

ESR study of radical products from 1,3-dimethyl-4-alkylamino-5-nitrosouracils

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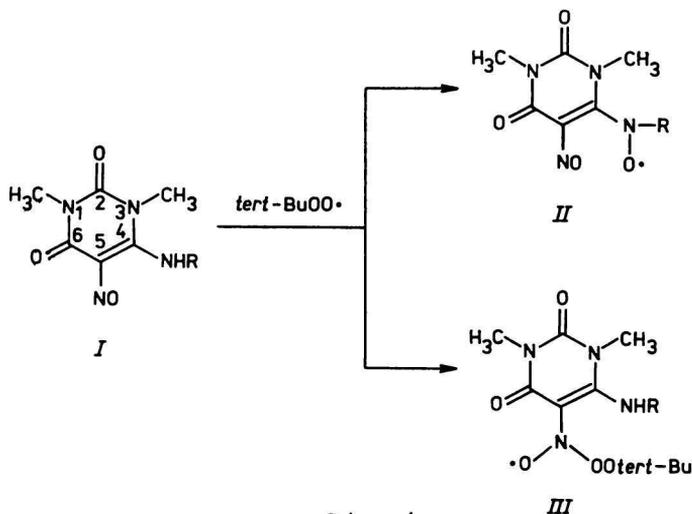
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Dedicated to Academician V Kellö, in honour of his 70th birthday

In the reaction of 1,3-dimethyl-4-alkylamino-5-nitrosouracils with peroxy radicals formation of radicals of the iminoxyl type has been proved by ESR spectroscopy. The splitting constant and the *g*-factor values were as follows: $a_N(\text{NO}) \doteq 3.2$ mT, $a_N(\text{NCH}_2\text{R}) \doteq 0.29$ mT, $a_H(\text{CH}_2\text{R}) \doteq 0.17$ mT, and $g = 2.0050$. In the reaction with $\text{Pb}(\text{CH}_3\text{COO})_4$ also formation of acyloxyl adducts to the nitroso group was observed.

С помощью спектроскопии ЭПР было доказано образование радикалов иминоксильного типа в реакции 1,3-диметил-4-алкиламино-5-нитрозоурацилов с перекисными радикалами. Значения константы расщепления и фактора *g* были следующие: $a_N(\text{NO}) \doteq 3,2$ мТ, $a_N(\text{NCH}_2\text{R}) \doteq 0,29$ мТ, $a_H(\text{CH}_2\text{R}) \doteq 0,17$ мТ, и $g = 2,0050$. В реакциях с $\text{Pb}(\text{CH}_3\text{COO})_4$ также наблюдалось образование ацилоксильных аддуктов по нитрозо-группе.

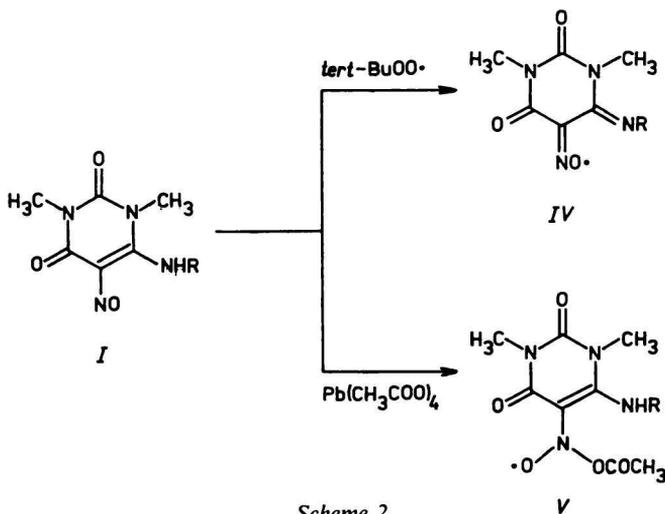
In the previous paper [1] the thermal conversion of 4-alkylamino-5-nitrosouracils to 8-substituted theophyllines, utilized in medicine [2], was described. The aim of the present work is to reinvestigate the reactions of uracils *I* with peroxy radicals. The structure type mentioned above can act as a secondary amine antioxidant, where a temporary formation of aminyl radicals, converted subsequently to nitroxyl radical *II*, may be expected [3]. On the other hand, the nitroso group in the position 5 may function as a radical trap to give the adduct *III* (Scheme 1). However, the results obtained in this work indicate that the aminyl radicals, formed primarily, were not converted into nitroxyl *II* and formation of the tertiary butylperoxy adduct *III* was not observed either.



Scheme 1

Experimental

1,3-Dimethyl-4-alkylamino-5-nitrosouracils **I** (alkyl: *Ia* — CH₃, *Ib* — (CH₂)₂OH, *Ic* — (CH₂)₂C₆H₅, *Id* — (CH₂)₃CH₃, *Ie* — CH₂CH(CH₃)₂, *If* — CH₂C(CH₃)₃, *Ig* — CH₂CH₃) were prepared according to [4] by the modified procedure [5]. After repeated crystallization the structures of the synthesized compounds were confirmed by elemental analysis, IR, UV, ¹H NMR, ¹³C NMR, and mass spectroscopy.



Scheme 2

The reactions of uracils *I* under the formation of radical products were performed in 10^{-2} M benzene solution of the substrate *I* (0.4 cm^3) with the system of PbO_2 (10 mg) and *tert*-BuOOH (30 mg) as the source of *tert*-BuOO• radicals [6] or with $\text{Pb}(\text{CH}_3\text{COO})_4$ (10 mg). ESR spectra were recorded and simulated on a Bruker ER 200 E-SRC spectrometer equipped with an Aspect 2000 computer.

Results and discussion

On the basis of general knowledge about oxidation of secondary amines, in the reaction of uracils *I* with peroxy radicals the formation of nitroxyl radicals *II* can be expected [3]. However, the results presented prove unambiguously the

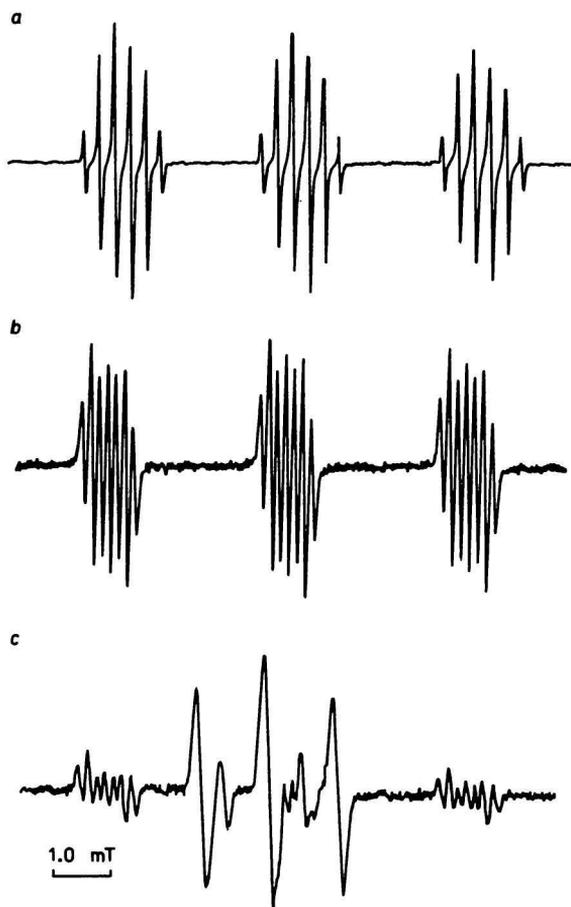
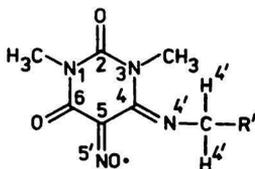


Fig. 1. Experimental ESR spectra of the radicals *IVa* (a), *IVb* (b), *IVd* and adduct *V* (c).

Table 1

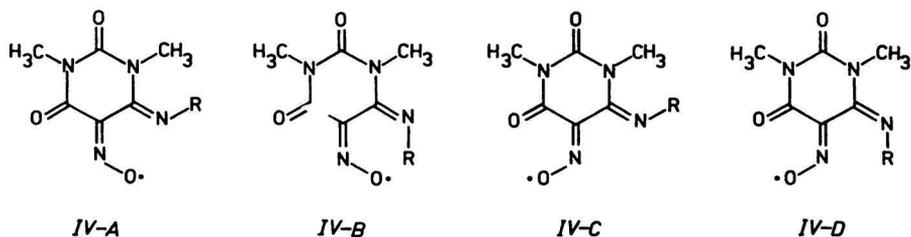
Iminoxyl radicals *IV* ($g = 2.0050$) and assignment of the splitting constants obtained by simulation



Radical	R'	Splitting constant/mT		
		$a_{N-5'}$	$a_{N-4'}$	$a_{H-4'}$
<i>IVa</i>	H	3.18	0.26	0.29
<i>IVb</i>	CH ₂ OH	3.15	0.294	0.16
<i>IVc</i>	CH ₂ C ₆ H ₅	3.155	0.30	0.192 (1H) 0.158 (1H)
<i>IVd</i>	(CH ₂) ₂ CH ₃	3.18	0.29	0.17
<i>IVe</i>	CH(CH ₃) ₂	3.18	0.29	0.17
<i>IVf</i>	C(CH ₃) ₃	3.18	0.29	0.177
<i>IVg</i>	CH ₃	3.18	0.29	0.17

formation of iminoxyl radicals *IV*. These were formed probably by subsequent isomerization of the aminyl radicals, *i.e.* the primary products of the reaction of *tert*-BuOO• radicals with the secondary amine group in the position 4 (Scheme 2).

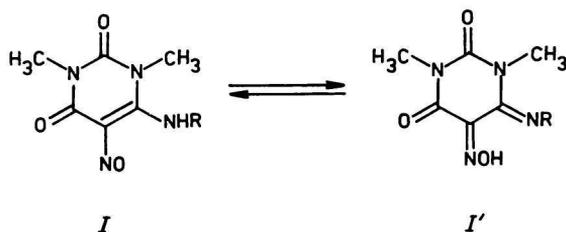
The ESR spectra of the iminoxyl radicals *IVa* and *IVb*, obtained by the reaction of *tert*-BuOO• radicals with the substrates *Ia* and *Ib*, are illustrated in Fig. 1. The values of splitting constants of the radicals *IVa*—*IVg*, obtained by simulation, are summarized in Table 1. The high values of splitting constants of the nitrogen atom in the position 5' ($a_{N} \doteq 3.2$ mT) point to radicals of the iminoxyl type and so does the measured value of the g -factor ($g = 2.0050$). Assignment of the splitting constant to the nitrogen atom in the position 4' is evident from the systematic replacement of substituents, that was adequately reflected in change of the hyperfine structure of the products *IV* (*IVa* — interaction with three protons, *IVb*—*IVg* — interaction with two protons). From the size of peak-to-peak values of the simulated spectra (0.04—0.05 mT) it follows that the splitting constants of further interacting nuclei are lower than the values mentioned above. From the structural point of view four different arrangements of the iminoxyl group are possible.



The ESR spectra point to formation of one isomer. *Caldabaru et al.* [7] obtained by oxidation of 1,3-dimethyl-2,6-dioxo-4-imino-5-nitrosohexahydropyrimidine the iminoxyl radical *IV* ($R = H$) as a mixture of 2 stereoisomers which, on the basis of quantum-chemical calculations, were ascribed to structures *IV-A* and *IV-C*. Their common characteristic is a strong interaction with endocyclic nitrogen atoms N-1 and N-3 ($a_N \approx 0.28$ mT), that was not observed in our spectra. From this it would follow that at our experimental conditions only one isomer was formed. However, the data presented are not sufficient to decide unambiguously whether it is *IV-B* or *IV-D*.

Theoretically the direct formation of iminoxyl radicals *IV* may be expected, provided that uracils *I* occur in the solution in the tautomeric form of hydroxyl-imines *I'* (Scheme 3). However, the presence of these tautomers in the solutions of uracils *I* has not been confirmed by 1H NMR analysis [8].

Moreover, it is to be noted that we failed to prepare nitroso radicals of the *II* type by the reaction of 1,3-dimethyl-4-alkylaminouracils with *tert*-BuOO \cdot radicals.



Scheme 3

In connection with the ability of the nitroso group to function as a trap of radicals, the possibility of addition of various types of radicals to uracils *I* was followed. The ESR spectra have shown that a mixture of radicals was formed only in the reaction of uracils *Ia*—*Ig* with $Pb(CH_3COO)_4$ (Fig. 1). The mixture included beside iminoxyl radicals also high concentration of acyloxynitroxyls *V*, characterized by unsplit nitrogen triplet with the splitting constant $a_N = 1.2$ mT (Scheme 2).

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