

N-ALKYLATION OF 3,5-DICYANO-2,4,4,6-TETRAMETHYL-
-1,4-DIHYDROPYRIDINE WITH SOME α,ω -DIHALOGENO-*n*-ALKENES*

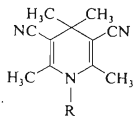
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Bis-1,4-dihydropyridine derivatives *Vc*–*Vf* can be obtained on reaction of α,ω -diiodo-*n*-alkanes with the sodio derivative *II* of compound *I*, while α,ω -dibromo-*n*-alkanes give a mixture of compounds *Vc*–*Vf* and *IVc*–*IVf*. Analogous products *IVa* and *Va,b* could not be prepared, owing to the predominating and disturbing elimination reactions. Spectral characteristics (UV, IR, NMR and mass spectra) of the compounds obtained are confronted with their structure.

In preceding studies on dihydropyridine derivatives it has been shown^{1,2} that penta-alkylated 3,5-dicyano-1,4-dihydropyridines display some optical and spectral properties, interesting from the point of view of practice. In connection with this we were interested in these properties in analogous, so far undescribed, compounds containing in their molecules always two 3,5-dicyano-1,4-dihydropyridine chromophore groupings, connected on the nitrogen atoms with a saturated carbon chain. In order to obtain the compounds of this type we decided to apply the procedure^{1,3} for N-alkylation of 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine (*I*), described earlier, on the reaction with dihalogeno derivatives of the general formula $X(CH_2)_2-nX$.

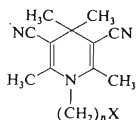


I, R = H

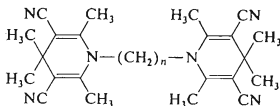
II, R = Na

III, R = $CH_2=CHCH_2-$

VI, R = CH_3CH_2-



IVa-f

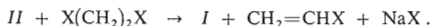


Va-f

Similarly as in refs^{1,3} the starting compound *I* was converted to sodio-derivative *II* under the effect of sodium hydride in dimethylformamide. Compound *II* was then

* Part XLIV in the series On Dihydropyridines; Part XLIII: This Journal 45, 2938 (1980).

exposed to the effect of alkylation agents $X(\text{CH}_2)_{2-7}X$. The results achieved are summarized in Table I. 1,2-Dichloro- and 1,2-dibromoethane did not alkylate compound *I*, because the sodium compound *II* causes only the dehydrohalogenation of both alkylating reagents.



Experiments aiming at the use of various phase-transfer catalysts and sodium hydroxide^{4,5} did not lead to a change in the reaction course either. It is probable that this is due to the steric interaction of 2,6-methyl groups in the reagent *II* with the 2-halogen atom of 1,2-dihalogen derivatives, preventing the formation of products *IVa* and *Va*. The fact that similar elimination reactions were already observed¹ in the experiments of N-alkylation of compound *I* with isopropyl and cyclohexyl halogenides, speaks in favour of this hypothesis. In the reaction of 1,3-dibromopropane with derivative *II* N-alkylation takes place in the first step, it is true, but the intermediate *IVb*, isolated in small amount, does not alkylate a further molecule of *II* under formation of the expected bis product *Vb*, but undergoes preferentially dehydrobromination.



TABLE I

N-Alkylation of Compound *I* with the Reagents $X(\text{CH}_2)_nX$

n	Reagent		Time h	Products (yields ^b , %)	
	X	mol ^a			
2	Cl	1	4		^c
2	Br	0.75	6		^c
3	Br	0.75	3	<i>III</i> (47)	<i>IVb</i> (<1)
4	Br	0.75	5.5	<i>IVc</i> (6)	<i>Vc</i> (47)
4	Br	1	3.25	<i>IVc</i> (42)	<i>Vc</i> (35)
4	Br	3	3	<i>IVc</i> (72)	<i>Vc</i> (16)
4	I	0.5	4		<i>Vc</i> (82)
5	Br	1.5	3	<i>IVd</i> (63)	<i>Vd</i> (18)
6	Br	1.5	2.5	<i>IVe</i> (60)	<i>Ve</i> (19)
6	I	0.75	1.25		<i>Ve</i> (76)
7	Br	1	2	<i>IVf</i> (56)	<i>Vf</i> (30)
7	I	0.75	2		<i>Vf</i> (48)

^a Referred to 1 mol of compound *I*; ^b referred to the reacted compound *I*; ^c the product of N-alkylation could not be identified in the reaction mixture.

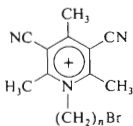
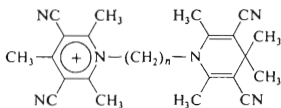
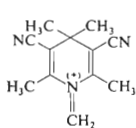
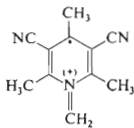
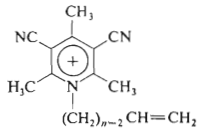
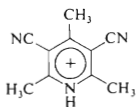
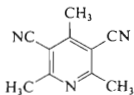
The main product of N-alkylation is thus 1-allyl-3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine (*III*) which can be obtained more easily by direct reaction of the sodium compound *II* with allyl bromide. Higher dihalogen derivatives $X(\text{CH}_2)_{4-7}X$ ($X = \text{Br}, \text{I}$) afford the products of N-alkylation exclusively, under formation of N-monoderivative *IVc-IVf* and N,N'-bis derivatives *Vc-Vf*. The effect of the type of halogen X on the isolated reaction products is evident from Table II. When dibromo derivative ($X = \text{Br}$) was used a mixture of both products *IVc-IVf* and *Vc-Vf* was always used, while in the reaction with diiodo compounds ($X = \text{I}$) bis-dihydropyridine derivatives *Vc-Vf* were isolated exclusively.

The structure of 1,4-dihydropyridine derivatives *IVb-IVf* and *Vc-Vf* was checked by analysing the corresponding spectral data. In Table II data for absorption spectra are given. It is evident that the $^1\text{H-NMR}$ spectra of all the substances investigated display characteristic signals of 2,4,4,6-methyl groups at 1.30 to 1.50 δ or 2.20 to 2.25 δ , in accordance with the data for analogous compounds¹. The methylene protons in the $\text{N-CH}_2\text{-C}$ and $\text{C-CH}_2\text{-Br}$ groupings display two mutually overlapped triplets in the 3.35 to 3.70 δ region, while other methylene protons appear as variously complex multiplets between 1.4 to 2.3 δ . The allyl group in compound *III* gives a characteristic multiplet at 4.95 to 5.40 δ for the terminal $\text{CH}_2=$ group and a multiplet of the -CH= group at 5.65 to 5.40 δ , as well as a centered doublet at 4.12 δ , corresponding to the $\text{N-CH}_2\text{-C}$ grouping. The maxima of the stretching bands of the $\text{C}\equiv\text{N}$ groups and the multiple bonds of the 1,4-dihydropyridine skeleton (C=C-N-C=C) are in agreement with the data for various 3,5-dicyano-1,4-dihydropyridines¹.

The ultraviolet spectra of compounds *IVc-IVf* and *Vc-Vf* are very similar (Table II) and in accordance with analogous spectra of 1-ethyl derivative *VI* (λ_{max} 220 and 345 nm, $\log \epsilon$ 4.40 and 3.79) and further pentaalkylated 3,5-dicyano-1,4-dihydropyridines¹. From this it may be concluded that under the conditions of measurement (methanolic solutions) mutual electronic interaction of both 1,4-dihydropyridine cycles in the molecule which would manifest itself on electron excitation does not take place in bis-derivatives *Va-Vf*.

The fragmentation of the molecules of compounds *IVc-IVf* and *Vc-Vf* under electron impact was investigated in greater detail. The ionic species found in the mass spectra are presented in the experimental part. Molecular ions of compounds *IVc-IVf* and *Vc-Vf* are cleaved by two alternative processes. In the first, predominating one, 4-methyl group is split off similarly as in other 4,4-dimethylated 1,4-dihydropyridine derivatives^{6,7} in the sense of the processes $[\text{IVc-IVf}]^+ \rightarrow \text{CH}_3 + \text{VIIc-VIIIf}$ and $[\text{Vc-Vf}]^+ \rightarrow \text{CH}_3 + \text{VIIIc-VIIIIf}$, while the m/e values and the abundance of the ionic species observed, *VIIc-VIIIf* and *VIIIc-VIIIIf* are dependent both on the type of the 1,4-dihydropyridine derivatives investigated (mono or bis), and on the structural characteristics of the substituent and n in formulae *IV* and *V*. The second process of the fragmentation of the molecular ions, which is,

however, a minor one, consists in the formation of ion *IX* (m/e 200) which is further fragmented independently of the starting compound, in the sense of the process $IX \rightarrow X$ (m/e 185) + CH_3 . In this case the structural difference in compounds *IVc*–*IVf* and *Vc*–*Vf* affects only the abundance, but not the mass of the identified fragments *IX* and *X*. The subsequent fragmentation of the cations *VIIc*–*VII f* and *VIIIc*–*VIII f* is remarkable. For the first type the elimination of hydrogen bromide is always characteristic, $VIIc$ –*VII f* \rightarrow *XIc*–*XI f*, in the second type protonized 3,5-dicyano-2,4,6-trimethylpyridine (*XII*) is formed in the sense of the process $VIIIc$ –*VIII f* \rightarrow *XIc*–*XI f* + *XII* (m/e 172).

*VIIc-f**VIIIc-f**IX* (m/e 200)*X* (m/e 185)*XIc-f**XII* (m/e 172)*XIII*

In formulae *IV*–*VIII* and *XI*: $a n = 2$, $b n = 3$, $c n = 4$, $d n = 5$, $e n = 6$, $f n = 7$.

The formation of the ionic species m/e 172 can also be explained by subsequent cleavage of the C–N bond and simultaneous hydrogen transfer in ions *XIc*–*XI f*. The conversions of ions *VIIc*–*VII f* and *VIIIc*–*VIII f*, consisting for example in the elimination of the considerably stable molecule of 3,5-dicyano-2,4,6-trimethylpyridine (*XIII*) in the sense of the process of the type $VIIc$ –*VII f* \rightarrow *XIII* + + $[\text{CH}_2=\text{CH}(\text{CH}_2)_{n-2}\text{X}]^{\ddagger}$ or $VIIc$ –*VII f* \rightarrow $[\text{XIII}]^{\ddagger} + \text{X}(\text{CH}_2)_n^{\ddagger}$ also seem less important from the point of view of the abundance of the ionic species formed.

EXPERIMENTAL

The temperature data are not corrected. The melting points were measured on a Boetius block. Samples for analysis were dried *in vacuo* at 130–260 Pa over phosphorus pentoxide for 12 to 15 h. The UV spectra were measured on a Specord UV-VIS spectrophotometer, the IR spectra on a Perkin-Elmer 325 apparatus, the $^1\text{H-NMR}$ spectra (CDCl_3 solutions) on a Varian XL 100 instrument (tetramethylsilane as reference) and the mass spectra on an LKB 9000 spectrometer at 70 eV.

N-Alkylation of 3,5-Dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine (*I*)

Sodium hydride (Merck) in paraffin oil (2 g of a 80% suspension) was added in portions to a stirred solution of 10 g of compound b *I* in 38 ml of dimethylformamide and the mixture was heated at 30–40°C (bath temperature) for one hour. After cooling to 0°C α,ω -dihalogeno-*n*-alkane

TABLE II

List of Dihydropyridine Derivatives Investigated and Their $^1\text{H-NMR}$, UV and IR Spectral Data

Compound	Formula (mol.mass)	M.p., °C methanol	Calculated/Found			
			% C	% H	% N	% Br
<i>IVc</i>	$\text{C}_{15}\text{H}_{20}\text{BrN}_3$ (322.3)	109–111	55.91 56.14	6.26 6.48	13.04 13.13	24.79 24.44
<i>Vc</i>	$\text{C}_{26}\text{H}_{32}\text{N}_6$ (428.6)	326–327 ^d	72.86 72.66	7.53 7.63	19.61 20.02	
<i>IVd</i>	$\text{C}_{16}\text{H}_{22}\text{BrN}_3$ (336.3)	81–83	57.14 57.46	6.59 6.70	12.50 12.47	23.76 23.59
<i>Vd</i>	$\text{C}_{27}\text{H}_{34}\text{N}_6$ (442.6)	212–213	73.27 73.28	7.74 7.89	18.99 19.03	
<i>IVe</i>	$\text{C}_{17}\text{H}_{24}\text{BrN}_3$ (350.3)	75–77	58.28 58.71	6.91 6.91	12.00 11.83	22.81 23.02
<i>Ve</i>	$\text{C}_{28}\text{H}_{36}\text{N}_6$ (456.6)	259–260 ^d	73.65 73.56	7.95 8.07	18.40 18.63	
<i>IVf</i>	$\text{C}_{18}\text{H}_{26}\text{BrN}_3$ (364.3)	62–64	59.34 59.44	7.19 7.20	11.53 11.57	21.93 21.38
<i>Vf</i>	$\text{C}_{29}\text{H}_{38}\text{N}_6$ (470.7)	161–163	74.00 73.81	8.14 8.41	17.86 18.04	
<i>III</i>	$\text{C}_{14}\text{H}_{17}\text{N}_3$ (227.3)	113–114	73.97 73.98	7.54 7.71	18.49 18.77	

^a Triplet $^3J_{\text{HH}} = 7\text{--}9$ Hz; ^b triplet $^3J_{\text{HH}} = 6\text{--}7$ Hz; ^c concentration $4 \cdot 10^{-5}$ mol l⁻¹, methanol; ^d crystallized from dimethylformamide; ^e owing to limited solubility the log ϵ value was not

was added to the yellow solution of compound *II* and the mixture was heated at 40–50°C for a limited time. After cooling and decomposition with water (about 50 ml) the separated crystals were filtered off under suction. The composition of the crude product was checked by thin-layer chromatography on silica gel (Kieselgel G; Merck), using detection with UV light or 1% solution of $\text{Ce}(\text{SO}_4)_2$ in 10% H_2SO_4 . In the case of the inhomogeneity of the product, this was chromatographed on alumina (act. III) with 20–50% of CHCl_3 in CCl_4 . In the case of the formation of compound *Vc*, *Vd*, insoluble in ethanol, they were suction-dried after suspension of the mixture in ethanol and then chromatographed. The conditions according to which the general procedure was modified in individual cases are evident from Table I. The characteristics of individual crystalline products, purified by crystallization until the melting point was constant, are presented in Table II.

Mass spectra of individual compounds: *m/e* (% r.i.):

IVb: 309/307 (0.9/0.9), 294/292 (10.2/10.2), 213 (16.7), 212 (100), 200 (2.5), 185 (9.3), 172 (9.5), 171 (18.5), 147 (12.0), 73 (27.8), 44 (25.9), 41 (31.5).

	δ (ppm), CDCl_3		$\tilde{\nu}$ (cm^{-1}), CHCl_3		λ_{max}^c , nm	$\log \epsilon$ l . mol ⁻¹ . cm ⁻¹
	$(\text{CH}_3)_2\text{—C}$ $\text{CH}_3\text{—C=}$	$\text{N—CH}_2\text{—C}^a$ $\text{C—CH}_2\text{—C}$	$\text{C—CH}_2\text{—C—Br}$ $\text{C—CH}_2\text{—Br}^b$	($\text{C}\equiv\text{N}$)		
1.39 s	3.49 t	1.7—1.9 m	2 200	1 650	224	4.36
2.25 s	1.6—1.7 m	3.43 t		1 580	344	3.81
1.39 s	3.46 t	—	2 205	1 635	225	^e
2.23 s	1.4—1.6 m			1 570	347	^e
1.32 s	3.46 t	1.7—1.9 m	2 210	1 655	224	4.39
2.23 s	1.4—1.6 m	3.41 t		1 585	346	3.79
1.35 s	3.45 t	—	2 210	1 655	225	4.62
2.21	1.4—1.6 m			1 585	346	4.13
1.37 s	3.43 t	1.8—1.9 m	2 215	1 650	224	4.43
2.22 s	1.4—1.6 m	3.37 t		1 585	345	3.84
1.37 s	3.47 t	—	2 200	1 630	225	4.48
2.23 s	1.4—1.6 m			1 580	347	3.93
1.37 s	3.45 t	1.8—1.95 m	2 205	1 630	223	4.39
2.23 s	1.4—1.6 m	3.41 t		1 585	346	3.79
1.39 s	3.46 t	—	2 205	1 650	225	4.62
2.24 s	1.4—1.6 m			1 580	346	4.13
1.41 s	4.1 d		2 210	1 655	223	4.43
2.20 s	4.95—5.40 m ^f	5.65—6.05 m ^g		1 585	347	3.85

determined; ^f $\text{CH}_2=$ grouping; ^g —CH= grouping.

IVc: 325/323 (0·9/0·9), 308/306 (17·1/17·1), 226 (22·2), 200 (4·2), 185 (7·3), 172 (33·1), 171 (8·5), 137/135 (22·1/22·0), 55 (100), 43 (33·3), 41 (18·8), 39 (13·7).

IVd: 337/335 (4·6/4·6), 323/321 (18·2/18·2), 322/320 (99·2/100), 240 (12·3), 200 (7·7), 198 (10·5), 195 (21·5), 173 (10·6), 172 (84·6), 171 (23·7), 151/149 (6·2/6·2), 110/108 (12·1/12·1), 70 (18·2), 69 (50·0), 55 (13·6), 53 (13·6), 44 (45·5), 42 (43·9), 41 (33·3), 39 (30·3), 29 (18·2), 27 (30·3).

IVe: 351/349 (4·4/4·5), 337/335 (10·6/10·6), 336/334 (86·5/87·0), 254 (30·4), 200 (6·5), 185 (13·0), 172 (57·0), 171 (17·5), 165/163 (2·0/2·0), 83 (39·0), 55 (100), 43 (34·8), 41 (56·5), 29 (21·7), 27 (13·0).

IVf: 365/363 (3·7/3·7), 351/349 (18·4/18·4), 350/348 (91·2/92·3), 269 (12·6), 268 (57·0), 200 (3·6), 185 (21·5), 172 (58·5), 171 (18·5), 97 (15·6), 69 (21·5), 56 (25·9), 55 (100), 43 (43·0), 42 (17·1), 41 (41·5), 39 (19·3), 29 (31·1), 27 (23·0).

Vc: 428 (3·3), 413 (9·2), 354 (30·6), 242 (4·4), 226 (19·4), 200 (4·7), 185 (31·9), 172 (55·6), 171 (9·7), 73 (36·1), 55 (100), 44 (22·2), 42 (19·4), 41 (11·1), 39 (11·1), 29 (19·4), 27 (16·7).

Vd: 442 (3·9), 428 (28·2), 427 (100), 256 (7·1), 240 (5·5), 226 (14·2), 206 (27·6), 200 (20·8), 185 (28·4), 172 (46·0), 171 (16·4), 69 (16·5), 55 (9·5), 42 (13·4), 41 (48·8), 27 (5·2).

Ve: 456 (0·3), 441 (3·4), 270 (2·6), 255 (16·2), 254 (81·2), 200 (6·8), 185 (12·8), 172 (57·3), 171 (16·2), 83 (29·9), 73 (70·5), 55 (100), 44 (65·2), 43 (18·4), 42 (38·0), 41 (56·5), 39 (11·7), 29 (18·4), 27 (12·3).

Vf: 470 (0·4), 465 (8·5), 284 (3·2), 269 (16·0), 268 (67·1), 200 (2·2), 185 (7·4), 172 (63·8), 171 (10·6), 97 (2·2), 69 (7·4), 55 (100), 43 (13·8), 42 (11·6), 41 (46·2), 39 (11·7), 27 (12·6).

Identification of Vinyl Halogenides in the Reaction of Compound *I* with 1,2-Dichloroethane and 1,2-Dibromoethane

The reaction of compound *I* with the mentioned dihalogenoethanes was carried out as in the preceding case, with the difference that the volatile components escaping from the reaction mixture were condensed by cooling to -78 to -80°C . Vinyl chloride or vinyl bromide obtained in this way were identified by means of mass spectra which were identical with the data published earlier⁹. After decomposition of the reaction mixture with water 90—95% of the starting 1,4-dihydro derivative *I* were isolated.

N-Alkylation of Compound *I* with Allyl Bromide

The reaction was carried out as in the example given above, starting from 2·67 g of compound *I* dissolved in 12 ml of dimethylformamide and 0·48 g of a 80% suspension of sodium hydride in paraffin oil, which gave compound *II*. This was heated with 1·73 g of allyl bromide at $35-40^{\circ}\text{C}$ for 3 h. After decomposition with water and crystallization of the crude product from a mixture of methanol and water 1-allyl derivative *III* (2·76 g; 85·1%) was obtained, m.p. $113-114^{\circ}\text{C}$, the NMR, IR and UV spectral data are given in Table II. Mass spectrum *m/e* (% r.i.): 227 (3·0), 214 (5·5), 213 (33·8), 171 (2·8), 51 (2·0), 42 (6·7), 41 (100).

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