sodium nitrite in 30 cc. of water at 0°. Then to the clear solution was added 15 g. of 50% hypophosphorous acid, and the solution was allowed to stand in an ice box for twenty hours. After making basic with sodium hydroxide, the mixture was extracted[5] with ether, the ether was removed by distillation, and the residue was dissolved in a solution of 70 cc. of benzene and one cc. of acetic anhydride. After removing some benzene and adding some petroleum ether (b. p. 60–68°), 4 g. (43%) of product melting at 130–132° was obtained. Recrystallization from a mixture of benzene and absolute ethanol gave an analytical sample melting at 133–134°.

Anal. Calcd. for $C_{12}H_{12}ON_2S$: N, 12.05; S, 13.74. Found: N, 12.26; S, 13.79.

From another deamination (of 22 g. or 0.089 mole of the amine) in which chloroform and ether were used in the extraction[5] the yield of product melting at 123–128° was 13 g. (65%). This material was hydrolyzed by refluxing for twenty minutes with 100 cc. of concd. hydrochloric acid. Neutralization and extraction with a large volume of benzene gave 8 g. (47%) of amine distilling at 152–153° (0.7 mm.), and melting at 76–78°. The same **8-amino-6-quinolyl methyl sulfide** was obtained by hydrochloric acid hydrolysis of some pure 8-acetamino-6-quinolyl methyl sulfide.

Anal. Calcd. for $C_{10}H_{10}N_2S$: N, 14.72. Found: N, 14.92.

In some subsequent preparations the acetamino compound was not isolated. Instead the chloroform and carbon tetrachloride (the mixture used in the later extractions) was removed, and the residue was hydrolyzed by 1:1 hydrochloric acid to give 51% of 8-amino-6-quinolyl methyl sulfide distilling at 143–145°(0.4 mm.) and melting at 78° (with softening at 74°).

5,8-Diacetamino-6-quinolyl Methyl Sulfide.– This diacetamino compound, prepared in benzene from 5-amino-8-acetamino-6-quinolyl methyl sulfide and acetic anhydride, melted at 242–248°.

Anal. Calcd. for $C_{14}H_{15}O_2N_3S$: N, 14.50. Found: N, 15.0 and 15.0.

8-(γ-Diethylaminopropylamino)-6-quinolyl Methyl Sulfide, Dihydrochloride. –Four grams of 8-amino-6-quinolyl methyl sulfide (0.021 mole), 3.75 g. (0.025 mole) of freshly distilled γ-diethylaminopropyl chloride and 5.4 g. (0.02 mole) of sodium citrate were added to 25 cc. of commercial absolute ethanol and the mixture was refluxed for forty-eight hours. It was then cooled, poured into 250 cc. of water, and made strongly basic with solid sodium hydroxide. The solution was extracted with ether, and after drying the ether layer over sodium sulfate it was filtered. Ethanolic hydrogen chloride was added to precipitate a yellow dihydrochloride. After several recrystallizations from a 95% ethanol–ether mixture, 3.0 g. (38%) of yellow needles were obtained melting at 214–218° in a rapidly heated bath, but with some preliminary softening. The analytical sample melted at 217–220°.

Anal. Calcd. for $C_{17}H_{25}N_3S.2HCl$: Cl, 18.9; S, 8.5. Found: Cl, 18.8; S, 8.3.

(5) The extractions were somewhat tedious due to the emulsions nd the large quantity of solvent needed.

Summary

In connection with studies on experimental avian malaria, 8-(γ-diethylaminopropylamino)-6-quinolyl methyl sulfide has been prepared. This compound is a sulfur analog of plasmocid.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Synthesis of 1-Alkylamino-4-bromopentane Derivatives and of Other Amino Halides[1]

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In a subsequent paper[2] the synthesis of a number of 8-(substituted aminoalkylamino)-quinoline derivatives is described. In the present paper we wish to present a description of the syntheses used for the preparation of the intermediate aminoalkyl halides required for the 8-aminoquinoline derivatives. The majority of the amino halides fall into two main structural groups, namely, those represented by the type formulas

$$X(CH_2)_nN\begin{matrix}R_1\\R_2\end{matrix} \quad \text{and} \quad CH_3CHBrCH_2CH_2CH_2NHR$$

I II

Variations in group I involved for the most part changes in R_1, representing an alkyl group, while R_2 remained constant as hydrogen, in the cases where $n = 3$ and 6. Bromides with $n = 5$ and 7 and $R_1 = R_2$ = ethyl were also prepared. Variations in group II involved variations of R.

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

(2) Elderfield, *et al.*, THIS JOURNAL, **68**, 1584 (1946).

For the synthesis of 3-*n*-propylamino-1-chloropropane advantage was taken of the greater reactivity of the bromine as compared to the chlorine in trimethylene chlorobromide,[3] and the desired aminochloride was thus prepared by condensation of trimethylene chlorobromide with *n*-propylamine. A similar synthesis with isopropylamine did not give favorable results, so that 3-isopropylamino-1-chloropropane was prepared by reaction of isopropylamine with trimethylene bromohydrin followed by replacement of the hydroxyl group in the intermediate 3-isopropylaminopropanol-1 by chlorine.

The general method used for preparing the aminohalides of Type I where $n = 5$, 6, and 7, R_1 is an alkyl group and R_2 is an alkyl group or hydrogen was based on a reaction originally used by Clarke[4] and extended by Drake, *et al.*,[5] for the synthesis of 6-diethylamino-1-bromohexane according to the following equations

(3) Drake *et al.*, *ibid.*, **68**, 1540 (1946).

(4) Clarke, *J. Chem. Soc.*, **103**, 1689 (1913).

(5) Drake, *et al.*, THIS JOURNAL, **68**, 1536 (1946).

$$CH_3O(CH_2)_nBr + R_2NH \longrightarrow CH_3O(CH_2)_nNR_2 \xrightarrow{HBr} Br(CH_2)_nNR_2$$

Alkylaminohexyl bromides containing methyl-, *n*-propyl- and isopropylamino and piperazyl groups in the terminal position have been prepared. As far as we can determine, the preparation of 5-diethylaminopentyl bromide has not been described, although its condensation product with 6-methoxy-8-aminoquinoline appears in the literature.[6] In the present work, it has been prepared from pentamethylene glycol by the same method as were the analogous hexyl compounds. Although it was impossible to obtain an analytically pure derivative of 5-diethylamino-1-bromopentane, the fact that its condensation product with 6-methoxy-8-aminoquinoline was pure[2] is strong evidence that the aminobromide was actually in hand. 7-Diethylamino-1-bromoheptane has been previously prepared by an alternate route.[7,8]

The usual method for the preparation of amino halides of type II in which a terminal tertiary amino group is present, as typified by the familiar 1-diethylamino-4-bromopentane, the intermediate required for manufacture of Pamaquine (Plasmochin), involves reaction of 1-chloropentanone-4 with diethylamine followed by reduction of the ketone group to hydroxyl and conversion of the resultant 1-diethylaminopentanol-4 to the halide. The corresponding reaction with a primary amine does not proceed in the above sense. In the case of the reaction of 1-bromopentanone-4 with a primary amine, such as ethyl or butyl amine, ring closure takes place with the formation of 1-alkyl-2-methyl-Δ^2-pyrrolines.[9,10,11] It has now been noted that the reaction of 1-chloropentanone-4 with a primary amine, isopropylamine, does not follow the course of either of the above reactions. Rather, the product is a viscous basic oil, presumably of polymeric nature.

For the synthesis of 1-amino-4-bromopentane derivatives containing a primary or secondary amino group we have utilized the series of reactions

$$CH_3COCH_2CH_2CH_2Cl \xrightarrow{Al(OisoPr)_3} \underset{III}{CH_3COCH_2CH_2CH_2Cl}$$

$$CH_3CHOHCH_2CH_2CH_2Cl + RNH_2 \longrightarrow \underset{IV}{CH_3CHOHCH_2CH_2CH_2NHR} \xrightarrow{SOBr_2} CH_3CHBrCH_2CH_2CH_2NHR$$

1-Chloropentanone-4 (III) was reduced smoothly to 1-chloropentanol-4 (IV) with aluminum isopropoxide provided conditions were so set that the reduction was completed as rapidly as possible. Catalytic reduction of III either with Raney nickel or platinum oxide resulted in the formation of 2-methyltetrahydrofuran exclusively. Ring closure of IV also occurred during the aluminum isopropoxide reduction to a certain extent, the amount of 2-methyltetrahydrofuran formed increasing with longer reaction times. IV is reasonably stable provided it is not heated unduly nor exposed to the action of mineral acids under either of which conditions ring closure takes place. Reaction of IV with ammonia or a primary amine yielded the amino carbinols which were converted to the bromides by the use of thionyl bromide. Use of hydrobromic acid for the preparation of the bromides or use of the more accessible thionyl chloride for preparation of the chlorides is not recommended for reasons set forth in an accompanying paper.[12] The amino-bromides thus prepared are summarized in Table II.

At the time this work was undertaken some doubt existed as to whether a 1-amino-4-bromopentane containing a primary or secondary amino group would couple with an 8-aminoquinoline without excessive pyrrolidine formation. Therefore as an alternate synthesis it was proposed to couple 1-acetoxy-4-chloro-(or bromo)-pentane with the 8-aminoquinoline and subsequently introduce the terminal amino group. While this approach proved to be unnecessary, the requisite 1-acetoxy-4-chloropentane was prepared. 1-Hydroxypentanone-4, prepared by an improvement of the procedure of Knunyantz, Chelintzev and Osetrova[13] was readily acetylated to 1-acetoxypentanone-4. This on reduction with Raney nickel gave 1-acetoxypentanol-4, from which the chloride was prepared with thionyl chloride.

In order to ascertain the effect on antimalarial action of a branch in the side chain in a substance of the Pamaquine type at the 4-carbon atom rather than at the 1-carbon atom, two aminobromides V and VI were prepared. The method

$$CH_3CH[N(C_2H_5)_2]CH_2Cl + CH_3COCH_2COOC_2H_5 \longrightarrow CH_3COCHCOOC_2H_5$$
$$\longrightarrow CH_2{-}CH[N(C_2H_5)_2]CH_3$$
$$CH_3COCH_2CH_2CH[N(C_2H_5)_2]CH_3 \xrightarrow{Ni} CH_3CHOHCH_2CH_2CH[N(C_2H_5)_2]CH_3 \xrightarrow{SOBr_2} \underset{V}{CH_3CHBrCH_2CH_2CH[N(C_2H_5)_2]CH_3}$$

used for preparing V is represented by the accompanying equations and needs no further comment. We were unable to secure a crystalline derivative of V, possibly due to the presence of two assymmetric centers. However, the condensation product of V with 6-methoxy-8-aminoquinoline[2] was satisfactory. VI was prepared by the reactions

(6) Fourneau, *et al.*, *Ann. Inst. Pasteur*, **50**, 731 (1933).

(7) Magidson, Madaeva and Rubtsov, *J. Gen. Chem.* (U. S. S. R.), **5**, 1506 (1935); *Arch. Pharm.*, **273**, 320 (1935).

(8) Altman, *Rec. trav. chim.*, **57**, 941 (1938).

(9) Adams and Mahan, THIS JOURNAL, **64**, 2588 (1942).

(10) Hielscher, *Ber.*, **31**, 277 (1898).

(11) Markwalder, *J. prakt. Chem.*, N. F., **75**, 329 (1907).

(12) Elderfield, *et al.*, THIS JOURNAL, **68**, 1516 (1946).

(13) Knunyantz, Chelintzev and Osetrova, *Compt. rend. acad. sci.* (U. S. S. R.) [H. S.], **1**, 312 (1934).

$$CH_3OCH_2CH_2CH_2MgCl + CH_3CH_2CHO \longrightarrow$$
$$CH_3CH_2CHOHCH_2CH_2CH_2OCH_3 \xrightarrow{SOCl_2}$$
$$CH_3CH_2CHClCH_2CH_2CH_2OCH_3 \xrightarrow{C_2H_5NH_2}$$
$$CH_3CH_2CH(NHC_2H_5)CH_2CH_2CH_2OCH_3 \xrightarrow{HBr}$$
$$CH_3CH_2CH(NHC_2H_5)CH_2CH_2CH_2Br$$
VI

Several 8-aminoquinolines containing ω-(α-piperidyl)-alkylamino side chains, prepared by Bergstrom,[14] are characterized by undesirable toxicity.[15] In order to provide additional information as to the grouping responsible other than that furnished by the drugs derived from the halides noted above, 1-bromo-4-aminooctane was prepared by cleavage of the ether in 1-methoxy-4-aminooctane.[16]

Finally two amino halides containing oxygen functions, 3-(3'-diethylaminopropoxy)-1-chloropropane and 1-bromo-2-hydroxy-4-ethylaminobutane, were prepared. The synthesis of the former is represented by the reactions

$$HOCH_2CH_2CH_2ONa + ClCH_2CH_2CH_2N(C_2H_5)_2 \longrightarrow$$
$$HOCH_2CH_2CH_2OCH_2CH_2CH_2N(C_2H_5)_2 \xrightarrow{SOCl_2}$$
$$ClCH_2CH_2CH_2OCH_2CH_2CH_2N(C_2H_5)_2$$

The latter was made by the reaction of 1-ethylaminobutene-3 with N-bromoacetamide.

Experimental[17,18]

1-Chloropentanol-4.—In a 2-liter round-bottomed flask fitted with a still head, dropping funnel and water condenser set downward for distillation, was placed 750 ml. of 3 *M* aluminum isopropoxide solution in isopropyl alcohol (commercial absolute isopropyl alcohol [99%] was used without further drying). The solution was heated to boiling on the steam-bath, 120.5 g. (1 mole) of freshly distilled 3-acetylpropyl chloride (U. S. Industrial Chemicals, Inc., b. p. 78–79° (20 mm.)) was added and the mixture was distilled as rapidly as possible (2–3 drops per second). During the distillation fresh isopropyl alcohol was continuously added through the dropping funnel at a ratio which maintained the volume in the flask constant. The reaction was continued for forty to forty-five minutes. The solution was then concentrated at water pump vacuum on the steam-bath, removing as much isopropyl alcohol as possible in fifteen to twenty minutes. It is important that the reaction mixture at this stage and at all subsequent operations be subjected to as little heat as possible, since the product readily undergoes cyclization to 2-methyltetrahydrofuran with evolution of hydrogen chloride. The residue was poured with stirring into a mixture of 300 ml. of hydrochloric acid (sp. gr. 1.19) and 400 g. of cracked ice. If the temperature rises above 50°, addition of more ice is necessary. The solution was filtered and the filtrate was extracted with five 400-ml. portions of ether. The combined ether extracts were washed with five 100-ml. portions of saturated magnesium sulfate solution. The last washing should be neutral to litmus paper. The ether solution was dried over anhydrous magnesium sulfate, and the solvent was removed at the water pump, taking care that the temperature did not exceed 60°. This distillation should not require more than one and one-half to two hours. The residue was again dissolved in an equal volume of anhydrous ether, dried with anhydrous magnesium sulfate, and the solvent removed as before. The residue was transferred to a distilling flask equipped with a 10-cm. packed column and an efficient water cooled condenser and distilled under reduced pressure. After a fore-run of low boiling material, the chlorohydrin was collected at 66–68° (3 mm.) with a bath temperature of 80–85°. The yield was 88 g. (72%). Subsequent runs using 2.4 molar amounts gave yields of 70–76%. The chlorohydrin is not particularly stable and gradually undergoes ring closure to 2-methyltetrahydrofuran. For example, a 370-g. batch of chlorohydrin which stood at room temperature for four weeks yielded only 150 g. of chlorohydrin on redistillation. Therefore the chlorohydrin should be stored in the refrigerator and used for subsequent steps as soon as possible.

Anal. Calcd. for $C_5H_{11}ClO$: C, 49.0; H, 9.0; Cl, 28.8. Found: C, 49.5; H, 8.9; Cl, 27.5.

1-Chloro-4-acetoxypentane.—A mixture of 61 g. of 1-chloropentanol-4 and 102 g. of acetic anhydride chilled in ice was allowed to stand overnight. The reaction mixture was distilled directly yielding 67.5 g. (82%) of material boiling at 102–106° (30 mm.)., $n^{25}D$ 1.4309.

Anal. Calcd. for $C_7H_{13}ClO_2$: C, 51.1; H, 8.0. Found: C, 51.4; H, 7.9.

Amination of 1-Chloropentanol-4.—The following procedure is typical of that used for condensing 1-chloropentanol-4 with all amines except ammonia. A mixture of the appropriate amounts of chloride and amine was allowed to stand at room temperature. Excess amine was removed by distillation from the steam-bath and the residue was poured onto a mixture of ice and hydrochloric acid. The acid solution was extracted twice with ether for removal of unreacted chloride. The aqueous layer was saturated with potassium hydroxide with strong cooling in an ice-bath. The amino alcohol layer was separated and the aqueous suspension of potassium chloride was thoroughly extracted with ether. The combined amino alcohol and ether extracts were dried with potassium hydroxide and distilled from barium oxide.

In the case of the reaction with ammonia, the chloride was placed in the glass liner of an American Instrument Company bomb and the appropriate amount of liquid ammonia was drawn from a tank and slowly condensed in the bomb by cooling the latter in a solid carbon dioxide bath. The bomb was then sealed and the reaction allowed to proceed at room temperature and worked up as before.

The results of a number of experiments with various amines are summarized in Table I.

1-Amino-4-bromopentane Derivatives.—These were all prepared by adding one molar equivalent of thionyl bromide dropwise to a solution of the alcohol in dry benzene below 10° over three hours. After stirring at room temperature for an additional three hours, the solvent was removed and the residue was recrystallized from acetone–ether (1:1). (The melting points and analyses of the substances prepared are given in Table II.)

Thionyl Bromide.—The following preparation using tank hydrogen bromide represents a substantial improvement over the procedure given in the literature.[19] Anhydrous hydrogen bromide from a tank (Dow Chemical Company) dried by passing through a calcium chloride tube and at a pressure of six inches of tetrachloroethane (regulated by a safety trap) was passed for three hours into one kilo of commercial thionyl chloride (Hooker Electrochemical Company) contained in a flask equipped with a very efficient reflux condenser and a totally immersed thermometer. The temperature of the thionyl chloride was held at 0–10° by an ice–salt-bath. The crude product was distilled from the reaction flask the fraction boiling at 48–56° (20–25 mm.) being collected. This was redistilled through a ten-inch Vigreux column yielding 1564 g. (90%) of thionyl bromide boiling at 55° (27 mm.).

(14) Bergstrom, *et al.*, THIS JOURNAL, **68**, 1572 (1946).

(15) Antimalarial Drugs 1941–1945, published by the Survey of Antimalarial Drugs, in press.

(16) Menschikoff and Schdanowitsch, *Ber.*, **69**, 1799 (1936).

(17) All melting points are corrected.

(18) Microanalyses by the Misses Lois May and Lathrope Baker.

(19) "Inorganic Syntheses," McGraw-Hill Book Co., Inc., New York, N. Y., 1939, Vol. 1, p. 113.

TABLE I

AMINATION OF 1-CHLOROPENTANOL-4

Amine	Chloropentanol, moles	Amine, moles	Time of standing, days	Yield, %	B. p. °C.	Mm.	$n^{25}D$	Analyses, % Calcd. C	H	Neut eq.	Found C	H	Neut eq.
NH_3	0.79	13.5	4	32	80–81	1.0	1.4551	58.2	12.7	103	58.5	12.7	105
$C_2H_5NH_2$	0.46	2.31	4	45	108–109	20	1.4458	64.1	13.1	131	64.4	13.1	130
n-$C_3H_7NH_2$	1.74	5.5	5	55	82–84	5	1.4463	66.2	13.2	145	65.9	13.1	145
i-$C_3H_7NH_2$	0.84	2.54	7	53	111–113	16	1.4435	66.2	13.2	145	66.0	13.0	144
i-$C_4H_9NH_2$	1.88	5.64	7.5	55	122–124	20		67.9	13.3	159	68.0	13.4	161
t-$C_4H_9NH_2$	1.00	2.94	18	25	109–110	16	1.4417	[a]					

[a] Satisfactory analytical figures were not obtained on the aminocarbinol. The di-*p*-nitrobenzoyl derivative melted at 121–121.5° after recrystallization from alcohol. *Anal.* Calcd. for $C_{23}H_{27}N_3O_7$: C, 60.4; H, 6.0; N, 9.2. Found: C, 60.7; H, 6.1; N, 9.3.

TABLE II

1-AMINO-4-BROMOPENTANE HYDROBROMIDES

Amino group	M. p., °C.	Analyses, % Calcd. C	H	Found C	H
NH_2	[a]				
C_2H_5NH	147–148	30.5	6.2	30.5	6.3
n-C_3H_7NH	210–212	33.2	6.6	33.1	6.4
i-C_3H_7NH	150–152	33.2	6.6	33.0	6.8
i-C_4H_9NH	235–237	35.6	6.9	35.8	7.0
t-C_4H_9NH	179–180	35.6	6.9	35.3	7.0

[a] No satisfactory salt could be found to characterize this substance. Therefore it was used as obtained for coupling with 6-methoxy-8-aminoquinoline and the product thus obtained was pure.[2]

1-Hydroxypentanone-4.—This was prepared by an improvement of the procedure of Knunyantz, Chelintzev and Osetrova.[13] To 3 liters of 5% hydrochloric acid (9.85 moles) in a 5-liter round bottom flask equipped with a reflux condenser and warmed on the steam-bath was added 1 kg. (7.81 moles) of acetobutyrolactone.[20] The mixture was heated gently for two and one-half hours during which carbon dioxide was evolved. The solution was cooled, made slightly alkaline (*p*H 8) with potassium hydroxide, and saturated with ammonium sulfate. The red oil which separated was drawn off and the aqueous solution was extracted repeatedly with ether. The combined red oil and ether extracts were dried overnight with anhydrous potassium carbonate, the solvent was removed and the product was distilled under water pump vacuum, the fraction boiling at 98–101° (15–17 mm.) (bath temperature 125–135°) being collected. The keto-alcohol is a water-white liquid soluble in ether and water and unstable in hot alkaline solution, $n^{20}D$ 1.4347.

1-Acetoxypentanone-4.—A mixture of 650 g. of 1-hydroxypentanone-4 and 750 g. of acetic anhydride was refluxed for two hours. After cooling the mixture was poured onto 1 liter of cracked ice, and made alkaline. The acetate was extracted with ether. The yield of material boiling at 105–107° (17–18 mm.) was 505 g. (55%) $n^{20}D$ 1.4259. Lipp[21] who prepared the compound from the alcohol and acetic acid in the presence of hydrobromic acid reports a boiling point of 213–214° (728 mm.). Karvonen[22] reports a boiling point of 109–110° (29 mm.) and $n^{20}D$ 1.4258.

1-Acetoxypentanol-4. A solution of 111 g. of 1-acetoxypentanone-4 in 300 ml. of absolute alcohol was shaken with 10 g. of Raney nickel at room temperature and hydrogen at 35 lb. pressure. The calculated amount of hydrogen was absorbed in about thirty-five hours. The product was distilled and the fraction boiling at 118–120° (18 mm.) was collected; yield, 77 g. or 70%; $n^{20}D$ 1.4314.

Anal. Calcd. for $C_7H_{14}O_3$: C, 57.5; H, 9.7. Found: C, 57.8; H, 9.7.

1-Acetoxy-4-chloropentane.—The above acetate was chlorinated with pure thionyl chloride in dry pyridine according to Whitmore, *et al.*[23] The chloride boiled at 96–98° (18 mm.) and 82° (10 mm.).

Anal. Calcd. for $C_7H_{13}O_2Cl$: C, 51.1; H, 7.9. Found: C, 51.1; H, 8.0.

3-*n*-Propylamino-1-chloropropane.—A mixture of 158 g. of trimethylene chlorobromide, 130 g. of *n*-propylamine and 125 ml. of dry ether was stirred for two hours during which the temperature rose to 30°. The mixture was then stirred for six hours at 40–45° and at room temperature for sixteen hours. After addition of sufficient water to dissolve salts, the organic layer was separated and washed with water. The organic layer was then acidified with hydrochloric acid (ice) and the aqueous layer extracted with ether for removal of unreacted trimethylene chlorobromide. After making the aqueous layer alkaline with 50% sodium hydroxide solution, the chloroamine was extracted with ether. The yield of product boiling at 68° (15 mm.) was 45 g. (33%).

Anal. Calcd. for $C_6H_{14}ClN$: C, 53.1; H, 10.4; neut. equiv., 135.5. Found: C, 52.9; H, 10.4; neut. equiv., 137.

3-Isopropylaminopropanol-1.—Freshly distilled trimethylene bromohydrin (209 g.) was added to isopropylamine (354 g.) during several hours at such a rate that the amine refluxed gently, after which refluxing was continued for eight hours. To the cooled mixture a solution of 90 g. of sodium hydroxide in 210 ml. of water was added. The organic layer was separated and the aqueous layer was extracted repeatedly with benzene. Fractionation of the combined organic layer and benzene extracts, after drying, yielded 120 g. (68.5%) of 3-isopropylaminopropanol-1 boiling at 93–95° (20 mm.). Neutral equiv. calcd. 117; found, 116.

3-Isopropylamino-1-chloropropane.—This was prepared from the above alcohol with thionyl chloride in benzene in excellent yield. The chloride hydrochloride melted at 178–180° after recrystallization from acetone-ether.

Anal. Calcd. for $C_6H_{15}Cl_2N$: C, 41.8; H, 8.7. Found: C, 41.4; H, 8.7.

1-Methylamino-6-methoxyhexane.—In a 500-ml. Pyrex liner for an American Instrument Company bomb chilled in a solid carbon dioxide-bath were placed 68 g. of 1-bromo-6-methoxyhexane[5] and 150 ml. of anhydrous methylamine. The liner was transferred to the bomb which was sealed and heated at 70° for two hours and allowed to stand at room temperature for sixteen hours. On working up as in the above cases 40 g. (79%) of material boiling at 83–84° (15 mm.) was obtained.

Anal. Calcd. for $C_8H_{19}NO$: C, 66.2; H, 13.2; neut. equiv., 145.2. Found: C, 66.1; H, 13.3; neut. equiv., 145.5.

1-*n*-Propylamino-6-methoxyhexane.—This was prepared as was the methylamino compound except that the

(20) We are indebted to Merck and Company for generous supplies of acetobutyrolactone.

(21) Lipp, *Ber.*, **22**, 1196 (1889).

(22) Karvonen, *Ann. Acad. Sci. Fennicae*, **10A**, No. 8, 1 (1916).

(23) Whitmore, *et al.*, THIS JOURNAL, **60**, 2536 (1938).

reaction mixture was refluxed for four hours. The yield of material boiling at 134–136° (28 mm.) was 71.5%.

Anal. Calcd. for $C_{11}H_{23}NO$: C, 69.3; H, 13.4; neut. equiv., 173. Found: C, 69.7; H, 13.7; neut. equiv., 172.

1-Isopropylamino-6-methoxyhexane.—The yield of material prepared as in the case of the *n*-propyl derivative and boiling at 124° (36 mm.) was 86%.

Anal. Calcd. for $C_{10}H_{23}NO$: C, 69.3; H, 13.4; neut. equiv., 173. Found: C, 69.4; H, 13.2; neut. equiv., 171.5.

1-Alkylamino-6-bromohexanes.—The above alkylaminomethoxyhexanes were boiled with 10 parts by weight of 48% hydrobromic acid for four hours. The hydrobromides were obtained on evaporation of the solutions to dryness and recrystallization from acetone-ether in substantially quantitative yield.

1-Methylamino-6-bromohexane hydrobromide, m. p. 55–60°. *Anal.* Calcd. for $C_7H_{17}Br_2N$: C, 30.6; H, 6.2. Found: C, 30.9; H, 6.2.

1-*n*-Propylamino-6-bromohexane hydrobromide, m. p. 159–160°. *Anal.* Calcd. for $C_9H_{21}Br_2N$: C, 35.6; H, 6.9. Found: C, 35.4; H, 7.0.

1-Isopropylamino-6-bromohexane hydrobromide, m. p. 125–127°. *Anal.* Calcd. for $C_9H_{21}Br_2N$: C, 35.6; H, 6.9. Found: C, 35.8; H, 6.9.

N-(6-Methoxyhexyl)-piperazine.—The method of Baltzly, *et al.*,[24] was adapted for this preparation. A mixture of 58 g. of anhydrous piperazine, 94 g. of 1-bromo-6-methoxyhexane and 600 ml. of 90% alcohol was refluxed for twenty hours. After removing the alcohol under reduced pressure, the residue was made strongly alkaline and extracted with several portions of ether. The material extracted by the ether was carefully fractionated and the part boiling at 136–137° (8 mm.) (41 g.) was collected as N-(6-methoxyhexyl)-piperazine. For characterization the dihydrochloride was prepared and melted at 227–229° after recrystallization from alcohol–ether.

Anal. Calcd. for $C_{11}H_{26}Cl_2N_2O$: C, 48.3; H, 9.6. Found: C, 48.5; H, 9.6.

A second fraction of about the same size boiling at 185–190° (8 mm.) was probably the dialkylated piperazine.

N-(6-Bromohexyl)-piperazine.—The dihydrobromide, melting at 211–213°, was prepared by cleavage of the ether in the above substance exactly as in the preceding cases.

Anal. Calcd. for $C_{10}H_{23}Br_3N_2$: C, 29.2; H, 5.6. Found: C, 28.7; H, 5.7.

1-Diethylamino-5-methoxypentane.—This was prepared by stirring 5-methoxy-1-bromopentane[1] (71 g.) with diethylamine (75 g.) at room temperature for thirty hours. The reaction was worked up as in the preceding cases yielding 62 g. (91%) of material boiling at 75–77° (18 mm.); $n^{20}D$ 1.2490.

Anal. Calcd. for $C_{11}H_{23}NO$: C, 69.4; H, 13.3; neut. equiv., 173. Found: C, 69.6; H, 13.6; neut. equiv., 174.

The ether in the above substance was cleaved as in the preceding cases. We were unsuccessful in obtaining a stable, non-hygroscopic salt of the bromoamine. It was therefore used as the crude hydrobromide for coupling with 6-methoxy-8-aminoquinoline.[2]

7-Methoxyheptanol-1.—Into the Grignard reagent prepared from 182 g. of 1-bromo-6-methoxyhexane and 26.7 g. of magnesium in 450 ml. of ether was passed formaldehyde generated by depolymerization of 50 g. of dry paraformaldehyde.[25] The addition compound was decomposed with 300 g. of ice and twice the calculated amount of 30% sulfuric acid. After warming the mixture on the steam-bath with vigorous stirring for two hours, the aqueous phase was saturated with sodium chloride. The ether layer was separated and the aqueous layer was extracted with two 100-ml. portions of ether. The combined ether extracts were dried over anhydrous potassium carbonate and the product was fractionally distilled under reduced pressure, yielding 47 g. (35%) of 7-methoxyheptanol-1, boiling at 108–110° (8 mm.); $n^{25}D$ 1.4334. Palomaa, Lehtimäki and Valkola[26] who prepared the compound from 5-methoxypentylmagnesium chloride and ethylene oxide, report a boiling point of 96–97° (3 mm.) and $n^{25}D$ 1.4332.

1-Bromo-7-methoxyheptane.—A solution of 39 g. of 7-methoxyheptanol-1 and 8 ml. of dry pyridine was added during six hours to 36 g. of phosphorus tribromide at 0°. The mixture was allowed to come to room temperature with stirring and then allowed to stand overnight. After pouring it onto cracked ice, the bromide was extracted with ether and distilled yielding 28 g. (50%) of material boiling at 95–97° (8 mm.); $n^{25}D$ 1.4592.

Anal. Calcd. for $C_8H_{17}BrO$: C, 45.9; H, 8.2. Found: C, 45.6; H, 8.1.

1-Methoxy-7-diethylaminoheptane.—This was prepared as in the preceding cases in 82% yield. The substance boiled at 140–142° (40 mm.); $n^{25}D$ 1.4333.

Anal. Calcd. for $C_{12}H_{27}NO$: C, 71.6; H, 13.5; neut. equiv., 201. Found: C, 71.6; H, 13.6; neut. equiv., 198.

1-Bromo-7-diethylaminoheptane Hydrobromide.—The ether in the above substance was cleaved with 48% hydrobromic acid as in the preceding cases. The yield of material melting at 83–85° was practically quantitative. Magidson, Madaeva and Rubtzov,[7] who prepared the compound by an alternate method report it melting at 81–84°.

1-Methoxyhexanol-4.—To the Grignard reagent prepared from 208 g. of 3-methoxypropyl chloride and 48 g. of magnesium turnings in 400 ml. of ether 116 g. of propionaldehyde was added at 0°. After hydrolysis with sulfuric acid, the product was extracted with ether and distilled yielding 122 g. (47%) of material boiling at 90–92° (15 mm.).

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.6; H, 12.1. Found: C, 63.5; H, 12.3.

1-Methoxy-4-chlorohexane.—To a stirred solution of 1-methoxy-4-hydroxyhexane (17 g.) in 10.2 g. of dry pyridine was added dropwise over one and one-half hours 23.8 g. of pure thionyl chloride. After heating the mixture at 60–70° for three hours, an excess of 6 *N* hydrochloric acid and ice was added. The oily layer was extracted with ether, dried and the product distilled giving 12.5 g. (65%) of material boiling at 68–70° (15 mm.).

Anal. Calcd. for $C_7H_{15}ClO$: C, 55.8; H, 10.0. Found: C, 56.1; H, 10.0.

1-Methoxy-4-ethylaminohexane.—A mixture of 93 g. of 1-methoxy-4-chlorohexane and 280 g. of ethylamine was heated in an American Instrument Company bomb at 90° for forty-four hours. The excess ethylamine was removed by distillation and the residue, which had separated into two layers, was poured into an excess of 10% hydrochloric acid. Extraction of the acid solution with 400 ml. of ether removed 20 g. of unreacted starting material. The acid solution was made strongly alkaline with potassium hydroxide with cooling and extracted with a liter of ether in several portions. The dried product was distilled yielding 60 g. (60%) of material boiling at 87–89° (16 mm.).

Anal. Calcd. for $C_9H_{21}NO$: C, 67.9; H, 13.2; neut. equiv., 159. Found: C, 67.5; H, 12.8; neut. equiv., 160.

1-Bromo-4-ethylaminohexane.—A mixture of 40 g. of the above amino-ether and 400 g. of 48% hydrobromic acid was refluxed for five hours and concentrated to dryness. The residual amine bromide hydrobromide was recrystallized from acetone–alcohol and melted at 115–117°.

Anal. Calcd. for $C_8H_{18}Br_2N$: C, 33.2; H, 6.6. Found: C, 32.9; H, 7.0.

1-Bromo-4-aminoöctane.—The ether in 1-methoxy-4-aminoöctane, prepared according to Menschikoff and Schdanowitsch[16] or by catalytic reduction of 1-methoxyoctanone-4 oxime over Raney nickel[27] was cleaved as in the above case. Because of the strong tendency of the bromo-amine to form the pyrrolidine, it was used directly as the crude hydrobromide without purification.

(24) Baltzly, *et al.*, THIS JOURNAL, **66**, 263 (1944).

(25) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1941, p. 188.

(26) Palomaa, Lehtimäki and Valkola, *Ber.*, **74**, 291 (1941).

(27) Courtesy of Dr. Nathan L. Drake.

1-Chloro-2-diethylaminopropane.—To a chilled solution of 182 g. of pure thionyl chloride in 500 ml. of dry benzene was added 100 g. of 2-diethylaminopropanol-1 at such a rate that the temperature did not exceed 25°. After heating the mixture at 50–60° for three hours, it was concentrated to dryness and the residue was made alkaline with 40% potassium hydroxide solution with cooling. The oily amino chloride was extracted with ether and distilled yielding 94 g. (82%) of material boiling at 79–80° (50 mm.) $n^{2}D$ 1.4310.

Anal. Calcd. for $C_7H_{16}ClN$: C, 56.2; H, 10.8. Found: C, 56.1; H, 10.8.

5-Diethylaminohexanone-2.—To a refluxing solution of ethyl sodio acetoacetate prepared from 11.5 g. of sodium and 65 g. of ethylacetoacetate in 250 ml. of absolute alcohol was added over one and one-half hours 75 g. of 1-chloro-2-diethylaminopropane. After refluxing for an additional fourteen hours, the precipitated sodium chloride was filtered off and the alcohol distilled from the filtrate. The crude ester was stirred for twenty hours at room temperature with 600 ml. of 5% sodium hydroxide solution. After separation of a small insoluble portion, the solution was acidified with hydrochloric acid and warmed on the steam-bath until evolution of carbon dioxide ceased. After cooling, the solution was made alkaline and saturated with potassium carbonate. The amino ketone was extracted with several portions of ether and distilled yielding 36 g. (42%) of material boiling at 94–95° (16 mm.) or 105–107° (22 mm.); $n^{25}D$ 1.4337.

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.1; H, 12.4. Found: C, 70.4; H, 12.3.

5-Diethylamino-hexanol-2.—The above ketone was reduced catalytically over Raney nickel,[27] yielding 85% of the alcohol boiling at 110° (15 mm.).

Anal. Calcd. for $C_{10}H_{23}NO$: C, 69.3; H, 13.4. Found: C, 69.0; H, 13.2.

2-Bromo-5-diethylaminohexane.—The above alcohol was converted to the oily bromide hydrobromide with thionyl bromide in benzene. Since no crystalline salt of the bromoamine could be found, it was used directly for subsequent work.[2]

3-(3′-Diethylaminopropoxy)-propanol-1.—To a solution of 50 g. of sodium in 400 g. of dry redistilled trimethylene glycol in 200 ml. of dry xylene at 120° was added 360 g. of 3-diethylamino-1-chloropropane. After cooling, the salt was filtered off and the filtrate was fractionated carefully yielding 192 g. (51%) of product boiling at 147–148° (10 mm.).

Anal. Calcd. for $C_{10}H_{23}NO_2$: C, 63.5; H, 12.2. Found: C, 63.7; H, 12.3.

3-(3′-Diethylaminopropoxy)-1-chloropropane.—This was prepared from the above alcohol with thionyl chloride in benzene. The free base boiled at 118–119° (10 mm.).

Anal. Calcd. for $C_{10}H_{22}ClNO$: C, 57.3; H, 10.6. Found: C, 57.5; H, 10.6.

1-Ethylaminobutene-3.—Reaction of 1-bromobutene-3[2] (77 g.) with ethylamine (300 ml.) in a bomb at 100° for twelve hours and then at room temperature for forty-eight hours as in the preceding cases gave 42% of 1-ethylaminobutene-3 boiling at 108–109°.

Anal. Calcd. for $C_6H_{13}N$: C, 72.7; H, 13.2. Found: C, 72.9; H, 13.3.

The acetyl derivative of the above amine boiled at 115–117° (30 mm.).

Anal. Calcd. for $C_8H_{15}NO$: C, 68.0; H, 10.7. Found: C, 68.1; H, 10.9.

1-Bromo-2-hydroxy-4-ethylaminobutane.—To a solution of 30 g. of 1-ethylaminobutene-3 in 27 ml. of acetic acid and 100 ml. of water was added over thirty minutes 42 g. of N-bromoacetamide.[29] After stirring for two hours the bromoacetamide all dissolved. After addition of 75 ml. of 48% hydrobromic acid the solution was concentrated under reduced pressure to a thick mush of oil and crystals. This was triturated with 20 ml. of absolute alcohol and the insoluble ammonium bromide was filtered off. The oily bromoamine hydrobromide was used for condensations with 6-methoxy-8-aminoquinoline without further purification because of its marked tendency to form a pyrrolidine derivative.

Summary

1. A general method for the synthesis of amino-halides of the type $CH_3CHX(CH_2)_3NR_2$, where R = alkyl or hydrogen, has been described.

2. The synthesis of a variety of other amino halides has been described.

(28) Linstead and Rydon, *J. Chem. Soc.*, 1995 (1934).

(29) Likhosherstov and Alekseev, *J. Gen. Chem.* (U. S. S. R.), **3**, 927 (1933), described the reaction of N-bromoacetamide with butene-2.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Synthesis of 5-Substituted Derivatives of 6-Methoxy-8-aminoquinoline and of 5-Chloro-6-methoxyquinoline[1]

BY ROBERT C. ELDERFIELD, WALTER J. GENSLER, THURMOND A. WILLIAMSON, JOHN M. GRIFFING, S. MORRIS KUPCHAN, JOHN T. MAYNARD, FRANK J. KREYSA AND JOHN B. WRIGHT

Derivatives of 5,6-dimethoxy-8-aminoquinoline, carrying alkylamino side chains in the 8-position have been reported in the literature[2,3] to possess antimalarial properties superior to those of similar substances not carrying the 5-methoxyl group. In a succeeding paper of this series, the synthesis of a number of such drugs is described. In the present communication we wish to present the results of a study of the synthesis of 5,6-dimethoxy-8-aminoquinoline itself. Various syntheses of this substance are given in the patent literature[4] of which the most direct consists in the reaction of 5-chloro- or 5-bromo-6-methoxy-8-nitroquinoline with sodium methoxide. However, possibly because of a lack of sufficient detail in the patents, we have been unable to duplicate the available syntheses.

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

(2) Schönhöfer and Andersag, German Patent 536,447; *Friedlander*, **18**, 2718 (1931).

(3) Schönhöfer, *Z. physiol. Chem.*, **274**, 1 (1942).

(4) Schönhöfer, U. S. Patent 1,879,538, Sept. 27, 1932.