[Contribution from the E. I. du Pont de Nemours & Company, Eastern Laboratory]

The Preparation of Amides from Salts of Secondary Nitroparaffins and Sodium Azide[1]

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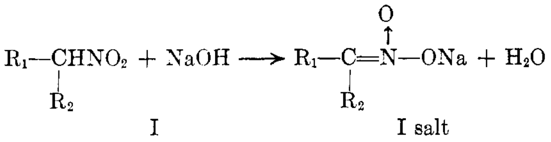
A new method for the preparation of amides from *aci* salts of secondary nitro paraffins has been discussed. Specifically, the preparations of N-methylacetamide, N-*n*-propyl-*n*-butyramide, N-*n*-hexylacetamide, ε-caprolactam, and δ-valerolactam from 2-nitropropane, 4-nitroheptane, 2-nitroöctane, nitrocyclohexane, and nitrocyclopentane, respectively, have been described. The possibility that the over-all reaction is a combination of the Nef reaction and the Schmidt reaction has been discussed. An explanation for the self-reduction of nitroparaffin *aci* salts by acidification has been offered.

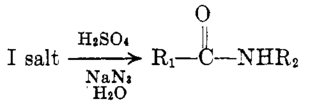
A new reaction for the preparation of amides from *aci* salts of secondary nitro paraffins has been reported in the patent literature.[2] Since the original disclosure, the reaction has been investigated further in order to extend its utility and to obtain a qualitative picture of the intermediates involved in the reaction.

When an aqueous solution containing an *aci* salt of a secondary nitro paraffin (I) and an equimolar quantity of sodium azide is added to concentrated sulfuric acid, at or near room temperature, a substituted amide (II) is formed.



$$\underset{\substack{|\\ R_2\\ \text{I}}}{R_1-CHNO_2} + NaOH \longrightarrow \underset{\substack{|\\ R_2}}{R_1-C}=\overset{\substack{O\\ \uparrow}}{N}-ONa + H_2O$$

I salt

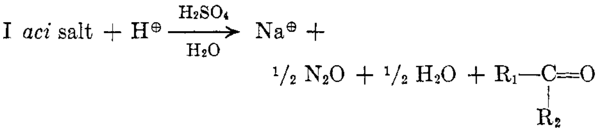


$$\text{I salt} \xrightarrow[\substack{NaN_3\\ H_2O}]{H_2SO_4} R_1-\overset{\substack{O\\ \|}}{C}-NHR_2$$

II

Listed in Table I are the yields of amides obtained when aqueous solutions of the nitronate salts of the five secondary nitro paraffins were treated with hydrazoic acid, formed *in situ* in the presence of concentrated sulfuric acid. The other products of the reaction were the ketone and the ketoxime corresponding to the nitro compound used.

The presence of a ketone in the product suggests that the amide may result from the reaction of the carbonyl derivative with hydrazoic acid by the Schmidt reaction[3] and ketone formation can be explained by the fact that carbonyl derivatives result from the acidification of *aci* salts *via* the Nef reaction.[4]



$$\text{I } \textit{aci} \text{ salt} + H^{\oplus} \xrightarrow[H_2O]{H_2SO_4} Na^{\oplus} + \tfrac{1}{2}N_2O + \tfrac{1}{2}H_2O + \underset{\substack{|\\ R_2}}{R_1-C}=O$$

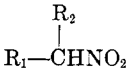
III

$$\text{III} + HN_3 \xrightarrow[H_2SO_4]{NaN_3} \text{II} + N_2$$

Support for the interpretation that the over-all reaction is the net result of these two steps was obtained by subjecting sodium *aci*-nitrocyclohexane to the same reaction conditions in the absence of sodium azide. The major product was cyclohexanone (40%). A small amount of cyclohexanone oxime (15%) was isolated also, but none of the amide (IId) was found. In addition to the ketone and the oxime, olefinic carbonyl compounds were obtained which might be related to cyclohexylidene cyclohexanone which is known to form from cyclo-

TABLE I

Preparation of Amides from Secondary Nitro Paraffins



$$R_1-\overset{\substack{R_2\\ |}}{C}HNO_2$$

No.	Nitroparaffin Used R₁	R₂	No.	Amide Produced Name	Yield, %
Ia	CH_3	CH_3	IIa	N-Methylacetamide	44
Ib	n-C_3H_7	n-C_3H_7	IIb	N-*n*-Propyl-*n*-butyramide	62
Ic	CH_3	n-C_6H_{13}	IIc	N-*n*-Hexylacetamide	47
Id	$-(CH_2)_5-$		IId	ε-Caprolactam	67
Ie	$-(CH_2)_4-$		IIe	δ-Valerolactam	81

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[1] Presented at the First Annual Delaware Valley Regional Meeting in Philadelphia, February 16, 1956.

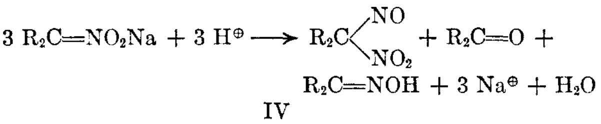
[2] Donaruma and Huber, U.S. Patent 2,702,801 (to du Pont), February 1955.

[3] Wolff, *Org. Reactions*, **3**, 307–335 (1951).

[4] Leitch, *Can. J. Chem.*, **33**, 400 (1955).

hexanone under these conditions.[5] Furthermore, it appears reasonable to assume that 10–20% conversion of the nitroparaffin to the unstable cyclohexyl pseudonitrole might occur.[6] When a mixture of sodium azide and sodium nitrocyclohexane was added to concentrated sulfuric acid as a solid rather than as a solution, the yield of ε-caprolactam (IId) was only 10%. This result may be attributed to the fact that the formation of ketones by the Nef reaction requires the presence of water.[4] However, the use of a large excess of water (the initial acid concentration was 95% and the final acid concentration 45%) in the sodium *aci*-nitrocyclohexane-sodium azide solution also gave a low yield of ε-caprolactam (IId) (36%), and it is known that the Schmidt reaction does not proceed well in dilute acid.[3] Therefore, it seems logical to assume that a certain minimum quantity of water is necessary to insure a satisfactory occurrence of the Nef reaction for a given amount of sulfuric acid. On the other hand, a high acid strength is desirable to carry out the Schmidt reaction. Obviously, the achievement of optimum conditions for both of these reactions in this case is not possible. Therefore, the practical experimental conditions which resulted in the highest yields of amide involved the use of a quantity of water sufficient to dissolve the required amount of *aci* salt and sodium azide and to give the best possible yield of ketone without diluting the acid employed to a point beyond which it would cease to function as a satisfactory catalyst for the Schmidt reaction.

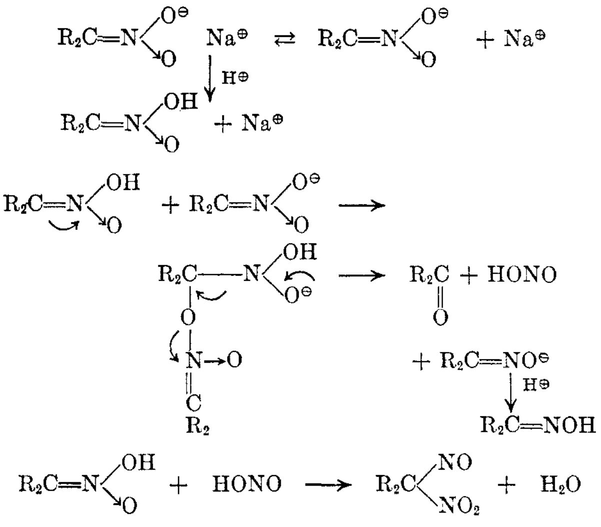
The ketoximes obtained as by-products probably were formed by a self-reduction of the *aci* form of the nitro paraffin employed. The reaction has been formulated as follows by Nygaard[6] who was the first to report the formation of oximes by the acidification of nitroparaffin *aci* salts.



$$3\ R_2C{=}NO_2Na + 3\ H^{\oplus} \longrightarrow \underset{\text{IV}}{R_2C\begin{smallmatrix}NO\\NO_2\end{smallmatrix}} + R_2C{=}O + R_2C{=}NOH + 3\ Na^{\oplus} + H_2O$$

The formation of pseudonitroles (IV) also was observed in this work. The reaction mixtures always were colored light blue or green and the characteristic odor of tertiary organic nitroso compounds was usually present. Attempts to isolate the pseudonitroles by distillation were unsuccessful due to the fact that the compounds decomposed when heated.

Pseudonitroles can be readily prepared by the acidification of nitroparaffin *aci* salts in the presence of nitrous acid.[7] With this fact in mind, the following rationalization is offered to explain the self-reduc tion of nitroparaffin *aci* salts.



The ketone formation shown in this rationalization should be considered subsidiary to that formed by the Nef reaction. This scheme also shows the possible formation of the ketone in a system which, unlike those used for the Nef reaction, does not require appreciable amounts of water. The ketone formed by this route may be the precursor of the caprolactam isolated when the anhydrous mixture of sodium *aci* nitrocyclohexane and sodium azide was added to concentrated sulfuric acid.

EXPERIMENTAL

N-Methylacetamide (IIa). A mixture consisting of 44.5 g. (0.5 mole) of 2-nitropropane, 20 g. (0.5 mole) of sodium hydroxide, and 250 ml. of water was heated with good agitation on a steam-bath until a homogeneous solution was obtained. To this hot solution was added 35 g. (0.55 mole) of sodium azide. Stirring was continued until the azide had dissolved. The solution containing the nitronate salt and sodium azide was slowly added to 750 g. of 95% sulfuric acid containing 375 ml. of chloroform. During the addition, the reaction mixture was stirred vigorously and cooled in an ice-bath. The rate of addition was such that the temperature stayed between 20–30°. When the addition of the solution containing the sodium 2-nitropropane and sodium azide was complete, the ice-bath was removed and the reaction mixture was stirred for one hour at room temperature. The mixture was then neutralized at or below 25° with concentrated ammonium hydroxide, filtered, and the filter cake was washed with chloroform. The chloroform layer was separated from the filtrate and the aqueous phase was extracted with three 100-ml. portions of chloroform. The combined chloroform solutions were dried, and the solvent was removed by distillation. The residue was distilled at atmospheric pressure to yield 16 g. (44%) of N-methylacetamide (b.p.$_{760}$ 204–206°). The infrared spectrum of the product was identical to the infrared spectrum of an authentic sample of N-methylacetamide.

N-n-Propyl-n-butyramide (IIb). Sodium hydroxide (4 g., 0.1 mole) was dissolved in 86 ml. of water. To this solution was added 14.5 g. (0.1 mole) of 4-nitroheptane and enough 95% ethanol to form a homogeneous solution. This solution was heated on the steam-bath in an open beaker with good agitation until the volume was reduced to 85–90 ml. The

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(5) Gault, Doltroff, and Ecktridan, *Bull. soc. chim. France*, 12, 952 (1945).

(6) Nygaard, U.S. Patent 2,401,267 (to Socony-Vacuum Oil Company), May 1946.

(7) Nametkin, *J. Russ. Phys.-Chem. Soc.*, 42, 581 (1910).

solution then was cooled to room temperature, and 7 g. (0.11 mole) of sodium azide was dissolved in the solution. The azide-*aci* salt solution was slowly added to a mixture of 180 g. of 95% sulfuric acid and 75 ml. of chloroform, cooled externally with an ice-bath, at a rate which kept the temperature of the reaction mixture between 20° and 30°. When the addition was complete, the ice-bath was removed and the mixture was stirred at room temperature for one hour. The isolation technique described in the previous example was employed again to obtain a product oil which, when fractionated at 10 mm. pressure, yielded the following products:

Fraction	B.P. at 10 mm., °C.	Wt. (g.)	Identity
1	25–88	0.2	Di-*n*-propyl ketone
2	88–110	3.01	Di-*n*-propyl ketoxime
3	110–124	7.93 (62%)	N-*n*-Propyl-*n*-butyramide

The identity of each of the products was confirmed by its infrared spectrum. Since the amide (IIb) had not been reported previously, it was synthesized from *n*-butyryl chloride and *n*-propylamine[8] in order to confirm its identity, and its infrared spectrum was compared with that of the material from Fraction 3. The spectra were identical.

Anal. (IIb) Calc'd for $C_7H_{15}NO$: N, 10.85. Found: N, 10.99, 10.94.

The amide (IIb) (14 g., 0.1 mole) was refluxed for three hours with 20% hydrochloric acid, diluted with 600 ml. of water, and extracted with ether. The solvent was removed from the dry extract by distillation to leave 5 g. of an oil which had an infrared spectrum identical to that of *n*-butyric acid. The aqueous solution from which the butyric acid was obtained was allowed to concentrate at room temperature in a large evaporating dish. The liquid residue was neutralized with 10% potassium hydroxide, an additional 0.3 mole of potassium hydroxide was added, and the *p*-toluenesulfonamide was prepared by the addition of 0.1 mole of *p*-toluenesulfonyl chloride. After the mixture was stirred for one hour at room temperature, it was filtered and acidified. An oil precipitated which solidified upon cooling. The solid product (12 g.) was removed by filtration and was recrystallized from water and ethanol. The product melted at 50–52° and had an infrared spectrum identical to that of an authentic sample of N-*n*-propyl-*p*-toluenesulfonamide, thus confirming the presence of *n*-propylamine in the amide.

N-Hexylacetamide (IIc). The procedure for the preparation of N-*n*-propylbutyramide (IIb) was repeated using 32 g. (0.2 mole) of 2-nitroöctane (Ic)[9] in place of 4-nitroheptane (Ib), 14 g. (0.22 mole) of sodium azide, 8 g. (0.2 mole) of sodium hydroxide, 172 ml. of water, 150 ml. of chloroform, and 360 g. of concentrated sulfuric acid. Vacuum distillation of the product oil yielded the fractions given in the preceding tabulation:

Fraction	B.P. at 3.25 mm., °C.	Wt. (g.)	Identity by Infrared Spectrum
1	25–80	2.29	Methyl hexyl ketone
2	80–86	2.41	Methyl hexyl ketoxime
3	86–120	2.10 ⎫ 47%	N-*n*-Hexylacetamide
4	120–126	11.22 ⎭	N-*n*-Hexylacetamide

The infrared spectra of Fractions 3 and 4 were identical to that of an authentic sample of N-*n*-hexylacetamide synthesized from acetyl chloride and *n*-hexylamine.[8] Since the properties of the amide (IIc) have not been described completely,[10] the amide (IIc) was hydrolyzed and extracted in the same manner as N-*n*-propylbutyramide (IIb) to yield an oil which, by its infrared spectrum, was shown to contain acetic acid. The aqueous phase was neutralized and extracted again to yield an oil which was essentially pure *n*-hexylamine, the infrared spectrum of which was identical to that of an authentic sample of *n*-hexylamine. No N-methylcaprylamide was isolated.

Anal. (IIc) Calc'd for $C_8H_{17}NO$: C, 67.11: H, 11.98; N, 9.79. Found: C, 67.31; H, 11.75; N, 10.27.

ε-Caprolactam (IId). A solution containing 25.8 g. (0.2 mole) of nitrocyclohexane, 8 g. (0.2 mole) of sodium hydroxide, 14 g. (0.22 mole) of sodium azide, and 172 ml. of water was added to a stirred mixture of 360 g. of 95% sulfuric acid and 150 ml. of chloroform under the conditions previously described. The chloroform extract yielded a product oil which upon vacuum distillation yielded a trace of cyclohexanone (b.p.$_{10}$ 35°; found in the cold trap), 4.4 g. of cyclohexanone oxime (b.p.$_{10}$ 105°) and 15.12 g. (67%) of ε-caprolactam (b.p.$_{10}$ 138°). The infrared spectra of the products matched the respective infrared spectra of cyclohexanone oxime and ε-caprolactam. The cyclohexanone was characterized by the preparation of its 2,4-dinitrophenylhydrazone.

δ-Valerolactam (IIe). A solution containing 86 ml. of water, 4 g. (0.1 mole) of sodium hydroxide, 7 g. (0.11 mole) of sodium azide, and 11.5 g. (0.1 mole) of nitrocyclopentane was added to 180 g. of 95% sulfuric acid mixed with 75 ml. of chloroform under the conditions previously outlined. After an identical work-up procedure was followed, there was obtained 8 g. (81%) of δ-valerolactam (b.p.$_9$ 94°). The infrared spectrum of the product was identical to that of an authentic sample of δ-valerolactam.

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[8] Shriner and Fuson, *The Systematic Identification of Organic Compounds*, 3rd ed., John Wiley and Sons, Inc., New York, 1948, p. 87.

[9] Mooberry, *A Study of the Reaction of Alkyl and Alicyclic Halides with Alkali Metal Nitrites*, Thesis, Purdue University, 1954, p. 128.

[10] Hantzsch, *Ber.*, **24**, 4021 (1891).