pyridine hydrochloride was removed by filtration. The ethereal filtrate was washed with 10% hydrochloric acid, water and 10% sodium hydroxide, and dried over Drierite. The solvent was removed and the residue distilled to give 43.5 g. (50%) of the ester, b.p. 52–54° at 10 mm., $n^{25}D$ 1.4052.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.71. Found: C, 69.93; H, 11.61.

Amide Formation *vs.* Alkylation with Various Esters of Diethylacetic Acid.—To a stirred solution of 0.11 mole of potassium amide[34] in 250 ml. of liquid ammonia was added 0.1 mole of the ester in 20 ml. of anhydrous ether and, after 0.5 hr., 15.1 g. (0.11 mole) of butyl bromide in 20 ml. of anhydrous ether was added. After stirring for 15 min., the liquid ammonia was evaporated as an equal volume of anhydrous ether was added, and the resulting suspension was stirred and refluxed for 1 hr. The mixture was cooled, and decomposed carefully with water. The ethereal solution of the reaction products was dried over Drierite, and the solvent distilled. The residue was dissolved in petroleum ether and the solution cooled on Dry Ice for 1 hr. The resulting precipitate of 2-ethylbutyramide (diethylacetamide) was collected on a funnel. The filtrate was evaporated and the residue fractionally distilled to yield the alkylated and unalkylated esters.

The yields of the two products and those of the recovered unalkylated esters are given in Table I. The 2-ethylbutyramide melted at 109.5–111° and, after recrystallization from petroleum ether, at 111–111.5°, reported m.p. 112°.[35] The alkylated ethyl ester, ethyl diethylbutylacetate (b.p. 91–92° at 10 mm., $n^{25}D$ 1.4265), was unaffected by refluxing 20% potassium hydroxide or 20% sulfuric acid (16 hr.), 98% of the ester being recovered.

Anal. Calcd. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.97; H, 11.96.

The three alkylated tertiary esters, *t*-butyl diethylbutylacetate (b.p. 99–100° at 10 mm., $n^{25}D$ 1.4250), *t*-amyl diethylbutylacetate (b.p. 117–118° at 10 mm., $n^{25}D$ 1.4320) and triethylcarbinyl diethylbutylacetate were hydrolyzed to form diethylbutylacetic acid (I) in yields of 92–96% by means of hydrochloric acid (see below). Data for the triethylcarbinyl ester are given in Table III, and those for acid I, in Table IV.

Alkylation of Triethylcarbinyl Esters.—To a stirred solution of 0.2 mole of potassium amide[34] in 500 ml. of liquid ammonia was added 0.2 mole of the triethylcarbinyl ester in 50 ml. of anhydrous ether. Within 5 min., the resulting mixture became green. After stirring 45 min., 0.2 mole of the alkyl halide in 50 ml. of anhydrous ether was added rapidly, and the stirring continued for 1 hr. Wet ether was then added carefully and the liquid ammonia was allowed to evaporate on the steam-bath as more ether was being added. Water was added with stirring, and the two layers separated. The ether layer (to which was added an ether extract of the aqueous layer) was dried over Drierite. The solvent was removed and the residue distilled *in vacuo* to give the alkylated esters.

The yields and other data are summarized in Table III. The esters were further identified by their conversion to the corresponding trialkylacetic acids as described below.

Hydrolysis of Alkylated Triethylcarbinyl Esters.—The alkylated ester (0.2 mole) was refluxed 2 hr. with a mixture of 30 ml. of 37% hydrochloric acid and 20 ml. of dioxane.[36] The resulting mixture was distilled through a short Vigreux column until the temperature rose to 100°, and the distillate discarded. The residue was cooled and dissolved in ether. The ethereal solution was extracted with three 50-ml. portions of 10% sodium hydroxide and then with 50 ml. of water. The combined aqueous alkaline extracts were made strongly acidic with 5 *N* sulfuric acid and the liberated carboxylic acid extracted with ether. After drying over Drierite, the solvent was removed from the ethereal extract, and the residue distilled *in vacuo* to give the trialkylacetic acid. The yields were 92–99%.

General Method of Synthesis of Trialkylacetic Acids.—Triethylcarbinyl esters of dialkylacetic acids were alkylated with alkyl halides by means of potassium amide or sodium amide on a 0.2-mole scale as described above. After replacing the liquid ammonia by ether and adding water, the mixture was acidified strongly with 5 *N* sulfuric acid. The layers were separated, and the solvent was removed from the ethereal layer. The residue of crude alkylated ester was hydrolyzed to the trialkylacetic acid and isolated[37] as described above.

The yields and other data are summarized in Table IV. The analyses, refractive indices and neutral equivalents given in this table are for redistilled samples. However, the refractive indices of the products on which the yields were based differed from the values given by less than ±0.0007. The neutral equivalents were determined in ethanol using phenolphthalein as indicator.

(34) R. S. Yost and C. R. Hauser, THIS JOURNAL, **69**, 2325 (1947).

(35) M. M. Tiffeneau and P. Weill, *Compt. rend.*, **204**, 592 (1937).

(36) The hydrogen chloride evolved was caught in a trap. Dilute hydrochloric acid was found unsatisfactory.

(37) The butylethyloctylacetic acid obtained from the alkylation of butylethylacetic ester with octyl bromide and hydrolysis of the crude alkylated product was not removed by the alkali extraction. Therefore, the ethereal solution was washed with dilute hydrochloric acid, dried, and the solvent removed. The crude acid was fractionally distilled.

DURHAM, NORTH CAROLINA

[CONTRIBUTION FROM THE RESEARCH DIVISION, ARMOUR AND COMPANY]

Alcoholysis of Esters with Aluminum Alcoholates[1]

BY EMIL KAISER AND ELLEN P. GUNTHER

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Two procedures are described for the complete exchange of the alkoxyl (or arylalkoxyl) groups between an ester and an aluminum alcoholate without the use of fractional distillation.

The exchange of alkoxyl groups between an ester and an aluminum alcoholate has been reported.[2,3] It was shown by Baker that the equilibrium

$$3R\cdot COOR' + Al(OR'')_3 \rightleftharpoons 3R\cdot COOR'' + Al(OR')_3 \quad (1)$$

could be forced to the right if the ester R·COOR′ has a higher boiling point than the ester R·COOR″. Thus the ester produced in the alcoholysis could be continuously removed from the reaction mixture and high yields of the desired products could be obtained.

This procedure is not suited for the completion of alkoxyl group interchanges in which the products are higher boiling than the starting materials. Also substances which decompose on distillation cannot be used in this type of alkoxyl exchange. A study was therefore conducted with the object of effecting

(1) Presented at the 14th International Congress for Pure and Applied Chemistry, Zurich, Switzerland, July, 1955.

(2) R. H. Baker, THIS JOURNAL, **60**, 2673 (1938). See this paper for earlier references.

(3) C. Barkenbus, M. B. Naff and K. E. Rapp, *J. Org. Chem.*, **19**, 1316 (1954).

complete alkoxyl interchange between an ester and an aluminum alcoholate without fractional distillation.

Two approaches seemed to have promise. One was based on the use of solvents in which the starting materials, shown on the left side of equilibrium 1, were soluble, while the aluminum alcoholate $Al(OR')_3$, produced in the reaction, was insoluble. Thus $Al(OR')_3$ would precipitate from the reaction mixture shifting the equilibrium toward completion of the alkoxyl exchange.

Another possibility for the removal of the product $Al(OR')_3$ from the reaction mixture was based on equilibrium 2

$$Al(OR')_3 + 3R''OH \rightleftarrows Al(OR'')_3 + 3R'OH \quad (2)$$

Using the alcohol corresponding to the alkoxyl of the starting aluminum alcoholate, $Al(OR'')_3$, as solvent, the aluminum alcoholate $Al(OR')_3$ produced in the reaction was reconverted to $Al(OR'')_3$. The excess of R″OH shifted the equilibrium 2 in the direction of the upper arrow resulting in a continuous removal of $Al(OR')_3$ from the reaction mixture and thus tending to force to completion the exchange of alkoxyl groups.

As model substances for these alkoxyl (or arylalkoxyl) exchange studies esters of N-*p*-toluoylsulfonylglycine (tosylglycine) were selected. The tosylglycine esters are well crystallized compounds which can be identified by their melting point, nitrogen content and saponification number. The exchange of alkoxyl groups could thus be followed by analysis and the products identified. Tosylglycine methyl ester was the starting material and toluene the solvent in the procedure in which an insoluble aluminum alcoholate was produced; aluminum methoxide is not soluble in toluene.

In the process, in which the alcohol corresponding to the alkoxyl of the aluminum alcoholate was the solvent, 2-propanol, 2-chloroethanol and methanol were used.

Experimental

Preparation of Tosylglycine Methyl Ester.—Tosylglycine (150 g.) prepared according to the procedure of McChesney and Swann,[4] was refluxed with a mixture of 1200 ml. of methanol and 12 ml. of concentrated sulfuric acid for 5 hr. After cooling, concd. aqueous ammonia solution was added to *p*H 7, and the ammonium sulfate which precipitated was removed by filtration. The filtrate was concentrated under reduced pressure; it was then chilled and the crystals were separated. After recrystallization from methanol, tosylglycine methyl ester, m.p. 92–93°, was obtained.

Anal. Calcd. for $C_{10}H_{13}SNO_4$: N, 5.76; mol. wt., 243.27. Found: N, 5.75; mol. wt., 243 (calcd. from sapn. no.).

Benzyl Ester and 1-Methylpentyl Ester of Tosylglycine.—To 50 ml. of dry toluene 0.198 g. (0.0067 mole + 10% excess) of aluminum shavings was added. The alcohol (0.06 mole), benzyl (6.48 g.) or 1-methylpentyl alcohol (6.12 g.), and catalytic amounts of carbon tetrachloride and mercuric chloride were added and the mixture was stirred and refluxed for 1 hr. In this aluminum alcoholate solution 4.8 g. (0.02 mole) of tosylglycine methyl ester was dissolved, and stirring and refluxing continued for 4 hr. The mixture was cooled and 100 ml. of water containing 6 ml. of concd. hydrochloric acid was added. The aqueous layer was extracted with toluene, then with ether and the combined toluene plus ether extracts dried over anhydrous sodium sulfate. The solvents were evaporated under reduced pressure, the residue was rubbed with petroleum ether (b.p. 40–60°) and kept in the cold until it solidified. The solids were dried in vacuum and analyzed without purification.

Tosylglycine benzyl ester, m.p. 79–81°, yield 5.3 g. (84%). *Anal.* Calcd. for $C_{16}H_{17}SNO_4$: N, 4.38; S, 10.04. Found: N, 4.41; S, 10.06.

Tosylglycine-1-methylpentyl ester, m.p. 56–58°, yield 5 g. (81%). *Anal.* Calcd. for $C_{15}H_{24}SNO_4$: N, 4.51; S, 10.20. Found: N, 4.49; S, 10.33.

Tosylglycine Isopropyl Ester. Reaction Time Study.—To obtain information regarding the time necessary for the completion of the exchange of alkoxyl residues, the reaction between tosylglycine methyl ester and aluminum isopropoxide was carried out in smaller individual batches and in larger batches, and the reaction stopped at various intervals. The molar ratio between tosylglycine methyl ester and aluminum isopropoxide also was varied.

(a) **Aluminum Isopropoxide Reaction in Toluene Molar Ratio 3 to 1.**—In 50 ml. of dry toluene 1.815 g. (0.075 mole) of tosylglycine methyl ester was dissolved. The solution was brought to reflux temperature and a boiling solution of 0.63 g. of freshly distilled aluminum isopropoxide (0.025 mole + 20% excess) in 25 ml. of dry toluene was added. The mixture was refluxed for the specified periods of time and then poured into 75 ml. of 0.1 *N* hydrochloric acid. The organic layer was separated, washed until neutral with water, dried over sodium sulfate and evaporated to dryness under reduced pressure. The solid residue was analyzed for nitrogen content. Results are shown in Table I (all values are averages of several determinations).

(b) **Aluminum Isopropoxide Reaction, Molar Ratio 3 to 5.**—The same procedure was used as described in part a, with the exception that 3.15 g. (0.125 mole) of aluminum isopropoxide was used instead of 0.63 g. This corresponds to a ratio of 3 moles of tosylglycine methyl ester to 5 moles of aluminum isopropoxide. Results of nitrogen determinations are shown in Table I.

TABLE I

EXCHANGE OF THE METHOXY GROUP OF TOSYLGLYCINE METHYL ESTER FOR THE ISOPROPOXY GROUP

Calcd. for tosylglycine methyl ester: N, 5.76. Calcd. for tosylglycine isopropyl ester: N, 5.16.

Reacn. time, min.	Nitrogen, %	Reacn. time, min.	Nitrogen, %
(a) 3 Moles of tosylglycine methyl ester, 1 mole of aluminum isopropoxide		(b) 3 Moles of tosylglycine methyl ester, 5 moles of aluminum isopropoxide	
0	5.75	0.5	5.47
2	5.75	1	5.35
4	5.70	2	5.27
6	5.67	3	5.25
8	5.63	4	5.19
10	5.62	7.5	5.14
15	5.60		
22	5.53		
30	5.39		
60	5.32		
120	5.31		
180	5.29		
240	5.25		
360	5.16		

Preparation of Tosylglycine Isopropyl Ester from the Methyl Ester in Isopropyl Alcohol.—In 30 ml. of 2-propanol 4.8 g. (0.02 mole) of tosylglycine methyl ester was dissolved by heating. Aluminum isopropoxide 1.5 g. (0.02 mole + 10% excess) was added and the mixture refluxed for 4 hr. After cooling, 200 ml. of water and 6 ml. of concd. hydrochloric acid were added. A crystalline product separated which was removed by filtration, washed with water and dried in vacuum. A yield of 5.1 g. of tosylglycine isopropyl ester (92.6% of theory) was obtained, m.p. 79–80°.

Anal. Calcd. for $C_{12}H_{17}SNO_4$: N, 5.16; S, 11.82; mol. wt., 271.3. Found: N, 5.15; S, 11.78; mol. wt., 271 (calcd. from sapn. no.).

(4) E. W. McChesney and W. K. Swann, Jr., THIS JOURNAL, **59**, 1116 (1937).

Preparation of Tosylglycine 2-Chloroethyl Ester from the Methyl Ester in 2-Chloroethanol.—A mixture of 4.8 g. of tosylglycine methyl ester, 0.2 g. of aluminum metal shavings, catalytic amounts of carbon tetrachloride and mercuric chloride and 20 ml. of 2-chloroethanol was stirred and refluxed for 4 hr. The 2-chloroethyl ester of tosylglycine was isolated in the same manner as the isopropyl ester; yield 4.4 g. (86%). The product was recrystallized from ether, m.p. 78–80°.

Anal. Calcd. for $C_{11}H_{14}SNO_4Cl$: N, 4.80; S, 10.99. Found: N, 4.87; S, 11.05.

Preparation of Tosylglycine Methyl Ester from Tosylglycine Isopropyl Ester in Methanol.—To 50 ml. of methanol 0.2 g. (0.0066 mole + 10% excess) of aluminum shavings, 2 ml. of carbon tetrachloride and a few crystals of mercuric chloride were added. The mixture was stirred and refluxed for 6 hr. Tosylglycine isopropyl ester, 2.7 g. (0.01 mole), was added and stirring and refluxing continued for 3 days (72 hr.). This prolonged reaction time was necessary for the completion of the alkoxyl exchange since shorter reaction times led to a mixture of isopropyl and methyl esters. The methanol solution was filtered (0.3 g. insoluble) and evaporated in vacuum. The residue was dissolved in 5 ml. of fresh methanol and a mixture of 50 ml. of water and 5 ml. of concd. hydrochloric acid was added. After chilling, the crystalline precipitate was isolated and dried; yield 2 g. (82.3%) of crude product which was recrystallized from ether; yield of crystalline tosylglycine methyl ester, 1.4 g. (57.6%). The substance had the m.p. 92–94° and did not depress the melting point of tosylglycine methyl ester prepared by the esterification of tosylglycine with methanol.

Anal. Calcd. for $C_{10}H_{13}SNO_4$: N, 5.76; S, 13.18. Found: N, 5.75; S, 13.25.

Preparation of Tosylglycine Methyl Ester from Tosylglycine Benzyl Ester in Methanol.—A solution of aluminum methoxide in methanol was prepared as described above from 0.1 g. (0.0033 mole + 10% excess) of aluminum shavings. Tosylglycine benzyl ester, 3.19 g. (0.01 mole) was added and the mixture refluxed for a day (26 hr.). The methanol solution was filtered and the filtrate poured into a mixture of 400 ml. of water and 6 ml. of concd. hydrochloric acid. After chilling the crystalline product was removed by filtration. The dried substance had the m.p. 91–93° and did not depress the melting point of tosylglycine methyl ester.

Anal. Calcd. for $C_{10}H_{13}SNO_4$: N, 5.76. Found: N, 5.70.

Discussion

According to the examples described in the Experimental part, the alcoholysis of an ester with an aluminum alcoholate can be brought to completion: (a) if the aluminum alcoholate produced in the reaction has a low solubility in the solvent in which the reaction is carried out, or (b) if the alcohol corresponding to the alkoxyl group to be exchanged is used as the solvent for the reaction.

Reaction time is an important factor in the alkoxyl exchange as shown by the change of the percentage of nitrogen in the reaction product as a function of time (Table I).

The nature of the alkoxyl residue of the aluminum alcoholate determines the time necessary for the ester interchange. A complete exchange of the methoxy group for an isopropoxy group in toluene takes place in about 6 hr. while the benzoxy and the 1-methylpentoxy group replaces the methoxy group in 4 hr. in the same solvent. In methanol solution the exchange of the benzoxy group for the methoxy group takes about 26 hr., while more than 70 hr. are needed to transform the isopropyl ester into the methyl ester.

The ratio of ester to aluminum alcoholate is also a factor which influences the reaction time. Using approximately equivalent amounts of reactants, the time for complete alcohol exchange between tosylglycine methyl ester and aluminum isopropoxide in toluene solution is about 6 hr. (Table Ia). When five equivalents of aluminum isopropoxide are treated with one equivalent of tosylglycine methyl ester the reaction is completed in 7.5 minutes (Table Ib).

As demonstrated the exchange of alkoxyl groups between an ester and an aluminum alkoxide can be completed under properly chosen conditions without fractional distillation.

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CHICAGO 9, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO]

Toxic Fluorine Compounds. VII.[1] ω-Fluoroalkyl Thiocyanates and ω-Fluoroalkyl Mercaptans

BY W. C. HOWELL, J. E. MILLINGTON AND F. L. M. PATTISON

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Representative members of the series of ω-fluoroalkyl thiocyanates and mercaptans were synthesized and their chemical, physical and toxicological properties determined. Evidence was obtained (a) for the reductive scission *in vivo* of aliphatic thiocyanates forming cyanide ion and the corresponding mercaptans and (b) for transthiolation of mercaptans to alcohols.

The pharmacological properties of the ω-fluorine atom have been described in earlier papers in this series.[2] The preparations of the ω-fluoroalkyl thiocyanates and mercaptans were undertaken in order to obtain information regarding the detoxication mechanism of aliphatic thiocyanates and mercaptans.

2-Fluoroethyl thiocyanate[3] and 3-fluoropropyl thiocyanate[4] have been prepared previously. Of the ω-fluoroalkyl mercaptans, only the 2-fluoroethyl derivative[5] has been mentioned in the literature. The preparation of the acetyl derivative of 2-fluoro-

(1) Issued as DRB Report No. SW-23.

(2) Part VI, THIS JOURNAL, **78**, 3487 (1956).

(3) B. C. Saunders, G. J. Stacey and I. G. E. Wilding, *J. Chem. Soc.*, 773 (1949).

(4) B. C. Saunders and F. L. M. Pattison, unpublished work (1947).

(5) E. K. Ellingboe, U. S. Patent 2,439,203; April 6, 1948.