OPEN-RING MODELS OF HETERO-CANNABINOIDS: SYNTHESIS OF 2-(ALKYLTHIO)-5-(2-AMINOETHYL)HYDROQUINONE DERIVATIVES

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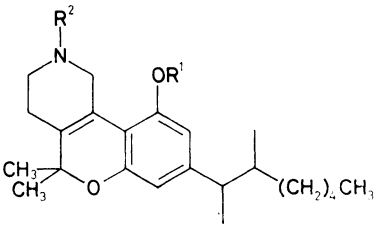
2,5-Dimethoxythiophenol was S-alkylated with pentyl bromide and heptyl bromide, the sulfides *IVa, b* were chloromethylated and the products were transformed to the nitriles *VIIa, b*. Reduction with aluminium hydride gave the amines *XIIIa, b* which were transformed to N-methyl- and N,N-dimethyl derivatives *XVa,b* and *XVIa,b*. Alkylation of the nitriles *VIIa,b* with 2-propyl bromide and the following reduction with aluminium hydride led under simultaneous partial demethylation to monophenolic amines *XVIIIa, b*. Methylation of these amines gave the N-(monomethyl) compound *XIXa* and the N,N-dimethyl compound *XXb*. The complete O-demethylation of *XXb* with boron tribromide or iodotrimethylsilane gave the hydroquinone *XXI* in the form of the corresponding salt (hydrobromide, hydroiodide). Compound *XIIIb* (hydrogen maleate VÚFB-16 519) exhibited interesting antireserpine activity in two tests and may be considered a potential antidepressant.

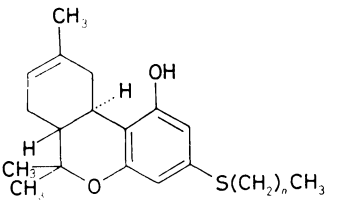
The motive of the huge amount of experimental work in the chemistry of cannabinoids[1,2] was the therapeutic potentiality of these compounds[3-6] which was indicated in the lines of sedative (tranquilizing), hypnotic, anticonvulsant, analgetic, cardiovascular, gastrointestinal (antiemetic), and other activities. In addition to carbocyclic cannabinoids some aza analogues[7,8], e.g. of the general formula *I* (R^1 = H or aminoacyl; R^2 = H, propargyl etc.) (refs[9-13]) and some thia analogues *II* (n = 3 or 5) (ref.[14]) were investigated with partly promising pharmacological results. Even some very simple cannabinoid models, lacking the ring B, showed considerable analgetic activity[15,16]. The object of this communication was the synthesis and pharmacological screening of the title compounds of formula *III* (R^1 = H or methyl, R^2 = H or 2-propyl, and n being 4 or 6).

2,5-Dimethoxythiophenol[17] was the starting material. It was transformed by sodium ethoxide to the sodium salt and this was S-alkylated with pentyl bromide and heptyl bromide in boiling ethanol to give the sulfides *IVa* and *IVb*. The following chloromethylation with aqueous formaldehyde and hydrogen chloride in dioxane (method[18]) led to the mixtures of the mono(chloromethyl) compounds and the corresponding diphenylmethane derivatives which were separated by crystallization from acetone utilizing the lower solubility of the diphenylmethanes. It was assumed

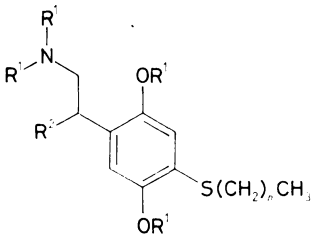
that the chloromethylation proceeded in position 4 (para to sulfur), considered to be the most activated position and the products were thus formulated as *Va*, *b*, *VIa*, *b*. The spectra were in agreement with these formulations without, however, representing an unequivocal proof of correctness of the structures assigned. The separations of *V* and *VI* were complete only after repeated recrystallizations and for further synthetic use, compounds *V*, slightly contaminated by *VI*, had to be used.



I



II

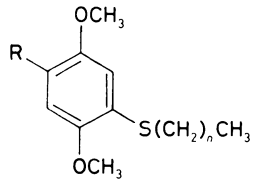


III

Compounds *Va* and *Vb* were transformed to nitriles *VIIa* and *VIIb* with sodium cyanide in dimethylformamide at 90–100°C. The nitriles were crystalline and were characterized by spectra. In the preparation of one batch of *VIIb* the crude product did not crystallize and chromatography on silica gel was necessary. The desired *VIIb* was eluted with the first fractions with benzene. In the last fractions, a small amount (some 3%) of a nitrogen-free and lower melting solid was eluted which was identified by spectra as the alcohol *VIIIb* which was evidently formed by hydrolysis of the starting *Vb*. Crystallization of *VIIb* of this experiment afforded a small amount (2–3%) of a different, higher melting solid which is assumed to be the ether *IXb*. This structure is in good agreement with the spectra. It could be formed from *VIIIb* by reaction with *Vb* in the presence of sodium cyanide as the base (Williamson reaction). An attempt to alkylate *VIIb* with diethyl bromomalonate[19] in dimethylformamide in the presence of sodium hydride was unsuccessful. The inhomogeneous product obtained was chromatographed on silica gel which recovered in the first fractions a part of the starting *VIIb*. From the last fractions some 5% of a higher

melting solid were isolated, identified by spectra as the dinitrile *Xb*. The IR spectrum showed the presence of the R—CN fragment (band at 2 245 cm^{-1}) and the ^1H NMR spectrum – in addition to all the other hydrogen atoms expected – proved only one hydrogen on the benzylic carbon. The carbanion, formed primarily from *VIIb* by the action of sodium hydride, was most likely the precursor of *Xb*. Participation of the bromomalonic ester cannot be excluded.

Both nitriles *VIIa, b* were hydrolyzed with potassium hydroxide in boiling ethanol and afforded the expected acids *XIa, b*. Both of them crystallized from benzene as 2 : 1 solvates with benzene and their identity was confirmed by spectra. A different acid was unexpectedly obtained as a minor product from an unsuccessful attempt to alkylate *VIIb* with the crude diethyl 3-chloroglutarate[20] in dimethylformamide in the presence of sodium hydride. It was identified by analysis and spectra as *XIIb* and its formation is considered obscure; most of the starting *VIIb* was recovered unchanged.



IV, R = H
V, R = CH_2Cl
VI, R = CH_2–(2,6-OCH_3, 4-$S(CH_2)_nCH_3$)
VII, R = CH_2CN
VIII, R = CH_2OH
IX, R = CH_2OCH_2–(2,6-OCH_3, 4-$S(CH_2)_nCH_3$)

X, R = CH(CN)–CH(CN)–(2-OCH_3, 5-$S(CH_2)_nCH_3$, 6-OCH_3)
XI, R = CH_2COOH
XII, R = COOH
XIII, R = $CH_2CH_2NH_2$
XIV, R = CH_2CH_2NHCHO
XV, R = $CH_2CH_2NHCH_3$
XVI, R = $CH_2CH_2N(CH_3)_2$

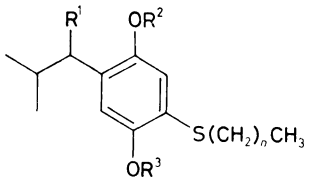
In formulae *IV–XX*: *a*, *n* = 4. *b*, *n* = 6

Nitriles *VIIa, b* were further reduced with aluminium hydride[21], obtained by reaction of lithium aluminium hydride and aluminium chloride, in a mixture of ether and tetrahydrofuran. Primary amines *XIIIa, b* were obtained. The oily bases were transformed to crystalline hydrogen maleates and the characterization was completed by recording the mass spectra. The amines *XIIIa, b* were formylated by the acetic-formic anhydride[22] to give in high yields the formamides *XIVa, b* as crystalline solids (structures confirmed by spectra). The following reduction with diborane, generated "in situ" by reaction of sodium borohydride with boron trifluoride etherate in tetrahydrofuran (method[23,24]), afforded the methylamino compounds

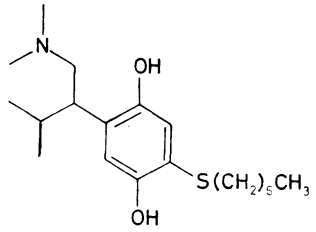
XVa, b. The oily bases were transformed to crystalline hydrogen maleates and characterization was again completed by the mass spectra. Methylation of the primary amines *XIIIa, b* by refluxing with formic acid and aqueous formaldehyde (Eschweiler–Clarke method[25]) gave the tertiary amines *XVIa, b*. The first of them (*XVIa*) was crystalline, its spectra were recorded and it was transformed to the hydrogen maleate. The second (*XVIb*) was oily, was transformed to the crystalline hydrogen maleate and the mass spectrum confirmed its composition.

In contrast to the mentioned unsuccessful attempts to alkylate *VIIb* with diethyl bromomalonate and diethyl 3-chloroglutarate, its alkylation with 2-propyl bromide in dimethylformamide in the presence of sodium hydride proceeded as expected and crystalline *XVIIb* was obtained in a satisfactory yield. Its structure was corroborated by spectra. Its reduction with aluminium hydride[21] to the primary amine was complicated by partial demethylation. We try to explain this demethylation by the presence of some unreacted aluminium chloride in the solution of aluminium hydride, obtained by reaction of lithium aluminium hydride with aluminium chloride in ether. In this connection it is surprising that similar reductions of *VIIa, b* proceeded without partial demethylation. We first assumed that the demethylation proceeded on the seemingly less hindered methoxyl, i.e. in *o*-position to heptylthio. The spectra, however, gave evidence of the opposite. The broad signal at 4·60 to 5·60 ppm in the ^{1}H NMR spectrum, corresponding to NH_2, is significantly shifted to lower values of the field and indicates rather the content of 3 H instead of 2 H. This has to be explained by the existence of a strong intramolecular hydrogen bond (see also the signal of CH_2N) between the amino group and the phenolic hydroxyl $H_2N\cdots H—O—Ar$. This is only possible if the demethylation took place on the methoxyl *ortho* to the aminoalkyl side chain and therefore we formulate the product as *XVIIIb*. IR spectrum shows a band at 2 622 cm^{-1} which can be explained as corresponding to the ammonium group NH_3^+ of the inner salt or more likely to the hydrogen bond mentioned. The nitrile *VIIa* was similarly alkylated with 2-propyl bromide but the product *XVIIa* did not crystallize and was, therefore, reduced with aluminium hydride in crude state. The reaction, likewise, was accompanied by partial demethylation and the product obtained is formulated "per analogiam" as *XVIIIa*. The oily base was transformed to the crystalline hydrogen maleate and the mass spectrum confirmed the elemental composition. The amine *XVIIIa* was formylated with acetic-formic anhydride[22] and the mixture obtained was chromatographed on silica gel. The main oily product, considered to be a mixture of the N-formyl derivative with the corresponding formic ester, was directly reduced with diborane similarly as in the synthesis of *XVa, b*. Chromatography of the crude product afforded the homogeneous oily *XIXa* which was transformed to the crystalline hydrogen maleate. The mass spectrum confirmed the elemental composition and also the structure. The amine *XVIIIb* was N-methylated by the Eschweiler–Clarke method[25] and gave the oily tertiary amine *XXb* whose characterization was similar like in the

preceding case. This amine (*XXb*) was demethylated first with boron tribromide in chloroform at 10°C. The crystalline product was identified as *XXI* hydrobromide hemihydrate by analysis and spectra; the mass spectrum confirmed the elemental composition. The demethylation of *XXb* was also carried out with iodotrimethylsilane (chlorotrimethylsilane/sodium iodide reagent[26]) in acetonitrile. The product was *XXI* hydroiodide which was soluble in chloroform and was eluted from the silica gel column with ethyl acetate. Its spectra were practically identical with those of the hydrobromide. Compound *XXI* is unstable and turns greenish on the air, evidently by formation of the corresponding quinhydrone.



XVII, R^1= CN ; R^2= R^3= CH_3
XVIII, R^1= CH_2NH_2 ; R^2= H ; R^3= CH_3
XIX, R^1= CH_2NHCH_3 ; R^2= H ; R^3= CH_3
XX, R^1= $CH_2N(CH_3)_2$; R^2= H ; R^3= CH_3



XXI

The acids and the amines (in the form of salts described in the Experimental) were pharmacologically tested, mainly for CNS effects. The compounds were administered orally and the doses given were calculated per bases. Acute toxicity in mice, LD_{50} in mg/kg: *XIa*, >1 000; *XIb*, >1 000; *XIIIa*, >1 000; *XIIIb* 2 000; *XVa*, 780; *XVb*, >1 000; *XVIa*, 718; *XVIb*, 933; *XIXa*, 476; *XXI*, 416.

Compounds *XIIIa*, *XVIa*, *XIXa*, and *XXI* significantly inhibited the spontaneous locomotor activity of mice (photo-cell method of Dews) at doses of 10 mg/kg; in the same doses *XIIIb*, *XVa*, *XVb*, and *XVIb* were inactive. Compounds *XIIIa*, *XVa*, and *XVIa* significantly increased the hypothermic effect of reserpine in mice: only *XVa* had in the same dose hypothermic effect "per se"; *XIIIb*, *XVb*, and *XVIb* were inactive. Only *XIIIb* in the dose of 25 mg/kg had significant antagonistic effect in the test of reserpine ptosis in mice. The same compound had significant antagonistic effect at 6·25 mg/kg in the test of reserpine-induced gastric ulcers in rats (*XVb* had a similar effect at 50 mg/kg; *XIIa*, *XVa*, *XVIa*, and *XVIb* were inactive at 50 mg/kg). The very active *XIIIb* was found devoid of anti-ulcer action towards indomethacine-induced gastric ulcers in rats (at 10 mg/kg), it had no significant anticholinergic activity in the oxotremorine test in mice (ED_{50} > 30 mg/kg), and it had only weak affinity to the muscarinic receptors in the brain (inhibition of binding of 0·5 nM [^{3}H]quinuclidinyl benzilate in the rat brain, IC_{50} = 8 931 nmol.

. l^{-1}). None of the amines had significant affinity to the imipramine and desipramine binding sites in the rat hypothalamus and to the dopamine receptors in the rat brain striatum ([^{3}H]spiperone was used as the ligand). Compounds *XVIa*, *XVIb*, *XIXa*, and *XXI* in doses of 10 mg/kg were devoid of analgetic activity in the writhing test in mice and *XIXa* and *XXI* were inactive in the same doses as anticonvulsants in the electroshock test in mice. The acids *XIa* and *XIb* in doses of 100 mg/kg were inactive as anti-inflammatory agents (carrageenan and adjuvant oedema in rats). In conclusion: only *XIIIb* (VÚFB-16 519) proved interesting pharmacodynamic properties, specifically in the line of antireserpine effects (potential antidepressant).

Some of the compounds were also tested for antimicrobial activity in vitro (minimum inhibitory concentrations in mg/l are given unless they exceed 100 mg/l): *Streptococcus β-haemolyticus*, *XIIIa* 100, *XIIIb* 50, *XVa* 100, *XVb* 50, *XVIb* 100; *Streptococcus faecalis*, *XIIIa* 100, *XIIIb* 25, *XVa* 100, *XVb* 12·5, *XVIb* 25; *Staphylococcus pyogenes aureus*, *XIIIa* 50, *XIIIb* 1·6, *XVa* 25, *XVb* 6·2, *XVIa* 100, *XVIb* 6·2; *Escherichia coli*, *XIIIa* 100, *XVb* 50, *XVIb* 100; *Proteus vulgaris*, *XIIIa*, 100, *XVb* 50, *XVIb* 100; *Saccharomyces pasterianus*, *XIIIb* 25, *XVb* 50, *XVIb* 25; *Trichophyton mentagrophytes*, *XIIIb* 25, *XVb* 25, *XVIa* 50, *XVIb* 12·5; *Candida albicans*, *XVIa* 50.

EXPERIMENTAL

The melting points were determined in the Mettler FP-5 melting point recorder; the samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at a suitably elevated temperature. UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (in Nujol, ν in cm^{-1}) with a Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (in $CDCl_3$ unless stated otherwise, δ in ppm, J in Hz) with the CW-NMR spectrometer Tesla BS 487C (80 MHz), and the mass spectra (m/z, fragments and/or %) with MCH 1 320 and/or Varian MAT 44S (GC–MS) spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

1,4-Dimethoxy-2-(pentylthio)benzene (*IVa*)

A solution of sodium ethoxide (from 9·75 g Na and 200 ml ethanol) was treated with 63·6 g 2,5-dimethoxythiophenol[17] and 67·4 g pentyl bromide and the mixture was stirred and refluxed for 5 h. Ethanol was distilled off, the residue was diluted with 250 ml water and the mixture was extracted with benzene. The dried extract was processed by distillation; 86·8 g (97%) b.p. 139 to 142°C/0·1 kPa, m.p. 38–39°C (methanol). UV spectrum; 251·5 (3·78), 303 (3·75). IR spectrum: 798, 810, 825, 884 (2 adjacent and solitary Ar–H); 1 040, 1 065, 1 188, 1 220 ($ArOCH_3$); 1 490, 1 582, 1 590, 3 000, 3 050, 3 080 (Ar). ^{1}H NMR spectrum: 0·85 bt, 3 H ($C-CH_3$); 1·10–1·70 m, 6 H (3 × CH_2 in positions 2, 3, 4 of pentyl); 2·82 t, 2 H (SCH_2, J = 7·0); 3·72 s and 3·78 s, 3 and 3 H (2 × OCH_3); 6·70 m, 3 H (ArH). For $C_{13}H_{20}O_2S$ (240·4) calculated: 64·95% C, 8·39% H, 13·34% S; found: 65·18% C, 8·49% H, 13·32% S.

2-(Heptylthio)-1,4-dimethoxybenzene (*IVb*)

Similar reaction of sodium ethoxide (from 6·30 g Na and 130 ml ethanol) with 46·7 g 2,5-dimethoxythiophenol[17] and 50·3 g heptyl bromide gave 73·5 g (theoretical) of homogeneous *IVb* melting at 46—47°C. The melting point remained unchanged after crystallization from methanol. UV spectrum: 250 (3·78), 301 (3·75). IR spectrum: 800, 810, 822, 832, 885 (2 adjacent and solitary Ar–H); 1 042, 1 065, 1 220 ($ArOCH_3$); 1 484, 1 580, 1 590, 3 045, 3 080, 3 100 (Ar). ^{1}H NMR spectrum: 0·88 bt, 3 H ($C–CH_3$); 1·30 bs, 8 H (4 × CH_2 in positions 2, 3, 4, 5 of heptyl); 1·60 m, 2 H (CH_2 in position 6 of heptyl); 2·88 t, 2 H (SCH_2, J = 7·0); 3·74 s and 3·80 s, 3 and 3 H (2 × OCH_3); 6·60—6·90 m, 3 H (ArH). For $C_{15}H_{24}O_2S$ (268·4) calculated: 67·12% C, 9·02% H, 11·94% S; found: 67·37% C, 9·18% H, 11·87% S.

2-(Chloromethyl)-1,4-dimethoxy-5-(pentylthio)benzene (*Va*)

A mixture of 10 ml 39% aqueous formaldehyde, 5 ml hydrochloric acid and 20 ml dioxane was saturated for 10 min with HCl (the temperature of the mixture rose spontaneously to 65°C). The stirred mixture was treated over 5 min with a solution of 12·2 g *IVa* in 10 ml dioxane, it was stirred for 30 min at 60—65°C, poured to 100 ml water, and extracted with ether. The extract was washed with water and processed. The residue (12·2 g) was crystallized from a mixture of acetone and light petroleum giving 0·6 g 2,2′,5,5′-tetramethoxy-4,4′-bis(pentylthio)diphenylmethane (*VIa*), m.p. 104—105°C (acetone). Mass spectrum: 492 (M^+, $C_{27}H_{40}O_4S_2$), 477 ($C_{26}H_{37}O_4S_2$), 461 ($C_{26}H_{37}O_3S_2$), 422 ($C_{22}H_{30}O_4S_2$), 390 ($C_{22}H_{30}O_4S$). IR spectrum: 859, 868 (solitary Ar–H); 1 040, 1 209 ($ArOCH_3$); 1 484, 1 590 (Ar). ^{1}H NMR spectrum: 0·88 bt, 6 H (2 × $C–CH_3$); 1·20—1·90 m, 12 H (6 × CH_2 in positions 2,3,4,2′,3′,4′ of the pentyls); 2·89 t, 4 H (2 × SCH_2, J = 7·0); 3·73 s and 3·78 s, 6 and 6 H (4 × OCH_3); 3·90 s, 2 H ($ArCH_2Ar$); 6·63 s, 2 H (H-3, H-3′); 6·88 s, 2 H (H-6, H-6′). For $C_{27}H_{40}O_4S_2$ (492·8) calculated: 65·81% C, 8·18% H, 13·02% S; found: 65·66% C, 8·39% H, 13·04% S.

Evaporation of the mother liquor and crystallization of the residue from light petroleum gave 9·4 g (64%) of *Va*, m.p. 64—66°C. IR spectrum: 865 (solitary Ar–H); 1 039, 1 210 ($ArOCH_3$); 1 490, 1 575, 1 598 (Ar). ^{1}H NMR spectrum: 0·80 bt, 3 H ($C–CH_3$); 1·10—1·70 bm, 6 H (3 × × CH_2 in positions 2, 3, 4 of pentyl); 2·80 bt, 2 H (CH_2S); 3·75 s, 6 H (2 × OCH_3); 4·52 s, 2 H ($ArCH_2Cl$); 7·60 s and 6·75 s, 1 and 1 H (2 ArH). For $C_{14}H_{21}ClO_2S$ (288·8) calculated: 58·22% C, 7·33% H, 12·27% Cl, 11·10% S; found: 58·49% C, 7·56% H, 12·03% Cl, 11·37% S.

2-(Chloromethyl)-5-(heptylthio)-1,4-dimethoxybenzene (*Vb*)

A mixture of 20 ml 38% aqueous formaldehyde, 10 ml hydrochloric acid and 40 ml dioxane was saturated for 10 min with HCl and the mixture was similarly reacted (cf. preceding experiment) with 26·8 g *IVb* in 20 ml dioxane and similarly processed. Crystallization of the inhomogeneous residue (31·3 g) from 100 ml acetone gave 6·7 g 4,4′-bis(heptylthio)-2,2′,5,5′-tetramethoxydiphenylmethane (*VIb*), m.p. 99—100°C (acetone). Mass spectrum: 548 (M^+, $C_{31}H_{48}O_4S_2$), 533 ($C_{30}H_{45}O_4S_2$), 517 ($C_{30}H_{45}O_3S_2$), 450 ($C_{24}H_{34}O_4S_2$), 418 ($C_{24}H_{34}O_4S$). IR spectrum: 866 (solitary Ar–H); 1 039, 1 210 ($ArOCH_3$); 1 487, 1 592 (Ar). ^{1}H NMR spectrum: 0·88 bt, 6 H (2 × $C–CH_3$); 1·30 bs, 16 H (8 × CH_2 in positions 2,3,4,5,2′,3′,4′,5′ of heptyls); 1·50 bm, 4 H (2 × CH_2 in positions 6,6′ of heptyls); 2·85 t, 4 H (2 × SCH_2, J = 7·0); 3·72 s and 3·78 s, 6 and 6 H (4 × OCH_3); 3·89 s, 2 H ($ArCH_2Ar$); 6·61 s, 2 H (H-3, H-3′); 6·84 s, 2 H (H-6, H-6′). For $C_{31}H_{48}O_4S_2$ (548·8) calculated: 67·84% C, 8·82% H, 11·68% S; found: 67·78% C, 9·06% H, 11·80% S.

Processing of the mother liquor gave 19·05 g (60%) of *Vb*, m.p. 66—69°C (light petroleum). UV spectrum: infl. 224 (4·16), 256 (3·88), 305 (3·90). IR spectrum: 869 (solitary Ar–H); 1 040,

1 215 ($ArOCH_3$); 1 490, 1 575, 1 600 (Ar). ^1H NMR spectrum: 0·79 bt, 3 H ($C-CH_3$); 1·20 bs, 8 H (4 × CH_2 in positions 2,3,4,5 of heptyl); 1·40 bm, 2 H (CH_2 in position 6 of heptyl); 2·80 bt, 2 H (CH_2S); 3·75 s, 6 H (2 × OCH_3); 4·51 s, 2 H ($ArCH_2Cl$); 6·68 s and 6·72 s, 1 and 1 H (H-3, H-6). For $C_{16}H_{25}ClO_2S$ (316·9) calculated: 60·64% C, 7·95% H, 11·19% Cl, 10·12% S; found: 60·90% C, 8·22% H, 10·90% Cl, 10·00% S.

(2,5-Dimethoxy-4-(pentylthio)phenyl)acetonitrile (*VIIa*)

The suspension of 82·2 g *Va* in 315 ml dimethylformamide was treated with 41·5 g NaCN, the mixture was stirred for 30 min at 40°C and for 5 h at 95°C. After cooling it was diluted with 500 ml water and extracted with benzene. Processing of the extract gave 90 g of a crude product which was crystallized first from 130 ml ethanol and then from 210 ml cyclohexane giving 68·2 g (86% of *VIIa*, m.p. 85—88°C (cyclohexane). UV spectrum: infl. 222 (4·15), 256 (3·87), 306 (3·89). IR spectrum: 820, 843 (solitary Ar–H); 1 035, 1 205, 1 215 ($ArOCH_3$); 1 497, 1 600 (Ar); 2 240 (R–CN). ^1H NMR spectrum: 0·88 bt, 3 H ($C-CH_3$); 1·20—1·80 m, 6 H (3 × CH_2 in positions 2,3,4 of pentyl); 2·88 t, 2 H (SCH_2, J = 7·0); 3·68 s, 2 H ($ArCH_2CN$); 3·82 s and 3·88 s, 3 and 3 H (2 × OCH_3); 6·84 s, 1 H (H-3); 6·88 s, 1 H (H-6). For $C_{15}H_{21}NO_2S$ (279·4) calculated: 64·48% C, 7·58% H, 5·01% N, 11·48% S; found: 64·67% C, 7·79% H, 4·91% N, 11·42% S.

(4-(Heptylthio)-2,5-dimethoxyphenyl)acetonitrile (*VIIb*)

A) A similar reaction of 25·3 g *Vb* with 12·65 g NaCN in 80 ml dimethylformamide gave 26 g of an inhomogeneous solid which was crystallized first from 50 ml methanol and then from 50 ml cyclohexane affording 17·3 g (71%) of *VIIb*, m.p. 69—71°C (light petroleum). UV spectrum: infl. 224 (4·14), 256 (3·86), 306 (3·88). IR spectrum: 860 (solitary Ar–H); 1 040, 1 212 ($ArOCH_3$); 1 490, 1 580, 1 598 (Ar); 2 240 (R–CN). ^1H NMR spectrum: 0·88 bt, 3 H ($C-CH_3$); 1·40 bs, 8 H (4 CH_2 in positions 2,3,4,5 of heptyl); 1·50 m, 2 H (CH_2 in position 6 of heptyl); 2·88 t, 2 H (SCH_2, J = 7·0); 3·65 s, 2 H ($ArCH_2CN$); 3·82 s and 3·87 s, 3 and 3 H (2 × OCH_3); 6·82 s, 1 H (H-3); 6·85 s, 1 H (H-6). For $C_{17}H_{25}NO_2S$ (307·5) calculated: 66·41% C, 8·20% H, 4·56% N, 10·43% S; found: 66·26% C, 8·41% H, 4·62% N, 10·48% S.

B) A similar reaction of 18·6 g crude *Vb* with 9·3 g NaCN in 60 ml dimethylformamide gave 19·2 g of an oily inhomogeneous product which was dissolved in 30 ml benzene and the solution was chromatographed on a column of 60 g silica gel using elution with benzene. The first fraction was 13·5 g of crude *VIIb* which was crystallized from ethanol. There were 0·5 g of an insoluble by-product which was purified by crystallization from a mixture of ethanol and benzene, melted then at 121·5—123°C and was identified as the non completely homogeneous bis(4-(heptylthio)-2,5-dimethoxybenzyl) ether (*IXb*). UV spectrum (saturated solution in methanol); 257, 306. IR spectrum: 860 (solitary Ar–H); 1 040, 1 109, 1 202 ($ArOCH_3$, ROR); 1 493, 1 598 (Ar). ^1H NMR spectrum: 0·88 bt, 6 H (2 × $C-CH_3$); 1·30 bs, 16 H (8 × CH_2 in positions 2,3,4,5,2′, 3′,4′,5′ of heptyls); 1·50 m, 4 H (2 × CH_2 in positions 6,6′ of heptyls); 2·88 t, 4 H (2 × SCH_2, J = 7·0); 3·77 s and 3·83 s, 6 and 6 H; 4·60 s, 4 H ($ArCH_2OCH_2Ar$); 6·82 s, 2 H (H-3, H-3′); 7·00 s, 2 H (H-6, H-6′). For $C_{32}H_{50}O_5S_2$ (578·8) calculated: 11·10% S; found: 11·22% S.

Processing of the ethanolic solution gave 8·8 g of *VIIb*, m.p. 67—70°C (light petroleum). The chromatography was continued and the last fractions afforded 0·65 g of a different crystalline substance melting after recrystallization from a mixture of cyclohexane and light petroleum at 56—57°C and identified as 4-(heptylthio)-2,5-dimethoxybenzyl alcohol (*VIIIIb*). Mass spectrum: 298 (M^+, $C_{16}H_{26}O_3S$), 281 ($C_{16}H_{25}O_2S$), 267 ($C_{15}H_{23}O_2S$), 200 ($C_9H_{12}O_3S$), 124 ($C_7H_8O_2$). UV spectrum: 255 (3·80), 304 (3·82). IR spectrum: 855, 863 (solitary Ar–H);

1 040, 1 200 (CH_2OH and $ArOCH_3$); 1 490, 1 600, 3 010 (Ar); 3 350, 3 465 (OH). ^1H NMR spectrum: 0·88 bt, 3 H (C–CH_3); 1·30 bs, 8 H (4 × CH_2 in positions 2,3,4,5 of heptyl); 1·50 m, 2 H (CH_2 in position 6 of heptyl); 2·40 bs, 1 H (OH); 2·81 t, 2 H (SCH_2, J = 7·0); 3·74 s and 3·78 s, 3 and 3 H (2 × OCH_3); 4·51 bs, 2 H ($ArCH_2O$); 6·79 s, 2 H (H-3, H-6). For $C_{16}H_{26}O_3S$ (298·4) calculated: 64·40% C, 8·78% H, 10·72% S; found: 64·54% C, 8·95H H, 10·60% S.

1,2-Bis(4-(heptylthio)-2,5-dimethoxyphenyl)ethane-1,2-dicarbonitrile (*Xb*)

A solution of 5·0 g *VIIb* in 50 ml dimethylformamide was treated at 55°C under nitrogen with 0·6 g 80% suspension of NaH in mineral oil, the mixture was stirred for 30 min, treated with 6·8 g diethyl bromomalonate[19], stirred for 6 h at 50°C, cooled, diluted with water and extracted with benzene. Processing of the extract gave 7·8 g of oil which was chromatographed on 200 g silica gel. A mixture of benzene and light petroleum eluted in the first fractions 3·0 g of the starting *VIIb* (m.p. 70·5—71·5°C). Benzene alone eluted then 0·5 g of a homogeneous fraction which crystallized from cyclohexane and was considered to be *Xb*, m.p. 125—127·5°C (cyclohexane). UV spectrum: infl. 227 (4·40), 262 (4·21), 310 (4·26). IR spectrum: 860 (solitary Ar–H); 1 038, 1 215 ($ArOCH_3$); 1 492, 1 564, 1 600, 3 015 (Ar); 2 245 (R–CN). ^1H NMR spectrum: 0·88 bt, 6 H (2 × C–CH_3); 1·00—1·80 m, 20 H (10 × CH_2 in positions 2,3,4,5,6,2′,3′,4′,5′,6′ of heptyls); 2·88 t, 4 H (2 × SCH_2, J = 7·0); 3·83 s and 3·89 s, 6 and 6 H (4 × OCH_3); 4·73 s, 2 H (2 × Ar–CH–CN); 6·80 s and 7·08 s, 2 and 2 H (H-3, H-3′, H-6, H-6′). For $C_{34}H_{48}O_4S_2$ (612·9) calculated: 66·60% C, 7·90% H, 4·57% N, 10·46% S; found: 66·55% C, 8·02% H, 4·51% N, 10·24% S.

2-(2,5-Dimethoxy-4-(pentylthio)phenyl)acetic Acid (*XIa*)

A mixture of 5·5 g *VIIa*, 15 ml ethanol, and 8·0 g KOH was refluxed for 7 h (bath temperature 140°C). After cooling it was diluted with water, the solution was washed with benzene and chloroform, acidified with hydrochloric acid, and the product was extracted with benzene. Processing of the extract gave 5·1 g (77%) of *XIa* which was purified by crystallization from a mixture of benzene and light petroleum, m.p. 100—101°C. The product is a 2 : 1 solvate with benzene. Mass spectrum: 298 (M^+, $C_{15}H_{22}O_4S$), 253 ($C_{14}H_{21}O_2S$), 227 ($C_{10}H_{11}O_4S$). IR spectrum: 860 (solitary Ar–H); 935, 1 210, 1 704, 2 540, 2 625, 2 720, infl. 3 150 (COOH); 1 040, 1 210 ($ArOCH_3$). ^1H NMR spectrum: 0·88 bt, 3 H (C–CH_3); 1·20—1·80 m, 6 H (3 × CH_2 in positions 2,3,4 of pentyl); 2·88 t, 2 H (SCH_2, J = 7·0); 3·60 s, 2 H ($ArCH_2CO$); 3·77 s and 3·82 s, 3 and 3 H (2 × OCH_3); 6·70 s, 1 H (H-3); 6·82 s, 1 H (H-6); 7·30 s, 3 H (0·5 C_6H_6); 10·75 bs, 1 H (COOH). For $C_{15}H_{22}O_4S$ + 0·5 C_6H_6 (337·5) calculated: 64·07% C, 7·47% H, 9·50% S; found: 64·16% C, 7·56% H, 9·68% S.

2-(4-(Heptylthio)-2,5-dimethoxyphenyl)acetic Acid (*XIb*)

Similar hydrolysis of 6·0 g *VIIb* with 8·0 g KOH in 10 ml ethanol gave 4·2 g (59%) of *XIb* solvate 2 : 1 with benzene, m.p. 85·5—86·5°C (benzene–light petroleum). Mass spectrum: 326 (M^+, $C_{17}H_{26}O_4S$), 281 ($C_{16}H_{25}O_2S$), 227 ($C_{10}H_{11}O_4S$). IR spectrum: 860 (solitary Ar–H); 935, 1 235, 1 705, 2 540, 2 620, 2 645, 2 720, infl. 3 100 (COOH); 1 040, 1 215 ($ArOCH_3$); 1 494, 1 600 (Ar). ^1H NMR spectrum: 0·88 bt, 3 H (C–CH_3); 1·30 bs, 8 H (4 CH_2 in positions 2,3,4,5 of heptyl); 1·50 bm, 2 H (CH_2 in position 6 of heptyl); 2·88 t, 2 H (SCH_2, J = 7·0); 3·61 s, 2 H ($ArCH_2COO$); 3·78 s and 3·83 s, 3 and 3 H (2 × OCH_3); 6·70 s, 1 H (H-3); 6·86 s, 1 H (H-6); 7·30 s, 3 H (0·5 C_6H_6); 10·15 flat band, 1 H (COOH). For $C_{17}H_{26}O_4S$ + 0·5 C_6H_6 (365·5) calculated: 65·72% C, 8·00% H, 8·77% S; found: 65·35% C, 8·10% H, 8·90% S.

4-(Heptylthio)-2,5-dimethoxybenzoic Acid (*XIIb*)

A solution of 15·0 g *VIIb* in 150 ml dimethylformamide was treated under nitrogen with 2·0 g 80% suspension of NaH in mineral oil, the mixture was stirred for 30 min at 40—45°C, treated with 42·5 g crude diethyl 3-chloroglutarate[20], stirred for further 5 h at 40—45°C, diluted with water, and extracted with benzene. Processing of the extract gave 55·1 g semi-solid residue from which 31·6 g volatile components (b.p. 95—98°C/0·2 kPa) were removed by distillation. The residue was chromatographed on 200 g silica gel. Benzene eluted 11·2 g of the starting *VIIb*, m.p. 70·5—71·5°C. Chloroform eluted then 4·7 g of a seemingly homogeneous fraction (TLC) from which a small amount (0·13 g) crystallized from light petroleum and was identified as *XIIb*, m.p. 142—144°C (ethanol). Mass spectrum: 312 (M^+, $C_{16}H_{24}O_4S$, 35), 214 ($C_9H_{10}O_4S$, 55), 199 ($C_8H_7O_4S$, 40). UV spectrum: 241 (4·27), 281·5 (4·22), 326 (4·24). IR spectrum: 879 (solitary Ar–H); 1 036, 1 220 ($ArOCH_3$); 952, 1 242, 1 268, 2 520, 2 600, infl. 3 100 (COOH); 1 491, 1 553, 1 600 (Ar); 1 680 (ArCOOH). ^{1}H NMR spectrum: 0·88 bt, 3 H ($C-CH_3$); 1·30 bs, 8 H (4 × CH_2 in positions 2,3,4,5 of heptyl); 1·60 bm, 2 H (CH_2 in position 6 of heptyl); 2·95 bt, 2 H (SCH_2, J = 7·0); 3·88 s, 3 H (OCH_3 in position 5); 4·05 s, 3 H (OCH_3 in position 2); 6·82 s, 1 H (H-3); 7·55 s, 1 H (H-6). For $C_{16}H_{24}O_4S$ (312·4) calculated: 61·52% C, 7·75% H,10·25% S; found: 61·62% C, 7·91% H, 10·14% S.

2-(2,5-Dimethoxy-4-(pentylthio)phenyl)ethylamine (*XIIIa*)

A solution of 15·7 g $AlCl_3$ in 110 ml ether was slowly added to a stirred solution of 5·7 g $LiAlH_4$ in 110 ml ether under nitrogen and the mixture was treated dropwise over 30 min with a solution of 22·4 g *VIIa* in 100 ml tetrahydrofuran. The mixture was stirred and refluxed for 6 h, after cooling decomposed with water and 20% NaOH, and extracted with benzene. Processing of the extract gave 22·7 g(theoretical) of oily *XIIIa*. Neutralization of 4·3 g of this product with 1·8 g maleic acid in acetone gave 5·3 g of hydrogen maleate, m.p. 158—161°C (ethanol). Mass spectrum:283 (M^+, $C_{15}H_{25}NO_2S$), 253 ($C_{14}H_{21}O_2S$), 183 ($C_9H_{11}O_2S$), 153 (C_8H_9OS). For $C_{19}H_{29}NO_6S$ (399·5) calculated: 57·12% C, 7·32% H, 3·51% N, 8·03% S; found: 56·96% C, 7·45% H, 3·58% N, 8·20% S.

2-(4-(Heptylthio)-2,5-dimethoxyphenyl)ethylamine (*XIIIb*)

The reagent was prepared from 11·0 g $AlCl_3$ and 4·0 g $LiAlH_4$ in 160 ml ether under nitrogen and was used to reduce similarly (like in the case of *XIIIa*) 17·3 g *VIIb*; 14·9 g (85%) of oily *XIIIb*. It was transformed to the hydrogen maleate, m.p. 156—158°C (ethanol). Mass spectrum: 311 (M^+, $C_{17}H_{29}NO_2S$), 281 ($C_{16}H_{25}O_2S$), 183 ($C_9H_{11}O_2S$). For $C_{21}H_{33}NO_6S$ (427·6) calculated: 58·99% C, 7·78% H, 3·28% N, 7·50% S; found: 59·06% C, 8·08% H, 3·44% N, 7·68% S.

N-(2-(2,5-Dimethoxy-4-(pentylthio)phenyl)ethyl)formamide (*XIVa*)

A mixture of 10·0 g acetic anhydride and 5·0 g 98% formic acid was heated for 2 h to 60°C and the reagent formed was added under stirring to 9·6 g *XIIIa*. The solution formed was allowed to stand at room temperature for 24 h, diluted with 50 ml water, neutralized with 100 ml 10% NaOH, and extracted with benzene. Processing of the extract gave 10·7 g of a solid residue which was crystallized from ethanol and then from cyclohexane; 10·5 g (theoretical) of *XIVa*, m.p. 81·5—83°C. UV spectrum: 254 (3·81), 304 (3·85). IR spectrum: 855 (solitary Ar–H); 1 040, 1 205, 1 258 ($ArOCH_3$); 1 495, 1 600, 3 010, 3 050 (Ar); 1 545, 1 650, 1 680 (RNHCHO); 3 275 (NH). ^{1}H NMR spectrum: 0·78 bt, 3 H ($C-CH_3$); 1·00—1·80 m, 6 H (3 × CH_2 in positions 2, 3,4 of pentyl); 2·70 m, 4 H (CH_2SArCH_2); 3·38 m, 2 H (NCH_2); 3·68 s and 3·72 s, 3 and 3 H (2 ×

× OCH_3); 5·90 bs, 1 H (NH); 6·58 s and 6·72 s, 1 and 1 H (H-3, H-6); 8·01 bs, 1 H (CHO). For $C_{16}H_{25}NO_3S$ (311·4) calculated: 61·70% C, 8·09% H, 4·50% N, 10·30% S; found: 62·02% C, 8·24% H, 4·55% N, 10·30% S.

N-(2-(4-Heptylthio)-2,5-dimethoxyphenyl)ethyl)formamide (*XIVb*)

The reagent was prepared from 6·0 g acetic anhydride and 3·0 g 99·7% formic acid and reacted similarly (like in the case of *XIVa*) with 6·8 g *XIIIb*; 6·2 g (83%) of *XIVb*, m.p. 83·5—84°C (cyclohexane–light petroleum). UV spectrum: infl. 223 (4·14), 254 (3·85), 303 (3·87). IR spectrum: 845 (solitary Ar–H); 1 034, 1 212 ($ArOCH_3$); 1 494, 1 594 (Ar); 1 546, 1 655 (RNHCHO); 3 030, 3 220 (NH). ^{1}H NMR spectrum: 0·80 bt, 3 H ($C-CH_3$); 1·00—1·70 m, 10 H (5 × CH_2 in positions 2,3,4,5,6 of heptyl); 2·80 m, 4 H (CH_2SArCH_2); 3·48 m, 2 H (NCH_2); 3·74 s and 3·80 s, 3 and 3 H (2 × OCH_3); 6·00 bs, 1 H (NH); 6·62 s and 6·78 s, 1 and 1 H (H-3, H-6); 8·09 bs, 1 H (CHO). For $C_{18}H_{29}NO_3S$ (339·5) calculated: 63·68% C, 8·61% H, 4·13% N, 9·44% S; found: 63·98% C, 8·89% H, 4·10% N, 9·58% S.

N-Methyl-2-(2,5-dimethoxy-4-(pentylthio)phenyl)ethylamine (*XVa*)

A stirred solution of 10·58 g *XIVa* in 100 ml tetrahydrofuran was treated under nitrogen with 3·7 g $NaBH_4$ and then 11·7 ml $BF_3.O(C_2H_5)_2$. The mixture was stirred for 1 h at room temperature and refluxed for 3 h. After standing overnight the mixture was decomposed under stirring by slow addition of 60 ml 1 : 1 dilute hydrochloric acid, made alkaline with 20% NaOH, and extracted with benzene. Processing of the extract gave 9·7 g of the crude base which was dissolved in 25 ml ether and the solution was neutralized with a solution of 3·78 g maleic acid in 20 ml acetone. The precipitated product was filtered and crystallized from 30 ml ethanol; 8·9 g (63%) of *XVa* hydrogen maleate, m.p. 121·5—123°C (ethanol). Mass spectrum: 297 (M^+, $C_{16}H_{27}NO_2S$), 254 ($C_{14}H_{22}O_2S$), 44 (C_2H_6N). For $C_{20}H_{31}NO_6S$ (413·5) calculated: 58·09% C, 7·56% H, 3·39% N, 7·75% S; found: 58·32% C, 7·78% H, 3·33% N, 7·69% S.

N-Methyl-2-(4-(heptylthio)-2,5-dimethoxyphenyl)ethylamine (*XVb*)

Compound *XIVb* (5·9 g) in 50 ml tetrahydrofuran was similarly reduced with diborane prepared "in situ" from 1·9 g $NaBH_4$ and 6·0 ml $BF_3.O(C_2H_5)_2$ and the mixture was similarly processed; 6·45 g (84%) of *XVb* hydrogen maleate, m.p. 123—124°C (ethanol–acetone). Mass spectrum: 325 (M^+, $C_{18}H_{31}NO_2S$), 282 ($C_{16}H_{26}O_2S$), 44 (C_2H_6N). For $C_{22}H_{35}NO_6S$ (441·6) calculated: 59·83% C, 7·99% H, 3·17% N, 7·26% S; found: 59·98% C, 8·17% H, 3·08% N, 7·37% S.

N,N-Dimethyl-2-(2,5-dimethoxy-4-(pentylthio)phenyl)ethylamine (*XVIa*)

A mixture of 8·3 g *XIIIa*, 8·0 ml formic acid and 6·5 ml 40% aqueous formaldehyde was heated for 5·5 h to 100°C. After cooling it was made alkaline with 80 ml 20% NaOH and extracted with benzene. Processing of the extract gave 8·8 g (96%) of practically pure *XVIa*, m.p 51—55°C (light petroleum). UV spectrum: infl. 222·5 (4·15), 254 (3·86), 304 (4·06). IR spectrum: 865 (solitary Ar–H); 1 040, 1 205 ($ArOCH_3$); 1 490, 1 600 (Ar); 2 760, 2 780, 2 820 ($N-CH_3$). ^{1}H NMR spectrum: 0·80 bt, 3 H ($C-CH_3$); 1·00—1·70 m, 6 H (3 × CH_2 in positions 2,3,4 of pentyl); 2·20 s, 6 H (2 × OCH_3); 2·20—2·90 m, 6 H ($CH_2SArCH_2CH_2N$); 3·70 s and 3·75 s, 3 and 3 H (2 × × OCH_3); 6·60 s and 6·73 s, 1 and 1 H (H-3, H-6). For $C_{17}H_{29}NO_2S$ (311·5) calculated: 65·55% C, 9·39% H, 4·50% N, 10·29% S; found: 65·45% C, 9·35% H, 4·32% N, 10·24% S.

Hydrogen maleate, m.p. 103—104·5°C (acetone–ether). For $C_{21}H_{33}NO_6S$ (427·5) calculated: 59·00% C, 7·78% H, 3·27% N, 7·50% S; found: 59·28% C, 7·99% H, 3·32% N, 7·62% S.

N,N-Dimethyl-2-(4-(heptylthio)-2,5-dimethoxyphenyl)ethylamine (*XVIb*)

Similar reaction of 5·0 g *XIIIb*, 5·0 ml 98% formic acid and 4·0 ml 40% aqueous formaldehyde gave 5·2 g of the crude base which was transformed to 5·05 g (69%) of *XVIb* hydrogen maleate, m.p. 105·5—107°C (acetone–ether). Mass spectrum: 339 (M^+, $C_{19}H_{33}NO_2S$), 295 ($C_{17}H_{27}O_2S$), 281 ($C_{16}H_{25}O_2S$), 183 ($C_9H_{11}O_2S$), 153 (C_8H_9OS), 58 (C_2H_6N). For $C_{23}H_{37}NO_6S$ (455·6) calculated: 60·63% C, 8·19% H, 3·07% N, 7·04% S; found: 60·73% C, 8·34% H, 3·23% N, 7·10% S.

2-(4-(Heptylthio)-2,5-dimethoxyphenyl)-3-methylbutyronitrile (*XVIIb*)

A solution of 5·0 g *VIIb* in 50 ml dimethylformamide was stirred and treated at 40°C under nitrogen with 0·6 g 80% NaH suspension (in mineral oil), the mixture was stirred for 30 min, treated with 3·5 g 2-propyl bromide, and heated for 6 h to 60°C. After cooling the mixture was diluted with water and extracted with benzene. Processing of the extract gave 5·8 g on inhomogeneous material which was chromatographed on 75 g silica gel. After an oily first fraction, a mixture of benzene and light petroleum(1 : 1) eluted 2·6 g (46%) of practically homogeneous *XVIIb*, m.p. 32·5—34·5°C (methanol). UV spectrum: infl. 225 (4·13), 257·5 (3·93), 307 (3·93). IR spectrum: 1 042, 1 204 ($ArOCH_3$); 1 490, 1 600, 3 010 (Ar); 2 240 (R–CN). ^{1}H NMR spectrum: 0·85 bt, 3 H (C–CH_3 of heptyl); 1·00 d, 6 H ($C(CH_3)_2$, J = 6·5); 1·10—1·80 m,10 H (5 × CH_2 in positions 2,3,4,5,6 of heptyl); 2·11 m, 1 H (CH in position 3 of butyronitrile); 2·89 t, 2 H (SCH_2, J = 7·0); 3·80 s and 3·88 s, 3 and 3 H (2 × OCH_3); 4·05 d, 1 H (Ar–CH–CN, J = 6·0); 6·80 s and 6·88 s, 1 and 1 H (H-3, H-6). For $C_{20}H_{31}NO_2S$ (349·5) calculated: 68·72% C, 8·94% H, 4·01% N, 9·17% S; found: 68·94% C, 9·24% H, 3·87% N, 9·16% S.

2-(4-(Heptylthio)-2-hydroxy-5-methoxyphenyl)-3-methylbutylamine (*XVIIIb*)

A solution of 6·0 g $AlCl_3$ in 40 ml ether was added dropwise to a stirred solution of 2·2 g $LiAlH_4$ in 40 ml ether under nitrogen and a solution of 10·8 g *XVIIb* in 50 ml ether was added dropwise over 1 h. The mixture was refluxed for 6 h, after cooling it was decomposed with 20 ml 20% NaOH, added dropwise, it was diluted with benzene, and the precipitated solid was filtered off. It was extracted with boiling benzene and the extract was combined with the organic layer of the filtrate. Processing gave the crude product which crystallized from ether; 5·5 g (52%) of *XVIIIb*, m.p. 110—111°C (benzene–light petroleum). IR spectrum: 855 (solitary Ar–H); 1 215 ($ArOCH_3$); 1 492, 1 589 (Ar); 2 620 ($H_2N\cdots H–O$ or NH_3^+); 3 280, 3 335 (NH_2). ^{1}H NMR spectrum: 0·75 bt, 3 H (C–CH_3 of heptyl); 0·70 d and 1·00 d, 3 and 3 H ($C(CH_3)_2$, J = 6·0); 1·10—1·80 m, 10 H (5 CH_2 in positions 2,3,4,5,6 of heptyl); 2·20 m, 2 H (Ar–CH–CH); 2·82 t, 2 H (SCH_2, J = 7·0); 2·88 dd and 3·48 dd, 1 and 1 H (NCH_2, J = 13·0; 2·0 and 13·0; 4·0); 3·76 s, 3 H (OCH_3); 4·60 to 5·60 flat signal, 3 H ($H_2N\cdots H–OAr$); 6·38 s, 1 H (H-6); 6·70 s, 1H (H-3). For $C_{19}H_{33}NO_2S$ (339·5) calculated: 67·22% C, 9·80% H, 4·13% N, 9·43% S; found: 67·41% C, 9·96% H, 4·36% N, 9·30% S.

Hydrogen maleate, m.p. 160—162°C (acetone–ether). Mass spectrum: 339 (M^+, $C_{19}H_{33}$·.NO_2S), 323 ($C_{18}H_{29}NO_2S$), 309 ($C_{17}H_{27}NO_2S$), 211 ($C_{11}H_{15}O_2S$). For $C_{23}H_{37}NO_6S$ (455·5) calculated: 60·64% C, 8·19% H, 3·08% N, 7·03% S; found: 60·79% C, 8·37% H, 3·14% N, 7·20% S.

2-(2-Hydroxy-5-methoxy-4-(pentylthio)phenyl)-3-methylbutylamine (*XVIIIa*)

A solution of 30 g *VIIa* in 200 ml dimethylformamide was treated at 40—50°C under nitrogen with 4·0 g 80% NaH over 30 min and then with 21 g 2-propyl bromide. The mixture was stirred

for 6 h at 60°C, cooléd, diluted with water and extracted with benzene. Processing of the extract gave a crude product which was chromatographed on 180 g silica gel. Elution with benzene gave 20·1 g of almost homogeneous *XVIIa* which was reduced without characterization with the reagent, prepared from 10 g $AlCl_3$ and 3·7 g $LiAlH_4$ in 240 ml ether under nitrogen. Similar processing like in the preceding case gave 18·2 g of crude *XVIIIa* which was transformed to the hydrogen maleate (18·4 g, 40%), m.p. 107—110°C (ethanol–ether). Mass spectrum: 311 (M^+, $C_{17}H_{29}$.NO_2S). For $C_{21}H_{33}NO_6S$ (427·6) calculated: 58·99% C, 7·78% H, 3·28% N, 7·50% S; found: 58·70% C, 7·83% H, 3·27% N, 7·62% S.

N-Methyl-2-(2-hydroxy-5-methoxy-4-(pentylthio)phenyl)-3-methylbutylamine (*XIXa*)

A mixture of 12 g acetic anhydride and 6·0 g 99% formic acid was heated for 2 h to 60°C and added to 12·6 g *XVIIIa*. After stirring for a few minutes the mixture was allowed to stand for 24 h at room temperature, poured into water, and extracted with benzene. Evaporation of the extract gave a mixture which was chromatographed on 220 g silica gel. The benzene and benzene–chloroform eluates were discarded and the chloroform eluates were combined and evaporated. The residue (11·8 g) was dissolved in 100 ml tetrahydrofuran and reduced with diborane, prepared from 3·8 g $NaBH_4$ and 12 ml $BF_3.O(C_2H_5)_2$. The mixture was stirred for 1 h at room temperature and refluxed for 4 h. After cooling it was diluted with 100 ml benzene and decomposed with 60 ml dilute hydrochloric acid (1 : 1), added dropwise. It was made alkaline with 50 ml 20% NaOH and at the end with NH_4OH and the mixture was extracted with benzene. The extract was evaporated and the residue was chromatographed on 250 g neutral Al_2O_3 (activity II). The benzene eluates were discarded and the chloroform eluates gave by evaporation 3·73 g (28%) of almost homogeneous *XIXa*. Neutralization with maleic acid in acetone afforded the hydrogen maleate, m.p. 138—139°C (acetone–ether). Mass spectrum: 325 (M^+, $C_{18}H_{31}NO_2S$, 10), 282 ($C_{16}H_{26}O_2S$, 39), 239 ($C_{13}H_{19}O_2S$, 10), 211 ($C_{11}H_{15}O_2S$, 8), 169 ($C_8H_9O_2S$, 4), 98 ($C_6H_{12}N$, 7), 44 (100). For $C_{22}H_{35}NO_6S$ (441·6) calculated: 59·84% C, 7·99% H, 3·17% N, 7·26% S; found: 60·01% C, 7·98% H, 3·34% N, 7·37% S.

N,N-Dimethyl-2-(4-(heptylthio)-2-hydroxy-5-methoxyphenyl)-3-methylbutylamine (*XXb*)

A mixture of 12·3 g *XVIIIb*, 13 ml 98% formic acid and 10 ml 40% aqueous formaldehyde was heated for 7 h to 100°C. After cooling it was made alkaline with 20% NaOH and extracted with benzene. Processing of the extract gave 13·0 g of crude oily *XXb* which was neutralized with 4·0 g maleic acid in ether giving 15·6 g (89%) of *XXb* hydrogen maleate, m.p. 134—136°C (acetone–ether). Mass spectrum: 367 (M^+, $C_{21}H_{37}NO_2S$), 324 ($C_{18}H_{30}NO_2S$), 309 ($C_{18}H_{29}O_2S$), 267 ($C_{14}H_{21}NO_2S$). For $C_{25}H_{41}NO_6S$ (483·6) calculated: 62·09% C, 8·55% H, 2·90% N, 6·62% S; found: 62·19% C, 8·58% H, 3·16% N. 6·34% S.

N,N-Dimethyl-2-(4-(heptylthio)-2,5-dihydroxyphenyl)-3-methylbutylamine (*XXI*)

A) A solution of 7·5 g *XXb* in 50 ml chloroform was stirred and treated over 1 h with a solution of 10 g BBr_3 in 15 ml chloroform, added dropwise at 10°C. The mixture was stirred for 5 h at room temperature, after standing overnight it was treated with 50 ml ethanol at 10°C, stirred for 8 h, and evaporated at 50°C in vacuo. The residue was triturated with water and crystallized slowly; 7·9 g (87%) of *XXI* hydrobromide, m.p. 96—104°C. Instability of the product prevented its purification by crystallization. Analysis identified the product to be the hemihydrate. Mass spectrum: 353 (M^+, $C_{20}H_{35}NO_2S$, 1·7), 58 (100). UV spectrum: 253 (3·81), 311 (3·89). IR spectrum: 877 (solitary Ar–H); 1 179, 1 200 (ArOH); 1 511, 1 607 (Ar); 2 600, 2 725 (NH^+); 3 090, 3 170, 3 365, 3 540 (OH). ^1H NMR spectrum (CD_3SOCD_3): 0·70—1·10 m, 9 H (3 ×

× C–CH_3); 1·10—3·20 m, 14 H (6 × CH_2 of heptyl and Ar–CH–CH); 2·80 s, 6 H ($N(CH_3)_2$); 3·45 bm, 2 H (NCH_2); 6·68 s and 6·82 s, 1 and 1 H (H-3, H-6).

B) A solution of 4·25 g *XXb* in 80 ml acetonitrile was treated with 13·2 g NaI and 9·6 g chlorotrimethylsilane. The mixture was stirred for 8 h at room temperature and refluxed for 16 h. It was then diluted with ether, washed with water and a solution of $Na_2S_2O_3$, dried, and evaporated. The residue was chromatographed on 170 g silica gel. Ethyl acetate eluted 2·95 g (53%) of homogeneous *XXI* hydroiodide, m.p. 131—135°C (benzene–ethanol). Mass spectrum: 353 (M^+, $C_{20}H_{35}NO_2S$), 58 (100). UV spectrum: 253 (3·81), 311 (3·88). IR spectrum: 876 (solitary Ar–H); 1 176, 1 190 (ArOH); 1 510, 1 610 (Ar); 2 600, 2 725 (NH^+); 3 065, 3 100, 3 205, 3 400, 3 590 (OH). ^{1}H NMR spectrum is practically identical with that of the hydrobromide. For $C_{20}H_{36}$·.INO_2S (481·5) calculated: 49·89% C, 7·53% H, 26·36% I, 2·91% N, 6·66% S; found: 49·61% C, 7·68% H, 26·22% I, 2·93% N, 6·92% S.

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