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Recyclization of Dimedone Adduct with 2-(2-Oxo-2-phenylethylidene)propanedinitrile in the Reaction with N-Nucleophiles

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Abstract—Three-component condensation of dimedone with phenylglyoxal hydrate and malononitrile gave a polyfunctional 5,6,7,8-tetrahydro-4*H*-chromene derivative, 2-amino-4-benzoyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile, which reacted with ammonium acetate to produce pyrrolo[3,4-*c*]quinoline ring system. Reactions of the condensation product with primary and secondary amines and hydroxylamine hydrochloride afforded polysubstituted pyrroles, whereas the reaction with hydrazine hydrate led to 3-amino-6-phenylpyridazine-4-carbonitrile.

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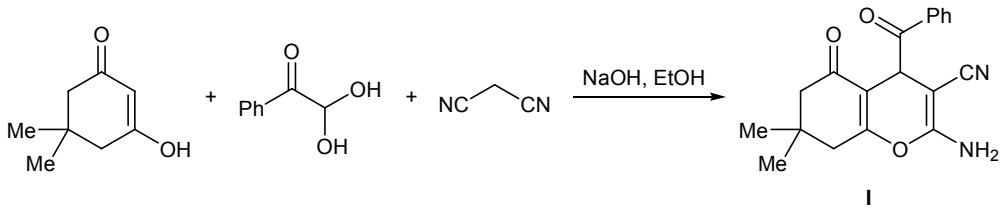
Numerous publications deal with Michael adducts derived from α,β-unsaturated components containing one or several cyano groups. In particular, adducts of cyclic 1,3-diketones with substituted benzylidenemalononitriles or their analogs are well known. These adducts are derivatives of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile, and they can be synthesized by both reaction of the two above listed compounds [1–4] and unsymmetrical three-component condensation of a cyclic 1,3-diketone with aromatic aldehyde (or ketone) and malononitrile, bypassing the isolation of unsaturated nitrile [5–10]. The resulting polyfunctional compounds attract interest from the viewpoint of their biological activity; for example, there are published data on their antibacterial effect [11].

A number of studies have been concerned with N-heterocyclizations of the aforesaid tetrahydro-4*H*-chromene derivatives; these heterocyclizations involve mainly fusion of pyridine [12] or pyrimidine ring [13] with participation of reactive amino and cyano groups. Recyclization into quinoline derivatives by the action of ammonium acetate [2] and isocyanates [14], as well as via Dimroth rearrangement [15], was also reported.

We previously studied N-heterocyclization of dimedone adducts with 1,1-diacetyl-2-benzoylethene [16], β-benzoylacrylic acid [17], and 1,2-dibenzoylethene [18]. The goal of the present study was to elucidate the direction of recyclization of dimedone adduct with 2-(2-oxo-2-phenylethylidene)propanedinitrile (compound **I**) in reactions with N-nucleophiles under different conditions. As nucleophiles we used ammonium acetate in acetic acid, primary amines (methylamine and benzylamine), secondary amines (morpholine and piperidine), and difunctional nucleophiles (hydroxylamine amine hydrochloride and hydrazine hydrate).

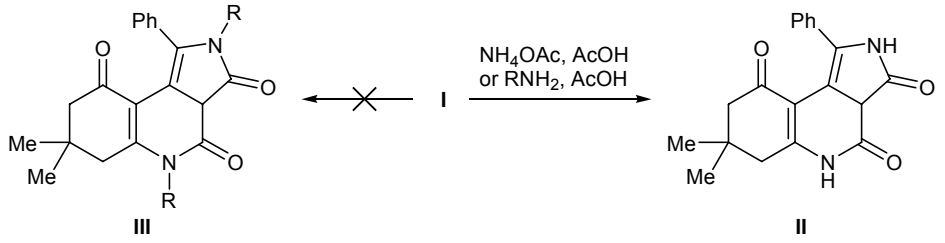
Initial tetrahydrochromene **I** was synthesized in 66% yield by three-component condensation of dimedone with equimolar amounts of phenylglyoxal hydrate and malononitrile. The condensation was carried

Scheme 1.



I

Scheme 2.



R = Me, $PhCH_2$.

out by heating the reactants in boiling ethanol for 4 h in the presence of sodium hydroxide (Scheme 1). Obviously, the reaction begins with formation of intermediate (2-oxo-2-phenylethylidene)propanedinitrile from phenylglyoxal hydrate and malononitrile, and the subsequent addition of dimedone and intramolecular cyclization involving the enolic hydroxy group in the dimedone fragment and one cyano group in the malononitrile fragment yield the final product.

Structural features of compound **I** imply the possibility for building up pyrrolo[3,4-*c*]quinoline system via closure of pyridine and pyrrole rings in one synthetic step in the reaction with ammonia. By heating compound **I** with ammonium acetate in boiling acetic acid (reaction time 1 h) we obtained 56% of pyrrolo[3,4-*c*]quinoline derivative **II** (Scheme 2).

We initially presumed that reactions of **I** with primary amines (aqueous methylamine and benzylamine) would lead to the corresponding *N*,*N*′-disubstituted derivatives **III**. However, these reactions in boiling acetic acid afforded the same product (~40%) as that isolated in the reaction with ammonium acetate, pyrrolo[3,4-*c*]quinoline **II**. Compound **II** was also formed when nitrile **I** reacted with secondary amines, piperidine and morpholine. These findings may be rationalized assuming a mechanism shown in Scheme 3, according to which both N-heterocyclization steps involve unsubstituted nitrogen atom in intermediate amidine.

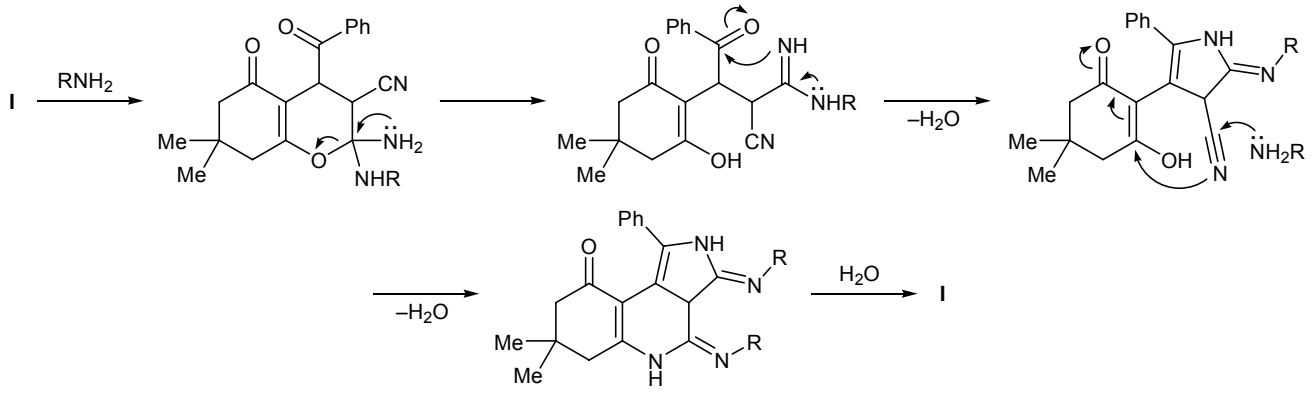
Different results were obtained when the reactions were carried out in a large excess of amine, i.e., when benzylamine, piperidine, or morpholine was used as solvent. By heating compound **I** in these amines at 85–90°C over a period of 2 h we obtained the corresponding substituted pyrroles **IVa**–**IVc** in 20–26% yield (Scheme 4).

Obviously, under these conditions the process stops at the step of recyclization of initial adduct **I** to pyrrole derivative. The low yields of **IVa**–**IVc** are likely to be determined by their donor character which favors tarring. We failed to improve the yield of **IVa**–**IVc** by varying the reaction conditions.

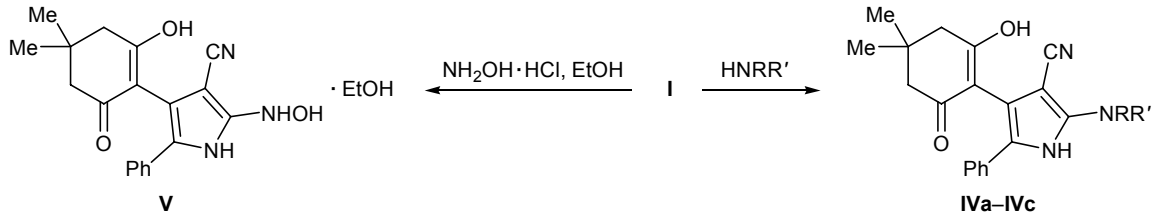
The reaction of **I** with hydroxylamine hydrochloride in ethanol followed a similar pattern, and the product was compound **V** which was obtained in a fairly good yield (67%); the product was isolated as solvate with one ethanol molecule (Scheme 4).

A different recyclization was observed in the reaction of **I** with hydrazine hydrate. Heating of the reactants at a **I**–$N_2H_4 \cdot H_2O$ ratio of 1 : 1.2 in boiling ethanol afforded previously described [19] pyridazine derivative **VI** (Scheme 5). Presumably, the reaction involves successive opening of the 4*H*-pyran ring, cyclization

Scheme 3.



Scheme 4.

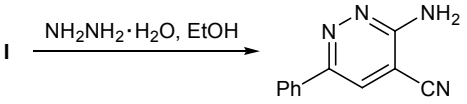


V **IVa–IVc**

R = $PhCH_2$, R′ = H (**a**); RR′N = piperidin-1-yl (**b**), morpholin-4-yl (**c**).

with participation of the fatty–aromatic carbonyl group and second nitrogen atom of hydrazine, and elimination of dimedone molecule with formation of aromatic pyridazine system.

Scheme 5.



VI

EXPERIMENTAL

The IR spectra were recorded in KBr on a Perkin Elmer Spectrum BX spectrometer. The ^1H NMR spectra were measured on a Bruker AC-400 instrument at 400 MHz using tetramethylsilane as internal reference. The mass spectra were obtained on an Agilent 1200 Series LC/MSD instrument (Zorbax XDB C18 column, 2.1×150 mm, 3.5 μm; eluent acetonitrile–water, 85:15; detector temperature 50°C). The progress of reactions was monitored by TLC on Sorbfil plates using chloroform as eluent; spots were visualized by treatment with iodine vapor.

2-Amino-4-benzoyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (I). A solution of 1.4 g (10 mmol) of dimedone, 1.52 g (10 mmol) of phenylglyoxal hydrate, 0.66 g (10 mmol) of malononitrile, and 50 mg (1.25 mmol) of sodium hydroxide in 50 ml of ethanol was heated for 4 h under reflux. After cooling, the precipitate was filtered off, washed with ethanol and diethyl ether, and dried in air. Yield 2.14 g (66%), colorless crystals, mp 204–206°C. IR spectrum, ν, cm^{-1}: 3400, 3321 (NH_2), 2193 (CN), 1689 (C=O), 1655 (C=O), 1594 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.12 s (3H, CH_3), 1.17 s (3H, CH_3), 2.28 s (2H, CH_2), 2.47 s (2H, CH_2), 4.68 s (2H, NH_2), 5.03 s (1H, 4-H), 7.49 t (2H, H_{arom}, J = 7.4 Hz), 7.59 t (1H, H_{arom}, J = 7.4 Hz), 8.07 d (2H, H_{arom}, J = 7.3 Hz). Mass spectrum: m/z 323 $[M + H]^+$. Found, %: C 71.02; H 5.78; N 8.81. $C_{19}H_{18}N_2O_3$. Calculated, %: C 70.79; H 5.63; N 8.69. M 322.36.

7,7-Dimethyl-1-phenyl-3,3a,4,5,6,7,8,9-octahydro-2*H*-pyrrolo[3,4-*c*]quinoline-3,4,9-trione (II). A solution of 0.2 g (0.62 mmol) of compound **I** and 0.2 g (2.6 mmol) of ammonium acetate in 5 ml of acetic acid was heated for 1 h under reflux. The mixture was poured into 100 ml of water and extracted with ethyl acetate (2×20 ml), the combined extracts were washed with water (2×20 ml) and dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was purified by express chromatography on silica gel using diethyl ether as eluent. Yield 0.112 g (56%), colorless crystals, mp 144–145°C. IR spectrum, ν, cm^{-1}: 3390 (NH), 3356 (NH), 1707 (C=O), 1670 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 s (3H, CH_3), 1.20 s (3H, CH_3), 2.45 d and 2.53 d (1H each, CH_2, J = 16.2 Hz), 2.82 d and 2.87 d (1H each, CH_2, J = 17.5 Hz), 5.00 s (1H, 3a-H), 5.56 br.s (1H, NH), 7.42–7.52 m (3H, H_{arom}), 7.80 d (2H, H_{arom}, J = 7.1 Hz), 7.95 br.s (1H, NH). Mass spectrum: m/z 323 $[M + H]^+$. Found, %: C 70.97; H 5.53; N 8.84. $C_{19}H_{18}N_2O_3$. Calculated, %: C 70.79; H 5.63; N 8.69. M 322.36.

2-Benzylamino-4-(4,4-dimethyl-2,6-dioxocyclohexyl)-5-phenyl-1*H*-pyrrole-3-carbonitrile (IVa). A solution of 0.2 g (0.62 mmol) of compound **I** in 3 ml of benzylamine was heated for 2 h at 85°C. The mixture was poured into 100 ml of water, 3 ml of concentrated aqueous HCl was added, and the precipitate was filtered off, washed with water, dried in air, and washed with cold methylene chloride. Yield 50 mg (20%), light yellow crystals, mp 150–152°C. IR spectrum, ν, cm^{-1}: 3414, 3258 (NH); 2620 (OH), 2196 (CN), 1639 (C=O), 1597 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.11 s (3H, CH_3), 1.19 s (3H, CH_3), 2.35 d and 2.47 d (2H each, CH_2, J = 16.8 Hz), 4.39 s (2H, C**H**$_2$NH), 4.73 s (1H, NH), 6.87–7.11 m (5H, H_{arom}), 7.23–7.45 m (5H, H_{arom}), 9.09 s (1H, NH). Mass spectrum: m/z 412 $[M + H]^+$. Found, %: C 75.64;

H 5.98; N 10.30. $C_{26}H_{25}N_3O_2$. Calculated, %: C 75.89; H 6.12; N 10.21. *M* 411.50.

4-(4,4-Dimethyl-2,6-dioxocyclohexyl)-5-phenyl-2-(piperidin-1-yl)-1*H*-pyrrole-3-carbonitrile (IVb). A solution of 0.2 g (0.62 mmol) of compound **I** in 3 ml of piperidine was heated for 2 h at 90°C. The mixture was poured into 100 ml of water, 4 ml of concentrated aqueous HCl was added, and the precipitate was filtered off, washed with water, dried in air, and purified by express chromatography on neutral aluminum oxide using methylene chloride as eluent. Yield 50 mg (21%), yellow crystals, decomposition point >180°C. IR spectrum, ν, cm^{-1}: 3150 (NH), 2650 (OH), 2217 (CN), 1644 (C=C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.77 s (6H, CH_3), 1.65–1.95 m (6H, CH_2), 2.16 s (2H, CH_2), 2.19 s (2H, CH_2); 3.38–3.55 m, 3.59–3.76 m, 3.88–4.04 m, and 4.37–4.53 m (1H each, CH_2N); 7.10–7.30 m (5H, H_{arom}), 8.42 br.s (1H, NH), 11.59 s (1H, OH). Mass spectrum: *m*/*z* 390 $[M + H]^+$. Found, %: C 73.60; H 7.07; N 10.88. $C_{24}H_{27}N_3O_2$. Calculated, %: C 74.01; H 6.99; N 10.79. *M* 389.49.

4-(4,4-Dimethyl-2,6-dioxocyclohexyl)-2-(morpholin-4-yl)-5-phenyl-1*H*-pyrrole-3-carbonitrile (IVc). A solution of 0.2 g (0.62 mmol) of compound **I** in 3 ml of morpholine was heated for 2 h at 90°C. The mixture was poured into 100 ml of water, 4 ml of concentrated aqueous HCl was added, and the precipitate was filtered off, washed with water, dried in air, and washed with cold methylene chloride. Yield 64 mg (26%), light yellow crystals, decomposition point >260°C. IR spectrum, ν, cm^{-1}: 3238 (NH), 2630 (OH), 2204 (CN), 1614 (C=C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.03 s (3H, CH_3), 1.07 s (3H, CH_3), 2.17 br.s (2H, CH_2), 2.41 br.s (2H, CH_2), 3.32 t (4H, CH_2N, *J* = 4.5 Hz), 3.73 t (4H, CH_2O, *J* = 4.5 Hz), 7.13 t (1H, H_{arom}, *J* = 7 Hz), 7.22–7.34 m (4H, H_{arom}), 10.50 br.s (1H, NH), 10.81 s (1H, OH). Mass spectrum: *m*/*z* 392 $[M + H]^+$. Found, %: C 70.28; H 6.55; N 10.80. $C_{23}H_{25}N_3O_3$. Calculated, %: C 70.57; H 6.44; N 10.73. *M* 391.46.

4-(4,4-Dimethyl-2,6-dioxocyclohexyl)-2-hydroxyamino-5-phenyl-1*H*-pyrrole-3-carbonitrile (solvate with one ethanol molecule) (V). A solution of 0.2 g (0.62 mmol) of compound **I** and 52 mg (0.75 mmol) of hydroxylamine hydrochloride in 5 ml of ethanol was heated for 1 h under reflux. The solvent was distilled off under reduced pressure, and the residue was ground with ice water, dried in air, and purified by express chromatography on neutral alumina using first methylene chloride and then ethyl acetate as eluent. Yield 0.16 g (67%), light yellow crystals, mp 166–168°C. IR spectrum, ν, cm^{-1}: 3456 (NH), 3335 (OH), 3175 (OH), 3134 (NH), 2640 (OH), 2208 (CN), 1641 (C=O), 1613 (C=C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.05 s (3H, CH_3), 1.07 s (3H, CH_3), 1.36 t (3H, C**H**$_3$CH$_2$, *J* = 7.1 Hz), 2.11–2.26 m (2H, CH_2), 2.36–2.50 m (2H, CH_2), 4.36 q (2H, C**H**$_2$CH$_3$, *J* = 7.1 Hz), 7.13 t (1H, H_{arom}, *J* = 7.2 Hz), 7.20–7.36 m (4H, H_{arom}), 10.56 br.s (1H, NH), 11.58 s (1H, OH). Mass spectrum: *m*/*z* 338 $[M - C_2H_5OH + H]^+$. Found, %: C 65.46; H 6.43; N 11.06. $C_{19}H_{19}N_3O_3 \cdot C_2H_5OH$. Calculated, %: C 65.78; H 6.57; N 10.96. *M* 383.44.

3-Amino-6-phenylpyridazine-4-carbonitrile (VI). A solution of 0.2 g (0.62 mmol) of compound **I** and 37 mg (0.74 mmol) of hydrazine hydrate in 2 ml of ethanol was heated for 0.5 h under reflux, 1 ml of water was added, the mixture was cooled, and the precipitate was filtered off and washed with cold ethanol. Yield 65 mg (53%), light yellow crystals. The spectral parameters of the product were consistent with published data [19]. Found, %: C 67.55; H 4.22; N 28.40. $C_{11}H_8N_4$. Calculated, %: C 67.34; H 4.11; N 28.55.

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