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RESEARCH ON LACTAMS.

XXXII.* ANOMALOUS FISCHER REACTION OF α-OXOCAPROLACTAM O-PHENYLOXIME

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The reaction of O-phenylhydroxylamine hydrochloride with α-oxocaprolactam gave α-oxocaprolactam O-phenyloxime, which gave two substances — 1,2,3,4-tetrahydropyrido[2,3-c]coumarin as the principal product and 1-oxo-10a-hydroxy-1H-2,3,4,5,5a,10a-hexahydrobenzofuro[2,3-c]azepine as the minor product — under the conditions of the Fischer reaction. The minor product was converted to 1-oxo-1H-2,3,4,5-tetrahydrobenzofuro[2,3-c]azepine in quantitative yield by dehydration in trifluoroacetic acid.

Like the corresponding arylhydrazones, the O-phenyloximes of carbonyl compounds undergo the Fischer reaction to give benzofuran derivatives [2]. In particular, 1-oxo-1H-2,3,4,5-tetrahydrobenzofuro[3,2-c]azepine derivatives were obtained by this method from substituted 2,4-dioxohexahydroazepines and O-phenylhydroxylamine [3].

In the present research we attempted to synthesize 1-oxo-1H-2,3,4,5-tetrahydrobenzofuro[2,3-c]azepine (I) with α-oxocaprolactam (II) as the starting compound [4]. α-Oxocaprolactam O-phenyloxime (IV) was obtained by reaction of II with O-phenylhydroxylamine hydrochloride (III). It follows from the PMR spectrum that phenyloxime IV is a mixture of two geometrical isomers, since doubling of the signals of the protons of the CH_2 group in the 4 position of the azepine ring (multiplets at 2.41 and 2.66 ppm) and of the NH group (triplets at 8.17 and 8.33 ppm) is observed in its spectrum, along with multiplets at 1.65 [5,6-$(CH_2)_2$], 3.11 (7-CH_2), and 6.85-7.35 ppm (aromatic protons).

In an attempt to convert phenyloxime IV to I under the conditions of the preparation of substituted benzofurans from O-phenyloximes [2] we isolated two substances: a major product (V) with empirical formula $C_{12}H_{11}NO_2$ and mp 141-143°C, and a minor product with empirical formula $C_{12}H_{13}NO_3$ and mp 188-190°C. On the basis of the spectral data it was established

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*See [1] for communication XXXI.

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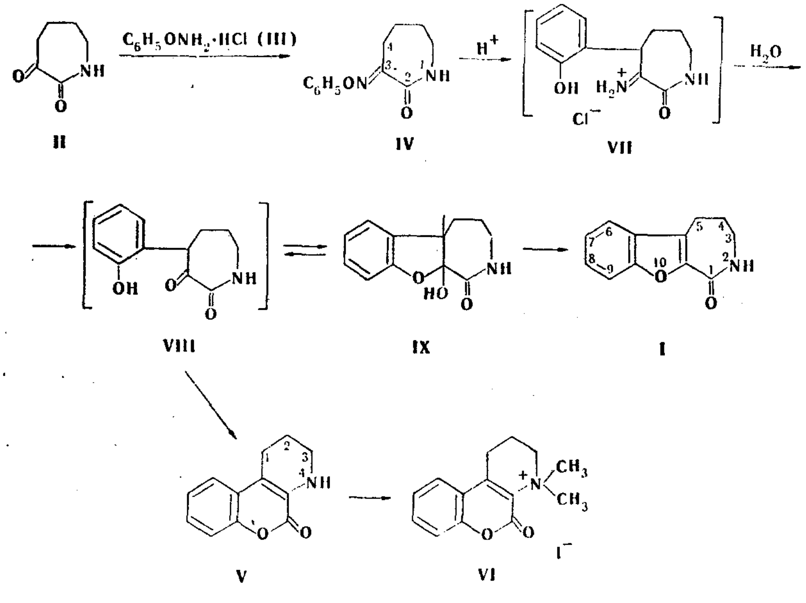
that the major product is tetrahydropyridocoumarin V. Its IR spectrum does not contain the absorption band of a lactam carbonyl group but does contain the band of a conjugated ester carbonyl group at 1700 cm^{-1}. In addition to multiplets from six protons of the piperidine ring at 1.92 (2-CH_2), 2.61 (1-CH_2), and 3.25 ppm (3-CH_2) and from four aromatic protons at 7.00-7.50 ppm, a broad singlet at 5.85 ppm (NH) is observed in the PMR spectrum of pyridocoumarin V. The singlet character of the latter is due to its rapid exchange due to the fact that V has the acidic properties (pK_α 11.40 ± 0.06, 50% alcohol) that are characteristic for 3-aminocoumarins [5]. The structure of V is confirmed by its mass spectrum, which contains a molecular ion (m/e 291) and daughter ions: $[M - H]^+$ (200), $[M - CH_3]^+$ (186), $[M - NHCH_2]^{+\bullet}$ (172), $[M - C_2H_5]^+$ (172), $[M - NHC_3H_5]^+$ (145), $[M - NHC_3H_6]^{+\bullet}$ (144). The presence in pyridocoumarin V of a secondary NH group rather than an amide NH group is also confirmed by its alkylation with excess methyl iodide in dimethylformamide (DMF) in the presence of sodium hydride to quaternary salt VI. Signals at 2.49 (2-CH_2, m), 3.33 (1-CH_2, t), 4.27 (3-CH_2, t), and 7.30-8.00 ppm (aromatic protons, m) are observed in the PMR spectrum of the latter [in $(CD_3)_2SO$], and the protons of the $N^+(CH_3)_2$ group form a singlet at 3.92 ppm with an intensity of six proton units. It may be assumed that phenyloxime IV is converted to pyridocoumarin via the following scheme: under the conditions of the Fischer reaction phenyloxime IV undergoes rearrangement to an immonium salt (VII), which is hydrolyzed by the water liberated in the reaction of the alcohol with hydrogen chloride to give an oxolactam (VIII); the latter undergoes alcoholysis at the 1 and 2 positions of the lactam fragment, which is accompanied by opening of the lactam ring to give α-oxo-β-(2-oxophenyl)-ε-aminocaproic acid ester. The conversion of the ester to pyridocoumarin V may evidently proceed via different pathways: by the formation of a coumarin ring with the subsequent formation of a piperidine fragment or in the reverse sequence. It should be emphasized that the conditions for the formation of V from phenyloxime IV correspond to the typical conditions under which substituted coumarins are usually synthesized [6].

According to the results of elementary analysis, the minor product, with mp 188-190°C, that is formed under the conditions of the Fischer reaction from phenyloxime IV corresponds to the structures of VIII and its cyclization product (IX). However, since the IR spectrum of the latter does not contain the absorption band of a ketone carbonyl group but does contain a narrow intense band at 1670 cm^{-1}, which corresponds to the absorption of a lactone CO group, we assumed that this compound has structure IX in the solid state.



It should be noted that the limited solubility of IX in organic solvents hindered the establishment of its fine structure. On the basis of the PMR spectrum (of a solution in CF_3COOH) it may be concluded that IX is an individual substance, since its spectrum contains only one signal of an NH proton (8.10 ppm, t), and the multiplets from the protons of the azepine ring have distinct character — 4-CH_2 and 5-CH_2 at 1.84 and 2.07 ppm respectively (four proton units), and 5a-CH and 3-CH_2 at 3.54 ppm (three proton units); the aromatic protons are represented by a multiplet with an intensity of four proton units at 6.7-7.3 ppm. An interesting phenomenon was observed during the recording of the PMR spectrum of IX in

CF_3COOH with time. It was found that this compound is converted quantitatively to benzofuroazepine I after standing at room temperature for 3 days. A broad triplet of an NH proton is observed at 8.90 ppm in the PMR spectrum of I; the methylene protons of the azepine ring are represented by multiplets at 2.41 (4-CH_2, two proton units), 3.32 (5-CH_2, two proton units), and 3.85 ppm (3-CH_2, two proton units); the four aromatic protons form a multiplet at 6.75-7.25 ppm. The data from the PMR spectra on the conversion of IX to benzofuroazepine I were confirmed by preparative synthesis of the latter. In a comparison of the mass spectra of I and IX it was established that the spectrum of the latter contains, in addition to a molecular ion peak with m/e 219, peaks of daughter ions: $[M - H_2O]^{+\bullet}$ (201), $[M - CO]^{+\bullet}$ (191), $[M - CO - OH]^{+}$ (174), $[M - CO - C_2H_4 - OH]^{+}$ (146), $[o\text{-}HOC_6H_4CH{=}CH_2]^{+\bullet}$ (120), $[o\text{-}HOC_6H_4{-}CH_2]^{+}$ (107). The presence in the spectrum of intense ion peaks with m/e 107 and 120 constitutes evidence that IX in the gas phase undergoes recyclization to oxolactam VIII. Because of this, the character of the fragmentation of IX differs substantially from the fragmentation of benzofuroazepine I. In the mass spectrum of the latter the most intense peak belongs to the molecular ion (m/e 201), whereas the subsequent fragmentation differs from the fragmentation of IX: $[M - NHCH_2]^{+\bullet}$ (172), $[M - NHC_2H_4]^{+\bullet}$ (158), $[M - CONHC_2H_3]^{+}$ (131), $[M - CONHC_3H_6]^{+\bullet}$ (116). In connection with the ability of IX to undergo recyclization it was assumed that it is capable of ring–chain tautomerism (VIII $\rightleftarrows$ IX) in solutions. This assumption is in agreement with the PMR spectrum [in $(CD_3)_2SO$] of IX, in which doubling of the NH (7.67 ppm, t; 7.89 ppm, t) and OH (7.42 ppm, s; 7.67 ppm, s) protons is observed. When 10 drops of CD_3OD are added, these signals decrease gradually until they disappear entirely. The assignment of the signals of the NH and OH protons to one or another tautomeric form is not possible, but on the basis of a comparison of the intensities of the signals it could be concluded that these tautomeric forms exist in a ratio of 1:2. It should be noted that the signals of the protons of the azepine ring are represented by markedly diffuse multiplets at 1.2-2.0 and 2.6-3.5 ppm, which also constitutes evidence in favor of the existence of two tautomeric forms (VIII and IX) in solution in $(CD_3)_2SO$.

EXPERIMENTAL

The UV spectra of the compounds were recorded with an EPS-3 spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer 457 spectrometer. The PMR spectra of solutions of the compounds in CF_3COOH, $(CD_3)_2NCOD$, and $(CD_3)_2SO$ were recorded with JNM-4H-100 and C-60 HL spectrometers with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples; the ionizing-electron energy was 30 eV, and the ionization-chamber temperature was 125°C.

α-Oxocaprolactam O-Phenyloxime (IV). A suspension of 8 g (55 mmole) of O-phenylhydroxylamine hydrochloride (III) and 7 g (55 mmole) of α-oxocaprolactam (II) in 70 ml of isopropyl alcohol was heated to 65-70°C for 15 min, after which it was decolorized with charcoal and cooled to 0°C. The resulting precipitate was removed by filtration, washed with isopropyl alcohol, and dried to give 9 g (75%) of phenyloxime IV with mp 125°C (dec., from ethyl acetate). IR spectrum: 3065 and 3200 (NH), 1600 (C=O), 1620 (C=N), and 1595 cm^{-1} (C=C). UV spectrum, λ_{max} (log ε): 245 nm (3.87). Mass spectrum: 218 ($M^{+\bullet}$), 189 $[M - NHCH_2]^{+\bullet}$, 148 $[M - CO - NHC_2H_3]^{+}$, 133 $[M - CO - NHC_2H_6]^{+\bullet}$, 119 $[M - CO - NHC_4H_8]^{+\bullet}$, 94 $[C_6H_5OH]^{+\bullet}$, 93 $[C_6H_5O]^{+}$. Found: C 66.0; H 6.4; N 12.7%. $C_{12}H_{14}N_2O_2$. Calculated: C 66.0; H 6.5; N 12.8%.

1,2,3,4-Tetrahydropyrido[2,3-c]coumarin (V) and 1-Oxo-10a-hydroxy-1H-2,3,4,5,5a,10a-hexahydrobenzofuro[2,3-c]azepine (IX). A solution of 3 g (14 mmole) of O-phenyloxime IV in a mixture of 15 ml of isopropyl alcohol and 15 ml of alcohol saturated at 0°C with hydrogen chloride was refluxed in a stream of nitrogen for 3 h, after which the mixture was cooled, and the precipitate was removed by filtration and suspended in 30 ml of water. The suspension was made alkaline to pH 8-9 with 1 N NaOH, and the resulting precipitate was removed by filtration, washed with water, and dried to give 1.9 g (69%) of pyridocoumarin V with mp 141-143°C (from alcohol). IR spectrum: 3390 (NH), 1700 (lactone C=O), and 1615 and 1595 cm^{-1} (C=C). UV spectrum, λ_{max} (log ε): 250 (3.92) and 344 nm (4.23). Found: C 71.6; H 5.5; N 6.9%. $C_{12}H_{11}NO_2$. Calculated: C 71.6; H 5.5; N 7.0%. The aqueous mother liquor from the isolation of pyridocoumarin V was acidified to pH 6 with 1 N HCl and maintained at 0°C for 12 h, and the resulting precipitate was removed by filtration, washed with water, and dried to give 0.8 g (26%) of IX with mp 188-190°C (from alcohol with ethyl acetate). IR spectrum: 3400 (OH), 3250 (NH), and 1670 cm^{-1} (lactam C=O). UV spectrum, λ_{max} (log ε): 277 nm (4.12). Found: C 66.1; H 5.9; N 6.3%. $C_{12}H_{13}NO_3$. Calculated: C 66.0; H 5.9; N 6.4%.

N-Methyl-1,2,3,4-tetrahydropyrido[2,3-c]coumarin Methiodide (VI). A 0.24-g (10 mmole) sample of sodium hydride was added to a solution of 1.3 g (6.4 mmole) of pyridocoumarin V in 10 ml of dimethylformamide at 20°C, and the mixture was allowed to stand for 20 min. Methyl iodide (6 ml) was then added, and the mixture was heated at 40-42°C for 4 h. It was then cooled to 0°C, and the resulting precipitate was removed by filtration, washed with water, and dried to give 0.76 g (33%) of methiodide VI with mp 168-170°C (from alcohol). IR spectrum: 1700 (lactone C=O) and 1605 cm^{-1} (C=C). UV spectrum, λ_{max} (log ε): 280 (3.98) and 316 nm (3.73). Found: C 47.4; H 4.7; I 35.4; N 3.9%. $C_{14}H_{16}INO_2$. Calculated: C 47.1; H 4.5; I 35.5; N 3.9%.

1-Oxo-1H-2,3,4,5-tetrahydrobenzofuro[2,3-c]azepine (I). A solution of 1 g (4.5 mmole) of IX in 10 ml of trifluoroacetic acid was maintained at 20°C for 3 days, after which it was vacuum evaporated to dryness, and the residue was crystallized from alcohol to give 0.88 g (95%) of benzofuroazepine I with mp 244-246°C. IR spectrum: 3205 (NH) and 1645 cm^{-1} (amide C=O). UV spectrum λ_{max} (log ε): 279 nm (3.73). Found: C 72.2; H 5.6; N 7.0%. $C_{12}H_{11}NO_2$. Calculated: C 71.6; H 5.5; N 7.0%.

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N-ALKYLATION OF 1,4-DIHYDROPYRIDINE-3,5-DICARBOXYLIC ACID ESTERS

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Alkylation of the anions of 1,4-dihydropyridines (1,4-DHP) formed by treatment of sodium hydride in aprotic solvents gave 1-alkyl(up to C_6H_{13})-3,5-bis(ethoxycarbonyl)- and 1-alkyl-3,5-bis(aryloxycarbonyl)-1,4-DHP. The presence of a substituent in the 4 position increases the reactivity of the 1,4-DHP anion in the alkylation reaction. The absorption maximum in the UV spectra of the 1,4-DHP anion is shifted ~100 nm bathochromically as compared with the neutral molecule. The long-wave absorption maximum in the UV spectra of 1-alkyl-1,4-DHP is shifted hypsochromically as compared with the 1-unsubstituted compounds; this is explained by steric hindrance of the conjugation of the C=O groups with the π-electron system of the ring. The introduction of an alkyl group at the nitrogen atom facilitates the electrical oxidation of 1,4-DHP.

1,4-Dihydropyridines (1,4-DHP) [1] have become important as antioxidants [2] and coronary-dilating [3] and hypotensive agents [4]. Less study has been devoted to 1-substituted 1,4-DHP, although as closer analogs of the redox enzyme NADH they may be of special interest.

Of the known methods for the preparation of 1-alkyl-1,4-DHP-3,5-dicarboxylic acid esters, the alkylation of 1,4-DHP anions is of greatest promise [5, 6]. The acid properties of 1,4-DHP-3,5-dicarboxylic acid esters (I) are weakly expressed, and a strongly alkaline agent such as sodium hydride is therefore necessary for the formation of anion II, and polar aprotic solvents promote the reactions [5-9].

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