

The Reaction of Isatin with Aromatic-*o*-diamines

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Although isatin (I) generally reacts with amines at the 3-position, *o*-phenylenediamine reacts with both carbonyl groups of isatin to form 6*H*-indolo[2,3-*b*]quinoxaline (II) (1). This reaction has been reported as being fairly general for a variety of isatins and *o*-phenylenediamines (1). The condensation is generally carried out in acetic acid or in ethanol (1b). In repeating this work we found that when the condensation of isatin and *o*-phenylenediamine was carried out in acetic acid, pure II was obtained. When ethanol was used as the solvent, however, the infrared spectrum of the crude product indicated the presence, in addition to II, of a small quantity of a carbonyl compound which was not isatin. Pure II could be easily isolated from

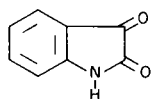
this reaction mixture by recrystallization or chromatography but the carbonyl compound could not be obtained in a pure form. A possible structure for this carbonyl compound was suggested by the work of Henseke and Lemke (2) who isolated III from the reaction of 2,3-diaminonaphthalene and isatin but obtained IV from the reaction of 1,2-diaminonaphthalene and isatin. With these results in mind, we decided to investigate the reaction of isatins with selected aromatic-*o*-diamines.

Using ethanol as solvent, spiro compounds of the type V were obtained when isatin was reacted with 4,5-diamino-1,3-dimethyluracil, 4,5-diaminopyrimidine, and as previously reported (2) 1,2-diaminonaphthalene. With 9,10-diaminophenanthrene a mixture of linear and spiro compounds was obtained, while 2,3-diaminonaphthalene gave as the only isolated product the previously reported (2) linear compound III, although a small carbonyl peak was noted in the infrared spectrum of the crude material.

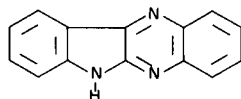
With *N*-methylisatin in ethanol, *o*-phenylenediamine gave mainly the spiro compound contaminated by a small amount of the linear *N*-methyl analogue of II which was the exclusive product when the reaction was carried out in acetic acid. 2,3-Diaminonaphthalene and *N*-methylisatin in ethanol gave the spiro compound. Recrystallization of this latter spiro compound from glacial acetic acid, however, caused rearrangement to the linear *N*-methyl analogue of III.

With *N*-acetylisatin in ethanol, *o*-phenylenediamine gave the spiro compound and 2,3-diaminonaphthalene gave the spiro compound together with a trace of material believed to be the *N*-acetyl analogue of III. In contrast to isatin, *N*-acetylisatin and 4,5-diamino-1,3-dimethyluracil in ethanol gave a linear product of the type VI although no attempt was made to prove which of the possible isomeric linear products was obtained. In contrast to other results in acetic acid, *N*-acetylisatin and 9,10-diaminophenanthrene gave the spiro type product V.

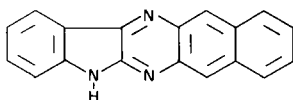
In view of the ease with which treatment of the spiro compound arising from *N*-methylisatin and 2,3-diaminonaphthalene with acetic acid gave rise to the linear compound it was felt that this might be a general reaction in



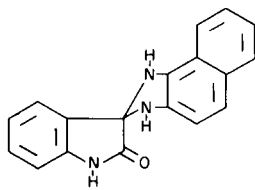
I



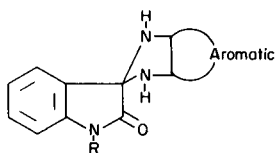
II



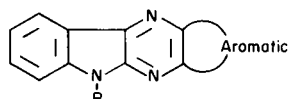
III



IV

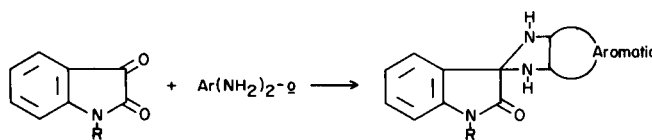


V



VI

TABLE I
Reactions Leading to Spiro Products (a)



R	Amine Used	Yield	M.p. (b)	Analyses						IR Potassium Bromide cm ⁻¹
				Calcd.			Found			
				C	H	N	C	H	N	
H	4,5-Diamino-1,3-dimethyluracil	82	356-357 (c)	56.18	4.38	23.40	56.18	4.46	23.33	1725 1695
H	4,5-diaminopyrimidine	80	342-344	60.24	3.79		60.14	3.88		1715
H	1,2-Diaminonaphthalene	75	359-362 (d)	75.24	4.56	14.63	75.61	4.27	14.82	1725
H	9,10-Diaminophenanthrene	77	347-350 (e)	78.32	4.48	12.46	78.35	4.47	12.42	1720
CH ₃	<i>o</i> -Phenylenediamine	70	167-170 (f)	71.69	5.21	16.72	71.45	5.07	16.78	1705
CH ₃	2,3-Diaminonaphthalene	80	186-188 (g)	75.73	5.02	13.94	75.45	5.13	13.75	1725
COCH ₃	<i>o</i> -Phenylenediamine	89	292-293 (h)	68.80	4.69	15.05	68.88	4.80	15.13	1690 1660
COCH ₃	2,3-Diaminonaphthalene	63	335-336 (i)	72.93	4.59	12.76	72.61	4.55	12.54	1680 1655
COCH ₃	9,10-Diaminophenanthrene	95	333-336 (j)	75.97	4.52	11.08	75.58	4.48	10.79	1710

(a) All condensations were carried out in ethanol with the exception of *N*-acetylisatin and 9,10-diaminophenanthrene which was carried out in acetic acid. (b) Recrystallizations from 95% ethanol unless otherwise noted. (c) Reaction product washed with hot dioxane and ethanol to give analytical sample. Mass spectra: 299 (7%), 297 (15%), 281 (100%), 271 (16%), 224 (15%), 197 (16%), 196 (89%), 181 (24%), 169 (20%), 168 (22%), 119 (19%), 102 (20%), 98 (18%), 68 (20%), 57 (17%). (d) Recrystallized from dioxane. (e) A small sample of linear product was obtained, see Table II. (f) IR of crude product indicated a trace of linear product. (g) Reaction product washed with hot CCl₄ to give analytical sample, recrystallization from acetic acid gave linear compound shown in Table II. (h) Refluxing in acetic acid for 2 hours gave the same product. Mass spectra: 279 (77%), 264 (19%), 237 (52%), 236 (52%), 220 (58%), 219 (74%), 210 (16%), 209 (100%), 208 (22%), 182 (13%), 181 (12%), 146 (15%), 91 (14%), 90 (22%), 65 (27%), 43 (39%). (i) Recrystallized from acetic acid; a trace of linear product (Table II) was obtained on an attempt to recrystallize from ethanol. (j) Recrystallized from dioxane.

the spiro series. When the spiro compound from *N*-acetylisatin and *o*-phenylenediamine was refluxed with glacial acetic acid for two hours, however, the spiro compound was recovered unchanged.

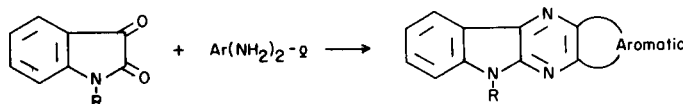
The mass spectrum of two of the spiro compounds V (R = H, and aromatic derived from 4,5-diamino-1,3-dimethyluracil; and R = COCH₃ and aromatic derived from *o*-phenylenediamine) were obtained and conversion to the linear product VI appears to be a major path with each compound (after loss of acetyl in the second case)

with M-18 being the strongest peak in the first compound and M-42 followed by a loss of 18 being strong peaks in the second compound. A path involving loss of CO and HCN after the acetyl, also plays a major role in the second compound

It would appear that the reaction of aromatic-*o*-diamines and isatins frequently gives spiro products in addition to or instead of linear ones. While formation of the spiro products are more prevalent in ethanol than in acetic acid such a path can on occasion also take place in acetic acid. We are currently investigating the extension of this work to the reaction of aliphatic diamines with isatins.

TABLE II

Reactions Leading to Linear Products (a)



R	Amine Used	M.p.	Analysis					
			Calcd.			Found		
			C	H	N	C	H	N
H	<i>o</i> -Phenylenediamine	293-295 (b)						
H	2,3-Diaminonaphthalene	365-366 (c)	80.28	4.12	15.60	80.00	4.48	15.50
COCH ₃	4,5-Diamino-1,3-dimethyluracil	332-335 (d)	59.44	4.05	21.66	59.37	4.07	21.39
H	9,10-Diaminophenanthrene	369-370 (e)			13.16			13.01
CH ₃	2,3-Diaminonaphthalene	233-234 (f)	80.54	5.62	14.83	80.20	4.55	14.73
COCH ₃	2,3-Diaminonaphthalene	245-247 (g)	77.15	4.21	13.50	76.25	4.10	13.19

(a) All reactions were carried out in ethanol. (b) Reported (G.M. Badger and P. J. Nelson, *J. Chem. Soc.*, 3926 (1962).) m.p. 295-296°. The IR of the crude product indicated the presence of a carbonyl containing component which could not be obtained in pure form. (c) Obtained in 80% yield and recrystallized from acetic acid. Reported (2) m.p. was 370°. The crude product had a weak carbonyl peak but this component could not be isolated. (d) Reaction was carried out in acetic acid to give 64% yield of material recrystallized from acetic acid. (e) Isolated as a minor component on recrystallization from dioxane. Reported (N.P. BuuHoi and P. Jacquignon, *Compt. Rend.*, 226, 2155 (1948).) m.p. > 360°. See also Table I. (f) Obtained in high yield when spiro product in Table I was recrystallized from acetic acid. (g) Very minor product soluble in hot ethanol and separated from compound in Table I by this method.

EXPERIMENTAL (3)

REFERENCES

Condensation of Isatins and Aromatic-*o*-diamines.

A mixture of 0.01 mole of the isatin and 0.01 mole of the aromatic-*o*-diamine in 20-30 ml. of ethanol were heated on the steam bath for 30 minutes and allowed to stand at room temperature until a solid precipitated (in some cases this solid appeared during heating). In some cases additional materials were obtained upon evaporation of the mother liquors. The products are included in Tables I and II.

Acknowledgment.

This work was supported by a research grant (CA 10345) from the National Cancer Institute, N.I.H.

(1a) See for example, W. C. Sumpter and F. M. Miller, "Heterocyclic compounds with Indole and Carbazole Systems," p. 125, Interscience, New York, 1954. (b) N. P. BuuHoi and G. Saint-Ruf, *Bull. Soc. Chim. France*, 1920 (1960) present a number of typical examples.

(2) G. Henseke and W. Lemke, *Chem. Ber.*, 91, 101 (1958).

(3) All melting points are corrected and taken in capillaries. Analyses are by Gnaps. Mass spectra by Morgan-Schaffer Corp.

Received October 23, 1968

Potsdam, N. Y. 13676