[Contribution from the Laboratory of Chemical Pharmacology,
National Cancer Institute]

PHENAZINE SYNTHESES. III.[1] MISCELLANEOUS PHENAZINES

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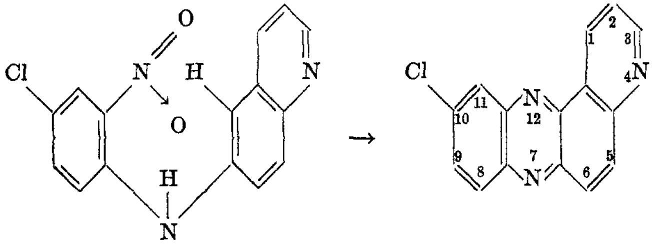
The present paper continues the illustration of the applicability to a wide variety of phenazines of the general method of ring closure through the nitro group (1). There are here described, in addition to the syntheses of various substituted phenazines, those of three compounds embodying another heterocyclic ring in addition to the pyrazine system. These compounds are shown in the following representation, in which the structures of two of these three compounds (II and VI) have been written as the angular isomers, on the reasonable assumption that ring closure of the corresponding intermediates (I and V) occurred across the double bond of the heterocyclic moiety. In the instance of IV, it is obvious that only one structure is possible.

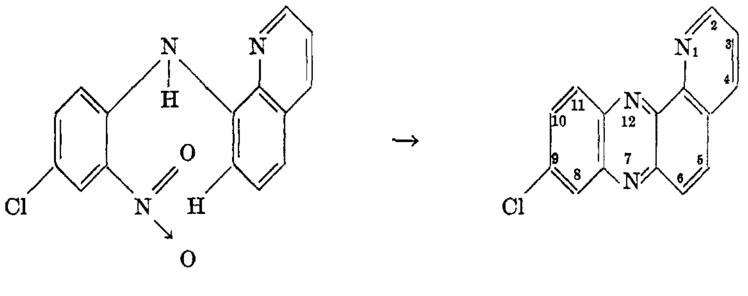


I

6-(4-Chloro-2-nitroanilino)quinoline

II

10-Chloropyridro[3,2-*a*]phenazine



III

8-(4-Chloro-2-nitroanilino)quinoline

IV

9-Chloropyrido [2, 3-*a*]phenazine

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[1] Phenazine Syntheses. II. *J. Org. Chem.*, **19**, 1136 (1954).

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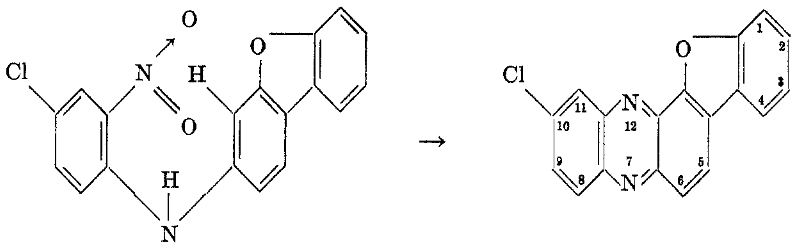

V
3-(4-Chloro-2-nitroanilino)dibenzofuran

VI
10-Chlorobenzofuro[2, 3-*a*]phenazine

Detailed methods of preparation for these three phenazines containing other heterocyclic groups follow in the experimental part. The methods of ring closure and of intermediate preparation are so similar for the other phenazines, however, that they are merely outlined in the accompanying tables. To make these tables as compact as possible, the phenazines are lettered A, B, etc., the diphenylamines from which they are respectively made being given the corresponding letters with primes appended. The yields of the phenazines are those of substantially pure products, but the yields of the intermediates are those of the crude compounds whenever such can be used without purification for the phenazine syntheses.

Since practically all of the phenazines form sulfur-yellow needles, the table does not list crystalline form or color.

EXPERIMENTAL[3]

10-Chloropyrido[3,2-a]phenazine (II). 1. *6-(4-Chloro-2-nitroanilino)quinoline* (I). A mixture of 37.5 g. of 6-aminoquinoline (2), 52.5 g. of 2,5-dichloronitrobenzene, and 52.5 g. of anhydrous sodium acetate was heated 40 hours under reflux in an oil-bath at 205–210°. Thorough steam-distillation, filtration of the residue, washing with water, and air-drying gave 76 g. of a black crude product which was satisfactory for ring closure. Several recrystallizations from alcohol and from benzene gave small, dull red, matted needles melting at 220–221°.

Anal.[4] Calc'd for $C_{15}H_{10}ClN_3O_2$: C, 60.1; H, 3.35.
Found: C, 59.7; H, 3.45.

2. *10-Chloropyrido[3,2-a]phenazine* (II). The above crude material (5 g.) was thoroughly mixed with 6.5 g. of ferrous oxalate dihydrate and 50 g. of granulated lead, and the mixture was heated in an open Erlenmeyer flask by an oil-bath at 256°. After 20 minutes' heating the internal temperature had risen to 259°; it held there for 1–2 minutes, then began to drop. The flask was removed from the bath, and the contents were subjected to vacuum sublimation. Thus there was obtained 1.44 g. of crude product, which on recrystallization from benzene gave 0.75 g. of very pale yellow needles, softening at 238°, darkening at 240°, and melting at 242–247°.

The recrystallized intermediate, in comparison with the above crude product, gave the following figures on ring closure: 1.66 g. yielded 0.81 g. of 10-chloropyrido[3,2-*a*]phenazine, melting at 246–248°, which on one recrystallization from benzene gave 0.55 g. of small,

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[3] All melting points are corrected.

[4] Analyses by the Microanalytical Laboratory, NIH, under the direction of Dr. William C. Alford.

TABLE I
SUBSTITUTED PHENAZINES

Phenazine	m.p.,[a] °C.	Yield, %	Formula	Analysis,[b] C		H	
				Calc'd	Found	Calc'd	Found
A. 2-Bromo-7-chloro-	254–255[c]	63	$C_{12}H_6BrClN_2$	49.1	49.5	2.06	2.23
B. 2-Chloro-6,8-dimethyl-	166–167[d]	37	$C_{14}H_{11}ClN_2$	69.3	69.6	4.57	4.77
C. 2-Chloro-1-methyl-	142–143[e]	45	$C_{13}H_9ClN_2$	68.3	68.6	3.96	3.70
D. 2-Chloro-8-methyl-	163.5–164.5[f]	44	$C_{13}H_9ClN_2$	68.3	67.8	3.96	4.21
E. 2-Chloro-8-phenyl-	199–201[c]	56	$C_{18}H_{11}ClN_2$	74.4	74.4	3.83	4.13
F. 7-Ethoxy-1-methoxy-	148–149[f]	30	$C_{15}H_{14}N_2O_2$	70.8	70.8	5.55	5.77
G. 1-Methyl-	108 (4)	29	$C_{13}H_{10}N_2$	80.4	80.4	5.17	5.46
H. 2-Methyl-	117–117.5 (5)	24	$C_{13}H_{10}N_2$	80.4	80.5	5.17	5.41

[a] Corrected. [b] Analyses by the Microanalytical Laboratory, NIH, under the direction of Dr. William C. Alford. Recrystallization Solvents: [c] Benzene. [d] Ethanol. [e] Ethyl acetate. [f] Methanol.

very pale yellow needles shrinking at 247.5°, and melting at 248.5–249°. These gave an orange-red color with concentrated sulfuric acid.

Anal. Calc'd for $C_{15}H_8ClN_3$: C, 67.8; H, 3.04.
Found: C, 68.0; H, 3.05.

9-Chloropyrido[2,3-a]phenazine (IV). a. *8-(4-Chloro-2-nitroanilino)quinoline* (III). The preparation and yield were substantially the same as those of the 6-isomer, above. However, the crude intermediate was not satisfactory for ring closure, and purification was effected by vacuum sublimation followed by recrystallization from chloroform. When 30 g. of unpurified material were sublimed at 5 mm. and 270–289°, 17.2 g. of raspberry-red product was obtained. This on recrystallization from chloroform gave 5 g. of a paler red compound, melting at 210–212° with earlier shrinking and darkening. Further recrystallization from chloroform gave very small red-orange needles, shrinking at 210.5°, and melting at 215–215.5°.

Anal. Calc'd for $C_{15}H_{10}ClN_3O_2$: C, 60.1; H, 3.35.
Found: C, 60.1; H, 3.75.

b. *9-Chloropyrido[2,3-a]phenazine* (IV). The yields of this compound were not nearly as satisfactory as were those of the 10-chloropyrido[3,2-*a*]phenazine, and purified intermediate rather than the crude material had to be used, as mentioned above, to secure any yield. Even with this purified intermediate, treated in the same way as was its isomer, there was obtained from 1.0 g. of the recrystallized compound, melting at 210–212°, only 0.05 g. of very pale small needles, shrinking and darkening at 264–265°, and melting with apparent decomposition to a dark brown liquid at 272–273°.

Anal. Calc'd for $C_{15}H_8ClN_3$: C, 67.8; H, 3.04.
Found: C, 68.0; H, 3.41.

10-Chlorobenzofuro[2,3-a]phenazine (VI). a. *3-(4-Chloro-2-nitroanilino) dibenzofuran* (V). A mixture of 32 g. of 3-aminodibenzofuran (3), 36 g. of 2,5-dichloronitrobenzene, and 30 g. of anhydrous sodium acetate was heated for 45 hours in an oil-bath at 206–212° (air-condenser). The usual steam-distillation to remove unreacted material, followed by washing with water and air-drying gave 55.8 g. of crude product (94%) softening and shrinking at 111°, and melting at 129–135°. Recrystallized twice from alcohol (Norit), the product formed deep red, silky needles, melting at 161–162°.

Anal. Calc'd for $C_{18}H_{11}ClN_2O_3$: C, 63.9; H, 3.27.
Found: C, 63.6; H, 3.44.

TABLE II

INTERMEDIATES

Diphenylamine	M.P.,[a] °C.	Method of Preparation	Yield, %	Formula	Analysis[b]			
					C		H	
					Calc'd	Found	Calc'd	Found
A'. 4-Bromo-5'-chloro-2'-methoxy-2-nitro-	196–197[c]	2,5-Dibromonitrobenzene; 5-chloro-2-anisidine; sodium acetate; 40 hours at 195–200°	77	$C_{13}H_{10}BrClN_2O_3$	43.7	43.4	2.82	2.91
B'. 4-Chloro-2',4'-dimethyl-2-nitro-	109–110[d]	2,5-Dichloronitrobenzene; 2,4-xylidine; sodium acetate; 40 hours at 180–190°	72	$C_{14}H_{13}ClN_2O_2$	60.8	60.7	4.74	4.60
C'. 5-Chloro-6-methyl-2-nitro-	107–109 (7)	2,3-Dinitro-6-chlorotoluene; aniline; 5 weeks in refluxing ethanol						
D'. 4-Chloro-4'-methyl-2-nitro-	120–122[e]	2,5-Dichloronitrobenzene; *p*-toluidine; sodium acetate 40 hrs. at 185–190°	60	$C_{13}H_{11}ClN_2O_2$	59.4	59.5	4.24	4.33
E'. 4-Chloro-2-nitro-4'-phenyl-	118–119[f]	2,5-Dichloronitrobenzene; *p*-xenylamine; sodium acetate; 40 hours at 185–190°	72	$C_{18}H_{13}ClN_2O_2 \cdot H_2O$	63.1	63.1	4.41	4.36
F'. 4'-Ethoxy-6-methoxy-2-nitro-	72–73[g]	2,3-Dinitroanisole; *p*-phenetidine; one week in refluxing ethanol	80	$C_{15}H_{16}N_2O_4$	62.5	62.4	5.56	5.70
G'. 2'-Methyl-2-nitro- (4)	76							
H'. 4'-Methyl-2-nitro- (6)	69–70							

[a] Corrected. [b] Analyses by the Microanalytical Laboratory, NIH, under the direction of Dr. William C. Alford. [c] Brown-orange microcrystals from ethanol. [d] Orange-red sparkling prisms from ethanol. [e] Red prisms from ethanol. [f] Small orange needles from ethanol. [g] Deep red prisms from n-hexane.

b. *10-Chlorobenzofuro[2,3-a]phenazine* (VI). The crude intermediate was satisfactory for ring closure. When 5 g. of this, intimately mixed with 6.5 g. of ferrous oxalate dihydrate and 50 g. of granulated lead, was heated in an open flask by an oil-bath at 270–275°, the reaction was complete within 14 minutes; the internal temperature reached a maximum of 275°. Vacuum sublimation from the entire reaction mixture gave 2.44 g. of the crude phenazine (54%). Recrystallization from benzene gave very small light yellow needles melting to a dark brown liquid at 277–286°.

Anal. Calc'd for $C_{18}H_9ClN_2O$: C, 71.0; H, 2.96.
Found: C, 71.0; H, 3.03.

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SUMMARY

A number of new phenazines have been synthesized through nitro-group ring-closure. Three of these latter embody additional fused heterocyclic rings.

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