SOME 2-NITROMETHYL-, 2,6-BIS(NITROMETHYL)-, 2-CYANO-, AND 2,6-DICYANO-SUBSTITUTED DERIVATIVES OF POLYALKYLATED 3,5-DICYANO-1,4-DIHYDROPYRIDINES

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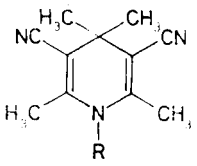
Received August 8, 1988
Accepted September 20, 1988

Nitration of polyalkyated 3,5-dicyano-1,4-dihydropyridines *Ia—Id* to the first and second degrees has been studied leading to compounds *II* and *III*, and conversion of nitromethyl groups of these compounds into nitrile groups with formation of tricyano derivatives *IV* and tetracyano-derivatives *V* has been followed. Also given is the fragmentation of the synthesized compounds *II—V* by an electron impact in mass spectrometer and further spectral characteristics.

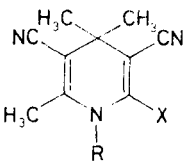
When studying the nitration of polyalkylated 3,5-dicyano-1,4-dihydropyridines we found[1-3] that the nitro group is introduced into 2- or 6-methyl groups. Depending on the 1- or 4-substituents it is possible to obtain the products of mononitration[1], dinitration[2], or further transformations[2,3]. The aim of this present work was to investigate the effect of alkyl group in 1-alkyl-3,5-dicyano-2,4,4,6-tetramethyl-1,4--dihydropyridines *I* on the nitration under various conditions and on spectral characteristics of the compounds prepared.

1-Methyl derivative *Ia* is known[1,2] to give 62% yield of mononitro compound *IIa* on nitration with 65% nitric acid in acetanhydride. Analogous nitration with fuming nitric acid converts compound *Ia* into dinitro derivative *IIIa*. The composition of products of nitration of 1,4-dihydropyridine *Ia* at various conditions was followed by means of HPLC. Table I shows that in acetanhydride medium increasing reaction time and increasing molar excess of the nitration agent increase the conversion of the nitro derivatives formed into subsequent products (conversions of nitro compound *IIa* by action of acetanhydride were studied earlier[4]). The nitration of compound *Ia* in chloroform gives somewhat higher yields of nitro compounds *IIa* and *IIIa*, and the products can be isolated more easily. Therefore, the nitration of 1,4-dihydropyridines *I* in chloroform medium was chosen for preparative purposes.

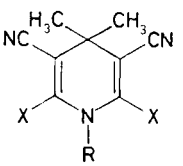
Out of different ways[5-7] of transformation of nitromethyl group into nitrile group the preparation of trinitrile *IVa* by reduction of nitro compound *IIa* with phosphorus trichloride in pyridine proved successful[4]. This method was applied[6] to syntheses of a series of trinitriles *IV* and tetranitriles *V*.



I



II, X = CH_2NO_2
IV, X = CN



III, X = CH_2NO_2
V, X = CN

In formulae *I–V*: *a*, R = CH_3; *b*, R = CH_2CH_3; *c*, R = $CH_2CH_2CH_3$; *d*, R = $CH_2CH_2CH_2CH_3$

Table II presents yields, melting temperatures, and elemental analyses of all the newly prepared 1,4-dihydropyridine derivatives *II – V*.

The proton signals in ^{1}H NMR spectra of compounds *II – V* (Table III) show the expected[8,9] chemical shifts. Also IR spectra of compounds *II – V* (Table III) exhibit the characteristic skeletal vibrations of 1,4-dihydropyridine nucleus in the region of 1 570 – 1 648 cm^{-1}. The absorption bands of C—H valence vibrations lie in the region of 2 880 – 3 058 cm^{-1}, those of C—H deformation vibrations in the region of 1 360 – 1 460 cm^{-1}. The spectra of nitro compounds *II* and *III* exhibit both characteristic bands of nitro group, the more intensive one in the region of 1 560 to 1 580 cm^{-1} and the less intensive one in the region of 1 310 – 1 315 cm^{-1}. The spectra of trinitriles *IV* and tetranitriles *V* contain two absorption bands in the region of 2 200 – 2 237 cm^{-1} corresponding to the valence vibrations of nitrile groups, the higher wavenumber corresponding to the nitrile groups at the positions 2 or 2 and 6 of the 1,4-dihydropyridine ring. In contrast to trinitriles *IV*, the tetranitriles *V* exhibit

TABLE I

Conditions and results of nitration of compound *Ia*

Experiment No.	Solvent	Nitration agent[a]	Molar ratio *Ia*: HNO_3	Reaction time, min	Product	Yield[b] %
1	Ac_2O	65	1 : 2·5	5	*IIa*	57
2	Ac_2O	100	1 : 3·6	5	*IIIa*	48
3	Ac_2O	100	1 : 3·6	150	*IIIa*	39
4	Ac_2O	100	1 : 3·6	1 440	*IIIa*	26
5	Ac_2O	100	1 : 7·2	150	*IIIa*	1
6	$CHCl_3$	65	1 : 3	5	*IIa*	63
7	$CHCl_3$	100	1 : 3	5	*IIIa*	58

[a] Percentage of HNO_3 is given; [b] determined by means of HPLC.

TABLE II

Physical characteristics of compounds *II*—*V*

Compound	Formula (M_r)	Melting point, °C Yield, %	Calculated/Found		
			% C	% H	% N
IIa		152—154[a] 70			
IIb	$C_{13}H_{16}N_4O_2$ (260·3)	100—103 58	59·99 59·88	6·20 6·48	21·52 21·25
IIc	$C_{14}H_{18}N_4O_2$ (274·3)	139—141 60	61·30 61·14	6·61 6·67	20·42 20·16
IId	$C_{15}H_{20}N_4O_2$ (288·3)	114—116 64	62·48 62·63	6·99 7·27	19·43 19·30
IIIa	$C_{12}H_{13}N_5O_4$ (291·3)	185—187 62	49·48 49·41	4·50 4·50	24·04 24·27
IIIb	$C_{13}H_{15}N_5O_4$ (305·3)	186—189 50	51·14 51·09	4·95 5·05	22·94 22·73
IIIc	$C_{14}H_{17}N_5O_4$ (319·3)	207—210 52	52·66 52·93	5·37 5·32	21·93 22·05
IIId	$C_{15}H_{19}N_5O_4$ (333·3)	149—152 71	54·05 54·24	5·74 5·87	21·01 20·87
IVa		107[b] 58			
IVb	$C_{13}H_{14}N_4$ (226·3)	139—142 50	69·00 69·19	6·24 6·34	24·76 24·80
IVc	$C_{14}H_{16}N_4$ (240·3)	61—63 52	69·97 69·57	6·71 6·86	23·32 23·57
IVd	$C_{15}H_{18}N_4$ (254·3)	42—44 48	70·84 70·83	7·13 6·93	22·03 22·15
Va	$C_{12}H_9N_5$ (223·2)	229—231 39	64·57 64·58	4·06 4·23	31·36 31·14
Vb	$C_{13}H_{11}N_5$ (237·3)	193—195 42	65·81 65·92	4·67 4·81	29·52 29·27
Vc	$C_{14}H_{13}N_5$ (251·3)	152—155 50	66·92 67·04	5·21 5·34	27·87 27·65
Vd	$C_{15}H_{15}N_5$ (265·3)	153—156 32	67·90 67·89	5·70 5·83	26·40 26·31

[a] Ref.[2] gives m.p. 149—152°C; [b] ref.[4] m.p. 107°C.

TABLE III

Spectral data of compounds *II*—*V*

Compound	^{1}H NMR ($CDCl_3$): δ, ppm				IR ($CHCl_3$): $\tilde{\nu}$, cm^{-1}		
	$(CH_3)_2$	CH_3	CH_2NO_2	R	C≡N	C=C	NO_2
IIb	1·24 s	2·28 s	5·39 s	3·58 q 1·20 t	2 214	1 647 1 568	1 582 1 315
IIc	1·44 s	2·28 s	5·40 s	3·45 t, 0·96 t 1·40—1·68 m	2 218	1 646 1 582	1 568 1 315
IId	1·40 s	2·25 s	5·36 s	3·45 t, 0·93 t 1·16—1·60 m	2 200	1 645 1 580	1 568 1 313
IIIa[a]	1·40 s		6·34 s	3·62 s	2 208	1 648 1 580	1 568 1 315
IIIb[a]	1·41 s		6·33 s	4·10 q 1·22 t	2 210	1 635 1 575	1 560 1 310
IIIc[a]	1·41 s		6·30 s	3·95 t, 0·75 t 1·25—1·72 m	2 222	1 630 1 575	1 559 1 310
IIId[a]	1·35 s		6·22 s	3·90 t, 0·69 t 1·00—1·30 m	2 210	1 635 1 572	1 566 1 315
IVb	1·43 s	2·24 s		3·72 q 1·29 t	2 239 2 210	1 635 1 572	
IVc	1·42 s	2·20 s		3·60 t, 0·97 t 1·48—1·84 m	2 239 2 217	1 635 1 573	
IVd[a]	1·37 s	2·08 s		3·54 t, 0·74 t 0·94—1·50 m	2 241 2 210	1 648 1 572	
Va	1·56 s			3·50 s	2 237 2 219	1 629 1 570	
Vb	1·54 s			3·90 q 1·42 t	2 242 2 200	1 622 1 568	
Vc	1·34 s			3·80 t, 1·03 t 1·62—1·96	2 248 2 225	1 622 1 568	
Vd	1·35			3·83 t, 1·01 t 1·24—1·85 m	2 249 2 225	1 622 1 568	

[a] The NMR spectrum measured in pentadeuteriopyridine and the IR spectrum by the KBr disc technique.

fluorescence in solution. Table IV gives their electronic spectra. The alkyl chain length at the 1-position of compounds *V* does not practically affect the properties of the chromophores in their ground and excited states.

Comparison of the mass spectra of the compounds *II* – *V* synthesized (Table V) shows common features of their fragmentation by the electron impact in mass spectrometer. In accordance with the results published[10,11] for compounds *Ia* – *Ic*, all the compounds *II* – *V* undergo aromatization of the 1,4-dihydropyridine ring with splitting off of methyl group from the 4-position. In contrast to the starting 1,4-dihydropyridines[10,11] *I*, this process does not always represent the main fragmentation pathway (Schemes 1 – 4); depending on 2- and 6-substituents the fragmentation of the molecular ion M of compounds *II* – *V* can also proceed by another way. In accordance with the earlier findings[4,10,11] also the alkyl R in 1-position can be split off at various phases of fragmentation of compounds *II* – *V*. The 1-methyl derivatives *IIa*, *IIIa*, *Va* split off the methyl radical, whereas the other compounds *II* – *V* split off the 1-alkyl either as the olefin $CH_2{=}CH{-}Y$ (Y = H, CH_3, C_2H_5) or as the ion R^+ which represents the main ion in the cases of compounds *IVd*, *Vc*, *Vd*. Beside the common features mentioned the mass spectra of compounds *II* – *V* also exhibit products of further splitting processes depending on nature of the substituents R and X. Table V gives selected characteristic ionic species in the mass spectra of compounds *II* – *V*, and Schemes 1 – 4 suggest possible fragmentation mechanisms. The fragmentation mechanisms of the mononitro and dinitro derivatives *II* and *III* (Schemes 1 and 2) are essentially analogous. A characteristic feature of both the mechanisms is a parallel splitting off of $CH_3^{\bullet}$ and $NO_2^{\bullet}$ radicals from the molecular ion giving very intensive ions *C* (Scheme 1) and *E* (Scheme 2). The fragmentation mechanisms of the tricyano and tetracyano derivatives *IV* and *V* (Schemes 3 and 4) are characterized by gradual splitting off of 4-methyl and 1-alkyl groups followed by a multiple splitting off of HCN. A somewhat different behaviour is observed

TABLE IV

Luminescence characteristics of compounds *V*

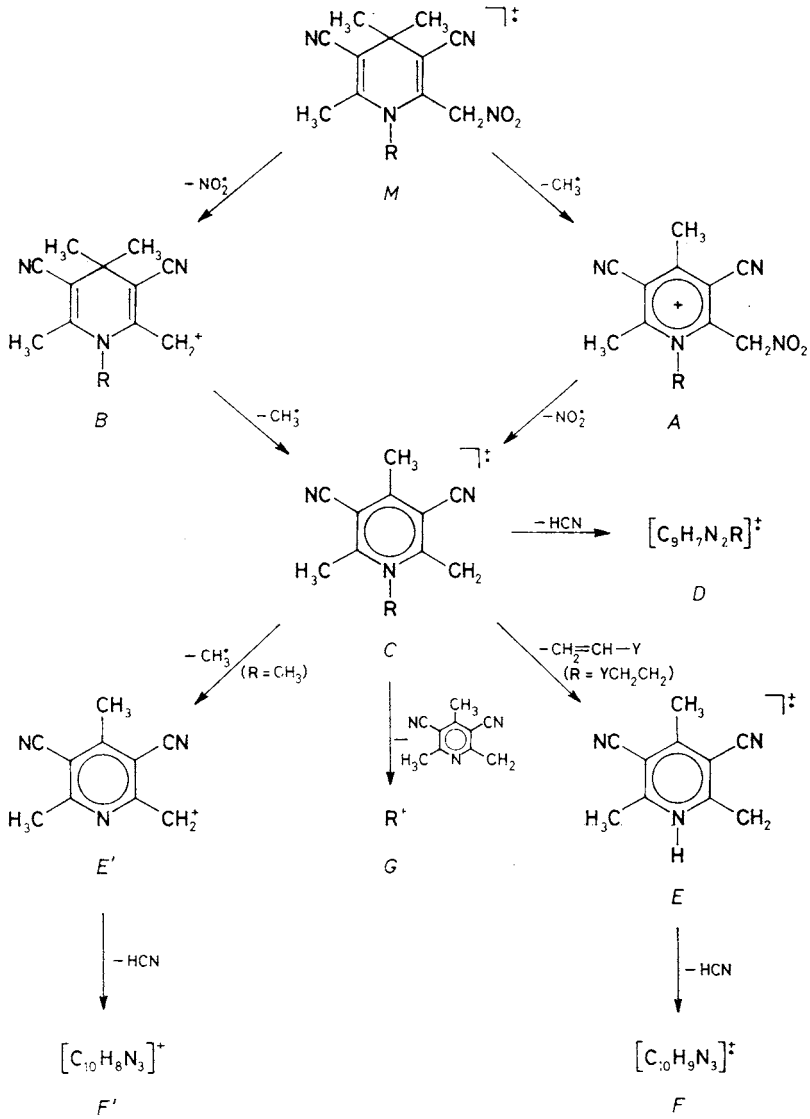
Compound	λ_{max}, nm			Quantum yield
	absorption	excitation	emission	
Va	380	381	423, 448	0·05
Vb	381	382	423, 448	0·05
Vc	381	382	423, 448	0·05
Vd	382	383	423, 448	0·04

TABLE V

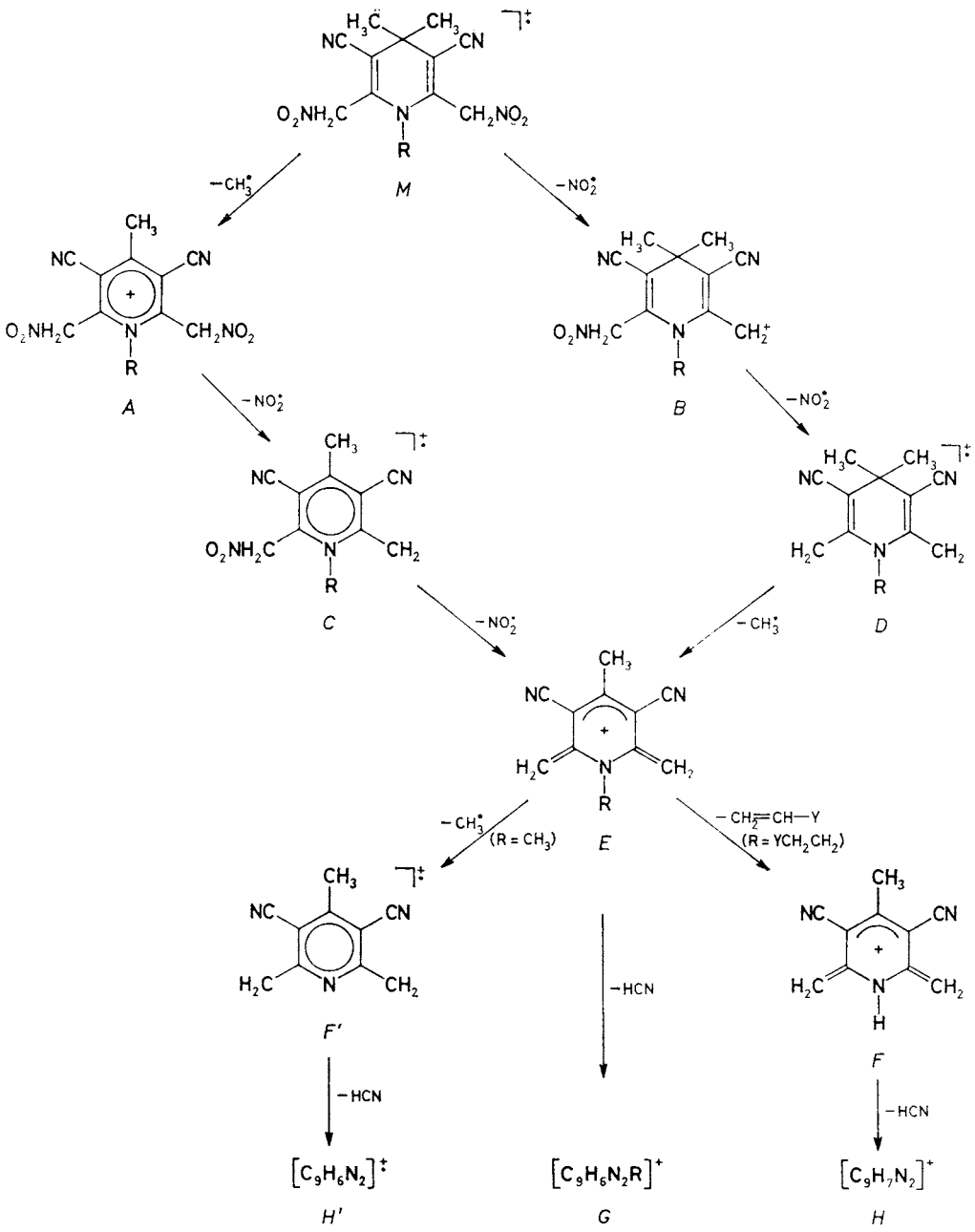
Selected characteristic ions in mass spectra of compounds *II* (Scheme 1), *III* (Scheme 2), *IV* (Scheme 3), and *V* (Scheme 3)

Compound	*m/z*, %								
	M	*A*	*B* or *B'*	*C*	*D*	*E* or *E'*	*F* or *F'*	*G*	*H* or *H'*
IIa	246 (5)	231 (17)	200 (7)	185 (100)	158 (6)	170 (4)	143 (2)		
IIb Y = H	260 (8)	245 (27)	214 (12)	199 (100)	172 (17)	171 (85)	144 (3)	29 (4)	
IIc Y = Me	274 (4)	259 (35)	228 (50)	213 (67)	186 (12)	171 (100)	144 (6)	443 (15)	
IId Y = Et	288 (5)	273 (30)	242 (25)	227 (52)	200 (8)	171 (100)	144 (5)	57 (42)	
IIIa	291 (4)	276 (14)	245 (1)	230 (33)	199 (22)	184 (100)	169 (1)	157 (8)	142 (5)
IIIb Y = H	305 (5)	290 (20)	259 (1)	244 (26)	213 (24)	198 (100)	170 (32)	171 (15)	143 (7)
IIIc Y = Me	319 (6)	304 (26)	273 (1)	258 (17)	227 (27)	212 (100)	170 (37)	185 (15)	143 (7)
IIId Y = Et	333 (9)	319 (39)	287 (1)	272 (16)	241 (30)	226 (100)	170 (16)	199 (8)	143 (8)
IVb Y = H	226 (10)	211 (86)	183 (100)	156 (13)	129 (11)	102 (8)	29 (65)		
IVc Y = Me	240 (7)	225 (35)	183 (100)	156 (7)	129 (4)	102 (3)	43 (41)		
IVd Y = Et	254 (6)	239 (4)	183 (56)	156 (5)	129 (4)	102 (2)	57 (100)		
Va	223 (5)	208 (100)	181 (5)	167 (8)	140 (6)	113 (2)			
Vb Y = H	237 (5)	222 (18)	184 (100)	167 (9)	140 (6)	113 (2)	29 (49)		
Vc Y = Me	251 (5)	236 (12)	194 (18)	167 (6)	140 (2)	113 (2)	43 (100)		
Vd Y = Et	265 (1)	250 (7)	194 (4)	167 (3)	140 (3)	113 (1)	57 (100)		

with the 1-methyl derivatives *IVa* (see ref.[4]) and *Va* where the ion *C* (Scheme 4) is formed directly from ion *A* by splitting off of acetonitrile (which was confirmed by finding a metastable ion in both the cases) and the fragment *B* (Scheme 4) is absent from the spectrum of compound *Va*.



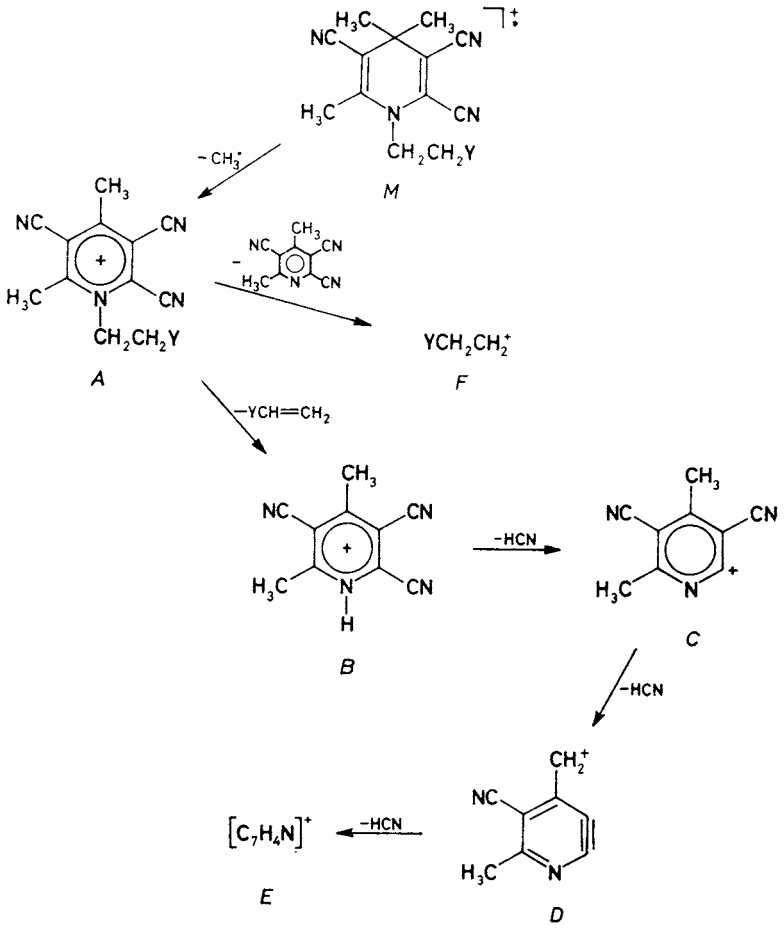
SCHEME 1



SCHEME 2

EXPERIMENTAL

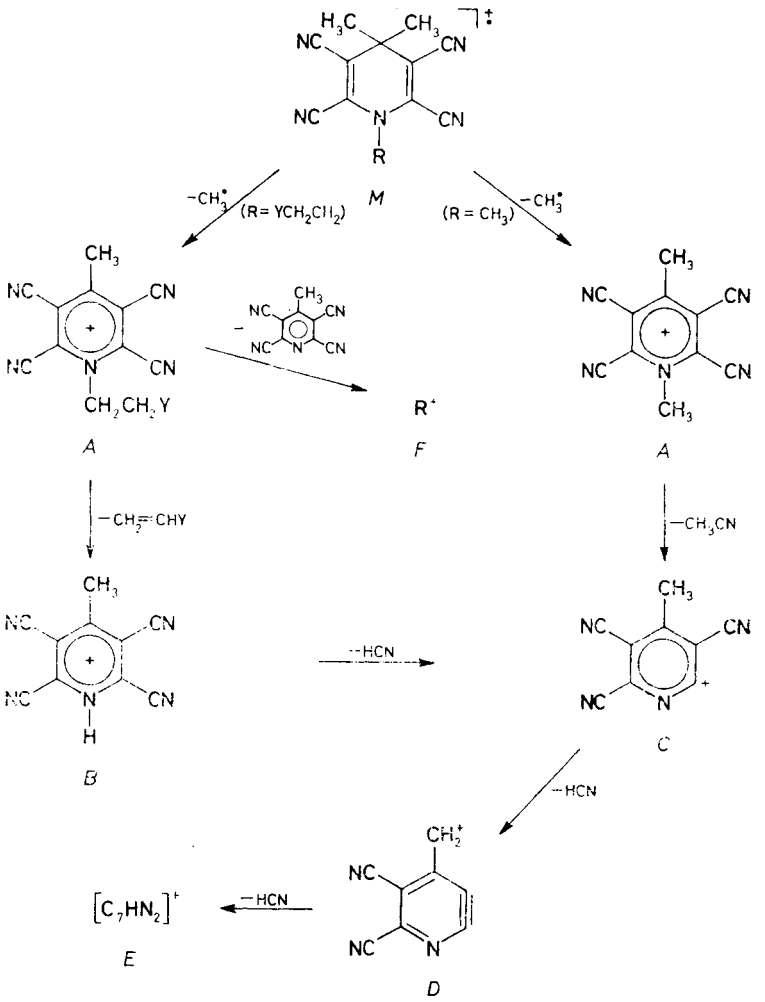
The temperature data were not corrected. The melting temperatures were measured with a Boetius apparatus. The IR spectra were measured with a Perkin–Elmer 325 apparatus in chloroform or by the KBr disc technique. The ^{1}H NMR spectra were measured with a Varian XL 100 (100 MHz) apparatus in deuteriochloroform or pentadeuteriopyridine with tetramethylsilane as the internal standard. The mass spectra were measured with a JEOL DX303/DA5000 apparatus (direct inlet, 70 eV). The HPLC analyses were carried out on a Chrom 500 apparatus (6 × 250 mm column with reverse phase Separon SI-C18, UV LCD 254 detector, solution of 1% water in methanol as the eluent, flow rate 2 ml min^{-1}). The electronic spectra of compounds *V* ($1 . 10^{-5}$ M solutions in cyclohexane) were measured with a Perkin–Elmer 330 (the absorption spectra) and Perkin–Elmer MPF-44B (the fluorescence spectra) apparatus. In order to find the quantum yield values we prepared solutions with concentrations as low as to maintain the ab-



SCHEME 3

sorbance values below 0·01. The spectra were corrected manually with respect to the parameters of apparatus. *p*-Terphenyl was chosen as the standard with the quantum yield value[12] in cyclohexane $q_F = 0{\cdot}93$. The excitation was carried out at the maxima of the excitation spectra of the individual compounds, nitrogen gas being bubbled through the solutions before and after the measurements. The individual values of quantum yields of fluorescence of compounds *V* are given in Table IV.

The starting 1,4-dihydropyridine derivatives *I* were prepared by alkylation[13] of 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine *I* (R = H) under the conditions of phase transfer catalysis. The first to be prepared was compound *Id*, m.p. 121–122°C; for $C_{15}H_{21}N_3$ (243·3) calculated: 74·03% C, 8·70% H, 17·27% N; found: 73·99% C, 8·81% H, 17·23% N.



SCHEME 4

1-*Alkyl*-3,5-*dicyano*-4,4,6-*trimethyl*-2-*nitromethyl*-1,4-*dihydropyridines* (II): A solution of 12 mmol 1,4-dihydropyridine *I* in 20 ml chloroform was treated with 36 mmol (2·5 ml) 65% nitric acid with stirring at 10°C. Then the reaction mixture was stirred at room temperature until disappearance of all the starting compound *I* (TLC — Silufol). The reaction mixture was decomposed by addition of 50 ml water, the organic layer was separated, the aqueous layer was extracted with 3 × 20 ml chloroform, the combined organic phases were washed twice with saturated aqueous sodium hydrogen carbonate (20 ml), twice with 20 ml water, and dried with anhydrous magnesium sulfate. The solvent was distilled off and the oily residue crystallized in vacuum. The product was recrystallized from ethanol (charcoal) until constant melting point.

1-*Alkyl*-3,5-*dicyano*-4,4-*dimethyl*-2,6-*bis*(*nitromethyl*)-1,4-*dihydropyridines* (III): A solution of 12 mmol 1,4-dihydropyridine *I* in 20 ml chloroform was treated with 72 mmol fuming nitric acid with stirring and cooling at 10°C. Then the reaction mixture was stirred at room temperature until disappearance of the starting compound *I* and mononitro derivative *II* (TLC — Silufol). The reaction mixture was decomposed with 100 ml water and treated as in the above case.

1-*Alkyl*-2,3,5-*tricyano*-4,4,6-*trimethyl*-1,4-*dihydropyridines* (IV): Phosphorus trichloride (3·8 mmol) was added dropwise to 3·8 mmol nitro compound *II* in 10 ml anyhdrous pyridine with cooling with water. The reaction mixture was heated under a reflux condenser equipped with a closure containing calcium chloride (the bath temperature 70°C) for 90 min. Then it was poured in 70 ml diluted (1 : 1) hydrochloric acid and extracted with 3 × 50 ml chloroform. The organic phases were combined, washed three times with 50 ml water, and dried with anhydrous magnesium sulfate. The solvent was distilled off, and the raw product was purified by column chromatography (silica gel, acetone–chloroform 1 : 99) and crystallization from ethanol until constant melting temperature.

1-*Alkyl*-2,3,5,6-*tetracyano*-4,4-*dimethyl*-1,4-*dihydropyridines* (V): Phosphorus trichloride (6·5 mmol) was added dropwise to 3·2 mmol dinitro compound *III* in 20 ml anhydrous pyridine (cooling with water). The further treatment was the same as in the above case.

The HPLC *analysis of the products of nitration of compound* Ia *under various conditions:* The nitration agent was added to 2·5 mmol 1,4-dihydropyridine *Ia* in 4 ml solvent (cooling with ice and water). The reaction mixture was thoroughly mixed and decomposed with 30 ml water after a definite time interval. The suspension obtained was extracted with 4 × 10 ml chloroform, the combined organic phases were washed twice with 20 ml saturated aqueous sodium hydrogen carbonate and twice with 20 ml water. After drying with anhydrous magnesium sulfate the solvent was distilled off and the solid residue was dissolved in methanol to make the final volume of 100 ml. The HPLC analysis was carried out at the above-given conditions by the method of internal standard. The results of analyses and reaction conditions chosen are presented in Table I.

REFERENCES

1. Kuthan J., Kurfürst A.: Tetrahedron Lett. *1976*, 1073.
2. Kurfürst A., Raclová F., Kuthan J.: Collect. Czech. Chem. Commun. *45*, 397 (1980).
3. Kurfürst A., Kuthan J.: Collect. Czech. Chem. Commun. *49*, 2620 (1984).
4. Kurfürst A., Kuthan J.: Collect. Czech. Chem. Commun. *48*, 1718 (1983).
5. Olah G. A., Vankar Y. D., Gupta B. G. B.: Synthesis *1979*, 36.
6. Wehrli P. A., Schaer B.: J. Org. Chem. *42*, 3956 (1977).
7. Lalancette J. M., Freche A., Brindle J. R., Laliberté M.: Synthesis *1972*, 526.
8. Eisner U., Kuthan J.: Chem. Rev. *72*, 1 (1972).

9. Kuthan J., Kurfürst A.: Ind. Eng. Chem., Prod. Res. Dev. *21*, 191 (1982).
10. Paleček J., Kuthan J.: Collect. Czech. Chem. Commun. *40*, 2632 (1975).
11. Paleček J., Kuthan J.: J. Radioanal. Chem. *30*, 221 (1976).
12. Berlman I. B.: *Handbook of Fluorescnece Spectra of Aromatic Molecules.* Academic Press, New York 1965.
13. Paleček J., Kuthan J.: Synthesis *1976*, 550.

Translated by J. Panchartek.