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Unusual Reaction of 3-Chloro-3-nitroalkylindolin-2-ones

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The reaction of 3-chloro-3-nitromethylindolin-2-one (**2a**) with aniline resulted the formation of 3-anilinomethylene-(**4a**) and 3-(*p*-phenylazo)anilinomethyleneindolin-2-one (**5**). Chromatographing of **2a**, **b** using Al_2O_3 in chloroform solution gave 3-nitromethyleneindolin-2-ones (**7a**, **b**), which were also reacted with amines to give 3-amino-methyleneindolin-2-ones (**4a**, **b** and **8a**, **b**).

In connection with our study on the synthesis of spiro[imidazolidine-4,3'-indoline] compounds,²⁾ the present authors investigated into the synthesis of various compounds derived from 3-hydroxy-3-nitroalkylindolin-2-ones³⁾ (**1**). Compound **1** was obtained easily by condensing indoline-2,3-dione with nitroalkane, and was chlorinated to 3-chloro derivative (**2**).⁴⁾ We thought that 3-amino compound **3** could be obtained by nucleophilic substitution reaction on **2** by amine and could be a suitable intermediate for the imidazole-ring formation. Although we could not have the desired compound **3** by this method, some unexpected results were obtained and are to be reported in this paper.

When 3-chloro-3-nitromethylindolin-2-one (**2a**) was allowed to react with two molar equivalents of aniline in benzene solution, a main product precipitated as yellow needles, mp 250° (**4a**) along with a small amount of orange yellow needles of mp 301° (**5**) were produced. The infrared (IR) spectrum of **4a** showed the peak of C=O group which was shifted to a lower frequency side compared with that of the compound **2a**, and showed no bands that could be assigned to NO_2 group. The molecular ion peak (M^+) thereof on the mass (MS) spectrum appeared at m/e 236, which did not agree with the molecular weight of the structure (**3**). The hydrogenation of **4a** with palladium-charcoal in methanol yielded 3-methylindolin-2-one (**6**). This behavior of hydrogenation reaction was found to be very similar to that of 3-amino-methyleneindolin-2-one as reported by Wenkert, *et al.*⁵⁾ From these results, the structure of the compound **4a** was postulated as 3-anilinomethyleneindolin-2-one. This compound was prepared by Friedlander, *et al.*,⁶⁾ by condensing 3-formylindolin-2-one with aniline and, later, by Seshadri, *et al.*,⁷⁾ who obtained the same product by the Vilsmeier Haack reaction of 2-indolinone with formanilide. The structure of the compound **4a** was identified by comparing the physical properties and spectral data with those of the authentic sample.

Another product **5** showed M^+ 340 on the MS spectrum and its IR and NMR spectra were very similar to those of compound **4a**. The NMR spectrum of **5**, with the exception of the aromatic protons integrated for thirteen, was almost superimposable on that of the compound **4a**, *viz.* doublet (1H, $J=13$ Hz) at 10.98, singlet (1H) at 10.57 and doublet (1H, $J=13$ Hz) at 8.70 ppm. After treatment with D_2O , the two signals at 10.98 and 10.57 ppm disappeared, while a doublet appeared as a singlet sharp peak at 8.60 ppm. The signal at 10.57 ppm could be assigned to the N-H proton of the indolin-2-one. The two doublet signals at 10.98 and

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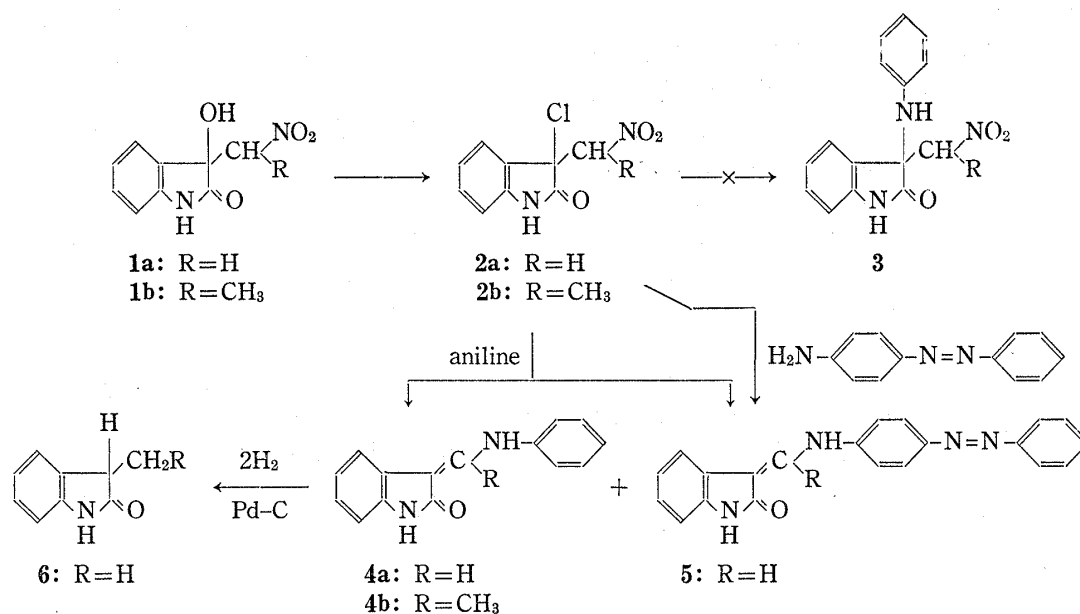


Chart 1

8.70 ppm were coupled and were assigned to the anilino and methin proton, respectively. Because the D₂O exchange spectrum was due to the deuteration of the anilino proton, the methin proton was decoupled and appeared as a sharp singlet at 8.60 ppm. In view of the above spectral and analytical data, it is supposed that the structure of **5** contains a phenylazo group at the *p*- or *o*-position of the anilino group of the compound **4a**. In order to verify this structural assignment, the reaction of **2a** with *p*-aminoazobenzene was carried out under the same conditions and 3-(*p*-phenylazo)anilinomethyleneindolin-2-one which coincided with the compound **5** was obtained.

Similarly, the reaction of 3-chloro-3-(α -nitro)ethylindolin-2-one (**2b**) with aniline gave a 50% yield of 3-(α -anilino)ethylideneindolin-2-one (**4b**). The corresponding 3-(*p*-phenylazo)-anilino compound was not isolated in this reaction.

When the compound **2a** was passed through the column of alumina employing chloroform as the solvent, it was observed that the chromatogram turned red immediately and the wine red effluent gave dark red plates, mp 156–157° (**7a**), which apparently had lost the chlorine atom. The ultraviolet (UV) spectrum of **7a** in ethanol showed a maximum absorption at 450 nm as the longest wave-length and the IR spectrum had the absorption peak of the C=O group which was shifted to a lower frequency side than the corresponding absorption of C=O in the compound **2a**. From the above analytical and spectral data, which support the formation of a conjugated 2-indolinone, the structure of **7a** was determined as 3-nitromethyleneindolin-2-one. Analogous treatment of **2b** yielded 3-(α -nitro)ethylideneindolin-2-one (**7b**),

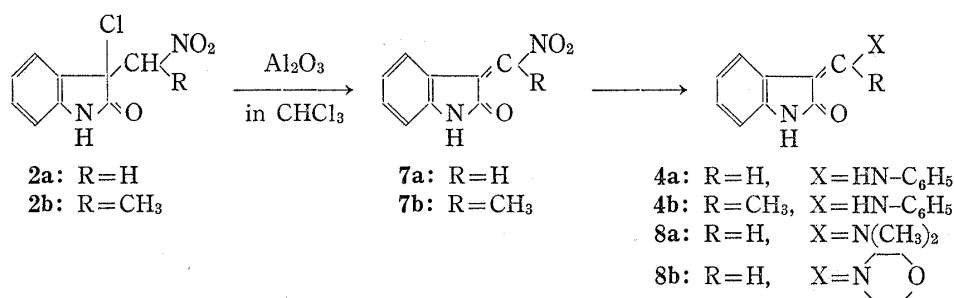


Chart 2

orange needles, mp 165–167° in a yield of 50%. Other reactions to try the elimination of the hydrogen chloride from the compound **2**, *i.e.*, refluxing with sodium hydroxide in ethanol

or heating with sodium acetate in acetic acid were attempted, but resulted in failure because the material decomposed. The elimination reaction of the hydrogen chloride from the compound **2** seemed to need a milder condition.

Concerning the formation of **4a** and **4b** respectively from **2a** and **2b**, it can be considered that the nitromethylene compounds **7a** and **7b** are the intermediates which react with aniline to give the corresponding 3-anilinomethylene compounds. Therefore, the reactions of these 3-nitromethylene compounds, **7a** and **7b**, with amines were carried out. The reactions of **7a** and **7b** with aniline under conditions similar to those for the compound **2** with aniline yielded, as we expected, yellow products of 3-anilinomethyleneindolin-2-ones (**4a**) and (**4b**), respectively.

Attempts were made to use secondary amines in this reaction. When **7a** was heated with dimethylamine in chloroform at 70° in a sealed tube, 3-dimethylaminomethyleneindolin-2-one⁵⁾ (**8a**) was obtained. The reaction of **7a** with morpholine in benzene gave 3-morpholinomethylene compound **8b**. In some runs, nitrous acid elimination was detected by starch-zinciodide paper, which indicated that the nitro group of the compound **7** was readily exchanged by amine.

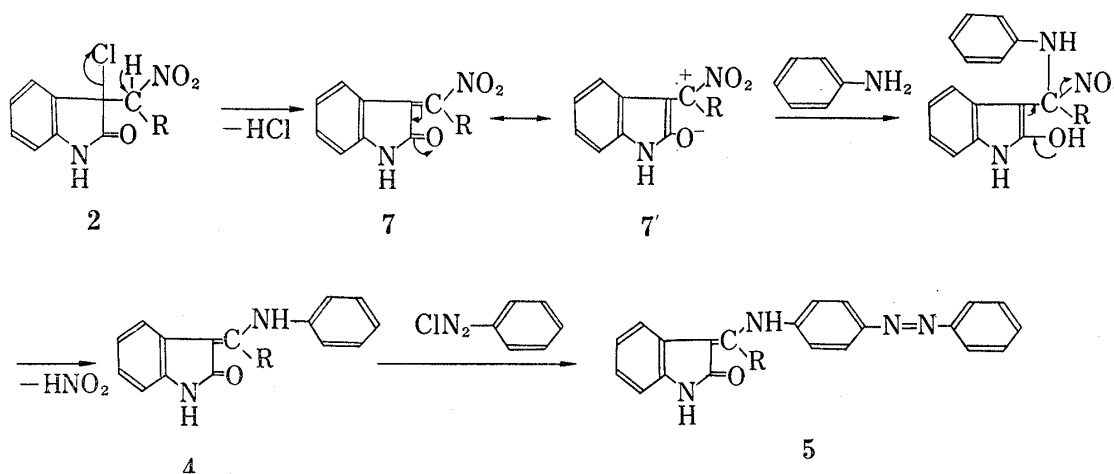


Chart 3

Consequently, the reaction course of the compounds **4** and **5** can be reasonably explained as illustrated in Chart 3; first, hydrogen chloride eliminated from **2** to the nitromethylene compound **7**, secondly, the polarized **7'** was attacked by aniline to give 3-aminomethylene compound **4** releasing nitrous acid. Hence, the presence of aniline hydrochloride in the reaction mixture gave the 3-(*p*-phenylazo)anilinomethylene compound **5**, as the result of the formation of diazonium chloride from aniline hydrochloride and nitrous acid and the coupling with the **4** at the *p*-position of the anilino group.

The other nucleophilic replacements of nitro group on the compounds **7a**, **b** with sodium methylate or phosphoroylchloride were unsuccessful and unworkable, and amorphous products were obtained.

Experimental

All melting points are uncorrected. IR spectra were recorded with a Hitachi Model-215 and UV spectra with a Shimadzu UV-200 instrument. NMR spectra were determined on a Hitachi-Perkin-Elmer R-20 spectrometer using trimethyl silane (TMS) as the internal standard. Mass spectra were run on a Hitachi RMS-4 spectrometer.

3-Anilinomethyleneindolin-2-one (4a)—To a solution of **2a** (1.0 g) in benzene (20 ml) was added aniline (0.4 g) at room temperature with stirring. The solution turned red-brown and separated yellow crystallines. The resulting mixture was further warmed at 60° for 30 min. The solvent was removed and the residue

was recrystallized from MeOH to give orange needles of mp 249°. Yield, 0.88 g or 85%. This was identical with the sample prepared by Vilsmeier-Haack reaction of 2-indolinone with formanilide.⁷⁾

3-(*p*-Phenylazo)anilinomethyleneindolin-2-one (5)—i) The mother liquor upon separation of **4a** was evaporated, the residue was taken up in CHCl₃ and run through a column of Al₂O₃. The effluent gave 40 mg of orange red needles of mp 301° (decomp.) (MeOH). IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1670 (C=O). NMR (*d*-DMSO) ppm: 10.98 (1H, d, *J*=13 Hz), 10.57 (1H, s), 8.7 (1H, d, *J*=13 Hz), 8.1–6.98 (13H, m). Mass Spectrum: 340 (M⁺). Anal. Calcd. for C₂₁H₁₆ON₄: C, 74.10; H, 4.74; N, 16.46. Found: C, 74.02; H, 4.79; N, 16.38.

ii) A mixture of **2a** (1.0 g) and *p*-aminoazobenzene (0.9 g) in benzene (30 ml) was warmed at 50° for 1 hr. The mixture was concentrated to dryness *in vacuo* and the residue was recrystallized from MeOH to give 0.35 g of orange red needles of mp 301°, which were identical with the above sample. From the mother liquor on recrystallization, 0.34 g of *p*-aminoazobenzene hydrochloride was obtained.

3-(α -Anilino)ethylideneindolin-2-one (4b)—A mixture of **2b** (1.2 g) and aniline (0.93 g) in benzene (30 ml) was refluxed for 1 hr. After evaporation of the solvent, the residue was recrystallized from MeOH to give yellow blades, mp 215–216°. Yield, 0.56 g or 47%. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3150 (NH), 1650 (C=O). NMR (*d*-DMSO) ppm: 12.20 (1H, s), 10.58 (1H, s), 7.52–7.0 (9H, m), 2.55 (3H, s). Mass Spectrum: 250 (M⁺). Anal. Calcd. for C₁₆H₁₄ON₂: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.74; H, 5.57; N, 10.89.

Hydrogenation of 4a: Formation of 3-Methylindolin-2-one (6)—A mixture of **4a** (0.3 g) and Pd-C (10%, 0.1 g) in MeOH (70 ml) was shaken with hydrogen at room temperature and atmospheric pressure. When the uptake of hydrogen became very slow, the hydrogenation was suspended and the mixture was filtered. Evaporation of the solvent gave colorless needles of mp 124°, which coincides with the description of 3-methylindolin-2-one.⁸⁾

3-Nitromethyleneindolin-2-one (7a)—A solution of **2a** (8.0 g) in CHCl₃ (100 ml) was run through a column (2.5 × 20 cm) packed with Al₂O₃ (Merck, Art 1097). The chromatogram turned red was developed with a mixture of CHCl₃ and MeOH (1:1). The effluent gave dark red plates of mp 155–157° (decomp.) (MeOH). Yield, 3.4 g or 50%. UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ): 209 (4.50), 255 (4.43), 337 (4.08), 450 (3.10). IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1715 (C=O), 1510 (ν_{as} NO₂). Mass Spectrum: 190 (M⁺). Anal. Calcd. for C₉H₆O₃N₂: C, 56.84; H, 3.18; N, 14.73. Found: C, 56.63; H, 2.91; N, 14.33.

3-(α -Nitro)ethylideneindolin-2-one (7b)—This compound was obtained from **2b** according to the similar procedure for the preparation of **7a**. Yield, 49%. Orange-red plates, mp 165–167° (MeOH). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ): 206 (4.15), 216 (4.15), 248 (4.41), 255 (4.38), 350 (3.14). IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1715 (C=O), 1530 (ν_{as} NO₂). Mass Spectrum: 204 (M⁺). Anal. Calcd. for C₁₀H₈O₃N₂: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.54; H, 3.63; N, 13.46.

Reaction of 7a with Aniline: Formation of 4a—A mixture of **7a** (1.0 g) and aniline (0.97 g) in benzene (40 ml) was heated at 60° for 10 min with stirring. After evaporation of the solvent *in vacuo*, the residue was recrystallized from MeOH to give 0.8 g (61%) of yellow needles of mp 249°, which undepressed the mixed fusion with the sample prepared from **2a** and aniline.

Reaction of 7b with Aniline: Formation of 4b—Similar treatment of **7b** (1.2 g) and aniline (0.93 g) gave 0.56 g (47%) of yellow blades, mp 215–216°, which coincides with the sample prepared from **2b** and aniline.

3-Dimethylaminomethyleneindolin-2-one (8a)—A mixture of **7a** (1.5 g) and dimethylamine (1.4 g) in CHCl₃ (50 ml) was heated in a sealed tube at 70° for 1 hr. After the reaction, the solvent was removed and the residue was recrystallized from benzene to give yellow crystal powder, mp 190–192°, which coincides with Wenkert, *et al.*,⁵⁾ description. Yield, 0.67 g or 46%.

3-Morpholinomethyleneindolin-2-one (8b)—A mixture of **7a** (1.5 g) and morpholine (0.8 g) in CHCl₃ (30 ml) was refluxed for 20 min. After evaporation of the solvent, the residue was recrystallized from benzene to give pale yellow needles of mp 202°. Yield, 60%. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1680 (C=O). Mass Spectrum: 230 (M⁺). Anal. Calcd. for C₁₃H₁₄O₂N₂: C, 67.71; H, 6.13; N, 12.17. Found: C, 68.10; H, 5.81; N, 12.05.

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