0.75 g. (93%) of colorless flat prisms (m. p. 114–115°) was obtained. The melting point was not changed by recrystallization from ethyl alcohol.

Anal. Calcd. for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20. Found: C, 58.68; H, 4.08.

2-Methoxy-3,5-dinitrobiphenyl was obtained as above using absolute methanol instead of ethanol. A nearly quantitative yield of small white plates was obtained, m. p. 113.5–114°.[12]

Anal. Calcd. for $C_{13}H_{10}N_2O_5$: C, 56.93; H, 3.68. Found: C, 57.41; H, 3.67.

2-Piperidino-3,5-dinitrobiphenyl was prepared by refluxing 2-chloro-3,5-dinitrobiphenyl for three minutes in piperidine solution. On cooling, the piperidino compound crystallized out in almost quantitative yield. The compound crystallized from methanol as small yellow-orange needles, m. p. 184.5–185°.

Anal. Calcd. for $C_{17}H_{17}N_3O_4$: C, 62.37; H, 5.23. Found: C, 62.13; H, 5.06.

2,2'-Diphenyl-4,4',6,6'-tetranitrobiphenyl (II).—A mixture of 2.8 g. of 2-chloro-3,5-dinitrobiphenyl and 3 g. of sand was heated to 215° and 2.8 g. of copper powder added over a period of about forty minutes. The mixture was stirred for two hours at 190° and then poured into 10–15 g. of sand. The sand was extracted repeatedly with hot acetic acid. After several recrystallizations, a small quantity of small yellow needles was obtained, m. p. 248–249°.

Anal. Calcd. for $C_{24}H_{14}N_4O_8$: C, 59.26; H, 2.90. Found: C, 59.27; H, 2.92.

Attempts to Condense 2-Chloro-3,5-dinitrobiphenyl with Sodio-malonic and Acetoacetic Esters in Ethanol Solution.—To a solution of approximately 0.23 g. of sodium in 75 cc. of absolute ethanol, 1.6 g. of ethyl malonate was added. To this, 3 g. of 2-chloro-3,5-dinitrobiphenyl was added with stirring and the mixture refluxed for eight hours. After evaporation of most of the alcohol, the residue was poured into cold dilute hydrochloric acid. The resulting product was recrystallized from ethanol, m. p. 114–115°. When mixed with the starting material, it melted below 95°, but it did not depress the melting point of 2-ethoxy-3,5-dinitrobiphenyl; yield 2.9 g. (93%).[13]

When the above reactions were repeated using an equimolecular quantity of acetoacetic ester instead of malonic ester, 2.3 g. (74%) of the ether was obtained.

Attempts to Condense 2-Chloro-3,5-dinitrobiphenyl with Sodio-esters in the Absence of Alcohol.—The sodio-esters were prepared in the usual way by the action of powdered sodium on the esters in an inert solvent. The halide was added and refluxed for a period after which the mixture was poured on ice and hydrochloric acid. The solvent layer was separated, the solvent distilled off, the ester recovered by distillation and the halide by crystallization of the residue. The results are reported in the accompanying table.

ATTEMPTED CONDENSATION WITH 2-CHLORO-3,5-DINITROBIPHENYL IN THE ABSENCE OF ALCOHOL

Sodio-ester	Solvent	Time of refluxing, hr.	Ester recovered, %	Chloride recovered, %
Malonic	Benzene	24	[a]	66[b]
Malonic	Dioxane	60	75	28
Aceto-acetic	Benzene–xylene (1:1)	72	0	50

[a] No attempt made to recover ester. [b] When this experiment was repeated using sodio-desoxybenzoin, 66% of the chloro compound was recovered.

Summary

In contrast to 2,4-dinitrochlorobenzene which is reported to undergo condensation with sodio-esters even in the presence of alcohol, 2-chloro-3,5-dinitrobiphenyl has been found to undergo ethoxylation under these conditions.

This difference in behavior has been attributed to steric hindrance.

(12) Hill and Hale (*Am. Chem. J.*, **33**, 1 (1905)) apparently obtained the same product, m. p. 114–115°, by methylation of 2-hydroxy-3,5-dinitrobiphenyl.

(13) The yield was calculated from the halide rather than from the sodium which was not weighed so accurately.

DURHAM, N. C. RECEIVED MAY 1, 1944

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Dialkylaminoalkyl Derivatives of Substituted Quinolines and Quinaldines

BY A. M. VANARENDONK AND H. A. SHONLE

Inasmuch as only four dialkylaminoalkyl derivatives of 4-amino-6-methoxyquinoline have been described,[1,2] it was decided to extend this series to include a representative group of dialkylaminoalkyl side chains to determine whether any suitably active compound could be evolved for use in the treatment of malaria. Several of these derivatives were demethylated to the corresponding 6-hydroxy derivatives since no compounds of this type had ever been described. In the course of the investigation, two substituted quinaldines were also prepared, since Holcomb and Hamilton[3] have reported recently that substituted quinaldines were active in avian malaria in contrast to the findings of early investigators.[4]

Accordingly, we have prepared the series of substituted 4-amino-6-methoxy- and 4-amino-6-hydroxyquinolines and the two quinaldines given in Table I.

Experimental Part

4-(γ-Diethylaminopropyl)-amino-6-methoxyquinoline Dihydrochloride.—A mixture of 9.5 g. (0.05 mole) of 4-chloro-6-methoxyquinoline[1] and 7 g. (0.06 mole) of γ-diethylaminopropylamine in 50 cc. of *p*-cymene was refluxed in an oil-bath for eight hours. The mixture was then cooled, shaken with about 100 cc. of water containing a little hydrochloric acid and extracted twice with ether. The aqueous layer was made alkaline and the 4-(γ-diethylaminopropyl)-amino-6-methoxyquinoline which separated as an oil was taken up in 200 cc. of ether, dried

(1) O. Y. Magidson and M. V. Rubtsov, *J. Gen. Chem.* (U. S. S. R.) **7**, 1896 (1937).

(2) E. P. Hal'perin, *Med. Parasitol. Parasitic Diseases* (U. S. S. R.) **9**, 44 (1940).

(3) W. F. Holcomb and C. S. Hamilton, THIS JOURNAL, **64**, 1309 (1942).

(4) I. L. Krichevskii, E. Y. Sternberg and E. P. Hal'perin, *J. Microbiol. Expidemiol. Immunobiol.* (U. S. S. R.) **14**, 642 (1935).

TABLE I

Compound: Amino-6-methoxyquinoline	Empirical formula	M. p., °C., uncor.	Analyses, % N Calcd.	Found
4-(β-Diethylaminoethyl)-·H_2O	$C_{16}H_{25}N_3O_2$	77–78	14.4	14.6
4-(β-Diisobutylaminoethyl)-·2HCl	$C_{20}H_{33}N_3OCl_2$	250–252	10.4	10.5
4-(γ-Diethylaminopropyl)-·$2H_2O$	$C_{17}H_{27}N_3OCl_2$	165–170	11.6	11.5
4-(δ-Diethylamino-α-methylbutyl)-·2HCl[a]	$C_{19}H_{31}N_3OCl_2$	Picrate 180–182		
4-(δ-N-Methyl-N-butylamino-α-methylbutyl)-·2HCl	$C_{20}H_{33}N_3OCl_2$	Hydrate 90–91	10.4	10.3
4-(δ-N-Isopropyl-N-isobutyl-amino-α-methylbutyl)-·2HCl[b]	$C_{22}H_{37}N_3OCl_2$	157–160	9.8	10.0
4-(δ-Diisobutylamino-α-methylbutyl)-·2HCl[b]	$C_{23}H_{39}N_3OCl_2$	Hydrate 104–106	9.5	9.5
4-(γ-N-Piperidinopropyl)-	$C_{18}H_{25}N_3O$	134–135	14.0	14.1
4-(γ-N-α-Pipecolinopropyl)-	$C_{19}H_{27}N_3O$	135–137	13.4	13.5
Amino-6-hydroxyquinoline				
4-(β-Diethylaminoethyl)-	$C_{15}H_{21}N_3O$	245–246	16.2	16.1
4-(β-Diisobutylaminoethyl)-·2HCl·$2H_2O$	$C_{19}H_{35}N_3O_3Cl_2$	138–140	10.8	10.7
4-(δ-Diethylamino-α-methylbutyl)-·2HCl	$C_{18}H_{29}N_3OCl_2$	150–153	11.2	10.9
4-(γ-N-Piperidinopropyl)-	$C_{17}H_{23}N_3O$	164–166	14.7	14.6
4-(β-Diethylaminoethyl)-amino-6-methoxyquinaldine	$C_{17}H_{25}N_3O$	145–147	14.6	14.4
4-(γ-Diethylaminopropyl)-amino-6-methoxyquinaldine·2HCl·$2H_2O$[c]	$C_{18}H_{33}N_3O_3Cl_2$	125–126		

[a] Magidson and Rubtsov, *J. Gen. Chem.* (U. S. S. R.) **7**, 1896 (1937). [b] Side chain prepared by J. W. Corse of our laboratories. [c] Holcomb and Hamilton, THIS JOURNAL, **64**, 1309 (1942).

over magnesium sulfate, and the ether evaporated on the steam-bath. The residual oil was distilled at less than 1 mm. pressure, the fraction boiling at 200–220° being collected. The crystalline base could be obtained by the slow evaporation of an ether solution but, since a soluble salt was desirable for pharmacological testing, the 4-(γ-diethylaminopropyl)-amino-6-methoxyquinoline dihydrochloride was prepared by passing dry hydrogen chloride gas into the dry ethereal solution. The precipitated dihydrochloride was extremely hygroscopic and was very difficult to analyze.

The other quinoline compounds were prepared in an analogous manner, with the exception of the dialkylaminoethyl and the piperidino- and α-pipecolinopropyl derivatives which tended to crystallize from the ethereal solution during the first extraction. These were more easily isolated as the bases and recrystallized from ethyl acetate. The yields obtained in the preparation of these compounds varied from 55 to 80%.

The quinaldines were prepared similarly, starting with 4-chloro-6-methoxyquinaldine.[5] The melting points and analyses of these compounds are given in Table I.

4-(β-Diethylaminoethyl)-amino-6-hydroxyquinoline.—Five grams of 4-(β-diethylaminoethyl)-amino-6-methoxyquinoline was refluxed in 50 cc. of 40% hydrobromic acid for six hours. The solution was then evaporated *in vacuo* until a residue of crude 4-(β-diethylaminoethyl)-amino-6-hydroxyquinoline dihydrobromide was obtained. This residue was dissolved in water, treated with decolorizing carbon, filtered and neutralized with sodium hydroxide solution to about *p*H 9. The gum which separated was dissolved in ether, and the ethereal solution was dried with magnesium sulfate and evaporated. The crystals of 4-(β-diethylaminoethyl)-amino-6-hydroxyquinoline which separated during the evaporation were recrystallized from ethyl acetate. The dihydrochloride was obtained by passing dry hydrogen chloride gas into a dry ethereal solution of the base.

The other hydroxy compounds were prepared in a similar manner. The melting points and analyses of these compounds are given in Table I.

Acknowledgment.—We are indebted to the late Mr. J. T. Bryant for the microanalyses.

Summary

A series of dialkylaminoalkyl derivatives of 4-amino-6-methoxyquinoline, 4-amino-6-hydroxyquinoline and 4-amino-6-methoxyquinaldine has been prepared. The pharmacological data will be reported elsewhere.

INDIANAPOLIS, INDIANA RECEIVED MAY 1, 1944

(5) J. N. Ashley, C. H. Browning, J. B. Cohen and R. Gulbransen, *Proc. Roy. Soc.* (London), **113B**, 295 (1933).