POTENTIAL ANTIDEPRESSANTS: 2-(PHENYLTHIO)ARALKYLAMINES

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Reactions of 2-(phenylthio)benzyl chloride with dimethylamine, diethylamine, pyrrolidine, piperidine, morpholine, and 1-methylpiperazine afforded the title compounds *VI*—*XI*. Reaction of 2-(penylthio)benzaldehyde with nitromethane gave the nitrostyrene *XIV* which was reduced with lithium aluminium hydride to 2-(2-(phenylthio)phenyl)ethylamine (*XVI*). This was transformed to the N-methyl and N,N-dimethyl derivatives *XVIII* and *XIX*. The Claisen reaction of (2-(phenylthio)phenyl)acetonitrile with ethyl acetate afforded compound *XXI* which was cleaved by phosphoric acid to (2-(phenylthio)phenyl)acetone (*XX*). The Leuckart–Wallach reaction afforded the formamide *XXIII* which was used as starting material for preparing the amines *XXIV*—*XXVI*. The alternative approach to these compounds starting by reaction of the aldehyde *XII* with nitroethane was complicated by the fact that in addition to the nitropropene *XV* 2-(phenylthio)benzonitrile was also formed. The synthetic use of the inhomogeneous *XV* resulted then in mixtures of amines *XXIV*—*XXVI* with *IV*—*VI* which was followed by means of mass and ^{1}H NMR spectra. The amines *XXIV*—*XXVI* were oxidized to the sulfoxides *XXVII*—*XXIX*. The oily bases were transformed to crystalline salts and spectra of all homogeneous bases were recorded. Pharmacological testing showed the amine *VI* (VÚFB-15 370) to be a promising potential antidepressant. The amines *XI* and *XXV* showed also pharmacological profile of potential antidepressants.

The high degree of psychotropic activity of substituted 10-(1-piperazinyl)-10,11-dihydrodibenzo[*b*,*f*]thiepins (*I*) (refs[1–3]) induced us many years ago to investigate some open-ring analogues *II* (ref.[4]) which, however, did not show psychotropic activity. More recently[5] we found in compound *III* a potential antidepressant which reanimated our interest in 2-(arylthio)benzylamines, open models of compounds *I* and *III*. This type of compounds was also mentioned in a fictitious patent[6] describing only *IV* as a single characterized substance but mentioning and claiming a vast area of related structures.

The present paper deals with the synthesis and preliminary pharmacology of some 2-(phenylthio)benzylamines, the homologous 2-(2-(phenylthio)phenyl)ethylamines and 1-(2-(phenylthio)phenyl)-2-propylamines. In the first line, compound *VI* was

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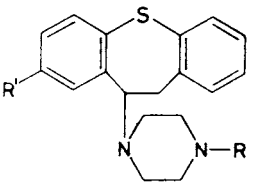
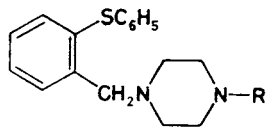
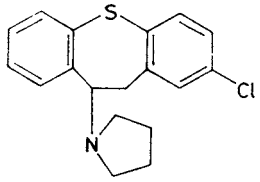
prepared by heating a solution of 2-(phenylthio)benzyl chloride[2,3] in chloroform, saturated with dimethylamine, to 75°C in autoclave. Compounds *VII*–*XI* were



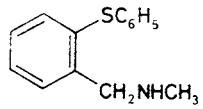
I



II

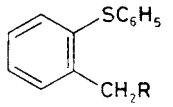


III



IV

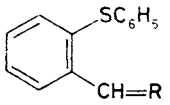
obtained by refluxing solutions of 2-(phenylthio)benzyl chloride[2,3] in chloroform with excessive diethylamine, pyrrolidine, piperidine, morpholine, and 1-methylpiperazine. The oily bases *VI*–*XI* were distilled and their ^{1}H NMR spectra were recorded. The bases were transformed to crystalline hydrogen maleates; the hydrogen maleate of *XI* was described[4] but the base *XI* was prepared differently.



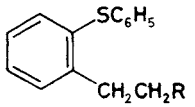
V, R = NH_2 *IX*, R = N⬡
VI, R = $N(CH_3)_2$ *X*, R = N⬡O
VII, R = $N(C_2H_5)_2$ *XI*, R = N⬡N–CH_3
VIII, R = N⬡

Further compounds to be prepared were the homologous 2-(2-(phenylthio)phenyl)-ethylamines. The aldehyde *XII* was chosen as the starting material. It was prepared by reaction of 2-chlorobenzaldehyde with thiophenol in hexamethylphosphoric triamide in the presence of aqueous sodium hydroxide according to a note in the literature[7] and was newly characterized by the semicarbazone. Refluxing the aldehyde *XII* with nitromethane in acetic acid in the presence of ammonium acetate (for method, cf. ref.[8]) gave the oily *XIV* which was characterized by spectra. It was reduced with lithium aluminium hydride in ether (for method, cf. refs[9,10]) to *XVI*.

This compound was formylated by heating with ethyl formate to 125–130°C in autoclave and the crude *XVII* obtained was reduced with lithium aluminium hydride to *XVIII*. Methylation of *XVI* by refluxing with formic acid and aqueous formaldehyde (Eschweiler–Clarke method[11]) gave *XIX*. The oily bases *XVI*, *XVIII*, and *XIX* were transformed to crystalline salts and the released homogeneous bases were used for recording the ^{1}H NMR spectra.



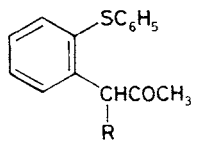
XII, R = =O
XIII, R = =N—NHCONH$_2$
XIV, R = =CH—NO$_2$
XV, R = =C(CH$_3$)—NO$_2$



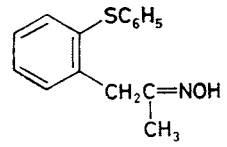
XVI, R = NH$_2$
XVII, R = NHCHO
XVII, R = NHCH$_3$
XIX, R = N(CH$_3$)$_2$

The last to be prepared were the 1-(2-(phenylthio)phenyl)-2-propylamines. Two approaches were used to this purpose. The first started with the preparation of (2-(phenylthio)phenyl)acetone (*XX*). The described transformation of phenylacetonitrile to phenylacetone[12] was used as a methodical model. (2-(Phenylthio)phenyl)-acetonitrile[2] was treated with sodium ethoxide in toluene and the anion formed was acylated with ethyl acetate to give *XXI*. Whereas its ^{1}H NMR spectrum confirmed clearly formula *XXI*, the IR spectrum indicated the product to be a mixture of *XXI* with the enol form (bands at 1 640 and 3 240 cm^{-1}). Reaction of *XXI* with phosphoric acid at 150–160°C gave *XX* which was characterized by spectra and transformed to the oxime *XXII*. The reduction of *XXII* with sodium and ethanol proceeded under an unusual cleavage reation: the obtained base afforded the hydrochloride $C_9H_{14}ClN$ (elemental analysis) and comparison of its melting point with the literature[13] value showed the product to be 1-phenyl-2-propylamine; thiophenol must have been the second cleavage product. Refluxing a mixture of *XX*, formamide and formic acid (Leuckart-Wallach reaction[11]) resulted in the formamide *XXIII* which was hydrolyzed with ethanolic potassium hydroxide to *XXIV*. Reduction of *XXIII* with lithium aluminium hydride afforded *XXV* and the Eschweiler–Clarke methylation[11] of *XXIV* gave *XXVI*. The bases *XXIV*–*XXVI* were oily, they were transformed to crystalline salts and ^{1}H NMR spectra of the released homogeneous bases were measured. The second approach to *XXIV*–*XXVI* started from *XII* which

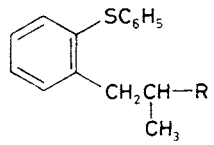
was reacted with nitroethane in boiling acetic acid in the presence of ammonium acetate (method, ref.[8]). The oily product was presumed to be *XV* but it was inhomogeneous and contained another important component. Its reduction with lithium aluminium hydride gave a mixture of bases which were transformed to hydrochlorides on the one hand, and to hydrogen maleates on the other. Repeated crystallization of these salts gave products with correct analyses but melting significantly lower than corresponding salts of *XXIV*, obtained by the first method. The ^{1}H NMR spectrum of the released base showed the presence of 30% of 2-(phenylthio)benzylamine (*V*). The precursor of this compound which was reduced and must have been the contaminant of *XV* was evidently 2-(phenylthio)benzonitrile. It was described in the literature[14] that aromatic aldehydes can afford directly nitriles by refluxing with nitroethane in acetic acid, especially in the presence of sodium acetate. For explaining this strange reaction it is necessary to assume the following steps: (i) rearrangement of nitroethane to ethanehydroxamic acid in the acid medium[15], (ii) cleavage of ethanehydroxamic acid to hydroxylamine, (iii) formation of the oxime of the starting aldehyde *XII*, and (iv) dehydration of the oxime. We met similar reaction quite recently[16]. Formylation of the inhomogeneous *XXIV* with ethyl formate at 120°C in autoclave gave inhomogeneous oily *XXIII* which was reduced with lithium aluminium hydride. The oily base obtained was transformed to the hydrogen oxalate which was characterized by the mass and ^{1}H NMR spectra. The mass spectrum identified the presence of two bases: *XXV*, $C_{16}H_{19}NS$ (*m/z* 257), and *IV* (cf. ref.[6]), $C_{14}H_{15}NS$ (*m/z* 229). The ^{1}H NMR spectrum determined the content of *IV* to be 40%. Repeated crystallization of this hydrogen oxalate afforded the homogeneous salt of *IV* (confirmed by the mass and ^{1}H NMR spectra). Methylation of the inhomogeneous *XXIV* with boiling formic acid and aqueous formaldehyde



XX, R = H
XXI, R = CN



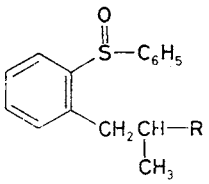
XXII



XXIII, R = NHCHO
XXIV, R = NH_2
XXV, R = $NHCH_3$
XXVI, R = $N(CH_3)_2$

gave inhomogeneous *XXVI* whose hydrogen maleate had the same melting point like the compound prepared by the first method and its analysis was correct. Nonetheless, the mass spectrum proved the presence of *VI* and ^{1}H NMR spectrum determined its content to be 35%.

Compounds *XXIV–XXVI* were oxidized with hydrogen peroxide in acetic acid at room temperature to the corresponding sulfoxides *XXVII–XXIX*. The oily bases were transformed to crystalline hydrogen maleates and the products were characterized by mass spectra, IR spectra (band of S—O at 1 030–1 058 cm^{-1}) and polarographic reduction.



XXVII, R = NH_2
XXVIII, R = $NHCH_3$
XXIX, R = $N(CH_3)_2$

The compounds prepared were pharmacologically tested on the one hand as potential antidepressants, and by methods of the general screening on the other. They were administered orally (unless stated otherwise) in the form of salts, described in Experimental; the doses given were calculated per bases.

Acute toxicity in mice (LD_{50} in mg/kg): *VI*, 211 (50 i.v.); *VII*, 243 (30 i.v.); *VIII*, 163 (30 i.v.); *IX*, 269 (50 i.v.); *X*, 804 (125 i.v.); *XI*, 360 (30 i.v.); *XVI*, 525; *XVIII*, 40 i.v.; *XIX*, 288 (40 i.v.); *XXIV*, 158, *XXV*, 216; *XXVI*, 173, *XXVII*, 352; *XXVIII*, 377; *XXIX*, 170. Doses (D in mg/kg) used in the screening: *VI*, 8 i.v.; *VII*, 6 i.v.; *VIII*, 6 i.v.; *IX*, 10 i.v.; *X*, 25 i.v.; *XI*, 6 i.v.; *XVI*, 200; *XVIII*, 8 i.v.; *XIX*, 8 i.v.

Antireserpine activities: (i) Antagonization of reserpine hypothermia in mice: *VI*, inactive at 10 mg/kg; *XVI*, significant activity at 100–250 mg/kg; *XXV*, significant activity at 10 mg/kg. (ii) Inhibition of reserpine-induced ptosis in mice, ED (significant effect) in mg/kg: *VI*, 12·5 (threshold active dose, 3 mg/kg); *VIII*, 25; *IX*, 25; *XI*, 12·5; *XVI* 50; *XXV*, 25; *VII*, *XIX*, *XXIV*, *XXVI–XXIX*, inactive at 25. (iii) Antagonization of the ulcerogenic effect of reserpine in rats (ED in mg/kg which significantly antagonized the effect): *VI*, 50 *XI*, 50 *XXV*, 50; *VII*, *XIII–X*, and *XVII* were inactive at 50–100. Potentiation of yohimbine toxicity in mice, ED_{50}: *VI*, 30 mg/kg.

Inhibition of binding of 4 nmol l^{-1} [^{3}H]imipramine in the rat hypothalamus, IC_{50} in nmol l^{-1}: *VI*, 13·5; *XVI*, 873; *VII–XI*, inactive at 500 nmol l^{-1}; *XIX*, *XXIV–XXIX*, inactive at 100 nmol l^{-1}. Inhibition of binding of 4 nmol l^{-1} [^{3}H]-

desipramine in the rat hypothalamus, IC_{50} in nmol l^{-1}: *VI*, 16·6; *XVI*, 711; *VII*, *VIII*, and *X* were active at 100 nmol l^{-1}; *IX*, *XI*, *XIX*, *XXIV–XXIX*, inactive at 100 nmol l^{-1}. Inhibition of reuptake of 10 nmol l^{-1} [^{3}H]5-hydroxytryptamine and [^{3}H]noradrenaline in the rat brain (in rat cortex): IC_{50} in nmol l^{-1}: *VI*, 0·30 and 0·53, respectively.

Inhibition of spontaneous locomotor activity in mice (test of Dews): *VI*, *VII*, *IX*, *XI*, *XIX*, *XXIV–XXVIII*, inactive at 10 mg/kg; *VIII* and *XXIX*, significant inhibition at 10 mg/kg; *X*, mild stimulation at 10 mg/kg; *XVI*, significant excitation at 10 mg/kg.

Hypotensive effect in normotensive anaesthetized rats (brief and sharp drops of the blood pressure after the dose D or the dose given): *VI*, 4 mg/kg i.v.; *VII–XI*, D.

Spasmolytic effects on the isolated rat duodenum (concentration in mg/l reducing the contractions to 50%) againts contractions induced by (i) acetylcholine: *VI*, 1; *VII*, 0·1–1·0; *VIII*, 0·1–1·0; *IX*, 0·1–1·0; *XI*, 0·01–0·1; (ii) barium chloride: *VI–VIII*, *XI*, 1–10.

Antitussive action in guinea-pigs with cough attacks elicited with an aerosol of citric acid solution; oral ED (in mg/kg) reducing significantly the number of the cough attacks: *VI*, 40; *IX*, 50; *X*, 100.

Anorectic activity in mice, oral doses (ED in mg/kg) reducing significantly the food consumption: *IX*, 25–50 (with excitation); *X*, 50–125; *XXV*, 100; *XXVII*, 100.

Potentiation of the thiopental sleeping time in mice: *XI*, 2·5–6·0 mg/kg i.v. prolonged to 200% of the control value (100%).

Antiulcer effect in rats; inhibition of the indomethacine-induced ulcer formation: *XI*, ED_{50} = 50 mg/kg.

In conclusion: Compound *VI* (VÚFB-15370) is a promising potential antidepressant which is active in two antireserpine tests, potentiates the toxicity of yohimbine, has high affinity to the imipramine as well as desipramine binding sites in the rat brain, and inhibits strongly the reuptake of 5-hydroxytryptamine as well as of noradrenaline in the rat brain structures. Further interesting compounds are *XI* (VÚFB-15377) which is active in two antireserpine tests, and also *XXV* (VÚFB-15486), active in three antireserpine tests and having some anorectic activity.

The compounds were also tested for antimicrobial activity in vitro (microorganisms and the minimum inhibitory concentrations in mg/l are given, unless they exceed 100 mg/l): *Streptococcus β-haemolyticus*, *IX* 50, *X* 50, *XVIII* 100, *XXIV* 100; *Streptococcus faecalis*, *XVIII* 100; *Staphylococcus pyogenes aureus*, *VIII* 100, *XI* 100, *XVI* 100, *XVIII* 100; *Proteus vulgaris*, *XVI* 50, *XIX* 100, *XXIV* 100, *XXVI* 100; *Escherichia coli*, *XXIV* 100; *Trichophyton mentagrophytes*, *VI* 50, *VII* 50, *VIII* 50, *IX* 50, *X* 50, *XI* 50, *XXIX* 50.

EXPERIMENTAL

The melting points were determined in the Mettler FP-5 melting point recorder or in a Kofler block; 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 ε)) were recorded with a Unicam SP 8 000 spectrophotometer, IR spectra (mostly in Nujol, ν in cm^{-1}) with a Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (in $CDCl_3$ unless stated otherwise, δ in ppm, J in Hz) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectra (m/z (%)) with MCH 1 320 and 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 $MgSO_4$, Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotating evaporator.

N,N-Dimethyl-2-(phenylthio)benzylamine (*VI*)

A solution of 11·7 g 2-(phenylthio)benzyl chloride[2,3] in 50 ml chloroform was saturated with 9·0 g dimethylamine and the mixture was heated for 12 h in autoclave to 75°C. After cooling chloroform was evaporated and the residue was distributed between benzene (150 ml) and water (150 ml) to which 10 ml 10% NaOH were aded. The benzene layer was washed with water and the base was extracted with 150 ml 1·5M-HCl. The aqueous layer together with the oily hydrochloride was made alkaline with NH_4OH and the base was extracted with benzene. Processing of the extract gave 12·0 g of crude *VI* which was distilled; 10·6 g (87%) of *VI*, b.p. 128–129°C/50 Pa. ^1H NMR spectrum: 2·24 s, 6 H ($N(CH_3)_2$); 3·55 s, 2 H ($ArCH_2N$); 7·00–7·50 m, 9 H (ArH). For $C_{15}H_{17}NS$ (243·4) calculated: 74·03% C, 7·04% H, 5·76% N, 13·17% S; found: 74·23% C, 7·11% H, 5·79% N, 13·24% S.

Hydrogen maleate, m.p. 144°C (acetone). For $C_{19}H_{21}NO_4S$ (359·4) calculated: 63·49% C, 5·89% H, 3·90% N, 8·92% S; found: 63·39% C, 5·94% H, 3·47% N, 9·05% S.

N,N-Diethyl-2-(phenylthio)benzylamine (*VII*)

A mixture of 11·7 g 2-(phenylthio)benzyl chloride[2,3], 50 ml chloroform, and 14·6 g diethylamine was refluxed for 8 h and processed similarly like in the preceding case; 10·8 g (80%) of *VII*, b.p. 133–135°C/50 Pa. ^1H NMR spectrum: 0·98 t, 6 H (2 CH_3); 2·48 q, 4 H (CH_2NCH_2, $J = 7·0$); 3·60 s, 2 H ($ArCH_2N$); 7·10 m, 8 H (C_6H_5, H-3, H-4, and H-5); 7·45 m, 1 H (H-6). For $C_{17}H_{21}NS$ (271·4) calculated: 75·23% C, 7·80% H, 5·16% N, 11·81% S; found: 75·17% C, 7·95% H, 5·16% N, 11·51% S.

Hydrogen maleate, m.p. 68–69°C (acetone–ether). For $C_{21}H_{25}NO_4S$ (387·5) calculated: 65·09% C, 6·50% H, 3·62% N, 8·27% S; found: 65·23% C, 6·51% H, 3·44% N, 8·29% S.

N-(2-(Phenylthio)benzyl)pyrrolidine (*VIII*)

A similar reaction of 11·7 g 2-(phenylthio)benzyl chloride[2,3] and 14·2 g pyrrolidine in 50 ml chloroform gave 10·2 g (76%) of *VIII*, b.p. 143–145°C/50 Pa. ^1H NMR spectrum: 1·80 bm, 4 H (CH_2CH_2 in positions 3, 4 of pyrrolidine); 2·55 bm, 4 H (CH_2NCH_2); 3·80 s, 2 H ($ArCH_2N$); 7·00–7·60 m, 9 H (ArH). For $C_{17}H_{19}NS$ (269·4) calculated: 75·79% C, 7·11% H, 5·20% N, 11·90% S; found: 76·06% C, 7·21% H, 5·24% N, 11·96% S.

Hydrogen maleate, m.p. 93–94°C (acetone–ether). For $C_{21}H_{23}NO_4S$ (385·5) calculated: 65·43% C, 6·01% H, 3·63% N, 8·32% S; found: 65·50% C, 6·11% H, 3·53% N, 8·60% S.

N-(2-(Phenylthio)benzyl)piperidine (*IX*)

A similar reaction of 11·7 g 2-(phenylthio)benzyl chloride[2,3] and 17·0 g piperidine in 50 ml chloroform gave 10·7 g (76%) of *IX*, b.p. 146–150°C/60 Pa. ^1H NMR spectrum: 1·50 bm, 6 H

(3 CH_2 in positions 3, 4, 5 of piperidine); 2·40 bm, 4 H (CH_2NCH_2); 3·60 s, 2 H ($ArCH_2N$); 7·00—7·50 m, 9 H (ArH). For $C_{18}H_{21}NS$ (283·4) calculated: 76·28% C, 7·47% H, 4·94% N, 11·31% S; found: 76·34% C, 7·52% H, 4·77% N, 11·31% S.

Hydrogen maleate, m.p. 102—103°C (acetone–ether). For $C_{22}H_{25}NO_4S$ (399·5) calculated: 66·14% C, 6·31% H, 3·51% N; 8·03% S; found: 66·04% C, 6·32% H, 3·22% N, 8·28% S.

N-(2-(Phenylthio)benzyl)morpholine (*X*)

A similar reaction of 11·7 g 2-(phenylthio)benzyl chloride[2,3] and 17·4 g morpholine in 50 ml chloroform gave 11·9 g (84%) of *X*, b.p. 159—161°C/50 Pa. ^{1}H NMR spectrum: 2·48 m, 4 H, (CH_2NCH_2 in the ring); 3·60 s, 2 H ($ArCH_2N$); 3·62 m, 4 H (CH_2OCH_2); 7·00—7·50 m, 9 H (ArH). For $C_{17}H_{19}NOS$ (285·4) calculated: 71·54% C, 6·71% H, 4·91% N, 11·23% S; found: 71·59% C, 6·80% H, 4·70% N, 11·30% S.

Hydrogen maleate, m.p. 118—119°C (acetone–ether). For $C_{21}H_{23}NO_5S$ (401·5) calculated: 62·82% C, 5·77% H, 3·49% N, 7·99% S; found: 62·85% C, 5·81% H, 3·19% N, 8·10% S.

1-Methyl-4-(2-(phenylthio)benzyl)piperazine (*XI*)

A similar reaction of 11·7 g 2-(phenylthio)benzyl chloride[2,3] and 20·0 g 1-methylpiperazine in 50 ml chloroform gave 11·7 g (79%) of *XI*, b.p. 164—165°C/50 Pa. ^{1}H NMR spectrum: 2·25 s, 3 H (NCH_3); 2·45 bm, 8 H (4 CH_2N of piperazine); 3·65 s, 2 H ($ArCH_2N$); 7·00—7·50 m, 9 H (ArH). For $C_{18}H_{22}N_2S$ (298·4) calculated: 72·44% C, 7·43% H, 9·39% N, 10·74% S; found: 72·34% C, 7·51% H, 9·70% N, 10·61% S.

Hydrogen maleate, m.p. 159—161°C (acetone–ethanol). Ref.[4], m.p. 160—162·5°C (the base was prepared differently).

2-(Phenylthio)benzaldehyde (*XII*) (Refs[7,17])

A stirred solution of 18·7 g thiophenol in 42 ml hexamethylphosphoric triamide was treated with a solution of 6·8 g NaOH in 13 ml water, after 10 min 22·5 g 2-chlorobenzaldehyde were added and the mixture was heated under reflux to 100°C for 3·5 h under nitrogen. The mixture was then poured into 300 ml ice-cold water and the product was isolated by extraction with benzene; 29·4 g (85%), b.p. 130—135°C/67 Pa.

Semicarbazone, m.p. 212—215°C (ethanol). UV spectrum: 247·5 (4·20), infl. 261 (4·18), 287 (4·32). IR spectrum: 690, 731, 740, 760 (5 and 4 adjacent Ar—H); 1 480, 1 580, 1 592 (Ar); 1 632 (CH=N); 1 691 ($CONH_2$); 3 150, 3 215, 3 270, 3 448 (NH, NH_2). ^{1}H NMR spectrum (CD_3SOCD_3): 6·55 bs, 3 H ($NHCONH_2$); 7·00—7·50 m, 8 H (C_6H_5, H-3, H-4, and H-5); 8·18 m, 1 H (H-6); 8·40 s, 1 H (Ar—CH=N). For $C_{14}H_{13}N_3OS$ (271·3) calculated: 61·97% C, 4·83% H, 15·49% N, 11·82% S; found: 62·20% C, 4·80% H, 15·64% N, 11·94% S.

1-Nitro-2-(2-(phenylthio)phenyl)ethene (*XIV*)

A mixture of 30·0 g *XII*, 12·8 g nitromethane, 120 ml acetic acid, and 12 g ammonium acetate was stirred and refluxed for 4 h. It was poured to water, the product was extracted with ether, the extract was washed with 5% Na_2CO_3 and water, dried, and evaporated; 34·7 g (96%) of almost homogeneous oily *XIV* (TLC). The sample for analysis was distilled; b.p. 180°C/0·2 kPa. UV spectrum: 243 (4·21), infl. 264 (4·06), infl. 299 (3·98), infl. 356 (3·48). IR spectrum (film):

690, 748 (5 and 4 adjacent Ar—H); 962 ((*E*)CH=CH); 1 336, 1 510 (=$CHNO_2$); 1 580, 3 050, 3 100 (Ar); 1 628 (C=C). ^{1}H NMR spectrum: 7·30 m, 9 H (ArH); 7·40 d, 1 H (ArCH=, J = = 14·0); 8·49 d, 1 H (=$CHNO_2$, J = 14·0). For $C_{14}H_{11}NO_2S$ (257·3) calculated: 65·34% C, 4·32% H, 5·44% N, 12·46% S; found: 65·74% C, 4·37% H, 5·14% N, 12·76% S.

2-(2-(Phenylthio)phenyl)ethylamine (*XVI*)

A solution of 25·0 g *XIV* in 150 ml ether was added dropwise to a stirred solution of 19 g $LiAlH_4$ in 300 ml ether over 3 h. The mixture was allowed to stand for 2 days at room temperature, decomposed by a slow addition of ethanol and water, the solid was filtered off, the filtrate was separated, and the organic layer was evaporated; 18·8 g (84%) of crude *XVI*. It was dissolved in ether, the solution was neutralized with a solution of 9·0 g maleic acid in ethanol, and the mixture was diluted with ether; crystallization gave 13·2 g of hydrogen maleate, m.p. 154—155°C (ethanol–ether). For $C_{18}H_{19}NO_4S$ (345·4) calculated: 62·58% C, 5·56% H, 4·06% N, 9·28% S; found: 62·28% C, 5·61% H, 3·96% N, 9·06% S.

A sample of the pure salt was decomposed with NH_4OH, the homogeneous oily base was isolated by extraction with ether, and used for recording the ^{1}H NMR spectrum: 1·35 s, 2 H (NH_2); 2·95 s, 4 H ($ArCH_2CH_2N$); 7·20 m, 9 H (ArH).

N-Methyl-2-(2-(phenylthio)phenyl)ethylamine (*XVIII*)

A mixture of 16·4 g *XVI* and 45 ml ethyl formate was heated for 6 h in autoclave to 125—130°C. The reaction mixture was dissolved in ether, the solution was washed with dilute hydrochloric acid, 5% $NaHCO_3$, dried, and evaporated; 16·2 g (88%) of crude *XVII* which was reduced in this state.

A solution of 16·2 g of crude *XVII* in 80 ml benzene was added dropwise to a stirred solution of 6·0 g $LiAlH_4$ in 70 ml ether, and the mixture was stirred and refluxed for 5 h. After cooling it was decomposed by slow addition of ethanol and water, the mixture was filtered, the organic layer of the filtrate was dried, and evaporated; 14·5 g (95%) of almost homogeneous *XVIII*. It was neutralized with oxalic acid dihydrate in ethanol and the solution was diluted with ether; 6·4 g of hydrogen oxalate, m.p. 190°C (ethanol–ether). For $C_{17}H_{19}NO_4S$ (333·4) calculated: 61·23% C, 5·76% H, 4·20% N, 9·62% S; found: 61·03% C, 5·82% H, 4·12% N, 9·92% S.

A sample of the released base was used for recording the ^{1}H NMR spectrum: 1·48 s, 1 H (NH); 2·40 s, 3 H (NCH_3); 2·90 m, 4 H ($ArCH_2CH_2N$); 7·20 m, 9 H (ArH).

N,N-Dimethyl-2-(2-(phenylthio)phenyl)ethylamine (*XIX*)

A mixture of 13·0 g *XVI*, 12 ml 80% formic acid, 21·5 ml 28% formaldehyde, and 10 ml water was stirred and refluxed for 11 h. After cooling it was poured into dilute NaOH, extracted with ether, the extract was washed with water and processed; 12·7 g (87%) of almost homogeneous *XIX*. It was transformed to hydrogen maleate, m.p. 100—102°C (ethanol–ether). For $C_{20}H_{23}$·.NO_4S (373·5) calculated: 64·31% C, 6·22% H, 3·75% N, 8·58% S; found: 64·05% C, 6·31% H, 3·82% N, 8·54% S.

^{1}H NMR spectrum of the released base: 2·25 s, 6 H ($N(CH_3)_2$); 2·50 m, 2 H (CH_2N); 2·98 m, 2 H ($ArCH_2$); 7·20 m, 9 H (ArH).

3-Oxo-2-(2-(phenylthio)phenyl)butyronitrile (*XXI*)

A suspension of 3·5 g 80% NaH in 50 ml toluene was stirred, heated to 70°C, and treated dropwise with 13·3 ml ethanol. A mixture of 20 g (2-(phenylthio)phenyl)acetonitrile[2] and 13·3 ml ethyl

acetate was added to the suspension of sodium ethoxide and the mixture was refluxed for 2 h. After cooling it was decomposed with 110 ml water, the toluene layer was washed three times with 30 ml water, the combined aqueous layers were cooled to 0°C and acidified with hydrochloric acid (pH 2–3). The separated oil was extracted with toluene, the extract was dried, and distilled; 13·5 g (57%) of *XXI*, b.p. 157–158°C/70 Pa. IR spectrum (film): 691, 753 (5 and 4 adjacent Ar—H); 1 473, 1 498, 1 580, 1 600, 3 050 (Ar); 1 640 (C=C of the enol form); 1 730 (CO); 2 200 (=C—CN of the enol form); 2 245 (R—CN); 3 240 (OH of the enol form). ^{1}H NMR spectrum: 2·20 s, 3 H ($COCH_3$); 5·48 s, 1 H (ArCH(CN)CO); 7·00–7·60 m, 9 H (ArH). For $C_{16}H_{13}NOS$ (267·3) calculated: 71·88% C, 4·90% H, 5·24% N, 11·99% S; found: 71·86% C, 4·95% H, 5·24% N, 12·21% S.

(2-(Phenylthio)phenyl)acetone (*XX*)

A stirred mixture of 12·0 g *XXI* and 10·4 g 85% H_3PO_4 was heated under reflux for 8 h in a bath of 200°C. After cooling the mixture was diluted with 50 ml water and the product was extracted with toluene. Processing of the extract and distillation gave 7·1 g (65%) of *XX*, b.p. 128–130°C/90 Pa, which crystallized, m.p. 50–51·5°C (ethanol). IR spectrum: 691, 749 (5 and 4 adjacent Ar—H); 1 475, 1 565, 1 580, 3 060 (Ar); 1 715 (R—CO—R'). ^{1}H NMR spectrum: 2·12 s, 3 H ($COCH_3$); 3·90 s, 2 H ($ArCH_2CO$); 7·20 m, 9 H (ArH). For $C_{15}H_{14}OS$ (242·3) calculated: 74·34% C, 5·82% H, 13·23% S; found: 74·04% C, 5·88% H, 13·30% S.

(2-(Phenylthio)phenyl)acetoxime (*XXII*)

A solution of 2·4 g *XX* in 5 ml pyridine was treated with a solution of 0·8 g hydroxylamine hydrochloride in 5 ml ethanol and the mixture was refluxed for 3 h. The solvents were evaporated in vacuo, the residue was washed with water, and the insoluble part was crystallized from ethanol; 1·9 g (75%) of *XXII*, m.p. 128–130°C. IR spectrum: 692, 745, 760 (5 and 4 adjacent Ar—H); 1 489, 1 581, 3 010, 3 055, 3 070 (Ar); 1 661 (C=N); 3 240 (OH). For $C_{15}H_{15}NOS$ (257·3) calculated: 70·00% C, 5·88% H, 5·44% N, 12·46% S; found: 69·77% C, 5·99% H, 5·32% N, 12·25% S.

1-Phenyl-2-propylamine (Ref.[13])

A solution of 16·5 g *XXII* in 285 ml ethanol was dropped to 16·5 g Na under reflux and the mixture was refluxed for 4 h (until Na dissolved). After partial cooling the mixture was decomposed by slow addition of 70 ml water, ethanol was evaporated and the aqueous residue was extracted with ether. Processing of the extract gave 3·6 g of oil which was treated with a solution of HCl in ether; 2·0 g of a hydrochloride melting at 145–148°C (ethanol–ether). The analysis indicated the composition $C_9H_{14}ClN$ and the product is thus 1-phenyl-2-propylamine hydrochloride; ref.[13], m.p. 147–148°C.

N-(1-(2-(Phenylthio)phenyl)-2-propyl)formamide (*XXIII*)

A mixture of 6·0 g *XX*, 15 g formamide, and 3·0 g 98% formic acid was refluxed for 12 h in a bath of 190–200°C. After partial cooling the mixture was poured into water and the product was extracted with ether. Processing of the extract gave 6·6 g (almost theoretical) of crude oily *XXIII* which was further used in this state. A sample (5·0 g) was chromatographed on 70 g silica gel. Benzene eluted 0·5 g of less polar impurities and chloroform eluted 4·2 g of homogeneous product (TLC) which crystallized from light petroleum, m.p. 66–68°C (benzene–hexane). IR spectrum (KBr): 690, 738 (5 and 4 adjacent Ar—H); 1 478, 1 580, 3 055 (Ar); 1 535, 1 650 (RNHCHO);

3 312 (NH). For $C_{16}H_{17}NOS$ (271·4) calculated: 70·81% C, 6·31% H, 5·16% N, 11·82% S; found: 71·03% C, 6·22% H, 5·37% N, 11·87% S.

1-(2-(Phenylthio)phenyl)-2-propylamine (*XXIV*)

A) Crude *XXIII* (6·6 g) was added to a solution of 6·6 g KOH in 8·8 ml ethanol and the mixture was refluxed for 4·5 h (bath of 120—130°C). After cooling it was diluted with 120 ml water, extracted with ether, and the extract was processed. The residue was dissolved in excessive 5% hydrochloric acid, the acid solution was washed with ether, was made alkaline with NH_4OH and the base was extracted again with ether. Processing gave 4·2 g (70%) of oily *XXIV* which was transformed to salts:

Hydrogen maleate, m.p. 140—141°C (ethanol). For $C_{19}H_{21}NO_4S$ (359·4) calculated: 63·49% C, 5·89% H, 3·90% N, 8·92% S; found: 63·67% C, 5·83% H, 3·96% N, 9·10% S.

Hydrochloride, m.p. 168—171°C (ethanol–ether). For $C_{15}H_{18}ClNS$ (279·8) calculated: 64·38% C, 6·48% H, 12·67% Cl, 5·00% N, 11·46% S; found: 64·30% C, 6·40% H, 12·75% Cl, 5·03% N, 11·51% S.

A sample of the hydrogen maleate was decomposed with NH_4OH and the released base was used for recording the ^1H NMR spectrum: 1·10 d, 3 H (CH_3, J = 6·0); 1·31 bs, 2 H (NH_2); 2·50—3·40 m, 3 H ($ArCH_2CHN$); 7·15 s, 9 H (ArH).

B) A mixture of 30·0 g *XII*, 15·8 g nitroethane, 120 ml acetic acid, and 12 g ammonium acetate was stirred and refluxed for 5 h. After partial cooling it was poured into water and the product was extracted with ether. Processing of the extract gave 34·5 g of *XV*, contaminated heavily with a second substance having a close R_F value (TLC). The mixture was processed in this state.

Crude *XV* (34·5 g) was dissolved in 200 ml ether and the solution was added dropwise over 2·5 h to a stirred solution of 25 g $LiAlH_4$ in 600 ml ether. The mixture was allowed to stand overnight at room temperature, decomposed by slow addition of ethanol and water, filtered, the organic layer of the filtrate was washed with water, dried, and evaporated; 29·1 g of inhomogeneous *XXIV*. Stirring a sample with dilute hydrochloric acid gave the hydrochloride which was recrystallized twice from a mixture of chloroform and heptane, m.p. 156—157°C. This melting point is at least by 10°C lower than that of the product obtained under *A*). It gave correct analytical values for Cl, N, and S but the ^1H NMR spectrum identified the presence of 2-(phenylthio)benzylamine (*V*) as an important impurity. The crude base was also transformed to the hydrogen maleate, m.p. 120—123°C (melting point lower by 20°C than that of the product obtained under *A*); it gave correct analytical values for $C_{19}H_{21}NO_4S$ but the ^1H NMR spectrum identified it as a mixture of 70% of *XXIV* hydrogen maleate and 30% of 2-(phenylthio)benzylamine (*V*) hydrogen maleate.

N-Methyl-1-(2-(phenylthio)phenyl)-2-propylamine (*XXV*)

A) A solution of 17·3 g of oily *XXIII* in 75 ml ether was added dropwise to a stirred solution of 7·2 g $LiAlH_4$ in 75 ml ether and the mixture was refluxed for 6 h. Under cooling it was decomposed by slow addition of 7·2 ml 15% NaOH and then 30 ml water. It was stirred for 30 min, the solid was filtered off, washed with ether, the filtrate was dried with $MgSO_4$, filtered with active carbon, and evaporated; 15·7 g (83%) of almost homogeneous oily *XXV*. It was transformed to hydrogen oxalate, m.p. 137—139°C (ethanol–ether). For $C_{18}H_{21}NO_4S$ (347·4) calculated: 62·22% C, 6·09% H, 4·03% N, 9·23% S; found: 62·21% C, 6·05% H, 4·24% N, 9·19% S.

^{1}H NMR spectrum of the released base: 1·05 bd, 3 H (CH_3, J = 6·0); 1·30 bs, 1 H (NH); 2·40 s, 3 H (NCH_3); 2·50–3·20 m, 3 H ($ArCH_2CHN$); 7·15 s, 9 H (ArH).

B) A mixture of 13·0 g of crude *XXIV* (obtained under *B*) and 45 ml ethyl formate was heated for 6 h in autoclave to 120°C. After cooling it was diluted with ether, the solution was washed with 5% hydrochloric acid and 5% $NaHCO_3$, dried, and evaporated; 12·7 g of inhomogeneous *XXIII*.

A solution of 12·7 g of this product in 60 ml benzene was reduced with 5·0 g $LiAlH_4$ in 55 ml ether (refluxing for 6 h). Processing like under *A*) gave 10·7 g of inhomogeneous *XXV*. The hydrogen oxalate melted at 124–132°C (aqueous ethanol–ether) and gave correct analytical values only for N and S. Mass spectrum: 257 (M^+, $C_{16}H_{19}NS$), 228, 200, 148, 58 (100), and 229 (M^+, $C_{14}H_{15}NS$), corresponding to *IV*. ^{1}H NMR spectrum (CD_3SOCD_3) with signals of *XXV* hydrogen oxalate: 1·10 d (CH_3, J = 6·0); 2·59 s (NCH_3); 2·90–3·50 m ($ArCH_2CHN$); 7·00 to 7·80 m (ArH); but also 4·29 s corresponding to $ArCH_2N$ of *IV*, present in the amount of 40%.

Repeated crystallization of this hydrogen oxalate from ethanol–ether gave finally homogeneous N-methyl-2-(phenylthio)benzylamine (*IV*) hydrogen oxalate, m.p. 142–144°C. Mass spectrum: 229 (M^+, $C_{14}H_{15}NS$, 65), 197 (100), 118 (82), 107 (97), 46 (38), 45 (76), 44 (76). ^{1}H NMR spectrum (CD_3SOCD_3): 2·60 s, 3 H (NCH_3); 4·30 s, 2 H ($ArCH_2N$); 7·10–7·50 m, 8 H (C_6H_5, H-3, H-4, and H-5); 7·80 m, 1 H (H-6); 9·40 s (NH_2^+, COOH). For $C_{16}H_{17}NO_4S$ (319·4) calculated: 60·16% C, 5·38% H, 4·39% N, 10·04% S; found: 59·88% C, 5·40% H, 4·50% N, 9·85% S. Ref.[6] described the synthesis of *IV* by an unequivocal method but only the hydrogen maleate was prepared.

N,N-Dimethyl-1-(2-(phenylthio)phenyl)-2-propylamine (*XXVI*)

A) A mixture of 11·0 g of oily *XXIV* (prepared under *A*), 8 ml water, 11·0 ml 80% formic acid, and 19 ml 28% formaldehyde was stirred and refluxed for 12 h. After cooling it was poured into 320 ml 5% NaOH, and the product was extracted with ether. The extract was washed with water, dried, filtered with active carbon, and evaporated; 10·8 g (88%) of almost homogeneous oily *XXVI*. It was transformed to hydrogen maleate, m.p. 84–86°C (ethanol–ether). For $C_{21}H_{25}$·.NO_4S (387·5) calculated: 65·09% C, 6·50% H, 3·61% N, 8·27% S; found: 65·23% C, 6·39% H, 3·89% N, 8·43% S.

^{1}H NMR spectrum of the released base: 0·91 d, 3 H (C–CH_3, J = 6·0); 2·28 s, 6 H ($N(CH_3)_2$); 2·50–3·60 m, 3 H ($ArCH_2CHN$); 7·15 s, 9 H (ArH).

B) Inhomogeneous *XXIV* (prepared under *B*) was similarly processed (like under *A*) and gave 10·5 g of inhomogeneous *XXVI*. It was transformed to the hydrogen maleate melting at 84–87°C (ethanol–ether) (the same melting point like that of the product under *A*) and giving correct analytical data for $C_{21}H_{25}NO_4S$. The mass spectrum, however, indicated in addition to the expected *m/z* 271 (M^+, $C_{17}H_{21}NS$) also *m/z* 243 (M^+, $C_{15}H_{17}NS$), corresponding to *VI*. The ^{1}H NMR spectrum determined the ratio of *XXVI* : *VI* to be 65 : 35.

1-(2-(Phenylthio)phenyl)-2-propylamine S-oxide (*XXVII*)

A solution of 1·2 g *XXIV* (under *A*) in 12 ml acetic acid was treated with 0·8 g 30% H_2O_2 and the mixture was allowed to stand for 24 h at room temperature. It was then diluted with 150 ml water, made alkaline with 45 ml 20% NaOH, and the product was isolated by extraction with benzene; 0·90 g (70%) of oily *XXVII*. It was transformed to the hydrogen maleate, m.p. 176 to 177°C (ethanol). Mass spectrum: 259 (M^+, $C_{15}H_{17}NOS$), 242, 216, 199, 197, 138, 44. IR spectrum: 695, 720, 759 (5 and 4 adjacent Ar–H); 1 030 (Ar–S–O); 1 570 (COO^-); 2 720, infl.

3 150 (COOH, NH_3^+). Polarographic reduction of the released base, which was dissolved in 0·25M-H_2SO_4, proceeded at $E_{1/2}$ — 0·84 V (S—O). For $C_{19}H_{21}NO_5S$ (375·4) calculated: 60·78% C, 5·64% H, 3·73% N, 8·54% S; found: 60·90% C, 5·64% H, 3·81% N, 8·33% S.

N-Methyl-1-(2-(phenylthio)phenyl)-2-propylamine S-Oxide (*XXVIII*)

Similar oxidation of 1·29 g *XXV* (under *A*) in 13 ml acetic acid with 0·8 g 30% H_2O_2 gave 1·3 g (94%) of oily *XVIII* which was transformed to the hydrogen maleate, m.p. 132—134°C (ethanol). Mass spectrum: 273 (M^+, $C_{16}H_{19}NOS$), 256, 216, 199, 197, 165, 138, 58. IR spectrum: 690, 750, 762 (5 and 4 adjacent Ar—H); 1 040, 1 058 (Ar—S—O); 1 575 (COO^-); 1 630 (C=C of maleic acid); 2 480, 2 730 (NH_2^+); 3 005, 3 030 (Ar). Polarographic reduction in 0·5M-HCl proceeded at $E_{1/2}$ — 0·84 V (S—O). For $C_{20}H_{23}NO_5S$ (389·5) calculated: 61·68% C, 5·95% H, 3·60% N, 8·23% S; found: 61·72% C, 6·03% H, 3·53% N, 8·22% S.

N,N-Dimethyl-1-(2-(phenylthio)phenyl)-2-propylamine S-Oxide (*XXIX*)

Similar oxidation of 1·4 g *XXVI* (under *A*) in 14 ml acetic acid with 0·7 g 30% H_2O_2 gave 1·4 g (97%) of oily *XXIX* which was transformed to the hydrogen maleate, m.p. 108—111°C (ethanol–ether). Mass spectrum: 287 (M^+, $C_{17}H_{21}NOS$), 270, 243, 227, 211, 197, 165, 72. IR spectrum: 689, 745, 760 (5 and 4 adjacent Ar—H); 1 040, 1 056 (Ar—S—O); 1 560 (COO^-); 1 612 (C=C of maleic acid); 2 400 (NH^+); 3 050 (Ar). Polarographic reduction in 0·5M-HCl proceeded at $E_{1/2}$ —0·84 V (S—O). For $C_{21}H_{25}NO_5S$ (403·5) calculated: 62·51% C, 6·24% H, 3·47% N, 7·95% S; found: 62·66% C, 6·31% H, 3·89% N, 7·88% S.

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REFERENCES

1. Protiva M., Jílek J., Metyšová J., Seidlová V., Jirkovský I., Metyš J., Adlerová E., Ernest I., Pelz K., Pomykáček J.: Farmaco, Ed. Sci. *20*, 721 (1965).
2. Jílek J. O., Seidlová V., Svátek E., Protiva M.: Monatsh. Chem. *96*, 182 (1965).
3. Jílek J. O., Svátek E., Metyšová J., Pomykáček J., Protiva M.: Collect. Czech. Chem. Commun. *32*, 3186 (1967).
4. Kopicová Z., Šedivý Z., Hradil F., Protiva M.: Collect. Czech. Chem. Commun. *37*, 1371 (1972).
5. Valenta V., Vlková M., Holubek J., Metyšová J., Protiva M.: Collect. Czech. Chem. Commun. *54*, 1979 (1989).
6. Christy M. E. (Merck & Co., Inc.): U.S. 4,018,830; Chem. Abstr. *87*, 22742 (1977).
7. Hori M., Kataoka T., Shimizu H., Ohno S.: Tetrahedron Lett. *1978*, 255.
8. Gairaud C. B., Lappin G. R.: J. Org. Chem. *18*, 1 (1953).
9. Rudinger J., Ferles M.: *Hydrid lithno-hlinitý a příbuzná činidla v organické chemii*, p. 147. Publishing House of the Czechoslovak Academy of Sciences, Prague 1956.
10. Gaylord N. G.: *Reduction with Complex Metal Hydrides*, p. 764. Interscience, New York 1956.

11. Moore M. L.: Org. React. *5*, 301 (1949).
12. Wajon J. F. M., Arens J. F.: Rec. Trav. Chim. Pays-Bas *76*, 65 (1957).
13. Gilsdorf R. T., Nord F. F.: J. Am. Chem. Soc. *74*, 1837 (1952).
14. Karmarkar S. N., Kelkar S. L., Wadia M. S.: Synthesis *1985*, 510.
15. Kornblum N., Brown R. A.: J. Am. Chem. Soc. *87*, 1742 (1965).
16. Kmoníček V., Vejdělek Z., Holubek J., Valchář M., Protiva M.: Collect. Czech. Chem. Commun. *54*, 1721 (1989).
17. Gosteli J. (Ciba-Geigy A.-G.): Ger. Offen. 2,165,260; Chem. Abstr. *77*, 114271 (1972).

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