1-ARYL- AND 1-(ARYLMETHYL)-4-GUANYLPIPERAZINES AND OTHER HETEROCYCLIC AND ALICYCLIC GUANIDINE DERIVATIVES*

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Reaction of the corresponding secondary and primary amines with S-methylisothiourea sulfate resulted in 1-aryl-4-guanylpiperazines *V*—*IX*, 1-(arylmethyl)-4-guanylpiperazines *Xa*—*XXIa*, 4-substituted 1-guanylpiperidines *XXII*—*XXV* and *XXIX*, bicyclic N-(2-guanidinoethyl)pyrrolidines *XXX* and *XXXI* and in N-guanyltryptamine (*XXXV*). The aminoguanidine derivative *XXVIII* was prepared analogously from 1-amino-4-phenylpiperidine. The guanidine derivative *XXXVI* and 2-aminoimidazolines *XL* and *XLI* were obtained from the corresponding thioureas (*XXXVIII*, *XLIII*) which were converted to S-methylisothiuronium salts which reacted with methylamine or ethylene diamine. Of the compounds prepared, only *XXX* resembled guanethidine (*I*) in its hypotensive activity but it did not fulfil the expectations in an orientative clinical testing.

Since 1960 guanidine derivatives blocking adrenergic neurones have represented one of the most important groups of antihypertensive drugs[1-6]. The prototypes of this group are guanethidine (*I*) (ref.[7-10]), debrisoquine (*II*) (ref.[11]) and betanidine (*III*) (ref.[12,13]); likewise, clonidine (*IV*) has the structure of a hypotensive cyclic guanidine but the mechanism of its action is at least partly different[14-16]. This team has done research in this field between 1960 and 1969. In some cases, other teams have published papers on the same topic after the termination of our work. In the present communication we have concentrated on material that has not been published so far.

Our studies in the group of piperazine derivatives (*cf.*[17,18]) and further the demonstration of antihypertensive activity of heterocyclic N-guanyl derivatives of the type of debrisoquine (*II*) (ref.[11]) have led to the preparation of a set of 1-aryl-4-guanylpiperazines. In the meantime, the same series has been studied and described by Japanese authors[19-22] who found the compounds to be myorelaxants as well as inhibitors of monoamine oxidase but some of the effects were opposite to what one would expect: The compounds cause a contraction of the cat nictitating membrane, an increase of blood pressure, they potentiate tyramine toxicity and increase the concentration of norepinephrine in brain and heart. Only those members of the series are described here that were not included in earlier communications[19-22]. Reactions of 1-(2-tolyl)piperazine[23], 1-(2-fluorophenyl)piperazine[24], 1-(2-nitrophenyl)piperazine[25], 1-(3-chlorophenyl)piperazine[23] and 1-(4-nitrophenyl)piperazine[26] with S-

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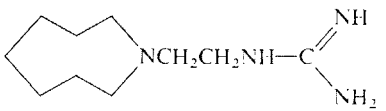
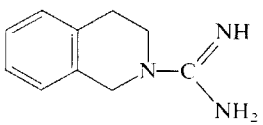
-methylisothiourea sulfate[27] in boiling water or aqueous ethanol (Method *A*) led to guanidine hemisulfates *V–IX*.

The work was then extended to include the series of 1-(arylmethyl)-4-guanylpiperazines *Xa–XXIa*. 1-Benzyl-4-guanylpiperazine itself was prepared before[28,29] and its pharmacology was examined[30–32]. Compounds *Xa–XXIa* were prepared by applying method *A* to 1-(arylmethyl)piperazines (*Xb–XXIb*), of which *XVb*, *XVIb* and *XVIIIb* were described on another occasion[18]. The others were prepared by alkaline hydrolysis of carbamates *Xc–XXIc* (method *B*) which were obtained by alkylation of 1-(ethoxycarbonyl)piperazine[33] with 2-, 3-, and 4-methylbenzyl bromide[34], 2-chlorobenzyl chloride[35], 3-chlorobenzyl chloride[36], 3-methoxybenzyl chloride[37], 2- and 3-(methylthio)benzyl chloride[38] and 4-(methylthio)benzyl chloride[39] (method *C*). The alcohols[38] required for the preparation of 2- and 3-(methylthio)benzyl chloride were obtained by reduction of 2-(methylthio)benzoic acid[40] and 3-(methylthio)benzoic acid[41] with sodium dihydrido-bis(2-methoxyethoxy)aluminate in benzene (method[42]). Of the monosubstituted piperazines *Xb–XXIb*, compounds *XIVb*, *XVIIb*, *XIXb–XXIb* are new. The preparation of the others has been described before but the procedures used here are novel: *Xb* (ref.[43–46]), *XIb* (ref.[44,46–48]), *XIIb* (ref.[45,47,49]), *XIIIb* (ref.[48,50,51]).



I



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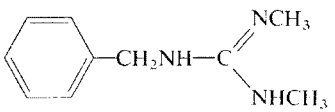

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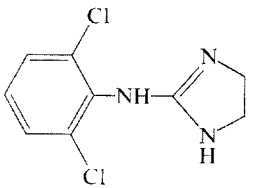
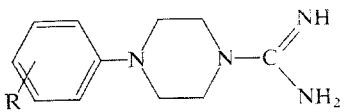
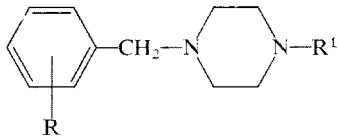


IV



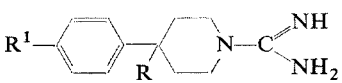
V, R = 2-CH_3
VI, R = 2-F
VII, R = 2-NO_2
VIII, R = 3-Cl
IX, R = 4-NO_2



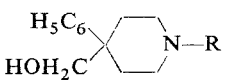
a, $R^1 = C(=NH)NH_2$
b, $R^1 = H$
c, $R^1 = COOC_2H_5$

X, R = 2-CH_3 *XIV*, R = 3-Cl *XVIII*, R = 4-OCH_3
XI, R = 3-CH_3 *XV*, R = 4-Cl *XIX*, R = 2-SCH_3
XII, R = 4-CH_3 *XVI*, R = 2-OCH_3 *XX*, R = 3-SCH_3
XIII, R = 2-Cl *XVII*, R = 3-OCH_3 *XXI*, R = 4-SCH_3

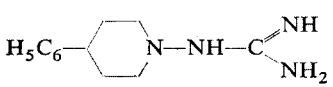
Another objective were the 1-guanyl-4-arylpiperidines, the starting compounds being 4-ethoxycarbonyl-4-phenylpiperidine[52] and substances derived from it, further 4-phenylpiperidines and 4-phenyl-1,2,3,6-tetrahydropyridines, accessible through a synthesis according to Schmidle and Mansfield[53] (see also ref.[54]). 1-Guanyl-4--(ethoxycarbonyl)-4-phenylpiperidine was described[55] even before the beginning of this work while the 1-guanyl derivatives of 4-phenylpiperidine and 4-phenyl-1,2,3,6--tetrahydropyridine were described only after termination of these experiments[56]. We describe here only substances which have not been reported until now. Application of method *A* to the corresponding 1-unsubstituted piperidines led to 1-guanylpiperidines *XXII*–*XXV*. Of the starting compounds used, 4-phenyl-4-piperidinol was prepared according to literature data[53,54]. 4-Phenylisonipecotinamide[57] was obtained by a catalytic debenzylation of 1-benzyl-4-phenylisonipecotinamide[58] on palladium. 4-Phenylpiperidine-4-methanol (*XXVI*) which had been obtained unexpectedly by reduction of 4-phenyl-1-(2-cyanoethyl)piperidine-4-carbaldehyde with lithium aluminium hydride[59] has now been prepared in two ways. In the first procedure, 4--(ethoxycarbonyl)-4-phenylpiperidine[52] was reduced with lithium aluminium hydride in ether or better in tetrahydrofuran. In the second procedure, a similar reduction of 1-benzyl-4-(ethoxycarbonyl)-4-phenylpiperidine[52] led to 1-benzyl-4-phenylpiperidine-4-methanol (*XXVII*) which was catalytically debenzylated in the second



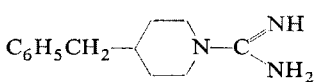
XXII, R = OH, R^1 = H
XXIII, R = $CONH_2$, R^1 = H
XXIV, R = CH_2OH, R^1 = H
XXV, R = H, R^1 = CH_3



XXVI, R = H
XXVII, R = $CH_2C_6H_5$



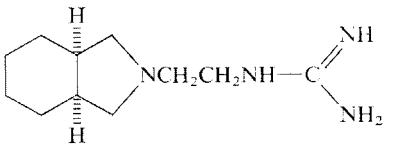
XXVIII



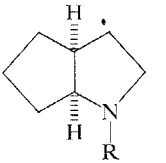
XXIX

step on palladium. Finally, the hitherto undescribed 4-(4-tolyl)piperidine was prepared by catalytic hydrogenation of 4-(4-tolyl)-1,2,3,6-tetrahydropyridine[54,60] and used in the crude state for a reaction with S-methylisothiourea sulfate. 4-Phenyl-1-guanidinopiperidine (*XXVIII*) was obtained from 1-amino-4-phenylpiperidine[61] by application of method *A*. Likewise, 4-benzyl-1-guanylpiperidine (*XXIX*) was prepared from 4-benzylpiperidine[62,63].

Guanidines *XXX* and *XXXI* were of interest as bicyclic analogues of guanethidine (*I*). The first of them was synthesized from *cis*-hexahydrophthalimide[64] which was reduced with lithium aluminium hydride in ether to *cis*-7-azabicyclo[4,3,0]nonane (prepared before in different ways[65,66]). By a modification of Strecker's reaction (see[67]) it was converted to 8-(cyanomethyl)-*cis*-7-azabicyclo[4,3,0]nonane which was reduced with lithium aluminium hydride to 8-(2-aminoethyl)-*cis*-8-azabicyclo-[4,3,0]nonane; application of method *A* resulted in guanidine *XXX*. After termination of this work, the synthesis of this compound by similar methods was described[68–73].



XXX

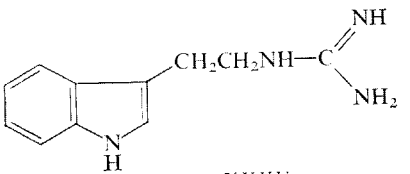


XXXI, R = $CH_2CH_2NHC(=NH)NH_2$

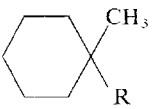
XXXII, R = H

XXXIII, R = CH_2CN

XXXIV, R = $CH_2CH_2NH_2$



XXXV



XXXVI, R = $NHC(=NCH_3)NHCH_3$

XXXVII, R = NH_2

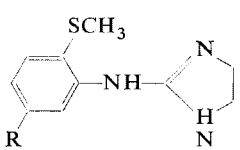
XXXVIII, R = $NHCSNHCH_3$

XXXIX, R = $NHC(=NCH_3)SCH_3$

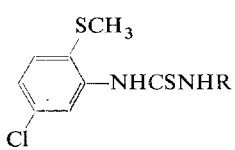
The *cis*-2-azabicyclo[3,3,0]octyl derivative *XXXI* was prepared analogously from *cis*-2-azabicyclo[3,3,0]octane[74,75] (*XXXII*). Alkylation with chloroacetonitrile[76] yielded the nitrile *XXXIII* which was reduced with lithium aluminium hydride to diamine *XXXIV* and this was processed in the crude state by method *A*. Application of the same method to tryptamine[77] led to the hemisulfate of guanidine *XXXV*; ref.[78–80] describe the preparation of hydroiodide of *XXXV* which was the subject of biological studies[30,81].

The trisubstituted guanidine *XXXVI* was prepared as an analogue of betanidine (*III*) (ref.[82]) and an analogous synthetic procedure was used[12]. 1-Methylcyclohexylamine (*XXXVII*) (ref.[83]) reacted with methyl isothiocyanate[84] to disubstituted thiorea *XXXVIII* which was methylated with methyl iodide to the hydroiodide of the substituted S-methylisothiourea *XXXIX*. Reaction with methylamine in aqueous methanol yielded *XXXVI*.

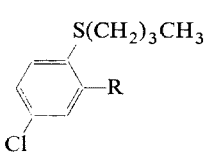
Substituted 2-anilino-2-imidazolines *XL* and *XLI* were synthesized as analogues of clonidine (*IV*), using analogous methods[14,85] which have as their last step the reaction of the corresponding isothiuronium salt with ethylenediamine. 2-(Methylthio)-aniline[86], boiled with an aqueous solution of ammonium thiocyanate, yielded N-(2-methylthiophenyl)thiourea (its preparation by a different procedure has been described[87]) which reacted with methyl iodide in methanol to the noncrystalline hydroiodide of the corresponding S-methylisothiourea; heating with ethylenediamine hydrate yielded the hydroiodide of *XL*. An analogous reaction of 5-chloro-2-(methylthio)-aniline[88] with ammonium thiocyanate did not result in the thiourea derivative *XLIII*; for this reason a modified method (for analogy see ref.[85]) was used. Reaction of 5-chloro-2-(methylthio)aniline with ammonium thiocyanate and benzoyl chloride in acetone yielded 1-benzoyl-3-(5-chloro-2-methylthiophenyl)thiourea (*XLII*) which was hydrolyzed under alkaline conditions to thiourea *XLIII*. The crude isothiuronium



XL, R = H
XLI, R = Cl

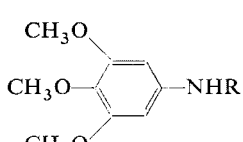


XLII, R = COC_6H_5
XLIII, R = H



XLIV, R = NO_2

XLV, R = NH_2



XLVI, R = $CSNH_2$

XLVII, R = $C(=NH)SCH_3$

salt obtained in a reaction with methyl iodide was treated with ethylenediamine to yield *XLI*. In a similar context, several potential intermediates were prepared. Reaction of 2,5-dichloronitrobenzene[89] with sodium butyl mercaptide in ethanol resulted in 2-(n-butylthio)-5-chloronitrobenzene (*XLIV*) which was reduced with stannous chloride to the aniline derivative *XLV*. Reaction of an aqueous solution of 3,4,5-trimethoxyaniline hydrochloride[90] with ammonium thiocyanate led to thiourea *XLVI* which, under the action of methyl iodide, yielded the hydroiodide of *XLVII*. Reaction with ethylene diamine did not result in a characterized product in this case.

Guanidine sulfates prepared by method A, as well as intermediate products prepared by methods *B* and *C*, are collected in Table I. The experimental section contains only examples of preparations by methods *A*—*C* and describes the preparation of intermediates and final products by other procedures.

The compounds prepared were evaluated for their hypotensive and adrenergic-neurone blocking activities (see ref.[3,6]) as well as by methods of general pharmacological screening. The first type included a series of six guanylpiperazine hemisulfates; the acute toxicity for mice on intravenous application (LD_{50} in mg/kg): *V*, 16·6; *XIIIa*, 12·2; *XVa*, 20·0; *XVIa*, 12·5; *XVIIa*, 20·7; *XVIIIa*, 19·5. With the exception of *V*, all the substances bring about in anaesthetized normotensive rats (administered *i.v.* in doses of 1·5—5·6 mg/kg) a drop of blood pressure by 10—60 Torr during the first 4 min after application, the drop being followed by an increase by 10—50 Torr lasting for 30—160 min. In anaesthetized cats, only *XVIa* at an *i.v.* dose of 3·0 mg/kg led to a short-term drop of blood pressure, the other compounds being without effect at a similar dose. For the sake of comparison, an *i.v.* dose of 5·0 mg/kg guanethidine leads with anaesthetized cats to an icnrease of blood pressure which persists for 10—20 min to return then to the initial value. Similarly, with normotensive unanaesthetized monkeys, *i.v.* doses of 3·0—5·6 mg/kg, or *p.o.* doses of 27 to 32 mg/kg of the above compounds did not affect the blood pressure; the same holds for guanethidine. Like guanethidine, compounds *XIIIa*, *XVa*, *XVIIa* and *XVIIIa* (a dose of 0·3 mg per 20 ml bath) potentiate the contractions of an isolated rat deferent duct brought about by 20 μg norepinephrine. Compounds *XIIIa* and *XVa*—*XVIIIa* in experiments on rats increase the pressor reaction to applied norepinephrine only at doses much greater than the correspondingly effective doses of guanethidine. Compound *V* brings about a slight relaxation of the nictitating membrane in cats, being much less effective in this test than is guanethidine.

Of the piperidine derivatives, four compounds (as hemisulfates) were tested in greater detail. Compound *XXII* (27 mg/kg *p.o.*), in contrast with guanethidine (25 mg/kg *p.o.*), did not affect the pressor reaction to an intravenous infusion of hypertensin in monkeys and, at a dose of 25 mg/kg *p.o.*, it did not affect the blood pressure of DOCA-hypertensive rats. Likewise, compounds *XXIV*, *XXVIII* and *XXIX* (LD_{50} 17·0 mg/kg *i.v.*) at doses of 25—30 mg/kg did not affect the blood pressure of hypertensive rats and in a test of relaxation of the nictitating membrane, their effect was much lower than that of guanethidine.

Among the bicyclic analogoues of guanethidine, compound *XXXI* (hemisulfate) had the characteristic effect of the standard but in only about 10% extent. Because of its relatively high toxicity it was not studied further. On the other hand, hemisulfate of *XXX* ("guanisoline") (LD_{50} in mg/kg for mice 21·5 *i.v.* and 920 *p.o.*, for rats 34·0 *i.v.* and 1 100 *p.o.*) showed in a number of tests properties similar to guanethidine. Its hypotensive effect was demonstrated with normotensive rabbits in a short-term experiment and further with rabbits with an experimental renal hypertension. In view of the fact that even the results of a parallel chronic application of guanisoline and guanethidine were comparable, guanisoline was used for an orientation clinical test

TABLE I

Hemisulfates of Guanidine Derivatives and Substituted Piperazines Prepared by Methods A—C

Compound[a] (method/ % yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol. wt.)	Calculated/Found			
			% C	% H	% N	% S
V-HS	267—268·5	$C_{12}H_{19}N_4O_2S_{0·5}$	53·92	7·16	20·96	5·99
(*A*/93)[b]	(water)	(267·3)	53·73	8·06	20·69	6·15
VI-HS[c]	262—269	$C_{11}H_{18}FN_4O_3S_{0·5}$	45·66	6·27	19·37	5·53[d]
(*A*/95)	(aqueous ethanol)	(289·3)	46·15	6·41	19·35	5·89
VII-HS	289—291	$C_{11}H_{16}N_5O_4S_{0·5}$	44·29	5·41	23·48	5·36
(*A*/79)	(aqueous ethanol)	(298·3)	44·45	5·48	23·52	5·34
VIII-HS	288—290[e]	$C_{11}H_{16}ClN_4O_2S_{0·5}$	45·92	5·60	19·48	5·56[f]
(*A*/92)	(aqueous ethanol)	(287·7)	45·80	5·71	19·23	5·75
IX-HS	304—306	$C_{11}H_{16}N_5O_4S_{0·5}$	44·29	5·41	23·48	5·36
(*A*/87)	(aqueous ethanol)	(298·3)	43·92	5·91	22·79	5·65
Xa-HS[g]	232—234	$C_{13}H_{22}N_4O_{2·5}S_{0·5}$	53·77	7·63	19·30	5·52
(*A*/60)	(aqueous ethanol)	(290·4)	54·30	7·48	19·15	5·75
XIa-HS[g]	231—234	$C_{13}H_{22}N_4O_{2·5}S_{0·5}$	53·77	7·63	19·30	5·52
(*A*/50)	(aqueous ethanol)	(290·4)	53·96	7·84	18·83	5·65
XIIa-HS	226—228	$C_{13}H_{21}N_4O_2S_{0·5}$	55·49	7·52	19·92	5·69
(*A*/65)	(aqueous ethanol)	(281·4)	55·33	7·47	19·56	5·93
XIIIa-HS	248—249	$C_{12}H_{18}ClN_4O_2S_{0·5}$	47·76	6·01	18·57[h]	—
(*A*/60)	(aqueous ethanol)	(301·8)	47·18	6·06	18·92	
XIVa-HS[g]	229—231	$C_{12}H_{19}ClN_4O_{2·5}S_{0·5}$	46·37	6·16	18·03	5·16[i]
(*A*/62)	(aqueous ethanol)	(310·8)	46·27	6·18	17·70	5·37
XVa-HS[c]	257—259	$C_{12}H_{20}ClN_4O_3S_{0·5}$	45·06	6·30	17·52	5·01[j]
(*A*/85)	(aqueous ethanol)	(319·8)	45·54	6·10	17·63	5·32
XVIa-HS	250—252	$C_{13}H_{21}N_4O_3S_{0·5}$	52·51	7·12	18·84	5·39
(*A*/62)	(aqueous ethanol)	(297·4)	52·38	7·17	18·90	5·61
XVIIa-HS	196—199	$C_{13}H_{21}N_4O_3S_{0·5}$	52·51	7·12	18·84	5·39
(*A*/60)	(aqueous ethanol)	(297·4)	52·17	7·20	18·73	5·30
XVIIIa-HS	231—235	$C_{13}H_{21}N_4O_3S_{0·5}$	52·51	7·12	18·84	5·39
(*A*/45)	(aqueous ethanol)	(297·4)	52·19	7·44	19·31	5·50
XIXa-HS	262—263	$C_{13}H_{21}N_4O_2S_{1·5}$	49·81	6·75	17·88	15·35
(*A*/68)	(aqueous ethanol)	(313·4)	49·82	6·71	18·26	15·63
XXa-HS[g]	207—209	$C_{13}H_{22}N_4O_{2·5}S_{1·5}$	48·42	6·88	17·38	14·92
(*A*/65)	(aqueous methanol)	(322·4)	48·39	7·01	17·35	14·82
XXIa-HS[g]	230—232	$C_{13}H_{22}N_4O_{2·5}S_{1·5}$	48·42	6·88	17·38	14·92
(*A*/62)	(aqueous ethanol)	(322·4)	48·00	6·70	17·21	14·75

TABLE I
(*Continued*)

Compound[a] (method/ % yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol. wt.)	Calculated/Found			
			% C	% H	% N	% S
Xb (*B*/86)	150–153/12[k]	—	—	—	—	—
Xb-M —	163–164 (ethanol)	$C_{16}H_{22}N_2O_4$ (306·4)	62·72 62·88	7·24 7·33	9·14 9·29	— —
XIb (*B*/84)	148–152/11[m]	—	—	—	—	—
XIb-MS —	125–126 (ethanol–ether)	$C_{13}H_{22}N_2O_3S$ (286·4)	54·52 54·53	7·74 7·76	9·78 9·90	—
XIIb (*B*/88)	156–158/15[n]	—	—	—	—	—
XIIb-2M —	174–176 (aqueous ethanol)	$C_{20}H_{26}N_2O_8$ (422·4)	56·86 56·43	6·20 6·34	6·63 6·49	— —
XIIIb-M[o] (*B*/90)	154–155/181–182 (ethanol)	$C_{15}H_{19}ClN_2O_4$ (326·8)	55·13 55·23	5·86 5·93	8·57 8·39	10·85[p] 11·06
XIVb (*B*/79)[b]	123–127/2	—	—	—	—	—
XIVb-2 HCl	227–230 decomp. (methanol)	$C_{11}H_{17}Cl_3N_2$ (283·6)	46·58 46·38	6·04 6·13	9·88 9·98	37·50[p] 37·55
XIVb-M —	125–126 (ethanol)	$C_{15}H_{19}ClN_2O_4$ (326·8)	55·13 54·87	5·86 5·99	8·57 8·67	10·85[p] 10·91
XVIIb-M[q] (*B*/91)	122–124 (ethanol)	$C_{16}H_{22}N_2O_5$ (322·3)	59·61 59·73	6·88 7·12	8·69 8·74	— —
XIXb (*B*/96)	96–97[r] (benzene)	$C_{12}H_{18}N_2S$ (222·3)	64·84 65·00	8·16 8·23	12·60 12·80	14·40 14·57
XIXb-M —	138–139 (ethanol)	$C_{16}H_{22}N_2O_4S$ (338·4)	56·78 56·84	6·55 6·62	8·28 8·31	9·47 9·30
XXb (*B*/69)	125–128/1	$C_{12}H_{18}N_2S$ (222·3)	64·84 65·00	8·16 8·40	12·60 12·20	14·40 14·18
XXb-M —	109–110 (ethanol)	$C_{16}H_{22}N_2O_4S$ (338·4)	56·78 56·41	6·55 6·79	8·28 7·98	9·47 9·36
XXIb (*B*/75)	135–138/1·5	—	—	—	—	—
XXIb-MS —	160–162 (ethanol)	$C_{13}H_{22}N_2O_3S_2$ (318·4)	49·03 49·14	6·96 7·03	8·79 8·72	20·14 20·24

TABLE I
(*Continued*)

Compound[a] (method/ % yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol. wt.)	Calculated/Found			
			% C	% H	% N	% S
Xc (*C*/81)[b]	202—205/12	—	—	—	—	—
Xc-M	166—167	$C_{19}H_{26}N_2O_6$	60·30	6·93	7·40	—
—	(ethanol)	(378·4)	60·42	6·92	7·37	—
XIc (*C*/84)	204—206/12	—	—	—	—	—
XIc-M	151—152	$C_{19}H_{26}N_2O_6$	60·30	6·93	7·40	—
—	(ethanol)	(378·4)	60·60	6·92	7·28	—
XIIc (*C*/79)	218—222/20	—	—	—	—	—
XIIc-M	153—154	$C_{19}H_{26}N_2O_6$	60·30	6·93	7·40	—
—	(ethanol)	(378·4)	60·60	7·07	7·53	—
XIIc-HCl	198—201	$C_{15}H_{23}ClN_2O_2$	60·29	7·76	9·37	11·87[p]
—	(acetonitrile–ether)	(298·8)	59·85	7·92	10·06	11·67
XIIIc-HCl[q]	171—173	$C_{14}H_{20}Cl_2N_2O_2$	52·67	6·32	8·78	22·21[p]
(*C*/65)	(ethanol–ether)	(319·2)	52·86	6·37	8·82	22·42
XIVc (*C*/82)	180—185/2·2	—	—	—	—	—
XIVc-M	153—154	$C_{18}H_{23}ClN_2O_6$	54·20	5·81	7·02	8·89[p]
—	(ethanol)	(398·8)	54·13	5·90	6·64	8·73
XIVc-HCl	181—183	$C_{14}H_{20}Cl_2N_2O_2$	52·67	6·32	8·78	22·21[p]
—	(ethanol–ether)	(319·2)	52·54	6·42	8·86	22·42
XVIIc-HCl[q]	157—159	$C_{15}H_{23}ClN_2O_3$	57·23	7·36	8·90	11·26[p]
(*C*/65)	(ethanol–ether)	(314·8)	57·16	7·40	8·80	11·66
XIXc (*C*/90)	181—183/1·2	$C_{15}H_{22}N_2O_2S$ (294.4)	61·19 61·45	7·53 7·79	9·51 9·52	10·89 10·96
XIXc-M	137—138	$C_{19}H_{26}N_2O_6S$	55·59	6·38	6·82	7·81
—	(ethanol)	(410·5)	55·63	6·37	6·88	8·15
XXc (*C*/89)	186—188/1·1	—	—	—	—	—
XXc-M	143—144	$C_{19}H_{26}N_2O_6S$	55·59	6·38	6·82	—
—	(ethanol)	(410·5)	55·66	6·59	6·73	
XXIc (*C*/74)	168—173/0·5	—	—	—	—	—

TABLE I
(*Continued*)

Compound[a] (method/ % yield)	B.p. °C/Torr or m.p. °C (solvent)	Formula (mol. wt)	Calculated/Found			
			% C	% H	% N	% S
XXIc-M	169–171	$C_{19}H_{26}N_2O_6S$	55·59	6·38	6·82	7·81
—	(ethanol)	(410·5)	55·52	6·41	6·58	7·93
XXII-HS	289–292	$C_{12}H_{18}N_3O_3S_{0·5}$	53·72	6·76	15·66	5·96
(*A*/58)	(water)	(268·3)	53·77	7·23	15·70	6·23
XXIII-HS	285–288	$C_{13}H_{19}N_4O_3S_{0·5}$	52·87	6·48	18·98	5·42
(*A*/30)	(aqueous ethanol)	(295·3)	53·08	6·84	18·72	5·60
XXIV-HS	294–296·5	$C_{13}H_{20}N_3O_3S_{0·5}$	55·30	7·14	14·89	5·67
(*A*/35)	(aqueous ethanol)	(282·3)	55·35	7·30	14·90	5·67
XXV-HS	285–287	$C_{13}H_{20}N_3O_2S_{0·5}$	58·63	7·57	15·78	6·00
(*A*/74)	(aqueous ethanol)	(266·3)	58·51	7·92	15·57	6·15
XXVIII-HS	240–244	$C_{12}H_{19}N_4O_2S_{0·5}$	53·91	7·16	20·96	6·00
(*A*/54)	(aqueous ethanol)	(267·3)	53·32	7·41	20·86	6·24
XXIX-HS	256–263 decomp.	$C_{13}H_{20}N_3O_2S_{0·5}$	58·63	7·57	15·78	6·01
(A/71)	(aqueous ethanol)	(532·6)	58·41	7·68	15·97	6·15
XXX-HS	227–229 decomp.[s]	$C_{11}H_{23}N_4O_2S_{0·5}$	50·94	8·94	21·60	6·18
(*A*/69)	(ethanol)	(259·4)	50·98	9·41	21·70	6·35
XXXI-HS	213–215[t]	$C_{10}H_{21}N_4O_2S_{0·5}$	48·95	8·63	22·84	6·53
(*A*/65)	(aqueous ethanol)	(245·3)	48·68	8·70	22·68	6·66
XXXV-HS	213–216	$C_{11}H_{15}N_4O_2S_{0·5}$	52·57	6·02	22·30	6·38
(*A*/80)	(aqueous ethanol)	(251·3)	52·59	6·42	22·20	6·57

[a] HS hemisulfate, M maleate, MS methanesulfonate. [b] See Experimental. [c] Monohydrate. [d] Calculated: 6·57% F; found: 6·53% F. [e] Ref.[19,20] report a m.p. of 280°C. [f] Calculated: 12·32% Cl; found: 12·28% Cl. [g] Hemihydrate. [h] Calculated: 11·75% Cl; found: 11·45% Cl. [i] Calculated: 11·41% Cl; found: 11·48% Cl. [j] Calculated: 11·09% Cl; found: 10·93% Cl. [k] Ref.[43–46] describe the preparation of the compound by alkylation of piperazine with 2-methylbenzyl bromide (or chloride) and report for the base a b.p. of 140–160°C/8 Torr. [m] Ref.[44,46–48] describe the preparation of the compound by other procedures and report for the base *e.g.* a b.p. of 150–160°C/8 Torr. [n] Ref.[45,47,49] describe the preparation of the compound by different procedures and report for the base *e.g.* a b.p. of 120–121°C/2 Torr. [o] The base was processed in the crude state (residue); ref.[48,50,51] report other preparative procedures. [p] Chlorine content. [q] The base was used for further work in the form of an undistilled residue (chromatographically homogeneous). [r] NMR spectrum ($CDCl_3$): δ 6·90–7·60 (m, 4 H, C_6H_4), 3·48 (s, 2 H, $ArCH_2$), 2·15–3·10 (m, 8 H, 4 CH_2 of piperazine), 2·37 (s, 3 H, SCH_3), 1·30–1·70 (m, disappears after D_2O, 1 H, NH). [s] The reported value of the m.p. refers to measurement in capillary; in Kofler's block the m.p. is 214–218°C, under decomposition; literature data for the m.p. are as follows (in °C); 238–240 (ref.[70]), 222–225 (ref.[72]), 220 (ref.[73]). [t] IR spectrum (Nujol): 1100 (C—N), 1465 (CH_2), 1630 to 1650 (NH_2), 1695 (C=N), 3200–3400 cm^{-1} (NH, NH_2).

with hypertonic patients using application *p.o.* The preparation was evaluated in tablets containing 10 and 25 mg substance in the Institute for Cardiovascular Diseases in Prague-Krč (presently the Institute of Clinical and Experimental Medicine) using a small group of hypertonic patients for 30 days, applying maximally 16 tablets per day. Only a small part of the patients showed a clear sign of reduced blood pressure, partly with symptoms of orthostatic hypotension (which is characteristic for guanethidine, as well). With most patients, guanisoline had no effect although guanethidine was effective.

Methanesulfonate of *XLI* (LD_{50} for the mice 9·0 mg/kg *i.v.*) was applied intravenously to unanaesthetized normotensive rats. At a dose of 0·34 mg/kg, the blood pressure was not affected, at a dose of 0·8 mg/kg there was a transient pressor reaction while doses of 1·6 and 3·4 mg/kg brought about a drop of blood pressure persisting for 1—1·5 h (some of the animals died). With anaesthetized cats, the compound blocked the effects of epinephrine but did not block the effects of isoprenaline; it has a hypotensive effect with normotensive monkeys (decreasing blood pressure by at least 20%).

The other substances (hemisulfates unless stated otherwise) were subjected to a systematic pharmacological screening; the mean lethal doses for mice are shown for an *i.v.* application (unless stated otherwise) and further also *i.v.* doses which were administered in tests *in vivo*: *VIII*, 15, 3; *Xa*, 7·5, 1·5; *XIa*, 10, 2; *XIIa*, 15, 3; *XIVa*, 11, 2; *XIXa*, 6·25, 1·25; *XX*a, *p.o.* > 2500, 300; *XXIa*, 12·5, 2·5; *XXXVI*-HI, 6·0, 1·0; *XL*-HI, 19, 3·0. Compound *VIII* brings about a slight increase of blood pressure in normotensive rats, it has a positive inotropic effect on the isolated rabbit atrium and shows a myorelaxing effect of curate type. Compound *Xa* depresses briefly the blood pressure of rats and shows a myorelaxing effect of curare type in rat gastrocnemius muscle. Compound *XIa* depresses briefly the blood pressure of normotensive rats and slightly potentiates the effect of epinephrine. With hypertensive rats, it does not cause a substantial drop of blood pressure at a dose of 40 mg/kg *p.o.* It has a pronounced antiarrhythmic effect in rats toward chloroform and aconitine arrhythmias. A similar profile was found with compounds *XIIa*, *XIVa* and *XIXa*, the last-named compound being rather toxic and characterized typically by a myorelaxing effect. Compound *XXa* applied *p.o.* showed only a slight antiarrhythmic effect toward chloroform arrhythmias. With *XXIa*, at higher doses there were signs of CNS depression but at the dose tested the compound slightly and briefly reduced the blood pressure of rats, having a slight positive inotropic effect and, most typically, a myorelaxing one. At the dose shown, the very toxic compound *XXXVI* brings about a brief but deep drop of blood pressure of normotensive rats. At a dose of 6 mg/kg it increases sharply and briefly the blood pressure of the dog, the rise being followed by a drop. In cats, it causes a pronounced relaxation of the nictitating membrane which persists for 24 h. It depresses briefly the level of norepinephrine in brain, more markedly than in heart. In general it may be said to possess the pharmacodynamic profile of guanethidine but quantitatively it is weaker than this standard. Likewise, *XL* is at least partly of guanethidine type. In an *i.v.* dose of 0·33 mg/kg it brings about a drop of blood pressure in anaesthetized rats persisting for about 1 h. In anaesthetized cats applied *i.v.*, it brings about a decrease of heartbeat frequency by 20—30%; applied *p.o.* it decreases the blood pressure. It does not block the effect of epinephrine and in only some animals it blocks the effect of isoprenaline. It decreases pronouncedly the blood pressure of normotensive monkeys. At a dose of 3·3 mg/20 ml, it potentiates the contractions of isolated rat deferent duct caused by norepinephrine, by 100%. A certain diuretic and antiinflammatory effect was observed.

The intermediate *XXVII* (maleate) (LD_{50} 65 mg/kg *i.v.*) brings about in an *i.v.* dose of 12 mg/kg a slight and protracted rise of blood pressure of normotensive rats. Also the secondary 1-(arylmethyl)piperazines (maleates unless stated otherwise) were tested, the mean lethal dose (LD_{50}) for an *i.v.* application to mice and doses used in tests *in vivo* being shown: *Xb*, 20, 4; *XIIb*, 100, 20; *XIIIb*, 40, 8; *XIVb*, 55, 11; *XVIIb*, 100, 20; *XIXb*, 35, 7; *XXb*, 50, 10; *XXIb* (methane-

sulphonate), 60, 12. Some of these substances are characterized by a central stimulating activity in mice which is displayed in higher doses (1-benzylpiperazine itself in ref.[18,91,92]); in agreement with this, compound *XIVb* was found to possess an antireserpine effect in a ptosis test in mice and compound *XVIIb* to possess a slight hyperthermic effect in rats. In several cases (*XIIIb*, *XIVb*, *XIXb*, *XXb*, *XXIb*), slight brief as well as protracted drops of blood pressure were observed in normotensive rats, followed by an occasional brief rise of preessure (*XXb*), further a negative chronotropic effect (*Xb*, *XIXb*), a negative inotropic effect (*XXb*) and an antiarrhythmic effect (*Xb*, *XIIIb*).

A similar testing was applied to carbamates of the 1-(arylmethyl)piperazine series (maleates) (LD_{50} and dose tested *i.v.*): *Xc* 125, 25; *XIc*, 110, 22; *XIIc*, 140, 30; *XIVc*, 110, 22; *XIXc*, 162, 30; *XXc*, 125, 25; *XXIc*, 125, 25. In contrast with the preceding series, the present one possesses a central depressant activity manifested by a slight hypothermic effect (*Xc*, *XIc*, *XXIc*), a slight potentiation of thiopental sleep (*XIc*) and an inhibition of motility in known surroundings (*XXc*). With *XIXc*, a short-term excitation was observed after high doses, followed by a protracted central depression; the compound raises slightly the body temperature of rats. Even in this group, practically all compounds display a slight hypotensive effect on normotensive rats, accompanied by bradycardia. Compound *XIXc* was found to show also an antiarrhythmic effect (toward chloroform arrhytmias).

The compounds prepared were tested for antimicrobial activity *in vitro* using a standard set of microorganisms (Dr A. Šimek, Dr J. Turinová, bacteriological department of this institute). Only a small part of the compounds showed a certain activity; the microorganisms and the minimum inhibitory concentrations in μg/ml are shown: *Streptococcus β-haemolyticus*, *XVIa*, 100, *XVIIa* 100, *XVIIb* 100, *XXXVI* 50; *Staphylococcus pyogenes aureus*, *XVIa* 100, *XVIIb* 100; *Klebsiella pneumoniae*, *XVIa* 100, *XVIIa* 100, *XVIIb* 100; *Pseudomonas aeruginosa*, *XVIa* 50, *XVIIa* 100; *Proteus vulgaris*, *XVIa* 50, *XVIIa* 100; *Escherichia coli*, *XVIIa* 100; *Salmonella typhi abdominalis*, *XVIIa* 100; *Mycobacterium tuberculosis* H37Rv, *XLI* 100.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried for 8 h *in vacuo* of about 0·2 Torr over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol) in a Unicam SP 200G spectrophotometer and the NMR spectrum in a ZKR 60 (Zeiss, Jena) spectrometer.

1-Guanyl-4-(2-tolyl)piperazine (*V*) (Method *A*)

A mixture of 14 ml water, 8·8 g 1-(2-tolyl)piperazine[23] and 7·0 g S-methylisothourea sulfate[27] was heated to 50°C, left overnight and on the following day it was refluxed for 8 h. After standing overnight, filtration yielded 12·5g (93%) crude hemisulfate of the product, m.p. 253—260°C. The analytical product melted at 267—268·5°C (50% aqueous ethanol). The analytical data are shown in Table I. In analogy, hemisulfates of guanidines *VI—IX*, *XXII—XXV*, and *XXVIII* to *XXXI* were synthesized. The remaining guanidine(hemisulfates) were prepared similarly, but using 50% aqueous ethanol as reaction medium.

2-(Methylthio)benzyl Alcohol

50% benzene solution of sodium dihydridobis(2-methoxyethoxy)aluminate[42] (240 ml) was added dropwise under stirring over a period of 60 min at 50—55°C to a suspension of 50 g 2-

-(methylthio)benzoic acid[40] in 500 ml benzene. The mixture was stirred for 3 h at room temperature, then 500 ml 10% NaOH was added under cooling with ice and water and the mixture was stirred for 30 min. After separation, the aqueous layer was extracted with benzene, the benzene phases were combined, washed with water, dried with K_2CO_3 and, after filtration, distilled; 39·6 g (87%), b.p. 148—150°C/10 Torr. For a product obtained by reduction of the methyl ester of the same acid with lithium aluminium hydride, ref.[38] reports a b.p. of 88°C/0·001 Torr.

3-(Methylthio)benzyl Alcohol

Like in the preceding case, reduction of 35·5 g 3-(methylthio)benzoic acid[41] yielded 26·0 g (80%) product boiling at 150—152°C/11 Torr. For a product obtained by reduction of the methyl ester of the same acid with $LiAlH_4$ ref.[38] reports a b.p. of 98°C/0·0001 Torr.

1-(Ethoxycarbonyl)-4-(2-methylbenzyl)piperazine (*Xc*) (Method *C*)

A mixture of 41 g 2-methylbenzyl bromide[34] and 70 g 1-(ethoxycarbonyl)piperazine[33] was heated for 2 h at 100°C. After cooling, it was mixed with 300 ml water and extracted with benzene. The extract was washed with water and shaken with excess dilute hydrochloric acid (1 : 3). The solution of the hydrochloride of the product formed was separated, made alkaline with NH_4OH and the product was isolated by extraction with benzene. Treatment of the extract yielded 47 g (81%) base, b.p. 202—205°C/12 Torr. Neutralization with maleic acid in ethanol yields hydrogen maleate, m.p. 166—167°C (ethanol). The analytical data are shown in Table I.

1-(3-Chlorobenzyl)piperazine (*XIVb*) (Method *B*)

Solid KOH (34 g) was added to a solution of 34 g *XIVc* (see Table I) in 35 ml ethanol and the mixture was refluxed under stirring for 3 h in a 120°C bath. After cooling, it was diluted with 150 ml water and extracted with benzene. Processing of the extract yielded 20·0 g (79%) base, boiling at 123—127°C/2 Torr. Neutralization with an ether solution of hydrogen chloride in methanol yielded the dihydrochloride, m.p. 227—230°C (decomp., methanol). Neutralization with maleic acid in ethanol yielded a maleate, m.p. 125—126°C (ethanol). The analytical data are shown in Table I.

4-Phenylpiperidine-4-carboxamide

A solution of 23·9 g 1-benzyl-4-phenylpiperidine-4-carboxamide hydrochloride[58] in a mixture of 200 ml ethanol and 50 ml water was hydrogenated at normal pressure on Pd/C (prepared from 1·6 g $PdCl_2 . 2 H_2O$). After 2 h of shaking, the theoretical consumption of hydrogen was reached and the mixture was processed to yield 7·8 g (56%) oil, from a sample of which the hydrochloride was prepared, m.p. 281—285°C (it softens from 277°C up; aqueous ethanol). For $C_{12}H_{17}ClN_2O$ (240·7) calculated: 59·87% C, 7·12% H, 14·73% Cl, 11·64% N; found: 59·70% C, 7·24% H, 14·65% Cl, 11·64% N. Ref.[57] reports a m.p. of 154—155°C (probably for the base).

1-Benzyl-4-phenylpiperidine-4-methanol (*XXVII*)

1-Benzyl-4-(ethoxycarbonyl)-4-phenylpiperidine[52] (28 g) was refluxed for 4 h with a solution of 3·3 g $LiAlH_4$ in 400 ml ether. After standing overnight, 3·3 ml water was added, followed with 3·3 ml 15% NaOH and 10 ml water; after 20 min of stirring, the precipitate was filtered and washed with ether. Evaporation of the ether solution, yielded 19·5 g (81%) product melting at 120—122°C.

The analytically pure base melts at 123–124°C (cyclohexane–benzene). UV spectrum: λ_{max} 214 nm (log ε 4·09), 241 nm (3·49). IR spectrum: 700, 749, 757 (C_6H_5), 1054 (CH_2OH), 1600 (Ar), 3150 cm^{-1} (OH). For $C_{19}H_{23}NO$ (281·4) calculated: 81·10% C, 8·24% H, 4·98% N; found: 81·15% C, 8·37% H, 5·17% N.

Hydrogen maleate, m.p. 142–143°C (ethanol–ether). For $C_{23}H_{27}NO_5$ (397·5) calculated: 69·50% C, 6·85% H, 3·52% N; found: 69·79% C, 6·86% H, 3·65% N.

4-Phenylpiperidine-4-methanol (*XXVI*)

A. A solution of 13·5 g 4-(ethoxycarbonyl)-4-phenylpiperidine[52] in 100 ml tetrahydrofuran was added dropwise under stirring to a solution of 4·0 g $LiAlH_4$ in 100 ml tetrahydrofuran and the mixture was refluxed for 4 h. After cooling, 4 ml water, 4 ml 15% NaOH and 12 ml water were added dropwise. After 20 min of stirring, the precipitate was filtered and washed with ether. Processing of the filtrate yielded 9·2 g (83%) crude product which crystallizes from benzene and, in a pure state, melts at 172–174°C. UV spectrum: λ_{max} 214 nm (log ε 3·80), 250 nm (3·18). IR spectrum: 693, 754 (C_6H_5), 1072 (CH_2OH), 1600 cm^{-1} (Ar). Ref.[59] reports a m.p. of 171°C for *XXVI* prepared by a different procedure.

B. Hydrochloride of *XXVII* (23 g, prepared by dissolving base *XXVII* in ethanolic solution of HCl and evaporation) was dissolved in 100 ml ethanol and 7 ml water and debenzylated by hydrogenation on Pd/C (from 2·1 g $PdCl_2 . 2 H_2O$) similarly as shown for the preparation of 4-phenyl-4-piperidinecarboxamide. A total of 8·2 g (52%) base melting at 169–172·5°C (acetone) was obtained. In mixture with the product according to *A* it melts without depression.

4-(4-Tolyl)piperidine

A solution of 20 g 4-(4-tolyl)-1,2,3,6-tetrahydropyridine[54,60] in 20 ml acetic acid was added to a suspension of platinum catalyst (from 2·0 g PtO_2) in 100 ml acetic acid. This was followed by five drops of perchloric acid and the mixture was hydrogenated on a shaker. The theoretical consumption of hydrogen was attained after 10 h. After filtration and evaporation of the filtrate at reduced pressure, the residue was made alkaline with 10% NaOH and the base was isolated by extraction with ether; 7·7 g (39%), b.p. 100–102°C/1·2 Torr. It was processed without further characterization.

8-(2-Aminoethyl)-*cis*-8-azabicyclo[4,3,0]nonane

Reduction of 129 g *cis*-hexahydrophthalimide[64] (m.p. 136–137°C) with $LiAlH_4$ (100 g) in 2400 ml ether yielded 72 g (69%) *cis*-8-azabicyclo[4,3,0]nonane, b.p. 70°C/10 Torr. Ref.[65,66] where a different preparation procedure is described, do not mention the boiling point. For $C_8H_{15}N$ (125·2) calculated: 76·74% C, 12·08% H, 11·19% N; found: 76·71% C, 12·04% H, 11·26% N.

A solution of 35·8 g $Na_2S_2O_5$ in 60 ml water was combined with 25 ml 38% aqueous formaldehyde; to the hot solution thus formed, 38·5 g *cis*-8-azabicyclo[4,3,0]nonane was added under stirring over a period of 2 min. The mixture was heated for 5 min on a boiling-water bath whereupon a solution of 31 g KCN in 60 ml water was added dropwise over a period of 2 min. The mixture was heated for further 5 min on a water bath and then left to cool slowly. The separated oil was extracted with ether, the extract was dried with K_2CO_3 and distilled; a total of 46·8 g (93%) 8-(cyanomethyl)-*cis*-8-azabicyclo[4,3,0]nonane was obtained; b.p. 135°C/13 Torr. Ref.[73] described the preparation of the compound by alkylation of 8-azabicyclo[4,3,0]nonane with chlorocetonitrile and reported a b.p. of 135°C/14 Torr. Neutralization of a sample of the base

with picric acid in ethanol resulted in a picrate, m.p. 144°C (ethanol). For $C_{16}H_{19}N_5O_7$ (393·3) calculated: 48·85% C, 4·87% H, 17·81% N; found: 49·17% C, 5·14% H, 17·95% N.

The nitrile (124 g) was refluxed for 5 h with 34·2 g $LiAlH_4$ in 600 ml ether. After cooling, it was combined with 35 ml water, 40 ml 20% NaOH and 100 ml water, all added dropwise. After 30 min of stirring, the precipitate was filtered and washed with ether. Processing of the filtrate led to 114·5 g (90%) 8-(2-aminoethyl)-*cis*-8-azabicyclo[4,3,0]nonane b.p. 128—130°C/17 Torr. For a compound prepared similarly, ref.[73] reports a b.p. of 148—150°C/15 Torr.

2-(Cyanomethyl)-*cis*-2-azabicyclo[3,3,0]octane (*XXXIII*)

A solution of 1·2 g chloracetonitrile[76] in 10 ml benzene and 0·9 g anhydrous Na_2CO_3 were added to a solution of 1·8 g *cis*-7-azabicyclo[3,3,0]octane[74,75] (*XXXII*) in 8 ml benzene. The mixture was refluxed for 4 h, cooled, and the inorganic fraction was filtered and washed with benzene. The filtrate was distilled; 1·2 g (50%), b.p. 110°C/12 Torr. From a sample of the base, a picrate was prepared; m.p. 128—130°C (ethanol). For $C_{15}H_{17}N_5O_7$ (379·3) calculated: 47·49% C, 4·51% H, 18·47% N; found: 47·72% C, 4·74% H, 18·62% N.

2-(2-Aminoethyl)-*cis*-2-azabicyclo[3,3,0]octane (*XXXIV*)

A solution of 4·6 g *XXXIII* in 20 ml ether was added dropwise to a solution of 2·0 g $LiAlH_4$ in 100 ml ether and the mixture was refluxed for 15 h. Processing as above yielded 3·4 g (73%) base; b.p. 96—100°C/12 Torr. It was used without further characterization.

1-Methyl-3-(1-methylcyclohexyl)thiourea (*XXXVIII*)

A solution of 11·3 g 1-methylcyclohexylamine[83] in 25 ml ether was added to a solution of 7·3 g methyl isothiocyanate[84] in 25 ml ether and the mixture was refluxed for 8 h. After standing overnight, the ether was evaporated and the resiude was filtered after mixing with a small amount of a mixture of ether and pentane; 14·8 g (80%), m.p. 68—70°C (ether–pentane). For $C_9H_{18}N_2S$ (186·3) calculated: 58·03% C, 9·74% H, 15·04% N, 17·18% S; found: 58·02% C, 9·75% H, 14·59% N, 17·23% S.

S-Methyl-1-methyl-3-(1-methylcyclohexyl)isothiourea (*XXXIX*)

Methyl iodide (4 ml) was added to a solution of 6·3 g *XXXVIII* in 20 ml methanol and the mixture was refluxed for 7 h. After standing overnight, it was evaporated at reduced pressure, the residue was dissolved in 120 ml water, the solution was washed with benzene, filtered with charcoal and evaporated *in vacuo*. The residue (9·3 g, 84%) is the crude hydroiodide of the product which, after crystallization from a mixture of ethanol and ether, melts at 113—115°C. For $C_{10}H_{21}IN_2S$ (328·3) calculated: 36·59% C, 6·45% H, 38·66% I, 8·53% N, 9·77% S; found: 36·62% C, 6·46% H, 38·44% I, 8·36% N, 9·90% S.

N,N′-Dimethyl-N″-(1-methylcyclohexyl)guanidine (*XXXVI*)

40% aqueous solution of methylamine (100 ml) was added to a solution of 30 g hydroiodide of *XXXIX* in 120 ml methanol and the mixture was refluxed for 7 h. After evaporation of the solvents *in vacuo* a sirup was obtained which was dissolved in ethanol and which crystallized after adding ether; 22·2 g hydroiodide, m.p. 130—131°C (ethanol–ether). For $C_{10}H_{22}IN_3$ (311·2) calculated: 38·60% C, 7·13% H, 13·51% N; found: 38·52% C, 7·29% H, 13·66% N.

2-(2-Methylthioanilino)-2-imidazoline (*XL*)

A mixture of 22·6 g 2-(methylthio)aniline[86], 24·4 g NH_4SCN, 70 ml water and 16 ml hydrochloric acid was refluxed for 5 h. After cooling, the precipitate was filtered, washed with water, extracted with 100 ml boiling chloroform, filtered again and washed with ether. A total of 30·0 g crude N-(2-methylthiophenyl)thiourea was obtained, m.p. 165–168°C; its preparation was described using a different procedure[87], the m.p. reported being 168°C. The product (30 g) was mixed with 125 ml methanol and with 40 g methyl iodide, the mixture was refluxed for 5 h. Evaporation *in vacuo* yielded the oily hydroiodide of the corresponding S-methylisothiourea, to which 35 ml 1,2-diaminoethane hydrate was added and the mixture was heated for 1·5 h to 150°C. The volatile fractions were then removed *in vacuo* at 120°C and the residue was mixed with dilute hydrochloric acid. The precipitated compound was filtered and recrystallized with charcoal from 280 ml water. A total of 24·0 g hydroiodide was obtained; m.p. 195–197°C (ethanol). For $C_{10}H_{14}IN_3S$ (335·2) calculated: 35·83% C, 4·21% H, 37·86% I, 12·54% N,, 9·56% S; found 36·13% C, 4·38% H, 37·74% I, 12·48% N, 9·82% S.

1-Benzoyl-3-(5-chloro-2-methylthiophenyl)thiourea (*XLII*)

Benzoyl chloride (18 g) was added dropwise under stirring to a solution of 11·0 g NH_4SCN in 300 ml acetone. A solution of 22·0 g 5-chloro-2-(methylthio)aniline[88] in 180 ml acetone was then added dropwise and the mixture was refluxed under stirring for 1·5 h. After evaporation of most of the acetone at reduced pressure the residue was diluted with 2 litres water. The precipitated product was filtered, washed with water and recrystallized from ethanol; 35 g, m.p. 169–170°C (ethanol). UV spectrum: λ_{max} 250 nm (log ε 4·45), infl. 300 nm (3·95). IR spectrum: 729, 741, 803, 863, 879 (5 and 2 adjacent and solitary Ar–H), 1 525 (NCS), 1 562, 1 680 (CONH), 3 345 cm^{-1} (NH). For $C_{15}H_{13}ClN_2OS_2$ (336·8) calculated: 53·48% C, 3·89% H, 10·53% Cl, 8·32% N, 19·03% S; found: 53·44% C, 4·00% H, 10·80% Cl, 8·05% N, 18·82% S.

1-(5-Chloro-2-methylthiophenyl)thiourea (*XLIII*)

A suspension of 35 g *XLII* in 250 ml 10% NaOH was refluxed for 3 h. The solution formed was cooled and acidified with hydrochloric acid, the precipitated mixture of product and of benzoic acid was filtered and separated by heating with excess dilute NH_4OH. The undissolved fraction was filtered, washed with water and dried; 14·7 g. Crystallization from a mixture of acetone and light petroleum yielded a pure product melting at 156–159°C. UV spectrum: λ_{max} 235·5nm (log ε 4·26). IR spectrum: 820, 836 (Ar–H), 1 520 (NCS), 1 619 (Ar), 3 260, 3 416 cm^{-1} (NH). For $C_8H_9ClN_2S_2$ (232·7) calculated: 41·28% C, 3·90% H, 15·23% Cl, 12·04% N; found: 41·60% C, 3·97% H, 15·62% Cl, 11·64% N.

2-(5-Chloro-2-methylthioanilino)-2-imidazoline (*XLI*)

A mixture of 12·0 g *XLIII*, 150 ml methanol and 15 g methyl iodide was refluxed for 3 h. The volatile fractions were then removed *in vacuo* and the residue was combined with 4·2 ml ethylenediamine. The mixture was refluxed for 2 h in a 125–130°C bath, dissolved while hot in dilute (2 : 1) acetic acid, cooled and made alkaline with 10% NaOH. The precipitated base was filtered on the following day, washed with water and dried *in vacuo*. It was dissolved in a small amount of ethanol and neutralized with methanesulfonic acid, yielding a methanesulfonate, m.p. 199–201°C (ethanol–ether). For $C_{11}H_{16}ClN_3O_3S_2$ (337·8) calculated: 39·10% C, 4·77% H, 10·50% Cl, 12·44% N, 18·98% S; found: 38·90% C, 4·81% H, 10·71% Cl, 12·17% N, 18·78% S.

2-(n-Butylthio)-5-chloronitrobenzene (*XLIV*)

A solution of 4·6 g Na in 300 ml ethanol was combined with 19·0 g *n*-butylmercaptan and a warm solution of 38·4 g 2,5-dichloronitrobenzene[89] in 100 ml ethanol was added dropwise under stirring. After standing overnight, the precipitated product was filtered and crystallized from ethanol; m.p. 89—90°C. For $C_{10}H_{12}ClNO_2S$ (245·7) calculated: 48·88% C, 4·92% H, 14·43% Cl, 5·70% N, 13·05% S; found: 48·87% C, 5·03% H, 14·48% Cl, 5·52% N, 13·28% S.

2-(n-Butylthio)-5-chloroaniline(*XLV*)

XLIV (2·0 g) was added to a stirred solution of 6·0 g $SnCl_2 . 2 H_2O$ in 6 ml hydrochloric acid and 18 ml ethanol. The solution was left to stand overnight, ethanol was then evaporated *in vacuo*, the residue was diluted with water and made alkaline with a 15% solution of NaOH. The product was isolated by extraction with benzene. Processing of the extract resulted in an oil which was dissolved in ether and converted to hydrochloride by adding an ether solution of hydrogen chloride; m.p. 96—99°C (ethanol–ether). For $C_{10}H_{15}Cl_2NS$ (252·2) calculated: 47·62% C, 5·99% H, 28·12% Cl, 5·55% N, 12·71% S; found: 47·48% C, 6·03% H, 27·95% Cl, 5·62% N, 12·80% S.

N-(3,4,5-Trimethoxyphenyl)thiourea (*XLVI*)

A mixture of 64·5 g 3,4,5-trimethoxyaniline[90], 53·2 g NH_4SCN, 580 ml water and 70 ml hydrochloric acid was refluxed for 3 h. After standing overnight, the precipitated fraction was filtered (treatment of the filtrate with Na_2CO_3 recovered 21 g of the starting trimethoxyaniline) and recrystallized from a large volume of ethanol; 29·2 g, m.p. 203·5—205°C. UV spectrum: λ_{max} 213 nm (log ε 4·42), 266 nm (4·15). IR spectrum: 856 (solitary Ar—H), 1135, 1180, 1234, 1276, 1342 (OCH_3), 1500 (NCS), 1594 (Ar), 1633 (NH_2), 3175, 3282, 3350 cm^{-1} (NH). For $C_{10}H_{14} . N_2O_3S$ (242·3) calculated: 49·57% C, 5·82% H, 11·56% N, 13·23% S; found: 49·60% C, 6·02% H, 11·47% N, 13·00% S.

N-(3,4,5-Trimethoxyphenyl)-S-methylisothiourea (*XLVII*)

Methyl iodide (12 ml) was added to a suspension of 16 g *XLVI* in 200 ml methanol and the mixture was refluxed for 4 h. The solution formed was evaporated at reduced pressure. The hydroiodide was obtained in a practically theoretical yield; after recrystallization from a mixture of ethanol and ether it melted at 184—186°C. For $C_{11}H_{17}IN_2O_3S$ (384·2) calculated: 34·38% C, 4·46% H, 33·03% I, 7·29% N, 8·35% S; found: 34·28% C, 4·46% H, 33·19% I, 7·11% N, 8·48% S.

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REFERENCES

1. Schlittler E., Druey J., Marxer A.: Progr. Drug Res. *4*, 341 (1962).
2. Copp F. C.: Advan. Drug Res. *1*, 161 (1964).
3. Mull R. P., Maxwell R. A. in the book: *Medicinal Chemistry*, Vol. 7. *Antihypertensive Agents* (E. Schlittler, Ed.), p. 115. Academic Press, New York and London 1967.
4. Schier O., Marxer A.: Progr. Drug Res. *13*, 110 (1969).
5. Comer W. T., Gomoll A. W. in the book: *Medicinal Chemistry*, 3rd Ed. (A. Burger, Ed.), Pt. II, p. 1043. Wiley-Interscience, New York 1970.
6. Durant G. J., Roe A. M., Green A. L.: *Progress in Medicinal Chemistry* (G. P. Ellis, G. B. West, Eds), Vol *7*, Pt. I., p. 124. Butterworths, London 1970.
7. Maxwell R. A., Mull R. P., Plummer A. J.: Experientia *15*, 267 (1959).
8. Mull R. P., Egbert M. E., Dapero M. R.: J. Org. Chem. *25*, 1953 (1960).
9. Maxwell R. A., Plummer A. J., Schneider F., Povalski H., Daniels A. I.: J. Pharmacol. Exp. Ther. *128*, 22 (1960).
10. Furst C. I.: Advan. Drug Res. *4*, 133 (1967).
11. Wenner W.: J. Med. Chem. *8*, 125 (1965).
12. Wellcome Foundation Ltd.: Fr. 1,302.943 (Brit. Appl. 23. XII. 1959 – 7. VII. 1960).
13. Boura A. L. A., Green A. F.: Brit. J. Pharmacol. *20*, 36 (1963).
14. C. H. Boehringer Sohn: Neth. Appl. 64/11.516 (Ger. Appl. 4. X. 1963 and 31. VII. 1964); Chem. Abstr. *63*. 18 102 (1965).
15. Hoefke W., Kobinger W.: Arzneim. - Forsch. *16*, 1038 (1966).
16. Kobinger W., Walland A.: Arzneim. - Forsch. *17*, 292 (1967).
17. Jílek J. O., Metyšová J., Němec J., Šedivý Z., Pomykáček J., Protiva M.: This Journal *40*, 3386 (1975).
18. Vejdělek Z. J., Němec J., Šedivý Z., Tůma L., Protiva M.: This Journal *39*, 2276 (1974).
19. Ozawa H., Iwatsuki K.: J. Pharm. Soc. Japan *88*, 330 (1968).
20. Ozawa H., Iwatsuki K.: Chem. Pharm. Bull. *16*, 2482 (1968).
21. Ozawa H., Iwatsuki K.: J. Pharm. Soc. Japan *90*, 1563 (1970).
22. Ozawa H., Iwatsuki K.: J. Pharm. Soc. Japan *91*, 1381 (1971).
23. Pollard C. B., Wicker T. H. jr: J. Amer. Chem. Soc. *76*, 1853 (1954).
24. Ratouis R., Boissier J. R., Dumont C.: J. Med. Chem. *8*, 104 (1965).
25. Schmutz J., Künzle F.: Helv. Chim. Acta *39*, 1144 (1956).
26. Bent R. L., Dessloch J. C., Duennebier F. C., Fassett D. W., Glass D. B., James T. H., Julian D. B., Ruby W. R., Snell J. M., Sterner J. H., Thirtle J. R., Vittum P. W., Weissberger A.: J. Amer. Chem. Soc. *73*, 3100 (1951).
27. Schildneck P. R., Windus W.: Org. Syn. Coll. Vol. *2*, 411 (1943).
28. Baltzly R., Buck J. S., Lorz E., Schön W.: J. Amer. Chem. Soc. *66*, 263 (1944).
29. Buck J. S., Baltzly R. (Burroughs Wellcome & Co.): U.S. 2,415.785 (11. II. 1947); Chem. Abstr. *41*, 3132 (1947).
30. Jerushalmy Z., Skoza L., Zucker M. B., Grant R.: Biochem. Pharmacol. *15*, 1791 (1966); Chem. Abstr. *66*, 9676 (1967).
31. Lubas A. A., Stankjavichjus A. P., Shadurskij K. S.: Farmakol. Toksikol. (Moscow) *33*, 17 (1970).
32. Stankevičjus A. P., Lubas A. A., Kost A. N.: Chim.-Farm. Zh. *5* (1), 13 (1971).
33. Moore T. S., Boyle M., Thorn V. M.: J. Chem. Soc. *1929*, 39.
34. Atkinson E. F. J., Thorpe J. F.: J. Chem. Soc. *91*, 1695 (1907).
35. Meisenheimer J., Zimmermann P., Kummer U. v.: Ann. Chem. *446*, 225 (1926).
36. Kenner J., Witham E.: J. Chem. Soc. *119*, 1460 (1921).
37. Pschorr R.: Justus Liebigs Ann. Chem. *391*, 44 (1912).

38. Grice R., Owen L. N.: J. Chem. Soc. *1963*, 1947.
39. Buu-Hoi N. P., Hoán N.: J. Org. Chem. *17*, 350 (1952).
40. Kucsman A., Kremmer T.: Acta Chim. (Budapest) *34*, 75 (1962).
41. Seidlová V., Metyšová J., Hradil F., Votava Z., Protiva M.: Česk. Farm. *14*, 75 (1965).
42. Černý M., Málek J., Čapka M., Chvalovský V.: This Journal *34*, 1025 (1969).
43. Morren H. G.: Belg. 549 420 (10. I. 1957); Chem. Abstr. *54*, 12 169 (1960).
44. Boggiano B. G., Jackman G. B., Petrow V., Stephenson O. (British Drug Houses Ltd.): Brit. 840 358 (6. VII. 1960); Chem. Abstr. *55*, 588 (1961).
45. Steck E. A.: J. Org. Chem. *27*, 306 (1962).
46. Sacha A.: Acta Pol. Pharm. *21*, 347 (1965); Chem. Abstr. *64*, 8180 (1966).
47. Morren H. G.: Belg. 506 695 (16. II. 1952); Chem. Abstr. *49*, 4732 (1955).
48. Shapiro S. L., Friedman L., Soloway H. (U.S. Vitamin & Pharmaceutical Corp.): Belg. 617 599 (U.S. Appl. 17. V. 1961); Chem. Abstr. *59*, 646 (1963).
49. Morren H. G., Trolin S., Denayer R., Grivsky E., Maricq J.: Bull. Soc. Chim. Belg. *60*, 282 (1951); Chem. Abstr. *46*, 8661 (1952).
50. Baltzly R., Ide W. S., Lorz E.: J. Amer. Chem. Soc. *77*, 4809 (1955).
51. Masuzawa K., Kitagawa M., Uchida H.: Bull. Chem. Soc. Jap. *40*, 244 (1967); Chem. Abstr. *66*, 104 983 (1967).
52. Eisleb O.: Ber. *74*, 1433 (1941).
53. Schmidle C. J., Mansfield R. C.: J. Amer. Chem. Soc. *78*, 1702 (1956).
54. Janssen P. A. J., Van De Westeringh C., Jageneau A. H. M., Demoen P. J. A., Hermans B. K. F., Van Daele G. H. P., Schellekens K. H. L., Van Der Eycken C. A. M., Niemegeers C. J. E.: J. Med. Pharm. Chem. *1*, 281 (1959).
55. Kwartler Ch. E., Lucas P.: J. Amer. Chem. Soc. *69*, 2582 (1947).
56. De Meglio P. G.: Farmaco (Pavia) Ed. Sci. *25*, 920 (1970).
57. Janssen P. A. J.: Belg. 601 228 (Appl. 31. III. 1961); Chem. Abstr. *56*, 10 107 (1962).
58. Wilson W.: J. Chem. Soc. *1950*, 2173.
59. Iorio M. A., Mazzeo P., Pinto-Scognamiglio W., Marotta M., Chiavarelli S.: Farmaco (Pavia) Ed. Sci. *22*, 12 (1967).
60. Schmidle C. J., Locke J. E., Mansfield R. C.: J. Org. Chem. *21*, 1194 (1956).
61. Allen & Hanburys Ltd.: Neth. Appl. 65/10 107 (Brit. Appl. 5. VIII. 1964); Chem. Abstr. *65*, 7154 (1966).
62. Tschitschibabin A. E.: J. Russ. Phys.-Chem. Ges. *34*, 511 (1902); Chem. Zentralbl. *1902*, II, 597.
63. Veer W. L. C., Goldschmidt S.: Rec. Trav. Chim. Pays-Bas *65*, 793 (1946); Chem. Abstr. *41*, 3100 (1947).
64. Hückel W., Müller H.: Ber. *64*, 1981 (1931).
65. Rice L. M., Grogan Ch. H.: J. Org. Chem. *20*, 1687 (1955).
66. Dunet A., Ratouis R., Cadiot P., Willemart A.: Bull. Soc. Chim. Fr. *1956*, 906.
67. Allen C. F. H.,: Van Allan J. A.: Org. Syn., Coll. Vol. *3*, 275 (1955).
68. Ciba Ltd.: Brit. 910 427 (U.S. Appl. 10. XI. 1959); Chem. Abstr. *58*, 7917 (1963).
69. Ciba Ltd.: Brit. 910 428 (U.S. Appl. 10. XI. 1959); Chem. Abstr. *58*, 7913 (1963).
70. Mull R. P. (Ciba Corp.): U.S. 3 252 972 (Appl. 8. IX. 1960); Chem. Abstr. *65*, 15 354 (1966).
71. Mull R. P. (Ciba Corp.): U.S. 3 522 240 (Appl. 23. V. 1966); Chem. Abstr. *73*, 77 086 (1970).
72. Wollweber H., Hiltmann R., Kroneberg H. G., Wilms H. (Farbenfabriken Bayer A.-G.): Belg. 608 905 (Ger. Appl. 19. XII. 1960); Chem. Abstr. *57*, 16 561 (1962).
73. Barron D. I., Bavin P. M. G., Durant G. J., Natoff I. L., Spickett R. G. W., Vallance D. K.: J. Med. Chem. *6*, 705 (1963).
74. Booth H., King F. E., Parrick J., Whitehead R. L. S. D.: Chem. Ind. (London) *1956*, 466.

75. Booth H., King F. E., Mason K. G., Parrick J., Whitehead R. L. S. D.: J. Chem. Soc. *1959* 1050.
76. Reisner D. B., Horning E. C.: Org. Syn., Coll. Vol. *4*, 144 (1963).
77. Abramovitch R. A., Shapiro D.: J. Chem. Soc. *1956*, 4589.
78. Kumagai T., Kawai S., Shikinami Y.: Proc. Acad. Tokyo *4*, 23 (1928); Chem. Zentr. *1928* I, 2843.
79. Kumagai T., Kawai S., Shikinami Y., Hosono T.: Scient. Pap. Inst. Phys. Chem. Res. *9*, 272 (1928); Chem. Zentr. *1929* I, 1439.
80. Suvorov N. N., Murasheva V. S.: Khim. Geterocikl. Soed., Sb. *1*, Azotsoderzhashchie Geterocikly *1967*, 25; Chem. Abstr. *70*, 77 701 (1969).
81. Geratz J. D.: Experientia *22*, 73 (1966).
82. Boura A. L. A., Copp F. C., Green A. F., Hodson H. F., Ruffell G. K., Sim M. F., Walton E., Grivsky E. M.: Nature *191*, 1312 (1961).
83. Vejdělek Z. J., Rajšner M., Protiva M.: This Journal *25*, 245 (1960).
84. Moore M. L., Crossley F. S.: Org. Syn., Coll. Vol. *3*, 599 (1955).
85. Kinoshita Y., Matsuda N., Sakai S., Oshima Y., Harada T., Nishihara T.: Agr. Biol. Chem. *30*, 447 (1966); Chem. Abstr. *65*, 7081 (1966).
86. Zincke T., Siebert G.: Ber. *48*, 1242 (1915).
87. Hofmann A. W.: Ber. *20*, 1795 (1887).
88. Brand K., Groebe W.: J. Prakt. Chem. [2] *108*, 5 (1924).
89. Fierz-David H. E., Blangey L.: *Grundlegende Operationen der Farbenchemie*, VI. Ed., p. 104. Springer, Wien 1946
90. Will W.: Ber. *21*, 612 (1888).
91. Bye C., Munro-Faure A. D., Peck A. W., Young P. A.: Eur. J. Clin. Pharmacol. *6*, 163 (1973).
92. Campbell H., Cline W., Evans M., Lloyd J., Peck A. W.: Eur. J. Clin. Pharmacol. *6*, 170 (1973).

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