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The Nitrolysis of N,N-Dialkylformamides

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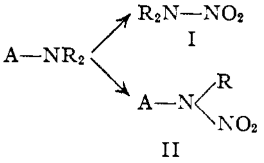
N,N-Dialkylformamides were shown to be very unstable in a nitrolysis medium of acetic anhydride and absolute nitric acid. Generally, poor yields of the dialkylnitramines were obtained and the corresponding nitrosamines were also formed. The use of phosphorus pentoxide or of zinc chloride catalyst in acetic anhydride failed to increase the yield of di-*n*-butylnitramine from the amide. However, formamides were found to be smoothly nitrolyzed to the nitramines in high yield when trifluoroacetic anhydride was used as solvent, and no nitrosamine formation was observed.

It was previously noted[1] that N,N′-dicyclohexyl-N-nitro-N′-formylethylenediamine was formed during the nitrolysis of N,N-dicyclohexylimidazolidine and at least partially survived the reaction. The formation of a formamide, even in low yield, was unexpected, and this study was undertaken to determine the stability of disubstituted formamides in nitrolysis media.

The behavior of a large number of disubstituted amides toward nitric acid has been studied and most of this work is very adequately reviewed by Backer.[2] Most of the previous work has been done using absolute or fuming nitric acid without solvent and the reactions followed one of two courses



A = Acyl, aroyl, sulfonyl, carbamyl or carbomethoxy

When R was methyl, or formed the ring systems of morpholine or piperazine, the secondary nitramine I was formed. In general, all other dialkylamides failed to react or yielded products of type II, where one N-alkyl group was replaced by a nitro group.

Table I gives the results of nitrolysis of several formamides in various media. As was expected, dimethyl formamide and N-formylmorpholine gave fair yields of dimethylnitramine and nitromorpholine when acetic anhydride medium was used. Diethyl and di-*n*-butyl formamides gave only small amounts of the corresponding nitramines in acetic anhydride and the nitrosamines also were formed. When catalytic amounts of zinc chloride were used in the acetic anhydride nitrolysis of di-*n*-butyl formamide,[3] the amount of nitramine was unchanged but the yield of di-*n*-butylnitrosamine was increased to 55%. Also, the use of phosphorus pentoxide as nitrolysis medium failed to improve yields and again dibutylnitrosamine was present in the products. It was surprising that N-formylpiperidine gave a good yield (65%) of the nitramine in acetic anhydride and that no nitrosamine was formed, since several workers[2] have shown that other amides of piperidine are very difficultly nitrolyzed.

TABLE I

Formamide	Nitrolysis medium	Yields, % Recd. amide	Nitramine	Nitrosamine
Dimethyl	Ac_2O		45	
Dimethyl	TFAA[a]		89	
Diethyl	Ac_2O		0	0
Diethyl	TFAA		80	0
Di-*n*-propyl	TFAA		91	0
Di-*n*-butyl	Ac_2O	27	13	
Di-*n*-butyl	P_2O_5	0	17	17
Di-*n*-butyl	$Ac_2O + ZnCl_2$	22	11	55
Di-*n*-butyl	TFAA	0	91	0
N-Formylpiperidine	Ac_2O		65	0
N-Formylpiperidine	TFAA		81	0
N-Formylmorpholine	Ac_2O		55	

[a] Trifluoroacetic anhydride.

Trifluoroacetic anhydride proved to be an excellent medium for the nitrolysis of the four dialkylformamides and for formylpiperidine. In all cases where attempts were made to isolate nitrosamine product or starting amide, these materials were shown to be absent. These reactions were very rapid at 0° and apparently were accompanied by very little by-product formation. The yields of purified dialkylnitramines ranged from 80 to 91%.

Trifluoroacetic anhydride has been shown to be an excellent reagent both for nitration and for esterification.[4] More recently acyl trifluoroacetates have been isolated from mixtures of carboxylic acids and trifluoroacetic anhydride.[5] In view of this mixed anhydride formation the unusual reactivity of nitric acid in trifluoroacetic anhydride might be due to nitronium ion furnished from nitronium trifluoroacetate, $CF_3COO^-NO_2^+$. Accordingly an attempt was made to isolate this product.

Absolute nitric acid reacted exothermically with trifluoroacetic anhydride at 0° after a short induction period. The principal product of reaction was nitrogen pentoxide, isolated simply by filtration of the cooled reaction mixture. From this it appears probable that the greater ease of nitrolysis in this medium is due to the increased activity of nitronium ion and that the mechanism may involve an S$_E$2 attack of nitronium ion on the amide. Further work is being done to determine the generality of the reaction as a preparative method for secondary nitramines.

Experimental[6]

Nitrolysis of Dimethylformamide. A. With Acetic Anhydride.—A solution of 5.0 g. (0.0686 mole) of freshly dis-

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(1) J. H. Robson and G. F Wright, THIS JOURNAL, **74**, 1608 (1952).

(2) H. J. Backer, *Sammlung Chem. und Chem. Tech. Vortrage*, **18**, 359 (1912); see also A. H. Lamberton, *Quart. Rev.*, **V**, No. 1 (1951).

(3) For the catalyzed nitration of amines see G. F. Wright, *et al.*, *Can. J. Research*, **B26**, 114 (1948).

(4) E. J. Bourne, *et al.*, *J. Chem. Soc.*, 2976 (1949); 1695 (1952).

(5) W. D. Emmons, K. S. McCallum and A. F. Ferris, THIS JOURNAL, **75**, 6047 (1953).

(6) All melting points are uncorrected.

tilled dimethylformamide in 40.0 cc. (0.412 mole) of acetic anhydride was added dropwise to 14.4 cc. (0.343 mole) of absolute nitric acid (99–100%) with stirring at −50°. When the addition was completed (40 minutes), another 10 cc. of acetic anhydride was added and the solution held at 25° for two hours, during which time there was a copious evolution of gas. After pouring into 75 cc. of ice–water mixture and making alkaline with 50% sodium hydroxide, the resulting crystalline slurry was extracted with four 40-cc. portions of ether. After drying over magnesium sulfate, the ethereal extracts were concentrated to yield 2.8 g. (45.5%) of white crystals, m.p. 54.0–56.0°. A mixture melting point with authentic dimethylnitramine gave no depression.

B. **With Trifluoroacetic Anhydride.**—To 91.7 cc. (0.663 mole) of trifluoroacetic anhydride was added 30.8 cc. (0.733 mole) of absolute nitric acid, cooling being required to maintain the temperature at −5° to 0°. This solution was cooled to −30° and 10.0 g. (0.137 mole) of distilled dimethylformamide was added cautiously. The resulting solution was distilled at 5 mm. to approximately half-volume, poured onto 150 g. of ice, basified to *p*H 10 and treated with ether in a liquid–liquid extractor for five hours. After drying and evaporating the ethereal phase there was obtained 10.92 g. of white crystals melting at 55.6–56.5°. A mixture melting point with dimethylnitramine was not depressed. The yield was 89%.

Nitrolysis of Di-*n*-butylformamide. A. With Acetic Anhydride.—A mixture of 30 cc. (0.31 mole) of acetic anhydride and 10 cc. (0.17 mole) of glacial acetic was cooled to −5°, 14.4 cc. of absolute nitric acid and then 10.8 g. (0.068 mole) of di-*n*-butylformamide added dropwise at that temperature. The reaction mixture was warmed to 25–30° for two hours, then the volatile components removed by distillation at 70° and 10 mm. pressure. The residual yellow oil was dissolved in 30 cc. of ether and extracted with eight 30-cc. portions of 12% hydrochloric acid. The combined aqueous extracts were basified to *p*H 10, extracted with ether and the dried ether extracts distilled to yield 2.92 g. (27%) of recovered di-*n*-butylformamide, b.p. 105–108° (8–10 mm.), n^{25}D 1.4435 (literature values[7] b.p. 76–78° (0.25 mm.), n^{25}D 1.4435).

The acid-extracted ether solution was dried and distilled to give 1.52 g. of yellow oil boiling at 105–130° (10 mm.). The presence of nitrosamine was indicated by the partial solubility of the oil in concentrated hydrochloric acid; the maximum possible yield of di-*n*-butylnitramine was 13%. No further purification was attempted.

B. **With Phosphorus Pentoxide.**—To 14.4 cc. (0.343 mole) of absolute nitric acid, cooled to 0°, was added 12.2 g. (0.086 mole) of phosphorus pentoxide and then, slowly with stirring, 10.8 g. (0.0686 mole) of di-*n*-butylformamide. After two hours at 25°, the semi-fluid mass was poured onto ice and extracted with three 20-cc. portions of ether. The ether solution was washed with 5% potassium hydroxide and water, dried and distilled to give 5.2 g. of oil boiling at 108–130° (8 mm.). Separation of the mixture by the method of Wright[3] yielded 2.05 g. (17%) of di-*n*-butylnitramine, m.p. −22°, n^{20}D 1.4562, and 2.00 g. (17%) of di-*n*-butylnitrosamine, n^{25}D 1.4451. That the latter compound was not di-*n*-butylformamide was shown by its insolubility in 12% hydrochloric acid. No dibutylformamide was found.

C. **With Acetic Anhydride and Zinc Chloride Catalyst.**—The reaction was carried out as in procedure A, except that 0.55 g. (0.004 mole) of zinc chloride was added to the reaction mixture. Extraction of the crude product with 12% hydrochloric acid gave a 22% recovery of di-*n*-butylformamide. The mixture of nitramine and nitrosamine was separated by the method of Wright[3] to yield 55% of di-*n*-butylnitrosamine and 11% of the nitramine.

D. **With Trifluoroacetic Anhydride.**—To 67.0 cc. (0.484 mole) of trifluoroacetic anhydride was added 22.5 cc. (0.535 mole) of absolute nitric acid and then 15.0 g. (0.095 mole of di-*n*-butylformamide, both additions being made dropwise at −5 to 0°. After stirring 80 minutes at −5° gas evolution had ceased. The solution was concentrated to 50% of its volume at 0° and reduced pressure, poured onto ice and basified with 10 *N* sodium hydroxide. Extraction with ether, followed by distillation of the ethereal phase gave 15.0 g. (90.5%) of di-*n*-butylnitramine, b.p. 129–132° (11 mm.), m.p. −18.5°. Extraction of this product with concentrated hydrochloric acid gave no acid-soluble material, proving both the formamide and nitrosamine to be absent.

Nitrolysis of Diethylformamide. A. With Acetic Anhydride.—The reaction was carried out as was the nitrolysis of di-*n*-butylformamide (A) except that a reaction time of six hours at 0° was allowed, during which the originally vigorous gas evolution nearly ceased. No water-insoluble products were formed.

B. **With Trifluoroacetic Anhydride.**—The reaction and purification procedure were the same as that used for di-*n*-butylformamide (D). Distillation gave only one fraction, b.p. 199–201° (700 mm.), 90–91° (14 mm.) (literature value[8] b.p. 206.5° (759 mm.)), n^{25}D 1.4528, no lower boiling nitrosamine fraction being found. The conversion to diethylnitramine was 80%.

Nitrolysis of N-Formylpiperidine. A. With Acetic Anhydride.—The nitrolysis was carried out by the method given in procedure A for dibutylformamide, using 15.5 g. (0.137 mole) of formylpiperidine. After a two-hour reaction period at 20–25°, the reaction mixture was poured into an ice–water mixture and made basic with 50% potassium hydroxide. After extracting the basic solution with ether and drying the ether extracts over magnesium sulfate, there was obtained 15.0 g. of a yellow oil. Distillation of this oil at 20 mm. gave 1.5 g. of a water-white low boiling fraction (70–120°) and 11.7 g. (65%) of N-nitropiperidine, b.p. 120–123°, n^{26}D 1.4958, m.p. −6.6 to −6.0° (literature values[9] b.p. 245°, m.p. −6°, $n^{26.4}$D 1.4954). Saturation of both fractions with anhydrous hydrogen chloride yielded no nitrosopiperidine hydrochloride. The lower boiling fraction was water insoluble, indicating the absence of formylpiperidine.

B. **With Trifluoroacetic Anhydride.**—The reaction and purification procedures were the same as those for di-*n*-butyl formamide (D). Distillation of the product gave only one fraction, boiling at 116–117° (17 mm.) and melting at −6.6 to 6.0°, n^{26}D 1.4958. The yield of nitropiperidine was 81%. Saturation of the product with dry hydrogen chloride gave no nitrosopiperidine hydrochloride.

Di-*n*-propylformamide.—A solution 74 g. (0.73 mole) of distilled di-*n*-propylamine in 183 g. (4.0 moles) of 98% formic acid was distilled through an 18-inch Vigreux column (a shorter column allows the formate salt to be carried over) to give 61 g. (65%) of the amide, b.p. 206–207° (715 mm.), n^{25}D 1.4384.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.33; H, 11.80; N, 10.57.

Nitrolysis of Di-*n*-propylformamide.—The nitrolysis was carried out in trifluoroacetic anhydride at 0°, following the method used for di-*n*-butyl formamide (D). A 91% yield of di-*n*-propylnitramine was obtained, b.p. 105–106° (10 mm.), m.p. 0.08°, n^{26}D 1.4540 (literature values[10] b.p. 103–104° (10 mm.), m.p. 1.0–1.6°, n^{20}D 1.4559). No lower boiling di-*n*-propylnitrosamine was found.

Nitrolysis of N-Formylmorpholine.—This nitrolysis was carried out in acetic anhydride, following the method given for di-*n*-butylformamide (A), except that a reaction time of six hours was allowed. Concentration of the reaction mixture at reduced pressure gave an oily solid which upon crystallization from water gave a 55% yield of nitromorpholine, m.p. 52–53°. A mixture melting point with authentic nitromorpholine was not depressed.

Nitrogen Pentoxide.—All work was carried out in a dry-box under nitrogen atmosphere. To 18.3 cc. (0.13 mole) of trifluoroacetic anhydride was added 11.7 cc. (0.28 mole) of absolute nitric acid dropwise, maintaining the temperature at 0–5°. When addition was completed, the yellow solution was cooled to −30° and the crystalline slurry filtered. The solid, which was washed twice with cold trifluoroacetic anhydride (−50°), was dried two hours at −30° and 1 mm. pressure. The resulting white solid had a neutral equivalent of 55.4 (found 54.3, 56.6; calcd. for N_2O_5, 54.0). Determination of nitrate ion as the nitron salt gave results of 98.61 and 101.28%, based on N_2O_5. Due to the difficulty of handling the product (nitrogen pentoxide decomposes above 0°), no yields were determined.

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[10] W. R. Kingdon and G. F Wright, THIS JOURNAL, **72**, 1030 (1950).