SYNTHESES AND SPECTRAL PROPERTIES OF UNSYMMETRICALLY 3,5-DISUBSTITUTED 2,6-DIMETHYL-1,4-DIHYDROPYRIDINES

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Unsymmetrically 3,5-disubstituted 4-(5-X-2-furyl)-2,6-dimethyl-1,4-dihydropyridines (where X = H, Br, NO_2) have been synthesized and characterized by spectral methods (IR, UV, ^{1}H NMR and MS). The modified Hantzsch method made it possible to prepare the title compounds as well as their *N*-alkylated derivatives. The paper also describes the *N*-alkylation of sodium salts of substituted 1,4-dihydropyridines using the phase-transfer catalysis.

Key words: 1,4-Dihydropyridines, alkylation; Hantzsch synthesis.

1,4-Dihydropyridines form a well-known group of chemotherapeutics – calcium antagonists, i.e. compounds with antihypertensive activity[1–8]. The original Hantzsch synthesis[9] is a suitable method for syntheses of symmetrically 3,5-disubstituted 2,6-dimethyl-1,4-dihydropyridines with various substituents at 4-position depending on the aldehyde used. Starting from the mechanism suggested for this reaction[1] we can devise possible syntheses of unsymmetrically 3,5-disubstituted 1,4-dihydropyridines: the molecule of 1,3-dicarbonyl compound reacting with the aldehyde can differ from that reacting with the amine, i.e. an α,β-unsaturated ketone and an enamine prepared separately from different 1,3-dicarbonyl compounds can give the expected unsymmetrically disubstituted product when reacting with each other. This possibility, which is particularly advantageous in the context of preparation of activated esters with different substituents at 3,5-positions before their subsequent partial hydrolysis[6], has been dealt with in a relatively small number of papers so far[7,8,10,11]. The aim of the present communication was to prepare 1,4-dihydropyridines carrying a 5-X-2-furyl substituent (X = H, Br, NO_2) at 4-position and different substituents at 3- and 5-positions (acetyl, alkoxycarbonyl) using the modified Hantzsch reaction, as well as to introduce an alkyl into the 1,4-dihydropyridine skeleton using *N*-alkylated enamines or alkylation of sodium salts of 1,4-dihydropyridines (Scheme 1).

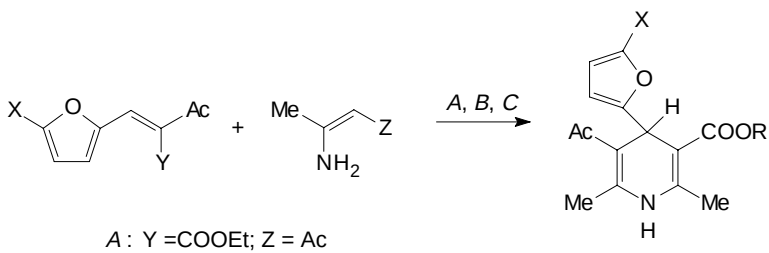
In a four-component reaction involving different 1,3-dicarbonyl compounds (differing distinctly in their reactivities) one can expect a reaction mixture with one of the products predominating. We prepared such a model mixture from equal molar amounts

of ethyl 3-oxobutanoate, 2,4-pentanedione, 5-furancarboxaldehyde and ammonia in ethanol, and its reaction gave the following products (determined by gas chromatography): only 41% unsymmetrically 3,5-disubstituted compound 2,6-dimethyl-3-acetyl-5-ethoxycarbonyl-4-(2-furyl)-1,4-dihydropyridine (**1a**) beside the symmetrically disubstituted compounds, viz. 3,5-diethoxycarbonyl derivative (36%) and diacetyl derivative (23%).

With the aim of avoiding the chromatographic separation of compounds of similar type, we tried to synthesize the unsymmetrically substituted 1,4-dihydropyridines making use of the well-known mechanism of the Hantzsch reaction. Ethyl and methyl 3-oxobutanoates react with 5-X-2-furancarboxaldehydes at the conditions of the Knoevenagel reaction to give the respective esters of 2-(5-X-2-furylidene)-3-oxobutanoic acid which are directly converted into dihydropyridines (as the only products) in the Michael reaction with equimolar amount of 2-amino-2-penten-3-one (Procedures *A*, *C*).

Starting from the mechanism of the Hantzsch reaction and from the finding that the formation of dihydropyridine **1** necessitates the presence of at least one acetyl group at the double bond in β-position with respect to 5-X-2-furyl residue, we carried out the syntheses of dihydropyridines of type **1** also by the second possible way, viz. by the reaction of ethyl 3-amino-2-butenoate with the 3-(5-X-2-furylidene)-2,4-pentanediones obtained by the Knoevenagel reactions of the corresponding 5-X-2-furancarboxaldehydes with 2,4-pentanedione (Method *B*). The yields of dihydropyridines **1** are approximately equal in the two synthetic methods (Table I).

The *N*-substituted 4-(5-X-2-furyl)-3-acetyl-5-ethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines **3a**, **3b**, **4a** were obtained by benzylation or methylation of the sodium salts of dihydropyridines **1a** and **1b** according to ref.[12] (Method *E*, Scheme 2). The alkylation of sodium salt of dihydropyridine **1c** was impossible at the reaction condi-



A : Y =COOEt; Z = Ac
B : Y =Ac; Z = COOEt
C : Y =COOMe; Z = Ac

1, R = Et
2, R = Me

1, **2**	X
a	H
b	Br
c	NO_2

SCHEME 1

TABLE I

Physico-chemical properties of 4-(5-X-2-furyl)-3-acetyl-5-alkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines **1–4**

Compound	Formula M.w.	M.p., °C R_F	Method Yield, %	Calculated/Found[a]		
				% C	% H	% N
1a	$C_{16}H_{19}NO_4$	118–120	*A*, *B*	66.42	6.62	4.84
	289.3	0.53[b]	85, 91	66.28	6.54	4.65
1b	$C_{16}H_{18}BrNO_4$	138–240	*A*, *B*	52.19	4.93	3.80
	368.3	0.56[b]	80, 72	51.99	4.89	3.68
1c[c]	$C_{16}H_{18}N_2O_6$	149–153	*A*, *B*	57.48	5.43	8.38
	334.3	0.50[b]	53, 49	57.32	5.21	8.12
2a	$C_{15}H_{17}NO_4$	164–165	*C*	65.44	6.22	5.09
	275.3	0.53[b]	63	65.22	6.07	4.96
2b	$C_{15}H_{16}BrNO_4$	162–164	*C*	50.87	4.55	3.95
	354.2	0.55[b]	68	50.68	4.32	3.78
2c	$C_{15}H_{16}N_2O_6$	182–184	*C*	56.25	5.03	8.75
	320.3	0.50[b]	62	56.04	4.87	8.56
3a	$C_{23}H_{25}NO_4$	150–151	*D*, F_1	72.80	6.64	3.69
	379.5	0.38[d]	24, 5[e]	72.65	6.46	3.43
3b	$C_{23}H_{24}BrNO_4$	134–136	F_1, F_2	60.27	5.28	3.06
	458.4	0.42[d]	8[e], 6[e]	60.09	5.13	2.86
4a	$C_{17}H_{21}NO_4$	52–53	*E*, F_1, F_2	67.31	6.98	4.62
	303.4	0.64[d]	38, 9[e], 7[e]	67.13	6.76	4.45
4b	$C_{17}H_{20}BrNO_4$	72–73	F_2	53.42	5.27	3.66
	382.3	0.70[d]	10[e]	53.21	5.08	3.48
4c	$C_{17}H_{20}N_2O_6$	96–100	F_1	58.61	5.79	8.04
	348.4	0.62[d]	8[e]	58.49	5.76	8.12

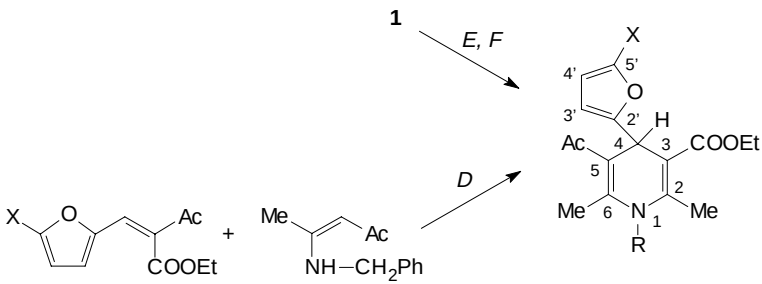
[a] % Br (calculated/found): for **1b**: 21.70/21.89; **2b**: 22.56/22.34; **3b**: 17.43/17.24; **4b**: 20.90/20.69. [b] Chloroform–ethanol 10 : 1. [c] Ref.[7] gives m.p. 149–150 °C. [d] Chloroform–ethanol 20 : 1. [e] Yields of chromatography.

tions mentioned because the reaction mixture turned black immediately upon formation of the respective sodium salt (due to the presence of the nitro group in the furan nucleus).

For this reason we tried to synthesize the *N*-benzyl derivative **3a** by a method using 2-benzylamino-2-penten-4-one instead of 2-amino-2-penten-4-one (which gives compound **3a** directly in the cyclocondensation reaction – Method *D*) but the dihydropyridines **3b**, **3c** could not be prepared in this way either.

The benzylation was also carried out by the method of phase transfer catalysis (Method *F*) using triethylbenzylammonium chloride (TEBA) (F_1) and dimethylbenzyldodecylammonium bromide (F_2) as the catalysts. Both the methods give approximately equal yields which, however, do not reach those of the cyclocondensation reaction. The yields of compound **4a** are higher in the methylation of sodium salt than in the phase-transfer catalysis method, which is probably connected with the fact that compound **4a** separates almost quantitatively from aqueous medium as a precipitate which merely needs to be recrystallized, whereas the reaction mixture obtained from the phase-transfer method has to be separated by chromatography. The yields of compounds **3b** and **4b** are about the same in the individual methods of preparation. In the case of methylation of compound **1c** by the phase-transfer catalysis method the reaction mixture turned black but, nevertheless, it was possible to isolate compound **4c** from it. Dihydropyridine **3c** could not be obtained by this method either. In all the cases, the alkylation agent was used in 50% excess.

The UV spectra of these compounds (Table II) represent a superposition of absorption bands of two chromophores: 1,4-dihydropyridine and furan. The bands were



3, R = CH_2Ph

4, R = Me

3, **4**	X
a	H
b	Br
c	NO_2

SCHEME 2

denoted as it is usual in literature. In all the cases the absorption bands represent a typical π–π^* transition of 1,4-dihydropyridine skeleton (band III) and furan or benzyl substituent (bands I and II). The interpretation of UV spectra of compounds **1**–**4** could start from the comparison of the UV spectra of these compounds with those of their analogues, i.e. 3,5-diacetyl- (λ_{max} = 404 nm), 3,5-diethoxycarbonyl- (λ_{max} = 369 nm, log ε = 2.88), 3,5-diacetyl-4-(2-furyl)- (λ_{max} = 376 nm, log ε = 2.96), and 3,5-diethoxycarbonyl-4-(2-furyl)-2,6-dimethyl-1,4-dihydropyridines (λ_{max} = 347, log ε = 2.96).

The introduction of a bulky substituent (furan nucleus) into 4-position causes a hypsochromic shift and intensity increase of the longest-wave band (III). This phenomenon agrees with available findings: an introduction of 4-substituent generally causes a hypsochromic shift of this band which represents the π–π^* transition of 1,4-dihydropyridine chromophore. The comparison of synthesized and model compounds shows that the position of the longest-wave band is closest to that of 4-furyl-3,5-diacetyl derivative. The bromo derivatives **1b** and **2b** show slight hypsochromic shift of band III, whereas this shift is considerable (about 35 nm) in nitro derivatives **1c** and **2c** with concomitant intensity increase of this band as compared with unsubstituted derivatives **1a** and **2a**.

TABLE II
UV spectra of 4-(5-X-2-furyl)-3-acetyl-5-alkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines **1–4**

Compound	Band I		Band II		Band III	
	λ_{max}	log ε	λ_{max}	log ε	λ_{max}	log ε
1a	223	3.45	245	3.26	366	3.00
1b	–	–	241	3.32	364	2.97
1c	–	–	242	3.40	331	3.30
2a	222	3.29	245	3.36	363	3.05
2b	–	–	238	3.44	363	3.00
2c	–	–	241	3.40	328	3.29
3a	212	3.28	225	3.04	329	3.21
3b	228	3.41	245	3.39	365	3.07
4a	219	3.10	250	3.11	364	2.88
4b	228	3.19	248	3.23	359	2.88
4c	208	3.10	253	3.32	327	3.30

[a] λ_{max} in nm, ε in $m^2\ mol^{-1}$.

The intensities of band II vary in the limits of 1 820–2 760 $m^2 mol^{-1}$ and those of the less intensive band III in the limits of 930–2 000 $m^2 mol^{-1}$. The values of molar absorption coefficient of band III are about the same as those of the model symmetrical compounds; for band II these values are in the middle between the values of the above-mentioned model substances.

The *N*-methylation causes a bathochromic shift in band II (by 5–11 nm), whereas band III is shifted hypsochromically (by 2–5 nm). The intensities of these bands are not substantially changed as compared with those of the nonalkylated derivatives. The 1-benzylation changes the shape of the whole absorption spectrum which becomes a superposition of absorption bands of three chromophores. A mild increase is observed in the intensity of band III (e.g. $\Delta \log \varepsilon = 0.21$ for compound **3a**).

The infrared spectra of 4-substituted 1,4-dihydropyridines (Table III) show absorption bands due to γ(C–H) vibrations in the regions of 852–885 and 925–965 cm^{-1}. The bands of symmetrical and asymmetrical vibrations ν(C–O–C) of furan nucleus are found in the regions of 993–1 013 and 1 207–1 235 cm^{-1}. This statement agrees with the results by Gross[13]: all 2-substituted and 5-nitro-2-substituted furan derivatives show two strong absorption bands in these regions which correspond to the above-mentioned vibrations.

TABLE III
Infrared spectra of 4-(5-X-2-furyl)-3-acetyl-5-alkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines **1–4**

Compound	ν(C–H)	ν(C–O–C)		δ(Me)s	ν(C=C)skel.		ν(C=O)	
		sym.	asym.				COMe	COOR
1a	880 w 940 m	1 008 m	1 225 m	1 380 m	1 465 s	1 580 m 1 635 w	1 665 s	1 685 s
1b	875 w 945 m	1 010 s	1 235 s	1 375 m	1 460 m	1 580 m 1 635 w	1 665 s	1 685 s
1c[a]	875 w 940 m	1 008 s	1 235 s	1 350 m	1 480 s	1 575 w 1 635 w	1 665 s	1 690 s
2a	885 w 935 m	1 004 s	1 220 s	1 375 s	1 460 s	1 580 s 1 635 w	1 665 s	1 685 s
2b	875 w 950 m	1 008 m	1 220 m	1 375 m	1 460 s	1 580 m 1 633 w	1 665 s	1 690 s
2c	875 w 960 w	1 013 s	1 235 s	1 375 m	1 480 s	1 575 m 1 633 w	1 670 s	1 695 s
3a	852 w –[b]	1 000 s	1 220 s	1 365 s	1 440 s	1 550 s 1 590 s	1 695 s[a]	
3b	860 w 935 s	1 000 s	1 213 s	1 367 s	1 450 s	1 575 s 1 625 s	1 655 s	1 675 s
4a	880 m 940 s	1 000 s	1 215 s	1 365 s	1 460 m	1 535 s 1 610 s	1 645 s	1 675 s
4b	860 w 965 s	1 000 s	1 215 s	1 368 s	1 460 m	1 535 s 1 608 s	1 645 s	1 675 s
4c	885 w 925 s	993 s	1 207 s	1 390 s	1 390 w	1 458 s 1 585 s[c]	1 630 s	1 660 s

[a] Ref.[7]: 3 375 (NH); 1 720, 1 690 (CO); 1 640–1 650 (C=C, NH); 1 495, 1 385 (NO_2). [b] Three bands with low intensity, not assigned. [c] Not resolved.

The peaks of deformation vibrations $\delta(CH_3)$ of methyl group are found in the region of 1 350–1 390 cm^{-1}. The bands of skeletal vibrations ν(C=C) of furan and dihydropyridine nuclei are found in the region of 1 450–1 635 cm^{-1}. Strong absorption bands of carbonyl groups ν(C=O) are found in the region of 1 630–1 695 cm^{-1} and are usually split (especially so for compounds **2** and **4**), which corresponds to vibrations of two different carbonyl groups (acetyl and ester). Starting from analogous wavenumbers of the model compounds, 4-furyl-3,5-diacetyl- and -diethoxycarbonyl analogues (ν(C=O) 1 670 and 1 705 cm^{-1}), we can assign the higher-energy band to carbonyl group of alkoxycarbonyl and the lower-energy one to that of acetyl.

The wavenumber values of vibrations of substituents in the dihydropyridine nucleus are lower than those in pyridine nucleus, which indicates a higher degree of conjugation of these substituents with dihydropyridine skeleton. *N*-Substitution of 1,4-dihydropyridine skeleton causes no distinct changes in positions of absorption bands.

No ν(NH) vibrations were recorded since these are usually found above 3 200 cm^{-1} while the range covered by the apparatus used was 700–3 100 cm^{-1} only.

In the ^{1}H NMR spectra (Table IV) of compounds **1** and **2** (except for **1b**) it is impossible to differentiate between the proton signals of methyl groups at 2- and 6-positions and that of methyl group in acetyl. The signals of these protons are found at

TABLE IV
^{1}H NMR spectra of 4-(5-X-2-furyl)-3-acetyl-5-alkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines **1–4**

Compound	H-4′	H-3′	H-5′	CH	$CH_3(CH_2)O$–	CH_3C=	CH_3CO–	NH, NR
1a	6.20 q	5.88 q	7.20 q	5.18 s	1.28 t, 4.21 q	2.30 s	2.30 s	7.11 s
1b	6.13 d	5.87 d	–	5.16 s	1.29 t, 4.22 q	2.32 s	2.30 s	6.68 s
1c[a]	7.19 q	6.27 d	–	5.32 s	1.30 t, 4.22 q	2.36 s	2.36 s	6.99 s
2a	6.19 q	5.92 d	7.20 q	5.17 s	3.74 s	2.31 s	2.31 s	6.89 s
2b	6.11 d	5.89 d	–	5.15 s	3.75 s	2.31 s	2.31 s	6.46 s
2c	7.18 d	6.24 d	–	5.31 s	3.76 s	2.35 s	2.35 s	7.35
3a	6.28 q	6.00 d	7.29 q	4.35 s	1.18 t, 4.18 q	1.25 s	1.88 s	4.43 s, 7.30 m
3b	6.11 d	5.88 d	–	5.13 s	1.28 t, 4.21 q	1.24 s	2.28 s	4.20 s, 7.33 m
4a	6.19 q	5.83 d	7.28 q	5.21 s	1.33 t, 4.28 q	2.45 s 2.48 s	2.38 s	3.19 s
4b	6.06 d	5.79 d	–	5.14 s	1.28 t, 4.22 q	2.41 s 2.45 s	2.33 s	3.17 s
4c	7.12 d	6.13 d	–	5.25 s	1.29 t, 4.22 q	2.43 s 2.48 s	2.33 s	3.23 s

[a] Ref.[7] ($CDCl_3$, TMS): 2.34 s, 3 H (CH_3); 1.21 t, 2 H (OCH_2); 4.11 q, 3 H (CH_3); 2 20 s, 3 H ($COCH_3$); 5.05 s, 1 H (CH); 6.20 d, 1 H (H-3′); 7.19 d, 1 H (H-4′).

2.30–2.36 ppm. The proton signals of alkoxycarbonyl groups are found about 4.21 and 1.29 ppm and at 3.75 ppm, respectively. The position of NH signal does not change: it is found at 6.47–7.04 ppm. The proton signals of furan nucleus are at 5.79–6.00 ppm and 6.06–6.28 ppm, respectively; for the nitro derivatives, these are shifted downfield by about 0.3 and 1.0 ppm, respectively. The $^3J_{AB}$ coupling constant values of furan protons vary in the limits of 3.30–3.80 Hz. The 4-H proton signal (at an sp^3 carbon of compounds **1** and **2**) shows the largest variability among all the measured chemical shifts of 1,4-dihydropyridine skeleton of the substances studied. It is found in the region of 5.15–5.32 ppm, which also characterizes a different effect of the 5-substituted furan on the carbon atom at 4-position.

The *N*-methyl signal is found in the region of 3.17–3.23 ppm. The derivatives having an *N*-methyl group show two signals of methyl groups at 2- and 6-positions which, at the same time, are different from the methyl signal of acetyl group. The signal of proton at the sp^3 carbon atom in 4-position is found at usual δ values (5.14–5.25) characteristic of 1,4-dihydropyridine skeleton. The signal of proton at 4-position of compound **3a** is shifted upfield. Similarly, the signals of methyl groups at 2- and 6-positions are shifted upfield, which is probably due to the presence of the phenyl nucleus in benzyl group.

In the mass spectra (Table V) of compounds **1**, **2** (except for **1a**, **2a**), the molecular ion has the intensity below 20%, however, the ($M^{+\bullet} - 1$) and ($M^{+\bullet} - 2$) peaks formed by splitting off of hydrogen atom and molecule, respectively, show even lower intensities, which means that the fragmentation does not involve the splitting off of neutral hydrogen molecule as the first step (as it is usual with symmetrical derivatives).

TABLE V
The most important peaks in mass spectra of 4-(5-X-2-furyl)-3-acetyl-5-alkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines **1–4**

Compound	Relative intensity
1a	289 (91), 260 (44), 246 (100), 216 (90), 206 (85)
1b	369 (14), 367 (13), 288 (100), 246 (100), 216 (46), 214 (38)
1c	334 (14), 206 (93), 71 (67), 57 (84), 43 (100)
2a	275 (59), 232 (100), 216 (52), 208 (26)
2b	355 (19), 353 (18), 312 (35), 310 (32), 274 (100), 232 (68)
2c	320 (6), 277 (11), 261 (20), 230 (42), 208 (39), 192 (63)
3a	379 (13), 336 (28), 306 (11), 91 (100)
4a	303 (7), 288 (4), 274 (5), 260 (49), 216 (9), 188 (12)
4b	383 (7), 340 (65), 338 (65), 308 (18), 302 (15), 230 (100), 56 (100), 43 (100)

In compounds **1a** and **2a**, the dominant process is splitting off of CH_3CO fragment ($M^{+\bullet} - 43$) and COOEt fragment ($M^{+\bullet} - 73$). Both these fragmentations are confirmed by metastable peaks. The bromo derivatives split off a bromine atom ($M^{+\bullet} - 79$, $M^{+\bullet} - 81$), whereas the nitro derivatives undergo the elimination of ammonia ($M^{+\bullet} - 17$) and subsequent splitting off of the nitrofuran fragment ($M^{+\bullet} - 111$). The other fragmentations are analogous to those in **1a** and **2a**. No differences were observed between the fragmentations of *N*-methyl derivatives and the corresponding *N*-unsubstituted analogues. Again, the CH_3CO and COOEt fragments are split off. In contrast to 3,5-dicyano substituted 1,4-dihydropyridines, no preference for splitting of *N*-methyl group is observed. The ($M^{+\bullet} - 15$) peak has only negligible intensities (below 2%) in both the spectra. Splitting off of a CH_4N fragment seems much more likely because it was found in both spectra. A similar fragmentation is also observed in compound **3a** where an additional splitting of alkyl–nitrogen bond takes place, which is proved by the presence of the tropylium cation (91 – the most intense peak) formed by splitting off of benzyl.

EXPERIMENTAL

The melting points were determined with a Kofler apparatus and were not corrected. The reaction course and purity of substances were monitored by means of TLC: Silufol 254 plates, detection in UV light or in iodine vapours. The elemental analyses of newly synthesized substances were carried out with a CHNO model 1102 (Carlo Erba, Milan, Italy). The reaction mixture from the four-component reaction was analyzed by GC using a Hewlett–Packard 7620A apparatus with flame ionization detector and a glass column (1.9 m length, 3 mm inner diameter) packed with 10% OU 101 on Chromosorb WHP DMCS (80–100 mesh). The inlet temperature 240 °C. The temperature regime for separation in column: 180 °C, 6 min, isothermal; 180–240 °C with the temperature increase of 10 °C min^{-1}. Carrier gas: nitrogen, 35 ml min^{-1} flow rate. Retention times: 3,5-diacetyl derivative – 13.14 min, 3-acetyl-5-ethoxycarbonyl derivative – 13.85 min, 3,5-diethoxycarbonyl derivative – 15.26 min. The UV spectra were measured with a double-beam UV-VIS spectrophotometer (Zeiss, Jena) in the range of 210–800 nm. The solutions measured were placed in 1 cm cells and their concentrations were in the limits of $1 \cdot 10^{-5}$–$7 \cdot 10^{-5}$ mol l^{-1}. The accuracy of measurements was ±1 nm. The IR spectra were measured with a double-beam spectrophotometer Perkin–Elmer 503 in the region of 700–3 100 cm^{-1} using 0.1 mm KBr cells. The accuracy of wavenumber readings was ±1 cm^{-1}. The ^1H NMR spectra were measured with an 80 MHz spectrometer BS 487 C Tesla at 25 °C in deuteriochloroform using tetramethylsilane as the internal standard. The mass spectra were measured with an MS 902 S apparatus with direct inlet. Ionization energy 70 eV, electron current 100 or 500 μA, temperature of ion source from 40 to 140 °C depending on the substance measured.

5-Bromo-2-furancarboxaldehyde was prepared by bromination of 2-furancarboxaldehyde in dichloroethane; 5-nitro-2-furancarboxaldehyde was prepared by hydrolysis of the 5-nitro-2-furylmethylene diacetate prepared by treating 2-furancarboxaldehyde with nitric acid in acetanhydride. Ethyl 3-amino-2-butenoate, 2-amino-2-penten-3-one, and 2-benzylamino-2-penten-3-one were prepared according to ref.[14]; the other starting materials used were commercial products.

Preparation of 4-(2-Furyl)-3-acetyl-5-ethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine (**1a**) by Hantzsch Reaction

A mixture of 2,4-pentanedione (1.0 g, 10 mmol), ethyl 3-oxobutanoate (1.3 g, 10 mmol), 2-furancarboxaldehyde (0.96 g, 10 mmol) in dry ethanol saturated with ammonia (30 ml) was refluxed on water bath 6 h, whereupon the reaction mixture was cooled and evaporated in vacuum until dry. The product was analyzed by means of TLC and GC, and the identification of substances in the mixture was verified by comparing with the authentic standards synthesized by the Hantzsch reaction. The mixture contained: 41% 4-(2-furyl)-3-acetyl-5-ethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine (**1a**), 36% 4-(2-furyl)-3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine, and 23% 4-(2-furyl)-3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridine.

4-(5-X-2-Furyl)-3-acetyl-5-alkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines **1**, **2** (Methods *A*–*C*)

5-X-2-Furylidene-1,3-dicarbonyl compound (10 mmol) was dissolved with enamine (2-amino-2-penten-4-one or ethyl 3-amino-2-butenoate; 10 mmol) in dry ethanol (30 ml) and the mixture was refluxed on water bath 6 h, cooled, and a part of the solvent was evaporated in vacuum. After some time, the product began to crystallize from the reaction mixture, which could be speeded up by undercooling or addition of water. The separated crystals were collected by suction and washed with cold dry ethanol. The recrystallization was carried out (by boiling with charcoal) from ethanol with water until constant melting point. The product forms yellow crystalline solid showing blue fluorescence in UV light. The yields and physical characteristics of the substances synthesized are presented in Table I.

1-Benzyl-4-(5-X-2-furyl)-3-acetyl-5-alkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines **3** (Method *D*)

Ethyl 2-(5-X-2-furylmethylidene)-3-oxobutanoate (10 mmol) was dissolved together with 2-benzylamino-2-penten-4-one (10 mmol) in dry ethanol (30 ml), and 5 drops of 10% sodium ethoxide was added. The reaction mixture was heated on a water bath 10 h. The reaction course and formation of product were monitored by TLC. When the reaction was finished, the mixture was cooled and a part of the solvent was evaporated in vacuum. After standing overnight, a voluminous crystalline precipitate (compound **3a**) was formed which was collected by suction and washed with cold methanol. The product was recrystallized from methanol (boiling with charcoal) until constant melting point. The obtained white fibrillar solid showed fluorescence in UV light. If the compound did not separate on standing overnight, the products were separated by chromatography (silica gel; benzene–chloroform 1 : 1) and recrystallized from methanol.

Alkylation of Sodium Salts of 4-(5-X-2-Furyl)-3-acetyl-5-alkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines **1** (Method *E*)

The sodium salt of nonalkylated dihydropyridine **1** was prepared in analogy to the method by Kuthan[12]. A solution of the respective dihydropyridine (20 mmol) in dry dimethylformamide (15 ml) was treated with sodium hydride (0.58 g, 25 mmol) added with continuous stirring and cooling with ice during 20 min in nitrogen atmosphere, whereupon the reaction mixture was heated at 35–40 °C 3 h.

N-Methylation of Sodium Salts of 4-(5-X-2-Furyl)-3-acetyl-5-alkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines **1**

The sodium salt of dihydropyridine (20 mmol) prepared in the previous experiment was cooled with ice with continuous stirring and treated with methyl iodide (3.6 g, 25 mmol). Then the reaction mix-

ture was refluxed 10 h. After the reaction was finished, the mixture (in the case of compound **1a**) was concentrated in vacuum to one half of the original volume and ice water was added thereto. The obtained precipitate was recrystallized from methanol (boiling with charcoal). In the case of compound **1b**, the reaction mixture was evaporated in vacuum until dry and separated by chromatography (silica gel; benzene–chloroform 1 : 1). The product was recrystallized from methanol.

N-Benzylation of Sodium Salts of 4-(5-X-2-Furyl)-3-acetyl-5-alkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines **1**

Benzyl chloride (3.2 g, 25 mmol) was added to sodium salt of dihydropyridine (20 mmol) with stirring and cooling with ice. The reaction mixture was heated at 35–40 °C 10 h. After concentrating to one half of the original volume in vacuum, 40 ml ice water was added, and the product was extracted with 3 × 50 ml benzene. The extract was dried with anhydrous sodium sulfate, evaporated until dry, and purified by chromatography (silica gel; benzene–hexane 2 : 1).

Alkylation of 4-(5-X-2-Furyl)-3-acetyl-5-alkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines **1** by Phase-Transfer Catalysis Method (Method *F*)

A mixture of dihydropyridine **1** (20 mmol), alkylating agent (methyl iodide or benzyl chloride, 30 mmol), catalyst (TEBA or dimethylbenzyldodecylammonium bromide, 10 mmol), 50% aqueous sodium hydroxide (5 ml), and benzene (40 ml) was heated with continuous stirring at 40–45 °C 10 h. Then the benzene layer was separated, washed with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuum and the residue was separated by chromatography (silica gel; benzene–hexane 1 : 1 for *N*-benzyl derivatives, benzene–chloroform 1 : 1 for *N*-methyl derivatives) and the product was recrystallized from methanol. The obtained white or yellow substances showed fluorescence in UV light (methyl derivatives showed fluorescence quenching).

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