Products Formed by the Reaction of *o*-Diacylbenzenes with Primary Amines

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The reactions of *o*-diacylbenzenes with primary amines or ammonia produced several isoindole derivatives in the presence or the absence of acid. From *o*-diacylbenzenes and hydroxylamine hydrochloride in the presence of triethylamine 1*H*-2,3-benzoxazine derivatives were obtained.

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The reactions of *o*-acetylbenzophenone (**1**) with several primary amines in the presence of acid produced one type of red and three types of deep blue pigments including isoindole moieties [1]. In a previous paper [2] we reported the structures of the yellow products formed by the reactions of **1** or *o*-diacetylbenzene (**2**) with aromatic amines in the absence of acid to be 1,2,3-trisubstituted isoindoles. The methanol solution of **1** and primary alkyl amines in the absence of acid afforded bis(2-alkyl-3-phenyl-1-isoindolyl)-methanes as pale brown compounds, which changed by addition of acid in methanol into deep blue pigments, namely isoindole derivatives [3].

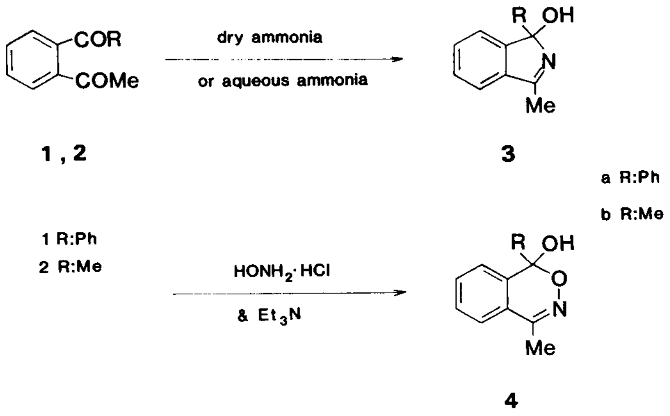
By bubbling dry ammonia through an ether solution of **1**, 1-hydroxy-3-methyl-1-phenyl-1*H*-isoindole (**3a**) was obtained in the yield of 90% [4]. On the treatment of **2** with dry ammonia, 1-hydroxy-1,3-dimethyl-1*H*-isoindole (**3b**) was definitely observed on the thin layer chromatogram. But the isolation of **3b** could not be carried out because of the two active methyl groups of **2** [2].

The methanol solution of **1** or **2** reacts with aqueous ammonia at room temperature for 3 or 0.5 hours to produce also **3a** or **3b** respectively. The column or preparative layer chromatography of the reaction mixture brought about decomposition of the product. The formation of **3a** in the reaction mixture was determined by thin layer chromatography on aluminium oxide and by mass and ^{1}H nmr spectra in deuteromethanol in comparison with the authentic product [4] from **1** and dry ammonia.

The structure of **3b** was decided by the behavior on thin layer chromatography and ^{1}H nmr as well as mass spectra. In the nmr spectrum of the reaction mixture in tetradeuteromethanol *two singlet* signals at δ 1.60 (3H) and δ 2.42 (3H) ppm assignable to methyl groups at the 1- and 3-positions and *a multiplet* at δ 7.45 (4H) assignable to the protons of *o*-disubstituted benzene are in agreement with the structure of **3b**. The existence of hydroxyl group was estimated by comparison of the mass spectra of the reaction mixtures in methanol and tetradeuteromethanol as well as **3a**; m/z reaction in methanol, 161 (M^+), 146 $(M-Me)^+$, 143 $(M-H_2O)^+$; reaction in tetradeuteromethanol, 162 (M^+), 147 $(M-Me)^+$, 143 $(M-HDO)^+$; **3a**, 223 (M^+), 205 $(M-H_2O)^+$, 146 $(M-Ph)^+$.

Isolation of **3b**-derivatives and their reactions in acidic media are to be subject of a further investigation.

The treatment of **1** or **2** and hydroxylamine in ethanol in the presence of triethylamine at room temperature afforded 1-substituted-1-hydroxy-4-methyl-1*H*-2,3-benzoxazine (**4**) in good yields. This reaction differs from the other reactions of **1** and **2** with primary alkyl and aryl amines as well as ammonia giving isoindole derivatives described above and is the simple and useful route to prepare 1*H*-2,3-benzoxazine derivatives.



EXPERIMENTAL

Melting points were determined on Yanaco micromelting point apparatus and are uncorrected. The infrared spectra were taken on a JASCO A-102 spectrometer using potassium bromide pellets. The proton nmr spectra were measured on a Varian XL-200 or Hitachi R-90 spectrometer, using tetramethylsilane as the internal standard. Mass spectra were obtained with LC-Mass M-2000 or ESCO EMD-05B spectrometer. For thin layer chromatography, aluminium oxide 60 plate (Merck) or silica gel 60 plate (Merck) and for preparative layer chromatography, silica gel precoated plate (Kieselgel 60 Merck) were used. Elemental analyses were performed at the Elemental Analysis Center in Kyoto University.

1-Hydroxy-1,3-dimethyl-1*H*-isoindole (**3b**).

Anhydrous ammonia was bubbled into an ether solution (150 ml) of **2** [5] (10 mmoles) in the ice-bath for 1 hour - in the case of **3a**, the reaction was carried out at room temperature [4]. Isolation of the product from the reaction mixture was unsuccessful because of the active methyl group. The structure of **3b** was decided in the following manner.

A methanol solution of 0.5 mmole of **2** was stirred with 2.0 mmoles of aqueous ammonia in methanol at room temperature for 30 minutes. On the thin layer chromatogram of aluminium oxide only one product was observed and the mass spectrum of the reaction mixture was measured (Mass-A). To a small portion of the reaction mixture deuterium oxide was added and the mass spectrum of the deuterated mixture was measured (Mass-B). After stirring the mixture for 3 hours three products were observed on the chromatogram.

To a deuteromethanol solution (0.5 ml) of **2** (0.2 mmoles) 0.1 ml of aqueous ammonia in 0.5 ml of deuteromethanol was added with stirring and after treating for 30 minutes at room temperature ^{1}H nmr and mass spectra (Mass-C) of the mixture was recorded.

Compound **3b** in the reaction mixture had ^{1}H nmr (deuteromethanol): δ 7.45 (m, 4H, aromatic H), 2.42 (s, 3H, 3-Me), 1.60 (s, 3H, 1-Me); Mass-A: m/z 161 (M^+, 53%), 146 ($(M-Me)^+$, 97%), 143 ($(M-H_2O)^+$, base peak); Mass-B: m/z 162 (M^+, 16%), 147 ($(M-Me)^+$, 91%), 143 ($(M-HDO)^+$, 72%); Mass-C: m/z 162 (M^+, 35%), 147 ($(M-Me)^+$, 88%), 143 ($(M-HDO)^+$, base peak).

The ^{1}H nmr and ms spectra of **3a** [4] were newly measured in order to compare with **3b**.

Compound **3a** had ^{1}H nmr (deuteromethanol): δ 7.65-7.26 (m, 9H, aromatic H), 2.50 (s, 3H, Me); ms: m/z 223 (M^+, 95%), 205 ($(M-H_2O)^+$, base peak), 146 ($(M-Ph)^+$, 60%).

The ^{1}H nmr of compound **3a** in the reaction of **1** with aqueous ammonia in deuteromethanol was: δ 7.68-7.23 (m, >9H, aromatic H), 2.50 (s, 3H, Me); ms: m/z 224 (M^+, 61%), 205 ($(M-HDO)^+$, base peak), 147 ($(M-Ph)^+$, 35%).

1-Hydroxy-4-methyl-1-phenyl-1*H*-2,3-benzoxazine (**4a**).

To an ethanol solution (8 ml) of **1** (1 mmole) 2 mmoles of hydroxylamine hydrochloride and 2.4 mmoles of triethylamine were added and stirred at room temperature for 24 hours. After evaporating the colorless clear mixture under reduced pressure, acetone was added to the residue and the resulting precipitate (triethylamine hydrochloride) was filtered off. The filtrate was chromatographed on the silica gel precoated plate using benzene-ethyl acetate (5:1) as the developing solvent. From the second band **4a** was obtained in the yield of 67%.

Compound **4a** had mp 169-170.5° (from benzene); ir: 3175 cm^{-1} (br, OH); ^{1}H nmr (deuterochloroform): δ 7.71 (m, 2H, aromatic H), 7.56-7.40 (m, 6H, aromatic H), 6.93 (m, 1H, aromatic H), 3.48 (s, 1H, OH), 2.49 (s, 3H, Me); ms: m/z 239 (M^+).

Anal. Calcd. for $C_{15}H_{13}NO_2$ (239.3): C, 75.30; H, 5.48; N, 5.85. Found: C, 75.46; H, 5.39; N, 5.86.

1-Hydroxy-1,4-dimethyl-1*H*-2,3-benzoxazine (**4b**).

By treating 1 mmole of **2** in ethanol with 2 mmoles of hydroxylamine hydrochloride and 2.4 mmoles of triethylamine for 5 hours in a similar manner as for the preparation of **4a**, **4b** was isolated in the yield of 51%.

Compound **4b** had mp 129-130.5° (from benzene); ir: 3230 cm^{-1} (br, OH); ^{1}H nmr (deuterochloroform): δ 7.68-7.51 (m, 4H, aromatic H), 2.98 (s, 1H, OH), 2.44 (s, 3H, 4-Me), 2.01 (s, 3H, 1-Me); ms: m/z 177 (M^+).

Anal. Calcd. for $C_{10}H_{11}NO_2$ (177.2): C, 67.78; H, 6.26; N, 7.90. Found: C, 67.93; H, 6.23; N, 7.93.

REFERENCES AND NOTES

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