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SHORT COMMUNICATIONS

Synthesis and Some Chemical Transformations of *N*-Cyclohexyl-2-imino-4-methyl-5,5-pentamethylene-2,5-dihydrofuran-3-carboxamide

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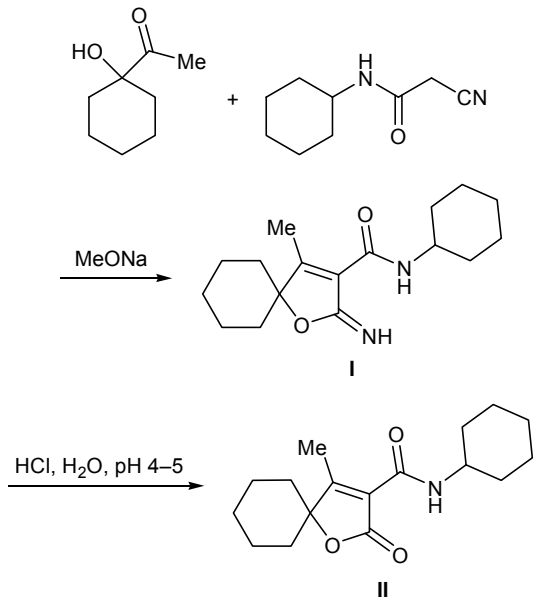
Functionally substituted derivatives of unsaturated γ-lactones are widespread in nature, and they often exhibit pronounced biological activity. Apart from monocyclic unsaturated γ-lactones, some natural compounds are derivatives of spiro and fused bicyclic systems including a six-membered ring. The natural terpenoid andirolactone is a spiro-fused unsaturated γ-lactone possessing valuable properties [1]. The natural alkaloid cerpegin in which unsaturated lactone ring is fused to a pyridine ring, exhibits antiphlogistic, analgesic, antiulcer, and tranquilizing activity and is used in folk medicine [2–4]. Therefore, synthesis of spiro systems including both γ-lactone and six-membered ring is an important problem.

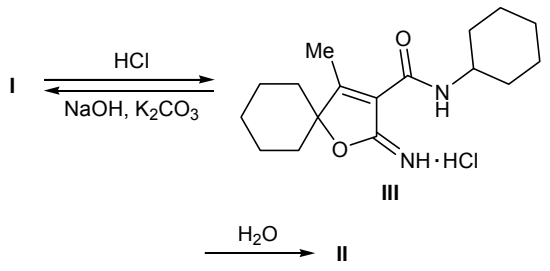
Scheme 1.



Taking into account that nitrogen analogs of various oxygen-containing biologically active substances often possess equally useful properties, we continued our studies on condensations of tertiary α-keto alcohols with compounds having an activated methylene group [5] and examined the reaction of 1-acetylcyclohexanol with *N*-cyclohexyl(cyano)acetamide. The reaction was carried out in anhydrous methanol in the presence of sodium methoxide at 40°C (reaction time 5 h). As a result, we isolated *N*-cyclohexyl-2-imino-4-methyl-5,5-pentamethylene-2,5-dihydrofuran-3-carboxamide (**I**) in high yield (Scheme 1). Imine **I** readily underwent hydrolysis in weakly acidic medium (pH 4–5, 85–90°C, 3 h) to produce 2,5-dihydrofuran-2-one **II**. This reaction sequence may be regarded as a new method for the synthesis of functionally substituted unsaturated γ-lactones.

Compound **I** was readily and quantitatively converted into the corresponding hydrochloride **III** by passing gaseous hydrogen chloride through a solution of **I** in benzene. Hydrochloride **III** can be titrated with a 0.1 N solution of sodium hydroxide, whereas treatment of **III** with a solution of potassium carbonate recovers initial 2-imino derivative **I**. Hydrolysis of

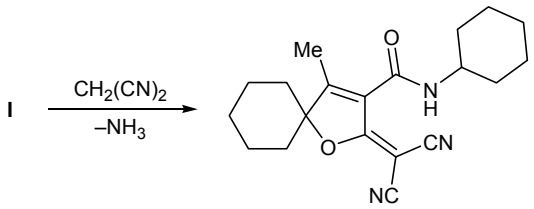
Scheme 2.



hydrochloride **III** at 85–90°C in 2 h also yields 2,5-dihydrofuran-2-one **II** (Scheme 2).

We also examined the reaction of 2-imino-2,5-dihydrofuran **I** with malononitrile. The reaction occurred at room temperature with equimolar amounts of the reactants and afforded 2-dicyanomethylidene-2,5-dihydrofuran **IV** in quantitative yield (ammonia no longer evolved by the end of the process; Scheme 3).

Scheme 3.



IV

The structure of the isolated compounds was proved by the IR and ^{1}H NMR spectra and elemental analyses. Compounds **I**–**IV** were tested for antibacterial activity at the Chemotherapy Laboratory, Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences of Armenian Republic. Moderate antibacterial activity of these compounds was revealed *in vitro*; therefore, further studies in this line seem to be promising.

***N*-Cyclohexyl-2-imino-4-methyl-5,5-pentamethylene-2,5-dihydrofuran-3-carboxamide (I).** 1-Acetylcyclohexanol and *N*-cyclohexyl(cyano)acetamide, 10 mmol each, were added to a solution of sodium methoxide in methanol prepared from 1 mmol of metallic sodium and 20 ml of methanol. The mixture was heated for 5 h at 40°C, the solvent was removed under reduced pressure, the residue was treated with water, and the precipitate was filtered off, washed with water, and recrystallized from ethanol. Yield 95%, mp 124–125°C. IR spectrum, ν, cm^{-1}: 3360, 3180 (NH); 1680 (C=O); 1670 (C=N); 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.19–1.49 m (6H, C_6H_{11}), 1.58–1.95 m (14H, C_6H_{11}), 2.33 s (3H, CH_3), 3.72 m (1H, NHC**H**), 7.23 s (1H, =NH), 9.35 d (1H, NH, *J* = 7.9 Hz). Found, %: C 70.44; H 9.14; N 9.77. $C_{17}H_{26}N_2O_2$. Calculated, %: C 70.31; H 9.02; N 9.65.

***N*-Cyclohexyl-4-methyl-5,5-pentamethylene-2-oxo-2,5-dihydrofuran-3-carboxamide (II).** A mixture of 1.5 mmol of compound **I** and 5 ml of water was adjusted to pH 4–5 by adding hydrochloric acid, and the mixture was heated for 3 h at 85–90°C, cooled, and extracted with diethyl ether (3×5 ml). The extract was dried over magnesium sulfate and evaporated, and the residue was recrystallized from petroleum ether. Yield 79%, mp 142–143°C. IR spectrum, ν, cm^{-1}: 3280 (NH), 1780 (C=O), 1680 (C=O), 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.19–1.49 m (6H, C_6H_{11}), 1.58–1.95 m (14H, C_6H_{11}), 2.33 s (3H, CH_3), 3.73 m (1H, NHC**H**), 9.35 d (1H, N**H**CH, *J* = 7.9 Hz). Found, %: C 70.24; H 8.73; N 4.94. $C_{17}H_{25}NO_3$. Calculated, %: C 70.07; H 8.65; N 4.81.

***N*-Cyclohexyl-2-imino-4-methyl-5,5-pentamethylene-2,5-dihydrofuran-3-carboxamide hydrochloride (III).** Gaseous hydrogen chloride was passed through a solution of 2 mmol of compound **I** in benzene. The precipitate was filtered off and washed with diethyl ether. Yield 97%, mp 236–240°C. ^{1}H NMR spectrum, δ, ppm: 1.19–1.49 m (6H, C_6H_{11}), 1.58–1.95 m (14H, C_6H_{11}), 2.33 s (3H, CH_3), 3.71 m (1H, NHC**H**), 9.22 d (1H, N**H**CH, *J* = 7.9 Hz), 10.34 br.s (2H, NH·HCl). Found, %: C 62.57; H 8.34; N 8.69. $C_{17}H_{27}ClN_2O_2$. Calculated, %: C 62.47; H 8.26; N 8.57.

Reaction of hydrochloride III with potassium carbonate. A concentrated aqueous solution of potassium carbonate was added to a solution of 0.5 mmol of hydrochloride **III** in water until pH 7–8. The precipitate was filtered off and washed with water. Yield of iminolactone **I** 95%, mp 124–125°C. No depression of the melting point was observed on mixing with a sample of **I** prepared as described above.

Hydrolysis of compound III. A mixture of 1 mmol of hydrochloride **III** and 5 ml of water was heated for 2 h at 85–90°C. The mixture was cooled and extracted with diethyl ether (3×5 ml), the extract was dried over magnesium sulfate and evaporated, and the residue was recrystallized from petroleum ether. Yield of compound **II** 82%; its melting point coincided with that given above.

***N*-Cyclohexyl-2-dicyanomethylidene-4-methyl-5,5-pentamethylene-2,5-dihydrofuran-3-carboxamide (IV).** A mixture of 2.5 mmol of compound **I**, 0.17 g (2.5 mmol) of malononitrile, and 5 ml of anhydrous ethanol was stirred at room temperature until ammonia no longer evolved. The solvent was distilled off, the residue was treated with water, and the precipitate was filtered off, washed with water, and recrystallized from benzene. Yield 90%, mp 166–167°C. IR spectrum, ν, cm^{-1}: 3280 (NH), 2225 (CN), 1680 (C=O), 1635 (C=C), 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.19–1.49 m (6H, C_6H_{11}), 1.58–1.95 m (14H, C_6H_{11}), 2.33 s (3H, CH_3), 3.72 m (1H, NHC**H**), 9.35 d

(1H, NH, J = 7.9 Hz). Found, %: C 70.92; H 7.51; N 12.44. $C_{20}H_{25}N_3O_2$. Calculated, %: C 70.77; H 7.42; N 12.38.

The IR spectra were recorded on a Specord 75IR spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were obtained on a Varian Mercury-300 spectrometer at 300 MHz using DMSO-d_6–CCl_4 (1:3) as solvent and tetramethylsilane as internal reference. The purity of the isolated compounds was checked by thin-layer chromatography on Silufol UV-254 plates using acetone–benzene (1:2) as eluent; spots were visualized under UV light and by treatment with iodine vapor.

REFERENCES

1. Orduna, A., Zepeda, L.G., and Tamariz, J., *Synthesis*, 1993, p. 375.
2. Adibatti, N.A., Thirugnanasambantham, P., Kulothungan, C., Viswanathan, S., Kameswaran, L., Balakrishna, K., and Sukumar, E., *Phytochemistry*, 1991, vol. 30, p. 2449.
3. Kelly, T.R. and Walsh, J.J., *J.Org. Chem*., 1992, vol. 57, p. 6657.
4. Villemin, D. and Liao, L., *Tetrahedon Lett*., 1996, vol. 37, p. 8733.
5. Avetisyan, A. and Karapetyan, L., *Synth. Commun*., 2009, vol. 39, p. 7.