SYNTHESIS OF 3-CHLORO-5-(4-METHYLPIPERAZINO)-6,7-DIHYDRO-5*H*-DIBENZO[*b,g*]THIOCIN, AN EIGHT-MEMBERED RING HOMOLOGUE OF THE NEUROLEPTIC AGENT OCTOCLOTHEPIN*

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Alkylation of diethyl malonate with 2-(4-chlorophenylthio)benzyl chloride, the following hydrolysis and decarboxylation gave 3-[2-(4-chlorophenylthio)phenyl]propionic acid (*IV*); its chloride was cyclized in low yield by treatment with aluminium chloride to 4-(4-chlorophenylthio)indanone (*V*). The corresponding methylpiperazine derivative *VIII* was prepared *via* intermediates *VI* and *VII*. A reaction of 3-(2-mercaptophenyl)propionic acid with 5-chloro-2-iodobenzoic acid and the following esterification resulted in the diester *XVI* which was cyclized by a Dieckmann reaction using sodium hydride in toluene to give ethyl 3-chloro-5-hydroxy-7*H*-dibenzo[*b,g*]thiocin-6-carboxylate (*XVII*). The acid hydrolysis afforded the ketone *XVIII* which was transformed *via* the intermediates *XX* and *XXI* to the title compound *II*. The product has a mild central depressant activity but it lacks the character of a neuroleptic agent.

The linearly condensed systems with a central six- or seven-membered ring are typical for the structures of tricyclic antipsychotics (neuroleptics, antidepressants). Until now only in the antidepressant group attempts to develop analogues with an eight-membered central ring were noted and derivatives of 5,6,7,12-tetrahydrodibenzo[*a,d*]cyclooctene[1], 5,6,11,12-tetrahydrodibenz[*b,f*]azocine[2-4], 5,6,7,12-tetrahydrodibenz[*b,e*]azocine[5], 5,6,7,12-tetrahydrodibenz[*b,g*]azocine[6], 5,6,7,12-tetrahydrodibenz[*c,f*]azocine[7], 6,7-dihydro-12*H*-dibenzo[*b,e*]thiocin[8,9] and 6,7-dihydro-5*H*-dibenzo[*b,g*]-1,4-thiazocine[10] were synthesized. In the present communication we are dealing with the synthesis of a potential neuroleptic agent, the molecule of which contains a new tricyclic system with a central eight-membered ring: 6,7-dihydro-5*H*-dibenzo[*b,g*]thiocin. The corresponding compound was dessigned by enlargement of the central seven-membered ring in the molecule of the neuroleptic clorothepin (octoclothepin) (*I*) (ref.[11]) and we are thus dealing here with the title compound *II*. In one of the preceding communications of this series[12], we described our preliminary experiments, which were directed to the synthesis of the mentioned new system leading, however, to derivatives of 2*H*-cyclopenta[*kl*]thioxanthene. The literature[13-15] reported the synthesis of derivatives of the analogous 5*H*-di-

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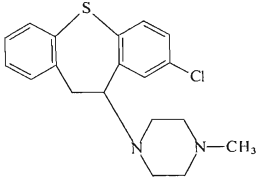
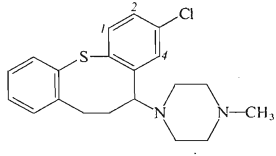
benz[*b*,*g*]oxocin and its 6,7-dihydro derivative without any connection with the chemistry of psychotropic agents.

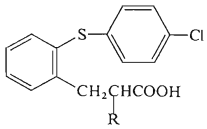


I

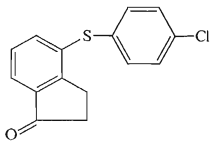


II

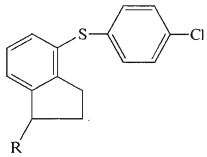
The first synthetic experiment, which was carried out, used a similar approach like in our preceding communication[12] and did not lead to the wanted result. Alkylation of diethyl malonate with 2-(4-chlorophenylthio)benzyl chloride[11] and the alkaline hydrolysis of the crude ester formed gave the acid *III* which exhibited a surprising stability. When refluxed with 40% sulfurid acid, it decarboxylated very slowly and only heating to 180°C led quantitatively to decarboxylation to 3-[2-(4-chlorophenylthio)phenyl]propionic acid (*IV*). After previous experience with attempts at cyclizing similar acids with polyphosphoric acid[12], different cyclization methods were tested in the present case. Attempts to cyclize the acid *IV* with trifluoroacetic anhydride[16] or with a mixture of phosphorus pentoxide and methanesulfonic acid[17] were unsuccessful. Only the Friedel–Crafts cyclization of the crude acid chloride (obtained by means of thionyl chloride) in carbon disulfide or dichloromethane with aluminium chloride gave a neutral product from which it was possible to isolate by column chromatography some 10% of a ketone $C_{15}H_{11}ClOS$. Its IR spectrum exhibited an absorption band at 1720 cm^{-1} corresponding to a conjugated keto group in a five-membered ring. After the results of our foregoing work[12], this product could unequivocally be formulated as 4-(4-chlorophenylthio)indanone (*V*). In agreement with this structure, the ^{1}H-NMR spectrum shows a singlet of 4 aromatic protons corresponding to the *4*-chlorophenylthio group, and the mass spectrum revealed a compatible fragmentation. In spite of the fact that the cyclization did not lead to the tricyclic ketone with an eight-membered ring, compound *V* was processed by reactions used in the synthesis of potential psychotropic drugs. Reduction with sodium borohydride in aqueous ethanol gave the alcohol *VI* which was transformed by treatment with hydrogen chloride in benzene to the oily chloride *VII* (its identity was confirmed by the mass spectrum). A substitution reaction with 1-methylpiperazine in boiling chloroform resulted in a theoretical yield of the base *VIII* which was characterized by spectra and transformed to a bis(hydrogen maleate).



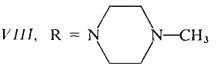
III, R = COOH
IV, R = H



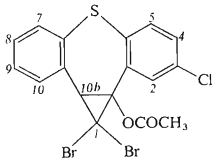
V



VI, R = OH
VII, R = Cl

VIII, R = 

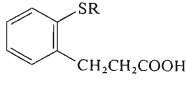
In a further experiment we attempted to use a reaction sequence in which a dihalocarbene is added to the enol acetate of a cyclic ketone and the condensed cyclopropane derivative formed is oppened under basic conditions and under a simultaneous ring enlargement[18]. 10-Acetoxy-8-chlorodibenzo[*b*,*f*]thiepin[19] was used as the enol acetate and out of the dihalocarbenes, dibromocarbene was selected and generated by decomposition of phenyl(tribromomethyl)mercury[20] in refluxing benzene[21]. Chromatography of the crude reaction product on silica gel afforded the dibenzo[*b*,*f*]cyclopropa[*d*]thiepin derivative *IX* (for the first report on the skeleton, *cf.*[22]), the structure of which was confirmed by spectra. For oppening the cyclopropane ring, reduction with lithium aluminium hydride (*cf.*[18]) was used, but from the mixture formed, we did not succeed in isolating any homogeneous product.



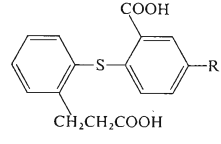
IX

Only the third synthetic attempt, using the Dieckmann cyclization with the high dilution technique, led to the desired result. The known 3-(2-mercaptophenyl)propionic acid (*X*) (ref.[23]), prepared from 3,4-dihydroquinolin-2(1*H*)-one[24] *via* sodium

3-(2-aminophenyl)-propionate[23,25], was used as the starting product. During the transformation of the last mentioned amino acid to the mercapto acid *X* by the xanthate method[23], the aryl xanthate *XI* was isolated as a minor product. It proved more suitable to prepare the acid *X* from the mentioned amino acid by diazotization, reaction of the diazonium salt solution with sodium disulfide and reduction of the product with zinc in acetic acid. A reaction of the acid *X* with 2-iodo-5-nitrobenzoic acid[26] in a boiling aqueous potassium hydroxide solution in presence of copper gave the nitro diacid *XII*. Its reduction with iron and aqueous acetic acid resulted in the amino diacid *XIII*, isolated in the form of a hydrochloride. The Sandmeyer reaction afforded then in a low yield the chloro diacid *XIV*.

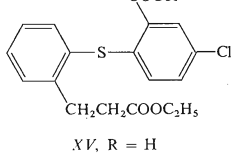


X, R = H
XI, R = $CSOC_2H_5$



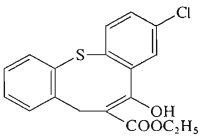
XII, R = NO_2
XIII, R = NH_2
XIV, R = Cl

For preparing the acid *XIV* and its diethyl ester *XVI*, it proved more suitable to start from a reaction of the acid *X* with 5-chloro-2-iodobenzoic acid[27] in a boiling aqueous potassium hydroxide solution in the presence of copper; crystallization of the crude product from ethanol gave the monoethyl ester of a diacid which was identified by means of the IR spectrum as the compound *XV*. The free dicarboxylic acid *XIV* is thus esterified by crystallization from ethanol to the monoethyl ester; the esterification takes place on the carboxyl group in the aliphatic chain. Esterification of the aromatic carboxyl group required catalysis with sulfuric acid and a long boiling with ethanol; the diester *XVI* was obtained in this manner. Even after 10 hours boiling, a part of the monoester *XV* remains unchanged and during its separation by extraction into a dilute sodium hydroxide solution, a complete hydrolysis to the diacid *XIV* took place, which was obtained by acidification of the aqueous solution.

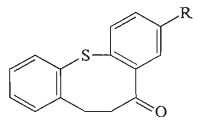


XV, R = H
XVI, R = C_2H_5

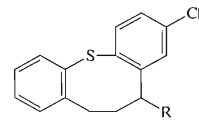
The Dieckmann cyclization of the diester *XVI* either by means of sodium hydride in toluene or with potassium tert-butoxide in xylene was carried out in an apparatus designed for the high dilution technique[13,28]. In the first case, the desired keto ester was obtained in a satisfactory yield. Its IR spectrum exhibits the ester band at 1649 cm^{-1} and further a broad band of the hydroxyl group at 2400–2800 cm^{-1}. Both bands indicate that we are dealing here with the enol form *XVII* stabilized by a hydrogen bond. A singlet of two benzylic protons in the ^{1}H-NMR spectrum is a further evidence of the structure of this enol form. Acid hydrolysis of this compound yielded the desired 3-chloro-6,7-dihydrodibenzo[*b*,*g*]thiocin-5-one (*XVIII*). The use of potassium tert-butoxide as the cyclizing agent proved much less suitable. In this case, it was necessary to subject the crude cyclization product directly to acid hydrolysis; the ketone *XVIII* was separated from the mixture in a low yield by chromatography. Additionally, a lower melting ketone was obtained, having according to the mass spectrum the composition $C_{17}H_{16}O_2S$. The IR and ^{1}H-NMR spectra indicated the presence of an ethoxyl group and the structure of the ethoxy ketone *XIX* was assigned. This compound was evidently formed *via* the corresponding benzyne intermediate and the position of the ethoxyl group is thus not fully established; the only source of the ethoxyl group was ethanol formed during the cyclization.



XVII



XVIII, R = Cl
XIX, R = OC_2H_5



XX, R = OH
XXI, R = Cl

The ketone *XVIII* was reduced with sodium borohydride in aqueous dioxane; the oily product formed was characterized by spectra as the alcohol *XX*. For transforming this alcohol to the chloride *XXI*, the usual treatment with hydrogen chloride in benzene at room temperature[11] is not sufficient and it was necessary to reflux it with thionyl chloride. The crude chloride *XXI* was subjected directly to the substitution reaction with an excess of boiling 1-methylpiperazine. In comparison with 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[11], the reaction of the present chloride *XXI* proceeds very slowly and a satisfactory yield on the oily base *II* was attained only after 48 hours refluxing. The base was transformed into the bis(hydrogen maleate), the decomposition of which gave the base *II*, used for recording the ^{1}H-NMR spectrum. In this spectrum, there is a typical signal of the benzylic proton, adjacent to the nitrogen atom, which appears as a quartet (doubled doublet) at δ 3·84 due to the magnetic non-equivalency of the adjacent two protons which have with it the coupling

constants of 5·0, and 12·0 Hz, respectively. Some rigidity of the tricyclic system remains thus preserved. The spectrum of compound *II* differs in this respect evidently from that of the isomeric base *VIII* in which the signal of the corresponding benzylic proton appears as a triplet at δ 4·38.

Compounds *II* [bis(hydrogen maleate) hemihydrate VÚFB-12.324] and *VIII* [bis(hydrogen maleate) VÚFB-10.650] were pharmacologically tested (Dr A. Dlabač, pharmacological department of this institute, and Dr M. Bartošová, affiliated unit of the institute at Rosice n/L); the doses marked with "b" were calculated for the base. Compound *II* is relatively little toxic (medium lethal doses in mice), LD_{50} = 200 mg/kg ("b") orally, 75 mg/kg *i.v.* In doses higher than 15 mg/kg *i.v.* it elicits strong symptoms of central depression in mice. In the rota-rod test, it brings about disturbances of coordination in mice; the medium effective dose causing ataxia, ED_{50} = 10 mg/kg ("b") orally. It is free of the cataleptic effect in rats; a dose of 50 mg/kg ("b") orally is completely ineffective. A concentration of 0·5% exhibits in 50% animals a complete anaesthesia in the test of corneal anaesthesia in rabbits (200% of the effect of trimecaine). In a dose of 15 mg/kg *i.v.*, it decreases the blood pressure of normotensive rats by 20% and in a dose of 7·5 mg/kg *i.v.*, it diminishes the adrenaline pressoric reaction to 50% (rats). In concentration of 1 — 10 μg/ml it inhibits acetylcholine and barium chloride contractions of the isolated rat duodenum by 50%; it has thus only a slight parasympatholytic antispasmodic action but a full musculotropic antispasmodic action of papaverine. In conclusion, the enlargement of the central ring in the molecule of the neuroleptic agent clorothepin (*I*) is connected with a loss of neuroleptic activity. The central depressant effect and some peripheral actions are being preserved but they appear in higher doses than with clorothepin (*I*). Compound *VIII* has an LD_{50} of 80 mg/kg *i.v.* In a dose of 15 mg/kg *i.v.*, it does not show any central effects. The antispasmodic action is similar like with the preceding compound.

Compounds *II* and *VIII* were also tested for antimicrobial activity *in vitro* (Dr A. Čapek and Dr J. Turinová, bacteriological department of this institute); the microorganisms used and the minimum inhibitory concentrations in μg/ml are given: *Streptococcus β-haemolyticus*, *II* 25, *VIII* 25; *Streptococcus faecalis*, *II* 50, *VIII* 25; *Staphylococcus pyogenes aureus*, *II* 25, *VIII* 50; *Mycobacterium tuberculosis* H37Rv, *II* 12·5, *VIII* 5; *Saccharomyces pasterianus*, *VIII* 25; *Trichophyton mentagrophytes*, *VIII* 50; *Candida albicans*, *VIII* 100; *Aspergillus niger*, *VIII* 100.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 70 Pa over P_2O_5 at room temperature or at 77°C. The UV spectra (mostly in methanol) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of silica gel or alumina.

[2-(4-Chlorophenylthio)benzyl]malonic Acid (*III*)

Sodium (4·6 g) was dissolved in 120 ml 1-butanol, the solution was treated with 32 g diethyl malonate and stirred at 70°C for 15 min. 2-(4-Chlorophenylthio)benzyl chloride[11] (55 g) was added and the mixture was refluxed for 2 h. After standing overnight, the mixture was treated with a solution of 25 g KOH in 25 ml H_2O and refluxed under stirring for 4 h. 1-Butanol was

then removed by steam distillation, the residue was cooled, filtered and the filtrate was acidified with 70 ml hydrochloric acid. The precipitated product was filtered, washed with water and dried *in vacuo*; 40 g (58%), m.p. 95–115°C. Analytical sample, m.p. 133·5°C (ethanol–benzene). IR spectrum (KBr): 758, 816 (4 and 2 adjacent Ar—H), 910, 1210, 1229, 1270, 1710, 1739, 2580 (COOH), 1574, 1589 cm^{-1} (Ar.) For $C_{16}H_{13}ClO_4S$ (336·8) calculated: 57·06% C, 3·89% H, 10·53% Cl, 9·52% S; found: 57·15% C, 3·96% H, 10·16% Cl, 9·26% S.

3-[2-(4-Chlorophenylthio)phenyl]propionic Acid (*IV*)

III (8·4 g) was heated to 180°C for 2 h. The residue was mixed with a small quantity of benzene and filtered; 6·75 g (92%), m.p. 141–142·5°C. Analytical sample, m.p. 141–143°C (benzene). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 12·25 (bs, 1 H, COOH), 7·00–7·50 (m, 8 H, Ar—H), 2·99 (t, 2 H, $ArCH_3$), 2·50 (t, 2 H, CH_2CO). For $C_{15}H_{13}ClO_2S$ (292·8) calculated: 61·53% C, 4·48% H, 12·11% Cl, 10·95% S; found: 61·98% C, 4·54% H, 11·98% Cl, 10·86% S.

4-(4-Chlorophenylthio)indanone (*V*)

A mixture of 46·4 g *IV* and 150 ml $SOCl_2$ was refluxed for 3 h and evaporated *in vacuo*. The remaining acid chloride was dissolved in 900 ml dichloromethane, the solution cooled to 10°C and treated under stirring with 36 g $AlCl_3$. The mixture was stirred for 7 h, decomposed under cooling with 500 ml 10% hydrochloric acid, the organic layer was separated, washed with dilute NH_4OH, dried with $MgSO_4$ and evaporated under reduced pressure; 50 g neutral oil. It was chromatographed on a column of 700 g SiO_2 (100/160). Benzene eluted 5·2 g least polar oil which did not show the typical fluorescence in the UV light. A mixture of benzene and chloroform eluted then 4·55 g (10%) ketone *V*, m.p. 105–112°. Analytical sample, m.p. 115–115·5°C (cyclohexane). Mass spectrum, *m/e* (corresponding to): 274 (M^+, $C_{15}H_{11}ClOS$), 246 ($C_{14}H_{11}ClS$), 162 (C_9H_6OS), 134 (base peak, C_8H_6S). UV spectrum: λ_{max} 244 nm (log ε 4·44), infl. 259 nm (4·16), infl. 281 nm (3·73), 312 nm (3·48). IR spectrum: 788, 807, 829 (3 and 2 adjacent Ar—H), 1583 (Ar), 1720 cm^{-1} (indanone CO). ^{1}H-NMR spectrum: δ 7·30–7·80 (m, 3 H, indanone Ar—H), 7·25 (s, 4 H, 4-chlorophenylthio Ar—H), 2·50–3·20 (m, 4 H, $ArCH_2CH_2CO$). For $C_{15}H_{11}ClOS$ (274·8) calculated: 65·56% C, 4·04% H, 12·91% Cl, 11·67% S; found: 65·68% C, 4·07% H, 12·62% Cl, 11·23% S.

4-(4-Chlorophenylthio)indane-1-ol (*VI*)

A stirred solution of 4·76 g *V* in 80 ml ethanol was treated dropwise with a solution of 0·66 g $NaBH_4$ in 3 ml H_2O containing 1 drop 20% NaOH. The mixture was refluxed for 5 h, ethanol was evaporated *in vacuo*, the residue diluted with water and extracted with benzene. Filtration of a solution of the residue in chloroform through a column of 150 g SiO_2 gave 4·1 g (86%) *VI*, m.p. 82–83°C. Analytical sample, m.p. 82–83°C (cyclohexane–light petroleum). IR spectrum: 793, 818 (3 and 2 adjacent Ar—H), 1064, 1092, 1128 (CHOH in a cycle), 3280 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·00–7·40 (m, 3 H, Ar—H in the indane residue), 7·15 (s, 4 H, 4-chlorophenylthio Ar—H), 6·18 (t, J = 6·0 Hz, 1 H, Ar—CH—O), 1·50–3·20 (m, 4 H, $ArCH_2CH_2$), 2·20 (s, 1 H, OH). For $C_{15}H_{13}ClOS$ (276·8) calculated: 65·09% C, 4·73% H, 12·81% Cl, 11·59% S; found: 65·37% C, 4·69% H, 12·82% Cl, 11·38% S.

4-(4-Chlorophenylthio)-1-(4-methylpiperazino)indane (*VIII*)

A solution of 4·0 g *VI* in 100 ml benzene was saturated for 3 h with anhydrous HCl in the presence of 3 g $CaCl_2$ at room temperature. After standing overnight, it was filtered and evaporated

in vacuo; 4·25 g (100%) oily *VII*. Mass spectrum, *m/e* (corresponding to): 294 (M^+, $C_{15}H_{12}Cl_2S$), 115 (base peak, C_9H_7).

A mixture of 4·1 g *VII*, 15 ml 1-methylpiperazine and 15 ml chloroform was refluxed for 8 h. After cooling, it was decomposed with 100 ml water and extracted with benzene. The extract was washed with water and the base was transferred by shaking with 10% hydrochloric acid into the aqueous layer. After separation, the acid layer was made alkaline with NH_4OH and the base extracted with benzene. The extract was dried (K_2CO_3) and evaporated *in vacuo*; 5·0 g (100%), m.p. 98—99°C (ethanol). Mass spectrum, *m/e* (corresponding to): 358 (M^+, $C_{20}H_{23}ClN_2S$), 147 (C_9H_7S). IR spectrum (KBr): 774, 816, 825 (3 and 2 adjacent Ar—H), 1012, 1087 (C—N), 1567 (Ar), 2768, 2838 cm^{-1} (N—CH_3). ^{1}H-NMR spectrum: δ 7·00—7·40 (m, 7 H, Ar—H), 4·38 (t, 1 H, Ar—CH—N), *c.* 2·75 (m, 2 H, $ArCH_2$), 2·50 (bs, 8 H, 4 NCH_2 of piperazine), 2·28 (s, 3 H, NCH_3), *c.* 2·10 (m, 2 H, remaining CH_2). For $C_{20}H_{23}ClN_2S$ (358·9) calculated: 66·92% C, 6·46% H, 9·88% Cl, 7·81% N, 8·93% S; found: 66·69% C, 6·46% H, 9·93% Cl, 7·93% N, 8·87% S.

Bis(hydrogen maleate), m.p. 193—193·5°C (aqueous ethanol). For $C_{28}H_{31}ClN_2O_8S$ (591·1 calculated: 56·90% C, 5·29% H, 6·00% Cl, 4·74% N, 5·42% S; found: 57·12% C, 5·43% H, 6·09% Cl, 4·67% N, 5·66% S.

1a-Acetoxy-1,1-dibromo-3-chloro-1a,10b-dihydro-1*H*-dibenzo[*b,f*]cyclopropa[*d*]thiepin (*IX*)

A solution of 7·1 g 10-acetoxy-8-chlorodibenzo[*b,f*]thiepin[19] in 30 ml benzene was treated with 29·4 g phenyl(tribromomethyl)mercury[20] and the mixture was stirred and refluxed under nitrogen for 3 h. The precipitated phenylmercuric bromide was filtered off and the filtrate was evaporated. The residue was chromatographed on a column of 300 g SiO_2. A mixture of benzene and light petroleum eluted first 3·2 g tetrabromoethylene. They were followed by 2·80 g (25%) *IX*, m.p. 168—172°C. Analytical sample, m.p. 171—172·5°C (cyclohexane–light petroleum). IR spectrum (KBr): 754, 818, 898 (4 and 2 adjacent and solitary Ar—H), 1087, 1113, 1201 (C—O of ester), 1550, 1572 (Ar), 1762 cm^{-1} (cyclopropyl-$OCOCH_3$). ^{1}H-NMR spectrum: δ 8·13 (mcs, J = 2·5Hz, 1 H, 2-H), 7·53 (d, J = 8·5 Hz, 1 H, 5-H), 7·18 (mcd, J = 8·5; 2·5 Hz, 1 H, 4-H), 7·15—7·65 (m, 4 H, 7,8,9,10-H_4), 3·51 (mcs, J = 1·0 Hz, 1 H, 10b-H), 2·10 (s, 3 H, $COCH_3$). For $C_{17}H_{11}Br_2ClO_2S$ (474·6) calculated: 43·02% C, 2·34% H, 33·67% Br, 7·47% Cl, 6·76% S; found: 42·11% C, 2·36% H, 33·30% Br, 7·39% Cl, 6·65% S. Continuation of the chromatography by elution with benzene led to the recovery of 3·0 g starting enol acetate; the yield on *IX* calculated "per conversion" is thus 44%.

3-(2-Mercaptophenyl)propionic Acid (*X*)

A) A solution of 28 g $NaNO_2$ and 72·5 g sodium 3-(2-aminophenyl)propionate[23,25] in 100 ml H_2O was added dropwise over 30 min to a stirred mixture of 150 ml hydrochloric acid and 150 g ice at 0°C. After an additional stirring for 1 h at 0°C, the diazonium salt solution was slowly poured at 0—5°C into a stirred solution of 120 g $Na_2S.9\,H_2O$, 16 g S and 20 g NaOH in 190 ml H_2O. It was then stirred for 2·5 h without cooling and acidified with 90 ml hydrochloric acid. The precipitated product was filtered and extracted with a boiling solution of 30 g Na_2CO_3 in 1 l H_2O, it was filtered again and the filtrate acidified with hydrochloric acid. The precipitated and purified disulfide diacid was filtered, dissolved in 200 ml acetic acid and the solution refluxed for 4 h with 30 g Zn. After evaporation of a part of acetic, acid, the residue was made alkaline with 20% NaOH, diluted with H_2O, filtered and the filtrate acidified with hydrochloric acid. The precipitated product was filtered, washed with water and dried *in vacuo*; 47·3 g (67%), m.p. 117—120°C. The literature[23] reported a m.p. of 118°C for a product prepared differently.

B) When the literature procedure[23] was followed, there were obtained 28·1 g (36%) *X* (m.p. 117–120°C) from 80 g sodium 3-(2-aminophenyl)propionate[23,25]. A small quantity (3·6 g) of another product was separated by crystallization which proved to be O-ethyl S-[2-(2-carboxyethyl)phenyl]xanthate (*XI*) and which evidently resisted to the step of the alkaline hydrolysis; m.p. 182·5–184°C (benzene–ethanol). For $C_{12}H_{14}O_3S$ (270·4) calculated: 23·72% S; found: 23·50% S.

3-[2-(2-Carboxy-4-nitrophenylthio)phenyl]propionic Acid (*XII*)

A mixture of 28·1 g *X*, 44·1 g 2-iodo-5-nitrobenzoic acid[26], 28 g KOH, 2 g Cu and 300 ml H_2O was stirred and refluxed for 7 h. It was then filtered and the filtrate was acidified with hydrochloric acid. The oil formed was separated and warmed with a small quantity of benzene to crystallize; 46·4 g (87%) crude product, m.p. 175–200°C. Analytical sample, m.p. 205–208°C (benzene–ethanol). UV spectrum: λ_{max} 250 nm (log ε 3·85), 343 nm (4·18). IR spectrum: 740, 760, 803, 837, 911 (4 and 2 adjacent and solitary Ar—H), 928, 1252, 1280, 1692, 2660 (COOH), 1340, 1520 (NO_2), 1570, 1600 cm^{-1} (Ar). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 8·59 (mcs, J = 3·0 Hz, 1 H, 3 H in the nitrophenyl residue), 8·08 (mcd, J = 8·0; 3·0 Hz, 1 H, 5-H in the nitrophenyl residue), *c.* 7·40 (m, 4 H, Ar—H in the phenylpropionic acid residue), 6·60 (d, J = 8·0 Hz, 1 H, 6-H in the nitrophenyl residue), 2·80 (t, J = 7·5 Hz, 2 H, $ArCH_2$), *c.* 2·40 (t, 2 H, CH_2COO). For $C_{16}H_{13}NO_6S$ (347·4) calculated: 55·33% C, 3·77% H, 4·03% N, 9·23% S; found: 55·71% C, 3·94% H, 3·96% N, 8·97% S.

3-[2-(4-Amino-2-carboxyphenylthio)phenyl]propionic Acid (*XIII*)

XII (21·4 g) was added to a mixture of 20 g Fe, 120 ml H_2O and 12 ml acetic acid and the mixture was stirred and refluxed for 5 h. After cooling, it was made alkaline with 20% NaOH, filtered and the filtrate was acidified with hydrochloric acid to give 17·0 g (74%) monohydrate of the hydrochloride. Crystallization from 5% hydrochloric acid gave the analytical sample, m.p. 195–197°C. UV spectrum: λ_{max} 267 nm (log ε 4·15), 325 nm (3·24). IR spectrum: 755, 766, 789, 825, 892 (4 and 2 adjacent and solitary Ar—H), 922, 1255, 1709, 3150 (COOH), 1472, 2595 cm^{-1} (NH_3^+). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 8·20 (bs, H_2O), 7·80 (mcs, J = 3·0 Hz, 1 H, 3-H in the aminophenyl residue), *c.* 7·30 (m, 5 H, 5-H in the aminophenyl residue and 4 Ar—H in the phenylpropionic acid residue). 6·50 (d, J = 8·0 Hz, 1 H, 6-H in the aminophenyl residue), 2·82 (t, 2 H, $ArCH_2$). *c.* 2·40 (t, 2 H, CH_2COO). For $C_{16}H_{18}ClNO_5S$ (371·8) calculated: 51·68% C, 4·87% H, 9·54% Cl, 3·77% N, 8·62% S; found: 51·78% C, 4·64% H, 9·26% Cl, 3·92% N, 8·78% S.

3-[2-(2-Carboxy-4-chlorophenylthio)phenyl]propionic Acid (*XIV*)

A suspension of 16·5 g *XIII*. $HCl.H_2O$ in 150 ml H_2O and 30 ml hydrochloric acid was heated to the boiling point, quickly cooled to 0°C and then diazotized under stirring with a solution of 3·5 g $NaNO_2$ in 10 ml H_2O at 0°C. The suspension was stirred for 1 h at 0°C and poured to a solution of 7·5 g CuCl in 40 ml hydrochloric acid. The mixture was stirred for 40 min at room temperature and then for 2 h at 70°C. After cooling, the precipitated solid was filtered, dissolved in 10% NaOH solution, filtered again, the filtrate was acidified with acetic acid, the solid filtered and recrystallized from aqueous ethanol with charcoal; 5·7 g (38%), m.p. 194–197°C with decomposition. Analytical sample, m.p. 211–213°C (benzene–dioxane). UV spectrum: λ_{max} 257 nm (log ε 4·09), 327 nm (3·58). IR spectrum: 723, 749, 753, 780, 829, 885 (4 and 2 adjacent and solitary Ar—H), 1242, 1299, 1708, 2540, 2650, 2710 (COOH), 1542 cm^{-1} (Ar). For $C_{16}H_{13}ClO_4S$

(336·8) calculated: 57·06% C, 3·89% H, 10·53% Cl, 9·52% S; found: 56·67% C, 4·07% H, 10·60% Cl, 9·38% S.

Ethyl 3-[2-(2-Carboxy-4-chlorophenylthio)phenyl]propionate (*XV*)

A mixture of 47·3 g *X*, 73·5 g 5-chloro-2-iodobenzoic acid[27], 50 g KOH, 4 g Cu and 500 ml H_2O was stirred and refluxed for 7 h, filtered and the filtrate acidified with hydrochloric acid. The product was filtered off and crystallized first from aqueous ethanol and then from a mixture of benzene and light petroleum to give 49·0 g (48%) benzene solvate of *XV*, m.p. 97–100°C. IR spectrum: 736, 759, 783, 896 (4 and 2 adjacent and solitary Ar—H), 926, 1 250, 1 310, 1 690 (ArCOOH), 1 176, 1 190, 1 730 (RCOOR), 1 542 (Ar), 2 540, 2 605, 2 645 cm^{-1} (dimeric COOH). ^{1}H-NMR spectrum: δ 10·88 (bs, 1 H, ArCOOH), 8·08 (mcs, J = 3·0 Hz, 1 H, 3-H in the benzoic acid residue), 7·00–7·60 (m, 7 H, 5-H in the benzoic acid residue, 4 Ar—H in the phenylpropionate residue and $1/3\ C_6H_6$), 6·50 (d, J = 8·0 Hz, 1 H, 6-H in the benzoic acid residue), 4·04 (*q*, J = 7·0 Hz, 2 H, $COOCH_2$), 3·00 (t, 2 H, $ArCH_2$), 2·60 (t, 2 H, CH_2COO), 1·20 (t, J = = 7·0 Hz, 3 H, CH_3). For $C_{18}H_{17}ClO_4S + 1/3\ C_6H_6$ (390·9) calculated: 61·45% C, 4·90% H, 9·07% Cl, 8·20% S; found: 61·39% C, 4·93% H, 9·40% Cl, 8·08% S.

Ethyl 3-[2-(4-Chloro-2-ethoxycarbonylphenylthio)phenyl]propionate (*XVI*)

A mixture of 48·3 g *XV* (benzene solvate), 500 ml ethanol and 5 ml H_2SO_4 was refluxed for 20 h. Benzene (100 ml) was added and the mixture distilled slowly through a column until 100 ml distillate were obtained. The solvents were then evaporated, the residue dissolved in benzene, the solution washed with 10% NaOH and H_2O, dried with $MgSO_4$ and evaporated; 33·8 g (70%) oily *XVI*. A sample was distilled for analysis, b.p. 200–205°C/50 Pa. ^{1}H-NMR spectrum: δ 7·85 (mcs, J = 3·0 Hz, 1 H, 3-H in the benzoate residue), *c.* 7·35 (m, 4 H, Ar—H of the phenylpropionate residue), 7·10 (mcd, J = 8·0; 3·0 Hz, 1 H, 5-H in the benzoate residue), 6·48 (d, J = = 8·0 Hz, 1 H, 6-H in the benzoate residue), 4·38 (q, J = 7·0 Hz, 2 H, benzoate $COOCH_2$), 4·01 (q, J = 7·0 Hz, 2 H, propionate $COOCH_2$), 2·98 (t, 2 H, $ArCH_2$), 2·50 (t, 2 H, CH_2COO), 1·40 and 1·15 (2 t, J = 7·0 Hz, 6 H, 2 CH_3). For $C_{20}H_{21}ClO_4S$ (392·9) calculated: 61·14% C, 5·39% H, 9·02% Cl, 8·16% S; found: 61·22% C, 5·51% H, 9·21% Cl, 8·02% S. Acidification of the aqueous solution from the alkaline washing gave 12·6 g diacid *XIV*, m.p. 211–213°C. The yield on *XVI* "per conversion" is thus becoming theoretical.

Ethyl 3-Chloro-5-hydroxy-7*H*-dibenzo[*b*,*g*]thiocin-6-carboxylate (*XVII*)

A suspension of 3·0 g NaH in 350 ml toluene was treated with 0·5 g tert-butyl alcohol and the reaction flask was connected with a high dilution technique apparatus[13,28] containing 350 ml toluene; it was stirred, refluxed and treated under nitrogen with a solution of 21·9 g *XVI* in 300 ml toluene over 48 h. It was refluxed for additional 3 h, decomposed with a mixture of 50 ml acetic acid and 50 ml toluene, and then with 200 ml H_2O. The toluene layer was washed with water, dried ($MgSO_4$) and evaporated. The residue was diluted with some benzene and deposited 2·72 g crystals of m.p. 197–211°C; this by-product was identified as the diacid *XIV*. The benzene solution was chromatographed on a column of 700 g SiO_2 (100/160) under elution with benzene; 12·52 g (65%) product, m.p. 107–110°C. Analytical sample, m.p. 110–112°C (benzene–light petroleum). UV spectrum: λ_{max} 231 nm (infl.) (log ε 4·39), infl. 260 nm (4·17), infl. 290 nm (3·82). IR spectrum (KBr): 763, 823, 871, 899 (4 and 2 adjacent and solitary Ar—H), 1 033, 1 103, (OH), 1 211, 1 248 (C—O), 1 561, 1 578 (Ar), 1 649 (COOR with a hydrogen bond), 3 030, 3 100 (Ar), 2 400–2 800 cm^{-1} (OH···O=). ^{1}H-NMR spectrum: δ 7·00–7·80 (m, 7 H, Ar—H), 4·18 (*q*,

J = 7·0 Hz, 2 H, $COOCH_2$), 3·20 (bs, 2 H, $ArCH_2$), 1·23 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{18}H_{15}ClO_3S$ (346·8) calculated: 62·34% C, 4·36% H, 10·22% Cl, 9·25% S; found: 62·73% C, 4·41% H, 10·36% Cl, 9·10% S.

3-Chloro-6,7-dihydrodibenzo[*b*,*g*]thiocin-5-one (*XVIII*)

A. A mixture of 2·80 g *XVII*, 50 ml ethanol and 50 ml 1 : 1 dilute hydrochloric acid was refluxed for 20 h. Ethanol was evaporated *in vacuo*, the residue dissolved in benzene, the solution washed with water, dried and evaporated; 2·20 g (almost 100%), m.p. 91—96°C. Analytical sample, m.p. 97—98°C (light petroleum). UV spectrum: λ_{max} 235 nm (log ε 4·25), infl. 261 nm, 324 nm (3.38). IR spectrum (KBr): 764, 774, 817, 835, 891 (4 and 2 adjacent and solitary Ar—H), 1236 (CO), 1349 (C—H in CH_2CO), 1458, 1550, 1583 (Ar), 1689 cm^{-1} (Ar—CO). ^{1}H-NMR spectrum: δ 6·90—7·65 (m, 7 H, Ar—H), 3·55 (m, 2 H, $ArCH_2$), 3·28 (m, 2 H, CH_2CO). For $C_{15}H_{11}ClOS$ (274·8) calculated: 65·56% C, 4·04% H, 12·91% Cl, 11·67% S; found: 65·46% C, 4·03% H, 13·00% Cl, 11·43% S.

B. Potassium (4·1 g) was dissolved in a mixture of 300 ml xylene and 22·2 g tert-butyl alcohol and the refluxing solution was treated over 48 h through a high dilution apparatus[13,28] with a solution of 18·7 g *XVI* in 300 ml xylene under nitrogen. The mixture was stirred and refluxed for additional 4 h, after cooling decomposed with a solution of 50 ml acetic acid in 50 ml xylene and then with 200 ml water. The organic layer was separated, washed with water, dried with $MgSO_4$ and evaporated; 15·8 g oily mixture. It was dissolved in benzene and chromatographed on a column of 700 g SiO_2 (100/160). Benzene eluted first 3·12 g mixture of two components and then 7·92 g starting diester *XVI*. The mixture (3·12 g) was refluxed with 60 ml ethanol and 60 ml 1 : 2 dilute hydrochloric acid for 3 h, ethanol was evaporated, the residue diluted with water and extracted with benzene. Processing of the extract gave 3·0 g residue which was dissolved in benzene and chromatographed on a column of 150 g Al_2O_3 (activity II). Elution with a mixture of benzene and light petroleum gave 0·48 g Solid, m.p. 97—98°C (light petroleum), being identical with the ketone *XVIII*, obtained according to *A*. The chromatography was continued under elution with benzene to give 0·23 g of a different compound, m.p. 72—74°C (light petroleum). This was identified as 3-ethoxy-6,7-dihydrodibenzo[*b*,*g*]thiocin-5-one (*XIX*). Mass spectrum, *m*/*e* (corresponding to): 284·0873 (M^+, $C_{17}H_{16}O_2S$), 149·0607 ($C_9H_9O_2$), 135·0260 (C_8H_7S). UV spectrum: λ_{max} 255 nm (infl.) (log ε 3·94), 236 nm (4·27), 334 nm (3·28). IR spectrum (KBr): 758, 819, 863 (4 and 2 adjacent and solitary Ar—H), 1040, 1164, 1220, 1238 (ArOR), 1306 (CO), 1590, 3060 (Ar), 1688 cm^{-1} (Ar—CO). ^{1}H-NMR spectrum: δ 6·70—7·60 (m, 7 H, Ar—H), 3·92 (q, J = 7·0 Hz, OCH_2), 3·10—3·70 (m, 4 H, $ArCH_2CH_2CO$), 1·31 (t, J = 7·0 Hz, 3 H, CH_3 in ethoxyl). For $C_{17}H_{16}O_2S$ (284·4) calculated: 71·80% C, 5·67% H, 11·28% S; found: 71·79% C, 5·84% H, 11·00% S.

3-Chloro-5-(4-methylpiperazino)-6,7-dihydro-5*H*-dibenzo[*b*,*g*]thiocin (*II*)

A solution of 2·3 g *XVIII* in 30 ml dioxane was treated under stirring with a solution of 0·4 g $NaBH_4$ in 2 ml H_2O containing a drop of 5% NaOH. The mixture was stirred for 30 min, dioxane was evaporated, the residue diluted with water and extracted with benzene. Processing of the extract gave 2·3 g (100%) oily *XX*. IR spectrum: 751, 819, 891 (4 and 2 adjacent and solitary Ar—H), 1039, 1060, 1071, 1100 (CHOH in a cycle), 1560, 1570, 1581, 3073 (Ar), 3390 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·80—7·60 (m, 7 H, Ar—H), 5·25 (bs, 1 H, Ar—CH—O), 1·00 to 3·00 (m, 4 H, $ArCH_2CH_2$).

A mixture of 6·3 g *XX* and 20 ml $SOCl_2$ was allowed to stand for 6 h at room temperature and then refluxed for 1 h. After standing overnight, $SOCl_2$ was completely evaporated *in vacuo*.

The remaining oily *XXI* (6·5 g) was treated with 30 ml 1-methylpiperazine and the mixture refluxed for 48 h (bath of 160°C). After cooling, it was diluted with 150 ml water and extracted with benzene. The extract was washed with water and the base transferred by shaking with 10% hydrochloric acid into the aqueous layer. The solution of the hydrochloride was separated, made alkaline with NH_4OH and the base isolated by extraction with benzene; 5·41 g (66%) oily base *II*. Neutralization with maleic acid in ethanol and addition of ether gave 7·8 g hemihydrate of bis(hydrogen maleate), m.p. 124—126°C (95% ethanol–ether). For $C_{28}H_{31}ClN_2O_8S + 0{\cdot}5\ H_2O$ (600·1) calculated: 56·04% C, 5·37% H, 5·91% Cl, 4·67% N, 5·34% S; found: 56·03% C, 5·21% H, 5·92% Cl, 4·60% N, 5·56% S.

A sample of the pure malcate was decomposed with NH_4OH and the pure base isolated by extraction with ether; it was used for recording the ^{1}H-NMR spectrum: δ 7·60 (mcs, $J = 2{\cdot}5$ Hz, 1 H, 4-H), 7·42 (d, $J = 8{\cdot}0$ Hz, 1 H, 1-H), 6·80—7·20 (m, 5 H, remaining Ar—H), 3·84 (dd, $J =$ $= 5{\cdot}0$; 12·0 Hz, 1 H, Ar—CH—N), 1·00—3·00 (m, 12 H, $ArCH_2CH_2$ and 4 NCH_2 of piperazine), 2·18 (s, 3 H, NCH_3).

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