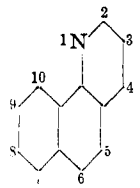
[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Some Derivatives of Benzo[h]quinoline

BY WILLIAM P. UTERMOHLEN, JR.,[1,2] AND CLIFF S. HAMILTON

In recent years, it has been found that a number of quinoline derivatives—plasmoquine, atebrin and certain quinolines and benzoquinolines substituted in the 2- and 4-positions with dialkylaminoalkylamino side chains[3,4]—possess a sufficiently strong antimalarial action to justify their therapeutic use. Therefore, it seemed desirable to investigate the synthesis of analogous compounds, containing a dialkylaminoalkylamino side chain attached to the 2- or 4-position of the benzo[h]quinoline nucleus.

Because of the existence of several conflicting systems of nomenclature among these types of compounds, the term "benzo[h]quinoline" as used here should be defined as referring to the benzoquinoline derived from 1-naphthylamine, and whose ring system is numbered as shown:



6-Bromobenzo[h]quinoline was prepared in fair yield from 4-bromo-1-naphthylamine, and 6-nitro- and 7-nitro-benzo[h]quinolines were prepared in poor yield from 4-nitro- and 5-nitro-1-naphthylamines, respectively, by means of the Skraup reaction. Application of the same reaction to 8-nitro-1-naphthylamine was entirely unsuccessful. The 7-nitro isomer is probably identical with one of the principal mono-nitro-benzo[h]quinolines obtained by Haid[5] from the nitration of benzo[h]-quinoline. These poor yields may be attributed in part to the inhibitory action of the nitro group, as both 4-bromo-1-naphthylamine (this work) and 8-chloro-1-naphthylamine (Adams and Steele)[6] give fair yields of the corresponding benzo[h]quinoline in the Skraup type synthesis.

2-Chloro-4-methyl- and 4-chloro-2-methylbenzo[h]quinolines were condensed with ethanolamine, piperidine, and morpholine to give the corresponding mono-quinolylamino derivatives. Condensations were also effected with β-hydroxyethylethylenediamine, but products in the desired state of purity could not be isolated. Condensations of these chlorobenzo[h]quinolines were not successful with *p*-arsanilic acid (probably due to the lack of a sufficiently reactive halogen atom[7]), with *p*-phenylenediamine, or with 2-methyl-2-aminopropanol-1 (85% solution). The reaction of chlorinating agents with the ethanolamine condensation products yielded 2-methyl-4-β-chloroethylamino-benzo[h]quinoline and 4-methyl-2-ethylidineaminobenzo[h]quinoline (dehydration in the side chain, followed by a hydrogen shift to give a bright yellow ethylidine type compound).

γ-N-Morpholino- and γ-diethylaminobutyronitriles, and β-N-morpholino- and β-diethylaminopropionitriles were prepared by condensations of morpholine and diethylamine with the proper chloronitrile. δ-Diethylamino- and δ-N-morpholino-butylamines were obtained in 50–60% yields by reduction of the corresponding nitriles with sodium and alcohol, according to the method reported for the preparation of 6-diethylamino-1-aminohexane.[8] γ-Diethylamino- and γ-N-morpholinopropylamines could not be prepared by this method, however, and therefore were synthesized by the more laborious Gabriel phthalimide type synthesis.[8,9] Diethylaminoacetonitrile likewise could not be reduced successfully with sodium and alcohol to the corresponding diamine. It would appear that the longer the alkyl chain between the amino and the nitrile groups, the better are the yields of diamine prepared by this method of reduction.

Condensations of 2-methyl-4-chloro- and 4-methyl-2-chloro-benzo[h]quinolines with the above four diamines yielded eight new dialkylaminoalkylamino-benzo[h]quinolines, which by analogy with previously reported compounds[3,4] should possess antimalarial properties. Their biological action is now being studied. 2-Methyl-4-chloro-benzo[h]quinoline and γ-N-morpholino-

(1) Parke, Davis and Company Fellow.

(2) Present address: Research Laboratories, Tennessee Eastman Corporation, Kingsport, Tennessee.

(3) I. G. Farbenindustrie A.-G., B.P. 481, 874.

(4) Magidson and Rubtzov, *J. Gen. Chem.* (U. S. S. R.), **7**, 1896, (1937); *Chem. Abs.*, **32**, 564 (1938).

(5) Haid, *Monatsh.*, **27**, 318 (1906).

(6) Adams and Steele, THIS JOURNAL, **52**, 4528 (1930).

(7) *Cf.* Slater, *J. Chem. Soc.*, 109 (1931).

(8) Magidson and Grigorowsky, *Ber.*, **69B**, 396 (1936).

(9) Shriner and Hickey, THIS JOURNAL, **61**, 888 (1939).

propylamine gave a di-quinolylamine, α-N-morpholino-γ-bis-(2-methyl-4-benzo[h]quinolyl)-aminopropane, instead of the mono-quinolylamine type of product obtained in the other seven similar reactions. An exactly analogous case already has been reported.[4]

The substitution of the morpholine ring for a dialkylamino group in antimalarial drugs has been studied but little. It is not to be expected that this grouping as such should have any particular effect, but it is possible that the ether linkage in the ring might serve to increase the solubility of the morpholine derivative in lipoids and so affect its antimalarial activity.

4-Bromo-1-naphthylamine was also condensed with acetoacetic ester to yield ethyl β-(4-bromo-1-naphthylamino)-crotonate. From this, 2-methyl-4-hydroxy-6-bromo- and 2-methyl-4-chloro-6-bromo-benzo[h]quinolines were synthesized by standard procedures.

Acknowledgment for assistance is due to Mr. Cliff M. Hollenbeck for performing the Kjeldahl analyses reported in this paper, and to Mr. E. J. Cragoe, Jr., for the preparation of β-chloro- and β-diethylamino-propionitriles.

Experimental

Nitrobenzo[h]quinolines.—4-Nitro-1-naphthylamine (10 g.), sirupy arsenic acid (10.5 g.), glycerol (25 g.), and acetic acid (25 ml.) were mixed together and heated in an oil-bath to 110°. Concentrated sulfuric acid (11 ml.) was added slowly, and the mixture was refluxed gently (120°) for ten hours, poured into water, and allowed to stand overnight. The tar and charcoal was filtered from the hot solution. A brownish-yellow solid separated from the filtrate upon cooling and addition of alkali. Two recrystallizations from ethyl alcohol, and one from a methanol–water mixture, gave 6-nitrobenzo[h]quinoline as a fluffy, light yellow product, in the form of fine needles, m. p. 149° (0.25 g.). Other modifications of the Skraup reaction, when applied to this amine, gave no product at all. *Anal.* Calcd. for $C_{13}H_8O_2N_2$: C, 69.6; H, 3.57. Found: C, 69.5; H, 3.62.

To a mixture of ferrous sulfate (1.5 g.) and 5-nitro-1-naphthylamine (7.0 g.) was added glycerol (13.5 g.) in which boric acid (4.5 g.) had been previously dissolved. Next, sirupy arsenic acid (10 g.) and finally concd. sulfuric acid (7.5 ml.) were added, the latter slowly and with stirring. The mixture was heated under reflux in an oil-bath at 140° for twelve hours, then poured into water and allowed to stand overnight. The suspension was warmed and filtered while hot, and the filtrate was discarded. Extraction of the residue with three successive portions (50 ml. each) of alcohol removed the crude 7-nitrobenzo-[h]quinoline. Alcohol recrystallization gave white feathery needles, m. p. 174.5–175° (0.3 g.). *Anal.* Calcd. for $C_{13}H_8O_2N_2$: C, 69.6; H, 3.57. Found: C, 69.6; H, 3.58.

6-Bromobenzo[h]quinoline.—Crude 4-bromo-1-naphthylamine (37 g.), sirupy arsenic acid (30 g.), and glycerol (90 g.) were mixed together and concd. sulfuric acid (57 g.) added dropwise with stirring. The mixture was heated in an oil-bath for one hour at a temperature gradually increasing from 95 to 125°, and then at 135° for six hours. The heating had to be controlled carefully during the early part of the reaction, as too sudden a temperature rise produced much foaming. The mixture was poured into cold water, allowed to stand overnight, and filtered. The cold filtrate upon basification yielded crude 6-bromobenzo[h]quinoline, purified by recrystallization from ligroin and from alcohol, from which it appeared as white fluffy needles, m. p. 115.5–116° (5 g.). *Anal.* Calcd. for $C_{13}H_8NBr$: Br, 30.97. Found: Br, 30.92.

Hydroxybenzo[h]quinolines.—4-Hydroxy-2-methylbenzo[h]quinoline was synthesized by the method of Limpach,[10] using a few drops of 6 *N* hydrochloric acid to catalyze the condensation between 1-naphthylamine and acetoacetic ester. Molar quantities of 4-bromo-1-naphthylamine and acetoacetic ester were condensed in the same fashion to yield ethyl β-(4-bromo-1-naphthylamino)-crotonate, which was recrystallized from alcohol–water to give a voluminous, light lavender solid, m. p. 113–114°, 51% yield. *Anal.* Calcd. for $C_{16}H_{16}O_2NBr$: N, 4.19. Found: N, 4.23. This ester when cyclized by the Limpach method yielded 4-hydroxy-2-methyl-6-bromobenzo[h]-quinoline, a lavender, amorphous solid, m. p. above 270° (60% yield). Methanol crystallization gave a pure white compound. *Anal.* Calcd. for $C_{14}H_{10}ONBr$: N, 4.85. Found: N, 4.80.

Chlorobenzo[h]quinolines.—From 2-methyl-4-hydroxybenzo[h]quinoline and from 4-methyl-2-hydroxybenzo[h]quinoline (Union Carbide and Carbon Co. product), the corresponding chlorobenzo[h]quinolines were prepared by reaction with phosphorus pentachloride in tetrachloroethane solution.[11] The yields were about 50% after recrystallization from alcohol. 2-Methyl-4-chloro-6-bromobenzo[h]quinoline was obtained from the corresponding hydroxy compound by the action of phosphorus pentachloride and phosphorus oxychloride.[12] Alcohol recrystallization gave fine white crystals, m. p. 146.5–147° (yield 25%). *Anal.* Calcd. for $C_{14}H_9NBrCl$: N, 4.57. Found: N, 4.41.

Aliphatic Aminonitriles.—β-Chloropropionitrile (20 g.) (one mole) was poured into diethylamine or morpholine (50 g.) (2 + moles) in small portions, to yield a precipitate of diethylamine or morpholine hydrochloride and solution containing the desired aminonitrile. The mixture had to be cooled due to the heat liberated by the reaction. The hydrochloride was filtered off and washed with ether. The combined filtrate and washings were fractionated under reduced pressure from a Claisen flask. Two fractionations gave the product in a pure form. γ-Chlorobutyronitrile was treated with diethylamine or morpholine in the same fashion, except that the reaction mixture was gently refluxed for eighteen hours, to give the corresponding aminobutyronitriles. The properties and analyses of these and the following liquid compounds are shown in Table I.

(10) Limpach, *Ber.*, **64B**, 969 (1931).

(11) Gibson, Hariharan, Menon and Simonsen, *J. Chem. Soc.*, 2247 (1926).

(12) Fischer, Diepolder and Wölfel, *J. prakt. Chem.*, **109**, 59 (1925).

TABLE I

ALIPHATIC AMINO COMPOUNDS AND PROPERTIES

	Name	B. p., °C.	Mm.	Yield, %	Sp. gr., d^{25}_4	$n^{25}D$	Formula	Mol. refractivity Calcd.	Mol. refractivity Found	Elem.	Analyses Calcd.	Analyses Found
1	β-Diethylamino-propionitrile	83.5–84.5	13	56	0.8761	1.4343	$C_7H_{14}N_2$	38.27	37.54	N	22.22	21.94
2	β-N-Morpholino-propionitrile	133–134	14	77	1.0375	1.4700	$C_7H_{12}ON_2$	37.85	37.71	N	20.00	19.83
3	γ-Diethylamino-butyronitile	91–100	14	69	0.8601	1.4353	$C_8H_{16}N_2$	42.87	42.56	C	68.57	68.38
4	γ-N-Morpholino-butyronitrile	142	15	55	1.0031	1.4648	$C_8H_{14}ON_2$	42.46	42.47	H	11.43	11.43
										N	18.18	18.27
5	γ-N-Morpholino-propylamine	103–105	15	26	0.9991	1.4755	$C_7H_{16}ON_2$	41.46	40.68	N	19.44	19.23
6	δ-Diethylamino-butylamine	85–86	16	50	.8331	1.4420	$C_8H_{16}N_2$	46.48	44.76	C	66.67	66.70
7	δ-N-Morpholino-butylamine	123–125	15	57	.9804	1.4720	$C_8H_{16}ON_2$	46.05	45.19	H	13.89	13.74
										N	17.72	17.48

TABLE II

BENZO[H]QUINOLYLAMINO—COMPOUNDS AND PROPERTIES

	-Benzo[h]quinoline	Description	M. p., °C.	Yield, %	Formula	Element	Analyses, % Calcd.	Analyses, % Found
1	2-N-Morpholino-4-methyl-	White needles	101.5	45	$C_{18}H_{18}ON_2$	N	10.07	9.85
2	4-N-Morpholino-2-methyl-	White needles	127.5	50	$C_{18}H_{18}ON_2$	N	10.07	9.98
3	2-β-Hydroxyethylamino-4-methyl-	White needles	108	50	$C_{16}H_{16}ON_2$	N	11.10	10.98
4	4-β-Hydroxyethylamino-2-methyl-	White, diamond-shaped crystals	181–181.5	55	$C_{16}H_{16}ON_2$	N	11.10	10.86
5	2-N-Piperidino-4-methyl-	White crystals	79–80	30	$C_{19}H_{20}N_2$	N	10.15	9.98
6	4-β-Chloroethylamino-2-methyl-	Long white needles	83–84	40	$(C_{16}H_{15}N_2Cl)_2 \cdot CH_3OH$	Cl	12.38	12.35
7	2-Ethylidineamino-4-methyl-	Bright yellow amorphous solid	184.5–186.5d	50	$C_{16}H_{14}N_2$	N	11.95	11.86
8	2-Methyl-4-γ-diethylaminopropyl-amino-	Cream colored solid	84–85	22	$C_{21}H_{27}N_3$	N	13.08	12.94
9	4-Methyl-2-γ-diethylaminopropyl-amino-	Brown fluorescent oil	B. p. 275–280 (5 mm.)	69	$C_{21}H_{27}N_3$	N	13.08	13.02
10	2-Methyl-4-δ-diethylaminobutyl-amino-	Cream colored solid	98–100	26	$C_{22}H_{29}N_3$	N	12.53	12.45
11	4-Methyl-2-δ-diethylaminobutyl-amino-	Brown fluorescent oil	B. p. 240–245 (2 mm.)	62	$C_{22}H_{29}N_3$	N	12.53	12.50
12	2-Methyl-4-δ-N-morpholinobutyl-amino-	Cream colored solid	110–112	28	$C_{22}H_{27}ON_3$	N	12.03	11.87
13	4-Methyl-2-δ-N-morpholinobutyl-amino-	Brown fluorescent oil	B. p. 285–290 (4 mm.)	61	$C_{22}H_{27}ON_3$	N	12.03	11.87
14	4-Methyl-2-γ-N-morpholinopropyl-amino-	Cream colored solid	83–84	57	$C_{21}H_{25}ON_3$	N	12.53	12.33
15	α-N-Morpholino-γ-bis-(2-methyl-4-benzo[h]quinolyl)-aminopropane	White crystals	151–152.5	38	$C_{35}H_{34}ON_4$	N	10.97	10.89

Aliphatic Diamines.—δ-Diethylamino- and δ-N-morpholino-butylamines were prepared by reduction of the corresponding nitriles, using sodium in an alcohol–toluene solution, following the general procedure of Magidson and Grigorowsky.[8] γ-Diethylamino- and γ-N-morpholino-propylamines were prepared by means of the Gabriel phthalimide type synthesis as directed by Shriner and Hickey,[9] except that the hydrolysis of the intermediate phthalimide compound was carried out with 10 *N* hydrochloric acid instead of the dilute acid used by the above authors. The morpholine hydrobromide by-product from the latter of these syntheses was recrystallized twice from alcohol, to give beautiful white needles, m. p. 214–215°. *Anal.* Calcd. for $C_4H_{10}ONBr$: N, 8.33. Found: N, 8.36.

All of these aliphatic aminonitriles and diamines were water-white liquids, with strong ammoniacal odors.

Alkylaminobenzo[h]quinolines.—A mixture of one of the two chloromethylbenzo[h]quinolines (10 g.) and ethanolamine (40 g.) was gently refluxed for eight hours, and the clear solution poured into an excess of water. A gum formed, which changed to a solid upon standing. Recrystallization from methyl or ethyl alcohol gave the product in a pure form. A similar procedure using the

chloromethylbenzo[h]quinoline (one part) and morpholine (two parts), gave the corresponding N-morpholinobenzo-[h]quinolines. When piperidine and 4-methyl-2-chlorobenzo[h]quinoline were refluxed together for two hours, the mixture treated with dilute sodium hydroxide solution, the basic solution extracted with ether, and the ether solution distilled, crude 4-methyl-2-N-piperidinobenzo-[h]quinoline was obtained. Treatment with hot 5% hydrochloric acid dissolved this product, leaving as a solid some less basic unreacted chloroquinoline. Filtration, basification of the filtrate, and methanol recrystallization of the precipitate gave a pure substance.

2-Methyl-4-β-chloroethylaminobenzo[h]quinoline was made by refluxing the corresponding hydroxy compound (3 g.) with phosphorus oxychloride (15 ml.) for three hours. The excess oxychloride was removed by distillation, and the residue poured into cold water. The solid product so obtained was a hydrochloride salt which upon treatment with alkali and recrystallization from methanol yielded the amine (containing methanol of crystallization, as evidenced by a low m. p. with evolution of vapor and by a halogen analysis). The free amine without alcohol of crystallization was obtained by ethanol–water recrystallization, and melted at 153°.

4-Methyl-2-β-hydroxyethylaminobenzo[h]quinoline (4.5 g.) and thionyl chloride (5 ml.) reacted violently when placed together. After being warmed for a short time, the mixture was poured into water. Neutralization with alkali gave a gummy solid, which after warming with more dilute alkali solution was free from halogen. Upon recrystallization from alcohol–water, followed by solution in dilute hydrochloric acid, filtration, and reprecipitation with base, a bright yellow material, 4-methyl-2-ethylidineaminobenzo[h]quinoline, was obtained. Its solutions in dilute acid were colorless.

These and the following aminobenzoquinoline compounds are listed in Table II, together with their properties and analyses.

Dialkylaminoalkylaminobenzo[h]quinolines.—The chloromethylbenzo[h]quinoline (two parts by weight, one mole) and the diamine such as γ-diethylaminopropylamine (three parts, 2 + moles) were mixed together in a Pyrex test-tube equipped with an air condenser, and the whole was gently refluxed (170–200°) for eight hours in an oil-bath. The reaction mixture was cooled and dissolved in 10% hydrochloric acid; after filtration from any insoluble matter, the filtrate was made strongly alkaline with ammonium hydroxide. The crude product separated as a gummy brown oil, which was extracted from the aqueous layer with ether. The ether solution was dried with anhydrous potassium carbonate, the ether evaporated with an air jet, and the residue placed in a vacuum desiccator for a day. If the crude product was still an oil, it was purified by vacuum distillation. If it had become a solid, it was dissolved in alcohol, boiled with charcoal, filtered, and reprecipitated by the careful addition of water; then it was recrystallized twice from ether, discarding the most ether-soluble gummy fraction. α-N-Morpholino-γ-bis-(2-methyl-4-benzo[h]quinolyl)-aminopropane was recrystallized twice from alcohol, and the ether crystallization was omitted.

All of these dialkylaminoalkylaminobenzo[h]quinolines displayed a strong greenish-yellow fluorescence in ether and in alcohol solutions, and a blue fluorescence in dilute hydrochloric acid solutions. They were either viscous brown oils with a green fluorescence, or cream-colored amorphous solids.

Summary

1. Several new benzo[h]quinolines have been obtained by application of the Skraup and Conrad–Limpach reactions to derivatives of 1-naphthylamine.

2. Four dialkylaminoalkylamines have been prepared through dialkylaminonitrile or dialkylaminoalkylaminoalkyl phthalimide intermediates.

3. Condensations have been effected between 2- and 4-chloro-benzo[h]quinolines and a number of amines, including the above diamines, to yield two series of new alkylaminobenzo[h]quinolines, some of which are closely analogous in structure to previously reported compounds possessing antimalarial properties.

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