Condensation of 2*H*-Indazole-4,7-dione Derivatives with 2-Aminophenol Derivatives

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A new type of 9-substituted-5-methyl-2-phenyl-4*H*-pyrazolophenoxazin-4-one derivatives was prepared by the condensation of 5-methyl- and 6-methyl-2-phenyl-2*H*-indazole-4,7-diones with 4-substituted-2-aminophenols in pyridine. Relative reactivity of 2-aminophenol derivatives in the condensation was studied.

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The phenoxazone and phenothiazone derivatives containing iminoquinone systems have been studied for the biological and pharmaceutical activities for example [1-3]. Recently we synthesized 4*H*-pyrrolo- [4] and 4*H*-pyrazolophenothiazin-4-one derivatives [5] including heterocyclic five-membered rings in good yields.

In this paper, the preparation of a new class of 4*H*-pyrazolophenoxazin-4-one derivatives was reported. The condensation of 5-methyl-, **2**, or 6-methyl-2-phenyl-2*H*-indazole-4,7-diones **3** [6] with 4-substituted-2-aminophenol derivatives **1** in pyridine at 60° afforded 9-substituted-5-methyl-2-pheny-4*H*-pyrazolo[5,4-*a*]phenoxazin-4-ones **4** or 9-substituted-5-methyl-2-phenyl-4*H*-pyrazolo[4,5-*a*]-phenoxazin-4-ones **5** in moderate yields respectively. Carrying out the reaction in refluxing ethanol or dimethylformamide at at 60° small amounts of **4** or **5** were obtained.

Because of the tendency of 2-aminophenol to be oxidized to 3*H*-phenoxazin-3-one and triphenodioxazine derivatives *etc.* [7,8], the condensations with **1** were complicated and the yields of expected products were lowered. This case is different from the case of the phenothiazone derivatives [5], however, we were able to separate the regioisomers **4** and **5** with an activated silica gel column from the reaction mixture in improved overall yields of these phenoxazones based on the mixture of **2** and **3** [9] notably for **5**.

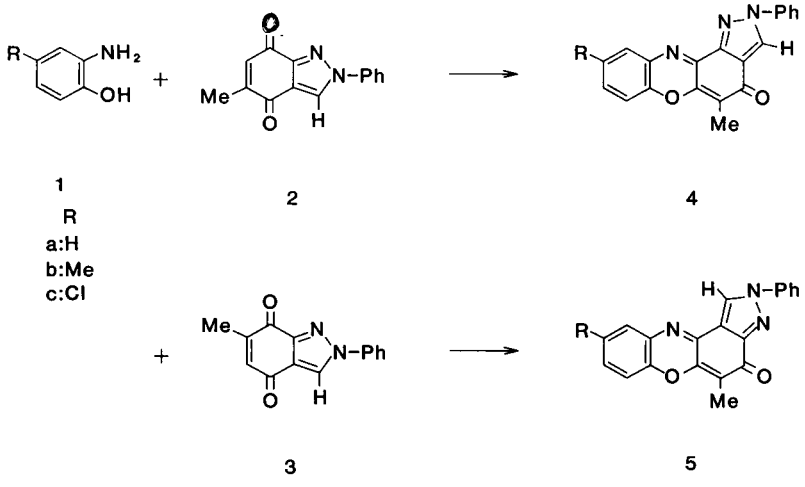
The relative reactivity of the three derivatives of **1** was measured by the competitive reaction of **1** with **2**. The results are: 4-methyl-, **1b**, and while 4-non-substituted-, **1a** have approximately the same reactivity, 4-chloro-2-aminophenol (**1c**) is less reactive.

The uv absorption maxima and the ir absorption bands at about 1630 cm^{-1} (*ca.* 6.1 μ) of **4** were shifted to longer wave lenghts than that of **5**.

With regard to nmr spectra, the characteristic singlet signals assignable to hydrogen at the 3-position of **2** and **3** moved to lower magnetic field for the condensation products **4** and **5**, especially for **5**.

EXPERIMENTAL

Melting points were determined on a Yanaco micro-melting point apparatus and are uncorrected. The infrared spectra were taken on a JASCO A-102 spectrometer using potassium bromide pellets and the ultraviolet spectra were recorded with a JASCO UVIDEC-505 spectrometer in chloroform solution. The nuclear magnetic resonance spectra were measured on a Varian XL-200 spectrometer operating in an FT mode in deuteriochloroform, using tetramethylsilane as the internal standard. Mass spectra were obtained with ESCO EMD-05B spectrometer. For column chromatography, silica gel (Kiesel-gel 60, Merck, 70-230



mesh ASTM; when necessary, it was activated by heating at 120° for 1 hour and cooled under argon) was used.

The relative reactivity was measured on a JASCO Series 800 liquid chromatograph equipped with an hplc pump 880-PU, variable wavelength detecter 875-UV and SIC Chromatocorder 11 using a JASCO SIL C_{18} column (4.6 mm i.d. x 10 cm) using methanol.

General Procedure for the Condensation of 2*H*-Indazole-4,7-diones **2** and **3** with 2-Aminophenol Derivatives **1**.

A mixture of 0.5 mmole of **2** or **3**, 1.5 mmoles of **1** and 2 ml of pyridine was stirred at 60° for 24 hours. After evaporating the pyridine under reduced pressure, the residue was washed with 1*N* hydrochloric acid and extracted with benzene. The resulting solid was purified by the column chromatography on silica gel using benzene and benzene-acetone (99:1) as the eluent.

5-Methyl-2-phenyl-4*H*-pyrazolo[5,4-*a*]phenoxazin-4-one (**4a**).

By the reaction of **1a** with **2**, **4a** was produced as orange needles in 36% yield. This compound had mp 309-314° (ethanol); ir: 1625 (C=O) cm^{-1}; uv: λ max, nm (log ε), 440 (4.03), 367 (4.24), 268 (4.63); ^1H nmr: δ 8.60 (s, 1H, pyrazole H), 7.93 (d, 2H), 7.85 (m, 1H), 7.61-7.46 (m, 4H), 7.38 (m, 2H), 2.20 (s, 3H, iminoquinone CH_3).

Anal. Calcd. for $C_{20}H_{13}N_3O_2$: C, 73.38; H, 4.00; N, 12.84. Found: C, 73.61; H, 3.75; N, 12.59.

5-Methyl-2-phenyl-4*H*-pyrazolo[4,5-*a*]phenoxazin-4-one (**5a**).

The equimolar mixture of **2** and **3** [9] and three times the molar quantity of **1** were treated as above. The orange yellow band was chromatographed on activated silica gel column using benzene-acetone (99:1). From the first yellow fraction **4a** was obtained in 18% yield and from the second orange yellow fraction **5a** was obtained as orange needles in 17% yield.

Compound **5a** had mp 261-263° (ethanol); ir: 1635 (C=O) cm^{-1}; uv: λ max, nm (log ε), 433 (4.16), 376 (4.28), 274 (4.52); ^1H nmr: δ 8.75 (s, 1H, pyrazole H), 7.94 (d, 2H), 7.72 (d, 1H), 7.60-7.43 (m, 4H), 7.37 (m, 2H), 2.25 (s, 3H, iminoquinone CH_3)).

Anal. Calcd. for $C_{20}H_{13}N_3O_2$: C, 73.38; H, 4.00; N, 12.84. Found: C, 73.31; H, 3.83; N, 12.66.

5,9-Dimethyl-2-phenyl-4*H*-pyrazolo[5,4-*a*]phenoxazin-4-one (**4b**).

From the reaction of **1b** and **2**, **4b** was prepared as oranges needles in 37% yield. This compound had mp 312-314° (ethanol); ir: 1632 (C=O) cm^{-1}; uv: λ max, nm (log ε), 454 (4.07), 371 (4.18), 273 (4.55); ^1H nmr: δ 8.59 (s, 1H, pyrazole H), 7.93 (d, 2H), 7.76 (s, 1H), 7.61-7.39 (m, 4H), 7.26 (s, 1H), 2.45 (s, 3H, aromatic CH_3), 2.21 (s, 3H, iminoquinone CH_3).

Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.85; H, 4.25; N, 12.03.

5,9-Dimethyl-2-phenyl-4*H*-pyrazolo[4,5-*a*]phenoxazin-4-one (**5b**).

The reaction of **1b** with the mixture of **2** and **3** was carried out by the same way described above. From the first band **4b** was obtained in 18% yield and from the second band **5b** was obtained as orange needles in 19% yield. Compound **5b** had mp 302-304° (ethanol); ir: 1643 (C=O) cm^{-1}; uv: λ max, nm (log ε), 444 (4.15), 377 (4.22), 275 (4.53); ^1H nmr: δ 8.77 (s, 1H, pyrazole H), 7.95 (d, 2H), 7.62-7.38 (m, 5H), 7.26 (s, 1H), 2.45 (s, 3H, aromatic CH_3), 2.26 (s, 3H, iminoquinone CH_3).

Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.80; H, 4.33; N, 12.12.

9-Chloro-5-methyl-2-phenyl-4*H*-pyrazolo[5,4-*a*]phenoxazin-4-one (**4c**).

By the reaction of **1c** and **2**, **4c** was produced as orange needles in 35% yield. This compound had mp 280-282° (ethanol); ir: 1632 (C=O) cm^{-1}; uv: λ max, nm (log ε), 449 (3.97), 371 (4.10), 275 (4.50); ^1H nmr: δ 8.60 (s, 1H, pyrazole H), 7.92 (d, 2H), 7.62-7.40 (m, 6H), 2.21 (s, 3H, iminoquinone CH_3); ms: m/e 361 (100%)/363 (36%).

Anal. Calcd. for $C_{20}H_{12}ClN_3O_2$: C, 66.40; H, 3.34; N, 11.61. Found: C, 66.24; H, 3.24; N, 11.42.

9-Chloro-5-methyl-2-phenyl-4*H*-pyrazolo[4,5-*a*]phenoxazin-4-one (**5c**).

The mixture of **1c**, **2** and **3** in pyridine was treated as described above. After repeated chromatography the first yellow band gave **4c** in 17% yield and the second orange yellow band provided **5c** as orange needles in 18% yield. Compound **5c** had mp 281-285° (ethanol); ir: 1642 (C=O) cm^{-1}; uv: λ max, nm (log ε), 438 (4.00), 376 (4.10), 277 (4.42); ^1H nmr: δ 8.78 (s, 1H, pyrazole H), 7.95 (d, 2H), 7.73 (d, 1H), 7.62-7.34 (m, 5H), 2.26 (s, 3H, iminoquinone CH_3); ms: m/e 361 (100%)/363 (42%).

Anal. Calcd. for $C_{20}H_{12}ClN_3O_2$: C, 66.40; H, 3.34; N, 11.61. Found: C, 66.21; H, 3.38; N, 11.39.

Measurement of the Relative Reactivity of *o*-Aminophenol Derivatives **1a-c**.

Competitive Reaction Between **1a** and **1b**.

An equimolar mixture of **1a** and **1b** with **2** (⅓ equivalent weight) in pyridine was stirred at 60 ± 1° for 24 hours. After the usual workup the residue was chromatographed on a silica gel column using benzene-acetone. The resulting solid was chromatographed (hplc) to give **4a** and **4b** in a ratio of 1.0:1.03 by calibration with known products.

Competitive Reaction Between **1b** and **1c**.

By the reaction of **1b** and **1c** with **2** as described above, **4b** and **4c** were obtained in the ratio of 4.0:1.0.

Consequently, condensation of **2** with **1a**, **1b** and **1c** took place in the ratio of 3.9:4.0:1.0 under the above conditions.

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[9] For the separation of the regioisomers **2** and **3** from the equimolar mixture were required repeated recrystallization and consequently pure **3** was obtained in low yield.