POTENTIAL ANTICONVULSANTS: SOME DERIVATIVES AND ANALOGUES OF 2-PROPYLPENTANOIC ACID

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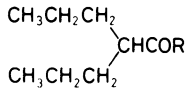
Reaction of 2-(ethoxycarbonylamino)ethanol with 2-propylpentanoyl chloride gave the ester *III*. N-(4-Piperidinyl)-2-propylpentanamide (*V*) was prepared via the 1-benzyl-4-piperidinyl derivative *IV* and was acylated with ethanesulfonyl chloride and 2-propylpentanoyl chloride to give the amides *VI* and *VII*. Malonic ester syntheses afforded diethyl 2-ethyl- and 2-propyl-2-(2-(methylthio)ethyl)malonate *VIII* and *XIII* which were hydrolyzed and decarboxylated to the acids *X* and *XV* which, in turn, were transformed to the amides *XII* and *XVII*. 3-Thiapentanenitrile was alkylated with propyl bromide to the nitrile *XIX* which was hydrolyzed to the acid *XX* and the amide *XXI*. The acids *X*, *XV*, and *XX*, and the amides *XII*, *XVII*, and *XXI* are analogues of the anticonvulsant agents valproic acid (*I*) and valpromide (*II*). Compounds *XX* (VÚFB-14 721) and *XXI* (VÚFB-14 722) potentiate, in doses in which they "per se" are ineffective as anticonvulsants in mice, significantly the anticonvulsant effect of diazepam.

Preparation of 2-propylpentanoic acid ("valproic acid") (*I*) by decarboxylation of dipropylmalonic acid[1,2] was described already in 1888 but its anticonvulsant activity was recognized only in 1963 (ref.[3]). Since 1967 it has been used in the treatment of some forms of epileptic seizures (absence, "petit mal") as the free acid or in the form of salts, especially sodium salts ("valproate sodium" and "valproate semisodium", refs[4-7]) and calcium salt (Convulsofin[R], ref.[8]). 2-Propylpentanamide ("valpromide" (*II*), ref.[9]) was also found to be an anticonvulsant[10,11] and is being also used as a prophylactic in the maniodepressive illness[12]. Because of the relatively low efficacy of *I* (oral daily doses are 0·6 – 1·8 g) and of some undesired side effects, the efforts to find more convenient anticonvulsants among its derivatives and analogues were quite comprehensible. The following types of analogues of *I* were investigated: straight-chain lower fatty acids[13], branched-chain acids with various alkyls[14,15], unsaturated acids[16,17] ((*E*)-2-propyl-2-pentenoic acid seems to be well comparable with *I* (ref.[17]), the isomeric 2-propyl-4-pentenoic acid is a toxic metabolite of *I* (refs[18,19])), cyclic analogues[20,21], compounds modified in the functional group (amides, ureas, amines, ketones, alcohols) (refs[22-24]). With the exception of 2-ethyl-3-methylpentanamide („valnoctamide", ref.[25]), none of the analogues prepared did find practical use. The present communication is a contribution to the efforts

mentioned and deals with (i) a carbamate group containing derivative of *I*, (ii) N-(4-piperidyl)amides of *I*, and (iii) thia analogues of *I* and *II*.

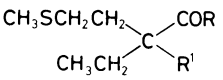


I, R = OH
II, R = NH_2
III, R = $OCH_2CH_2NHCOOC_2H_5$
IV, R = NH–  –$NCH_2C_6H_5$
V, R = NH–  –NH
VI, R = NH–  –$NSO_2C_2H_5$
VII, R = NH–  –$NCOCH(CH_2CH_2CH_3)_2$

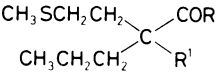
The carbamate fragment is a rather typical moiety of moleculs of the anticonvulsant agents[26]. This fact induced us to design the structure *III* and to synthesize this ester. It was obtained by reaction of 2-propylpentanoyl chloride[9] with 2-(ethoxycarbonylamino)ethanol[27] at 70–80°C. The oily product *III* was purified by distillation in vacuo and was characterized by spectra. In order to prepare a basic amide of *I* which would be soluble in water in the form of salts, 2-propylpentanoyl chloride was reacted with 4-amino-1-benzylpiperidine[28] (for the base, cf. also ref.[29]) in 2-butanone under cooling; crystalline hydrochloride of *IV* was obtained in a high yield. Treatment with aqueous ammonia released the crystalline base *IV* whose identity was confirmed by spectra. Catalytic hydrogenolysis of *IV* on the Adams catalyst in ethanol afforded the secondary amine *V* which was purified by sublimation in vacuo, characterized by spectra and transformed to the hydrochloride. Treatment of *V* with ethanesulfonyl chloride[30] in boiling acetone in the presence of potassium carbonate gave the sulfonamide *VI*. A similar reaction of *V* with 2-propylpentanoyl chloride afforded *VII*, containing two valproic acid residues in the molecule. Structures of *VI* and *VII* were corroborated by spectra.

Substitution of the methylene group in molecules of pharmacologically active compounds by the atom of sulfur ("thia isosterism") leads often to interesting analogues. Our first attempt in this line started from the known diethyl 2-(methylthio)-ethylmalonate[31,32] which was treated with sodium ethoxide in ethanol and alkylated with ethyl iodide. The distilled product[31] *VIII* (purity was checked by gas chromatography) was hydrolyzed with potassium hydroxide in aqueous ethanol and after acidification gave the crystalline malonic acid *IX* which was characterized by the IR and ^1H NMR spectra. Heating of *IX* to 120–150°C effected decarboxylation and the valproic acid-related *X* was purified by distillation. Its structure was corroborated by spectra. Reaction with thionyl chloride in boiling benzene gave the

crude chloride *XI* which was distilled and was further used without characterization. Its ammonolysis with ammonia in chloroform led to the crystalline amide *XII*. In the second attempt, diethyl 2-(methylthio)ethylmalonate was alkylated with propyl bromide and the diester *XIII* obtained was hydrolyzed to the malonic acid *XIV*. Thermic decarboxylation afforded the valproic acid analogue *XV* which was oily and whose structure was confirmed by spectra. Transformation to the crude acid chloride *XVI* proceeded similarly like in the preceding case. Its reaction with ammonia in chloroform afforded in addition to the desired crystalline amide *XVII* a considerable amount of a liquid by-product which was identified as the ethyl ester *XVIII*. Its formation has to be explained by the presence of ethanol in the chloroform used and by the preferential ethanolysis in comparison with the desired ammonolysis.

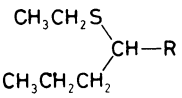


VIII, R = OC_2H_5; R^1 = $COOC_2H_5$ *XI*, R = Cl; R^1 = H
IX, R = OH; R^1 = COOH *XII*, R = NH_2; R^1 = H
X, R = OH; R^1 = H



XIII, R = OC_2H_5; R^1 = $COOC_2H_5$ *XVI*, R = Cl; R^1 = H
XIV, R = OH; R^1 = COOH *XVII*, R = NH_2; R^1 = H
XV, R = OH; R^1 = H *XVIII*, R = OC_2H_5; R^1 = H

The third attempt aimed at 3-thiavalproic acid and its amide. The known 3-thiapentanenitrile[33,34] was alkylated with propyl bromide in the presence of sodium or potassium hydroxide and the phase transfer catalyst. The use of 50% sodium hydroxide or powdered potassium hydroxide together with tetrabutylammonium iodide led to mixtures with high participation of the starting 3-thiapentanenitrile. The combination of 50% sodium hydroxide with triethylbenzylammonium chloride led to recovery of 41% of the starting 3-thiapentanenitrile and to the desired *XIX* in the yield of 80% (per conversion). It is a liquid, distilling in vacuo without decomposition, containing about 98·5% of *XIX* according to gas chromatography, and confirmed structurally by the IR and ^{1}H NMR spectra. Its hydrolysis to *XX* was carried out by heating with a boiling mixture of hydrochloric acid and dioxane. 3-Thiavalproic acid (*XX*) – similarly like valproic acid (*I*) itself and its thia analogues *X* and *XV* – is a liquid which was distilled and characterized by spectra. Hydrolysis of *XIX* with sodium hydroxide in aqueous ethanol led to a mixture of the amide *XXI* and the acid *XX*.



XIX, R = CN
XX, R = COOH
XXI, R = $CONH_2$

Compounds *III*, *VII*, *XII*, *XVII*, *XX*, and *XXI* (the acid *XX* in the form of the sodium salt) were subjected to preliminary pharmacological evaluation (oral administration) and partially compared with *I* and *II*. Acute toxicity in mice, LD_{50} in mg/kg: *IV*, 162; *V*, 354; *VI*, 602; *VII*, >1 000; *XII*, 1 000; *XVII*, >1 000; *XX*, >2 500; *XXI*, >500 (for comparison *I*, 1 000). Test of corneal electroshock in mice: *III*, *V*, *XII* and *XVII*, ineffective at 100 mg/kg; *IV* and *VI*. at 10 mg/kg partial protection from the lethal effect of the electroshock but no anticonvulsant effect; *VII*, ineffective at 10 mg/kg; *XX* (VÚFB – 14 721) and *XXI* (VÚFB – 14 722), ineffective at 300 and 500 mg/kg but potentiate significantly the anticonvulsatn effect of diazepam (for comparison *I*, at 25–100 mg/kg ineffective as an anticonvulsant but reducing lethality; 500 mg/kg protect 100% of the animals from convulsions; ED_{50} 490 mg/kg (ref.[35]); *II*, PD_{50} 83·9 mg/kg, potentiates significantly the anticonvulsant activity of diazepam). Affinity to the benzodiazepine receptors (1 nmol l^{-1} [^{3}H]-flunitrazepam used as the ligand): *IV*, *VI*, *VII*, and *XVIII* were found ineffective. The data available did not warrant any more detailed studies of the synthesized compounds as potential anticonvulsants.

EXPERIMENTAL

The melting points of analytical samples were determined mostly in the Kofler block (they are not corrected), partly in the Mettler FP-5 melting point recorder; the samples were dried in vacuo of about 60 Pa at room temperature or at a suitably elevated temperature. IR spectra (mostly in Nujol, wave numbers in cm^{-1}) were recorded with the Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (in $CDCl_3$, δ in ppm, J inHz) with a TESLA BS 487C (80 MHz) spectrometer, and the mass spectrum (m/z, %) with the MCH 1320 spectrometer. The homogeneity of the substances 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.

2-(Ethoxycarbonylamino)ethyl 2-Propylpentanoate (*III*)

2-(Ethoxycarbonylamino)ethanol[27] (13·3 g) was stirred and treated over 15 min with 16·7 g 2-propylpentanoyl chloride[9], added dropwise. The temperature of the mixture rose spontaneously and the mixture was then heated for 6 h to 70–80°C. After cooling the mixture was dissolved in 70 ml ether, the solution was washed with a mixture of a saturated NaCl solution and 20% Na_2CO_3, dried, and processed by distillation; 23·2 g (90%) of *III*, b.p. 138–139°C/0·13 kPa. IR spectrum (film): 1 145, 1 170, 1 251, infl. 1 705, 1 729 (RCOOR', RNHCOOR');

1 530 (RNHCOOR'); 3 345 (NH). ^{1}H NMR spectrum: 0·85 bt, 6 H (2 × CH_3 of two propyls); 1·25 t, 3 H (CH_3 of ethyl; J = 7·0); 1·40 bm, 8 H (4 × CH_2 of two propyls); 2·35 bm, 1 H (CHCOO); 3·40 m, 2 H (CH_2N); 4·10 q, 2 H (CH_2O of ethoxycarbonylamino; J = 7·0); 4·15 s, 2 H (the ester $COOCH_2$; J = 7·0); 4·90 bs, 1 H (NH). For $C_{13}H_{25}NO_4$ (259·3) calculated: 60·20% C, 9·72% H, 5·40% N; found: 60·43% C, 10·00% H, 5·50% N.

N-(1-Benzyl-4-piperidinyl)-2-propylpentanamide (*IV*)

A solution of 10·0 g 4-amino-1-benzylpiperidine[28,29] in 70 ml 2-butanone was cooled to −2°C and treated under stirring with a solution of 9·4 g 2-propylpentanoyl chloride[9] in 60 ml 2-butanone, added dropwise over 30 min. The temperature of the mixture was maintained for further 30 min at −2—+5°C and, finally, it was stirred for 3 h at room temperature. The precipitated hydrochloride of *IV* was filtered, washed with a mixture of acetone and ether, and crystallized from a mixture of 70 ml ethanol and 50 ml ether; 12·0 g (65%), m.p. 241—242°C (ethanol). The analytical sample was dried at 150°C. Mass spectrum, CI: 316 (M^+, $C_{20}H_{32}N_2O$, 2·5); EI: 299 (0·3), 287 (0·2), 274 (0·6), 245 (1), 225 (2), 173 (15), 144 (14), 132 (18), 91 (50), 82 (100). For $C_{20}H_{33}ClN_2O$ (352·9) calculated: 68·06% C, 9·42% H, 10·05% Cl, 7·94% N; found: 67·77% C, 9·58% H, 10·30% Cl; 7·74% N.

The base *IV* was released from the hydrochloride with NH_4OH and was purified by crystallization from aqueous ethanol, m.p. 134—135°C. IR spectrum: 699, 741 (5 adjacent Ar–H); 1 492, 1 524, 1 583, 1 620, 3 022, 3 080 (Ar); 1 552, 1 639 (NHCO); 2 675, 2 735, 2 790 (CH_2–N); 3 275 (NH). ^{1}H NMR spectrum: 0·91 bt, 6 H (2 × CH_3 of two propyls); 1·00—3·00 m, 16 H ($CH_2CH_2NCH_2CH_2$ and 4 × CH_2 of two propyls); 3·50 s, 2 H ($ArCH_2N$); 3·85 bm, 1 H (CH–N); 5·42 bd, 1 H (NH); 7·30 s, 5 H (C_6H_5). For $C_{20}H_{32}N_2O$ (316·5) calculated: 75·90% C, 10·19% H, 8·85% N; found: 76·20% C, 10·48% H, 8·71% N.

N-(4-Piperidinyl)-2-propylpentanamide (*V*)

A solution of 20·0 g *IV* in 420 ml ethanol was treated with 3·0 g PtO_2 and the mixture was hydrogenated under shaking at normal conditions (temperature, pressure). After the consumption of 2·71 l H_2 (calculated 2·62 l) the reaction stopped, the mixture was filtered and the filtrate was evaporated; 14·3 g (theoretical) of *V*, m.p. 154—155°C (benzene–hexane). For analysis, the sample was sublimated in vacuo at 110—120°C (at 50 Pa), m.p. 163°C. IR spectrum: 1 550, 1 629 (RNCOOR'); 3 270 (NH). ^{1}H NMR spectrum: 0·89 bt, 6 H (2 × terminal CH_3); 1·00—2·00 m, 13 H ($CH_2CH_2CHCH_2CH_2$ in the acyl residue and 2 × CH_2 in positions 3 and 5 of piperidinyl); 1·48 s, 1 H (the piperidine NH); 2·65 m, 2 H (H-2ax and H-6ax of piperidinyl); 3·02 m, 2 H (H-2eq and H-6eq of piperidinyl); 3·85 m, 1 H (H-4 of piperidinyl); 5·50 bd, 1 H (CONH; J = 9·0). For $C_{13}H_{26}N_2O$ (226·4) calculated: 68·98% C, 11·58% H, 12·38% N; found: 69·15% C, 11·55% H, 12·17% N.

Hydrochloride, m.p. 174—175°C (2-propanol–ether). For $C_{13}H_{27}ClN_2O$ (262·8) calculated: 56·41% C, 10·36% H, 13·49% Cl, 10·66% N; found: 56·31% C, 10·27% H, 13·16% Cl, 10·52% N.

N-(1-(Ethanesulfonyl)-4-piperidinyl)-2-propylpentanamide (*VI*)

A stirred solution of 4·2 g *V* in 250 ml acetone was treated with 5·5 g K_2CO_3 and 2·4 g ethanesulfonyl chloride[30], added dropwise, and the mixture was refluxed for 4 h. The inorganic salts were filtered off while hot and the filtrate was evaporated in vacuo. The residue was dissolved in 150 ml warm benzene, the solution was washed with dilute hydrochloric acid and with 10% NaOH, dried, and evaporated to a volume of 10 ml. The crystallized product was filtered,

washed with ether, and dried in vacuo; 5·2 g (88%), m.p. 193–194°C (ethanol–hexane). IR spectrum: 1 135, 1 324 (RSO_2N); 1 550, 1 636 (RCONHR·); 3 285 (NH). ^{1}H NMR spectrum: 0·90 bt, 6 H (2 × terminal CH_3); 1·00–2·00 m, 13 H ($CH_2CH_2CHCH_2CH_2$ in the acyl residue and 2 × CH_2 in positions 3 and 5 of piperidinyl); 1·38 t, 3 H (CH_3 of ethylsulfonyl; J = 7·0); 2·98 q, 2 H (CH_2SO_2; J = 7·0); 2·90 m, 2 H (H-2ax and H-6ax of piperidinyl); 3·80 m, 2 H (H-2eq and H-6eq of piperidinyl); 4·05 m, 1 H (H-4 of piperidinyl); 5·98 bd, 1 H (CONH; J = 9·0). For $C_{15}H_{30}N_2O_3S$ (318·5) calculated: 56·57% C, 9·50% H, 8·80% N, 10·06% S; found: 56·86% C, 9·67% H, 8·75% N, 10·18% S.

N-(1-(2-Propylpentanoyl)-4-piperidinyl)-2-propylpentanamide (*VII*)

A stirred solution of 4·2 g *V* in 200 ml acetone was treated with 5·5 g K_2CO_3 and 3·1 g 2-propylpentanoyl chloride[9], added dropwise, and the mixture was refluxed for 4 h. It was diluted with 100 ml acetone, the salts were filtered off while warm and the filtrate was evaporated in vacuo. The residue was dissolved in 100 ml ether, the solution was washed with dilute hydrochloric acid and 10% NaOH, dried, and evaporated. The residue was crystallized from a mixture of 15 ml benzene and 40 ml hexane; 5·50 g (84%) of *VII*, m.p. 98–99°C (benzene–hexane). IR spectrum: 1 535, 1 635 (RCONHR' and RCON); 3 295 (NH). ^{1}H NMR spectrum: 0·90 bt, 12 H (4 × CH_3 in the two acyl residues); 1·00–2·00, 22 H (2 × $CH_2CH_2CHCH_2CH_2$ in the two acyl residues and 2 × CH_2 in positions 3 and 5 of piperidinyl); 4·10 m, 1 H (H-4 of piperidinyl); 3·00 m, 2 H (H-2ax and H-6ax of piperidinyl); 4·60 bm and 4·00 bm, 1 and 1 H (H-2eq and H-6eq of piperidinyl); 5·60 bd, 1 H (CONH; J = 9·0). For $C_{21}H_{40}N_2O_2$ (352·5) calculated: 71·54% C, 11·44% H, 7·95% N; found: 71·33% C, 11·27% H, 7·92% N.

Diethyl 2-Ethyl-2-(2-(methylthio)ethyl)malonate (*VIII*)

Alkylation of 50·0 g diethyl 2-(2-(methylthio)ethyl)malonate[31,32] with 25·1 g ethyl bromide in the presence of sodium ethoxide (from 4·8 g Na) in 125 ml ethanol according to ref.[31] gave 42·7 g (77%) of *VIII*, b.p. 91–93°C/40 Pa. The product consisted of 92% *VIII* (gas chromatographic evaluation).

Diethyl 2-(2-(Methylthio)ethyl)-2-propyl malonate (*XIII*)

A stirred solution of sodium ethoxide (4·8 g Na in 100 ml ethanol) was treated at 50°C over 75 min with 50·0 g diethyl 2-(2-(methylthio)ethyl)malonate[31,32], the mixture was refluxed for 1 h, then treated at 65°C with 29·5 g propyl bromide, added dropwise over 50 min, and the mixture was refluxed for 4·5 h. The precipitated NaBr was filtered off and the filtrate was processed by distillation; 46·8 g (80%) of *XIII*. The product consisted of 94% of *XIII* (gas chromatographic evaluation). IR spectrum (film): 1 177, 1 210, 1 230, 1 250, 1 730 (RCOOR'). ^{1}H NMR spectrum: 0·90 bt, 3 H (CH_3 of propyl); 1·20 bm, 2 H (CH_2 in position 1 of propyl); 1·24 t, 6 H (2 × CH_3 of ethyls; J = 7·0); 1·60–2·20 m, 4 H (CH_2 in position 2 of propyl and CH_2 in position 1 of methylthioethyl); 2·10 s, 3 H (CH_3S); 2·30 m, 2 H (CH_2S); 4·18 q, 4 H (2 × CH_2O; J = 7·0). For $C_{13}H_{24}O_4S$ (276·4) calculated: 56·49% C, 8·75% H, 11·60% S; found: 56·19% C, 8·97% H, 11·78% S.

2-Ethyl-2-(2-(methylthio)ethyl)malonic Acid (*IX*)

A solution of 42·7 g *VIII* in 180 ml ethanol was treated with a solution of 92·5 g KOH in 95 ml water and the mixture was refluxed for 4 h. Aqueous ethanol (210 ml) was distilled off, the residue

was diluted with 100 ml water and the solution was washed with ether. The aqueous layer was acidified under stirring and cooling with 250 ml 2·5M-HCl. The product was extracted with ether; processing of the extract gave 32·0 g (94%) of crystalline *IX*, m.p. 110—113°C (benzene). IR spectrum: 923, 1 252, 1 271, 1 340, 1 708, 2 620, infl. 3 050 (COOH). ^{1}H NMR spectrum: 1·00 t, 3 H (CH_3 of ethyl); 2·14 s, 3 H (CH_3S); 1·80—2·70 m, 6 H (CH_2CH_2–C–CH_2); 12·10 bs, 2 H (2 COOH). For $C_8H_{14}O_4S$ (206·3) calculated: 46·58% C, 6·84% H, 15·55% S; found: 46·83% C, 6·96% H, 15·28% S.

2-(2-(Methylthio)ethyl)-2-propylmalonic Acid (*XIV*)

A similar hydrolysis of 16·7 g *XIII* in 70 ml ethanol with 33·5 g KOH in 35 ml water gave 13·2 g (theoretical) of crude *XIV*, m.p. 83—88°C. Analytical sample, m.p. 90—93°C (benzene–hexane). IR spectrum: 910, 1 193, 1 237, 1 262, 1 299, 1 709, 2 630, 3 075 (COOH). ^{1}H NMR spectrum: 1·02 bt, 3 H (CH_3 of propyl); 1·35 bm, 2 H (CH_2 in position 1 of propyl); 2·15 s, 3 H (CH_3S); 1·80—2·30 m, 6 H (SCH_2CH_2 and CH_2 in position 2 of propyl); 12·15 bs, 2 H (2 COOH). For $C_9H_{16}O_4S$ (220·3) calculated: 49·06% C, 7·32% H, 14·56% S; found: 48·78% C, 7·44% H, 14·51% S.

2-Ethyl-5-thiahexanoic Acid (*X*)

Diacid *IX* (32·0 g) was heated for 1 h to 120°C, for 20 min to 130°C, for 20 min to 140°C, for 30 min to 150°C, and the residue was distilled; 22·5 g (89%), b.p. 91—93°C/40 Pa. IR spectrum (film): 945, 1 231, 1 289, 1 704, 2 670, infl. 3 200 (COOH). ^{1}H NMR spectrum: 1·00 t, 3 H (CH_3 of ethyl; J = 7·0); 1·30—2·00 m, 4 H (CH_2 of ethyl and CH_2 in position 3); 2·10 s, 3 H (CH_3S); 2·52 t (J = 7·0) and 2·55 bm, $\sum$ 3 H (CH_2S and CHCO); 11·70 bs, 1 H (COOH). For $C_7H_{14}O_2S$ (162·3) calculated: 51·81% C, 8·70% H, 19·77% S; found: 51·60% C, 8·88% H, 19·85% S.

2-Propyl-5-thiahexanoic Acid (*XV*)

A similar thermic decarboxylation of 37·4 g *XIV* gave 24·2 g (81%) of *XV*, b.p. 100—103°C/40 Pa. IR spectrum (film): 950, 1 246, 1 286, 1 704, 2 670, infl. 3 200 (COOH). ^{1}H NMR spectrum: 0·90 bt, 3 H (CH_3 of propyl); 1·20—2·00 m, 6 H (CH_2CH_2 of propyl and CH_2 in position 3); 2·10 s, 3 H (CH_3S); 2·52 t (J = 7·0) and 2·55 bm, $\sum$ 3 H (CH_2S and CHCO); 11·70 bs, 1 H (COOH). For $C_8H_{16}O_2S$ (176·3) calculated: 54·50% C, 9·15% H, 18·19% S; found: 54·21% C, 9·04% H, 18·30% S.

2-Ethyl-5-thiahexanamide (*XII*)

A solution of 22·5 g *X* in 110 ml benzene was slowly treated with 24 g $SOCl_2$, the mixture was refluxed for 1·5 h and processed by distillation; 22·7 g of crude *XI*, b.p. 98—100°C/2·7 kPa. A solution of this intermediate (22·7 g) in 25 ml chloroform was treated with 80 ml chloroform which was saturated with NH_3. The mixture was stirred and saturated with NH_3 for 1·5 h at 40°C. Then it was treated with 50 ml NH_4OH and refluxed for 30 min. After cooling the mixture was extracted with chloroform, the extract was washed with water, dried, and evaporated. The residue crystallized from light petroleum; 8·1 g (36%), m.p. 78·5—79°C (benzene–light petroleum). IR spectrum (KBr): 1 655 ($CONH_2$); 3 185, 3 375 (NH_2). ^{1}H NMR spectrum: 0·92 t, 3 H (CH_3 of ethyl; J = 7·0); 1·00—2·70 m, 7 H ($SCH_2CH_2CHCH_2$); 2·10 s, 3 H (CH_3S); 5·65 bs and 6·00 bs, 1 and 1 H ($CONH_2$). For $C_7H_{15}NOS$ (161·3) calculated: 52·13% C, 9·38% H, 8·69% N, 19·89% S; found: 52·20% C, 9·25% H, 8·39% N, 19·59% S.

2-Propyl-5-thiahexanamide (*XVII*)

A similar reaction of 24·2 g *XV* with 25 g $SOCl_2$ in 80 ml boiling benzene gave 23·1 g of crude *XVI*, b.p. 113—116°C/2·7 kPa. This product was subjected to a similar treatment with NH_3 in chloroform and NH_4OH and gave 10·6 g (44%) of crude *XVII*, m.p. 85—90°C. Analytical sample, m.p. 94—95·5°C (benzene–hexane). IR spectrum: 1 655 ($CONH_2$); 3 180, 3 375 (NH_2). ^{1}H NMR spectrum: 0·90 bt, 3 H (CH_3 of propyl); 1·00—2·80 m, 9 H ($SCH_2CH_2CHCH_2CH_2$); 2·10 s, 3 H (CH_3S); 5·75 bs and 6·18 bs, 1 and 1 H ($CONH_2$). For $C_8H_{17}NOS$ (175·3) calculated: 54·81% C, 9·78% H, 7·99% N, 18·29% S; found: 54·57% C, 9·57% H, 8·28% N, 18·04% S.

The mother liquor after the crystallization of *XVII* was evaporated and the remaining oil was distilled; 4·6 g, b.p. 122—123°C/2·7 kPa. This product was purified by chromatography on 100 g neutral Al_2O_3 (activity II) and the fraction, obtained by elution with benzene, was redistilled; b.p. 110°C/2·1 kPa. It was identified as ethyl 2-propyl-5-thiahexanoate (*XVIII*). IR spectrum (film): 1 152, 1 183, 1 729 (RCOOR'). For $C_{10}H_{20}O_2S$ (204·3) calculated: 58·78% C, 9·86% H, 15·70% S; found: 59·08% C, 9·60% H, 15·71% S.

2-Propyl-3-thiapentanenitrile (*XIX*)

A mixture of 51·5 g 3-thiapentanenitrile[33,34], 96 g propyl bromide, 150 g NaOH, 150 ml water, and 10 g benzyltriethylammonium chloride was stirred for 8 h at 45°C, diluted with 250 ml water, and extracted with benzene. The extract was washed with water, diluted hydrochloric acid and water, dried, and distilled through a 70 cm column. The first fraction (40·6 g, b.p. 83—95°C/1·6 kPa) was the recovered 3-thiapentanenitrile. It was followed by 34·8 g (80% per conversion) of the crude *XIX* (consisted of 98·5% *XIX* according to gas chromatography), b.p. 96—97°C/1·3 kPa, a sample of which was redistilled, b.p. 102°C/2·0 kPa. IR spectrum (film): 2 240 (R–CN). ^{1}H NMR spectrum: 0·90 bt, 3 H (CH_3 of propyl), 1·30 t, 3 H (remaining CH_3, J = 7·0); 1·40—2·00 m, 4 H (CH_2CH_2 of propyl); 2·71 q, 2 H (CH_2S; J = 7·0); 3·00 t, 1 H (SCHCN; J = 7·0). For $C_7H_{13}NS$ (143·3) calculated: 58·69% C, 9·15% H, 9·78% N, 22·38% S; found: 58·48% C, 8·93% H, 9·84% N, 22·16% S.

2-Propyl-3-thiapentanoic Acid (*XX*)

A mixture of 25·7 g *XIX*, 240 ml hydrochloric acid and 240 ml dioxane was refluxed for 12 h. After cooling the mixture was diluted with water and extracted with ether. From the extract the product was re-extracted into 10% NaOH. Processing of the organic layer led to recovery of 7·45 g of *XIX* (b.p. 92—94°C/1·33 kPa). Acidification of the aqueous alkaline solution with hydrochloric acid, extraction with ether, and processing of the extract gave 12·2 g (59% per conversion) of *XX*, b.p. 148—152°C/2 kPa. IR spectrum (film): 940, 1 209, 1 286, 1 710, 2 680, infl. 3 260 (COOH). ^{1}H NMR spectrum: 0·88 bt, 3 H (CH_3 of propyl); 1·20 t, 3 H (remaining CH_3; J = 7·0); 1·30—2·00 m, 4 H (CH_2CH_2 of propyl); 2·60 q, 2 H (CH_2S; J = 7·0); 3·20 t, 1 H (SHCO; J = 7·0); 11·40 bs, 1 H (COOH). For $C_7H_{14}O_2S$ (162·2) calculated: 51·82% C, 8·69% H, 19·76% S; found: 51·49% C, 8·56% H, 19·43% S.

2-Propyl-3-thiapentanamide (*XXI*)

A solution of 15·9 g *XIX* in 100 ml ethanol was refluxed with a solution of 4·0 g NaOH in 20 ml water for 15 h. Ethanol was partly evaporated, the residue was diluted with water and extracted with benzene. The extract was washed with 10% NaOH and water, dried, and evaporated. The residue was crystallized from a mixture of benzene and light petroleum giving 6·6 g (37%) of

XXI, m.p. 106—107°C (benzene–light petroleum). IR spectrum: 1 652 ($CONH_2$); 3 180, 3 368 (NH_2). ^1H NMR spectrum: 0·90 bt, 3 H (CH_3 of propyl); 1·25 t, 3 H (remaining CH_3; $J = 7·0$); 1·30—2·00 m, 4 H (CH_2CH_2 of propyl); 2·59 q, 2 H (CH_2S; $J = 7·0$); 3·29 t, 1 H (SCHCO; $J = 7·0$); 6·60 bs, 2 H ($CONH_2$). For $C_7H_{15}NOS$ (161·3) calculated: 52·13% C, 9·38% H, 8·69% N, 19·88% S; found: 52·25% C, 9·36% H, 8·70% N, 19·88% S.

Acidification of the alkaline washings with hydrochloric acid, extraction with ether and processing of the extract gave 7·80 g (44%) of the acid *XX*, b.p. 145—150°C/2 kPa.

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REFERENCES

1. Fuerth E.: Monatsh. Chem. *9*, 319 (1888).
2. Smith H. A.: J. Am. Chem. Soc. *62*, 1136 (1940).
3. Meunier H., Carraz G., Meunier Y., Eymard P., Aimard M.: Therapie *18*, 435 (1963); Chem. Abstr. *62*, 13738 (1965).
4. Pinder R. M., Brogden R. N., Speight T. M., Avery G. S.: Drugs *13*, 81 (1977).
5. Anonym: Drugs Future *9*, 595 (1984).
6. Robinson C. P.: Med. Actual. (Drugs Today) *20*, 423 (1984).
7. Fischer F. E. (Abbott Laboratories): Can. 1,144,558; Chem. Abstr. *99*, 86761 (1983).
8. Waesser S.: *Medicamentum 1985*, No. 75, 10.
9. Lukeš R., Hofman J.: Chem. Listy *52*, 1747 (1958).
10. Carraz G., Darbon M., Lebreton S., Beriel H.: Therapie *19*, 468 (1964); Chem. Abstr. *63*, 7536 (1965).
11. Anonym: Med. Actual. (Drugs Today) *8*, 58 (1972).
12. Souček K., Vencovský E., Žatecká I.: Cesk. Psychiat. *79*, 200 (1983).
13. Perlman B. J., Goldstein D. B.: Mol. Pharmacol. *26*, 83 (1984).
14. Chapman A. G., Meldrum B. S., Mendes E.: Life Sci. *32*, 2023 (1983).
15. Chapman A. G., Croucher M. J., Meldrum B. S.: Biochem. Pharmacol. *33*, 1459 (1984).
16. Taillandier G., Benoit-Guyod J.-L., Laruelle C., Boucherle A.: Arch. Pharm. *310*, 394 (1977).
17. Loescher W., Nau H., Marescaux C., Vergnes M.: Eur. J. Pharmacol. *99*, 211 (1984).
18. Granneman G. R., Wang S. I., Madhinist J. M., Kesterson J. W.: Xenobiotica *14*, 375 (1984).
19. Rettenmeier A. W., Gordon W. P., Prickett K. S., Levy R. H., Lockard J. S., Thummel K. E., Baillie T. A.: Drug Metabol. Dispos. *14*, 443 (1986); Chem. Abstr. *105*, 145594 (1986).
20. Brana M. F., Martinez M., Garrido J., Roldan C. M.: An. Quim. *79*, 47 (1983); Chem. Abstr. *100*, 44882 (1984).
21. Scott K. R., Moore J. A., Zalucky T. B., Nicholson J. M., Lee J. A. M., Hinko C. N.: J. Med. Chem. *28*, 413 (1985).
22. Benoit-Guyod J.-L., Boucherle A., Carraz G.: Bull. Soc. Chim. Fr. *1965*, 1660.
23. Benoit-Guyod M., Benoit-Guyod J.-L., Boucherle A., Broll M., Eymard P.: Chim. Ther. *7*, 388, 393 (1972); *8*, 412 (1973).
24. Benoit-Guyod M., Benoit-Guyod J.-L., Broll M., Boucherle A., Broll M., Werbenec J. P., Eymard P.: Chim. Ther. *8*, 419 (1973).

25. Haj-Yehia A., Bialer M.: J. Pharm. Sci. *77*, 831 (1988).
26. Spinks A., Waring W. S. in: *Progress in Medicinal Chemistry* (G. P. Ellis and G. B. West, Eds), Vol. 3, p. 261. Butterworths, London 1963.
27. Bortnick N. M. (Rohm and Haas Co.): U.S. 2,718,516; Chem. Abstr. *50*, 1371 (1956).
28. Brookes P., Terry R. J., Walker J.: J. Chem. Soc. *1957*, 3165.
29. Maragues J., Prieto J., Spickett R. G. W., Vega A., Salazar W., Roberts D. J.: Farmaco, Ed. Sci. *35*, 951 (1989).
30. Sprague J. M., Johnson T. B.: J. Am. Chem. Soc. *59*, 1837 (1937).
31. Zima O., Werder F. V. (E. Merck Chem. Fabr.): Ger. 946,804; Chem. Abstr.*52*, 18477 (1958).
32. Abe K., Matsui K.: J. Pharm. Soc. Jpn. *75*, 896 (1955); Chem. Abstr. *50*, 4980 (1956).
33. Kiprianov A. I., Suitnikov P., Suich E. D.: J. Gen. Chem. (U.S.S.R.) *6*, 576 (1936); Chem. Abstr. *30*, 5583 (1936).
34. Boehme H.: Ber. Dtsch. Chem. Ges. *69*, 1610 (1936).
35. Frey H.-H., Loescher W.: Arzneim.-Forsch. *26*, 299 (1976).

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