[CONTRIBUTION FROM THE LION OIL CO., A DIVISION OF MONSANTO CHEMICAL CO.]

Formylation of Amines

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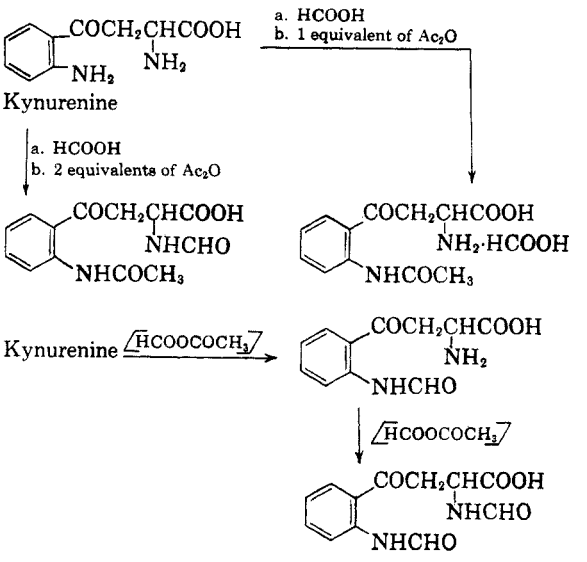
A wide variety of amines were formylated by acetic formic anhydride.

Many procedures have been used to formylate amines, but the range of applicability appears to be limited. Formamido compounds were required for biological testing, so that a general formylation procedure was desired. The results of this research show that acetic formic anhydride is an excellent general reagent for the preparation of formyl derivatives of amines.

A brief summary of the shortcomings of various formylation procedures (particularly as applied to heterocyclic amines in this study) will be of interest. Formamide[2] serves to formylate some aniline derivatives and amines such as benzylamine. It did not give the formyl derivative of 2-amino-5-nitrothiazole. Esters[3] of formic acid gave good results with a number of amines, but sealed tubes or autoclaves are often required. Chloral[4] reacts with many amines to furnish the formamido compound and chloroform. Again, this reagent did not react with 2-amino-5-nitrothiazole. Sometimes chloral gives addition products. For example,[5] 2-aminopyridine and chloral formed the addition compound $C_7H_7Cl_3N_2O$ which sublimed under vacuum (11 mm.) and melted at 106.5°. An odd complex resulted from a reaction between 2-aminoquinoxaline and chloral. This complex decomposed at 176°. It could be crystallized from benzene, but an attempted crystallization from 2-propanol gave the starting 2-aminoquinoxaline (m.p. 154°). Therefore chloral fails to formylate some amines. Formic acid alone formylates varied aniline derivatives such as 3,4-dichloroaniline.[6] Even weakly basic anilines such as 3,5-dinitroaniline[7] gave moderate (50%) yields of the formyl derivative upon reflux with a large excess (8 moles) of formic acid. In some cases, acetic anhydride has been added to a solution of amine in an excess of formic acid. Such a procedure was used to prepare 2-(5-nitrothiazolyl)formamide.[8]

Dalgliesch[9] made a study of the use of mixtures of formic acid and acetic anhydride. Acetylation sometimes occurred rather than formylation. For example, the addition of acetic anhydride to a formic acid solution of anthranilic acid gave the acetyl derivative. Yet these conditions gave the formyl derivative with phenylalanine, phenacylglycine, and tryptophane. His interesting studies with kynurenine are illustrated below.

Formylation and Acetylation of Kynurenine[9]



The simple addition of two equivalents of acetic anhydride to a formic acid solution of kynurenine resulted in the formylation of the aliphatic amino group and the acetylation of the aromatic amino group. Acetic formic anhydride proved to be a better formylation agent. In fact, it was possible to selectively formylate the aromatic amino group by the use of one mole of acetic formic anhydride. A further formylation of aliphatic amino group occurred upon the addition of more acetic formic anhydride. The acetic formic anhydride need not be isolated. Merely allowing a mixture of acetic anhydride and formic acid to warm spontaneously causes the formation of acetic formic anhydride.

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TABLE I
FORMAMIDO COMPOUNDS

Compound	Yield, %	M.P., °C.	Crystallized from	Formula	Analysis							
					Calcd.				Found			
					C	H	Cl	N	C	H	Cl	N
2-Quinoxalinoformamide	91	192.5–194 (dec.)	Benzene and ethyl acetate	$C_9H_7N_3O$	62.4	4.07	—	24.3	62.1	3.95	—	24.1
3′,4′-Dichloroformanilide[6]	96	110–112	Benzene and carbon tetrachloride	$C_7H_5Cl_2NO$	44.2	2.65	37.3	7.37	44.4	2.55	37.3	7.17
2-Thiazolylformamide[13]	64	156–161	Benzene	$C_4H_4N_2OS$	37.5	3.14	—	21.9	37.6	3.07	—	20.9
2-(5-Nitrothiazolyl)-formamide[3]	84	192–194	Ethyl acetate	$C_4H_3N_3O_3S$	27.7	1.74	—	—	27.8	1.52	—	—
2-Benzimidazolylformamide	83	260.2–260.8	Dimethylformamide	$C_8H_7N_3O$	59.6	4.38	—	26.0	59.9	4.17	—	25.6
2-Benzothiazolylformamide	94	254.2–256.2 (dec.)	Ethyl acetate	$C_8H_6N_2OS$	53.9	3.39	—	15.7	54.2	3.37	—	15.0

If desired, an excellent[10] preparation of pure acetic formic anhydride can be made from ketene and formic acid. A formylation of 2-amino-3-methylpyridine was accomplished[11] with one mole of acetic formic anhydride in ether. A similar treatment of 2-aminoquinoxaline gave a low yield of crude 2-quinoxalinoformamide which was purified with difficulty. Some of starting 2-aminoquinoxaline was recovered. However, when the quantity of acetic formic anhydride was doubled, an excellent yield (91%) of high purity product was obtained by filtration of the reaction mixture. Evidently, the three basic nitrogen atoms of 2-aminoquinoxaline require that the reaction mixture contain more than a mole of acetic formic anhydride and a mole of acetic acid. It is noteworthy that 2-quinoxalinoformamide and 2-acetamidoquinoxaline[12] have the same melting point (194°). A mixture of the two gave a sharp lowering of the melting point.

The versatility of the acetic formic anhydride formylation procedure is shown by the results given in Table I. All types of amines—especially amines of heterocyclic compounds—gave good yields of the desired formamido derivatives. The experimental section describes the preparation of 2-quinoxalinoformamide as an illustration of the method. In all other cases, an overnight reaction period was satisfactory. Experimental details are given also for 3′,4′-dichloroformanilide because it was the only formyl compound which was soluble in the reaction mixture.

EXPERIMENTAL

Microanalysis by Clark Microanalytical Laboratories, Urbana, Ill. Melting points (uncorrected) were taken with Anschutz thermometers using a Hershberg-type apparatus.

2-Quinoxalinoformamide. The acetic formic anhydride was prepared (but not isolated) by heating acetic anhydride (20.4 ml.) and formic acid (8.6 ml., 98%) for two hours at 50–60° in a flask equipped with a stirrer and drying tube. The solution was cooled to 27°. A gradual addition of 2-aminoquinoxaline (14.6 g., 0.1 mole, Merck) was made over a 15-min. period using a water bath to maintain a temperature below 39°. Some of the 2-aminoquinoxaline dissolved. The reaction mixture was cooled to 30° and ether (50 ml.) was added to the suspension. The mixture was allowed to stir about 60 hr. (no doubt a shorter time would be satisfactory) at room temperature. A filtration removed the product, which was washed with ether (25 ml.). The crude product weighed 15.9 g. (91%). It sintered at 175° and melted at 190–192° (dec.).

A preliminary run with one-half the above quantity of acetic formic anhydride gave a very low yield of 2-quinoxalinoformamide along with recovered 2-aminoquinoxaline.

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An analytical sample was obtained by crystallization of the crude material from benzene followed by 3 recrystallizations from ethyl acetate. It softened at 150° and melted at 192.5–194.0°.

A mixed melting point of 2-quinoxalinoformamide and 2-acetamidoquinoxaline (m.p. 192.6–193.8°)[12] showed a sharp depression.

3′,4′-Dichloroformanilide. Acetic formic anhydride was prepared from acetic anhydride (40.8 ml.) and 98% formic acid (17.2 ml.). This mixture was cooled in an ice bath to 12°. A gradual addition of 3,4-dichloroaniline (32.4 g., 0.2 mole) was made so that the temperature did not rise above 40°. The dark red solution was held at room temperature (35°) for five hours after which ether (100 ml.) was added. The following day the dark purple solution was extracted with 2 × 100 ml. of water. The ether layer was evaporated on the steam bath to furnish 36.7 g. (96.5%) of crude material, m.p. 94–103°. A hot benzene (150 ml.) solution of the crude product was treated with Nuchar C. The filtrate was cooled for several hours prior to collecting the product by filtration. A cold benzene wash was applied to the gray solid. The purified 3′,4′-dichloroformanilide weighed 30.4 g. It sintered at 99° and melted at 110–112°. Recrystallization from a large volume of carbon tetrachloride furnished off-white crystals with no change in melting point. The product is soluble in chloroform and cyclohexene but insoluble in petroleum ether or cyclohexane. Possibly a reduction in the quantity of acetic formic anhydride to slightly over one mole would give a satisfactory result for this type of preparation.

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[CONTRIBUTION FROM THE RESEARCH CENTER, HERCULES POWDER COMPANY]

Preparation of Ethenesulfonamide[1]

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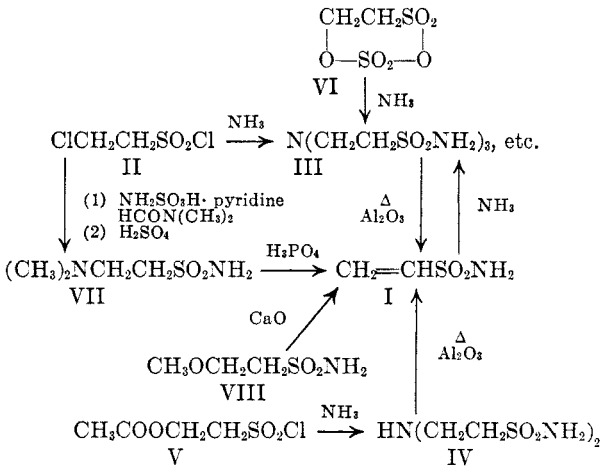
Ethenesulfonamide has been prepared in moderate yields by heating 2-sulfamylethylamines and their salts.

The literature records three different sets of properties for ethenesulfonamide (I).[2–9] None of these are those that would be predicted from the properties of the closely related ethanesulfonamide.[10,11] These discrepancies prompted a reinvestigation of the preparation of I.



Ethenesulfonamide has now been prepared in 53% yield by heating with alumina a mixture obtained by ammonolysis of 2-chloroethanesulfonyl chloride (II). After crystallization from ether it melted at 24° and was soluble in ethanol, water, ethyl acetate, and acetone but insoluble in benzene and hexane. Ammonia added readily to I to form tris(2-sulfamylethyl)amine (III) and thiophenol added to I to form 2-phenylthioethanesulfonamide. No Diels-Alder reaction occurred with anthracene on heating with I at 100° for 72 hr.

The formation of I on heating is believed to occur by elimination of ammonia from the mixture of 2-sulfamylethylamines obtained by ammonolysis of II.[12] The preparation of I (in 35% yield) from bis-(2-sulfamylethyl)amine (IV) under the same conditions lends support to this view. Heating the hydrochloride of IV also gave I in 30% yield. The sample of IV used was prepared by ammonolysis of 2-acetoxyethanesulfonyl chloride (V).

Another source of mixtures containing 2-sulfamylethylamines was the reaction of ammonia

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(1) Presented in part at the Delaware Chemical Symposium, University of Delaware, February 19, 1955.

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(6) H. F. Park, U.S. Patent **2,700,055** (1955).

(7) H. F. Park, U.S. Patent **2,715,142** (1955).

(8) H. F. Park, U.S. Patent **2,709,707** (1955).

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(12) H. W. Coover and N. H. Shearer, Jr. [U.S. Patent **2,719,178** (1955)] report the preparation of *N,N*-dimethylmethacrylamide by passing its dimethylamine adduct over alumina at 550°.