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The preparation and properties of (+)- and (−)-guanoxan

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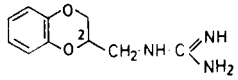
(±)-2-Aminomethyl-1,4-benzodioxan has been resolved into its optically active isomers: (+)- and (—)-guanoxan have been synthesized from these. The pharmacological effects of racemic-guanoxan and of the two optical isomers have been compared on the isolated central ear artery of the rabbit, on the pithed rat in which pressor responses were evoked by stimulation of the thoraco-lumbar sympathetic outflow, and on the pre- and post-ganglionically stimulated nictitating membrane of the cat. The two isomers were equipotent in producing adrenergic neuron blockade. Initial catecholamine release was weak in the cat, but occurred more powerfully in the rabbit ear artery and in the rat. Ability to produce this effect resided mainly with the (+)-isomer. α-Adrenoreceptor blocking activity was detectable in the rat and was produced mainly by the (+)-isomer suggesting that its stereochemical configuration corresponds to that of D-(—)-noradrenaline. Ganglion blockade was an unimportant action of the compounds, but both isomers possessed weak atropine-like activity in the rat.

GUANOXAN, (±)-guanidinomethyl-1,4-benzodioxan (I) is an antihypertensive agent (Augstein & Green, 1964; Peart & MacMahon, 1964), which acts primarily by preventing the release of noradrenaline from adrenergic nerve endings (Davey & Reinert, 1965; Augstein, Green & others, 1965; Baines, Cobb & others, 1965), although it also has some α-adrenoreceptor blocking activity, especially in the dog (Davey & Reinert, 1965). Its action resembles that of guanethidine (II) in that it depletes peripheral adrenergic neurons of their stores of noradrenaline. In contrast to guanethidine, however, it also depletes noradrenaline stores in the hypothalamus (Augstein & others, 1965; Davey & Reinert, 1965).



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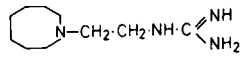

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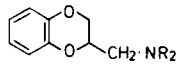

III

Guanoxan (I) possesses an asymmetric centre at the 2-position, and hitherto has not been resolved into its optical isomers. The stereoisomers of adrenaline, noradrenaline and other sympathomimetic amines show marked differences in pharmacological action, and similar differences

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have been observed in the potency of isomeric pairs of various anti-adrenaline drugs, including the benzodioxan (III R = Et) (Trefouel, Trefouel & Dunant, 1935), of which the (−)-isomer is about six times as effective as the (+)-isomer in blocking the pressor actions of adrenaline in the cat (Bovet & Simon, 1935). Since guanoxan also possesses an asymmetric centre at position 2, it was considered of interest to isolate the two optical isomers of (±)-guanoxan for pharmacological evaluation.

Chemistry

Although guanoxan readily forms salts with many of the optically active acids used as resolving agents, the salts are insoluble in most organic solvents. For this reason direct resolution of guanoxan proved impossible; 2-methylamino-1,4-dioxan (III, R = H), however, was successfully resolved.

Salts with several acids, including D-tartaric acid, D-dibenzoyltartaric acid, D-camphorsulphonic acid, D-quinic acid and L-mandelic acid, were prepared by the general procedure of Greenstein & Winitz (1961). Of these, the (−)-2-aminomethyl-1,4-benzodioxan L-(+)-mandelate crystallized preferentially from ethyl acetate-absolute ethanol (3:1), whilst the (−)-2-aminomethyl-1,4-benzodioxan D-(−)-dibenzoyltartrate crystallized from methanol.

Decomposition of these purified salts as described in the experimental procedures gave (+)- and (−)-2-aminomethyl-1,4-benzodioxans; the rotations of the derived hydrochlorides were $[\alpha]_D^{21}$ + 72·2° (*c*, 0·483 MeOH) and $[\alpha]_D^{21}$ − 72·9° (*c*, 0·461 MeOH) respectively, thus confirming their optical purity.

(+)- and (−)-Guanoxan sulphates were synthesized by treating the corresponding (+)- and (−)-2-aminomethyl-1,4-benzodioxans with *S*-methylisothiourea sulphate. The chemical purity of the products was confirmed by elementary analysis and thin-layer chromatography in two separate solvent systems. Both isomers showed complete absence of traces of the respective (+)- and (−)-2-aminomethyl-1,4-benzodioxans, and *S*-methylthiourea sulphate, and also had the same Rf values as authentic (±)-guanoxan sulphate. The optical purity follows from the specific rotations of the two isomeric guanoxan sulphates which were $[\alpha]_D^{22}$ + 54·8° (*c*, 0·485 water) and $[\alpha]_D^{22}$ − 55·0° (*c*, 0·487 water) respectively.

EXPERIMENTAL

(±)-2-*Aminomethyl*-1,4-*benzodioxan* (III, R = H) may be obtained from guanoxan (I) as follows. The method used is that described by Carter, Clarke & others (1946) for the degradation of streptidine to streptamine. Guanoxan sulphate (54 g) was refluxed (30 hr) with sodium hydroxide solution (6N; 200 ml). Ether extraction in the usual way yielded (±)-2-aminomethyl-1,4-benzodioxan (20·9 g; 60·4%), b.p. 105°/0·5 mm; n_D^{17} 1·5512. Augstein & others (1965) quote

b.p. 92–94°/0·4 mm; n_D^{25} 1·5583. Hydrochloride, m.p. 219° (decomp.). Augstein & others (1965) give m.p. 220–222°.

(+)-2-*Aminomethyl*-1,4-*benzodioxan* L-(+)-*mandelate*. (±)-2-Aminomethyl-1,4-benzodioxan (17·5 g; 0·106 mole) in a mixture of ethyl acetate and ethanol (3:1; 400 ml) at 50° was added to L-(+)-mandelic acid (8·09 g; 0·053 mole) in the same solvent (350 ml) also at 50°. Crystallization (64 hr) at room temperature yielded a crude product (10·5 g), $[\alpha]_D^{21}$ + 80·5° (*c*, 0·796 MeOH), which after three re-crystallizations from the same solvent gave (+)-2-*aminomethyl*-1,4-*benzodioxan* L-(+)-*mandelate* (5·2 g; 31·4%), m.p. 167–168°, $[\alpha]_D^{22}$ + 90·5° (*c*, 0·772 MeOH). Found: C, 64·3; H, 5·7; N, 4·45. $C_{17}H_{19}NO_5$ requires C, 64·3; H, 6·0; N, 4·4%.

The mother liquors, cooled in the refrigerator for 24 hr, yielded further amine mandelate (1·3 g), $[\alpha]_D^{22}$ + 73·2° (*c*, 0·786 MeOH). Concentration of the remaining solution to 25 ml *in vacuo* gave a further crop of amine mandelate (3·5 g), $[\alpha]_D^{21}$ + 41·2° (*c*, 0·785 MeOH).

(−)-2-*Aminomethyl*-1,4-*benzodioxan* D-(−)-*dibenzoyltartrate*. The concentrated collected mother liquors from the preparation of (+)-2-aminomethyl-1,4-benzodioxan L-(+)-mandelate were diluted with methanol (25 ml), warmed to 50°, and mixed with a solution of D-(−)-dibenzoyltartaric acid (9·46 g; 0·265 mole) in methanol (40 ml) also at 50°. Crystallization (12 hr) at 0° yielded a crude product (12·3 g), $[\alpha]_D^{22}$ − 98·0° (*c*, 0·55 MeOH), which after three re-crystallizations from the same solvent gave (−)-2-*aminomethyl*-1,4-*benzodioxan* D-(−)-*dibenzoyltartrate* (5·6 g; 31·2%), m.p. 175–176°, $[\alpha]_D^{21}$ − 108·2° (*c*, 0·621 MeOH). Found: C, 62·6; H, 5·0; N, 4·1. $C_{36}H_{36}O_{12}N_2$ requires C, 62·8; H, 5·3; N, 4·1%.

(+)-2-*Aminomethyl*-1,4-*benzodioxan hydrochloride*. (+)-2-Aminomethyl-1,4-benzodioxan L-(+)-mandelate was treated with sodium hydroxide solution (2%), the liberated amine extracted with ether (3 × 25 ml). Treatment with dry HCl, gave (+)-2-*aminomethyl*-1,4-*benzodioxan hydrochloride*, m.p. 251° (decomp.), $[\alpha]_D^{21}$ + 72·2° (*c*, 0·483 MeOH). Found: C, 54·2; H, 6·2; N, 6·9%. $C_9H_{12}ClNO_2$ requires C, 53·6; H, 6·0; N, 7·0%.

(−)-2-*Aminomethyl*-1,4-*benzodioxan hydrochloride* similarly obtained from the dibenzoyltartrate had m.p. 251° (decomp.), $[\alpha]_D^{21}$ − 72·9° (*c*, 0·461 MeOH). Found: C, 53·9; H, 6·0; N, 7·2. $C_9H_{12}ClNO_2$ requires C, 53·6; H, 6·0; N, 7·0%.

(+)-*Guanoxan sulphate*. (+)-2-Aminomethyl-1,4-benzodioxan (2·46 g; 0·0149 mole) was stirred with a solution of *S*-methylisothiourea sulphate (Shildneck & Windus, 1943) (2·07 g; 0·0075 mole) in water (18 ml) at room temperature during three days. The product obtained by adding acetone was recrystallized from aqueous acetone, and dried *in vacuo* over phosphorus pentoxide. (+)-*Guanoxan sulphate* resulted (2·52 g; 63·4%), m.p. 225°, $[\alpha]_D^{22}$ + 54·8° (*c*, 0·485 water). Found: C, 47·1; H, 5·6; N, 16·5%. $C_{20}H_{28}N_6O_8S$ requires C, 46·9; H, 5·5; N, 16·4%.

(−)-*Guanoxan sulphate*. (−)-2-Aminomethyl-1,4-benzodioxan (2·3 g) treated with *S*-methylisothiourea sulphate as above gave, after three

recrystallizations, (−)-guanoxan sulphate (1·68 g; 47·2%), m.p. 224–224·5°, $[\alpha]_D^{22}$ − 55·0° (*c*, 0·487 water). Found: C, 47·0; H, 5·5; N, 16·4%. $C_{20}H_{28}N_6O_8S$ requires C, 46·9; H, 5·5; N, 16·4%.

Thin-layer chromatography on silica gel in chloroform–methanol–0·88 ammonia (75:20:5) gave Rf values for (+)- and (−)-guanoxan sulphate, 0·15 and 0·17; (+)- and (−)-2-aminomethyl-1,4-benzodioxan, 0·95; *S*-methylisothiourea sulphate, 0·64. Iodine vapour was used for visualization. n-Propanol–aqueous ammonium carbonate (M) (40:30) gave Rf values for (+)- and (−)-guanoxan sulphate, 0·40; for (+)- and (−)-2-aminomethyl-1,4-benzodioxan, 0·54. (Concentrated sulphuric acid was used as a spray reagent).

Pharmacology

EXPERIMENTAL

The effects of the two isomers and of the racemate were examined on three preparations.

1. *The isolated central artery preparation of the rabbit's ear* (de la Lande & Rand, 1965). Isolated arteries from 45 ears were perfused at a constant rate of 8 ml/min, with McEwen (1956) solution warmed to 36–37° and gassed with 5% carbon dioxide in oxygen. Sympathetic nerve endings within the artery wall were stimulated through periarterial electrodes with rectangular pulses of 1 or 2 msec duration at a frequency of 2/sec for 10 sec in every 3 min. The stimulus strength was greater than that required to produce maximal responses at this frequency. The preparations were left for 1–1½ hr until responses to nerve stimulation were constant. Injections of noradrenaline were made into the perfusion fluid just before it entered the lumen of the artery. (±)-, (+)- or (−)-Guanoxan sulphate was added to the reservoir of perfusion fluid, the final concentrations ranging from 0·07–0·2 μg/ml.

In a further series of experiments on this preparation, the paired ear arteries from 7 rabbits were perfused simultaneously. One artery of each pair was perfused successively with 3 concentrations of the (+)-isomer while the other was similarly and simultaneously perfused with the same 3 concentrations of the (−)-isomer to compare the ability of the two isomers to cause catecholamine release. The concentrations of the isomers used were 0·2, 0·5 and 1·0 μg/ml and each concentration was perfused for 20 min.

2. *The blood pressure of the rat.* Ten rats were pithed and prepared to record pressor responses from a carotid artery evoked by stimulation of the thoraco-lumbar sympathetic outflow by the method described by Gillespie & Muir (1967). Pressor responses were elicited every 5 min by stimulating for 10 sec at a frequency of 10/sec with pulses of 2 msec duration. The voltage output from the stimulator was 50 V and at this strength the pressor responses were submaximal. Drugs were injected through a cannula in a jugular vein.

The α-adrenoreceptor blocking action of guanoxan and of the isomers

was tested on similar pithed preparations in which the sympathetic outflow was not stimulated. Two of these rats were pretreated with reserpine (1·5 mg/kg intraperitoneally) on the evening before the experiment.

Three rats were anaesthetized with urethane (0·55 ml of a 25% solution per 100 g body weight) injected intraperitoneally, and the ECG was recorded. At 2 min intervals the left vagus nerve was stimulated for 5 sec with trains of rectangular pulses of 100 μsec duration. The frequency of the trains was such as to produce complete heart block and was constant in each experiment. Every 6 min, instead of vagal stimulation, acetylcholine (15 μg) was injected intravenously. (±)-Guanoxan sulphate and the two isomers were injected intravenously in doses of 0·5 to 2·0 mg/kg.

3. *Nictitating membrane of the cat.* Two cats were anaesthetized with a mixture of chloralose (80 mg/kg) and sodium pentobarbitone (6 mg/kg) injected intravenously. Contractions of both nictitating membranes were recorded simultaneously on smoked paper by means of isotonic frontal writing levers which magnified the contractions about 12 times. One nictitating membrane was excited by stimulation of the pre-ganglionic cervical sympathetic trunk after sectioning the nerve centrally to the electrodes, while the other was excited by stimulating the post-ganglionic trunk after crushing the superior cervical ganglion. Both stimulating electrodes were connected to the same output of the stimulator and contractions were evoked by stimulation at a frequency of 5/sec for 10 sec in every 2 min with rectangular pulses of 0·5 msec duration and of a strength greater than that necessary to produce maximal contractions at this frequency. Blood pressure was recorded from a femoral artery. Drugs were injected intravenously. The effects of (+)-guanoxan were studied in one cat and the effects of the (−)-isomer in the other.

The drugs used were: (−)-adrenaline (British Drug Houses), (−)-noradrenaline bitartrate (Koch-Light), acetylcholine chloride (Roche), (±)-guanoxan sulphate (Pfizer) and the two isomers of guanoxan prepared as described above. The doses quoted refer to the sulphates in the case of guanoxan and its isomers, and to the base or cation for the other drugs.

Results

Adrenergic neuron blockade. Since the adrenergic neuron blocking action of this type of compound is not readily reversed, only one of the isomers or the racemate was examined in each preparation. Fig. 1 expresses the mean results of experiments on 45 isolated rabbit ear arteries in which the time taken for each compound to reduce the constrictor response to nerve stimulation by 50% was noted. These experiments showed that there was little if any difference between the potencies of (±)-, (+)- and (−)-guanoxan as adrenergic neuron blocking drugs in this preparation, and similar results were obtained in the rat and the cat.

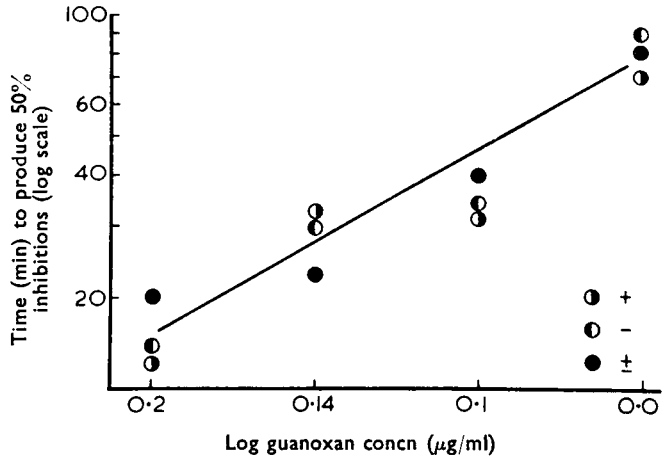

FIG. 1. Potencies of (+)-, (−)- and (±)-guanoxan in blocking responses of the isolated central artery of the rabbit's ear to periarterial nerve stimulation.

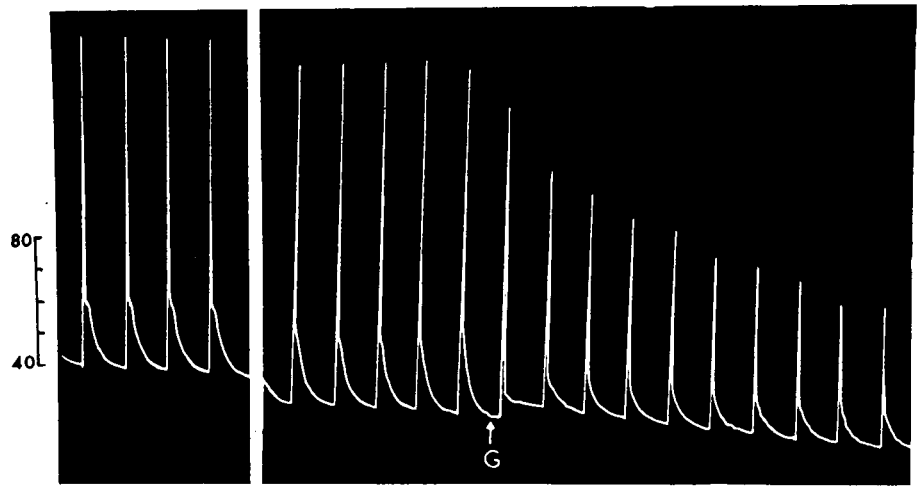

FIG. 2. Pressor responses (mm Hg) in the pithed rat to stimulation of the thoracolumbar sympathetic outflow (10/sec for 10 sec every 5 min). The gap in the record corresponds to 1 hr. At G, 0·5 mg/kg (±)-guanoxan intravenously.

In the pithed rat, pressor responses evoked by spinal cord stimulation usually increased in size during the first 30–60 min and then remained constant for several hours (Fig. 2). In each experiment, (±)-guanoxan, or one of the isomers, was initially injected in a dose of 0·25 mg/kg, and this dose reduced the pressor response in only 1 rat out of 10, and then only by 10%. Twenty min later, a dose of 0·5 mg/kg was injected and 20 min after that, a dose of 1 mg/kg was injected. The decrease in pressor response produced was noted 15–18 min after each injection and the results obtained for the racemate and the two isomers are expressed

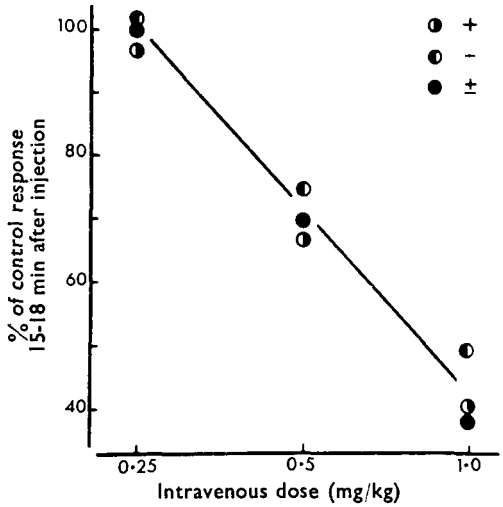

FIG. 3. Potencies of (+)-, (−)- and (±)-guanoxan in blocking pressor responses to spinal cord stimulation in the pithed rat.

graphically in Fig. 3. No account of cumulative effects could be taken and the graphs are therefore not meant to represent dose-response lines, but merely to illustrate that, as with the rabbit ear artery, there was little or no difference in the potencies of the three compounds.

In the two cats, the (+)- or the (−)- isomer were each injected at a dose level of 5 mg/kg intravenously. Responses of the nictitating membrane to both pre- and post-ganglionic stimulation were depressed at a similar rate and to a similar extent. In the dose used, both isomers produced about 80% depression of the nictitating membrane contractions within 20 min after injection. Fig. 4 illustrates the effects of the (+) isomer.

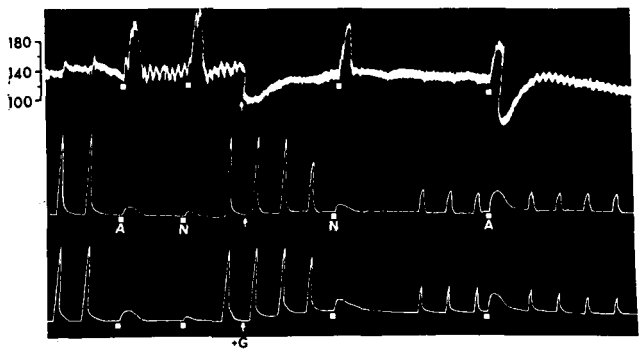

FIG. 4. Cat, 3·4 kg. Upper record, blood pressure (calibration in mm Hg); middle record, contractions of the right nictitating membrane in response to post-ganglionic stimulation; lowest record, contractions of the left nictitating membrane in response to pre-ganglionic stimulation (5/sec for 10 sec every 2 min). At A, 30 μg adrenaline; at N, 30 μg noradrenaline and at +G, 5 mg/kg (+)-guanoxan. All injections intravenously.

Davey & Reinert (1965) reported a similar potency of the racemic compound on the contractions of the cat nictitating membrane.

Catecholamine release. In concentrations of 0·2 μg/ml and above, (±)-guanoxan or the isomers usually produced constriction of the isolated rabbit ear artery. This effect of the (+)-isomer is illustrated in Fig. 8. Experiments on paired ear arteries showed that the (+)-isomer was more potent than the (−)-isomer in producing this effect (Figs 5 and 6) and the activity of the racemate is therefore primarily due to the (+)-isomer.

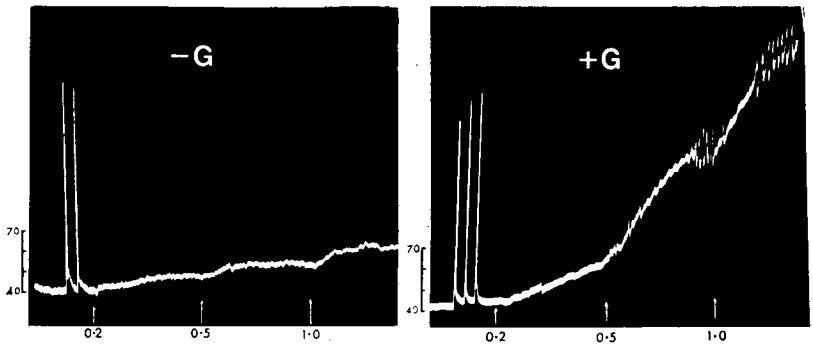

FIG. 5. Paired isolated central ear arteries of a rabbit. Responses on the left are to periarterial nerve stimulation. The left panel shows the effect of perfusion with (−)-guanoxan and the right with (+)-guanoxan. The concentrations, in μg/ml, are given below the arrows. Each concentration was perfused for 20 min. Calibration in mm Hg.

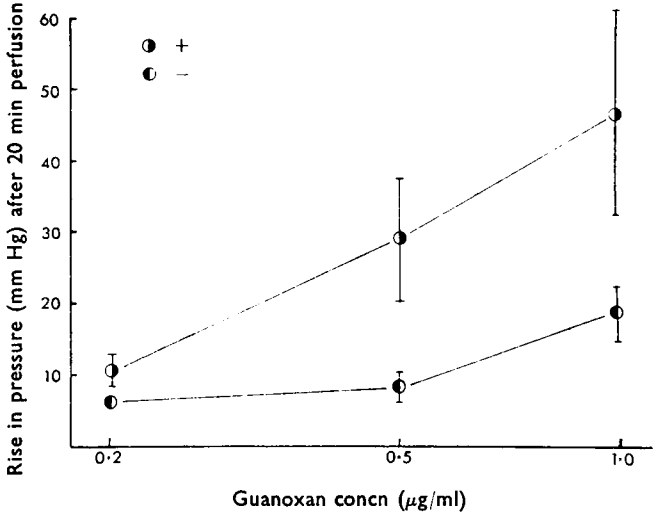

FIG. 6. Results of perfusion with (+)- or (−)-guanoxan obtained on 7 pairs of isolated central ear arteries of rabbits. The vertical lines are the standard errors.

In the pithed rat, a transient rise (5–10 min) in blood pressure was produced immediately after intravenous injection of the compounds (Fig. 7A). With repeated injections, tachyphylaxis to this pressor effect was evident (Fig. 7A) but the results showed that the order of potency of the compounds in producing this effect was again (+) > (±) > (−). In pithed rats that had been pretreated with reserpine to deplete the stores of catecholamine, the pressor response to the compounds was weak or absent (Fig. 7B) indicating that it was probably the result of catecholamine release.

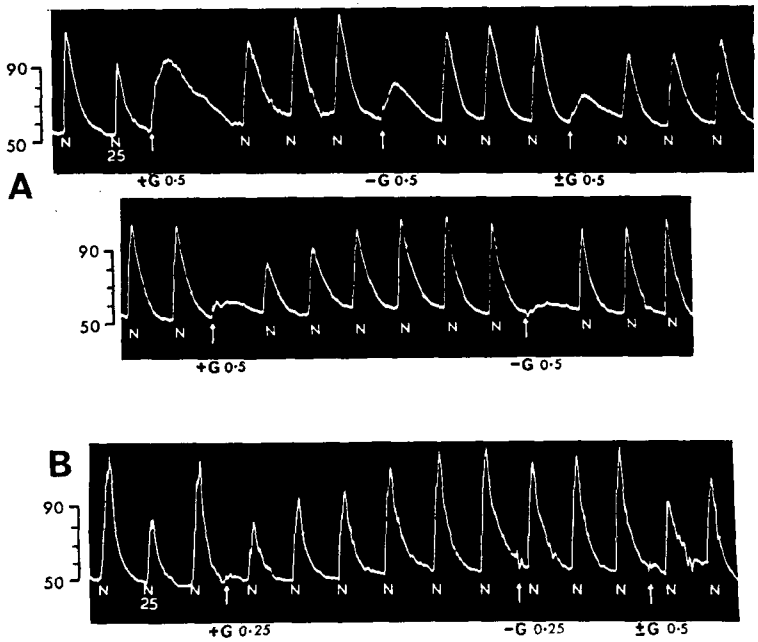

FIG. 7. Blood pressure of pithed rats (calibration in mm Hg); the record labelled B was obtained from a rat pretreated with reserpine. At N, 50 ng of noradrenaline; at N/25, 25 ng of noradrenaline; at +G, −G and ±G, (+)-, (−)- and (±)-guanoxan respectively. The doses of guanoxan and its isomers were as illustrated, in mg/kg. All injections intravenously. Noradrenaline was injected every 5 min except after guanoxan. The gap between the two panels of Fig. 7A corresponds to 30 min.

Catecholamine release by the (+)-isomer in a cat was evidenced by a small and gradually developing increase in the resting tone of the nictitating membrane (Fig. 4). This effect was not produced in the cat treated with the (−)-isomer, and neither isomer produced an initial rise in blood pressure. In fact, the immediate blood pressure response to the isomers in the two cats was a small and transient depressor effect (Fig. 4). No evidence of an initial pressor effect or of contraction of the nictitating membrane in the cat was reported to follow intravenous injection of the racemate by Davey & Reinert (1965), and in general the results confirm that catecholamine release following intravenous injection

in the cat is very much less than that following intravenous injection of guanethidine.

α-Adrenoreceptor blocking action. Davey & Reinert (1965) described a marked α-receptor blocking action of the racemate in the dog, but this effect was very weak in the cat. The present experiments on two cats confirmed that the α-receptor blocking action of the isomers is weak in this species. Fig. 4 illustrates a slight reduction in the pressor response to noradrenaline and the unmasking of a secondary depressor component of the response to adrenaline after injection of 5 mg/kg of the (+)-isomer. At the same time, however, the contractions of the nictitating membrane produced by the amines were enhanced. In the same cat, a further dose of 10 mg/kg of the (+)-isomer did not produce a stronger blocking action. This dose was more than sufficient to abolish the responses of the membrane to nerve stimulation. In the other cat no evidence of α-receptor block by the (−)-isomer was obtained.

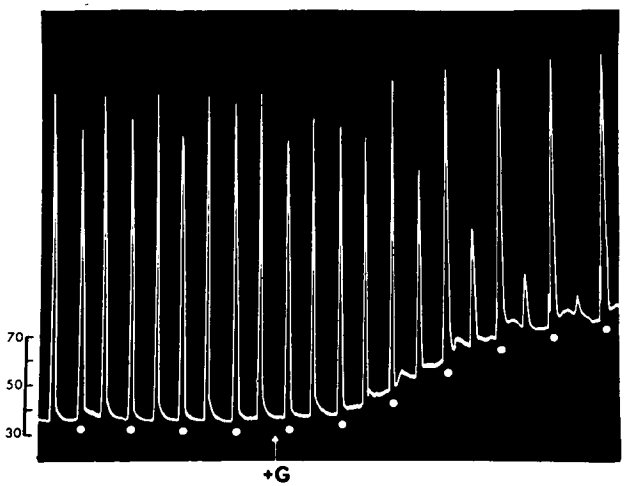

FIG. 8. Responses (calibration in mm Hg) of the isolated central ear artery of the rabbit to periarterial nerve stimulation (unlabelled responses) and to 30 ng noradrenaline (at the dots). Responses to one or the other were evoked every 2 min. At +G, perfusion with (+)-guanoxan (0·2 μg/ml) was commenced and continued throughout the rest of the record. Note that responses to noradrenaline were not depressed whereas those to nerve stimulation were blocked. Guanoxan caused an increase in the background resistance to perfusion.

In the isolated ear artery of the rabbit no evidence of α-receptor blockade by racemic guanoxan or either of its isomers was obtained. Fig. 8 illustrates persisting responses to noradrenaline during abolition of the responses to nerve stimulation by perfusion with 0·2 μg/ml of (+)-guanoxan. Even in concentrations up to 2 μg/ml of the compounds, responses to noradrenaline were never reduced but were increased in most experiments.

Of the preparations from the three species studied, definite evidence of α-receptor block was produced only in the rat. (±)-Guanoxan in a

dose of 0·5 mg/kg intravenously reduced the pressor response to noradrenaline in the pithed rat by 40–60%. Full recovery occurred within 20–30 min. Most, but not all, of the α-receptor blocking action of the racemate was displayed by the (+)-isomer, the (−)-isomer having a relatively weak effect. Fig. 7 illustrates the antagonistic action of the compounds against the pressor responses to noradrenaline in the pithed rat. In the experiment illustrated by Fig. 7B, the rat had been pretreated with reserpine to avoid the complication due to the pressor action of the compounds resulting from catecholamine release. It is of interest that the (+)-isomer was the most potent both in producing an initial pressor effect and in producing α-receptor block. Since these two actions are antagonistic, the catecholamine release is probably greater than that reflected by the pressor response.

α-Receptor block probably did not contribute greatly to the reduction in response to stimulation of the sympathetic outflow in the pithed rat. The time courses of the two actions were different; maximum α-receptor block was evident immediately after injection of guanoxan (Fig. 7) but the effect wore off quickly. Maximum adrenergic neuron block took about an hour to develop (Fig. 2) and was irreversible.

Ganglion blockade and atropine-like action. Davey & Reinert (1965) recorded only a weak and transient depressant effect of guanoxan, compared with that of guanethidine, on the evoked ganglionic action potential recorded from the superior cervical ganglion of the cat, and it is possible that ganglion block was responsible for the initial transient depressor effect of the isomers in the present experiments on cats. However, no difference could be detected between the rate of onset of block of contractions of the nictitating membrane evoked by pre- or post-ganglionic stimulation (Fig. 4) showing that any contribution by ganglion block is unimportant in the cat.

Spinal stimulation of the pithed rat excites pre-ganglionic sympathetic fibres (Gillespie & Muir, 1967) and the possibility that ganglion block was a contributory factor in this species was investigated by recording the heart block produced by vagal stimulation or by acetylcholine. Doses of (±)-, (+)- or (−)-guanoxan ranging from 0·5–2·0 mg/kg intravenously reduced, but did not abolish, the response to vagal stimulation. However, the response to acetylcholine was always reduced more than that to nerve stimulation, suggesting that a weak atropine-like action was mainly responsible. This effect persisted for up to 15–60 min depending on the dose. There appeared to be no difference in the potencies of the two isomers in producing this atropine-like effect but insufficient experiments were done to detect small differences.

Discussion

The results showed that in the preparations from the three species studied, (±)-guanoxan and its two isomers are equipotent in producing adrenergic neuron block, indicating that the stereochemical configuration at the 2 position of the compound is unimportant in this action.

Species difference is evident in the α-adrenoreceptor blocking action of guanoxan. Of the species studied, it is most pronounced in the dog (Davey & Reinert, 1967) and the rat, weakly evident in the cat, and undetectable in the rabbit. It is of interest that both the α-receptor blocking action and the ability to cause catecholamine release reside mainly in the (+)-isomer. The absolute stereochemical configuration of the compounds has not yet been elucidated.

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