POLYCONDENSED NITROGEN HETEROCYCLES. PART XI. 1,3-DISUBSTITUTED 2-METHYLPYRROLO [3,2-c] CINNOLINE AND 2-ACETYL-3-METHYLPYRROLO [1,2-c] - BENZO [1,2,3] TRIAZINE.

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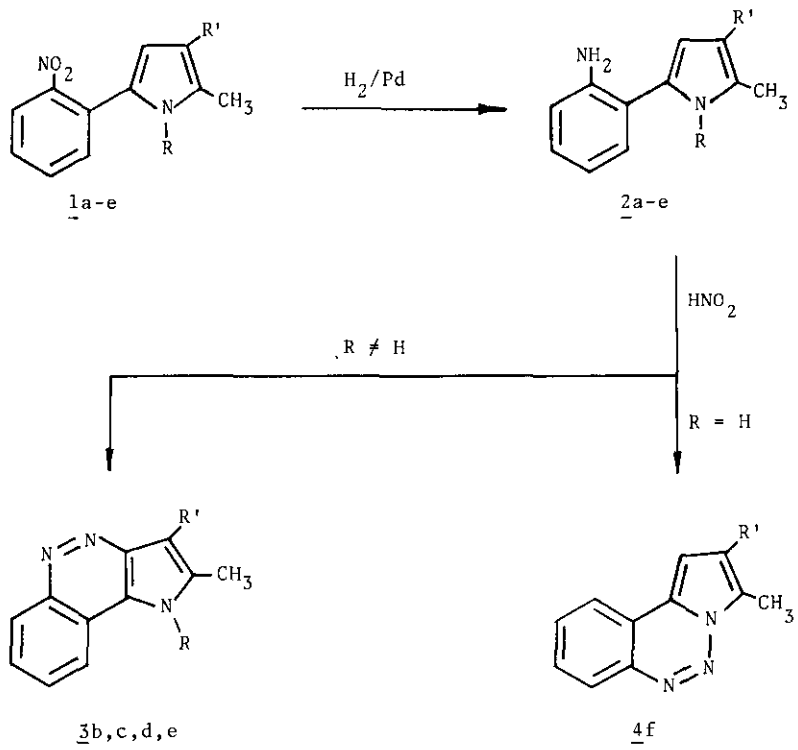
Abstract- The diazotization of 1,3-disubstituted 2-methyl-5-(2-aminophenyl)pyrroles (2) and the intramolecular coupling reaction of the resulting diazonium salts lead to pyrrolo[1,2-c]benzo[1,2,3]triazine 4 when R = H. Pyrrolo[3,2-c]cinnolines 3, a new ring system, were obtained when R ≠ H. Compound 3d inhibited the germination of seeds of Echinochloa crus-galli.

Cinnoline derivatives have shown to possess several properties which space from biological activity[1-8] to appliances in agriculture for the suppression of the growth of the grass[9-10] or in the industry in direct positive emulsions[11]. Moreover, there are many heterocyclic systems condensed with cinnoline nucleus, but very few examples of pyrrolo-cinnolines are reported[12-15] likely owing to difficulty with which these derivatives may be obtained.

In connection with our investigations on polycondensed nitrogen heterocyclic compounds with potential pharmaceutical properties[16] we became interested to synthetize a new ring system i.e. pyrrolo[3,2-c]cinnoline, structurally related to the 3-aryl-4-alkylaminocinnolines which are claimed to possess antiulcer activity, to be pepsin inhibitor and antialgal agent[5].

In this paper we report the synthesis of the new ring system. Compounds 1a[17], b[18], c[18], d and e, were reduced over 10% palladium on charcoal to give the corresponding amino derivatives 2a-e.

The amines 2a-e underwent diazotization with sodium nitrite in acetic acid. The coupling reaction takes two different pathways depending on the substituent in the 1-position of the pyrrole ring. When 1-substituted 5-(2-aminophenyl)pyrroles 2 having a hydrogen at 4-C were diazotized, the intramolecular coupling reaction leads to the pyrrolo[3,2-c]cinnoline derivatives 3.



1a-e 2a-e

3b,c,d,e 4f

a R=H,R'=$COCH_3$; b R=CH_3,R'=$COCH_3$; c R=C_6H_5,R'=$COCH_3$; d R=CH_3,R'=$COOC_2H_5$; e R=C_6H_5,R'=$COOC_2H_5$; f R'=$COCH_3$.

Evidences for the assigned structures 3 were, besides analytical data, molecular weight determined by mass spectrometry, as well as spectral data. IR spectra did not display any absorption band in the 4-5μ range attributable to a diazonium group stretching frequency and nmr spectra showed signals at 1.46-4.57δ attributable to alkyl substituents and at 6.70-8.60δ due to the aromatic protons.

Pyrrolic CH signal was lacking, confirming that the 4-position of the pyrrole system is involved in the cyclization of cinnoline nucleus. When NH pyrroles 2 were diazotized, the intramolecular coupling reaction with iminic nitrogen preferentially took place[19] and 2-acetyl-3-methylpyrrolo [1,2-c] benzo [1,2,3] triazine 4f was obtained in 88% yield. In fact the ir spectrum did not show pyrrolic NH band and nmr spectrum, besides expected signals, exhibited a singlet at 7.11δ due to pyrrolic CH. These spectral evidences as well as analytical data, confirmed the structure of pyrrolo [1,2-c] benzo [1,2,3] triazine for the compound 4f obtained. The pyrrolo-cinnolines 3 did not show to have any significant biological activity, but the compound 3d evaluated by Diamond Shamrock Corporation for preemergent herbicide activity demonstrates antigerminative properties on seeds of Echinochloa crus-galli.

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.

1-Methyl- (1d) and 1-phenyl-3-ethoxycarbonyl-2-methyl-5-(2-nitrophenyl)pyrrole(1e). The preparation of these compounds was carried out according to the procedure described for 1b[18].

Compound 1d (R=CH_3; R'=$COOC_2H_5$): This compound was recrystallized from ethanol (yield 70%), mp 86°C; ir 1695 (CO) cm^{-1}; nmr ($CDCl_3$): 1.32 (3H,t,$CH_2\underline{CH_3}$),2.58 (3H, s,CH_3),3.29 (3H,s,CH_3),4.25 (2H,q,$\underline{CH_2}CH_3$),6.52 (1H,s,CH),7.45-7.96 (4H,m,C_6H_4)δ; ms M^+= 288; Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72; Found: C, 62.61; H, 5.67; N, 9.81.

Compound 1e (R=C_6H_5; R'=$COOC_2H_5$): This compound was recrystallized from ethanol (yield 60%), mp 95°C; ir 1690 (CO) cm^{-1}; nmr ($CDCl_3$): 1.35 (3H,t,$CH_2\underline{CH_3}$),2.35 (3H, s,CH_3),4.25 (2H,q,$\underline{CH_2}CH_3$),6.60 (1H,s,CH),6.80-7.70 (9H,m,C_6H_5 and C_6H_4)δ; ms M^+=

350; Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00; Found: C, 68.71; H, 5.25; N, 7.92.

General method for the preparation of 1,3-disubstituted 3-methyl-5-(2-aminophenyl)pyrroles (2b,c,d and e).

These compounds were performed according to the procedure described for 2a[17].

Compound 2b (R=CH_3; R'=$COCH_3$): This compound was recrystallized from benzene (yield 71%), mp 135°C; ir: 3440 and 3360 (NH_2) 1640 (CO) cm^{-1}; nmr ($CDCl_3$): 2.35 (3H,s,CH_3),2.55 (3H,s,CH_3),3.30 (3H,s,CH_3),3.77 (2H,s,exchangeable NH_2),6.45 (1H, s,CH),6.60-7.35 (4H,m,C_6H_5)δ; ms M^+= 228; Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27; Found: C, 73.70; H, 7.11; N, 12.40.

Compound 2c (R=C_6H_5; R'=$COCH_3$): This compound was recrystallized from benzene (yield 90%), mp 153°C; ir: 3460 and 3340 (NH_2) 1650 (CO) cm^{-1}; nmr ($CDCl_3$): 2.37 (3H,s,CH_3),2.42 (3H,s,CH_3),3.82 (2H,s, exchangeable NH_2),6.55 (1H,s,CH),6.35-7.25 (9H,m,C_6H_5 and C_6H_4)δ; ms M^+= 290; Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65; Found: C, 78.65; H, 6.17; N, 9.72.

Compound 2d (R=CH_3; R'=$COOC_2H_5$): This compound was isolated as hydrochloride and recrystallized from absolute ethanol (yield 82%), mp 218°C; ms M^+-HCl = 258; Anal. Calcd. for $C_{15}H_{19}ClN_2O_2$: C, 61.11; H, 6.50; N, 9.50; Found: C, 61.35; H, 6.64; N, 9.32.

Compound 2e (R=C_6H_5; R'=$COOC_2H_5$): This compound was recrystallized from ethanol (yield 82%), mp 153°C; ir: 3460 and 3360 (NH_2) 1675 (CO) cm^{-1}; nmr ($CDCl_3$): 1.40 (3H,t,CH_2CH_3),2.40 (3H,s,CH_3),3.90 (2H,s,exchangeable NH_2),4.30 (2H,q,CH_2CH_3),6.67 (1H,s,CH),6.35-7.25 (9H,m,C_6H_5 and C_6H_4)δ; ms M^+= 320; Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.74; Found: C, 75.03; H, 6.37; N, 8.83.

General method for the preparation of 1,3-disubstituted 3-methylpyrrolo[3,2-c]cinnolines (3b,c,d and e) and 2-acetyl-3-methylpyrrolo[1,2-c]benzo[1,2,3]triazine(4f).

To a stirred solution of 2a-e(10 mmoles) and acetic acid(15 ml),a solution of sodium nitrite(10 mmoles) in water(20 ml) was added dropwise at 0-5°C. After 1 hour the mixture was allowed to room temperature and adjusted to pH 7 with aqueous sodium hydroxide(5%).The precipitate was filtered off,air dried and recrystallized.

Compound 3b (R=CH_3; R'=$COCH_3$): This compound was recrystallized from ethanol (yield 88%), mp 225°C; ir: 1660 (CO) cm^{-1}; nmr ($CDCl_3$): 2.83 (3H,s,CH_3),3.13 (3H, s,CH_3),4.08 (3H,s,CH_3),7.27-8.59 (4H,m,C_6H_4)δ; ms M^+= 239; Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.48; N, 17.56; Found: C, 70.47; H, 5.59; N, 17.63.

Compound 3c (R=C_6H_5; R'=$COCH_3$): This compound was recrystallized from ethanol (yield 77%), mp 278°C; ir: 1660 (CO) cm^{-1}; nmr ($CDCl_3$): 2.55 (3H,s,CH_3),3.12 (3H, s,CH_3),6.70-8.60 (9H,m,C_6H_5 and C_6H_4)δ;ms M^+= 301; Anal. Calcd. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.95; Found: C, 75.88; H, 5.11; N, 14.02.

Compound 3d (R=CH_3; R'=$COOC_2H_5$): This compound was recrystallized from ethanol (yield 86%), mp 227°C; ir: 1695 (CO) cm^{-1}; nmr ($CDCl_3$): 1.46 (3H,t,$CH_2\underline{CH_3}$),2.53 (3H,s,CH_3),3.75 (3H,s,CH_3),4.43 (2H,q,$\underline{CH_2}CH_3$),7.41-8.46 (4H,m,C_6H_4)δ; ms M^+= 269; Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61; Found C, 66.78; H, 5.79; N, 15.56.

Compound 3e (R=C_6H_5; R'=$COOC_2H_5$): This compound was recrystallized from ethanol (yield 85%), mp 231°C; ir: 1710 (CO) cm^{-1}; nmr ($CDCl_3$): 1.52 (3H,t,$CH_2\underline{CH_3}$),2.60 (3H,s,CH_3) 4.57 (2H,q,$\underline{CH_2}CH_3$),6.97-8.58 (9H,m,C_6H_5 and C_6H_4)δ; ms M^+= 331; Anal. Calcd. For $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68; Found: C, 72.65, H, 5.33; N, 12.72.

Compound 4f (R'=$COCH_3$): This compound was recrystallized from ethanol (yield 88%), mp 181°C; ir: 1665 (CO) cm^{-1}; nmr ($CDCl_3$): 2.61 (3H,s,CH_3),3.03 (3H,s,CH_3),7.11 (1H,s,CH),7.53-8.24 (4H,m,C_6H_4)δ;ms M^+= 225; Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66; Found : C, 69.57; H, 5.13; N, 18.57.

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