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POLYCONDENSED NITROGEN HETEROCYCLES. PART XIV[1]. REACTIVITY OF 3-DIAZOPYRROLES: PYRROLO [3,4-c] PYRIDAZINE

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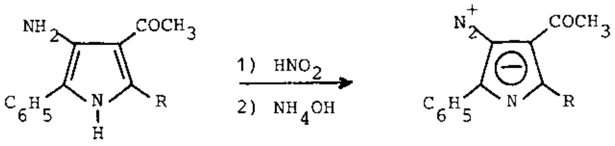
Abstract- 3-Diazopyrroles 2a,b were prepared in excellent yields by diazotization of the corresponding amines 1a,b.
Compounds 2a,b, by acid catalyzed intramolecular coupling reaction led to the new ring system pyrrolo [3,4-c] pyridazine 3a,b.

In view of the several biological properties and herbicide activity[2] of cinnoline derivatives, we recently synthetized 1-substituted pyrrolo [3,2-c] cinnolines[3], which demonstrate to inhibite the germination of seeds of Echinochloa crus-galli. In order to search structure-activity relationship, we became interested in the synthesis of 1-unsubstituted pyrrolo [3,2-c] cinnoline derivatives.
On the basis of the reaction used by Angelico in the synthesis of pyrrolo [3,4-c]-cinnolines[4], the diazopyrroles of type 2 appeared to be suitable intermediates for the purpose in mind.
Therefore the diazotization of the amino derivatives 1a,b afforded the 3-diazopyrroles 2a,b in good yield (75-80%). These products were quite stable if sheltered from the light.

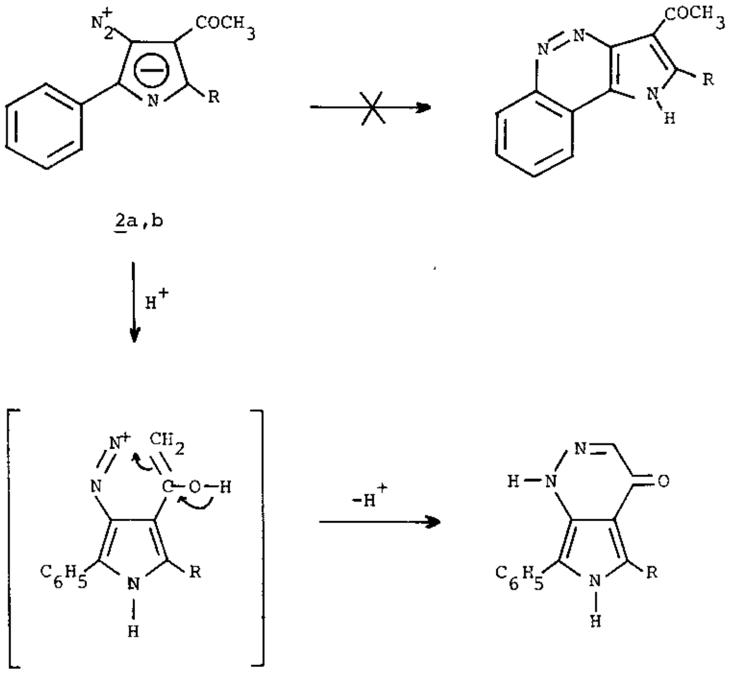


1a,b 2a,b

a R = CH_3; b R = C_6H_5.

The structure of diazopyrroles 2 was assigned on the basis of elemental analyses, molecular weight, determined by mass spectrometry, as well as ir and nmr data. In fact the ir spectra didn't show any absorption in the NH stretching region, but exhibited a strong band in the triple bond range at 2130-2120 cm^{-1} attributable to diazo group. The nmr spectra only showed signals due to the aromatic and CH_3 protons.

According to the Angelico's reaction[4], the diazopyrrole 2a has been refluxed with sulphuric acid: 1H-pyrrolo[3,2-c]cinnoline couldn't be found, but the main product isolated (yield 30%) was identified as 5-methyl-7-phenyl-1,6-dihydropyrrolo-[3,4-c]pyridazin-4-one 3a. In fact the ir spectrum showed two broad bands at 3390 and 3210 cm^{-1} due to the pyridazine and pyrrole NH stretchings and a broad band at 1615 cm^{-1} attributable to the C=O stretching.



2a,b

3a,b

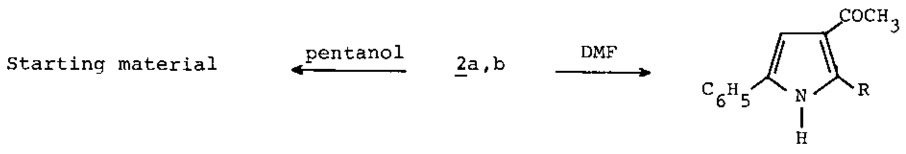
a R = CH_3; b R = C_6H_5.

The nmr spectrum exhibited only a singlet for three protons at 2.67δ and, in addition to the aromatic protons multiplet, two exchangeable singlets at 12.43 and 12.70δ.

Evidently, despite the competing coupling reaction with the phenyl in the 2-position, the diazonium group, formed in sulphuric acid, couples preferentially with the enolic form of the acetyl group, and this did not permit the formation of pyrrolo [3,2-c] cinnoline derivatives.

At this point the path of the reaction was considered and the hypothesis that the preliminary formation of the diazonium group wasn't necessary and that a mesoionic structure of type 2 could equally lead to the pyrrolo [3,4-c] pyridazines 3 was formulated.

To verify this supposition, different experimental conditions that couldn't permit the preliminary formation of the diazonium salt were chosen. Therefore the diazopyrroles 2a,b have been refluxed in pentanol or in an aprotic dipolar solvent like N,N-dimethylformamide. In these conditions no cyclization products were observed but unreacted starting material was isolated when pentanol was used and the pyrroles 4a,b were obtained when DMF was the medium.



4a,b

a R = CH_3; b R = C_6H_5.

These findings suggest that acid catalysis seems to be necessary for the pyridazine ring closure and considering that in sulphuric acid several resinous gums and untractable solids were obtained, the reaction was perfomed in a different acid medium.

Therefore, the diazopyrroles 2a,b have been refluxed in acetic acid: the main products were again the pyrrolo [3,4-c] pyridazines 3a,b (yield 50%).

These experimental data demonstrate that 3-diazopyrroles are unable to couple without the preliminary formation of diazonium salts.

This agrees with the few examples reported in literature on the reactivity of the 3-diazopyrroles which failed to give coupling reaction when it wasn't possible to assume that the diazonium salt was preliminarily formed[4,5]. The sole example of reactivity of the mesoionic form was verified in cycloaddition reaction[6].

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected; ir spectra were determined in nujol mull with a Perkin-Elmer 299 spectrophotometer; uv spectra were recorded in ethanol using a Perkin-Elmer Hitachi 200 spectrophotometer; nmr spectra were obtained with a Varian FT 80 spectrometer (TMS as internal reference). Mass spectra were run on a JEOL JMS-01 SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and 10 KW accelerating voltage. Exact mass measurement were performed at 20,000 resolving power and carried out to an accurancy of ± 10 ppm. The chromatography was performed on columns of silica gel deactivated with water (15%).

Preparation of 2-phenyl-3-amino-4-acetyl-5-methylpyrrole (1a).

This compound was prepared according to the procedure described[7]. It was recrystallized from ethanol, mp 223°C (lit.[7] mp 218-220°C); hydrochloride mp 290-295°C dec.; nmr (DMSO): 2.33 and 2.50 (6H,2s,CH_3), 5.25 (2H,s,exchangeable NH_2), 6.95-7.65 (5H,m,C_6H_5), 10.88 (1H,broad,exchangeable NH)δ; ms M^{+}= 214.

Preparation of 2,5-diphenyl-3-amino-4-acetylpyrrole (1b).

2,5-Diphenyl-3-acetylpyrrole 4b[8] was nitrated by using nitric acid-acetic anhydride mixture in nitromethane at -15°C according to the procedure described previously.[9] 2,5-Diphenyl-3-nitro-4-acetylpyrrole precipitated during the reaction, was filtered off, washed with nitromethane and recrystallized from ethanol, (yield 88%); mp 208°C; ir: 3200 (NH) 1670 (CO) cm^{-1}; nmr (DMSO): 2.31 (3H,s,CH_3), 7.10-7.60 (10H,m,C_6H_5), 12.61 (1H,broad,exchangeable NH)δ; ms M^{+}= 306.308; Anal.Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15; Found: C, 70.76; H, 4.46; N, 9.32.

The reduction of the nitro derivative was performed in ethanol in a Parr apparatus at 45 psi at room temperature and 10% palladium on charcoal as catalyst. After 12 hours the catalyst was filtered off and evaporation of the solution gave compound 1b (yield 73%), mp 203°C; ir: 3440 and 3340 (NH_2) 3200 (NH) 1615 (CO) cm^{-1}; nmr (DMSO): 1.92 ($3H,s,CH_3$), 5.36 (2H,s,exchangeable NH_2) 6.97-7.87 (10H, m,C_6H_5), 11.33 (1H,broad,exchangeable NH) δ; ms M^{+}= 276.221; Anal.Calcd. for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14; Found: C, 78.44; H, 5.99; N, 10.32.

General method for the preparation of 2-phenyl-3-diazo-4-acetyl-5-R-pyrroles (2a,b).

To a solution of amines 1a,b, (10 mmoles) in the minimum volume of acetone, diluted hydrogen chloride (20 mmoles, 0.5 N) was added and then the mixture was cooled at 0°C with stirring. An aqueous solution of sodium nitrite (10 mmoles, 18%) was added dropwise and the reactants were allowed to stir at room temperature for 3 hours. The mixture was neutralized with aqueous ammonia (2 N). In the case of 1a, the mixture was stirred overnight and extracted with diethyl ether (3 x 100 ml). The organic layer, dried on sodium sulphate, was evaporated under reduced pressure and purified by chromatography (eluant light petroleum (bp 50-70°C): ethyl acetate 7:3). In the case of 1b, the solid precipitate was filtered off, air dried and recrystallized.

Compound 2a ($R=CH_3$): This compound was recrystallized from light petroleum (bp 50-70°C) (yield 80%), mp 65°C (with decomposition); ir: 2120 (N≡N) 1620 (CO) cm^{-1}; uv: 244 (ε 12080) nm; nmr ($CDCl_3$): 2.49 and 2.62 ($6H,2s,CH_3$), 7.39-7.71 (5H,m, C_6H_5) δ; ms M^{+}= 225.212; Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66; Found: C, 69.54; H, 5.01; N, 18.79.

Compound 2b ($R=C_6H_5$): This compound was recrystallized from ethanol (yield 75%), mp 148°C (with decomposition); ir: 2130 (N≡N) 1640 (CO) cm^{-1}; uv: 250 (ε 15090) nm; nmr (DMSO): 2.10 ($3H,s,CH_3$), 7.47-8.05 ($10H,m,C_6H_5$) δ; ms M^{+}= 287.190; Anal. Calcd. for $C_{18}H_{13}N_3O$: C, 75.24; H, 4.56; N, 14.63; Found: C, 75.43; H, 4.69; N, 14.88.

Action of sulphuric acid on the 3-diazopyrrole 2a.

The 3-diazopyrrole 2a (10 mmoles) has been refluxed for 36 hours in aqueous sulphuric acid (25%). The reaction mixture was diluted with water (250 ml), neutralized with hydrogen sodium carbonate and extracted with diethyl ether (3 x 100 ml). Evaporation of the organic layer was chromatographed. The first 200 ml of eluant, light petroleum (bp 50-70°C): ethyl acetate 1:1, gave 2-methyl-3-acetyl-5-phenylpyrrole (4a). Further elution (500 ml) with ethyl acetate gave 5-methyl-7-phenyl-1,6-dihydropyrrolo[3,4-c]pyridazin-4-one (3a).

Compound 4a (R=CH_3): This compound, (yield 5%), had mp in agreement with published value[10] and was fully characterized by ir and nmr spectroscopy: ir: 3130 (NH) 1630 (CO) cm^{-1}; nmr (DMSO): 2.37 and 2.53 (6H,2s,CH_3), 7.03 (1H,d(J=2.5Hz),CH,s upon exchange with deuterium oxide), 7.23-7.97 (5H,m,C_6H_5), 11.86 (1H,broad,exchangeable NH)δ.

Compound 3a (R=CH_3): This compound was recrystallized from ethanol (yield 30%), mp 315°C (with decomposition); ir: 3390 and 3210 (NH) 1615 (CO) cm^{-1}; uv: 217 (ε 15970) 222 (ε 14240) 297 (ε 19060) nm; nmr (DMSO): 2.67 (3H,s,CH_3), 7.19-7.71 (6H,m,C_6H_5 and CH), 12.43 and 12.70 (2H,2 broad,exchangeable NH)δ; ms M^+= 225.181; Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66; Found: C, 69.42; H, 4.80; N, 18.71.

Action of pentanol on the 3-diazopyrroles 2a,b.

The 3-diazopyrroles 2a,b have been refluxed in pentanol for 1 hour. The solvent was evaporated under reduced pressure and the residue was identified as unreacted starting compounds 2a,b by tlc, mps and ir.

Action of N,N-dimethylformamide on the 3-diazopyrroles 2a,b.

The 3-diazopyrroles 2a,b have been refluxed in N,N-dimethylformamide until the tlc showed no starting material (30 minutes). The solution was poured onto crushed ice and the precipitate was filtered off, air dried and recrystallized to give the pyrroles 4a,b, the authenticity of which was established by tlc, mps and ir.

Action of acetic acid on the 3-diazopyrroles 2a,b.

The 3-diazopyrroles 2a,b have been refluxed for 1 hour in acetic acid. The solution was poured onto crushed ice. The crude products were filtered off, air dried and chromatographed. In the case of 2a, the first 200 ml of eluant, light petroleum (bp 50-70°C): ethyl acetate 1:1, gave compound 4a (yield 5%). Further elution (500 ml) with ethyl acetate gave compound 3a (yield 50%). In the case of 2b, the first 200 ml of eluant, light petroleum (bp 50-70°C): ethyl acetate 7:3, gave 3-acetyl-2,5-diphenylpyrrole (4b). Further elution (500 ml) with ethyl acetate gave 5,7-diphenyl-1,6-dihydropyrrolo[3,4-c]pyridazin-4-one (3b).

Compound 4b (R=C_6H_5): This compound, (yield 3%), had mp in agreement with published value[8] and was fully characterized by ir and nmr spectroscopy: ir: 3240 (NH) 1610 (CO) cm^{-1}; nmr (DMSO): 2.29 (3H,s,CH_3), 7.10 (1H,d (J=2.5Hz),CH,s upon exchange with deuterium oxide),7.14-7.88 (10H,m,C_6H_5), 11.83 (1H,broad,exchangeable NH)δ.

Compound 3b (R=C_6H_5): This compound was recrystallized from ethanol (yield 50%), mp 290°C (with decomposition); ir: 3430 and 3250 (NH) 1590 (broad CO) cm^{-1}; uv: 217 (ε 15980) 228 (ε 16420) 295 (ε 19820) nm; nmr (DMSO): 7.40-8.40 (11H,m,C_6H_5 and CH), 12.83 and 13.00 (2H,2 broad,exchangeable NH)δ; ms M^+=287.021; Anal. Calcd. for $C_{18}H_{13}N_3O$: C, 75.24; H, 4.56; N, 14.63; Found: C, 75.39; H, 4.70; N, 14.51.

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