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

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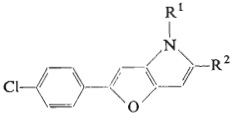
Reduction, hydrolysis, N-alkylation and N-acylation of 2-(chlorophenyl)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate are described. The HMO method was used to calculate compounds *I*, *II*, *IV* and *X* as model substances furo[3,2-*b*]pyrrole, 2-phenylfuro[3,2-*b*]pyrrole and methyl furo[3,2-*b*]pyrrole-5-carboxylate. The stability and reactivity of the synthesized compounds are discussed on the basis of indexes of chemical reactivity.

Our preceding papers[1,2] dealt with the preparation of some ethyl 2-aryl-4*H*-furo[3,2-*b*]pyrrole-5-carboxylates of which the derivative bearing a 2-nitrophenyl group in position 2 of furo[3,2-*b*]pyrrole system was of interest[2]. This paper concerns the



	R^1	R^2
I	H	$COOC_2H_5$
II	H	COOH
III	H	CH_3
IV	CH_3	$COOC_2H_5$
V	C_2H_5	$COOC_2H_5$
VI	C_2H_5	CH_2OH
VII	C_2H_5	COOH
VIII	C_2H_5	COCl
IX	C_2H_5	$CONH_2$

	R^1	R^2
X	$COCH_3$	$COOC_2H_5$
XI	CH_2CH_2CN	$COOC_2H_5$
XII	CH_2CH_2COOH	COOH
XIII	$CH_2-CH-CH_2$ (O)	$COOC_2H_5$
XIV	$CH_2-CH(OH)-CH_2NH_2$ HCl	$COOC_2H_5$
XV	$CH_2CH(OH)CH_2NH.HCl$ $CH(CH_3)_2$	$COOC_2H_5$
XVI	$CH_2-CH(OH)-CH_2NH.HCl$ $C(CH_3)_3$	$COOC_2H_5$

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reactions of 2-(4-chlorophenyl)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate from which the series of compounds *II*–*XVI* was prepared (Table I)

TABLE I

Substituted 2-(Chlorophenyl)furo[3,2-*b*]pyrroles (*II*—*XVI*)

Compound	Formula (mol. weight)	Calculated/Found				M.p., °C (yield, %)
		% C	% H	% N	% Cl	
II	$C_{13}H_8ClNO_3$ (261·7)	59·67 / 59·49	3·08 / 3·12	5·35 / 5·29	13·55 / 13·72	210 (70)
III	$C_{13}H_{10}ClNO$ (231·7)	67·39 / 67·48	4·35 / 4·26	6·04 / 6·05	15·30 / 14·81	217 (24)
IV	$C_{16}H_{14}ClNO_3$ (303·7)	63·28 / 63·52	4·64 / 4·58	4·64 / 4·82	11·67 / 11·45	140 (73)
V	$C_{17}H_{16}ClNO_3$ (318·8)	64·05 / 64·30	5·06 / 4·98	4·41 / 4·13	11·12 / 10·91	110 (68)
VI	$C_{15}H_{14}ClNO_2$ (275·7)	65·34 / 65·26	5·11 / 5·01	5·07 / 4·86	12·85 / 12·63	75 (26)
VII	$C_{15}H_{12}ClNO_3$ (289·7)	62·19 / 62·09	4·17 / 4·07	4·83 / 4·93	12·24 / 11·97	165 (74)
VIII	$C_{15}H_{11}Cl_2NO_2$ (308·2)	58·47 / 58·37	3·59 / 3·49	4·54 / 4·48	23·00 / 22·84	—
IX	$C_{15}H_{13}ClN_2O_2$ (288·7)	62·39 / 62·64	4·53 / 4·48	9·70 / 9·76	12·27 / 11·97	155 (52)
X	$C_{17}H_{14}ClNO_4$ (331·7)	61·15 / 61·30	4·25 / 4·20	4·20 / 4·00	10·69 / 10·46	131 (73)
XI	$C_{18}H_{15}ClN_2O_3$ (342·8)	63·07 / 62·87	4·41 / 4·24	8·17 / 8·07	10·34 / 10·36	169 (76)
XII	$C_{16}H_{12}ClNO_5$ (333·7)	57·59 / 57·70	3·87 / 3·78	4·20 / 4·36	10·62 / 10·42	200—202 (54)
XIII	$C_{18}H_{16}ClNO_4$ (345·6)	62·25 / 62·50	4·66 / 4·48	4·05 / 4·12	10·26 / 10·30	109 (96)
XIV	$C_{18}H_{20}Cl_2N_2O_4$ (399·3)	54·14 / 54·17	5·05 / 4·95	7·01 / 7·12	17·75 / 17·36	247—248 (32)
XV	$C_{21}H_{26}Cl_2N_2O_4$ (441·3)	57·71 / 57·59	5·94 / 5·82	6·34 / 6·54	16·06 / 15·92	245—247 (80)
XVI	$C_{22}H_{28}Cl_2N_2O_4$ (455·4)	58·02 / 59·92	6·19 / 6·09	6·15 / 6·02	15·57 / 15·36	226—228 (53)

Reduction of *I* with $LiAlH_4$ afforded at room temperature a mixture of 5-methyl- and 5-hydroxymethyl derivatives. At temperature of boiling ether the pure 2-(4-chlorophenyl)-4*H*-5-methylfuro[3,2-*b*]pyrrole (*III*) was obtained.

Hydrolysis of *I* furnished 2-(4-chlorophenyl)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid (*II*), the decarboxylation of which was investigated under various conditions. Thus, in quinoline in the presence of copper powder resinous products were isolated. The decarboxylation was monitored directly in the cell by means of ^{1}H-NMR spectroscopy in pentadeuteriopyridine. The decarboxylation without catalyst did not take place up to 110°C, whilst in the presence of copper powder opening of the furo-[3,2-*b*]pyrrole ring system occurred. Similarly, opening of the system was observed in xylene in the presence of Ba^{2+}. The 2-nitrophenyl residue, as an electron-accepting substituent, might influence more substantially the stability of the skeleton than 4-chlorophenyl. This fact would explain the successful decarboxylation reported in our previous paper[2].

Further experiments were pointed to the alkylation at nitrogen of the substituted furo[3,2-*b*]pyrrole system. The interphase transfer catalysis was successfully applied to preparation of ethyl 2-(chlorophenyl)-4-ethylfuro[3,2-*b*]pyrrole-5-carboxylate (*V*), which hydrolyzed in an alkaline medium to give the corresponding acid *VII*. 2-(4--Chlorophenyl)-4-ethylfuro[3,2-*b*]pyrrole-5-carboxylic acid yielded with thionyl chloride the chloride, which afforded with ammonia the corresponding amide *IX*.

The reaction of *I* with lithium hydride in dimethylformamide furnished the N-lithium derivative, which gave with acetyl chloride the N-acetyl compound *X*. The N-methyl derivative of *IV* was prepared under analogous conditions as *V*. The reaction of *I* with acrylonitrile in pyridine afforded in the presence of benzyltrimethylammonium hydroxide the compound *IX*. Cyano and ethoxycarbonyl groups hydrolyzed to give the dicarboxylic acid *XII*. (Chloromethyl)oxirane reacted with *I* under formation of 4-(2,3-epoxypropyl) derivative *XIII*. The latter opens its oxirane ring with nitrogen bases to furnish the amino-hydroxy derivatives; these afforded with ethanolic HCl derivatives *XIV*, *XV*, *XVI*, which are, at the time being, biologically tested. The IR, UV, and ^{1}H-NMR spectra data are listed in Tables II and III. The IR spectral data revealed that the effect of N-substitution on the ν(C=O) band position of the ethoxycarbonyl group was more pronounced in compound *X* only. The chemical shifts of protons of *II* and *III* showed that replacement of the substituent in position 5 of the furo[3,2-*b*]pyrrole system influenced the chemical shift of H_6. The alteration of the substituent in position 5 little influenced chemical shifts of H_3. Also the substituent at nitrogen affected very little the chemical shift of H_6. The more significant shift of the δH_6 value toward lower field occurred when introducing acetyl group into position 4.

A long distance coupling constant between protons H_3 and H_6 was found to be $J_{3,6} = 0{\cdot}7$ Hz. The efficacy of the spin-spin interaction transmission well increased both in unsaturated systems with the W shaped skeleton and in saturated systems

TABLE II

Infrared (ν, cm^{-1}) and Ulraviolet Spectra (λ_{max}, nm) of Compounds *II*—*XVI*

Compound	ν(C=O)	ν(C=C)	λ_{max}	log ε	λ_{max}	log ε
II	1 680	1 535	343·0	4·67	357·1	4·66
III	—	1 490	348·2	4·51	—	—
IV	1 680	1 520	341·6	4·49	358·1	4·69
V	1 695	1 520	336·1	4·25	357·1	4·56
VI	—	1 530	341·3	4·69	—	—
VII	1 660	1 520	343·3	4·78	—	—
IX	1 640	1 610	342·8	4·75	359·4	4·70
X	1 710	1 525	341·6	4·77	357·1	4·74
XI	1 680	1 525	341·0	4·56	357·1	4·70
XII	1 617	1 520	341·6	4·69	357·1	4·65
XIII	1 690	1 520	342·1	4·75	358·1	4·71
XIV	1 685	1 525	343·3	4·76	359·1	4·68
XV	1 685	1 525	343·3	4·71	358·1	4·71
XVI	1 685	1 527	343·3	4·75	359·1	4·66

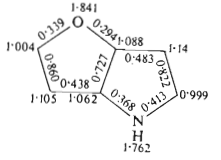
TABLE III

^{1}H-NMR Spectra of Compounds *II*—*XVI* (δ, ppm)

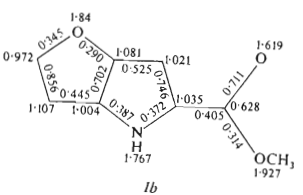
Compound	H_A[a]	H_B[a]	H_3[b]	H_4[b]	Further signals		
II	7·81	7·49	7·12	6·67		11·62	
III	7·70	7·40	6·89	5·83		2·34	
IV	7·75	7·42	7·18	6·77		3·91	
V	7·71	7·41	7·19	6·75	4·47		1·36
VI	7·68	7·38	7·21	5·98	4·41	4·05	1·36
VII	7·78	7·47	7·39	6·80	4·48		1·36
VIII	7·82	7·50	7·34	6·68	4·46		1·36
IX	7·88	7·53	7·30	6·91	4·48		1·36
X	7·63	7·47	7·41	7·05		2·65	
XI	7·76	7·46	7·33	6·88	4·69		2·97
XII	7·76	7·46	7·33	6·86			
XIII	7·75	7·47	7·31	6·86	2·80	4·8	4·47
XIV	7·75	7·48	7·30	6·86	4·27	4·32	
XV	7·78	7·50	7·38	6·85	4·47	4·22	1·22
XVI	7·76	7·48	7·42	6·85	4·48		1·25

[a] $J_{A,B} = 8·5$ Hz; [b] $J_{3,6} = 0·7$ Hz.

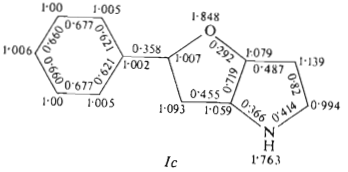
by the C-mechanism. Therefore, one can observe in the spectrum an interaction through 5 bonds. The magnitude of this coupling constant is comparable with that of naphthalene $J_{1,5} = 0{\cdot}8$ Hz.



Ia

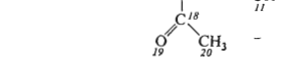


Ib



Ic

Compounds *Ia*–*Ic*, *II*, *IV* and *X* were subjected to calculation by the standard HMO method. The distribution of π-electrons on the unsubstituted furo[3,2-*b*]pyrrole system proved that a compound with a not well pronounced aromatic character (the order of double bonds 0·98–0·73, the order of single bonds 0·44–0·48) was involved. The introduction of a strong electron-accepting substituent (COOH, COOR) into position 5 increased the aromatic character of the skeleton this being



indicated by the more uniform distribution of π-electrons along the bonds. Substitution of the skeleton at carbon 2 by phenyl influenced the charge distribution only feebly and more at furan ring than at pyrrole. The π-charge density of compounds *I*, *II*, *IV* and *X* is very similar to each other; a little alteration after introduction of an acetyl group on nitrogen of compound *X* was observed in the ^{1}H-NMR spectrum as a shift of the proton signal of carbon 6. Table IV lists the calculated indexes

TABLE IV

HMO Indexes of Chemical Reactivities of Atoms 1—20 in Compounds *I*, *II*, *IV* and *X*

Index		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	18	19	20
	I	1·85	0·98	1·10	1·77	1·03	1·02	1·00	1·07	0·63	1·62	1·93	1·01	1·00	1·01	0·99	—	—	—
Q	*II*	1·85	0·98	1·10	1·77	1·02	1·03	1·00	1·07	0·72	1·56	1·89	1·00	1·00	1·01	0·99	—	—	—
	IV	1·85	0·98	1·10	1·75	1·04	1·03	1·01	1·08	0·63	1·62	1·93	1·01	1·00	1·01	1·99	0·99	—	—
	X	1·84	0·98	1·10	1·72	1·04	1·01	1·00	1·07	0·63	1·62	1·93	1·01	1·00	1·01	0·99	0·57	1·60	1·91
	I	—	0·25	0·47	—	0·21	0·46	0·19	0·22	—	—	—	0·13	0·43	0·40	0·30	—	—	—
F	*II*	—	0·25	0·47	—	0·20	0·47	0·19	0·22	—	—	—	0·13	0·43	0·40	0·30	—	—	—
	IV	—	0·25	0·48	—	0·21	0·46	0·19	0·22	—	—	—	0·13	0·43	0·40	0·30	—	—	—
	X	—	0·25	0·47	—	0·22	0·47	0·20	0·22	—	—	—	0·13	0·43	0·40	0·30	—	—	—
	I	0·15	0·90	0·75	0·25	0·71	1·03	0·78	0·64	1·83	0·59	0·11	0·76	0·91	0·82	0·89	—	—	—
S_N	*II*	0·15	0·92	0·75	0·25	0·70	1·08	0·81	0·64	1·97	0·81	0·20	0·76	0·92	0·82	0·89	—	—	—
	IV	0·15	0·90	0·75	0·27	0·69	1·00	0·76	0·63	1·82	0·58	0·11	0·76	0·91	0·82	0·89	0·02	—	—
	X	0·16	0·92	0·75	0·26	0·74	1·11	0·82	0·66	1·84	0·60	0·11	0·76	0·92	0·82	0·89	1·75	0·51	0·11
	I	0·94	0·94	1·18	0·88	1·03	0·90	0·91	1·12	0·30	0·77	0·64	0·80	0·93	0·86	0·91	—	—	—
S_E	*II*	0·94	0·99	1·18	0·88	1·03	0·93	0·92	1·12	0·39	1·23	0·64	0·80	0·93	0·86	0·91	—	—	—
	IV	0·94	0·99	1·19	0·95	1·03	0·94	0·91	1·14	0·29	0·77	0·64	0·80	0·93	0·86	0·91	1·10	—	—
	X	0·93	0·98	1·17	0·82	1·04	0·87	0·91	1·13	0·30	0·77	0·64	0·80	0·93	0·86	0·91	0·20	0·68	0·92
Bond		8–7	1–2	2–3	4–5	5–6	6–8	3–7	1–8	4–18	5–9	9–10	9–11	2–12	12–13	13–14	14–15	18–19	18–20
	I	0·69	0·32	0·80	0·37	0·76	0·53	0·46	0·29	—	0·41	0·71	0·31	0·36	0·62	0·68	0·65	—	—
p_{ij}	*II*	0·69	0·32	0·80	0·37	0·74	0·53	0·46	0·29	—	0·43	0·72	0·36	0·36	0·62	0·68	0·65	—	—
	IV	0·69	0·32	0·80	0·38	0·73	0·54	0·46	0·29	0·10	0·41	0·71	0·31	0·36	0·62	0·68	0·65	—	—
	X	0·70	0·33	0·79	0·36	0·75	0·52	0·47	0·29	0·31	0·41	0·71	0·31	0·36	0·62	0·68	0·65	0·76	0·05

of chemical reactivity of compounds under study (for numbering see Fig. 2): F the index of free valence, S_N and S_E the nucleophilic and electrophilic superdelocalizations. Basing both at these indexes and values of localization energies the nucleophilic attack for model *Ia* is anticipated at carbons 5 and 2 and the electrophilic one to heteroatoms of the skeleton: oxygen > nitrogen. Introduction of a methoxycarbonyl group into position 5 predicts a nucleophilic attack at carbon 9 (reactions of the methoxycarbonyl group – hydrolysis, reesterification, preparation of chlorides, amides) or to positions 6 and 2 and an electrophilic attack at heteroatoms. This would evidence the possible furan ring cleavage by reactions in acid medium. Basing upon S_E the attack at position 8 and for model *Ic* at position 3 are very probable (possible electrophilic substitution reactions). Nucleophilic reactions for derivatives *I*, *II*, *IV* and *X* are predicted to positions 6 and 9 (L_N and S_N) and electrophilic reactions at heteroatoms (L_N) and in position 3 (S_E).

EXPERIMENTAL

2-(4-Chlorophenyl)-5-methyl-4*H*-furo[3,2-*b*]pyrrole (*III*)

Compound *I* (ref.[1], 1·45 g, 5 mmol) was added to a suspension of $LiAlH_4$ (0·38 g, 10 mmol) in ether at room temperature with stirring, which was continued at reflux for 90 min. The unreacted $LiAlH_4$ was decomposed, the ethereal layer separated and the aqueous one extracted with ether. The combined ethereal layers were washed with water, dried with anhydrous sodium sulfate, ether removed under diminished pressure and the residue crystallized from benzene. 2-(4-Chlorophenyl)-4-ethyl-5-hydroxymethylfuro[3,2-*b*]pyrrole (*VI*) was synthesized in an analogous way.

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

A solution of sodium hydroxide (50%, 30 ml), ethyl iodide (1·2 g, 7·7 mmol) and triethylbenzylammonium chloride (0·4 g) was added to a stirred solution of *I* (1·94 g, 6·7 mmol) in benzene. The solution was heated to 65%C for 4 h, then cooled, diluted with water and the organic layer separated. The aqueous layer was extracted with ether. The combined organic layers were washed with water, dried with anhydrous sodium sulfate, organic solvents were distilled off and the product crystallized from methanol. Ethyl 2-(4-chlorophenyl)-4-methylfuro[3,2-*b*]pyrrole-5-carboxylate (*IV*) was prepared by this procedure, as well.

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

A solution of NaOH (5%, 20 ml) was added to *V* (2·13 g, 6·7 mmol) dissolved in ethanol (100 ml) and heated on a steam bath for 2 h. The solution was concentrated to one half of its volume, the precipitate filtered off, dissolved in aqueous ethanol, acidified with hydrochloric acid (1 : 1) and poured on a crushed ice. The separated precipitate was filtered off and crystallized from methanol. 2-(4-Chlorophenyl)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid (*II*) was obtained from *I* in the same way.

2-(4-Chlorophenyl)-4-ethylfuro[3,2-*b*]pyrrole-5-carboxamide (*IX*)

Compound *VII* (1·45 g, 5 mmol) was heated at reflux with thionyl chloride for 4 h, the excess of the reagent was distilled off *in vacuo* and the residue chromatographed on a silica gel packed column with benzene–ether 2 : 3. The chloride *VIII* was crystallized from benzene. Solution of *VIII* (1 g, 3·3 mmol) in benzene (40) ml) saturated with gaseous ammonia was left to stand at room temperature for 30 min, the separated ammonium chloride was filtered off, the filtrate concentrated and *IX* crystallized from ethanol.

Ethyl 2-(4-chlorophenyl)-4-acetylfuro[3,2-*b*]pyrrole-5-carboxylate (*X*)

Lithium hydride (48 mg, 6 mmol) was added at room temperature to the solution of *I* (1·45 g, 5 mmol) in dimethylformamide (30 ml). The mixture was stirred at 30°C till the evolution of hydrogen ceased, then acetyl chloride was added (0·39 g, 5 mmol) and stirring was continued at 60°C for 2 h. The solution was poured into cool water (10 ml) and the precipitate crystallized from ethanol.

Ethyl 2-(4-chlorophenyl)-4-(2-cyanoethyl)furo[3,2-*b*]-pyrrole-5-carboxylate (*XI*)

Acrylonitrile (1·5 g, 30 mmol) and a 40% solution of triethylbenzylammonium hydroxide (0·5 ml) were added to a solution of *I* (1·16 g, 4 mmol) in pyridine (40 ml) and heated at reflux for 20 min. The solution was cooled, the solvent removed *in vacuo* and the product crystallized from ethanol.

2-(4-Chlorophenyl)-4-(2-carboxyethyl)furo[3,2-*b*]pyrrole-5-carboxylic Acid (*XII*)

The solution of *XI* (1·14 g, 3·3 mmol) in ethanol was heated at reflux with sodium hydroxide (2·12 g) in water (10 ml), till the evolution of NH_3 ceased. Ethanol was distilled off under reduced pressure and the concentrated solution, hot-dissolved in ethanol and precipitated with dilute hydrochloric acid 1 : 1, poured onto ice; the green precipitate was suction-filtered, washed with water and crystallized from ethanol.

Ethyl 2-(4-chlorophenyl)-4-(2,3-epoxypropyl)furo[3,2-*b*]pyrrole-5-carboxylate (*XIII*)

Triethylbenzylammonium hydroxide (0·5 ml) was added to a suspension of *I* (5 g, 17 mmol) in a fresh-distilled (chloromethyl)oxirane (100 ml). The mixture heated at reflux till the starting *I* disolved was then filtered and the solvent removed *in vacuo*. The obtained product was crystallized from ethanol.

2-(4-Chlorophenyl)-4-(3-isopropylamio-2-hydroxypropyl)-5-ethoxycarbonylfuro[3,2-*b*]pyrrole Hydrochloride (*XV*)

Solution of *XIII* (1·14 g, 3·3 mmol) and isopropylamine (1·2 g, 20 mmol) heated at reflux in ethanol (50 ml) for 6 h was then concentrated under reduced pressure. The pH of the residue dissolved in ethanol was adjusted with ethanolic HCl to 4—5. The volatile constituents were distilled off *in vacuo* and the remaining hydrochloride was crystallized from ethanol. According to this procedure following substances were also prepared: 2-(4-chlorophenyl)-4-(t-butylamino-2-hydroxypropyl)ethoxycarbonyl[3,2-*b*]pyrrole hydrochloride (*XVI*) and 2-(4-chlorophenyl)-4-(3-amino--2-hydroxypropyl)-5-ethoxycarbonylfuro[3,2-*b*]pyrrole hydrochloride (*XIV*).

Spectral Measurements

The IR spectra were measured with a Zeiss, Jena spectrophotometer using the KBr technique (1 mg per 1 g of KBr). The electronic absorption spectra were recorded with a Specord UV-VIS (Zeiss, Jena) spectrophotometer in methanol at a $2 . 10^{-5}$—$5 . 10^{-5}$ mol l^{-1} concentration at ambient temperature. The ^{1}H-NMR spectra were taken with a Tesla BS 487 C spectrometer operating at 80 MHz in hexadeuteriodimethyl sulfoxide with hexamethylsiloxane as an internal reference.

Calculations

The standard Hückel HMO method[3-7] was used for calculation of derivatives *Ia—Ic*, *II*, *IV* and *X*. The employed parameters were taken from the paper by Purcell and Singer[4].

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