POTENTIAL ANTIDEPRESSANT AND ANTI-INFLAMMATORY AGENTS: 4-(2-PROPYLTHIO)ACETOPHENONE OXIMES AND 4-(2-PROPYLTHIO)PHENYLALKANOIC ACIDS

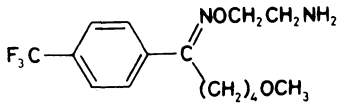
Jiří Jílek, Karel Šindelář, Jaroslava Grimová, Eva Maturová, Jiří Holubek, Emil Svátek, Jiřina Metyšová, Jan Metyš, Marta Hrubantová and Miroslav Protiva

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

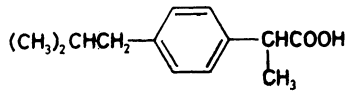
Received August 10, 1989
Accepted September 11, 1989

4-(2-Propylthio)acetophenone oxime (*IV*) was reacted with 2-aminoethyl chloride and 3-dimethylaminopropyl chloride to give the O-(aminoalkyl)oximes *V* and *VI* which are analogues of the antidepressant agent fluvoxamine (*I*). Kindler–Willgerodt reaction of 4-(2-propylthio)-acetophenone (*III*) gave the thiomorpholide *VII* which was hydrolyzed to the acid *IX*. Friedel–Crafts reaction of (2-propylthio)benzene with ethoxalyl chloride afforded ethyl 4-(2-propylthio)-benzoylformate (*X*) which was transformed by reaction with methylmagnesium iodide, by the following hydrolysis and reduction with hydroiodic acid to 2-(4-(2-propylthio)phenyl)propionic acid (*XII*), a thia isostere of the anti-inflammatory and analgesic agent ibuprofen (*II*); acid *XII* was also obtained by reaction of 2-(4-mercaptophenyl)propionic acid (*XVII*) with 2-bromopropane and by the following hydrolysis. The acids *IX* and *XII* were converted to the amides *XIII*–*XV*. The fluvoxamine analogue *V* (VÚFB-16 650) showed some pharmacological properties of potential antidepressants. The acids *IX* and *XII* (VÚFB-16 603) have comparable anti-inflammatory activity with that of ibuprofen (*II*); in addition, *XII* has lower acute toxicity and higher analgetic activity than ibuprofen.

In the present communication structures of the therapeutic agents *I* and *II* were used as the lead for further pharmaco-chemical research. The first of them is the antidepressant agent "fluvoxamine" (refs[1,2]) with typical 5-hydroxytryptamine uptake inhibiting properties ("a serotonergic antidepressant") (refs[3,4]). The latter is the famous anti-inflammatory and mild analgesic agent "ibuprofen" (refs[5–7]).



I

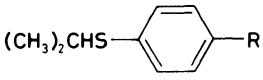


II

It was the first intention to use 4-(2-propylthio)acetophenone (*III*) as the starting compound in the synthesis of analogues of *I* and *II*. Compound *III* is readily avai-

lable[8] from (2-propylthio)benzene, which is obtained by reaction of thiophenol with 2-bromopropane in ethanol in the presence of sodium hydroxide[9]. The Friedel–Crafts acylation of (2-propylthio)benzene with acetyl chloride in the presence of aluminium chloride was carried out on the one hand in 1,2-dichloroethane[8], and in carbon disulfide on the other; the results were similar: yields on the distilled product were 73% and 67%, respectively. The reaction is evidently complicated by side reactions: (i) Gas chromatography of the distilled product showed the presence of about 5% of a contaminant which could be the *o*-isomer; (ii) the smell of thiophenol indicates cleavage of the 2-propyl-S bond in a part of the starting (2-propylthio)benzene; (iii) there was an important distillation residue not distilling until 200°C/0·15 kPa which was not further studied. The ketone *III* was characterized by the crystalline and known 2,4-dinitrophenylhydrazone[10]. The oxime *IV* was prepared by heating a mixture of *III*, hydroxylamine hydrochloride, and sodium acetate in aqueous ethanol. It is a crystalline, homogeneous (TLC) substance whose configuration could not be assigned only on the basis of the UV and IR spectra recorded; on the basis of analogy[11] it is assumed to be the "anti-phenyl" isomer.

The oxime *IV* was O-alkylated with 2-chloroethylamine hydrochloride[12] in ethanol in the presence of sodium ethoxide (for the method, cf. ref.[13]); some of the starting *IV* was recovered and the oily *V* was obtained in the yield of 67% (per conversion). It was transformed to the hydrogen maleate whose mass spectrum confirmed the identity. Similar alkylation of *IV* with 3-dimethylaminopropyl chloride gave the oily *VI* which, likewise, was transformed to the crystalline hydrogen maleate. Also in this case, the mass spectrum confirmed the identity. Compounds *V* and *VI* are analogues of fluvoxamine (*I*).

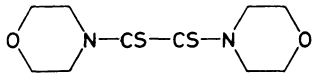


III, R = $COCH_3$
IV, R = $C(=NOH)CH_3$
V, R = $C(=NOCH_2CH_2NH_2)CH_3$
VI, R = $C(=NO(CH_2)_3N(CH_3)_2)CH_3$
VII, R = CH_2CSN(morpholine)O
VIII, R = $COCSN$(morpholine)O
IX, R = CH_2COOH

X, R = $COCOOC_2H_5$
XI, R = $CH(OH)COOH$
XII, R = $CH(CH_3)COOH$
XIII, R = CH_2CONH_2
XIV, R = $CH(CH_3)CONH_2$
XV, R = $CH(CH_3)CON$(piperazine)NCH_3

The ketone *III* was subjected to the Kindler–Willgerodt reaction[14], i.e. to heating with morpholine and sulfur (for analogy, cf. ref.[15]). Crystallization of the crude

product from ethanol gave 65% of the thiomorpholide *VII* which was characterized by spectra. The mother liquors after *VII* were processed by crystallization from benzene and by chromatography which led to the isolation of the oxothiomorpholide (*VIII*), the rather important by-product. The mentioned chromatography afforded in the last fraction a minor by-product, a yellow high-melting (264–265°C) solid $C_{10}H_{16}N_2O_2S_2$ (analysis) to which the structure *XVI* was assigned (spectra are in agreement). This compound (dithio-oxalodimorpholide) had already been isolated and identified as a by-product of the Kindler–Willgerodt reaction[16]. It was also obtained by a direct reaction of morpholine with sulfur[17] (both references gave lower melting point values than found by us), and was also isolated from a reaction of acetylene with morpholine and sulfur[18] (m.p. 263–265°C given). TLC of the mother liquors after *VII* revealed a higher number of spots than corresponding only to the presence of *VIII* and *XVI*; this is in agreement with the published finding[19] that acetomorpholide and thioacetomorpholide are also products of reaction of morpholine with sulfur.



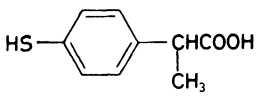
XVI

Hydrolysis of the crude *VII* with potassium hydroxide in aqueous ethanol gave the crude acid *IX* which was chromatographed on silica gel affording the homogeneous *IX* melting constantly at 49–50°C. This melting point value is at variance with that published in patents[15,20]. Because the spectra of our product fully support its identity, we must be dealing here with a case of polymorphism. Similar hydrolysis of homogeneous *VII* afforded *IX* having the melting point identical with the published value (77–78°C).

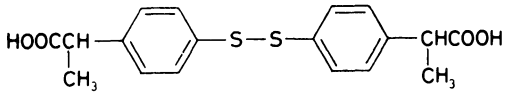
The synthesis of the 4-(2-propylthio)phenyl analogue ("thia isostere") of ibuprofen (*II*) requested a different synthetic approach. The synthesis started with the Friedel–Crafts acylation of (2-propylthio)benzene[9] with ethoxalyl chloride[21] in 1,2-dichloroethane in the presence of aluminium chloride. The desired *X* was obtained in a rather low yield (27% of redistilled product). The reaction was accompanied again by the cleavage of the 2-propyl–S bond because the first fraction of the distillate consisted mainly of thiophenol. Reaction of *X* with methylmagnesium iodide in a mixture of ether and toluene and the following hydrolysis of the ester group with aqueous potassium carbonate gave the hydroxy acid *XI* w ich was obtained in the yield of 46% and was characterized by spectra. Its reduction with hydroiodic acid, generated from phosphorus and iodine in boiling acetic acid containing a small amount of water, afforded in a high yield the desired ibuprofen analogue *XII* whose structure was corroborated by spectra. The acid *XII* is new, i.e. it was never before

described as a characterized substance. Its structure, however, was included in the general formulae in the Boots' patents[15,20]. The synthesis described here is an analogy of the procedure mentioned in refs[15,20] together with a series of other possible methods which were not substantiated by description of the experiments. For having a completely independent procedure for our acid *XII*, we started from the acid *XVII* (cf. ref.[22]) which was obtained from the hydrochloride of 2-(4-aminophenyl)-propionic acid[23] by diazotization, the following reaction with potassium ethyl xanthate at 55°C and by the final alkaline hydrolysis of the corresponding aryl ethyl xanthate (for method, cf. ref.[24]). A very inhomogeneous product was obtained which was separated by chromatography on silica gel. Elution with chloroform gave 38% of crystalline *XVII* which was fully characterized by spectra and which differs from the product described in ref.[22] (this was characterized as an oil distilling in vacuo without decpmposition). From the last chromatographic fraction (eluted with chloroform containing 5% of ethanol), a small amount of a high-melting solid was isolated which was characterized as the disulfide *XVIII*. Reaction of *XVII* with 2-bromopropane in dimethylformamide at 60°C in the presence of potassium carbonate and the following hydrolysis with sodium hydroxide in aqueous ethanol afforded the acid *XII* in a fair yield; its identity was confirmed by comparison (analysis and melting point) with the acid *XII* obtained by the synthesis described above.

The acids *IX* and *XII* were transformed by refluxing with thionyl chloride in hexane to the acid chlorides which were not characterized and were converted by treatment with ammonia in ether to the crystalline amides *XIII* and *XIV*, characterized by spectra. The crude chloride of the acid *XII* was reacted with 1-methylpiperazine in ether and gave the oily amide *XV* which was transformed to the crystalline hydrochloride and hydrogen maleate. The latter salt proved to be the 3 : 1 solvate with toluene which was proven by recording the mass spectrum.



XVII



XVIII

The fluvoxamine analogues *V* and *VI* were pharmacologically tested in the form of the hydrogen maleates. They were administered orally and the doses given were calculated per bases. Compound *V* (VÚFB-16 650) antagonized significantly the reserpine ptosis in mice starting with the dose of 3 mg/kg which is a very important effect. In the dose of 50 mg/kg it inhibited significantly the hypothermic effect of reserpine in mice. The toxicity of yohimbine was potentiated in 40% of mice by the relatively high dose of 100 mg/kg. The dose of 10 mg/kg elicited a significant increase

of spontaneous locomotor activity in mice which must be explained by a central stimulating effect. On the other hand, compound *VI* did not antagonize reserpine ptosis in the dose of 30 mg/kg and did not potentiate the toxicity of yohimbine in mice in doses of 10–100 mg/kg. Both compounds (*V* and *VI*) were inactive in the rotarod test in mice in doses of 100 mg/kg (no ataxic effect) and both did not inhibit in concentrations of 100 nmol l^{-1} the binding of 4 nM [^{3}H] imipramine and 4 nM [^{3}H] desipramine in the rat hypothalamus in vitro. Compound *V* may be considered a potential antidepressant.

Compounds *IX*, *XII* (VÚFB-16 603) and *XV* (hydrochloride) were tested as potential anti-inflammatory and analgetic agents in comparison with ibuprofen (*II*), used as the standard. The anti-inflammatory activity was evaluated in three models of experimental oedema in rats (carrageenan oedema[25], kaolin oedema[26], and adjuvant oedema[27]), the doses in mg/kg p.o. are given, and the results are expressed as % of inhibition of the oedema ($^+$ means statistical significance). Carrageenan oedema: *IX*, 100, 54$^+$; *XII*, 100, 58$^+$; *XV*, 50, 16$^+$; ibuprofen, 100, 55$^+$. Kaolin oedema: *IX*, 100, 29$^+$; *XII*, 100, 40$^+$; ibuprofen, 100, 40$^+$. Adjuvant oedema: *IX*, 100, 49$^+$; *XII*, 100, 36$^+$; *XV*, 50, 20$^+$; ibuprofen, 100, 53$^+$. The analgetic activity was assessed in three tests of experimental pain in rodents: (i) test of inhibition of the writhing syndrome in male mice using stimulation with intraperitoneal 0·7% acetic acid[28] (results in % of inhibition of the pain after the dose given or in the ED_{50} values in mg/kg); (ii) model of inflammatory hyperalgesia (algesimeter) in rats[29] (doses and % of inhibition of the pain, $^+$ means statistical significance), and (iii) model of pressure analgesia on the rat's foot[30] (results in % of increase of the pain threshold in comparison with the untreated control in 1 h and 3 h after the administration). Inhibition of the writhing syndrome: *IX*, ED_{50} 180 p.o.; *XII*, ED_{50} 82 p.o.; *XV*, 10 i.v., 41$^+$; ibuprofen, ED_{50} 170 p.o. Algesimeter: *XII*, 150 p.o., 37$^+$; *XV*, 20 i.v., 53$^+$; ibuprofen, 150 p.o., 45$^+$. Pressure analgesia: *XII*, 200 mg/kg p.o., 129%, 87%; ibuprofen, 200 mg/kg p.o., 100%, 81%. Acute toxicity in mice (dose and % of lethality or LD_{50} given): *IX*, 1 g/kg p.o., 0%; *XII*, LD_{50} 2 240 mg/kg p.o.; *XV*, 10 mg/kg i.v., 0%; 100 mg/kg i.v., 60%; ibuprofen, LD_{50} 1 350 mg/kg p.o.. Gastrotoxicity was tested with the standard method[31] in rats and the ulcerogenic index (UI) for three doses in mg/kg p.o. is given: *XII*, 50, UI 97·5; 100, UI 270; 200, UI 300; ibuprofen, 50, UI 208; 100, UI 233; 200, UI 300. In conclusion: the acids *IX* and *XII* have comparable anti-inflammatory activity with that of ibuprofen (*II*); *XII* has lower acute toxicity in mice and higher analgetic activity than ibuprofen. Compound *XV* which was considered a possible prodrug of *XII*, has lower anti-inflammatory activity and considerable analgetic activity (direct comparison is not possible because of the intravenous administration used with *XV*). The compound *XII* was also compared with ibuprofen in the line of possible central effects. In the test of inhibition of spontaneous locomotor activity in male mice, ibuprofen (D_{50} 254 mg/kg p.o.) had stronger central depressant activity than *XII*. With the apparatus

Varimex (evaluation of the total activity), *XII* in the dose of 500 mg/kg p.o. had significant depressant activity. In the rotarod test in mice evaluating the ataxic activity, ibuprofen (ED_{50} 356 mg/kg p.o.) was more active than *XII* (ED_{50} above 500 mg/kg p.o.). In the test of potentiation of the thiopental sleeping time in mice ibuprofen, likewise, is more active (the dose of 100 mg/kg p.o. prolonged significantly) than *XII* (the dose of 200 mg/kg p.o. prolonged only mildly (to 160% of the control value)). Compound *XII* has thus less central side effects than ibuprofen.

The amides *XIII* and *XIV* were tested for ataxic and anticonvulsant activity. Their acute toxicity in mice is very low (LD_{50} in both cases above 1 g/kg p.o.). In the rotarod test in mice the doses of 50 mg/kg p.o. brought about ataxia in 20–30% of the animals. In the test of maximum electroshock in mice the doses of 2 and 10 mg/kg p.o. had no protective effect.

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 ε)) were recorded with a Unicam SP 8000 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 CW-NMR spectrometer TESLA BS 487C (80 MHz), and the mass spectra (m/z, %) with MCH 1320 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 $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

4-(2-Propylthio)acetophenone (*III*)

A) A stirred solution of 91·5 g (2-propylthio)benzene[9] and 60 g acetyl chloride in 450 ml 1,2-dichloroethane was treated under external cooling (10–15°C) with 105 g pulverized $AlCl_3$, added in small portions over 1 h. The mixture was stirred for 6 h at room temperature, was allowed to stand overnight, and was poured into a mixture of 1·2 kg ice and 300 ml hydrochloric acid. The separated organic layer was washed with 2 × 200 ml 10% hydrochloric acid, with water and 10% Na_2CO_3, dried, and distilled; 85·8 g (73%) of crude *III*, b.p. 108–115°C/26 Pa. According to gas chromatography the product consisted of 95% of the main component (evidently *III*) and 5% of a contaminant. Ref.[8], b.p. 121–123°C/40 Pa.

2,4-Dinitrophenylhydrazone, m.p. 172°C (ethyl acetate). Ref.[10], m.p. 173–174°C.

B) A solution of 91·3 g (2-propylthio)benzene[9] and 70 g acetyl chloride in 400 ml CS_2 was similarly treated at 0–10°C over 45 min with 93 g $AlCl_3$. After 4 h stirring at the same temperature, the mixture was poured into a mixture of 1 kg ice and 200 ml hydrochloric acid. Similar processing gave 78·3 g (67%) of crude *III*, b.p. 108–110°C/20 Pa, which was identical with the product obtained under *A* (gas chromatography).

4-(2-Propylthio)acetophenone Oxime (*IV*)

A solution of 30 g $NH_2OH.HCl$ and 58·5 g sodium acetate trihydrate in 90 ml water was added

to a solution of 30 g *III* in 400 ml ethanol and the mixture was refluxed for 1 h. A part of ethanol (250 ml) was distilled off and the residue was diluted with 500 ml water. The separated oily product crystallized on standing, was filtered, washed with water, and dried in vacuo; 32·3 g (theoretical) of *IV*, m.p. 67–71°C. Crystallization from hexane (250 ml, undissolved component was removed by filtration), then from aqueous ethanol, and finally once more from hexane gave the completely homogeneous *IV* crystallizing in great prisms, m.p. 74·5°C. UV spectrum: 283 (3·77), 690 (4·16). IR spectrum: 820 (2 adjacent Ar–H); 1 490, 1 590 (Ar); 1 643 (Ar—C=N); 3 210 (OH). For $C_{11}H_{15}NOS$ (209·3) calculated: 63·12% C, 7·22% H, 6.69% N, 15·32% S; found: 63·17% C, 7.30% H, 6·60% N, 15·41% S.

O-(2-Aminoethyl)-4-(2-propylthio)acetophenone Oxime (*V*)

Oxime *IV* (10·45 g) was added to a solution of sodium ethoxide (from 2·53 g Na and 80 ml ethanol), the solution obtained was stirred for 30 min and treated dropwise with a solution of 6·4 g 2-chloroethylamine hydrochloride[12] in 25 ml ethanol. The mixture was stirred for 4 h at room temperature and allowed to stand overnight. Precipitated NaCl was filtered off, the filtrate was heated for 30 min to 60–70°C and evaporated. The residue was treated with 100 ml water and 3M-HCl to pH 1–2. The precipitated solid (4·15 g, m.p. 72–73°C) was filtered off and identified as the starting *IV*. The acid filtrate was made alkaline with NH_4OH and extracted with benzene. The extract was washed with water, dried, and evaporated; 5·1 g (67% per conversion) of oily *V*. It was dissolved in 20 ml ether and reacted with a solution of 2·4 g maleic acid in 120 ml ether; 4·8 g of hydrogen maleate of *V*, m.p. 122–124°C (ethanol). Mass spectrum: 252 (M^+, $C_{13}H_{12}NOS$). For $C_{17}H_{24}N_2O_5S$ (368·4) calculated: 55·41% C, 6·57% H, 7·61% N, 8·70% S; found: 55·21% C, 6·53% H, 7·50% N, 8·77% S.

O-(3-Dimethylaminopropyl)-4-(2-propylthio)acetophenone Oxime (*VI*)

Oxime *IV* (10·45 g) was dissolved in a solution of sodium ethoxide (from 1·4 g Na and 100 ml ethanol), the solution was stirred for 30 min, treated with 8·0 g 3-dimethylaminopropyl chloride and the mixture was refluxed for 7 h. Similar processing gave 9·7 g (66%) of crude oily *VI*.

Hydrogen maleate, m.p. 93–94°C (ethanol). Mass spectrum; CI: 295 ($(M + H)^+$, $C_{16}H_{26}N_2OS$ + H), 194, 99; EI: 194 (7), 100 (21), 71 (100), 58 (66), 43 (21). For $C_{20}H_{30}N_2O_5S$ (410·5) calculated: 58·51% C, 7·37% H, 6·83% N, 7·81% S; found: 58·35% C, 7·58% H, 6·77% N 7·67% S.

(4-(2-Propylthio)phenyl)acetothiomorpholide (*VII*)

A stirred mixture of 38·8 g *III*, 12·8 g S, and 80 g morpholine was heated under reflux for 9 h in a bath (150°C). After cooling the mixture was diluted with 300 ml benzene, the solution was washed with 2 × 150 ml 1·5M-HCl and water, dried, and evaporated. The oily residue was dissolved in 180 ml ethanol and the solution was allowed to crystallize for 48 h at room temperature; 37·7 g (65%) of *VII*, m.p. 86–87°C (ethanol). IR spectrum: 800 (2 adjacent Ar–H); 1 129 (R–O–R); 1 492 (RCSN); 1 592, 3 030, 3 060 (Ar). ^1H NMR spectrum: 1·23 d, 6 H (2 × CH_3 of 2-propyl, $J = 7·0$); 3·10–4·50 m, 11 H (CHS, $ArCH_2$, and 4 × CH_2 of morpholine); 7·30 m, 4 H (ArH). For $C_{15}H_{21}NOS_2$ (295·5) calculated: 60·97% C, 7·17% H, 4·74% N, 21·70% S; found: 61·08% C, 7·17% H, 4·64% N, 21·78% S.

Two similar batches from 68·0 and 120 g *III* gave 68 and 125 g *VII*, respectively. Mother liquors from all the three experiments were combined and evaporated to a volume of about 250 ml. Standing for 4 days led to crystallization of 16·6 g crude 2-(4-(2-propylthio)phenyl)-2-

-oxoacetothiomorpholide (*VIII*), m.p. 117–127°C. Two crystallizations from benzene and one from ethanol gave the product melting at 128–130°C containing still some more polar impurity. A sample (2·0 g) was chromatographed on 60 g silica gel. Benzene eluted 1·5 g of homogeneous *VIII*, m.p. 133–134°C (yellow plates). Mass spectrum: 309 (M^+, $C_{15}H_9NO_2S_2$, 11·2), 179 (100), 137 (57·6), 130 (20), 109 (20), 86 (48). UV spectrum: 268 (4·20), 325 (4·28). IR spectrum: 809 (2 adjacent Ar–H); 1 236, 1 268 (R–O–R); 1 500 (NCS); 1 500, 1 547, 1 581, 3 020, 3 040, 3 050 (Ar); 1 641 (ArCOSN). ^{1}H NMR spectrum: 1·38 d, 6 H (2 × CH_3 of 2-propyl, J = 6·5); 3·40–4·40 m, 9 H (CHS, 2 × CH_2O, and 2 × CH_2N); 7·30 d, 2 H (H-2 and H-6, J = 9·0); 7·88 d, 2 H (H-3 and H-5, J = 9·0). For $C_{15}H_{19}NO_2S_2$ (309·4) calculated: 58·22% C, 6·19% H, 4·53% N, 20·72% S; found: 58·27% C, 6·13% H, 4·38% N, 20·78% S.

Continued elution with chloroform gave 0·20 g of the yellow dithio-oxalodimorpholide (*XVI*), m.p. 264–265°C (chloroform). UV spectrum: 1 233 (R–O–R); 1 483, 1 509 (NCS). ^{1}H NMR spectrum: 3·40–4·30 m (CH_2 groups of morpholine). The analysis is in agreement with $C_{10}H_{16}N_2O_2S_2$. Ref.[18], m.p. 263–265°C.

(4-(2-Propylthio)phenyl)acetic Acid (*IX*)

A) A mixture of 33 g crude *VII* (oily), 110 ml ethanol, 27 g KOH and 5 ml water was stirred and refluxed for 7 h. Ethanol was evaporated under reduced pressure. The residue was dissolved in 200 ml water, the solution was washed benzene, filtered with active carbon and the filtrate was acidified with 55 ml hydrochloric acid. The separated oil was extracted with benzene, the extract was washed with water, filtered, and evaporated. The oily residue (18·9 g, 83%) crystallized on standing but the attempts at its recrystallization were not successful. A part (10·0 g) was therefore chromatographed on 200 g silica gel. Elution with chloroform gave 8·1 g of a homogeneous substance which crystallized from hexane and melted constantly at 49–50°C. Because of the spectral and analytical data, this substance is considered to be crystal modification *A* of *IX*. IR spectrum: 811 (2 adjacent Ar–H); 903, 1 245, 1 700, 2 555, 2 650, 2 730, infl. 3 100 (COOH); 1 497, 1 602, 3 025 (Ar). ^{1}H NMR spectrum: 1·30 d, 6 H (2 × CH_3 of 2-propyl, J = 6·0); 3·35 m, 1 H (CHS); 3·60 s, 2 H ($ArCH_2CO$); 7·18 d, 2 H (H-3 and H-5, J = 8·5); 7·38 d, 2 H (H-2 and H-6, J = 8·5); 11·30 bs, 1 H (COOH). For $C_{11}H_{14}O_2S$ (210·3) calculated: 62·83% C, 6·71% H, 15·25% S; found: 62·80% C, 6·87% H, 15·24% S. Refs[15,20], m.p. 78–79°C.

B) A similar hydrolysis of 36·7 g homogeneous, crystalline *VII* (m.p. 86–87°C) with 30 g KOH in 170 ml ethanol and 30 ml water gave the crude crystalline product which was recrystallized from 200 ml hexane; 23·5 g (90%) of crystal modification *B* of *IX*. It gave correct analysis for $C_{11}H_{14}O_2S$ and its melting point is identical with the published value (refs[15,20], m.p. 78–79°C).

Ethyl 4-(2-Propylthio)benzoylformate (*X*)

Ethoxalyl chloride[21] (108 g) was added at 10°C to a solution of 152 g (2-propylthio)benzene[9] in 650 ml 1,2-dichloroethane and the stirred solution was treated over 45 min with 140 g $AlCl_3$, added in small portions (temprature 10–15°C). The mixture was stirred for 4·5 h at 20°C and poured into a mixture of 1·6 kg ice and 440 ml hydrochloric acid. The separated aqueous layer was extracted with 1,2-dichloroethane, organic layers were combined, washed with saturated NaCl solution, 10% hydrochloric acid, and water, dried and evaporated. The residue gave by first distillation 64 g of a fraction boiling at 135–155°C/0·1 kPa and containing about 80% of *X* (gas chromatography). Redistillation gave 55·1 g (27%) of almost homogeneous *X*, b.p. 130–140°C/40 Pa. UV spectrum: 327 (4·10). IR spectrum (film): 829, 843 (2 adjacent Ar–H); 1 088,

1 180, 1 210 (C–O–C of ester); 1 490, 1 552, 1 589, 3 060 (Ar); 1 675 (ArCO); 1 733 (COOR). For $C_{13}H_{16}O_3S$ (252·3) calculated: 61·88% C, 6·39% H, 12·71% S; found: 61·58% C, 6·39% H, 12·97 % S.

2-Hydroxy-2-(4-(2-propylthio)phenyl)propionic Acid (*XI*)

Grignard reagent was prepared from 7·0 g Mg and 38·3 g methyl iodide in 50 ml ether and was diluted with 80 ml toluene. After cooling this solution was added dropwise to a stirred solution of 55·0 g *X* in 60 ml toluene; the temperature was maintained at 0—3°C. The mixture was then stirred for 3 h at room temperature and was poured to a mixture of 800 g ice and 60 ml H_2SO_4. The organic layer was separated (after removal of a small amount of a yellow solid by filtration), washed with 5% hydrochloric acid, 5% Na_2CO_3, and 5% $K_2S_2O_5$, dried and evaporated. The residue (63 g) was dissolved in 130 ml methanol, the solution was treated with a solution of 37 g K_2CO_3 in 130 ml water and the mixture was stirred and refluxed for 6 h. Methanol was evaporated, the residue was dissolved in 200 ml water, the solution was washed with benzene, filtered with active carbon, and the filtrate was acidified under stirring with dilute H_2SO_4 (1 : 4). The separated product was extracted with warm benzene (50°C) and the extract was processed. The crude crystalline product (40 g) was dissolved in 450 ml boiling benzene, a small amount of undissolved material (3·8 g) was filtered off, the filtrate was evaporated, the residue was dissolved in 70 ml benzene and the addition of 40 ml hexane induced crystallization; 23·9 g (46%) of *XI*, m.p. 111—112°C (benzene). IR spectrum: 838 (2 adjacent Ar–H); 879, 1 242, 1 289, 1 723, 2 573, 2 740, 3 120 (COOH); 1 485, 1 592 (Ar); 1 107, 1 143 (C–OH); 3 430 (OH). ^{1}H NMR spectrum: 1·28 d, 6 H (2 × CH_3 of 2-propyl, J = 6·0); 1·80 s, 3 H (remaining CH_3); 3·38 m, 1 H (CHS); 7·30 d, 2 H (H-3 and H-5, J = 8·5); 7·50 d, 2 H (H-2 and H-6, J = 8·5); 7·70 flat band, 1 H (COOH). For $C_{12}H_{16}O_3S$ (240·3) calculated: 59·97% C, 6·71% H, 13·34% S; found: 60·20% C, 6·83% H, 13·42% S.

2-(4-Mercaptophenyl)propionic Acid (*XVII*)

2-(4-Aminophenyl)propionic acid[23] (58 g in the form of the hydrochloride) was dissolved in dilute hydrochloric acid (175 ml water and 70 ml hydrochloric acid), the solution was cooled and was diazotized at 0°C under stirring with a solution of 24·2 g $NaNO_2$ in 130 ml water. The mixture was stirred for 45 min at 0°C and was added dropwise to a solution of 65·0 g potassium ethyl xanthate in 270 ml water and 270 ml ethyl acetate at 55°C over 30 min. The mixture was stirred for 30 min, cooled, the separated aqueous layer was extracted with ethyl acetate, organic layers were combined, and evaporated. The residue (73 g) was dissolved in 440 ml ethanol, a solution of 79·1 g KOH in 440 ml water was added and the mixture was refluxed under nitrogen for 12 h. Ethanol was evaporated, the aqueous residue was acidified at 10—15°C with 100 ml hydrochloric acid, and the separated product was extracted with ether. Processing gave 58·3 g of residue which was dissolved in 50 ml benzene and chromatographed on 1 kg silica gel. The benzene eluates were discarded. The following chloroform eluates gave 24·09 g (38%) of *XVII*, m.p.59—63°C (light petroleum). IR spectrum (KBr): 800, 830 (2 adjacent Ar–H); 945, 1 229, 1 700, 2 625, 2 720, infl. 3 150 (COOH). ^{1}N NMR spectrum: 1·46 d, 3 H (CH_3, J = 7·0); 3.40 s, 1 H (SH); 3·65 q, 1 H (ArCHCO, J = 7·0); 7·15 s, 4 H (ArH); 11·70 bs, 1 H (COOH). For $C_9H_{10}O_2S$ (182·2) calculated: 59·32% C, 5·53% H, 17·60% S; found: 59·49% C, 5·60% H, 17·42% S. Ref.[22], b.p. 160°C/0·47 kPa.

Chromatography was concluded by elution with chloroform containing 5% of ethanol which gave 0·8 g of di(4-(1-carboxyethyl)-phenyl)disulfide (*XVIII*), m.p. 184—186°C (ethanol–benzene). Mass spectrum: 362 (M^+, $C_{18}H_{18}O_4S_2$, 50), 317 (10), 316 (10), 273 (10), 245 (5), 182 (20),

167 (50), 137 (100), 135 (90), 125 (20), 105 (25), 104 (30), 103 (28). IR spectrum: 800 (2 adjacent Ar–H); 940, 1 230, 1 695, 2 535, 2 620, 2 718, infl. 3 100 (COOH); 1 490, 1 564, 1 590 (Ar). ^{1}H NMR spectrum (CD_3SOCD_3): 1·35 d, 6 H (2 × CH_3, J = 7·0); 3·69 q, 2 H (2 × ArCHCO, J = 7·0); 7·32 d, 4 H (H-2, H-6, H-2′, and H-6′, J = 8·5); 7·53 d, 4 H (H-3, H-5, H-3′, and H-5′, J = 8·5). For $C_{18}H_{18}O_4S_2$ (362·5) calculated: 59·65% C, 5·01% H, 17·69% S; found: 59·83% C, 5·16% H, 17·88% S.

2-(4-(2-Propylthio)phenyl)propionic Acid (*XII*)

A) A mixture of 23·9 g *XI*, 150 ml acetic acid, 2 ml water, 7·0 g red phosphorus, and 2·0 g *I* was stirred and refluxed for 5 h. After cooling the mixture was filtered and the filtrate was poured into 600 ml water containing 20 g $K_2S_2O_5$. The separated oil crystallized on standing, was filtered, washed with water, and dried in vacuo; 21·2 g (95%) of *XII*, m.p. 66–67°C (light petroleum). IR spectrum: 805, 833 (2 adjacent Ar–H); 946, 1 167, 1 232, 1 243, 1 685, 1 701, 1 722, 2 630, infl. 3 150 (COOH); in chloroform: 1 709 (COOH). ^{1}H NMR spectrum: 1·32 d, 6 H (2 × CH_3 in 2-propyl, J = 7·0); 1·50 d, 3 H (remaining CH_3, J = 7·0); 3·38 m, 1 H (CHS); 3·72 q, 1 H (ArCHCO, J = 7·0); 7·20 d, 2 H (H-3 and H-5, J = 8·5); 7·40 d, 2 H (H-2 and H-6, J = 8·5); 11·90 bs, 1 H (COOH). For $C_{12}H_{16}O_2S$ (224·3) calculated: 64·24% C, 7·19% H, 14·29% S; found: 64·14% C, 7·38% H, 14·08% S.

B) A mixture of 2·55 g *XVII*, 3·8 g K_2CO_3, 3·44 g 2-bromopropane, and 10 ml dimethylformamide was stirred and heated to 60°C for 5 h. After cooling the mixture was diluted with 20 ml water, the separated intermediate was extracted with benzene, and the extract was processed. The residue (3·04 g) was dissolved in 5 ml ethanol, a solution of 3·0 g NaOH in 10 ml water was added and the mixture was refluxed for 5·5 h. Ethanol was evaporated, the residue was dissolved in 80 ml water, the solution was washed with benzene and was acidified with hydrochloric acid. The seaprated *XII* was isolated by extraction with benzene; 2·2 g (70%), m.p. 56–63°C. Recrystallization from light petroleum gave the pure product melting at 63·5–66°C which was found identical with the product obtained under *A*.

(4-(2-Propylthio)phenyl)acetamide (*XIII*)

A solution of 6·0 g *IX* in 60 ml hexane was treated with 17 g $SOCl_2$ and the mixture was stirred and refluxed for 4 h. Hexane and the excess of $SOCl_2$ were removed by evaporation, the remaining oily acid chloride was dissolved in 80 ml ether, and the solution was saturated for 30 min with NH_3 which was introduced to the surface of the solution. After standing overnight ether was distilled off, the residue was distributed between 150 ml chloroform and 70 ml dilute NH_4OH, the chloroform layer was filtered, and evaporated; 5·4 g (90%) of *XIII*, m.p. 155°C (benzene). IR spectrum: 802 (2 adjacent Ar–H); 1 500, 1 600, 3 040 (Ar); 1 640, infl. 1 670 ($RCONH_2$); 3 180, 3 350 (NH_2). ^{1}H NMR spectrum (CD_3SOCD_3): 1·28 d, 6 H (2 × CH_3 of 2-propyl, J = 6·0); 3·40 s and 3·40 m, 2 and 1 H ($ArCH_2CO$ and CHS); 7·20 d, 2 H (H-3 and H-5, J = = 8·5); 7·35 d, 2 H (H-2 and H-6, J = 8·5); 6·85 bs and 7·45 bs, 1 and 1 H ($CONH_2$). For $C_{11}H_{15}NOS$ (209·3) calculated: 63·12% C, 7·22% H, 6·69% N, 15·32% S; found: 62·85% C, 7·30% H, 6·68% N, 15·46% S.

2-(4-(2-Propylthio)phenyl)propionamide (*XIV*)

Acid *XII* (6·0 g) in 60 ml hexane was similarly transformed by treatment with 16·2 g $SOCl_2$ to the crude acid chloride which was dissolved in 80 ml ether, and the solution was similarly saturated with NH_3. Similar processing gave 5·6 g (93%) of *XIV*, m.p. 112–113°C (benzene). IR spectrum:

832 (2 adjacent Ar–H); 1 492, 1 594, 3 015 (Ar); 1 630, 1 655 ($CONH_2$); 3 180, 3 350 (NH_2). ^{1}H NMR spectrum: 1·30 d, 6 H (2 × CH_3 of 2-propyl, J = 7·0); 1·50 d, 3 H (remaining CH_3 J = 7·0); 3·35 m, 1 H (CHS); 3·60 q, 1 H (ArCHCO, J = 7·0); 5·65 bs and 6·38 bs, 1 and 1 H ($CONH_2$); 7·20 d, 2 H (H-3 and H-5, J = 8·5); 7·40 d, 2 H (H-2 and H-6, J = 8·5). For $C_{12}H_{17}NOS$ (223·3) calculated: 64·53% C, 7·67% H, 6·27% N, 14·35% S; found: 64·58% C, 7·89% H, 6·11% N, 14·27% S.

2-(4-(2-Propylthio)phenyl)propiono(4-methylpiperazide) (*XV*)

The crude acid chloride was prepared from 7·0 g *XII* and 17·8 g $SOCl_2$ in 70 ml hexane, after evaporation of the volatile components the residue was dissolved in 70 ml ether and the solution was treated dropwise over 30 min with a solution of 6·3 g 1-methylpiperazine in 20 ml ether. The solvent was evaporated and the residue was distributed between 100 ml chloroform and dilute NH_4OH. The chloroform layer was washed with water, dried, and evaporated; 8·8 g (93%) of oily *XV*.

Hydrogen maleate, 3 : 1 solvate with toluene, m.p. 132–134°C (ethanol denaturated with toluene). Mass spectrum: 306 (M^+, $C_{17}H_{26}N_2OS$, 20), 249 (18), 220 (5), 206 (10), 179 (40), 137 (37), 127 (38), 99 (28), 83 (50), 70 (100); the presence of toluene was proven. For $C_{21}H_{30}N_2O_5S + 1/3\ C_7H_8$ (453·2) calculated: 61·83%'C, 7·27% H, 6·18% N, 7·07% S; found: 61·86% C, 7·19% H, 6·19% N, 7·14% S.

Hydrochloride, m.p. 200–203°C (ethanol). IR spectrum: 832 (2 adjacent Ar–H); 1 590, 3 060 (Ar); 1 640 (CON); 2 415, 2 500, 2 540, 2 575 (NH^+); 2 720 ($N-CH_2$, $N-CH_3$). For $C_{17}H_{27}ClN_2OS$ (342·9) calculated: 59·54% C, 7·94% H, 10·34% Cl, 8·17% N, 9·35% S; found: 59·80% C, 8·00% H, 10·57% Cl, 8·39% N, 9·51% S.

The authors wish to thank their colleagues at the Research Institute for Pharmacy and Biochemistry for their contributions to the present study: Mr J. Pomykáček (help with the synthesis); Mrs J. Komancová, Mrs V. Šmídová, and Mrs A. Svatošová (elemental analyses); Dr B. Schneider, Mrs A. Hrádková, and Mrs Z. Janová (some of the spectral data); Drs M. Ryska, I. Koruna, and O. Matoušová (mass spectra); Dr M. Valchář, Mrs M. Jandová, Mrs J. Ezrová, Mrs J. Horáková, and Mrs E. Šulcová (pharmacology and biochemical pharmacology).

REFERENCES

1. N. V. Philips' Gloeilampenfabrieken: Belg. 839,744; Neth Appl. 75 03,310; Chem. Abstr. *86*, 72203 (1977).
2. Thorpe P. J.: Drugs Future *3*, 288 (1978); *4*, 303 (1979); *6*, 255 (1981); *7*, 287 (1982); *8*, 363 (1983); *9*, 295 (1984).
3. Claassen C., Davies J. E., Hertting G., Placheta P.: Br. J. Pharmacol. *60*, 505 (1977).
4. Benfield P., Ward A.: Drugs *32*, 313 (1986).
5. Nicholson J. S., Adams S. S. (Boots Pure Drug): Brit. 971,700; U.S. 3,228,831; 3,385,886; Chem. Abstr. *61*, 14591 (1964).
6. Adams S. S., Cliffe E. E., Lessel B., Nicholson J. S.: J. Pharm. Sci. *56*, 1686 (1967).
7. Adams S. S., McCullough K. F., Nicholson J. S.: Arch. Int. Pharmacodyn. Ther. *178*, 115 (1969).
8. Gregory W. A. (E. I. du Pont de Nemours): U.S. 2,763,692; Chem. Abstr. *51*, 4429 (1957).
9. Zimmerman H. E., Thyagarajan B. S.: J. Am. Chem. Soc. *82*, 2505 (1960).
10. Gasparič J., Večeřa M., Jureček M.: Chem. Listy *52*, 1720 (1958).

11. Rekker R. F., Veenland J. U.: Rec. Trav. Chim. Pay-Bas *78*, 739 (1959).
12. Seitz O.: Ber. Dtsch. Chem. Ges. *24*, 2626 (1891).
13. Exner O.: Collect. Czech. Chem. Commun. *20*, 202 (1955).
14. Carmack M.: Org. React. *3*, 85 (1946).
15. Nicholson J. S., Adams S. S. (Boots Pure Drugs): Neth. Appl. 65 295, 860; Chem. Abstr. *63*, 14774 (1965).
16. McMillan F. H., King J. A.: J. Am. Chem. Soc. *69*, 1207 (1947).
17. Horton W. J., Van den Berghe J.: J. Am. Chem. Soc. *70*, 2425 (1948).
18. Levesque C. L. (Rohm and Haas): U.S. 2,525,416; Chem. Abstr. *45*, 1623 (1951).
19. Brace N. O.: J. Am. Chem. Soc. *75*, 357 (1953).
20. Nicholson J. S., Adams S. S.: Brit. 1,012,480.
21. Southwick P. L., Seivard L. L.: J. Am. Chem. Soc. *71*, 2532 (1949).
22. Societe des Usines Chimiques Rhone-Poulenc: Fr. M6,444, Addn 0296; Chem. Abstr. *75*, 5528 (1971); *78*, 58068 (1973).
23. Nerdel F., Fischer L.: Chem. Ber. *87*, 217 (1954).
24. Tarbell D. S., Fukushima D. K.: Org. Synth., Coll. Vol. *3*, 809 (1955).
25. Winter J.: Proc. Soc. Exp. Biol. Med. *111*, 544 (1962).
26. Hillebrecht N. P.: Arzneim.-Forsch. *9*, 625 (1959).
27. Pearson C. M.: Arthr. Rheum. *2*, 440 (1959).
28. Witkins L. B., Heubner C. F., Galdi F., O'Keefe E., Spitaletta P., Plummer A. J.: J. Pharmacol. Exp. Ther. *133*, 400 (1961).
29. Jezdinský J., Hálek J.: Cesk. Fysiol. *22*, 363 (1973).
30. Randall L. O., Selitto J. J.: Arch. Int. Pharmacodyn. Ther. *111*, 409 (1957).
31. Robert A., Nezamis J. E.: Proc. Soc. Exp. Biol. Med. *99*, 443 (1958).

Translated by the author (M.P.).