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Reduction of 5-Arylidenebarbiturate Derivatives by Thiols

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Abstract : The electrophilic olefin function of 5-arylidenebarbiturates is reduced by thiols in the presence of triethylamine. Mechanistic aspects of the reaction are discussed.

The oxidation of thiols by 5-arylidene-1,3-dimethylbarbituric acid has been reported by Tanaka et al.² and applied to the synthesis of unsymmetrical disulfide systems. These authors have proposed an unconventional mechanism in which the reducing species, namely a hydride ion, is generated by attack of the thiolate anion upon the sulfur atom of a second thiol molecule. This amounts to a nucleophilic displacement of the thiol hydrogen as a hydride species, which is directly transferred to the electrophilic olefin function of 5-arylidene-barbiturates.

In connection with our studies on models of the thymidylate synthase reaction, we have recently shown that 5-uracilylmethylenepyridinium salts are reduced to thymine derivatives by reaction with benzyl mercaptans. The hydride equivalent in this reaction is derived from the benzyl methylene group, as supported by deuterium-labelling experiments. Further studies, including the influence of galvinoxyl reagent on the rate of thymine (derivative) formation has led to the proposal of a radical mechanism in which the C(5)-exocyclic methylene group is reduced by the thiol³. The latter reduction step bears resemblance to the reported reduction of 5-arylidene barbituric acid by thiols². In view of this fact and because of the unusual characteristics of the suggested mechanism², we have examined the reaction of suitably substituted selected 5-arylidenebarbiturates **1a,b** with benzyl mercaptans **2a,2a'** and phenyl thiol **2b** and have especially directed our attention to the fate of the barbituric acid substrate rather than to that of the thiol. The results of this investigation (Scheme 1) are discussed in the present communication.

The reaction of barbiturates **1a,1b** with benzyl mercaptan **2a**, in refluxing dioxane, under nitrogen, led to the formation of Michael adducts **3a** and **3c**, respectively. An analogous reaction between **1a** and thiophenol **2b** gave the corresponding adduct **3b**. While the addition of thiols **2a,b** to barbiturate **1a** proceeded in high yields, in about 20 hours, the addition of **2a** to **1b** was incomplete even after 50 hours. This is in line with the expectation since the *p*-methoxy substituted arylidene barbiturate **1b** is a poorer Michael acceptor than **1a**. When the reactions of **1a,b** with **2a, 2a'** and **2b** were carried out in the presence of 2.5 eq. of triethyl amine, in refluxing dioxane (24 hours) the reduction products **4a,b** were initially formed. Since **4a,b** are readily oxidized during chromatographic separation, they were isolated and identified as the corresponding (more stable) hydroxylated products **5a,b**, respectively. This product isolation procedure, however, involved considerable losses, as a consequence of which the observed conversions of **1a,b** to **5a,b** were around 40%. The structure of **5a** was established by independent synthesis⁴.

(type AM1) on an IBM computer using the SPARTAN programme, version 3 (Table I). The ionization potential (IP) was defined as the difference in energy between the HOMO and LUMO. The ionization enthalpy was calculated from the ionization potential according to the relationship $\Delta H_i = IP \cdot 3.83 \cdot 10^{-20} N_A$. An examination of the ionization enthalpies reveals that the thiolate ions, when compared with the corresponding thiols, are highly prone to lose a single electron to give the corresponding radicals.

Table I

Calculated ionization enthalpies (ΔH_i) for **2a,b** and the corresponding thiolates.

				IP	ΔH_i kcal/mole
2a	$\text{PhCH}_2\text{SH} \rightarrow \text{PhCH}_2\text{S}^+\text{H} + \text{e}^-$			8.92 eV	206
	$\text{PhCH}_2\text{S}^- \rightarrow \text{PhCH}_2\text{S}^\cdot + \text{e}^-$			6.58 eV	152
2b	$\text{PhSH} \rightarrow \text{PhS}^+\text{H} + \text{e}^-$			9.11 eV	210
	$\text{PhS}^- \rightarrow \text{PhS}^\cdot + \text{e}^-$			7.75 eV	179

The difference in the ΔH_i values is consistent with the proposed radical mechanism (Scheme 2) for the reduction step.

Scheme 2

The mechanism explains the difference between the reactivity patterns leading to the kinetic products, namely Michael adducts - clearly formed *via* an ionic mechanism- and the thermodynamic products **4a,b**. Most importantly, it explains how the base (triethylamine) directs the reaction to proceed in the reduction mode.

The aforementioned reduction mechanism and the results previously reported from our laboratory³ suggest that reductions by thiols *via* radical processes may be a general phenomena.

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1. Taken in part from the doctorate thesis of J.W.G. Meissner, University of Amsterdam 1993.
2. Tanaka, K.; Chen, X.; Yoneda, F. *Tetrahedron* **1988**, *11*, 3241-3249.
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4. Compound **5a** was synthesized by oxidation of **4a** with *m*-chloroperbenzoic acid. **5a**: m.p.: 165-167°C; ¹H-NMR (CDCl₃, 200 MHz) ppm: 3.24 (s, 6H, N-CH₃), 3.34 (s, 2H, CH₂Ph), 3.66 (s, 1H, OH), 7.23 (d, *J* = 8.6 Hz, 2H, H3' en H5'), 8.28 (d, *J* = 8.6 Hz, 2H, H2' en H6'); ¹³C-NMR (CDCl₃, 400 MHz) ppm: 28.9 (N-CH₃), 48.3 (CH₂), 76.3 (C-OH), 123.7 (Ph-CH), 130.6 (Ph-CH), 139.3 (Ph-C), 147.9 (Ph-C), 149.9 (C=O), 169.13 (C=O). **5a** has been reported by Tanaka, K.; Chen, X.; Kimura, T.; Yoneda, F. *Chem. Pharm. Bull.* **1986**, *34*, 3945-3948 without giving its spectral data.

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