Barbiturate Glucosides

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Nitrogen barbiturate glucosides of barbital, phenobarbital, amobarbital, secobarbital, and pentothal were prepared from acetobromoglucose and the potassium barbiturate. Proof of the nitrogen glucosidic linkages was obtained by direct condensation of sym-di-(tetra-O-acetyl-β-D-glucopyranosyl)urea with diethylmalonyldichloride. The lack of hypnotic activity of the barbiturate glucosides was demonstrated with intraperitoneal injections of 6 to 25 times the hypnotic dose of the corresponding barbiturate salt.

IT IS WELL KNOWN that many glycosides have very pronounced and widely varied pharmacological effects. The type of pharmacological response always depends on the specific structure of the aglycone but the sugar moiety contributes important absorption and distribution characteristics. However, a survey of the literature pertaining to glucosides of pharmacologically active compounds showed no consistent change in the varied responses of the compounds studied.

Many investigators have studied the effect of glucose and its metabolic products on barbiturate anesthesia. Lamson and his co-workers (1) were the first to publish their observations made when glucose was injected into dogs which recovered from pentobarbital anesthesia. They found that the dogs returned to anesthesia and remained in this state for an average time of 1 hour. Upon subsequent injections of glucose, the duration of anesthesia decreased until eventually further anesthesia could not be produced. Some other substances which will also cause this return to barbiturate anesthesia are products of glycolysis and the Krebs cycle, vitamins, malonic acid, glycerin, and epinephrine (2–5). Bester and Nelson (6) found that normal blood glucose levels did not affect pentobarbital anesthesia and proposed a competitive inhibition mechanism to explain the significant increase in sleeping time when glucose was injected with pentobarbital. Further evidence supporting an oxidative inhibitory mechanism is animal protective studies with cytochrome C injected with pentothal (7) and the need for greater quantities of pentothal to produce anesthesia in insulin-treated animals (8).

The present study was undertaken in order to determine whether glucose would have a potentiating effect if chemically combined with barbiturates. Furthermore, stable water-soluble barbiturate glucosides would be advantageous for liquid pharmaceutical dosage forms.

Only three barbiturate glycosides are reported in the literature. The mono-glucoside of barbital was prepared by reacting diethylmalonyldichloride with tetra-O-acetylglucose-urea (9). Bodendorf (10) prepared 5,5-diethyl-1,3-di-(tetra-O-acetyl-β-D-glucopyranosyl)barbituric acid from tetra-O-acetyl-α-D-glucopyranosylbromide and potassium barbital with subsequent deacetylation by sodium methoxide. Only one enolic barbiturate glucoside has been prepared utilizing the enolizing influence of silver oxide. Snyder and Link (11) prepared 5,5-diethyl-4-(tetra-O-acetyl-β-D-glucopyranosyloxy)-2,6-pyrimidinedione in 2.6% yield from 5,5-diethylbarbituric acid and tetra-O-acetyl-α-D-glucopyranosylbromide in the presence of silver oxide and a catalytic amount of quinoline.

EXPERIMENTAL[1]

Tetra-O-acetyl-α-D-glucopyranosylbromide.—Tetra-O-acetyl-α-D-glucopyranosylbromide, commonly known as acetobromoglucose, was prepared by a combination of two known methods (12, 13). Two hundred grams of β-D-glucose pentaacetate prepared by a standard procedure (14) was mixed with 350 ml. of 30% hydrogen bromide in glacial acetic acid and kept at room temperature for 4 hours. Hydrogen bromide was removed under reduced pressure at 40–50°, passing dry nitrogen through the capillary. Excess acetic acid was distilled at the bath temperature of 55–60° and 15 mm. Hg. The dark brown residue was crystallized twice from dry ether giving white needles; yield 127 Gm. (60%), m.p. 89–90°.

Glucosides of Barbital, Phenobarbital, Amobarbital, and Secobarbital.—These four nitrogen glucosides were prepared by following general procedure. Fifteen milliliters of 2 *N* potassium hydroxide was added to 50 ml. of an acetone solution containing acetobromoglucose (0.030 mole) and the barbiturate (0.015 mole). After 4 days reaction time, the absence of acetobromoglucose was shown by a negative silver nitrate test. The acetone was then evaporated and the resulting syrup was dissolved in 50

Received October 19, 1961, from the Research Dept., White Laboratories, Inc., Kenilworth, N. J.
Accepted for publication November 3, 1961.
Abstracted in part from the dissertation presented to the Graduate School, Ohio State University, for the degree of Doctor of Philosophy.
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[1] Melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected. Analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

ml. benzene and extracted with three 50-ml. portions of 20% sodium hydroxide, followed by water extraction until all the base was removed. After drying the benzene solution over anhydrous sodium sulfate, the solvent was evaporated giving hard, white, glassy products. Yields and physical constants are listed in Table I. Only the acetylated glucoside of barbital was crystallizable. Two crystallizations from absolute ethanol gave 1.8 Gm. (14%) of fine needles. None of the four acetylated nitrogen glucosides reduced hot Benedict's reagent.

Elemental analyses shown in Table I indicate that a di-glucoside was formed in every case except with amobarbital. Infrared spectra support this by the presence of imino group absorption at 3.1 μ with the acetylated amobarbital glucoside and the absence of this absorption in the spectra of phenobarbital, secobarbital, and barbital acetyl glucosides.

Deacetylations were done by partially dissolving the acetylated glucoside (0.002 mole) in 100 ml. of absolute ethanol, adding 6 ml. of sodium methoxide solution (1 mg. sodium per ml. of methanol) and distilling the methylacetate and alcohols. After decolorizing with charcoal, white hard amorphous compounds were obtained which were very water soluble but were not crystallizable. After acid hydrolysis, they reduced hot Benedict's reagent. Deacetylation of the crystalline barbital glucoside was also accomplished with ammonia in absolute methanol. The acetylated compound (0.0015 mole) was partially dissolved in 60 ml. of absolute methanol and saturated with dry ammonia gas at 5°. After 1 day, the ammonia and methanol were evaporated and the acetamide was removed from the white residue with 10 ml. of chloroform. The yield was 0.50 Gm. (0.0010 mole) of a white, brittle, amorphous solid.

Anal.—Calcd. for $C_{20}H_{32}N_2O_{13}$: N, 5.51. Found: N, 5.12.

5 - Ethyl - 5 - (1 - methylbutyl) - 1,3 - di - β - D - glucopyranosyl-2-thiobarbituric Acid.—Acetobromoglucose (8.2 Gm., 0.02 mole) was added to 60 ml. of a dry acetone solution containing 6.0 Gm. (0.02 mole) of sodium pentothal. After 1 day at room temperature, the sodium bromide was filtered out and the acetone evaporated. The resulting yellow syrup was dissolved in 30 ml. of benzene and extracted with three 10-ml. portions of 2% sodium hydroxide solution, followed by extraction with water until the base was removed. After drying over anhydrous sodium sulfate, the benzene was evaporated, giving 7.8 Gm. (87%) of a hard yellow amorphous powder. Analytical data shown in Table I and the absence of imino group absorption at 3.1μ in the infrared spectrum indicate the formation of a di-glucoside. Deacetylation was accomplished by the standard sodium methoxide method resulting in a yellow amorphous solid which was very water soluble but noncrystallizable.

SYNTHETIC PROOF OF NITROGEN GLUCOSIDE BOND

It is obvious that the glucoside bonds could be either through the nitrogen or enolic oxygen atoms of the barbiturate. Therefore, the acetylated di-nitrogen glucoside of barbital was synthesized in an unambiguous manner. The physical properties of this compound are identical to those of the glucoside synthesized from acetobromoglucose and barbital, indicating that a di-nitrogen glucoside was actually formed. The synthetic approach which was chosen involves the following steps: (*a*) synthesis of sym-di-(tetra-O-acetyl-β-D-glucopyranosyl)-urea, and (*b*) condensation of the acetylated diglucose-urea derivative with diethylmalonyldichloride.

(*a*) **Sym-di-(tetra-O-acetyl-β-D-glucopyranosyl)-urea.**—A mixture of urea (0.60 Gm., 0.01 mole), powdered Drierite (10 Gm.), silver oxide (2.32 Gm., 0.01 mole), and acetobromoglucose (8.22 Gm., 0.02 mole) in 10 ml. of dimethylsulfoxide (DMS) was

TABLE I.—BARBITURATE GLYCOSIDES

Compound	Yield, %	M.p., °C.	$[\alpha]_D^{25}$	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
5,5-Diethyl-1,3-di-(tetra-O-acetyl-β-D-glucopyranosyl)-barbituric acid	14.0	173–174	−28.7° (C, 4.17; $CHCl_3$)	$C_{36}H_{48}N_2O_{21}$	...	...	...	...	3.31	3.29
5-Allyl-5-(1-methylbutyl)-1,3-di-(tetra-O-acetyl-β-D-glucopyranosyl)barbituric acid	15.3	77–82	−29.3° (C, 2.49; $CHCl_3$)	$C_{40}H_{54}N_2O_{21}$	53.45	53.30	6.01	6.02	3.12	3.27
5-Ethyl-5-phenyl-1,3-di-(tetra-O-acetyl-β-D-glucopyranosyl)-barbituric acid	7.5	90–96	−8.4° (C, 4.05; $CHCl_3$)	$C_{40}H_{48}N_2O_{21}$	...	...	...	...	3.14	2.93
5-Ethyl-5-isoamyl-1-(tetra-O-acetyl-β-D-glucopyranosyl)-barbituric acid	7.5	47–52	−18.6° (C, 4.24; $CHCl_3$)	$C_{25}H_{36}N_2O_{12}$	54.25	53.35	6.51	6.68	5.06	5.35
5-Ethyl-5-(1-methylbutyl)-1,3-di-(tetra-O-acetyl-β-D-glucopyranosyl)-2-thiobarbituric acid	87.0	62–67	Due to yellow color, optical rotation could not be determined	$C_{39}H_{18}N_2O_{20}S$	52.24	52.57	5.36	5.67	3.12	3.46
5,5-Diethyl-4-(tetra-O-acetyl-β-D-glucopyranosyloxy)-2,6-pyrimidinedione[a]	5.3	178–179	+8.04° (C, 4.17; $CHCl_3$)	$C_{22}H_{30}O_{12}N_2$	51.35	51.20	5.88	5.75	5.45	5.66

[a] Synthesized by procedure of Snyder and Link (11).

TABLE II.—PHARMACOLOGICAL RESULTS

Barbiturate	Anesthetic Dose of Sodium Barbiturate,[a] mg.	Type of Glucoside	Dose of Barbiturate Glucoside,[a] mg.	Results
Barbital	200	Di-nitrogen	1500	Inactive
Barbital	200	Mono-enolic tetraacetate[a]	1200	Inactive
Phenobarbital	100	Di-nitrogen	1000	Inactive
Secobarbital	40	Di-nitrogen	1000	Inactive, painful
Amobarbital	200	Mono-nitrogen	2000	Inactive
Thiopental	40	Di-nitrogen	500	Inactive

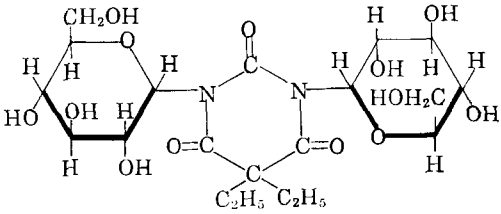
[a] All were intraperitoneal injections of aqueous solutions except the mono-enolic glucoside tetraacetate of barbital which was in the form of a 1% acacia aqueous suspension. The doses are in mg. of compound per Kg. of rat.

stirred for 12 hours (reaction of all acetobromoglucose was indicated by negative test with silver nitrate T.S.). After filtering and washing with dry ether, the DMS was distilled (58°, 5 mm.) resulting in an opaque syrup. It was not possible to crystallize the syrup which was used in the following reaction with diethylmalonyldichloride.

(*b*) **Condensation of Sym-di-(tetra-O-acetyl-β-D-glucopyranosyl)-urea with Diethylmalonyldichloride.**—Diethyldiethylmalonate was prepared from 0.5 mole of diethylmalonate according to the procedure of Vogel (15), but was not isolated. The alcoholic filtrate containing diethyldiethylmalonate was then saponified with 2.5 moles of sodium hydroxide and the alcohol distilled. After extraction with ether and crystallization from chloroform, the yield of diethylmalonic acid was 15.1 Gm. (19%), m.p. 124–125°.

Diethylmalonyldichloride was prepared from 8.0 Gm. of diethylmalonic acid and 20.8 Gm. of phosphorus pentachloride according to standard procedure. The acid chloride was distilled at 85–89° (14 mm.); yield 9.1 Gm. (92%), b.p. 199°.

Diethylmalonyldichloride, 1.37 Gm. (0.007 mole) was added to 50 ml. of an ether solution containing 3.5 Gm. of the syrup obtained in (*a*) and 1.2 Gm. (0.015 mole) of pyridine. After 20 hours reaction time at room temperature, the mixture was filtered and residue washed with dry ether. The ether filtrate was then extracted with two 50-ml. portions of 5% sodium carbonate solution and two 50-ml. portions of water. After drying the ether solution with anhydrous sodium sulfate, the solvent was removed *in vacuo*. Crystallization occurred very slowly after 2 days from alcohol-water, after seeding with the acetylated barbital diglucoside which was obtained by the Bodendorf procedure. The crystals were filtered after 10 days and washed with 10 ml. water. After recrystallization from absolute methanol, the yield of fine needles was 480 mg.; m.p. 174–175°. A mixed melting point with the acetylated barbital diglucoside obtained by direct condensation of acetobromoglucose and barbital showed no depression. This unambiguous synthesis indicated that the structure of the barbital di-nitrogen glucoside is that shown below



PHARMACOLOGICAL TESTING

A comparison was made between the barbiturate glucosides and the corresponding sodium barbiturate salts for hypnotic activity in albino rats. The lack of hypnotic activity of the barbiturate glucosides was demonstrated with intraperitoneal injections of 6 to 25 times the hypnotic dose of the corresponding barbiturate salt. Both the enolic tetraacetate and nitrogen-type glucosides were inactive. The results are summarized in Table II.

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