NEUROTROPIC AND PSYCHOTROPIC COMPOUNDS. XLVI.* SEVERAL DERIVATIVES OF CYCLOHEXYLPHENYL SULFIDE

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Reaction of 2-(phenylthio)cyclohexanone (*I*) with methyl cyanoacetate yielded the cyano ester *II* which underwent alkaline hydrolysis to give a low yield of 2-(phenylthio)cyclohexene-1-acetic acid (*IX*). The reaction of 2-(phenylthio)cyclohexanol (*III*) with phosphorus tribromide resulted in crystalline cyclohexanonebis(phenylthio) ketal (*X*). While the lactone of *cis*-2-hydroxycyclohexylacetic acid does not react with sodium thiophenolate, the lactone of the corresponding *trans*-acid yields in this reaction 6% of 2-(phenylthio)cyclohexylacetic acid (*XI*). Attempts at cyclization of *IX* and *XI* with polyphosphoric acid to the tricyclic ketones were not successful.

In its original scope this communication proceeds from some previous papers of this series[1-3] as it describes the initial phases of experiments with the synthesis of partly saturated analogues of the neuroleptic and central depressant perathiepin, *i.e.* 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin[4]. These experiments, proceeding in two directions, met with considerable preparative difficulties and were stopped after the information had been obtained that the problem had been solved elsewhere by a different approach[5] and that the saturation of one of the benzene rings of the dibenzo[*b*,*f*]thiepin system is associated with the loss of neuroleptic activity in the series of analogues of perathiepin. In the present paper we describe the preparation of several other compounds not connected with the above program and intended only for a systematic pharmacological screening.

The first experiments proceeded from 2-(phenylthio)cyclohexanone[6] (*I*) obtained in a reaction of sodium thiophenolate with 2-chlorocyclohexanone[7]. Analogously, using butanthiol, 4-chlorothiophenol[8] and 4-thiocresol[9] in place of thiophenol, the ketones *VI*–*VIII* were obtained[10]. Reaction of ketone *I* with methyl cyanoacetate (for methods see[11,12]) led to the cyano ester *II* which was hydrolyzed with

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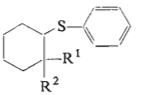
an aqueous–ethanolic solution of potassium hydroxide. During subsequent acidification thiophenol appeared so that, in addition to hydrolysis and decarboxylation, the cyclohexyl—S bond is also cleaved. The acid was obtained in only a 19% yield – according to its NMR spectrum it is 2-(phenylthio)cyclohexene-1-acetic acid (*IX*). The attempt at cyclization of acid *IX* with polyphosphoric acid at 110°C is accompanied by further splitting off of thiophenol; the neutral product formed is not homogeneous and could not be made to crystallize even after chromatography.

Reduction of 2-(phenylthio)cyclohexanone (*I*) with sodium borohydride gave rise to oily 2-(phenylthio)cyclohexanol (*III*), apparently as a mixture of *cis* and *trans* isomers. Upon treatment with phosphorus tribromide in benzene and in the presence of pyridine further thiophenol is split off. Elimination and addition of thiophenol to the elimination product play a role here since, from the neutral product of reaction, some 20% of crystalline $C_{18}H_{20}S_2$ was obtained. The NMR spectrum (only two multiplets at 7·15–8·00 and 1·73 p.p.m., each corresponding to 10 H) showed unequivocally that we are dealing here with the heretofore unknown bis(phenylthio) ketal of cyclohexanone (*X*).

The reaction of 2-(phenylthio)cyclohexanone (*I*) with 3-dimethylaminopropylmagnesium chloride in ether yields a low amount of oily amino alcohol *IV* which



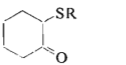
I, $R^1 = R^2 = =O$

II, $R^1 = R^2 = =C(CN)(COOCH_3)$

III, $R^1 = H$, $R^2 = OH$

IV, $R^1 = OH$, $R^2 = (CH_2)_3N(CH_3)_2$

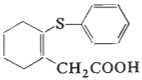
V, $R^1 = OCOCH_3$, $R^2 = (CH_2)_3N(CH_3)_2$



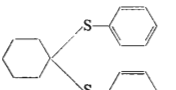
VI, $R = C_4H_9$

VII, $R = 4\text{-}C_6H_4Cl$

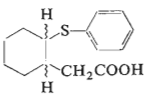
VIII, $R = 4\text{-}C_6H_4CH_3$



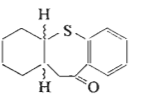
IX



X



XI



XII

apparently represents a mixture of stereoisomers. Treatment with hydrogen chloride gives rise to a crystalline hydrochloride which is readily purified to a homogeneous substance with a constant melting point. Decomposition of this hydrochloride by alkalinization can then provide one of the stereoisomers of *IV* in the crystalline form. Alcohol *IV* shows no tendency to dehydration since during heating with acetyl chloride in chloroform the only characterized product obtained was the amino ester *V* (in the form of crystalline hydrochloride).

In further experiments we attempted to achieve a reaction of the lactone of *cis*-2-hydroxycyclohexylacetic acid[13] and of the lactone of the corresponding *trans* acid[14] with sodium thiophenolate. A similar reaction with γ-lactones derived from primary alcohols (see *e.g.* γ-butyrolactone[15] or phthalide[16]) proceeds smoothly and yields the corresponding phenylthiocarboxylic acids. Substitution at the carbon bearing the oxygen atom of the alcoholic function complicates the reaction. Thus *e.g.* 3,3-dimethylphthalide does not react with sodium thiophenolate in boiling ethanol.* Similarly, the lactone of *cis*-2-hydroxycyclohexylacetic acid[13] does not react with sodium thiophenolate under these conditions (the starting lactone was practically completely regenerated). On the other hand, the lactone of *trans*-2-hydroxycyclohexylacetic acid[14] yielded approximately 6% of 2-(phenylthio)cyclohexylacetic acid (*XI*) on direct heating with thiophenolate to 200°C. In an attempt at cyclization of acid *XI* with the aid of polyphosphoric acid at 110–120°C a relatively high yield of a neutral product is obtained which, even in a crude state, displays a band in the IR spectrum at 1675 cm^{-1}, which might correspond to a conjugated keto group in the seven-membered ring. This product thus apparently contains the desired ketone *XII*, probably both stereoisomers, but even after chromatography none of the fractions could be made to crystallize.

The oxime of ketone *I*, hydrochloride of amino alcohol *IV*, semicarbazones of ketones *VI*– *VIII* and the acid *IX* (as a solution of its sodium salt) were evaluated pharmacologically in a broad spectrum of tests using methods of general screening under the direction of Dr F. Hradil and Dr J. Němec at the unit of this Institute at Rosice n/L. They were further tested as to their inhibitory potency toward typical microorganisms *in vitro* at the bacteriological department of this institute (Drs A. Šimek and J. Turinová).

Acute toxicity (LD_{50}) was determined in mice, with readily soluble compounds after intravenous injection (*IV*·HCl 50 mg/kg; *IX* Na-salt 150 mg/kg), with less soluble compounds after oral application (oximes and semicarbazones all >2·5 g/kg). The oxime and the semicarbazones show in high doses (300 mg/kg *p.o.*) an indication of central depressant effect in mice and anticonvulsant effect in the electro-shock test in mice. The oxime inhibits *in vitro* at a concentration of 100 μg/ml the growth of a number of microorganisms (*Streptococcus* β-*haemolyticus*, *Staphylococcus pyogenes aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus vulgaris*, *Mycobacterium tuberculosis* H 37 Rv). Hydrochloride *IV* at a dose of 10 mg/kg *i.v.* shows a pronounced hypothermic effect on rats and a spasmolytic effect against barium chloride contractions of rat duodenum *in vitro*. The sodium salt of acid *IX*, in addition to a weak

* Finding of Dr M. Rajšner in this laboratory.

central depressant and anticonvulsant effect in mice (30 mg/kg *i.v.*) shows an antiarhythmic effect (chloroform technique) in mice and, at a concentration of 50 μg/ml *in vitro* it inhibits the growth of *Mycobacterium tuberculosis* H 37 Rv. Generally the effects are too weak to warrant a detailed pharmacological investigation.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block. The samples were dried for 8 h *in vacuo* (about 0·2 Torr) over phosphorus pentoxide at a temperature proportional to the melting point of the substance (at most 100°C). The NMR spectra shown were recorded in a ZKR 60 (Zeiss-Jena) apparatus in a 6% solution in deuteriochloroform. As reference standard served hexamethyldisiloxane; the values shown in the paper are referred to tetramethylsilane.

2-(Phenylthio)cyclohexanone (*I*)

The compound was prepared by a slightly modified procedure previously described[6]: 44·0 g thiophenol was added to a solution of 9·2 g sodium in 350 ml ethanol and, at 0°C under stirring, this was followed over 3 h with 53·0 g 2-chlorocyclohexanone[7] (b.p. 80°C, 10 Torr) in 150 ml ethanol. The mixture was stirred for 2 h at room temperature, refluxed for 8 h in a water bath, cooled, filtered and the filtrate distilled: 72·2 g (88%) b.p. 130—132°C/0·6 Torr. Ref.[6] gives b.p. 184°C/12 Torr.

The *oxime* was obtained by heating a solution of 4·1 g ketone and 4·2 g hydroxylamine hydrochloride in a mixture of 15 ml ethanol and 8 ml pyridine for 3 h on a boiling-water bath: m.p. 94—95° (aqueous ethanol). NMR spectrum: δ 7·55—6·96 (mult., 5 H, phenyl), 3·89 (triplet, 1 H, on tertiary carbon of cyclohexane ring), 3·00—2·20 (multiplet, 2 H, CH_2 group adjacent to C=NOH), 2·20—1·70 (multiplet, 6 H, remaining CH_2 groups of the cyclohexane ring), 8·00—9·00 (broad singlet, disappearing after deuterization, NOH). For $C_{12}H_{15}NOS$ (221·3) calculated: 65·12% C, 6·83% H, 6·33% N, 14·49% S; found: 65·36% C, 6·76% H, 6·06% N, 14·58% S.

2-(n-Butylthio)cyclohexanone (*VI*)

Similarly to the preceding case, 24 g 1-butanethiol (commercial product) reacted with 39·8 g 2-chlorocyclohexanone[7] to yield 33·7 g product boiling at 93°C/0·9 Torr. For $C_{10}H_{18}OS$ (186·3) calculated: 64·47% C, 9·73% H; found: 63·78% C, 9·70% H.

Semicarbazone, m.p. 169—171°C (ethanol). NMR spectrum: δ 5·92 (singlet disappearing after deuterization, 2 H, NH_2), 3·50 (singlet, 1 H, at tertiary carbon of cyclohexane ring), 2·80 to 2·15 and 2·15—1·05 (two multiplets, 14 H, CH_2 groups of cyclohexane ring and butyl), 0·90 (deformed triplet, CH_3), 9·23 (singlet, NH). For $C_{11}H_{21}N_3OS$ (243·4) calculated: 54·28% C, 8·70% H, 17·27% N, 13·17% S; found: 54·59% C, 8·69% H, 17·50% N, 13·27% S.

2-(4-Chlorophenylthio)cyclohexanone (*VII*)

As before, yield of 89%: b.p. 158°C/1 Torr. Mentioned also in the patent[10] where the reported b.p. was 154—156°C/1 Torr. For $C_{12}H_{13}ClOS$ (240·8) calculated: 59·85% C, 5·44% H, 14·73% Cl, 13·32% S; found: 59·41% C, 5·36% H, 14·84% Cl, 13·15% S.

Semicarbazone, m.p. 204—206°C (1-butanol). For $C_{13}H_{16}ClN_3OS$ (297·8) calculated: 52·43% C, 5·42% H, 11·91% Cl, 14·11% N, 10·77% S; found: 52·50% C, 5·48% H, 12·00% Cl, 13·96% N, 10·87% S.

2-(4-Methylphenylthio)cyclohexanone (*VIII*)

As before, in a yield of 79%: b.p. 154°C/0·8 Torr. Patent[10] gives a b.p. of 130—130·5°C/0·45 Torr. For $C_{13}H_{16}OS$ (220·3) calculated: 70·88% C, 7·32% H, 14·56% S; found: 70·88% C, 7·53% H, 14·41% S.

Semicarbazone, m.p. 190—192°C (ethanol). For $C_{14}H_{19}N_3OS$ (277·4) calculated: 60·62% C, 6·90% H, 15·15% N, 11·56% S; found: 60·79% C, 7·01% H, 15·26% N, 11·45% S,

Methyl 2-(Phenylthio)cyclohexylidenecyanoacetate (*II*)

A mixture of 31·0 g ketone *I*, 15·0 g methyl cyanoacetate, 4·2 g ammonium acetate, 16 ml acetic acid and 240 ml benzene was distilled for 12 h using an attachment for separation of water formed in the reaction; a total of 9 ml water was separated. After cooling, the reaction mixture was washed with water and with 5% sodium hydroxide, dried ($MgSO_4$) and distilled; 34·4 g (80%), b.p. 192—196°C/1·5 Torr. For $C_{16}H_{17}NO_2S$ (287·3) calculated: 66·88% C, 5·96% H, 4·88% N, 11·14% S; found: 67·17% C, 6·10% H, 4·96% N, 11·08% S.

2-(Phenylthio)cyclohexene-1-acetic Acid (*IX*)

A solution of 40·0 g ester *II* and 50 g potassium hydroxide in 160 ml ethanol and 80 ml water was refluxed for 15 h. Ethanol was then distilled off, the remainder was mixed with 500 ml water and, by washing with benzene, the neutral fraction was removed (10·7 g). The alkaline aqueous solution was slightly acidified with 200 ml 3M-HCl under cooling in an ice bath and stirring, the separated oil was extracted with benzene, the extract was washed with water, dried ($MgSO_4$) and evaporated. The residue (18·0 g) was freed of thiophenol by steam distillation, extracted with benzene and the solution was evaporated. The residue yielded 6·5 g (19%) crystalline product, m.p. 84—85°C (cyclopentane). NMR spectrum: δ 7·21 (singlet, 5 H, phenyl), 3·51 (singlet, 2 H, CH_2 group at α-position to carboxyl), 2·20 (singlet, 4 H, CH_2 groups of cyclohexane ring adjacent to double bond), 1·90—1·35 (multiplet, 4 H of remaining CH_2 groups of cyclohexane ring), 10·64 (singlet, 1 H, carboxyl). For $C_{14}H_{16}O_2S$ (248·3) calculated: 67·73% C, 6·50% H, 12·89% S; found: 67·75% C, 6·75% H, 12·58% S.

2-(Phenylthio)cyclohexanol (*III*)

A solution of 1·83 g sodium borohydride and 0·2 ml 15% sodium hydroxide in 15 ml 70% methanol was added dropwise under stirring at a temperature less than 30°C to a solution of 10·0 g ketone *I* in 150 ml methanol. The mixture was stirred for 3 h under a reflux condenser at 70°C, methanol was then distilled off and the residue divided between 70 ml water and 70 ml benzene. Distillation of the benzene solution yielded 8·1 g (80%) of a compound boiling at 125—127°C/0·7 Torr. For $C_{12}H_{16}OS$ (208·2) calculated: 69·21% C, 7·74% H, 15·37% S; found: 69·11% C, 7·81% H, 15·42% S.

Cyclohexanonebis(phenylthio) ketal (*X*)

One ml pyridine was added to a solution of 3·5 g phosphorus tribromide in 5 ml benzene and, under external cooling with ice-cold water, a solution of 7·5 g alcohol *III* in 10 ml benzene was added dropwise. The mixture was stirred for 2 h at room temperature, heated for 1 h to 50°C, cooled and diluted with 10 ml benzene and finally washed with 20 ml 3M-HCl (intense smell of thiophenol). The benzene solution was washed with water, dried ($MgSO_4$) and distilled. A total of 4·1 g product boiling at 120—130°C/0·9 Torr was obtained. On standing the product gave rise to 0·8 g of a crystalline compound: m.p. 83—85°C (light petroleum). NMR spectrum: δ 7·15 to

8·00 (multiplet, 10 H, phenyl), 1·73 (multiplet, 10 H, CH_2 groups of cyclohexane ring). For $C_{18}H_{20}S_2$ (300·3) calculated: 71·98% C, 6·71% H, 21·31% S; found: 72·21% C, 6·69% H, 21·18% S.

On heating the compound with ethanolic solution of hydrochloric acid thiophenol is split off only slowly. Thiophenol is identified by its smell and can be steam-distilled and demonstrated in the distillate after gentle oxidation with hydrogen peroxide as diphenyldisulfide (m.p. 57°C).

1-(3-Dimethylaminopropyl)-2-(phenylthio)cyclohexanol (*IV*)

Reaction of 24·2 g 3-dimethylaminopropyl chloride with 4·86 g magnesium in 60 ml ether gave rise to a Grignard reagent, using a small amount of iodine and 0·5 ml ethyl bromide for starting the reaction. The mixture was refluxed for 4 h. After cooling, the reagent was diluted with 100 ml ether and, over a period of 10 min, a solution of 20·6 g ketone *I* in 100 ml ether was added dropwise. The mixture was refluxed for 8 h and, after cooling, decomposed with 260 ml 10% solution of ammonium chloride. The basic product was extracted from the ether layer into excess dilute hydrochloric acid, liberated from the hydrochloride solution and isolated by extraction with ether. A total of 4·3 g oily product was obtained; this was dissolved in ether and left to react with an ether solution of hydrogen chloride, giving rise to the hydrochloride, m.p. 187—188°C (ethanol–ether). For $C_{17}H_{28}ClNOS$ (329·9) calculated: 61·89% C, 8·55% H, 10·75% Cl, 4·25% N, 9·71% S; found: 62·17% C, 8·60% H, 10·73% Cl, 4·14% N, 9·85% S.

Decomposition of the pure hydrochloride with ammonia and extraction with ether yielded the base, m.p. 71—72°C (light petroleum). UV spectrum (methanol): λ_{max} 257 nm (log ε 3·848). IR spectrum (Nujol): 698, 750 and 760 (monosubstituted benzene), 1 105 (tertiary alcohol), 1 584 (Ar), 3 160 cm^{-1} (OH). NMR spectrum: δ 7·30 (multiplet, 5 H, phenyl,) 5·15 (broad singlet, disappears after deuterization, OH), 3·05 (triplet, 1 H on tertiary carbon of cyclohexane ring), 2·20 (singlet, 6 H, $N(CH_3)_2$), 2·50—0·80 (multiplet, 14 H, CH_2 groups in ring and aliphatic chain). For $C_{17}H_{27}NOS$ (293·5) calculated: 69·57% C, 9·28% H, 4·77% N, 10·93% S; found: 69·77% C 9·32% H, 4·74% N, 11·20% S.

1-(3-Dimethylaminopropyl)-1-acetoxy-2-(phenylthio)cyclohexane (*V*)

Five ml acetyl chloride were added to a solution of 2·9 g alcohol *IV* in 30 ml chloroform and the solution was refluxed for 3 h. After evaporation of chloroform at reduced pressure the residue was made alkaline with aqueous ammonia and the base was isolated by extraction with ether. Evaporation of the extract yielded 2·8 g nonhomogeneous base which was chromatographed on a column of 70 g alumina (activity II) and the course of chromatography was checked by chromatography of the individual samples on a thin layer of alumina. This yielded 0·52 g homogeneous base which gave a crystalline *hydrochloride*, m.p. 151—154°C (ethanol–ether). For $C_{19}H_{30}ClNO_2S$ (371·9) calculated: 61·35% C, 8·13% H, 9·53% Cl, 3·77% N, 8·62% S; found: 60·98% C, 8·10% H, 9·85% Cl, 4·24% N, 8·78% S. From the crystalline hydrochloride the *base* was liberated in the conventional way, its NMR spectrum being as follows: δ 7·30 (multiplet, 5 H, phenyl), 3·46 (triplet, 1 H, at tertiary carbon of cyclohexane ring), 3·16 (singlet, 6 H, $N(CH_3)_2$), 2·00 (singlet, $COCH_3$), 2·00—0·80 (multiplet, 14 H, CH_2 groups of ring and chain).

2-(Phenylthio)cyclohexylacetic Acid (*XI*)

Thiophenol (5·5 g) and 7·0 g lactone of *trans*-2-hydroxycyclohexylacetic acid[14] (b.p. 139°C/12 Torr) were added to a solution of sodium ethoxide (1·2 g sodium in 25 ml ethanol). Ethanol was slowly distilled from the solution and the residue was heated in an open flask on a 180—200°C bath for 3 h. After cooling, the melt was mixed with 70 ml warm water, the mixture was extracted

with benzene to remove neutral fractions and the alkaline aqueous solution was made acid with 5 ml concentrated hydrochloric acid. The liberated thiophenol was removed by steam distillation, the residue was extracted with benzene, the extract was shaken with excess 5% sodium hydroxide, the acid product was released from the alkaline solution by hydrochloric acid and re-extracted with benzene. Evaporation of the extract yielded 1·7 g oily product which, after several days of standing, gave rise to 0·78 g (6·2%) crystalline compound, m.p. 89—91°C (light petroleum). NMR spectrum: δ 10·53 (singlet, 1 H, carboxyl), 7·32 (multiplet, 5 H, phenyl), 3·20 (split doublet, 1 H, at tertiary carbon adjacent to sulfur atom, $J = 12·0$ Hz). For $C_{14}H_{18}O_2S$ (250·3) calculated: 67·18% C, 7·25% H, 12·78% S; found: 67·00% C, 7·27% H, 11·97% S.

When attempting a cyclization, the mixture of 3·5 g acid *XI* and 35 g polyphosphoric acid was heated under stirring for 5 h at 110—120°C. After decomposition with water, an oily neutral product was isolated in the usual way (2·5 g), its IR spectrum (chloroform) showing absorption bands at 1 460 (Ar, CH_2CO), 1 675 (conjugated ketone) and 2 980 (CH_2 groups) cm^{-1}). This suggests the presence of 1,2,3,4,4a,11a-hexahydro-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*XII*). However, even chromatography on alumina did not isolate the compound in a pure state.

The authors are indebted for registration and for interpretation of a part of the NMR spectra to Dr B. Kakáč, and of UV and IR spectra to Dr E. Svátek, of the physico-chemical laboratories of this Institute.

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