SYNTHESIS OF SOME 1-OXO-1H-2,3,4,5-TETRAHYDROBENZOFURO[3, 2-c]AZEPINES

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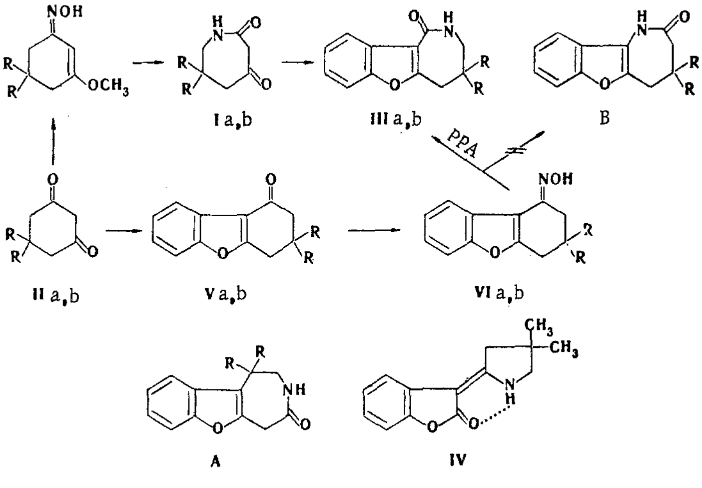
Condensation of O-phenylhydroxylamine with 1H-2,3,4,5,6,7-hexahydroazepine-2,4-dione in alcoholic hydrogen chloride solution gave 1-oxo-1H-2,3,4,5-tetrahydrobenzofuro[3,2-c]-azepine, while a similar condensation with 6,6-dimethyl-1H-2,3,4,5,6,7-hexahydroazepine-2,4-dione gave a mixture of 4,4-dimethyl-1H-2,3,4,5-tetrahydrobenzofuro[3,2-c]azepine and 2-oxo-3-(3',3'-dimethyl-5'-pyrrolidylidene)benzofuran. Tetrahydrobenzofuroazepines were also synthesized by Beckmann rearrangement of oximes of 1-oxo-1,2,3,4-tetrahydrobenzofuran and 3,3-dimethyl-1-oxo-1,2,3,4-tetrahydrodibenzofuran, which were obtained in turn by condensation of O-phenylhydroxylamine with dihydroresorcinol and dimedone.

In our preceding communications [1-4] we described the synthesis of benzofuran systems condensed with various heterorings. We simultaneously investigated problems associated with the stepwise character of the ring closing of some O-aryl ethers of ketoximes to benzofurans [5].

It seemed of interest to us to study the cyclization of O-aryl ethers of ketoximes of some unsymmetrical ketones of the azepine-2,4-dione type; this would make it possible to clear up a number of problems of the effect of the structure of these compounds on the direction of closing of the benzofuran ring.

Since the mechanism of the closing of the furan ring is similar to the mechanism of the Fischer indole synthesis, a comparison of these reactions using unsymmetrically constructed ketones may give new material for a more detailed study of the indicated processes.

We selected 1H-2,3,4,5,6,7-hexahydroazepine-2,4-dione (Ia) and 6,6-dimethyl-1H-2,3,4,5,6,7-hexahydroazepine-2,4-dione (Ib), which were obtained by Beckmann rearrangement of the oximes of dihydroresorcinol (IIa) and dimedone (IIb), respectively [6], as the starting ketones.



I, II, III, V, VI a R=H; b R=CH$_3$

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The condensation of O-phenylhydroxylamine with ketones Ia,b was carried out without isolation of the intermediate phenyl ethers of the oximes. The cyclization of the latter could lead to the formation of two possible isomers of the III or A type.

One substance, to which the 1-oxo-2,3,4,5-tetrahydrobenzofuro[3,2-c]azepine structure (IIIa) was assigned on the basis of a study of the UV, IR, and PMR spectra, was isolated as a result of the reaction of O-phenylhydroxylamine with 1H-2,3,4,5,6,7-hexahydroazepine-2,4-dione (Ia). The IR spectrum of IIIa (in $CHCl_3$) is characterized by $\nu_{C=O}$ 1650 cm^{-1} and ν_{NH} 3435 cm^{-1}. The UV spectrum has a specific curve without expressed absorption maxima (Fig. 1, curve 1); this curve differs from the curve of the spectrum of the model compound 1,2,3,4-tetrahydrodibenzofuran (VII) (Fig. 1, curve 2). As compared with the spectrum of IIIa, the spectrum of VII is characterized by a lower intensity of the long-wave portion of the curve. A compound with a structure of the A type would have a UV spectrum similar to the spectrum of VII. The PMR spectrum of IIIa (in nitrobenzene) has signals at 3.50 ppm (2H, quartet with somewhat broadened components, J = 5 Hz, $3\text{-}H_2$), 3.1 ppm (2H, triplet, J = 7 Hz, $5\text{-}H_2$), and 1.9-2.4 ppm (2H, multiplet, $4\text{-}H_2$). On deuteration, the quartet from $3\text{-}H_2$ is converted to a triplet (J = 5 Hz). The singlet (at weak field) of two $5\text{-}H_2$ protons that should appear if the substance obtained had a structure of the A type was not observed. The absence of an isomer (type A) is confirmed by a study of the reaction mass by means of thin-layer chromatography (TLC) on aluminum oxide. All of these data are evidence that structure IIIa should be assigned to the compound obtained.

Condensation of 6,6-dimethyl-1H-2,3,4,5,6,7-hexahydroazepine-2,4-dione (Ib) with O-phenylhydroxylamine gives a mixture of two substances, which are separated by repeated crystallization into individual compounds with mp 163-164° and 173-174° and identical elemental compositions. Analysis of the reaction mixture by means of PMR spectroscopy demonstrated that these compounds are formed in a ratio of about 1:1. The UV spectrum of the compound with mp 163-164° has the same curve as IIIa (see Fig. 1, curve 3). The IR spectrum (in $CHCl_3$) is characterized by $\nu_{C=O}$ 1650 cm^{-1} and ν_{NH} 3438 cm^{-1}, a narrow intense band with a half width of 21 cm^{-1}. The PMR spectrum (in $CDCl_3$) has the following signals: 1.05 ppm [singlet, $4\text{-}(CH_3)_2$], 2.86 ppm (singlet, $5\text{-}H_2$), 3.06 ppm (doublet, $3\text{-}H_2$, J = 6 Hz; it is converted to a singlet when CD_3OD is added), 6.8 ppm (1H, a broad NHCO signal that vanishes when CD_3OD is added).

On the basis of these data and a comparison of them with the data obtained for IIIa, the 4,4-dimethyl-1-oxo-1H-2,3,4,5-tetrahydrobenzofuro[3,2-c]azepine structure (IIIb) should be assigned to the substance with mp 163-164°.

The UV spectrum of the compound with mp 173-174° has λ_{max} 246-254 nm (log ε 4.14) and 320-322 nm (log ε 4.2). The IR spectrum contains the following bands: 1710 cm^{-1} ($\nu_{C=O}$), 1626 cm^{-1} (a very intense band of a conjugated double bond), and 3344 cm^{-1} (ν_{NH}, a band with a half width of 36 cm^{-1} that remains in practically the same place as the concentration changes from 0.1 to 0.01 M). The PMR spectrum (in $CDCl_3$) contains the following signals: 1.1 ppm (6H, singlet, $2\text{-}CH_3$), 2.8 (2H, singlet), 3.4 ppm (2H, doublet, J ≃ 1 Hz; it is converted to a singlet when CD_3OD is added), and 8.2 ppm (1H, a broad NH signal that vanishes on deuteration). On the basis of these data, a structure of the A type cannot be assigned to the compound with mp 171-173°. It is most likely 2-oxo-3-(3',3'-dimethyl-5'-pyrrolidylidene)benzofuran (IV), the formation of which can be visualized if one assumes the alcoholysis of the seven-membered lactam with cleavage of the amide bond in one of the intermediate stages of the reaction.

With the aim of obtaining compounds with possible structures III and B, we simultaneously studied the cyclization of dihydroresorcinol (IIa) and dimedone (IIb) with O-phenylhydroxylamine. We obtained one substance in both cases. Their 1-oxo-1,2,3,4-tetrahydrodibenzofuran (Va) and 1-oxo-3,3-dimethyl-1,2,3,4-tetrahydrobenzofuran (Vb) structures were confirmed by the spectral data. The UV spectra of both compounds (Fig. 2, curves 1 and 2) have λ_{max} 224-228 nm (log ε 4.3) and 260-264 nm (log ε 3.9) and are definitely similar to the spectrum (Fig. 2, curve 3) of a genuine sample of 2-methyl-3-acetylbenzofuran (VIII) obtained by condensation of acetylacetone with O-phenylhydroxylamine. The IR spectra of Va,b are characterized by $\nu_{C=O}$ 1667 and 1671 cm^{-1}, respectively. In the IR spectrum of model compound VIII, $\nu_{C=O}$ is 1670 cm^{-1}. The PMR spectrum of Va (in CCl_4) contains the following peaks: 2.98 ppm (2H, triplet, J ≃ 6 Hz), and 1.9-2.85 ppm (4H, multiplet). The PMR spectrum of Vb (in CCl_4) contains the following signals: 1.0 ppm (6H, singlet, $2\text{-}CH_3$), 2.22 (2H, singlet, $4\text{-}H_2$), and 2.75 ppm (2H, singlet, $2\text{-}H_2$).

The oximes (VIa,b) were obtained from Va,b and were subjected to the Beckmann rearrangement with polyphosphoric acid (PPA) to give individual substances that were identical to IIIa,b with respect to their melting points and UV, IR, and PMR spectra; this is an additional proof of the correctness of the structures assigned to them. The formation of substances of the B types does not occur in the Beckmann rearrangement under the indicated conditions.

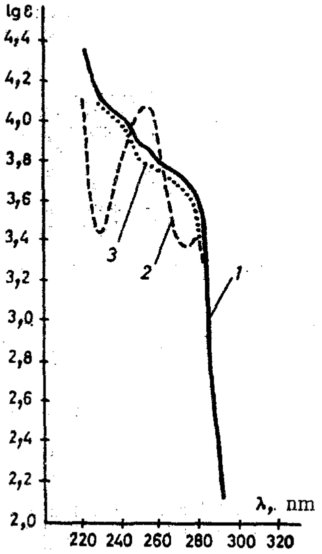

Fig. 1. UV spectra (in alcohol, c 1 · 10^{-5}–1 · 10^{-2}): 1) 1-oxo-1H-2,3,4,5-tetrahydrobenzofuro[3,2-c]azepine (IIIa); 2) 1,2,3,4-tetrahydrodibenzofuran (VII); 3) 1-oxo-4,4-dimethyl-1H-2,3,4,5-tetrahydrobenzofuro-[3,2-c]azepine (IIIb).

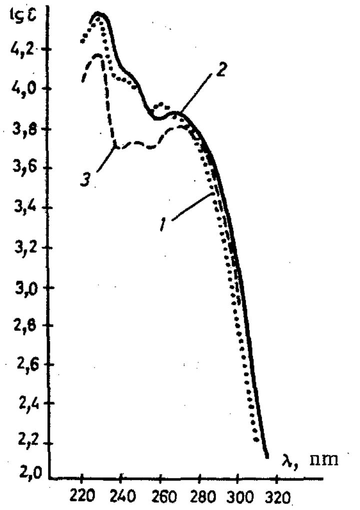

Fig. 2. UV spectra (in alcohol, c 1 · 10^{-5}–1 · 10^{-2}): 1) 1-oxo-1,2,3,4-tetrahydrobenzofuran (Va); 2) 1-oxo-3,3-dimethyl-1,2,3,4-tetrahydrodibenzofuran (Vb); 3) 2-methyl-3-acetylbenzofuran (VIII).

EXPERIMENTAL

The UV spectra were recorded with an SF-4 spectrophotometer, the IR spectra were recorded with a UR-10 spectrograph, and the PMR spectra were recorded with a Varian T-60 radiospectrometer (operating frequency 60 MHz, readings on the δ scale). Thin-layer chromatography was carried out on alkaline Al_2O_3.

1-Oxo-1H-2,3,4,5-tetrahydrobenzofuro[3,2-c]azepine (IIIa). A mixture of 0.7 g (5.5 mmole) of Ia and 0.8 g (5.5 mmole) of O-phenylhydroxylamine hydrochloride was refluxed for 3 h in 15 ml of a 20% solution of hydrogen chloride in absolute ethanol, after which the mixture was cooled, and the precipitated substance was removed by filtration, washed with a small amount of cold alcohol and water, and vacuum dried to give 0.7 g (64%) of IIIa with mp 195-196° (from alcohol). Found, %: C 71.6; H 5.5; N 7.0. $C_{12}H_{11}NO_2$. Calculated, %: C 71.6; H 5.5; N 7.0.

1-Oxo-1,2,3,4-tetrahydrobenzofuran (Va). A mixture of 2.5 g (21 mmole) of dihydroresorcinol and 2.4 g (22 mmole) of O-phenylhydroxylamine [7] in 40 ml of a 25% solution of hydrogen chloride in methanol was refluxed for 16 h and poured into water. The precipitate, which began to crystallize, was removed by filtration, washed with water, dried, and dissolved in ether. The ether solution was passed through a column containing 60 g of activity IV Al_2O_3 [elution with ether and monitoring by TLC (R_f 0.78)]. The ether solutions were evaporated to give 2.52 g (60%) of Va with mp 57-58°. Found, %: C 77.3; H 5.4. $C_{12}H_{10}O_2$. Calculated, %: C 77.4; H 5.4.

1-Oxo-1,2,3,4-tetrahydrodibenzofuran Oxime (VIa). A solution of 6.4 g (90 mmole) of hydroxylamine hydrochloride in 10 ml of water and a solution of 3.7 g (90 mmole) of sodium hydroxide in 10 ml of water were added successively to a solution of 3.8 g (20 mmole) of Va in 40 ml of alcohol, and the mixture was refluxed for 3.5 h and cooled. The resulting precipitate was removed by filtration and washed with water. The mother liquor was diluted with water to provide another 0.6 g of VIa to give an overall yield of 88% of a substance with mp 135-136.5° (from alcohol). Found, %: C 71.9; H 5.5; N 6.9. $C_{12}H_{11}NO_2$. Calculated, %: C 71.6; H 5.5; N 7.0.

1-Oxo-1H-2,3,4,5-tetrahydrobenzofuro[3,2-c]azepine (IIIa). A mixture of 3 g (15 mmole) of VIa and 90 g of PPA was heated at 110-115° for 1 h, after which it was cooled, poured over ice, and made alkaline with 10% potassium carbonate solution. The resulting precipitate was removed by filtration and washed with water to give 2.85 g (95%) of IIIa with mp 194.5-196° (from alcohol). Found, %: C 71.6; H 5.6; N 7.1. $C_{12}H_{11}NO_2$. Calculated, %: C 71.6; H 5.5; N 7.0.

2-Methyl-3-acetylbenzofuran (VIII). A mixture of 2.4 g (24 mmole) of acetylacetone and 3.45 g (24 mmole) of O-phenylhydroxylamine hydrochloride in 30 ml of a 10-12% solution of hydrogen chloride in absolute alcohol was refluxed for 30 min, after which it was poured into water. The aqueous mixture was extracted with ether, and the extract was washed with sodium hydroxide solution and water and dried. The solvent was evaporated, and the residue was distilled to give 1.45 g of VIII with bp 140-142° (5 mm) and mp 48-49.5°. Found, %: C 75.7; H 5.6. $C_{11}H_{10}O_2$. Calculated, %: C 75.8; H 5.8. PMR spectrum (in CCl_4), ppm: 2.58 (3H, singlet, CH_3), 2.78 (3H, singlet, CH_3), 7.32 and 7.9 (multiplets of aromatic protons).

1-Oxo-4,4-dimethyl-1H-2,3,4,5-tetrahydrobenzofuro[3,2-c]azepine (IIIb) and 2-Oxo-3-(3',3'-dimethyl-5'-pyrrolidylidene)benzofuran (IV). A mixture of 5 g (32 mmole) of Ib and 5 g (34 mmole) of O-phenylhydroxylamine hydrochloride in 50 ml of a 20% alcohol solution of hydrogen chloride was refluxed for 3 h, after which the reaction mass was poured into warm water, and the resulting precipitate was removed by filtration to give 6.7 g (90.7%) of a mixture of IIIb and IV with mp 132-145° and R_f 0.46 and 0.19, respectively (TLC on activity IV Al_2O_3 in chloroform). The mixture was crystallized three times from alcohol to give IV with mp 173-174° and R_f 0.19. Found, %: C 73.3; H 6.6; H 6.2. $C_{14}H_{15}NO_2$. Calculated, %: C 73.3; H 6.6; N 6.1. The alcohol mother liquors were evaporated, and the residue was recrystallized three times from heptane containing benzene to give IIIb with mp 162-163°. Found, %: C 73.2; H 6.5; N 6.2. $C_{14}H_{15}NO_2$. Calculated, %: C 73.3; H 6.6; N 6.1.

1-Oxo-3,3-dimethyl-1,2,3,4-tetrahydrobenzofuran (Vb). A mixture of 4 g (28 mmole) of dimedone and 4 g (27 mmole) of O-phenylhydroxylamine hydrochloride in 50 ml of a 20% solution of hydrogen chloride in alcohol was refluxed for 18 h. It was then cooled, and the resulting precipitate was removed by filtration and washed with water to give 5 g (83%) of Vb with mp 118-119° (from alcohol). Found, %: C 78.2; H 6.6. $C_{14}H_{14}O_2$. Calculated, %: C 78.4; H 6.6.

1-Oxo-3,3-dimethyl-1,2,3,4-tetrahydrodibenzofuran Oxime (VIb). A solution of 3 g (43 mmole) of hydroxylamine hydrochloride and a solution of 6 g (0.04 mole) of sodium hydroxide in 5 ml of water were added successively to a solution of 3 g (14 mmole) of Vb in 35 ml of alcohol, and the mixture was refluxed for 2 h and poured into water. The resulting precipitate was removed by filtration to give 2.3 g (71.9%) of VIb with mp 168-170° (from alcohol). Found, %: C 73.3; H 6.6; N 6.4. $C_{14}H_{15}NO_2$. Calculated, %: C 73.3; H 6.6; N 6.1.

1-Oxo-4,4-dimethyl-1H-2,3,4,5-tetrahydrobenzofuro[3,2-c]azepine (IIIb). A mixture of 1 g (4 mmole) of VIb and 40 g of PPA was heated at 120° for 1 h, after which it was cooled, poured into water, and made alkaline with potassium carbonate solution. The precipitate was removed by filtration to give 0.8 g (80%) of IIIb with mp 163-164° (from heptane containing benzene). Found, %: C 73.3; H 6.7; N 6.2. $C_{14}H_{15}NO_2$. Calculated, %: C 73.3; H 6.6; N 6.1.

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