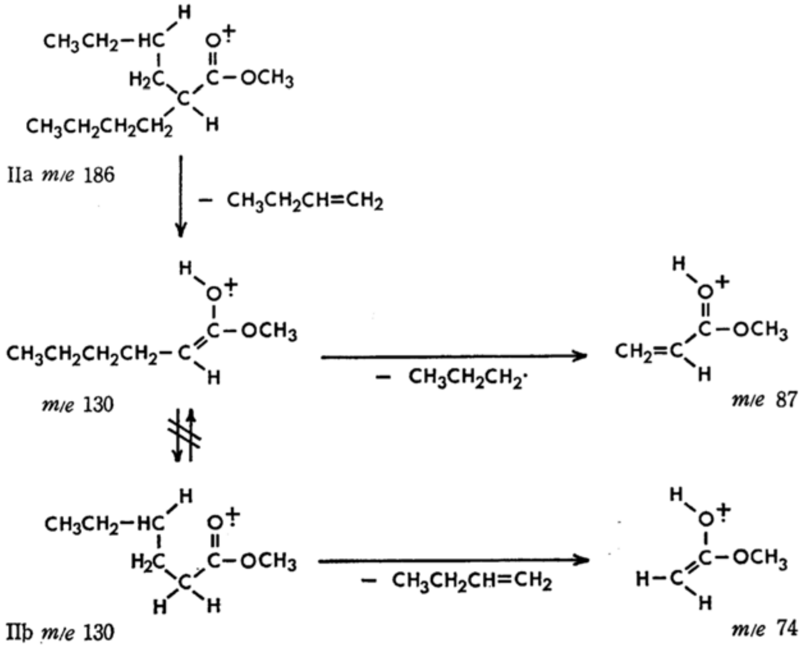


Fig. 3. Mass spectrum of methyl 2-*n*-butylhexanoate (IIa).
Fig. 4. Mass spectrum of methyl hexanoate (IIb).



Scheme II

tive (IIIa) also exhibited an M−42 peak at *m/e* 182. This ion must be represented as an enol structure because its formation is ascribable to the similar McLafferty rearrangement. If enol→keto tautomerism took place in this *m/e* 182 ion, the 2,2-di-*n*-propyl derivative (IIIa) would have afforded the intense *m/e* 140 peak. Although there are several common peaks in the spectra of IIIa and IIIb, the absence of this double McLafferty rearrangement peak at *m/e* 140 in the IIIa spectrum (Fig. 5) clearly excludes the possibility of keto-enol tautomerism in the *m/e* 182 ions.

In conclusion, we have no evidence for tautomeric changes in the molecular and fragment ions in a

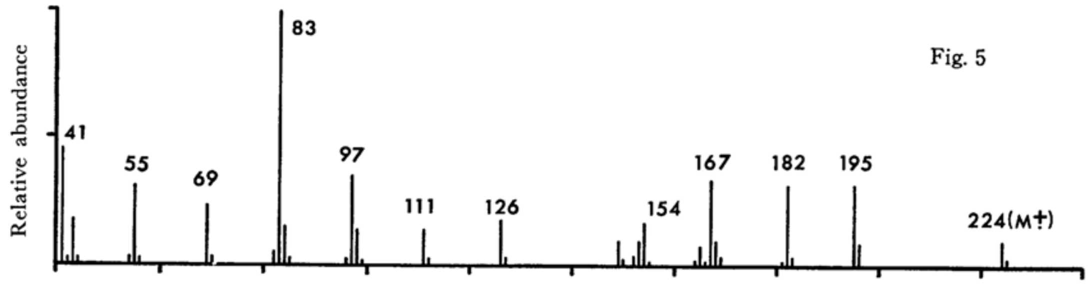


Fig. 5

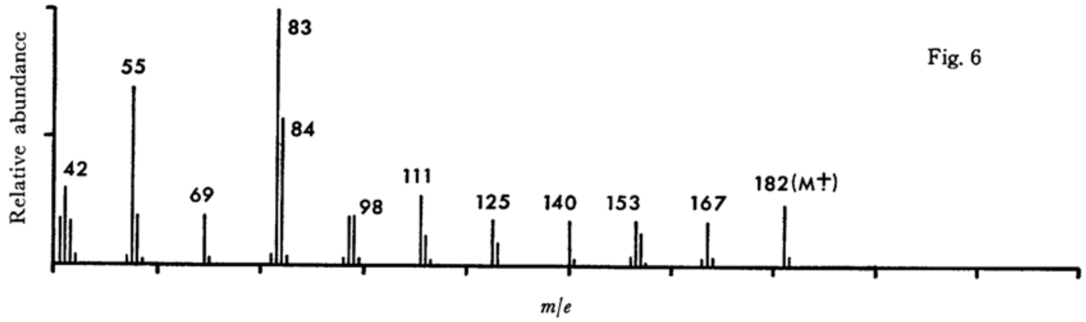


Fig. 6

Fig. 5. Mass spectrum of 2,2-di-*n*-propyl-5,5-dimethyl-1,3-cyclohexanedione (IIIa).
Fig. 6. Mass spectrum of 2-*n*-propyl-5,5-dimethyl-1,3-cyclohexanedione (IIIb).

mass spectrometer.[10] From the viewpoint of the quasi-equilibrium theory of mass spectra[11] these results are not unexpected, for the production of ions in a mass spectrometer is usually considered to be a very rapid process and the average life time of ordinary ions is roughly in the range of 10^{-12}—10^{-5} sec.

One corollary from the present results is the argument against the arbitrary postulation for the structure of the molecular ion of tautomeric compounds. The fact that keto and enol forms of a given compound show different fragmentaion patterns should be noted in the formulation of the molecular ion. For the compounds we have examined, the molecular ion seems to have the structure of the most stable form that predominates in solution and in solid state. For other compounds, however, the molecular ion may not necessarily be the same as the most stable structure in solution, because several environmental factors such as hydrogen-bonding and solvation would affect the tautomeric equilibrium in solution. Conversely, the stability of each tautomeric form in gas phase may well be studied by applying the technique of mass spectrometry.

Experimental

The mass spectra were measured with a Hitachi RMU-7 mass spectrometer by using an all-glass inlet system heated at 200°C. The ionizing energy was maintained at 70 eV and the total ionizing current 80 μA. The infrared spectra were recorded with a JASCO model IR-G spectrophotometer. All melting points and boiling points are uncorrected.

Diethyl *n*-Butylmalonate (Ib). Diethyl *n*-butylmalonate (Ib) was prepared from diethyl malonate and *n*-butyl bromide.[12] Bp 128—129°C/20 mmHg. $\nu_{\mathrm{C=O}}^{\mathrm{neat}}$ 1755, 1736 cm^{-1}.

Found: C, 60.72; H, 9.66%. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32%.

Diethyl Di-*n*-butylmalonate (Ia). Diethyl di-*n*-butylmalonate (Ia) was synthesized from 38 g of Ib and 34 g of *n*-butyl bromide in the presence of sodium ethoxide (6 g of sodium in 130 m*l* of ethanol). The procedure was essentially the same as described for alkylation of diethyl methylmalonate with *n*-decyl bromide.[13] The material boiling at 155°C/23 mmHg[14] was collected. Yield 26 g. $\nu_{\mathrm{C=O}}^{\mathrm{neat}}$ 1730 cm^{-1} (broad).

Found: C, 65.96; H, 10.63%. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36%.

Methyl 2-*n*-Butylhexanoate (IIa). Alkaline hydrolysis and subsequent decarboxylation of Ia were carried out in a similar manner as described for the synthesis of 2-methyldodecanoic acid.[13] Re-esterification of the product with methanol afforded IIa. Thus, 38 g of diethyl di-*n*-butylmalonate (Ia) was treated with a solution of 40 g of potassium hydroxide in 200 m*l* of 95% ethanol and the mixture heated at reflux, with

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[10] A recent report by Djerassi and co-workers also indicated the absence of keto-enol tautomerism in fragment ions. See, J. K. MacLeod, J. B. Thomson and C. Djerassi, *Tetrahedron*, **23**, 2095 (1967).

[11] H. M. Rosenstock and M. Krauss, "Mass Spectrometry of Organic Ions," ed. by F. W. McLafferty, Academic Press, New York (1963), p. 1.

[12] R. Adams and R. M. Kamm, "Organic Syntheses," Coll. Vol. I, p. 250 (1941).

[13] C. F. Allen and M. J. Kalm, "Organic Syntheses," Coll. Vol. IV, p. 616 (1963).

[14] R. Dolique, *Ann. Chim.*, [10] **15**, 425 (1931); *Chem. Abstr.*, **26**, 2971 (1932).

stirring, for 3 hr. About 10 m*l* of water was added to the refluxed mixture when a white jelly solid appeared during the hydrolysis. About two-thirds of the solvent was removed by distillation, 100 m*l* of water was added, and the solution was acidified, under cooling, with 6 N sulfuric acid to bring the pH of the solution to 1—2. A white, precipitated solid was collected and dissolved in ether, and the aqueous layer was extracted with ether. Combined ether solutions were washed with water and with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded crystalline di-*n*-butylmalonic acid. This material was carefully heated over its melting point under reflux for 3 hr to perform decarboxylation.

The crude 2-*n*-butylhexanoic acid, after checked by its IR spectrum,[15] was dissolved in 150 m*l* of methanol containing 5 m*l* of concentrated sulfuric acid. The mixture was refluxed for 3 hr, and then 50 m*l* of benzene was added and about 50 m*l* of azeotropic mixture was distilled, and the residue was again refluxed for 1 hr. The esterification was effected by repeating the above procedure three times to remove water produced. Finally the mixture was cooled and poured onto ice-water. The organic phase was separated and aqueous phase was extracted with ether. The organic phase and the ether extracts were combined, washed with sodium bicarbonate solution, and dried over anhydrous sodium sulfate. The solvent was removed and the residue was distilled under reduced pressure. The material boiling at 112—116°C/32 mmHg was collected. Redistillation gave 13 g of pure methyl 2-*n*-butylhexanoate (IIa), bp 108—109°C/25 mmHg.[16] $\nu_{C=O}^{CHCl_3}$ 1739 cm^{-1}.

Found: C, 71.06; H, 11.84%. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90%.

Methyl Hexanoate (IIb). The commercially available methyl hexanoate (IIb) was purified by repeated distillation. Bp 148.5°C.

2,2-Di-*n*-propyl-5,5-dimethyl-1,3-cyclohexanedione (IIIa). About 9 g of 5,5-dimethyl-1,3-cyclohexanedione[17] was dissolved in a solution of 5 g of sodium bicarbonate in 200 m*l* of water and 10 m*l* of ethanol. To this solution was added 50 m*l* of allyl bromide and the mixture was refluxed for 5 hr. A sufficient amount of crystalline sodium bicarbonate was added to the reaction mixture for every 30 min during this period in order to maintain the water layer neutral or slightly basic. After cooling, the mixture was extracted with ether and the ether extracts were washed with sodium bicarbonate solution and dried over anhydrous sodium sulfate. Removal of the solvent gave a yellow oil. This material was chromatographed on 150 g of silica gel (40×400 mm column). Elution of the first band with chloroform afforded 12.6 g of 2,2-diallyl-5,5-dimethyl-1,3-cyclohexanedione as colorless needles, mp 65—75°C.[18] $\nu_{C=O}^{CHCl_3}$ 1724, 1693 cm^{-1}. Catalytic hydrogenation of 6.5 g of this 2,2-diallyl derivative in ethanol under atmospheric hydrogen over platinum oxide yielded 6.8 g of a colorless oil. After chromatographed on 150 g of silica gel (40×400 mm column), pure 2,2-di-*n*-propyl-5,5-dimethyl-1,3-cyclohexanedione (IIIa) was obtained. The pure material solidified on cooling, mp 42—43°C. $\nu_{C=O}^{CHCl_3}$ 1721, 1690 cm^{-1}.

Found: C, 74.95; H, 10.96%. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78%.

2-*n*-Propyl-5,5-dimethyl-1,3-cyclohexanedione (IIIb). Mono-allylation of 5,5-dimethyl-1,3-cyclohexanedione was conveniently carried out according to the directions of Lukeš and Hofman.[19] 2-Allyl-5,5-dimethyl-1,3-cyclohexanedione was obtained as colorless plates, mp 152—154°C.[18,19] $\nu_{C=O}^{CHCl_3}$ 1739, 1707 cm^{-1}. Catalytic hydrogenation of this 2-allyl derivative and recrystallization of the product from aqueous ethanol gave pure 2-*n*-propyl-5,5-dimethyl-1,3-cyclohexanedione (IIIb) as colorless, flattened needles, mp 167—168°C.[18,20] $\nu_{C=O}^{CHCl_3}$ 1741, 1709 cm^{-1}.

Found: C, 72.28; H, 10.06%. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96%.

The authors wish to express their gratitude to Mr. Hideo Yoshizumi of Meijo University for his measurements of mass spectra. This work was supported in part by a grant from the Ministry of Education.

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[15] D. L. Guertin, S. E. Wiberley and W. H. Bauer, *Anal. Chem.*, **28**, 1194 (1956).

[16] V. Franzen, *Chem. Ber.*, **87**, 1219 (1954).

[17] R. L. Shriner and H. R. Todd, "Organic Syntheses," Coll. Vol. II, p. 200 (1943).

[18] R. D. Desai, *J. Chem. Soc.*, **1932**, 1079.

[19] R. Lukeš and J. Hofman, *Chem. Listy*, **51**, 2309 (1957); *Chem. Abstr.*, **52**, 6172 (1958).

[20] W. E. Silbermann and T. Henshall, *J. Am. Chem. Soc.*, **79**, 4107 (1957).