

SPECTROSCOPIC PROPERTIES OF 1-SUBSTITUTED 3,5-DICYANO-2,4,4,6-TETRAMETHYL-1,4-DIHYDROPYRIDINES*

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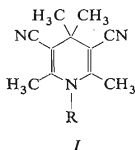
The synthesis of 1,4-dihydropyridine derivatives *Ib–Ig* is described, based on alkylation of 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine (*Ia*) or on condensation of N-substituted 3-amino-crotononitriles *IIf–IIg* with ace.one. The relationships between the structure of the dihydro derivatives obtained and their spectral characteristics are discussed.

In connection with the possibility of practical utilisation of luminescent properties of suitably substituted 1,4-dihydropyridine derivatives¹ we were interested in the variation of the structure of 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine (*Ia*) carried out by introduction of substituents onto the heterocyclic nitrogen atom. Two routes are given in literature leading to this goal: the first is based on alkylation^{2,3} or acylation² of the corresponding 1,4-dihydropyridine derivative, the second starts with the substitution of the amino group in the starting enamino derivative and continues with a condensation with an aldehyde or ketone, affording 1-alkylated 1,4-dihydro derivative⁴.

In experiments aiming at 1-substitution of compound *Ia* we started from two corresponding 1-metallo derivatives *Ii* and *Ik* (Table I; for the structure of the compounds of this type see⁵). 1-Bromomagnesium derivative *Ii* is formed by prolonged reaction of ethylmagnesium bromide in dioxan with substance *Ia* at an elevated temperature. On reaction with corresponding alkylating reagents it afforded in the last mentioned case 1-alkyl derivatives *Ib, Ic* and *Ie* in a very low yield. Preparatively more advantageous was 1-alkylation of the sodium derivative *Ik* obtained on reaction of compound *Ia* with sodium hydride in dimethylformamide or in hexamethylphosphorotriamide at room temperature⁶. The substitution with more bulky substituents gives relatively lower yields even in this case while attempts at the preparation of 1-isopropyl derivative *Ih* failed completely. The modification of the preparation of the starting 1,4-dihydro derivative *Ia*, based on the substitution of enamionitrile *IIa* by cyanoacetone during the condensation reaction with acetone⁷, does not lead to a satisfactory yield of the product. In the second, analogous, variant of the pre-

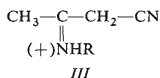
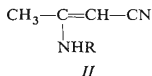
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paration of 1-alkylated dihydro derivatives we started with N-substituted enamino-nitriles *IIf–IIh* (see⁸) which we converted to compounds *Ib–Ih* by condensation with acetone. The yields of dihydropyridine products are increased substantially if the reaction is carried out in strongly acid medium, which is evidently due to the formation of reactive protonized forms *III*, because the enamino-nitriles behave as C-bases⁹. Another factor is the presence of substances capable of substracting the reaction water. For instance, the presence of 10% (vol.) of water in the reaction mixture prevents the formation of compound *Ic* completely. By changing the reaction conditions⁹ we found optimum conditions and applied them to the preparation of the series of 1-substituted 1,4-dihydro derivatives *Ib–Ig*. From Table I it is evident that the yield of the product is distinctly affected by the volume of the substituent R. Neither in this case were we able to prepare compound *Ih* by cyclization of N-isopropyl derivative *IIh*, which is a consequence of the sterical hindrance between the substituent R and 2,6-methyl groups in the molecules *Ib–Ih*.



a, R = H
b, R = CH₃
c, R = C₂H₅
d, R = n-C₃H₇

e, R = C₆H₅CH₂
f, R = C₆H₅
g, R = C₆H₁₁
h, R = i-C₃H₇



i, R = MgBr
k, R = Na
m, R = MgOH

The ultraviolet spectra of ethanolic solutions of 1,4-dihydro derivatives *Ia–If* contain two absorption maxima at 218–220 or 340–345 nm (Table II) with a bathochromic shift of 7–12 nm only, in comparison with non-alkylated 3,5-dicyano-1,4-dihydropyridine¹⁰. Hence, the spectral phenomenon may be assigned to the same π -electron chromophore and, in agreement with quantum chemical calculations¹¹, the corresponding electronic transitions may be characterized as $\pi \rightarrow \pi^*$ transitions. A further bathochromic shift of the long-wave absorption maximum in 1-cyclohexyl derivative *Ig* can be connected with conformational changes of the chromophoric system, caused by steric interaction of the saturated six-membered ring with the 2,6-methyl groups. Further the changes are remarkable which are displayed in the ultraviolet spectrum of solid-state substance. In Table III the characteristics of reflection spectra of 1,4-dihydro derivatives *Ia–Ic* on carriers are given in comparison with the data obtained for ethanolic solutions. It is interesting that 1-ethyl derivative *Ic* which gives the highest yield of luminescence in solid state has

its absorption curve of solid phase minimally distorted. Therefore it may be judged that its crystal structure affects the absorption properties of its molecules minimally. In contrast to this, for substances *Ia* and *Ib* characteristic differences of reflection and solution spectra may be observed. The effect on the spectral manifestation in solid phase is also due to the possible interactions with the carrier used for obtaining the reflection spectrum. From Table III and Fig. 1 it is evident that in compound *Ia* such an interaction with strongly basic magnesium oxide takes place which manifests itself by the formation of a new band with its maximum at 396 nm. This is due, most probably, to a partial formation of 1-magnesium derivative *Im* connected with a hypsochromic shift of the mentioned long-wave absorption. This type of interpretation is to a considerable extent supported by the fact that the non-basic silica gel, used as carrier, does not cause the formation of the 396 nm maximum.

All 1,4-dihydro derivatives studied (*Ia–Ig*) give a blue fluorescence in crystalline state, but in contrast to the series of 3,5-dicarbonyl 1,4-dihydropyridine derivatives^{12–15} this does not take place in solutions. In Table IV the relative intensities

TABLE I

Preparation of 1-Substituted 3,5-Dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridines *Ib–Ih*

Product	Alkylation of <i>Ia</i>			Cyclisation of <i>Iib–Iih</i>	
	reagents	solvent ^a	yield, %	procedure ^b	yield, %
<i>Ib</i>	NaH + (CH ₃) ₂ SO ₄	DOX	60	<i>A</i>	40
<i>Ib</i>	NaH + CH ₃ I	HMPT	81	—	—
<i>Ib</i>	C ₂ H ₅ MgBr + (CH ₃) ₂ SO ₄	DOX	60	—	—
<i>Ic</i>	NaH + (C ₂ H ₅) ₂ SO ₄	DOX	47	<i>A</i>	58
<i>Ic</i>	NaH + C ₂ H ₅ I	DMF	77	<i>B</i>	72
<i>Ic</i>	C ₂ H ₅ MgBr + (C ₂ H ₅) ₂ SO ₄	DOX	21	<i>C</i>	78
<i>Id</i>	NaH + <i>n</i> -C ₃ H ₇ I	DMF	79	<i>A</i>	46
<i>Ie</i>	NaH + C ₆ H ₅ CH ₂ Cl	DMF	76	<i>A</i>	25
<i>Ie</i>	C ₂ H ₅ MgBr + C ₆ H ₅ CH ₂ Cl	DOX	24	—	—
<i>If</i>	^c			<i>C</i>	22
<i>Ig</i>	^c			<i>A</i>	2.0
<i>Ih</i>	NaH + <i>i</i> -C ₃ H ₇ I	HMPT	0	<i>A, B, C</i>	0

^a Symbols: DOX dioxane, DMF dimethylformamide, HMPT hexamethylphosphorictriamide;

^b condensation reagents: *A* HCl + CH₃COOH + C₂H₅OH, *B* as *A* + (CH₃CO)₂O, *C* CH₃COCl + C₆H₆; ^c not investigated.

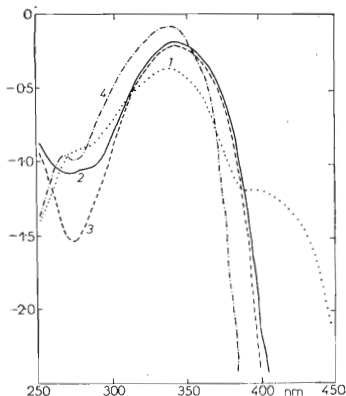


FIG. 1
Reflection Ultraviolet Spectra of Dihydro
Derivatives Ia-Ic

1, 2, 3 Compounds Ia, Ib, Ic — carrier
magnesium oxide; 4 compound Ia — carrier
silica gel.

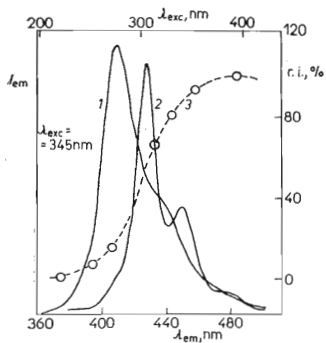


FIG. 2

Fluorescence Spectra of Microcrystalline
State

1 Dihydro derivative Ic, 2 anthracene, 3
dependence of the luminescence intensity
of compound Ic on the wave-length of the
primary radiation λ_{exc} (upper scale applies
for the dotted line).

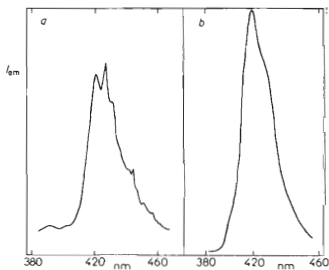


FIG. 3

Fluorescence Spectrum of Dihydro Deriva-
tive Ic at Different Wave-Length of the Pri-
mary Radiation

a λ_{exc} 220 nm, value I_{em} 9 times increased;
b λ_{exc} 250 nm.

TABLE II
1-Substituted 3,5-Dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridines *Ib-Ig*

Compounds	Formula	Calculated/Found		λ_{\max} , nm ^d (log ϵ)	$\bar{\nu}_{\max}$, cm ^{-1b} (CHCl ₃)		δ , p.p.m. (CDCl ₃) ^c (CH ₃) ₂ C R-CH ₂ -N CH ₃ -C= R	
		% C	% H		% N	C=C		N-R
<i>Ib</i>	C ₁₂ H ₁₅ N ₃	71.60	7.52	20.88	1 650	1 220	1.36	6.84
169-170	(201.3)	71.47	7.55	21.08	1 585		2.26	
<i>Ic</i>	C ₁₃ H ₁₇ N ₃	72.52	7.96	19.52	1 655	1 240	1.42	6.42
152-153	(215.3)	72.28	7.98	20.00	1 585		2.25	8.84
<i>Id</i>	C ₁₄ H ₁₉ N ₃	73.32	8.35	18.33	1 650	1 220	1.36	6.58
111-112	(229.3)	73.21	8.45	18.34	1 580		2.20	8.42, 9.08
<i>Ie</i>	C ₁₈ H ₂₉ N ₃	77.94	6.91	15.15	1 640	1 215	1.40	5.30
133-134	(277.4)	77.69	7.27	14.78	1 582		2.20	2.72
<i>If</i> ^d	C ₁₇ H ₁₇ N ₃	—	—	—	1 650	1 340	1.50	—
146-147	(263.6)	—	—	—	1 590		1.78	2.71
<i>Ig</i>	C ₁₇ H ₂₃ N ₃	75.79	8.61	15.50	1 635	1 230	1.27	—
210-211	(269.4)	75.97	8.67	15.90	1 570	-1 210 ^f	2.28	8.16 ^g

^a In ethanol (ϵ 4 · 10⁻⁵ M); ^b in all substances a further band at 2200 cm⁻¹ of the C≡N and bands at 2970-2980, 2915-2925, and 1385 to 1395 cm⁻¹ of the methyl groups were also found; ^c with tetramethylsilane as reference; ^d literature data; m.p. 146-148°C, λ_{\max} (log ϵ) 217.5 (4.61), 258 (3.50), 339 (3.82), $\bar{\nu}_{\max}$ 2190, 1640, 1579, 1382 and 1340 cm⁻¹, 2.4-2.9 τ , 8.23 τ and 8.57 τ ; ^e absorption of the phenyl chromophore; ^f broadened band; ^g approximate center of the multiplet.

of the fluorescence of compounds *Ia–Ig* are given which are obtained at such wave lengths of the incident radiation λ_{exc} which give a maximum emission. It is evident that the emission maxima are in the 396–445 nm region, while the derivatives *Ia–Ic* with small substituents on the heterocyclic nitrogen display the most intense fluorescence. With increasing size and conformational flexibility of the substituent the emission decreases, due evidently to better possibility of thermal deactivation *via* more favourable vibrational cascades of the crystals. In connection with this it is worth mentioning that neither does 1-phenyl derivative *If* represent an exception in this respect. In its ^1H NMR spectrum (Table II) the signal of the methyl groups in the positions 2 and 6 at 1.18δ is shifted by 0.42 to 0.50 p.p.m. upfield with respect to analogous signals in the spectra of other dihydro derivatives, which is in agreement with similar data in ref.⁴ This finding may be explained by the fact that the mentioned methyl protons in substance *If* are in the diamagnetic region of the phenyl group the plane of which is approximately perpendicular to the plane of the dihydropyridine ring. Therefore, a conjugation which could increase the effectivity of the fluorescence does not take place between both cyclic systems in molecule *If*.

The most effective luminophore in the series investigated is 1-ethyl derivative *Ic*. Further characteristics of the investigated fluorescence spectra may be demonstrated on this substance. In Fig. 2 the emission curve of the microcrystalline state of substance *Ic* is shown at the wave-length of incident radiation which is identical with the absorption maximum, *i.e.* 345 nm (Table III) and it is compared with the emission curve of anthracene obtained under the same conditions. Simultaneously, the dependence of the intensity of the emission on the wave-length of the primary radiation λ_{exc} is also shown in this figure. From the figure it is evident that the strongest fluorescence takes place for λ_{exc} lower by ~ 20 nm than the position of the strongest emission maximum. The shape of the emission curve is also dependent to a considerable extent on the λ_{exc} value (Fig. 3). At $\lambda_{\text{exc}} \approx 220$ nm the strongest emission maximum is λ_{max} 426 nm in addition to a second one at λ_{max} 420 nm, and the vibrational structure is evident on the curve. At $\lambda_{\text{exc}} > 250$ nm this vibrational structure disappears and the most intensive maximum becomes that at λ_{max} 420 nm, while the relative intensity of the longer-wave maximum decreases with increasing λ_{exc} and leads to the formation of a shoulder only, located on the longer-wave arm of the emission band (Figs. 2 and 3). Therefore, we consider it probable that the fluorescence spectra of the microcrystalline state of the substance *Ia–If* are connected with minimally two vibrationally separated transitions at 430–450 nm and 400–420 nm, of which the last mentioned is preferentially excited by the longer-wave primary radiation. In 1-cyclohexyl derivative *Ig* fluorescence is almost suppressed and shifted bathochromically for reasons which were already considered during the discussion of its electronic absorption spectrum.

EXPERIMENTAL

Temperature data are not corrected. The melting points were measured on a Boetius melting point block. The following instruments were used for the measurement of spectral characteristics: Perkin-Elmer 325 (IR), Optica Milano NI 4CF (UV), Perkin-Elmer-Hitachi MPF-2A (fluorescence), and Tesla 477B (NMR).

The purity of the preparations was checked by thin-layer chromatography on Silufol (Lachema, Brno; detection under UV light).

Reaction of 1-Magnesium Derivative *Ii* with Alkylating Reagents

An ethereal solution of ethylmagnesium bromide ($8 \cdot 10^{-3}$ mol) was added under stirring to a solution of $2 \cdot 10^{-3}$ mol of compound *Ia* in 70 ml of dioxan and the suspension of the yellow precipitate of the intermediate *Ii* was refluxed for 30 minutes. Alkylating agent ($1 \cdot 2 \cdot 10^{-2}$ mol) was then added dropwise and the mixture heated for 8 hours. After 24 hours' standing at room temperature it was decomposed with $8 \cdot 10^{-2}$ mol of water under stirring and the insoluble part was filtered off and the filtrate evaporated. 1-Methyl and 1-ethyl derivatives *Ib* and *Ic* were obtained by crystallization of the residue from cyclohexane-benzene (1 : 1), 1-benzyl derivative *Ie* was isolated by column chromatography on 30 g of alumina, activity II according to Brockmann, using benzene as eluent, and by crystallization from light petroleum-benzene (1 : 1). The yields and the properties of the products are given in Tables I and II.

Reaction of 1-Sodium Derivative *Ik* with Alkylating Reagents

To a solution of $2 \cdot 10^{-2}$ mol of compound *Ia* in 15 ml of a corresponding solvent (Table I) $2 \cdot 5 \cdot 10^{-2}$ mol of sodium hydride were added over 20 minutes under stirring and cooling with ice and water. The operation was carried out under nitrogen. The mixture was stirred for 4 hours

TABLE III

Comparison of the Ultraviolet Absorption Spectra of 1,4-Dihydro Derivatives *Ia*–*Ic* in Solid State and in Solution

Compound	Reflection spectrum			Spectrum in ethanol	
	carrier ^a	λ_{\max} , nm	$\log \epsilon^b$	λ_{\max} , nm	$\log \epsilon$
<i>Ia</i>	MgO (3.50)	279 ^c	3.09	340 ^d	3.81 ^d
		338	3.53		
		396 ^c	2.80		
<i>Ia</i>	SiO ₂ (3.56)	268	3.04	340 ^d	3.81 ^d
		338	3.91		
<i>Ib</i>	MgO (3.70)	280	2.94	342	3.79
		342	3.81		
<i>Ic</i>	MgO (3.50)	342	3.79	345	3.79

^a In parenthesis: mg of compound/600 mg of carrier; ^b calculated according to the empirical equation: $\log \epsilon = \log \epsilon_{\text{exp}} + 4.00$; ^c shoulder; ^d other value¹⁶: λ_{\max} 239 nm ($\log \epsilon$ 4.14).

TABLE IV
Effect of 1-Substitution in 1,4-Dihydro Derivatives Ia–Ig on Fluorescence in Microcrystalline State

Compound	Substituent	λ_{exc} , nm	λ_{max} , nm	Rel. inten., % ^a
Ia	H	375	404	69.9
Ib	CH ₃	380	408	56.4
Ic	C ₂ H ₅	395	418	100.0
Id	n-C ₃ H ₇	395	417	32.7
Ie	C ₆ H ₅ CH ₂	375	402	21.8
If	C ₆ H ₅	380	402	15.1
Ig	C ₆ H ₁₁ ^b	360	396 445	1.2 1.0

^a Approximated by the height of the emission maximum; ^b cyclohexyl.

at 35–40°, then cooled and added with $2.5 \cdot 10^{-2}$ mol of the corresponding alkylating agent. After heating at 35–40°C for 10 hours the mixture was concentrated *in vacuo* to half its volume and the residue was poured into 40 ml of ice-cold water. Dihydro derivatives Ib–Id were filtered off under suction and crystallized from methanol or dilute ethanol; 1-benzyl derivative was extracted with benzene and crystallized after evaporation of the solvent. For the yields and the properties of the products see Table I and II.

Condensation of Enaminonitriles IIb–IIg with Acetone

The preparation of N-substituted 3-aminocrotonitriles IIb–IIg is described in papers^{4,17}. The variation of the cyclisation procedures A, B, C (Table I) is illustrated by the preparation of 1-ethyl derivative Ic, the yields and the properties of all products obtained are given in Tables I and II.

A) 272 ml of 6M ethanolic HCl were added to a stirred mixture (30 min) of 200 g of enamino-nitrile IIc, 97 g of acetone, 340 ml of ethanol and 52 ml of glacial acetic acid at room temperature over 2 hours, keeping the temperature within the 40–50°C interval. The mixture was stirred for half an hour at room temperature and then refluxed for another half an hour. After cooling it was poured onto 1600 g of ice and the precipitated products was filtered off under suction, washed gradually with 50 ml of 5% sodium hydroxide, water and light petroleum. Crystallization from dilute ethanol gave 115 g (58%) of dihydro derivative Ic, m.p. 152–153°C.

B) A solution of 6M-HCl (12 ml) was added to a mixture of 10 g of compound IIc, 5.2 g of acetone, 15 ml of ethanol, 1.4 ml of glacial acetic acid, and 1 ml of acetic anhydride at room temperature after 30 minutes' stirring. The addition took 20 minutes. After 30 minutes' refluxing the reaction mixture was worked up as under A). Yield 7 g (72%) of dihydro derivative Ic, m.p. 152–153°C.

C) 7.8 g of acetyl chloride in 10 ml of benzene were added to a solution of 7 g of compound IIc, 3.5 g of acetone and 10 ml of benzene under stirring. After one hour's stirring at room

temperature the mixture was refluxed for another 30 minutes and the excess acetyl chloride was decomposed by addition of ethanol. After concentration *in vacuo* the residue was mixed with 80 ml of icy water and the separated product isolated as in the preceding cases. Yield 5.3 g (78%) of dihydro derivative *Ic*, m.p. 152–153°C.

Condensation of Cyanoacetone with Acetone

A mixture of 1.16 g of cyanoacetone¹⁸, 0.81 g of acetone and 1.08 g of ammonium acetate was heated at 90–100°C for one hour. After cooling the reaction mixture was filtered off under suction and washed with 5 ml of cold water. Crystallization from methanol gave 0.60 g of dihydro derivative *Ia* the identity of which was confirmed by comparison of its spectral characteristics with those of an authentic specimen. Analogous results were achieved on reaction with cyclopentanone and cyclohexanone.

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