

SYNTHESIS IN THE PHENOTHIAZINE SERIES

XXVII.* 1-NITRO-3-BROMOPHENOTHIAZINE AND

2-BROMO-4-NITROPHENOTHIAZINE

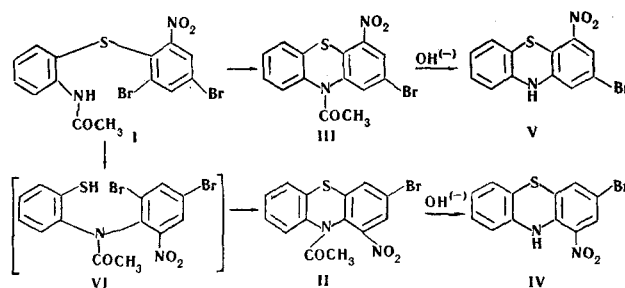
A. N. Gritsenko, Z. I. Ermakova,
and S. V. Zhuravlev

UDC 547.869.2:542.949

10-Acetyl-1-nitro-3-bromophenothiazine and 10-acetyl-2-bromo-4-nitrophenothiazine were synthesized by heating 2-acetamido-2'-nitro-4',6'-dibromodiphenyl sulfide at 160-170°C in nitrobenzene in the presence of a copper catalyst. Saponification of these products led to 1-nitro-3-bromophenothiazine and 2-bromo-4-nitrophenothiazine.

We have previously shown [1-3] that the intramolecular cyclization of 2,2'-substituted diphenyl sulfides to the corresponding phenothiazines proceeds differently depending on the conditions used to carry out the reaction. 2-Acetamido-2'-nitro-6'-bromodiphenyl sulfide and 2-acetamido-2'-nitro-4',6'-dibromodiphenyl sulfide (I) form 10-acetyl-1-bromo- and 10-acetyl-1-nitrophenothiazines [1] and 10-acetyl-1,3-dibromophenothiazine [3], respectively, when they are heated in nitrobenzene in the presence of Ullmann catalysts and alkaline reagents (potassium carbonate, sodium hydroxide). The reaction apparently proceeds through intermediate 2-mercapto-2'-bromo-6'-nitro-N-acetamidodiphenylamine and 2-mercapto-2',4'-dibromo-6'-nitro-N-acetamidodiphenylamine (VI), which form as a result of a Smiles rearrangement, and cyclization of these intermediates leads to the corresponding substituted phenothiazines. In the absence of alkaline agents 2-acetamido-2'-nitro-6'-bromodiphenyl sulfide cyclized to 10-acetyl-4-nitrophenothiazine [2], while sulfide I cyclized to III and II. The formation of the latter is probably associated with rearrangement of sulfide I to VI and subsequent cyclization to phenothiazine II.

The presence of a nitro group and two bromine atoms in the ortho and para positions with respect to the C-S bond in one of the benzene rings of sulfide I weakens this bond and makes it possible to carry out the Smiles rearrangement even without participation of an alkaline agent. The reaction is carried out in nitrobenzene at 160-170° in the presence of copper powder and potassium iodide.



Two substances were isolated from the reaction mass; they have close analytical data and the same R_f values in determining their properties by thin-layer chromatography on a loose layer of aluminum oxide. Their melting points were also extremely close. One substance melted at 186-187°, while the other melted

*For Communication XXVI see [1].

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from *Khimiya Geterotsiklicheskikh Soedinenii*, No. 10, pp. 1337-1338, October, 1970. Original article submitted December 8, 1968.

at 180–181°. However, a mixed sample of these two substances had a deep (150–152°) melting point depression. This provided us with a basis for assuming that we had obtained the two isomeric 10-acetylbromonitrophenothiazines, II and III. The yields of these substituted 10-acetylphenothiazines were about 10–15%. The major portion of the starting sulfide remains unchanged. Attempts to raise the yields of the products by changing the temperature conditions or the heating time of the reaction mixture did not give positive results.

A study of the IR spectra of IV and V established that the absorption band of the NH group in V ($\nu = 3340\text{ cm}^{-1}$, in carbon disulfide, c 0.01 mole, l 1 mm) is shifted to the short-wave side as compared with the unsubstituted compound, which indicates the formation of a hydrogen bond between the imino and nitro groups. A similar deviation was previously observed in a study of the IR spectrum of 1-nitrophenothiazine [1]. The IR spectral data and the lower melting point, characteristic for compounds which have hydrogen bonds, indicate that we have assigned the correct structure to compound IV. As for V, it has a higher melting point, and the absorption band of the NH group lies in the region characteristic for it – 3420 cm^{-1} (in chloroform, c 0.01 mole, l 1 mm). We also observed the same absorption region for 4-nitrophenothiazine [2].

EXPERIMENTAL

10-Acetyl-1-nitro-3-bromophenothiazine (II) and 10-Acetyl-2-bromo-4-nitrophenothiazine (III). A mixture of 17.84 g (0.04 mole) of 2-acetamido-2',4'-dibromo-6'-nitrodiphenyl sulfide (I), 0.8 g of copper powder, and 1.0 g of potassium iodide in 130 ml of nitrobenzene was heated with stirring for 28 h at 160–170°. The hot reaction mixture was filtered, and the nitrobenzene was removed from the filtrate in vacuo. The residue was refluxed in toluene, activated charcoal was added, and the mixture was filtered. The starting sulfide (7.2 g, mp 164–165°) was isolated from the cooled toluene solution and melted at 168–170° after recrystallization. A mixture of this substance with a known sample of I did not give a melting point depression. The toluene filtrate was evaporated, and the solid residue was triturated in a small amount of alcohol and filtered to give 7.0 g of solid, which was crystallized from a toluene–alcohol mixture to give 3.3 g of a substance with mp 150–152°. Compound III was obtained in the form of bright-yellow crystals with mp 186–187° after recrystallization from alcohol. Found %: Br 21.79, 21.84; S 8.75, 8.81. Compound II (0.6 g) with mp 180–181° was isolated from the filtrate on further cooling. Found %: Br 21.89, 22.0; S 8.68, 8.61. $\text{C}_{14}\text{H}_9\text{BrN}_2\text{O}_3\text{S}$. Calculated %: Br 21.88; S 8.78. A mixture of the two substances gave a melting point depression (150–152°).

2-Bromo-4-nitrophenothiazine (V). Sodium hydroxide (2 ml of a 2 N solution) was added to a solution of 1.0 g (0.003 mole) of 10-acetyl-2-bromo-4-nitrophenothiazine (III) in 10 ml of ethanol and 5 ml of tetrahydrofuran, and the mixture was refluxed with stirring for 30 to 40 min, during which the reaction mixture gradually darkened. The precipitate was filtered and recrystallized from toluene to give 0.7 g (80%) of a dark-violet, crystalline substance with mp 265–267° which was quite soluble in hot toluene, less soluble in alcohol, and insoluble in water. Found %: Br 24.82, 24.93; N 8.58, 8.60. $\text{C}_{12}\text{H}_7\text{BrN}_2\text{O}_2\text{S}$. Calculated %: Br 24.73; N 8.67.

1-Nitro-3-bromophenothiazine (IV). A substance (0.8 g, 90%) with mp 180–181° was obtained from 1.0 g (0.003 mole) of 10-acetyl-1-nitro-3-bromophenothiazine (II) under the conditions described above. After recrystallization from toluene the substance melted at 189° (with decomposition) and was isolated in the form of lustrous, dark needles which were quite soluble in toluene. Found %: Br 24.73; S 9.83, 9.74. $\text{C}_{12}\text{H}_7\text{BrN}_2\text{O}_2\text{S}$. Calculated %: Br 24.73; S 9.91.

LITERATURE CITED

1. V. A. Skorodumov, S. V. Zhuravlev, A. N. Gritsenko, and V. G. Vinokurov, *Khim. Geterotsikl. Soed.*, 1333 (1970).
2. S. V. Zhuravlev, A. N. Gritsenko, and Z. I. Ermakova, *Khim. Geterotsikl. Soed.*, No. 3 (in press).
3. S. V. Zhuravlev, A. N. Gritsenko, Z. I. Ermakova, and G. A. Khutornenko, *Khim. Geterotsikl. Soed.*, 1041 (1970).