Azo Compounds Derived from 1H-5-amino-4-ethoxycarbonyl-3-methylpyrazole and Phenols or Phenolic Derivatives and Possibilities of Their Cyclization to Pyrazolo[5,1-c]benzo[1,2-e][1,2,4]triazines

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The coupling reaction of 1H-4-ethoxycarbonyl-3-methylpyrazol-5-yl-diazonium chloride (2) with phenols and phenolic derivatives leads to 1H-5-arylazo-4-ethoxycarbonyl-3-methylpyrazoles, which were characterized by TLC, MS, IR, VIS, 1H-NMR and 13C-NMR spectroscopy. The cyclization of one of the synthesized azo compounds [1H-4-ethoxycarbonyl-5-(4,6-dimethoxy-2-hydroxy-phenylazo)-3-methylpyrazole] led to the corresponding pyrazolo[5,1-c][1,2,4]triazinic derivative.

Keywords: azo compounds, 1H-4-ethoxycarbonyl-3-methylpyrazol-5-yl-diazonium chloride, 1H-5-amino-4-ethoxycarbonyl-3-methylpyrazole, pyrazolo[5,1-c][1,2,4]triazines.

This work is part of our studies on the synthesis and properties of polycondensed heterocyclic systems, pyrazolo[5,1-c][1,2,4]triazine and pyrazolo[5,1-c][benzo[1,2-e]][1,2,4]triazine [1,2].

The literature includes a relatively large number of pyrazolyl-azo-phenolic dyes, obtained mainly through the coupling of aromatic or heterocyclic diazonium salts to the reactive position (4) of pyrazole and 5-pyrazolone compounds [3-10], but also through condensation reactions [11-16]. These 4-aryl(hetaryl)-azo-pyrazoles are used as pigments and dyes [5,15], fluorescent brightening agents [3], ligands [4,6-10], compounds with antimicrobial activity [9,11,12], intermediated in the synthesis of polycondensed heterocyclic systems [16].

Surprisingly, azo compounds derived from 3(5)-amino-pyrazoles are scarcely reported in the literature, probably due to, among other things, their limited availability. Thus, to our knowledge, the literature includes only azo compounds obtained through the coupling of diazonium salts obtained from 3(5)-amino-pyrazoles with naphthols, phenols or aromatic ethers [17-20], and azo compounds obtained through the coupling of diazonium salt derived from 5-amino-4-ethoxycarbonyl-3-methyl-pyrazole with phenols, naphthols and phenolic derivatives, published by us previously [1,2]. A singular case is represented by the intramolecular coupling of a 3,4-disubstituted 1-aryl-5-amino-pyrazole, with the formation of a pyrazolo[3,4-c]-cinnoline [21].

Previously it was proved that in the coupling of 1H-4-ethoxycarbonyl-3-methylpyrazol-5-yl-diazonium chloride (2) with reactive phenols (resorcinol, phloroglucine) the corresponding azo compounds (4) cannot be isolated, because of their cyclization to the corresponding pyrazolo[5,1-c][benzo[1,2-e]][1,2,4]triazines (5) [1], and recently it was also shown that the azo dyes derived from the diazonium salt of 1H-3-amino-4-ethoxycarbonylpyrazole and aromatic ethers can be cyclized to the corresponding pyrazolo[5,1-c][benzo[1,2-e]][1,2,4]triazines (5) [20].

For the investigation of the effect of the substituents on the phenolic rings on the cyclization reaction to pyrazolo[5,1-c][benzo[1,2-e]][1,2,4]triazines (5), a number of 8 new azo compounds (4a-h) were synthesized through the coupling of 1H-4-ethoxycarbonyl-3-methylpyrazol-5-yl-diazonium chloride (2) with phenols and phenolic derivatives (3) (scheme 1).

Scheme 1. Coupling of 1H-4-ethoxycarbonyl-3-methylpyrazol-5-yl-diazonium chloride (2) with phenols and phenolic derivatives (3).

R=H, X,Y=3,4(MeO)2 (3a); R=OMe, X=H, Y=4-Me,N (3b); R=H, X=H, Y=4-Me,N (3c); R=X=H, Y=4-COOCH3 (3d); R=H, X=3-OH, Y=4-COOH(3e); R=H, X=H, Y=4-NH2 (3f); R=H, X=4-COOCH2(3g); R=H, X=H, Y=4-NO2 (3h)

R=H, X,Y=3,4(MeO)2 (4a); R=Me, X=H, Y=5-NMe2 (4b); R=H, X=H, Y=5-NMe2 (4c); R=X=H, Y=5-COOCH3 (4d); R=H, X=4-OH, Y=5-COOH (4e); R=H, X=H, Y=5-NH2 (4f); R=H, X=H, Y=5-COOCH2(4g); R=H, X=H, Y=5-NO2 (4h)

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R=H, X,Y=3,4(MeO)2 (4a); R=Me, X=H, Y=5-NMe2 (4b); R=H, X=H, Y=5-NMe2 (4c); R=X=H, Y=5-COOCH3 (4d); R=H, X=4-OH, Y=5-COOH (4e); R=H, X=H, Y=5-NH2 (4f); R=H, X=H, Y=5-COOCH2(4g); R=H, X=H, Y=5-NO2 (4h)
The preparation of 1H-4-ethoxycarbonyl-3-methyl-pyrazol-5-il-diazonium chloride (2) was performed following the indications from literature [22,23], and the coupling with phenolic derivatives (3a-j) was carried out in aqueous-alcoholic solution, at pH = 10-11 or in an organic solvent in the presence of pyridine. The mass spectra, IR spectroscopic analysis, 1H-NMR, 13C-NMR and MS confirm the structure of these compounds, while the visible spectra display an intense absorption maximum characteristic to the azo group between 340-404 nm.

The preliminary attempts to cyclize the azo dye (4a) were carried out by refluxing in cyclohexanol or in acetic acid, in the presence of p-toluenesulfonic acid.

Experimental part
Materials and instruments
Phenols (3f,h) utilized were commercial products (Merck, Fluka) and used as received, while the following were obtained according to the literature [23], [25], [26], [27], [28], [29].

A mixture of 0.85g (5 mmol) 1H-5-aminolethoxycarbonyl-3-methyl-pyrazole (1) was prepared following the indications from literature [23].

Melting points were determined on a Böetius PHMK apparatus (Vebl Analitik Dresden), and thin-layer chromatography was performed on 60F<sub>254</sub> Merck silicagel plates using benzene:metanol = 7:3 (vol) as eluant.

The mass spectra ESI-MS were recorded on a Varian GC-MS instrument using methanol as carrier.

The UV-VIS spectra were recorded in methanolic solution on a Jasco instrument using methanol as carrier.

The IR spectra were recorded in KBr pellet on a Jasco FT/IR-410 spectrophotometer, and the electronic spectra in visible were recorded in methanolic solution on a Varian V-530 UV/VIS spectrophotometer. 1H- and 13C-NMR spectra were recorded on a Bruker Avance AC200 spectrometer at 25°C in DMSO-d<sub>6</sub>, using TMS as reference, the chemical shifts being expressed in ppm and the coupling constants in Hz.

Procedures
Preparation of 1H-4-ethoxycarbonyl-3-methyl-pyrazol-5-il-diazonium chloride (2)

A mixture of 0.85g (5 mmol) 1H-5-amino-4-ethoxycarbonyl-3-methyl-pyrazole (1), 1.1 mL water and 1.5 mL concd. HCl is heated to approximately 40°C, filtered with active charcoal and the obtained solution is cooled to 0-5°C. To the fine suspension formed a solution containing 0.36 g (6 mmol) NaNO<sub>2</sub> in 1.4 mL water is added dropwise under stirring over a period of about 15 min. The solution of diazonium salt (2) thus obtained is treated with active charcoal and filtered cold, being used immediately in the coupling step.

Coupling of 1H-4-ethoxycarbonyl-3-methyl-pyrazol-5-il-diazonium chloride (2) with phenols (3a-h)

Method A

To a solution of 5 mmoles phenol (3a,d,f-h) in 5 mL ethanol and 18 mL sol. NaOH 5% the solution of diazonium salt (2) is added dropwise under stirring, at 0-5°C. The colored solution (suspension) formed (pH = 10-11) is kept for half an hour at room temperature, then diluted with 10 mL water and brought to pH = 1 with HCl 15%, and the suspension formed is filtered. Products (4) were purified by recrystallization.

Method B

To a solution of 5 mmoles phenol (3a-f) in 10 mL acetone or 5 mmoles phenol (3f) in 10 mL isopropanol and 3 mL pyridine, the solution of diazonium salt (2) is added dropwise under stirring, at 0.5°C. The colored solution formed is kept for half an hour at room temperature, then diluted with 10 mL water, brought to pH = 1 with HCl 15%, and filtered (4a,d) or extracted with 3 x 10 mL chloroform (4b,c). The chloroform solution is washed successively with 2 x 5 mL HCl 2M, 5 mL water, dried on Na<sub>2</sub>O, then concentrated to dryness. Products (4) were purified by recrystallization.

Cyclization of 1H-5-(4,6-dimethoxy-2-hydroxy-phenylazo)-4-ethoxycarbonyl-3-methyl-pyrazole (4a)

This was performed by heating 1 g compound 4a in 10 mL cyclohexanol for 7 h at reflux, followed by distillation to dryness and recrystallization from ethyl alcohol (procedure 1), or by heating to reflux a mixture of 2 mmoles compound 4a and 0.2 mmoles p-toluenesulfonic acid in 10 mL CH<sub>3</sub>COOH for 3 h, followed by cooling and filtration (procedure 2), respectively.

Results and discussions
Characterization of compounds
1H-5-(4,6-dimethoxy-2-hydroxy-phenylazo)-4-ethoxycarbonyl-3-methyl-pyrazole (4a)

Orange powder, m.p. 214-217°C; 72% (method A)

Brick-red crystals; 82% m.p. 213-216°C (method B)

ESI-MS (M/z): 355 (M+1), 289 [M-45 (C,H,O)]

ESI-MS (M/z): 335 (M+1), 289 [M-45 (C,H,O)]

UV-VIS: λ max [nm] (ε x 10<sup>4</sup>): 305.5 (2.54)

IR (KBr): 3427, 3255, 3062, 2985, 2938, 2361, 1683, 1636, 1595, 1540, 1455, 1410, 1282, 1230, 1205, 1157, 1124, 1056, 1015, 933, 869, 835, 786, 695, 605, 574, 545, 525, 514.

1H-NMR<sub>δ</sub> (DMSO-d<sub>6</sub>, 200 MHz): 15.53 (s, 1H, -NH); 6.05 (d, 1H, J=2.1Hz, 5H); 5.97 (d, 1H, J=2.1Hz, 3H); 2.17 (s, 3H, -CH<sub>3</sub>); 1.31 (t, 3H, J=7.1Hz, -O-CH<sub>2</sub>-CH3).

13C-NMR<sub>δ</sub> (DMSO-d<sub>6</sub>, 200 MHz): 157.7 (C=O); 162.6 (C); 161.9 (C); 159.7 (C); 146.5 (C); 144.1 (C); 130.2 (C); 59.9 (C); 57.0 (C).

1H-5-(5-N,N-dimethylamino-2-methoxy-phenylazo)-4-ethoxycarbonyl-3-methyl-pyrazole (4b)

Red-brick powder, m.p. 228-234°C; 60% (method B)

ESI-MS (M/z): 317 (M), 288 [M-29 (C,H,O)]

UV-VIS: λ max [nm] (ε x 10<sup>4</sup>): 341 (1.44)
Scheme 2. Cyclization of 1H-5-(4,6-dimethoxy-2-hydroxy-phenylazo)-4-ethoxycarbonyl-3-methyl-pyrazole (4a)

IR (KBr): 3199m, 2981m, 1713i, 1583s, 1555s, 1505m, 1447m, 1380s, 1323s, 1255i, 1171s, 1106i, 1020s, 945s, 876s, 836s, 776m.

**1H-4-ethoxycarbonyl-5-(2-hydroxy-5-methoxycarbonyl-phenylazo)-3-methyl-pyrazole (4d)**
Orange powder, m.p. 192-194°C; \( \eta = 36\% \) (method B)
Black crystals, m.p. 201-214°C; \( \eta = 94\% \) (method A)

IR (KBr): 3270i, 2931m, 2856m, 1703i, 1616m, 1552i, 1477m, 1437i, 1371i, 1292m, 1236i, 1165i, 1061i, 978m, 881s, 851s, 789m, 754s, 640s, 477s.

**1H-5-(5-carboxy-2,4-dihydroxy-phenylazo)-4-ethoxycarbonyl-3-methyl-pyrazole (4e)**
Black powder, m.p. 175°C (dec.); \( \eta = 29\% \) (method A)

IR (KBr): 3422s, 3064s, 2983s, 2936s, 2879s, 2685m, 1681m, 1524i, 1458i, 1275i, 1231m, 1132i, 1109i, 1063s, 1012s, 784s, 752s, 679s.

**1H-5-(5-amino-2-hydroxy-phenylazo)-4-ethoxycarbonyl-3-methyl-pyrazole (4f)**
Black powder, m.p. 147-150°C (dec.); \( \eta = 29\% \) (method A)

IR (KBr): 3427m, 2931m, 2985m, 1703i, 1616m, 1552i, 1449m, 1417i, 1306m, 1260m, 1138m, 1086m, 1023s, 966s, 806s, 81i, 681s, 603s.

**1H-4-ethoxycarbonyl-5-(5-ethoxycarbonyl-2-hydroxy-phenylazo)-3-methyl-pyrazole (4g)**
Orange powder, m.p. 192-194°C; \( \eta = 96\% \) (method A)

UV VIS: \( \lambda \) max [nm] (\( \epsilon \) x 10^4): 393 (1.27)

**6,8-dimethoxy-3-ethoxycarbonyl-2-methyl-benzo[1,2-e]pyrazolo[5,1-c][1,2,4]triazine (5a)** (procedure 1)
Brick-red powder; \( \eta = 87.5\% \)

**M.p.** 210-214°C

**ESI-MS** (M/z): 317 (M+1), 289.1 (M-28; H2C=CH2), 288 (M-29; H2C=CH2 + H)

**GC-MS** (M/z): 316 (M 100%), 286 [M-30; 13% (CH2O)], 257 [M=45; 32% (C2H5O)]

**UV VIS** \( \lambda \) max [nm] (\( \epsilon \) x 10^4): 394 (1.991)

**IR** (KBr): 3421s, 3054s, 2980s, 2934s, 2905s, 2730m, 1707m, 1621i, 1557i, 1472m, 1449m, 1418s, 1375m, 1308s, 1270s, 1206i, 1186m, 1127i, 1086s, 1031s, 940s, 912s, 849s, 786s, 765s, 655s.

**1H-NMR** (DMSO-d6, 200 MHz): 7.10 (d, 1H, J=1.5Hz, 10H): 6.76(d, 1H, J=1.5Hz, 12H); 4.39(q, 2H, J=7.1Hz, -O-CH-CH3); 4.08(s, 6H, -OH-CH2); 2.70(s, 3H, -3-C3H3); 1.39(t, 3H, J=7.1Hz, -O-CH-CH3).

**13C-NMR** (DMSO-d6, 50 MHz): 162.2 (>C=O); 159,3 (13-C); 155,6 (12-C); 146,4(9-C); 99,2(10-C), 99,1(10-C); 92,8(4-C); 59,9(-O-CH3); 56,6(2x-O-CH3); 14,5(-O-CH2-CH3); 14,2(3-C3H3).

6,8-dimethoxy-3-ethoxycarbonyl-2-methyl-benzo[1,2-e]pyrazolo[5,1-c][1,2,4]triazine (5a) (procedure 2)
Brick-red powder; \( \eta = 94\% \)

**M.p.** 210-220°C

**UV VIS** \( \lambda \) max [nm] (\( \epsilon \) x 10^4): 395 (1.953)

**IR** (KBr): 3420s, 3077s, 3052s, 2981s, 2935s, 1727m, 1707m, 1619i, 1582s, 1557i, 1533s, 1472m, 1452m, 1443m, 1419s, 1379m, 1309s, 1273m, 1297i, 1174m, 1129i, 1087s, 1031s, 982s, 940s, 912s, 850s, 786s, 765s, 684s.

**Conclusions**

The coupling reaction of 1H-4-ethoxycarbonyl-3-methyl-pyrazol-5-5-il-diazonium chloride (2) with phenols and phenolic derivatives leads, in most cases, to the formation of azo compounds (4), with reaction yields between 37-82%. The obtained products show azo pigments properties, having their \( \lambda \) max values in the 340-404 nm range, values that are specific for this class of compounds.

The coupling of 1H-4-ethoxycarbonyl-3-methyl-pyrazol-5-il-diazonium chloride (2) with \( p \)-amino-phenol leads to an unitary product, as yet unidentified, which does not display the characteristics expected for the normal coupling product, 1H-5-(5-amino-2-hydroxyphenylazo)-4-ethoxycarbonyl-3-methyl-pyrazole (4f).

The attempt to cyclize the azo compound 4a to pyrazolo[5,1-c]benzo[1,2-e][1,2,4]triazine (5a) succeeded due to the presence on the phenol ring of substituents having +E and +I effect, i.e., -OH and -OCH3, respectively.

This shows that their effect is sufficient to shift the nucleus into the enol form, which allows for the
nucleophilic attack of the pyrazole -NH- group (similarly to the mechanism of the Bücherer reaction), as it is the case for the compounds containing two or three -OH groups attached to the benzene ring, which can be cyclized as previously reported (X = H, Y = 4-OH; X = 4-OH, Y = 6-OH) [1], their tendency to display the tautomeric enol form being known.

The attempt to cyclize the azo compound 4a using the method recently reported in the literature [20] lead to product 5a, identical to the one obtained by refluxing in cyclohexanol. The facts supporting the formation of 5a are the following:

- the shift of $\lambda_{\text{max}}$ (~5 nm) in the VIS spectrum relative to the initial compound;
- the disappearance of the valence vibration characteristic for the amino group ($\nu_{\text{NH2}}$ 3255 cm$^{-1}$);
- the presence of the molecular peak in the GC-MS spectra and of M+1 in the ESI-MS spectra. It is worth mentioning that the starting material (4a) displays in the GC-MS spectrum a molecular peak M-18, which is the cyclized product (5a), and shows the same defragmentation behaviour.
- chemical shifts (δ) for the endociclic -NH- group of the compound 4a at 15.53 p.p.m. disappears in the ¹H-NMR spectra of the compound 5a.

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