The Solution of a Classical Problem. Tautomerism and Isomerism in the α-Methylglutaconic Acid Series

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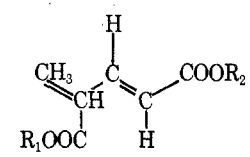
All four isomeric diethyl α-methyl- and γ-methylglutaconates (diethyl 3-methyl-1-propene-1,3-dicarboxylate and 1-methyl-1-propene-1,3-dicarboxylate, respectively) have been prepared for the first time, and their interconversions studied under acid-catalyzed, base-catalyzed, thermal, and photochemical conditions. The compounds previously believed to belong to the α-methyl series were actually γ-methyl derivatives, but were readily converted thermally into the α-methyl isomers, the *Z* product predominating largely. Base-catalyzed reactions, on the other hand, converted the diethyl α-methylglutaconates into the (*E*)-γ-methylglutaconate. The pure α-methylglutaconic acids could not be isolated. The readily obtained (*E*)-γ-methylglutaconic acid was converted into its *Z* isomer, through the anhydride, by treatment with either heat or acid followed by hydrolysis. The stable form of the anhydride was not the expected hydroxypyrone isomer(s), although the latter were observed by NMR in strong acids. No interconversion of 2-methyleneglutaric acid or ester with α- or γ-methylglutaconic acids or esters was observed in the presence of heat, light, acid, or base. However, the interconversion in the presence of a hydrogen transfer catalyst was confirmed.

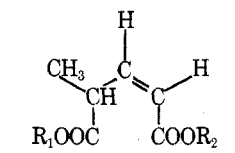
For half a century following the first preparation of the parent compound,[1] heated polemics were associated with the progress toward understanding the tautomerism and isomerism of glutaconic acids. Three research groups were more particularly involved, those of Feist, Thorpe, and Kon, who contributed a total of 49 publications on this subject, and for a long time the debate was centered on the existence of a special type of tautomerism for the three-carbon system, comprising the "normal" and "labile" forms. In the former, a "mobile" hydrogen was attached to the central carbon of the system, which still remained acyclic, while in the latter there was one localized double bond, with the possibility of cis–trans isomerism about it. Five isomeric forms were thus recognized, two cis, two trans, and one "normal", this last one being due to "retarded mobility". The concept of "normal" structures passed away around 1930, and the remaining problem consisted in establishing the position of the double bond in unsymmetrical systems, and determining the stereochemistry about it. The last piece of structural work with acyclic, alkyl-substituted, glutaconic acids was due to Fitzgerald and Kon, and appeared in 1937.[2] The field became dormant until 1952, when the long-debated structure of Feist's acid was finally shown to be 3-methylenecyclopropane-*trans*-1,2-dicarboxylic acid,[3] and thus proved not to be that of a glutaconic acid after all. However, the structures of the other alkylglutaconic acid derivatives were not reinvestigated at that time. The isolation of unsymmetrically substituted glutaconic acids from natural sources[4] made such a study particularly desirable, and we therefore decided to isolate and study the interconversion of the four α-methyl- and γ-methylglutaconic acids, the simplest monosubstituted members of this group. In this traditional nomenclature, the α position refers to the allylic carbon, and the β and γ positions to the vinylic carbons of the propene-1,3-dicarboxylic acid system.

Until this work was completed, only two isomers were known, one cis and one trans, which had been shown by ozonolysis to belong to different tautomeric series.[2] During the preparation of this article a publication appeared which described some isomerization reactions of methylglutaconic esters,[5] but confused the situation even further by claiming the participation of the isomeric methyleneglutaric esters (**5**), which had not been previously implicated, and which we proved not to be involved at all.

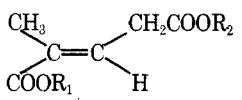
We repeated the condensation of diethyl malonate with chloroform,[1] followed by methylation and hydrolysis, and obtained the crystalline product melting at 144–145°. The assignment to the α-methylglutaconic acid structure **1a** had been essentially based on the assumption that no double bond migration had occurred during the hydrolysis and decarboxylation, and had been supported by ozonolysis, which yielded (from the diester) oxalic and methylmalonic esters.[2] The NMR analysis has now proved this product to belong to the γ-methyl series instead, with one methyl as a singlet, only one vinyl, and two methylene protons. That it was indeed the *E* isomer **3a** became apparent from subsequent chemical observations and NMR data (Table I). The mother solution could be crystallized, and melted at 112–113°, giving the appearance of a pure compound, while being actually a mixture of **1a, 3a,** and **4a** as shown by NMR. Through the anhydride, the conversion of **3a** into an



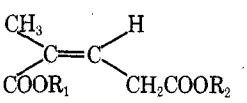
1a, $R_1 = R_2 = H$
m, $R_1 = R_2 = CH_3$
e, $R_1 = R_2 = C_2H_5$



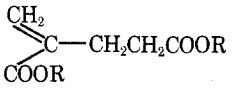
2a, $R_1 = R_2 = H$
m, $R_1 = R_2 = CH_3$
e, $R_1 = R_2 = C_2H_5$



3a, $R_1 = R_2 = H$
m, $R_1 = R_2 = CH_3$
e, $R_1 = R_2 = C_2H_5$
11m, $R_1 = H$; $R_2 = CH_3$
e, $R_1 = H$; $R_2 = C_2H_5$
16m, $R_1 = CH_3$; $R_2 = H$
e, $R_1 = C_2H_5$; $R_2 = H$



4a, $R_1 = R_2 = H$
m, $R_1 = R_2 = CH_3$
e, $R_1 = R_2 = C_2H_5$
12m, $R_1 = H$; $R_2 = CH_3$
e, $R_1 = H$; $R_2 = C_2H_5$
17m, $R_1 = CH_3$; $R_2 = H$
e, $R_1 = C_2H_5$; $R_2 = H$



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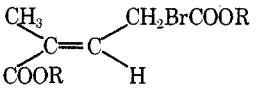

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Table I
NMR (Coupling Constants) of the Glutaconic Acid Derivatives

Compd	Solvent	CH_3	OCH_2CH_3[a]	OCH_3	CH_2	β-Vinyl	γ-Vinyl	C–H
1e	$CDCl_3$	1.34	1.27, 4.19			7.06	5.90	3.38
		(7)	1.30, 4.22			(8, 16)	(1.5, 16)	(1.5, 7, 8)
2e	$CDCl_3$	1.31	1.21, 4.00			6.37	5.84	4.48
		(7)	1.23, 4.16			(9, 11.5)	(11.5)	(7, 9)
3a	Me_2SO-d_6	1.74[c]			3.22[b]	6.78[b]		
3m	$CDCl_3$	1.90[c]		3.74	3.31[b]	6.81[b]		
				3.78				
3e	$CDCl_3$	1.87	1.27, 4.19		3.23	6.97[b]		
		(1)	1.30, 4.22		(7)			
11e	$CDCl_3$	1.87[c]	1.27, 4.23		3.27[b]	7.09[b]		
15e	$CDCl_3$	1.93	1.33, 4.22			7.04		5.05
		(1)	4.25			(1, 11)		(11)
15m	$CDCl_3$	2.03		3.88		7.13		5.16
		(1)		3.92		(1, 11)		(11)
16e	$CDCl_3$	1.86[c]	1.27, 4.18		3.28[b]	6.92[b]		
4a	Me_2SO-d_6	1.85[c]			3.48[b]	6.18[b]		
4m	$CDCl_3$	1.99[c]		3.74	3.61[b]	6.26[b]		
				3.78				
4e	$CDCl_3$	1.99[c]	1.26, 4.25		3.60[b]	6.28[b]		
			1.30, 4.20					
12m	$CDCl_3$	1.98[c]		3.73	3.65[b]	6.42[b]		
12e	$CDCl_3$	1.98	1.27, 4.18		3.62	6.40[b]		
		(1, 1.5)			(1.5, 7)			
17e	$CDCl_3$	1.96[c]	1.29, 4.23		3.63[b]	6.20[b]		

[a] J = 7 Hz. [b] J = 1 and 7 Hz. [c] J = 1 and 1 Hz.

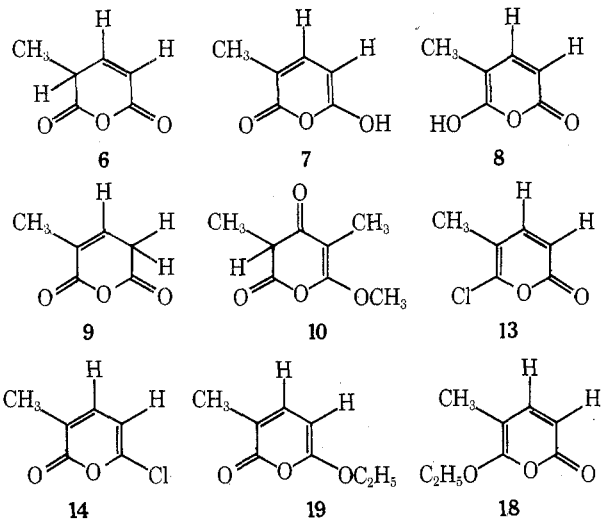
isomer melting at 125–126° could be performed as reported by Fitzgerald and Kon, and the NMR proved this to be the *Z* isomer **4a**, in agreement with the conclusions derived from ozonolysis.

The Anhydride of (*Z*)-γ-Methylglutaconic Acid. Prior to Fitzgerald and Kon's work, two isomeric acids were known, melting at 145[1,6–13] and 118°,[7] which were obtained by saponification of ester precursors, and which were believed to be the *trans*- and *cis*-α-methylglutaconic acids, respectively. It is probable that the latter was very similar to our sample melting at 113°. Feist and Pomme reported that an anhydride could not be formed by treating either acid with acetyl chloride at reflux, or with thionyl chloride in refluxing ether.[6] However, they obtained an anhydride melting at 85° which was formulated as **6**, when either acid was treated with phosphorus pentachloride in order to form their monoacid chloride. They found the hydrolysis of **6** with water not to proceed readily, and they also found that its treatment with aqueous base containing some casein yielded the then expected acid melting at 118°.[6] Thole and Thorpe agreed with the above formulation of the anhydride, and reported the same product to be formed by treatment of the acid melting at 145° with 2 equiv of acetyl chloride in a sealed tube at 100°.[3] However, they believed that this compound was enolized to **7** during distillation, and ruled out the isomeric structure **8** on the basis of a permanganate oxidation reaction.

Thole and Thorpe agreed with Feist and Pomme on the results of the alkaline hydrolysis,[7] but they also observed the slow formation of the trans acid by treatment with warm water. Unfortunately, the melting point of this product was not recorded, and structure **9** was not considered for the anhydride. Fitzgerald and Kon observed that the hydrolysis of the "hydroxy anhydride" with cold water yielded a small amount of what they believed to be a purer cis acid, melting at 125–126°.[2] Unfortunately, their structure determination of the isomeric acids by ozonolysis involved prior conversion to the methyl esters with diazomethane, and distillation of the methyl esters. The thermal isomerization reactions discussed below could only give misleading results, although the published experimental results cannot even be reconciled in detail with the now expected outcome.

Since the trans acid is now known to be **3a** rather than **1a**, a reformulation of the anhydride was desirable. As noted earlier, the acetyl chloride reaction with **3a** yielded mixtures rich in chlorinated products, and was not convenient for obtaining the anhydride itself, which we first encountered during the distillation of the monoester **16e**, and later in the thermolysis of the acid **4a**. The anhydride, which melted at 75°, was unquestionably that of a γ-methylglutaconic acid and had structure **9**, since its NMR spectrum showed one vinyl proton at 6.74, the two methylene protons at 3.58, and the methyl at 2.30 ppm. The isomeric structures **6**, **7**, and **8** are clearly ruled out by this spectrum.

Surprisingly, the enolization of this anhydride proved quite difficult. It did not occur upon distillation, as claimed earlier, and no change in the NMR was apparent when hydrogen chloride was bubbled into the $CDCl_3$ solution for 5 min, or when the compound was heated in trifluoroacetic acid for 62 hr at 100°. Compound **10** is another example in which the enolization to a hydroxypyrone system is known not to occur readily.[14] However, the facile thermal enolization of an acyclic anhydride was described,[15] but is most certainly benefiting from the stabilization of the monoenol by intramolecular hydrogen bending to the other carbonyl. The enolization of **9** was observed when 1 drop of concentrated sulfuric acid was added to the trifluoroacetic acid solution. The NMR then showed a singlet at 2.28 ppm for the methyl, and doublets at 6.72 and 8.38 ppm for the ring protons. The coupling constant of 8 Hz suggested a rapid exchange between the two enolic structures **7** and **8**, in which the values of ca. 9 and 7 Hz, respectively, would have been expected.[7,16]



Treatment of the acidic solution with ice water gave a mixture of the two γ-methylglutaconic acids containing 29% of **3a** and 71% of **4a**, from which a pure sample of the latter was obtained by fractional crystallization. It melted at 125–126°, and thus was probably identical with Fitzgerald and Kon's material.[2] The comparison between the NMR spectra of the products melting at 145 and 125° clearly supported the formulation as trans and cis acids, respectively (Table I). The only other reaction which we performed on this anhydride was a treatment with ethanol at reflux, which gave **12e** in good yield, resulting from nucleophilic attack at the less hindered carbonyl.

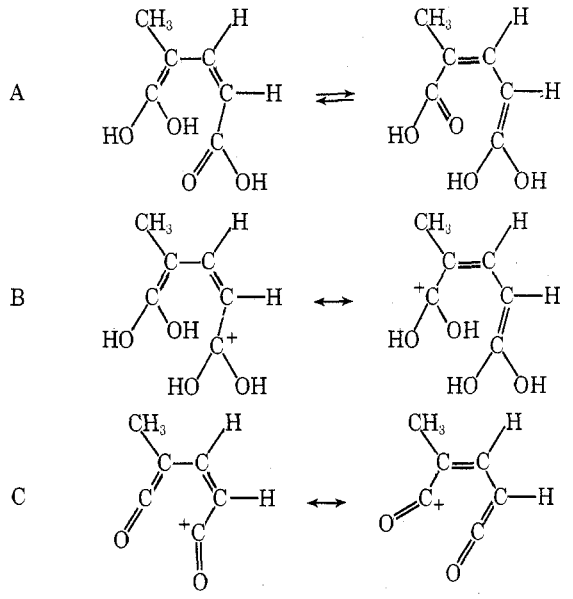
The treatment of **3a** with an excess of acetyl chloride yielded a crystalline product, mp 39–40°, which was an equimolar mixture of **13** and **14**, as shown by the mass spectral and NMR analyses. The separation of the components of this mixture proved difficult, but pure **13**, mp 69–70°, was found to be the only product eluted by column chromatography over silica gel. It was probably identical with the product melting at 71°, and believed by Thole and Thorpe to have structure **14**. We did not investigate whether **13** had isomerization into **14** on the column or had been selectively hydrolyzed. It is now known that the isomer **13**, melting at 75°, may be obtained pure by acid-catalyzed isomerization of **14** in the presence of acetyl chloride.[5]

The (*E*)- and (*Z*)-γ-Methylglutaconic Acids. A. Acid-Catalyzed Reactions. As indicated above, the pure acids **3a** and **4a** were obtained in this work, and the ozonolysis of the latter was uneventful, yielding pyruvic and malonic acids, in contrast to the published reports with the corresponding esters.[2] In order to explore the possibility of isomerizing the double bond to the less substituted positions, **3a** was treated with acid, and the reaction followed by NMR.

Very little change was observed in fluorosulfonic acid at room temperature, but after 10 min at 100° new peaks appeared, a singlet at 1.72 (3 H) and two doublets at 6.18 (1 H) and 7.76 ppm (1 H), with a coupling constant of 8 Hz (after cooling of a similar sample to the usual probe temperature, the chemical shifts were 2.20, 6.62, and 8.28 ppm, respectively). Quenching of the hot solution with ice water yielded a 1:2.5 mixture of **3a** and **4a**, and a similar behavior was observed for a solution of **3a** in concentrated sulfuric acid.

When pure **4a** was dissolved in either of the two acids, the spectrum of the above intermediate was obtained immediately. The mode of formation of this intermediate, as well as its reaction with ethanol to yield the monoester **12**, suggested it to be the anhydride or an equivalent. This was supported by the spectrum of **9** in these acids, which was indistinguishable from that generated from either **3a** or **4a**, and which probably represented **7** and **8** in rapid equilibrium. Furthermore, when a sample of **3a** was heated for 40 hr at 100° in trifluoroacetic acid, a 1:1 mixture of the starting material and the anhydride **9** *in its ketonic form* was obtained.

The conversion of **3a** into a *Z* species in acid could be rationalized by the formation of any of the three sets of structures A, B, or C, in addition to the enolized forms **7** and **8** of the cyclic anhydride **6** or **9**. All have the proton distribution required by the observed NMR spectrum (note that the hydroxyl peaks were not detected experimentally, and thus cannot be used for structural assignments).



Structures A and B follow from the well-known protonation of carboxylic acids in mineral acids.[17] Structure C may be viewed as vinylogous to the methylketenylacylium ion observed by Conrow and Morris upon acid treatment of methylmalonic acid.[18]

We have no direct proof for dismissing the structures A–C. There is a need for a driving force which will explain the formation of the *Z* intermediate from the *E* diacid. In the absence of any obvious stabilizing elements for the *Z* configuration in the acyclic structures A–C, their thermal isomerization to the electronically preferred *E* configuration should have taken place. Consequently, the most satisfying explanation involves a structure in which the *Z* configuration is locked, such as in the anhydride, which is obtained here in its enolized forms **7** and **8** in a manner similar to that described for maleic acid.[19]

Unsaturated and aromatic anhydrides have been reported to be quite stable in superacids,[20] and to undergo reversible protonation at the oxygen rather than at the carbon atoms, and this also applied to unsaturated acids.[19] The same is seen here with **9**, judging from the chemical shifts of the pyrone ring protons in comparison with those of the vinyl protons in the starting material.

The kinetics of the thermal reaction of **3a** to the anhydride could be easily followed by NMR from the disappearance of the methyl signal at 1.50 and the appearance of the signal at 1.70 ppm. A good first-order plot was obtained, and from the rate constants at four different temperatures, an activation energy of 16.5 kcal/mol was determined for the overall cis–trans isomerization about the double bond.

B. Base-Catalyzed Reactions. Since the acid-catalyzed isomerization of **3a** and **4a** did not yield any detectable quantity of the α-methylglutaconic acid isomers, we turned to base-catalyzed treatments. The conversion of α,β-unsat-

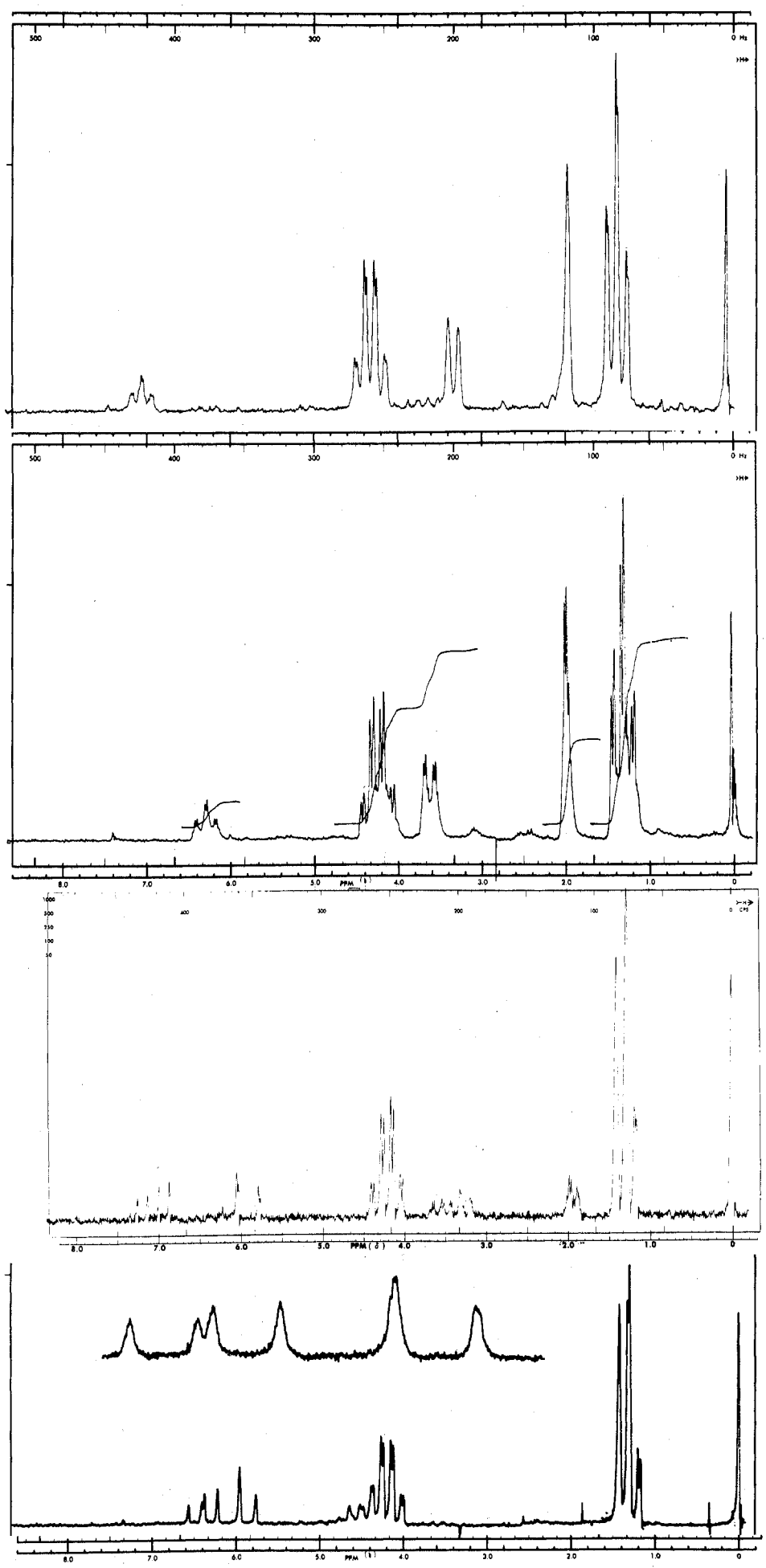


Figure 1. NMR spectra of the four isomeric diethyl α-methyl- and γ-methylglutaconates. From top to bottom: **3e, 4e, 1e,** and **2e.** (The sample of **1e** is contaminated with small amounts of **3e** and **4e.**)

urated acids into their β,γ-unsaturated isomers has long been known, most notably through the early work of Fittig and his group, followed by Kon and Linstead and their coworkers.[21]

The acidic nature of the methylene protons in **3a** was indicated by their exchange in deuterium oxide, which was complete after 20 min at 90°.[22] When **3a** was refluxed in alkaline solution for 6 days a mixture containing 75% of a 5:1 mixture of **3a** and **4a** and 25% of one α-methylglutaconic acid isomer was obtained. The new acid was recognized in the NMR by a methyl doublet at 1.20 (J = 6 Hz), and the γ-vinyl proton as a doublet at 5.73 ppm (J = 16 Hz). Although the other signals were masked by those of the starting material, the magnitude of this coupling constant indicated the E configuration for the product, which was therefore **1a**. Unfortunately, it could not be obtained pure following either fractional crystallization or chromatography.

C. Thermal Reactions. When a pure sample of **3a** was heated under vacuum at 160°, its isomer **4a** slowly sublimed in the pure state. After 12 hr at ca. 30 Torr, 60% of the original sample had been isomerized and this procedure was the simplest for obtaining pure **4a**. When there was no cold area for the product to condense on, the anhydride **9** was found to be the major product, and the thermal treatment of the Z acid **4a** under the same conditions also yielded the anhydride **9**. It appeared, therefore, that the cis–trans isomerization of **3a** was followed by anhydride formation, but no double bond migration to the α-methylglutaconic acid system was detected in these experiments.[23]

D. Photochemical Reactions. The irradiation of either **3a** or **4a** in anhydrous ether at 253.7 nm for 2 hr yielded an equimolar mixture of these two acids, without the formation of any detectable quantity of the isomeric α-methylglutaconic acids **1a** or **2a**, as observed by NMR.[24]

Diethyl Methylglutaconates. The difficulties encountered in attempting to isolate the acid **1a** which was produced in the base-catalyzed isomerization of **3a** prompted us to handle the esters instead, with the hope that their preparative gas chromatographic separation would be feasible, and would allow the isolation of **1e** and **2e** in pure form.

The Wittig reaction is usually the method of choice for introducing a double bond regiospecifically, but the condensation of ethyl 2-formylpropionate with carboethoxymethylenetriphenylphosphorane, at room temperature or below, actually yielded an equimolar mixture of **2e** and **3e**, rather than the expected mixture of **1e** and **2e**. The slow isomerization of **2e** into **3e** by the basic phosphorane reagent[25] was demonstrated in a control experiment, and thus explained the formation of the latter product. The distillation of the reaction mixture under vacuum in a spinning band column afforded three fractions, pure **2e** in the first, and mixtures of **1e** and **4e** in the second and third (95:5 and 20:80, respectively). The residue contained a mixture of all four isomers **1e–4e**.

Essentially pure samples of **1e** and **4e** were obtained by preparative gas chromatography, and the independent existence of all four isomeric α-methyl- and γ-methylglutaconic esters was thus finally demonstrated experimentally, as shown in Figure 1.

Other synthetic approaches toward the α-methylglutaconic ester series were not as successful. For example, the Doebner condensation of ethyl 2-formylpropionate with monoethyl malonate[12] yielded **3e** exclusively, as did the zinc reduction of the allylic bromide **15e**.

A. Thermal Isomerization Reactions. Surprisingly, the distillation of a sample of **3e** which was pure from NMR yielded a major fraction which was the pure Z isomer **4e**. Some starting material, as well as **1e** and **2e**, was observed in the other fractions. This isomerization was completely suppressed by lowering the pot temperature from 230 to 150° during the distillation, and this thermal reaction therefore provided an inviting avenue into the α-methylglutaconic acid series. It also created problems for the GLC analyses, and made a sample of either **3e** or **4e**, which was known to be pure from NMR, appear to be contaminated by three other components. This was corrected by lowering the temperature of the injection block to ca. 180°, and in these conditions none of the esters **1e–4e** was found to be isomerized in the gas chromatography. Unfortunately, we did not succeed in obtaining a complete separation of the peaks for the isomers **1e** and **4e**. However, the separation was sufficient for qualitative measurements, which closely paralleled the NMR analyses.

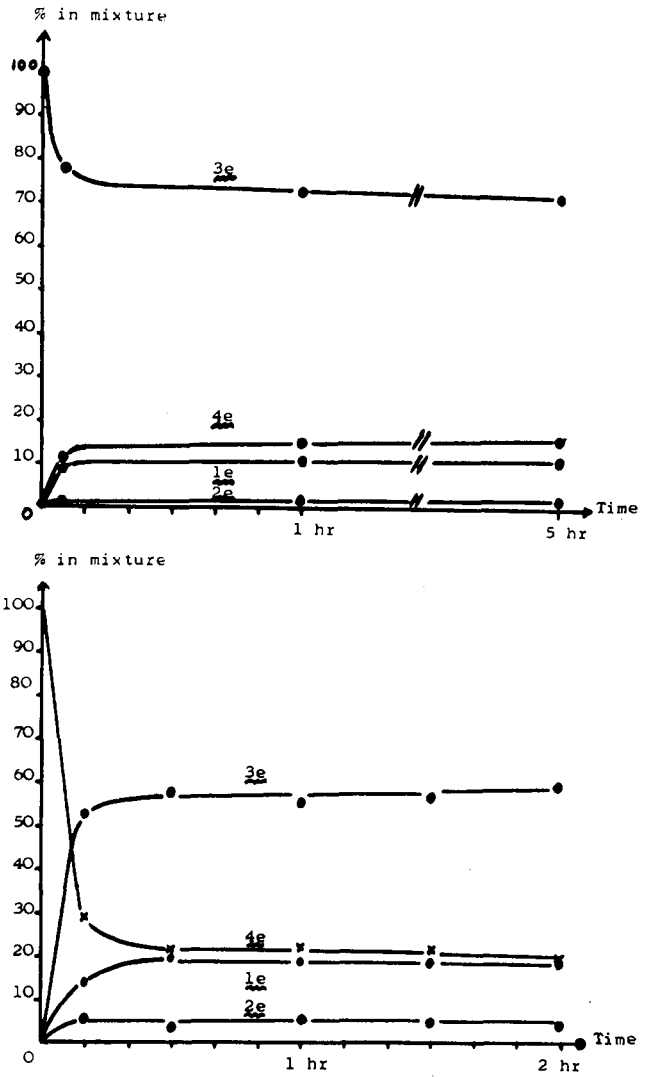


Figure 2. The thermal isomerization of **3e** at 260°, and of **4e** at 265°. (The accuracy of the GLC analyses is ca. ±10%, and the small amounts of polymeric materials were neglected.)

While the occurrence of the thermal isomerization of the esters had been dramatically demonstrated, the kinetics and equilibrium concentrations were more difficult to measure, because of competing polymerization and/or decomposition reactions which yielded insoluble materials, especially at higher temperatures. Smooth curves were obtained for the isomerization of **3e** at 260° and **4e** at 265°, which showed that the cis–trans isomerization proceeded faster than the double bond migration (Figure 2). Poorer results were obtained in the thermal treatment of the other isomers, which was accompanied by extensive polymerization. These thermal reactions require further study, and we hope to be able to report on their course in the near future.

The thermal isomerization reactions described above un-

Table II
NMR of the Anhydride Derivatives

Compd	Solvent	CH_3	CH_2	Vinyl	Ethyl
9	$CDCl_3$	2.03 (m)	3.58 (m)	6.74 (m)	
7 ⇌ 8	H_2SO_4	2.30		6.74 (8), 8.32 (8)	
	FSO_3H	2.20		6.62 (8), 8.28 (8)	
13	$CDCl_3$	2.05		6.15 (9), 7.21 (9)	
14	$CDCl_3$	2.05 (1)		6.09 (7), 7.05 (7, 1)	
18	$CDCl_3$	1.99 (1.5)		5.34 (9), 7.24 (9, 1.5)	1.41 (7), 4.20 (7)

doubtedly help explain the results of Fitzgerald and Kon's experiments.[2] As a check, the acid **3a** was esterified with diazomethane and yielded **3m** which was pure from NMR. Vacuum distillation with a pot temperature of 210–230° yielded **4m** as the major product, but one fraction containing about 40% of **1m** was also obtained. The residue was a mixture of all four isomers.

B. Acid-Catalyzed Reactions. The only attempt at isomerizing the diethyl γ-methylglutaconate system into the α-methyl isomer was by treating **4e** with concentrated sulfuric acid for 10 min at 100°. Dilution with water and extraction yielded a 1:1 mixture of the *E,Z* pair of **3a** and **4a,** without any evidence for double bond migration.

C. Photochemical Isomerization Reactions. A photoequilibrium of all four isomeric esters was observed upon irradiation of either **2e** or **3e** at 253.7 nm in benzene for 70 hr. The equilibrium mixture contained 6% of **1e,** 2% of **2e,** 47% of **3e,** and 45% of **4e.**

D. Base-Catalyzed Isomerization Reactions. All the chemical syntheses which utilized base-catalyzed reactions had yielded the pure (*E*)-γ-methylglutaconic diester **3e,** resulting from isomerization of the initially formed α-methylglutaconic diester. The facile isomerization of the *Z* diester **2e** was confirmed by an independent treatment with pyridine, which resulted in complete disappearance of the starting material, and formation of **3e.**

Monoethyl γ-Methylglutaconates. The treatment of the anhydride **9** with ethanol had yielded a monoethyl ester, identified as **12e,** and the synthesis of the isomeric monoesters was desirable for spectroscopic comparison. One single isomer was isolated from the Doebner condensation of ethyl 2-formylpropionate with malonic acid.[11,12,27] The NMR analysis showed it to belong to the γ-methyl series, and to be *E* from the allylic coupling constant of 7.5 Hz. This product was therefore **16e** and the original assignment of **12e** was confirmed by the comparison of the NMR spectra as well as the ultraviolet spectra. As expected for the conjugated acid **12e,** the absorption maximum shifted from 213 to 218 nm in going from pH 1 to 9, whereas there was no bathochromic shift in the spectrum of the nonconjugated acid **16e** when base was added. Cis–trans isomerization but no appreciable double bond migration took place in **16e,** either thermally during distillation, or photochemically upon irradiation at 253.7 nm in benzene for 15 hr. In the thermal treatment, the formation of both the anhydride **9** and the ethoxypyrone **18** competed with the isomerization. The structural assignment of this latter was based mainly on the NMR spectrum, which showed the two adjacent ring protons with a coupling constant of 9 Hz. As seen in the chloroanhydride **14,** the isomeric ethoxypyrone **19** would have been expected to show a coupling constant of 7 Hz for these adjacent protons. The 1.3:1 mixture of **16e** and **17e** which was formed by irradiation of **16e** could not be separated into its components by chromatography over silica gel. Similarly, a mixture of **11e** and **12e** (1:1.3) was obtained by photolysis of the former in the same conditions, but could not be separated into its components. However, all four isomeric monoesters could be easily identified by their NMR spectra (Table I).

Conclusion

Although the synthesis of the α-methylglutaconic acids is still to be performed, the main part of this article described the synthesis and interconversion of the four isomeric diethyl α-methyl- and γ-methylglutaconates.

Diethyl methyleneglutarate (**5**) was not detected in this work by either NMR or GLC analyses, and its independent treatment under thermal, photochemical, or base-catalyzed conditions did not result in any noticeable isomerization to the methylglutaconic esters. The Swiss workers' claim to the contrary[5] needed to be explained. We repeated their hydrogen transfer reaction in the presence of rhodium chloride, and confirmed that both **3e** and **5** yielded a mixture of **5, 3e, 4e,** and **1e,** and that **2e** was not a reaction product. A major additional component was obtained, however, which was identified as diethyl α-methylglutarate, the product of reduction. Contamination by some rhodium catalyst and/or difficulties with the NMR analyses are therefore the most logical explanations for the recently published results.

Experimental Section

(*E*)-γ-Methylglutaconic Acid (3a). From 227.4 g of diethyl malonate and 56 ml of chloroform,[1] there was obtained 70 g of recrystallized sodio-1,1,3,3-tetracarboethoxypropene: NMR (Me_2SO-d_6) 1.23 (t, 7 Hz, 12 H), 4.04 (q, 7 Hz, 8H), and 8.06 ppm (s, 1 H). Methylation of 49.0 g with 9.1 ml of methyl iodide yielded 38.0 g of 1,1,3,3-tetracarboethoxybutene: bp 160–161° (0.5 Torr); NMR ($CDCl_3$) 1.28 (m, 12 H), 1.67 (s, 3 H), 4.23 (m, 8 H), and 7.52 ppm (s, 1 H). Reflux overnight in a solution of 38 g of potassium hydroxide in 200 ml of water, followed by acidification to pH 3 and ether extraction, yielded 11.4 g of recrystallized **3a:** mp 144–145°; ir 3100 (br), 1700, 1600, 1450, 1370, 1280, 1140, 900 cm^{-1}; mol wt 144 (mass spectrum). Anal. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.55. Found: C, 49.72, H, 5.40. The NMR of the mother liquor showed a mixture of **1a, 3a,** and **4a.**

(*Z*)-γ-Methylglutaconic Acid (4a). A solution of 0.598 g of **3a** in 1 ml of either fluorosulfonic acid or sulfuric acid was heated at 100° in an oil bath for 2 hr. The light brown solution was quenched with 5.0 g of ice water and extracted with 25 ml of ether, which was dried and concentrated, yielding 0.278 g of a mixture of 29% **3a** and 71% **4a** by NMR. Repeated crystallizations from chloroform yielded 0.202 g of **4a:** mp 125–126° (lit. 125–126°); ir (Nujol) 3100 (br), 1690, 1670, 1630, 1360, 1310, 930 cm^{-1}. The starting material (0.028 g) was recovered from the mother solution.

Ozonolysis of 3a. A solution of 4.7 g of **3a** in 150 ml of ethyl acetate was ozonized at −80°, concentrated under vacuum at room temperature, treated with 100 ml of water, and warmed over a steam bath for 15 min. The solution was concentrated, and the residue esterified with ethanol and sulfuric acid at reflux for 24 hr. Distillation yielded 0.620 g of ethyl pyruvate, bp 153–155°, and 0.460 g of diethyl malonate, bp 198–199°, identified by comparison of their NMA and GLC with authentic samples.

γ-Methylglutaconic Anhydride (9). A. A solution of 3.0 g of **3a** in 10 ml of acetic anhydride was refluxed for 2 hr. The dark brown solution was distilled and yielded 1.0 g of **9** at 140–144° (3 Torr). After recrystallization from CCl_4 **9** had mp 74–76°; mol wt 126 (mass spectrum); ir ($CHCl_3$) 1820, 1760, 1380, 1220, 1070 cm^{-1}. Anal. Calcd for $C_6H_6O_3$: C, 57.10; H, 4.76. Found: C, 57.00; H, 4.73.

B. A solution of 0.050 g of **3a** in 0.5 ml of trifluoroacetic acid was heated in an NMR tube at 100° for 62 hr. The NMR spectrum showed a 1:1 mixture of **3a** and **9**.

Reaction of (*E*)-γ-Methylglutaconic Acid with Acetyl Chloride. A solution of 3 g of **3a** in 6 ml of acetyl chloride was refluxed for 24 hr, concentrated, and distilled, and yielded 2.2 g, bp 80–81° (4 Torr), mp 39–40°, mol wt 144 (mass spectrum), of a mixture of **13** and **14**. Chromatography over silica gel of 1.0 g of this mixture yielded 0.70 g of crude **13**, eluted with chloroform–ether. After recrystallization from petroleum ether it had mp 69–70°; NMR ($CDCl_3$) 2.05 (s, 3 H), 6.15 (d, J = 9 Hz, 1 H), and 7.21 ppm (d, J = 9 Hz, 1 H); ir ($CHCl_3$) 3000, 1640, 1555, 1530, 1100, and 935 cm^{-1}. Anal. Calcd for $C_6H_5O_2Cl$: C, 49.82; H, 3.47; Cl, 24.30. Found: C, 49.92; H, 3.35; Cl, 24.00. By difference, the NMR of **14** was 7.05 (d, d, J = 7, 2 Hz, 1 H), 6.09 (d, J = 7 Hz, 1 H), and 2.05 ppm (d, J = 2 Hz).

Deuterium Exchange of 3a. A solution of 0.050 g of **3a** in 0.5 ml of deuterium oxide had the following NMR at room temperature: 1.48 (s, 3 H), 3.01 (d, J = 6 Hz, 2 H), and 6.52 ppm (t, J = 6 Hz, 1 H). Complete disappearance of the methylene protons was observed after 20 min at 90°, and the 6.52-ppm signal had become a broad singlet.

Deuterium Exchange with 4a. A solution of 0.302 g of **4a** in 2 ml of 40% sodium deuteroxide (prepared by careful reaction of sodium hydride with deuterium oxide) was stirred at room temperature for 5 min. I was acidified with deuterium chloride and extracted with 5 ml of ether which was dried and evaporated, yielding 0.175 g of **3a**-d_4: NMR (Me_2SO-d_6) 1.73 (s, 3 H) and 6.66 ppm (br s, 1 H); mol wt 148 (mass spectrum).

Kinetic Study of the Reaction of 3a in Sulfuric Acid. The NMR probe temperature was adjusted to 75, 80, 85, and 90° utilizing the relative chemical shifts of the ethylene glycol protons. All rate determinations were run in duplicate starting from 0.050 g of **3a** in 0.5 ml of concentrated sulfuric acid. The progress of the reaction was followed by the decrease in the integration for the methyl peak at 1.50 ppm in the starting material. The plot of log $(I_t - I_e)$ vs. time was linear, where I_t and I_e are the values of the integration at time t and at equilibrium. The rate constants were derived from the slope of this plot at each temperature and were 4, 5.29, 7.06, and 10.3 × 10^{-2} min^{-1} at 75, 80, 85, and 90°, respectively. The equilibrium constants were 1.25, 1.41, 1.67, and 2.16 at these temperatures. The activation energy of 16.5 kcal/mol was obtained from the plot of log k vs. $1/T$.

Reaction of 4a with Concentrated Acids. A solution of 0.300 g of **2a** in 1 ml of concentrated sulfuric acid at room temperature showed NMR peaks at 1.70 (s, 3 H), 6.11 (d, J = 8 Hz, 1 H), and 7.76 ppm (d, J = 8 Hz, 1 H). The hydroxyl proton was not seen even at −80°. The solution was quenched with 5 g of ice–water and extracted with 10 ml of ethyl acetate which was washed, dried, and evaporated. There was obtained 0.240 g of starting material, mp 125–126°. A similar result was observed with fluorosulfonic acid.

(*Z*)-γ-Methylglutaconic Acid-d_3. A solution of 0.250 g of **4a** in 1 ml of concentrated sulfuric acid was quenched immediately in deuterium oxide. After work-up as above, there was obtained 0.212 g of **4a**-α-d_1-dicarboxyl-d_2: NMR (Me_2SO-d_6) 1.88 (s, 3 H), 3.48 (d, J = 6 Hz, 1 H), 6.16 (br s, 1 H); mol wt 147 (mass spectrum).

Isomerization of 3a in Base. A solution of 0.242 g of **3a** in 8 ml of 30% aqueous potassium hydroxide was refluxed for 6 days, acidified to pH 1, and extracted with 10 ml of ether, which was dried and evaporated. The NMR of the crude product indicated 75% of a 5:1 mixture of **3a** and **4a** and 25% of **1a**. From this, there was obtained 0.132 g of a solid, which was a 3:1 mixture of **3a** and **4a** from NMR. It could not be fractionated by crystallization or TLC.

Isomerization of 4a in Base. A solution of 0.050 g of **4a** in 5 ml of 40% aqueous potassium hydroxide was stirred at room temperature for 5 min. Following work-up as as above, the crude solid product gave an NMR spectrum identical with that of **3**, and melted at 144–145° after recrystallization from water.

Thermal Isomerization of 3a. A Pyrex vessel containing 1.0 g of **3a** was heated in a sand bath at 160° for 12 hr at 30 Torr. Part of the sample had sublimed and was mostly **4a**. The latter was purified by fractional crystallization from 1:1 chloroform–hexane, and melted at 125–126°. In another experiment, the anhydride **9** was the major product when **3a** was placed in a tube which was sealed under 30 Torr and heated at 180° for 8 hr.

Thermal Isomerization of 4a. A Pyrex vessel containing 0.500 g of **4a** was heated in a sand bath at 170–175° for 7 hr at 30 Torr. After cooling, 25 ml of hot carbon tetrachloride was added. The solution yielded 0.214 g of **9**, mp 75–76°.

Photochemical Isomerization of 3a. A solution of 1.0 g of **3a** in 20 ml of anhydrous ether was irradiated at 254 nm in a Rayonet reactor for 2 hr. After evaporation of the solvent, a 1:1 mixture of **3a** and **4a** (NMR) was obtained.

Photochemical Isomerization of 4a. The above procedure was followed, using 0.033 g of **4a** in 5 ml of ether, and yielded an equimolar mixture of **3a** and **4a**. Although there were signals in the region of 0.9–1.4 ppm, the corresponding vinyl doublets expected from **1a** of **2a** were not detected.

(*Z*)-4-Carbomethoxy-2-methyl-2-butenoic Acid (12m). A solution of either **4a** (0.180 g) or **9** (0.102 g) in 2 ml of concentrated sulfuric acid at room temperature was quenched immediately in 5 ml of chilled methanol. After dilution with 10 ml of water and extraction with three 10-ml portions of ether which were subsequently dried and concentrated, 0.106 g of **12m** was obtained: mp 71–72° after recrystallization from chloroform–hexane (1:4); ir ($CHCl_3$) 3600 (br), 3100, 1720, 1680, 1640, and 1510 cm^{-1}; uv (EtOH) λ_{max} 218 nm (ε 3800) in a buffer at pH 9, 213 nm (ε 3400) at pH 1. Anal. Calcd for $C_7H_{10}O_4$: C, 53.10; H, 6.34. Found: C, 52.80; H, 6.30.

(*Z*)-4-Carboethoxy-2-methyl-2-butenoic Acid (12e). A. A solution of 0.514 g of **4a** or 0.259 g of **9** treated with ethanol as above yielded **12e** (0.245 and 0.208 g, respectively): mp 56–58° after recrystallization from hexane; ir ($CHCl_3$) 3600 (br), 3100, 1720, 1680, and 1515 cm^{-1}. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found: C, 55.71; H, 7.00.

(*E*)-4-Carboethoxy-3-pentenoic Acid (16e). A solution of 13.0 g of freshly distilled ethyl formylpropionate, 11.0 g of malonic acid, and 10 ml of purified pyridine was heated on a steam bath for 4 hr, poured over 50 g of ice, stirred until the ice melted, and acidified to pH 2 with cooling. The precipitate was washed with a small amount of cold water, dried, and recrystallized from hexane, yielding 8.0 g of **16e**: mp 66–67°; ir ($CHCl_3$) 3500 (br), 2900, 1710, 1700, 1640, 1360, 1080, and 1030 cm^{-1}; uv (EtOH) λ_{max} 225 nm (ε 8590) at pH 9, 225 nm (ε 8045) at pH 1. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found: C, 55.73; H, 7.03.

Photolysis of 16e. A solution of 3.0 g of **16e** in 50 ml of spectrograde benzene was irradiated at 254 nm for 15 hr, and yielded a 1.3:1 mixture of **16e** and **17e**. These isomers could not be separated by chromatography or selective extraction with base.

Photolysis of 12e. A solution of 0.974 g of **12e** in 5 ml of benzene was irradiated at 254 nm for 15 hr, and yielded a 1.31:1 mixture of **12e** and **11e** which could not be separated.

Thermolysis of 16e. Distillation of 3.0 g of **16e** in a spinning band apparatus gave a major fraction (1.44 g) of **9**, bp 102–103° (3.5 Torr). It was recrystallized from carbon tetrachloride and melted at 75–76°. A minor fraction (0.031 g), bp 142–144° (3.5 Torr), contained mainly **18** with a trace of **9**. When this experiment was repeated, only **9** was isolated. The residual liquid was a ca. 1:1 mixture of **16e** and **17e**.

Wittig Reaction of Ethyl Formylpropionate with Carboethoxymethylenetriphenylphosphorane. A solution of 21.4 g of the phosphorane in 250 ml of absolute ethanol was added dropwise with stirring at room temperature to 8.0 g of ethyl formylpropionate.[28] After stirring for 48 hr the solution was concentrated under vacuum at room temperature, and 250 ml of petroleum ether was added. The precipitate was filtered and washed with an additional 50 ml of solvent. The combined extracts were concentrated at room temperature, and yielded 5.14 g of **2e** and **3e** in equal amounts (NMR), with a trace of triphenylphosphine oxide. The same results were obtained at −5°. Distillation in a spinning band apparatus (pot temperature 225°) yielded three fractions. The first was 1.64 g of pure **3e** (NMR and GLC): bp 70–72° (4.7 Torr); ir (neat) 3000, 1730, 1710, 1640, 1410, 1390, 1370, 1310, 1300, 1290, 1210, 1030, 945, and 830 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00. Found: C, 59.85; H, 7.83. The second fraction, 2.12 g, bp 77–80° (4.7 Torr), contained ca. 95% of **4e** and 5% of **1e**. The former was purified by preparative GLC, and had ir (neat) 2995, 1730, 1710, 1645, 1450, 1440, 1365, 1315, 1230, 1180, 1135, 1030, 855, and 840 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00. Found: C, 59.72; H, 7.89. The last fraction [0.73 g, bp 83–86° (4.7 Torr)] was a mixture of 20% **4e** and 80% **1e**, and the latter was obtained at least 95% pure by preparative GLC. The residue from distillation was a mixture of the four isomers **1e**–**4e**.

Condensation of Ethyl Formylpropionate with Monoethyl Malonate. A mixture of 26.0 g of freshly distilled ethyl formylpropionate, 26.4 g of monoethyl malonate, and 20 ml of pyridine was refluxed overnight,[12] diluted with water, acidified to pH 2, extracted with two 50-ml portions of ether, which were dried and concentrated at 30°, and yielded 14 g of **3e** pure from NMR and GLC: ir (neat) 2980, 1730, 1710, 1645, 1440, 1380, 1260, 1180, 1120, 1050, 860, 740 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00. Found:

C, 59.82; H, 7.92. Distillation of this product in a 6-in. Vigreux column with a pot temperature of 230° yielded 1.9 g at 78–82° (4.7 Torr) which contained 20% of **2e**, 30% of **1e**, and 50% of **4e** from GLC. There was also obtained 3.0 g, bp 82–83° (4.7 Torr), which was pure **4e**.

Diethyl (*E*)-α-Bromo-γ-methylglutaconate (15e). A mixture of 12.0 g of **3e**, 13.0 g of *N*-bromosuccinimide, a trace of benzoyl peroxide, and 150 ml of carbon tetrachloride was refluxed for 48 hr. The filtrate was washed with 100 ml of 10% bicarbonate and 100 ml of water. The organic phase was dried and concentrated. Distillation yielded 5.0 g of starting material and 4.3 g of **15e**: bp 130–133° (0.25 Torr); ir (neat) 2995, 1735, 1710, 1640, 1440, 1365, 1255, 1280, 1210, 1025, 980, 860, and 750 cm^{-1}. Anal. Calcd for $C_{10}H_{15}O_4Br$: C, 43.00; H, 5.37; Br, 28.25. Found: C, 42.91; H, 5.30; Br, 27.97.

Reduction of 15e. Zinc dust (2.3 g) was added to 1.3 g of **15e** in 2 ml of glacial acetic acid, and the mixture was stirred for 1 hr.[26] It was filtered, diluted with 50 ml of water, and extracted with 25 ml of ether which was dried and concentrated, yielding 0.7 g of **3e**.

Thermal Isomerizations. Neat samples of diesters (ca. 0.050 g) in sealed tubes were heated in a sand bath for various lengths of time. After cooling, the tubes were opened, acetone was added, and the solution was analyzed by GLC utilizing a 4 ft × 0.25 in. glass column of 15% diethylene glycol succinate on Chromosorb W, an injection temperature of 180°, and an oven at 50° which was heated at 4°/min. In all these experiments, a dark, insoluble material had been formed.

Irradiation of 4e. A solution of 0.200 g of **4e** in 5 ml of benzene was irradiated at 254 nm for 70 hr, and was shown by GLC to contain 2% of **2e**, 6% of **1e**, 44% of **4e**, and 48% of **3e**.

Irradiation of 3e. A solution of 0.300 g of **3e** in 5 ml of benzene was irradiated at 254 nm for 70 hr, and was shown by GLC to contain 2% of **2e**, 5% of **1e**, 46% of **4e**, and 47% of **3e**.

Dimethyl (*E*)-γ-Methylglutaconate (3m). Diazald (42 g) was used to prepare an ether solution of diazomethane, and 6.5 g of **3a** was added to it. Concentration under vacuum yielded 8.72 g of **3m**, judged to be pure from NMR: ir (neat) 2950, 1740, 1720, 1660, 1440, 1260, 1200, 1180, 1130, 1020, 1010, and 740 cm^{-1}. Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 6.99. Found: C, 55.54; H, 6.92. A 3-g sample of the ester was distilled in a spinning band apparatus with a pot temperature of 210–230°, and yielded 2.3 g of **4m:** bp 68–69° (6 Torr); ir (neat) 2950, 1740, 1710, 1650, 1420, 1240, 1200, 1180, 1140, 1020, 1000, and 850 cm^{-1}. Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 6.99. Found: C, 55.61; H, 6.84. A minor fraction (0.240 g), bp 73–76° (6 Torr), contained ca. 40% of **1m** and 60% starting material from GLC.

Dimethyl 2-Methyleneglutarate (5m). A mixture of 34.0 g of methyl acrylate, 1.0 g of tributylphosphine, and 0.2 g of hydroquinone in 80 ml of *tert*-butyl alcohol was refluxed for 7.5 hr,[29] concentrated under vacuum, and distilled to yield 9.5 g of **5m:** bp 74–77° (9.5 Torr); NMR ($CDCl_3$) 2.62 (m, 4 H), 3.70 (s, 3 H), 3.80 (s, 3 H), 5.64 (s, 1 H), and 6.24 ppm (s, 1 H); ir ($CHCl_3$) 3000, 2950, 1710, 1610, 1430, 990, and 950 cm^{-1}.

Diethyl 2-Methyleneglutarate (5e). A mixture of 20.0 g of ethyl acrylate, 1.0 g of tributylphosphine, and 0.2 g of hydroquinone in 80 ml of *tert*-butyl alcohol was refluxed for 7.5 hr, concentrated under vacuum, and distilled to yield 12.5 g of **5e:** bp 92–94° (3 Torr); NMR ($CDCl_3$) 1.25 (t, J = 7 Hz, 3 H), 1.30 (t, J = 7 Hz, 3 H), 2.58 (broad s, 4 H), 4.16 (q, J = 7 Hz, 2 H), 4.20 (q, J = 7 Hz, 2 H), 5.20 (s, 1 H), and 6.20 ppm (s, 1 H); ir (neat) 2900, 1730, 1720, 1630, 1370, 1300, 1260, 1190, 1140, 1045, 950, 890, 860, and 820 cm^{-1}.

2-Methyleneglutaric Acid (5a). A mixture of 8.0 g of **5m,** 7.82 g of potassium hydroxide, and 25 ml of water was refluxed for 2 hr, cooled, and brought to pH 1. The precipitate was filtered and recrystallized from ether to yield 3.1 g of **5a:** mp 130–136° (lit.[29] mp 129–130°); NMR (Me_2SO-d_6) 2.43 (m, 4 H), 5.62 (s, 1 H), 6.07 (s, 1 H), and 12.40 ppm (br s, 2 H); ir ($CHCl_3$) 3500, 3000, 2950, 2400, 1710, 1620, 1430, 990, and 950 cm^{-1}.

Acid Treatment of 5a. A solution of 0.30 g of **5a** in 3 ml of concentrated sulfuric acid was heated in an oil bath at 100° for 1 hr. The dark brown solution was diluted with 10 ml of water and extracted with 10 ml of ether. The extract was dried and concentrated and yielded 0.17 g of crystalline starting material.

Base Treatment of 5a. A solution of 0.500 g of **5a,** 0.600 g of potassium hydroxide, and 20 ml of water was refluxed for 18 hr, cooled, adjusted to pH 1, and extracted with 20 ml of ether. The extract was dried and concentrated, and yielded pure starting material.

Irradiation of 5a. A solution of 0.200 g of **5a** in 5 ml of methanol was irradiated at 254 nm for 15 hr. Evaporation of the solvent yielded the starting material.

Rhodium Chloride Treatment of 5e. A mixture of 0.050 g of **5e,** 0.030 g of rhodium(III) chloride dihydrate, 0.010 g of hydroquinone, and 0.5 ml of ethanol was heated in a sealed glass tube for 4.5 hr at 210°.[5] The mixture was concentrated and filtered after addition of 2 ml of carbon tetrachloride. The filtrate was shown by GLC to contain 25% of an unknown component, 8% of starting material, 10% of **4e,** 8% of **1e,** and 49% of **3e**.

Rhodium Chloride Treatment of 3e. The above procedure was repeated exactly with **3e.** GLC analysis showed the reaction mixture to contain 13% of the unknown, 7% of **5e,** 9% of **4e,** 8% of **1e,** and 63% of **3e.**

Diethyl 2-Methylglutarate. The unknown product in the rhodium chloride experiments gave no peaks above *m/e* 156 in the mass spectrum, compared to *m/e* 154 for each of the isomers **1e**–**4e,** which were not distinguishable by this technique, and **5e.** The diethyl 2-methylglutarate structure was therefore indicated and this product was prepared in 83% yield by hydrogenation of **5e** over 5% palladium on charcoal catalyst. It had bp 121–122° (3.3 Torr), NMR ($CDCl_3$) 1.18 (d, J = 6 Hz, 3 H), 1.25 (t, J = 7.5 Hz, 6 H), 1.7–2.7 (complex, 5 H), and 4.16 ppm (q, J = 7.5 Hz, 4 H), and was identical (GLC and mass spectrum) with the above unknown.

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Registry No.—**1e,** 53358-20-6; **2e,** 56298-60-3; **3a,** 53358-21-7; **3e,** 53358-19-3; **3m,** 53358-16-0; **4a,** 53358-22-8; **4e,** 53358-18-2; **4m,** 53358-15-9; **5a,** 3621-79-2; **5e,** 5621-43-2; **5m,** 5621-44-3; **7,** 56298-61-4; **8,** 56298-62-5; **9,** 56298-63-6; **11e,** 56298-64-7; **12e,** 56298-65-8; **12m,** 56298-66-9; **13,** 53358-24-0; **14,** 53358-25-1; **15e,** 56298-67-0; **15m,** 56298-68-1.

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Torsional Isomerism and Configurational Assignments in Amides Containing Three Asymmetric Centers. A Method for Distinguishing Meso and DL Secondary Amines[1a,b]

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The amides of 1-methoxyphenylacetic acid (*O*-methylmandelic acid) and *dl*- and *meso*-bis(1-phenylethyl)amine were prepared and their NMR spectra obtained under conditions of both slow and rapid torsion about amide bonds. The diastereomeric amides prepared from the meso amine could be interconverted by torsion about the configurationally labile amide bond. The diastereomeric amides prepared from the racemic amine could be separated since they differed in configuration at asymmetric carbon atoms, while the amide bond was not a configurational unit. The free energies of activation for torsion about the amide bond were determined using NMR spectroscopy. The values obtained for the amides prepared from the meso amine (15.6–15.9 kcal/mol) were nearly the same as those obtained for the two amides prepared from the *dl* amine (15.6 and 16.0 kcal/mol), although the stereochemical processes were different, isomerization in the former and topomerization in the latter two compounds. The configurations of the four amides were assigned and it was shown how the stereochemical behavior of the amides could be used to distinguish between meso and *dl* secondary amines.

Torsion about carbonyl to nitrogen bonds is slow enough on the NMR time scale to render this moiety a labile stereochemical unit. Since barriers to rotation generally fall within the range of 5–25 kcal/mol, the stereochemistry of amides is most conveniently studied by observing the coalescence of NMR resonances from diastereotopic groups, although in some cases the barrier is high enough to permit the isolation of a single isomer and the measurement of the rate of isomerization using conventional kinetics.[2] The diastereotopic groups whose NMR resonances coalesce can reside either in the same molecule (for example, in *N,N*-dimethylacetamide) or in different, isomeric molecules (for example, in *N*-methyl-*N*-ethylacetamide). In the former case, we speak of groups which are diastereotopic by internal comparison and the stereochemical process which results in coalescence is a topomerization, while in the latter case, the two groups are diastereotopic by external comparison and the stereochemical process is an isomerization which reversibly interconverts two diastereomeric molecules.

This paper deals with amides which exhibit chemical shift nonequivalence and undergo coalescence which is a reflection of either isomerization or topomerization *depending upon the stereochemistry of the substituents attached to the amide moiety.*

In addition, the ability to distinguish between topomerization and isomerization using NMR spectroscopy can be used to distinguish between diastereomeric meso and *dl* secondary amines 1.[3] NMR methods based upon the magnetic nonequivalence of diastereotopic groups[4] and upon the introduction of pseudo-asymmetry[5] have been developed. The symmetry arguments used in the present approach offer some advantages over those of previous methods.

The method of Hill and Chan[4] involves conversion of the secondary amines 1 into tertiary amines 2, which bear a prochiral atom, such as that in a benzyl group, attached to nitrogen. The two benzyl methylene protons in *dl*-2 are diastereotopic and appear as an AB quartet while those in *meso*-2 are enantiotopic. The observation of chemical shift nonequivalence allows an unambiguous assignment of the *dl* configuration to the parent amine. However, the obser-