SYNTHESIS OF ARYLTHIOACETAMIDOXIMES AS POTENTIAL ANTIDEPRESSANTS*

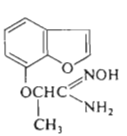
Irena ČERVENÁ, Marta HRUBANTOVÁ, Marie BARTOŠOVÁ and Miroslav PROTIVA

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

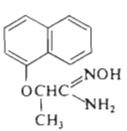
Received August 25th, 1980

Reactions of thiophenol and 16 of its derivatives with chloroacetonitrile afforded arylthioacetonitriles *IVb—XXb* which were treated with hydroxylamine and gave arylthioacetamidoximes *IVa—XXa*. Compounds *VIIa—IXa*, *XIIa*, *XVIa* and *XVIIIa* exhibited antireserpine activity in the test of ptosis in mice and compounds *IXa* and *XVIIa* in the test of reserpine hypothermia in mice.

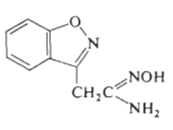
The literature reported for several relatively simple amidoximes interesting psychotropic effects. The benzofuran derivative L-7526 (*I*) was described as a potential antidepressant with significant antireserpine and antiaggressive effects[1]. Its naphthalene analogue L-7660 (*II*) revealed antireserpine activity only in the test of reserpine hypothermia and showed also antiaggressive activity[2]. The benzisoxazole derivative PF-257 (*III*) was characterized as a potential antidepressant with a unique spectrum of activity[3-5].



I



II

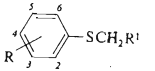


III

In the present communication the synthesis of a series of arylthioacetamidoximes *IVa–XXa* is being described; the compounds have been prepared for the purpose of the general pharmacological screening oriented especially to psychotropic activities. Out of these compounds only the unsubstituted one (*IVa*) was described in a different connection[6] and only after the termination of our experiments a patent[7] disclosed the analogous 3,4-dichlorophenyl derivative for which the psychotropic and antiaggressive activity was claimed. In the syntheses of the title compounds

* Part CXLIX in the series Neurotropic and Psychotropic Agents; Part CXLVIII: This Journal *46*, 781 (1981).

we used as starting materials thiophenol, 4-methylthiophenol, 4-ethylthiophenol[8], 4-chlorothiophenol, 2-methoxythiophenol[9], 3-methoxythiophenol[10], 4-methoxythiophenol[11], 4-ethoxythiophenol[12], 4-(methylthio)thiophenol[13], 4-(ethylthio)thiophenol[13], 4-chloro-2-methoxythiophenol[14], 4-chloro-3-methoxythiophenol[15], 3,4-dimethoxythiophenol[16], 1-thionaphthol[17], 2-thionaphthol[18], 5,6,7,8-tetrahydronaphthalene-1-thiol[19,20] and 5,6,7,8-tetrahydronaphthalene-2-thiol[21,22] (the preparation of this compound by reduction of 5,6,7,8-tetrahydronaphthalene-2-sulfonyl chloride[22] with phosphorus and iodine in acetic acid is being described in the Experimental). These thiophenols were transformed by treatment with sodium methoxide in methanol to sodium salts which were processed by reactions with chloroacetonitrile in boiling methanol (method *A*) and afforded the arylthioacetonitriles *IVb* to *XXb*. Out of these, the literature reported the synthesis of compounds *IVb* (ref.[23]), *Vb* (ref.[24,25]), *VIIb* (ref.[26]), *Xb* (ref.[26]), and *XVIIIb* (ref.[25]), partly using different synthetic procedures. For the transformation of nitriles *IVb*–*XXb* to amidoximes *IVa*–*XXa* a method was used which was described[6] for *IVa*, consisting in reactions of nitriles with hydroxylamine in boiling methanol (method *B*). A part of the amidoximes was obtained in the form of crystalline bases; the hydrochlorides were the final products in all cases. The nitriles and amidoximes *IVab*–*XXab* are summarized in Table I with the usual experimental data. The Experimental describes only examples of preparations.



a, $R^1 = C(=NOH)NH_2$

b, $R^1 = CN$

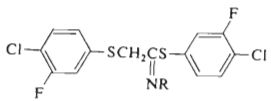
IV, R = H
V, R = 4-CH_3
VI, R = 4-C_2H_5
VII, R = 4-Cl
VIII, R = 2-OCH_3
IX, R = 3-OCH_3
X, R = 4-OCH_3
XI, R = 4-OC_2H_5

XII, R = 4-SCH_3
XIII, R = 4-SC_2H_5
XIV, R = 2-OCH_3-4-Cl
XV, R = 3-OCH_3-4-Cl
XVI, R = 3,4-$(OCH_3)_2$
XVII, R = 2,3-benzo
XVIII, R = 3,4-benzo
XIX, R = 2,3-$(CH_2)_4$

XX, R = 3,4-$(CH_2)_4$

A reaction of 4-chloro-3-fluorothiophenol[27] with chloroacetonitrile under the conditions of method *A* gave an inhomogeneous product which was treated in crude state with hydroxylamine. As a single crystalline product a compound $C_{14}H_9Cl_2F_2NOS_2$ (analyses and mass spectrum) was obtained in a low yield which was identified by means of the ^{1}H-NMR spectrum as S-(4-chloro-3-fluorophenyl)4-chloro-3-fluorophenylthioacetothiohydroxamate (*XXI*). As demonstrated on the case of a reaction of hydrogen cyanide with benzyl mercaptan[28],

nitriles afford by treatment with thiols in the presence of hydrogen chloride the corresponding imino-thioethers which react with hydroxylamine under the formation of thiohydroxamates. In our case the imino-thioether *XXII* was probably formed in the first stage in addition to the desired (4-chloro-3-fluorophenyl)acetonitrile by reaction with a further molecule of 4-chloro-3-fluorothiophenol; it reacted then with hydroxylamine to give the isolated thiohydroxamate *XXI*.



XXI, R = OH
XXII, R = H

The hydrochlorides of compounds *IVa*–*XXa* were subjected to a general pharmacological screening on parenteral administration. The acute toxicity was estimated in mice on intravenous administration. The values of LD_{50} and doses D (in mg/kg *i.v.*), used in the screening, are given: *IVa*, 132·5, 25; *Va*, 120, 24; *VIa*, 100, 20; *VIIa*, 125, 25; *VIIIa*, 125, 25; *IXa*, 120, 24; *Xa*, 150, 30; *XIa*, 125, 25; *XIIa*, 120, 24; *XIIIa*, 87·5, 17; *XIVa*, 100, 20; *XVa*, 125, 25; *XVIa*, 175, 35; *XVIIa*, 80, 16; *XVIIIa*, 120, 24; *XIXa*, 65, 14; *XXa*, 80, 16. Most of the compounds (*IVa*, *VIIa*–*IXa*, *XIVa*, *XVa*, *XVIIa*–*XXa*) in doses higher than D increase the activity and reactivity of mice, higher doses bring about ataxia and tremor; some of the compounds (*Va*, *VIa*, *Xa*–*XIIIa*, *XVIa*) exhibit under similar conditions a central depression. Only few of the compounds bring about central excitation (increase significantly the spontaneous motility of mice in known surroundings) in doses D administered subcutaneously (*XVa*, *XVIIa*, *XVIIIa*, *XXa*); compound *XVIa* shows this effect in a dose lower than D (ED = 15 mg/kg *s.c.*). The antireserpine activity, which is the criterion for the potential antidepressant effect, was estimated in two most common tests in mice, *i.e.* in the test of reserpine ptosis and in the test of reserpine hypothermia. With compounds *VIIa*, *VIIIa*, *IXa*, *XIIa*, *XVIa* and *XVIIIa*, a significant inhibition of the reserpine ptosis was found in doses D. administered intraperitoneally (for amphetamine as a standard, ED = 0·5 mg/kg *i.p.*). The effect towards reserpine hypothermia was found only with compounds *IXa* (ED = 24 mg/kg *i.p.*) and *XVIIa* (ED = 10 mg/kg *i.p.*) (ED is a dose increasing the rectal temperature in mice by 1°C in comparison with the reserpine control group; for amphetamine as a standard, ED = 0·75 mg/kg *i.p.*). The antireserpine activity found is thus of a relatively low degree. With compounds *XIXa* the α-adrenolytic effect was proven (a dose of 10 mg/kg *i.v.* inhibits the adrenaline pressor reaction in rats by 50%). Compound *VIIa* exhibits a hypotensive action (a dose of 25 mg/kg *i.v.* decreases the blood pressure of normotensive rats by 20% for at least 10 min), a negativelly inotropic

TABLE I

Arylthioacetonitriles *IVb—XXb* and Arylthioacetamidoximes *IVa—XXa*

Compound	Method (yield, %)	B.p., °C/kPa or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
				% C	% H	% Cl	% N	% S
IVb	*A*	154—157/2·4[a]	—	—	—	—	—	—
	(88)			—	—	—	—	—
Vb	*A*	168—170/4·27[b]	—	—	—	—	—	—
	(91)			—	—	—	—	—
VIb	*A*	138/0·13	$C_{10}H_{11}NS$	67·75	6·26	—	7·90	18·09
	(56)		(177·3)	68·03	6·46	—	7·74	18·28
VIIb	*A*	88—89[c]	—	—	—	—	—	—
	(63)			—	—	—	—	—
VIIIb	*A*	132—134/0·07	C_9H_9NOS	60·30	5·06	—	7·82	17·89
	(75)		F(179·2)	60·14	5·30	—	8·08	17·25
IXb	*A*	164—168/0·31	C_9H_9NOS	60·30	5·06	—	7·82	17·89
	(48)		(179·2)	60·99	5·16	—	7·13	18·04
Xb	*A*	164/0·27[d]	C_9H_9NOS	60·30	5·06	—	7·82	17·89
	(79)		(179·2)	60·92	5·38	—	7·73	17·46
XIb	*A*[e]	67—68	$C_{10}H_{11}NOS$	62·14	5·74	—	7·25	16·59
	(80)	(ethanol)	(193·3)	62·30	5·70	—	7·19	16·33
XIIb	*A*	62—64[f]	$C_9H_9NS_2$	55·34	4·64	—	7·17	32·84
	(69)	(ethanol)	(195·3)	55·31	4·71	—	7·19	33·09
XIIIb	*A*	168—170/0·11	$C_{10}H_{11}NS_2$	57·37	5·30	—	6·69	30·64
	(66)		(209·3)	57·76	5·42	—	6·27	30·74
XIVb	*A*	176/0·33	C_9H_8ClNOS	50·58	3·77	16·59	6·56	15·00
	(38)		(213·7)	51·45	4·09	16·38	6·13	15·19

TABLE I
(*Continued*)

Compound	Method (yield, %)	B.p., °C/kPa or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
				% C	% H	% Cl	% N	% S
XVb	*A* (70)	168/0·19	C_9H_8ClNOS (213·7)	50·58 51·39	3·77 3·96	16·59 16·38	6·56 6·57	15·00 14·30
XVIb	*A* (74)	101—103[g] (ethanol)	$C_{10}H_{11}NO_2S$ (209·2)	57·39 57·64	5·30 5·32	— —	6·69 6·57	15·32 15·15
XVIIb	*A* (70)	167/0·21[h]	$C_{12}H_9NS$ (199·2)	— —	— —	— —	— —	16·08 16·36
XVIIIb	*A* (54)	81—84[i] (ethanol)	$C_{12}H_9NS$ (199·2)	72·32 72·65	4·55 4·61	— —	7·03 6·80	16·09 16·34
XIXb	*A* (78)	160—162/1·33	$C_{12}H_{13}NS$ (203·3)	— —	— —	— —	— —	15·77 16·00
XXb	*A* (70)	173/0·19	$C_{12}H_{13}NS$ (203·3)	70·89 71·09	6·45 6·84	— —	6·89 7·04	15·77 16·18
IVa-HCl	*B* (60)	128—130[j] (ethanol–ether)	$C_8H_{11}ClN_2OS$ (218·7)	43·93 44·34	5·07 5·33	16·21 16·16	12·81 13·08	14·66 14·84
Va	*B* (90)	67·5—69·5[k] (hexane)	$C_9H_{12}N_2OS$ (196·3)	55·07 55·29	6·16 5·69	— —	14·28 14·36	16·34 16·57
Va-HCl	—	142—145 (ethanol–ether)	$C_9H_{13}ClN_2OS$ (232·7)	46·44 46·75	5·63 5·72	15·23 15·32	12·04 12·24	13·78 13·72
VIa-HCl	*B* (90)	125—128 (ethanol–ether)	$C_{10}H_{15}ClN_2OS$ (246·8)	48·67 48·70	6·13 6·05	14·37 14·16	11·36 11·49	12·99 12·69
VIIa-HCl	*B* (77)	140·5—142[l] (ethanol–ether)	$C_8H_{10}Cl_2N_2OS$ (253·1)	37·96 38·38	3·98 3·85	28·01 27·68	11·07 11·06	12·66 12·79

TABLE I
(*Continued*)

Compound	Method (yield, %)	B.p., °C/kPa or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
				% C	% H	% Cl	% N	% S
VIIIa	*B* (75)	113—115[m] (benzene)	$C_9H_{12}N_2O_2S$ (212·3)	50·92 51·51	5·70 5·79	— —	13·20 13·29	15·11 15·05
VIIIa-HCl	—	120—122 (ethanol–ether)	$C_9H_{13}ClN_2O_2S$ (248·7)	43·46 43·92	5·27 5·21	14·25 14·40	11·26 11·31	12·89 13·19
IXa-HCl	*B* (40)	114—116 (ethanol–ether)	$C_9H_{13}ClN_2O_2S$ (248·7)	43·46 43·64	5·27 5·38	14·25 14·40	11·26 11·57	12·89 13·02
Xa-HCl	*B* (75)	119—121 (ethanol–ether)	$C_9H_{13}ClN_2O_2S$ (248·7)	43·46 43·84	5·27 5·32	14·25 14·37	11·26 11·33	12·89 13·13
XIa	*B*[e] (65)	52—55 (hexane–ether)	$C_{10}H_{14}N_2O_2S$ (226·3	53·07 53·03	6·24 6·33	— —	12·38 12·34	14·17 14·45
XIa-HCl	—	127—129 (ethanol–ether)	$C_{10}H_{15}ClN_2O_2S$ (262·8)	45·71 45·87	5·75 5·72	13·49 13·42	10·66 10·91	12·20 12·40
XIIa	*B* (79)	70—72[n] (benzene)	$C_9H_{12}N_2OS_2$ (228·4)	47·33 47·98	5·30 5·48	— —	12·27 12·12	28·09 27·53
XIIa-HCl	—	143—146 (ethanol–ether)	$C_9H_{13}ClN_2OS_2$ (264·8)	40·82 41·51	4·95 5·11	13·39 13·64	10·58 10·80	24·22 24·21
XIIIa	*B* (80)	63—66[o] (benzene–light petroleum)	$C_{10}H_{14}N_2OS_2$ (242·2)	49·55 49·71	5·82 5·93	— —	11·56 11·42	26·46 26·26
XIIIa-HCl	—	117—119 (ethanol–ether)	$C_{10}H_{15}ClN_2OS_2$ (278·8)	43·07 43·01	5·42 5·42	12·72 12·58	10·05 10·28	23·00 23·07

TABLE I
(*Continued*)

Compound	Method (yield, %)	B.p., °C/kPa or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
				% C	% H	% Cl	% N	% S
XIVa-HCl	*B* (70)	152—154 (ethanol–ether)	$C_9H_{12}Cl_2N_2O_2S$ (283·2)	38·17 38·31	4·27 4·50	25·04 25·32	9·89 10·39	11·32 11·15
XVa	*B* (60)	139—141[p] (benzene)	$C_9H_{11}ClN_2O_2S$ (246·7)	43·81 44·02	4·49 4·64	14·37 14·45	11·36 11·47	12·99 12·81
XVa-HCl	—	143—145 (ethanol–ether)	$C_9H_{12}Cl_2N_2O_2S$ (283·2)	38·17 38·12	4·27 4·31	25·04 24 88	9·89 10·04	11·32 11·31
XVIa	*B* (66)	142—144[q] (ethanol)	$C_{10}H_{14}N_2O_3S$ (242·3)	49·57 49·22	5·82 5·88	— —	11·56 11·90	13 24 13 18
XVIa-HCl	—	179—182 (methanol–ether)	$C_{10}H_{15}ClN_2O_3S$ (278·8)	43·08 43·46	5·42 5·58	12·72 12·90	10·05 10 32	11·50 11·54
XVIIa-HCl	*B* (48)	139—141 (ethanol–ether)	$C_{12}H_{13}ClN_2OS$ (268·8)	53·62 53·73	4·87 4·98	13·19 13·13	10·43 10·67	11 93 11·98
XVIIIa	*B* (88)	93—96[r] (benzene)	$C_{12}H_{12}N_2OS$ (232·3)	62·04 62·18	5·21 5·17	— —	12·06 11·80	13·80 13·45
XVIIIa-HCl	—	149—152 (ethanol–ether)	$C_{12}H_{13}ClN_2OS$ (268·8)	53·62 53·83	4·87 4·86	13 19 13 32	10·43 10·64	11·93 12·12
XIXa-HCl	*B* (70)	148—152 (ethanol–ether)	$C_{12}H_{17}ClN_2OS$ (272·8)	52·83 53·26	6·28 6·40	13·00 12·89	10·27 10·37	11·75 11·85
XXa-HCl	*B* (75)	139—141 (ethanol–ether)	$C_{12}H_{17}ClN_2OS$ (272·8)	52·83 52·58	6·28 6·48	13·00 13·32	10·27 10·25	11 75 12·00

[a] Lit.[23], b.p. 146—147°C/1·87 kPa. [b] Lit.[25], b.p. 91—93°C/133 Pa. [c] Lit.[26], m.p. 88—90°C. [d] Lit.[26], b.p. 163—173°C/0·4 kPa. [e] See Experimental. [f] IR spectrum: 818 (2 adjacent Ar—H), 1481, 1580, 3048 (Ar), 2252 cm^{-1} (R—CN); ^{1}H-NMR spectrum ($CDCl_3$) δ 7·45 (d, J =

= 8·5 Hz, 2 H, 2,6-H_2), 7·18 (d, J = 8·5 Hz, 2 H, 3,5-H_2), 3·45 (s, 2 H, SCH_2CN), 2·44 (s, 3 H, SCH_3). [g] IR spectrum: 769, 810, 820, 864, 880 (2 adjacent and solitary Ar—H), 1021, 1140, 1231, 1258 (ArOR), 1506, 1582, 1590, 3020, 3033, 3080 (Ar), 2255 cm^{-1} (R—CN); ^{1}H-NMR spectrum ($CDCl_3$): δ 7·18 (mcd, 1 H, 6-H), 7·10 (mcs, 1 H, 2-H), 6·82 (d, 1 H, 5-H), 3·86 (s, 6 H, 2 OCH_3), 3·45 (s, 2 H, SCH_2CN). [h] IR spectrum (film): 773, 800 (4 and 3 adjacent Ar—H), 1504, 1564, 1590 (Ar), 2252 cm^{-1} (R—CN). [i] Lit[25], m.p. 83—84°C; IR spectrum: 740, 820, 866 (4 and 2 adjacent and solitary Ar—H), 1506, 1589, 1626, 3048 (Ar), 2250 cm^{-1} (R—CN). [j] IR spectrum: 680, 740 (C_6H_5), 1370 (N—OH), 1482, 1519, 1579, 1588 (Ar), 1680 (C=N), 2620 (NH_3^+), 3185, 3230, 3285, 3353 cm^{-1} (amidoxime); the literature[6] reported the m.p. of 140 to 143°C. [k] IR spectrum: 810 (2 adjacent Ar—H), 1376 (N—OH), 1496, 1570 (Ar), 1663 (C=N), 2770 (OH···N), 3160, 3350, 3390, 3460, 3500 cm^{-1} (amidoxime); ^{1}H-NMR spectrum: δ 9·10 (s, 1 H, NOH), 7·25 (d, J = 8·0 Hz, 2 H, 3,5-H_2), 7·02 (d, J = 8·0 Hz, 2 H, 2,6-H_2), 5·36 (bs, 2 H, NH_2), 3·45 (s, 2 H, SCH_2), 2·18 (s, 3 H, CH_3). [l] IR spectrum: 810 (2 adjacent Ar—H), 1478, 1590 (Ar), 1682 (C=N), 2705, 2770 (NH_3^+), 3132, 3190, 3245, 3345 cm^{-1} (amidoxime); ^{1}H-NMR spectrum: δ 11·20 (bs, 1 H, NOH), 8·80 (bs, NH_3^+), 7·52 (s, 2 H, 3,5-H_2), 7·35 (d, 2 H, 2,6-H_2), 4·00 (s, 2 H, SCH_2). [m] IR spectrum: 761 (4 adjacent Ar—H), 1250 (ArOR), 1480, 1580 (Ar), 1690 (C=N), 3120, 3180, 3230, 3365, 3468 cm^{-1} (amidoxime); ^{1}H-NMR spectrum: δ 9·10 (s, 1 H, NOH), 6·70—7·40 (m, 4 H, Ar—H), 5·48 (bs, 2 H, NH_2), 3·72 (s, 3 H, OCH_3), 3·42 (s, 2 H, SCH_2). [n] IR spectrum: 822 (2 adjacent Ar—H), 1130 (C—O), 1482, 1507, 1572, 1586 (Ar), 1610 (NH_2), 1659 (C=N), 3318, 3450 cm^{-1} (amidoxime). [o] UV spectrum: λ_{max} 273 nm (log ε 4·21); IR spectrum: 810 (2 adjacent Ar—H), 1483, 1580 (Ar), 1673 (C=N), 3220, 3348, 3440, 3460 cm^{-1} (amidoxime); ^{1}H-NMR spectrum: δ 9·18 (bs, 1 H, NOH), 7·40 and 7·20 (ABq, J = 8·5 Hz, 4 H, Ar—H), 5·50 (bs, 2 H, NH_2), 3·55 (s, 2 H, SCH_2), 2·98 (q, J = 7·0 Hz, 2 H, SCH_2 in ethylthio), 1·25 (t, J = 7·0 Hz, 3 H, CH_3). [p] IR spectrum: 806, 846 (2 adjacent and solitary Ar—H), 1062, 1260 (ArOR), 1488, 1576 (Ar, NH_2), 1670 (C=N), 3150, 3400, 3500 cm^{-1} (amidoxime); ^{1}H-NMR spectrum: δ 9·20 (s, 1 H, NOH), 7·35 (d, J = 8·5 Hz, 1 H, 5-H), 7·21 (mcs, J = 2·0 Hz, 1 H, 2-H), 6·98 (mcd, J = 8·5; 2·0 Hz, 1 H, 6-H), 5·55 (bs, 2 H, NH_2), 3·90 (s, 3 H, OCH_3), 3·61 (s, 2 H, SCH_2). [q] IR spectrum: 770, 810, 860 (2 adjacent and solitary Ar—H), 1022, 1228, 1258 (ArOR), 1502, 1599, 3000, 3020, 3053, 3080 (Ar), 1663 (C=N), 3100, 3360, 3480 cm^{-1} (amidoxime); ^{1}H-NMR spectrum: δ 9·06 (s, 1 H, NOH), 6·90 (m, 3 H, Ar—H), 5·40 (bs, 2 H, NH_2), 3·71 and 3·69 (2 s, 6 H, 2 OCH_3), 3·40 (s, 2 H, SCH_2). [r] IR spectrum: 741, 810, 866, 898 (4 and 2 adjacent and solitary Ar—H), 1502, 1569, 3050 (Ar), 1650 (C=N), 3240, 3345, 3468 cm^{-1} (amidoxime); ^{1}H-NMR spectrum: δ 9·19 (s, 1 H, NOH), 7·20—8·00 (m, 7 H, Ar—H), 6·53 (bs, 2 H, NH_2), 3·68 (s, 2 H, SCH_2).

effect (a concentration of 25–50 μg/ml decreases the inotropy of the isolated rabbit atrium by 25%), diuretic effect (an oral dose of 100 mg/kg increases the diuresis in mice by 100% as compared with the control; for hydrochlorothiazide as a standard, ED = 100 mg/kg *p.o.*) and a mild antitussive effect (an oral dose of 125 mg/kg reduces to 52% the coughing activity in rats elicited by the aerosol of an aqueous citric acid solution in comparison with the control).

The compounds were also tested for antimicrobial activity *in vitro* (Dr L. Langšádl and Dr J. Turinová, bacteriological department of this institute). The used microorganisms, numbers of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *XIIIa* 25, *XIVa* 25, *XVa* 25, *XIXa* 50; *Streptococcus faecalis*, *XIIIa* 100, *XVa* 100; *Escherichia coli*, *IVa* 100, *Va* 100, *VIIIa* 100, *Xa* 100; *Proteus vulgaris*, *XIIIa* 100, *XIVa* 50, *XVa* 50; *Mycobacterium tuberculosis* H37Rv, *VIIa* 50, *XIa* 50, *XIIa* 100, *XIIIa* 50, *XIVa* 100, *XVa* 100, *XVIIa* 100, *XVIIIa* 100, *XIXa* 100, *XXa* 100; *Trichophyton mentagrophytes*, *VIIa* 50, *IXa* 50, *XIVa* 50, *XVIIa* 50, *XVIIIa* 50, *XIXa* 50, *XXa* 50. All the compound were inactive towards *Staphylococcus pyogenes aureus*, *Pseudomonas aeruginosa*, *Saccharomyces pasterianus*, *Candida albicans and Aspergillus niger*.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at about 70 Pa at room temperature or at 77°C. UV spectra (in CH_3OH) were registered with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in CD_3SOCD_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectrum was recorded with a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of silica gel. Analyses of compounds *IVab*—*XXab* are summarized in Table I.

5,6,7,8-Tetrahydronaphthalene-2-thiol

5,6,7,8-Tetrahydronaphthalene-2-sulfonyl chloride[22] (44·6 g, m.p. 53—55°C) was dropped over 1 h into a refluxing mixture of 56 ml acetic acid, 15·6 g red phosphorus and 0·68 g iodine and the mixture was refluxed for 3 h. After standing overnight, it was treated with 10 ml water and refluxed for 1 h. After cooling it was poured into 500 ml cold water and extracted with chloroform. The extract was filtered, dried (Na_2SO_4) and evaporated. The residue gave by distillation 18·4 g (58%) product, b.p. 144—148°C/1·6 kPa. The literature[21] reported a b.p. of 146—148°C/1·87 kPa for a product prepared differently.

(4-Ethoxyphenylthio)acetonitrile (*XIb*) (Method *A*)

A solution of 30·9 g 4-ethoxythiophenol[12] in 60 ml methanol was treated with CH_3ONa (4·6 g Na, 115 ml methanol), the solution was stirred for 15 min at room temperature and treated slowly with 15·1 g chloroacetonitrile. The mixture was stirred for 2 h at room temperature and for 5 h at 50°C, filtered while warm and the filtrate was evaporated under reduced pressure. The residue was crystallized from 35 ml ethanol; 31·0 g (80%), m.p. 67—68°C. Analytical sample had the same melting point. IR spectrum: 816, 850 (2 adjacent Ar—H), 1050, 1252 (ArOR),

1480, 1498, 1575, 1600, 3060, 3086, 3172 (Ar), 2252 cm^{-1} (R—CN). ^{1}H-NMR spectrum ($CDCl_3$): δ 7·58 (d, J = 8·5 Hz, 2 H, 2,6-H_2), 6·90 (d, J = 8·5 Hz, 2 H, 3,5-H_2), 4·08 (q, J = = 7·0 Hz, 2 H, SCH_2CN), 3·48 (s, 2 H, CH_2O), 1·46 (t, J = 7·0 Hz, 3 H, CH_3).

(4-Ethoxyphenylthio)acetamidoxime (*XIa*) (Method *B*)

A solution of sodium methoxide (4·4 g Na, 75 ml methanol) was treated with 13·2 g $NH_2OH.HCl$, 140 ml methanol and 31·0 g *XIb* and the mixture was refluxed for 5 h. It was filtered while hot and the filtrate was evaporated under reduced pressure. The residue was crystallized from a mixture of hexane and ether; 29·5 g (65%), m.p. 52—55°C. Further crystallization did not raise this melting point. IR spectrum: 806, 822 (2 adjacent Ar—H), 1059, 1250 (ArOR), 1560, 1581, 1600 (Ar), 1670 (C=N), 3190, 3255, 3340, 3430, 3453 cm^{-1} (amidoxime). ^{1}H-NMR spectrum: δ 9·13 (s, 1 H, NOH), 7·39 (d, J = 8·5 Hz, 2 H, 2,6-H_2), 6·89 (d, J = 8·5 Hz, 2 H, 3,5-H_2), 5·45 (bs, 2 H, NH_2), 4·01 (q, J = 7·0 Hz, 2 H, CH_2O), 3·45 (s, 2 H, SCH_2), 1·35 (t, J = 7·0 Hz, 3 H, CH_3).

A solution of 29·5 g base in 70 ml ethanol was neutralized with a solution of anhydrous HCl in ether and gave 21·5 g hydrochloride, m.p. 125—128°C. Analytical sample, m.p. 127—129°C (ethanol–ether).

S-(4-Chloro-3-fluorophenyl) 4-Chloro-3-fluorophenylthioacetothiohydroxamate (*XXI*)

A solution of 16·2 g 4-chloro-3-fluorothiophenol[27] in 30 ml methanol was treated with sodium methoxide (2·3 g Na, 50 ml methanol), the mixture was stirred for 15 min at room temperature, treated dropwise with 7·55 g chloroacetonitrile, stirred for 30 min at room temperature, for 2 h at 50°C and refluxed for 1 h. It was filtered while hot and the filtrate was evaporated. The residue was fractionally distilled *in vacuo*; 5·94 g product, b.p. 146°C/0·31 kPa. This product (5·82 g) was added to a solution of NH_2OH (2·01 g $NH_2OH.HCl$ and CH_3ONa from 0·67 g Na and 30 ml methanol) and the mixture was refluxed for 4 h. It was filtered while hot and the filtrate was evaporated. The residue was extracted with 20 ml boiling benzene, the insoluble solid (0·6 g) was filtered off and the filtrate treated with 30 ml light petroleum. The separated semi-solid product was crystallized from a mixture of benzene and light petroleum; 2·1 g, m.p. 122—135°C. An attempt to transform the product to a hydrochloride by treatment with HCl in a mixture of ethanol and ether did not lead to a crystalline product. It was therefore evaporated and the residue crystallized from a mixture of ethanol and ether, 0·90 g, m.p. 149—150°C. Mass spectrum, *m/e*: 379 (M^+, corresponds to $C_{14}H_9Cl_2F_2NOS_2$), 218, 201, 190, 173. UV spectrum: λ_{max} 227 nm (log ε 4·26), 263 nm (4·06), infl. 280 nm (3·95). IR spectrum: 811, 860, 900 (2 adjacent and solitary Ar—H), 1486 (SC=N), 1571, 1591, 1614, 3070, 3088 (Ar), 1670 (C=N), 3200, 3300, 3475 cm^{-1} (C=NOH in a H-bond). ^{1}H-NMR spectrum: δ 7·70 (bs, 1 H, NOH), 7·10 to 7·55 (m, 6 H, Ar—H), 5·45 (s, 2 H, SCH_2). For $C_{14}H_9Cl_2F_2NOS_2$ (380·3) calculated: 44·22% C, 2·39% H, 18·65% Cl, 9·99% F, 16·86% S; found: 44·12% C, 2·40% H, 18·75% Cl, 10·23% F, 16·96% S.

Compound VIIa *has been prepared by Mr J. Pomykáček in our laboratory. The authors are indebted to Drs E. Svátek, J. Holubek and M. Ryska (department of physical chemistry of this institute) for recording and interpreting the spectra and to Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech and Mrs J. Kropáčová (analytical department of this institute) for carrying out the analyses.*

REFERENCES

1. Areschka A., Mahaux J.-M., Verbruggen F., Houben Ch., Descamps M., Broll M., Werbenec J.-P., Charlier R., Simiand J., Eymard P.: Eur. J. Med. Chem.-Chim. Therap. *10*, 398 (1975).
2. Areschka A., Mahaux J.-M., Verbruggen F., Houben Ch., Descamps M., Werbenec J.-P., Broll M., Simiand J., Eymard P.: Eur. J. Med. Chem.-Chim. Therap. *10*, 463 (1975).
3. Shimizu M., Yoshida K., Karasawa T., Masuda M., Oka M., Ito T., Kamei C., Hori M., Sohji Y., Furukawa K.: Experientia *30*, 405 (1974).
4. Uno H., Kurokawa M., Natsuka K., Yamato Y., Nishimura H.: Chem. Pharm. Bull. *24*, 632, (1976).
5. Karasawa T., Furukawa K., Yoshida K., Shimizu M.: Chem. Pharm. Bull. *24*, 2673 (1976).
6. Bruderlein F. T. (American Home Products Corp).: U.S. 3 334 137 (Appl. 29. 12. 1965); Chem. Abstr. *68*, 59 328 (1968).
7. Lafon V. (Laboratoire L. Lafon): Belg. 866·314 (Fr. Appl. 29. 04. 1977); Ger. Offen. 2 818 498; Chem. Abstr. *90*, 71 905 (1979).
8. Pelz K., Protiva M.: This Journal *32*, 2161 (1967).
9. Mauthner F.: Ber. Deut. Chem. Ges. *39*, 1348 (1906).
10. Mauthner F.: Ber. Deut. Chem. Ges. *39*, 3596 (1906).
11. Suter C. M., Hansen H. L.: J. Amer. Chem. Soc. *54*, 4100 (1932).
12. Protiva M., Rajšner M., Adlerová E., Seidlová V., Vejdělek Z. J.: This Journal *29*, 2161 (1964).
13. Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *39*, 3338 (1974).
14. Jlek J. O., Pomykáček J., Metyšová J., Bartošová M., Protiva M.: This Journal *43*, 1747 (1978).
15. Červená I., Šindelář K., Metyšová J., Svátek E., Ryska M., Hrubantová M., Protiva M.: This Journal *42*, 1705 (1977).
16. Fries K., Koch H., Stuckenbrock H.: Justus Liebigs Ann. Chem. *468*, 172 (1929).
17. Taboury F.: Bull. Soc. Chim. Fr. [3] *29*, 761 (1903); Chem. Zentralbl. *1903*, II, 620; C. R. Acad. Sci. *138*, 982 (1904); Ann. Chim. Phys. [8] *15*, 5 (1908).
18. Dann O., Kokorudz M.: Chem. Ber. *91*, 172 (1958).
19. Braun J. v.: Ber. Deut. Chem. Ges. *56*, 2332 (1923).
20. Krollpfeifer F., Schultze H., Schlumbohm E., Sommermeyer E.: Ber. Deut. Chem. Ges. *58*, 1654 (1925).
21. Schroeter G., Svanoe, Einbeck H., Geller H., Riebensahm E.: Justus Liebigs Ann. Chem. *426*, 83 (1922).
22. Davies W., Porter Q. N.: J. Chem. Soc. *1956*, 2609.
23. Dijkstra R., Backer H. J.: Rec. Trav. Chim. Pays-Bas *73*, 569 (1954).
24. Schonberger C., Voinescu V., Balogh A.: Rev. Chim. (Bucharest) *14*, 688 (1963); Chem. Abstr. *60*, 15 772 (1964).
25. Santilli A. A., Osdene T. S., Childress S. J. (American Home Products Corp.): U.S. 3 553 198 (Appl. 07. 01. 1966); Chem. Abstr. *75*, 5935 (1971).
26. Falco E. A., Roth B., Hitchings G. H.: J. Org. Chem. *26*, 1143 (1961).
27. Červená I., Metyšová J., Svátek E., Kakáč B., Holubek J., Hrubantová M., Protiva M.: This Journal *41*, 881 (1976).
28. Houben J., Zivadinovitsch R.: Ber. Deut. Chem. Ges. *69*, 2352 (1936).

Translated by the author (M. P.).