CYCLIZATION OF O-ARYLHYDROXYLAMINES WITH β-DICARBONYL COMPOUNDS

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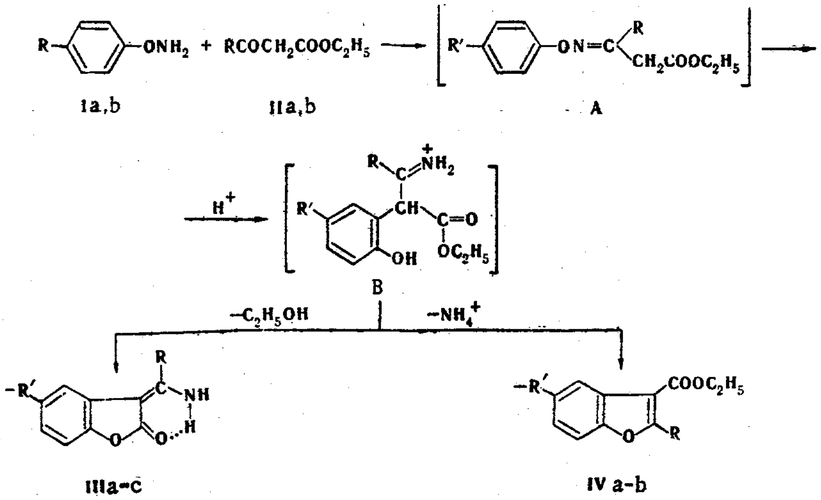
The reaction of O-arylhydroxylamines (AH) with β-dicarbonyl compounds, which can lead to substituted benzofurans, has been insufficiently investigated. Earlier it was shown that the reaction of O-phenylhydroxylamine (Ia) with acetoacetic ester (IIa) [1] or with acetylacetone [1, 2] in the presence of acids gives 2-methyl-3-ethoxycarbonylbenzofuran or 2-methyl-3-acetylbenzofuran respectively. Condensed benzofurans were obtained by the reaction of cyclohexanedione, dimedone, or hexahydro-2,4-azepinediones in an acidic medium [2].

We found that the reaction of AH with certain β-keto esters occurs in a different direction. When O-(4-nitrophenyl)hydroxylamine (Ib) was heated with benzoylacetic ester (IIb) in a 9:1 mixture of glacial acetic and concentrated sulfuric acids, 3-(α-aminobenzylidene)-5-nitro-2,3-dihydro-2-benzofuranone (IIIa) was obtained with a 74% yield. If a 25% solution of hydrogen chloride in alcohol is used as medium, 4% of compound (IIIa) is formed together with 2-phenyl-3-ethoxycarbonyl-5-nitrobenzofuran (IVa) and 2-phenyl-5-nitrobenzofuran (V). By replacement of the initial compound by (Ia) it is possible to increase the yield of the benzofuran type of compound to 45%. Condensation of the hydroxylamine (Ib) with (IIa) in a mixture of acetic and sulfuric acids is accompanied by strong resinification; in a 25% solution of hydrogen chloride in alcohol we obtained 52% of compound (IVb) and 9% of the benzofuranone (IIIc).



I a $R=H$, b $R=NO_2$; II a $R=CH_3$, b $R=C_6H_5$; III a $R=C_6H_5$, $R'=NO_2$; b $R=C_6H_5$, $R'=HO_2$; c $R=CH_3$, $R'=NO_2$; IV a $R=C_6H_5$, $R'=NO_2$; b $R=CH_3$, $R'=NO_2$

The structure of compounds (IIIa-c) was confirmed by the absence of reactions with aqueous acids and alkalis, by the UV, IR, and PMR spectra, and also by molecular weight determination. Thus, the IR spectrum of a 0.01 M solution of compound (IIIc) in chloroform contains strong absorption bands at 1630 and 1730 cm^{-1}, which must be assigned to the stretching vibrations of the alkylidene double bond and the carbonyl of the unsaturated five-membered lactam. In the regions of 3300 and 3490 cm^{-1} there are two bands for the vibrations of the NH_2 group, and the first of them is broader (half-widths 41 and 25 cm^{-1} respectively). These frequencies do not obey Bellamy's equation [3], and this must be explained by the presence of an intramolecular bond between the carbonyl and one of the hydrogen atoms in the

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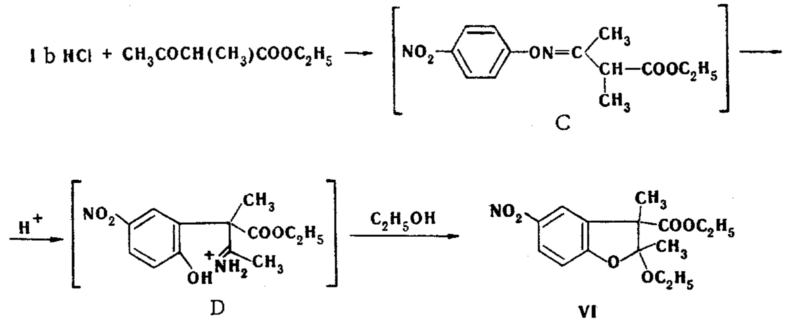
NH_2 group. The existence of such a bond in 3-(α-aminoalkylidene)-2,3-dihydro-2-furanones was reported earlier (e.g., [2, 4, 5]). The spectral characteristics of compounds (IIIa-c) are given in the experimental section.

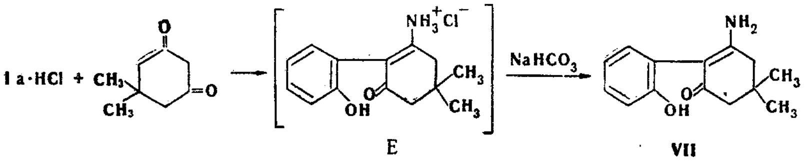
The benzofuranones (IIIa-c) are formed after rearrangement of the O-aryloximes of the β-dicarbonyl compounds (A) to the intermediate compounds (B), which are capable of lactonization. A different path for the conversion of compounds (B) into benzofurans of type (IVa, b) was observed earlier, and here ammonia (the ammonium ion in an acidic medium) or water (if there is a possibility of hydrolysis of the imines B) is eliminated. The direction of cyclization in compounds B must clearly depend on the reaction conditions (the presence of water in the reaction mixture, the position and degree of protonation of the imine or ketone, etc.).

It is known that in contrast to arylhydrazines O-aryloximes of ketones with the CH_2COCH fragment rearrange exclusively on the side of the methylene group (e.g., [6, 7]). The results from the rearrangement of the 4-nitrophenyloxime of α-methylacetoacetic ester (C) were therefore somewhat unexpected. 2,3-Dimethyl-2-ethoxy-3-ethoxycarbonyl-5-nitro-2,3-dihydrobenzofuran (VI) was isolated with a 30% yield. In the IR spectrum of the acetal (VI) (a 0.5 M solution in carbon tetrachloride) there is a strong band at 1735 cm^{-1} (the ester C=O group), and there are no bands in the region of 3100-3700 cm^{-1}. (The absence of a phenolic hydroxyl is also confirmed by a negative reaction with alkalis.) The UV spectrum of compound (VI) (in alcohol), like the spectrum of 4-nitroanisole, is characterized by a long-wave absorption maximum at 307 nm (log ε 3.98). (For the PMR spectrum, see the experimental section.)



Thus, this is the first case of the rearrangement of O-aryloximes involving the methine unit of the ketone part of the molecule.

The intermediate products from the rearrangement of the O-aryloximes of β-dicarbonyl compounds have not so far been isolated, and this would be important for investigating the mechanism of cyclization. However, we obtained 1-amino-2-(2-hydroxyphenyl)-5,5-dimethyl-1-cyclohexen-3-one (VII) with a 41% yield from phenylhydroxylamine (Ia) and dimedone under mild conditions.



Under the investigated conditions compound (VII) exists in the form of the enamino ketone. In the region of 1500-1700 cm^{-1} the IR spectrum (in Vaseline oil or in tablets with potassium bromide) is characteristic of β-aminovinyl ketones of such a type [8] and has absorption at 1644, 1560, and 1520 cm^{-1}. In the UV spectrum the long-wave absorption maximum has a value of 290 nm (log ε 4.29). In the PMR spectrum (see the experimental section) there is no signal for the methine proton of the possible imino ketone form. The imino form is also refuted by the fact that the signals of the two CH_3 groups and the two CH_2 groups remain singlets in the transition to other solvents. Compound (VII) dissolves in dilute alkalis and mineral acids (for the base pK_a = 3.1 in 50% alcohol at 20°C). Protonation of the enamino ketone (VII) clearly does not occur at the carbon atom, since the proton at C_3 is not observed in the PMR spectrum in trifluoroacetic acid, and the singlet character of the signals for the protons of the CH_3 (δ 1.3 ppm) and CH_2 (δ 2.75 and 2.85 ppm) groups is retained (as also in trifluoroacetic acid—deuteromethanol solution).

During electron impact the molecular ion formed from (VII) (m/e 231) loses NH_3 and is converted into a comparatively stable ion with m/e 214 (the maximum peak).

Thus, the fundamental possibility of synthesizing enamino ketones with an aryl substituent at position 2 has been demonstrated for the case of the rearrangement of dimedone O-phenyloxime.

EXPERIMENTAL

The UV spectra were recorded on a Perkin-Elmer 402 spectrophotometer in alcohol (c = 10^{-4}-10^{-5} M). The IR spectra were recorded on a Perkin-Elmer 457 spectrometer in carbon tetrachloride or chloroform, in Vaseline oil, or in tablets with potassium bromide. The PMR spectra were recorded on a Varian T-60 radiospectrometer with TMS as standard. The mass-spectroscopic measurements were made on a Varian MAT-112 instrument with direct introduction of the sample into the source at an ionization potential of 50-70 eV. The pK_a values were determined by potentiometry on a pH-340 instrument. For TLC we used aluminum oxide (alkaline form, grade 4 activity, with chloroform as eluent).

Reaction of Benzoylacetic Ester (IIb) with O-(4-Nitrophenyl)hydroxylamine (Ib). A. A solution of 1 g (5.2 mmole) of the hydrochloride of (Ib) and 1 g (5.2 mmole) of the keto ester (IIb) in 7.5 ml of glacial acetic acid and 0.8 ml of concentrated sulfuric acid was boiled for 6 min. The mixture was cooled, the precipitate was filtered off, and 1.1 g (74%) of compound (IIIa) was obtained in the form bright-yellow crystals; mp 299-300.5°C (from acetic acid), R_f = 0.51. UV spectrum, λ_{max} (log ε): 249 (4.42), 342 nm (4.26). IR spectrum (in chloroform, c = 0.005 M, d = 1 mm): 1620 (benzylidene double bond), 1726 (lactone C=O), 3300 and 3480 cm^{-1} (ν_{NH_2}). PMR spectrum (in DMSO-d_6): 6.7 (d, J = 3 Hz, 4-H), 7.3 (d, J = 9 Hz, 7-H), 7.9 (q, J_1 = 9 Hz, J_2 = 3 Hz, 6-H), 7.5-7.8 (C_6H_5), 9.0 and 9.4 ppm (two broadened singlets, NH_2, disappearing with the addition of CD_3OD). Found %: C 64.0; H 3.4; N 10.0. Mol.wt. 282 (by mass spectrometry). $C_{15}H_{10}N_2O_4$. Calculated %: C 63.8; H 3.6; N 9.9. Mol.wt. 282.2. From the mother solution we isolated 0.13 g of the reaction product, in which a small amount of (IVa) was detected by TLC together with other unidentified substances.

B. A mixture of 3 g (15.7 mmole) of the hydrochloride of (Ib) and 3.03 g (15.7 mmole) of the keto ester (IIb) (not containing acetophenone, according to GLC) in 30 ml of a 25% solution of hydrogen chloride in absolute alcohol was boiled for 75 min. The mixture was then cooled, the precipitate was filtered off and washed with water and with alcohol, and the residue (1.7 g) was chromatographed on a column of aluminum oxide (grade 2 activity) with chloroform as eluent. We obtained 0.2 g (4%) of compound (IIIa), identical with that described above in a mixed melting test and in its R_f value, and also 1.4 g of a mixture of compounds (mixture A), in which the presence of compounds (IVa) and (V) in a ratio of 1:2 was established by TLC and PMR spectra. [For comparison compound (IVa) was obtained as described below, and compound (V) was obtained by condensation of (Ib) with acetophenone [9], mp 157-159°C.] The mother solution contained a mixture of four substances, two of which were compounds (IVa) and (V) (according to TLC).

A 1-g sample of mixture A was boiled for 30 min in 15 ml of an alcohol solution of sodium hydroxide. 2-Phenyl-3-carboxy-5-nitrobenzofuran was isolated in the usual way. It was esterified by boiling for 2 h in 15 ml of a 25% solution of hydrogen chloride in absolute alcohol. After cooling, the ester (IVa) separated; mp 145-146°C (from alcohol). Found %: C 65.5; H 4.2; N 4.5. $C_{17}H_{13}NO_5$. Calculated %: C 65.6; H 4.2; N 4.5.

The characteristic signals of the protons in the PMR spectra were as follows: (IVa) 1.4 (t, J = 7 Hz, CH_3), 4.4 (q, J = 7 Hz, CH_2), 8.8 (d, J = 3 Hz, 4-H); (V) 6.9 (s, 3-H), 8.3 ppm (d, J = 3 Hz, 4-H).

Reaction of Acetoacetic Ester (IIa) with O-(4-Nitrophenyl)hydroxylamine (Ib). A mixture of 5.4 g (28 mmole) of the hydrochloride (Ib) and 4.16 g (32 mmole) of the keto ester (IIa) in 60 ml of a 25% solution of hydrogen chloride in absolute alcohol was boiled for 2 h 15 min. The reaction mass was filtered while hot, the precipitated ammonium chloride was washed with absolute alcohol, and the filtrate was cooled. The precipitate was separated, washed with alcohol, and chromatographed on a column with aluminum hydroxide (grade 4 activity) with chloroform as eluent. We obtained 3.7 g (52%) of compound (IVb) and 0.57 g (9%) of (IIIc). Compound (IVb), mp 120-121°C (from alcohol), R_f 0.84, is insoluble in aqueous acids and alkalis. UV spectrum, λ_{max} (log ε): 242 (4.29), 282 nm (3.65). IR spectrum (in carbon tetrachloride, c = 0.5 M, d = 0.04 mm): 1350 and 1535 (ν_{NO_2}), 1605 (benzofuran ring), 1723 cm^{-1} ($\nu_{C=O}$ of ester). PMR spectrum (in carbon tetrachloride): 1.35 (t, J = 7.5 Hz, 3-CH_3), 2.7 (s, 2-CH_3), 4.45 (q, J = 7.5 Hz, 3-CH_2), 7.6 (d, J = 9 Hz, 7-H), 8.4 (q, J_1 = 9 Hz, J_2 = 3 Hz, 6-H), 9.0 ppm (d, J = 3 Hz, 4-H). Found %: C 57.8; H 4.5; N 5.7. $C_{12}H_{11}NO_5$. Calculated %: C 57.8; H 4.5; N 5.6. Compound (IIIc) formed yellow crystals; mp 253-255°C, R_f 0.39. PMR spectrum (in DMSO-d_6): 3.3 (s, CH_3), 7.3 (d, J = 9 Hz, 7-H), 8.0 (q, J_1 = 9 Hz, J_2 = 2.5 Hz, 6H), 8.1 (signal from 5-H, overlapping with the downfield components of the signal of 6-H), 9.2 and 9.4 ppm (broad signals of two nonequivalent NH_2 protons). Found %: C 54.6; H 3.6; N 12.8. Mol.wt. 220 (by mass spectrometry). $C_{10}H_8N_2O_4$. Calculated %: C 54.5; H 3.7; N 12.7. Mol. wt. 220.2.

Reaction of Benzoyl Acetic Ester (IIb) with O-Phenylhydroxylamine (Ia). A mixture of 0.76 g (5.2 mmole) of the hydrochloride of (Ia) and 1 g (5.2 mmole) of the keto ester (IIb) in 10 ml of a 23% solution of hydrogen chloride in absolute alcohol was boiled for 1 h. The solution was filtered while hot, and 0.57 g (45%) of compound (IIIb) was obtained by cooling the filtrate and by partial evaporation; mp 201-202.5°C (from alcohol), R_f 0.38 (aluminum oxide, grade 2 activity, chloroform). A mixture of unidentified substances remained in the mother solution. UV spectrum of compound (IIIb), λ_{max} (log ε): 252 (4.20), 348 nm (4.09). IR spectrum (in chloroform, c = 0.01 M, d = 1 mm): 1602 and 1623 (C=C bonds), 1710 ($\nu_{C=O}$ of lactone), 3300 and 3480 cm^{-1} (ν_{NH_2}). In the PMR spectrum (in chloroform) the signals of the nonequivalent NH_2 protons appear at 5.0 and 8.9 ppm. (In DMSO one broad signal with an intensity of two proton units appears at 8.8 ppm.) The addition of deuteromethanol leads to the disappearance of the NH_2 signals. Found %: C 75.9; H 4.7; N 5.8. $C_{15}H_{11}NO_2$. Calculated %: C 76.0; H 4.7; N 5.9.

Reaction of α-Methylacetoacetic Ester with O-(4-Nitrophenyl)hydroxylamine (Ib). A mixture of 3 g (21 mmole) of α-methylacetoacetic ester and 4 g (21 mmole) of the hydrochloride of (Ib) in 30 ml of 19% solution of hydrogen chloride in absolute alcohol was boiled for 2 h. The solution was filtered from the ammonium chloride, and the filtrate was cooled, added to water (~ 150 ml), and extracted with benzene. The benzene solution was washed with a solution of potassium carbonate in water and evaporated. A 2-g yield (31%) of the crude acetal (VI) was obtained. It was crystallized from petroleum ether; mp 86-87°C, R_f = 0.8. PMR spectrum: 1.4 (s, 3-CH_3), 1.7 (s, 2-CH_3), 1.0 and 1.22 (two CH_2 groups, two t, J = 7.5 Hz), 7.1 (d, J = 9 Hz, 7-H), 8.5 (J_1 = 9 Hz, J_2 = 3 Hz, 6-H), 8.6 ppm (4-H overlapsed with the signal of 6-H). Found %: C 58.3; H 6.2; N 4.7. Mol. wt. 309 (by mass spectrometry). $C_{15}H_{19}NO_6$. Calculated %: C 58.2; H 6.2; N 4.5. Mol.wt. 309.3. According to the UV, IR, and PMR spectra and also to the ability to dissolve in alkalis, the intermediate compound D (in the keto form) and the products from its acid and ketone cleavage are formed in addition to compound (VI). Further heating of the mixture with an alcohol solution of hydrogen chloride only led to the formation of a small amount of (VI).

Reaction of Dimedone with O-Phenylhydroxylamine (Ia). A mixture of 1 g (6.9 mmole) of the hydrochloride of (Ia) and 0.96 g (6.9 mmole) of dimedone in 10 ml of absolute alcohol was boiled for 20 min. The alcohol was distilled, and the residue was rubbed with ether. The solution was filtered, the precipitate (1.7 g) was crystallized from absolute alcohol with the addition of ether, and 1.25 g of the crude hydrochloride E was obtained. It was dissolved in water and converted into the base (VII) by the addition of aqueous sodium bicarbonate. The yield was 0.65 g (41%); mp 207-208°C (from 50% alcohol). PMR spectrum (in DMSO-d_6): 1.05 (s, $2CH_3$), 2.1 and 2.3 (two s, $2CH_3$), 3.3 (s, H_2O impurity), 6.0 (broad s, 2H, NH_2), 6.6-6.7 (C_6H_4), 8.6 ppm (s, 1H, phenol OH with hydrogen bond). Found %: C 72.8; H 7.2; N 6.2. $C_{14}H_{17}NO_2$. Calculated %: C 72.7; H 7.4; N 6.1.

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SYNTHESIS OF SOME 3-CHROMANONE DERIVATIVES

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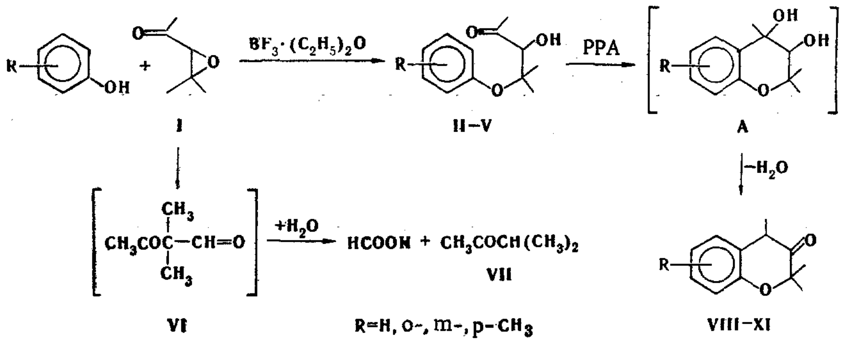
As shown in [1], in reaction with phenol in the presence of sulfuric acid 3,3-dimethyl-2-acetyloxirane (I) forms a mixture of products containing small amounts of 2,2,4-trimethyl-3-chromanone, the formation of which was explained by cyclization of the unisolated 4-methyl-3-hydroxy-4-phenoxy-2-pentanone.

In the present work it was possible to obtain the phenoxy ketols (II-V) required for cyclization to chromanones with satisfactory yields by the reaction of oxirane (I) with phenol and o-, m-, and p-cresols in dichloroethane solution in the presence of boron trifluoride etherate at 0-5°C. In the reaction of the above-mentioned oxirane with phenol in ether in the presence of perchloric acid the yield of the phenoxy ketol (II) amounted to only 8%. The low yields of the phenoxy ketols (II-V) were due to isomerization [2] of the oxirane (I), occurring in parallel with the main reaction and leading to the ketoaldehyde (VI), which undergoes ketone cleavage into methyl isopropyl ketone (VII) and formic acid when the reaction mixture is treated with sodium hydroxide solution to remove the excess of phenol. The ketone (VII) was identified by its 2,4-dinitrophenylhydrazone [3] by treatment of the dichloroethane, distilled from the reaction mixture, with a hydrochloric acid solution of 2,4-dinitrophenylhydrazine.

The yield of the phenoxy ketol (III) was considerably lower than that of its analogs (II, IV, V), and this was evidently due to steric hindrances created by the methyl group of o-cresol during attack by the unshared electron pair of the phenolic oxygen at the β-carbon atom of the oxirane (I).

The structures of the phenoxy ketols (II-V) were established on the basis of data from quantitative periodate oxidation of the acyloin group [4] (the content of the α-ketol amounted to 98-100%) and the IR spectra, in which there were absorption bands for the hydroxyl group combined by a hydrogen bond (3470-3480 cm^{-1}), a band for the stretching vibrations of the carbonyl group (1715-1725 cm^{-1}), bands for the vibrations of the phenyl fragment in the regions of 1600, 1500, 700, and 3050 cm^{-1}, and strong absorption bands in the region of 1230-1240 cm^{-1}, due to the asymmetric stretching vibrations of the C—O bond of the phenyl ether, and a band for the stretching vibrations of the C—OH bond of a secondary hydroxyl (1100 cm^{-1}) [5].



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