

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 Aldehyde 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

Glycolaldehyde, 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 aldehyde 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).

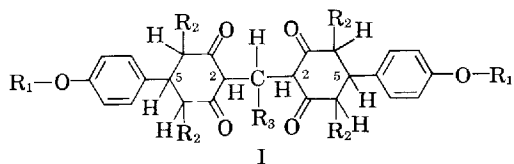
In the present work 5-(*p*-hydroxyphenyl)-4,6-dicarbethoxycyclohexane-1,3-dione was condensed with each of the following carbohydrates (or derivatives) to give bis-derivatives which may be represented by the general formula (I): glycolaldehyde, glyoxal, *dl*-glyceraldehyde, L-

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arabinose, 4,6-*O*-benzylidene-*D*-glucose, *D*-mannose, and *D*-galactaric dialdehyde.



$R_1 = \text{H}$ in experiments 1, 2, 3, 5, 7; $-\text{CH}_3$ in 4 and $-\text{COCH}_3$ in 6 and 8. $R_2 = -\text{COOC}_2\text{H}_5$ in 1, 2, 3, 5, 6, 7, 8 and H in 4. The value of R_3 is shown in Table I.

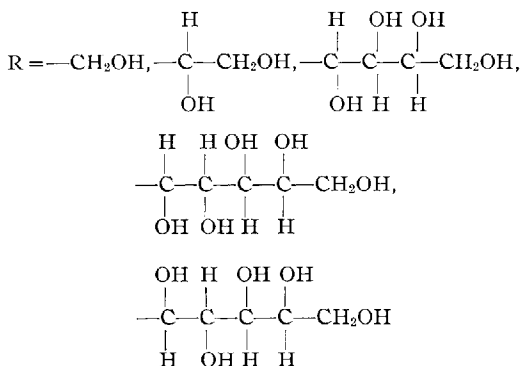
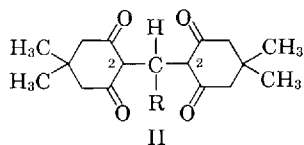
The method of preparation described under *Experimental* is similar to that used by Horning and Horning (2) with some modifications (1).

Other β -diketones are known to condense with aldehydes to give bis-derivatives (3-6).

Vorlander (7) treated dimedone (5,5-dimethylcyclohexane-1,3-dione) with each of the following: glycolaldehyde, glyoxal, and *dl*-glyceraldehyde and obtained (bis-derivatives) anhydrides. His method consisted in dissolving the diketone with each of the respective substances and allowing it to stand at room temperature several hours whereby a precipitate was formed which was purified and analyzed. He failed to obtain precipitates with tetroses and higher aldoses. Bourne *et al.* (8) have reported that, under the conditions which they used, *D*-xylose does not react with dimedone.

Fletcher (9) and co-workers found that: "*D*-xylose and dimedone containing a trace of quino-

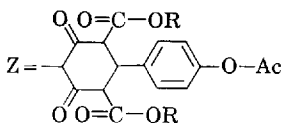
line mutarotates slowly over an extended period and yields a crystalline product which has the analysis of xylose-dimethone anhydride. A crystalline benzoate has also been obtained." In the present work aldosylidene-bis-dimedone derivatives were obtained, general formula (II), by condensing dimedone with each of the following carbohydrates in 75% methanol containing 2 drops of piperidine: glycolaldehyde, *dl*-glyceraldehyde, *D*-arabinose, *D*-mannose, and *D*-glucose. (*Experiments A-E*.)



The results of the experiments *A* and *B* indicate that glycolaldehyde and glyceraldehyde react with dimedone to form (bis-derivatives)

TABLE I.—VALUE OF R_3

Expt.	R_3	Expt.	R_3
1	$-\text{CH}_2\text{OH}$		
2	$-\text{CHO}$		
3	$-\text{CHOHCH}_2\text{OH}$		
4	$\begin{array}{c} \text{OH} \quad \text{H} \quad \text{H} \\ \quad \quad \\ -\text{C}-\text{C}-\text{C}-\text{CH}_2\text{OH} \\ \quad \quad \\ \text{H} \quad \text{OH} \quad \text{OH} \end{array}$	6	$\begin{array}{c} \text{C}_6\text{H}_5 \\ \\ \text{O}-\text{C}-\text{H} \\ \quad \\ \text{OH} \quad \text{OH} \\ \quad \\ -\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{H} \\ \quad \quad \quad \quad \\ \text{H} \quad \text{OH} \quad \text{H} \quad \text{H} \quad \text{H} \end{array}$
5	$\begin{array}{c} \text{OH} \quad \text{H} \quad \text{OH} \quad \text{OH} \\ \quad \quad \quad \\ -\text{C}-\text{C}-\text{C}-\text{C}-\text{CH}_2\text{OH} \\ \quad \quad \quad \\ \text{H} \quad \text{OH} \quad \text{H} \quad \text{H} \end{array}$	7	$\begin{array}{c} \text{H} \quad \text{H} \quad \text{OH} \quad \text{OH} \\ \quad \quad \quad \\ -\text{C}-\text{C}-\text{C}-\text{C}-\text{CH}_2\text{OH} \\ \quad \quad \quad \\ \text{OH} \quad \text{OH} \quad \text{H} \quad \text{H} \end{array}$
		8	$\begin{array}{c} \text{OAc} \quad \text{H} \quad \text{H} \quad \text{OAc} \quad \text{Z} \\ \quad \quad \quad \quad \\ -\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{H} \\ \quad \quad \quad \quad \\ \text{H} \quad \text{OAc} \quad \text{OAc} \quad \text{H} \quad \text{Z} \end{array}$



anhydrides. This is in agreement with Vorlander's work. Experiments *C*, *D*, and *E* indicate that contrary to Vorlander's findings the dimesone can condense with pentoses and hexoses. Analogous reactions have already been shown in Table I of this report where 5-(*p*-hydroxyphenyl)-4,6-dicarbethoxy-1,3-cyclohexanedione reacted with pentoses and hexoses to form bis-derivatives. (Experiments 6-8.)

EXPERIMENTAL

5-(*p*-Acetoxyphenyl)-4,6-dicarbethoxy-1,3-cyclohexanedione, 1, 3, and 5-(*p*-hydroxyphenyl)-1,3-cyclohexanedione and related materials were prepared according to methods previously described (10).

METHOD

The method used for the condensation of the aldehydoform of the sugars to form aldositylene-bis-derivatives with the above cyclic 1,3-diketones and with dimesone (type formula I and II) is similar to that used previously by the present author (1). In a general way, the molar proportions of the diketone to the aldose were 2:1. The materials were dissolved in hot 75% methyl alcohol, 1 or 2 drops of piperidine were added, and the mixture refluxed 2 hr. and then allowed to stand 3 days at room temperature, and in some cases, in the refrigerator.

Besides this method of procedure, experiments 5 and 7 were repeated and modified. After the reagents and solvents were mixed, they were allowed to stand at room temperature; compound 5 for 6 months and compound 7 for 13.5 months.

After evaporation of the solvents under reduced pressure using a water bath, the residue was purified by recrystallization from 50% methanol and in some cases from boiling distilled water. Details of purification varied, depending on the solubilities of the reagents and products in the different solvents.

1.—2,2-(2'-Hydroxyethylidene)-bis-[5-(*p*-hydroxyphenyl)-4,6-dicarbethoxy-1,3-cyclohexanedione].—Glycolaldehyde, 60 Gm., 5-(*p*-hydroxyphenyl)-4,6-dicarbethoxy-1,3-cyclohexanedione, 6.96 Gm., and 1 drop of piperidine were dissolved and refluxed in 75% methanol for 1 to 2 hr. The mixture was allowed to stay at room temperature 3 days. The solution was concentrated by evaporation on a water bath to an oily liquid which solidified upon addition of water. It was recrystallized from 75% methanol. It softens at 120° to a waxy consistency; it melts and decomposes at 143°. The bubbles formed are opalescent but clear at 156°.

Anal.—Calcd. for $C_{38}H_{42}O_{15} \cdot \frac{1}{2} H_2O$: C, 61.03; H, 5.61. Found: C, 60.81; H, 5.74.

2.—2,2-Formalformylidene-bis-[5-(*p*-hydroxyphenyl)-4,6-dicarbethoxy-1,3-cyclohexanedione].—To 6.96 Gm. of 5-(*p*-hydroxyphenyl)-4,6-dicarbethoxy-1,3-cyclohexanedione dissolved in hot 75% methanol, 2 ml. of 30% glyoxal and 1 drop of piperidine were added. The mixture was refluxed 0.5 hr., then cooled and allowed to stand in the refrigerator 3 days. A precipitate was formed which was processed. It was recrystallized from 75% methanol, m.p. 145°, dec. 156°. This compound is analogous to the bis-derivative of

glyoxal with dimesone (5,5-dimethyl-1,3-cyclohexanedione) obtained by Vorlander.

Anal.—Calcd. for $C_{38}H_{40}O_{15} \cdot H_2O$: C, 60.41; H, 5.60. Found: C, 60.07; H, 5.45.

3.—2,2-(2',3'-Dihydroxypropylidene)-bis-[5-(*p*-hydroxyphenyl)-4,6-dicarbethoxy-1,3-cyclohexanedione].—To 2.32 Gm. of 5-(*p*-hydroxyphenyl)-4,6-dicarbethoxycyclohexane-1,3-dione dissolved in 75% hot methanol, 0.30 Gm. of *dl*-glyceraldehyde and 1 drop of piperidine were added with stirring. The mixture was refluxed 2 hr., then the solvents were evaporated and the residue recrystallized from hot distilled water. It melted at 90° and decomposed at 110°.

Anal.—Calcd. for $C_{39}H_{44}O_{16}$: C, 60.93; H, 5.76. Found: C, 61.17; H, 5.70.

The above product treated with phenylhydrazine gave an orange-red precipitate, a small part of which dissolved in ether. The residue was dissolved in alcohol and reprecipitated with distilled water, m.p. 161-163°.

Anal.—Calcd. for $C_{31}H_{56}N_4O_{14}$: N, 5.90. Found: N, 6.27.

From the ether solution after evaporation of the solvent, the small amount of material obtained was dissolved in alcohol and reprecipitated with distilled water, m.p. 129°.

Anal.—Calcd. for $C_{37}H_{60}N_6 \cdot 3H_2O$: N, 7.68. Found: N, 7.66.

4.—2,2-(*L*-Arabosylidene)-bis-[5-(*p*-methoxyphenyl)-1,3-cyclohexanedione].—5-(*p*-Methoxyphenyl)-1,3-cyclohexanedione, 4.36 Gm., *L*-arabinose, 1.5 Gm., and 2 drops of piperidine were dissolved in 75% methanol. The mixture was refluxed for 1 hr., then allowed to stand 3 days at room temperature. After evaporation of the solvents, the residue was recrystallized from boiling distilled water. At 138° it changed to a waxy consistency and melted and decomposed at 140°.

Anal.—Calcd. for $C_{31}H_{38}O_{10} \cdot \frac{1}{2} H_2O$: C, 64.75; H, 6.29. Found: C, 64.76; H, 6.30.

5.—2,2-(*p*-Glucosylidene)-bis-[5-(*p*-hydroxyphenyl)-4,6-dicarbethoxy-1,3-cyclohexanedione].—5-(*p*-Hydroxyphenyl)-4,6-dicarbethoxy-1,3-cyclohexanedione, 6.96 Gm. (0.02 mole), and dextrose, 1.80 Gm. (0.01 mole), were placed in a ground-stoppered bottle with 200 ml. of 75% methanol and 3 drops of piperidine, and the mixture was allowed to stand 7 months in a cupboard at room temperature. Then the solvents were evaporated in a rotating evaporator under reduced pressure using a water bath. The solid residue was recrystallized from boiling water, m.p. 187-188°. The product was dried under reduced pressure at 100°. Yield, 67%. $[\alpha]_D^{20} = +11.65$ (c 3.0896; acetone).

Anal.—Calcd. for $C_{42}H_{50}O_{19} - 2H_2O$: C, 61.30; H, 5.63. Found: C, 61.49; H, 5.70.

6.—2,2-(4',6'-*O*-Benzylidene-glucosylidene)-bis-[5-(*p*-acetoxyphenyl)-4,6-dicarbethoxy-1,3-cyclohexanedione].—5-(*p*-Acetoxyphenyl)-4,6-dicarbethoxy-1,3-cyclohexanedione, 7.8 Gm., and 2.68 Gm. of 4,6-*O*-benzylidene-glucose (11) and 2 drops of piperidine were dissolved in 75% methanol and refluxed for 2 hr. The solvents were distilled off under reduced pressure and the product recrystallized from methyl alcohol, m.p. 168°.

Anal.—Calcd. for $C_{33}H_{38}O_{21}$: C, 61.73; H, 5.67. Found: C, 61.45; H, 5.74.

A phenylhydrazine derivative of the product above was formed in the usual way. It was dissolved in alcohol and reprecipitated with distilled water, m.p. 121°.

Anal.—Calcd. for $C_{74}H_{82}N_8O_{17} \cdot 2H_2O$: C, 64.79; H, 6.03; N, 7.85. Found: C, 64.40; H, 6.19; N, 7.59.

7.—2,2 - (D - Mannosylidene) - bis - [5 - (p-hydroxyphenyl) - 4,6 - dicarbethoxy - 1,3 - cyclohexanedione] - $2H_2O$.—5 - (p - Hydroxyphenyl) - 4,6-dicarbethoxy-1,3-cyclohexanedione, 6.96 Gm. (0.02 mole), and mannose, 1.80 Gm. (0.01 mole), were placed in a ground-stoppered bottle with 200 ml. of 75% methanol and 3 drops of piperidine. The mixture was allowed to stand 13.5 months at room temperature in a closed cupboard. After the solvents were evaporated under reduced pressure using a water bath, the solid residue was recrystallized from boiling water. The product was dried at 100° under reduced pressure, m.p. 180°. $[\alpha]_D^{18} = 0$ (c 1.328; acetone).

Anal.—Calcd. for $C_{42}H_{50}O_{19} - 2H_2O$: C, 61.30; H, 5.63. Found: C, 61.37; H, 5.97. C, 61.13; H, 5.98. C, 61.04; H, 5.82.

8.—2,2 and 2,2-(Galactar-di-ylidenetetraacetate)-tetrakis - [5 - (p - hydroxyphenyl) - 4,6 - dicarbethoxy-1,3-cyclohexanedione].—Tetraacetyl galactaric dialdehyde, 0.346 Gm., and 1.392 Gm. of 5-(p - acetoxyphenyl) - 4,6 - dicarbethoxy - 1,3 - cyclohexanedione and 1 drop of piperidine were dissolved in 75% hot methanol and allowed to stand at room temperature. After 2 days the solvents were evaporated under reduced pressure and the product recrystallized from methanol, m.p. 184°.

Anal.—Calcd. for $C_{94}H_{102}O_{40}$: C, 60.31; H, 5.49. Found: C, 60.41; H, 5.94.

Aldosylidene-bis-dimedone Derivatives

2,2 - (2' - Hydroxyethylidene) - bis - [5,5 - dimethyl - 1,3 - cyclohexanedione] - H_2O .—*Experiment A.*—Dimedone, 2.33 Gm. (0.0166 mole), glycolaldehyde, 0.50 Gm. (0.0083 mole), 15 ml. of methanol, and 5 ml. of water and 1 drop of piperidine were refluxed for 2 hr. and allowed to stand at room temperature 3 days. The solution was concentrated and cooled. The crystals formed were separated and recrystallized from 50% methanol, m.p. 233°. (Vorlander found m.p. 227°.)

Anal.—Calcd. for $C_{18}H_{26}O_5 - H_2O$: C, 71.02; H, 7.97. Found: C, 70.73; H, 7.92.

2,2 - (2',3' - Dihydroxypropylidene) - bis - [5,5-dimethyl - 1,3 - cyclohexanedione] - H_2O .—*Experiment B.*—Dimedone, 1.4 Gm. (0.01 mole), *dl*-glyceraldehyde, 0.45 Gm. (0.005 mole), 15 ml. of CH_3OH , 5 ml. of water, and 1 drop of piperidine were heated at refluxing temperature for 1 hr. and allowed to stand at room temperature for 3 days. The solution was concentrated to 7 ml. and cooled. The crystals formed were recrystallized from 50% methanol, m.p. 209°. (Vorlander found m.p. 197°.)

Anal.—Calcd. for $C_{19}H_{25}O_6 - H_2O$: C, 68.26; H, 7.83. Found: C, 68.17; H, 7.50.

2,2 - (D - Arabosylidene) - bis - [5,5 - dimethyl-1,3-cyclohexanedione].—*Experiment C.*—Dimedone, 2.80 Gm. (0.02 mole), D-arabinose, 1.5 Gm. (0.01 mole), 15 ml. of methanol, 5 ml. of water, and 1 drop of piperidine were placed in a ground-stoppered flask and allowed to stand for 1 week. Then the solution was refluxed 1 hr. and concentrated almost to dryness. The residue, after cooling, was stirred with ether. The ether was decanted and the residue stirred with ethanol and filtered. The white residue was recrystallized from boiling distilled water, m.p. 146°. $[\alpha]_D^{21} = -274.9^\circ$ (c 1.98; water).

Anal.—Calcd. for $C_{21}H_{22}O_8$: C, 61.14; H, 7.82. Found: C, 61.05; H, 7.81.

2,2 - (D - Mannosylidene) - bis - [5,5 - dimethyl-1,3-cyclohexanedione] - $2H_2O$.—*Experiment D.*—Dimedone, 5.60 Gm. (0.04 mole), and D-mannose, 3.60 Gm. (0.02 mole), were dissolved in 50 ml. of 70% methanol containing 2 drops of piperidine. The solution was refluxed 2 hr. and allowed to stand at room temperature 3 days. The solvents were evaporated under reduced pressure to a thick jelly-looking material which was soluble in alcohol but insoluble in ether. On stirring, it became like taffy. The material was dried on a porous plate and recrystallized from boiling water. It sinters at 87°, froths at 90°, and becomes clear at 112°.

Anal.—Calcd. for $C_{22}H_{24}O_9 \cdot 2H_2O$: C, 55.21; H, 8.00. Found: C, 54.76; H, 8.18.

2,2 - (D - Glucosylidene) - bis - [5,5 - dimethyl-1,3 - cyclohexanedione] - H_2O .—*Experiment E.*—Dimedone, 5.60 Gm. (0.04 mole), and D-glucose, 3.60 Gm. (0.02 mole), were dissolved in 50 ml. of 75% methanol containing 2 drops of piperidine. The solution was refluxed 2 hr., then it was allowed to stand at room temperature for 2 weeks. The solution was concentrated under reduced pressure on a water bath. Alcohol and benzene were added for azeotropic distillation. After partial distillation, the solution was cooled, ether was added, and the precipitate formed was filtered, washed with ether, and dried, m.p. 189°, dec. 190°. Yield, 62%. $[\alpha]_D^{21} = 173.58^\circ$ (c, 4.01536; water).

Anal.—Calcd. for $C_{22}H_{34}O_9 - H_2O$: C, 62.07; H, 7.59. Found: C, 61.90; H, 7.67. C, 62.11; H, 7.78.

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