PREPARATION OF MONOMERIC 2,2-DIMETHYL-1,3-PRO-PYLENE DIMETHYLMALONATE ; POTENTIAL EXAMPLE OF CONFORMATIONAL ISOMERISM AND AN EXAMPLE OF THE USE OF MOLECULAR MODELS IN RESEARCH STUDIES

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ICHTISAR

Dengan penggunaan model² molekul dapat dilihat kemung-kinan untuk adanja suatu isomeri jang stabil dalam senjawa lingkar berinti delapan jalah monomer 2,2-dimetilpropilen dimetilmalonat (1).

Senjawa ini dibuat dengan djalan reaksi pertukaran ester antara 2,2-dimetil-1,3-propandiol dan etil dimetilmalonat, de-ngan dibutilstanni dibutoxida sebagai katalisator.

Suatu hasil jang lumajan dapat diperoleh dengan teknik destilasi bertingkat jang lambat sekali dari hasil tjampuran reaksi.

Hasil tersebut telah diselidiki dan terbukti adalah senjawa lingkar berinti delapan jang diharapkan, jalah suatu matjam bentuk jang biasanja sukar sekali dibuat.

Kenjataan telah diperoleh dengan penggunaan chromatografi gas bahwa isomer² konformasi dari 1 tidak stabil pada 150°C.

Belum didapat keterangan² lebih landjut mengenai kesta-bilan isomer² konformasi pada suhu kamar.

Because individual molecules obviously cannot be made visible, there have been efforts made for many years to prepare three-dimensional models which afford a visible representation of a molecule. Many of the efforts have been directed toward the making of models useful in elementary teaching, particularly in organic chemistry. The primary purpose of such models is to give the elementary student an approximate understanding of the special arrangement of atoms in the molecule and of the bonds between these atoms. In such cases the relative sizes of the different atoms are frequently ignored and the lengths of the bonds exaggerated ; because in an accurately scaled model the bonds, as such, are not visible, and it is very difficult — in some cases almost impossible — for the elementary student clearly to visualize the real spacial relationships within the molecule, particularly the location and types of bonds between atoms (see Figs. 1 and 2).

In addition to the teaching applications of models, research applications have long been recognized. For research applications a serious effort has been made to prepare models constructed exactly to scale. Use of such models facilitates many structural studies, particularly stereochemical studies. Typical uses of such models are found in (a) prediction of the possible existence or non-existence of a particular structure, (b) prediction of the steric effect of a certain group in hindering or aiding the chemical reactions of a neighboring group, and (c) prediction of the relative proba-
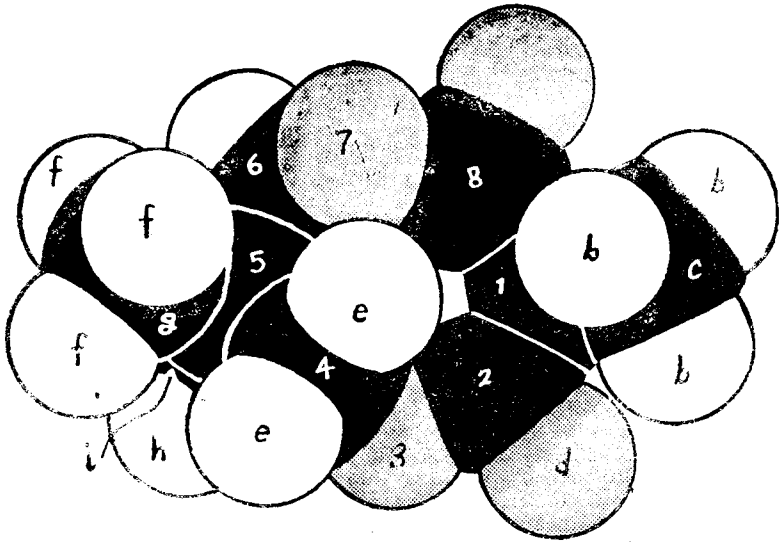
(a)
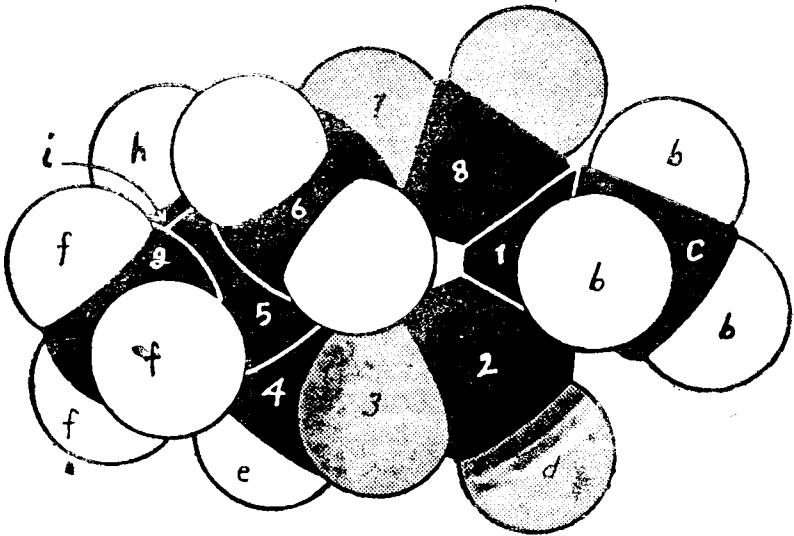
(b)

Fig. 1.

bility of internal as opposed to external hydrogen bonding in a given compound. Of course the accurately scaled models are also useful in teaching.

Real chemical bonds in real molecules have a certain flexibility which unfortunately has never satisfactorily been introduced into models. Thus, particularly in the case of strained rings, it is difficult to get a correlation between actual experimental findings and the predictions based upon the use of models. For example, the use of models alone would lead one to predict that the cyclopropane ring cannot exist. The fact is that cyclopropane is well known to the chemist, and many of its derivatives are well known in nature. A further defect of models is that one cannot by the use of a composite of several atomic models arrive at a useful representatition of a molecule which has a large resonance energy.

In efforts to overcome these difficulties sets of models have been prepared and are commercially available with several different kinds of atomic models for a single element, each kind to be used in a different kind of molecular structure. For example, the set of models used in the present investigation contains five different types of carbon atom models — one each for paraffinic, olefinic, acetylenic, aromatic and carboxyl structures. Additional types would be required if the user desired to make models of cyclobutane, cyclopropane, etc. Obviously this multiplicity of types of atom models for a single element has serious limitations in the attempted construction of a model of an unknown molecule.

Instead of using models, one can make calculation based upon values for bond length, bond angle, atomic radius, etc., obtained through X-ray studies, spectral studies, and other methods. In fact, this is the way in which the models were designed in the first place. These calculations have two serious limitations. First, the method is quite tedious and time-consuming. Second, it is beyond the mathematical ability of the typical organic chemist. Furthermore, except in the cases of strained rings and highly mesomeric structures, it is doubtful whether the results of the calculations are much more reliable than those obtained through the use of models, provided the models are well designed. Thus, in spite of their many limitations, models are very useful in molecular structure studies of a variety of sorts.

During the course of an experimental attempt to prepare monomeric 2,2-dimethyl-1,3-propylene dimethylmalonate (I), a model of the compound

(I)
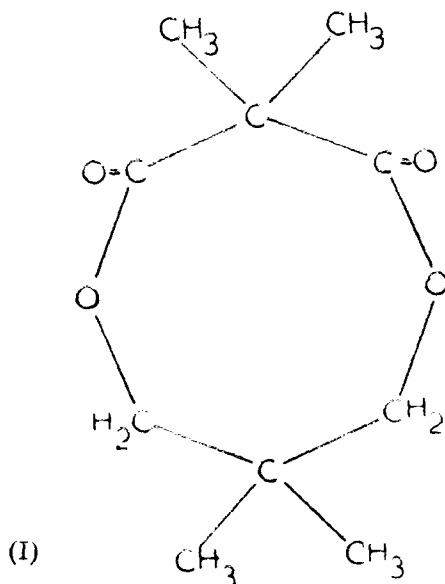
was prepared using *Fisher-Hirschfelder-Taylor* molecular models. The rather surprising result was that apparently, if the models can be trusted (see limitations already discussed), the compound should exist in two types of conformational isomers, one, a pair of asymmetric isomers which constitute a racemic modification (Fig. 1a and 1b), the other, a symmetric meso form (Fig. 2). From these models it would appear that:

a. The two conformational forms should have an approximately equal energy content, because they are completely strainless and are equally easy to construct. Hence, in the equilibrium mixture the relative amounts of the two forms should be roughly equal, or at least in the same order of magnitude.

b. In the model the two forms are not interchangeable without breaking either a carbon-carbon bond or a carbon-oxygen bond; hence an energy barrier toward interconversion should exist, although it perhaps is not large.

c. The two structures are closely similar, so that the two isomers, if they exist at all, should be very similar in physical properties and not readily separable.

d. If the isomerism exists at ordinary temperatures, the racemic modification should be very nearly impossible to resolve, and if resolved, the optical isomers should show a rather low value for the specific rotation because of the overall symmetry in the shape of the molecule.

It can be said with reasonable assurance that this type of conformational isomerism should occur at very low temperatures; however, if the conformational isomers could be shown to be rather stable at ordinary temperatures and separable in the laboratory, this would be a case of very unique type of isomerism. The present investigation was undertaken to determine (a) whether this highly hindered ester link will form at a great enough rate to permit a practical synthesis of the eight-membered ring compound and (b) whether the conformational isomerism exists at ordinary temperatures.

GENERAL PROCEDURE

From the very outset it was apparent that several problems must be solved. Since the pioneering studies of condensation polymerization by Carothers [1]) it has been wellknown that virtually all ringforming reactions can also lead to the formation of linear polymers and that the polymerization alternative is much more probable whenever the ring would contain seven or more atoms. It is particularly difficult to form rings containing eight to twelve carbon atoms. Since, in the present case, there should be very little of the eight-membered ring compound in the equilibrium mixture of cyclic and linear polymeric compounds, the method of synthesis of monomeric dimethylpropylene dimethylmalonate must utilize continuous separation of the desired compound from the reaction mixture. This is probably best accomplished by continuous fractional distillation during the course of the reaction. Fortunately for this case, ester links are more flexible than carbon chains and hence facilitate ring formation, and *gem*-dimethyl groups specifically promote ring formation. The desired compound contains two ester links and two pairs of *gem*-dimethyl groups in one ring, hence the precentage of the eight-membered ring compound in the equilibrium mixture should be larger than in mist such cases.

Because ester interchange normally occurs faster and under milder conditions than direct esterification, it should be most practical to carry out the synthesis by the base-catalyzed reaction of 2,2-dimethyl-1,3-propanediol (II) with dimethyl or diethyl dimethylmalonate (III), the mechanism of which is assumed to be as follows:
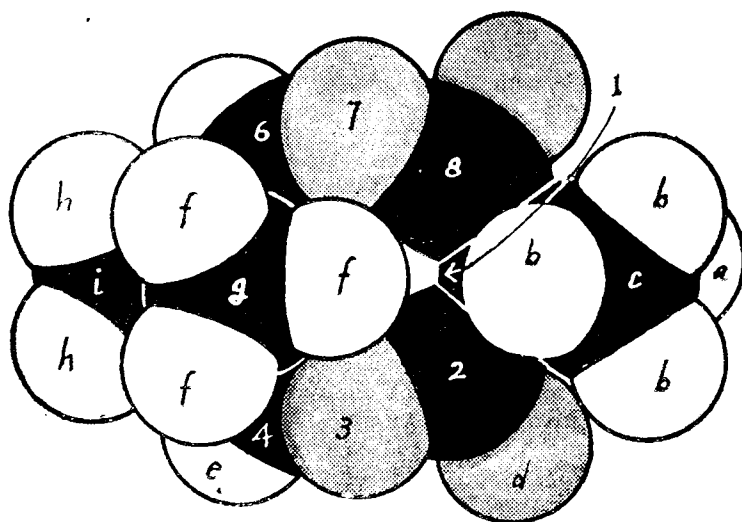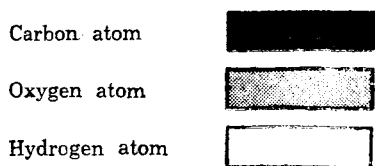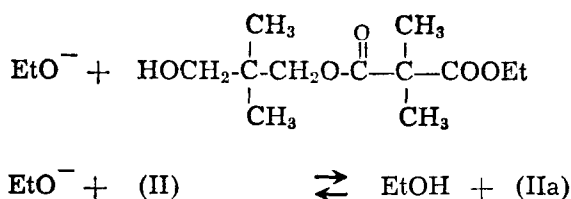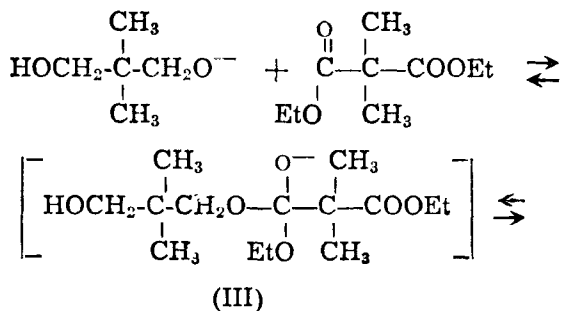

Fig. 2.

Carbon atom	
Oxygen atom	
Hydrogen atom	

$$\underset{\underset{\text{(II)}}{\underset{\overset{|}{\text{CH}_3}}{\overset{\overset{\text{CH}_3}{|}}{\text{HOCH}_2\text{-C-CH}_2\text{OH}}}}}{} + \text{B}^- \quad \rightleftarrows \quad \underset{\underset{\text{(IIa)}}{\underset{\overset{|}{\text{CH}_3}}{\overset{\overset{\text{CH}_3}{|}}{\text{HOCH}_2\text{-C-CH}_2\text{O}}}}}{} + \text{BH}$$

$$\underset{\overset{|}{\text{CH}_3}}{\overset{\overset{\text{CH}_3}{|}}{\text{HOCH}_2\text{-C-CH}_2\text{O}^-}} + \underset{\text{EtO}}{\overset{\overset{\text{O}}{\|}}{\text{C}}}\underset{\overset{|}{\text{CH}_3}}{\overset{\overset{\text{CH}_3}{|}}{\text{-C-COOEt}}} \rightleftarrows$$

$$\left[\underset{\overset{|}{\text{CH}_3}}{\overset{\overset{\text{CH}_3}{|}}{\text{HOCH}_2\text{-C-CH}_2\text{O}}}-\underset{\overset{|}{\text{EtO}}}{\overset{\overset{\text{O}^-}{|}}{\text{C}}}-\underset{\overset{|}{\text{CH}_3}}{\overset{\overset{\text{CH}_3}{|}}{\text{C}}}\text{-COOEt} \right]^- \rightleftarrows$$

(III)

$$\text{EtO}^- + \underset{\overset{|}{\text{CH}_3}}{\overset{\overset{\text{CH}_3}{|}}{\text{HOCH}_2\text{-C-CH}_2\text{O}}}\text{-}\underset{\overset{|}{\text{CH}_3}}{\overset{\overset{\text{O}}{\|}}{\text{C}}}\text{-}\underset{\overset{|}{\text{CH}_3}}{\overset{\overset{\text{CH}_3}{|}}{\text{C}}}\text{-COOEt}$$

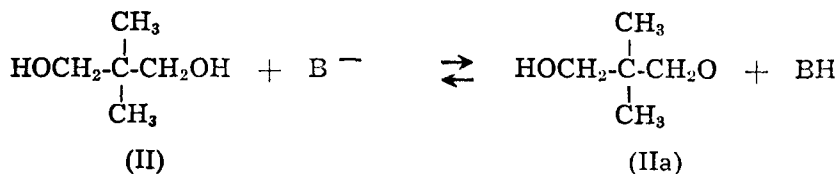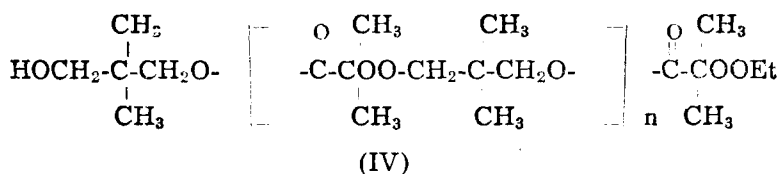$$\text{EtO}^- + \text{(II)} \quad \rightleftarrows \quad \text{EtOH} + \text{(IIa)}$$
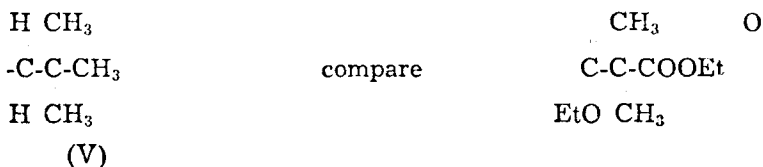
Other ester interchange steps should occur by like mechanism to produce the eight-membered ring compound (I), larger ring compounds, or linear polymers of the type structure IV, which actually may be terminated by either dimethyl-

$$\underset{\overset{|}{\text{CH}_3}}{\overset{\overset{\text{CH}_3}{|}}{\text{HOCH}_2\text{-C-CH}_2\text{O-}}} \left[\underset{\overset{|}{\text{CH}_3}}{\overset{\overset{\text{O}}{}}{\text{-C-COO-CH}_2}}\underset{\overset{|}{\text{CH}_3}}{\overset{\overset{\text{CH}_3}{|}}{\text{-C-CH}_2\text{O-}}} \right]_n \underset{\overset{|}{\text{CH}_3}}{\overset{\overset{\text{O CH}_3}{}}{\text{-C-COOEt}}}$$

(IV)

malonic ester or by dimethylpropanediol residues. Through reversible base-catalyzed interchange reactions the larger ring compounds and polymer (IV) should be in equilibrium with the cyclic monomer (I), although the equilibrium should greatly favor the polymer.

This proposed ester interchange mechanism should exhibit a quite slow reaction rate, since it involves a bimolecular nucleophilic substitution reaction on a carboxyl group structurally very similar to the neopentyl group (V). In studies of bimolecular nucleophilic aliphatic substitutions,

$$\begin{array}{ccc} \text{H CH}_3 & & \text{CH}_3 \quad\ \text{O} \\ \text{-C-C-CH}_3 & \quad\text{compare}\quad & \text{C-C-COOEt} \\ \text{H CH}_3 & & \text{EtO CH}_3 \\ \quad\text{(V)} & & \end{array}$$

the neopentyl group has been shown to be the most highly sterically hindered of the simple aliphatic groups and almost incapable of undergoing the bi-molecular substitution reaction [2]).

It does not seem reasonable to predict that conformational isomers should be separable at all by fractional distillation (unless by repeated molecular distillation carried out at relatively very low temperature). Not only should the isomers differ only extremely slightly in boiling point, but also, even if the isomers were quite stable at room temperature, they should undergo extensive interconversion during the long periods of heating required for efficient fractionation. The most likely separation methods should be counter-current distribution, solution adsorption chromatography, and gas-liquid partition chromatography (if rapidly carried out). Of these methods the first two are different techniques for the same basic process. Countercurrent distribution would probably be the preferred method, not only because it is capable of handling larger samples than can be handled by laboratory scale apparatus for any of the other three techniques listed, but also because the conditions are very mild. Unfortunately the equipment for countercurrent distribution is not available to the authors of this paper. It was decided to attempt gas chromatography, the least likely of these techniques to succeed because of the temperatures involved, but by far the simplest to carry out of the four techniques. If gas chromatography proves unsuccessful, then column partition chromatography could be tried. Paper partition chromatography would not allow a sufficiently large sample, and adsorption chromatography might well cause isomer interconversion at the heterogeneous surface.

EXPERIMENTAL

The starting materials and catalyst were prepared by known procedures.

Ethyl dimethylmalonate (III) was prepared by the alkylation of malonic ester [3]). The product had the following properties:

$$b. \ p. \ = 72.0 - 73.8°C/7 \ mm.$$
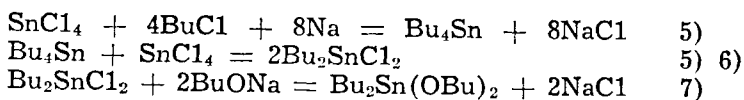$$n^{24.1} = 1.4144$$

2.2-Dimethyl-1.3-propanediol (II) was prepared from isobutyraldehyde and formaldehyde by a combination of aldol and "crossed" Cannizaro reactions [4]). The product had the following properties:

$$b. \ p. \ = 110-113°C/10 \ mm.$$
$$capillary \ m. \ p. \ = 123-125°C \ (uncorr.)$$

Dibutyltin dibutoxide was prepared in three steps by the following reactions:

$$SnCl_4 + 4BuCl + 8Na = Bu_4Sn + 8NaCl \quad \quad 5)$$
$$Bu_4Sn + SnCl_4 = 2Bu_2SnCl_2 \quad \quad 5) \ 6)$$
$$Bu_2SnCl_2 + 2BuONa = Bu_2Sn(OBu)_2 + 2NaCl \quad \quad 7)$$

The product was not isolated, but was used as a solution in butanol at a concentration of 0.625 mole per liter of butanol.
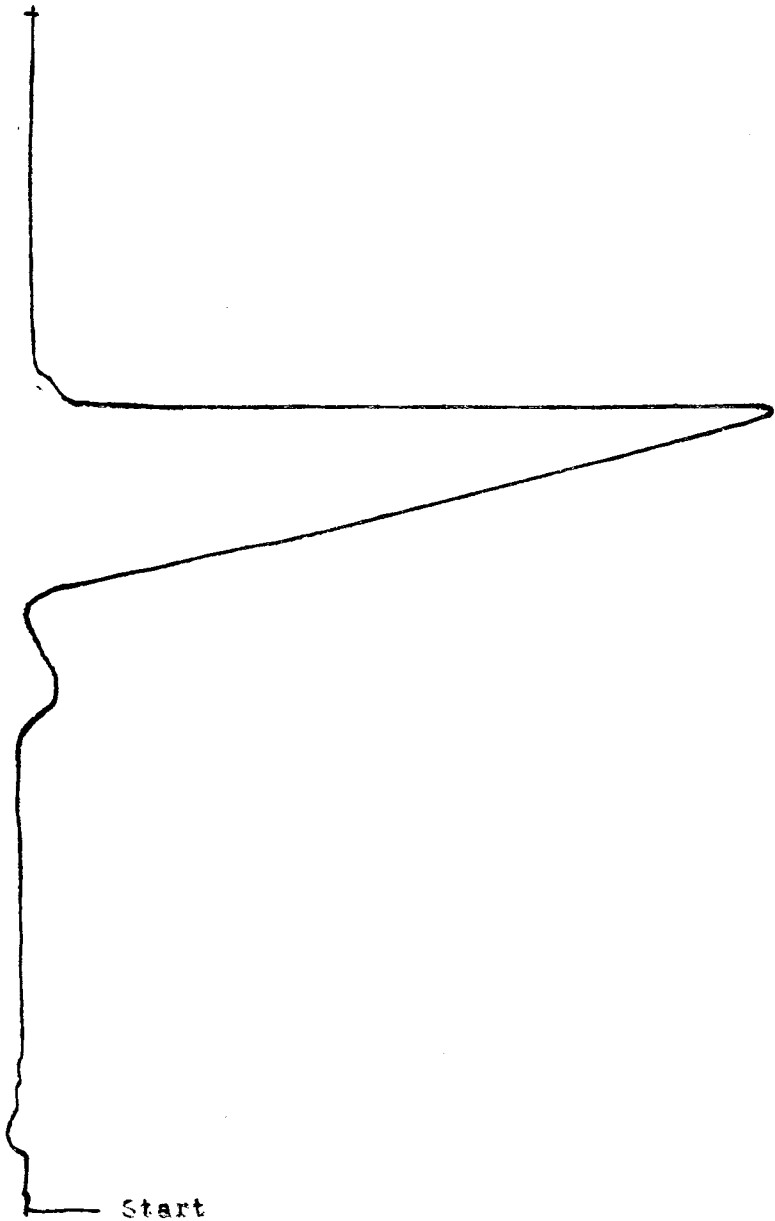
Start

Fig. 3

Preparation of 2,2-dimethyl-1,3-propylene dimethylmolanate (I).

The reaction was carried out in a 150 ml. round-bottomed flask equipped with a thermometer well and a fine capillary air-inlet tube to prevent bumping during the vacuum distillation. The flask was fitted with an inside-silvered vacuum-jacketed fractionating column of 12 mm. inside diameter and packed with glass helices for a length of 30 cm. The column was topped with a water-cooled take-off head suitable for vacuum distillation and adjustable for any desired reflux ratio. The flask was heated in a bath of molten Wood's metal.

A mixture of 9.0 g. (0.087 mol.) 2,2-dimethyl-1,3-propanediol, 15.6 g. (0.087 mol.) ethyl dimethylmalonate, and three drops of the solution of dibutyl tin dibutoxide was put into the flask and heated at 150°C. A little alcohol distilled out ; and after about two hours, when no more alcohol reached the column head, the bath was allowed to cool to 80° and the system evacuated to a pressure of 20 mm. The reaction product was distilled slowly at this pressure and at a reflux ratio of 50:1. After about eleven hours no more of the desired product was obtained. At this point in the preparation there were 9.0 g. of a liquid product boiling over the range 101-103°C/20 mm. (uncorr.). To this product were added another three drops of the catalyst solution, and the product was distilled a second time under the same conditions to eliminate all open-chain material. Yield : 5,0 g (0,025 mol. ; 29% of theory); b.p. = 101,5-102,8° C/20 mm (uncorr.). The product was a colorless liquid of fragrant odor.

In earlier attempts at the preparation sodium butoxide was used as catalyst. The product could not be freed from considerable amounts of open-chain material. Apparently the sodium butoxide is not stable under the conditions of the distillation and rapidly loses its catalytic activity.

Characterization of the product.

The saponification equivalent of a 0.5123 g. sample of the product was
determined calcd. for $C_{10}H_{16}O_4$: 100.12 ; found : 98.9

A cryoscopic measurement of the molecular weight was made in benzene.
calcd. for $C_{10}H_{16}O_4$: 200.24 ; found : 200.7 $\pm$ 2.0 (avg. of 2 determination).

The infrared spectrum of the compound was determined with a Leitz Infrared Spectrograph which is a double-beam, single monochromator, optical null balance instrument with "half-automatic" recording of the data. The spectrum showed no significant absorption band in the range from 2.0 to 3.25 microns. Primary alcoholic groups absorb strongly in this range.

The compound was analyzed by the gas-liquid partition chromatographic method using a locally constructed instrument consisting of a copper tube in gaschromatograph 180 cm copper tube of 3 mm. inside diameter packed with Sil-O-Cel C-22 brick support (manufactured by Johns-Manville Corp.) impregnated with dioctyl phthalate (30% by weight). The tube was spirally wound and immersed in a constant-temperature oil bath at 150°C. The detection cell was a katharometer with platinum thermistors, and the data were recorded by a Brown electronic recorder. Nitrogen was used as carrier gas.

Asymmetric form

Symmetric form

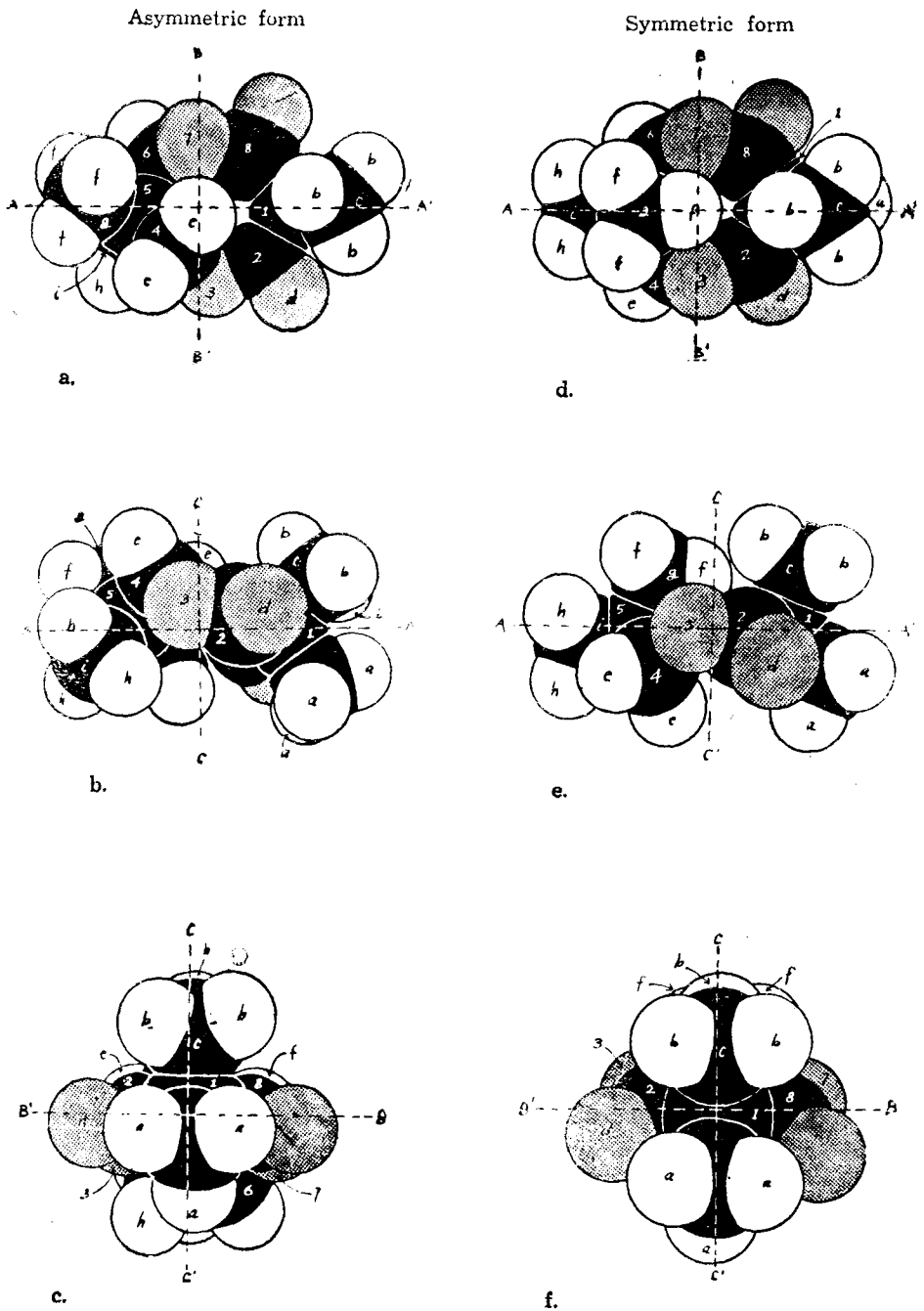

a.

d.

b.

e.

c.

f.

Fig. 4. A comparison of the overall shape of the asymmetric and symmetric forms of the cyclic ester, each form viewed from three directions.

The gas chromatogram (Fig. 3) indicates a purity of 98.3% with no evidence of isomerism.

DISCUSSION AND CONCLUSIONS

The fact that no evidence was found by gas chromatography for the existence of stable conformational isomerism does not necessarily rule out the possibility of such isomerism. As stated earlier, this method should be the least likely to succeed of the methods considered. Clearly the conformational isomers would have to be very stable indeed to resist interconversion at the temperature of 150° required to develop the chromatogram. Any lowering of this temperature would result in prolongation of the heating period, so little could be accomplished in that way.

An obvious alternative is that which has already been mentioned, i.e. room temperature column partition chromatography of a solution of the compound. Unfortunately there is no simple detection cell for this case, such as that used in gas chromatography. Probably the most satisfactory analysis for the very small quantities of ester which appear in the eluate would be infrared spectrographic analysis of a large number of fractions of the eluate. Just prior to the completion of the present investigation, unfortunately, the only available infrared spectrograph (the instrument described in the experimental section) became inoperative with no prospect of repair for several months. The simple aliphatic esters, such as the compound under discussion, do not show any absorption band within the range of the usual ultraviolet spectrophotometers ; so that in the present investigation no further attempt was made to detect the possible existence of stable conformational isomerism in monomeric dimethypropylene dimethylmalonate.

It is necessary to take into account also that the structural difference between the conformational isomers in this case is very small and that the overall shape of the molecules of the two isomers is not significantly different (see Fig. 4). It is entirely possible for such isomerism to exist and yet be essentially undetectable by the methods employed in the present investigation. This seems unlikely, however, since even very small differences in adsorption (or more precisely in the vapor-liquid partition coefficient) should cause at least some irregularity in the peak of the chromatogram.

It should be quite worth while to continue this investigation along the lines already discussed when the infrared spectrograph again becomes operable. If evidence were obtained for stable conformational isomerism in this case, then the problem of demonstrating the optically active forms would be a very challenging and difficult one. Conventional methods of resolution would probably all fail. It might be possible to cause selective saponification of one of the optical isomers by the use of an asymmetric base catalyst. Adsorption chromatography might be successful if the adsorbant were asymmetric (a natural polysaccharide, for example). This again would depend upon the use of a suitable detector such as the infrared spectrograph. The eluate solution would probably be too dilute for a polarimeter to be used as detector.

Conclusions

1. The desired monomeric ester can be prepared on a small scale at a slow, but useful rate.

2. Conformational isomers of this ester almost certainly are not stable at a temperature of 150°C. No evidence was obtained concerning the stability of the conformational isomers of the ester at room temperature.

The use of molecular models indidates the possibility of stable conformational isomerism in the eight-membered ring compound monomeric 2,2-dimethylpropylene dimethyllonate (I). This compound was prepared by the ester interchange reaction of 2,2-dimethyl-1,3-propanediol with ethyl dimethylmalonate using dibutyltin dibutoxide as catalyst. An acceptable yield was obtained by the technique of very slow fractional distillation of the product from the reaction mixture. The compound was characterized and shown to be the desired eight-membered ring, a type of structure normally very difficult to prepare. Evidence was obtained through the use of gas chromatography that the conformational isomers of are not stable at 150°C. No evidence has yet been obtained concerning the stability of the conformational isomers at room temperature.

SUMMARY

The use of molecular models indicates the possibility of stable comformational isomerism in the eight-membered ring compound monomeric 2,2-dimethylpropylene dimethylmalonate (I). This conpound was prepared by the ester interchange reaction of 2,2-dimethyl-1,3-propanediol with ethyl dimethylmalonate using dibutyltin dibutoxide as catalyst. An acceptable yield was obtained by the technique of very slow fractional distillation of the product from the reaction mixture. The compound was characterized and shown to be the desired eight-membered ring, a type of structure normally very difficult to prepare. Evidence was obtained through the use of gas chromatography that the conformational isomers of I are not stable at 150°C. No evidence has yet been obtained concerning the stability of the conformational isomers at room temperature.

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