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THE DISTRIBUTION OF SOME QUATERNARY AMMONIUM SALTS IN THE PERIPHERAL NERVOUS SYSTEM OF CATS IN RELATION TO THE ADRENERGIC BLOCKING ACTION OF BRETYLIUM

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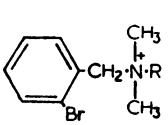
The concentrations of bretylium in the peripheral nervous system of cats after subcutaneous dosage have been compared with those drugs bearing either chemical or pharmacological resemblance to bretylium. *o*-Bromobenzyltrimethylammonium iodide (383C57), a chemical homologue of bretylium with feeble adrenergic blocking activity, selectively accumulated in adrenergic neurones to attain concentrations comparable with those found for bretylium, but it did not persist in the neurones. {2-(4-Benzoyl-2,6-dimethylphenoxy)ethyl}trimethylammonium, the 4-benzoyl derivative of 2,6-xylyl choline ether (172C58), a pharmacological analogue of bretylium but with little chemical resemblance, had a less marked selective affinity for adrenergic neurones and the concentrations after an effective dose were much lower than found for bretylium. Pentacynium {N¹-5-cyano-5,5-diphenylpentyl)-N¹N¹N²-trimethylethylene-1-ammonium-2-morpholinium di-iodide}, a bis-quaternary ammonium-type ganglion blocking agent, had no selective affinity for adrenergic neurones. Bretylium was not displaced from adrenergic neurones by a subsequent dose of 172C58. The potency and duration of local anaesthetic action of bretylium, 383C57 and 172C58 were roughly parallel to the potency and duration of their adrenergic blocking action. The results are discussed in relation to the role of selective accumulation in adrenergic neurones by bretylium in its adrenergic blocking activity.

Selective inhibition of the peripheral adrenergic system by bretylium (I ; R = ethyl) (Boura & Green, 1959) seems to be related to a specific affinity of the drug for adrenergic neurones (Boura, Copp, Duncombe, Green & McCoubrey, 1960b). The rise and fall of concentration of the ^{14}C-labelled drug in the adrenergic nerves and ganglia of cats showed a fair parallelism to the time course of the adrenergic block, and high concentrations of the drug persisted in these structures when levels in other organs had fallen considerably.



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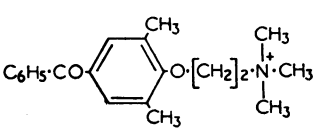

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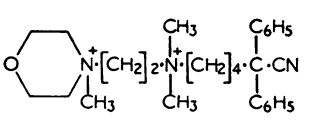

III

{2-(4-Benzoyl-2,6-dimethylphenoxy)ethyl}trimethylammonium, the 4-benzoyl derivative of 2,6-xylyl choline ether, referred to as 172C58 (II), has a similar pharmacological effect to bretylium in cats at one-tenth of the subcutaneous dosage

needed for bretylium. The effects are more rapid in onset. The adrenergic neurone block caused by 172C58, in the *in vitro* preparation described by Finkleman (1930), unlike that caused by bretylium, is readily abolished by washing. The drug has little adrenergic blocking action in man (Boura, Coker, Copp, Duncombe, Elphick, Green & McCoubrey, 1960a). By contrast, *o*-bromobenzyltrimethylammonium, referred to as 383C57 (I ; R = methyl), has very little adrenergic neurone blocking action in cats in spite of its close chemical resemblance to bretylium (Boura & Green, unpublished). The distribution of these quaternary salts in cats has therefore been compared to those of bretylium and pentacynium (III), a ganglion blocking agent of the bis-quaternary ammonium type (Adamson, Billinghurst, Green & Locket, 1956).

METHODS

Chemicals

The ^{14}C-labelled drugs were prepared by Dr F. C. Copp (383C57 and 172C58) and Mr J. W. Billinghurst (pentacynium) by quaternizing the appropriate tertiary amine with [^{14}C]-methyl iodide. Pentacynium was labelled at the morpholine nitrogen atom. They were checked for purity as described for bretylium (Boura *et al.*, 1960b).

o-Bromobenzyltrimethylammonium (383C57). The product had a specific activity of 1 mC/mmole. For doses of 10 mg/kg it was diluted with an equal part of inactive carrier. For the 50 mg/kg dose it was diluted with ten parts of carrier.

{2-(4-Benzoyl-2,6-dimethylphenoxy)ethyl}trimethylammonium (172C58). The product, 5 mC/mmole, was used without dilution by carrier.

Pentacynium. The product, 1 mC/mmole, was used without dilution by carrier.

Experimental

Cats received the drugs subcutaneously and were killed at the stated times by exsanguination from the aorta under ether anaesthesia. Doses were, for 383C57, 10 and 50 mg/kg ; for 172C58, 1 mg/kg ; and for pentacynium, 2 mg/kg. Tissue sampling and radioactivity determinations were performed as described for bretylium (Boura *et al.*, 1960b).

Cats under chloralose anaesthesia were prepared for preganglionic stimulation of the superior cervical sympathetic nerve on both sides (10 cycles/sec for 1 min every 3 min), and contractions of the nictitating membranes were recorded on a smoked drum. The response was constant at the fourth stimulation. Labelled bretylium (2.5 mg/kg) was given intravenously and after 5 min a further 2.5 mg/kg. When the height of the trace on the drum was reduced by half (in 15 to 20 min), the left superior cervical sympathetic nerve and ganglion and the vagus and nodose ganglia were excised and prepared for counting. A further 2.5 mg/kg bretylium was given, followed by either saline or 172C58 (unlabelled) (2 mg/kg). After 172C58 the membrane response was completely inhibited in a few minutes. With bretylium alone, inhibition was complete in a further 30 min. The right superior cervical sympathetic nerve and ganglia and the vagus and nodose ganglia were removed 50 min after the first dose and prepared for counting.

Local anaesthetic activity after intradermal injection into guinea-pigs was tested by the method of Bülbring & Wajda (1945).

RESULTS

Distribution of {2-(4-benzoyl-2,6-dimethylphenoxy)ethyl}trimethylammonium (172C58). The general pattern of distribution of 172C58 in the glands and larger organs of cats killed at 2, 12 and 18 hr after 1 mg/kg is shown in Table 1. The dose fully relaxed the nictitating membranes of all the four cats, within 30 min of

TABLE 1

DISTRIBUTION OF {2-(4-BENZOYL-2,6-DIMETHYLPHENOXY)ETHYL}TRIMETHYL-AMMONIUM IODIDE IN CAT TISSUES

1 mg/kg of the *N*-[^{14}C]-methyl-labelled drug was given subcutaneously. Concentrations are expressed in mμmoles/g wet tissue. 1 mμmole=0·439 μg 172C58

	Time in hr			
Tissue	2	12	18	18
Adrenal gland	0·3	0·4	0·0	0·2
Parotid gland	4·2	1·3	0·5	0·2
Thyroid gland	1·7	—	0·1	—
Heart	6·4	3·4	0·8	0·8
Kidney	2·2	1·6	0·8	—
Spleen	2·3	1·8	0·9	0·4
Liver	9·5	6·0	4·3	4·4
Lung	0·9	1·5	1·3	1·2
Plasma	0·1	0·06	0·4	—

injection. The concentrations of 172C58 in a variety of other tissues, not given in Table 1, at 18 hr after the dose were between 0.1 and 0.4 mμmoles/g. There was none in perirenal fat.

The drug appeared to be rapidly absorbed by the liver, which achieved the highest concentration of any tissue examined, and relatively high levels tended to persist. A relatively high proportion of the dose was found in the bile of one cat killed at 18 hr (130 μg.≡6% of the dose). Unfortunately, urine was not obtainable from this animal. The kidney contained a relatively small proportion of the dose at all time intervals studied. In the one specimen of urine obtained at 18 hr there was 350 μg≡20% of the dose.

TABLE 2

DISTRIBUTION OF {2-(4-BENZOYL-2,6-DIMETHYLPHENOXY)ETHYL}TRIMETHYL-AMMONIUM IODIDE IN NERVES AND GANGLIA OF CATS

1 mg/kg of the *N*-[^{14}C]-methyl-labelled drug given subcutaneously. Concentrations are expressed in mμmoles/g wet tissue. 1 mμmole=0·439 μg 172C58

	Time in hr			
Tissue	2	12	18	18
Sympathetic ganglia				
Superior cervical	3·7	5·4	5·1	4·6
Stellate	4·7	3·8	2·0	2·8
Coeliac	5·6	4·9	2·5	3·0
Superior mesenteric	5·4	6·7	1·2	—
Inferior mesenteric	4·0	3·4	1·9	—
Other ganglia				
Sympathetic chain	1·0	1·0	1·8	—
Dorsal root	0·8	0·9	0·6	—
Nodose	1·0	1·3	0·3	1·0
Adrenergic nerves				
Post-ganglionic cervical	0·9	2·0	2·0	2·2
Inferior cardiac	1·7	1·3	2·3	2·1
Splenic and gastric	0·4	1·4	0·8	—
Cholinergic nerves				
Pre-ganglionic cervical	0·4	0·4	0·2	—
Splanchnic	0·2	0·7	0·0	—
Optic	—	—	0·2	—
Vagus	0·1	—	0·2	—
Phrenic	—	—	0·1	—
Sciatic	—	0·1	0·04	—

The concentrations of 172C58 found in the sympathetic ganglia were higher than in most tissues (1.2 to 5.6 mμmoles/g) and the drug tended to persist in these structures (Table 2). By contrast, the adrenal glands took up very little of the drug. Concentrations in the adrenergic nerves were not outstandingly high, though they exceeded those in non-adrenergic nerves. Thus the concentrations in the pre-ganglionic cervical sympathetic nerves were one-fifth to one-tenth of those in the post-ganglionic nerves at 12 and 18 hr after the dose. Ganglia other than those of the sympathetic system contained up to 1.3 mμmoles/g, the highest being in the nodose ganglion at 12 hr after the dose. Among tissues not mentioned in the table, the ciliary and gasserian ganglia, the cerebral and cerebellar cortices and the spinal cord did not accumulate the drug. The hypothalamus had a trace (0.1 mμmole/g) at 12 hr. There was no evidence for radioactive metabolic products in urine after autoradiography of chromatograms of whole urine or trichloroacetic acid extracts of liver in *s*-butanol–acetic acid–water mixture (12:5:3).

Distribution of o-bromobenzyltrimethylammonium (383C57). The concentration of 383C57 in representative tissues at 3, 12 and 18 hr after 10 mg/kg is summarized in Tables 3 and 4. One of the three cats used, that killed at 12 hr, showed just noticeable relaxation of the nictitating membranes. No relaxation had been seen in a previous series of five cats that had received the same dose level of unlabelled drug. After 50 mg/kg a near maximal relaxation of the nictitating membranes occurred, but they had almost regained their normal tone when the animal was killed at 12 hr after the dose. A similar brief effect was seen in three other cats receiving the unlabelled drug at the same dose level. This near toxic dose caused salivation and vomiting.

Concentrations of 383C57 in the larger organs after 10 mg/kg were highest at 3 hr after the dose, though the blood levels were fairly constant in all three cats used. Fairly high concentrations were found in the adrenal glands and (in one cat only) in the thyroid.

TABLE 3

DISTRIBUTION OF *o*-BROMOBENZYLTRIMETHYLAMMONIUM IODIDE (383C57) IN CAT TISSUES

10 mg/kg of the *N*-[^{14}C]-methyl-labelled drug was given subcutaneously. Concentrations are expressed in mμmoles/g wet tissue. 1 mμmole=0·356 μg 383C57

Tissue	Time in hr		
	3	12	18
Adrenal gland	67	59	39
Parotid gland	—	0	6
Thyroid gland	—	120	2
Heart	63	13	9
Kidney	21	9	5
Spleen	44	17	16
Liver	51	9	6
Lung	—	10	6
Blood	7	8	9
Skeletal muscle	18	12	12
Area postrema	7	5	12
Cerebral cortex	1	0	—
Cerebellar cortex	0	0	—
Hypothalamus	0	7	0
Spinal cord	—	0	0

TABLE 4

DISTRIBUTION OF *o*-BROMOBENZYLTRIMETHYLAMMONIUM IODIDE (383C57) IN NERVES AND GANGLIA OF CATS

10 mg/kg of the *N*-[^{14}C]-methyl-labelled drug was given subcutaneously. Concentrations are expressed in mμmoles/g wet tissue. 1 mμmole=0·356 μg 383C57

	Time in hr			
Tissue	3	12	18	50 mg 12
Sympathetic ganglia				
Superior cervical	149	164	105	312
Stellate	213	468	97	219
Inferior mesenteric	—	39	47	93
Coeliac	213	120	72	207
Other ganglia				
Dorsal root	21	6	5	15
Nodose	17	9	39	18
Ciliary	63	—	2	25
Adrenergic nerves				
Post-ganglionic cervical	28	76	63	103
Inferior cardiac	193	176	71	162
Splenic and gastric	—	—	70	193
Hypogastric	71	0	30	203
Cholinergic nerves				
Pre-ganglionic cervical	18	14	20	49
Splanchnic	—	14	—	—
Vagus	13	9	23	12
Phrenic	—	13	3	22
Sciatic	—	2	7	9

The highest concentrations were found in the sympathetic ganglia at 12 hr after the dose. The levels in the cat killed at 18 hr were much lower. Other ganglia had lower concentrations of the drug. Similarly, the levels in adrenergic nerves considerably exceeded those in non-adrenergic nerves.

There was good recovery of the dose from urine in the cat killed at 18 hr (76%). Chromatography of this urine and of a trichloroacetic acid extract of the liver in *s*-butanol–acetic acid–water mixture (12:5:3) followed by autoradiography revealed only one radioactive spot at R_F 0.8 corresponding to the unchanged drug.

TABLE 5

DISTRIBUTION OF PENTACYNIUM IN THE NERVES AND GANGLIA OF CATS

2 mg/kg of *N*-[^{14}C]-methyl-labelled pentacynium given subcutaneously. Tissues were sampled at 3 hr after the dose. Concentrations in mμmoles/g wet tissue. 1 mμmole=0·679 μg pentacynium iodide

Tissue	Concentration
Ganglia	
Superior cervical	1·4
Stellate	1·9
Superior mesenteric	0·0
Coeliac	Trace
Nodose	4·5
Ciliary	5·5
Nerves	
Post-ganglionic cervical sympathetic	Trace
Splenic and gastric	2·0
Hypogastric	3·8
Inferior cardiac	Trace
Greater splanchnic	3·8
Vagus	1·3
Pre-ganglionic cervical sympathetic	5·1
Sciatic	Trace

The level of 383C57 in nerves and ganglia after 50 mg/kg was roughly doubled compared to the 10 mg/kg dose at the same time interval. Notable exceptions were the stellate ganglion with a lower concentration and the hypogastric nerve with a much higher concentration.

Distribution of pentacynium. The dose of pentacynium (2 mg/kg) had relaxed the nictitating membranes and dilated the pupils maximally when the cat was killed at 3 hr after the dose. The levels in nerves and ganglia are given in Table 5. Counting rates were low and errors in estimation of the concentrations amounted to ±10% for the more active samples to ±50% for those of low activity. There was little radioactivity in the larger organs, except kidney. The result indicates that pentacynium had no affinity for the adrenergic ganglia or their post-ganglionic nerves in excess of that shown for cholinergic nervous tissue.

Local anaesthetic activity. The duration of local anaesthesia after intradermal injection of bretylium, 172C58 and 383C57 is shown in Fig. 1. While 383C57 was equiactive to bretylium in potency as measured by maximum effect, it had little

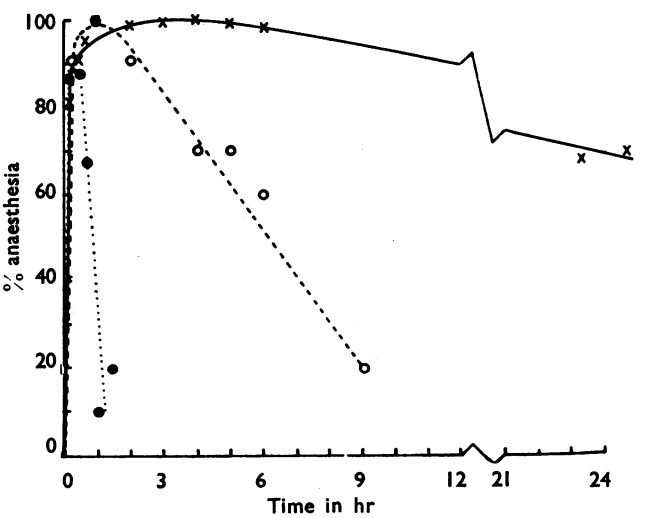

Fig. 1. Local anaesthetic activity of 3% *o*-bromobenzyltrimethylammonium (383C57) (●.... ●), 0·3% {2-(4-benzoyl-2,6-dimethylphenoxy)ethyl}trimethylammonium (172C58) (○ - - - ○), and 3% bretylium (X——X) after intradermal injection in guinea-pigs.

persistence. Indeed, the persistence of the local anaesthetic effect of bretylium is outstanding. Dose for dose, 172C58 had greater potency than bretylium, but at an equipotent dose its persistence was much less marked.

Influence of {2 - (4 - benzoyl - 2,6 - dimethylphenoxy)ethyl} trimethylammonium (172C58) on the accumulation of bretylium. Table 6 shows that the concentrations of bretylium in the superior cervical ganglion and its post-ganglionic nerve at 50% inhibition of contraction of the nictitating membranes were 70 mμmoles/g (mean of 4 results) and 18 mμmoles/g (mean of 2 results) respectively. At full inhibition of contraction a mean concentration of 148 mμmoles/g was found in the ganglion,

TABLE 6

CONCENTRATION OF BRETYLIUM IN NERVES AND GANGLIA OF CATS AT PARTIAL AND FULL INHIBITION OF THE CERVICAL SYMPATHETIC NERVE AND THE LACK OF INFLUENCE OF {2-(4-BENZOYL-2,6-DIMETHYLPHENOXY)ETHYL}TRIMETHYL-AMMONIUM (172C58)

Cats under chloralose anaesthesia given 2 × 2·5 mg/kg doses of [^{14}C]-labelled bretylium intravenously. The left cervical sympathetic and vagus nerves were sampled at approx. 50% inhibition. A further 2·5 mg/kg labelled bretylium was given, followed by either saline or 172C58 (2 mg/kg) intravenously and the nerves of the right side sampled at 50 min. Concentration in mμmoles/g

	Bretylium+saline		Bretylium+172C58	
Tissue	At 50% block	At full block	At 50% block	At full block
Superior cervical ganglion	79, 15	125, 171	101, 86	204, 139
Post-ganglionic cervical sympathetic nerve	19, —	17, —	79, —	39, —
Pre-ganglionic cervical sympathetic nerve	—, 7	—, 22	—, 13	—, 18
Nodose ganglion	20, 32	28, 39	33, 29	38, 28
Vagus	8, 8	9, 22	8, 11	12, 13
Stellate ganglion	— —	153, —	— —	212, —
Coeliac ganglion	— —	154, —	— —	237, —
Blood	4, —	7, 2·4	20, —	4, 4

and this was not significantly altered (172 mμmoles/g) by a dose of 172C58. A maximum concentration in the nodose ganglia and the vagus nerves (about 10 mμmoles/g) was achieved virtually within 20 min.

DISCUSSION

The marked affinity of bretylium for the peripheral adrenergic neurones of cats (Boura *et al.*, 1960b) undoubtedly contributes to its adrenergic neurone blocking action in this species. This discussion is concerned mainly with the problem whether the mechanism of this selective localization is an integral part of the adrenergic blocking mechanism or whether the localization is a fortuitous property ensuring the presence of adequate levels of drug at its site of action.

Pentacynium, a ganglion blocking agent, inhibits the effect of pre-ganglionic stimulation of the superior cervical sympathetic nerve, but its mode of action clearly differs from that of bretylium (Boura & Green, 1959). Its failure to accumulate selectively in adrenergic ganglia suggests that the localization of bretylium is a

TABLE 7

COMPARATIVE ACTIVITIES OF {2-(4-BENZOYL-2,6-DIMETHYLPHENOXY)ETHYL}-TRIMETHYLAMMONIUM (172C58), BRETYLIUM AND *o*-BROMOBENZYLTRIMETHYL-AMMONIUM (383C57)

	172C58	Bretylium	383C57
Adrenergic neurone			
Accumulation in	Low	High	High
Persistence in	Moderate	High	Low
Persistence of block	Moderate	High	Low
Finkleman preparation			
Activity	High	Moderate	Low
Persistence after washing	Low	High	Low
Local anaesthesia			
Activity	High	Moderate	Low
Persistence	Moderate	High	Low

specific property of this type of adrenergic blocking drug. The results with *o*-bromobenzyltrimethylammonium and {2-(4-benzoyl-2,6-dimethylphenoxy)ethyl}-trimethylammonium, however, show that any relation between adrenergic blocking mechanism and selective localization is not a simple one.

In Table 7, ratings have been given to the degrees of selective accumulation in adrenergic nervous tissue relative to dosage for *o*-bromobenzyltrimethylammonium, {2-(4-benzoyl-2,6-dimethylphenoxy)ethyl}trimethylammonium and bretylium, to their relative potencies and persistence of adrenergic block in the whole animal and to their intrinsic adrenergic blocking activity as indicated by the Finkleman preparation. {2-(4-Benzoyl-2,6-dimethylphenoxy)ethyl}trimethylammonium appears to have an intrinsic activity some ten times that of bretylium and about fifty times that of *o*-bromobenzyltrimethylammonium. The levels of {2-(4-benzoyl-2,6-dimethylphenoxy)ethyl}trimethylammonium in adrenergic neurones were about one-hundredth of those found for bretylium at comparable pharmacological effect, but were only about five times those found in cholinergic nerves and ganglia. There is nevertheless a clear selective localization of {2-(4-benzoyl-2,6-dimethylphenoxy)-ethyl}trimethylammonium in adrenergic nervous tissue. Conversely, *o*-bromobenzyltrimethylammonium, with very low intrinsic activity, accumulated in adrenergic neurones to about the same degree as bretylium, but it lacked persistence. Since all three drugs accumulated in tissues to levels considerably higher than those in blood, there must be a degree of non-specific accumulation in adrenergic neurones analogous to that in liver or cholinergic nerves. Table 8 shows the excess of

TABLE 8

"SPECIFIC" ACCUMULATION OF QUATERNARY AMMONIUM SALTS IN THE SUPERIOR CERVICAL GANGLIA AND POST-GANGLIONIC CERVICAL SYMPATHETIC NERVES

The figures are the excess concentration {2-(4-benzoyl-2,6-dimethylphenoxy)ethyl}trimethylammonium (172C58), *o*-bromobenzyltrimethylammonium (383C57) and bretylium in mμmoles/g wet tissue for (a) superior cervical ganglia over nodose ganglia, (b) post- over pre-ganglionic cervical sympathetic nerve

	172C58			383C57			Bretylium		
Time in hr	2	12	18	3	12	18	3	12	18
Superior cervical ganglia	2·7	4·1	4·8	132	155	166	159	255	860
Post-ganglionic cervical sympathetic nerve	0·5	1·7	1·8	10	52	43	14	49	620

concentration in the superior cervical ganglia over that in the nodose ganglia and the excess in post-ganglionic cervical sympathetic nerves above that in the pre-ganglionic nerves at the time intervals studied. The figures indicate that *o*-bromobenzyltrimethylammonium was little inferior to bretylium in this "specific" accumulatory capacity up to 12 hr after the dose, but that it did not continue to accumulate after this time as did bretylium. "Specific" accumulation of {2-(4-benzoyl-2,6-dimethylphenoxy)ethyl}trimethylammonium apparently occurred rapidly to a low constant level. There is clearly a dissociation between intrinsic activity and degree of specific accumulation.

The relatively low intrinsic activity of bretylium compared with {2-(4-benzoyl-2,6-dimethylphenoxy)ethyl}trimethylammonium is probably compensated by its greater

persistence, while *o*-bromobenzyltrimethylammonium is probably virtually inactive because its very low intrinsic activity is not compensated by persistence. The mechanism of persistence is conceivably distinct from that of *initial* accumulation, which indeed may be no more specific than occurs in other organs. On these grounds the accumulation of bretylium could be the consequence rather than the cause of adrenergic block, and its binding in the tissue could result from some change in the tissue. The accumulation of bretylium was not influenced by a subsequent dose of {2 - (4 - benzoyl - 2,6 - dimethylphenoxy)ethyl}trimethylammonium—it was neither displaced nor was accumulation enhanced. Though application of bretylium to sensory nerve endings in the skin causes persistent local anaesthesia, there is clearly no marked accumulation of bretylium by these nerve endings after systemic administration, since bretylium does not cause generalized cutaneous sensory loss. It seems reasonable to conclude that persistence, which can lead to retention and slow accumulation, is more related to adrenergic blocking mechanism than accumulation itself and that this persistence is likely to be a reflection of specific binding at some hypothetical receptor. Thus, {2-(4-benzoyl-2,6-dimethylphenoxy)-ethyl}trimethylammonium, with a high intrinsic activity, has a relative inability to persist, for it can be readily washed out of *in vitro* preparations, and this may go some way to explain its failure to effect adrenergic block in man.

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