The Reaction of *o*-Phthalaldehydic Acid with 5-Amino-1,3-dimethylpyrazole

Leo R. Swett and George H. Aynilian

Department of Medicinal Chemistry, Abbott Laboratories, North Chicago, Illinois 60064

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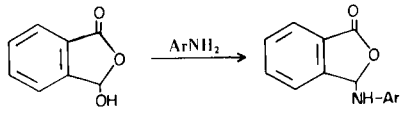
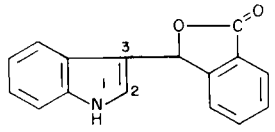
o-Phthalaldehydic acid reacted with 5-amino-1,3-dimethylpyrazole to yield 5-amino-1,3-dimethyl-4-phthalidylpyrazole. The latter was transformed to a tricyclic system; 1,3-dimethylpyrazolo[3,4-*b*]benzazepin-9-one, which in turn was reduced with lithium aluminum hydride to 9,10-dihydro-1,3-dimethylpyrazolo[3,4-*b*]benzazepine.

Anilines and a series of selected non-benzenoid aromatic amines are reported (1) to react with *o*-phthalaldehydic acid **1** to yield 3-arylaminophthalides **2**.



1 2

Other investigators (2,3,4) have reported on the reaction of *o*-phthalaldehydic acid with simple indoles. If the indole 3-position was free, the 3-phthalidyl derivative, *e.g.* **3** was formed.



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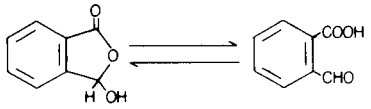
Using various substituted indoles, the preferred orientation in the indole ring was found to be 3 > 1 > 2. It was postulated that (4) the mechanism of this reaction proceeded by a nucleophilic attack of the indole on the aldehydic carbon of the open-ring form *o*-formylbenzoic acid **4** which in solution is in rapid equilibrium with the cyclic form, 3-hydroxyphthalide **1**. This mechanism was favored



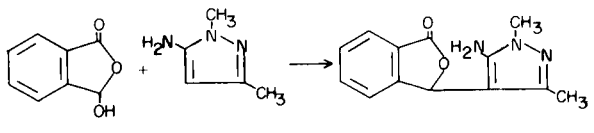
1 4

over the electrophilic substitution of the indole ring by the cyclic form **1**, since neither 3-phthalidyl acetate nor 3-ethoxyphthalide, both of which cannot exist in open ring forms, reacted with indoles under the same conditions. The reaction of the 3-phthalidyl acetate with indole was unaffected by the use of acid catalysts such as *p*-toluenesulphonic acid (4).

In view of the condensation products obtained by reacting *o*-phthalaldehydic acid with nucleophiles like aromatic amines and indoles which possess high electron density centers, studies were initiated to determine the course of the reaction of *o*-phthalaldehydic acid with 5-aminopyrazoles unsubstituted at the 4-positions. Molecular orbital calculations (5) predict that maximum electron density occurs at the 4-position of the 5-aminopyrazole ring, which is in agreement with the case of electrophilic substitutions at this site.

Assuming that the reaction between 5-aminopyrazoles and *o*-phthalaldehydic acid proceeds in the same manner as in the case of indoles, the resulting condensation products might be valuable intermediates toward the synthesis of tricyclic systems.

The compound 5-amino-1,3-dimethylpyrazole **5** was heated under reflux with equimolar amounts of *o*-phthalaldehydic acid in benzene or toluene. Work-up of the reaction mixture afforded 5-amino-1,3-dimethyl-4-phthalidylpyrazole **6** in high yields (Scheme I).



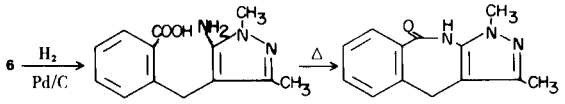
1 5 6

Scheme I

The high yield (75%) of product **6** indicated that the amino group of the pyrazole ring was not involved in the reaction to any appreciable extent. However, no effort was made to isolate the minor products of the reaction mixture.

The lactone moiety in **6** was readily cleaved by hydrogenation using palladium/carbon as catalyst to yield the

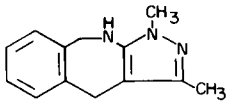
amino acid **7**, which in turn when heated neat or under reflux in xylene formed a new tricyclic system, 1,3-dimethylpyrazolo[3,4-*b*]benzazepin-9-one **8** (Scheme II). Compound **6** is also a key intermediate in the synthesis of another new heterocyclic system, namely pyrazolothiazepine (6).



7 **8**

Scheme II

Finally, lithium aluminum hydride reduction of **8** yielded 9,10-dihydro-1,3-dimethylpyrazolo[3,4-*b*]benzazepine **9**.



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EXPERIMENTAL

Melting points were determined with a Thomas Hoover Capillary melting point apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Model 521.

Absorption bands are reported in reciprocal centimeters (cm^{-1}). Proton magnetic resonance spectra were recorded on Varian HA-100 and HA-60 spectrometers using tetramethylsilane (TMS) as the internal standard. The chemical shifts are reported in parts per million (δ). Elemental analyses were performed by Abbott Laboratories, North Chicago, Illinois. All solvents and chemicals used were of reagent and analytical grade.

5-Amino-1,3-dimethyl-4-phthalidylpyrazole (**6**).

A mixture of 5-amino-1,3-dimethylpyrazole (11.1 g., 0.1 mole) and *o*-phthalaldehydic acid (15.0 g., 0.1 mole) in toluene (150 ml.) was heated under reflux for four hours, using a Dean-Stark water separator. At the end of three hours, a precipitate had already formed. The reaction mixture was cooled, the toluene decanted and to the gummy residue, ethanol (50 ml.) was added and the mixture heated on a steam bath until all the residue crystallized. Finally, the suspension was cooled, filtered, and the precipitate, after being washed with ethanol, afforded 18.3 g. of crystals (75% yield). Recrystallization from ethyl acetate-hexane mixture afforded an analytical sample of **6** (11.3 g.), m.p. 170-172°; ir (nujol): γ max at 3440, 3360, 1750 and 1623 cm^{-1}; pmr (DMSO): δ 1.33 (s, 3H, C-CH_3), 3.52 (s, 3H, N-CH_3), 5.50 (s, 2H, NH_2), 6.80 (s, 1H, CH-benzylic) and 7.70 (m, 4H, aromatic).

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.27. Found: C, 63.83; H, 5.24; N, 17.38.

5-Amino-4-(*o*-carboxybenzyl)-1,3-dimethylpyrazole (**7**).

A Parr hydrogenation bottle was charged with 5-amino-1,3-dimethyl-4-phthalidylpyrazole (21.1 g., 0.087 mole), 250 ml. of absolute ethanol and 4.0 g. of 5% palladium/carbon. Hydrogenation was effected in less than an hour with three atmospheres of pressure. The warm mixture was filtered to remove the catalyst and the filtrate concentrated to induce cyrstallization. The harvested crystals, after washing several times with ethanol, afforded an analytical sample of **7** in a yield of 17.1 g. (70%), m.p. 193-194°; ir (nujol): γ max at 3345, 3220, 1690 and 1650 cm^{-1}; pmr (DMSO): δ 1.83 (s, 3H, C-CH_3), 3.47 (s, 3H, N-CH_3), 3.94 (s, 2H, CH_2-benzylic), 7.24 (m, 3H, aromatic), 7.75 (m, 1H, arom. *ortho* to COOH).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.51; H, 5.93; N, 17.20.

1,3-Dimethylpyrazolo[3,4-*b*]benzazepin-9-one (**8**).

5-Amino-4-(*o*-carboxybenzyl)-1,3-dimethylpyrazole (2 g., 0.0081 mole) was heated at reflux in xylene (150 ml.) for 18 hours with constant stirring. Dissolution was effected in six hours. The reaction mixture was filtered hot, the filtrate concentrated *in vacuo* to 30 ml. and cooled. This resulted in a copious precipitate (1.7 g.) (yield 75%), having a m.p. of 236-239°. Recrystallization from aqueous ethanol afforded an analytical sample melting at 238-240°; ir (nujol); γ max at 3120 and 1655 cm^{-1}; pmr (DMSO): δ 2.10 (s, 3H, C-CH_3), 3.60 (s, 3H, N-CH_3), 3.64 (s, 2H, benzylic-CH_2), 7.35 (m, 3H, aromatic), 7.72 (m, 1H, arom. *ortho* to carbonyl) and 10.70 (s, 1H, NH).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.76; N, 18.49. Found: C, 68.98; H, 5.67; N, 18.76.

9,10-Dihydro-1,3-dimethylpyrazolo[3,4-*b*]benzazepine (**9**).

1,3-Dimethylpyrazolo[3,4-*b*]benzazepin-9-one (11.4 g., 0.05 mole) was added in portions to lithium aluminum hydride (3.8 g., 0.1 mole) in 200 ml. of THF with constant stirring. The mixture was heated at reflux for two hours, cooled to room temperature, 3.6 ml. of water, followed by 3.6 ml. of 15% sodium hydroxide and finally 10.8 ml. of water were added respectively. The mixture was stirred for one hour, filtered, and the solvent removed *in vacuo* to afford 7.1 g. of a colorless residue exhibiting a m.p. of 165-170°. Recrystallization from ethyl acetate yielded 5.2 g. of an analytical sample of **9** having a m.p. of 168-170° (yield 66%).

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 72.93; H, 7.32; N, 19.81.

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