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A Study of the Nicotinic Action of 3-Phenyltropane and Related Compounds

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Introduction

For several years our laboratories have been actively interested in the chemical and pharmacological properties of tropine and its derivatives. This has involved the determination of the conformation of tropine and some related compounds[1,2] and the effect of configuration and conformation of tropine on the potency of pharmacologically active derivatives.[3-5] Recently, one of us has synthesized 3β-phenyltropane and the corresponding α-isomer, compounds with nicotinic properties which are quite marked in the case of the former. This communication describes the synthesis and gives the results of a pharmacological investigation of the structure–activity relationships involved.

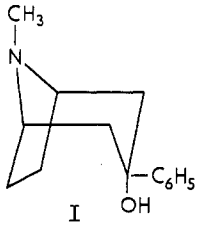
Chemistry

The two isomeric 3-phenyltropanes were prepared from a common starting material, 3β-phenyltropine (I).[6] Bonner *et al.*[7] suggested that the Raney nickel catalysed dehydroxylation of atrolactic acid, a tertiary benzylic alcohol, to 2-phenylpropionic acid proceeded with practically complete retention of configuration. It was expected that the analogously constituted benzylic alcohol (I) would dehydroxylate in the same way. The compound obtained from the reaction of (I) with Raney nickel was a liquid which furnished a crystalline hydrochloride, m.p. 207–209°. The base was formulated as (II).

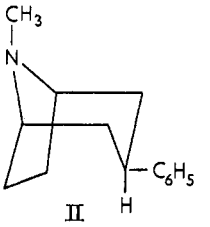
Zirkle *et al.*[8] reported that methyl Δ^2-tropidene-3-carboxylate gave methyl tropane-3α-carboxylate on catalytic hydrogenation. Addition of hydrogen occurred in the 'exo' sense as with tropinone.[9] 3-Phenyltropidene on catalytic hydrogenation afforded

a crystalline base, the hydrochloride of which depressed the melting point of the corresponding salt of (II). These substances were therefore clearly different and if hydrogenation occurred by 'exo' addition as expected, then the product is 3α-phenyltropane (IV).

It has been demonstrated that certain 3α-phenyltropanes such as (V) and (VI) exist in the boat form,[10] as evidenced by nitrogen–carbonyl interaction in (V) and carbinolamine formation in (VI).



I



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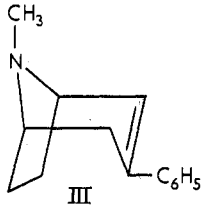
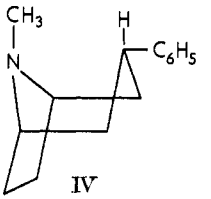
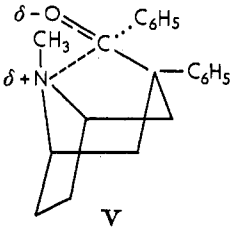


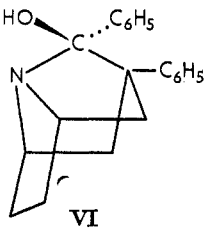
III



IV



V



VI

It was suggested that the non-bonded interactions of the phenyl group and the ethylene-bridge carbon atoms in the chair form were severe enough to force the tropine ring system to adopt the boat conformation. This phenomenon was not noted in the piperidine series. It is probable that these same non-bonded interactions would force 3α-phenyltropane to adopt the boat form as in (IV).

Experimental

3β-Phenyltropane hydrochloride (*II*). Moist Raney nickel catalyst (90 g) was covered with ethanol (125 ml) and 3-phenyltropine (6·0 g) was added to the suspension. After four hours of reflux the mixture was filtered and the metal was washed with fresh alcohol. The combined filtrates were concentrated and the residue was distilled to give an oil (4·2 g.), b.p. 92–94°/0·2 mm.

A portion of the oil was converted to the hydrochloride in ether with alcoholic hydrogen chloride. The crystalline solid was filtered and recrystallized from acetone. The white prisms melted at 207–209°, after drying *in vacuo* for 16 h at 100°.

Anal. Calcd. for $C_{14}H_{19}N \cdot HCl$: C, 70·70; H, 8·49; N, 5·89. Found: C, 70·72; H, 8·13; N, 6·00.

3α-Phenyltropane hydrochloride (*IV*). A solution of 3-phenyltropidene (32·7 g) in ethanol was hydrogenated at 50° in the presence of Raney nickel catalyst at 1000 lb/in^2 pressure. After half an hour the mixture was covered and filtered. The filtrate was concentrated to dryness leaving a residue which was distilled. An oil, b.p. 128–131°/2·0 mm was obtained, which solidified; m.p. 55–57° after crystallization from hexane.

A portion of the base furnished a *hydrochloride* which melted at 217–219° after recrystallization from 2-propanol. When mixed with the hydrochloride of (II) the melt was clear at 195°.

Anal. Calcd. for $C_{14}H_{19}N \cdot HCl$: C, 70·70; H, 8·49; N, 5·89. Found: C, 70·90; H, 8·47; N, 5·91.

Pharmacology

Methods

Dogs were anaesthetized by the intravenous administration of thiopental sodium (15 mg/kg) followed immediately by barbital sodium (250 mg/kg). One common carotid artery was cannulated for the recording of blood pressure and the trachea cannulated and arranged for the recording of respiration. All injections were made into the exposed femoral vein. The resultant blood pressure responses to the injected drugs are shown in Tables I and II. Inasmuch as the results obtained are only approximate values,

Table I. Effect on blood pressure in dogs and acute toxicity in mice of several tropine derivatives

	Compound	Salt	Blood pressure effect after i.v. injection			Acute toxicity—mouse i.v. $LD_{50} \pm$ S.E. mg/kg (base)[b]
			dose mg/kg	effect	intensity[a]	
1	3β-Phenyltropane	HCl	0·08–0·16	pressor	+++	0·77±0·06
2	3β-Phenyltropane	CH_3I	0·10–0·15	pressor	++, +++	3·17±0·23
3	3α-Phenyltropane	HCl	0·30–0·60	pressor	++	4·9 ±0·5
4	3α-Phenyltropane	CH_3I	>1·00	inactive		7·14±0·8
6	3-Phenyltropine acetate	HCl	1·6	inactive		35·8 ±1·8
7	Methyl 3α-phenyltropane-3β-carboxylate	HCl	0·8 –1·6	pressor	++	
8	β-Tropine	HCl	1·6	pressor	++	164±8
9	α-Tropine	HCl	1·6	depressor	++	270±18
10	α-Tropine	CH_3I	1·6	depressor	+++	
11	Nicotine	$2C_4H_6O_6$	0·08–0·16	pressor	+++	0·53±0·05
12	Nicotine	CH_3I	0·08–0·16	pressor	+++	0·58±0·02

[a] Pressor responses have been graded as follows: 10–20 mm Hg (+), 20–40 (++), 40–60 (+++).
[b] The 'base' of the quaternary salt has been computed as the molecular weight minus the weight of the halogen atom.

Table II. Effect on blood pressure in dogs and acute toxicity in mice of derivatives of 1-methylpiperidine

	Compound	Salt	Blood pressure effect after i.v. injection			Acute toxicity—mouse i.v. $LD_{50} \pm$ S.E. mg/kg (base)[b]
			dose mg/kg	effect	intensity[a]	
13	1-Methylpiperidine	HCl	1·6	none		131 ± 8
14		CH_3I	0·8 –1·6	pressor	+ + +	13·5 ± 0·6
15		C_2H_5I	1·0 –5·0	depressor	+ +	35 ± 2
16	1-Methyl-4-piperidyl-methanol	CH_3I	0·25–1·0	depressor	+	7 ± 0·5
17	1-Methyl-4-phenyl-piperidine	HCl	1·0 –2·0	pressor	+, + + +	15·8 ± 6·6
18		CH_3I	0·01–0·02	pressor	+ + +	0·8 ± 0·07
19	4-Hydroxymethyl-1-methyl-4-phenyl-piperidine	base	1·6	inactive		143 ± 7
20	1-Methyl-4-piperidyl-methyl acetate	CH_3I	0·01–0·1	depressor	+ + +	6·7 ± 0·2

[a] Pressor responses have been graded as follows: 10–20 mm Hg (+), 20–40 (+ +), 40–60 (+ + +).
[b] The 'base' of the quaternary salt has been computed as the molecular weight minus the weight of the halogen atom.

changes in blood pressure, either a rise or fall, are expressed as + (10–20 mm Hg), + + (20–40 mm) and + + + (40–60 mm or more). At least three animals were used for each determination and in the case of the most active compounds as many as 14–17 experiments were performed. In some instances, an adrenolytic agent, piperidinomethylbenzodioxane (F 933), was administered intravenously to cause complete blockade or reversal of the pressor action of epinephrine, followed by a second series of injections of the nicotinic agents.

Cats were anaesthetized with pentobarbital sodium (35 mg/kg) administered intraperitoneally and arranged for kymographic recording, as described above for the dog. In some experiments, the abdominal cavity was opened and the uterus arranged for the recording of motility. After obtaining responses to the nicotinic compounds, the adrenal glands were removed and the nicotinic compounds again injected.

In a few experiments, the nictitating membrane of the cat was arranged for kymographic recording and the carotid artery on the same side cannulated for direct injection without the interruption of blood flow during subsequent experimentation. The test drugs were injected into the carotid stream and the nictitating membrane and blood pressure responses compared with those following intravenous injection.

Acute intravenous toxicity was determined in albino mice. The dose that killed 50 per cent (LD_{50}) of the mice at 24 h was determined in the usual manner. Ten mice were used at each dose level and three or more dose levels were used in each determination, the doses being graded at 0·1 log intervals. The values computed are expressed as the $LD_{50} \pm$ S.E. in mg/kg.

Results

The intravenous injection of 3β-phenyltropane hydrochloride (II·HCl) in dogs produced a nicotine-like increase in mean arterial blood pressure along with respiratory stimulation. This action is not increased by quaternization. The corresponding 3α-phenyltropane hydrochloride (IV·HCl) is distinctly less potent and again quaternization does not increase this action (Table I). The administration of an adrenolytic (F 933), in doses that cause

reversal of epinephrine, reduces the pressor action of small doses (40–80 μg/kg) and converts the pressor response of larger doses (80–160 μg/kg) into a depressor response (Fig. 1). Similar reversals of the pressor action of nicotine ditartrate were obtained at these dose levels.

Similar results have been obtained in the anaesthetized cat. The intravenous administration of II·HCl caused a marked increase in mean carotid blood pressure at doses of 20–40 μg/kg. This action is diminished or abolished by a ganglionic blocking agent, Win 12,512 [3-(2-diethylaminoethylamino)-8-(2-chlorobenzyl)nortropane bismethiodide]. The nictitating membrane responses to the ipsilateral carotid injection of II·HCl and IV·HCl were compared. The II·HCl is 10–20 times more potent than IV·HCl. Doses initiating the response were ineffective when administered intravenously. These small doses (0·4–1·0 μg/kg and 5–20 μg/kg respectively) were probably below the threshold for adrenal medullary stimulation. In some experiments, responses of the uterus were recorded simultaneously. Pressor doses of II·HCl caused a prompt relaxation of the uterus. Bilateral adrenalectomy reduced the pressor action and abolished the uterine response.

The above data establish that 3β-phenyltropane has a nicotine-like action which is of the same order of potency as that of nicotine. A comparison of the pharmacological action of this compound with its geometric isomer indicates that there is a preferred configuration. The pressor potency of 3α-phenyltropane is distinctly less than that of the β-isomer (approximately one-fifth). Similar activity ratios have been found for pressor action in the anaesthetized cat. Quaternization, to form the methohalide salt, did not increase pressor action of the β-isomer and in the case of the α-isomer there was a reduction in activity.

A comparison of the acute intravenous toxicity in mice has been made (Table I). The most toxic tropane (i.e., the β-isomer) is also the most pressor. Quaternization caused a distinct reduction in this toxicity. The β-isomer is 6·4 times more toxic than the corresponding α-isomer which in turn is more toxic on a molar basis than the α-isomer methiodide. Death from the β-isomer hydrochloride salt was preceded by convulsions and there was no significant difference between the convulsant and lethal

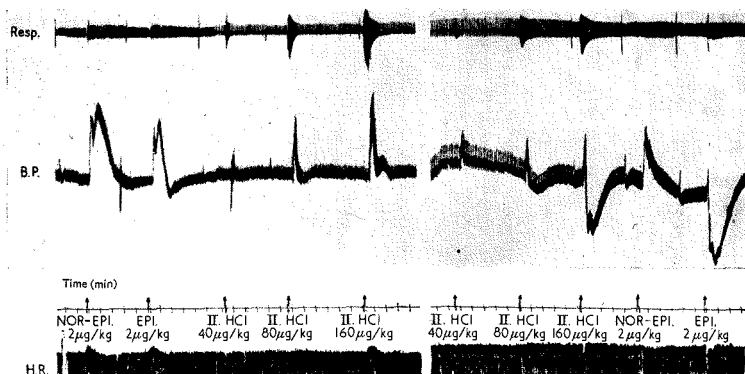


Fig. 1. A comparison of the pressor action of 3β-phenyltropane HCl (II·HCl) and 3α-phenyltropane (IV·HCl) on respiration, blood pressure and heart rate in the anaesthetized dog following intravenous administration. Between the first and second segments of the kymogram, F 933 (2·0 mg/kg, i.v.) was administered. Respiratory changes were recorded by a membrane manometer directly from the tracheal cannula; carotid blood pressure was recorded by a conventional mercury manometer equipped for ink writing; the heart rate was recorded from the carotid artery–mercury manometer line with the pulse recorder devised by Grumbach [*Arch. int. pharmacodyn.*, **109**, 280 (1957)].

doses. Some excitement and respiratory stimulation were noted among survivors receiving both II·HCl and IV·HCl. The corresponding quaternary salts caused convulsions, but these were preceded by respiratory paralysis and may have been caused by asphyxia.

Structure–Activity Considerations

The preceding section has described the nicotine-like action of 3β-phenyltropane. The structural requirements for this action show a high degree of specificity; the α-configuration is clearly less favourable than the β-isomer. Removal of the benzene ring greatly reduces both pressor action and toxicity, the α-isomer now actually causing a reduction in blood pressure at a dose of 1·6 mg/kg. The presence of a second substituent in the 3-position (No. 7, Table I) reduces potency.

Reduction of the ring structure to the corresponding 1-methyl-4-phenylpiperidine results in a compound with weak pressor action and comparatively low toxicity (No. 17, Table II). The methiodide quaternary salt of this base is a potent pressor (nicotine-like) agent with an activity about 8 times greater than that of 3β-phenyltropane HCl. Quaternization also increases toxicity, but this increase is relatively less than expected from the increase in nicotine-stimulating action. The presence of a benzene ring in a position corresponding to that in the tropines (II and IV) is important for the action described. No pressor response was obtained with 1-methylpiperidine HCl at doses up to 1·6 mg/kg. The methiodide salt is pressor but requires doses of 0·8–1·6 mg/kg to induce an 'assay' rise in blood pressure. Substitution of a hydroxymethyl group on the carbon bearing the phenyl group (No. 19, Table II) does not favour pressor action and this is also noted in the case of the smaller methanol derivative (No. 16, Table II). The acetate of this compound is a depressor and this action probably is cholinomimetic inasmuch as it is blocked by atropine.

We have included in this series, for purposes of comparison, 1-methylpiperidine ethiodide (No. 15, Table II). This compound is a depressor at doses up to 5·0 mg/kg and causes ganglionic blocking.

The acute toxicities reflect, in a general way, the nicotinic activity as measured by blood pressure changes. The most potent nicotine-like stimulating compounds are also most toxic. As with the tropines, the cause of death appears to be related to nicotine-like stimulation.

Discussion

A comparison of the actions of various synthetic compounds at 'muscarine-sensitive' sites, at the neuromyal junction and on sympathetic ganglia (and adrenal gland) discloses specific structural requirements for optimal activity at each site.[11, 12] In general, optimum nicotine-stimulating action with monoquaternary compounds requires somewhat greater chain length in one of the N-substituents than that which characterizes the optimum structure for stimulation at the muscarine-sensitive sites or at the neuromyal junction. Thus, *n*-butyryl- and isobutyrylcholine increase blood pressure in the spinal cat more than do acetyl- and propionylcholine. Similarly, Winbury *et al.*[13] have noted that the ganglionic stimulating action of imidazolepropionylcholine is about five times greater than imidazoleacetylcholine. At the same time, such change usually causes a reduction in the stimulating action on skeletal muscle. Thus, 3-(ethylmercapto)propyltrimethylammonium iodide and 3-dimethylammoniumpropylisopropyl sulphide methiodide have more effect on blood pressure and are less effective at the neuromyal junction and at muscarine-sensitive sites than the shorter 3-(methylmercapto)propyltrimethylammonium iodide.[11]

The inclusion of a terminal benzene ring favours ganglionic stimulation and potencies equal to or exceeding that of nicotine have been obtained with *p*-aminophenethyltrimethylammonium[14] and phenoxyethyltrimethylammonium[12] salts, the latter compound being about 10 times more pressor (cat) than nicotine. A potency equal to the latter was observed in the present series of experiments with 1-methyl-4-phenylpiperidine methiodide. The related 1,1-dimethyl-4-phenylpiperazinium iodide is somewhat less potent.[15]

Construction and measurement of the molecular model of nicotine indicates a length less than the optimum, as given above

(5·5 Å *vs.* 9·0 Å approx.) for activity. An additional important difference is noted in the effect of methohalide quaternization. This does not increase the pressor activity of nicotine and the phenyltropines studied in this investigation as is usually found for the phenylalkylamines (*op. cit.*). Our results, obtained with 3β-phenyltropane, resemble nicotine in these respects, suggesting that both compounds may be acting on the same receptor mechanisms. The conformation represented by the β-isomer can thus be pictured as providing a better fit to the receptor than does that found in the α-isomer. Our results with 1-methyl-4-phenylpiperidine differ from the above in that quaternization is again important for high potency. Possibly there is more than a single receptor system providing for ganglion-adrenal medullary stimulation. The present results suggest either that this is the case with two optimum molecular lengths or that length is not critical within an over-all N-to-terminal-carbon distance of about 5–9 Å.

Summary. Some of the pharmacological actions of 3-phenyltropane hydrochloride have been determined. The β-isomer is nicotine-like and of a potency comparable to that of nicotine base. The structural requirements for this action are quite specific. The α-isomer is much less potent. Methohalide quaternization did not increase and the presence of a second substituent in the 3-position reduced activity. Removal of the phenyl ring from the 3-position greatly reduced or abolished nicotine-like actions. Reduction of the ring structure of tropine to 1-methyl-4-phenylpiperidine provided a weakly nicotinic compound. However, quaternization to the corresponding methiodide salt led to a 100-fold increase in potency. Removal of the phenyl ring, as above, reduced or abolished this characteristic action. Other modifications of structure represented by 4-hydroxymethyl-1-methyl-4-phenylpiperidine, 1-methyl-4-phenylpiperidylmethanol methiodide and 1-methyl-4-piperidylmethyl acetate methiodide did not favour nicotinic action.

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