POLAROGRAPHIC REDUCTION
OF 2-NITROMETHYL-4,4,6-TRIMETHYL-3,5-DICYANO-
-1,4-DIHYDROPYRIDINE AND OF ITS 4,4-SPIROANALOGUES*

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The reduction of 2-nitromethyl substituted 1,4-dihydropyridines at a dropping mercury electrode and their electron absorption spectra were studied. The probable mechanism of the electro-reduction is discussed.

Recently, this Laboratory prepared the 4,4-disubstituted 2-nitromethyl-6-methyl--3,5-dicyano-1,4-dihydropyridines $Ia-c$ by nitrating the corresponding 2,6-dimethyl derivatives[1,2]. The latter compounds reduce at a dropping mercury electrode either at considerably negative potentials in an ill-defined irreversible reduction wave[3,4] or are irreducible. On the other hand, it is known[5-7] that substances with a nitro group in an aliphatic bond are relatively easily reduced at a dropping mercury electrode[8]. The aim of this contribution was a verification of the polarographic behaviour of substances $Ia-c$ as aliphatic nitro compounds. In addition to this, we were also interested in the way how this behaviour is affected by their ionization at extreme pH values of the solution.

EXPERIMENTAL

Chemicals. Substances *Ia—c, VIIb, VIIIc, IXa* are prepared[1,2] by nitrating the corresponding 2,6-dimethyl derivatives. Their purity has been checked by thin-layer chromatography (Silufol--sorbent Silpearl, UV 254, chloroform + acetone 20 : 1, detection by UV and iodine vapours) and by determining their melting points in a Kofler block (m.p.: *Ia* 149—150°C, *Ib* 156—158°C, *Ic* 111·5—113°C, *VIIb* 150·5—152·5°C, *VIIIc* 255—258°C, *IXa* 272—276°C). All the other chemicals used in this investigation were normal commercial products.

Polarography. The dc-polarographic measurements of current-voltage curves were carried out with a three-electrode circuit, *i.e.* with a dropping mercury indicator electrode, a platinum working anode and a reference saturated calomel electrode. The curves were recorded with

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a Hungarian Radelkis OH 102 polarograph. The base solutions contained either 20 or 50% (by vol.) dimethylformamide (with 80 or 50% by vol. supporting electrolyte solution, respectively), the concentration of the substance to be investigated being, as a rule, $5 . 10^{-4}$M. As supporting electrolytes sulphuric acid solutions (pH 1.2) and hydrochloric acid solutions (pH 1.6) were used or simple buffers such as 0.1M acetate (pH 4.9), 0.05M phosphate (pH 7.2), 0.05M borate (pH 9.7), and 0.1M sodium hydroxide (pH 10.6). The final pH values were measured with a glass electrode making use of a PHK-1 pH meter (produced by Radiometer); the recording of each polarographic curve was followed by measuring the pH of the studied solution. The plots of the polarographic curves in $\log I/(I_d - I) - E$ coordinates leading to the so-called logarithmic analysis were calculated with a Hewlett–Packard AP 9820 desk calculator according to a programme worked out[9] in the Heyrovský Institute.

UV *Spectrophotometry*. The UV spectra of the substances studied in this communication were measured with a Specord UV Vis (Carl Zeiss, Jena) instrument. Since in dimethylformamide only the dihydropyridine band at longer wave lengths can be measured the UV spectra of the studied substances were measured at a $4 . 10^{-5}$M concentration level in 96% ethanol. The required pH values (from 0.4 to 13.2) of the solutions were attained by using ethanolic solutions of sulphuric acid and sodium hydroxide. In order to make possible an assessment of the polarographic behaviour of substances *Ia—c*, additional measurements of UV spectra in dimethylformamide (50% by vol. dimethylformamide) were performed and the pH values were adjusted by titrating with aqueous solutions of sulphuric acid and sodium hydroxide. The concentration of the substance to be studied was again $4 . 10^{-5}$M.

The pK_a values were determined from equivalence points of the titration curves of these substances in 80% (by vol.) ethanol in their titration with an ethanolic 0.05M sodium hydroxide solution making use of an automatic recording titrator Radiometer RTS 622. For *Ia* a pK_a value of 7.2 was obtained, for *Ib* and *Ic* a value of 7.5.

RESULTS

The results of the polarographic investigation of the reduction of *Ia—c* are summarized in Table I and the character of the polarographic curves of substance *Ic* is demonstrated in Fig. 1. It follows from Table I that three kinds of waves can be observed on the polarographic curves of *Ia—c* in aqueous dimethylformamide containing the corresponding buffers (this observation has been made over the range from pH 0 to pH 10.6);

The first wave appears within the range of $E_{1/2}$ from -0.36 to -0.62 V, it is strongly pH-dependent, irreversible (*e.g.* $\alpha n = 1.08$ for *Ic* at pH 1.2) and corresponds to an uptake of 4 electrons (this follows from a comparison with the analogous waves of *m*-dinitrobenzene and *m*-nitrobenzoic acid which have been investigated in detail[10]). Up to about pH 5 this wave exhibits a diffusion-controlled behaviour (from the $\bar{I}_1 - \sqrt{h}$ plot) and its height only slightly decreases between pH 0 and 5. The second wave possesses a kinetic character, its $E_{1/2}$ varies from -0.89 to -0.94 V and the wave appears at slightly higher pH values than the first one. It vanishes jointly with the first wave at a pH value higher than the pK_a value of substances *Ia—c* (*cf.* Experimental). As far as the first and the second wave appear simultane-

TABLE I

Values of $E_{1/2}$ and I_d of the Investigated Substances at Different pH-Values

$5 . 10^{-4}$M Reactant, 20% (by vol.) dimethylformamide, 80% (by vol.) solution of supporting electrolyte; $E_{1/2}$ values are referred to an aqueous saturated calomel electrode.

pH	$E_{1/2}$, V			I_d 10^6, A		
		Ia				
1·2	—0·36	—	—	2·8	—	—
1·6	—0·37	—	—	2·8	—	—
4·9	—0·53	—0·89	—	2·3	0·7	—
7·2	—0·60	—	—1·36	0·15	—	0·8
9·7	—	—	—1·63	—	—	4·2
10·6	—	—	—1·64	—	—	3·7
		Ib				
1·2	—0·34	—	—	3·0	—	—
4·9	—0·52	—0·94	—	2·2	0·5	—
7·2	—0·62	—	—1·41	0·1	—	0·8
9·7	—	—	—1·72	—	—	3·7
		VIIb				
1·2	—0·29	—	—	5·6	—	—
1·6	—0·31	—	—	4·7	—	—
4·9	—0·51	—0·92	—	4·9	0·9	—
7·2	—0·69	—	—	0·4	—	—
9·7	—	—	—1·69	—	—	6·8
10·6	—	—	—1·72	—	—	6·6
		Ic				
1·2	—0·37	—0·84	—	3·2	1·5	—
1·6	—0·38	—0·86	—	3·0	1·2	—
4·9	—0·53	—0·90	—	2·4	0·5	—
7·2	—0·62	—	—1·36	0·1	—	1·9
9·7	—	—	—1·64	—	—	4·2
10·6	—	—	—1·64	—	—	2·9
		VIIIc				
1·2	—0·37	—	—	5·1	—	—
1·6	—0·40	—	—	4·9	—	—
4·9	—0·59[a]	—	—	3·8[a]	—	—
7·2	—0·63[a]	—1·22	—	0·3[a]	3·9	—
9·7	—	—1·19	—1·62	—	2·2	2·9
10·6	—	—1·38	—1·64	—	2·7	2·1

[a] Double wave.

ously on the polarogram the sum of their limiting currents is approximately constant.

The third wave appears on the polarogram of substances $Ia-c$ at pH 7·2 and above this value, and its half-wave potentials are rather negative, i.e. from $-1·36$ to $-1·72$ V.

Characteristically, the values of $E_{1/2}$ at pH higher than 9·7 are pH-independent and the diffusion-controlled limiting currents — the measurement of which is rather problematic over this region — probably acquire its maximum value at pH from 8 to 10.

As with the polarographic curves, the absorption curves of the substances $Ia-c$ in the near ultraviolet and visible region undergo a conspicuous change with changing the pH-value of the solutions. The spectral data for ethanolic solutions and in presence of buffers are summarized in Table II and are illustrated by the shape of the whole envelope curves for substance Ic in Fig. 2. Over the pH-range from 0 to 7·5 the absorption curves considerably resemble each other by the presence of the conspicuous less intense long-wave maximum at about 350 nm and of the more intense
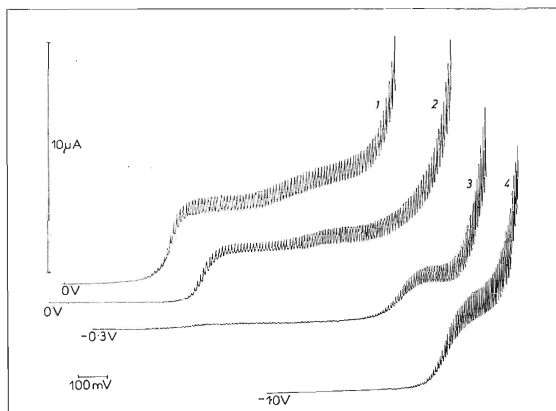

Fig. 1

Polarographic Waves of Substance Ic at Different pH

$5 . 10^{-4}$M Substance Ic, 20% (by vol.) dimethylformamide, 80% (by vol.) supporting electrolyte pH: 1 1·2; 2 4·9; 3 7·2; 4 9·7.

short-wave maximum at about 220 nm. In the spectra obtained with solutions of pH 9·0 and higher, new, clear-cut maxima appear at about 320 nm and at 200—215 nm whose intensity increases with increasing basicity of the solution.

In order to confirm these spectral characteristics also under conditions approaching as much as possible those of the polarographic investigation, an investigation was

TABLE II

UV Spectra of Substances Ia—c

Solutions in 96% (by vol.) ethanol or in 50% (by vol.) dimethylformamide contain the substances at a $4 . 10^{-5}$M concentration.

Substance	pH	λ, nm					log ε				
	0·86[b]			292	—	360			3·31[c]	—	3·49
	2·7[b]			283	—	354			3·39[c]	—	3·52
	3·15[b]			283	—	354			2·95[c]	—	3·75
Ia^{a}	4·81[b]			—	—	354			—	—	3·41
	6·4[b]			292	—	342			3·31	—	3·54
	7·2[b]			300	328	365			3·72	3·77	3·59
	10·2[b]			299	320	361			3·89	3·82	3·54
	12·6[b]			297	318	367			3·87	3·80	3·52
	0·4	220	225	—	—	352	4·24	4·24	—	—	3·75
	4·8	221	—	—	—	350	4·24	—	—	—	3·37
Ia	7·75	220	—	—	—	340	4·18	—	—	—	3·61
	9·0	216	220	296	325	360	4·12	4·10	3·75	3·87	3·41
	12·7	214	—	296[d]	319	352	4·13	—	3·8	3·92	3·49
	13·2	208	—	296[d]	319	352	4·39	—	3·9	3·94	3·52
	0·5	227	—	—	—	351	4·14	—	—	—	3·54
	2·39	224	—	—	—	351	4·15	—	—	—	3·51
Ib	7·75	220	—	—	—	343	4·15	—	—	—	3·52
	12·6	214	—	300[d]	320	363	4·32	—	3·95	3·86	3·57
	13·0	213	—	300[d]	311	355	4·38	—	4·0	3·91	3·66
	0·5	228	—	—	—	343	4·38	—	—	—	3·57
	2·9	228	—	—	—	340	4·19	—	—	—	3·70
Ic	6·65	219	223	—	—	335	4·38	4·39	—	—	3·67
	9·95	215	—	305[d]	324	354[d]	4·15	—	3·8	4·05	3·8
	12·5	204	—	305[d]	322	354[d]	4·41	—	3·9	4·12	3·8

[a] Measurements carried out in 50% (by vol.) dimethylformamide; [b] band overlapped by solvent absorption; [c] this weak absorption at low pH value has not been assigned; [d] shoulder.

undertaken of the influence of pH on the spectra of *Ia* in aqueous dimethylform-amide (1 : 1). It follows from Fig. 3 that the changes in the long-wave region of the spectra correspond to the above findings with ethanolic solutions. Moreover, it is evident that a new broad absorption between 270 and 330 nm results already at pH from 4·8 to 6·4; here, with increasing pH the absorption maximum at about 318 nm grows more rapidly whereas that at 297 nm starts to increase at higher pH--values with the pH-region in which the first and the second polarographic waves vanish. As a whole, the formation of this new absorption can be brought together becoming prevalently controlled by the kinetics of a chemical reaction (in contrast to the diffusion-controlled character at lower pH-values) and where the third wave starts to appear.

DISCUSSION

A comparison of the parallels in the changes of the polarographic and spectral behaviour of the substances to be investigated at different pH-values reveals that, over the whole pH-region under study, more than a single form of the organic electroactive substance plays a role. At pH from 0 to 5 the prevailing form is the
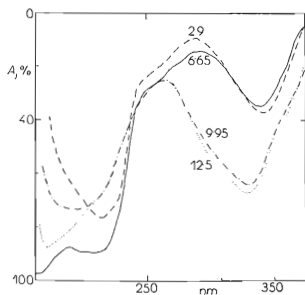
FIG. 2

UV Spectra of Substance *Ic* in 96% (by vol.) Ethanol as a Function of pH

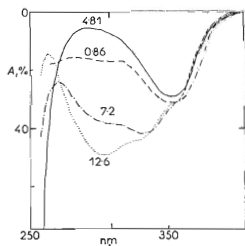$4 \cdot 10^{-5}$M Substance *Ic*; length of the cuvette: 0·996 mm.

FIG. 3

UV Spectra of *Ia* in 50% (by vol.) Dimethyl-formamide as a Function of pH

$4 \cdot 10^{-5}$M Substance *Ia*; length of the cuvette: 0·996 mm.

molecule of the nitro compounds $Ia-c$. This interpretation is supported by the overall character of the electronic spectra which in this case closely resemble those of the analogous spectra of the corresponding 2,6-dimethyl derivatives[2,11]. The influence of the strongly electron-attracting nitro group in the side-chain of the 2-substituent is probably reflected in a somewhat higher decrease of the energy of π^*--LUMO as compared to that the π-HOMO and consequently in a slight shift of the maximum of the long-wave absorption band (caused in essence merely by a HOMO--LUMO transition[12]) to higher wave-lengths by about 5 nm. Taking into account the non-basic properties of alkylated 3,5-dicyano-1,4-dihydropyridines[13] one can, in accordance with these spectral characteristics, conclude that the polarographic reduction primarily attacks the unprotonated form[14] of the molecules $Ia-c$. This is why one can assume that in general the first polarographic wave corresponds to the reactions $I + 4e + 5H^+ \rightarrow II \cdot H^+ + H_2O$ (or $I + 4e + 4H^+ \rightarrow II + H_2O$) in accordance with the above-mentioned assumptions about the polarographic reduction of aliphatic nitro compounds[5-8]. In fact the electron uptake occurs in several steps and is preceded by the protonation of the particle. It is worth mentioning that at the same pH-values the $E_{1/2}$-values reported in this contribution are somewhat more positive than those of already investigated substances[5-8]. This fact can be interpreted by the overall π-electron donor capacity of the 1,4-dihydropyridine system.

The changes in the electron spectra reflected in the new broad absorption between 270 and 330 nm (Table II and Fig. 2 and 3) at pH above 5 evidently bear upon the ionization of the starting molecules according to equation of the following type $I + H_2O \rightarrow III + H_3O^+$ (or, $I + OH^- \rightarrow III + H_2O$), or, as the case may be, with the corresponding participation of the buffer and solvent molecules. One knows that the anions of nitro compounds[15,16] give rise to the corresponding iso-nitro compounds on acidifying the solution; this compound only slowly isomerizes to a nitro compound. If this information is applied to the case of anions III one can, in particular over the region from pH 5 to pH 10, assume further equilibria of the type $III + H_2O \rightleftarrows IV + OH^-$ (or, $III + H_3O^+ \rightleftarrows IV + H_2O$). Evidently, it is obvious that under given conditions three potential depolarizers can be taken into account: nitro compounds $Ia-c$, isonitro compounds $IVa-c$ and the corresponding anions $IIIa-c$. With respect to the negative charge on the last of them and in accordance with[8] one can assume that these species will be irreducible at a dropping mercury electrode. Consequently, only the isonitro form $IVa-c$ can be considered the second active depolarizer to which the third polarographic wave is to be ascribed; this wave only appears in more alkaline media where the inactive precursors $IIIa-c$ are generated at the electrode to a sufficient degree. This interpretation is supported by the tendency of the limiting current of the third polarographic wave to decrease at a relatively high pH of 10·6 (Table I) which can be explained by a decreasing rate of protonation of the anions $IIIa-c$ and, consequently, by a decrease in the concentration of the polarographically reducible molecules $IVa-c$. The gradual increase

in the height of both maxima at about 318 and 297 nm in the spectra of *I* (Fig. 3) with increasing pH can be explained in a similar way: the first maximum belongs to a band of the isonitro form *IVa* and the other to the band of the ionized form *IIIa*. In the spectra of ethanolic *Ia − c* solutions these two bands overlap to a considerable degree and on the envelope curve one can observe a distinct maximum of the first band (Fig. 2 and Table II). One cannot exclude, however, that as a result of an *ortho* effect of the cyano group in position 3 the isonitro forms *IVa − c* can be rapidly and irreversibly transformed to the bicyclic adduct *Va − c*; the latter would no more isomerize to the nitro form *Ia − c*. In agreement with this supplementary explanation one can understand the absence of the first polarographic wave at higher pH-values and the independence of the half-wave potential of the third wave on pH which could be *e.g.* interpreted by the irreversible reaction of *V → VI* at the dropping mercury electrode.
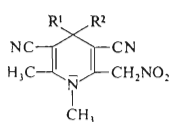
I

a, R¹ = R² = CH₃
b, R¹,R² = (CH₂)₄
c, R¹,R² = (CH₂)₅
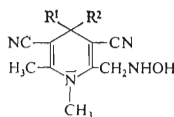
IIa − c
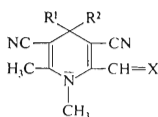
IIIa − c, X = NO₂⁽⁻⁾
IVa − c, X = NO₂H
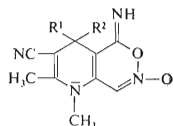
Va − c
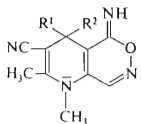
VIa − c
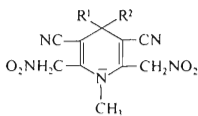
VIIb
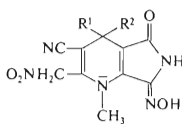
VIIIc
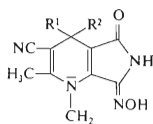
IXa

With respect to the above interpretation of the formation of the first and third waves it is worth investigating the origin of the second, kinetic wave. It is probable that it is related to the prototropic isomerization *IV → I* which may be acid catalyzed[15,16]. In agreement with this assumption the above-mentioned polarographic phenomenon vanishes at pH values above 7 where the proton activity is evidently not sufficient for the catalysis giving rise to the kinetic current in the second wave. The conspicuous decrease in the sum of the limiting currents of the first and second wave in this pH-region (Table I) follows from the prevailingly kinetic character of both waves in this situation.

Analytical Aspects

In order to verify the possibilities of electrochemical identification of the 2-nitro-methyl group in substances of type *I* the compounds *VIIb* and *VIIIc* were investigated by polarography; both these substances are products of follow-up reactions after the nitration[2] of mononitro derivatives *Ib* and *Ic*. The results obtained for a 20% (by vol.) dimethylformamide solution (80% by vol. of the solution of the supporting electrolyte) are summarized in Table I.

It is characteristic of the 2,6-bis-nitromethyl derivative *VIIb* that its polarographic waves are analogous to the waves of the mononitro derivatives *Ia — c*, the only difference being their approximately double height. This allows a conclusion to be made that both nitro groups in *VIIb* are reduced at the dme. either simultaneously or in two processes coalescing in a single wave. In strongly acidic media, the wave corresponding to the reduction of the nitro tautomer *VIIb* is shifted by about 0·5 V to less negative potentials as compared to substance *Ib*. This finding can be considered — in addition to the increased limiting current — a suitable means of identifying the presence of two nitromethyl groups in position 2 and 6. It evidently bears connection with a further decrease in the LUMO energy in substance *VIIb* as compared to *Ib*; this change is due to the introduction into the 6-methyl group of a second, strongly electron-attracting nitro group. It is evident that in *VIIIc* the diffusion-controlled wave in strongly acidic media has virtually the same half-wave potential as the waves of the mononitro derivatives *Ia — c* but the diffusion current is higher. One can there-fore assume that this wave corresponds not only to the reduction of the nitromethyl group but also to that of the whole grouping CO—NH—C=NOH. In agreement with this the wave is split into a double wave at pH 4·9 to 7·2; this phenomenon

TABLE III
Polarographic Identification of Some Molecular Fragments in Substances *Ic*, *VIIIc*, *IXa*

Substance	pH	$E_{1/2}$, V	I_d 10^6, A	Assignment
Ic	1·9	—0·48	1·65	CH_2NO_2
	11·1	—1·76	3·8	$CH=NO_2H$ ($CH=NO_2^-$)
VIIIc	1·9	—0·45	4·07	CH_2NO_2 and $CONHC=NOH$
	11·1	—1·36	1·8	$CONHC=NO^-$ ($CONHC=NOH$)
		—1·78	2·38	$CH=NO_2H$ ($CH=NO_2^-$)
IXa	1·9	—0·47	2·9	$CONHC=NOH$
	11·1	—1·32	2·53	$CONHC=NO^-$ ($CONHC=NOH$)

can be interpreted in terms of different $-dE_{1/2}/dpH$ values of the two, originally coalescing waves. Only at high pH values a clear distinction of the two polarographically active groupings in the molecule *VIIIc* sets in. Whereas the nitro group reduces in its tautomeric isonitro form at $-1\cdot6$ V as with *Ia*$-c$, the grouping CO—NH—C= =NOH gives a different wave with $E_{1/2}$ between $-1\cdot2$ to $-1\cdot4$ V which is pH-dependent. Since with increasing pH the height of this wave clearly increases one can assume that the reduction wave is due to the reduction of an ionized group derived from CO—NH—C=NOH, *i.e.* CO—$\overline{N}$—C=NOH or CO—NH—C=NO$^{(-)}$. Between pH 4·9 and 7·2 the behaviour of *VIIIc* is less transparent because of a number of overlapping waves of partly kinetic origin.

The analytical application of the polarographic curves as a proof for the presence of the two alternative groupings —CH$_2$NO$_2$ and —CO—NH—C=NOH in substances *VIIb*, *VIIIc* and *IXa* is finally demonstrated with 50% (by vol.) dimethylformamide solutions in Table III. In the first instance, it is evident that a transition from 20% to 50% solutions does not lead to a change in the polarographic behaviour in substances *Ic* and *VIIIc* but only to a systematic shift of $E_{1/2}$ to more negative potentials by about 100 to 140 mV (Table I and III). If the kinetic currents in the intermediate region are excluded and only those obtained at pH 1·9 and 11·1 are considered one can unambiguously identify the present groupings basing on Table III.

In conclusion one can state that the most transparent course of the polarographic reduction has been observed for acid media where a four-electron reduction occurs of the unprotonated form of the reactant giving rise to the hydroxylamino derivatives *IIa*$-c$. In the intermediate alkaline region (pH 9 to 11) substances *Ia*$-c$ ionize giving rise to the corresponding anions *IIIa*$-c$ which rapidly hydrolyze to the labile isonitro forms *IVa*$-c$; these probably yield the bisheterocycles *Va*$-c$ as a second type of electroactive reactant. The most difficult orientation in the problem results from the situation in neutral media around pH 7 where the reduction waves are kinetically controlled and instead of the formation of *Va*$-c$ an isomerization of the above-mentioned isonitro forms *IVa*$-c$ to the nitro forms *Ia*$-c$ is operative here. For the polarographic detection of the nitro groups in substances of type *I* one must only use acid media.

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