EtOH) 247 nm (ε 10,300) and 296 (476); nmr (CCl_4) δ 2.4–1.0 (m, all protons, with CH_3 singlets at 1.90 and 1.72); mass spectrum (70 eV) *m/e* 218 (molecular ion).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.02; H, 8.22.

Tricyclo[4.4.2.0]dodecane-2,7-dione (12).—A solution of 0.886 g (5.39 mmol) of enedione **7** in 150 ml of CH_2Cl_2 saturated with ethylene was irradiated (Pyrex filter) at low temperature[27] for 1.5 hr. Progress of the addition was monitored by glpc (3% DEGS, 8 ft × 0.125 in., 135°, 30 cc/min of He). The reaction solution was dried ($MgSO_4$) and the solvent was removed to leave 1.11 g of clear oil which solidified upon standing. The material was eluted through a 2-g plug of alumina[22] with ether–hexane and recrystallized (hexane) at low temperature[23] to yield 0.707 g (68%) of **12**. A portion of **12** was sublimed [60° (0.15 mm)] for elemental analysis. Adduct **12** had mp 45–48°; ir (CCl_4) 1705 cm^{-1} (C=O); uv max (95% EtOH) 296 nm (ε 59); nmr (CCl_4) δ 2.5–1.2 (m); mass spectrum (70 eV) *m/e* 192 (molecular ion).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.91; H, 8.22.

Tricyclo[4.3.3.0]dodecane-2,7-dione (13).—A solution of 0.076 g (0.395 mmol) of **12** and 0.5 g of $TsOH \cdot H_2O$ in 45 ml of benzene was heated at reflux for 1 hr with azeotropic removal of water. Progress of the rearrangement was monitored by glpc (3% DEGS, 8 ft × 0.125 in., 135°, 30 cc/min of He). The cool reaction mixture was washed with saturated $NaHCO_3$ (30 ml) and water (10 ml), dried ($MgSO_4$), and concentrated to leave 0.070 g (92%) of **13**. Dione **13** was collected from preparative glpc (20% SE-30, 5 ft × 0.25 in., 170°, 85 cc/min of He) for characterization: mp 115–118°; ir (CCl_4) 1740 (cyclopentanone C=O) and 1705 cm^{-1} (cyclohexanone C=O); uv max (95% EtOH) 292 nm (ε 42); nmr (CCl_4) δ 2.5–1.2 (m); mass spectrum (70 eV) *m/e* 192 (molecular ion).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.92; H, 8.27.

Preparation of Transient 2,3-Dimethyltricyclo[6.4.0.$0^{3,8}$]dodec-1-ene-4,9-dione (14) and Its Acid-Catalyzed Conversion to 1,3-Dimethyltricyclo[7.3.0.$0^{4,9}$]dodec-3-ene-2,8-dione (15).—A 0.814-g (4.96 mmol) quantity of enedione **7** was converted to adduct **10** as described, using a base-washed irradiation vessel. The uranium glass filter was removed and irradiation (Pyrex) was continued for 3.75 hr, until glpc (3% DEGS, 8 ft × 0.125 in., 135°, 30 cc/min of He) indicated a mixture of static integral intensity numbers. Collection of the smaller of the two major peaks (present in *ca.* a 1:3 ratio) from glpc (10% Apiezon M, 8 ft × 0.25 in., 220°, 85 cc/min of He) showed it to be enedione **11**, which had been formed from enedione **10** on the column. [This was proved by collection of **10** from another glpc system (20% SE-30, 5 ft × 0.25 in., 180°, 85 cc/min of He) which did not cause this conversion.] Collection of the larger peak yielded enedione **15**: bp 100° (0.2 mm); ir (CCl_4) 1705 (C=O) and 1650 cm^{-1} (C=C); uv max (95% EtOH) 251 nm (ε 7890), 221 (4470), and 315 (305); nmr (CCl_4) δ 3.0–1.0 (m, with CH_3 singlets at 1.71 and 1.07); mass spectrum (70 eV) *m/e* 218 (molecular ion).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.09; H, 7.90.

The finding that **14** was a labile precursor of **15** and the determination of the photostationary mixture of **10** and **14** (as 1:3, respectively) are presented in the discussion section.

Registry No.—**1**, 22242-82-6; **3**, 42249-31-0; **4**, 42245-83-0 **6a**, 42245-84-1; **6b**, 42245-85-2; **7**, 42245-86-3; monochloro-**7**, 42249-11-6; dichloro-**7**, 42249-12-7; **8**, 42245-87-4; **10**, 42245-88-5; **11**, 42245-89-6; **12**, 42245-90-9; **13**, 42245-91-0; **14**, 42245-92-1; **15**, 42245-93-2; cyclohexenone, 930-68-7; 2-butyne, 503-17-3; ethylene, 74-85-1.

(27) Low temperature was maintained by immersing the irradiation vessel in a Dry Ice–isopropyl alcohol bath, and circulating isopropyl alcohol, cooled indirectly with Dry Ice, through the probe.

Photochemical Addition of Dimethyl Maleate to 2,3-Dimethyl-2-butene. Use of a Chiral Shift Reagent

GERALD L. GOE[1]

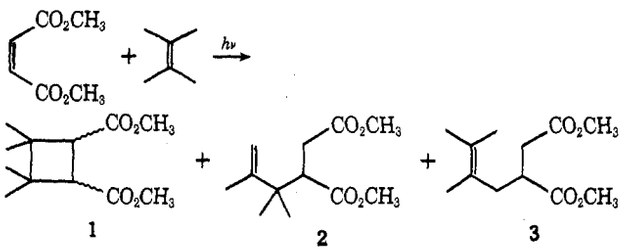
Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

Received May 30, 1973

Irradiation (253.7 nm) of dimethyl maleate with excess 2,3-dimethyl-2-butene gave dimethyl (1,1,2-trimethylallyl)succinate (49% of product), dimethyl (2,3-dimethyl-2-butenyl)succinate (33%), and dimethyl 3,3,4,4-tetramethylcyclobutane-*trans*-1,2-dicarboxylate (18%) in 33% yield. The stereochemistry of the cyclic ester was proven by conversion to the corresponding cis ester by way of the cyclic anhydride. Proton nmr spectra of the trans ester with added tris(trifluoroacetylcamphorato)europium showed different shifts for the hydrogens of the enantiomers in the racemic modification of the compound; the corresponding cis (meso) ester, similarly treated, showed different shifts for the enantiotopic nuclei, the differential shifts being intramolecular as shown by coupling between the nonequivalent methine hydrogens in the shifted spectra.

In spite of the increasing number of ways in which instrumental methods can be applied to problems of structure elucidation, chemical degradations and even independent syntheses of degradation products are frequently necessary in difficult structure problems. In connection with another problem we recently required authentic samples of *cis*- and *trans*-3,3,4,4-tetramethylcyclobutane-1,2-dicarboxylic acid, and in the process of identifying these compounds practiced a recently proposed instrumental method that promises great savings in time and material as compared with traditional chemical methods.

The dimethyl ester (**1**) of one of the desired acids was produced, albeit as a minor product, by irradiation of a mixture of dimethyl maleate and 2,3-dimethyl-2-butene (tetramethylethylene, TME). The structures of the other products, **2** and **3**, were determined unambiguously by instrumental methods (see Experimental Section) and are consistent with the allylic abstraction–radical recombination mechanism proposed for the photoaddition of dimethyl maleate to cyclohexene[2] that was confirmed by labeling studies.[2d] Only a single isomer of **1** was produced in this reaction;



1 2 3

(1) Address correspondence to Reilly Tar and Chemical Corp., Indianapolis, Ind. 46204.

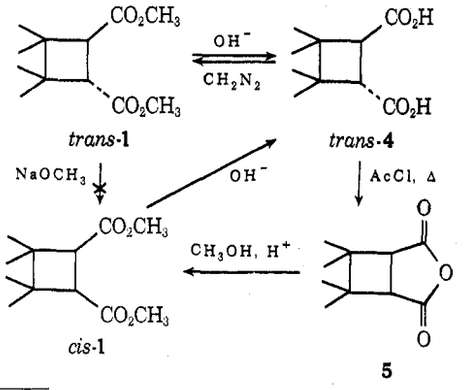
(2) (a) P. de Mayo, R. W. Yip, and S. T. Reid, *Proc. Chem. Soc., London*, 54 (1963); (b) J. A. Barltrop and R. Robson, *Tetrahedron Lett.*, 597 (1963); (c) P. de Mayo, *Pure Appl. Chem.*, **9**, 597 (1964); (d) G. Ahlgren and B. Åkermark, *Tetrahedron Lett.*, 1885 (1970).

since maleate and fumarate esters are rapidly interconverted under the reaction conditions and both are present in the reaction mixture, it made no difference whether maleate or fumarate esters were used as starting material.[3]

It remained to prove the stereochemistry of the isomer of **1** produced in the photochemical reaction and to prepare the other isomer, if possible. There are four classical methods for determining the stereochemistry of a vicinally disubstituted cyclic compound. The coupling constant in the proton nmr is frequently a useful guide to the stereochemistry of the substituents, and can sometimes be determined by examination of the ^{13}C satellite peaks in the case of identical disubstitution. Unfortunately, the cis and trans coupling constants in cyclobutanes are too similar to be used for this purpose.[4] A second method relies on conversion of the substituents to a cyclic functionality (*e.g.*, an ahydride) to demonstrate the spatial proximity of the original substituents. A third method depends on the symmetry properties of the substituted compound; in the absence of other unsuitable substituents, a cyclic compound with trans-like substituents possesses a twofold symmetry axis (before allowing for conformational effects) and no other symmetry element and therefore is not superposable with its mirror image and can support optical activity. Similarly, a suitable cis disubstituted compound will have a plane of symmetry and will be meso, incapable of supporting optical activity. Therefore, successful resolution of an unknown compound of suitable constitution to give observable optical activity can provide definitive proof of trans stereochemistry. The fourth method depends on conversion of the thermodynamically less stable isomer to the more stable, if the substituents are such that interconversion can take place and if the relative stabilities of the isomers are known. In the case of the cyclic vicinal dicarboalkoxy compounds, cis isomers are converted to trans isomers by alkoxide base.[5] Of these methods, all except the nmr method require considerable amounts of material and time, and, since a negative result is not always conclusive, the availability of both isomers is frequently a necessity.

The stereochemistry of **1** was proven to be trans by the reactions outlined in Scheme I. Treatment of the

SCHEME I



ester with sodium methoxide gave no detectable amount of another isomer, consistent with the trans stereochemistry. Since the equilibrium constant for the unsubstituted dimethyl cyclobutane-1,2-dicarboxylate is only 7.7–8.6 (temperature dependent),[5] the lack of detectable isomerization in the present case is consistent with much greater steric hindrance in *cis*-**1** than in the less substituted compound, because of the four methyl groups.

Saponification of the ester gave the diacid, *trans*-**4**, which could be transformed into the cis cyclic anhydride **5** by treatment with acetyl chloride under forcing conditions. Acid-catalyzed methanolysis of **5** gave the ester *cis*-**1**. Attempted saponification of *cis*-**1** gave concomitant isomerization, yielding *trans*-**4** exclusively;[6] this result was confirmed by esterification of the acid thus produced, to give back *trans*-**1**.

Recently, an instrumental substitute for optical resolution for proof of stereochemistry has been developed. Although a number of lanthanide compounds cause differential changes in the chemical shift of nonequivalent nuclei in the nmr spectra of compounds containing polar groups, if the ligands on the metal are chiral, then nuclei in enantiomeric molecules are shifted by different amounts.[7] Thus, as was first pointed out by Pirkle, *et al.*,[8] the racemic modification of a compound capable of supporting optical activity should demonstrate differential shifts for the two enantiomers when treated with a chiral shift reagent. A meso compound, under similar circumstances, might naively be expected to give no differential shifts. However, it must be noted that the symmetry plane common to meso stereoisomers causes symmetry-related groups to have an enantiotopic relationship to one another; although equivalent in achiral media, enantiotopic groups will reside in diastereomeric environments in a chiral medium and therefore will not be chemically equivalent; in principle, the enantiotopic nuclei will be anisochronous in the nmr.[9] Thus it should be expected that meso stereoisomers will also show differential shifts when treated with chiral shift reagents.

There is an important and observable difference between the ways in which *dl* and meso compounds are shifted, however, since the differential shifts in the *dl* compound are *inter*molecular—nuclei in the (+) and (−) molecules are shifted by different amounts—and the differential shifts in the meso compound are *intra*molecular—enantiotopic nuclei within the *same* molecule are shifted by different amounts. This difference allows a simple distinction between the two types of compounds, since nuclei in different molecules cannot couple with one another while nonequivalent nuclei within a single molecule can be coupled. If this coupling can be observed in shifted spectra, the stereochemistry of a meso compound can be confirmed.

This prediction and the stereochemistry elucidated by chemical means were confirmed by examining the

(3) Attempted photochemical cycloaddition of TME to maleic anhydride was unsuccessful.

(4) H. Weitkamp and F. Korte, *Tetrahedron, Suppl.*, **No. 7**, 75 (1966).

(5) D. S. Seigler and J. J. Bloomfield, *J. Org. Chem.*, **38**, 1375 (1973), and references cited therein.

(6) Partial isomerization of cyclobutane-*cis*-1,2-dicarboxylic acid to the trans isomer under conditions of acid or heat has been observed: E. R. Buchman, A. O. Reims, T. Skei, and M. J. Schlatter, *J. Amer. Chem. Soc.*, **64**, 2696 (1942).

(7) Review: R. von Ammon and R. D. Fischer, *Angew. Chem., Int. Ed. Engl.*, **11**, 675 (1972).

(8) M. Kainosho, K. Ajisaka, W. H. Pirkle, and S. D. Beare, *J. Amer. Chem. Soc.*, **94**, 5924 (1972).

(9) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).

nmr spectra of *cis*- and *trans*-**1** as influenced by the chiral shift reagent tris(trifluoroacetylcamphorato)-europium [Eu(tfac)$_3$]. Both isomers gave differentially shifted spectra for all the kinds of protons, but, while the methine hydrogens in *trans*-**1** gave differential shifts that were clearly intermolecular, the methine hydrogens of *cis*-**1** gave an obvious AB pattern [J_{AB} = 9.8 Hz, $\delta_A - \delta_B$ = 18.1 Hz at 100 MHz and 0.4 equiv of Eu(tfac)$_3$] in the shifted spectra (see Figure 1), confirming that the groups are enantiotopic by internal comparison, and therefore that the compound has a plane of symmetry and is meso and cis disubstituted. It is also worthy of note that the cis isomer is more shifted than the trans, as noted by Pirkle, *et al.*,[8] in a known system, probably because of greater ease of approach of the cis isomer to the metal.

Thus the use of chiral shift reagents to elucidate stereochemistry promises great savings in time and amounts of material needed, *if* the compounds of interest are such that additional coupling in the shifted spectra of the meso isomer can be observed. In contrast with other methods, assignment made by this method should always be reliable even if only one isomer is available, providing that the above conditions are met.

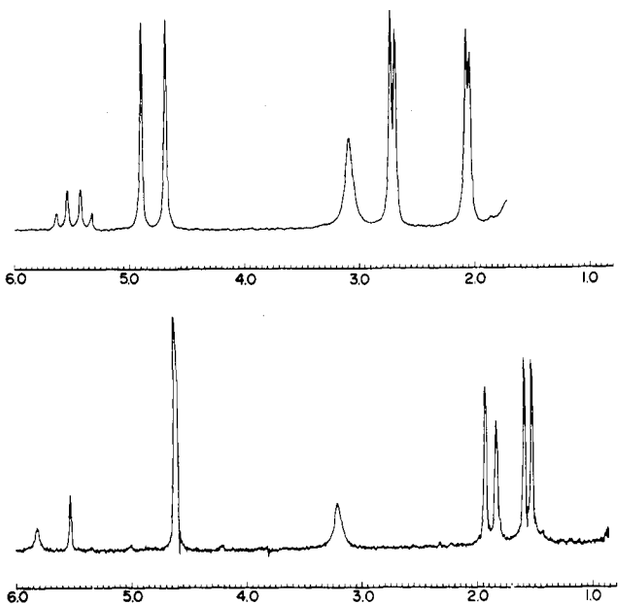


Figure 1.—Nmr spectra (100 MHz) of *cis*-**1** (top) and *trans*-**1** (bottom), each with 0.4 equiv of Eu(tfac)$_3$. Scale is in ppm downfield from TMS. Peak at 3.1–3.2 is due to shift reagent. The downfield peak for methine hydrogen in *trans*-**1** (δ 5.8 in the bottom spectum) is observably broader than other peaks at all shift reagent concentrations. Expansion of the peak at δ 4.6 in the spectrum of *trans*-**1** shows it to consist of two peaks separated by 0.6 Hz.

Experimental Section[10]

Irradiation of Dimethyl Maleate and 2,3-Dimethyl-2-butene.—A solution of 12.0 g (0.083 mol) of dimethyl maleate, 15.0 g (0.18 mol) of TME, and 2 ml of absolute EtOH (necessary for homogeneous solution) was sealed in a quartz tube with a serum cap and deaerated by nitrogen bubbling. The resulting solution was irradiated with a circular array of 16 G15T8 germicidal lamps for 14 days; aliquots were taken periodically for analysis by glpc [6 ft × 0.125 in. 5% diethylene glycol succinate (DEGS) on Chromosorb G, 140°]. Solvent and excess TME were removed under reduced pressure at room temperature, and the residue was distilled under reduced pressure. After a small forerun of maleate and fumarate esters a mixture of **1**, **2**, and **3** (6.2 g, 33%; glpc area ratio 18:49:33, using flame ionization detector) was distilled, bp 135–150° (18–20 mm). Pure samples of the products were obtained by preparative glpc (8 ft × 0.375 in. 10% DEGS on Chromosorb P, 150°); order of elution was **1**, **2**, and **3**. No *cis*-**1** could be detected in the mixture (limit of detection ~1%).

Dimethyl 3,3,4,4-Tetramethylcyclobutane-*trans*-1,2-dicarboxylate (*trans*-**1**).—The compound was further purified by recrystallization from MeOH–H$_2$O: mp 75.0–75.5°; ir 1735 cm^{-1}; nmr (60 MHz) δ 0.95 (s, 3), 1.05 (s, 3), 3.04 (s, 1), and 3.63 (s, 3); mass spectrum *m/e* (rel intensity) 228.136 (M$^+$, 9, calcd for $C_{12}H_{20}O_4$ 228.135), 115 (100), 114 (52), 84 (48), 83 (60).

Dimethyl (1,1,2-Trimethylallyl)succinate (**2**).—The liquid compound was further purified by preparative glpc (3 ft × 0.25 in. 10% silicone rubber SE-30 on Chromosorb P, 130°): ir (film) 3080, 1735, and 895 cm^{-1}; nmr (60 MHz) δ 1.05 and 1.08 (2s, 6), 1.77 (br s, 3), 2.03–3.05 (m, 3), 3.60 and 3.63 (2s, 6), and 4.76 (br s, 2); mass spectrum *m/e* (rel intensity) 228.139 (M$^+$, 3, calcd for $C_{12}H_{20}O_4$ 228.135), 83 (100).

Dimethyl (2,3-Dimethyl-2-butenyl)succinate (**3**).—The liquid compound was further purified by preparative glpc (conditions as for **2**, above): ir 1740 cm^{-1}; nmr (60 MHz) δ 1.63 (s, 9), 2.12–2.67 (m, 4), 2.72–3.17 (m, 1), and 3.62 (s, 6); mass spectrum *m/e* (rel intensity) 228.124 (M$^+$, 28, calcd for $C_{12}H_{20}O_4$ 228.135), 83 (100).

Attempted Isomerization of *trans*-1 with Sodium Methoxide.—A mixture of 5.6 mg (0.025 mmol) of *trans*-**1**, 5 ml of dry MeOH, and 0.1 ml (0.002 mmol of NaOMe) of a MeOH solution 0.02 *M* in NaOMe was heated under reflux in a nitrogen atmosphere. Aliquots (0.04 ml) were removed periodically and quenched with H$_2$O and CH$_2$Cl$_2$, the layers were separated, and the dried (MgSO$_4$) CH$_2$Cl$_2$ layers were analyzed by glpc. After 20 hr another 0.4 ml of NaOMe solution was added (total base 0.011 mmol) and heating was continued. After another 26 hr, the trans ester remained unchanged, and no *cis*-**1** could be detected by glpc.

3,3,4,4-Tetramethylcyclobutane-*trans*-1,2-dicarboxylic Acid (*trans*-**4**).—A mixture of 187 mg (0.82 mmol) of *trans*-**1**, 2 g of KOH, and 20 ml of 80% EtOH was heated under reflux for 4 hr. Most of the solvent was evaporated and the residue was diluted with H$_2$O. The resulting basic solution was extracted with CH$_2$Cl$_2$ and the organic layer discarded, acidified with concentrated HCl, and extracted continuously with CH$_2$Cl$_2$ for 48 hr. The extract was evaporated to yield 160 mg (98%) of crude *trans*-**4**, which was recrystallized from acetone–hexane, mp 212.5–213.5°.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found (Schwarzkopf Microanalytical Laboratory): C, 59.82; H, 8.05.

3,3,4,4-Tetramethylcyclobutane-*cis*-1,2-dicarboxylic Anhydride (**5**).—A mixture of *trans*-**4** (126 mg, 0.63 mmol) and 2.0 ml of acetyl chloride was heated under reflux with protection from atmospheric moisture for 4 hr. Excess acetyl chloride was removed by distillation and the residue was heated at 150° for 2 hr. This material was sublimed at 180–200° (0.1 mm) to yield 92 mg (~80%) of crude **5** (mp 124–130°) which appeared to contain some trans mixed anhydride (see below) but which was not further purified: ir 1857 and 1780 cm^{-1}; mass spectrum *m/e* (rel intensity) 182.094 (M$^+$, 0.1, calcd for $C_{10}H_{14}O_3$ 182.093), 154 (4), 110 (2), 83 (100).

Dimethyl 3,3,4,4-Tetramethylcyclobutane-cis-1,2-dicarboxylate (*cis*-**1**).—A mixture of 52 mg (0.29 mmol) of crude **5**, 5 ml of dry MeOH, and 0.05 ml of concentrated H$_2$SO$_4$ was heated under reflux with protection from moisture for 2 hr. The resulting solution was diluted with H$_2$O and extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ solution was washed with saturated aqueous NaHCO$_3$ solution, dried (MgSO$_4$), and evaporated to yield 45 mg (69%) of *cis*-**1**, found to be contaminated with 27% (by nmr and glpc) of *trans*-**1**. Pure liquid *cis*-**1** was isolated by preparative glpc (9 ft × 0.25 in. 10% DEGS on Chromosorb P, 155°): ir 1740 cm^{-1}; nmr (60 MHz) δ 1.11 (br s, 6), 2.95 (s, 1), and 3.60 (s, 3); mass spectrum *m/e* (rel intensity) 228.138 (M$^+$, 1, calcd for $C_{12}H_{20}O_4$ 228.135), 115 (100), 114 (53), 84 (47), 83 (77).

(10) Melting points were taken on a Fisher-Johns apparatus that had been calibrated with known compounds. Nmr spectra were recorded using Varian A-60A (60 MHz) or XL-100 (100 MHz) spectrometers and CCl$_4$ solutions. Ir spectra were taken on CCl$_4$ solutions except as noted. Mass spectra were recorded on an AEI MS902 mass spectrometer at an ionizing voltage of 70 eV; the masses of molecular ions were measured by peak matching with the appropriate peak of tris(perfluorobutyl)amine reference.

Nmr Spectra of *cis*-1 and *trans*-1 with Eu(tfac)$_3$.—Solutions of *cis*-1 (18 mg) and *trans*-1 (26 mg), each in 0.35 ml of CCl_4 containing TMS, were prepared, and solutions of Eu(tfac)$_3$ (Willow Brook Laboratories) in CCl_4 were prepared such that 0.01 ml would contain 0.05 molar equiv of the shift reagent. Nmr spectra (100 MHz) of the esters were recorded after each addition of 0.01- or 0.02-ml aliquots of the shift reagent solution. The esters were recovered from the resulting solutions by column chromatography on silica gel, eluted with benzene. (The shift reagent could not be recovered by this procedure.)

3,3,4,4-Tetramethylcyclobutane-*trans*-1,2-dicarboxylic Acid (*trans*-4) from *cis*-1.—A mixture of *cis*-1 (16 mg, 0.07 mmol, recovered from the shifted nmr sample as described above) and 3 ml of a solution of 10% KOH in 80% EtOH was heated under reflux for 2 hr and diluted with H_2O. The basic solution was extracted with CH_2Cl_2 and the organic layer discarded, acidified with concentrated HCl, and extracted continuously with CH_2Cl_2 for 29 hr. The CH_2Cl_2 solution was evaporated to give 11 mg (79%) of crude *trans*-4, mp 210–211.5°, mmp with authentic *trans*-4 212–213°. A 2-mg sample of acid was esterified in MeOH solution with ethereal diazomethane to give only *trans*-1, identical with an authentic sample by glpc and ir.

Acknowledgment.—I wish to thank Mr. Don Schifferl for the mass spectra and for assistance with the 100-MHz nmr spectra.

Registry No.—*trans*-1, 42151-26-8; *cis*-1, 42151-27-9; 2, 42151-28-0; 3, 42151-29-1; *trans*-4, 42151-30-4; 5, 42151-31-5; dimethyl maleate, 624-48-6; 2,3-dimethyl-2-butene, 563-79-1; acetyl chloride, 75-36-5.

N-Acylation during the Addition of Carboxylic Acids to *N-tert*-Butylacylketenimines and the Use of the Reagent *N-tert*-Butyl-5-methylisoxazolium Perchlorate for Peptide Synthesis

DARRELL J. WOODMAN* AND A. I. DAVIDSON

Department of Chemistry, University of Washington, Seattle, Washington 98195

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Diacylamide precursors of amide impurities have been detected in spectral tests of the addition of carboxylic acids to *N-tert*-butylacylketenimines. Variations in the product distribution with an inefficient acylketenimine in media of differing acidity suggest that diacylamide formation involves a second intermediate adduct that does not convert rapidly to the desired enol ester. A high free acid concentration results in interception of the intermediate to give acid anhydrides. Partial deuterium incorporation at the vinylic position of the enol esters indicates that intramolecular *O,O*-acyl migration is relatively slow for the adducts of *N-tert*-butylacylketenimines, and possible substituent influences are discussed. The preparation of β-acyloxy-*N-tert*-butylcrotonamide enol ester acylating agents from *N-tert*-butyl-5-methylisoxazolium perchlorate succeeds with unprotected hydroxyl groups and the carboxamide function of glutamine. However, amide dehydration was observed in the case of asparagine and competing azlactone formation was detected with benzoylleucine. Crystalline esters were not obtained with Z-Ala-OH, Z-Tyr-OH, and Z-Met-OH. Test couplings have established compatibility of the enol esters with unprotected hydroxyl groups in the amine component but results are not markedly improved relative to *N*-ethyl-5-phenylisoxazolium 3′-sulfonate. A new side reaction, condensation of the amine component with the coupling by-product, is shown to be a likely source of impurities in the use of the esters of hindered carboxylic acids. The original zwitterionic isoxazolium salt reagent is much less susceptible to the side reaction.

Since the discovery of the facile conversion of carboxylic acids to enol ester acylating agents upon reaction with 3-unsubstituted isoxazolium salts,[1] there have been continuing attempts to obtain isoxazolium cations with superior properties for application as reagents in peptide synthesis. Following the development of the zwitterion *N*-ethyl-5-phenylisoxazolium 3′-sulfonate (NEPIS),[2] structural modifications have centered on the substituent on nitrogen,[3,4] benzisoxazolium cations,[5,6] and other ring-fused isoxazolium salts.[7] The issues of concern underlying these efforts have been the avoidance of rearrangement of the enol esters to diacylamides, the efficiency of enol ester formation, and the prevention of racemization *via* azlactones during the formation and reactions of enol esters of N-protected peptide acids. In contrast to the *N*-aryl heterocycles,[3] the *N-tert*-butyl compounds (**1**) were found to stabilize the enol esters relative to rearrangement.[4] However, examination of the reagent *N-tert*-butyl-5-methylisoxazolium (**1a**) perchlorate revealed *N-tert*-butylamides (**7**) as a side reaction product.[4] Our further examination of the *N-tert*-butyl system has led to the partial elucidation of the side reaction, the discovery of new complications in the reaction of the *N-tert*-butylacylketenimine intermediates (**2**) with carboxylic acids, and a definition of the limits of synthetic utility for **1a**.

A likely explanation of the side reaction observed in the *N-tert*-butyl series would involve *N-tert*-butyldiacylamides (**6**) as precursors of the amides **7**. Since the diacylamides were not themselves detected in the previous study, they would have to be relatively labile compounds. Consistent with this possibility, an attempt to force thermal rearrangement of the enol ester **4a** (R_3 = $ZNHCH_2$) of carbobenzoxyglycine to the corresponding diacylamide **6a** gave only the decomposition fragments amide **7** and *N-tert*-butylacetoacetamide (**5a**).[8] Spectral data in support of the proposed

(1) R. B. Woodward and R. A. Olofson, *J. Amer. Chem. Soc.*, **83**, 1007 (1961); *Tetrahedron, Suppl.*, **7**, 415 (1966).

(2) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Amer. Chem. Soc.*, **83**, 1010 (1961); *Tetrahedron Suppl.*, **No. 8**, 321 (1966).

(3) R. B. Woodward, D. J. Woodman, and Y. Kobayashi, *J. Org. Chem.*, **32**, 388 (1967).

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(8) Other workers[9] have reported that the enol ester of 3,5-diamino-6-chloropyrazine-2-carboxylic acid similarly gives the *N-tert*-butylamide on treatment with triethylamine, but a compound assigned the diacylamide structure was obtained with methoxide in polar media. If the latter structure is correct, it remains unclear why fragmentation took place only in the former medium and what special factors account for imide stability in the latter experiment.

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