matography showed only one radioactive spot which corresponded with an authentic sample of I.

2-Butyl-1-C^{14}-aminomethyl-8-ethoxy-1,4-benzodioxane Hydrochloride (III).—Sodium butyrate-1-C^{14} (0.5 mmole, 860 μc), 5 ml. of dry benzene, 0.05 ml. of thionyl chloride and one drop of pyridine were stirred at room temperature for 2 hr. One and one-half grams of 2-aminomethyl-8-ethoxy-1,4-benzodioxane (free base) in 5 ml. of benzene was added and the mixture refluxed for 5 hr. After cooling, ether and 1N NaOH were added and the whole transferred to a separatory funnel. The organic layer was separated and washed with additional 1N NaOH, 1N HCl and water. By evaporation to dryness the radioactive amide was recovered as an oil which crystallized upon standing, m.p. 99–101°.

Anal. Calcd. for $C_{15}H_{21}O_4N$: N, 5.02. Found: N, 4.84.

Reduction of the intermediate amide was effected by refluxing 16 hr. with 100 mg. of lithium aluminum hydride in a mixture of 25 ml. of ether and 25 ml. of benzene. After cooling, 1N NaOH (10 ml.) was added and the organic layer recovered by centrifugation. The product was extracted into 1N HCl and after neutralization re-extracted into ether. The crude hydrochloride obtained by saturation of the ether with dry hydrogen chloride was purified by recrystallization from ethyl ether–methanol. The product, 2-butyl-1-C^{14}-aminomethyl-8-ethoxy-1,4-benzodioxane hydrochloride (III), weighed 134 mg. (89%) and melted at 196–198°. This material had the same X-ray pattern as II and an authentic sample of I and was one spot material when paper chromatographed.

2-Carboxy-8-ethoxy-1,4-benzodioxane (VI).—This acid was prepared by the procedure described by Koo[9] for the preparation of the unsubstituted analog. Oxidation of 9.5 g. of 2-hydroxymethyl-8-ethoxy-1,4-benzodioxane yielded 5.9 g. (58%) of 2-carboxy-8-ethoxy-1,4-benzodioxane (VI). The acid after purification by sublimation melted at 126–127°.

Anal. Calcd. for $C_{11}H_{12}O_6$: C, 58.93; H, 5.40. Found: C, 58.72; H, 5.43.

Animal Experiments.—Methods for collecting and counting urine and respiratory carbon dioxide samples from rats[10] and from dogs[4] (chihuahua) have been described. The dose level in rats was 10 mg./kg. and 2.5 mg./kg. in dogs. The dose was administered intraperitoneally in aqueous solution. Each set of rat data in Table I represents the mean of four animals (the standard deviation was less than 5% of observed mean values in most cases). The dog data is based on a single animal.

(9) J. Koo, S. Avakian and G. J. Martin, THIS JOURNAL, **77**, 5373 (1955).

(10) R. E. McMahon, *ibid.*, **80**, 411 (1958).

For the purposes of paper chromatography studies, each urine sample was extracted with ether at neutral pH and again at pH 2. The neutral extracts were chromatographed using the buffered system described earlier.[4,11] The acid extracts were chromatographed on Whatman #1 paper using a 1:1 1-butanol–1.5 N ammonium hydroxide system. Carboxylic acids were visualized by spraying with brom phenol blue. The radioactive spots on chromatograms were located in an automatic scanning device. Phenol spots were found by spraying with diazotized sulfanilamide.[12]

Isolation of 2-Carboxy-8-ethoxy-1,4-benzodioxane (VI) **from Dog Urine.**—A total of 400 mg. of I containing tracer amounts of II was administered to dogs at a dose level of 2.5 mg./kg. (i.p.) and 24-hr. urine collections made. The urine (800 ml.) was then made pH 2 and extracted continuously with diethyl ether to yield after evaporation a black tar (150 mg.) When warmed with benzene (25 ml.) part of the tar dissolved. The benzene solution after cooling was placed on a prepared silica gel (Davidson) column and the column developed with benzene–ethylacetate mixtures. The fractions containing peak radioactivity were combined and sublimed at 90° (0.1 mm.) to yield 15 mg. of white crystals m.p. 124–127°. These were identical in X-ray diffraction pattern, infrared and ultraviolet spectra and R_f value to authentic 2-carboxy-8-ethoxy-1,4-benzodioxane.

Studies on Human Urine.—Morning urine collections from 12 patients receiving 25 mg. of ethoxybutamoxane per day were made. The urine samples were then extracted with ether first at pH 2 and then at pH 8.

Whether or not VI was present in the acid extract could not be settled by paper chromatography so that it was necessary to resort to column chromatography. To the acid extract was added, as a tracer, 1 mg. of radioactive acid VI obtained from dog urine (see above). The acid extract was then chromatographed in the same manner as described above. The peak radioactive fractions were combined and found to weigh slightly less than 1 mg., showing that no VI was present in human urine.

The extracts made at pH 8 were paper chromatographed and sprayed with phenol reagent.

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(11) A. Brossi, O. Hafliger and O. Schnider, *Arzneim. Forsch.*, **5**, 62 (1955).

(12) R. J. Block, R. LeStrange and G. Zweig, "Paper Chromatography," Academic Press, Inc., New York, N. Y., 1952, p. 64.

[CONTRIBUTION OF THE CHEMISTRY RESEARCH DEPARTMENT, U. S. NAVAL ORDNANCE LABORATORY, WHITE OAK, SILVER SPRING, MD.]

Transesterification in Sulfuric Acid[1a]

BY MARION E. HILL[1a]

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2,4,6-Trichlorophenol or its acetate and some exemplary halogen substituted alcohols and their acetates produce good yields of esters by transesterification with negatively substituted methyl esters or the free acids in 100% or fuming sulfuric acid solution. Evidence is presented that the reaction proceeds by cleavage of the starting ester in the sulfuric acid solution followed by establishment of new equilibria which favor the formation of the product ester.

Introduction

Previous studies have shown that simple esters of carboxylic acids in general undergo cleavage in sulfuric acid and the free acids can be recovered by pouring the reaction solutions into water.[2–4] However we have observed that esters such as 2,4,6-trichlorophenyl and 2,2,2-tribromoethyl 4′-nitrobenzoates were only partly cleaved in 100% sulfuric acid and, in an extreme case, 2,4,6-trichlorophenyl 3′,5′-dinitrobenzoate was almost com-

(1) Presented in part before the Organic Division, 131st National A.C.S. Meeting, Miami, Fla., April, 1957.

(1a) Stanford Research Institute, Menlo Park, California.

(2) For a good review of organic bases in sulfuric acid see J. R. Gillespie and J. A. Leisten, *Quart. Revs.*, **8**, 40 (1954).

(3) M. S. Newman, R. A. Craig and A. B. Garrett, THIS JOURNAL, **71**, 869 (1944).

(4) (a) M. S. Newman, H. G. Kuivila and A. B. Garrett, *ibid.*, **67**, 704 (1945); (b) L. P. Kuhn and A. H. Corwin, *ibid.*, **70**, 3370 (1948); (c) A. Bradley and M. E. Hill, *ibid.*, **77**, 1575 (1955).

TABLE I
TRANSESTERIFICATION IN SULFURIC ACID

Product	M.p., °C.	Ratio, reactants	H_2SO_4 concn., method	Yield, %	Composition,[a] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Other Element	Other Calcd.	Other Found
2,4,6-Trichlorophenyl											
3',5'-dinitrobenzoate[b]	162–163	1–1, methyl ester–alcohol	4% fuming, A[c]	55							
		1–1, acid–alcohol acetate	4% fuming, B	80							
		1–1, methyl ester–alcohol acetate	4% fuming, A	70							
4'-Nitrobenzoate	105–106	1–1, methyl ester–alcohol	4% fuming, A[d]	42							
		1–1, methyl ester–alcohol	4% fuming, B	40							
		1–1, acid–alcohol acetate	4% fuming, A	46							
		2–1, acid–alcohol acetate	4% fuming, A	73							
		2–1, acid–alcohol acetate	100%, A	44							
		2–1, acid–alcohol acetate	96%, A	5							
		2–1, methyl ester–alcohol acetate	4% fuming, A	72							
3'-Nitrobenzoate	135–135.5	2–1, acid–alcohol acetate	4% fuming, B	45							
		2–1, acid–alcohol acetate	100%, B	16							
2'-Nitrobenzoate[b]	171–172	2–1, acid–alcohol acetate	100%, A	60	45.01	45.12	1.73	1.93	Cl	30.72	30.90
4'-Chlorobenzoate	92.5–93	2–1, methyl ester–alcohol	4% fuming, A	20	46.46	46.31	1.80	2.00	Cl	42.21	42.42
2'-Chlorobenzoate	62–62.5	2–1, acid–alcohol acetate	100%, A	10	46.46	46.60	1.80	2.11	Cl	42.21	42.50
Terephthalate[b]	190–191	1–2, acid–alcohol acetate	4% fuming, A	53	45.75	46.00	1.54	1.70	Cl	40.52	40.70
1',3',5'-Benzene-tricarboxylate[b]	197–198	1–3, acid–alcohol acetate	4% fuming, B	55	43.32	43.12	1.21	1.38	Cl	42.64	42.69
2,4,6-Tribromophenyl											
3',5'-Dinitrobenzoate[b]	177–178	1–1, methyl ester–alcohol	4% fuming, B	40	29.74	29.76	0.96	1.26	N	5.34	5.53
2,2,2-Tribromoethyl											
4'-Nitrobenzoate	100–101	2–1, methyl ester–alcohol	100%, B	33							
2'-Chlorobenzoate	54–54.5	2–1, acid–alcohol acetate	100%, A	41	25.72	25.98	1.53	1.70			
		2–1, acid–alcohol acetate	96%, A	58							
2'-Methylbenzoate	64.5–65	2–1, acid–alcohol acetate	100%, A	15	30.00	30.13	2.26	2.23	Br	59.79	59.46
2,2,2-Trifluoroethyl											
4'-Nitrobenzoate	47–48	1–3, methyl ester–alcohol	100%, A	32	43.80	43.78	2.46	2.62	N	5.68	5.85
Terephthalate	112–113	1–3, acid–alcohol acetate	100%, A	12	43.65	43.75	2.45	2.65			
2,2,3,3-Tetrafluoropropyl											
4'-Nitrobenzoate[e]	43–44	2–1, acid–alcohol acetate	100%, A	45	42.70	42.75	2.49	2.66	N	4.98	5.20

[a] Analyses by Dr. Mary Aldridge, American University, Washington, D. C. [b] Product precipitated from solution. [c] In 100% sulfuric acid, no yield; in 10% fuming H_2SO_4, 10% yield. [d] 40% recovery after hydrolysis of this ester under the same conditions. [e] 2,2,3,3-Tetrafluoropropanol was furnished by E. I. du Pont de Nemours and Co.

pletely unaffected by 4% fuming sulfuric acid. The cleavage of the corresponding methyl esters, on the other hand, was more easily achieved and, if carried out in the presence of a negatively substituted phenol such as 2,4,6-trichlorophenol or a polyhalogenated alcohol, a new ester was formed *in situ*. These findings prompted a study of the equilibria involved in sulfuric acid solutions of esters negatively substituted in the acid and alcohol portions.

Discussion and Results

The transesterification procedure consisted simply of heating a nearly saturated solution of the ester to be transesterified and the reaction component in anhydrous or fuming sulfuric acid at 70° until cleavage of the starting ester and establishment of a new equilibrium system had occurred. After completion of the reaction, the product was isolated by pouring the reaction mixture into ice and water and followed by purification. As indicated in Table I, nearly the same yields were obtained in comparable systems by alcoholysis of a methyl ester, acidolysis of an alcohol acetate or ester interchange of a methyl ester and alcohol acetate. Of the three transesterification procedures studied, the reaction of acids with alcohol acetates proceeded at the highest rate, requiring less than an hour in comparison to six hours or more when methyl esters were used as starting esters.

The strength of sulfuric acid required for optimum yield varied markedly with the extent of negative substitution in the reactants. The acetates of halogen-substituted aliphatic alcohols transesterified readily in 100% sulfuric acid, but optimum reaction in the preparation of derivatives of 2,4,6-trichlorophenol required 4% fuming sulfuric acid. The latter was necessary in order to obtain any yield at all in the preparation of 2,4,6-trichlorophenyl 3',5'-dinitrobenzoate, but no advantage was gained by using 10% fuming sulfuric acid containing more than an equimolar amount of sulfur trioxide.

In a series of trichlorophenyl benzoate preparations under standard conditions varying only the substituent group and ring position, nitro and carboxyl groups in the *p*-position were effective in enhancing product formation, but chlorine was much less so. For the mono-*o*-substituted benzoates in which a limited degree of steric hindrance was involved, the reaction proceeded well, as in the case of 2,4,6-trichlorophenyl 2'-nitrobenzoate. In comparing the effect of halogens in the alcohol portion, not much variance was observed in the results of the 2,2,2-tribromoethanol and fluoroalcohol 4-nitrobenzoate preparations.

The existence of an equilibrium was demonstrated by comparison of the preparation and cleavage reactions of 2,4,6-trichlorophenyl 4'-nitrobenzoate in which the 40% yield realized in the preparation of the ester was the same as the amount of uncleaved ester remaining after its hydrolysis under the same conditions in a separate experiment. Alternatively, the same equilibrium

point was reached by first cleaving the starting ester and then adding the reactant. Although the yields of the acid-soluble esters were limited by the equilibrium degree of conversion of the intermediates to product and varied from 5–73%, in some cases the equilibrium was upset by the precipitation of the product from solution. Esters such as 2,4,6-trichlorophenyl 3′,5′-dinitrobenzoate and terephthalate were insoluble to the extent that very little remained dissolved in the reaction solution. Introducing an excess of one reactant forced the reaction toward higher conversion to product in the normal manner of an equilibrium process.

In considering a mechanism for the transesterification reaction, experimental results do not indicate the actual reacting species in sulfuric acid solutions since there are a number of possible ionic reactants from the starting ester equilibrium and from the equilibria resulting from the introduced reactants. A possible mode of reaction involves an initial cleavage of the starting ester followed by formation of a new equilibrium system which favors the product ester, summarized in equations 1–4 for the alcoholysis reaction.

$$RCOOCH_3 + H_2SO_4 \rightleftharpoons [RCOOCH_3]H^+ + HSO_4^- \quad (1)$$

$$[RCOOCH_3]H^+ + H_2SO_4 \rightleftharpoons [RCOOH]H^+ + CH_3OSO_3H \quad (2)$$

$$[RCOOH]H^+ + R'OH \rightleftharpoons [RCOOR']H^+ + H_2O \quad (3)$$

$$[RCOOR']H^+ + HSO_4^- \rightleftharpoons RCOOR' + H_2SO_4 \quad (4)$$

These equations are in agreement with the formation of product ester by either alcohol–ester, acid–ester or ester–ester interchange in which the common reactants are some form of the negatively substituted acid and alcohol. A principal factor which influences the extent of reaction is the weak basicity of the product ester relative to sulfuric acid, with the forward reaction represented in equation 3 favored. The protonation equilibrium of the product with sulfuric acid, equation 4, accounts for the formation of the un-ionized form which may or may not precipitate from solution. Otherwise the reaction would not proceed beyond ester cleavage represented by equations 1 and 2. This interpretation is consistent with the effect of electron-withdrawing substituents in the reactants, namely a decrease in basicity of the ester grouping with concomitant increase in stability toward sulfuric acid.

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Experimental

The preparation of 2,4,6-trichlorophenyl 4′-nitrobenzoate by alcoholysis of methyl 4-nitrobenzoate exemplifies the general method used for the ester interchange reactions in sulfuric acid solution:

Method A.—A solution of 1.81 g. (0.010 mole) of methyl 4-nitrobenzoate and 1.97 g. (0.010 mole) of 2,4,6-trichlorophenol in 16 g. of fuming sulfuric acid containing 0.008 mole of sulfur trioxide was heated 6 hours at 70°. (Alternatively, 2,4,6-trichlorophenyl acetate was heated for 30 minutes with 4-nitrobenzoic acid or for 6 hours with methyl 4-nitrobenzoate.) After cooling, the solution was poured onto ice and filtered. The crude wet product mixture was slurried with sodium carbonate solution for several hours, filtered, dried, and recrystallized from aqueous methanol. There was obtained 1.45 g., 42%, of 2,4,6-trichlorophenyl 4′-nitrobenzoate, m.p. 105–106°. This product proved to be identical to the ester obtained by metal halide catalysis of the reaction of 4-nitrobenzoyl chloride with 2,4,6-trichlorophenol[5] by lack of reduction in melting point when mixed and by identical infrared traces.

The same experiment was run using 32 g. of 4% fuming sulfuric acid instead of 16 g. The yield was reduced to 24%.

Method B.—A solution of 1.81 g. (0.010 mole) of methyl 4-nitrobenzoate in 16 g. of fuming sulfuric acid containing 0.008 mole of sulfur trioxide was heated at 70° for 6 hours, the required period for complete cleavage of the methyl 4-nitrobenzoate. To this solution was added 1.97 g. (0.010 mole) of 2,4,6-trichlorophenol and the resulting reaction solution was heated an additional 30 minutes. (Alternatively 2,4,6-trichlorophenyl acetate was heated 5 minutes, an acid added and the solution heated for 1 hour.) After cooling, the product was isolated as in method A. A yield of 1.38 g., 40%, of 2,4,6-trichlorophenyl 4′-nitrobenzoate, m.p. 105–106°, was obtained.

The results of other reactions are summarized in Table I which also contains elemental analyses of new compounds.

(5) M. E. Hill, THIS JOURNAL, **76**, 2329 (1954).

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT, PENNSALT CHEMICALS CORP.]

Novel Elimination Reactions of Telomer Iodides of 1,1-Difluoroethylene[1]

BY MURRAY HAUPTSCHEIN AND ROBERT E. OESTERLING

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Telomer iodides having $-CF_2CH_2CF_2I$ end groups have been found to undergo dehydroiodination preferentially when treated with a wide variety of strong and weak bases and nucleophiles. Only the relatively non-basic halide ion nucleophiles have been shown to produce the dehydroiodination product $-CF_2CH{=}CF_2$ exclusively. Lithium chloride in dimethylformamide, in particular, gave high conversions in a rapid and selective elimination reaction, and the synthesis of a series of the olefins $R_f(CH_2CF_2)_nCH{=}CF_2$ is described. The preparations of some of the related chlorides and fluorides $R_f(CH_2CF_2)_nX$ where X = Cl or F are reported.

During the course of investigations on ultraviolet-catalyzed chlorinations of telomer iodides of 1,1-difluoroethylene[2]; *i.e.*, $R_f(CH_2CF_2)_nI$ where R_f = perfluoroalkyl and n = 1–10, the reaction products were found to be contaminated with olefinic by-products. Thus, when $C_3F_7CH_2CF_2I$ was chlorinated at room temperature in the presence of ultraviolet irradiation, the organic products were

(1) Presented at the 136th Meeting of the American Chemical Society, Atlantic City, N. J., September, 1959.

(2) M. Hauptschein, M. Braid and F. E. Lawlor, THIS JOURNAL, **80**, 846 (1958). It should be noted that substitution chlorination of hydrogen atoms does not occur under the present conditions; iodine replacement by chlorine is much more energetically favored.