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Anticonvulsant Properties of α-, γ-, and α,γ-Substituted γ-Butyrolactones

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SUMMARY

Derivatives of γ-butyrolactone (GBL) substituted on the α- and/or γ-positions were synthesized and tested for their effects on behavior in mice, on the electroencephalographs and blood pressure of paralyzed-ventilated guinea pigs, and on electrical activity of incubated hippocampal slices. Several compounds, including α-ethyl-α-methyl GBL (α-EMGBL), α,α-dimethyl GBL, α,γ-diethyl-α,γ-dimethyl GBL, and γ-ethyl-γ-methyl GBL, prevented seizures induced by pentylenetetrazol, β-ethyl-β-methyl-γ-butyrolactone (β-EMGBL), picrotoxin, or all three compounds in mice and guinea pigs but had no effect on seizures induced by maximal electroshock or bicuculline. Neither γ-hydroxybutyrate (GHB) nor α-isopropylidene GBL had any anticonvulsant activity. The anticonvulsant α-substituted compounds had a potent hypotensive effect and antagonized the hypertensive effect of β-EMGBL. α-EMGBL was tested in incubated hippocampal slices and was found to depress basal activity and antagonize excitation induced by β-EMGBL. These results demonstrate that α-alkyl-substituted GBL and, to a lesser extent, γ-substituted derivatives are anticonvulsant agents and that their effects are strikingly different from those of GHB or β-alkyl-substituted GBLs, which are epileptogenic. Possibly β- and α-substituted GBLs act at the same site as agonists and antagonists, respectively.

INTRODUCTION

GHB[2] and GBL produce effects in experimental animals which have been suggested to be similar to petit mal absence seizures in humans (1–3). The effects of GHB and GBL are prevented by drugs such as ESM and TMO, which are effective in the treatment of petit mal absence seizures. Structural similarities between the five-membered heterocyclic rings of GBL, ESM, and TMO led to the hypothesis that alkyl-substituted GBLs may have actions very different from those of the unsubstituted compound. In the preceding report (4), we studied the behavioral and electrophysiological effects of β-substituted GBLs and found them to be potent convulsants. In the present study, α-, γ-, and α,γ-substituted GBLs (Fig. 1) were examined and found to have anticonvulsant activity. In a following report (5), the activities of α,β-substituted GBLs are examined and the structure-activity relationships of GBLs are discussed.

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[2] The abbreviations used are: GBL, γ-butyrolactone; GHB, γ-hydroxybutyrate; ESM, ethosuximide; TMO, trimethadione; PHT, phenytoin; PTZ, pentylenetetrazol; PTX, picrotoxin; BIC, bicuculline; γ-EMGBL, γ-ethyl-γ-methyl-γ-butyrolactone; α-EMGBL, α-ethyl-α-methyl-γ-butyrolactone (α-EMGHB, the corresponding hydroxy analogue); α-DMGBL, α,α-dimethyl-γ-butyrolactone; DMSM, dimethylsuccinimide; β-EMGBL, β-ethyl-β-methyl-γ-butyrolactone; β-DMGBL, β,β-dimethyl-γ-butyrolactone; α,γ-DEMGBL, α,γ-diethyl-α,γ-dimethyl-γ-butyrolactone; α-IPGBL, α-isopropylidene-γ-butyrolactone; EEG, electroencephalograph(ic).

MATERIALS AND METHODS

Drugs and Chemicals

ESM (Zarontin) and PHT (Dilantin) were obtained from Parke-Davis (Morris Plains, N. J.). PTZ, PTX, and BIC were obtained from Sigma Chemical Company (St. Louis, Mo.). γ-EMGBL was obtained from Aldrich Chemical Company (Milwaukee, Wisc.).

Chemical Syntheses

General chemical methods. All chemical methods were identical with those previously reported (4).

Synthesis of α-EMGBL, α-DMGBL, α,γ-DEMGBL, and DMSM. α-EMGBL and α-DMGBL were synthesized by alkylation of α-methyl-GBL (Aldrich) with the appropriate alkyl iodide by the method of Rathke and Lindert (6). α,γ-DEMGBL was synthesized by successive ethylation and methylation of γ-EMGBL by the same procedure. DMSM was prepared from 2,2-dimethylsuccinic acid (Aldrich) by conversion of the anhydride (7) to the imide by the method of Miller and Long (8). All compounds had satisfactory IR and proton magnetic resonance spectra.

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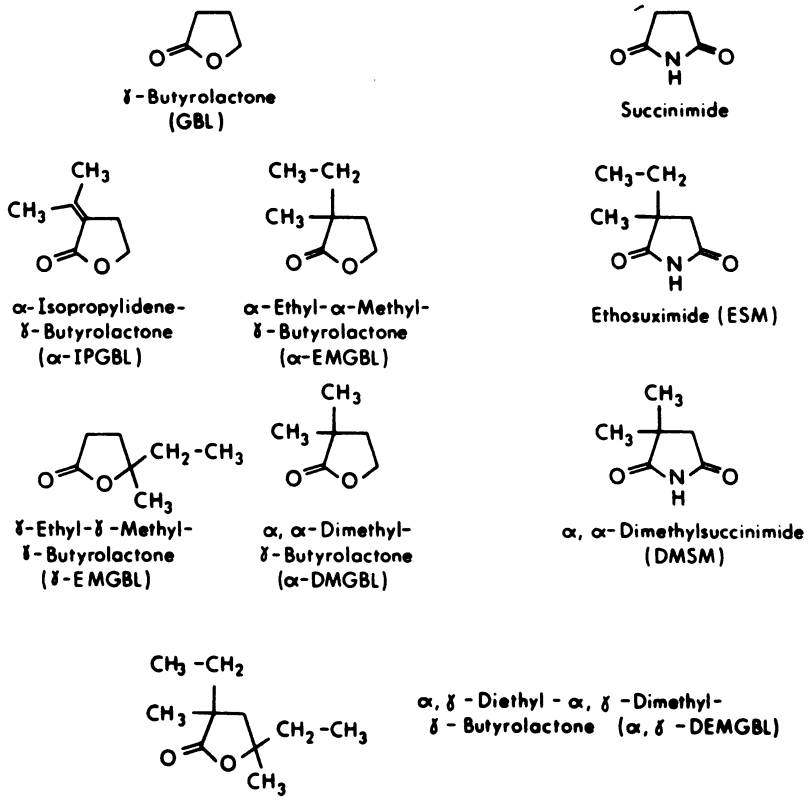

FIG. 1. *Chemical structures of α- and γ-substituted GBLs and α-substituted succinimides*

Synthesis of α-IPGBL. α-IPGBL was synthesized by a modification of the method of Grieco and Hiroi (9) for the synthesis of α-methylene-GBL. GBL (Aldrich) was converted to α-(2-hydroxyisopropyl)-GBL by a modification of the method of Rathke (10). Briefly stated, GBL was added to a solution of lithium *N*-isopropylcyclohexylamide in tetrahydrofuran at −78°. After 15 min, 2-propanone (Aldrich) was added rapidly and the mixture was stirred for 5 min. The mixture was allowed to reach room temperature and was quenched with excess HCl and then concentrated on a rotary evaporator at 60° (20 mm Hg). The residue was extracted with ether and filtered, and the organic layer was dried over Na_2SO_4 and then reconcentrated. Vacuum distillation gave the hydroxy lactone, b.p. 100–103° (0.8 mm Hg), as a colorless, odorless oil. The IR spectra showed a single, strong carbonyl absorption at 1770 cm^{-1} and a broad hydroxyl absorption at 3500 cm^{-1}. The proton NMR in $CDCl_3$ showed the following: δ1.30 (*d*, 6, 2*x*, —CH_3); 2.0–2.8 (*m*, 3, α-CH— plus β-CH_2—); 3.45 (broad *s*, 1, —OH); 4.21 (*m*, 2, γ-CH_2—).

This compound was then dehydrated to α-IPGBL by conversion to the mesylate (11) and subsequent refluxing in pyridine. After purification on a silica gel column eluted with methylene chloride, the product was a clear, slightly yellow liquid, b.p. 67–70° (0.7 mm Hg), with a very unpleasant odor. The IR spectra showed a single, strong carbonyl absorption at 1745 cm^{-1} and a double-bond absorption at 1670 cm^{-1}. The proton NMR in $CDCl_3$ showed the following: δ1.9 (*t*, 3, —CH_3); 2.26 (*t*, 3, —CH_3); 2.86 (broad *s*, 2, β-CH_2—); 4.29 (*t*, 2, γ-CH_2—).

Testing of Behavioral and Electrophysiological Effects

Effects on behavior in mice. Female Swiss-Webster mice (20–30 g, Lab Supply) received i.p. injections or i.v. injections (in the lateral tail vein) of drugs in a volume of 10 μl/g. Anticonvulsants were given 30 min before convulsant challenge except for PHT, which was given 60 min before. ESM and DMSM were given as aqueous solutions in the doses indicated. PTZ was given as an aqueous solution in a dose of 100 mg/kg i.p. PHT was given as a suspension in 30% propylene glycol in a dose of 50 mg/kg. All other drugs were given as solutions in 30% propylene glycol in the doses indicated. Propylene glycol (30%) alone produced no anticonvulsant effect in this system.

Chemically induced seizures were recorded by three markers: myoclonic twitches, generalized clonic seizures, and tonic seizures. Maximal electroshock seizures were induced by applying square-wave pulses with a duration of 2 msec, frequency of 50 Hz, and amplitude of 70 V with a train duration of 2–3 sec through moistened ear clips. All untreated mice had tonic seizures after this treatment.

Neurotoxicity was determined by the standard rotorod procedure (12). In this method, a mouse must remain on a 1-inch diameter rod rotating at 6 rpm for at least 1 min in each of three trials.

Effects on the EEG of paralyzed-ventilated guinea pigs. The procedure was the same as was reported previously (4).

Effects on incubated hippocampal slices. The effects on hippocampal slices were determined as previously reported (4).

RESULTS

Effects on behavior in mice. When given alone, α-EMGBL produced no effect in doses up to 200 mg/kg i.p. Doses of 250–350 mg/kg produced slight ataxia and drow-

siness which lasted 10–15 min after injection. Hyperexcitability was also sometimes seen during this period. A dose of 500 mg/kg caused marked sedation for at least 30 min, and all animals were neurotoxic as judged by their inability to pass the rotorod test. ESM produced very similar effects at the same doses. DMSM and α-DMGBL also caused very similar effects but were less potent. Doses of α,γ-DEMGBL up to 200 mg/kg had no effect on behavior; 250–300 mg/kg produced short periods of hyperexcitability before the mice became ataxic and slightly sedated. At a dose of 450 mg/kg, the period of hyperexcitability was increased to 15–20 min and the reaction was more severe, sometimes resembling dystonic posturing; the mice eventually became very ataxic and sedated. The most striking effect of α-IPGBL was its toxicity. A dose of 250 mg/kg caused extreme sedation and labored breathing; 500 mg/kg caused death due to respiratory paralysis in less than 10 min after injection. None of these drugs alone ever produced seizures similar to those seen with β-substituted compounds.

The most notable property of these drugs was their ability to prevent experimental seizures such as those induced by PTZ. At a PTZ dose of 100 mg/kg i.p., the mice exhibited myoclonic twitches, clonic seizures, and usually a fatal tonic seizure. The time course for anticonvulsant activity against this seizure model was tested in mice treated with α-EMGBL (250 mg/kg). One hundred per cent protection from tonic seizures was observed at both 15 and 30 min after injection of α-EMGBL, whereas only 25% of mice were protected at 60 min. Therefore, dose-response studies were carried out with a 30-min pretreatment. The anticonvulsant effect, determined by prevention of the tonic seizure, was clearly dose-dependent (Fig. 2), with an ED_{50} of 150 mg/kg (1.17 mmoles/kg) for α-EMGBL. Similar effects were observed with α,γ-DEMGBL and α-DMGBL. The ED_{50} of α,γ-DEMGBL for prevention of tonic seizures was 1.47 mmoles/kg; α-DMGBL had an ED_{50} of 3.51 mmoles/kg, which was 3 times that of α-EMGBL. The γ-substituted derivative, γ-EMGBL, had very little activity, producing only 25% protection from tonic seizures at a dose of 3.91 mmoles/kg (Fig. 2).

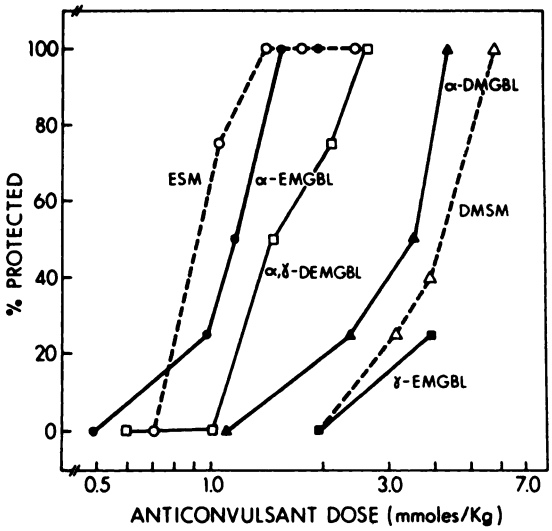

FIG. 2. *Dose-response curve of the ability of various anticonvulsants to prevent the tonic phase of the seizure induced by PTZ (100 mg/kg i.p.)*

All drugs were given i.p. 30 min before PTZ.

TABLE 1

Effect of ESM, PHT, and α-EMGBL on maximal electroshock seizures

Drugs were given i.p. in the following doses: ESM, 350 mg/kg (2.5 mmoles/kg) 30 min before shock; PHT, 50 mg/kg 60 min before shock; α-EMGBL, 350 mg/kg (2.7 mmoles/kg) 30 min before shock.

Pretreatment	Animals exhibiting a tonic extension
None	5/5
ESM	5/5
PHT	0/5
α-EMGBL	5/5

ESM also showed a very similar dose-dependent ability to prevent the PTZ-induced tonic seizures (Fig. 2). The ED_{50} was 130 mg/kg (0.92 mmoles/kg), a value which agrees very well with that reported by others (12). The dimethyl derivative, DMSM, was less potent, having a 4-fold higher ED_{50} of 4.2 mmoles/kg (Fig. 2).

Neither GBL itself nor α-IPGBL provided any protection against PTZ-induced seizures, even at neurotoxic doses.

At a dose of 350 mg/kg, neither ESM nor α-EMGBL had any effect on maximal electroshock seizures. This dose is more than twice the ED_{50} in PTZ-induced seizures. PHT, 50 mg/kg, a dose which had no protective effect against PTZ, completely prevented both the tonic and the clonic portions of maximal electroshock seizures (Table 1).

Both α-EMGBL and ESM provided protection against seizures induced by β-EMGBL. This seizure was described in the preceding report (4). In mice treated with β-EMGHB (50 mg/kg i.p.), ESM (250 mg/kg) had little effect, but α-EMGBL (250 mg/kg) delayed the onset of myoclonic twitches and clonic seizures in all animals tested and prevented tonic seizures entirely in 60%. A 500 mg/kg dose of ESM prevented tonic seizures in 100% of the animals, but only slightly delayed myoclonic twitches and clonic seizures. A 500 mg/kg dose of α-EMGBL had a similar effect on myoclonic twitches, but totally prevented all clonic and tonic seizures.

α-EMGBL was tested at the higher dose (500 mg/kg) to determine its effects on the dose-response curves of β-EMGBL and PTX in mice. In both cases, α-EMGBL provided complete protection from tonic seizures caused by supramaximal doses of both drugs and shifted the CD_{50} from 3.7 to 12 μmoles/kg for PTX and from 230 to 789 μmoles/kg for β-EMGBL (Fig. 3). This is a 3.2-fold shift for picrotoxin and a 3.4-fold shift for β-EMGBL.

Some degree of ataxia and sedation was produced by α-DMGBL, γ-EMGBL, α,γ-DEMGBL, and DMSM at doses close to their ED_{50} for protection from PTZ-induced tonic seizures. However, α-EMGBL produced no signs of neurological deficit 30 min after a dose of 1.95 mmoles/kg, which is more than that needed to produce 100% seizure protection (Fig. 2). α-EMGBL also compared favorably with ESM in the rotorod test (Table 2).

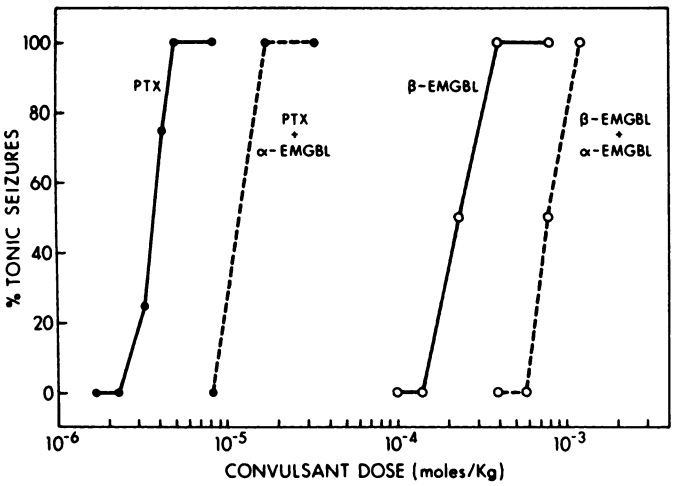

FIG. 3. *Effect of α-EMGBL on the dose-response curves of i.v. PTX and i.p. β-EMGBL*

Curves were obtained before (——) and after (– – –) a 30-min pretreatment with α-EMGBL (500 mg/kg i.p.).

Effects on the EEG of paralyzed-ventilated guinea pigs. Effects comparable to those seen in mice were observed electroencephalographically in paralyzed-ventilated guinea pigs (Fig. 4). When given alone, α-EMGBL, α-DMGBL, and ESM caused no change in the EEG at the doses indicated except for some transient and variable changes immediately after injection. α-IPGBL produced an irregular slowing of the EEG when given alone.

TABLE 2

Comparison of anti-PTZ activity and rotorod toxicity of ESM and α-EMGBL

Drug	ED_{50} (PTZ)	TD_{50} (rotorod)	TD_{50}/ED_{50}
	mmoles/kg	*mmoles/kg*	
ESM	0.92[a]	3.1[b]	3.4
α-EMGBL	1.17[a]	3.1	2.7

[a] From Fig. 2.
[b] From ref. 12.

As noted above, this compound was very toxic in mice.

As reported in the preceding paper (4), a 50 mg/kg dose of β-EMGHB caused paroxysmal bursts of spikes and slow waves, generalized high-frequency discharges, and polyspike bursts followed by electrical silence. ESM, α-EMGBL, and α-DMGBL prevented all three stages of epileptoform activity induced by β-EMGHB (Fig. 4). No protection was seen with α-IPGBL.

α-EMGBL had the striking ability to stop rapidly a seizure already in progress. When β-EMGHB (75 mg/kg) was given to a paralyzed-ventilated guinea pig, seizure activity began about 15 sec after injection and lasted for more than 45 min. During the first 15 min, a generalized, high-frequency seizure occurred about once per minute. When α-EMGBL was given i.v. after the seizure activity had begun, the seizure discharge stopped within seconds and the EEG initially became almost flat. Normal EEG activity then returned within about 2–3 min (Fig. 5), and no further seizures were observed during the following 10-min period.

Neither α-EMGBL nor ESM prevented seizures caused by BIC (0.30 mg/kg i.v.) (the lowest dose which caused seizures in all animals tested). This was observed even at doses of 250 mg/kg, which would always protect against seizures caused by β-EMGHB or PTZ.

Both the β-substituted compounds (4) and the α-substituted GBLs had profound cardiovascular effects. β-EMGHB caused a large and rapid increase in blood pressure (Fig. 6), but α-EMGBL reversed this effect and stopped the epileptiform discharges. Alone, a 200 mg/kg dose of α-EMGBL initially caused a large and rapid decrease in blood pressure (Fig. 6). This effect gradually diminished, but the blood pressure stabilized below control levels (Fig. 6). When a 100 mg/kg dose of β-EMGHB was given after treatment with α-EMGBL, blood pressure increased to normal or slightly above normal levels (Fig. 6); however, all stages of epileptiform activity normally observed were prevented. ESM had cardiovascular effects which were similar to but less dramatic than those of α-EMGBL. A 250 mg/kg dose of ESM alone reduced both systolic and diastolic pressures by about 30% (versus

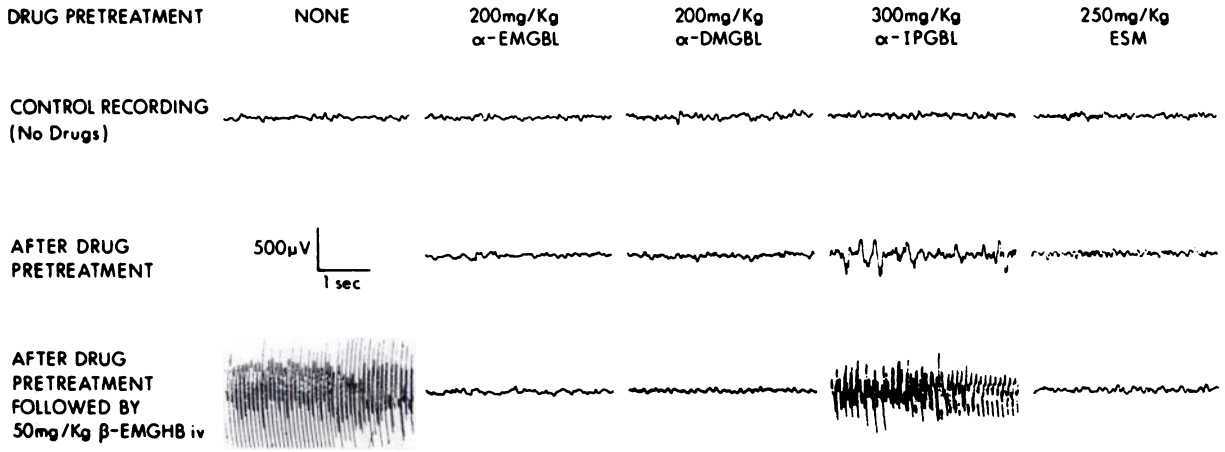

FIG. 4. *Effects of α-substituted GBLs and ESM on seizures induced by β-EMGHB (50 mg/kg i.v.) in guinea pigs*

The *top line* represents the control recording before any drugs. The *middle line* shows recording 14 min after a 200 mg/kg i.v. dose of α-EMGBL, 10 min after a 200 mg/kg i.v. dose of α-DMGBL, 30 min after a 300 mg/kg i.v. dose of α-IPGBL, and 45 min after a 250 mg/kg i.v. dose of ESM. The *bottom line* shows recording 1 min (control), 1 min (α-EMGBL), 1 min (α-DMGBL), 7 min (α-IPGBL), and 6 min (ESM) after a 50 mg/kg dose of β-EMGHB given immediately after the *middle* recording.

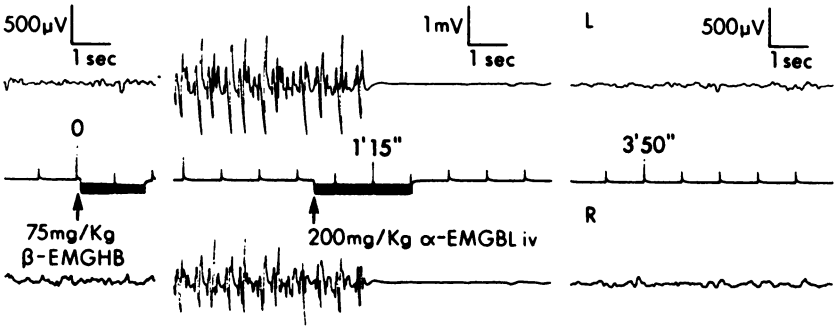

FIG. 5. *Rapid reversal of β-EMGHB-induced seizure activity by intravenous α-EMGBL*
Times indicated are from the injection of β-EMGHB. The *upper tracing* shows sequential periods from the left parietal cortex. The *lower tracing* is from the right parietal cortex.

50% by α-EMGBL), but the effect was of shorter duration than that produced by α-EMGBL. However, ESM was equally active in preventing the β-EMGHB-induced rise in blood pressure.

Effects on electrical activity of incubated hippocampal slices. Activity was evoked and recorded as previously described (4). Concentrations of α-EMGBL of 1–100 μM had no effect. Concentrations of 1–10 mM caused a slight suppression of normal spontaneous activity and evoked potential. As was previously reported (4), 1 mM β-EMGBL increased the evoked potential and produced epileptiform discharges. When given in combination with 1 mM β-EMGBL, 1 mM α-EMGBL had no effect. However, 10 mM α-EMGBL prevented the excitatory effect of 1 mM β-EMGBL, and this effect of 10 mM α-EMGBL was reversible. ESM had an effect on the β-EMGBL-induced excitation very similar to that of α-EMGBL; i.e., 1 mM ESM had little or no effect and 10 mM prevented the excitatory effect of 1 mM β-EMGBL. The hydroxy acid analogue of α-EMGBL, α-EMGHB, did not prevent β-EMGBL-induced excitation at all, even at a concentration of 10 mM. This is consistent with the fact that the lactone is the active form of these alkyl-substituted GBLs (4).

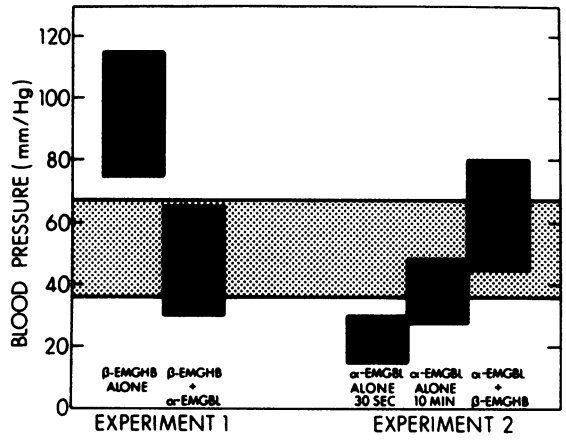

FIG. 6. *Effects of β-EMGHB and α-EMGBL on the blood pressure of paralyzed-ventilated guinea pigs*
Guinea pigs were paralyzed and ventilated as indicated under Materials and Methods. Blood pressure was recorded from a cannula in the femoral artery. Results represent the mean systolic and diastolic pressures of two to five animals. Standard deviations were less than 10%. Control values are indicated by the *stippled area* and were 67 ± 3/6 ± 2 mm Hg. Experiment 1: *first bar*, 1 min after β-EMGHB (75 mg/kg); *second bar*, 30 sec after (200 mg/kg) α-EMGBL given 1 min after treatment with β-EMGHB. Experiment 2: *first bar*, 30 sec after α-EMGBL (200 mg/kg) given with no pretreatment; *second bar*, 10 min after α-EMGBL (200 mg/kg); *third bar*, 1 min after β-EMGHB (100 mg/kg) given 10 min after α-EMGBL (200 mg/kg).

DISCUSSION

GBL is an asymmetrical molecule with two non-equivalent positions which can be substituted, i.e., α and β to the carbonyl. In the preceding study (4), we reported that the β-substituted GBLs had potent convulsant activity distinct from that of GBL itself. The present results demonstrate that the corresponding α-substituted GBLs have essentially the opposite effect and are anticonvulsant. To our knowledge, this is the first report of the anticonvulsant properties of these compounds.

The markedly different properties of α- and β-substituted GBLs are surprising in view of their similar structural and chemical properties. The α- and β-substituted GBLs proved to be antagonistic in every situation in which they were tested. The β-compounds caused seizures in mice (4) whereas the α-compounds caused depression when given alone and subsequently antagonized the β-substituted GBL-induced seizures. In paralyzed-ventilated guinea pigs, β-EMGBL caused epileptiform discharges and increased blood pressure. The α-compounds caused little change in the EEG and a decrease in blood pressure. They also prevented or immediately reversed the blood pressure and EEG effects of the β-

TABLE 3
Anticonvulsant profiles of ESM, PHT, phenobarbital, and α-EMGBL

Drug	Convulsant stimulus				
	PTZ	PTX	β-GBLs	Maximal electro shock	BIC
ESM	+	+	+	0	0
α-EMGBL	+	+	+	0	0
PHT	0	0	0	+	ND[a]
Phenobarbital[b]	+	ND	ND	+	ND

[a] ND, not determined.
[b] From ref. 12.

compounds. The effects observed in hippocampal slices *in vitro* support the *in vivo* observations.

ESM and PHT are the classical representatives of the extreme poles of the anticonvulsant spectrum. For example, ESM is active against human petit mal absence epilepsy and inactive against partial seizures and generalized tonic-clonic convulsions. Conversely, PHT is effective in the treatment of partial seizures and generalized tonic-clonic convulsions but ineffective against petit mal absence seizures. The anticonvulsant activities of ESM and PHT are also opposite in several other experimental seizure models (13). Comparison of the effect of the α-substituted GBLs with the effects of ESM, PHT, and phenobarbital demonstrate that the α-substituted compounds have an anticonvulsant profile very similar to that of ESM and very different from that of PHT (Table 3).

The protective index of α-EMGBL in mice was very close to that of ESM when determined by protection from PTZ-induced seizures and the rotorod neurotoxicity test. This suggests a potential clinical usefulness of α-EMGBL. However, the immediate utility of α-EMGBL lies in its potential for the study of the mechanism of action of anticonvulsant drugs used to treat petit mal absence seizures. Its structural similarity to convulsants such as β-EMGBL and PTX (5) may also be helpful in elucidating the pathophysiological mechanisms of absence seizures.

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