[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Introduction of Alkylamino and Dialkylamino Groups into the Quinoline Nucleus

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It has been shown that quinine is detoxified in the body by oxidation to the 2-hydroxy derivative which has much less therapeutic activity.[3] Since antimalarials containing a quinoline nucleus may suffer a similar fate, the problem of introducing groups into the 2-position in order to block this mode of detoxification was undertaken. It was hoped that amino and substituted alkylamino groups would overcome such objections, and so a study was made on the ease of substitution of such groups in the 2-position of quinoline and of finding the optimum conditions for such introduction.

The direct introduction of the amino group by the use of alkali amides in liquid ammonia, tertiary amines, or inert solvents has become a well established reaction.[4] It has been shown also, that alkylamino groups can be introduced by the use of the fused sodium–potassium amide eutectic in the presence of an excess of a primary amine.[5] It has now been shown that in some cases 2-aminoquinoline may also be produced in this reaction. In this Laboratory 2-methylaminoquinoline has been produced by the reaction of quinoline with lithium methylamide in ether solution and nitrogen atmosphere. However, the methods for the direct introduction of 2-dialkylamino groups have not been so well established. Roser[6] and Cohen, *et al.*,[7] alkylated the methiodide of 2-aminoquinoline stepwise to obtain 2-dimethylaminoquinoline. Quinoline 2-sulfonic acid (prepared from 2-chloroquinoline and sodium sulfite solution) when heated with an aqueous solution of a dialkylamine will yield compounds of the type of 2-dialkylaminoquinoline.[8] Fourneau, *et al.*,[9] combined 2-chloroquinoline itself with a benzene solution of diethylamine in a heated sealed tube to obtain 2-diethylaminoquinoline hydrochloride. Buchman and Hamilton[10] found that both halogen atoms in 2,4-dichloroquinoline were quite reactive and gave good yields of 2,4-di-(N-morpholino)-quinoline. Magidson and Rubtsov[11] and certain patent literature[12] make reference to the successful reaction of 2-chloroquinoline and 2-chloroquinoline derivatives with various basically substituted amines such as 1-diethylamino-4-aminopentane. In addition certain aromatic amino derivatives have been made by the reaction of 2-chloroquinoline with substituted anilines.[13]

We have not been able as yet to accomplish the direct introduction of dialkylamino groups into the quinoline nucleus using alkali dialkylamides. Even in a sealed two-legged tube, potassium dimethylamide in methylamine gave no reaction with quinoline, while only unreacted starting material could be obtained when quinoline was treated with lithium dimethylamide in anhydrous ether, benzene, or toluene. Therefore, it seemed advisable to investigate the general nature of the reaction of 2-chloroquinoline with dialkylamines and to study the properties of the compounds produced. The results are summarized in Tables I and II.

Experimental

Accordingly a series of compounds ranging from 2-dimethylamino- to diamylaminoquinoline was prepared by treating 2-chloroquinoline with the corresponding amine either in a sealed tube or, if the boiling point of the amine was sufficiently high, by refluxing. Hydrolysis of the hydrochlorides so formed was effected by 20% sodium carbonate solution, and after the free base was separated by benzene extraction, it was purified by vacuum distillation.

In this series with the exception of the first compound, all were pale-yellow, stable oils boiling from 140–170° at 2 mm. forming only monomethiodides and hydrochlorides. As the alkyl group became larger, higher temperatures were needed to bring about the reaction of 2-chloroquinoline with the dialkylamine. The salts of the resulting compounds were crystallized with greater difficulty and their melting points tended to become lower.

In a similar manner 2-methylamino-, 2-propylamino- and 2-piperidinoquinoline were also prepared. By treating 4-chloroquinoline with methylamine in a sealed tube heated at 100° for five hours, a 96% yield of 4-methylaminoquinoline was obtained.

The monoalkylaminoquinolines were white crystalline solids which formed only mono-salts. Mono-salt formation may be explained by postulating an amidine type resonance (Fig. 1) in which the positive charge prevents the approach of another molecule of methyl iodide. That

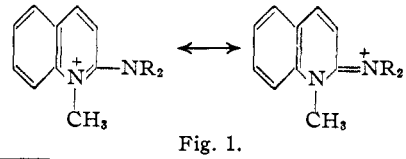

Fig. 1.

(1) Material herein presented based on the M.S. Thesis of Nydia Goetz, Stanford University, August, 1945, and on the Ph.D. Thesis of Nydia Goetz-Luthy, Stanford University, August, 1948.

(2) Deceased March 29, 1946.

(3) Kelsey, Geiling, Oldham and Dearborn, *J. Pharmacol. and Exp. Therap.*, **80**, 391 (1944).

(4) Leffler, "The Amination of Heterocyclic Bases by Alkali Amides" in "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942.

(5) Bergstrom, Sturz and Tracy, *J. Org. Chem.*, **11**, 239 (1946).

(6) Roser, *Ann.*, **282**, 384 (1894).

(7) Cohen, Cooper and Marshall, *Proc. Roy. Soc.* (*London*), **108**, 130 (1931).

(8) German Patent 615,184 (I. G. Farbenindustrie) (1935).

(9) Fourneau, Tréfouel and Benoit, *Ann. Inst. Pasteur*, **44**, 719 (1930).

(10) Buchman and Hamilton, THIS JOURNAL, **64**, 1357 (1942).

(11) Magidson and Rubtsov, *J. Gen. Chem.* (*U. S. S. R.*), **7**, 1896 (1937); *Chem. Abst.*, **32**, 564 (1938).

(12) Zerweck and Kunze, U. S. Patent 2,086,691 (July 13, 1937); German Patent 615,184 (June 28, 1935); British Patent 437,137 (Oct. 28, 1935).

(13) Narang and Ray, *J. Chem. Soc.*, 976 (1931).

TABLE I

REACTION OF 2-CHLOROQUINOLINE WITH ALKYL AND DIALKYLAMINES

Amine	Yield, %	Product[a] M. p. or b. p., °C.	Mm.	Picrate[b] M. p., °C.	Formula	Analyses,[c] % Calculated Carbon	Calculated Hydrogen	Found Carbon		Found Hydrogen	
Dimethyl-[d]	90	70.5–71[l]		215–217	$C_{11}H_{12}N_2$	76.69	7.02	76.68	76.75	7.00	7.07
Diethyl-[e]	30	154–155	4	184–185	$C_{14}H_{19}N_2I$	49.1	5.6	49.34	49.21	5.73	5.71
Di-*n*-propyl-[f]	60	140–145	2	188–190.5	$C_{16}H_{23}N_2I$	51.9	6.26	51.52	51.8	6.29	6.31
Di-*n*-butyl-[g]	60	155–157	2	176–178	$C_{18}H_{27}N_2I$	54.28	6.83	54.27	54.09	6.73	6.65
Di-*n*-amyl-[h]	57	165–167	2	180–185	$C_{20}H_{31}N_2I$	56.33	7.33	55.87	55.8	7.28	7.2
Monomethyl-[i]	98	71–71.5		228–230							
Mono-*n*-propyl-[j]	60	78–78.5									
		140–145	3	196–196.5	$C_{12}H_{14}N_2$	77.38	7.58	77.03	76.92	7.50	7.46
Piperidine[k]	98	49–50		173–176	$C_{14}H_{16}N_2$	79.21	7.6	79.36		7.62	

[a] Where no pressure is given, the value is for the m. p. [b] Recrystallization generally from ethyl alcohol or methyl isobutyl ketone. [c] Analyses on the methiodide derivative or free base by Huffman Microanalytical Laboratories, Denver, Colorado. [d] Sealed tube heated six hours at 90°. *Anal.* Calcd.: N, 16.22. Found: N, 16.31. [e] Sealed tube heated eighteen hours at 120°. [f] Reaction in ground glass apparatus refluxed at 111° for two hours. [g] Reaction in ground glass apparatus refluxed at 160° for four hours. [h] Refluxed at 205° for four hours. [i] Sealed tube heated for six hours at 100°. See Bergstrom, *Chem. Rev.*, **35** 177 (1944). [j] Sealed tube heated for seven hours at 130°. The reaction with isopropylamine was poor; approximately 10% yield of 2-isopropylaminoquinoline was obtained identified only by its gold salt. [k] Sealed tube heated at 100° for one hour; base recrystallized from aqueous alcohol after vacuum distillation at 130–135°, 0.4–0.45 mm. [l] See reference 8.

TABLE II

DERIVATIVES OF 2-ALKYLAMINO- AND 2-DIALKYLAMINOQUINOLINES

Quinoline derivatives	Monomethiodide[a] M. p., °C.	% Iodine[b] Calcd.	Found		Monohydrochloride[c] M. p., °C.	Neutral equiv.[d] Calcd.	Found		Platinum salt[e] M. p., °C.	% Platinum Calcd.	Found	
2-Dimethylamino-	197–197.5	40.41	40.43	40.12	232–234	208.6	210.6					
2-Diethylamino-	195–195.5	37.1	36.71	36.78	169–170.5[i]	236.6	235.4	235.9				
2-Di-*n*-propylamino-	160.5–161	34.78	33.87	34.32	145–146	264.8	265.3	266.1				
2-Di-*n*-butylamino-	151.5–152	31.87	31.87	31.95	(Oil)							
2-Di-*n*-amylamino-	136–137.5								192–194	19.59	19.23	19.62
2-Monomethylamino-[g]	195–196[h]								199–200[f]	39.56	39.54	39.45
2-Monopropylamino-	249–250	38.67	38.46	38.86					198–198.5	24.45	24.82	24.88
2-Piperidino-									198.5–199.5			

[a] Monomethiodides were all formed by treating the 2-alkylamino- or di-alkylaminoquinoline with excess methyl iodide in a sealed tube at 100°. [b] Quantitative determination of percentage iodine made according to method of Willard and Furman, "Elementary Quantitative Analyses," 3rd ed., Van Nostrand Co., New York, N. Y., 1940, p. 320. [c] Hydrochlorides generally recrystallized from isopropyl alcohol or methyl isobutyl ketone, followed by drying over phosphorus pentoxide in a vacuum desiccator. [d] The neutral equivalent determined by dissolving sample in neutralized alcohol and titrating with standardized sodium hydroxide using phenolphthalein as indicator. [e] Calculated as $PtCl_6 \cdot 2$ Base. [f] Gold salt, per cent. gold calculated on the basis of $C_{10}H_{10}N_2 \cdot HAuCl_4$. [g] The positional isomer 4-methylaminoquinoline was prepared by treating 4-chloroquinoline with methylamine in a sealed tube heated at 100° for five hours. The purified compound melted at 227–227.5°, 96% yield. The compound sublimes readily; the picrate recrystallized from alcohol gives m. p. 249–250°. *Anal.* Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37. Found: C, 76.04; H, 6.15. The methiodide recrystallized from methyl isobutyl ketone, m. p. 310°. [h] Roser, ref. 6, reports a hydrate melting at 160°. [i] Fourneau, *et al.*, ref. 9, reported the m. p. as 165–170° after decomposition at about 155°.

it is the ring nitrogen which forms the quaternary salt is indicted by the fact that both 2-aminoquinoline methiodide and 2-dimethylaminoquinoline methiodide are converted to 1-methyl-2-quinolone by boiling in aqueous alkaline solution.[7]

Summary

1. A series of 2-dialkylaminoquinolines and 2-alkylaminoquinolines has been prepared by heating 2-chloroquinoline with the corresponding anhydrous amine in a sealed tube. 4-Methylaminoquinoline was obtained from 4-chloroquinoline in a similar manner.

2. Only monomethiodides and monohydrochlorides could be formed from these quinoline bases. The platinum, gold, and picrate derivatives are described for a number of compounds of this series.

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