would be necessary. In the present work, no direct test for completeness of combustion by measurement of carbon dioxide or carbon monoxide formation was made on any of the compounds.

The accuracy of the values reported here is almost certainly poorer than the precision of the determinations, since the purity of the samples—in spite of the effort to obtain high-grade materials—probably is the limiting factor. The compounds were all taken as 100% pure even though in some instances the analysis throws some doubt on this, and in the case of the liquids no attempt was made to correct for any dissolved gases. This appears to be the best policy to follow, first, because the significance of the analysis may be questioned and, second, because the kind and amount of impurity is indeterminate. The cyanamide, dicyandiamide and melamine figures are considered to be the most reliable in this respect.

The heats of combustion of cyanamide, dicyandiamide and melamine were measured by Lemoult,[12] his figures being 171.6, 328.7 and 469 kcal./mole, respectively. These values are nominally 5.6, 3.2 and 2.8 kcal./mole lower than those obtained here. Since the corresponding heats of formation have rather low absolute values, these differences naturally result in large percentage differences between the old and new heats of formation. The present values are considered to be the more trustworthy. No values have been located in the literature for the other substances.

Acknowledgment.—Acknowledgment is made to Mr. P. Adams, Dr. P. R. Averell, Dr. I. Heckenbleikner, Dr. R. F. Stamm, and members of the Analytical Department of these Laboratories for the preparation, purification, and analysis of the compounds used, and to the Directors of these Laboratories for permission to publish these results.

Summary

A bomb calorimeter, calibrated with benzoic acid, has been used for determining the heats of combustion of eight organic nitrogen compounds at 25° and constant volume. From these data, the corresponding heats of combustion and of formation at constant pressure have been calculated. The substances burned were cyanamide, dicyandiamide, melamine, 3-cyanopyridine, phthalonitrile, dimethylol urea, diisopropyl cyanamide, and diisopropyl carbodiimide.

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[12] P. Lemoult, *Ann. chim. phys.*, [7] **16**, 338 (1898). See also F. R. Bichowsky and F. D. Rossini, "Thermochemistry of Chemical Substances," Reinhold Publishing Corp., New York, N. Y., 1936, p. 50.

[CONTRIBUTION FROM THE STAMFORD LABORATORIES OF THE AMERICAN CYANAMID CO.]

Some Amides and Esters of Fluoroacetic Acid

BY J. C. BACON, C. W. BRADLEY,[1] E. I. HOEGBERG, PAUL TARRANT[2] AND J. T. CASSADAY

The toxicity of certain derivatives of fluoroacetic acid to insects and rodents was established in these Laboratories several years ago and has led to the synthesis of additional compounds of this type.

The problem of preparing economically a simple derivative of α-fluoroacetic acid to be used as a starting material for the rest of these syntheses was solved by the discovery of a method for converting chloroacetamide into fluoroacetamide by reaction with potassium fluoride. This method is discussed below. The literature[3-5] has subsequently indicated that during the course of our investigations methods were simultaneously in the process of development in England, Poland, and elsewhere in the United States for the large-scale production of methyl, ethyl and sodium fluoroacetates, the latter being known as rodenticide "1080." Analytical methods have been reported[4] for the determination of extremely small traces of fluorine in these and similar types of materials and reports[6,7] have also been published covering the effect of "active" fluorine compounds on warm-blooded animals.

Numerous unsuccessful attempts were made to replace the chloro group of chloroacetic acid and ethyl chloroacetate using hydrogen fluoride alone or in combination with antimony trifluoride.

Fluoroacetamide was finally prepared by the reaction of chloroacetamide with potassium fluoride. A mixture of the fluoro- and chloroamides was obtained both by dry distillation under reduced pressure and by distillation at atmospheric pressure using xylene as a carrier. The yields of fluoroacetamide based upon the chloroacetamide consumed were greater than 50%. The mixture of amides was converted into a

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[3] H. McCombie and B. C. Saunders, *Nature*, **158**, No. 4011, 382 (1946).

[4] W. B. Reed for R. L. Jenkins and E. E. Hardy, Office of Technical Service Report, PB 24903; C. W. Mason and C. B. De La-Mater, PB 5484; J. H. Yoe, Jason M. Salsbury and James W. Cole, PB 5955, PB 4220, PB 6020, PB 6021; John H. Yoe and Lyle G. Overholser, PB 4216; Benjamin Witten, Bernard Gehauf and Melvin M. Falkof, PB 17207; Joseph M. Sanchis, PB 9511; Irving S. Goldman, Mary Catherine Flannery, Louis J. Arent, John B. Hoag, Arthur M. Buswell, PB 9510; Charles C. Price and William G. Jackson, PB 5904; Nathan L. Drake, PB 5863, R. H. Kimball and Lewis E. Tufts, PB 52707.

[5] E. Gryszkiewics-Trochimowski, A. Sporzynski and J. Wnuk, *Rec. trav. chim.*, **66**, 413–418 (1947).

[6] Maynard B. Chenoweth and Alfred Z. Gilman, PB 9577; Sidney P. Colowick, Louis Berger and Milton W. Slein, PB 5873.

[7] Marais and Onderstepoort, *J. Vet. Sci. Animal Ind.*, **18**, 203 (1943); **20**, 67 (1944).

mixture of ethyl chloro- and fluoroacetates by the use of ethanol and hydrogen chloride or sulfuric acid, and the combined esters were separated by fractional distillation. The pure ethyl fluoroacetate was then converted by customary methods into other esters or amides.

A similar conversion of ethyl bromoacetate into the corresponding fluoro ester was effected by refluxing with potassium fluoride or, in lower yield, with thallous fluoride. The use of bismuth trifluoride produced none of the desired ester.

Since potassium fluoride had proved useful in the production of fluoroacetamide from chloroacetamide as outlined above, other fluorides were tested. Sodium fluoride, when tried in the fusion method for the production of the amide and in the attempted conversion of ethyl bromoacetate to the fluoroacetate, gave none of the desired products. When ammonium fluoride was used in the fusion method, a small amount of fluoroacetamide was isolated.

Another relatively economical material, ammonium glycolamide sulfate, has been converted into fluoroacetamide by fusion with potassium fluoride.[8]

Experimental

The Preparation of Fluoroacetamide from Chloroacetamide

A. Dry Fusion Method.—Chloroacetamide, 187 g. (2.0 moles), and anhydrous potassium fluoride, 200 g. (3.5 moles), were ground together in a ball mill for two hours. The reagents were placed in a one-liter three-necked flask and heated with a Glas-Col mantle. The reaction was carried out at a pressure of about 25 mm. produced by a water pump. When the temperature of the mixture reached 130°, distillation began and continued until 121 g. of solid condensed in the receiver. This material, based on a fluorine analysis, appeared to be 82.2% fluoroacetamide, a yield of 64.5%.

B. Inert Carrier Method.—A method for preparing fluoroacetamide in xylene has been described by one of the authors.[9] Although the yield (55%) was somewhat lower than that obtained in the dry fusion method, a purer product was obtained. The use of tetrachloroethylene (b. p. 121°) instead of xylene resulted in a slightly lower yield of product.

The Preparation of Ethyl Fluoroacetate Using Potassium Fluoride.—Ethyl bromoacetate, 110 g. (0.66 mole), and 75 g. (1.32 moles) of anhydrous potassium fluoride were placed in a 500-ml., round-bottomed flask equipped with a 12″ Vigreux column and a variable take-off fractionating head. The column was maintained under total reflux until the vapor temperature reached 120°, whereupon the ethyl fluoroacetate was stripped off. Heating was continued for sixteen hours, during which time 59 g. of distillate was collected. Refractionation gave 32 g. (45% yield) of ethyl fluoroacetate, b. p. 117.5°.

The Preparation of Ethyl Fluoroacetate Using Thallous Fluoride.—Ethyl bromoacetate, 60 g. (0.36 mole), thallous fluoride, 72 g. (0.32 mole), and ethanol, 50 ml., were placed in a round-bottomed flask with a reflux condenser and heated on a steam-bath for twenty-eight and one-half hours. At the end of this period the mixture was filtered and the liquid distilled under reduced pressure. A refractionation gave 5 g. (13% yield) of ethyl fluoroacetate, b. p. 115.5–118°.

The Esterification of Crude Fluoroacetamide.—The esterification of fluoroacetamide was carried out by allowing it to react with ethanol in the presence of enough acid to neutralize the ammonia formed. A typical example of an experiment using gaseous hydrogen chloride as the neutralizing agent follows:

The esterification of the crude amides prepared from a mixture of chloroacetamide and potassium fluoride in a 1:2 ratio was carried out in a two-liter, three-necked flask equipped with reflux condenser, stirrer and inlet for hydrogen chloride. The hydrogen chloride was passed slowly into a mixture of 462 g. of crude amide and 328 g. (410 ml.) of absolute ethanol. During the first two hours 90 g. of hydrogen chloride was absorbed; 200 g. was added during the next hour. The mixture was then allowed to stand for about thirty-six hours.

The slurry of ammonium chloride and esters was centrifuged and the solid washed with 75 ml. of ethanol. The filtrate and wash solutions were treated with about 400 ml. of saturated calcium chloride solution. The organic layer was separated and washed with 400 ml. of a saturated sodium bicarbonate solution and again with a calcium chloride solution. The product was dried with anhydrous sodium sulfate and distilled at atmospheric pressure through a 24″ column packed with glass helices, giving 272 g. of ethyl fluoroacetate boiling at 115.5–120° and 133 g. of ethyl chloroacetate. Since analysis had shown the crude amide to contain 64.7% fluoroacetamide and 32.9% chloroacetamide, the conversions of the two amides to the corresponding esters were 66 and 67%, respectively.

It was later found that sulfuric acid could be substituted for hydrogen chloride without decreasing the yield of ethyl fluoroacetate. Although the recovery of ethyl chloroacetate was not complete, the ease with which the reaction could be carried out offset this disadvantage.

Preparation of Purified Fluoroacetamide.—Fluoroacetamide was prepared from ethyl fluoroacetate and aqueous ammonia by a method analogous to one commonly used for the preparation of chloroacetamide.[10] However, presumably because of the more stable fluorine atom in the molecule, the yields were usually 90% or better. Several small batches were synthesized to give a total of 457 g. melting at 107–108°.

Ammonium Glycolamide Sulfate.—Anhydrous glycolonitrile was added gradually with vigorous stirring to an equimolecular quantity of 100% sulfuric acid below 60°; then the reaction mixture was added to a slight excess of aqueous ammonia with cooling.[11] Because the reaction product of glycolonitrile and sulfuric acid often solidified immediately to a hard cake, a modification of this procedure was also used, whereby anhydrous glycolonitrile (114 g., 2 moles) was added gradually at 55–65° to 95.5% sulfuric acid (392 g., 3.8 moles) with mechanical stirring. The viscous, liquid reaction mixture was then added with ice-bath cooling to a slurry of powdered calcium carbonate (200 g., 2 moles) in 28% aqueous ammonia (750 ml., 11 moles), and the reaction mixture was allowed to stand for about twelve hours, followed by warming to 80° for one-half hour to insure complete reaction. The calcium sulfate was removed by filtration and the filtrate was concentrated under water pump vacuum to a small volume, cooled and filtered to give 402 g. of ammonium glycolamide sulfate contaminated with a little ammonium sulfate. Recrystallization of the crude product from hot water gave a purified product as colorless crystals melting at 183–185° (cor.).

Anal. Calcd. for $C_2H_8N_2O_5S$: N, 16.4; SO_4, 55.8. Found: N, 16.3; SO_4, 56.3.

Conversion of Ammonium Glycolamide Sulfate to Fluoroacetamide.—Ammonium glycolamide sulfate (180 g., 1.05 moles) and potassium fluoride (116 g., 2 moles) were mixed in a ball mill for three hours, during which time some ammonia was liberated. The resulting powdered mixture was placed in a one-liter, two-necked distilling flask equipped with a thermometer and air conden-

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[8] J. C. Bacon, U. S. Patent 2,416,607 (1946).

[9] C. W. Bradley, U. S. Patent 2,403,576 (1946).

[10] Gilman and Blatt, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., p. 153.

[11] Attempts to add concentrated sulfuric acid to anhydrous glycolonitrile, rather than the reverse procedure, caused violent exothermic decomposition and carbonization.

TABLE I

ESTERS OF FLUOROACETIC ACID, FCH_2COOR

R	% Yield	B. p., °C.	$n^{25}D$	Sap. equiv. Calcd.	Sap. equiv. Found	% Analyses Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Fluorine Calcd.	Fluorine Found
2-Ethylhexyl[12]	79.5[a]	65–68 (2 mm.)	1.4173			63.1	62.5	10.1	10.1 9.9	10.0	9.9
1-Dodecyl	59	106–128[b] (1 mm.)	1.4317	246	244	68.2	68.9	11.0	11.2 11.4	7.7	7.7

[a] On the basis of ethyl fluoroacetate converted. [b] Distilled without fractionation.

TABLE II

AMIDES OF FLUOROACETIC ACID, FCH_2CONHR

R	Yield, %	M. p.,[c] °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Fluorine[e] Calcd.	Fluorine[e] Found
Cyclohexyl[a]	61	99–100	60.3	60.3 60.3	8.9	9.0 9.2		
1-Dodecyl[a]	74	63–66	68.5	68.8	11.5	11.5	7.7	8.0
1-Octadecyl[a]	39	73–75	72.8	72.5 72.4	12.2	12.1 12.2	5.8	5.9
4-Tolyl[b]	77[d]							

[a] Prepared by Procedure A. [b] Prepared by Procedure B; synthesized by a different method by C. C. Price and W. G. Jackson, PB 5904 (1946); THIS JOURNAL, **69**, 1065 (1947). [c] Corrected. [d] Crude yield; m. p. of purified sample checks with that of Price and Jackson. [e] Difficulties were sometimes encountered in obtaining fluorine analyses which checked closely.

ser. The flask was heated under reduced pressure with the temperature maintained below 200°. Twenty-nine grams of solid sublimed from the mixture at a vapor temperature of about 140°. The crude solid was recrystallized from ethanol to give 20 g. (25% of the theoretical) of fluoroacetamide, m. p. 104°.

Esters of Fluoroacetic Acid.—Esters of greater chain length than ethyl were prepared by heating ethyl fluoroacetate (usually in about 5% excess) with an equivalent amount of the higher alcohol to 100–170° in the presence of a trace of *p*-toluenesulfonic acid as catalyst, and distilling the liberated ethanol as it was formed, thus driving the reaction to completion. Two or three hours were normally required. The reaction product was washed with saturated sodium bicarbonate solution, dried over calcium sulfate, and distilled. Examples of esters prepared by this method are listed in Table I.

Amides of Fluoroacetic Acid.—Either of two procedures was used: **Procedure A.** Ethyl fluoroacetate was heated with an equivalent amount of the proper amine to 100–160° until approximately the theoretical amount of ethanol had been distilled off and measured. The reaction product was purified by distillation if a liquid, or by recrystallization from heptane if a solid. **Procedure B.** Fluoroacetamide and the proper amine were heated in equivalent amounts in glacial acetic acid on a steam-bath for about three hours, then thrown into excess cold water and separated. The crude product was recrystallized from aqueous ethanol for purification.

Several of the amides prepared are listed in Table II.

Acknowledgment.—We are indebted to the Analytical Laboratories for the analyses shown above, to the Chemotherapy Division for preliminary toxicological data, and to the Agricultural Chemicals Laboratories for numerous insecticidal evaluations as well as to Drs. R. C. Swain and J. T. Thurston who offered considerable helpful advice during the course of this problem.

Summary

1. Some new methods for the preparation of fluoroacetamide are described. Two convenient methods for the preparation of N-substituted fluoroacetamides are also given.

2. Three new amides and one new ester of fluoroacetic acid are listed.[13]

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(12) J. L. Horsfall, U. S. Patent, 2,409,859 (1946).

(13) The toxicity of these types of compounds to warm-blooded animals both orally and by skin absorption is high, and due caution should be exercised in handling them.