CHEMICAL TRANSFORMATIONS OF ETHYL 3,5-DICYANO-2,4,4,6-TETRAMETHYL-1,4-DIHYDRO-1-PYRIDYL ACETATE. SYNTHESIS OF A NEW N-VINYL MONOMER*

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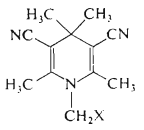
Ethoxycarbonyl group in the title compound *I* undergoes regioselective functional transformations to give the amide *II* and the carboxylic acid *III*. Reduction with lithium aluminium hydride gave the alcohol *V* whose *p*-toluenesulfonate was converted directly or *via* the 2-iodoethyl derivative *VIII* into the N-vinyl monomer *IX*. Absorption molecular spectra of the synthesized compounds *I*–*IX*, as well as their fragmentation by electron impact, are discussed.

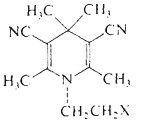
In our preceding communication[1] we have shown that the easily accessible 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine can be N-substituted with ethyl bromoacetate to give the corresponding 1-ethoxycarbonylmethyl derivative *I* in very high yield. This finding gave us an impetus to investigate experimentally the conversion of the ethoxycarbonyl group into related functional derivatives including its reduction. In the series of Hantzsch 1,4-dihydropyridines, such experiments have not been performed as yet and the possible participation of the heterocyclic system and/or the 3,5-cyano group in the studied reaction was of interest. As shown below, there was no such participation.

Ethyl ester *I* was converted into the N,N-dimethylamide *II* and the carboxylic acid *III* by standard synthetic procedures, consisting in reaction of *I* with dimethyl-



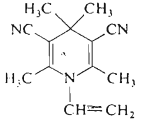
I–*IV*

I, X = $COOC_2H_5$
II, X = $CON(CH_3)_2$
III, X = COOH
IV, X = H



V–*VIII*

V, X = OH
VI, X = OTs
VII, X = OC_2H_5
VIII, X = I



IX

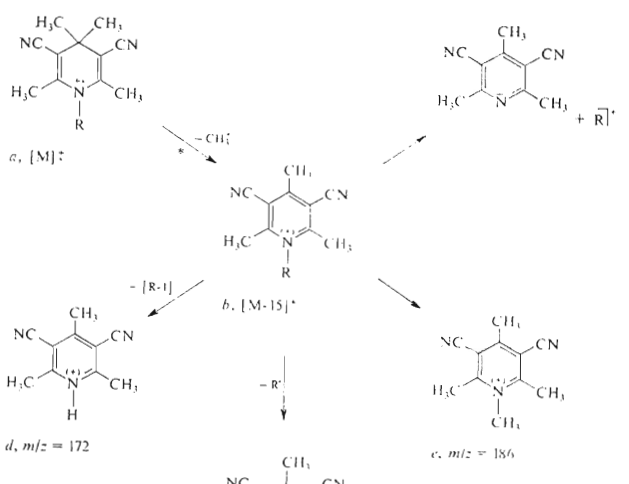
* Part LII in the series On Dihydropyridines; Part LI: This Journal *48*, 608 (1983).

amine at elevated temperature and saponification with potassium hydroxide at 20°C. The very good preparative yields of both products *II* and *III* (81% and 68%) indicate a high regioselectivity of the reactions. The free carboxylic acid *III* was a stable compound and was decarboxylated into the known[2] 1,4-dihydropyridine derivative *IV* only on heating to 200°C.

Reduction of the ester *I* with lithium aluminium hydride was also highly regioselective, affording 92% of the alcohol *V* which was used in the attempted preparation of the potential 1,4-dihydropyridine N-vinyl monomer *IX*. To this end we investigated the following synthetic procedures[3-6]: In the first reaction path, the alcohol *V* was treated with *p*-toluenesulfonyl chloride in pyridine to give in 95% yield the corresponding *p*-toluenesulfonate *VI* which was then subjected to elimination of *p*-toluenesulfonic acid[4] by potassium tert-butoxide in tert-butyl alcohol. The desired 3,5-dicyano-2,4,4,6-tetramethyl-1-vinyl-1,4-dihydropyridine (*IX*) was thus obtained in 95% yield. The second method, treatment with sodium ethoxide in ethanol as dehydrotosylation reagent[5] afforded 71% of the 1-vinyl derivative *IX* and 15% of a side-product which on the basis of its spectra was assigned the structure *VII*. Its formation can be explained by a concurrent nucleophilic substitution with the ethoxide ion. In the third method, the same reagent was successfully employed in the dehydroiodination of the iodo derivative *VIII* which gave the desired 1-vinyl derivative *IX* as the sole product in 92% yield. The intermediate *VIII* was obtained in 85% yield by the known[6] method, consisting in reaction of the *p*-toluenesulfonate *VI* with sodium iodide. These results indicate that compounds of the type *IX* can be prepared also from other Hantzsch 1,4-dihydropyridine derivatives.

The IR and ^{1}H NMR spectra of the synthesized compounds are in full accord with the structural formulae *I*–*III* and *V*–*IX* (Table I). The UV spectrum of the 1-vinyl derivative *IX* is very interesting since, in contrast with the other compounds exhibiting two maxima at 218–222 nm and 333–340 nm, it displays three maxima at 216, 260 and 333 nm. The second maximum is probably due to conjugation of the 1-vinyl group with the π-electron system of the 1,4-dihydropyridine skeleton in the molecule of *IX*. In accord with this assumption, a similar additional maximum at 255 nm was found also in the spectrum of the analogous 1-ethoxycarbonyl derivative[1] in which a similar conjugation with π-electrons of the C=O bond can be expected.

The probable fragmentation mechanism for cleavage of compounds *I*–*III* and *V*–*IX* on electron impact is depicted in Scheme 1. Similarly as for 3,5-dicyano-1,4-dihydropyridines of the type *IV* (ref.[7,8]), the key process is an aromatization of the molecular radical-ion *a*, $[M]^{+\cdot}$, to the quaternary pyridinium ion *b*, $[M-15]^+$. The substituent R can be cleaved off either as the radical-cation *c*, *m*/*z* 171, the protonated pyridinium ion *d*, *m*/*z* 172, or a single carbonium ion R^+, $[M-186]^+$. In the case of the carboxylic acid *III*, we observed also decarboxylation of the ion *b* to the ion *e*, *m*/*z* 186.



SCHEME 1

EXPERIMENTAL

The temperature data are uncorrected. The melting points were determined on a Boetius block (G.D.R.). Analytical samples were dried over phosphorus pentoxide for 12—15 h at 130—260 Pa. Spectral characteristics were measured on the following instruments: Specord UV-VIS, Perkin Elmer 325, Varian 100 XL and LKB 9000 (70 eV). Composition of reaction mixtures was followed by liquid chromatography on a chromatograph type 501 (Laboratorní přístroje, Prague) on a column filled with Separon SI with methanol as eluant. Spectral data of the synthesized compounds are given in Table I.

3,5-Dicyano-1-(N,N-dimethylaminocarbonylmethyl)-2,4,4,6-tetramethyl-1,4-dihydropyridine (*II*)

A mixture of the ethyl ester *I* (ref.[1]) (2·16 g), dimethylamine (0·8 ml) and ethanol (15 ml) was heated in a sealed tube to 110°C for 11 h. After cooling, the separated crystals were collected on filter and crystallized from ethanol, yielding 1·7 g (81%) of the amide *II*, m.p. 258—259°C. For $C_{15}H_{20}N_4O$ (272·4) calculated: 66·14% C, 7·41% H, 20·57% N; found: 65·91% C, 7·43% H, 20·44% N.

3,5-Dicyano-1-hydroxycarbonylmethyl-2,4,4,6-tetramethyl-1,4-dihydropyridine (*III*)

A saturated solution of the ethyl ester *I* (3·0 g) in methanol was mixed with a solution of potassium hydroxide (1·8 g) in methanol (25 ml). After standing for three days at room temperature, the separated crystals of potassium salt of *III* were filtered and dissolved in water (25 ml). The solution was acidified (pH 4—5) with 5% hydrochloric acid, the precipitate was filtered and crystallized from water, yielding 1·8 g (68%) of the acid *III*, m.p. 180—183°C. For $C_{13}H_{15}N_3O_2$ (245·3) calculated: 63·65% C, 6·17% H, 17·13% N; found: 63·33% C, 6·20% H, 17·09% N.

3,5-Dicyano-1,2,4,4,6-pentamethyl-1,4-dihydropyridine (*IV*)

The carboxylic acid *III* (0·3 g) was heated to 200°C for 20 min. After cooling, the mixture was triturated with hot water (10 ml), the insoluble portion was filtered and exposed on a porous

TABLE I

Spectral data of the studied compounds

Compound	UV, nm λ_{max}	log ε	IR ν(C≡N) ν(C=C)	$\tilde{\nu}_{max}$, cm^{-1} ν(C=O) ν(C—O)	^1H NMR, $(CH_3)_2C$ CH_3C=	δ, ppm N—CH_2
II	218	4·51	2 200 s		1·40 s	4·26 s
	339	3·78	1 660 s		2·08 s	3·00[a]
			1 640 s			
III	219	4·46	2 210 s	1 735 s	1·42 s	4·29 s
	340	3·85	1 670 s	1 275 w	2·18 s	
			1 590 m	1 210 m		
V	222	4·57	2 200 s	—	1·38 s	3·71—3·74[b]
	340	3·81	1 650 s	1 050 m[c]	2·27 s	
			1 585 m			
VI	222	4·57	2 200 s	—	1·33 s	4·05 t/5 Hz[d]
	333	3·80	1 655 s	1 180 s	2·17 s	3·85 t/5 Hz
			1 590 m			
VIII	221	4·41	2 200 s	—	1·36 s	3·76 t/8 Hz[d]
	337	3·80	1 655 s		2·20 s	3·03 t/8 Hz
			1 590 m			
IX	216	4·36	2 200 s	—	1·39 s	6·00—6·22 m[c]
	260	3·78	1 660 s	970[e]	2·09 s	4·98—5·36 m
	333	3·75	1 640 s			

[a] Due to $N(CH_3)_2$ group; [b] non-resolvable multiplet due to NCH_2CH_2OH group; [c] the band at 3 420—3 480 cm^{-1} due to OH group vibration; [d] signal of NHC_2CH_2O—; [e] due to CH_2= =CH— group.

tile to ethanol vapours for 5 h. In this way, 0·1 g (40%) of the 1,4-dihydro derivative *IV*, m.p. 166—168°C, was obtained (reported[2] m.p. 169—170°C). Chromatographic and spectral characteristics of the product were identical with those of an authentic sample[2].

3,5-Dicyano-1-(2-hydroxyethyl)-2,4,4,6-tetramethyl-1,4-dihydropyridine (*V*)

To a stirred suspension of the ethyl ester *I* (2·73 g) in ether (150 ml), 0·78M solution (12·8 ml) of lithium aluminium hydride in diethyl ether was added dropwise during 30 min. The mixture was refluxed for 2 h, cooled and decomposed with water (2 ml) and 20% sulfuric acid (30 ml). The aqueous layer was separated and extracted with ether (50 ml total). The combined ethereal extracts were washed with saturated aqueous sodium chloride solution (30 ml) and dried over magnesium sulfate. After evaporation, the residue was dissolved in chloroform, containing 2% of methanol, and chromatographed on a column of silica gel (150 g). Fractions, containing the alcohol *V*, were combined and taken down. Crystallization of the residue from benzene–light petroleum afforded 1·4 g (92%) of the hydroxy derivative *V*, m.p. 111—114°C. For $C_{13}H_{17}N_3O$ (231·3) calculated: 67·49% C, 7·42% H, 18·17% N; found: 67·50% C, 7·51% H, 18·42% N.

3,5-Dicyano-1-(*p*-toluenesulfonyl-2-ethyl)-2,4,4,6-tetramethyl-1,4-dihydropyridine (*VI*)

p-Toluenesulfonyl chloride (3·0 g) was added to a solution of the hydroxy derivative *V* (1·77 g) in pyridine (10 ml) and the mixture was set aside at room temperature for 24 h. After evaporation of pyridine *in vacuo*, the residue was dissolved in ethanol (10 ml) and the product was precipitated with water (100 ml). Filtration and crystallization from benzene gave 2·8 g (95%) of the *p*-toluenesulfonate *VI*, m.p. 150—152°C. For $C_{20}H_{23}N_3O_3S$ (385·3) calculated 62·30% C, 6·03% H, 10·90% N, 8·32% S; found: 62·13% C, 5·93% H, 10·89% N, 7·89% S.

3,5-Dicyano-1-(2-iodoethyl)-2,4,4,6-tetramethyl-1,4-dihydropyridine (*VIII*)

Anhydrous sodium iodide (2·4 g) was added to a solution of the *p*-toluenesulfonate *VI* (2 g) in 2-butanone (100 ml) and the mixture was refluxed for 3 h. After cooling, the precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was mixed with benzene (50 ml) and the undissolved sodium salts were removed by filtration. The benzene solution was again taken down and the residue was crystallized from benzene–heptane, affording 1·51 g (85%) of the iodo derivative *VIII*, m.p. 130—131°C. For $C_{13}H_{16}IN_3$ (341·2) calculated: 12·32% N; found: 11·93% N.

3,5-Dicyano-2,4,4,6-tetramethyl-1-vinyl-1,4-dihydropyridine (*IX*)

A: The *p*-toluenesulfonate *VI* (1·9 g) was added to a solution of potassium tert-butoxide prepared from potassium (0·31 g) and tert-butyl alcohol (30 ml). The mixture was refluxed for 10 h, taken down *in vacuo* and the residue was extracted several times with benzene (100 ml total). The benzene solution was filtered, taken down and crystallized from the same solvent, yielding 1·01 g (95%) of the 1-vinyl derivative *IX*, m.p. 85—86°C. For $C_{13}H_{15}N_3$ (213·3) calculated: 73·20% C, 7·10% H, 19·70% N; found: 73·35% C, 7·18% H, 19·62% N.

B: The *p*-toluenesulfonate *VI* (0·38 g) was added to a solution of sodium (0·23 g) in ethanol (10 ml) and the mixture was heated for 10 h. After evaporation of the solvent, the residue was mixed with benzene (50 ml) and chromatographed on a column of silica gel (100 g) with 1% methanol in chloroform as eluant. Fractions, containing the 1-vinyl derivative *IX*, were com-

bined, taken down and the residue was crystallized from benzene, affording 0·15 g (71%) of compound *IX*, m.p. 85–86°C. Further fractions, containing the ethoxy derivative *VII*, were combined and taken down. The residue was applied on a porous tile and set aside in contact with hexane vapours, affording 0·04 g (15%) of *VII*, m.p. 100–105°C. For $C_{15}H_{22}N_3O$ (259·4) in mass spectrum found molecular ion *m/z* 259. ^{1}H NMR spectrum displayed signals due to $(CH_3)_2C$ (singlet at 1·37δ), $CH_3C=$ (singlet at 2·21δ), NCH_2CH_2O (triplet centered at 3·66δ and 3·39δ; J_{HH} = 5 Hz) and CH_3CH_2O grouping (quartet at 3·42δ and triplet at 1·18δ; J_{HH} = 6 Hz).

C: The iodo derivative *VIII* (1·7 g) was added to a solution of sodium (1·15 g) in ethanol (80 ml). The mixture was refluxed for 10 g and poured into water (150 ml). After extraction with benzene (4 × 30 ml), the combined organic layers were dried over magnesium sulfate and concentrated, yielding crystals of the 1-vinyl derivative *IX* (0·98 g; 93%), m.p. 85–86°C.

Mass Spectra (ions, relative %)

II: 272[a] (5·2), 258 (19·0), 257[b] (100), 243$^+$ (—), 185 (12·1), 86 (77·0), 72 (10·3). *III*: 245[a] (3·3), 244 (8·3), 231 (4·3), 230[b] (100), 229 (23·3), 186 (9·7), 185 (17·0), 184 (10·7), 171[c] (33·3), 170 (12·0), 128 (6·3), 115 (6·3), 42 (15·7), 39 (11·3), *V*: 231[a] (9·1), 217 (18·2), 216[b] (100), 202$^+$ (—), 173 (9·1), 172 (68·2), 81 (13·7), 69 (22·7), 57 (22·7), 55 (18·2), 43 (22·7), 41 (22·7). *VI*: 386 (5·7), 385[a] (7·1), 372 (21·4), 371 (61·4), 370[b] (100), 200 (15·7), 199[g] (70·0), 198 (15·7), 185 (28·6), 172[f] (15·7), 171[c] (18·6), 157 (11·4), 156 (10·0), 155 (71·4), 92 (21·4), 91 (100), 90 (17·1), 89 (14·3), 77 (11·4), 65 (42·8), 63 (12·8). *VIII*: 341[a] (2·3), 327 (3·1), 326[b] (22·3), 297 (6·9), 272$^+$ (—), 214 (13·0), 172[f] (5·4), 171[c] (12·3), 155[g] (100), 143 (2·1), 65 (1·8), *IX*: 213[a] (5·8), 199 (16·1), 198[b] (100), 184$^+$ (—), 172[f] (10·0), 171[c] (3·8), 99$^+$ (—). ([a–g] ions interpreted by the fragmentation mechanism; $^+$ metastable ions).

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