REACTIVITY OF 3-DIAZOPYRROLES. PART 2[1].

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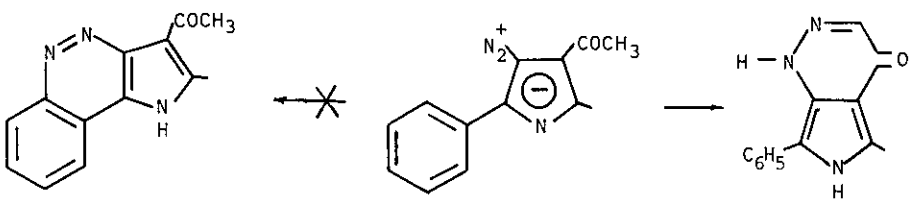
Abstract- 3-Diazopyrroles 8 were prepared as key compounds for an alternative route to synthetize 1H-pyrrolocinnoline. However under the acidic conditions, decomposition and intermolecular coupling reactions were only observed.

As a part of our investigation on pyrrolocinnoline derivatives, a class of compounds which is assuming a relevant importance in agriculture and in medicinal chemistry[2-9] we recently described the synthesis and the reactivity of 3-diazopyrroles of type 1[1]. We attempted to synthetize 1H-pyrrolo[3,2-c]cinnoline 2 via intramolecular coupling reaction of 2-phenyl-3-diazopyrroles of type 1.



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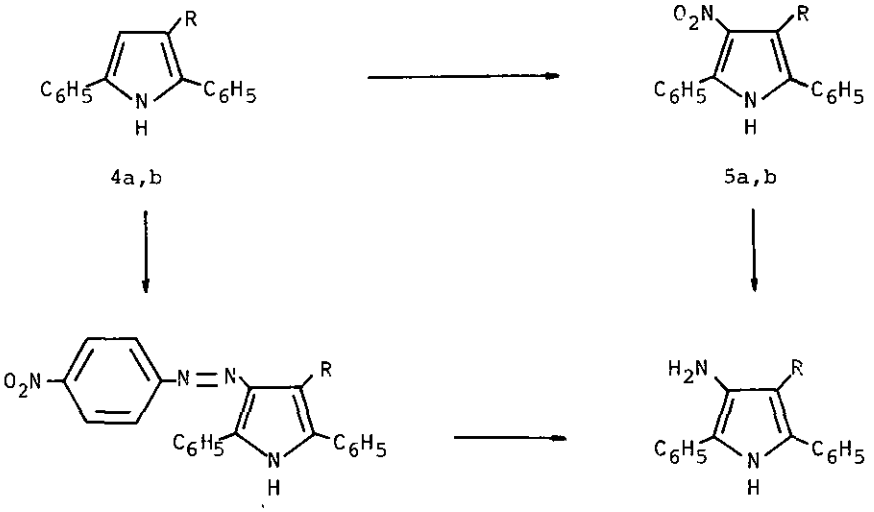
These compounds, under the conditions of Angelico's reaction[10] first and in a milder acidic medium then, did not lead to the expected pyrrolocinnoline derivatives 2, but afforded the new ring system pyrrolo[3,4-c]pyridazine 3. Evidently the coupling reaction took place preferentially with the acetyl substituent in the 4 position rather than with the phenyl in the 2 position.
In view of these findings, to obtain 1H-pyrrolocinnoline it appeared useful to synthetize 3-diazopyrroles bearing in their 4 position substituents different

from the acetyl group.

To this purpose the amino derivatives 7a,b were prepared, in two steps, from the corresponding pyrroles 4a,b by catalytic reduction of the nitro compounds 5a,b or, to obtain 7a in higher yields, by reduction of the azo derivative 6a with stannous chloride in acetic acid.

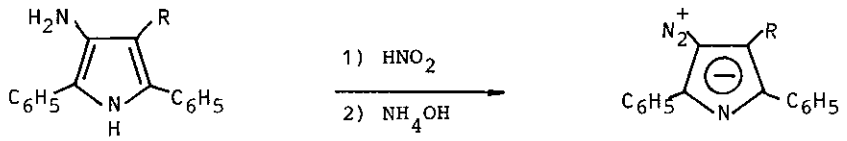


4a,b 5a,b

6a 7a,b

a R=$COOC_2H_5$; b R=CN.

The diazotization of the amino derivatives 7a,b afforded in good yield the 3-diazopyrroles 8a,b.



7a,b 8a,b

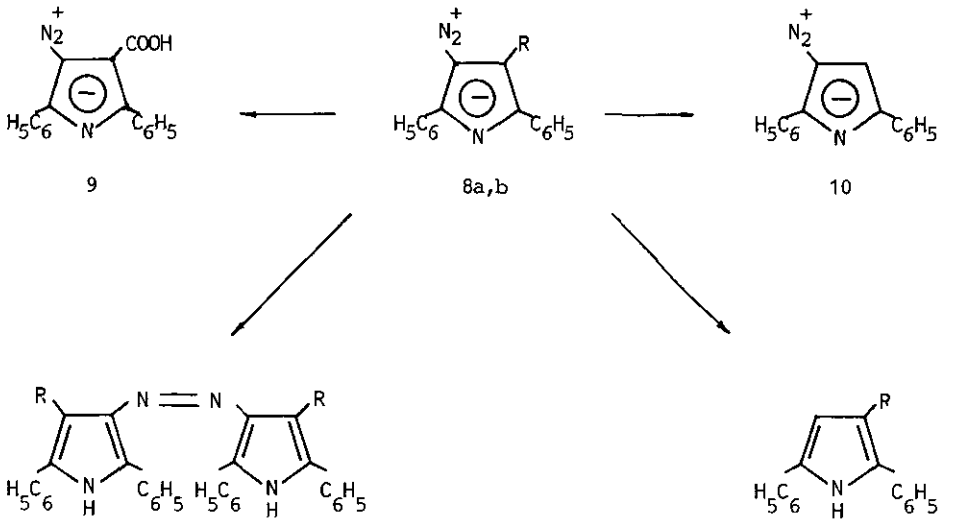
a R=$COOC_2H_5$; b R=CN.

The structure of the 3-diazopyrroles 8 was confirmed by analytical as well as ir and nmr data. The ir spectra showed a strong band in the range 2130-20 cm^{-1} due

to the N≡N stretching, while no absorptions were observed in the NH stretching region. The nmr spectra did not show any signal due to the iminic protons, but only signals due to aromatic and substituent protons.

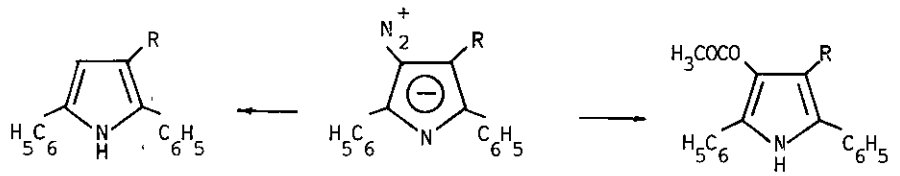
Using the Angelico's procedure[10], the 3-diazopyrroles 8a,b were refluxed in aqueous sulphuric acid for 36 h. From the complex reaction mixture, it was possible to isolate the products 9,10,11c and 4c in comparable yields, in the case of 8a. A reasonable sequence for the reaction pathway would expect the initial hydrolysis of the ethoxycarbonyl group of the 3-diazopyrrole 8a. The acid derivative 9 was then decarboxylated to give compound 10 which lost nitrogen affording the 2,5-diphenylpyrrole (4c). The observation that after 7 h the reaction mixture showed compounds 8a and 9 with traces of compound 10 is a support of the formulated pathway.

In the case of 8b, the compounds 10,11b and 4b were isolated. The 3-diazopyrrole 8b mainly lost nitrogen to give compound 4b, which coupled with the unreacted starting compound affording the azo derivative 11b. The hydrolysis of the cyano group and subsequent decarboxylation originated the diazo compound 10.



a R=$COOC_2H_5$; b R=CN; c R=H.

To limit the formation of by-products, milder reaction conditions were chosen and the 3-diazopyrroles 8a,b were refluxed in acetic acid. From the reaction, together with unreacted 3-diazopyrroles 8, compounds of type 4 and 12 were isolated.
In acetic acid, the hydrolysis of the substituent in the 4 position was actually avoided, whilst the dediazotization was again observed. The replacement of the diazo group by OR affording the 4-acetyloxy derivatives 12 is an usual reaction of diazonium group.



4a,b 8a,b 12a,b

a R=$COOC_2H_5$; b R=CN.

In conclusion, under the employed experimental reaction conditions, the 3-diazopyrroles did not demonstrate any reactivity toward the phenyl substituent in the 2 position. Decomposition and intermolecular coupling reactions were only observed, the behaviour of 3-diazopyrroles appearing from this point of view, like the aromatic diazonium salts.

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; 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. The chromatography was performed on columns of silica gel deactivated with water (15%).

2,5-Diphenyl-3-nitro-4-R-pyrroles (5a,b).

The nitration of pyrroles 4a[11],b[12] was carried out by using nitric acid-acetic anhydride mixture in nitromethane at -15°C according to the procedure described

previously[13]. In the case of 4a the residue underwent a base-acid purification before the recrystallization.

Compound 5a (R=$COOC_2H_5$).

This compound was recrystallized from ethanol (yield 47%), mp 139°C; ir: 3280 (NH) 1675 cm^{-1} (CO); nmr (DMSO-d_6): 1.18 (3H,t,$CH_2\underline{CH_3}$) 4.24 (2H,q,$\underline{CH_2}CH_3$) 7.21-7.75 (10H,m,C_6H_5) 12.70 (1H,br exchangeable NH)δ; ms M^+=336; Anal. Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.80; N, 8.33; Found: C, 68.05; H, 4.96; N, 8.39.

Compound 5b (R=CN).

This compound was recrystallized from ethanol (yield 85%), mp 276°C; ir: 3190 (NH) 2230 cm^{-1} (CN); nmr (DMSO-d_6): 7.54-7.94 (10H,m,C_6H_5) 13.05 (1H,very br exchangeable NH)δ; ms M^+=289; Anal. Calcd. for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53; Found: C, 70.72; H, 3.95; N, 14.61.

Ethyl 3-(4-nitrophenylazo)-2,5-diphenylpyrrole-4-carboxylate (6a).

To a stirred solution of 4-nitroaniline (40 mmoles) in 6N hydrochloric acid (30 ml), a solution of sodium nitrite in water (30%, 15 ml) was added dropwise, at 0 - 5°C. The mixture, cooled at 0°C, was treated with pyrrole 4a (40 mmoles) dissolved in buffered acetic acid (200 ml with sodium acetate (10 g) added). After being stirred for 1 hour, the mixture was poured onto crushed ice. The solid product was collected and washed with water and ethanol (9:1). Compound 6a was recrystallized from ethanol (yield 100%), mp 249°C; ir: 3380 (NH) 1720 cm^{-1} (CO); nmr ($CDCl_3$): 1.31 (3H,t,$CH_2\underline{CH_3}$) 4.37 (2H,q,$\underline{CH_2}CH_3$) 7.30-8.41 (14H,m,C_6H_5 and C_6H_4) 8.98 (1H,br exchangeable NH)δ; ms M^+=440; Anal. Calcd. for $C_{25}H_{20}N_4O_4$: C, 68.17; H, 4.58; N, 12.72; Found: C, 68.40; H, 4.72; N, 12.80.

Preparation of 3-amino-2,5-diphenyl-4-R-pyrroles (7a,b).

METHOD A. Pyrroles 5a,b were reduced over 10% palladium on charcoal in ethanol in a Parr apparatus at 45 psi. After standing overnight at room temperature, the catalyst was filtered off and the solvent was evaporated under reduced pressure. The solid was recrystallized from the appropriate solvent.

Compound 7a (R=$COOC_2H_5$).

This compound was recrystallized from benzene (yield 69%), mp 133°C; ir: 3420 and

3340 (NH) 1660 cm^{-1} (CO); nmr (DMSO-d_6): 1.06 (3H,t,$CH_2\underline{CH_3}$) 4.07 (2H,q,$\underline{CH_2}CH_3$) 4.93 (2H,s exchangeable NH_2) 7.09-7.72 (10H,m,C_6H_5) 11.17 (1H,s exchangeable NH) δ; ms M^+=306; Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15; Found: C, 74.71; H, 6.05; N, 9.26.

Compound 7b (R=CN).

This compound was recrystallized from ethanol (yield 76%), mp 218°C; ir: 3400 and 3330 (NH_2) 3260 (NH) 2210 cm^{-1} (CN); nmr (DMSO-d_6): 4.51 (2H,s exchangeable NH_2) 7.19-7.90 (10H,m,C_6H_5) 11.44 (1H,s exchangeable NH) δ; ms M^+=259; Anal. Calcd. for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.21; Found: C, 78.80; H, 5.12; N, 16.26.

METHOD B. To a stirred solution of $SnCl_2.2H_2O$ (80 g) in acetic acid (80 ml) heated at 80°C (steam bath), compound 6a (40 mmoles) was added in small portions. The reactants were stirred until it became colourless, then they were cooled to room temperature. The mixture was added to a solution of aqueous potassium hydroxyde (20%) with stirring. After 0.5 hour, the solid precipitate was filtered off and recrystallized from benzene to give compound 7a (yield 58%).

General method for the preparation of 3-diazo-4-R-2,5-diphenylpyrroles (8a,b).

These compounds were prepared according to the procedure described previously[1].

Compound 8a (R=$COOC_2H_5$).

This compound was recrystallized from ethanol (yield 90%), mp 115°C; ir: 2130 (N≡N) 1670 cm^{-1} (CO); nmr ($CDCl_3$): 1.23 (3H,t,$CH_2\underline{CH_3}$) 4.30 (2H,q,$\underline{CH_2}CH_3$) 7.35-8.20 (10H,m,C_6H_5) δ; ms M^+=317; Anal. Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24; Found: C, 72.01; H, 4.82; N, 13.31.

Compound 8b (R=CN).

This compound was recrystallized from ethanol (yield 85%), mp 150°C; ir: 2210 (CN) 2120 cm^{-1} (N≡N); nmr ($CDCl_3$): 7.35-8.45 (10H,m,C_6H_5) δ; ms M^+=270; Anal. Calcd. for $C_{17}H_{10}N_4$: C, 75.54; H, 3.37; N, 20.73; Found: C, 75.62; H, 3.80; N, 20.78.

Action of sulphuric acid on the 3-diazopyrrole 8a.

The 3-diazopyrrole 8a (10 mmoles) was refluxed for 36 hours in aqueous sulphuric acid (25%, 30 ml). The reaction mixture was poured onto crushed ice, neutralized

with solid sodium bicarbonate and extracted with diethyl ether. The organic layer was dried (sodium sulphate) and the solvent removed under reduced pressure to give an oil. The reaction mixture was very complex and several products could be detected by tlc in that oil which was chromatographed using as eluant light petroleum (bp 50-70°C)-ethyl acetate (7:3). The first product to be eluted was 2,5-diphenylpyrrole (4c) which was identified by comparison of its ir and mass spectra with those of an authentic sample[14]. The second product to be eluted was 3-diazo-2,5-diphenylpyrrole (10) which was identified as the above product[14]. The third product to be eluted was 2,2',5,5'-tetraphenyl-3,3'-azopyrrole (11c) which had mp in agreement with published value[15] and was fully characterized by ir and nmr spectroscopy: ir: 3450 cm^{-1} (NH); nmr (DMSO-d_6): 6.83 (2H,d,CH,s upon exchange with deuterium oxide) 7.26-8.18 (20H,m,C_6H_5) 11.58 (2H,br exchangeable NH)δ. Further elution with light petroleum (bp 50-70°C)-ethyl acetate (1:1), gave 3-diazo-2,5-diphenylpyrrol-4-carboxylic acid (9) which was recrystallized from ethanol; mp 189°C (dec.); ir: 2620 (broad OH) 2120 (N≡N) 1645 cm^{-1} (CO); nmr (DMSO-d_6): 7.37-8.01 (10H,m,C_6H_5) 11.3 (1H,very br exchangeable OH)δ; ms M^+=269; Anal. Calcd. for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53; Found: C, 70.80; H, 3.97; N, 14.61. The same diazopyrrole 8a was refluxed for 7 hours in aqueous sulphuric acid (25%, 30 ml). The reaction mixture was poured onto crushed ice and a solid precipitated upon neutralization with solid sodium bicarbonate. The solid was collected, air dried and chromatographed. Elution with light petroleum (bp 50-70°C)-ethyl acetate (8:2) gave unreacted starting material (yield 36%). Further elution with light petroleum (bp 50-70°C)-ethyl acetate (1:1) gave compound 9 (yield 31%). The neutralized aqueous solution was extracted with diethyl ether. The organic layer, dried and evaporated, gave compound 10.

Action of sulphuric acid on the 3-diazopyrrole 8b.

The 3-diazopyrrole 8b (10 mmoles) was refluxed for 36 hours in aqueous sulphuric acid (25%, 30 ml). The brown solid was filtered off, air dried and chromatographed using light petroleum (bp 50-70°C)-ethyl acetate (7:3) as eluant. The first product to be eluted was 3-cyano-2,5-diphenylpyrrole (4b) (yield 7%) which was iden-

tified by comparison of its ir and mass spectra with those of an authentic sample[12]. The second product to be eluted was 2,2',5,5'-tetraphenyl-4,4'-dicyano-3,3'-azopyrrole (11b) which was recrystallized from ethanol (yield 25%), mp 320°C; ir: 3220 (NH) 2210 cm^{-1} (CN); nmr (DMSO-d_6): 7.42-8.20 (20H,m,C_6H_5) 12.64 (2H,br exchangeable NH) δ; ms M^+=514; Anal. Calcd. for $C_{34}H_{22}N_6$: C, 79.36; H, 4.31; N, 16.33; Found: C, 79.47; H, 4.38; N, 16.37.

The solid which precipitated upon neutralization of the aqueous solution with aqueous ammonia was collected, air dried and identified as 3-diazo-2,5-diphenylpyrrole (10) (yield 7%) by comparison of its ir and mass spectra with those of an authentic sample[14].

Action of acetic acid on the 3-diazopyrroles 8a,b.

The 3-diazopyrroles 8a,b (10 mmoles) were refluxed in acetic acid (30 ml) for 18 hours. The solution was poured onto crushed ice. The crude products were collected, air dried and chromatographed using light petroleum (bp 50-70°C)-ethyl acetate (9:1) as eluant. The first products to be eluted were unreacted compounds 8a,b. The second products to be eluted were 3-R-2,5-diphenylpyrroles (4a,b) which were identified as above. The third products to be eluted were the 2,5-diphenyl-3-acetyloxy-4-R-pyrroles (12a,b).

Compound 12a (R=$COOC_2H_5$).

This compound was recrystallized from ethanol (yield 30%), mp 150°C; ir: 3260 (NH) 1770 and 1670 cm^{-1} (CO); nmr ($CDCl_3$): 1.13 (3H,t,$CH_2\underline{CH_3}$) 2.25 (3H,s,CH_3) 4.15 (2H,q,$\underline{CH_2}CH_3$) 7.23-7.75 (10H,m,C_6H_5) 8.90 (1H,s exchangeable NH) δ; ms M^+=349; Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01; Found: C, 72.36; H, 5.59; N, 4.16.

Compound 12b (R=CN).

This compound was recrystallized from ethanol (yield 30%), mp 170°C; ir: 3260 (NH) 2210 (CN) 1760 cm^{-1} (CO); nmr ($CDCl_3$): 2.30 (3H,s,CH_3) 7.25-7.80 (10H,m, C_6H_5) 9.36 (1H,br exchangeable NH) δ; ms M^+=302; Anal.Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27; Found: C, 75.70; H, 4.81; N, 9.41.

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