RING CLOSURE OF SOME O-ARYL ETHERS OF KETOXIMES TO BENZOFURANS

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The action of alcohol solutions of hydrogen chloride on aryl ethers of the oximes of N-substituted 4-piperidones (Ia-c) yielded rearrangement products – 3-(2-hydroxyaryl)-4-piperidones (IIa, b) and (or) 4a-alkoxy-1,2,3,4,4a,9b-hexahydrobenzofuro[3,2-c]pyridines (IIIa-c), which, under certain conditions, are readily converted to 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridines (IVa, b). Ketones of the II type are ketalized to dihydrobenzofurans III by alcohol solutions of hydrogen chloride.

The method of closing the furan ring in aryl ethers of ketoximes discovered several years ago [1-5] is beginning to assume importance for the synthesis of various condensed furan systems, including compounds with a furan ring fused with other heterorings [5-9]. Two papers on the elucidation of the mechanism of this interesting transformation were presented simultaneously [10, 11]. It is assumed [1, 2, 10], even though somewhat arbitrarily, that the mechanism of this closing of the furan ring is similar to the mechanism of the Fischer indole synthesis.

Of course, every bit of new information on the products of the conversion of O-aryl oximes of ketones should be used in the plans for establishing the mechanism of the furan ring closure, especially since the parallel study of this process and the Fischer cyclization of arylhydrazones will undoubtedly have a positive effect on the definitive solution of the problem of the detailed mechanisms of the elementary reactions of both multistep transformations.

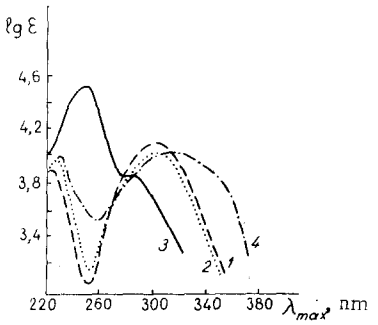

Fig. 1. UV spectra (in alcohol, c $1 \cdot 10^{-5}$ to $1 \cdot 10^{-2}$ M): 1) 2-methyl-4a-ethoxy-8-nitro-1,2,3,4,4a,9b-hexahydrobenzofuro[3,2-c]pyridine (IIIb); 2) 4-nitroanisole; 3) 2-methyl-1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridine (IVa); 4) 2-methyl-3-(2-hydroxy-5-nitrophenyl)-4-piperidone (IIa).

We have previously [9] worked out the synthesis of 1,2,3,4-tetrahydrobenzofuro[3,2-c]pyridines by the intramolecular cyclization of the aryl ethers of the oximes of 4-piperidones under the influence of a mixture of sulfuric and acetic acids or boron trifluoride etherate. However, these compounds cannot be obtained when the reaction is carried out in alcohol solutions of hydrogen chloride, although, under similar conditions, the cyclization of O-aryl oximes of tetrahydro-4-thiopyrone, i.e., the analog of 4-piperidone, to the corresponding thiopyrano [4,3-b]benzofurans proceeded without complications [8].

In this study, we have ascertained the structures of the products of the reaction of O-aryl oximes of 4-piperidones with alcohol solutions of hydrochloric acid.

The starting materials were the 4-nitro- and 4-carbethoxyphenyl ethers of 1-methyl-4-piperidone (Ia, b) and the 4-nitrophenyl ether of 1,2,5-trimethyl-4-piperidone oxime (Ic). The compounds

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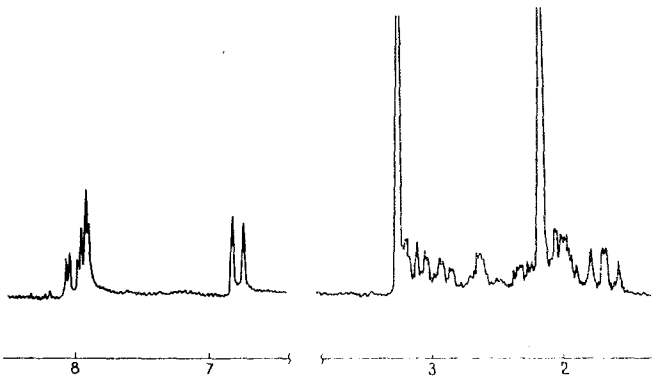
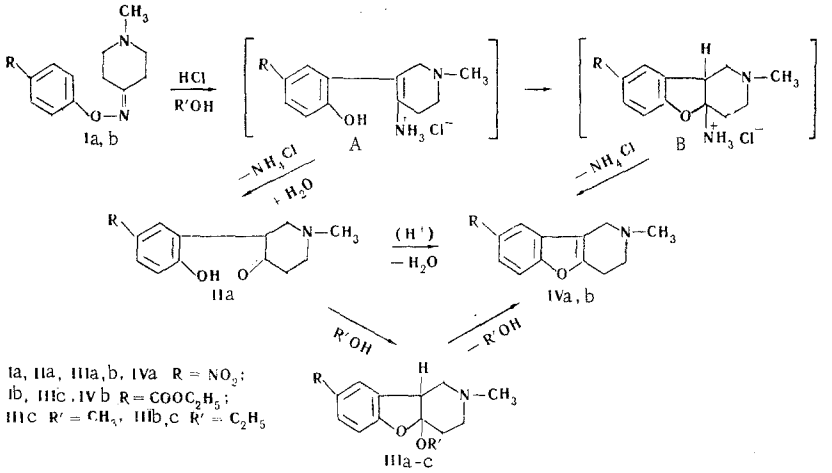


Fig. 2. PMR spectrum of 2-methyl-4a-methoxy-8-nitro-1,2,3,4,4a,9b-hexahydrobenzofuro[3,2-c]pyridine (IIIa).

isolated were 3-(2-hydroxyaryl)-4-piperidones (IIa, b) and (or) 4a-alkoxy-1,2,3,4,4a,9b-hexahydrobenzofuro[3,2-c]pyridines (IIIa-c). Thus, for example, 72% IIa and 21% IIIa were obtained when a mixture of Ia and 28% hydrogen chloride in absolute methanol was refluxed for ~1 h. Similar treatment of Ia with a 29% solution of hydrogen chloride in ethanol gave 12% IIa and 39% IIIb. The final cyclization products – benzofurans IV – are not formed under these conditions. Traces of benzofuran derivative IVa, previously [9] synthesized by the cyclization of Ia in a mixture of acetic and sulfuric acids, could be detected in the reaction mass by means of thin-layer chromatography only after refluxing for ~6 h in an alcohol solution of hydrogen chloride.



Compounds IIIa, b are not crystal solvates (with a molecule of alcohol) of IVa. The curves of the UV spectra of IIIa, b, which have a 4-alkoxynitrobenzene fragment, are similar to the curve of 4-nitroanisole, but differ substantially from the spectral curve of benzofuran IVa (see Fig. 1). The signals of the protons of the alicyclic portion of the molecule in the PMR spectrum of IVa [9] are broad peaks at 2.8 and 3.4 ppm, while the complex signals of the protons of the alicycle in the spectra of IIIa, b occupy the 1.4-3.2 ppm region (see Fig. 2 for the spectrum of IIIa).

The IR spectra (in mineral oil) of ketones IIa, b are characterized by $\nu_{C=O}$ at 1713 cm^{-1} and a broad band at 1800-2000 cm^{-1} caused by hydrogen bonding. In chloroform solution (c 10^{-3} M), the vibrations of a free hydroxyl group are also absent, which attests to a strong intramolecular hydrogen bond between the phenolic hydroxyl group and, apparently, the nitrogen atom of the piperidine ring. The UV spectrum of IIa (see Fig. 1, curve 4) is similar to the spectrum of 4-nitrophenol (for the latter, λ_{max} 310-312 nm, log ε 4.10).

Hydroxy ketones II are apparently formed from intermediate enamines A by hydrolytic cleavage of the amino group by the action of the moisture present in the reaction mixture. It is less likely that the hydrolysis occurs during workup of the reaction products with water. This is partly confirmed by the isolation of ammonium chloride from the reaction solution in amounts up to 88% of the theoretical and by the fact that the IR spectrum of the residue from the evaporation of the solution (in the case of the reaction

TABLE 1. Conversion of II and III to IV

Starting compound	Amount of II or III, g	Vol. of the acid mixture, ml	Substance obtained	mp, °C	Yield, %
IIa	0,15	1,5	IVa	145—146a	65
IIb	0,20	3,0	IVb	54—56c	64
IIIa	0,10	1,0	IVa	145—146a	90
IIIb	3,0	30,0	IVa	145—146a	62
IIIc	0,7	10,0	IVc	111—112b	80

a) From alcohol; R_f 50% alcohol. c) From petroleum ether.

with Ia), with protection from external moisture, contains bands that are characteristic for the hydrochloride of IIa: 1737, 1626, and 1600 cm^{-1}.

It is essential to note that the 4-nitrophenyl ethers of tetrahydro-4-thiopyrone [8] and other ketones [11] that do not have an amino group in the β position do not form alcohol-addition products in the presence of hydrogen chloride. Alkoxy derivatives III are most likely formed by either prior replacement of the H_3N^+ group by an alkoxy group in intermediates A or B (compounds of similar structure were previously isolated along with ketones of the II type in the rearrangement of the phenyl ether of 1-cyclohexyl-3-oxo-2-pyrrolidone oxime [10]) or by ketalization of hydroxyaryl ketones II. Under the conditions of the reaction of I with alcohol solutions of hydrogen chloride, benzofurans IV do not add an alcohol molecule at the site of the double bond of the furan ring. The comparatively high stability of ketals III should be explained by the electron-acceptor effect of the protonated amino group of the ring (for simplicity, this amino group is depicted in the unprotonated form in the scheme), which leads to an increase in the positive charge on the C_{4a} atom in III or, correspondingly, on the C atom of the carbonyl group in II. In our opinion, the relative amounts of ketones II and ketals III in the reaction mixture are determined not only by the reaction time and temperature but also by the concentration of water in the alcohols and the nucleophilicity of the alkoxy groups.

Special experiments demonstrated that ketone IIa can be partially converted to ketal IIIa by heating in methanolic hydrogen chloride.

Both IIa and IIIa, b smoothly give benzofuran derivatives IVa, b when they are heated with a mixture of acetic and sulfuric acids, i.e., under conditions that are sufficiently favorable for the preparation of IV directly from the ethers of the ketoximes, particularly the nitro-substituted ones [9].

Thus, in the general case, the cyclization of ethers of oximes to benzofurans can proceed not only through intermediate B but also via the other paths indicated in the scheme.

EXPERIMENTAL

The UV spectra of alcohol solutions were recorded with an SF-4 spectrometer. The IR spectra were recorded with a UR-10 spectrometer. The PMR spectra (in CCl_4) were obtained with a Varian-HA-100 spectrometer with an operating frequency of 100 MHz. The purity of the compounds obtained was monitored by thin-layer chromatography on Al_2O_3 (alkaline form, activity IV, elution with chloroform). The hydrochlorides were applied on the adsorbent without conversion to the bases.

Transformations of Aryl Ethers Ia-c in the Presence of Alcohol Solutions of Hydrogen Chloride. A) A mixture of 6.6 g (0.026 mole) of ether Ia and 100 ml of a 28% solution of hydrogen chloride in absolute methanol was refluxed for 1 h and cooled. The mixture was filtered to give 0.84 g (60%) of ammonium chloride, and the filtrate was vacuum-evaporated at ~ 40°. The residue was dissolved in 50 ml of water, and the solution was made alkaline with ammonium hydroxide to give 4.85 g of precipitate. The aqueous solution was partially evaporated in vacuo to give another 1.4 g of precipitate. (This and the first precipitate gave two spots with R_f 0.05 and 0.50.) The combined precipitates were refluxed for 15 min with 200 ml of benzene, and the hot mixture was filtered to give 3.15 g of pure 2-methyl-3-(2-hydroxy-5-nitrophenyl)-4-piperidone (IIa) with mp 157-158° and R_f 0.05. Another 1.6 g of IIa was isolated from the benzene solution on cooling to give an overall yield of 4.75 g (72%). Found: C 57.8; H 5.7; N 10.9%. $C_{12}H_{14}N_2O_4$. Calculated: C 57.6; H 5.6; N 11.2%. UV spectrum, λ_{max}, nm (log ε): 230-232 (4.01), 312-318 (4.04). IR spectrum: $\nu_{C=O}$ 1713 cm^{-1}. The benzene solution was evaporated to dryness to give 1.5 g (21%) of 2-methyl-4a-methoxy-8-nitro-1,2,3,4,4a,9b-hexahydrobenzofuro[3,2-c]pyridine (IIIa) with mp 111-112° (from heptane) and R_f 0.50. Found: C 59.0; H 6.1; N 10.5%. $C_{13}H_{16}N_2O_4$. Calculated: C 59.1; H 6.1; N 10.6%. UV spectrum, λ_{max}, nm (log ε): 228 (3.99), 302-306 (3.99). The hydrochloride decomposed at ~ 120°. Found N 9.0; Cl 11.9%. $C_{13}H_{16}N_2O_4 \cdot HCl$. Calculated: N 9.3; Cl 11.8%.

B) A mixture of 1.6 g (6 mmole) of ether Ia in 16 ml of a 29% solution of hydrogen chloride in absolute alcohol was refluxed for 1 h and cooled. The mixture was filtered to give 0.3 g (88%) of ammonium chloride, and the filtrate was evaporated to dryness in vacuo at ~ 40°. The residue was crystallized from absolute alcohol to give 0.85 g (39%) of the crystal solvate of the hydrochloride of 2-methyl-4a-ethoxy-8-nitro-1,2,3,4,4a,9b-hexahydrobenzofuro[3,2-c]pyridine (IIIb) with mp 191-192° and R_f 0.55. Found: C 53.2; H 6.5; N 8.3; Cl 10.5%. $C_{14}H_{18}N_2O_4 \cdot HCl \cdot 0.5C_2H_5OH$. Calculated: C 53.3; H 6.6; N 8.3; Cl 10.5%. All of this compound was dissolved in 10 ml of water, and the solution was made alkaline with ammonium hydroxide. The resulting precipitate was removed by filtration, washed with water, dried, and crystallized from heptane to give 0.6 g of IIIb with mp 81-82° and R_f 0.55. Found: C 60.4; H 6.5; N 10.1%. $C_{14}H_{18}N_2O_4$. Calculated: C 60.4; H 6.6; N 10.1%. UV spectrum, λ_{max}, nm (log ε): 228-230 (3.97), 307 (4.04). IR spectrum: 1622, 1603, 1512, 1381 cm^{-1}. The hydrochloride (obtained from an ether solution of a pure sample of IIIb by precipitation with an ether solution of hydrogen chloride) decomposed at ~ 130° and had R_f 0.55. Found: N 8.8; Cl 11.1%. $C_{14}H_{18}N_2O_4 \cdot HCl$. Calculated: N 8.9; Cl 11.3%. When this hydrochloride was recrystallized from absolute alcohol, a hydrochloride containing 0.5 mole of solvate alcohol and melting at 191-192° was obtained. (A sample of this product did not depress the melting point of the compound obtained above.)

The alcohol mother liquor remaining after removal of 0.85 g of $IIIb \cdot HCl \cdot 0.5C_2H_5OH$ was evaporated to dryness. The residue was dissolved in 5 ml of water, and the solution was made alkaline with ammonium hydroxide. The aqueous solution was decanted from the viscous precipitate, and the latter was triturated twice with a mixture of 5 ml of water and 0.5 ml of concentrated ammonium hydroxide. The combined aqueous ammonia solutions were evaporated to dryness, and the residue was treated with boiling toluene. The toluene solution was filtered hot and cooled. The precipitated crystals were removed by filtration and washed with ether to give 0.2 g (12%) of IIa with mp 157-158° and R_f 0.05. This product did not depress the melting point of the sample obtained in the experiment with methanol.

C) A mixture of 3 g (1 mmole) of ether Ib and 60 ml of a 25% solution of hydrogen chloride in absolute alcohol was refluxed for 1 h and cooled. The mixture was filtered to give 0.5 g (86%) of ammonium chloride, and the solution was poured into absolute ether. The precipitated hydrochloride was removed by filtration and recrystallized three times from absolute alcohol to give 2.8 g (77%) of the hydrochloride of 2-methyl-4a-ethoxy-8-carbethoxy-1,2,3,4,4a,9b-hexahydrobenzofuro[3,2-c]pyridine (IIIc) with mp 191-192°. Found: C 59.9; H 7.2; N 4.2; Cl 10.3%. $C_{17}H_{23}NO_4 \cdot HCl$. Calculated: C 59.7; H 7.1; N 4.1; Cl 10.4%.

D) A solution of 3 g (11 mmole) of ether Ic in 30 ml of a 20% solution of hydrogen chloride in absolute methanol was refluxed for 1 h, and the methanol was removed by vacuum distillation. The residue was dissolved in water and gradually made alkaline with ammonia during periodic extraction with ether. The ether extracts were dried and evaporated, and the residue was triturated with a small amount of ether and filtered to give 1.75 g (58%) of 1,2,5-trimethyl-3-(2-hydroxy-5-nitrophenyl)-4-piperidone (IIb) with mp 146-147° (from aqueous alcohol). Found: C 60.0; H 6.4; N 10.3%. $C_{14}H_{18}N_2O_4$. Calculated: C 60.4; H 6.5; N 10.1%. IR spectrum: $\nu_{C=O}$ 1713 cm^{-1}.

Conversion of IIa to IIIa. A mixture of 1 g (4 mmole) of IIa and 10 ml of a 28% solution of hydrogen chloride in absolute methanol was refluxed for 1 h, and the mixture was worked up as above to give 0.49 g (41%) of unchanged IIa with mp 157-158° (from toluene) and R_f 0.05 and 0.14 g (13%) of IIIa with mp 111-112° (from heptane) and R_f 0.50.

Tetrahydrobenzofuro[3,2-c]pyridines (IV). Compound II or III was refluxed with a mixture of glacial acetic and concentrated sulfuric acids (9 : 1 by volume) for 5 min (15 min in the preparation of IVc), and the mixture was poured into water. The resulting mixture was made alkaline with ammonium hydroxide solution, and IV was removed by filtration (see Table 1).

Compounds IVa-c were identical (according to mixed melting-point determinations) to the compounds obtained in [9].

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