having β-disubstituted aminoethyl, α-methyl-β-disubstituted aminoethyl and γ-disubstituted aminopropyl side chains.

INDIANAPOLIS, INDIANA RECEIVED JUNE 14, 1944

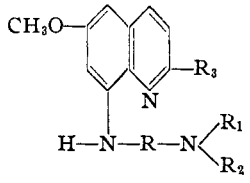
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Derivatives of 6-Methoxy-8-aminoquinoline and 2-Methyl-6-methoxy-8-aminoquinoline. II

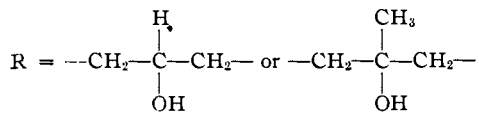
BY EWALD ROHRMANN AND H. A. SHONLE

There have been comparatively few substituted 8-aminoquinolines reported containing a free hydroxyl group in the side chain.[1,2] Magidson and Strukov[2] observed that the compound 6-methoxy-8-(β-hydroxy-γ-diethylaminopropylamino)-quinoline was highly active but was somewhat more toxic than the corresponding desoxy compound.

The present work was undertaken in order to obtain a better correlation between compounds of the type prepared by Magidson and Strukov[2] and the corresponding desoxy derivatives. The present paper concerns the preparation of quinoline derivatives of the type



where R_1 and R_2 = alkyl, cycloalkyl or alkene



and R_3 = H or CH_3.

The dialkylaminohydroxyalkyl chlorides which were coupled with 6-methoxy-8-aminoquinoline or 2-methyl-6-methoxy-8-aminoquinoline to yield the desired quinoline derivatives were prepared by treating epichlorohydrin or β-methylepichlorohydrin with the desired secondary amine in a suitable solvent such as ethanol. In most cases, the reaction proceeds readily at room temperature. In many cases the dialkylaminohydroxyalkyl chlorides can be purified by distillation, but this is not necessary since the crude reaction mixture may be used directly. Certain of the dialkylaminohydroxyalkyl chlorides such as the β-hydroxy-γ-diethylaminopropyl chloride and the β-hydroxy-γ-piperidinopropyl chlorides tend to decompose rather vigorously on vacuum distillation and this procedure for these compounds should be avoided.

Coupling of the dialkylaminohydroxyalkyl chlorides with the desired quinoline nucleus was carried out by refluxing in ethanol solution at 110–115° for two days. The yield of product varied from 40 to 65%. The reaction products were purified by distillation *in vacuo* and subsequent conversion to the dihydrochlorides.

These compounds have been tested in ducklings infected with *Plasmodium lophurae* by Mr. C. L. Rose of these Laboratories. Full details of the activities and toxicities of these compounds will be reported later.

The details of the preparation and properties of the secondary amines used in this work will be published at a later date in THIS JOURNAL.

We wish to thank Miss Shirley Crandall and the late Mr. J. T. Bryant of these Laboratories for the micro Dumas analyses reported herein. We also wish to thank Mr. R. D. Stayner for his assistance in the preparation of 6-methoxy-8-aminoquinoline and 2-methyl-6-methoxy-8-aminoquinoline.

Experimental[3]

6-Methoxy-8-aminoquinoline.—This was prepared by the usual Skraup synthesis[4] from 1-amino-2-nitro-6-methoxybenzene and the resulting 6-methoxy-8-nitroquinoline reduced with iron and hydrochloric acid.[5] The product was purified by distillation *in vacuo*.

2-Methyl-6-methoxy-8-aminoquinoline.—This was prepared essentially by the method described by Mathur and Robinson.[6] The nitro compound was reduced with iron and hydrochloric acid.[5] The product was purified by distillation *in vacuo*.

Dialkylaminohydroxyalkyl Chlorides.—To a solution of 0.25 mole of secondary amine dissolved in 25 cc. of ethanol and cooled to 20° was added 0.25 mole of epichlorohydrin or β-methylepichlorohydrin. The mixture may become warm spontaneously and external cooling may be required. This was particularly so with the lower alkyl amines and with the piperidines. The mixture was allowed to stand at about 25–30° overnight. The reaction mixture may be used directly in the subsequent condensation or in some cases it may be purified by distillation *in vacuo*. Distillation *in vacuo* is not advisable if the secondary amine is a rather reactive one, such as diethyl, methyl, *n*-propyl, pyrrolidine or the piperidines. The yields are about 70–75%.

Condensation with 8-Aminoquinolines.—A mixture of 0.1 mole of 6-methoxy-8-aminoquinoline or 2-methyl-6-methoxy-8-aminoquinoline and approximately 0.11 mole of the dialkylaminohydroxyalkyl chloride (a considerable excess does not appear to be detrimental to the reaction) was dissolved in 60 cc. of absolute ethanol and the solution refluxed on an oil-bath at a temperature of 110–115° for

(1) British Patent 267,169 (1927); German Patents 486,079, 488,945 (1942).

(2) Magidson and Strukov, *Arch. Pharm.*, **371**, 369 (1933).

(3) All melting points are uncorrected.

(4) Magidson and Strukov, *Arch. Pharm.*, **371**, 359 (1933).

(5) West, *J. Chem. Soc.*, **127**, 494 (1925).

(6) Mathur and Robinson, *ibid.*, 1520 (1934).

TABLE I

6-METHOXY-8-(β-HYDROXY-γ-R₁R₂-AMINOPROPYLAMINO)-QUINOLINES

	R_1	R_2	M. p., °C.	Formula	N analyses, % Calcd.	Found
1	Methyl	*n*-Propyl	183–185	$C_{17}H_{25}N_3O_2 \cdot 2HCl$	11.17	10.7
2	Ethyl	Isopropyl	217–219	$C_{18}H_{27}N_3O_2 \cdot 2HCl$	10.77	10.78
3	*n*-Propyl	*n*-Propyl	209–211	$C_{19}H_{29}N_3O_2 \cdot 2HCl$	10.40	10.25
4	Isopropyl	Isobutyl	183–186	$C_{20}H_{31}N_3O \cdot 2HCl$	10.03	9.85
5	Isopropyl	*n*-Butyl	173–176	$C_{20}H_{31}N_3O_2 \cdot 2HCl$	10.03	9.90
6	*n*-Butyl	*s*-Butyl	190–192	$C_{21}H_{33}N_3O_2 \cdot 2HCl$	9.73	9.89
7	*n*-Butyl	*n*-Butyl	155–157	$C_{21}H_{33}N_3O_2 \cdot 2HCl$	9.73	9.75
8	*n*-Butyl	Isobutyl	180–182	$C_{21}H_{33}N_3O_2 \cdot 2HCl$	9.73	9.60
9	Isobutyl	Isobutyl	197–199	$C_{21}H_{33}N_3O_2 \cdot 2HCl$	9.73	9.60
10	Isobutyl	*s*-Butyl	185–187	$C_{21}H_{33}N_3O_2 \cdot 2HCl$	9.73	9.82
11	Isobutyl	1-Methyl-butyl	190–192	$C_{22}H_{35}N_3O_2 \cdot 2HCl$	9.42	9.48
12	Isobutyl	Cyclopentyl	181–184	$C_{22}H_{33}N_3O_2 \cdot 2HCl$	9.45	9.56
13	*n*-Amyl	*n*-Amyl	134–136	$C_{23}H_{37}N_3O_2 \cdot 2HCl$	9.13	9.09
14	Isoamyl	Isoamyl	135–138	$C_{23}H_{37}N_3O_2 \cdot 2HCl$	9.13	9.27
15	Allyl	Allyl	175–177	$C_{19}H_{25}N_3O_2 \cdot 2HCl$	10.50	10.32
16	2-Methylpiperidino		162–165	$C_{19}H_{27}N_3O_2 \cdot 2HCl$	10.44	10.48
17	3-Methylpiperidino		208–211	$C_{19}H_{27}N_3O_2 \cdot 2HCl$	10.44	10.49
18	2,4-Dimethylpiperidino		163–166	$C_{20}H_{29}N_3O_2 \cdot 2HCl$	10.1	9.5
19	2,3-Dimethylpiperidino		171–174	$C_{20}H_{29}N_3O_2 \cdot 2HCl$	10.1	9.84
20	2,6-Dimethylpiperidino		212–215	$C_{20}H_{29}N_3O_2 \cdot 2HCl$	10.1	9.9

TABLE II

6-METHOXY-8-(β-HYDROXY-β-METHYL-γ-R₁R₂-AMINOPROPYLAMINO)-QUINOLINES

	R_1	R_2	M. p., °C.	Formula	N analyses, % Calcd.	Found
1	Methyl	*n*-Propyl	236–239	$C_{18}H_{27}N_3O_2 \cdot 2HCl$	10.76	10.6
2	Ethyl	Ethyl	230–233	$C_{18}H_{27}N_3O_2 \cdot 2HCl$	10.76	10.66
3	Ethyl	Isopropyl	231–233	$C_{19}H_{20}N_3O_2 \cdot 2HCl$	10.39	10.33
4	*n*-Propyl	*n*-Propyl	228–230	$C_{20}H_{31}N_3O_2 \cdot 2HCl$	10.02	9.91
5	Allyl	Allyl	165–168	$C_{20}H_{27}N_3O_2 \cdot 2HCl$	9.86	10.0
6	Isopropyl	Isobutyl	211–213	$C_{21}H_{33}N_3O_2 \cdot 2HCl$	9.73	9.74
7	*n*-Butyl	*n*-Butyl	185–187	$C_{22}H_{35}N_3O_2 \cdot 2HCl$	9.42	9.50
8	*n*-Butyl	Isobutyl	151–154	$C_{22}H_{35}N_3O_2 \cdot 2HCl$	9.42	9.31
9	Isobutyl	Isobutyl	135	$C_{22}H_{35}N_3O_2 \cdot 2HCl$	9.42	9.37
10	Isobutyl	*s*-Butyl	192–195	$C_{22}H_{35}N_3O_2 \cdot 2HCl$	9.13	9.29
11	*n*-Amyl	*n*-Amyl	172–174	$C_{24}H_{39}N_3O_2 \cdot 2HCl$	8.86	9.1
12	Isoamyl	Isoamyl	210–213	$C_{24}H_{39}N_3O_2 \cdot 2HCl$	8.86	8.68
13	Piperidino		247–250	$C_{19}H_{27}N_3O_2 \cdot 2HCl$	10.43	10.63
14	2-Methylpiperidino		232–235	$C_{20}H_{29}N_3O_2 \cdot 2HCl$	10.1	10.23
15	3-Methylpiperidino		214–216	$C_{20}H_{29}N_3O_2 \cdot 2HCl$	10.1	9.91
16	2,4-Dimethylpiperidino		232–235	$C_{21}H_{31}N_3O_2 \cdot 2HCl$	9.77	9.89
17	2,3-Dimethylpiperidino		239–241	$C_{21}H_{31}N_3O_2 \cdot 2HCl$	9.77	9.6
18	Pyrrolidino		255–258	$C_{18}H_{25}N_3O_2 \cdot 2HCl$	10.82	10.75

TABLE III

2-METHYL-6-METHOXY-8-(β-HYDROXY-β-R-γ-R₁R₂-AMINOPROPYLAMINO)-QUINOLINES

	R	R_1	R_2	M. p., °C.	Formula	N analyses, % Calcd.	Found
1	H	Isopropyl	Isobutyl	190-193	$C_{21}H_{33}N_3O_2 \cdot 2HCl$	9.73	9.43
2	H	*n*-Butyl	*n*-Butyl	159-162	$C_{22}H_{35}N_3O_2 \cdot 2HCl$	9.42	9.56
3	H	*n*-Butyl	Isobutyl	175–177	$C_{22}H_{35}N_3O_2 \cdot 2HCl$	9.42	9.47
4	H	Isobutyl	Isobutyl	209–211	$C_{22}H_{35}N_3O_2 \cdot 2HCl$	9.42	9.7
5	CH_3	Isobutyl	Isobutyl	211–214	$C_{23}H_{37}N_3O_2 \cdot 2HCl$	9.42	9.32
6	CH_3	Isobutyl	*s*-Butyl	192–195	$C_{23}H_{37}N_3O_2 \cdot 2HCl$	9.13	9.21

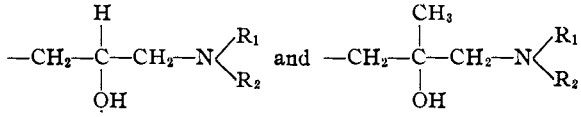
approximately forty-eight hours. The reaction mixture was then diluted with about 300 cc. of water and made strongly alkaline with sodium hydroxide. The liberated base was taken up in ether and the ethereal solution dried over anhydrous magnesium sulfate. The ether was evaporated on a steam-bath and the residual material distilled *in vacuo* from a Claisen flask heated on an oil-bath. The main fraction of high boiling material forms a viscous yellow oil. This was dissolved in about 60 cc. of absolute ethanol and saturated with dry hydrogen chloride. Anhydrous ether was now added until crystallization began. The mixture was then cooled at 0°. Recrystallization was

effected from ethanol-ether. The products form yellow or orange colored crystals.

Samples for analysis were dried at 100–120° *in vacuo* for one hour. Some of the compounds contained a molecule of water of crystallization which was lost with difficulty.

Summary

Forty-four new disubstituted amino derivatives of 8-aminoquinolines have been prepared. These cover compounds having the groupings



in the side chain.

INDIANAPOLIS, INDIANA RECEIVED JUNE 14, 1944

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

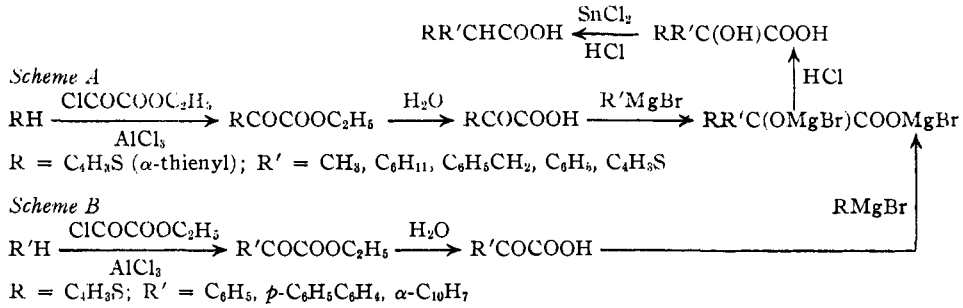
Antispasmodics. VII[1]

BY F. F. BLICKE AND M. U. TSAO[2a,b]

The pharmacological equivalence of certain compounds which contain a benzene ring and corresponding α-thienyl derivatives has been demonstrated, at least in a qualitative sense, in a number of instances,[3] however, the literature contains little information with regard to quantitative comparisons or to the possible clinical merits of thiophene derivatives.

Basic-alkyl esters of diphenyl-, cyclohexylphenyl-, benzylphenyl-, α-naphthylphenyl- and *p*-xenylphenylacetic acid have been shown to be active antispasmodics.[4] During this investigation we have synthesized α-thienyl analogs of these types of esters, that is, basic-alkyl esters of di-α-thienyl-, phenyl-α-thienyl-, benzyl-α-thienyl-, α-naphthyl-α-thienyl- and *p*-xenyl-α-thienylacetic acid. We obtained the disubstituted acetic acids from the corresponding disubstituted hydroxyacetic acids, and in some instances the latter also were converted into basic-alkyl esters, and examined pharmacologically; esters of the following disubstituted hydroxyacetic acids were obtained: methyl-α-thienyl-, cyclohexyl-α-thienyl-, phenyl-α-thienyl-, α-naphthyl-α-thienyl- and *p*-xenyl-α-thienylhydroxyacetic acid. The basic-alkyl groups in the esters were represented by such radicals as β-diethylaminoethyl, β-morpholinoethyl, β-piperidinoethyl, γ-diethylaminopropyl and γ-dibutylaminopropyl. The esters were tested pharmacologically in the form of their water-soluble hydrochlorides, hydrobromides or methobromides.

The antispasmodic activity of our esters was determined by Dr. A. M. Lands and Miss V. L. Nash in the Frederick Stearns and Company Laboratories.[5] In general, the spasmolytic activity of the esters of hydroxyacetic acids on the isolated intestinal strip which had been stimulated with acetylcholine was found to be much greater than that of the esters of acetic acids. The remarkable effectiveness of some of these esters, especially those which contain a cyclohexyl group, is shown in Table V. Several of the esters are equal to, or exceed, atropine in activity, a potency seldom found hitherto in synthetic antispasmodics.



The required disubstituted hydroxyacetic and disubstituted acetic acids were prepared in the manner indicated above.

The acetic acids were converted into the basic-

(1) Presented before the Division of Medicinal Chemistry at the 108th Meeting of the American Chemical Society in New York, N. Y., Sept. 11–15, 1944.

(2) (a) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by M. U. Tsao in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan. (b) Frederick Stearns and Company Fellow.

(3) Finzi, *Gazz. chim. ital.*, **45**, 11, 280 (1915); Steiukopf and Wolfram, *Ann.*, **437**, 22 (1924); Erleumeyer, Berger and Leo, *Helv. Chim. Acta*, **16**, 733 (1933); Blicke and Zienty, THIS JOURNAL, **63**, 2945 (1941); Rhodehamel and Degering, *J. Am. Pharm. Assoc.*, **31**, 281 (1942); Blicke and Burckhalter, THIS JOURNAL, **64**, 477 (1942); Warren, Marsh, Thompson, Shelton and Becker, *J. Pharmacol. Exptl. Therap.*, **79**, 187 (1943); and Dann, *Ber.*, **76**, 419 (1943).

(4) For a discussion of these compounds see Blicke, *Ann. Rev. Biochem.*, **13**, 549 (1944).

(5) See Lands and Nash, *Proc. Soc. Exptl. Biol. Med.*, (in press) 1944.