N-ALKYLATION OF HANTZSCH 1,4-DIHYDROPYRIDINES WITH ESTERS OF HALOGENOCARBOXYLIC ACIDS

Jaroslav PALEČEK, Manfred PAVLÍK and Josef KUTHAN

Department of Organic Chemistry,
Prague Institute of Chemical Technology, 166 28 Prague 6

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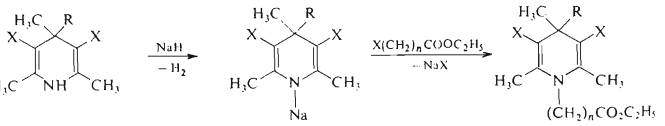
Dedicated to Academician J. Mostecký on the occasion of his 60th birthday.

1,4-Dihydropyridine derivatives *IIIa,b,d,e* and *IVa,b,e* were prepared from the corresponding Hantzsch dihydropyridines *I* and *II* by alkylation with ethyl halogenocarboxylates after deprotonation of the starting compounds with sodium hydride in dimethylformamide. Attempts to prepare compounds *IIIc* and *IVc,d* by this method failed. Spectral characteristics of the products and their fragmentation on electron impact are discussed.

Recently, considerable attention has been paid to 1-alkylation of 1,4-dihydropyridine derivatives[1,2] in connection with possible modification of their properties. In this communication we decided to study the hitherto disregarded possibility of attaching a carbon chain, bearing a terminal ester group, to the heterocyclic nitrogen atom. Further transformations of the products could then give new dihydropyridines. We describe several versions of introduction of an ethoxycarbonylalkyl group into two Hantzsch dihydropyridines, namely 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine (*I*) and 3,5-diethoxycarbonyl-2,4,6-trimethyl-1,4-dihydropyridine (*II*),



I, R = CH_3, X = CN *V*, R = CH_3, X = CN *IIIa–e*, R = CH_3, X = CN
II, R = H, X = $COOC_2H_5$ *VI*, R = H, X = $CO_2C_2H_5$ *IVa–e*, R = H, X = $CO_2C_2H_5$
a, $n = 0$; *b*, $n = 1$; *c*, $n = 2$; *d*, $n = 3$; *e*, $n = 4$.

SCHEME 1

* Part LI in the series On Dihydropyridines; Part L: J. Electroanal. Chem. Interfacial Electrochem. *132*, 131 (1982).

under formation of the corresponding N-substituted derivatives *IIIa–e* and *IVa–e* according to Scheme 1. The starting compounds were deprotonated with sodium hydride in dimethylformamide under formation of the corresponding 1-sodio-1,4-dihydropyridines *V* and *VI* which then reacted with ethyl chloroformate ($n = 0$) or ω-bromoalkanoates ($n = 1-4$) to give 1,4-dihydropyridine ester-dinitriles of the type *III* and triesters of the type *IV*. The experimental results are summarized in Table I. It is obvious that the reaction of both the starting compounds *I* and *II* with ethyl chloroformate and ethyl bromo acetate ($n = 0$ and 1, respectively) proceeds smoothly, giving very good yields of compounds *IIIa,b* and *IVa,b*. Also the reaction of ethyl 5-bromopentanoate ($n = 4$) afforded the desired products *IIIe* and *IVe*. On the contrary, all attempts to prepare compounds *IIIc* and *IVc* ($n = 2$) by reaction with ethyl 3-bromopropanoate failed and the reaction mixtures afforded only the starting dihydro derivatives *I* or *II* together with ethyl acrylate, identified by gas–liquid chromatography and mass spectrometry. In these experiments the 1-sodio-1,4-dihydro derivatives *V* and *VI* (or their ionized forms) evidently act as nucleophilic dehydrobrominating reagents according to the following scheme:

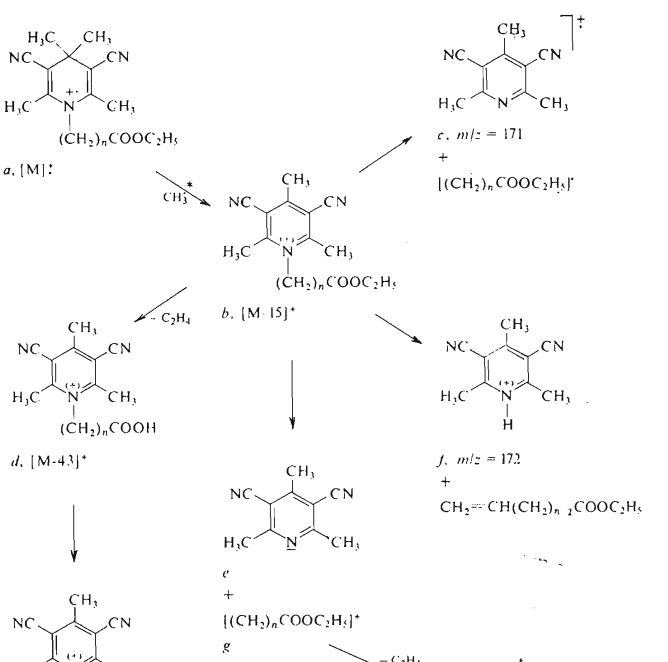
$$V(VI) + Br(CH_2)_2COOC_2H_5 \rightarrow I(II) + CH_2{=}CHCOOC_2H_5 + NaBr$$

A similar elimination was already observed[3,4] in the case of 1,3-dibromopropane. The fact that the N-alkylation reaction does not take place even at higher temperatures, in higher dilution or with an excess of sodium hydride indicates that the dihydropyridines *I* and *II* do not undergo even the Michael addition to ethyl acrylate. This was confirmed by experiments with the authentic α,β-unsaturated ester as well as with acrylonitrile showing that compounds of the type *III* and *IV* with $n = 2$ cannot be prepared by cyanoethylation.

Results of the attempted N-substitution of compounds *I* and *II* with ethyl 4-bromobutanoate ($n = 3$) were less interpretable. Although the 3,5-dicyano derivative *I* gave the expected N-substituted product *IIId* in good yield, in repeated experiments with the 3,5-diester *II* the desired analogous derivative *IVd* was neither isolated nor detected.

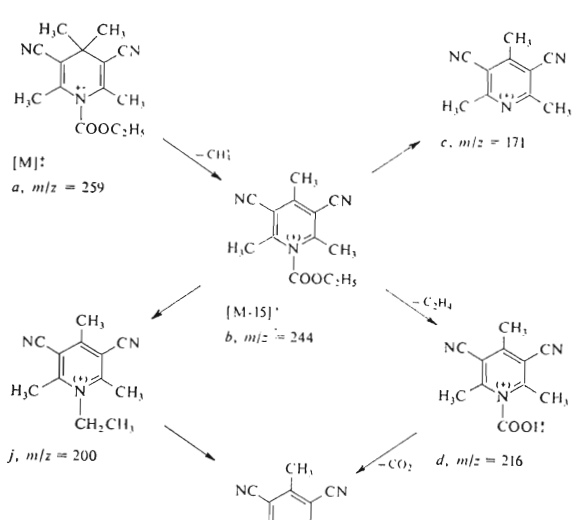
Chemical and physical characteristics of the N-substituted 1,4-dihydro derivatives *IIIa,b,d,e* and *IVa,b,e* are summarized in Table II. Their UV, IR and ^{1}H NMR spectra agree with the molecular structures *III* and *IV*.

Typical fragmentation mechanisms, derived from the mass spectra of compounds *IIIa,b,d,e* and *IVa,b,e*, taking into account the known[5–9] behaviour of analogous 1,4-dihydropyridines, are given in Scheme 2 to 4. The basic fragmentation pattern for the structure *III* ($n = 1-4$), depicted in Scheme 2, is analogous to the fragmentation of 1-alkyl-3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridines[6,7]. In all cases the molecular ion *a* has a low relative intensity (2–10%). The main fragmentation consists in elimination of a methyl radical in position 4 under formation of the ion



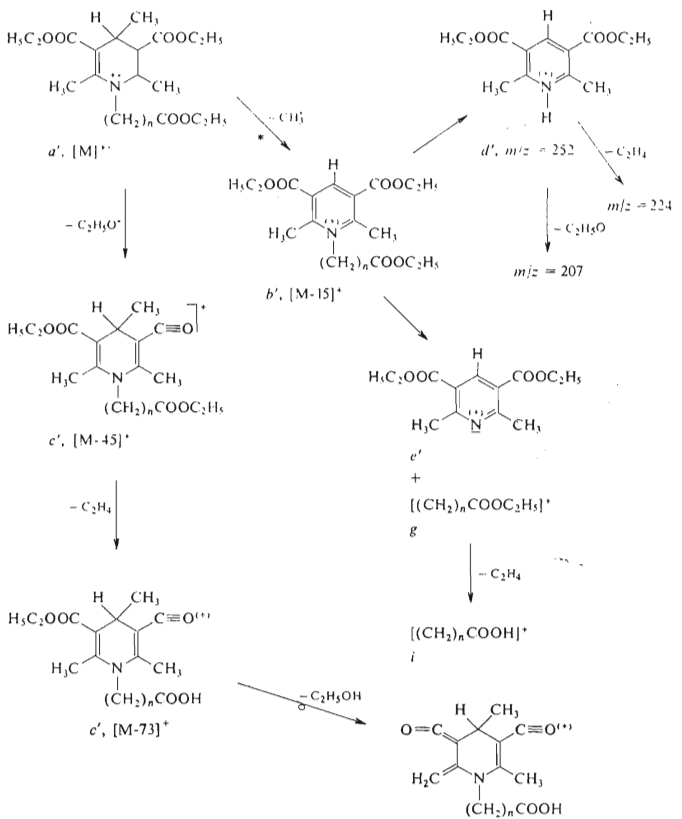
SCHEME 2

species b $(M-15^+)$. For this aromatization process a metastable peak was observed in all cases (Table III). The heteroaromatic ion b can lose the 1-substituent and give the ionic species c, m/z 171 and the fragment e, and/or lose an ethene molecule from the ethoxycarbonyl group affording the ion d $(M-43)^+$. Formation of the ion h, m/e 186, can be best explained by cleavage of the alkyl chain of the 1-substituent in the ion d. In case of compound *IIIb* $(n = 1)$ the ion h is formed by mere decarboxylation of the mentioned ion d. The latter thermal reaction was also carried



SCHEME 3

out preparatively[10]. As expected, the cleavage of the parent member of the series *III*, *i.e.* compound *IIIa* ($n = 0$), shows some different features (see Scheme 3)). In this case, the ion *b* affords by decarboxylation and McLafferty rearrangement the ion *j*, *m/z* 200. The fragmentation mechanism for compounds *IVa,b,e*, depicted in Scheme 4, was explained with regard to the analogous fragmentation[8] of compound *II* into two main branches. In the first, heteroaromatization again takes place by loss of a methyl radical from the position 4 to give the ion *b'* $(M-15)^+$, which invariably represents the base peak. The second branch begins by elimination of an ethoxy radical from one of the ethoxycarbonyl groups in positions 3 and 5 under formation of the ion *c'* $(M-45)^+$. This ion loses ethene molecule and is converted into the ion *e'* $(M-73)^+$, which by an *ortho*-rearrangement gives the ion *f'* $(M-119)^+$. Loss of the 1-substituent leads to ions *g* or *d'*. Further fragmentation of the ion *d'* proved to be identical with the corresponding region of the mass spectrum[8] of compound *II*.



SCHEME 4

EXPERIMENTAL

Temperature data are uncorrected, melting points were taken on a Boetius block (G.D.R.). Analytical samples were dried over phosphorus pentoxide at 130—260 Pa (1—2 Torr) for 12 to 15 h. UV spectra were recorded in $4 . 10^{-5}$—$2 . 10^{-5}$ mol l^{-1} ethanolic solutions on a Specord UV-VIS instrument, IR spectra were taken in chloroform on a Perkin-Elmer 325 spectrophoto-

meter. ^{1}H NMR spectra were measured on a Varian 100 XL spectrometer in deuteriochloroform and mass spectra were taken on an LKB 9000 instrument (at 70 eV).

The 1,4-dihydro derivatives *I* and *II* were prepared by described[11,12] cyclocondensations. The compound *I* melted at 242°C (reported[13] m.p. 244°C), compound *II* had m.p. 130–131°C (reported[14] m.p. 131°C).

Ethyl chloroformate was prepared from phosgene and ethanol[15], b.p. 91–93°C (reported[15] b.p. 94–95°C). Ethyl bromobutanoate was obtained by reaction of γ-butyrolactone with hydrogen bromide and ethanol[16]; b.p. 89°C/2·7 kPa (reported[16] b.p. 97–99°C/3·4 kPa). The remaining halogeno esters were commercial products and were distilled prior to use: ethyl bromo acetate, b.p. 153–154°C (ref.[17] b.p. 154–155°C); ethyl bromopropanoate, b.p. 70°C/2·7 kPa (ref.[18] b.p. 89°C/5·4 kPa); ethyl 5-bromopentanoate, b.p. 95–98°C/1·35 kPa (ref.[19] b.p. 102–103°C/1·62 kPa).

N-Substitution of 1,4-Dihydropyridines *I* and *II*

An 80% suspension of sodium hydride in paraffin oil (2 g; Merck) was added under nitrogen to a stirred solution of the dihydro derivative *I* or *II* ($5{\cdot}34 \cdot 10^{-2}$ mol) in dimethylformamide (50 ml) under cooling with an ice–salt mixture. After warming to 30–40°C for 1 h, the mixture was cooled to 0°C and the corresponding amount of the halogeno ester was added dropwise. The mixture was again warmed to 30–40°C for the time specified in Table I, cooled to room temperature and decomposed by dropwise addition of water (100 ml). The precipitated product was filtered and the filtrate was extracted three times with ether (50 ml). The combined organic extracts were washed with saturated aqueous sodium chloride solution (50 ml), the crude product was combined with the ethereal extract, the solution was dried over magnesium sulfate and taken down. The residue was analyzed by thin-layer chromatography on Silufol (in chloroform with

TABLE I

Products of reaction of Hantzsch 1,4-dihydropyridine *I* and *II* with esters of the type $X(CH_2)_n.COOC_2H_5$ according to Scheme 1

n, X	Starting compound	Amount of reagent, mol	Time	Product	Yield, %[a]
0, Cl	*I*	1·3	0·5	*IIIa*	72
0, Cl	*II*	1·2	0·5	*IVa*	75
1, Br	*I*	1·5	1·0	*IIIb*	70
1, Br	*II*	2·0	2·0	*IVb*	83
2, Br	*I*	1·2–6·0	0·5	*IIIc*	0
2, Br	*II*	1·2	0·5	*IVc*	0
3, Br	*I*	3·0	3·0	*IIId*	68
3, Br	*II*	0·5–2·0[b]	0·5–3·0	*IVd*[b]	0
4, Br	*I*	1·1	4·0	*IIIe*	29
4, Br	*II*	1·1	1·0	*IVe*	61

[a] Based on the reacted starting compound; [b] compound *IVd* was not formed even when using a greater excess of sodium hydride and toluene–dimethylformamide as solvent.

TABLE II

New 1,4-dihydropyridines of the type *III* and *IV*

Dihydro-pyridine	M.p., °C solvent[a]	Formula (mol.wt.)	Found/Calculated			UF, nm λ_{max}	log ε	IR, ν(C=N) ν(C=O)	$\tilde{\nu}_{max}$, cm^{-1} ν(C=C) ν(C—O)	^{1}H NMR, CH_3/R/C^b CH_3C=	δ, ppm NCH_2 CH_2CO	J_{HH} Hz CH_3C^c CH_2O
			% C	% H	% N							
IIIa	53—54	$C_{14}H_{17}N_3O_2$	64·78	6·61	16·14	212	4·32	2 220 s	1 655 s	1·45 s	—	1·46 t
	A					255	4·13	1 750 s	1 610 m	2·43 s		7·0
		(259·3)	64·86	6·62	16·12	310	3·45		1 190 s			4·41 q
									1 265 s			7·0
IIIb	98—100	$C_{15}H_{19}N_3O_2$	66·17	7·03	15·28	217	4·63	2 210 s	1 655 s	1·41 s	4·25 s	1·31 t
	B	(273·3)	65·99	7·03	15·38	332	3·99	1 750 s	1 590 m	2·15 s		7·0
									1 195 s			4·29 q
									1 280 v			7·0
IIId	94—94·5	$C_{17}H_{23}N_3O_2$	67·68	7·72	13·77	222	4·45	2 200 s	1 650 s	1·34 s	3·45 t	1·24 t
	A	(301·4)	67·71	7·71	13·91	341	3·82	1 730 s	1 585 m	2·19 s	8·0	7·0
									1 230 m		2·29 t	4·06 q
									1 175 m		6·5	7·0
IIIe	41—43	$C_{18}H_{25}N_3O_2$	68·81	8·15	13·71	222	4·48	2 200 s	1 650 s	1·32 s	3·50 t	1·23 t
	A	(315·7)	68·49	8·00	13·32	341	3·86	1 730 s	1 585 s	2·20 s	7·0	7·0
									1 225 m		2·32 t	4·10 q
									1 165 m		8·0	7·0

IVa	[d]	$C_{17}H_{25}NO_6$	60·22	7·47	3·97	221	4·14	—	1 660 m	1·01 d/7·0	—	1·31 t
		(339·3)	60·17	7·44	4·13	261	4·10	1 725 s	1 620 m	3·84 q/7·0	—	7·0
								1 710 s	1 270 m	2·45 s		4·23 q
									1 220 s			7·0
IVb	102–104	$C_{18}H_{27}NO_6$	61·27	7·86	3·79	231	4·19	—	1 645 m	0·97 d/6·5	4·31 s	1·29 t
	C	(353·4)	61·17	7·70	3·96	258	4·03	1 755	1 590 m	3·82 q/6·5		7·0
						340	3·87	1 685 s	1 220 s	2·32 s		4·18 q
									1 145 m			7·0
IVc	53–56	$C_{21}H_{33}NO_6$	64·43	8·56	3·42	233	3·71	—	1 635	0·94 d/6·5	3·60 t	1·29 t
	A	(395·5)	64·11	8·60	3·51	263	3·54	1 730 m	1 580 m	3·82 q/6·5	7·0	7·0
						347	3·43	1 680 s	1 215 m	2·37 s	2·30 t	4·16
									1 140 s		7·0	7·0

[a] A heptane, B ethanol–water, C benzene; [b] R = CH_3 in compounds *III*, R = H in compounds *IV*; [c] CH_3C and CH_2O of the ethyl group in position 1; [d] oil, isolated by chromatography.

0—4% methanol, detection with UV-light and iodine vapours) and, according to its composition, either crystallized or chromatographed on a column of silica gel (50—100 g, elution with 0—4% methanol). The product-containing fractions were combined, taken down and the residue was crystallized from a suitable solvent. Results of the experiments are summarized in Table I and characteristics of the compounds *IIIa,b,d,e* and *IVa,b,e* are given in Table II.

Mass spectra (the superscripts at the *m/z* values denote the ions, described in the fragmentation mechanisms, + denotes a metastable peak, relative % in parentheses): *IIIa*: 259[a] (12·5), 244[b] (37·5), 200[j] (20·0), 186 (6·3), 173 (16·3), 172[f] (100), 171[c] (11·3), 77 (7·0), 65 (7·5), 64 (7·2), 51 (7·0), 42 (20·0), 41 (6·5), 39 (13·8); *IIIb*: 273[a] (5·9), 258[b] (100), 230[d] (51·0), 205[+] (3·9), 200 (9·8), 186[h] (11·8), 172[e] (5·9), 97 (13·8), 85 (11·8), 83 (13·8), 81 (13·8), 71 (15·8), 69 (25·5), 57 (25·5); *IIId*: 301[a] (16·7), 287 (10·0), 286[b] (41·7), 272[+] (—), 258[d] (10·0), 186[h] (9·2), 172[f] (9·2), 171[c] (8·3), 116 (8·3), 115[g] (91·7), 88 (8·3), 87[i] (100), 69 (10·0), 43 (37·5); *IIIe*: 315[a] (2·9), 301 (12·1), 300[b] (68·9) 285[+] (—), 272[d] (15·0), 213 (10·7), 208 (22·1), 186[h] (10·0), 172[f] (17·8), 171[c] (17·8), 129[g] (71·4), 101[i] (100), 84 (37·1), 55 (58·6); *IVa*: 339[a] (2·0), 325 (18·3), 324[b] (100), 311[+] (—), 294[c] (34·6), 280 (20·8); 224 (58·7); 222 (11·5), 206 (24·0), 200[+] (—), 196 (39·4), 178 (18·3), 150 (13·5), 148 (11·5), 147 (10·6), 120 (8·6), 79 (11·5), 77 (18·3), 42 (19·2); *IVb*: 353[a] (8·9), 339 (20·5), 338[b] (100), 324[+] (—), 310 (17·9), 280 (25·3), 254 (12·6), 234[f] (11·0), 208 (7·9), 95 (6·8), 77 (6·3), 69 (8·9), 55 (13·2), 43 (15·3); *IVe* 395[a] (3·6), 394 (3·0), 381 (21·4), 380[b] (64·3), 366[+] (—), 351 (6·4), 350[c] (28·6), 276[f] (10·7), 196 (6·4), 130 (15·7), 129[g] (100), 101[i] (78·6), 83 (21·4), 78 (8·6), 59 (14·3), 55 (35·7), 43 (10·0), 41 (11·4).

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