REACTIONS OF ETHYL 2-(NITROPHENYL)-4*H*-FURO[3,2-*b*]PYRROLE-5-CARBOXYLATE*

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Reactions of ethyl 2-(2-nitrophenyl)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate were studied. The preparation of a new heterocyclic system -pyrrolo[2',3' : 4,5]furo[3,2-*b*]indole- is described.

In our previous paper[1] we described the preparation of ethyl 2-aryl-4*H*-furo[3,2-*b*]-pyrrole-5-carboxylates; the derivative with a 2-nitrophenyl group attached to position 2 of the furo[3,2-*b*]pyrrole seemed to be of great interest as a starting material for further syntheses. This paper concerns the alkylation of the furo[3,2-*b*]pyrrole system at nitrogen. The interfacial catalysis[2,3] was found to be successful; under its conditions the ethyl 2-(2-nitrophenyl)-4-ethylfuro[3,2-*b*]pyrrole-5-carboxylate (*III*) was prepared and hydrolyzed to yield the corresponding acid *IV*. The latter gave the chloride *V* upon reaction with thionyl chloride and the amide *VI* with ammonia. The direct preparation of amide *VI* starting from the ester *III* and ammonia was unsuccessful. The reaction of *III* with hydrazine hydrate involves the reduction of nitro group and led to hydrazide of 2-(2-aminophenyl)-4-ethylfuro-[3,2-*b*]pyrrole-5-carboxylic acid (*VII*).

Hydrazine hydrate reacts with *I* under formation of the hydrazide of 2-(2-nitrophenyl)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid (*VIII*). Acid *II*, prepared by hydrolysis of *I*, decarboxylates in the presence of quinoline and an electrolytic Cu to afford 2-(2-nitrophenyl)-4*H*-furo[3,2-*b*]pyrrole (*IX*), which leads upon Vilsmeier formylation to 2-(2-nitrophenyl)-4*H*-furo[3,2-*b*]pyrrole-5-carbaldehyde (*X*).

The Cadogan method[4-6] of production of nitrene intermediates from nitro derivatives by means of trivalent phosphorus was used when preparing the pyrrolo[2',3' : : 4,5]furo[3,2-*b*]indole grouping. Toluene as solvent was found to be inconvenient for triethylphosphite deoxygenation of *I*; nevertheless the reaction proceeds in xylene at an optimum reaction time 7 h giving a 30% yield. Even more advantageous was found the reaction of *I* in an excess of triethylphosphite without any solvent for 7 h.

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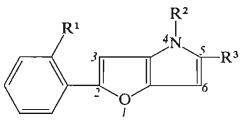
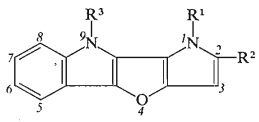
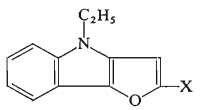
A further extent of the reaction time resulted in an increase of unidentified products in favour of the desired product – ethyl 1, 9-dihydropyrrolo[2′,3′ : 4,5]furo[3,2-*b*]-indole-2-carboxylate (*XI*). Similarly, the triethylphosphite deoxygenation of *IV* furnished ethyl 1-ethyl-9*H*-pyrrolo[2′,3′ : 4,5]furo[3,2-*b*]indole-2-carboxylate (*XII*), which afforded by further alkylation the corresponding diethyl derivative *XVI*. The latter could also be achieved from 4-ethylfuro[3,2-*b*]indole-2-carbaldehyde (*XIII*), the preparation of which was published recently[7]. Condensation of *XIII* with ethyl azidoacetate gave ethyl 2-azido-3-[2-(4-ethylfuro[3,2-*b*]indolyl)]acrylate (*XIV*); *XIV* undergoes a cyclization leading to ethyl 9-ethyl-1*H*-pyrrolo[2′,3′ - 4,5]-furo[3,2-*b*]indole-2-carboxylate (*XV*) which, upon further alkylation, afforded *XVI*.



I – X



XI, XII, XV, XVI



XIII, XIV

We did not succeed to hydrolyze *XI* to the corresponding acid which might decarboxylate to the unsubstituted 1,9-dihydropyrrolo[2′,3′ : 4,5[furo[3,2-*b*]indole; this fact could be rationalized by a considerable lability of the unsubstituted system.

EXPERIMENTAL

Ethyl 2-(2-Nitrophenyl)-4-ethylfuro[3,2-*b*]pyrrole-5-carboxylate (*III*)

A 50% aqueous solution of sodium hydroxide (30 ml) was poured into ethyl 2-(2-nitrophenyl)--4*H*[furo 3,2-*b*]pyrrole-5-carboxylate (*I*, 2 g, 6·7 mmol) in benzene (60 ml) and while stirred, ethyl iodide (1·2 g, 7·7 mmol) and triethylbenzylammonium bromide (0·4 g) were added. The solution was kept stirred at 60°C for 4 h. The cooled mixture was then diluted with water, the organic layer separated and the aqueous one extracted with ether. The combined organic solutions were washed with water and dried with anhydrous sodium sulfate. The work-up gave *III* (1·87 g, 85%), m.p. 91°C (methanol). For $C_{17}H_{16}N_2O_5$ (328·3) calculated: 62·18% C, 4·87% H, 8·53% N; found: 62·32% C, 4·92% H, 8·28% N. IR: ν_{max} (KBr, cm^{-1}): 1695 (C=O). UV: λ_{max} (methanol,

nm): 322 (log ε 4·64). ^{1}H-NMR: 7·25 (1 H, d, $C_{(3)}$—H), 6·75 (1 H, d, $C_{(6)}$—H), $J_{3,6}$ = 0·7 Hz; 4·46 (2 H, q, O—CH_2), 1·30 (3 H, t, CH_3), 4·49 (2 H, q, N—CH_2), 1·36 (3 H, t, CH_3).

2-(2-Nitrophenyl)-4-ethylfuro[3,2-*b*]pyrrole-5-carboxylic Acid (*IV*)

Compound *III* (2 g, 6·7 mmol) in ethanol (50 ml) and 5% sodium hydroxide (20 ml) was heated on a steam bath for 1 h and concentrated to a half of its original volume. The precipitate was dissolved in dilute ethanol, acidified with hydrochloric acid 1 : 1 and poured onto ice. Yield 1·77 g (88%), m.p. 215–216°C (methanol). For $C_{15}H_{12}N_2O_5$ (300·3) calculated: 60·00% C, 4·03% H, 9·32% N; found: 59·88% C, 3·99% H, 9·25% N. IR: ν_{max} (nujol, cm^{-1}): 1 675 (C=O). UV: λ_{max} (methanol, nm): 328 (log ε 4·44). ^{1}H-NMR: 7·29 (1 H, d, $C_{(3)}$—H), 6·79 (1 H, d, $C_{(6)}$—H), 6·79 , $J_{3,6}$ = 0·7 Hz; 7·94–7·65 (4 H, m, C—H_{arom}).

Chloride of 2-(2-Nitrophenyl)-4-ethylfuro[3,2-*b*]pyrrole-5-carboxylic Acid (*V*)

2-(2-Nitrophenyl)-4-ethylfuro[3,2-*b*]pyrrole-5-carboxylic acid (*IV*, 1 g, 3 mmol) was refluxed with thionyl chloride (5·4 g, 4·5 mmol) for 4 h and the excess of thionyl chloride was distilled off under reduced pressure. The crude product crystallized to yield 0·68 g (72%) of *V*, m.p. 137 to 139°C (light petroleum). For $C_{15}H_{11}ClN_2O_4$ (318·7) calculated: 56·52% C, 3·48% H, 8·79% N; found: 56·72% C, 3·36% H, 8·39% N. IR: ν_{max} ($CHCl_3$, cm^{-1}): 1 695 (C=O), 795 (C—Cl). UV: λ_{max} (n-heptane, nm): 351 (log ε 4·40), ^{1}H-NMR: 7·32 (1 H, d, $C_{(3)}$=H), 6·79 (1 H, d, $C_{(6)}$—H), $J_{3,6}$ = 0·7 Hz; 7·88–7·67 (4 H, m, C—H_{arom}), 4·49 (2 H, q, N—CH_2), 1·36 (3 H, t, CH_3).

2-(2-Nitrophenyl)-4-ethylfuro[3,2-*b*]pyrrole-5-carboxamide (*VI*)

The solution of *V* (0·7 g, 2·2 mmol) in benzene (20 ml) was saturated with gaseous ammonia and allowed to stand for half an hour at room temperature. The separated ammonium chloride was filtered off and the product crystallized. Yield 0·57 g (87%) of *VI*, m.p. 139–140°C (methanol). For $C_{15}H_{13}N_3O_4$ (299·3) calculated: 60·19% C, 40·37% H, 14·03% N; found: 60·32% C, 4·51% H, 13·80% N. IR: ν_{max} (nujol, cm^{-1}): 1 670 (C=O). UV: λ_{max} (methanol, nm): 329 (log ε 4·42). ^{1}H-NMR: 7·28 (1 H, d, $C_{(3)}$—H), 6·85 (1 H, d, $C_{(6)}$—H), $J_{3,6}$ = 0·7 Hz; 6·92–7·65 (4 H, m, C—H_{arom}), 4·49 (2 H, q, N—CH_2), 1·36 (3 H, t, CH_3).

Hydrazide of 2-(2-Aminophenyl)-4-ethylfuro[3,2-*b*]pyrrole-5-carboxylic Acid (*VII*)

A 60% solution of hydrazine hydrate (1·8 g) was added to the solution of *III* (1 g, 3·4 mmol) in methanol (20 ml). After 40 h of boiling the crystalline red-brown product *VII* was filtered off. Yield 0·58 g (60%), m.p. 183–184°C (methanol). For $C_{15}H_{16}N_4O_2$ (284·5) calculated: 63·31% C, 5·66% H, 19·69% N; found: 63·62% C, 5·86% H, 19·39% N. IR: ν_{max} (nujol, cm^{-1}): 1 620 (C=O). UV: λ_{max} (methanol, nm): 357 (log ε 4·44). ^{1}H-NMR: 7·05 (1 H, d, $C_{(3)}$—H), 6·75 (1 H, d, $C_{(6)}$—H), $J_{3,6}$ = 0·7 Hz; 4·49 (2 H, q, N—CH_2), 1·36 (3 H, t, CH_3).

Hydrazide of 2-(Nitrophenyl)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylic Acid (*VIII*)

A 80% solution of hydrazine hydrate (3·1 g) and *I* (1 g, 3·7 mmol) in methanol (30 ml) were boiled for 20 h, cooled and the red-brown *VIII* filtered off. Yield 0·8 g (75%), m.p. 230–231°C (methanol). For $C_{12}H_{10}N_4O_4$ (290·2) calculated: 49·65% C, 3·47% H, 19·51% N; found: 49·70% C, 3·50% H, 19·56% N. IR: ν_{max} (nujol, cm^{-1}): 1 625 (C=O), 3 465 (N—H). UV: λ_{max} (methanol, nm): 325 (log ε 4·40). ^{1}H-NMR: 7·09 (1 H, d, $C_{(3)}$—H, 6·88 (1 H, d, $C_{(6)}$—H), $J_{3,6}$ = 0·7 Hz.

2-(2-Nitrophenyl)-4*H*-furo[3,2-*b*]pyrrole (*IX*)

The solution of *II* (0·5 g, 1·8 mmol) in a fresh distilled quinoline (20 ml) and electrolytic copper were heated at 170°C for 2 h. Quinoline was distilled off under reduced pressure and the residue chromatographed on a silica gel column (eluant benzene–ethyl acetate 1 : 2). Yield 0·29 g (71%), m.p. 102°C ether–light petroleum). For $C_{12}H_8N_2O_3$ (228·2) calculated: 63·15% C, 3·53% H, 12·27% N; found: 63·20% C, 3·49% H, 12·15% N. IR: ν_{max} ($CHCl_3$, cm^{-1}): 3465 (N—H). UV: λ_{max} (methanol, nm): 332 (log ε 4·67). ^{1}H-NMR: 7·53—7·35 (4 H, m, C—H_{arom}), 7·06 (1 H, d, $C_{(3)}$—H), 6·94 (1 H, dd, $C_{(5)}$—H), 6·09 (1 H, dd, $C_{(6)}$—H), $J_{3,6}$ = 0·7 Hz, $J_{5,6}$ = 3·0 Hz, $J_{4,5}$ = 2·8 Hz.

2-(2-Nitrophenyl)-4*H*-furo[3,2-*b*]pyrrole-2-carbaldehyde (*X*)

Dimethylformamide (3 g, 0·04 mmol) and phosphorus oxychloride (1·7 g, 0·011 mmol) were stirred at 0°C for 20 min. A solution of *IX* (0·9 g, 0·04 mmol) in dimethylformamide (3 g) was added to this mixture so as the temperature did not exceed 10°C. The stirring was continued at 5°C for 1 h, at 20°C for additional 1 h; the content was then poured into ice-cold water and neutralized with sodium hydrogen carbonate. The product was extracted with chloroform, dried with sodium sulfate and concentrated to crystallization. Yield 0·87 g (85%), m.p. 204°C (methanol). For $C_{13}H_8N_2O_4$ (256·4) calculated: 60·88% C, 3·14% H, 10·94% N; found: 60·92% C, 3·20% H, 10·87% N. IR: ν_{max} ($CHCl_3$, cm^{-1}): 1650 (CH=O), 3450 (N—H). UV: λ_{max} (methanol, nm): 357 (log ε 4·5). ^{1}H-NMR: 7·17 (1 H, d, $C_{(3)}$—H), 7·00 (1 H, d, $C_{(6)}$—H), $J_{3,6}$ = 0·7 Hz; 9·44 (1 H, s, CHO).

Ethyl 1,9-Dihydropyrrolo[2′,3′ : 4,5]furo[3,2-*b*]indole-2-carboxylate (*XI*)

The mixture of *I* (2 g, 6·6 mmol) and triethylphosphite (15 g, 90 mmol) were refluxed under nitrogen for 7 h. Triethylphosphite and triethylphosphate were distilled off under reduced pressure and the residue crystallizing at 0°C within 24 h was washed with a hot benzene–ether mixture to yield *XI* (0·9 g, 51%), m.p. 221°C (chloroform). For $C_{15}H_{12}N_2O_3$ (268·3) calculated: 67·15% C, 4·51% H, 10·44% N; found: 67·10% C, 4·76% H, 10·21% N. IR: ν_{max}($CHCl_3$, cm^{-1}): 1691 (C=O), 3461 (N—H). UV: λ_{max} (methanol, nm): 355 (log ε 4·3). ^{1}H-NMR: 6·87 (1 H, s, $C_{(3)}$—H), 4·31(2 H, q, O—CH_2), 1·33 (3 H, t, CH_3).

Ethyl 1-Ethyl-9*H*-pyrrolo[2′,3′ : 4,5]furo[3,2-*b*]indole-2-carboxylate (*XII*)

The mixture of *III* (0·8 g, 2·5 mmol), triethylphosphite (6·3 g, 38 mmol) and xylene (30 ml) were refluxed under nitrogen for 7 h; xylene, triethylphosphite and triethylphosphate were removed and the oily product chromatographed on a silica gel column (eluant benzene–ether 2 : 3). For $C_{17}H_{16}N_2O_3$ (296·3) calculated: 68·90% C, 5·45% H, 9·44% N; found: 68·79% C, 5·35% H, 9·27% N. IR: ν_{max} (KBr, cm^{-1}): 1670 (C=O), 3350 (N—H). UV: λ_{max} (methanol, nm): 360 (log ε 4·47). ^{1}H-NMR: 6·91 (1 H, s, $C_{(3)}$—H), 4·70 (2 H, q, O—CH_2), 1·32 (3 H, t, CH_3), 4·27 (2 H, q, N—CH_2), 1·43 (3 H, t, CH_3).

Ethyl 2-Azido-3-[2-(4-ethylfuro[3,2-*b*]indolyl)]acrylate (*XIV*)

A solution of ethyl azidoacetate (3·8 g, 31 mmol) and 4-ethylfuro[3,2-*b*]indole-2-carbaldehyde (*XIII*, 0·8 g, 3·8 mmol) in ethanol was added to a solution of sodium metal (0·75 g, 35 mgat) in ethanol (20 ml) at 0°C during 30 min. The temperature was then risen to 15°C for 30 min and then cooled to 0°C at which temperature ammonium chloride was added, the solution

concentrated to a half of its volume and poured into ice-cold water (30 ml). The product was extracted with ether, dried with sodium sulfate and the solvents were evaporated. Yield 0·8 g (65%), m.p. 118–120°C (ethanol). For $C_{17}H_{15}N_4O_3$ (323·3) calculated: 63·15% C, 4·48% H, 17·33% N; found: 63·36% C, 4·76% H, 17·04% N. IR: ν_{max} (KBr, cm^{-1}): 1 700 (C=O), 2120 (N_3). UV: λ_{max} (methanol, nm): 420 (log ε 4·39).

Ethyl 9-Ethyl-1*H*-pyrrolo[2′,3′ : 4,5]furo[3,2-*b*]indole-2-carboxylate (*XV*)

A solution of *XIV* (0·5 g, 1·5 mmol) in xylene (50 ml) was refluxed for 30 min. The solvent was distilled off to furnish *XV* (0·36 g, 82%), m.p. 197–200°C (benzene). For $C_{17}H_{16}N_2O_3$ (296·3) calculated: 68·18% C, 5·44% H, 9·45% N; found: 68·70% C, 5·54% H, 9·30% N. ^{1}H-NMR: 6·85 (1 H, s, $C_{(3)}$—H), 4·41 (2 H, q, O—CH_2), 1·35 (3 H, t, CH_3), 4·24 (2 H, q, N—CH_2), 1·50 (3 H, t, CH_3).

Ethyl 1,9-Diethylpyrrolo[2′,3′ : 4,5]furo[3,2-*b*]indole-2-carboxylate (*XVI*)

To a solution of *XII* (0·5 g, 1·7 mmol) in benzene (90 ml) a 50% sodium hydroxide (10 ml) and triethylbenzylammonium bromide (0·2 g) were added. Ethyl iodide (0·3 g, 2 mmol) was added to this solution under stirring. After 5 h of refluxing the solution was cooled and diluted with water, the organic layer separated and the aqueous one extracted with ether. The combined organic layers were washed with water to a neutral reaction, dried with sodium sulfate and evaporated *in vacuo*. Yield 0·43 g (78%), m.p. 112–113°C (benzene). For $C_{19}H_{20}N_2O_3$ (324·4) calculated: 70·35% C, 6·21% H, 8·64% N; found: 70·39% C, 6·30% H, 8·56% N. IR: ν_{max} (KBr, cm^{-1}): 1 670 (C=O). UV: λ_{max} (methanol, nm): 361 (log ε 4·59). ^{1}H-NMR: 6·90 (1 H, s, $C_{(3)}$—H), 4·55 (2 H, q, O—CH_2), 1·38 (3 H, t, CH_3), 4·22 (2 H, q, N—CH_2), 1·42 (3 H, t, CH_3), 4·55 (2 H, q, N—CH_2), 1·38 (3 H, t, CH_3).

Spectral Measurements

The infrared absorption spectra were recorded with a UR-20 spectrophotometer Zeiss, Jena, the ultraviolet spectra were measured with a Specord UV VIS Zeiss, Jena apparatus at room temperature. The ^{1}H-NMR spectra were taken with a Tesla BS-487 C instrument operating at 80 MHz and 25°C in hexadeuteriodimethyl sulfoxide. The internal refence substance was hexamethyldisiloxane, chemical shifts are given in ppm at the δ scale.

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