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## Indole Compounds. VI\*. Syntheses of Indole Thioethers by Direct Cyclization of Phenylhydrazine Hydrochlorides and Aliphatic Acetals Under Mild Conditions

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The ease of Fischer indolization, into several types of indole thioethers, with respect to the nature of the starting arylhydrazine and acetal components in 25% acetic acid at 80° is investigated. 3-Benzyloxy- and 3,4-dimethyl-phenylhydrazine hydrochlorides indolize with 4-benzylthiobutanal diethyl acetal into isomeric mixtures of 4- and 6-benzyloxy-, and 4,5- and 5,6-dimethyl-3-(2-benzylthioethyl) indoles (I and II, and III and IV, respectively); separation and structure assignment of the isomers is reported. Debenzylation of III and IV gives the corresponding 3-(2-mecaptoethyl)- and bis[3-(2-thioethyl)indoles]. Indolization of 3-benzylthiopropional diethyl acetal with several arylhydrazine hydrochlorides results in the formation of the corresponding 3-benzylthiomethylindoles in low yield; a subsequent decomposition of the products under the conditions of the indolization reaction has been established. 4-Benzylthiophenylhydrazine hydrochloride and 4-aminobutanal diethyl acetal cyclize smoothly into 5-benzylthiotryptamine hydrochloride.

In Part V of this series<sup>1</sup> it has been reported that phenylhydrazine hydrochlorides bearing an electron-releasing group in *para*- or less favourably in the *ortho*- position indolize under mild conditions (25% acetic acid, 80°) with 4-benzylthiobutanal diethyl acetal into the corresponding 3-(2-benzylthioethyl)indoles. Our previous experiments have shown<sup>2</sup> that under the conditions used, the determinant factor for a successful reaction is the nature of the phenylhydrazine moiety (with 2,4-dinitro-, unsubstituted- and 3-benzyloxy- phenylhydrazine hydrochlorides the reaction failed<sup>2,3</sup>), and that the aliphatic acetal component (unsubstituted, 4-amino-, *N,N*-disubstituted-4-amino-, 3- and 4-acylamino- or 3-cyano-) does not affect substantially the relative ease of indolization. The results were rationalized<sup>2</sup> by assuming that in this Fischer indole synthesis using mild catalytic conditions the substituent on the phenylhydrazine moiety should exert an appreciable contribution to the formation and polarizability of the enhydrazine intermediate<sup>4</sup>.

The fact that the unsubstituted phenylhydrazine hydrochloride indolized with 4-benzylthiobutanal diethyl acetal into the corresponding indole thioether<sup>1</sup> in a 45% yield suggests that the sulphur atom in the acetal moiety has an influence on the polarizability of the enhydrazine moiety. In the present work the relative ease of indolization into indole thioethers with respect to the

\* Part V: Lit. cit.<sup>1</sup>

nature of the starting arylhydrazine and acetal components has been studied, and the syntheses, isomer separations and characterization of several types of indole thioethers are reported.

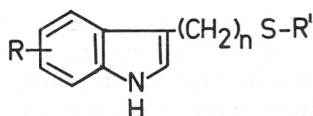
While indolization of 3-benzyloxyphenylhydrazine hydrochloride with several acetals has been unsuccessful<sup>2,3</sup>, identical treatment of this aryl hydrazine with 4-benzylthiobutanal diethyl acetal gave a mixture of 4- and 6-benzyloxy-3-(2-benzylthioethyl)indoles (I and II) in low yield. The isomers were separated by column chromatography, and their structures were assigned on the basis of correlation with various 4- and 6-substituted indole isomers as well as from spectroscopic data.

The relative differences in yields<sup>5,6</sup> and melting points<sup>6,7</sup> suggested the higher melting isomer I (m. p. 90—91°, 4% yield) as the 4- and the lower melting isomer II (m. p. 79—81°, 10% yield) as the 6-substituted 3-(2-benzylthioethyl)indole. The specific colour reagent<sup>8</sup> for 6-hydroxy- and 6-alkoxyindoles gave a positive colour reaction only with the lower melting isomer II. Further evidence for the structural assignments for I and II was obtained from the following spectroscopic data: a) in the ultraviolet spectrum the isomer II absorbs at higher wavelengths than I which is consistent with the general observation<sup>6,7,9</sup> that the ultraviolet spectra of 6-substituted indoles show a bathochromic shift relative to those of their 4-substituted isomers; b) the infrared spectrum of isomer II shows small but well defined bands at 1631, 1580, 1500 and 1462 cm.<sup>-1</sup> which are claimed<sup>10</sup> as a characteristic group of bands for 6-methoxyindoles; c) the nuclear magnetic resonance spectra of both isomers show clearly the expected signals for O- and S-methylene and ethylene protons but in the aromatic proton region they are not very informative owing to the presence of signals caused by aromatic protons of the two protecting benzylic groups. However, the fact that in the spectrum of the higher melting isomer I, one benzene proton of the indolic ring appears separated from the others as a pair of doublets ( $J = 1.5$  and  $6.5$  Hz) at higher field than H-2 while in the spectrum of isomer II, H-2 and two benzene protons overlap and fall into an unresolvable multiplet, could be explained by the shielding effect of the benzyloxy substituent: substitution in position 4-should result in an upfield shift of H-5 while in the case of the 6-benzyloxy isomer both adjacent protons, H-5 and H-7 should be shifted to a higher field.

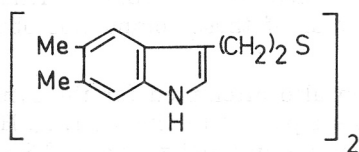
The indolization of 3,4-dimethylphenylhydrazine hydrochloride and 4-benzylthiobutanal diethyl acetal resulted in an isomeric mixture of 4,5- and 5,6-dimethyl-3-(2-benzylthioethyl)indoles (III and IV) in high yield, thus indicating that the positive inductive effect of the two methyl groups in the aryl moiety enhances the indole ring formation. However, the separation of the two isomers proved to be rather tedious. On thin-layer chromatography (TLC) the isomeric mixture behaved as a single spot material in all the solvents tried and was discernible only by a different shade of colour developed with Ehrlich reagent. Only after repeated alumina column chromatography followed by fractional crystallisation was a clean separation of the greatest part of the isomeric mixture achieved, the yields on the pure 4,5-isomer III and 5,6-isomer IV obtained in this manner being 14 and 21%, respectively.

The UV and IR spectra of the two isomers show only small differences which are insufficient for an unequivocal structure assignment, but conclusive evidence for assignment was obtained from the nuclear magnetic

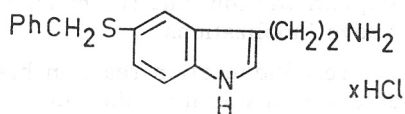
resonance spectra. The spectrum of the isomer III reveals two magnetically nonequivalent methyl groups appearing in  $\text{CDCl}_3$  and  $\text{CCl}_4$  at  $\tau$  7.50 and 7.67, and at  $\tau$  7.62 and 7.74, respectively, whereas in the spectrum of IV the protons of both methyl groups give rise to a sharp singlet appearing in  $\text{CDCl}_3$  and  $\text{CCl}_4$  at  $\tau$  7.67 and  $\tau$  7.74, respectively. The paramagnetic shift of one methyl group has been ascribed to the ring current effect<sup>11</sup> the magnitude of which should be higher in position 4- than in position 6- of the indole ring. Furthermore, the two aromatic protons of the benzene moiety give rise in the spectrum of IV to two separate singlets, thus indicating that they are in the *para*- relationship to each other (the peak at higher field may be assigned to H-7 which due to the shielding effect of the adjacent indolic nitrogen group would be expected<sup>12</sup> to appear at higher field than H-4) whereas in III the two benzene protons, give rise to one peak (the absence of the *ortho*- coupling suggests that this is a deceptively simple spectrum<sup>11</sup> in which the two hydrogens have fortuiously the same chemical shift).



	R	R'	n
I	4—OCH <sub>2</sub> Ph	CH <sub>2</sub> Ph	2
II	6—OCH <sub>2</sub> Ph	CH <sub>2</sub> Ph	2
III	4,5- <i>di</i> -Me	CH <sub>2</sub> Ph	2
IV	5,6- <i>di</i> -Me	CH <sub>2</sub> Ph	2
V	5,6- <i>di</i> -Me	H	2
VII	4,5- <i>di</i> -Me	H	2
VIII	H	CH <sub>2</sub> Ph	1
IX	5—OCH <sub>2</sub> Ph	CH <sub>2</sub> Ph	1
X	5—OMe	CH <sub>2</sub> Ph	1



VI



XI

Debenzylation of the 5,6- isomer IV with sodium in liquid ammonia yielded a mixture of 5,6-dimethyl-3-(2-mercaptoethyl)indole (V) and bis-[5,6-dimethyl-3-(2-thioethyl)indole] (VI) which were separated by column chromatography and characterized spectroscopically.

Analogous debenzoylation of the 4,5- isomer III resulted in the isolation of 4,5-dimethyl-3-(2-mercaptoethyl)indole (VII), the NMR spectrum of which proved to be consistent with the proposed structure. The corresponding disulphide of VII was detected in the reaction mixture by TLC but, owing to the lack of material, its isolation was not attempted. On paper chromatography

in basic solvents the thiols V and VII, as already observed<sup>1</sup> for this class of compounds, undergo oxidation to the corresponding disulphides. The two types of compounds have identical  $R_f$  values but they give different colours with Ehrlich reagent.

In order to investigate whether the direct indolization under mild conditions could be extended to 3-benzylthiomethylindoles, the indolization of 3-benzylthiopropional diethyl acetal with several phenylhydrazine hydrochlorides was attempted. Jardine and Brown<sup>13</sup> prepared by a similar method 3-ethylthioindole, (*i. e.* the thioether with sulphur directly linked to the pyrrole part of the ring) by indolizing ethylthioacetaldehyde diethyl acetal and phenylhydrazine in acetic acid in the presence of boron trifluoride as the catalyst. 3-Benzylthiomethylindole has been already described by Poppelsdorf and Holt<sup>14</sup> who synthesized the compound by two routes; one involving the condensation of indole, formaldehyde and benzylthiol in acetic acid which gave the thioether in a 14% yield, while a 87% yield was achieved by fusion of gramine and benzylthiol.

Under our reaction conditions the expected 3-benzylthiomethylindoles VIII, IX and X were formed in very low yields from the corresponding arylhydrazines. The reaction mixture darkened considerably, and TLC revealed several indolic spots some of which were negative on the sulphur test. Column chromatography of the reaction products on alumina resulted in the isolation of the pertinent indole thioether together with benzylthiol and dibenzyl-disulphide; the latter two compounds accounting for up to 25% of the initial amount of the acetal used in the reaction. The remaining indolic products decomposed subsequently during the separation procedure and were not further investigated.

When pure crystalline VIII, IX and X, respectively, were subjected to the conditions of the indolization reaction, TLC revealed the subsequent appearance of several indole-positive spots with  $R_f$  values identical to those detected in the indolization reaction, and benzylthiol and dibenzyl-disulphide. The easiness by which in acid media 3-benzylthiomethylindoles undergo fission of the C—S bond at the methylene group linked to the aromatic ring may partly explain the low but rather similar yields of these compounds obtained in the above indolizations.

The direct indolization reaction has been also attempted for the synthesis of thioethers with sulphur linked to the benzene part of the indole ring. Horner and Skinner<sup>15</sup> synthesized 5-benzylthiotryptamine by indolization of 2,3-piperidone-3-(4'-benzylthio)phenylhydrazone which was obtained through the Japp-Klingemann reaction with subsequent hydrolysis followed by decarboxylation of the product. The smooth reaction by which we obtained 5-benzylthiotryptamine (XI) from 4-benzylthiophenylhydrazine hydrochloride and 4-aminobutanal diethyl acetal under standard conditions indicates that the electron-donating ability of sulphur in the *para*-benzylthio group of the aryl moiety exerts a qualitatively similar influence to that of the corresponding alkoxy substituents. Since 4-benzylthiophenylhydrazine hydrochloride proved to be an easily accessible compound, the above reaction is a convenient route for the synthesis of indole thioethers which have the sulphur atom linked directly to the C-5 of the ring.

## EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 137 infrared spectrophotometer. UV spectra were recorded in ethanol solutions (10<sup>-4</sup> mole/l.) on a Beckmann D. U. G. 2400 spectrophotometer. NMR spectra were obtained in the solvent specified, using a Varian A-60A spectrometer, chemical shifts refer to an internal standard of tetramethylsilane ( $\tau$  10.00) and coupling constants ( $J$ ) are measured in Hz. Thin-layer chromatography (TLC) was carried out on chromatoplates of silicagel G (E. Merck) using the solvent system specified and the components were detected with: a) Ehrlich reagent (2% *p*-dimethylaminobenzaldehyde in 5% hydrochloric acid), b) 10% sulphuric acid, c) iodo-platinate reagent, d) acidic diazo reagent<sup>8</sup>. Column chromatography was conducted on alumina (E. Merck, neutral) and silicagel (E. Merck, 0.2—0.5 mm). Paper chromatography (descending, one-dimensional) was performed on Whatman No. 1 paper in: A. *n*-butanol-acetic acid-water (4 : 1 : 2), B. *iso*-propanol-ammonia-water (10 : 1 : 1), and the spots were developed with Ehrlich reagent.

3,4-Dimethylphenylhydrazine hydrochloride<sup>16</sup> was obtained in a considerably higher yield (70%) when instead of the original procedure, the general method given by Hunsberger *et al.*<sup>17</sup> for the preparation of arylhydrazines was used.

4-Benzylthioaniline hydrochloride was synthesized after Lantz *et al.*<sup>18</sup>. The ethanolic solution of the base was acidified with 15% hydrochloric acid, and the precipitated hydrochloride was recrystallized from ethanol; colourless crystals, m. p. 236—238°.

*Anal.* C<sub>13</sub>H<sub>14</sub>ClNS (251.771) calc'd.: C 62.01; H 5.64; N 5.56%  
found: C 62.14; H 5.55; N 5.41%

3-Benzylthiopropional diethyl acetal<sup>19</sup> was prepared from 3-benzylthiopropional<sup>20</sup> and triethyl orthoformate according to Fischer and Baer<sup>21</sup>; colourless oil, 67% yield, b. p. 106—108°/0.15 mm.

*Anal.* C<sub>14</sub>H<sub>22</sub>O<sub>2</sub>S (254.38) calc'd.: C 66.10; H 8.72%  
found: C 66.29; H 8.68%

## 4-Benzylthiophenylhydrazine hydrochloride

To finely powdered 4-benzylthioaniline hydrochloride (8 g., 31.7 mmoles) in 62 ml. of water and 92 ml. of conc. hydrochloric acid a solution of sodium nitrite (2.4 g., 35 mmoles) in 12 ml. of water was added dropwise under stirring at 0°. The solution was stirred for one hr. at 0—5°, filtered and cooled to —7°; stannous chloride hydrate (21.5 g., 31.7 mmoles) dissolved in 30 ml. of conc. hydrochloric acid was then added under stirring. The stirring was continued for one hr. at —7° and then for 3 hr. at 0°. The precipitate was filtered off, washed with small amounts of cold water and ether and dried. Recrystallization from hot ethanol followed by addition of ether gave colourless plates of 4-benzylthiophenylhydrazine hydrochloride; yield 5.5 g., 65%, m. p. 194—196°. A second crystallisation afforded the analytically pure sample, m. p. 196—198°.

*Anal.* C<sub>13</sub>H<sub>15</sub>ClN<sub>2</sub>S (266.793) calc'd.: C 58.52; H 5.67; Cl 13.29; N 10.50; S 12.02%  
found: C 58.67; H 5.51; Cl 13.15; N 10.38; S 11.97%

## 4- and 6-Benzylthioxy-3-(2-benzylthioethyl)indoles (I and II)

To a stirred solution of 3-benzylthioxyphenylhydrazine hydrochloride (1.126 g., 4.48 mmoles) in 40 ml. ethanol-acetic acid-water (30 : 25 : 25) 4-benzylthiobutanol diethyl acetal (1.203 g., 4.48 mmoles) dissolved in 10 ml. of ethanol was added dropwise at 80°. The stirring and heating was continued for 3 hr. and after cooling the reaction mixture was concentrated *in vacuo* to about one-third of the volume and extracted with benzene. The extracts were washed with aq. sodium hydrogen carbonate and water, dried over sodium sulphate and evaporated to dryness. The oily residue was dissolved in the minimum amount of benzene and chromatographed on an alumina (40 g.) column with petroleum ether-benzene (3 : 1) and (1 : 1). The first solvent (250 ml.) eluted 90 mg. of unidentified oils and the second (350 ml.) displaced subsequently (monitoring by TLC in benzene): a) the 4-substituted isomer I (48

mg.,  $R_f \sim 0.3$ , blue-violet spot with Ehrlich reagent), b) a mixture of isomers I and II (114 mg.), and c) the 6-substituted isomer II (92 mg.,  $R_f \sim 0.2$ , blue-green spot with Ehrlich reagent). The mixture b) was re-chromatographed on a silicagel (10 g.) column with benzene whereby a nearly complete separation of I from II was achieved. Fractions containing chromatographically homogenous isomer I were pooled evaporated to dryness, and the oily residue (60 mg., 3.6%) was recrystallized from benzene-petroleum ether yielding colourless crystals of 4-benzyloxy-3-(2-benzylthioethyl)indole (I), m. p. 90–91°. TLC, colour reaction with acidic diazo reagent: brown. IR spectrum (KBr): 3350s (NH), 1590m, 1510s, 1450m, 1370m, 1260vs, 1090s, 1080m, 778s, 768m, 745vs, 724m and 703s  $\text{cm}^{-1}$ . UV spectrum:  $\lambda_{\text{max}}$  232, 268–275, 278–285 and 293 ( $\log \epsilon$  3.89, 3.83, 3.80 and 3.77)  $\text{m}\mu$ . NMR spectrum ( $\text{CDCl}_3$ ):  $\tau = 2.05$ – $2.30$  broad s (1H, exchangeable with  $\text{D}_2\text{O}$ , NH), 2.58–2.80 m (11H), 3.02 d, 3.17 t (2H, H-2 partly obscured with one indolic proton), 3.42 d.d (1H,  $J_{5,7} = 1.5$ , and  $J_{5,6} = 6.5^{22}$ , H-5), 4.84 s (2H,  $\text{OCH}_2$ ), 6.47 s (2H,  $\text{SCH}_2$ ), 6.82–7.35 m (4H,  $\text{CH}_2\text{CH}_2$ ); ( $\text{CCl}_4$ ):  $\tau = 2.26$ – $2.56$  broad s (1H, NH, exchangeable with  $\text{D}_2\text{O}$ ), 2.63–2.88 m (10H), 3.13 t (2H, H-6 and H-7), 3.31 d (1H,  $J = 2.4$ , collapses to a singlet on deuteration, H-2), 3.57 d.d (1H,  $J_{5,7} = 1.5$  and  $J_{5,6} = 6.5$ , H-5), 4.90 s (2H,  $\text{OCH}_2$ ), 6.50 s (2H,  $\text{SCH}_2$ ), 6.92–7.50 m ( $\text{CH}_2\text{CH}_2$ ).

Anal.  $\text{C}_{24}\text{H}_{23}\text{NOS}$  (373.494) calc'd.: C 77.17; H 6.21; N 3.75; S 8.59%  
found: C 77.35; H 6.05; N 3.81; S 8.87%

Fractions containing the chromatographically homogenous isomer II were pooled, evaporated to dryness, and the oily residue (148 mg., 8.8%) was recrystallized from benzene-petroleum ether giving crystals of 6-benzyloxy-3-(2-benzylthioethyl)indole, m. p. 79–81°, mixed m. p. with I: 68–76°. TLC, colour reaction with acidic diazo reagent: immediate red, turning purple on standing. IR spectrum (KBr): 3380s (NH), 1630s, 1580w, 1500m, 1460vs, 1420m, 1300s, 1250 m, 1180vs, 1020vs, 808s, 778m, 768m, 747s, 708vs  $\text{cm}^{-1}$ . UV spectrum:  $\lambda_{\text{max}}$  237 and 292–296 ( $\log \epsilon$  3.97 and 3.70)  $\text{m}\mu$ . NMR spectrum ( $\text{CDCl}_3$ ):  $\tau = 2.10$ – $2.35$  broad s (1H, NH), 2.57–2.72 m (11H), 3.10 m (3H, indolic protons), 4.88 s (2H,  $\text{OCH}_2$ ), 6.26 s (2H,  $\text{SCH}_2$ ), 7.00 t, 7.22 t (4 H,  $\text{CH}_2\text{CH}_2$ ).

Anal.  $\text{C}_{24}\text{H}_{23}\text{NOS}$  (373.494) calc'd.: C 77.17; H 6.21; N 3.75; S 8.59%  
found: C 77.24; H 6.06; N 3.76; S 8.51%

#### 4,5- and 5,6- Dimethyl-3-(2-benzylthioethyl)indole (III and IV)

3,4-Dimethylphenylhydrazine hydrochloride (1.727 g., 10 mmoles) was brought into reaction with equimolar amount of benzylthiobutanal diethyl acetal in 80 ml. of acetic acid-ethanol-water (1:2:1) as described for I and II. After working up, the oily residue was dissolved in a minimum amount of petroleum ether-benzene (2:1) and chromatographed on an alumina (80 g.) column (55  $\times$  1.2 cm.) with petroleum ether; 15 ml. fractions were collected, and after the fraction 124 the system was changed to petroleum ether-benzene (3:1). The ratio of the isomers was estimated from chromatoplates run in petroleum ether-benzene-methanol (40:30:4),  $R_f \sim 0.7$  for the both isomers. Ehrlich reagent develops with the 5,6-isomer a yellow spot which turns navy-blue and with the 4,5-isomer it gives a yellow-brown spot which turns at a slower rate to violet-blue.

Fractions 45–80 (824 mg.) consisting predominantly of the 5,6-isomer IV were pooled, evaporated to dryness and crystallized from petroleum ether; colourless plates 469 mg., m. p. 57–59° deposited. Fractions 81–90 (332 mg.) containing the mixture of the two isomers in nearly equal ratio were combined with the above mother liquor and subjected to a second alumina column chromatography; after crystallization an additional crop of the 5,6-isomer (150 mg., total yield 21%) was obtained. Two further crystallizations afforded pure 5,6-dimethyl-3-(2-benzylthioethyl)indole (IV), m. p. 59–61°.  $R_f$  values: A 0.96; B 0.88. IR spectrum (KBr) 3370s (NH), 2870m ( $\text{CH}_2$ ), 864s, 808s, 768s, 702s. UV spectrum  $\lambda_{\text{max}}$ : 237 and 288 ( $\log \epsilon$  3.76 and 3.71)  $\text{m}\mu$ ,  $\lambda_{\text{infl}}$  297  $\text{m}\mu$ . NMR spectrum ( $\text{CDCl}_3$ ):  $\tau = 2.40$ – $2.55$  broad s (1H, NH), 2.73 s (5H, aromatic benzyl protons), 2.77 s (1H, partly overlapped with the singlet 2.73, ?H-4), 3.03 s (1H, ?H-7), 3.28 broad s (1H, H-2), 6.30 s (2H,  $\text{SCH}_2$ ), 7.09 t, 7.29 t (4H,  $\text{CH}_2\text{CH}_2$ ), 7.67 s (6H, 2 $\text{CH}_3$ ); ( $\text{CCl}_4$ ):  $\tau = 2.78$  s (6H, aromatic benzyl protons and NH), 2.88 s (1H, ?H-4), 3.10 s (1H, ?H-7), 3.32 d (1H,  $J = 2.4$ , collapses to singlet on deuteration, H-2), 6.38 s (2H,  $\text{SCH}_2$ ), 7.13 t, 7.38 t (4H,  $\text{CH}_2\text{CH}_2$ ), 7.74 s (6H, 2  $\text{CH}_3$ ).

*Anal.* C<sub>19</sub>H<sub>21</sub>NS (295.43) calc'd.: C 77.24; H 7.17; N 4.74; S 10.85%  
found: C 77.49; H 7.12; N 4.76; S 10.65%

Fractions 91—144 (999 mg.) containing the isomeric mixture with prevailing 4,5-isomer III and some coloured material were re-chromatographed on an alumina column whereby 455 mg. of chromatographically homogenous material, highly enriched in the 4,5-isomer III was obtained. Crystallization from petroleum ether afforded white needles (270 mg., 9.1%, m. p. 60—63°) of III and re-treatment of the remaining isomeric mixtures raised the yield on isomer III to 14%. A second crystallization gave pure 4,5-dimethyl-3-(2-benzylthioethyl)indole (III), m. p. 64—66°. *R<sub>f</sub>* values: *A* 0.96; *B* 0.88. IR spectrum (KBr) 3400s (NH), 2900m (CH<sub>2</sub>), 777s, 763s, 703s cm<sup>-1</sup>. UV spectrum: λ<sub>max</sub>: 237 and 275—290 (log ε 3.76 and 3.65) mμ, λ<sub>infl</sub>: 298 mμ. NMR spectrum (CDCl<sub>3</sub>): τ = 2.20—2.40 broad s (1H, exchangeable with D<sub>2</sub>O, NH), 2.70 s (5H, aromatic benzyl protons), 2.98 s (2H, H-6 and H-7), 3.10 d (1H, *J* = 2.2, collapses to singlet on deuteration, H-2), 6.27 s (2H, SCH<sub>2</sub>), 6.68—7.34 m (4H, CH<sub>2</sub>CH<sub>2</sub>), 7.50 s (3H, CH<sub>3</sub>), 7.67 s (3H, CH<sub>3</sub>); (CCl<sub>4</sub>): τ = 2.50—2.68 broad s (1H, NH), 2.90 s (5H, aromatic benzyl protons), 3.14 s (2H, H-6 and H-7), 3.36 d (1H, *J* = 2.4, H-2), 6.47 s (2H, SCH<sub>2</sub>), 7.01 t, 7.45 t (4H, CH<sub>2</sub>CH<sub>2</sub>), 7.62 s (3H, CH<sub>3</sub>), 7.74 s (3H, CH<sub>3</sub>).

*Anal.* C<sub>19</sub>H<sub>21</sub>NS (295.43) calc'd.: C 77.24; H 7.17; N 4.74; S 10.85%  
found: C 77.06; H 7.07; N 4.99; S 10.57%

5,6-Dimethyl-3-(2-mercaptoethyl)indole (V) and bis-[5,6-Dimethyl-3-(2-thioethyl)indole] (VI)

To 5,6-dimethyl-3-(2-benzylthioethyl)indole (IV, 715 mg., 2.42 mmoles) in 50 ml. of dry ammonia, sodium (0.4 g., 17.4 mmoles) was added under stirring at —40°. The mixture was stirred for additional one hr., ammonium chloride (930 mg., 17.4 mmoles) was added, and ammonia was evaporated by a stream of dry nitrogen. The residue was dissolved in 20 ml. of water, the mixture adjusted with 2*N* HCl to pH 5 and extracted with peroxide-free ether. After the removal of the solvent the oily residue was chromatographed on an alumina (18 g.) column, elution being carried with: petroleum ether, petroleum ether-benzene (3:1), benzene and chloroform; the displacement was followed by TLC in xylene. The thiol V emerged with the second solvent (with Ehrlich reagent yellow spot turning blue), and further elution displaced the disulphide VI (blue spot with Ehrlich reagent), contaminated with some coloured material.

Fractions containing chromatographically homogenous thiol V were pooled, evaporated to dryness, and the residue (260 mg., 53%) was crystallized from a small volume of petroleum ether; on cooling at —10° white crystals, m. p. 44—46° deposited. *R<sub>f</sub>* values: *A* 0.96; *B* 0.86; with Ehrlich reagent in *A* yellow spot turning blue-green on standing, in *B* immediate blue spot. IR spectrum (KBr): 3370s (NH), 2880m (CH<sub>2</sub>), 2530w (SH), 870s (1, 2, 4, 5 tetrasubstituted benzene) cm<sup>-1</sup>. NMR spectrum (CCl<sub>4</sub>): τ = 2.5—2.75 broad s (1H, NH), 2.78 s (1H, ?H-4), 3.13 s (1H, ?H-7), 3.30 d (1H, *J* = 2.4, H-2), 6.9—7.4 m (4H, CH<sub>2</sub>CH<sub>2</sub>), 7.72 s (6H, 2CH<sub>3</sub>), 8.79 t (1H, *J* = 7.5, SH).

*Anal.* C<sub>12</sub>H<sub>15</sub>NS (205.314) calc'd.: C 70.19; H 7.36; N 6.82; S 15.62%  
found: C 70.43; H 7.35; N 7.01; S 15.68%

Fractions containing the disulphide VI were pooled, evaporated to dryness and the residue was chromatographed on a silica gel (10 g.) column with benzene whereupon chromatographically homogenous VI (150 mg., 30.3%) was obtained. Recrystallization from benzene-petroleum ether afforded analytically pure compound, m. p. 158—159°. *R<sub>f</sub>* values: *A* 0.96; *B* 0.86; with Ehrlich reagent in both solvents blue spot. IR spectrum (KBr): 3350s (NH), 2860m (CH<sub>2</sub>), 870s (1, 2, 4, 5 tetrasubstituted benzene) cm<sup>-1</sup>.

*Anal.* C<sub>24</sub>H<sub>25</sub>N<sub>2</sub>S<sub>2</sub> (408.600) calc'd.: C 70.54; H 6.91; N 6.86; S 15.69%  
found: C 70.76; H 6.87; N 6.64; S 15.81%

4,5-Dimethyl-3-(2-mercaptoethyl)indole (VII)

4,5-Dimethyl-3-(2-benzylthioethyl)indole (III, 479 mg., 1.62 mmoles) was debenzylated in 30 ml. of dry ammonia with 0.25 g of sodium as described for III. After

working up, the residue was extracted with hot petroleum ether, the extracts were evaporated to dryness and the remaining solid was crystallized from benzene-petroleum ether; on cooling 104 mg. (31.3%) of crystals deposited. A second crystallization afforded the analytically pure 4,5-dimethyl-3-(2-mercaptoethyl)indole (VII), m. p. 108—110°.  $R_f$  values: A 0.96; B 0.86; with Ehrlich reagent in A yellow spot turning blue-green on standing, in B immediate blue-green spot. IR spectrum (KBr): 3370s (NH), 2880m ( $\text{CH}_2$ ) 2550w (SH), 809vs (1, 2, 3, 4 tetrasubstituted benzene)  $\text{cm}^{-1}$ . NMR spectrum ( $\text{CDCl}_3$ ):  $\tau$  = 2.1—2.4 broad s (1H, exchangeable with  $\text{D}_2\text{O}$ ), 2.98 s (2H, H-6 and H-7), 3.02 d (1H,  $J$  = 2.4, collapses to singlet on deuteration, H-2), 6.68—7.28 m (4H,  $\text{CH}_2\text{CH}_2$ ), 7.48 s (3H,  $\text{CH}_3$ ), 7.66 s (3H,  $\text{CH}_3$ ), 8.52 t (1H,  $J$  = 7.5, SH).

Anal.  $\text{C}_{12}\text{H}_{15}\text{NS}$  (205.314) calc'd.: C 70.19; H 7.36; N 6.82; S 15.62%  
found: C 69.97; H 7.14; N 7.04; S 15.64%

### Synthesis of 3-Benzylthiomethylindoles

3-Benzylthiopropional diethyl acetal was brought into reaction with the equimolar amount of the corresponding phenylhydrazine hydrochloride as described for I and II. After working up, the dark oily residue was fractionated on an alumina column; elution was carried with petroleum ether, petroleum ether-benzene (3:1), (1:1) and benzene. The first solvent displaced dibenzyldisulphide (m. p. 68—69°, no depression with a commercial sample) and benzylmercaptan (identified as the 2,4-dinitrophenyl derivative, m. p. 128—129°) while the following solvents displaced subsequently heterogenous oily material which on TLC revealed several Ehrlich positive spots. Fractions containing the predominant indolic spot were pooled and rechromatographed on a second alumina column whereby the chromatographically homogenous benzylthiomethylindoles were isolated as oils which crystallized on standing. For analysis they were recrystallized from benzene-petroleum ether.

### 3-Benzylthiomethylindole (VIII)

Yield: 5.5%, m. p. 67—69°, lit.<sup>14</sup>: 74°. UV spectrum:  $\lambda_{\text{max}}$  282 and 290 ( $\log \epsilon$  3.72 and 3.66  $\text{m}\mu$ ,  $\lambda_{\text{infl}}$  275  $\text{m}\mu$ . IR spectrum (KBr): 3400s (NH), 2900w ( $\text{CH}_2$ ), 750vs (mono- and o-substituted benzene)  $\text{cm}^{-1}$ .

Anal.  $\text{C}_{16}\text{H}_{15}\text{NS}$  (253.354) calc'd.: C 75.84; H 5.79; N 5.53; S 12.66%  
found: C 76.07; H 6.02; N 5.69; S 12.90%

### 5-Benzylloxy-3-benzylthiomethylindole (IX)

Yield: 14.5%, m. p. 72—74°. UV spectrum:  $\lambda_{\text{max}}$  278 ( $\log \epsilon$  3.72)  $\text{m}\mu$ ,  $\lambda_{\text{infl}}$  289, 295 and 308  $\text{m}\mu$ .

Anal.  $\text{C}_{23}\text{H}_{21}\text{NOS}$  (359.474) calc'd.: C 76.84; H 5.89; N 3.90; S 8.82%  
found: C 76.60; H 5.88; N 4.00; S 8.91%

### 5-Methoxy-3-benzylthiomethylindole (X)

Yield: 12%, m. p. 89—90°. UV spectrum:  $\lambda_{\text{max}}$  278 ( $\log \epsilon$  3.72)  $\text{m}\mu$ ,  $\lambda_{\text{infl}}$  296, 302 and 308  $\text{m}\mu$ .

Anal.  $\text{C}_{17}\text{H}_{17}\text{NOS}$  (283.384) calc'd.: C 72.03; H 6.05; N 4.94; S 11.31%  
found: C 71.78; H 5.79; N 5.15; S 11.38%

### 5-Benzylthiotryptamine hydrochloride (XI)

To 4-benzylthiophenylhydrazine hydrochloride (1.334 g., 5 mmoles) in 50 ml. of acetic acid-ethanol-water (1:2:1), a solution of 4-aminobutanal diethyl acetal (805 mg., 5 mmoles) in 10 ml. of the same solvent was added under stirring at 80° followed by conc. hydrochloric acid (1.29 ml., 15 mmoles). The reaction mixture was further stirred at 80° for 4 hr., concentrated *in vacuo* to about 10 ml. and left at 0° whereupon 5-benzylthiotryptamine hydrochloride (XI) precipitated; yield 711 mg., 44.6%. After recrystallization from ethanol-water the compound was analytically pure, m. p. 212—214°, lit.<sup>15</sup>: 213—214°.

Anal.  $\text{C}_{17}\text{H}_{19}\text{ClN}_2\text{S}$  (318.863) calc'd.: C 64.03; H 6.01; N 8.79%  
found: C 64.20; H 6.06; N 8.75%



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## IZVOD

**Indolski spojevi. VI. Sinteze indolskih tioetera direktnom ciklizacijom fenilhidrazin hidroklorida i alifatskih acetala pod blagim reakcionim uvjetima**

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Studirana je relativna lakoća stvaranja indolskih tioetera metodom Fischerove indolizacije pod blagim reakcionim uvjetima, i to s obzirom na prirodu arilhidrazinske i acetalne komponente. Arilhidrazin hidrokloridi (3-benziloksi- i 3,4-dimetil-) indoliziraju s 4-benziltiobutanal dietil acetalom u izomerne smjese 4- i 6-benziloksi-, odnosno 4,5- i 5,6-dimetil- 3-(2-benziltioetil)indole; izomeri su odvojeni i karakterizirani. Debenzilacijom dobiveni su odgovarajući 3-(2-merkaptioetil)indoli i bis[3-(2-tioetil)indoli]. Indolizacija 3-benziltiopropanal dietil acetala i arilhidrazin hidroklorida teče u mnogo slabijim iskorištenjima, nego analogne reakcije s 4-benziltiobutanal dietil acetalom; utvrđeno je da se pod uvjetima reakcije indolski produkt spontano raspada. Indolizacija 4-benziltiofenilhidrazin hidroklorida i 4-aminobutanal dietil acetala dala je u vrlo dobrom iskorištenju 5-benziltiotriptamin hidroklorid.

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