New Derivatives of Quinuclidine as Potential Antihypertensive Agents

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Five new 3-aminoalkoxy derivatives of quinuclidine have been synthesized. All compounds reduced blood pressure in dogs to varying degrees, the most effective being 3-(3-dimethylaminopropoxy) quinuclidine. The evidence points to ganglionic blockade as the principal mechanism of action with the possibility that it may also be due to some direct depressant action on the cardiovascular system

QUINUCLIDINE, 1-azabicyclo[2.2.2]octane, is an integral part of the quinine molecule. Because of the many and varied responses produced by quinine and the other cinchona alkaloids, there has been a great interest in the quinuclidine nucleus as a possible therapeutic agent. Quinuclidine itself, as the hydrochloride salt, has been found to be a potent hypotensive and smooth muscle relaxant (1).

Therapeutically active quinuclidine derivatives have been synthesized and pharmacological activity has been found in both mono- and disubstituted products. The range in activity is quite varied.

The greatest volume of synthetic work involved the preparation of 3-substituted quinuclidines. Series of esters of bicyclic aminoalcohols, including 3-quinuclidinol have been prepared by Martell and Soine (2), by Sternbach and Kaiser (3), and by Mikhlina and Rubtsov (4). These derivatives have marked spasmolytic activity, one of the most active being 3-diphenylacetoxyquinuclidine.

Several 3-substituted derivatives of quinuclidine have been reported by Grob (5) to stimulate the central nervous system.

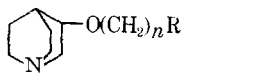
A series of 2-aminomethyl quinuclidines have been prepared and tested by Nikitskaya *et al.* (6). Some members of the series were found to have strong ganglionic blocking activity. Diethylaminoethyl-quinuclidine-2-carboxylate was found to be a good hypotensive. Ganglionic blocking was also noticed with 2,3-disubstituted products (7), the greatest activity being shown by 2-*N*-phenylaminomethyl-3-(2-*N*-phenylaminoethyl) quinuclidine. Perrine (8) synthesized a series of 4-phenyl substituted compounds for investigation as possible analgesics.

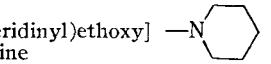
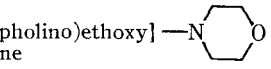
This investigation is involved with the synthesis of a series of 3-aminoalkoxy derivatives of quinuclidine and the pharmacological testing of their dimethiodide salts. All of the compounds showed antihypertensive activity, the most effective being 3-(3-dimethylaminopropoxy) quinuclidine.

DISCUSSION

Five new compounds were synthesized and are represented by the general formula shown. All products were prepared as the dimethiodide salts.

All compounds were prepared by the Williamson synthesis. A mixture of sodium and 3-quinuclidinol was refluxed in dry benzene to give sodium 3-quinuclidinoxide. This was reacted with the various aminoalkyl chlorides to give the corresponding ethers. These compounds were high boiling, colorless liquids which darkened upon standing.



	R	*n*
I, 3-(2-diethylaminoethoxy) quinuclidine	$-N(C_2H_5)_2$	2
II, 3-(2-dimethylaminoethoxy) quinuclidine	$-N(CH_3)_2$	2
III, 3-(3-dimethylaminopropoxy) quinuclidine	$-N(CH_3)_2$	3
IV, 3-[2-(1-piperidinyl)ethoxy] quinuclidine		2
V, 3-[2-(1-morpholino)ethoxy] quinuclidine		2

An attempt was made to isolate the ethers as their hydrochloride salts. This was done by bubbling dry HCl into a cold benzene solution of the ethers. The oily residues which formed were extremely hygroscopic and could not be crystallized.

The products were ultimately isolated as their dimethiodide salts which were stable in air and very soluble in water.

The infrared spectra showed characteristic alkyl ether bands between 8.9–9.4 mμ. Elemental analysis further confirmed the preparation of the desired products (Table I).

EXPERIMENTAL

All melting points are uncorrected. Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Sodium 3-Quinuclidinoxide—Into a 300-ml. 3-necked flask equipped with stirrer, dropping funnel, and condenser (drying tube) were placed 10.0 Gm. (0.08 mole) of 3-quinuclidinol[1] and 100 ml. of dry benzene. This mixture was heated until the 3-quinuclidinol was completely dissolved. Then 1.0 Gm. (0.08 mole) of sodium, cut into small strips, was added over a period of 1 hr. while heating and stirring. The mixture was refluxed until all the sodium had reacted (about 48 hr.) whereupon a light yellow slurry resulted.

Aminoalkyl Chlorides—These were prepared by the neutralization of the hydrochloride salts with sodium hydroxide according to the method of

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[1] Supplied by U. S. Army Chemical Center, Edgewood, Md. Can be prepared by the method described by Aaron, H. S., Elkin, S., Owens, O. O., Rosenstock, P. D., Leonard, S., and Miller, J. I., *J. Org. Chem.*, **30**, 1331(1965).

TABLE I—ANALYSIS OF THE 3-AMINOALKOXY DERIVATIVES OF QUINUCLIDINE

	Compd.	Yield, %	B.p.	Yield, % (Dimethiodide)	M.p., °C.	Anal. (Dimethiodide) Calcd.	Found
I	3-(2-Diethylaminoethoxy) quinuclidine	79	129–132°/6 mm.	63.3	214–216°	$C_{15}H_{32}I_2N_2O$	
						C, 35.31	35.77
						H, 6.32	6.46
						N, 5.49	5.14
						I, 49.47	49.57
II	3-(2-Dimethylaminoethoxy) quinuclidine	55	110/112°/4 mm.	57.3	282–283°	$C_{13}H_{28}I_2N_2O$	
						C, 32.38	32.33
						H, 5.85	5.86
						N, 5.81	5.40
						I, 52.64	51.66
III	3-(Dimethylaminopropoxy) quinuclidine	40	102–103°/2 mm.	62.2	258–259°	$C_{14}H_{30}I_2N_2O$	
						C, 33.89	33.59
						H, 6.09	6.06
						N, 5.65	5.43
						I, 51.15	50.18
IV	3-[2-(1-Piperidinyl)ethoxy] quinuclidine	35	128–132°/1 mm.	24	233–235°	$C_{16}H_{32}I_2N_2O$	
						C, 36.79	36.73
						H, 6.18	6.22
						N, 5.35	5.22
						I, 48.60	47.92
V	3-[2-(1-Morpholino)ethoxy] quinuclidine	12	137–138°/1 mm.	19	241–243°	$C_{15}H_{30}I_2N_2O$	
						C, 34.36	35.13
						H, 5.34	5.87
						N, 5.51	5.32
						I, 48.41	47.55

Shirley (9). *N*-(β-Chloroethyl) piperidine could not be isolated in pure form as heating produced a viscous nondistillable substance. An ether solution of the crude material was used in the reaction.

Preparation of Ethers—The aminoalkyl chloride (0.08 mole) was added dropwise, over a period of 1 hr., to a refluxing suspension of sodium 3-quinuclidinoxide (0.08 mole) in dry benzene. The mixture was refluxed for 48 hr., cooled, filtered, and the residue washed with 10–20 ml. of dry benzene. After removing the benzene the residue was distilled under reduced pressure to give the ether and unreacted 3-quinuclidinol. The distillate, cooled in a dry ice–acetone bath, was treated with 10–20 ml. of anhydrous ether, and the precipitated 3-quinuclidinol was removed by filtration. The filtrate, after removal of the ether, was distilled under reduced pressure.

Preparation of Dimethiodides—Excess methyl iodide was added dropwise, with stirring, to a cold benzene solution of the ether whereupon a white precipitate formed. The mixture was filtered and the residue recrystallized from hot absolute ethanol.

PHARMACOLOGY

Preliminary pharmacological evaluation showed that all of the compounds evoked some degree of antihypertensive activity, the most effective being the dimethiodide of 3-3-dimethylaminopropoxy quinuclidine. The pharmacological study of the latter is described.

Method—Mongrel dogs weighing 8 to 13 Kg. were anesthetized with sodium pentobarbital, 30 mg./Kg., given intravenously. Mean arterial blood pressure was monitored from an exposed cannulated femoral artery, using a Statham pressure transducer attached to a multichannel recorder (Electronics for Medicine); heart rate was measured with a lead 2 to electrocardiogram and cardiac output using a standard indocyanine green[2] dye dilution technique. Injections of drugs were made into a cannulated femoral vein.

TABLE II—CARDIOVASCULAR DYNAMICS OF 3-(3-DIMETHYLAMINOPROPOXY) QUINUCLIDINE

	Normal	After Drug Adm. 5 min.	25 min.
B.P.[a]	131	99	90
H.R.[b]	184	144	128
C.O.[c]	2.715	1.564	1.546
S.V.[d]	14.7	10.7	12.0
T.P.R.[e]	3.13	3.97	3.72
No. animals	5	4	5

[a] Mean blood pressure in mm. Hg. [b] Mean heart rate in beats per minute. [c] Mean cardiac output in liters per minute. [d] Mean stroke volume in ml. [e] Mean calculated total peripheral resistance in arbitrary units.

Following control measurements of the various parameters described, the compound was injected intravenously at a dose of 3.0 mg./Kg. in one animal and at 5.0 mg./Kg. in 9 other animals since the latter dose produced greater and more prolonged effects.

Results—Blood pressure usually fell precipitously reaching a nadir within 30 to 40 sec. following injection, then rose slightly but generally stabilized within 3 to 4 min. at a level significantly lower than the control. Along with the hypotension there occurred a significantly reduced heart rate and cardiac output and some depression in stroke volume. The calculated total peripheral resistance showed a slight increase (Table II). Pressure gradually rose over a period of 2 hr. but was still significantly reduced at the end of this time interval.

[2] Cardio-green.

In an attempt to delineate the mechanism of action of this compound a number of pharmacologic techniques were employed. Atropine sulfate, 0.5 mg./Kg., did not alter the action of the compound. It was subsequently determined that the compound could effectively block the following procedures: electrical stimulation of the peripheral end of the right vagus, the carotid occlusion pressor reflex, and the pressor effect of nicotine salicylate. In addition, potentiation of the pressor response to epinephrine was noted as well as elimination of the reflex vagal effect that usually develops at the height of the epinephrine response. These findings were observed in 3 animals 20 to 30 min. following administration of the compound.

CONCLUSIONS

The evidence points to ganglionic blockade as the principal mechanism of action of this agent, however, the possibility that it may also exert some direct depressant action on the cardiovascular system has not been eliminated.

SUMMARY

Five new derivatives of quinuclidine have been prepared by reacting 3-quinuclidinol with various aminoalkyl halides *via* the Williamson synthesis. The resulting ethers, as the dimethiodide salts, were tested for antihypertensive activity. All showed varying degrees of activity, the most effective being 3-(3-dimethylaminopropoxy) quinuclidine.

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Determination of Moisture in Crude Drugs by Gas–Liquid Chromatography

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The use of gas–liquid chromatography was investigated as a means of determining the moisture content of crude drugs. Sixteen crude drugs representing a variety of plant parts and products were analyzed using this technique. Water was extracted from the crude drugs by disintegration with anhydrous methanol in a Waring blender and analyzed with a column of Teflon-6 coated with 10 percent polyethylene glycol 1500, using *n*-propanol as an internal standard. Peak height ratios were used to calculate the moisture content. The results obtained with the gas–liquid chromatographic procedure were quantitatively in accord with the results obtained by oven drying at 105° and toluene distillation methods. In addition, the new chromatographic procedure is simpler, more rapid, and has a very good precision (the maximum standard deviation was 0.36).

THE USE of gas–liquid chromatography for the direct analysis of moisture in a number of materials has been reported by many investigators. This technique was found to be reliable and convenient. Most of these studies utilized the method for the analysis of aqueous solutions of organic compounds (1–8). In only a few instances has this method been applied to the determination of water in natural products. The National Bureau of Standards (9) has adopted gas–liquid chromatography for moisture determination of grains. Schwecke and Nelson (10) used gas–liquid chromatography in determining the moisture content of cereal pellets, dried raisins, flour, and other food, and Brekke and Conrad (11) measured the water content of fruits and fruit products employing the same technique.

The simplicity, rapidity, and accuracy of the gas chromatographic process should also make the method well suited to the estimation of moisture in crude drugs. The methods currently recognized in the USP and NF for moisture content measurement of crude drugs include oven drying and toluene distillation. Both of these methods are time-consuming, and in the case of toluene distillation, the use of a comparatively large sample of the crude drug is a further disadvantage. The present investigation was, therefore, undertaken in order to develop an alternate procedure for the rapid measurement of moisture content in crude drugs utilizing a direct gas–liquid chromatographic technique.

EXPERIMENTAL

The crude drugs used in this work were obtained from S. B. Penick and Co., New York, N.Y. All drugs, except digitalis and peppermint leaves, were in powdered form. The leaf samples of digitalis and peppermint were powdered, before analysis, according to the NF XII (12) specification.

Moisture Determination by Oven Drying—The moisture content of all of the crude drugs, except

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