base with aqueous potassium hydroxide. The solution was extracted with chloroform, the chloroform extracts dried with potassium carbonate, filtered and evaporated. The residue was triturated with ether and crystallized twice from an acetone–ether mixture; m. p. 78–80°.

Method B.—A mixture of 5 g. of 2-amino-4-chloro-6-γ-piperidinopropylamino-*s*-triazine (VI) and 20 g. of γ-piperidinopropylamine was heated at 100° on the steam-bath for two and a half hours and at 135° for five minutes. Solid potassium hydroxide was added and the solution, after warming on the steam-bath for five minutes, was filtered and the filtrate was freed of γ-piperidinopropylamine by heating to 120° at 3 mm. pressure for twenty minutes. The residue was triturated with ether to give 5.7 g. of material melting at 78–82°. Recrystallization from a ligroin–alcohol mixture gave a product melting at 78–80°. A mixed melting point with this and the compound prepared in Method A was 78–80°. This product formed a picrate with melting point of 183–184° which, when mixed with the picrate from the sample in Method A, melted at 182–3°.

2-Amino-4-ethoxy-6-γ-piperidinopropylamino-*s*-triazine.—Into a sodium ethylate solution, obtained from 0.175 g. of sodium and 50 ml. of absolute ethanol, was dropped 1.00 g. of 2-amino-4-chloro-6-γ-piperidinopropylamino-*s*-triazine (VI). This was refluxed for twenty-four hours, cooled and the precipitated sodium chloride filtered. The alcoholic filtrate was concentrated to a sirup which crystallized upon stirring with ether; crude yield, 0.875 g., m. p. 125–128°. This was recrystallized from absolute ethanol and again from methanol to give the pure ethoxy derivative melting at 130.0–130.5°. *Anal.* Calcd. for $C_{13}H_{24}N_6O$: C, 55.70; H, 8.63. Found: C, 55.31, H, 8.68.

2,4-Dichloro-6-γ-piperidinopropylamino-*s*-triazine (V).—Freshly distilled cyanuric chloride, 18.35 g., was dissolved in 500 ml. of anhydrous ether and cooled to 0°. To this solution was added with stirring a solution of 14.2 g. of γ-piperidinopropylamine in 50 ml. of anhydrous ether. After fifteen minutes of stirring, the precipitate was filtered, washed with three 200-ml. portions of ether, stirred with a fourth portion of boiling ether, filtered and dried in a vacuum; weight 30.0 g. This material melted with bubbling at approximately 90°. All attempts to purify this material further led to products with a low nitrogen content. On standing, this material evolves hydrogen chloride and slowly decomposes.

2,4-Diamino-6-γ-morpholinopropylamino-*s*-triazine.—The following description is more or less typical of the method by which the remaining compounds in Table I were prepared. A mixture of 7.3 g. of γ-morpholinopropylamine[10] (0.05 mole), 12 g. of the damp filter cake of 2-chloro-4,6-diamino-*s*-triazine (III)[4] (0.05 mole) and 8 g. of pyridine was heated in a sealed tube at 160° for three hours. After cooling, the contents of the bomb tube were stirred with solid sodium hydroxide and a little pyridine until the mass solidified. About 20 ml. of water was cautiously added to dissolve the excess sodium hydroxide and sodium chloride and the mixture was filtered. The crystalline precipitate was washed with saturated sodium carbonate solution, acetone, and finally four times with ether. On drying at 90° for one hour, the resultant white product weighed 8.3 g. and melted at 160–164°. This was crystallized from acetone–water mixture after treating with Norit to give a total yield of 65% of product melting at 163–164°. Further crystallization did not raise this melting point. *Anal.* Calcd. for $C_{10}H_{19}ON_7$: C, 47.44; H, 7.56. Found: C, 47.14; H, 7.31.

The Reaction of Cyanuric Chloride with Excess γ-piperidinopropylamine.—In an attempt to replace each of the three chlorine atoms in cyanuric chloride with an aliphatic, basically-substituted side chain, several reactions under various conditions were performed. We did not, however, isolate an analytically pure sample from the reactions. The following was a typical experiment.

An ether solution of 28 g. of γ-piperidinopropylamine was added to a solution of 6.2 g. of freshly distilled cyanuric chloride in 200 ml. of anhydrous ether over a fifteen-minute period. The mixture was heated in an open flask on the steam-bath for one hour and finally in an oil-bath at 140° for one hour. The resultant viscous liquid was extracted with ether and the ether discarded. It was then thoroughly washed with three portions of saturated potassium carbonate solution. The chloroform was replaced with acetone and dry hydrogen chloride gas bubbled through the solution, which was cooled by the addition of Dry Ice. The precipitated hydrochloride weighed 17.5 g. This was recrystallized four times from absolute ethanol–ether mixtures and once from *n*-propanol to give a product melting at 177–180°. *Anal.* Calcd. for $C_{27}H_{51}N_9 \cdot 3HCl$: C, 53.1; H, 8.4; N, 20.6. Found: C, 49.8; H, 8.7; N, 19.2. A picrate prepared from this material melted at 148–150°. *Anal.* Calcd. for $C_{27}H_{51}N_9 \cdot 6C_6H_3O_7N_3$: C 40.0; H, 3.7. Found: C, 38.4; H, 3.3.

Summary

The reaction of cyanuric chloride with ammonia and various basically-substituted aliphatic amines, in particular γ-piperidinopropylamine, has been studied and nine new basically-substituted 1,3,5-triazine derivatives have been described.

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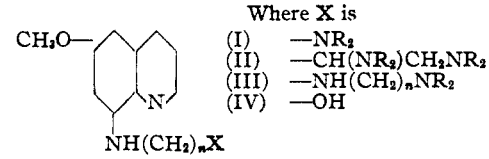
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Heterocyclic Basic Compounds. III. Basically-substituted Quinoline Derivatives[1]

BY WILLIAM H. YANKO,[2] HARRY S. MOSHER AND FRANK C. WHITMORE

In extending the research on the type of compound represented by 8-γ-diethylaminopropylamino-6-methoxyquinoline,[3] we have prepared a series of related quinoline compounds represented by the general formulas.



In the above formulas, —NR_2 may represent either a dialkylamino group, such as the diethylamino radical, or a heterocyclic amino group, such as the piperidino or morpholino radicals.

(1) Presented before the Medicinal Section of the American Chemical Society in Cleveland, April 6, 1944.

(2) Parke, Davis Research Fellow, 1942. The following work is taken in part from a thesis submitted by William H. Yanko to The Pennsylvania State College in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Present address: Central Research, Monsanto Chemical Co., Dayton, Ohio.

(3) (a) Magidson and Strukov, *Arch. Pharm.*, **271**, 359–369 (1933); (b) Kritchevskii and Sternberg, *Z. Immunitäts.*, **80**, 438–459 (1933); (c) Fourneau, Trefouel, Bovet and Benoit, *Ann. inst., Past.*, **46**, 514–541 (1931); **50**, 731–744 (1933).

Similar compounds are found in the work of Robinson,[4] Fourneau,[3c] Magidson,[3a] and many others. In particular, compounds of types I and III above have recently been reported by Robinson.[5]

The basically-substituted alkyl halides necessary for the synthesis of the members of group I were prepared either by the reaction of a secondary amine with trimethylene chlorobromide,[6] or by the reaction of a secondary base with trimethylene chlorohydrin and treatment of the resultant tertiary aminohydrin with thionyl chloride.[7] It is of particular interest to note that most of the aminoalkyl chlorides were distilled and yields of from 52 to 87% of the distilled products were obtained in spite of their tendency to undergo intra- or inter-molecular alkylation.

The dibasic "side chains" were prepared from the corresponding dibromoalcohols. Thus 2,3-dibromopropanol reacted with morpholine to give a 41% yield of 2,3-dimorpholinopropanol and this was converted to 2,3-dimorpholinopropyl chloride in 61% yield with thionyl chloride. The low yield is a result of olefin formation from the removal of hydrogen bromide from the 2,3-dibromopropanol by the base.

$$BrCH_2CHBrCH_2OH + HNC_4H_8O \longrightarrow BrCH{=}CHCH_2OH + HBr\,HNC_4H_8O$$
(or isomer)

The resultant bromopropenol mixture contains an unreactive "vinyl bromide" and as such does not react further with the morpholine. When the stronger base, diethylamine, reacted with 2,3-dibromopropanol, the removal of hydrogen bromide with the formation of the unsaturated bromoalcohol was the major reaction and a 74% yield of the bromopropenols was obtained and only a 15% yield of the desired metathetical reaction product, 2,3-di-(diethylamino)-propanol, resulted.

It has been found throughout this work that, from a chemical standpoint, the morpholino compounds were generally preferable to work with, for they gave better yields and more readily crystallizable products.

Allylmethylcarbinol[8] was prepared in a 62% yield by adding a mixture of allyl bromide and acetaldehyde to magnesium. This reacted with bromine to give 1,2-dibromo-4-pentanol in 67% yield, which in turn reacted with morpholine to give a 34% yield of the desired 1,2-dimorpholino-4-pentanol and a 43% yield of the olefin mixture resulting from the removal of hydrogen bromide.

(4) Robinson and Tomlinson, *J. Chem. Soc.*, 1524–1530 (1934).

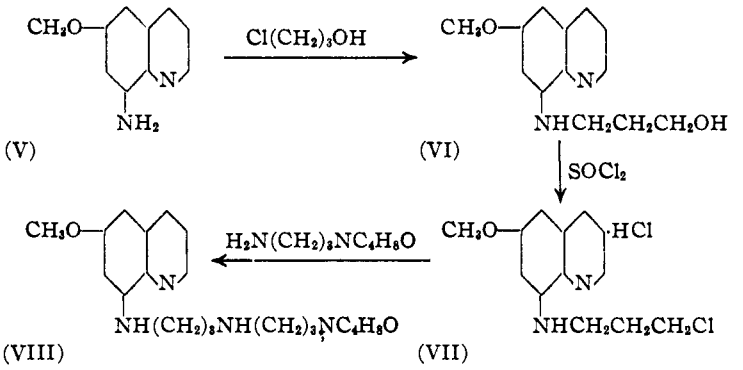
(5) (a) Quin and Robinson, *ibid.*, 555 (1944); (b) Glen and Robinson, *ibid.*, 557 (1944); (c) Crum and Robinson, *ibid.*, 561 (1944).

(6) Adams, Ph.D. thesis, The Pennsylvania State College, February, 1944.

(7) Slotta and Behnisch, *Ber.*, **68B**, 754–761 (1935).

(8) Kuin-Houo, *Ann. Chem.*, **13**, 175–241 (1940).

The compounds in groups I, II, and IV were all prepared in the conventional manner by causing the appropriate aliphatic chloro compound or its hydrochloride to react with 8-amino-6-methoxyquinoline (V) at approximately 130–160° without solvent and with stirring in an open flask. In a few cases the reaction was carried out in Cellosolve solvent to advantage. With the compounds of class III, this method of coupling the aliphatic chloro compound and the 8-amino-6-methoxyquinoline was unsuccessful and these products were synthesized by the following indicated steps:



This is essentially the same method recently reported independently by Crum and Robinson.[5c] The yields are generally good; the initial alkylation to produce the alcohol VI without solvent at 126° in 79% yield and the conversion to the chloro compound VII in 80% yield. The final reaction was performed in a sealed tube at 150° and in one case resulted in a 91% yield of the product (VIII).

Crum and Robinson[5c] reported that the reaction of thionyl chloride with the free base of VI resulted in the formation of the thioether, bis-(8-γ-chloropropylamino-6-methoxy-5-quinolyl)-thioether, as by-product, especially when the reaction time was over one-half hour. Our yield was considerably better than theirs and, although in one case the reaction was refluxed for six hours, at no time was this troublesome by-product observed in our work. This is undoubtedly because we used the hydrochloride salt, VI.

In addition to the compounds of the above types, one derivative of 8-amino-6-chloroquinoline and two derivatives of 6-amino-8-methoxyquinoline, isomeric with compounds number 1 and 4 in Table I, were prepared.

8-Methoxy-6-nitroquinoline was prepared by the Strukov modification of the Skraup reaction[9] in 68% yield and reduced to 6-amino-8-methoxyquinoline in 84% yield. 6-Chloro-8-nitroquinoline was made by the same modification in 50% yield.

Experimental

2,3-Dimorpholinopropanol.—A mixture of 358 g. of morpholine, 4.12 moles, and 208 g. of 2,3-dibromopropanol,

(9) Strukov, *Org. Chem. Ind.* (U. S. S. R.), **4**, 523 (1937); *Chem. Abs.*, **32**, 4987 (1938).

0.955 mole, was allowed to react spontaneously. After a short period at room temperature, the mixture warmed to the boiling point and was then cooled during the remainder of the reaction. By adding 100 ml. of dry benzene to the brown, thick reaction mixture, the morpholine hydrobromide was precipitated. After washing the precipitate with benzene and drying, it weighed 260 g., 1.5 moles. The filtrate was refluxed for ten more hours, but only 3 more grams of morpholine hydrobromide precipitated. The benzene was removed from the reaction mixture by distillation and the residue vacuum distilled to give 94 g. of product, b. p. 170–190° (3 mm.), which formed a white crystalline hydrochloride, m. p. 225–227°. *Anal.* Calcd. for $C_{11}H_{22}O_3N_2 \cdot 2HCl$: Cl, 23.46. Found: Cl, 23.50. The low yield is a result of olefin formation, 135 g. of which was collected at 60° (15 mm.).

2,3-Dimorpholinopropyl Chloride.—To a solution of 92.5 g. of the 2,3-dimorpholinopropanol in 210 g. of anhydrous chloroform at 0° was added 60 g. of redistilled thionyl chloride in a period of three and a half hours. It was refluxed on the steam-bath for eight hours after which time the chloroform was removed by distillation and the residue crystallized and recrystallized from a methanolic hydrogen chloride solution to give 79 g. of white crystals melting at 206–209° dec. *Anal.* Calcd. for $C_{11}H_{22}O_2N_2Cl \cdot HCl$: N, 8.70. Found: N, 8.50.

In a similar manner, piperidine and diethylamine reacted with 2,3-dibromopropanol. In the first case a 15% yield of 2,3-dipiperidinopropanol, b. p. 130–140° (1 mm.), picrate, m. p. 173–175° dec., was obtained and in the second case a 15% yield of 2,3-di-(diethylamino)-propanol, b. p. 119° (17 mm.), picrate m. p. 163–164°, was produced. *Anal.* Calcd. for $C_{11}H_{26}ON_2 \cdot C_6H_3O_7N_3$: N, 16.22. Found: H, 15.86. In each case the by-product was the mixed bromopropenols, b. p. 55–70° (15 mm.); 78 and 70% yields, respectively. Both of the amino-alcohols were converted to the chloro compounds by the above method in 78 and 68% yield, respectively. The hydrochlorides of these compounds could not be crystallized, but both formed picrates melting, respectively, at 192–194° and 126–127°. *Anal.* Calcd. for $C_{11}H_{25}N_2Cl \cdot C_6H_3O_7N_3$: N, 15.54. Found: N, 15.68. *Anal.* Calcd. for $C_{13}H_{25}N_2Cl \cdot C_6H_3O_7N_3$: N, 14.77. Found: N, 14.71.

1,2-Dimorpholino-4-pentanol.—A mixture of 847 g. of allyl bromide and 308 g. of acetaldehyde in 1 liter of anhydrous ether was added with rapid stirring to 200 g. of magnesium in 2.5 liters of anhydrous ether after it was made certain that the Grignard reaction had started. The reaction mixture was filtered and hydrolyzed with 3 kg. of ice and 6 moles of sulfuric acid. The ether layer and ether extracts of the water layer were fractionated to give 379 g. of allylmethylcarbinol,[7] b. p. 114° (740 mm.). This was converted in 67% yield to 1,2-dibromo-4-pentanol, b. p. 103° (2 mm.), by the addition of bromine at 0°. The product loses hydrogen bromide spontaneously on standing and was used immediately after distillation for the preparation of 1,2-dimorpholino-4-pentanol. This was obtained by the same method as used for the preparation of 1,2-dimorpholinopropanol outlined above; yield 34%, b. p. 155–165° (2 mm.), picrate m. p. 194–195°. *Anal.* Calcd. for $C_{13}H_{26}O_3N_2 \cdot C_6H_3N_3O_7$: N, 14.65. Found: N, 14.41. As a by-product in this reaction there was obtained a 43% yield of the olefin mixture, 1-(or 2)-bromopentene-1(or 2)-ol-4. The 1,2-dimorpholino-4-pentanol was converted to the chloride hydrochloride, m. p. 254–255°, with thionyl chloride in 97% yield, melting point of the picrate 257° dec. *Anal.* Calcd. for $C_{13}H_{25}O_2N_2Cl \cdot 2C_6H_3N_3O_7$: N, 15.24. Found: N, 15.32. *Anal.* Calcd. for $C_{13}H_{25}O_2N_2Cl \cdot 2HCl$: N, 8.07. Found: N, 8.17.

γ-(γ′-Morpholinopropyl)-aminopropanol.—A mixture of 43.2 g. of γ-morpholinopropylamine[10] and 28.2 g. of trimethylene chlorohydrin was heated at 130° for eight hours. After one-half hour, the solution had turned black. Less decomposition would probably have resulted if the reaction had been carried out in a solvent. The reaction mixture was dissolved in 100 ml. of absolute ethanol and made basic with a solution of 17 g. of potassium hydroxide in 50 ml. of ethanol. Anhydrous ether was added and the potassium chloride that precipitated filtered from the solution. The filtrate was freed of solvent by distillation and the residue distilled at 1 mm. pressure to give 23 g. of γ-(γ′-morpholinopropyl)-amino propanol boiling at 140°. *Anal.* Calcd. for $C_{10}H_{22}O_2N_2$: N, 9.26. Found: N, 9.31. In addition to this there was obtained 4 g. of material boiling at 225–235° (1 mm.) which was assumed to be N-[γ-di-(γ′-hydroxypropyl)-amino]-propylmorpholine.

γ-(γ′-Morpholinopropyl)-aminopropyl Chloride Hydrochloride.—The 23 g. of γ-(γ′-morpholinopropyl)-aminopropanol was dissolved in 50 ml. of anhydrous chloroform and 14 g. of thionyl chloride in 35 ml. of chloroform was added to this solution at 10°. After the addition was complete, the reaction mixture which contained a tan, gummy precipitate, was refluxed on the steam-bath for two hours. The precipitate crystallized on cooling. It was filtered and recrystallized from 7 *N* alcoholic hydrogen chloride solution and finally from methanol; yield 27 g., 79.8%, m. p. 208–210°. *Anal.* Calcd. for $C_{10}H_{21}ON_2Cl$: N, 9.55. Found: N, 9.67.

γ-Dicyclohexylaminopropanol.—A solution of 186 g. of dicyclohexylamine, 94 g. of trimethylene chlorohydrin and 200 ml. of toluene was refluxed for eight hours and the dicyclohexylamine hydrochloride, 32 g., filtered. Most of the toluene was then distilled from the reaction mixture and the residue refluxed for three more hours. The solution was cooled and the second crop of 73 g. of dicyclohexylamine hydrochloride removed by filtration and the residue distilled to give 93 g., 77.5% yield, of γ-dicyclohexylaminopropanol, b. p. 160–167° (5 mm.) $n^{20}D$ 1.5006. This formed a picrate which, when crystallized from dilute methanol and recrystallized from ethanol, melted at 68–69° *Anal.* Calcd. for $C_{15}H_{29}ON \cdot C_6H_3O_7N_3$: N, 11.95. Found: N, 11.72.

γ-Dicyclohexylaminopropyl Chloride.—The chloride hydrochloride was prepared by the action of thionyl chloride in the usual manner. The hydrochloride of the product did not crystallize but formed a crystalline picrate which melted at 139–140°. *Anal.* Calcd. for $C_{15}H_{28}NCl \cdot C_6H_3O_7N_3$: N, 11.52. Found: N, 11.39.

2-(γ-Hydroxypropylamino)-pyridine.—To a warm mixture of 47 g. of sodamide, 450 ml. of toluene and 113 g. of 2-aminopyridine which had been refluxed for five hours, was added 95.6 g. of trimethylene chlorohydrin dissolved in 50 ml. of toluene and the reaction mixture was heated for six hours on the steam-bath. The reaction was thoroughly mixed with water, the water layer extracted with ether, and the ether–toluene solution distilled under reduced pressure to give 43.5 g. of 2-(γ-hydroxypropylamino)-pyridine, b. p. 175–185° (5 mm.). A portion of this was converted into the hydrochloride salt in absolute ethanol and recrystallized from methanol–ether; m. p. 125–128°. *Anal.* Calcd. for $C_8H_{12}ON_2 \cdot 2HCl$: Cl, 18.8. Found: Cl, 18.7.

2-(γ-Bromopropylamino)-pyridine.—The 2-(γ-hydroxypropylamino)-pyridine, 41 g., was treated with 142 g. of phosphorus tribromide in 60 ml. of anhydrous benzene at 0° and the mixture stirred at 0° for one hour followed by heating on the steam-bath for ten hours. The reaction mixture was carefully decomposed with ice, neutralized with sodium carbonate, and extracted with benzene. The extracts on evaporation gave 18 g. of light tan oil, 31.9% crude yield. This material was used in the coupling reaction with 8-amino-6-methoxyquinoline without further purification.

β-Hydroxy-γ-morpholinopropyl Chloride Hydrochloride.—This was prepared from morpholine and epichlorohydrin by the general method employed by Drozdov and Cherntzov[11]; m. p. 160–161°, yield 60%. *Anal.* Calcd. for $C_7H_{14}O_2NCl \cdot HCl$: Cl, 16.4. Found: Cl, 16.4.

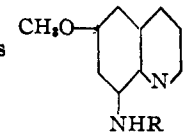
The quinoline nuclei were all made by the Strukov[9]

(10) Whitmore, Mosher, Adams, Taylor, Chapin, Weisel and Yanko, THIS JOURNAL, **66**, 725 (1944).

(11) Drozdov and Cherntzov, *J. Gen. Chem.* (U. S. S. R.), **4**, 969-974 (1934).

TABLE I

8-AMINO-6-METHOXYQUINOLINE DERIVATIVES



No.	Side chain equals R	B. p., °C.	Mm.	M. p., °C.	Yield, %	Derivative	and m. p., °C.	Formula	N Analyses, % Calcd.	Found
1	—$CH_2CH_2CH_2NEt_2$[a]	182	1.0	Oil	71.8	2HCl	218–220	$C_{17}H_{28}ON_2 \cdot 2HCl$	11.62	11.14
2	—$CH_2CH_2CH_2N(n\text{-}Pr)_2$[f]			Oil	76.0	2HCl	190–192	$C_{19}H_{32}ON_2 \cdot 2HCl$	10.79	10.77
3	—$CH_2CH_2CH_2N(n\text{-}Bu)_2$[f]	210–215	1.5	Oil	43.8	2HCl	128	$C_{21}H_{36}ON_2 \cdot 2HCl$	10.05	10.03
4	—$CH_2CH_2CH_2NC_4H_8O$[c,f]	207–210	1.5	81.5	93.2	2HCl	223	$C_{17}H_{28}O_2N_2$	13.92	13.96
5	—$CH_2CH_2CH_2NC_5H_{10}$[d,f]	202	1.5	Oil	69.3	2HCl	233	$C_{18}H_{30}ON_2 \cdot 2HCl$	11.27	11.24
6	—$CH_2CH_2CH_2NH$-2-pyridyl	250–260	1.0	Oil	49.4	2HCl	202–206	$C_{18}H_{20}ON_4$		
7	—CH_2CH_2-2-pyridyl	208–214	1.0	Oil	78.5	2HCl	216–218	$C_{17}H_{17}ON_3$	16.52	16.38
8	—$CH_2CHOHCH_2NC_4H_8O$	235–240	1.0	Oil	91.3	2HCl	217–218	$C_{17}H_{28}O_3N_2 \cdot 2HCl$	9.87	9.92
9	—$CH_2CH(NEt_2)CH_2(NEt_2)$	210	1.0	Oil	30.5	3HCl	115–120	$C_{29}H_{54}ON_4 \cdot 3HCl$	12.29	11.97
10	—$CH_2CH(NC_4H_8O)CH_2NC_4H_8O$	255–260	1.5	Oil	38.9	3HCl	210–212[b]	$C_{21}H_{30}O_3N_4 \cdot 3HCl$	11.29	11.00
11	—$CH_2CH(NC_5H_{10})CH_2NC_5H_{10}$	235–250	1.5	87–88	62.8	3pic.	118–120	$C_{11}H_{34}ON_4$	14.65	14.21
12	—$(CH_2)_3NH(CH_2)_3NC_4H_8O$[e]	235–260	1.5	Oil	90.7	3HCl	220–222	$C_{20}H_{30}O_2N_4 \cdot 3HCl \cdot 1/_2H_2O$	11.75	11.36
13	—$(CH_2)_3NHCH(CH_3)(CH_2)_3NEt_2$	230	1.5	Oil	54.5	3HCl	70–72[b]	$C_{21}H_{36}ON_4 \cdot 3HCl$	11.64	11.50
14	—$(CH_2)_3N[(CH_2)_3NEt_2]_2$[e]			Oil	76.4	3HCl	88–90[b]	$C_{27}H_{42}ON_5 \cdot 4HCl$	11.59	11.95
15	—$CH_2CH_2CH_2OH$[g]	205–210	1.5	58.0–58.5	78.8	HCl	170–172	$C_{18}H_{16}O_2N_2 \cdot HCl$	10.41	10.40
16	—$CH_2CH_2CH_2Cl \cdot HCl$[g]			179–180	95	pic.	141–142	$C_{18}H_{18}ON_2Cl \cdot HCl$	9.77	9.67

[a] See ref. 3. [b] This melting point is not sharp and is accompanied by decomposition. [c] —NC_4H_8O represents the 4-morpholinyl radical (morpholino radical). [d] —NC_5H_{10} represents the 1-piperidyl radical (piperidino radical). [e] For the side chains used in the preparation of these compounds see ref. 10. [f] For the aminoalkyl chlorides used in the preparation of these compounds see ref. 6. [g] See ref. 5.

modification of the Skraup reaction: 8-nitro-6-methoxyquinoline, 78% yield, 6-nitro-8-methoxyquinoline,[12] 87% yield crude, 68% yield purified, and 8-nitro-6-chloroquinoline,[13] 50% yield.

6-Nitro-8-methoxyquinoline.—Concentrated sulfuric acid, 180 ml., was added in 50-ml. portions to a homogeneous mixture of 334 g. of powdered arsenic acid, 336 g. of 5-nitro-2-aminoanisole and 740 g. of glycerol. The reaction mixture was heated under a vacuum (15 to 25 mm. press.) in an oil-bath to a temperature of 105° during which time the loss in weight of the reaction mixture was 200 g. The vacuum was removed and stirring started while 134 ml. of concd. sulfuric acid was added over a two-hour period and the temperature was maintained at 105–115°. It is not safe to add the sulfuric acid any faster than this or to allow the temperature to rise much higher. The reaction mixture was held at 110° for ten hours and then raised to 120° for three additional hours. The reaction mixture was cooled to about 90° and 2 kg. of crushed ice added with vigorous stirring. It was then neutralized with 600 ml. of 50% sodium hydroxide solution with stirring and cooling; the resultant yellow precipitate was filtered, dried, and extracted with chloroform. The chloroform extracts were decolorized with Norit, the solvent distilled, and the residue of 362 g. of yellow solid crystallized from ethylene dichloride to give 284 g. of 8-methoxy-6-nitroquinoline, m. p. 149°.

Compounds 1–11 in Table I were prepared by a typical coupling reaction of 8-amino-6-methoxyquinoline and a basically-substituted alkyl chloride according to the example described below.

8-(β-Hydroxy-γ-morpholinopropylamino)-6-methoxyquinoline.—β-Hydroxy-γ-morpholinopropyl chloride hydrochloride, 21.6 g., was fused with 17.4 g. of 8-amino-6-methoxyquinoline for twelve hours at 130°. The resultant black mass was dissolved in warm water, cooled, made basic with sodium hydroxide solution, saturated with potassium carbonate, and extracted with three 500-ml. portions of ether. The ether extracts were dried with anhydrous potassium carbonate, and the solvent removed on the steam-bath. The residue was distilled from a small Claisen flask to give 2 g. of recovered β-hydroxy-γ-morpholinopropyl chloride; b. p. 65–77° (1 mm.), hydrochloride derivative m. p. 160–1°, and 18 g. of product; b. p. 235–240° (1 mm.). This product did not crystallize on standing and so was converted to the dihydrochloride in absolute alcoholic hydrogen chloride solution and crystallized by adding anhyd. ether and cooling; yield 22 g. of yellow orange crystals, m. p. 217–218°; picrate, m. p. 165–166°. *Anal.* Calcd. for $C_{17}H_{28}O_3N_3 \cdot 2HCl$: N, 9.87. Found: N, 9.92.

8-γ-Hydroxypropylamino-6-methoxyquinoline[5c] **(VI).**—A mixture of 100 g. of 8-amino-6-methoxyquinoline and 54 g. of trimethylene chlorohydrin was heated with stirring in an oil-bath at 126° for sixteen hours and the resultant brown oil dissolved in dilute hydrochloric acid, cooled, and neutralized with sodium hydroxide solution. The heterogeneous mixture was extracted with benzene and the extracts dried with potassium carbonate and distilled to give 20 g. of recovered 8-amino-6-methoxyquinoline and 84 g. of 8-(γ-hydroxypropylamino)-6-methoxyquinoline, b. p. 210° (1.5 mm.). This was converted to the hydrochloride by bubbling dry hydrogen chloride into its ether solution and recrystallizing the precipitate from an ether-alcohol mixture; m. p. 171–172°, picrate, m. p. 115–116°. *Anal.* Calcd. for $C_{13}H_{16}O_2N_2 \cdot HCl$: N, 10.41. Found: N, 10.40.

8-γ-Chloropropylamino-6-methoxyquinoline[5c] **(VII).**—A solution of 60 g. of redistilled thionyl chloride and 60 ml. of chloroform was dropped into an ice-cold mixture of 117 g. of 8-γ-hydroxypropylamino-6-methoxyquinoline hydrochloride in 750 ml. of chloroform over a one-hour period. The orange solution was stirred and heated to 40° for one-half hour and then to boiling for an additional half hour The solution was filtered from a small amount of yellow precipitate (4.8 g., m. p. 210–214°, uninvestigated) and the filtrate concentrated under reduced pressure in a water-bath at 50° until the total volume was approximately 100 ml. The reaction mixture was cooled and the product filtered to give 117 g. of crude product, m. p. 168–170°, yield 95%. This was recrystallized from methanol to give 99 g. melting at 176–177°, 80% yield. A sample, after recrystallizing from methanol–ether, melted at 179–180°. *Anal.* Calcd. for $C_{13}H_{15}ON_2Cl \cdot HCl$: N, 9.77. Found: N, 9.67. This forms a picrate which melts at 141–142°. Robinson[5c] reports a melting point for this picrate of 128°. *Anal.* Calcd. for $C_{13}H_{15}ON_2Cl \cdot 2C_6H_3O_7N_3$: N, 14.10. Found: N, 13.94. The above method, which treats the hydrochloride instead of the free base with thionyl chloride, results in a considerably better yield than that re-

(12) Fourneau, Trefouel and Benoit, *Ann. inst. Past.*, **44**, 719–751 (1930).

(13) Magidson and Bobyshev, *J. Gen. Chem.* (U. S. S. R.), **8**, 911 (1938).

ported by Crum and Robinson[50] and in addition, none of the objectionable thioether described by these authors was observed by us.

8-γ-(γ'-Morpholinopropylamino)-propylamino-6-methoxyquinoline (VIII).—A mixture of 10.0 g. of 8-(γ-chloropropylamino)-6-methoxyquinoline hydrochloride from above, 12 g. of γ-morpholinopropylamine[10] and 12 ml. of absolute ethanol was heated in a sealed tube at 147° for seven hours. The contents of the tube were mixed with 100 ml. of water and the aqueous layer saturated with potassium carbonate and extracted with five 150-ml. portions of benzene. The wet extracts were dried over potassium carbonate, the solvent removed on the steam-bath, and the residue distilled through a small Claisen flask to give 10.0 g. of material boiling at 235-236° (1.5 mm.), 90.7% yield. This was converted to the hydrochloride by bubbling dry hydrogen chloride into an anhydrous ether–alcohol solution of the base, and the precipitate recrystallized, after treating with Norit, from methanol–ether; light orange crystals, m. p. 226-227°. *Anal.* Calcd. for $C_{20}H_{30}O_2N_4 \cdot 3HCl \cdot 1/2H_2O$: C, 50.35; H, 7.19; N, 11.75. Found: C, 50.15; H, 7.19; N, 11.36. Although the original precipitated hydrochloride of this compound was very hygroscopic, after recrystallization it could be stored in the atmosphere indefinitely. Compounds 12, 13, and 14 in Table I were made by this same procedure.

8-(γ-Morpholinopropylamino)-6-chloroquinoline.—A homogeneous mixture of 20.8 g. of γ-morpholinopropyl chloride hydrochloride and 20.8 g. of 8-amino-6-chloroquinoline was heated with stirring in an oil-bath at 150° for five hours. The reaction mixture was taken up in 50 ml. of 2.5 *N* HCl, treated with Norit and made alkaline with potassium carbonate. The resultant heterogeneous mixture was extracted with ether and the ether extracts dried over anhydrous potassium carbonate, concentrated on the steam-bath, and distilled from a small Claisen flask at 2 mm. pressure to give 8.5 g. of recovered 8-amino-6-chloroquinoline and 17 g. of clear, yellow product boiling at 185-195° (2 mm.), yield 71%. The base was crystallized from hot methanol, m. p. 84.5-86.0°. *Anal.* Calcd. for $C_{16}H_{20}ON_3Cl$: N, 13.73. Found: N, 13.59. The hydrochloride salt made in the usual manner melted at 210-212°. *Anal.* Calcd. for $C_{16}H_{20}ON_3Cl \cdot 2HCl$: N, 11.10. Found: N, 10.89.

6-(γ-Diethylaminopropylamino)-8-methoxyquinoline.—A well-stirred mixture of 12.4 g. of 6-amino-8-methoxyquinoline hydrochloride, 9.3 g. of γ-diethylaminopropyl chloride hydrochloride and 8 ml. of pyridine was heated at 150° for twelve hours. After dissolving the reaction mixture in dilute hydrochloric acid, neutralizing with sodium hydroxide, extracting with ether, and distilling the ether extracts, 5.0 g. of 6-(γ-diethylaminopropylamino)-8-methoxyquinoline, b. p. 175–82° (1.5 mm.) was obtained. The hydrochloride was recrystallized from absolute ethanol and ether, orange crystals m. p. 205–7°. *Anal.* Calcd. for $C_{17}H_{25}ON_3 \cdot 2HCl$: N, 11.62. Found: N, 12.03.

In a similar fashion, 6-(γ-morpholinopropylamino)-8-methoxyquinoline hydrochloride was prepared, 37.4% yield, m. p. 230–5°. *Anal.* Calcd. for $C_{17}H_{23}O_2N_3 \cdot HCl$: N, 12.13. Found: N, 12.12.

Summary

1. A series of sixteen derivatives of 8-amino-6-methoxyquinoline has been reported along with the necessary intermediates for their preparation. Seven of these derivatives contain two or more basic groups in the side chain.

2. Two derivatives of 6-amino-8-methoxyquinoline were prepared.

3. One derivative of 8-amino-6-chloroquinoline was prepared.

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Some Chemotherapeutically Active Sulfones.[1] I

BY L. L. BAMBAS

The antistreptococcal activity of 4,4'-diaminodiphenyl sulfone was found to be approximately one hundred times that of sulfanilamide.[2] Rist, Block and Hamon[3] reported the inhibitory effect of this drug on experimental tuberculosis in animals. Feldman, Hinshaw and Moses[4,5,6] in studies on this compound and two derivatives which are readily decomposed to the parent 4,4'-diaminodiphenyl sulfone conclude that it has chemotherapeutic efficacy in experimental tuberculosis and that some modification of this compound should be made to obtain drugs more suitable for clinical application. Since the toxic manifestations of 4,4'-diaminodiphenyl sulfone preclude its use as a drug in clinical tuberculosis, analogs of this compound were prepared with the hope of reducing the toxicity and retaining the antistreptococcal and antitubercular activity. Thus one or both phenyl rings were replaced by heterocyclic rings.

Changing the amine from the 4-position to the 2- or 3-positions on one of the phenyl rings of 4,4'-diaminodiphenyl sulfone decreased the antibacterial activity of the resultant compounds.[7] Therefore, the compounds investigated were limited to heterocycles in which the amine could be placed in an equivalent para position to the sulfone. That principle of vinylogy was used in which the vinylene group (—CH=CH—) may be replaced by the thio (—S—), the iminomethylene (—N=CH—) and the hydrazo (=N—N=) groups. Thus substitution on the 2 and 5 positions on the pyridine, thiazole,[8] thiophene and

(1) Presented in part before the Division of Medicinal Chemistry, Memphis meeting of the American Chemical Society, April 20, (1942).

(2) Buttle, Stephenson, Smith, Dewing and Foster, *Lancet*, **1**, 1331 (1937).

(3) Rist, Block and Hamon, *Ann. Inst. Pasteur*, **64**, 203 (1940).

(4) Feldman, Hinshaw and Moses, *Am. J. Med. Sci.*, **207**, 290 (1944).

(5) Feldman, Hinshaw and Moses, *Am. Rev. Tuberc.*, **45**, 303 (1942).

(6) Feldman, Hinshaw and Moses, *Arch. Path.*, **36**, 64 (1943).

(7) Tullar and Banks, Abstracts of the St. Louis meeting of the American Chemical Society, Paper no. 5, The Division of Medicinal Chemistry, April, 1941.

(8) The preparation of the thiazole compounds will be given in a subsequent paper.