[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

SUBSTITUTED 1,10-PHENANTHROLINES. VI. CHLORO DERIVATIVES[1]

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This investigation was undertaken to provide new chloro-1,10-phenanthrolines which might have use in the detection of Fe^{++} or Cu^{+}, or which, in the form of their ferrous salts, might be employed as oxidation-reduction indicators. At present the known chloro-1,10-phenanthrolines include only the 2- (1), the 4- (2), and the 5- (3) mono-, and the 4,4′- (2) dichloro derivatives.

The synthesis of 3-chloro-1,10-phenanthroline (VII) was accomplished by subjecting 8-amino-3-chloroquinoline (V) to the Skraup reaction. Since the preparation of the necessary intermediate, 3-chloro-8-nitroquinoline by the Skraup reaction described below gave low yields (See Table I) recourse was had to a modification of the method of Riegel (4). It was found in this connection, that the yield is much improved if considerably less than the molar amount of chlorine relative to the sulfur monochloride is used.

The synthesis of 5,6-dichloro-1,10-phenanthroline (III) involved preparation of the hitherto-unreported 5,6-dichloro-8-nitroquinoline (II), by the Skraup reaction on 4,5-dichloro-2-nitroacetanilide (I) (5), reduction to the amine, and subjection of this to another Skraup reaction.

It was felt that a convenient source of 3-chloroquinolines and phenanthrolines would be the reaction of α-chloroacrolein, first prepared by Moreu and Boismenu (6), with suitable amines. One instance of the successful use of this reagent in this manner was the synthesis of 3-chloro-6-methoxy-8-nitroquinoline from 4-amino-3-nitroanisole in concentrated hydrochloric acid (7). Furthermore, the analogous α-bromoacrolein in the form of its diacetate has been successfully employed to make 3-bromo derivatives (8). However, in our hands, only in some cases could the reaction be made to yield any of the desired product, whether under Skraup or Doebner-Miller conditions, and low yields were always obtained. Thus under Skraup conditions, *o*-nitroaniline was converted in low yield to 3-chloro-8-nitroquinoline; 4-chloro-2-nitroacetanilide to 3,6-dichloro-8-nitroquinoline (XIV); 2-nitro-4-phenylacetanilide to 3-chloro-8-nitro-6-phenylquinoline; and 8-amino-5,6-dichloroquinoline to 3,5,6-trichloro-1,10-phenanthroline (IV). Under Doebner-Miller conditions, 3,8-dichloro-1,10-phenanthroline (VI) was obtained from 8-amino-3-chloroquinoline (V), and 3,5-dichloro-1,10-phenanthroline (IX) from 8-amino-6-chloroquinoline (VIII).

By the use of methylacrolein diacetate (9), a number of chloro-3-methylquinolines and phenanthrolines were prepared. Thus from 4-chloro-2-nitroaniline (XI) was obtained 6-chloro-3-methyl-8-nitroquinoline (XII), and by reduction, the corresponding amine. From the action of the amine with α-methylacrolein

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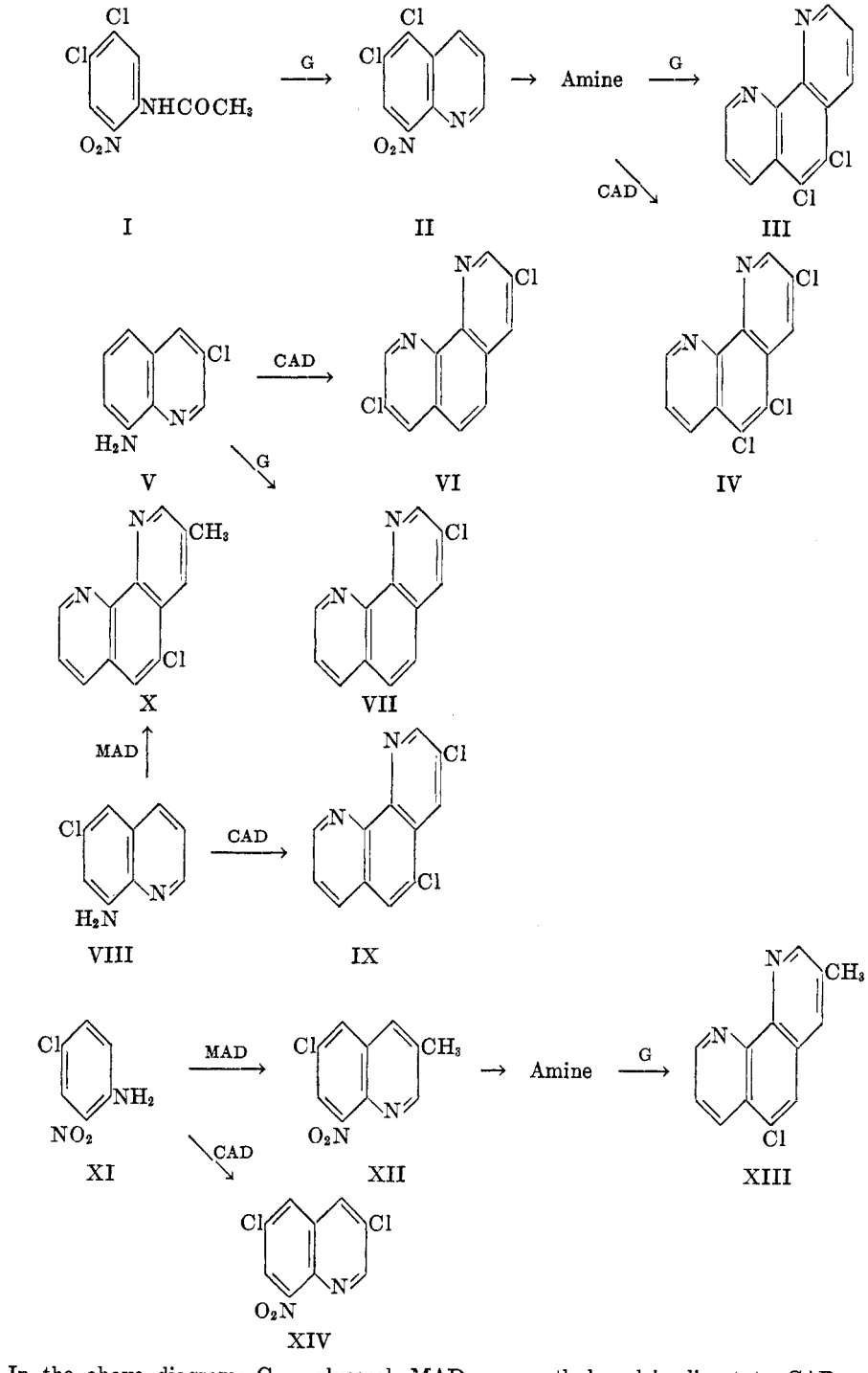
TABLE I

PREPARATION OF QUINOLINES BY THE SKRAUP REACTION

QUINOLINE PREPARED	1ST COMPONENT	2ND COMPONENT[a]	M.P., °C.	YIELD, %	CRYST'N SOLVENT	MOLECULAR FORMULA	ANALYSIS CHLORINE	
							Calc'd	Found
5,6-Dichloro-8-nitro	4,5-Dichloro-2-nitroaniline	G	175–176	67.8	Benzene	$C_9H_4Cl_2N_2O_2$	29.18	29.00
3,6-Dichloro-8-nitro	4-Chloro-2-nitroacetanilide	CAD	160–161	13.6	Ethanol	$C_9H_4Cl_2N_2O_2$	29.18	28.88
3-Chloro-8-nitro-6-phenyl-	4-Acetamino-3-nitrobiphenyl	CAD	159–160	4.9	Ethanol	$C_{15}H_9ClN_2O_2$	12.45	12.35
6-Chloro-3-methyl-8-nitro-	4-Chloro-2-nitroaniline	MAD	203–204	56	Ethanol	$C_{10}H_7ClN_2O_2$	15.92	15.73
6-Chloro-3-methyl	*p*-Chloroaniline	MAD	81–82	58	Ethanol	$C_{10}H_8ClN$	19.97	19.74
3-Chloro-8-nitro	*o*-Nitroaniline	CAD	137–139	4.8	Ethanol	$C_9H_5ClN_2O_2$	Known compound	

[a] G = glycerol; MAD = α-methylacrolein diacetate; CAD = α-chloroacrolein diacetate.



I II III IV V VI VII VIII IX X XI XII XIII XIV

In the above diagram: G = glycerol; MAD = α-methylacrolein diacetate; CAD = α-chloroacrolein diacetate.

TABLE II

PREPARATION OF 1,10 PHENANTHROLINES BY THE SKRAUP REACTION

1,10-PHENANTHROLINE PREPARED	1ST COMPONENT 8-AMINOQUINOLINE	2ND COMPONENT	M.P., °C.	YIELD, %	CRYST'N SOLVENT	MOLECULAR FORMULA	ANALYSIS			
							CHLORINE			
							Calc'd		Found	
6-Chloro-3-methyl-	6-Chloro-3-methyl	G	165–166	38.0	Benzene	$C_{13}H_9ClN_2$	15.50		15.75	
5-Chloro-3-methyl-	6-Chloro-	MAD	184–185	23.0	Benzene	$C_{13}H_9ClN_2$	15.50		15.33	
5,6-Dichloro-	5,6-Dichloro-	G	234–235	26.2	Benzene	$C_{12}H_6Cl_2N_2$	28.47		28.37	
3,5,6-Trichloro-	5,6-Dichloro-	CAD	207–208	7.9	Benzene	$C_{12}H_5Cl_3N_2$	37.52		37.38	
							C		H	
							Calc'd	Found	Calc'd	Found
3-Chloro-	3-Chloro-	G	170	26.7	Benzene	$C_{12}H_7ClN_2$	67.14	67.19	3.29	3.38
3,8-Dichloro-	3-Chloro-	CAD	268–269	2.5	Benzene	$C_{12}H_6Cl_2N_2$	57.86	57.70	2.43	2.37
3,5-Dichloro-	6-Chloro-	CAD	226–227	2.0	Ethanol-water	$C_{12}H_6Cl_2N_2$	57.86	58.05	2.43	2.56

[a] G = glycerol; MAD = α-methylacrolein diacetate; CAD = α-chloroacrolein diacetate.

diacetate, no 5-chloro-3,8-dimethyl-1,10-phenanthroline was isolated. With glycerol, however, 6-chloro-3-methyl-1,10-phenanthroline (XIII) was obtained. From 8-amino-6-chloroquinoline (VIII) and α-methylacrolein diacetate, 5-chloro-3-methyl-1,10-phenanthroline (X) was obtained. With the same reagent, *p*-chloroaniline yielded 6-chloro-3-methylquinoline, previously unreported.

EXPERIMENTAL PART

General procedure for the synthesis of quinolines and 1,10-phenanthrolines:

A. Skraup method. A mixture of one molar proportion of the appropriate aniline or aminoquinoline derivative, one mole of arsenic acid, 4 moles of sulfuric acid in 96.8% solution, and a volume of water equal to one-third of the volume of sulfuric acid was heated to 100° and treated with 1.5 moles of glycerol, α-chloroacrolein diacetate, or α-methylacrolein diacetate at such a rate that the temperature did not exceed 140°. This reaction temperature was maintained for two hours. The mixture was then poured into water, made alkaline, and the tarry precipitate was removed by filtration. The filtrate was extracted three times with hot benzene (in case of the phenanthrolines only), which was then used to extract the quinoline or phenanthroline from the solid material. After the removal of the benzene, the residue was crystallized from the solvent indicated in the table.

B. Doebner-Miller method. (This was used only for the preparation of 3,8- and of 3,5-dichloro-1,10-phenanthrolines.) A mixture of 0.1 mole of 8-amino-chloroquinoline, 11.5 g. of arsenic acid, 10 g. of anhydrous zinc chloride, and 200 ml. of concentrated hydrochloric acid was heated with stirring on a steam bath. During 30 minutes, 48 g. of α-chloroacrolein diacetate was added for the 3,8-dichloro-1,10-phenanthroline, and 58 g. for the 3,5-derivative. Heating was then continued for two hours. The mixture was made strongly alkaline, and extracted with hot benzene as before. The residue, after removal of the benzene was crystallized from the solvent indicated in Table II.

4,5-Dichloro-2-nitroacetanilide. The following procedure was found to be an improvement over that previously recorded (5): To a mixture of 48 g. of 3,4-dichloroacetanilide (10) and 468 ml. of concentrated sulfuric acid, 21.4 g. of ethyl nitrate was gradually added with stirring, the temperature being kept below 2°. After one hour's standing at this temperature, the reaction mixture was poured onto ice, and the resulting precipitate was crystallized from ethanol. The yield was 36 g., m.p. 122–124°, or 61.3%.

3-Chloro-8-nitroquinoline. To the solution prepared by passing 19 g. of chlorine into 68 g. of sulfur monochloride, was added 30 g. of 8-nitroquinoline. The mixture was allowed to stand one hour and then refluxed for three hours. Dry ether (250 ml.) was next added, and the resulting precipitate, after washing with another 250-ml. portion of ether, was suspended in water and the mixture was made strongly alkaline with sodium hydroxide. The precipitate was recrystallized several times from ethanol yielding 10.8 g. of material melting at 134–135°. This was sufficiently pure for further use.

8-Amino-6-chloro-3-methylquinoline. A solution of 30 g. of 6-chloro-3-methyl-8-nitroquinoline and 90.6 g. of stannous chloride dihydrate in 600 ml. of ethanol was refluxed for three hours. After removal of the ethanol, the residue was made strongly alkaline and was extracted with ether. After removal of the ether, the base was crystallized from ethanol. The yield of pure product, melting at 104–105° was 16.1 g., or 61%.

Anal. Calc'd for $C_{10}H_9ClN_2$: Cl, 18.40. Found: Cl, 18.08.

5,6-Dichloro-8-aminoquinoline. This was prepared from 5,6-dichloro-8-nitroquinoline in the manner described above. The yield of pure base, crystallized from methanol, melting at 124–125°, was 55.7%.

Anal. Calc'd for $C_9H_6Cl_2N_2$: Cl, 33.28. Found: Cl, 33.21.

SUMMARY

The preparation of the following 1,10-phenanthrolines is described: 3-chloro-; 6-chloro-3-methyl; 5-chloro-3-methyl; 5,6-dichloro-; 3,5-dichloro-; 3,8-dichloro-; and 3,5,6-trichloro-.

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REFERENCES

(1) KARRER AND PLETSCHER, *Helv. Chim. Acta*, **31**, 793 (1948).
(2) SNYDER AND FREIER, *J. Am. Chem. Soc.*, **68**, 1320 (1946).
(3) RICHTER AND SMITH, *J. Am. Chem. Soc.*, **66**, 396 (1944).
(4) RIEGEL AND CO-WORKERS, *J. Am. Chem. Soc.*, **68**, 1532 (1946).
(5) BEILSTEIN AND KURBATOV, *Ann.*, **196**, 225 (1879).
(6) MOREU AND BOISMENU, *Ann. chim.*, [9], **15**, 209 (1921).
(7) YALE, *J. Am. Chem. Soc.*, **70**, 1982 (1948).
(8) CASE, *J. Org. Chem.*, **16**, 941 (1951).
(9) CASE, *J. Am. Chem. Soc.*, **70**, 3994 (1948).
(10) HODGSON AND KERSHAW, *J. Chem. Soc.*, 2922 (1929).