

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.

Gaetano Dattolo, Girolamo Cirrincione, Anna Maria Almerico,

Isabella D'Asdia and Enrico Aiello^o

II Cattedra di Chimica Farmaceutica e Tossicologica dell'Università di Palermo, Via Archirafi 32, 90123 Palermo, Italy

Abstract- The diazotization of 1,3-disubstituted 2-methyl-5-(2-amino-phenyl)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*.

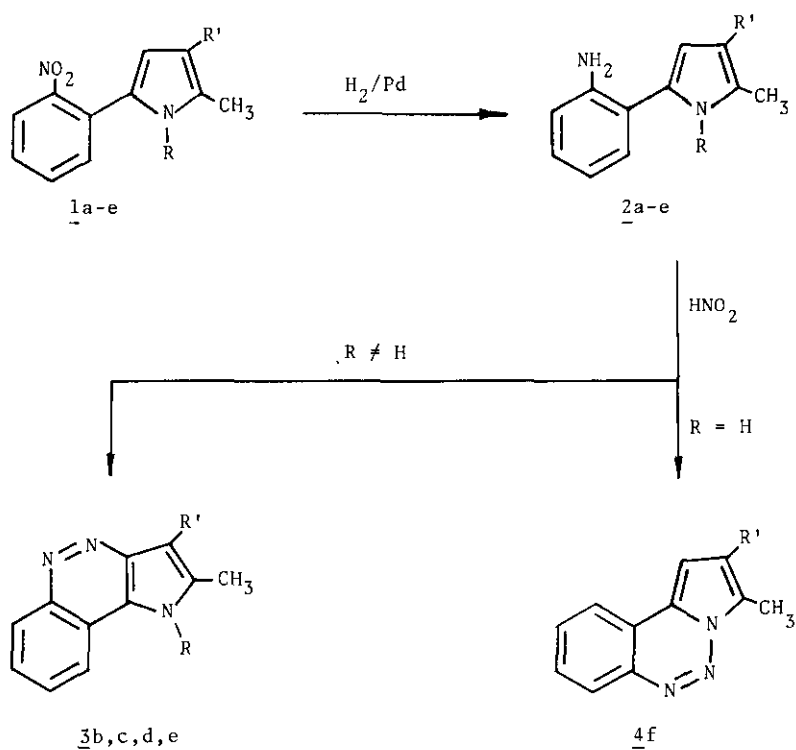
Cinnoline derivatives have shown to possess several properties which range from biological activity¹⁻⁸ to applications in agriculture for the suppression of the growth of the grass⁹⁻¹⁰ or in the industry in direct positive emulsions¹¹.

Moreover, there are many heterocyclic systems condensed with cinnoline nucleus, but very few examples of pyrrolo-cinnolines are reported¹²⁻¹⁵, likely owing to difficulty with which these derivatives may be obtained.

In connection with our investigations on polycondensed nitrogen heterocyclic compounds with potential pharmaceutical properties¹⁶ we became interested to synthesize 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 agent⁵.

In this paper we report the synthesis of the new ring system. Compounds Ia¹⁷, b¹⁸, c¹⁸, 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.



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 $4-5\mu$ range attributable to a diazonium group stretching frequency and nmr spectra showed signals at $1.46-4.57\delta$ attributable to alkyl substituents and at $6.70-8.60\delta$ 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 place¹⁹ 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 7.11 δ 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-O1 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 1b¹⁸.

Compound 1d (R=CH₃; R'=COOC₂H₅): This compound was recrystallized from ethanol (yield 70%), mp 86°C; ir 1695 (CO) cm⁻¹; nmr (CDCl₃): 1.32 (3H,t,CH₂CH₃), 2.58 (3H,s,CH₃), 3.29 (3H,s,CH₃), 4.25 (2H,q,CH₂CH₃), 6.52 (1H,s,CH), 7.45-7.96 (4H,m,C₆H₄) δ ; ms M⁺ = 288; Anal. Calcd. for C₁₅H₁₆N₂O₄: C, 62.49; H, 5.59; N, 9.72; Found: C, 62.61; H, 5.67; N, 9.81.

Compound 1e (R=C₆H₅; R'=COOC₂H₅): This compound was recrystallized from ethanol (yield 60%), mp 95°C; ir 1690 (CO) cm⁻¹; nmr (CDCl₃): 1.35 (3H,t,CH₂CH₃), 2.35 (3H,s,CH₃), 4.25 (2H,q,CH₂CH₃), 6.60 (1H,s,CH), 6.80-7.70 (9H,m,C₆H₅ and C₆H₄) 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 prepared according to the procedure described for 2a¹⁷.

Compound 2b (R=CH₃; R'=COCH₃): This compound was recrystallized from benzene (yield 71%), mp 135°C; ir: 3440 and 3360 (NH₂) 1640 (CO) cm⁻¹; nmr (CDCl₃): 2.35 (3H,s,CH₃), 2.55 (3H,s,CH₃), 3.30 (3H,s,CH₃), 3.77 (2H,s,exchangeable NH₂), 6.45 (1H,s,CH), 6.60-7.35 (4H,m,C₆H₅) δ ; ms M⁺ = 228; Anal. Calcd. for C₁₄H₁₆N₂O: C, 73.65; H, 7.06; N, 12.27; Found: C, 73.70; H, 7.11; N, 12.40.

Compound 2c (R=C₆H₅; R'=COCH₃): This compound was recrystallized from benzene (yield 90%), mp 153°C; ir: 3460 and 3340 (NH₂) 1650 (CO) cm⁻¹; nmr (CDCl₃): 2.37 (3H,s,CH₃), 2.42 (3H,s,CH₃), 3.82 (2H,s, exchangeable NH₂), 6.55 (1H,s,CH), 6.35-7.25 (9H,m,C₆H₅ and C₆H₄) δ ; ms M⁺ = 290; Anal. Calcd. for C₁₉H₁₈N₂O: C, 78.59; H, 6.25; N, 9.65; Found: C, 78.65; H, 6.17; N, 9.72.

Compound 2d (R=CH₃; R'=COOC₂H₅): This compound was isolated as hydrochloride and recrystallized from absolute ethanol (yield 82%), mp 218°C; ms M⁺-HCl = 258; Anal. Calcd. for C₁₅H₁₉ClN₂O₂: C, 61.11; H, 6.50; N, 9.50; Found: C, 61.35; H, 6.64; N, 9.32.

Compound 2e (R=C₆H₅; R'=COOC₂H₅): This compound was recrystallized from ethanol (yield 82%), mp 153°C; ir: 3460 and 3360 (NH₂) 1675 (CO) cm⁻¹; nmr (CDCl₃): 1.40 (3H,t,CH₂CH₃), 2.40 (3H,s,CH₃), 3.90 (2H,s,exchangeable NH₂), 4.30 (2H,q,CH₂CH₃), 6.67 (1H,s,CH), 6.35-7.25 (9H,m,C₆H₅ and C₆H₄) δ ; ms M⁺ = 320; Anal. Calcd. for C₂₀H₂₀N₂O₂: 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]cinolines (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_2CH_3), 2.53 (3H,s, CH_3), 3.75 (3H,s, CH_3), 4.43 (2H,q, CH_2CH_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_2CH_3), 2.60 (3H,s, CH_3) 4.57 (2H,q, CH_2CH_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.

Acknowledgment- A part of this work was supported by a Grant from the C.N.R.(Rome).

REFERENCES AND NOTES

*A preliminary account of this work was presented at the I Convegno Nazionale Divisione Chimica Farmaceutica della Società Chimica Italiana, Pisa Dec. 1979.

1) R.N.Castle, Intern. Congr. Chemotherapy, Proc., 3rd, Stuttgart, 1963, 2, 1064-8.

2) F.Miyazawa, T.Hashimoto, S.Iwahara, T.Itai, I.Suzuki, S.Sako, S.Kamiya, S.Natsume, T.

- Nakashima and G.Okusa,Eisei Shikenjo Hokoku,1963,81,98-100.
- 3) K.Koshinuma,S.Iwahara,T.Nakashima,K.Nato and I.Suzuki,Eisei Shikenjo Hokoku,1970,18, (88),116-17.
 - 4) J.K.Horner and D.W.Henry,J.Med.Chem.,1968,11,946.
 - 5) H.S.Lowrie(G.D. Searle and Co.),U.S. Pat.3,239,526(C1.260-250),Mar.8,1966,Chem.Abstr.,1966,64,P17616h.
 - 6) N.B.Chapman,K.Clarke and K.Wilson,J.Chem.Soc.,1963,2256.
 - 7) S.Suzuki,K.Ueno and K.Mori,Yakugaku Kenkyu,1962,34,224.
 - 8) G.M.Singerman in "The Chemistry of Heterocyclic Compounds",J.Wiley,New York 1973,27,222.
 - 9) H.S.Lowrie(G.D.Searle and Co.),U.S. Pat. 3,265,693(C1.260-247.5),Aug.9,1966,Chem.Abstr.,1966,65,P15395c.
 - 10) H.D.Bidlack and W.T.Irvine,U.S.Pat.893,002(C1.71-92,A01n),Dec.14,1971,Chem.Abstr.,1972,76,P82192v.
 - 11) J.D.Kendall,H.W.Wood and S.F.W.Welford(Ilford Ltd),U.S.Pat.2,669,515,Feb.16,1954,Chem.Abstr.,1954,48,6892f.
 - 12) F.Angelico and C.Labisi,Gazz.Chim.Ital.,1910,40,411 and references cited therein.
 - 13) D.E.Ames,H.R.Ausari and A.W.Ellis,J.Chem.Soc.,1969,1795.
 - 14) L.Caglioti,G.Rosini,P.Tundo and A.Vigevani,Tetrahedron Letters,1970,2349.
 - 15) W.A.Remers,R.H.Roth and M.J.Weiss,J.Med.Chem.,1971,14,860.
 - 16) G.Dattolo,G.Cirrincone and E.Aiello,J.Heterocyclic Chem.,1980,17,701.
 - 17) E.Aiello,G.Dattolo,G.Cirrincone,S.Plescia and G.Daidone,J.Heterocyclic Chem.,1979,16,209.
 - 18) E.Aiello,G.Dattolo and G.Cirrincone,J.Chem.Soc.Perkin Trans.I,1981,1.
 - 19) E.Aiello,Atti Accad.Sci.Lettere Arti Palermo,1970,30,237.

Received, 3rd December, 1981