5(OR 4)-ARYLTHIO-2-METHYLTHIOPYRIMIDINES AS POTENTIAL INTERMEDIATES IN THE SYNTHESIS OF TRICYCLIC PYRIMIDO SYSTEMS*

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Reaction of 5-chloro-2-methylthiopyrimidine-4-carboxylic acid with thiophenols led to 5-arylthio--2-methylthiopyrimidine-4-carboxylic acids *I*—*VII*. The phenylthio acid *I* was converted to derivatives *VIII*—*XI*; its reduction with complex hydrides results in 1,6-dihydropyrimidine--4-methanol *XIII* which was dehydrogenated with *p*-benzoquinone to the pyrimidine derivative *XII*. Thermal decarboxylation of acids *I*—*IV* led to aryl 5-pyrimidyl sulfides *XV*—*XVIII*. Acids *I* and *II*, being heated with polyphosphoric acid, are cyclized with concomitant decarbonylation, resulting in [1]benzothieno[3,2-*d*]pyrimidines *XIX* and *XX*. Cyclization of chloride *VIII* with the aid of aluminium chloride yielded 2-methylthio-[1]benzothiopyrano[3,2-*d*]pyrimidin-10-one (*XXI*). Reaction of ethyl 4-chloro-2-methylthiopyrimidine-5-acetate with 4-chlorothiophenolates and hydrolysis leads to acid *XXII* which does not cyclize under the action of polyphosphoric acid or in the form of chloride under the action of aluminium chloride. Its reaction with trifluoroacetic anhydride leads to trifluoroacetylation in the α-position of the side chain. Acid hydrolysis of the primary product yields the enol form of ketone *XXV* while alkaline hydrolysis in aqueous ethanol results in acid-forming cleavage, accompanied by ethanolysis which gives rise to the ethoxy derivative *XXIII*.

When designing molecules of neurotropically active substances, tricyclic, linearly condensed, systems with two external aromatic rings often come into play. Besides carbocyclic aromates heterocyclic rings may be used. Much attention has been devoted to tricyclic pyrido and thieno systems (*e.g.*[1-4]). Less is known about tricyclic pyrimido systems, due apparently to the relative inaccessibility of the pyrimido analogues of benzo-drugs (see *e.g.*[5]), as well as to the fact that pyrimido analogues usually substantially differ from the benzo-prototypes in their overall character and hence in their pharmacodynamic activity. In spite of this there are literature reports on pharmaceutically motivated syntheses of derivatives of 10*H*-pyrimido[5,4-*b*]--1,4-benzothiazine (1,3-diazaphenothiazine)[6-13], 10*H*-pyrimido[4,5-*b*]-1,4-benzothiazine (2,4-diazaphenothiazine)[14], 10*H*-pyrido[2,3-*b*]pyrimido[4,5-*e*]-1,4-thiazine

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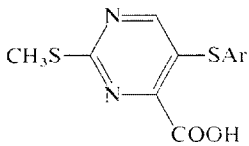
(1,3,6-triazaphenothiazine)[15], 10*H*-[1]benzothiopyrano[3,2-*d*]pyrimidine (1,3-diazathioxanthene)[16], 5*H*-pyrimido[4,5-*b*]-1-benzazepine[17,18], pyrimido[4,5-*b*]-1,5-benzothiazepine[19], 6*H*-pyrimido[4,5-*b*]-1,5-benzodiazepine[19], 11*H*-pyrimido[4,5-*b*]-1,4-benzodiazepine[20-22] and others. During the synthesis of these systems the last step may be *a*) closure of the central ring by formation of a new bond between C and the heteroatom (see[6-15,19,20]), *b*) closure of the central ring by formation of a new C—C bond (see[16]) and *c*) building up the pyrimidine ring on a bicyclic system (see[17,18,21,22]). The main part of the present communication deals with attempts at synthesis of derivatives of hitherto unknown systems of pyrimido[5,4-*b*]-1-benzothiepin and pyrimido[4,5-*b*]-1-benzothiepin using path (*b*) which has not yet been used for building up systems with a seven-membered central ring. Both approaches remained unfinished at the stage of potential intermediates.

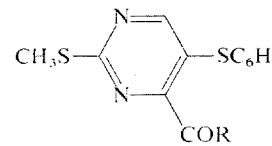
The starting reaction of the first group of experiments was a substitution of 5-chloro-2-methylthiopyrimidine-4-carboxylic acid[23] with thiophenol, *p*-thiocresol, 4-chlorothiophenol, 4-bromothiophenol[24,25], 4-methoxythiophenol[26], 4-nitrothiophenol[27] and 2-thionaphthol[28,29], carried out in the presence of sodium methoxide in boiling dimethylformamide, and giving rise to acids *I*–*VII*. Only after this work had been terminated, the preparation of acids *II*, *III* and *V* was described by Bennur and Badiger[16] who used 5-bromo-2-methylthiopyrimidine-4-carboxylic acid as the starting compound. According to IR spectra, acids *I*–*VII* behave partly as internal salts; the carboxyl bands in the region of 1 690–1 710 cm^{-1} are surprisingly low while there appear bands of the ammonium group NH^+ at 2500 cm^{-1} and bands which may be attributed to the carboxylate COO^- group (about 1400 and 1550 cm^{-1}). Acid *I* was converted by conventional methods to chloride *VIII* and ethyl ester *IX*. Reaction of chloride *VIII* with 1-methylpiperazine yielded amide *X* which was isolated in the form of hydrogen maleate. Chloride *VIII* reacted with activated sodium azide (for method see[30]) in boiling toluene, giving rise to isocyanate *XI* which is contaminated by the correspondding amine according to analysis and spectra.

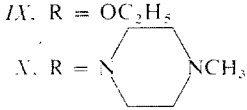
To attain the goal it was necessary to transform acid *I* and compounds *II*–*VII* to the nearest homologous acids, (pyrimidine-4-acetic) acids. For this purpose acid *I* was reduced with lithium aluminium hydride in boiling ether, and with sodium dihydridobis(2-methoxyethoxy)aluminate in benzene at room temperature. In both cases the product was apparently a carbinol of the 1,6-dihydropyrimidine series *XIII*. This is in agreement with the previous[31] experience with the reduction of pyrimidine derivatives by complex hydrides when the formation of 1,6-dihydropyrimidines has been established. Action of thionyl chloride converted the product to the hydrochloride of the chloromethyl derivative *XIV*, the structure of which was also established by spectra. The authors quoted above[31] carried out in one case a dehydrogenation of the 1,6-dihydropyrimidine derivative to the corresponding pyrimidine with the aid of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone. In our case it was possible to dehydrogenate compound *XIII* to the corresponding pyrimidine-4-methanol *XII* with the aid

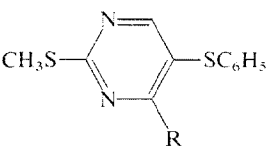
of *p*-benzoquinone in boiling ethanol; the same agent was previously used for dehydrogenation of α-hydroxyaminonitriles to α-oximinonitriles[32], *i.e.* also for a conversion of the C—N bond to a C=N one. Attempts at further transformation of *XII via* the chloromethyl and cyanomethyl derivatives to the corresponding pyrimidine-4--acetic acid resulted merely in mixtures of oily or resinous compounds which could not be resolved into chemical individuals. Likewise, the attempt at converting chloride *VIII* to the desired pyrimidine-4-acetic acid with the aid of the Arndt–Eistert procedure[33] did not lead to the desired product.



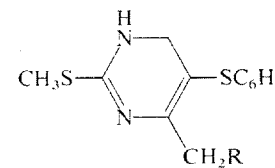
I, Ar = C_6H_5 *V*, Ar = 4-$C_6H_4OCH_3$
II, Ar = 4-$C_6H_4CH_3$ *VI*, Ar = 4-$C_6H_4NO_2$
III, Ar = 4-C_6H_4Cl *VII*, Ar = 2-naphthyl
IV, Ar = 4-C_6H_4Br



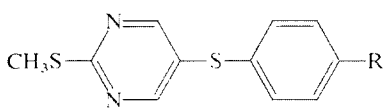
VIII, R = Cl
IX, R = OC_2H_5
X, R = 



XI, R = N=CO
XII, R = CH_2OH



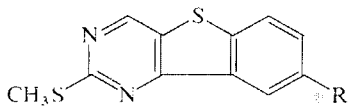
XIII, R = OH
XIV, R = Cl



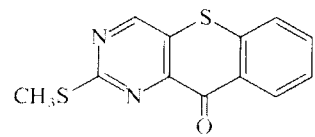
XV, R = H *XVII*, R = Cl
XVI, R = CH_3 *XVIII*, R = Br

When heated above the melting point (200°C) acids *I*–*IV* are decarboxylated and yield aryl-5-pyrimidyl sulfides *XV*–*XVIII*. Application of polyphosphoric acid to acids *I* and *II* at 120–125°C results in yellow crystalline products which contain no oxygen and the analysis of which indicates that, in contrast with the starting compounds, they are poorer in $CO_2 + H_2$ or $CO + H_2O$. Their spectra define them as derivatives of the little known system of [1]benzothieno[3,2-*d*]pyrimidine *XIX* and

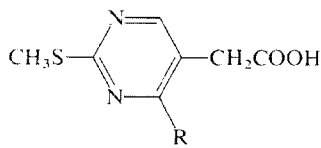
XX (RRI-3039, see[34]). Their formation is to be explained by decarbonylation of the primarily formed acylium cations and by subsequent stabilization of the resulting carbocations through cyclization, *i.e.* in fact an alkylation into the activated *o*-position of the benzene ring[35]. A normal course of cyclization is found only with chloride *VIII* when using aluminium chloride in nitrobenzene as described by Bennur and Badiger[16] for chlorides of acids *II* and *III* and some analogues. In the present case the product was a hitherto unknown 2-methylthio-[1]benzothiopyrano[3,2-*d*]pyrimidin-10-one (*XXI*). Attempts at using this ketone for synthesis of compounds of the type of 1,3-diaza-analogue of prothixene (for method see[36]) were not successful.



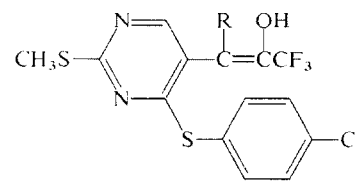
XIX, R = H
XX, R = CH_3



XXI



XXII, R = 4-SC_6H_4Cl
XXIII, R = OC_2H_5



XXIV, R = COOH
XXV, R = H

In view of the difficulties encountered in the attempts at transforming substituted pyrimidinecarboxylic acids to the corresponding pyrimidineacetic acids, in the second part of the present experiments the starting compound was the known derivative of pyrimidineacetic acid, *i.e.* the ethyl ester of 4-chloro-2-methylthio-5-pyrimidineacetic acid[36,37]. Reaction of this compound with 4-chlorothiophenol and with potassium hydroxide in the presence of copper in boiling water yielded a satisfactory amount only of acid *XXII*. This acid is unstable in an alkaline medium in aqueous ethanol where the arylthio group is replaced by the ethoxy group. If the same reaction is conducted in the presence of sodium ethoxide in ethanol and the product is saponified with an aqueous–ethanolic solution of sodium hydroxide, the main product obtained is the ethoxy acid *XXIII* while the acid *XXII* is only a minor product isolated from the reaction mixture before saponification. In the attempt at a reaction of the ester of the starting chloro acid[36,37] with excess 4-chlorothiophenol in hexamethylphosphoramide in the presence of potassium carbonate at 120°C, an oily product was obtained, the main part of which was found to be unsaponifiable with boiling aqueous

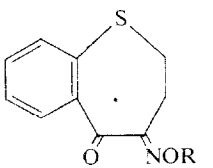
sodium hydroxide and showed a relatively low boiling point. It was identified with the aid of analyses and ^{1}H-NMR spectrum as an incompletely pure 4-(ethylthio)-chlorobenzene[38,39]. Even if the mechanism of formation of this compound is not completely clear it is apparent that the ethyl in the ethylthio group derives from the ethoxycarbonyl group of the starting compound. Here it should be noted that one of the two ways of formation of 4-(ethylthio) chlorobenzene described in the literature consisted in an alkylation of 4-chlorothiophenol with the ethyl ester of carboxylic acid; prolonged heating of ethyl trichloroacetate with sodium 4-chlorothiophenolate to 70°C yielded 4-(ethylthio)chlorobenzene[39].

Attempts were made to cyclize acid *XXII* to 8-chloro-3-methylthiopyrimido-[4,5-*b*]-1-benzothiepin-10(11*H*)-one with the aid of polyphosphoric acid, first at 130°C, then at 160–170°C. In the first case the starting acid *XXII* was recovered almost quantitatively, in the second by more than 50%; however, no other characterized product could be isolated. It was similarly unsuccessful to convert acid *XXII* first with thionyl chloride to chloride which was then processed in the crude state by treatment with aluminium chloride in carbon disulfide. The last attempt to be carried out was cyclization of acid *XXII* with trifluoroacetyl anhydride (in another critical case this method was successful[40]). Acid *XXII* was heated with excess trifluoroacetic anhydride in tetrachloromethane. No cyclization was observed but analysis of the product indicates that the trifluoroacetyl group entered the molecule. The IR spectrum excludes the presence of the trifluoroacetyl in the keto form —$COCF_3$; on the contrary, it agrees with the presence of the enolic form =C(OH) . . CF_3. Hence trifluoroacetylation occurred apparently in the α-position of the acetic acid residue and the isolated product is a sodium salt of the enol form of β-keto acid *XXIV*. This was confirmed by other experiments. Reaction with sulfuric acid results in ketone-forming cleavage, giving rise to the enol form of the trifluoroacetonyl derivative *XXV*. On the other hand, heating of the sodium salt with an aqueous-ethanolic solution of sodium hydroxide results in an acid-forming cleavage with concomitant ethanolysis leading to the formation of the above ethoxy acid *XXIII*. Here again the lability of the bond between the 4-chlorophenylthio group and the pyrimidine ring in an aqueous-ethanolic alkaline solution is apparent. The construction of a tricyclic pyrimido system through the formation of a new C—C bond was thus again unsuccessful.

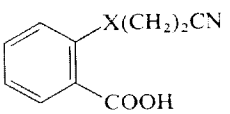
The last attempt at synthesis proceeds from the work of Galantay[41–45] who succeeded in annealing an oxazole ring to the benzocycloheptene system in a reaction of 6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one or of its O-acetyl derivative with the so-called Beckmann mixture[46] (hydrogen chloride in a mixture of acetic anhydride and acetic acid); the result was a simple synthesis of 2-methyl-9,10-dihydro-4*H*-benzo[5,6]cyclohepta[1,2-*d*]oxazol-4-one which was found to be a versatile intermediate of syntheses of neurotropic and psychotropic agents. In view of the fact that so far no analogous 2-methyloxazolo[5,4-*c*]-1-benzothiepin-4(10*H*)-one is

known we attempted to synthesize it, proceeding from work in the group of 1-benzothiepin derivatives[47] and particularly of its benzo and thieno derivatives[48,49]. Using 2,3,4,5-tetrahydro-1-benzothiepin-5-one[50] and treatment with butyl nitrite we prepared the 4-oximino derivative *XXVI* which reacted with a mixture of acetic acid and acetic anhydride at 110°C smoothly to the O-acetyl derivative *XXVII*. Reaction of *XXVI* and *XXVII* with a mixture of acetic acid and acetic anhydride in the presence of a small amount of concentrated sulfuric acid (with hydrogen chloride no identified product was obtained) gave an acid-reacting substance which was identified by analysis and spectra as S-(2-cyanoethyl)thiosalicylic acid[51] (*XXVIII*). During its reduction with sodium dihydridobis(2-methoxyethoxy)aluminate (Synhydrid) in benzene, the cyanoethyl residue is split off and the product is bis(2-hydroxymethylphenyl) disulfide[52,53] (*XXX*); the same product was obtained by reduction of dithiosalicylic acid[54]. It is probable that the primary product of both reductions is 2-mercaptobenzyl alcohol[55]; disulfide *XXX* is apparently a product of auto-oxidation caused by access of air.

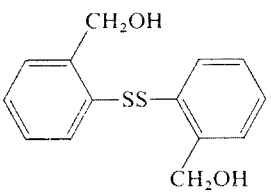
Compound *XXVIII* is evidently a product of Beckmann rearrangement of second order[46]. To check whether the predominance of this type of reaction over the expected annealion of the oxazole ring was caused by using sulfuric acid instead of hydrogen chloride in Beckmann's mixture we carried out a similar reaction with 6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one[41-45]. Here again the only product isolated was the nitrilo-acid *XXIX*, *i.e.* again a product of Beckmann's rearrangement of second order. To ensure a required course of Galantay's reaction one must thus use hydrogen chloride in a mixture with acetic acid and acetic anhydride; replacement of hydrogen chloride with a small amount of sulfuric acid results solely in a second-order Beckmann rearrangement.



XXVI, R = H
XXVII, R = $COCH_3$



XXVIII, X = S
XXIX, X = CH_2



XXX

Acids *I* – *V* were evaluated both for their antiinflammatory activity and in connection with a general pharmacological screening at the affiliated unit of this institute at Rosice n/L (Dr J. Němec). The results are summarized in Table I. Orientation data on acute toxicity after intravenous and oral application to mice are shown. The antiinflammatory activity was followed in two tests; firstly using the model of acute inflammation after an injection of kaolin suspension into the hind leg with a single administration of the compound tested and secondly using the model of a subchronic inflammation in an implanted pellet test (here the inhibiton of growth of granular tissue in the vicinity of the pellets was followed and the compounds tested were administered repeatedly for 7 days). For pharmacological methods see[56-58]. The results indicate that acid *I* is significantly active in both types of inflammation, while acids *II* and *III* display a significant activity only in the kaolin inflammation test. The effect of *I* is roughly comparable with that of kebuzone (Ketazon ®)[59]. Of the other effects mention should be made of the central depressant effect at high doses and further of the positively inotropic effect of all the five acids.

TABLE I

Pharmacological Properties of Acids *I* – *V* (doses in mg/kg)

Compound[a]	Acute toxicity LD_{50}[b]		Screening dose D	Antiinflammatory activity[d]		Further effects
	i.v.	*p.o.*	*i.v.*[c]	kaolin edema	implanted pellets	
I	270	500–1000	55	12+	36+	*e, f, g, h*
II	300	>1000	60	13+	2	*e, h*
III	125	>1000	25	10+	18	*e, h*
IV	200	>1000	40	8	26	*e, h*
V	315	>1000	60	8	2	*e, h*

[a] *P.o.* application used the compounds as such (aqueous suspension with gum arabic), parenterally they were applied as aqueous solutions of sodium salts. [b] Acute toxicity was evaluated in groups of five female mice (weight 18–22 g). [c] Dose at which the compound was administered in *in vivo* tests within general pharmacological screening. [d] Antiinflammatory activity was evaluated in groups of eight female rats (Wistar strain, weight 140–190 g); the figures represent the percentage of inflammation inhibition after a dose of 100 mg/kg compound tested (*p.o.*) in comparison with untreated control; + denotes statistical significance of the activity. [e] In doses greater than D the compound brings about signs of central depression in mice. [f] In dose D a brief incoordinating effect in the rotating-rod test in mice is observed. [g] At dose D, a brief peripheral-vasodilating effect is observed, evaluated according to rising temperature of the ear lobe of guinea pig registered with a skin thermo-couple. [h] At 50 μg/ml it has a positive inotropic effect on isolated rabbit atrium.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at 0·1—0·5 Torr over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, IR spectra (in Nujol) in a Unicam SP 200 G spectrophotometer. The ^{1}H-NMR spectra were obtained in CD_3 . . $SOCD_3$ in a ZKR-60 (Zeiss, Jena) spectrometer and the mass spectra in a MS 902 (AEI) spectrometer unless stated otherwise. The homogeneity of the compounds was tested by thin-layer chromatography on silica gel (mostly Silufol).

2-Methylthio-5-phenylthiopyrimidine-4-carboxylic Acid (*I*)

Sodium (8·1 g) was dissolved in 200 ml methanol and the solution was evaporated *in vacuo*. The residue was combined with 200 ml dimethylformamide, 19·3 g thiophenol and 36·0 g 5-chloro-2-methylthiopyrimidine-4-carboxylic acid[23] and the mixture was refluxed under stirring for 6 h. After cooling, it was diluted with 600 ml water and acidified with hydrochloric acid to pH 2. After standing overnight, the yellow precipitate was filtered, washed with water and dried in air; 41·1 g (82%). For analysis the product was recrystallized from ethanol, m.p. 169—170°C. UV spectrum: λ_{max} 273 nm (log ε 4·21), 286 nm (4·22), 372 nm (3·29). IR spectrum (KBr): 692, 708, 722, 743, 758 (C_6H_5), 997, 1697, 3080 (COOH), 1227 (C—O), 1414 (COO^-), 1555 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 8·40 (s, 1 H, 6-H of pyrimidine), 7·46 (s, 5 H, C_6H_5), 2·50 (s, 3 H, SCH_3). For $C_{12}H_{10}N_2O_2S_2$ (278·2) calculated: 51·80% C, 3·62% H, 10·07% N, 23·02% S; found: 51·56% C, 3·56% H, 9·70% N, 22·85% S.

Of the compounds described[16] the following were prepared in analogy to *I*: 2-methylthio-4-(4-tolylthio)pyrimidine-4-carboxylic acid (*II*), yield 70%, m.p. 176—178°C (ethanol) (ref.[16] reports a m.p. of 171—172°C); 5-(4-chlorophenylthio)-2-methylthiopyrimidine-4-carboxylic acid (*III*), yield 52%, m.p. 188—190°C (ethanol) (ref.[16] reports a m.p. of 188—189°C); 5-(4-methoxyphenylthio)-2-methylthiopyrimidine-4-carboxylic acid (*V*), yield 71%, m.p. 190—192°C (ref.[16] reports a m.p. of 199—200°C).

5-(4-Bromophenylthio)-2-methylthiopyrimidine-4-carboxylic Acid (*IV*)

Like in the preparation of *I*, reaction of 3·78 g 4-bromothiophenol[24,25] and 4·08 g 5-chloro-2-methylthiopyrimidine-4-carboxylic acid[23] yielded 5·50 g (82%) acid *IV*, m.p. 186—187°C (ethanol). UV spectrum: λ 267·5 nm (log ε 4·33), 289 nm (4·22). IR spectrum: 820 (2 adjacent Ar—H), 1010, 1694 (COOH), 1225 (C—O), 1557 (COO^-, Ar), 2520 (NH^+), 3440 cm^{-1} (OH). ^{1}H-NMR spectrum (Tesla BC-487, 80 MHz): δ 8·40 (s, 1 H, 6-H of pyrimidine), 7·50(d, J = = 8·0 Hz, 2 H, 3,5-H_2 of phenyl), 7·20 (d, J = 8·0 Hz, 2 H, 2,6-H_2 of phenyl), 2·40 (s, 3 H, SCH_3). For $C_{12}H_9BrN_2O_2S_2$ (357·3) calculated: 40·34% C, 2·54% H, 22·37% Br, 7·84% N, 17·95% S; found: 40·67% C, 2·69% H, 22·23% Br, 7·65% N, 18·22% S.

2-Methylthio-5-(4-nitrophenylthio)pyrimidine-4-carboxylic Acid (*VI*)

Like in preceding cases, reaction of 1·55 g 4-nitrothiophenol[27] and 2·04 g 5-chloro-2-methylthiopyrimidine-4-carboxylic acid[23] yielded 1·50 g (47%) acid *VI*, m.p. 183—184·5°C (ethanol). For $C_{12}H_9N_3O_4S_2$ (323·3) calculated: 44·59% C, 2·81% H, 13·00% N; found: 44·10% C, 2·87% H, 13·22% N.

2-Methylthio-5-(2-naphthylthio)pyrimidine-4-carboxylic Acid (*VII*)

Like in the preceding cases, reaction of 6·4 g 2-thionaphthol[28,29] with 8·16 g 5-chloro-2-methylthiopyrimidine-4-carboxylic acid[23] yielded 10·0 g (76%) product: m.p. 183—184°C (ethanol). UV spectrum: λ_{max} 265 nm (log ε 4·39). IR spectrum: 740, 820, 852, 880 (4 and 2 adjacent and solitary Ar—H), 1180, 1225, 1700 (COOH), 1555 (COO^-, Ar), 2500 cm^{-1} (NH^+). ^{1}H-NMR spectrum (Tesla 80 MHz): δ 8·42 (s, 1 H, 6-H of pyrimidine), 7·80 (m, 4 H, 1,4,5,8-H_4 of naphthyl), 7·40 (m, 3 H, 3,6,7-H_3 of naphthyl), 2·56 (s, 3 H, SCH_3). For $C_{16}H_{12}N_2O_2S_2$ (328·4) calculated: 58·52% C, 3·68% H, 8·53% N, 19·53% S; found: 58·65% C, 3·67% H, 8·71% N, 19·24% S.

2-Methylthio-5-phenylthiopyrimidine-4-carbonyl Chloride (*VIII*)

A mixture of 60 ml thionyl chloride and 14·0 g acid *I* was refluxed for 30 min. The volatile fractions were then evaporated at reduced pressure, the residue was diluted with 30 ml benzene and, by adding 150 ml light petroleum, the product was induced to crystallize; 11·1 g (75%), orange-yellow crystals, m.p. 72—74°C (toluene–light petroleum). UV spectrum: λ_{max} 269 nm (log ε 4·20), 287 nm (4·25), 365 nm (3·29). For $C_{12}H_9ClN_2OS_2$ (296·8) calculated: 48·56% C, 3·06% H, 11·95% Cl, 9·44% N, 21·60% S; found: 48·66% C, 3·07% H, 11·73% Cl, 9·16% N, 21·37% S. Ref.[16] reports a reaction of acids *II* and *III* with thionyl chloride but does not describe the products.

Ethyl 2-methylthio-5-phenylthiopyrimidine-4-carboxylate (*IX*)

A solution of 0·85 g acid *I* in 220 ml ethanol was saturated with hydrogen chloride and the mixture was left at room temperature overnight. Most of the ethanol was then evaporated *in vacuo*, the residue was diluted with 50 ml chloroform, the solution was washed with water and 10% $NaHCO_3$, dried with Na_2SO_4 and evaporated. Crystallization of the residue from ethanol yielded 0·60 g (64%) ester *IX*, m.p. 47·5—48·5°C. For $C_{14}H_{14}N_2O_2S_2$ (306·4) calculated: 54·88% C, 4·60% H, 9·14% N, 20·93% S; found: 54·75% C, 4·54% H, 9·00% N, 20·64% S.

4-(4-Methylpiperazinocarbonyl)-2-methylthio-4-phenylthiopyrimidine (*X*)

A solution of 1·2 g chloride *VIII* in 25 ml benzene was combined with 1 ml 1-methylpiperazine and the mixture was refluxed for 1 h. After cooling, it was washed with water and the benzene solution was evaporated. The residue (1·4 g) was dissolved in 25 ml ethanol and the solution was neutralized with a solution of an equivalent amount of maleic acid in ethanol. Addition of ether and standing resulted in crystalline hydrogen maleate of product *X*: 1·4 g (73%), m.p. 163—164·5°C (ethanol). ^{1}H-NMR spectrum: δ 8·78 (s, 1 H, 6-H of pyrimidine), 7·40 (s, 5 H, C_6H_5), 6·10 (s, 2 H, CH=CH of maleic acid), 2·85—4·00 (m, 8 H, 4 CH_2 of piperazine), 2·75 (s, 3 H, SCH_3), 2·51 (s, 3 H, NCH_3). For $C_{21}H_{24}N_4O_5S_2$ (476·5) calculated: 52·93% C, 5·07% H, 11·75%N, 13·48% S; found: 52·97% C, 5·29% H, 11·85% N, 13·70% S.

2-Methylthio-5-phenylthio-4-pyrimidyl Isocyanate (*XI*)

A solution of 9·0 g chloride *VIII* in 100 ml toluene was combined with 13·0 g activated NaN_3 (ref.[30]) and the mixture was refluxed under stirring for 8 h. After standing overnight the solid was filtered and the filtrate was evaporated *in vacuo*. The residue was then chromatographed on a column of 300 g silica gel, using elution with a mixture of benzene and acetone (49 : 1). After removal of the less polar noncrystalline fractions, elution yielded 6·0 g (72%) product which crystallized first from toluene and then from a mixture of acetone and ethanol, m.p. 142—144°C.

The mass spectrum displays a molecular ion corresponding to the expected composition C_{12} . . $H_9N_3OS_2$; in addition, there is an ion at *m/e* 249, corresponding to $C_{11}H_{11}N_3S_2$ which corresponds to the 4-amino-2-methylthio-5-phenylthiopyrimidine present. ^{1}H-NMR spectrum ($CDCl_3$): δ 8·54 (s, 1 H, 6-H of pyrimidine), 7·26 (s, 5 H, C_6H_5), 2·51 (s, 3 H, SCH_3); besides, it exhibits a bs at 10·26 ppm which disappears after D_2O (it corresponds apparently to the NH_2 group of amine). Likewise, the analysis indicates a contamination with a lower molecular weight product containing more hydrogen. For $C_{12}H_9N_3OS_2$ (275·2) calculated: 52·37% C, 3·30% H, 15·27% N, 23·28% S; found: 52·52% C, 3·85% H, 15·94% N, 23·78% S.

2-Methylthio-5-phenylthio-1,6-dihydropyrimidine-4-methanol (*XIII*)

A. A solution of 5·0 g $LiAlH_4$ in 100 ml ether was combined under stirring for a 20 min period with 5·6 g acid *I*. After dilution with 50 ml ether it was stirred for 6 h at room temperature and refluxed for 1 h. After cooling, it was decomposed slowly under stirring by adding dropwise 30 ml of a 3% solution of NaOH. After filtration, the ether solution was washed with water and, after drying, partly evaporated. The residue yielded 3·0 g (63%) crystalline product melting at 140—141°C (ether). UV spectrum: λ_{max} 236 nm (log ε 4·01), 290 nm (3·78). IR spectrum (KBr): 698, 741, 750 (C_6H_5), 1042 (CH_2OH), 1199 (NH), 1493, 1581, 1609 (Ar), 1656 (C=N), 3130, 3180 cm^{-1} (OH, NH). NMR spectrum: δ 8·60 (bs, 1 H, NH in position 1 of pyrimidine), 7·30 (s, 5 H, C_6H_5), 4·86 (bs, 1 H, OH), 4·21 (s, 2 H, CH_2O), 3·96 (s, 2 H, CH_2 in position 6 of pyrimidine), 2·30 (s, 3 H, SCH_3). For $C_{12}H_{14}N_2OS_2$ (266·3) calculated: 54·13% C, 5·30% H, 10·52% N, 24·06% S; found: 54·31% C, 5·47% H, 10·56% N, 24·09% S.

B. A solution of 62·7% sodium dihydridobis(2-methoxyethoxy)aluminate in benzene containing 12·0 g of the agent was added to a suspension of 5·6 g acid *I* in 100 ml benzene. The temperature rose to 35°C and the mixture was stirred at room temperature for 7 h and decomposed with 100 ml 5% NaOH. The benzene layer was washed with water and dried. After partial evaporation of benzene *in vacuo* and after cooling, 1·3 g crystalline compound (25%) was isolated; m.p. 140—141°C which is identical with the product prepared according to *A*. The mother liquor yielded 3·1 g residue from which no characterized product could be prepared by chromatography on a silica gel column.

4-Chloromethyl-2-methylthio-5-phenylthio-1,6-dihydropyrimidine (*XIV*)

PCl_3 (6 ml) was added dropwise under stirring at 10°C over a period of 20 min to a solution of 0·90 g alcohol *XIII* in 100 ml chloroform. The mixture was heated and briefly refluxed, the volatile fractions were removed by evaporation *in vacuo*. The residue crystallized to 0·60 g hydrochloride of the product, m.p. 186—190°C (ethanol–ether). UV spectrum: λ_{max} 241·5 nm (log ε 4·08), 312 nm (3·82). IR spectrum: 700, 750 (C_6H_5), 1558, 1610 (Ar), 1670 (C=N), 2750 (NH^+), 3230 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 7·40 (s, 5 H, C_6H_5), 4·63 (s, 2 H, CH_2Cl), 3·95 (s, 2 H, CH_2 in position 6 of pyrimidine), 2·73 (s, 3 H, SCH_3). For $C_{12}H_{14}Cl_2N_2S_2$ (321·3) calculated: 44·86% C, 4·39% H, 22·07% Cl, 8·72% N, 19·96% S; found: 44·75% C, 4·53% H, 22·40% Cl, 8·44% N, 20·20% S.

2-Methylthio-5-phenylthiopyrimidine-4-methanol (*XII*)

A mixture of 30 ml ethanol, 0·5 g *XIII* and 0·5 g *p*-benzoquinone was refluxed for 1 h, left to stand overnight at room temperature, diluted with 300 ml water and left to stand for 48 h. The precipitated product was filtered: 0·4 g (81%), which was purified for analysis by filtration of the

solution in ethanol with charcoal and recrystallized from aqueous ethanol: m.p. 70—71°C. IR spectrum (KBr): 690, 749 (C_6H_5), 1095 (CH_2OH), 1555 (Ar), 3255 cm^{-1} (OH). NMR spectrum (CD_3COCD_3): δ 8·55 (s, 1 H, 6-H of pyrimidine), 7·36 (s, 5 H, C_6H_5), 4·69 (d, $J = 5·0$ Hz, after deuterization s, 2 H, CH_2O), 4·22 (t, $J = 5·0$ Hz, disappears after deuterization, 1 H, OH), 2·55 (s, 3 H, SCH_3). For $C_{12}H_{12}N_2OS_2$ (264·2) calculated: 54·54% C, 4·58% H, 10·60% N, 24·24% S; found: 54·59% C, 4·61% H, 10·36% N, 24·49% S.

2-Methylthio-5-phenylthiopyrimidine (*XV*)

Acid *I* (5·0 g) was melted and heated for 20 min to 200°C. Cooled melt was recrystallized from ethanol; 3·78 g (90%), m.p. 46·5—49°C. ^{1}H-NMR spectrum ($CDCl_3$): δ 8·60 (s, 2 H, 4,6-H_2 of pyrimidine), 7·35 (s, 5 H, C_6H_5), 2·50 (s, 3 H, SCH_3). For $C_{11}H_{10}N_2S_2$ (234·2) calculated: 56·41% C, 4·30% H, 11·96% N, 27·33% S; found: 56·89% C, 4·42% H, 12·06% N, 27·26% S.

2-Methylthio-5-(4-tolylthio)pyrimidine (*XVI*)

Like in the preceding case, thermal decarboxylation of 5·0 g acid *II* yielded 3·82 g (90%) product: m.p. 57·5—58·5°C (ethanol). ^{1}H-NMR spectrum ($CDCl_3$): δ 8·50 (s, 2 H, 4,6-H_2 of pyrimidine), 7·00—7·55 (m, 4 H, protons of phenylene), 2·51 (s, 3 H, SCH_3), 2·30 (s, 3 H, Ar—CH_3). For $C_{12}H_{12}N_2S_2$ (248·2) calculated: 58·06% C, 4·87% H, 11·29% N, 25·78% S; found: 58·35% C, 5·00% H, 11·28% N, 25·60% S.

5-(4-Chlorophenylthio)-2-methylthiopyrimidine (*XVII*)

Like in the preceding cases, thermal decarboxylation of acid *III* resulted in a product melting a 46—51°C (ethanol). For $C_{11}H_9ClN_2S_2$ (268·8) calculated: 49·20% C, 3·37% H; found: 49·28% C 3·30% H.

5-(4-Bromophenylthio)-2-methylthiopyrimidine (*XVIII*)

Like in the preceding cases, thermal decarboxylation of acid *IV* resulted in a product melting at 51—56°C (ethanol). For $C_{11}H_9BrN_2S_2$ (313·2) calculated: 42·10% C, 2·88% H; found: 42·56% C, 2·95% H.

2-Methylthio-[1]benzothieno[3,2-*d*]pyrimidine (*XIX*)

85% H_3PO_4 (20 ml) was combined under stirring with 33 g P_2O_5 added in parts and the mixture was heated for 2 h to 120—125°C. Acid *I* (5·0 g) was then added and the mixture was heated for 6 h to 120—125°C. After cooling, it was decomposed with 250 g of a mixture of ice and water and the product was isolated by extraction with benzene. The extract was washed with a 5% solution of NaOH and water, dried with Na_2SO_4 and evaporated at reduced pressure. Crystallization of the residue from acetic acid yielded 1·6 g (38%) yellowish needles, melting at 125—127°C (ethanol). UV spectrum: λ_{max} 249 nm (log ε 4·40), 268 nm (4·38), 298 nm (3·88), 307 nm (3·85), 362 nm (3·49). IR spectrum: 750 (4 adjacent Ar—H), 1512, 1550, 1563 (pyrimidine), 1600 cm^{-1} (Ar). ^{1}H-NMR spectrum ($CDCl_3$): δ 9·05 (s, 1 H, 4-H), 8·50 (m, 1 H, 9-H), c. 7·70 (m, 3 H, 6,7,8-H_3), 2·69 (s, 3 H, SCH_3). For $C_{11}H_8N_2S_2$ (232·2) calculated: 56·90% C, 3·47% H, 12·07% N, 27·56% S; found: 56·71% C, 3·54% H, 11·78% N, 27·61% S. The same product was obtained in a reaction of the ethyl ester *IX* with polyphosphoric acid at 150°C (33%, m.p. 124—126°C).

8-Methyl-2-methylthio-[1]benzothieno[3,2-*d*]pyrimidine (*XX*)

Like in the preceding case, 7·2 g acid *II* yielded 2·25 g (37%) product melting at 129–130°C (ethanol). UV spectrum: λ_{max} 248 nm (log ε 4·44), 269 nm (4·42), 304 nm (3·92), 312·5 nm (3·93), 366 nm (3·45). IR spectrum: 803, 881, 905 (2 adjacent and solitary Ar—H), 1512, 1550, 1563 (pyrimidine), 1610 cm^{-1} (Ar). ^{1}H-NMR spectrum ($CDCl_3$): δ 9·04 (s, 1 H, 4-H), 8·30 (mcs, 1 H, 9-H), 7·77 (d, J = 8·0 Hz, 1 H, 6-H), 7·45 (mcd, J = 8·0; 1·5 Hz, 1 H, 7-H), 2·69 (s, 3 H, SCH_3), 2·51 (s, 3 H, $ArCH_3$). For $C_{12}H_{10}N_2S_2$ (246·2) calculated: 58·53% C, 4·09% H, 11·38% N, 25·99% S; found: 58·70% C, 4·17% H, 11·36% N, 26·08% S.

2-Methylthio-[1]benzothiopyrano[3,2-*d*]pyrimidin-10-one (*XXI*)

A mixture of 7·0 g acid *I* and 30 ml $SOCl_2$ was refluxed for 30 min. The volatile fractions were evaporated *in vacuo*, the residue was dissolved in 50 ml nitrobenzene, 16 g $AlCl_3$ was added and the mixture was heated for 3 h to 100°C. It was then cooled, poured into ice and water, the nitrobenzene was removed by steam-distillation and the product was obtained from the cooled residue by filtration. After crystallization from dioxane, a total of 3·0 g (48%) product was obtained; m.p. 218–221°C. UV spectrum: λ_{max} 230·5 nm (log ε 4·12), infl. 261 nm (4·15), 292·5 nm (4·51), 417·5 nm (3·60). IR spectrum (KBr): 739 (4 adjacent Ar—H), 1500, 1550, 1590 (pyrimidine, Ar) 1639 cm^{-1} (Ar—CO—Ar). For $C_{12}H_8N_2OS_2$ (260·2) calculated: 55·39% C, 3·10% H, 10·77% N, 24·60% S; found: 55·64% C, 3·14% H, 10·58% N, 24·41% S.

4-(4-Chlorophenylthio)-2-methylthiopyrimidine-5-acetic Acid (*XXII*)

A. A solution of 45 g KOH in 450 ml water was combined one after another with 67 g 4-chlorothiophenol, 46·2 g ethyl 4-chloro-2-methylthio-5-pyrimidineacetate[36,37] and with 3·0 g "molecular" copper and the mixture was refluxed for 6 h. After filtration, it was made acid with acetic acid, the nonreacted 4-chlorothiophenol was steam-distilled (recovery 38 g) and the residue in the flask was cooled yielding 52·7 g (86%) product, m.p. 137–139°C (benzene–light petroleum). UV spectrum: λ_{max} 256·5 nm (log ε 4·35), 307·5 nm (3·87). IR spectrum: 813, 821 (2 adjacent Ar—H), 1229, 1680, 1719, 2500–3200 (COOH), 1510, 1559, 1569 cm^{-1} (Ar). ^{1}H-NMR spectrum (Tesla 80 MHz): δ 8·20 (s, 1 H, 6-H of pyrimidine), 7·47 (s, 4 H, protons of *p*-phenylene), 3·58 (s, 2 H, CH_2CO), 2·00 (s, 3 H, SCH_3). For $C_{13}H_{11}ClN_2O_2S_2$ (326·8) calculated: 47·77% C, 3·39% H, 10·85% Cl, 8·57% N, 19·62% S; found: 48·14% C, 3·46% H, 10·59% Cl, 8·78% N, 19·68% S.

In another experiment, crystallization of the product from a mixture of benzene and ethanol resulted in a higher-melting modification, m.p. 153·5–155·5°C. Its UV and IR spectra are identical with those of the lower-melting modification. For $C_{13}H_{11}ClN_2O_2S_2$ (326·8) calculated: 47·77% C, 3·39% H, 10·85% Cl, 8·57% N, 19·62% S; found: 47·68% C, 3·45% H, 10·84% Cl, 8·57% N, 19·38% S.

B. Ethyl 4-chloro-2-methylthio-5-pyrimidineacetate[37] (3·15 g) and 5·24 g 4-chlorothiophenol were dissolved in 13 ml hexamethylphosphoramide whereupon 1·8 g K_2CO_3 was added and the mixture was heated for 5 h to 120°C. After dilution with water, it was extracted with benzene, the extract was washed with 10% NaOH and with water, dried with $MgSO_4$ and evaporated. The oily residue (7·2 g) was refluxed for 6 h with 20 ml 20% NaOH. After cooling, it was extracted with benzene. The aqueous layer was acidified and yielded 1·9 g starting 4-chlorothiophenol, m.p. 52–53°C. Evaporation of the benzene extract yielded 2·0 g (91%) oil, b.p. 110–115°C/10 Torr which was identified as incompletely pure 4-(ethylthio)chlorobenzene. ^{1}H-NMR spectrum (Tesla 80 MHz, $CDCl_3$): δ c. 7·15 (s, 4 H, protons of *p*-phenylene), 2·85 (q, 2 H, SCH_2), 1·23

(t, 3 H, C—CH_3). For C_8H_9ClS (172·7) calculated: 55·64% C, 5·26% H, 20·53% Cl, 18·57% S; found: 54·75% C, 5·11% H, 19·33% Cl, 19·02% S. Ref.[38] reports for a product obtained in a reaction of 4-chlorothiophenol with diethyl sulfate a b.p. of 123°C/18 Torr, for the product obtained in a reaction of ethyl trichloroacetate with sodium *p*-chlorothiophenolate[39], b.p. 125 to 126°C/23 Torr.

2-[4-(4-Chlorophenylthio)-2-methylthio-5-pyrimidyl]-2-(trifluoroacetyl)acetic Acid (*XXIV*)

A solution of 10·0 g *XXII* in 400 ml CCl_4 was combined with 84 g trifluoroacetic anhydride, the mixture was stirred for 4 h at room temperature and refluxed for 32 h (a 60°C bath). After 48 h of standing it was shaken with 300 ml 20% NaOH and the precipitated solid was filtered, washed with water and dried; 11·8 g (87%). After crystallization from a mixture of ethanol and benzene it melts at 202—204°C, under decomposition. Incinerated it leaves 14% ash. It is a sodium salt of the enol form of *XXIV*. UV spectrum: λ_{max} 226 nm (log ε 4·17), 257 nm (4·32), 307 nm (3·93). IR spectrum: 821 (2 adjacent Ar—H), 1097 (C—OH), 1274 (C—O), 1370, 1552, 1610 (COO^-), 1480, 1500 (Ar), 1665 (CO—C=C—OH), 3200 and 3360 cm^{-1} (OH). For $C_{15}H_9 . ClFN_2NaO_3S_2$ (444·8) calculated: 7·97% Cl, 12·81% F, 6·30% N, 14·42% S; found: 8·17% Cl, 13·36% F, 6·37% N, 14·05% S.

4-(4-Chlorophenylthio)-2-methylthio-5-(3,3,3-trifluoro-2-oxopropyl)pyrimidine (*XXV*)

Concentrated H_2SO_4 (10 ml) was combined with 1·0 g sodium salt of *XXIV* and left to stand at room temperature overnight. Then it was diluted with water, made alkaline with 20% NaOH and finally acidified with acetic acid. Filtration yielded 0·8 g (94%) compound crystallizing from a mixture of benzene and light petroleum either as a solvate (needles) melting at 60—70°C or unsolvated (prisms), melting at 101—103°C. The solvate is converted by drying to the compound melting at 101—103°C. The mass spectrum with a molecular ion at *m/e* 378 supports the formula $C_{14}H_{10}ClF_3N_2OS_2$. UV spectrum: λ_{max} 257 nm (log ε 4·34), 307 nm (3·89). IR spectrum (KBr): 818, 863 (Ar—H), 1091 (C—OH), 1180, 1386 (CF_3), 1477, 1510, 1562 (Ar), 2660 (NH^+), 3150, 3430, 3519 cm^{-1} (OH). For $C_{14}H_{10}ClF_3N_2OS_2$ (378·8) calculated: 44·39% C, 2·66% H, 9·36% Cl, 15·05% F, 7·39% N, 16·93% S; found: 44·13% C, 2·78% H, 9·70% Cl, 14·97% F, 7·45% N, 16·97% S.

4-Ethoxy-2-methylthiopyrimidine-5-acetic Acid (*XXIII*)

A. Sodium (0·35 g) was dissolved in 20 ml ethanol and the solution combined with 2·17 g 4-chlorothiophenol and 3·36 g ethyl 4-chloro-2-methylthio-5-pyrimidineacetate[37]. The mixture was refluxed for 6 h, diluted with water and extracted with benzene. Acidification of the aqueous layer with acetic acid yielded 0·26 g of a lower-melting form of acid *XXII*, m.p. 137—139°C (benzene–light petroleum). The benzene extract was dried, evaporated and the oil (4·9 g) was dissolved in 50 ml ethanol. After adding 12 ml 20% aqueous NaOH it was refluxed for 2 h. The ethanol was evaporated *in vacuo* and the residue was dissolved in 40 ml water and filtered. The filtrate was acidified with acetic acid whereupon 1·9 g 4-chlorothiophenol (m.p. 52—53°C) precipitated and was filtered. The oil remained in the filtrate wherefrom it was isolated by extraction with dichloromethane and the extract was dried and evaporated. The residue (2·0 g, 67%) crystallized from a mixture of benzene and cyclohexane, m.p. 144—146°C (benzene–light petroleum) and was identified as *XXIII*. IR spectrum: 923, 1710 (COOH), 1029, 1228, 1331, 1350 (Ar—O—R), 1551, 1590 (Ar), 2630, 2735 cm^{-1} (NH^+). ^{1}H-NMR spectrum (Tesla 80 MHz): δ 8·10 (s, 1 H, 6-H of pyrimidine), 4·25 (q, J = 7·0 Hz, 2 H, OCH_2), 3·34 (s, 2 H, CH_2CO), 2·40 (s, 3 H, SCH_3),

1·20 (t, J = 7·0 Hz, 3 H, C—CH_3). For $C_9H_{12}N_2O_3S$ (228·2) calculated: 47·35% C, 5·30% H, 12·27% N, 14·05% S; found: 47·60% C, 5·34% H, 12·64% N, 14·57% S.

B. A mixture of 2·0 g sodium salt of *XXIV*, 30 ml ethahol and 30 ml 20% aqueous NaOH was refluxed for 5 h. After evaporation of ethanol the residue was diluted with water, the solution was neutralized with hydrochloric acid and washed with chloroform and acidified with acetic acid. Extraction with chloroform yielded 0·21 g (21%) compound, m.p. 142—145°C, identical with that according to *A*.

4-Oximino-2,3,4,5-tetrahydro-1-benzothiepin-5-one (*XXVI*)

Sodium (2·3 g) was dissolved in 70 ml ethanol, a solution of 17·8 g 2,3,4,5-tetrahydro-1-benzothiepin-5-one[50] in 90 ml ethanol was added and the mixture was cooled to 0°C. Butyl nitrite (15 g) was added dropwise under stirring over 30 min. The mixture was stirred for 4 h at 0°C, left to stand overnight at room temperature, ethanol was evaporated in vacuo, the residue was diluted with 200 ml water and acidified with 2M-HCl to pH 5. After 5 h of standing the precipitated product was filtered, washed with water and dried in air; 18·5 g (89%), after crystallization from ethanol m.p. 161—164°C. UV spectrum (ethanol): λ_{max} 245 nm (log ε 4·26), 263 nm (3·97), 343 nm (3·27). IR spectrum: 752, 756 (4 adjacent Ar—H), 915, 1046, 3240 (C=N—OH), 1580 (Ar), 1675 cm^{-1} (Ar—CO). ^{1}H-NMR spectrum (CD_3OD): δ 7·80 (m, 1 H, aromatic 6-H), 7·35—7·70 (m, 3 H, aromatic 7,8,9-H_3), 3·00 (m, 4 H, SCH_2CH_2). For $C_{10}H_9NO_2S$ (207·2) calculated: 57·96% C, 4·37% H, 6·75% N, 15·47% S; found: 58·00% C, 4·34% H, 6·66% N, 15·45% S.

4-(Acetoximino)-2,3,4,5-tetrahydro-1-benzothiepin-5-one (*XXVII*)

A mixture of 40 ml acetic acid and 7 ml acetic anhydride was combined at 110°C with 2·6 g *XXVI* and the mixture was kept at this temperature for 20 min. After cooling it was poured over ice and water, left to stand for 2 h and the solid was filtered, washed with water and dried in air; 2·5 g (80%), after crystallization from aqueous acetic acid it melted at 110—111°C. UV spectrum (ethanol): λ_{max} 245 nm (log ε 4·34), 346 nm (3·36). IR spectrum ($CHCl_3$): 1190, 1200 (N—O—C), 1586 (Ar), 1677 (ArCO), 1770 cm^{-1} (=NOCOR). ^{1}H-NMR spectrum ($CDCl_3$): δ 8·03 (m, 1 H, aromatic 6-H), 7·30—7·70 (m, 3 H, remaining aromatic protons), 3·24 (m, 4 H, SCH_2CH_2), 2·23 (s, 3 H, CH_3CO). For $C_{12}H_{11}NO_3S$ (249·3) calculated: 57·82% C, 4·44% H, 5·61% N, 12·86% S; found: 57·84% C, 4·25% H, 5·62% N, 13·00% S.

2-(2-Cyanoethylthio)benzoic Acid (*XXVIII*)

A. XXVI (0·5 g) was dissolved in a mixture of 7·5 ml acetic acid and 3 ml acetic anhydride, followed by an addition of 5 drops of H_2SO_4 and the mixture was left to stand overnight at room temperature. The precipitated product was filtered, washed with light petroleum and recrystallized from ethanol; it melts at 186—187°C and appear homogeneous on thin-layer chromatography on Silufol. Mass spectrum with a molecular ion at m/e 207 supports the formula $C_{10}H_9NO_2S$. IR spectrum (KBr): 755 (4 adjacent Ar—H), 910, 2360, 2570, 2660 (COOH), 1558, 1590 (Ar), 1690 cm^{-1} (Ar—COOH). ^{1}H-NMR spectrum: δ 8·06 (m, 1 H, aromatic 6-H), 7·15—7·80 (m, 3 H, remaining aromatic protons), 3·26 and 2·90 (2t, 4 H, SCH_2CH_2). For $C_{10}H_9NO_2S$ (207·2) calculated: 57·97% C, 4·38% H, 6·76% N, 15·45% S; found: 58·02% C, 4·54% H, 6·75% N, 15·58% S. Ref.[51] describes the preparation of the substance by cyanoethylation of thiosalicylic acid but reports a m.p. of 214°C for the product.

B. A mixture of 15 ml acetic acid, 3 ml acetic anhydride, 0·3 g *XXVII* and 2 drops of H_2SO_4 was processed similarly to *A*. The product obtained melts at 183—186°C and is identical with that obtained under *A*.

Bis(2-hydroxymethylphenyl) Disulfide (*XXX*)

A. A 40% benzene solution of sodium dihydridobis(2-methoxyethoxy)aluminate containing 7·0 g agent was added dropwise under stirring to a suspension of 1·5 g *XXVIII* in 40 ml benzene at room temperature. After three hours of stirring the solution cleared, was diluted with 20 ml 10% hydrochloric acid, the benzene solution was washed with water, dried with Na_2SO_4 and evaporated. The residue was recrystallized from 2-propanol; 0·8 g (40%), m.p. 140—141°C. IR spectrum (KBr): 750 (4 adjacent Ar—H), 1038, 1055 (CH_2OH), 1575, 1595 (Ar), 3240 and 3320 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·10—7·60 (m, 8 H, aromatic protons), 5·35 (t, J = 5·0 Hz, disappears after D_2O, 2 H, 2 OH), 4·56 (d, J = 5·0 Hz, after D_2O s, 4 H, 2 CH_2O). For C_{14} . . $H_{14}O_2S_2$ (278·3) calculated: 60·43% C, 5·07% H, 23·00% S; found: 60.38% C, 5·01% H, 22·83%S. Ref.[52,53] report for a product prepared differently a m.p. of 144 and of 141—142°C, respectively.

B. A 70% solution of sodium dihydridobis(2-methoxyethoxy)aluminate in benzene (containing 14 g agent) was added dropwise to a suspension of 5·4 g dithiosalicylic acid[54] in 80% benzene. The mixture was refluxed for 30 min, cooled and decomposed with 30 ml 10% hydrochloric acid; the benzene layer was washed with water, dried and evaporated. A total of 3·1 g (67%) compound melting at 139—141·5°C was obtained, this being identical with the product prepared under *A*.

2-(3-Cyanopropyl)benzoic Acid (*XXIX*)

A mixture of 7 ml acetic acid and 3 ml acetic anhydride was combined with 0·50 g 6-oximino--6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one[41—45] and with 0·1 ml H_2SO_4. The mixture was left at room temperature for 48 h, diluted with 30 ml ether and washed with water. The ether layer was dried with Na_2SO_4 and evaporated *in vacuo*. The residue was extracted with a 5% solution of NaOH, the insoluble fractions were removed with ether and the product was precipitated from the alkaline solution by acidification with hydrochloric acid; 0·4 g (80%), m.p. 81—83·5°C (water). UV spectrum: λ_{max} 229 nm (log ε 3·89), 278 nm (3·51). IR spectrum (KBr): 748 (4 adjacent Ar—H), 913, 1275, 2515, 2690, 2815 (COOH), 1483, 1575 (Ar), 1680 (ArCOOH), 2245 cm^{-1} (CN). For $C_{11}H_{11}NO_2$ (189·2) calculated: 69·84% C, 5·85% H, 7·40% N; found: 69·67% C, 5·99% H, 7·42% N.

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