chemical reduction[5] of carbon–carbon unsaturated compounds. Both reactions involve the trapping of organometallic reagents formed from an alkali metal and an unsaturated organic compound. A protic solvent serves as trapping agent in the chemical reduction, and a chlorosilane is the trapping agent in the disilylation reaction. The unusual phenomenon noted in the latter synthesis,[3] whereby the disilylation of aryl olefins with lithium in tetrahydrofuran (THF) could be directed toward monomolecular or bimolecular products by minor changes in trapping agent to olefin ratio, prompted a short reinvestigation of the chemical reduction of an aryl olefin at various ratios of proton source to olefin. We now wish to report that the same phenomenon is noted in the chemical reduction of α-methylstyrene and to suggest a convenient method for directing the chemical reduction of aryl olefins to monomolecular or bimolecular products.

The chemical reduction of monoaryl olefins has usually given the monomolecular product. Thus, styrene yields ethylbenzene with lithium and ethylaniline,[6] sodium in ammonia,[7] or $Ca(NH_3)_6$ in ether[8] and yields 1-ethylcyclohexene with lithium in methylamine.[9] In these typical reduction procedures a large excess of the proton source is employed. A bimolecular reduction of α-methylstyrene to 2,5-diphenylhexane was accomplished by Frank, *et al.*,[10] *via* a two-step procedure.

$$\mathrm{PhMeC{=}CH_2 + Na \xrightarrow[THF]{-70^\circ} \underset{A}{NaCPhMe(CH_2)_2CPhMeNa}}$$

$$\mathrm{A + H_2O \longrightarrow (PhMeCHCH_2)_2}$$

In the current study the reduction of α-methylstyrene in tetrahydrofuran with lithium and varying amounts of ethanol was investigated. Changing the ratio of olefin to alcohol from the stoichiometry required for monomolecular reduction to that required for bimolecular reduction had a dramatic effect on the course of the reduction. Whereas a 2:1 ratio of alcohol to olefin gave mainly monomolecular reduction, an equal molar ratio of alcohol and olefin gave mainly bimolecular reduction. The structural assignment for

$$\mathrm{PhMeC{=}CH_2 + 2EtOH + 2Li \xrightarrow{THF} PhCMe_2H}$$

$$\mathrm{2PhMeC{=}CH_2 + 2EtOH + 2Li \xrightarrow{THF} \underset{65\%}{(PhMeCHCH_2)_2}}$$

the 2,5-diphenylhexane from the latter reaction was confirmed by its relatively simple H^1 n.m.r. pattern. The *d,l* and *meso* isomers of this compound were separated by fractional crystallization.

This tendency for the reagents to combine in the ratio present in the solution was also noted in the disilylation of styrene and α-methylstyrene under the above conditions and again confirms the similarity between these two synthetic procedures. The reasons for this interesting phenomenon have been discussed.[3]

Experimental

Bimolecular Reduction.—The addition of a mixture of 18.4 g. (0.4 mole) of ethanol and 47.2 g. (0.4 mole) of α-methylstyrene to 5.6 g. (0.8 g.-atom) of lithium in 200 ml. of THF during 10 min. gave an extremely exothermic reaction. The temperature was maintained at 20–40° by external cooling. Distillation after filtration and extraction with dilute hydrochloric acid gave less than 1 g. of cumene, 30.9 g. (65%) of 2,5-diphenylhexane (b.p. 140° at 1.5 mm.; $n^{25}\mathrm{D}$ 1.5392), and 8.85 g. (19%) of residue.

Anal. Calcd. for $C_{18}H_{22}$: C, 90.7; H, 9.3. Found: C, 90.9, 91.2; H, 9.52, 9.51.

Fractional crystallization from MeOH at 0° gave a crystalline isomer (m.p. 44.5–46.2° after two recrystallizations) and a liquid isomer (m.p. below 0°). The infrared solution spectra of the two isomers and the original mixture were identical from 2–15 μ. The H^1 n.m.r. spectra showed the CH_3 doublets at τ 8.86, multiplets for CH_2 at 8.55, multiplets for CH at 7.46, and $C_{ar}H$ at 2.95 in a ratio of 3:2:1:5. The spectra for the two isomers were identical except for different splitting patterns for CH_2.

Monomolecular Reduction.—The rapid addition of a mixture of 23.6 g. (0.2 mole) of α-methylstyrene and 18.4 g. (0.4 mole) of ethanol to 5.3 g. (0.76 g.-atom) of lithium in 200 ml. of THF gave a mildly exothermic reaction. The reduction, which was complete in 1.5 hr., gave a 4:1 ratio of cumene to 2,5-diphenylhexane by v.p.c. analysis.

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(5) For an excellent review of chemical reduction see H. Smith, "Organic Reactions in Liquid Ammonia," Vol. I, Part 2, Interscience Publishers, Inc., New York, N. Y., 1963., pp. 151–280.

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Synthesis and Properties of Fluorine-Containing Heterocyclic Compounds. III. Substituted Tetrahydropyrans[1]

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When ethyl trifluoroacetoacetate was treated with various aliphatic and aromatic aldehydes using the usual Knoevenagel conditions, the products obtained appeared to be monohydrates of the expected bisesters based on their elemental analysis. All the compounds obtained were white crystalline solids with fairly low melting points (95–125°), and no signs of decomposition were observed on melting. The one molecule of water which was included in the empirical formula of all the products could not be removed by prolonged drying at 0.1 mm. or by azeotropic distillation. When these compounds were treated with a ferric chloride solution or ceric nitrate reagent, they did not give a positive test as would be expected if they contained hydroxyl groups. The infrared spectra of these compounds did not show evidence for enolic double bonds. Attempts to prepare copper chelates also failed thus indicating the absence of β-keto structures. Oximes or 2,4-dinitrophenylhydrazones of some of the compounds could not be obtained under the normal conditions used to prepare these derivatives. This showed the absence of normal carbonyl groups. A molecular weight determination on the product formed from ethyl trifluoro-

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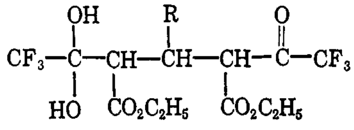
(1) Preceding paper in this series: A. S. Dey and M. M. Joullié, *J. Heterocyclic Chem.*, in press.

(2) Abstracted from a portion of the Ph.D. thesis of A. S. Dey, University of Pennsylvania, 1964.

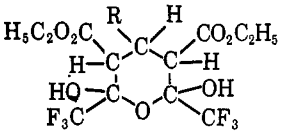
acetoacetate and formaldehyde agreed well with the empirical formula $C_{13}H_{16}F_6O_7$.

On the basis of the analytical data, two possible structures can be written for these compounds.



$CF_3-C(OH)_2-CH(CO_2C_2H_5)-CH(R)-CH(CO_2C_2H_5)-C(=O)-CF_3$

A



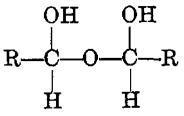
B

I, R = H
II, R = CH_3
III, R = C_2H_5
IV, R = C_6H_5
V, R = p-FC_6H_4
VI, R = p-$CH_3OC_6H_4$

Structure A can be ruled out for a number of reasons. It is difficult to see why only one trifluoroacetyl group would become hydrated and not the other. The compounds are unchanged after standing in air for long periods of time. This might be explained if the compounds were highly enolic, but this is ruled out by the negative ferric chloride test and the absence of the appropriate bands in the infrared spectra. A nonenolic trifluoroacetoacetate group as shown in structure A should absorb near 1780 cm.$^{-1}$ in the infrared because of the electron-withdrawing trifluoroacetyl group.[3] Yet none of the infrared spectra of compounds I–VI show any absorption above 1740 cm.$^{-1}$.

Thus, the products of the condensation of ethyl trifluoroacetoacetate with aldehydes appear to be best represented by structure B. Once one of the trifluoroacetyl groups is hydrated, it is in a very favorable position to react with the trifluoroacetyl group at the other end of the molecule to form a six-membered ring. Such a ring should be unusually stable.

It has been found recently that several aldehydes form hemihydrates of the type



$R-CH(OH)-O-CH(OH)-R$

n-Dodecanal hemihydrate is an example of this type of compound.[4] Fluoral also forms a white hydrate whose analysis and molecular weight fit the formula $[CF_3CH(OH)]_2O$ better than $CF_3CH(OH)_2$.[5]

The infrared spectra of compounds I–VI were determined in different media, but the best spectra were obtained in chloroform solution. The most striking features of these spectra are the presence of different hydroxyl peaks and splitting of the ester carbonyl absorption. In chloroform solution, all of the spectra showed two peaks of roughly equal intensity at 1740–1732 and at 1715–1705 cm.$^{-1}$. The compounds with aliphatic substituents (I–III) showed no other absorptions between 1700 and 1450 cm.$^{-1}$ excluding the presence of an enolic β-keto ester. Compounds IV–VI had bands near 1610 and 1500 cm.$^{-1}$, but these must be assigned to the aromatic ring. There are several possible explanations for split carbonyls.[6] The most appropriate one, in this case, seems to be the different conformational assignments of the ester groups although Fermi resonance was not ruled out. Examination of the hydroxyl region of the infrared spectra of compounds I–VI, in several media, shows absorptions which can be assigned to associated hydroxyl groups (3375–3340 cm.$^{-1}$), free hydroxyl groups (3610–3595 cm.$^{-1}$), and intramolecularly hydrogen-bonded hydroxyl groups (3350–3540 cm.$^{-1}$).

The limited solubility of compounds I–VI restricted n.m.r. examination, but a spectrum of I in DMSO contained two singlet peaks, τ 6.78 and 6.94 p.p.m., which were assigned to hydroxyl groups since they disappeared on addition of trifluoroacetic acid. The spectrum of III in DMSO also showed two hydroxyl resonances at τ 6.65 and 7.07 p.p.m.

Because of the possibility of several optical and geometric isomeric forms for compounds I–VI, rigorous proof of their structures could not be obtained. However, to give some support to the cyclic nature of B, the chemical reactions of some of the compounds were investigated.

The basic hydrolysis of compounds II and V yielded 3-substituted glutaric acids. This reaction probably proceeds by saponification of the carbethoxy groups and cleavage of the hemihydrate followed by a haloform type of cleavage to give a methylenebismalonic acid which would be easily decarboxylated to give the final product.

Acid hydrolysis was complicated because several reactions may occur. Both the ester and the trifluoromethyl groups may be hydrolyzed to carboxylic acids and these may in turn decarboxylate. The hemihydrate may be cleaved, or dehydration to a 4H-pyran may occur. The dehydration of 2,4-dihydroxy-5-methyl-2,4,6-tris(trifluoromethyl)tetrahydropyran to 5-methyl-2,4,6-tris(trifluoromethyl)-2H-pyran has been carried out by slow distillation of the starting material from concentrated sulfuric acid or phosphorus pentoxide.[7] Similar dehydrations have been accomplished by heating tetrahydropyrans with concentrated sulfuric acid at 150° for 12 hr.[8]

Treatment of compound I with concentrated sulfuric acid at 100° resulted in complete decomposition of the mixture. However, compound II under the same conditions yielded 3,5-dicarboxy-2,6-dihydroxy-2,6-ditrifluoromethyl-4-methyltetrahydropyran. This reaction furnishes additional evidence against structure A since, if this structure were correct, a β-keto acid or its decomposition products would be formed.

Since the reactions of 2-methyl-4,6-dialkyl-4H-pyrans with 2,4-dinitrophenylhydrazine sulfate have been shown to give 2,4-dinitrophenylhydrazones of the corresponding 1,5-dicarbonyl compounds,[9] a similar reaction was tried on our compounds. It was possible

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TABLE I

4-SUBSTITUTED 3,5-DICARBETHOXY-2,6-DIHYDROXY-2,6-DITRIFLUOROMETHYLTETRAHYDROPYRANS

Compound no.	Substituent R	Yield, %	M.p., °C.	Formula	Calcd., %			Found, %		
					C	H	F	C	H	F
I	H	52.5	103–105	$C_{13}H_{16}F_6O_7$[a]	39.20	4.02	28.64	39.11	3.92	28.82
II	CH_3	54.7	95.5–98	$C_{14}H_{18}F_6O_7$[a]	40.78	4.40	27.65	40.55	4.39	27.60
III	C_2H_5	62.2	125–127.5	$C_{15}H_{20}F_6O_7$[a]	42.45	4.73	26.74	42.17	4.80	26.90
IV	C_6H_5	19	116–118.5	$C_{19}H_{20}F_6O_7$[a,b]	48.10	4.25	24.03	48.22	4.10	24.26
V	p-F–C_6H_4	29.8	124–125	$C_{19}H_{19}F_7O_7$[b]	46.35	3.89	27.01	46.27	3.84	27.01
VI	p-CH_3O–C_6H_4	37.5	95–96	$C_{20}H_{22}F_6O_8$[c]	47.62	4.40	22.60	47.58	4.38	22.48

[a] Recrystallized from aqueous ethanol. [b] Recrystallized from petroleum ether (b.p. 60–110°). [c] Recrystallized from benzene–petroleum ether.

to isolate pure products from the reaction of compounds II and III with 2,4-dinitrophenylhydrazine sulfate in refluxing ethanol, but these were not the expected derivatives of the corresponding 1,5-diones. Both the ester and trifluoromethyl groups underwent hydrolysis and decarboxylation to give bis(2,4-dinitrophenylhydrazones) of 3-substituted glutaraldehydes. The properties of the compounds prepared are recorded in Table I.

Experimental[10]

Preparation of Substituted Tetrahydropyrans. A. Condensation of Ethyl Trifluoroacetoacetate with Aldehydes in the Presence of Piperidine.—The general method[11] will be illustrated with the preparation of I. Ethyl trifluoroacetoacetate (18.4 g., 0.100 mole) and 40% aqueous formaldehyde solution (4.5 g., 0.06 mole) were mixed in a flask fitted with a condenser and immersed in an ice–salt bath at −6°. Three drops of piperidine were added; the mixture was kept at −10° for 4 hr. with occasional shaking. The flask was stoppered and kept in the refrigerator for 2 days until its contents had solidified. The mixture was then kept at room temperature for 2 days. The white solid formed was suspended in 10 ml. of water, removed by filtration, and recrystallized from aqueous ethanol. Addition of water to the filtrate yielded additional material which was also recrystallized from aqueous ethanol. The molecular weight was found to be 383 (calcd. 398).

B. Condensation of Ethyl Trifluoroacetoacetate with Aldehydes in the Presence of Potassium Fluoride.—The general method[12] will be illustrated with the preparation of IV. Ethyl trifluoroacetoacetate (17.1 g., 0.093 mole), benzaldehyde (9.85 g., 0.093 mole), anhydrous potassium fluoride (1.45 g., 0.025 mole), and 50 ml. of anhydrous ethanol were placed in a 250-ml. round-bottomed flask fitted with a condenser and calcium chloride tube. The mixture was refluxed for 6 hr. and stirred with a magnetic stirrer. It was then poured into 100 ml. of cold water and the organic layer extracted with ether. The ether layer was shaken with 40% sodium bisulfite, washed with water, and evaporated to give an oil which became a semisolid under a pressure of 0.2 mm. This substance was triturated with water to give 4.18 g. of a white product which was first recrystallized from 50% aqueous ethanol and then recrystallized from petroleum ether (b.p. 60–110°).

Basic Cleavage of Some Substituted Tetrahydropyrans. A. Preparation of 3-Methylglutaric Acid.—Compound II (3.82 g., 0.00927 mole) was placed in 30 ml. of 10% aqueous sodium hydroxide, and the mixture was refluxed for 2 hr. A small amount of solid was removed by filtration and the filtrate acidified with 15 ml. of 50% aqueous sulfuric acid and extracted with ether. The ether layer was dried over magnesium sulfate, the drying agent removed by filtration, and the solvent evaporated to yield 1.1 g. (76%) of 3-methylglutaric acid. This compound was recrystallized from benzene to yield white crystals, m.p. 86–88° (lit.[13] m.p. 86°; lit.[14] m.p. 87°). The infrared spectrum of this compound showed a strong carbonyl band at 1690 cm.$^{-1}$ and bands at 1415, 1220, and 927 cm.$^{-1}$ which are typical of a carboxylic acid.

B. Preparation of 3-p-Fluorophenylglutaric Acid.—Compound V (4.0 g., 0.0081 mole) was placed in 30 ml. of 10% aqueous sodium hydroxide and the mixture refluxed for 2 hr. The solution was acidified with 15 ml. of 50% aqueous sulfuric acid, and the white precipitate formed was removed by filtration to yield 1.76 g. (96%) of product. This solid was recrystallized from benzene to give a white powder, m.p. 144–147°.

Anal. Calcd. for $C_{11}H_{11}FO_4$: C, 58.40; H, 4.90; F, 8.40. Found: C, 58.43; H, 5.09; F, 8.22.

The infrared spectrum of this compound showed bands at 1700, 1440, 1213, and 920 cm.$^{-1}$ typical of a carboxylic acid.

Acid Hydrolysis of II. Preparation of 3,5-Dicarboxy-2,6-dihydroxy-2,6-ditrifluoromethyl-4-methyltetrahydropyran.—Compound II (1.0 g., 0.0024 mole) was dissolved in 5 ml. of concentrated sulfuric acid. The mixture was kept on a steam bath for 19 hr. It was then poured into 50 ml. of ice–water. The yellow solution obtained was extracted with ether. The ether layer was dried over magnesium sulfate. Removal of the drying agent and evaporation of the solvent gave a thick oil which crystallized to yield 0.4 g. (46%) of 3,5-dicarboxy-2,6-dihydroxy-2,6-ditrifluoromethyl-4-methyltetrahydropyran, m.p. 148–151°, with evolution of gas.

Anal. Calcd. for $C_{10}H_{10}F_6O_7$: C, 33.72; H, 2.83; F, 32.01. Found: C, 33.90; H, 2.90; F, 31.98.

3-Methylglutaraldehyde Bis(2,4-dinitrophenylhydrazone).—A solution of compound II (1.0 g., 0.0024 mole) in 15 ml. of absolute ethanol was added to a solution of 2,4-dinitrophenylhydrazine (1.0 g., 0.005 mole) in 5 ml. of concentrated sulfuric acid and 20 ml. of absolute ethanol. The solution was refluxed on the steam bath for 2 hr. and then cooled. The excess of 2,4-dinitrophenylhydrazine was removed by filtration and the filtrate evaporated to yield 0.23 g. (20%) of 3-methylglutaraldehyde bis(2,4-dinitrophenylhydrazone) which was fractionally recrystallized from 50% aqueous ethanol, m.p. 193–196° (lit.[15] m.p. 198°). The lower melting point exhibited by our compound is probably due to a slight amount of 2,4-dinitrophenylhydrazine still present in this product.

3-Ethylglutaraldehyde Bis(2,4-dinitrophenylhydrazone).—A solution of compound III (1.0 g., 0.0023 mole) in absolute ethanol was added to a solution of 2,4-dinitrophenylhydrazine in 5 ml. of concentrated sulfuric acid and 20 ml. of absolute ethanol. The solution was refluxed on the steam bath for 2 hr. and then cooled. The solid formed was removed by filtration and fractionally recrystallized from ethanol to yield 0.63 g. (55%) of 3-ethylglutaraldehyde bis(2,4-dinitrophenylhydrazone), m.p. 123–126°.

Anal. Calcd. for $C_{19}H_{20}N_8O_8$: C, 46.72; H, 4.13; N, 22.94. Found: C, 46.65; H, 4.09; N, 23.11.

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[10] Melting points were determined in a Thomas–Hoover capillary melting point apparatus. Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tenn., and Dr. A. Bernhardt, Max Planck Institut, 433 Mülheim (Ruhr), West Germany. Infrared spectra were determined with a Perkin-Elmer Model 421. N.m.r. spectra were determined with a Varian A-60 high-resolution recording n.m.r. spectrometer at a frequency of 60 Mc./sec. Measurements were made in dimethyl sulfoxide using tetramethylsilane as an internal standard.

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