NEUROTROPIC AND PSYCHOTROPIC COMPOUNDS. LIII.*

1-(1,3-DIARYLPROPYL)PIPERAZINES AND 1-(1-ARYL-2-PHENYLTHIOETHYL)PIPERAZINES

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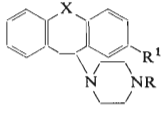
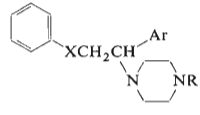
Ketones *III*—*V* and *VII*—*IX* were used to prepare chlorides *XIb*—*XVIb via* alcohols *XIa*—*XVIa*. The chlorides reacted with 1-methylpiperazine to yield methylpiperazino derivatives *XVIII* to *XXIII*. Starting from 1-(4-methoxyphenyl)-3-phenylpropyl chloride (*XIIb*), reactions with other monosubstituted piperazines yielded *XXIV*—*XXVIII*. Hydrolysis of the carbamate *XXVIII* produced the secondary amine *XXIX* which was further transformed to 1,4-disubstituted piperazines *XXX*—*XXXIV*. The central neurotropic activity of the compounds is insignificant. They are of greater interest as parasympatholytics (*XVIII*, *XVIII* — CH_3I, *XXII*, *XXIII*), hypotensive, vasodilating and antiarrhythmic agents (*XVIII*, *XXV*, *XXXIV*), as hypoglycaemics (*XXIX*) and as antimicrobial agents (*XVIII*—*XXII*).

The central depressant and neuroleptic activity of tricyclic piperazine derivatives of the general formula *I* described in this laboratory[1] in a number of communications brings us gradually to the derivation of more distant structural analogues of these compounds[2]. In the present paper we describe the synthesis and pharmacological properties of a series of piperazine derivatives *II* which were derived from compounds *I* by opening the central ring and by shifting the bridge element *X*.



I



II

$C_6H_5XCH_2COAr$

III, X = CH_2, Ar = C_6H_5
IV, X = CH_2, Ar = 4-$C_6H_4OCH_3$
V, X = CH_2, Ar = 4-$C_6H_4SCH_3$
VI, X = 0, Ar = 4-$C_6H_4OCH_3$
VII, X = S, Ar = 4-$C_6H_4OCH_3$
VIII, X = CH_2, Ar = 2-thienyl
IX, X = S, Ar = 2-thienyl

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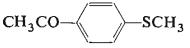


X

(Series *a*, R = OH)

(Series *b*, R = Cl)

XI, X = CH_2, Ar = C_6H_5
XII, X = CH_2, Ar = 4-$C_6H_4OCH_3$
XIII, X = CH_2, Ar = 4-$C_6H_4SCH_3$
XIV, X = S, Ar = 4-$C_6H_4OCH_3$
XV, X = CH_2, Ar = 2-thienyl
XVI, X = S, Ar = 2-thienyl

The starting compounds were ketones *III*–*IX*, of which compound *III* is available through catalytic hydrogenation of benzalacetophenone[3,4] and the others can be obtained by a Friedel–Crafts reaction of the chlorides of hydrocinnamic acid[5], phenoxyacetic acid[6] and phenylmercaptoacetic acid[7] with anisol, thioanisol or with thiophene. For the preparation of 1-(4-methoxyphenyl)-3-phenylpropan-1-one (*IV*) we used Rothstein's procedure[8] with aluminium chloride in benzene (method A). The same procedure was applied successfully to the synthesis of a novel 1-(4-methylthiophenyl)-3-phenylpropan-1-one (*V*), as well as to the preparation of the ketone *VII*, the synthesis of which has already been described[9,10] using a different approach. The application of the method to the reaction of phenoxyacetyl chloride[6] with anisol did not give the desired product. Ketone *VI* was obtained in a 12% yield using carbon disulfide as the medium[11]. Similarly, in the case of the reaction of phenylmercaptoacetyl chloride[7] with thioanisol method A was not successful. The only crystalline product obtained was 4-methylthioacetophenone[12,13] (*X*). The compound is apparently formed by the cleavage of a primarily formed 4-methylthio-ω-phenylthioacetophenone (pronounced smell of thiophenol accompanies the hydrolysis of the reaction mixture). 1-(2-Thienyl)-3-phenylpropan-1-one (*VIII*) is formed through a reaction of the components in carbon disulfide[14] but in a yield markedly lower than reported in the literature. A substantially better yield was obtained on using stannic chloride in benzene (method in[15,16]; method B). Analogously, 2-(phenylmercaptoacetyl)thiophene[10,17] (*IX*) was prepared. All the ketones were characterized as crystalline semicarbazones (*III*-S to *IX*-S), only *III*-S being known from the literature[18]. The ketones and the semicarbazones are summarized in Table I.

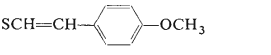
Ketones *III*–*V* and *VII*–*IX* were reduced with sodium borohydride in aqueous ethanol in the presence of a small amount of sodium hydroxide (method C) to secondary alcohols *XIa*–*XVIa* (Table I). Of these alcohols only the preparation of the first two is known from the literature (*XIa*[19–23], *XIIa*[24,25]) where different methods were used. Of the new alcohols only *XIIIa* is crystalline, *XVa* is oily but distils without decomposition. When attempting to purify the alcohol *XIVa* by distillation it was dehydrated. The oily product was analyzed as 4-methoxystyryl phenyl sulfide (*XVII*). Alcohols *XIVa* and *XVIa* were used for further work in the

TABLE I

Ketones *III*—*IX* and Alcohols *XIa*—*XVIa*

Compound[a]	Method (yield, %)	M.p., °C (ethanol) and/or b.p., °C/Torr	Formula (m.w.)	Calculated/Found			
				% C	% H	% N	% S
III	Ref.[4] (95)	71·5—72·5[b]	—	—	—	—	—
III-S	—	146—148[c]	$C_{16}H_{17}N_3O$ (267·3)	71·88 71·85	6·41 6·56	15·72 16·00	— —
IV	A[8] (85)	98—99[d]	—	—	—	—	—
IV-S	—	138—140[e]	$C_{17}H_{19}N_3O_2$ (297·4)	68·66 68·96	6·44 6·35	14·13 13·85	— —
V	A[f] (74)	85·5—87	$C_{16}H_{16}OS$ (256·4)	74·96 74·95	6·29 6·36	— —	12·51 12·41
V-S	—	165—167	$C_{17}H_{19}N_3OS$ (313·4)	65·14 65·13	6·11 6·04	13·41 13·21	10·23 10·18
VI	A[g] (12)	64—65[h] 194—210/21	$C_{15}H_{14}O_3$ (242·3)	74·36 74·48	5·83 5·84	— —	— —
VI-S	—	166—168[i]	$C_{16}H_{17}N_3O_3$ (299·3)	64·20 64·39	5·73 5·51	14·04 13·90	— —
VII	A (60)	89—90[j]	$C_{15}H_{14}O_2S$ (258·3)	69·74 69·93	5·46 5·35	— —	12·41 12·37
VII-S	—	148—152	$C_{16}H_{17}N_3O_2S$ (315·4)	60·93 61·21	5·43 5·36	13·32 12·80	10·17 10·07
VIII	B[16] (75)	46—47[k] 168—182/10	$C_{13}H_{12}OS$ (216·3)	72·18 72·66	5·59 5·61	— —	14·83 14·83
VIII-S	—	151—153	$C_{14}H_{15}N_3OS$ (273·4)	61·51 61·45	5·53 5·61	15·37 15·32	11·73 11·73
IX	B[f] (66)	54—56	$C_{12}H_{10}OS_2$ (234·3)	61·50 61·64	4·30 4·33	— —	27·37 27·12
IX-S	—	117—118	$C_{13}H_{13}N_3OS_2$ (291·4)	53·58 53·36	4·50 4·44	14·42 14·41	22·01 21·88
XIa	C (92)	160—176/8[m]	$C_{15}H_{16}O$ (212·3)	84·86 84·68	7·60 7·71	— —	— —
XIIa	C (95)	53—54[n] (hexane)	$C_{16}H_{18}O_2$ (242·3)	79·31 79·67	7·48 7·57	— —	— —
XIIIa	C (97)	54—56 (hexane)	$C_{16}H_{18}OS$ (258·4)	74·37 74·62	7·02 7·19	— —	12·41 12·59
XVa	C (79)	182—185/16[o]	$C_{13}H_{14}OS$ (218·3)	71·52 71·50	6·46 6·51	— —	14·69 14·32

crude form. Alcohols *XIa–XVIa* were converted to chlorides *XIb–XVIb* by treatment with thionyl chloride in tetrachloromethane (method D)[21], or by treatment with hydrogen chloride in benzene (method E). Literature contains reports[21,26] only on the preparation of 1,3-diphenylpropyl chloride (*XIb*).



XVII

The crude chlorides *XIb–XVIb* were heated with excess 1-methylpiperazine to 110–120°C and converted in high yields to oily methylpiperazino derivatives *XVIII* to *XXIII* (method F) which, for the sake od characterization and for biological evaluation were converted to crystalline di(hydrogen maleates). In several cases the monomethoiodides were prepared in the usual way (Table II). In view of the fact that preliminary tests indicated a clear neurotropic activity for *XIX*, its araliphatic skeleton was preserved during the subsequent phase of the work and several alterations were performed in the piperazine residue. Reactions of 1-(4-methoxyphenyl)-3-phenylpropyl chloride (*XIIb*) with 1-(2-hydroxyethyl)piperazine[27], 1-(3-tolyl)-piperazine[28], 1-(4-tolyl)piperazine[28], 1-benzylpiperazine[29] and 1-(ethoxycarbonyl)-piperazine[27] (method F) yielded compounds *XXIV–XXVIII*. Alkaline hydrolysis of the carbamate *XXVIII* provided the secondary amine *XXIX* which was heated with acetic anhydride and acetic acid to give the acetyl derivative *XXX*. Reduction

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[a] S semicarbazone. [b] Ref.[4] gives m.p. 72–73°C. [c] Ref.[18] gives m.p. 141–143°C. [d] Ref.[8] gives m.p. 101–102°C. [e] Ref.[8] gives m.p. 135°C. [f] See Experimental. [g] Carbon disulfide was used instead of benzene as solvent. The main product was coumaranone, m.p. 100°C. [h] Ref.[11] gives m.p. 67°C and b.p. 230–233°C/20 Torr. UV spectrum: λ_{max} 271 nm (log ε 4·24); IR spectrum: 690, 750 (C_6H_5), 832 (1,4–C_6H_4), 1 030, 1 220, 1 250, 1 263, (Ar–O–R), 1 602, (Ar), 1 688 cm^{-1} (ArCO). [i] NMR spectrum (hexadeuteriodimethyl sulfoxide): ϑ 9·95 (s. 1 H of NH) 7·80 and 6·90 (2 d. 4 H, J = 9·0 Hz, aromatic protons in C_6H_4) 7·50–6·75 (m. 5 H, C_6H_5), 6·60 (b. s. 2 H of NH_2), 5·15 (s. 2 H of OCH_2C), 3·75 (s., 3 H of OCH_3). [j] Ref.[9] gives m.p. 89–90°C for a compound prepared by a different procedure; UV spectrum: λ_{max} 254 nm (log ε 4·10), 280 nm (4·24); IR spectrum: 690, 740 (C_6H_5), 820, 830 (1,4-C_6H_4), 1 024, 1 266 (Ar–O–R), 1 420 (SCH_2), 1 570, 1 602 (Ar), 1 660 cm^{-1} (Ar–CO). [k] Crystallized from light petroleum. Ref.[16] gives m.p. 45–45·5°C; in a number of batches we obtained a product melting at 33·5–35°C (light petroleum) which is probably a crystal modification. UV spectrum: λ_{max} 260 nm (log ε 3·97), 285 nm (3·87). IR spectrum: 700, 725 (C_6H_5), 850, 860 (1,4-C_6H_4), 1 500, 1 570, 1 609 (Ar), 1 666 cm^{-1} (Ar–CO). [m] Ref.[19–23] give for b.p. values of 152°C/2 Torr, 156°C/1·5 Torr, 186°C/14 Torr. [n] Ref.[24,25] give m.p. either 46–48°C or 52·3–53·3°C, for products obtained by different procedures. UV spectrum: λ_{max} 225 nm (log ε 4·04), 274 nm (3·17), 281 nm (3·09). [o] UV spectrum: λ_{max} 233·5 nm (log ε 3·90), 260 nm (2·38), 263 nm (2·28), 267 nm (2·27). IR spectrum (film): 700, 750 (C_6H_5), 838 (2-thienyl), 1 030, 1 065 (sec. alcohol), 1 602 (Ar), 3 390, 3 550, 3 585 cm^{-1} (OH).

TABLE II

Piperazine Derivatives *XVIII*—*XXXIV* (Method F)

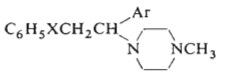
Compound[a] (yield, %)[b]	M.p., °C (Solvent)	Formula (M. w.)	Calculated/Found			
			% C	% H	% N	% S(Hal)
XVIII-2 HM	178—182	$C_{28}H_{34}N_2O_8$	63·86	6·51	5·32	—
(84)	(aqueous ethanol)	(526·6)	64·47	6·62	5·33	—
XVIII-MeI	212—214	$C_{21}H_{29}IN_2$	57·80	6·70	6·42	29·08
	(methanol–ether)	(436·4)	57·82	6·87	6·36	29·29
XIX-2 HM	173—175	$C_{29}H_{36}N_2O_9$	62·58	6·52	5·03	—
(69)	(aqueous ethanol)	(556·6)	62·36	6·65	4·79	—
XIX-2 MS	187—189	$C_{23}H_{36}N_2O_7S_2$	53·46	7·02	5·42	12·41
	(ethanol–ether)	(516·7)	53·32	7·06	5·11	12·05
XIX-MeI	200	$C_{22}H_{31}IN_2O$	56·65	6·70	6·01	27·21
	(methanol–ether)	(466·4)	56·61	6·80	5·67	27·43
XX-2 HM	179—182	$C_{29}H_{36}N_2O_8S$	60·82	6·34	4·89	5·60
(66)	(aqueous ethanol)	(572·7)	60·74	6·47	4·88	5·79
XXI-2 HM	157—159	$C_{28}H_{34}N_2O_9S$	58·52	5·96	4·88	5·58
(72)	(aqueous ethanol)	(574·6)	58·59	6·03	4·82	5·80
XXI-MeI	192	$C_{21}H_{29}IN_2OS$	52·06	6·03	5·79	6·62[c]
	(methanol–ether)	(484·5)	51·98	5·96	5·68	6·44
XXII-2 HM	163—166	$C_{26}H_{32}N_2O_8S$	58·63	6·06	5·26	6·02
(63)	(aqueous ethanol)	(532·6)	58·54	5·98	5·04	6·26
XXIII-2 HM	135—138	$C_{25}H_{30}N_2O_8S_2$	54·53	5·49	5·09	11·65
(49)	(ethanol)	(550·6)	54·50	5·52	4·93	11·56
XXIV-2 HM	152—154	$C_{30}H_{38}N_2O_{10}$	61·42	6·53	4·78	—
(49)	(aqueous ethanol)	(586·6)	61·47	6·64	4·78	—
XXV-HCl[d]	195—199	$C_{27}H_{33}ClN_2O$	74·20	7·61	6·41	8·11
	(methanol)	(437·0)	74·31	7·78	6·42	7·99
XXVI M[d]	137—138	$C_{31}H_{36}N_2O_5$	72·07	7·03	5·42	—
	(ethanol)	(516·6)	71·64	7·23	5·63	—
XXVII-2 HM	190—192	$C_{35}H_{40}N_2O_9$	66·44	6·37	4·43	—
(35)	(aqueous methanol)	(632·7)	66·66	6·56	4·27	—
XXVIII-HM	139	$C_{27}H_{35}N_2O_{1·5}$	63·89	6·95	5·52	—
(69)[e,f]	(ethanol)	(507·6)	63·76	7·02	5·87	—
XXIX[f]	69—70	$C_{20}H_{26}N_2O$	77·38	8·44	9·03	—
	(light petroleum)	(310·4)	77·39	8·41	8·99	—
XXIX-2 HM[f]	149—151	$C_{28}H_{34}N_2O_9$	61·98	6·32	5·16	—
	(methanol)	(542·6)	61·96	6·56	5·19	—

TABLE II
(*Continued*)

Compound[a] (yield, %)[b]	M.p., °C (Solvent)	Formula (M.w.)	Calculated/Found			
			% C	% H	% N	% S(Hal)
XXX-HM[f]	137 (ethanol–ether)	$C_{26}H_{32}N_2O_6$ (468·5)	66·65 66·88	6·88 6·94	5·98 5·92	—
XXXI-2 HM[f]	179–182 (aqueous ethanol)	$C_{30}H_{38}N_2O_9$ (570·6)	63·14 63·03	6·71 6·86	4·91 4·88	—
XXXII-HM[f]	129 (methanol)	$C_{25}H_{32}N_2O_7S$ (504·6)	59·50 59·32	6·39 6·49	5·55 5·57	6·36 6·51
XXXIII-2 HM[f]	163 (ethanol)	$C_{31}H_{37}N_3O_9$ (595·6)	62·51 62·50	6·26 6·33	7·06 6·92	—
XXXIV-3 HM[f]	171–173 (aqueous ethanol)	$C_{35}H_{45}N_3O_{13}$ (715·7)	58·73 58·69	6·34 6·46	5·87 5·95	—

[a] HM hydrogen maleate, M maleate, MeI methoiodide, MS methanesulfonate. [b] The yield shown refer to crude bases. [c] Calculated: 26·20% I; found: 26·31% I. [d] The yield was low because of difficulties with the separation of the product from the starting tolylpiperazine. [e] Hemihydrate. [f] See Experimental.

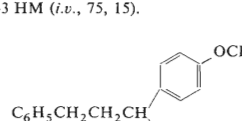
of this amide with lithium aluminium hydride in ether provided the ethylpiperazino derivative *XXXI*. Reaction of amine *XXIX* with methanesulfonyl chloride in pyridine gave rise to the sulfonamide *XXXII*. Addition of the amine *XXIX* to acrylonitrile resulted in the cyanoethyl derivative *XXXIII* which was reduced with lithium aluminium hydride to the triamine *XXXIV*. The bases *XXIV*–*XXXIV* are mostly oily and the compounds were isolated in the form of crystalline maleates (with the exception of *XXV* which was isolated as hydrochloride).



XVIII, X = CH_2, Ar = C_6H_5
XIX, X = CH_2, Ar = 4-$C_6H_4OCH_3$
XX, X = CH_2, Ar = 4-$C_6H_4SCH_3$
XXI, X = S, Ar = 4-$C_6H_4OCH_3$
XXII, X = CH_2, Ar = 2-thienyl
XXIII, X = S, Ar = 2-thienyl

The following compounds were evaluated pharmacologically by general screening methods (way of administration, acute toxicity in mice LD_{50} in mg/kg and finally the dose in mg/kg generally used in the *in vivo* tests; abbreviations: S semicarbazone, HM hydrogen maleate, M maleate, MeI methiodide): *III*-S (*p.o.*, > 2500, 300), *IV*-S (*p.o.*, 2500, 300), *V*-S (*p.o.*, > 2500, 300), *VII*-S (*p.o.*, > 2500, 300), *VIII*-S (*p.o.*, > 2500, 300), *IX*-S (*p.o.*, > 2500, 300), *XVIII*-2 HM

(*i.v.*, 55, 11), *XVIII*-MeI (*i.v.*, 4·25, 0·8), *XIX*-2 HM (*p.o.*, 750, 150), *XIX*-MeI (*i.v.*, 4·25, 0·8), *XX*-2 HM (*p.o.*, 1 000, 200), *XXI*-2 HM (*p.o.*, 750, 150), *XXII*-2 HM (*p.o.*, 1 000, 200), *XXIII*-2 HM (*p.o.*, 1 000, 200), *XXIV*-2 HM (*i.v.*, 87·5, 18), *XXV*-HCl (*p.o.*, > 2 500, 300), *XXVI*-M (*p.o.*, > > 2 500, 300), *XXVII*-2 HM (*i.v.*, 90, 18), *XXVIII*-HM (*p.o.*, 1 500, 300), *XXIX*-2 HM (*p.o.*, 1 000, 200), *XXX*-HM (*i.v.*, 75, 15), *XXXI*-2 HM (*p.o.*, 1 000, 200), *XXXII*-HM (*i.v.*, > 300, 60), *XXXIII*-2 HM (*i.v.*, 100, 20), *XXXIV*-3 HM (*i.v.*, 75, 15).



XXIV, R = CH_2CH_2OH — *XXIX*, R = H
XXV, R = 3-$C_6H_4CH_3$ — *XXX*, R = $COCH_3$
XXVI, R = 4-$C_6H_4CH_3$ — *XXXI*, R = CH_2CH_3
XXVII, R = $CH_2C_6H_5$ — *XXXII*, R = SO_2CH_3
XXVIII, R = $COOC_2H_5$ — *XXXIII*, R = CH_2CH_2CN
XXXIV, R = $CH_2CH_2CH_2NH_2$

It follows from the values that semicarbazones *III*-S to *IX*-S are little toxic and pharmacologically uninteresting. Only traces of mydriatic, vasodilating, antiarrhythmic (toward chloroform) and anticonvulsant (toward pentazol) activities were observed.

All the amines *XVIII*—*XXXIV* showed a certain central neurotropic activity displayed by excitation at values higher than those shown as the test doses. When using the doses shown, excitation did not take place or was replaced by depression (*e.g. XVIII*, *XXI*, *XXII*). In several cases, a slight potentiation of thiopental sleep in mice was observed (*XVIII*, *XIX*, *XX*, *XXVI*) and a slight to pronounced hypothermic activity in rats (*XIX*, *XX*, *XXII*, *XXVIII*). Compounds *XIX*, *XX* and *XXII* showed a slight anticonvulsant activity toward pentetrazol in mice. Rather typical of the whole group is a parasympatholytic effect displayed either by mydriasis (mouse pupils) (*e.g. XIX*—*XXIII*), or by antispasmodic effect toward acetylcholine in isolated rat intestine (*XVIII* comparable with adiphenine, *XXIII* and *XXIV* being weaker). In several compounds a myotropic spasmolytic activity in isolated rat intestine was observed toward barium chloride spasms comparable with the effect of papaverine (*XVIII*, *XXIII*, *XXIV*, *XXVIII*, *XXX*). A parasympatholytic effect was observed also with the highly toxid quaternary salts (*XVIII*-MeI and *XIX*-MeI), the spasmolytic effect of which toward acetylcholine is higher than with adiphenine. In high doses the compounds show a myorelaxant activity of the curare type in a neuromuscular preparation of the rat *m. gastrocnemius in vivo*.

Some of the piperazine derivatives showed in the test with normotensive rats a slight hypotensive effect (*XXIV*—*XXVII*, *XXX*) which was protracted with *XVIII* and *XXXIV*. *XXXIII* has a slight hypertensive and hyperthermic effect. A certain vasodilating effect (characterized by the rise of skin temperature of mice) was observed with *XXII* and *XXIII*. An antiarrhythmic effect in rats was observed with *XVIII* (toward aconitine) and *XXXIV* (toward chloroform and aconitine). Compound *XXIV* significantly prolongs the survival of mouse asphyctic myocard and compound *XXVII* has a positive inotropic effect on isolated rabbit auricle. Several compounds were found to show a hypoglycaemic effect on rats (*XIX*, *XIX*-MeI, most significant with *XXIX*),

others had a slight hyperglycaemic effect (*XXIV*, *XXVII*, *XXVIII*, *XXX–XXXII*). In several cases antimicrobial activity was observed *in vitro*, partly with a wide spectrum. The values of minimum inhibitory concentrations for several microbial species are shown in Table III.

TABLE III

Antimicrobial Efficiency of Some Compounds Prepared Here *in Vitro*

Minimum inhibitory concentration (μg/ml). Unless a numerical value is given, the compound was not effective at the concentrations shown. All the compounds were ineffective toward *Saccharomyces pasteurianus*, *Trichophyton mentagrophytes*, *Candida albicans* and *Aspergillus niger*.

Compound[a]	1[b]	2	3	4	5	6	7	8	9	10
VII-S	50	50	50	50	100	100	100	100	100	—
XVIII-2 HM	25	25	25	25	50	100	100	100	100	50
XVIII-MeI	50	50	50	50	—	—	—	—	—	—
XIX-2 HM	25	25	25	25	50	100	100	50	100	50
XIX-MeI	25	25	50	50	50	—	—	—	50	—
XX·2 HM	25	25	25	25	50	100	100	100	100	25
XXI 2 HM	25	25	25	25	50	100	100	100	100	—
XXII 2 HM	50	50	50	50	50	100	100	100	100	50

[a] S semicarbazone, MH hydrogen maleate, MI methiodide. [b] 1 *Streptococcus* β-*haemolyticus*, 2 *Streptococcus* β-*haemolyticus* WARD, 3 *Staphylococcus pyogenes aureus*, 4 *Staphylococcus pyogenes aureus* resistant against penicillin, 5 *Klebsiella pneumoniae*, 6 *Pseudomonas aeruginosa*, 7 *Escherichia coli*, 8 *Salmonella typhi abdominalis*, 9 *Proteus vulgaris*, 10 *Mycobacterium tuberculosis* H 37 Rv.

EXPERIMENTAL

The melting points of the analytical preparations were estimated in Kofler's block. The samples were dried in the usual way. The analyses of most of the compounds prepared here are shown in Tables I and II. The UV spectra (methanol) were recorded on a Unicam SP 700 spectrophotometer, the IR spectra (Nujol) on a Unicam SP 200 G spectrophotometer and the NMR spectra (in deuteriochloroform unless otherwise stated) on a ZKR 60 (Zeiss, Jena) spectrometer.

1-(4-Methylthiophenyl)-3-phenylpropan-1-one (*V*) (Method A)

A solution of 29·4 g hydrocinnamyl chloride[5] (b.p. 118–120°C/17 Torr) in 60 ml benzene was added dropwise over a period of 75 min to a mixture of 110 ml benzene, 35 g anhydrous aluminium chloride and 44·8 g thioanisol under stirring. The mixture was stirred for 3 h at room temperature, left to stand overnight and poured into a mixture of 500 g ice and 150 ml concentrated hydrochloric acid. After separation of the benzene layer the aqueous phase was extracted with benzene, the combinated benzene fractions were washed with 10% sodium carbonate and dried with sodium sulfate. By evaporating the benzene and mixing the residue with ethanol a product was obtained: 32·9 g (74%), m.p. 85·5–87°C (ethanol). UV spectrum: λ_{max} 229 nm (log ε 3·83), 305 nm (4·30). IR spectrum: 700, 750, 775 (C_6H_5), 820 (1,4-C_6H_4), 1 500, 1 556,

1 592 (Ar), 1 668 cm^{-1} (Ar-CO). The *semicarbazone* (V—S) was obtained in a practically theoretical yield by a reaction of free semicarbazide (liberated from the hydrochloride with sodium acetate) with the ketone in boiling ethanol; m.p. 165—167°C (ethanol).

4-Methylthioacetophenone (*X*)

A solution of 33·6 g phenylmercaptoacetyl chloride[7] (b.p. 121—123°C/10 Torr) in 60 ml benzene was added dropwise under stirring over a period of 90 min at 20°C to a mixture of 120 ml benzene, 37·5 g aluminium chloride and 48 g thioanisol. The mixture was stirred for 2·5 h at room temperature, left to stand overnight and processed as under (*A*): 14·2 g m.p. 81·5—82·5°C (ethanol). For $C_9H_{10}OS$ (166·2) calculated: 65·05% C, 6·07% H, 19·26% S; found: 64·87% C, 6·27% H, 19·08% S. Ref.[12] gives a m.p. of 80°C for the compound prepared by a reaction of acetic anhydride with thioanisol and aluminium chloride in carbon disulfide. *Semicarbazone* (X—S), m.p. 205—209°C (ethanol) (ref.[13] gives m.p. 212—213°C). NMR spectrum (in hexadeuteriodimethyl sulfoxide): 7·25 (d. 2 H, J = 9·0 Hz, aromatic protons in *o*-positions to SCH_3), 7·85 (d. 2 H, J = 9·0 Hz, the remaining two aromatic protons), 6·55 (b. s. 2 H, terminal NH_2), 2·48 (s. 3 H of SCH_3), 2·17 (s. 3 H, C—CH_3), 9·46 (s. 1 H, N—NH—CO). For $C_{10}H_{13}N_3OS$ (223·2) calculated: 53·80% C, 5·87% H, 18·83% N, 14·34% S; found: 54·16% C, 5·90% H, 18·54% N, 14·35% S.

2-(Phenylmercaptoacetyl)thiophene (*IX*) (Method B)

A mixture of 12·0 ml thiophene, 25·2 g phenylmercaptoacetyl chloride[7] and 150 ml benzene was cooled to 0°C and 17·4 ml stannic chloride was added dropwise over a period of 45 min. The mixture was stirred for 1 h at room temperature and decomposed by the slow addition of a mixture of 12 ml HCl and 75 ml water. The benzene layer was separated, washed with water, dried with calcium chloride and distilled; b.p. 174°C/1 Torr. The distillate crystallized and was recrystallized from 20 ml ethanol; 21·0 g (66%), m.p. 54—56°C (ref.[10,17] give b.p. 165—170°C/3 Torr, and 150—170°C/1 Torr, and m.p. of 54°C). UV spectrum: λ_{max} 254 nm (log ε 4·25), 286 nm (3·93). IR spectrum: 699, 732, 740 (C_6H_5), 860 (2-thienyl), 1 410 (CH_2S), 1 580 and 1 610 (Ar), 1 654 cm^{-1} (Ar—CO). *Semicarbazone IX*-S, m.p. 117—118°C (ethanol).

1-(4-Methylthiophenyl)-3-phenylpropanol (*XIIIa*) (Method C)

A solution of 1·2 g sodium borohydride in 10 ml water with 0·2 ml 15% NaOH was added to a solution of 20·5 g ketone *V* in 150 ml ethanol. The mixture was refluxed for 3 h, evaporated at reduced pressure, the residue was decomposed with water and extracted with benzene. The extract was washed (3% solution of NaOH and water), dried with Na_2SO_4 and evaporated. The residue crystallized from hexane; 19·9 g (97%), m.p. 54—56°C (hexane). UV spectrum: λ_{max} 257 nm (log ε 3.78). IR spectrum: 700, 750 (C_6H_5), 820 (1,4-C_6H_4), 1 090 (sec. alcohol). 1 600 (Ar), 3 300 cm^{-1} (OH).

4-Methoxystyryl Phenyl Sulfide (*XVII*)

Crude oily alcohol *XIVa* was distilled under water-pump vacuum. It was decomposed, giving rise to an oily substance boiling at 196°C/10 Torr. For $C_{15}H_{14}OS$ (242·3) calculated: 74·36% C, 5·83% H, 13·20% S; found: 74·61% C, 5·94% H, 12·81% S.

1-(2-Thienyl)-3-phenylpropyl Chloride (*XVb*) (Method D)

Thionyl chloride (9 ml) was added slowly to a warm solution of 13·1 g alcohol *XVa* in 75 ml tetrachloromethane and the mixture was stirred for 30 min with refluxing at 65°C. After cooling, the clear solution was washed with water, with 8% sodium hydrogen carbonate and again with water. After drying with $CaCl_2$ the tetrachloromethane was evaporated at reduced pressure. The residue (14·0 g, 98%) is a crude product. Similar methods were used for preparing the chlorides *XIb*–*XIIIb*.

1-(4-Methoxyphenyl)-2-(phenylthio)ethyl Chloride (*XIVb*) (Method E)

A solution of 16·8 g crude alcohol *XIVa* in 100 ml benzene with 7 g powdery calcium chloride added, was saturated with anhydrous hydrogen chloride. After standing overnight it was filtered and the filtrate was carefully evaporated at reduced pressure. The remaining oil (18 g, 100%) represents a crude product. Chlorides *XIIb* and *XVIb* were prepared analogously.

1-[1-(4-Methoxyphenyl)-3-phenylpropyl]-4-ethoxycarbonylpiperazine (*XXVIII*) (Method F)

A mixture of 74·0 g crude chloride *XIIb* and 90·0 g 1-ethoxycarbonylpiperazine[27] was heated for 4 h to 110°C. After cooling the mixture was separated by shaking between 100 ml benzene and 100 ml water, the aqueous phase was extracted with benzene and the combined benzene solutions were shaken with 250 ml dilute (3 : 1) hydrochloric acid. The aqueous acid phase together with the oily hydrochloride at the bottom were made alkaline with aqueous ammonia, the base was re-extracted with benzene, the extract was dried with Na_2SO_4 and evaporated. A total of 75·3 g (69%) crude oily base was obtained. A part of this base (20·5 g) was neutralized with a solution of 6·2 g maleic acid in 55 ml ethanol. After adding 250 ml ether a total of 18·1 g *hydrogenmaleate* precipitated, which was analyzed as hemihydrate melting at 139°C (ethanol). Decomposition of the salt with aqueous ammonia, extraction with chloroform and distillation yielded the pure *base*, b.p. 176–180°C/0·25 Torr. IR spectrum: 700, 752 (C_6H_5), 835 (1,4-C_6H_4), 1245 (C—O—C), 1510, 1610 (Ar), 1700 cm^{-1} ($NCOOC_2H_5$). NMR spectrum: δ 7·40–7·05 (m., 5 H of C_6H_5), 6·98 (d., 2 H, J = 9·0 Hz, aromatic protons at *o*-positions toward OCH_3), 7·18 (d. 2 H, J = 9·0 Hz, remaining 2 aromatic protons), 4·06 (q., 2 H, $COOCH_2C$), 3·78 (s., 3 H, OCH_3), 3·65–3·15 (m., 5 H, $-CH_2CH_2CH-$), 2·60–1·90 (m. 8 H, CH_2 groups of piperazine), 1·18 (t. 3 H, $C-CH_3$). For $C_{23}H_{30}N_2O_3$ (382·5) calculated: 72·22% C, 7·90% H, 7·33% N; found: 72·10% C, 8·05% H, 7·34% N.

1-[1-(4-Methoxyphenyl)-3-phenylpropyl]piperazine (*XXIX*)

A mixture of 53·5 g crude base *XXVIII*, 50 ml ethanol and 27 g potassium hydroxide was refluxed under stirring for 2·5 h in a bath at 120–125°C. After cooling, it was diluted with 100 ml water and extracted with 100 ml benzene and 100 ml chloroform, the extract was dried with K_2CO_3 and evaporated. A total of 41·7 g (96%) crude oily base *XXIX* was obtained which crystallized from light petroleum, m.p. 69–70°C. NMR spectrum: δ 7·24 (b. s. 5 H, C_6H_5), 6·90 and 7·21 (2 d., 4 H, J = 9·0 Hz, aromatic protons of C_6H_4), 3·81 (s. 3 H of OCH_3), 3·26 (m., 1 H of Ar—CH—N), 2·80 (m., 4 H of the CH_2 group of piperazine adjacent to NH), 2·60–1·90 (m., 8 H of CH_2 group of the aliphatic chain and the remaining two CH_2 groups of piperazine), 1·46 (s. 1 H of NH). *Di(hydrogen maleate)*, m.p. 149–151°C (methanol).

1-[1-(4-Methoxyphenyl)-3-phenylpropyl]-4-acetylpiperazine (*XXX*)

A mixture of 6·2 g crude base *XXIX*, 40 ml acetic acid and 4 ml acetic anhydride was refluxed for 2 h (bath at 150–155°C). After cooling, the volatile fractions were evaporated *in vacuo*, the residue after alkalinization with aqueous ammonia was extracted with benzene and the solution was shaken with 125 ml 3M-HCl. After removal of the benzene phase, alkalinization with ammonium hydroxide liberated the base which was isolated by extraction with benzene: 4·7 g (67%) of crude oily base. *Hydrogen maleate*, m.p. 137°C (ethanol–ether).

1-[1-(4-Methoxyphenyl)-3-phenylpropyl]-4-ethylpiperazine (*XXXI*)

A solution of 4·7 g crude base *XXX* in 35 ml ether was added dropwise to a suspension of 1·26 g lithium aluminium hydride in 35 ml ether and the mixture was refluxed for 8 h. After cooling it was decomposed under stirring by gradually adding 1·3 ml water, 1·3 ml 15% NaOH and 3·8 ml water. After 1 h of standing it was filtered and the ether filtrate was evaporated: 4·27 g (95%) oily base. *Di(hydrogen maleate)*, m.p. 179—182°C (aqueous ethanol).

1-[1-(4-Methoxyphenyl)-3-phenylpropyl]-4-methanesulfonylpiperazine (*XXXII*)

Methanesulfonyl chloride (2·4 ml) was added dropwise to a solution of 6·2 g crude base *XXIX* in 12 ml pyridine and the mixture was heated for 2 h to 90°C. After cooling it was decomposed with 100 ml water, made alkaline with ammonium hydroxide and extracted with benzene. Processing of the extract yielded 7·5 g (96%) crude oily base. *Hydrogen maleate*, m.p. 129°C (methanol).

1-[1-(4-Methoxyphenyl)-3-phenylpropyl]-4-(2-cyanoethyl)-piperazine (*XXXIII*)

A solution of 40·3 g crude base *XXIX* in 130 ml tert-butyl alcohol was treated with 3 ml of 50% triethylbenzylammonium hydroxide in methanol and, under stirring, 26 ml acrylonitrile in 130 ml tert-butyl alcohol was added dropwise at 30°C. The mixture was stirred for 4 h in a bath at 50 to 65°C, the volatile fractions were evaporated *in vacuo*, the residue was dissolved in benzene, the solution was washed with water and then shaken with 300 ml 3M-HCl. After removong the benzene phase it was made alkaline with ammonium hydroxide and the base was isolated by extraction with benzene: 44·2 g (94%) oil. *Di(hydrogen maleate)*, m.p. 163°C (ethanol).

1-[1-(4-Methoxyphenyl)-3-phenylpropyl]-4-(3-aminopropyl)piperazine (*XXXIV*)

Reduction of 7·26 g crude base *XXXIII* with 2·3 g lithium aluminium hydride in 170 ml ether was done by 3 h of refluxing. The reaction mixture was processed as during preparation of *XXXI*. A total of 5·9 g (80%) crude oily base was obtained. *Tri(hydrogen maleate)*, m.p. 171—173°C (aqueous ethanol).

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