SUBSTITUTED 4-BENZYLFURO[3,2-*b*]PYRROLES

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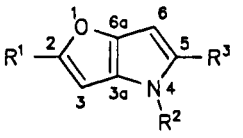
Preparation of 4-benzylfuro[3,2-*b*]pyrroles is described and their reactions with selected dienophiles are discussed. Utilization of 4-acetylfuro[3,2-*b*]pyrroles for preparation of 4-substituted derivatives of furo[3,2-*b*] pyrrole and the synthesis of ethyl 4-(2- and 4-nitrobenzyl)furo[3,2-*b*]pyrrole-5-carboxylates for fusing to a 1,4-diazepine system is presented.

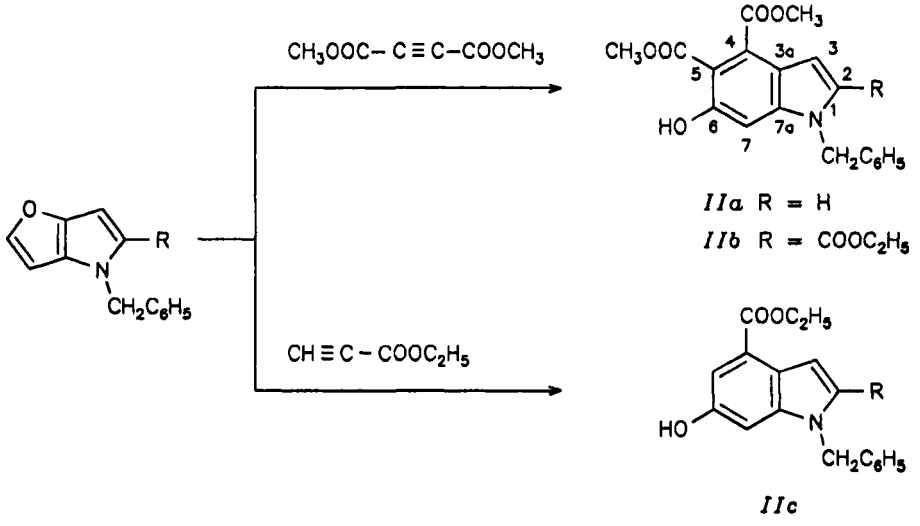
Addition and cycloadditions of furo[3,2-*b*]pyrrole and its derivatives were already published[1-4]. As found, substituents bound to this ring system influence the course of the above-mentioned reactions leading to products of Michael addition at the pyrrole ring, or products of [4 + 2] cycloadditions at furan or pyrrole rings. The unstable products of [4 + 2] addition were transformed into benzo[*b*]furans or indoles.

This paper describes the preparation and reactions of 4-benzyl and 4-(2- or 4-nitrobenzyl)furo[3,2-*b*]pyrroles. Ethyl 4-benzylfuro[3,2-*b*]pyrrole-5-carboxylate (*Ia*) was obtained by benzylation of ethyl furo[3,2-*b*]pyrrole-5-carboxylate under conditions of phase-transfer catalysis. Hydrolysis of the ester *Ia* produced the corresponding acid *Ib*, which decarboxylated to 4-benzylfuro[3,2-*b*]pyrrole (*Ic*) alternatively prepared from 4-acetylfuro[3,2-*b*]pyrrole under conditions of phase-transfer catalysis; 4-methylfuro[3,2-*b*] pyrrole (*Id*) was formed similarly.

We found that the reaction course of 4-benzylfuro[3,2-*b*]pyrroles with dienophiles (Scheme 1) was influenced by substituents attached to this system. Thus, 4-benzyl[3,2-*b*]-pyrrole reacted with dimethyl butynedioate in acetonitrile exothermally to give a [4 + 2] cycloaddition product at the furan moiety of the furo[3,2-*b*]pyrrole system. The structure of dimethyl 1-benzyl-6-hydroxyindole-4,5-dicarboxylate (*IIa*) was deduced from the ^{1}H NMR spectra. Ethyl 4-benzylfuro[3,2-*b*]pyrrole-5-carboxylate (*Ia*) reacted under the same conditions at the reflux temperature of the solvent only. The resulting [4 + 2] cycloaddition product – ethyl 4,5-dimethyl-1-benzyl-6-hydroxyindole-2,4,5-tricarboxylate (*IIb*) – was obtained after 80 h of reacting. The lowered reaction ability of the compound is associated with the electron-accepting effect of the ethoxycarbonyl group, which lowers the diene character of the furo[3,2-*b*]pyrrole system.



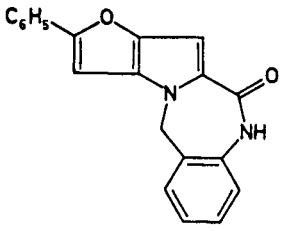
	R^1	R^2	R^3
Ia	H	$C_6H_5CH_2$	$COOC_2H_5$
Ib	H	$C_6H_5CH_2$	COOH
Ic	H	$C_6H_5CH_2$	H
Id	H	CH_3	H
IIIa	H	$4\text{-}NO_2C_6H_4CH_2$	$COOC_2H_5$
IIIb	H	$2\text{-}NO_2C_6H_4CH_2$	$COOC_2H_5$
IIIc	CH_3	$4\text{-}NO_2C_6H_4CH_2$	$COOC_2H_5$
IIId	CH_3	$2\text{-}NO_2C_6H_4CH_2$	$COOC_2H_5$
IIIe	C_6H_5	$4\text{-}NO_2C_6H_4CH_2$	$COOC_2H_5$
IIIf	C_6H_5	$2\text{-}NO_2C_6H_4CH_2$	$COOC_2H_5$
IIIg	C_6H_5	$2\text{-}NH_2C_6H_4CH_2$	$COOC_2H_5$



SCHEME 1

Regioselectivity of the reaction involving an asymmetric dienophile was investigated with *Ia* and ethyl propynoate. The crude reaction product, obtained by a 25 h reflux in acetonitrile, was analysed by ^{1}H NMR spectroscopy showing this compound to be ethyl 1-benzyl-6-hydroxyindole-5-carboxylate (*IIc*). Formation of this regioisomer was evidenced by the coupling constant $J(5,7)$ = 2.2 Hz. This value is in accordance with that published in ref.[4]. The lowered dienophilic character of ethyl propynoate (the increased energetic level of LUMO) can be the reason why the reaction with ethyl 4-benzylfuro[3,2-*b*]pyrrole-5-carboxylate (*Ia*) did not take place.

Preparation of ethyl 4-(2- and 4-nitrobenzyl)furo[3,2-*b*]pyrrole-5-carboxylates *III* was not succeeded under the given conditions for *Ia*. Satisfying yields of compounds *IIIa* – *IIIf* afforded the utilization of sodium carbonate and tetrabutylammonium bromide under conditions of a phase-transfer catalysis. Reduction of *IIIf* furnished the corresponding amino derivative *IIIg*, which, on condensative cyclization in the presence of 2-hydroxypyridine yielded 2-phenylfuro[2',3':4,5]pyrrole[2,1-*c*]-benzo[1,4]diazepin-11-one (*IV*). Compound *IV* is an isoelectronic analogue of indole[2,1-*c*][1,4]benzodiazepines[5] exhibiting, like furo[3,2-*b*]indoles[6], antiallergic properties.



IV

Structure of compounds prepared (Table I) was proved by IR, UV (Table II) and ^{1}H NMR spectra. The ^{13}C NMR and mass spectra were taken with compounds *Id* and *IIIb*, respectively.

EXPERIMENTAL

Infrared spectra of compounds *IIa* – *IIc* were measured in chloroform, the remaining substances were measured by a KBr technique (0.5 – 1.0 mg per 300 mg KBr) with a Specord 71 IR (Zeiss, Jena) apparatus. The UV spectra of methanolic solutions (10^{-4} mol l^{-1}) were taken with a Specord UV VIS (Zeiss, Jena) at room temperature. The ^{1}H NMR spectra (δ, ppm) of *IIIc*, *IIId*, *IIIg* in hexadeuterioacetone and the others in hexadeutoriodimethyl sulfoxide, tetramethylsilane and hexamethyldisiloxane being the respective internal references, were recorded with a Tesla BS 487 C (80 MHz) spectrometer. The ^{13}C NMR spectrum of *Id* in deuteriochloroform was run with a Bruker AM-300 instrument operating at 75.43 MHz. The mass

TABLE I
Characteristic data for compounds *Ia – Id*, *IIa – IIc*, *IIIa – IIIf*

Compound	Formula (M. w.)	M. p., °C (Yield, %)	Calculated/Found		
			% C	% H	% N
Ia	$C_{16}H_{15}NO_3$	29 – 30	71.36	5.61	5.20
	(269.3)	(75)	71.61	5.51	5.53
Ib	$C_{14}H_{11}NO_3$	129 – 130	69.70	4.60	5.81
	(241.2)	(86)	69.62	4.68	5.95
Ic[a]	$C_{13}H_{11}NO$	45 – 46	79.17	5.62	7.10
	(197.2)	(61)	79.21	5.82	7.11
Id[b]	C_7H_7NO		69.43	5.78	11.57
	(121.1)	(51)	69.19	5.90	11.60
IIa	$C_{19}H_{17}NO_5$	123 – 124	67.25	5.05	4.13
	(339.3)	(50)	67.38	5.18	4.38
IIb	$C_{22}H_{21}NO_7$	177 – 178	64.23	5.15	3.41
	(411.4)	(16)	64.42	5.28	3.62
IIc	$C_{18}H_{17}NO_3$	171 – 172	73.20	5.80	4.74
	(295.3)	(48)	73.10	5.95	4.88
IIIa	$C_{16}H_{14}N_2O_5$	88 – 89	61.14	4.49	8.91
	(314.3)	(70)	60.21	4.80	9.15
IIIb	$C_{16}H_{14}N_2O_5$	140 – 141	61.14	4.49	8.91
	(314.3)	(67)	61.15	4.44	9.11
IIIc	$C_{17}H_{16}N_2O_5$	129 – 130	62.21	4.88	8.54
	(328.2)	(66)	62.31	4.89	8.69
IIId	$C_{17}H_{16}N_2O_5$	111 – 112	62.21	4.88	8.54
	(328.2)	(59)	62.33	4.95	8.61
IIIe	$C_{22}H_{18}N_2O_5$	173 – 174	67.71	4.62	7.18
	(390.3)	(91)	67.53	4.73	7.31
IIIf	$C_{22}H_{18}N_2O_5$	211 – 212	67.71	4.62	7.18
	(390.3)	(75)	67.83	4.79	7.26
IIIg	$C_{22}H_{20}N_2O_3$	124 – 125	73.32	5.59	7.77
	(360.4)	(45)	73.42	5.61	7.73
IV	$C_{20}H_{14}N_2O_2$	295 – 299	76.44	4.45	8.91
	(314.2)	(87)	76.42	4.49	8.81

[a] Yield 44 % by method *B*; [b] b.p. 83 °C/2 kPa.

spectrum of *IIIb* was measured with an MS 902 S (AEI, Manchester) spectrometer at 70 eV ionizing ion energy, 100 μA trap current and 100 °C ion-source temperature.

The starting compounds were synthesized as follows: ethyl furo[3,2-b]pyrrole-5-carboxylate according to ref.[7], ethyl 2-methylfuro[3,2-*b*]pyrrole-5-carboxylate according to ref.[8], ethyl 2-phenylfuro[3,2-*b*]pyrrole-5-carboxylate according to ref.[9], 4-acetylfuro[3,2-*b*]pyrrole according to ref.[10] and furo[3,2-*b*] pyrrole according to ref.[11].

Ethyl 4-Benzylfuro[3,2-*b*]pyrrole-5-carboxylate (*Ia*)

Sodium hydroxide (50%, 90 ml) and benzyl chloride (1.75 ml, 21 mmol) were added to a stirred solution of ethyl furo[3,2-*b*]pyrrole-5-carboxylate (3 g, 17 mmol) in benzene (300 ml), Finally, triethylbenzylammonium bromide (1.2 g) was added and the mixture was kept stirred at 60 °C for 4 h. The cooled organic layer was separated, the aqueous one was three times extracted with benzene, the collected benzene layers were washed with water and dried with sodium sulfate. The product was crystallized after benzene had been distilled off under reduced pressure. ^{1}H NMR: 1.30 t, 3 H (CH_3); 4.01 q, 2 H (OCH_2); 5.67 s, 2 H ($CH_2C_6H_5$); 6.48 dd, 1 H (H-3, J(3,6) = 0.8); 6.85 d, 1 H (H-6); 7.21 bs, 5 H (H_{arom}); 7.60 dd, 1 H (H-2, J(2,3) = 2.2).

TABLE II
IR and UV spectra of compounds *Ia – Ic*, *IIa – IIc*, *IIIa – IIIf*

Compound	ν(C=O)	ν(C=C)	$\nu_{as}(NO_2)$	$\nu_s(NO_2)$	λ_{max}, nm (log ε)		
Ia	1 700	1 560			300.1 (3.41)	268.7 (2.98)	
Ib	1 675	1 570			294.1 (3.43)	276.5 (3.10)	
Ic	–	1 550			251.8 (3.10)	200.1 (3.08)	
IIa	1 732 1 674	1 620			349.6 (2.68)	303.8 (2.79)	247.8 (3.52)
IIb	1 730 1 722 1 670	1 620			350.6 (3.05)	269.1 (3.39)	246.9 (3.30)
IIc	1 705	1 620			345.8 (2.86)	312.5 (2.76)	229.4 (3.38)
IIIa	1 695	1 610	1 350	1 610	293.4 (3.50)	267.0 (3.28)	
IIIb	1 690	1 610	1 347	1 610	295.5 (3.51)	265.3 (3.21)	
IIIc	1 678	1 610	1 348	1 610	304.5 (3.56)	269.5 (3.29)	
IIId	1 688	1 612	1 358	1 612	306.4 (3.55)	262.1 (3.19)	
IIIe	1 695	1 605	1 343	1 605	354.1 (3.62)	337.4 (3.61)	277.5 (3.13)
IIIf	1 691	1 605	1 346	1 605	351.6 (3.68)	335.1 (3.73)	268.1 (3.04)

4-Benzylfuro[3,2-*b*]pyrrole-5-carboxylic Acid (*Ib*)

Sodium hydroxide (5%, 35 ml) was added to a solution of ethyl 4-benzylfuro[3,2-*b*]pyrrole-5-carboxylate (2.6 g, 10 mmol) in ethanol (100 ml). The mixture was refluxed for 2 h, concentrated and diluted with hot 50% ethanol. The hot solution was acidified with 17% hydrochloric acid to a weakly acidic reaction, poured on ice, the precipitate was filtered off and washed with water. The product was crystallized from ethanol–ethyl acetate 1 : 1. ^{1}H NMR: 5.61 s, 5 H ($CH_2C_6H_5$); 6.60 dd, 1 H (H-3, J(3,6) = 0.8); 6.83 d, 1 H (H-6); 7.16 bs, 5 H (H_{arom}); 7.70 d, 1 H (H-2, J(2,3) = 2.2).

4-Benzylfuro[3,2-*b*]pyrrole (*Ic*)

Method A. A mixture of acid *Ib* (3.4 g, 14 mmol) and copper chromite (0.98 g) in quinoline (28.8 ml) was stirred under nitrogen at 150 °C till the evolution of carbon dioxide ceased (about 4 h, monitored by introducing the reaction gases into lime milk). The mixture was then cooled to 0 °C and poured into ether (400 ml). The ethereal solution was first washed with 0.1M hydrochloric acid till all quinoline was removed and then with water to neutral reaction. Benzene was distilled off after being dried with sodium sulfate and the product was crystallized from hexane.

Method B. 4-Acetylfuro[3,2-*b*]pyrrole (7 g, 50 mmol) in benzene (270 ml) was added to 50% NaOH (150 ml). Benzyl chloride (6.4 g, 51 mmol) and triethylbenzylammonium bromide (2.3 g) were added to the well stirred mixture, which was heated to 60 °C for 6 h. The organic layer was separated after cooling and the aqueous one extracted with benzene (3 × 100 ml). The combined organic layers were worked up and the product was crystallized from hexane. ^{1}H NMR spectrum: 5.12 s, 2 H ($CH_2C_6H_5$); 6.04 dd, 1 H (H-6); 6.45 dd, 1 H (H-3, J(3,6) = 0.8); 6.91 dd, 1 H (H-5, J(5,6) = 3.0); 7.23 bs, 5 H (H_{arom}); 7.43 dd, 1 H (H-2, J(2,3) = 2.2, J(2,5) = 1.2).

4-Methylfuro[3,2-*b*]pyrrole (*Id*) was obtained in an analogous way employing methyl iodide instead of benzyl chloride. ^{1}H NMR spectrum: 3.56 s, 3 H (CH_3); 6.03 dd, 1 H (H-6); 6.39 dd, 1 H (H-3, J(3.6) = 0.8); 6.53 dd, 1 H (H-5, J(5.6) = 3.0); 7.31 dd, 1 H (H-2, J(2.3) = 2.2, J(2.5) = 1.2). ^{13}C NMR: 144.1 (C-2); 98.16 (C-3); 126.38 (C-3a); 123.90 (C-5); 90.69 (C-6); 144.90 (C-3a); 34.86 (CH_3). ^1J(C-2,H-2) = 202.2, ^2J(C-2,H-3) = 10.5, ^1J(C-3,H-3) = 177.4, ^2J(C-3,H-2) = 13.7, ^1J(C-5,H-5) = 184.0, ^2J(C-5,H-6) = 7.6, ^1J(C-6,H-6) = 175.9, ^2J(C-6,H-5) = 8.5, ^3J(C-5,CH_3N) = 3.6.

Dimethyl 1-Benzyl-6-hydroxyindole-4,5-dicarboxylate (*IIa*)

Methyl butynedioate (2.41 g, 17 mmol) was added to 4-benzylfuro[3,2-*b*]pyrrole (3 g, 15 mmol) in acetonitrile (10 ml). After the exothermal reaction the solvent was distilled off and the product was crystallized from methanol. ^{1}H NMR spectrum: 3.75 s, 3 H (CH_3); 3.85 s, 3 H (OCH_3); 5.37 s, 2 H ($CH_2C_6H_5$); 6.69 dd, 1 H (H-3, J (3.7) = 0.7); 6.98 – 7.42 m, 5 H (H_{arom}); 7.06 dd, 1 H (H-7); 7.52 d, 1 H (H-2); 9.80 s, 1 H (OH).

Ethyl 4,5-Dimethyl-1-benzyl-6-hydroxyindole-2,4,5-tricarboxylate (*IIb*)

This compound was prepared analogously as *IIa* starting from ethyl 4-benzylfuro[3,2-*b*]pyrrole-5-carboxylate and dimethyl butynedioate, 80 h reaction time and reflux temperature of the solvent. ^{1}H NMR spectrum: 3.75 s, 3 H (OCH_3); 3.86 s, 3 H (OCH_3); 5.77 s, 2 H ($CH_2C_6H_5$); 6.90 – 7.40 m, 5 H (H_{arom}); 7.12 d, 1 H (H-7); 7.55 d, 1 H (H-3).

Ethyl 1-benzyl-6-hydroxyindole-4-carboxylate (*IIc*) was obtained by the same procedure employing ethyl propynoate and 25 h reaction time at reflux temperature. ^{1}H NMR spectrum: 1.30 t, 3 H (CH_3); 4.02 q, 2 H (OCH_2); 5.37 s, 2 H ($CH_2C_6H_5$); 6.86 dd, 1 H (H-3, J(3,7) = 0.7); 7.03 dd, 1 H (H-7); 7.03 – 7.22 m, 5 H (H_{arom}); 7.37 d, 1 H (H-5, J(5,7) = 2.2); 7.46 d, 1 H (H-2, J(2,3) = 3.2); 9.37 s, 1 H (OH).

Ethyl 2-*R*-4-(4-Nitrobenzyl)furo[3,2-*b*]pyrrole-5-carboxylates *IIIa*, *IIIc*, *IIIe*

Na_2CO_3 (32%, 350 ml) and 4-nitrobenzyl bromide (3.9 g, 18 mmol) were added to the respective ethyl 2-*R*-furo[3,2-*b*]pyrrole-5-carboxylate (17 mmol) in benzene (300 ml) with vigorous stirring. After addition of tetrabutylammonium bromide (1.2 g) the stirred mixture was heated to 60 °C for 7 h, cooled and the organic layer was separated. The aqueous layer was extracted three times with benzene, the combined benzene solutions were washed with water, dried with sodium sulfate, the solvent was distilled off under diminished pressure and the product was crystallized from ethanol.

Ethyl 2-*R*-4-(2-nitrophenyl)furo[3,2-*b*]pyrrole-5-carboxylates *IIIb*, *IIId*, *IIIf* were synthesized using 2-nitrobenzyl chloride (3.1 g, 18 mmol) and 16 h reaction time. ^{1}H NMR spectra of compounds *IIIa* – *IIIf* are listed in Table III. Mass spectrum of *IIIb*, *m/z* (%): 314 (88), 284 (9), 269 (6), 241 (42), 225 (18), 213 (54), 195 (18), 179 (45), 157 (12), 151 (27), 133 (100), 122 (40), 119 (39), 115 (15), 106 (35), 92 (24), 89 (18), 78 (67), 65 (24), 63 (18), 51 (20), 44 (36), 28 (61).

Ethyl 2-Phenyl-4-(2-aminobenzyl)furo[3,2-*b*]pyrrole-5-carboxylate (*IIIg*)

Palladium on charcoal (10%, 0.15 g) was added to methanolic solution of *IIIf* (2.34 g, 60 mmol, 30 ml). The stirred mixture was hydrogenated at 350 kPa and 45 °C till consumption of hydrogen ceased. The catalyst was filtered off, the solvent was removed in vacuo and the product was crystallized from ethanol. ^{1}H NMR spectrum: 1.30 t, 3 H (CH_3); 4.01 q, 2 H (OCH_2); 5.61 s, 2 H ($CH_2C_6H_5$); 6.59 d, 1 H (H-3, J(3,6) = 0.88); 6.90 d, 1 H, (H-6); 7.62 – 7.69 m, 9 H (H_{arom}); 7.75 s, 2 H (NH_2).

TABLE III
^{1}H NMR spectra (δ, ppm) of compounds *III*

Compound	R	H-3	H-6	CH_2	H_{arom}	J, Hz
IIIa	7.69 d	6.78 dd	6.91 d	5.84 s	7.36 d 8.16 d	J(2,3) = 2.2 J(H_{arom}) = 9 J(3,6) = 0.9
IIIb	7.77 d	6.69 dd	6.92 d	5.94 s	6.32 – 6.44 m 7.43 – 7.58 m 8.03 – 8.15 m	J(2,3) = 2 J(3,6) = 0.8
IIIc	2.40 s	6.30 d	6.83 d	5.81 s	7.38 d 8.17 d	J(3,6) = 0.9 J(H_{arom}) = 8.6
IIId	2.41 s	6.28 d	6.93 d	6.00 s	6.40 – 6.62 m 7.47 – 7.62 m 8.07 – 8.10 m	J(3,6) = 0.8
IIIe	7.32 – 7.79 m	6.93 d	7.27 d	5.75 s	7.36 d 8.13 d	J(3,6) = 0.8 J(H_{arom}) = 8.6
IIIf	7.25 – 7.72 m	6.89 d	6.98 d	5.94 s	6.55 – 6.72 m 7.40 – 7.57 m 7.97 – 8.10 m	J(3,6) = 0.8

2-Phenylfuro[2',3':4,5]pyrrolo[2,1-c][1,4]benzodiazepin-11-one (*IV*)

2-Hydroxypyridine (2.5 g, 20 mmol) was added to compound *IIIg* (1.8 g, 5 mmol) in xylene (10 ml). The mixture was refluxed for 70 h, cooled and the precipitate was crystallized from dimethylformamide. ^{1}H NMR spectrum: 5.31 s, 2 H (CH_2); 6.82 s, 1 H (=CH); 7.39 – 7.73 m, 7 H (H_{arom}); 10.22 s, 1 H (NH).

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