CONDENSATION OF O-PHENYLHYDROXYLAMINE WITH SOME UNSYMMETRICAL HETEROCYCLIC KETONES

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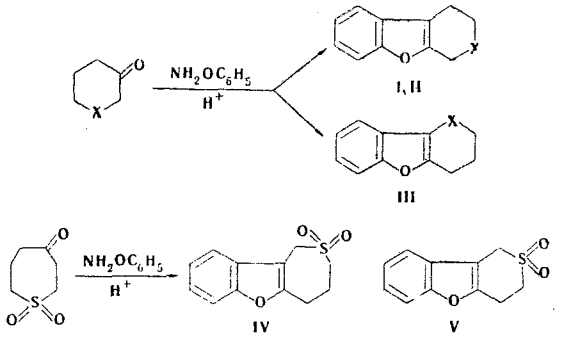
UDC 547.728.2'83

2-Methyl-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine, 3,4-dihydro-1H-thiopyrano[3,4-b]benzofuran, 2,3-dihydro-4H-thiopyrano[3,2-b]benzofuran 1,1-dioxide, and 1,3,4,5-tetrahydrothiepino[4,3-b]benzofuran 2,2-dioxide, respectively, were synthesized by condensation of O-phenylhydroxylamine with N-methyl-3-piperidone, tetrahydro-3-thiopyrone, tetrahydro-3-thiopyrone S,S-dioxide, and 4-thiepanone S,S-dioxide.

Continuing our syntheses of condensed benzofuran systems [1-3] containing various heterocycles, we have investigated the cyclization of aryl ethers of oximes (without isolation of them) of unsymmetrical heterocyclic ketones with the aim of creating new heterocyclic systems and studying the direction of closing of the benzofuran ring. In addition, we were interested in the possibility of comparing the direction of formation of the benzofuran ring of aryl ethers of unsymmetrical heterocyclic ketones with the orientation of closing of the indole ring (via the Fischer reaction) of arylhydrazones of the same ketone [4-6], since it is assumed that the mechanisms of the "benzofuranization" and "indolization" reactions have certain similarities.

In all cases of the cyclization, only one of the two possible isomers was isolated. The structures of these isomers were established by means of the PMR spectra.

2-Methyl-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine (I) was obtained by refluxing (1 h) a mixture of hydrochlorides of N-methyl-3-piperidone [7] and O-phenylhydroxylamine, initially in alcohol and then (after removal of the solvent by distillation) in glacial acetic acid–concentrated sulfuric acid.



I X = NCH_3; II X = S; III X = SO_2

The PMR spectrum of I in CCl_4 contains singlet signals of $N-CH_3$ groups (2.5 ppm), $1-CH_2$ groups (3.6 ppm), and an unresolved multiplet of the A_2B_2 system of CH_2CH_2 protons (2.7 ppm). It is important to point out that the PMR spectrum of these molecular fragments is quite similar to the spectrum of 2,6-dimethyl-1,2,3,4-tetrahydro-β-carboline, which was obtained by Fischer cyclization of N-methyl-3-pip-

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 315-318, March, 1973. Original article submitted March 6, 1972.

eridone p-tolylhydrazone [6]. The chemical shifts of the 3-H and 4-H protons in the PMR spectrum (in CD_3OD+D_2O) of the hydrochloride of I differ markedly with respect to magnitude and appear as two groups of signals at 3.6 and 3.1 ppm (in the latter case, the signal is overlapped with the $N-CH_3$ signal), while the 1-H signal appears at δ 4.2 ppm.

The reaction of tetrahydro-3-thiopyrone with O-phenylhydroxylamine was carried out in an alcohol solution of hydrogen chloride. We isolated 3,4-dihydro-1H-thiopyrano[3,4-b]benzofuran (II), the PMR spectrum of which (in $CHCl_3$) contains a singlet signal of two 1-H protons at 3.7 ppm and an unresolved signal of an A_2B_2 system at 2.9 ppm (CH_2CH_2).

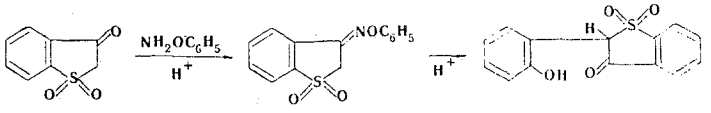
The condensation of O-phenylhydroxylamine with tetrahydro-3-thiopyrone S,S-dioxide (under the same conditions) gave 2,3-dihydro-4H-thiopyrano[3,2-b]benzofuran 1,1-dioxide (III). The PMR spectrum of III (in pyridine) contains signals at 3.45 (a distorted triplet with a subsplit center component, $J\simeq 6$ Hz, $2-CH_2$), 2.8 (distorted triplet, $J\simeq 6$ Hz, $4-CH_2$), and at 2.0-2.6 ppm (multiplet, $3-CH_2$; the signals of protons of CH_3 groups of picoline impurities appear in this same region). The spectrum of this compound in nitrobenzene has the same character, but the last two groups of signals are found at somewhat weaker field.

1,3,4,5-Tetrahydrothiepino[4,3-b]benzofuran 2,2-dioxide (IV) was synthesized by condensation of O-phenylhydroxylamine with 4-thiepanone in an alcohol solution of hydrogen chloride. The PMR spectrum of IV (in pyridine) contains signals at 4.85 (singlet, $1-CH_2$), 3.65 (distorted triplet with a low-intensity center component, $J\simeq 6$ Hz, $3-CH_2$), 3.1 (distorted triplet, $J\simeq 6$ Hz, $5-CH_2$), and 2.1-2.5 ppm (multiplet, $4-CH_2$).

We synthesized 3,4-dihydro-H-thiopyrano[4,3-b]benzofuran 2,2-dioxide (V) for comparison of the PMR spectra. The spectrum of V (in pyridine) contains a singlet $1-CH_2$ signal at 4.6 ppm and an unresolved CH_2CH_2 signal at 3.2-3.8 ppm.

We note that the cyclization of tetrahydro-3-thiopyrone phenylhydrazone gave 2,3-dihydro-4H-thiopyrano[3,2-b]indole, while 3,4-dihydro-1H-thiopyrano[3,4-b]indole was isolated in the condensation of phenylhydrazine with tetrahydro-3-thiopyrone S,S-dioxide [4]. 1,2,4,5-Tetrahydrothiepino[4,5-b]indole 3,3-dioxide was obtained by cyclization of 4-thiepanone S,S-dioxide phenylhydrazone [5]. Consequently, substances with structures analogous to those of the products of Fischer cyclization of arylhydrazones of the same ketones are not formed in all cases of the cyclization of phenyl ethers of oximes of unsymmetrical heterocyclic ketones. In the indicated examples, we observed coincidence of the direction of the formation of benzofuran and indole rings only for N-methyl-3-piperidone.

We also studied the reaction of 3-benzothiophanone S,S-dioxide with O-phenylhydroxylamine. The O-phenyl ether of 3-benzothiophanone oxime (VI) was isolated when equimolar amounts of these substances were refluxed in an alcohol solution of hydrogen chloride (30 min).



VI VII

Prolonged refluxing (> 20 h) in the same medium gave a rearrangement product – 2-(2-hydroxyphenyl)-3-benzothiophanone S,S-dioxide (VII). The following bands were observed in the IR spectrum of VII (in mineral oil): $\nu_{C=O}$ 1726 cm^{-1} and ν_{OH} in the form of two broad bands at 3443 and 3377 cm^{-1}. The PMR spectrum (in dimethyl sulfoxide) of VII contains a narrow singlet of one proton at 5.6 ppm, a broad signal at 9.8 ppm (OH), two groups of multiplet signals with intensities of two proton units at 6.8 and 7.1 ppm (the phenol portion of the molecule), and a multiplet (4H) at 8.0 ppm (benzothiophene portion of the molecule). Compound VII could not be converted to a benzofuran system by refluxing with $ZnCl_2$ in acetic acid, refluxing in toluene containing p-toluenesulfonic acid, or by brief heating with a mixture of glacial acetic and concentrated sulfuric acid (9 : 1). Starting VII was recovered in all cases. The difficulty involved in closing the benzofuran ring in this case is apparently associated with steric factors. We direct attention to the fact that the Fischer cyclization of phenyl- and p-tolylhydrazones of 3-benzothiophanone S,S-dioxide also does not give the corresponding indoles under various conditions.

EXPERIMENTAL

The PMR spectra were recorded with a Varian T-60 spectrometer, the UV spectrum was recorded with an SF-4 spectrophotometer, and the IR spectrum was recorded with a UR-10 spectrograph.

2-Methyl-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine (I). A mixture of 1.2 g (8 mmole) of N-methyl-3-piperidone hydrochloride and 1.3 g (9 mmole) of O-phenylhydroxylamine hydrochloride in 15 ml of absolute alcohol was refluxed for 1 h, after which the solvent was vacuum-evaporated. The residue was refluxed for 5 min with 10 ml of glacial acetic acid–concentrated H_2SO_4 (9 : 1 by volume), and the mixture was poured into water. The aqueous mixture was made alkaline with ammonium hydroxide solution and extracted with ether. Treatment of the dried extract with a solution of hydrogen chloride in alcohol precipitated 0.7 g (39%) of the hydrochloride of I with mp 295° (dec., from absolute alcohol). Found: C 64.4; H 6.2; Cl 16.0%. $C_{12}H_{13}NO \cdot HCl$. Calculated: C 64.4; H 6.2; Cl 15.8%.

1,2-Dihydro-1H-thiopyrano[3,4-b]benzofuran (II). A mixture of 2 g (1.7 mmole) of tetrahydro-3-thiopyrone and 2.5 g (1.7 mmole) of O-phenylhydroxylamine hydrochloride in 30 ml of 5% solution of hydrogen chloride in alcohol was refluxed for 15 min. The mixture was then poured into water and extracted with ether. The extract was dried and evaporated, and the residue was dissolved in chloroform. The chloroform solution was passed through a column filled with Al_2O_3 (activity IV) to give 0.6 g (18%) of II with mp 94.5-95° (from alcohol with decolorization with activated charcoal). λ_{max}, nm (log ε): 250 (4.06), 276 (3.55), 282 (3.54). Found: C 69.5; H 5.0; S 17.6%. $C_{11}H_{10}OS$. Calculated: C 69.4; H 5.3; S 16.8%.

2,3-Dihydro-4H-thiopyrano[3,2-b]benzofuran 1,1-Dioxide (III). A 0.45-g (3 mmole) sample of O-phenylhydroxylamine hydrochloride and 0.46 g (3 mmole) of tetrahydro-3-thiopyrone S,S-dioxide were refluxed for 1 h in 25 ml of a 27% solution of hydrogen chloride in alcohol. The mixture was then poured into water, and the precipitate was removed by filtration, washed with water, and air-dried to give 0.4 g (58%) of III with mp 143-145° (from absolute alcohol). Found: C 59.0; H 4.3; S 14.7%. $C_{11}H_{10}O_3S$. Calculated: C 59.4; H 4.5; S 14.4%.

1,3,4,5-Tetrahydrothiepino[4,3-b]benzofuran 2,2-Dioxide (IV). Similarly, 0.6 g (41%) of IV with mp 217-218° (from absolute alcohol) was obtained from 0.1 g (6 mmole) of 4-thiepanone S,S-dioxide and 0.9 g (6 mmole) of O-phenylhydroxylamine hydrochloride in 30 ml of a 25% solution of hydrogen chloride in alcohol. Found: C 61.0; H 5.1; S 14.0%. $C_{12}H_{12}O_3S$. Calculated: C 61.0; H 5.1; S 13.6%.

3,4-Dihydro-1H-thiopyrano[4,3-b]benzofuran 2,2-Dioxide (V). Similarly, 1.2 g (74%) of V with mp 201-202° (from absolute alcohol) was obtained from 1 g (6.8 mmole) of tetrahydro-4-thiopyrone S,S-dioxide and 0.98 g (6.8 mmole) of O-phenylhydroxylamine hydrochloride. Found: C 59.2; H 4.6; S 14.9%. $C_{11}H_{10}O_3S$. Calculated: C 59.5; H 4.5; S 14.4%.

O-Phenyl Ether of 3-Benzothiophanone S,S-Dioxide Oxime (VI). A mixture of 1.5 g (10 mmole) of O-phenylhydroxylamine hydrochloride and 1.9 g (10 mmole) of 3-benzothiophanone S,S-dioxide in 15 ml of a 30% solution of hydrogen chloride was refluxed for 30 min, after which it was cooled and 2.15 g (76%) of VI with mp 152.5-153° (from absolute alcohol) was removed by filtration. Found: N 5.2; S 12.1%. $C_{14}H_{11}NO_3S$. Calculated: N 5.1; S 11.7%.

2-(2-Hydroxyphenyl)-3-benzothiophanone 1,1-Dioxide (VII). A. A 2.5-g (13 mmole) sample of 3-benzothiophanone S,S-dioxide and 2 g (13 mmole) of O-phenylhydroxylamine hydrochloride were refluxed for 21 h in 100 ml of 20% solution of hydrogen chloride in alcohol. The resulting precipitate was removed by filtration, washed with water, and dried to give 3 g (80%) of VII with mp 226-227° (from alcohol). Found: C 61.4; H 4.0; S 12.1%. $C_{14}H_{10}O_4S$. Calculated: C 61.3; H 3.7; S 11.7%.

B. Compound VI was refluxed for 5 min in glacial acetic acid–concentrated H_2SO_4 (9 : 1) to give 30% of VII. More prolonged heating gave water-soluble substances.

3-Benzothiophanone S,S-Dioxide p-Tolylhydrazone. A 1-g (5.5 mmole) sample of 3-benzothiophanone S,S-dioxide and 0.9 g (5.6 mmole) of p-tolylhydrazine hydrochloride were refluxed for 5 h in 30 ml of 20% alcohol solution of hydrogen chloride. The mixture was cooled, and the resulting precipitate was removed by filtration and washed with water, alcohol, and ether to give 1.35 g (86%) of the p-tolylhydrazone with mp 253-254° (from alcohol). Found: N 10.0; S 10.9%. $C_{15}H_{14}N_2O_2S$. Calculated: N 9.8; S 11.2%. The hydrazone could not be cyclized by refluxing with solutions of hydrogen chloride in alcohol and glacial acetic acid, by refluxing in benzene with the passage of a stream of hydrogen chloride, or by refluxing in glacial acetic acid–concentrated H_2SO_4.

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