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SYNTHESES OF 1-(2-BROMO-3-HYDROXYPROPYL)- AND 1-(2-BROMO-2-PROPENYL)ISATINS AND THEIR β-THIOSEMICARBAZONES

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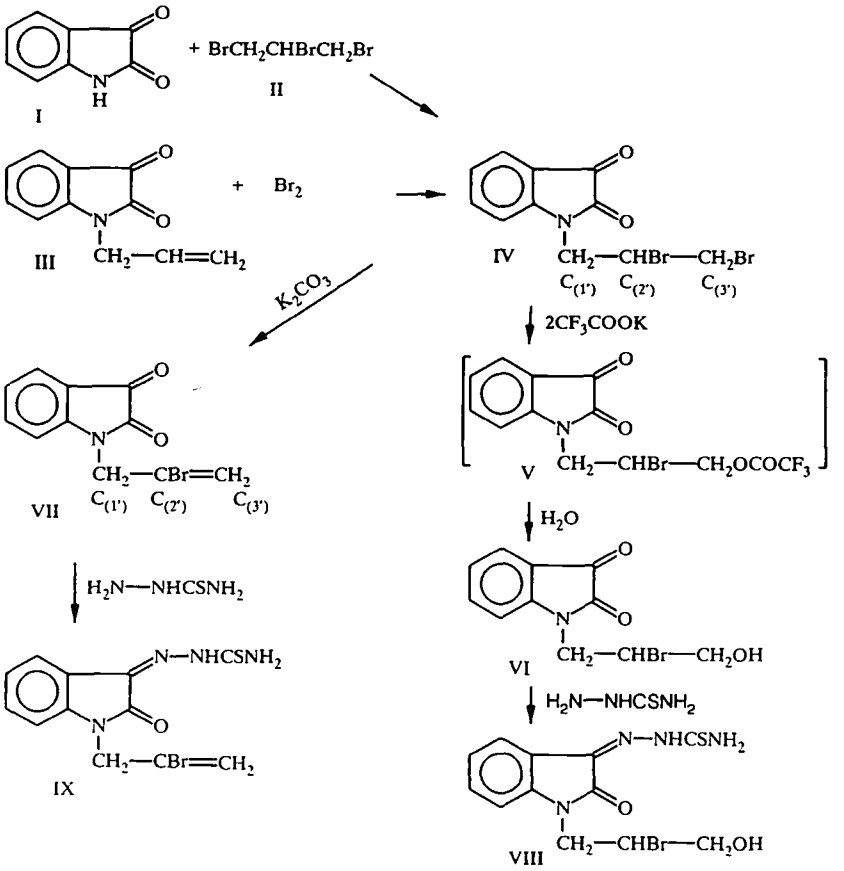
Only the bromine atom at the primary carbon atom participates in nucleophilic replacement by a trifluoroacetate ion and elimination of HBr in 1-(2,3-dibromopropyl)isatin.

The β-thiosemicarbazone of 1-(2-hydroxyethyl)isatin displays antiviral activity comparable to Metisazon [1]. We might have expected that the introduction of hydroxyl group into the substituent at the nitrogen atom would lead to enhancement of this activity and better solubility in polar solvents. In order to obtain the β-thiosemicarbazone of 1-(2,3-dihydroxypropyl)isatin, we used the product of the N-alkylation of isatin I with excess 1,2,3-tribromopropane (II) at 20°C or product of the addition of bromine at the double bond in N-allylisatin (III), namely, 1-(2,3-dibromopropyl)isatin (IV). We expected that both bromine atoms would be replaced by trifluoroacetate groups upon condensation of IV with anhydrous potassium trifluoroacetate in absolute DMSO and that the trifluoroacetate groups would be readily saponified in water or, better, in 5% aqueous $NaHCO_3$.



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However, we isolate a compound with the chemical formula $C_{11}H_{10}BrNO_3$. In determining the structure of this product by ^{13}C NMR spectroscopy, we consider two alternative structures corresponding to the multiplicity of the observed signals: 1-(2-bromo-3-hydroxypropyl)isatin VI or its isomer, 1-(2-hydroxy-3-bromopropyl)isatin. Calculation of the chemical shifts for the methylene group carbon nuclei for these structures using the bromine increments taken from Pretsch et al. [2] and isatin increments ($C\alpha$ = 26.5, $C\beta$ = 5, and $C\gamma$ = −4.3 ppm) obtained by comparison of the ^{13}C NMR chemical shifts of propane with N-propylisatin [3], gives values of 68.0 and 38.0 ppm, respectively. The experimental value for the single methylene group (67.2 ppm) corresponds to structure VI.

The N-alkylation of isatin I by 1,2,3-tribromopropane at 50-90°C instead of IV gives its dehydrobromination product. PMR and ^{13}C NMR spectral data indicate that this product is 1-(2-bromo-2-propenyl)isatin (VII). This result was unexpected since a secondary bromine atom is usually eliminated more readily than a primary bromine atom.

Our experiments with isatin IV showed that only the bromine atom at the primary carbon atom participates in nucleophilic replacement by a trifluoroacetate ion and elimination of HBr. The secondary bromine atom is apparently shielded by the 1-isatinylmethyl residue and, thus, remains inert to the action of potassium trifluoroacetate and K_2CO_3.

Thiosemicarbazones VIII and IX were obtained from VI and VII. A study of these compounds will be published later. We only note that isatin β-thiosemicarbazones with such functional groups in the alkyl substituent at the nitrogen atom as found in VIII and IX have not yet been reported.

EXPERIMENTAL

A sample of DMSO was dried by distillation twice in vacuum over CaH_2. A sample of potassium trifluoroacetate was dried in vacuum over P_2O_5 to constant weight. 1,2,3-Tribromopropane II was prepared from equimolar amounts of freshly distilled allyl bromide and bromine in benzene at +5°C. After standing overnight, the solution was washed with 5% aq. $Na_2S_2O_3$ and water and dried over anhydrous Na_2SO_4. Benzene was evaporated in vacuum and the product was used without further purification. The purity of the products was checked by thin-layer chromatography on Silufol plates using benzene and 4:1 benzene−acetone as the eluents. The plates were developed with iodine vapor and aq. $KMnO_4$. The melting points were determined on a Boetius block and were not corrected.

The ^1H and ^{13}C NMR spectra were taken on a Bruker AC-80 spectrometer at 80 MHz for the ^1H NMR spectra and 20 MHz for the ^{13}C NMR spectra using 5 and 30% solutions in DMSO-d_6, respectively.

The ^{13}C NMR spectra were taken with complete and partial suppression of coupling. The chemical shifts are given on the δ scale relative to TMS. The DMSO-d_6 signal was used as the internal standard (2.50 ppm for ^1H and 39.5 ppm for ^{13}C).

1-(2,3-Dibromopropyl)isatin (IV). A. A sample of 84.3 g (0.3 mole) 1,2,3-dibromopropane II and 20.7 g (0.15 mole) K_2CO_3 were added to a solution of 14.7 g (0.1 mole) isatin I in 100 ml DMF and stirred for 6 h at 20°C. The reaction mixture was poured into 1000 ml water. Excess 1,2,3-tribromopropane was removed by extraction with four 100-ml portions of hexane. The aqueous layer was acidified to pH 1 and extracted with four 100-ml portions of benzene. The combined benzene extract was evaporated and subjected to chromatography on a column packed with 300 g silica gel L 160/100 μ using 4:1 benzene−acetone as the eluent. The yield of chromatographically pure isatin IV was 67%, mp 132-137°C. Found, %: C, 38.44; H, 2.49; Br, 45.47. Calculated for $C_{11}H_9Br_2NO_2$, %: C, 38.07; H, 2.62; Br, 46.05; N, 4.04. PMR spectrum in DMSO-d_6: 4.12 (2H, d, ^3J = 5.34 Hz, CH_2-N), 4.25 (2H, d, ^3J = 6.9 Hz, CH_2-Br), 4.52-4.86 (1H, m, CH_2Br), 7.13-7.87 ppm (4H, m, H_{arom}). ^{13}C NMR in DMSO-d_6: $C_{(2)}$ 158.23 (s), $C_{(3)}$ 182.47 (s), $C_{(4)}$ 138.06 (d), $C_{(5)}$ 123.39 (d), $C_{(6)}$ 124.45 (d), $C_{(7)}$ 110.92 (d), $C_{(7a)}$ 117.47 (s), $C_{(3a)}$ 150.09 (s), $C_{(1')}$ 44.96, $C_{(2')}$ 49.33 (d), $C_{(3')}$ 36.17 (t).

B. A sample of 16 g (0.1 mole) bromine was added dropwise to a suspension of 18.7 g (0.1 mole) N-allylisatin III [4] in 100 ml dry CCl_4. After standing overnight, the solution was washed with 5% aq. $Na_2S_2O_3$ and water and dried over anhydrous Na_2SO_4. Benzene was evaporated and the residue was crystallized from 2-propanol. The yield of IV was 82%.

1-(2-Bromo-3-hydroxypropyl)isatin (VI). A sample of 12.1 g (80 mmoles) potassium trifluoroacetate was added to a solution of 13.88 g (40 mmoles) 1-(2,3-dibromopropyl)isatin IV in 50 ml absolute DMSO and the reaction mixture was heated for 4 h at 120-130°C. After cooling, the solution was poured into 500 ml 5% aq. $NaHCO_3$. After 2 h, the mixture was extracted with ten 100-ml chloroform portions. The combined extract was washed with two 50-ml water portions and dried over anhydrous Na_2SO_4. Chloroform was evaporated to give 11.3 g of a bright red viscous syrup consisting mainly of the reaction product and isatin IV.

Chromatography was carried out on a column packed with 300 g silica gel L 160/100 μ using pure benzene as the eluent to give starting isatin IV and using 4:1 benzene–acetone to give VI, R_f 0.43 (5:1 benzene–acetone), 0.75 (5:1 chloroform–acetone), 0.60 (1:1 ethyl acetate–hexane). Found,%: C, 46.32; H, 3.40; Br, 28.50; N, 4.81. Calculated for $C_{11}H_{10}BrNO_3$,%: C, 46.50; H, 3.55; Br, 28.12; N, 4.93.

1-(2-Bromo-2-propenyl)isatin (VII). A sample of 14.7 g (0.1 mole) isatin I was dissolved in 100 ml freshly distilled DMF and 84.3 g (0.3 mole) 1,2,3-tribromopropane (II) and 27.6 g (0.2 mole) finely ground K_2CO_3 were added. The reaction mixture was heated at 60-70°C for 4 h. After cooling, the mixture was poured into 1000 ml water and excess 1,2,3-tribromopropane was removed by extraction with hexane. The aqueous layer was acidified to pH 1 by adding concentrated hydrochloric acid. The precipitate of VII was separated, dried in the air and then over P_2O_5, and crystallized from anhydrous benzene. The yield of VII was 70%, mp 113-115°C. Found,%: C, 49.43; H, 2.91; Br, 29.46; N, 5.18. Calculated for $C_{11}H_8BrNO_2$,%: C, 49.65; H, 3.03; Br, 30.03; N, 5.26. PMR spectrum (DMSO-d_6): 0.21 (1H, d.t, ^2J = 2.66, ^4J = 1.5 Hz, $=CH_2$), 4.61 (2H, d.d, ^4J = 1.51, ^4J = 1.16 Hz, CH_2-N), 5.70 (1H, d.t, ^2J = 2.66, ^4J = 1.16 Hz, $=CH_2$), 7.13-7.86 ppm (4H, m, H_{arom}). ^{13}C NMR spectrum in DMSO-d_6: $C_{(2)}$ 157.63 (s), $C_{(3)}$ 182.38 (s), $C_{(4)}$ 138.10 (d), $C_{(5)}$ 123.52 (d), $C_{(6)}$ 124.46 (d), $C_{(7)}$ 111.04 (d), $C_{(8)}$ 117.39 (s), $C_{(9)}$ 149.72 (s), $C_{(1')}$ 46.97 (t), $C_{(2')}$ 125.48 (s), $C_{(3')}$ 120.14 (t).

β-Thiosemicarbazone of 1-(2-Bromo-2-propenyl)isatin (IX). A mixture of 5.32 g (20 mmoles) isatin VII and 2 g (24.7 mmoles) thiosemicarbazide in 150 ml 2-propanol was heated for 4 h at 50-60°C and left overnight. The precipitate was removed and crystallized from 2-propanol to give 5.56 g (82%) IX, mp 220-225°C. Found,%: C, 42.53,%: H, 3.30; N, 16.42. Calculated for $C_{12}H_{11}BrN_4OS$,%: C, 42.49; H, 3.27; N, 16.52.

β-Thiosemicarbazone of 1-(2-Bromo-3-hydroxypropyl)isatin (VII) was obtained in 78% yield from VI using the procedure for the synthesis of IX. The mp of VII was 188-189°C (after crystallization twice from 2-propanol). Found: C, 40.44; H, 4.16; N, 15.21. Calculated for $C_{12}H_{13}BrN_4O_2$,%: C, 40.34; H, 3.67; N, 15.68.

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