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Reactions of Dimedone–β-Benzoylacrylic Acid Adduct with Nitrogen-Containing Binucleophiles

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Abstract—2-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-4-oxo-4-phenylbutanoic acid (dimedone adduct with β-benzoylacrylic acid) reacted with ethylenediamine and benzidine to give bis-quinoline derivatives. In the reaction with tryptamine a product containing hexahydroquinoline and indole fragments was obtained, while the reaction with phenylhydrazine hydrochloride afforded pyridazine derivative. The reactions with *o*- and *p*-phenylenediamines involved retro-Michael decomposition of the initial adduct and formation of enamino derivatives of dimedone.

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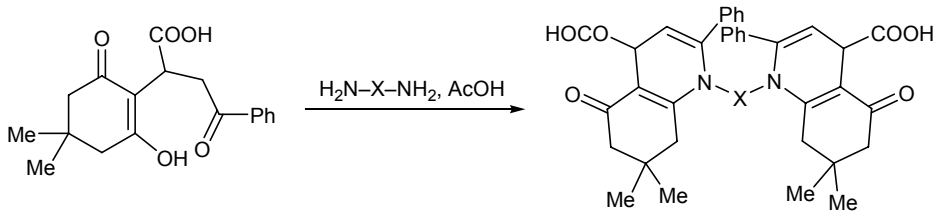
Polycarbonyl compounds derived from cyclic 1,3-diketones and electron-deficient 1,2-disubstituted ethylenes possess 1,3-, 1,4-, or 1,5-dicarbonyl fragment and are convenient model structures for various heterocyclizations, e.g., in reactions with nitrogen-centered nucleophiles. These reactions could lead to the formation of heterocyclic compounds belonging to the pyrrole, quinoline, pyrroloquinoline, and pyridazine series, and they attract much interest from the viewpoint of molecular design. Some products obtained as a result of the above heterocyclization are important as potential physiologically active substances. For example, data on the use of tetra- and hexahydroquinoline derivatives as analgesic, antiallergic, antiphlogistic, and antipyretic agents have been reported [1–3].

It was shown previously that 2-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-4-oxo-4-phenylbutanoic acid (**I**, Michael adduct of dimedone and β-benzoylacrylic acid) reacts with ammonia to give pyrrolo[4,3,2-*de*]quinoline derivative [4] and that hexahydroquinoline derivatives are formed in reactions of **I** with primary amines [5]. N-Heterocyclizations of other polycarbonyl compounds, products of Michael addition of dimedone to 1,2-dibenzoylethylene [6] and 1,1-diacetyl-2-benzoylethylene [7], were also studied, and the resulting nitrogen-containing heterocycles were identified as pyrrole, quinoline, and pyrrolo[3,4-*c*]quinoline derivatives.

In the present work we examined reactions of adduct **I** with some nitrogen-centered binucleophiles, in particular ethylenediamine, benzidine, phenylhydrazine hydrochloride, *o*- and *p*-phenylenediamines, and a biogenic amine, tryptamine, with a view to determine their regioselectivity. The reactions with ethylenediamine and benzidine were carried out by heating the reactants in boiling acetic acid; the substrate–diamine molar ratio was 1:1.5 for ethylenediamine and 2:1 for benzidine. As a result, we obtained the corresponding bis-quinoline derivatives **IIa** and **IIb** (Scheme 1);

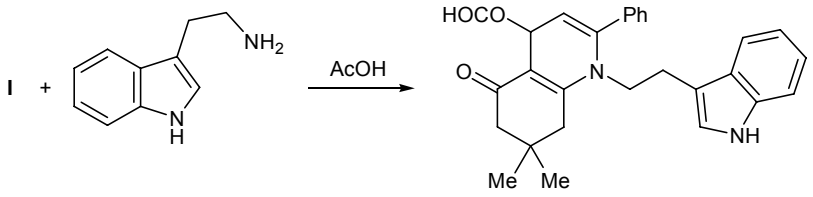
Scheme 1.



I **IIa**, **IIb**

X = CH_2CH_2 (**a**), *p*-$C_6H_4C_6H_4$-*p*′ (**b**).

Scheme 2.



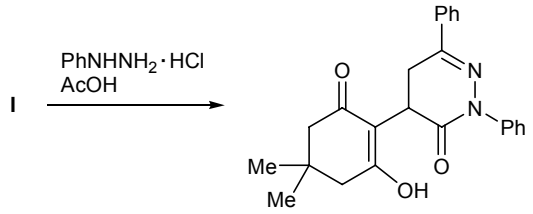
III

compound **IIa** was formed as a mixture of atropisomers at a ratio of 1:2. The poor yield of **IIa** (9%) may be rationalized assuming that the main process is retro-Michael decomposition of initial adduct **I** and subsequent formation of water-soluble enamines from dimedone; in this case, the expected heterocyclization of **I** to compound **IIa** is a minor process. We failed to improve the yield of **IIa** by varying the reaction conditions.

By reaction of adduct **I** with an equimolar amount of tryptamine in acetic acid we obtained 65% of compound **III** possessing both hexahydroquinoline and indole fragments (Scheme 2). We can conclude that adduct **I** in the above reactions acts as 1,5-diketone whose N-heterocyclization gives rise to compounds with a 1,4-dihydropyridine fragment.

A different regioselectivity was observed in the reaction of adduct **I** with phenylhydrazine hydrochloride. Heating of equimolar amounts of the reactants in boiling acetic acid led to the formation of pyridazine derivative **IV** in which the dimedone fragment remained unchanged (Scheme 3). The synthesis of simpler pyridazinones from γ-keto acids is well known [8].

Scheme 3.



IV

As nitrogen-containing binucleophiles we also used *o*- and *p*-phenylenediamines. The reaction with *o*-phenylenediamine was expected to give compound **V** as double cyclization product, whereas *p*-phenylenediamine was presumed to produce bis-quinoline **VII**. However, contrary to the expectations, the products of the above reactions were the corresponding enamines **VI** and **VIII** (Scheme 4) which were reported previously [9–11]. Obviously, compounds **VI** and **VIII** were formed via retro-Michael decomposition of initial adduct **I** and subsequent reaction of dimedone with *o*- and *p*-phenylenediamines. The latter are likely to act as bases which catalyze retro-Michael reaction.

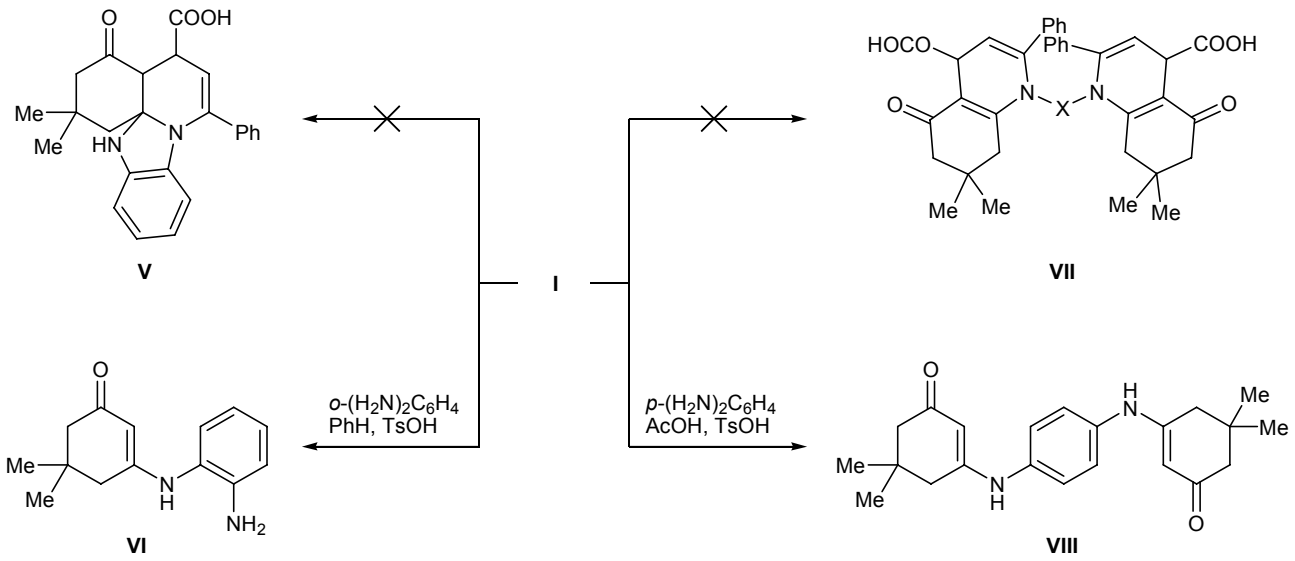
The structure of the isolated compounds was proved by the IR, NMR, and mass spectra (HPLC–MS data).

EXPERIMENTAL

The IR spectra were recorded in KBr on a Perkin–Elmer Spectrum BX spectrometer. The ^{1}H NMR spectra were measured on a Bruker AC-400 spectrometer (400 MHz) from solutions in $CDCl_3$ and DMSO-d_6 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, grain size 3.5 μm, eluent methanol–water (70:30), detector temperature 50°C. The progress of reactions was monitored by TLC on Sorbfil plates using ethyl acetate–ethanol (10:1) as eluent; development with iodine vapor.

1,1′-(Ethane-1,2-diyl)bis(7,7-dimethyl-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline-4-carboxylic acid) (IIa). A solution of 0.2 g (0.63 mmol) of adduct **I** and 0.114 g (0.95 mmol) of 50% aqueous ethylenediamine in 5 ml of acetic acid was heated for 20 min under reflux. The mixture was poured into 100 ml of a dilute aqueous solution of sodium chloride, and the precipitate was filtered off, washed with water, dried in air, and ground with diethyl ether. Yield 18 mg (9%), colorless crystals, mp 225–227°C. IR spectrum, ν, cm^{-1}: 2300 br (OH, assoc.), 1606 (C=O in CO_2^-). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: atropisomer **A**: 1.10 s (12H, CH_3), 2.31 s (4H, CH_2), 2.47 s (4H, CH_2), 2.84 d and 3.96 d (2H each, NCH_2, J = 9.8 Hz), 5.32 d (2H, 4-H, J = 1.5 Hz), 7.14 t (4H, H_{arom}, J = 7 Hz), 7.29–7.38 m (6H, H_{arom}), 8.18 d (2H, 3-H, J = 1.5 Hz), 14.92 s (2H, OH); atropisomer **B**: 1.10 s (12H, CH_3), 2.32 s (4H, CH_2), 2.48 s (4H, CH_2), 3.07 d and 3.76 d

Scheme 4.



X = *p*-C_6H_4.

(2H each, NCH_2, J = 9.8 Hz), 5.10 d (2H, 4-H, J = 1.5 Hz), 7.04 t (4H, H_{arom}, J = 7 Hz), 7.29–7.38 m (6H, H_{arom}), 8.33 d (2H, 3-H, J = 1.5 Hz), 15.00 s (2H, OH). Mass spectrum: m/z 621 $[M + H]^+$. Found, %: C 73.25; H 6.64; N 4.60. $C_{38}H_{40}N_2O_6$. Calculated, %: C 73.53; H 6.50; N 4.51. M 620.

1,1′-(Biphenyl-4,4′-diyl)bis(7,7-dimethyl-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline-4-carboxylic acid) (IIb). A solution of 0.4 g (1.27 mmol) of adduct **I** and 0.117 g (0.63 mmol) of benzidine in 5 ml of acetic acid was heated for 1 h under reflux. The mixture was poured into ice water, and the precipitate was filtered off, washed with water, dried in air, and purified by express chromatography on silica gel using ethyl acetate as eluent. Yield 0.25 g (53%), light yellow crystals, mp 187–188°C. IR spectrum, ν, cm^{-1}: 2400 br (OH, assoc.), 1640 (C=O), 1619 (C=O in CO_2^-). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.05 s (12H, CH_3), 2.05 s (4H, CH_2), 2.40 s (4H, CH_2), 6.22 d (2H, 4-H, J = 1 Hz), 7.17–7.37 m (10H, H_{arom}), 7.41 d (2H, 3-H, J = 1 Hz), 7.56 d (4H, H_{arom}, J = 8 Hz), 7.63 d (4H, H_{arom}, J = 8 Hz), 12.29 s (2H, OH). Mass spectrum: m/z 745 $[M + H]^+$. Found, %: C 77.07; H 6.12; N 3.88. $C_{48}H_{44}N_2O_6$. Calculated, %: C 77.40; H 5.95; N 3.76. M 744.

1-[2-(1*H*-Indol-3-yl)ethyl]-7,7-dimethyl-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline-4-carboxylic acid (III). A solution of 0.2 g (0.63 mmol) of adduct **I** and 0.1 g (0.63 mmol) of tryptamine in 5 ml of acetic acid was heated for 1 h under reflux. The mixture was poured into 100 ml of ice water, and the precipitate was filtered off, washed with water, dried in air, and recrystallized from chloroform. Yield 0.182 g (65%), colorless crystals, mp 283–284°C (decomp.). IR spectrum, ν, cm^{-1}: 3290 (NH), 2750 br (OH, assoc.), 1637 (C=O), 1616 (C=O in CO_2^-). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.98 s (6H, CH_3), 2.20 s (4H, CH_2), 2.63 t (1H, NCH_2, J = 9.5 Hz), 2.72–2.79 m (2H, CH_2), 2.89 d (1H, 4-H, J = 11.9 Hz), 3.92 t (1H, NCH_2, J = 9.5 Hz), 4.29 d (1H, 3-H, J = 11.9 Hz), 7.00 d (1H, H_{arom}, J = 7.6 Hz), 7.09 t (1H, H_{arom}, J = 7.6 Hz), 7.34–7.40 m (8H, H_{arom}), 10.84 s (1H, NH), 11.31 s (1H, OH). Mass spectrum: m/z 441 $[M + H]^+$. Found, %: C 76.13; H 6.63; N 6.47. $C_{28}H_{28}N_2O_3$. Calculated, %: C 76.34; H 6.41; N 6.36. M 440.

4-(4,4-Dimethyl-2,6-dioxocyclohexyl)-2,6-diphenyl-2,3,4,5-tetrahydropyridazin-3-one (IV). A solution of 0.2 g (0.63 mmol) of adduct **I** and 92 mg (0.63 mmol) of phenylhydrazine hydrochloride in 5 ml of acetic acid was heated for 30 min under reflux. The mixture was poured into 100 ml of a dilute aqueous solution of sodium chloride, and the precipitate was filtered off, washed with water, dried in air, and ground with diethyl ether. Yield 73 mg (30%), Colorless crystals, mp 215–216°C. IR spectrum, ν, cm^{-1}: 2600 br (OH, enol), 1637 (NC=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.03 s (6H, CH_3), 2.28 s (4H, CH_2), 3.06 d.d (1H, 5-H, J = 16.8, 7.6 Hz), 3.24 d.d (1H, 5-H, J = 13.0, 16.8 Hz), 3.98 d.d (1H, 4-H, J = 7.6, 13.0 Hz), 7.26 t (1H, H_{arom}, J = 7.4 Hz), 7.34–7.47 m (5H, H_{arom}), 7.53 d (2H, H_{arom}, J = 7.7 Hz),

7.80 d (2H, H_{arom}, J = 7.3 Hz), 11.02 s (1H, OH). Mass spectrum: m/z 389 $[M + H]^+$. Found, %: C 74.35; H 6.39; N 7.32. $C_{24}H_{24}N_2O_3$. Calculated, %: C 74.21; H 6.23; N 7.21. M 388.

3-(2-Aminophenylamino)-5,5-dimethylcyclohex-2-en-1-one (VI). Benzene, 10 ml, was added to a mixture of 0.1 g (0.32 mmol) of adduct **I**, 34 mg (0.32 mmol) of *o*-phenylenediamine, and 30 mg (0.16 mmol) of *p*-toluenesulfonic acid. The mixture was heated for 1.5 h under reflux with stirring, the solvent was distilled off under reduced pressure, the residue was dissolved in 5 ml of alcohol, the solution was poured into 50 ml of a dilute aqueous solution of sodium chloride, and the precipitate was filtered off, washed with water, dried in air, and ground with diethyl ether. Yield 37 mg (51%). Light yellow crystals, mp 176–177°C; published data [10]: mp 178–179°C. Mass spectrum: m/z 231 $[M + H]^+$. Found, %: C 72.86; H 8.08; N 12.33. $C_{14}H_{18}N_2O$. Calculated, %: C 73.01; H 7.88; N 12.16. M 230.

***N*,*N*′-(Benzene-1,4-diyl)bis(3-amino-5,5-dimethylcyclohex-2-en-1-one) (VIII).** A solution of 0.1 g (0.32 mmol) of adduct **I**, 17 mg (0.16 mmol) of *p*-phenylenediamine, and 30 mg (0.16 mmol) of *p*-toluenesulfonic acid in 5 ml of acetic acid was stirred for 1.5 h at 100°C. The mixture was poured into 100 ml of a dilute aqueous solution of sodium chloride, and the precipitate was filtered off, washed with water, dried in air, and ground with diethyl ether. Yield 36 mg (65%), light gray crystals decomposing above 350°C. The spectral parameters were consistent with published data [11]. Mass spectrum: m/z 353 $[M + H]^+$. Found, %: C 74.70; H 8.20; N 8.09. $C_{22}H_{28}N_2O_2$. Calculated, %: C 74.97; H 8.01; N 7.95. M 352.

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