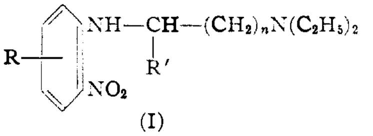
[CONTRIBUTION FROM THE POLYTECHNIC INSTITUTE OF BROOKLYN AND THE RESEARCH LABORATORY OF ENDO PRODUCTS, INC.]

The Preparation of Substituted *o*-Nitranilines

BY FRANK KIPNIS,[1] NATHAN WEINER AND PAUL E. SPOERRI

In the course of an investigation on the synthesis of certain heterocyclic compounds of possible therapeutic value, it was found desirable to prepare a series of ring-substituted N-(dialkylaminoalkyl)-*o*-nitranilines (I). The methods described in the literature for the preparation of this type of compound suffer from the circumstance that the intermediates are usually unstable, or that by-products, difficult to eliminate, contaminate the final product.



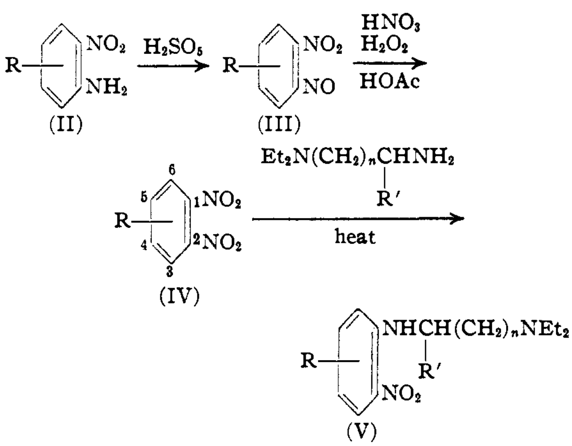
(I)

R = H, CH_3, di(CH_3), Cl, OCH_3
R' = H or CH_3
n = 2 or 3

It is known that the replacement of one nitro group of an *o*-dinitrobenzene by an amine residue is a synthetic method which has been applied successfully with simple primary and secondary monoamines. The yields are reasonably good and the final product is usually free of isomers. There seems to be no precise basis for predicting the location of the entering amine residue, but earlier studies with ammonia and simpler amines have definitely fixed the position in these cases and it is assumed that the more complex diamines used in the work to be described substitute at the same point.[2,3,4,5,6,7]

The following scheme, depending in the last stage upon this replacement of one nitro group of an *o*-dinitrobenzene by an appropriate diamine, has, therefore, been studied.

Compounds of structure II are dyestuff intermediates and readily available. After oxidation with Caro acid to the nitroso compound, it was found unnecessary to purify highly the nitroso-nitro derivatives (III) before oxidation to IV. The method of Kuhn and van Klaveren,[8] using 30% hydrogen peroxide and nitric acid in glacial acetic acid was found preferable to the use of fuming nitric acid for the oxidation to the dinitro derivative (IV), since a cleaner product in better yield was produced. Over-all yields from II to IV were about 65%.



3,4-Dinitroanisole,[9] 3,4-dinitrochlorobenzene[1] and 3-diethylaminopropylamine[11] were prepared by known methods. 1-Methyl-4-diethylaminobutylamine was purchased from the Winthrop Chemical Company.

In the past sealed tube reactions[2,3,4,5,7] have been used in replacing one nitro group of IV by NH_2, while ethanol was usually the solvent for the less volatile amines, in the replacement reaction.[6] In certain cases, fusion of the reactants in the absence of solvent gave acceptable results.[9] In the present work, *p*-cymene, boiling under slightly reduced pressure, has proved to be a most suitable medium. The boiling point of cymene (176°) is close to the boiling range of the diamines used; it is a mutual solvent for the reactants and the final product, is unreactive toward the nitrous fumes generated during the reaction, and, finally, its use appears to shorten the reaction period to about three hours, in contrast to approximately eight hours required in the absence of solvent. The use of slightly reduced pressure is advantageous in that it promotes the elimination of nitrous fumes, which are thus prevented from reacting with the starting diamine or with the final product.

Experimental

***o*-Dinitrobenzene.**—Purchased from the Eastman Kodak Co. and used without further purification.

3,4-Dinitrochlorobenzene (IV, R = 5-Cl).—The procedure[10] mentioned earlier was used. The crude product was distilled at 160° (4 mm.) giving colorless crystals melting at 39° (cor.). The literature reports a melting point of 38.8° for the crystalline α-modification of this compound; yield, 81%.

3,4-Dinitroanisole (IV, R = 5-OCH_3).—To 35 g. of 3-nitro-4-aminoanisole suspended in 70 ml. of water, 35 ml. of concentrated sulfuric acid was added in small por-

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(1) From a thesis submitted by Frank Kipnis in partial fulfillment of the requirements for the Degree of Doctor of Philosophy, Polytechnic Institute of Brooklyn, 1944.

(2) Laubenheimer, *Ber.*, **11**, 1155 (1875).

(3) Blanksma, *Rec. trav. chim.*, **25**, 162 (1906).

(4) Laubenheimer, *Ber.*, **9**, 768, 1826 (1876).

(5) Bantlin, *ibid.*, 11, 2099 (1878).

(6) Mangini and Colonna, *Gazz. chim. ital.*, **68**, 543 (1938).

(7) Hodgson and Smith, *J. Chem. Soc.*, 500 (1933).

(8) Kuhn and van Klaveren, *Ber.*, **71**, 779 (1938).

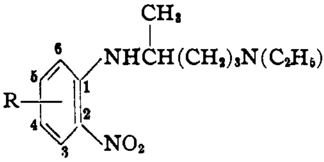
(9) Topchiev, *Compt. rend. acad. sci. U. R. S. S.* [N. S.], **4**, 201 (1935).

(10) Mangini and Deliddo, *Gazz. chim. ital.*, **63**, 612 (1933).

(11) Holcomb and Hamilton, THIS JOURNAL, **64**, 1309 (1942).

TABLE I

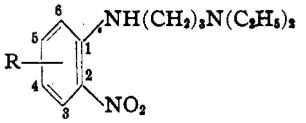
SUBSTITUTED *o*-NITRANILINES



	B. p.,		Yield,		M. p.,[b]		Analyses			
							Calculated		Found	
R	°C.	Mm.	%	Derivative	°C.	Formula	C	H	C	H
H	185	3.5	89	Picrate	126–6.5	$C_{21}H_{28}N_6O_9$	49.60	5.55	49.75	5.40
6-CH_3	184	2.5	60	.... [a]	.....	$C_{16}H_{27}N_3O_2$	65.49	9.28	65.56	9.52
5-CH_3	195–200	4	57	Picrate	95–96	$C_{22}H_{30}N_6O_9$	50.57	5.79	50.59	5.69
4,6-DiCH_3	208–12	2	51.5	.... [a]	.....	$C_{17}H_{29}N_3O_2$	66.41	9.54	66.86	9.13
4,5-DiCH_3	209–11	2	56.5	.... [a]	.....	$C_{17}H_{29}N_3O_2$	66.41	9.54	66.25	9.41
5-Cl	208	2.5	35.2	.... [a]	.....	$C_{15}H_{24}ClN_3O_2$	57.42	7.68	57.53	7.35

[a] Oily picrate and hydrochloride. Analyzed as liquid base. [b] All m. p. corrected.

SUBSTITUTED *o*-NITRANILINES



H	168–70	2	59	Picrate	122–3	$C_{19}H_{24}N_6O_9$	47.50	5.04	47.73	5.12
6-CH_3	176	3	96.5	Picrate	98.5–99	$C_{20}H_{26}N_6O_9$	48.58	5.31	48.45	5.30
5-CH_3	184–7	4	64.5	Picrate	158–9.5	$C_{20}H_{26}N_6O_9$	48.58	5.31	48.98	5.13
4,6-DiCH_3	168–75	2	54.5	Picrate	109–11	$C_{21}H_{28}N_6O_9$	49.60	5.55	49.60	5.54
5-OCH_3	198	2	50	Picrate	143.5–5.5	$C_{20}H_{26}N_6O_{10}$	47.06	5.13	47.25	5.16
5-Cl	210	4	63	Hydrochloride	225.7 dec.	$C_{13}H_{21}Cl_2N_3O_2$	48.45	6.57	48.38	6.42

tions with constant swirling. The heat of reaction caused the amine to dissolve. The hot solution was immediately poured over 300 g. of ice with mechanical stirring and 100 ml. of water was added to the suspension. The mixture was cooled to 2–5° with an ice-bath and was diazotized with 16 g. of sodium nitrite in 40 ml. of water.[12]

The vigorously stirred solution was treated cautiously with powdered barium carbonate until alkaline to congo red paper. The barium carbonate and barium sulfate were removed by centrifuging in the cold and the residues in the cups were washed thoroughly with water. The cold supernatant liquids were combined for the following operations.

During the centrifugation, the catalyst solution was prepared as follows: forty grams of Chevreul salt[13] ($CuSO_3 \cdot Cu_2SO_3 \cdot 2H_2O$) was added slowly to a well-stirred solution of 120 g. of sodium nitrite in 200 ml. of water. After the red coloration of the original salt had disappeared, the solution of the diazotized amine was added from a dropping funnel, to the vigorously stirred catalyst solution during one hour and the mixture was then stirred for an additional hour. The precipitated product was filtered by suction and washed thoroughly with water. The wet cake was transferred to a large beaker and covered with about 300 ml. of water. An equal volume of concentrated hydrochloric acid was added with brisk but careful stirring (nitrous fumes are evolved—hood) whereupon the dinitroanisole came down as a tacky mass, which was washed several times by decantation with a total of 1000 ml. of water.

The crude material may be crystallized from a small volume of ethanol or may be distilled under reduced pressure. Both procedures are rather unsatisfactory. Certain batches have yielded a good product after one recrystallization, while others have given oils. During distillation, a distinct tendency toward explosion was evident; however, several runs were distilled at 168° (3 mm.) to produce a solid distillate which was recrystallized from aqueous ethanol to give white needles melting at 71° (cor.). Topchiev reported golden-yellow needles with the same melting point; yield, 48–49%.

2,3-Dinitrotoluene (IV, R = 6-CH_3).—The procedure of Meisenheimer and Hesse[14] was used for the preparation of the nitroso-nitro compound, which was then oxidized to the dinitro derivative by the method of Kuhn.[8] The overall yield from the amine was 65%; m. p. 61° (cor.).

3,4-Dinitrotoluene (IV, R = 5-CH_3).—The amine was oxidized to the nitroso compound by the method of Langley[15] and the latter further oxidized as usual[8]; over-all yield, 70.5%; m. p. 60° (cor.).

1,3-Dimethyl-4,5-dinitrobenzene (IV, R = 4,6-di-CH_3).—The method of Kuhn, Desnuelle and Weygand[16] was used for oxidation to the nitroso derivative but the peroxysulfuric acid was not neutralized prior to use as recommended by these workers. Further oxidation followed the usual procedure[8]; over-all yield, 68%; m. p. 132.5° (cor.).

1,2-Dimethyl-4,5-dinitrobenzene (IV, R = 4,5-di-CH_3).—1,2-Dimethyl-4-aminobenzene was nitrated according to the procedure of Noelting, Braun and Thesmar:[17] The 4-amino-5-nitro-1,2-dimethylbenzene thus produced was oxidized to the nitroso-nitro derivative and then to the dinitro compound by the usual method.[8] Over-all yield from the nitro-amine was 67.5%; m. p. 139° (cor.).

Substituted Nitranilines.—One example will suffice to indicate the method followed in the entire series of compounds except those derived from 3,4-dinitrochlorobenzene. In the latter series of compounds, it was found that cleaner final products in higher yields could be produced by using ethanol instead of cymene as the reaction medium.

1-(3′-Diethylaminopropyl)-2-nitraniline (V, R = H, R′ = H, *n* = 2).—One-tenth mole of *o*-dinitrobenzene was suspended in 450 ml. of cymene contained in a 1000-ml. interjoint flask fitted with a short, efficient reflux con-

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(12) After this operation was completed, solution was complete. If the directions of Topchiev were followed, a considerable portion of the starting nitraniline was recovered at this point.

(13) Abegg and Auerbach "Handbuch der anorganischen Chemie," Vol. II, part I, p. 556.

(14) Meisenheimer and Hesse, *Ber.*, **52**, 1161 (1919).

(15) Langley, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1942, Vol. XXII, page 44.

(16) Kuhn, Desnuelle and Weygand, *Ber.*, **70**, 1293 (1937).

(17) Noelting, Braun and Thesmar, *ibid.*, **34**, 2242 (1901).

denser; 0.125 mole of 3-diethylaminopropylamine was added with swirling, and the exit of the condenser was connected to a suitable trap for nitrous fumes. The flask was heated gently with a free flame, until a vigorous reaction began, as indicated by rapid boiling and a sharp evolution of nitrous fumes. The flame was removed at this point and the reaction was allowed to proceed until boiling became gentle (four to five minutes). The flame was replaced and the mixture refluxed briskly until a piece of starch–potassium iodide paper at the exit of the trap showed no more oxidizing fumes (two to three hours).

Heating was discontinued, the flask cooled under running water and the contents transferred to a 1000-ml. separatory funnel. The flask was washed four times with 50-ml. portions of 20% hydrochloric acid and the washings added to the cymene solution in the separatory funnel, followed by 150 ml. of ethyl ether. The mixture was shaken vigorously and separated; the aqueous layer was washed with an additional 150 ml. of ether. The ethereal layers were combined and washed with 100 ml. of saturated sodium chloride solution.[18] The aqueous layers were combined and run carefully into 100 ml. of 60% sodium hydroxide solution with swirling. The mixture was filtered by suction through a bed of dicalite (this procedure avoids serious emulsions during subsequent extractions) and the filtrate extracted six times with 150-ml. portions of chloroform. The combined extracts were washed through the dicalite bed and the filtrate was distilled to dryness from the steam-bath, the last traces of solvent being removed under reduced pressure. The residue was dissolved in anhydrous chloroform, filtered through a dicalite bed to remove traces of inorganic salts, and the filtrate distilled to dryness as above. The dry residue was distilled at 168–70° (2 mm.) to give a rich, red oil which could not be induced to crystallize; yield, 59%. Table I summarizes the properties, yields and analytical data for the various nitranilines prepared during this work.

Derivatives of the Nitranilines

Picrates.—The free base was dissolved in anhydrous ethanol and treated with an excess of picric acid in the same solvent. The picrate came down as an oil which was washed with anhydrous ether and then crystallized from ethanol or methanol to give a bright yellow product.

Hydrochlorides.—The free base was dissolved in anhydrous ethyl ether and treated with a solution of dry hydrogen chloride in the same solvent. The product was worked up as above. Several bases were analyzed directly, since neither crystalline picrates nor hydrochlorides could be obtained.

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Summary

1. Six known *o*-dinitrobenzene derivatives were prepared in approximately 65% yield by oxidizing *o*-nitranilines with Caro acid to the nitroso-nitro compounds, followed by further oxidation of these compounds with hydrogen peroxide and nitric acid. Other difficultly available *o*-dinitrobenzenes were prepared by a Sandmeyer reaction on a nitro-diazonium hydroxide, or by direct nitration.

2. Twelve new *o*-(dialkylaminoalkyl)-nitranilines were then prepared by the direct replacement of one nitro group of an *o*-dinitrobenzene by a diamine.

3. The use of cymene as a reaction medium for the above replacement reaction was found to be highly advantageous in increasing the yield and purity of the final product and shortening the reaction time.

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[18] Cymene and unreacted *o*-dinitrobenzene may be recovered from the ethereal layers.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF BRYN MAWR COLLEGE AND COLUMBIA UNIVERSITY]

Benzoates, *p*-Aminobenzoates and Phenylurethans of 2-Alkylaminoethanols

BY ARTHUR C. COPE AND EVELYN M. HANCOCK[1]

The reduction of ethanolamine with ketones and aldehydes provides an easy synthesis for 2-alkylaminoethanols,[2] which is particularly satisfactory for the secondary alkyl homologs, $RR'CHNHCH_2CH_2OH$. This paper reports a practical method for converting these aminoalcohols into esters (I, as hydrochlorides). The local anesthetic action of the esters has been investigated.

Compared to the very large number of esters of *tertiary* aminoalcohols which have been prepared, relatively few esters of alcohols substituted by *secondary* amino groups have been investigated. Aminoalcohols of the latter class have not been readily available, and their reaction with acid chlorides can lead either to esters (I) or to amides (II). Further reaction can produce ester-amides (III).[3] An additional complication noted by

$$\underset{\text{I}}{RCOOCH_2CH_2NHR'} \qquad \underset{\text{II}}{RCON(R')CH_2CH_2OH}$$

$$\underset{\text{III}}{RCOOCH_2CH_2N(R')COR}$$

several investigators is the fact that esters containing primary or secondary amino groups (such as I, R' = hydrogen or alkyl) are stable as salts but the bases rearrange rapidly into the corresponding amides (II).[4] Certain of the substituted

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[1] Sharp and Dohme Research Associate.

[2] Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942).

[3] Mannich and Wieder, *Ber.*, **65**, 389 (1932).

[4] (a) Wolfheim, *Ber.*, **47**, 1447 (1914); (b) Gabriel, *Ann.*, **409**, 326 (1915); (c) Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 403 (1915); (d) Kanao, *J. Pharm. Soc. Japan*, **48**, 1070 (1928); (e) Hartung, Munch and Kester, THIS JOURNAL, **54**, 1526 (1932); (f) Immediata and Day, *J. Org. Chem.*, **5**, 512 (1940).