8. Smith, C. H., *Pediatrics,* 1956, v17, 596.

9. Bothwell, T. H., and Mallett, B., *Clin. Sci.,* 1955, v14, 235.

10. Høyer, K., *Acta med. scand.,* 1944, v119, 562.

11. Waldenström, J., *Acta med. scand.,* 1946, Suppl. 170, 252.

12. Schaefer, K.-H., and Boenecke, I., *Arch. f. exp. Path. u Pharmakol.,* 1949, v207, 666.

13. Hemmeler, G., *Métabolisme du fer,* 1951, Masson et Cie., Paris.

14. Josephson, B., and Larsson, H., *Skand. Arch. f. Physiol.,* 1934, v69, 227.

15. Forsgren, E., *Über die Rhythmik der Leberfunktion, des Stoffwechsels und des Schlafes,* 1935, Marcus, Stockholm.

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Anticonvulsant Activity of Some Substituted Ethylene Glycols. (23404)

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The clinical utility of diols such as mephenesin and 2,2-diethyl-1,3-propanediol (DEP) (I) has been limited by the short duration of action of these otherwise interesting drugs. Riley and Berger(1), and Berger and Ludwig(2) showed that rapid oxidation of the hydroxyl groups is responsible for this brief effect. Therefore it seemed desirable to synthesize structural variants less vulnerable to oxidative detoxication.

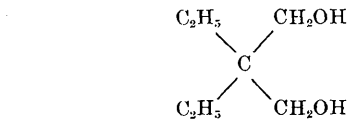
In this study a structural modification was considered favorable when the compound was effective against both electroshock and Metrazol convulsions at a dose below 100 mg/kg and had a duration of not less than 3 hours.

Methods. All compounds examined were administered orally as 5% gum acacia suspensions to Wistar-strain rats of either sex. The anticonvulsant activity of the compounds was measured at a predetermined time of peak activity by the maximal electroshock seizure test (M.E.S.) of Toman *et al.*(3), and by the subcutaneous Metrazol seizure test (Met.) described by Goodman *et al.*(4). The animals were observed before and after the convulsive challenges. Particular emphasis was placed on detection of motor impairment and other manifestations of central depression when present. Dose-response curves were established for active compounds whenever supply permitted. At least 3 dosage groups of 8 animals each were used to complete the median effective doses (ED_{50}) by the method of Bliss(5).

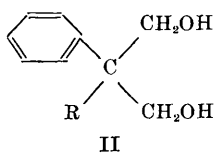
TABLE I. Effect of DEP Modification on Activity.

Compound	$ED_{50} \pm$ S.E. (mg/kg) Maximal electroshock seizure	Metrazol seizure	Peak action (min.)
I (DEP)	154.4 ± 7.7	155.2 ± 8.4	30
II a	159.0 ± 9.9	229.3 ± 17.2	30–60
II b	142.8 ±11.4	235.3 ± 30.6	30
III	120.7 ± 9.3	181.0 ± 15.4	30–90

Results. Table I shows the effect of modification of the DEP molecule upon anticonvulsant activity. Replacement of one ethyl group by phenyl (IIb) enhanced the depressant effect. A similar observation has been reported by Berger(6). In a further variation, the 1,3-diol arrangement of IIa was changed to 1,2-diol (III). Although this alteration diminished the depressant effect, the anticonvulsant activity of the new compound was superior to that of either I or II (Table I).

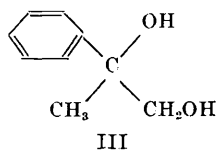


I (DEP)



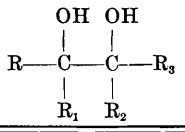
II

a) R = CH_3
b) R = C_2H_5



III

TABLE II. Effect of Glycol Substituents on Activity.



	R	R_1	R_2	R_3	$ED_{50} \pm$ S.E. (mg/kg) Maximal electroshock seizure	$ED_{50} \pm$ S.E. (mg/kg) Metrazol seizure	Peak action (min.)
1	C_6H_5	H	H	H	300	300	
2	"	CH_3	H	H	120.7 ± 9.3	181.0 ± 15.4	30– 90
3	"	C_2H_5	H	H	190.6 ± 21.5	173.8 ± 22.6	30
4	"	nC_3H_7	H	H	250	200	
5	"	C_6H_5	H	H	99.0 ± 11.1	200	30– 60
6	"	CH_3	CH_3	H	121.3 ± 20.0	137.9 ± 23.4	30–180
7	"	C_2H_5	"	H	119.1 ± 11.4	125.1 ± 12.5	30– 90
8	"	C_6H_5	"	H	107.6 ± 7.5	308.9 ± 38.6	30– 90
9	"	H	C_3H_7	C_3H_7	400	200	
10	"	CH_3	CH_3	CH_3	75.1 ± 10.1	150.5 ± 12.3	30–120
11	"	C_2H_5	"	"	100	69.2 ± 7.3	60
12	"	CH_3	C_2H_5	"	146.2 ± 8.5	88.7 ± 7.8	30– 90
13	"	"	C_3H_7	"	>160	73.5 ± 5.1	60
14	"	"	C_2H_5	C_2H_5	Tremors at 400 mg/kg		
15	Isoamyl	"	CH_3	CH_3	89.7 ± 9.4	86.3 ± 8.0	30
16	nC_3H_7	nC_3H_7	"	"	160	>160	
17	Cyclohexyl		"	"	100	>200	

In view of the enhanced anticonvulsant activity, systematic study of substituted ethylene glycols was undertaken.

In Table II may be seen the effect upon anticonvulsant potency afforded by alteration of the groups attached to the ethylene glycol nucleus. From these studies, 5 monophenyl substituted 1,2-diols were chosen and further altered by the substitution of halogen, methyl, or methoxy radicals in the phenyl ring. Completely substituted ethylene glycols are more potent anticonvulsant agents than tri-, di-, or monosubstituted analogues. The l-phenyl-l-methyl configuration seems particularly desirable, for all l-phenyl-l-ethyl compounds have short duration of action and the l-l-diphenyl variants lack anti-Metrazol efficacy.

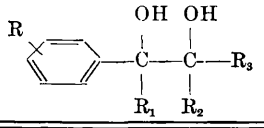
The optimal substitution of the second carbon atom of the ethylene glycols seems to be either monomethyl, dimethyl, or ethyl methyl. Larger groups cause loss of activity or other toxic effects, as observed in the diethyl compound No. 14.

Further modifications by substitution in the phenyl ring of compounds 2, 6, 10, 11 and 12 are summarized in Table III. In general, meta- or para-chlorination markedly improves anticonvulsant activity, whereas methyl or methoxy substitution reduces activity from that of the parent compound. Two analogues are of special interest. Compound 25, 2-*m*-chlorophenyl - 3 - methyl-2,3-butanediol, the most potent of the entire series, is equally effective as an anti-electroshock and anti-Metrazol agent. This equipotency is also observed in other meta-substituted phenyl compounds. Compound 26, 2-*p*-chlorophenyl-3-methyl - 2,3 - butanediol (phenaglycodol), though less potent than Compound 25, has the longest duration of action of the diols studied. It is devoid of manifestations of toxicity at effective dose levels. Studies by Slater *et al.* (7) indicate that this compound acts as a polysynaptic depressant.

Gruber and Mosier(8) have found the phenaglycodol to be an effective anticonvulsant. In addition, extensive clinical trials have shown that it is a useful neurosedative agent.

Discussion. The purpose of this investigation was the synthesis of structural variants of the DEP molecule that were longer in duration without sacrifice of potency. Phenaglycodol (2-*p*-chlorophenyl-3-methyl-2, 3-butanediol) is more potent and longer acting than DEP.

TABLE III. Effect of Aromatic Substituents on Activity.



	R	R_1	R_2	R_3	$ED_{50} \pm$ S.E. (mg/kg) Maximal electroshock seizure	$ED_{50} \pm$ S.E. (mg/kg) Metrazol seizure	Peak action (min.)
2	H	CH_3	H	H	120.7 ± 9.3	181.0 ± 15.4	30– 90
18	*o*-Cl	"	H	H	>125	>100	
19	*m*-Cl	"	H	H	111.9 ± 11.4	118.5 ± 14.2	30
20	*p*-Cl	"	H	H	>100	>100	
21	*o*-CH_3	"	H	H	>140	>400	
22	*m*-CH_3	"	H	H	144.2 ± 14.1	149.0 ± 23.8	30
23	*p*-CH_3	"	H	H	>250	>200	
6	H	"	CH_3	H	121.3 ± 20	137.9 ± 23.4	30–180
24	*p*-Cl	"	"	H	104.8 ± 11.5	73.8 ± 10	30–180
10	H	"	"	CH_3	75.1 ± 10.1	150.5 ± 12.3	30–120
25	*m*-Cl	"	"	"	35.8 ± 2.1	34.1 ± 4.3	60–180
26	*p*-Cl	"	"	"	63.0 ± 6.6	45.1 ± 7.7	60–240
27	*p*-F	"	"	"	77.9 ± 3.9	58.0 ± 6.7	30–120
28	*m*-CH_3	"	"	"	>100	>160	
29	*p*-CH_3	"	"	"	>100	>200	
30	*p*-OCH_3	"	"	"	>200	>250	
31	*m*-Cl	"	C_2H_5	"	92.4 ± 8.1	91.0 ± 10.9	30– 90
32	*p*-Cl	"	"	"	88.8 ± 7.4	74.8 ± 10.1	60–180
33	*p*-Cl	C_2H_5	CH_3	"	>250	>250	

This interesting activity seems dependent upon full substitution of the ethylene glycol nucleus. Such a configuration should reduce susceptibility to oxidative biotransformation. Current studies are directed toward elucidation of the metabolic fate of phenaglycodol.

Summary. 1. A series of substituted ethylene glycols has been studied for anticonvulsant activity by both the maximal electroshock seizure and subcutaneous Metrazol seizure tests. 2. Fully substituted ethylene glycols are more potent anticonvulsant agents than mono-, di-, or trisubstituted analogues. 2-*p*-Chlorophenyl - 3 - methyl-2, 3-butanediol (phenaglycodol) has been selected for clinical trial since it has high potency and long duration of action. It is suggested that the long duration of action may be related to full substitution of the ethylene glycol nucleus which should reduce the probability of oxidative detoxification.

1. Riley, R. F., and Berger, F. M., *Arch. Biochem.*, 1949, v20, 159.

2. Berger, F. M., and Ludwig, B. J., *J. Pharmacol. Exp. Therap.*, 1950, v100, 27.

3. Toman, J. E. P., Swinyard, E. A., and Goodman, L. S., *J. Neurophysiol.*, 1946, v9, 231.

4. Goodman, L. S., Toman, J. E. P., and Swinyard, E. A., *Am. J. Med.*, 1946, v1, 213.

5. Bliss, C. I., *Quart. J. Pharm. and Pharmacol.*, 1939, v11, 192.

6. Berger, F. M., PROC. SOC. EXP. BIOL. AND MED., 1951, v78, 277.

7. Slater, I. H., Jones, G. T., and Young, W. K., *ibid.*, 1956, v93, 528.

8. Gruber, C. M., Jr., and Mosier, J. M., *ibid.*, 1957, v94, 384.

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