POLYCONDENSED NITROGEN HETEROCYCLES. PART 15. REACTIVITY OF 3-DIAZOPYRROLES. 3[1]. 1H-PYRROLO [3,2-c] CINNOLINE AND PYRROLO-[3,4-c] PYRIDAZINE

Gaetano Dattolo, Girolamo Cirrincione, Anna Maria Almerico, Giuseppe Presti, and Enrico Aiello
II Cattedra di Chimica Farmaceutica e Tossicologica della Università di Palermo, Via Archirafi 32, 90123 Palermo, Italy

Abstract- 3-Diazopyrroles of type 5 were prepared and refluxed in acetic acid. In the case of 5a, an intramolecular coupling reaction between the diazonium group and the methoxyphenyl substituent in the 2-position leads to the 1H-pyrrolo [3,2-c]-cinnoline derivative 6, whilst in the case of 5b an intramolecular coupling with the acetyl group in the 4-position affords the pyrrolo [3,4-c] pyridazine derivative 7.

In connection with our investigations on pyrrolo-cinnoline derivatives, which demonstrated antigerminative properties[2], and on possible structure-activity relationships, we became interested in the synthesis and reactivity of 3-diazo-2-phenylpyrroles as intermediates to 1H-pyrrolo [3,2-c] cinnoline derivatives. In preceding papers in this series[1,3], we reported that the 3-diazopyrroles behave like the aromatic diazonium salts to give coupling reactions and decomposition, but the diazo group did not couple, under acid conditions, with the phenyl in the 2-position.

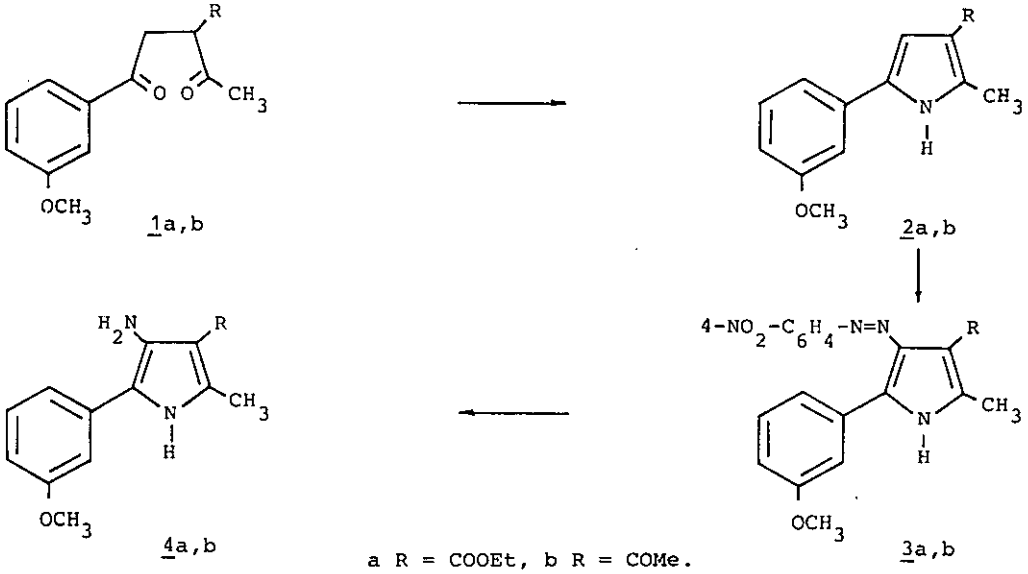
A possible explanation could be that the benzene ring was not sufficiently activated for the electrophilic reaction to take place.

In this paper the synthesis and the reactivity of 3-diazopyrroles of type 5, in

which the phenyl in the 2-position was made more reactive by the introduction of a methoxy group in the opportune position, are reported.

It is to be expected that compound 5a, which bears in the 4-position an ethoxycarbonyl group, unreactive towards the diazo group, would cyclize to give the 1H-pyrrolo [3,2-c] cinnoline ring system. In compound 5b, on the other hand, it would be interesting to observe the competition between the two possible intramolecular coupling reactions.

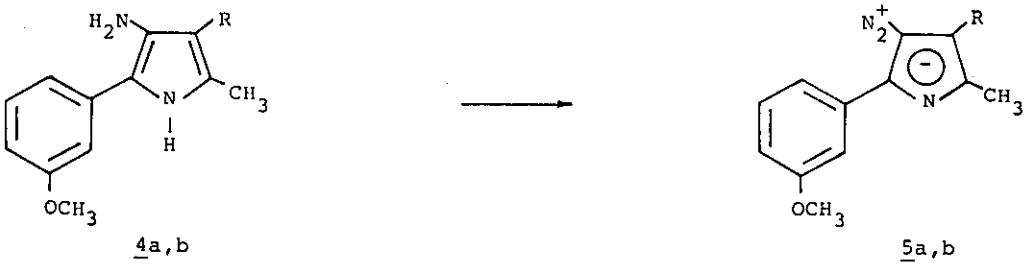
To this purpose the pyrroles 2a,b were prepared from the corresponding diketones 1a,b. Copulation of compounds 2a,b with the diazonium salt of 4-nitroaniline afforded the azo derivatives 3a,b, which upon reduction with stannous chloride in acetic acid, gave the aminopyrroles 4a,b (overall yield 56-71 %).



1a,b 2a,b 3a,b 4a,b

a R = COOEt, b R = COMe.

The diazotization of compounds 4a,b gave the 3-diazopyrroles 5a,b which were isolated from the neutralized reaction mixture.



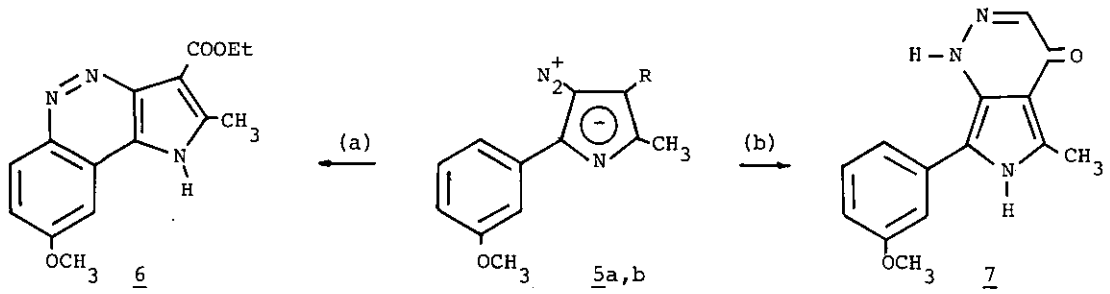
4a,b 5a,b

a R = COOEt, b R = COMe.

The diazopyrroles were characterized by analytical and spectral data. The ir spectra showed a strong absorption at 2120 cm^{1} due to the diazo group stretching, while in the nmr spectra there were no signals attributable to NH group.

The 3-diazopyrroles 5a,b were refluxed in acetic acid until no starting compounds were detected by t.l.c.

With compound 5a the expected 1H-pyrrolo [3,2-c] cinnoline derivative 6 was isolated in 70% yield, whilst in the case of 5b the pyrrolo [3,4-c] pyridazin-4-one 7 was obtained in 60% yield.



a R = COOEt, b R = COMe.

The structures of compounds 6 and 7 were assigned on the basis of spectral data. The nmr spectrum of derivative 6 showed, besides substituent bands, signals due to three aromatic protons, confirming the ring closure had occurred onto the methoxyphenyl substituent and that the methoxy group occupied the 8-position of the polycondensed ring system.

The ir spectrum of the derivative 7 showed two absorption bands at 3430 and 3240 cm^{-1} due to the NH stretchings, while in the nmr spectrum, there were all the expected signals including two exchangeable singlets for one proton each attributable to NH group, but the signal due to the acetyl methyl group was missing, confirming that intramolecular coupling to the acetyl group had taken place.

Evidently, when the 3-diazopyrrole bears an acetyl group in the 4 position, intramolecular coupling with the enolic form of the acetyl group is preferred, and the phenyl group in the 2-position, even if activated towards electrophilic substitutions, is less reactive than the acetyl. But when there is no competition with the substituent in the 4 position, the diazonium group, formed in acid medium,

intramolecularly couples with the 3-methoxyphenyl group in the 2-position, affording the 1H-pyrrolo[3,2-c]cinnoline derivative.

3-Diazopyrroles, in the intramolecular coupling reported so far[3,5], always showed a preferential reactivity towards the substituents on the 4-position of the nucleus. The low availability of the phenyl in the 2-position to undergo coupling reaction could be explicated according to the larger transmission of electronic effects between the 2- and 3-position (hyper-ortho) than between the 3- and 4-position (hypo-ortho) due to the high "bond fixation" which give rise to a C-2 — C-3 bond with a high π bond order as already pointed out in thiophen ring[6].

EXPERIMENTAL

All melting points were taken on a Büchi-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 KV accelerating voltage. The chromatography was performed on columns of silica gel deactivated with water (15%).

Preparation of 3-ethoxycarbonyl- (1a) and 3-acetyl-1-(3-methoxyphenyl)-1,4-pentanedione (1b).

To a mixture of sodium ethoxide (40 mmoles) in absolute ethanol and ethyl acetoacetate (40 mmoles) or acetylacetone (40 mmoles), 3-methoxyphenacyl bromide (40 mmoles) was added in small portions with stirring and cooling on an ice bath. After standing at room temperature overnight, the solid was filtered off and the ethanol solution was evaporated under reduced pressure to give an oil in the case of 1a. In the case of 1b, the diketone was isolated by complexing it with aqueous cupric acetate. The collected solid was dissolved in dilute sulphuric acid (25%) and extracted with diethyl ether. The evaporated solution gave compound 1b.

Compound 1a was isolated as an oil in 60% yield, bp 202°C, ir: 1740, 1715 and 1680 (CO) cm^{-1}; nmr (DMSO-d_6) δ: 1.26 (3H,t,$CH_2\underline{CH_3}$) 2.40 (3H,s,CH_3) 3.70 (2H,d, $\underline{CH_2}CH$) 3.86 (3H,s,OCH_3) 4.26 (2H,q,$\underline{CH_2}CH_3$) 4.33 (1H,t,$CH_2\underline{CH}$) 7.20 - 7.90 (4H,m,

C_6H_4). Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.90; H, 6.45.

Compound 1b was recrystallized from ethanol (yield 40%), mp 70 C, ir: 1710 and 1680 (CO) cm^{-1}; The nmr spectrum was in agreement with the presence of two tautomeric structures, $ArCO-CH_2-\underset{COCH_3}{CH}-COCH_3$ (A) and $ArCO-CH-\underset{COCH_3}{C}=C(OH)CH_3$ (B), in equilibrium in DMSO-d_6 in ratio 4:1 respectively δ: 2.10 (3H,s,$COCH_3$,B) 2.36 (6H,s,$COCH_3$,A) 3.50 (2H,s,CH_2,B) 3.70 (2H,d,CH_2,A) 3.76 (3H,s,$C(OH)CH_3$,B) 3.90 (6H,s,OCH_3,A and OCH_3,B) 4.25 (1H,s,OH,B) 4.56 (1H,t,CH,A) 7.20 - 7.90 (8H,m,C_6H_4,A and C_6H_4,B). Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.49; H, 6.38.

Preparation of 4-substituted 2-(3-methoxyphenyl)-5-methylpyrroles (2a,b).

The preparation of these compounds was carried out according to the procedure described previously[4].

Compound 2a (R=$COOC_2H_5$) was recrystallized from ethanol (yield 90%), mp 137 C; ir: 3320 (NH) 1655 (CO) cm^{-1}; nmr (DMSO-d_6) δ: 1.30 (3H,t,$CH_2\underline{CH_3}$) 2.53 (3H,s,CH_3) 3.83 (3H,s,OCH_3) 4.28 (2H,q,$\underline{CH_2}CH_3$) 6.93 (1H,d,CH,J=2.5 Hz, a singlet appeared upon exchange with deuterium oxide) 6.80 - 7.50 (4H,m,C_6H_4) 11.70 (1H,broad, exchangeable NH); ms: M^+= 259. Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.78; H, 6.49; N, 5.61.

Compound 2b (R=$COCH_3$) was recrystallized from ethanol (yield 80%), mp 159°C; ir: 3190 (NH) 1625 (CO) cm^{-1}; nmr (DMSO-d_6) δ: 2.36 (3H,s,CH_3) 2.45 (3H,s,CH_3) 3.83 (3H,s,OCH_3) 7.05 (1H,d,CH,J=2.5 Hz, a singlet appeared upon exchange with deuterium oxide) 6.75 - 7.50 (4H,m,C_6H_4) 11.70 (1H,broad,exchangeable NH); ms: M^+= 229. Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.51; H, 6.51; N, 6.00.

Preparation of 4-substituted 2-(3-methoxyphenyl)-5-methyl-3-(4-nitrophenylazo) pyrroles (3a,b).

The preparation of these compounds was carried out according to the procedure described previously[1].

Compound 3a (R=$COOC_2H_5$) was recrystallized from ethanol (yield 85%), mp 203°C; ir: 3290 (NH) 1685 (CO) cm^{-1}; nmr (DMSO-d_6) δ: 1.26 (3H,t,$CH_2\underline{CH_3}$) 2.43 (3H,s,CH_3) 3.93 (3H,s,OCH_3) 4.33 (2H,q,$\underline{CH_2}CH_3$) 7.06 - 8.66 (8H,m,2xC_6H_4) 11.35 (1H,broad,

exchangeable NH); ms: M^+= 408; Anal. Calcd. for $C_{21}H_{20}N_4O_5$: C, 61.76; H, 4.94; N, 13.72. Found: C, 61.44; H, 4.99; N, 13.71.

Compound 3b (R=$COCH_3$) was recrystallized from ethanol (yield 70%), mp 203°C; ir: 3210 (NH) 1645 (CO) cm^{-1}; nmr (DMSO-d_6) δ: 2.25 (3H,s,CH_3) 2.29 (3H,s,CH_3) 3.84 (3H,s,OCH_3) 7.42 - 8.42 (8H,m,2xC_6H_4) 12.23 (1H,s,exchangeable NH); ms: M^+= 378. Anal. Calcd. for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.80; N, 14.81; Found: C, 63.61; H, 4.98; N, 14.78.

Preparation of 4-substituted 3-amino-2-(3-methoxyphenyl)-5-methylpyrroles (4a,b). These compounds were prepared according to the procedure described previously (method B)[1].

Compound 4a (R=$COOC_2H_5$) was recrystallized from benzene (yield 83%), mp 146°C; ir: 3440 and 3350 (NH_2) 3280 (NH) 1640 (CO) cm^{-1}; nmr (DMSO-d_6) δ: 1.30 (3H,t, CH_2CH_3) 2.50 (3H,s,CH_3) 3.83 (3H,s,OCH_3) 4.30 (2H,q,CH_2CH_3) 4.93 (2H,s,exchangeable NH_2) 6.70 - 7.45 (4H,m,C_6H_4) 11.00 (1H,s,exchangeable NH); ms: M^+= 274; Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.44; H, 6.41; N, 10.21.

Compound 4b (R=$COCH_3$) was recrystallized from ethanol (yield 80%), mp 215°C (decomp.); ir: 3440 and 3340 (NH_2) 3180 (NH) 1680 (CO) cm^{-1}; nmr (DMSO-d_6) δ: 2.33 (3H,s,CH_3) 2.50 (3H,s,CH_3) 3.80 (3H,s,OCH_3) 5.36 (2H,s,exchangeable NH_2) 6.70 - 7.50 (4H,m,C_6H_4) 11.00 (1H,s,exchangeable NH); ms: M^+= 244. Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.04; H, 6.71; N, 11.40.

Preparation of 4-substituted 3-diazo-2-(3-methoxyphenyl)-5-methylpyrroles (5a,b). These compounds were prepared according to the procedure described previously[3]. The neutralized reaction mixture was 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 8:2 for 5a and light petroleum (bp 50 - 70°C)- ethyl acetate 1:1 for 5b).

Compound 5a (R=$COOC_2H_5$) was recrystallized from light petroleum (bp 50 - 70°C) (yield 70%), mp 73°C (decomp.); ir: 2120 (N≡N) 1670 (CO) cm^{-1}; nmr (DMSO-d_6) δ: 1.30 (3H,t,CH_2CH_3) 2.50 (3H,s,CH_3) 3.86 (3H,s,OCH_3) 4.35 (2H,q,CH_2CH_3) 7.10 - 7.60

(4H,m,C_6H_4); ms: M^+= 285; Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.89; H, 5.19; N, 14.49.

Compound 5b (R=$COCH_3$) was recrystallized from light petroleum (bp 50 - 70°C) (yield 70%), mp 73°C (decomp.); ir: 2120 (N≡N) 1625 (CO) cm^{-1}; nmr (DMSO-d_6) δ: 2.46 (3H,s,CH_3) 2.56 (3H,s,CH_3) 3.85 (3H,s,OCH_3) 7.05 - 7.56 (4H,m,C_6H_4); ms: M^+= 255. Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.66; H, 4.99; N, 16.21.

Action of acetic acid on the 3-diazopyrroles 5a,b.

The 3-diazo compounds 5a,b (10 mmoles) were refluxed in acetic acid until no starting material was detected by t.l.c. (8 h in the case of 5a and 0.5 h in the case of 5b). The mixture was poured onto crushed ice. The solid precipitate was collected. In the case of 5a the solid was purified by refluxing in ethanol for a long time. The insoluble residue was identified as ethyl 8-methoxy-2-methylpyrrolo [3,2-c] cinnolin-3-carboxylate (6) (yield 70%), mp 272°C; ir: 3410 (broad NH) 1700 (CO) cm^{-1}; nmr (DMSO-d_6) δ: 1.39 (3H,t,$CH_2\underline{CH_3}$) 2.85 (3H,s,CH_3) 4.03 (3H,s, OCH_3) 4.41 (2H,q,$\underline{CH_2}CH_3$) 7.54 (1H,dd,J_o=9.38 and J_m=2.64 Hz,H-7) 7.91 (1H,d,J_m= 2.64 Hz,H-9) 8.40 (1H,d,J_o=9.38,H-6); ms: M^+= 285. Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.35; H, 5.21; N, 14.49. The ethanol solution was evaporated under reduced pressure. The residue was chromatographed on p.l.c. plate using light petroleum (bp 50 - 70°C)-ethyl acetate (8:2) as eluant to give compound 2a (yield 3%).

In the case of 5b the crude solid was chromatographed: elution with light petroleum (bp 50 - 70°C)-ethyl acetate (3:7) gave compound 2b (yield 5%). Further elution with ethyl acetate gave 7-(3-methoxyphenyl)-5-methyl-1,6-dihydropyrrolo [3,4-c] pyridazin-4-one (7). This compound was recrystallized from ethanol (yield 60%), mp 273 C°(decomp.); ir: 3430 and 3220 (NH) 1600 (broad CO) cm^{-1}; nmr (DMSO-d_6) δ: 2.68 (3H,s,CH_3) 3.86 (3H,s,OCH_3) 6.64 - 7.48 (5H,m,C_6H_4 and CH) 12.46 (1H,s,exchangeable NH) 12.76 (1H,s,exchangeable NH); ms: M^+= 255. Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.80; H, 5.24; N, 16.61.

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REFERENCES AND NOTES

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