INDOLE DERIVATIVES

XXXIII.* THE DIRECTION OF THE CYCLIZATION OF ARYLHYDRAZONES OF TETRAHYDROTHIOPYRAN-3-ONE AND ITS S,S-DIOXIDE

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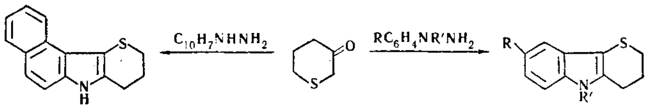
It has been shown by means of PMR spectra that the Fischer cyclization of arylhydrazones of tetrahydrothiopyran-3-one forms 2,3-dihydrothiopyrano[3,2-b]indoles; the cyclization of arylhydrazones of tetrahydrothiopyran-3-one S, S-dioxide leads to the formation of 1,2-dihydrothiopyrano[3,4-b]indole S, S-dioxides.

We found previously [1] that the cyclization of arylhydrazones of tetrahydrothiophen-3-one leads to the formation of 2,3-dihydro-4H-thieno[3,2-b]indoles in which the sulfur atoms are connected directly to the β position of the indole ring. The cyclization of arylhydrazones of a seven-membered sulfur-containing ketone – thiepan-4-one – forms 4,5-dihydro-1,3,6H-thiepino[4,3-b]indoles [2] in which the sulfur atoms occupy the closest possible positions to the β atoms of the indole rings. Under these conditions, tetrahydrothiophen-3-one S,S-dioxides are converted into 1,2,4,5-tetrahydro-6H-thiepino[3,4-b]indole S,S-dioxides in which the SO_2 group is located symmetrically with respect to the 2,3-bond of the indole ring.

It may be assumed that the direction of the cyclization of the arylhydrazones of unsymmetrical sulfur-containing cyclic ketones depends on the electronic state of the sulfur atom. In view of this, we have performed the Fischer condensation of arylhydrazones of tetrahydrothiopyran-3-one and its S,S-dioxide. In the case of tetrahydrothiopyran-3-one itself, the reaction was mainly performed without the isolation of the extremely unstable arylhydrazones by briefly boiling equimolar amounts of the arylhydrazine hydrochloride and tetrahydrothiopyran-3-one in ethanol. The reaction was accompanied by the resinification of the mixture and the formation of polymeric products. In each case, only one isomer (I-IV) was isolated.



IV

I–III

R=R'=H I; R=CH_3, R'=H II; R=H, R'=CH_3 III

We were unable to select conditions for the cyclization of the p-ethoxycarbonylphenylhydrazine of tetrahydrothiopyran-3-one. When the latter was heated with 5-30% solutions of hydrogen chloride in ethanol, and also with concentrated hydrochloric acid, complete resinification took place.

It is known that the arylhydrazones of tetrahydrothiopyran-4-one are more stable and cyclize to form 1,3,4,5-tetrahydrothiopyrano[4,5-b]indoles smoothly with good yields [3]. The Fischer cyclization of arylhydrazones of 2-thiochroman-4-one takes place under considerably milder conditions than the cyclization of 1-thiochroman-4-one [4]. The cyclization of arylhydrazones of $RCOCH_2SR'$, leading to the formation of

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*For Communication XXXII, see [8].

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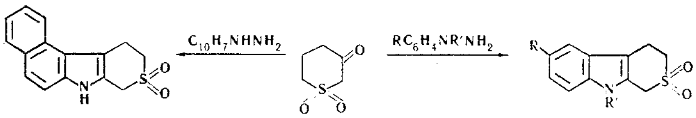
β-sulfides of indole, is carried out with cooling. All these facts, and also the similarity of the nature of the cyclization of arylhydrazones of tetrahydrothiophen-3-one and tetrahydrothiopyran-3-one have permitted the assumption that cyclization takes place in the direction of the formation of 2,3-dihydrothiopyrano-[3,2-b]indoles (I-IV), i.e., substances in which the sulfur atoms are connected directly with the β position of the indole ring.

The PMR spectrum of compound I has a peak at 2.5-3.0 ppm (4H) from the two CH_2 groups in position 2 and 4 split because of coupling with the protons of the CH_2 group in position 3. A complex multiplet at 1.9-2.5 ppm may be assigned to the protons of the methylene group in position 3, interacting with the four protons at C_2 and C_4. The absence of a singlet corresponding to the CH_2 group in position 4 of the alternative structure with the sulfur atom in position 3 is a proof of the structure of the substance as 2,3-dihydrothiopyrano[3,2-b]indole (I). The structures of compounds II-IV were adopted by analogy.

The Fischer reaction with tetrahydrothiopyran-3-one S,S-dioxide takes place when equimolar amounts of the ketone and an arylhydrazine hydrochloride are heated in 20-30% ethanolic hydrogen chloride. In each case, a single isomer was isolated in high yield. As in the case of the nonoxide compound, we were unable to select conditions for the cyclization of the p-ethoxycarbonylphenylhydrazone of tetrahydrothiopyran-3-one S,S-dioxide.



VIII

V-VII, IX

R=R'=H V; R=CH_3, R'=H VI; R=H, R'=CH_3 VII; R=H, R'=CH_2Ph IX

Substance (IX) was synthesized by the alkylation of the Na derivative of V with benzyl chloride in dimethylformamide. The structure of compounds V-VIII was shown on the basis of that of 1,2-dihydrothiopyrano[3,4-b]indole S,S-dioxide (V). The PMR spectrum of substance V has a singlet at 4.6 ppm from the two protons in position 4 and a multiplet at 3.0-3.4 ppm (4H) from the two CH_2 groups at C_1 and C_2, interacting with one another, which confirms the structure of the 1,2-dihydrothiopyrano[3,4-b]indoles (V-IX). Thus, the Fischer cyclization of arylhydrazones of tetrahydrothiopyran-3-one and of its S,S-dioxide leads to heterocycles of different structures: I-IV and V-VIII, respectively.

On the basis of the behavior of five- [1], six- [3], and seven-membered [2] sulfur-containing ketones a general tendency for the Fischer cyclization of their arylhydrazones to form cyclization products in which the sulfur atoms strive to occupy the closest possible position to the β-atom of the indole ring has been established. In contrast to this, in the cyclization of arylhydrazones of the S,S-dioxides of these ketones cyclization products are formed in which the sulfur occupies the position most remote from the β-atom of the indole ring. The reason for this phenomenon is apparently connected with the electronic nature and stereochemistry of the initial ketones.

EXPERIMENTAL

The PMR spectra were taken on an RS-60 spectrometer with a working frequency of 60 MHz. Substance I was studied in $CDCl_3$ and V in pyridine. Tetramethylsilane was used as internal standard.

2,3-Dihydrothiopyrano[3,2-b]indole (I). A mixture of 3 g (0.0257 mole) of tetrahydrothiopyran-3-one [6] and 3.7 g (0.0257 mole) of phenylhydrazine hydrochloride in 25 ml of absolute ethanol was heated to the boil. The mixture boiled vigorously and continued boiling for 2-3 min after the burner had been removed. It darkened and became black, and ammonium chloride separated out. The hot reaction mixture was poured into 100 ml of water and the mixture was acidified with dilute hydrochloric acid (1 : 1), decanted from the resin formed, and extracted with ether. The ethereal extract was washed with water, dried and evaporated, and the residue was recrystallized from the minimum amount of benzene. This gave 0.5 g (10.3%) of I with mp 129-130°C (from ethanol). Found %: N 7.61, 7.65; S 16.91, 16.94. $C_{11}H_{11}NS$. Calculated %: N 7.40; S 16.93.

8-Methyl-2,3-dihydrothiopyrano[3,2-b]indole (II). In a similar manner to the preceding case, 2.1 g (0.018 mole) of tetrahydrothiopyran-3-one and 2.9 g (0.018 mole) of p-tolylhydrazine in 15 ml of methanol yielded 0.6 g (16.7%) of II with mp 148-149°C (from ethanol). Found %: N 7.13, 7.09; S 16.01, 16.05. $C_{12}H_{13}NS$. Calculated %: N 6.89; S 15.77.

5-Methyl-2,3-dihydrothiopyrano[3,2-b]indole (III). A mixture of 2 g (0.017 mole) of tetrahydrothiopyran-3-one and 2.1 g (0.017 mole) of N-methyl-N-phenylhydrazine in 12 ml of absolute 10% ethanolic hydrogen chloride was boiled for 15 min and poured into water,and the precipitate was filtered off, washed with water, and dried. This gave 2.3 g (65.5%) of III with mp 117-118°C (from a mixture of heptane and benzene). Found %: N 6.97, 7.02; S 15.40, 15.43. $C_{12}H_{13}NS$. Calculated %: N 6.89; S 15.77.

2,3-Dihydro-4H-benzo[e]thiopyrano[3,2-b]indole (IV). A mixture of 1.4 g (0.012 mole) of tetrahydrothiopyran-3-one and 2.34 g (0.012 mole) of β-naphthylhydrazine hydrochloride in 10 ml of absolute ethanol was boiled for 10 min and poured into water, and the precipitate was filtered off, washed with hot water, and recrystallized from ethanol with the addition of carbon. This gave 0.8 g (27.8%) of IV with mp 144-145°C (from ethanol). N 5.90, 5.97; S 13.34, 13.40. $C_{16}H_{13}NS$. Calculated %: N 5.86; S 13.40.

Tetrahydrothiopyran-3-one p-Ethoxycarbonylphenylhydrazone. A mixture of 3.2 g (0.0275 mole) of tetrahydrothiopyran-3-one and 4.97 g (0.0275 mole) of p-ethoxycarbonylphenylhydrazine in 75 ml of absolute ethanol was boiled for 15 min and, after cooling, 5 g (65%) of p-ethoxycarbonylphenylhydrazone, mp 140-141°C (from ethanol), was filtered off. Found %: N 10.13, 10.11; S 11.47, 11.76. $C_{14}H_{18}N_2O_2S$. Calculated %: N 10.07; S 11.52.

1,2-Dihydrothiopyrano[3,4-b]indole S,S-Dioxide (V). A mixture of 3 g (0.02 mole) of tetrahydrothiopyran-3-one S,S-dioxide [7] and 3 g (0.02 mole) of phenylhydrazine hydrochloride in 40 ml of absolute 22% ethanolic hydrogen chloride was boiled for 10 min and poured into water, and the precipitate was filtered off, washed with hot water, and dried. This gave 3.7 g (82%) of V, mp 272-272°C (decomp., from dioxane). Found %: N 6.66, 6.76; S 14.21, 14.28. $C_{11}H_{11}NO_2S$. Calculated %: N 6.33; S 14.49.

8-Methyl-1,2-dihydrothiopyrano[3,4-b]indole S,S-Dioxide (VI). As in the preceding case, 2 g (0.013 mole) of tetrahydrothiopyran-3-one S,S-dioxide and 2.1 g (0.013 mole) of p-tolylhydrazine hydrochloride in 45 ml of absolute 29% ethanolic hydrogen chloride (with boiling for 15 min) gave 2.5 g (79%) of VI, mp 262-264°C (decomp., from aqueous dioxane). Found %: N 6.14, 6.18; S 13.68, 13.53. $C_{12}H_{13}NO_2S$. Calculated %: N 5.95; S 13.62.

1,2-Dihydrobenzo[e]thiopyrano[3,4-b]indole S,S-Dioxide (VIII). A mixture of 1 g (0.068 mole) of tetrahydrothiopyran-3-one S,S-dioxide and 1.3 g (0.0068 mole) of β-naphthylhydrazine hydrochloride in 30 ml of absolute 29% ethanolic hydrogen chloride was boiled for 30 min and poured into water, and the precipitate was filtered off, washed with hot water, and dried in the air. This gave 1.57 g (86%) of VIII with mp 302-303°C (decomp., from dioxane). Found %: N 5.33, 5.37; S 11.51, 11.59. $C_{15}H_{13}NO_2S$. Calculated %: N 5.16; S 11.80.

5-Benzyl-1,2-dihydrothiopyrano[3,4-b]indole S,S-Dioxide (IX). A solution of 2 g (0.009 mole) of V in 20 ml of dimethylformamide was added dropwise to 0.3 g (0.009 mole) of 75% sodium hydride in 20 ml of dimethylformamide and the mixture was stirred for 1 h 30 min at 25-30°C, after which 1.14 g (0.009 mole) of benzyl chloride was added and the resulting mixture was stirred at 40°C for 2 h, poured into water, and extracted with chloroform. The extract was evaporated, the residue was treated with ethanol and ether, and 1.9 g (68%) of IX was filtered off with mp 203-204°C (from aqueous dioxane). Found %: N 4.69, 4.66; S 10.03, 9.94. $C_{18}H_{17}NO_2S$. Calculated %: N 4.50; S 10.29.

5-Methyl-1,2-dihydrothiopyrano[3,4-b]indole S,S-Dioxide (VII). A mixture of 2 g (0.013 mole) of tetrahydrothiopyran-3-one S,S-dioxide and 1.6 g (0.013 mole) of N-methyl-N-phenylhydrazine in 20 ml of absolute 20% ethanolic hydrogen chloride was boiled for 25 min, and the hot mixture was poured into water, after which the precipitate was filtered off, washed with water, and dried. This gave 2.8 g (88%) of VII with mp 195-197°C (decomp., from aqueous dioxane). Found %: N 6.16, 5.97; S 13.72, 13.86. $C_{12}H_{13}NO_2S$. Calculated %: N 5.95; S 13.62.

Tetrahydrothiopyran-3-one S,S-Dioxide p-Ethoxycarbonylphenylhydrazone. A mixture of 3 g (0.02 mole) of tetrahydrothiopyran-3-one S,S-dioxide and 3.65 g (0.02 mole) of p-ethoxycarbonylphenylhydrazine in 200 ml of absolute ethanol was boiled for 15 min and, after cooling, the precipitate was filtered off and washed with ether. This gave 6.3 g (100%) of hydrazone, mp 226.5-227°C (from absolute ethanol). Found %: N 9.15, 9.29; S 10.37, 10.14. $C_{14}H_{18}N_2SO_4$. Calculated %: N 9.03; S 10.34.

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