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SHORT COMMUNICATIONS

Selective Monobromination in the Series of Quinoid Pyrido[1,2-*a*]benzimidazole Derivatives

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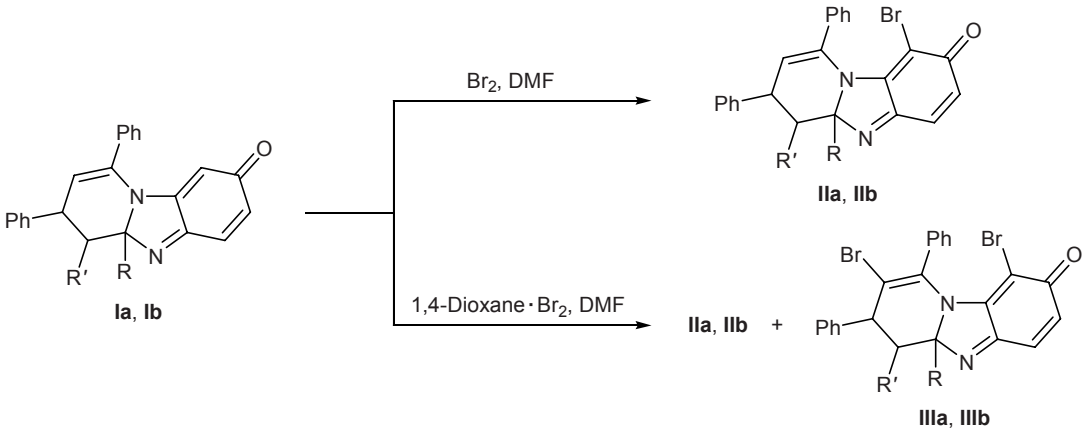
Bromo-substituted quinoid compounds are widespread in nature (examples are alkaloids discorhabdins, verongiaquinol, components of plant pigments, etc.), and they exhibit pronounced antibacterial activity [1]. Synthetic analogs of natural compounds could also be expected to display various kinds of biological activity. Furthermore, regioselective introduction of bromine atoms into quinoid ring should make further nucleophilic functionalization of the bromination products more unambiguous with a view to obtain compounds having pharmacophoric groups. On the other hand, heterocyclic compounds whose molecules contain quinoid fragments are convenient substrates for various transformations due to their fairly rare ability to undergo functionalization under mild conditions by the action of both nucleophilic and electrophilic reagents, as well as of radical species.

Halogenation of *para*-quinones and quinone imines has been studied in sufficient detail [2]. As a rule, such reactions follow the addition–elimination pattern, and in most cases the process is difficult to terminate at the stage of formation of monohalo derivative, so that polyhalogenated products are formed. Published data on the halogenation of heterocyclic quinone imines are rather scanty. Most examples refer to halogenation of phenothiazinones and phenazinones [3]. However, halogenation of such systems is sufficiently selective only in the presence of an oxidant; otherwise, mixtures of polyhalo derivatives are obtained. Moreover, there are no data on the bromination of such rare quinoid compounds as heterocyclic methylenequinone imines.

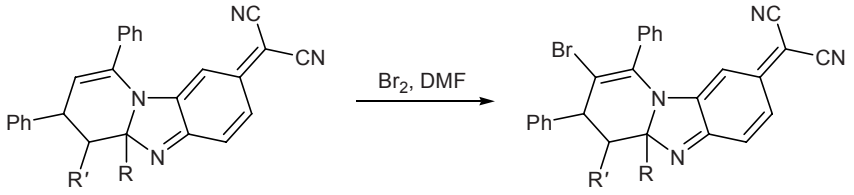
Bromination of quinone imines **I** of the pyrido[1,2-*a*]benzimidazole series with a solution of bromine in carbon tetrachloride was not selective, and it resulted in the formation of a mixture of 3,9-di- and 3,8,9-tribromo-substituted quinoid derivatives which were difficult to separate by chromatography; the reaction was carried out in the absence of an oxidant [4].

Scheme 1.



RR′ = $(CH_2)_4$ (**a**); R = Ph, R′ = H (**b**).

Scheme 2.



IVa, **IVb** **Va**, **Vb**

RR′ = $(CH_2)_4$ (**a**); R = Ph, R′ = H (**b**).

With a view to enhance the regioselectivity of bromination of heterocyclic quinones we were the first to use a milder brominating agent, namely 1,4-dioxane–bromine complex in chloroform. However, analogous results were obtained.

The bromination of **Ia** and **Ib** with a solution of bromine in dimethylformamide gave the corresponding 9-bromo derivatives **IIa** and **IIb** as the major products. The reactions took 2 h at room temperature, and the substrate-to-reagent ratio was 1:2. In the reactions of the same substrates with 1 or 2 equiv of dioxane dibromide mixtures of 9-mono- (**IIa**, **IIb**) and 2,9-dibromo derivatives (**IIIa**, **IIIb**) at a ratio of 1:2 were formed, and we failed to find conditions ensuring predominant formation of one or another product.

We also examined bromination of [4,4a-dihydropyrido[1,2-*a*]benzimidazol-8(3*H*)-ylidene]malononitriles **IVa** and **IVb** with a solution of bromine in DMF. We previously showed [4] that bromination of **IVa** and **IVb** with a solution of bromine in chloroform at a substrate-to-reagent ratio of 1:2 results in quantitative formation of the corresponding 2,9-dibromo derivatives. The bromination of the same substrates in DMF at room temperature (reaction time 2 h) gave exclusively [2-bromo-1,3-diphenyl-4,4a-dihydropyrido[1,2-*a*]benzimidazol-8(3*H*)-ylidene]malononitriles **Va** and **Vb**.

According to the IR data, the quinoid structure was conserved in the bromination products, and their ^{1}H NMR spectra were also consistent with the assumed structures. The ^{1}H NMR spectra of mixtures of compounds **II** and **III** contained doublets from 2-H and 7-H in **II** and doublets from 6-H and 7-H in **III**, the latter being twice as intense, while no 9-H signal was observed. The spectra of compounds **Va** and **Vb** lacked doublet signal assignable to olefinic proton on C^2, while signals from protons in the quinoid fragment remained almost unchanged. The chemical ionization mass spectra of all compounds **II**, **III**, and **V** contained peaks from the $[M + H]^+$ pseudomolecular ions with *m*/*z* values corresponding to the calculated ones.

Thus, the use of a solution of bromine in DMF ensures regioselective bromination of quinone imines of the pyrido[1,2-*a*]benzimidazole series with formation of 6-bromo-substitued derivatives. Analogous results were obtained in ethanol as solvent, but the conversion was not complete because of poor solubility of the initial quinone imines. It may be concluded that the regioselectivity in the examined reactions is determined mainly by solvent polarity rather than by the reagent nature. We believe that polar solvents induce polarization of bromine molecule so that the latter becomes capable of forming a complex at the N^{10} nitrogen atom ($Br^{\delta-}$–$Br^{\delta+}\cdots N^{10}$). Decomposition of the complex is accompanied by bromine addition at the nearest nucleophilic carbon atom (C^9 in the quinoid fragment). The C^9 atom in molecules **IVa** and **IVb** is shielded by the cyano groups; therefore, bromine atom adds at the other nearest carbon atom in position *2*.

To conclude, the proposed procedure makes it possible to introduce bromine atoms into different positions of quinoid pyrido[1,2-*a*]benzimidazole derivatives, depending on the solvent nature, which is promising from the viewpoint of subsequent selective functionalization of these compounds.

Initial compounds **Ia**, **Ib** [5], **IVa**, and **IVb** [6] were synthesized according to known methods.

Bromination of compounds I and IV with a solution of bromine in dimethylformamide (*general procedure***).** A solution of an equimolar amount of bromine in 5 ml of DMF was added dropwise over a period of 15 min to a solution of 0.24 mol of compound **Ia** or **IVa** or 0.33 mol of **Ib** or **IVb** in 5 ml of DMF under stirring at room temperature. The mixture was stirred for 1 h, an additional 1 equiv of bromine in DMF was added, and the mixture was stirred until the initial compound disappeared according to the TLC data. The mixture was then diluted with two volumes of water, and the red (compounds **II**) or violet (**V**) precipitate was filtered off, washed with water, and dried. The products were purified by preparative thin-

layer chromatography (**II**) or by heating in boiling acetone–hexane (1 : 10) over a period of 30 min to remove impurities (**V**).

9-Bromo-4,4a-tetramethylene-1,3-diphenyl-3,4,4a,8-tetrahydropyrido[1,2-*a*]benzimidazol-8-one (IIa). Yield 68%, mp 177–179°C. ^{1}H NMR spectrum, δ, ppm: 1.50–2.25 m (9H), 3.73 d.d (1H, 3-H, J = 9.1, 4.7 Hz), 6.03 d (1H, 2-H, J = 4.7 Hz), 6.84 d (1H, 7-H, J = 9.6 Hz), 7.15–7.30 m (11H, 6-H, C_6H_5). Found, %: C 69.35; H 5.05; N 5.63. Mass spectrum: m/z 471 $[M + H]^+$. $C_{27}H_{23}BrN_2O$. Calculated, %: C 68.79; H 4.92; N 5.94. M 471.39.

9-Bromo-1,3,4a-triphenyl-3,4,4a,8-tetrahydropyrido[1,2-*a*]benzimidazol-8-one (IIb). Yield 84%, mp 183–185°C. ^{1}H NMR spectrum, δ, ppm: 1.68 d.d (1H, 4-H_{ax}, J = 11.8, –13.2 Hz), 3.48 d.d (1H, 4-H_{eq}, J = 7.1, –13.2 Hz), 3.63 q.d (1H, 3-H, J = 11.8, 7.1, 3.3 Hz), 5.98 d (1H, 2-H, J 3.3 Hz), 6.82 d (1H, 7-H, J = 9.9 Hz), 7.15–7.65 m (16H, 6-H, C_6H_5). Found, %: C 70.58; H 4.39; N 5.53. Mass spectrum: m/z 491 $[M + H]^+$. $C_{29}H_{21}BrN_2O$. Calculated, %: C 70.59; H 4.29; N 5.68. M 493.39.

(2-Bromo-4,4a-tetramethylene-1,3-diphenyl-3,4,4a,8-tetrahydropyrido[1,2-*a*]benzimidazol-8-ylidene)malononitrile (Va). Yield 72%, mp 251–253°C. ^{1}H NMR spectrum, δ, ppm: 1.50–2.40 m (9H), 3.96 d (1H, 3-H, J = 9.9 Hz), 4.85 d (1H, 9-H, J = 1.7 Hz), 7.07 d (1H, 6-H, J = 9.6 Hz), 7.37 d.d (1H, 8-H, J = 9.6, 1.7 Hz), 7.20–7.60 m (10H, C_6H_5). Found, %: C 69.84; H 4.79; N 10.66. Mass spectrum: m/z 519 $[M + H]^+$. $C_{30}H_{23}BrN_4$. Calculated, %: C 69.37; H 4.46; N 10.79. M 519.43.

(2-Bromo-1,3,4a-triphenyl-3,4,4a,8-tetrahydropyrido[1,2-*a*]benzimidazol-8-ylidene)malononitrile (Vb). Yield 75%, mp 257–259°C. ^{1}H NMR spectrum, δ, ppm: 1.98 d.d (1H, 4-H_{ax}, J = 12.9; –12.4 Hz), 3.41 d.d (1H, 4-H_{eq}, J = 6.1, –12.4 Hz), 3.65 d.d (1H, 3-H, J = 12.9, 6.1 Hz), 4.92 s (1H, 9-H), 7.04 d (1H, 6-H, J = 9.9 Hz), 7.15–7.65 m (16H, 7-H, C_6H_5). Found, %: C 71.37; H 4.12; N 10.08. Mass spectrum: m/z 541 $[M + H]^+$. $C_{32}H_{21}BrN_4$. Calculated, %: C 70.99; H 3.91; N 10.35. M 541.44.

Bromination of compounds Ia and Ib with 1,4-dioxane–bromine complex in DMF. An equimolar amount of dioxane dibromide was added under stirring to a solution of 0.1 g of compound **Ia** (0.24 mmol) or **Ib** (0.33 mmol) in 5 ml of DMF. The mixture was stirred for 1 h, an additional equivalent of dioxane dibromide was added, and the mixture was stirred for 1 h until the initial compound disappeared (TLC). The mixture was then diluted with two volumes of water, and the red precipitate was filtered off, washed with water, and dried. We failed to separate compounds **II** and **III** by chromatography.

The ^{1}H NMR spectra were recorded on a Bruker AC-250 spectrometer at 250 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The elemental compositions were determined on a Flash EA 1112 CHN/MAS200 analyzer. HPLC analysis was performed on a an HP 1100 LC/MSD system (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 chemical ionization).

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