SYNTHESIS OF SOME CONDENSED BENZOFURANS

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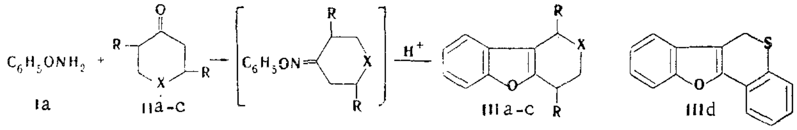
UDC 547.728.2.818

The condensation of O-phenylhydroxylamine (Ia) with tetrahydro-4-thiopyrone, 1-methyl-4-piperidone (IIb), 1,2,5-trimethyl-4-piperidone, and 4-thiochromanone and of O-(4-tolyl)-hydroxylamine with IIb was used to synthesize the corresponding benzofuran derivatives (IIIa-e), from which IIIa and IIIb were obtained by deamination of 8-amino-3,4-dihydro-1H-thiopyrano-[4,3-b]benzofuran and 2-methyl-8-amino-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine.

The cyclization of 4-nitrophenyl ethers of oximes of tetrahydro-4-thiopyrone and 4-piperidones, which leads to derivatives of new heterocyclic systems – 3,4-dihydro-1H-thiopyrano[4,3-b]benzofuran and 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine – that contain a nitro group in the benzene ring, has been described in previous communications [1-3]. In a study of the cyclization of 4-piperidones, the peculiarities of this reaction, which contribute to the elucidation of its mechanism, were established [4].

In a continuation of these investigations, we have studied the condensation of unsubstituted O-phenylhydroxylamine (Ia) with heterocyclic ketones – tetrahydro-4-thiopyrone (IIa), 1-methyl-4-piperidone (IIb), 1,2,5-trimethyl-4-piperidone (IIc), and 4-thiochromanone (IId). Several examples of the condensation of Ia with ketones to give the corresponding phenyl ethers of the oximes with subsequent cyclization of them to benzofurans are presented in [5-7]. We have obtained benzofuran derivatives (IIIa-d) as a result of the condensation of Ia with IIa-d without isolation of the intermediate ethers. The condensation of Ia with IIa and IId was carried out in alcohol solutions of hydrogen chloride. Under similar conditions, the reaction with IIb and IIc leads to the formation of a mixture of several substances, from which the final products of the reaction (IIIb and IIIc) cannot be isolated. Compounds IIIb, c were obtained only on subsequent heating of the residue formed after evaporation of the reaction mass with a mixture (9:1) of acetic and sulfuric acids.



II, III a R = H, X = S; b R = H, X = NCH$_3$; c R = CH$_3$, X = NCH$_3$

Consequently, as in the case of the 4-nitrophenyl ethers of 4-piperidones [1, 3], to complete the cyclization of phenyl ethers of 4-piperidones it is expedient to use a mixture of the indicated acids, which is a more active catalyst for the conversion of the intermediate products of the condensation to the benzofuran system [4]. The use of this mixture of acids from the very start of the reaction of O-phenylhydroxylamine with IIb, c gives somewhat poorer results. This same route was used for the reaction of O-(4-tolyl)hydroxylamine (Ib) with IIa to give 2,8-dimethyl1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine (IIIe).

The melting point of the hydrochloride of IIIb (265-266°) differs considerably from that of the compound (228°) obtained in low yield (6%) by Cattanach and Rees [5] by the reaction of Ia with IIb in alcohol with subsequent heating in alcoholic hydrogen chloride solution. In order to confirm the structure of III (in the case of IIIa, b) and to search for a different path for their preparation, we undertook the synthesis of IIIa, b from the previously described [3] 8-nitro-3,4-dihydro-1H-thiopyrano[4,3-b]benzofuran (IVa) and 2-methyl-

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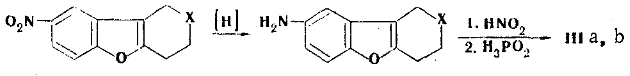
Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 740-742, June, 1972. Original article submitted June 14, 1971.

8-nitro-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine (Va) by reduction to the corresponding 8-amino derivatives (IVb and Vb) and deamination of the latter through the diazonium salts.



IVa, Va IVb, Vb

IV a, b X=S; V a, b X=NCH_3

The reduction of the nitro compounds (IVa and Va) proceeds extremely smoothly by the action of hydrazine hydrate in the presence of Raney nickel. In contrast to IVa [2], Va can also be reduced in good yield with hydrogen over Pd black. The diazo group was replaced by hydrogen by the action of hypophosphorous acid. Both samples of the hydrochloride of IIIb and both samples of IIIa obtained by these two methods proved to be completely identical. The PMR spectrum of IIIc (a solution of the base in CD_3OD, Varian T-60 spectrophotometer, δ scale), as in the case of the corresponding 8-nitro derivative [3], is characterized by the presence of two doublet signals with $J \simeq 6.5$ Hz at 1.53 and 1.26 ppm from the 1-CH_3 and 4-CH_3 groups, respectively, and by the appearance of a long-range spin–spin coupling ($J \simeq 2$ Hz) between the 1-H and 4-H protons, the signals of which are at 3.0-3.7 and 2.0-2.7 ppm (overlapped, respectively, with the signals of the 3-H_2 and 2-CH_3 protons). The PMR spectral data exclude the assumption that the product of the condensation of Ia with IIc is an isomeric compound that might have formed if the cyclization had occurred at the 5 position of piperidone IIc.

EXPERIMENTAL

2-Methyl-8-amino-1,2,3,4-tetrahydro[3,2-c]pyridine (Vb). A. A 10-g (42 mmole) sample of Va in 200 ml of ethanol was hydrogenated over 0.2 g of Pd black. After hydrogen absorption had ceased, the catalyst was removed by filtration, and the alcohol was vacuum-evaporated. The residue was dissolved in ether, and alcoholic hydrogen chloride solution was added to precipitate 9.5 g (76%) of the monohydrate of the dihydrochloride of Vb with mp 271-273° (dec., from aqueous isopropyl alcohol). Found: C 49.1; H 6.3; Cl 24.3; N 9.7%. $C_{12}H_{14}N_2O \cdot 2HCl \cdot H_2O$. Calculated: C 49.1; H 6.2; Cl 24.2; N 9.6%.

B. A 1-1.5-g sample of Raney nickel was added to a solution of 3.8 g (16 mmole) of Va in 130 ml of methanol, and 7 ml of hydrazine hydrate was then added dropwise with stirring in the course of 30 min. The mixture was stirred for 1 h, the catalyst was removed by filtration, and the methanol was evaporated to give 3.1 g (96%) of Vb with mp 131-131.5° (from heptane–benzene). Found: C 71.2; H 7.0; N 13.5%. $C_{12}H_{14}N_2O$. Calculated: C 71.3; H 7.0; N 13.3%.

8-Amino-3,4-dihydro-1H-thiopyrano[4,3-b]benzofuran (IVb). An 8-g (34 mmole) sample of IVa in 300 ml of methanol was reduced over Raney nickel with 15 ml of hydrazine hydrate as in the preparation of Vb to give 6.5 g (91%) of IVb with mp 153-154° (from heptane–benzene). Found: C 64.4; H 5.3; N 6.9; S 15.4%. $C_{11}H_{11}NOS$. Calculated: C 64.4; H 5.4; N 6.9; S 15.6%.

2-Methyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine (IIIb). A. A mixture of 1.2 g (11 mmole) of Ia and 1.3 g (11 mmole) of IIb [8] was refluxed in 15 ml of 15% absolute alcoholic hydrogen chloride solution, and the mixture was poured into water. The acid solution was made alkaline with ammonium hydroxide and extracted with ether. The extract was dried and evaporated, and the residue was refluxed for 5 min with glacial acetic acid–concentrated H_2SO_4 (9 : 1). The mixture was poured into water, and the acid solution was made alkaline with ammonium hydroxide and extracted with ether. The extract was dried and treated with absolute alcoholic hydrogen chloride solution to precipitate 1.25 g (51%) of the hydrochloride of IIIb with mp 265-266° (from absolute alcohol). Found: C 64.3; H 6.3; Cl 15.8; N 6.4%. $C_{12}H_{13}NO \cdot HCl$. Calculated: C 64.3; H 6.3; Cl 15.8; N 6.3%.

B. A 3.5-g (11.9 mmole) sample of the dihydrochloride of Vb in 80 ml of water and 20 ml of concentrated H_2SO_4 was diazotized at 0° with 0.9 g (13 mmole) of $NaNO_2$ in 10 ml of water, and H_3PO_2, prepared from 22 g of $Ba(H_2PO_2)_2$ and 12 ml of concentrated H_2SO_4 in 80 ml of water, was added to the diazonium solution. The mixture was held at 0-5° for 12 h and at 20° for 36 h. It was then made alkaline with 10% KOH and extracted with ether. The ether solution was dried with $MgSO_4$ and treated with alcoholic hydrogen chloride solution to precipitate 7 g (64%) of the hydrochloride of IIIb with mp 265-266° (from absolute alcohol). Samples of IIIb obtained by these two methods did not depress one another's melting points, had identical IR spectra (in mineral oil) at 400-3600 cm^{-1}, and gave identical R_f values during thin-layer chromatography (TLC) on the alkaline form of Al_2O_3.

1,2,4-Trimethyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine (IIIc). As in the synthesis of IIIb, the reaction of 2.7 g (19 mmole) of the hydrochloride of Ia with 2.6 g (19 mmole) of IIc in 15 ml of 20% absolute alcoholic hydrogen chloride solution with subsequent treatment with 20 ml of glacial acetic acid–concentrated sulfuric acid (9 : 1) gave 3.6 g (77%) of the hydrochloride of IIIc with mp 276-277° (dec., from absolute alcohol). Found: C 66.9; H 7.2; Cl 14.1; N 5.7%. $C_{14}H_{17}NO \cdot HCl$. Calculated: C 66.8; H 7.2; Cl 14.1; N 5.6%.

2,8-Dimethyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine (IIIe). Similarly, 3.2 g (0.02 mole) of the hydrochloride of Ib [9] and 2.25 g (20 mmole) of IIb gave 1.85 g (39%) of the hydrochloride of IIIe with mp 257-258° (from absolute alcohol). Found: C 65.8; H 6.7; Cl 14.6; N 5.9%. $C_{13}H_{15}NO \cdot HCl$. Calculated: C 65.7; H 6.8; Cl 14.9; N 5.9%.

3,4-Dihydro-1H-thiopyrano[4,3-b]benzofuran (IIIa). A. A mixture of 1.2 g (11 mmole) of Ia and 1.3 g (11 mmole) of IIa in 10 ml of 7.5% absolute alcoholic hydrogen chloride solution was refluxed for 10 min and poured into water. The aqueous mixture was extracted with ether, the extract was dried and evaporated, and the residue was crystallized three times from hexane to give 0.4 g (18%) of IIIa with mp 71-72°. Found: C 69.2; H 5.2; S 16.8%. $C_{11}H_{10}OS$. Calculated: C 69.4; H 5.3; S 16.9%. The UV spectrum (in alcohol, c 10^{-5} M) was similar to the spectrum of the benzofuran reported in [10]: there is a series of bands at 244-256 nm (log $\varepsilon \cong 4.11$) in addition to λ_{max} 248 nm (log ε 4.15).

B. A 2-g (9.7 mmole) sample of IVb in 25 ml of water and 25 ml of concentrated HCl was diazotized at 0° with a solution of 0.8 g of $NaNO_2$ in 10 ml of water and was then deaminated, as in the case of Vb, by means of H_3PO_2, prepared from 11 g of $Ba(H_2PO_2)_2$, 12 ml of concentrated H_2SO_4, and 80 ml of water, to give 1 g (54%) of IIIa with mp 71-72° (from hexane). The product did not depress the melting point of a sample of IIIa obtained as indicated above and was identical to it with respect to mobility during TLC on Al_2O_3.

6H-Benzo[5,6]thiopyrano[4,3-b]benzofuran (IIId). As in the preparation of IIIa, 2.7 g (19 mmole) of the hydrochloride of Ia and 3.0 g (18 mmole) of IId in 30 ml of 26% absolute alcoholic hydrogen chloride solution (refluxing for 30 min) gave 1.5 g (34%) of IIId with mp 54-55° (from hexane). Found: C 75.6; H 4.1; S 12.9%. $C_{15}H_{10}OS$. Calculated: C 75.6; H 4.2; S 13.4%.

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