REACTIONS OF 4-CHLORO-6-OXO-2,3-DIHYDRO-5-

AZABENZOFURANS WITH AMINES

M. Ya. Uritskaya, V. A. Loginova, and L. N. Yakhontov UDC 547.728.2'75'822.5'824

The reaction of 7-nitro- and 7-unsubstituted 4-chloro-6-oxo-2,3-dihydro-5-azabenzofurans with primary and secondary amines proceeds with substitution of the chlorine atoms by amine residues and with recyclization of the compounds to 5- and 7-azaindoline derivatives.

Methods for the preparation of 5-azabenzofuran derivatives containing functional substituents in the 4 and 7 positions and the conversion of 6-oxo-dihydro-5-azabenzofurans to 5-azaindoles were previously described in [1-3]; it was shown that 4-chloro-6-oxo-2,3-dihydro-5-azabenzofuran (Ia) and its N-alkyl (N-methyl-Ib) derivatives are capable of readily undergoing substitution of the chlorine atom by an alkoxy group.

It was subsequently made clear that the latter transformation, which proceeds smoothly on treatment of I with dimethyl sulfate in aqueous alkaline media, cannot be realized by the action of sodium methoxide on Ia or its N-alkyl-substituted derivatives because of the complete destruction of I even under mild conditions.



In the reaction of Ia and Ib with primary and secondary amines (aniline, benzylamine, diethylamine, and dibutylamine), replacement of the chlorine atom begins at 120° C, as judged from the appearance in the reaction mass of ionic chlorine; however, 4-amino-6-oxo-2,3-dihydro-5-azabenzofurans cannot be isolated. When I is heated with dibenzylamine or ammonia for 8 h at 180° , the starting compounds undergo quantita-tive conversion.* With aniline at 180° , in addition to replacement of the chlorine atoms, there is also conversion of the dihydrofuran ring to a 1-phenylpyrroline ring, as observed in the case of 6-oxo-2,3-dihydro-5-azabenzofuran [3]. The resulting 1-phenyl-4-phenylamino-6-oxo-5-azaindolines (IIa and IIb) are stable and can be isolated in pure form.

*We have previously observed a similar order of nucleophilicity in reactions with other haloheteroaromatic compounds in [4], in which the dependence of these processes on the basicity of the amines and the steric factors was examined in greater detail.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1311-1313, October, 1973. Original article submitted November 16, 1972.

© 1975 Plenum Publishing Corporation, 227 West 17th Street, New York, N.Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for \$15.00.

Bands of NH groups at 3330-3340 cm⁻¹ and of carbonyl groups at 1640-1660 cm⁻¹, which attest to the lactam structure of these substances, are observed in the IR spectra of IIa and IIb. The PMR spectra (in CF₃COOH) contain two triplet signals (2H each) of the $-CH_2 - CH_2 - group of the pyrroline ring (2.82 and 4.27 ppm) with J = 8 Hz, a singlet (1H) for the proton attached to C₇ at 5.82-5.83 ppm, and two multiplets (10H) of phenyl rings at 7.20-7.50 ppm.$

As expected, the introduction of the electron-acceptor nitro group into the 7 position of the dihydro-5-azabenzofuran system facilitates nucleophilic substitution of chlorine and stabilizes the resulting 4-amino derivatives (IV-VI). The reaction proceeds at 100°, and amines IV-VI are isolated in 30-64% yields. In the reaction of IIIa with aniline at 100°, in addition to replacement of the chlorine atom by an aniline residue and the formation of VI, there are also transformations associated with opening of the dihydrofuran ring and the formation of VIIa. In contrast to VIa, VIIa does not form salts with picric acids, and its IR spectrum contains bands at 3120 (with KBr), 3380 (in CHCl₃), and 3450 cm⁻¹ (with KBr), which are characteristic for the stretching vibrations of NH and OH groups, an amide carbonyl band at 1680 cm⁻¹ (in CHCl₃), which corresponds (according to the integral intensity) to the absorption of one carbonyl group, and a band of stretching vibrations of C == C bonds at 1609 cm⁻¹.

Two triplets (2H each) at 3.36 and 4.46 ppm with J = 8 Hz, which are characteristic for the CH_2CH_2 group of the pyrroline ring, a multiplet (5H) of the phenyl ring at 7.58 ppm, and a singlet (1H) at 7.45 ppm, which can be ascribed to the proton bonded to the nitrogen of the amide group, are observed in the PMR spectrum of VIIa (in CF₃COOH).

All of the above makes it possible to suppose that VIIa has the 1-phenyl-4-hydroxy-5-nitro-6oxo-7-azaindoline structure. The formation of VIIa in the investigated reaction can be conceived of as being the result of replacement of the chlorine atom in IIIa by an aniline residue with subsequent opening of the dihydrofuran ring and closing of the new 1-phenylpyrroline ring. The structure of VIIa is also confirmed by reduction of it over a palladium catalyst in acetic anhydride to 1-phenyl-4-acetoxy-5-acetamido-6-oxo-7H-7-azaindoline (VIIIa).

EXPERIMENTAL

The PMR spectra were recorded with a JNM-4H-100 (100 MHz) spectrometer with tetramethylsilane as the internal standard. The IR spectra were recorded with a UR-10 spectrophotometer. The UV spectra of ethanol solutions were recorded with an EPS-3 spectrophotometer.

<u>1-Phenyl-4-phenylamino-6-oxo-5-azaindoline (IIa)</u>. A mixture of 0.5 g (3 mmole) of Ia [1] and 6 ml of aniline was heated at 180° for 7 h, after which it was cooled, and the resulting crystals were removed by filtration to give 0.37 g (39%) of the hydrochloride of IIa as colorless crystals with mp 253-254° (from alcohol). The product was only slightly soluble in water and acetone, but more soluble in alcohol. Found, %: Cl 10.5; N 12.7. $C_{18}H_{17}N_{3}O \cdot HCl$. Calculated, %: Cl 10.8; N 12.8. The base was obtained as a white crystalline substance with mp 242-243° [dec., from dimethylformamide (DMF)]; it was insoluble in ether, benzene, chloroform, and water, but soluble in hot DMF. Found, %: C 74.4; H 5.6; N 14.2. $C_{18}H_{17}N_{3}O$. Calculated, %: C 74.2; H 5.8; N 14.4. In a similar experiment carried out at 160° for 6 h, the yield of IIa was reduced to 11.7%.

<u>1-Phenyl-4-phenylamino-5-methyl-6-oxo-5-azaindoline (IIb)</u>. A solution of 0.25 g (1.36 mmole) of Ib [1] in 0.6 ml (7 mmole) of aniline was heated at 180° for 6 h, after which the excess aniline was evaporated in vacuo, and the residue was triturated with ether. The resulting substance was dissolved in water, and the solution was extracted with benzene. The extract was dried with potassium carbonate and vacuum evaporated to give 0.15 g (35.8%) of IIb as a white crystalline substance that was only slightly soluble in water, ether, benzene, and chloroform, but more soluble in alcohol. Found, %: C 75.2; H 5.9; N 13.3. $C_{20}H_{19}N_3O$. Calculated, %: C 75.5; H 5.9; N 13.2. In a similar experiment carried out at 120° for 6 h, the yield of IIb was 12%.

<u>4-(N-Phenyl-N-ethylamino)-6-oxo-7-nitro-2,3-dihydro-5-azabenzofuran (IVa)</u>. A 1 g (5 mmole) sample of IIIa [2] was heated in 5 ml of N-ethylaniline at 100° for 7 h, after which the precipitate was removed by filtration, washed with ether, and dissolved in DMF. Dilution of the DMF solution gave 0.45 g (35.6%) of the monohydrate of IVa as yellow crystals that did not melt up to 360°. The product was insoluble in water, ether, benzene, alcohol, acetone, and chloroform, but soluble in DMF. Found, %: C 56.8; H 5.3; N 13.6. $C_{15}H_{15}N_2O_2 \cdot H_2O$. Calculated, %: C 56.7; H 5.3; N 13.2.

<u>4-Chloro-5-methyl-6-oxo-7-nitro-2,3-dihydro-5-azabenzofuran (IIIb)</u>. A 0.25 g (1.3 mmole) sample of Ib was added gradually with stirring to cooled (to -10°) 3 ml sample of fuming nitric acid, after which the mixture was held at this temperature for 1 h. It was then carefully made alkaline to pH 10 (with stirring and ice cooling) with 25% ammonium hydroxide and allowed to stand in a refrigerator for 10 h. The precipitate was removed by filtration to give 0.17 g (55%) of IIIb as colorless crystals with mp 251-252° (from water). The substance was only slightly soluble in ether and benzene, but more soluble in chloroform, alcohol, and water. Found,%: C 41.8; H 3.0; Cl 15.4; N 11.8. C₈H₇ClN₂O₄. Calculated,%: C 41.6: H 3.0; Cl 15.4; N 12.1.

<u>4-Benzylamino-5-methyl-6-oxo-7-nitro-2,3-dihydro-5-azabenzofuran (Vb)</u>. A mixture of 0.25 g (1 mmole) of IIIb and 0.25 ml (2.5 mmole) of benzylamine in 22 ml of acetone was refluxed for 5.5 h, after which the precipitate was removed by filtration, and the acetone was vacuum evaporated to give 0.1 g (29.5%) of the monohydrate of Vb with mp 219-220° (from alcohol). The substance was only slightly soluble in ether, benzene, and ethyl acetate, more soluble in chloroform and alcohol, and soluble in DMF and acetone. Found,%: C 56.8; H 5.2; N 13.6. $C_{15}H_{15}N_3O_4 \cdot H_2O$. Calculated,%: C 56.7; H 5.4; N 13.2. The picrate was obtained as light-yellow crystals with mp 195-196° (from alcohol). The substance was only slightly soluble in ether, benzene, and chloroform, but more soluble in alcohol. Found,%: C 47.6; H 3.6; N 16.2. $C_{15}H_{15}N_3O_4 \cdot C_6H_3N_3O_7$. Calculated,%: C 47.5; H 3.4; N 15.8.

<u>4-Phenylamino-5-oxo-6-nitro-2,3-dihydro-5-azabenzofuran (VIa)</u>. A mixture of 0.8 g (3 mmole) of IIIa and 8 ml of aniline was heated at 100° for 15 h, after which it was cooled, and the precipitate was removed by filtration to give 0.05 g (10%) of VIIa. The filtrate was diluted with 80 ml of ether and filtered to give 0.7 g (64%) of VIa as light-yellow crystals with mp 255° (dec., from alcohol). The substance was only slightly soluble in ether, benzene, and water, but more soluble in alcohol and chloroform. Found,%: C 56.8; H 4.1; N 15.0. $C_{13}H_{11}N_3O_4$. Calculated,%: C 57.1; H 4.0; N 15.4. The picrate was obtained as light-yellow crystals with mp 182.5-184° (from alcohol). It was only slightly soluble in ether and benzene, but more soluble in alcohol. Found,%: C 45.1; H 3.1; N 16.8. $C_{13}H_{11}N_3O_4 \cdot C_6H_3N_3O_7$. Calculated,%: C 45.4; H 2.8; N 16.7.

<u>1-Phenyl-4-hydroxy-5-nitro-6-oxo-7-azaindoline (VIIa)</u>. A mixture of 2 g (8 mmole) of IIIa and 20 ml of aniline was heated at 100° for 6 h, after which it was cooled and the precipitate was removed by filtration to give 0.95 g (37.8%) of VIIa as a bright-red crystalline substance with mp 208-208.5° (from benzene). The product was only slightly soluble in ether and water, but more soluble in alcohol and benzene. Found,%: C 57.4; H 4.2; N 15.2. $C_{13}H_{11}N_{3}O_{4}$. Calculated,%: C 57.2; H 4.0; N 15.4. The mother liquor from the separation of VIIa was diluted with 150 ml of ether and filtered to give 0.64 g (24%) of VIa with mp 255° (decomp.).

<u>1-Phenyl-4-acetoxy-5-acetamido-6-oxo-7H-7-azaindoline (VIIIa)</u>. A palladium catalyst (obtained by reduction of 1.5 g of PdCl₂ with hydrogen in 18% hydrochloric acid, removal by filtration, and washing thoroughly with alcohol) was added to a solution of 2 g (7 mmole) of VIIa in 150 ml of acetic anhydride. The material was hydrogenated under normal conditions until hydrogen absorption ceased. The catalyst was removed by filtration, and the solution was evaporated to dryness in vacuo. The product (VIIIa) was extracted from the residue with 500 ml of boiling ether, and the extract was evaporated to one fourth of its original volume and cooled. The resulting crystals were removed by filtration to give 0.15 g of VIIIa. The product, which was insoluble in ether, was introduced (as a solution in 1 ml of chloroform) into a column filled with Al₂O₃ (h 40 cm, d 2.5 cm) and eluted with 200 ml of ether to give 0.15 g of VIIIa; the overall yield of VIIIa was 0.3 g (12.5%). The colorless crystals had mp 178-178.5° (from benzene). The product was only slightly soluble in ether and water, but more soluble in alcohol, acetone, and chloroform. Found,%: C 61.8; H 5.1; N 12.9. C₁₇H₁₇N₃O₄. Calculated,%: C 62.1; H 5.2; N 12.8.

We thank Yu. N. Sheinker, E. M. Peresleni, L. M. Alekseeva, N. A. Zosimova, and Yu. I. Pomerantsev for their assistance in conducting the spectral investigations.

LITERATURE CITED

- 1. L. N. Yakhontov, M. Ya. Uritskaya, E. I. Lapan, and M. V. Rubtsov, Khim. Geterotsikl. Soed., 18 (1968).
- 2. L. N. Yakhontov, M. Ya. Uritskaya, V. A. Loginova, and M. V. Rubtsov, Khim. Geterotsikl. Soed., 456 (1969).
- 3. L. N. Yakhontov and E. I. Lapan, Khim. Geterotsikl. Soed., 27 (1970).
- 4. L. N. Yakhontov, D. M. Krasnokutskaya, A. N. Akalaev, I. N. Palant, and Yu. I. Vainshtein, Khim. Geterotsikl. Soed., 789 (1971).