

## 1-ARYL-3,3-DIALKYLTRIAZENE COMPOUNDS. VII.\*

## TWO-ELECTRON REVERSIBLE OXIDATION OF SOME 4-SUBSTITUTED 1-PHENYL-3,3-DIMETHYLTRIAZENES

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Received December 15th, 1970

Chemical and electrochemical oxidations of 1-(4-hydroxyphenyl)-3,3-dimethyltriazene, 1-(4-aminophenyl)-3,3-dimethyltriazene and 1-(N,N-dimethyl-4-aminophenyl)-3,3-dimethyltriazene have been studied. Potassium diperiodatocuprate(III) has been used as the oxidation agent and platinum rotation disc microelectrode has been used for electrochemical oxidation. It has been found that the oxidation is of two-electron type, it proceeds stage by stage through radical semiquinone to the respective quinoneimine form, and it is reversible. The quinoid compounds formed are very unstable and decompose readily with simultaneous N-demethylation and reduction of the system. The participation of this quinoneimine compound in cancerogenesis of 1-aryl-3,3-dimethyltriazene compounds is discussed. Within the framework of the studies which we devoted in our laboratories to problems of chemical and physiological behaviour of 1-aryl-3,3-dialkyltriazene compounds<sup>1-11</sup>, we prepared 1-(4-hydroxyphenyl)-3,3-dimethyltriazene<sup>12</sup>, 1-(4-aminophenyl)-3,3-dimethyltriazene and 1-(N,N-dimethyl-4-aminophenyl)-3,3-dimethyltriazene<sup>12</sup>. All these compounds are noted for their low stability, they undergo a splitting of triazene bond (to give aryldiazonium salt and dimethylamine) eventually are oxidized (especially the hydroxyderivative) by air oxygen in the light. N-Coupling of the respective aryldiazonium salts with dimethylamine was the principle of preparation in all the cases.

In the present work we have focused our attention on the chemical and electrochemical oxidation of these compounds. As the oxidation can be carried out in alkaline medium only (with respect to a possible splitting of the triazene bond<sup>13</sup>), it was necessary to use such an oxidizing agent, which would have a sufficiently high oxidation potential in the given medium and would be of the one-electron type as far as possible. The complex salt of trivalent copper-potassium diperiodatocuprate(III) proved to be the only possibility; its oxidation potential is sufficiently high in alkaline medium<sup>14</sup> ( $E_{OH}^0 = +0.80$  V).

The proper oxidation-reduction potentials of the triazene compounds studied do not differ from each other very much. With respect to the ready splitting of the triazene bond at higher hydroxonium ion concentration, the pH ranges 7-12 and 8-10 were used for electrochemical and chemical oxidations respectively. The reversibility was verified by cathodic reduction of the oxidized

\* Part VI: This Journal 35, 1598 (1971).

product. Absorption spectra of the original triazene compounds studied and quinoneimine forms were measured. It was found by orientation experiments that the oxidized forms are unstable; they are transformed easily to the respective 1-aryl-3-monomethyltriazenes with simultaneous splitting off of a methyl group in the form of formaldehyde. It was, however, impossible to identify the monomethyltriazene compound due to its instability<sup>15</sup>. Only formaldehyde and the respective aromatic amine<sup>15,16</sup> were found.

A further aim of this study was to clear up, at least in part, the relatively high toxicity observed earlier and presumed carcinogenicity of 1-phenyl-3,3-dimethyltriazenes carrying electropositive substituents in *p*-position of the phenyl group<sup>17</sup>.

## EXPERIMENTAL

A valve potentiometer Precision pH Meter type OP-205 (Radelkis, Budapest) was used for the potentiometric measurements. Anodic oxidation was studied by means of a Polarograph LP 60 and the platinum rotation disc microelectrode which we have already described<sup>19</sup>. A commercial saturated calomel electrode (Lachema, Prague) was used as the reference electrode. The spectrophotometric measurements were carried out with the use of a Spectromom 201 apparatus (MOM, Budapest). The Britton-Robinson buffer solutions were used in all the measurements.

### Reagents and Methods

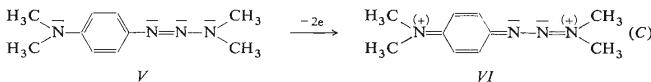
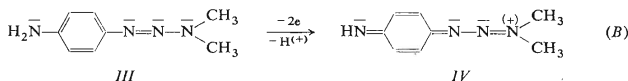
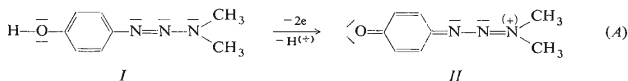
1-(4-Hydroxyphenyl)-3,3-dimethyltriazene and 1-(*N,N*-dimethyl-4-aminophenyl)-3,3-dimethyltriazene were prepared according to the method given in literature<sup>12</sup> and recrystallized from benzene and hexane respectively; the respective melting points 93.5°C and 92°C agreed with the literature data<sup>12</sup>. 1-(4-Aminophenyl)-3,3-dimethyltriazene was prepared in an analogous way, the mono-diazotization of *p*-phenylenediamine being carried in the medium of 2.0M-HCl. The raw product was recrystallized from benzene to give white crystals melting at 42–43.5°C (yield about 12%). For C<sub>8</sub>H<sub>12</sub>N<sub>4</sub> (164.2) calculated: 58.6% C, 7.35% H, 34.23% N; found: 58.7% C, 7.6% H, 33.6% N. The other chemicals used were commercial samples of p.a. or c.p. purity grade (Lachema, Merck and Bayer). 0.1M-K<sub>7</sub>[Cu(IO<sub>6</sub>)<sub>2</sub>] was prepared according to the method described by Jenšovský<sup>18</sup>.

The formation of the semiquinone resulting from oxidation of 4-substituted 1-phenyl-3,3-dimethyltriazenes was followed with the use of a potentiometric method: 5 · 10<sup>-4</sup> mol of the respective triazene was dissolved in 50 ml of the respective Britton-Robinson buffer solution at 20°C with stirring and titrated with 0.1M-K<sub>7</sub>[Cu(IO<sub>6</sub>)<sub>2</sub>] until steady potential (potentiometric indication); the reduction-oxidation potential system established sufficiently rapidly). The calculation of the constant of semiquinone formation,  $k = [\text{sem}]^2/[\text{ox}][\text{red}]$ , was carried out on the basis of analysis of the obtained potentiometric curve of the oxidation course from the so called index potentials  $E_i$  by the method described by Michaelis<sup>20</sup>. At the same time, the maximum content of this compound (in %) was calculated ( $S_M\%$ )<sup>21</sup>. The values measured are presented in Table I. *Electrochemical oxidation* of 1-phenyl-3,3-dimethyltriazenes on the platinum rotation disc microelectrode was carried out by the method described earlier<sup>19</sup>. 0.02M solutions were used for the measurements which were carried out at room temperature 20°C. The results are presented in Table II. *Spectrophotometric measurements* were carried out with the solutions of the original 1-phenyl-3,3-dimethyltriazene derivatives as well as with the respective oxidized forms at pH 7-9.2. The concentration was 5 · 10 mol/l in the both cases.

The presence of formaldehyde in the reaction solution after the oxidation of the respective *p*-substituted derivative of 1-phenyl-3,3-dimethyltriazene was proved by means of a colour reaction with 1,8-dihydroxynaphthalene-3,6-disulfonic acid<sup>22</sup>.

## RESULTS AND DISCUSSION

From the consumption of the oxidation agent it was possible to suggest the following reaction mechanism (Eqs (A)–(C)).



In all the cases a two-electron mechanism is operating, which is (from the point of view of the oxidation potential) dependent on hydroxonium ion concentration in the cases of 1-(4-hydroxyphenyl)-3,3-dimethyltriazenes and 1-(4-aminophenyl)-3,3-dimethyltriazenes, whereas it is independent of the hydroxonium ion concentration in the case of 1-(N,N-dimethyl-4-aminophenyl)-3,3-dimethyltriazenes. The participa-

TABLE I

Dependence of Values of  $E_i$  (mV),  $k$  and  $S_M\%$  of Oxidation of 1-(4-Hydroxyphenyl)-3,3-dimethyltriazenes (*I*), 1-(4-Aminophenyl)-3,3-dimethyltriazenes (*III*) and 1-(N,N-Dimethyl-4-aminophenyl)-3,3-dimethyltriazenes (*V*)

For the symbols see Experimental.

pH	<i>I</i>			<i>III</i>			<i>V</i>		
	$E_i$ , mV	$k$	$S_M$ , %	$E_i$ , mV	$k$	$S_M$ , %	$E_i$ , mV	$k$	$S_M$ , %
7.5	31	5.60	54.2	—	—	—	—	—	—
7.96	32	6.48	56.2	—	—	—	—	—	—
8.36	34	8.22	58.8	38	13.01	64.3	43	21.4	69.8
8.70	36	10.55	61.7	50	29.25	73.0	34	8.22	57.8
9.15	60	94.09	82.9	36	10.55	61.7	31	5.60	54.2
9.37	40	15.95	66.6	32	6.43	56.2	25	2.13	42.2
9.62	32	6.48	56.2	30	4.92	42.2	23	1.42	37.2
9.91	28	3.63	48.8	25	2.14	42.2	22	1.22	35.7
10.38	20	0.58	27.5	14	—	—	—	—	—

TABLE II

Values of  $E_{1/2}$  of Oxidation of 1-(4-Hydroxyphenyl)-3,3-dimethyltriazine (*I*), 1-(4-Aminophenyl)-3,3-dimethyltriazine (*III*) and 1-(*N,N*-Dimethyl-4-aminophenyl)-3,3-dimethyltriazine (*V*) at Various pH

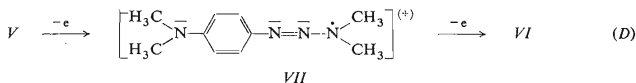
Measured with platinum rotating disc microelectrode and saturated calomel electrode at 20°C.

pH	<i>I</i>		<i>III</i>		<i>V</i>	
	$E_{1/2}$ , V	<i>i</i> , cm	$E_{1/2}$ , V	<i>i</i> , cm	$E_{1/2}$ , V	<i>i</i> , cm
7.0	0.4	1.7	0.42	0.2	—	—
8.0	0.36	2.7	0.38	4.7	0.34 <sup>a</sup>	1.1
					0.60 <sup>a</sup>	0.7
9.0	0.33	2.2	0.37	9.5	0.34	4.6
					0.60	4.4
10.0	0.24	3.1	0.33	8.6	0.34	5.7
					0.60	5.4
11.0	0.21	6.0	0.28	6.7	0.34	6.4
					0.59	5.4
12.0	0.19	5.0	0.23	6.2	—	—

<sup>a</sup> Twofold wave characteristic for semiquinone formation.

tion of the protons follows from the Eq. (A) and (B) most clearly. This is confirmed by the results of half-wave oxidation potentials obtained with the use of the platinum rotation disc microelectrode (Table I).

The oxidation potential value decreases with increasing pH which stands in accord with the reactions (A) and (B). This is not the case with 1-(*N,N*-dimethyl-4-aminophenyl)-3,3-dimethyltriazine which, again, confirms the mechanism given in Eq. (C). The value of limit current *i* given in Table II rather reflects the stability of the compounds studied in the medium given. This problem was discussed in our previous report<sup>23</sup>. It is interesting that, in the case of 1-(*N,N*-dimethyl-4-aminophenyl)-3,3-dimethyltriazine a marked disjoining of anodic wave occurs, the chromatographic purity of the sample and the height ratio of limit current of individual waves being sufficient evidence for the two-step oxidation leading to a formation of unstable intermediate with unpaired electron — the semiquinone *VII*. Thus the reaction (B) can be written as follows:



This is also supported by the potentiometric course of the oxidation of triazene *V* with potassium diperiodatocuprate(III) wherefrom the respective constants ( $k$ ) of semiquinone formation and maximum semiquinone percentage ( $S_M\%$ ) were calculated (Table II). It is very interesting that the maximum semiquinone formation occurs at pH about 9 in the case of triazenes *I* and *III*, whereas in the case of triazene *V* this occurs at pH below 8. Otherwise the semiquinone amounts attain the maximum values 82.9%, 73.0% and 69.8% in the cases of *p*-hydroxy-, *p*-amino- and *p*-dimethylamino derivatives of 1-phenyl-3,3-dimethyltriazene respectively. In the last case the value given is probably not the optimum, because measurements at lower pH (where the amount of the semiquinone formed would be substantially higher) were not possible due to the instability of the original oxidized substance.

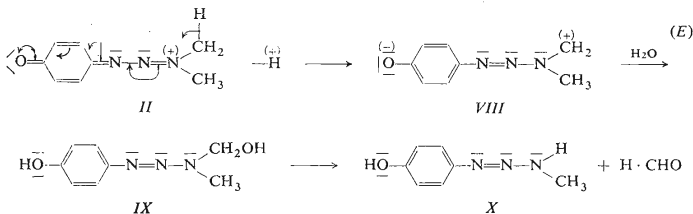
The only disjoining of anodic wave, which occurs in the case of 1-(*N,N*-dimethyl-4-aminophenyl)-3,3-dimethyltriazene, is probably caused by higher stability of the semiquinone derived from this compound, rather than by its higher amount formed in the course of the oxidation. The stability of the semiquinone formed can be ascribed to an easier delocalization of its spin density.

It is rather surprising that, even in the case of the abovementioned 1-(*N,N*-dimethyl-4-aminophenyl)-3,3-dimethyltriazene, the oxidation potential depends on the hydroxonium ion concentration during the chemical oxidation with potassium diperiodatocuprate(III), although the oxidation equation (C) does not suggest any participation of hydroxonium ions in the oxidation. This fact can be explained either by an oxidation mechanism involving an intermediate adduct of the triazene compound with the oxidation agent, or by a too slow course of the oxidation potentiometrically indicated which results in a partial decomposition of the oxidized quinoneimine form *VI*, the subsequent oxidation of these decomposition products being then dependent (in the value of oxidation potential) on pH. The same can, of course, apply to the other compounds, too, because the oxidation products *II*, *IV* and *VI* are really unstable and may behave in an analogous way. For that reason, the quantitative data of the oxidation-reduction potentials measured might, of course, be incorrect.

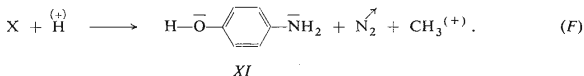
In spite of the instability of the oxidized forms *II*, *IV* and *VI*, we succeeded in measuring their absorption spectra which extend as far as to the visible region. We were interested especially in the difference between the absorption of the original non oxidized *p*-substituted 1-phenyl-3,3-dimethyltriazenes and the corresponding oxidized forms. For this purpose we have chosen the main absorption band in the ultraviolet region<sup>8</sup>. The differences found were 184 nm, 199 nm and 236 nm for the compounds *I-III*, *III-IV* and *V-VI* respectively. This increase stands in accord with  $E_{1/2}$  values: the greater the  $E_{1/2}$  value (in the case of 1-(*N,N*-dimethyl-4-aminophenyl)-3,3-dimethyltriazene the value between  $E_{1/2}$  of the first and second wave must be considered) the greater the bathochromic shift in absorption spectra between the original compound and its oxidized form.

The instability of the oxidized forms *II*, *IV* and *VI* stands in accord with a similar

behaviour of the quinoneimonium salts derived from *N,N,N',N'*-tetramethylbenzidine; we described the mechanism of their decomposition earlier<sup>24</sup>. In that case, too, the aromatization proceeded with simultaneous *N*-demethylation giving formaldehyde which was found in the reaction solution in a sufficient amount. We suppose that the mechanism of decomposition of *e.g.* oxidized form *II* can be expressed by Eq. (E).



In the first phase the proton is split off and the unstable intermediate *VIII* is formed having an electron deficit at methyl carbon atom. Further reaction with a water molecule gives the compound *IX* with methylol group  $-\text{CH}_2\text{OH}$ , and this, in turn, decomposes to formaldehyde and 1-(4-hydroxyphenyl)-3-methyltriazene *X*. This compound is relatively hard to isolate or prove, as it decomposes in practically neutral media already (in accord with findings of Dimroth<sup>15</sup> and some of our previous studies on 1-aryl-3-methyltriazene compounds<sup>23</sup>) giving 4-aminophenol, elementary nitrogen and methyl cation  $\text{CH}_3^+$  (Eq. (F)).



In conclusion, it would be of use to mention the studies of Preussmann and co-workers<sup>16,25</sup> dealing with the mechanism of carcinogenic action of 1-aryl-3,3-dialkyltriazene compounds *in vivo*. The authors suppose that the carcinogenesis of these, compounds consists in a primary enzymatic oxidation of 1-aryl-3,3-dimethyltriazene, which is an alkylating agent for desoxyribonucleic acids and is thus the cause of immediate interference with genetic informations of living cell. On the basis of this theory, all the three triazenes *I*, *III* and *V* studied should be extraordinary active, as they can act as twofold alkylating agents which was proved in the present paper. This consideration does not differentiate as to what kind of alkylation mechanism is operating, because this mechanism was not proved definitively even in the case of 1-aryl-3-methyltriazene. We are studying these problems now and intend to publish the results in a further report.

We are indebted to Mr J. Diviš and Mrs E. Rambousková technical assistance, and to Dr L. Synek, for carrying out the elemental analyses.

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Translated by J. Panchartek.