Surfactant–Base–Barbiturate Suppositories I

Rectal Absorption in Rabbits

By J. H. FINCHER, D. N. ENTREKIN, and C. W. HARTMAN

A series of petrolatum–paraffin–surfactant suppository bases were tested in rabbits under carefully controlled conditions with a series of barbiturates included. Each surfactant had a different HLB value and each barbiturate had a different distribution coefficient. The depression of the respiratory rate was measured for a period of 2.5 hr. to determine absorption rates. A comparative analysis of the data is presented. The effects of the chemical type of the drug and the surfactant are shown in the comparative studies. Surfactants enhanced the release and absorption of the barbiturate in some bases; however, binding of the drug is suspected in some bases. The relationships of the HLB of the surfactant and the distribution coefficient of the drug to release and absorption are presented. Further work, using different approaches to this problem, is indicated.

THE PRIMARY purpose of this work was to investigate the relationship of some of the physicochemical properties of the drug and the base on the efficacy of base–drug suppository formulations *in vivo*.

The hydrophile–lipophile balance (HLB), as a system of classifying and evaluating surfactants, was proposed and expanded by Griffin (1, 2). The effect of this property has been studied *in vitro* by Spittle and Hartman (3) and Rhyne *et al.* (4). Base composition has been long recognized as having an influence on the therapeutic activity of base–drug combinations (5–9). Emulsification of the base has been shown to effect drug release by many researchers (10–19). Others have shown that the chemical type of the ingredients in a formulation influences the desired clinical response (1, 2, 20). Other factors that have been considered are the distribution coefficient of the drug between the base and body fluids and the pKa of the drug (21–25). While some of the research cited above was conducted *in vivo*, the greater portion was conducted *in vitro*. The need for studies on animals is apparent. For this reason a series of 8 barbiturates were evaluated in a series of petrolatum–paraffin–surfactant suppository bases differing with respect to the emulsifiers which had different HLB values. Since each barbiturate was evaluated under the same conditions, a comparison could be made. A suppository formulation containing an emulsifier and medicament when placed in the rectum produces a complex system indeed. However, it is felt that such a comparative study as described above will reveal some of the major factors to consider when conducting further research intended to place drug diffusion, release, and absorption on a predictable basis.

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EXPERIMENTAL

Preparation of Bases.—Bases were prepared utilizing white petrolatum, white paraffin, polyethylene glycol (PEG), and surfactants. Surfactants with established HLB values (1, 2) were added to obtain a concentration of 10% by weight in each base. To produce anhydrous bases all materials except the emulsifiers were dried to constant weight. The consistency of all bases was standardized by varying the proportion of petrolatum and paraffin, or in the case of the PEG, by varying the proportion of PEGs of different molecular weights. The standard consistency selected was a penetration depth of 60 mm. (±6 mm.), when tested by the U.S.P. method at 25°.

Ten per cent by weight of surfactant was incorporated by fusion methods into lots of petrolatum and paraffin. Portions of these two emulsifier–base mixtures were then combined by trial and error to obtain the desired consistency. An HLB value of 0 was represented by using only petrolatum and paraffin as a base, and a water-soluble base was represented by use of a mixture of PEGs. Base composition and properties are shown in Table I. Table II gives a list of the barbiturates and their chemical properties. Several days before the time of the *in vivo* experiments the barbiturate was incorporated into the various bases using a glass mortar and pestle. The bases were stored in a temperature controlled room (21–23°) until the time of the experiments.

In Vivo Experimental Procedure.—The experimental animals were New Zealand white male rabbits weighing 1.5 to 2.3 Kg.

Seven to ten rabbits were used for each suppository base–barbiturate combination. One rabbit receiving the PEG base plus the drug and one rabbit receiving the petrolatum–paraffin base plus the drug were used as controls. All bases contained 0.0008 mole of the barbiturate per Gm. of suppository, thus regulating the concentration so that 1 Gm. of base would provide a dose of (0.0004 mole/Kg. body weight) for a rabbit weighing 2 Kg. This dose would be lethal to the rabbit if it were available for complete absorption in a short period of time.

A plastic injector having a tube length of 6.35 cm.

TABLE I.—COMPOSITION AND PROPERTIES OF SUPPOSITORY BASES[a]

Base No.	Ingredients	% by Wt.	Consistency in mm. Penetration	HLB Value of the Surfactant
I	Petrolatum	70.0		Approx. zero
	Paraffin (hard)	30.0	59.4	
II	Sorbitan trioleate[b]	10.0		1.8
	Petrolatum	59.4		
	Paraffin (medium)	30.6	62.4	
III	Sorbitan monolaurate[b]	10.0		8.6
	Petrolatum	59.4		
	Paraffin (hard)	30.6	59.1	
IV	Polyoxycthylene sorbitan tristearate[b]	10.0		10.5
	Petrolatum	61.2		
	Paraffin (hard)	28.8	58.5	
V	Polyoxyethylene sorbitan monolaurate[b]	10.0		16.7
	Petrolatum	59.4		
	Paraffin (hard)	30.6	62.8	
VI	Polyoxyethylene lauryl ether[b]	10.0		16.9
	Petrolatum	58.5		
	Paraffin (medium)	31.5	63.2	
VII	Polyoxycthylene monostearate[b]	10.0		17.9
	Petrolatum	59.0		
	Paraffin (medium)	31.0	58.0	
VIII	Polycthylene glycol 1500	98.2		Water soluble
	Polycthylene glycol 4000	1.8	66.8	

[a] Barbiturates were added to these bases. [b] Supplied by Atlas Chemical Co., Wilmington, Del.

TABLE II.—pKa AND DISTRIBUTION COEFFICIENTS[a,b] OF BARBITURATES

Barbiturate			Distribution
Generic Name	Chemical Name	pKa	Coefficient
Allylbarbituric acid	5-Allyl-5-iso-butyl BA[c]	7.86	10.5
Butethal[d]	5-Butyl-5-ethyl BA[c]	8.10	11.7
Pentobarbital	5-Ethyl-5-(1-methyl-butyl) BA	8.17	28.0
Aprobarbital	5-Allyl-5-iso-propyl BA	7.54	4.8
Secobarbital	5-Allyl-5-(1-methyl-butyl) BA		50.0

[a] From *Reference 21.* [b] Chloroform to water. [c] BA, barbituric acid. [d] Supplied by Abbott Laboratories.

and a diameter of 0.63 cm. was used to inject the suppository into the rectum.

All the rabbits used in a given experiment were fasted for 12 to 13 hr. before the time of the studies to render the rectum free of excess fecal matter and bladder free of excess urine. Fasting was begun at 7:30 p.m. (±30 min.) and each experiment was begun at 9:30 a.m. (±30 min.), thus keeping the time of day reasonably uniform. The rabbits were weighed, marked, and tied to a rabbit board (47.0 × 73.7 cm.) at least 45 min. before the injection of the suppository.

After weighing each injector an excess of the base–barbiturate mixture was molded directly into the injector and the exact calculated dose was adjusted by trial and error weighings.

The injector containing the base was then inserted into the rectum 1.3 cm. (indicated by a mark on the plastic tube) using no lubricant except the base itself. The plunger was then used to eject the suppository from the injector into the rectum. Polishing the sharp edge of the injector closed the end just enough to prevent the insertion of the plunger beyond this point, thus geometrically placing the suppository 1.3 cm. into the rectum as measured from the caudal end of the suppository. To prevent expulsion of the suppository a rubber hose clamp was used to hold the anus closed. Each animal was used only one time.

The barbiturates were released from the bases in sufficient quantity to cause marked changes in the respiratory rate. Administration of varying amounts of sodium pentobarbital by intravenous injection showed the change of respiration rate with a change of the dose (Fig. 1).

After administration of the suppository, the respiratory rate per minute was measured at time intervals ranging from 2 to 30 min., depending on the rate of change. Measurement of the respiratory rate was accomplished using a stopwatch and visually counting chest expansions. The respiratory counts were continued through a minimum period of 2.5 hr.

A constant time interval between 50 and 60 min. after rectal administration was arbitrarily selected as the end point for the comparative studies. The lowest respiratory rate within this interval for each

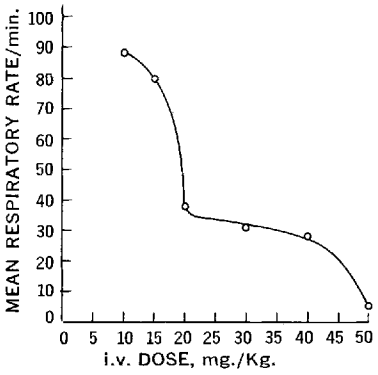

Fig. 1.—Mean respiratory rate as a function of i.v. dose of sodium pentobarbital 10 min. after administration to rabbits

TABLE III.—MEAN RESPIRATORY RATES AND RESULTS OF ERROR CALCULATIONS DETERMINED BETWEEN 50 AND 60 min. AFTER RECTAL ADMINISTRATION OF VARIOUS BASE–BARBITURATE COMBINATIONS TO RABBITS

Base[a]	Barbiturate	Mean Respiratory Rate, 1 min.	Animals, No.	$\pm\sigma m$[b]
I	Pentobarbital	100.3	4	9.8
	Sodium pentobarbital	50.7	3	10.9
	Calcium pentobarbital	105.4	5	15.5
	Butethal	110.0	9	5.5
	Secobarbital	98.5	6	7.2
	Allylbarbituric acid	108.0	8	7.1
	Aprobarbital	97.7	7	14.2
II	Pentobarbital	92.5	7	7.9
	Sodium pentobarbital	18.0	2	6.0
	Calcium pentobarbital	49.6	7	3.2
	Butethal	54.5	8	4.0
	Secobarbital	40.0	8	2.6
	Allylbarbituric acid	50.4	7	3.8
	Aprobarbital	43.3	8	2.5
III	Pentobarbital	128.8	7	17.73
	Sodium pentobarbital	106.9	2	6.0
	Calcium pentobarbital	96.8	7	15.35
	Butethal	97.0	6	12.4
	Secobarbital	71.3	7	5.8
	Allylbarbituric acid	77.3	8	9.8
	Aprobarbital	93.3	8	8.2
IV	Pentobarbital	105.1	7	11.9
	Sodium pentobarbital	64.0	3	7.4
	Calcium pentobarbital	64.1	7	8.5
	Butethal	128.8	6	6.7
	Secobarbital	65.5	8	5.7
	Allylbarbituric acid	99.4	8	8.1
	Aprobarbital	75.4	8	4.4
V	Pentobarbital	94.8	8	9.9
	Sodium pentobarbital	54.0	2	10.0
	Calcium pentobarbital	64.2	6	8.6
	Butethal	111.1	7	6.3
	Secobarbital	87.9	8	8.2
	Allylbarbituric acid	79.8	6	10.7
	Aprobarbital	80.3	7	16.9
VI	Pentobarbital	98.3	7	9.1
	Sodium pentobarbital	59.0	2	5.0
	Calcium pentobarbital	62.8	8	8.6
	Butethal	49.4	10	5.0
	Secobarbital	30.9	9	6.1
	Allylbarbituric acid	98.4	9	8.0
	Aprobarbital	66.8	8	6.53
VII	Pentobarbital	69.3	7	9.4
	Sodium pentobarbital	33.6	5	2.3
	Calcium pentobarbital	61.9	7	7.7
	Butethal	84.9	10	7.2
	Secobarbital	45.1	7	5.0
	Allylbarbituric acid	62.6	9	5.3
	Aprobarbital	47.8	10	4.2
VIII	Pentobarbital	14.3	4	3.9
	Sodium pentobarbital	0	6	0
	Calcium pentobarbital	0	6	0
	Butethal	32.4	8	2.8
	Secobarbital	23.4	7	6.0
	Allylbarbituric acid	37.3	8	3.3
	Aprobarbital	15.8	8	2.8

[a] See Table I for composition. [b] σm = standard error of the mean.

of the animals tested with a given base–drug formulation was used to evaluate the base. The mean respiratory rate was calculated, and from this the individual standard errors of the mean (σm) were determined. Appropriate t tests were performed for the data where quantitative comparisons of data are presented (26).

RESULTS AND DISCUSSION

The comparative results of the surfactant–base–barbiturate studies are summarized in Table III. The availability of pentobarbital is much less than that of calcium and sodium pentobarbital in all bases used with the exception of the petrolatum–paraffin base containing calcium pentobarbital (Fig. 2). This is in partial agreement with Riegelman and Crowell (17), who found the absorption of anions to be enhanced by the presence of surfactants while the absorption of an undissociated molecule was markedly retarded. The solubility of the sodium and calcium salts of pentobarbital in normal rectal fluids is probably much greater than the solubility of pentobarbital. The drug molecule having the

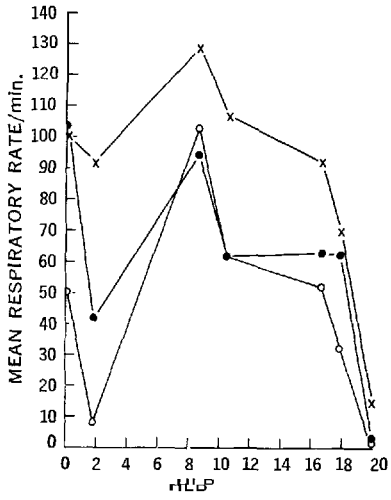

Fig. 2.—Mean respiratory rate as a function of the surfactant HLB value in the base. Comparison of a relatively undissociated barbituric acid to its partial or completely dissociated salts. Key: ×, pentobarbital; ●, calcium pentobarbital; ○, sodium pentobarbital. Statistical analysis: test of significance of difference of means nearest each other (t test) at the respective HLB values. Data are obtained from Table III. The probability of error (p) in the statement that the two means are different is tabulated as follows: × and ●, p <0.4> 0.35, 0 (HLB value); ● and ○, p <0.01> 0.005, 0 (HLB value); × and ●, p <0.005, 1.8 (HLB value); ● and ○, p <0.025> 0.01, 1.8 (HLB value); × and ○, p <0.15> 0.1, 8.6 (HLB value); ○ and ●, p <0.35> 0.20, 8.6 (HLB value); × and ●, p <0.01> 0.005, 10.5 (HLB value); ○ and ●, p ≃100, 10.5 (HLB value); × and ●, p <0.025> 0.01, 16.7 (HLB value); ● and ○, p <0.35> 0.2, 16.7 (HLB value); × and ●, p <0.35> 0.2, 17.9 (HLB value); ○ and ●, p <0.005, 17.9 (HLB value); × and ●, p <0.005, 20 (HLB value); ● and ○, p ≃100, 20 (HLB value). (The symbols consist of drugs compared.)

greater solubility would then be more available for absorption through the rectal membrane, if the drug were released from the base. Binding or complexing is suspected in all forms of pentobarbital, as well as of other barbiturates, used in the sorbitan monolaurate base (Table III).

In an effort to determine the effect of the distribution coefficient (DC) of the drug on release and absorption of barbiturates from suppositories after rectal administration, barbituric acids having varying DCs were chosen (Table II) and studied in bases containing different surfactants. Graphical presentation of the mean respiratory rate as a function of DC (chloroform/water) shows that those surfactants with a close chemical similarity (polyoxyethylene sorbitan tristearate and polyoxyethylene monostearate) yielded curves with approximately the same shape (Fig. 3). Sorbitan trioleate and sorbitan monolaurate yielded similar shaped curves (Fig. 4). When comparing Fig. 3 (polyoxyethylene sorbitan tristearate and polyoxyethylene monostearate) with Fig. 4 (sorbitan monolaurate and sorbitan trioleate), representing a more varied chemical structure, this similarity in the shape of the curves does not exist.

To study the effect of the HLB of the surfactants on release and absorption of barbiturates from the suppositories, surfactants with HLB values covering a large part of the HLB scale were utilized (Table II). A plot of the mean respiratory rate as a function of HLB of the surfactant shows that the two barbituric acids, aprobarbital and secobarbital, which have almost identical chemical structures, exhibited curves very similar in shape, and the degree of respiratory depression at the various HLB values was also similar (Fig. 5). Aprobarbital (5-allyl-5-isopropylbarbituric acid) and secobarbital (5-allyl-5[1-methyl butyl]barbituric acid) differ by 2 carbon atoms in the side chain. When comparing the results obtained with pentobarbital with

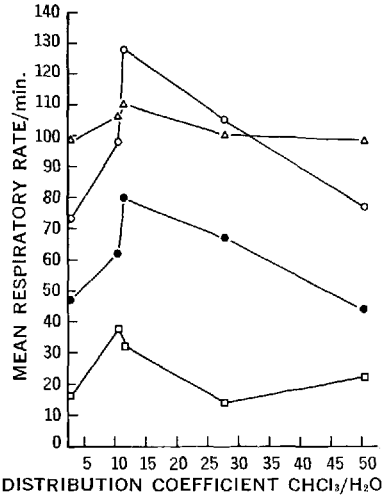

Fig. 3.—The mean respiratory rate as a function of the distribution coefficient of barbiturates. Comparison of surfactant chemical type. Key: ○, polyoxyethylene sorbitan tristearate; ●, polyoxyethylene monostearate; △, petrolatum–paraffin; □, polyethylene glycol.

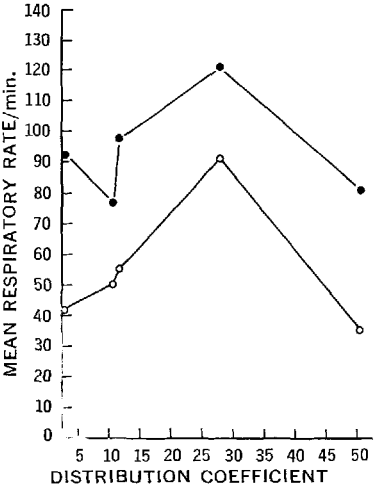

Fig. 4.—The mean respiratory rate as a function of distribution coefficient of the barbiturates. Comparison of surfactant chemical type. Key: ●, sorbitan monolaurate; ○, sorbitan trioleate.

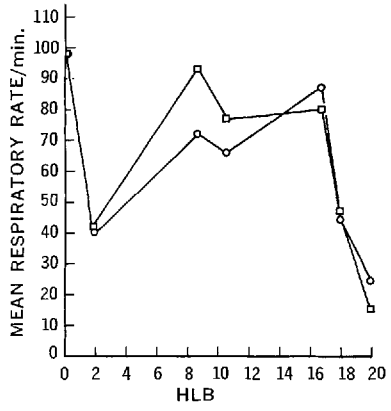

Fig. 5.—The mean respiratory rate as a function of the HLB of the surfactant in the base. Comparison of the chemical type of the barbiturates. Key: □, 5-allyl-5-isopropyl barbituric acid; O, 5-allyl-5-(1-methylbutyl) barbituric acid. Null hypothesis: the mean respiratory rates at each HLB value are different. Accept the null hypothesis if our probability of error is equal to or less than 0.2; reject the null hypothesis if our probability of error is greater than 0.2. Result: HLB value 0, reject; 1.8, reject; 8.6, accept; 10.5, accept; 16.9, reject; 17.9, reject; 20, reject.

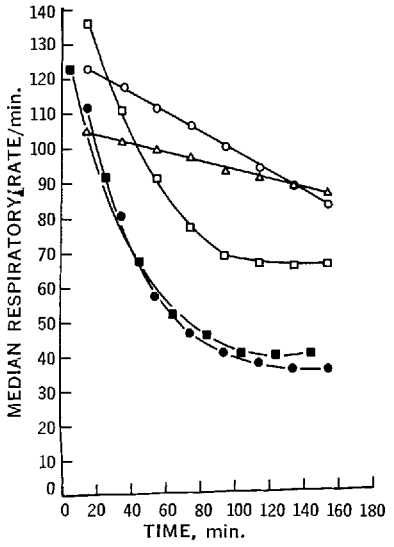

Fig. 6.—The median respiratory rate as a function of time using various bases containing surfactants with different HLB values and 5-ethyl-5-butyl-barbituric acid. Key: O, polyoxyethylene sorbitan monolaurate; □, polyoxyethylene stearate; △, sorbitan monolaurate; ■, sorbitan trioleate; ●, polyoxyethylene lauryl ether.

those obtained with secobarbital and aprobarbital (Figs. 2 and 5), this closeness in structure does not seem significant. The influence of the HLB of the surfactant, however, is not conclusive.

Since the HLB of a surfactant largely determines the type of emulsion formed and the degree of emulsification (27), and since some emulsification probably takes place in the rectum, when using suppository bases which contain surfactants, the effect on drug release at different HLB values may be quite significant. The predicted points of inflection are: (*a*) the point at which the most stable water-in-oil emulsion is formed, (*b*) the inversion point (point of changing from water-in-oil to an oil-in-water emulsion or vice-versa), and (*c*) the point at which the most stable oil-in-water emulsion is formed. The relative solubilities of the drug in the oil and water phases (distribution coefficient) would determine if these inflection points occur at a maximum or minimum biological response.

The change of the median respiratory rate in rabbits as a function of time and the type surfactant used in the bases is exemplified in Fig. 6. It is interesting to note that the laurates[1] exhibited linear relationships, whereas the oleate, stearate, and lauryl ether exhibited similarly shaped curves. The effect of similar chemical types of the surfactant on absorption is obvious here.

The change of the median respiratory rate of rabbits with time using various barbiturates in a base containing a polyoxyethylene lauryl ether[2] are exemplified in Fig. 7.

A complete analysis of the kinetic data will be presented for publication in the near future.

[1] Marketed as Tween 20 and Span 20 by Atlas Chemical Industries, Wilmington, Del.

[2] Marketed as Brij 35 by Atlas Chemical Industries, Inc., Wilmington, Del.

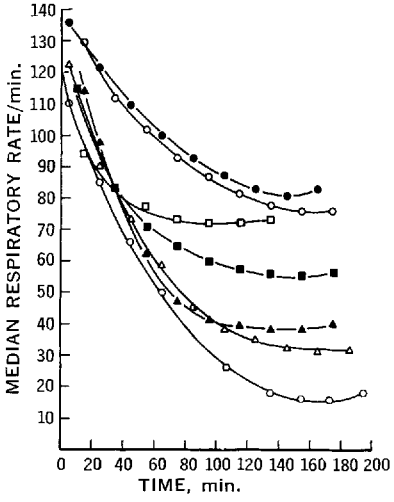

Fig. 7.—The median respiratory rate as a function of time using various barbituric acids in polyoxyethylene lauryl ether base (VI). Key: ●, 5-allyl-5-isobutyl barbituric acid; O, 5-ethyl-5-(1-methyl butyl) barbituric acid; □, 5-allyl-5-isopropyl barbituric acid; ■, calcium 5-ethyl-5-(1-methylbutyl) barbituric acid; ▲, 5-butyl-5-ethyl barbituric acid; △, sodium 5-ethyl-5-(1-methylbutyl) barbituric acid; O, 5-allyl-5-(1-methylbutyl) barbituric acid.

SUMMARY AND CONCLUSIONS

1. The absorption of barbiturates from eight suppository bases, which differed only by including surfactants with different HLB values, has been determined. Seven different barbiturates were used in

the suppositories which were administered to rabbits.

2. The salts of pentobarbital are more available for absorption from most bases containing surfactants based on the results of this study.

3. The relationship between the distribution coefficient of the drug and the HLB value of the surfactants used in the bases and their combined effects on absorption are inconclusive.

4. The chemical type of the surfactant and drug greatly influences the degree of release or absorption of barbiturates from suppositories in rabbits.

5. The addition of a surfactant to a base in most cases affects the availability of the drug from the base to the tissues. Complexation or binding may be one major factor causing these marked changes.

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Condensation of Aldoses and Their Aldehydo Derivatives with Compounds of the Type 1,3-Cyclohexanedione

Synthesis of 2,2-Aldosylidene-bis-[5-(*p*-hydroxyphenyl)-4,6-dicarbethoxy-1,3-cyclohexanedione] and 2,2-Aldosylidene-bis-[5,5-dimethyl-1,3-cyclohexanedione] and Derivatives

By PHILIPPOS E. PAPADAKIS

Glycoaldehyde, glyoxal, *dl*-glyceraldehyde, D-arabinose, D-glucose, and D-mannose react with compounds of the 1,3-cyclohexanedione type to form 2,2-aldosylidene-bis-1,3-cyclohexanedione derivatives.

THE PREPARATION of various 2,2-alkylidene or arylidene bis[5-(*p*-hydroxyphenyl)-1,3-cyclohexanedione] by the condensation of an aliphatic or an aromatic aldehyde with 5-(*p*-hydroxyphenyl)-1,3-cyclohexanedione or its derivatives was reported in a previous publication (1). It was also shown in that report that 5-(*p*-hydroxyphenyl)-1,3-cyclohexanedione could condense with 1,2-acetone-D-xylotrihydroxyglutaric dialdehyde to give [5,5-bis-<2′,2′-{5′,5′-(*p*-hydroxyphenyl)-cyclohexanedione-1′, 3′}>-1,2-isopropylidene-5-desoxy-D-xylofuranose]$_2$ monohydrate. This suggests that the aldehydo form of aldoses and of metabolic products of carbohydrates having a carbonyl group may condense with cyclic 1,3-diketones to form bis-derivatives. Such reactions should be of scientific and pharmacological interest (9).

In the present work 5-(*p*-hydroxyphenyl)-4,6-dicarbethoxycylohexane-1,3-dione was condensed with each of the following carbohydrates (or derivatives) to give bis-derivatives which may be represented by the general formula (I): glycolaldehyde, glyoxal, *dl*-glyceraldehyde, L-

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