Synthesis and Reactivity of 1-Methyl-3-phenyl-4-diazo-5-benzoylamidopyrazole. A Potential Antitumor Agent

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The title compound **2** was prepared in excellent yield by diazotation of the parent amino derivative. Compound **2** was found to react with a variety of acyclic and cyclic active methylene compounds to yield the corresponding pyrazolo-4-ylhydrazones.

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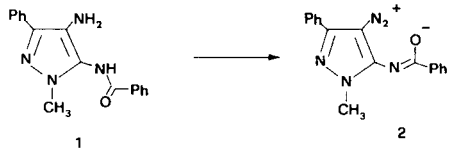
Heterocyclic diazo compounds and their diazonium salts are an interesting class of reactive substrates and their synthetic potentialities have reaceived recent attention [1-2].

As part of our program aimed at the synthesis of potential antitumor agents containing the pyrazole ring [3-5] we have recently described the synthesis of 1-methyl-3-phenyl-4-amino-5-benzoylamidopyrazole (**1**) [6]. We now report the synthesis and reactivity of its 4-diazo derivative which can be regarded as a potential antitumor agent. In fact it has been shown that the cytostatic activity of dacarbazine is to be attributed to the "*in vivo*" formation of a diazo compound [7]. Our interest in compound **2** further depends on the fact that to our knowledge it is the first reported stable *N*-substituted diazopyrazole.

Compound **2** can be easily prepared with good yield by diazotation of the parent compound **1**. The reaction was carried out at room temperature and a yellow product was separated upon standing. Compound **2** did not contain halogen and its analytical and spectroscopical data prompted us to attribute to it the zwitterionic structure reported below. In fact the ir spectrum of **2** showed an absorption

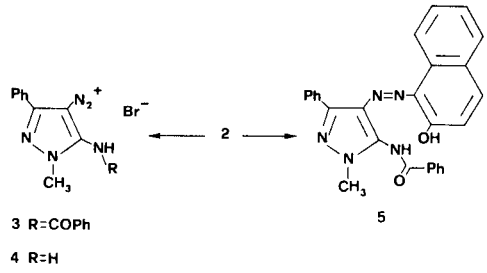
Scheme 1



band at 2160 cm^{-1} and the absence of the absorption band corresponding to the C=O amidic group, which may be ascribed to the formation of a zwitterionic compound.

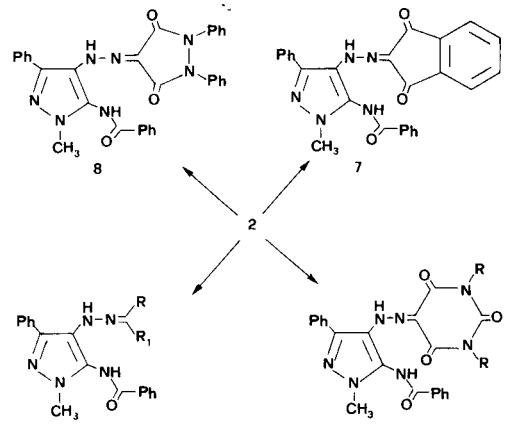
When **2** was allowed to react at room temperature with hydrobromic acid benzoylamidodiazonium bromide **3** was obtained. The structure of **3** was also confirmed by the presence of the C=O amidic absorption band at 1690 cm^{-1}. When **2** was refluxed with the above-mentioned reactant 5-amino-4-diazonium monobromide **4** was obtained because of the presence of the electron withdrawing diazonium group. The 4-diazopyrazole **2** coupled readily at room temperature in ethanol with β-naphthol to give the corresponding diazo-dye **5**. Moreover an ethanolic solution of **2**, when treated with acetylacetone, ethyl cyanoacetate or malononitrile easily gave rise to the corresponding hydrazones **6a-c**. Cyclic active methylene compounds

Scheme 2



like indan-1,3-dione, 1,2-diphenylpyrazolidin-3,5-dione, barbituric acid and its 1,3-dimethyl, diphenyl and dicyclohexyl derivatives also reacted readily to yield compounds **7-8** and **9a-d**, respectively.

Scheme 3



6a R=R$_1$=COCH$_3$
6b R=CN; R$_1$=COOEt
6c R=R$_1$=CN

9a R=H
9b R=CH$_3$
9c R=C$_6$H$_5$
9d R=C$_6$H$_{11}$

All compounds of this type can be regarded as aza compounds or as hydrazones. On the basis of ir and nmr data we attribute the hydrazone structure to them, and this attribution is further borne out by the literature [8].

EXPERIMENTAL

All melting points were determined on a Buchi capillary melting point apparatus and are uncorrected. The ir spectra were measured for potassium bromide discs with a Perkin-Elmer 283 spectrophotometer. The nmr spectra were recorded with a Varian EM-360 instrument: chemical shifts are reported in δ (ppm) downfield from internal tetramethylsilane. Silicagel plates (Merck F_{254}) were used for analytical tlc.

1-Methyl-3-phenyl-4-diazo-5-benzoylamidopyrazole (**2**).

To a solution of **1** (0.8 g) in glacial acetic acid (2 ml) and concentrated hydrochloric acid (0.8 ml) a solution of sodium nitrite (0.2 g) in water (1 ml) was added dropwise under stirring. The solution was set aside for half an hour. Upon addition of water a yellow precipitate was formed, yellow needles, mp 128-130° (from ethanol) 92% yield; ir: 2160, 1605, 1565, 1500, 1380, 1280, 900, 770, 720 and 695 cm^{-1}; nmr (acetone-d_6): 8.4-8.2 (m, 2H, benzene protons), 7.8-7.3 (m, 8H, benzene protons), 3.87 (s, 3H, NCH_3).

Anal. Calcd. for $C_{17}H_{13}N_5O$: C, 67.31; H. 4.31; N, 23.09. Found: C, 67.05; H, 4.33; N, 23.02.

1-Methyl-3-phenyl-5-benzoylamidopyrazole-4-diazonium Bromide (**3**).

A suspension of **2** (0.1 g) in 48% hydrobromic acid (2 ml) was stirred at room temperature until the mixture became colorless. Upon standing a precipitate was obtained, white crystals, mp 209° dec (from acetonitrile) 80% yield; ir: 2190, 1690, 1565, 1455, 1380, 1270, 770 and 710 cm^{-1}; nmr (dimethyl-d_6 sulfoxide): 9.1 (br s, 1H, NH, it exchanges with deuterium oxide), 8.3-8.1 (m, 2H, benzene protons), 8.0-7.4 (m, 8H, benzene protons), 4.03 (s, 3H, NCH_3).

Anal. Calcd. for $C_{17}H_{14}BrN_5O$: C, 53.15; H, 3.67; N, 18.23. Found: C, 53.17; H, 3.67; N, 18.33.

1-Methyl-3-phenyl-5-aminopyrazole-4-diazonium Bromide (**4**).

A suspension of **2** (0.1 g) in 48% hydrobromic acid (5 ml) was refluxed for 1 hour. Upon cooling 70 mg (58% yield) of yellow product was recovered, yellow crystals, mp 240° dec (from acetonitrile); ir: 3310, 3200 (br), 3000 (br), 2160, 1645, 1590, 1480, 1450, 1400, 770, 680, 655 and 630 cm^{-1}; nmr (deuteriochloroform + dimethyl-d_6 sulfoxide): 9.2 (br s, 2H, NH_2, it exchanges with deuterium oxide), 7.8-7.4 (m, 5H, benzene protons), 3.80 (s, 3H, NCH_3).

Anal. Calcd. for $C_{10}H_{10}BrN_5$: C, 41.38; H, 3.79; N, 24.14. Found: C, 41.70; H, 3.45; N, 24.52.

1-(1-Methyl-3-phenyl-5-benzoylamidopyrazolo-4-ylazo)-2-naphthole (**5**).

A solution of β-naphthol (0.15 g) in diluted sodium hydroxide was added under stirring to a solution of **2** (0.3 g) in ethanol. A red-orange precipitate was obtained by careful addition of glacial acetic acid, red needles, mp 220-222° dec (from ethanol) 34% yield; ir: 3600-3100 (v br), 1695, 1625, 1550, 1530, 1465, 1265, 935, 815, 690 and 630 cm^{-1}; nmr (deuteriochloroform + dimethyl-d_6 sulfoxide): 14.1 (br s, 1H, OH or NH, it exchanges with deuterium oxide), 10.6 (br s, 1H, NH or OH, it exchanges with deuterium oxide), 8.4-6.6 (m, 16H, 10 benzene protons + 6 naphthalene protons), 3.94 (s, 3H, NCH_3).

Anal. Calcd. for $C_{27}H_{21}N_5O_2$: C, 72.47; H, 4.69; N, 15.65. Found: C, 72.36; H, 4.72; N, 15.26.

General Procedure for the Reaction Between **2** and Acyclic and Cyclic Active Methylene Compounds.

A solution of **2** (1 mmole) in ethanol (10 ml) was treated with the equivalent amount of active methylene compound. The mixture was refluxed and the reaction was followed by tlc. Upon standing a crude product was obtained.

Compound **6a**.

This compound was obtained as orange needles, mp 205-207° dec (from ethanol) 70% yield; ir: 3220, 1675, 1600, 1510, 1480, 1320, 1290, 1200, 1190, 770, 710, 690 and 620 cm^{-1}; nmr (deuteriochloroform): 15.1 and 8.5 (2 br singlets containing 1 H each, both exchange with deuterium oxide), 8.1-7.8 (m, 2H, benzene protons), 7.7-7.2 (m, 8H, benzene protons), 3.80 (s, 3H, NCH_3), 2.45 (s, 3H, CH_3), 1.90 (s, 3H, CH_3).

Anal. Calcd. for $C_{22}H_{21}N_5O_3$: C, 65.50; H, 5.25; N, 17.36. Found: C, 65.12; H, 5.54; N, 17.74.

Compound **6b**.

This compound was obtained as yellow needles, mp 170-173° dec (from ethanol) 53% yield; ir: 3410, 2220, 1695, 1680, 1610, 1550, 1520, 1470, 1315, 1275, 1230, 1015, 770, 710 and 685 cm^{-1}; nmr (deuteriochloroform): 13.2 and 8.6 (2 br singlets containing 1H each, both exchange with deuterium oxide), 8.1-7.8 (m, 2H, benzene protons), 7.7-7.2 (m, 8H, benzene protons), 4.26 (q, 2H, CH_2), 3.81 (s, 3H, NCH_3), 1.32 (t, 3H, CH_3).

Anal. Calcd. for $C_{22}H_{20}N_6O_3$: C, 63.45; H, 4.84; N, 20.18. Found: C, 63.30; H, 4.87; N, 19.95.

Compound **6c**.

This compound was obtained as yellow crystals, mp 189-190° dec (from ethanol) 73% yield; ir: 3320, 2230, 1670, 1515, 1275, 765, 710, 700 and 680 cm^{-1}; nmr (acetone-d_6): 11.2 and 9.9 (2 br singlets containing 1H each, both exchange with deuterium oxide), 8.2-8.0 (m, 2H, benzene protons), 7.9-7.3 (m, 8H, benzene protons), 3.92 (s, 3H, NCH_3).

Anal. Calcd. for $C_{20}H_{15}N_7O$: C, 65.03; H, 4.09; N, 26.54. Found: C, 65.32; H, 4.19; N, 26.12.

Compound **7**.

This compound was obtained as red crystals, mp 241° dec (from dimethyl sulfoxide) 66% yield; ir: 3400, 1715, 1695, 1665, 1600, 1555, 1520, 1495, 1265, 1210, 1025, 1000, 755 and 685 cm^{-1}; nmr (dimethyl-d_6 sulfoxide): 13.2 and 10.6 (2 br singlets containing 1H each, both exchange with deuterium oxide), 8.3-7.3 (m, 14H, benzene protons), 3.88 (s, 3H, NCH_3).

Anal. Calcd. for $C_{26}H_{19}N_5O_3$: C, 69.48; H, 4.26; N, 15.58. Found: C, 69.29; H, 4.28; N, 15.54.

Compound **8**.

This compound was obtained as yellow-orange crystals, mp 223-225° dec (from ethanol) 57% yield; ir: 3600-3300 (br), 1730, 1690, 1605, 1565, 1530, 1490, 1270, 760, 690 and 640 cm^{-1}; nmr (deuteriochloroform): 9.2 (br s, 1H, NH, it exchanges with deuterium oxide), 8.2-8.0 (m, 2H, benzene protons), 7.8-7.1 (m, 19H, 18 benzene protons + NH, the latter exchanges with deuterium oxide), 3.93 (s, 3H, NCH_3).

Anal. Calcd. for $C_{32}H_{25}N_7O_3$: C, 69.18; H, 4.54; N, 17.75. Found: C, 69.14; H, 4.70; N, 17.54.

Compound **9a**.

This compound was obtained as yellow needles, mp 267-268° dec (from ethanol) 97% yield; ir: 3600-3000 (br), 1745, 1730, 1710, 1675, 1600, 1515, 1470, 1445, 1410, 1275, 765, 715, 690 and 500 cm^{-1}; nmr (dimethyl-d_6 sulfoxide): 14.2, 11.4, 11.1 and 10.6 (4 br singlets containing 1H each, all are exchangeable with deuterium oxide), 8.2-7.9 (m, 2H, benzene protons), 7.9-7.3 (m, 8H, benzene protons), 3.83 (s, 3H, NCH_3).

Anal. Calcd. for $C_{21}H_{17}N_7O_4$: C, 58.42; H, 3.97; N, 22.71. Found: C, 58.50; H, 3.74; N, 22.94.

Compound **9b**.

This compound was obtained as yellow needles, mp 222-225° dec (from ethanol) 98% yield; ir: 3395, 2960, 1730, 1695, 1665, 1635, 1595, 1510, 1470, 1450, 1290, 1090, 770, 750, 710, 690 and 470 cm^{-1}; nmr (deuteriochloroform): 14.9 and 9.5 (2 br singlets containing 1H each, both exchange with deuterium oxide), 8.3-8.1 (m, 2H, benzene protons), 7.8-7.2

(m, 8H, benzene protons), 3.95 (s, 3H, pyrazole NCH_3), 3.40 (s, 3H, barbituric NCH_3), 3.30 (s, 3H, barbituric NCH_3).

Anal. Calcd. for $C_{25}H_{21}N_7O_4$: C, 60.12; H, 4.61; N, 21.34. Found: C, 60.27; H, 4.65; N, 21.60.

Compound **9c**.

This compound was obtained as yellow needles, mp 249-252° dec (from ethanol) 95% yield; ir: 3360, 1740, 1690, 1680, 1640, 1600, 1510, 1490, 1470, 1410, 1290, 1240, 945, 800, 690, 565 and 530 cm^{-1}; nmr (deuteriochloroform): 14.7 and 9.5 (2 br singlets containing 1H each, both exchange with deuterium oxide), 8.4-8.0 (m, 2H, benzene protons), 7.8-7.1 (m, 18H, benzene protons), 3.94 (s, 3H, NCH_3).

Anal. Calcd. for $C_{33}H_{25}N_7O_4$: C, 67.92; H, 4.32; N, 16.80. Found: C, 67.57; H, 4.33; N, 16.50.

Compound **9d**.

This compound was obtained as yellow needles, mp 209-210° dec (from ethanol) 93% yield; ir: 3350, 2930, 2850, 1730, 1695, 1670, 1635, 1590, 1520, 1470, 1415, 1270, 1250, 980, 795, 765, 690, 570 and 530 cm^{-1}; nmr (deuteriochloroform): 14.8 and 9.6 (2 br singlets containing 1H each, both exchanges with deuterium oxide), 8.4-8.1 (m, 2H, benzene protons), 7.9-7.3 (m, 8H, benzene protons), 3.96 (s, 3H, NCH_3), 2.8-1.0 (m, 22H, cyclohexane protons).

Anal. Calcd. for $C_{33}H_{38}N_7O_4$: C, 66.69; H, 6.27; N, 16.49. Found: C, 66.38; H, 6.17; N, 16.20.

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