9-CHLORO-10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b,f*]--THIEPIN AND SOME RELATED SYNTHETIC EXPERIMENTS* **

K.ŠINDELÁŘ, B.KAKÁČ, E.SVÁTEK, J.HOLUBEK, M.RAJŠNER, J.METYŠOVÁ and M.PROTIVA

Research Institute of Pharmacy and Biochemistry, 130 00 Prague 3

Received April 20th, 1973

The synthesis of 9-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*I*) was accomplished. The decisive step of the synthesis was the oxidation of 1-chloro-9-methylenethioxanthene (*IX*) with thallic nitrate in methanol; the principal product was the enol-ether *X* which was hydrolyzed to 9-chlorodibenzo[*b,f*]thiepin-10(11*H*)-one (*II*). The by-product of the oxidation reaction were 1-chloroketone *IV* and compounds *XVI*—*XVIII*. Ketone *II* was converted to the piperazine derivative *I*. Compound *I* is practically inactive as a central depressant and as a cataleptic agent. The synthesis was preceded by a number of experiments described here. An attempt at cyclization of 2-(2-acetamido-5-chlorophenylthio)phenylacetic acid (*XXIX*) with polyphosphoric acid in the presence of toluene yielded 2-chloro-5*H*-dibenzo[*b,g*]-1,4-thiazocin-6(7*H*)-one (*XXXII*) and two other products resulting from interaction of the amide group with toluene and characterized as *XXXIX* and *XL*.

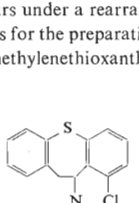
After establishing the high degree of central depressant activity of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin ("perathiepin")[1-4] the problem of most suitable substitution of its molecule to increase further its activity was tackled. For substitution the chlorine atom was used and the 1-, 2-, 3-, 4-, 6-, 7- and 8-chloro-derivatives were systematically prepared[1,5,6]. A favourable effect on activity was found only with substitution in position 8, the 8-chloro derivative ("octoclothepin") functioning as a perphenazine-type neuroleptic both as regards its intensity and character of action[7]. The effect of substitution in position 9 of the perathiepin molecule on its activity remained unclear since the 9-chloro derivative *I* has resisted for some time all attempts at its synthesis. To obtain at least indirect information on the effect of substitution in position 9 in the perathiepin molecule on activity, the 6,8--dichloro derivative and the 6,9-dichloro derivative of the parent compound were synthesized and their activity was compared. It was found that substitution in position 9 has an unfavourable effect on activity[8]. Work on the synthesis of the 9-chloro

* Part LXVIII in the series Neurotropic and Psychotropic Agents; Part LXVII: This Journal *38*, 3879 (1973).

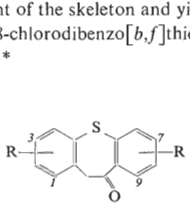
** Preliminary communication: Farmaco (Pavia), Ed. Sci. 28(*3*), 256 (1973).

derivative *I* was successfully terminated and a description of the synthesis and of some unsuccessful attempts is presented in this paper.

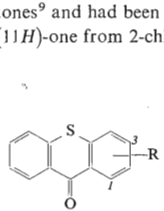
The principal problem of synthesis of *I* was the preparation of 9-chlorodibenzo[*b,f*]-thiepin-10(11*H*)-one (*II*) as the key intermediate. The usual method of preparation of this type of ketones, *i.e.* cyclization of the corresponding chlorinated 2-(phenylthio)-phenylacetic acids with the aid of polyphosphoric acid[1], does not yield the desired product in this particular case. 2-(3-Chlorophenylthio)phenylacetic acid yields a high amount of a single reaction product, *viz.* the corresponding 7-chloroketone[5] *III*. After a number of futile attempts at preparing ketone *II* in various ways to be mentioned later the method of olefin oxidation with thallic nitrate was applied. This occurs under a rearrangement of the skeleton and yields ketones[9] and had been used by us for the preparation of 8-chlorodibenzo[*b,f*]thiepin-10(11*H*)-one from 2-chloro--9-methylenethioxanthene[10]. *



I



II, R = 9-Cl
III, R = 7-Cl
IV, R = 1-Cl
V, R = 3-Cl

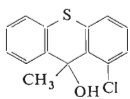


VI, R = 1-Cl
VII, R = 3-Cl

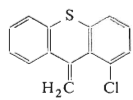
As a starting compound, 1-chlorothioxanthone (*VI*) was required which had been reported as the product of cyclization of 2-(3-chlorophenylthio)benzoic acid with sulfuric acid[11]. Although another reference[12] reports as the sole product of this reaction the isomeric 3-chlorothioxanthone (*VII*), the mentioned paper[11] indicated that in the thioxanthene series the cyclization does not take place as unequivocally as in the dibenzo[*b,f*]thiepin series[5]. Cyclization of 2-(3-chlorophenylthio)benzoic acid[5,11] with sulfuric acid at 50°C yielded a nonhomogeneous neutral product which crystallized from benzene to give approximately 50% of crude 3-chlorothioxanthone[11,12] (*VII*). Treatment of the mother liquor and repeated recrystallization yielded a compound of the same empirical formula but with a lower melting point than reported[11] for 1-chlorothioxanthone (*VI*). The IR spectrum of the present compound displays in the aromatic region heavy bands at 784 and 812 cm^{-1}, corresponding to 3 vicinal aromatic C—H bonds, which are missing in the spectrum of *VII*. On the other hand, bands at 862 (1 C—H), 825 and 836 cm^{-1} (2 C—H) clearly present in the spectrum of the 3-chloroketone *VII*, are represented in the spectrum of our lower-melting substance by some 20% and this lends support to the view that we are dealing here with 1-chlorothioxanthone (*VI*) contaminated with some 20% of the 3-chloro isomer *VII*. Assuming the possibility of removal of the minor contaminant in several further steps we experimented with the compound further.

* See also ref.[44] (added in proof).

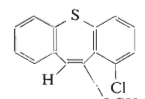
Reaction with methylmagnesium iodide in ether yielded a product which was chromatographed on a column of alumina. Most of the compound was eluted with light petroleum; distillation of the eluate yielded crude olefin *IX* containing the 3-chloro isomer which was used for further work. A more polar compound eluted with chloroform was a crystalline substance characterized by analysis and by IR spectroscopy as carbinol *VIII*. Oxidation of the low-polarity compound with thallic nitrate in methanol and subsequent hydrolysis of the product with 1M-H_2SO_4 at room temperature yielded a mixture of products which was separated by chromatography on alumina. The least polar compound eluted with benzene was $C_{15}H_{11}ClOS$ (in a small amount) which was identified as the enol-ether *X*. Further compounds eluted with chloroform were 3-chlorothioxanthone (*VII*), 3-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one[5](*V*) and 7-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one[5] (*III*). The last three products originate from 3-chlorothioxanthone (*VII*) present as contaminant in the starting material which is evidently not suitable for our purposes.



VIII



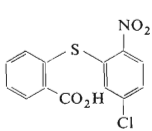
IX



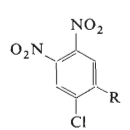
X

Pure ketone *VI* was synthesized from 2-(2-nitro-5-chlorophenylthio)benzoic acid[13] (*XI*) obtained through a modified procedure by the substitution reaction of thiosalicylic acid[14] with 3,4-dinitrochlorobenzene[15] (*XII*) in the presence of potassium carbonate in aqueous ethanol at room temperature. Mangini's procedure[15] for the preparation of *XII* by nitration of 3-chloronitrobenzene was not found to be suitable since a substantial amount of 2,4,5-trinitrochlorobenzene (*XIII*) is formed[16]. The formation of this by-product was suppressed by reducing the excess of the nitration mixture. Acid *XI* was cyclized according to Mayer[13] to 1-chloro-4-nitrothioxanthone (*XIV*) which was further reduced with stannous chloride in boiling hydrochloric acid and acetic acid to 1-chloro-4-aminothioxanthone (*XV*). Diazotization and reduction of the diazonium salt with hypophosphorous acid eliminated the amino group and gave rise to 1-chlorothioxanthone (*VI*) which was shown to be homogeneous by spectral analysis.

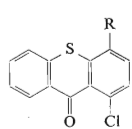
Reaction of ketone *VI* with methylmagnesium iodide in ether and dehydration of the crude product by heating with sulfuric acid in methanol gave rise to almost



XI



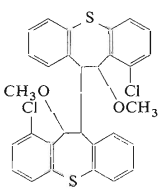
XII, R = H
XIII, R = NO_2



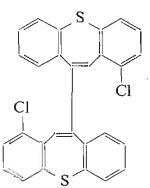
XIV, R = NO_2
XV, R = NH_2

90% 1-chloro-9-methylenethioxanthene (*IX*) (for unsubstituted 9-methylenethioxanthene see ref.[17]). This product was also oxidized by thallic nitrate[9] in methanol at room temperature and the crude product was hydrolyzed with 1M-H_2SO_4 for 5 min. The mixture obtained gave rise to some crystalline enol-ether *X* whereafter the remaining mixture was chromatographed on alumina. The least polar component to be eluted was another portion of the enol-ether *X* (a total of about 30%). Further to be eluted were small amounts of high-melting compounds $C_{28}H_{16}Cl_2S_2$ and $C_{30}H_{24}Cl_2O_2S_2$, approximately 35% of 1-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one[5] (*IV*), a small amount of $C_{15}H_{11}ClO_2S$ and finally a small amount of 9-chlorodibenzo-[*b*,*f*]thiepin-10(11*H*)-one (*II*). It appears that while the sterically hindered enol–ether *X* resisted the relatively gentle hydrolysis, the analogous enol-ether corresponding to ketone *IV* was hydrolyzed. Hydrolysis of the enol–ether *X* with a boiling mixture of dilute hydrochloric acid and acetic acid yielded the 9-chloro-ketone *II*. The empirical composition of the substance $C_{30}H_{24}Cl_2O_2S_2$ was confirmed by its mass spectrum, on the basis of which the structure *XVI* was derived. The compound was readily split thermically and, under formation of two molecules of methanol, it yields a compound with the formula $C_{26}H_{16}Cl_2S_2$ which is ascribed the structure of *XVII* (for the nonchlorinated analogue see ref.[4]). The compound $C_{15}H_{11}ClO_2S$ was identified on the basis of the IR and NMR spectra as the methyl ester of 1-chlorothioxanthene-9-carboxylic acid (*XVIII*).

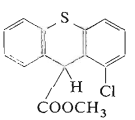
Reduction of ketone *II* with sodium borohydride in aqueous ethanol yielded almost quantitatively the alcohol *XIX* which was transformed by the action of hydrogen chloride in a mixture of benzene and chloroform at room temperature to 9,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XX*). During reaction of this chloride with excess 1-methylpiperazine in boiling chloroform the substitution reaction was accomplished by only 50%, resulting in the desired 9-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*I*) which was characterized by the NMR spectrum in the form of the base and, for pharmacological testing, was converted to the dimethanesulfonate. As a neutral product of the strongly represented elimination reaction two crystalline modifications of 1-chlorodibenzo[*b*,*f*]thiepin (*XXI*) were isolated[5].



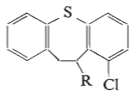
XVI



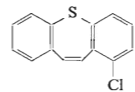
XVII



XVIII



XIX, R = OH
XX, R = Cl



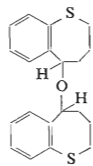
XXI

The synthesis described here was preceded by several experiments which did not lead to the desired product but which were interesting enough to be mentioned here.

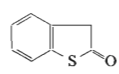
One of these, aimed at the iodo-analogue of alcohol *XIX*, proceeded from the work of Taylor and coworkers[18] who had described a practically quantitative conversion of benzyl alcohol to 2-iodobenzyl alcohol through the action of thallic trifluoroacetate and then potassium iodide. The reaction performed with 5-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin[19] (*XXII*) as substrate, yielded, in addition to a prevalent amount of the starting compound, ether *XXIII* as the single product.

Another experiment proceeded from the reaction of 3,4-dinitrochlorobenzene (*XII*) with the potassium salt of 2-mercaptophenylacetic acid, obtained by alkaline hydrolysis of 2,3-dihydro-1-benzothiophen-2-one[20] (*XXIV*). The resulting product was 2-(2-nitro-5-chlorophenylthio)phenylacetic acid (*XXV*) which could not be cyclized with the aid of polyphosphoric acid at 140° or 170°C, or with polyphosphoric acid in boiling toluene or with hydrofluoric acid. Using the conditions described by Mayer[13] for the cyclization of the lower homologue *XI*, *i.e.* conversion of the acid to the chloride and subsequent treatment with aluminium chloride in benzene, yielded a neutral product of keto character which was identified as substituted deoxybenzoin *XXVI*. Thus, instead of cyclization, a Friedel–Crafts reaction with the benzene present in the mixture took place.

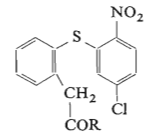
XXII



XXIII



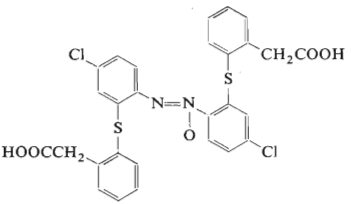
XXIV



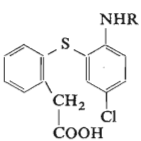
XXV, R = OH
XXVI, R = C_6H_5

In further work, it was attempted to use the corresponding amino acid and its derivatives as intermediates of the synthesis. After the attempt at reduction of the nitro acid *XXV* by hydrogenation on platinum ended with the azoxy compound *XXVII*, the amino acid *XXVIII* was prepared by an independent procedure. According to ref.[21–23] 6-chlorodehydro-1,2,3-benzdithiazolium chloride was hydrolyzed under alkaline conditions[24,25] to 2-amino-5-chlorothiophenol (*XXX*) (its formation is apparently accompanied by the formation of the disulfide *XXXI*), which was condensed, without isolation, with 2-iodophenylacetic acid[26]. The desired amino acid

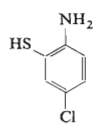
XXVIII can be obtained in this way but the procedure is not suitable for preparative purposes. The amino acid was then prepared by reduction of the nitro acid *XXV* with stannous chloride and, most suitably, by reduction with iron in acetic acid.



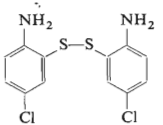
XXVII



XXVIII, R = H
XXIX, R = $COCH_3$



XXX

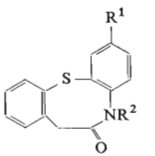


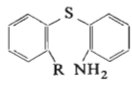
XXXI

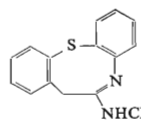
The amino acid *XXVIII* is cyclized by the action of polyphosphoric acid smoothly to the neutral product of expected empirical formula which, however, is not a cyclic ketone but rather a lactam. It was characterized as 2-chlorodibenzo[*b*,*g*]-1,4-thiazocin-6(5*H*,7*H*)-one (*XXXII*). This result aroused the interest in the derivatives of this little-known system, some of which had been recently described[27-30]. Their synthesis was made possible by the Beckmann rearrangement of the oxime of dibenzo[*b*,*f*]thiepin-10(11*H*)-one to dibenzo[*b*,*g*]-1,4-thiazocin-6(5*H*,7*H*)-one (*XXXIII*)[27]. This last compound was now prepared by a novel procedure: condensation of the potassium salt of 2-aminothiophenol with 2-iodophenylacetic acid[26] in an aqueous solution of potassium hydroxide in the presence of copper led to 2-(2-aminophenylthio)-phenylacetic acid (*XXXVI*) which is readily cyclized by the action of polyphosphoric acid to the lactam *XXXIII*. A novel procedure was also used for the preparation of the known 2-(2-aminophenylthio)benzoic acid[31] (*XXXVII*): condensation of the potassium salt of 2-aminothiophenol with 2-iodobenzoic acid[32]. Reaction of lactam *XXXIII* with isobutylamine in the presence of titanium tetrachloride in tetrahydrofuran led to the cyclic amidine *XXXVIII*.

In view of the fact that the amino acid *XXVIII* prefers in the reaction with polyphosphoric acid rather understandably the formation of an eight-membered lactam to that of the sterically hindered seven-membered ketone, we attempted to prepare its

derivatives with a blocked amino group. Heating of the amino acid *XXVIII* with acetic anhydride gives rise to a mixture of two neutral products that were identified as lactam *XXXII* and its N-acetyl derivative *XXXIV*, and the desired acetamido acid *XXIX*. This acetamido acid becomes the main product of the reaction of *XXVIII* with acetic anhydride at room temperature. In the reaction of amino acid *XXVIII* with methanesulfonyl chloride in a solution of sodium carbonate lactam *XXXII* is again the only product identified. In an attempt to prevent the interaction of the carboxyl with the amino group, Kriecheldorf's method was employed[33]; the reaction of amino acid *XXVIII* with trimethylchlorosilane in a mixture of chloroform with acetonitrile gave the trimethylsilyl ester which – after addition of dicyclohexylethylamine[34] was heated with 4-toluenesulfonyl chloride. In spite of the masking of the carboxyl group the only products isolated were lactam *XXXII* and its N-(4-toluenesulfonyl) derivative *XXXV*.







XXXII, $R^1 = Cl$, $R^2 = H$ *XXXVI*, $R = CH_2COOH$

XXXIII, $R^1 = R^2 = H$ *XXXVII*, $R = COOH$

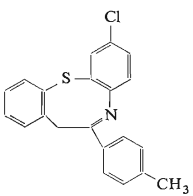
XXXIV, $R^1 = Cl$, $R^2 = COCH_3$

XXXV, $R^1 = Cl$, $R^2 = 4\text{-}SO_2C_6H_4CH_3$

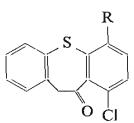
XXXVIII

Since the attempts at cyclization of the acetamido acid *XXIX* with polyphosphoric acid and with hydrogen fluoride at 130°C did not yield any defined products, attempts were made to achieve cyclization with polyphosphoric acid in boiling toluene. In the course of this, a mixture of neutral compounds was obtained from which a small amount of lactam *XXXII* crystallized. The following two compounds were then separated from the residue by chromatography on alumina. The less polar compound of empirical formula $C_{21}H_{16}ClNS$; mass spectrum as well as NMR spectrum indicates the presence of the toluene residue attached to the remaining part of the molecule by the *para*-position toward methyl. The more polar product has the empirical formula $C_{23}H_{18}ClNOS$; the IR spectrum indicates the presence of a keto group conjugated with the ring and further the presence of a C=N bond; the NMR spectrum shows the presence of ten aromatic protons and of two C-methyl groups, one of which belongs to the toluene fragment. The experimental findings are interpreted as indicating the origin of both products in an interaction of the toluene molecule

with the amide group. In the first case the amide group belongs to lactam *XXXII* and the product is formulated as 2-chloro-6-(4-tolyl)-7*H*-dibenzo[*b*,*g*]-1,4-thiazocine (*XXXIX*). In the second case apparently a cyclization to the ketone took place accompanied by an interaction of the toluene molecule with the acetamide group in position 6 of the newly formed skeleton. The product is thus taken to be a Schiff base *XL*. In both cases we were dealing here with an intermolecular analogy of the Bischler-Napieralsky reaction, for which no analogy has been found in the literature. The usual intramolecular form of the reaction is readily feasible with the aid of polyphosphoric acid[35–37]. Attempts at converting the Schiff base *XL* to the desired aminochloroketone were not successful. Heating of *XL* with dilute hydrochloric acid gives rise only to the hydrochloride of the starting compound *XL*. Heating even with concentrated sulfuric acid to 75°C does not result in the desired hydrolysis; after dilution with water and treatment with alkali only the starting compound was recovered. Likewise, an attempt at alkaline hydrolysis was unsuccessful. An attempt to hydrogenate *XL* on palladium resulted in the uptake of one hydrogen molecule whereafter hydrogenation stopped. On the basis of analyses and spectra the dihydro derivative is assumed to have the structure *XLI*.



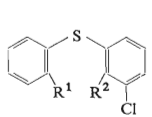
XXXIX



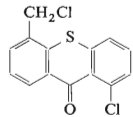
XL, R = —N=C(CH3)—C6H4—CH3

XLI, R = —NHCH(CH3)—C6H4—CH3

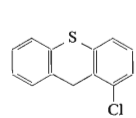
Our last synthetic attempt had the objective of preparing a suitably 2,2′-disubstituted 3-chlorodiphenylsulfide in which the formation of the required CH_2CO bridge (like in *II*) would be accomplished by joining the 2- and 2′-substituents. We proceeded from the reaction of 2-chloro-6-iodobenzoic acid[5] with the potassium salt of thiosalicylalcohol[38,39] which led to the hydroxyacid *XLII*. Reaction with thionyl chloride in boiling benzene in the presence of dimethylformamide led to 2-(2-chloromethylphenylthio)-6-chlorobenzoyl chloride (*XLIII*). In a similar experiment where no dimethylformamide was added, the crude product spontaneously cyclized during



XLII, $R^1 = CH_2OH$, $R^2 = COOH$
XLIII, $R^1 = CH_2Cl$, $R^2 = COCl$
XLIV, $R^1 = CH_2Cl$, $R^2 = COOCH_3$



XLV



XLVI

distillation. The product is probably 1-chloro-5-chloromethylthioxanthone (*XLV*) Reaction of the chlorochloride *XLIII* with methanol at room temperature led to the methyl ester *XLIV*; an attempt at further transformation of the compound by a reaction with potassium cyanide with the objective of obtaining an intermediate suitable for a Dieckmann cyclization, had no effect. In an attempt to form the necessary CH_2CO bridge the chlorochloride *XLIII* was left to react with magnesium in tetrahydrofuran; after hydrolysis of the mixture a product with formula $C_{13}H_9ClS$ was isolated. Although no concept about the mechanism of formation of the compound exists it is considered to be 1-chlorothioxanthene (*XLVI*) which is not at variance with experimental findings (UV and IR spectra).

The dimethanesulfonate (hemihydrate) of 9-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*] thiepin (*I*) was evaluated pharmacologically; the figures shown refer to the base. The acute toxicity for mice on *i.v.* application was $LD_{50} = 46$ mg/kg. In the rotating-rod test in mice the mean effective dose that would bring about disturbance of motor coordination was determined on *i.v.* application; $ED_{50} = 18$ mg/kg. The corresponding value for octoclothepin (*i.e.* the 8-chloro-analogue)[6,7] is 0·06 mg/kg. In the catalepsy test in rats the *i.p.* dose of 10 mg/kg brings about a cataleptic state only in two out of ten animals. For octoclothepin[6,7] the mean effective dose $ED_{50} = 2{\cdot}4$ mg/kg.

Compound *I* can thus be considered as inactive neuroleptically. This result represents a definitive confirmation of the fact that substitution in position 9 of the perathiepin molecule has a pronounced negative effect on neuroleptic activity.

The lactam *XXXII* and the hydrogen maleate of the cyclic amidine *XXXVIII* were subjected to a general pharmacological screening at the affiliated unit of this insttitute at Rosice n/L., under the direction of Dr J. Němec. Compound *XXXII* was applied per os; its LD_{50} is higher than 2·5 g/kg. For *in vivo* tests it was applied in a dose of 300 mg/kg and, with the exception of an insignificant potentiation of thiopental sleep in mice it showed no interesting pharmacodynamic effects. The salt of *XXXVIII* was administered parenterally; its LD_{50} on *i.v.* application to mice is 30 mg/kg; for *in vivo* tests it was then used in a dose of 6 mg/kg *i.v.* It slightly increases the motility of the experimental animals. Furthermore, it has a locally anaesthetic effect, an antiarrhythmic effect (toward aconitine) and a spasmolytic effect (toward barium chloride spasms in the *in vitro* test) approximately at the level of papaverine. It reduces slightly and briefly the blood pressure of rats. At the bacteriological department of this institute (Dr A. Šimek, Dr J. Turinová) the compound was found to possess at concentrations of 25—100 μg/ml a rather broad antimicrobial spectrum. An experiment *in vivo* using mice infected with *Escherichia coli* was completely negative.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at room temperature at 0·5 Torr over P_2O_5. The UV spectra (in methanol unless stated otherwise) were recorded in a Unicam SP 700 spectrophotometer, IR spectra (in Nujol unless stated otherwise) in a Unicam SP 200G or in an Infrascan (Hilger and Watts) spectrophotometer, the NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR 60 (Zeiss, Jena) spectrometer and the mass spectra partly in a MS 902 (AEI) mass spectrometer.

3,4-Dinitrochlorobenzene (*XII*)

A. Nitration of 25·0 g 3-chloronitrobenzene with a mixture of 500 ml H_2SO_4 and 250 g KNO_3 according to ref.[15] gave a mixture containing the desired compound *XII* which remains in the mother liquor on crystallization from a larger amount of ethanol, and a substantial amount of 2,4,5-trinitrochlorobenzene (*XIII*) which can be obtained by repeated crystallization from ethanol in the analytically pure state, m. p. 117—118.5°C. Ref.[16] shows for the compound a m. p. of 116°C.

B. 3-Chloronitrobenzene (100 g) was dissolved in 200 ml concentrated H_2SO_4 and then 100 g KNO_3 was added to the solution under stirring over 30 min. The mixture was heated for 90 min in a 170°C bath and, after partial cooling, poured into 2 kg ice and water. The product precipitated overnight was filtered and recrystallized from ethanol; 100 g (78%), m.p. 36—40°C. Ref.[15] gives a m.p. of 38·8°C.

2-(2-Nitro-5-chlorophenylthio)benzoic Acid (*XI*)

A solution of 76 g thiosalicylic acid[14] and 140 g K_2CO_3 in 400 ml water was added under stirring over a period of 10 min to a solution of 100 g 3,4-dinitrochlorobenzene (*XII*) in 1000 ml ethanol. The mixture was stirred for 4 h, left to stand overnight, alcohol was then evaporated at reduced pressure, the residue was diluted with 500 ml water and, after filtration, it was acidified with hydrochloric acid. The precipitated product was recrystallized from acetic acid; 125·2 g (82%) of a yellow compound melting at 185—192°C. Mayer[13] carried out a similar reaction in boiling benzene in the presence of Na_2CO_3 and Cu and reported a m.p. of 188—189°C.

1-Chloro-4-aminothioxanthone (*XV*)

A mixture of 75·9 g 1-chloro-4-nitrothioxanthone[13] (*XIV*) (m.p. 207—209°C), 235 g $SnCl_2.2\,H_2O$, 300 ml concentrated hydrochloric acid and 800 ml acetic acid was refluxed for 3 h. After cooling, the precipitated compound was filtered, extracted for 1·5 h by stirring with 500 ml 10% NaOH, the suspension was left to stand overnight, the product was filtered again, washed with ethanol and dried; 68·0 g (almost quantitative yield), m.p. 194—196°C. The analytical sample was obtained by recrystallization from ethanol, m.p. 196—198°C. UV spectrum: λ_{max} 210 nm (log ε 4·37), 257 nm (4·57), 326 nm (3·93), 404 nm (3·66). IR spectrum (KBr): 750 and 762 (4 vicinal aromatic C—H), 814 and 824 (2 vicinal aromatic C—H), 1575 and 1595 (Ar), 1625 (thioxanthone CO), 3330 and 3400 cm^{-1} (NH_2). NMR spectrum (CD_3SOCD_3): δ 8·35 (m, 1 H, aromatic proton in position 8), 7·50—7·90 (m, 3 H, aromatic protons in positions 5, 6 and 7), 7·40 (d, J = 9·0 Hz, 1 H, aromatic proton in position 2), 7·10 (d, J = 9·0 Hz, 1 H, aromatic proton in position 3), 4·14 (s, 2 H, NH_2). For $C_{13}H_8ClNOS$ (261·7) calculated: 59·66% C, 3·08% H, 13·55% Cl, 5·35% N 12·25% S; found: 60·08% C, 3·18% H, 13·38% Cl, 5·21% N, 12·21% S.

1-Chlorothioxanthone (*VI*)

A. 2-(3-Chlorophenylthio)benzoic acid[5,11] (70 g) was added at 50°C to 350 ml H_2SO_4, the mixture was stirred at that temperature for 30 min and decomposed by pouring over ice. Filtration yielded 64 g of a crude product melting at 100—140°C, which was recrystallized from benzene. A total of 28·3 g 3-chlorothioxanthone (*VII*) melting at 155—167°C was obtained. After recrystallization from cyclohexane the m.p. was 176·5—177°C. Ref.[12] gives a m.p. of 176—178°C. IR spectrum (KBr): 742 (4 vicinal aromatic C—H), 825 and 837 (2 vicinal aromatic C—H), 862 (isolated aromatic C—H), 1312 (CO), 1438 and 1592 (Ar), 1648 cm^{-1} (thioxanthone CO). Evaporation of the mother liquor yielded 33·7 g compound melting at 105—106°C; after recrystallization from a mixture of methanol and acetic acid the m.p. remains unchanged. According to the IR spectrum (KBr) we are dealing here with 1-chlorothioxanthone (*VI*), contaminated with some 20% of isomer *VII*: 744 (4 vicinal aromatic C—H), 785 and 810 (3 vicinal aromatic C—H), weak bands at 827 and 838 (2 vicinal aromatic C—H), a weak band at 862 (isolated aromatic C—H), 1303 (CO), 1436 and 1585 (Ar), 1648 cm^{-1} (thioxanthone CO). For $C_{13}H_7ClOS$ (246·7) calculated: 63·28% C, 2·86% H, 14·37% Cl, 13·00% S; found: 63·07% C, 2·93% H, 14·60% Cl, 12·98% S.

B. A solution of 0·84 g $NaNO_2$ in 2 ml water was added dropwise at 0°C to a suspension of 2·62 g aminoketone *XV* in 30 ml concentrated hydrochloric acid and 30 ml ethanol. The mixture was stirred for 1 h at the above temperature, then a solution of 5·3 g $NaH_2PO_2.2\,H_2O$ in 20 ml water was then added and the mixture was stirred for 2 h at 0°C. After standing overnight in a refrigerator, the precipitated compound was filtered and extracted with benzene. The benzene solution was evaporated and the residue recrystallized from ethanol (with charcoal added); 1·7 g (68%), m.p. 115—116°C. UV spectrum: λ_{max} 285 nm ($\log \varepsilon$ 4·51), 304 nm (3·61), 380 nm (3·62). IR spectrum (KBr): 742 (4 vicinal aromatic C—H), 783 and 810 (3 vicinal aromatic C—H), 1300 (CO), 1435, 1582 and 1597 (Ar), 1648 cm^{-1} (thioxanthone CO). NMR spectrum: δ 8·43 (m, 1 H, aromatic proton in position 8), *c*. 7·50 (m, 6 H, remaining aromatic protons). For $C_{13}H_7ClOS$ (246·7) calculated: 63·28% C, 2·86% H, 14·37% Cl, 13·00% S; found: 63·48% C, 2·85% H, 14·25% Cl, 13·05% S. During preparation of this manuscript a synthesis of 1-chlorothioxanthone (*VI*) by cyclization of 2-phenylthio-6-chlorobenzoic acid with sulfuric acid has been described[40,41], the melting point reported being 112—114°C (see also[42,43]).

1-Chloro-9-methylthioxanthene-9-ol (*VIII*)

A solution of 12·4 g crude 1-chlorothioxanthone (prepared according to *A*) in 100 ml benzene was added dropwise over a period of 10 min to a solution of methylmagnesium iodide which was prepared by reaction of 4·86 g magnesium and 28·4 g methyl iodide in 150 ml ether. The mixture was refluxed for 9 h, cooled and decomposed with a solution of NH_4Cl; after filtration, the organic phase was separated, dried with $MgSO_4$ and evaporated. The oily residue (11·7 g) was chromatographed on a column of 430 g alumina (activity II). Light petroleum was used to eluate 7·35 g of the least polar components which are distilled at 135—140°C/0·2 Torr. After recrystallization from ethanol, the distillate melts at 78—80°C. Its analysis indicates that we are dealing here with crude 1-chloro-9-methylenethioxanthene (*IX*); this was used in the first oxidation experiment with $Tl(NO_3)_3$ (see below). As the chromatography was continued, benzene eluted a smaller amount of coloured compounds and chloroform then 3·77 g of the polar fractions from which crystallization from cyclohexane yielded pure alcohol *VIII*, m.p. 71—72°C. IR spectrum (film): 760 (4 vicinal aromatic C—H), 779 and 793 (3 vicinal aromatic C—H), 1035 (C—OH), 1560 and 1575 (Ar), 3345 cm^{-1} (OH). For $C_{14}H_{11}ClOS$ (262·8) calculated: 63·99% C, 4·22% H, 13·50% Cl, 12·20% S; found: 64·12% C, 4·26% H, 13·31% Cl, 12·01% S.

1-Chloro-9-methylenethioxanthene (*IX*)

A solution of 16·5 g pure 1-chlorothioxanthone (prepared according to *B*) in 100 ml benzene was added dropwise over a period of 30 min to a solution of methylmagnesium iodide prepared from 19·0 g methyl iodide and 3·2 g Mg in 100 ml ether. After 5 h of refluxing, it was decomposed with 20% NH_4Cl, filtered, the ether layer was dried and evaporated. The residue (19 g) was dissolved in 200 ml methanol, 10 ml H_2SO_4 was added and the mixture was refluxed for 1 h. After cooling, it was diluted with 200 ml water and made slightly alkaline with 15% NaOH, and extracted with benzene. The extract was dried with $MgSO_4$ and evaporated. The residue was chromatographed on a column of 450 g alumina (activity II). Elution with light petroleum yielded 14·2 g (87%) compound *IX*, m.p. 72—73·5° (benzene–light petroleum). UV spectrum (ethanol): λ_{max} 228 nm (log ε 4·35), 269 nm (4·05), 325 nm (3·09). IR spectrum ($CHCl_3$): 918 (C=CH_2), 1550 and 1570 (Ar), 1615 cm^{-1} (C=C). NMR spectrum: δ 6·90—7·75 (m, 7 H, aromatic protons), 5·85 and 5·77 (2s, 2 H, C=CH_2). For $C_{14}H_9ClS$ (244·7) calculated: 68·70% C, 3·71% H, 14·49% Cl, 13·10% S; found: 68·93% C, 3·72% H, 14·55% Cl, 13·23% S.

9-Chloro-10-methoxydibenzo[*b,f*]thiepin (*X*)

A. A solution of 7·25 g $Tl(NO_3)_3.3\ H_2O$ in 50 ml methanol was added to 4·0 g crude olefin *IX* (the least polar product from the preparation of alcohol *VIII*) in 300 ml methanol, the mixture was left for 1 h at room temperature, the inorganic fractions were filtered, the filtrate was shaken for 5 min with 200 ml 1M-H_2SO_4 and the mixture was extracted with benzene. The extract was dried with $MgSO_4$ and evaporated. A total of 3·9 g oil was obtained and this was chromatographed on a column of 300 g alumina (activity II). Benzene eluted 0·91 g of a substance which, after recrystallization from cyclohexane melts at 149—150°C and was identified as the enol-ether *X*. The UV spectrum (ethanol): λ_{max} 263 nm (log ε 4·21), infl. 292 nm (3·78). IR spectrum ($CHCl_3$): 1200, 1240 and 1268 (C=C—OCH_3), 1553 and 1570 (Ar), 1630 cm^{-1} (C=C). NMR spectrum: δ 7·00—7·70 (m, 7 H, aromatic protons), 6·47 (s, 1 H, Ar—CH=C), 3·86 (s, 3 H, OCH_3). For $C_{15}H_{11}ClOS$ (274·8) calculated: 65·57% C, 4·04% H, 12·90% Cl, 11·67% S; found: 65·57% C, 4·05% H, 12·79% Cl, 11·87% S.

On continuing the chromatography, chloroform eluted 0·30 g 3-chlorothioxanthone (*VII*), m.p. 176·5—177°C (cyclohexane). UV spectrum: λ_{max} infl. 218·5 nm (log ε 4·15), 223 nm (4·23), 261·5 nm (4·69), 377 nm (3·78). The IR spectrum is identical with the spectrum of the substance reported under (*A*) in the preparation of 1-chlorothioxanthone (*VI*). For $C_{13}H_7ClOS$ (246·7) calculated: 63·28% C, 2·86% H, 14·37% Cl, 13·00% S; found: 63·70% C, 2·94% H, 14·19% Cl, 12·86% S.

Chloroform eluted further 0·64 g substance which crystallized from ethanol to yield 65 mg 3-chlorodibenzo[*b,f*] thiepin-10(11*H*)-one (*V*) ,m.p. 145—146°C. Ref.[5] reports a m.p. of 143—145°C. UV spectrum: λ_{max} 230 nm (log ε 4·32), infl. 255 nm (4·07), 328 nm (3·56). IR spectrum (KBr): 751 (4 vicinal aromatic C—H, 822 (2 vicinal aromatic C—H), 863 and 880 (isolated aromatic C—H), 1585 (Ar), 1679 cm^{-1} (ArCO). For $C_{14}H_9ClOS$ (260·7) calculated: 64·49% C, 3·48% H, 13·60% Cl, 12·30% S; found: 64·33% C, 3·49% H, 13·68% Cl, 12·41% S.

From the mother liquor after the preceding compound, evaporation and recrystallization from cyclohexane yielded 110 mg 7-chlorodibenzo[*b,f*]thiepin-10(11*H*)-one (*III*), m.p. 132—134°C. Ref.[5] reports a m.p. of 132—133·5°C. UV spectrum: λ_{max} 252·5 nm (log ε 4·37), 329 nm (3·63). IR spectrum (KBr): 749 and 766 (4 vicinal aromatic C—H), 811 and 826 (2 vicinal aromatic C—H), 869 (isolated aromatic C—H), 1579 (Ar), 1680 cm^{-1} (ArCO). For $C_{14}H_9ClOS$ (260·7) calculated: 64·49% C, 3·48% H, 13·60% Cl, 12·30% S; found: 64·44% C, 3·54% H, 13·42% Cl, 12·50% S.

B. A solution of 12·45 g pure olefin *IX* in 800 ml methanol was oxidized similarly to the preceding case with the aid of a solution of 22·6 g $Tl(NO_3)_3.3\ H_2O$ in 150 ml methanol. The mixture was left to stand for 3·5 h at room temperature and then processed analogously to the preceding case (hydrolysis by shaking with 500 ml 1M-H_2SO_4 for 5 min). The oily product was mixed with cyclohexane to yield directly 2·6 g enol-ether *X*, m.p. 149–150°C, which was identical with the product prepared under *A*. Evaporation of the mother liquor yielded 11·3 g oil which was chromatographed on a column of 450 g alumina (activity II). Mixture of benzene and light petroleum eluted further 2·04 g enol-ether *X*, the total yield thus amounting to 4·64 g.

A further benzene–light petroleum fraction was crystallized from ethanol to obtain 0·11 g substance melting at 264–266°C which appears to have the structure of bi(1-chlorodibenzo[*b,f*] thiepin-10-yl) (*XVII*). UV spectrum: λ_{max} 248, 316 and 376 nm. IR spectrum (KBr): 738 and 753 (4 vicinal aromatic C—H), 765 (3 vicinal aromatic C—H), 900, 1425 and 3020 cm^{-1} (C=C—H). For $C_{28}H_{16}Cl_2S_2$ (487·4) calculated: 68·99% C, 3·31% H, 14·55% Cl, 13·16% S; found: 67·95% C, 3·48% H, 14·35% Cl, 13·19% S.

Benzene and chloroform eluted 4·94 g of a practically homogeneous more polar substance. After addition of ethanol a fraction remained undissolved (50 mg) which, after crystallization from a mixture of benzene and ethanol shows a m.p. 231–234°C and which has apparently the structure of bi(1-chloro-11-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl) (*XVI*). The mass spectrum shows a molecular ion of *m/e* 550, indicating the composition $C_{30}H_{24}Cl_2O_2S_2$. The spectrum further indicates a thermal splitting to $C_{28}H_{16}Cl_2S_2$ (*m/e* 486) and methanol. It is assumed that the fragment is identical with *XVII*. Thermal degradation takes place already at 140°C. For $C_{30}H_{24}Cl_2O_2S_2$ (551·6) calculated: 65·33% C, 4·39% H 12·85% Cl, 11·62% S; found: 65·30% C, 4·45% H, 12·90% Cl, 11·40% S. On cooling the above ethanolic solution a product precipitates which melts at 128–130°C and which was identified as 1-chlorodibenzo[*b,f*] thiepin-10(11*H*)-one (*IV*). The compound represents a greater part of the above polar fraction. In mixture with an authentic ketone[5] *IV* it shows no m.p. depression. UV spectrum (ethanol): λ_{max} 240 nm (log ε 4·28), 288 nm (3·47), 330 nm (3·49). IR spectrum ($CHCl_3$): 1560 and 1588 (Ar), 1675 cm^{-1} (Ar—CO). NMR spectrum: δ 8·32 (m, 1 H, aromatic proton in position 9), 6·90–7·80 (m, 6 H, remaining aromatic protons), 4·56 (s, 2 H, $ArCH_2CO$). For $C_{14}H_9ClOS$ (260·7) calculated: 64·49% C, 3·48% H, 13·60% Cl, 12·30% S; found: 64·20% C, 3·43% H, 13·64% Cl, 12·39% S. The mother liquor after the preceding compound yielded 0·45 g of a substance which, after recrystallization from ethanol, melts at 116–117·5°C, apparently methyl 1-chlorothioxanthene-9-carboxylate (*XVIII*). IR spectrum: 1565 and 1585 (Ar), 1740 cm^{-1} (R—COOR). NMR spectrum: δ 7·00–7·60 (m, 7 H, aromatic protons), 5·66 (s, 1 H, Ar_2CH), 3·50 (s, 3 H, OCH_3). For $C_{15}H_{11}ClO_2S$ (290·8) calculated: 61·96% C, 3·81% H, 12·19% Cl, 11·03% S; found: 62·08% C, 3·88 H, 12·20% Cl, 11·02% S.

Elution with a mixture of chloroform and ether yielded 0·7 g of the most polar fractions which crystallized from ethanol to yield a substance melting at 120–123°C, identified as 9-chlorodibenzo[*b,f*]thiepin-10(11*H*)-one (*II*). It is identical with the product of hydrolysis of enol-ether *X* (see below).

9-Chlorodibenzo[*b,f*]thiepin-10(11*H*)-one (*II*)

A mixture of 7·8 g enol-ether *X*, 100 ml acetic acid, 1 ml concentrated hydrochloric acid and 15 ml water was refluxed for 4·5 h, filtered while hot and the filtrate was left to crystallize. A total of 6·5 g (88%) of the desired ketone melting at 120–122°C precipitated. The sample for analysis was recrystallized from cyclohexane, m.p. 121–123°C. UV spectrum (ethanol): λ_{max} 246 nm (log ε 4·10), 332 nm (3·42). IR spectrum ($CHCl_3$): 1692 cm^{-1} (ArCO). NMR spectrum: δ 7·00–7·70 (m, 7 H, aromatic protons), 4·20 (s, 2 H, $ArCH_2CO$). For $C_{14}H_9ClOS$ (260·7) cal-

culated: 64·49% C, 3·48% H, 13·60% Cl, 12·30% S; found: 64·10% C, 3·55% H, 13·71% Cl, 12·15% S.

9-Chloro-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XIX*)

A solution of 0·90 g $NaBH_4$ in 2 ml water with a drop of 20% NaOH was slowly added to a solution of 5·73 g ketone *II* in 150 ml ethanol. The mixture was refluxed for 4·5 h, ethanol was evaporated, the residue was diluted with water and extracted with benzene. The extract was washed with dilute hydrochloric acid, dried with $MgSO_4$ and evaporated. Crystallization of the residue from a mixture of benzene and cyclohexane yielded 5·64 g (98%) of a compound melting at 115—116°C. IR spectrum (KBr): 750—762 (4 vicinal aromatic C—H), 773 (3 vicinal aromatic C—H), 1050 (CHOH), 1556 and 1576 (Ar), 3340 cm^{-1} (OH). NMR spectrum: δ 6·90—7·70 (m, 7 H, aromatic protons), 5·45 (m, after deuterization dd, J = 4·0; 6·0 Hz, 1 H, CH—O), 3·70 and 3·45 (2dd, J = 4·0; 14·0 and 6·0; 14·0 Hz, 2 H, $ArCH_2$), 2·65 (d, J = 8·0 Hz, disappears on deuterization, 1 H, OH). For $C_{14}H_{11}ClOS$ (262·8) calculated: 63·99% C, 4·22% H, 13·50% Cl, 12·20% S; found: 64·24% C, 4·46% H, 13·37% Cl, 12·30% S.

9,10-Dichloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XX*)

Anhydrous powdery $CaCl_2$ (2·0 g) was added to a solution of 5·5 g alcohol *XIX* in 100 ml benzene and 20 ml chloroform and the suspension was saturated under stirring for 1 h with anhydrous HCl. After standing overnight, the mixture was filtered and the filtrate evaporated. The residue (5·83 g, 99%) was purified by recrystallization from cyclohexane, m.p. 129—131°C. NMR spectrum: δ 7·00—7·80 (m, 7 H, aromatic protons), 5·90 (dd, J = 7·0; 5·5 Hz, 1 H, CH—Cl), 4·08 and 3·30 (2 dd, J = 14·0; 5·5 and 14·0; 7·0 Hz, 2 H, $ArCH_2$). For $C_{14}H_{10}Cl_2S$ (281·2) calculated: 59·79% C, 3·58% H, 25·22% Cl; found: 59·64% C, 3·64% H, 24·83% Cl.

9-Chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[b,*f*]thiepin (*I*)

A mixture of 5·6 g chloride *XX*, 20 ml 1-methylpiperazine and 20 ml chloroform was refluxed for 8 h. After cooling, it was diluted with 100 ml water and extracted with benzene. The extract was washed with water and then shaken with 100 ml dilute hydrochloric acid (1 : 3). Evaporation of the benzene layer yielded 2·43 g crude elimination product which crystallized from ethanol to 1·55 g 1-chlorodibenzo[*b,f*]thiepin (*XXI*), m.p. 90—91°C. From cyclohexane a prismatic modification crystallizes, melting at 99°C. Previously[5], the m.p. reported for this compound was 95—96°C. The two modifications were compared with the aid of their IR spectra and found to be identical. IR spectrum (KBr): 738 (4 vicinal aromatic C—H), 780 (3 vicinal aromatic C—H), 1417 (*cis*-CH=CH), 1543 and 1568 cm^{-1} (Ar). NMR spectrum: δ 7·00—7·70 (m, 9 H, aromatic and olefinic protons). For $C_{14}H_9ClS$ (244·7) calculated: 68·70% C, 3·71% H, 14·49% Cl, 13·10% S; found: 68·78% C, 3·87% H, 14·69% Cl, 13·08% S.

The acid aqueous layer after separation of the benzene phase was made alkaline with a 20% solution of NaOH and base *I* was isolated by extraction with benzene; 3·43 g (50%), m.p. 155 to 156°C (ethanol). NMR spectrum: δ 6·80—7·70 (m, 7 H, aromatic protons), 4·40 and 4·09 (2 dd, J = 12·0; 4·0 and 12·0; 12·0 Hz, 2 H, $ArCH_2$), 3·06 (dd, 1 H, J = 12·0; 4·0 Hz, Ar—CH—N), 2·73 (t, J = 4·0 Hz, 4 H, $CH_2N^1CH_2$), 2·33 (t, J = 4·0 Hz, 4 H, $CH_2N^4CH_2$), 2·22 (s, 3 H, NCH_3). For $C_{19}H_{21}ClN_2S$ (344·9) calculated: 66·16% C, 6·14% H, 10·28% Cl, 8·12% N, 9·30% S; found: 66·32% C, 6·51% H, 10·32% Cl, 7·91% N, 9·39% S.

Dimethanesulfonate (hemihydrate), m.p. 120—125°C (ethanol–ether). For $C_{21}H_{30}ClN_2O_{6\cdot5}S_3$ (546·1) calculated: 46·19% C, 5·54% H, 6·49% Cl, 5·13% N; found: 46·21% C, 5·78% H, 6·20% Cl, 5·20% N.

Di(2,3,4,5-tetrahydro-1-benzothiepin-5-yl) Ether (*XXIII*)

5-Hydroxy-2,3,4,5-tetrahydro-1-benzothiepin[19] (*XXII*) (4·0 g, 22·2 mmol) was added to 15·6 ml solution of thallic trifluoroacetate[18] (20 mmol) in trifluoroacetic acid. The mixture was stirred for 4 h at 20°C, heated briefly in a 90°C bath and the trifluoroacetic acid was evaporated. The residue was combined with 8·3 g KI in 50 ml water, the mixture was stirred for 30 min, made alkaline with 15% NaOH and an aqueous solution of 1·0 g $Na_2S_2O_3$ was added. After another 30 min of stirring, 100 ml benzene were added and the mixture stirred for further 30 min. It was then filtered, the benzene layer separated from the filtrate, washed with a solution of $Na_2S_2O_3$ and evaporated. A total of 2·9 g oily mixture was obtained which, according to thin-layer chromatography on silica gel, consists of the starting compound *XXII* and a less polar compound. After dissolving in a small volume of methanol this less polar component crystallized; 0·32 g, m.p. 158–159°C (ethanol). According to analysis and spectra, we are dealing here with ether *XXIII*. IR spectrum (KBr): 750 and 760 (4 vicinal aromatic C—H), 1082 and 1208 (C—O—C) 1570 cm^{-1} (Ar). NMR spectrum: δ 7·05–7·90 (m, 8 H, aromatic protons), 4·92 (m, 2 H, 2 CH—O), c. 2·65 (m, 4 H, 2 SCH_2), c. 2·00 (m, 8 H, 2C—CH_2CH_2C). For $C_{20}H_{22}OS_2$ (342·5) calculated: 70·13% C, 6·47% H, 18 72% S; found: 70·32% C, 6·38% H, 18·48% S.

2-(2-Nitro-5-chlorophenylthio)phenylacetic Acid (*XXV*)

2,3-Dihydro-1-benzothiophen-2-one[20] (*XXIV*) (30 g) was boiled for 30 min with a solution of 55·2 g K_2CO_3 in 200 ml water, the potassium salt solution was cooled and, at 20°C, a solution of 40·1 g 3,4-dinitrochlorobenzene (*XII*) in 800 ml ethanol was added to it dropwise under stirring. The mixture was stirred for 2 h, left to stand overnight, ethanol was then evaporated at reduced pressure, the residue was diluted with water and the solution was acidified with hydrochloric acid. The yellow precipitate formed was filtered, washed with water, dried and recrystallized from a mixture of benzene and light petroleum; 57·8 g (89%), m.p. unsharp to 148°C. After recrystallization from a mixture of benzene and cyclohexane the m.p. is 152–155°C (it softens from 138°C). IR spectrum (KBr): 760 and 772 (4 vicinal aromatic C—H), 798 (2 vicinal aromatic C—H), 872 (isolated aromatic C—H), 1248, 1300, 1705, 3080 and 3120 (COOH), 1340 and 1562 (NO_2), 1518 and 1595 cm^{-1} (Ar). NMR spectrum: δ 8·55 (s, 1 H, COOH), 8·24 (d, 1 H, aromatic proton in *o*-position toward NO_2), 7·35–7·80 (m, 4 H, aromatic protons of the phenylacetic residue), 7·18 (d, 1 H, aromatic proton in position 4 of the phenylthio group), 6·64 (s 1 H, aromatic proton in position 6 of the phenylthio group), 3·83 (s, 2 H, $ArCH_2COO$). For $C_{14}H_{10}ClNO_4S$ (323·8) calculated: 51·94% C, 3·11% H, 10·95% Cl, 4·33% N, 9·99% S; found: 52·58% C, 3·24% H, 10·88% Cl, 4·19% N, 10·04% S.

2′-(2-Nitro-5-chlorophenylthio)deoxybenzoin (*XXVI*)

Phosphorus pentachloride (3·4 g) was added to a solution of 5·0 g acid *XXV* in 50 ml benzene. The mixture was refluxed for 1 h, 2·6 g $AlCl_3$ were added and refluxing continued for 4 h. After cooling, it was decomposed with water, filtered, the benzene layer of the filtrate was washed with a 5% solution of NaOH and water, dried and evaporated. The oily residue crystallized after mixing with benzene and light petroleum: 1·7 g, m.p. 133·5–134·5°C (benzene–light petroleum). UV spectrum: λ_{max} 246 nm (log ε 4·44), infl. 276 nm (4·05), 362 nm (3·67). IR spectrum (KBr): 745, 752, and 760 (4 and 5 vicinal aromatic C—H), 823 (2 vicinal aromatic C—H), 865 (isolated aromatic C—H), 1330 and 1497 (NO_2), 1580 (Ar), 1680 cm^{-1} (ArCO). NMR spectrum: δ 8·15 (d, J = 9·0 Hz, 1 H, aromatic proton in position 3 of the phenylthio group), 7·98 (m, 2 H, aromatic protons in *o*-positions toward the keto group), 7·25–7·80 (m, 7 H, remaining aromatic protons of deoxybenzoin), 7·14 (dd, J = 9·0; 2·5 Hz, 1 H, aromatic proton in position 4 of the

phenylthio group), 6·72 (d, $J = 2·5$ Hz, 1 H, aromatic proton in position 6 of the phenylthio group), 4·50 (s, 2 H, $ArCH_2CO$). For $C_{20}H_{14}ClNO_3S$ (383·9) calculated: 62·58% C, 3·68% H, 9·24% Cl, 3·65% N, 8·35% S; found: 62·68% C, 3·80% H, 9·17% Cl, 3·76% N, 8·46% S.

2,2'-Bis(2-carboxymethylphenylthio)-4,4'-dichlorazoxybenzene (*XXVII*)

A solution of 6·5 g acid *XXV* in 50 ml ethyl acetate and 40 ml ethanol was hydrogenated under normal conditions on a platinum catalyst, obtained by reduction of 0·1 g PtO_2, until cessation of hydrogen absorption. It was then filtered and the filtrate evaporated. The dark oily residue was dissolved in ethanol and crystalized to 0·48 g red product, m.p. unsharp at 241—254°C, in a capillary at 238—243°C (ethanol). IR spectrum: 765 (4 vicinal aromatic C—H), 815 and 850 (2 vicinal aromatic C—H), 870 (isolated aromatic C—H), 939 and 1241 (COOH + N=N—O), 1560 and 1580 (Ar), 1640 (N=N), 1700, 2650, 2730 and 3200 cm^{-1} (COOH). For $C_{28}H_{20}Cl_2N_2O_5S_2$ (599·5) calculated: 56·10%C, 3·36% H, 11·83% Cl, 4·67% N, 10·70% S; found: 56·38% C, 3·33% H, 12·00% Cl, 4·34% N, 10·70% S.

2-Amino-5-chlorothiophenol (*XXX*)

A mixture of 13·0 g 6-chlorodehydro-1,2,3-benzdithiazolium chloride[24,25] and 70 ml ethanol was stirred for 30 min, then a solution of 10 g NaOH and 3·0 g $Na_2S_2O_5$ in 40 ml water was added, the mixture was stirred for 1 h and left to stand for 2 days. After evaporation of ethanol the residue was filtered, acidified with acetic acid and extracted with ether. Evaporation of the extract yielded 8·1 g oil which passed only partly to an aqueous solution of NaOH. Acidification of the alkaline solution and extraction with ether led to the acidic product. Its distillation proceeds with signs of decomposition; only 1·0 g crude product was obtained which was purified by crystallization from cyclohexane; m.p. 75—77°C. The analysis indicates that we are dealing here with an incompletely pure thiol *XXX*. For C_6H_6ClNS (159·6) calculated: 45·14% C, 3·79% H, 8·77% N, 20·09% S; found: 46·15% C, 3·97% H, 8·89% N, 20·34% S.

The NaOH-insoluble fraction was isolated by extraction with ether and, after evaporation of the solvent, purified by crystallization from a mixture of benzene and cyclohexane; m.p. 108—111°C. Anylysis and NMR spectrum indicate it to be di(2-amino-5-chlorophenyl)disulfide (*XXXI*). NMR spectrum: δ 6·95—7·25 (m, 2 H, aromatic protons in positions 6 and 6'), 6·60 and 7·15 (d, $J = 9·5$ Hz, 4 H, aromatic protons in positions 3,4,3' and 4'), 4·21 (s, 4 H, 2 NH_2). For $C_{12}H_{10}Cl_2N_2S_2$ (317·3) calculated. 45·43% C, 3·18% H, 22·35% Cl, 8·83% N, 20·21% S; found: 45·72% C, 3·33% H, 22·10% Cl, 8·59% N, 20·55% S.

2-(2-Amino-5-chlorophenylthio)phenylacetic Acid (*XXVIII*)

A. A solution of 75 g KOH in 250 ml water was added slowly to a solution of 70 g 6-chlorodehydro-1,2,3-benzdithiazolium chloride[24,25] in 250 ml ethanol, the mixture was stirred for 1 h, filtered and the filtrate combined with 24·5 g 2-iodophenylacetic acid[26] in a solution of 10 g KOH in 100 ml water and 2 g "molecular" copper were added. The mixture was refluxed under stirring for 8 h, cooled, filtered, and the filtrate was acidified with acetic acid. The precipitated product was filtered and recrystallized from aqueous ethanol; 19·5 g (71%), m.p. 150—165°C. The compound was dissolved in benzene, the solution was decolorized with silica gel and $CaSO_4$ and the residue after evaporation crystallized from aqueous ethanol; m.p. 174—176·5°C. IR spectrum: 735 and 752 (4 vicinal aromatic C—H), 830 (2 vicinal aromatic C—H), 890 (isolated aromatic C—H), 925, 1222, 1694, 1699 and 3080 (COOH), 1620, 3375 and 3485 cm^{-1} (NH_2).

For $C_{14}H_{12}ClNO_2S$ (293·8) calculated: 57·24% C, 4·12% H, 12·07% Cl, 4·77% N, 10·91% S; found: 57·64% C, 4·07% H, 12·03% Cl, 4·79% N, 10·95% S.

B. A solution of 10·0 g acid *XXV* in 300 ml ether was combined with 30 g $SnCl_2.2\,H_2O$ and 10 ml concentrated hydrochloric acid were added dropwise under refluxing and the mixture was further refluxed for 5 h. After cooling, concentrated hydrochloric acid was added, the ether layer was separated and the aqueous phase was treated with a conc. aqueous solution of Na_2S until formation of precipitate ceased. After filtration of the precipitate, the filtrate was made strongly alkaline with a solution of NaOH, filtered again and the alkaline filtrate was acidified with acetic acid. The required compound was obtained in a yield of 2·2 g, m.p. 168—175°C.

C. Acid *XXV* (57·8 g) was added under stirring over a period of 15 min to a mixture of 360 ml water, 62·5 g powdered iron and 45 ml acetic acid at 100°C. The mixture was refluxed for 6 h, left to stand overnight, and then 650 ml 10% Na_2CO_3 was added and the mixture refluxed for 1 h until the solid dissolved. After filtration, the filtrate was acidified with acetic acid and the precipitated product recrystallized from ethanol with an addition of charcoal; 48·8 g (92%), m.p. 157—176°C. Recrystallization from aqueous ethanol yielded a solid melting at 173—176°C, identical with the product prepared under A. For $C_{14}H_{12}ClNO_2S$ (293·8) calculated: 57·24% C, 4·12% H, 12·07% Cl, 4·77% N, 10·91% S; found: 57·07% C, 4·12% H, 11·82% Cl, 4·85% N, 11·17% S.

2-Chlorodibenzo[*b,g*]-1,4-thiazocin-6(5*H*,7*H*)-one (*XXXII*)

A. Polyphosphoric acid was prepared by reaction of 50 g P_2O_5 and 30 ml 85% H_3PO_4 (4 h, 130°C). During 20 min of stirring at 130°C, 4·0 g acid *XXVIII* was added, the mixture was stirred for 75 min at 130°C and then poured into 300 ml water with ice. On the following day, the solid was filtered, suspended in 5% Na_2CO_3, filtered, washed with water, dried and recrystallized from a mixture of chloroform and ethanol; 2·85 g (76%), m.p. 277—279°C. IR spectrum (KBr): 764 (4 vicinal aromatic C—H), 831 (2 vicinal aromatic C—H), 893 (isolated aromatic C—H), 1112 and 1187 (NH), 1271, 1673, 1680, 2925, 3100 and 3200 cm^{-1} (—CONH—). For $C_{14}H_{10}ClNOS$ (275·8) calculated: 60·98% C, 3·65% H, 12·86% Cl, 5·08% N, 11·63% S; found: 61·25% C, 3·55% H, 13·15% Cl, 5·10% N, 11·80% S.

B. A solution of 0·24 g methanesulfonyl chloride in 5 ml acetone was added dropwise over 5 min to a solution of 0·62 g acid *XXVIII* in 10 ml 5% Na_2CO_3. The mixture was stirred for 2·5 h at room temperature, diluted with 15 ml water and acidified with 2 ml concentrated hydrochloric acid. Filtration yielded 0·40 g crude lactam *XXXII* which was purified by crystallization from ethanol; m.p. 275—277°C. For $C_{14}H_{10}ClNOS$ (275·8) calculated: 60·98% C, 3·65% H, 12·86% Cl, 5·08% N, 11·63% S; found: 61·19% C, 3·80% H, 12·96% Cl, 5·16% N, 11·94% S.

2-(2-Aminophenylthio)phenylacetic Acid (*XXXVI*)

A mixture of 26·2 g 2-iodophenylacetic acid[26], 13·8 g 2-aminothiophenol, 17 g KOH, 170 ml water and 1 g "molecular" copper was refluxed for 10 h. It was filtered while hot and the filtrate was acidified with acetic acid. After cooling, the precipitate was filtered and recrystallized from aqueous ethanol with an addition of charcoal; 14·5 g (56%), m.p. 110—115°C. An analytical sample was obtained by recrystallization from benzene; according to analysis it was a solvate with $^1/_3$ of a benzene molecule. NMR spectrum: δ 6·50—7·50 (m, 8 H, aromatic protons), *c.* 6·75 (s, 1 H, COOH), 6·60 (s, 2 H, NH_2), 3·79 (s, 2 H, $ArCH_2COO$). For $C_{16}H_{15}NO_2S$ (285·3) calculated: 67·36% C, 5·30% H, 4·91% N, 11·22% S; found: 67·59% C, 5·39% H, 4·77% N, 11·39% S.

2-(2-Aminophenylthio)benzoic Acid (*XXXVII*)

A mixture of 24·8 g 2-iodobenzoic acid[32], 13·4 g 2-aminothiophenol, 21 g KOH, 210 ml water and 1·5 g "molecular" copper was refluxed for 6·5 h, and processed similarly to the preceding case. A total of 17·9 g (73%) product melting at 157–158°C (acetic acid) was obtained. Ref.[31] reports a m.p. of 157·5°C for a compound obtained by reduction of the corresponding nitro acid. For $C_{13}H_{11}NO_2S$ (245·2) calculated: 63·67% C, 4·52% H, 5·71% N, 13·05% S; found: 63·78% C, 4·58% H, 5·72% N, 12·91% S.

Dibenzo[*b,g*]-1,4-thiazocin-6(5*H*,7*H*)-one (*XXXIII*)

A mixture of 225 g polyphosphoric acid and 14·9 g acid *XXXVI* was heated for 1·5 h under stirring to 130–140°C. After pouring the mixture into 1 000 ml water the precipitate was filtered, dissolved in chloroform, the solution was washed with Na_2CO_3 and evaporated. A total of 11·0 g (79%) crude product melting at 248–253°C was obtained which, after recrystallization from dioxane, melts at 253–255°C. For the product of a Beckmann rearrangement of the corresponding oxime ref.[27] reports a m.p. of 253–256°C. IR spectrum: 758 (4 vicinal aromatic C—H), 1585 (Ar), 1670 (CONH in a ring), 3270 cm^{-1} (NH). For $C_{14}H_{11}NOS$ (241·2) calculated: 69·70% C, 4·59% H, 5·80% N, 13·27% S; found: 69·11% C, 4·74% H, 5·58% N, 12·90% S.

6-Isobutylamino-7*H*-dibenzo[*b,g*]-1,4-thiazocine (*XXXVIII*)

A solution of 4·3 g $TiCl_4$ in 30 ml benzene was added dropwise to a mixture of 5·6 g lactam *XXXIII* and 20 g isobutylamine in 100 ml tetrahydrofuran. The mixture was left to stand for 2 days and then refluxed under stirring for 16 h. After cooling, it was decomposed with 10 ml water, the solid was filtered, washed with benzene and dioxane and the filtrate was evaporated. The residue was dissolved in benzene, the solution was washed with aqueous ammonia and evaporated again. The residue was dissolved in a small amount of ethanol, a solution of 2·6 g maleic acid in ethanol was added and crystallization was initiated by an addition of ether. A yield of 3·9 g (41%) of hydrogen maleate was obtained; m.p. 153–154·5°C (ethanol–ether). NMR spectrum: δ 7·00–7·90 (m, 8 H, aromatic protons), 6·20 (s, 2 H, CH=CH of maleic acid), 3·62 and 3·75 (2 s, 2 H, $ArCH_2$), 2·90–3·50 (m, 2 H, CH_2 of isobutyl), c. 1·65 (m, 1 H, CH of isobutyl), 0·85 and 0·72 (2 d, 6 H, 2 CH_3 of isobutyl). For $C_{22}H_{24}N_2O_4S$ (412·4) calculated: 64·06% C, 5·87% H, 6·79% N, 7·76% S; found: 63·88% C, 5·97% H, 6·57% N, 7·73% S.

2-Chloro-5-acetyldibenzo[*b,g*]-1,4-thiazocin-6(5*H*,7*H*)-one (*XXXIV*)

A mixture of 5·0 g acid *XXVIII* and 40 ml acetic anhydride was refluxed for 1 h and poured into 500 ml water. After 2 days of standing the precipitate was filtered, dissolved in chloroform and the solution was washed with a solution of Na_2CO_3. Acidification of the alkaline solution and recrystallization of the product from a mixture of benzene and light petroleum yielded 1·33 g acid *XXIX*, m.p. 165–169°C, a more suitable preparation of which is described later. The chloroform solution was evaporated and the residue (1·45 g) was separated by fractional crystallization into a small amount of lactam *XXXII*, m.p. 278–281°C (ethanol) and a major part of acetylated lactam *XXXIV*; prisms melting at 183–186°C (ethanol–chloroform). NMR spectrum: δ 7·74 (s, 1 H, aromatic proton in position 1), 7·00–7·70 (m, 6 H, remaining aromatic protons), 3·55 (s, 2 H, $ArCH_2CO$), 2·68 (s, 3 H, $COCH_3$). For $C_{16}H_{12}ClNO_2S$ (317·8) calculated: 60·47% C, 3·80% H, 11·16% Cl, 4·41% N, 10·09% S; found: 60·37% C, 3·84% H, 11·51% Cl, 4·39% N, 10·19% S.

2-(2-Acetamido-5-chlorophenylthio)phenylacetic Acid (*XXIX*)

Acid *XXVIII* (5·0 g) was dissolved in warm 30 ml acetic anhydride and the solution was left to stand for 12 h at room temperature. Then it was decomposed by pouring into excess warm water, left to stand for 12 h and the precipitate was filtered. It was purified by dissolving in a dilute solution of NaOH, precipitation by acidification with dilute hydrochloric acid and finally by recrystallization from aqueous ethanol; 4·05 g (71%), m.p. 169–170·5°C. IR spectrum (KBr): 740 and 760 (4 vicinal aromatic C—H), 832 (2 vicinal aromatic C—H), 1193 (COOH), 1300 (CONH), 1512 and 1574 (Ar), 1647 (CONH), 1718 and 2910 (COOH), 3310 cm^{-1} (CONH). NMR spectrum (CD_3SOCD_3): δ 9·55 (s, 1 H, COOH), 6·90–7·70 (m, 7 H, aromatic protons), 3·80 (s, 2 H, $ArCH_2COO$), 2·00 (s, 3 H, $COCH_3$). For $C_{16}H_{14}ClNO_3S$ (335·8) calculated: 57·23% C, 4·20% H, 4·17% N, 9·55% S; found: 57·55% C, 4·20% H, 4·01% N, 9·74% S.

2-Chloro-5-(4-toluenesulfonyl)dibenzo[*b,g*]-1,4-thiazocin-6(5*H*,7*H*)-one (*XXXV*)

A mixture of 5·9 g acid *XXVIII*, 2,4 g trimethylchlorosilane, 30 ml chloroform and 10 ml acetonitrile was refluxed for 2 h. After cooling, 7·0 g dicyclohexylethylamine[34] was added together with 5·7 g 4-toluenesulfonyl chloride in 10 ml chloroform, the mixture was refluxed for further 9 h and, after cooling, it was shaken with a 10% solution of Na_2CO_3. The precipitated lactam *XXXII* (1·3 g, m.p. 277–280°C) was filtered, the organic phase of the filtrate was separated, washed with 15% NaOH, 5% hydrochloric acid and water, dried and evaporated. From the oily residue 0·7 g crystalline compound separated. This was recrystallized from a mixture of ethanol and benzene to melt at 220–223°C and characterized as *XXXV*. IR spectrum: 750 and 759 (4 vicinal aromatic C—H), 815 and 840 (2 vicinal aromatic C—H), 872 (isolated aromatic C—H), 1175 and 1370 (SO_2N), 1552 and 1595 (Ar), 1680, 1720 cm^{-1} (—CON—). NMR spectrum: δ 6·90–8·05 (m, 11 H, aromatic protons), 3·49 (d, $J = 7·0$ Hz, 2 H, $ArCH_2$), 2·42 (s, 3 H, $C—CH_3$). For $C_{21}H_{16}ClNO_3S_2$ (430·0) calculated: 58·66% C, 3·75% H, 8·25% Cl, 3·25% N, 14·92% S; found: 58·82% C, 3·89% H, 8·21% Cl, 3·42% N, 15·04% S.

Cyclization of Acid *XXIX* in Toluene

Polyphosphoric acid was prepared from 18 g P_2O_5 and 10 ml 85% H_3PO_4, 1·06 g acid *XXIX* and 50 ml toluene were added and the mixture was refluxed under stirring for 13 h. After decomposition with water it was filtered, the toluene layer was washed with a 5% solution of NaOH and water, dried and evaporated. The residue was dissolved in cyclohexane, 50 mg lactam *XXXII*, m.p. 273–275°C, remaining undissolved. The cyclohexane solution was evaporated and the residue (1·25 g) was chromatographed on a column of 100 g alumina (activity II). A mixture of benzene and light petroleum eluted 0·40 g compound which was crystallized from a mixture of ethanol and benzene; m.p. 219–221°C, 2-chloro-6-(4-tolyl)-7*H*-dibenzo[*b,g*]-1,4-thiazocine (*XXXIX*). The molecular ion of the mass spectrum corresponds to $C_{21}H_{16}ClNS$, fragments of *m/e* 334 and 258 indicate the presence of methyl and the whole toluene residue. NMR spectrum: δ 7·85 (d, 2 H, aromatic protons in positions 2 and 6 of toluene), 7·68 (s, 1 H, aromatic proton in position 1 of the skeleton), 6·90–7·50 (m, 8 H, remaining aromatic protons), 3·75 (bs, 2 H, $ArCH_2$), 2·28 (s, 3 H. $C—CH_3$). For $C_{21}H_{16}ClNS$ (349·9) calculated: 72·09% C, 4·61% H, 10·13% Cl, 4·00% N, 9·17% S; found: 72·31% C, 4·81% H, 10·09% Cl, 3·75% N, 9·11% S.

Benzene eluted 0·46 g of a compound which was crystallized from a mixture of benzene and light petroleum, m.p. 149–150·5°C, 6-[1-(4-tolyl)-1-ethylideneamino]-9-chlorodibenzo[*b,f*]thiepin 10(11*H*)-one (*XL*). UV spectrum: λ_{max} 252 nm (log ε 4·46). IR spectrum: 748 (4 vicinal aromatic C—H), 806, 820 and 858 (2 vicinal aromatic C—H), 1570 and 1602 (Ar), 1628 (C=N conjug.),

1 688 cm^{-1} (Ar—CO). NMR spectrum: δ 8·02 (d, 2 H, aromatic protons in positions 7 and 8 of the system), 7·05—7·55 (m, 8 H, remaining aromatic protons), 4·56 (s, 2 H, $ArCH_2CO$), 2·64 (s, 3 H, C—CH_3 of ethylidene), 2·43 (s, 3 H, C—CH_3 of toluene). For $C_{23}H_{18}ClNOS$ (391·9) calculated: 70·49% C, 4·63% H, 9·05% Cl, 3·57% N, 8·18% S; found: 70·62% C, 4·62% H, 9·19% Cl, 3·72% N, 8·30% S. Heating of the substance with aqueous ethanolic solution of HCl yielded only the hydrochloride, m.p. in a capillary 207—209°C (ethanol). For $C_{23}H_{19}Cl_2NOS$ (428·4) calculated: 64·49% C, 4·47% H, 16·55% Cl, 3·27% N, 7·49% S; found: 64·84% C, 4·62% H, 16·42% Cl, 3·20% N, 7·40% S.

6-[1-(4-Tolyl)ethylamino]-9-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XLI*)

A solution of 2·25 g base *XL* in a mixture of 100 ml ethanol and 100 ml ethyl acetate was hydrogenated under normal conditions on a palladium catalyst (0·1 g $PdCl_2$ and 1 g charcoal) until cessation of hydrogen uptake. After filtration, the filtrate was evaporated to yield 2·2 g compound which crystallized from a mixture of ethanol and benzene; m.p. 178—180°C. IR spectrum (KBr): 722 (4 vicinal aromatic C—H), 810 and 818 (2 vicinal aromatic C—H), 1 580 and 1 602 (Ar), 1 662 (Ar—CO) 3 480 cm^{-1} (NH). NMR spectrum: δ 6·10—8·20 (m, 10 H, aromatic protons), 4·45 (s, 2 H, $ArCH_2$), 3·60 (bs, 1 H, NH), 2·40 (s, 3 H, C—CH_3 of toluene), 1·55 (d, J = 6·0 Hz, 3 H, C—CH_3, 1,1-disubstituted ethyl). For $C_{23}H_{20}ClNOS$ (393·9) calculated: 70·12% C, 5·12% H 9·00% Cl, 3·56% N, 8·14% S; found: 70·27% C, 5·23% H, 9·00% Cl, 3·60% N, 8·15% S.

2-(2-Hydroxymethylphenylthio)-6-chlorobenzoic Acid (*XLII*)

Thiosalicylalcohol[38,39] (22·4 g) was dissolved in a solution of 27 g KOH in 350 ml water and, at 100°C, 2·2 g "molecular" copper and 41·4 g 2-chloro-6-iodobenzoic acid[5] was added. The mixture was stirred for 6 h at 100°C, filtered while hot and the filtrate acidified with 100 ml dilute hydrochloric acid (1 : 1). The precipitated crude product was filtered and recrystallized from aqueous ethanol with an addition of charcoal; 35·8 g (83%), m.p. 175—177°C. For $C_{14}H_{11}ClO_3S$ (294·8) calculated: 57·04% C, 3·76% H, 12·03% Cl, 10·88% S; found: 56·95% C, 3·84% H, 11·82% Cl, 10·77% S.

2-(2-Chloromethylphenylthio)-6-chlorobenzoyl Chloride (*XLIII*)

A mixture of 5·9 g acid *XLII*, 9 ml thionyl chloride, 60 ml benzene and 2 ml dimethylformamide was refluxed for 4 h. On the following day, distillation yielded 5·7 g (86%) product boiling at 170—174°C/0·1 Torr. For $C_{14}H_9Cl_3OS$ (331·6) calculated: 50·70% C, 2·74% H, 32·07% Cl, 9·67% S; found: 50·91% C, 2·83% H, 31·64% Cl, 9·65% S.

1-Chloro-5-chloromethylthioxanthone (*XLV*)

A mixture of 20·0 g acid *XLII*, 200 ml benzene and 30 ml thionyl chloride was refluxed for 4 h. After evaporation of benzene and excess $SOCl_2$ a decomposition took place and the distillation residue solidified; m.p. 190—192°C (benzene). UV spectrum (saturated solution in methanol): λ_{max} 226, 260, 304 and 382 nm. IR spectrum: 790, 799 and 808 (3 vicinal aromatic C—H), 1 580 and 1 589 (Ar), 1 641 cm^{-1} (CO of thioxanthone). For $C_{14}H_8Cl_2OS$ (295·2) calculated: 56·96% C, 2·73% H, 24·02% Cl, 10·87% S; found: 57·06% C, 2·66 H, 24·19% Cl, 10·63% S.

Methyl 2-(2-chloromethylphenylthio)-6-chlorobenzoate (*XLIV*)

A solution of chloride *XLIII* (4·0 g) in 10 ml methanol was left to stand for 12 h at room temperature. After evaporation at reduced pressure the product was distilled; 3·6 g (91%), b.p. 170 — 175°C/0·5 Torr. For $C_{15}H_{12}Cl_2O_2S$ (327·2) calculated: 55·05% C, 3·70% H, 21·67% Cl, 9·80% S; found: 54·97% C, 3·68% H, 21·76% Cl, 9·62% S.

1-Chlorothioxanthene (*XLVI*)

A grain of iodine and several drops of ethylene dibromide were added to 5·0 g Mg in 30 ml tetrahydrofuran. After initiation of the reaction, a solution of 6·6 g chloride *XLIII* in 300 ml tetrahydrofuran was added dropwise over 1 h under refluxing and stirring. The mixture was further refluxed for 1·5 h. It was then cooled, diluted with ether, filtered, the filtrate was washed with 10% NaOH and evaporated. The residue (3·9 g) was chromatographed on a column of 60 g alumina (activity II). The only crystalline compound to be obtained was eluted with the first 60 ml benzene; 1·7 g, m.p. 67—68°C (ethanol). The mass spectrum corresponds to $C_{13}H_9ClS$ and the course of fragmentation is not at variance with the formulation of the product as *XLVI*. UV spectrum: λ_{max} 250 nm (log ε 3·82), 266 nm (3·99). IR spectrum: 751 (4 vicinal aromatic C—H), 779 (3 vicinal aromatic C—H), 1 580 cm^{-1} (Ar). For $C_{13}H_9ClS$ (232·7) calculated: 67·09% C, 3·90% H, 15·23% Cl, 13·78% S; found: 67·05% C, 3·99% H, 14·99% Cl, 13·55% S.

The authors are indebted to Dr V. Hanuš, Institute of Physical Chemistry, Czechoslovak Academy of Sciences, Prague, and to Dr M. Ryska, Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences, Prague, for measuring and interpreting the mass spectra. The technical cooperation in the preparative part of work by Mrs H. Nováková and Mrs E. Princová, in the spectral analysis by Mrs P. Vejdělková is acknowledged. The analyses were done by Mr K. Havel, Mrs J. Komancová, Mrs V. Šmídová, Mrs J. Hrdá, Mrs A. Slaviková and Mrs E. Dvořáková of the analytical department of this institute.

REFERENCES

1. Protiva M., Jilek J. O., Metyšová J., Seidlová V., Jirkovský I., Metyš J., Adlerová E., Ernest I., Pelz K., Pomykáček J.: Farmaco (Pavia), Ed. Sci. *20*, 721 (1965).
2. Jilek J. O., Seidlová V., Svátek E., Protiva M.: Monatsh. Chem. *96*, 182 (1965).
3. Metyšová J.: Activitas Nervosa Super. *8*, 388 (1966).
4. Jilek J. O., Svátek E., Metyšová J., Pomykáček J., Protiva M.: This Journal *32*, 3186 (1967).
5. Pelz K., Ernest I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1852 (1968).
6. Jilek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *33*, 1831 (1968).
7. Metyš J., Metyšová J., Votava Z., Benešová O., Dlabač A., Kazdová E., Franz Z., Queisnerová M., Kraus P., Vaněček M., Hradil F., Jilek J. O., Protiva M.: Farmakoterap. zprávy 17(3), 131 (1971).
8. Šindelář K., Kakáč B., Svátek E., Holubek J., Metyšová J., Hrubantová M., Protiva M.: This Journal *38*, 3321 (1973).
9. McKillop A., Hunt J. D., Taylor E. C., Kienzle F.: Tetrahedron Letters *1970*, 5275.
10. Jilek J. O., Šindelář K., Pomykáček J., Horešovský O., Pelz K., Svátek E., Kakáč B., Holubek J., Metyšová J., Protiva M.: This Journal *38*, 115 (1973).
11. Mahishi N. B., Sattur P. B., Nargund K. S.: J. Karnatak Univ. *2*, 50 (1957); Chem. Abstr. *53*, 14 101 (1959).
12. Sandoz Ltd.: Belg. Pat. 617.251; Chem. Abstr. *58*, 12 518 (1963).
13. Mayer F.: Ber. *43*, 595 (1910).

14. Allen C. F. H., MacKay D.D.: Org. Syn., Coll. Vol. *2*, 580 (1943).
15. Mangini A., Deliddo C.: Gazz. Chim. Ital. *63*, 612 (1933); Chem. Zentr. *1934*, I, 848.
16. Nietzki R., Zänker W.: Ber. *36*, 3953 (1903).
17. Decker H., Fellenberg T. v.: Ber. *38*, 2511 (1905).
18. Taylor E. C., Kienzle F., Robey R. L., McKillop A., Hunt J. D.: J. Am. Chem. Soc. *93* (*19*), 4845 (1971).
19. Traynelis V. J., Love R. F.: J. Org. Chem. *26*, 2728 (1961).
20. Grewald K., Neumann G.: Chem. Ber. *101*, 1933 (1968).
21. Cassella & Co.: German Pat. 367.346; Chem. Zentr. *1923*, II, 919; Friedl. Fortschr. Teerfarbenfabr. *14*, 748 (1926).
22. Cassella & Co.: German Pat. 398.877; Chem. Zentr. *1925*, I, 1657; Friedl. Fortschr. Teerfarbenfabr. *14*, 918 (1926).
23. König W.: Ber. *61*, 2067, 2069 (1928).
24. Cassella & Co.: German Pat. 360.690; Chem. Zentr. *1923* II, 190; Friedl. Fortschr. Teerfarbenfabr. *14*, 910 (1926).
25. Cassella & Co.: German. Pat. 367.344; Chem. Zentr. *1923* II, 527; Friedl. Fortschr. Teerfarbenfabr. *14*, 913 (1926).
26. Šindelář K., Metyšová J., Protiva M.: This Journal *37*, 1734 (1972).
27. Schindler W., Schmid E. (J. R. Geigy AG.): Swiss Pat. 455.782 (Appl. 23. IX. 1965); Chem. Abstr. *70*, 78 034 (1969).
28. Schindler W., Schmid E. (J. R. Geigy AG.): Swiss Pat. 455.783 (Appl. 23. IX. 1965); Chem. Abstr. *70*, 4 159 (1969).
29. Schindler W., Schmid E. (J. R. Geigy AG.): Swiss Pat. 454.865 (Appl. 23. IX. 1965); Chem. Abstr. *69*, 96 798 (1968).
30. Schindler W., Schmid E. (J. R. Geigy AG.): Swiss. Pat. 454.866 (Appl. 23. IX. 1965); Chem. Abstr. *69*, 96 794 (1968).
31. Mayer F.: Ber. *42*, 3060 (1909).
32. Wachter W.: Ber. *26*, 1744 (1893).
33. Kricheldorf H. R.: Synthesis *1970*, 592.
34. Hünig S., Kiessel M.: Chem. Ber. *91*, 380 (1958).
35. Popp F. D., McEwen W. E.: Chem. Rev. *58*, 321 (1958).
36. Pratt E. F., Rice R. G., Luckenbaugh R. W.: J. Am. Chem. Soc. *79*, 1212 (1957).
37. Snyder H. R., Werber F. X.: J. Am. Chem. Soc. *72*, 2962 (1950).
38. Grice R., Owen L. N.: J. Chem. Soc. *1963*, 1947.
39. Pelz K., Jirkovský I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1895 (1968).
40. Okabayashi I., Miyoshi F., Arimoto M.: J. Pharm. Soc. Japan *92*, 1386 (1972).
41. Collins J. Ch., Rosi D., Miller T. Ch. (Sterling Drug Inc.): S. African Pat. 71/06, 590 (U.S. Appl. 5. X. 1970); Chem. Abstr. *78*, 29 624 (1973).
42. Schulenberg J. W. (Sterling Drug Inc.): US-Pat. 3,711,513 (Appl. 5. X. 1970); Chem. Abstr. *78*, 84 258 (1973).
43. Laidlaw G. M., Collins J. C., Archer S., Rosi D., Schulenberg J. W.: J. Org. Chem. *38*(*9*), 1743 (1973).
44. McKillop A., Hunt J. D., Kienzle F., Bigham E., Taylor E. C.: J. Am. Chem. Soc. *95* (*11*), 3635 (1973).

Translated by A. Kotyk.