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Reduction of 5-Arylidenebarbiturate Derivatives by Thiols

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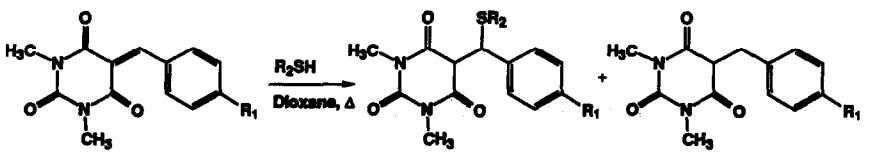
Abstract : The electrophilic olefin function of 5-arylidenebarbiturates is reduced by thiols in the presence of triethylamine. Mechanistic aspects of the reaction are discussed.

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 thiol[3]. The latter reduction step bears resemblance to the reported reduction of 5-arylidene barbituric acid by thiols[2]. In view of this fact and because of the unusual characteristics of the suggested mechanism[2], 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 synthesis[4].



1a R_1 = NO_2
1b R_1 = OCH_3

2a R_2 = CH_2Ph
2a' R_2 = CD_2Ph
2b R_2 = Ph

3a R_1 = NO_2, R_2 = CH_2Ph
3b R_1 = NO_2, R_2 = Ph
3c* R_1 = OCH_3, R_2 = CH_2Ph

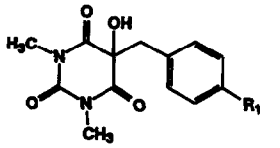
4a R_1 = NO_2
4b R_1 = OCH_3

[O]

Reaction of 5-arylidenebarbiturates with thiols

Barbituric acid	Thiol	Product: Dioxane, Δ	h	Product: Dioxane, Et_3N, Δ
1a	2a	3a (96%)	22	4a --> 5a
1a	2a'			4a --> 5a
1a	2b		20	4a --> 5a
1b	2a	3b (92%)	50	4b --> 5b
1b	2a'	3c (< 50%)*		4b --> 5b
1b	2b			4b --> 5b

* Estimated (NMR) in a mixture (1 : 1) of 1b and 3c



5a R_1 = NO_2
5b R_1 = OCH_3

Scheme 1

It is highly significant that reactions of **1a,b** with deuterium labelled thiol **2a'** did not lead to products **5a,b**, bearing a deuterium atom at the benzyl position. Such labelling would have been the result if a mechanism analogous to the one found for reduction of the uracilylmethylenepyridinium salt (by thiols) had been operative[3]. Further evidence that a different mechanism is involved is derived from the observation that thiophenol **2b**, which lacks a methylene group, also mediates the reduction of **1a,b** to **4a,b**.

These results strongly suggest a role for the dissociable hydrogen of the thiol reagent (RSH) in the reduction process. Unfortunately, our attempts to establish this directly by employing freshly prepared PhSD (60% D) and $PhCH_2SD$ (~ 90% D) in the reactions, were thwarted by deuterium exchange, prior to the reduction step, under the reaction conditions.

Another noteworthy result was the conversion of **3a** to **4a** (identified as **5a**) upon refluxing it with triethylamine and **2a** in dioxane, implying that under these conditions the primary Michael adduct reverts to **1a**, which subsequently undergoes reduction.

The results of our study may be summarized as follows: (i) in dioxane, the reaction of thiols with arylidenebarbiturates leads to Michael adducts; (ii) in the presence of base (triethyl amine) the same reaction results in reduction of the double bond; (iii) the Michael adduct is converted into the reduction product, upon treatment with the thiol *in the presence* of triethyl amine and (iv) in case of benzyl mercaptan, the hydride equivalent is not derived from the benzyl methylene group. Observations (ii) and (iii) suggest that the Michael adduct dissociates into the starting components in the presence of base and subsequently, as expected, undergoes reduction under the reaction conditions. From the results of (iv) it follows that the most likely source of the reduction equivalent is the thiol hydrogen (RS-H).

In considering the mechanism of reduction, the fate of the substrates (**1a,b**) is of primary relevance. Because of the tendency of thiols to oxidize to disulfide with facility, the measurement of disulfide formation alone, does not necessarily give a good measure of the formation of an equivalent amount of reduced substrate. Our results, involving the study of substituted arylidene barbiturates and labelled thiols, while clearly suggesting a role for the thiol hydrogen, do not directly allow a distinction between a hydride transfer or a radical (hydrogen) transfer mechanism. In order to gain further information on this point, we have examined the ionization potentials of neutral thiols and thiolate ions for both PhSH and $PhCH_2SH$. The ionization enthalpies (ΔH_i) were calculated on basis of molecular models, employing a semi-empirical molecular calculation

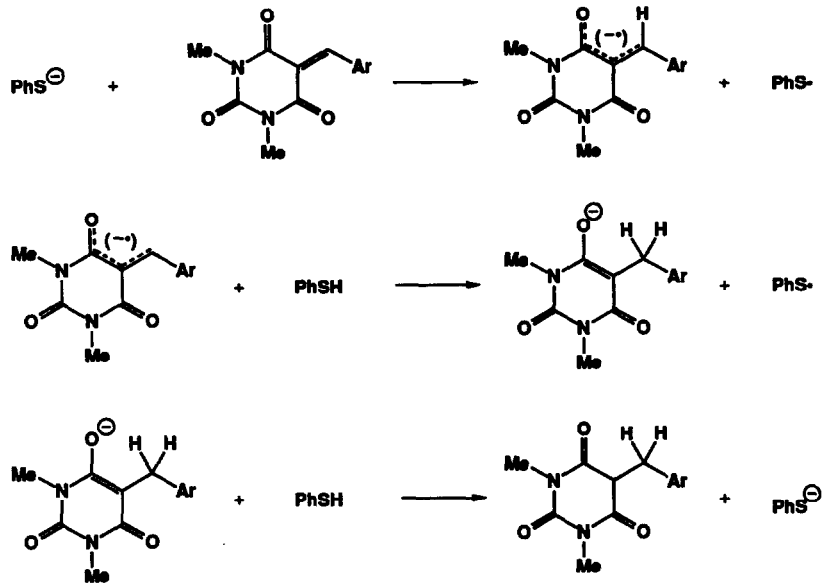
(type AM1) on an IBM computer using the SPARTAN programme, version 3 (Table I). The ionization potential (IP) was defined as the difference in energy between the HOMO and LUMO. The ionization enthalpy was calculated from the ionization potential according to the relationship $\Delta H_i = IP.\ 3.83\ .\ 10^{-20}\ N_A$. 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	$PhCH_2SH$	→	$PhCH_2S^{\cdot}H^+$	+	e^-	8.92 eV	206
	$PhCH_2S^-$	→	$PhCH_2S^{\cdot}$	+	e^-	6.58 eV	152
2b	PhSH	→	$PhS^{\cdot}H^+$	+	e^-	9.11 eV	210
	PhS^-	→	$PHS^{\cdot}$	+	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 laboratory[3] 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.
3. Meissner, J. W. G.; Pandit, U. K. *Tetrahedron Letters* **1992**, *21*, 2999-3002.
4. Compound **5a** was synthesized by oxidation of **4a** with *m*-chloroperbenzoic acid. **5a**: m.p.: 165-167°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) ppm: 3.24 (s, 6H, N-CH_3), 3.34 (s, 2H, CH_2Ph), 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'); ^{13}C-NMR ($CDCl_3$, 400 MHz) ppm: 28.9 (N-CH_3), 48.3 (CH_2), 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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