CURARIFORM ACTIVITY AND CHEMICAL STRUCTURE

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I. Introduction

It has been known for many years that the material called curare has the effect of causing muscular paralysis when injected into frogs or mammals. This material had been brought from South America to Europe in small quantities by explorers, and was known to have been prepared by the natives in the form of aqueous extracts and concentrates for use as an arrow poison. The samples available for scientific examination have varied so widely in botanical origin, physiological potency, and chemical constitution that it is only in recent years

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that definite information has been obtained about the chemical compounds responsible for the "curare activity" of the South American curare.

The physiological effect of curare (curare or curariform activity) has been found to have useful applications in surgery and in the treament of spastic and other paralytic conditions. Furthermore, a large number of synthetic and naturally occurring organic compounds have been studied which have physiological effects similar to, although in practically all cases less intense than, the active materials present in South American curare.

The object of the present paper is to review the literature and to tabulate the compounds which have been reported to exhibit curare or curare-like activity in order to deduce, if possible, what units of chemical structure are responsible for, enhance, or reduce this activity. Other types of physiological actions which frequently accompany curare activity have been recorded.

II. Historical

The paralyzing action of curare has been known for centuries. The first record of the primitive use of curare is in Hakluyt's description of Sir Walter Raleigh's contact with Indians of the Orinoco in 1595. Watterton and Brodie in 1815 demonstrated that death from curare was due to respiratory failure. Bernard in 1844 first described the location of the physiological action of curare as being at the junction of the nerve and muscle (myoneural junction). The paralytic action of curare led to its early investigation in causing relaxation of muscles in such convulsive conditions as epilepsy, rabies, tetanus, strychnine poisoning, and various tics. The non-homogeneity of the crude curare preparations made physiological investigations and clinical use difficult, with the result that chemical investigations were started (8, 74).

The chemical examination of curare preparations was first carried out in 1829 by Roulin and Boussingault (187), who isolated a syrupy mass which they called curarine. In the period following, Buchner (18), Preyer (158), Sachs (188), and other workers isolated amorphous alkaloids for which they proposed various structures. Boehm (12) brought some order into the curare field when he showed that the South American curare preparations were of three kinds, distinguished by the type of container in which they were packed. They were (*a*) para, tube, or bamboo curare, packed in bamboo tubes, (*b*) pot curare, exported in small earthenware pots, and (*c*) gourd or calabash curare, packed in small gourds. Furthermore, Boehm showed that curare preparations contained several alkaloids of two general types: amorphous quaternary bases which produced the curare action, and tertiary bases which were inactive. The constitution of the various curare preparations depended on the botanical origin, which not only differed among the three types of curare but also differed from sample to sample of the same type. Curare was first believed to be prepared from South American *Strychnos* species, but later chemical evidence indicated that the alkaloids also occur in menispermaceous plants (86).

King (129) isolated the first crystalline active alkaloid, *d*-tubocurarine chloride, from tube curare, and found that a dose of 0.5 mg./kg. produced complete curare paralysis of frogs, as compared to doses of 2.5–5 mg./kg. required of various curare preparations. He (129, 130) was able to show that *d*-tubocurarine

chloride was a diquaternary base with a bisbenzyltetrahydroisoquinoline type structure (see Section IV,D,1 on page 351 *et seq.* for the chemistry of the curare alkaloids). King's chemical evidence (131) indicated that there was a close relationship between the alkaloids of pot and tube curare.

More recently, Wintersteiner and Dutcher (223) isolated *d*-tubocurarine chloride from a sample of South American curare which was known to have been prepared from only one plant species, *Chondodendron tomentosum* Ruiz and Pavon. This gave a source of a pure, active curare alkaloid and of standardized curare preparations, so that physiological and clinical investigations could be carried out with a greater degree of certainty.

Investigations of gourd curare have not been as extensive as those of the other types. Wieland and coworkers (217–220) isolated a group of very active quaternary alkaloids from gourd curare, which have been shown by preliminary examination to be different in chemical nature from the other curare alkaloids (see Section IV,D,1). Although these alkaloids are very active physiologically, some even more active than *d*-tubocurarine, no reports of any investigations as to their possible therapeutic value were found.

III. Curariform Activity

A. Physiological Aspects

Since Bernard's discovery of the peripheral location of the action of curare, many investigations as to the mechanism of curare action have been carried out. It is generally agreed that the curare action is one of prevention, in some manner, of the transfer of impulses from the nerve to the muscle at the myoneural junction.

The most widely accepted theory for the mechanism of neuromuscular transmission is the acetylcholine theory, which states that an impulse from the nerve causes the formation of acetylcholine which in turn causes stimulation of the muscle. The acetylcholine formed by each impulse is quickly hydrolyzed by cholinesterase, and the process, which takes place at the myoneural junction, is repeated for each impulse of the nerve. Rosenblueth and coworkers (186a, 210) postulated that there is a range of concentrations of acetylcholine to which the muscle responds. Response by the muscle does not occur if the concentration is below the "threshold of excitation" or above the "upper paralytic boundary". This postulate explains why the injection of acetylcholine or drugs that are known to inhibit the action of cholinesterase cause curare-like paralysis, since the acetylcholine would be present in concentrations above the upper paralytic boundary. Because curare does not interfere with the liberation of acetylcholine and does not inhibit the action of cholinesterase, they believed that the action of curare was one of raising the threshold of excitation of the muscle. Thus, it is postulated that although the usual amount of acetylcholine is produced by the impulse from the nerve, it is not enough to cause response by the muscle.

The peripheral paralysis due to curare occurs in a definite order, so that the first signs of curare poisoning are dropping of the eyelids, drowsiness, loss of speech, and paralysis of the neck muscles. The extremities are then affected, followed by the muscles of the diaphragm; finally, death occurs from respiratory failure. A compound which produces a true curariform action has no effect on

the central nervous system or the heart. Reflexes are diminished but not abolished, and a paralyzed muscle returns to its normal state without showing any harmful effects. That death occurs from respiratory failure before other toxic manifestations are noted has been shown by giving dogs up to fifty times the ordinary lethal dose of a curare preparation without fatality by maintaining artificial respiration (8, 74).

The nature of the action of curare led to early investigations as to the possible therapeutic use in treatment of various neuromuscular disorders. Some success has been attained in the use of curare for relaxation of muscles during surgery and for treatment of various convulsive states. The difficulties encountered because of non-homogeneity of preparations have been alleviated by the availability of purified, standardized preparations; however, the margin of safety is still low. Another disadvantage has been that it is ineffective orally (8, 86). Because of these difficulties, many other compounds which produce a curare-like effect have been investigated clinically, the most notable being certain erythrina alkaloids. Erythroidine and dihydro-β-erythroidine, the two erythrina alkaloids which have been used extensively, have shown considerable promise as therapeutic agents, particularly because they are effective orally (20, 57). Their main disadvantage is that they do not have as intense and prolonged an action as the curare alkaloids (19, 20).

Since the known drugs exhibiting curariform activity have certain disadvantages, it was hoped that a literature survey would furnish chemical information that could be used in preparing new drugs or improving old ones.

B. TYPES OF COMPOUNDS EXHIBITING CURARIFORM ACTIVITY

Since the active curare alkaloids were quaternary, Brown and Fraser (15, 16) in 1868 attributed curariform action to the onium ion. Since that time many quaternary salts have been investigated, and it has been found that quaternary ammonium, sulfonium, phosphonium, arsonium, and stibonium salts all possess curare activity (5, 32, 102). The onium salts in the order of decreasing intensity of curare action are as follows (167):

$$(CH_3)_4N^+ > (CH_3)_3S^+ > (CH_3)_4P^+ > (CH_3)_4As^+ > (CH_3)_4Sb^+$$

Actually, the ammonium, potassium, and sodium ions and ions of other alkali metals have been shown to exhibit curare activity in varying degrees (5, 32). Attempts have been made, though with little success, to relate quantitatively the intensity of the curare action with the size (5, 117) and the mobility (167) of the cation, since it was the ionic nature of the material which seemed to be essential for the physiological action.

Folkers and Major (57) isolated an active principle, which they called β-erythroidine, from an extract of the seeds of *Erythrina americana* Mill., which had been known for some time to possess curare activity. Subsequent chemical investigations showed that this compound contains a tertiary nitrogen instead of a quaternary nitrogen. This was the first example of a tertiary nitrogen compound that exhibited a marked curare action and, as stated above, the action was of such a nature that the drug has been used clinically rather extensively.

During a systematic investigation of the pharmacological properties of α-glycerol ethers, Berger and Bradley (9) in 1946 observed that certain of the compounds produced paralysis and marked muscular reaction. Further investigations of the most effective of these ethers, α-(*o*-tolyl)glycerol ether, showed that while the action was partially curare-like, it was mostly a depressant action in the spinal cord (9, 10). However the net effect, muscular paralysis, was the same, and this type of compound was proposed as a curare substitute.

C. OTHER PHYSIOLOGICAL ACTIONS FREQUENTLY ACCOMPANYING CURARIFORM ACTIVITY

Hunt and coworkers (99–116) and Renshaw and coworkers (163–183) published a series of papers on onium compounds and their effect on the autonomic nervous system. They attributed three general types of action to quaternary ammonium compounds: curare action, muscarinic action, and nicotinic action.

A muscarinic action is one of direct stimulation of smooth muscles, which is manifest in mammals by slowing of the heartbeat, depression of the blood pressure, vasodilatation, miosis, bronchial constriction, salivation, and sweating (74). Renshaw (163) and Hunt (101, 102) used as a criterion for muscarinic activity the production of a fall in blood pressure which was prevented by atropine, the latter being a specific antagonist to muscarinic activity.

A nicotinic action consists of a primary transient stimulation and a secondary more persistent depression of all sympathetic and parasympathetic ganglia. Thus, the first signs of a nicotinic action are a rise in blood pressure due to peripheral vasoconstriction, followed by a falling of the blood pressure due to vasomotor paralysis. In the stage of paralysis, nicotine thus manifests a curare-like paralysis which largely explains the fact that death from nicotine is due to respiratory failure (74). Renshaw (163) and Hunt (101, 102) distinguished between stimulating and paralyzing nicotinic actions of the onium compounds. Their criterion for a stimulating nicotinic action was a rise in blood pressure which was prevented by a large dose of nicotine. A compound was said to exhibit a paralyzing nicotinic action if it prevented the stimulating action of a small dose of nicotine.

Since these physiological actions are exhibited by the same compounds which give curariform paralysis, they must be taken into consideration when investigating compounds for possible therapeutic use. The presence of a stimulating nicotinic action would probably prevent the clinical use of a compound, although the paralyzing nicotinic action might not interfere and muscarinic action could be abolished by use of atropine. In the tabulation of compounds which possess curariform activity, the above physiological actions, when reported, have been indicated.

D. METHODS OF MEASUREMENT

The abolition of response of muscle to electrical stimulation of motor nerves has been used as a qualitative determination of curare activity (163). Several methods have been used in testing quantitatively for curare action. The most widely used has been the determination of the minimum dose necessary, when

injected into the lymph sac, to cause complete paralysis in the frog. Other animals have been used to a lesser extent in complete paralysis experiments, but such a determination is more convenient with frogs.

The rabbit head-drop procedure (8, 31) is a rapid, accurate method for determining the intensity of curare paralysis. The solution of the compound to be tested is injected slowly into the ear vein of a rabbit and the dose adjusted so that the neck muscles fail to lift the chin in $2\frac{1}{2}$ to 3 min. The end-point is very clear and reproducible. The dose required to produce the above effect can be reported in milligrams per kilogram of body weight, or the volume of test solution necessary to reach the end-point can be compared to a standard curare solution required to reach the same end-point in the same rabbit on the day preceding or following. In the second case the effectiveness of a compound is reported in units per milligram of the compound. A unit is defined as the activity of 1 milligram of the standard curare powder; hence the larger the value in units per milligram for a compound, the more effective it is.

Ing and coworkers (118–121) used isolated sartorius nerve–muscle preparations to determine the intensity of curare action. They measured the time for paralysis of the isolated nerve sartorius immersed in solutions of various compounds in concentrations of 0.1, 1, and 10 millimoles per liter.

IV. Compounds Exhibiting Curariform Activity

Although all onium ions, in general, exhibit curariform activity to some extent, a literature survey of only the most effective of these, the quaternary ammonium compounds, seemed worthwhile. The quaternary ammonium compounds (tables 1 to 19) have been organized into four large groups: alkylammonium compounds, arylalkylammonium compounds, heterocyclic ammonium compounds, and alkaloids. Each of these groups has been subdivided, with a table of related compounds for each subdivision. A definite order for listing compounds has been used in each table. The simplest and, in the case of the heterocyclic compounds, the most unsaturated derivatives appear first. That is, in the tetraalkylammonium derivatives the tetramethylammonium salt is listed first, followed by the compounds in which one methyl group is replaced by alkyl groups of increasing length, then by compounds in which two methyl groups have been replaced, etc. In the arylalkylammonium compounds the same general order is used with respect to the number of methyl groups on the nitrogen. In the heterocyclic compounds, the parent compound with simplest substituent is listed first, followed by increasing size and number of substituents, then by compounds of increasing saturation,—dihydro-, tetrahydro-, etc.

The alkaloids have been subdivided according to types, with various derivatives of each series listed in order of empirical formula or increasing substitution. The only alkaloids occurring naturally as the quaternary salts are the curare alkaloids. Although the erythrina alkaloids are effective as tertiary bases, the other types of alkaloids must be converted to quaternary derivatives before marked curariform activity is exhibited.

Table 20 contains the α-glycerol ethers, which have recently been proposed as possible curare substitutes.

In the discussion which follows each table the type of compound is taken up, with particular attention being given not only to the compounds which are most effective in their curariform activity but also to the effect of change of chemical structure or substituents on the various types of physiological action. Toxic doses of the various compounds have been recorded where possible in order to have this information readily available for consideration of margins of safety if any of the compounds are ever considered for drug use.

Explanation of symbols in the tables

The relative intensities of the types of actions are indicated by use of plus (+) signs. Three plus (+++) signs indicate a very pronounced action; two, a pronounced action; and one, a weak action. If the action is reported to be present and no notation is given as to the intensity, it is indicated by the symbol ⊕. A negative (−) sign indicates that the action was tested for and found to be absent. A question mark (?) indicates that the presence of the action is doubtful. In table 12 the letters d and p indicate depressor and pressor actions on the blood pressure.

The salt used in determining paralyzing or toxic doses is indicated in the same column with the dose. The letters and underlined numbers in the toxic dose columns indicate whether the lethal dose is the minimum lethal dose (M) or the dose required to kill a certain per cent of the animals (50 = lethal dose for 50 per cent of the animals; 80 = LD 80, etc.). The absence of any of these symbols indicates that the dose was merely reported as the lethal dose. The method of injection is indicated by the following:

EL = endolymphal
IP = intraperitoneal
IV = intravenous
OS = oral
SC = subcutaneous

The rabbit head-drop method and tests with the isolated nerve sartorius were discussed on page 290.

A. ALKYLAMMONIUM COMPOUNDS

1. Tetraalkylammonium compounds (table 1)

In general, all of the tetraalkylammonium salts possess both curare and nicotinic action in varying degree. Muscarinic action may or may not be present.

Tetramethyl- and trimethylalkyl-ammonium salts have very pronounced curare actions, a maximum effectiveness in the trimethylalkyl series being reached with the butyl and amyl derivatives. The paralyzing power of these derivatives compares favorably with curare, as shown by comparison of the effectiveness of trimethylbutylammonium iodide on the isolated nerve preparation with that of curare (see table 14). Trimethyloctylammonium iodide was investigated clinically (19), but it caused vomiting. The muscarinic and stimu-

TABLE 1

Alkylammonium compounds

Tetraalkylammonium compounds

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSES			PARALYZING DOSES		REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions	Frogs	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius (millimoles/liter: 1 | 10)	
							mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*minutes*	
Tetramethyl-	$(CH_3)_4N^+$	++	++	++	++		Cl 10 EL	I 50 30 IP I 3 IV I 33–50 SC Cl 20 SC	Cats Cl 100 SC	Cl 5 EL	I 5.7	(5, 21, 32, 101, 102, 117, 120, 122, 146, 162, 211)
Trimethylethyl-	$(CH_3)_3N^+C_2H_5$	+	+	⊕				I 50 43 IP		Cl 10 EL	I 15 | 3.5	(5, 120, 146, 203, 211)
Trimethylpropyl-	$(CH_3)_3N^+C_3H_7$	+	⊕	+				I 50 68 IP			I 10	(5, 120, 162, 211)
Trimethylbutyl-	$(CH_3)_3N^+C_4H_9$	++	+++	++	−			I 50 19 IP			I 2.5	(5, 101, 117, 120, 162, 211)
Trimethylamyl-	$(CH_3)_3N^+C_5H_{11}$	++	++	⊕			1 EL	I 50 18 IP	Cats 8–10 SC Rabbits 10–12 SC		I 5.5	(5, 32, 120, 162, 192, 193, 211)
Trimethylisoamyl-	$(CH_3)_3N^+isoC_5H_{11}$	⊕	++				1 EL			Cl <10		(32, 193, 211)
Trimethylhexyl-	$(CH_3)_3N^+C_6H_{13}$	++	++	++				I 50 24 IP			I 6	(5, 117, 120, 123, 162)
Trimethylheptyl-	$(CH_3)_3N^+C_7H_{15}$	++	+	⊕				I 50 28 IP			I 6.5	(5, 120, 162, 211)
Trimethyloctyl-	$(CH_3)_3N^+C_8H_{17}$	++	+	?	−			I 50 60 IP			I 6	(4, 5, 117, 120, 162, 211)

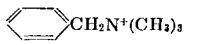
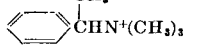
Trimethylnonyl-	$(CH_3)_3N^+C_9H_{19}$		+	?	−			I 50	46	IP					(4, 5)
Trimethylduodecyl-	$(CH_3)_3N^+C_{12}H_{25}$	+	⊕									Br 20	I 30		(24, 120)
Trimethylcetyl-	$(CH_3)_3N^+C_{16}H_{33}$	⊕													(161)
Dimethyldiethyl-	$(CH_3)_2N^+(C_2H_5)_2$	+										Cl 13 EL	I	34	(120, 146, 162)
Methyltriethyl-	$CH_3N^+(C_2H_5)_3$	+										Cl 20 EL	I	255	(117, 120, 146, 162)
Methyltributyl-	$CH_3N^+(C_4H_9)_3$		−	⊕	−				30	SC					(101)
Tetraethyl-	$(C_2H_5)_4N^+$	+	−	−	⊕		Cl 25 EL	Cl	107–120	SC	Cats Cl >250 SC	Cl 20 EL	I	300	(21, 32, 101, 102, 111, 120, 123, 146, 162, 211)
Triethylpropyl-	$(C_2H_5)_3N^+C_3H_7$	+													(136)
Triethylbutyl-	$(C_2H_5)_3N^+C_4H_9$	⊕	+	−	++				71	SC					(101, 136)
Triethylamyl-	$(C_2H_5)_3N^+C_5H_{11}$	⊕													(136)
Triethyloctyl-	$(C_2H_5)_3N^+C_8H_{17}$	⊕													(136)
Diethyldibutyl-	$(C_2H_5)_2N^+(C_4H_9)_2$		−	−	++				17	SC					(101)
Ethyltributyl-	$C_2H_5N^+(C_4H_9)_3$		−	−	++				24	SC					(101)
Tetrapropyl-	$(C_3H_7)_4N^+$	⊕	−	−	++				52	SC		Cl 20–60	I 11.5		(32, 101, 117, 121, 162, 211)
Tripropylbutyl-	$(C_3H_7)_3N^+C_4H_9$		−	⊕	++				25	SC					(101)
Tetrabutyl-	$(C_4H_9)_4N^+$	++	−	+	⊕				19	SC			I 6.5		(101, 117, 121, 162)
Tetraamyl-	$(C_5H_{11})_4N^+$	⊕													(211)
Benzyltrimethyl-		⊕	+++	++	++			I 50	41.5	IP		Br 40			(4, 24, 39, 101, 140, 161)
									35	SC					
p-Nitrobenzyltrimethyl-												Br 100			(24)
α-Phenylethyltrimethyl-			⊕	⊕				I 50	44	IP					(4, 39, 111)
								Br	55	SC					

TABLE 1—*Continued*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSES			PARALYZING DOSES		REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions	Frogs	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius (Millimoles/liter: 1 | 10)	
							mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*minutes*	
β-Phenylethyltrimethyl-	$C_6H_5CH_2CH_2N^+(CH_3)_3$	⊕	++	+++	−			I $\underline{50}$ 18.5 IP Br 80 SC		Br 15		(4, 24, 111, 140, 161)
(β-Phenyl-α-methylethyl)trimethyl-	$C_6H_5CH_2CH(CH_3)N^+(CH_3)_3$		−	++				I $\underline{50}$ 31 IP				(4)
(β-Phenyl-β-methylethyl)-trimethyl-	$C_6H_5CH(CH_3)CH_2N^+(CH_3)_3$		−					I $\underline{50}$ 92 IP		I 30		(4, 24)
γ-Phenylpropyltrimethyl-	$C_6H_5(CH_2)_3N^+(CH_3)_3$		−	++	−			I $\underline{50}$ 10.5 IP				(4)
(γ-Phenyl-α-methylpropyl)-trimethyl-	$C_6H_5(CH_2)_2CH(CH_3)N^+(CH_3)_3$		−	++				I $\underline{50}$ 26 IP				(4)
4-Phenylbutyltrimethyl-	$C_6H_5(CH_2)_4N^+(CH_3)_3$		−	⊕	−			I $\underline{50}$ 29 IP				(4)
5-Phenylamyltrimethyl-	$C_6H_5(CH_2)_5N^+(CH_3)_3$		−	+	−			I $\underline{50}$ 33 IP				(4)

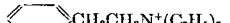
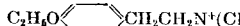
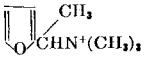
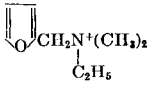
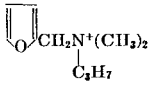
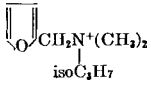
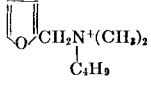
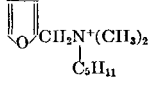
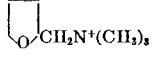
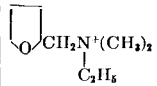
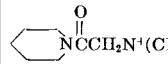
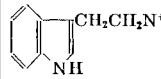
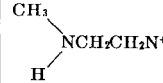
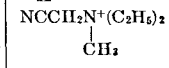
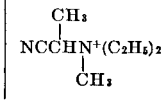
Benzyltriethyl-			–	–	++				160	SC					(101)
β-Phenylethyltriethyl-		⊕	–	–	⊕			I	80	SC			I	5.7	(111, 117, 120)
β-(*p*-Hydroxyphenyl)ethyltrimethyl-		⊕	–	+++	+++			I	50 55	IP	I	5–10			(3, 6, 111, 140, 211)
β-(*p*-Ethoxyphenyl)ethyltrimethyl-			–	+											(140)
β-(3,4-Dihydroxyphenyl)ethyltrimethyl-			–	+++	+++										(6, 111)
β-(3,4-Dimethoxyphenyl)ethyltrimethyl-			–	⊕											(140)
(Phenylcyanomethyl)methyldiethyl-			–	–				I	M 380	SC					(111)
(Phenylcyanomethyl)triethyl-			–	+	⊕			I	M 200	SC					(111)
Furfuryltrimethyl-			++	⊕	⊕			I	50 10	SC					(37, 150)

TABLE 1—*Concluded*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSES			PARALYZING DOSES		REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions	Frogs	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius; Millimoles/liter 1 | 10	
							mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*minutes*	
α-Furylethyltrimethyl-			⊕	+								(39)
Furfuryldimethylethyl-			++	+	⊕			I $\underline{50}$ 400 SC				(37, 38, 39)
Furfuryldimethylpropyl-			+									(37)
Furfuryldimethylisopropyl-			+									(37)
Furfuryldimethylbutyl-			+									(37)
Furfuryldimethylamyl-			+									(37)
Tetrahydrofurfuryltrimethy-			⊕	⊕	⊕			I $\underline{50}$ 100 SC				(37, 38)

Tetrahydrofurfuryldimethylethyl.....			⊕	⊕	⊕			I	50	700	SC	(37, 38)
Carbopiperidinomethyltrimethyl.....			⊕	−	−							(196a)
β-(3-Indole)ethyltrimethyl.....			⊕	++								(140, 196a)
Hydroxymethyltrimethyl.....	$HOCH_2N^+(CH_3)_3$	(See formocholine, table 4)										
Iodomethyltrimethyl.....	$ICH_2N^+(CH_3)_3$		++	++				I	M	80	SC	(102)
Nitromethyltrimethyl.....	$NO_2CH_2N^+(CH_3)_3$		+	+	−			Br	M	>1500	SC	(111)
β-Hydroxyethyltrimethyl.....	$HOCH_2CH_2N^+(CH_3)_3$	(See choline, table 4)										
β-Chloroethyltrimethyl.....	$ClCH_2CH_2N^+(CH_3)_3$	⊕	⊕	⊕		Central depressant						(30, 153)
β-Bromoethyltrimethyl.....	$BrCH_2CH_2N^+(CH_3)_3$	⊕	⊕	⊕				I	M	250	SC	(30, 35, 116, 211)
β-Cyanoethyltrimethyl.....	$NCCH_2CH_2N^+(CH_3)_3$	⊕	⊕									(30, 35)
β-Aminoethyltrimethyl.....	$H_2NCH_2CH_2N^+(CH_3)_3$	⊕	⊕			Central depressant						(30, 35, 153)
β-(Methylamino)ethyltrimethyl		?	⊕			Central depressant						(153)
Cyanomethyldiethylmethyl...								I		250	SC	(99)
α-Cyanoethyldiethylmethyl...								I		400	SC	(99)

lating nicotinic actions shown by these compounds would probably prevent any therapeutic use.

The successive replacement of methyl groups with other alkyl groups reduces the muscarinic action to such an extent that tetraalkyl derivatives other than tetramethyl are devoid of muscarinic action. The replacement of methyl groups with ethyl groups reduces the intensity of curare action; however, the intensity again increases in the tetrapropyl- and tetrabutyl-ammonium compounds. The nicotinic action shows no general trends in these variations of the molecular structure.

Substitution of one alkyl group by an alkyl group containing a phenyl group, such as benzyl, β-phenylethyl, etc., in most cases eliminates the muscarinic action without affecting appreciably the other actions. However, triethyl-benzyl- and triethyl-β-phenylethyl-ammonium salts possess neither muscarinic nor stimulating nicotinic actions, and the latter possesses a very pronounced curare action on the isolated nerve sartorius. Alles (4) showed that the introduction of a methyl group in the phenylalkyl chain in the position α to the nitrogen greatly decreases both muscarinic and nicotinic actions.

Furfuryltrialkylammonium salts possess both muscarinic and nicotinic actions, but no information is available on their curare action. Fellows and Livingston (37) reported that saturation of the furan ring decreases the physiological potency with little effect on the toxicity.

2. Neurine derivatives and analogues (table 2)

Neurine acts in accord with the rule concerning the relation between the physiological actions of compounds containing saturated and unsaturated groups (32), which states that the unsaturated compounds are more toxic and generally more effective physiologically than the corresponding saturated compounds. Neurine is more toxic and has more pronounced muscarinic and nicotinic actions than ethyltrimethylammonium salts. Hunt and Renshaw (102) reported that neurine also possesses a depressant action on autonomic ganglia. In general, all derivatives and analogues of neurine possess curare actions, but they also have marked muscarinic and nicotinic actions. Of this series, only ethynyl-trimethylammonium salts are reported to possess a very pronounced curare action (191).

3. Muscarine derivatives and analogues (table 3)

Muscarine is the drug responsible for the poisonous effects of certain species of mushrooms. It has no curare or nicotinic action. It has such a definite action that the term "muscarinic" is used to designate the particular response of heart, smooth muscle, and glands to its stimulation. The criterion for muscarinic action was discussed on page 289. The analogues of muscarine have never been found to possess any marked curare activity (68, 74).

4. Choline derivatives and analogues (table 4)

Choline possesses the three pharmacological actions of quaternary ammonium bases,—muscarinic, nicotinic, and curariform. Derivatives of choline may

TABLE 2

Alkylammonium compounds

Neurine derivatives and analogues

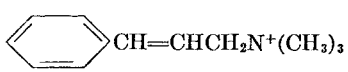
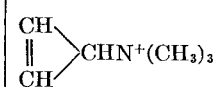
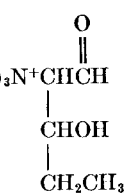
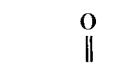
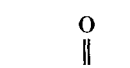
AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSES			PARALYZING DOSES	REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions	Frogs	Mice	Miscellaneous	Frogs	
							mg./kg.	*mg./kg.*	*mg./kg.*		
Vinyltrimethyl-... (Neurine)	$CH_2{=}CHN^+(CH_3)_3$	⊕	++	++	⊕		1–2 SC	Br M 73 SC OH M 46 SC 2.5 IP	Rabbits 40–50 SC		(101, 102, 107, 211)
Allyltrimethyl-... (Homoneurine)	$CH_2{=}CHCH_2N^+(CH_3)_3$		++	++	⊕			Cl M 200 SC I M 250 SC OH M 130 SC			(101, 107, 116)
Isocrotyltrimethyl-.....	$CH_3CH{=}CHCH_2N^+(CH_3)_3$									>20 mg.	(211)
γ-Phenylallyltrimethyl-.....			−	+++				I 50 21 IP			(4)
β-Methoxyallyltrimethyl-.....	$CH_2{=}C(OCH_3)CH_2N^+(CH_3)_3$	−	++	−	−	Cathartic			Cats Br 1–5		(85)
Trimethinetrimethyl-.....		+									(211)
Ethynyltrimethyl-	$HC{\equiv}CN^+(CH_3)_3$	++					M 30 EL			1 mg.	(32, 191, 211)

TABLE 3

Alkylammonium compounds

Muscarine derivatives and analogues

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSE	PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Frogs	Frogs	
						mg./kg.	*mg./kg.*	
(α-Formyl-β-hydroxybutyl)trimethyl- (Muscarine)		−	+++	−	−	1 EL		(2, 30, 32)
Formylmethyltrimethyl-			⊕					(14, 66)
Acetonyltrimethyl			−				Cl 300	(14, 24)
β-Formylethyltrimethyl-			⊕					(14)
β-Formylethyltriethyl-			⊕					(14)

Benzoylmethyltrimethyl-						50	(24)
2,4-Dihydroxybenzoylmethyltrimethyl-				⊕	⊕	Cl 30	(6,24)

TABLE 4

Alkylammonium compounds

Choline derivatives and analogues

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
Choline	$HOCH_2CH_2N^+(CH_3)_3$	+	⊕	⊕	⊕			Cl M 740–50 SC	Cats M 250 IV	Mice 500	(32, 74, 102, 115, 116, 117)
Formylcholine	$HCOOCH_2CH_2N^+(CH_3)_3$	⊕	++								(30, 35)
Acetylcholine	$CH_3COOCH_2CH_2N^+(CH_3)_3$	⊕	+++	⊕	−			Cl M 310 SC Br M 300 SC Cl 50 20 IV Cl 50 170 SC Cl 5000 OS	Rats 22 IV 250 SC 2500 OS		(35, 74, 102, 108, 115, 135, 149)
Acetyl-d_3-choline	$Cd_3COOCH_2CH_2N^+(CH_3)_3$		++		⊕						(34, 115)
Chloroacetylcholine	$ClCH_2COOCH_2CH_2N^+(CH_3)_3$		⊕	++				Br M 700 SC			(30, 102)
Propionylcholine	$C_2H_5COOCH_2CH_2N^+(CH_3)_3$		++	⊕							(194)
Butyrylcholine	$C_3H_7COOCH_2CH_2N^+(CH_3)_3$		+	++							(115, 194)
Isobutyrylcholine	iso-$C_3H_7COOCH_2CH_2N^+(CH_3)_3$		+	+							(115)
Valerylcholine	$C_4H_9COOCH_2CH_2N^+(CH_3)_3$		+	⊕							(115)
Lactylcholine	$CH_3CHOHCOOCH_2CH_2N^+(CH_3)_3$	⊕	++								(30, 35)
Phenylacetylcholine	 $CH_2COOCH_2CH_2N^+(CH_3)_3$		+	++				Cl M >500 SC			(87, 115)

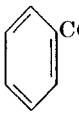
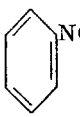
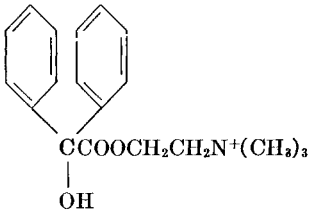
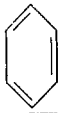
Phenylpropionylcholine	 $CH_2CH_2COOCH_2CH_2N^+(CH_3)_3$		⊕	++								(115)
Succinoylcholine	$CH_2COOCH_2CH_2N^+(CH_3)_3$ | $CH_2COOCH_2CH_2N^+(CH_3)_3$		+		⊕							(115)
Benzoylcholine	 $COOCH_2CH_2N^+(CH_3)_3$		+		++			Cl	M	2000	SC	(115, 116)
Anisoylcholine	OCH_3  $COOCH_2CH_2N^+(CH_3)_3$				⊕							(115)
p-Nitrobenzoylcholine	NO_2  $COOCH_2CH_2N^+(CH_3)_3$		+									(115)
m-Nitrobenzoylcholine	 NO_2 $COOCH_2CH_2N^+(CH_3)_3$		++									(115)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
Benzilylcholine.....							⊕				(119)
Carbamylcholine..... (Carbaminoylcholine)	$H_2NCOOCH_2CH_2N^+(CH_3)_3$		++	++	++			Cl 0.5 IV Cl 1.5 SC Cl 50 0.3 IV Cl 50 3 OS	Rats 4 SC 0.1 IV 40 OS		(2, 37, 38, 74, 135, 149)
Dibutylcarbamylcholine.....	$N(C_4H_9)_2$ $COOCH_2CH_2N^+(CH_3)_3$		−		−		⊕				(203)
Diamylcarbamylcholine.....	$N(C_5H_{11})_2$ $COOCH_2CH_2N^+(CH_3)_3$						⊕				(203)
Diphenylcarbamylcholine.....	$N(C_6H_5)_2$ $COOCH_2CH_2N^+(CH_3)_3$						⊕				(203)

Glycylcholine.....	$H_2NCH_2COOCH_2CH_2N^+(CH_3)_3$	−	−		−	−	−						(224)
N-Trimethylglycyl-choline bromide.....	$Br^-N^+(CH_3)_3$ | $CH_2COOCH_2CH_2N^+(CH_3)_3$	−	+		−	−	−						(224)
Choline nitrite.....	$(CH_3)_3N^+CH_2CH_2ON{=}O$	⊕	++	⊕									(2, 30, 35, 128)
Choline nitrate.....	$(CH_3)_3N^+CH_2CH_2ON$ (=O, →O)	⊕	++	++	⊕				M	210	SC	Frogs 20 EL	Frogs 2 EL	(30, 32, 35, 102)
Choline sulfate.....	$(CH_3)_3N^+CH_2CH_2O$ \ / SO_2 / \ $(CH_3)N^+CH_2CH_2O$		−	−	−				M	1000	SC			(105)
Choline dimethylphosphate.....	$(CH_3)_3N^+CH_2CH_2OPO(OCH_3)_2$		+		+++			Cl	M	44	SC			(105, 174)
Choline methyl ether..	$CH_3OCH_2CH_2N^+(CH_3)_3$	⊕	++	⊕										(35, 194)
Choline ethyl ether...	$C_2H_5OCH_2CH_2N^+(CH_3)_3$	⊕	++	⊕										(35, 194)
Choline propyl ether..	$C_3H_7OCH_2CH_2N^+(CH_3)_3$	⊕	++											(30, 35)
Choline butyl ether...	$C_4H_9OCH_2CH_2N^+(CH_3)_3$		+		++									(194)
Choline hydroxyethyl ether.....	$HOCH_2CH_2OCH_2CH_2N^+(CH_3)_3$												Frogs Cl 30	(24)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
Choline vinyl ether...	$CH_2{=}CHOCH_2CH_2N^+(CH_3)_3$		++		++						(194)
Choline benzyl ether..	 $CH_2OCH_2CH_2N^+(CH_3)_3$		–		–			Br M 38 SC			(114)
Choline phenyl ether..	 $OCH_2CH_2N^+(CH_3)_3$		–	+++				Cl M 85 SC			(105, 114)
Choline *o*-tolyl ether..	 $OCH_2CH_2N^+(CH_3)_3$ CH_3		–		++	++		Br M 20 SC			(114)
Choline *m*-tolyl ether..	 $OCH_2CH_2N^+(CH_3)_3$ CH_3		–		⊕			Br M 42 SC			(114)
Choline *p*-tolyl ether..	CH_3  $OCH_2CH_2N^+(CH_3)_3$		–		⊕			Br M 29 SC			(114)
Choline *p*-ethylphenyl ether.....	C_2H_5  $OCH_2CH_2N^+(CH_3)_3$		–		⊕			Br M 85 SC			(114)
Choline *p-tert*-butylphenyl ether.....	$(CH_3)_3C$  $OCH_2CH_2N^+(CH_3)_3$		–		–			Br M 500 SC			(114)

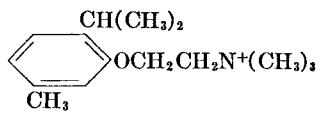
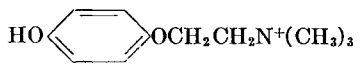
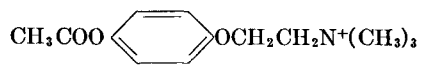
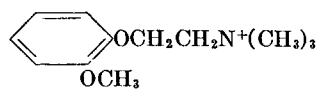
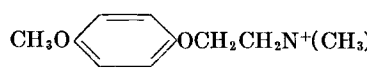
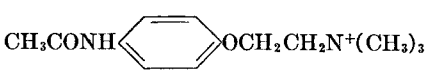
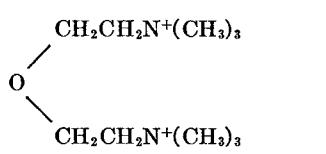
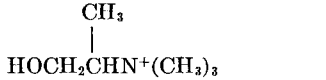
Choline 2-isopropyl-5-methylphenyl ether.			–		+			Br	M	500	SC		(114)
Choline *p*-hydroxyphenyl ether.....			–		⊕			Br	M	230	SC		(107)
Choline *p*-acetoxyphenyl ether.....			–		⊕			Br	M	>1400	SC		(107)
Choline *o*-methoxyphenyl ether.....			–		⊕			Br	M	100	SC		(107)
Choline *p*-methoxyphenyl ether.....			–		⊕			Br	M	600	SC		(107)
Choline *p*-acetaminophenyl ether.....			–		–			Br	M	170	SC		(107)
β-Ethoxycholine ethyl ether.....			–										(14)
Dicholine ether.....		⊕	⊕										(30, 35)
α-Methylcholine.....								Cl	M	1000	SC		(100)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
Acetyl-α-methylcholine	$CH_3COOCH_2CH(CH_3)N^+(CH_3)_3$	−	⊕		⊕			Cl M 350 SC			(75, 100, 125)
Propionyl-α-methylcholine	$C_2H_5COOCH_2CH(CH_3)N^+(CH_3)_3$							Cl M 1600 SC			(100)
Isovaleryl-α-methylcholine	$(CH_3)_2CHCH_2COOCH_2CH(CH_3)N^+(CH_3)_3$							Cl M 1600 SC			(100)
α-Bromoisocapryl-α-methylcholine	$(CH_3)_2CHCH_2CH(Br)COOCH_2CH(CH_3)N^+(CH_3)_3$							Cl M 1000 SC			(100)
Benzoyl-α-methylcholine	$C_6H_5COOCH_2CH(CH_3)N^+(CH_3)_3$							Cl M 900 SC			(100)

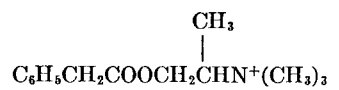
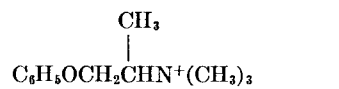
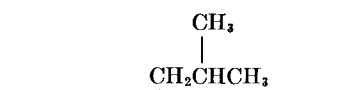
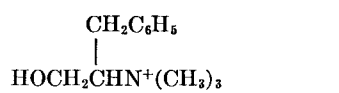
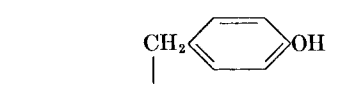
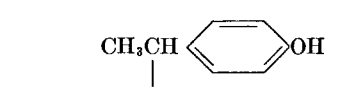
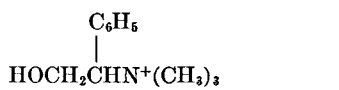
Phenylacetyl-α-methylcholine									Cl M >2000 SC		(100)
α-Methylcholine phenyl ether					⊕						(114)
Acetyl-α-isobutylcholine			⊕		⊕						(75, 125)
α-Benzylcholine		+	⊕	⊕							(141)
Acetyl-α-(p-hydroxybenzyl)choline			⊕		⊕						(75, 125)
Acetyl-α-(α-p-hydroxyphenylethyl)choline			⊕		⊕						(75, 125)
α-Phenylcholine		+	⊕	⊕							(141)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
β-Methylcholine......	$HOCHCH_2N^+(CH_3)_3$ CH_3		⊕		⊕			Cl M 630 SC	Cats 75 SC 20 IV 750 OS		(74, 113, 116)
Acetyl-β-methylcholine................	$CH_3COOCHCH_2N^+(CH_3)_3$ CH_3		+++	−	+	+		Cl M 175 SC Cl 50 90 SC Cl 50 20 IV			(2, 38, 74, 113, 116, 141)
Propionyl-β-methylcholine...........	$C_2H_5COOCHCH_2N^+(CH_3)_3$ CH_3		++	−							(113, 194)
Benzoyl-β-methylcholine................	CH_3 $C_6H_5COOCHCH_2N^+(CH_3)_3$							Cl M 1080 SC			(116)
Carbamyl-β-methylcholine	CH_3 $H_2NCOOCHCH_2N^+(CH_3)_3$			−			⊕	Cl 50 120 SC Cl 50 10 IV			(149, 203)

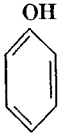
β-Methylcholine methyl ether	$CH_3OCHCH_2N^+(CH_3)_3$ (CH₃ on O)	⊕	++	+				I	M	110	SC			(114, 195)
β-Methylcholine ethyl ether	$C_2H_5OCHCH_2N^+(CH_3)_3$ (CH₃ on O)		++	−	−			Cl	50	250	SC			(2, 114, 140, 149, 194)
								Cl	50	30	IV			
								I	M	140	SC			
β-Methylcholine isopropyl ether	$CHOCHCH_2N^+(CH_3)_3$ (CH₃ and CH₃ on O)		⊕		+			I	M	220	SC			(114)
β-Methylcholine butyl ether	$C_4H_9OCHCH_2N^+(CH_3)_3$ (CH₃ on O)	⊕	+	+										(195)
β-Chloromethylcholine	$HOCHCH_2N^+(CH_3)_3$ (CH_2Cl on C)							Cl	M	500	SC			(116)
Acetyl-β-chloromethylcholine	$CH_3COOCHCH_2N^+(CH_3)_3$ (CH_2Cl on C)							Cl	M	365	SC			(116)
Benzoyl-β-chloromethylcholine	$C_6H_5COOCHCH_2N^+(CH_3)_3$ (CH_2Cl on C)							Cl	M	356	SC			(116)
β-Hydroxymethylcholine	$HOCHCH_2N^+(CH_3)_3$ (CH_2OH on C)							Cl	M	1800	SC			(116)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
Acetyl-β-acetoxymethylcholine.....	$CH_3COOCHCH_2N^+(CH_3)_3$ (CH₂OCOCH₃)							Cl M 1000 SC			(116)
Benzoyl-β-benzoyloxymethylcholine.....	$C_6H_5COOCHCH_2N^+(CH_3)_3$ (CH₂OCOC₆H₅)							Cl M 1200 SC			(116)
Acetyl-β-ethylcholine..	$CH_3COOCHCH_2N^+(CH_3)_3$ (C_2H_5)		++	+							(195)
β-Ethylcholine methyl ether.....	$CH_3OCHCH_2N^+(CH_3)_3$ (C_2H_5)		⊕	−							(195)
β-Ethylcholine ethyl ether.....	$C_2H_5OCHCH_2N^+(CH_3)_3$ (C_2H_5)		⊕	−							(195)
β-Ethylcholine propyl ether.....	$C_3H_7OCHCH_2N^+(CH_3)_3$ (C_2H_5)	++	−	−							(195)

β-Ethylcholine butyl ether	$C_4H_9OCH(C_2H_5)CH_2N^+(CH_3)_3$	++	−	−								(195)
Acetyl-β-propylcholine	$CH_3COOCH(C_3H_7)CH_2N^+(CH_3)_3$		⊕									(196)
β-Propylcholine methyl ether	$CH_3OCH(C_3H_7)CH_2N^+(CH_3)_3$		+	−								(195)
β-Propylcholine ethyl ether	$C_2H_5OCH(C_3H_7)CH_2N^+(CH_3)_3$		⊕	−								(195)
β-Propylcholine butyl ether	$C_4H_9OCH(C_3H_7)CH_2N^+(CH_3)_3$	++	−	−								(195)
β-Propylcholine amyl ether	$C_5H_{11}OCH(C_3H_7)CH_2N^+(CH_3)_3$	++	−	−								(195)
Acetyl-β-butylcholine	$CH_3COOCH(C_4H_9)CH_2N^+(CH_3)_3$		⊕									(196)
β-Butylcholine methyl ether	$CH_3OCH(C_4H_9)CH_2N^+(CH_3)_3$		⊕	⊕								(195)
β-Butylcholine ethyl ether	$C_2H_5OCH(C_4H_9)CH_2N^+(CH_3)_3$		−	−								(195)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
β-Butylcholine butyl ether	$C_4H_9OCHCH_2N^+(CH_3)_3$ (C₄H₉ above O)	⊕	−	−							(196)
β-Benzylcholine	$C_6H_5CH_2$ / $HOCHCH_2N^+(CH_3)_3$	⊕	−	−							(196)
β-Phenylcholine	 $HOCHCH_2N^+(CH_3)_3$		⊕		⊕						(140)
β-(*p*-Hydroxyphenyl)-choline	OH  $HOCHCH_2N^+(CH_3)_3$		⊕		+						(140)
β-(*p*-Methoxyphenyl)-choline	OCH_3  $HOCHCH_2N^+(CH_3)_3$		⊕		⊕						(136, 140)

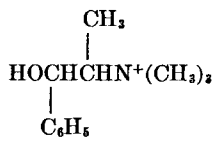
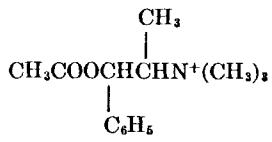
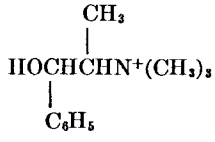
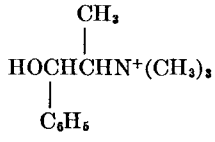
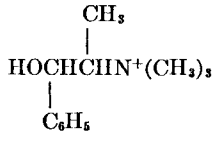
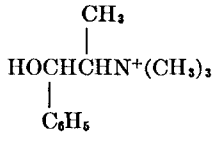
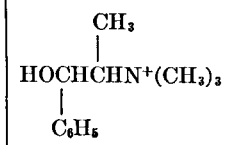
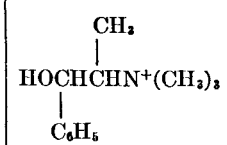
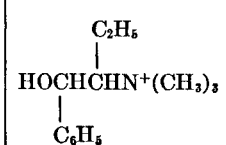
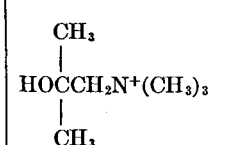
N-Methylephedrine methohydroxide.....		–										Frogs I 30 Rabbits 15	(24, 117)
Acetyl-*N*-methylephedrine methohydroxide.....			–		–			M	270	SC			(114)
d-*N*-Methylephedrine methohydroxide.....			–		⊕								(140)
l-*N*-Methylephedrine methohydroxide.....			–		+								(140)
dl-*N*-Methylephedrine methohydroxide.....			–		+								(140)
d-*N*-Methyl-ψ-ephedrine methohydroxide			–		⊕								(140)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
l-*N*-Methyl-ψ-ephedrine methohydroxide			–		⊕						(140)
dl-*N*-Methyl-ψ-ephedrine methohydroxide			–		⊕						(140)
α-Ethyl-β-phenylcholine			⊕		⊕						(140)
β,β-Dimethylcholine			⊕		⊕			Cl M 700 SC			(116, 140)

β-Methyl-β-ethyl-choline	$HOC(CH_3)(C_2H_5)CH_2N^+(CH_3)_3$							Cl	M	610	SC				(116)
β-Methyl-β-phenyl-choline	$HOC(CH_3)(C_6H_5)CH_2N^+(CH_3)_3$				⊕			Cl	M	450	SC				(116, 136)
Formocholine	$HOCH_2N^+(CH_3)_3$							Cl	M	70–75	SC				(107, 116)
Acetylformocholine	$CH_3COOCH_2N^+(CH_3)_3$		++		⊕			Cl	M	> 170	SC				(102)
Formocholine methyl ether	$CH_3OCH_2N^+(CH_3)_3$	⊕	⊕		⊕			Cl Cl	M M	37 40	SC SC				(35, 107, 110, 116)
Formocholine ethyl ether	$C_2H_5OCH_2N^+(CH_3)_3$	⊕													(35)
Formocholine propyl ether	$C_3H_7OCH_2N^+(CH_3)_3$	⊕	++		⊕										(35, 110)
Formocholine allyl ether	$CH_2{=}CHCH_2OCH_2N^+(CH_3)_3$		⊕		⊕			I	M	52	SC				(107)
Formocholine butyl ether	$C_4H_9OCH_2N^+(CH_3)_3$	⊕	⊕		⊕			I	M	71	SC				(35, 107)
Formocholine isobutyl ether	iso-$C_4H_9OCH_2N^+(CH_3)_3$		⊕		⊕			I I	M M	54 52	SC SC				(107, 110)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES					PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice				Miscellaneous		
								mg./kg.				*mg./kg.*	*mg./kg.*	
γ-Homocholine	$HO(CH_2)_3N^+(CH_3)_3$		++	+				Cl	M	170	SC			(116, 153)
Acetyl-γ-homocholine	$CH_3COO(CH_2)_3N^+(CH_3)_3$							Cl	M	70	SC			(116)
Benzoyl-γ-homocholine	$C_6H_5COO(CH_2)_3N^+(CH_3)_3$							Cl	M	270	SC			(116)
γ-Homocholine methyl ether	$CH_3OCH_2CH_2CH_2N^+(CH_3)_3$	⊕	⊕		⊕	⊕								(193b)
γ-Homocholine allyl ether	$CH_2{=}CHCH_2O(CH_2)_3N^+(CH_3)_3$		−											(211)
γ-Homocholine phenyl ether	$C_6H_5OCH_2CH_2CH_2N^+(CH_3)_3$		−	⊕	+			Cl	M	180	SC			(105)
γ-Phenylhomocholine methyl ether	$CH_3OCH(C_6H_5)CH_2CH_2N^+(CH_3)_3$	⊕	−	++										(193a)
Ammonium compounds related to choline														
(α-Methyl-β-phenyl-β-hydroxyethyl)dimethylethyl	$HOCH(C_6H_5)CH(CH_3)N^+(CH_3)_2(C_2H_5)$		⊕		⊕									(140)

β-Benzilyloxyethyldimethylethyl.....	$(C_6H_5)_2COHCOO(CH_2)_2N^+(CH_3)_2$ $\vert$ C_2H_5						⊕	Cl 50 Cl 50 Cl 50	40 160 1000	IP SC OS			(119)
β-Benzilyloxyethyldimethylisopropyl...	$(C_6H_5)_2COHCOO(CH_2)_2N^+(CH_3)_2$ $\vert$ CH_3CHCH_3						⊕	Cl 50 Cl 50	40 75	IP SC			(119)
β-Benzilyloxyethyldimethylpropyl.....	$(C_6H_5)_2COHCOO(CH_2)_2N^+(CH_3)_2$ $\vert$ C_3H_7						⊕						(119)
β-Benzilyloxyethyldimethylallyl.....	$(C_6H_5)_2COHCOO(CH_2)_2N^+(CH_3)_2$ $\vert$ $CH_2CH{=}CH_2$						⊕						(119)
β-Benzilyloxyethyldimethylbutyl.....	$(C_6H_5)_2COHCOO(CH_2)_2N^+(CH_3)_2$ $\vert$ C_4H_9						⊕						(119)
β-Benzilyloxyethyldimethylamyl	$(C_6H_5)_2COHCOO(CH_2)_2N^+(CH_3)_2$ $\vert$ C_5H_{11}						⊕						(119)
β-Acetoxyethyldimethylbenzyl.....	$CH_3COO(CH_2)_2N^+(CH_3)_2$ $\vert$ $CH_2C_6H_5$		++		⊕	⊕		Br M	750	SC			(108)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
(α-Methyl-β-phenyl-β-hydroxyethyl)dimethylbenzyl.....	$C_6H_5CHOHCHN^+(CH_3)_2$ (H$_3$C; CH$_2$C$_6$H$_5$)		⊕		++						(140)
γ-Benzilyloxypropyldimethylethyl.....	$(C_6H_5)_2COHCOO(CH_2)_3N^+(CH_3)_2$ (C_2H_5)						⊕	Cl 50 90 IP Cl 50 550 SC			(119)
β-(Dibutylcarbamyloxy)ethyldimethylethyl.....	$(C_4H_9)_2NCOO(CH_2)_2N^+(CH_3)_2$ (C_2H_5)		−			−	⊕				(155)
β-(p-Aminobenzoyloxy)ethylmethyldiethyl.....	$COOCH_2CHN^+(C_2H_5)_2$ (CH_3; NH_2)	⊕		⊕							(83, 84)

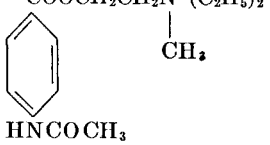
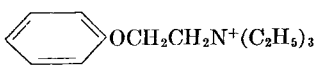
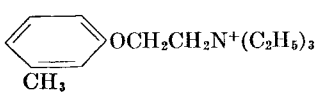
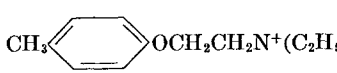
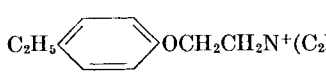
β-(*p*-Acetaminobenzoyloxy)ethylmethyldiethyl.....		+		⊕									(83, 84)
β-Benzilyloxyethylmethyldiethyl.....	$(C_6H_5)_2COHCOO(CH_2)_2N^+(C_2H_5)_2$ $\vert$ CH_3						⊕	Cl	50	130	SC		(119)
								Cl	50	625	IP		
γ-Benzilyloxypropylmethyldiethyl.....	$(C_6H_5)_2COHCOO(CH_2)_3N^+(C_2H_5)_2$ $\vert$ CH_3						⊕	Cl	50	650	SC		(119)
β-Hydroxyethyltriethyl.....	$HOCH_2CH_2N^+(C_2H_5)_3$							Cl	M	70	SC		(116)
β-Acetoxyethyltriethyl.....	$CH_3COOCH_2CH_2N^+(C_2H_5)_3$		−		−	++		Br	M	100	SC		(108)
β-Benzoyloxyethyltriethyl.....	$C_6H_5COO(CH_2)_2N^+(C_2H_5)_3$							Cl	M	280	SC		(116)
β-Benzilyloxyethyltriethyl.....	$(C_6H_5)_2COHCOO(CH_2)_2N^+(C_2H_5)_3$						⊕	Br	50	150	SC		(119)
β-Methoxyethyltriethyl.....	$CH_3OCH_2CH_2N^+(C_2H_5)_3$		−		−	−		I	M	100	SC		(112)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES					PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice				Miscellaneous		
								mg./kg.				*mg./kg.*	*mg./kg.*	
β-Ethoxyethyltriethyl	$C_2H_5OCH_2CH_2N^+(C_2H_5)_3$		−		−	−		I	M	320	SC			(112)
β-Butoxyethyltriethyl	$C_4H_9OCH_2CH_2N^+(C_2H_5)_3$	−	−		+	⊕		I	M	230	SC			(112)
β-Phenoxyethyltriethyl			−			⊕		I	M	180	SC			(112)
β-(2-Methylphenoxy)-ethyltriethyl			−		−	⊕		Br	M	210	SC			(114)
β-(3-Methylphenoxy)-ethyltriethyl			−		−	⊕		Br	M	25	SC			(114)
β-(4-Methylphenoxy)-ethyltriethyl			−		−	⊕		Br	M	70	SC			(114)
β-(4-Ethylphenoxy)-ethyltriethyl			−		−	⊕		Br	M	90	SC			(114)

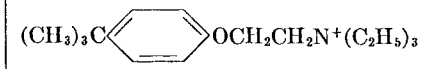
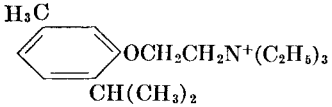
β-(4-*tert*-Butylphenoxy)ethyltriethyl			–		–	⊕		Br	M	35	SC		(114)
β-(2-Isopropyl-5-methylphenoxy)-ethyltriethyl			–		–	⊕		Br	M	190	SC		(114)
β-Hydroxypropyltriethyl	$HOCHCH_2N^+(C_2H_5)_3$							Cl	M	180	SC		(116)
β-Acetoxypropyltriethyl	$CH_3COOCHCH_2N^+(C_2H_5)_3$							Cl	M	101	SC		(116)
(β-Benzoyloxypropyltriethyl	$C_6H_5COOCHCH_2N^+(C_2H_5)_3$							Cl	M	320	SC		(116)
(β-Hydroxy-γ-chloropropyl)triethyl	$HOCHCH_2N^+(C_2H_5)_3$							Cl	M	370	SC		(116)
(β-Acetoxy-γ-chloropropyl)triethyl	$CH_3COOCHCH_2N^+(C_2H_5)_3$							Cl	M	209	SC		(116)
(β-Benzoyloxy-γ-chloropropyl)triethyl	$C_6H_5COOCHCH_2N^+(C_2H_5)_3$							Cl	M	122	SC		(116)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES					PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice				Miscellaneous		
								mg./kg.				*mg./kg.*	*mg./kg.*	
β,γ-Dihydroxypropyltriethyl	CH_2OH | $HOCHCH_2N^+(C_2H_5)_3$							Cl	M	620	SC			(116)
β,γ-Diacetoxypropyltriethyl	CH_2OCOCH_3 | $CH_3COOCHCH_2N^+(C_2H_5)_3$							Cl	M	460	SC			(116)
β,γ-Dibenzoyloxypropyltriethyl	$CH_2OCOC_6H_5$ | $C_6H_5COOCHCH_2N^+(C_2H_5)_3$							Cl	M	150	SC			(116)
Methoxymethyltriethyl	$CH_3OCH_2N^+(C_2H_5)_3$		−		−	−		I	M	85	SC			(112)
Ethoxymethyltriethyl	$C_2H_5OCH_2N^+(C_2H_5)_3$	⊕	−		−	⊕		I	M	100	SC			(112)
Alloxymethyltriethyl	$CH_2{=}CHCH_2OCH_2N^+(C_2H_5)_3$	++	−		−	++		I	M	120	SC			(112)
β-Benzilyloxyethyldiethylpropyl	$(C_6H_5)_2COHCOO(CH_2)_2N^+(C_2H_5)_2$ | C_3H_7						⊕							(119)

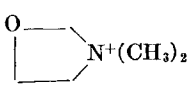
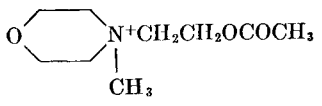
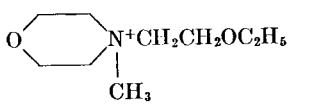
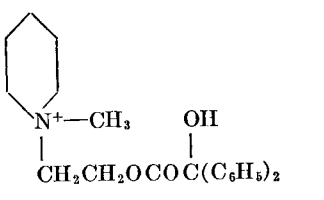
β-Hydroxyethyldiethylisoamyl	$HOCH_2CH_2N^+(C_2H_5)_2$ $\vert$ C_5H_{11}(iso)							Cl	M	630	SC					(116)
β-Acetoxyethyldiethylisoamyl	$CH_3COOCH_2CH_2N^+(C_2H_5)_2$ $\vert$ C_5H_{11}(iso)							Cl	M	400	SC					(116)
β-Benzoyloxyethyldiethylisoamyl	$C_6H_5COOCH_2CH_2N^+(C_2H_5)_2$ $\vert$ C_5H_{11}(iso)							Cl	M	1200	SC					(116)
β-Hydroxyethyltripropyl	$HOCH_2CH_2N^+(C_3H_7)_3$							Cl	M	170	SC					(116)
β-Benzoyloxyethyltripropyl	$C_6H_5COOCH_2CH_2N^+(C_3H_7)_3$							Cl	M	180	SC					(116)
β-Hydroxypropyltripropyl	$HOCHCH_2N^+(C_3H_7)_3$ $\vert$ CH_3							Cl	M	110	SC					(116)
β-Acetoxypropyltripropyl	$CH_3COOCHCH_2N^+(C_3H_7)_3$ $\vert$ CH_3							Cl	M	160	SC					(116)
β-Benzoyloxypropyltripropyl	$C_6H_5COOCHCH_2N^+(C_3H_7)_3$ $\vert$ CH_3							Cl	M	52	SC					(116)
(β-Hydroxy-γ-chloropropyl)tripropyl	$HOCHCH_2N^+(C_3H_7)_3$ $\vert$ CH_2Cl							Cl	M	65	SC					(116)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
(β-Acetoxy-γ-chloropropyl)tripropyl	$CH_3COOCH(CH_2Cl)CH_2N^+(C_3H_7)_3$							Cl M 170 SC			(116)
(β-Benzoyloxy-γ-chloropropyl)tripropyl	$C_6H_5COOCH(CH_2Cl)CH_2N^+(C_3H_7)_3$							Cl M 60 SC			(116)
β,γ-Dihydroxypropyltripropyl	$HOCH(CH_2OH)CH_2N^+(C_3H_7)_3$							Cl M 250 SC			(116)
β,γ-Diacetoxypropyltripropyl	$CH_3COOCH(CH_2OCOCH_3)CH_2N^+(C_3H_7)_3$							Cl M 200 SC			(116)
β,γ-Dibenzoyloxypropyltripropyl	$C_6H_5COOCH(CH_2OCOC_6H_5)CH_2N^+(C_3H_7)_3$							Cl M 100 SC			(116)
β-Hydroxyethyltriamyl	$HOCH_2CH_2N^+(C_5H_{11})_3$							Cl M 150 SC			(116)
β-Acetoxyethyltriamyl	$CH_3COOCH_2CH_2N^+(C_5H_{11})_3$							Cl M 145 SC			(116)

β-Benzoyloxyethyltriamyl	$C_6H_5COOCH_2CH_2N^+(C_5H_{11})_3$							Cl	M	36	SC				(116)
β-Hydroxypropyltriamyl	$HOCHCH_2N^+(C_5H_{11})_3$ (CH₃ on CH)							Cl	M	90	SC				(116)
β-Acetoxypropyltriamyl	$CH_3COOCHCH_2N^+(C_5H_{11})_3$ (CH₃ on CH)							Cl	M	150	SC				(116)
β-Benzoyloxypropyltriamyl	$C_6H_5COOCHCH_2N^+(C_5H_{11})_3$ (CH₃ on CH)							Cl	M	38	SC				(116)
(β-Hydroxy-γ-chloropropyl)triamyl	$HOCHCH_2N^+(C_5H_{11})_3$ (CH_2Cl on CH)							Cl	M	210	SC				(116)
(β-Acetoxy-γ-chloropropyl)triamyl	$CH_3COOCHCH_2N^+(C_5H_{11})_3$ (CH_2Cl on CH)							Cl	M	150	SC				(116)
(β-Benzoyloxy-γ-chloropropyl)triamyl	$C_6H_5COOCHCH_2N^+(C_5H_{11})_3$ (CH_2Cl on CH)							Cl	M	39	SC				(116)
β,γ-Dihydroxypropyltriamyl	$HOCHCH_2N^+(C_5H_{11})_3$ (CH_2OH on CH)							Cl	M	400	SC				(116)
β,γ-Diacetoxypropyltriamyl	$CH_3COOCHCH_2N^+(C_5H_{11})_3$ (CH_2OCOCH_3 on CH)							Cl	M	250	SC				(116)
β,γ-Dibenzoyloxypropyltriamyl	$C_6H_5COOCHCH_2N^+(C_5H_{11})_3$ ($CH_2OCOC_6H_5$ on CH)							Cl	M	144	SC				(116)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
Tetra(β-hydroxyethyl)	$N^+(CH_2CH_2OH)_4$		++		−	−		Cl M > 1500 SC			(108)
β-Acetoxyethyltri(β-hydroxyethyl)	$CH_2CH_2OCOCH_3$ | $N^+(CH_2CH_2OH)_3$		−		−	−					(108)
Dimethyloxazolium		⊕									(35)
β-Acetoxyethylmethylmorpholinium			+++		−						(140)
β-Ethoxyethylmethylmorpholinium			⊕		⊕						(140)
β-Benzilyloxyethylmethylpiperidinium							⊕				(119)

Ammonium compounds related to sulfur derivatives of choline

β-Sulfhydrylethyltrimethyl	$HSCH_2CH_2N^+(CH_3)_3$	++	+		−	++		Br	M	26	SC		(110)
β-Acetylthioethyltrimethyl	$CH_3COSCH_2CH_2N^+(CH_3)_3$	++	+			++						Cats 0.15–2.2	(173, 179)
β-Sulfhydrylpropyltrimethyl	$HSCHCH_2N^+(CH_3)_3$ (CH₃ branch)	⊕	+			⊕							(87, 172)
Acetylthiomethyltrimethyl	$CH_3COSCH_2N^+(CH_3)_3$		++										(119)
Methylthiomethyltrimethyl	$CH_3SCH_2N^+(CH_3)_3$	⊕	++		−			I	M	120	SC		(110)
Ethylthiomethyltrimethyl	$C_2H_5SCH_2N^+(CH_3)_3$		++		++	−		Cl	M	40	SC		(110)
Propylthiomethyltrimethyl	$C_3H_7SCH_2N^+(CH_3)_3$		++		++			I	M	66	SC		(110)
Isopropylthiomethyltrimethyl	$iso\text{-}C_3H_7SCH_2N^+(CH_3)_3$	⊕	⊕		⊕			I	M	66	SC		(110)
Butylthiomethyltrimethyl	$C_4H_9SCH_2N^+(CH_3)_3$		⊕		⊕			I	M	80	SC		(110)
Isobutylthiomethyltrimethyl	$iso\text{-}C_4H_9SCH_2N^+(CH_3)_3$		++		⊕			I	M	67	SC		(110, 112)

TABLE 4—*Concluded*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES				PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice			Miscellaneous		
								mg./kg.			*mg./kg.*	*mg./kg.*	
Ethylsulfonylmethyltrimethyl	$C_2H_5S(=O)(=O)CH_2N^+(CH_3)_3$		+					SO_4 M	60	SC			(110)
Propylsulfonylmethyltrimethyl	$C_3H_7S(=O)(=O)CH_2N^+(CH_3)_3$		+					SO_4 M	50	SC			(110)
Butylsulfonylmethyltrimethyl	$C_4H_9S(=O)(=O)CH_2N^+(CH_3)_3$		+					SO_4 M	28	SC			(110)
Isobutylsulfonylmethyltrimethyl	iso-$C_4H_9S(=O)(=O)CH_2N^+(CH_3)_3$							SO_4 M	43	SC			(110)

Methylthiomethyltriethyl	$CH_3SCH_2N^+(C_2H_5)_3$	++	−		−	++		I	M	80	SC		(112)
Ethylthiomethyltriethyl	$C_2H_5SCH_2N^+(C_2H_5)_3$		−		−			I	M	120	SC		(112)
Isopropylthiomethyltriethyl	$CH_3CH(CH_3)SCH_2N^+(C_2H_5)_3$	⊕	−		−	⊕		I	M	95	SC		(112)
Isobutylthiomethyltriethyl	iso-$C_4H_9SCH_2N^+(C_2H_5)_3$	++	−		−	++		I	M	95	SC		(112)

possess all, none, or varying combinations of these actions. Esterification of the hydroxyl group greatly increases the muscarinic action. Acetylcholine and acetyl-β-methylcholine have such effective muscarinic action that they have been used clinically in the treatment of various diseases, particularly those of blood vessels (74). Carbaminoylcholine is less readily hydrolyzed in the body than the above esters, and therefore has a more prolonged action and is effective orally.

Unna and coworkers (213) reported that carbaminoylcholine in extremely small doses greatly enhances and prolongs the curarizing effect of β-erythroidine.

The alkyl ethers of choline have a somewhat more effective muscarinic action than choline but are less effective than the esters. The aromatic ethers are devoid of muscarinic action and have very marked nicotinic actions.

A methyl group in the α- or β-position on the hydroxyethyl chain seems to have little effect on the activity. Acetyl-β-methylcholine is as effective as acetylcholine and has a more prolonged action, since it is somewhat less readily hydrolyzed. Other alkyl groups in the β-position abolish the nicotinic, reduce the muscarinic, and enhance the curare action, particularly in the case of the choline ethers. Derivatives containing a phenyl group in the hydroxyethyl chain, such as ephedrine derivatives, have only weak nicotinic and no muscarinic activity.

The formocholines are somewhat less active physiologically than the corresponding choline derivatives. γ-Homocholine has a greater muscarinic action than choline itself. The various derivatives of γ-homocholine, however, seem to be less effective than the corresponding derivatives of choline.

Benzilyl derivatives of choline in which one or more of the methyl groups on the nitrogen has been replaced by another alkyl group have atropine-like actions. Choline derivatives with the three methyl groups replaced by ethyl, propyl, and butyl groups lack both muscarinic and stimulating nicotinic actions. The ethers of the triethyl derivatives are reported to have only curare activity (74).

The replacing of the oxygen of choline with sulfur to form thiocholine greatly enhances the curare and paralyzing nicotinic actions and abolishes the stimulating nicotinic action. The ethers of the thioformocholine derivatives containing three ethyl groups on the nitrogen possess marked curare actions. The isobutyl ether has a very powerful but brief curare action (112).

5. Betaine derivatives and analogues (table 5)

Betaine itself is pharmacologically inert, but its esters have marked physiological action, chiefly muscarinic with some nicotinic. Replacement of the three methyl groups on the nitrogen in the betaine esters with ethyl, propyl, butyl, and other alkyl groups abolishes the muscarinic action. Thus, as was true in the tetraalkylammonium derivatives, the methyl groups on the nitrogen appear to play a part in causing muscarinic action. The amide of betaine possesses both muscarinic and nicotinic actions; substitution on the nitrogen of the amide diminishes the muscarinic action.

Very few data are available on the curare action of the betaine derivatives. Betaine itself and true betaine-type compounds, such as benzbetaine, the methyl betaine of nicotinic acid, tryptophan betaine, taurobetaine, and thiohistidine betaine, are pharmacologically inert. The fact that they do not exhibit a curare action may be due to the quaternary nitrogen not being a free ion, since a negative charge is present in the same molecule. Some of the esters of substituted betaines do have marked curare action, and these esters are onium ions of the ordinary type.

6. Diammonium compounds (table 6)

The few compounds of this type which have been reported have only weak pharmacological actions.

B. ARYLALKYLAMMONIUM COMPOUNDS

1. Aryltrialkylammonium compounds (table 7)

Aryltrialkylammonium compounds exhibit muscarinic, nicotinic, and weak curare actions. The replacement of an alkyl group on a quaternary nitrogen with an aryl group reduces the curare activity.

2. Prostigmine derivatives and analogues (table 8)

Prostigmine is a synthetic compound which is used as a physostigmine substitute in the treatment of eye and intestinal disorders. Its pharmacological action is due to the inhibition of cholinesterase in body fluids and tissues, thus preventing enzymatic hydrolysis of acetylcholine. Its effect on skeletal muscle in small doses is opposite to that of curare; indeed, it has been found to be an antagonist to curare paralysis (74), with the result that the effects of too large a dose of curare can be alleviated by injection of prostigmine.

Large doses of prostigmine, however, have been found to cause a peripheral paralysis similar to that of curare. Rosenblueth and Morison (186a) postulated that the cholinesterase inhibition of prostigmine allowed the acetylcholine formed at the myoneural junction to build up to concentrations above which the muscle does not respond (see page 287 for a discussion of their theories).

The cholinesterase inhibition of prostigmine is attributed to the carbamyl group. Stedman (199, 200) showed that the urethans of the isomeric dimethylaminophenols and of the isomeric hydroxybenzyldimethylamines possess miotic activity, which is a result of cholinesterase inhibition. He found that conversion of the tertiary bases of the dimethylaminophenol derivatives to the quaternary compounds intensifies the miotic action of the meta compounds and abolishes the actions of the ortho and para compounds. In the benzyl derivatives, the conversion to the quaternary compounds increases the miotic action of the ortho derivative, diminishes that of the meta, and abolishes that of the para compound. Stedman, Schweitzer, and Wright (201) reported that the tertiary bases are central convulsants, but the quaternary compounds are central depressants.

TABLE 5

Alkylammonium compounds

Betaine derivatives and analogues

AMMONIUM COMPOUND	STRUCTURE	CURARIFORM ACTION	MUSCARINIC ACTION	STIMULATING NICOTINIC ACTION	PARALYZING NICOTINIC ACTION	TOXIC DOSES MICE	REFERENCES
						mg./kg.	
Carboxymethyltrimethyl- (Betaine)	$(CH_3)_3N^+CH_2COO^-$	−	−	−		M 2000 SC Cl M 3000 SC	(103, 105, 116, 117, 211)
Carbomethoxymethyltrimethyl-	$(CH_3)_3N^+CH_2COOCH_3$		++	+	+	Br M 110 SC	(103, 178)
Carbethoxymethyltrimethyl-	$(CH_3)_3N^+CH_2COOC_2H_5$		++	+	+	Br M 170 SC	(103, 108, 153)
Carbobutoxymethyltrimethyl-	$(CH_3)_3N^+CH_2COOC_4H_9$		⊕	+	+	Br M 420 SC	(103)
Carbobenzoxymethyltrimethyl-	$(CH_3)_3N^+CH_2COOCH_2C_6H_5$		⊕	+	+	Br M 290 SC	(103)
Carboxymethyltriethyl-	$(C_2H_5)_3N^+CH_2COO^-$		+	−	+	Br M > 1500 SC	(108)
Carbomethoxymethyltriethyl-	$(C_2H_5)_3N^+CH_2COOCH_3$		−	−	+	Br M 400 SC	(108, 178)
Carbethoxymethyltriethyl-	$(C_2H_5)_3N^+CH_2COOC_2H_5$		−	−	⊕	Br M 430 SC	(108)
Carboxymethyltripropyl-	$(C_3H_7)_3N^+CH_2COO^-$		−	−	−	Br M > 2000 SC	(108)
Carbomethoxymethyltripropyl-	$(C_3H_7)_3N^+CH_2COOCH_3$		−	−	++	Br M 180 SC	(108)
Carbethoxymethyltripropyl-	$(C_3H_7)_3N^+CH_2COOC_2H_5$		−	−	++	Br M 120 SC	(108)

Carbomethoxymethyltributyl-	$(C_4H_9)_3N^+CH_2COOCH_3$		−	+++		Br M	90 SC	(108, 178)
Carbethoxymethyltributyl-	$(C_4H_9)_3N^+CH_2COOC_2H_5$		−	+++	−	Br M	100 SC	(108, 178)
Carboxymethyltriisoamyl-	$(iso\text{-}C_5H_{11})_3N^+CH_2COO^-$		+	+	−	Br M	120 SC	(108)
Carbethoxymethyltriisoamyl-	$(iso\text{-}C_5H_{11})_3N^+CH_2COOC_2H_5$		−	++	⊕	Br M	120 SC	(108)
Carboxymethyltri(β-hydroxyethyl)-	$(HOCH_2CH_2)_3N^+CH_2COO^-$		+	−	−	Br M	> 1500 SC	(108)
Carbethoxymethyltri(β-hydroxyethyl)-	$(HOCH_2CH_2)_3N^+CH_2COOC_2H_5$		−	−	−	Br M	> 1500 SC	(108)
Carbomethoxymethylbenzyldimethyl-	$(CH_3)_2N^+(CH_2C_6H_5)CH_2COOCH_3$		+	+	⊕	Br M	380 SC	(108)
Carbethoxymethylbenzyldimethyl-	$(CH_3)_2N^+(CH_2C_6H_5)CH_2COOC_2H_5$		++	++	⊕	Br M	730 SC	(108)
Carbomethoxymethyldibenzylmethyl-	$(C_6H_5CH_2)_2N^+(CH_3)CH_2COOCH_3$					Br M	170 SC	(108)
Carbethoxymethyldibenzylmethyl-	$(C_6H_5CH_2)_2N^+(CH_3)CH_2COOC_2H_5$		+	⊕	⊕	Br M	32 SC	(108)

TABLE 5—*Continued*

Ammonium compound	Structure	Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Toxic doses mice		References
							mg./kg.	
(α-Carbethoxyethyl)trimethyl-..	$(CH_3)_3N^+CH(CH_3)COOC_2H_5$	++	⊕	+	+	Br M	560 SC	(103)
(α-Carbethoxybutyl)trimethyl-.	$(CH_3)_3N^+CH(C_3H_7)COOC_2H_5$	++	⊕	+	+	Br M	260 SC	(103)
(α-Carbethoxyamyl)trimethyl-..	$(CH_3)_3N^+CH(C_4H_9)COOC_2H_5$	++	⊕	+	+	Br M	220 SC	(103)
(α-Carbethoxybenzyl)trimethyl-	$(CH_3)_3N^+CH(C_6H_5)COOC_2H_5$	++	⊕	+	+	Br M	170 SC	(103)
(γ-Carboxypropyl)trimethyl-...	$(CH_3)_3N^+CH_2CH_2CH_2COO^-$	⊕						(211)
Formylmethyltrimethyl-........	$(CH_3)_3N^+CH_2CHO$		⊕					(14, 66)
Dimethoxymethyltrimethyl-....	$(CH_3)_3N^+CH(OCH_3)_2$		+					(66)
Carbamylmethyltrimethyl-.....	$(CH_3)_3N^+CH_2CONH_2$		++	+	+	Cl M	420 SC	(103, 105, 153)
N-Methylcarbamylmethyltrimethyl......................	$(CH_3)_3N^+CH_2CONHCH_3$		++	+	+	Cl M	420 SC	(105)

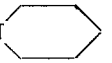
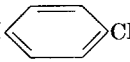
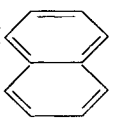
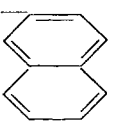
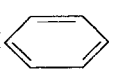
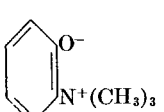
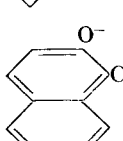
N-Ethylcarbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONHC_2H_5$		++	+	+	Cl M	680 SC	(105)
N-Propylcarbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONHC_3H_7$		−	+	⊕	Cl M	770 SC	(105)
N-Butylcarbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONHC_4H_9$		−	+	⊕	Cl M	750 SC	(105)
Carbopiperidinomethyltrimethyl-	$(CH_3)_3N^+CH_2CON$ 		++	−	⊕	Cl M	370 SC	(105)
N-Phenylcarbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONH$ 		+	++	⊕	Cl M I M	670 SC 39 SC	(105, 111)
N-(*p*-Tolyl)carbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONH$  CH_3		−	−	++	Cl M	440 SC	(105)
N-(*p*-Hydroxyphenyl)carbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONH$  OH		−	⊕		Cl M	230 SC	(105)
N-(*p*-Methoxyphenyl)carbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONH$  OCH_3		−	−		Cl M	430 SC	(105)
N-(*o*-Methoxyphenyl)carbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONH$  CH_3O		−	−	⊕	Cl M	470 SC	(105)
N-(*p*-Ethoxyphenyl)carbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONH$  OC_2H_5		−	−		Cl M	350 SC	(105)
N-(*o*-Ethoxyphenyl)carbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONH$  C_2H_5O		−	−	⊕	Cl M	180 SC	(105)

TABLE 5—*Continued*

AMMONIUM COMPOUND	STRUCTURE	CURARIFORM ACTION	MUSCARINIC ACTION	STIMULATING NICOTINIC ACTION	PARALYZING NICOTINIC ACTION	TOXIC DOSES MICE	REFERENCES
						mg./kg.	
N-(α-Naphthyl)carbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONH$ 		−	−	⊕	Cl M 650 SC	(105)
N-(β-Naphthyl)carbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONH$ 		−	−	⊕	Cl M 260 SC	(105)
N-Phenylcarbamylmethyltriisoamyl-	$(iso\text{-}C_5H_{11})_3N^+CH_2CONH$ 		−	−	−	Cl M 90 SC	(105)
Carbureidomethyltrimethyl-	$(CH_3)_3N^+CH_2CONHCONH_2$		++	⊕	+	Cl M 40 SC	(105)
Carb(phenylureido)methyltrimethyl-	$(CH_3)_3N^+CH_2CONHCONHC_6H_5$		+	−		Cl M 1000 SC	(105)
o-Hydroxyphenyltrimethyl- (Benzbetaine)		−	−	−	−		(88, 211)
2-Hydroxynaphthaltrimethyl-		−	−	−	−		(32)

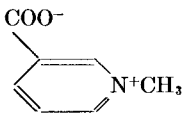
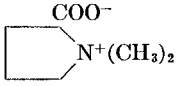
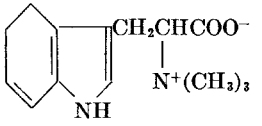
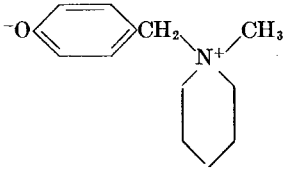
3-Carboxy-*N*-methylpyridinium.		–	–	–	–		(211)
2-Carboxy-*N*,*N*-dimethylpyrrolidinium.....		–	–	–	–		(211)
(Tryptophan betaine).....		–	–	–	–		(211)
N-Methyl-*N*-(*p*-hydroxybenzyl) piperidinium.....		–	–	–	–		(32)
β-Sulfoethyltrimethyl-..... (Taurobetaine)	$(CH_3)_3N^+CH_2CH_2SO_3^-$	–	–	–	–		(211)
(Thiohistidine betaine).....	$C_9H_{15}O_2N_3S$	–	–	–	–		(211)

TABLE 6

Alkylammonium compounds

Diammonium compounds

DIAMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSE CATS	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Other actions			
						mg./kg.	*mg./kg.*	
N,N,N,N′,N′,N′-Hexamethyldimethylene-	$(CH_3)_3N^+(CH_2)_2N^+(CH_3)_3$	+	⊕	⊕	Central depressant			(1, 193, 211)
N,N,N,N′,N′,N′-Hexamethyltrimethylene-	$(CH_3)_3N^+(CH_2)_3N^+(CH_3)_3$	+					Cl 300	(24)
N,N,N,N′,N′,N′-Hexamethyltetramethylene-	$(CH_3)_3N^+(CH_2)_4N^+(CH_3)_3$	⊕						(1, 211)
N,N,N,N′,N′,N′-Hexamethylpentamethylene-	$(CH_3)_3N^+(CH_2)_5N^+(CH_3)_3$	⊕						(1, 211)
N,N,N,N′,N′,N′-Hexamethyl-2-hydroxytrimethylene-	$(CH_3)_3N^+CH_2CHOHCH_2N^+(CH_3)_3$	−						(211)
Oblitin	$(CH_3)_3N^+CH_2CHCH_2COOC_2H_5$ | O | $(CH_3)_3N^+CH_2CHCH_2COOC_2H_5$	−				2000		(211)

Stevens and Beutel (202) showed that an alkyl group on the benzene ring makes the quaternary bases of the ortho and para compounds effective. It is remarkable that the methiodide of the dimethylcarbamyl derivative of *p*-dimethylaminophenol has a toxicity in mice of 120 mg./kg., whereas the corresponding compound with an isopropyl group on the ring in the position ortho to the nitrogen has a toxicity of 0.075 mg./kg. This represents an increase in toxicity by a factor of 1600.

Prostigmine has been used clinically in the treatment of infantile paralysis (124), but it is necessary to use atropine along with the prostigmine to suppress its muscarinic effects. Kabat and Knapp (124) reported that prostigmine acts at the spinal cord as well as at the myoneural junction.

C. HETEROCYCLIC AMMONIUM COMPOUNDS

1. Pyridinium compounds (table 9)

The alkylpyridinium salts possess weak curare activity, in some cases marked muscarinic activity, and in general, no nicotinic activity. The benzylpyridinium salt is the most effective of the pyridine derivatives. The ethyl- and propyl-pyridinium salts are less effective than the methyl derivatives. The isoamyl and cetyl derivatives have an action comparable to the methyl derivative.

The presence of an alkyl group on the ring seems to have little effect, as methyl-α-picolinium iodide has an activity comparable to that of methylpyridinium odide.

2. Piperidinium compounds (table 10)

Dimethylpiperidinium iodide is more effective in paralyzing the isolated nerve sartorius than is methylpyridinium iodide. Santesson and Koraen (190) observed that reduction of the pyridine ring increases the curare action, while Hunt and Renshaw (104) reported that reduction of the ring reduces the muscarinic and nicotinic actions and the toxicity.

3. Quinolinium compounds (table 11)

Unsubstituted alkylquinolinium salts possess a curare action but no muscarinic or nicotinic action. Increasing the length of the alkyl group increases the intensity of the curare action. Octylquinolinium iodide is half as effective as curarine in paralyzing the isolated nerve sartorius.

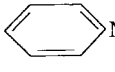
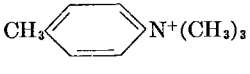
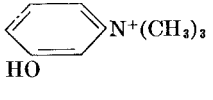
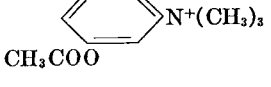
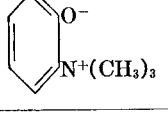
An alkyl group on the quinoline ring in the 2-, 4-, or 6-position renders the compound pharmacologically inert.

Dimethyl- and methylethyl-tetrahydroquinolinium salts are about equal in action to the ethylquinolinium salt and are more effective than the methylquinolinium salt. *N*,*N*-Dimethyl-6-methoxytetrahydroquinolinium chloride (dimethylthallinium chloride) is ten times more effective than methylquininium chloride. Since such a marked increase is not noted in the reduction of the unsubstituted quinolines, it seems probable that the methoxyl group acts to enhance the curare action.

TABLE 7

Arylalkylammonium compounds

Aryltrialkylammonium compounds

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSES			PARALYZING DOSES			REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Mice		Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius: Millimoles/liter 1	Minutes to paralyze isolated nerve sartorius: Millimoles/liter 10	
						mg./kg.		*mg./kg.*	*mg./kg.*	*minutes*		
Phenyltrimethyl-		⊕	++	++	++	I 50 55 IP 49 SC Cl 80 15 IV Cl 80 200–300 OS		Rabbits 80 OS	I 150	I 5.5		(3, 4, 24, 32, 101, 117, 120, 161)
p-Methylphenyltrimethyl-									I 80			(24)
m-Hydroxyphenyltrimethyl-						I 80 25–30 IV I 80 200–250 OS						(3)
m-Acetoxyphenyltrimethyl-						CH_3SO_4 80 7.5–10 CH_3SO_4 80 1000 OS						(3)
o-Hydroxyphenyltrimethyl-		−	−	−	−							(88)

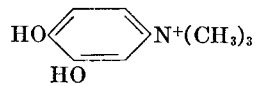
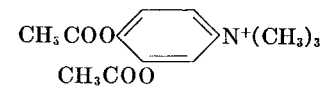
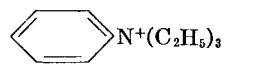
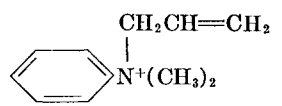
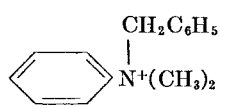
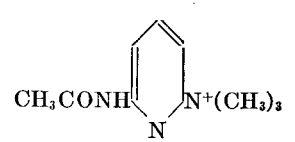
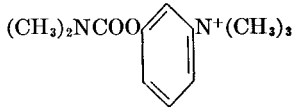
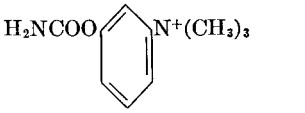
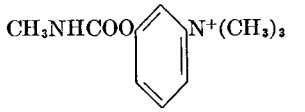
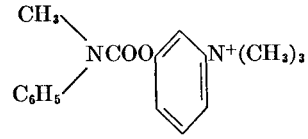
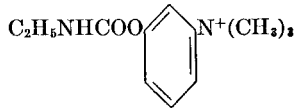
3,4-Dihydroxyphenyltrimethyl-				⊕						(211)
3,4-Diacetoxyphenyltrimethyl-				⊕						(211)
Phenyltriethyl-		⊕								(211)
Phenyldimethylallyl-		+								(211)
Phenyldimethylbenzyl-		+						Cl 35		(32, 211)
(α-Acetaminopyridyl)trimethyl-								Cl 200		(24)

TABLE 8

Arylalkylammonium compounds

Prostigmine derivatives and analogues

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE				REFERENCES
		Miotic action	Other actions					
					mg./kg.			
3-(Dimethylcarbamyloxy)phenyltrimethyl- (Prostigmine)		⊕	Weak curariform	I CH_3SO_4	50 80	0.55 0.5	 IV	(3, 74, 202)
3-(Carbamyloxy)phenyltrimethyl-		—		CH_3SO_4 CH_3SO_4	80 80	0.7 500	IV OS	(3)
3-(Methylcarbamyloxy)phenyltrimethyl-		⊕	Central depressant	Br I CH_3SO_4 CH_3SO_4	80 80 80 80	0.15 0.1 0.1 2.5	IV IV IV IV	(3, 201)
3-(Methylphenylcarbamyloxy)-phenyltrimethyl-			Central depressant	CH_3SO_4	80	3.5	IV	(3, 201)
3-(Ethylcarbamyloxy)phenyltrimethyl-				CH_3SO_4	80	1	IV	(3)

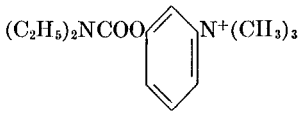
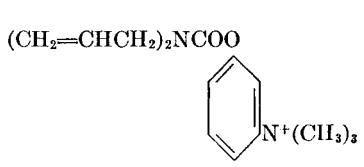
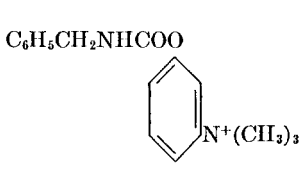
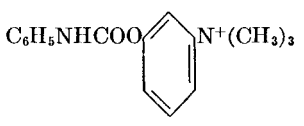
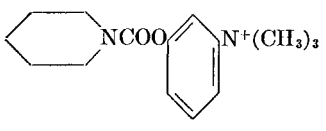
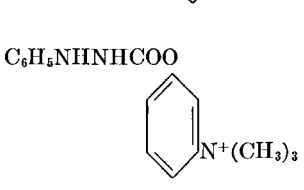
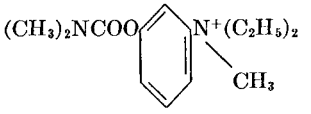
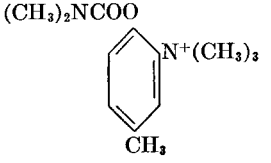
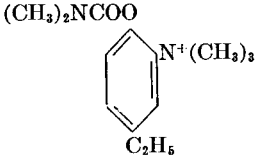
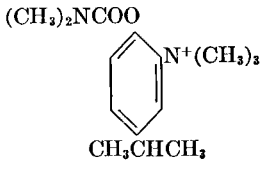
3-(Diethylcarbamyloxy)phenyltrimethyl-				CH_3SO_4	80	8	IV	(3)
3-(Diallylcarbamyloxy)phenyltrimethyl-				CH_3SO_4	80	10	IV	(3)
3-(Benzylcarbamyloxy)phenyltrimethyl-				CH_3SO_4	80	0.1	IV	(3)
3-(Phenylcarbamyloxy)phenyltrimethyl-				CH_3SO_4	80	2	IV	(3)
3-(Pentamethylenecarbamyloxy)-phenyltrimethyl-				CH_3SO_4	80	6	IV	(3)
3-(Phenylhydrazinoformyloxy)-phenyltrimethyl-				CH_3SO_4	80	0.25	IV	(3)

TABLE 8—*Continued*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE			REFERENCES
		Miotic action	Other actions		*mg./kg.*		
3-(Dimethylcarbamyloxy)phenyldiethylmethyl-			Physostigmine action				(201)
2-(Dimethylcarbamyloxy)-5-methylphenyltrimethyl-				I	50	2	(202)
2-(Dimethylcarbamyloxy)-5-ethylphenyltrimethyl-				I	50	1.25	(202)
2-(Dimethylcarbamyloxy)-5-isopropylphenyltrimethyl-				I	50	4.8	(202)

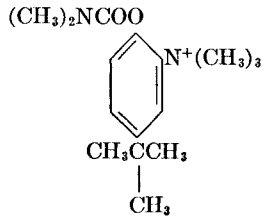
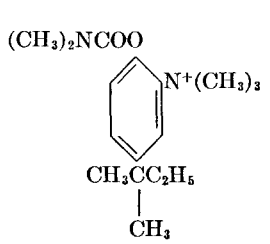
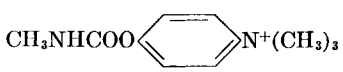
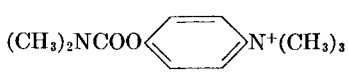
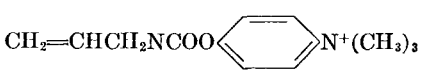
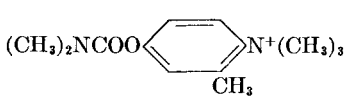
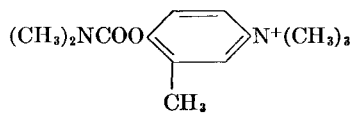
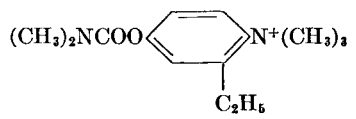
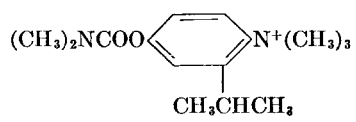
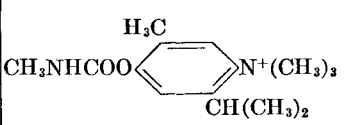
2-(Dimethylcarbamyloxy)-5-*tert*-butylphenyltrimethyl-				I	50	13.5		(202)
2-(Dimethylcarbamyloxy)-5-*tert*-amylphenyltrimethyl-				I	50	12		(202)
4-(Methylcarbamyloxy)phenyltrimethyl-				I	80	2	IV	(3)
4-(Dimethylcarbamyloxy)phenyltrimethyl-				I	50	120		(202)
4-(Allylcarbamyloxy)phenyltrimethyl-				CH_3SO_4	80	0.75	IV	(3)
4-(Dimethylcarbamyloxy)-2-methylphenyltrimethyl-				I	50	13		(202)

TABLE 8—*Continued*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE			REFERENCES
		Miotic action	Other actions				
					mg./kg.		
4-(Dimethylcarbamyloxy)-3-methylphenyltrimethyl-				I	50	6.5	(202)
4-(Dimethylcarbamyloxy)-2-ethylphenyltrimethyl-				I	50	1.15	(202)
4-(Dimethylcarbamyloxy)-2-isopropylphenyltrimethyl-				I	50	0.075	(202)
4-(Methylcarbamyloxy)-2-methyl-5-isopropylphenyltrimethyl-				I	50	0.22	(202)
4-(Methylcarbamyloxy)-3-methyl-6-isopropylphenyltrimethyl-				I	50	0.09	(202)

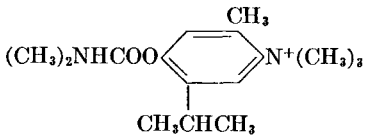
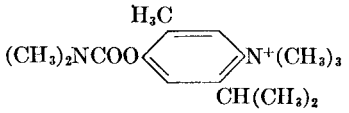
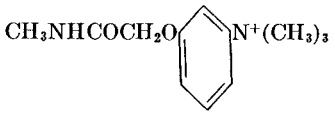
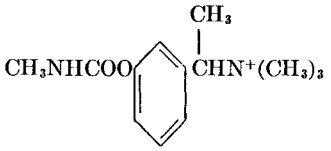
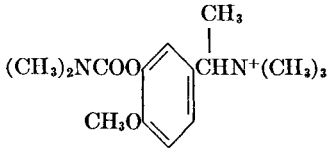
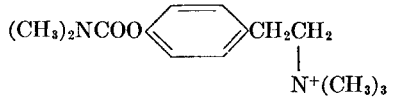
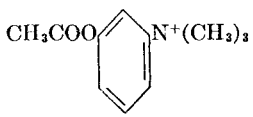
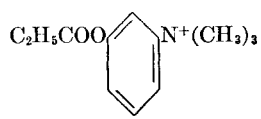
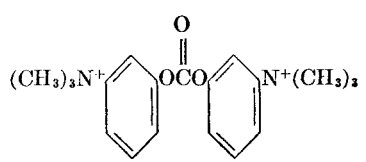
4-(Dimethylcarbamyloxy)-2-methyl-5-isopropylphenyltrimethyl-				I	50	0.72		(202)
4-(Dimethylcarbamyloxy)-3-methyl-6-isopropylphenyltrimethyl-				I	50	0.24		(202)
3-(Methylcarbamylmethoxy)-phenyltrimethyl-			Central depressant	CH_3SO_4 CH_3SO_4	80 80	7.5 1000	IV OS	(3, 201)
α-(3-Methylcarbamyloxyphenyl)-ethyltrimethyl- (Miotine)		++	Weak muscarinic					(201)
α-(3-Dimethylcarbamyloxy-4-methoxyphenyl)ethyltrimethyl-				I	80	5	IV	(3)
β-(4-Dimethylcarbamyloxyphenyl)ethyltrimethyl-			Central depressant					(201)

TABLE 8—*Concluded*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE				REFERENCES
		Miotic action	Other actions			*mg./kg.*		
3-Acetoxyphenyltrimethyl-				CH_3SO_4	80	7.5	IV	(3)
				CH_3SO_4	80	1000	OS	
3-Propionyloxyphenyltrimethyl-		–		I	80	25	IV	(3, 201)
				I	80	500	OS	
(Bis(3-trimethylammonium-phenyl)carbonate)				CH_3SO_4	80	12.5	IV	(3)
				CH_3SO_4	80	1000	OS	

4. Isoquinolinium compounds (table 12)

Hjort and coworkers (89–97) and Takase and coworkers (204–206) published a series of papers on the pharmacology of various substituted isoquinolines, dihydroisoquinolines, and tetrahydroisoquinolines. No mention was made of any peripheral curare paralysis. The effect of substituents on the toxicity and blood pressure was shown. In three homologous series of 2-alkyltetrahydroisoquinoline derivatives it was shown that the toxicity increases with increasing length of the 2-alkyl group. 6,7-Dihydroxy compounds are less toxic than 6,7-dimethoxy compounds. Substituents in the 6- and 7-positions have less effect on toxicity and blood pressure response than substituents on the nitrogen.

Takase and Sato (205) found that certain 2-methyldihydro- and 2-methyltetrahydro-isoquinoline derivatives have anesthetic and antispasmodic actions. Since the blood pressure effect of the compounds is not prevented by atropine (not a muscarinic action), the action must be on the central nervous system.

The paralyzing doses for frogs indicate that *N*-methylisoquinolinium chloride is less effective than *N*-methylquinolinium iodide. However, Santesson (189) reported that the order of intensity of curare paralysis is 1:2.5:3.75:25 for methylpyridinium, methylquinolinium, methylisoquinolinium, and dimethylthallinium chlorides, respectively.

Various workers (93, 206) have noted the similarity of action between isoquinolines and β-phenylethylamines, which may be regarded as the parent compound of isoquinolines. Further discussion of this observation and of other isoquinolines is included under isoquinoline alkaloids (see page 388).

5. Miscellaneous heterocyclic compounds (table 13)

Some pyrazolium salts have been reported to possess a curare action. These compounds also paralyze the central nervous system, possibly because of the secondary nitrogen present. Two isoxazolium salts have been reported to possess curare activity.

D. ALKALOIDS

1. Curare alkaloids (table 14)

Preparations from South American curare have a powerful and prolonged peripheral paralyzing action; the mechanism of the action has already been discussed (see page 287).

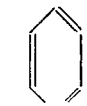
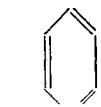
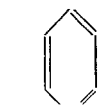
Boehm (12) isolated from tube curare the inactive, tertiary alkaloid curine in a crystalline form and assigned to it the formula $C_{18}H_{19}NO_3$. This formula was accepted by Späth, Leithe, and Ladeck (198), who proposed a benzyltetrahydroisoquinoline structure, which was later doubled to a bisbenzyltetrahydroisoquinoline by Späth and Kuffner (197) on the basis of molecular-weight determinations.

The active, amorphous alkaloid "tubocurarine" obtained by Boehm (12) from tube curare was obtained as a crystalline chloride by King (129). Since

TABLE 9

Heterocyclic ammonium compounds

Pyridinium compounds

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSES		PARALYZING DOSES			REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius: Millimoles/liter 1	10	
						mg./kg.	*mg./kg.*	*mg./kg.*	*minutes*		
N-Methylpyridinium	 CH_3N^+	⊕					Cats Cl 500 SC Frogs Cl 500	I 300 SC Cl 300–400	I	26	(121, 144, 211)
N-Ethylpyridinium	 $C_2H_5N^+$						Rabbits Cl 200 Frogs Cl 40	I 1500 SC	I 60		(121, 211)
N-Propylpyridinium	 $C_3H_7N^+$	⊕						I 600 SC			(144)
N-Isoamylpyridinium	iso-$C_5H_{11}N^+$	⊕						I 300 SC			(144)

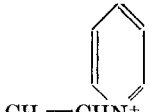
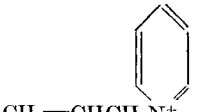
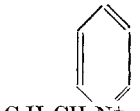
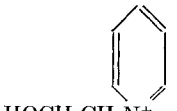
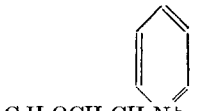
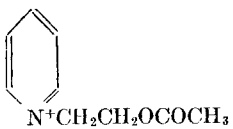
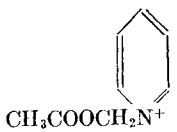
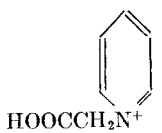
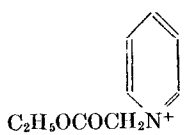
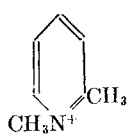
N-Cetylpyridinium	 $C_{16}H_{33}N^+$	⊕		⊕		Cl M 2 IP	Rabbits Cl M 20 IV Rats 50 30 IV 50 200 OS	Br 300			(24, 152 215)
N-Vinylpyridinium	 $CH_2{=}CHN^+$	⊕					Rabbits Cl 15 Frogs Cl 5				(211)
N-Allylpyridinium	 $CH_2{=}CHCH_2N^+$	⊕						I 1500 SC			(144)
N-Benzylpyridinium	 $C_6H_5CH_2N^+$							Cl 90 SC			(144)
N-(β-Hydroxyethyl)pyridinium	 $HOCH_2CH_2N^+$	⊕									(211)
N-(β-Phenoxyethyl)pyridinium	 $C_6H_5OCH_2CH_2N^+$	+	+			Br M 220 SC					(106)

TABLE 9—*Continued*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSES		PARALYZING DOSES		REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius; Millimoles/liter 1 | 10	
						mg./kg.	*mg./kg.*	*mg./kg.*	*minutes*	
N-(β-Acetoxyethyl)pyridinium			+++							(143)
N-Acetoxymethylpyridinium			++	+		Cl 130 SC				(101, 104)
N-Carboxymethylpyridinium			+	−	−	Br >2000 SC				(104)
N-Carbethoxymethylpyridinium			++		−	Br 370 SC				(101, 104)
N-Methyl-α-picolinium								I 300		(24)

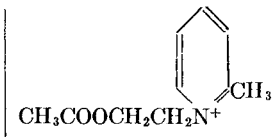
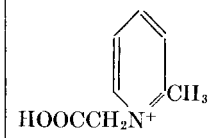
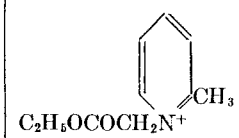
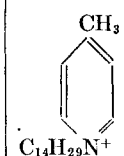
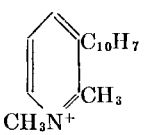
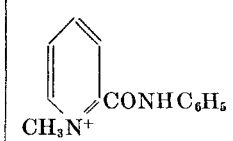
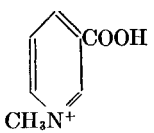
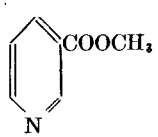
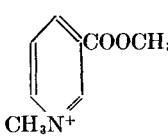
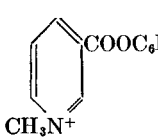
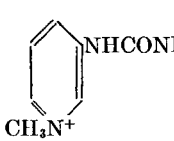
N-(β-Acetoxyethyl)-α-picolinium			+++									(143)
N-Carboxymethyl-α-picolinium		−				SO_4	M	>1600	SC			(106)
N-Carbethoxymethyl-α-picolinium			−	−	+	Br		700	SC			(104)
N-Myristyl-γ-picolinium										Rats 50 7.5 IP 50 30 IV 50 200 SC 50 250 OS		(152)
N-Methyl-β-naphthyl-α-picolinium											Br 300	(24)
N-Methyl-α-(phenylcarbamyl)pyridinium		−	−	−	−	I	M	1000	SC			(162)

TABLE 9—*Continued*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSES		PARALYZING DOSES		REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius (Millimoles/liter 1 | 10)	
						mg./kg.	*mg./kg.*	*mg./kg.*	*minutes*	
N-Methyl-β-carboxypyridinium								I 300		(24)
Methyl ester of nicotinic acid			++	−	−	>1000 SC				(104)
N-Methyl-β-carbomethoxypyridinium			++	−	−	I 600 SC				(104)
N-Methyl-β-carbophenoxypyridinium			−	+		I M 1000 SC				(106)
N-Methyl-β-carbamidopyridinium			+	−		I M 1400 SC				(106)

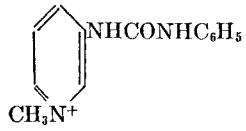
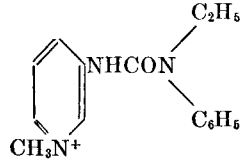
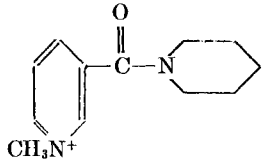
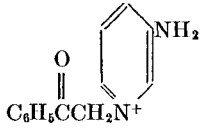
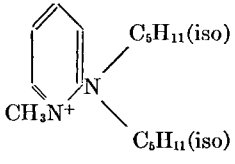
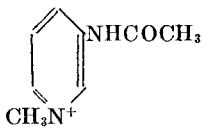
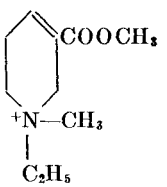
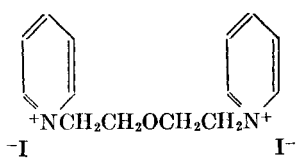
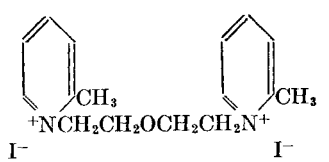
N-Methyl-β-phenylcarbamidopyridinium				—	—		I	M	>1600 SC				(106)
N-Methyl-β-ethylphenylcarbamidopyridinium				—	—		I	M	1350 SC				(106)
N-Methyl-β-carbopiperidinopyridinium		—	—	—	—		I	M	440 SC				(106)
N-Phenacyl-β-aminopyridinium											Br 300		(24)
N-Methyl-α-diisoamylaminopyridinium											I 600		(144)

TABLE 9—*Concluded*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSES		PARALYZING DOSES		REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius (Millimoles/liter: 1 | 10)	
						mg./kg.	*mg./kg.*	*mg./kg.*	*minutes*	
N-Methyl-β-acetaminopyridinium		+	−			I M 850 SC				(106)
N-Methyl-*N*-ethyl-β-carbomethoxytetrahydropyridinium			+++	−	+	Br M 65 SC				(104)
N,N'-2,2'-Bis(pyridinium iodide) diethyl ether								238 EL		(160)
N,N'-2,2'-Bis(2-methylpyridinium iodide)diethyl ether								227 EL		(160)

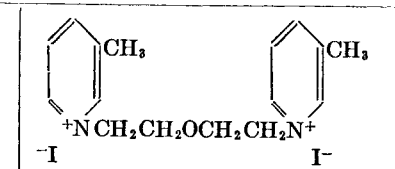
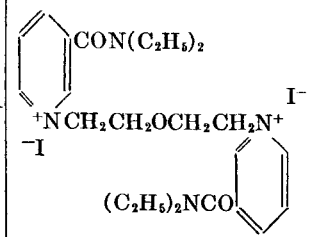
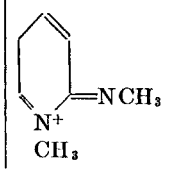
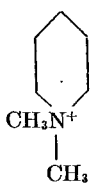
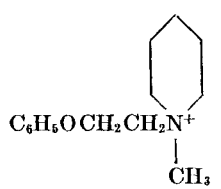
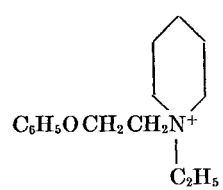
N,N'-2,2'-Bis(3-methylpyridinium iodide)diethyl ether									185 EL				(160)
N,N'-2,2'-Bis(3,3'-bis(diethylcarbamyl)pyridinium iodide)-diethyl ether									>1900 EL				(160)
Methiodide of α-pyridonemethylimide			⊕						I	300 SC			(144)

TABLE 10

Heterocyclic ammonium compounds

Piperidinium compounds

PIPERIDINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTIONS					TOXIC DOSE MICE	MINUTES TO PARALYZE ISOLATED NERVE SARTORIUS 10 millimoles/liter	REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action			
							mg./kg.	*minutes*	
N,*N*-Dimethyl-		⊕						I 8	(121)
N-Methyl-*N*-(β-phenoxyethyl)-			−	−	+		I M 900 SC		(106)
N-Ethyl-*N*-(β-phenoxyethyl)-			−	−			Br M 160 SC		(106)

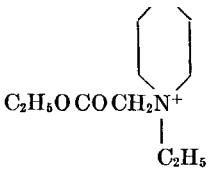
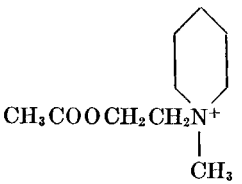
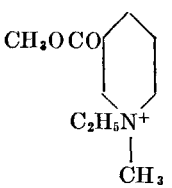
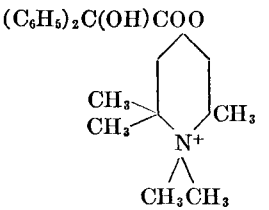
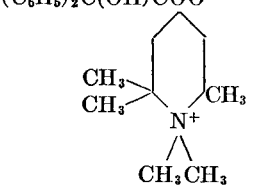
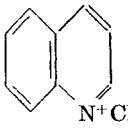
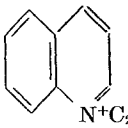
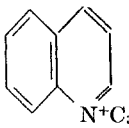
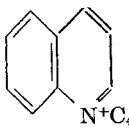
[illegible]-Carbethoxymethyl-4-ethyl-			+				Br	M	180 SC	(104)
N-(β-Acetoxyethyl)-*N*-methyl-			++	−	−		I	M	270 SC	(104)
3-Carbomethoxy-*N*-ethyl-*N*-methyl-			⊕				Br	M	180 SC	(104)
4-Benzilyloxy-*N*,*N*,2,2,6-pentamethyl- (β-isomer)						⊕	Cl Cl Cl	50 50 50	75 IP 325 SC 1000 OS	(119)
4-Benzilyloxy-*N*,*N*,2,2,6-pentamethyl- (α-Isomer)						⊕	Cl Cl	50 50	80 IP 325 SC	(119)

TABLE 11

Heterocyclic ammonium compounds

Quinolinium compounds

QUINOLINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSE	PARALYZING DOSES			REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action		Frogs	Isolated nerve sartorius, Millimoles/liter		
								1	10	
		⊕				*mg./kg.*	*mg./kg.*	*minutes*		
N-Methyl-							I 300 340	I	9.25	(24, 121)
N-Ethyl-		+	−	−	−	Mice M 120 SC		I 14	4	(106, 121)
N-Propyl-		⊕						I 6		(121)
N-Butyl-		⊕						I 6		(121)

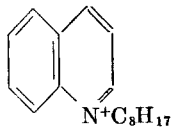
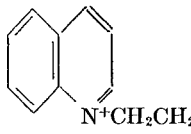
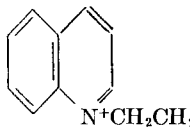
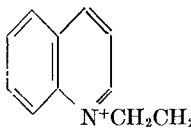
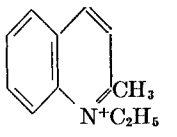
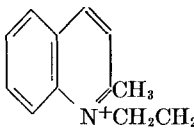
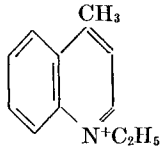
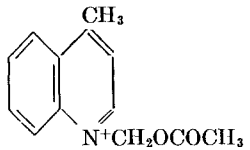
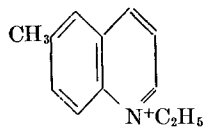
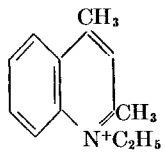
N-Octyl-		⊕						I 5.8		(121)
N-(β-Hydroxyethyl)-		⊕								(211)
N-(β-Aminoethyl)-						Rabbits Cl 27 IV				(211)
N-(β-Acetoxyethyl)-			+++							(143)
N-Ethyl-2-methyl-		−	−	−	−	Mice M 100 SC				(106)
N-(β-Acetoxyethyl)-2-methyl-			+++							(143)

TABLE 11—*Concluded*

QUINOLINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSE	PARALYZING DOSES			REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action		Frog	Isolated nerve sartorius		
								Millimoles/liter		
								1	10	
						mg./kg.	*mg./kg.*	*minutes*		
N-Ethyl-4-methyl-		—	—	—	—	Mice M 120 SC				(106)
N-Acetoxymethyl-4-methyl-			—	—	—	Mice Br 280 SC				(104)
N-Ethyl-6-methyl-		—	—	—	—	Mice M 85 SC				(106)
N-Ethyl-2,4-dimethyl-		—	—	—	—	Mice M 110 SC				(106)

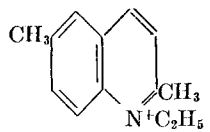
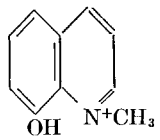
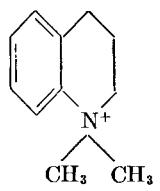
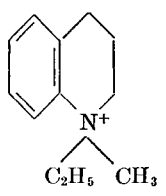
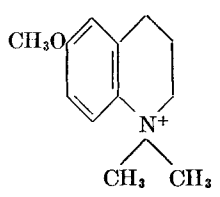
N-Ethyl-2,6-dimethyl-		−	−	−	−	Mice M 120 SC				(106)
N-Methyl-8-hydroxy-						Mice I 80 0.1 IV				(194)
(Diquinolyl dimethylsulfate)	Structure undetermined	⊕	−	−	−	Rabbits 30				(98, 211)
N,*N*-Dimethyltetrahydro-								I 12.25		(121)
N-Ethyl-*N*-methyltetrahydro-								I 20		(120)
N,*N*-Dimethyl-6-methoxytetrahydro-(Dimethylthallinium)		⊕								(190)

TABLE 12

Heterocyclic ammonium compounds

Isoquinolinium compounds

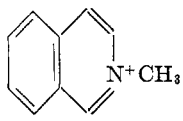
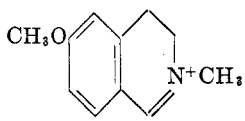
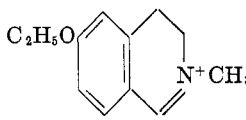
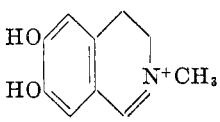
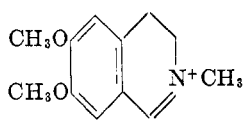
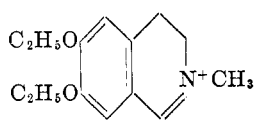
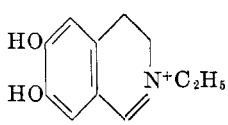
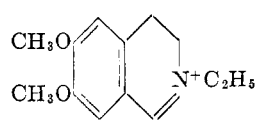
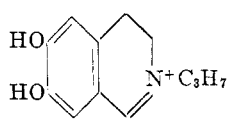
ISOQUINOLINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Effect on blood pressure			
				mg./kg.	*mg./kg.*	
N-Methyl-		+			Cl 500	(190, 211)
N-Methyl-6-methoxy-3,4-dihydro-			d p	Cl 50 166 IP		(91)
N-Methyl-6-ethoxy-3,4-dihydro-			d p	Cl 50 184 IP		(91)
N-Methyl-6,7-dihydroxy-3,4-dihydro-			p	Cl 50 120 IP		(91)
N-Methyl-6,7-dimethoxy-3,4-dihydro-		⊕	p	Cl 50 92 IP		(91, 211)
N-Methyl-6,7-diethoxy-3,4-dihydro-			d	Cl 50 124 IP		(91)
N-Ethyl-6,7-dihydroxy-3,4-dihydro-			p	Cl 50 116 IP		(91)
N-Ethyl-6,7-dimethoxy-3,4-dihydro-			d p	Cl 50 99 IP		(91)
N-Propyl-6,7-dihydroxy-3,4-dihydro-			p	Cl 50 134 IP		(91)

TABLE 12—*Continued*

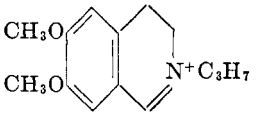
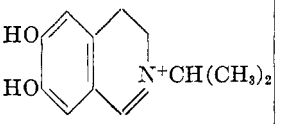
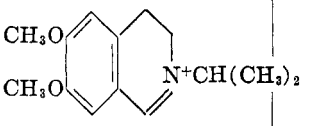
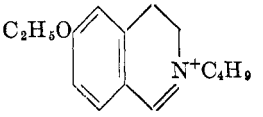
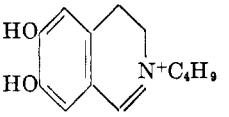
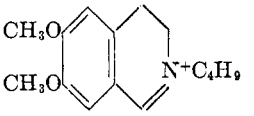
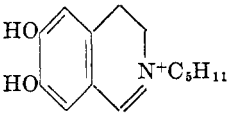
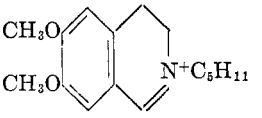
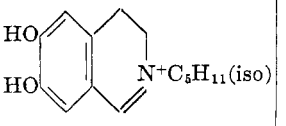
ISOQUINOLINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Effect on blood pressure	*mg./kg.*	*mg./kg.*	
N-Propyl-6,7-dimethoxy-3,4-dihydro-			d	Cl 50 73 IP		(91)
N-Isopropyl-6,7-dihydroxy-3,4-dihydro-			d p	Cl 50 109 IP		(91)
N-Isopropyl-6,7-dimethoxy-3,4-dihydro-			d	Cl 50 86 IP		(91)
N-Butyl-6-ethoxy-3,4-dihydro-			d			(91)
N-Butyl-6,7-dihydroxy-3,4-dihydro-			d p	Cl 50 179 IP		(91)
N-Butyl-6,7-dimethoxy-3,4-dihydro-			d	Cl 50 126 IP		(91)
N-Amyl-6,7-dihydroxy-3,4-dihydro-			d p	Cl 50 159 IP		(91)
N-Amyl-6,7-dimethoxy-3,4-dihydro-			d	Cl 50 108 IP		(91)
N-Isoamyl-6,7-dihydroxy-3,4-dihydro-			d	Cl 50 170 IP		(91)

TABLE 12—*Continued*

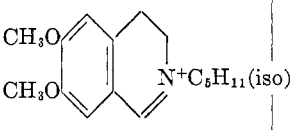
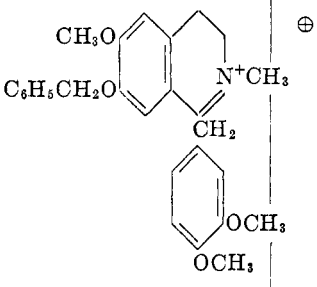
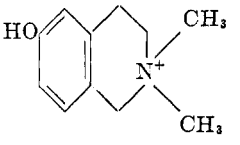
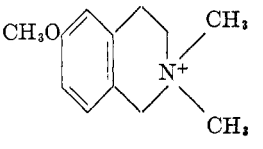
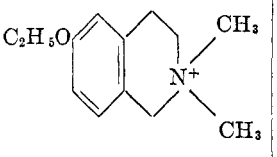
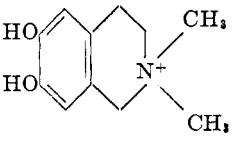
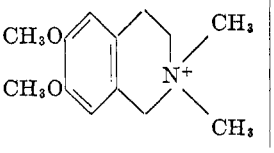
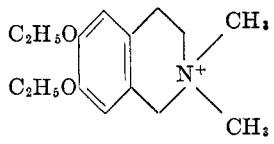
ISOQUINOLINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Effect on blood pressure	*mg./kg.*	*mg./kg.*	
N-Isoamyl-6,7-dimethoxy-3,4-dihydro-			d	Cl 50 130 IP		(91)
N-Methyl-6-methoxy-7-benzyloxy-1-(3,4-dimethoxybenzyl)-3,4-dihydro-		⊕				(204)
N,*N*-Dimethyl-6-hydroxytetrahydro-			d p	Cl 50 25 IP		(90)
N,*N*-Dimethyl-6-methoxytetrahydro-			p	Cl 50 31 IP		(90)
N,*N*-Dimethyl-6-ethoxytetrahydro-			p	Cl 50 58 IP		(90)
N,*N*-Dimethyl-6,7-dihydroxytetrahydro-			d p	Cl 50 33 IP		(90)
N,*N*-Dimethyl-6,7-dimethoxytetrahydro-			p	Cl 50 20 IP		(90)

TABLE 12—*Concluded*

ISOQUINOLINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Effect on blood pressure			
				mg./kg.	*mg./kg.*	
N,*N*-Dimethyl-6,7-diethoxy-tetrahydro-			p	Cl 50 69 IP		(90)

it was found to be dextrorotatory, it was called *d*-tubocurarine chloride. King (129, 130) showed that *d*-tubocurarine chloride and *l*-curine methochloride are isomeric, and proved by a series of Hofmann degradations that *d*-tubocurarine chloride has the following structure:

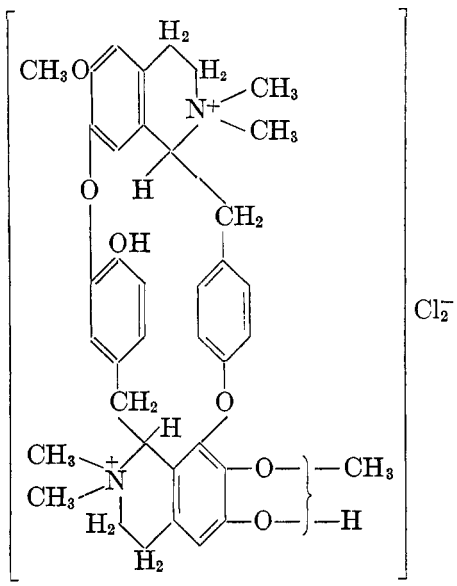
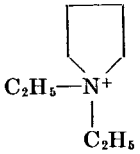
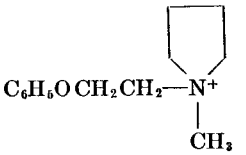
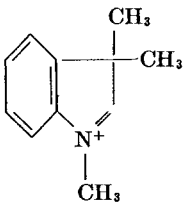


TABLE 13

Heterocyclic ammonium compounds

Miscellaneous compounds

QUATERNARY COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions			
							mg./kg.	*mg./kg.*	
N,*N*-Diethylpyrrolidinium			−						(104)
N-Methyl-*N*-(β-phenoxyethyl)pyrrolidinium			−	++	⊕		Mice I M 140 SC		(106, 107, 178)
N,3,3-Trimethylindolinium							Rabbits Cl 200–500 SC		(211)

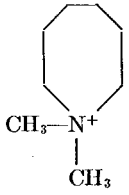
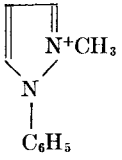
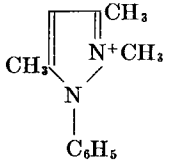
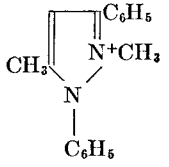
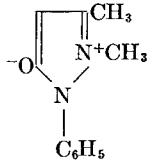
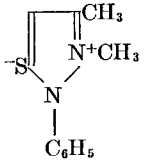
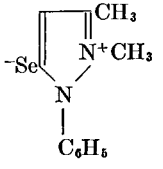
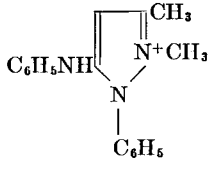
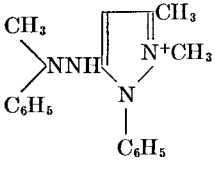
N,*N*-Dimethylhexahydroazepinium			−	+	+		Mice Br M 23 SC		(104)
1-Phenyl-2-methylpyrazolium		⊕							(211)
1-Phenyl-2,3,5-trimethylpyrazolium		−				Central paralysis			(207, 211)
1,3-Diphenyl-2,5-dimethylpyrazolium		+				Central paralysis			(208)
Antipyrine		−	−	−	−				(134)

TABLE 13—*Continued*

QUATERNARY COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions			
							mg./kg.	*mg./kg.*	
Thiopyrine						Central nervous poison			(208)
Selenopyrine						Central nervous poison			(134)
1-Phenyl-2,3-dimethyl-5-anilinopyrazolium						Stimulation followed by paralysis of central nervous system			(134)
1-Phenyl-2,3-dimethyl-5-(phenylmethylhydrazino)-pyrazolium		—				Central paralysis			(134)

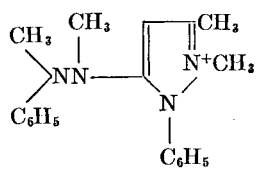
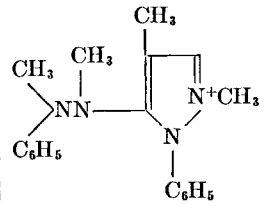
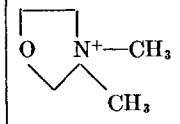
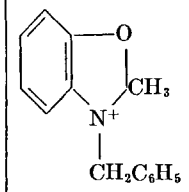
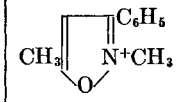
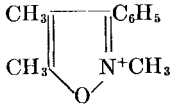
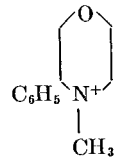
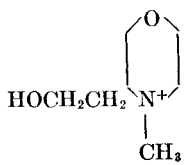
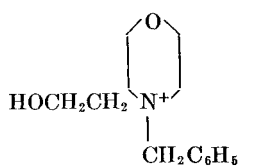
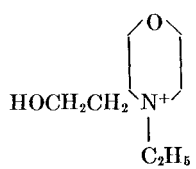
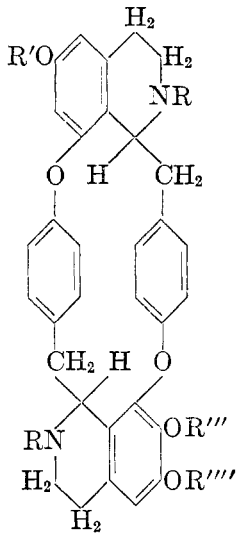
1-Phenyl-2,3-dimethyl-5-(phenyldimethylhydrazino)pyrazolium		⊕							(134)
1-Phenyl-2,4-dimethyl-5-(phenyldimethylhydrazino)pyrazolium		⊕							(211)
N,N-Dimethyloxazolium			−	−	−				(30)
2-Methyl-3-benzylbenzoxazolium								300	(24)
2,5-Dimethyl-3-phenylisoxazolium		+				Central paralysis			(208)

TABLE 13—*Concluded*

QUATERNARY COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions			
							mg./kg.	*mg./kg.*	
2,4,5-Trimethyl-3-phenylisoxazolium		⊕						Cl 200	(211)
N-Methyl-*N*-phenylmorpholinium								I 300	(24)
N-Methyl-*N*-(β-hydroxyethyl)morpholinium								I 300	(24)
N-Benzyl-*N*-(β-hydroxyethyl)morpholinium		+						I 300	(24)
N-Ethyl-*N*-(β-hydroxyethyl)morpholinium		+						I 300	(24)

King (128–133), Wintersteiner and Dutcher (223), and Dutcher (31) showed that various curare alkaloids have structures of the following two types:

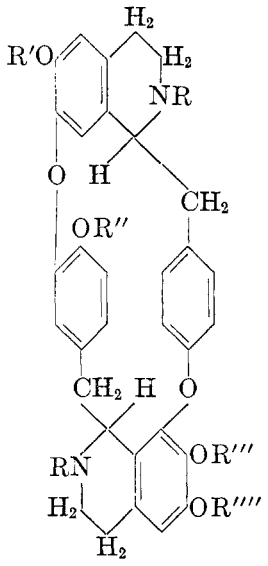


Type I

Protocuridine: R is CH_3; R′ or R′′′′ or both are CH_3; R″ or R′′′ or both are H (133)

Neoprotocuridine: R is CH_3; R′ and R′′′′ are H; R″ and R′′′ are CH_3 (132)

Isochondodendrine: R is CH_3; R′ or R′′′′ or both are CH_3; R″ or R′′′ or both are H (133)



Type II

l-Curine (*l*-bebeerine) and *d*-bebeerine: R is CH_3; R′ and R′′′′ are CH_3; R″ and R′′′ are H (131, 132)

d-Tubocurarine chloride: R is $(CH_3)_2$, making nitrogen quaternary; R′ is CH_3; R″ is H; one of R′′′ and R′′′′ is CH_3 and the other is H (129)

d-Chondocurine: R is CH_3; R′ is CH_3; R″ is H; R′′′ and R′′′′ are H and CH_3 in reverse of *d*-tubocurarine chloride (31)

d-Chondocurarine chloride: R is $(CH_3)_2$; R′, R″, R′′′, and R′′′′ are the same as in chondocurine (31)

Wieland and coworkers (217–220) have isolated a group of very active alkaloids from gourd or calabash curare, which they have named calabashcurarines and toxiferines. The different alkaloids are indicated by numerals placed after the names, such as calabashcurarine I, calabashcurarine II, etc. They were able to establish the empirical formulas for these alkaloids and to show that only one of the two nitrogens present is quaternary.

Karrer and coworkers (126, 127) recently published two papers describing preliminary work on structural determinations of these alkaloids. From titration data and preparation of an *N*-nitroso derivative they showed that the non-

TABLE 14

Alkaloids

Curare alkaloids

ALKALOID	EMPIRICAL FORMULA	PHARMACOLOGICAL ACTION		TOXIC DOSES			PARALYZING DOSES				SAFETY INDEX RABBITS LD 50 / HDrD 50	REFERENCES
		Curariform action	Other actions	Frogs	Mice	Rabbits	Frogs	Minutes to paralyze isolated nerve sartorius (Millimoles/liter 1 | 0.1)	Rabbit head-drop: Units/mg.	Rabbit head-drop: HDrD 50		
				mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*minutes*		*mg./kg.*		
Standard ampulled curare		++			50 4.4–6 SC 100 7 SC	50 1.3 IV	2.5 –5 EL			0.6	47	(13, 19, 25, 87)
Curarine	$C_{19}H_{26}N_2O$	++	Paralyzing nicotinic action	150	0.38–0.41 SC	0.34	Cl 0.2 –0.5 EL	3.7 | 7.0				(13, 86, 87, 117, 118, 210, 213, 216)
Eucararine	$C_{20}H_{23}N_2O$			0.13								(86)
Strychnolethaline	$C_{22}H_{27}NO_4$	–	Central paralysis									(22, 139)
Curine (Bebeerine)	$C_{36}H_{38}N_2O_6$	+	Central depressant									(86, 216)
l-Curine dimethiodide	$(C_{38}H_{44}H_2O_6)^{++}I_2^-$	+++							5			(31)
d-Curine dimethiodide	$(C_{38}H_{44}N_2O_6)^{++}I_2^-$			20			20					(86, 129)
O-Dimethyl-*l*-curine dimethiodide	$(C_{40}H_{48}N_2O_6)^{++}I_2^-$	+++							18.3			(31)

d-Isochondodendrine (*d*-Isobebeerine)	$C_{36}H_{38}N_2O_6$	−	Central depressant														(69)
d-Isochondodendrine dimethiodide	$(C_{38}H_{44}N_2O_6)^{++}I_2^-$	++													<0.4		(69, 223)
O-Dimethylisochondodendrine dimethiodide	$(C_{40}H_{48}N_2O_6)^{++}I_2^-$	++													1.6		(69, 223)
O-Diethylisochondodendrine dimethiodide	$(C_{42}H_{52}N_2O_6)^{++}I_2^-$	⊕															(69)
d-Chondocurine	$C_{36}H_{38}N_2O_6$	⊕															(223)
d-Chondocurarine chloride	$(C_{38}H_{44}N_2O_6)^{++}Cl_2^-$	+++													19.75		(31, 223)
Protocurine	$C_{20}H_{23}NO_3$	+															(131)
Protocurarine	$(C_{21}H_{26}NO_3)^+$	++		1.5			0.24										(13, 86, 131)
Neoprotocuridine	$C_{36}H_{38}N_2O_6$	+						HCl	45								(86, 131)
d-Tubocurarine chloride	$(C_{38}H_{44}N_2O_6)^{++}Cl_2^-$	+++		0.5			1 SC		0.5						6.5		(13, 86, 129, 216, 223)
O-Dimethyl-*d*-tubocurarine chloride	$(C_{40}H_{48}N_2O_6)^{++}Cl_2^-$	+++													60		(223)
O-Diethyl-*d*-tubocurarine iodide	$(C_{42}H_{52}N_2O_6)^{++}I_2^-$	++															(223)
O-Dibutyl-*d*-tubocurarine iodide	$(C_{46}H_{60}N_2O_6)^{++}I_2^-$	−															(223)
Calabashcurarine I	$C_{20}H_{21}N_2^+$	+++						HCl	0.12–0.16	EL							(86, 217, 219)
Bromocalabashcurarine I	$C_{20}H_{20}BrN_2^+$	+++						HCl	0.04	EL							(220)
Nitrocalabashcurarine I	$(C_{20}H_{20}N_3O_2)^+$	+++						HCl	0.008	EL							(220)

TABLE 14—*Concluded*

ALKALOID	EMPIRICAL FORMULA	PHARMACOLOGICAL ACTION		TOXIC DOSES			PARALYZING DOSES				SAFETY INDEX RABBITS LD 50 / HDrD 50	REFERENCES
		Curariform action	Other actions	Frogs	Mice	Rabbits	Frogs	Minutes to paralyze isolated nerve sartorius (Millimoles/liter 1 | 0.1)	Rabbit head-drop: Units/mg.	Rabbit head-drop: HDrD 50		
				mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*minutes*		*mg./kg.*		
Calabashcurarine III	$C_{20}H_{21}N_2^+$	−										(220)
Toxiferine I	$C_{20}H_{21}N_2^+$	+++					0.23–0.6 EL					(217, 218)
Calabashcurarine II	$C_{20}H_{23}N_2^+$	++					HCl 2–4 EL					(86, 217, 219)
Bromocalabashcurarine II	$C_{20}H_{22}BrN_2^+$	+++					0.6 EL					(220)
Nitrocalabashcurarine II	$(C_{20}H_{22}N_3O_2)^+$	++					8 EL					(220)
Calabashdihydrotoxiferine I	$C_{20}H_{23}N_2^+$	+++					0.06 EL					(217)
Calabashisodihydrotoxiferine I	$C_{20}H_{23}N_2^+$	+++					0.12–0.16 EL					(217)
Toxiferine II	$C_{20}H_{23}N_2^+$	+++					0.2 EL					(217)
Toxiferine IIa	$C_{20}H_{23}N_2^+$	+++					0.8–1.2 EL					(217)
Toxiferine IIb	$C_{20}H_{23}N_2^+$	++					4–6 EL					(217)
Calabashtoxiferine II	$C_{20}H_{23}N_2^+$	+++					0.4 EL					(217)

quaternary nitrogen was secondary and not basic. Heating the quaternary chloride gave them methyl chloride and a tertiary base, a result which indicated that there was a methyl group on the quaternary nitrogen. They interpreted titration data on the tertiary base as indicating that the tertiary nitrogen is in a reduced isoquinoline ring system and is common to two rings.

Freise (67) and Carneiro (22) have isolated alkaloids from various South American plants believed to be associated with curare: eucurarine from *Strychnos spp.*, macowbeine from *Macoubea guyanensis*, and lethaline and curalethaline from *Strychnos lethalis*. No information was found about their physiological action or chemical nature.

The active constituents of curare preparations are quaternary alkaloids; the tertiary alkaloids have a very weak or no paralyzing action, but become very effective on conversion to the quaternary bases. *d*-Tubocurarine chloride is the active ingredient of the curare preparations which have been most widely used and has a paralyzing action on frogs from five to ten times that of standard ampuled curare. Chondocurine, which is a tertiary alkaloid, has only a weak curariform action; however, when it is converted to the dimethochloride, it has an effectiveness about three times that of *d*-tubocurarine chloride. Wintersteiner and Dutcher (223) stated that this is the first instance in which a tertiary alkaloid of this type has been converted to a quaternary base which approximates or exceeds in potency the naturally occurring active constituents of curare.

When the two free hydroxyl groups of *d*-tubocurarine chloride are methylated, the resulting compound has a paralyzing action much greater than that of the original compound. Ethylation does not show this marked effect, and butylation abolishes the activity completely (223).

The effectiveness of some of the calabashcurarines is greater than that of *d*-tubocurarine. Calabashcurarine I paralyzes frogs in doses of 0.12–0.16 mg./kg. as compared to a dose of 0.5 mg./kg. for *d*-tubocurarine chloride. Calabashcurarine I can be readily converted to monobromo or mononitro derivatives which paralyze frogs in doses of 0.04 and 0.008 mg./kg., respectively. These are extremely low paralyzing doses.

The effective paralyzing action of the curare preparations, as was stated in the introduction, led to early clinical investigations for treatment of various muscle spasms and for relaxation of muscles during surgical operations (7, 17, 20, 23, 29, 70, 74, 77, 80, 147, 186), with promising results in some cases. The fact that the composition of various curare preparations was not uniform has caused unreproducible results in clinical applications. Three things that would be desirable in a drug of this type are (*1*) a powerful and prolonged paralyzing action, (*2*) a relatively large margin of safety, and (*3*) effectiveness when given orally. Intocostrin, which is a standardized, purified curare preparation, has the powerful and prolonged action desired but is ineffective orally and has a relatively small margin of safety.

Cohnberg (27) reported recently that intocostrin and *d*-tubocurarine chloride have an effect on the central nervous system. The action is one of stimulation of the central nervous system so that hyperexcitability and clonic convulsions

are produced. Signs of stimulation are more conspicuous in some animals than others. Central nervous depressants such as sodium amytal or cyclopropane decrease or prevent intocostrin convulsions, but artificial respiration has little effect in controlling convulsions. This central stimulation is another disadvantage of curare.

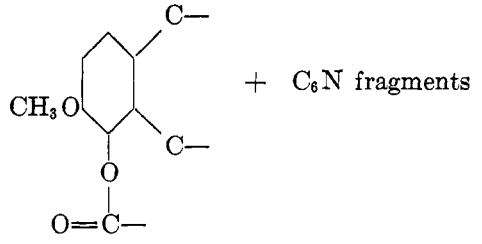
Clinically, standardized curare preparations in doses of 25 mg. given intravenously and 10–40 mg. given intramuscularly have an effect lasting 1 to 2 days, so that injections are given about three times a week. Patients still show some signs of curare paralysis up to 12 days after administration. The paralyzing effect occurs immediately after intravenous injection and in 20 to 30 min. after intramuscular injection (19).

2. Erythrina alkaloids (table 15)

The extracts of seeds of plants of the *Erythrina* species have been known for many years to exhibit a paralyzing action in animals. Only recently, however, has their paralyzing action been shown to be curare-like (213).

Folkers and Major (57) isolated an active alkaloid erythroidine from *Erythrina americana* Mill., and found that it consisted of at least two isomeric dextrorotatory alkaloids, which were designated as α- and β-erythroidine. Since the β-form is more readily obtained in pure state, it has been investigated chemically and physiologically to the greater extent. In further examination of various *Erythrina* species, some twelve different alkaloids, most of which show curare-like paralysis, have been isolated (40, 43–48, 54–57, 61, 63–65). A series of patents have been issued to Folkers and coworkers on procedures for isolating and purifying these various alkaloids (41–42, 49–53, 58–60, 62).

β-Erythroidine has been shown to have the empirical formula $C_{16}H_{19}NO_3$ and to contain a tertiary nitrogen common to two rings, a methoxyl group, two olefinic double bonds, and a lactone ring. It was shown to contain an indole nucleus by isolation of indole from a potassium hydroxide fusion. After demethylation, hydrolysis, methylation, and oxidation of β-erythroidine, 3-methoxyphthalic anhydride was obtained. After dehydrogenation, hydrolysis, methylation, and oxidation, hemipinic anhydride (3,4-dimethoxyphthalic anhydride) was obtained. These facts would indicate that a partial structure for β-erythroidine might be as follows:

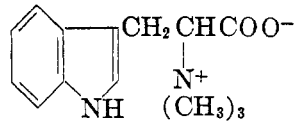


It is highly probable that the ring system of erythroidine differs from that of the other erythrina alkaloids (52, 213).

By catalytic hydrogenation β-erythroidine is converted into dihydro-β-ery-

throidine and two tetrahydro isomers, which are called α-tetrahydro-β-erythroidine and β-tetrahydro-β-erythroidine (52, 58, 213).

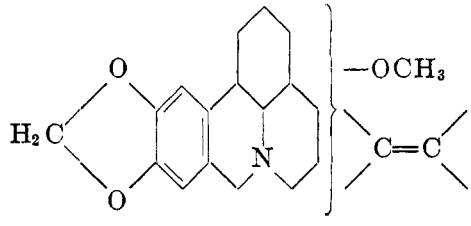
One of the compounds isolated from *Erythrina* extracts was called hypaphorine. It was shown to be the betaine of tryptophan (44).



Hypaphorine

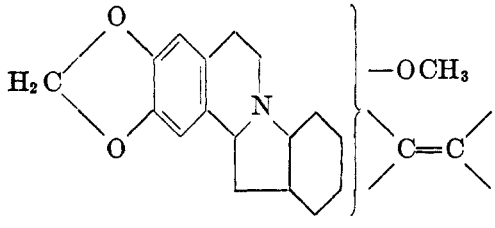
Hypaphorine does not possess curare activity, but the methyl ester does. This is in line with observations of other betaine-type compounds.

Of the other alkaloids isolated from *Erythrina* species, the first structural investigation was carried out on erythramine ($C_{18}H_{21}NO_3$), which was shown to have a tertiary nitrogen common to two rings, a methoxyl group, one olefinic double bond, and five fused rings, one of which was aromatic (45). Because of the close similarity of the ultravioletabsorption curves of dihydroerythramine and 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, the following structure was proposed (47):



It was pointed out, however, that one ring might be five-membered.

In later degradation studies, indole was isolated from potassium hydroxide fusions (55). Interpretation of the indole formation suggested that erythramine might be one of the following:



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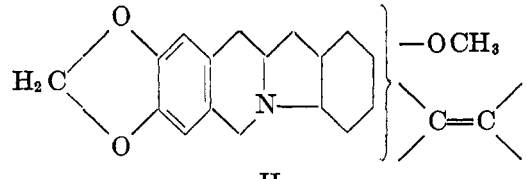


II

TABLE 15

Alkaloids

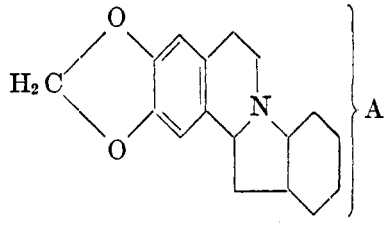
Erythrina alkaloids

ALKALOID	EMPIRICAL FORMULA	CURARIFORM ACTION	OTHER ACTIONS	TOXIC DOSES			PARALYZING DOSES		SAFETY INDEX FOR RABBITS LD 50 / HDrD 50	REFERENCES
				Mice	Rats	Miscellaneous	Frogs	Rabbit head-drop HDrD 50		
				mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*		
Hypaphorine... (Tryptophan betaine)	$C_{14}H_{17}N_2O_2$	−								(44)
Hypaphorine methyl ester.	$(C_{15}H_{20}N_2O_2)^+$	⊕		I 50 450			I 100 EL			(44)
β-Erythroidine.	$C_{16}H_{19}NO_3$	++	Muscarinic	HCl 50 45 SC HCl 100 50 SC HCl 50 120 OS HCl 100 140 OS Na^+ 50 230 SC	HCl 50 1260 SC HCl 50 510 OS HCl 50 39.9 IV	Rabbits HCl M 5 HCl 50 8.6 IV Dogs HCl M < 3.5 HCl 50 8.8 IV	HCl 3–8 EL Na^+ 75 EL	7.6	88%	(20, 24, 25, 26, 57, 231)
β-Erythroidine methiodide..	$(C_{17}H_{22}NO_3)^+I^-$	+					I 200 EL			(213)
Dihydro-β-erythroidine.	$C_{16}H_{21}NO_3$	++		HCl 50 9.3 SC HCl 50 7.5 OS	HCl 230 SC HCl 320 OS HCl 8.9 IV	Rabbits HBr M 1 HBr 50 2.1 IV Dogs HBr M 1 HBr 50 1.1 IV	HCl 0.6 EL Na^+ 0.5 EL	1.5	73%	(24, 25, 26, 52, 213)
α-Tetrahydro-β-erythroidine.....	$C_{16}H_{23}NO_3$	+					HBr 200 EL			(213)

β-Tetrahydro-β-erythroidine	$C_{16}H_{23}NO_3$	++		HBr	50	9.5	SC						HBr	0.5	EL			(213)
Erysopine	$C_{17}H_{19}NO_3$	++		HCl	50	15	SC						HCl	4	EL			(48, 56, 212)
				HCl	50	18	OS											
Tetrahydroerysopine	$C_{17}H_{23}NO_3$	+											HBr	40	EL			(212)
Erysonine	$C_{17}H_{19}NO_3$	+											HCl	100	EL			(48, 63)
Erythraline	$C_{18}H_{19}NO_3$	++		HBr	50	72	SC						HBr	10	EL			(212, 213)
				HBr	50	80	OS											
Erythraline methiodide	$(C_{19}H_{22}NO_3)^+I^-$	+											I	100	EL			(55, 212)
													I	50	EL			
Dihydroerythraline	$C_{18}H_{21}NO_3$	+		HBr		300							HBr	300	EL			(55)
Erythramine	$C_{18}H_{21}NO_3$	++											HBr	10	EL			(44, 46)
Erythramine methiodide	$(C_{19}H_{24}NO_3)^+I^-$	++											I	40	EL			(55, 219)
Dihydroerythramine	$C_{18}H_{23}NO_3$	+		HBr	50	104	SC						HBr	300	EL			(45, 212)
Erythratine	$C_{18}H_{21}NO_4$	+											HBr	75	EL			(46)
Erythratine methiodide	$(C_{19}H_{24}NO_4)^+I^-$												I	300	EL			(212)
Dihydroerythratine	$C_{18}H_{23}NO_4$												HBr	100	EL			(212)
Erysodine	$C_{18}H_{21}NO_3$			HCl	50	100	SC						HCl	10–15	EL			(48, 56, 212)
				HCl	50	155	OS											
Tetrahydrocrysodine	$C_{18}H_{25}NO_3$												HBr	> 300	EL			(219)
Erysovine	$C_{18}H_{21}NO_3$	++											HCl	3	EL			(48, 56, 212)
													Na^+	3	EL			
Erysocine	$C_{18}H_{21}NO_3$	++																(48)
Erysothiopine	$C_{19}H_{21}NO_7S$	++		Na^+	50	76	SC						Na^+	1	EL			(56, 212)
Erysothiovine	$C_{20}H_{23}NO_7S$	++											Na^+	1	EL			(56)

Structure I was favored over II because of biogenetical relationships, that is, I is a 1-benzyltetrahydroisoquinoline derivative, many of which occur naturally.

Erythramine, erythraline, and erythratine were shown to have carbon skeletons containing five fused rings, four of which were identical for all three of the alkaloids. The fifth ring differed in unsaturation and substitution (55). The following structures were proposed for these three alkaloids:



Erythramine: A = CH_3O— and one double bond
Erythraline: A = CH_3O— and two double bonds
Erythratine: A = CH_3O—, HO—, and one double bond

The alkaloids isolated from various *Erythrina* species are of two types: those occurring as free alkaloids, and those which must be liberated by hydrolysis. The stem *erythr-* has been used in naming the first group, while the stem *eryso-* has been used for the liberated alkaloids (48). Thus, erysodine, erysopine, and erysonine were isolated after hydrolysis of extracts with hydrochloric acid. Erysodine, erysopine, and erysovine have identical nuclear structures, as the complete methylation of the alkaloids produces identical compounds (54). By chromatographic purification, erysocine, which was thought to be a single alkaloid, was shown to be a mixture of erysodine and erysovine, possibly a molecular complex (61). Since these liberated alkaloids contain a phenolic hydroxyl group and the free alkaloids do not, it was believed that the liberated alkaloids were tied up through this group (56). No indication has been given as to whether these "eryso-" alkaloids have the same general ring system as erythramine, erythradine, and erythratine. The substituents found for these alkaloids are as follows: erysopine has one —OCH_3, one alcoholic —OH, and one phenolic —OH; erysodine has two —OCH_3 groups and one phenolic —OH; and erysovine has two —OCH_3 groups and one phenolic —OH (48).

Folkers, Koniuszy, and Shavel (56) isolated two sulfur-containing alkaloids, erysothiovine and erysothiopine, which were found to give erysovine and erysopine on acid hydrolysis. The other compound formed in the hydrolysis was found to be sulfoacetic acid. Since the sulfur-containing alkaloids were weakly basic, the sulfoacetic acid residue was believed to be attached as a sulfonic ester to the phenolic hydroxyl group.

The erythrina alkaloids are the first compounds containing a tertiary nitrogen that exhibit a pronounced curariform action. In all other cases, the conversion of a tertiary base which has a curare action to a quaternary compound greatly enhances the action. This is not the case with the erythrina alkaloids, as β-erythroidine is reduced in effectiveness by a factor of about twenty on con-

version to the methiodide. This is also true to a lesser extent with erythraline, erythramine, and erythratine.

β-Erythroidine paralyzes frogs in doses of 3–8 mg./kg. as compared to doses of 0.5 mg./kg. of *d*-tubocurarine chloride. Dihydro-β-erythroidine is five to ten times more effective than β-erythroidine itself. The β-tetrahydro-β-erythroidine also has an action greater than that of the unsaturated alkaloid, but the α-isomer is very much less effective.

Erysothiopine and erysothiovine are three to four times as effective as erysopine and erysovine, and differ from them only by the presence of a sulfoacetic residue on the ring. This indicates that the sulfoacetic group, attached as a sulfonic ester, enhances curare activity.

Because of the effectiveness of β-erythroidine and dihydro-β-erythroidine and particularly because they are effective orally, they have been investigated clinically with some success as possible curare substitutes (17, 19, 28, 33, 37, 70, 71, 72, 73, 77, 79, 81, 82, 148, 184, 185, 221, 222). The paralyzing action of β-erythroidine is not as intense or prolonged as that of standardized curare preparations, but it has a greater margin of safety. β-Erythroidine given intravenously has an effect lasting at most 24 hr., making it necessary to give injections daily. Burman (20) reported that it has a hypnotic effect when given orally that is not shown when given by injection.

3. Quaternary derivatives of cinchona alkaloids (table 16)

Quaternary salts of quinine and cinchonine have been prepared and are found to possess marked curare activity. The nitrogen of the quinuclidine ring is the most basic and is in the quaternary form in the monoalkylquininium salts. The diquaternary salts have only about half the curare activity of the monoalkylquininium salts.

In the series of monoalkylquinium salts, a maximum effectiveness is shown by the amyl derivative in paralysis of both frogs and rabbits. If the ratio of the dose in the rabbit head-drop test to the toxic dose for a rabbit is taken as an indication of margin of safety, the amylquininium salt is the safest to use. The amylquininium salt is about one-sixth as effective in frogs or rabbits as standardized curare; compared to β-erythroidine, it is less effective in frogs but more effective in rabbits. Using the above ratio as the margin of safety, the quininium salt is safer than either curare or β-erythroidine.

The quininium salts have an action of about one-third the duration of that of curare (25). Harvey (78) found that quinine itself has a weak curare action which is greatly increased by formation of the monoquaternary salt, the central and other effects being greatly reduced or abolished. He found that methylquininium chloride is effective orally, a dose of 150–200 mg. producing in cats a sequence of events similar to those caused by curare injected into humans.

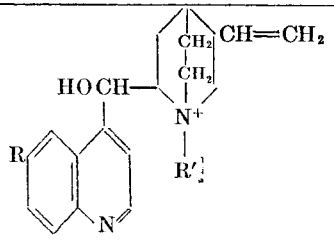
Methylcinchoninium sulfate has about the same action as the corresponding quininium salt; however, the amylcinchoninium salt is less effective than the corresponding quininium salt.

Quinine methochloride and ethochloride have been investigated clinically as

TABLE 16

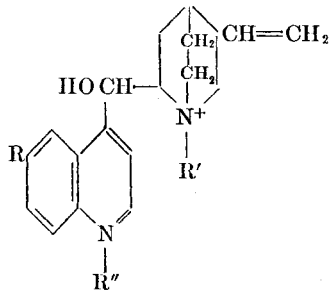
Alkaloids

Quaternary derivatives of cinchona alkaloids

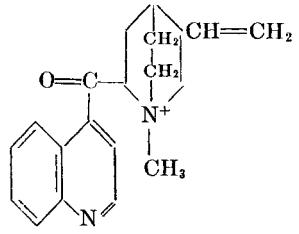


QUATERNARY ALKALOID	R	R′	PHARMACOLOGICAL ACTION: Curariform action	PHARMACOLOGICAL ACTION: Other actions	TOXIC DOSES: Rabbits	TOXIC DOSES: Dogs	TOXIC DOSES: Rats	PARALYZING DOSES: Frogs	PARALYZING DOSES: Rabbits	PARALYZING DOSES: Rabbit head-drop HDrD 50	SAFETY INDEX RABBITS LD 50 / HDrD 50	REFERENCES
					mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*		
N-Methylquininium	—OCH$_3$	—CH$_3$	++		Cl 50 7 IV	Cl M 15 IV Cl 50 16.3 IV	Cl M <5 IV Cl 50 5 IV	Cl 40 EL Br 50 I 60	Cl 7.5 Br 5	Cl 5	72	(24, 25, 26, 78, 211)
N-Ethylquininium	—OCH$_3$	—C$_2$H$_5$	++		Cl 50 7.6 IV	Cl 50 12.9 IV Cl M 8.5 IV	Cl 50 5.2 IV Cl M <5 IV	Cl 30 EL	Cl 5	Cl 3.3	44	(25, 26)
N-Propylquininium	—OCH$_3$	—C$_3$H$_7$	++		Br 50 3.4 IV Cl 50 2.9 IV	Br 50 5.9 IV Cl 50 4.3 IV	Br 50 4.2 IV Cl 50 6.9 IV	Br 50 EL Cl 70 EL		Br 3.2 Cl 2.4	Br 93 Cl 81	(25)
N-Isopropylquininium	—OCH$_3$	—C$_3$H$_7$(iso)	+		Cl 50 13.2 IV	Cl 50 9.3 IV	Cl 50 20.8 IV	Cl 200 EL		Cl 8.6	65	(25)
N-Butylquininium	—OCH$_3$	—C$_4$H$_9$	++		Cl 50 9.5 IV	Cl 50 5.8 IV	Cl 50 7.2 IV	Cl 50 EL		Cl 4.2	44	(25)
N-Amylquininium	—OCH$_3$	—C$_5$H$_{11}$	++		Br 50 10 IV	Br 50 15.6 IV	Br 50 4.5 IV	Br 30 EL		Br 3.9	39	(25)
N-Isoamylquinin-										Cl 4.2	41	(25)

N-Hexylquininium	—OCH_3	—C_6H_{13}	+		Br 50 10 IV	Br 50 20.8 IV	Br 50 9.3 IV	Br 80 EL		Br 4.1	41	(25)
N-Methylcinchoninium	—H	—CH_3	++					SO_4 26–40				(32, 87)
N-Amylcinchoninium	—H	—C_5H_{11}	++					I 50–80				(32, 87)
N-Carbomethoxymethylcinchoninium	—H	—CH_2COOCH_3	++					I 50				(87)



	R	R′	R″										
N,*N*-Dimethylquininium	—OCH_3	—CH_3	—CH_3	+					I 150				(24, 211)
N,*N*-Dimethylcinchoninium	—H	—CH_3	—CH_3	⊕									(211)
N-Methylcinchonicinium				⊕	Convulsant								(211)



curare substitutes (8, 79, 81). The results were described as "adequate" in the treatment of spastic paralysis and in shock therapy; the margin of safety, however, is uncertain.

4. Quaternary derivatives of pyridine alkaloids (table 17)

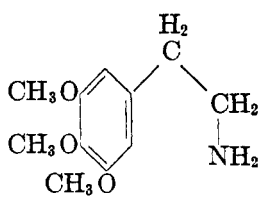
Various alkylconiinium, alkylconhydrinium, and alkylnicotinium salts possess curare actions. The most effective salt reported, ethylbenzylconiinium iodide, has a paralyzing action in frogs about one-fiftieth of that of curare or about the same as that of methylquininium iodide.

The presence of two different alkyl groups on the nitrogen of coniine and conhydrine gives rise to two stereoisomers, since the quaternary nitrogen and the adjacent carbon are now asymmetric. The higher-melting or β-isomer is always more effective than the lower-melting or α-isomer. In the benzylalkylconiinium series through the benzylbutyl derivative, the effectiveness decreases with increasing length of the alkyl group. However, the isoamylbenzyl derivative has an action comparable to that of the ethylbenzyl derivative. In general, the conhydrinium salts are less effective than the coniinium.

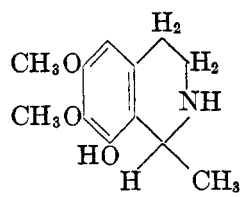
The nicotinium salts have only a weak curare action. *N*,*N'*-Diethylnicotinium iodide is about one-third as effective as *N*-ethylnicotinium iodide. This observation is in line with results in the quininium series, where conversion of both nitrogens to the quaternary form reduced the intensity of the curare action. It is interesting to note that a quaternary nitrogen in a saturated ring system caused marked curare action, which is reduced when a nitrogen in an unsaturated ring in the same molecule is converted to a quaternary nitrogen.

5. Isoquinoline alkaloids (table 18)

The simple isoquinolinium compounds were discussed on page 351. In that discussion, mention was made of the similarity in physiological action of the isoquinolines and β-arylethylamines. This is also borne out by the similarity of action of mescaline and the cactus alkaloid, anhalonidine.



Mescaline



Anhalonidine

Both have a depressant action on the central nervous system. Anhalonidine is reported to have a curariform action in large doses (86).

Laidlaw (138) reported that isoquinoline derivatives substituted in the 6-, 7-, and 8-positions with methoxy and methylenedioxy groups are convulsant when the nitrogen is tertiary, but devoid of this effect when the nitrogen is quaternary. Pyman (159) made these same observations with 6,7-dimethoxy derivatives; no mention was made in either case of peripheral paralyzing actions.

Macht (142) found that papaverine and related alkaloids tend to inhibit contractions and to relax the tonus of smooth muscle. The inhibitory or depressor effect seems to reside in the benzyl portion of the molecule. Papaverine, narcotine, hydrastine, and hydrastinine exhibit this depressor effect, but isoquinolines which do not have the 1-benzyl group do not have this relaxing effect and may cause contractions.

Pohl (157) reported that papaverinium salts have no curare action, but give a central paralysis. However, Takase (204) reported that papaverinium salts paralyze motor nerve endings. In this case, the nitrogen is present in an unsaturated ring.

Coclaurine, which has the nitrogen present in a saturated ring, has a weak curare action (156) although it is only a secondary base. No information on the quaternary salt could be found, but in view of previous results, it should have a marked curare action.

The alkylation of canadine leads to two stereoisomers, and again the higher-melting or β-isomer is more effective (ten times) than the α-isomer. β-*l*-Canadine methochloride paralyzes frogs in a dose of 2.5 mg./kg., an effect which is comparable to that of standardized curare. This compound is particularly interesting, since it contains a quaternary nitrogen which is common to two rings.

On the other hand, palmatine paralyzes the central nervous system and the respiratory center. This is also true of columbamine and jatrorrhizine, which are isomers and differ only from palmatine in that one methoxy group is replaced by hydroxyl (11, 86). These compounds also contain a quaternary nitrogen common to two rings, but one ring is unsaturated.

The quaternary salts of some of the morphine alkaloids are reported to have curare activity; the intensity of their action, however, is not great enough to make them of interest.

6. Quaternary derivatives of miscellaneous alkaloids (table 19)

Quaternary salts of some of the tropine alkaloids possess curare activity. Benzyl- and methyl-atropinium bromides paralyze frogs in doses almost equivalent to that of β-erythroidine. The only example found where there is any significant difference in the effectiveness of different salts of the same onium ion is that of benzylatropinium bromide and iodide. The bromide is reported to be sixty times as effective as the iodide, an observation that seems doubtful.

Quaternary salts of some of the indole alkaloids possess curare activity. Of the strychninium and brucinium salts reported, the benzyl derivatives are the most effective, benzylstrychninium bromide being comparable to β-erythroidine in paralyzing frogs.

Quaternary salts of two alkaloids of indefinite structure, dendrobine and veratrine, have been reported but have little curare activity.

E. α-GLYCEROL ETHERS (TABLE 20)

Most of the 143 compounds of this type which were investigated by Berger and Bradley (9) give paralysis only in doses which are lethal to some of the

TABLE 17

Alkaloids

Quaternary derivatives of pyridine alkaloids

CONIINIUM COMPOUND	 R	R′	CURARIFORM ACTION	TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
				mg./kg.	*mg./kg.*	
N,*N*-Dimethyl	$-CH_3$	$-CH_3$	+	Mice I 30–60	I 60	(117,211)
N-Benzyl-*N*-ethyl- (β-Isomer)	$-CH_2C_6H_5$	$-C_2H_5$	++		I 25	(87,211)
N-Benzyl-*N*-ethyl- (α-Isomer)	$-CH_2C_6H_5$	$-C_2H_5$	++		I 43	(87)
N-Benzyl-*N*-propyl- (β-Isomer)	$-CH_2C_6H_5$	$-C_3H_7$	+		I 64	(87,211)
N-Benzyl-*N*-propyl- (α-Isomer)	$-CH_2C_6H_5$	$-C_3H_7$	+		I 77	(87)
N-Benzyl-*N*-butyl- (β-Isomer)	$-CH_2C_6H_5$	$-C_4H_9$	+		I 107	(87,211)
N-Benzyl-*N*-butyl- (α-Isomer)	$-CH_2C_6H_5$	$-C_4H_9$	+		I 120	(87)
N-Benzyl-*N*-isoamyl- (β-Isomer)	$-CH_2C_6H_5$	$-C_5H_{11}$(iso)	++		I 33	(87,211)
N-Benzyl-*N*-isoamyl- (α-Isomer)	$-CH_2C_6H_5$	$-C_5H_{11}$(iso)	++		I 42	(87)
N-Allyl-*N*-ethyl- (β-Isomer)	$-CH_2CH{=}CH_2$	$-C_2H_5$	++		I 45	(87)
N-Allyl-*N*-ethyl- (α-Isomer)	$-CH_2CH{=}CH_2$	$-C_2H_5$	++		I 52	(87)

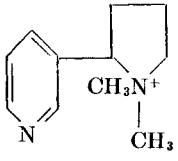
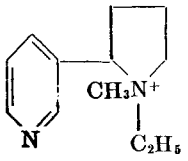
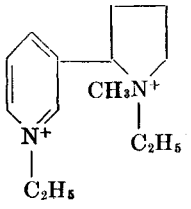
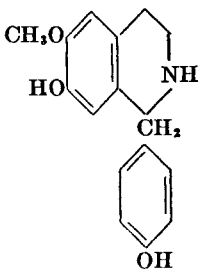
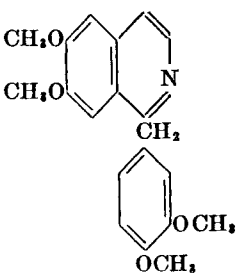
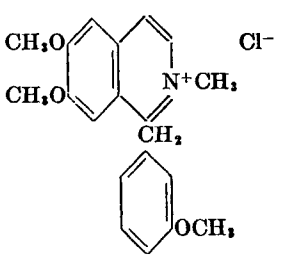
CONHYDRINIUM COMPOUND	$R-N^+(R')(CHOHCH_2CH_3)$ R	R′					
N-Benzyl-*N*-ethyl- (β-Isomer)	$-CH_2C_6H_5$	$-C_2H_5$	+		I	59	(87)
N-Benzyl-*N*-ethyl- (α-Isomer)	$-CH_2C_6H_5$	$-C_2H_5$	+		I	65	(87)
N-Benzyl-*N*-propyl- (β-Isomer)	$-CH_2C_6H_5$	$-C_3H_7$	+		I	67	(87)
N-Benzyl-*N*-propyl- (α-Isomer)	$-CH_2C_6H_5$	$-C_3H_7$	+		I	80	(87)
N-Benzyl-*N*-isoamyl- (β-Isomer)	$-CH_2C_6H_5$	$-C_5H_{11}$(iso)	+		I	72	(87)
N-Benzyl-*N*-isoamyl- (α-Isomer)	$-CH_2C_6H_5$	$-C_5H_{11}$(iso)	+		I	86	(87)
NICOTINIUM COMPOUND	STRUCTURE						
N-Methyl-			+	Rabbits I 800–1200 SC	I SO_4	180 1000–1670	(32,87,211)
N-Ethyl-			+		I SO_4	150–250 200–333	(32,87,211)
N,*N*′-Diethyl-			+		I	500	(87,211)

TABLE 18

Alkaloids

Isoquinoline alkaloids

ALKALOID	STRUCTURE OR TYPE	PHARMACOLOGICAL ACTION		TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Other actions			
				mg./kg.	*mg./kg.*	
Coclaurine		+				(129)
Papaverine		−	Central paralysis			(142, 157)
Papaverine methochloride		?	Central paralysis			(117, 157, 204)

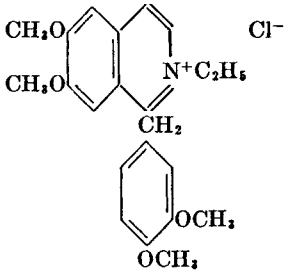
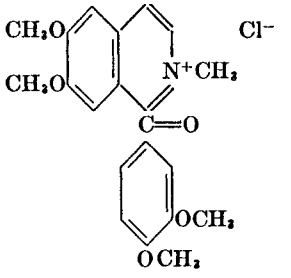
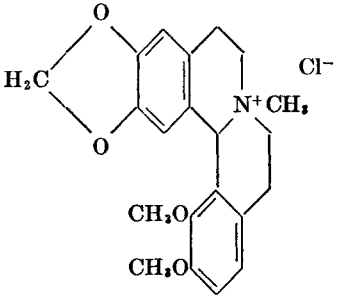
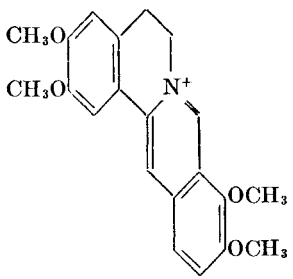
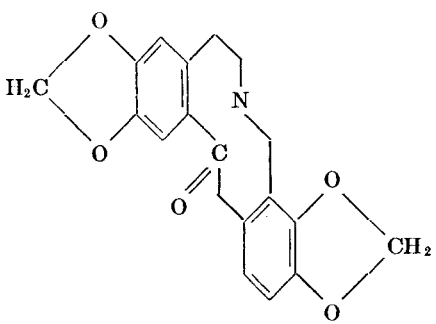
Papaverine ethochloride		?	Central paralysis			(157, 211)
Papaveraldine methochloride		?	Central paralysis			(117, 157)
α-*l*-Canadine methochloride		++			Cl 25	(137, 211)
β-*d*-Canadine methochloride		⊕				(137)
α-*l*-Canadine methochloride		++			Cl 2.5	(137, 211)
β-*d*-Canadine methochloride		⊕				(137)

TABLE 18—*Continued*

ALKALOID	STRUCTURE OR TYPE	PHARMACOLOGICAL ACTION		TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Other actions			
				mg./kg.	*mg./kg.*	
Palmatine			Central paralysis			(11, 86)
Protopine		⊕				(86)
Tetrandrine methiodide	$(C_{39}H_{45}N_2O_6)^+I^-$ (Bisbenzylisoquinoline type)		Muscarinic and nicotinic actions			(140)

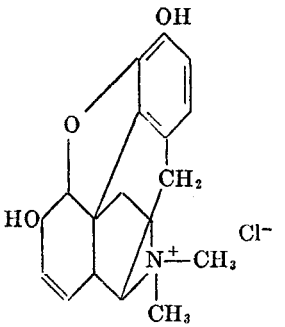
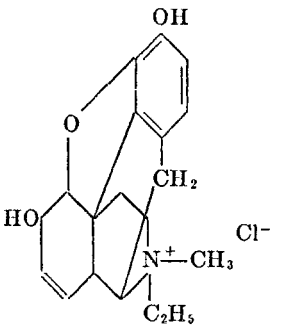
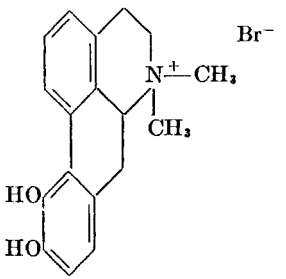
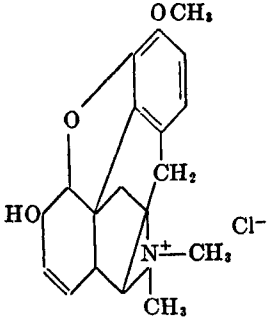
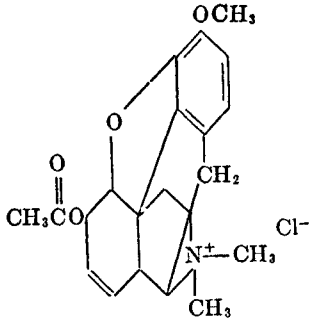
Morphine methochloride		⊕		Mice Cl 7.5–10 SC	Cl 167	(117, 122, 211)
Morphine ethochloride		⊕				(211)
Apomorphine methobromide		⊕			Br 100	(211)

TABLE 18—*Concluded*

ALKALOID	STRUCTURE OR TYPE	PHARMACOLOGICAL ACTION		TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Other actions			
				mg./kg.	*mg./kg.*	
Codeine methochloride		⊕		Mice Cl 17 SC Br 30 SC		(117, 122, 211)
Acetylcodeine methochloride				Mice Cl 9 SC		(211)

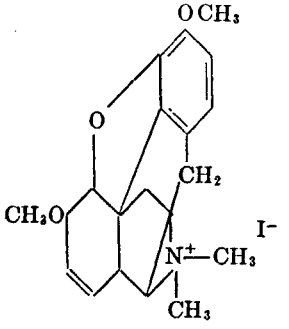
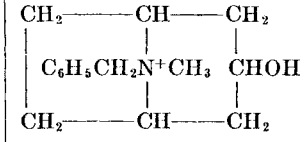
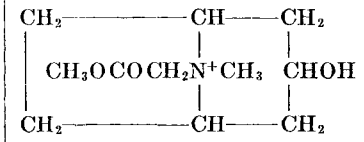
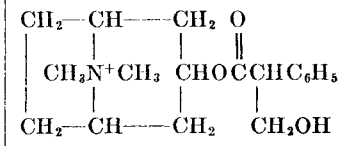
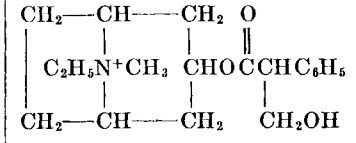
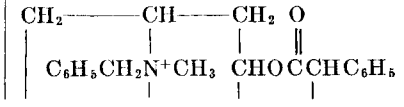
Thebaine methiodide		⊕		Rabbits I 200	SO_4 200	(117,122, 211)

TABLE 19

Alkaloids

Quaternary derivatives of miscellaneous alkaloids

QUATERNARY ALKALOID	STRUCTURE OR EMPIRICAL FORMULA	PHARMACOLOGICAL ACTION		TOXIC DOSE	PARALYZING DOSES			REFERENCES
		Curariform action	Other actions		Frogs	Minutes to paralyze isolated nerve sartorius		
						Millimoles/liter		
						1	10	
				mg./kg.	*mg./kg.*	*minutes*		
N-Benzyltropinium		+			I 1000			(87)
N-Carbomethoxymethyltropinium		+			I 1670			(87)
N-Methylatropinium		++		Rabbits I 180 SC SO_4 150 SC	Br 6–10			(32,87,117,211)
N-Ethylatropinium		+						(211)
N-Benzylatropinium		++			Br 10–16 I 600			(32,87,211)

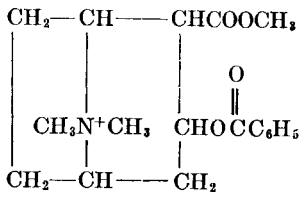
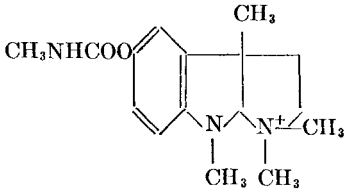
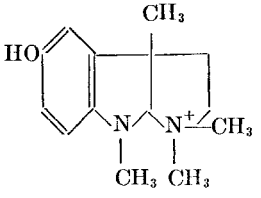
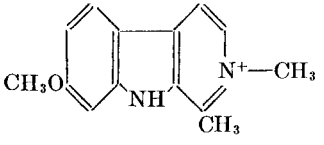
N-Methylcocainium.....		⊕						(211)
N-Methylphysostigminium..... (*N*-Methyleserinium)			Marked miotic; central depressant	Mice I 80 0.75–1 IV I 80 250–300 OS				(3,201,202)
N-Methyleserolinium.....		⊕						(201)
N-Methylharminium.....			Weak nicotinic					(140)
N-Methylisocalycanthinium.....	$(C_{13}H_{17}N_2)^+$ Indole type	+	Convulsant; respiratory paralysant		50–100			(86,151, 211)

TABLE 19—*Concluded*

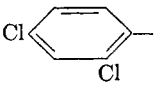
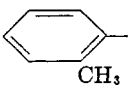
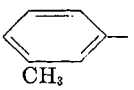
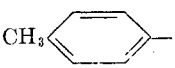
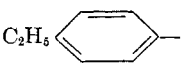
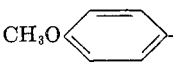
QUATERNARY ALKALOID	STRUCTURE OR EMPIRICAL FORMULA	PHARMACOLOGICAL ACTION		TOXIC DOSE	PARALYZING DOSES			REFERENCES
		Curariform action	Other actions		Frogs	Minutes to paralyze isolated nerve sartorius, Millimoles/liter		
						1	10	
				mg./kg.	*mg./kg.*	*minutes*		
N-Methylstrychninium	$(C_{22}H_{25}N_2O_2)^+$ Indole type	++		Mice Cl 5 SC	SO_4 8–13	I 3–3.6	6.3	(32,87,117,118,121,122,211)
N-Ethylstrychninium	$(C_{23}H_{27}N_2O_2)^+$	++			SO_4 25–40	I 5.5		(32,87,121,211)
N-(β-Hydroxyethyl)strychninium	$(C_{23}H_{27}N_2O_3)^+$	++			Cl 16–23			(211)
N-Benzylstrychninium	$(C_{28}H_{29}N_2O_2)^+$	++			Br 6–10			(32,87)
N-Carbomethoxymethylstrychninium	$(C_{24}H_{27}N_2O_4)^+$	++			I 25			(87)
N-Methylbrucinium	$(C_{24}H_{29}N_2O_4)^+$ Indole type	+			Br 60 I 25–70			(24,32,87,117,122)

N-Ethylbrucinium	$(C_{25}H_{31}N_2O_4)^+$	++			SO_4 25–40			(32,87,211)
N-Benzylbrucinium	$(C_{30}H_{33}N_2O_4)^+$	++			Br 15–25			(32,87,211)
N-Methyldendrobinium	$(C_{17}H_{28}NO_2)^+$ Undetermined		Weak muscarinic and nicotinic					(140)
N-Methylveratrinium	$(C_{33}H_{52}NO_9)^+$ Undetermined	+			>100			(211)
N-Amylveratrinium	$(C_{37}H_{60}NO_9)^+$ Undetermined	⊕	Convulsant					(211)

animals. They reported that they were unable to make any correlation between chemical structure and paralyzing activity. Some of the most effective and least toxic of the ethers are listed in table 20. α-(*o*-Tolyl)glycerol ether, which

TABLE 20

α-Glycerol ethers

$ROCH_2CH(OH)CH_2OH$		TOXIC DOSE MICE LD50 SC	PARALYZING DOSE MICE PD50 SC	THERAPEUTIC INDEX MICE LD50/PD50
Ether	R			
		mg./kg.	*mg./kg.*	
Butyl	C_4H_9—	2800 ± 150	1480 ± 54	1.89
Amyl	C_5H_{11}—	2000 ± 100	870 ± 49	2.30
Isoamyl	$(CH_3)_2CHCH_2CH_2$—	2100 ± 130	1240 ± 80	1.69
Hexyl	C_6H_{13}—	2230 ± 50	1060 ± 70	2.15
Phenyl	C_6H_5—	1680 ± 65	920 ± 98	1.82
p-Chlorophenyl		920 ± 86	420 ± 46	2.19
2,4-Dichlorophenyl		840 ± 44	540 ± 53	1.55
p-Bromophenyl		1160 ± 57	840 ± 44	1.38
o-Tolyl		1000 ± 56	325 ± 20	3.07
m-Tolyl		1470 ± 89	570 ± 51	2.58
p-Tolyl		1270 ± 61	530 ± 39	2.39
p-Ethylphenyl		1450 ± 67	820 ± 38	1.77
p-Methoxyphenyl		1610 ± 50	940 ± 74	1.72

has been given the name myanesin, is the most effective and has the greatest margin of safety.

The action of myanesin has been shown to be partially curare-like but mostly a depression of reflexes in the spinal cord (9, 10). That the action is somewhat

curare-like is shown by the action of high concentrations on nerve-muscle preparations and the weak antagonism of physostigmine and prostigmine toward it. Large and nearly lethal doses are necessary to produce curare-like actions. Physostigmine and prostigmine accelerate the recovery of animals from myanesin paralysis, but do not abolish the effect of lethal doses of the drug. This suggests that the curare-like action accounts for only part of the effect produced.

The depressant action on the central nervous system is shown by the antagonism to convulsions produced by central nervous system stimulants. Myanesin does not appear to act on the brain, as it does not effect consciousness; hence it is not an anesthetic. In minimum paralyzing doses, myanesin appears not to affect blood pressure or respiration. With sufficiently large doses, death is due to respiratory failure.

Table 21 gives the periods of induction and the duration of paralysis for various doses of myanesin given intraperitoneally in mice. As shown in this

TABLE 21

Duration of myanesin paralysis of mice

DOSE	PARALYZED	DIED	MEAN DURATION OF INDUCTION	MEAN DURATION OF PARALYSIS
mg./kg.	*per cent*	*per cent*		
150	0	0		
175	65	0	2 hr. ± 6 min.	12 hr. ± 1 hr. 42 min.
200	70	0	2 hr. ± 6 min.	13 hr. ± 4 hr. 18 min.
225	90	0	1 hr. 48 min. ± 12 min.	23 hr. ± 4 hr. 12 min.
300	100	0	1 hr. 36 min. ± 12 min.	25 hr. ± 2 hr. 48 min.
350	100	0	1 hr. 12 min. ± 6 min.	56 hr. ± 6 hr. 42 min.
500	100	5	48 min. ± 2 min.	61 hr. ± 12 hr. 42 min.
550	100	35		
600	100	45	48 min. ± 6 min.	120 hr. ± 4 hr. 18 min.
650	100	60		

table, the duration of paralysis is relatively short, but repeated doses show no cumulative effects, and tolerance is not built up.

Mallinson (145) investigated myanesin as a possible curare substitute in clinical use. He observed that the injection of 13 mg. per kilogram of body weight in a conscious patient caused no narcosis, although some is produced in animals. A dose of 27 mg./kg. in a patient produced some weakness of limbs and full abdominal relaxation without narcosis. The action of myanesin is enhanced by pentothal, so that full abdominal relaxation is easily obtained in man in doses of 10–15 mg./kg.

In therapeutically effective doses, there has been no evidence of toxic effects on any organ of the body. No effect has been noted on the tonus and contraction of intestinal muscle. Myanesin has well-marked advantages over curare in certain applications, having a much greater margin of safety and bringing about relaxation without distress. It is much more effective with barbiturate anesthesia than curare, apparently enhancing the action of the barbiturates.

V. Summary

1. The peripheral curare paralysis is commonly associated with onium compounds, of which quaternary ammonium salts are the most effective.

2. A few nitrogen compounds which are not quaternary possess weak curare action. In general, the conversion of such a compound to a quaternary compound greatly increases the curare action.

3. The erythrina alkaloids, which contain a tertiary nitrogen common to two rings, possess a pronounced curare action. Conversion of this nitrogen to a quaternary nitrogen abolishes the curare activity. This is the only class of compounds which loses curare activity on conversion of a tertiary nitrogen to a quaternary nitrogen.

4. The length of the alkyl groups on the quaternary nitrogen has an effect on the intensity of curare action. Tetraethylammonium salts are less effective than tetramethyl, but the effectiveness is again increased with the tetrapropyl and tetrabutyl derivatives. In the series of alkyltrimethylammonium salts, the maximum effectiveness is reached with the butyl and amyl derivatives; in the quininium derivatives, the maximum is reached with the amyl derivative; and the curare action increases from the methyl to the butyl derivative of quinolinium salts.

5. The replacing of one alkyl group of tetraalkylammonium salts with a chain containing a phenyl group (benzyl or β-phenylethyl) reduces the muscarinic and nicotinic actions. Benzyltriethyl- and β-phenylethyltriethylammonium salts possess pure and pronounced curare activity.

6. The replacing of an alkyl group on a quaternary nitrogen with an aryl group reduces the curare activity.

7. The benzyl group is frequently associated with paralyzing action. In pyridinium, strychninium, coniinium, and brucinium salts, the *N*-benzyl derivatives have the most intense curare actions; further, 1-benzylisoquinolines have relaxing actions, whereas the same isoquinolines without the benzyl group may even cause contractions. The curare alkaloids, which possess a very pronounced peripheral paralyzing action, are of the bisbenzylisoquinoline type.

8. The degree of unsaturation of a ring containing the nitrogen, quaternary or otherwise, influences the intensity of the curare action. Piperidinium, tetrahydroquinolinium, and tetrahydroisoquinolinium salts have more intense curare-like actions than the corresponding pyridinium, quinolinium, or isoquinolinium salts. The canadinium salts, which have a quaternary nitrogen common to two saturated rings, possess pronounced curare activity. However, quaternary salts of palmatine, columbamine, and jatrorrhizine, which differ from canadine in that one of the rings which contains the quaternary nitrogen is unsaturated, exhibit a central paralysis rather than a peripheral one. In general, all of the really effective curare-like compounds have the nitrogen present in a saturated ring.

9. When a compound containing one nitrogen in an unsaturated ring and one in a saturated ring has both nitrogens quaternary, the compound is less effective than when only the nitrogen in the saturated ring is quaternary. This is shown in nicotinium and quininium derivatives.

10. The methoxyl group enhances curare action. Methylation of the two free hydroxyl groups in *d*-tubocurarine chloride greatly enhances its paralyzing action, whereas ethylation decreases and butylation abolishes the action. A methoxyl group in the 6-position enhances the curare action in quinolinium salts. The quininium salts are somewhat more effective than cinchoninium salts, the former containing a methoxyl group in the 6-position. β-Erythroidine and other erythrina alkaloids contain methoxyl groups.

11. When the conversion of a compound to a quaternary nitrogen compound produces two isomers, the higher-melting or β-isomer is invariably more effective than the lower-melting or α-isomer. This is true in numerous quaternary derivatives of coniine, conhydrine, and canadine, and in the tetrahydroerythroidine derivatives.

12. The sulfoacetic acid group enhances curare activity in some of the erythrina alkaloids.

13. The replacing of oxygen in choline with sulfur greatly enhances the curare action and abolishes the stimulating nicotinic action.

14. Certain α-glycerol ethers exhibit paralyzing actions. Of those tested, α-(*o*-tolyl)glycerol ether has the strongest action. These compounds do not possess a true curare-like action, but are the only compounds which do not contain nitrogen that have been reported to have possible therapeutic value as paralyzing agents.

15. The calabashcurarines, of unknown structure, are the most effective compounds reported. Nitration and bromination in some cases markedly increase their activity.

16. Curare alkaloids, erythrina alkaloids, quininium salts, and prostigmine have been used clinically for producing relaxation of muscles in various types of neuromuscular disorders involving spasm or contraction.

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VI. References

(1) Ackermann, D.: Münch. med. Wochschr. **68,** 12 (1921).
(2) Addinall, C. R.: J. Am. Pharm. Assoc. **26,** 156 (1937).
(3) Aeschlimann, J. A., and Reinert, M.: J. Pharmacol. **43,** 413 (1931).
(4) Alles, G. A.: Univ. Calif. (Berkeley) Pubs. Pharmacol. **2,** 161 (1944).
(5) Alles, G. A., and Knoefel, P. K.: Univ. Calif. (Berkeley) Pubs. Pharmacol. **1,** 187 (1939).
(6) Barger, G., and Dale, H. H.: J. Physiol. **41,** 19 (1910).
(7) Bennett, A. E.: J. Am. Med. Assoc. **114,** 322 (1940).
(8) Bennett, A. E.: Am. J. Psychiat. **97,** 1040 (1941).
(9) Berger, F. M., and Bradley, W.: Brit. J. Pharmacol. **1,** 265 (1946).
(10) Berger, F. M., and Bradley, W.: Lancet **252,** 97 (1947).
(11) Biberfield, J.: Z. exptl. Path. Pharm. **7,** 569 (1910).
(12) Boehm, R.: Arch. Pharm. **235,** 660 (1897).
(13) Boehm, R.: A. Heffter's *Handbuch der experimentellen Pharmakologie* **2.1,** 179 (1920).
(14) Brabant, V.: Arch. intern. pharmacodynamie **25,** 295 (1921).
(15) Brown, A. C., and Fraser, T.: Trans. Roy. Soc. Edinburgh **25,** 151 (1868–9).

(16) BROWN, A. C., AND FRASER, T.: Trans. Roy. Soc. Edinburgh **25,** 693 (1868–9).
(17) BROWN, J. R., ESSEX, H. E., AND MOERSCH, F. P.: Proc. Staff Meetings Mayo Clinic **16,** 264 (1941).
(18) BUCHNER, E.: Jahresber. **1861,** 767.
(19) BURMAN, M. S.: Arch. Neurol. Psychiat. **41,** 307 (1939).
(20) BURMAN, M. S.: J. Pharmacol. **69,** 143 (1940).
(21) BURN, J. H., AND DALE, H. H.: J. Pharmacol. **6,** 417 (1915).
(21a) CANNON, W. B., AND ROSENBLUETH, A.: Am. J. Physiol. **119,** 221 (1937).
(22) CARNEIRO, P. DE B.: Compt. rend. **206,** 1202 (1938).
(23) CHASE, H. F., AND LEHMAN, A. J.: Federation Proc. **1,** 157 (1942).
(24) CHASE, H. F., AND LEHMAN, A. J.: J. Pharmacol. **75,** 265 (1942).
(25) CHASE, H. F., LEHMAN, A. J., AND RICHARD, E. E.: J. Pharmacol. **82,** 266 (1944).
(26) CHASE, H. F., LEHMAN, A. J., AND YONKMAN, F. F.: J. Pharmacol. **75,** 270 (1942).
(27) COHNBERG, R. E.: J. Lab. Clin. Med. **31,** 866 (1946).
(28) COTTINGTON, F.: Am. J. Psychiat. **98,** 397 (1941).
(29) CULLEN, S. C., AND QUINN, C. S.: Surgery **14,** 256 (1943).
(30) DALE, H. H.: J. Pharmacol. **6,** 147 (1914).
(31) DUTCHER, J. D.: J. Am. Chem. Soc. **68,** 419 (1946).
(32) DYSON, G. M.: *The Chemistry of Chemotherapy,* pp. 105–20. Ernest Benn Ltd., London (1928).
(33) EISENSTEIN, V. W., AND TARLAU, M.: Arch. Neurol. Psychiat. **45,** 649 (1941).
(34) ERLENMEYER, H., AND LOBECK, H.: Helv. Chim. Acta **20,** 142 (1937).
(35) EWINS, A. J.: Biochem. J. **8,** 266 (1914).
(36) FASSETT, D. W., AND HJORT, A. M.: J. Pharmacol. **63,** 253 (1938).
(37) FELLOWS, E. J., AND LIVINGSTON, A. E.: J. Pharmacol. **68,** 231 (1940).
(38) FELLOWS, E. J., AND LIVINGSTON, A. E.: J. Pharmacol. **71,** 187 (1941).
(39) FELLOWS, E. J., AND LIVINGSTON, A. E.: J. Pharmacol. **74,** 65 (1942).
(40) FOLKERS, K.: J. Am. Pharm. Assoc. **27,** 689 (1938).
(41) FOLKERS, K.: U. S. patent 2,226,528 (1940).
(42) FOLKERS, K.: U. S. patent 2,391,014 (1945).
(43) FOLKERS, K., AND DIETZ, E. M.: J. Am. Pharm. Assoc. **35,** 48 (1946).
(44) FOLKERS, K., AND KONIUSZY, F.: J. Am. Chem. Soc. **61,** 1232 (1939).
(45) FOLKERS, K., AND KONIUSZY, F.: J. Am. Chem. Soc. **61,** 3053 (1939).
(46) FOLKERS, K., AND KONIUSZY, F.: J. Am. Chem. Soc. **62,** 436 (1940).
(47) FOLKERS, K., AND KONIUSZY, F.: J. Am. Chem. Soc. **62,** 1673 (1940).
(48) FOLKERS, K., AND KONIUSZY, F.: J. Am. Chem. Soc. **62,** 1677 (1940).
(49) FOLKERS, K., AND KONIUSZY, F.: U. S. patent 2,252,709 (1941).
(50) FOLKERS, K., AND KONIUSZY, F.: U. S. patent 2,273,031 (1942).
(51) FOLKERS, K., AND KONIUSZY, F.: U. S. patent 2,280,816 (1942).
(52) FOLKERS, K., AND KONIUSZY, F.: U. S. patent 2,370,651 (1945).
(53) FOLKERS, K., AND KONIUSZY, F.: U. S. patent 2,391,013 (1945).
(54) FOLKERS, K., KONIUSZY, F., AND SHAVEL, J.: Abstract of paper presented at the 102nd Meeting of the American Chemical Society, Atlantic City, New Jersey, September, 1941.
(55) FOLKERS, K., KONIUSZY, F., AND SHAVEL, J.: J. Am. Chem. Soc. **64,** 2146 (1942).
(56) FOLKERS, K., KONIUSZY, F., AND SHAVEL, J.: J. Am. Chem. Soc. **66,** 1083 (1944).
(57) FOLKERS, K., AND MAJOR, R. T.: J. Am. Chem. Soc. **59,** 1580 (1937).
(58) FOLKERS, K., AND MAJOR, R. T.: U. S. patent 2,280,837 (1942).
(59) FOLKERS, K., AND MAJOR, R. T.: U. S. patent 2,373,952 (1945).
(60) FOLKERS, K., AND MAJOR, R. T.: U. S. patent 2,385,266 (1945).
(61) FOLKERS, K., AND SHAVEL, J.: J. Am. Chem. Soc. **64,** 1892 (1942).
(62) FOLKERS, K., AND SHAVEL, J.: U. S. patent 2,391,015 (1945).
(63) FOLKERS, K., SHAVEL, J., AND KONIUSZY, F.: J. Am. Chem. Soc. **63,** 1544 (1941).
(64) FOLKERS, K., AND UNNA, K.: J. Am. Pharm. Assoc. **27,** 693 (1938).

(65) FOLKERS, K., AND UNNA, K.: J. Am. Pharm. Assoc. **28,** 1019 (1939).
(66) FOURNEAU, F., AND BOVET, D.: Compt. rend. soc. biol. **138,** 469 (1944).
(67) FREISE, F. W.: Pharm. Ztg. **81,** 818 (1936).
(68) FÜHNER, H.: A. Heffter's *Handbuch der experimentellen Pharmakologie* **1,** 640–83 (1923).
(69) GABBE, E.: Arch. intern. pharmacodynamie **24,** 327 (1914–18).
(70) GIRDEN, E.: J. Exptl. Psychol. **31,** 219 (1942).
(71) GIRDEN, E.: J. Exptl. Psychol. **31,** 232 (1942).
(72) GIRDEN, E.: J. Exptl. Psychol. **31,** 322 (1942).
(73) GIRDEN, E.: Proc. Soc. Exptl. Biol. Med. **53,** 163 (1943).
(74) GOODMAN, L., AND GILMAN, A.: *The Pharmaceutical Basis of Therapeutics,* pp. 350–87. The Macmillan Company, New York (1941).
(75) GORDONOFF, T.: Biochem. Z. **160,** 451 (1925).
(76) GRIFFITH, H. R., AND JOHNSON, G. E.: Anesthesiology **3,** 418 (1942).
(77) HARRIS, M. M., AND HARRIS, R. S.: Proc. Soc. Exptl. Biol. Med. **46,** 619 (1941).
(78) HARVEY, A. M.: Bull. Johns Hopkins Hosp. **66,** 52 (1940).
(79) HARVEY, A. M., LANDIS, E. E., AND MASLAND, R. L.: Trans. Am. Neurol. Assoc. **66,** 154 (1940).
(80) HARVEY, A. M., AND MASLAND, R. L.: J. Pharmacol. **73,** 304 (1941).
(81) HARVEY, A. M., MASLAND, R. L., AND WIGTON, R. S.: Am. J. Med. Sci. **199,** 878 (1940).
(82) HARVEY, R. W.: Clinics **1,** 490 (1942).
(83) HAZARD, R., AND CARTEGGIANI, E.: Compt. rend. **216,** 779 (1943).
(84) HAZARD, R., AND SEVIN, A.: Compt. rend. **217,** 52 (1943).
(85) HECHT, G.: Klin. Wochschr. **14,** 957 (1935).
(86) HENRY, T. A.: *The Plant Alkaloids,* 3rd edition, pp. 372–83. P. Blakiston's Son and Co., Inc., Philadelphia (1939).
(87) HILDEBRANDT, H.: Arch. exptl. Path. Pharmakol. **53,** 76 (1905).
(88) HILDEBRANDT, H.: Beitr. Chem. Physiol. Path. **9,** 470 (1907).
(89) HJORT, A. M., DE BEER, E. J., BUCK, J. S., AND RANDALL, L. O.: J. Pharmacol. **76,** 64 (1942).
(90) HJORT, A. M., DE BEER, E. J., BUCK, J. S., AND RANDALL, L. O.: J. Pharmacol. **76,** 71 (1942).
(91) HJORT, A. M., DE BEER, E. J., BUCK, J. S., AND RANDALL, L. O.: J. Pharmacol. **76,** 252 (1942).
(92) HJORT, A. M., DE BEER, E. J., BUCK, J. S., AND RANDALL, L. O.: J. Pharmacol. **76,** 263 (1942).
(93) HJORT, A. M., DE BEER, E. J., AND FASSETT, D. W.: J. Pharmacol. **62,** 165 (1938).
(94) HJORT, A. M., DE BEER, E. J., AND FASSETT, D. W.: J. Pharmacol. **63,** 432 (1938).
(95) HJORT, A. M., DE BEER, E. J., AND FASSETT, D. W.: J. Pharmacol. **68,** 69 (1940).
(96) HJORT, A. M., DE BEER, E. J., AND FASSETT, D. W.: J. Pharmacol. **68,** 73 (1940).
(97) HJORT, A. M., DE BEER, E. J., AND RANDALL, L. O.: J. Pharmacol. **76,** 258 (1942).
(98) HOPPE-SEYLER, G.: Arch. exptl. Path. Pharmakol. **24,** 241 (1887–8).
(99) HUNT, R.: Arch. intern. pharmacodynamie **12,** 447 (1904).
(100) HUNT, R.: J. Pharmacol. **6,** 477 (1914).
(101) HUNT, R.: J. Pharmacol. **28,** 267 (1926).
(102) HUNT, R., AND RENSHAW, R. R.: J. Pharmacol. **25,** 315 (1925).
(103) HUNT, R., AND RENSHAW, R. R.: J. Pharmacol. **29,** 17 (1926).
(104) HUNT, R., AND RENSHAW, R. R.: J. Pharmacol. **35,** 75 (1929).
(105) HUNT, R., AND RENSHAW, R. R.: J. Pharmacol. **35,** 99 (1929).
(106) HUNT, R., AND RENSHAW, R. R.: J. Pharmacol. **37,** 177 (1929).
(107) HUNT, R., AND RENSHAW, R. R.: J. Pharmacol. **37,** 193 (1929).
(108) HUNT, R., AND RENSHAW, R. R.: J. Pharmacol. **37,** 309 (1929).
(109) HUNT, R., AND RENSHAW, R. R.: J. Pharmacol. **44,** 63 (1932).
(110) HUNT, R., AND RENSHAW, R. R.: J. Pharmacol. **44,** 151 (1932).
(111) HUNT, R., AND RENSHAW, R. R.: J. Pharmacol. **48,** 51 (1933).

(112) HUNT, R., AND RENSHAW, R. R.: J. Pharmacol. **48**, 105 (1933).
(113) HUNT, R., AND RENSHAW, R. R.: J. Pharmacol. **51**, 237 (1934).
(114) HUNT, R., AND RENSHAW, R. R.: J. Pharmacol. **58**, 140 (1936).
(115) HUNT, R., AND TAVEAU, R. DE M.: Brit. Med. J., **2**, 1788 (1906).
(116) HUNT, R., AND TAVEAU, R. DE M.: J. Pharmacol. **1**, 303 (1909).
(117) ING, H. R.: Physiol. Revs. **16**, 527 (1936).
(118) ING, H. R., AND COWAN, S. L.: J. Physiol. **82**, 432 (1934).
(119) ING, H. R., DAWES, G. S., AND WAZDA, I.: J. Pharmacol. **85**, 85 (1945).
(120) ING, H. R., AND WRIGHT, W. M.: Proc. Roy. Soc. (London) **B109**, 337 (1931).
(121) ING, H. R., AND WRIGHT, W. M.: Proc. Roy. Soc. (London) **B114**, 48 (1933).
(122) IODLBAUER, A.: Arch. intern. pharmacodynamie **7**, 183 (1900).
(123) JORDAN, S. N.: Arch. exptl. Path. Pharmakol. **8**, 15 (1878).
(124) KABAT, H., AND KNAPP, M. E.: J. Am. Med. Assoc. **122**, 989 (1943).
(125) KARRER, P.: Helv. Chim. Acta **5**, 469 (1922).
(126) KARRER, P., AND MATTER, E.: Helv. Chim. Acta **29**, 1871 (1946).
(127) KARRER, P., AND SCHMID, H.: Helv. Chim. Acta **29**, 1853 (1946).
(128) KING, H.: J. Chem. Soc. **121**, 1743 (1922).
(129) KING, H.: J. Chem. Soc. **1935**, 1381.
(130) KING, H.: J. Chem. Soc. **1936**, 1276.
(131) KING, H.: J. Chem. Soc. **1937**, 1472.
(132) KING, H.: J. Chem. Soc. **1939**, 1157.
(133) KING, H.: J. Chem. Soc. **1940**, 737.
(134) KOBERT, K.: Z. exptl. Path. Therap. **9**, 614 (1911).
(135) KREITMAR, H.: Arch. exptl. Path. Pharmakol. **164**, 346 (1932).
(136) KÜLZ, F.: Arch. ges. Physiol. **195**, 623 (1922).
(137) LAIDLAW, P. P.: J. Pharmacol. **4**, 461 (1913).
(138) LAIDLAW, P. P.: Biochem. J. **5**, 243 (1911).
(139) LAPICQUE, L.: Compt. rend. **208**, 857 (1939).
(140) LEE, H. M., VAN ARENDANK, A. M., AND CHEN, K. K.: J. Pharmacol. **56**, (1936).
(141) LESTRANGE, Y. DE, AND LEVY, J.: Bull. sci. pharmacol. **36**, 353 (1929).
(142) MACHT, D. I.: J. Pharmacol. **11**, 389 (1918).
(143) MACOWSKI, E., AND RAMONTEANU, E.: J. prakt. Chem. **138**, 92 (1933).
(144) MAGIDSON, O., AND MENSCHIKOFF, G.: Ber. **59**, 1209 (1926).
(145) MALLINSON, F. B.: Lancet **152**, 98 (1947).
(146) MARSHALL, C. R.: Trans. Roy. Soc. Edinburgh **50**, 17, 379, 481 (1915).
(147) MAUTNER, H., AND LUISADA, A.: J. Pharmacol. **72**, 386 (1941).
(148) MILLER, W. R.: Arch. Neurol. Psychiat. **47**, 508 (1942).
(149) MOLITOR, H.: J. Pharmacol. **58**, 337 (1936).
(150) MYERSON, A., RINKEL, M., LAMAN, J., AND DAMESHEK, W.: J. Pharmacol. **68**, 476 (1940).
(151) MCGUIGAN, H., AND HESS, C. L. VON: J. Pharmacol. **3**, 441 (1911).
(152) NELSON, J. W., AND LYSTER, S. C.: J. Am. Pharm. Assoc. **35**, 89 (1946).
(153) OETTINGEN, W. F. VON, AND EVETETH, D. V.: J. Pharmacol. **44**, 465 (1932).
(154) OETTINGEN, W. F. VON, AND BOWMAN, R. O.: J. Pharmacol. **48**, 333 (1933).
(155) PETERSON, C. G., AND PETERSON, D. R.: J. Pharmacol. **84**, 236 (1945).
(156) PLUGGE, P. C.: Arch. exptl. Path. Pharmakol. **32**, 266 (1893).
(157) POHL, J.: Arch. intern. pharmacodynamie **13**, 479 (1904).
(158) PREYER, R.: Compt. rend. **60**, 1346 (1865).
(159) PYMAN, F. L.: J. Chem. Soc. **95**, 1738 (1909).
(160) RAHMAN, C., AND ZIETAN, K.: Ber. **71**, 296 (1938).
(161) RAVENTOS, J.: Quart. J. Exptl. Pharmacol. **26**, 361 (1937).
(162) RAVENTOS, J.: Quart. J. Exptl. Pharmacol. **27**, 89 (1937).
(163) RENSHAW, R. R.: Science **62**, 384 (1925).
(164) RENSHAW, R. R., AND ARMSTRONG, W. D.: J. Biol. Chem. **103**, 187 (1933).

(165) RENSHAW, R. R., AND BACON, N.: J. Am. Chem. Soc. **48**, 1726 (1926).
(166) RENSHAW, R. R., BACON, N., AND ROBLYER, J. H.: J. Am. Chem. Soc. **48**, 517 (1926).
(167) RENSHAW, R. R., AND BENCOWITZ, I.: J. Am. Chem. Soc. **47**, 1904 (1925).
(168) RENSHAW, R. R., AND BENCOWITZ, I.: J. Am. Chem. Soc. **48**, 2146 (1926).
(169) RENSHAW, R. R., AND BISHOP, R. A.: J. Am. Chem. Soc. **60**, 946 (1938).
(170) RENSHAW, R. R., AND CASS, W. E.: J. Am. Chem. Soc. **61**, 1195 (1939).
(171) RENSHAW, R. R., AND CONN, R. C.: J. Am. Chem. Soc. **59**, 297 (1937).
(172) RENSHAW, R. R., DREISBACK, P. F., ZIFF, M., AND GREEN, D.: J. Am. Chem. Soc. **60**, 1765 (1938).
(173) RENSHAW, R. R., GREEN, D., AND ZIFF, M.: J. Pharmacol. **62**, 430 (1938).
(174) RENSHAW, R. R., AND HOPKINS, C. Y.: J. Am. Chem. Soc. **51**, 953 (1929).
(175) RENSHAW, R. R., AND HOPKINS, C. Y.: J. Am. Chem. Soc. **55**, 1524 (1933).
(176) RENSHAW, R. R., AND HOTCHKISS, H. T., JR.: J. Am. Chem. Soc. **48**, 2698 (1926).
(177) RENSHAW, R. R., AND HOTCHKISS, H. T., JR.: J. Biol. Chem. **103**, 183 (1933).
(178) RENSHAW, R. R., AND MCGREAL, M. E.: J. Am. Chem. Soc. **54**, 1471 (1932).
(179) RENSHAW, R. R., AND SEARLE, D. S.: J. Am. Chem. Soc. **55**, 4951 (1933).
(180) RENSHAW, R. R., AND SEARLE, D. S.: J. Am. Chem. Soc. **59**, 2056 (1937).
(181) RENSHAW, R. R., AND SKAND, E. W.: J. Am. Chem. Soc. **54**, 1474 (1932).
(182) RENSHAW, R. R., AND WARE, J. C.: J. Am. Chem. Soc. **47**, 2989 (1925).
(183) RENSHAW, R. R., ZIFF, M., BRODIE, B., AND KORNBLUM, N.: J. Am. Chem. Soc. **61**, 638 (1939).
(184) ROSEN, S. R., AND BORENSTEIN, M. V.: Psychiat. Quart. **15**, 163 (1941).
(185) ROSEN, S. R., CARVERON, D. E., AND ZIEGLER, J. B.: Psychiat. Quart. **14**, 477 (1940).
(186) ROSEN, S. R., ZIEGLER, J. B., AND CORINOLE, B.: J. Am. Pharm. Assoc. **29**, 164 (1940).
(186a) ROSENBLUETH, A., AND MORISON, R. S.: Am. J. Physiol. **119**, 236 (1937).
(187) ROULIN, J., AND BOUSSINGALT, J.: Ann. chim. **39**, 24 (1929).
(188) SACHS, T.: Ann. **191**, 354 (1878).
(189) SANTESSON, C. G.: Arch. exptl. Path. Pharmakol. **35**, 23 (1894).
(190) SANTESSON, C. G., AND KORAEN, G.: Skand. Arch. Physiol. **10**, 201 (1900).
(191) SCHMIDT, E.: Ann. **267**, 244 (1892).
(192) SCHMIDT, E.: Ann. **337**, 37 (1904).
(193) SCHMIEDEBERG, O., AND HARNACK, E.: Arch. exptl. Path. Pharmakol. **6**, 101 (1876).
(193a) SIMONART, A.: Arch. intern. pharmacodynamie **34**, 15 (1928).
(193b) SIMONART, A.: Arch. intern. pharmacodynamie **34**, 375 (1928).
(194) SIMONART, A.: J. Pharmacol. **46**, 157 (1932).
(195) SIMONART, A.: J. Pharmacol. **50**, 1 (1934).
(196) SIMONART, A.: Arch. intern. pharmacodynamie **48**, 328 (1934).
(196a) SIMONART, A.: J. Pharmacol. **54**, 105 (1935).
(197) SPÄTH, E., AND KUFFNER, F.: Ber. **67B**, 55 (1934).
(198) SPÄTH, E., LEITHE, W., AND LADECK, F.: Ber. **61B**, 1698 (1928).
(199) STEDMAN, E.: Biochem. J. **20**, 719 (1926).
(200) STEDMAN, E.: Biochem. J. **23**, 17 (1929).
(201) STEDMAN, E., SCHWEITZER, A., AND WRIGHT, S.: J. Physiol. **96**, 302 (1939).
(202) STEVENS, J. R., AND BEUTEL, R. H.: J. Am. Chem. Soc. **63**, 308 (1941).
(203) SWAN, K. E., AND WHITE, N. G.: J. Pharmacol. **80**, 285 (1944).
(204) TAKASE, T.: Tôhoku J. Exptl. Med. **18**, 443 (1932).
(205) TAKASE, T., AND SATO, H.: J. Pharm. Soc. Japan **49**, 1096 (1929).
(206) TAKASE, T., AND TERAUCHI, K.: J. Pharm. Soc. Japan **48**, 978 (1928).
(207) TAPPEINER, H.: Arch. exptl. Path. Pharmakol. **28**, 295 (1891).
(208) TAPPEINER, H.: Arch. exptl. Path. Pharmakol. **37**, 323 (1896).
(209) TAYLOR, K. B.: Ann. chim. anal. chim. appl. **19**, 5 (1937).
(210) TAYLOR, K. B.: Ann. chim. anal. chim. appl. **19**, 33 (1937).
(211) TRENDELENBURG, P.: A. Heffter's *Handbuch der experimentellen Pharmakologie* **1**, 564, 640 (1923).

(212) UNNA, K., AND GRESLIN, J. G.: J. Pharmacol. **80,** 53 (1944).
(213) UNNA, K., KNIAZUK, M., AND GRESLIN, J. G.: J. Pharmacol. **80,** 39 (1944).
(214) UNNA, K., AND PICK, E. P.: J. Pharmacol. **83,** 59 (1945).
(215) WARREN, M. R., BECKER, T. J., MARSH, D. G., AND SHELTON, R. S.: J. Pharmacol. **74,** 401 (1942).
(216) WEST, R.: Proc. Roy. Soc. Med. **28,** 565 (1935).
(217) WIELAND, H., BÖHR, K., AND WITKOP, B.: Ann. **547,** 156 (1941).
(218) WIELAND, H., KONZ, W., AND SONDERHOFF, R.: Ann. **527,** 160 (1937).
(219) WIELAND, H., AND PISTOR, H. J.: Ann. **536,** 68 (1938).
(220) WIELAND, H., PISTOR, H. J., AND BÖHR, K.: Ann. **547,** 140 (1941).
(221) WILLIAMS, J. M.: Med. Ann. Dist. Columbia **10,** 171 (1941).
(222) WILLIAMS, J. M.: Ohio State Med. J. **37,** 849 (1941).
(223) WINTERSTEINER, O., AND DUTCHER, J. D.: Science **97,** 467 (1943).
(224) WORK, T. S.: J. Chem. Soc. **1941,** 190.