REVIEW ARTICLE

THE PHARMACOLOGY OF TROPANE COMPOUNDS IN RELATION TO THEIR STERIC STRUCTURE*

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ATROPINE, hyoscine and cocaine are the best know naturally occurring tropane alkaloids. The first two are active inhibitors of structures innervated by postganglionic cholinergic nerves: cocaine, in suitable concentrations, prevents conduction in all nerves. Because of this specific biological activity, their pharmacological properties and those of several other tropane alkaloids, and also their degradation and synthetic products, were investigated.

Research over the last thirty years in the field of atropine-like structures has led to the discovery of many synthetic parasympathetic blocking agents. With the knowledge of the structure of cocaine originated the wide search for new local anaesthetic compounds.

The naturally occurring tropane compounds are tropine esters which act both centrally and peripherally. Atropine stimulates some areas in the brain and blocks the action of muscarine-like parasympathomimetic drugs and most postganglionic cholinergic nerve end-organs. Hyoscine is unlike atropine in its central actions because it is usually depressant, and in its more widespread central action, for example on cortical and subcortical areas. But it is like atropine in its peripheral actions. Cocaine causes intense central nervous stimulation and a blockade of conduction in nerve, at synapses and at neuromuscular junctions.

The aim of this work is to survey the compounds of tropane and related structures, collecting and collating the available data relating chemical structure and pharmacological action. Much valuable information has been derived from the study of the stereostructure of the tropane alkaloids.

CHEMISTRY AND NOMENCLATURE OF TROPANE COMPOUNDS

The basic skeleton of the tropane alkaloids is the ring system tropane (I) which is an *N*-methylated 8-aza-bicyclo-3:2:1-octane. Pharmacologically the oxyderivatives of tropane have most significance: these are tropine and ψ-tropine, 6-oxytropine, 6:7-dioxytropine or teloidine, 6:7-epoxytropine or scopine and ecgonine.

Stereostructure of Tropine and ψ-Tropine

Tropine and ψ-tropine are chemically 3-oxytropanes. The two compounds are isomers[1]. They differ in the position of the OH group in relation to the nitrogen, tropine being the *trans* form (II) and ψ-tropine the *cis* form (III).

* Dedicated to Professor B. Issekutz on his 70th birthday.

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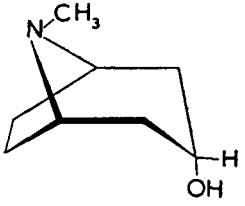
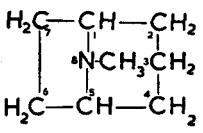
The steric position of the OH group was first determined by Fodor and Nador[2] and independently by Nickon and Fieser[3]. Fodor and Nador found that in the case of *N*-acetyl- or *N*-benzoyl-nor ψ-tropine the N → O or O → N directed acyl migration can be effected by H^+ and OH^- ions respectively. On the other hand this reaction does not succeed with *N*-acetyl or *N*-benzoyl-nor-tropine. From this it follows that in ψ-tropine



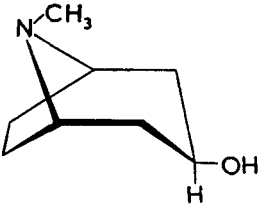
(II)

Tropine
(*trans*)



(I)

Tropane



(III)

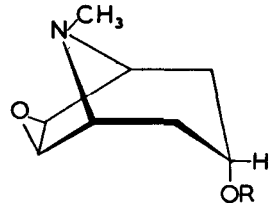
ψ-Tropine
(*cis*)

the OH group and the nitrogen are in spatial proximity, that is, in the *cis* position; with tropine the OH is distal to the nitrogen and *trans*. For these reasons the authors assigned formula II to tropine and III to ψ-tropine. A proof of the validity of these proposed formulae was given by Hardegger and Ott[4] who prepared a ring oxamine ψ-tropine derivative. The structures of tropine and ψ-tropine have since been established by the physical and chemical measurements of others[5,6]. By analogy with the nomenclature of steroids, tropine is 3α-tropanol or 3α-oxytropane, and ψ-tropine is 3β-tropanol or 3β-oxytropane. Here, α assigns a *trans* configuration of the grouping to the nitrogen and β a *cis* configuration.

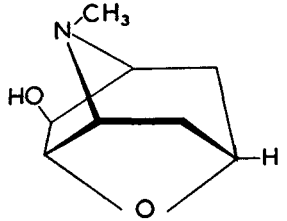
It follows that in atropine, hyoscyamine, convolvamine, poroidine and *iso*poroidine, all of which on hydrolysis yield tropine, and also in convolvine which yields nor-tropine, the esterified OH group of the tropane ring is *trans* to the nitrogen. In tropacocaine and tigloidine, which on hydrolysis yield ψ-tropine, the esterified OH group occupies the *cis*-position in relation to the nitrogen.

Stereostructure of Hyoscine (Scopolamine)

Hyoscine is the (−)-tropic acid ester of scopine, the latter being a 3-oxytropane which contains an epoxy ring (IV). The observation that scopine can easily be transformed into the ring structure scopoline (V)



(IV)



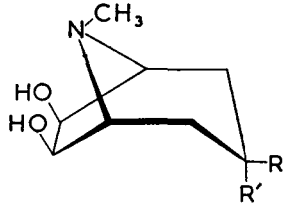
(V)

(R = H = scopine : R = $COCH{\cdot}(CH_2OH)C_6H_5$ = hyoscine)

proves the *trans*-position of the 3-oxy group to the nitrogen. This reaction can take place with the epimeric ψ-scopine only with difficulty. On the basis of this and further investigations made by Fodor and colleagues[7–10], which showed the epoxy group to be in the β-position, hyoscine is 6:7β-epoxy-3α-tropyloxytropane and its stereostructure is represented by (IV).

Teloidine (3:6:7-*trioxytropane*) *and its* 3-*Tiglic Acid Ester Meteloidine*

The stereochemistry of teloidine may be elucidated using the following arguments. Teloidine can be prepared according to the classic synthesis of Robinson starting from *meso* tartaric acid-dialdehyde. This synthesis proves that the two OH groups at C(6) and C(7) are in *cis*-position to each other. This was first demonstrated by Schöpf[11], but the position of these OH groups to the nitrogen was still questionable, as there were four possible steric structures of teloidine (VI*a* and *b*; VII*a* and *b*). Fodor[9] determined the steric position of the 6:7-dihydroxy groups to the nitrogen, and Heusner[12] and Sheehan and Bissel[13] ascertained the configuration of the OH group on C(3) to the nitrogen. Correlation of this data showed the correct stereostructure of teloidine to be represented by formula VI*a*, where the 6:7-OH groups are in *cis*-position to each other and in the *cis*-position to the nitrogen. Therefore teloidine is 3α:6β:7β-trioxytropane.



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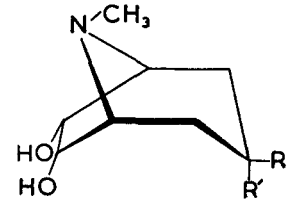
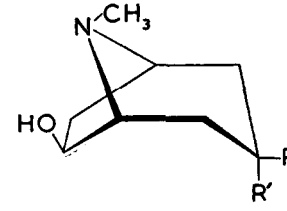


(VII)

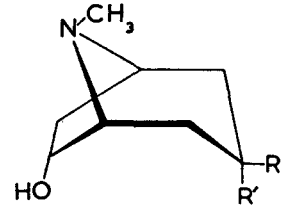
(*a*, R = H, R′ = OH: *b*, R = OH, R′ = H)

6-*Oxytropine and* 6-*Oxy-*ψ-*tropine*

Naturally occurring valeroidine is the *iso*valerianic acid ester of the 6-oxytropine. Its stereostructure was ascertained by Stoll and colleagues[14]. Stereochemically four different structures may be supposed (VIII*a* and *b*; IX*a* and *b*). Two of the formulae are sterically similar to



(VIII)



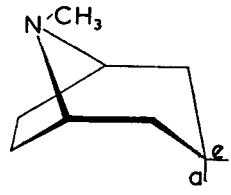
(IX)

(*a* R = H, R′ = OH: *b*, R = OH, R′ = H)

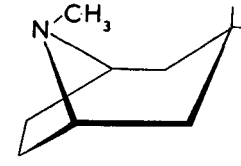
tropine and two to ψ-tropine in the relation of OH groups on C(3), while the position of the OH group at C(6) may be *cis* or *trans* to the nitrogen. The steric position of both of these OH groups was determined by Martin, Mitchell and Tranter[15,16]. According to these authors and latterly Fodor and colleagues[9], who by the results of the catalytic hydrogenation of scopolamine added a further proof to the 6-oxytropine stereostructure, the position of the OH on C(6) is *cis* and that of the OH on C(3) is *trans* to the nitrogen. Therefore the configuration (VIII*a*) was assigned to 6-oxytropine. Thus valeroidine is 3α-valeroyloxy-6β-oxytropane.

The Conformation of the Piperidine Ring in the Tropane Compounds

In the preceding sterostructural formulae the piperidine ring is represented by a "chair" form (X*a*). However, acyl migration experiments which established the steric position of the C(3)–OH group in tropine and ψ-tropine on the one hand, and the development of a cyclic oxazine structure according to Hardegger and Ott[4] in ψ-tropine on the other, can be explained only by the "boat" form (X*b*). The reduction of tropinone to ψ-tropine can be explained on the basis of an assumption of the chair-form, because a reduction with complex metal hydrides, for example lithium aluminium hydride, gives an equatorial OH group relative to the axis of the ring system which has a *cis*-position relative to the nitrogen. Reduction with catalytic agents, however, produces an axial OH group in



(X*a*)
Chair-form

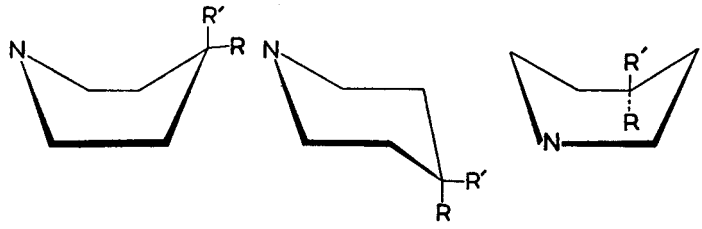


(X*b*)
Boat-form

the *trans*-position. The differences between the rate of saponification of the ester linkages in tropine and ψ-tropine compounds can be explained by a chair-form structure. This contradiction is explicable in that tropane can be thought of as either a piperidine ring strengthened by an ethylene chain, or as a *cyclo*heptane ring which is fixed by an N-CH_3 bridge. In this hypothesis the chair-form of the piperidine structure is also simultaneously the boat-form of the *cyclo*heptane ring. Work to solve the problem is still in progress. The present opinion is that, considerations of dynamic equilibria suggest the chair conformation of the piperidine ring the more frequent and the more probable.

Many difficulties have arisen in solving conformational arrangements in the piperidinium compounds investigated by us[17]. Some experimental data allow the hypothesis that 4-oxypiperidine and its compounds can be characterised by one of the chair-forms or by the *trans* boat-form among the possible six varieties of conformation. (XI*a* and *b*; XII*a* and *b*;

XIII*a* and *b*.) It is important to know the correct steric relations of piperidine compounds to the naturally occurring tropane derivatives. Only with this knowledge is it possible to establish the relation between chemical structure and pharmacological action.



(XI) (XII) (XIII)

(*a*, R = H, R′ = OH: *b*, R = OH, R′ = H)

Steric Configuration about the Tropane Nitrogen

Fodor[9,18] and Findlay[19] independently described quaternary tropine compounds which were pseudoasymmetric about the nitrogen. Findlay did not prove the steric position of the substituents on the nitrogen. According to Fodor[9,18], the *N*-carbethoxymethylscopolaminium iodide prepared from hyoscine with iodoacetic ester, hydrolysed by acid gives the same lactone of *N*-carbethoxymethyl scopoline as that obtained from (±)-scopoline. This indicates that the carbethoxymethyl group is bound to the nitrogen of these compounds from the direction of the endoethylene bridge. The experimental results indicate that in these compounds the *N*–CH_3 group is orientated towards the piperidine ring. Fodor and colleagues[18] stated further that ψ-tropine, with ethyl bromoacetate, yields only a single quaternary ammonium salt. When the sequence of the quaternisation is reversed, by preparing the *N*-carbethoxymethyl-nor-ψ-tropine first and then quaternising with methylbromide, a different *N*-epimeric tropinium salt is obtained. Each of these compounds proved to be uniform but not the same by crystallographic and X-ray studies. The situation is the same with the two quaternary carbethoxymethyl tropinium compounds obtained by two different ways.

The results concerning the *N*–CH_3 group show that the ring system in tropane compounds leads to a strong configurational stability of the methyl group attached to the tertiary nitrogen, and it is orientated towards the piperidine ring. The consequence of this is that in quaternising the tropeines, the second substituent, that is, the quaternary one, is given a determined steric orientation towards the pyrrolidine ring, and whether the two substituents—tertiary and quaternary—can change their position by transvibration and under what circumstances has yet to be elucidated.

Stereochemistry of Cocaine and Related Compounds

The stereostructure of cocaine is more complicated than that of the tropane alkaloids, because cocaine epimers must be considered to belong to one of two different systems. It is known that the acid hydrolysis of

cocaine yields ecgonine. Neglecting stereochemistry, this latter is 3-oxytropane-2-carboxylic acid. Wilstätter[20] stated that oxidation of ecgonine gives tropinone through the β-ketonic acid. Einhorn and Marquardt[21] observed that as a result of treatment with alkali, ecgonine is transformed into (+)-ψ-ecgonine, which proved to be the diastereoisomeric form of the ecgonine. Based on these results Willstätter[22] denoted (+)-ecgonine as (+)-ψ-ecgonine without having proved C(3) epimerism. Recent investigations in organic chemistry have almost completely elucidated the stereochemistry of ecgonine and related compounds. There were two important questions to be solved: (i) the relative steric position of C(3)–OH group to the nitrogen, and (ii) the establishment of the relative position of the functional groups on C(2) and (3) in cocaine.

The configuration of the C(3)–OH group relative to the nitrogen was investigated in ecgonine using methods similar to those for tropine and ψ-tropine derivatives. These are acyl migration, and oxazine formation by *p*-nitrobenzaldehyde. This research led to the conclusion that in both ecgonine and ψ-ecgonine the C(3)–OH group has a *cis*-position to the nitrogen[23–27]. The investigations also dealt with 2-methyl-3-tropanol epimers, prepared from the ecgonines, and showed that ecgonine and ψ-ecgonine are C(2) epimers.

Findlay[25] showed that ecgonine methyl ester reacts with methyl iodide to give a methiodide identical with that obtained from the ψ-ecgonine methyl ester (the positive charge on the nitrogen atom facilitating the epimerisation). It is known that the α-hydrogen of esters of this type is more labile than that of the corresponding acid under alkaline conditions. Ecgonine can be converted to the ψ-isomer in 2 per cent yield with 10 per cent alcoholic potash, but in 39 to 54 per cent yield from the methyl ester (or cocaine) under the same conditions. These results also indicate that ecgonine and ψ-ecgonine are C(2) epimers.

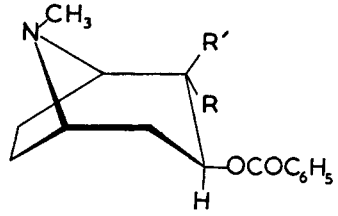
The determination of the relative steric position of the substituents of C(2) and C(3) atoms required much research. Fodor[9,23] showed that acyl migration does not succeed with the *N*-benzoyl derivative of 2-amino-3-tropanol which was prepared from ψ-ecgonine by the Curtius reaction. But 2-benzamido-3-tropanol obtained from ecgonine showed a quantitative and reversible N → O acyl migration.

When studying the chemistry of nor-ecgonine, in preparing *O*-benzoyl-nor-ecgonine Findlay[25] found that inadvertent use of insufficient acid yielded an isomer not previously reported. He confirmed that the new compound was the result of rearrangement to give the *N*-benzoyl nor-ecgonine, proving a *cis* arrangement of the C(3) OH group to the nitrogen.

On the basis of this and other work[28] it can be stated that in ecgonine the C(2) and C(3) groups are in the *cis*-position to each other, while in ψ-ecgonine they are *trans*. Also cocaine and ψ-cocaine differ only in the configuration of the C(2) grouping.

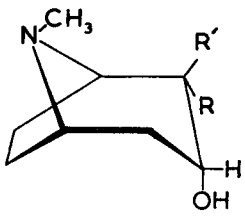
Thus cocaine is 2-β-carbomethoxy-3β-benzoyloxypropane (XIV*a*) and ψ-cocaine is 2α-carbomethoxy-3β-benzoyloxytropane (XIV*b*). In the cocaine group four racemic pairs may exist, two racemates being well

known for a long time, one of them being used clinically as the local anaesthetic psicaine. The third racemate of ecgonine was prepared in a small quantity by Willstätter[29] by the large-scale reduction of 2-carbomethoxytropinone. Its configuration is represented by XV*a*[25]. The fourth racemate was prepared recently by Fodor[30] and has the structure (XV*b*).



(XIV)

(*a*, R = H, R′ = $COOCH_3$:
b, R = $COOCH_3$, R′ = H)



(XV)

(*a*, R = COOH, R′ = H:
b, R = H, R′ = COOH)

Thus most of the structural problems of tropane and related compounds have been successfully resolved in recent years, and the up-to-date nomenclature of tropane compounds expresses these stereochemical features. This nomenclature should be introduced into pharmacology without delay, because of the great importance of the relation of steric structure to activity.

Atropine-like Tropane Compounds

The tropane alkaloids are widely distributed in nature especially in plants of the Solanaceae. Of the alkaloids, atropine [(±)-tropyl-tropine] has been the most studied pharmacologically. Atropine is a racemic mixture of hyoscyamine, the (−)-isomer of which is considerably more active than the (+)-isomer in its peripheral anti-acetylcholine effects; on the central nervous system the isomers are equiactive[31]. (—)-Hyoscine [(−)-tropyl-α-scopine], is much more active than (+)-hyoscine. Its peripheral actions are very like those of atropine but central effects differ in that it has a direct depressant effect on the central nervous system in reducing excitement and fear. The (+)-isomer has a much weaker atropine-like effect but its central depressant activity is similar to that of the (−)-isomer[32,33].

This review will endeavour to describe only the correlation of the most characteristic pharmacological effects and chemical structure, and therefore it will not cover many of the actions which these alkaloids possess. There are several reviews which deal with this aspect[31,34,35].

Groups

The Role of the Acid Ester Groups in the Pharmacological Activity of Tropine Esters (Tropeines)

The high activity of atropine (an ester) and the relative inactivity of its parent amino alcohol, tropine, led to the preparation and investigation of many tropeines in which tropine was esterified by acids other than tropic

acid. The role of the acid ester group in the α-tropine compounds has been summarised by von Oettingen[31]. In general it can be stated that in blocking post-ganglionic parasympathetic effects, tropine esters of oxy-aromatic acids are the most active. But, in view of the diversity of methods used by the authors quoted by von Oettingen in his review, no absolute quantitative comparison of their results can be made.

Tropeines can be divided into three groups of differing atropine-like potency shown in Table I. It seems that the requirement for high activity is an asymmetric carbon atom in the aromatic acids esterifying tropine. The activity can be enhanced by an OH group[31]. Substitution of the oxyaromatic tropic acid in hyoscine by other acids, i.e., acetic, cinnamic, benzoic, greatly diminishes the atropine-like activity[36].

TABLE I

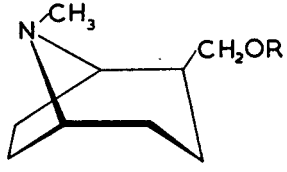
ATROPINE-LIKE ACTIVITY OF TROPEINES RELATED TO ESTER GROUPING

Tropeines without activity	Tropeines with mild activity	Tropeines with a high activity
Glycolyl tropine	Acetyl tropine	(±)-Tropyl tropine
Tartaryl tropine	Lactyl tropine	(−)-Tropyl tropine
Fumaryl tropine	Succinyl tropine	Acetyltropyl tropine
Phthaloyl tropine	Methylparaconyl tropine	(±)-Mandelyl tropine
	α-Phenyl-β-chlorpropionyl tropine	(−)-Mandelyl tropine
	α-Phenyl-β-brompropionyl tropine	*o*-Methylmandelyl tropine
	Atrolactyl tropine	*m*-Methylmandelyl tropine
	Atroglyceryl tropine	*p*-Methylmandelyl tropine
	Atropyl tropine	Fluorenyl tropine[64]
	Hydratropyl tropine	Oxyfluorenyl tropine[64]
	Phenylacetyl tropine	Xanthen 9-carboxyl tropine[86]
	Phenylaminoacetyl tropine	Phenyl-thienyl tropine[63]
	Cinnamyl tropine	Diphenylacetyl tropine[63]
	*iso*Cumarin-carboxyl tropine	
	α-Phenyl-β-hydroxypropionyl tropine	
	α-2-Pyridyl-β-hydroxypropionyl tropine	
	Hippuryl tropine	
	Phenylcarbamyl tropine	
	Dibenzylacetyl tropine	
	Benzylyl-β-tropine	

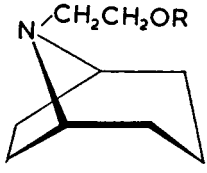
Note: The data without references were collected from the review of von Oettingen.[31].

The Position of the Ester Group on the Tropane Ring System and Activity

von Braun and Müller[37] synthetised various homatropanol esters with general formula XVI (where R = (±)-atropyl, (±)-mandelyl or benzoyl). Wichura[38] found these esters weaker and not identical in their action with 3 α-tropanol esters. Of the compounds of von Braun and Räth[39] (the



(XVI)



(XVII)

esters of *N*-alkyl nor-tropane with general formula XVII where R = acyl), only the tropic acid ester of *N*-oxyethyl-nor-tropane has atropine-like effect[26]. By the application of the principle of heterotopy to these compounds a wide range of investigations developed with compounds of the

general formula R_2N alkyl-COO-aryl, where R_2N is usually a piperidine ring or dialkylamino groups. From these series of substances which do not contain the tropane ring system have come many of the so-called neurotropic spasmolytics.

The Steric Position of Ester Groups attached to the C(3) of Tropane and activity

The pseudoderivative of (−)-hyoscyamine has been mentioned as a mydriatic[40], but the (±)-tropyl and (±)-mandelyl β-tropines[41] do not show any mydriatic activity. Benzoyl β-tropine is a much weaker atropine-like agent than benzoyl α-tropine, and this applies to their alkyl quaternary derivatives also[42,43].

Although the relation of stereostructure of the esterifying group to activity has not yet been investigated systematically, it seems that an aromatic acid ester group on the C(3) of tropane directed in the α-position to the nitrogen is necessary for activity. According to Pfeiffer's theory[44] acetylcholine acts at cholinergic neuro-effector junctions by three functional groups, a "cationic head" ^{+}N–CH_3 group and an ether and a ketone O atom displaced from the ^{+}N–CH_3 group by 5 and 7 Å respectively. Most of the specific and typical antagonists of acetylcholine at the autonomic post-ganglionic receptor site contain both the ^{+}N–CH_3 group and the ether and ketone O atoms again at a distance of 5 and 7 Å. But these antagonists have the active groups protected sterically to give a large umbrella-like molecule by aromatic groups as with tropane and some piperidine compounds, or surrounded by simple aliphatic groups. A ring system around the nitrogen is not essential for atropine-like effect, as can be seen from the commercially available compounds which have alkyl groups attached to the nitrogen and no saturated ring system, for example in methantheline, oxyphenonium or lachesine. With these compounds the steric flexibility of the carbon chain between the functional groups can assure the correct fit on the receptor surfaces, but with tropane compounds, the rigid ring system 3-tropanol and the directed localisation of the ester groups attached to its C(3)–OH group determine the steric position of the functional groups. The difference between the α- and β-position of C(3)–OH group appears to be of importance for atropine-like activity.

The Effect of an Ester Group on Atropine-like Activity

The hydrolysis products (tropine and ψ-tropine) of the naturally occurring tropeines, were mentioned as almost devoid of atropine-like activity[45,46]; in addition, both 3α- and 3β-tropanol have only slight activity at ganglia[17,47]. Thus it may be deduced that this activity also is connected with an ester function.

The Nitrogen of Tropine Esters in Atropine-like Activity

Secondary amine derivatives of tropeines. Demethylation of the nitrogen in atropine and (−)-hyoscyamine to give the secondary amines noratropine and nor-(−)-hyoscyamine reduces the activity about eight times. The latter compound occurs in a natural form in *Scopolia japonica*[31].

Quaternary ammonium derivatives of tropeines. Our recent experience shows that the most pronounced alterations in the pharmacological effects of tropane compounds can be obtained by varying the groupings on the quaternised nitrogen.

Methyl quaternary derivatives of atropine were first investigated as early as 1869 by Crum Brown and Fraser[48]. In 1906 Hildebrand[49] described the curare-like effect of the methyl- and benzyl-quaternaries of atropine. Issekutz[50] dealing with the methyl quaternary derivatives of atropine and homatropine pointed out that, especially in the case of homatropine, quaternisation with a methyl group enhances the vagus-blocking and curare-like capacity and diminishes the central stimulant activity. In 1948 Kimura, Unna and Pfeiffer[51,52] described various bis-quaternary derivatives of atropine. Among these the decamethylene bis-atropinium diiodide was most active, having very pronounced curare-like activity besides a strong atropine-like effect. In 1950 Issekutz and Nador[53] found that the 1:4-xylilene quaternary derivative of atropine, (±)-mandelyl- and benzoyl-tropines are very active curare-like compounds. These have only relatively moderate atropine-like activity[54]. In 1951 Gyermek and Sztanyik drew attention to the ganglion-blocking activity of quaternary tropeines of the atropine group[55]. This was confirmed later by others[56,57]. The following year we prepared several new tropane compounds, with aralkyl quaternary groups, which were the most active ganglion-blocking agents then known. At the same time, Wick[58] independently dealt with the quaternary derivatives of hyoscine and made some new observations on their mode of action. These investigations led to the derivative butyl scopolammonium bromide (buscopan) being used in therapy. Between 1952–54, parallel with the development of sterochemistry of tropane compounds, we made systematic investigations for anticholinergic nerve actions with tropane and related compounds. In 1954, Rothlin and his colleagues[59] made new observations with the 6-alkoxytropine compounds and their quaternary salts prepared by Stoll and Jucker[60]. Recently Archer, Cavallito and Gray[61] and Lape, Fort and Hoppe[62] described asymmetric bis-quaternary compounds of tropane structure. The latter group especially seems to merit attention.

The changes in the pharmacological activity of quaternary tropane derivatives effected by alterations of chemical structure will now be described.

The Methyl Quaternary Group in the Tropine Esters

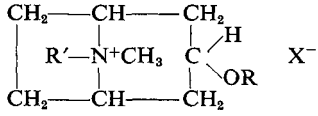
Aliphatic acid esters of tropine such as acetyl and dimethylcarbaminoyl tropines quaternised with methyl halides yield compounds with parasympathomimetic activity. They cause a blood pressure fall and spasm of isolated organs which can be antagonised by atropine. Their effects are 100 to 500 times weaker than those of acetylcholine. These tropine compounds are similar in action to the acetyl ester of 1-methyl piperidine[63]. Thus it is not essential for the parasympathomimetic activity of acetyl and dimethylcarbaminoyl esters of basic alcohols to have CH_3 groups on the nitrogen, which itself can be in a ring system. The "umbrella"-like

structure of the tropine compounds only decreases and does not abolish the parasympathomimetic activity. For atropine-like activity it is unnecessary for the nitrogen-containing basic esters to have a ring structure. Neither parasympathomimetic nor atropine-like activity in the basic ester type of compounds appears to be dependent upon a rigid saturated ring system around the terminal nitrogen.

A summary of the changes which can be observed with the methyl quaternisation of aromatic acid tropine esters can be seen in Table II.

TABLE II

THE EFFECT OF METHYL QUATERNARY GROUPS ON THE ESTERS WITH ATROPINE-LIKE PROPERTIES



R	R′	X	Atropine-like activity Atropine = 1*	Ganglion-blocking activity Tetraethyl-ammonium bromide = 1†	Curare-like activity Tubocurarine = 1‡
C_6H_5–CO–	H	HCl	0·006	0·1	—
,,	CH_3	Br	0·04	2·0	0·10
C_6H_5–CH(OH)–CO–	H	HCl	0·08	0·35	—
,,	CH_3	Br	0·3	4·5	0·07
C_6H_5–CH(CH_2OH)–CO–	H	H_2SO_4	1·0	0·35	—
,,	CH_3	Br	1·0	4·0	0·15
$(C_6H_5)_2$–CH–CO–	H	HCl	0·06	—	—
,,	CH_3	I	0·08	5·3	0·05
C_6H_5–CH(2-thienyl)–CO–	H	HCl	0·2[43]	—	—
,,	CH_3	Br	0·5	—	—

* Isolated rabbit and rat gut; † cat nictitating membrane; ‡ frogs.

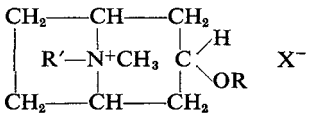
The methyl quaternisation, besides introducing curare-like activity, enhances atropine-like and especially ganglion-blocking activity. This alteration in atropine-like activity is general, not only with the compounds having a tropane ring but also with 6-methoxytropine compounds[59] and with hyoscine[35]. An increase in this activity can be induced by the methyl quaternisation of compounds containing a piperidine ring, or *N*-aliphatic groups[64]. Quaternisation of tropine esters by aralkyl groups gives compounds with very different actions: atropine-like activity diminishes, ganglion-blocking activity increases, and the curare-like effect alters (Table III).

Quaternisation with the groups of the general formula X_1–Ar–CH_2–X (where X_1 = a halogen or phenyl group, Ar = aryl group and X =

halogen group) containing the halogen or phenyl group in the *para* position, yields active ganglion-blocking compounds. Among the quaternary compounds containing condensed rings the most active were those that were coaxially condensed.

TABLE III

THE PHARMACOLOGICAL PROPERTIES OF SOME ARALKYL QUATERNARY TROPEINES



R	R′	X	Atropine-like activity Atropine = 1*	Ganglion-blocking activity Tetraethyl-ammonium bromide = 1†	Curare-like activity Tubocurarine = 1‡
C_6H_5–CO–	C_6H_5–CH_2–	Br	0·004	3·0	0·10
,,	*p*BrC_6H_5–CH_2–	Br	0·003	8·2	0·17
p$NH_2C_6H_5$–CO–	C_6H_5–CH_2–	Br	0·005	8·0	0·20
,,	*p*ClC_6H_5–CH_2–	Br	0·0025	22·0	0·40
C_6H_5–CH(OH)–	C_6H_5–CH_2–	Br	0·005	3·0	0·10
,,	*o*BrC_6H_5–CH_2–	Br	0·015	4·1	0·17
,,	*m*BrC_6H_5–CH_2–	Br	0·025	6·8	0·20
,,	*p*BrC_6H_5–CH_2–	Br	0·015	19·0	0·12
,,	C_6H_5–C_6H_5–CH_2–	Br	0·015	40·0	0·12
C_6H_5–CH(CH_2OH)–	C_6H_5–CH_2–	Br	0·10	2·1	0·18
,,	*p*BrC_6H_5–CH_2–	Br	0·07	8·5	0·17
,,	C_6H_5–C_6H_5–CH_2–	Br	0·15	28·0	0·10

* Isolated rabbit and rat gut; † cat nictitating membrane; ‡ frogs.

Between 1951 and 1955 we determined the relation between the structure and effect of more than 50 mono-quaternary tropine ester compounds[17,65], and found that the various anti-acetylcholine activities changed quite independently of each other and of the type of quaternisation. We observed that several parasympathetic blocking tropine esters could be changed into selectively acting ganglion-blocking or curare-like compounds.

Some examples of ganglion-blocking selectivity can be seen in Table IV.

p-*Diphenylmethyl Quaternary Groups*

All the compounds investigated containing benzyl quaternary groups with or without halogen and alkyl substituents show only blocking activity on autonomic ganglia. Some *p*-diphenylmethyl quaternary derivatives of benzoyl and *p*-aminobenzoyl-tropine and ψ-tropine,

however, have ganglion-stimulating effects too. The diphenylmethyl quaternary derivative of *p*-aminobenzoyl α-tropinium bromide is so effective that its stimulant activity exceeds that of nicotine by about 50 times. It has the highest ganglion-stimulating activity hitherto known. The tropane skeleton is only partly responsible for this activity. The *p*-amino group on the benzoic acid ester seems to be of importance[66].

TABLE IV

GANGLION-BLOCKING SELECTIVITY

Compounds	Ratio of Ganglionic blocking activity† to	
	Curare-like action‡	Atropine-like action*
p-Chlorbenzyl(*p*-aminobenzoyl) α-tropinium bromide ..	55	8,800
p-Brombenzyl[(±)-mandelyl]-α-tropinium bromide ..	160	1,250
p-Diphenylmethyl[(±)-mandelyl] α-tropinium bromide ..	235	2,700
p-Diphenylmethyl[(±)-tropyl] α-tropinium bromide ..	168	280
p-Brombenzyl[(±)-tropyl] α-tropinium bromide	50	57
Tubocurarine	3	—
Atropine	—	0·3
Tetraethylammonium bromide	15	—

* Isolated rabbit gut; † cat nictitating membrane; ‡ frogs.

The changes effected in the structure of the mono-quaternary tropeines have produced the most active ganglion-blocking and stimulating compounds known until 1954, and the results suggest the use of these compounds as starting materials for further research.

Quaternary Compounds of Hyoscine

With atropine and homatropine, the higher alkyl quaternary derivatives proved to be weaker atropine-like and ganglion-blocking agents than the methyl quaternary derivatives[65]. Contrary to this, the butyl quaternary compound of hyoscine is a highly active ganglion-blocking agent[58]. Its atropine-like side effects, mydriasis and tachycardia, are weak, and it is used clinically. The successful experiments with *p*-diphenylmethyl quaternary derivatives of atropine[67] and hyoscine[68] show that these tropeines are more potent than butyl scopolammonium bromide and they advantageously unite important and therapeutically useful pharmacological effects. The atropine derivative was clinically tested and proved to be therapeutically active[69].

In our opinion, the specific quaternary group attached to the tropane nitrogen of hyoscine is more important for activity than the epoxy group[68,70]. We have observed several instances in which the epoxy group decreases ganglion-blocking activity. This effect is shown in Table V.

Rothlin and his colleagues[59] reporting the activity of the compounds of 6-alkoxytropine esters described by Stoll and Jucker[60] stated that some of these have favourable pharmacological properties. Therapeutically useful hyoscine and butyl scopolammonium bromide-like compounds were sought. Although some of the 6-methoxytropine compounds have a marked atropine-like activity they do not show the central actions characteristic of hyoscine. Apparently the (−)-tropic acid ester of

6-methoxytropine was not prepared. This compound would have given valuable information had it shown hyoscine-like central depressant effects.

TABLE V

ATROPINE-LIKE AND GANGLION-BLOCKING ACTIVITY OF SOME ATROPINE AND HYOSCINE QUATERNARY DERIVATIVES*

Compound	Atropine-like activity*	Ganglion-blocking activity†
Atropine sulphate	1·0	0·35
Methyl atropinium bromide	1·5	4·0
Butyl atropinium bromide	0·02	—
p-Diphenylmethyl atropinium bromide	0·1	23·0
Hyoscine hydrobromide	2·0	0·1
Methyl scopolammonium bromide	4·0	0·4
Butyl scopolammonium bromide	0·025	3·0
p-Diphenylmethyl scopolammonium bromide	0·2	10·0
Tetraethylammonium bromide	—	1·0

* Rabbit and rat gut; † cat nictitating membrane.

Bis-quaternary Tropeines

Results of the investigations into the structure of naturally occurring curare alkaloids led to a search for new curare-like derivatives. Many bis-quaternary ammonium compounds were prepared and tested. Because of the competitive nature of tubocurarine for acetylcholine receptors it seemed interesting to produce and investigate bis-quaternary atropine compounds. Kimura, Unna and Pfeiffer[51,52] described the first of such compounds. Two atropine molecules were connected by the OH groups of their tropic acid moieties or by their nitrogen atoms by quaternisation. The most active compound was the 1 : 10-decamethylene-bis-atropinium diiodide, which showed about the same activity as tubocurarine but also had a very pronounced atropine-like effect. The aim of the investigations of Issekutz and Nador with bis-quaternary tropeines[71,72] was to find compounds with practical value. The bis-atropinium, mandelyl, and benzoyl tropinium compounds prepared with 1 : 4-xylylene dibromide showed a high curare-like activity. It was noteworthy, however, that these compounds had only relatively mild atropine-like activity compared with their methyl quaternary compounds[54]. The *cis*-position of the benzoyl ester group and the lack of other ester groups decreases the curare-like effect[71]. However, of the α- and β-forms of the hexamethylene-1 : 6-bis-benzoyltropinium halides, the β-form proved to be the more effective[73].

Many authors consider the chain length between the two nitrogen atoms, the so-called interquaternary distance, as the most important structural requirement for the curare-like activity of the bis-quaternary ammonium compounds; we have found with several bis-quaternary tropeines that the character of the quaternary group is at least as important. In the case of bis-quaternary tropeines prepared by quaternisation with alkyl or aralkyl dihalides, the reaction predetermines the structure of the quaternary ammonium group. Therefore it was decided to prepare bis-quaternary tropeines in which, besides an optimal quaternary

distance, a choice of quaternary groups could be made. The investigations with some succinyl and phthaloyl tropeines resulted in compounds with curare-like effect which were equal to, or more active than, tubocurarine[74]. Also, recently some bis-quaternary belladonnine compounds of Hotovy and colleagues[75] were mentioned as being very active.

There are not yet enough of the bis-quaternary tropane compounds to decide which kind has the optimal characteristic for curare-like action. Because some of them have proved to be very potent curare-like compounds, a comparison of a few derivatives is made in Table VI.

TABLE VI

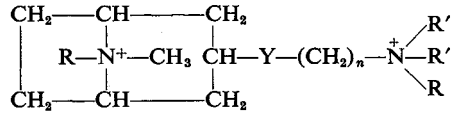
BIS-QUATERNARY TROPANE DERIVATIVES

Compound	Curare-like effect Tubocurarine = 1		Atropine-like activity Atropine = 1*	Ganglion-blocking activity Tetraethyl-ammonium bromide = 1†
	Frogs	Rabbit head drop		
Methyl atropinium bromide	0·05	0·015	1·0	4·0
1:10-Decamethylen-bis-atropinium diiodide ..	0·25	2·5	2·0	—
1:4-Xylylene bis-atropinium dibromide ..	1·5	1·0	0·2	0·4
1:4-Xylylene bis-benzoyl α-tropinium dibromide	1·0	1·5	0·01	0·4
m-Brombenzyl-succinyl α-tropinium dibromide	2·0	2·5	0·02	3·0
1:6-Hexamethylen-bis-benzoyl β-tropinium dibromide	2·0	3·0	0·002	<0·5

* Rabbit and rat gut; † cat nictitating membrane.

Asymmetric Bis-quaternary Ammonium Compounds with the Tropane Ring System

Two series of these compounds are known. The first one can be characterised by the general formula: $(CH_3)_3$–$^+$N–$(CH_2)_3$–$^+$N–R where $^+$N–R = tropane, tropine, tropinone or atropine[61]. The preparation of these compounds was suggested by the observation that various asymmetric bis-quaternary compounds containing –$(CH_2)_3$–chain and hydrated *iso*quinoline and carboline rings proved to be strong and long-lasting vasodepressants. The other group of compounds[62] has the general formula XVIII. Some members of this series show very strong and



(XVIII)

(R′ = Alkyl or aralkyl; R = Alkyl; Y = NH, *N*-alkyl or 0; n = 2 or 3)

long-lasting blocking activity on autonomic ganglia and on vasopressor reflexes. It is interesting to mention that the intensity and duration of action were the greatest with those compounds having an aralkyl group, with halogen substituent (*m*–Cl–benzyl group), on the chain nitrogen. In this respect the compounds are similar to the active mono-quaternary tropane compounds described previously by us[17]. None of these asymmetric compounds with $(CH_2)_n$, where $n = 2$ or 3, have significant curare-like activity in spite of their bis-quaternary character.

The Tropane Ring System and its Stereostructure in Relation to Pharmacological Activity

Changes in structure of tropane derivatives and synthesis of new compounds did not show more effective atropine-like activity than that produced by atropine, hyoscyamine and hyoscine. The many active alkylamine compounds not possessing a tropane ring system on the one hand, and the relative inefficacy of the tropane compounds without ester groups on the other, showed that the tropane ring system is not responsible for the atropine-like activity of the tropane alkaloids.

The role of the tropane skeleton in the synaptic (ganglion-blocking and curare-like) effects remained unsolved even after the preparation of the highly active tropine ester compounds. Knowledge of the stereostructure of the tropane ring system appeared necessary to solve this problem.

In 1951 on the basis of observations on a few quaternary derivatives of tropine we supposed that, in the ganglion-blocking actions, the C(3)–OH group of the tropine compounds depressed activity[53]. The striking difference in the ganglion-blocking activity between some alkyl tropinium salts and the corresponding quaternaries of 2-6-dimethylpiperidines led to a search for correlation of stereostructure and anti-acetylcholine effects in tropane and some piperidine compounds.

The Steric Position of the C(3)–OH Group of the Tropane Skeleton and Activity

As previously mentioned, the C(3)–OH group in tropine may be in a *trans-* (α) or *cis-* (β) position to the ring nitrogen, its configuration determining the steric position of ester groups connected to it.

To study the pharmacological effect of the configuration of the C(3)–OH group, benzoyl-α-tropine (benzoyltropine) and benzoyl-β-tropine (tropacocaine) seemed to be most suitable. Preparation of several quaternary derivatives of these was undertaken, and their atropine-like, and ganglion-blocking, and local anaesthetic effects were assessed.

As the distance of the ketone and ether O atoms in the ester linkage from the nitrogen seems to be an important factor for atropine-like activity[44], it appeared from experiments that the optimum distance is present only in α-tropine and not in the β-tropine esters. Further, the effectiveness of a group of compounds is already determined by the configuration of tropine, and no quaternary group is capable of influencing this in β-tropine compounds, in which the steric structure probably does not permit the O atoms to be at the required distances from the ring nitrogen[42,43]. The configuration of the C(3) grouping of the tropine derivatives does not affect ganglion-blocking activity as the members of the benzoyl β-tropinium series are no less active in this respect than those of the α-tropinium series. Curare-like effect appears to run parallel with ganglion-blocking activity. Because the steric position of the aromatic ester groups on C(3) has no significant influence on these latter two actions it was assumed and later confirmed that the presence of these groups was unnecessary for activity.

The Effect of the C(3)–OH Group of Tropine on Activity

This was investigated using the quaternary derivatives of 3-tropanol (tropine) and tropane series. Parallelism on ganglion-blocking activity is found between the members of both series and the corresponding quaternary derivatives of aromatic acid tropine esters. The correlations obtained can be seen in Table VII, which also shows the depressant effect of C(3)–OH groups on ganglion-blocking activity. The aromatic ester group is not responsible for this effect as the tropane compounds are similar in activity to the esterified compounds. For ganglion-blocking activity in tropane compounds, the nature of the quaternary group appears to be the most important factor.

TABLE VII

THE GANGLION-BLOCKING ACTIVITY OF TROPINE, TROPANE AND TROPINE ESTER COMPOUNDS. CAT NICTITATING MEMBRANE

Tetraethylammonium bromide = 1

Quaternary group	Tropine	Tropane	Mandelyl-α-tropine	Tropyl-α-tropine
Tertiary	0·5	2·0	0·2	0·35
Methyl	1·0	2·4	4·5	4·0
Benzyl	0·8	4·0	3·0	2·1
p-Brombenzyl	2·5	17·0	19·0	8·5
p-Diphenylmethyl ..	6·0	28·0	40·0	28·0

2:6-DIMETHYLPIPERIDINIUM COMPOUNDS

The "opening" of the endoethylene bridge in the tropane ring by substituting two methyl groups not only breaks the chain character but it may also affect the conformation of the ring system. Therefore the 2:6-dimethylpiperidine compounds may serve as only imperfect paper-plane models of the tropane compounds.

Among the 2:6-dimethylpiperidine compounds three kinds of derivatives are known: (i) 2:6-dimethyl-4-acyloxypiperidinium compounds, (ii) 2:6-dimethylpiperidinium compounds[76], (iii) 2:6-dimethylpiperidino-1-(ethan-2-ol) esters[77].

The first compounds were made for comparison with α- and β-tropine esters, and were found to have great similarity in atropine-like activity to the β-tropine esters[17]. From this it may be deduced that an ester grouping on C(4) has a β- rather than an α-configuration assuming the existance of the unproved chair conformation of the piperidine ring. The ganglion-blocking and curare-like effects of the compounds were not comparable to those of the α- and β-tropine esters. This fact shows that the 2:6-dimethylpiperidine ring, which stereochemically is not a rigid ring system as is tropane, under certain circumstances alters its steric form; for example, besides the alternations of the chair and boat conformations the steric orientation of the 2:6-dimethyl groups can change in addition. This view is confirmed by the results with 2:6-(*cis*- and *trans*-)dimethylpiperidinium compounds.

The members of this series were used to answer the following questions: (i) can one replace the endoethylene bridge of tropane compounds by methyl groups in the 2 and 6 position of the piperidine ring?; (ii) has the

possible *cis* and *trans* position of methyl groups in C(2) and C(6) of piperidine a significant role on the synaptic-blocking effects?; (iii) can the change in the order of the substituents (primary and secondary) on the nitrogen alter the pharmacological activity?

Some results of experiments made with 2:6-dimethylpiperidine quaternary derivatives are shown in Table VIII when it can be seen that the

TABLE VIII

GANGLION-BLOCKING ACTIVITY OF 2:6-DIMETHYL(*cis*)*N*-METHYL-PIPERIDINIUM AND TROPINIUM COMPOUNDS. CAT NICTITATING MEMBRANE

Tetraethylammonium bromide = 1

Compound	2:6-Dimethylpiperidine group	Tropane group
Tertiary	2·0	2·0
Methyl quaternary	2·5	2·4
Benzyl quaternary	3·4	4·0
p-Diphenylmethyl quaternary ..	8·0	28·0

cis members of the series have an activity similar to the corresponding members of the tropane series except for the *p*-diphenylmethyl quaternary compound which is weaker than the similar tropane compound. The difference between the two diphenylmethyl quaternary compounds can be explained by the postulation that this large group, with a greater steric requirement, deforms the "original" *cis* configuration of the methyl groups on C(2) and C(6) which in normal circumstances seems to be sterically similar to the endoethylene bridge. Evidence for this supposition is the observation that compounds with *trans* methyl groups are weaker than those with *cis* methyl groups, only the latter being similar in ganglion-blocking activity to tropane compounds.

These observations show that for ganglion-blocking action the stereostructure of the rigid ring system of tropane with the endoethylene bridge is a very favourable basic chemical structure. Therefore building up various quaternary groups on this skeleton may give promising results.

Similarly Winbury[76] stated that for ganglion-blocking activity in aliphatic quaternary ammonium compounds an α-branched aliphatic chain attached to the nitrogen is necessary. In our opinion this statement is valid only if the stereostructure of such a branched aliphatic carbon chain is known. Very probably this steric orientation is similar to that of the α-branched tropane ring system.

The 2:6-dimethylpiperidinium ring, in contrast to the tropane ring, is not a rigid ring system. Therefore in piperidinium compounds which differ in the position of the quaternary groups about the nitrogen, the steric position of these groups and their relation to the elastic ring system is not the same as in the rigid quaternary tropane compounds. The results obtained with 2:6-dimethylpiperidinium derivatives showed indeed that in one instance the potency of the R′–$^{+}$N–R and the R–$^{+}$N–R′ epimeric form, was exchanged[17].

From data on the 2:6-dimethylpiperidinium compounds, some having ester groups on C(4) and other attached to a carbon chain on the nitrogen,

one can state that generally they do not have such a high ganglion-blocking activity as tropane compounds[17,77,78]. This also applies to their curare-like activity[17].

N-Alkyl and Aralkyl-nor-tropine Compounds

The problem of the role of the absolute steric position of the substituents on the nitrogen in relation to pharmacological activity can be investigated only in nor-tropine or tropane compounds which have the desired substituents in a different order. The investigation of these compounds can answer the question whether with the tropine and tropane compounds, the presence of, and the steric position of, the N–CH_3 group is optimal for pharmacological activity or not.

Pharmacological data for this kind of tropine compound have been limited until recently. Stoll and Jucker[60] mention the observation of Rothlin and colleagues[59] with the butyl-quaternary derivative of benzylyl-6-methoxytropine and its N-epimeric methyl-quaternary N-butyl-benzylyl-6-methoxy-nor-tropine. They did not find significant differences in the spasmolytic action of these compounds. Our experiments with some aralkyl tropinium compounds quaternised in a reversed order resulted in compounds exhibiting marked differences in atropine- and curare-like and ganglion-blocking effects[17,79].

Piperidinium Compounds

Experiments made with compounds containing simple piperidine (piperidinium) rings show that their structure does not fulfil the requirements necessary for synaptic-blocking activity compared with the tropane compounds[17].

The Tropane Compounds and Local Anaesthetic Activity

Local anaesthetic tropane compounds can be divided into three groups: compounds with (*a*) ecgonine, (*b*) tropine and (*c*) 6-alkoxytropine ring systems.

The best known and one of the most active among these is cocaine (2β-carbomethoxy-3β-benzoyloxytropane)[80]. As psicaine (2α-carbomethoxy-3β-benzoyloxytropane) has about the same local anaesthetic activity as cocaine[81], the configuration of the carbomethoxy group in C(2) is not important for this activity. In fact tropacocaine, which has no carbomethoxy group, is a potent local anaesthetic. However, in all of these substances the benzoyl ester group is found in the 3β-position. Compounds with ester groups attached to the OH group in the 3α-position have weaker activity. It seems that for the blockade of (sensory) nerve conduction, ester groups in the 3β-position are important. The benzoyl ester prepared from the third racemate of ecgonine has no local anaesthetic properties according to Wick[82]. Ecgonine proved to be ineffective too.

Considering the role of nitrogen in compounds with the ecgonine ring, the secondary amine derivative corresponding to cocaine is more effective than cocaine itself, but the methyl-quaternary cocaine derivative shows little activity[83]. von Braun and Müller[37] investigated some nor-ecgonidine derivatives (compounds not having a substituent on C(3), their benzoyl

ester group being on an aliphatic chain attached to the nitrogen). One of these compounds, Ekkain [*N*-(3-benzoyloxy-*n*-propyl)2-carbethoxy-nortropidine], proved to be more effective and to possess a better therapeutic index than cocaine[84].

In the group of local anaesthetic compounds with the tropine ring system, tropacocaine, benzoyltropine and *p*-aminobenzoyl-α-tropine are known. Methyl quaternisation of these compounds, as with cocaine, decreases their activity, but higher alkyl and aralkyl quaternary groups retain or even increase the local anaesthetic activity in comparison with the tertiary compounds[42,43]. Recently it has been pointed out[85] that some higher alkyl and aralkyl quaternaries of atropine were absorbed from the gastrointestinal tract more efficiently than the methyl derivative. Presumably in other tissues the rate of penetration depends significantly on the nature of the quaternary groups.

Of the 6-methoxytropine derivatives, the 3α-benzoyloxy-6-methoxy tropane and the 3α-diphenylglycolyl-6-methoxy-tropane show a definite local anaesthetic activity[59]. Their methyl and butyl quaternary derivative were, however, inactive. The activity of the former compounds proves that the methoxy group at C(6) does not affect local anaesthetic activity.

From a practical point of view, the stereochemical features of tropane and ecgonine compounds with local anaesthetic activity do not seem to be of as great an importance as those of ganglion-blocking and curare-like substances. The large number of synthetic local anaesthetics of high activity and their wide application shows that for local anaesthetic effect, unlike atropine-like activity, some simple alkamines without a complicated ring system can exert optimal effects. However, in the search for new local anaesthetics, without undesirable side effects, the derivatives of tropane and ecgonine, with their elucidated stereostructure, still merit further attention.

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