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NEW SEDATIVES AND ANTICONVULSANTS

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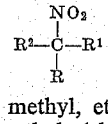
4 Claims. (Cl. 167—65)

My invention relates to new sedative and anticonvulsant compounds and more particularly it relates to the use of substituted primary nitroalcohols as sedative and anticonvulsants.

In recent years a number of new drugs have been made available for use in the treatment of various types of mental disorders. These are generally classified as relaxant, ataraxic or antiphobic drugs depending upon the particular form of mental ailment for which they have been found to be most suitable.

The relaxant drugs ordinarily produce reversible paralysis of the voluntary muscles without significantly affecting autonomic functions. One of the most widely used drugs of this type at the present time is 2-methyl-2-n-propyl-1,3-propanediol dicarbamate, generally known as meprobamate. Like most drugs, however, meprobamate is not equally effective with all patients and it produces undesirable side effects in many cases including such unfavorable effects as cutaneous, muscular, gastrointestinal, and paradoxical cerebral effects. The desirability of having available drugs not subject to all or even a portion of these undesirable effects and in general are even more effective as relaxants appears obvious.

I have discovered that the compounds designated by the structural formula



where R is hydrogen, methyl, ethyl, n-propyl, and isopropyl, R^1 is hydroxymethyl, 1-hydroxyethyl, and 1-hydroxypropyl, and R^2 is methyl, ethyl and hydroxymethyl, are effective sedatives and anticonvulsants which act on the central nervous system below the cerebrum. For this reason they exert their relaxant effects without marked sedation, as is caused by the barbiturates. Specific examples of such compounds include 2-nitro-2-n-propyl-1,3-propanediol, 2-nitro-2-isopropyl-1,3-propanediol, 2-nitro-2-methyl-1-propanol, 2-nitro-2-methyl-1-butanol, 3-nitro-2-butanol, and 4-nitro-3-hexanol.

My new sedative and anticonvulsant drugs were evaluated by comparing the anticonvulsant action of the drugs in male, white mice, weighing 18 to 22 g. The compounds being evaluated were dissolved in pyrogen free water or suspended in 10% acacia and the desired dose administered either orally or intraperitoneally. When the compounds were administered intraperitoneally, 100 mgs./kg. of Metrazol were given intraperitoneally simultaneously with the test compound. In the oral studies, 100 mgs./kg. of Metrazol were given intraperitoneally 30 minutes after the compound. All mice were observed one hour for convulsions and 18–24 hours for death. Five mice were employed at each level and a maximum dose of 500 mgs./kg. was used. Compounds incapable of preventing Metrazol convulsions at this level were considered too inactive to warrant additional studies. Table I below gives the results of convulsant studies on my new relaxants and compares them with the previously known relaxant Tridione and myanesin. The upper row of figures following each compound represents results from oral administration, and the lower row intraperitoneal administration.

Table I

	LD_{50}, mg./kg.	ACD_{50}, mg./kg.	ALD_{50}, mg./kg.	$\frac{LD_{50}}{ACD_{50}}$	$\frac{LD_{50}}{ALD_{50}}$
2-nitro-2-propyl-1,3-propanediol	1,220±101	168±36	140±25	7.3	8.8
	612±25	184±45	56±10	3.3	10.9
2-nitro-2-isopropyl-1,3-propanediol	820±110	298±38	108±26	2.8	7.6
	960±93	213±93	91±11	4.5	10.5
2-nitro-2-methyl-1-propanol	1,020±112	325±63	178±28	2.8	5.7
	800±121	175±33	86±22	4.6	9.3
2-nitro-2-methyl-1-butanol	820±78	205±40	142±30	4.0	5.8
Tridione	1,360±96	380±48	122±31	3.6	11.1
Myanesin-3-(o-toloxy)-1,2-propanediol	610±10	----------	80	----------	7.6

ACD=Anticonvulsant dose.
ALD=Antilethal dose.
$\frac{LD_{50}}{ACD_{50}}$=Anticonvulsant index.

Table II shows the duration of anticonvulsant activity of my new relaxants in mice.

Table II

	Route of Administration	Dose, mg./kg.	Duration of Activity in Hours	
			Anticonvulsant	Antilethal
2-nitro-2-n-propyl-1,3-propanediol.	IP	400	1	1
2-nitro-2-isopropyl-1,3-propanediol.	IP	500	2	2
2-nitro-2-isopropyl-1,3-propanediol.	Oral	500	2	2
2-nitro-2-methyl-1-butanol	IP	300	(1)	----------

[1] Control mice given Metrazol simultaneously with 300 mg./kg. of this compound had typical Metrazol convulsions 82-120 minutes after Metrazol was administered.

Certain of my compounds were tested by the method of E. A. Swinyard (J. Am. Pharm. Assoc., scientific ed., 38, 201, (1949)), to determine the electroshock convulsive threshold of mice determined by using a stimulus delivered from an electroshock apparatus. The mice were stimulated with a small rat electrode placed on the parietal lobes just behind the eyes. They were restrained only by the hand and released immediately after a stimulation lasting 0.2 second. The compound tested was dissolved in water and 300 mg./kg. administered intraperitoneally to the test animal. Twenty minutes after administration of the compound maximal electroshock seizure (MES) and normal electroshock threshold (NET) tests were made. The end point for MES tests was abolition of the extension of the hind legs during the

tonic phase of the seizure when a stimulus five times the threshold was employed. Absence of facial clonus for a period of 10 seconds following stimulation with a shock 20% greater than threshold was taken as the end point for the NET tests.

Table III below gives results for certain of my compounds tested in this manner.

Table III

Compound	TD_{50}[1]	Percent Protected, 300 mg./kg. NET Test	Percent Protected, 300 mg./kg. MES Test
2-nitro-2-methyl-1-propanol	420±75	100	100
2-nitro-2-isopropyl-1,3-propanediol	423±62	60	60
2-nitro-2-n-propyl-1,3-propanediol	345±60	80	100
2-nitro-2-methyl-1-butanol	235±55	[2] 100	[2] 100

[1] Toxic doses.
[2] At 200 mg./kg.

Table IV below shows a comparison of certain of my compounds with the relaxant meprobamate. In each case the compound was administered orally to the test animals (mice) and the time of reaction determined. The values are in minutes except where otherwise indicated.

Table IV

	2-methyl-2-n-propyl-1,3-propanediol (meprobamate)			2-nitro-2-n-propyl-1,3-propanediol dicarbamate			4-nitro-3-hexanol
	1,600 mg./kg.	800 mg./kg.	400 mg./kg.	1,600 mg./kg.	800 mg./kg.	400 mg./kg.	400 mg./kg.
Time of first evidence of disturbance.	2-3	2-3	3-4	<1	1	2	2.
Time of greatest depression	7	10	15	3	6	18	2.
Time of hypnosis	12	20	none	7	15	none	none.
Time of catalepsy	<40	none	none	<30	none	none	none.
Time of onset of recovery	4 hrs.	2 hrs.	1½ hrs.	4½ hrs.	1½ hrs.	1 hr.	30.
Time of complete recovery	8 hrs.	5½ hrs.	2 hrs.	8 hrs.	5 hrs.	2 hrs.	2 hrs.

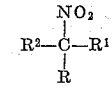
I am aware of the fact that certain substituted diols and dicarbamates of substituted diols possess central depressant properties. I have now discovered, however, that the introduction of the NO_2 group into substituted diols gives central nervous system depressants of equal and in some cases decidedly higher effectiveness than previously known drugs of this type and which possess the additional advantage of being relatively free from the concomitant depression or anesthesia generally induced by previously available drugs of this class.

The results with animals shown in the tables above have been confirmed by clinical use in man. One to two 0.25 g. doses administered four times daily produced a generally tranquilizing effect and in some patients an hypnotic effect as well.

My new sedatives and anticonvulsants are preferably administered orally in the form of tablets, capsules or other suitable forms. Preferred doses range from 0.25 to 0.50 gm., two to four times daily, or single doses of 0.5 to 1.0 gm. daily.

Now having described my invention what I claim is:

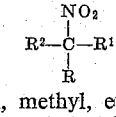
1. A composition in unit dosage form for use in producing ataraxia containing as the essential active ingredient 0.25–0.5 g. of a compound having the structural formula:



where R is hydrogen, methyl, ethyl, n-propyl, and isopropyl, R^1 is hydroxymethyl, 1-hydroxyethyl, and 1-hydroxypropyl, and R^2 is methyl, ethyl and hydroxymethyl.

2. A composition in unit dosage form for use in producing ataraxia containing as the essential active ingredient 0.25–0.5 g. of 2-nitro-2-propyl-1,3-propanediol.

3. The process of effecting ataraxic effects in the living human body which comprises administering a compound having the structural formula:



where R is hydrogen, methyl, ethyl, n-propyl, and isopropyl, R^1 is hydroxymethyl, 1-hydroxyethyl, and 1-hydroxypropyl, and R^2 is methyl, ethyl and hydroxymethyl.

4. A process of effecting ataraxic effects in the living human body which comprises administering in oral unit dosage form 2-nitro-2-propyl-1,3-propanediol in amounts ranging from 1.0 g. to 2.0 g. per day.

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UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 2,902,404 September 1, 1959

Joseph N. Spencer

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Columns 3 and 4, Table IV, the heading over columns 2, 3, and 4 thereof, for "2-methyl-2-n-propyl-1,3-propanediol (meprobamate)" read -- 2-methyl-2-n-propyl-1,3-propanediol dicarbamate (meprobamate) --; same columns 3 and 4, Table IV, the heading over columns 5, 6, and 7 thereof, for "2-nitro-2-n-propyl-1,3-propanediol dicarbamate" read -- 2-nitro-2-n-propyl-1,3-propanediol --.

Signed and sealed this 9th day of August 1960.

(SEAL)
Attest:

KARL H. AXLINE
Attesting Officer

ROBERT C. WATSON
Commissioner of Patents