[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE]

PHENAZINE SYNTHESES. IV.[1] NITRILES

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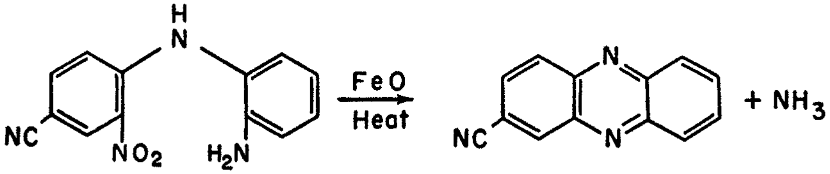
In continuation of the project of demonstrating the general applicability of ring closure through the nitro group to the synthesis of a wide variety of phenazines, the formation of phenazinecarbonitriles was studied. The present paper describes the findings in this investigation.

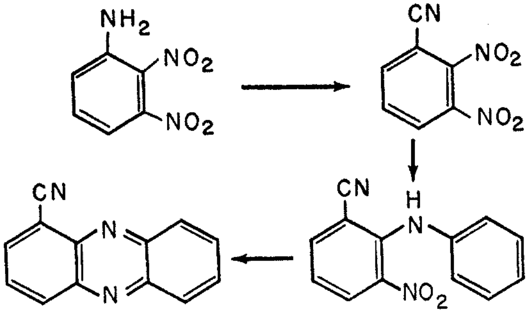
The reactions all take the usual course (1), with the exception of the ring closure as applied to 2′-amino-4-cyano-2-nitrodiphenylamine (4-*o*-aminoanilino-3-nitrobenzonitrile). In this reaction the amino group is eliminated (at least in part as ammonia) and unsubstituted 2-phenazinecarbonitrile results:



No trace of any aminophenazine could be found in the reaction products.

This behavior of the amino group *ortho* to the imino linkage of the unnitrated benzene ring parallels that of alkoxy groups in the same position, whose elimination occurs in the "Type B" reaction previously reported (1). While no generalization can be drawn from the single example given herein, it seems likely, in view of the general behavior of the 2′-alkoxy compounds, that all 2′-amino groups will likewise be eliminated whenever 2-nitrodiphenylamines containing them are subjected to ring closure.

Because it was desirable to have an intermediate bearing the nitrile group in the same ring as the nitro group, the following method of synthesis of 1-phenazinecarbonitrile was devised:



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[1] Paper III: *J. Org. Chem.*, **19**, 1641 (1954).

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The 1-phenazinecarbonitrile so obtained melted at 170–172°,[3] and underwent the expected normal hydrolysis to give the well-known 1-phenazinecarboxylic acid.

The other isomer, 2-phenazinecarbonitrile, does not seem to have been completely characterized hitherto. Although Maffei (2) has recently reported it, giving the melting point as 160°, his carbon analysis does not agree with the true calculated value but with his own calculated value, which is almost 3 % too low. Also, he states that hydrolysis of his compound gave him 2-phenazinecarboxylic acid melting at 191° (this is almost certainly merely a typographical error). Kögl, Tönnis, and Gronewegen (3) give the melting point of 2-phenazinecarboxylic acid as 292–293°, and Clemo and McIlwain (4), who prepared it by a different method, give 292°. The 2-phenazinecarbonitrile reported in this paper melts, with darkening, at 232–234°, and the acid obtained from it by alkaline hydrolysis melts at 295–296.5°.

McIlwain (5) obtained a sublimate by heating N-methyldihydro-2-phenazinenitrile or N-methyl-2-phenazylnitrile to 200° for 12 hours; this sublimate (which he did not identify by name), when recrystallized from alcohol, gave yellow needles melting at 226°. On alkaline hydrolysis these yielded 2-phenazinecarboxylic acid which had a m.p., in this instance, of 284°. There seems little doubt, in view of this conversion, the crystalline form and color, and the fairly good agreement in melting point with that of the 2-phenazinecarbonitrile reported herein, that McIlwain's compound was 2-phenazinecarbonitrile.

TABLE I

PHENAZINECARBONITRILES

Phenazine[a]	M.p., °C.[c]	Yield, %	Formula	Analysis, %[d]			
				Carbon		Hydrogen	
				Calc'd	Found	Calc'd	Found
A. 7-Methoxy-2-phenazinecarbonitrile	267–268	25	$C_{14}H_9N_3O$	71.5	71.2	3.86	3.67
B. 8-Methoxy-2-phenazinecarbonitrile	224–225.5	19	$C_{14}H_9N_3O$	71.5	71.5	3.86	3.67
C. 7-Chloro-2-phenazinecarbonitrile	318.5–319	20	$C_{13}H_6ClN_3$	65.2	64.8	2.52	2.57
D. 8-Chloro-2-phenazinecarbonitrile (6)	310–324(d)	26	$C_{13}H_6ClN_3 \cdot 1/4H_2O$	64.0	63.9[b] 64.0 63.9 64.1	2.69	2.74 2.68 2.74 2.77

[a] All of these were pale yellow needles and were recrystallized from ethanol, except D, which was recrystallized from benzene. [b] These four analyses are of four different samples, to substantiate the formula with 1/4 mole H_2O. Also, the following additional values were found for one of the four: Calc'd for $C_{13}H_6ClN_3 \cdot 1/4\ H_2O$: Cl, 14.5; N, 17.2. Found: Cl, 14.4; N, 16.8. [c] Corrected. [d] See footnote 4 in text regarding analyses.

TABLE II

INTERMEDIATES

Diphenylamine	M.p., °C.[g]	Method of Preparation	Yield, [e]%	Formula	Analysis,[h] % Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found
A'.[f] 4-Cyano-2',5'-dimethoxy-2-nitrodiphenylamine	195.5–196[a]	4-Chloro-3-nitrobenzonitrile (8) 2,5-Dimethoxyaniline Sodium acetate trihydrate 7 days in refluxing 95% ethanol	88	$C_{15}H_{13}N_3O_4$	60.2	60.2	4.40	4.42
B'. 4-Cyano-4'-methoxy-2-nitrodiphenylamine	125.5–127[b]	4-Chloro-3-nitrobenzonitrile (8) *p*-Anisidine Sodium acetate trihydrate 16 hours in refluxing 95% ethanol	83	$C_{14}H_{11}N_3O_3$	62.4	62.5	4.15	4.01
C'. 5'-Chloro-4-cyano-2'-methoxy-2-nitrodiphenylamine	250–252[c]	4-Chloro-3-nitrobenzonitrile (8) 4-Chloro-2-anisidine Sodium acetate trihydrate 10 days in refluxing 95% ethanol	60	$C_{14}H_{10}ClN_3$-O_3	55.4	55.6	3.32	3.62
D' 4-Chloro-4'-cyano-2-nitrodiphenylamine	178–179[d]	*p*-Aminobenzonitrile 2,5-Dichloronitrobenzene Sodium acetate 60 hours at 190–200°	60	$C_{13}H_8ClN_3$-O_2	57.1	56.8	2.95	2.93

[a] Small red felted needles. All of the recrystallizations reported in this table are from ethanol. [b] Long lustrous orange prisms. [c] Dark raspberry-red prisms. [d] Small saffron prisms. [e] Yields are of the crude intermediates. [f] Compound A, Table 1, was prepared from A', etc. [g] Corrected. [h] See footnote 4 in text.

The preparation of the other compounds dealt with in the present paper, chloro- and methoxy-2-phenazinecarbonitriles, affords no point of special interest, unless it be that yields of these cyano-substituted compounds tend to run lower than has been our general experience with the yields of other substituted phenazines, the yield of unsubstituted phenazine from 2'-amino-4-cyano-2-nitrodiphenylamine being especially poor. The accompanying tables summarize the preparation and properties of the compounds not reported in detail in the experimental part. The phenazines are, of course, prepared by the usual reaction (1), as carried out by means of ferrous oxalate and granulated lead with oil-bath heating.

EXPERIMENTAL[3]

1-PHENAZINECARBONITRILE

(*a*) *2,3-Dinitroaniline.* In accordance with the method of Kremer and Bendich (7), *m*-nitroacetanilide was nitrated at 16–18° by gradually adding 1200 g. of it to 2500 cc. of fuming nitric acid (*sp. gr.* 1.50, 90% HNO_3) with good stirring. Pouring onto crushed ice, filtering, and washing to neutrality gave a quantitative yield of the mixture of isomers, but we were not able to get nearly as high a yield of the 2,3-dinitroacetanilide, m.p. 186–187°, from one recrystallization from alcohol as was reported by Kremer and Bendich. It was noted, however, that yields from one manufacturer's fuming HNO_3 were much poorer than from another's, suggesting that use of anhydrous HNO_3 might be advantageous. The better yield obtained was 350 g. of 2,3-dinitroacetanilide, m.p. 186–187° (darkening at 173°), from 1681 g. of the mixture of isomers, recrystallized from 13 l. of 99% alcohol with cooling only to room temperature. In the poorer preparation, only 175 g. of 2,3-dinitroacetanilide was obtained from 1417 g. of the isomer mixture. For conversion of the 2,3-dinitroacetanilide to the free amine, advantage was taken of the catalytic method of Verkade and Witjens (8), generally applicable to acetamido compounds with an *ortho* or *para* nitro group, though these authors did not deacetylate 2,3-dinitroacetanilide. When 87.5 g. of the latter compound was refluxed for 2½ hours with 1800 cc. of methanol containing 2 g. of sodium methoxide, pouring the hot solution into cold water, washing and air-drying gave 66.5 g. (93%) of 2,3-dinitroaniline, m.p. 126–127°.

(*b*) *2,3-Dinitrobenzonitrile.* Diazotization of the 2,3-dinitroaniline followed the method of Hodgson and Walker (9), and conversion to the nitrile was patterned after the method used by Storrie (10) for 2,4-dinitroaniline. A solution of 31.9 g. of 2,3-dinitroaniline in 350 cc. of glacial acetic acid was added dropwise to a stirred and cooled solution of 16.4 g. of $NaNO_2$ in 117 cc. of conc'd H_2SO_4, keeping the temperature at 15–20° by external cooling. The diazonium solution then was added, in a thin stream, to a well-stirred solution, gently heated on the stream-bath, made up by adding 61.25 g. of KCN in 265 cc. of H_2O to one of 52.5 g. of $NiSO_4 \cdot 6H_2O$ in 87.5 cc. of H_2O, and mixing with a solution of 350 g. of Na_2CO_3 in 1,050 cc. of H_2O. When the addition was complete, the whole mixture was cooled to room temperature, giving a precipitate of crude 2,3-dinitrobenzonitrile weighing 22.9 g. (64%). No completely satisfactory recrystallization solvent was found for this crude material, but dissolving in 550 cc. of a 2:1 mixture by volume of ethanol-water, refluxing with Norit, and cooling to −8°, gave about 10 g. of small, light buff-colored leaflets, melting at about 96°. Further recrystallization gave light buff micro-crystals, melting at 97–98°.

Anal.[4] Calc'd for $C_7H_3N_3O_4$: C, 43.5; H, 1.57.
Found: C, 43.3; H, 1.74.

(*c*) *6-Cyano-2-nitrodiphenylamine* (*2-anilino-3-nitrobenzonitrile*). A mixture of 12.4 g. of once-recrystallized 2,3-dinitrobenzonitrile and 18 g. of aniline was refluxed in 100 cc. of ethanol for six weeks. Steam-distillation of the excess aniline left a black tar weighing slightly more than the 15.4 g. theoretical yield. This very crude material could be used for conversion to the 1-phenazinecarbonitrile despite its softness. Recrystallized twice from 2:1 ethanol-H_2O (Norit), it formed brown-orange micro-crystals, melting at 89–91°.

Anal. Calc'd for $C_{13}H_9N_3O_2$: C, 65.2; H, 3.79; N, 17.6.
Found: C, 65.0; H, 3.68; N, 17.5.

(The optimum period of refluxing was not determined. Four weeks of refluxing seemed to give almost as good results as did six weeks.)

(*d*) *1-Phenazinecarbonitrile.* When 1.0 g. of the crude, soft 6-cyano-2-nitrodiphenylamine was mixed with 1.3 g. of ferrous oxalate dihydrate and 10 g. of lead, and the mixture was heated in an oil-bath at 260°, the reaction was complete in about 8 minutes, a maximum

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[3] All melting points reported by us are corrected.

[4] Microanalyses by the Microanalytical Laboratory of the National Institutes of Health, under the supervision of Dr. W. C. Alford.

internal temperature of 267° being attained. Sublimation at about 3 mm. from the 260° oil-bath gave 0.4 g. dark yellow product, which on two recrystallizations from absolute alcohol gave light yellow needles melting at 170–172°.

Anal. Calc'd for $C_{13}H_7N_3$: C, 76.1; H, 3.43; N, 20.5.

Found: C, 76.4; H, 3.78; N, 20.1.

Hydrolysis of 1-phenazinecarbonitrile to 1-phenazinecarboxylic acid. To a solution of 0.75 g. of crude 1-phenazinecarbonitrile in 75 cc. of absolute alcohol there was added 7.5 g. of KOH in 4 cc. of water, and the mixture was refluxed for 3½ hours in a stainless steel flask. During this refluxing NH_3 was evolved, turning red litmus blue. Evaporation of the alcohol, and acidification of the cooled solution with dilute HCl gave 0.67 g. of greenish-yellow solid melting at 213–216°. This, on two recrystallizations from methanol, melted at 241–242°. Kögl and Postowsky (11) give 238–239° as the m.p. of 1-phenazinecarboxylic acid.

Anal. Calc'd for $C_{13}H_8N_2O_2$: C, 69.6; H, 3.60.

Found: C, 69.9; H, 3.66.

2-Phenazinecarbonitrile. A mixture of 5 g. of 4-cyano-2-nitrodiphenylamine (12), 6.5 g. of ferrous oxalate dihydrate, and 50 g. of granulated lead was heated in an open flask by immersion in an oil-bath held at 273–274°. The temperature inside the mixture rapidly climbed to a maximum of 294°, and copious yellow fumes were evolved. When the fumes ceased and the internal temperature began to drop, which occurred after 10 minutes' heating, the reaction flask was withdrawn from the bath. The contents were pulverized and then submitted to vacuum sublimation at 3–4 mm. from an oil-bath at 230–235°. There was thus obtained 0.75 g. (18%) of crude 2-phenazinecarbonitrile, shrinking at 184° and melting to a dark brown liquid at 232–233°. Recrystallization from ethanol gave small sulfur-yellow needles, shrinking at 229°, darkening at 235°, and melting to a clear brownish-gray liquid at 236–238°.

Anal. Calc'd for $C_{13}H_7N_3$: C, 76.1; H, 3.43.

Found: C, 76.2; H, 3.77.

Conversion of 2-phenazinecarbonitrile to 2-phenazinecarboxylic acid. Alkaline hydrolysis was employed, as was done by McIlwain (5). A mixture of 0.75 g. of 2-phenazinecarbonitrile, 75 cc. of ethanol, 7.5 g. of KOH, and 4 cc. of water was triturated in a mortar, and then refluxed for 2 hours in a stainless steel flask. Evaporation of the alcohol left a semi-solid residue, which was put into solution in water, and filtered through fine porosity paper. Acidification by 1:5 HCl gave 0.6 g. of pale yellow precipitate melting to a black liquid at 294–302 . Recrystallization of 0.1 g. of the product from 30 cc. of acetone gave 0.03 g. of small sulfur-yellow needles of 2-phenazinecarboxylic acid, melting at 295–296.5° (lit. (3), 292–293°).

Anal. Calc'd for $C_{13}H_8N_2O_2$: C, 69.6; H, 3.60.

Found: C, 69.1; H, 3.84.

Loss of the amino group in ring closure on 2'-amino-4-cyano-2-nitrodiphenylamine. (*a.*) The intermediate was prepared by refluxing for 16 hours a mixture of 27.5 g. of 4-chloro-3-nitrobenzonitrile (13), 23 g. of *o*-phenylenediamine, 21 g. of sodium acetate trihydrate, and 325 cc. of 95% ethanol. The solution deposited on cooling 31.5 g. of small raspberry-red plates. Recrystallized from 95% alcohol, the sparkling deep-red crystals melted at 160–161°.

Anal. Calc'd for $C_{13}H_{10}N_4O_2$: C, 61.4; H, 3.96; N, 22.0.

Found: C, 61.7; H, 4.24; N, 21.9.

(*b*) *Ring closure.* A mixture of 1.0 g. of the above intermediate, 1.3 g. of ferrous oxalate dihydrate, and 10 g. of granulated lead was heated in an open flask immersed in an oil-bath at 243–248°. Within 12 minutes the internal temperature had risen to a maximum of 280°, and as soon as it began to drop the flask was removed from the bath. During the reaction vapors of NH_3 were evolved, as shown by their ammoniacal odor, and by their turning moistened red litmus blue. The usual vacuum sublimation gave a yield of only 0.03 g. of reddish material which on recrystallization from alcohol still retained more color than that possessed by the sulfur-yellow needles of 2-phenazinecarbonitrile, but which melted at about 235°, and showed no depression of the melting-point on admixture with 2-phenazinecarbonitrile made from 4-cyano-2-nitrodiphenylamine.

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SUMMARY

1. A number of new phenazinecarbonitriles have been synthesized through nitro-group ring closure.

2. The loss of an amino group in the 2′ position, during closure, is reported.

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REFERENCES

(1) Waterman and Vivian, *J. Org. Chem.*, **14**, 289 (1949).
(2) Maffei, *Gazz. chim. ital.*, **80**, 651 (1950).
(3) Kögl, Tönnis, and Gronewegen, *Ann.*, **497**, 265 (1932).
(4) Clemo and McIlwain, *J. Chem. Soc.*, 738 (1935).
(5) McIlwain, *J. Chem. Soc.*, 1704 (1937).
(6) Coker, Plant, and Turner, *J. Chem. Soc.*, 110 (1951).
(7) Kremer and Bendich, *J. Am. Chem. Soc.*, **61**, 2660 (1939).
(8) Verkade and Witjens, *Rec. trav. chim.*, **62**, 201 (1943).
(9) Hodgson and Walker, *J. Chem. Soc.*, 1620 (1933).
(10) Storrie, *J. Chem. Soc.*, 1746 (1937).
(11) Kögl and Postowsky, *Ann.*, **480**, 280 (1930).
(12) Borsche, Stackmann, and Makaroff-Semljanski, *Ber.*, **49**, 2229 (1916).
(13) Mataar, *Rec. trav. chim.*, **41**, 25 (1922).