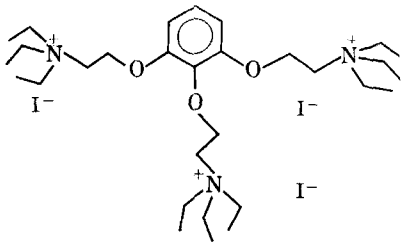
Quaternary Salts of 2,4-Bis(dialkylaminoalkoxy)quinazolines. Potential Curaremimetics

By RONALD E. ORTH

Bis-quaternary salts of 2,4-bis(dialkylaminoalkoxy)quinazolines were prepared from the corresponding bis-tertiary amines as potential curaremimetic agents.

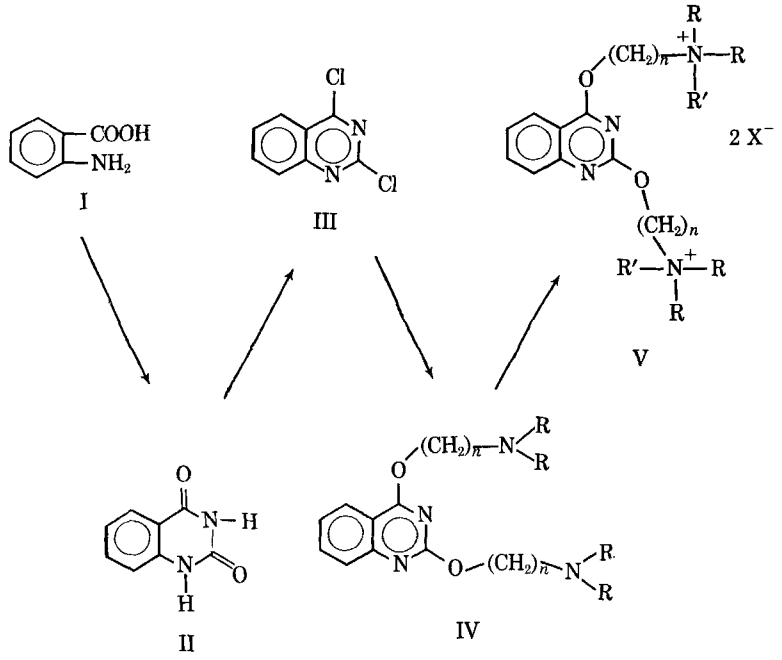
TUBOCURARINE CHLORIDE and drugs which act in a similar manner are utilized to induce muscle relaxation in neuromuscular disorders and during abdominal surgery. These applications were made only after it was demonstrated that the drug acts at the myoneural junction. However, tubocurarine chloride exerts undesirable autonomic ganglionic effects which have led investigators to continue the quest for a more specific myoneural blocking agent. Numerous investigations have ensued. Brown and Fraser suggested the pharmacological activity of various quaternary salts (1) and Craig found that all "onium" containing compounds may be expected to exhibit curare-like activity (2). Two or more quaternized moieties within a single substance were shown to produce higher activity by virtue of a more firm attachment at the site of action (3, 4). A distance of approximately 15 Å. between "onium" heads in a homologous series was suggested for maximum curariform activity. Stenlake *et al.* studied linear chemicals with three, four, and five "onium" heads and found that the number of these centers influenced potency, reversibility, and the duration of action



Gallamine Triethiodide N.F. XII

(5, 6). In 1949 Bovet *et al.* attempted to reproduce synthetically a simplified version of the tubocurarine molecule (7). They achieved the synthesis of a series of bis-quinoline derivatives wherein the aromatic structures were connected through a methylene chain by ether linkages. The same group examined some simple mono- and polyphenolic ethers of certain aminoalcohols and found that these substances also possessed a striking curariform activity. The best-known of this latter series is the triethiodide of tris(β-diethylaminoethoxy)-1,2,3-benzene (gallamine triethiodide).

Hohmann and Jones demonstrated high curare-like activity in several quaternary salts of 2,4,6-tris(dialkylaminoalkoxy)-1,3,5-triazines and 2,4-bis(dialkylaminoalkoxy)quinazolines (8). The paralyzing doses required in the mouse sloping-screen and rabbit head drop tests were calculated and sum-

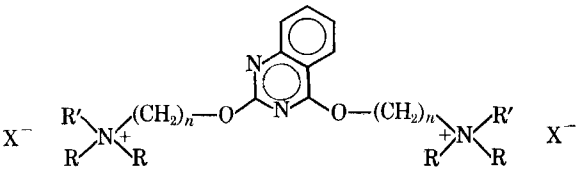


I, anthranilic acid; II, 2,4-(1*H*,3*H*)quinazolinedione (9); III, 2,4-dichloroquinazoline (10); IV, 2,4-bis(dialkylaminoalkoxy)quinazoline (8); V, title compounds. *n* is 2 or 3; R is methyl or ethyl; R′ is ethyl or benzyl; X is chloride, iodide.

Scheme I

Received January 3, 1967 from the Department of Pharmaceutical Chemistry, College of Pharmacy, University of Kentucky, Lexington, KY 40506
Accepted for publication March 22, 1967.

TABLE I—BIS-QUATERNARY SALTS OF 2,4-BIS(DIALKYLAMINOALKOXY)QUINAZOLINES



	Quaternary Salt				% N		% Halide			
	n	R	R′	X⁻	Calcd.	Found[b]	Calcd.	Found[b]	Dec. Pt., °C.	% Yield
I	2	Me	Et	I⁻	9.09	8.77	41.2	40.1	261–263	71
II	2	Me	Bzyl[a]	Cl⁻	10.0	10.0	12.7	12.0	257–258	85
III	2	Et	Et	I⁻	8.33	8.31	36.3	36.3	232–233	68
IV	2	Et	Bzyl[a]	Cl⁻	9.07	9.02	11.6	11.4	244	81
V	3	Et	Et	I⁻	8.00	7.83	36.3	36.3	254–256	77
VI	3	Et	Bzyl[a]	Cl⁻	8.73	8.67	11.1	11.2	271–273	91

[a] Benzyl. [b] Elemental analysis by Dr. G. Weiler and Dr. F. B. Strauss, Microanalytical Laboratory, Oxford, England.

marized using gallamine as a standard. In both tests 2,4,6-tris(β-diethylaminoethoxy)-1,3,5-triazine tribenzchloride proved superior to gallamine and other salts of the triazine and quinazoline series. Unfortunately, the LD_{50} for this substance was 5.05 mg./Kg. The quinazolines, however, were potent and much less toxic than the corresponding triazines. No obvious increase in potency was attributed to the trimethylene side chain moiety over dimethylene in the quinazoline series. It was noted in both series that *N,N*-diethyl substitution produced more potent activity than *N,N*-dimethyl. Since only the methiodides of the quinazolines were prepared, several of the potentially more active ethiodides and benzchlorides are synthesized. (Scheme I.)

EXPERIMENTAL

2, 4 - Bis (dialkylaminoalkoxy) quinazolines—Twelve grams of 2,4-dichloroquinazoline, prepared by the method of Lange *et al.* (10), was dissolved in 50 ml. of dry benzene and added to a cooled suspension of sodium aminoalkoxide prepared by reacting 2.8 Gm. (0.12 *M*) of sodium with 0.18 *M* of the dialkylaminoalkanol. The mixture is refluxed for 2 hr., cooled, washed with water, and dried over Na_2SO_4. Most of the benzene is then removed at atmospheric pressure. The remaining mixture is distilled twice to obtain the pure amine (8). 2,4-Bis(diethylaminoethoxy)quinazoline: 225–226°/4 mm. (54% yield). 2,4-Bis(diethylaminopropoxy)quinazoline: 230–233°/2 mm. (40% yield). 2,4-Bis(dimethylaminoethoxy)quinazoline: 234–236°/9 mm. (35% yield).

Diethiodide and Dibenzchloride Salts—Reflux 0.1 *M* of the amine and 0.5 *M* of the halide in 50 ml. of absolute ethanol for 2 hr. Absolute ether is then added until the quaternary salt precipitates. The solid is collected on a filter, washed with dry ether, and dried in a vacuum oven at 60°. The yields, melting points, and analytical data are given in Table I.

REFERENCES

(1) Brown, A. C., and Fraser, T., *Tr. Roy. Soc. Edinburgh*, **25**, 151, 693(1868–1869).
(2) Craig, L. E., *Chem. Rev.*, **42**, 285(1948).
(3) Phillips, A. P., and Castillo, J. C., *J. Am. Chem. Soc.*, **73**, 3949(1951).
(4) Cavallito, C. J., Soria, A. E., and Hoppe, J. O., *ibid.*, **72**, 2661(1950).
(5) Edwards, D., Stenlake, J. B., Lewis, J. J., and Stothers, F., *J. Med. Pharm. Chem.*, **3**, 369(1961).
(6) Carey, F. M., Furst, C. I., Lewis, J. J., and Stenlake, J. B., *J. Pharm. Pharmacol.*, **16**, Suppl. 89T(1964).
(7) Bovet, D., Depierre, F., Courvoisier, S., and deLestrange, Y., *Arch. Intern. Pharmacodyn.*, **80**, 172(1949).
(8) Hohmann, J. R., and Jones, J. W., *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 453(1954).
(9) Lange, N. A., and Sheibley, F. E., "Organic Synthesis," coll. vol. II, Blatt, A. H. ed., John Wiley & Sons, Inc., New York, N. Y., 1943, pp. 79–80.
(10) Lange, N. A., Roush, W. E., and Asbeck, H. J., *J. Am. Chem. Soc.*, **52**, 3696(1930).