SYNTHESIS OF N-(2-CHLOROETHYL)ISATINS AND THEIR β-ETHYLENEACETALS AND β-THIOSEMICARBAZONES

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The nitrogen atoms of isatin, its 5-bromo derivative, and their β -ethyleneacetals are alkylated by 1,2-dichloroethane in K₂CO₃-DMF and LiH(NaH)-DMF.

Several bis(β -chloroethyl)amines have been used to treat malignant tumors [1]. In the search for equally potent compounds, it seemed expedient to synthesize isatins, their β -ethyleneacetals, and β -thiosemicarbazones with the 2-chloroethyl group on the nitrogen atom. These compounds are practically unknown except for N-(chloroethyl)isatin, which is prepared by substitution of the hydroxy group by chlorine in the reaction of difficultly accessible N-(2-hydroxyethyl)isatin with thionyl chloride [2].

We developed a simple route for synthesis of these compounds *via* direct N-alkylation of isatin Ia, its 5-bromo derivative Ib, and their β -ethyleneacetals IIa,b with an excess of 1,2-dichloroethane (see Scheme 1). The condensations were performed using K₂CO₃ or LiH(NaH) in DMF [3, 4]. DMF can be replaced by DMSO or dioxane.



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Data from the biological tests of IIIa-c, IV, and Va,b will be reported separately. We are reporting only preliminary data for the clearly evident antiviral activity of N-(2-chloroethyl)isatin β -thiosemicarbazone (IVa) and its high toxicity, which is due to the lability of the chlorine atom. This lability causes IVa to behave *in vivo* as an alkylating agent, similar to the aforementioned bis(β -chloroethyl)amines. This hypothesis was checked by synthesis of N-(4-chlorobutyl)isatin (IIIa) and its β -thiosemicarbazone (IVb) by the described method. The latter exhibits sharply decreased toxicity and elevated antiviral activity.

EXPERIMENTAL

IR spectra were recorded in vaseline oil on a IR-71 instrument. Mass spectra were measured on a MX-1320 instrument from a direct probe with 100 mA ion-source current at 70 eV ionizing potential. The purity of the isolated compunds was monitored using TLC with benzene and benzene: acetone (4:1) eluent. Compounds Va,b were identified visually using iodine vapor. Bands of IIIa,c were identified visually. Freshly distilled DMF, 1,2-dichloroethane, and 1,4-dichlorobutane were used.

N-(2-Chloroethyl)isatin (IIIa). A solution of isatin (7.35 g, 50 mmol) in DMF (50 ml) was treated with stirring with finely ground K₂CO₃ (17.25 g, 125 mmol) and 1,2-dichloroethane (98.9 g, 1 mmol). The reaction mixture was stirred for 5 h at 80°C, cooled, and treated with water (500 ml) and conc. HCl (13 ml). The organic layer was separated. The aqueous layer was extracted with 1,2-dichloroethane (3 × 100 ml). The combined extracts were washed with water until neutral, dried with Na₂SO₄, and evaporated to dryness. The solid was recrystallized from ethanol. Yield 8.46 g (80%); mp 111-112°C, which agrees with the literature [2]. IR spectrum: 1728 (α -CO and β -CO); 1610 and 1340 cm⁻¹ (C=C benzene ring). UV spectrum, λ_{max} (ϵ): 213 (15,000), 244 (22,000), 251 (18,800), 301 (2,800), 420 nm (500). Mass spectrum (*m*/*z*): 209, 211 (M⁺), 181, 183 (M - CO), 153, 155 (M - 2CO), 180, 182 (M - CO, - H), 146 (M - C₂H₄Cl, M - CO, - Cl), 145 (146 - H), 132 (M - CO, -CH₂Cl), 105 (132 - HCN), 104 (132 - CO), 77 (104 - HCN).

N-(2-Chloroethyl)isatin β -Thiosemicarbazone (IVa). Boiling solutions of N-(2-chloroethyl)isatin (2.09 g, 10 mmol) in ethanol (20 ml) and thiosemicarbazide (1.09 g, 12 mmol) in ethanol (110 ml) were mixed. One drop of conc. HCl was added. The reaction mixture was cooled to room temperature and stirred for an additional 14 h. The precipitate (IVa) was separated, washed successively with ethanol (20 ml), boiling water (70 ml), and boiling ethanol (30 ml), and dried for 24 h over KOH. Yield 2.66 g (94%); mp 232°C, which agrees with the literature [2].

5-Bromo-N-(2-chloroethyl)isatin (IIIb). Powdered lithium hydride (0.79 g, 100 mmol) is added in portions with stirring to a solution of 5-bromoisatin (11.3 g, 50 mmol) in DMF (70 ml) cooled to -5°C. After 20 min 1,2-dichloroethane (49.5 g, 0.5 mmol) is added. The reaction mixture is held for 5 h at 50°C, poured after cooling to 0°C into water (700 ml) acidified with conc. H₂SO₄ (1 ml), and extracted with ether. The combined ether extract (800 ml) is washed with water and dried over Na₂SO₄. The solvent is removed. The solid is chromatographed on silica gel (λ 100/160 μ , 400 g) using benzene containing CHCl₃ (5 %). Yield 6.06 g (42%). Found, %: C 41.8; H 2.4; N 4.90; (Cl + Br) 40.7. C₁₀H₇BrClNO₂. Calculated, %: C 41.6; H 2.4; N 4.8; (Cl + Br) 40.0.

N-(4-Chlorobutyl)isatin (IIIc). Powdered lithium hydride (1.2 g, 0.15 mol) is added in portions with vigorous stirring to a cooled solution of isatin (14.7 g, 0.1 mol) in DMF (60 ml). After 20 min, 1,4-dichlorobutane (62.3 g, 0.5 mol) is added in one batch. The reaction mixture is held for 3 h at 55-60°C, cooled to 0°C, treated with ice water (600 ml) acidified with conc. H₂SO₄ (2 ml), and extracted with ether. The combined washed ether extract is dried over Na₂SO₄. The ether is removed. The solid is chromatographed on silica gel (λ 100/250 μ , 500 g) using a benzene–CHCl₃ (9:1) mixture as eluent. Yield 13.26 g (55%) of compound IIIc; mp 38-39°C. IR spectrum: 1735 (C₂=O), 1730 (C₃=O), 1610 cm⁻¹ (C=C benzene ring). Found, %: C 60.9; H 5.0; N 5.8; Cl 14.6. C₁₂H₁₂ClNO₂. Calculated, %: C 60.6; H 5.1; N 5.9; Cl 14.9.

N-(4-Chlorobutyl)isatin β -Thiosemicarbazone (IVb). Boiling solutions of N-(4-chlorobutyl)isatin (3.55 g, 15 mmol) in ethanol (50 ml) and thiosemicarbazide (1.36 g, 15 mmol) in water (25 ml) are mixed and treated with conc. HCl (one drop). The reaction mixture is stirred for 8 h at room temperature. The precipitate of compound IVb is filtered off, washed successively with ethanol (20 ml), boiling water (100 ml), and boiling ethanol (30 ml),

and dried under vacuum over KOH. Yield 90%; mp 187-188°C. IR spectrum: 3340, 3240, 3150 (N-H), 1700 (C₂=O), 1625 (C=N), 1600 cm⁻¹ (C=C benzene ring). Found, %: C 50.1; H 4.8; N 17.8. $C_{13}H_{15}CIN_4OS$. Calculated, %: C 50.2; H 4.9; N 18.0.

N-(2-Chloroethyl)isatin β -Ethyleneacetal (Va). Finely ground KOH and then 1,2-dichloroethane (49.5 g, 0.5 mol) are added to a solution of isatin β -ethyleneacetal (5.73 g, 3 mmol) in DMF (30 ml). The reaction mixture is stirred for 20 h at 80°C, cooled, and treated with water (250 ml) acidified with conc. HCl (4 ml). The organic layer is separated. The aqueous layer is extracted with 1,2-dichloroethane (3 × 70 ml). The organic layer and the combined extracts are washed with water until the washings are neutral and dried over Na₂SO₄. The solvent is removed. The solid (9.5 g) is dissolved in benzene and chromatographed on silica gel (λ 100/160 μ , 270 g). The isolated compound Va is crystallized from alcohol. Yield 4 g (61%); mp 71-73°C. Found, %: C 57.6; H 4.7; N 5.4; Cl 14.2. Cl₂H₁₂ClNO₃. Calculated, %: C 56.8; H 4.8; N 5.5; Cl 14.0.

5-Bromo-N-(2-chloroethyl)isatin β -Ethyleneacetal (Vb). Powdered lithium hydride (0.19 g, 24 mmol) is added in portions to a solution of 5-bromoisatin β -ethyleneacetal (5.4 g, 20 mmol) in DMF (25 ml) cooled to 0°C. The mixture is held for 4.5 h at 50°C, cooled, treated with ice water, and extracted with CHCb. The extract is dried over Na₂SO₄ and then evaporated to dryness. The resulting viscous oil is dissolved in benzene and chromatographed on silica gel (λ 100/250 μ , 180 g) using benzene as eluent. Yield 5.14 g (77.3%); mp 96-98°C. Found, %: C 43.5; H 3.0; N 4.3. C₁₂H₁₁BrClNO₃. Calculated, %: C 43.3, H 3.3, N 4.2.

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