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PYRROLOINDOLES.
16*. SOME ELECTROPHILIC SUBSTITUTION REACTIONS OF 2,7-DICARBETHOXY-1H,6H-PYRROLO[2,3-e]INDOLES

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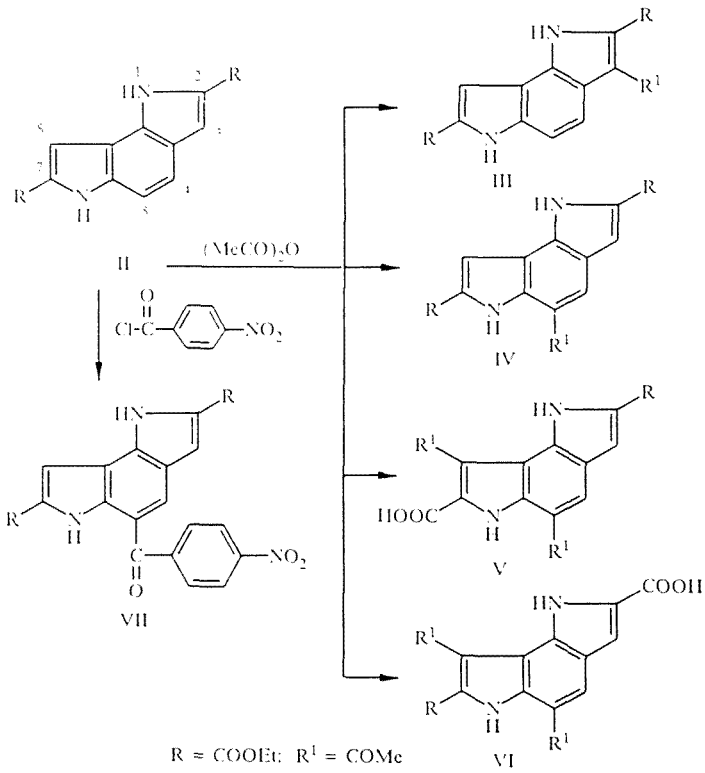
Electrophilic substitutions of 2,7-dicarbethoxy-1H,6H-pyrrolo[2,3-e]indole (Friedel–Crafts acylation, nitration, bromination) take place both at position 3 of the indole ring and at positions 5 and 8 in the benzene ring.

It has already been shown [2, 3] that certain electrophilic substitutions (Mannich aminomethylation, azo coupling, Vilsmeier-Haack N and C acetylation) of 1H,6H-pyrrolo[2,3-e]-indole (I) and its 2,7-dicarbethoxy derivative (II) occur at positions 3 and 8. In Vilsmeier-Haack acetylation of the unsubstituted heterocycle the substituent is directed to the 2, 3, and 8 positions [3]. Carbethoxy groups decrease the reactivity of II but do not change substituent orientation [2].



*For communication 15 see [1].

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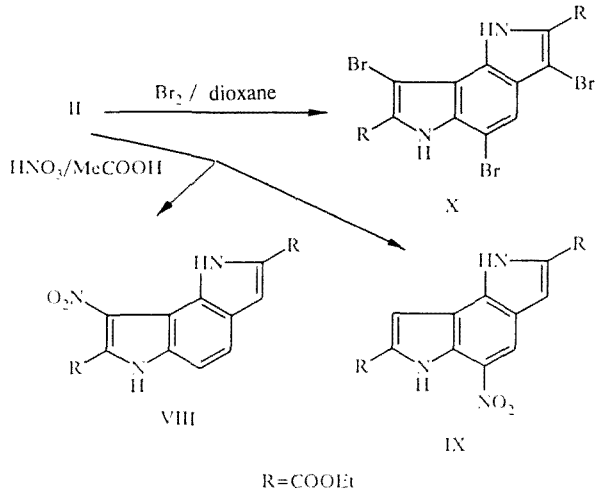
It was therefore of interest to investigate the orientation of substitution of 2,7-dicarbethoxy derivatives when treated with strong electrophiles. Under these reaction conditions the unsubstituted 1H,6H-pyrrolo[2,3-e]indole (I) and indole itself [4, 5] undergo much tarring.

Acetylation of the pyrroloindole II by acetic anhydride in dichloroethane in the presence of $AlCl_3$ under reflex occurs with formation of the mono- and disubstituted products III-VI. The ratio of III-VI in the mixture depends on the sequence of addition of the reagents. When $AlCl_3$ is added to a mixture of reagents (A) the reaction products are formed in overall 44% yield in the ratio 5:4:1:1. Addition of the starting diester II to the Friedel–Crafts complex (B) increases the yield of disubstitution products III-VI to 4:13:8:8. However, the overall yield is lowered to 29% because of tarring of the reaction mixture.

Pyrroloindole II reacts with p-nitrobenzoyl chloride under conditions (A) to form only the mono substituted VII.

Nitration of II at room temperature gives a mixture of three products. Using column chromatography it was possible to isolate pure only 2,7-dicarbethoxy-8-nitro-1H,6H-pyrrolo[2,3-e]indole (VIII) and 2,7-dicarbethoxy-5-nitro-1H,6H-pyrrolo[2,3-e]indole (IX).



Bromination of II with dioxane dibromide in dioxane at room temperature gives principally the 3,5,8-tribromo derivative X.

The structures of the compounds synthesized were confirmed spectroscopically.

The PMR spectrum of III was similar to that of the starting diester II with the exception of the absence of the 3-H proton signal at 7.23 ppm and the presence of a singlet signal at 2.63 ppm which we assign to the protons of the $COCH_3$ group. Hence the acetyl group is situated at position 3.

The PMR spectrum of IV shows a singlet signal at 2.75 ppm for $COCH_3$. The aromatic proton signals occur as two doublets at 7.45 and 7.70 ppm (J = 2.19 Hz) and are assigned to 3-H and 8-H respectively whereas the singlet signal at 8.52 can be assigned to 4-H. Hence IV is the 5-acetyl derivative.

The PMR spectrum of V shows a doublet signal at 7.41 ppm (J = 1.83 Hz) and a singlet at 8.47 ppm in the aromatic proton region which are assigned to 3-H and 4-H respectively. There are also two singlet signals for the acetyl group protons at 2.62 and 2.78 ppm

The low field shift for 4-H in IV (8.52 ppm) when compared with the analogous proton in starting diester II (7.49 ppm) and 3-acetyl derivative III (7.68 ppm) can be explained by the deshielding effect of the electron acceptor acetyl group at position 5. The larger shift (8.76 ppm) for the 5-nitro derivative IV is due to the stronger effect of the nitro group. On the whole, the spectra of the acetyl derivatives III and IV are almost identical to those of the nitro derivatives VIII and IX with the exception of the larger downfield shift of the latter.

The spectrum of tribromo X has one singlet signal at 7.65 ppm. Following the above rationale this can be assigned to 4-H so the substituents must have been directed to positions 3, 5, and 8.

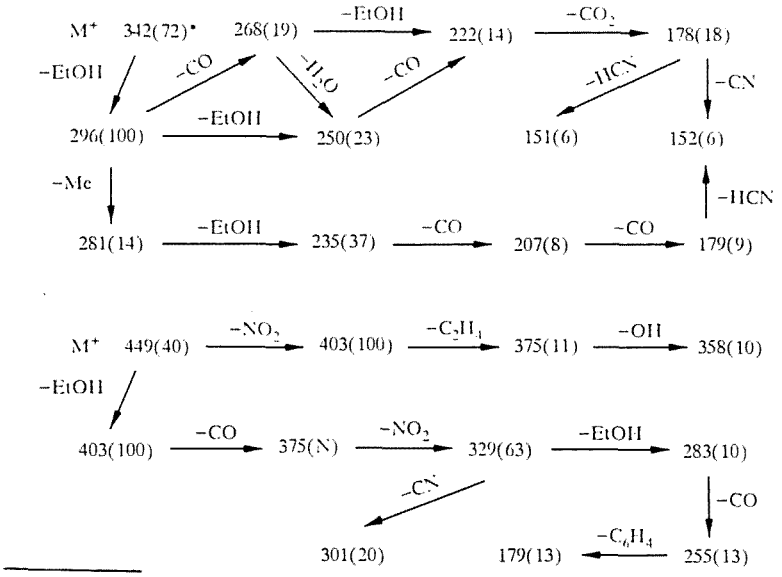
The nature of the fragmentation of the molecular ions under electron impact does not conflict with the structures proposed. As an example we show the scheme for IV and VII. Fragmentation of these ions occurs via several routes including loss of C_2H_5O, C_2H_5OH, CO, Br, and HCN in different sequences. The initial fragmentation step is dominated by loss of ethoxy and carbonyl groups.

TABLE 1. Physicochemical and Spectroscopic Data for III-X

Compound	mp, °C	M⁺	R_f*	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum,*2 chemical shift, δ, ppm	PMR spectrum,*2 spin–spin coupling, J, Hz	Yield, %
III	250...251	342	0.85[a]	3290, 3310 (NH), 1670 (C=O ester), 1650 (C=O ketone)	204(4.4), 250(4.4), 303(4.5), 344(4.3)	12.73 (1H, s), 7.68 (4H, d), 7.30 (5H, d), 12.26 (6H, s), 7.65 (8H, d), 4.35, 4.42 (CH_2, q), 1.36, 1.39 (CH_3, t), 2.63 ($COCH_3$, s)	J_{68} = =1.83, J_{45} = =9.1	20 (A) 4 (B)
IV	218...219	342	0.64[a]	3290, 3410 (NH), 1670 (C=O ester), 1650 (C=O ketone)	205(4.2), 274(4.4), 295(4.45)	11.16 (1H, s), 7.45 (3H, d), 8.52 (4H, s), 11.78 (6H, s), 7.70 (8H, d), 4.42, 4.39 (CH_2, q), 1.39, 1.41 (CH_3, t), 2.75 ($COCH_3$, s)	J_{13} = =2.19, J_{68} = =2.55	16 (A) 4 (B)
V	295...296	356	0.35[a]	3300 (NH), 1745 (C=O ester), 1650 (C=O ketone)	217(4.4), 312(4.1), 357(4.0)	11.33 (1H, s), 7.41 (3H, d), 8.47 (4H, s), 11.78 (6H, s), 4.40 (CH_2, q), 1.39 (CH_3, t), 2.70, 2.78 ($COCH_3$, s)	J_{13} = =1.83	4 (A) 13 (B)
VI	306...307	356	0.21[a]	3300(NH), 1745(C=O ester), 1650(C=O ketone)	204(4.3), 250(4.3), 312(4.2)	11.28 (1H, s), 7.36 (3H, d), 8.42 (4H, s), 11.68 (6H, s), 4.40 (CH_2, q), 1.39 (CH_3, t), 2.69, 2.78 ($COCH_3$, s)	J_{13} = =1.83	4 (A) 8 (B)
VII	278...279	449	0.49[b]	3310(NH), 1740(C=O ester), 1710(C=O ketone)	204(4.3), 270(4.5), 371(4.1)	11.93 (1H, s), 7.43 (3H, br.s), 8.16 (4H, d), 11.16 (6H, s), 7.79 (8H, d), 4.39, 4.45 (CH_2, q), 1.37, 1.43 (CH_3, t), 8.09 (2^1H, d), 8.48 (3^1H, d)	J_{68} = =2.2, $J_{ортно}$ = =8.8	52 (A)
VIII	275...276	345	0.49[c]	3310, 3450(NH), 1680(C=O ester), 1550, 1330(NO_2)	203(4.3), 270(4.5), 385(4.0)	12.42 (1H, s), 8.13 (4H, d), 7.37 (3H, s), 7.63 (5H, d), 4.48, 4.44 (CH_2, q), 1.39, 1.37 (CH_3, t)	J_{45} = =9	13
IX	228...229	345	0.52[d]	3440, 3410(NH), 1710(C=O ester), 1510, 1340(NO_2)	204(4.2), 272(4.5), 385(3.9)	1300 (1H, s), 7.51 (3H, d), 8.76 (4H, s), 11.24 (6H, s), 7.83 (8H, d), 4.41, 4.39 (CH_2, q), 1.38, 1.37 (CH_3, t)	J_{68} = =2.4, J_{13} = =2.1	9
X	192...193	534, 536, 538, 540	0.48[e]	3440, 3305(NH), 1710(C=O ester)	288(5.72), 333(5.1), 350(3.9)	12.44 (1H, s), 7.65 (4H, s), 10.87 (6H, s), 4.41, 4.38 (CH_2, q), 1.39, 1.36 (CH_3, t)	—	52

*Chromatographic system: a) benzene–acetone 5:1; b) benzene–acetone 2:1; c) benzene–ether 5:1; d) benzene–ether 5:2; e) benzene–acetone 10:1.

*2Spectrum recorded in dimethylsulfoxide-D_6 and acetone-D_6.



*Values of m/z, intensities relative to the maximum ion current are given in brackets.

EXPERIMENTAL

Reaction progress and compound purity were monitored on Silufol UV-254 plates. UV spectra were recorded on a Specord spectrophotometer using ethanol as solvent. IR spectra were measured on a UR-20 instrument in vaseline oil and PMR spectra on a WP-200-SY spectrometer with internal standard TMS. Mass spectra were taken on a Ribermag R-10-10-B chromatographic mass spectrometer. Column chromatography was performed on silica gel having particle size 100-250 microns.

Elemental analytical data for the synthesized compounds agreed with that calculated.

Acetylation of 2,7-Dicarbethoxy-1H,6H-pyrrolo[2,3-e]-indole (II). A. Acetic anhydride (0.84 ml, 9 mmole) was added to a solution of II (1.35 g, 4.5 mmole) in dry dichloroethane (100 ml). A solution of $AlCl_3$ (1.2 g, 9 mmole) in dry dichloroethane (40 ml) was added dropwise with cooling and stirring and the product was refluxed for 5 h.

B. Acetic anhydride (0.84 ml, 9 mmole) was added to a solution of $AlCl_3$ (1.2 g, 9 mmole) in dry dichloroethane (40 ml). A solution of II (1 g, 3.3 mmole) in dry dichloroethane (50 ml) was added dropwise with cooling and stirring and the product refluxed for 5 h. The mixture was poured into ice (100 g), acidified with HCl to pH 1, and filtered. The filtrate was extracted with chloroform, dried with $CaCl_2$, and evaporated to dryness to give 0.7 g of a mixture of III-VI which was separated chromatographically.

2,7-Dicarbethoxy-5-P-nitrobenzoyl-1H,6H-pyrrolo[2,3-e]indole (VII). A solution of p-nitrobenzoyl chloride (1.11 g, 6 mmole) in dichloroethane (50 ml) was added to II (0.9 g, 3 mmole) in dry dichloroethane (30 ml). A solution of $AlCl_3$ (1.6 g, 12 mmole) in dry dichloroethane (60 ml) was then added dropwise with cooling and stirring and the product was refluxed for 5 h. Compound VII was separated similarly.

Nitration of 2,7-Dicarbethoxy-1H,6H-pyrrolo[2,3-e]indole (II). HNO_3 (d 1.42 g/cm^3, 0.75 ml, 16 mmole) was added dropwise to a solution of II (1 g, 3.3 mmole) in acetic acid (30 ml) and the product stirred at room temperature for 1 h. It was poured into ice (300 g) and the precipitate filtered, washed to neutrality, and dried to give a mixture (0.5 g) which was separated chromatographically.

2,7-Dicarbethoxy-3,5,8-tribromo-1H,6H-pyrrolo[2,3-e]indole (X). Bromine (0.5 ml) in dioxane (50 ml) was added dropwise with stirring at room temperature to a solution of II (1 g, 3.3 mmole) in dioxane (70 ml) and the product was stirred for 0.5 h. Solvent was evaporated to 30 ml and the product diluted with ether. The precipitated crystals were filtered, washed with ether, and dried to give 0.9 g).

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