

SYNTHESIS OF ARYLTHIOACETAMIDOXIMES AS POTENTIAL ANTIDEPRESSANTS*

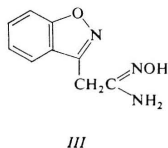
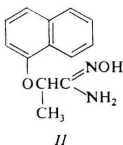
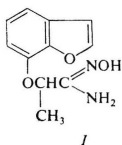
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Reactions of thiophenol and 16 of its derivatives with chloroacetonitrile afforded arylthioacetamidoximes *IVb–XXb* which were treated with hydroxylamine and gave arylthioacetamidoximes *IVa–XXa*. Compounds *VIIa–IXa*, *XIIa*, *XVIa* and *XVIIIa* exhibited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

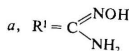
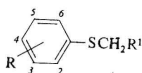
The literature reported for several relatively simple amidoximes interesting psychotropic effects. The benzofuran derivative L-7526 (*I*) was described as a potential antidepressant with significant antireserpine and antiaggressive effects¹. Its naphthalene analogue L-7660 (*II*) revealed antireserpine activity only in the test of reserpine hypothermia and showed also antiaggressive activity². The benzisoxazole derivative PF-257 (*III*) was characterized as a potential antidepressant with a unique spectrum of activity^{3–5}.



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 connection⁶ and only after the termination of our experiments a patent⁷ disclosed the analogous 3,4-dichlorophenyl derivative for which the psychotropic and antiaggressive activity was claimed. In the syntheses of the title compounds

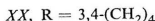
* Part CXLIX in the series Neurotropic and Psychotropic Agents; Part CXLVIII: This Journal 46, 781 (1981).

we used as starting materials thiophenol, 4-methylthiophenol, 4-ethylthiophenol⁸, 4-chlorothiophenol, 2-methoxythiophenol⁹, 3-methoxythiophenol¹⁰, 4-methoxythiophenol¹¹, 4-ethoxythiophenol¹², 4-(methylthio)thiophenol¹³, 4-(ethylthio)thiophenol¹³, 4-chloro-2-methoxythiophenol¹⁴, 4-chloro-3-methoxythiophenol¹⁵, 3,4-dimethoxythiophenol¹⁶, 1-thionaphthol¹⁷, 2-thionaphthol¹⁸, 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 chloride²² 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 arylthioacetoneitriles *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 described⁶ 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.



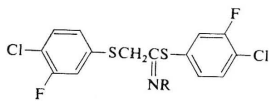
- IV*, R = H
V, R = 4-CH₃
VI, R = 4-C₂H₅
VII, R = 4-Cl
VIII, R = 2-OCH₃
IX, R = 3-OCH₃
X, R = 4-OCH₃
XI, R = 4-OC₂H₅

- XII*, R = 4-SCH₃
XIII, R = 4-SC₂H₅
XIV, R = 2-OCH₃-4-Cl
XV, R = 3-OCH₃-4-Cl
XVI, R = 3,4-(OCH₃)₂
XVII, R = 2,3-benzo
XVIII, R = 3,4-benzo
XIX, R = 2,3-(CH₂)₄



A reaction of 4-chloro-3-fluorothiophenol²⁷ 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 C₁₄H₉Cl₂F₂NOS₂ (analyses and mass spectrum) was obtained in a low yield which was identified by means of the ¹H-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 mercaptan²⁸,

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 LD₅₀ 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 negatively inotropic

TABLE I
Arylthioacetoneitriles 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 (88)	154—157/2.4 ^a	—	—	—	—	—	—
Vb	A (91)	168—170/4.27 ^b	—	—	—	—	—	—
VIb	A (56)	138/0.13	C ₁₀ H ₁₁ NS (177.3)	67.75 68.03	6.26 6.46	—	7.90 7.74	18.09 18.28
VIIb	A (63)	88—89 ^c	—	—	—	—	—	—
VIIIb	A (75)	132—134/0.07	C ₉ H ₉ NOS F(179.2)	60.30 60.14	5.06 5.30	—	7.82 8.08	17.89 17.25
IXb	A (48)	164—168/0.31	C ₉ H ₉ NOS (179.2)	60.30 60.99	5.06 5.16	—	7.82 7.13	17.89 18.04
Xb	A (79)	164/0.27 ^d	C ₉ H ₉ NOS (179.2)	60.30 60.92	5.06 5.38	—	7.82 7.73	17.89 17.46
XIb	A ^e (80)	67—68 (ethanol)	C ₁₀ H ₁₁ NOS (193.3)	62.14 62.30	5.74 5.70	—	7.25 7.19	16.59 16.33
XIIb	A (69)	62—64 ^f (ethanol)	C ₉ H ₉ NS ₂ (195.3)	55.34 55.31	4.64 4.71	—	7.17 7.19	32.84 33.09
XIIIb	A (66)	168—170/0.11	C ₁₀ H ₁₁ NS ₂ (209.3)	57.37 57.76	5.30 5.42	—	6.69 6.27	30.64 30.74
XIVb	A (38)	176/0.33	C ₉ H ₈ ClNOS (213.7)	50.58 51.45	3.77 4.09	16.59 16.38	6.56 6.13	15.00 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 ₉ H ₈ ClNOS (213·7)	50·58 51·39	3·77 3·96	16·59 16·38	6·56 6·57	15·00 14·30
XVlb	A (74)	101—103 ^g (ethanol)	C ₁₀ H ₁₁ NO ₂ S (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 ₉ NS (199·2)	—	—	—	—	16·08 16·36
XVIIIb	A (54)	81—84 ⁱ (ethanol)	C ₁₂ H ₉ NS (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 ₈ H ₁₁ ClN ₂ OS (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 ₉ H ₁₂ N ₂ OS (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 ₉ H ₁₃ ClN ₂ OS (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 ₂ OS (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 ₈ H ₁₀ Cl ₂ N ₂ OS (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 ₉ H ₁₂ N ₂ O ₂ S (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 ₉ H ₁₃ ClN ₂ O ₂ S (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 ₉ H ₁₃ ClN ₂ O ₂ S (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 ₉ H ₁₃ ClN ₂ O ₂ S (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 ₂ O ₂ S (226.3)	53.07 53.3	6.24 6.33	—	12.38 12.34	14.17 14.45
XIa-HCl	—	127—129 (ethanol-ether)	C ₁₀ H ₁₅ ClN ₂ O ₂ S (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 ₉ H ₁₂ N ₂ OS 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 ₉ H ₁₃ ClN ₂ OS 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 ₂ OS 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 ₂ OS 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 11.58
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.^{2,3}, b.p. 146—147°C/1.87 kPa. ^b Lit.^{2,5}, b.p. 91—93°C/133 Pa. ^c Lit.^{2,6}, m.p. 88—90°C. ^d Lit.^{2,6}, 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); ¹H-NMR spectrum (CDCl₃) δ 7.45 (d, J =

= 8.5 Hz, 2 H, 2,6-H₂), 7.18 (d, *J* = 8.5 Hz, 2 H, SCH₂CN), 2.44 (s, 3 H, SCH₃). ^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); ¹H-NMR spectrum (CDCl₃): 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 OCH₃), 3.45 (s, 2 H, SCH₂CN). ^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 (C₆H₅), 1370 (N—OH), 1482, 1519, 1579, 1588 (Ar), 1680 (C≡N), 2620 (NH₃⁺), 3185, 3230, 3285, 3353 cm⁻¹ (amidoxime); the literature⁶ 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); ¹H-NMR spectrum: δ 9.10 (s, 1 H, NOH), 7.25 (d, *J* = 8.0 Hz, 2 H, 3,5-H₂), 7.02 (d, *J* = 8.0 Hz, 2 H, 2,6-H₂), 5.36 (bs, 2 H, NH₂), 3.45 (s, 2 H, SCH₂), 2.18 (s, 3 H, CH₃). ^l IR spectrum: 810 (2 adjacent Ar—H), 1478, 1590 (Ar), 1682 (C≡N), 2705, 2770 (NH₃⁺), 3132, 3190, 3245, 3345 cm⁻¹ (amidoxime); ¹H-NMR spectrum: δ 11.20 (bs, 1 H, NOH), 8.80 (bs, NH₃⁺), 7.52 (s, 2 H, 3,5-H₂), 7.35 (d, 2 H, 2,6-H₂), 4.00 (s, 2 H, SCH₂). ^m IR spectrum: 761 (4 adjacent Ar—H), 1250 (ArOR), 1480, 1580 (Ar), 1690 (C≡N), 3120, 3180, 3230, 3365, 3468 cm⁻¹ (amidoxime); ¹H-NMR spectrum: δ 9.10 (s, 1 H, NOH), 6.70–7.40 (m, 4 H, Ar—H), 5.48 (bs, 2 H, NH₂), 3.72 (s, 3 H, OCH₃), 3.42 (s, 2 H, SCH₂). ⁿ IR spectrum: 822 (2 adjacent Ar—H), 1130 (C—O), 1482, 1507, 1572, 1586 (Ar), 1610 (NH₂), 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); ¹H-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, NH₂), 3.55 (s, 2 H, SCH₂), 2.98 (q, *J* = 7.0 Hz, 2 H, SCH₂ in ethylthio), 1.25 (t, *J* = 7.0 Hz, 3 H, CH₃). ^p IR spectrum: 806, 846 (2 adjacent and solitary Ar—H), 1062, 1260 (ArOR), 1488, 1576 (Ar, NH₂), 1670 (C≡N), 3150, 3400, 3500 cm⁻¹ (amidoxime); ¹H-NMR spectrum: δ 9.20 (s, 1 H, NOH), 7.35 (d, *J* = 8.5 Hz, 1 H, 5-H), 7.21 (mes, *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, NH₂), 3.90 (s, 3 H, OCH₃), 3.61 (s, 2 H, SCH₂). ^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); ¹H-NMR spectrum: δ 9.06 (s, 1 H, NOH), 6.90 (m, 3 H, Ar—H), 5.40 (bs, 2 H, NH₂), 3.71 and 3.69 (2 s, 6 H, 2 OCH₃), 3.40 (s, 2 H, SCH₂). ^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); ¹H-NMR spectrum: δ 9.19 (s, 1 H, NOH), 7.20–8.00 (m, 7 H, Ar—H), 6.53 (bs, 2 H, NH₂), 3.68 (s, 2 H, SCH₂).

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 CH₃OH) were registered with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ¹H-NMR spectra (in CD₃SOCN₃ 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 chloride²² (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 (Na₂SO₄) and evaporated. The residue gave by distillation 18.4 g (58%) product, b.p. 144–148°C/1.6 kPa. The literature²¹ 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-ethoxythiophenol¹² in 60 ml methanol was treated with CH₃ONa (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). $^1\text{H-NMR}$ 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 $\text{NH}_2\text{OH}\cdot\text{HCl}$, 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 ($\text{C}=\text{N}$), 3190, 3255, 3340, 3430, 3453 cm^{-1} (amidoxime). $^1\text{H-NMR}$ 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-fluorothiophenol²⁷ 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 $\text{NH}_2\text{OH}\cdot\text{HCl}$ 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 $\text{C}_{14}\text{H}_9\text{Cl}_2\text{F}_2\text{NOS}_2$), 218, 201, 190, 173. UV spectrum: λ_{max} 227 nm ($\log \epsilon$ 4.26), 263 nm (4.06), infl. 280 nm (3.95). IR spectrum: 811, 860, 900 (2 adjacent and solitary Ar—H), 1486 ($\text{SC}=\text{N}$), 1571, 1591, 1614, 3070, 3088 (Ar), 1670 ($\text{C}=\text{N}$), 3200, 3300, 3475 cm^{-1} ($\text{C}=\text{NOH}$ in a H-bond). $^1\text{H-NMR}$ 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 $\text{C}_{14}\text{H}_9\text{Cl}_2\text{F}_2\text{NOS}_2$ (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.

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