Hydrolysis of Barbituric Acid Derivatives. Part 6.[1] Hydrolysis of Spirocyclopropane- and Spiro-2′-methylcyclopropane-1′,5-barbituric Acids

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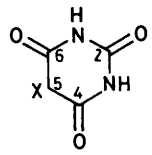
The title barbiturates are hydrolysed by pyrimidine ring degradation or by cyclopropane ring opening. The cyclopropane ring decreases the hydrolytic reactivity of the pyrimidine moiety in relation to other spirobarbiturates, owing to conjugation between the cyclopropane ring and the C-4 or C-6 carbonyl group. The kinetics and the products of the alcoholysis of these barbiturates have been investigated. The influence of the cyclopropane moiety on the pK_{a_1} values and ^{13}C n.m.r. spectra has also been discussed.

The effect of C-5 substituents on the hydrolytic degradation of barbiturates has been widely investigated. These investigations allow two general conclusions. First, that unsaturated or aromatic substituents are responsible for an increase in the hydrolytic reactivity of barbiturates because of their electron withdrawing character.[2–8] The second is that the steric effect of C-5 alkyl or cycloalkyl substituents causes a decrease in the hydrolytic reactivity of barbiturates, and this effect, rather than the electronic effect predominates.[2–9] Substituents larger than methyl at the 5-position shield the ring against nucleophilic attack. In a previous paper[10] we showed that barbiturates in which such steric shielding is impossible (*i.e.* spirocycloalkane-1′,5-barbituric acids with 4-, 5-, and 6-membered rings) are hydrolysed 10^3—10^4 times faster than the other 5,5-dialkylbarbiturates, while a cyclobutane ring, more strained than cyclopentane and cyclohexane rings, and which can thus affect the deformation of the barbituric acid ring, causes only a five-fold increase in the rate of hydrolysis. We extended these studies to investigate the influence of a 5-spirocyclopropane moiety on the rates of hydrolysis and alcoholysis of barbiturates. We also discuss the ^{13}C n.m.r. spectra of the four spirobarbiturates (**1**)—(**4**) (see Table 1).

Acid Strengths.—The first dissociation constants were determined spectrophotometrically, and are: for (**1**), pK_{a_1} = 8.54 ± 0.03 (lit.,[11] 8.73); and for (**2**), pK_{a_1} = 8.94 ± 0.03. These values are comparable with those for 5,5-dimethylbarbituric acid (pK_{a_1} = 8.51) and 5-spirobarbiturates containing 4-, 5-, and 6-membered cycloalkane rings (pK_{a_1} = 8.82 – 8.88), respectively.[10,11] On the other hand, compounds (**1**) and (**2**) are weaker acids by 0.5—1.0 units of pK_a in relation to other 5,5-disubstituted barbiturates. This acidity-weakening effect in a series of 5-spirobarbiturates is attributed to increased solvation in the undissociated molecules which is possible because of the lack of the steric shielding effect of a C-5 substituent.[10–13] Compound (**2**) has a pK_{a_1} value higher than that of (**1**) by 0.40 units; this results from the introduction of a methyl group into the cyclopropane ring. However, a methyl group in the α-position of the C-5 alkyl chain increases the pK_{a_1} by about 0.2 units.[14–16] Thus, the observed polar effect of the methyl group can be considered to operate by electron release across the cyclopropane ring to the heterocyclic moiety.

^{13}C N.m.r. Spectra.—The ^{13}C n.m.r. chemical shifts (relative to Me_4Si) for the studied spirobarbiturates (**1**)—(**4**) are listed in Table 1. These were assigned by comparison with the spectra of other 5,5-dialkylbarbiturates[17,18] and appropriate cyclo-

Table 1. ^{13}C N.m.r. data for spirobarbiturates (**1**)—(**4**)



C atom	(**1**) X = 1′CH_2–1′CH_2–	(**2**) X = 1′ 1″MeCH–2′CH_2–	(**3**) X = 1′CH_2–2′CH_2–1′CH_2–	(**4**) X = 1′CH_2–2′CH_2–2′CH_2–1′CH_2–
1′	23.51	32.24	28.76	37.25
2′		26.53	15.50	26.94
1″		11.48		
2	150.87	151.03	150.65	150.64
4,6	170.27	168.40; 170.40	172.97	174.70
5	27.10	35.51	48.53	55.63

alkanes,[19] and by analysis of the signal multiplicity obtained from proton coupled spectra.

The typical chemical shifts of the C-5 atom for the 5,5-disubstituted barbiturates are δ 50—62 p.p.m.[18,20–22] However, for compounds (**1**) and (**2**) the resonance signals for the C-5 atom show strong upfield shifts. Similarly, the signals due to C-4 and C-6 of compounds (**1**) and (**2**) are shifted upfield by 2–4 p.p.m. as compared with the other 5,5-dialkylbarbiturates.[17,18] These changes are associated with the electronic nature of the cyclopropane ring. The C-4 and C-6 carbonyl groups of (**2**) appear as separate signals as a result of the molecular assymetry in the methylcyclopropane moiety and the chemical shift difference of 2 p.p.m. is significantly higher than those observed (0.1—1.1 p.p.m.) for other 5,5-disubstituted barbiturates containing substituents with the chiral centre at the C-1′ position.[18,20,21,23]

Hydrolysis of Spirobarbiturates (**1**) *and* (**2**).—The hydrolysis of (**1**) with water and (**2**) with an equimolar amount of sodium hydroxide in water at 80 °C yielded 5-(2-hydroxyethyl)-barbituric acid (**5**) and 5-(2-hydroxypropyl)barbituric acid (**6a**). However, the hydrolyses of (**1**) and (**2**) in strongly alkaline

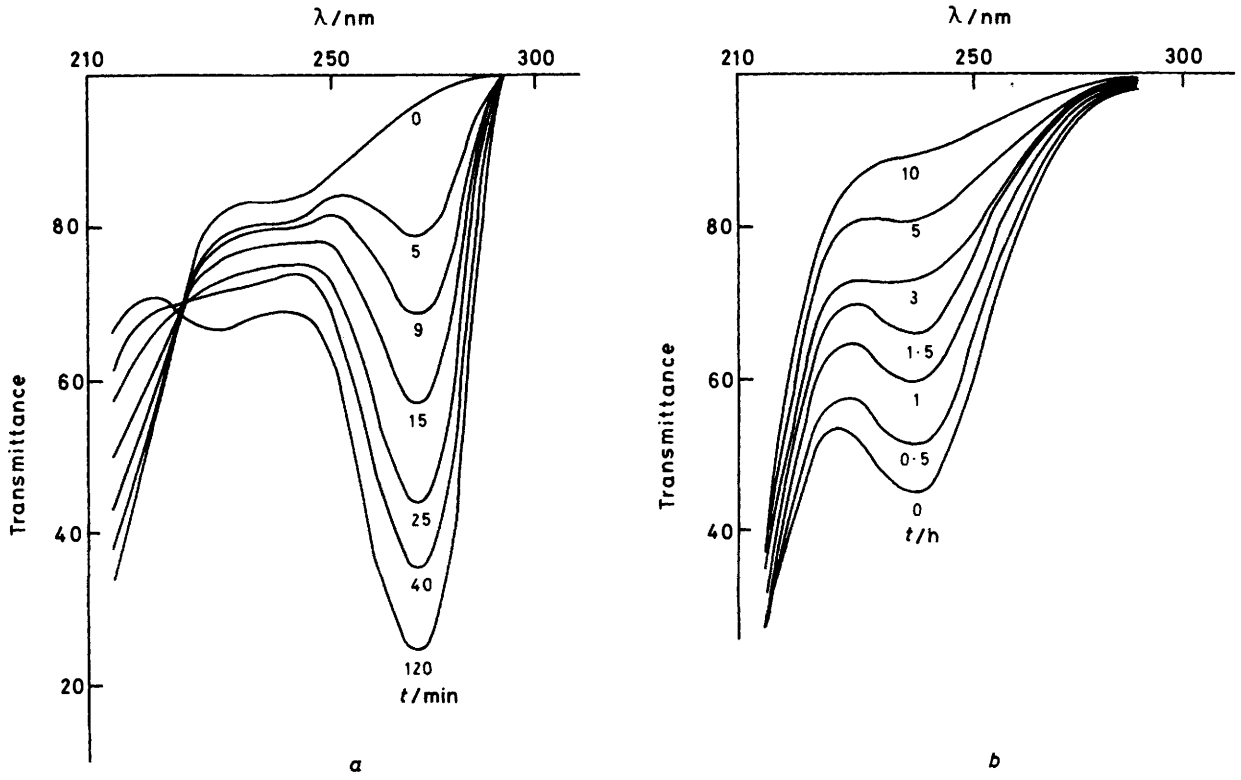
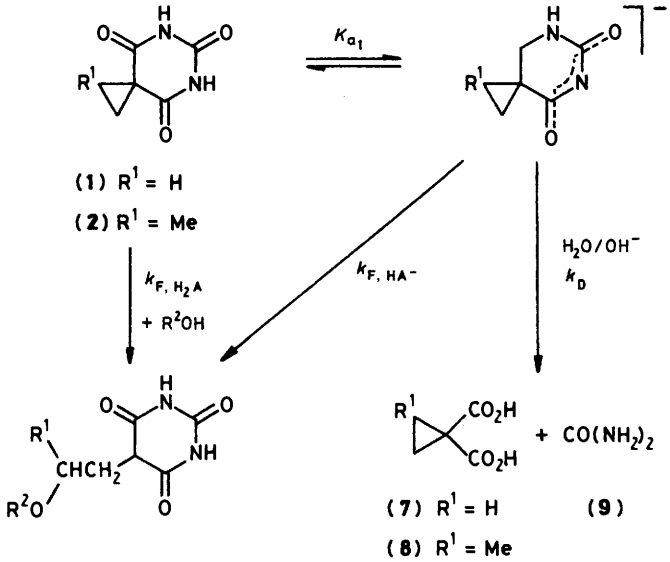


Figure 1. Scanning u.v. study of the reaction of the spirobarbiturate (**2**) (3×10^{-5}M) with water at 50 °C: (*a*) at pH 8.15, (*b*) at pH 11.20.



	R^1	R^2
(5)	H	H
(6a)	Me	H
(6b)	Me	Me
(6c)	Me	Et
(6d)	Me	Pr
(6e)	Me	Bu
(6f)	Me	Pr^i

Scheme 1.

media yielded the corresponding cyclopropane-1,1-dicarboxylic acids (**7**) and (**8**), and urea (**9**) (Scheme 1).

The rate constants for the hydrolysis of the investigated spirobarbiturates (**1**) and (**2**) were determined at different pH values within the range 5.0—11.6 in the appropriate buffer solutions at 50 ± 0.2 °C. The course of the reaction was monitored by u.v. spectroscopy over the range 215—290 nm. During hydrolysis the formation of the 5-monosubstituted barbiturates ($\lambda_{max.}$ 268 or 270 nm) as the final product was observed for (**5**) up to pH 8.94 and for (**6**) up to pH 9.99 (Figure 1*a*). Above the given pH limits, the formation of (**5**) and (**6**) becomes less obvious and the disappearance of the spirobarbiturates (**1**) and (**2**) ($\lambda_{max.}$ 239—240 nm) was observed. However, from pH 9.66—10.92 only the disappearance of the absorption band of (**1**) and (**2**), respectively, was observed (Figure 1*b*).

Plots of log *A versus* time for all investigated pH values were linear to the end of the reaction. The pseudo-first-order rate constants of the degradation (k_D) of (**1**) and (**2**) and the formation (k_F) of (**5**) and (**6a**) were calculated by a single linear regression according to equations (1) and (2).

$$\ln (A_t - A_\infty) = \ln (A_0 - A_\infty) - k_D t \quad (1)$$

$$\ln (A_\infty - A_t) = \ln (A_\infty - A_0) - k_F t \quad (2)$$

where A_0, A_t, and A_∞ are absorbances measured at the $\lambda_{max.}$ of spirobarbiturates (**1**) and (**2**) or 5-monosubstituted barbiturates (**5**) and (**6a**) at time $t = 0$, t, and $= \infty$, respectively. The individual rate constants are listed in Table 2 and the log *k*–pH profiles are shown in Figure 2.

The observed cyclopropane ring opening reaction which occur under nucleophilic attack by water remains a non-catalytic process within the investigated pH ranges, 6.50—9.32 and 5.00—10.65 for (**1**) and (**2**), respectively. Within the above

Table 2. Rate constants[a] for hydrolysis of compounds (1) and (2) at 50 ± 0.2 °C

(1)			(2)		
pH	$10^5k_D/s^{-1}$ [b]	$10^5k_F/s^{-1}$ [c]	pH	$10^5k_D/s^{-1}$ [b]	$10^5k_F/s^{-1}$ [c]
6.50		1.41	5.00		68.5
6.83		1.35	6.00		73.7
7.43		1.27	7.00		75.1
7.86		1.12	8.15		55.0
8.30		0.672	8.35		39.7
8.55		0.534	8.58		33.6
8.94		0.376	8.78		23.5
9.32		0.405	8.98		15.3
9.66	0.506		9.18		12.4
9.71	0.755		9.38		9.54
9.91	0.836		9.71		4.59
9.99	1.51		9.99	0.69[d]	3.85
10.72	4.07		10.40	1.89[d]	2.72
10.92	7.72		10.65	3.66	2.73
11.62	39.5		10.92	6.89	
			11.03	6.67	
			11.20	16.2	
			11.62	32.7	

The slope of log k_D = f(pH) (and correlation coefficient)

0.91 (0.992) 1.04 (0.993)

[a] Correlation coefficients are within the limits $0.99 \leqslant r \leqslant 1.00$ and the reproducibility of measurement is within the range 4—7%. [b] Degradation of (1) or (2). [c] Formation of (5) or (6a). [d] The values calculated from equation are $k_D = k_{D,obs.} - k_F$.

Table 3. The k_{F,H_2A}, k_{F,HA^-}, and pK_{a_1} values[a] for (1) and (2), calculated from equation (4)

	(1)	(2)
$k_{F,H_2A}/s^{-1}$	1.45×10^{-5}	7.24×10^{-4}
$k_{F,HA^-}/s^{-1}$	3.50×10^{-6}	2.32×10^{-5}
pK_{a_1}	8.01	8.42

[a] At 50 ± 0.2 °C.

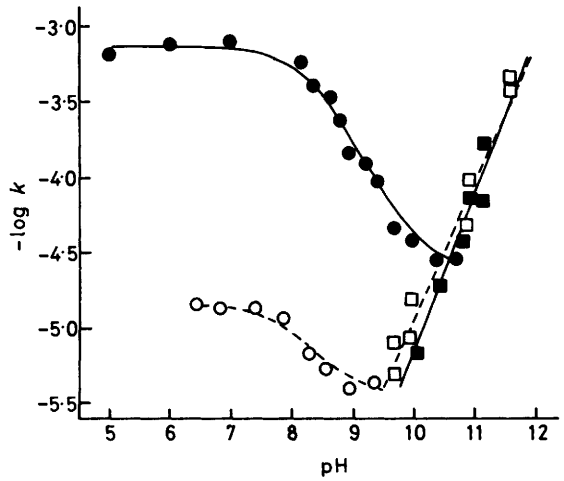


Figure 2. log k–pH profiles: ● formation of (6a), ○ formation of (5), ■ pyrimidine ring opening of (2), □ pyrimidine ring opening of (1).

pH ranges the observed pseudo-first-order rate constants ($k_{F,obs.}$) (Table 2) are dependent on the concentrations of the un-ionized and mono-ionized forms of (1) and (2), and are described by equation (3), where k_{F,H_2A} and k_{F,HA^-} are cyclopropane ring opening rate constants for the un-ionized and mono-ionized species of (1) or (2), and x_{H_2A} and x_{HA^-} are the molar fractions of these species, respectively. Equation (3) was transformed into equation for the purposes of computation.

$$k_{F,obs.} = k_{F,H_2A}/[10^{(pH-pK_{a_1})} + 1] + k_{F,HA^-}\{1 - 1/[10^{(pH-pK_{a_1})} + 1]\} \quad (4)$$

The rate constants k_{F,H_2A} and k_{F,HA^-} and the pK_{a_1} value were calculated, based on $k_{F,obs.}$ and the pH values listed in Table 2, from equation (4) using the MINUIT program for the Cyber 72 computer system. The results of these calculations are presented in Table 3.

Addition of the water molecule to the cyclopropane ring occurs more slowly for the mono-ionized species than for the un-ionized ones by about four-fold and 31-fold for (1) and (2), respectively. The increased electron density in the mono-ionized form of the pyrimidine moiety involves a similar effect in the cyclopropane ring, decreasing its susceptibility towards nucleophilic attack. Introduction of a methyl group into the cyclopropane ring, however, results in an increase in k_{F,H_2A} and k_{F,HA^-} values by about 50- and seven-fold, respectively (Table 3). Such a significant difference in the k_{F,H_2A} and k_{F,HA^-} values for (2) in relation to (1) may indicate a significant decrease in the electron density at the reaction centre caused by the methyl group.

The pK_{a_1} values at 50 °C calculated from equation (4) (Table 3) are lower by about 0.5 units than those measured for (1) and (2) at 20 °C. This temperature effect on the pK_a value is consistent with that observed for the other barbiturates.[24] It should also be noted that the difference between the pK_{a_1} values calculated for (1) and (2) at 50 °C is essentially the same ($\Delta pK_{a_1} = 0.41$) as that at 20 °C.

The degradation of the investigated barbiturates by pyrimidine ring opening occurs at the 1—6 position, as indicated by the isolated products (Scheme 1), and is typical for the hydrolysis of 5,5-disubstituted barbiturate monoanions.[2,8,10] The slopes of log k_D = f(pH) profiles for (1) and (2) (Table 2, Figure 2) indicate an OH^- ion catalysed reaction. Moreover, the introduction of the methyl group into the cyclopropane ring does not involve changes in the particular k_D constants in this process within the investigated pH range.

Table 4. The observed pseudo-first-order and the secondary rate constants[a] for hydrolysis and alcoholysis of (6a—f) and σ* and E_s constants[25]

Compound	R^2OH	$10^5k_F/s^{-1}$	$10^6k_n^{II}/l\cdot mol^{-1}s^{-1}$	σ*	E_s
(6a)	HOH	77.2	15.0	+0.49	+1.24
(6b)	MeOH	4.55	2.03	0	0
(6c)	EtOH	2.31	1.48	−0.10	−0.07
(6d)	PrOH	1.66	1.36	−0.115	−0.36
(6e)	BuOH	1.44	1.41	−0.13	−0.39
(6f)	Pr^iOH	1.25	1.02	−0.19	−0.47

[a] Measured at 50 ± 0.2 °C

Alcoholysis of (2).—The reaction of (2) with the alcohols given in Scheme 1 was carried out preparatively to obtain authentic samples for the kinetic studies. Spectral data (u.v. and ^1H n.m.r.) and elemental analyses were in accord with the expected structures (6b—f). The reaction was followed by u.v. spectroscopy and the pseudo-first-order rate constants were calculated by equation (2) from changes in absorbance observed during the formation of (6b—f) ($\lambda_{max.}$ 268—269 nm). The differences between the observed k_F values (Table 4) under the

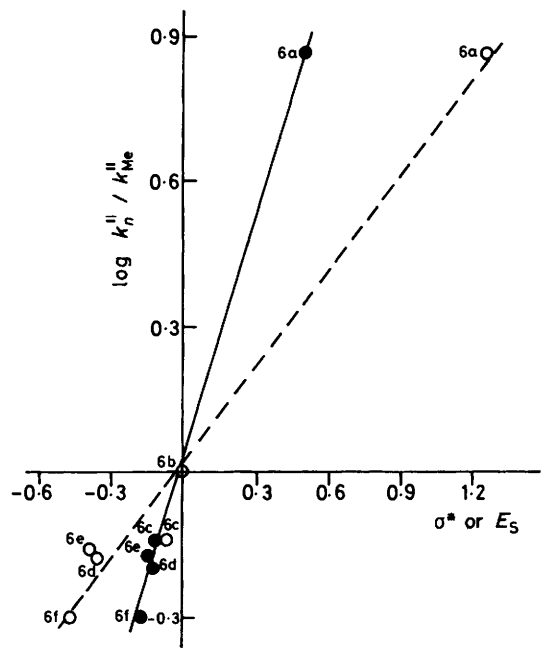


Figure 3. The plots of log k_n^{II}/k_{Me}^{II} *versus* σ* (●) or E_s (○) values.

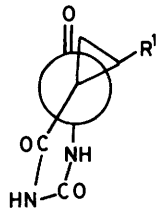


Figure 4. The synclinal arrangement of the C-1′–C-2′ bond of the cyclopropane ring in relation to the C-4 or C-6 carbonyl group in (**1**) and (**2**).

$$\log k_n^{II}/k_{Me}^{II} = 0.03 + 1.70\cdot\sigma^* \quad (7)$$
$$r = 0.999, \text{ c.l.} = 99.9\%, s = 0.023$$

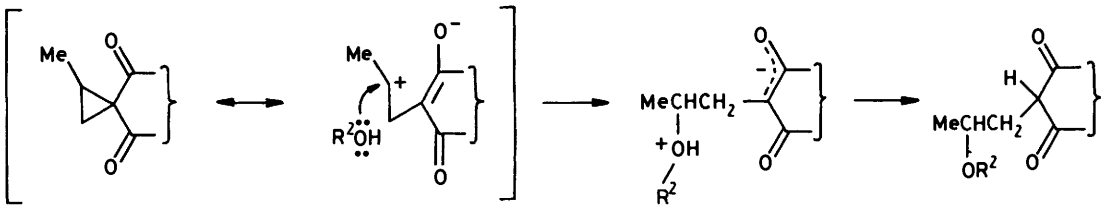
$$\log k_n^{II}/k_{Me}^{II} = 0.02 + 0.68\cdot E_s \quad (8)$$
$$r = 0.988, \text{ c.l.} = 99.9\%, s = 0.074$$

The calculations indicate that there is excellent correlation between the second-order rate constants of hydrolysis and alcoholysis and the polar substituent constants. Correlation with the steric substituent constants shows a lower correlation coefficient, which is still highly significant; it should be pointed out however that the E_s scale also contains a large 'polar' component. Thus, one can conclude that both substituent polar and steric effects in the nucleophile reagent are required in the investigated reactions. The positive ρ* value [equation (7)] indicates a low electron density at the reaction centre, which facilitates the nucleophilic attack of water or alcohols. On the other hand, bulkier R^2 substituents hinder the nucleophilic attack at the cyclopropane moiety [equation (8)].

Conclusions

The investigated spirocyclopropane-1′,5-barbiturates (**1**) and (**2**) are hydrolysed in two ways, *i.e.* by pyrimidine ring opening at the 1—6 position and by cyclopropane ring opening.

The degradation rate constants of the barbituric acid moiety, under the same conditions, are lower by *ca.* 20-fold than those for the other spirobarbiturates containing cyclopentane and cyclohexane rings and for 5,5-dimethylbarbituric acid (k = 1.1—1.7 × 10^{-3} s^{-1} at pH 11.02),[10] which also show no steric shielding effect. Moreover, steric deformation of the pyrimidine ring by the spirocyclobutane moiety results in a *ca.* 50-fold increase in the hydrolysis rate (k = 4.7 × 10^{-3} s^{-1} at pH 11.02)[10] in relation to (**1**) and (**2**). Both steric strain and the inductive effect of the cyclopropane ring, which shows the unsaturated character,[25] should accelerate hydrolysis of the pyrimidine ring.[4,5,8,10] The cyclopropane ring, however, shows a tendency to conjugation with the adjacent carbonyl



Scheme 2.

same conditions, appear to be significant and indicate the undoubted influence of nucleophiles on the alcoholysis rate. The results were correlated with the polar (σ*) and steric (E_s) Taft's constants of the nucleophiles using the Hammett equations:

$$\log k_n^{II}/k_{Me}^{II} = \rho^*\cdot\sigma^* \quad (5)$$

$$\log k_n^{II}/k_{Me}^{II} = \delta\cdot E_s \quad (6)$$

where $k_n^{II} = k_F/c_{Nu}$ represents the secondary rate constant for the nth nucleophile, k_{Me}^{II} is the secondary rate constant for methanol, k_H is the observed pseudo-first-order rate constant (Table 4), and c_{Nu} is the concentration of the nucleophile: ρ* and δ are reaction and steric susceptibility constants, respectively. A straight line was fitted by the standard least squares method and the correlation coefficient (r) was evaluated using the Student's test (c.l. = confidence level; s = standard deviation). The results are presented in Figure 3 and in equations (7) and (8).

group.[26–29] The angle deformations introduced into the pyrimidine moiety by the cyclopropane ring can favour, in (**1**) and (**2**), a synclinal conformation of the C-1′–C-2′ and carbonyl group bonds, as shown by an analysis of Dreiding models. In this conformation, the π-orbitals of the carbonyl group and the cyclopropane ring p-orbital[26] can be arranged in the same plane (Figure 4). Thus, conjugation between the cyclopropane ring and the carbonyl groups in (**1**) and (**2**) can exist, and this hinders OH^- ion attack at the C-4 or C-6 carbonyl atoms. Moreover, one can assume that the conformation shown in Figure 4 might be additionally favoured, owing to the existing conjugation.

The cyclopropane ring opening reaction seems to be bimolecular (Scheme 2), and involves a significant steric effect [equation (8)] of the R^2 substituents, which is typical for such types of reaction.[30] Additional evidence for the bimolecular mechanism of this reaction lies in the comparison of the pseudo-first-order rate constants at different concentrations of nucleo-

phile. A 3-fold decrease in the water concentration in the water–dioxane mixture results in a *ca.* 14-fold decrease in the pseudo-first-order rate constant ($k_{F,obs.}$ = 5.7 × 10^{-5} s^{-1}). The observed difference can be attributed both to a decrease in nucleophile concentration and to solvent effects.[30] On the other hand, the nucleophilic attack in the cyclopropane ring is facilitated by the presence of a methyl group at the 2′-position.

This effect can be also explained by the existence of conjugation between the cyclopropane ring and the carbonyl group, because the methyl group stabilizes the resonance structure because of the electron deficiency at the C-2′ atom.

Experimental

U.v. spectra were recorded with a Specord UV-VIS (Zeiss, Jena) and i.r. spectra with a Specord 75 IR (Zeiss, Jena) instrument. A Nicolet Magnetic Corporation apparatus was used for recording ^{13}C n.m.r. spectra and a Varian EM-360 spectrometer for ^{1}H n.m.r. spectra. Elemental analyses were carried out by Regional Laboratory of Physico-chemical Analysis, Poznán. M.p.s. were determined with a Boethius apparatus. Kinetic runs were carried out in the ultrathermostat U-7 and pH measurements were taken on the pH-meter N517 (Mera Elwro) with the combined electrode OSH-10-10. The ^{13}C n.m.r. data for the compounds (**1**)—(**4**) are summarised in Table 1.

Materials.—Syntheses of the investigated barbiturates are described as follows: (**1**),[31] (**2**),[32] (**3**),[33] and (**4**).[34] The following buffer solutions according to the NBS standards were used for kinetic investigations: pH (measured at 50 °C) 5.00—8.55 (phosphate), 8.58—10.40 (borate), 10.65—11.03 (phosphate), 11.20 and 11.62 (NaOH + KCl). The ionic strength was kept at 0.1. The buffers were prepared using double-distilled water and analytical grade reagents. Anhydrous dioxane and alcohols were used for kinetic experiments. T.l.c. experiments were carried out using commercial plates (5 × 10 cm) with silica gel 60 F_{254} (Merck).

pK_a *Measurements.*—The pK_{a_1} values of (**1**) and (**2**) were determined spectrophotometrically[35] at 20 ± 0.2 °C using 0.1M HCl and buffer solution (pH 11.60) for un-ionized and monoionized species, respectively. Seven borate buffers [pH 8.08—9.18 for (**1**) and pH 8.42—9.57 for (**2**)] were used for partly ionized species.

Kinetic Procedure.—Method A. Kinetic experiments were carried out at 50 ± 0.2 °C. Samples of dioxane stock solutions of the investigated compounds (**1**) and (**2**) (5 × 10^{-3} mol l^{-1}) were diluted with the appropriate buffer pre-equilibrated at the temperature of the experiment to a final concentration 3 × 10^{-5} mol l^{-1}. At appropriate time intervals samples were withdrawn and the u.v. spectra were recorded within the range 210—290 nm.

Method B. A 1.5 ml aliquot portion of dioxane stock solution of (**2**) (1.25 × 10^{-2} mol l^{-1}) were diluted with water or the appropriate alcohol pre-equilibrated at 50 ± 0.2 °C to 25 ml in the volumetric flask to produce a concentration of 8 × 10^{-4} mol l^{-1}. At appropriate times 0.2 ml samples were withdrawn and diluted to 5 ml with buffer of pH 7.0. Reactions were followed by monitoring the appearance of the characteristic absorbances at 268—270 nm of the ionized form of the 5-monosubstituted barbituric acid derivative (**6a**—**f**).

Preparative Hydrolyses of (**1**) *and* (**2**) *in Alkaline Medium.*—The spirobarbiturates (**1**) or (**2**) (3 mmol) were added to 0.2M NaOH (30 ml) solution and the reaction mixtures were kept at 85 °C for 4 h. After cooling the mixtures were acidified with concentrated HCl to pH 1 and ether extraction (3 × 20 ml) yielded *cyclopropane-1,1-dicarboxylic acid* (**7**) as colourless crystals from water (0.3 g, 77%), m.p. 139—141 °C (lit.,[36] m.p. 140—141 °C); $\nu_{max.}$(KBr) 3 200—2 300, 1 710, 1 410, and 895 cm^{-1}; *2-methylcyclopropane-1,1-dicarboxylic acid* (**8**), as colourless crystals from benzene (0.35 g, 81%), m.p. 107—108.5 °C (lit.,[37] m.p. 113.5 °C); $\nu_{max.}$(KBr) 3 200—2 300, 1 715, 1 440, and 880 cm^{-1}.

Identification of Urea (**9**).—The formation of urea during the hydrolysis of (**1**) and (**2**) was confirmed by t.l.c. using a standard. Solvent system: chloroform–methanol (4:1); visualization: 1% *p*-(*N*,*N*-dimethylamino)benzaldehyde in concentrated HCl–ethanol (1:1).

5-(2-*Hydroxyethyl*)*barbituric Acid* (**5**).—The spirobarbiturate (**1**) (1.5 mmol) was hydrolysed with an equimolar amount of sodium hydroxide (7.5 ml of 0.1M aqueous solution) at 80 °C for 120 h. After cooling, the reaction mixture was acidified with concentrated HCl to pH 1 and extracted with ether (3 × 20 ml). The ether layer was evaporated and the precipitate was crystallized from water giving colourless microcrystals (0.2 g, 78%), m.p. 330 °C (decomp.) (lit.,[38] m.p. 300 °C), $\lambda_{max.}$ (pH 10.0) 268 nm ($\varepsilon_{max.}$ 19 800); $\nu_{max.}$(KBr) 3 850—2 950, 2 860, 1 710, 1 430, 1 380, 1 310, and 1 220 cm^{-1}.

Preparation of the 5-Monosubstituted Barbiturates (**6a**—**f**).—The spirobarbiturate (**2**) (0.4 g, 2.4 mmol) was added to water or an appropriate alcohol (50 ml), and the reaction mixture was refluxed for 6—8 h and the solvent evaporated to give 5-(2-*hydroxypropyl*)*barbituric acid* (**6a**) as colourless microcrystals from propan-2-ol–ethyl ether (1:1) (0.26 g, 58%), m.p. 174—176 °C (Found: C, 44.8; H, 5.5; N, 14.8. $C_7H_{10}N_2O_4$ requires C, 45.2; H, 5.4; N, 15.0%); $\lambda_{max.}$ (pH 10.0) 270 nm ($\varepsilon_{max.}$ 19 400); δ ($CDCl_3$–CF_3COOH) 1.45 (3 H, d, *Me*CHCH$_2$), 2.8 (2 H, d, MeCHC*H*$_2$), 3.7—4.1 (1 H, m, MeC*H*CH$_2$), and 5.5 (1 H, br s, OH); 5-(2-*methoxypropyl*)*barbituric acid* (**6b**), as colourless crystals from propan-2-ol (0.46 g, 96%), m.p. 170—173 °C (Found: C, 47.8; H, 6.0; N, 14.0. $C_8H_{12}N_2O_4$ requires C, 48.0; H, 6.0; N, 14.0%); $\lambda_{max.}$ (pH 10.0) 268 nm ($\varepsilon_{max.}$ 18 700); δ ($CDCl_3$–CF_3COOH) 1.25 (3 H, d, *Me*CHCH$_2$), 2.7 (2 H, d, MeCHC*H*$_2$), 3.5—4.0 (1 H, m, MeC*H*CH$_2$), and 3.5 (3 H, s, OMe); 5-(2-*ethoxypropyl*)*barbituric acid* (**6c**), as colourless crystals from propan-2-ol–ether (1:1) (0.48 g, 93%), m.p. 134—138 °C (Found: C, 50.2; H, 6.5; N, 13.1. $C_9H_{14}N_2O_4$ requires C, 50.5; H, 6.6; N, 13.1%); $\lambda_{max.}$ (pH 10.0) 269 nm ($\varepsilon_{max.}$ 16 400); δ ($CDCl_3$–CF_3COOH) 1.35 (3 H, d, *Me*CHCH$_2$), 2.75 (2 H, d, MeCHC*H*$_2$), 3.45—4.1 (1 H, m, MeC*H*CH$_2$), 3.75 (2 H, q, OC*H*$_2$Me), and 1.3 (3 H, t, OCH$_2$*Me*); 5-(2-*propoxypropyl*)-*barbituric acid* (**6d**), as colourless crystals from propanol–ether (1:1) (0.48 g, 88%), m.p. 145—148 °C (Found: C, 52.3; H, 7.2; N, 12.2. $C_{10}H_{16}N_2O_4$ requires C, 52.6; H, 7.1; N, 12.3%); $\lambda_{max.}$ (pH 10.0) 268 nm ($\varepsilon_{max.}$ 18 400); δ($CDCl_3$–CF_3COOH) 1.25 (3 H, d, *Me*CHCH$_2$), 2.8 (2 H, d, MeCHC*H*$_2$), 3.4—4.1 (3 H, m, MeC*H*CH$_2$ and OCH$_2$), 1.5—2.1 (2 H, m, C*H*$_2$Me), and 0.95 (3 H, t, CH$_2$*Me*), 5-(2-*butoxypropyl*)*barbituric acid* (**6e**), as colourless crystals from propan-2-ol (0.45 g, 77%), m.p. 143—145 °C (Found: C, 54.1; H, 7.6; N, 11.4. $C_{11}H_{18}N_2O_4$ requires C, 54.5; H, 7.5; N, 11.6%); $\lambda_{max.}$ (pH 10.0) 268 nm. ($\varepsilon_{max.}$ 12 800); δ($CDCl_3$–CF_3COOH) 1.25 (3 H, d, *Me*CHCH$_2$), 2.8 (2 H, d, MeCHC*H*$_2$), 3.35—4.2 (3 H, m, MeC*H*CH$_2$ and OCH$_2$), 1.4—1.9 (4 H, m, CH$_2$CH$_2$), and 0.95 (3 H, t, CH$_2$*Me*); 5-(2-*isopropoxypropyl*)*barbituric acid* (**6f**), as colourless crystals from propan-2-ol (0.52 g, 95%), m.p. 156—158 °C (Found: C, 52.4; H, 7.2; N, 12.2. $C_{10}H_{16}N_2O_4$ requires C, 52.6; H, 7.1; N, 12.3%); $\lambda_{max.}$ (pH 10.0) 269 nm ($\varepsilon_{max.}$ 18 800); δ($CDCl_3$–CF_3COOH) 1.3 (3 H, d, *Me*CHCH$_2$), 2.75 (2 H, d, MeCHC*H*$_2$), 3.8—4.35 (2 H, m, MeC*H*CH$_2$ and OCH=), and 1.2 (6 H, d, CH*Me*$_2$).

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References

1 Part 5. M. Paluchowska, L. Ekiert, K. Jochym, and J. Bojarski, *Pol. J. Chem.*, 1983, **57**, 799.
2 F. Fretwurst, *Arzneim.-Forsch.*, 1958, **8**, 44.
3 C. Stanier, J. Bosly, F. Dutrieux, and R. Stainier, *Acta Pharm. Helv.*, 1963, **38**, 587.
4 S. O. Eriksson and A. Holmgren, *Acta Pharm. Suec.*, 1965, **2**, 293.
5 S. O. Eriksson, *Acta Pharm. Suec.*, 1965, **2**, 305.
6 E. Gotto, T. Furukawa, and S. Goto, *Arch. Pract. Pharm.*, 1967, **27**, 311.
7 J. Knabe and H. Junginger, *Dtsch. Apoth.-Ztg.*, 1971, **111**, 1415.
8 E. R. Garrett, J. T. Bojarski, and G. J. Yakatan, *J. Pharm. Sci.*, 1971, **60**, 1145.
9 J. M. A. Sitsen and J. A. Fresen, *Pharm. Weekbl.*, 1974, **109**, 61.
10 J. Mokrosz and J. Bojarski, *Pol. J. Chem.*, 1982, **56**, 491.
11 R. H. McKeown and R. J. Prankerd, *J. Chem. Soc., Perkin Trans. 2*, 1981, 481.
12 R. H. McKeown, *J. Chem. Soc., Perkin Trans. 2*, 1980, 504.
13 R. H. McKeown, *J. Chem. Soc., Perkin Trans. 2*, 1980, 515.
14 D. A. Doornbos and R. A. de Zeeuw, *Pharm. Weekbl.*, 1969, **104**, 233.
15 D. A. Doornbos and R. A. de Zeeuw, *Pharm. Weekbl.*, 1971, **106**, 134.
16 J. M. A. Sitsen and J. A. Fresen, *Pharm. Weekbl.*, 1973, **108**, 1053.
17 J. Okada and T. Esaki, *Chem. Pharm. Bull.*, 1974, **22**, 1580.
18 F. I. Carroll and C. G. Moreland, *J. Chem. Soc., Perkin Trans. 2*, 1974, 374.
19 J. J. Burke and P. C. Lauterbur, *J. Am. Chem. Soc.*, 1964, **86**, 1870.
20 A. Fratiello, M. Mardirossian, and E. Chavez, *J. Magn. Reson.*, 1973, **12**, 221.
21 F. I. Carroll, A. Philip, and C. G. Moreland, *J. Med. Chem.*, 1976, **19**, 521.
22 S. Asada and J. Nishijo, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 3379.
23 H. W. Avdovich and G. A. Neville, *Can. J. Pharm. Sci.*, 1980, **15**, 75.
24 M. E. Krahl, *J. Phys. Chem.*, 1940, **44**, 449.
25 J. Shorter, 'Correlation Analysis of Organic Reactivity,' Research Studies Press, Chichester, New York, Brisbane, Toronto, Singapore, 1982.
26 M. Yu. Lukina, *Russ. Chem. Rev.*, 1962, **31**, 419.
27 M. T. Rogers and J. D. Roberts, *J. Am. Chem. Soc.*, 1946, **68**, 483.
28 M. T. Rogers, *J. Am. Chem. Soc.*, 1947, **69**, 2544.
29 A. D. Walsh, *Trans. Faraday Soc.*, 1949, **45**, 179.
30 R. W. Alder, R. Baker, and J. M. Brown, 'Mechanism in Organic Chemistry,' Wiley-Interscience, London, New York, Sydney, Toronto, 1971.
31 Ya. M. Slobodin and I. N. Shokhor, *Sb. Stat. Obsch. Khim.*, 1953, **2**, 850 (*Chem. Abstr.*, 1955, **49**, 6960c.)
32 J. L. Mokrosz, *Pharmazie*, 1985, **40**, 359.
33 A. W. Dox and H. Yoder, *J. Am. Chem. Soc.*, 1921, **43**, 677.
34 G. S. Skinner, G. Limperos, and R. H. Pettebone, *J. Am. Chem. Soc.*, 1950, **72**, 1648.
35 A. Albert and E. P. Serjeant, 'Ionozation Constants of Acids and Bases,' Methuen, London, 1967.
36 W. H. Perkin, *J. Chem. Soc.*, 1910, **47**, 817.
37 R. Marburg, *Ann.*, 1897, **294**, 89.
38 J. Johnson and W. Shepard, *J. Am. Chem. Soc.*, 1913, **35**, 994.

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