SYNTHESIS AND PROPERTIES OF 4-ALKYLAMINOMETHYL AND 4-ALKOXYMETHYL DERIVATIVES OF 5-METHYL-2-FURANCARBOXYLIC ACID

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New β-substituted amines and ethers of the furan series (*II*—*V*) were prepared by reaction of methyl 4-bromomethyl-5-methyl-2-furancarboxylate (*I*) with nucleophiles such as pyrrolidine, piperidine, morpholine, N-phenylpiperazine, cyclohexylamine, 2-methylcyclohexylamine, N-ethylaniline, *p*-toluidine, ethanol, butanol and salicylaldehyde. The structure of the products was confirmed by their analytical and spectral data. Kovats indices *I* for the products were determined using gas–liquid chromatography.

Recently, there is an increasing interest in β-substituted furan derivatives, concerning not only theoretical aspects but also practical utilization. To this group of compounds belong also biologically highly active amides of 2,5-dimethyl-3-furancarboxylic acid such as "Xyligen" (N-cyclohexyl-N-methoxyamide), used as fungicide and insecticide in the protection of wood[1]. In the present study we prepared some new 4-alkylaminomethyl, 4-alkoxymethyl, and 4-aryloxymethyl derivatives of 5-methyl-2-furancarboxylic acid.

The starting methyl 4-bromomethyl-4-methyl-2-furancarboxylate (*I*) is a reactive compound that has been utilized, *e.g.* in the synthesis of furan-substituted benzoindolizines[2]. Compound *I* reacted with primary and secondary nitrogen nucleophiles such as pyrrolidine, piperidine, morpholine, N-phenylpiperazine, cyclohexylamine, 2-methylcyclohexylamine, and N-ethylaniline, to afford the corresponding 4-alkylaminomethyl derivatives *IIa*—*IIg* (Table I). The reaction was performed with two molar equivalents of the amine; the second equivalent of the amine bonded the liberated hydrogen bromide. Compounds *II* were obtained in 52—70% yields at room temperature in benzene, except compound *IIg* which was prepared only in 44% yield. A temperature study showed that slightly higher temperatures had a beneficial effect (70% yield at 40—50°C but 61% at reflux temperature).

In the reaction of *I* with *p*-toluidine, both at room and elevated temperature, the intermediate more basic secondary amine reacts with another molecule of *I* under

formation of N,N-bis(5-methoxycarbonyl-2-methyl-3-furylmethyl)-*p*-toluidine (*III*). In accord with the results of Mocelo and Kováč[3], who on reaction of *I* with 5-nitro--2-furfuryl bromide at room temperature isolated only the obviously less basic toluidinomethyl derivative, we found that the replacement of the nitro group by the less electron-accepting methoxycarbonyl group, as well as the shift of the reaction center

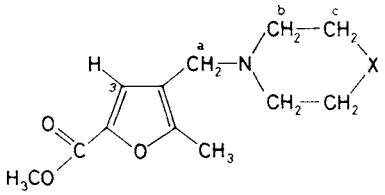
TABLE I

β-Substituted furan amines and ethers *II*—*V* and their UV spectral data

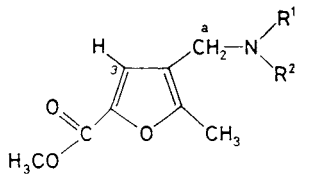
Compound	Formula (mol. wt.)	B.p., °C/p, Pa (yield, %)	Calculated/found			λ_{max}, nm (log ε, m^2 mol^{-1})
			% C	% H	% N	
IIa	$C_{12}H_{17}NO_3$ (223·3)	100/66·6 (54)	64·56 64·85	7·68 7·94	6·27 6·32	266 (3·13)
IIb	$C_{13}H_{19}NO_3$ (237·3)	120/79·8 (61)	65·74 65·90	8·10 8·25	5·90 5·71	266 (3·21)
IIc	$C_{12}H_{17}NO_4$ (239·3)	47[a,b] (63)	60·23 60·52	7·16 7·23	5·85 6·05	265 (3·19)
IId	$C_{18}H_{22}O_3N_2$ (314·4)	50—53[a,b] (64)	68·76 68·53	7·05 7·12	8·91 9·09	255 (3·28)
IIe	$C_{14}H_{21}NO_3$ (251·3)	156/26·6 (52)	66·90 —	8·42 —	5·57 5·95	252[c] (3·28)
IIf	$C_{15}H_{23}NO_3$ (265·3)	152/16 (68)	67·89 —	8·74 —	5·28 5·43	266 (3·06)
IIg	$C_{16}H_{19}NO_3$ (273·3)	164—166/133 (70)	70·31 —	7·01 —	5·13 6·27	256 (2·71)
III	$C_{23}H_{25}NO_6$ (411·4)	140[a,d] (49)	67·14 67·91	6·12 6·36	3·40 4·08	264 (3·53)
IVa	$C_9H_{12}O_4$ (184·2)	83—84[a,e] (63)	58·68 58·43	6·57 6·35	— —	261 (3·09)
IVb	$C_{11}H_{16}O_4$ (212·2)	66[a,e] (87)	62·25 62·12	7·60 7·17	— —	264 (3·26)
V	$C_{15}H_{14}O_5$ (274·3)	85[a,f] (73)	65·67 65·33	5·14 4·99	— —	265 (3·32) 318 (2·65)

[a] M.p.; [b] from ether–hexane (1 : 1); [c] shoulder at 266 nm; [d] from ethanol; [e] from water; [f] from acetone–hexane.

from α- to β-position, decreases the deactivation effect of the substituent on the amine basicity.

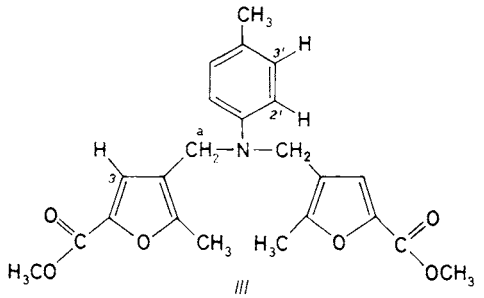


II a, X missing
II b, X = CH_2
II c, X = O
II d, X = N—C_6H_5

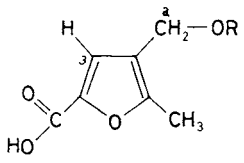


II e, R^1 = H; R^2 = cyclohexyl
II f, R^1 = H; R^2 = 2-methylcyclohexyl
II g, R^1 = C_2H_5; R^2 = C_6H_5

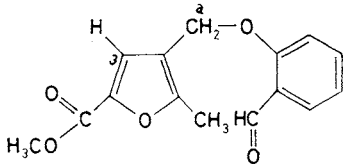
In the reaction of *I* with an alcohol in the presence of an alkali metal hydroxide, the nucleophilic substitution is accompanied by hydrolysis of the ester group. Thus, treatment with ethanol or butanol and potassium hydroxide afforded the corresponding 4-alkoxymethyl-5-methyl-2-furancarboxylic acids *IVa* and *IVb*.



III



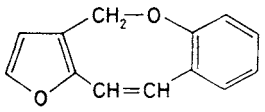
IV a, R = C_2H_5
IV b, R = $CH_3(CH_2)_3$



V

From the halogenomethyl derivative *I* and sodium salt of salicylaldehyde we prepared methyl 4-(2-formylphenoxymethyl)-5-methyl-2-furancarboxylate (*V*) as the starting compound for synthesis of 4*H*-benzo[*b*]furo[2,3-*f*]oxocine (*VI*), compound

with potentially aromatic carbanion. However, due to the low acidity of the methyl hydrogen in the position 5, as well as the possible mutually unfavorable position of the methyl and formyl groups, no closure of the eight-membered ring took place on treatment with methanolic sodium methoxide or potassium acetate in acetic acid and acetic anhydride, or with potassium tert-butoxide in butanol.



VI

Structure of the β-substituted furan amines and ethers *II* – *V* was confirmed by elemental analysis and spectral data; their purity was checked by gas–liquid chroma-

TABLE II

^{1}H NMR data (δ, ppm) for derivatives *II* – *V*

Compound	CH_3	OCH_3	$(CH_2)_a$	H_3	Other signals
IIa	2·35	3·84	3·39	7·13	1·75 m (CH_2)$_c$; 2·47 m (CH_2)$_b$
IIb	2·34	3·85	3·26	7·12	1·13 m (CH_2)$_c$; 2·34 m (CH_2)$_b$
IIc	2·33	3·84	3·28	7·08	2·44 t (CH_2)$_b$; 3·66 t (CH_2)$_c$
IId	2·34	3·84	3·35	7·16	2·56 t (CH_2)$_b$; 3·20 t (CH_2)$_c$; 6·77–7·40 m (C_6H_5)
IIe	2·35	3·86	3·58	7·14	1·00–2·00 m (CH_2)[a]; 2·35 m (CH—N); 1·51 s (NH)
IIf	2·36	3·86	3·55	7·15	0·97 d (CH_3—CH); 2·37 m (CH—N); 1·06–2·27 m (CH_2, CH)[a], NH
IIg	2·31	3·80	4·21	7·00	1·12 t (CH_3—CH_2); 3,35 q (CH_2—CH_3); 6·50–7·37 m (C_6H_5)
III	2·20	3·81	4·11	6·95	2·22 s (CH_3—C_6H_4); 6·72 d (H_3'); 7·00 d (H_2'); J (H_2', H_3') = 9 Hz
IVa	2·39	—	4·34	7·29	1·25 t (CH_2—CH_3); 3·52 q (CH_2—CH_3); 9·92 bs (OH)
IVb	2·41	—	4·33	7·28	0·92 m (CH_3—CH_2); 1·52 m (CH_2—CH_2—CH_3); 3·33 t (CH_2—O); 9·25 bs (OH)
V	2·40	3·87	4·98	7·20	6·92–7·93 m (C_6H_4); 10·42 s (CHO)

[a] Cyclohexane ring.

tography (GLC). Spectra of the synthesized compounds have similar features. The infrared spectra of derivatives *II*–*V* exhibit characteristic furan absorption bands at 1 001–1 036 cm^{-1} and 840–871 cm^{-1}. Bands due to $\delta_s(CH_3)$ and $\delta_{as}(CH_3)$ frequently overlap with the corresponding vibrations of the methylene group. The strongest band due to $\nu(C{=}O)$ appears at 1 688–1 731 cm^{-1}, in the spectra of free acids *IVa* and *IVb* at 1 688 cm^{-1} and 1 698 cm^{-1}. The phenoxy derivative *V* has two C=O bands at 1 688 cm^{-1} ($COOCH_3$) and 1 728 cm^{-1} (CHO). The UV spectra of *II*–*V* (Table I) display a maximum in the region 252–266 nm, corresponding to electron transitions in the furan part of the molecule. The UV spectrum of *V* is complicated by the presence of isolated *o*-formylphenoxymethylene grouping and exhibits another, less strong band at 318 nm.

Table II contains ^1H NMR data for the synthesized compounds. All the spectra display the characteristic furan $H_{(3)}$ proton signal at δ 6·95–7·29. Proton signals of the methyl on the furan nucleus appear at δ 2·20–2·41, the ester methyl signals at δ 3·81–3·87. Chemical shifts of the methylene group bonded in the furan β-position, $(CH_2)_a$, depend on the character of substituents on the benzene ring or nitrogen atom, large difference occurring when the nitrogen is replaced by oxygen.

We determined Kovats indices *I* for derivatives *I*–*II* and *IV*–*V* on a non-polar stationary phase UCW-98 and a semi-polar phase OV-17. As seen from Table III, the retention indices, determined on the latter phase are 300–400 units higher than those found on UCW-98; this is in accord with higher interaction of more polar compounds with the phase allowing an induced interaction with the electron cloud of the aromatic ring (polymethylphenylsiloxane).

TABLE III
Kovats indices *I* for compounds *I*–*II*, *IV*–*V*

Compound	$I^{180\,°C}_{UCW}$	$I^{180\,°C}_{OV\text{-}17}$	ΔI
I	1483·7	1790·5	306·8
IIa	1725·3	2000·5	248·2
IIb	1797·1	2083·4	286·3
IIc	1811·7	2136·8	325·1
IId	2433·1[a]	2688·1[a]	255·0
IIe	1969·1	2270·1	301·0
IIg	2122·5[a]	2506·2[a]	384·0
IVa	1513·5	1776·1	262·6
IVb	1692·5	1949·2	256·7
V	2242·3[a]	2692·2[a]	449·9

[a] Column temperature 230°C.

EXPERIMENTAL

Melting points were determined on a Boetius block, microanalyses were performed on a Carlo Erba (Italy) analyser. The IR spectra were taken in chloroform on a UR-20 (Carl Zeiss, Jena) spectrophotometer, UV spectra in methanol on a UV VIS (Carl Zeiss, Jena) spectrometer. ^{1}H NMR spectra were measured at 25—80°C on a Tesla BS 487C (80 MHz) instrument in deuteriochloroform with tetramethylsilane as internal standard. Gas–liquid chromatography was performed on a Hewlett–Packard 7620A (U.S.A.) chromatograph (flame-ionization detector) on 1·2 m × 4 mm glass columns packed with 5% UCW-98 (silicone elastomer, Hewlett–Packard) on Chromosorb WHP (80—100 mesh) or 5% OV-17 (polymethylphenylsiloxane; Supelco, U.S.A.) on Chromosorb WHP (80—100 mesh; flow rate of carrier nitrogen 50 ml/min, injection chamber and detector temperature 220°C, column temperature 180°C and 230°C).

Methyl 4-bromomethyl-5-methyl-2-furancarboxylate (*I*) was prepared from methyl 2-furancarboxylate[4] *via* methyl 5-chloromethyl-2-furancarboxylate[5] and methyl 5-methyl-2-furancarboxylate[6].

Methyl 4-*Alkylaminomethyl*-5-*methyl*-2-*furancarboxylates* (IIa—IIg). An alkylamine (20 mmol) in benzene (10 ml) was gradually added to compound *I* (2·33 g; 10 mmol) in benzene (20 ml) at 5—10°C and the reaction mixture was stirred at room or elevated temperature. Derivatives *IIa*, *IIc*, and *IId* reacted at room temperature for 14 h, *IIb*, *IIe* for 28 h, *IIf* for 48 h, and *IIg* for 14 h at 40—50°C. The precipitated amine hydrobromide was filtered and washed with benzene (3 × × 10 ml). The benzene solutions were combined and the solvent was evaporated under diminished pressure. The final product was distilled or crystallized from an appropriate solvent (Table I).

N,N-*Bis*(5-*methoxycarbonyl*-2-*methyl*-3-*furylmethyl*)-*p*-*toluidine* (III). A solution of *p*-toluidine (1·6 g; 15 mmol) in benzene (10 ml) was added dropwise to compound *I* (2·33 g; 10 mmol) in benzene (20 ml) at 5—10°C. The reaction mixture was vigorously stirred at 45—50°C for 9 h and worked up as described in the preceding experiment.

4-Alkoxymethyl-5-methyl-2-furancarboxylic Acids (IVa—IVb). A solution of potassium hydroxide (2·8 g; 50 mmol) in an alcohol (30 ml) was added to compound *I* (1·39 g; 6 mmol) in the same alcohol (20 ml) and the reaction mixture was refluxed for 5 h. The precipitated inorganic material was removed by filtration, washed with alcohol (2 × 10 ml) and the solvent was evaporated under diminished pressure. The residue was dissolved in a minimum amount of water, treated with charcoal and the corresponding acid was isolated after acidification with dilute (1 : 1) hydrochloric acid.

Methyl 4-(2-*Formylphenoxymethyl*)-5-*methyl*-2-*furancarboxylate* (V). Sodium salt of salicylaldehyde[7] (3·3 g; 23 mmol) in dimethylformamide (15 ml) was added to compound *I* (5·4 g; 23 mmol) in acetone (100 ml) and the reaction mixture was refluxed for 4 h. The inorganic material was filtered, washed with acetone (3 × 10 ml) and the solvent was evaporated under diminished pressure. Water (40 ml) was added to the residue and the mixture was extracted with chloroform (3 × 30 ml). The combined organic extracts were dried over sodium sulfate and, after removal of the solvent, the product was crystallized from acetone–hexane.

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