THE PHARMACOLOGY OF SOME HYDROXYBENZYL*ISO*QUINOLINE DERIVATIVES

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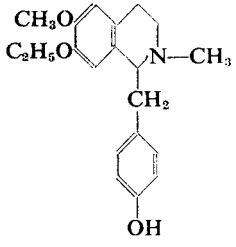
(±)-1-(4′-Hydroxybenzyl(-2-methyl-6-methoxy-7-ethoxy-1:2:3:4-tetrahydro-*iso*quinoline and its dextrorotatory and laevorotatory isomers and methochloride, (±)-1-(4′-hydroxybenzyl)-2-methyl-7-methoxy-6-ethoxy-1:2:3:4-tetrahydro-*iso*quinoline, its laevorotatory isomer and methochloride and a berberine-like compound related to tetrahydroworenine have been tested for curare-like activity. Little activity was noted, but on the rat diaphragm and frog rectus muscle quaternisation of the racemic compounds increased this. The tertiary bases possessed potent convulsant properties.

THE compounds I and II were synthesised by Jeffreys[1] during studies on the constitution of the di-tertiary alkaloid *iso*chondrodendrine (III). These compounds are related chemically to armepavine[2], coclaurine[3], *iso*coclaurine[3] and magnocurarine[4] (IV-VII). *iso*Coclaurine and magnocurarine have been reported to possess some curare-like activity. Coclaurine is inactive. Compounds I and II are possible degradation products of *iso*chondrodendrine which is chemically somewhat similar to tubocurarine (a di-quaternary base). We thought it worth-while to test



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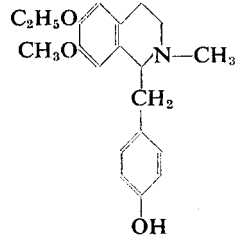

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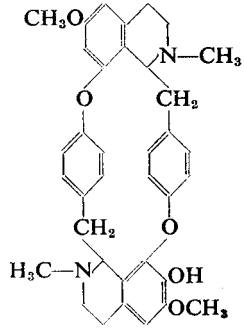

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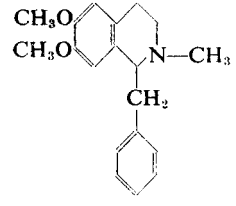

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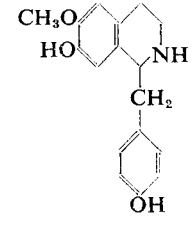

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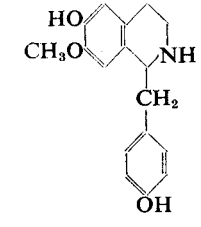

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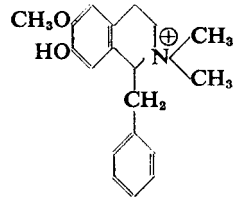

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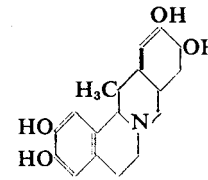

(VIII)

these compounds for curare-like activity and also to test the corresponding quaternary salts, especially since magnocurarine, which is a quaternary base, has been reported to possess some curare-like activity[4]. We have made some comparisons with tubocurarine and with a berberine-like compound (VIII) which contains an *iso*quinoline ring system[5].

Materials, Methods and Results

The composition of the perfusion fluids used in this investigation was as follows:—

Frog Ringer's solution: NaCl 6·5 g., KCl 0·138 g., $CaCl_2$ (anhydrous) 0·12 g., $NaHCO_3$ 0·2 g., dextrose 1·0 g., distilled water to 1000 ml. Locke's solution: NaCl 9·0 g., KCl 0·42 g., $CaCl_2$ (anhydrous) 0·24 g., $NaHCO_3$ 0·5 g., dextrose 1·0 g., distilled water to 1000 ml. Tyrode's solution: NaCl 8·0 g., KCl 0·198 g., $CaCl_2$ (anhydrous) 0·2 g., $NaHCO_3$ 1·0 g., $MgCl_2$ 0·1 g., NaH_2PO_4 0·005 g., dextrose 1·0 g., distilled water to 1000 ml.

Drugs used were as follows: acetylcholine chloride (ACh), (−)-adrenaline hydrochloride (Ad), (−)-noradrenaline hydrochloride (NA), tubocurarine chloride (TC), decamethonium iodide (C10), histamine acid phosphate (Hm), 5-hydroxytryptamine creatinine sulphate (5-HT), phentolamine, dibenamine and hydergine.

The compounds investigated were: 1, (±)-1-(4′-hydroxybenzyl)-2-methyl-6-methoxy-7-ethoxy-1:2:3:4-tetrahydro*iso*quinoline (I) and its dextrorotatory (I*d*) and laevorotatory isomers (I*l*) and the quaternary derivative (I*q*) (methochloride); 2, (±)-1-(4′-hydroxybenzyl)-2-methyl-7-methoxy-6-ethoxy-1:2:3:4-tetrahydro-*iso*quinoline (II) and its laevorotatory (II*l*) isomer and the quaternary derivative (II*q*) (methochloride); 3, a compound related to tetrahydroworenine[5], 5:6:13:13a-tetrahydro-2:3:10:11-tetrahydroxy-8H-dibenzo-(a, g)-pyridocholine hydrochloride, described as (VIII).

The tertiary compounds are insoluble in water but can be dissolved in dilute hydrochloric acid at about pH 5. The quaternary compounds are freely soluble in water.

Frog Rectus Abdominis Muscle

The rectus muscle was dissected and suspended in a 20 ml. bath containing oxygenated frog Ringer's solution at room temperature. Reproducible submaximal contractions were obtained to ACh (0·1 to 0·2 μg./ml.) and C10 (2·0 to 2·5 μg./ml.) added at 5 minute intervals and left in contact

with the tissue for 1·5 minutes. Drugs in doses of 12·5 to 250 μg./ml. were added ½ minute before the next addition of ACh or C10 and left in contact with the tissue for 2 minutes.

There was antagonism by all compounds to ACh-induced contractions and a graded effect was seen. Comparing the potency against TC, I was one fiftieth, II about one four hundredth, VIII about one hundredth, and I*l*, I*d* and II*l* had a potency of one four hundredth, one sixtieth and one four hundred and fiftieth respectively. I*q* and II*q* had respectively about one thirtieth and one fiftieth of the potency of TC. None of these compounds had any direct effects on the rectus. All antagonised contractions by 2 to 2·5 μg./ml. C10, but high doses were needed. The effects of these compounds were additive to those of TC.

Frog Sartorius Muscle Ischiad Nerve Preparation

The sartorius muscle with the ischiad nerve was dissected. The nerve was drawn through the membrane of a fluid electrode and the muscle nerve preparation suspended in an 80 ml. bath containing oxygenated frog Ringer's solution at room temperature. The muscle was stimulated indirectly by using square pulses at a frequency of 12/minute at 10 V., pulse width 0·5 msec. Drugs at doses of 25 to 200 μg./ml. were added to the bath and kept in contact with the muscle for 3 minutes.

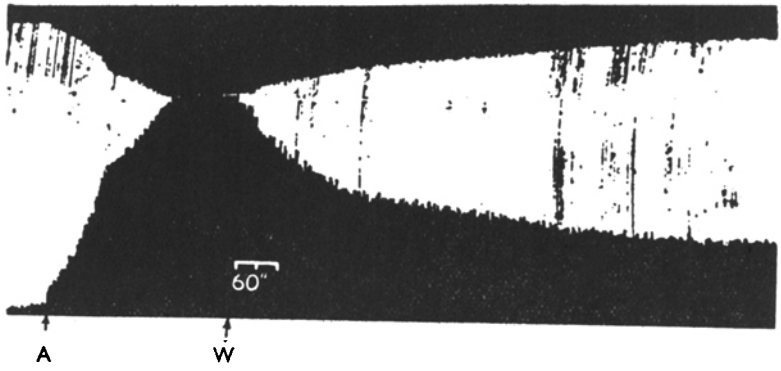

FIG. 1. Frog sartorius muscle-ischiad nerve preparation. Contractions due to indirect square pulses, 12/min. 12 V., 0·5 msec. width.
At A, 62·5 μg./ml. compound II. At W, wash out.

Only I, II and VIII were tested. The doses given of these three compounds inhibited the response to indirect stimulation. They were much less potent than TC. After washing there was complete recovery of the contraction (Fig. 1).

Rat Phrenic Nerve Diaphragm Preparation

The dissection was made as described by Bülbring[6] and the muscle-nerve preparation suspended in an 80 ml. bath containing Tyrode's solution at 29° and gassed with 95 per cent O_2 and 5 per cent CO_2. A Collison's electrode was used and the muscle stimulated indirectly using square

pulses at a frequency of 6/minute at 12 V.; pulse width 1·0 msec. Drugs were added to the bath and kept in contact with the muscle for 3 minutes.

On this preparation these compounds had only very weak curare-like activity. I*q* and II*q*, the quaternary salts of I and II were about five times more potent than the tertiary bases from which they were prepared. Complete neuromuscular block could be produced but high doses of about 0·25 mg./ml. had to be used. After the response to indirect

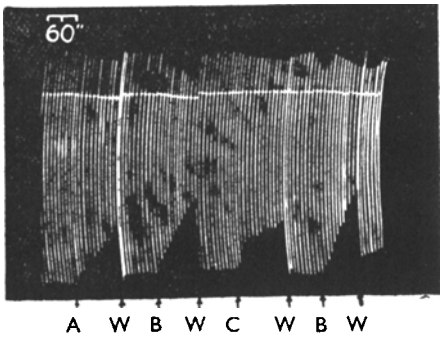

FIG. 2*a*. Rat phrenic nerve-diaphragm preparation. Contractions due to indirect square pulses, 6/min., 12 V. 1 msec. width.

At A, 2·5 μg./ml. tubocurarine chloride.
At B, 3·0 μg./ml. tubocurarine chloride.
At C, 0·6 mg./ml. compound I.
At W, wash out.

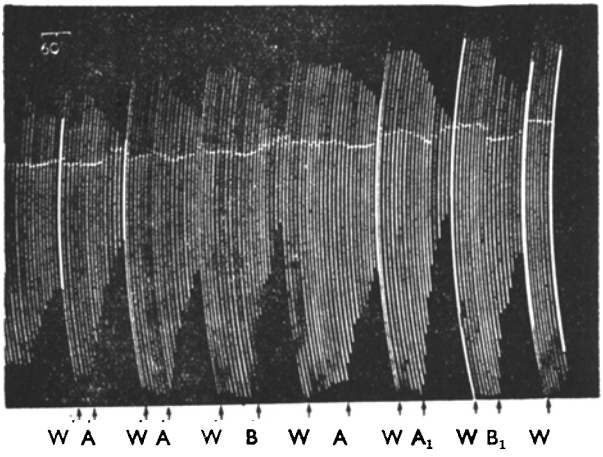

FIG. 2*b*. Rat phrenic nerve-diaphragm preparation as Fig. 2*a*.

At A, 5 μg./ml. tubocurarine chloride.
At A_1, 10 μg./ml. tubocurarine chloride.
At B, 300 μg./ml. compound II.
At B_1, 250 μg./ml. compound II.
At W, wash out.

stimulation had failed, the muscle still responded to direct stimulation. The tertiary bases were about 250 times less potent (Fig. 2*a*) and compound (VIII) had about one fourtieth of the potency of TC (Fig. 2*b*).

Isolated Kitten Heart

Kitten hearts were perfused by Langendorff's method[7] using oxygenated Locke's solution at 37°. The outflow was measured by collecting the perfusate for periods of 5 minutes into a measuring cylinder. Drugs were administered by injection into the aortic cannula.

Ten to 20 μg. of II*l* increased the rate and amplitude of the heart; 20 μg. of I*l* had a similar effect. These effects were reversible. II and VIII had no effect.

Guinea Pig Ileum

About 3 cm. of the terminal ileum was suspended in a 4 ml. bath containing oxygenated Tyrode's solution at 31°. Reproducible submaximal contractions were obtained by adding ACh (0·05 to 0·2 μg./ml.) or Hm (0·05 to 0·2 μg./ml.) at 3 minute intervals and leaving in contact for $\frac{1}{2}$ minute at doses of 25 to 250 μg. Drugs were added $\frac{1}{2}$ or 1 minute before the next addition of ACh or Hm. Contact of drug with tissue was for 1 or 1·5 minutes.

All compounds inhibited contractions by ACh or Hm. There was a graded inhibition according to dose. No direct effects were seen.

Cat Gastrocnemius Muscle Sciatic Nerve Preparation

In cats weighing 2·0 to 3·5 kg. anaesthesia was induced by ether and maintained by intravenous chloralose (80 mg./kg.). The gastrocnemius muscle was partially freed from the surrounding tissues and the achilles tendon severed just above its insertion into the calcaneus. The tendon was attached by means of a strong linen thread to a myograph lever. The sciatic nerve was partly dissected on the lateral aspect of the thigh and stimulated by means of platinum electrodes which were placed on the nerve just above the emergence of the anterior tibial nerve. Stimulation was by square pulses at a frequency of 6/minute at 12 V.; pulse width 2·5 msec. A Dobbie McInnes square wave generator was used. Drugs were administered by the cannulated external jugular vein.

The quaternary bases at doses of 1 to 2 mg./kg. did not depress the response of the muscle to indirect stimulation. Similarly the tertiary bases at 1 to 4 mg./kg. had no neuromuscular blocking activity. There was some spontaneous muscular twitching.

Cat Blood Pressure

In cats weighing 2·0 to 3·5 kg. anaesthesia was induced by ether and maintained by intravenous chloralose (80 mg./kg.). Blood pressure was recorded from the common carotid artery. Drugs were administered by the cannulated external jugular vein. In some experiments the spinal cat was used.

Results showed that I (1·0 to 2·0 mg./kg.) always caused a biphasic depressor-pressor response. The fall in blood pressure was marked but the ensuing rise was small (Fig. 3). I*d* and I*l* showed qualitatively similar effects but both depressor and pressor components were less. When I was given after bilateral mid-cervical vagotomy, the depressor component was lost and only a rise in blood pressure was seen (Fig. 3). In a few

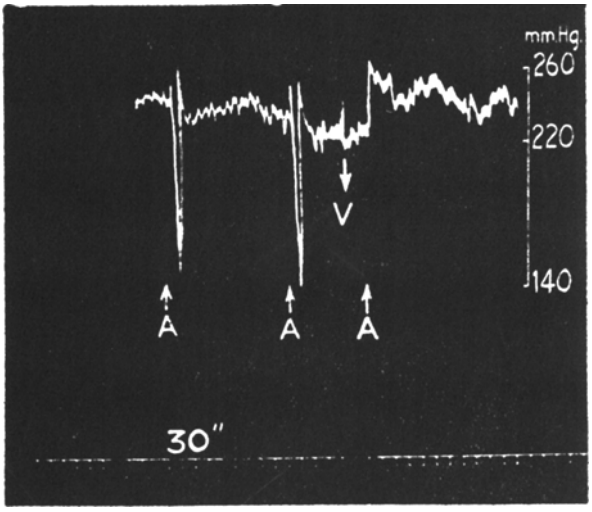

FIG. 3. Cat 2·5 kg. anaesthetised with ether-chloralose. Record of blood pressure from common carotid artery.
At A, 0·8 mg./kg. compound I intravenously.
At V, bilateral cervical vagotomy.

experiments I*l* caused a rise only in blood pressure. I*q* (0·5 to 1·0 mg./kg.) caused a rise in blood pressure (Fig. 4). II and II*l* at dose levels of 1·0 to 2·0 mg./kg. caused respectively a slight rise in blood pressure and a biphasic depressor-pressor effect. II*q* (0·5 to 1·0 mg./kg.) also caused a rise in blood pressure (Fig. 4). VIII (1·0 to 2·0 mg./kg.) had no effects on the blood pressure. The pressor responses were not blocked by phentolamine (up to 5 mg./kg.), dibenamine (up to 25 mg./kg.) or hydergine (up to 0·4 mg./kg.). These compounds did not antagonise the characteristic effects on the blood pressure of ACh (0·5 to 1·0 μg./kg.), Hm (0·5 to 1·0 μg./kg.), Ad (1·0 to 2·0 μg./kg.) or 5-HT (1·0 to 2·0 μg./kg.).

Higher doses when given repeatedly in anaesthetised cats caused respiration to stop and artificial respiration had to be given.

When doses of 1 mg./kg. or more were given at intervals of $\frac{1}{4}$ to $\frac{1}{2}$ hour in anaesthetised or spinal cats, convulsions were caused. Convulsant activity was not shown following the first dose but on repeated administration of each drug convulsant activity became apparent. This appeared to be a cumulative effect. Convulsions were preceded by twitching movements which became clonic convulsions. There were periods of quiet between convulsions.

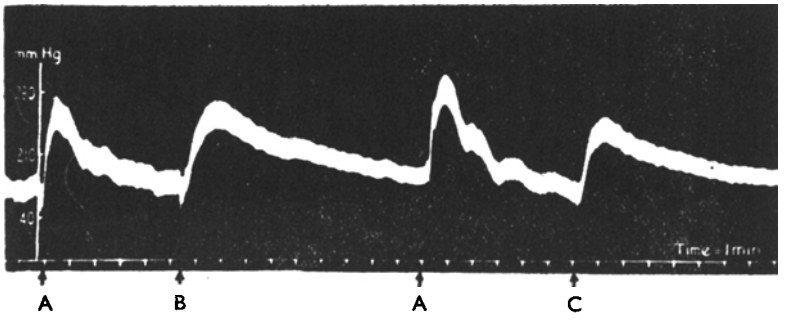

FIG. 4. Cat female, 4·0 kg. anaesthetised by intraperitoneal chloralose. Record of blood pressure from common carotid artery.

At A, 0·2 μg./kg. noradrenaline hydrochloride intravenously.

At B, 0·5 mg./kg. compound I*q* intravenously.

At C, 0·5 mg./kg. compound II*q* intravenously.

Toxicity

Drugs were given by intraperitoneal injection into groups of mice weighing 40 to 50 g.

In mice I, II and VIII showed potent convulsant activity. These compounds were roughly equipotent with leptazol. The mice showed tonic-clonic convulsions with maximal hind leg extensor spasm.

DISCUSSION

The compounds which we have tested possess little or no skeletal neuromuscular blocking activity but the preparation of the quaternary salts of I and II increased their potency on the rat diaphragm and frog rectus muscle. Compound II is less potent than compound I which would indicate that transposition of the ethoxy and methoxy groups had altered activity.

All of the tertiary bases were convulsants but we have had insufficient supplies of the quaternary compounds to test them for convulsant activity.

Acknowledgment. We are indebted to Dr. J. A. D. Jeffreys for samples of the compounds tested.

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DISCUSSION

The paper was presented by DR. M. S. ZOHA.

DR. J. B. STENLAKE (Glasgow). What was the activity of the quaternary salts of isochondrodendrine which would be structurally related to tubocurarine?

DR. M. S. ZOHA replied. The quaternary salts of isochondrodendrine were not examined.