

## FORMATION OF ACETALS AND CLEAVAGE OF THE FIVE-MEMBERED RING IN THE BROMINATION OF ISATIN IN ALCOHOLS

Jiří GASPARIČ<sup>a</sup>, Tomáš VONTOR<sup>a</sup>, Antonín LYČKA<sup>b</sup> and Dobroslav ŠNOBL<sup>b</sup>

<sup>a</sup> Faculty of Pharmacy, Charles University, 501 65 Hradec Králové

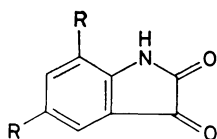
<sup>b</sup> Research Institute of Organic Syntheses, 532 18 Pardubice-Rybitví

Received January 24, 1990

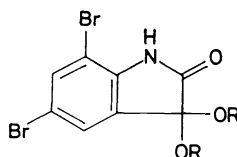
Accepted May 17, 1990

Bromination of isatin (*I*) in alcohols affords in good yield 5,7-dibromo-3,3-dialkoxy-2-indolinones (*IIIa* and *IIIb*) which arise by reaction catalysed with hydrogen bromide liberated in the bromination. The reaction affords also minor amounts of 2,4,6-tribromoaniline (*IV*) formed by splitting off of two carbon atoms from the isatin five-membered ring.

As described in the literature, isatin (*I*) can be brominated with bromine either in ethanol<sup>1</sup> or in acetic acid<sup>2</sup>. When brominating isatin in acetic acid, we obtained the corresponding brominated derivative *II* in good yield. When, however, the



*I*, R = H  
*II*, R = Br



*IIIa*, R = CH<sub>3</sub>  
*IIIb*, R = C<sub>2</sub>H<sub>5</sub>

bromination was performed in methanol, thin-layer chromatography revealed gradual formation of yellow spots of mono- and dibromoderivatives of isatin. In order to achieve a complete bromination, we heated the mixture with another portion of bromine. After some time the intense orange colour of isatins disappeared. After the usual work-up we isolated in 75% yield a substance of composition C<sub>10</sub>H<sub>9</sub>Br<sub>2</sub>NO<sub>3</sub>, which was shown by <sup>1</sup>H and <sup>13</sup>C NMR spectra to be 5,7-dibromo-3,3-dimethoxy-2-indolinone (*IIIa*). This compound represents an analogy to the 5,7-diiodo derivative isolated by Bass<sup>3</sup> in small amount (3%) in the iodination of 5-iodoisatin in methanol.

Our bromination of isatin afforded minor quantities of another compound, identified by <sup>1</sup>H and <sup>13</sup>C NMR spectra and comparison with an authentic sample as 2,4,6-tribromoaniline (*IV*).

These facts show that in the bromination of isatin in methanol the liberated hydrogen bromide catalyzes the formation of the dimethyl acetal on the C(3) carbon atom. The higher reactivity of the carbonyl group in position 3 agrees with the literature data<sup>4-6</sup>. The structure of the arising acetal *IIIa* was confirmed by hydrolysis to 5,7-dibromoisatin (*II*). The formation of 2,4,6-tribromoaniline (*IV*) can be explained by removal of two carbon atoms from the five-membered isatin ring during the reaction. When performing the bromination in ethanol, we obtained the analogous diethyl acetal *IIIb*.

### EXPERIMENTAL

The melting points were determined on a Koffler block and are uncorrected. Samples were dried at about 100 Pa over phosphorus pentoxide. Thin-layer chromatography was performed on Silufol<sup>®</sup> UV 254 sheets in acetone-hexane (3 : 7); colourless compounds were detected at 254 nm. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured at 25°C on a Jeol JNM FX 100 instrument (99.602 MHz for <sup>1</sup>H, 25.047 MHz for <sup>13</sup>C) in hexadeuteriodimethyl sulfoxide. The <sup>1</sup>H and <sup>13</sup>C chemical shifts were referenced to the solvent signal ( $\delta(^1\text{H}) - 2.55$ ;  $\delta(^{13}\text{C}) - 39.6$ ) and are given in ppm ( $\delta$ -scale). <sup>13</sup>C NMR spectral data for compounds *I-IV* are given in Table I.

#### Bromination of Isatin (*I*) in Acetic Acid

Bromine (7.5 g; 47 mmol) was added at 70°C to a solution of isatin (*I*, 3.0 g; 20 mmol) in acetic acid (70 ml). The reaction mixture was then heated to 70–80°C for 1 h, poured into water and the product collected on filter and purified by crystallization from ethanol. Yield 5.1 g (82%) of 5,7-dibromoisatin (*II*), m.p. 248–249°C (reported<sup>1</sup> m.p. 247–248°C). <sup>1</sup>H NMR spectrum: 7.79 d, 1 H (H-4,  $J(4, 6) = 2.0$ ); 8.04 d, 1 H (H-6,  $J(4, 6) = 2.0$ ); 11.51 bs, 1 H (H-1).

TABLE I  
<sup>13</sup>C chemical shifts in spectra of compounds *I-IV* in hexadeuteriodimethyl sulfoxide

Carbon	Compound			
	<i>I</i> <sup>a</sup>	<i>II</i>	<i>IIIa</i> <sup>b</sup>	<i>IV</i> <sup>c</sup>
2	159.3	159.1	171.2	108.0
3	184.4	182.4	96.9	133.6
3a	117.7	120.9	128.2	—
4	124.6	125.9	127.0	106.5
5	122.7	114.6	114.3	133.6
6	138.4	141.2	135.4	108.0
7	112.2	105.8	104.7	—
7a	150.7	148.6	140.6	—

<sup>a</sup> Values taken from ref.<sup>7</sup>; <sup>b</sup> other signal 50.5 (2 × OCH<sub>3</sub>); <sup>c</sup> other signal 142.6 (C-NH<sub>2</sub>).

Bromination of Isatin (*I*) in Methanol

Isatin (*I*, 3 g; 20 mmol) was dissolved in boiling methanol (40 ml) and bromine (7.5 g; 47 mmol) was added to the hot solution. After 1 h another portion of bromine (5.0 g; 31 mmol) was added and the mixture refluxed for further 2 h. During this time, the mixture decolorized and was poured into water. The product was collected on filter and separated by chromatography on a column of silica gel in hexane-ethyl acetate 3 : 1, affording 5.3 g (75%) of 5,7-dibromo-3,3-dimethoxy-2-indolinone (*IIIa*), m.p. 200–201°C. <sup>1</sup>H NMR spectrum: 3.45 s, 6 H (2 × OCH<sub>3</sub>); 7.65 d, 1 H (H-4, *J*(4, 6) = 2.0); 7.84 d, 1 H (H-6, *J*(4, 6) = 2.0); 11.10 bs, 1 H (H-1). For C<sub>10</sub>H<sub>9</sub>Br<sub>2</sub>NO<sub>3</sub> (351.0) calculated: 34.22% C, 2.58% H, 3.99% N; found: 34.31% C, 2.61% H, 4.02% N.

The reaction mixture further afforded 0.36 g (5.5%) of 2,4,6-tribromoaniline, m.p. 121–122°C (reported<sup>8</sup> m.p. 122°C). <sup>1</sup>H NMR spectrum: 5.58 bs, 2 H (NH<sub>2</sub>); 7.68 s, 2 H (2 × H-arom.).

5,7-Dibromo-3,3-dimethoxy-2-indolinone (*IIIa*)

*A*) Gaseous hydrogen bromide was introduced for 20 min into a refluxing solution of 5,7-dibromoisatin (*II*, 1.0 g; 3.2 mmol) in methanol (50 ml). Work-up of the reaction mixture gave 0.91 g (79%) of acetal *IIIa*, m.p. 200–201°C.

*B*) The reaction was performed as described under *A*) except that instead of the gaseous hydrogen bromide it was catalyzed with concentrated sulfuric acid (2 ml). Yield 0.94 g (83%) of acetal *IIIa*, m.p. 200–201°C.

*C*) Bromine (5.0 g; 31 mmol) was gradually added to a boiling solution of 5,7-dibromoisatin (*II*, 1.0 g; 3.2 mmol) in methanol (50 ml). Work-up of the reaction mixture, followed by chromatography afforded 0.84 g (73%) of acetal *IIIa*, m.p. 200–201°C and 41 mg (4%) of 2,4,6-tribromoaniline (*IV*), m.p. 121–122°C.

Hydrolysis of 5,7-Dibromo-3,3-dimethoxy-2-indolinone (*IIIa*)

A mixture of acetal *IIIa* (0.50 g; 1.4 mmol), 10% aqueous methanol (50 ml) and concentrated sulfuric acid (1 ml) was refluxed for 1 h. Work-up of the reaction mixture gave 5,7-dibromoisatin (*II*), m.p. 247–248°C.

Bromination of Isatin (*I*) in Ethanol

The bromination in ethanol was performed in the same manner as described for the reaction in methanol (*vide supra*). The same processing of the reaction mixture furnished 5.3 g (68%) of 5,7-dibromo-3,3-diethoxy-2-indolinone (*IIIb*), m.p. 173–174°C. For C<sub>12</sub>H<sub>13</sub>Br<sub>2</sub>NO<sub>3</sub> (379.1) calculated: 38.02% C, 3.46% H, 3.69% N; found: 38.12% C, 3.51% H, 3.62% N.

2,4,6-Tribromoaniline (*IV*), m.p. 121–122°C, was obtained as the second product (0.49 g; 7.5%).

## REFERENCES

1. Lindwall H. G., Bandes J., Weinberg I.: J. Am. Chem. Soc. 53, 317 (1931).
2. Bayer A., Oekonomides S.: Ber. Dtsch. Chem. Ges. 15, 2098 (1882).
3. Bass R. J.: Tetrahedron Lett. 1971, 1087.
4. Bredford G. R., Partridge M. W.: J. Chem. Soc. 1959, 1633.

5. Palazzo G., Rosnati V.: *Gazz. Chim. Ital.* **83**, 211 (1953).
6. Campaigne E., Archer L. W.: *J. Am. Chem. Soc.* **74**, 5801 (1952).
7. Winkler T., Fenini P. G., Haas G.: *Org. Magn. Reson.* **12**, 101 (1979).
8. Fuchs W.: *Monatsh. Chem.* **36**, 113 (1915).

Translated by M. Tichý.