BENZOCYCLOHEPTENES AND HETEROCYCLIC ANALOGUES AS POTENTIAL DRUGS. VII.*

4-PHENYL-2,3,4,5-TETRAHYDRO-1-BENZOTHIEPINS AND SOME RELATED COMPOUNDS

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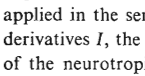
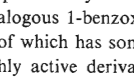
Alkylation of phenylacetonitrile with 2-(phenylthio)ethyl chloride and 2-(4-tolylthio)ethyl chloride yielded monoalkylated nitriles *III* and *IV* and dialkylated nitriles *VIII* and *IX*. Hydrolysis of nitriles *III* and *IV* gave rise to acids *V* and *VI* which were heated with polyphosphoric acid; *V* yields benz[*b*]indeno[2,1-*d*]thiopyran (*XVII*), *VI* the ketone *XVI*. Ketone *XV* was obtained in a minute yield by cyclization of acid *V* with anhydrous hydrogen fluoride. The methylpiperazine derivative *XX* was synthesized from ketone *XVI*. Aminoalkylation of nitrile *III* produced aminonitriles *X*—*XII* which are rather toxic and display no useful pharmacodynamic effects.

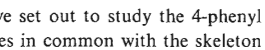
Various types of amines derived from 2,3,4,5-tetrahydro-1-benzothiepin and from its 5-phenyl derivative that have been prepared by our group[1,2] showed all a low degree of desired neurotropic activity. On the basis of a similar consideration as applied in the series of analogous 1-benzoxepins[3] we set out to study the 4-phenyl derivatives *I*, the skeleton of which has some features in common with the skeleton of the neurotropically highly active derivatives of dibenzo[*b*,*f*]thiepin of type *II*.



I



II



III, $R^1 = H$, $R^2 = CN$
IV, $R^1 = CH_3$, $R^2 = CN$
V, $R^1 = H$, $R^2 = COOH$
VI, $R^1 = CH_3$, $R^2 = COOH$
VII, $R^1 = CH_3$, $R^2 = CONH_2$

The principal potential intermediate of the work described was likely the ketone *XV* which should be available by cyclization of 2-phenyl-4-(phenylthio)butyric acid (*V*).

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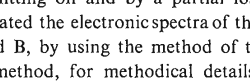
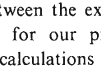
Alkylation of phenylacetonitrile with 2-(phenylthio)ethyl chloride[4] in ether or in toluene with the aid of sodium amide yielded as the main product 2-phenyl-4-(phenylthio)butyronitrile (*III*). The product of double alkylation *VIII* was isolated from the distillation residue. During the reaction a small part of thiophenol was split off as indicated by the isolation of 1,2-di(phenylthio)ethane[5] from the intermediate fraction. Hydrolysis of nitrile *III* with a boiling mixture of dilute sulfuric acid and acetic acid resulted in acid *V* which was also prepared by reaction of sodium thiophenolate with α-phenyl-γ-butyrolactone[6,7] in boiling ethanol. An attempt at cyclization of acid *V* with polyphosphoric acid at 150–160°C produced a good yield of an orange substance $C_{16}H_{10}S$ instead of the expected ketone *XV*. It follows from the composition of the product that, besides cyclization reactions, dehydrogenation must have taken place. Both the colour and the UV spectrum of the substance indicate the presence of an extensive system of conjugated double bonds present in the form of a polycyclic condensed aromate. Since the UV spectrum is similar to that of benz[*b*]indeno[1,2-*e*]thiopyran[8,9] which is a heterocyclic analogue of dibenz[*a*,*g*]azulene we considered as possible the structure of the isomeric benz[*b*]indeno[2,1-*d*]thiopyran (*XVII*). The formation of this compound from acid *V* would require first of all splitting of the phenylthio residue from carbon 4 (numbering of the butyric acid chain) and its subsequent attachment to carbon 1. There is no clear pattern for the mechanism of such transformation but the fact is that the reaction is accompanied by splitting off and by a partial loss of thiophenol as indicated by its smell. We calculated the electronic spectra of the structure *XVII*, as well as of the possible isomers A and B, by using the method of the limited configuration interaction (LCI-SCF, PPP-method, for methodical details[10,11]). Very good accord between the theory for the structure *XVII* and between the experimental curve (Fig. 1) was obtained, and hence the structure *XVII* for our product appears to be confirmed. It is necessary to mention that the calculations excluded the possibility of the presence of both the structures A, and B. Not even the attempt at cyclization of acid *V* in the form of chloride with aluminium chloride in nitrobenzene did give the desired



VIII, $R^1 = H$, $R^2 = (CH_2)_2SC_6H_5$

IX, $R^1 = CH_3$, $R^2 = (CH_2)_2S$– 

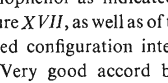
X, $R^1 = H$, $R^2 = (CH_2)_2N(CH_3)_2$

XI, $R^1 = H$, $R^2 = (CH_2)_2N(C_2H_5)_2$

XII, $R^1 = H$, $R^2 = (CH_2)_3N(CH_3)_2$

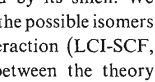
XIII, $R^1 = CH_3$, $R^2 = (CH_2)_2N(C_2H_5)_2$

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

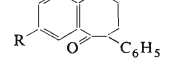


XV, R = H

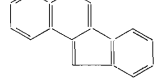
XVI, R = CH_3



XVII



A



B

product. Only when the acid *V* reacted with anhydrous hydrogen fluoride at room temperature a minute amount of crystalline $C_{16}H_{14}OS$ was obtained which appears to be the desired ketone *XV*. However, the procedure is not applicable to preparatory purposes.

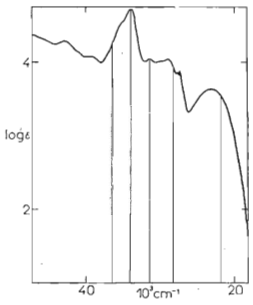


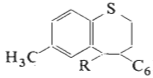
FIG. 1

Absorption Spectrum of *XVII* in Heptane; the Vertical Lines Indicate the Calculated Positions and Intensities of the Maxima

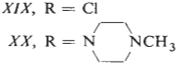
Even before the elucidation of the structure of the cyclization product of acid *V* we considered the possibility that one of the causes of side reactions and hence unsuccessful cyclization attempts might be the unblocked and very reactive *para* position with respect to the sulfur atom in compound *V*. For this reason further preparative work was done using compounds with the *p*-position blocked by methylation. Alkylation of phenylacetonitrile with 2-(4-tolylthio)ethyl chloride[12] yielded nitriles *IV* and *IX*, the first of which underwent acid hydrolysis to acid *VI* (a by-product of the hydrolysis was amide *VII*). Reaction of the acid *VI* with polyphosphoric acid at 150–160°C resulted smoothly in the desired 4-phenyl-7-methyl-2,3-dihydro-4*H*-1-benzothiepin-5-one (*XVI*). Its reduction with sodium borohydride yielded an oily mixture of stereoisomeric alcohols *XVIII* which was treated with acetic anhydride in acetic acid at 100°C to yield as the only isolated product 4-phenyl-7-methyl-2,3-dihydro-1-benzothiepin (*XXI*). The product not characterized here formed by the action of hydrogen chloride on the mixture of alcohols *XVIII* in benzene was considered as a mixture of chlorides *XIX*. Its reaction with 1-methylpiperazine in boiling chloroform in the presence of anhydrous potassium carbonate resulted in a 45% yield of a base with a NMR spectrum supporting structure *XX*. It yields a di-(hydrogen maleate) crystallizing as a monohydrate, the unsharp melting point of which indicates that here, too, we are dealing with a mixture of stereoisomers.

Several further experiments were done to obtain samples for pharmacological screening and for a detailed characterization of some of the compounds prepared.

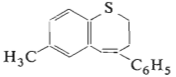
Thus, alkylation of the nitriles *III* and *IV* with 2-dimethylaminoethyl chloride, 2-diethylaminoethyl chloride and 3-dimethylaminopropyl chloride resulted in aminonitriles *X*–*XIV*. Oxidation of sulfide-nitriles *III* and *IV* with hydrogen peroxide in acetic acid at 100°C resulted in sulfones *XXII* and *XXIV*. The first of these was hydrolyzed in an acid medium to acid *XXIII*.



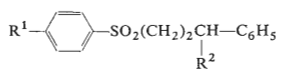
XVIII, R = OH
XIX, R = Cl



XX, R = N NCH$_3$



XXI



XXII, R^1 = H, R^2 = CN
XXIII, R^1 = H, R^2 = COOH
XXIV, R^1 = CH_3, R^2 = CN

Maleate of *XX* (toxicity for mice on intravenous administration: LD_{50} = 49 mg/kg) was evaluated pharmacologically from the point of view of assumed neurotropic effects. It was found to be ineffective as central depressant, cataleptic and antiapomorphine in mice and rats. In a dose of 10 mg/kg *i.p.*, it antagonizes slightly the reserpine ptosis in mice but is ineffective in the test of influencing the reserpine-caused gastric ulcers of rats. On the whole, it is uninteresting neurotropically. Five compounds were subjected to a pharmacological systematic screening using a wider spectrum of tests (mode of administration, acute toxicity LD_{50} in mice and the tested dose D are shown): *V* (*i.v.*, as sodium salt, 150, 30), *X*-HCl (*i.v.*, 30, 6), *XI*-HCl (*i.v.*, 10, 2), *XII*-HCl (*i.v.*, 20, 4) and *XXII* (*p.o.*, 2500, 300). With compounds *V* and *XXII* no significant activities were found. The aminonitriles *X*–*XII* are rather toxic. Besides a mild hypotensive and a suggested vasodilatory effect they, too, showed no marked effects. Compounds *V*, *X*–*XII*, and *XX* were tested for their antimicrobial activity *in vitro*. They were found to be inhibitory against *Streptococcus* β-*haemolyticus* at 12·5–50 μg/ml, *Staphylococcus pyogenes aureus* (25–100), *Klebsiella pneumoniae* (50–100), *Mycobacterium tuberculosis* H 37 Rv (12·5–50).

EXPERIMENTAL

The melting points of analytical preparations were not corrected and were determined in a capillary. The samples were dried in the usual way. The UV spectra (in methanol, unless stated otherwise) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol, unless stated otherwise) in a Unicam SP 200 G spectrophotometer and the NMR spectrum (in deuteriochloroform) in a ZKR 60 (Zeiss, Jena) spectrometer.

2-Phenyl-4-(phenylthio)butyronitrile (*III*)

A solution of 78·0 g phenylacetonitrile in 300 ml ether was added slowly under stirring to a suspension of 31·2 g sodium amide in 200 ml ether. After subsiding of the vigorous reaction the mixture was refluxed for 90 min. After partial cooling, 130 g 2-(phenylthio)ethyl chloride[4] (b.p. 87–88°C/0·9 Torr) in 150 ml ether was added dropwise and the mixture was refluxed for 2 h. After cooling it was decomposed by adding 500 ml water, the organic phase was washed with water, dried and distilled. The main fraction boiling at 152–162°C/0·01 Torr and a minor fraction boiling at 180–190°C/0·01 Torr were collected. The main fraction represents the desired product in a yield of 115 g (68%). For analysis it was redistilled: b.p. 168–171°C/0·2 Torr. For $C_{16}H_{15}NS$ (253·3) calculated: 75·87% C, 5·97% H, 5·53% N, 12·63% S; found: 75·22% C,

5·79% H, 6·01% N, 13·22% S. The intermediate fraction was boiled for 1 h with a mixture of 50 ml sulfuric acid, 50 ml water and 50 ml acetic acid. The acid fraction formed was removed on the basis of solubility in 5% NaOH and the neutral fraction was isolated in the usual way which was then identified as 1,2-di(phenylthio)ethane, m.p. 68·5—69°C (ethanol). For $C_{14}H_{14}S_2$ (246·2) calculated: 68·28% C, 5·73% H, 25·99% S; found: 68·08% C, 5·73% H, 25·80% S. Ref.[5] reports a m.p. of 65°C for the compound obtained by a reaction of sodium thiophenolate with ethylene dibromide. Crystallization of the distillation residue from a mixture of acetone and ether yielded 15·0 g α,α-*bis*(2-*phenylthioethyl*)*phenylacetonitrile* (VIII), m.p. 62·5—63·5°C. UV spectrum: λ_{max} 253 nm (log ε 4·21). IR spectrum: 692, 704 and 739 (C_6H_5), 1600 (Ar), 2250 cm^{-1} (CN). For $C_{24}H_{23}NS_2$ (389·4) calculated: 74·02% C, 5·95% H, 3·60% N, 16·43% S; found: 73·82% C, 6·11% H, 3·78% N, 16·42% S. An analogously conducted preparation of *III* in boiling toluene resulted in a 45% yield.

1-Phenyl-4-(4-tolylthio)butyronitrile (*IV*)

In analogy with the preceding case, alkylation of 117 g phenylacetonitrile with 47 g sodium amide and 187 g 2-(4-tolylthio)ethyl chloride[12] (b.p. 110—112°C/1 Torr) yielded 205 g (77%) of a product boling at 160—165°C/0·1 Torr. The sample for analysis was redistilled; b.p. 162°C/ : 0·1 Torr. For $C_{17}H_{17}NS$ (267·3) calculated: 76·38% C, 6·41% H, 5·24% N, 11·97% S; found: 76·26% C, 6·40% H, 5·13% N, 12·15% S. The distillation residue yielded 35 g α,α-*bis*[2-(4-*tolylthio*)*ethyl*]*phenylacetonitrile* (IX), m.p. 88—89°C (acetone–ethanol). UV spectrum: λ_{max} 255 nm (log ε 4·20). IR spectrum: 702, 741, 759, 768 (C_6H_5), 800 (1,4-C_6H_4), 2232 cm^{-1} (CN). For $C_{26}H_{27}NS_2$ (417·5) calculated: 74·80% C, 6·52% H, 3·36% N, 15·33% S; found: 74·90% C, 6·61% H, 3·32% N, 15·23% S.

1-Phenyl-4-(phenylthio)butyric Acid (*V*)

A) *Hydrolysis of nitrile* III: Mixture of 15 ml water, 15 ml acetic acid, 15 ml sulfuric acid and 14 g nitrile *III* was refluxed for 1 h in a 130°C bath. After cooling, the mixture was diluted with 500 ml water and the precipitated acid was filtered on the following day: 14·5 g (95%). Crystallization from a mixture of toluene and light petroleum yielded the pure product, m.p. 102—103°C. UV spectrum: λ_{max} 253·5 nm (log ε 3·61). IR spectrum: 700, 730 and 740 (C_6H_5), 960, 1210 and 1695 cm^{-1} (COOH). For $C_{16}H_{16}O_2S$ (272·3) calculated: 70·57% C, 5·92% H, 11·75% S; found: 70·72% C, 6·02% H, 11·68% S. B) *Reaction of thiophenolate with α-phenylbutyrolactone*: Thiophenol (22 g) was added to a solution of 4·6 g sodium in 200 ml ethanol. This was followed by an addition of 39 g α-phenyl-γ-butyrolactone[6,7] (b.p. 145—147°C/0·6 Torr). The mixture was refluxed for 6 h, diluted with 500 ml water and the blue solution formed was made acid with hydrochloric acid. Filtration yielded 54·5 g (100%) of a crude product which was dried and recrystallized from a mixture of toluene and light petroleum; m.p. 102—103°C. The compound is identical with the compound prepared under *A*).

1-Phenyl-4-(4-tolylthio)butyric Acid (*VI*)

In analogy with the preceding case according to *A*), 100 g nitrile *IV* was hydrolyzed with a mixture of 200 ml water, 200 ml acetic acid and 200 ml sulfuric acid. A total of 75 g (70%) of the desired acid was obtained, m.p. 130—132°C (ethanol). UV spectrum: λ_{max} 255·5 nm (log ε 3·97). IR spectrum: 701, 727, 741, 757 (C_6H_5), 809 (1,4-C_6H_4), 926, 1240 and 1694 (COOH), 1600 (Ar), 2600—2700 cm^{-1} (COOH). For $C_{17}H_{18}O_2S$ (286·3) calculated: 71·31% C, 6·34% H, 11·18% S; found: 71·32% C, 6·29% H, 10·94% S. As a neutral product of hydrolysis was obtained a 5·1 g amount of 1-*phenyl*-4-(4-*tolylthio*)*butyramide* (VII), m.p. 120—121°C (ethanol). UV spectrum:

λ_{max} 255 nm (log ε 3·96). IR spectrum: 699, 728, 751 (C_6H_5), 806 and 826 (1,4-C_6H_4), 1 597 (Ar), 1 645 and 1 659 ($CONH_2$), 3 353 cm^{-1} (NH). For $C_{17}H_{19}NOS$ (285·3) calculated: 71·56% C, 6·71% H, 4·91% N, 11·22% S; found: 71·51% C, 6·76% H, 4·85% N, 11·11% S.

Aminoalkylation of Nitriles *III* and *IV*

α-(2-*Phenylthioethyl*)-α-(2-*dimethylaminoethyl*)*phenylacetonitrile* (X): A solution of 30·0 g nitrile *III* in 400 ml toluene was heated for 50 min to 80°C with 5·0 g finely pulverized sodium amide. 2-Dimethylaminoethyl chloride (15·2 g) was then added dropwise and the mixture was heated with stirring for 4 h to 80—100°C. After cooling it was decomposed with water, the basic product was extracted from the toluene phase with excess dilute hydrochloric acid from which it was liberated with a solution of NaOH and isolated by extraction with benzene: 15·0 g (40%), b.p. 165—175°C/0·1 Torr. Hydrochloride, m.p. 191—193°C (ethanol–ether). For $C_{20}H_{25}ClN_2S$ (360·7) calculated: 66·59% C, 6·93% H, 9·82% Cl, 7·76% N, 8·89% S; found: 66·53% C, 7·03% H, 9·94% Cl, 7·71% N, 8·98% S.

α-(2-*Phenylthioethyl*)-α-(2-*diethylaminoethyl*)*phenylacetonitrile* (XI): Similarly to the above procedure, from nitrile *III* and 2-diethylaminoethyl chloride in a 57% yield; b.p. 190—200°C : : 0·15 Torr. Hydrochloride, m.p. 133—135°C (ethanol–ether). For $C_{22}H_{29}ClN_2S$ (383·7) calculated: 9·24% Cl, 7·29% N, 8·36% S; found: 9·23% Cl, 7·37% N, 8·29%S.

α-(2-*Phenylthioethyl*)-α-(3-*dimethylaminopropyl*)*phenylacetonitrile* (XII): Similarly to the above procedure, from nitrile *III* and 3-dimethylaminopropyl chloride on a 33% yield; b.p. 180—185°C : : 0·05 Torr. Hydrochloride, m.p. 150—151°C (ethanol–ether). For $C_{21}H_{27}ClN_2S$ (374·7) calculated: 67·30% C, 7·20% H, 9·46% Cl, 7·47% N, 8·55% S; found: 67·19% C, 7·29% H, 9·51% Cl, 7·27% N, 8·62% S.

α-[2-(4-*Tolylthio*)*ethyl*]-α-(2-*diethylaminoethyl*)*phenylacetonitrile* (XIII): Similarly to the above procedure, from nitrile *IV* and 2-diethylaminoethyl chloride; b.p. 188—195°C/0·3 Torr. Hydrochloride, m.p. 188—190°C (ethanol–ether). For $C_{23}H_{31}ClN_2S$ (403·0) calculated: 8·80% Cl, 6·95% N; found: 9·10% Cl, 7·32% N.

α-[2-(4-*Tolylthio*)*ethyl*]-α-(3-*dimethylaminopropyl*)*phenylacetonitrile* (XIV): Similarly to the preceding, from nitrile *IV* and 3-dimethylaminopropyl chloride in a 66% yield; b.p. 185—195°C : : 0·5 Torr. Hydrochloride, m.p. 168—170°C (ethanol–ether). For $C_{22}H_{29}ClN_2S$ (389·0) calculated : 67·92% C, 7·52% H, 9·12% Cl, 7·20% N, 8·24% S; found: 67·65% C, 7·56% H, 9·24% Cl, 7·10% N, 8·26% S.

4-Phenyl-2,3-dihydro-4*H*-1-benzothiepin-5-one (*XV*)

Acid *V* (5·0 g) was added over a 5 min period under stirring and cooling with dry ice to 50 ml anhydrous hydrogen fluoride. The mixture was left for 8 h at 20°C in a closed polyethylene vessel and hydrogen fluoride was then evaporated at room temperature. The residue was dissolved in a mixture of benzene and chloroform. The solution was washed with water and then with a solution of soda. Acidification of the soda solution regenerated 1·4 g of the starting acid *V*. Evaporation of the organic phase yielded 3·7 g neutral product which was not homogeneous and was therefore chromatographed on a column of 90 g alumina (activity II). Evaporation of the benzene eluate yielded 0·54 g of an oil which was dissolved in ether. An addition of light petroleum precipitated 0·2 g of ketone *XV*, m.p. 86—88°C. UV spectrum: λ_{max} 240 nm (log ε 4·30), 260 nm (3·83), 321 nm (3·54). IR spectrum (KBr): 709 and 720 (C_6H_5), 749, 757 and 769 (1,2-C_6H_4), 1 496 and 1 588 (Ar), 1 684 cm^{-1} (CO—Ar). For $C_{16}H_{14}OS$ calculated: 75·57% C, 5·55% H, 12·60% S; found: 75·44% C, 5·68% H, 12·43% S.

4-Phenyl-7-methyl-2,3-dihydro-4*H*-1-benzothiepin-5-one (*XVI*)

Acid *VI* (5·0 g) was added to polyphosphoric acid, prepared from 40 g 85% phosphoric acid and 35 g phosphorus pentoxide, and the mixture was stirred for 1 h at 150—160°C. After partial cooling, the mixture was decomposed with water and extracted with benzene. The red extract was washed with water and with 5% NaOH, dried and evaporated: 4·1 g crude product. Recrystallization from ethanol and acetone yielded the pure product: needles, m.p. 167—169°C. UV spectrum: λ_{max} 241 nm (log ε 4·33), 262 nm (3·87), 329 nm (3·52). IR spectrum: 710, 730 and 760 (C_6H_5), 835, 899 (1,2,4-C_6H_3), 1 600 (Ar), 1 682 cm^{-1} (CO—Ar). For $C_{17}H_{16}OS$ (268·3) calculated: 76·10% C, 6·01% H, 11·93% S; found: 76·15% C, 6·07% H, 11·88% S.

Benz[*b*]indeno[2,1-*d*]thiopyran (*XVII*)

Acid *V* (5·0 g) was added at 150—160°C to polyphosphoric acid prepared from 40 g 85% phosphoric acid and 40 g phosphorus pentoxide. The mixture was stirred at 150—160°C for 2·5 h. It turned intensely orange and the reaction was accompanied by a thiophenol smell. After partial cooling it was decomposed with 300 ml water, extracted with benzene, the extract was washed with water and with 5% NaOH and evaporated. A total of 3·1 g orange substance was obtained which was crystallized from a mixture of benzene and light petroleum or from acetone, m.p. 166—169°C. The molecular weight from mass spectrum is 234. UV spectrum (heptane): λ_{max} 210·5 nm (log ε 4·37), 229·5 nm (4·31), 248·5 nm (4·09), 284 nm infl. (4·58), 292 nm (4·75), 313·5 nm (4·07), 342·4 nm (4·01), 358·5 nm (3·87), 364·5 nm (3·89), 427 nm (3·63). IR spectrum: 751 (1,2-C_6H_4), 827, 851, 877, 939, 1 019, 1 039, 1 080, 1 130, 1 150, 1 207, 1 254, 1 350, 1 383, 1 448, 1 472, 1 542, 1 596 (Ar), 1 635 cm^{-1}. For $C_{16}H_{10}S$ (234·2) calculated: 82·04% C, 4·30% H, 13·66% S; found: 81·88% C, 4·43% H, 13·24% S.

4-Phenyl-7-methyl-2,3,4,5-tetrahydro-1-benzothiepin-5-ol (*XVIII*)

A solution of 6·0 g sodium borohydride and 1 g NaOH in 30 ml water was added dropwise under stirring to a solution of 30·0 g ketone *XVI* in a mixture of 600 ml ethanol and 200 ml benzene. The mixture was refluxed for 10 h, after cooling it was decomposed with dilute hydrochloric acid and extracted with benzene. The extract was washed with water, dried, filtered with charcoal and evaporated. A total of 21·0 g oily product was obtained which, according to thin-layer chromatography on alumina, does not contain the starting ketone. The product is apparently a mixture of stereosiomers and was used for further work in the crude state.

4-Phenyl-7-methyl-2,3-dihydro-1-benzothiepin (*XXI*)

Acetic anhydride (15 g) and several drops sulfuric acid were added to a solution of 10·0 g alcohol *XVIII* in 100 ml acetic acid. The mixture was stirred for 3 h at 90—100°C. The volatile fractions were then evaporated at reduced pressure, the residue was dissolved in benzene, the solution was washed with water, filtered with charcoal and evaporated. A total of 8·2 g oil was obtained, which was chromatographed on alumina. Elution with light petroleum resulted in 3·8 g crystalline product, m.p. 49—50·5°C (acetic acid). UV spectrum: λ_{max} 219·5 nm (log ε 4·22), 261·5 nm (4·39), 289 nm (4·18). IR spectrum: 700 and 745 (C_6H_5), 819 and 873 (1,2,4-C_6H_3), 1 597 (Ar), 1 630 cm^{-1} (C=C—Ar). For $C_{17}H_{16}S$ (252·3) calculated: 80·92% C, 6·39% H, 12·68% S; found: 80·79% C, 6·54% H, 12·47% S.

4-Phenyl-5-(4-methylpiperazino)-7-methyl-2,3,4,5-tetrahydro-1-benzothiepin (*XX*)

Powdery anhydrous calcium chloride (15 g) was added to a solution of 13·5 g alcohol *XVIII* in 100 ml benzene and the suspension was saturated for 14 h with anhydrous HCl at room temperature. After adding charcoal, it was filtered and the filtrate was evaporated at reduced pressure at 30°C to dryness. A total of 13·5 g oily mixture of stereoisomeric chlorides *XIX* was obtained. The whole product was dissolved in 150 ml chloroform, 7·0 g 1-methylpiperazine and 6·5 g anhydrous potassium carbonate were added and the mixture was refluxed for 24 h. After cooling, charcoal was added, the mixture was filtered, and from the filtrate the basic product was extracted with excess HCl (1 : 5). Alkalinization of the acid aqueous solution with ammonium hydroxide liberated the base which was isolated by ether extraction. The extract was dried with K_2CO_3 and evaporated: 7·5 g (45%) crude oily base. Its neutralization with maleic acid in ethanol yielded di(hydrogenmaleate) monohydrate. After recrystallization from ethanol the compound melts at 135—145°C, the melt crystallizes again below 165°C and then melts at 188 to 191°C. For $C_{30}H_{38}N_2O_2S$ (602·7) calculated: 59·78% C, 6·36% H, 4·64% N, 5·33% S; found: 59·91% C, 6·20% H, 4·70% N, 5·60% S. Decomposition of a sample with the maleate by making alkaline liberated the base which was isolated by extraction with ether. NMR spectrum: δ 7·19 (singlet, 5 H of the phenyl protons), 6·70—7·40 (multiplet, 3 H of the remaining aromatic protons), 4·38 (doublet, 1 H of the CH carrying the piperazine residue), 2·95—3·50 (multiplet, 1 H of the phenyl-carrying CH), 2·68 (triplet, 2 H of CH_2S), 2·25—2·38 (multiplet, 11 H of the CH_2 group of piperazine and Ar—CH_3), 2·13 (singlet, 3 H of NCH_3), 1·68 (quadruplet, 2 H of the remaining CH_2 group in the seven-membered ring).

1-Phenyl-4-(benzenesulfonyl)butyronitrile (*XXII*)

30% hydrogen peroxide (15 ml) was added dropwise over 30 min at 85—90°C to a solution of 10·0 g nitrile *III* in 100 ml acetic acid and the mixture was stirred for 2 h at 100°C. After cooling, it was diluted with water and the precipitated solid was filtered; 9·0 g (80%) crude product. Crystallization from ethanol yielded the pure product, m.p. 87—91°C. IR spectrum: 690, 700, 749, 769 (C_6H_5), 1159, 1310, 1329 (sulfone), 2248 cm^{-1} (CN). For $C_{16}H_{15}NO_2S$ (285·3) calculated: 67·36% C, 5·30% H, 4·91% N, 11·22% S; found: 66·89% C, 5·49% H, 4·95% N, 11·59% S.

1-Phenyl-4-(4-toluenesulfonyl)butyronitrile (*XXIV*)

Similarly to the preceding case, oxidation of *IV* yielded 56% sulfone *XXIV*, m.p. 98·5—100°C (ethanol). For $C_{17}H_{17}NO_2S$ (299·3) calculated: 68·21% C, 5·73% H, 4·68% N, 10·69% S; found: 67·83% C, 5·72% H, 4·39% N, 10·83% S.

1-Phenyl-4-(benzenesulfonyl)butyric Acid (*XXIII*)

Compound *XXII* (5·0 g) was heated for 1 h with a mixture of 25 ml water, 25 ml acetic acid and 25 ml sulfuric acid and the acid product was isolated in the usual way; 3·0 g (55%), m.p. 113 to 114°C (benzene). For $C_{16}H_{16}O_4S$ (304·3) calculated: 63·15% C, 5·30% H, 10·52% S; found: 62·97% C, 5·48% H, 10·73% S.

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