SYNTHESIS OF POTENTIAL NEUROLEPTICS AND TRANQUILLIZERS: 2-(TERT.AMINO)-9-(3-DIMETHYLAMINOPROPYLIDENE)-THIOXANTHENES

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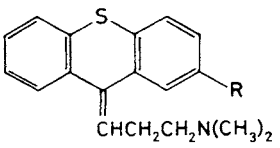
4-Dimethylamino-, 4-pyrrolidino-, 4-piperidino-, 4-morpholino- and 4-(4-methylpiperazino)-thiophenol (*IIIa*—*IIIe*), which were prepared by two methods and characterized as the 2,4-dinitrodiphenyl sulfides *IVb*—*IVe*, were transformed by treatment with 2-iodobenzoic acid and copper in aqueous potassium hydroxide to 2-(4-tert.aminophenylthio)benzoic acids (*Va*—*Ve*). Cyclization with polyphosphoric acid gave thioxanthones *VIa*—*VIe* which were treated with 3-dimethylaminopropylmagnesium chloride to give the diamino alcohols *VIIa*—*VIId*. *VIIa*, *VIIc* and *VIId* were dehydrated by heating with dilute sulfuric acid which resulted in mixtures of geometrical isomers of the olefinic bases *Ia*, *Ic* and *Id*. Crystallization of bases or salts led to homogeneous or almost homogeneous (*Z*)-isomers belonging to the "active chlorprothixene series". The products are devoid of cataleptic and antiapomorphine activities and show only some properties of mild tranquillizers.

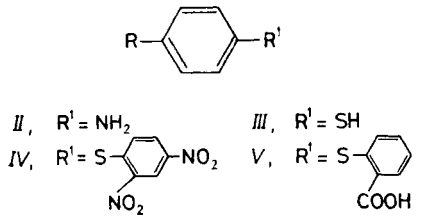
In two recent communications[1,2] we have surveyed the psychotropic thioxanthene derivatives substituted in position 2 of the skeleton and carrying in position 9 the typical 3-dimethylaminopropylidene side chain. Until now, the influence of tertiary amino group as substituent in position 2 on the psychotropic activity has been unknown. The present communication represents an attempt to fill up this gap and outlines the synthesis of three title compounds in which dimethylamino (*Ia*), piperidino (*Ic*) and morpholino (*Id*) were the tertiary amino groups. The set of intermediates included also the pyrrolidino (series *b*) and 4-methylpiperazino derivatives (series *e*).



I

In formulae *I*–*VII*: *a*, R = $N(CH_3)_2$; *b*, R =  ; *c*, R =  ; *d*, R =  ; *e*, R =  .

The syntheses started from the thiophenols *IIIa–IIIe*, out of which only 4-(dimethylamino)thiophenol (*IIIa*) was described in the literature[3]; 4-piperidinothiophenol (*IIIc*) was mentioned in a patent[4] without specification of the synthetic method and properties of the compound. 4-(Dimethylamino)thiophenol (*IIIa*) was prepared according to the cited paper[3] by reaction of 4-thiocyanodimethylaniline[5] with sodium sulfide and sodium hydroxide in boiling ethanol. 4-Pyrrolidinothiophenol (*IIIb*) was obtained similarly; the starting 1-(4-thiocyanophenyl)pyrrolidine has been synthesized by treatment of 1-phenylpyrrolidine[6] with potassium thiocyanate and bromine in acetic acid. Thiophenol *IIIb* was obtained also from 1-(4-aminophenyl)-pyrrolidine (*IIb*) (refs[7,8]) by the xanthate method[9,10]. This method (method A) was then used for the preparation of the remaining 4-(tert.amino)thiophenols, *i.e.* compounds *IIIc–IIIe*. The starting 1-(4-aminophenyl)piperidine (*IIc*) (ref.[8]) was obtained by the described catalytic hydrogenation of 1-(4-nitrophenyl)piperidine[8] on Raney nickel, 4-(4-aminophenyl)morpholine (*IId*) (ref.[8]) by reduction of 4-(4-nitrophenyl)-morpholine[8] with iron and hydrochloric acid, undescribed for this case until now, and finally 1-(4-aminophenyl)-4-methylpiperazine (*IIe*) (ref.[7]) by hydrogenation of 1-methyl-4-(4-nitrophenyl)piperazine[7] on Raney nickel. Thiophenols *IIIa–IIIe* distill *in vacuo* with partial decomposition. For this reason they were used for further work in crude state and for characterization they were transformed by reactions with 2,4-dinitrofluorobenzene in acetone in the presence of triethylamine (method B) to corresponding crystalline S-(2,4-dinitrophenyl) derivatives *IVb–IVe*.



The syntheses were continued like in our previous and mentioned investigations[1,2]. Thiols *IIIa–IIIe* were subjected to reactions with 2-iodobenzoic acid in boiling aqueous solutions of excessive potassium hydroxide in the presence of copper (method C); 2-(4-tert.aminophenylthio)benzoic acids *Va–Ve* were obtained. Their cyclization to thioxanthones *VIa–VIe* was carried out by heating with polyphosphoric acid to 130–140°C (method D). The following step was the reaction of the ketones obtained with 3-dimethylaminopropylmagnesium chloride, carried out in mixtures of tetrahydrofuran and benzene (method E); products were the 2-(tert.amino)-9-(3-dimethylaminopropyl)thioxanthen-9-ols (*VIIa–VIId*). The intermediates *III* to *VII* are assembled in Table I with the usual experimental data; the Experimental discloses only examples of proceeding in the individual steps.

TABLE I

Thiophenols *III*, diaryl sulfides *IV*, *V*, and thioxanthenes *VI* and *VII*

Compound[a]	Method (yield, %)	M.p., °C (solvent) or b.p., °C/kPa	Formula (mol.wt.)	Calculated/found			
				% C	% H	% N	% S
IIIb	A (26)	172–175/4[b]	—	—	—	—	—
IIIc[c]	A (66)	172–175/2·3	$C_{11}H_{15}NS$ (193·3)	68·34 68·24	7·82 7·87	7·25 7·37	16·59 16·45
IIId	A (80)	[d]	—	—	—	—	—
IIIe	A (30)	185–188/1·87[b]	—	—	—	—	—
IVb	B (60)	213–215[e] (pyridine)	$C_{16}H_{15}N_3O_4S$ (345·4)	55·64 56·06	4·38 4·34	12·17 12·39	9·28 9·03
IVc	B (55)	190–191[f] (pyridine)	$C_{17}H_{17}N_3O_4S$ (359·4)	56·81 56·42	4·77 4·75	11·69 11·54	8·92 8·91
IVd	B (60)	283–285[g] (pyridine)	$C_{16}H_{15}N_3O_5S$ (361·4)	53·18 53·46	4·18 4·20	11·64 11·55	8·87 9·00
IVe[c]	B (31)	211–213 (pyridine)	$C_{17}H_{18}N_4O_4S$ (374·4)	54·53 54·52	4·89 5·01	14·96 15·10	8·56 8·51
IVe-M[h]	—	174–176 (ethanol–ether)	$C_{21}H_{22}N_4O_8S$ + 0·5 H_2O (499·5)	50·49 50·88	4·64 4·66	11·22 11·03	6·42 6·57
Va	C (80)	261–263[i] (aqueous dimethylformamide)	$C_{15}H_{15}NO_2S$ (273·3)	65·92 65·70	5·53 5·55	5·13 5·01	11·72 11·63
Vb	C (84)	275–276[j] (dimethylformamide)	$C_{17}H_{17}NO_2S$ (299·4)	68·20 67·87	5·72 5·94	4·68 4·79	10·71 10·90
Vc[c]	C (72)	236–238 (ethanol)	$C_{18}H_{19}NO_2S$ (313·4)	68·98 68·81	6·11 5·95	4·47 4·38	10·23 10·05
Vd	C (40)	244–246[k] (aqueous ethanol)	$C_{17}H_{17}NO_3S$ (315·4)	64·74 64·44	5·43 5·48	4·44 4·08	10·17 10·01
Ve	C (61)	293–295[l] (dimethylformamide)	$C_{18}H_{20}N_2O_2S$ (328·4)	65·82 65·25	6·14 6·29	8·53 8·95	9·76 9·46
VIa[c]	D (90)	122–124 (ethanol)	$C_{15}H_{13}NOS$ (255·3)	70·56 70·08	5·13 5·16	5·49 5·26	12·56 12·52
VIb	D (81)	153–155[m] (aqueous ethanol)	$C_{17}H_{15}NOS$ (281·4)	72·56 72·39	5·37 5·45	4·98 4·80	11·40 11·68
VIc	D (88)	108–110[n] (aqueous ethanol)	$C_{18}H_{17}NOS$ (295·4)	73·18 73·09	5·80 5·74	4·74 4·58	10·86 10·57
VId	D (89)	177·5–178·5[o] (aqueous ethanol)	$C_{17}H_{15}NO_2S$ (297·4)	68·66 67·96	5·08 4·91	4·71 4·51	10·78 10·57

TABLE I
(*Continued*)

Compound[a]	Method (yield, %)	M.p., °C (solvent) or b.p., °C/kPa	Formula (mol.wt.)	Calculated/found			
				%C	%H	%N	%S
VIe	D (70)	97–99[p] (benzene–light petroleum)	$C_{18}H_{18}N_2OS$ (310·4)	69·64 69·90	5·85 6·06	9·03 8·81	10·33 10·46
VIe-M		177–179 (ethanol–ether)	$C_{22}H_{22}N_2O_5S$ (426·6)	61·97 61·50	5·20 5·34	6·57 6·63	7·52 7·75
VIIa	E (79)	147–149[q] (ethanol)	$C_{20}H_{20}N_2OS$ (342·5)	70·13 70·26	7·65 7·84	8·18 8·04	9·36 9·43
VIIb[c]	E (90)	168–170 (toluene)	$C_{22}H_{28}N_2OS$ (368·5)	71·70 72·32	7·66 7·78	7·60 7·52	8·70 8·81
VIIc	E (76)	138–140[r] (toluene)	$C_{23}H_{30}N_2OS$ (382·6)	72·21 72·11	7·90 7·94	7·32 7·31	8·38 8·41
VIId	E (86)	139–141[s] (aqueous ethanol)	$C_{22}H_{28}N_2O_2S$ (384·5)	68·71 69·39	7·34 7·23	7·29 7·23	8·34 8·20

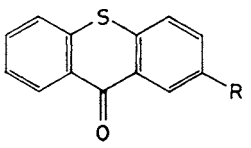
[a] M maleate. [b] Distillation under partial decomposition. [c] See Experimental. [d] The crude undistilled product was used for further work; it was characterized as the S-(2,4-dinitrophenyl) derivative. [e] UV spectrum: λ_{max} 280 nm (log ε 4·45), inflexes at 317 nm (4·05) and 342 nm (4·06); IR spectrum: 815, 830, 860 (2 adjacent and solitary Ar—H), 1 337, 1 509 ($ArNO_2$), 1 592, 3 095 cm^{-1} (Ar). [f] UV spectrum: λ_{max} 274 nm (log ε 4·40), infl. 324 nm (4·15); IR spectrum: 818, 831, 859 (2 adjacent and solitary Ar—H), 1 335, 1 501 ($ArNO_2$), 3 075, 3 108 cm^{-1} (Ar); ^{1}H NMR spectrum: δ 9·01 (d, J = 3·0 Hz, 1 H, 3-H), 8·05 (dd, J = 9·0; 3·0 Hz, 1 H, 5-H), 7·34 (d, J = 9·0 Hz, 2 H, 2′,6′-H_2), 7·03 (d, J = 9·0 Hz, 1 H, 6-H), 6·96 (d, J = 9·0 Hz, 2 H, 3′,5′-H_2), 3·30 (bm, 4 H, CH_2NCH_2), 1·70 (bs, 6 H, remaining 3 CH_2 of piperidine). [g] UV spectrum (saturated solution in methanol): λ_{max} 277 nm, infl. 325 nm; IR spectrum: 820, 831, 863 (2 adjacent and solitary Ar—H), 1 336, 1 501 ($ArNO_2$), 1 590, 3 100 cm^{-1} (Ar). [h] Hemihydrate. [i] UV spectrum: λ_{max} 278 nm (log ε 4·39), infl. 310 nm (3·93); IR spectrum: 745, 810 (4 and 2 adjacent Ar—H), 929, 1 252, **1 670**, 2 555, 2 640, 2 720, infl. 3 100 (ArCOOH), 1 510, 1 555, 1 595 cm^{-1} (Ar); ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·92 (q, J = 8·5; 2·5 Hz, 1 H, 6-H), 7·38 (d, J = 8·5 Hz, 2 H, 2′,6′-H_2), c. 7·20 (m, 2 H, 4,5-H_2), 6·82 (d, J = 8·5 Hz, 2 H, 3′,5′-H_2), c. 6·80 (m, 1 H, 3-H), 3·02 (s, 6 H, CH_3NCH_3). [j] UV spectrum (saturated solution in methanol): λ_{max} 279 nm, infl. 315 nm; IR spectrum: 750, 810 (4 and 2 adjacent Ar—H), 931, 1 256, **1 667**, 2 555, 2 665, 2 720, infl. 3 120 (ArCOOH), 1 504, 1 556, 1 595 cm^{-1} (Ar). [k] UV spectrum: λ_{max} 273 nm (log ε 4·29), infl. 320 nm (3·78); IR spectrum (KBr): 750, 810 (4 and 2 adjacent Ar—H), 925, 1 230, 1 249, 1 263, **1 662**, 2 550, 2 635, infl. 3 100 (ArCOOH), 1 130, 1 151 (R—O—R), 1 500, 1 550 ,1 590 (Ar), 2 810 cm^{-1} (CH_2—N). [l] UV spectrum: λ_{max} 270 nm (log ε 3·89); IR spectrum: 752, 819 (4 and 2 adjacent Ar—H), 1 250 (COOH), 1 340, 1 589 (COO^-), 1 492, 3 050 cm^{-1} (Ar). [m] UV spectrum: λ_{max} 269 nm (log ε 4·59), 300 nm (4·37), infl. 335 nm (3·63); IR spectrum: 740, 814, 855, 869 (4 and 2 adjacent and solitary Ar—H), 1 481, 1 490, 1 590,

TABLE I
(*Continued*)

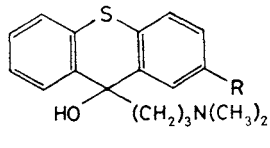
1 600, 3 048 (Ar), 1 630 cm^{-1} (ArCOAr'); ^1H NMR spectrum: δ 7·64 (d, J = 2·0 Hz, 1 H, 2-H), 7·20—7·60 (m, 5 H, 4,5,6,7,8-H_5), 6·88 (dd, J = 8·5; 2·0 Hz, 1 H, 3-H), 3·30 (bm, 4 H, CH_2. .NCH_2), 2·00 (bm, 4 H, remaining 2 CH_2 of pyrrolidine). [n] UV spectrum: λ_{max} 266 nm (log ε 4·56), 292 nm (4·39), 421 nm (3·58); IR spectrum: 742, 812, 873 (4 and 2 adjacent and solitary Ar—H), 1 480, 1 590 (Ar), 1 630 (ArCOAr'), 2 790 cm^{-1} (CH_2—N); ^1H NMR spectrum: δ 8·60 (m, 1 H, 8-H), 8·01 (d, J = 3·0 Hz, 1 H, 1-H), 7·10—7·60 (m, 5 H, remaining ArH), 3·20 (bm, 4 H, CH_2NCH_2), 1·60 (bs, 6 H, remaining 3 CH_2 of piperidine). [o] UV spectrum: λ_{max} 263 nm (log ε 4·57), 416 nm (3·63), infl. 288 nm (4·40); IR spectrum: 749, 811, 869, 879 (4 and 2 adjacent and solitary Ar—H), 1 119 (R—O—R), 1 479, 1 589, 1 598 (Ar), 1 630 cm^{-1} (ArCOAr'); ^1H NMR spectrum: δ 8·59 (m, 1 H, 8-H), 8·01 (d, J = 3·0 Hz, 1 H, 1-H), 7·10—7·60 (m, 5 H, remaining Ar—H), 3·85 (m, 4 H, CH_2OCH_2), 3·20 (m, 4 H, CH_2NCH_2). [p] UV spectrum: λ_{max} 263 nm (log ε 4·57), 416 nm (3·56), infl. 282 nm (4·41); IR spectrum: 740, 821, 828, 868 (4 and 2 adjacent and solitary Ar—H), 1 478, 1 582, 1 590 (Ar), 1 621 cm^{-1} (ArCOAr'); ^1H NMR spectrum: δ 8·58 (m, 1 H, 8-H), 8·00 (d, J = 2·5 Hz, 1 H, 1-H), c. 7·40 (m, 4 H, 4,5,6,7-H_4), 7·20 (dd, J = 8·5; 2·0 Hz, 1 H, 3-H), 3·40 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·60 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·30 (s, 3 H, CH_3N). [q] IR spectrum: 750, 765, 805, 848 (4 and 2 adjacent and solitary Ar—H), 1 100 (R_3C—OH), 1 485, 1 550, 1 595 (Ar), 2 620, infl. 3 050 cm^{-1} (O—H···N); ^1H NMR spectrum: δ 7·89 (dd, J = 8·0; 3·0 Hz, 1 H, 8-H), 7·00—7·40 (m, 5 H, 3,4,5,6,7-H_5), 6·54 (dd, J = 8·0; 3·0 Hz, 1 H, 1-H), 2·89 [s, 6 H, $ArN(CH_3)_2$], 2·30 (s, 6 H, CH_3NCH_3 in the aliphatic chain), c. 2·10 (m, 5 H, 2 external CH_2 in propyl and OH), 1·20 (bm, 2 H, CH_2 in the middle of propyl). [r] IR spectrum: 750, 764, 805, 811, 846, 857, 899 (4 and 2 adjacent and solitary Ar—H), 1 126 (R_3C—OH), 1 550, 1 568, 1 591, 3 045 (Ar), 2 630 (O—H···N), 3 380 cm^{-1} (OH). [s] IR spectrum: 757, 769, 815, 845, 855, 876 (4 and 2 adjacent and solitary Ar—H), 1 130 (R_3C—OH), 1 135, 1 260 (Ar—NR_2), 1 475, 1 551, 1 568, 1 595, 3 052 (Ar), 2 630, 2 700, 3 100 cm^{-1} (O—H···N); ^1H NMR spectrum: δ 7·89 (bd, 1 H, 8-H), 7·55 (d, J = 3·0 Hz, 1 H, 1-H), 7·20 (m, 4 H, 4,5,6,7-H_4), 6·72 (dd, J = 8·5; 3·0 Hz, 1 H, 3-H), 3·82 (m, 4 H, CH_2OCH_2), 3·15 (m, 4 H, CH_2NCH_2), 2·31 (s, 6 H, CH_3NCH_3), 1·90—2·30 (m, 4 H, 2 external CH_2 in propyl), 1·20 (m, 2 H, CH_2 in the middle of propyl).

The acid catalyzed dehydration of amino alcohols *VII* by heating with 1·25M- or 2·5M-H_2SO_4 was carried out successfully (*i.e.* afforded characterized products) only in series *a*, *c* and *d*. In series *a* a crystalline dihydrochloride (solvate with water) was obtained whose mass spectrum confirmed the presence of the base *Ia* (*m/z* 324, $C_{20}H_{24}N_2S$). The base, which was released from the salt, was oily; according to the ^1H NMR spectrum we are dealing here with a mixture of (*Z*)- and (*E*)-isomer (signal of the single olefinic proton is splitted); the IR spectrum (in carbon disulfide) with the inflex at 862 cm^{-1} (appears as a weak band in the spectrum of (*Z*)-chlorprothixene[11]) and lacking the band at 877 cm^{-1} (typical for (*E*)-chlorprothixene[11]) indicates that (*Z*)-form predominates in the substance *Ia*. In series *c* the crystalline base could be prepared and was recrystallized to the constant melting point. The signal of the olefinic proton in the ^1H NMR spectrum is not splitted which indicates the homogeneity of the compound. IR spectrum (in carbon disulfide) has a strong band at

901 cm^{-1}, belonging to the Ar—H bond in the solitary C—H group, which corresponds to a similar band in the spectrum of (*Z*)-chlorprothixene at 894 cm^{-1} (ref.[11]); (*Z*)-configuration was thus assigned to the compound *Ic*. It afforded crystalline salts (succinate and maleate). In series *d*, likewise, a crystalline base *Id* was prepared. In spite of the fact that crystallization did not increase its melting point, the ^1H NMR spectrum identified it to be a mixture of (*Z*)- and (*E*)-isomer. The IR spectrum with an intensive band at 909 cm^{-1} indicated again the (*Z*)-isomer as the prevailing one. Crystalline salts (maleate and succinate) were also obtained from this base.



VI



VII

Compounds *Ia*, *Ic* and *VIe* were pharmacologically evaluated in basic tests with regard to the expected psychotropic and neurotropic activity; compounds *Id* and *IVe* were subjected to a general pharmacological screening. All compounds were administered orally and tested in the form of salts described in the Experimental or in Table I; in the case of the first three compounds the doses were calculated per bases. All doses given are in mg/kg. Acute toxicity in mice, LD_{50}: *Ia*, 190; *Id*, 750–1 000; *IVe*, 2 500; *VIe*, 418. Incoordinating activity in the rotarod test in mice, ED_{50}: *Ia*, 11·4; *Ic*, 12·3; *Id*, >150; *IVe*, >100. The compounds were noncataleptic in rats in the following doses: *Ia*, 50; *Ic*, 50 (catalepsy with 10% of animals); *Id*, 150. The compounds did not affect apomorphine-induced stereotypies in rats in the following high doses: *Ia*, 80; *Ic*, 40; *Id*, 150. Compound *Id* potentiated thiopental effect in mice (doses of 10–25 mg/kg prolonged the thiopental sleeping time to 200% of the control), had hypothermic effect in rats (the dose of 150 mg/kg decreased the body temperature by 1°C) and exhibited antihistamine effect in guinea-pigs (doses of 10 to 25 mg/kg protected 50% of the animals from the lethal effect of the dose of 5 mg/kg histamine, administered intrajugularly). Compound *IVe* did not show any interesting activity in the dose of 100 mg/kg. Compound *VIe* was considered a potential antidepressant but proved inactive: in the dose of 25 mg/kg it did not affect the reserpine ptosis in mice. In receptor-binding assays its IC_{50} for inhibition of (^3H)-imipramine binding in rat hypothalamus was >100 nmol l^{-1}, for inhibition of (^3H)-desipramine binding in rat hypothalamus >100 nmol l^{-1}, and for inhibition of (^3H)-spiperone binding in rat striatum >200 nmol l^{-1}. On the basis of data available, compounds *Ia*, *Ic* and *Id* may be characterized as mild tranquillizers but not as neuroleptics. Tertiary amino groups, located in position 2 of the skeleton, did not prove the character of "neuroleptic substituents".

The compounds prepared were also tested for antimicrobial activity *in vitro* (microorganisms and the minimum inhibitory concentrations in μg/ml are given unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus, Ia* 100, *Ic* 25, *VIe* 100; *Streptococcus faecalis, Ia* 100, *Ic* 25, *VIe* 100; *Staphylococcus pyogenes aureus, Ia* 100, *Ic* 12·5, *VIe* 100; *Pseudomonas aeruginosa, Ic* 100; *Proteus vulgaris, Ic* 50; *Saccharomyces pasterianus, Ic* 50; *IVe* 50; *Trichophyton mentagrophytes, Ia* 50, *Ic* 50, *IVe* 6·2, *VIe* 25.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in Nujol) with a Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectrum with a Varian MAT 44S spectrometer. The homogeneity of the products 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 rotating evaporator.

1-(4-Thiocyanophenyl)pyrrolidine

A solution of 6·0 g 1-phenylpyrrolidine[6] and 8·4 g KSCN in 25 ml acetic acid was stirred, cooled to 10°C and treated dropwise with a solution of 6·6 g Br in 10 ml acetic acid (the temperature maintained between 10 and 20°C). The mixture was stirred for 1 h without cooling and poured into 250 ml water. The precipitated crude product was filtered, washed with water and dried; 7·0 g (84%), m.p. 96–98°C. Crystallization from aqueous ethanol gave the pure substance melting at 101–102°C. For $C_{11}H_{12}N_2S$ (204·3) calculated: 64·67% C, 5·92% H, 13·71% N, 15·70% S; found: 64·55% C, 5·86% H, 14·30% N, 15·29% S.

4-(4-Aminophenyl)morpholine (*IId*)

A suspension of 150 g Fe in 900 ml water was treated with 18 ml hydrochloric acid and the boiling mixture was stirred and slowly treated with 103 g 4-(4-nitrophenyl)morpholine[8]. The mixture was refluxed for 4 h, filtered while hot and the filtrate was allowed to crystallize; 34·0 g *IId*, m.p. 130–132°C. A second product was obtained by extraction of the solid, which was filtered off from the original reaction mixture, with benzene. The total yield was 54·5 g (61%) of the base *IId*, m.p. 133–134°C (cyclohexane). UV spectrum: λ_{max} 250 nm (log ε 4·15), 305 nm (3·40). IR spectrum: 830 (2 adjacent Ar—H), 1 119 (R—O—R), 1 510 (Ar), 1 638 ($ArNH_2$), 3 218, 3 318, 3 380, 3 400 cm^{-1} (NH_2). ^{1}H NMR spectrum: δ 6·80 (d, J = 8·5 Hz, 2 H, 2,6-H_2 in phenyl), 6·60 (d, J = 8·5 Hz, 2 H, 3,5-H_2 in phenyl), 3·80 (m, 4 H, CH_2OCH_2), 3·40 (bs, 2 H, NH_2), 3·00 (m, 4 H, CH_2NCH_2). For $C_{10}H_{14}N_2O$ (178·2) calculated: 67·38% C, 7·92% H, 15·72% N; found: 67·30% C, 8·03% H, 15·82% N.

1-(4-Aminophenyl)-4-methylpiperazine (*IIe*)

A solution of 131 g 1-methyl-4-(4-nitrophenyl)piperazine[7] in 2 l ethanol was treated with 5·0 g Raney Ni and hydrogenated in a 5 l autoclave at 60°C and hydrogen pressure of approximately 50 MPa. The reaction was finished after 5 h stirring, after cooling the catalyst was filtered off

and the solution evaporated *in vacuo*; 107 g (94%) crystalline *IIe*, m.p. 90–92°C (cyclohexane). Ref.[7], m.p. 90–92°C.

4-Pyrrolidinothiophenol (*IIIb*)

1-(4-Thiocyanophenyl)pyrrolidine (6·4 g) and 13·0 g $Na_2S.9\,H_2O$ were added to a solution of 1·6 g NaOH in 70 ml ethanol and the mixture was stirred and refluxed under nitrogen for 4 h. After cooling it was poured into a mixture of 500 ml water and 100 g ice, containing 35 g NH_4Cl. The separated crude product was extracted with ether, the extract was washed with water and processed; 5·0 g (89%) semisolid base *IIIb* (m.p. approximately 30°C) which was characterized by transformation to *IVb* (*cf.* Table I).

4-Piperidinothiophenol (*IIIc*) (Method A)

Ice (100 g) was added to a stirred solution of 54·4 g *IIc* (ref.[8]) in 100 ml hydrochloric acid and the mixture was diazotized at 0–5°C with a solution of 22·5 g $NaNO_2$ in 60 ml water, added dropwise. The obtained diazonium salt solution was slowly added to a stirred solution of 86 g potassium ethyl xanthate and 10 g Na_2CO_3 in 100 ml water which was maintained at 60°C. The mixture was stirred for another 2 h at 60°C and allowed to stand overnight at room temperature. The separated oil was extracted with benzene, the extract washed with water, dried and evaporated. The residue was dissolved in 200 ml ethanol, the stirred solution was treated with a solution of 68·5 g KOH in 70 ml water and the mixture was refluxed for 16 h under nitrogen. Ethanol was distilled off, the residue was dissolved in water, and the solution washed with benzene. The aqueous solution was cooled, acidified with acetic acid and the crude *IIIc* was isolated by extraction with benzene; 39·6 g (66%). A sample was distilled *in vacuo*; b.p. 172–175°C/2·4 kPa. For characterization, the crude product was transformed to *IVc* (*cf.* Table I).

4′-(4-Methylpiperazino)phenyl 2,4-Dinitrophenyl Sulfide (*IVe*) (Method B)

A solution of 5·0 g crude *IIIe* and 5·0 g 2,4-dinitrofluorobenzene in 60 ml acetone was treated with 20 ml triethylamine, the mixture was refluxed for 30 min and poured into water. The precipitated product was filtered and crystallized from pyridine; 2·8 g (31%) *IVe*, m.p. 211–213°C. UV spectrum: λ_{max} 274 nm (log ε 4·38), infl. 323 nm (3·03). IR spectrum: 832 (2 adjacent Ar–H), 1 326, 1 505 ($ArNO_2$), 1 590, 3 100 (Ar), 2 760, 2 800 cm^{-1} (N–CH_2, N–CH_3). Neutralization of the base with maleic acid in boiling ethanol and crystallization induced by addition of ether gave the maleate. Recrystallization from a mixture of 95% ethanol and ether gave the hemihydrate, m.p. 174–176°C. Analyses of the base and of the maleate are included in Table I.

2-(4-Piperidinophenylthio)benzoic Acid (*Vc*) (Method C)

IIIc (9·0 g) was dissolved in a stirred solution of 10·0 g KOH in 110 ml water, 12·4 g 2-iodobenzoic acid and 0·2 g Cu were added and the mixture was refluxed for 8 h. It was filtered while hot with active carbon, the filtrate was cooled and acidified with acetic acid. The precipitated product was filtered, washed with water and dried; 10·5 g (72%), m.p. 220–225°C. Analytical sample, m.p. 236–238°C (ethanol). UV spectrum: λ_{max} 279 nm (log ε 4·31), infl. 313 nm (3·92). IR spectrum: 745, 810 (4 and 2 adjacent Ar–H), 915, 1 240, 1 255, 1 270, **1 677**, 2 550, 2 640, infl. 3 070 (ArCOOH), 1 500, 1 590 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·90 (dd, J = 9·0; 2·0 Hz, 1 H, 6-H), 7·00–7·40 (m, 2 H, 4,5-H_2), 7·30 (d, J = 9·0 Hz, 2 H, 2′,6′-H_2), 6·95 (d, J = 9·0 Hz, 2 H, 3′,5′-H_2), 6·65 (bd, J = 8·5 Hz, 1 H, 3-H), 3·20 (bm, 4 H, CH_2NCH_2), 1·60 (bs, 6 H, remaining 3 CH_2 of piperidine). Analysis is included in Table I.

2-(Dimethylamino)thioxanthone (*VIa*) (Method D)

Polyphosphoric acid was prepared from 71 g 85% H_3PO_4 and 84 g P_2O_5, 15·6 g *Va* were added and the mixture was stirred and heated for 2 h to 130°C. It was decomposed by pouring into a mixture of 600 g ice and 1·2 l water, a slight excess of Na_2CO_3 was slowly added and the precipitated product was filtered; 13·0 g (90%) crude *VIa*. Crystallization from ethanol gave the pure substance, m.p. 122–124°C. UV spectrum: λ_{max} 268 nm (log ε 4·58), 297·5 nm (4·37), 450 nm (3·61). IR spectrum: 750, 802, 810, 852 (4 and 2 adjacent and solitary Ar—H), 1 586, 1 599 (Ar), 1 628 cm^{-1} (ArCOAr'). ^1H NMR spectrum: δ 8·48 (m, 1 H, 8-H), 7·78 (d, J = 2·5 Hz, 1 H, 1-H), 7·40 (m, 3 H, 5,6,7-H_3), 7·32 (d, J = 8·5 Hz, 1 H, 4-H), 7·00 (dd, J = 8·5; 2·5 Hz, 1 H, 3-H), 2·98 (s, 6 H, CH_3NCH_3). The analysis is included in Table I.

9-(3-Dimethylaminopropyl)-2-pyrrolidinothioxanthen-9-ol (*VIIb*) (Method E)

A solution of Grignard reagent was prepared by reaction of 0·6 g Mg with 3·0 g 3-dimethylaminopropyl chloride (initiation by a grain of iodine and a drop of 1,2-dibromoethane) in 50 ml tetrahydrofuran, and was treated with a suspension of 3·4 g *VIb* in 30 ml benzene. The stirred mixture was refluxed for 2 h, cooled, decomposed by addition of 50 ml saturated NH_4Cl solution, the organic layer was separated and the aqueous one extracted with benzene. The combined organic layers were washed with water, dried with Na_2SO_4 and evaporated. The oily residue crystallized by standing; 4·0 g (90%) crude *VIIb*, m.p. 160–162°C. Crystallization from toluene gave the pure substance, m.p. 168–170°C. IR spectrum: 755, 792, 844, 872 (4 and 2 adjacent and solitary Ar–H), 1 102 (R_3C–OH), 1 500, 1 566, 1 600, 3 048, 3 095 (Ar), 2 640, 2 700, infl. 3 140 (OH and O—H...N), 2 770, 2 820 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 7·85 (bd, 1 H, 8-H), 6·90–7·40 (m, 5 H, 1,4,5,6,7-H_5), 6·35 (dd, J = 8·5; 3·0 Hz, 1 H, 3-H), 3·20 (m, 4 H, CH_2NCH_2 in pyrrolidinyl), 2·30 (s, 6 H, CH_3NCH_3), 1·70–2·30 (m, 9 H, 2 remaining CH_2 in pyrrolidinyl, 2 external CH_2 of propyl and OH), 1·15 (m, 2 H, CH_2 in the middle of propyl). Analysis is included in Table I.

2-(Dimethylamino)-9-(3-dimethylaminopropylidene)thioxanthene (*Ia*)

VIIa (5·1 g) was dissolved in 50 ml 2·5M-H_2SO_4 and the solution was stirred and heated to 100°C for 2 h. After cooling it was made alkaline by NH_4OH and extracted with benzene. The extract was washed with water, dried and evaporated. The residue (4·4 g, 91%) is the oily mixture of geometrical isomers of *Ia*. It was dissolved in 10 ml 95% ethanol, the solution was neutralized with a solution of HCl in ether, and addition of ether led to precipitation of the dihydrochloride. It was crystallized from a mixture of 95% ethanol and ether and appeared to be a 2 : 3 solvate with water, m.p. 178–181°C. Mass spectrum, m/z (%): 324 (M^+ corresponding to $C_{20}H_{24}N_2S$), 266, 221 (7), 58 (100). For $C_{20}H_{26}Cl_2N_2S + 1·5\ H_2O$ (424·4) calculated: 56·59% C, 6·89% H, 16·71% Cl, 6·60% N; found: 56·66% C, 6·36% H, 16·56% Cl, 6·18% N. Treatment of this dihydrochloride with NH_4OH and extraction with ether led to the oily base *Ia* which was used for recording the spectra. IR spectrum (CS_2): 742, 759, 839, infl. 862 cm^{-1}; it indicates that the main component in the mixture is (*Z*)-*Ia*. ^1H NMR spectrum: δ 6·40–7·50 (m, 5 H, ArH), 5·88 and 5·81 (2 t, 1 H, =CH; proved that the substance consisted in the mixture of geometrical isomers), 2·88 [s, 6 H, Ar–$N(CH_3)_2$], c. 2·50 (m, 4 H, CH_2CH_2N), 2·15 (s, 6 H, CH_3NCH_3 in the aliphatic chain).

9-(3-Dimethylaminopropylidene)-2-piperidinothioxanthene (*Ic*)

VIIc (21·0 g) was dissolved in 210 ml 1·25M-H_2SO_4 and the solution was refluxed for 6 h. After cooling it was made alkaline with NH_4OH and the bases (19 g) were isolated by extraction with

benzene. This product was chromatographed on a column of 250 g neutral Al_2O_3 (activity II); elution with a 1 : 1 mixture of benzene and light petroleum gave 13·3 g (67%) pure mixture of geometrical isomers of *Ic*. After its dissolution in hexane 5·1 g homogeneous (*Z*)-*Ic* crystallized, m.p. 108–110°C. UV spectrum: λ_{max} 233 nm (log ε 4·51), 282 nm (4·27), 342 nm (3·45). IR spectrum (CS_2): 739, 757, 804, **901** (4 and 2 adjacent and solitary Ar—H), 2 760, 2 780, 2 808 cm^{-1} (N—CH_3); in Nujol: 1 550, 1 560, 1 590 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·00–7·50 (m, 5 H, 4,5,6,7,8-H_5), 6·90 (d, *J* = 3·0 Hz, 1 H, 1-H), 6·78 (dd, *J* = 8·5; 3·0 Hz, 1 H, 3-H), 5·80 (t, *J* = 7·0 Hz, 1 H, =CH), 3·10 (bm, 4 H, CH_2NCH_2 in piperidine), 2·30–2·70 (m, 4 H, =C—CH_2CH_2N), 2·18 (s, 6 H, CH_3NCH_3), 1·60 (bs, 6 H, remaining 3 CH_2 of piperidine). For $C_{23}H_{28}N_2S$ (364·5) calculated: 75·77% C, 7·74% H, 7·69% N, 8·80% S; found: 75·75% C, 7·82% H, 7·71% N, 9·02% S.

Succinate, m.p. 162–164°C (ethanol–ether). For $C_{27}H_{34}N_2O_4S$ (482·6) calculated: 67·19% C, 7·10% H, 5·80% N, 6·65% S; found: 68·61% C, 7·14% H, 6·02% N, 6·83% S.

Maleate, m.p. 158–160°C (ethanol–ether). For $C_{27}H_{32}N_2O_4S$ (480·6) calculated: 67·47% C, 6·71% H, 5·83% N, 6·67% S; found: 67·39% C, 6·83% H, 5·83% N, 7·03% S.

9-(3-Dimethylaminopropylidene)-2-morfolinothioxanthene (*Id*)

A solution of 4·8 g *VIId* in 150 ml 1·25M-H_2SO_4 was refluxed for 8 h, cooled, made alkaline with NH_4OH and extracted with benzene. Processing of the extract gave 4·6 g oily residue which was chromatographed on a column of 150 g neutral Al_2O_3 (activity II). Benzene eluted 4·0 g (88%) mixture of geometrical isomers of *Id*. Trituration with hexane afforded 2·6 g crystalline base with prevailing (*Z*)-*Id*, m.p. 100–102°C (heptane). UV spectrum: λ_{max} 234 nm (log ε 4·52), 279 (4·27), 342 nm (3·49). IR spectrum (CS_2): 739, 759, 804, **909** (4 and 2 adjacent and solitary Ar—H), 1 121 (R—O—R), 2 760, 2 775, 2 810 (N—CH_3); in Nujol: 1 550, 1 560, 1 590 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·60–7·50 (m, 7 H, ArH), c. 5·82 (m, 1 H, =CH), 3·80 (bt, 4 H, CH_2OCH_2), 3·10 (bt, 4 H, CH_2NCH_2), 2·30–2·70 (m, 4 H, =C—CH_2CH_2N), 2·18 (s, 6 H, CH_3NCH_3). For $C_{22}H_{26}N_2OS$ (366·5) calculated: 72·09% C, 7·15% H, 7·64% N, 8·75% S; found: 72·04% C, 7·25% H, 7·56% N, 8·42% S.

Succinate, m.p. 162–164°C (ethanol–ether). For $C_{26}H_{32}N_2O_5S$ (484·6) calculated: 64·44% C, 6·66% H, 5·78% N, 6·62% S; found: 65·19% C, 6·93% H, 6·11% N, 7·10% S.

Maleate, m.p. 163–165°C (ethanol–ether). For $C_{26}H_{30}N_2O_5S$ (482·6) calculated: 64·71% C, 6·27% H, 5·80% N, 6·64% S; found: 64·38% C, 6·35% H, 5·73% N, 6·73% S.

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