Diazocine Chemistry. V. Synthesis and Rearrangement of Dibenzo(*b,f*)(1,4)diazocine-6,11(5H,12H)-dione

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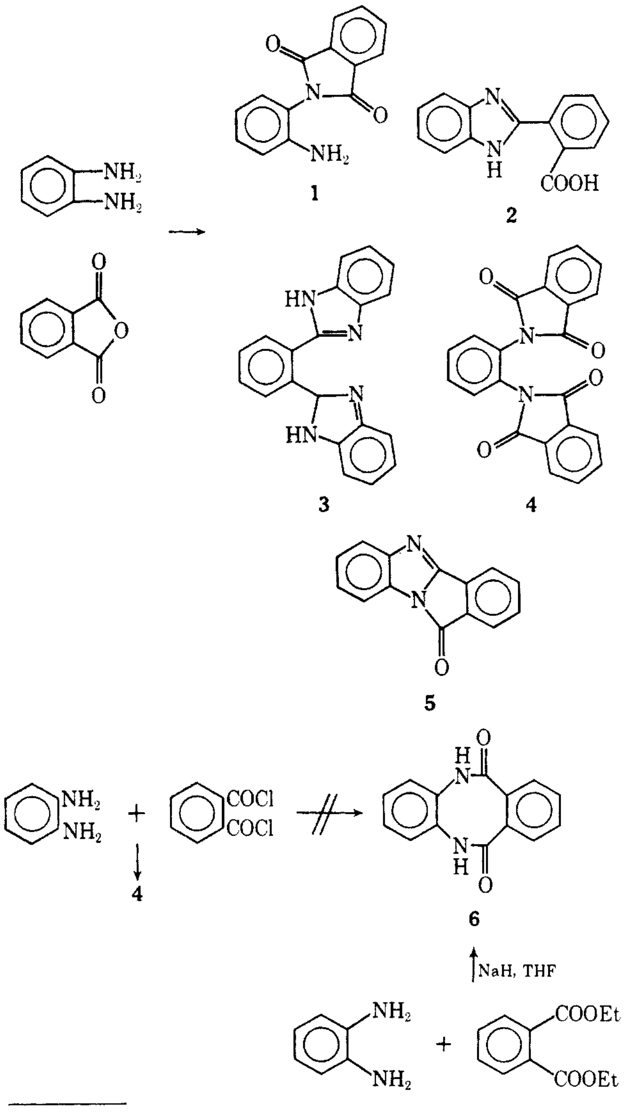
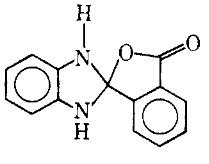
It has been shown that the condensation of *o*-phenylenediamine with diethyl phthalate, in the presence of sodium hydride, yields the dibenzo-1,4-diazocine derivative **6**. Contrary to reports in the literature, this compound has never been prepared. Diazocine **6**, when heated at its melting point, forms the dehydrated and ring-contracted compound **5**. Base hydrolysis of **6** yields the benzimidazole derivative **2**. A similar ring-contracted compound **13** (isolated as ester**14**) is obtained when **6** is treated with phosphorus pentachloride. The N,N′-dimethyl derivative of **6** (compound **10**), when treated with base, yields the zwitterionic ring-contracted compound **15**, which, upon heating, is converted into the methyl *o*-2-(3-methylbenzimidazoyl)benzoate (**16**). Monobenzo-1,4-diazocine (**18**) was prepared from diethy succinate and *o*-phenylenediamine and was thermally rearranged to the ring-contracted compound **19**.

The condensation of *o*-phenylenediamine with various derivatives of phthalic acid has been the subject of numerous publications.[1] The use of phthalic anhydride and *o*-phenylenediamine affords, depending upon the reaction conditions, compounds **1**–**5** (Scheme I). Stetter and coworkers[2] have reported that the condensation of *o*-phenylenediamine with phthaloyl chloride, under high-dilution conditions, affords the dibenzodiazocine derivative **6**. Compounds **1**, **2**, and **6** are clearly isomeric, while substances **3** and **4** are formed from the condensation of 2 mol of the diamine with 1 mol of phthalic anhydride and *vice versa*, respectively. Imidazopyrrole **5** can be envisioned to be formed from the dehydration of compounds **1** and/or **2**.

Scheme I



There remains the possibility of the existence of yet a fourth compound that is isomeric with the one to one condensation products **1**, **2**, and **6**. This substance would be lactone **7**.



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Stetter's compound (presumably **6**) was described as melting at 300° and as being readily soluble in benzene and ethanol. The appropriate elemental analysis and molecular weight of this compound were also reported.

In view of our interest in diazocine chemistry, this substance became of some interest to us as a potential precursor for other 1,4-diazocine derivatives. Repetition of the reported condensation procedure afforded a compound which melts at 298° and has the reported solubility characteristics. The mass spectrum of this compound is, however, *not in agreement* with the assigned structure, since the mass spectrometric molecular weight (m/e) is 368 and not the expected 238 mass units. This molecular weight is in agreement with that expected if the compound is in fact the phthalimide derivative **4**. In fact, the melting point and solubility properties of "Stetter's compound" are also in agreement with the phthalimide structure **4**.[1d] This rather disappointing result made it necessary to consider the development of a new synthetic approach to the preparation of the desired diazocine **6**.

In a preliminary communication[3] we have described the synthesis of dibenzo(*b,f*)(1,5)diazocine (**9**) from

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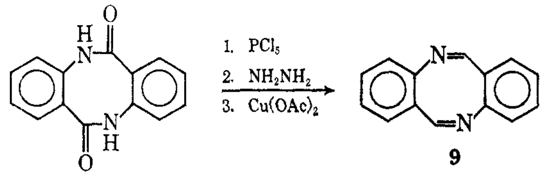
(1) (a) J. Arient and J. Marhan, *Collect. Czech. Chem. Commun.*, **26**, 98 (1961); (b) L. Guglialmelli, P. Chanussot, and C. L. Ruiz, *Bull. Soc. Chim. Fr.*, **51**, 80 (1932); (c) R. Meyer and H. Luders, *Ann.*, **415**, 29 (1918); (d) B. A. Porai-Koshits and M. M. Antoshul'skaya, *J. Gen. Chem. USSR*, **13**, 339 (1943), *Chem. Abstr.*, **38**, 1234 (1944).

(2) H. Stetter, L. Marx-Moll, and H. Rutzen, *Chem. Ber.*, **91**, 1775 (1958).

(3) W. W. Paudler and A. G. Zeiler, *Chem. Commun.*, 1077 (1967).



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diamide **8**. The latter compound was prepared by condensing ethyl anthranilate with itself in the presence of sodium hydride. The application of this condensation to the preparation of the 1,4-diazocine **6** represents a logical extension. In fact, when *o*-phenylenediamine was condensed with diethyl phthalate, there was obtained a 71% yield of a compound which analyzed correctly for diamide **6**. The mass spectrometric molecular weight of this compound, 238, is also in agreement with the diamide structure. The alternate lactone structure **7** can be eliminated from consideration since the condensation product is insoluble in acid and its infrared spectrum is void of a lactone carbonyl absorption peak. The carbonyl absorption in the infrared region (1695 cm^{-1}) of compound **6** is the same as that observed for the 1,5-diazocine derivative **8**. These data confirm the assigned structure (**6**) for the condensation product of *o*-phenylenediamine and diethyl phthalate in the presence of sodium hydride.

The conversion of diamide **6** into dichloro derivative **11** was attempted in a fashion similar to that described for the preparation of 6,12-dichlorodibenzo(*b*,*f*)(1,5)-diazocine.[4] However, the product resulting from the action of phosphorus pentachloride on diamide **6** had a mass spectrometric molecular weight of 256 and showed the typical "doublet" due to the presence of one chlorine atom.

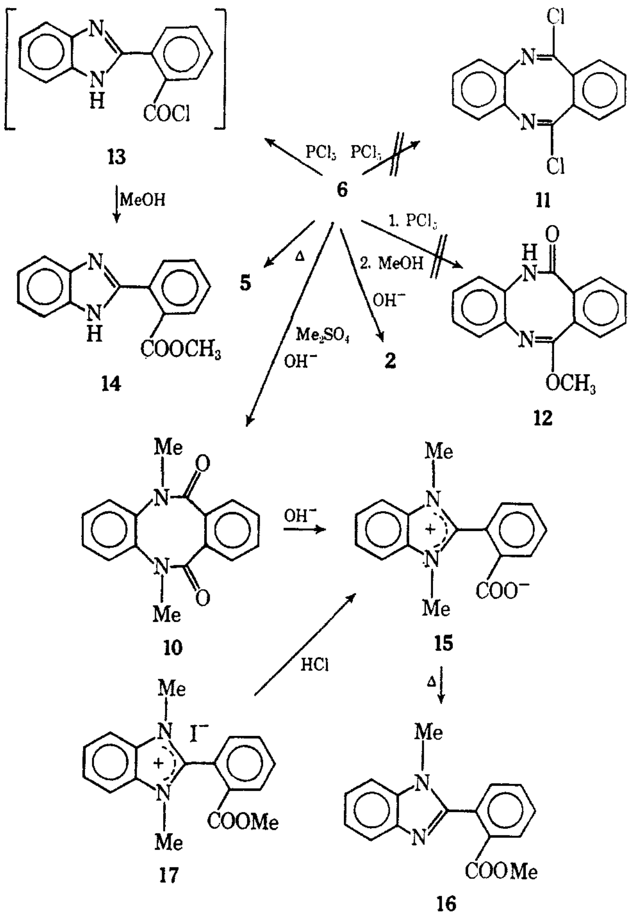
Treatment of this unstable compound with methanol gave a monomethyl derivative whose pmr spectrum is considerably different from that expected for a structure such as **12**. The aromatic protons, which appear as two peaks in the parent compound and in its dimethyl derivative (**10**) (*cf.* Experimental Section), appeared as a rather complex multiplet with a one-proton deshielded multiplet as a distinct feature suggesting rearrangement of the ring skeleton during the halogenation reaction.

Consideration of the possible rearrangement paths open to diazocine **6** and the established ring contractions observed in diazepine derivatives[5] indicate that the chloro compound and the methyl derivative might be compounds **13** and **14**, respectively. Ester **14** is a known compound and can be prepared[6] from the imidazopyrrole derivative **5**. The identity of the methyl ester was readily established by a comparison of the melting point and infrared and pmr spectra.

Since an analysis of the mass spectrum of diazocine **6** revealed the curious fact that it loses 18 mass units with great facility, we decided to study its thermal stability. When compound **6** was heated at 300°, the yellow crystalline material which sublimed was shown to be identical with an authentic sample of compound **5**.[1a] Thus, a facile thermal ring contraction takes place in analogy with the ring contraction that occurs upon treatment of compound **6** with phosphorus pentachloride.

The base hydrolysis of diazocine **6** also reveals its tendency toward ring contraction, since the only product that is obtained is the known *o*-2-benzimidazoylbenzoic acid **2** (*cf.* Scheme II).[1a]

SCHEME II



The N,N′-dimethyl derivative **10**, when treated with sodium hydroxide, yields a compound that is isomeric with the starting material (**10**). The pmr spectrum of this substance reveals two identical methyl groups and the complex aromatic proton system typical of the various ring-contracted products described earlier. The infrared spectrum of the new compound shows absorption peaks typical for the carboxylate anion. Thus structure **15** is suggested as the most likely one for this hydrolysis product and is confirmed by an unequivocal synthesis of this zwitterionic compound from the known[7] ester **17**.

Finally, compound **15** can be thermally rearranged to methyl ester **16** whose structure proof rests upon a comparison of its pmr and infrared spectra with that of compound **14** (*cf.* Experimental Section).

An extension of the condensation reaction which, ultimately, could have some bearing upon a better understanding of the stability of these ring systems, involves the condensation of diethyl succinate with *o*-phenylenediamine under the conditions which afford dibenzo compound **6** in such excellent yield. When this reaction was investigated, there was obtained a compound which analyzed correctly for the expected

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(4) G. Schroeter, *Chem. Ber.*, **52**, 2224 (1919).

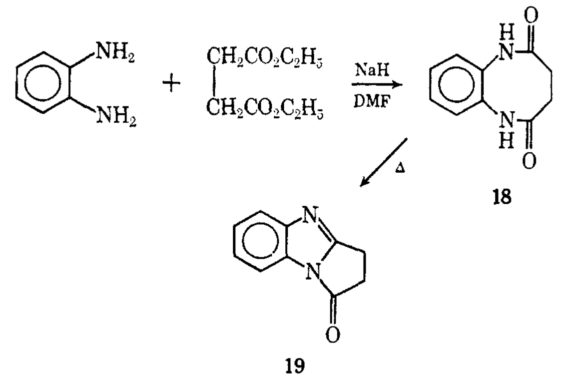
(5) M. Israel, L. C. Jones, and E. J. Modest, *Tetrahedron Lett.*, 4811 (1968).

(6) J. Arient, L. Havlickova, and J. Slosar, *Collect. Czech. Chem. Commun.*, **29**, 3115 (1964).

(7) H. Rupe and K. G. Thiess, *Ber.*, **42**, 4287 (1909).

benzodiazocine **18**. The pmr spectrum of this substance shows the presence of a four-proton singlet (based upon the molecular formula) at δ 2.92 typical of slightly deshielded methylene protons. In addition to this singlet there appears a typical A_2B_2 aromatic proton multiplet centered at δ 7.54. These data clearly confirm the assigned structure **18** (*cf.* Scheme III).

SCHEME III



That this compound, in analogy with the dibenzo derivative **6**, is also subject to facile ring contraction was shown by the observation that it is readily transformed into the known imidazopyrrole **19**[1c] when it is heated at its melting point.

Experimental Section[8]

Dibenzo(*b,f*)(1,4)diazocine-6,11(5H,12H)-dione (**6**).—To a stirred solution of 32.4 g (0.3 mol) of *o*-phenylenediamine and 66.6 g (0.3 mol) of diethyl phthalate in 600 ml of dry tetrahydrofuran in a 2-l. flask was added 29 g (0.6 mol) of a 50% oil dispersion of sodium hydride. The reaction mixture was stirred at room temperature until a vigorous reaction began. The mixture was then cooled in ice and stirred for 12 hr, followed by stirring at room temperature. The resulting dark solution was diluted with 500 ml of water and acidified with aqueous HCl. The white solid that precipitated was filtered and washed with ethanol and benzene to afford 50.8 g (71%) of compound **6**. An analytical sample was obtained by recrystallization from dimethylformamide: mp 301–302.5°; ir (KBr) 3180 cm^{-1} (N–H), 1695 (C=O); pmr (CF_3COOH) δ 7.59 (s), 7.35 (s); mol wt, 238 (mass spectrum).

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.22; N, 11.76. Found: C, 70.71; H, 4.39; N, 11.72.

5,12-Dimethyldibenzo(*b,f*)(1,4)diazocine-6,11-dione 10.—To a cooled, stirred suspension of 10 g (0.042 mol) of diamide **6** in 100 ml of 20% NaOH was added 10 ml of dimethyl sulfate. The reaction mixture was stirred for 2 hr at room temperature and the resulting precipitate was filtered and recrystallized from ethanol to afford 6.8 g (60%) of compound **10**: mp 262–265°; ir (KBr) 1695 cm^{-1} (C=O); pmr ($CDCl_3$) δ 7.25 (d, 8), 3.45 (s, 6); mol wt, 266 (mass spectrum).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.23; N, 10.52. Found: C, 72.08; H, 5.44; N, 10.55.

Reaction of Compound 6 with Phosphorous Pentachloride.—A suspension of 3 g (0.012 mol) of **6** and 6 g (0.029 mol) of PCl_5 in 100 ml of $CHCl_3$ was refluxed for 0.5 hr. Removal of the solvent gave a pale yellow residue. A small portion of this material was washed with tetrahydrofuran to afford a white solid (**13**) which rapidly turns yellow on standing: mp 211–212° dec; mass spectrum *m/e* (per cent of P) 256 (100), 258 (25).

The remaining solid was warmed with 100 ml of methanol and the resulting solution was diluted with 100 ml of water and 10 ml of aqueous ammonia. The white solid that precipitated was collected and afforded 2.7 g (86%) of methyl *o*-2-benzimidazoyl benzoate (**14**): mp 193°; ir (KBr) 1718 cm^{-1} (C=O); pmr ($CDCl_3$) δ 8.28 (m, 1), 7.45 (m, 7), 3.83 (s, 3). This material was identical with an authentic sample prepared by the method of Arient, Havlickova and Slosar.[6]

Thermal Dehydration of Compound 6.—A 1-g sample of diamide **6** was heated at 300° (0.1 mm), affording 0.75 g (85%) of isoindolo(2,1-*a*)benzimidazol-11-one (**5**) as a yellow sublimate. This material (mp 213–214°) was identical in every respect (mp 213–214°, ir, pmr) with a sample prepared by the method of Arient and Marhan.[1a]

Base Hydrolysis of Compound 6.—A solution of 3 g (0.012 mol) of **6** in 30 ml of 10% NaOH was refluxed for 48 hr. After cooling, the solution was neutralized with acetic acid and the resulting precipitate of *o*-2-benzimidazoylbenzoic acid was collected (2.2 g, 73%). This material (**2**) (mp 271–272°) was identical (mp 271–272°, ir, pmr) with a sample prepared by the method of Arient and Marhan.[1a]

Base Hydrolysis of the Dimethyl Compound 10.—A suspension of 3 g (0.011 mol) of compound **10** in a solution of 1 g of NaOH in 20 ml of water and 10 ml of dioxane was refluxed for 12 hr. The mixture was cooled, acidified with acetic acid, and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave a heavy oil which, when boiled with tetrahydrofuran, yielded 1.85 g (61%) of *o*-2-(1,3-dimethylbenzimidazolium) benzoate (**15**). An analytical sample was obtained by recrystallization from a mixture of dioxane and water (20:1, v/v): mp 294–295°; ir (KBr) 1618 and 1580 cm^{-1} (COO^-); pmr (D_2O) δ 7.35 (m, 1), 7.00 (m, 7), 2.95 (s, 6); mol wt, 266 (mass spectrum).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.23; N, 10.52. Found: C, 72.08; H, 5.44; N, 10.44.

***o*-2-(1,3-Dimethylbenzimidazolium) Benzoate** (**15**).—Methyl *o*-2-(1-methylbenzimidazoyl)benzoate methiodide (**17**) was prepared by the method of Rupe and Thiess.[7] This material (1.5 g, 3.7 mmol) was dissolved in 50 ml of 4 *N* HCl and refluxed for 12 hr. The solution was basicified with NaOH, neutralized with acetic acid, and exhaustively extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated to yield 0.73 g (75%) of **15** as white crystals. This compound was identical in every respect (melting point, ir, pmr, mass spectra) with that obtained from the hydrolysis of compound **10**.

Thermal Rearrangement of Compound 15.—A 1-g sample of **15** was heated at 320° (0.1 mm) for 12 hr. The resulting oily sublimate was recrystallized from a mixture of acetone and water (1/1, v/v) to afford 0.6 g (60%) of methyl *o*-2-(3-methylbenzimidazoyl)benzoate: mp 132–133°; ir (KBr) 1718 cm^{-1} (C=O); pmr ($CDCl_3$) δ 8.2–7.20 (m, 8), 3.64 (s, 3), 3.53 (s, 3).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.23; N, 10.52. Found: C, 71.88; H, 5.38; N, 10.59.

3,4-Dihydro-1,6-benzodiazocine-2,5(1H,6H)-dione 18.—To a solution of 10.8 g (0.1 mol) of *o*-phenylenediamine and 17.4 g (0.1 mol) of diethyl succinate in 50 ml of dimethylformamide was added 10 g of a 50% oil dispersion of NaH. After a few minutes and exothermic reaction began and the reaction mixture was cooled in an ice bath. After the initial reaction had subsided, the mixture was heated on a steam bath for 1 hr. Water (200 ml) and concentrated HCl (50 ml) were added and the resulting precipitate was collected and washed with benzene. Recrystallization from dimethylformamide gave 4.7 g (25%) of pure **18**: mp 264–265.5° dec; ir (KBr) 3180 cm^{-1} (N–H), 1700 (C=O); pmr (CF_3COOH) δ 7.94 (A_2B_2, 4), 2.92 (s, 4); mol wt, 190 (mass spectrum).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.14; H. 5.30; N, 14.73. Found: C, 63.23; H, 5.44; N, 14.76.

Thermal Dehydration of Compound 18.—When a 0.5-g sample of compound **18** was heated for 5 min at 270° there sublimed 0.28 g (62%) of compound **19**, mp 171–172°. This material is identical with a sample prepared by the method of Meyer and Luders.[1c]

Registry No.—**6**, 4482-14-8; **10**, 19799-45-4; **13**, 19766-46-2; **14**, 1780-94-5; **15**, 19779-46-5; **18**, 19766-48-4; methyl *o*-2-(3-methylbenzimidazoyl)benzoate, 19766-49-5.

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[8] Nmr spectra were obtained with a Varian A-60 spectrometer. Mass spectra were obtained with a Hitachi-Perkin Elmer RMU-6E instrument equipped with a solid sample injector. The ionizing voltage employed was 80 V. Elemental analyses were done by Mrs. K. Decker of this department.