Anticonvulsants. 2. Acyloxymethyl and Halomethyl Derivatives of Barbituric Acid and Diphenylhydantoin

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Acyloxymethyl, bis(acyloxymethyl), and bis(halomethyl) derivatives of 5-ethyl-5-phenylbarbituric acid displayed marked anticonvulsant activity. The bis(acyloxymethyl) derivatives of phenobarbital were active against maximal electroshock seizures as well as pentylenetetrazole, while the bis(halomethyl) derivatives of phenobarbital were effective anticonvulsants against pentylenetetrazole only. The 1,3-bis(acetoxymethyl) derivatives of 5,5-diethylbarbituric acid and diphenylhydantoin showed anticonvulsant activity against maximal electroshock seizures.

In the preceding article we reported[1] that 1,3-bis(alkoxymethyl)phenobarbitals possess marked anticonvulsant activity against electrically and chemically induced seizures, yet are devoid of hypnotic activity. It was of interest, therefore, to determine whether acyloxymethyl or halomethyl derivatives of barbiturates had the same properties. We reported, also,[1] that alkoxymethyl-5,5-diphenylhydantoins were active against electrically as well as chemically induced seizures. This was surprising since the parent compound, 5,5-diphenylhydantoin, inhibits maximal electroshock seizures, but is totally inactive against pentylenetetrazole. We were curious, therefore, to learn whether acyloxymethyl derivatives of 5,5-diphenylhydantoin resembled the activity of the parent compound, 5,5-diphenylhydantoin, or the alkoxymethyl derivatives of 5,5-diphenylhydantoins.

We found that the 1,3-bis(acyloxymethyl)phenobarbitals resembled the 1,3-bis(alkoxymethyl)phenobarbitals rather than the parent compound, phenobarbital, in that they were effective against electrically and chemically induced seizures, yet were devoid of hypnotic activity. We also found that 1,3-bis(acetoxymethyl)-barbital resembled 1,3-bis(methoxymethyl)barbital rather than barbital itself since both barbital derivatives displayed marked anticonvulsant activity against maximal electroshock seizures, yet were devoid of hypnotic activity.

On the other hand, 3-acetoxymethyl-5,5-diphenylhydantoin resembled the parent compound, 5,5-diphenylhydantoin, not the 3-alkoxymethyl-5,5-diphenylhydantoins, *i.e.*, the acyloxymethyl derivative, like 5,5-diphenylhydantoin, showed good activity against maximal electroshock seizures but was inactive against pentylenetetrazole.

We also found that 1,3-bis(halomethyl) derivatives of phenobarbital were effective anticonvulsants against pentylenetetrazole. At the same time, these compounds, unlike phenobarbital, were completely devoid of hypnotic activity.

The acid- or base-catalyzed reaction of phenobarbital and formaldehyde yielded a mixture of 1,3-bis(hydroxymethyl)phenobarbital and 1-hydroxymethylphenobarbital. Attempts to separate these two compounds have failed, and only phenobarbital was isolated. This is not surprising since retroaldol condensation takes place readily, giving rise to phenobarbital and formaldehyde. The mixture of 1-hydroxymethylphenobarbital and 1,3-bis(hydroxymethyl)phenobarbital could readily be acetylated. Separation of the acetyl derivatives provided 1-acetoxymethylphenobarbital (**1**) and 1,3-bis(acetoxymethyl)phenobarbital (**2**).

The mixture of methylol compounds described above was treated with trichloroacetyl isocyanate. The compound 1,3-bis(carbamoylmethyl)phenobarbital (**3**) was the only product isolated from that reaction.

Compound **2** was also formed from 1,3-bis(methoxymethyl)phenobarbital (**4**)[1] and Ac_2O in the presence of catalytic amounts of $SnCl_4$. When **4** was treated with BzCl or AcCl in the presence of anhyd $SnCl_4$ 1,3-bis(chloromethyl)-5-ethyl-5-phenylbarbituric acid (**5**) was obtained. Similarly 1,3-bis(bromomethyl)-5-ethyl-5-phenylbarbituric acid (**6**) was prepared from **4** and AcBr in the presence of anhyd $SnBr_4$.

Compound **6** could be converted into **5** in good yield with $Ag(OCOCF_2Cl)$.[2] 1,3-Difluoromethyl-5-ethyl-5-phenylbarbituric acid (**7**) was obtained from **6** and AgF.

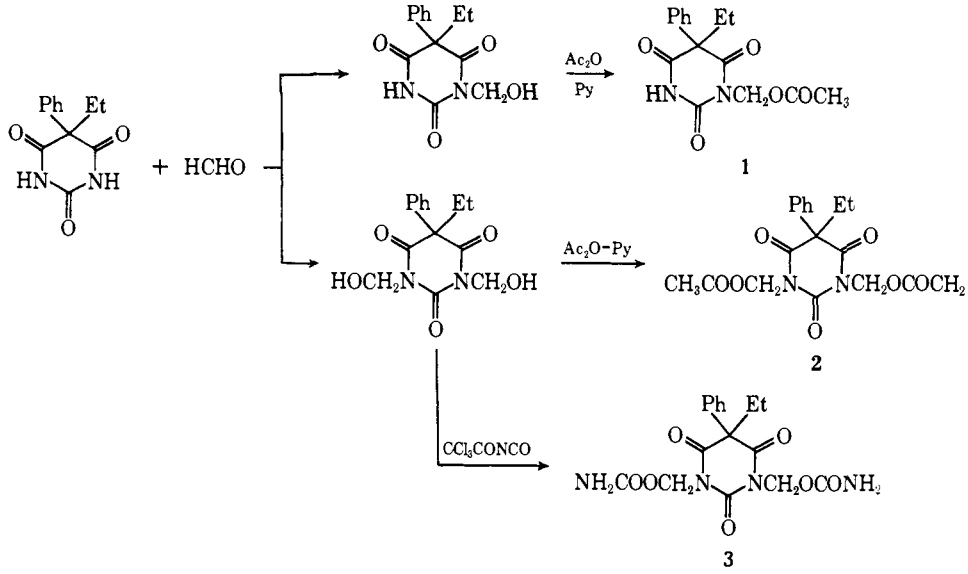
Compound **6** was easily solvolyzed in boiling EtOH to yield 1,3-bis(ethoxymethyl)-5-ethyl-5-phenylbarbituric acid (**8**). From the base-catalyzed reaction of 5,5-diphenylhydantoin with excess CH_2O 1,3-bis(hydroxymethyl)-5,5-diphenylhydantoin was obtained, which was converted into 1,3-bis(acetoxymethyl)-5,5-diphenylhydantoin (**9**) as shown.

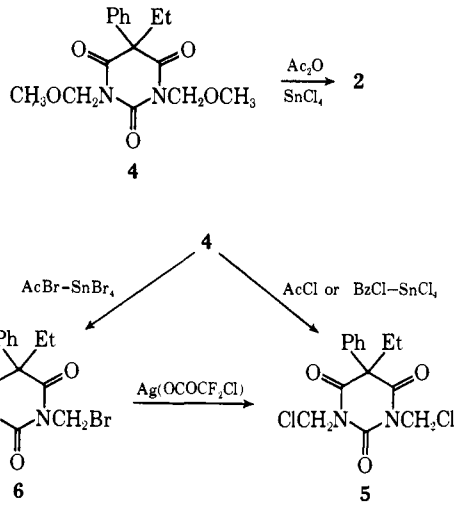
On the other hand, 3-methoxymethyl-5,5-diphenylhydantoin[1] could be converted into 3-acetoxymethyl-5,5-diphenylhydantoin (**6**) with Ac_2O in the presence of $SnCl_4$.

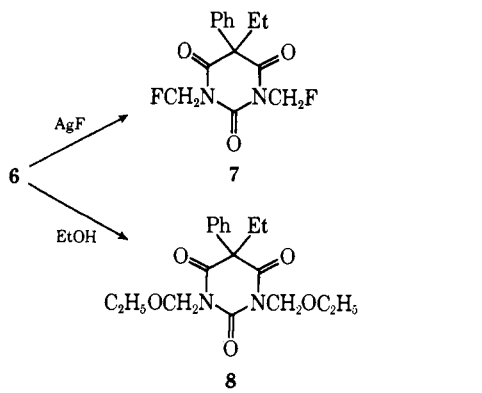
We became interested also in finding out whether some higher mol wt compounds, prepared from phenobarbital derivatives would display anticonvulsant properties. Compound **5** was treated with Ag phenobarbital to provide a compound of high mol wt (**11**). Mass spectral data indicated the presence of a pentamer. Determination of the mol wt indicated that the compound is a mixture of two compounds containing

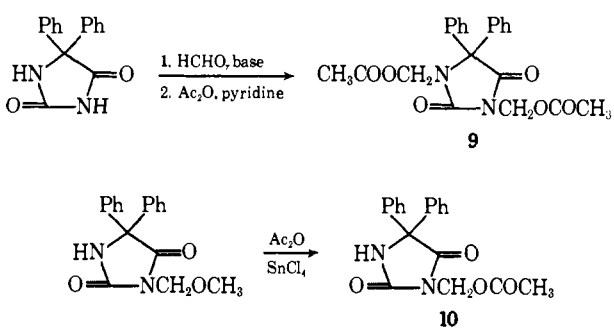
(1) C. M. Samour, J. Reinhard and J. A. Vida, *J. Med. Chem.*, **14**, 187 (1970).

(2) J. A. Vida, *Tetrahedron Lett.*, 3447 (1970).

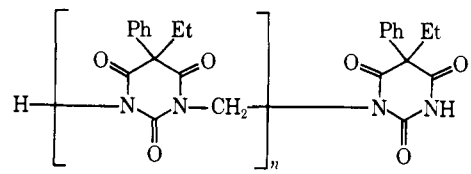








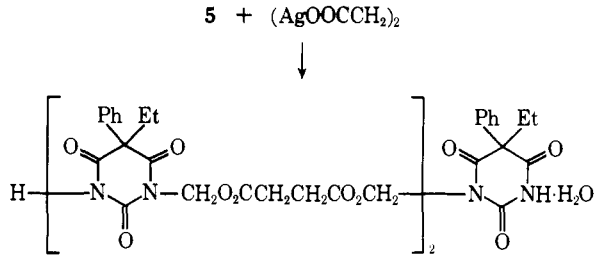
30% of a pentamer and 70% of a trimer with the following structure, where $n = 2$ and 4:



11, $n = 2$ and 4
12, $n = 6$

In a separate experiment, **3** was heated in MeCN with Ag_2CO_3 to produce the heptamer (**12**, $n = 6$), as established by mol wt measurement (calcd mol wt of heptamer = 1697.68, found **1660** ±50).

The only compound isolated from the reaction of **5** and Ag succinate was a high mol wt compound containing 3 units of the barbituric acid structure, as shown:



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Mol wt measurement gave a value of 995±30. The calcd mol wt of *N*-bis[(5-ethyl-5-phenyl-1-barbituryl)-methyleneoxysuccinyloxymethyl]phenobarbital monohydrate (**13**) is 998. Interestingly some of the high mol wt compounds, especially **11**, displayed good activity against maximal electroshock seizures.

Pharmacological Studies.—Protection against maximal electroshock (MES) and pentylenetetrazole (Met) and toxicity (LD_{50}) were determined according to Swinyard, *et al.*[3]

Results summarized in Table I indicate marked activity against MES following administration of **2**, **9**, **10**, **14**, and **15** suggesting potential therapeutic effectiveness

(3) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, **106**, 319 (1952).

TABLE I

PHARMACOLOGICAL PROPERTIES OF ACYLOXYMETHYL AND HALOMETHYL DERIVATIVES OF BARBITURIC ACID AND DIPHENYLHYDANTOIN AND THEIR POLYMERIC PRODUCTS

Compd	MES ED_{50}, mg/kg	Met ED_{50}, mg/kg	Peak time, hr	LD_{50}, mg/kg
1				>500
2	28.0 (22.4–35.0)	104.0 (80.0–135.0)	1.5	640 (474–864)
3	~50		2	>500
5	Inactive	>100		>500
6	Inactive	~27	1	
7		>100	2	
9	<25		2	
10	<12.5	Inactive	1	<500
11	~25		2	>500
12	>200			<1000
13	>200		2	>500
14	16.5 (12.1–22.4)		3	570 (259.1–1254.0)
15	~25		3	>500

in grand mal epilepsy. Only **2** and **10** were tested against pentylenetetrazole. Typical of hydantoins, **10** was inactive against pentylenetetrazole. On the other hand **2** was active against both MES and pentylenetetrazole, suggesting a broader spectrum of anticonvulsant activity than that of diphenylhydantoin. Margins of safety (LD_{50}/ED_{50}) were satisfactory and, in some instances, remarkably high, ratios of 3–5 being fairly representative of therapeutically active CNS agents.

The phenobarbital polymer **11** had marked potency against electroshock seizures. The dibromo, dichloro, and difluoro derivatives (**6**, **5**, and **7**, respectively) had satisfactory activity against chemoshock (Met).

Compounds **2**, **3**, **5**, **6**, **7**, **11**, **12**, **13**, **14**, and **15** were tested for hypnotic activity. The pattern of toxicity in mice disclosed progressive depression of the CNS, death resulting from respiratory paralysis. Sleep, however, did not appear except at lethal doses.

Experimental Section

Molecular weight was determined by a Hitachi-Perkin-Elmer vapor pressure osometer. For other methods, see the preceding article.

1-Acetoxymethyl-5-ethyl-5-phenylbarbituric Acid (1).—Phenobarbital (9.28 g, 0.04 mole) was suspended in H_2O (40 ml). A 37% aq HCHO soln (17.6 ml, 6.0 g, 0.2 mole) and triethanolamine (2 g) were added and the mixt was refluxed for 150 min then allowed to cool. The product was extd into Et_2O. The Et_2O soln was washed first with aq HCl, then with H_2O. After drying (Na_2SO_4), the solvent was evapd to yield a pale yellow oil. Ac_2O (10 g) and pyridine (45 ml) were added, and the soln was allowed to stand overnight. The soln was poured into 500 mg of ice–H_2O containing 50 ml of 38% HCl and stirred for 2 hr. An oily solid pptd, which was extd into CH_2Cl_2 and washed with 2 *N* HCl, dil $NaHCO_3$ soln, and H_2O. The dried (Na_2SO_4) CH_2Cl_2 soln was evapd to yield an oil. Trituration of the oil with Et_2O produced a solid consisting mainly of **2**, mp 136–137° which was removed by filtrn. This product was further purified according to procedure A, given for the prepn of 1,3-bis(acetoxymethyl)-5-ethyl-5-phenylbarbituric acid, to yield pure **2**, characterized in the same manner as described below.

The resulting soln containing mainly **1** was chromatographed on silica gel. Elution with a C_6H_6–EtOAc mixt (9:1 by vol) provided fractions containing fairly pure **1**. This material was crystd repeatedly from hexane using a Soxhlet app. The combined material was chromatographed on silica gel. Elution with a C_6H_6–EtOAc mixt (9:1 by vol) provided a solid material, which was crystd several times from $PhCH_3$. Finally, crystn from Et_2O using a Soxhlet app provided pure **1** (1.7 g, 13.8% yield), mp 126–127°. *Anal.* ($C_{16}H_{16}N_2O_5$) C, H, N.

1,3-Bis(acetoxymethyl)-5-ethyl-5-phenylbarbituric Acid (2). Procedure A.—Phenobarbital (11.5 g) was dissolved in 20 ml of dioxane. To the soln 100 ml of 37% aq HCHO and 1 ml of 38% aq HCl[4] were added and the soln was heated at reflux for 16 hr. The soln was cooled to 25°, the product was extd into EtOAc, and the dried (Na_2SO_4) EtOAc soln was evapd. To the oily residue 12.5 ml of Ac_2O and 12.5 ml of pyridine were added and the soln was allowed to stand at 25° overnight. The soln was poured into 500 ml of ice–H_2O containing 12.5 ml of 38% aq HCl and was stirred for 3 hr. The solid product was filtered and washed with H_2O, then crystd from EtOH (100 ml) to yield 10.1 g of crude **2** (53% yield), mp 136–137°. From the aq mother liquor extn with EtOAc and evapn of the solvent gave an oily residue. Chromatography and crystn according to the procedure described for the prepn of **1**, ultimately gave **1** identical in all respects with the same product described above. Further purification was achieved by dissolving crude **2** in 100 ml of EtOAc, washing the soln several times with cold, satd soln of K_2CO_3, then H_2O. The dried (Na_2SO_4) EtOAc soln was evapd to give a solid which was crystd from 100 ml of EtOH to give 8.9 g (47% yield) of **2**, mp 146–148°. *Anal.* ($C_{18}H_{20}N_2O_7$) C, H, N.

Procedure B.—1,3-Bis(methoxymethyl)phenobarbital[1] (**4**) (2.0 g) was suspended in 5 ml of Ac_2O. Two drops of $SnCl_4$ was added, the suspension was stirred for 20 hr and then poured into 20 ml of ice-H_2O. The mixt was then stirred for 3 hr and the solid product filtered. The solid was crystd from EtOH to give **2** (2.0 g, 85% yield) identical with the same product as described in procedure A.

1,3-Bis(carbamoyloxymethyl)-5-ethyl-5-phenylbarbituric Acid (3).—Phenobarbital (11.5 g) was treated with HCHO in the manner described in procedure A for **2**. After extn and evapn of the solvent an oily residue was obtd to which CCl_3CONCO (25 g) was added and the soln was allowed to stand at 25° overnight. MeOH was then added and the product was extd into CH_2Cl_2. The solvent was evapd to yield an oil, to which EtOH was added. Upon standing, crystals appeared, which were filtered. Recrystn from 50% aq MeOH gave 7.6 g (40% yield) of **3**, mp 213–215°. *Anal.* ($C_{16}H_{18}N_4O_7$) C, H, N.

1,3-Bis(chloromethyl)-5-ethyl-5-phenylbarbituric Acid (5). Procedure A.—**4** (16.0 g, 0.05 mole) was suspended in AcCl (32 g, 0.4 mole). To the suspension was added slowly, drop by drop, 0.2 ml of anhyd $SnCl_4$. The suspension was stirred at 25° and soon became a homogeneous soln, but after about 60 hr of stirring, a solid material began to ppt. After 110 hr of stirring the reaction mixt was poured into 500 g of ice–H_2O and stirred for an addl 6 hr. The pptd solid material was sepd from the reaction mixt by filtrn, washed with cold H_2O, and dried (25°). This crude product was crystd from abs EtOH (500 ml) to yield 13.26 g (81%) of **5**, mp 154–156°. *Anal.* ($C_{14}H_{24}Cl_2N_2O_3$) C, H, Cl, N.

Procedure B.—The procedure was conducted in the manner described in procedure A, except that an equiv wt of BzCl was substituted for AcCl. The product **5**, obtd in 75% yield, was identical in all respects with the same product obtained in procedure A.

(4) Similar results were obtained when AcOH, Na_2CO_3, triethanolamine, Et_3N, DABCO, etc. were substituted for HCl.

Procedure C.—**6** (4.2 g, 0.01 mole) was dissolved in MeCN (50 ml). To the soln $Ag(OCOCF_2Cl)$ (4.8 g, 0.02 mole) was added and the reaction mixt was stirred at reflux overnight. The pptd Ag salt was removed by filtrn and the solvent was evapd to yield a solid product. Crystn first from CCl_4, then from abs EtOH, provided 2.2 g (68.5% yield) of **5**, mp 154–156°. *Anal.* ($C_{14}H_{24}O_3N_2Cl_2$) C, H, Cl, N.

1,3-Bis(bromomethyl)-5-ethyl-5-phenylbarbituric Acid (6).—**4** (16 g, 0.05 mole) was suspended in AcBr (36.5 g, 0.28 mole). Anhyd $SnBr_4$ (4 g) was added to the suspension slowly over a period of 10 min. The suspension was heated to 55° with stirring, whereupon it became a homogeneous soln; stirring was continued while maintaining the mixt at that temp. After about 70 hr a solid material began to ppt. When the stirring had continued for a total of 150 hr, the reaction mixt was poured into 300 g of ice–H_2O and stirring was continued for another 4 hr. The solid ppt was sepd from the reaction mixt by filtrn, washed with cold H_2O, and dried (25°). The material was crystd from $CHCl_3$ (120 ml) to yield 18 g (86%) of **3**, mp 160–161.5°. *Anal.* ($C_{14}H_{24}Br_2N_2O_3$) C, H, Br, N.

1,3-Bis(fluoromethyl)-5-ethyl-5-phenylbarbituric Acid (7).—**6** (4.2 g, 0.01 mole) was dissolved in MeCN (100 ml). AgF (5.1 g, 0.04 mole) was added to the soln and the mixt was stirred at reflux for 20 hr, after which the hot soln was filtered through a Büchner funnel containing a compacted layer of finely divided diatomaceous silica, and the filtrate was passed directly into 1 kg of ice–H_2O. An oily ppt formed which solidified when allowed to stand overnight. The solid ppt was sepd from the reaction mixt by filtrn, washed with H_2O, and dried. The resulting crude product was crystd from EtOH (50 ml) to yield 1.5 g of **7**, mp 148–149°. *Anal.* ($C_{14}H_{24}F_2N_2O_3$) C, H, N, F.

Solvolysis of 1,3-Bis(bromomethyl)-5-ethyl-5-phenylbarbituric Acid (6).—**6** (4.2 g, 0.01 mole) was dissolved in boiling abs EtOH (20 ml) and kept at reflux for 30 min. Upon cooling, crystals pptd, which were filtered and recrystd from 20 ml of abs EtOH to yield 3.16 g (90.5%) of **8**, mp 65–66°, identical in all respects with an authentic sample of the same compound.[1]

1,3-Bis(acetoxymethyl)-5,5-diphenylhydantoin (9).—5,5-Diphenylhydantoin (25.2 g, 0.1 mole) was dissolved in a mixt of 25 ml of dioxane and 100 ml of H_2O. To the soln, 37% aq HCHO (44 ml) and triethanolamine (5 ml) were added and the soln was heated at reflux for 7 hr. It was cooled to 25°, then acidified with dil HCl to pH 1. The soln was extrd with Et_2O; the Et_2O was evapd to yield an oil consisting of 1,3-bis(hydroxymethyl)-5,5-diphenylhydantoin. The oil was treated with 25 ml of Ac_2O and 25 ml of pyridine and allowed to stand at 25° overnight, then poured into ice–H_2O containing 25 ml of 38% HCl. A solid material pptd. The product was removed by filtrn, then washed (H_2O), and crystd from MeOH (500 ml) to yield **9**, mp 150–151° (yield 53.5%). *Anal.* ($C_{21}H_{20}N_2O_6$) C, H, N.

3-Acetoxymethyl-5,5-diphenylhydantoin (10).—3-Methoxymethyl-5,5-diphenylhydantoin[1] (6 g) was suspended in Ac_2O (20 ml). To the suspension was added 4 drops of anhyd $SnCl_4$. The suspension was stirred at 25° overnight, then poured into ice–H_2O (600 ml), whereupon a solid material pptd. The resulting crystals were filtered and then recrystd from abs EtOH to to yield 4.7 g (71% yield) of **10**, mp 162–163°. *Anal.* ($C_{18}H_{16}N_4O_4$) C, H, N.

Polymeric Phenobarbital Mixture (11).—**5** (3.2 g, 0.01 mole) was dissolved in DMF (100 ml). To the soln dry Ag phenobarbital (6.8 g) was added which in turn was obtained by pptn from an aq soln of Na phenobarbital and 1 equiv of $AgNO_3$ soln. The Ag phenobarbital was removed by filtrn, dried, and titrated iodometrically. The reaction mixt was stirred at 25° for 20 hr, the Ag salt was removed by filtrn and the filtrate was poured into H_2O (1000 ml). A solid pptd was removed by filtrn and dissolved in 100 ml of DMF. The soln was treated with activated C; C was removed by filtrn and the filtrate was poured into H_2O (1000 ml). The pptd product was filtered and dried under reduced pressure (25°) to yield 1.45 g of **6**. Mass spectral data indicated the presence of a pentameric product, mass unit of 120 g; mol wt: calcd for pentamer; 1209.20; for trimer; 720.72; calcd for mixt containing 30% pentamer and 70% of trimer; 866.7. Found, 870 (±20). *Anal.* (30% of $C_{64}H_{60}O_{15}N_{10}$, 70% of $C_{38}H_{36}O_7N_6$) C, H, N.

TABLE II
ANALYSES

Compd	Formula	Analysis
1	$C_{15}H_{16}N_2O_5$	C, H, N
2	$C_{18}H_{20}N_2O_7$	C, H, N
3	$C_{16}H_{18}N_4O_7$	C, H, N
5 (procedure A)	$C_{14}H_{24}Cl_2N_2O_3$	C, H, N, Cl
5 (procedure C)	$C_{14}H_{24}Cl_2N_2O_3$	C, H, N, Cl
6	$C_{14}H_{24}Br_2N_2O_3$	C, H, N, Br
7	$C_{14}H_{24}F_2N_2O_3$	C, H, N, F
9	$C_{21}H_{20}N_2O_6$	C, H, N
10	$C_{18}H_{16}N_2O_4$	C, H, N
11	30% of $C_{64}H_{60}N_{10}O_{15}$ 70% of $C_{38}H_{36}N_6O_9$	C, H, N
12	Unit of $C_{13}H_{12}N_2O_3$	C, H, N
13	$C_{48}H_{50}N_6O_{18}$	C, H, N
14	$C_{14}H_{20}N_2O_7$	C, H, N
15	$C_{20}H_{24}N_2O_7$	C, H, N

Phenobarbital Heptamer (12).—**6** (4.2 g, 0.01 mole) was dissolved in MeCN (150 ml). To the soln Ag_2CO_3 (2.75 g, 0.01 mole) was added and the reaction mixt was stirred at reflux for 5 hr. The Ag salt was removed by filtrn and the filtrate was poured into ice–H_2O (1000 ml) whereupon an oily substance pptd. The H_2O was decanted and the residue was dissolved in CH_2Cl_2 (20 ml). To this soln abs EtOH was added (200 ml), and the soln was concd to 150 ml. A white product (1.3 g) pptd which was collected by filtrn, then dissolved in C_6H_6, and chromatographed on silica gel. Elution with a C_6H_6–EtOAc (8:2 by vol) gave a solid material (900 mg) which was crystd from a 50% mixt of Me_2CO and EtOH to yield crystals: mp 205°; mol wt: calcd for heptamer, 1697.68. Found, 1660 (±50). *Anal.* (unit of $C_{13}H_{12}N_2O_3$), C, H, N.

***N*-Bis[(5′-ethyl-5′-phenyl-1′-barbituryl]methyleneoxysuccinyloxymethyl]phenobarbital Monohydrate (13).**—**5** (6 g) was dissolved in 100 ml of DMF. To the soln was added dry disilver succinate (6 g), which was obtained by pptn from a soln of Na succinate with 2 equiv of $AgNO_3$ in H_2O. The reaction mixt was heated at 110° overnight. The AgCl which pptd overnight was filtered off and the DMF soln was poured into 1000 ml of H_2O. The solid material was filtered and purified first by dissolving it in 10 ml of DMF and then treating the resulting soln with activated C. The C was removed by filtrn and the soln poured into H_2O (1000 ml). The ppt was filtered and dried to give 4.1 g of product (41% yield): mol wt: calcd for trimer monohydrate, 998. Found, 995 ±30. *Anal.* ($C_{48}H_{50}N_6O_{18}$) C, H, N.

1,3-Bis(acetoxymethyl)-5,5-diethylbarbituric Acid (14).—This compd was prepared from 5,5-diethylbarbituric acid and HCHO, followed by acetylation with Ac_2O in pyridine in the same manner described in procedure A for **2**. After acetylation an oily product was obtd which was extd into CH_2Cl_2. The solvent was evapd and the oily residue was chromatographed on silica gel. Elution with a C_6H_6–EtOAc mixt (9:1 by vol) provided a semicryst product which was crystd from hexane, then pentane to yield **14** (14.6 g, 57% yield), mp 64–65°. *Anal.* ($C_{14}H_{20}N_2O_7$) C, H, N.

1,3-Bis(propionoxymethyl)-5-ethyl-5-phenylbarbituric Acid (15).—The procedure was carried out as described in procedure A for **2** except that $(EtCO)_2O$ was substituted for Ac_2O, providing 4 g (20% yield) of **15**, mp 93.5–94.5°. *Anal.* ($C_{20}H_{24}N_2O_7$) C, H, N.

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