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The synthesis and pharmacology of some 1,4,5,6-tetrahydropyrimidines

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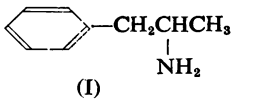
1. Several 1- and 2-substituted, and 1,2-disubstituted, 1,4,5,6-tetrahydropyrimidines have been prepared and their toxicological and pharmacological properties have been investigated.

2. In general the compounds were neuromuscular blocking agents with the monosubstituted members of the series showing a depolarizing type of activity and the disubstituted compounds a non-depolarizing type.

3. The toxicity to mice of some of the monosubstituted compounds was increased by pretreatment of the animals with SKF 525A, but the toxicity of the disubstituted compounds was unaffected.

4. The results obtained with these compounds are not at variance with a suggestion made previously that nicotinic action at the neuromuscular junction can result from an interaction between drug and receptor at two points separated by about 4 Å.

Many drugs like amphetamine (I) and ephedrine (II), containing the phenylethylamine skeleton, Ph–C–C–N, exhibit pressor activity. There do not appear to be many examples of compounds where the nitrogen atom has been incorporated into a ring system, but Tolazoline (III), in which the nitrogen atom forms part of an imidazoline ring, exhibits depressor rather than pressor activity (Hartmann & Isler, 1939) and in a U.S. patent (Langis & Pilkington, 1964) bronchodilator and antihistaminic activity has been claimed for 1-(β-phenylethyl)-2-benzyl-3,4,5,6-tetrahydropyrimidine (IV). It seemed of interest, therefore, to study the tetrahydropyrimidine derivative (V) corresponding to Tolazoline and also related compounds substituted in the 1-, as well as in the 2-, position. This paper describes the synthesis of a number of such compounds (VI) and the results of their pharmacological testing.



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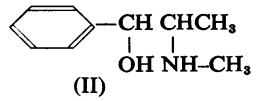

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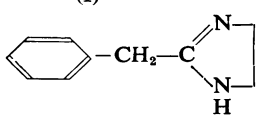

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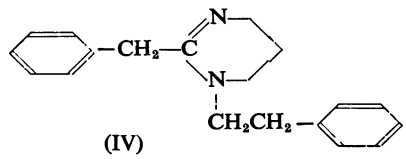

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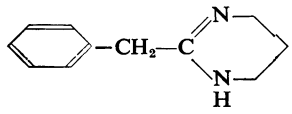

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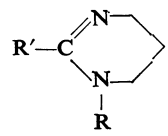


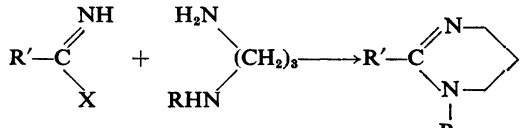
(VI)

The substituents R and R′ were methyl, phenyl, benzyl, phenethyl, phenoxyethyl, phenylpropyl and some substituted benzyl and phenethyl groups.

Methods

Chemical syntheses

All the 1,4,5,6-tetrahydropyrimidines, with the exception of the compound mentioned below, were prepared according to the method described by Brown & Evans (1962) by refluxing equimolar quantities of the appropriate amidine (VIIa) or imino ether (VIIb) with the appropriate diamine (VIII) in ethanol for a few hours until the evolution of ammonia had ceased.



(VIII)

(VI)

(VII) a, X=NH_2
b, X=OC_2H_5

One compound, 1-*p*-nitrophenylethyl-2-benzyl-1,4,5,6-tetrahydropyrimidine, was prepared by aralkylation of 2-benzyl-1,4,5,6-tetrahydropyrimidine with *p*-nitrophenethyl bromide.

Methiodides were prepared from the parent base by reaction with methyl iodide in acetone.

The amidines, imino ethers, and propane diamines were obtained either commercially or by standard preparative methods.

The physical properties of the 1,4,5,6-tetrahydropyrimidine (VI) are recorded in Table 1.

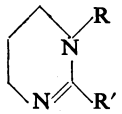
Biological methods

Toxicology

All the compounds were tested for their intravenous toxicity to female albino mice (18–25 g). Injections were made into a tail vein and a volume of 5 ml./kg was used. The LD50 was determined using up to six groups, each consisting of five mice. The ratio between doses was 1 : 1·2 and the LD50s were calculated using the method of probit analysis (Finney, 1947).

In some experiments, mice used in toxicity studies were pretreated with the metabolic inhibitor 2-diethylaminoethyl diphenylpropylacetate (proadifen, SKF 525A). This was given by the intraperitoneal route, in a dose of 50 mg/kg, 30 min before the intravenous administration of the tetrahydropyrimidine.

TABLE 1. *Tetrahydropyrimidines*



Compound No.	R	R′	Salt	Melting point (° C)	Yield (%)	Solvent	Analysis or melting point in literature (% Calc.) C	H	N		(% Found) C	H	N
1	H	H	HCl	188–190	88	F	—	—	—	189–190*	—	—	—
2	H	Me	HCl	145–148	96	D	—	—	—	146–149*	—	—	—
3	H	Ph	HCl	241–244	76	E	—	—	—	244–246*	—	—	—
4	H	Ph.CH_2	HCl	208–209	76	B	—	—	—	212–213*	—	—	—
			Free base	112–114						107–109†			
5	H	$Ph(CH_2)_2$	HCl	190–192	93	B	64·1	7·62	12·5		64·1	8·22	12·7
6	H	$Ph(CH_2)_3$	HCl	142–144	90	C	65·4	8·02	11·7		65·4	8·22	12·0
7	H	4-$MeOC_6H_4.CH_2$	HCl	195–198	98	B	59·9	7·12	11·6		59·5	7·19	12·0
8	H	3,4-$DiMeOC_6H_3.CH_2$	HCl	210–212	85	C	57·7	7·07	10·4		58·0	6·99	10·6
9	Me	H	Acetate	b.p. 88–90° /0·2 mm	100	—	—	—	—		—	—	—
			Picrate	103–105						104–106*			
10	Ph.CH_2	H	Free base	b.p. 130° /0·3 mm	95	—	75·8	8·10	16·1		75·5	8·49	15·6
				67–69		G							
11	$Ph(CH_2)_2$	H	Acetate	—	90	—	—	—	—		—	—	—
			Picrate	105–107	—	A	51·8	4·59	16·8		52·3	4·98	16·6
12	$Ph(CH_2)_3$	H	Free base	b.p. 128–130° /0·3 mm	97	—	—	—	—		—	—	—
			Picrate	67–69	—	A	52·9	4·91	16·2		52·4	4·94	16·5
13	Ph.O.$(CH_2)_2$	H	Free base	52–54	97	G	—	—	—		—	—	—
			Picrate	120–122	—	A	49·9	4·42	16·2		49·5	4·86	16·6
14	$PhCH_2$	Ph	HCl	194–196	78	E	71·2	6·68	9·77		71·5	6·77	9·72
15	$Ph(CH_2)_2$	Ph	HCl	220–222	94	C	71·9	7·04	9·32		71·7	7·51	9·05
16	$Ph(CH_2)_2$	Ph.CH_2	HCl	196–198	95	C	72·5	7·36	8·90		72·8	7·76	8·87
17	$Ph(CH_2)_2$	$Ph(CH_2)_2$	HCl	157–159	98	C	73·0	7·66	8·52		73·4	8·26	8·25
18	4-$NO_2.C_6H_4(CH_2)_2$	Ph.CH_2	HBr	216–218	39	A	56·4	5·48	10·40		56·6	5·89	10·07
19	$Ph(CH_2)_3$	Ph	H_2SO_4	205–207	47	C	60·6	6·43	7·44		60·6	6·61	7·80
20	$Ph(CH_2)_3$	Ph.CH_2	HCl	133–135	98	E	73·0	7·66	8·52		73·2	7·92	8·04
21	$PhO(CH_2)_2$	Ph	$HCl,\frac{1}{2}H_2O$	231–233	92	C	66·4	6·81	8·60		66·7	6·90	8·88
22	$PhO(CH_2)_2$	Ph.CH_2	HCl	167–169	85	C	69·0	7·01	8·47		69·3	7·22	8·97
23	4-$MeO.C_6H_4O(CH_2)_2$	Ph	HCl,H_2O	167–169	88	C	62·7	6·92	7·71		62·4	6·99	7·96
24	$Ph(CH_2)_2$	H	CH_3I	143–145	—	A	—	—	—		—	—	—
25	$Ph(CH_2)_2$	Ph	CH_3I	138–140	—	C	—	—	—		—	—	—

* Brown & Evans (1962). † Skinner & Wanz (1951).

A=EtOH; B=MeOH/Et_2O; C=EtOH/Et_2O; D=EtOH/EtOAc; E=MeOH/C_6H_6; F=iPrOH/EtOAc; G=Petrol (40°–60°).

Pharmacology

Isolated tissues

All the compounds were tested for their effects on isolated chick semi-spinalis muscle and some were tested on an isolated chick biventer cervicis nerve-muscle preparation.

The chick spinalis preparation was used as described by Child & Zaimis (1960). The muscle was removed from 3–10 day old chicks anaesthetized with ether and was suspended in a 5 ml. organ bath containing oxygenated Ringer-Tyrode solution at 40° C. Contractions of the muscle in response to depolarizing substances were recorded on a smoked drum using a light isotonic lever, and the activities of these substances were expressed in terms of the activity of nicotine using a four-point assay procedure; the activities of non-depolarizing blocking substances were assessed by comparing the concentrations which, when allowed to act for 1 min, blocked the contracture produced by 5×10^{-4}M nicotine.

The biventer-cervicis preparation was used as described by Ginsborg & Warriner (1960). The nerve-muscle preparation was removed from a chick anaesthetized with ether and suspended in a 30 ml. organ bath containing oxygenated Ringer-Tyrode solution at 40° C. Muscle twitches in response to nerve stimulation (6–12 c/min, 900 μsec duration, voltage adjusted to give maximal contractions) were recorded on a smoked drum using a light semi-isometric lever. Both depolarizing and non-depolarizing neuromuscular blocking agents reduce the contractions of the muscle evoked by nerve stimulation, but depolarizing drugs, in addition, cause a contracture of the muscle.

Anaesthetized cat experiments

All the compounds were tested for their effects on an anaesthetized cat preparation. Cats weighing between 1·8 and 2·4 kg were used. Anaesthesia was induced with halothane and followed by slow intravenous injection of chloralose (80–100 mg/kg) into the cephalic vein of the fore-limb.

Blood pressure was recorded from the left femoral artery using a Statham Physiological Transducer Model P23AA. Changes in tension of the nictitating membrane were recorded using an E and M Myograph Type C (maximum sensitivity 5 g) with a resting tension on the membrane of 1 g. In some experiments nictitating membrane contractions evoked by stimulation of the superior cervical nerve (12 c/s, 4 msec pulse width, 0·5 V) were measured. Needle electrodes, one on either side of the chest wall, enabled respiratory movements to be recorded with an E and M Impedance Pneumograph. All signals were suitably amplified and displayed on a pen recorder (Physiograph "Six", E and M Instrument Company Inc.). Drugs were injected through a cannula in the right femoral vein. In one experiment the animal was adrenalectomized before drugs were given.

A few compounds were given by intra-arterial injection direct to the superior cervical ganglion. The method used was essentially that described by Brimblecombe & Sutton (1968), with ganglion stimulant activity being assessed in terms of the nictitating membrane contraction.

Anaesthetized rabbit experiments

Rabbits weighing between 1·8 and 2·5 kg were anaesthetized with urethane (1·8 to 2 g/kg into the marginal vein of the ear). Following intubation of the trachea,

about 2 cm of the phrenic nerve was carefully dissected out on the right side of the neck. The nerve was cut and the central end laid across platinum recording electrodes. The compound action potentials were recorded using a Tektronix type 122 AC coupled amplifier and a Telequipment cathode ray oscilloscope type D43. The signals were stored on 1 inch magnetic tape using an Epsylon multi-track FM recording system and subsequently photographed.

The peripheral end of the phrenic nerve was placed across silver stimulating electrodes. Diaphragm movements, both spontaneous and those resulting from phrenic nerve stimulation, were recorded using the Head slip method (Head, 1889) and employing an E and M Type C myograph (maximum sensitivity 5 *g*). Tetanus of the diaphragm was achieved by stimulating at 60 c/s, 250 msec pulse width with voltages varying between 0·5 and 6 V. Tracings were made with a pen recorder (E and M Physiograph "Six"). Drugs were injected via a cannula in the right jugular vein.

Effects on chickens

Chickens aged between 2 and 4 weeks were used to distinguish between non-depolarizing and depolarizing neuromuscular blocking agents. The method used was essentially that described by Buttle & Zaimis (1949) in which the test compound was injected into the wing vein. Non-depolarizing blockers produced a flaccid type of paralysis with a head-drop while depolarizing blockers gave a spastic paralysis with a typical retraction of the head. An initial dose of 2 mg was used and if this had no effect a further dose of 5 mg was given 5 min later. Compounds producing no effect at a dose of 5 mg were considered inactive.

Results

Toxicity

The intravenous LD50s to mice of all the compounds are shown in Table 2. The signs of poisoning were similar for all compounds: weakness of the hind limbs and difficulty in respiration were followed by convulsions which occurred within 1–2 min. Very high doses resulted in immediate collapse and death within 1 min.

Twelve of the compounds were tested for their toxicity to mice treated with the metabolic inhibitor SKF 525A. The results, also in Table 2, indicate that the LD50s of six of the compounds, which were 1- and 2-monosubstituted derivatives (Nos. 1, 3, 4, 5, 11 and 12) were significantly decreased by this treatment while the LD50s of the remainder, the 1-phenoxyethyl and 1,2-disubstituted derivatives (Nos. 13, 14, 15, 19, 20 and 22) were unchanged.

Effects on isolated tissues

Effects on the isolated chick semi-spinalis muscle are shown in Table 3. Some of the compounds were without activity at the highest concentration used (10^{-5}M). Some others showed depolarizing activity and were assayed for their potency relative to nicotine. Others showed activity in blocking nicotine-induced contractures of the muscle—that is, non-depolarizing neuromuscular blocking activity.

Eight compounds were studied for their effects on the isolated chick biventer cervicis nerve-muscle preparation. Five of these, monosubstituted compounds

TABLE 2. *Summary of toxicological results*

Compound number	LD50 i.v. mice (mg/kg±95% limits)	LD50 after SKF525A (mg/kg±95% limits)
1	5·9 (5·0–6·9)	2·6 (2·2–3·1)
2	88·5 (75·2–104)	—
3	12·6 (9·1–17·3)	4·7 (3·4–6·4)
4	9·4 (7·7–11·4)	5·0 (4·3–5·9)
5	3·3 (2·6–4·1)	2·0 (1·7–2·4)
6	4·7 (3·3–6·4)	—
7	12·3 (9·5–16·6)	—
8	21·3 (17·5–26·0)	—
9	58·5 (31·1–85·6)	—
10	62·7 (53·5–73·7)	—
11	3·0 (2·8–3·3)	1·0 (0·65–1·5)
12	13·1 (11·1–15·4)	8·7 (7·4–10·3)
13	38·4 (31·5–46·9)	49·0 (39·0–61·6)
14	9·6 (7·4–12·4)	10·4 (8·5–12·7)
15	3·6 (2·6–5·1)	3·6 (2·9–4·6)
16	15·3 (14·2–16·4)	—
17	10·5 (7·7–14·9)	—
18	17·7 (13·4–23·4)	—
19	8·2 (5·9–11·3)	7·5 (5·8–9·7)
20	9·1 (6·6–13·5)	10·1 (7·3–13·8)
21	10·4 (8·5–12·7)	—
22	9·6 (7·9–11·7)	9·9 (8·3–11·9)
23	12·6 (10·7–14·8)	—
24	11·8 (10·0–13·9)	—
25	12·1 (8·7–16·7)	—

TABLE 3. *Summary of pharmacological results*

Compound number	Blocking action on chickens	Effect on chick biventer-cervicis preparation. Concentration for neuro-muscular block (M)	Activity on chick semi-spinalis relative to nicotine
1	D	10^{-3} (D)	0·009
2	D	—	Inactive
3	D	—	0·28
4	D	3×10^{-4} (D)	0·015
5	D	10^{-4} (D)	0·08
6	D	—	Inactive
7	D	—	Inactive
8	D	—	Inactive
9	No effect	—	Inactive
10	D	—	Inactive
11	D	3×10^{-4} (D)	0·12
12	D	—	0·005
13	D	—	Inactive
14	N	—	Block at 10^{-4}M
15	N	10^{-5} (N)	Block at 10^{-5}M
16	N	3×10^{-4} (N)	Block at 5×10^{-5}M
17	N	3×10^{-8} (N)	Block at 2×10^{-5}M
18	N	—	Block at 10^{-5}M
19	N	—	Block at 10^{-4}M
20	N	—	Block at 10^{-4}M
21	N	—	Inactive
22	N	—	Block at 3×10^{-4}M
23	N	—	Block at 10^{-4}M
24	D	—	Inactive
25	N	—	Block at 10^{-4}M

D=Depolarizing block; N=non-depolarizing block; Inactive=no activity at 100 μM.

(Nos. 1, 4, 5, 9 and 11), showed activity typical of depolarizing neuromuscular blocking agents. The remaining three, di-substituted compounds (Nos. 15, 16 and 17), showed a non-depolarizing type of activity. The detailed results are given in Table 3.

Effects on anaesthetized cats

Several of the compounds produced a rise in blood pressure of the anaesthetized cat. The most active compounds were Nos. 4, 11, 12 and 16 with phenyl or aralkyl groups in positions 1 or 2, all of which produced hypertension at doses of 0·1 μ-moles/kg (about 30 μg/kg) or less. The more active compounds also simultaneously caused a small contraction of the nictitating membrane. These effects were completely blocked by the ganglion blocking agent hexamethonium and by the α-adrenoceptor blocking drug, phentolamine. When given after phentolamine, some of the drugs caused a long-lasting fall in blood pressure. A typical record is shown in Fig. 1.

One compound, No. 1, the unsubstituted tetrahydropyrimidine, caused a transient fall in blood pressure which was blocked by atropine sulphate.

Several compounds were studied for their effects on the superior cervical ganglion when given into the external carotid artery. Three of these, all disubstituted compounds (Nos. 15, 22 and 23), blocked the contraction of the nictitating membrane produced by electrical stimulation of the preganglionic nerves. In each, a dose of 100 μg (about 0·3 μ-moles) reduced the extent of the contraction by about 50%.

Other compounds tested in this way (Nos. 3, 4, 5, 7 and 11, all monosubstituted with alkyl or aralkyl substituents) caused contractions of the nictitating membrane. The threshold doses were 2, 10, 5, 0·5 and 2 μg (about 6, 30, 15, 1·5 and 6 μ-moles) respectively. These contractions were completely blocked by pretreatment with hexamethonium bromide (1 mg, 5 μ-moles) but were unaffected by pretreatment with atropine sulphate (10 μg, 0·025 μ-moles). A typical tracing is shown in Fig. 2.

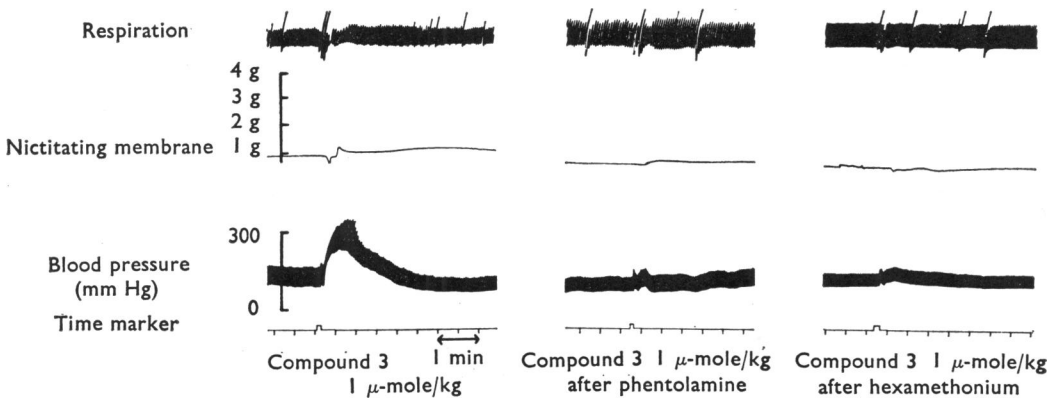


FIG. 1. Effects of compound 3 (2-phenyl-1,4,5,6-tetrahydropyrimidine) on anaesthetized cat preparation.

Effects on anaesthetized rabbits

The compounds tested on this preparation fall clearly into two groups. One group caused an asynchronous discharge in the phrenic nerve, but the activity soon reverted to the normal rhythmical discharge. This effect occurred at doses which had no effect on spontaneous movements of the diaphragm or on responses of the diaphragm to phrenic nerve stimulation. After higher doses, neuromuscular blockade occurred and just before death there was a marked decrease in the rate of phrenic nerve discharge. Compounds acting in this way included the benzyl and phenethyl compounds, Nos. 4, 5 and 11.

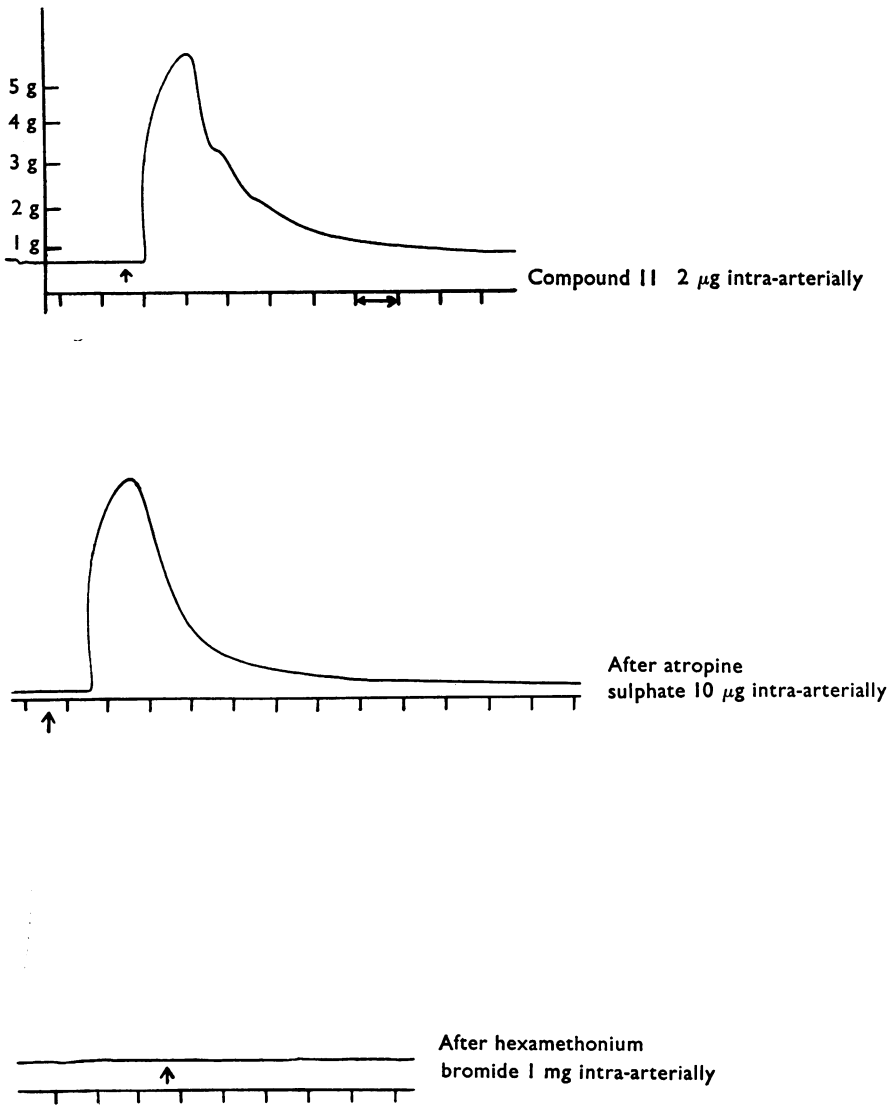


FIG. 2. Effect of compound 11 (1-phenylethyl-1,4,5,6-tetrahydropyrimidine) on contraction of cat nictitating membrane.

The other groups of compounds did not produce the asynchronous discharge but gave rise to a slowing in the rate of rhythmical discharge. In animals which died this became progressively slower until death ensued. Neuromuscular blockade preceded death. Compounds in this category were the disubstituted compounds, Nos. 15 and 16.

Nicotine was studied on this preparation for comparative purposes, but it was found that its effects were not exactly similar to either of the above groups of compounds. While producing the asynchronous discharge in the phrenic nerve it also caused a dramatic increase in depth, and often rate, of respiration.

Figure 3 shows the results of an experiment in which the effects of two tertiary bases (Nos. 15 and 11) were compared with those of their corresponding quaternary ammonium salts (respectively Nos. 25 and 24). The effects of Nos. 15 and 25 were very similar—slowing of rate of phrenic nerve discharge. The quaternary salt No. 24 did not, however, produce the asynchronous discharge which occurred after administration of its corresponding tertiary base No. 11.

Effects on chickens

The results are given in Table 3. With the exception of the 1-methyl compound (No. 9), which was inactive at a dose of 4 mg, all the compounds produced a neuromuscular blockade either of the non-depolarizing or of the depolarizing type.

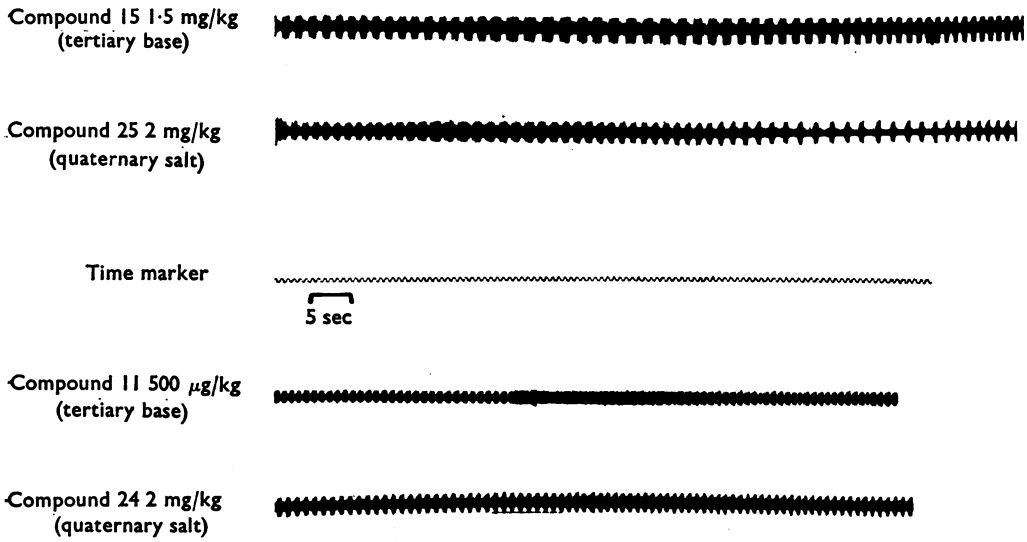


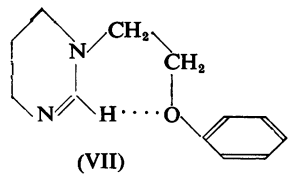
FIG. 3. Comparison of activity of tertiary bases with their corresponding quaternary salts on phrenic nerve discharge. Compound 15, 1-phenylethyl-2-phenyl-1,4,5,6-tetrahydropyrimidine; compound 11, 1-phenylethyl-1,4,5,6-tetrahydropyrimidine.

Discussion

It is clear from the results of the experiments reported here that compounds in this series do not show pressor activity of the type normally associated with phenylethylamines. The rise in blood pressure observed in the anaesthetized cat preparation is due to stimulation of the autonomic ganglia because the effect is blocked by hexamethonium. It seems possible that there was also some stimulation of the adrenal medulla to release adrenaline, since after α-adrenoceptor blockade with phentolamine, some of the pyrimidines produced a fall in blood pressure which was unaffected by atropine and thus presumably due in part to stimulation of β-adrenoceptors, since the fall was less in adrenalectomized animals.

The results of other tests confirm that the main pharmacological action of the compounds is of the " nicotinic " type. They produced a neuromuscular blockade in anaesthetized rabbits, in chickens and in the biventer cervicis nerve-muscle preparation. It was possible from the results of the latter two tests and from the results of experiments using the isolated chick semi-spinalis muscle to divide the compounds clearly into those having a depolarizing effect at the neuromuscular junction and those exerting a non-depolarizing type of neuromuscular blockade. From the results in Table 3 it is clear that those compounds with substituents only in either position 1 or position 2 of the pyrimidine ring were depolarizing blockers while those with substituents in both positions were non-depolarizing blockers.

There is another difference between the mono- and the di-substituted compounds. The toxicities of the latter were unchanged by pretreatment of the animals with SKF 525A, while the toxicities of the former increased after this pretreatment, suggesting that the metabolic processes concerned with detoxication were blocked by SKF 525A. One compound, No. 13, was an exception to this general rule in that its toxicity was unchanged following pretreatment with SKF 525A despite the fact that it was substituted only in position 1. It is probably relevant that the 1-substituent in this case was a phenoxyethyl group which can reasonably be assumed to take up a position whereby hydrogen bonding can occur between the ether oxygen and the hydrogen atom in the 2-position of the tetrahydropyrimidine to form a 6-membered ring system (VII) which can be considered to be a disubstituted tetrahydropyrimidine.



(VII)

There is no evidence at present to account for these differences in pharmacological activity and in metabolism between the mono- and di-substituted compounds.

There was also the suggestion of one more difference between mono- and di-substituted compounds. Of the five compounds examined in the rabbit preparation, the three monosubstituted ones produced a burst of asynchronous firing of the phrenic nerve, while the two disubstituted ones did not. The asynchronous discharge appeared to result from a central action, since the quaternary ammonium salt examined, which presumably did not penetrate into the central nervous system, had no such effect. Nicotine also produced this effect but it also altered the respiratory pattern.

The present results do not seem to be at variance with the suggestion made by Barrass *et al.* (1968) that for activity at the neuromuscular junction, interaction with two receptor sites separated by about 4 Å is necessary. In the compound (No. 3) with the highest nicotine-like activity at the neuromuscular junction and, incidentally, bearing the closest structural resemblance to nicotine, the aromatic nucleus and the amidino residue in the pyrimidine ring are presumably involved in this interaction. It is also of interest in this context that the unsubstituted tetrahydropyrimidine (No. 1), which would be capable of interaction with only one of the postulated receptor sites, was relatively weak as a nicotinic agent.

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