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Acid Hydrolysis of Amides Obtained by Beckmann Rearrangement of Methyl Ketones Oximes of Unsaturated γ-Lactone, Aromatic, and Alicyclic Series

G. G. Tokmadzhyan

Erevan State University, Erevan, 375025 Armenia
e-mail: tokmajyang@yahoo.com

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Abstract—Beckmann rearrangement was performed of oximes of substituted 3-acetyl-4-methyl-5,5-dimethyl(pentamethylene)-2-oxo-2,5-dihydrofuranes in the presence of boron trifluoride etherate. Aiming at establishing the spatial arrangement of the oximes the hydrolysis was carried out of acid amides obtained by Beckmann rearrangement of oximes of methyl ketones belonging to unsaturated γ-lactone series and also to aromatic and alicyclic series. The hydrolysis with 20% sulfuric acid led to the formation of the corresponding acid and amine, and the hydrolysis with acetic and hydrochloric acids resulted in retrobeckmann rearrangement giving the initial oximes.

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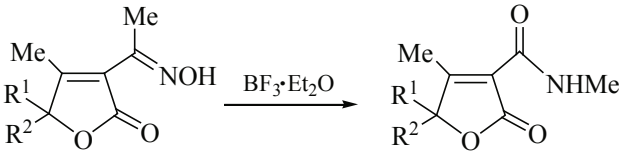
Beckmann rearrangement of ketoximes since its discovery in 1886 [1] up till now has attracted the attention of researchers for it occupies a special place among the nucleophilic rearrangements at electron-deficient sites (so-called sextet rearrangement). Beside the widely known practical application for the production of caprolactam from cyclohexanone oxime, the rearrangement provides a possibility to establish the spatial configuration of oximes of unsymmetrical ketones from the structure of their rearrangement products.

We formerly performed under UV irradiation the rearrangement of oximes of substituted 3-acetyl-4,5,5-trimethyl-2-oxo-2,5-dihydrofurans in acetonitrile resulting in N-methylamides of the corresponding 2,5-dihydrofuran-3-carboxylic acid [2]. We regarded as interesting to carry out Beckmann rearrangement in the series of the mentioned oximes in the presence of commonly used acid catalysts. We tested a number of known catalysts (concn. H_2SO_4, PCl_5, boron trichloride etherate, "Beckmann mixture": HCl in the mixture AcOH–Ac_2O [3]) of this rearrangement, and we succeeded in performing Beckmann rearrangement of oximes of 3-acetyl-4-methyl-5,5-dimethyl(pentamethylene)-2-oxo-2,5-dihydrofurans only in the presence of boron trifluoride etherate. The reaction proceeded with high yields in anhydrous ether at room temperature over 1 h.



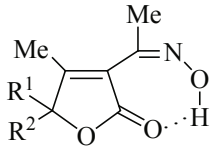
Ia, Ib **IIa, IIb**

$R^1 = R^2 = Me$ (**a**); $R^1,R^2 = (CH_2)_5$ (**b**).

The structure of amides obtained was established from IR and ^1H NMR spectra, and also from the results of their acid hydrolysis. For instance, the hydrolysis of amides **IIa, IIb** with 20% H_2SO_4 along the known procedure [4] led to the formation of the corresponding acids completely identical by the physicochemical constants to the data of the previously obtained acids [5, 6].

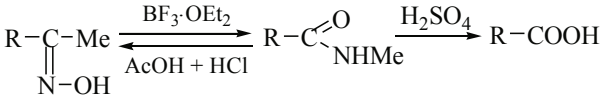
Therefore the proof of the structure of amides obtained by Beckmann rearrangement shows the anti-structure (with respect to the methyl group) of the initial oximes that may be due to the formation of an intramolecular

hydrogen bond between the lactone carbonyl and the hydroxy group of the initial oxime.

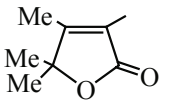
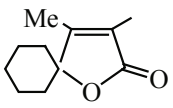


Yet we obtained unexpected results when in order to prove the structure of amides obtained we performed their hydrolysis not by 20% H_2SO_4, but by a mixture of 80% AcOH and concn. HCl, 10:1 [7]. In this event the hydrolysis resulted not in the expected 4-methyl-5,5-dimethyl(pentamethylene)-2-oxo-2,5-dihydrofuran-3-carboxylic acids but in the corresponding initial oximes as was unambiguously proved by the comparison of the spectral and physicochemical characteristics of compounds obtained and the products of the independent synthesis from 3-acetyl-4-methyl-5,5-dimethyl-(pentamethylene)-2-oxo-2,5-dihydrofurans and hydroxylamine.

To exmine this phenomenon we investigated the hydrolysis of N-methylamides of aromatic and alicyclic series. Thus from the oximes of acetophenone [8] and *p*-hydroxyacetophenone in the presence of boron trifluoride etherate we obtained N-methylamides of benzoic [9] and *p*-hydroxybenzoic acids which on hydrolysis with 20% H_2SO_4 formed benzoic [10] and *p*-hydroxybenzoic acids [11] respectively identified by their physicochemical constants whereas the hydrolysis in the mixture AcOH–HCl resulted in the initial oximes. The same behavior was observed at the hydrolysis of cyclohexanecarboxylic acid N-methylamide.

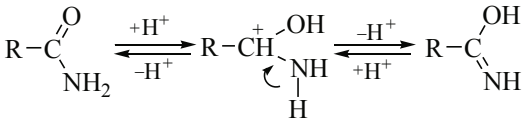


Ia–Ie **IIa–IIe**

R =  (**a**),  (**b**),

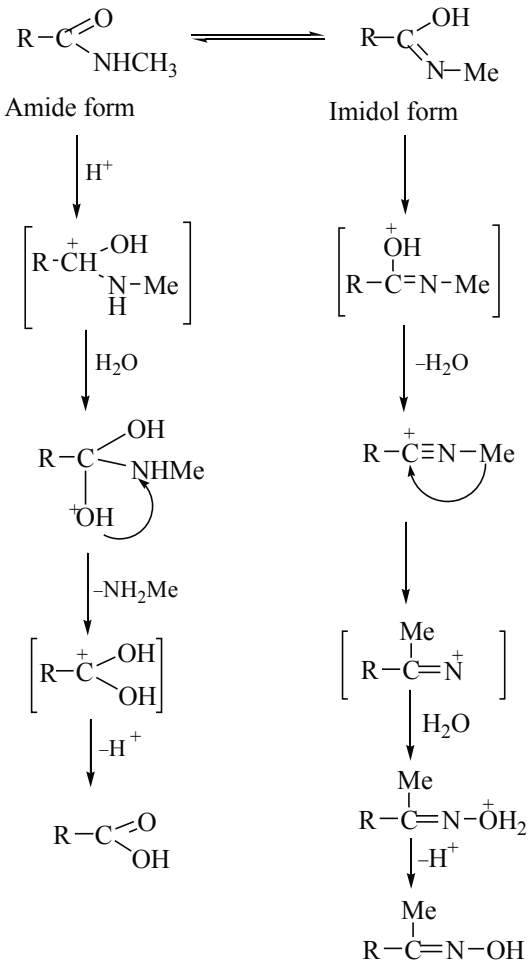
Ph (**c**), *n*-HOC_6H_4 (**d**), cyclohexyl (**e**).

We suggest for the explanation of this interesting phenomenon the following scheme clearly showing the routes of formation of both types of the reaction products.



The acid amides are known to participate in a tautomerism type known as amide-imidol triade prototropy [12]. It is considered that the rate of enolization is governed by the rate of the first stage which occurs the easier the greater is the electron density on the oxygen atom of the carbonyl group [13]. Taking into account the sharp difference in the proton concentrations in both media (20% H_2SO_4 and AcOH–HCl) we presume that in this case the governing stage of enolization is the second one: the rupture of a proton from the nitrogen atom and its transfer into the medium. The high proton concentration in 20% H_2SO_4 considerably retards the second stage and prevents the formation of the imidol form, i.e., the equilibrium is shifted to the side of the amide form. Accordingly, the low proton concentration in the mixture AcOH–HCl favors the nitrogen deprotonation, i.e., the proceeding of the second enolization stage and the formation of imidol form. As seen from the scheme in the case of prevailing amide form of the compound its hydrolysis results in the

Scheme.



corresponding acid, and at the predominant presence of the imidol form a retrobeckmann rearrangement occurs with the formation of the initial oxime. Apparently in the case of the products of Beckmann rearrangement of methyl ketone oximes of unsaturated γ-lactone, aromatic and alicyclic series the acid amides in the mixture AcOH–HCl exist prevailingly in the imidol form which results in the formation of the initial oximes.

EXPERIMENTAL

IR spectra of compounds synthesized were recorded on a spectrophotometer Specord 75 IR from mulls in mineral oil, ^{1}H NMR spectra, on a spectrometer Varian Mercury-300 (300 MHz), internal reference TMS. Mass spectrum of an electron impact (direct sample admission) was obtained on an instrument M-1321 A at the energy of ionizing electrons 50–70 eV. The purity of compounds synthesized was checked by TLC on Silufol UV-254 plates, eluent acetone–benzene, 1:2, development in iodine vapor and under UV irradiation.

Oximes **Ia–Ic, Ie** were synthesized by known methods [2, 8, 14].

Methyl *p*-hydroxyphenyl ketone oxime (Id). To a solution in alcohol of 1.36 g (0.01 mol) of the ketone was added 0.7 g (0.01 mol) of hydroxylamine hydrochloride and 0.7 g (0.005 mol) of potassium carbonate as a saturated water solution. The mixture was stirred at room temperature for 1 h, the precipitate was filtered off, the filtrate was evaporated at a reduced pressure. Yield 1.26 g (83%), mp 143°C (from ethanol). IR spectrum, ν, cm^{-1}: 3580 (OH), 1630 (C=N conjug.), 1600 (arom). ^{1}H NMR spectrum, δ, ppm: 2.3 s (3H, CH_3–C=N), 6.8–7.7 m ($4H_{arom}$), 9.8 s (1H, OH), 10.2 s (1H, OH).

***N*-Methylamides IIa–IIe.** A mixture of 1.5 mmol of oxime, 5 ml of anhydrous ether, and 5 ml of boron trifluoride etherate was stirred for 1 h at room temperature. The precipitated crystals were filtered off.

4,5,5-Trimethyl-2-oxo-2,5-dihydrofuran-3-carboxylic acid *N*-methylamide (Ia). Yield 0.25 g (93%), white crystals, mp 65–66°C [2], R_f 0.60. IR spectrum, ν, cm^{-1}: 3370 (NH), 1755 (C=O), 1685 (C=O), 1630 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.44 s (6H, 5,5-CH_3), 2.28 s (4-CH_3), 2.40 d (CH_3NH, *J* 4.9 Hz), 7.50 br.s (NH).

4-Methyl-2-oxo-5,5-pentamethylene-2,5-dihydrofuran-3-carboxylic acid *N*-methylamide (Ib). Yield 0.25 g (76%), white crystals, mp 104–105°C [2], R_f 0.68. IR spectrum, ν, cm^{-1}: 3365 (NH), 1755 (C=O), 1690 (C=O), 1625 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.0–2.0 m [10H, $(CH_2)_5$], 2.27 s (4-CH_3), 2.45 s (CH_3NH), 6.60 br.s (NH).

***N*-Methylbenzamide (Ic).** Yield 1.68 g (83%), mp 114–115°C [9], R_f 0.63. IR spectrum, ν, cm^{-1}: 3350 (NH), 1690 (C=O), 1600–1500 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 2.47 d (CH_3NH, *J* 4.9 Hz), 7.06–7.14 m ($5H_{arom}$), 9.60 br.s (NH).,

***p*-Hydroxybenzoic acid *N*-methylamide (Id).** Yield 2.15 g (95%), mp 123–125°C, R_f 0.65. IR spectrum, ν, cm^{-1}: 3580 (OH), 3370 (NH), 1690 (C=O), 1600–1500 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 2.48 d (CH_3NH, *J* 4.9 Hz), 6.61 d ($2H_{arom}$, *J* 8.0 Hz), 6.89 d ($2H_{arom}$, *J* 8.0 Hz), 9.40 s (1H, OH), 9.58 br.s (1H, NH).

***N*-Methylcyclohexylamide (Ie).** Yield 0.3 g (67%), mp 140°C [8], R_f 0.60. IR spectrum, ν, cm^{-1}: 3370 (NH), 1690 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.7–0.95 m (6H, C^3H_2, C^4H_2, C^5H_2), 1.27 and 1.39 d.d (2H, $H^{2a,6a}$, *J* 8.1, *J* 4.9 Hz), 1.49 and 1.52 d.d (2H, $H^{2b,6b}$, *J* 5.4, *J* 5.4 Hz), 2.47–2.83 m (1H, H^1), 3.01 d (CH_3NH, *J* 4.9 Hz), 9.58 br.s (1H, NH).

Hydrolysis of N-methylamides in sulfuric acid. A mixture of 3 mmol of N-methylamide **IIa–IIe** and 10 ml of 20% H_2SO_4 was heated over 10 h at 75°C, evaporated at a reduced pressure, and the residue was recrystallized.

4,5,5-Trimethyl-2-oxo-2,5-dihydrofuran-3-carboxylic acid (IIIa). Yield 0.45 g (88%), mp 113°C (from xylene) [5].

4-Methyl-2-oxo-5,5-pentamethylene-2,5-dihydrofuran-3-carboxylic acid (IIIb). Yield 0.48 g (76%), mp 144°C (from heptane) [6].

Benzoic acid (IIIc). Yield 0.195 g (80%), mp 121°C (from water) [10].

***p*-Hydroxybenzoic acid (IIId).** Yield 0.215 g (78%), mp 216–217°C (from methanol) [11].

Cyclohexanecarboxylic acid (IIIe). Yield 0.15 g (55%), mp 235–238°C (from ethanol) [15].

No depression of the melting point was observed in mixed samples of compounds **IIIa–IIIe** with the corresponding acids prepared by known methods [5, 6, 10, 11, 15].

Hydrolysis of *N*-methylamides IIa–IIe in the presence of acetic and hydrochloric acids. A mixture of 3 mmol of N-methylamide **IIa–IIe**, 15 ml of 80% AcOH, and 1.5 ml of concn. HCl was heated for 10 h at 75°C, evaporated at a reduced pressure, treated with 75 ml of cold 10% solution of NH_4OH, and excess water

was removed. To the residue ether was added, the crystals insoluble in ether were filtered off. The filtrate was evaporated, the residue was recrystallized.

3-Acetyl-4,5,5-trimethyl-2-oxo-2,5-dihydrofuran oxime (Ia). Yield 0.3 g (59%), R_f 0.52, mp 116°C (from xylene) [2]. IR spectrum, ν, cm^{-1}: 3360 (OH), 1735 (C=O), 1655 (C=N), 1620 (C=C). ^1H NMR spectrum, δ, ppm: 1.1 s (6H, 5,5-CH_3), 1.95 s (4-CH_3), 2.30 s (Ac), 13.1s (OH).

3-Acetyl-4-methyl-2-oxo-5,5-pentamethylene-2,5-dihydrofuran oxime (Ib). Yield 0.4 g (64%), mp 129°C (from xylene) [2], R_f 0.6. IR spectrum, ν, cm^{-1}: 3320 (OH), 1730 (C=O), 1645 (C=N), 1620 (C=C). ^1H NMR spectrum, δ, ppm: 1.5–1.9 m [10H, $(CH_2)_5$], 1.95 s (4-CH_3), 2.10 s (Ac), 11.5 s (OH).

Methyl phenyl ketone oxime (Ic). Yield 0.22 g (81%), mp 58–60°C (from water) [8], R_f 0.58.

Methyl *p*-hydroxyphenyl ketone oxime (Id). Yield 0.24 g (80%), mp 143°C (from ethanol), R_f 0.6. IR spectrum, ν, cm^{-1}: 3580 (OH), 1630 (C=N conjug.), 1600 (arom). ^1H NMR spectrum, δ, ppm: 2.3 s (3H, CH_3), 6.8–7.7m ($4H_{arom}$), 9.8 s (1H, OH), 10.2 s (1H, OH).

Methyl cyclohexyl ketone oxime (Ie). Yield 0.2 g (66%), mp 62°C [14], R_f 0.65.

No depression of the melting point was observed in mixed samples of compounds **Ia–Ie** with the corresponding oximes prepared by known methods [2, 8, 14].

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