Anticonvulsants. 1. Alkoxymethyl Derivatives of Barbiturates and Diphenylhydantoin

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Alkoxymethyl derivatives of barbiturates and 5,5-diphenylhydantoin are effective anticonvulsants. Particularly effective are 1,3-bis(alkoxymethyl)-5-ethyl-5-phenylbarbituric acids which possess marked anticonvulsant activity against both electrically and chemically induced seizures. 3-Alkoxymethyl-5,5-diphenylhydantoins were also active against both maximal electroshock and pentylenetetrazole-induced seizures.

Phenobarbital and diphenylhydantoin are the most widely used drugs in the treatment of epilepsies.[3] However, phenobarbital has the disadvantage of being hypnotic, and occasionally produces a paradoxical exciting effect both in children and in the elderly.[4] Diphenylhydantoin, on the other hand, is known to have a multiplicity of side effects, including hypertrophic gingivitis, hirsutism, toxic psychoses, and megaloblastic anemia.[5]

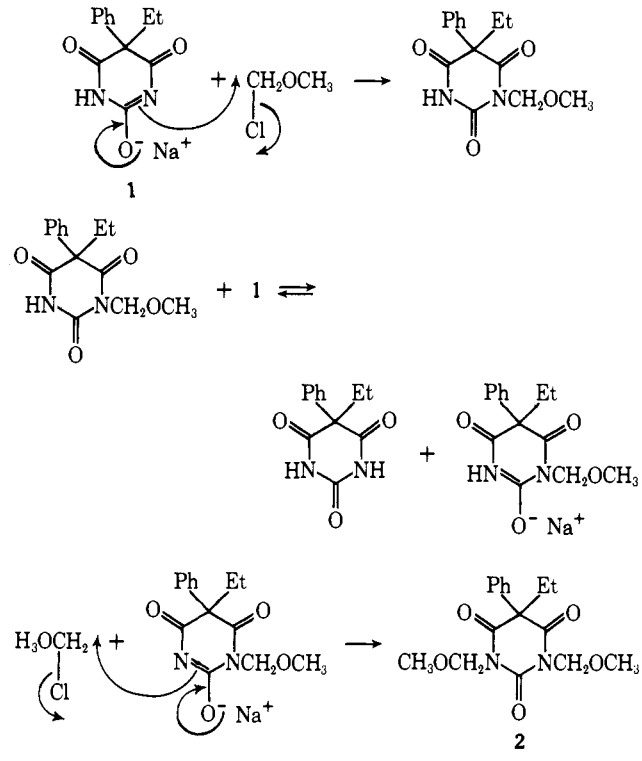
Our findings reveal that alkoxymethyl derivatives of barbiturates and diphenylhydantoin are effective anticonvulsants which possess potential advantages over their respective parent compounds.

The 1,3-bis(alkoxymethyl)phenobarbitals had marked anticonvulsant activity, yet were devoid of the hypnotic effects associated with the parent compound. Similarly the 1,3-bis(alkoxymethyl)barbitals had good activity against a convulsive dose of pentylenetetrazole, yet were devoid of hypnotic activity. In the 5,5-diphenylhydantoin series the 3-methoxymethyl derivative had the potency of the parent compound against maximal electroshock seizures and, unlike 5,5-diphenylhydantoin, was weakly active against pentylenetetrazole. Even more surprising was the finding that 3-benzyloxymethyl-5,5-diphenylhydantoin, and 3-butoxymethyl-5,5-diphenylhydantoin, like 5,5-diphenylhydantoin, displayed good activity against maximal electroshock seizures but, unlike 5,5-diphenylhydantoin, were effective against chemoshock as well.

The 1,3-bis(alkoxymethyl)barbiturates may be prepared conveniently by treating a barbiturate salt with an alkyl halomethyl ether. Thus the reaction of equimolar amounts of Na phenobarbital (**1**) and $ClCH_2OCH_3$ provided 1,3-bis(methoxymethyl)phenobarbital (**2**) in 50% yield. Fifty per cent of unreacted phenobarbital was recovered. The use of excess $ClCH_2OCH_3$ did not improve the yield of **2**. This may be explained by the sequence of reactions shown in Scheme I.

1-Methoxymethylphenobarbital, the first product of the reaction sequence is transformed into its Na salt through equilifiration with the excess of **1**. In turn, sodium 1-methoxymethylphenobarbital reacts with $ClCH_2OCH_3$ to produce **2**. The recovery of 50% phenobarbital is also accounted for in the reaction sequence.

SCHEME I

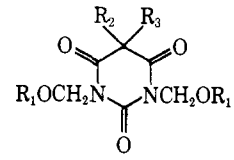


The dissociation constants of 5,5-disubstituted barbituric acids range from pK 7.1 to 8.1.[6] The acids can undergo a second ionization as well. The pK values are in the range of 11.7–12.7.[7] It appeared reasonable, therefore, to assume that a dialkali metal salt of a 5,5-disubstituted barbituric acid could be prepared. The dialkali metal salt of a 5,5-disubstituted barbituric acid, in turn, could be converted (without isolating the salt) into 1,3-bis(alkoxymethyl)-5,5-disubstituted barbituric acids upon reaction with an alkyl chloromethyl ether. Indeed the disodium salt of phenobarbital, obtained from phenobarbital and 2 moles of NaH in DMF, could be converted in nearly quantitative yield into **2** by treating the disodium salt *in situ* with 2 moles of $ClCH_2OCH_3$, as shown:

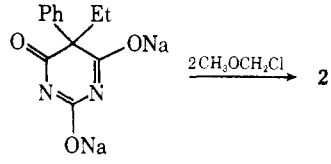
(1) Kendall Co., Cambridge, Mass.
(2) Northeastern University, Boston, Mass.
(3) (a) B. Wyke, "Principles of General Neurology," Elsevier, Amsterdam, 1969, p 288; (b) D. M. Woodbury "Basic Mechanisms of the Epilepies," H. H. Jasper, A. A. Ward, and A. Pope, Ed., Little Brown and Co., Boston, Mass., 1969, pp 647–688.
(4) R. P. Schmidt and B. J. Wilder, "Epilepsy," F. A. Davis, Philadelphia, Pa., 1968, p 148.
(5) L. Meyler, Ed., "Side Effects of Drugs," Volume V, Excerpta Medica Foundation, Amsterdam, 1966, pp 78–82.
(6) W. J. Doran, *Med. Chem.*, **4**, 8 (1959).
(7) T. C. Butler, J. M. Ruth, and G. F. Tucker, *J. Amer. Chem. Soc.*, **77**, 1488 (1955).

TABLE I

PHARMACOLOGICAL ACTIVITY OF 1,3-BIS(ALKOXYMETHYL)-5,5-DISUBSTITUTED BARBITURIC ACIDS



R_1	R_2	R_3	MES, ED_{50} mg/kg	Met ED_{50} mg/kg	Peak time, hr	LD_{50}, mg/kg
CH_3	C_2H_5	C_6H_5	13.5 (8–22.7)	47.0 (29.4–75.2)	2	470 (376–588)
$C_6H_5CH_2$	C_2H_5	C_6H_5	~25	~50	1	>500
n-C_4H_9	C_2H_5	C_6H_5	>50 <100			>500
C_2H_5	C_2H_5	C_6H_5	>12.5 <25		1.5	>375 <500
n-$C_{12}H_{25}$	C_2H_5	C_6H_5	~50		2	>500
CH_3	C_2H_5	C_2H_5	~50	6.2 (4.6–8.4)	1	>1000
n-$C_{12}H_{25}$	C_2H_5	C_2H_5		>200		
CH_3	Allyl	2-Pentyl	<200	~100		>500 <1000
$C_6H_5CH_2$	Allyl	2-Pentyl	>200	>200		>1000



Pharmacological Studies. Maximal Electroshock Seizures (MES) and Time of Peak Effect in the Mouse.—The procedure was the same as that of Swinyard, *et al.*,[8] except that (1) Charles River mice were used and (2) a current of 60 mA was employed for corneal stimulation. The time of peak anticonvulsant activity (MES) was determined according to Swinyard, *et al.*[8]

Antipentylenetetrazole Activity (Met).—The procedure of Swinyard, *et al.*,[8] was followed, except for using Charles River mice, and a dosage of 106 mg/kg of pentylenetetrazole.

Acute Toxicity.—The compound was suspended or dissolved in 10% aq acacia and administered orally to adult male albino mice at 1–5 dosage levels. Deaths were recorded daily for 1 week.

Median effective and lethal dose (ED_{50} and LD_{50}) was determined according to Litchfield and Wilcoxon.[9]

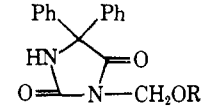
Hypnotic Activity.—The pattern of toxicity in mice and rats disclosed progressive depression of the CNS; death resulting from respiratory paralysis. Sleep, however, did not appear except at lethal doses.

The results of these studies have been summarized in Tables I and II. The anticonvulsant activity of the aliphatic alkoxymethylbarbiturates decreased as the size of the alkoxy group increased (see Table III). In the methoxy-, ethoxy-, *n*-butoxy-, and *n*-dodecyloxymethyl series the methoxymethyl derivatives were the most potent anticonvulsants. Alkoxymethyl-substituted derivatives, where the alkoxy substituent is branched aliphatic or alicyclic, offered no advantage over the methoxymethyl derivative.

In the 5,5-diphenylhydantoin series (see Table IV) activity against maximal electroshock seizures decreased as the size of the alkoxy group increased. Thus, while the methoxymethyl derivative was weakly active against pentylenetetrazole, both the *n*-butoxymethyl and benzyloxymethyl derivatives displayed good activity against chemoshock.

TABLE II

PHARMACOLOGICAL PROPERTIES OF 3-ALKOXYMETHYL-5,5-DIPHENYLHYDANTOINS



R	MES ED_{50}, mg/kg	Met ED_{50}, mg/kg	Peak time, hr	LD_{50}, mg/kg
CH_3	~6	Weakly active	3	
n-C_4H_9	<25	~50	1	>500
$C_6H_5CH_2$	>25	<50	1	

Experimental Section

Microanalyses were within ±0.3% of the theoretical values as performed by Galbraith Laboratories, Knoxville, Tenn. Melting points were obtained on a Fisher-Johns hot stage and are corrected. Ir spectra were recorded on a Perkin-Elmer 337 grating infrared spectrophotometer. Nmr spectra were run on a Varian Associates A60A spectrometer in $(CD_3)_2SO$ using Me_4Si as internal reference. All ir and nmr spectra were obtained as expected. Mass spectra were determined on a Hitachi RMU-6D double focusing spectrometer at 70 eV.

Chromatographic separations were obtained using silica gel, Davison Type 950, 60-200 mesh. Evapns were carried out on a Büchi Rotavapor apparatus. Merck HF-254 + 366 silica gel, according to Stahl, was used for tlc development with PhH–EtOAc mixts.

1,3-Bis(alkoxymethyl)-5,5-disubstituted Barbituric Acids.—The following examples illustrate the procedures used in the preparation of these compds, shown in Table III.

Procedure A.—To a suspension of 1 (25.4 g, 0.1 mole) in DMF (100 ml) was added a 2.2 equiv wt of $ClCH_2OCH_3$. The reaction mixt was stirred at 25° for 20 hr, then poured into ice–H_2O (200 ml). The product was removed by filtrn, washed with H_2O, and crystd from EtOH to yield 14.8 g of **2**, mp 116–118°.

Procedure B.—Sodium barbital (4.1 g, 0.02 mole) was suspended in DMF (20 ml). $ClCH_2OCH_3$ (2.2 equiv wt) was added over a period of 15 min. The reaction mixt was stirred for 4 hr and poured into ice–H_2O (100 ml), and the product was extd into EtOAc. The dried (Na_2SO_4) EtOAc soln was evapd and the product was purified by column chromatography on silica gel. Elution with a C_6H_6–EtOAc mixt (9:1 by vol) yielded pure 1,3-bis(methoxymethyl)-5,5-diethylbarbituric acid (2.2 g), an oil.

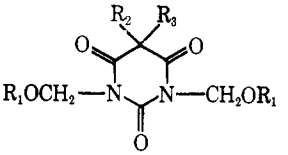
Procedure C.—Phenobarbital (23.2 g, 0.1 mole) was dissolved in DMF (250 ml). To the soln was added KO-*tert*-Bu (11.29 g)

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

(9) J. T. Litchfield, Jr. and F. Wilcoxon, *ibid.*, **96**, 99 (1949).

TABLE III

1,3-BIS(ALKOXYMETHYL)-5,5-DISUBSTITUTED BARBITURIC ACIDS

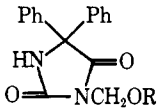


Procedure	Base	R_1	R_2	R_3	Mp, °C	Yield, %	Formula[b]
A		CH_3	C_2H_5	C_6H_5	116–118	46.5	$C_{16}H_{20}N_2O_5$
A		$C_6H_5CH_2$	C_2H_5	C_6H_5	74–75	10	$C_{28}H_{28}N_2O_5$
A		n-C_4H_9	C_2H_5	C_6H_5	71–72	30	$C_{22}H_{32}N_2O_5$
A		C_2H_5	C_2H_5	C_6H_5	65–66	19	$C_{18}H_{24}N_2O_5$
A		n-$C_{12}H_{25}$	C_2H_5	C_6H_5	48–50	21	$C_{38}H_{64}N_2O_5$
B		CH_3	C_2H_5	C_2H_5	Oil	40	$C_{12}H_{20}N_2O_5$
B		n-$C_{12}H_{25}$	C_2H_5	C_2H_5	Oil	30	$C_{34}H_{64}N_2O_5$
B		CH_3	Allyl	2-Pentyl	Oil	10	$C_{16}H_{26}N_2O_5$
B		$C_6H_5CH_2$	Allyl	2-Pentyl	Oil	15	$C_{28}H_{34}N_2O_5$
C	KOBu	CH_3	C_2H_5	C_6H_5	116–118	63.5	$C_{16}H_{20}N_2O_5$
C	LiOH[a]	CH_3	C_2H_5	C_6H_5	116–118	66	$C_{16}H_{20}N_2O_5$
D	NaH	CH_3	C_2H_5	C_6H_5	116–118	92	$C_{16}H_{20}N_2O_5$
D	LiH	CH_3	C_2H_5	C_6H_5	116–118	94	$C_{16}H_{20}N_2O_5$
D	KH	CH_3	C_2H_5	C_6H_5	116–118	80	$C_{16}H_{20}N_2O_5$
E	LiH	n-$C_{12}H_{25}$	C_2H_5	C_2H_5	Oil	55	$C_{34}H_{64}N_2O_5$
E	LiH	$C_6H_5CH_2$	Allyl	2-Pentyl	Oil	79	$C_{28}H_{34}N_2O_5$

[a] This experiment was carried out at room temp. [b] All compds were analyzed for C, H, N.

TABLE IV

3-ALKOXYMETHYL-5,5-DIPHENYLHYDANTOINS



R	Mp, °C	Yield, %	Formula[a]
CH_3	127–128	67	$C_{17}H_{16}O_3N_2$
n-C_4H_9	108–110	26	$C_{20}H_{22}O_3N_2$
$C_6H_5CH_2$	151–152	35	$C_{23}H_{20}O_3N_2$

[a] See Table I, footnote *b*.

and the mixt was warmed to 100° at which temp all solids had dissolved. The soln was cooled to 50°, and $ClCH_2OCH_3$ (8 g) was added, and the mixt was stirred for 1 hr. To the suspension another amt of KO-*tert*-Bu (11.29 g) was added and the mixt was heated to 50°. Another portion of $ClCH_2OCH_3$ (16 g) was added, the mixt was stirred for 1 hr and then pured into ice–H_2O, and the ppt was removed by filtrn and washed with H_2O. The crude product was crystd from EtOH to yield 20 g of **2**, mp 116–118°.

Procedure D.—Phenobarbital (23.2 g, 0.1 mole) was dissolved in DMF (250 ml). To the cooled soln LiH (1.6 g, 0.2 mole) was added and the mixt was stirred for 30 min. $ClCH_2OCH_3$ (2.2 equiv wt) was added to the mixt over a period of 30 min. The reaction mixt was stirred for 1 hr, then poured into ice–H_2O (120 ml). The solid ppt was filtered, washed with H_2O, and crystd from EtOH. The yield of **2** was 29.4 g (92%), mp 116–118°.

Procedure E.—Barbital (1.87 g, 0.01 mole) was dissolved in DMF (20 ml). To the soln was added LiH (176 mg, 0.022 mole), the mixt was stirred for 20 min, then n-dodecyl chloromethyl ether[10] (5.1 g, 0.0218 mole) was added, and the reaction mixt was warmed to 100°, stirred for 30 min, allowed to cool to 25° overnight, and poured into ice–H_2O. The product was extd into EtOAc, the solvent evapd, and the crude product purified by column chromatography on silica gel. Elution with a C_6H_6–EtOAc mixt (8:2 by vol) provided pure 1,3-bis(n-dodecyloxymethyl)-5,5-diethylbarbituric acid (3.2 g).

3-Alkoxymethyl-5,5-diphenylhydantoin.—The following example illustrates the procedure used in the prepn of 3-alkoxymethyl-5,5-diphenylhydantoins. 5,5-Diphenylhydantoinsodium (27.5 g, 0.1 mole) was suspended in DMF (250 ml). To the suspension $ClCH_2OCH_3$ (8.8 g, 0.11 mole) was added over a period of 30 min. The reaction mixt was stirred at 25° overnight, then poured into H_2O (1000 ml). The solid ppt was removed by filtrn, washed with H_2O, and crystd from aq EtOH (50%) to yield pure 3-methoxymethyl-5,5-diphenylhydantoin, (20 g, 67%), mp 127–128°.

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(10) All alkyl chloromethyl ethers were prepared according to A. J. Hill and De W. T. Keach, *J. Amer. Chem. Soc.*, **48**, 257 (1926). Compare German Patent 578,568 (1931) and U. S. Patent 2,012,073 (1931).