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5-Arylidene 1,3-Dimethylbarbituric Acid Derivatives, Mild Organic Oxidants for Allylic and Benzylic Alcohols[1)]

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Various 5-arylidene 1,3-dimethylbarbituric acid derivatives and closely related compounds were synthesized as models of redox coenzymes and used for oxidation of alcohols.

Under mild neutral conditions, 5-arylidene 1,3-dimethylbarbituric acid derivatives, especially those having an electron-withdrawing group on the aromatic ring, effectively oxidized allylic and benzylic alcohols to the corresponding carbonyl compounds. The relationship between the oxidizing ability and the structure of the oxidant (coenzyme model) was investigated and it was found that the electron density on the carbon–carbon double bond is a critical factor for the oxidation. In the case of the deuterium-labeled compound, the observed value of normal and primary isotope effect was 3.3 and so it was concluded that mechanism of this oxidation mainly involves the hydride transfer from the alcohol. An electrochemical investigation was also carried out and the redox potentials of the coenzyme models, 5-arylidene 1,3-dimethylbarbituric acid derivatives and related compounds, were measured.

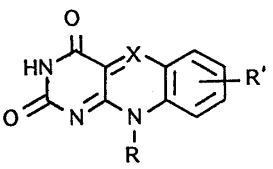
Keywords——5-arylidene 1,3-dimethylbarbituric acid; coenzyme model; oxidation; allylic alcohol; benzylic alcohol; oxidation mechanism; hydride transfer; primary isotope effect; cyclic voltammetry; redox potential

It is well known that redox coenzymes, such as flavin adenine dinucleotide (FAD) and nicotinamide adenine dinucleotide (NAD^+), play important roles in the energy metabolism of organisms. Recently, 5-deazaflavin derivatives, which had been elaborated as part of a search for antagonists of riboflavin, were isolated from a natural source and shown to be redox coenzymes.[2)] These coenzymes have received considerable attention from a number of biochemists because of their close relationship to the origin of life.

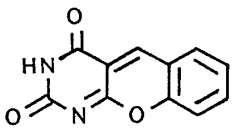
In the course of our investigations on the exploitation of new model compounds possessing coenzyme-like functions, we chose 5-arylidene barbituric acid derivative as a simple coenzyme model. All the above mentioned redox coenzymes have electron-deficient conjugated double bonds surrounded by carbonyl and/or imino groups as common characteristic structural feature, which should be the crucial functional center of these coenzymes. A similar electron-deficient conjugated double bond to that found in redox coenzymes is preserved in 5-arylidene 1,3-dimethylbarbituric acid derivatives, which are regarded as a simplified model of 5-deazaflavin as well as 5-deazaoxaflavin,[3)] a model previously developed for oxidation.

A related aza analogue of 5-arylidene 1,3-dimethylbarbituric acid has appeared in the literature[4)] in connection with a simplified model of FAD, and was used to obtain mechanistic insight into the reaction of FAD.

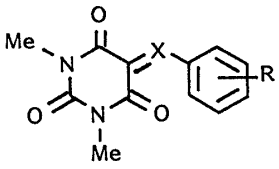
We now report in detail the results of oxidation of some alcohols using 5-arylidene 1,3-dimethylbarbituric acid derivatives and their analogues as redox coenzyme models. Mechanistic aspects will also be described.



X=N: flavin
X=CH: 5-deazaflavin



5-deazaoxaflavin

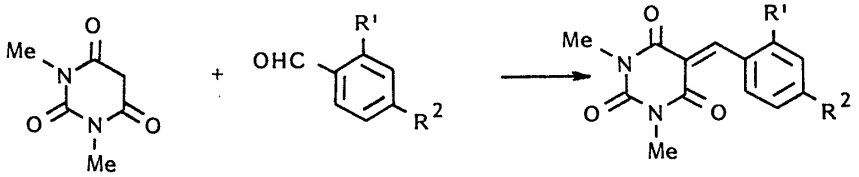


X=N
X=CH

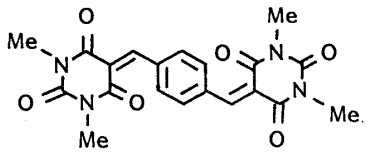
Chart 1

Preparation of 5-Arylidene 1,3-Dimethylbarbituric Acid Derivatives and Related Compounds

One of the authors (F.Y.) has already reported that 5-arylidene barbituric acid derivatives can be prepared readily just by heating a barbituric acid derivative and an appropriate aromatic aldehyde in ethanol.[5] This simple procedure makes it possible to get various kinds of 5-arylidene derivatives which differ in the position and identity of the functional group on the aromatic ring. This diversity may substantially influence the electron density and steric environment of the carbon–carbon double bond. Most compounds were synthesized by this procedure (method A), whereas **13**—**15** were obtained by Knoevenagel condensation *via* the Mannich base (method B).[6] Beside 5-arylidene 1,3-dimethylbarbituric acid derivatives, compounds of another type (**10**—**19**) were also prepared to explore the oxidation–structure relationship (Chart 2). These compounds include the double-headed compound (**10**), the Meldrium's acid derivatives (**14**, **15**), the extended conjugated compound (**12**) and the heteroaromatic compound (**11**). In these synthetic procedures, most of the



	R^1	R^2
1	H	OMe
2	H	H
3	OAc	H
4	H	OAc
5	H	F
6	H	CF_3
7	Cl	Cl
8	H	NO_2
9	NO_2	NO_2



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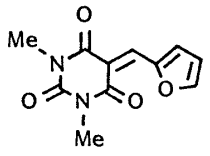

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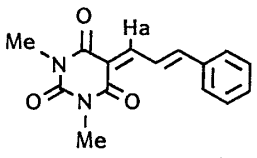

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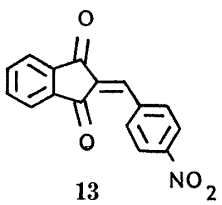

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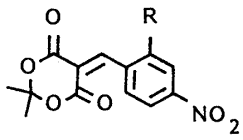
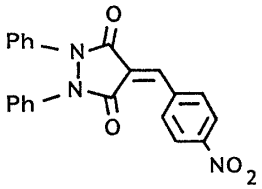


14 : R=H
15 : R=NO_2



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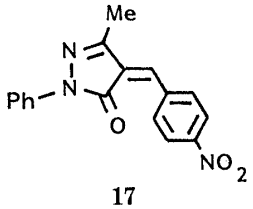

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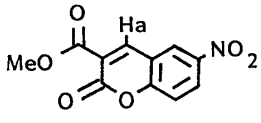

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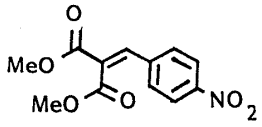

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Chart 2

TABLE I. Preparation and Spectral Data of 5-Arylidene 1,3-Dimethylbarbituric Acid and Related Compounds

Compd. No.	Method of preparation	Isolated yield (lit. yield, %)	mp (°C) (lit. mp)	IR: max ($CHCl_3$, cm^{-1})	^{1}H-NMR ($CDCl_3$, δ)[a] =CH– on arylidene carbon
1	A[5]	98 (84)	151 (151)	1665	8.46
2	A[5]	97 (82)	164 (164)	1670, 1585	8.55
3	A	57	126—128	1765, 1675	8.58
4	A	97	156—157.5	1765, 1660	8.53
5	A	38	167—170	1670, 1590	8.52
6	A	40	140—142	1675, 1625	8.57
7	A	92	183—184	1675, 1605	8.63
8	A	90	200	1675, 1590	8.57
9	A	70	205—207	1680, 1600	8.82
10	A	68	>300	1675, 1630	8.55
11	A	94	201—202	1660, 1580	8.44
12	A	93	202—203.5	1660, 1570	8.20[b]
13	B	83	236—237	1690, 1625	7.91
14	B	77	216—219	1730, 1595	8.45
15	B	65	149—150	1735, 1600	8.76
16	Ref. 7	78 (52)[7]	254—255 (243)[7]	1695, 1630	8.50
17	Ref. 8	32 (—)[8]	185.5—187 (171)[8]	1595	7.36
18	D	44	220—221	1775, 1620	8.62[b]
19	E	57	93—95	1725, 1640	7.80

D, E: See experimental section. *a*) A ^{13}C-NMR study of a closely related compound has appeared.[9] *b*) Ha in Chart 2.

condensed compounds were easily obtained nearly quantitatively as crystalline compounds whose physical data are included in Table I.

Oxidation of Alcohols with Model Compounds

Benzylic alcohols can be oxidized with aromatic alcohol oxidase isolated from the microorganism *Polystictus versicolor*, but the structure of this flavin-dependent enzyme is obscure.[10]

Thus, readily available 5-arylidene 1,3-dimethylbarbituric acid derivatives and their analogues were used to oxidize benzylic and allylic alcohols in a suitable solvent under neutral conditions. Most reactions were carried out in dioxane under reflux for 3 d and the products were isolated by preparative thin layer chromatography (p-TLC). The oxidation also runs well in other solvents, such as chloroform, toluene and ethyl acetate, resulting in a comparable or slightly less satisfactory yields of products.

At first, oxidation of cinnamyl alcohol with a series of model compounds (**1**—**19**) was investigated and the results are presented in Table II. As can be seen, there seems to be a good correlation of oxidation yield with Hammett substituent constant (σ_p or σ^-) in the series of 5-arylidene 1,3-dimethylbarbituric acid derivatives. The greater the number and the stronger the nature of electron-withdrawing substituents on the aromatic ring in the models, the higher the oxidation ability. Thus, oxidation with **1**—**4** was not so good, whereas the yields (62 and 70%) with the electron deficient compounds, **8** and **9**, were satisfactory. The double-headed compound (**10**) shows some oxidation potential, but not as high as would be expected. From the table, it can be seen that **13**—**16**[6] have moderate oxidation ability, whereas **17**[7]—**19** turned out to have no ability.

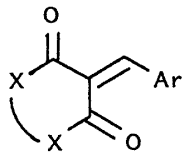
These results suggest that the partial structure in Fig. 1 is the essential structural unit for the oxidation.

TABLE II. Oxidation of Cinnamyl Alcohol with 5-Arylidene 1,3-Dimethylbarbituric Acid and Related Compounds

	1	2	3	4	5	6	7	8	9
	Substitutent group								
	OMe	H	*o*-OAc	*p*-OAc	F	CF_3	Cl	*p*-NO_2	*o*,*p*-NO_2
σ_p [a]	−0.12	0	—	0.31	0.15	0.53	0.24	0.81	0.81
σ^- [a]	—	0	—	—	—	0.74	—	1.23	1.23
% yield of cinnamaldehyde	5	35	30	40	38	39	52	62	70

	10	11	12	13	14	15	16	17	18	19
% yield of cinnamaldehyde	40	<1.0	<1.0	8.0	33	40	12	<1.0	<1.0	<1.0

a) Values of Hammett substituent constants (σ_p and σ^-) are taken from reference 11.



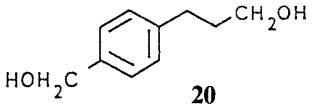
X=N or O

Fig. 1

TABLE III. Oxidation of Some Alcohols with **8** or **9**

		p-Methoxybenzyl alcohol	Carveol	4-Cholesten-3β-ol	Octyl alcohol	Menthol	Cholestenol	**20**
		Product						
		p-Anisaldehyde	Carvone	4-Cholesten-3-one	Octyl aldehyde[a]	Menthone[a]	Cholestenone[a]	**21**
Isolated yield (%)	**8**	25	29	30	<1	<1	<1	—
	9	39	35	—	<1	<1	<1	34

a) Because of their poor yield, these products were not identified.



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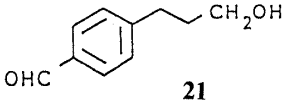

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Since **8** and **9** showed a high oxidation potential toward cinnamyl alcohol, their action on other alcohols was examined. *p*-Methoxybenzyl alcohol, carveol and 4-cholesten-3-ol were oxidized to the corresponding carbonyl compounds with **8** and/or **9** in 25—45% yield. Unlike allylic and benzylic alcohols, aliphatic alcohols, such as octyl alcohol, menthol and cholesterol resisted the oxidation, and therefore a selective oxidation of the diol (**20**) was achieved (34% yield of **21**, 89% yield based on the consumed diol (**20**)) with **9**. These results are summarized in Table III. Since no products other than the carbonyl compounds and the starting alcohols were isolated, the chemical yield based on the consumed starting alcohol may be much higher in the oxidation. Furthermore, when excess model compound (oxidant) was used, a higher yield of the oxidized product was observed.

Table IV. Redox Potentials[a] of **1**—**7**

	1	**2**	**3**	**4**	**5**	**6**	**7**
Redox potential (mV)	−905	−900	−880	−895	−885	−740	−765

a) 0.5 mmol/0.1 mol $(n\text{-Bu})_4NClO_4$/DMF *vs.* S.C.E.

Electrochemical Studies of Model Compounds

In order to investigate whether there are any relationships between the structures of a series of compounds and the oxidation potentials or not, an electrochemical study using cyclic voltammetry (C.V.) was carried out. It was difficult to analyze clearly the redox potentials for all of the compounds having a nitro group on a benzene ring, because the nitro group itself appeared to have been reduced at the first electron transfer so that the shape of the C.V. curve became complex and the exact potential could not be determined. On the other hand, the redox potentials of **1**—**7**, having no nitro group, were measured and the values are shown in Table IV. The table suggests that the values correlate closely with the oxidation ability toward cinnamyl alcohol. Under the same conditions (0.5 mmol/DMF–$(n\text{-Bu})_4NClO_4$), the redox potentials of these compounds are generally higher than those of 5-deazaflavin (*ca.* −1080 mV) and pyridodipyrimidine (*ca.* −930 mV) by about 100 to 300 mV.

Mechanistic Aspects of the Oxidation

Next, we turned our attention to the interpretation of the oxidation mechanisms with 5-arylidene 1,3-dimethylbarbituric acid derivatives. In this case, the oxidation can be interpreted in terms of an ionic mechanism,[12] since a change of the electronic situation on the aromatic ring of the model greatly influences the oxidation potential. To explore the reaction mechanism, after attempts to isolate intermediates in these oxidations were unsuccessful, oxidation products of *p*-methoxybenzyl alcohol with **8** were examined in some detail. Beside *p*-anisaldehyde and the starting *p*-methoxybenzyl alcohol, **22** and **23** were isolated together with a trace amount of an unidentified compound (Chart 3). Compound **23** was probably derived from the reduced compound (**22**) by air-oxidation during the reaction and/or the isolation step. In fact, the 5-position of the reduced compound (**22**) is so nucleophilic that it can react easily with *m*-chloroperbenzoic acid (mcpba) to give **23** quantitatively.[13]

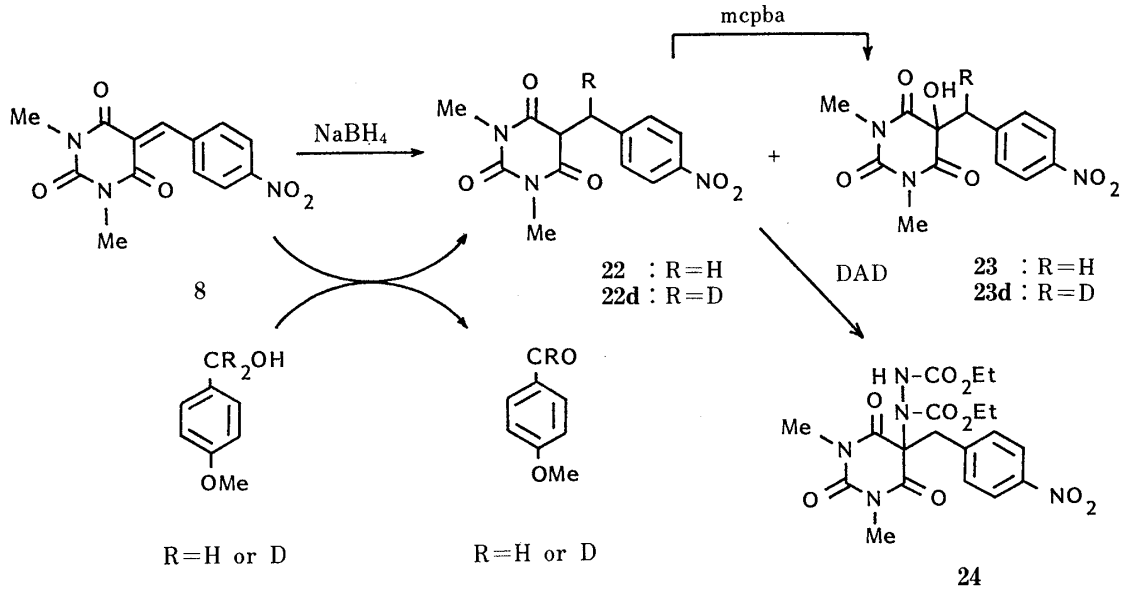

Chart 3

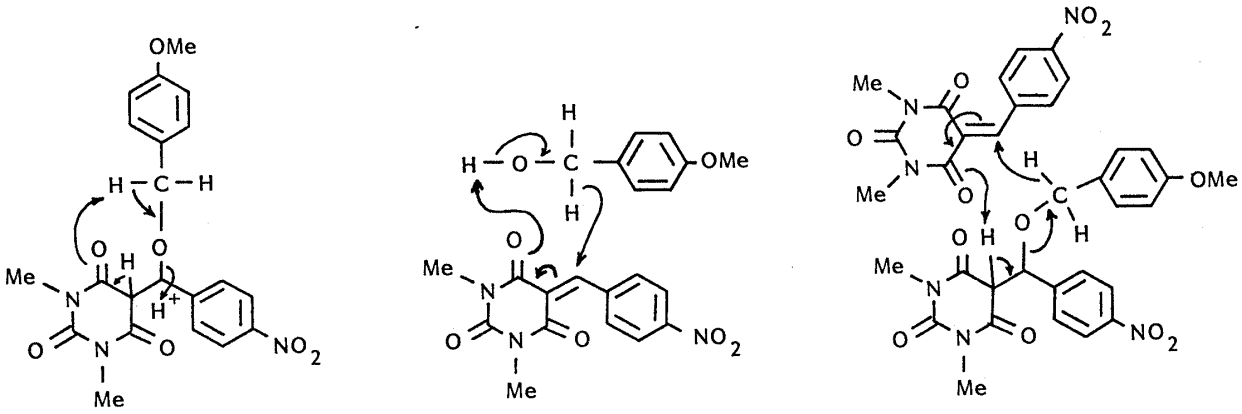

Fig. 2

There are two general ionic mechanisms for the oxidation of alcohol, one involving proton shift, as can be seen in oxidation *via* chromate ester intermediate, and the other involving hydride shift in the transition state, typically found in Oppenauer oxidation.[14] Enzymatic oxidation involving NAD^+ in biological systems belongs to the latter category.[15] In order to clarify and classify our oxidation mechanism, the following experiments were carried out. Oxidation was performed under an atmosphere of argon, from which atmospheric oxygen was strictly excluded, and it was found that this had no effect upon the oxidation outcome. Subsequently, *p*-methoxybenzyl alcohol-d_2 was prepared by the lithium aluminum deuteride reduction of ethyl *p*-methoxybenzoate and subjected to oxidation with **8**. Two deuterium-labeled compounds (**22d** and **23d**) were isolated in addition to *p*-anisaldehyde-d_1 (Chart 3). Judging from their proton nuclear magnetic resonance (^{1}H-NMR) spectra and mass spectra (MS), incorporation of deuterium was almost complete, and both **22d** and **23d** were contaminated by less than 5% of **22** and **23**. Furthermore the rate of this oxidation was retarded in comparison with that of unlabeled *p*-methoxybenzyl alcohol probably due to the isotope effect.

Next, a kinetic study was carried out and the normal and primary isotope effect in this oxidation was confirmed. The value of k_H/k_D is 3.3, suggesting that a bond to the isotopically substituted atom is broken in the rate-determining step. From the experimental evidence, it is deduced that the oxidation with 5-arylidene 1,3-dimethylbarbituric acid derivatives can not be a chromic acid type oxidation (A in Fig. 2) involving proton shift of the intermediate chromate ester, but an Oppenauer type of reaction including hydride transfer from the alcohol. This is also consistent with the proposed oxidation mechanism for NAD^+ and 5-deazaflavin.[15,16] The transition state may be B or C, as shown in Fig. 2, but so far no evidence of a termolecular mechanism has been found.

Conclusion

Though pyridodipyrimidine and 5-deazaflavin derivatives are known to be excellent organic oxidants, and some can be used in "autorecycling oxidation" where they function as catalysts,[17] it is interesting that these oxidants fail to oxidize *p*-methoxybenzyl alcohol under the same neutral reaction conditions as described above.

Another characteristic and important feature of a redox coenzyme is its function as a turn-over catalyst. Both flavin and 5-deazaflavin act as catalysts in the redox reaction of various substrates in biological systems. We attempted to oxidize the reduced compound (**22**) in order to examine whether 5-arylidene 1.3-dimethylbarbituric acid derivative acts as a turn-

over catalyst in the oxidation or not. As described previously, the 5-position of the reduced compound (**22**) was readily accessible to electrophiles including molecular oxygen, but air oxidation and oxidation with diethyl azodicarboxylate[18] (DAD) of **22** gave **23** and **24**, respectively (Chart 3), and no reoxidized compound (**8**) was formed in this reaction. Transformation of these compounds (**23** and **24**) into **8** was also unsuccessful. These results show 5-arylidene 1,3-dimethylbarbituric acid derivatives can not act as turn-over catalysts.

In conclusion, the present study suggests that the readily available 5-arylidene 1,3-dimethylbarbituric acid derivatives, especially compounds bearing an electron-withdrawing substituent on the aromatic ring (*e.g.* **8**, **9**), are effective and selective stoichiometric organic oxidants for allylic and benzylic alcohols under neutral conditions.

Further studies are in progress on the activation of molecular oxygen with nucleophilic compounds, such as **22**, the oxidation of other type of substrates (thiols and amines) and the preparation of analogues of **8** and **9** having optical activity.

Experimental

Commercially available organic and inorganic chemicals were used. Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu IR-400 spectrophotometer. ^{1}H-NMR spectra were obtained in chloroform-*d* at 200 MHz on a JEOL FX 200 instrument with chemical shifts being reported in δ units from tetramethylsilane as an internal standard and couplings in hertz. MS were taken on a JEOL JMS 01SG-2 instrument by direct insertion at 75 eV. High-performance liquid chromatography (HPLC) was done on a Waters Associates ALC/GPC 244 instrument equipped with a μ-Porasil column (3.9 × 300 mm) for kinetic studies. C.V. was performed with an MCL AS-01 C.V. analyzer (Mitsubishi Kasei Ltd.) and current-potential curves were recorded on an X-Y recorder (Watanabe Ltd., WX 1000). Before each measurement, a sufficient amount of pure nitrogen gas was bubbled through the electrolytic solution to remove any dissolved oxygen. p-TLC was run on 20 × 20 cm plates coated with a 0.1—1.5 mm layer of Merck Silica gel PF_{254} and/or GF_{254}. Gas-liquid chromatography (GLC) was done on a Shimadzu GC-7AG with a capillary column (FQ type, OV-101, 25 m × 0.2 mm).

General Methods for Preparation of 5-Arylidene 1,3-Dimethylbarbituric Acid and Related Compounds (1—19)——Method A: A mixture of 1,3-dimethylbarbituric acid (1.0 g, 6.58 mmol), an equimolar amount of an aromatic aldehyde and 10 ml of ethanol was refluxed for 1 h. In the case of the preparation of **10**, 0.5 eq of the aldehyde was used. After cooling, the precipitated product was collected by filtration and washed with ethanol three times. The crystalline 5-arylidene 1,3-dimethylbarbituric acid and related compounds thus obtained were pure enough for use in the next reaction.

Method B: 1,3-Dimethylbarbituric acid or an analogous active methylene compound (1.0 g) was added portionwise to a solution of an equimolar amount of an aldehyde and pyrrolidine in 10 ml of anhydrous methylene chloride at 0 °C under an atmosphere of argon. The mixture was stirred for 2 h at the same temperature and then *p*-toluenesulfonic acid (1.1 eq) was added. The whole was stirred for 10 min at 0 °C, poured into ice-water and extracted with chloroform. The chloroform layer was washed with water, dried over magnesium sulfate and then concentrated to leave a residual solid. Recrystallization from benzene or ether gave the pure sample.

5-(2′-Acetoxybenzylidene)-1,3-dimethylbarbituric Acid (3)——57% yield. This unsatisfactory yield is probably due to impurities in the 2-acetoxybenzaldehyde. mp 126—128 °C, IR ν_{max} cm^{-1}: 1765, 1675, 1375, 1180. ^{1}H-NMR δ: 2.31 (3H, s, –COMe), 3.35 (3H, s, –NMe), 3.42 (3H, s, –NMe), 7.15—8.05 (4H, m, Ar), 8.58 (1H, s, =CH–). *Anal.* Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.43; H, 4.60; N, 10.47.

5-(4′-Acetoxybenzylidene)-1,3-dimethylbarbituric Acid (4)——mp 156—157.5 °C, IR ν_{max} cm^{-1}: 1765, 1660, 1380, 1165. ^{1}H-NMR δ: 2.33 (3H, s, –COMe), 3.38 (3H, s, –NMe), 3.42 (3H, s, –NMe), 7.22 (2H, d, J=9, Ar), 8.19 (2H, d, J=9, Ar), 8.53 (1H, s, =CH–). *Anal.* Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.87; H, 4.67; N, 9.40.

5-(4′-Fluorobenzylidene)-1,3-dimethylbarbituric Acid (5)——mp 167—170 °C, IR ν_{max} cm^{-1}: 1670, 1590, 1425, 1380. ^{1}H-NMR δ: 3.39 (3H, s, –NMe), 3.44 (3H, s, –NMe), 7.15 (2H, t, J=9, Ar), 8.20 (2H, dd, J=5.5, 9.0, Ar), 8.52 (1H, s, =CH–). *Anal.* Calcd for $C_{13}H_{11}FN_3O_3$: C, 59.54; H, 4.23; N, 10.68. Found: C, 59.26; H, 4.09; N, 10.79.

5-(4′-Trifluoromethylbenzylidene)-1,3-dimethylbarbituric Acid (6)——mp 164—165 °C, IR ν_{max} cm^{-1}: 1675, 1320. ^{1}H-NMR δ: 3.36 (3H, s, –NMe), 3.44 (3H, s, –NMe), 7.70 (2H, d, J=8, Ar), 7.98 (2H, d, J=8, Ar), 8.57 (1H, s, =CH–). *Anal.* Calcd for $C_{14}H_{11}F_3N_2O_3$: C, 53.85; H, 3.55; N, 8.97. Found: C, 53.95; H, 3.31; N, 9.11.

5-(2′,4′-Dichlorobenzylidene)-1,3-dimethylbarbituric Acid (7)——mp 183—184 °C, IR ν_{max} cm^{-1}: 1675, 1465, 1375. ^{1}H-NMR δ: 3.35 (3H, s, –NMe), 3.44 (3H, s, –NMe), 7.30 (1H, dd, J=9, 2, Ar), 7.48 (1H, d, J=2, Ar), 7.73 (1H, d, J=9, Ar), 8.63 (1H, s, =CH–). *Anal.* Calcd for $C_{13}H_{10}Cl_2N_2O_3$: C, 49.84; H, 3.19; N, 8.94. Found: C, 49.92;

H, 2.94; N, 8.78.

5-(4′-Nitrobenzylidene)-1,3-dimethylbarbituric Acid (8)——mp 200 °C, IR ν_{max} cm^{-1}: 1675, 1520, 1375, 1345. ^{1}H-NMR δ: 3.35 (3H, s, –NMe), 3.44 (3H, s, –NMe), 7.96 (2H, d, J=9, Ar), 8.28 (2H, d, J=9, Ar), 8.57 (1H, s, =CH–). *Anal.* Calcd for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53. Found: C, 53.72; H, 3.58; N, 14.28.

5-(2′,4′-Dinitrobenzylidene)-1,3-dimethylbarbituric Acid (9)——mp 205—207 °C, IR ν_{max} cm^{-1}: 1680, 1600, 1530, 1375, 1345. ^{1}H-NMR δ: 3.22 (3H, s, –NMe), 3.45 (3H, s, –NMe), 8.56 (1H, d, J=8.5, Ar), 8.54 (1H, dd, J=8.5, 2, Ar), 8.82 (1H, s, =CH–), 9.12 (1H, d, J=2, Ar). *Anal.* Calcd for $C_{13}H_{10}N_4O_7$: C, 46.71; H, 3.02; N, 16.76. Found: C, 46.71; H, 2.94; N, 16.47.

5,5′-Terephthaliylidene Bis(1,3-dimethylbarbituric Acid) (10)——mp 300 °C, IR ν_{max} cm^{-1}: 1675, 1380. ^{1}H-NMR δ: 3.38 (6H, s, 2×–NMe), 3.43 (6H, s, 2×–NMe), 8.02 (4H, s, Ar), 8.55 (2H, s, =CH–). *Anal.* Calcd for $C_{20}H_{18}N_4O_6$: C, 58.53; H, 4.42; N, 13.65. Found: C, 58.36; H, 4.30; N, 13.59.

5-Furfurylidene 1,3-Dimethylbarbituric Acid (11)——mp 201—202 °C, IR ν_{max} cm^{-1}: 1660, 1580, 1360. ^{1}H-NMR δ: 3.42 (6H, s, 2×–NMe), 6.74 (1H, dd, J=2, 4, =CH–), 7.85 (1H, d, J=2, =CH–), 8.44 (1H, s, =CH–), 8.64 (1H, d, J=4, =CH–). *Anal.* Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.41; H, 4.06; N, 12.03.

5-Cinnamylidene 1,3-Dimethylbarbituric Acid (12)——mp 202.5—203.5 °C, IR ν_{max} cm^{-1}: 1660, 1570, 1380. ^{1}H-NMR δ: 3.40 (6H, s, 2×–NMe), 7.40—7.65 (5H, m, Ar), 7.43 (1H, d, J=15.5, =CH–), 8.20 (1H, d, J=12, =CH–), 8.60 (1H, dd, J=12, 15.5, =CH–). *Anal.* Calcd for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.86; H, 5.10; N, 10.30.

2-(4′-Nitrobenzylidene)-1,3-diketohydrindene (13)——mp 236—237 °C, IR ν_{max} cm^{-1}: 1690, 1520, 1345. ^{1}H-NMR δ: 7.91 (1H, s, =CH–), 8.00 (4H, m, Ar), 8.33 (2H, d, J=9, Ar), 8.55 (2H, d, J=9, Ar). *Anal.* Calcd for $C_{16}H_9NO_4$: C, 68.82; H, 3.25; N, 5.02. Found: C, 68.80; H, 3.11; N, 5.07.

5-(4′-Nitrobenzylidene)-2,2-dimethyl 1,3-Dioxane-4,6-dione (14)——mp 216—218 °C, IR ν_{max} cm^{-1}: 1730, 1525, 1350, 1285. ^{1}H-NMR δ: 1.82 (6H, s, 2×–NMe), 8.15 (2H, d, J=9, Ar), 8.30 (2H, d, J=9, Ar), 8.45 (1H, s, =CH–). *Anal.* Calcd for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found: C, 56.39; H, 3.75; N, 4.94.

5-(2′,4′-Dinitrobenzylidene)-2,2-dimethyl 1,3-Dioxane-4,6-dione (15)——mp 149—150 °C, IR ν_{max} cm^{-1}: 1735, 1600, 1535, 1345, 1285. ^{1}H-NMR δ: 1.82 (6H, s, 2×–NMe), 7.69 (1H, d, J=8.5, Ar), 8.57 (1H, dd, J=8.5, 2, Ar), 8.76 (1H, s, =CH–), 9.12 (1H, d, J=2, Ar). *Anal.* Calcd for $C_{13}H_{10}N_2O_8$: C, 48.46; H, 3.13; N, 8.69. Found: C, 48.64; H, 3.03; N, 8.62.

3-Methoxycarbonyl 6-Nitrocoumarin (18)——The procedure described here corresponds to method D in Table I. 2-Hydroxy-5-nitrobenzaldehyde (83 mg, 0.5 mmol) was added to a solution of dimethyl malonate (61 mg, 0.5 mmol) and triethylamine (55 mg, 0.5 mmol) in 10 ml of tetrahydrofuran, and the solution was refluxed for 4 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was crystallized from methanol and collected by filtration. mp 220—221 °C, IR ν_{max} cm^{-1}: 1775, 1620, 1530, 1345. ^{1}H-NMR δ: 3.99 (3H, s, –OMe), 7.51 (1H, d, J=9, Ar), 8.50 (1H, dd, J=9, 2.5, Ar), 8.57 (1H, d, J=2.5, Ar), 8.62 (1H, s, =CH–). *Anal.* Calcd for $C_{11}H_7NO_6$: C, 53.02; H, 2.83; N, 5.62. Found: C, 52.89; H, 2.66; N, 5.38.

Dimethyl 2-(4′-Nitrobenzylidene)malonate (19)——The procedure described here corresponds to method E in Table I. A mixture of 4-nitrobenzaldehyde (3.5 g, 0.023 mol), dimethyl malonate (2.8 g, 0.021 mol), piperidine (0.2 ml) and benzene (80 ml) was refluxed for 48 h in a Dean–Stark type apparatus. The solution was washed successively with 5% aqueous solutions of hydrochloric acid and sodium carbonate and then concentrated under reduced pressure to give a crystalline residue, which was recrystallized from a mixture of benzene and ehter. mp 93—95 °C, IR ν_{max} cm^{-1}: 1725, 1520, 1350, 1260. ^{1}H-NMR δ: 3.84 (3H, s, –OMe), 3.89 (3H, s, –OMe), 7.58 (2H, d, J=9, Ar), 7.80 (1H, s, =CH–), 8.25 (2H, d, J=9, Ar). *Anal.* Calcd for $C_{12}H_{11}NO_6$: C, 54.34; H, 4.18; N, 5.28. Found: C, 54.24; H, 4.11; N, 5.26

5-(4′-Nitrobenzyl)-1,3-dimethylbarbituric Acid (22) from 8——Sodium borohydride (200 mg) was added portionwise to a solution of **8** (200 mg) in methanol (10 ml) and the mixture was stirred for 10 min at room temperature. Water (50 ml) was added and the mixture was washed with chloroform. After acidification of the aqueous layer with 5% hydrochloric acid, the layer was extracted with chloroform. The chloroform extract was dried over $MgSO_4$ and then concentrated to give crystalline residue, which was recrystallized from methanol. The yield was 200 mg (99%). mp 152—153 °C, IR ν_{max} cm^{-1}: 1690, 1525, 1350. ^{1}H-NMR δ: 2.22 (6H, s, 2×NMe), 3.60 (2H, d, J=5, CH_2–Ar), 3.88 (1H, t, J=5, –CH–), 7.35 (2H, d, J=9, Ar), 8.10 (2H, d, J=9, Ar). *Anal.* Calcd for $C_{13}H_{13}N_3O_5$: C,.53.61; H, 4.50; N, 14.43. Found: C, 53.40, H, 4.45, N, 14.28.

5-Hydroxy-5-(4′-nitrobenzyl)-1,3-dimethylbarbituric Acid (23)——A solution of **22** (200 mg, 0.68 mmol) and *m*-chloroperbenzoic acid (300 mg, 1.92 mmol) in methylene chloride (10 ml) was stirred for 4 h at room temperature. An aqueous solution of Na_2SO_3 (1.0 g) was added and the mixture was stirred for 10 min. The mixture was extracted with chloroform and the chloroform layer was washed successively with 10% aqueous $NaHCO_3$ and water, and then dried over $MgSO_4$. Concentration of the solution give a residue, which was crystallized from methanol. Yield, 190 mg (90%). mp 177—179 °C, IR ν_{max} cm^{-1}: 1690, 1520, 1345. ^{1}H-NMR δ: 3.24 (6H, s, 2×NMe), 3.32 (2H, s, CH_2Ar), 7.22 (2H, d, J=9, Ar), 8.17 (2H, d, J=9, Ar). *Anal.* Calcd for $C_{13}H_{13}N_3O_6$: C, 50.81; H, 4.26; N, 13.68. Found: C, 50.76; H, 4.11; N, 13.42.

If $NaBD_4$ was used for reduction of **8** in place of $NaBH_4$, **22d** (which contains deuterium at the α-benzyl

position) was obtained. Compound **23d** was obtained similarly.

5-(4′-Nitrobenzyl-α-d_1)-1,3-dimethylbarbituric Acid (22d)——The IR spectral data are the same as those of **22**. ^{1}H-NMR δ: 3.24 (6H, s, 2 × NMe), 3.58 (1H, d, J=5, –CHD–), 3.84 (1H, d, J=5, =CH–), 7.33 (2H, d, J=9, Ar), 8.10 (2H, d, J=9, Ar). MS m/z: 291 (M^+).

5-Hydroxy 5-(4′-Nitrobenzyl-α-d_1)-1,3-dimethylbarbituric Acid (23d)——The IR spectral data are the same as those of **23**. ^{1}H-NMR δ: 3.24 (6H, s, 2 × NMe), 3.31 (1H, s, –CHD–), 7.22 (2H, d, J=9, Ar), 8.18 (2H, d, J=9, Ar). MS m/z: 308 (M^+). Compounds **22**, **22d**, **23** and **23d** were identical with the samples which were derived from the oxidation of alcohol with **8** in terms of TLC behavior, and IR and ^{1}H-NMR spectra.

Oxidation of 22 with DAD——A mixture of **22** (115 mg, 0.4 mmol) and 2 ml of diethyl azodicarboxylate was heated at 70 °C for 1 h, and concentration of the mixture under reduced pressure yielded a residue, which was subjected to p-TLC on silica gel, developed with hexane–ethyl acetate (1 : 1). The crystalline adduct (**24**) (170 mg) was obtained in 93% yield as a sole product. mp 210—211 °C (from ether), IR ν_{max} cm^{-1}: 1690, 1610, 1525, 1350. ^{1}H-NMR δ: 1.28, 1.36 (each 3H, t, J=7, 2 × CMe), 3.14 (6H, s, 2 × NMe), 3.28 (2H, s, CH_2), 4.18, 4.32 (each 2H, t, J=7, 2 × –OCH_2C), 6.88 (1H, s, NH), 7.19 (2H, d, J=9, Ar), 8.14 (2H, d, J=9, Ar). *Anal.* Calcd for $C_{19}H_{23}N_5O_9$: C, 49.03; H, 4.98; N, 15.05. Found: C, 48.85; H, 4.92; N, 14.88.

Oxidation of Alcohols with 5-Arylidene 1,3-Dimethylbarbituric Acid or Related Compounds (Coenzyme Model), (1—19)——General Procedure: A solution of 5-arylidene 1,3-dimethylbarbituric acid or a related compound (0.75 mmol) and an alcohol (0.75 mmol) was refluxed in 1,4-dioxane (8 ml) for 3 d. Then the solution was concentrated and the residue was separated by p-TLC, developed with hexane–ethyl acetate (4 : 1). The products thus obtained, the corresponding carbonyl compounds and the recovered alcohol, were characterized and identified by comparison with authentic samples (TLC, GLC and/or HPLC).

Use of excess oxidant resulted in a higher yield of oxidized products. For example, the use of two equivalents of **8** (1.5 mmol) for the oxidation of cinnamyl alcohol (0.75 mmol) gave 68% yield of cinnamaldehyde in 2 d under the reaction conditions described above.

Kinetic Studies: The oxidation of the alcohol with **8** is regarded as a simple first-order reaction with respect to each reactant. The kinetic isotope effect was determined by measuring the decrease in concentration of the alcohol, by HPLC of definite volumes of reaction mixture sampled at regular intervals. A plot of 1/[A] against reaction time was found to be linear ([A] refers to the concentration of the alcohol), and this graphic analysis provided a value for the appropriate rate constant. According to this procedure, k_H and k_D were determined in the oxidation of *p*-methoxybenzyl alcohol-d_2 with **8** to obtain the value of the isotope effect.

α,α-Dideuterio *p*-Methoxybenzyl Alcohol——Lithium aluminum deuteride (170 mg) was added portionwise to a stirred mixture of methyl 4-methoxybenzoate (660 mg) in ethyl ether (30 ml) and the mixture was refluxed for 20 min with stirring. Ice-water was carefully added to the mixture, which was then filtered, and the precipitate was washed with ether several times. The filtrate and washings were combined and the whole was concentrated to dryness to give an oily residue (537 mg), which was pure enough to use for the next reaction. IR ν_{max} cm^{-1}: 1610, 1510, 1245. ^{1}H-NMR δ: 3.31 (1H, s, OH), 3.73 (3H, s, OMe), 6.81 (2H, d, J=8, Ar), 7.18 (2H, d, J=8, Ar). MS m/z: 140 (M^+), 123, 110.

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References and Notes

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