POTENTIAL ANTIDEPRESSANTS: 4-(AMINOALKOXY)THIOXANTHONES

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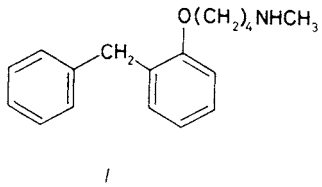
Four different approaches were used for preparing a series of the title compounds. Reactions of the sodium salt of 4-hydroxythioxanthone (*V*) with dimethylaminoalkyl chlorides gave the ethers *VI* and *VII*. Partial demethylation of *VII* via the carbamate *IX* afforded the secondary amine *VIII*. Reactions of the 4-bromobutoxy compound *XI* with amines resulted in *II*, *XII*, and *XIII*. Reaction of *V* with 1-chloro-2,3-epoxypropane and the following treatment of the resulting *XIV* with 2-propanamine gave the amino alcohol *XV*. The xanthone *III* was obtained via *XVIII* similarly like *II*. The products, especially *II* and *III* are cyclic analogues of the antidepressant and cerebral activator "bifemelane" (*I*) but they do not exhibit the pharmacological profile of antidepressants.

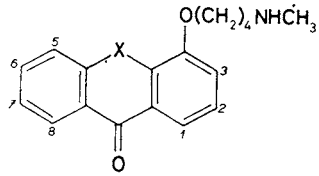
The research team of Mitsubishi[1] developed a series of 2-(aminoalkoxy) derivatives of diphenylmethane, diphenyl ether, diphenyl sulfide, and diphenylamine showing antireserpine potency in tests using the reserpine-induced hypothermia in mice. Compound *I* (bifemelane, MCI-2016) was selected for preclinical studies which showed it to be not only potential antidepressant[2,3] but also a general cerebral activator[4]. Using the sulfide and ether analogues of *I* as prototypes, we designed a series of tricyclic analogues derived by bridging the *o*-positions of the benzene nuclei by a —CO— group. The compounds to be synthesized were thus *II* and *III* as well as additional 4-(aminoalkoxy)thioxanthones.

2-(2-Methoxyphenylthio)benzoic acid[5] was cyclized with polyphosphoric acid at 110–120°C to *IV* (ref.[5] described this cyclization with trifluoroacetic acid anhydride) which was demethylated by heating with pyridine hydrochloride to 230–235°C to give *V* in excellent yield. Compound *V* was used as a common intermediate in the synthesis of a series of ethers. Refluxing the sodium salt of *V* (obtained from *V* and sodium ethoxide) with 2-dimethylaminoethyl chloride and 3-dimethylaminopropyl chloride in ethanol gave the amino ethers *VI* and *VII* which were transformed to hydrochlorides. In order to prepare the secondary amine *VIII*, *VII* was partially demethylated by treatment with ethyl chloroformate in boiling benzene. A mixture was formed from which the first component to be separated was identified as the hydrochloride of *VII* (this crystallized from the benzene solution). The benzene filtrate was washed with dilute hydrochloric acid for removing

the basic components and the solution of neutral products was separated by chromatography on aluminium oxide. The less polar, minor product, which easily crystallized, was identified by analysis and spectra as the 3-chloropropyl ether *X*. It was

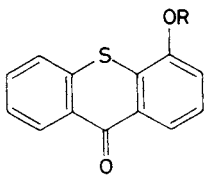


I



II, X = S
III, X = O

followed by the desired carbamate *IX* as the main product. Its formation together with methyl chloride is evidently accompanied by a second-type C—N cleavage affording *X* and the non-isolated ethyl N,N-dimethylcarbamate. Hydrolysis of *IX* with refluxing ethanolic potassium hydroxide resulted in *VIII*, characterized by spectra and transformed to the hydrochloride.



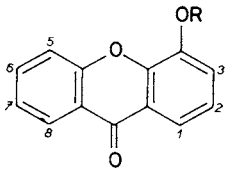
IV, R = CH_3
V, R = H
VI, R = $CH_2CH_2N(CH_3)_2$
VII, R = $(CH_2)_3N(CH_3)_2$
VIII, R = $(CH_2)_3NHCH_3$
IX, R = $(CH_2)_3N(CH_3)COOC_2H_5$

X, R = $(CH_2)_3Cl$
XI, R = $(CH_2)_4Br$
XII, R = $(CH_2)_4NHC_4H_9$
XIII, R = $(CH_2)_4NH$—⬡
XIV, R = $CH_2CH(O)CH_2$
XV, R = $CH_2CH(OH)CH_2NHCH(CH_3)_2$

Reactions of the potassium salt of *V* with 1,4-dibromobutane in boiling methanol gave 83% of the 4-bromobutyl ether *XI* (method according to literature[1]) which was subjected in ethanol to a substitution reaction with 40% aqueous methylamine at room temperature. Crystalline *II* was obtained in satisfactory yield, its structure was corroborated by spectra, and it was transformed to the hydrochloride. Similar substitution reactions of *XI* with butylamine and cyclohexylamine in boiling ethanol afforded the amino ethers *XII* and *XIII*. Heating of *V* with 1-chloro-2,3-epoxy-

propane in toluene in the presence of potassium carbonate gave *XIV* which reacted with 2-propanamine in ethanol and gave the amino alcohol *XV*.

For preparing the xanthone derivative *III*, 2-(2-methoxyphenoxy)benzoic acid[6] was cyclized with polyphosphoric acid at 110–115°C to *XVI* (ref.[6] described the cyclization of the acid chloride with aluminium chloride) which was demethylated by heating with pyridine hydrochloride to 220°C to give *XVII* (for different methods, cf. refs[6–8]). Its transformation to *III* via *XVIII* used similar methods like in the thioxanthone series.



XVI, R = CH_3
XVII, R = H
XVIII, R = $(CH_2)_4Br$

Most of the compounds prepared were subjected to general pharmacological screening and/or microbiological screening in vitro. They were tested in the form of hydrochlorides together with hydrochloride of *I* which was synthesized[1] to this purpose and used as the standard. Acute toxicity in mice on intravenous administration, LD_{50} in mg/kg: *I*, 55·1 (400 on oral administration); *II*, 50; *VII*, 75; *VIII*, 76·2. Toxic symptoms were sedation and convulsions. Doses used in the screening, D in mg/kg (i.v.): *II*, 10; *VII*, 15. Antireserpine activity in the test of ptosis in mice: *I*, significant blockade of the ptosis starting with the dose of 30 mg/kg orally; *II* and *VIII* inactive in doses D administered intraperitoneally. Potentiation of yohimbine toxicity in mice: *I*, ED_{50} = 62 mg/kg p.o. Inhibition of the reserpine-induced hypothermia in mice using doses D (i.p.): *II*, inactive; *VII*, indication of effect. Inhibition of reserpine-induced gastric ulcer formation in rats: oral doses of 25 and 100 mg/kg of *I* had statistically insignificant effect. Anticataleptic effect towards perphenazine-induced catalepsy in rats: *I*, inactive at 50 mg/kg orally; *VIII*, 100 mg/kg p.o. without effect. Compounds *I* and *VIII* proved inactive in the test for antiserotonin action (rat paw oedema) in oral doses of 10 mg/kg. Compounds *II* and *VII* in doses D brought about brief and deep drops of the blood pressure in normotensive rats. The same compounds showed spasmolytic effects on the isolated rat duodenum in concentrations of 10 μg/ml against acetylcholine as well as barium chloride contractions. In conclusion, compound *I* showed the character of an atypical and weak antidepressant agent; the new compounds lack this character.

Antimicrobial activity tested in vitro (microorganisms and the minimum inhibitory concentrations in μg/ml given unless they exceed 125 μg/ml): *Streptococcus β-haemolyticus, I* 50, *II* 25, *III* 50, *VII* 25, *XIII*, 25; *Streptococcus faecalis, I* 100, *II* 25, *III* 6·25, *VI* 2, *VII* 25, *XIII* 25, *XV* 50; *Staphylococcus pyogenes aureus, I* 25, *II* 25, *III* 50, *VI* 4, *VII* 25, *XIII* 25, *XV* 6·25; *Pseudomonas aeruginosa, I* 100, *VI* 128; *Escherichia coli, I* 50, *VI* 8; *Proteus vulgaris, I* 100, *II* 100, *III* 50, *VI* 16, *VII* 100, *XV* 50; *Trichophyton mentagrophytes, III* 50, *VI* 50, *XV* 50.

EXPERIMENTAL

The melting points were determined in 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. The UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8 000 spectrophotometer, IR spectra (mostly in Nujol, ν in cm^{-1}) with Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (in C^2HCl_3 unless stated otherwise, δ, J in Hz) with a Tesla BS 487 C (80 MHz) spectrometer, and the mass spectra with MCH 1 320 and varian MAT 44S spectrometers (m/z, composition and/or % given). 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 Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotating evaporator.

4-Methoxythioxanthone (*IV*)

A stirred mixture of 33·9 g 2-(2-methoxyphenylthio)benzoic acid[5] and 185 g polyphosphoric acid was heated for 45 min to 110–120°C and poured into a mixture of 400 g ice and 370 ml NH_4OH. After 2 h standing the yellow product was filtered, washed with water, dried in vacuo, and crystallized from a mixture of 500 ml ethanol and 100 ml benzene; 30·9 g (98%) of *IV*, m.p. 167–169°C. Ref.[5], m.p. 166–168°C.

4-Methoxyxanthone (*XVI*)

A stirred mixture of 15·9 g 2-(2-methoxyphenoxy)benzoic acid[6] and 90 g polyphosphoric acid was heated for 45 min to 110–116°C and processed similarly like in the preceding case. The crude product (9·3 g) was crystallized by dissolving in 70 ml boiling benzene and by addition of light petroleum; 7·9 g (54%) of *XVI*, m.p. 170–175°C. Ref.[6], m.p. 173°C.

4-Hydroxythioxanthone (*V*)

A mixture of 21·6 g *IV* and 67·5 g pyridinium chloride was heated under stirring for 45 min in a bath of 230°C (temperature of the mixture was 207°C). After cooling to 100°C, the mixture was decomposed with 400 ml water, the suspension obtained was allowed to stand for 2 h at room temperature, the yellow solid was filtered, washed with water, and crystallized from 1 400 ml methanol; 18·0 g of *V*, m.p. 280–285°C. Processing of the mother liquor afforded further 2·0 g product of the same quality; total yield was thus 20·0 g (98%). Analytical sample, m.p. 281–283°C (methanol). UV spectrum: 233 (4·08), infl. 253 (4·56), 259 (4·63), infl. 301 (3·92), 310 (4·03), 3·88 (3·79). IR spectrum: 744, 818 (4 and 3 adjacent Ar—H); 1 180, 1 286 (ArOH); 1 569, 1 590 (Ar); 1 616 ($Ar_2CO\cdots H—O$ intermol.); 3 110 (OH). ^1H NMR spectrum ($C^2H_3SOC^2$.

$.H_3$): 7·20—7·90 m, 5 H (H-2,3,5,6,7); 8·02 dd, 1 H (H-1, J = 8·5; 1·5); 8·50 dd, 1 H (H-8, J = 8·5; 1·5). For $C_{13}H_8O_2S$ (228·3) calculated: 68·40% C, 3·53% H, 14·05% S; found: 68·14% C, 3·63% H, 14·07% S.

4-Hydroxyxanthone (*XVII*)

A mixture of 7·7 g *XVI* and 26 g pyridinium chloride was heated for 45 min under stirring in a bath of 230°C. Similar processing like in the preceding case gave 6·9 g crude product which was dissolved in 400 ml boiling ethanol, the solution was filtered with charcoal, and the filtrate was partly evaporated; 5·8 g (81%) of *XVII*, m.p. 243—245°C. Refs[6,7], m.p. 241 and 245—246°C, respectively.

4-(4-Bromobutoxy)thioxanthone (*XI*)

A stirred solution of 2·8 g KOH in 100 ml methanol was treated with 9·1 g *V* and then over 10 min with a solution of 17·3 g 1,4-dibromobutane in 20 ml methanol. The mixture was refluxed for 9 h, evaporated in vacuo, and the residue was extracted with benzene. The extract was washed with 2M-NaOH and water, dried, and evaporated in vacuo. The residue gave by crystallization from 90 ml ethanol 8·4 g (58%) of *XI*, m.p. 97·5—101·5°C. Analytical sample, m.p. 101—103°C (ethanol). UV spectrum: 258·5 (4·74), infl. 298 (3·91), 307·5 (4·07), 386 (3·92). IR spectrum: 710, 744, 817 (4 and 3 adjacent Ar—H); 1 055, 1 070, 1 263 (ArOR); 1 570, 1 590, 3 010, 3 053 (Ar); 1 621 (Ar_2CO). ^{1}H NMR spectrum: 2·10 m, 4 H (O—C—CH_2CH_2—C—Br); 3·60 bt, 2 H (CH_2Br, J = 6·0); 4·18 bt, 2 H (OCH_2, J = 6·0); 7·09 dd, 1 H (H-3, J = 8·0; 2·0); 7·40 t, 1 H (H-2, J = 8·0); 7·60 m, 3 H (H-5, 6, 7); 8·25 dd, 1 H (H-1, J = 8·0; 2·0); 8·62 bd, 1 H (H-8, J = = 8·0). For $C_{17}H_{15}BrO_2S$ (363·3) calculated: 56·20% C, 4·16% H, 22·00% Br, 8·83% S; found: 56·62% C, 4·24% H, 22·02% Br, 9·04% S.

4-(4-Bromobutoxy)xanthone (*XVIII*)

A solution of 1·7 g KOH in 100 ml methanol was treated with 5·3 g *XVII* and 11·2 g 1,4-dibromobutane, the mixture was refluxed for 6 h, and processed similarly like in the preceding case. The crude product was crystallized from 25 ml ethanol; 4·9 g (57%) of *XVIII*, m.p. 91—95°C. Analytical sample, m.p. 95—98°C (ethanol). UV spectrum: 246 (4·56), infl. 275 (3·76), 345 (3·72). IR spectrum (KBr): 687, 729, 755, 772, 813 (4 and 3 adjacent Ar—H); 1 072, 1 229, 1 253, 1 272 (ArOR and ArOAr'); 1 492, 1 572, 1 593, 1 606, 3 020 (Ar); 1 660 (Ar_2CO). ^{1}H NMR spectrum: 2·15 m, 4 H (O—C—CH_2CH_2—C—Br), 3·60 bt, 2 H (CH_2Br); 4·18 bt, 2 H (OCH_2); 7·10 to 7·80 m, 5 H (H-2, 3, 5, 6, 7); 7·90 m, 1 H (H-1); 8·32 bd, 1 H (H-8). For $C_{17}H_{15}BrO_3$ (347·2) calculated: 58·80% C, 4·35% H, 23·02% Br; found: 58·94% C, 4·57% H, 22·78% Br.

4-(2,3-Epoxypropoxy)thioxanthone (*XIV*)

A mixture of 6·8 g *V*, 21·6 g 1-chloro-2,3-epoxypropane, 6·4 g K_2CO_3, and 15 ml toluene was stirred for 2 h at 80°C and then under reflux for 1 h in a bath of 135°C. The excess of 1-chloro--2,3-epoxypropane was distilled off in vacuo, the residue was distributed between water and chloroform, the chloroform solution was dried and evaporated. The crude product obtained was dissolved in a mixture of 300 ml ethanol and 50 ml benzene, the solution was filtered through a layer of charcoal, the filtrate was partly evaporated and allowed to crystallize in the refrigerator; 6·7 g (80%) of *XIV*, m.p. 130—134°C. Analytical sample, m.p. 136—138°C (ethanol). UV spectrum: 222 (4·12), 256·5 (4·65), 295 (3·81), 305·5 (3·95), 383 (3·80). IR spectrum: 708, 736, 770, 810 (4 and 3 adjacent Ar—H); 1 269 (ArOR); 1 569, 1 592 (Ar); 1 632 (Ar_2CO), 3 050 (CH_2

of epoxide). ^{1}H NMR spectrum: 2·85 m, 2 H (CH_2 of epoxide); 3·40 m, 1 H (CH of epoxide); 4·02 dd and 4·40 dd, 1 + 1 H ($ArOCH_2$, J = 11·0; 5·0 and 11·0; 3·0); 7·05 dd, 1 H (H-3, J = 8·5; 2·0); 7·31 t, 1 H (H-2, J = 8·5); c. 7·50 m, 3 H (H-5, 6, 7); 8·20 dd, 1 H (H-1, J = 8·5; 2·0); 8·52 m, 1 H (H-8). For $C_{16}H_{12}O_3S$ (284·3) calculated: 67·58% C, 4·26% H, 11·28% S; found: 67·22% C, 4·03% H, 11·31% S.

4-(2-Dimethylaminoethoxy)thioxanthone (*VI*)

2-Dimethylaminoethyl chloride hydrochloride (7·0 g) was added to a solution of sodium ethoxide (from 2·0 g Na and 100 ml ethanol), the mixture was stirred for 10 min and treated with 7·3 g *V*. Under stirring the mixture was refluxed for 10 h, after cooling the solid was filtered off, washed with ethanol and benzene, and the filtrate was acidified with hydrochloric acid. The precipitated crude hydrochloride was filtered off, the filtrate was evaporated, the residue was combined with the hydrochloride, the mixture was dissolved in water, the solution was washed with benzene, and made alkaline with NH_4OH. The released base was extracted with benzene and processing of the extract gave 6·0 g (63%) of *XI*, m.p. 93–95°C (ethanol). UV spectrum: 223 (4·48), infl. 252 (4·58), 258 (4·66), infl. 296 (3·87), 306 (3·98), 382 (3·86). IR spectrum: 742, 814 (4 and 3 adjacent Ar—H); 1 052, 1 067, 1 261, 1 275 (ArOR); 1 555, 1 572, 1 594, 3 050 (Ar); 1 633 (Ar_2CO); 2 780 (N—CH_2). ^{1}H NMR spectrum: 2·35 s, 6 H ($N(CH_3)_2$); 2·80 t, 2 H (CH_2N, J = 6·0); 4·20 t, 2 H (OCH_2, J = 6·0); 7·03 dd, 1 H (H-3, J = 8·0; 1·5); 7·31 t, 1 H (H-2, J = 8·0); c. 7·50 m, 3 H (H-5, 6, 7); 8·19 dd, 1 H (H-1, J = 8·0; 1·5); 8·53 m, 1 H (H-8). For $C_{17}H_{17}NO_2S$ (299·4) calculated: 68·20% C, 5·72% H, 4·68% N, 10·71% S; found: 68·32% C, 5·80% H, 4·54% N, 10·84% S.

Hydrochloride, m.p. 258–262°C (methanol). For $C_{17}H_{18}ClNO_2S$ (335·8) calculated: 60·79% C, 5·40% H, 10·56% Cl, 4·17% N, 9·55% S; found: 61·02% C, 5·50% H, 10·45% Cl, 4·28% N, 9·80% S.

4-(3-Dimethylaminopropoxy)thioxanthone (*VII*)

A similar reaction of 9·7 g 3-dimethylaminopropyl chloride hydrochloride with sodium ethoxide (2·6 g Na and 300 ml ethanol) and 10·3 g *V* gave 10·9 g (77%) of *VII*, m.p. 97–99°C (cyclohexane). UV spectrum: 257 (4·65), infl. 297 (4·10), 307 (4·26), 384 (4·09). IR spectrum: 715, 733, 815 (4 and 3 adjacent Ar—H); 1 053, 1 273 (ArOR); 1 550, 1 570, 1 591, 3 060, 3 070 (Ar); 1 632 (Ar_2CO); 2 750, 2 783, 2 815 (N—CH_3). ^{1}H NMR spectrum: 2·10 m, 2 H (O—C—CH_2—C—N); 2·28 s, 6 H ($N(CH_3)_2$); 2·55 t, 2 H (CH_2N, J = 7·0); 4·20 t, 2 H (OCH_2, J = 7·0); 7·10 dd, 1 H (H-3, J = 8·5; 2·0); 7·40 t, 1 H (H-2, J = 8·5); 7·60 m, 3 H (H-5, 6, 7); 8·22 dd, 1 H (H-1, J = 8·5; 2·0); 8·62 bd, 1 H (H-8). For $C_{18}H_{19}NO_2S$ (313·4) calculated: 68·98% C, 6·11% H, 4·47% N, 10·23% S; found: 68·75% C, 6·11% H, 4·22% N, 10·10% S.

Hydrochloride, m.p. 207–209°C (ethanol). For $C_{18}H_{20}ClNO_2S$ (349·9) calculated: 61·79% C, 5·76% H, 10·13% Cl, 4·00% N, 9·17% S; found: 61·84% C, 5·69% H, 10·27% Cl, 3·80% N, 9·04% S.

4-(3-(N-Ethoxycarbonyl-N-methylamino)propoxy)thioxanthone (*IX*)

A solution of 10·2 g *VII* in 65 ml benzene was treated with 7·2 g ethyl chloroformate in 20 ml benzene, the mixture was stirred for 30 min at room temperature, and then refluxed for 5·5 h. After cooling the separated solid was filtered off (2·9 g) and identified as *VII* hydrochloride (m.p. 200–204°C; the released base *VII*, m.p. 94–97°C). The filtrate was washed with dilute hydrochloric acid and with water, dried, and evaporated. The inhomogeneous residue (7·3 g)

was chromatographed on a column of 215 g neutral Al_2O_3 (activity II). Benzene eluted 0·4 g (4%) of homogeneous neutral product which crystallized on standing, m.p. 153–155°C (benzene) and was identified as 4-(3-chloropropoxy)thioxanthone (*X*). UV spectrum: 223 (4·10), 257 (4·67), infl. 298 (3·82), 306·5 (3·98), 384 (3·82). IR spectrum: 712, 748, 780, 819 (4 and 3 adjacent Ar—H); 1 050, 1 260 (ArOR); 1 573, 1 590, 3 060 (Ar); 1 620 (Ar_2CO). ^{1}H NMR spectrum: 2·35 m, 2 H (OC—CH_2—C—Cl); 3·80 t, 2 H (CH_2Cl, J = 6·0); 4·20 t, 2 H (OCH_2, J = 6·0); 7·00 dd, 1 H (H-3, J = 2·0; 8·0); 7·30 t, 1 H (H-2, J = 8·0); 7·50 m, 3 H (H-5, 6, 7); 8·18 dd, 1 H (H-1, J = 2·0; 8·0); 8·50 m, 1 H (H-8). For $C_{16}H_{13}ClO_2S$ (304·8) calculated: 63·05% C, 4·30% H, 11·63% Cl, 10·52% S; found: 63·15% C, 4·43% H, 11·87% Cl, 10·75% S.

The elution was continued with a 1 : 1 mixture of benzene and chloroform which gave 1·1 g mixture of *X* and *IX*. The chromatography was concluded by elution with chloroform affording 4·8 g (40%) of *IX*, m.p. 82–85°C. UV spectrum: 223 (4·09), 257·5 (4·65), infl. 298 (3·83), 307 (3·98), 383 (3·95). IR spectrum: 715, 752, 778, 784 (3 and 4 adjacent Ar—H); 1 068, 1 251, 1 263 (ArOR and C—O of NCOOR); 1 488, 1 570, 1 591, 3 060 (Ar); 1 630 (Ar_2CO); 1 705 (NCOOR). ^{1}H NMR spectrum: 1·18 t, 3 H (CH_3 in ethyl, J = 7·0); 2·10 m, 2 H (O—C—CH_2—C—N); 2·91 s, 3 H (NCH_3); 3·51 t, 2 H (CH_2N, J = 6·0); 4·05 q, 2 H ($COOCH_2$, J = 7·0); 4·12 t, 2 H ($ArOCH_2$, J = 6·0); 7·00 dd, 1 H (H-3, J = 2·0; 8·0); 7·31 t, 1 H (H-2, J = 8·0); 7·50 m, 3 H (H-5, 6, 7); 8·20 dd, 1 H (H-1, J = 2·0; 8·0); 8·55 m, 1 H (H-8). For $C_{20}H_{21}NO_4S$ (371·5) calculated: 64·67% C, 5·70% H, 3·77% N, 8·63% S; found: 64·55% C, 5·87% H, 3·48% N, 8·57% S.

4-(3-Methylaminopropoxy)thioxanthone (*VIII*)

A mixture of 4·8 g *IX*, 3·8 g KOH, and 7·5 ml ethanol was refluxed under stirring for 11 h (bath temperature 120°C). Ethanol was evaporated, the residue was distributed between water and benzene, the benzene solution was shaken with 3M-HCl, the obtained solution of the hydrochloride was made alkaline with NH_4OH, and the base was isolated by extraction with benzene; 3·8 g (100%) of *VIII* which crystallized from cyclohexane, m.p. 98–101°C. UV spectrum: 222·5 (4·43), 257 (4·62), 295 (3·83), 305 (3·96), 383 (3·81). IR spectrum: 715, 730, 812 (4 and 3 adjacent Ar—H); 1 263, 1 275 (ArOR); 1 571, 1 592, 3 060 (Ar); 1 632 (Ar_2CO); 2 795 (N—CH_3); 3 260 (NH). ^{1}H NMR spectrum: 1·42 bs, 1 H (NH); 2·10 m, 2 H (O—C—CH_2—C—N); 2·48 s, 3 H (NCH_3); 2·85 t, 2 H (CH_2N, J = 7·0); 4·20 t, 2 H (OCH_2, J = 7·0); 7·03 dd, 1 H (H-3, J = 8·5; 2·0); 7·28 t, 1 H (H-2, J = 8·5); 7·00 m, 3 H (H-5, 6, 7); 8·18 dd, 1 H (H-1, J = 8·5; 2·0); 8·58 bd, 1 H (H-8, J = 8·5). For $C_{17}H_{17}NO_2S$ (299·4) calculated: 68·20% C, 5·72% H, 4·68% N, 10·71% S; found: 68·41% C, 5·92% H, 4·66% N, 10·68% S.

Hydrochloride, m.p. 205–208°C (ethanol–ether). Mass spectrum: 299 (M^+, $C_{17}H_{17}NO_2S$, 10), 228 ($C_{13}H_8O_2S$, 35), 212 ($C_{13}H_8OS$, 5), 171 ($C_{11}H_7S$, 15), 72 ($C_4H_{10}N$, 95), 44 (100). For $C_{17}H_{18}ClNO_2S$ (335·8) calculated: 60·79% C, 5·40% H, 10·56% Cl, 4·17% N, 9·55% S; found: 60·04% C, 5·21% H, 11·02% Cl, 4·32% N, 9·57% S.

4-(4-Methylaminobutoxy)thioxanthone (*II*)

A solution of 11·0 g *XI* in a mixture of 400 ml ethanol and 40 ml benzene was treated with 50 ml 40% aqueous methylamine and the mixture was stirred for 5 h at room temperature. After standing for 2 days, further 50 ml 40% methylamine were added and the mixture was stirred for another 5 h at room temperature. It was then evaporated in vacuo, the residue was treated with 100 ml 10% NaOH, and the product was extracted with a mixture of benzene and ether. Processing of the extract gave the crude product which was crystallized from cyclohexane;

7·0 g (74%) of *II*, m.p. 94–97°C (benzene–hexane). UV spectrum: 223 (4·09), 257 (4·66), infl. 298 (3·83), 307 (3·97), 384 (3·81). IR spectrum: 690, 748, 818 (4 and 3 adjacent Ar—H); 1 066, 1 270 (ArOR); 1 570, 1 590, 3 055 (Ar); 1 620 (Ar_2CO); 2 800 (N—CH_2, N—CH_3); 3 320 (NH). ^{1}H NMR spectrum: 1·15 s, 1 H (NH); 1·75 bm, 4 H (O—C—CH_2—CH_2C—N); 2·40 s, 3 H (NCH_3); 2·62 t, 2 H (CH_2N, J = 6·0); 4·05 t, 2 H (OCH_2, J = 6·0); 6·95 dd, 1 H (H-3, J = 2·0; 8·0); 7·30 t, 1 H (H-2, J = 8·0); 7·50 m, 3 H (H-5, 6, 7); 8·15 dd, 1 H (H-1, J = 2·0; 8·0); 8·52 m, 1 H (H-8). For $C_{18}H_{19}NO_2S$ (313·4) calculated: 68·98% C, 6·11% H, 4·47% N, 10·23% S; found: 69·43% C, 6·00% H, 4·04% N, 10·41% S.

Hydrochloride hemihydrate, m.p. 214–218°C (methanol–ether). Mass spectrum: 313 (M^+, $C_{18}H_{19}NO_2S$, 0·3), 269 ($C_{16}H_{13}O_2S$, 3), 228 ($C_{13}H_8O_2S$, 3·5), 86 ($C_5H_{12}N$, 100), 44 (55). For $C_{18}H_{20}ClNO_2S + 0{\cdot}5\ H_2O$ (357·8) calculated: 60·41% C, 5·91% H, 9·63% Cl, 3·91% N, 8·96% S; found: 61·03% C, 5·57% H, 9·60% Cl, 3·90% N, 9·28% S.

4-(4-Methylaminobutoxy)xanthone (*III*)

A similar reaction of 29 g *XVIII* with 40% methylamine (230 and 200 ml) in 1 500 ml methanol afforded 20·0 g (80%) oily *III* which was transformed to hydrochloride crystallizing from a mixture of ethanol and light petroleum as a 2 : 1 solvate with ethanol, m.p. 195–198°C. Mass spectrum: 297 (M^+, $C_{18}H_{19}NO_3$, 0·1), 254 (0·6), 253 (0·7), 224 (2·4), 212 (12), 128 (10), 127 (10), 86 (100). For $C_{18}H_{20}ClNO_3 + 0{\cdot}5\ C_2H_6O$ (356·8) calculated: 63·95% C, 6·49% H, 9·94% Cl, 3·93% N; found: 63·89% C, 6·10% H, 10·18% Cl, 3·67% N.

A sample of the pure hydrochloride was decomposed with NH_4OH and the homogeneous oily base was isolated by extraction with ether. It was used for recording the spectra. UV spectrum: 245 (4·54), infl. 278 (3·73), 346 (3·72). IR spectrum: 752 (4 adjacent Ar—H); 1 069, 1 229, 1 286, 1 270 (ArOR, ArOAr'); 1 492, 1 573, 1 595, 1 605, 3 060 (Ar); 1 666 (Ar_2CO); 2 790 (N—CH_3); 3 220 (NH). ^{1}H NMR spectrum: 1·45 bs, 1 H (NH); 1·80 m, 4 H (O—C—CH_2CH_2—C—N); 2·48 s, 3 H (NCH_3); 2·70 bt, 2 H (CH_2N, J = 7·0); 4·15 t, 2 H (OCH_2, J = 7·0); 7·10–7·70 m, 5 H (H-2, 3, 5, 6, 7); 7·85 m, 1 H (H-1); 8·30 bd, 1 H (H-8).

4-(4-(Butylamino)butoxy)thioxanthone (*XII*)

A solution of 3·6 g *XI* in 50 ml ethanol and 5 ml benzene was treated with 3·3 g butylamine and the mixture was refluxed for 8 h. The solvents were evaporated in vacuo, the residue was treated with 50 ml 10% NaOH, and the product was extracted with benzene. Processing of the extract gave 3·3 g of the crude *XII* which was dissolved in 15 ml ethanol and the solution was acidified with a solution of HCl in ether; 3·5 g (90%) of hydrochloride which crystallized from a mixture of methanol and ether, m.p. 174–177°C. Mass spectrum: 355 (M^+, $C_{21}H_{25}NO_2S$, 0·3), 312 ($C_{18}H_{18}NO_2S$, 2·5), 228 ($C_{13}H_8O_2S$, 75). 200 ($C_{12}H_8OS$, 26), 172 ($C_{11}H_8S$, 28), 171 ($C_{11}H_7S$, 50), 128 ($C_8H_{18}N$, 27), 84 ($C_5H_{10}N$, 100). UV spectrum: 222 (4·12), 256 (4·63), 297 (3·82), 306 (3·97), 382 (3·81). IR spectrum: 710, 745, 814 (4 and 3 adjacent Ar—H); 1 079, 1 282 (ArOR); 1 571, 1 592 (Ar); 1 628 (Ar_2CO); 2 472, 2 560, 2 730 (NH_2^+); 3 420 (NH).

4-(4-Cyclohexylaminobutoxy)thioxanthone (*XIII*)

A warm solution of 3·6 g *XI* in 40 ml ethanol was treated with 5·0 g of cyclohexylamine and the mixture was stirred and refluxed for 9 h. After standing for 3 days, the mixture was filtered, the filtrate was evaporated in vacuo, the residue was treated with 50 ml 10% NaOH, and the product was extracted with benzene. From the organic solvent the base was transferred into

aqueous solution by shaking with an excess of 3M-HCl, the solution of the hydrochloride was separated, treated with NH_4OH, and extracted with benzene. Processing of the extract gave the crude product which crystallized by standing; 3·2 g (84%) of *XIII*, m.p. 83–85°C (cyclohexane). UV spectrum: 223 (4·11), 257 (4·63), 306 (3·98), 382 (3·83). IR spectrum: 688, 735, 770, 813 (4 and 3 adjacent Ar—H); 1 065, 1 272 (ArOR); 1 570, 1 592, 3 065 (Ar); 1 630 (Ar_2CO); 3 410 (NH). ^{1}H NMR spectrum: 0·70–2·00 m, 15 H (5 CH_2 of cyclohexyl, NH and O—C—CH_2CH_2—C—N); 2·40 bm, 1 H (N—CH); 2·70 t, 2 H (CH_2N, J = 6·0); 4·10 t, 2 H (OCH_2, J = 6·0), 7·00 dd, 1 H (H-3, J = 2·0; 8·0); 7·30 t, 1 H (H-2, J = 8·0); 7·50 m, 3 H (H-5, 6, 7); 8·15 dd, 1 H (H-1, J = 2·0; 8·0); 8·55 m, 1 H (H-8). $C_{23}H_{27}NO_2S$ (381·5) calculated: 72·40% C, 7·13% H, 3·67% N, 8·41% S; found: 72·45% C, 7·36% H, 3·56% N, 8·40% S.

Hydrochloride, m.p. 210–213°C (methanol). For $C_{23}H_{28}ClNO_2S$ (418·0) calculated: 66·09% C, 6·75% H, 8·48% Cl, 3·35% N, 7·67% S; found: 65·71% C, 6·92% H, 8·59% Cl, 3·32% N, 7·95% S.

4-(2-Hydroxy-3-(2-propylamino)propoxy)thioxanthone (*XV*)

A solution of 1·8 g *XIV* in 80 ml ethanol was aded dropwise to a stirred solution of 1·2 g isopropylamine in 15 ml ethanol at 60–70°C. The mixture was stirred and refluxed for 2 h, evaporated in vacuo, the residue was distributed between water and warm benzene, and the benzene solution was shaken with an excess of 3M-HCl. The aqueous solution of the hydrochloride was treated with NH_4OH and the base was extracted with chloroform. Processing of the extract gave the crude product which was crystallized from 20 ml ethanol; 1·6 g (74%), m.p. 139–141°C (ethanol). UV spectrum: 221·5 (4·22), 256 (4·65), 295·5 (3·88), 304·5 (3·99), 382 (3·80). IR spectrum: 705, 733, 743, 788, 807 (4 and 3 adjacent Ar—H); 1 068 (CHOH); 1 256 (ArOR); 1 550, 1 570, 1 591, 3 050 (Ar); 1 629 (Ar_2CO); infl. 3 130 (OH); 3 275 (NH). ^{1}H NMR spectrum: 1·15 d, 6 H (2 CH_3, J = 6·5); 2·50 bs, 2 H (NH and OH); 2·90 m, 3 H (CH_2NCH); 4·15 m, 3 H (OCH_2CHO); 7·08 dd, 1 H (H-3, J = 8·5; 2·0); 7·31 t, 1 H (H-2, J = 8·5); 7·50 m, 3 H (H-5, 6, 7); 8·20 dd, 1 H (H-1, J = 8·5; 2·0); 8·58 bd, 1 H (H-8). For $C_{19}H_{21}NO_3S$ (343·4) calculated: 66·44% C, 6·16% H, 4·08% N, 9·34% S; found: 66·82% C, 6·18% H, 4·14% N, 9·43% S.

Hydrochloride, m.p. 203–206° (methanol–ether). For $C_{19}H_{22}ClNO_3S$ calculated: 60·06% C, 5·84% H, 9·33% Cl, 3·69% N, 8·44% S; found: 60·36% C, 5·84% H, 9·24% Cl, 3·53% N, 8·52% S.

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