INDOLE DERIVATIVES

XXXIV.* THE FISCHER CYCLIZATION OF ARYLHYDRAZONES OF 3-METHYLTETRAHYDROTHIOPYRAN-4-ONE AND ITS S,S-DIOXIDE

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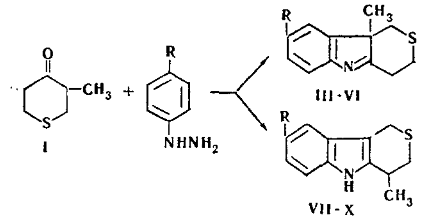
The Fischer cyclization of arylhydrazones of 3-methyltetrahydrothiopyran-4-one and its S,S-dioxide has been studied. It has been found that the direction of cyclization depends on the nature of the heteroatom of the ketonic component.

We have previously established that the Fischer cyclization of arylhydrazones of 2-(β-methoxycarbonylethyl)cyclohexanone and 3-(β-methoxycarbonylethyl)tetrahydrothiopyran-4-one takes place in the usual way, leading to indole and 3H-indole derivatives [1,2]. In contrast to this, the condensation of α-methylpyridin-4-ones and of 3-(β-ethoxycarbonylethyl)-1-methylpiperidin-4-one with arylhydrazines is accompanied by a rearrangement with the formation of the new system of 1,2,3,4-tetrahydropyrimido[3,4-a]indole [1,3].

In order to determine further whether the nature of the heteroatom affects the direction of cyclization, we selected as ketonic components in the Fischer reaction 3-methyltetrahydrothiopyran-4-one (I) and its S,S-dioxide (II). Compound I was obtained by the Dieckmann cyclization of β-(2-methoxycarbonylethylmercapto)-α-methylpropionic acid [4]. The constants of the ketone obtained corresponded to those given in the literature. However, a study of the product by gas-liquid chromatography showed that it consisted of a mixture of tetrahydrothiopyran-4-one and 3-methyltetrahydrothiopyran-4-one in a ratio of 1 : 1. We separated these ketones by freezing out the tetrahydrothiopyran-4-one from a solution in a mixture of ether and petroleum ether, followed by chromatography on alumina.

Compound II was obtained by the oxidation of ketone I with peracetic acid and it had a melting point differing from that given in the literature [4]. All the cyclization reactions were carried out with chromatographically pure ketones.

The hydrazine components used were p-tolyl-, p-methoxyphenyl-, p-ethoxycarbonylphenyl-, phenyl-, and naphthylhydrazines. Cyclization was carried out in the majority of cases without the isolation of the arylhydrazones. On cyclization, the arylhydrazones of ketones I and II can form both indoles and 3H-indoles.



III $R = H$; IV $R = CH_3$; V $R = OCH_3$; VI $R = COOC_2H_5$;
VII $R = H$; VIII $R = CH_3$; IX $R = OCH_3$; X $R = COOC_2H_5$

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*For Communication XXXIII, see [1].

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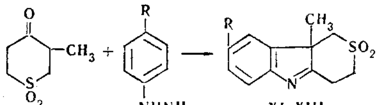
The condensation of I with p-tolyl- and phenylhydrazines was brought about by means of a 5-10% solution of hydrogen chloride in ethanol. In each case, a mixture of two substances in approximately equal proportions was obtained. The structure of substances VII and VIII as indole derivatives was confirmed by elementary analysis and IR and UV spectra. In the IR spectra of VII and VIII there are bands in the 3400 cm^{-1} region corresponding to the stretching vibrations of N–H bonds. The UV spectra of these compounds each have the absorption maximum at 275-280 nm that is characteristic for indoles. The 3H-indole structure of III and IV was confirmed by the capacity of these substances for forming hydrochlorides, by the absence of the characteristic vibrations of a N–H bond from the IR spectra, and by their UV spectra. The most favorable conditions for this cyclization of I with p-methoxyphenylhydrazine proved to be boiling the hydrochloride of the hydrazine and I in absolute ethanol. This gave a mixture of the two substances IX and V with yields of 58 and 15%, respectively, i.e., in this case the reaction is directed mainly to the formation of the indole IX. The use of 15-20% ethanolic solutions of hydrogen chloride or of other cyclizing agents for cyclization led to pronounced resinification of the reaction mixture and to a fall in the yields of the indole and the 3H-indole.

We performed the cyclization of the p-ethoxycarbonylphenylhydrazone of ketone I under various conditions. On cyclization with a 28% solution of hydrogen chloride in ethanol and on cyclization in benzene with the passage of hydrogen chloride, ~15% of the indole X and ~43% of the 3H-indole VI were formed. Cyclization of the hydrazone in concentrated hydrochloric acid led to the indole X, the corresponding 3H-indole not being formed under these conditions.



II

XI-XIII

XI R = H; XII R = CH_3; XIII R = COOH

The cyclization of ketone II with phenyl- and p-tolylhydrazines was effected by boiling the components with 25% ethanolic hydrogen chloride. The cyclization of the p-ethoxycarbonylphenylhydrazone of ketone II was carried out in concentrated hydrochloric acid.

In each case, only one substance was obtained. The 3H-indole structure of compounds XI–XIII was confirmed by their capacity for forming hydrochlorides, and also by their IR and UV spectra. The IR spectra of the 3H-indoles XI–XIII lacked the band of the vibrations of NH group in 3300-3500 cm^{-1} region. The UV spectra of these compounds each have an absorption maximum in the ~260 nm region.

Thus, we were able to observe an anomalous course of the condensation of aryl hydrazones of 3-substituted ketones only in the case of ketones of the piperidin-4-one series [1,3]. Later we hope to determine whether this rearrangement [1,3] is caused by the strong electron-accepting influence of the protonated amino group of the heterocycle or, conversely, by the considerable electron-donating effect of the nonprotonated amino group which exists in certain amounts in the acid medium used for performing the reaction.

EXPERIMENTAL

4-Methyl-1,3,4,5-tetrahydrothiopyrano[4,3-b]indole (VII) and 9b-Methyl-3,4-dihydro-1H-thiopyrano-[4,3-b]indole (III). A mixture of 1.3 g (0.01 mole) of 3-methyltetrahydrothiopyran-4-one (I) and 1.37 g (0.095 mole) of phenylhydrazine hydrochloride was heated in 12 ml of about 10% ethanolic hydrogen chloride for 30 min and was then poured into water and left overnight. The precipitate was filtered off, giving 0.32 g (15.2%) of the indole (VII), mp 88-89°C (from benzene and heptane). Found %: N 7.07; S 15.98. $C_{12}H_{13}NS$. Calculated %: N 6.89; S 15.77. IR spectrum (in paraffin oil): 3400 cm^{-1} (NH). UV spectrum, λ_{max}, nm (log ε): 226 (4.72); 282-284 (3.99).

The acid solution was made alkaline with potassium carbonate solution and extracted with ether, and the extract was washed with water and dried with magnesium sulfate. From the ethereal solution the hydrochloride of the 3H-indole III was precipitated, and this was converted into the base. Yield 0.58 g (28%), mp 82.5-83.5°C (from petroleum ether and a drop of diethyl ether). Found %: N 6.78; S 15.78. $C_{12}H_{13}NS$. Calculated %: N 6.89; S 15.77. UV spectrum, λ_{max}, nm (log ε): 254-260 (3.86).

Hydrochloride of 3H-indole III, found %: Cl 14.57; S 12.96. $C_{12}H_{13}NS \cdot HCl$. Calculated %: Cl 14.66; S 13.30.

4,8-Dimethyl-1,3,4,5-tetrahydrothiopyrano[4,3-b]indole (VIII) and 8,9b-Dimethyl-3,4-dihydro-1H-thiopyrano[4,3-b]indole (IV). A mixture of 1 g (0.0075 mole) of ketone I and 1.1 g (0.007 mole) of p-tolylhydrazine hydrochloride was heated in 15 ml of 5% ethanolic hydrogen chloride for 1 h, poured into water, and left overnight. Then the precipitate was filtered off, giving 0.44 g (29%) of the indole VIII, mp 144-145°C (from absolute ethanol). Found %: N 6.49; S 14.91. $C_{13}H_{15}NS$. Calculated %: N 6.45; S 14.75. IR spectrum (in oil): 3400 cm^{-1} (NH). UV spectrum, λ_{max}, nm (log ε): 228 (4.56); 284-288 (3.86).

The acid solution was made alkaline with potassium carbonate and extracted with ether, the ethereal solution was washed with water and dried with magnesium sulfate, and the solvent was distilled off to give 0.48 g (28%) of the 3H-indole IV, mp 102-103°C (from heptane). Found %: N 6.28; S 14.78. $C_{13}H_{15}NS$. Calculated %: N 6.45; S 14.75. UV spectrum: λ_{max}, nm (log ε): 258-260 (3.90).

Hydrochloride of the 3H-Indole IV, mp 138-140°C. Found %: Cl 13.37; N 5.67; S 12.45. $C_{13}H_{15}NS \cdot HCl$. Calculated %: Cl 13.97; N 5.52; S 12.63.

8-Methoxy-4-methyl-1,3,4,5-tetrahydrothiopyrano[4,3-b]indole (IX) and 8-Methoxy-9b-methyl-3,4-dihydro-1H-thiopyrano[4,3-b]indole (V). In a similar manner to the preceding case, 1.2 g (0.007 mole) of p-methoxyphenylhydrazine hydrochloride and 1.2 g (0.009 mole) of ketone I in 15 ml of absolute ethanol (with boiling for 1 h) gave 0.93 g (58%) of the indole IX, mp 136-137°C (from ethanol). Found %: N 6.14; S 14.06. $C_{13}H_{15}NOS$. Calculated %: N 6.00; S 13.74.

On being made alkaline and extracted with ether, the acid solution yielded 0.25 g (15.6%) of the 3H-indole V, mp 120-121°C (from heptane). Found %: N 5.90; S 13.58. $C_{13}H_{15}NOS$. Calculated %: N 6.00; S 13.74.

Hydrochloride of the 3H-Indole Derivative (V). Found %: Cl 13.04; N 5.17; S 11.76. $C_{13}H_{15}NOS \cdot HCl$. Calculated %: Cl 13.14; N 5.19; S 11.88.

3-Methyltetrahydrothiopyran-4-one p-Ethoxycarbonylphenylhydrazone (XIV). A mixture of 3.8 g (0.03 mole) of the ketone I and 4.9 g (0.027 mole) of p-ethoxycarbonyl phenylhydrazone in 15 ml of absolute ethanol was boiled for 30 min and was then cooled, and the precipitate that deposited was filtered off, giving 6.9 g (87%) of hydrazone with mp 148-150°C (from absolute ethanol). Found %: N 9.83; S 11.09. $C_{15}H_{20}N_2O_2S$. Calculated %: N 9.58; S 10.96.

Cyclization of 3-Methyltetrahydrothiopyran-4-one p-Ethoxycarbonylphenylhydrazone. a. With heating, 3 g (0.01 mole) of the hydrazone XIV was dissolved in 50 ml of anhydrous benzene, and dry hydrogen chloride was passed in at the boil for 4 h. After cooling, the solution was poured into water (~300 ml) and extracted with benzene. After the benzene had been distilled off, the residual oil was dried over P_2O_5 and treated with an ethereal solution of hydrogen chloride. The precipitate was filtered off (filtrate A), repeatedly washed with absolute ether, converted into the base with potassium carbonate, and extracted with ether, and 1.5 g of the substance was chromatographed on Al_2O_3 (activity grade ~4). Elution with a mixture of petroleum ether and benzene (4 : 1) gave 8-ethoxycarbonyl-9b-methyl-3,4-dihydro-1H-thiopyrano[4,3-b]-indole (VI), yield 1.32 g (41%).

Hydrochloride of the 3H-Indole Derivative VI, mp 160-161.5°C. Found %: Cl 11.33; N 4.23; S 10.05. $C_{15}H_{17}NO_2S \cdot HCl$. Calculated %: Cl 11.37; N 4.49; S 10.28.

The ethereal solution (A) was washed with water and dried with magnesium sulfate, and the solvent was distilled off. The residue was recrystallized from benzene to give 0.45 g (16%) of 8-ethoxycarbonyl-4-methyl-1,3,4,5-tetrahydrothiopyrano[4,3-b]indole (X), mp 175-176°C. Found %: N 5.28; S 11.71. $C_{15}H_{17}NO_2S$. Calculated %: N 5.09; S 11.64.

b. A mixture of 2.8 g (0.01 mole) of the hydrazone XIV and 20 ml of 26-28% ethanolic hydrogen chloride was boiled for 1 h 30 min, poured into water (about 300 ml), and extracted with ether. From the ethereal solution, hydrogen chloride precipitated 1.4 g (43.7%) of the hydrochloride of 8-ethoxycarbonyl-9b-methyl-3,4-dihydro-1H-thiopyrano-[4,3-b]indole (VI), mp 160-161.5°C. A mixture with the sample described above gave no depression of the melting point. Distillation of the ether yielded 0.4 g (15%) of 8-ethoxycarbonyl-4-methyl-1,3,4,5-tetrahydrothiopyrano[4,3-b]indole (X), mp 175-176°C (from benzene). A mixture with the sample described above gave no depression of the melting point.

c. A mixture of 0.9 g (0.003 mole) of the hydrazone XIV and 9 ml of concentrated hydrochloric acid was boiled for 10 min and cooled, and the precipitate was filtered off and washed with water. This gave 0.4 g (50%) of X, mp 175-176°C (from absolute ethanol).

3-Methyltetrahydrothiopyran-4-one S,S-Dioxide (II). A solution of 5 g (0.038 mole) of 3-methyltetrahydrothiopyran-4-one in 10 ml of glacial acetic acid was added to 6.8 g of peracetic acid in 66 ml of glacial acetic acid at such a rate that the temperature of the reaction mixture was maintained at 70-80°C. The solution was evaporated to two-thirds of its original volume and cooled, and the precipitate that deposited was filtered off. This gave 3.1 g (50%) of the ketone II, mp 141-142°C (from acetic acid). Found %: S 19.84. $C_6H_{10}O_3S$. Calculated %: S 19.75.

9b-Methyl-3,4-dihydro-1H-thiopyrano[4,3-b]indole S,S-Dioxide (XI). A mixture of 0.5 g (0.003 mole) of 3-methyltetrahydrothiopyran-4-one S,S-dioxide and 0.44 g (0.003 mole) of phenylhydrazine hydrochloride was boiled in 15 ml of 24% ethanolic hydrogen chloride for 1 h. Then the precipitate was filtered off and washed with absolute ethanol and then with water. This gave 0.4 g (57%) of the 3H-indole derivative XI in the form of the base, mp 166-167°C (from absolute ethanol). Found %: N 6.28; S 13.66. $C_{12}H_{13}NO_2S$. Calculated %: N 5.95; S 13.62. UV spectrum, λ_{max}, nm (log ε): 262 (3.72).

The hydrochloride of the 3H-indoline derivative XI was obtained in a methanolic solution of hydrogen chloride, mp 202-204°C. Found %: Cl 12.96. $C_{12}H_{13}NO_2S \cdot HCl$. Calculated %: Cl 13.04.

8,9b-Dimethyl-3,4-dihydro-1H-thiopyrano[4,3-b]indole S,S-Dioxide (XII). In a similar manner to the preparation of XI, 0.48 g (0.003 mole) of p-tolylhydrazine hydrochloride and 0.55 g (0.0034 mole) of the ketone II gave 0.6 g (71%) of the 3H-indole derivative XII, mp 172.5-173.5°C (from ethanol). Found %: N 5.88; S 12.90. $C_{13}H_{15}NO_2S$. Calculated %: N 5.62; S 12.86. UV spectrum, λ_{max}, nm (log ε): 222 (4.21); 268-270 (3.82).

3-Methyltetrahydrothiopyran-4-one S,S-Dioxide p-Ethoxycarbonylphenylhydrazone (XV). A mixture of 2.2 g (0.012 mole) of p-ethoxycarbonylphenylhydrazine and 2 g (0.012 mole) of the ketone II was boiled in absolute ethanol for 30 min and cooled, and the precipitate was filtered off, giving 3.7 g (92.5%) of the hydrazone, mp 216-218°C (from absolute ethanol). Found %: S 9.67. $C_{15}H_{20}N_2O_4S$. Calculated %: S 9.88.

9b-Methyl-3,4-dihydro-1H-thiopyrano[4,3-b]indole-8-carboxylic Acid S,S-Dioxide (XIII). A mixture of 0.6 g (0.0018 mole) of the hydrazone XV and 6 ml of concentrated hydrochloric acid was boiled for 3 h and poured into water, and the precipitate was filtered off. Yield 0.3 g (55.5%), mp 272-274°C (from ethanol). Found %: N 5.29; S 11.40. $C_{13}H_{13}NO_4S$. Calculated %: N 5.02; S 11.48. UV spectrum, λ_{max}, nm (log ε): 274-276 (4.03).

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