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Emylcamate,* A Potent Tranquillizing Relaxant

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Introduction

As part of our mental health programme we have for a number of years studied neuro-psychopharmacological and biochemical aspects of nervous and mental diseases.

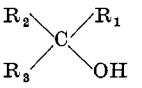
The present study has been directed at finding the minimum structural requirements for a compound with a full range of muscle-relaxing and tranquillizing properties. In our screening programme meprobamate has been the standard drug used for comparison.

A survey of the literature has shown that at the turn of the century a parallelism was established between muscle-relaxant effect in laboratory animals and a favourable influence upon the symptoms of anxiety and tension neurosis. Dreser[1] introduced Hedonal (*sec*-amylurethan) as a hypnotic. Because of the muscle-relaxing properties of the drug it was used as pre-medication prior to surgical operations. Huber[2,3] proceeded further along the same line and arrived at Aponal (*t*-amylene carbamate), which for a number of years was used in the treatment of sleep disturbances, anxiety and tension states.

No systematic study of the potential tranquillizing activity of tertiary alcohol carbamates seems to have been carried out. The independent development of meprobamate from mephenesin made it of interest to study more closely tranquillizing and muscle-relaxant properties of a full series of tertiary alcohols and their esters. Table I gives details about the alcohols studied and also about different types of esters investigated.

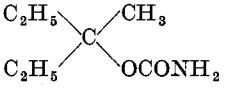
* NUNCITAL ® KABI. The trade mark Striatran has been adopted in the United States by Merck & Co., Inc. for its brand of emylcamate.

Table I. Alcohols studied. Besides the alcohols listed below, the following derivatives were studied: acetates, chloroacetates, *N*-diethylaminoacetates, *N*-diallylaminoacetates, phenyl carbonates and carbamates.



R_1	R_2	R_3
CH_3	CH_3	C_2H_5
CH_3	CH_3	C_3H_7
CH_3	C_2H_5	C_2H_5
etc.		
CH_3	$CH_2CH(CH_3)CH_3$	C_2H_5
C_2H_5	C_2H_5	C_2H_5
C_3H_7	C_3H_7	C_3H_7
C_4H_9	C_4H_9	C_4H_9
CH_3	CH_3	$C\equiv CH$
CH_3	C_2H_5	$C\equiv CH$
CH_3	C_2H_5	$CH=CH_2$
CH_3	$CH_2CH(CH_3)CH_3$	$C\equiv CH$

As a result of the screening, the compound 1-ethyl-1-methylpropyl carbamate (I), to which the generic name emylcamate has been assigned, was selected.



(I)

Chemistry

The synthetic procedures used for the preparation of emylcamate and its congeners will be described in patents by Melander and Hanshoff which are now pending. Since tertiary alcohols like 1-ethyl-1-methylpropanol behave differently from, e.g., the primary diol used in the preparation of meprobamate, the most convenient methods, re-esterification and direct use of phosgene, could not be applied for the emylcamate synthesis. Pathways

found to be applicable included reacting phosgene with phenol to form phenyl chlorocarbonate. This intermediate was reacted with 1-ethyl-1-methylpropanol to form the corresponding phenyl carbonate which, autoclaved with liquid ammonia, yielded emylcamate.

The molecular weight of emylcamate is 145·2. The melting point is 55 to 56°C. It is slightly soluble in water, 4·0 mg/ml at 20°C. Emylcamate is very soluble in organic solvents such as methanol, ethanol, petroleum ether, benzene and *cyclo*hexane. Emylcamate shows the following absorption maxima in infrared in the region 1,800–750 cm^{-1} dissolved in carbon disulphide to make a 5 per cent solution: 1,710 (s), 1,590 (m), 1,355 (s), 1,322 (s), 1,306 (m), 1,288 (m), 1,156 (m), 1,134 (s), 1,070 (m), 1,036 (s), 997 (m), 890 (w), 843 (w), 768 (w). ((s) = strong absorption, (m) = medium absorption and (w) = weak absorption.)

For chemical assay emylcamate can be hydrolysed by refluxing with hydrochloric acid followed by neutralization, distillation and titration of the liberated ammonia.

Pharmacology

Spontaneous and Increased Motor Activity in Mice

In order to study the effect of emylcamate and meprobamate at dose levels not relaxing skeletal muscles to any observable degree in the test animals, 50 mg/kg orally of emylcamate and of meprobamate were given to groups of 5 white mice. The effect on spontaneous motor activity 1 h after medication was recorded. Since mice might change behaviour when moved to new surroundings the standard plastic mouse cages were used for the study. To reach a numerical value for the motor activity, a photocell set-up was used. This technique was introduced by Winter and Flataker[4] and a similar device was discussed by Dews[5] and applied by Brown *et al.*[6] In order to register even minor motor activity changes the device as used by us consists of four pairs of photocells placed centrally on the sides of the cage and in both diagonals. Because of time-to-time variations in the spontaneous motor activity relatively short observation periods were employed. Individual counts were obtained during a 5 min period. After

this count was obtained the compounds were administered and a new count was taken 60 min later for another 5 min period. The results are given in Table II.

In order to get some additional information about mouse behaviour in the dark the photocell technique was combined with a photographic one. Rothlin and Cerletti[7] have employed such a method in their study of waltzing mice but no details facilitating the reproduction of the method used are given.

Table II. Influence of emylcamate and of meprobamate dissolved in propylene glycol on spontaneous motor activity in mice recorded with a photocell counter.

Compound	Control count 60 min interval	Post-medication count 60 min interval	Motor activity decrease % 'tranquillity'
	49	30	
Meprobamate	74	40	
50 mg/kg	114	98	32
orally	69	59	
	74	32	
	73	39	
Emylcamate	133	65	
50 mg/kg	103	59	63
orally	139	35	
	171	31	

We found it suitable to utilize our standard plastic cages also in this experiment. Individual mice were painted with a dye that upon activation by ultraviolet light emits visible light. The ultraviolet light was filtered off by means of a standard yellow ultraviolet filter and the movement of the mouse was exposed in the dark on a panchromatic film during 5 min. This exposure took place immediately after the corresponding photocell count was obtained; thus both a numerical value and visible behaviour changes have been recorded.

Fig. 1 supplies details for emylcamate. Below each photo the corresponding photocell count is given. The numerical values showing the reproducibility of the method are from a parallel experiment of the one given in Table II.

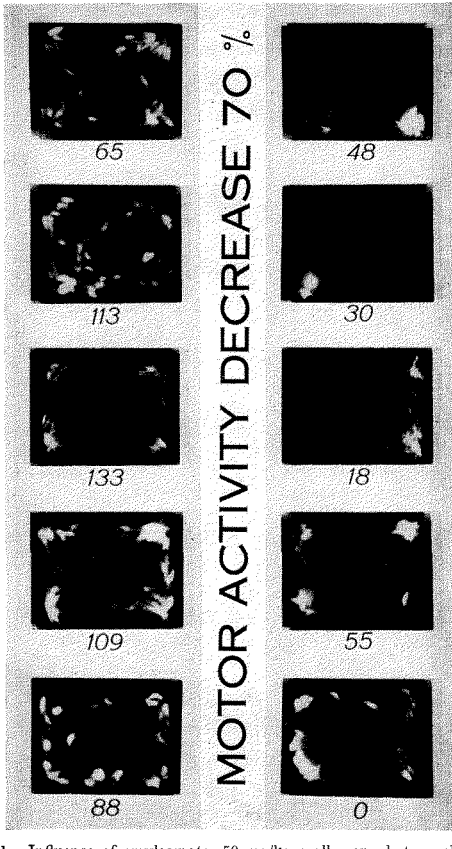


Fig. 1. Influence of emylcamate, 50 mg/kg orally, on photographically recorded spontaneous motor activity in mice. Figures at bottom refer to corresponding photocell counts

In order to study the effect of emylcamate and of meprobamate on pipradrol-induced increased motor activity, simultaneous injection of 10 mg/kg of pipradrol and 100 mg/kg of the test compound were given intraperitoneally to groups of 5 mice and the number of mice showing side position after varying intervals was recorded. The results are given in Table III.

Table III. Effect of emylcamate and meprobamate dissolved in propylene glycol in mice at the dose level of 100 mg/kg i.p. on simultaneous administration of 10 mg/kg i.p. of pipradrol.

	No. of mice in side position after:						
	15	30	45	60	90	120	150 min
Meprobamate	1/5	2/5	1/5	1/5	1/5	0/5	0/5
Emylcamate	4/5	3/5	3/5	2/5	2/5	1/5	0/5

Muscle-relaxing Effect

Emylcamate and meprobamate were given i.p. to groups of 10 mice at dose levels from 50 to 900 mg/kg. The paralysing dose (PD) producing side position in 50 per cent of the animals was estimated as the LD50 within 24 h. Furthermore, the time between injection and side position at the experimental PD100 was recorded. Details are given in Table IV.

Table IV. Muscle-relaxing effect, paralysing dose 50%, PD50, and acute toxicity, LD50, within 24 h of i.p. administration of emylcamate and meprobamate in aqueous suspension as well as time of onset of action. 11 dose levels, 10 animals at each level.

Compound	PD50	LD50	No. of mice	Therap. index	Time for onset of action, min
Meprobamate	175±15 mg/kg	600±32 mg/kg	110	3·4	35
Emylcamate	125±55 mg/kg	550±16 mg/kg	110	4·4	3

Anticonvulsant Effect

The effect of administration of emylcamate and meprobamate prior to the injection of the convulsants strychnine and pentylenetetrazol was studied.

Strychnine. Graded doses of emylcamate and meprobamate ranging from 25 to 125 mg/kg i.p. were administered to groups of 10 white mice prior to the i.v. administration of 0·60 mg/kg of strychnine. The mortality rate in the different groups was compared at various intervals after strychnine injection.

As shown in Table IV, a full muscle-relaxant effect of emylcamate is obtained within 3 min after administration. In contrast there is a 35 min delay in the onset of action of meprobamate.

Table V. Mortality rates in groups of 10 white mice given aqueous suspension of emylcamate 3 min or meprobamate 35 min prior to strychnine.

Compound	Dose level mg/kg i.p.	Strychnine administration of 0·60 mg/kg i.v. Mortality rate at 2 min	30 min	
Controls	—	9/10	9/10	
Meprobamate	25	10/10	10/10	
Time interval	50	9/10	10/10	
to strychnine	75	9/10	9/10	Protective dose 50=
35 min	100	3/10	3/10	79·5±3·1 mg/kg
	125	1/10	1/10	
Emylcamate	25	9/10	9/10	
Time interval	50	6/10	6/10	
to strychnine	75	4/10	4/10	=56·3±5·4 mg/kg
3 min	100	2/10	2/10	
	125	1/10	1/10	

Thus emylcamate was given 3 min prior to strychnine and meprobamate 35 min prior to the convulsant. Details of the experiment are found in Table V.

Pentylenetetrazol. The protecting effect of graded doses of emylcamate and meprobamate against pentylenetetrazol maximal seizures was investigated. As in the strychnine test, emylcamate was administered 3 min prior to pentylenetetrazol and meprobamate was administered 35 min prior to pentylenetetrazol. Details are given in Table VI.

Electroshock. Details regarding the device used have been given by de Jongh.[8] It allows administration of electroshock to

10 mice simultaneously. Every second mouse served as control and the others were given the compounds orally dissolved in

Table VI. Number of convulsions per group of 10 white mice given aqueous suspensions of emylcamate 3 min or meprobamate 35 min prior to pentylenetetrazol, 90 mg/kg i.p. Observation period, 10 min during which all 10 control mice succumb.

Compound	Dose level mg/kg i.p.	No. of maximal seizures per 10 mice during 10 min
Meprobamate	75	18
Time interval to pentylenetetrazol 35 min	100	10
	125	0
Emylcamate	60	10
Time interval to pentylenetetrazol 3 min	75	2
	90	0

propylene glycol 60 min prior to shock. Details are given in Table VII.

Barbiturate activation. The influence of pre-medication with emylcamate or meprobamate upon the anaesthesia time in white

Table VII. Influence on electroshock convulsions by pre-medication 60 min before shock of emylcamate and meprobamate in propylene glycol. Results given as number of convulsed animals/groups of 10 mice.

Compound	Dose level mg/kg p.o.	Number of animals with maximal seizures
Controls	—	40/40
Meprobamate	100	8/10
	150	5/10
Emylcamate	100	8/10
	150	0/10

mice after i.v. administration of thiopental sodium was studied. The duration of anaesthesia is judged from loss to return of the righting reflex. Previous experiments indicate that prolongation of anaesthesia time does not necessarily reflect the hypnotic activity of the compound used for pre-medication. Results are given in Table VIII.

Table VIII. Influence upon anaesthesia time in white mice of oral pre-medication with emylcamate and meprobamate in aqueous propylene glycol 60 min prior to i.v. injection of 40 mg/kg of thiopental sodium.

Compound	Dose level mg/kg p.o.	No. of mice per group	Average anaesthesia time, min	Relative anaesthesia time
Controls	—	20	8·5	1
Meprobamate	25	15	16	1·9
	35	10	37·5	4·4
Emylcamate	25	15	17·7	2·1
	35	10	38	4·5

Paralysing activity in rabbits. All compounds were screened also with regard to paralysing activity in rabbits after oral or i.p. administration of doses ranging from 200 to 400 mg/kg. Oral administration was considered to mimic clinical conditions best since it answered at the same time questions regarding absorption rate, time for onset of action, duration of action, and degree of skeletal muscle relaxation. Two dose levels were usually employed for each compound. Two to five rabbits were used for every compound in each test series. The rabbits were observed for impairment of the righting reflex at short intervals during several hours after administration.

In these tests comprising 125 rabbits, it was found that upon oral administration flaccid paralysis was obtained for emylcamate in the dose range of 200 to 300 mg/kg. A dose of 400 mg/kg of meprobamate was required to produce the same effect. Parallel to the observations in mice it was found in rabbits that the onset of action started within a few minutes of emylcamate administration, whereas between 30 to 45 min were required for meprobamate to exert its paralysing activity. The duration of activity was approximately the same for both compounds and amounted to 2 to 4 h.

Compared with meprobamate, emylcamate has a considerably shorter onset of action, shows effect at about one-half to two-thirds of the meprobamate paralysing dose, and produces a more profound muscle relaxation.

Cardiovascular action. The effect of emylcamate and of meprobamate both dissolved in saline upon the blood pressure of

anaesthetized rabbits was determined. At dose levels up to 8 mg/kg no hypotensive effect was recorded with either of the two compounds. Due to the low solubility in water of the compounds, 4·0 mg/ml for emylcamate and 3·9 mg/ml for meprobamate, it became impractical to administer higher doses without employing solvents complicating the evaluation of the results.

Chronic Toxicity and Pathology

Mice. Groups of 10 mice were daily injected subcutaneously with 5 per cent propylene glycol solutions of emylcamate and meprobamate at a dose level of 25 mg/kg. A control group received the same volume of the solvent propylene glycol.

The groups were weighed daily and upon termination of the experiment after 30 days every second mouse was subjected to pathological-anatomical examination.*

The weight increase of the three test groups is recorded in Table IX. Figures are given as average mouse weight. To save space every second value is given. No untoward influence upon the weight increase was observed. The post-mortem examination revealed no macroscopic or microscopic pathological changes that could be considered as caused by the medication.

Rabbits. Rabbits in groups of three were given emylcamate and meprobamate in propylene glycol by stomach tube at the high dose level of 100 mg/kg daily for 35 weeks. The control group received corresponding amounts of the solvent.

The rabbits were weighed weekly and in addition to clinical observations, blood counts and liver function tests (G.O.T.) were made weekly during the first month of study and every seond week thereafter until the termination of the experiment.

Upon termination of the experiment every animal in the groups was subjected to macroscopic and microscopic pathological-anatomical examination.*

No untoward reaction whatever was caused by the medication and no considerable differences with regard to weight increase were found between the three test groups. One rabbit in the

* Courtesy of Dr. Axel Isaksson, Veterinary Surgeon, the State Veterinary Medical Institute, Stockholm.

Table IX. Chronic toxicity in white mice, groups of 10. Emylcamate and meprobamate given subcutaneously daily at the dose level of 25 mg/kg in a volume of 0·05 ml of propylene glycol. Controls receive a corresponding amount of solvent. Figures refer to average mouse weight in g.

Day No.	1	3	5	6	8	10	12	13	17	19	20	22	24	26	27	29	31
Controls	22·9	23·2		23·0	23·7	23·7		23·8	24·3	25·4		25·4	25·9		25·4	25·3	26·2
Meprobamate	23·0	23·6		23·5	24·6	25·2		24·6	25·7	26·4		26·2	26·6		26·6	26·4	27·1
Emylcamate	23·0	22·6		22·2	23·5	24·1		23·9	25·5	25·6		25·5	26·2		25·6	25·3	25·6

emylcamate group died in the eleventh week of the study of causes unrelated to the drug administration. The pathological-anatomical examination of this rabbit revealed rhinitis and sinusitis.

Discussion

Among the alcohols and various derivatives as shown in Table I we have observed a sharp increase in activity up to the molecular structure of emylcamate. With increasing carbon chain length there is a similar swift decrease in activity. The muscle-relaxant and anticonvulsant effect runs parallel among the tertiary alcohols and their esters. There is, however, a steep activity increase in the carbamates.

In order to elucidate more fully the differences in pharmacodynamic spectrum and activity between the original tertiary alcohol carbamate, Aponal and emylcamate, Aponal was run through the screening programme simultaneously with emylcamate and meprobamate. Since the highly unsaturated acetylenic alcohol 3-methylpentynol-3 has been used as a hypnotic for some time and partly replaced by its more stable carbamate, special attention was given also to the last-mentioned compound.

Emylcamate in these experiments proved to be superior to both Aponal and the carbamate of 3-methylpentynol-3. The differences were most marked with regard to therapeutic index, to 'tranquillity' where spontaneous motor activity was evaluated, in the electroshock test and in the barbiturate prolongation test.

The therapeutic index was below 2·5 for both Aponal and the carbamate of methylpentynol compared to 4·4 for emylcamate. With regard to 'tranquillity' in mice the carbamate of methylpentynol was half as potent as emylcamate. In the electroshock test Aponal and the carbamate of methylpentynol were found to be slightly less active than meprobamate. Only emylcamate gave full protection against electroshock. In the barbiturate anaesthesia prolongation test the carbamate of methylpentynol caused twice the anaesthesia prolongation of emylcamate.

The comparison between emylcamate and meprobamate supplies the following overall picture. The tranquillity as judged from the tests regarding spontaneous motor activity in mice after

administration of nonparalytic doses of the compounds is twice as high for emylcamate as for meprobamate. The same results are obtained also if pipradrol-induced increased motor activity is taken in account.

The time for onset of action is considerably shorter after emylcamate than after meprobamate, up to tenfold. As far as the anticonvulsant effect is measured against the chemical convulsants strychnine and pentylenetetrazol and also against electroshock, emylcamate seems to be twice as active as meprobamate.

Long-range comparative toxicity studies in mice and in rabbits of emylcamate and meprobamate accompanied by haematological and liver function studies in rabbits show that none of the compounds has any untoward influence upon the test animals.

Emylcamate, according to Stone,*[9] selectively blocks reflexes mediated over polysynaptic reflex arcs at doses not inhibiting monosynaptic pathways. This effect together with the nature of its anticonvulsant and muscle-relaxing properties supports the conclusion that emylcamate acts as an internuncial blocking agent.

Studying the electroencephalographic effects in cats, Vernier and O'Neill*[10] found emylcamate and meprobamate to cause a similar slowing of the spontaneous activity of the EEG. No apparent changes were noted in the specific sensory pathway conduction, and even at the highest dose tested emylcamate was only rarely capable of abolishing the activating patterns. Studying the EEG and concomitant behavioural effects in monkeys with chronically implanted electrodes, Brodie *et al.**[11] found that slowing of spontaneous rhythms of the EEG following emylcamate or meprobamate was rarely associated with attenuation or abolishing of the alerting responses to sensory stimulation. Such findings suggest that emylcamate will not produce sedation in man in doses which produce useful skeletal muscle relaxation.

Jonsson and Andersén[12] carrying out a double blind study on emylcamate, meprobamate and placebo utilizing a battery of 18 psychological tests found that at the high dose level of 1,200 mg given in a single dose emylcamate did not affect the normal performance, skill or precision, whereas meprobamate significantly

* Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories, West Point, Pa., U.S.A.

affected the results on several observation points. Increasing the single dose to 1,800 mg both compounds impaired performance.

Mårtens[13] utilized the double blind technique for comparing the effect of emylcamate, meprobamate and placebo in severe neurotic ambulatory alcoholics who had earlier been kept sober by means of meprobamate medication. Emylcamate was found to be significantly superior to meprobamate at the dose level of 400 mg three times daily. Mårtens also found that at the same dose level given daily for over six months no significant haematological or liver function changes occurred.

As indicated in the psychological test, emylcamate does not produce sedation or dullness even at single doses corresponding to one to two days' dose of the drug, 1,200 mg. This is in good accordance with the clinical results reached so far. Thus the safety factor is high for the use of emylcamate in ambulant patients carrying on their normal activities. Emylcamate according to accumulating data produces a desired clinical response at the dose level of 200 mg three times daily without sedation or impairment of precision, skill and judgement.

These data have demonstrated the minimum structural requirements for a potent tranquillizing relaxant, emylcamate. Despite the complex psychological mechanisms involved in anxiety neurosis and tension states the experimental screening system employed allows a good predictability as far as the clinical effect of a new compound is concerned.

Summary. (1) Screening a series of tertiary alcohols and their acetates, chloroacetates, *N*·diethylaminoacetates, *N*·diallylaminoacetates, phenyl carbonates and carbamates for the minimum structural requirements for full tranquillizing and relaxant activity, 1·ethyl-1·methylpropyl carbamate, was selected.

(2) Utilizing meprobamate as a standard, emylcamate proved to be about twice as active as, and to have an onset of action down to one·tenth that of meprobamate.

(3) Chronic toxicity studies in mice for 30 days and in rabbits for 35 weeks revealed no untoward influence of either emylcamate or meprobamate as compared with controls.

(4) Results from separate psychological, psychotechnical and clinical studies parallel the experimental results regarding superiority of emylcamate over meprobamate.

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