Chemistry of Heterocyclic Compounds, Vol.35, No. 1, 1999

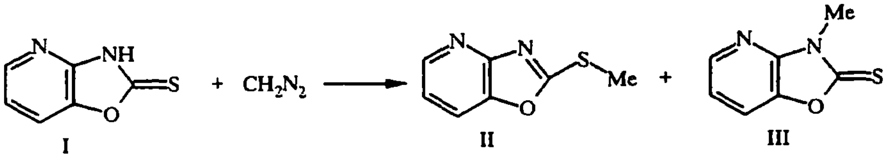
AZABENZENE CHEMISTRY.
PART 2*. METHYLATION OF 2,3-DIHYDROOXAZOLO[4,5-*b*]PYRIDIN-2-THIONE

N. A. Aliev, M. G. Levkovich, E. L. Kristallovich, N. D. Abdullaev, and V. G. Kartsev

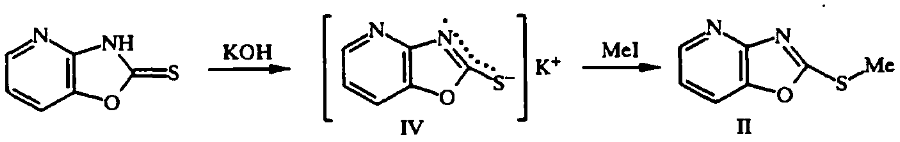
*Studies have been made on the reactions of 2,3-dihydrooxazolo[4,5-*b*]pyridin-2-thione and of its potassium and sodium salts with methylating agents under various conditions.*

We have previously reported [1] the synthesis and structure of 2,3-dihydrooxazolo[4,5-*b*]pyridin-2-thione (I). This paper deals with the methylation of I and of its potassium and sodium salts by diazomethane, methyl iodide, dimethyl sulfate, and methyl tosylate. Interest attaches to the effects of the alkylating agent and solvent on the reaction direction.

Methylation of thione I by an excess of an ether solution of diazomethane is almost quantitative, but the mixture of 2- (II) and 3-methylated derivatives (III) in a ratio of 2:1 (from PMR data) is formed.



Thione I reacts with methyl iodide in acetone at room temperature giving a yield of 30% only of product II. Similar selective methylation occurs on treating the K salt of compound I (IV) in methanol with methyl iodide: in this case product II is formed with a yield of 66%. These results are due to the mildness of the alkylating agent.



Different results were obtained when the methylating agent was dimethyl sulfate, which when used with a potassium salt IV under the same conditions as for methyl iodide gave a mixture of products II and III (2.5:1) with overall yield 66%. Compounds II and III are formed in the same ratio on treating salt IV with dimethyl sulfate in the solid state, but then the overall yield is only 36%.

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* See [1] for Part 1.

Plant Substance Chemistry Institute, Uzbekistan Academy of Sciences, Tashkent 700170. Organic Nitrogen Technology Association, Interbioskrin, Moscow a/ya 218, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 87-89, January, 1999. Original article submitted July 2, 1997; revision submitted July 3, 1998.

Methylation with methyl tosylate of salt IV in acetone and of salt V in hexamethylphosphortriamide (HMPTA) leads mainly to the S-alkylation product II: the yields are 73 and 66% respectively. In both cases, the N-alkylation product III is formed with yields of 2 and 7%.

The trend in the alkylation of thione I is thus dependent on the methylating agent and solvent.

In the experiment with HMPTA, the reaction mixture contained not only the initial compound I but also on TLC showed 2,3-dihydrooxazolo[4,5-*b*]pyridin-2-one (VI) [1], which is evidently due to the hydrolysis of the initial thione I. It is known that the benzthiazolinthiones are transformed by hydrolysis in alkaline medium into benzthiazolinones [2], and also that benzoxazolinthione is transformed to benzoxazolinone [3].

The structures of compounds II and III were confirmed by the PMR data, UV spectra, and elemental analysis. For example, the UV spectrum of III coincides with that of thione I: the two have their absorption maxima at 315 nm; whereas in the case of II, the maximum is at 290 nm. The PMR spectra of the two compounds contain signals from protons in the pyridine ring as condensed with the oxazole in the form of three one-proton doublets in the region 7.50-8.39 ppm. Each spectrum also has a three-proton singlet from the methyl group at 2.74 or 3.70 ppm (for II and III respectively). The integral intensity relation between those methyl group signals was used to estimate the ratio of the products II and III in the reaction mixtures.

EXPERIMENTAL

The UV spectra were recorded with an EPS-3T spectrometer (Hitachi) in ethanol, while the PMR spectra were recorded with a Tesla BS-567 in deuteromethanol. Working frequency 100 MHz, internal standard HMDS.

We checked the course of the reactions and the distinctness of the synthesized compounds, and also determined R_f, by using Silufol UV-254 plates in a 10:1 benzene-methanol solvent mixture, developer 0.5 g $KMnO_4$ - 2 ml of concentrated H_2SO_4 - 48 ml H_2O.

Methylation of 2,3-dihydrooxazolo[4,5-*b*]pyridin-2-thione (I). With diazomethane. We treated 0.2 g (1.3 mmole) of thione I with vigorous stirring with small batches of an ether solution of diazomethane (until nitrogen release ceased). When the yellow color had vanished, the reaction mixture was treated with 2% aqueous NaOH and the organic layer was dried over $CaCl_2$. The solvent was evaporated off to give 0.21 g (about 100%) of a mixture of products II and III in a 2:1 ratio (PMR data).

With methyl iodide. To a solution of 0.152 g (1 mmole) of thione I in 5 ml of acetone we added with vigorous stirring 0.2 g (1.4 mmole) of methyl iodide. The stirring at room temperature was continued for 6 h, and then the solvent was evaporated off and the residue was treated with 2% aqueous NaOH. The resulting mass was extracted three times with benzene and the extract was dried with $CaCl_2$. The residue after evaporating off the benzene crystallized on standing and was transferred to a porous plate. We obtained 0.05 g (30%) of II, R_f 0.50, mp 56-58°C. Found, %: N 17.05; S 19.60. $C_7H_6N_2OS$. Calculated, %: N 16.76; S 19.16.

Methylation of the K salt of thione I (IV). With methyl iodide. The potassium salt IV was obtained from 0.76 g (5 mmole) of thione I and 0.28 g (5 mmole) of KOH in 10 ml of CH_3OH, and to this we added with stirring 0.71 g (5 mmole) of methyl iodide. The reaction mixture was stirred for 30 min on a boiling water bath and for 1 day at room temperature. We evaporated off about 5 ml of methanol, and to the residue we added 7 ml of H_2O and treated the resulting mass as described above. This gave 0.55 g (66%) of the product, melting point 57-58°C, R_f 0.50.

With dimethyl sulfate. We used a solution of the K salt obtained from 0.76 g (5 mmole) of thione I and 0.28 g (5 mmole) of KOH in 8 ml of CH_3OH, and we added with stirring 0.55 g (4.4 mmole) of dimethyl sulfate in 2 ml of CH_3OH. The reaction mixture was kept on a boiling water bath for 2 h and then for 16 h at room temperature. The slight precipitate was filtered off and the filtrate was treated with 15 ml of 2% aqueous KOH and then extracted three times with benzene. The extract was dried over $CaCl_2$ and the benzene was evaporated off. Distilling the residue under vacuum gave 0.49 g (66%) of a 2.5:1 mixture of products II and III as indicated by PMR.

With methyl tosylate. To a solution of 10 mmole of the K salt IV obtained by treating 1.52 g (10 mmole) of compound I with 2% aqueous KOH we added a solution of 1.72 g (9 mmole) of methyl tosylate in 5 ml of acetone. The resulting mass was kept for 4 h on a boiling water bath and then for 16 h at room temperature. The reaction mixture was treated with 2% aqueous KOH and extracted three times with benzene; the extract was dried over $CaCl_2$. Then the solvent was removed and the residue was recrystallized from hexane, which gave 1.1 g (73%) of product II, melting point 56-57°C, R_f 0.50. The mother liquor after isolating compound II was evaporated and the residue was treated with a small amount of acetone, with filtration, which gave 0.03 g (2%) of 3-methyl-1,3-dihydrooxazolo[4,5-*b*]pyridin-2-thione (III), melting point 135-137°C, R_f 0.78. Found, %: N 17.11; S 19.66. $C_7H_6N_2OS$. Calculated, %: N 16.76; S 19.16.

With dimethyl sulfate in the solid state. We distributed uniformly on a glass filter 0.95 g (50 mmole) of dry potassium salt IV, which was kept for 7 days in a vacuum desiccator over 1.26 g (10 mmole) of dimethyl sulfate. Then the reaction mass was washed with 10 ml of H_2O and extracted with benzene, with the extract dried over $CaCl_2$. The TLC and PMR spectra showed that the residue (0.3 g) after evaporating off the benzene contained products II (R_f 0.50) and III (R_f 0.78) in a ratio of 2.5:1, yield 36%. When the aqueous solution was acidified with 15% HCl, we obtained 0.3 g of thione I.

Methylation of the Na salt (V) of thione I. We methylated 10 mmole of the Na salt V made from 1.52 g (10 mmole) of compound I and 0.24 g (10 mmole) of NaH by the action of 1.72 g (9 mmole) of methyl tosylate in 10 ml of HMPTA using the method described above for salt IV, which gave 0.98 g (66%) of product II and 0.1 g (7%) of product III. After acidification with 15% HCl, the water layer was extracted with benzene to isolate 0.2 g of a mixture of two substances (TLC), which were identified by the use of known specimens as the initial compound I (R_f 0.32) and 1,3-dihydro[1,3]oxazolo[4,5-*b*]pyridin-2-one (VI) (R_f 0.21).

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