SYNTHETIC EXPERIMENTS AIMING AT 1,2,4,5-TETRAHYDRO--3-BENZOTHIEPIN DERIVATIVES

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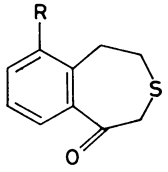
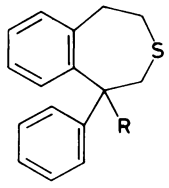
Some derivatives of 2,3,4,5-tetrahydro-1*H*-3-benzazepine proved interesting pharmacological properties, especially in the line of dopaminomimetic and antidopaminergic activity (cf. reference cited in literature[1]). This fact induced our interest in the structurally related and unknown 1,2,4,5-tetrahydro-3-benzothiepin derivatives leading to two preliminary synthetic experiments which are described in the present short paper.

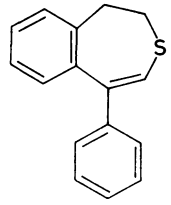
4,5-Dihydro-3-benzothiepin-1(2*H*)-one (*I*), which was obtained by cyclization of S-(2-phenylethyl)-2-mercaptoacetyl chloride according to ref.[2], was reacted with phenylmagnesium bromide in ether and gave in a high yield the tertiary alcohol *III*. Its dehydration by heating with a solution of hydrochloric acid in ethanol proceeded normally and afforded the crystalline *V* whose structure was confirmed by the UV and ^{1}H NMR spectra. Reduction of *III* with hydroiodic acid (mixture of boiling acetic acid, red phosphorus, iodine, and water) gave a homogeneous oily product which distilled without decomposition and whose analysis corresponded to the



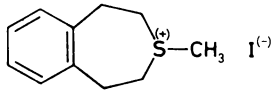
I, R = H
II, R = Cl



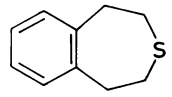
III, R = OH
IV, R = H



V



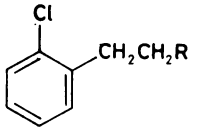
VI



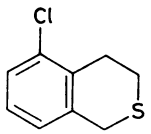
VII

elemental composition $C_{16}H_{16}S$, i.e. of the desired *IV*. Its reaction with methyl iodide afforded a crystalline sulfonium salt whose analysis did not correspond to the methiodide of *IV* but to a compound $C_{11}H_{15}IS$. This is the elemental composition of *VI* and this structure is supported by the mass spectrum. The compound is cleaved by heating and the spectrum (CI) showed the peaks with m/z 142, corresponding to methyl iodide, and 164, corresponding to *VII* (with the respective fragments). In the EI spectrum occurring peak with m/z 179 and 127 were interpreted as corresponding to the methylsulfonium ion $C_{11}H_{15}S$ and to the atom of iodine. We have no explanation of this strange cleavage of phenyl from the molecule but structure *IV* is considered doubtfull. The source of complications could be the carbonium cation which is evidently formed from *III* by abstraction of the hydroxyl anion on treatment with acidic reagents and which could undergo various transformations.

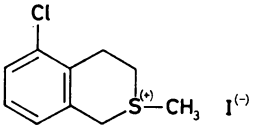
The second experiment aimed in the first line at the chloroketone *II*. It started from 2-(2-chlorophenyl)ethyl bromide[3] which was transformed to the thiol *VIII* via the hydrobromide of *IX*. Reaction of the sodium salt of *VIII* with sodium chloroacetate in aqueous sodium hydroxide at 100°C gave almost quantitatively the oily *X* which solidified to a low-melting crystalline compound (characterized by IR and ^{1}H NMR spectra). The oily product of reaction of *X* with thionyl chloride at 80 to 90°C, which could not be distilled without decomposition and therefore was used without purification and characterization, was considered to be the acid chloride *XI*. It was treated with aluminium chloride in 1,1,2,2-tetrachloroethane at room temperature in order to carry out the cyclization to *II*. A neutral and inhomogeneous oily product was obtained which was chromatographed on aluminium oxide. Some 90% of the product were eluted with the first benzene fractions and crystallized. It



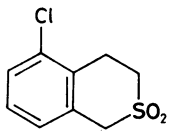
VIII, R = SH
IX, R = SC(=NH)NH$_2$
X, R = SCH_2COOH
XI, R = SCH_2COCl



XII



XIII



XIV

was characterized by analysis and the mass spectrum as an oxygen-free substance C_9H_9ClS which was identified by the ^1H NMR spectrum as 5-chloro-3,4-dihydro--1*H*-2-benzothiopyran (5-chloroisothiochroman) (*XII*). The observed loss of CO can be explained by decarbonylation of the intermediate acylium cation. Such decarbonylation should be facilitated by the lower reactivity of the aromatic acceptor (cf. our papers[4,5] and references therein). In our case, the meta standing atom of chlorine could be responsible for this lower reactivity. Compound *XII* reacted with methyl iodide normally and afforded the sulfonium salt *XIII*. Oxidation of *XII* with excessive hydrogen peroxide in acetic acid at 75–80°C gave the sulfone *XIV*.

EXPERIMENTAL

The melting points of analytical samples were determined in the Kofler block and were not corrected. The samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at a suitably elevated temperature. UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unican SP 8000 spectrophotometer, the IR spectra (in NUJOL, ν in cm^{-1}) were recorded with the Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (in $CDCl_3$, δ in ppm, J in Hz) with a CW-NMR TESLA BS 487C (80 MHz) spectrometer, and the mass spectra (m/z, %) with Varian MAT 44S (GC-MS) spectrometer. The homogeneity of the substances and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

1-Phenyl-1,2,4,5-tetrahydro-3-benzothiepin-1-ol (*III*)

Grignard reagent was prepared from 2·7 g Mg and 18·1 g bromobenzene in 50 ml ether, it was cooled to room temperature and treated under stirring over 1 h with a solution of 9·0 g *I* (ref.[2]) in 35 ml ether, and the mixture was refluxed for 3 h. After cooling it was decomposed under stirring with a solution of 10 g NH_4Cl in 30 ml water, the organic layer was separated and the aqueous layer was extracted with ether. The combined ethereal solutions were dried with Na_2SO_4, filtered, and evaporated. The residue was triturated with hexane and the crystalline product was filtered; 11·3 g (88%) of *III*, m.p. 93°C (benzene–hexane). IR spectrum: 700, 758 (4 and 5 adjacent Ar–H); 1 071 (C–OH); 1 485, 1 600, 3 020, 3 045, 3 070, 3 090 (Ar); 3 435, 3 465 (OH). ^1H NMR spectrum: 2·60–3·70 m, 7 H ($CH_2CH_2SCH_2$ and OH); 7·25 m, 9 H (ArH). For $C_{16}H_{16}OS$ (256·4) calculated: 74·96% C, 6·29% H, 12·51% S; found: 74·81% C, 6·42% H, 12·55% S.

1-Phenyl-4,5-dihydro-3-benzothiepin (*V*)

A solution of 1·0 g *III* in 6 ml warm ethanol was treated with 0·4 ml hydrochloric acid and the mixture was stirred and heated for 30 min to 70–80°C. After standing overnight, the crystallized solid was filtered, washed with 15 ml aqueous ethanol, and dried, 0·8 g (86%) of *V*, m.p. 117 to 118°C (ethanol). UV spectrum: 244 (4·16), infl. 260 (3·91), 311 (3·83). ^1H NMR spectrum: 3·10 bt, 2 H ($ArCH_2$); 3·55 bt, 2 H (CH_2S); 6·75 s, 1 H (C=CH—S); 6·90–7·50 m, 9 H (ArH). For $C_{16}H_{14}S$ (238·3) calculated: 80·63% C, 5·92% H, 13·45% S; found: 80·69% C, 6·11% H, 13·34% S.

3-Methyl-1,2,4,5-tetrahydro-3-benzothiepinium Iodide (*VI*)

A mixture of 30 ml acetic acid, 4·0 g red P, and 1·7 g iodine was stirred for 20 min at room tem-

perature, a suspension of 20·0 g *III* in 40 ml acetic acid and 1·3 ml water was added, and the mixture was refluxed for 7 h. It was filtered while hot, the filtrate was poured into a solution of 16 g Na_2SO_3 in 400 ml water and the mixture was allowed to stand overnight in the refrigerator. The separated oil was extracted with benzene, the extract was washed with 10% $Na_2S_2O_3$, filtered, and the filtrate was evaporated in vacuo. The oily residue was distilled in vacuo; 17·4 g (93%) of $C_{16}H_{16}S$ (*IV*), b.p. 175–178°C/0·13 kPa. For $C_{16}H_{16}S$ (240·4) calculated: 79·95% C, 6·71% H, 13·34% S; found: 79·86% C, 7·01% H, 13·58% S.

A mixture of 3·0 g of the oily product and 10 ml methyl iodide was allowed to stand at room temperature for 2 weeks, the separated solid was filtered, washed with ether, and dried; 3·65 g of *VI*, m.p. 151–152°C (ethanol). Mass spectrum (CI): 164 ($C_{16}H_{16}S$, i.e. *VII*, 43), 149 (100), 142 (CH_3I, 80), 117 (18), 116 (19), 115 (55), 91 (18), EI: 179 ($C_{11}H_{15}S$, 3), 127 (I, 30). IR spectrum: 772 (4 adjacent Ar–H). For $C_{11}H_{15}IS$ (306·2) calculated: 43·15% C, 4·94% H, 41·44% I, 10·47% S; found: 42·93% C, 5·03% H, 41·38% I, 10·67% S.

2-(2-Chlorophenyl)ethanethiol (*VIII*)

A mixture of 104 g 2-(2-chlorophenyl)ethyl bromide[3], 36 g thiourea, and 400 ml ethanol was stirred and refluxed for 6 h. After standing overnight in the refrigerator, the solid product was filtered, washed with 150 ml of a mixture of ethanol and ether (1 : 1), and dried; 106·2 g, m.p. 172°C. Processing of the mother liquor gave further 9·3 g of product, the total yield being 115·5 g (83%) of S-(2-(2-chlorophenyl)ethyl)isothiourea hydrobromide (*IX*.HBr). For $C_9H_{12}BrClN_2S$ (295·6) calculated: 36·56% C, 4·09% H, 27·03% Br, 12·00% Cl, 9·48% N, 10 84% S; found: 36·85% C, 4·00% H, 27·13% Br, 11·82% Cl, 9·70% N, 10·87% S.

A mixture of 115 g *IX*.HBr and 450 ml water was heated under reflux to 100°C, under nitrogen and with stirring it was treated with a solution of 17 g 95% NaOH in 25 ml water and refluxing was continued for 30 min. After cooling to room temperature a solution of 5 ml H_2SO_4 in 35 ml water was added dropwise, the mixture was stirred for 10 min by a stream of nitrogen and extracted with a mixture of benzene and ether. The extract was dried with Na_2SO_4, filtered, the filtrate was evaporated and the remaining crude *VIII* was distilled in a stream of nitrogen; 60·4 g (90%), b.p. 119–120°C/1·6 kPa. Because of the extremely pungent smell of this product, its characterization proved very uneasy and the product was used in the further step in the crude state.

S-(2-(2-Chlorophenyl)ethyl)-2-mercaptoacetic Acid (*X*)

To a stirred solution of 42 g NaOH in 85 ml water there were added dropwise under stirring 60·5 g of crude *VIII*, the mixture was stirred under nitrogen for 5 min at 10°C, then a solution of 33 g chloroacetic acid and 15 g NaOH in 70 ml water was added over 50 min at 10°C (nitrogen) and the mixture was stirred and heated to 95°C for 50 min. After cooling to 20°C the suspension was treated under cooling with 110 ml hydrochloric acid, and the mixture was extracted with ether. The extract was dried (Na_2SO_4), filtered, and the filtrate was evaporated. The residue was diluted with 120 ml benzene which was thereafter distilled off for removing water. The oily residue (80·4 g, almost quantitative) represented the practically homogeneous *X*. It crystallized after trituration with a mixture of benzene and hexane, m.p. 41–42°C (benzene–hexane). IR spectrum: 745 (4 adjacent Ar–H); 940, 1 295, 1 710, 2 560, 2 670, infl. 3 200 (COOH), ^{1}H NMR spectrum: 3·00 m, 4 H ($ArCH_2CH_2S$); 3·30 s, 2 H (SCH_2CO); 7·20 m, 4 H (ArH); 11·75 s, 1 H (COOH). For $C_{10}H_{11}ClO_2S$ (230·7) calculted: 52·06% C, 4·81% H, 15·37% Cl, 13·90% S; found: 51·97% C, 4·73% H, 15·52% Cl, 13·88% S.

5-Chloro-3,4-dihydro-1*H*-2-benzothiopyran (*XII*)

A mixture of 80 g *X* and 63 g $SOCl_2$ was stirred and heated to 80—90°C until the formation of gaseous products (SO_2, HCl) was finished. The excess of $SOCl_2$ was completely distilled off in vacuo and the oily residue (86 g) which was considered to be the crude *XI*, was used in the further step. It was dissolved in 100 ml 1,1,2,2-tetrachloroethane and the solution was added dropwise to a stirred mixture of 97 g $AlCl_3$ and 130 ml 1,1,2,2-tetrachloroethane over 100 min at 1—5°C. The mixture was stirred for 7·5 h at room temperature and was allowed to stand overnight. Then it was poured into 500 g ice, the mixture was heated for 30 min to 60°C, cooled, and separated. The organic layer was washed with 200 ml 10% Na_2CO_3 and the solvent was evaporated in vacuo. The residue (71 g of oil) was dissolved in benzene and the solution was chromatographed on 1 kg of neutral Al_2O_3 (activity II). Benzene eluted in the first fractions 63 g (98%) of crystalline *XII*, m.p. 64—65°C (ethanol). Mass spectrum: 184 (M^+, C_9H_9ClS, 99), 169 (29), 151 (21), 149 (100), 138 (76), 115 (49), 103 (58), 77 (29). UV spectrum: 263 (3·60), 300 (2·80), 340 (2·52). IR spectrum (KBr): 783 (3 adjacent Ar–H); 1 562, 1 589, 3 010, 3 050 (Ar). ^{1}H NMR spectrum: 2·95 m, 4 H ($ArCH_2CH_2S$); 3·70 s, 2 H ($ArCH_2S$); 6·80—7·40 m, 3 H (ArH). For C_9H_9ClS (184·7) calculated: 58·53% C, 4·91% H, 19·20% Cl, 17·36 S; found: 58·73% C, 4·79% H, 19·20% Cl, 17·36% S.

5-Chloro-2-methyl-3,4-dihydro-1*H*-2-benzothiopyranium Iodide (*XIII*)

Compound *XII* (1·0 g) was dissolved in 5 ml methyl iodide and the solution was allowed to stand at room temperatue for 20 days. The excess of methyl iodide was evaporated in vacuo, the residue was mixed with 10 ml acetone and the solid product was filtered. It was washed with acetone and dried in vacuo; 1·3 g (74%) of *XIII*, m.p. 167—170°C. Analytical sample, m.p. 173—175°C (methanol). For $C_{10}H_{12}ClIS$ (326·6) calculated: 36·77% C, 3·70% H, 10·86% Cl, 38·86% I, 9·81% S; found: 36·80% C, 3·73% H, 11·16% Cl, 38·89% I, 10·11% S.

5-Chloro-3,4-dihydro-1*H*-2-benzothiopyran 2,2-Dioxide (*XIV*)

A mixture of 10·3 g *XII*, 100 ml acetic acid, and 35 ml 30% H_2O_2 was stirred and heated for 6 h to 75—80°C. After cooling to 40°C the mixture was poured to 1·2 l ice-cold water, it was stirred for 40 min and allowed to stand overnight at room temperature. The precipitated product was filtered, the filtrate was extracted with chloroform, the extract was processed and the residue was combined with the filtered part of the product. Crystallization from benzene gave 10·7 g (89%) of *XIV* m.p. 158—159°C (benzene). IR spectrum: 775 (3 adjacetn Ar–H); 1 123, 1 295, 1 320 (SO_2); 1 567, 1 591, 3 070 (Ar). ^{1}H NMR spectrum: 3·30 m, 4 H ($ArCH_2CH_2SO_2$); 4·20 s, 2 H ($ArCH_2SO_2$); 6·80—7·40 m, 3 H (ArH). For $C_9H_9ClO_2S$ (216·7) calculated: 49·88% C, 4·19% H, 16·36% Cl, 14·80% S; found: 49·64% C, 4·29% H, 16·64% Cl, 14·99% S.

The spectra were recorded and interpreted by Drs J. Holubek, E. Svátek, M. Ryska, I. Koruna, O. Matoušová, Mrs A. Hrádková, and Mrs Z. Janová. The elemental analyses were carried out by Mrs J. Komancová, Mrs V. Šmídová, Mrs A. Svatošová, and Mr M. Čech.

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