

## The Reaction of Isatin with Cycloalkylamines

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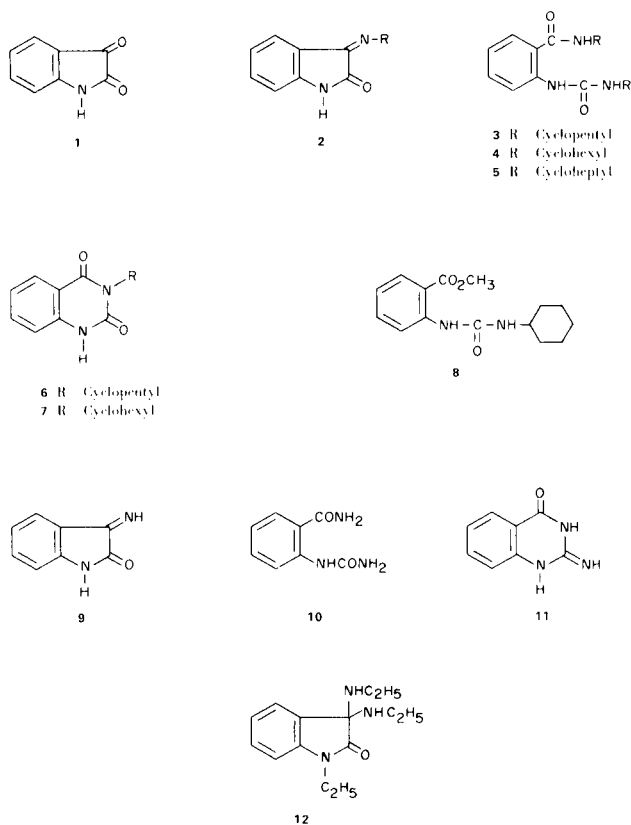
The reaction of isatin (**1**) with a 1:1 molar ratio of cyclopentylamine leads to the imine (**2**, R = cyclopentyl) (**1**). This reaction of isatin and primary amines to give imines has been observed by many workers (**2**). We now find that use of a ten fold excess of cyclopentylamine with isatin in 95% ethanol leads to a compound of the formula  $C_{18}H_{25}N_3O_2$  to which we have assigned structure (**3**). Reaction of isatin with an excess of cyclohexyl- and cycloheptylamine proceeds in a similar oxidative aminolysis to give **4** and **5** respectively.

The reaction proceeds in the dark but when run under a nitrogen atmosphere no crystalline product (**3**) is obtained until the reaction mixture is exposed to the air. If the ethanol and excess of amine are removed *in vacuo* before exposure to air, the imine (**2**) but no **3** is present in the gum obtained. Compound **3** is also obtained when **2** (R = phenyl, ethyl, cyclopentyl, or cyclohexyl) is treated with an excess of cyclopentylamine in ethanol. Reaction of **2** (R = cyclopentyl) with an excess of cyclohexylamine similarly gives **4**.

The structures **3**, **4**, and **5** are supported by both spectrophotometric and chemical evidence. The nmr and ir data which are shown in the Experimental Section are consistent with the structures. The mass spectral data for **3** are also shown in the Experimental Section and can be rationalized by one or more simple cleavages of amide type linkages or cleavage with H migration. Reaction of **3** and **4** with hydrochloric acid leads to the quinazoline-diones **6** and **7** respectively.

In an attempt to confirm the structure **4** by synthesis, **8** was treated with cyclohexylamine. Rather than **4** this reaction gave **7** and dicyclohexylurea. Compound **4** was synthesized, however, by treating cyclohexyl anthranilamide with cyclohexylisocyanate. In addition to **4**, a very small amount of product,  $C_{27}H_{40}N_4O_3$ , from the reaction of two moles of the isocyanate with one mole of the amide was obtained.

The reaction leading to **3**, **4**, and **5** does not appear to be general. With an excess of *sec*-butylamine, isopropylamine, and aniline the only products were imines (**2**). With an excess of *n*-propylamine and *n*-butylamine, neat or in ethanol, a purple gum is obtained. This same



type of gum is isolated from the reaction of isatin with an excess of ethylamine in ethanol. One might cite the formation of aldehydes from isatin and amines (**5**) as being responsible for this gum from which no crystalline products could be isolated.

Although a ring opening of isatin with amines has not been previously reported, there appears to be some precedent in the literature for this oxidative ring opening. Jacini (**3**) states that the reaction of the imine of isatin (**9**) with hydrogen peroxide under basic conditions gives **10** which is somewhat analogous to our reaction. In some later work there is an observation (**4**) that isatin in aqueous ammonia standing in sunlight for three months gives **11**. This reaction is also analogous since **11** must be formed by cleavage of the 2,3-bond of isatin.

The reaction of isatin and an excess of ethylamine neat has been reported (6) to give rise to a compound,  $C_{14}H_{21}N_3O$ , which was assigned (6) the unlikely structure **12**. We are currently investigating the structure of this isatin-excess ethylamine product.

#### EXPERIMENTAL

Analyses by Spang Microanalytical Laboratory, Ann Arbor, Michigan. All melting points are corrected.

##### Formation of Imines (**2**).

Isatin (1.47 g., 0.01 mole) and the appropriate amine (0.01 mole) in 40-100 ml. of 95% ethanol were heated in an open flask on a steam bath for 30 minutes and allowed to stand overnight. The products were collected by filtration (in some cases a small amount of water was added to induce precipitation) and recrystallized from ethanol or ethanol-water. The following imines have not been previously reported: (**2**, R = cyclopropyl), m.p. 202-203°; ir (potassium bromide): 1725, 1610  $cm^{-1}$ , was formed in 56% yield.

*Anal.* Calcd. for  $C_{11}H_{10}N_2O$ : C, 70.95; H, 5.41. Found: C, 70.81; H, 5.44.

(**2**, R = *n*-butyl), m.p. 107-108°; ir (potassium bromide): 1740, 1620  $cm^{-1}$ , was formed in 60% yield.

*Anal.* Calcd. for  $C_{12}H_{14}N_2O$ : C, 71.26; H, 6.98. Found: C, 71.01; H, 7.03.

(**2**, R = *sec*-butyl), m.p. 122-123°; ir (potassium bromide): 1740, 1620  $cm^{-1}$  was prepared in 50% yield.

*Anal.* Calcd. for  $C_{12}H_{14}N_2O$ : N, 13.95. Found: N, 14.01.

##### Reaction of Isatin with an Excess of Primary Amine.

Isatin and a ten-fold excess of the primary amine in 95% ethanol (50-100 ml. per 0.01 mole of isatin) were heated in an open flask on a steam bath for 30 minutes and allowed to stand overnight. *n*-Propyl, ethyl, and *n*-butylamine gave only a purple gum. *sec*-Butylamine and aniline gave only the imines (**2**).

Cyclopentylamine gave a 50% yield of **3**, m.p. 202-203° from ethanol; ir (potassium bromide): 2090, 1700, 1650  $cm^{-1}$ ; nmr (deuteriochloroform): 10.1 (1), 8.6 (2), 7.4 (4), 4.2 (2), 1.6  $\delta$  (16); mass spectra *m/e* (rel. int.): 315 (5%), 231 (19%), 230 (5%), 205 (19%), 204 (72%), 163 (40%), 162 (20%), 147 (6%), 146 (70%), 145 (8%), 137 (6%), 136 (60%), 121 (9%), 120 (100%), 119 (36%), 93 (9%), 92 (21%), 90 (13%), 84 (60%), 69 (12%), 67 (10%), 65 (15%).

*Anal.* Calcd. for  $C_{18}H_{25}N_3O_2$ : C, 68.54; H, 7.99; N, 13.32. Found: C, 68.61; H, 7.84; N, 13.28.

When the reaction was carried out under nitrogen and the product stored under nitrogen for two weeks no solid was obtained. Exposure of the reaction mixture to the air for a few days resulted in the crystallization of **3** in 46% yield. When the reaction was again carried out under nitrogen and the solvent and excess amine removed *in vacuo* before exposure to air, a crude material whose ir spectra and tlc indicated the presence of **2** (R = cyclopentyl) and absence of **3** was obtained. When the reaction was carried out in the dark the product **3** was obtained. When the reaction was carried out in the absence of ethanol a gum was obtained which crystallized to give **3** when treated with ethanol.

Cyclohexylamine gave **4**, m.p. 227-229° from ethanol; ir (potassium bromide): 1710, 1620  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{20}H_{29}N_3O_2$ : C, 69.94; H, 8.51; N, 12.23. Found: C, 70.03; H, 8.29; N, 11.99.

Cycloheptylamine gave **5**, m.p. 216-217° from ethanol.

*Anal.* Calcd. for  $C_{22}H_{33}N_3O_2$ : C, 71.12; H, 8.95; N, 11.31. Found: C, 70.98; H, 8.83; N, 11.32.

##### Reaction of Imines (**2**) with an Excess of Primary Amine.

Reaction of imines (**2**, R = phenyl, ethyl, cyclohexyl, and cyclopentyl) with a ten-fold excess of cyclopentylamine as described for the reaction of isatin with an excess of amine in ethanol gave **3** in yields of about 40%. In a similar manner **2** (R = cyclopentyl) and an excess of cyclohexylamine gave **4** in 40% yield.

##### Acid Hydrolysis of **3**.

A mixture of 0.35 g. of **3** and 20 ml. of 25% hydrochloric acid was heated on a steam bath for 1 hour. The reaction mixture was cooled and filtered to give 0.12 g. (48%) of **6**, m.p. 234-235° from ethyl acetate, reported (7) m.p. 234°; ir (potassium bromide): 2960, 1720, 1660  $cm^{-1}$ ; nmr (DMSO- $d_6$ ): 11.2 (1), 7.5 (4), 5.3 (1), 1.8  $\delta$  (8).

*Anal.* Calcd. for  $C_{13}H_{14}N_2O_2$ : C, 67.80; H, 6.12; N, 12.18. Found: C, 67.86; H, 6.09; N, 12.19.

##### Acid Hydrolysis of **4**.

In a similar manner, **4** and 25% hydrochloric acid gave **7** in a 50% yield, m.p. 269-270°, reported (7), m.p. 273-274°.

##### Reaction of **8** with Cyclohexylamine.

A mixture of 2.76 g. of **8** (8) and 25 ml. of cyclohexylamine was heated at 130° for 2 days and then stirred at room temperature for 2 days. Filtration gave 1.67 g. (75%) of cyclohexylurea, m.p. 227-229°, reported (9) m.p. 229-230°. Chloroform was added to the filtrate and the chloroform solution was washed with 5% hydrochloric acid, dried and concentrated to give 0.65 g. (27%) of **7**, m.p. 268-270°.

##### Independent Synthesis of **4**.

To 2.18 g. of cyclohexyl anthranilamide (**10**) in 5 ml. of high boiling ligroin was added 3.0 g. of cyclohexylisocyanate and a few drops of triethylamine. The reaction mixture was heated on a steam bath for 2 hours, cooled, and filtered to give 1.55 g. (45%) of **4**. A small amount of compound,  $C_{27}H_{40}N_4O_3$ , m.p. 195-196° was also obtained. This latter compound was obtained in 60% yield when 1.25 g. of cyclohexyl anthranilamide, 0.75 g. of cyclohexylisocyanate, and 1 ml. of triethylamine in 30 ml. of high boiling ligroin were refluxed for 21 hours; ir (potassium bromide): 3450, 1750, 1640  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{27}H_{40}N_4O_3$ : C, 69.20; H, 8.60; N, 11.96. Found: C, 69.25; H, 8.56; N, 11.94.

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