SYNTHESIS OF N-ALKYL-N'-(4-DIAZO-5-PYRAZOLYL)UREAS AND THEIR CONVERSION INTO PYRAZOLO[3,4-*d*][1,2,3]TRIAZOLE AND PYRAZOLO[3,4-*d*]OXAZOLE DERIVATIVES

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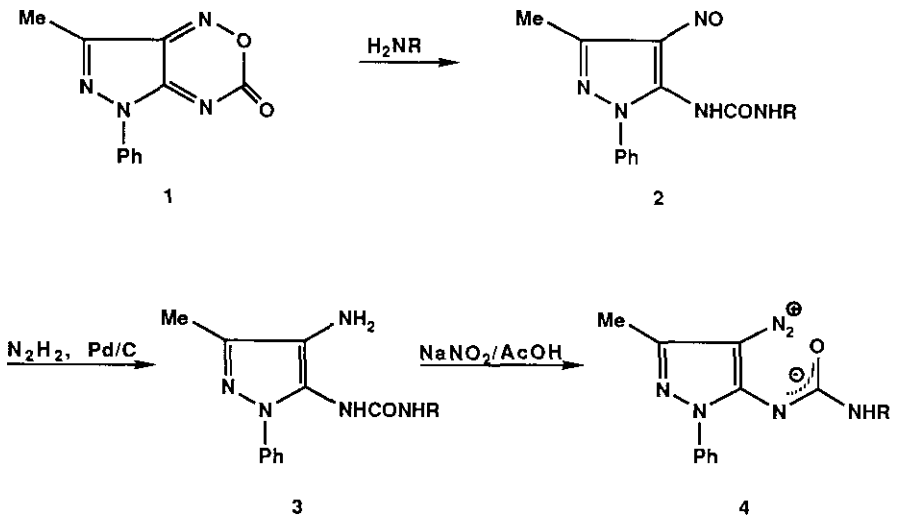
Abstract- The synthetic route to N-alkyl-N'-(4-diazo-5-pyrazolyl)ureas (**4**) starting from pyrazolo[4,3-*c*][1,2,5]oxadiazin-3(5H)-one (**1**) is described. Compounds (**4**) undergo thermal and photochemical reactions affording pyrazolo[3,4-*d*][1,2,3]triazoles (**5**) and pyrazolo[3,4-*d*]oxazoles (**7**) respectively.

In recent years considerable efforts have been expended on the search for antitumor agents based on 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (dacarbazine) and analogous dimethyltriazenes which are useful in treating several human malignancies.[1-4] It has been shown that the real cytostatic agent is not dacarbazine itself but its metabolic product 5-diazoimidazole-4-carboxamide, probably because of the ability of the diazo group to interfere with bionucleophiles.[5-7] In connection with these findings a number of diazoazoles were investigated, including 4-diazo-5-pyrazolylcarboxamides.[8,9]

In the present paper we describe the synthesis of N-alkyl-N'-(4-diazo-5-pyrazolyl)-ureas (**4**) which were considered of interest as potential antitumor agents. Furthermore we investigated the chemical and photochemical reactivities of compounds (**4**) which, according to the literature on diazoazoles,[10,11] could be worthy synthons in heterocyclic chemistry.

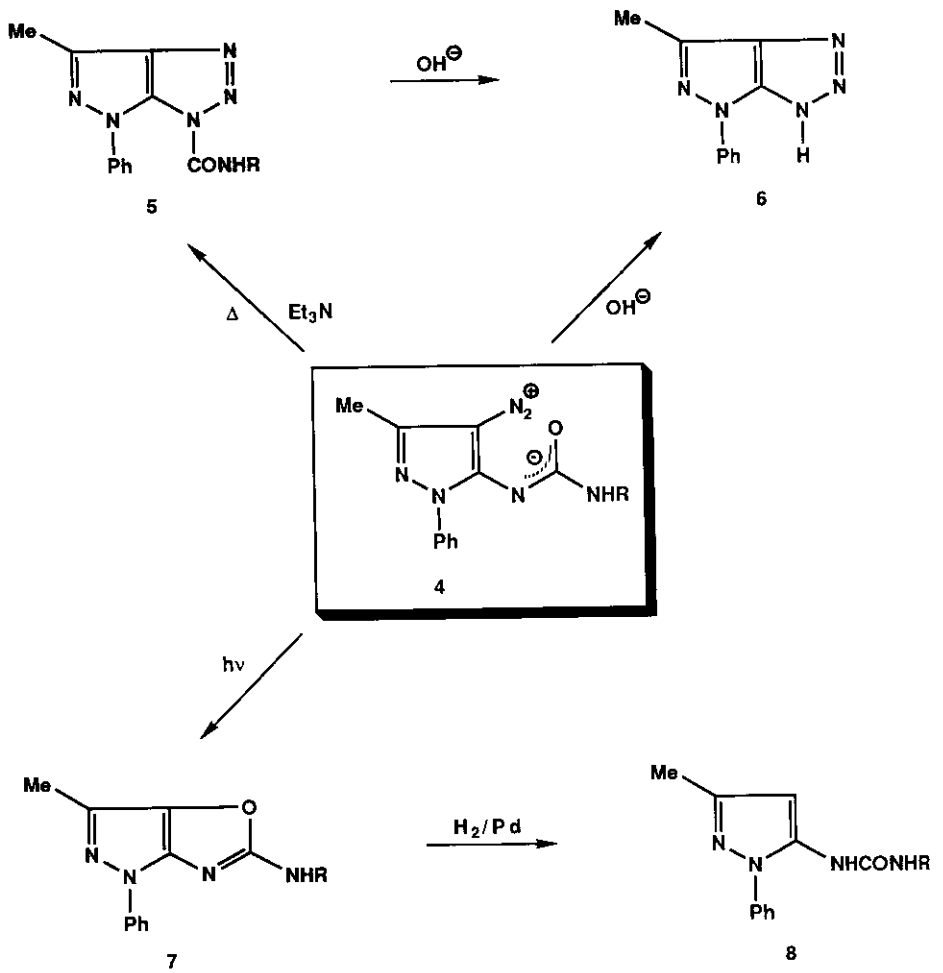
The target products (**4**) were prepared as shown in Scheme 1. The reaction of pyrazolo[4,3-*c*][1,2,5]oxadiazin-3(5H)-one[12] (**1**) with methylamine and benzylamine afforded the green coloured N-alkyl-N'-(4-nitroso-5-pyrazolyl)ureas (**2**).[13] Reduction of **2** with hydrazine hydrate in the presence of palladized charcoal gave the corresponding N-alkyl-N'-(4-amino-5-pyrazolyl)ureas (**3**). Treatment of **3** with one equivalent of sodium nitrite in acetic acid provided the required diazo derivatives which exist in the zwitterionic structure (**4**).



R= Me, CH_2Ph

Scheme 1

This structure is supported by the following spectral data: infrared spectra show a sharp absorption peak at 2140-2120 cm^{-1} indicating the presence of a diazo group; the ^1H-nmr spectra evidence the absence of the absorption by the NH group linked to ring. The key feature of the ^{13}C-nmr spectrum of **4a** is the shift value (71 ppm) of the carbon atom in position 4. The upfield shift of this diazo carbon agrees with the data previously reported for analogous structures.[14] Compounds (**4**) are crystalline yellow solids which are quite stable when stored at room temperature and sheltered from light.



R= Me, CH_2Ph

Scheme 2

When heated under reflux in anhydrous tetrahydrofuran in the presence of triethylamine, compounds (**4**) afforded fluorescent white products which were characterized as pyrazolo[3,4-*d*][1,2,3]triazole-1-(N-alkyl)carboxamides (**5**) (Scheme 2). The alkaline hydrolysis of both diazo derivatives (**4**) and carboxamides (**5**) gave nearly quantitative yields of the same product, the known pyrazolo[3,4-*d*]-[1,2,3]triazole (**6**).[15,16]

When ethanolic solution of **4** was irradiated with a 250 W mercury lamp for 2 h, 5-alkylaminopyrazolo[3,4-*d*]oxazoles (**7**) were obtained in high yields. Compounds (**7**) could be generated by the intramolecular nucleophilic attack of the $C\text{-}O^{\ominus}$ of **4** to the C_4 cation formed by the N_2 loss.[17] Evidence for the structure of compounds (**7**) was obtained from analytical and spectral data (see Experimental) and from their catalytic reduction which led to the oxazole ring opening affording the N-alkyl-N'-5-pyrazolylureas (**8**).

Biological tests on the compounds (**4**) are in progress and will be reported in due course.

EXPERIMENTAL

Melting points were determined using a Reichert Köfler block and are uncorrected. The ir spectra were recorded from potassium bromide discs on a Perkin-Elmer 299B spectrophotometer. The ^{1}H-nmr and ^{13}C-nmr spectra were recorded on a Bruker AC 200 spectrometer; chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane as internal standard and coupling constans in Hz. For column chromatography, silica gel (Kieselgel 60 Merck, 70-230 mesh ASTM) was used. The irradiation of the samples was performed with the light of a T Q 120K Hanau mercury lamp.

N-Methyl-N'-(4-nitroso-3-methyl-1-phenylpyrazol-5-yl)urea (2a).

A 40% solution of methylamine in water (0.91 ml, 11 mmol) was added dropwise to a stirred solution of **1** (2.28 g, 10 mmol) in tetrahydrofuran (50 ml). After stirring for 20 min, the solution was acidified with 2N hydrochloric acid and the solvent was evaporated. Yield 2.0 g, 77%, mp 162-163°C (toluene); ir (KBr) cm^{-1}: 3340, 1650, 1555; ^{1}H-nmr (DMSO-d_6) δ: 2.50 (s, 3H, Me), 2.60 (d, J=4.5 Hz, 3H, NMe), 7.00 (q, J=4.5 Hz, 1H, NH), 7.40-7.67 (m, 5H, Ph), 10.20 (br, 1H, NH). Anal. Calcd for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.01. Found: C, 55.25; H, 5.17; N, 26.80.

N-Benzyl-N'-(4-nitroso-3-methyl-1-phenylpyrazol-5-yl)urea (2b).

This compound was prepared by reacting **1** with benzylamine, according to the procedure described for **2a**. Yield 87%, mp 134-135°C (toluene) (lit.,[18] mp 134-135°C); ir (KBr) cm^{-1}: 3340, 3360, 1700, 1560, 1540, 1520; ^{1}H-nmr ($CDCl_3$) δ: 2.58 (br, 3H, Me), 4.26 (d, J=5.5 Hz, 2H, CH_2), 7.11-7.48 (m, 11H, 2Ph + 1NH), 9.93 (br, 1H, NH). Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.62; H, 5.21; N, 20.64.

N-Methyl-N'-(4-amino-3-methyl-1-phenylpyrazol-5-yl)urea (3a).
99% Hydrazine hydrate (0.98 ml, 20 mmol) and 5% palladized charcoal (0.30 g) were added to a solution of **2a** (1.04 g, 4 mmol) in methanol (80 ml). After heating under reflux for 5 min, the catalyst was filtered off and the filtrate was evaporated to a solid residue that was purified by recrystallization from ethyl acetate. Yield 0.93 g, 95%, mp undetected (decomposition at 100°C); ir (KBr) cm^{-1}: 3300, 1640, 1600, 1500; ^{1}H-nmr (DMSO-d_6) δ: 2.14 (s, 3H, Me), 2.61 (d, J=4.5 Hz, 3H, NMe), 3.64 (br s, 2H, NH_2), 6.13 (q, J=4.5 Hz, 1H, NH), 7.25-7.53 (m, 5H, Ph), 7.87 (br s, 1H, NH); ^{13}C-nmr (DMSO-d_6) δ: 11.53 (q, J=126 Hz, Me), 26.56 (q, J=136 Hz, Me), 121.77 (d, J=159 Hz, Ph), 122.51 (s, C-NH), 124.86 (s, C-NH), 125.38 (d, J=158 Hz, Ph), 128.75 (d, J=160 Hz, Ph), 138.53 (s, C-3), 139.51 (s, Ph), 156.22 (s, CO). Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.94; H, 6.06; N, 28.38.

N-Benzyl-N'-(4-amino-3-methyl-1-phenylpyrazol-5-yl)urea (3b).
This compound was obtained by reduction of **2b** according to the procedure described for **3a**. Yield 98%, mp 183-184°C (ethyl acetate); ir (KBr) cm^{-1}: 3300, 1650, 1560, 1505; ^{1}H-nmr (DMSO-d_6) δ: 2.11 (s, 3H, Me), 3.66 (br s, 2H, NH_2), 4.23 (d, J=5.8 Hz, 2H, CH_2), 6.75 (t, J=5.7 Hz, 1H, NH), 7.15-7.50 (m, 10H, 2Ph), 7.90 (s, 1H, NH). Anal. Calcd for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.61; N, 27.01. Found: C, 60.38; H, 6.44; N, 27.26.

N-Methyl-N'-(4-diazo-3-methyl-1-phenylpyrazol-5-yl)urea (4a).
A solution of sodium nitrite (0.31 g, 4.4 mmol) in water (5 ml) was added dropwise to a stirred solution at 0°C of **3a** (0.98 g, 4 mmol) in a mixture of 1N hydrochloric acid (40 ml) and methanol (50 ml). After stirring for 2 h, the mixture was made alkaline with 20% ammonium hydroxide and the yellow precipitate was collected and washed with water. Yield 0.73 g, 71%, mp 180-181°C (methanol); ir (KBr) cm^{-1}: 3280, 2150, 1645, 1630, 1545; ^{1}H-nmr ($CDCl_3$) δ: 2.36 (s, 3H, Me), 2.81 (d, J=5.0 Hz, 3H, NMe), 5.30 (br q, J=5.0 Hz, 1H, NH), 7.20-7.44 (m, 3H, Ph), 7.82-7.86 (m, 2H, Ph); ^{13}C-nmr (DMSO-d_6) δ: 11.88 (q, J=129 Hz, Me), 26.41 (q, J=139 Hz, Me), 71.00 (s, C-4), 122.42 (d, J=166 Hz, Ph), 125.72 (d, J=162 Hz, Ph), 128.88 (d, J=161 Hz, Ph), 139.86 (s, Ph), 146.76 (s, C-3), 153.79 (s, C-5), 164.29 (s, CO). Anal. Calcd for $C_{12}H_{12}N_6O$: C, 56.24; H, 4.72; N, 32.79. Found: C, 56.47; H, 4.58; N, 32.48.

N-Benzyl-N'-(4-diazo-3-methyl-1-phenylpyrazol-5-yl)urea (4b).
This compound was prepared by diazotization of **3b** according to the procedure described for **4a**. Yield 96%, mp 146-147°C (methanol); ir (KBr) cm^{-1}: 3250, 2120,

1610, 1520, 1485; ^{1}H-nmr ($CDCl_3$) δ: 2.41 (s, 3H, Me), 4.48 (d, J=6.0 Hz, 2H, CH_2), 5.68 (t, J=6.0 Hz, 1H, NH), 7.23-7.47 (m, 8H, Ph), 7.88 (d, J=8.0 Hz, 2H, Ph). Anal. Calcd for $C_{18}H_{16}N_6O$: C, 65.05; H, 4.85; N, 25.29. Found: C, 65.30; H, 4.93; N, 25.50.

4-Methyl-6-phenylpyrazolo[3,4-*d*][1,2,3]triazole-1-(N-methyl)-carboxamide (5a).

A solution of **4a** (0.77 g, 3 mmol) and triethylamine (0.1 ml, 0.7 mmol) in anhydrous tetrahydrofuran (50 ml) was heated under reflux for 8 h. The solvent was evaporated and the solid residue was submitted to column chromatography (eluent: ethyl acetate / light petroleum 8:2 v/v). The fractions having Rf=0.8 were pooled and evaporated to give a fluorescent white solid characterized as **5a**. Yield 0.35 g, 46%, mp 175-176°C (ethyl acetate); ir (KBr) cm^{-1}: 3480, 1760, 1560, 1530, 1505; ^{1}H-nmr (DMSO-d_6) δ: 2.56 (s, 3H, Me), 2.91 (d, J=4.6 Hz, 3H, NMe), 7.29-7.61 (m, 3H, Ph), 7.96-8.00 (m, 2H, Ph), 9.17 (q, J=4.6 Hz, 1H, NH); ^{13}C-nmr (DMSO-d_6) δ: 13.29 (q, J=129 Hz, Me), 26.90 (q, J=138 Hz, Me), 116.20 (d, J=163 Hz, Ph), 125.13 (d, J=162 Hz, Ph), 126.82 (s, C-6a), 129.56 (d, J=155 Hz, Ph), 130.81 (s, C-4), 137.81 (s, Ph), 147.64 (s, C-3a), 156.35 (s, CO). Anal. Calcd for $C_{12}H_{12}N_6O$: C, 56.24; H, 4.72; N, 32.79. Found: C, 56.00; H, 4.84; N, 32.87.

4-Methyl-6-phenylpyrazolo[3,4-*d*][1,2,3]triazole-1-(N-benzyl)-carboxamide (5b).

This compound was prepared from **4b** according to the procedure described for **5a**. Yield 42%, mp 148-150°C (ethanol); ir (KBr) cm^{-1}: 3360, 1740, 1600, 1550, 1520; ^{1}H-nmr ($CDCl_3$) δ: 2.70 (s, 3H, Me), 4.71 (d, J=6.1 Hz, 2H, CH_2), 7.24-7.53 (m, 9H, Ph + NH), 8.05-8.09 (m, 2H, Ph). Anal. Calcd for $C_{18}H_{16}N_6O$: C, 65.05; H, 4.85; N, 25.29. Found: C, 64.86; H, 4.82; N, 25.17.

4-Methyl-6-phenylpyrazolo[3,4-*d*][1,2,3]triazole (6).

A solution of **5a** (0.51 g, 2 mmol) in 1N methanolic potassium hydroxide (30 ml) was heated under reflux for 15 min. The solvent was evaporated, the residue was taken up with water and acidified with 2N hydrochloric acid. The product was collected, dried over phosphorous pentoxide and purified by recrystallization. Yield 0.38 g, 96%; mp 208°C (benzene). The product was identical to that obtained by the known methods.[15,16]

By the same procedure each compound (**5b**), (**4a**) and (**4b**) gave **6**; yields ranged from 90% to 98%.

5-Methylamino-3-methyl-1-phenylpyrazolo[3,4-*d*]oxazole (7a).

A solution of **4a** (1,02 g, 4 mmol) in ethanol (280 ml) and water (50 ml) was irradiated for 2 h with a mercury lamp. The organic layer was evaporated and the precipitate was collected. Yield 0.92 g, 90%; mp 145-146°C (*tert*-butyl methyl ether); ir (KBr) cm^{-1}: 3300, 3210, 1660, 1580, 1540, 1510; ^{1}H-nmr ($CDCl_3$) δ: 2.40 (s, 3H, Me), 3.08 (d, J=4.8 Hz, 3H, NMe), 5.37 (br q, J=4.8 Hz, 1H, NH), 7.13-7.94 (m, 5H, Ph); ^{13}C-nmr (DMSO-d_6) δ: 11.44 (q, J=127 Hz, Me), 28.77 (q, J=138 Hz, Me), 116.33 (d, J=163 Hz, Ph), 124.50 (d, J=154 Hz, Ph), 127.62 (s, C-3), 129.36 (d, J=159 Hz, Ph), 133.92 (s, C-6a), 139.02 (s, Ph), 149.08 (s, C-3a), 167.65 (s, C-5). Anal. Calcd for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.32; H, 5.18; N, 24.78.

5-Benzylamino-3-methyl-1-phenylpyrazolo[3,4-*d*]oxazole (7b).

This product was obtained from **4b** according to procedure described for **7a**. Yield 88%, mp 137-139°C (*tert*-butyl methyl ether); ir (KBr) cm^{-1}: 3300, 1640, 1580, 1545, 1510; ^{1}H-nmr ($CDCl_3$) δ: 2.39 (s, 3H, Me), 4.63 (d, J=5.7 Hz, 2H, NCH_2), 5.49 (br s, 1H, NH), 7.12-7.44 (m, 8H, Ph), 7.94 (d, J=8.2 Hz, 2H, Ph). Anal. Calcd for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. Found: C, 69.87; H, 5.40; N, 18.40.

N-Methyl-N'-(3-methyl-1-phenylpyrazol-5-yl)urea (8a).

A solution of **7a** (0.91 g, 4 mmol) in a mixture of methanol (80 ml) and acetic acid (4 ml) was hydrogenated for 2 h in the presence of 5% palladized charcoal (0.10 g). The catalyst was filtered off and the filtrate was evaporated to a solid residue which was recrystallized from ethyl acetate. Yield 0.78 g, 85%, mp 192-193°C; ir (KBr) cm^{-1}: 3330, 3280, 1650, 1595, 1505; ^{1}H-nmr (DMSO-d_6) δ: 2.16 (s, 3H, Me), 2.58 (d, J=4.5 Hz, 3H, NMe), 6.15 (s, 1H, CH), 6.34 (q, J=4.5 Hz, 1H, NHMe), 7.36-7.49 (m, 5H, Ph), 8.22 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6) δ: 13.74 (q, J=127 Hz, Me), 26.21 (q, J=138 Hz, Me), 98.97 (d, J=178 Hz, C-4), 123.87 (d, J=160 Hz, Ph), 126.91 (d, J=156 Hz, Ph), 129.07 (d, J=161 Hz, Ph), 138.19 (s, C-5), 138.58 (s, Ph), 147.71 (s, C-3), 155.02 (s, CO). Anal. Calcd for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.32; H, 6.20; N, 24.52.

N-Benzyl-N'-(3-methyl-1-phenylpyrazol-5-yl)urea (8b).

This compound was prepared by reduction of **7b** according to the procedure described for **8a**. Yield 80%, mp 212-14°C (ethyl acetate); ir (KBr) cm^{-1}: 3300, 1640, 1585, 1570, 1520, 1505; ^{1}H-nmr (DMSO-d_6) δ: 2.16 (s, 3H, Me), 4.23 (d, J=5.7 Hz, 2H, NCH_2), 6.19 (s, 1H, CH), 6.98 (br t, J=5.7 Hz, 1H, NH), 7.19-7.49 (m, 10H, 2Ph), 8.29 (s,

1H, NH). Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.33; H, 5.80; N, 18.41.

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