SYNTHESIS OF A SERIES OF 5-METHYL-1*H*-IMIDAZOLE-4-YLMETHYL SULFIDES

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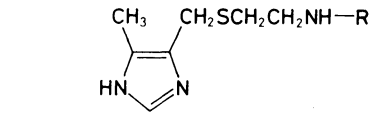
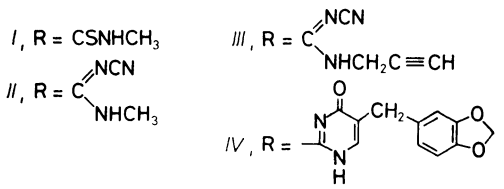
5-Methyl-1*H*-imidazole-4-ylmethanethiol (*V*) hydrochloride was reacted with benzyl chloride, 4-fluorobenzyl bromide, 4-chlorobenzyl chloride, 4-(2-dimethylaminoethoxy)benzyl chloride hydrochloride, 1-chloro-2,3-epoxypropane, 4-fluorophenacyl chloride, 1-bromo-3-phenylpropane, 1-bromo-4-phenylbutane, 1-bromo-5-phenylpentane, 1-bromo-2-methyl-4-phenylbutane, 1-bromo-6-phenylhexane, 1-(benzhydryloxy)-2-bromoethane, 1-bromo-2-(bis(4-fluorophenyl)methoxy)-ethane, 2-(4-chloromethyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene, 2-(4-chlorobutyryl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene, and 4-(chloromethyl)-*s*-hydrindacene in the presence of sodium hydroxide to give the title sulfides *VII*—*XXII*, most of which were transformed to salts. Only compounds *X* and *XIII* showed some pharmacological activity in tests which are considered predictive of antidepressant action.

Some 5-methyl-1*H*-imidazole-4-ylmethyl sulfides with hydrophilic thiourea or guanidine residues in their molecules became in recent years very famous for their histamine H_2-receptor antagonistic properties which was the basis for their therapeutic utility in the treatment of gastric ulcers[1]. The following four experimental or practically used agents may be mentioned as examples: metiamide (*I*) (ref.[2]), cimetidine (*II*) (ref.[3]), etintidine (*III*) (ref.[4]), and oxmetidine (*IV*) (ref.[5]). The hydrophilicity of these compounds is evidently connected with the peripheral character of their pharmacodynamic actions. In the present communication the synthesis of a series of 5-methyl-1*H*-imidazole-4-ylmethyl sulfides with lipophilic residues is being presented. The purpose of the work was to make such compounds available for pharmacological testing especially for the central effects.



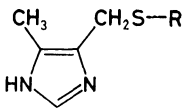


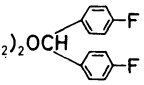
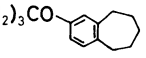
The starting material used was 5-methyl-1*H*-imidazole-4-ylmethanethiol (*V*) hydrochloride[6] which is accessible from 4-(chloromethyl)-5-methylimidazole hydrochloride[7]. We considered also the preparation of *V* via *VI* and prepared *VI* dihydrochloride from 4-(chloromethyl)-5-methylimidazole hydrochloride[7] by reaction with thiourea in boiling ethanol. In fact, *VI* had already been prepared[8] but was used only as an intermediate without having been characterized.

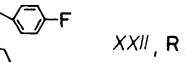
5-Methyl-1*H*-imidazole-4-ylmethanethiol (*V*) hydrochloride[6] was reacted with benzyl chloride, 4-fluorobenzyl bromide[9], 4-chlorobenzyl chloride, 4-(2-dimethylaminoethoxy)benzyl chloride hydrochloride, 1-chloro-2,3-epoxypropane, 4-fluorophenacyl chloride[10], 1-bromo-3-phenylpropane, 1-bromo-4-phenylbutane[11], 1-bromo-5-phenylpentane[12], 1-bromo-2-methyl-4-phenylbutane[13], 1-bromo-6-phenylhexane[11], 1-(benzhydryloxy)-2-bromoethane[14,15], 1-bromo-2-(bis(4-fluorophenyl)methoxy)ethane[15], 2-(chloromethyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[16], 2-(4-chlorobutyryl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[17], and 4-(chloromethyl)-*s*-hydrindacene[18] to give the sulfides *VII*–*XXII*. The reactions were carried out in the presence of aqueous sodium hydroxide either in 2-propanol (method *A*), in 2-propanol and in the presence of triethylbenzylammonium chloride (method *B*), or in dioxane (method *C*). The crude products were chromatographed on aluminium oxide and the homogenenous bases (crystalline or oily) were characterized by spectra and mostly transformed to crystalline salts (hydrochlorides, oxalates, maleates). The products are assembled in Table I with the usual experimental data and their spectra are assembled in Table II. In the Experimental, the description of synthesis of *VII*, *XIII*, and *XXII* is presented as examples of the used methods *A*–*C*. Comparison of yields attained by methods *A*, *B*, and *C* (cf. Table I) indicates practically no difference between *A* and *B* what means that the phase-transfer catalysis, used in method *B*, was not necessary. Yields attained by method *C* are lower but the method was used only in two cases. Reaction of *V*.HCl with 1-(2-chloroethyl)piperazine dihydrochloride[19] using method *B* did not lead to the product wanted; a high-melting solid (m.p. 190–192°C) was obtained whose analysis corresponded to the elemental composition $C_{10}H_{14}N_4S_2$. It is considered to be the disulfide *XXIII* (the fragmentation pattern of the mass spectrum is in agreement) which was described in the literature[6] but the melting point was given by 15°C lower (174–175°C) than our value.

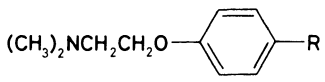
The starting material for the synthesis of *X*, i.e. *XXVI*.HCl, was prepared from *XXIV* which was only mentioned in a patent[20] and obtained now by reaction of the sodium salt of methyl 4-hydroxybenzoate with 2-dimethylaminoethyl chloride in boiling methanol. The oily *XXIV* was distilled and was characterized by spectra. It was reduced with lithium aluminium hydride in ether and gave the oily *XXV* in a high yield. It was also distilled and transformed to the crystalline hydrochloride whose spectra were registered. Reaction of this hydrochloride with thionyl chloride in 1,2-dichloroethane gave directly *XXVI*.HCl (mass spectrum recorded). An at-

tempt to N-alkylate 4(5)-methylimidazole with 1-chloro-4-(2-chloroethylthio)-benzene[21] in dimethylformamide in the presence of sodium hydride led only to elimination of hydrogen chloride and 1-chloro-4-(vinylthio)benzene (*XXVII*) (cf. ref.[22]) was obtained. The easy elimination of hydrogen chloride from 1-chloro-4--(2-chloroethylthio)benzene was described[23].

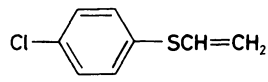


V, R = H
VII, R = $CH_2C_6H_5$
IX, R = 
XI, R = 
XIII, R = $(CH_2)_3C_6H_5$
XV, R = $(CH_2)_5C_6H_5$
XVII, R = $(CH_2)_6C_6H_5$
XIX, R = 
XX, R = 
XXI, R = 

VI, R =
VIII, R =
X, R = 
XII, R =
XIV, R = $(CH_2)_4C_6H_5$
XVI, R = 
XVIII, R = 
XXII, R =
XXIII, R = 



XXIV, R = $COOCH_3$
XXV, R = CH_2OH
XXVI, R = CH_2Cl



XXVII

Most of the compounds prepared were subjected to a preliminary pharmacological and microbiological screening. They were tested in the form of salts, described in Table I, and the doses given (in mg/kg) were calculated per bases. Oral administration was used (unless otherwise stated). Acute toxicity in mice, LD_{50} in mg/kg: *VII*, 123; *VIII*, 291; *IX*, 75 i.v.; *X*, 467; *XIII*, 309; *XIV*, 521; *XV*, 464; *XVIII*, 564; *XIX*, 632.

In concentrations of 100 nmol l^{-1} *VII*, *VIII*, *X*, *XIII*–*XV*, *XVIII*, and *XIX* did not show affinity to imipramine and desipramine binding sites in the rat brain hypothalamus (ligands were 4 nmol l^{-1} [^{3}H]imipramine and 4 nmol l^{-1} [^{3}H]desipramine). Compound *XIII* showed in the dose of 25 mg/kg a weak antireserpine

effect against the reserpine-elicited ptosis in mice; in the same doses *VII*, *VIII*, *XV*, *XVIII*, and *XIX* were inactive. Compound *X* in the dose of 10 mg/kg significantly antagonized the reserpine-induced hypothermia in mice; *VII* in the same dose significantly potentiated the reserpine hypothermia. Compounds *VII*, *VIII*, *XIII*, and *XIV* in doses of 10 mg/kg significantly inhibited the spontaneous locomotor activity of mice in the intervals of 1 or 3 h (or both) after the administration; *X*, *XV*, *XVIII*, and *XIX* in the same doses were inactive. Compound *IX* in the i.v. dose of 15 mg/kg brought about brief and deep drops of the blood pressure in normotensive, anaesthetized rats; in concentration of 1–10 mg/l it had spasmolytic effect against the acetylcholine and barium chloride contractions of the isolated rat duodenum.

Antimicrobial effects in vitro (microorganisms and the minimum inhibitory concentrations in mg/l (unless they exceed 100 mg/l) given): *Streptococcus faecalis*, *XVI* 100, *XVII* 100, *XX* 100; *Staphylococcus pyogenes aureus*, *VII* 25, *XV* 50; *Proteus vulgaris*, *XV* 100, *XVI* 100; *Pseudomonas aeruginosa*, *VII* 100; *Saccharomyces pasterianus*, *XV* 50, *XVII* 50; *Trichophyton mentagrophytes*, *VIII* 50, *XIII*, 50, *XIV* 50, *XV* 50, *XVI* 50, *XVII* 12·5, *XVIII* 50, *XX* 50, *XXII* 50; *Aspergillus niger*, *XVII* 50.

EXPERIMENTAL

The melting points of analytical samples were determined in the Kofler block and were not corrected. The samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at a suitably elevated temperature. UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in NUJOL unless otherwise stated, ν in cm^{-1}) were recorded with the Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (mostly in $CDCl_3$, δ in ppm, J in Hz) with a CW-NMR TESLA BS 487C (80 MHz) spectrometer, and the mass spectra (*m/z*, fragments and/or %) with MCH 1320 and Varian MAT 44S (GC-MS) spectrometers. The homogeneity of the substances and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator. For preparative chromatographic separations neutral Al_2O_3 (activity II) was used.

S-(5-methyl-1*H*-imidazole-4-ylmethyl)isothiuronium Chloride Hydrochloride (*VI*.2 HCl)

A mixture of 2·79 g thiourea, 5·76 g *V*.HCl (ref.[6]), and 50 ml ethanol was stirred and refluxed for 6 h. After cooling the precipitated product was filtered, washed with acetone, and dried in vacuo; 5·4 g of *VI*.2 HCl, m.p. 201–202°C (aqueous ethanol–acetone). Further 2·7 g of the product were obtained by processing of the mother liquors; total yield was 8·1 g (97%) of *VI*. .2 HCl. IR spectrum (KBr): 1 583 (imidazolyl as Ar); 1 635, 1 648 (C=N); 2 735 (=NH_2^+); 3 115, 3 250 (NH_2). For $C_6H_{12}Cl_2N_4S$ (243·2) calculated: 29·64% C, 4·98% H, 29·16% Cl, 23·04% N, 13·18% S; found: 29·90% C, 5·10% H, 29·19% Cl, 23·07% N, 13·26% S.

5-Methyl-4-(benzylthiomethyl)-1*H*-imidazole (*VII*) (Method *A*)

A mixture of 6·8 g *V*.HCl (ref.[6]), 60 ml 2-propanol, and 5·3 g benzyl chloride was stirred, treated with a solution of 3·6 g NaOH in 5 ml water and heated to 60°C for 4 h. After standing overnight

the precipitated NaCl was filtered off, the filtrate was evaporated and the residue was dissolved in 1,2-dichloroethane. The solution was washed with 5% NaOH and water, dried, and evaporated. The oily residue (8·6 g) was chromatographed on 200 g Al_2O_3. Elution with 1,2-dichloroethane and with this solvent containing 20% of chloroform gave 6·3 g of almost homogeneous product which was crystallized from a mixture of 10 ml ether and 10 ml hexane; 6·2 g (61%) of *VII*, m.p. 83–85°C (benzene–hexane). Hydrochloride, m.p. 192–194°C (ethanol–ether). Hydrogen maleate, m.p. 80–82°C (acetone–ether). Analyses and the ^{1}H NMR spectrum are included in Tables I and II.

5-Methyl-4-(3-phenylpropylthiomethyl)-1*H*-imidazole (*XIII*) (Method *B*)

A stirred mixture of 8·4 g *V*.HCl (ref.[6]), 60 ml 2-propanol, and 0·1 g triethylbenzylammonium chloride was treated with a solution of 3·4 g NaOH in 5 ml water. In nitrogen atmosphere the mixture was stirred for 30 min at room temperature, treated with 6·6 g 1-bromo-3-phenylpropane, and stirred for 1 h at room temperature. Then it was heated for 4 h to 80°C (bath temperature). After standing overnight the precipitated mixture of salts was filtered off, washed with 2-propanol and the filtrate was evaporated in vacuo. The residue was dissolved in 30 ml 1,2-dichloroethane, the solution was washed with 20% NaOH, saturated NaCl, and water and was processed. The residue (9·8 g) was chromatographed on 200 g Al_2O_3. Elution with 1,2-dichloroethane and with a mixture of 1,2-dichloroethane and chloroform (1 : 1) gave 5·2 g (53%) of an almost homogeneous oily product which crystallized from a mixture of ether and light petroleum, m.p. 69 to 71°C. Hydrochloride, m.p. 187–189°C (ethanol–ether). Analyses and spectra are included in Tables I and II.

4-(*s*-Hydrindacen-4-ylmethylthiomethyl)-5-methyl-1*H*-imidazole (*XXII*) (Method *C*)

A stirred mixture of 8·5 g 79% *V*.HCl (ref.[6]) and 60 ml dioxane was treated with a solution of 3·8 g NaOH in 10 ml water and over 30 min a solution of 9·4 g 4-(chloromethyl)-*s*-hydrindacene[18] in 30 ml dioxane was added dropwise. The mixture was refluxed for 4 h, evaporated in vacuo, the residue was diluted with 20 ml water and extracted with 1,2-dichloroethane. The extract was washed with 20% NaOH, saturated NaCl, water, and was processed. The oily residue was chromatographed on 150 g Al_2O_3. Elution with 1,2-dichloroethane and with a mixture of 1,2-dichloroethane and chloroform (1 : 1) gave 5·3 g (45%) of crystalline *XXII* which was recrystallized from a mixture of benzene and light petroleum, m.p. 180–182°C. Hydrochloride, m.p. 224–226°C (ethanol–ether). Analyses and spectra are included in Tables I and II.

Bis(5-methyl-1*H*-imidazole-4-ylmethyl) Disulfide (*XXIII*)

A solution of 10·0 g 79% *V*.HCl (ref.[6]), 11·5 g 1-(2-chloroethyl)piperazine dihydrochloride[19], and 0·1 g triethylbenzylammonium chloride in 80 ml 2-propanol was stirred for 30 min, then treated under nitrogen with a solution of 8·4 g NaOH in 10 ml water (added over 15 min), the mixture was stirred for 30 min without heating and finally heated for 5·5 h to 80°C (bath temperature). After standing overnight the precipitated NaCl was filtered off, washed with 2-propanol and the filtrate was evaporated in vacuo. The dark residue was chromatographed on 300 g Al_2O_3. Elution with chloroform containing 3% of ethanol gave first 6·3 g of inhomogeneous oily fractions which were followed by 2·7 g of a homogeneous oil which crystallized from ethanol, m.p. 190–192°C. Experimental data suggested that we are dealing here with *XXIII*. Mass spectrum: 218, 128, 126, 125, 95, 83, 76, 68, 54. For $C_{10}H_{14}N_4O_2$ (254·4) calculated: 47·22% C, 5·55% H, 22·03% N, 25·20% S; found: 47·07% C, 5·63% H, 21·83% N, 25·20% S. Ref.[6], m.p. 174–175°C.

TABLE I

5-Methyl-1H-imidazole-4-ylmethyl Sulfides

Compound Method; yield, %	M.p., °C solvent	Formula (M.w.)	Calculated/Found			
			% C	% H	% N	% S
VII	83—85	$C_{12}H_{14}N_2S$	66·02	6·46	12·83	14·60
A[a]; 61	benzene–hexane	(218·3)	65·88	6·43	12·62	14·69
VII-HCl	192—194	$C_{12}H_{15}ClN_2S$[b]	56·57	5·93	11·00	12·58
	ethanol–ether	(254·8)	56·28	6·00	11·25	12·80
VII-MH[c]	80—82	$C_{16}H_{18}N_2O_4S$	57·46	5·43	8·38	9·59
	acetone–ether	(334·4)	57·23	5·39	8·43	9·58
VIII	120—122	$C_{12}H_{13}FN_2S$[d]	61·00	5·54	11·85	13·57
B; 42	benzene–hexane	(236·3)	61·07	5·66	11·80	13·49
VIII-HCl	192—194	$C_{12}H_{14}ClFN_2S$[e]	52·83	5·17	10·27	11·76
	ethanol–ether	(272·8)	52·62	5·06	10·39	11·96
IX	100—102	$C_{12}H_{13}ClN_2S$[f]	57·02	5·18	11·07	12·69
A; 47	benzene–hexane	(252·8)	57·05	5·19	11·14	12·94
IX-HCl	210—212	$C_{12}H_{14}Cl_2N_2S$[g]	49·83	4·88	9·69	11·09
	ethanol–ether	(289·2)	49·73	4·83	9·98	11·40
X-DO[h]	153—155	$C_{20}H_{27}N_3O_9S$	49·47	5·61	8·65	6·60
A; 69	aqueous ethanol	(485·5)	49·40	5·78	8·52	6·80
XI-HH[i]	125—127[j]	$C_8H_{12}N_2OS$	49·73	6·78	14·50	16·56
C; 45	aqueous ethanol	$+ 0·5\ H_2O$	50·03	6·65	14·36	16·85
		(193·2)				
XII	161—163	$C_{13}H_{13}FN_2OS$[k]	59·07	4·96	10·60	12·13
A; 58	ethanol	(264·3)	59·18	5·05	10·40	12·20
XIII	69—71	$C_{14}H_{18}N_2S$	68·25	7·36	11·37	13·02
B[a]; 53	ether–light petroleum	(246·4)	67·98	7·33	11·20	12·96
XIII-HCl	187—189	$C_{14}H_{19}ClN_2S$[l]	59·45	6·77	9·90	11·34
	ethanol–ether	(282·8)	59·19	6·77	10·25	11·60
XIV	65—67	$C_{15}H_{20}N_2S$	69·18	7·74	10·76	12·31
B; 36	di(2-propyl) ether	(260·4)	68·95	7·59	10·69	11·92
XIV-HCl	180—182	$C_{15}H_{21}ClN_2S$[m]	60·68	7·13	9·44	10·80
	methanol–ether	(296·9)	60·65	6·84	9·24	10·72
XV-HCl	188—190	$C_{16}H_{23}ClN_2S$	61·83	7·45	9·01	10·31
B; 65	ethanol–ether	(310·9)	61·81	7·41	8·95	10·46
XVI-HCl	188—190	$C_{16}H_{23}ClN_2S$[n]	61·83	7·45	9·01	10·31
B; 58	methanol–ether	(310·9)	61·45	7·39	9·10	10·47

TABLE I
(*Continued*)

Compound Method; yield, %	M.p., °C solvent	Formula (M.w.)	Calculated/Found			
			% C	% H	% N	% S
XVII-HCl	186—188	$C_{17}H_{25}ClN_2S^o$	62·84	7·75	8·62	9·87
B; 41	acetone	(324·9)	62·59	7·55	8·85	10·12
XVIII	115—116·5	$C_{20}H_{22}N_2OS$	70·96	6·55	8·28	9·47
A; 33	1,2-dichloro-ethane–light petroleum	(338·5)	70·66	6·34	8·33	9·69
XVIII-HO[p]	180—182	$C_{21}H_{23}N_2O_3S$	65·77	6·05	7·31	8·36
	ethanol–ether	(383·5)	65·51	6·21	7·26	8·49
XIX-OX[q]	120—122	$C_{22}H_{22}F_2N_2O_5S^r$	56·90	4·77	6·03	6·90
A; 30	ethanol–ether	(464·5)	56·60	4·83	6·09	7·17
XX-HCl	186—188	$C_{17}H_{23}ClN_2S^s$	63·23	7·18	8·68	9·93
B; 25	ethanol–ether	(322·9)	62·91	7·17	8·77	9·98
XXI-HCl	151—153	$C_{20}H_{27}ClN_2OS^t$	63·38	7·18	7·39	8·50
A; 20	ethanol–ether	(379·0)	63·21	7·20	7·38	8·63
XXI	180—182	$C_{18}H_{22}N_2S$	72·44	7·43	9·39	10·74
C; 45	1,2-dichloro-ethane	(298·4)	72·14	7·55	9·35	10·83
XXII-HCl	224—226	$C_{18}H_{23}ClN_2S^u$	64·55	6·92	8·37	9·57
	ethanol–ether	(334·9)	64·26	6·97	8·40	9·80

[a] See Experimental; [b] calculated: 13·92% Cl, found: 13·86% Cl; [c] hydrogen maleate; [d] calculated: 8·04% F, found: 8·33% F; [e] calculated: 13·00% Cl, 6·97% F, found: 13·28% Cl, 7·18% F; [f] calculated: 14·03% Cl, found: 13·92% Cl; [g] calculated: 24·52% Cl, found: 24·66% Cl; [h] dioxalate; [i] hemihydrate; [j] first melting at 110—112°C; [k] calculated: 7·19% F, found: 7·42% F; [l] calculated: 12·54% Cl, found: 12·25% Cl; [m] calculated: 11·94% Cl, found: 12·09% Cl; [n] calculated: 11·40% Cl, found: 11·47% Cl; [o] calculated: 10·91% Cl, found: 10·90% Cl, [p] hemioxalate; [q] oxalate; [r] calculated: 8·18% F, found: 8·47% F; [s] calculated: 10·98% Cl, found: 11·04% Cl; [t] calculated: 9·35% Cl, found: 9·42% Cl; [u] calculated: 10·59% Cl, found: 10·62% Cl.

Methyl 4-(2-Dimethylaminoethoxy)benzoate (*XXIV*)

Methyl 4-hydroxybenzoate (15·2 g) was added to a solution of sodium methoxide (from 2·3 g Na and 40 ml methanol) and after 30 min stirring the solution obtained was evaporated in vacuo. The residue was dried in vacuo at 90°C, after cooling it was suspended in 130 ml dimethyl sulfoxide and the stirred suspension was treated with 12·5 g 2-dimethylaminoethyl chloride, added dropwise. The mixture was stirred for 8 h at 80°C, treated with further 2·0 g 2-dimethylaminoethyl chloride and heated for 8 h to 95—100°C (bath temperature). The solvent was evaporated in

TABLE II

Spectra of 5-methyl-1*H*-imidazole-4-ylmethyl sulfides

Compound	Spectrum	Data
VII	^{1}H NMR	2·14 s, 3 H (CH_3); 3·62 s and 3·65 s, 2 and 2 H ($ArCH_2SCH_2$); 7·28 s, 5 H (C_6H_5); 7·57 s, 1 H (H-2 of imidazole); 12·30 s, 1 H (NH)
VIII	UV	261 (2·84), 267·5 (2·90), 274 (2·82)
	IR	825, 854 (2 adjacent Ar–H); 1 222 (Ar–F); 1 570, 1 600, 3 035 (Ar); infl. 3 100 (NH)
	^{1}H NMR	2·15 s, 3 H (CH_3); 3·63 s, 4 H ($ArCH_2SCH_2$); 6·95 t, 2 H (H-3 and H-5 of fluorophenyl, $J_{H-H} = J_{H-F} = 9·0$); 7·25 dd, 2 H (H-2 and H-6 of fluorophenyl, $J_{H-H} = 9·0$; $J_{H-F} = 5·5$); 7·55 s, 1 H (H-2 of imidazole); 11·62 s, 1 H (NH)
IX	UV	infl. 268 (2·79), infl. 277 (2·55)
	IR	820, 840 (2 adjacent Ar–H); 1 486, 1 605, 3 010, 3 075 (Ar); infl. 3 100 (NH)
	^{1}H NMR	2·15 s, 3 H (CH_3); 3·60 s, 4 H ($ArCH_2SCH_2$); 7·20 s, 4 H (ArH of chlorophenyl); 7·54 s, 1 H (H-2 of imidazole); 11·50 s, 1 H (NH)
X-DO[a]	MS	305 (M^+, $C_{16}H_{23}N_3OS$, 0·1), 234 ($C_{12}H_{14}N_2OS$, 2·8), 210 ($C_{11}H_{16}NOS$, 4·5), 128 ($C_5H_8N_2S$, 7·8), 72 ($C_4H_{10}N$, 30), 58 (C_3H_8N, 100)
XI-HH[b]	MS	184 (M^+, $C_8H_{12}N_2OS$, 100), 169 ($C_7H_9N_2OS$, 10), 151 ($C_8H_{11}N_2O$, 7), 137 ($C_7H_9N_2O$, 20), 109 ($C_6H_9N_2$, 41), 95 ($C_5H_7N_2$, 90), 67 (C_4H_5N, 40)
	IR	1 500, 1 590 (imidazole as Ar); 3 110, 3 160, 3 390, 3 585 (NH, H_2O)
	^{1}H NMR[c]	2·00 s, 3 H (CH_3); 2·80 m, 2 H (SCH_2–C); 3·65 m, 1 H (CH–O); 3·70 s, 2 H ($ArCH_2S$); 4·05 m, 2 H (CH_2O); 7·40 s, 1 H (H-2 of imidazole)
XII	MS	264 (M^+, $C_{13}H_{13}FN_2OS$, 3), 138 (6), 127 (59), 123 (41), 95 (100)
	UV	243 (4·07), 328 (2·76)
	IR	780, 820 (2 adjacent Ar–H); 1 287 (Ar–F); 1 480, 1 510, 1 600 (Ar); 1 670 (ArCOR); 3 100 (NH)

TABLE II
(*Continued*)

Compound	Spectrum	Data
XIII	IR (KBr)	700, 750 (5 adjacent Ar–H); 1 498, 1 604, 3 030 (Ar); 3 100 (NH)
	^{1}H NMR	1·90 m, 2 H (CH_2 in position 2 of propyl); 2·19 s, 3 H (CH_3); 2·48 t, 2 H (SCH_2 of propylthio, J = 7·0); 2·68 t, 2 H ($ArCH_2$, J = 7·0); 3·69 s, 2 H (imidazolyl–CH_2S); 7·20 m, 5 H (C_6H_5); 7·50 s, 1 H (H-2 of imidazole); 9·90 bs, 1 H (NH of imidazole)
XV	^{1}H NMR	1·50 m, 6 H (3 × CH_2 in positions 2, 3 and 4 of pentyl); 2·20 s, 3 H (CH_3); 2·50 m, 4 H (SCH_2 and $ArCH_2$ of pentyl); 3·68 s, 2 H (4-imidazolyl–CH_2S); 7·20 s, 5 H (C_6H_5); 7·53 s, 1 H (H-2 of imidazole); 9·70 bs, 1 H (NH)
XVI	^{1}H NMR	1·00 d, 3 H (CH_3 of methylbutyl); 1·60 m, 3 H ($CHCH_2$ in positions 2 and 3 of butyl); 2·18 s, 3 H (imidazole-5-CH_3); 2·50 m, 4 H (SCH_2 and $ArCH_2$ of butyl); 3·62 s, 2 H (imidazole–CH_2S); 7·20 bs, 5 H (C_6H_5); 7·34 bs, 1 H (H-2 of imidazole); 10·55 bs, 1 H (NH)
XVII	^{1}H NMR	1·40 bm, 8 H (4 × CH_2 in positions 2, 3, 4, and 5 of hexyl); 2·18 s, 3 H (CH_3); 2·50 m, 4 H (SCH_2 and $ArCH_2$ of hexyl); 3·65 s, 2 H (imidazole–CH_2S) 7·20 s, 5 H (C_6H_5); 7·55 bs, 1 H (H-2 of imidazole); 9·55 bs, 1 H (NH)
XVIII	^{1}H NMR	2·10 s, 3 H (CH_3); 2·65 t, 2 H (SCH_2 of ethylthio, J = 7·0); 3·55 t, 2 H (CH_2O, J = 7·0); 3·68 s, 2 H (imidazole–CH_2S); 5·30 s, 1 H (Ar_2CHO); 7·25 bs, 10 H (2 × C_6H_5); 7·30 s, 1 H (H-2 of imidazole); 10·40 bs, 1 H (NH)
XIX-OX[d]	MS	374 (M^+, $C_{20}H_{20}F_2N_2OS$, 0·01), 279, 219, 203, 201, 183, 95
XX-HCl	MS	286 (M^+, $C_{17}H_{22}N_2S$, 3·4), 253 ($C_{17}H_{21}N_2$, 0·5), 159 ($C_{12}H_{15}$, 17), 95 ($C_5H_7N_2$, 100), 96 ($C_5H_8N_2$, 78)
XXI-HCl	MS	342 (M^+, $C_{20}H_{26}N_2OS$, 1), 248 (1), 230 (0·6), 201 (3), 188 (33), 173 (24), 127 (24), 96 (85), 95 (100)
XXII	IR	867 (solitary Ar–H); 1 610, 3 010 (Ar); 2 620 (=NH^+); 3 110 (NH)
	^{1}H NMR	1·96 bt, 4 H (2 × CH_2 in positions 2 and 6 of hydrindacene); 2·12 s, 3 H (CH_3); 2·75 bt, 8 H (4 × $ArCH_2$ of hydrindacene); 3·65 s, 4 H (CH_2SCH_2Ar); 6·92 s, 1 H (H-8 of hydrindacene); 7·40 s, 1 H (H-2 of imidazole); 10·48 bs, 1 H (NH)

[a] Dioxalate; [b] hemihydrate; [c] in CD_3SOCD_3; [d] oxalate.

vacuo, the residue was diluted with 20 ml saturated NaCl and extracted with benzene. The extract was washed with 20% NaOH and saturated NaCl, and processed. The residue was distilled giving 13·4 g (60%) of *XXIV*, b.p. 134–136°C/0·13 kPa. UV spectrum: 254 (4·28). IR spectrum (film): 771, 850 (2 adjacent Ar–H); 1 030, 1 252 (ArOR); 1 103, 1 169, 1 278, 1 716 (ArCOOR); 1 510, 1 570, 1 604, 3 068 (Ar); 2 770, 2 818 (N–CH_3). ^{1}H NMR spectrum: 2·35 s, 6 H ($N(CH_3)_2$); 2·75 t, 2 H (CH_2N, J = 6·0); 3·90 s, 3 H ($COOCH_3$); 4·14 t, 2 H ($ArOCH_2$, J = 6·0); 6·96 d, 2 H (H-3 and H-5, J = 8·5); 8·00 d, 2 H (H-2 and H-6, J = 8·5). For $C_{12}H_{17}NO_3$ (223·3) calculated: 64·55% C, 7·68% H, 6·27% N; found: 64·69% C, 7·85% H, 6·25% N.

4-(2-Dimethylaminoethoxy)benzyl Alcohol (*XXV*)

A solution of 13·0 g *XXIV* in a mixture of 100 ml ether and 30 ml tetrahydrofuran was added dropwise to a stirred solution of 3·0 g $LiAlH_4$ in 30 ml ether and the mixture was refluxed for 2 h. After cooling the stirred mixture was decomposed by 12 ml 20% NaOH, the organic solution was separated by decantation from the semisolid salts and evaporated. The residue was distilled giving 10·1 g (89%) of crude *XXV*, b.p. 160–165°C/0·45 kPa. Neutralization with HCl in a mixture of ethanol and ether gave the hydrochloride, m.p. 154–156°C (ethanol). IR spectrum: 819 (2 adjacent Ar–H); 1 030, 1 047, 1 064 (CH_2OH); 1 170, 1 243 (ArOR); 1 510, 1 585, 1 610, 3 023, 3 058 (Ar); 2 490, 2 525, 2 680 (NH^+); 3 330 (OH). ^{1}H NMR spectrum (D_2O): 3·00 s, 6 H ($N(CH_3)_2$); 3·60 t, 2 H (CH_2N, J = 5·0); 4·35 t, 2 H ($ArOCH_2$, J = 5·0); 4·60 s, 2 H ($ArCH_2O$); 7·03 d, 2 H (H-3 and H-5, J = 8·5); 7·40 d, 2 H (H-2 and H-6, J = 8·5). For $C_{11}H_{18}ClNO_2$ (231·7) calculated: 57·01% C, 7·83% H, 15·30% Cl, 6·05% N; found: 56·85% C, 7·74% H, 15·58% Cl, 5·96% N.

4-(2-Dimethylaminoethoxy)benzyl Chloride (*XXVI*)

A suspension of 8·4 g *XXV*.HCl in 50 ml 1,2-dichloroethane was stirred and treated at 80°C with a solution of 6·0 g $SOCl_2$ in 5 ml 1,2-dichloroethane, added dropwise. The mixture was refluxed for 6 h, allowed to stand overnight, the volatile components were evaporated in vacuo and the residue was crystallized from a small volume of 1,2-dichloroethane giving 7·3 g (82%) of *XXVI*.HCl, m.p. 134–136°C. Mass spectrum: 213 (M^+, $C_{11}H_{16}ClNO$, 1·8), 133 (C_9H_9O, 0·5), 125 (C_7H_6Cl, 1·2), 89 (C_7H_5, 3), 72 ($C_4H_{10}N$, 3·2), 58 (100). For $C_{11}H_{17}Cl_2NO$ (250·2) calculated: 52·81% C, 6·85% H, 28·35% Cl, 5·60% N; found: 52·87% C, 6·91% H, 28·09% Cl, 5·52% N.

1-Chloro-4-(vinylthio)benzene (*XXVII*)

A solution of 4·1 g 4(5)-methylimidazole in 40 ml dimethylformamide was stirred and treated with 1·44 g NaH (in the form of suspension in mineral oil), the mixture was stirred for 1 h at room temperature, treated with a solution of 11·9 g 1-chloro-4-(2-chloroethylthio)benzene[21], and heated for 5 h to 100°C (bath temperature). After cooling NaCl was filtered off and the filtrate was evaporated in vacuo. The residue (12·5 g) was dissolved in ether and the solution was acidified with HCl in ether. The precipitated solid was filtered off and the filtrate was distilled; 5·1 g (55%) of *XXVII*, b.p. 92–95°C/1·1 kPa. For C_8H_7ClS (170·7) calculated: 56·30% C, 4·13% H, 20·78% Cl, 18·79% S; found: 56·01% C, 4·22% H, 20·86% Cl, 18·50% S. Ref.[22], b.p. 66–67°C/0·13 kPa.

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REFERENCES

1. Ganellin C. R., Parsons M. E. (Eds): *Pharmacology of Histamine Receptors.* Wright, Bristol 1982.
2. Black J. W., Duncan W. A. M., Emmett J. C., Ganellin C. R., Heseslbo T., Parsons M. E., Wyllie J. H.: Agents Actions *3*, 133 (1973).
3. Durant G. J., Emmett J. C., Ganellin C. R., Miles P. D., Parsons M. E., Prain H. D., White G. R.: J. Med. Chem. *20*, 901 (1977).
4. Meyers W. M., Peterson W. L.: Clin. Res. *28*, 30A (1980).
5. Blakemore R. C., Brown T. H., Durant G. J., Emmett J. C., Ganellin C. R., Parsons M. E., Rasmussen A. C.: Br. J. Pharmacol. *70*, 105P (1980).
6. Toso R., Sega A., Mihalić M., Kajfez F., Sunjić V.: Gazz. Chim. Ital. *109*, 529 (1979).
7. Durant G. J., Emmett J. C., Ganel in C. R., Roe A. M. (Smith Kline and French Laboratories): Brit. 1,341,376; Chem. Abstr. *80*, 95958 (1974).
8. Jenko B., Langof I., Habjan J. (LEK, Tov. Farm. Kem. Izdel.): Belg. 875,845; Brit. Appl. 2,019,842; Ger. Offen. 2,916,610; Fr. Demande 2,424,261; Chem. Abstr. *92*, 76095, 76508, 198400 (1980); *93*, 71768 (1980).
9. Oláh G. A., Pavláth A. E., Oláh J. A., Herr F.: J. Org. Chem. *22*, 879 (1957).
10. Hann R. M., Wetherill J. P.: J. Washington Acad. Sci. *24*, 526 (1934); Chem. Zentralbl. *1935*, II, 1537.
11. Braun J. v.: Ber. Dtsch. Chem. Ges. *44*, 2867 (1911).
12. Braun J. v., Deutsch H., Schmatloch A.: Ber. Dtsch. Chem. Ges. *45*, 1258 (1912).
13. Bateman L., Cunneen J. I., Lyons J. A.: J. Chem. Soc. *1951*, 2290.
14. Rieveschl G. Jr. (Parke–Davis Co.): U.S. 2,437,711; Chem. Abstr. *42*, 4610 (1948).
15. Vejdělek Z., Metyš J., Holubek J., Svátek E., Protiva M.: Collect. Czech. Chem. Commun. *49*, 2649 (1984).
16. Aspinall G. O., Baker W.: J. Chem. Soc. *1950*, 743.
17. Vejdělek Z., Rajšner M., Svátek E., Holubek J., Protiva M.: Collect. Czech. Chem.Commun. *44*, 3604 (1979).
18. Vejdělek Z. J., Holubek J., Bartošová M., Protiva M.: Collect. Czech. Chem. Commun. *42*, 3094 (1977).
19. Vigelius W. D., Marinis S. (Goedecke A.-G.): Ger. Offen. 2,246, 279; Chem. Abstr. *81*, 63680 (1974).
20. Copp F. C., Elphick A. R., Coker G. G. (Wellcome Foundation Ltd.): Brit. 919,126; Chem. Abstr. *59*, 1531 (1963).
21. Moszew J., Moskal J.: Roczniki Chem. *45*, 1899 (1971).
22. Kuliev A. M., Usubova E. N., Sultanov Yu. M., Kuliev A. B.: Zh. Org. Khim. *4*, 822 (1968).
23. Oae S., Yano Y.: Tetrahedron *24*, 5721 (1968).

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