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QUINOLINE DERIVATIVES FROM 2- AND 4-CHLOROQUINOLINES[1]

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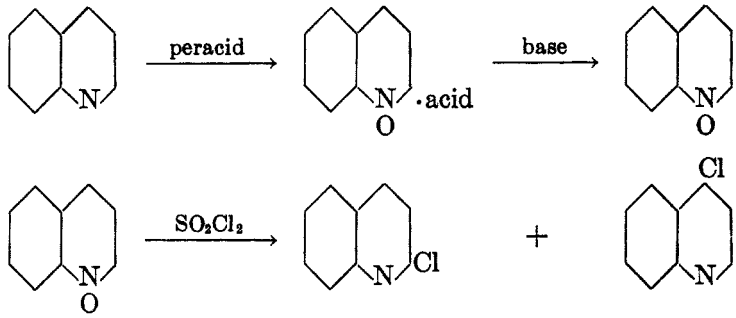
PREPARATION OF CHLOROQUINOLINES

Quinoline and related N-heterocycles react readily with peracids to give N-oxides, and these in turn react with various chlorinating agents to give a mixture of *alpha*- and *gamma*-chloro derivatives



These reactions, first studied by Meisenheimer (4) and later by Bobranski (1), give ready access to the 4-position of quinolines in which the pyridine ring is otherwise unsubstituted.

The ratio of 2-chloro to 4-chloro derivatives formed is about 1:1.7 for quinoline itself and 1:0.6 for 6-methoxyquinoline. In applying this reaction to various quinolines, we have found that the nature of a substituent already present on the benzenoid nucleus is the primary factor influencing the ratio of *alpha*- to *gamma*-chloro derivative obtained. Thus with 6-nitroquinoline the 4-chloro derivative predominates and the ratio is about 1:3.5. On the other hand, changes in the reaction conditions appear to have very little influence on the ratio. Thus, with 6-methoxyquinoline N-oxide, the use of an inert solvent, such as carbon tetrachloride, does not appreciably affect the course of the reaction. Other solvents and possible catalysts such as sulfuric acid, acetic acid, or phosphorus pentoxide cause undesirable side reactions. Also, whether the oxide, oxide dihydrate, or oxide hydrochloride is used, the amounts of *alpha* and *gamma* derivatives formed are about the same. It should be noted, however, that it is possible to reduce 2-chloro-6-methoxyquinoline catalytically to 6-methoxyquinoline and to recycle this material and obtain more of the 4-chloro derivative.

In Table I will be seen the results of applying the Meisenheimer reactions to 6-methoxy-, 6-chloro-, 6-nitro-, and benzo-(*f*)-quinolines. In all of these syntheses the Meisenheimer procedure was greatly simplified by the preparation of the N-oxide phthalate by the method of Bobranski(1), but converting this salt to the

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free base instead of the hydrochloride. The latter is more difficult to obtain. It is surprising to note that a third isomer, possibly the 3-chloro compound, was

TABLE I

QUINOLINE DERIVATIVES

FORMULA	M.P. (COR.) °C.	YIELD %	RATIO ISOMERS	ANALYSIS, %	
				Calc'd	Found
N-OXIDES					
6-MeO-quinoline N-oxide[b]	108–109				
6-Cl-quinoline N-oxide[a]	126.5			N, 7.8	7.8, 7.7
6-NO_2-quinoline N-oxide[a]	220–222			N, 14.8	15.1, 15.0
Benzo-(*f*)-quinoline N-oxide[a]	132			C, 80.0	80.2, 80.0
				H, 4.7	4.7, 4.7
CHLOROQUINOLINES[c]					
2-Cl-6-MeO-quinoline[b]	106–107	55	1.00		
4-Cl-6-MeO-quinoline[b]	79	35	.63		
2,6-dichloroquinoline[d]	161.5	49	1.00	C, 54.6	55.0, 55.3
				H, 2.6	2.7, 2.6
4,6-dichloroquinoline[a]	104	35	1.38	C, 54.6	54.8, 54.7
				H, 2.6	2.6, 2.8
2-Cl-6-NO_2-quinoline[e]	230	16	1.00		
3(?)Cl-6-NO_2-quinoline[a]	145	3.5	.22	Cl, 17.0	16.8, 17.0
4-Cl-6-NO_2-quinoline[a]	142.5	56.5	3.53	N, 13.4	13.2, 13.3
3-Cl-benzo-(*f*)-quinoline[f]	112.5	32	1.54		
1-Cl-benzo-(*f*)-quinoline[g]	66–67	21[h]	1.00		
HYDROXYQUINOLINES					
2-OH-6-Cl-quinoline[i]	267.5				
4-OH-6-Cl-quinoline[a]	269			C, 60.2	60.7, 60.9
				H, 3.4	3.4, 3.5
2-OH-6-NO_2-quinoline[j]	280				
4-OH-6-NO_2-quinoline[a]	325			N, 14.7	14.7, 14.8

[a] New compound. All were white in color except the hydroxyl and N-oxide derivatives of 6-nitroquinoline which were yellow.

[b] Magidson, *J. Gen. Chem.* (USSR), **7,** 1896 (1937).

[c] In each group the isomers are listed in the order of their precipitation from acidic solution by alkali.

[d] Fischer, *Ber.*, **35,** 3683 (1902); m.p. 156°.

[e] Fischer and Guthmann, *J. prakt. Chem.*, (2), **93,** 381 (1916); m.p. 235°.

[f] Hamer and Kelly, *J. Chem. Soc.*, 777 (1931); m.p. 114°.

[g] Brit. Patent 481,874 (March 14, 1943): m.p. 66–67°. Mueller and Hamilton, *J. Am. Chem. Soc.*, **65,** 1017 (1943); m.p. 62–63°.

[h] Higher yields should be possible; only one trial was made.

[i] Einhorn and Lauch, *Ann.*, **243,** 345; m.p. 262–263°.

[j] Fischer and Guthmann, *loc. cit.*; m.p. 280°.

isolated in the case of 6-nitroquinoline. The hydroxy compounds listed were obtained by acid hydrolysis of the *alpha-* and *gamma*-chloro derivatives.

TABLE II

DERIVATIVES FROM CHLOROQUINOLINES

FORMULA	TEMP. °C	REACTION TIME, HOURS	YIELD, %	B.P. °C. (MM.)	M.P. (COR.) °C	ANALYSIS %	
						Calc'd	Found
A. *R=6-methoxyquinolyl*							
R-4-NHCH(C_2H_5)CH_2N(C_2H_5)$_2$	175	50	32[a]	195 (0.5)	117		
Dipicrate					198	C, 47.4	47.3, 47.5
						H, 4.4	4.3, 4.4
R-4-NHCH(C_2H_5)CH_2N(CH_2CH_2)$_2$O	175	24	22[b]		170	N, 13.3	13.5, 13.5
R-4-NH(CH_2)$_6$N(C_2H_5)$_2$	175	4	60[b]		oil	N, 12.8	12.9
Monohydrate					83	C, 69.1	68.6, 68.6
						H, 9.6	9.7, 9.7
R-4-NHCH$_2$C(CH_3)$_2$$CH_2N$($CH_3$)$_2$	145–170[c]	14	16[a]	200 (0.1)		C, 71.0	70.6, 70.9
						H, 8.8	8.4, 8.4
Dihydrochloride					222	C, 56.4	56.4, 56.3
						H, 7.6	7.6, 7.5
R-2-NHCH[CH_2N(CH_3)$_2$]$_2$	173	12	41[a]	185–190 (0.3)			
Picrate					182–183	N, 18.4	17.8, 18.2
Dihydrochloride					245–246	C, 54.4	53.8, 54.1
						H, 7.5	7.1, 7.3
R-4-NHCH[CH_2N(CH_3)$_2$]$_2$	150	20	72[c]		140	C, 67.5	66.5, 66.8
						H, 8.7	8.5, 8.8
Trihydrochloride					255	N, 12.0	12.2, 11.9
Trihydrochloride hydrate					245 (dec.)	N, 11.5	11.3
R-4-NHCH[CH_2N(C_2H_5)$_2$]$_2$	175	8	50[a]	205 (0.3)	85		
Trihydrochloride					255	N, 12.0	12.17, 11.94
R-4-NHCH[CH_2N(C_3H_7)$_2$]$_2$	155	17	56[a]	222 (0.15)	56	C, 73.0	72.13, 72.08
						H, 9.8	10.20, 10.27
R-4-NHCH[CH_2N(C_4H_9)$_2$]$_2$	175	13	62[a]	240 (0.04)		C, 74.0	73.2, 73.4
						H, 10.7	10.2, 10.3

Trihydrochloride					103	C, 60.1 H, 9.2	59.0, 58.9 9.2, 9.4
Dihydrochloride					145	C, 64.1 H, 9.6	63.6, 63.2 9.7, 9.6
R-4-NHCH{$CH_2N[CH_2CH(CH_3)_2]_2$}$_2$	175	15	44[b]		116	C, 74.0 H, 10.7	73.84, 73.78 10.76, 10.80
R-4-$OCH_2CH_2N(C_2H_5)_2$·2HCl	140	5	89[d]		188	C, 55.4 H, 7.0	54.9, 54.9 7.0, 6.8
R-4-OCH[$CH_2N(C_2H_5)_2$]$_2$	135	3	55[a]	190 (0.1)		C, 70.2 H, 9.0	71.4, 71.5 9.6, 9.4
Trihydrochloride					191	C, 53.8 H, 7.7	53.7, 53.0 7.8, 7.7
R-4-(6′-methoxy-8′-quinolylamino)-H_2O	140	7	62[c]		178.5	C, 68.8 H, 5.5	68.5, 69.0 5.6, 5.6
R-4-(8′-quinoxy)·2HCl	172	3	58[d]		268	C, 60.8 H, 4.3	61.2, 61.3 4.6, 4.3
B. *Q=6-hydroxyquinolyl*							
Q-4-$NHCH_2C(CH_3)_2CH_2N(CH_3)_2$	120	2.5	56	240 (0.03)	225	C, 70.3 H, 8.5 N, 15.4	70.6, 70.9 8.6, 8.6 15.2, 15.4
Dihydrobromide					226–227	C, 44.2 H, 5.8	43.9, 43.8 6.2, 6.1
Q-4-NHCH[$CH_2N(CH_3)_2$]$_2$·3HBr	120	2			270	C, 36.2 H, 5.1	36.5, 36.7 5.3, 5.4
Q-4-NHCH[$CH_2N(C_2H_5)_2$]$_2$·3HBr	120	2			242	C, 40.8 H, 6.2	40.8, 41.2 6.3, 5.8
C. U=6-chloroquinolyl							
U-2-$NH(CH_2)_3N(C_2H_5)_2$	152	6	60[a]	202 (0.3)		N, 14.4	14.3, 14.1
Dihydrochloride					229–230	N, 11.5	11.8, 11.5
Dihydrochloride hydrate					75 (dec.)	N, 10.5	10.8, 10.6

TABE II—*Concluded*

FORMULA	TEMP. °C	REACTION TIME, HOURS	YIELD, %	B.P. °C (MM.)	M.P. (COR.) °C	ANALYSIS, %	
						Calc'd	Found
U-2-NHCH[$CH_2N(CH_3)_2$]$_2$	175	6	45[a]	188 (0.3)		C, 62.6	62.4, 62.4
						H, 7.6	7.7, 7.2
Trihydrochloride					257	C, 46.2	46.1, 45.8
						H, 6.3	6.3, 6.4
U-2-$OCH_2CH_2N(C_2H_5)_2$	132	4	55[a]	164 (0.3)		C, 64.6	64.2, 65.3
						H, 6.9	6.9, 6.8
Monohydrochloride					164.5	C, 57.1	57.4, 57.1
						H, 6.4	6.4, 6.4
D. W=6-Nitroquinolyl							
W-4-$NH(CH_2)_3N(C_2H_5)_2$	100	8	45[a]	220 (0.15)	67	N, 18.5	18.5, 18.8
Monohydrate					68		
W-4-NHCH[$CH_2N(CH_3)_2$]$_2$	100	21	65[c]		140.5	C, 60.5	60.5, 60.5
						H, 7.3	7.3, 7.4
						N, 22.1	21.6, 21.6

[a] By distillation.
[b] By concentration of ether extract.
[c] By precipitating from acidic solution by alkali.
[d] By addition of alcoholic HCl to ether extract.
[e] Solution refluxed; temperature range due to rising boiling point.

DERIVATIVES FROM CHLOROQUINOLINES

The 2- and 4-chloroquinolines are readily converted into the corresponding quinoline amines and ethers through reaction with amines and the sodium derivatives of alcohols. A series of such compounds was prepared for the purpose of studying their pharmacological activity, especially towards the plasmodia of malaria.

In general, the compounds prepared were characterized by the difficulty with which they were obtained crystalline. The free bases were usually difficultly crystallizable oils and the hydrochlorides tended to be hygroscopic. Those derivatives containing several basic nitrogen atoms formed more than one hydrochloride and more than one picrate and it was often difficult to obtain a suitable material for analysis. Distillation of the free base under high vacuum was almost essential to obtain crystalline products.

TABLE III

TRIAMINES

FORMULA	B.P. °C (MM.)	d_4^{30}	n_D^{30}
$[(C_3H_7)_2NCH_2]_2CHNH_2$	115(0.2)	0.8473	1.4458
$[(C_4H_7)_2NCH_2]_2CHNH_2$	135(0.2)	.8505	1.4488
$\{[(CH_3)_2CHCH_2]_2NCH_2\}_2CHNH_2$	165(13)	.8377	1.4439

SYNTHESIS OF TRIAMINES

Some of the side chains employed were derived from new triamines obtained by reducing the Mannich condensatiom products between various secondary amines, formaldehyde, and nitromethane.

$$2R_2NH + 2H_2CO + CH_3NO_2 \longrightarrow (R_2NCH_2)_2CHNO_2$$

$$(R_2NCH_2)_2CHNO_2 \xrightarrow[\text{Raney nickel}]{H_2} (R_2NCH_2)_2CHNH_2$$

These reactions have been studied by Henry (3) and Cerf de Mauny (2) who used dimethylamine and diethylamine in the synthesis. We found that the higher secondary amines give equally good results, although the initial condensation may be somewhat more sluggish. The physical properties of the new members of this series are given in Table III.

EXPERIMENTAL

Perphthalic acid. This was prepared according to the procedure given in Organic Syntheses (5). It was found advantageous to use very concentrated alkali (40%) and add finely crushed ice directly to the mixture. A single extraction with 100 ml. of ether for each 17 g. of phthalic anhydride taken was found to extract most (86%) of the perphthalic acid formed, resulting in an economy of ether and giving a more concentrated solution.

N-oxide phthalates. The quinoline base was added in a suitable form to a quantity of the ether solution of perphthalic acid corresponding to a 50% excess. Liquid bases, as 6-methoxyquinoline, were added directly, using stirring and slow addition. 6-Chloro-

quinoline was melted, supercooled to room temperature, then added in a like manner. For benzo-(*f*)-quinoline, a saturated ether solution of the solid was prepared. Since 6-nitroquinoline is insoluble in ether, a saturated solution in dioxane was used.

Such additions usually resulted in a turbidity, marking the precipitation of an oil, probably a complex (perphthalate salt) of the acid and the base. It was found best not to permit this oil to settle as a separate layer, because its subsequent transformation to the solid N-oxide phthalate is an exothermic reaction, and the heat evolved may cause decomposition if not dissipated. Stirring in a bath of tap water (15°) until the transformation was complete gave good results. 6-Nitroquinoline did not give such an oily precipitate. Its N-oxide phthalate separated directly as a solid when the clear solution was allowed to stand in the ice-box for 2 to 4 days.

The resulting crystalline N-oxide phthalates were filtered and washed with ether, and were then pure enough to be converted directly to the free oxides.

N-oxides. The oxide phthalate, finely ground in a mortar, was covered with a liberal excess of 5% aqueous ammonia and stirred mechanically for fifteen minutes. The insoluble free oxide, in most cases a hydrate, was collected on a filter, washed with water, and dried in the air. Continued drying of the hydrate results in a slow conversion to the anhydrous form. It is usually difficult to determine exactly when a water content corresponding to the hydrate has been reached in the drying process. 6-Nitroquinoline N-oxide apparently does not form a stable hydrate. The oxide hydrates which were isolated are listed below (see Table I for anhydrous forms).

6-Methoxyquinoline N-oxide·$2H_2O$, white, m.p. 88–89° (cor.).

6-Chloroquinoline N-oxide·$2(?)H_2O$, white, m.p. 55–59° (cor.).

Benzo-(*f*)-quinoline N-oxide·$2(?)H_2O$, white m.p. 75–79° (cor.).

Chloroquinolines. Oxides, oxide hydrates, and oxide hydrochlorides all gave essentially the same results in their conversions to chloroquinolines. In all cases the material was added in portions to a volume of phosphorus oxychloride, chilled in ice, corresponding to 5 ml. for each 1 gram of the base. After addition was complete, the mixture was warmed gently under a condenser until refluxing began. An ice-bath was kept at hand in case the reaction became suddenly violent. Refluxing was continued for thirty minutes. The cooled reaction mixture was poured with stirring on crushed ice (500 g. for each 100 ml. of $POCl_3$), the solution diluted if necessary to dissolve any sparingly soluble chloroquinoline hydrochloride, and then filtered from any weakly basic chloroquinoline (6-nitro-2-chloroquinoline and 2,6-dichloroquinoline) which was present. Successive partial neutralizations of the filtrate with concentrated aqueous ammonia gave a series of precipitates of chloroquinoline derivatives in the order of increasing basicity. Usually only two products were formed: the 2- and 4-chloro isomers, and usually the 2-chloro was least basic and separated first. The isomers are listed in the order of their precipitation by alkali in Table I.

Aliphatic triamines. The diaminonitro compounds were prepared by the procedure of Cerf de Mauny (2) except that the longer reaction times indicated were used: di-*n*-propylamine 3 hrs; di-*n*-butylamine 48 hrs; di-isobutylamine 24 hrs. The products were yellow oils in all cases and were obtained uniformly in crude yields of 85%. All attempts at purification by distillation, even at very low pressures, resulted in decomposition. However, the products were pure enough for reduction.

For this step the nitro compound, dissolved in an equal volume of absolute ethanol, was reduced in a Parr hydrogenator at 60 lbs. pressure, using a Raney nickel catalyst. Reduction proceeded at once and the highly exothermic reaction was controlled by passing a rapid air blast through a copper jacket surrounding the reduction bottle. Reduction usually required from 45 to 60 minutes. Absorption of hydrogen was 80–90% of the theoretical amount.

The filtered mixture was dried over Drierite and distilled. The triamines obtained were colorless liquids with a characteristic amine odor. Their properties are given in Table III.

Derivatives from chloroquinolines. The derivatives of 6-methoxy-, 6-chloro-, and 6-nitroquinolines were prepared in all cases by heating, without a solvent, the corresponding active

chloro derivative with an excess (100%) of an amine, the sodium derivative of an amino alcohol, or, in one case, with 8-hydroxyquinoline. The temperatures and reaction times (listed in Table II) had to be varied according to the activity of the chloroquinoline and the nature of the side chain. Where the required reaction temperature was higher than the boiling point of the mixture, the reaction was conducted in a sealed tube. Heating was best achieved by surrounding the reaction tube with the vapor of a refluxing liquid of suitable boiling point. Chlorobenzene, *o*-dichlorobenzene, and *o*-xylene were among the compounds found useful for this purpose.

The cooled reaction mixture, often very viscous, was dissolved in three volumes of concentrated hydrochloric acid, and the free base was precipitated in a separatory funnel with aqueous alkali. It was then extracted with ether and dried. Such extracts were usually distilled under a high vacuum, but in certain cases (noted in Table II) it was advantageous to crystallize out the free base by concentrating the extract, or to precipitate a hydrochloride of the base by the addition of alcoholic hydrogen chloride. In a few cases the base as precipitated by alkali was a solid. One or two recrystallizations from pentane, heptane, or other solvent then usually gave the pure compound.

The distilled free bases sometimes solidified upon standing, in which case they were recrystallized from a suitable solvent. More often the oils were dissolved in ether and treated with alcoholic hydrogen chloride to form the hydrochlorides. Frequently these separated as oils which could be obtained crystalline only by chilling and scratching, washing with another solvent, reprecipitation from a good solvent by addition of a poor one, or by long standing. Once a solid salt was obtained, alcohol, sometimes mixed with dioxane or dibutyl ether, was usually the best recrystallizing solvent for the hydrochlorides.

The derivatives of 6-hydroxyquinoline were obtained from the corresponding 6-methoxy compounds by refluxing a solution of the derivative in concentrated hydrobromic acid (Baker's C.P., 5 ml. for each 1 g. of base) for two hours. The solution was then diluted with four volumes of water. In most cases cooling and scratching induced the separation of a nicely crystalline hydrobromide hydrate which was removed and recrystallized from ethanol. When this procedure was not effective, the reaction mixture was evaporated to dryness under a vacuum on a steam cone, and the solid residue recrystallized from ethanol.

SUMMARY

1. A number of *alpha*- and *gamma*-chloroquinolines have been prepared by treatment of their N-oxides with phosphorus oxychloride. Several of these are new.

2. A number of aminoalkylamino, diaminoalkylamino, and aminoalkoxy derivatives have been prepared from these chloroquinolines and characterized.

3. Three new aliphatic triamines have been prepared and characterized.

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