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Synthesis of Quaternary 3-(1,3-Dioxo-1*H*-isoindol-2-ylmethyl)-5,6-dihydroimidazo[2,1-*b*]thiazolium Salts

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Abstract—The reaction of dihydroimidazole-2-thiol with *N*-(3-chloro-2-oxopropyl)phthalimide gave 2-[3-(4,5-dihydroimidazol-2-ylsulfanyl)-2-oxopropyl]-1,3-dioxo-1*H*-isoindole which underwent intramolecular heterocyclization to dihydroimidazothiazole system by the action of a dehydrating agent. Treatment of 3-(1,3-dioxo-1*H*-isoindol-2-ylmethyl)-5,6-dihydroimidazo[2,1-*b*]thiazole with concentrated hydrochloric acid led to the formation of dihydroimidazo[2,1-*b*]thiazol-3-ylmethanamine. Water-soluble quaternary 3-(1,3-dioxo-1*H*-isoindol-2-ylmethyl)-5,6-dihydroimidazo[2,1-*b*]thiazolium salts were obtained by alkylation of 3-(1,3-dioxo-1*H*-isoindol-2-ylmethyl)-5,6-dihydroimidazo[2,1-*b*]thiazole with alkyl halides.

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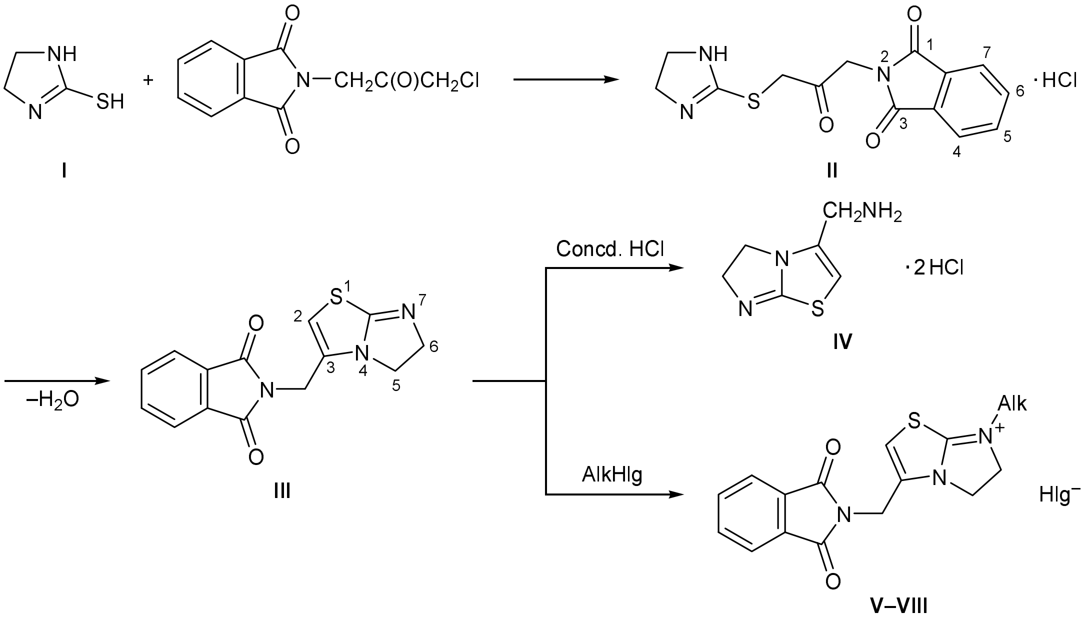
Many pharmaceutical agents are water-soluble organic ammonium salts. It is known that quaternary salts produce fewer side effects; in addition, water-soluble compounds are convenient for the preparation of injections. In continuation of our studies in the series of thiazoloazole derivatives [1, 2], the present communication reports on the synthesis of 3-phthalimidomethyl-substituted 5,6-dihydroimidazo[2,1-*b*]thiazoles **III** and **IV** and their quaternary salts **V–VIII**. The starting compound was 4,5-dihydroimidazole-2-thiol (**I**) which is known to readily undergo alkylation with various α-halo ketones [3, 4]. The reaction of 3-chloro-1-phthalimidoacetone with imidazolethiol **I** in boiling acetone or dioxane gave compound **II**. The latter underwent intramolecular heterocyclization with elimination of water molecule to produce dihydroimid-

Scheme 1.



V, **VI**, Hlg = I; **VII**, **VIII**, Hlg = Br; **V**, Alk = Me; **VI**, Alk = Pr; **VII**, Alk = $PhCOCH_2$; **VIII**, Alk = $MeCOCH_2$.

azo[2,1-*b*]thiazole **III** on heating in orthophosphoric acid (Scheme 1). Attempts to effect hydrolysis of the phthalimide fragment in **III** by heating in hydrazine hydrate or concentrated acetic acid were unsuccessful. In the first case, only tars were obtained, and in the second, the initial compound was recovered from the reaction mixture. Dihydrochloride **IV** was isolated only when compound **III** was heated for 5–6 h in boiling concentrated hydrochloric acid. Treatment of compound **III** with alkyl halides in boiling acetone or methyl ethyl ketone gave the corresponding quaternary ammonium salts **V**–**VIII**.

The structure of the newly synthesized compounds was confirmed by the IR and NMR spectra. The IR spectrum of **II** contained three carbonyl absorption bands in the region 1750–1680 cm^{-1} and a band at 3195–3150 cm^{-1} due to stretching vibrations of the N–H bond. Compound **II** showed in the ^{1}H NMR spectrum a signal at δ 4.0 ppm (d.d.d) from one diastereotopic proton in the methylene group on C^4. The remaining three protons of the dihydroimidazole ring gave a multiplet at δ 4.3–4.5 ppm. Protons of the SCH_2CO and $OCCH_2N$ groups appeared in the spectrum as singlets at δ 4.20 and 4.85 ppm, respectively. In addition, downfield multiplets from aromatic protons in the isoindole fragment were observed in the region δ 7.45–8.61 ppm.

The ^{1}H NMR spectrum of **III** contained two triplets at δ 3.85 and 4.18 ppm ($J = 9.3$ Hz), which correspond to methylene protons in the dihydroimidazole ring. The two-proton singlet at δ 4.5 ppm was assigned to the 3-CH$_2$ group, the 2-H proton at the double C=C bond gave a singlet at δ 5.75 ppm, and two two-proton multiplets from the isoindole benzene fragment were present in the region δ 7.72–7.90 ppm.

In the ^{1}H NMR spectrum of **IV** (in DMSO), two triplets at δ 4.29 and 4.53 ppm ($J = 10.2$ Hz) from the imidazole ring, a singlet from the aminomethyl protons (δ 4.03 ppm), and a one-proton singlet from the thiazole 2-H proton (δ 6.82 ppm) were observed. In going to D_2O, the ^{1}H NMR spectral pattern characteristically changes: methylene protons in the dihydroimidazole ring become diastereotopic, so that each methylene group shows a geminal coupling constant ^2J of 11.5 Hz, and the vicinal coupling constants become nonequivalent ($^3J = 3.1$, 8.4 Hz). The ^{13}C NMR spectrum of **IV** recorded with the ^{13}C–^{1}H coupling modulation is given in Experimental.

The IR spectra of salts **V**–**VIII** contained absorption bands in the region 2680–2450 cm^{-1} due to quaternary nitrogen atoms.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument at 300 and 75 MHz, respectively; the chemical shifts were measured relative to DSS (D_2O, DMSO) or TMS ($CDCl_3$). The IR spectra were obtained on a UR-20 spectrometer from samples dispersed in mineral oil. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates (1-butanol–acetic acid–water, 4 : 1 : 2; development with iodine vapor).

2-[3-(4,5-Dihydroimidazol-2-ylsulfanyl)-2-oxopropyl]-1,3-dioxo-1*H*-isoindole-1,3(2*H*)-dione hydrochloride (II). Compound **I**, 8.16 g (80 mmol), was dissolved on heating in 200 ml of dioxane or acetone, 19.2 g (80 mmol) of 3-chloro-1-phthalimidoacetone was added, and the mixture was heated for 2 h under reflux (on a water bath). The precipitate was filtered off. Yield 20.4 g (75%), colorless crystals, mp 262–265°C (from ethanol). IR spectrum, ν, cm^{-1}: 1750–1680 (C=O), 3195–3150 (NH). ^{1}H NMR spectrum (D_2O), δ, ppm: 4.0 d.d.d (1H, 4-H$_a$, $^2J = 11.2$, $^3J = 5.5$, 2.0 Hz), 4.3–4.55 m (3H, 4-H$_b$, 5-H), 4.2 s (2H, SCH_2CO), 4.85 s (2H, $OCCH_2N$), 7.90–8.00 m (4H, H$_{arom}$). Found, %: C 50.15; H 4.63; N 12.52. $C_{14}H_{13}N_3O_3S \cdot HCl$. Calculated, %: C 49.49; H 4.15; N 12.37.

3-(1,3-Dioxo-1*H*-isoindol-2-ylmethyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (III). A mixture of 28.9 g (85 mmol) of compound **II** and 50 ml of orthophosphoric acid was heated for 1 h at 120–130°C. The mixture was poured onto ice and neutralized with a solution of ammonia (according to universal indicator paper), and the precipitate was filtered off. Yield 21.0 g (87%), yellow crystals, mp 201–203°C (from aqueous ethanol). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.85 t (2H, 4-H, $J = 9.3$ Hz), 4.18 t (2H, 5-H, $J = 9.2$ Hz), 5.57 s (2H, 3-CH$_2$), 5.73 s (1H, 2-H), 7.72–7.90 m (4H, H$_{arom}$). Found, %: C 58.65; H 3.63; N 14.22. $C_{14}H_{11}N_{23}O_2S$. Calculated, %: C 58.93; H 3.89; N 14.73.

5,6-Dihydroimidazo[2,1-*b*]thiazol-3-ylmethanamine dihydrochloride (IV). A mixture of 2.0 g (5.8 mmol) of compound **III** and 25 ml of concentrated hydrochloric acid was heated for 5 h at the boiling point. The mixture was poured into ice water, the precipitate was filtered off, the filtrate was evaporated to dryness on a water bath, and the residue was treated with ethanol and cooled. After 12 h, the precipitate was filtered off. Yield 1.1 g (83%), pale pink crystals, mp 234–236°C (from ethanol). ^{1}H NMR spectrum

(DMSO-d_6), δ, ppm: 4.29 t (2H, 5-H, J = 10.2 Hz), 4.53 t (2H, 6-H, J = 10.2 Hz), 4.03 s (2H, CH_2NH_2), 6.82 s (1H, CH=C). ^{13}C NMR spectrum (D_2O–DMSO-d_6), δ, ppm: 47.57 s (C^5), 52.16 s (C^6), 112.71 s (C^2), 131.08 s (C^3), 172.21 s (C^8). Found, %: C 31.40; H 4.45; N 18.02. $C_6H_9N_3S \cdot 2HCl$. Calculated, %: C 31.59; H 4.86; N 18.42.

3-(1,3-Dioxo-1*H*-isoindol-2-ylmethyl)-7-methyl-5,6-dihydroimidazo[2,1-*b*]thiazol-7-ium iodide (V). A mixture of 0.9 g (3.5 mmol) of compound **III** and 0.7 g (5 mmol) of methyl iodide in 40–50 ml of acetone or methyl ethyl ketone was heated for 3 h under reflux. The precipitate was filtered off. Yield 1.45 g (97%), yellow crystals, mp 287–290°C. IR spectrum: ν($-N^+\equiv$) 2675–2450 cm^{-1}. Found, %: C 42.40; H 3.45; I 29.52; N 9.72. $C_{15}H_{14}IN_3O_2S$. Calculated, %: C 42.17; H 3.30; I 29.70; N 9.83.

Compounds **VI–VIII** were synthesized in a similar way.

3-(1,3-Dioxo-1*H*-isoindol-2-ylmethyl)-7-propyl-5,6-dihydroimidazo[2,1-*b*]thiazol-7-ium iodide (VI). Yield 13.5 g (95%), yellowish crystals, mp 278–280°C. IR spectrum: ν($-N^+\equiv$) 2680–2455 cm^{-1}. Found, %: C 44.40; H 3.45; I 27.52; N 9.72. $C_{17}H_{18}IN_3O_2S$. Calculated, %: C 44.84; H 3.98; I 27.87; N 9.22.

3-(1,3-Dioxo-1*H*-isoindol-2-ylmethyl)-7-(2-oxo-2-phenylethyl)-5,6-dihydroimidazo[2,1-*b*]thiazol-7-ium bromide (VII). Yield 1.2 g (71%), colorless crystals, mp 262–264°C. IR spectrum: ν($-N^+\equiv$) 2660–2450 cm^{-1}. Found, %: C 54.40; H 3.45; Br 16.52; N 8.72. $C_{22}H_{18}BrN_3O_3S$. Calculated, %: C 54.55; H 3.74; Br 16.50; N 8.67.

3-(1,3-Dioxo-1*H*-isoindol-2-ylmethyl)-7-(2-oxopropyl)-5,6-dihydroimidazo[2,1-*b*]thiazol-7-ium bromide (VIII). Yield 1.24 g (84%), light pink crystals, mp 254–258°C. IR spectrum: ν($-N^+\equiv$) 2675–2460 cm^{-1}. Found, %: C 48.40; H 3.65; Br 19.02; N 9.72. $C_{17}H_{16}BrN_3O_3S$. Calculated, %: C 48.35; H 3.82; Br 18.92; N 9.95.

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