previously described and the dry weight of the secondary amine hydrochloride fraction was found to be 3.98 g (13 mmoles). The solid was made up to 100 ml: α_D −1.23 ± 0.02°, $[\alpha]_D$ −15.5 ± 0.2°. On the same basis of calculation as in the previous experiment this corresponds to 84.7% L (reasonably, 80–90%) of the D-(−) isomer. The solution was evaporated to 31 g giving crop I, then to 14 g for II, to 7.5 g for III, and to 4 g for IV in which a different type of crystal was apparent. The first crops were recrystallized serially from 15 ml of H_2O giving crops of 1.8 g and 0.5 g, respectively, which were combined and recrystallized again from 20 g of H_2O. The product, 1.6 g, was identical with the previously prepared D-(−) isomer.

sec-Butyl mesylate was prepared by the method of Hoffmann.[22]

*sec*BuOH was resolved by literature methods[23] by fractional crystallization of the brucine half-phthalates. We were not successful in attempts to purify brucine L-*sec*-butyl acid phthalate but highly enriched L half-ester could be obtained by crystallization of racemic half-ester from material recovered from the more soluble brucine salt fractions. The oily ester remaining after no more DL ester crystallized on refrigeration was estimated by rotation (in EtOH) to be about 80% L and 20% D isomer.

Recovery of optically active alcohol from half-ester or directly from brucine salt by alkaline hydrolysis, distillation, etc., entailed, in our hands, unacceptable losses. A more convenient and efficient procedure was found to be distillation with excess benzylamine.

D-*sec*-**BuOH.**—D-*sec*-Butyl acid phthalate (61.5 g, 0.27 mole) was heated with 80 ml of benzylamine. A thermometer registered the temperature of the liquid and a second surmounted a 5-cm Vigreux column leading to a condenser. The receiver was protected from moisture. The internal temperature was raised during 18 min to 140°. At this point there was some refluxing (but not distillation) of liquid. During the next few minutes the internal temperature fell and after 58 min of constant heating it was 125°. Some distillation took place during this period. Heating was increased gradually over 3.5 hr until the temperature of the melt was 206° and high-boiling liquid was condensing in the lower part of the fractionating column. The condenser was rinsed with pentane into the receiving flask, the volume in the flask was increased with pentane to about 50 ml, and the distillate (which contained some water and benzylamine) was dried ($CaSO_4$). The distillate was removed from the desiccant and distilled through a short fractionating column. There was obtained 17 g of pure D-*sec*-BuOH. In several preparations by this method, yields were consistently 85–90%. Examination of the (solidified) residue in the reaction flask showed it to be mainly N,N′-dibenzylphthalamide. Benzylamine was selected for this reaction on the basis of availability and boiling point. Presumably, any other simple, primary aliphatic amine boiling well over 150° could replace it.

2-Amino-2-methylhexane[24] required for the preparation of LXX was prepared by the Hoffmann reaction from the corresponding amide. The Jeffreys[25,26] modification of the Hoffmann reaction was most advantageous but even this variation gave inferior yields (around 50%). Considerable amounts of amide were recovered and it is suspected that hindrance slowed the initial step of N-halogenation.

Acknowledgment.—The authors wish to express their gratitude to Dr. S. W. Blackman for the many microanalyses required and to Mrs. Justina Strelitz and Messrs. Joseph Horodniak and Thomas McInerny for technical assistance.

(22) H. M. R. Hoffmann, *J. Chem. Soc.*, 1249 (1964).

(23) *Cf.* especially S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **75**, 1744 (1953).

(24) O. S. Urbenskaya, *Zh. Obshch. Khim.*, **29**, 174 (1959); *Chem. Abstr.*, **53**, 21661 (1959).

(25) E. Jeffreys, *Ber.*, **30**, 898 (1897); *Am. Chem. J.*, **22**, 14 (1899).

(26) The hydrolysis of the urethan obtained by the Jeffreys method is discussed by E. Magnien and R. Baltzly, *J. Org. Chem.*, **23**, 2039 (1958).

Adrenergic Neurone Blocking Agents. III.[1] Heterocyclic Analogs of Guanoxan

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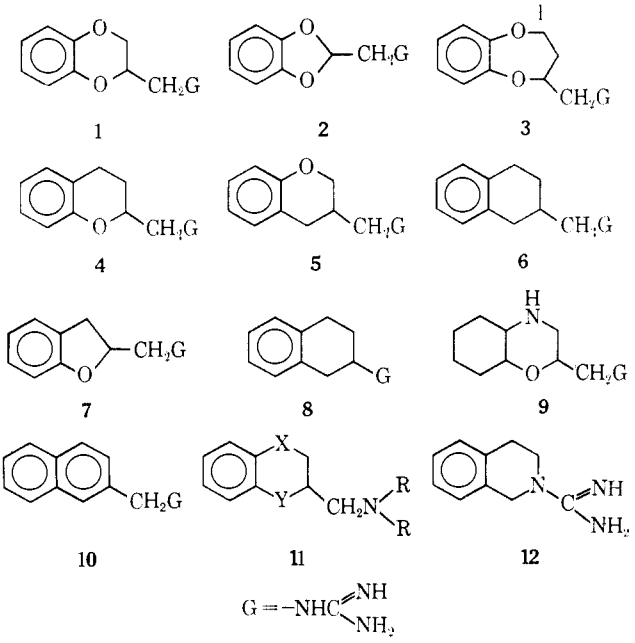
Analogs of guanoxan modified in the heterocyclic ring have been compared with respect to their adrenergic neurone blocking potencies, their effects *vs.* epinephrine and norepinephrine in the cat, and their antihypertensive effects in the dog.

It has been reported[2] that the antihypertensive agent guanoxan (**1**) displayed, like guanethidine, adrenergic neurone blocking properties in the cat, but in contrast to guanethidine, guanoxan also displayed a classical blockade of α receptors. The effects on these properties upon introduction of substituents to the aromatic ring[1a] or to the dioxane ring,[1b] and of modification of the side chain,[1a] have already been discussed.

This paper is concerned with the adrenergic neurone blocking activity of **2–10** in which the heterocyclic ring of guanoxan has been modified. Syntheses of most of these compounds have already been described in the literature. Additional features of interest, and details of those syntheses not already reported, are described in the Experimental Section.

Biological Results and Discussion.—Adrenergic neurone blocking activity of the compounds was measured



(1) (a) Paper I in this series: J. Augstein, S. M. Green, A. M. Monro, G. W. H. Potter, C. R. Worthing, and T. I. Wrigley, *J. Med. Chem.*, **8**, 446 (1965); (b) paper II: A. M. Monro, G. W. H. Potter, and M. J. Sewell, *ibid.*, **10**, 880 (1967).

(2) M. J. Davey and H. Reinert, *Brit. J. Pharmacol.*, **24**, 29 (1965).

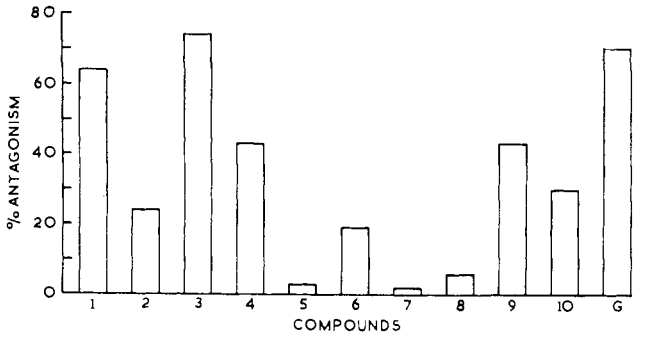


Figure 1.—Histogram showing the effect of a dose of 5 mg/kg iv of **1–10** and guanethidine (G) on the contractions of the nictitating membrane in response to preganglionic cervical sympathetic stimulation (10 v_1 500 μs, 16 cps for 40 sec) in cats anesthetized with chloralose. Responses were measured 1 hr after compound administration. The height of each column represents the percentage antagonism of the control response to stimulation and the numbers of the compounds are situated below the columns.

(a) by observing the degree of relaxation of the nictitating membrane of the conscious cat 20 hr after subcutaneous injection of the compound at two dose levels (Table I), and (b) by observing the drug-induced antagonism to the contraction of the nictitating membrane caused by stimulation of the preganglionic[3] cervical sympathetic nerve in the anesthetized cat (Figure 1).

TABLE I

ADRENERGIC NEURONE BLOCKING ACTIVITY OF SOME GUANIDINES IN CONSCIOUS CATS[a]

	Relaxation of nictitating membrane[b] at 20 hr	
No.	5 mg/kg	20 mg/kg
1	+	+++
2	0	0
3	+	+++[c]
4	0	+++
5	0	0
6	0	0
7	0	0
8	0	+
9	++[d]	++[d]
10	0	0

[a] Four cats were used at each dose level. [b] Percentage of eye covered: 0 (<15%), + (15–30%), ++ (30–50%), +++ (>50%). On this scale guanethidine was rated ++ (5 mg/kg) and +++ (20 mg/kg). [c] This compound (20 mg/kg) showed ++ activity at 92 hr. [d] This compound (at both dose levels) showed +++ activity at 44 and 68 hr diminishing to ++ at 92 hr.

The antiadrenergic properties of the compounds were compared by observing the reduction of the blood pressure response to intravenously injected epinephrine and norepinephrine in the anesthetized cat (Figures 2 and 3).

About 30 years ago, Benoit and Bovet[4] compared the adrenolytic properties of a series of dialkylaminomethylbenzoheterocycles (**11**, X and/or Y = NH, O, S) with those of the corresponding 1,4-benzodioxan derivatives (**11**, X = Y = O), and observed in general,

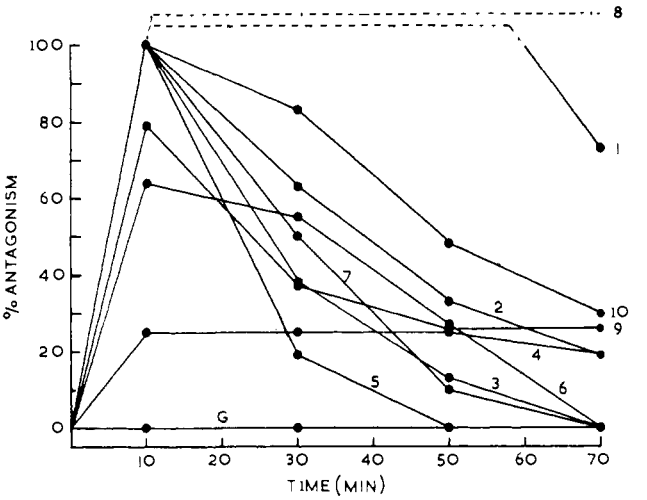


Figure 2.—Graph showing the effects of **1–10** and guanethidine (G) (5 mg/kg iv) on the pressor responses to epinephrine (8 μg iv) in cats anesthetized with chloralose. The ordinate represents the percentage antagonism of the control response to epinephrine, and the abscissa represents the time in minutes after compound administration. The broken line in the case of **1** and **8** signifies "epinephrine reversal."

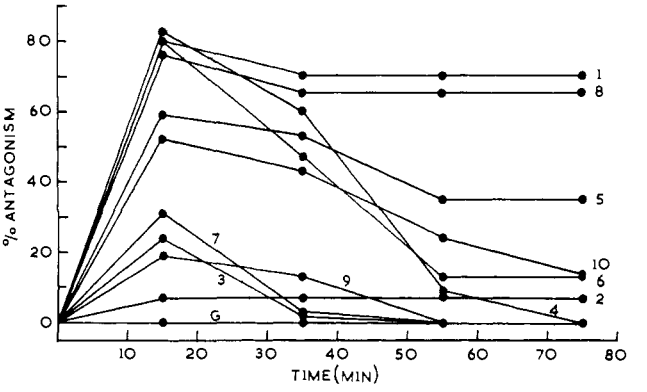


Figure 3.—Graph showing the effect of **1–10** and guanethidine (G) (5 mg/kg iv) on the pressor responses to norepinephrine (5 μg iv) in cats anesthetized with chloralose. The ordinate represents the percentage antagonism of the control response to epinephrine, and the abscissa represents the time in minutes after compound administration.

a similar, although somewhat reduced, activity in the former compounds. Thus it was reasonable to expect that variations in the heterocyclic ring of guanoxan would lead to compounds which retained an affinity for adrenergic structures, and which might show interesting modifications of activity.

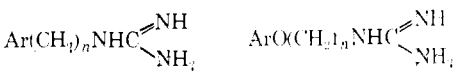
Our results indicate the importance of the heteroatoms in the ring, for replacement of the oxygen atoms in guanoxan (**1**) led to a distinct modification of the pharmacological properties studied. Thus the only compounds which retained a pronounced adrenergic neurone blocking property as measured in the above tests were **3**, **4**, and **9**. These compounds contain six- or seven-membered heterocyclic rings with the grouping Ar–O–C–C–guanidine. Contraction of the ring resulted in a loss in activity in both the dioxane (**1** → **2**)[5] and chroman (**4** → **7**) series.

(3) Qualitatively similar results were obtained from postganglionic stimulation in the same preparation, confirming the mode of action of these compounds as being *via* adrenergic neurone blockade.

(4) G. Benoit and M. D. Bovet, *J. Pharm. Chim.*, **22**, 544 (1935); G. Benoit and M. D. Bovet, *Bull. Sci. Pharmacol.*, **40**, 97 (1938).

(5) Compound **2** (10 mg/kg) has been reported by M. W. Baines, D. B. Cobb, R. J. Eden, R. Fielden, J. N. Gardner, A. M. Roe, W. Tertiuk, and G. L. Willey [*J. Med. Chem.*, **8**, 81 (1965)] to antagonize completely the contraction of the nictitating membrane caused by electrical stimulation of the postganglionic cervical nerve, but we were unable to confirm this effect.

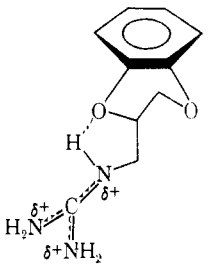
These results are reminiscent of the structure activity relationships already commented upon[6] in the acyclic series. Thus the adrenergic neurone blocking



13 14

activity of **13** (n = 1) is lost upon chain extension (**13**, n = 2 or 3), yet **14** (n = 2 or 3) are active. If one considers the shortest path between the guanidine group and the aromatic ring, then **13** (n = 1) is analogous to debrisoquin (**12**),[7] and the homologs (**13**, n = 2, 3) correspond to compounds **8** and **6**, respectively; debrisoquin is active, and **8** and **6** are essentially inactive, thus behaving in a parallel manner to the compounds in the acyclic series. In the same way, guanoxan (**1**) and its longer chain homolog[1a] correspond to **14** (n = 2 and 3), both series being active.

It is tempting to suggest that in guanoxan efficacy is attained by the guanidine group being able to interact with the oxygen atom (*e.g.*, as **15**) in the same manner (and with the same reservations) as postulated[6] for di-*ortho*-substituted aryloxyalkylguanidines. If this has any significance then an explanation must be sought for the relative inactivity of **2** and **7** as adrenergic neurone blocking agents, for it is not immediately obvious why a similar interaction should not occur also in these compounds. Analogy can be drawn with the significance of *ortho* substitution in the acyclic series of **14**. It was



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pointed out[6] that only compounds with weak uv absorption, and presumably an increased oxygen basicity, were biologically effective. Measurement of the uv spectra of **1**–**4** and **7** revealed a similar pattern (Table II).

It can be seen that **2** and **7** absorbed with approximately 50% greater intensity than the corresponding six-membered ring homologs **1** and **4**, while the seven-membered ring compound **3** showed considerably less absorption than **1**. Clark and Williams[8] have recently analyzed the conformations of a series of cyclic aryl ethers (**16**) by studying their uv spectra. They con-

16 17

cluded that if the two rings in 2,3-dihydrobenzofuran are considered to be essentially coplanar, then the O–C_2 bonds in **16** (n = 2 and 3) are, respectively, 34 and 63° twisted from the plane of the aromatic ring. It is reasonable to interpret our data for the dioxo compounds as indicating a similar increased buckling of the heterocyclic ring with increase in ring size, *i.e.*, as **2** → **1** → **3**. The changes in absorption intensity may also be taken to indicate that as ring size increases then contributions from canonical forms such as **17** become less important, *i.e.*, that the oxygen atom is more basic in the larger ringed compounds. This increased basicity combined with a more buckled conformation would be expected to facilitate interactions of type **15**, and hence may explain why compounds **2** and **7** are less active than **1** (and **3**) and **4**.[9] Alternatively it may be that these changes in electron density at the oxygen atom merely affect in some subtle, yet critical, manner the orientation of the π-delocalized aryloxy group at the receptor site.[10]

Replacement of the heterocyclic ring by a benzenoid ring (**10**) led also to a loss of activity, suggesting that an electron-rich group *per se* between the aromatic ring and the guanidine group is insufficient to confer activity in this series of compounds.

The pattern of adrenolytic activity was somewhat different (Figures 2 and 3). Guanoxan (**1**) and **8** were the most effective antagonists against both epinephrine and norepinephrine, both causing a reversal of the pressor effects of epinephrine. Compounds **5**, **6**, and **10** were all effective antagonists of epinephrine but their effects *vs.* norepinephrine, although marked, were relatively short-lived. Compounds **2**, **3**, **7**, and **9**, although effective antagonists of epinephrine, gave rise to only weak effects against norepinephrine. Compound **4** was notable in being the only compound which was markedly more effective *vs.* norepinephrine than epinephrine. In general there was some adrenolytic activity throughout the series, and no distinctive trends were apparent.

Compounds **1** and **3**–**6** were administered daily as a single oral dose of 10 mg/kg (base) to ten conscious beagles with chronic neurogenic or nephrogenic hypertension. The systolic blood pressure was recorded immediately before and 6 hr after administration of

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA[a]

Compd	λ_{max}, mμ	ε
1	274, 280	2300, 2050
2	287	3400
3	273	1090
4	274, 280	1850, 1850
7	278	2780, 2460

[a] Measured in MeOH on a Perkin-Elmer Ultracord 137 instrument.

(6) J. Augstein, S. M. Green, A. M. Monro, T. I. Wrigley, A. R. Katritzky, and G. J. T. Tiddy, *J. Med. Chem.*, **10**, 391 (1967).

(7) R. A. Moe, H. M. Bates, Z. M. Palkoski, and R. Banziger, *Current Therap. Res.*, **6**, 299 (1964).

(8) E. R. Clark and S. G. Williams, *J. Chem. Soc., B*, 859 (1967).

(9) It is interesting to note that Clark and Williams[8] found that introduction of a 7-methyl group into **16** (n = 1) and an 8-methyl group into **16** (n = 2) led in each case to a reduction in absorption intensity, attributed in these compounds to steric interference of the methyl groups with the oxygen lone pairs and not to increased buckling of the rings. Such an intensity reduction correlates well with our finding[1a] that an 8-methyl substituent enhances the adrenergic neurone blocking activity of guanoxan (8-methylguanoxan has λ_{max} 278 mμ (ε 1460), *cf.* **1**) and with the reported increase in adrenergic neurone blocking activity upon *o*-methyl substitution in a series of quaternary ammonium or guanidine-3-substituted 2,3-dihydrobenzofurans [R. Fielden, A. M. Roe, and G. L. Willey, *Brit. J. Pharmacol.*, **28**, 486 (1964)].

(10) E. R. Clark, P. M. Dawes, and S. G. Williams [*ibid.*, **32**, 113 (1968)] later applied similar considerations of conformational flexibility and oxygen basicity (based on their spectroscopic findings[8]) to a correlation of the pharmacological properties of **16** (R = $CH_2N^+R_3$).

TABLE III
ANTIHYPERTENSIVE ACTIVITY IN CONSCIOUS DOGS

Compd	No. of dogs	Systolic pressure, mm ± SE: Mean control	Treated mean	Mean fall	Mean % act.,[a] mm ± SE
1	10	167.0 ± 5.0	128.0 ± 4.7	39.0 ± 3.9	118.4 ± 13.7
3	10	163.5 ± 4.8	120.5 ± 3.4	43.0 ± 2.9	149.1 ± 18.7
4	10	164.0 ± 4.2	137.5 ± 4.2	26.5 ± 2.7	86.8 ± 11.3
5	10	166.0 ± 4.6	150.0 ± 4.9	16.0 ± 3.3	49.0 ± 10.9
6	4	160.0 ± 9.4	133.8 ± 5.5	26.2 ± 5.5	108.3 ± 31.7

[a] Per cent activity was calculated as follows: (control − treated systolic pressure)/(control systolic pressure − 130) × 100. The figure in the table is the mean of the per cent activity calculated for each dog in the group.

each compound. The systolic blood pressure of normotensive dogs in our colony is *ca.* 130 mm, and it can be seen that compounds **1**, **4**, and **6** effectively reduced the blood pressure of the hypertensive dogs to an approximately normotensive level (Table III); compound **3** was the most active compound, producing a hypotensive effect. The maximum antihypertensive effect was achieved by the fifth day of treatment with all compounds, and there were no signs of tolerance up to 10 days treatment. With the exception of **6**, the compounds caused diarrhea and vomiting, although these effects became less pronounced as treatment progressed.

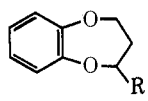
Experimental Section[11]

The preparations of **1**,[12a] **2**,[12] **6**,[13] **8**,[13] and **9**[14] have already been reported and required no further comment.

The following syntheses presented features of interest.

2-Guanidinomethyl-3,4-dihydro-2H-1,5-benzodioxepine Sulfate (3).—The compound was prepared[15] by guanylation of the corresponding primary amine, the preparation of which has already been reported.[16] The Geigy patent reported that the acid **18a**, obtained as a precursor to a series of **18d**, was isolated in two forms, mp 78–80° and mp 124–126°. It claims that the acid of lower melting point was converted to derivatives of the 2-substituted 1,5-benzodioxepine series.

We were only able to isolate acid of mp 125–126°, which, from its nmr spectrum, obviously had structure **18a** [quartet (1 H) centered at τ 5.21 ($OCHCO_2H$), multiplet (2 H) at 5.48–6.05 (OCH_2CH_2), multiplet (2 H) at 7.30–7.70 ($CH_2CH_2CHCO_2H$)]. It gave a methyl ester and amide (mp 157–160°, lit.[16] 169–170°) with similar nmr spectra, and the amide was converted to the required primary amine (hydrochloride mp 309–312°, lit.[16] mp 311–312°).



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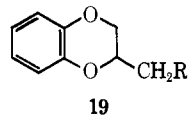
a, R = CO_2H
b, R = CO_2Et



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c, R = $CONH_2$
d, R = CH_2NHR

However, during the preparation of **18c** from the crude ester **18b** resulting from the ring closure reaction,[16] we obtained a second amide (mp 97–100°) as the major product. This compound was shown to be 1,4-benzodioxan-2-acetamide (**19c**) by comparison (mixture melting point, ir) with an authentic specimen.[17] This suggests that the reaction between catechol and ethyl 2,4-dibromobutyrate yields a mixture of **19b** (the major product) and **18b**, although on conversion of the mixture to the amides, **18c** is isolated more readily than **19c**. As the acid **19a** has mp 100–101°,[17] it would seem that the acid of low melting point reported by the Geigy workers was probably a mixture of **18a** and **19a**.

2-Guanidinomethylchroman Sulfate (4).—Chroman-2-carboxylic acid, used as the starting point in the synthesis already reported for **4**,[18] was originally prepared by the laborious route of Baddeley and Cooke.[19] A greatly improved procedure is catalytic hydrogenation over Pd–C in AcOH at 70° of the readily accessible chromone-2-carboxylic acid.[20] This procedure gave chroman-2-carboxylic acid in 87% yield.

2-Aminomethylchroman, not characterized in the earlier report,[18] had bp 173–182° (1.3 mm), $n^{25}D$ 1.5560.

3-Guanidinomethylchroman Sulfate (5).—2H-1-Benzopyran-3-carboxylic acid was used as the starting point in the reported synthesis[21] of **5**. During the preparation of this acid we observed that earlier workers had assigned an incorrect structure to a compound intermediate in the synthesis. Two groups considered that one of the products (mp 151–153°,[22] mp 153°[23]) from the reaction of salicylaldehyde with acrylonitrile under basic conditions was 3-cyano-4-chromanol. Inspection of the ir, uv, and nmr spectra of this compound clearly indicates that it has the structure of the isomeric conjugated amide, 2H-1-benzopyran-3-carboxamide [ν_{max} 3525, 3410, 1665 cm^{-1}, no absorption near 2200 cm^{-1}; λ_{max} 236, 285, 336 mμ (ϵ 21,500, 10,150, 6225); multiplet (5 H) at τ 2.6–3.2 (4 aromatic + 1 olefinic H), broad singlet (2 H) at 4.2 (NH_2), doublet (2 H, J = 1.3 cps) at 4.92 ($OCH_2C{=}CH$)].

Hydrolysis of a compound with either the hydroxynitrile or the conjugated amide structure would be expected to give the 2H-1-benzopyran-3-carboxylic acid reported by Taylor and Tomlinson.[23] The amide's structure was confirmed by its preparation from the conjugated acid by a standard procedure.

2-Guanidinomethyl-2,3-dihydrobenzofuran sulfate (7)[24] was prepared by the following steps. 2-Bromomethyl-1,2-dihydrobenzofuran was heated with a fivefold excess of benzylamine at 100° for 16 hr. The mixture was cooled, basified with aqueous NaOH, and extracted with ether. Solvent was evaporated from the dried extract, and benzylamine was removed by distillation. To the residue was added 2 *N* HCl, and the hydrochloride which formed was recrystallized from EtOH–Et_2O to give **2-benzylaminomethyl-2,3-dihydrobenzofuran hydrochloride,** mp 217–220°. *Anal.* ($C_{17}H_{17}NO \cdot HCl$) C, H.

(11) Melting points were taken on an Electrothermal melting point apparatus, Series IA, and are corrected. Infrared spectra were obtained in $CHCl_3$ on a Perkin-Elmer Infracord 237 instrument, uv spectra in MeOH on a Perkin-Elmer Ultracord 137 instrument, and nmr spectra in $CDCl_3$ on a Varian A60 instrument. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(12) This compound was isolated as the nitrate by M. W. Baines, *et al.*[5] We isolated the compound as the sulfate, mp 237–239°.

(13) Pfizer Corp., Belgian Patent 660,538 (Sept 3, 1965); *Chem. Abstr.*, **64**, 2033 (1966).

(14) Pfizer Ltd., British Patent 1,057,568 (Feb 1, 1967); *Chem. Abstr.*, **66**, 95058 (1967).

(15) Pfizer Ltd., Belgian Patent 659,663 (Aug 12, 1965); *Chem. Abstr.*, **64**, 744 (1966).

(16) J. R. Geigy, S. A., Belgian Patent 613,212 (July 30, 1962); *Chem. Abstr.*, **57**, 16639 (1962).

(17) C. Milani, R. Landi-Vittory, and G. B. Marini-Bettolo, *Rend. Ist. Super. Sanita*, **22**, 207 (1959); *Chem. Abstr.*, **54**, 1522 (1960).

(18) Pfizer Ltd., British Patent 1,004,468 (Sept 15, 1965); *Chem. Abstr.*, **63**, 18036 (1965).

(19) G. Baddeley and J. R. Cooke, *J. Chem. Soc.*, 2797 (1958).

(20) V. A. Zagorevskii, D. A. Zykov, and L. P. Pronina, *Zh. Obshch. Khim.*, **29**, 1026 (1959); *J. Gen. Chem. USSR*, **29**, 1004 (1959).

(21) Pfizer Ltd., British Patent 1,043,857 (Sept 28, 1966); *Chem. Abstr.* **65**, 18562 (1966).

(22) G. B. Bachman and H. A. Levine, *J. Am. Chem. Soc.*, **70**, 599 (1948).

(23) H. V. Taylor and M. L. Tomlinson, *J. Chem. Soc.*, 2724 (1950).

(24) This compound, prepared by a different method, has been described as the nitrate salt by Ward Blenkinsop and Co. Ltd., South Africa Patent 66/7036 (June 16, 1967).

The benzylamino derivative was hydrogenated in AcOH over Pd-C at room temperature and pressure. The catalyst was filtered, the solvent was evaporated, and the residue was basified and distilled to give the product, **2-aminomethyl-2,3-dihydrobenzofuran,** bp 86° (0.01 mm), $n^{25}D$ 1.5575. *Anal.* ($C_9H_{11}NO$) C, H. The hydrogen maleate had mp 147° (from EtOH–Et_2O).

The primary amine was converted to the guanidine by a standard procedure (A, ref 1a). The product had mp 204–206° (from aqueous acetone). *Anal.* ($C_{10}H_{13}N_3O \cdot 0.5H_2SO_4$) C, H, N.

2-Guanidinomethylnaphthalene Tosylate (10).—2-Aminomethylnaphthalene (2.5 g) and guanidine tosylate (3.6 g) were heated together at 150°. NH_3 was evolved while the temperature of the reaction was raised to 190° over 45 min. When cold, the mixture was crystallized from H_2O and then EtOH to give the product, mp 198–200°. *Anal.* ($C_{12}H_{13}N_3 \cdot C_7H_8SO_3$) C, H, N.

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Sympathetic Nervous System Blocking Agents. IV. Synthesis of 2-(2-Methylthioethylamino)ethylguanidine Sulfate and Related Compounds[1,2]

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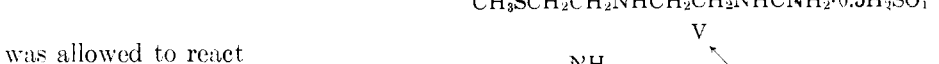
The reaction between N-(2-aminoethyl)aziridine and 2-methyl-2-thiopseudourea sulfate failed to give the expected 2-(1-aziridinyl)ethylguanidine sulfate (I, $n = 2$). The product isolated proved to be 2-(2-methylthioethylamino)ethylguanidine sulfate (V), and it caused an effective blockade of the sympathetic nervous system as determined by its effect on the nictitating membrane of the unanesthetized cat following oral administration. Eight homologs and analogs were prepared in order to study the structure–activity relationships in this series of compounds. The title compound proved to be the most active member of the series and was subjected to extensive pharmacological evaluation. The mechanism of formation of the title compound was studied. The reaction appears to proceed *via* 2-(1-aziridinyl)ethylguanidine followed by opening of the aziridine ring with methanethiol, rather than by a one-step intramolecular reaction.

The first guanidine reported to be effective in blocking the sympathetic nervous system was guanethidine[3] (I, $n = 7$). Lower homologs (I, $n = 4$–6) have been

I

prepared,[4] but not those with $n = 2$, 3. We were interested in preparing the smallest homolog of the guanethidine series. Therefore, the reaction between N-(2-aminoethyl)aziridine (II) and 2-methyl-2-thiopseudourea sulfate (III) was investigated (Scheme I). The product of this reaction, however, was not the desired 2-(1-aziridinylethyl)guanidine sulfate (I, $n = 2$) but proved to be 2-(2-methylthioethylamino)ethylguanidine sulfate (V), on the basis of elemental analyses, ir, and nmr spectra. The same substance was obtained when N-(2-methylthioethyl)ethylenediamine (VII), obtained from II and methanethiol, was allowed to react with III.



VII

At first glance it seems logical that I ($n = 2$) did form, and then underwent ring opening to V by reaction with methanethiol. Indeed, the evolution of some

SCHEME I

I, $n = 2$

methanethiol during the course of this reaction was evident. On the other hand, the intermediacy of I ($n = 2$) is not essential to formation of V. One could visualize a concerted mechanism in which liberation of methanethiol does not occur. If I ($n = 2$) is actually an intermediate in this reaction then any other thiol present should compete with the methanethiol to open the aziridine ring. On the other hand if VI, or some-

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(2) Presented before the Division of Medicinal Chemistry at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

(3) R. A. Maxwell, R. P. Mull, and A. J. Plummer, *Experientia*, **15**, 267 (1959).

(4) R. P. Mull, M. E. Egbert, and M. R. Dapero, *J. Org. Chem.*, **25**, 1953 (1960).