International Journal of Pharmaceutics, 3 (1979) 341–353

PRO-DRUGS AS DRUG DELIVERY SYSTEMS III. ESTERS OF MALONURIC ACIDS AS NOVEL PRO-DRUG TYPES FOR BARBITURIC ACIDS *

HANS BUNDGAARD, ANNE BAGGER HANSEN and CLAUS LARSEN

The Royal Danish School of Pharmacy, Department of Pharmaceutics, 2 Universitetsparken, DK-2100 Copenhagen (Denmark)

(Received March 6th, 1979)
(Revised version received April 3rd, 1979)
(Accepted April 26th, 1979)

SUMMARY

A series of malonuric acid esters were synthesized and evaluated as potential pro-drugs of barbituric acids. The esters were found to undergo a rapid and quantitative cyclization in neutral and alkaline aqueous solution to the corresponding barbituric acids by an intramolecular nucleophilic attack of the terminal ureido nitrogen anion on the ester carbonyl moiety. At pH 7.4 and 37°C the half-time of conversion is from 8 to 63 min for various methyl malonurates, suggesstting that malonuric acid esters are possible candidates as pro-drugs of their respective barbituric acids. Besides the kinetics of the cyclization, the L-octanol–water partition coefficients and aqueous solubilities of the esters were determined. It is proposed that by appropriate selection of the alcohol moiety of malonuric acid esters it may be feasible to obtain pro-drugs of barbiturates with varying physicochemical properties, such as lipophilicity and rate of cyclization, and hence to control and modify the delivery and overall activity characteristics of the parent drugs.

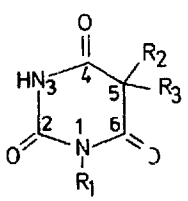
INTRODUCTION

Bioreversible derivatization of drug substances to produce compounds (pro-drugs) with altered and, with respect to delivery from the site of administration to the site of action within the body, enhanced physicochemical properties is a means by which substantial improvements in the overall efficacy of drugs often can be achieved (for recent reviews see Sinkula and Yalkowsky, 1975; Stella, 1975). Chemical transformation of active drug substances into per se inactive derivatives which convert to the parent compounds within

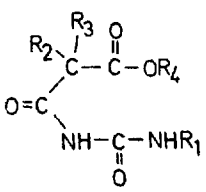
* Part 2 of this series: Bundgaard, H. and Larsen, C., Open-ring ester derivatives as novel pro-drug candidates of trimethadione. Arch. Pharm. Chem., Sci. Ed., 7 (1979) 41–50.

the body systems is a relatively simple task for drug substances possessing, for example, hydroxyl or carboxylic acid groups which are readily esterifiable in a bioreversible manner. For a large number of drugs, however, no apparently readily derivatizable functional groups or entities are present in the molecules.

A study was initiated to identify potentially useful transport forms of such not easily derivatizable drug molecules. To this category belong barbituric acids (I), for which no transient pro-drug forms have been described hitherto. We have found that esters of one of the hydrolysis products of barbituric acids, malonuric acids (II, R_4 = H) may be promising pro-drug candidates, since they are capable of undergoing a fast and quantitative cyclization to the respective barbituric acids at physiological conditions of pH and temperature. In a preliminary communication (Bundgaard et al., 1978) we have described the kinetics of cyclization of methyl 2,2-diethylmalonurate to barbital. In this paper the synthesis of a series of malonuric acid esters (III–XIV) (Table 1) is reported along with the kinetics of their cyclization to the corresponding barbituric acids (Table 2) and determinations of the lipophilicity and aqueous solubility (Table 3) of the pro-drug candidates and the parent drugs.



I



II

MATERIALS AND METHODS

(A) Apparatus

Ultraviolet spectra were recorded using a Perkin–Elmer Model 124 spectrophotometer and kinetic measurements were made on a Zeiss PMQ II spectrophotometer equipped with a thermostatically controlled cell compartment and a Servogor potentiometric recorder. One-cm quartz cells were used. PMR spectra were run on a JEOL C-60-HL instrument using tetramethylsilane as an internal standard and infrared spectra on a Unicam SP 200 spectrophotometer. Readings of pH were carried out on a Radiometer Type PHM 26 meter at the temperature of study. Melting points were taken on a capillary melting-point apparatus and are uncorrected. Thin-layer chromatography was done on precoated 0.25 mm silica gel 60 F_{254} glass plates (E. Merck, G.F.R.). Microanalysis was carried out by P. Hansen, Microanalytical Department of Chemical Laboratory II, University of Copenhagen.

(B) Synthesis

The malonuric acids (II, R_4 = H) of barbital, phenobarbital, allobarbital, aethallobarbital and hexobarbital were prepared by alkaline hydrolysis of the respective barbituric acids according to a previously described procedure (Aspelund and Skoglund, 1937) and were recrystallized from aqueous ethanol.

The methyl esters of the malonuric acids were prepared by esterification with diazomethane as follows. To a stirred suspension of 10 mmol of the malonuric acid in 50 ml of anhydrous ether were added 40 ml of an ethereal solution of diazomethane (prepared from 4.28 g (20 mmol) of N-methyl-N-nitroso-p-toluenesulfonamide). Immediate effervescence occurred, and stirring was continued for 15 min after complete addition. After destruction of excess diazomethane with formic acid the solution was evaporated to dryness under reduced pressure. The residue was recrystallized from ether–petroleum ether and after filtering the crystals were dried over phosphorous pentoxide in vacuo. Yields were from 75 to 90%.

The other malonuric acid esters investigated in this study were synthesized by alkylation of the triethylammonium salts of the acids in N,N-dimethylformamide with the appropriate alkyl halogenides (ethyl iodide, isopropyl iodide, benzyl bromide, chloromethyl methyl ether and methyl bromoacetate). To a solution of 5 mmol of the malonuric acid in 10 ml of N,N-dimethylformamide were added 5 mmol of triethylamine and 10 mmol of the alkyl or substituted alkyl halogenide. The solution was stirred at room temperature overnight, poured into 100 ml of water and then extracted with two 75-ml portions of ether. The combined ether extracts were washed with 50 ml of 2% sodium bicarbonate solution followed by 50 ml of water. After drying with anhydrous sodium sulphate the ether extract was evaporated under reduced pressure to give a white solid or, in some cases, an oily residue which crystallized during standing at 4°C for 1 or 2 days. After recrystallization from ether-petroleum ether or chloroform–petroleum ether the crystalline esters were dried over phosphorous pentoxide in vacuo. Yields ranged from 60 to 90%.

The melting points of the esters are listed in Table 1. Elemental analyses for C, H, and N and the PMR ($CDCl_3$) and IR (KBr) spectra were in agreement with the indicated structures [1].

(C) Kinetic measurements

All kinetic measurements were carried out in the thermostated cell compartment of the spectrophotometer at 24 and 37 ± 0.1°C using aqueous buffer solutions with a constant ionic strength of 0.5. The buffers used were phosphate (pH 6.5–7.4), borate (pH 8.4–9.5) and carbonate (pH 10.0–10.5) and, except in those experiments in which buffer effects were specifically investigated, the total concentration of the buffers was 0.1 M. The reactions were performed in 2.5 ml aliquot portions of buffer solution and were initiated by adding 25 μl of malonuric acid ester dissolved in acetonitrile to give a final concentration of about 10^{-4} M (pH > 8.3) or $3–10 \times 10^{-4}$ M (pH < 8). The reaction progress was followed spectrophotometrically by monitoring the formation of the corresponding barbituric acid at its λ_{max} (244 nm for hexobarbital, 238 nm for the other compounds). First-order rate constants were determined from plots of log $(A_\infty - A_t)$ versus time, where A_∞ and A_t are the absorbance readings at infinity and at time t, respectively. Rate constants for some slower reactions were determined by the method of Guggenheim (1926).

[1] These data are available upon request from the authors.

(D) Measurement of partition coefficients

The apparent partition coefficients (P) of the various malonuric acid esters and their parent barbituric acids were determined in a L-octanol–water system. The aqueous phase was 0.1 M sodium acetate buffer solution of pH 3.5. Exactly weighed quantities of the compounds were dissolved in a mixture of 20 ml of the aqueous phase previously saturated with L-octanol and 10 ml of L-octanol previously saturated with the aqueous phase. The initial concentrations of the compounds in the aqueous phase were $1-3 \times 10^{-3}$ M except for the ester VI where a concentration of about 10^{-2} M was used. The mixtures were shaken in stoppered flasks at 23°C for 1–2 h to achieve complete equilibration. After separation of the two phases the aqueous layer was centrifuged at 3000 rpm for 10 min. The solute concentrations in this phase were finally determined by appropriate dilution of an aliquot with 0.2 M borate buffer pH 10.2 and reading of absorbance of the dilution at 238 or 244 nm. For the malonurate esters the solutions were allowed to stand at room temperature (5–30 min depending on the ester) before reading of absorbance in order to get complete conversion to the corresponding barbituric acid. The concentration of the compounds was calculated from the measured absorbances by reference to standard curves obtained with the same borate buffer as solution medium. The partition coefficients were calculated from Eqn. 1:

$$P = \frac{C_o V_w}{C_w V_o} = \left(\frac{C_i - C_w}{C_w}\right) \frac{V_w}{V_o} \qquad (1)$$

where C and V represent the concentration and volume of the aqueous (subcript w) and organic (subscript o) phases, respectively, and C_i is the initial concentration in the aqueous phase. For each compound, determinations were carried out in triplicate, the log P values thereby obtained being reproducible to within ±2%.

(E) Solubility determinations

The solubility of the malonuric acid esters and the corresponding barbituric acids in a 0.1 M aqueous acetate buffer pH 3.5 was determined by placing 10–100 mg of the compounds in 10 ml of the buffer. The mixtures were rotated for 24 h (where equilibrium was reached) at constant temperature (23°C) and filtered. An aliquot of the filtrate was diluted with an appropriate amount of 0.02 M borate buffer pH 10.2, and the absorbance of the dilution read at 238 or 244 nm after a waiting period as described above. The concentration of the compounds in the saturated solutions was calculated from the measured absorbances and by reference to standard curves.

RESULTS AND DISCUSSION

Cyclization of malonuric acid esters to their respective barbituric acids

In neutral and basic aqueous solutions all the 12 esters prepared from 5 different malonuric acids (Table 1) were found to undergo cyclization to their respective barbituric acid derivatives. Taking the methyl ester of 2-ethyl-2-phenylmalonuric acid (IX) as an example this was demonstrated in the following ways. (a) Upon standing of aqueous solu-

TABLE 1

MALONURIC ACID ESTERS INVESTIGATED IN THIS STUDY WITH R_1, R_2, R_3 AND R_4 REFERRING TO THE GROUPS IN FORMULA II

Compound number	Chemical name	R_1	R_2	R_3	R_4	m.p. (°C)
III	Methyl 2,2-diethylmalonurate	H	C_2H_5	C_2H_5	CH_3	112 –113
IV	Ethyl 2,2-diethylmalonurate	H	C_2H_5	C_2H_5	C_2H_5	84.5– 85
V	Isopropyl 2,2-diethylmalonurate	H	C_2H_5	C_2H_5	$(CH_3)_2CH$	99.5–100
VI	Benzyl 2,2-diethylmalonurate	H	C_2H_5	C_2H_5	$C_6H_5CH_2$	107 –108
VII	Methoxymethyl 2,2-diethylmalonurate	H	C_2H_5	C_2H_5	CH_3OCH_2	113 –113.5
VIII	Methoxycarbonylmethyl 2,2-diethylmalonurate	H	C_2H_5	C_2H_5	CH_3OOCCH_2	89 – 89.5
IX	Methyl 2-ethyl-2-phenylmalonurate	H	C_2H_5	C_6H_5	CH_3	105
X	Methyl 2,2-diallylmalonurate	H	CH_2=$CHCH_2$	CH_2=$CHCH_2$	CH_3	84 – 84.5
XI	Methyl 2-ethyl-2-allylmalonurate	H	C_2H_5	CH_2=$CHCH_2$	CH_3	78.5– 79
XII	Methyl 2-methyl-2-cyclohexenyl-6-methylmalonurate	CH_3	CH_3	C_6H_9	CH_3	94 – 94.5
XIII	Ethyl 2-methyl-2-cyclohexenyl-6-methylmalonurate	CH_3	CH_3	C_6H_9	C_2H_5	97.5– 98
XIV	Methoxymethyl 2-methyl-2-cyclohexenyl-6-methylmalonurate	CH_3	CH_3	C_6H_9	CH_3OCH_2	73 – 73.5

tions (pH 7–11) of IX ($1–5 \times 10^{-4}$ M) an absorption band with maximum at 238 nm developed, more rapidly the higher the pH. The final ultraviolet spectrum superimposed that of phenobarbital and showed the same changes in peak intensity with varying pH as the barbituric acid (due to its ionization and the different absorptivities of the ionized and unionized forms). (b) A 50 mg quantity of IX was added to 100 ml of 0.1 M borate buffer (pH 9.2) and the mixture kept at 37°C for 1 h under continuous shaking. The solution was then acidified with 2 M hydrochloric acid to pH 5 and extracted with two 25-ml portions of ether. The combined ether extracts were dried over anhydrous sodium sulphate and evaporated to dryness. The melting point (172–174°C) of the residue was found to be identical to that of phenobarbital, and also the IR spectrum obtained (in KBr) of the residue was the same as that of phenobarbital.

Kinetics and mechanism of the cyclizations

The kinetics of the ring closure of the esters III–XIV to their respective barbituric acids was studied in the pH range 6.5–10.5 and at temperatures of 24 and 37°C. At constant pH and temperature the reactions displayed good first-order kinetics over more than 3 half-lives, and in all kinetic runs the barbituric acids were formed in quantitative amounts, as determined from the final absorptions at 238 nm (or at 244 nm for the esters XII–XIV). In the pH range investigated, the observed pseudo-first-order rate constants

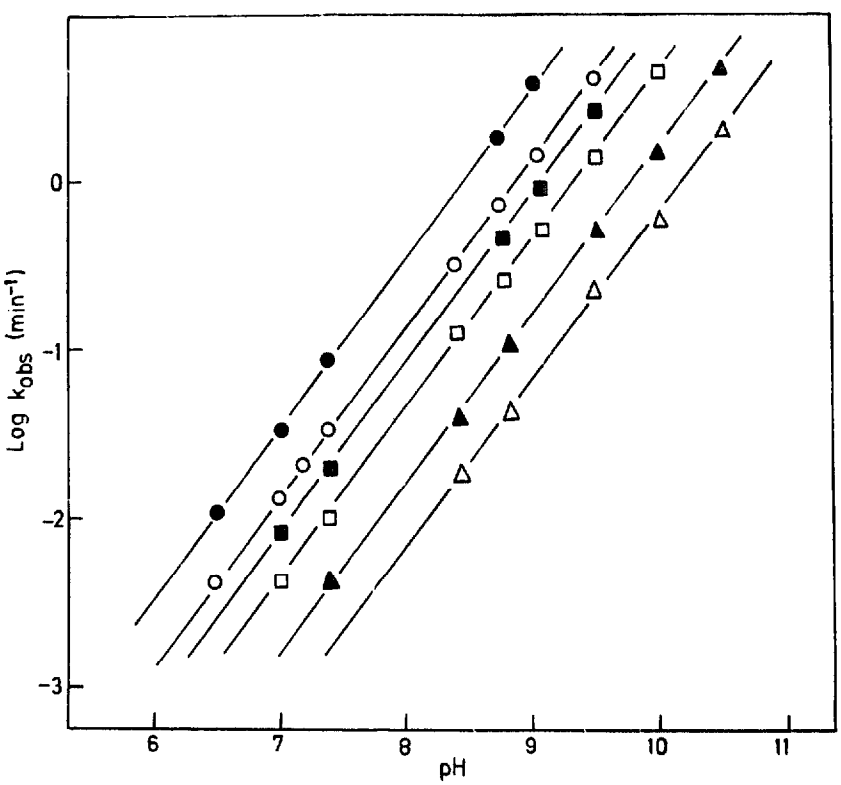


Fig. 1. pH–rate profiles for the cyclization of various malonuric acid esters to their respective barbituric acids in aqueous solutions (μ = 0.5) at 37°C. Key: ●, X; ○, III; ■, IX; □, XII; ▲, XIII; △, V.

(k_{obs}) were found to be directly proportional to the hydroxide ion activity as demonstrated for some of the esters in Fig. 1 in which log k_{obs} has been plotted against pH. The plots are linear with slopes of 1.0, suggesting that the reactions are first-order dependent on hydroxide ions and that Eqn. 2 is valid:

$$k_{obs} = k_1 a_{OH} \quad (2)$$

where a_{OH} refers to the hydroxide ion activity. This was calculated from the measured pH according to the following equations (Harned and Hamer, 1933):

$$a_{OH} = 10^{(pH - 14.03)} \ (24°C) \quad (3)$$

$$a_{OH} = 10^{(pH - 13.62)} \ (37°C) \quad (4)$$

The values of the second-order rate constants, k_1, for the apparently specific base-catalyzed cyclization of the various esters are given in Table 2 together with half-times for the reactions at pH 7.4 at 37 and 24°C.

The rate of cyclization was for all esters found to be independent of buffer concentration from 0.02 to 0.2 M at constant ionic strength, and thus no general acid–base catalysis appears to be involved.

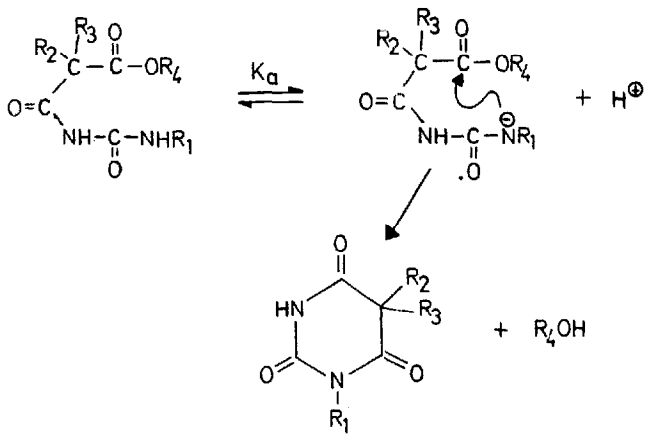
TABLE 2

SECOND-ORDER RATE CONSTANTS FOR THE APPARENT SPECIFIC BASE-CATALYZED CYCLIZATION OF ESTERS III–XIV TO THEIR RESPECTIVE BARBITURIC ACIDS IN AQUEOUS SOLUTION (μ = 0.5) AT 37 AND 24°C AND HALF-TIMES FOR THE CYCLIZATION AT pH 7.40 (μ = 0.5)

Ester	37°C		24°C	
	$k_1 \times 10^{-4}$ (M^{-1} min^{-1})	$t_{1/2}$ [a] (min)	$k_1 \times 10^{-4}$ (M^{-1} min^{-1})	$t_{1/2}$ [a] (min)
III	5.5	21	2.5	120
IV	2.3	50	1.0	300
V	0.29	395	0.12	2480
VI	4.4	26	1.8	1650
VII	8.5	14	3.8	80
VIII	10.2	11	5.1	60
IX	3.7	32	1.4	210
X	14.6	8	6.6	45
XI	9.5	12	3.8	80
XII	1.9	63	1.0	300
XIII	0.68	170	0.31	960
XIV	2.4	48	1.0	300

[a] At pH 7.40. The figures were calculated from Eqn. 2 and the experimentally determined values of k_1. Some values obtained experimentally in 0.1 M phosphate buffer solutions agreed within ±10% with the calculated ones.

The results obtained can be rationalized in terms of a kinetic scheme in which the ring closure proceeds through an intramolecular nucleophilic attack of the ureido nitrogen anion upon the ester carbonyl moiety (Scheme 1). The first-order dependence on



Scheme 1

hydroxide ion activity is consistent with the active nucleophile in the attack being the ureido nitrogen anion. Since the plots of log k_{obs} against pH over the pH range studied are linear and do not tend to plateau at low pH, reactions involving participation by the neutral ureido group are not involved under these pH conditions. The lack of general acid–base catalysis also indicates that the cyclizations proceed via pre-equilibrium ionization of the ureido group as depicted in Scheme 1. The pK_a value of the ureido group in the malonurates might be expected to be greater than 14 (Hegarty and Bruice, 1970), which agrees with the observed linearity between k_{obs} and a_{OH} up to pH 10.5. According to the suggested mechanism, Eqn. 2 should be written as (for $a_H >> K_a$):

$$k_{obs} = k_1' \cdot \frac{K_a}{a_H} \tag{5}$$

where K_a refers to the ionization constants of the ureido groups, a_H is the hydrogen ion activity, and k_1' represents a first-order rate constant for the intramolecular attack of the ionized ureido group on the ester carbonyl moiety. As K_a was not determinable, k_1' cannot be calculated.

Several precedents exist of intramolecular nucleophilic displacement reactions by ureido groups at the carbonyl moiety of esters and amides. Thus, various esters of o-ureidobenzoic acid have been described to undergo an apparently specific base-catalyzed cyclization to quinazolines (Hegarty and Bruice, 1970) and 6-(N-phenylureido)penicillanic acids to the corresponding 3-phenylhydantoin-thiazolidines (Bundgaard, 1973). Similarly, formation of hydantoins from alkyl esters of the corresponding hydantoic acids has been observed in neutral and alkaline aqueous solutions (Stella and Higuchi, 1973).

Malonuric acids have previously been reported to be capable of undergoing a reversible cyclization to the corresponding barbituric acids in aqueous solutions. Thus, Aspelund (1969) has described the cyclization of malonuric acids derived from 1,3,5,5-tetrasub-

stituted barbituric acids and the formation of barbital (Garrett et al., 1971), butalbital (Maulding et al., 1972) and thiobarbital (Bojarski, 1974) from the respective malonuric acids in alkaline solutions has been reported. With the exception of the tetrasubstituted derivatives these reactions are very slow and do not proceed in a quantitative fashion. As expected the cyclization of malonuric acid esters as demonstrated herein is much more efficient, which can be ascribed to the better leavability of alkoxide ions compared to O^{2-} and possibly also to the electrostatic barrier to attack by an ureido anion upon a carboxylate anion apparently involved in the reaction of the malonuric acids.

Influence of substituents on cyclization rate

As appears from Table 2, the various esters differ in their rates of cyclization to the corresponding barbituric acids. The relatively small influence on the reactivity of C-2 substituents in the malonurates studied can be seen by comparing the rate data for the methyl esters III, IX, X and XI. Compared with ethyl groups in the C-2 position a phenyl substituent leads to a lower reactivity whereas allyl substituents increase the cyclization rate. This may possibly be ascribed to the difference in steric effects of these groups. The least reactive of the methyl esters studied is compound XII in which the terminal ureido group is N-methylated.

The influence of variation in the alkyl portion of the esters on the rate of ring closure appears to be similar to that found in other nucleophilic reactions as, for example, alkaline hydrolysis, and thus be controlled by polar and steric effects. By comparing the rate data for the 2,2-diethylmalonuric acid esters III–VIII it is seen that the order of reactivity relative to that of methylester is 1.85 ($-CH_2COOCH_3$), 1.55 ($-CH_2OCH_3$), 1 ($-CH_3$), 0.80 ($-CH_2C_6H_5$), 0.42 ($-C_2H_5$) and 0.053 ($i-C_3H_7$). For the alkaline hydrolysis of 3,5-dinitrobenzoate esters with some of the same alcohols the relative rates are 1 ($-CH_3$), 0.74 ($-CH_2C_6H_5$), 0.35 ($-C_2H_5$) and 0.071 ($i-C_3H_7$) (Robinson, 1967). Thus, the effect of variation in the alcohol portion of the malonurate esters on the rate of intramolecular cyclization is seen to parallel closely the effect on alkaline ester hydrolysis. On the basis of the vast amount of data on substituent effects in alkaline hydrolysis of esters (e.g. Robinson, 1967; Washkuhn et al., 1971) it may therefore be possible to predict with some confidence the cyclization rate of a given malonuric acid ester.

Influence of serum on cyclization

For the evaluation of the malonuric acid esters as being potential pro-drugs of barbituric acids it is important to ascertain whether serum enzymes would be able to hydrolyze the ester linkage at such a rate that the ring closure reaction would be seriously ousted. This possibility was investigated for the methyl ester derivatives III and XI. The compounds (10 mg) were incubated in a phosphate buffer pH 7.4 containing 75% human serum at 37°C. After 3 h in which the reactions had gone to completion, the solutions were acidified to pH 3 and extracted with chloroform. The dried extracts were evaporated to dryness in vacuo and after dissolution in methanol the residue was subjected to TLC analysis as previously described (Bundgaard et al., 1978). The analysis revealed the formation, respectively, of barbital and ethallobarbital, and no indication of

the formation of the corresponding malonuric acids was obtained. These acids, which would have been the products of an enzymatic hydrolysis of the esters, were in separate experiments shown to be unable to cyclize to barbituric acid under the experimental conditions or in aqueous acidic solutions. It appears, therefore, that under physiological conditions of pH and temperature the spontaneous cyclization of these malonuric acid esters proceeds much more rapidly than a possible enzymatic hydrolysis of the ester group. For certain other esters, however, enzymatic hydrolysis may be of significance and compete with the intramolecular cyclization.

The lipophilicity and solubility of barbituric acids and their pro-drugs

Apparent partition coefficients for the various esters and the corresponding barbituric acids were measured using the widely used L-octanol–water system. In order to prevent cyclization of the esters during the measurements an acetate buffer of pH 3.5 was used as the aqueous phase instead of water or a buffer of pH 7.4. Since the esters are neutral the same results should be expected with an aqueous phase of pH 7.4. The values found for log P and the molar solubilities in aqueous acetate buffer of pH 3.5 are listed in Tables 3 and 4. The log P values for barbital and phenobarbital are identical to those determined by Hansch and Anderson (1967) in a L-octanol–water system, and for the other barbituric acids the experimentally determined log P values agree with calculated values (Hansch and Anderson, 1967; Hansch et al., 1968b; Leo et al., 1971).

The results obtained show that the malonuric acid esters studied are all more lipophilic than the parent barbituric acids. For the methyl esters the increase in log P amounts to about 0.3 except for phenobarbital where the difference between log P (methyl ester) and log P (phenobarbital) is only 0.17. Compared with the methyl esters the log P values

TABLE 3

PARTITION COEFFICIENTS AND AQUEOUS SOLUBILITIES OF MALONURIC ACID ESTERS

Ester	log P [a]	$S \times 10^3$ [b] (M)
III	0.95	11
IV	1.45	8.4
V	1.99	1.7
VI	2.74	0.22
VII	1.00	6.8
VIII	0.99	9.7
IX	1.58	1.8
X	1.37	6.8
XI	1.19	12
XII	1.75	2.1
XIII	2.25	1.0
XIV	1.80	3.8

[a] Between L-octanol and 0.1 M acetate buffer solution pH 3.5 at 23°C.
[b] The molar solubility in 0.1 M acetate buffer solution pH 3.5 at 23°C.

TABLE 4

PARTITION COEFFICIENTS AND AQUEOUS SOLUBILITIES OF BARBITURIC ACIDS

Barbituric acid	log P [a]	S x 10^3 [b] (M)
Barbital (I, R_1 = H; R_2 = R_3 = ethyl)	0.66	37
Phenobarbital (I, R_1 = H; R_2 = ethyl; R_3 = phenyl)	1.41	4.6
Ethallobarbital (I, R_1 = H; R_2 = ethyl; R_3 = allyl)	0.83	26
Allobarbital (I, R_1 = H; R_2 = R_3 = allyl)	1.08	8.5
Hexobarbital (I, R_1 = R_2 = methyl; R_3 = cyclohexenyl)	1.45	2.2

[a] Between L-octanol and 0.1 M acetate buffer solution pH 3.5 at 23°C.
[b] The molar solubility in 0.1 M acetate buffer solution pH 3.5 at 23°C.

for the other esters are in excellent agreement with values calculated on basis of π substituent values (Leo et al., 1971). For example, on going from the methyl esters III and XII to the corresponding ethyl esters IV and XIII log P increases with 0.50, which is equal to π for a methylene group. Similarly, the difference in log P between VI and III (1.79) is identical to π for the phenyl group (1.77).

An increase in lipophilicity is generally accompanied by a decrease in water solubility. In Fig. 2 the logarithm of the molar aqueous solubilities (S) of the various compounds

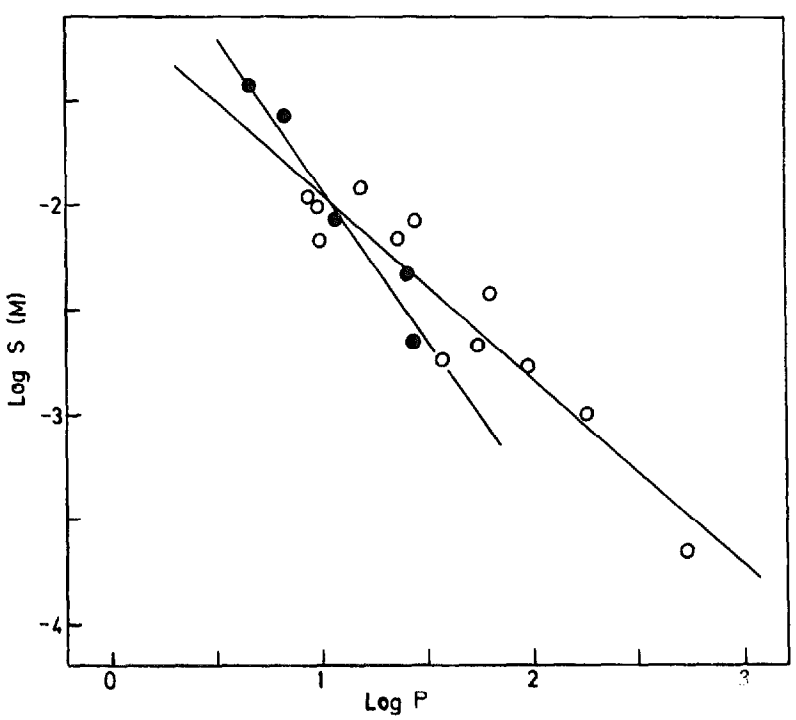


Fig. 2. Plots of the logarithm of the molar aqueous solubility (S) versus log P for the malonuric acid esters (○) and barbituric acids (●) investigated in this study.

has been plotted against log P. The regression equations between log S and log P for the esters and the barbituric acids are given by Eqns. 6 and 7:

$$\log S = -(0.89 \pm 0.10) \log P - (1.05 \pm 0.17) \text{ (esters III–XIV)} \quad (6)$$

$$\log S = -(1.44 \pm 0.17) \log P - (0.45 \pm 0.19) \text{ (barbituric acids)} \quad (7)$$

The coefficients of log P are in the same range as that (1.34) obtained by Hansch et al. (1968a) for a large number of different liquids. In the above equations a term for melting point (cf. Yalkowsky, 1977) was not included, because within the two sets of compounds the melting points do not differ appreciably. On basis of Eqn. 6 and from values of log P nated on the basis of the additive substituent principle, it may be possible to predict approximate aqueous solubilities of barbituric acid pro-drugs.

The hypnotic acitivity of a large number of 5-substituted barbituric acids has been reported to depend amlost entirely on their lipophilic character as defined by their L-octanol–water partition coefficients, the activity increasing with log P up to a value of about 2 (Hansch et al., 1968b). Also, the ability of barbiturates to inhibit various biochemical reactions has been shown to depend strongly on the lipophilicity (Hansch and Anderson, 1967) and, further, in situ gastric absorption rates of barbiturates were demonstrated to depend significantly on the lipophilic properties as expressed by partition coefficients (Kakemi et al., 1967; Plá-Delfina et al., 1975). Consequently, the delivery and activity characteristics of barbiturates can to a great extent be controlled by variation in the lipophilicity. In practice, this can be done and has been done by changing the 5-substituents giving new analogues. This study shows, however, that the same may be achieved by making use of the pro-drug concept and thus permitting control of the physicochemical properties, and hence the delivery, pharmacokinetic and activity characteristics, of a given barbituric acid derivative.

REFERENCES

Aspelund, H., Einwirkung von Alkali auf einige 1,3,5,5-tetrasubstituierte Barbitursäuren. Acta Acad. Aboensis Math. Phys., Ser. B, 29 (1969) 1–13.

Aspelund, H. und Skoglund, L., Die Beständigkeit der Natriumsalze einiger Schlafmittel der Barbitursäure-Reihe in Lösung. Acta Acad. Aboensis Math. Phys., 10 (1937) 1–22.

Bojarski, J., Hydrolysis of barbituric acid derivatives. Part II. Hydrolysis of thiobarbital. Roczn. Chem., 48 (1974) 619–626.

Bundgaard, H., Intramolecular nucleophilic attack of an ureido group on the β-lactam carbonyl moiety of penicillins. Acta Pharm. Suec., 10 (1973) 309–316.

Bundgaard, H., Hansen, A.B. and Larsen, C., Pro-drugs as drug delivery systems. I. Esters of malonuric acids as novel pro-drug candidates of barbituric acids. Arch. Pharm. Chem., Sci. Ed., 6 (1978) 231–240.

Garrett, E.R., Bojarski, J.T. and Yakatan, G.J., Kinetics of hydrolysis of barbituric acid derivatives. J. Pharm. Sci., 60 (1971) 1145–1154.

Guggenheim, E.A., On the determination of the velocity constant of a unimolecular reaction. Phil. Mag., 2 (1926) 538–543.

Hansch, C. and Anderson, S.M., The structure–activity relationship in barbiturates and its similarity to that in other narcotics. J. Med. Chem., 10 (1967) 745–753.

Hansch, C., Quinlan, J.E. and Lawrence, G.L., The linear free-energy relationship between partition coefficients and the aqueous solubility of organic liquids. J. Org. Chem., 33 (1968a) 347–350.

Hansch, C., Steward, A.R., Anderson, S.M. and Bentley, D., The parabolic dependence of drug action upon lipophilic character as revealed by a study of hypnotics. J. Med. Chem., 11 (1968b) 1–11.

Harned, H.S. and Hamer, W.J., The ionization constant of water and the dissociation of water in potassium chloride solutions from electromotive forces of cells without liquid junction. J. Am. Chem. Soc., 55 (1933) 2194–2206.

Hegarty, A.F. and Bruice, T.C., Acyl transfer reactions from and to the ureido functional group. III. The mechanism of intramolecular nucleophilic attack of the ureido functional group upon acyl groups. J. Am. Chem. Soc., 92 (1970) 6575–6588.

Kakemi, K., Arita, T., Hori, R. and Konishi, R., Absorption and excretion of drugs. XXX. Absorption of barbituric acid derivatives from rat stomach. Chem. Pharm. Bull., 15 (1967) 1534–1539.

Leo, A., Hansch, C. and Elkins, D., Partition coefficients and their uses. Chem. Rev., 71 (1971) 525–616.

Maulding, H.V., Nazareno, J., Polesuk, J. and Michaelis, A., Investigations of hydrolytic products of butalbital. J. Pharm. Sci., 61 (1972) 1389–1393.

Plá-Delfina, J.M., Morena, J., Durán, J. and del Pozo, A., Calculation of the gastric absorption rate constants of 5-substituted barbiturates through the R_m values or substituent $\triangle R_m$ constants in reversed-phase partition chromatography. J. Pharmacokin. Biopharm., 3 (1975) 115–141.

Robinson, J.R., Identification of alcohols from rates of alkaline hydrolysis of their 3,5-dinitrobenzoate esters. Anal. Chem., 39 (1967) 1178–1180.

Sinkula, A.A. and Yalkowsky, S.H., Rationale for design of biologically reversible drug derivatives: prodrugs. J. Pharm. Sci., 64 (1975) 181–210.

Stella, V., Pro-drugs: an overview and definition. In Higuchi, T. and Stella, V. (Eds.), Pro-Drugs as Novel Drug Delivery Systems, American Chemical Society, Washington, D.C., 1975, pp. 1–115.

Stella, V. and Higuchi, T., Esters of hydantoic acids as prodrugs of hydantoins. J. Pharm. Sci, 62 (1973) 962–967.

Washkuhn, R.J., Patel, V.K. and Robinson, J.R., Linear free energy models for ester solvolysis with a critical examination of the alcohol and phenol dissociation model. J. Pharm. Sci., 60 (1971) 736–744.

Yalkowsky, S.H., Solubility and melting point considerations in drug design. In Roche, E.B. (Ed.), Design of Biopharmaceutical Properties through Prodrugs and Analogs, American Pharmaceutical Association, Washington, D.C., 1977, pp. 392–408.