The ether extracts were washed with water, dilute sodium hydroxide solution, and water, then treated with methanol (10 ml), and evaporated to dryness under vacuum at 100°, leaving 2.92 g of brown liquid. This was dissolved in petroleum ether (bp 30–60°) and the solution was passed through a 1.8 × 9 cm column of silica gel G, eluting with petroleum ether until the dark brown band was about to emerge. Solvent removal from the eluate left 2.58 g of amber oil which was chromatographed again on a 1.8 × 25.5 cm column of silica gel G. Progress of the colorless fraction could be followed visually by change in the appearance of the absorbent, and elution of this material was accomplished using 100 ml of petroleum ether, collected in seven fractions. The first 5-ml fraction afforded 0.14 g of mobile colorless oil, and the remaining six fractions afforded 0.77 g. The column was further eluted with benzene (152 ml), from which eluate 1.20 g of viscous liquid resulted on evaporation.

Vapor phase chromatography (5-ft analytical column of 20% silicone rubber on 45–60 mesh firebrick, 200°) of the first fraction above showed two constituents. The leading fraction was isolated by preparative vapor phase chromatography, and proved to be *cis*-1,3-diphenylpropene, as shown by comparison of its retention time and its infrared and ultraviolet spectra with those of an authentic sample. Its catalytic reduction (30% Pd–C, ethanol) yielded a sample whose infrared and ultraviolet spectra and vapor phase chromatographic retention time corresponded to those of authentic 1,3-diphenylpropane.

From a similar acetolysis, 1.7 g of hydrocarbon fraction was obtained from 10 g of tosylate. Vapor phase chromatography again showed two components, 15% of the above *cis*-1,3-diphenylpropene and 85% of a component with longer retention time. The latter was isolated and repeatedly recrystallized from hexane (Dry Ice–methanol), yielding a sample of *trans*-1,3-diphenylpropene, mp 15–17°, which was chromatographically homogeneous and displayed an infrared spectrum identical with that of an authentic sample. Its catalytic hydrogenation, as before, resulted in the uptake of 1 molar equiv of hydrogen and the formation of a product whose infrared and ultraviolet spectra and gas chromatographic retention time corresponded again to those of 1,3-diphenylpropane. Its bromination in chloroform afforded the crystalline 1,2-dibromo-1,3-diphenylpropane, mp 107–109.5°, reported by Dieckmann and Kämmerer.[35] The product had an infrared spectrum identical with and showed no mixture melting point depression with an authentic sample of this dibromide.

The infrared spectra of the above 1.2 g of viscous syrup from the original benzene eluate showed strong bands at 1730 and 1245 cm^{-1}, suggesting a mixture of acetates. Vapor phase chromatography of the product (the above analytical column, 200°) showed seven peaks with retention times (in minutes) (relative intensity) as follows: (a) 2 (3.7), (b) 3.5 (3.1), (c) 4.3 (4.7), (d) 6.5 (6.0), (e) 7.8 (13.4), (f) 9.5 (2.8), and (g) 12.0 (0.5). Under the same conditions a crude sample of 2-tropyl-2-phenylethyl acetate showed a retention time of 7.8 min. The identities of these presumably ester products are currently under investigation.

Acetolysis of 2,3-Diphenyl-1-propyl *p*-Toluenesulfonate.—A solution containing the above tosylate (1.0 g), anhydrous sodium acetate (0.5 g), and a trace of hydroquinone in acetic acid (20 ml) was heated under reflux for 16 hr, then was cooled and poured into ice and water (175 g) containing sodium hydroxide (16 g). The mixture was extracted with ether, and the extract was washed with water, treated with methanol (5 ml), and evaporated to dryness under vacuum. Vapor phase chromatographic examination of the crude residue showed three peaks in a ratio of 25:120:196, the retention times of the first two matching those of *cis*- and *trans*-1,3-diphenylpropene. The entire sample was placed on a 1.8 × 2.0 cm column of silica gel G, which was eluted with petroleum ether (50 ml) followed by benzene (75 ml). Evaporation of the petroleum ether eluate yielded 0.20 g of colorless oil whose ultraviolet and infrared spectra matched those of the crude 1,3-diphenylpropene fraction from the previous acetolysis. Rechromatographing on silica gel G gave 0.15 g of colorless oil whose vapor phase chromatography showed two peaks corresponding in retention time to *cis*- and *trans*-1,3-diphenylpropene. Evaporation of the above benzene eluate afforded 0.50 g of colorless liquid whose infrared spectrum was consistent with that of an acetate. Vapor phase chromatography showed two peaks in a ratio of 1:5.3. The crude material was reduced to an alcohol (0.37 g) using lithium aluminum hydride in ether. The infrared spectrum of the alcohol product was identical with that of a sample of 1,3-diphenyl-2-propanol prepared by the lithium aluminum hydride reduction of dibenzyl ketone.

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(35) W. Dieckmann and M. Kämmerer, *Ber.*, **39**, 3046 (1906).

Organic Fluorine Compounds. I. Reinvestigation of the Action of Perchloryl Fluoride on Diethyl Malonate[1]

HERMAN GERSHON, J. A. A. RENWICK, W. K. WYNN, AND RICHARD D'ASCOLI

Boyce Thompson Institute for Plant Research, Inc., Yonkers, New York 10701

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The reaction of perchloryl fluoride on diethyl malonate in the presence of strong base has been reexamined. Whereas it was previously reported that only one product, diethyl difluoromalonate, resulted from this reaction in ethanol, the present study established the presence of five products: diethyl difluoromalonate (I), diethyl ethylmalonate (II), diethyl malonate (III), diethyl ethylfluoromalonate (IV), and diethyl fluoromalonate (V). In an aprotic solvent, toluene, the reaction yielded only I, III, and V. The alcohol was shown to participate in a competing reaction. That these reactions are general was established by comparable studies with diethyl ethylmalonate and diethyl fluoromalonate.

It was reported by Inman and co-workers[2–5] that compounds containing active methylene groups could be fluorinated by perchloryl fluoride in the presence of strong base. These authors[3] stated that on fluorination of the sodium salt of diethyl malonate in ethyl alcohol only the difluoromalonate was produced. Even if insufficient sodium was used, the difluoromalonate and unreacted starting material were obtained. A quantitative yield of diethyl difluoromalonate was produced when 2 equiv of sodium/mole of diethyl malonate was employed. No monofluoromalonic ester was recovered under any of the fluo-

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(1) This investigation was supported, in part, by the Cancer Chemotherapy National Service Center, National Institutes of Health, under Contract No. PH 43-63-579.

(2) C. E. Inman, E. A. Tyczkowski, R. E. Oesterling, and F. L. Scott, *Experientia*, **14**, 355 (1958).

(3) C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Am. Chem. Soc.*, **80**, 6533 (1958).

(4) C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, U. S. Patent 3,030,408 (1962).

(5) C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, U. S. Patent 3,141,040 (1964).

TABLE I

COMPOSITION OF FLUORINATION MIXTURES

Reaction conditions[a]			Products, % of solvent-free mixture					
Reaction	Ester	Base	I	II	III	IV	V	VI
A	III	Na (C_2H_5OH)	36.1	25.2	14.4	15.3	8.7	
B	III	Na (C_2H_5OH)	26.2	5.2	40.2	0.5	28.2	
C	III	Na (toluene)	29.2	0	29.3	0	41.6	
D	II	Na (C_2H_5OH)		33.3		51.5		15.2
E	II	Na (toluene)		4.0		96.0		0
F	V	Na (C_2H_5OH)	85.6			6.7	7.6	
G	V	Na (toluene)	95.5[b]					

[a] The ester, base, and ClO_3F are all in the molecular proportion of 1:1:1 except A which is 1:2:2. [b] The remaining 4.5% of the mixture was composed of two unidentified materials.

rinating conditions, although it undoubtedly was formed as an intermediate. This was explained by stating that, since diethyl monofluoromalonate is a stronger acid than diethyl malonate, it competes successfully for the available base and undergoes difluorination before monofluorination of another molecule of diethyl malonate could take place.

In the course of our work on the preparation of amino acid analogs and small fluorinated molecules as potential chemotherapeutic agents,[6,7] it was desired to prepare a supply of diethyl difluoromalonate. After several attempts with the procedure,[3] we invariably obtained products deficient in fluorine. Upon examination of the reports of Inman, Oesterling, and Tyczkowski,[3-5] it can be seen that although the carbon and hydrogen values for the compound were correct no fluorine assay was reported in ref 3.[8]

As a result of our inability to prepare the desired product in a satisfactory state of purity by the method described,[3] along with the unsatisfactory data characterizing the compound,[3,8] we decided to reinvestigate the reaction of perchloryl fluoride on the sodium salt of diethyl malonate. Three variations of the conditions of fluorination were attempted. The first two reactions were conducted in anhydrous ethyl alcohol, and the molar ratios of diethyl malonate:sodium:perchloryl fluoride were (A) 1:2:2 and (B) 1:1:1. The third reaction was carried out in dry toluene, and the molar ratio of the reactants was (C) 1:1:1. The first two variations were designed to test the conclusion that only diethyl difluoromalonate could be obtained regardless of the ratio of reactants, and the third variation was included to determine if the solvent affected the course of the reaction. Toluene was selected because it is an aprotic solvent and possesses a low dielectric constant.

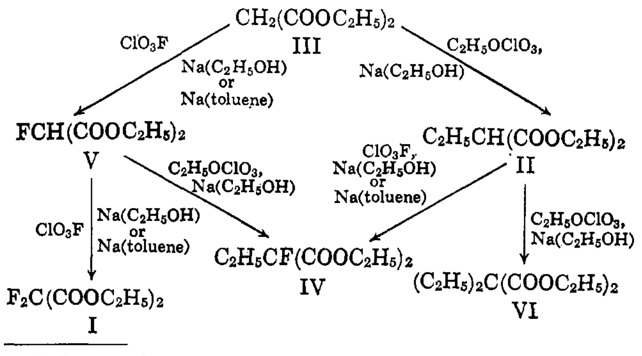
Upon completion of each fluorination, the mixture was freed of solvent and of inorganic salts and was subjected to gas chromatography. The results are presented in Table I. Mixture A is composed of five products which were identified as diethyl difluoromalonate (I), diethyl ethylmalonate (II), diethyl malonate (III), diethyl ethylfluoromalonate (IV), and diethyl fluoromalonate (V). B shows the same five peaks but in different proportions, and C has three peaks composed of I, III, and V. These compounds were identified by means of retention times, refractive indices, and infrared spectra. Elemental composition was established where necessary.

For the identification of the diethyl ethylfluoromalonate (IV), we referred to the previously cited literature.[3-5]

Since this compound was not properly identified,[9] it became desirable to repeat a study on the fluorination of diethyl ethylmalonate (II), similar to the one on diethyl malonate (III). The first fluorination (D) was carried out in anhydrous ethyl alcohol, and the molecular ratio of reactants, II:sodium:perchloryl fluoride was 1:1:1, whereas the second fluorination (E) was conducted in dry toluene, employing the reactants in the same ratio. The reaction mixtures were prepared as previously described and resolved by gas chromatography. These results are also listed in Table I. Mixture D was composed of three products. The compounds were identified as diethyl ethylmalonate (II), diethyl diethylmalonate (VI), and diethyl ethylfluoromalonate (IV). E showed only two products, II and IV.

Upon examination of the products obtained from reactions A and B, it is clear how I, III, and V arose. Product II was formed by alkylation. The alkylating agent was undoubtedly ethyl perchlorate which was shown by Inman, *et al.*,[2] to be formed on reaction of perchloryl fluoride with sodium ethoxide. IV was obtained from II and/or V. Reaction C was characterized by the absence of II and IV. In reaction D product VI was produced from II by alkylation with ethyl perchlorate, and reaction E was also characterized

SCHEME I



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(6) H. Gershon and A. Scala, *J. Org. Chem.*, **27**, 463 (1962).

(7) H. Gershon, S. G. Schulman, and A. D. Spevack, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964, p 15-K.

(8) Whereas ref 4 and 5 reported the same analytical data for carbon and hydrogen, a fluorine assay was also included. *Anal.* Calcd: F, 19.37. Found: F, 17.20.

(9) Compound IV was mentioned in ref 3 but was not characterized. Its presence was established by means of the derivative, 5-ethyl-5-flourobarbituric acid. In ref 4 and 5, the details of the fluorination were presented, but the elemental composition of the product was unsatisfactory: *Anal.* Calcd: C, 52.42; H, 7.33. Found: C, 54.69; H, 7.31. No fluorine assay was reported. Since this work was completed, IV was described by F. L. M. Pattison, R. L. Buchanan, and F. H. Dean, *Can. J. Chem.*, **43**, 1700 (1965).

TABLE II

PHYSICAL DATA

Compound	Retention time, min	Obsd, $n^{25}\text{D}$	Lit. $n\text{D}$(°C)	$\nu_{\text{max}}^{\text{C=O}}$ (liquid), cm^{-1} Obsd	Lit.
Diethyl difluoromalonate (I)	3.3	1.3750	1.3800 (20)[a]	1770, 1785	1765, 1785[a]
Diethyl ethylmalonate (II)	6.4	1.4138	1.4138 (25)[b]	1740, 1758	1742, 1759[c]
Diethyl malonate (III)	7.9	1.4123	1.4142 (20)[d]	1738, 1758	1742, 1760[c]
Diethyl ethylfluoromalonate (IV)	9.7	1.4064	1.4060 (25)[e]	1760	
Diethyl fluoromalonate (V)	13.5	1.4035	1.4040 (27)[f]	1755, 1772	1750, 1780[f]
Diethyl diethylmalonate (VI)	6.8	1.4218	1.4252 (16.6)[g]	1735, 1749	1737, 1751[c]

[a] Reference 3. [b] Since no $n\text{D}$ for this compound could be found in the literature, the result reported was taken of a chromatographically homogeneous commercial sample. [c] R. A. Abramovitch, *Can. J. Chem.*, **36**, 151 (1958). [d] C. Contzen-Crowet, *Bull. Soc. Chim. Belges*, **35**, 165 (1926). [e] Footnote 9. [f] Reference 15. [g] K. von Auwers, *Ber.*, **46**, 494 (1913).

by the absence of VI. These reactions are summarized in Scheme I.

The results indicate that the solvent influenced the course of the reaction Toluene appeared to be inert, while ethyl alcohol became involved. In toluene, the action of perchloryl fluoride on III involved two competing reactions, the formation of V from III and of I from V, and the yield of V was nearly 1.5 times that of I. On fluorination of II in toluene, only one anion could be formed, and, consequently, IV was obtained in nearly quantitative yield. On the other hand, the action of perchloryl fluoride on III in ethyl alcohol involved four competing reactions: the formation of V from III, I from V, II from III, and IV from II and/or V. The yields of products were influenced by the amount of base present. In reaction B, I and V were formed in nearly equal yield, II and IV were present in very low yield, and a high per cent of unreacted starting material (III) remained. In reaction A, where the level of base was double that in B, the yield of I was increased at the expense of III and V, and the yields of II and IV were also markedly increased at the expense of III. In the case of D, there were only two competing reactions: IV was formed from II by fluorination and VI was produced by alkylation of II. In E, IV was formed in nearly quantitative yield.

Since it was still desired to prepare diethyl difluoromalonate (I), a similar study of the action of perchloryl fluoride on diethyl fluoromalonate (V)[10] was made. In alcohol, the reaction mixture was composed of products I, IV, and V, and in toluene, I was present in nearly quantitative yield.

The physical data establishing the identities of I–VI obtained by preparative gas chromatography are listed in Table II.

Experimental Section[11]

Fluorination of Diethyl Malonate in Ethyl Alcohol. A.—To a solution of 4.6 g (0.2 g-atom) of sodium in 500 ml of absolute ethyl alcohol was added 16.0 g (0.1 mole) of diethyl malonate. A stream of perchloryl fluoride[12] (11.3 g, 0.11 mole) was passed into the mixture, keeping the temperature between 10 and 15° by external cooling.[3] Upon completion of the reaction as evidenced by no further heat of reaction and loss of alkalinity of the mixture, the inorganic salts were removed by filtration. The solvent was flash evaporated, and the residue was passed through a fine sintered-glass filter and chromatographed.

B.—This reaction was carried out as above, except that the molecular ratio of reactions was 1:1:1.

Fluorination of Diethyl Malonate in Toluene. C.—Sodium dispersion[13] (2.3 g, 0.1 g-atom of sodium) was suspended in 200 ml of dry toluene and was titrated with 16.8 g (0.105 mole) of diethyl malonate.[14] Perchloryl fluoride (11.3 g, 0.11 mole) was added to the suspension in a rapid stream, keeping the temperature at 10–15° by means of an ice bath. Upon completion of addition of the gas, the inorganic materials were removed by filtration and the toluene was flash evaporated under vacuum. The residue was filtered through a fine sintered-glass filter and assayed by gas chromatography.

Fluorination of Diethyl Ethylmalonate in Ethyl Alcohol. D.—This procedure was similar to B.

Diethyl Ethylfluoromalonate (IV).—The procedure was similar to C, but 80% of product was recovered on distillation, bp 95–96° (10 mm), lit.[9] bp 96–99.5° (13 mm).

Anal. Calcd for $C_9H_{15}FO_4$: C, 52.42; H, 7.33; F, 9.21. Found: C, 52.50; H, 7.54; F, 8.78.

Fluorination of Diethyl Fuoromalonate in Ethyl Alcohol. F.—The procedure was similar to B.

Diethyl Difluoromalonate (I).—The procedure was similar to C, except that the sodium salt of diethyl fluoromalonate was formed at 85–90°. On distillation, 82% of product was recovered, boiling at 90–94° (23 mm), lit.[15] bp 94–95° (23 mm).

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(10) H. Machleidt, *Ann.*, **676**, 66 (1964).

(11) Infrared data were obtained with a Perkin-Elmer Model 221 spectrophotometer, and refractive indices were taken in a Bausch and Lomb, Abbe-3L refractometer. Analytical gas chromatography was performed on an Aerograph Model 204 with a flame-ionization detector to which was attached a Leeds and Northrup Speedomax H recorder fitted with a Model 207 disk integrator. A stainless steel column, 5 ft × 1/8 in. o.d. was packed with 20% diethylene glycol succinate coated on 80–100 mesh Chromosorb W previously treated with hexamethylsilazane. The instrument was operated at a column temperature of 113° and a flow rate of nitrogen of 30 cc/min. Preparative gas chromatography was carried out with an Aerograph Autoprep Model A-700 fitted with a 20 ft × 3/8 in. o.d. aluminum column packed with 25% Apiezon L on acid-washed 30–60 mesh Chromosorb W. The column was operated at 190° with a flow rate of helium of 200 cc/min. Compounds II and IV were collected as a mixture free of I, III, and V by means of this column. To separate II from IV, a second column was prepared using 20 ft × 3/8 in. o.d. aluminum tubing packed with 30% diethylene glycol succinate coated on 45–60 mesh acid-washed firebrick. This column was operated at 185° with a flow rate of helium of 200 cc/min.

(12) Perchloryl fluoride was obtained from Pennsalt Chemical Corp., Philadelphia 2, Pa., along with technical pamphlet DC-1819, "Perchloryl Fluoride," on details of safety and handling.

(13) Purchased from Gray Chemical Co., Gloucester, Mass., as 50% sodium in mineral spirits.

(14) The end point of the titration was determined by cessation of hydrogen evolution, since there was no way to measure the exact quantity of sodium to be transferred. A slight excess of malonic ester was always employed to ensure complete utilization of the sodium.

(15) E. D. Bergmann, S. Cohen, and I. Shahak, *J. Chem. Soc.*, 3286 (1959).