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Reactions of *p*-Quinone Diimines of the 1,2,3,4,4a,5-Hexahydro-10*H*-benzimidazo[2,1-*j*]quinolin-10-imines with Some Compounds Having an Activated Methylene Group

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Abstract—Reactions of *N*-(1,2,3,4,4a,5-hexahydro-10*H*-benzimidazo[2,1-*j*]quinolin-10-ylidene)amines with malononitrile and cyanoacetamide gave the corresponding 12-methylidene derivatives.

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Reactions of *p*-quinone diimines with carbon-centered nucleophiles have been studied insufficiently. A few reactions of symmetric *N*,*N*′-diacyl-*p*-quinone diimines with 1,3-dicarbonyl compounds (dibenzoylmethane, cyclohexane-1,3-dione, etc.) were reported to occur as addition at the quinoid ring with formation of benzoid structures [1–3]. Even less data are available on analogous reactions with heterocyclic quinone derivatives. We found only one example of reaction of heterocyclic quinone imine (benzophenoxazinone) with anionic C-nucleophiles, which followed aromatic nucleophilic substitution pattern, and the subsequent tautomerization gave products having methylenequinone imine structure [4]; no analogous reactions with quinone diimines were reported. Baxter et al. [5] described the addition of acetylacetone at the quinoid fragment of 4-arylsulfonylimino-6*H*-1,3-benzoxazol-2-one with formation of benzoid structure.

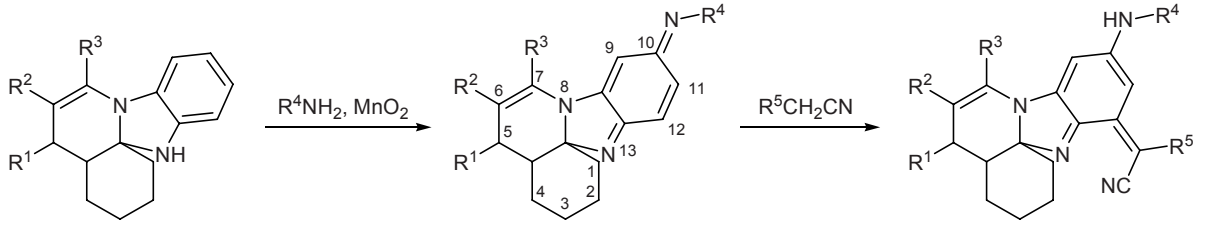
We previously showed [6] that pyrido[1,2-*a*]benzimidazole derivatives having a quinone imine or *N*-phenylquinone diimine fragment react with indan-1,3-dione, barbituric acid, malononitrile, and cyanoacetamide to give the corresponding substitution products at the 8-position of the pyridobenzimidazole system. By contrast, the reactions with *N*-cyclohexylquinone diimines of the same series occurred at the 9-position with subsequent tuatomerization to *o*-methylenequinone imine derivatives. Presumably, initial 1,4-addition at the quinoid ring is followed by oxidation (e.g., with atmospheric oxygen) which regenerates quinoid structure. It was presumed that the different directions of nucleophilic addition to quinone diimines is related to the presence of an electron-withdrawing phenyl ring or electron-donating cyclohexane ring on the exocyclic nitrogen atom. Taking into account that the addition at position *9* (and subsequent tautomerization) was observed only once, it seemed to be reasonable to examine reactions of CH acids with a larger number of *N*-substituted quinone diimines with a view to elucidate whether the above direction is general.

Initial quinone diimines **IIa**, **IIIa**, **IVa**, and **IVb** were prepared by oxidative coupling of 1,2,3,4,4a,5-hexahydro-13*H*-benzimidazo[2,1-*j*]quinolines **Ia** and **Ib** with primary aliphatic amines in the presence of manganese(IV) oxide. Compounds **IIIa** [7] and **IVa** and **IVb** [8], which were obtained by coupling with 2,2,6,6-tetramethylpiperidin-4-amine and 2-amino-2-methylpropan-1-ol, respectively, were described previously. Condensation product **IIa** derived from methanamine was synthesized for the first time.

We found that compounds **IIa**, **IIIa**, **IVa**, and **IVb** readily react with malononitrile and cyanoacetamide to give compounds **V**–**IX** having a methylene-*p*-quinone imine fragment (Scheme 1). The reactions occurred at high rate at room temperature, i.e., under milder conditions than in the reactions with quinone imines and *N*-phenylquinone diimine (the latter were slow even at elevated temperature) [6].

Taking into account that the isolation of compound **IIa** was difficult due to its thermal and chromatographic instability, we tried to synthesize compounds **Va** and **VIIIa** directly from 1,2,3,4,4a,5-hexahydro-

Scheme 1.



R^1 = H, R^2R^3 = $(CH_2)_4$ (**a**); R^1 = R^3 = Ph, R^2 = H (**b**); **II**, **V**, **VIII**, R^4 = Me; **III**, **VI**, **IX**, R^4 = 2,2,6,6-tetramethylpiperidin-4-yl; **IV**, **VII**, R^4 = $HOCH_2CMe_2$; **V**–**VII**, R^5 = CN; **VIII**, **IX**, R^5 = $CONH_2$.

13*H*-benzimidazo[2,1-*j*]quinolines **Ia** and **Ib** and the corresponding CH acids without intermediate isolation of imines **IIa** and **IIIa**. For this purpose, the reaction mixture containing imine **IIa** or **IIIa** was filtered from MnO_2, and malononinitrile or cyanoacetamide was added to the filtrate. This one-pot procedure was also used to obtain compounds **VIa** and **IXa** from *N*-(2,2,6,6-tetramethylpiperidin-4-yl)imine **IIIa**.

All compounds **V**–**VII** obtained by condensation with malononitrile were stable, in contrast to those derived from cyanoacetamide (compounds **VIIIa** and **IXa**); the yields of the latter were lower due to their thermal and photochemical lability. Solutions of all compounds **V**–**IX** were bright green.

We previously showed [8] that *N*-(2-hydroxyethyl)-quinone diimines formed as a result of oxidative coupling of pyridobenzimidazole derivatives with substituted aminoethanols are capable of undergoing intramolecular cyclization to give products having an oxazine ring fused at the 7,8-position. However, we failed to obtain analogous cyclization products from compounds **VIIa** and **VIIb** on heating or on treatment with potassium *tert*-butoxide. Presumably, the presence of an electron-donating amino group at C^{10} deactivates the neighboring C^{11} atom toward nucleophilic attack; on the other hand, some contribution of steric hindrances is also possible.

The IR spectra of **V**–**IX** contained an absorption band typical of secondary amino group, while absorption bands belonging to vibrations of the double C^6=C^7 bond and quinoid C=N and C=C bonds were retained, indicating formation of *ortho*-quinoid structure. Compounds **V**–**VII** displayed absorption bands due to conjugated cyano groups, and bands typical of conjugated cyano and carbamoyl groups were observed in the IR spectra of **VIIIa**, **IXa**. The presence of OH absorption in the spectra of **VIIa** and **VIIb** confirmed that no fusion at positions *7,8* occurred.

The *m*/*z* values of pseudomolecular $[M + H]^+$ ions in the mass spectra of **V**–**IX** were consistent with those calculated for the assumed structures.

The ^{1}H NMR spectra of **V**–**IX** lacked signal assignable to 12-H, a signal typical of NH group appeared, and the 11-H signal changed its multiplicity from doublet of doublets (as in the spectra of initial compounds **II**–**IV**) to a doublet with a long-range coupling constant ^4J of 1.7 Hz. These findings also confirmed the presence of a methylenequinone imine fragment in molecules **V**–**IX**.

In the ^{1}H NMR spectra of **Va**, **VIa**, **VIIa**, and **VIIb**, signals from the quinoid 9-H and 11-H protons, as well as from protons in the NH and CH_3 groups, were doubled at a ratio of 1.5:1 (**Va**, **VIa**), 1:1 (**VIIa**), or 6:1 (**VIIb**). Nuclear Overhauser effect experiments showed the existence of stable conformers **A** and **B** with respect to the single C^{10}–N bond. Signals from protons in the quinoid fragments and NH groups in the spectra of **Va**, **VIa**, **VIIa**, and **VIIb** were assigned using heteronuclear double resonance technique (INDOR). Increased fraction of one conformer of compound **VIIb** (6:1) is likely to be related to restricted inversion of the aminoethanol fragment located in the vicinity of the 7-phenyl group.

Analogous signal doubling in the spectra of **VIIIa** and **IXa** could result from the presence of *Z* and *E* stereoisomers with respect to the exocyclic C^{12}=C double bond, as was the case of *p*-methylenequinone imine derivatives reported previously [9]. We believe that these compounds also exist as mixtures of stable conformers **A** and **B** having more favorable *E* configuration of the exocyclic double bond. The latter follows from the downfield position of the 11-H signal (δ 7.40–7.50 ppm against δ 6.90 ppm in the spectrum of **IIa**) due to deshielding by the $CONH_2$ fragment.

Our results demonstrate that the regioselectivity of nucleophilic addition to *p*-quinone diimines of the

pyridobenzimidazole series is determined by the electronic nature of substituent on the exocyclic nitrogen atom.

EXPERIMENTAL

The IR spectra were recorded on a Perkin–Elmer Spectrum BX-II spectrometer from solutions in methylene chloride or samples prepared as KBr pellets. The ^{1}H NMR spectra were measured from solutions in DMSO-d_6 on a Bruker AC-250 spectrometer at 250 MHz using tetramethylsilane as internal reference. The elemental compositions were determined on a Flash EA 1112 CHN/MAS200 analyzer. HPLC analysis was performed on an HP 1100 LC/MSD instrument equipped with a Hypersil ODS column (4× 125 mm); eluent propan-2-ol–water (60:40), flow rate 0.3 ml/min, temperature 55°C, diode matrix; atmospheric pressure corona discharge ionization source; positive or negative (**VIIa**) ion mode. The mass spectra were also recorded under electron impact (70 eV) with direct sample admission into the ion source.

The melting points were determined in capillaries or using a Boetius melting point apparatus. The progress of reactions and the purity of products were monitored by TLC using Silufol UV-254 and Sorbfil plates; hexane–ethyl acetate (1:1), ethyl acetate, ethanol, and AcOH–water (1:10) were used as eluents. Preparative thin-layer chromatography was performed on 25×30-cm plates coated with a 1.5-mm layer of aluminum oxide of activity grade II according to Brockmann; sample amount 0.25 g.

All compounds were synthesized according to the general procedure (see below) with different isolation and purification methods. Compounds **Ia** and **Ib** [10], **IIIa** [7], and **IVa** [8] were reported previously.

***N*-(6,7-Tetramethylene-1,2,3,4,4a,5-hexahydro-10*H*-benzimidazo[2,1-*j*]quinolin-10-ylidene)methanamine (IIa).** Compound **Ia**, 1 mmol, was dissolved in 20 ml of ethanol, a solution of 1.5 mmol of methanamine hydrochloride in 10 ml of ethanol saturated with Na_2CO_3 was added under stirring, and 3 g of MnO_2 was then added. The mixture was stirred for 3 h at room temperature until the initial compound disappeared (TLC), the precipitate of MnO_2 was filtered off and washed with ethanol until slightly colored washings, the filtrate was diluted with three volumes of water, 3 ml of a saturated solution of Na_2CO_3 was added, and the precipitate was filtered off, washed with two portions of water, and dried. The product was purified by chromatography using petroleum ether–ethyl acetate (3:1) as eluent. Yield 62%, red crystals, mp 120–122°C. IR spectrum, ν, cm^{-1}: 1666 (C^6=C^7); 1629 (C=N); 1595, 1535 (C=C_{quin}). ^{1}H NMR spectrum, δ, ppm: 1.20–2.20 m (19H), 3.16 s (3H, CH_3), 5.82 s (1H, 9-H), 6.90 d (1H, 11-H, J = 10.0 Hz), 7.15 d (1H, 12-H, J = 10.0 Hz). Found, %: C 78.07; H 8.42; N 13.21. Mass spectrum: m/z 308 $[M + H]^+$. $C_{20}H_{25}N_3$. Calculated, %: C 78.14; H 8.20; N 13.67. M 307.43.

General procedure for the synthesis of compounds V–IX. *a*. Compound **IIa**, **IIIa**, **IVa**, or **IVb**, 1 mmol, was dissolved in 10 ml of ethanol, 1.5 mmol of malononitrile or cyanoacetamide was added, and the mixture was stirred at room temperature until the initial compound disappeared according to the TLC data (for 1 h in the sunthesis of **VIa**, for 2 h in the synthesis of **VIIa** and **VIIb**, for 3 h in the synthesis of **VIIIa** and **IXa**, and for 5 h in the synthesis of **Va**). By the end of the process, the mixture turned dark green. In the synthesis of **VIIa**, the mixture was cooled, and the precipitate was filtered off and recrystallized from hexane–acetone. In the other cases, the mixture was diluted with three volumes of water, 3 ml of a saturated solution of Na_2CO_3 was added, and the precipitate was filtered off, washed with water (2×5 ml), dried, and subjected to chromatography using petroleum ether–ethyl acetate (2:1) (**Va**, **VIIb**), acetone–ethanol (1:2) (**VIIIa**, **IXa**), or pure ethanol (**VIa**) as eluent. The products were green finely crystalline substances which were readily soluble in ethanol, acetone, and ethyl acetate and very poorly soluble in hexane and chloroform.

b. *One-pot procedure for the synthesis of compounds **Va**, **VIa**, **VIIIa**, and **IXa**.* Compound **Ia**, 1 mmol, was dissolved in 10 ml of ethanol, 1.5 mmol of the corresponding amine and 3 g of MnO_2 were added in succession, and the mixture was stirred at room temperature until the initial compound disappeared according to the TLC data. The precipitate of MnO_2 was filtered off and washed on a filter with ethanol until slightly colored washings. Malononitrile, or cyanoacetamide, 1.5 mmol, was added to the filtrate, and the mixture was stirred at room temperature until compound **IIa** or **IIIa** disappeared according to the TLC data. The mixture was then diluted with three volumes of water, 3 ml of a saturated solution of Na_2CO_3 was added, and the precipitate was filtered off, washed with water (2×5 ml), and dried. The product was purified by preparative thin-layer chromatography as described above in *a*.

(10-Methylamino-6,7-tetramethylene-1,2,3,4,4a,5-hexahydro-12*H*-benzimidazo[2,1-*j*]-quinolin-12-ylidene)malononitrile (Va) (A:B ratio 3:2**).** Yield 51 (*a*), 67 (*b*); mp 266–268°C (decomp.). IR spectrum, ν, cm^{-1}: 3263 (NH); 2186, 2155 (CN); 1666 (C^6=C^7); 1633 (C=N); 1590, 1549 (C=C_{quin}). ^{1}H NMR spectrum, δ, ppm: 0.80–2.40 m (19H), 1.20 s (3H, CH_3, **B**), 1.28 s (3H, CH_3, **A**), 5.60 d (1H, 9-H, **A**, *J* = 1.7 Hz), 5.66 d (1H, 9-H, **B**, *J* = 1.5 Hz), 5.80 d (1H, 11-H, **B**, *J* = 1.5 Hz), 5.97 d (1H, 11-H, **A**, *J* = 1.7 Hz), 8.73 m (1H, NH, **B**), 8.97 m (1H, NH, **A**). Found, %: C 74.45; H 6.99; N 18.39. Mass spectrum: *m*/*z* 372 $[M + H]^+$. $C_{23}H_{25}N_5$. Calculated, %: C 74.36; H 6.78; N18.85. *M* 371.48

[6,7-Tetramethylene-10-(2,2,6,6-tetramethylpiperidin-4-ylamino)-1,2,3,4,4a,5-hexahydro-12*H*-benzimidazo[2,1-*j*]quinolin-12-ylidene]malononitrile (VIa) (A:B ratio 3:2**).** Yield 65 (*a*), 53 (*b*); mp 252–254°C (decomp.). IR spectrum, ν, cm^{-1}: 3317, 3244 (NH); 2193, 2170 (CN); 1668 (C^6=C^7); 1633 (C=N); 1593, 1537 (C=C_{quin}). ^{1}H NMR spectrum, δ, ppm: 1.00–2.50 m (24H), 1.02 s (12H, CH_3, **A**), 1.20 s (12H, CH_3, **B**), 5.61 d (1H, 9-H, **A**, *J* = 1.5 Hz), 5.69 d (1H, 9-H, **B**, *J* = 1.2 Hz), 5.85 d (1H, 11-H, **B**, *J* = 1.2 Hz), 5.99 d (1H, 11-H, **A**, *J* = 1.5 Hz), 8.62 br.s (1H, NH, **B**), 8.85 br.s (1H, NH, **A**). Found, %: C 75.38; H 8.15; N 16.66. Mass spectrum: *m*/*z* 497 $[M + H]^+$. $C_{31}H_{40}N_6$. Calculated, %: C 74.96; H 8.12; N16.92. *M* 496.69.

[10-(2-Hydroxy-1,1-dimethylethylamino)-6,7-tetramethylene-1,2,3,4,4a,5-hexahydro-12*H*-benzimidazo[2,1-*j*]quinolin-12-ylidene]malononitrile (VIIa) (A:B ratio 1:1**).** Yield 72%, mp 270–272°C (decomp.) IR spectrum, ν, cm^{-1}: 3289 br (NH, OH); 2195, 2176 (CN); 1668 (C^6=C^7); 1640 (C=N); 1591, 1588 (C=C_{quin}). ^{1}H NMR spectrum, δ, ppm: 1.00–2.50 m (21H), 1.31 s (6H, CH_3, **A**), 1.33 s (6H, CH_3, **B**), 5.20 t (1H, OH, **B**, *J* = 5.4 Hz), 5.25 t (1H, OH, **A**, *J* = 5.2 Hz), 5.79 br.s (1H, 9-H, **B**), 5.86 br.s (1H, 9-H, **A**), 6.07 br.s (1H, 11-H, **B**), 6.12 br.s (1H, 11-H, **A**), 8.09 br.s (1H, NH, **A**), 8.41 br.s (1H, NH, **B**). Found, %: C 72.81; H 7.39; N 16.25. Mass spectrum: *m*/*z* 428 $[M - H]^-$. $C_{26}H_{31}N_5O$. Calculated, %: C 72.70; H 7.27; N 16.30. *M* 429.56.

[10-(2-Hydroxy-1,1-dimethylethylamino)-5,7-diphenyl-1,2,3,4,4a,5-hexahydro-12*H*-benzimidazo-[2,1-*j*]quinolin-12-ylidene]malononitrile (VIIb) (A:B ratio 6:1**).** Yield 66%, mp 255–257°C (decomp.). IR spectrum, ν, cm^{-1}: 3262 br (NH, OH); 2193, 2167 (CN); 1653 (C^6=C^7); 1631 (C=N); 1590 (C=C_{quin}). ^{1}H NMR spectrum, δ, ppm: 1.10–2.20 m (11H), 1.14 s (3H, CH_3, **A**), 1.22 s (3H, CH_3, **A**), 1.28 s (3H, CH_3, **B**), 1.30 s (3H, CH_3, **B**), 4.00 d.d (1H, 5-H, **B**, $J_{5,4a}$ = 10.0, $J_{5,6}$ = 3.0 Hz), 4.07 d.d (1H, 5-H, **A**, $J_{5,4a}$ = 10.0, $J_{5,6}$ = 3.0 Hz), 4.52 d (1H, 9-H, **A**, *J* = 1.7 Hz), 4.75 d (1H, 9-H, **B**, *J* = 1.7 Hz), 4.99 t (1H, OH, **A**, *J* = 5.6 Hz), 5.15 t (1H, OH, **B**, *J* = 5.6 Hz), 5.50 d (1H, 6-H, **B**, *J* = 3.0 Hz), 5.55 d (1H, 6-H, **A**, *J* = 3.0 Hz), 6.08 d (1H, 11-H, **B**, *J* = 1.7 Hz), 6.10 d (1H, 11-H, **A**, *J* = 1.7 Hz), 7.20–7.50 m (10H, H_{arom}), 8.18 br.s (1H, NH, **B**), 8.48 br.s (1H, NH, **A**). Found, %: C 77.72; H 6.11; N 13.20. Mass spectrum: *m*/*z* 528 $[M + H]^+$. $C_{34}H_{33}N_5O$. Calculated, %: C 77.39; H 6.30; N 13.27. *M* 527.66

2-Cyano-2-[(12*E*)-10-methylamino-6,7-tetramethylene-1,2,3,4,4a,5-hexahydro-12*H*-benzimidazo[2,1-*j*]quinolin-12-ylidene]acetamide (VIIIa) (A:B ratio 1:1**).** Yield 48 (*a*), 64 (*b*); mp 167–169°C (decomp.). IR spectrum, ν, cm^{-1}: 3483, 3410 (NH_2); 3247 (NH); 2162 (CN); 1700 (C=O); 1669 (C^6=C^7); 1644 (C=N); 1585 (C=C_{quin}). ^{1}H NMR spectrum, δ, ppm: 0.90–2.50 m (19H), 1.14 s (3H, CH_3, **A**), 1.22 s (3H, CH_3, **B**), 5.50 s (1H, 9-H, **A**), 5.52 s (1H, 9-H, **B**), 6.03 br.s (2H, NH_2, **A**), 6.36 br.s (2H, NH_2, **B**), 7.40 br.s (1H, 11-H, **A**), 7.50 br.s (1H, 11-H, **B**), 8.09 br.s (1H, NH, **A**), 8.60 br.s (1H, NH, **B**). Found, %: C 70.97; H 7.43; N 18.19. Mass spectrum: *m*/*z* 390 $[M + H]^+$. $C_{23}H_{27}N_5O$. Calculated, %: C 70.92; H 6.99; N 17.98. *M* 389.49.

2-Cyano-2-[(12*E*)-6,7-tetramethylene-10-(2,2,6,6-tetramethylpiperidin-4-ylamino)-1,2,3,4,4a,5-hexahydro-12*H*-benzimidazo[2,1-*j*]-quinolin-12-ylidene]acetamid (IXa) (A:B ratio 3:2**).** Yield 63 (*a*), 54 (*b*); mp 240–242°C (decomp). IR spectrum, ν, cm^{-1}: 3480, 3420 (NH_2); 3248 (NH); 2163 (CN); 1673 (C=O); 1653 (C^6=C^7); 1631 (C=N); 1580, 1576 (C=C_{quin}). ^{1}H NMR spectrum, δ, ppm: 1.02 s (6H, CH_3, **A**), 1.05 s (6H, CH_3, **A**), 1.14 s (6H, CH_3, **B**), 1.20 s (6H, CH_3, **B**), 1.50–2.70 m (24H), 5.57 s (1H, 9-H, **A**), 5.59 s (1H, 9-H, **B**), 6.07 br.s (2H, NH_2, **B**), 6.34 br.s (2H, NH_2, **A**), 7.50 br.s (1H, 11-H, **B**), 7.67 br.s (1H, 11-H, **A**), 8.00 d (1H, NH, **A**, *J* = 7.0 Hz), 8.55 d (1H, NH, **B**, *J* = 7.0 Hz). Found, %: C 72.45; H 8.01; N 16.67. Mass spectrum: *m*/*z* 515 $[M + H]^+$. $C_{31}H_{42}N_6O$. Calculated, %: C 72.34; H 8.22; N16.33. *M* 514.71.

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