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PHARMACOLOGY OF SCOPINIUM BROMIDE

BY

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By oxidizing hyoscine (scopolamine) with hydrogen peroxide, Polonovski & Polonovski (1927) obtained hyoscine amine oxide, scopoline amine oxide and a quaternary compound which they isolated as the bromide and termed " scopinium." These authors established the physical and chemical properties of the last compound and proposed its structure. By hydrogenation of scopinium they obtained pseudoscopine, the stable cis-isomer of scopine, in a 90% yield. Polonovski & Polonovski (1927) proposed the hypothesis that scopinium was changed to an unstable tautomeric ketone (scopinone) which in turn was reduced to pseudoscopine. By treatment of scopinium bromide with silver hydroxide or with hot alkali, metahydroxybenzaldehyde was obtained by the rearrangement of the seven-membered ring to a six-membered one.

As far as we know there have been no papers on the pharmacology of scopinium. Since this compound is an oxidation product of hyoscine, we thought it would be of great interest to study its general pharmacology in several species, using classical techniques. In addition, before using the drug, we carried out many chemical and physical tests to make certain that the compound was scopinium and not one of its unstable conversion products.

A previous short report on this subject was presented at the Second International Pharmacological Congress held in Prague, August 20 to 23, 1963.

METHODS

Chemical methods

We used a sample of scopinium bromide that was originally obtained by Polonovski & Polonovski (1927). To ascertain the purity of this compound, we did a series of physical and chemical tests.

Scopinium bromide is a white, crystalline substance, very hygroscopic, and easily soluble in water. It may be recrystallized from ethanol. The melting point (208 to 210° C) and the percentage of bromine and nitrogen which we determined for this substance were in full agreement with the results given by Polonovski & Polonovski (1928).

Treating scopinium bromide in water with a solution of picric acid, we were able to obtain a well-crystallized picrate, not previously described, with a melting point of 256 to 257° C. The purity of this picrate was verified by its analysis: C; calculated 43.9%, found 44.0%. This picrate was used to determine the molecular weight of the scopinium base by the method of Cunningham, Dawson & Spring (1951). The molecular weight we found was 154.2 (the calculated value is 154.08).

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Using the method described for hydrogenation of scopinium, we were able to obtain pseudoscopine, with melting point 124 to 126° C; Polonovski & Polonovski (1928) found 125 to 126° C, and Heusner & Zeile (1958) 122 to 123° C.

We failed to obtain pseudoscopine from scopinium, using the reducing agent potassium borohydride, which is known to reduce selectively carbonyl groups.

From pseudoscopine, its hydrochloride, methiodide and picrate were obtained. The properties of these substances completely coincided with those already described by Polonovski & Polonovski (1928). For scopinium bromide and pseudoscopine hydrochloride infrared spectra were also obtained.

Pharmacological methods

Twenty dogs, thirty cats, sixteen rabbits, fifty rats, eighty mice and ten pigeons were used. All the dogs were anaesthetized with sodium pentobarbitone (30 to 35 mg/kg, intraperitoneally). Twenty of the cats were anaesthetized with the same drug (30 to 35 mg/kg, intraperitoneally) and five with Dial (diallylbarbituric acid-urethane) (0.8 ml./kg, intraperitoneally). Rabbits, rats, mice and pigeons were conscious.

Scopinium bromide was injected intravenously, intraperitoneally or intracisternally in doses ranging from 0.1 to 50 mg/kg of the salt.

Autonomic nervous system. Contraction of the nictitating membrane in cats was elicited by preganglionic or postganglionic electrical stimulation, or both, with rectangular shocks, 0.1 to 1 msec duration, 10 to 20 shocks/sec, for 10 sec to 2 min, at 5 to 7V; or by intravenous injection of dimethylphenylpiperazinium iodide (15 to 25 μg/kg). The contraction of the nictitating membrane was recorded by means of an isotonic lever with a tenfold amplification.

In three dogs and three cats the peripheral stump of the cut vagus nerve was electrically stimulated in the neck (1 msec, 10 to 20 shocks/sec, 10 to 15 sec, and 7 to 9 V).

By means of a mercury manometer arterial blood pressure was recorded from a femoral or an iliac artery in dogs and cats. Electrocardiograms were obtained in five dogs and three cats, using conventional leads. Respiration was recorded from a tracheal cannula connected to a Marey manometer.

In bitches, in addition to blood pressure and respiration, urinary bladder contraction produced by the intravenous injection of dimethylphenylpiperazinium (15 to 25 μg/kg) was also recorded. For recording bladder contraction the abdomen was opened and both ureters were ligated; an intravesical catheter was inserted through a small incision in the urethra and connected to a straight water-manometer provided with a light float.

In five dogs Wharton's duct was cannulated and the salivary flow was measured by means of a drop recorder. In rabbits and cats salivary flow was assessed from visual observation.

Pupil diameter was measured in the unanaesthetized mouse by means of a calibrated eye-piece in a microscope, using a constant light intensity. The eye-piece was marked with 0.2 mm divisions to allow comparative measurements of pupil diameter changes. Hyoscine hydrobromide was used as the standard drug.

Scopinium bromide was tested in rats to see if it produced chromodacryorrhea or whether it antagonized that elicited by the intraperitoneal injection of 250 μg/kg of carbachol.

Segments of guinea-pig ileum and rat duodenum were suspended in a Dale organ-bath in aerated Tyrode solution maintained at 37° C. Contractions were elicited by appropriate doses of acetylcholine and recorded with an isotonic lever on a kymograph.

Peripheral nervous system. Twitch responses of the gastrocnemius muscle to maximal electrical stimulation of the sciatic nerve were recorded in cats. In these experiments scopinium bromide was injected into the femoral artery.

Central nervous system. Cats were chronically implanted with epidural and deep electrodes to record the electroencephalograph. The electrodes were introduced stereotaxically following the atlas of Snider & Niemer (1961). After termination of the experiments the brains were fixed in 10% formalin solution to permit histological determination of the position of the electrode tip.

Movements and tremor in mice were recorded by means of a pick-up operating through an electro-encephalographic amplifier and recorder (Vidal-Beretevide & Monti, 1963).

Rectal temperature in rabbits was measured with a clinical thermometer.

RESULTS

Autonomic nervous system

In twelve cats after receiving scopinium bromide (1 to 10 mg/kg, intravenously) a clear relaxation of the nictitating membrane was noted during continuous electrical stimulation of the preganglionic sympathetic trunk in the neck (Fig. 1). The contraction

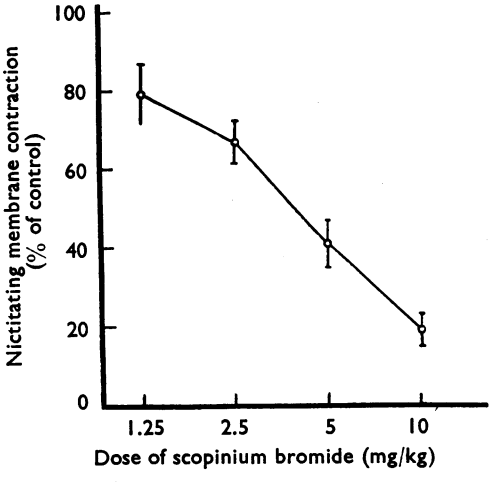

Fig. 1. Effect of scopinium bromide on the contractile response of the nictitating membrane, induced by electrical stimulation of the preganglionic sympathetic trunk of an anaesthetized cat. Abscissa: intravenous dose of scopinium bromide in mg/kg. Ordinate: contraction of the nictitating membrane as a percentage of the control contraction. Each point represents the mean values of five experiments. Vertical lines indicate standard errors.

of the postganglionically stimulated nictitating membrane was not changed by the drug. This sharp contrast was clearly seen when the preganglionic trunk on one side and the postganglionic on the other were stimulated simultaneously and the contractions of both membranes were recorded, as shown in a typical experiment in Fig. 2.

In only three of these cats after intravenous injection of scopinium bromide (2.5 to 5 mg/kg), either a contraction of the unstimulated nictitating membrane or an initial peak superimposed on the tracing obtained during continuous preganglionic sympathetic stimulation was observed.

The blood pressure drop produced by electrical stimulation of the peripheral stump of the vagus nerve in the neck was not significantly modified by intravenous injection of scopinium bromide in three dogs and three cats in doses up to 25 mg/kg.

A contraction of the urinary bladder was noted consistently in ten dogs after injection of 2 to 5 mg/kg of the drug (Fig. 3, left side). This response was clear but transient;

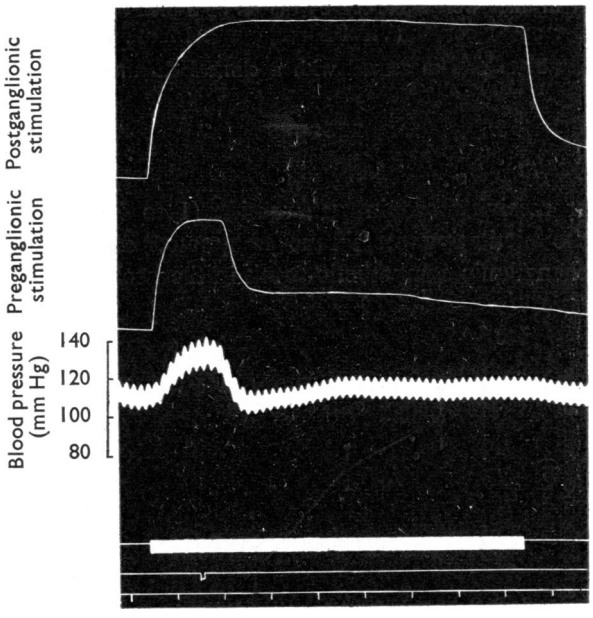

Fig. 2. Comparison of the effects of scopinium bromide on contractions of both nictitating membranes produced by electrical stimulation of the preganglionic trunk on one side and the postganglionic trunk on the other side. Cat, male, 3.4 kg. Sodium pentobarbitone, 35 mg/kg, intraperitoneally. From top to bottom: contraction of the left nictitating membrane, postganglionically stimulated; contraction of the right nictitating membrane, preganglionically stimulated; arterial blood pressure; signal of electrical stimulation (1 msec; 10 shocks/sec; 5 V) of pre- and postganglionic trunks; signal of injection; and time (30 sec). At the signal, 4.5 mg/kg of scopinium bromide were injected intravenously. Note the relaxation of the preganglionically stimulated nictitating membrane without change of the postganglionically stimulated one.

it diminished upon repeated injections of scopinium bromide and was even sometimes abolished by previous intravenous injection of hexamethonium chloride (5 to 8 mg/kg) (Fig. 3, right side).

Contractions of the nictitating membrane and arterial hypertension in six cats and urinary bladder contractions in four dogs produced by intravenous injection of dimethylphenylpiperazinium (15 to 25 μg/kg) were antagonized by scopinium bromide (15 to 20 mg/kg).

The peripheral blood-pressure responses in six cats after intravenous doses of acetylcholine chloride (1 to 5 μg/kg) and adrenaline bitartrate (5 to 20 μg/kg) were not modified by previous intravenous injection of scopinium bromide up to 25 mg/kg. In addition the contraction of the nictitating membrane produced by similar doses of adrenaline was also not changed by scopinium bromide.

In most of the animals after an intravenous injection of scopinium bromide (0.7 to 5 mg/kg) a brief decrease in arterial blood pressure lasting from 2 to 10 min was observed and this effect was dose-dependent (Table 1). This drop in blood pressure was reproducible after each successive injection of the drug.

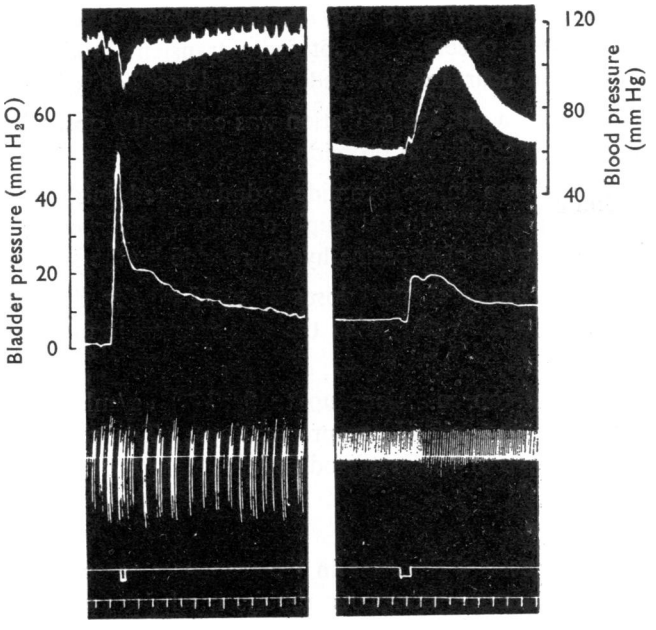

Fig. 3. Effects of scopinium bromide on contractions of the urinary bladder before and after hexamethonium. Bitch, 6 kg. Sodium pentobarbitone anaesthesia, 35 mg/kg, intravenously. From top to bottom: blood pressure; contraction of the urinary bladder; respiration; signal of injection; time (30 sec). At the signal marks 3.5 mg/kg of scopinium bromide were injected intravenously. Hexamethonium bromide, 8 mg/kg, was given intravenously 10 min before the second record. As is usual, the blood pressure dropped and respiratory rate increased. Note after hexamethonium the marked hypertension and feeble urinary bladder contraction produced by scopinium.

TABLE 1

EFFECT OF SCOPINIUM BROMIDE ON MEAN ARTERIAL BLOOD PRESSURE IN CATS AND DOGS

Scopinium bromide was injected intravenously. Values are means and standard errors, and are expressed as percentages of controls

	Cats		Dogs	
Dose (mg/kg)	Number	Decrease in blood pressure (%)	Number	Decrease in blood pressure (%)
1	5	19·4±2·2	6	17·6±1·8
2	8	30·0±3·8	6	21·6±2·6
4	6	56·6±8·6	4	43·8±5·2

Only one dog and three cats responded with hypertension to the first injection of scopinium bromide. This blood pressure rise could not be repeated by injecting further doses of the substance; instead, a hypotensive response was obtained. The brief hypotension was markedly diminished or abolished by intravenous injections of atropine sulphate (1 mg/kg) in three of five animals, and of hexamethonium chloride (5 to 10 mg/kg). After the injection of hexamethonium the subsequent administration of scopinium bromide (3 to 5 mg/kg) produced a marked and protracted arterial hypertension in six of nine animals (Fig. 3).

After scopinium bromide (0.7 to 5 mg/kg, intravenously) no important changes in the electrocardiogram were observed except for a transient bradycardia lasting 2 to 3 min. In these animals the heart rate was reduced by 15 to 27% of its initial level.

In rabbits, cats and dogs a marked salivation was constantly observed after intravenous doses of 5 to 20 mg/kg of scopinium bromide.

In mice 25 mg/kg of scopinium bromide, administered intraperitoneally, caused a mydriasis of about 2.5-times the initial pupil diameter. This effect was equivalent to that caused by 30 to 35 μg/kg of hyoscine hydrobromide by the same route.

Scopinium bromide, in intraperitoneal doses up to 25 mg/kg, did not produce chromodacryorrhea in rats nor did it antagonize the response to intraperitoneal injections of 250 μg/kg of carbachol.

Scopinium bromide, in concentrations up to 5×10^{-5} μg/ml., had no action on rat isolated duodenum or guinea-pig ileum preparations. The response to acetylcholine chloride (1 to 2×10^{-7} μg/ml.) was not modified.

Peripheral nervous system

There were marked species differences in the responses to scopinium bromide at the neuromuscular junction. In five conscious rabbits head drop and generalized paralysis without previous muscle fasciculations were observed 2 to 5 min after the intravenous injection of the drug (25 to 50 mg/kg).

In twenty rats, intraperitoneal injection of the same doses caused similar effects. Tremor, as described later, was superimposed on the muscle weakness.

The muscle paresis could be antagonized in rabbits and rats with neostigmine sulphate, 100 and 200 μg/kg, intravenously and intraperitoneally respectively.

When the sciatic nerve-gastrocnemius muscle preparation in the cat was used (five animals), intra-arterial injection of 0.2 to 10 mg of scopinium bromide produced only transient twitches or fasciculations, but neuromuscular transmission was not impaired.

Intravenous injection of scopinium bromide in ten pigeons in doses of 20 to 25 mg/kg gave rise to a strong contracture of the leg muscles, which lasted some minutes.

Central nervous system

In twenty mice, twenty rats and five rabbits generalized and marked tremor was observed within a few minutes after the injection of the drug (25 to 50 mg/kg, intraperitoneally or intravenously). The typical pattern for a mouse after the drug is shown in Fig. 4. Usually the tremor was intermingled with muscle weakness, giving rise, especially in rats and rabbits, to a picture of paresis, tremor and dypsnoea.

When the drug was injected intracisternally in five rabbits (15 to 20 mg) the tremor was observed within only a few seconds.

Tremor was not modified by previous intraperitoneal injection of atropine sulphate (up to 2.5 mg/kg).

In five conscious cats with chronically implanted electrodes to record the electroencephalogram an intraperitoneal dose of 25 mg/kg of the drug was injected. Four

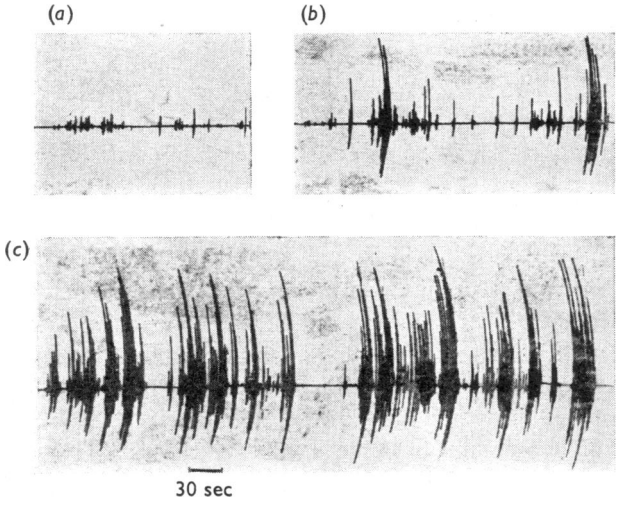

Fig. 4. " Actographic " record of the effect of scopinium bromide in a conscious mouse. (*a*) Normal movements ; (*b*) 5 min after 25 mg/kg of scopinium bromide, intraperitoneally and (*c*) 20 min after (*b*). Note that the tremor has a clear pattern.

of them developed a state of marked sedation, or a " taming " effect, and a tendency to maintain imposed uncomfortable postures. This clinical sedation or sleep-like state was not reflected by major changes in the electroencephalogram.

Neither the arousal reaction to external stimuli (sound and touch) nor the activation produced by intraperitoneal injection of 50 to 100 μg/kg of physostigmine sulphate was modified.

In six rabbits intravenous injection of up to 25 mg/kg of scopinium bromide did not significantly change rectal temperature.

DISCUSSION

Chemistry

Since there has been much controversy as to the stability of scopinium bromide, we had to be certain of the identity and purity of the compound used in these experiments.

Following the papers published by Polonovski & Polonovski (1927, 1928), several authors (Polonovski & Lespagnol, 1934 ; Holmes, 1950 ; Fódor, 1952 ; Cookson, 1953 ; Meinwald, 1953 ; Lebeau & Janot, 1955 ; Boit, 1961) admitted the existence and the manner of formation of scopinium bromide.

However, different authors after Polonovski & Polonovski (1927, 1928) failed to obtain scopinium bromide (Fódor, 1955 ; Meinwald & Chapman, 1959). Using a different method, Heusner & Zeile (1958) were able to obtain scopinone by oxidizing scopine with Sarett's reactive. This ketone could be reduced by potassium borohydride to give pseudoscopine (50% yield). These authors thought that scopinone must be a compound different from scopinium and, in general, they admitted that their results agreed with

those published by Polonovski & Polonovski (1928). It is interesting to stress again that Polonovski & Polonovski (1928) had already proposed the possibility of the transformation of scopinium to an unstable ketone which, reduced, would give pseudoscopine.

Meinwald & Chapman (1959), who failed to obtain scopinium bromide, observed that scopinone obtained by Heusner & Zeile (1958) is remarkably unstable, giving rise easily to the formation of metahydroxybenzaldehyde. This same aldehyde may also be obtained from scopine methylbromide. Thus, these authors confirmed the essential authenticity of the rearrangement reported by Polonovski & Polonovski (1927, 1928).

According to our results scopinium bromide is a substance definitely different from scopinone hydrobromide. The melting point of scopinone picrate is 175° C (Heusner & Zeile, 1958) but that of scopinium picrate that we have obtained is 256 to 257° C. We were not able to reduce scopinium with potassium borohydride, but we successfully obtained pseudoscopine, using the method of Polonovski & Polonovski (1928). The infrared spectrum of scopinium bromide lacks typical carbonyl and tertiary amine absorption bands in 5.81 μ and 3.65 to 3.73 μ respectively. For all the above-mentioned reasons we have the striking fact that scopinium bromide obtained in 1927 showed no changes of its physical and chemical properties after more than 35 years. This is in sharp contrast to the instability described for scopinone, which, at least in solution, decomposes within hours. The pseudoscopine we have obtained has practically the same melting point described by Polonovski & Polonovski (1928) and by Heusner & Zeile (1958). The melting point and quantitative composition of its hydrochloride and methiodide agreed with calculated values.

In the infrared spectrum of pseudoscopine hydrochloride bands were present which correspond to those of the hydroxyl group, to those of a tertiary amine salt and to those of oxirane.

Thus we have shown a series of facts which certainly assert that scopinium bromide corresponds to the formula given by Polonovski & Polonovski (1927, 1928) and that its pharmacological properties can be attributed to that structure.

Pharmacology

Scopinium bromide, a monoquaternary compound, gave rise in several species to a wide variety of effects. We shall try to classify them as follows.

Autonomic nervous system. A short acting but definite ganglionic-blocking action was demonstrated by nictitating membrane experiments, especially those with simultaneous pre- and postganglionic stimulation. Contraction to preganglionic stimulation was blocked, while that to postganglionic stimulation was unaltered by the drug. Although the response to the stimulation of the peripheral end of the cut vagus nerve was not blocked, antagonism of parasympathetic ganglionic stimulation was demonstrated by the abolition of the contraction of the urinary bladder produced by dimethylphenylpiperazinium after repeated or large doses (15 to 20 mg/kg) of scopinium bromide.

The contraction of the urinary bladder (which was blocked by previous injection of hexamethonium), the contraction of the nictitating membrane and the initial hypertensive peak after the drug in some experiments indicated a ganglionic-stimulating action of the substance.

In other words, scopinium bromide acted as a ganglionic stimulating drug mainly on parasympathetic ganglia, and as a ganglionic blocking drug, especially for sympathetic ganglia. Sympathetic stimulation and parasympathetic block at ganglionic sites existed but were not so sharply demonstrable.

The substance was devoid of atropine-like, adrenergic nerve blocking, or adrenolytic properties. Mydriasis in mice may therefore not be ascribed to atropine-like or adrenergic nerve blocking actions.

The arterial hypotension observed with scopinium bromide seemed not to be due to cardiac depression, since the electrocardiogram was not qualitatively modified and because atropine and hexamethonium diminished or abolished the hypotension in most of the animals. The arterial hypotension could be partly explained by parasympathetic ganglionic stimulation or sympathetic ganglionic block. Using atropine and hexamethonium in fully effective doses, we were not able to establish beyond doubt the part played by ganglionic effects in scopinium-induced bradycardia and arterial hypotension.

After hexamethonium a new injection of scopinium bromide produced a relative long-lasting arterial hypertension. This result may not be ascribed to antagonism of ganglionic block, since the urinary bladder and the nictitating membrane were not responsive during the hypertension. This action could be ascribed to a smooth muscle contraction of the vessels caused by scopinium bromide.

Neuromuscular junction. With the methods employed by us, the drug could not be clearly classified as depolarizing or as a competitive curare-like substance. In rats and rabbits it did not give rise to muscle fasciculations and it was antagonized by neostigmine, but in cats it produced twitches and fasciculations, without further block. In pigeons a clear-cut contracture was observed.

Central nervous system. The appearance of generalized, co-ordinated, symmetrical and sustained tremor indicated the central nervous system as a site of action of scopinium bromide. This hypothesis was reinforced by the fact that tremor ensued only some seconds after the intracisternal introduction of the drug, while more time (maybe due to difficulty in crossing the blood-brain barrier) was required for the appearance of tremor when other routes of injection were used. The spontaneous electroencephalogram was not modified by scopinium bromide ; it did not produce activation or hypersynchronization in the record. It did not block activation responses produced by peripheral stimuli or by physostigmine.

In conclusion, the variegated properties of scopinium bromide (arterial hypotension, bradycardia, salivation, ganglionic stimulation and block, and tremor) had features in common with the actions of nicotine and tremorine. In some aspects scopinium bromide acted as a cholinergic drug (bradycardia, arterial hypotension and marked salivation), but it did not produce typical cholinergic responses like contraction of the isolated intestine and chromodacryorrhea.

SUMMARY

1. Scopinium bromide was obtained from scopolamine by Polonovski & Polonovski (1927). It is undoubtedly different from its tautomeric ketone, scopinone, obtained in

1958 by Heusner & Zeile, as determined by the infrared spectra and the melting points of their picrates.

2. Following the technique of Polonovski & Polonovski (1928) for reduction of scopinium bromide we have been able to obtain pseudoscopine.

3. The pharmacological properties of scopinium bromide were studied in mice, rats, pigeons, rabbits, cats and dogs.

4. Scopinium bromide, in doses ranging from 1 to 50 mg/kg caused: autonomic ganglionic blockade (more marked for the sympathetic ganglia); autonomic ganglionic stimulation (more marked for the parasympathetic ganglia); arterial hypotension and bradycardia; marked salivation; and mydriasis in mice.

5. Scopinium bromide did not produce chromodacryorrhea or contracture of the isolated intestine, nor did it show atropine-like, adrenergic nerve blocking or adrenolytic properties.

6. The drug appeared to have a direct constrictor action on vascular smooth muscle.

7. The drug caused irregular, scattered muscle twitches in the cat, rigidity-paresis with co-ordinated tremor in mice, rats and rabbits, and muscle contracture in pigeons. Tremor in rabbits rapidly developed after intracisternal injection of the drug. Electroencephalographic changes in animals with implanted electrodes were not significant.

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REFERENCES

BOIT, H. G. (1961). *Ergebnisse der Alkaloid-Chemie bis* 1960. Berlin: Akademie-Verlag.

COOKSON, R. C. (1953). Stereochemistry of alkaloids. *Chem. Ind.*, **47**, 337–340.

CUNNINGHAM, K. G., DAWSON, W. & SPRING, F. S. (1951). Microdetermination of the molecular weights of picrates by a spectrophotometric method. *J. chem. Soc.*, 2305–2306.

FÓDOR, G. (1952). Stereochemistry of the propane alkaloids. *Nature* (*Lond.*), **170**, 278–279.

FÓDOR, G. (1955). Steric structure of tropane alkaloids. *Acta chim. hung.*, **5**, 379–442.

HEUSNER, A. & ZEILE, K. (1958). Partial synthesis of scopinone and pseudoscopine. *Chem. Ber.*, **91**, 2399–2405.

HOLMES, H. L. (1950). In *The Alkaloids*, ed. MANSKE, R. H. F., & HOLMES, H. L., vol. 1, pp. 304–306. New York: Academic Press.

LEBEAU, P. & JANOT, M. M. (1955). *Traité de Pharmacie Chimique*, vol. 4, p. 2793. Paris: Masson.

MEINWALD, J. (1953). The stereochemistry of scopolamine. *J. chem. Soc.*, 712.

MEINWALD, J. & CHAPMAN, O. L. (1959). Elimination reaction of bicyclic quaternary salts. IV. The conversion of scopinone into m-hydroxybenzaldehyde. *J. Amer. chem. Soc.*, **81**, 5800–5803.

POLONOVSKI, M. & LESPAGNOL, A. (1934). *Elements de Chimie Organique Biologique.* Paris: Masson.

POLONOVSKI, M. & POLONOVSKI, M. (1927). A scopinium derivative: reduction to pseudoscopine and degradation into m-hydroxybenzaldehyde. *C. R. Acad. Sci.* (Paris), **185**, 277–279.

POLONOVSKI, M. & POLONOVSKI, M. (1928). The constitution of pseudoscopine. *Bull. Soc. chim.*, **43**, 590–603.

SNIDER, R. S., & NIEMER, W. T. (1961). *A Stereotaxic Atlas of the Cat Brain.* Chicago: University Press.

VIDAL-BERETEVIDE, K. & MONTI, M. (1963). Pharmacological Study of tropyl-chromone-2-carboxylate and some of its derivatives. *Arz. Forsch.*, **13**, 452–454.