CHEMISTRY AND PHARMACOLOGY OF ESTERS OF METHYLPENTYNOL AND RELATED COMPOUNDS

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The narcotic action of a range of methylpentynol esters has been investigated. In general, esterification reduces or abolishes narcotic activity, but the carbamate possesses increased and more prolonged activity and higher oral toxicity than the parent carbinol, though their therapeutic indices are similar. Contrary to previous claims, the *N*-methyl carbamate is inactive by our method of test. Carbamates of methylpentynol homologues and near relatives also possess increased narcotic properties compared with the parent carbinols. The anticonvulsant properties of methylpentynyl carbamate against leptazol in mice are superior to those of aloxidone. Chronic toxicity tests in mice over 4 to 5 months have shown no untoward effects, and the average weight gain follows a normal pattern: there is no effect on blood pressure or respiration in therapeutic doses. Methylpentynyl carbamate shows no analgesic activity on intravenous administration in mice compared with that of salicylamide. Bemegride acts as an antagonist. A new method[2] for the preparation of carbamates of tertiary alcohols is described.

In a search for an active solid ester of methylpentynol suitable for tabletting we found the acetate to be a liquid with reduced activity, and the benzoate, a liquid and inactive, as was the *N*-methyl carbamate[1]. Of the solid esters, the hydrogen phthalate and *N*-phenyl carbamate were inactive, the allophanate possessed slight activity, only the carbamate possessed high activity. Methylpentynyl carbamate was therefore investigated in detail, and the narcotic activity of the carbamates of certain homologues and related saturated carbinols was also determined. The difficulties in preparing carbamates of tertiary alcohols have been described by McLamore, P'an, and Bavley[3], who obtained methylpentynyl carbamate in 21 per cent yield by splitting the phenylcarbonate with ammonia.

The results of our attempts to prepare the intermediate chloroformates of methylpentynol and ethinyl*cyclo*hexanol, before reaction with ammonia, emphasised the instability of these esters and neither could be isolated. Thus, from the reaction of ethinyl*cyclo*hexanol with phosgene in pyridine at 0° 1-ethinyl*cyclo*hexene alone was obtained. Reaction of methylpentynol with phosgene, without a base, in a sealed tube at 150° yielded carbon dioxide and an unstable oil, b.p. 54° at 13 mm., which had the molecular formula $C_6H_{10}Cl_2$ and would result from the addition of two molecules of hydrogen chloride to the dehydration product of methylpentynol. The ready decomposition of tertiary butyl chloroformate to give *iso*butylene, carbon dioxide and hydrogen chloride has been described by Choppin and Rogers[4].

The preparation of methylpentynyl carbamate by the reaction of carbamyl chloride with methylpentynol in ether has been described in the patent literature[5], but a yield of only 16·5 per cent is claimed; we have confirmed this low yield. In the same specification a general method is described for the preparation of carbamates of tertiary acetylenic alcohols by the action of ammonia on the chloroformates, which were obtained (but not isolated) by the reaction of phosgene with the carbinol in ether or toluene and in the presence of a tertiary base, preferably trimethylamine. Using this method, with trimethylamine as base, we have obtained a yield of 50 per cent of methylpentynyl carbamate. Heterocyclic bases are less satisfactory, with both methylpentynol and ethinyl*cyclo*hexanol.

Attempted ester interchange between methylpentynol and ethyl carbamate, with both acidic and basic catalysts, was unsuccessful. Reaction of methylpentynol with cyanate in the presence of hydrogen chloride under a variety of conditions failed to yield the carbamate. Reaction of methylpentynol with sodium cyanate and trichloroacetic acid in an excess of methylpentynol as solvent gave the carbamate in about 65 per cent yield based on the sodium cyanate. This could be carried out at 20° for several days or at 50° for 24 hours. Carbon tetrachloride could be used as solvent instead of excess methylpentynol with only a small decrease in yield. Methylene dichloride, however, could only be used at 20° as at higher temperatures trichloroacetic acid and cyanate react in this solvent with the formation of carbon dioxide and trichloroacetamide. This reaction takes place in dioxan even at room temperature and gives a much lower yield of carbamate. A similar reaction takes place using acetic or monochloroacetic acids instead of trichloroacetic acid, and with these acids no carbamate is formed.

Preparation of Chemical Compounds

Methylpentynyl acetate was obtained by treating methylpentynol with acetic anhydride and acetic acid in the presence of boron trifluoride-acetic acid complex, as a liquid, b.p. 146 to 147° at 763 mm. (*cf.* Heilmann, Glénat, and Gaudemaris[6], 149° at 745 mm., and Keil, Muschawek and Rademacher[7], 148 to 150° at 760 mm.).

Methylpentynyl benzoate. Benzoyl chloride (35 g.) was added gradually to methylpentynol (19·6 g.) in pyridine (50 ml.) with cooling and stirring. The mixture was refluxed for 1 hour, then poured into water and extracted with ether. After drying, the ether was removed and the residue was distilled. Yield, 29·6 g. (73 per cent), b.p. 65 to 67° at 0·05 mm. Found: C, 77·2; H, 7·2. Calc. for $C_{13}H_{14}O_2$, C, 77·2; H, 7·0 per cent. Keil[7] gives b.p. 127·5 to 132·5° at 11 mm.

Methylpentynyl allophanate. Cyanuric acid (10 g.) was depolymerised by heating at *ca.* 400° in a slow stream of CO_2 in an electrically heated tube (*cf.* Blohm and Becker)[8], and the cyanic acid vapour passed into a solution of methylpentynol (9·8 g.) in anhydrous ether (20 ml.), protected from atmospheric moisture and cooled in ice. A loose cotton wool plug in the delivery-tube served to minimise sublimation of cyanuric

acid into the solution. The depolymerisation required approximately 6 hours, after which time the ether solution had becomed cloudy. The next day the separated crystals were recrystallised from ethanol (charcoal) giving needles, m.p. 135 to 137° decomp. (evolution of gas). Found: C, 52·5; H, 6·6; N, 15·0. Calc. for $C_8H_{12}O_3N_2$, C, 52·2; H, 6·6; N, 15·2 per cent. Keil[7] gives m.p. 148° but no preparative details.

TABLE I

OTHER CARBAMATES OF ACETYLENIC CARBINOLS

Carbamates of	Yield per cent	m.p.	Analysis
3-Methylbut-1-yn-3-ol	49	106–107·5°	Found: C, 57·2 H, 7·2 N, 10·7
			$C_6H_9O_2N$ requires: C, 56·7 H, 7·1 N, 11·0
3-Methylhept-1-yn-3-ol	49	44–45° b.p. 93–94°/0·2 mm.	Found: C, 63·9 H, 8·9 N, 8·55
			$C_9H_{15}O_2N$ requires: C, 64·0 H, 8·9 N, 8·3
3-Methyloct-1-yn-3-ol	42	42·5–43·5°	Found: C, 65·9 H, 9·1 N, 7·95
			$C_{10}H_{17}O_2N$ requires: C, 65·6 H, 9·3 N, 7·65
3:5-Dimethylhex-1-yn-3-ol	37	28·5–29·5° b.p. 78–79°/0·3 mm.	Found: C, 63·7 H, 8·8 N, 8·55
			$C_9H_{15}O_2N$ requires: C, 64·0 H, 8·9 N, 8·3
3-Ethylpent-1-yn-3-ol	38	38·5–40°	Found: C, 62·3 H, 8·5 N, 9·5
			$C_8H_{13}O_2N$ requires: C, 62·0 H, 8·4 N, 9·05
3-Methylhex-1-yn-3-ol	43	53·5–54°	Found: C, 62·2 H, 8·5 N, 9·5
			$C_8H_{13}O_2N$ requires: C, 62·0 H, 8·4 N, 9·05
1-Ethinyl *cyclo*hexanol	22*	95–96°	Found: C, 64·7 H, 7·9 N, 8·1
			Calc. for $C_9H_{13}O_2N$: C, 64·7 H, 7·8 N, 8·4

* Reaction carried out with potassium cyanate and dioxan as solvent.

Methylpentynyl N-*phenylcarbamate.* Methylpentynol (4·9 g., 0·05 mole) was refluxed with phenyl *iso*cyanate (6.5 g., 0·055 mole) for 2 hours, and the product was dissolved in light petroleum (b.p. 40 to 60°), filtered from some *s*-diphenylurea, and the filtrate concentrated to crystallising point. Yield, 6·25 g. (57·5 per cent), m.p. 65 to 66° (*cf.* Young and Webb[9]).

Methylpentynyl N-*methylcarbamate.* Methylpentynol (9·8 g., 0·1 mole) was heated with methyl *iso*cyanate (5·7 g., 0·1 mole) in a sealed

tube at 170° for 4 hours, the contents added to water and extracted with ether. The ether was removed from the dried extract, and the residue was distilled. Yield, 5·2 g. (35 per cent), b.p. 100° at 11 mm. Found: C, 62·3; H, 8·5; N, 8·85; Calc. for $C_8H_{13}O_2N$, C, 61·9; H, 8·4; N, 9·0 per cent. The preparation of this ester at room temperature has been described[1], with the following constants: b.p. 103° at 11 mm., m.p. 54 to 55°, but no analysis was given.

Reaction of ethinylcyclohexanol with phosgene in pyridine. Ethinyl-*cyclo*hexanol (12·4 g.) in pyridine (20 ml.) was added with stirring to a suspension prepared by gradually adding phosgene (10 ml.) to pyridine

TABLE II

ACUTE ORAL TOXICITY OF METHYLPENTYNYL CARBAMATE IN FEMALE ALBINO MICE

Dose mg./kg.	No. of mice	Deaths (after 5 days)
400	27	25
333	27	9
277	26	3

LD 50 = 337 mg./kg.
Fiducial limits = 322–353 mg./kg.

(40 ml.) with cooling. After stirring at room temperature for 2 hours, the mixture was allowed to stand overnight, poured into water, and the product extracted with ether. After removal of the ether from the dried extract, the residue was distilled and 1-ethinyl*cyclo*hexene (6·3 g., 60 per cent) was obtained, b.p. 84° at 100 mm. Found: C, 90·5; H, 9·4. Calc. for C_8H_{10}, C, 90·5; H, 9·4 per cent.

Reaction of methylpentynol with phosgene. Methylpentynol (9·8 g.) and phosgene (8 ml.) were heated in a sealed tube at 150° for 1 hour. After cooling and releasing the carbon dioxide, the contents were poured

TABLE III

RED AND WHITE BLOOD CELL COUNTS OF ANIMALS IN SUB-ACUTE TOXICITY TEST

	Controls	Test
Average red blood cell count (millions/cu. mm.)	10·16	11·92
Average white blood cell count (thousands/cu. mm.) ..	16·63	16·97

into water, and the separated oil was extracted with ether. Working up in the usual manner yielded an *oil*, b.p. 54° at 13 mm. The structure was not elucidated. Found: C, 46·9; H, 6·5; Cl, 45·8. $C_6H_{10}Cl_2$ requires C, 47·1; H, 6·6; Cl, 46·3 per cent.

Methylpentynyl carbamate. To trichloroacetic acid (1634 g.), dried *in vacuo* in the reaction vessel, was added methylpentynol (2175 g., 2·5 l.) and sodium cyanate (650 g.), also thoroughly dried. The suspension, protected from moist air and mechanically stirred, was heated at 45 to 50° for 20 hours, and then neutralised to *ca.* pH 7 by the gradual addition

of anhydrous sodium carbonate. The mixture was cooled to 30°, filtered using a filter aid, and the vessel rinsed with carbon tetrachloride (200 ml.) which was then used to wash the filter cake (mainly sodium trichloroacetate). Carbon tetrachloride was then removed from the filtrate and washings. Excess of methylpentynol was then distilled off at *ca.* 6 mm. pressure whilst the temperature was gradually raised to 50°. Approximately 1240 g. of methylpentynol was recovered. Two volumes of water were then added to the residue with stirring. The oil which separated solidified on cooling to room temperature. The yellowish powder was collected and dried. Yield, 1138 g., m.p. *ca.* 40°. Recrystallisation

TABLE IV

NARCOTIC ACTIVITY OF METHYLPENTYNYL CARBAMATE

Expt.	Compound	No. of mice	Route	Dose g./kg.	Time after injection in hours: ½ N	½ D	1 N	1 D	2 N	2 D	3 N	3 D	4 N	4 D	5 N	5 D	6 N	6 D	24 N	24 D
1.	Methylpentynol	20	oral	1·140	20	–	20	–	19	1	15	5	7	13	5	15	5	15		
				0·760	16	–	19	–	19	–	19		19		20		19	1		
				0·506	12	–	13	–	16	–	10		9		9		4			
				0·338	2	–	1	–	0	–	0		0		0		0			
2.	Methylpentynyl carbamate	19	oral	0·506	19		19		19		18	1	16	3	15	4	14	5	13	5
				0·338	10		10		7		6	1	7	1	6	1	6	1	0	1
				0·225	0		0		0		0		0		0		0		0	

N = Narcotised
D = Dead (total)

from *cyclo*hexane gave an almost white product, the carbamate of 3-methylpent-1-yn-3-ol (940 g.), m.p. 53 to 55°. The aqueous medium from the solidified oil was cooled in ice for 24 hours and afforded a further 22 g. of pure material, giving a total yield of 962 g. (68 per cent). Found: C, 59·5; H, 7·9; N, 10·2. Calc. for $C_7H_{11}O_2N$, C, 59·5; H, 7·85; N, 9·9 per cent.

Other carbamates of acetylenic carbinols (Table I). The carbamates of tertiary acetylenic alcohols were prepared by the above method, except that the crude compounds were extracted with ether, and the extracts were washed with aqueous sodium bicarbonate and water, dried, and evaporated. Excess of the carbinol was removed at $\nearrow$ 100° at 20 mm., and the residue was crystallised from light petroleum or *cyclo*hexane. Approximately 80 per cent of the unreacted carbinols was recovered. In addition to these in Table I *tert.*-butyl carbamate was prepared in low yield by an analogous method using potassium cyanate, and with dioxan as solvent. This is known to be less satisfactory than the method detailed above for methylpentynol. The product had m.p. 106 to 107° (*cf.* Choppin and Rogers[4] 108 to 108·5°).

BIOLOGICAL METHODS

Female mice of Schofield strain and weighing approximately 20 g. were used for all estimations involving this species.

Acute Toxicity

Food was witheld from mice 18 hours before use. Methylpentynyl carbamate was administered orally as a suspension in 5 per cent gum acacia solution, at a concentration such that 0·5 ml. was given per 20 g. of body weight. The animals were kept under observation for 5 days

TABLE V

NARCOTIC ACTIVITY OF ESTERS OF METHYLPENTYNOL AND RELATED COMPOUNDS
(5 mice in each case except where otherwise stated)

No.	Compound	Oral dose g./kg.	Time after injection in hours ½ N	½ D	1 N	1 D	2 N	2 D	3 N	3 D	4 N	4 D	5 N	5 D	6 N	6 D	7 N	7 D	24 N	24 D
327	Methylpentynyl acetate ..		ED 50 approx. 1·17 g./kg. Later time of onset, shorter duration																	
496	Methylpentynyl benzoate ..	1·17	0		0		0		0		0		0		0		–		–	
502	Methylpentynyl *N*-phenyl carbamate	1·17	0		0		0		0		–		–		–		–		–	
511	Methylpentynyl *N*-methyl carbamate	1·17	0		0		0		0											
521	Methylpentynyl allophanate ..	1·17	0		2		2	2	1	3	2	3	1	4						
		0·78	0		0		3		3		2	1	1	2						
		0·52	0		0		0		0		0		2							
	Methylpentynyl hydrogen phthalate	1·14			0	1	0	2	0	3	0	4	0	4	0	4				
533	Carbamate of 2-methylbutan-2-ol	1·14	0		0		0		0		0		0		0					
522	Carbamate of 3-methylhex-1-yn-3-ol	1·14	4	1	2	3	2	3	2	3	1	4	1	4	1	4				
		0·76	3	2	3	2	3	2	1	4	1	4	0	5	0	5				
		0·506	5		5		4	1	4	1	4	1	4	1	4	1				
		0·338	4		5		5		4		4		4		4					
		0·225	0		0		0		0		0		0		0					
555	Carbamate of 3-ethylpent-1-yn-3-ol 30/dose	0·506	28		29	1	29	1	28	2	27	2	23	5	23	5				
		0·338	28		29		29		28		26		14		4					
		0·225	5		4		2		0		0		0		0					
		0·150	0		0		0		0		0		0		0					
558	Carbamate of 3:5-dimethylhex-1-yn-3-ol	1·14	0		0		0		0		0		0		0					
559	Carbamate of 3-methyloct-1-yn-3-ol	0·506	0		0		0		0		0		0		0					
561	Carbamate of 3-methylhept-1-yn-3-ol	0·506	5		5		3		2		0		0		0					
		0·338	3		3		1		0		0		0		0					
		0·225	2		1		0		0		0		0		0					
		0·150	0		0		0		0		0		0		0					
566	Carbamate of 3-methylbut-1-yn-3-ol	1·14	5		5		5		5		5		5						1	4
		0·76	5		5		5		5		5		5						4	1
		0·506	5		5		5		5		5		5						5	
		0·338	0		1		0		0		0		0						0	
519	Carbamate of 1-ethinylcyclohexanol[13]	1·17	3	2	3	2	2	3	2	3	1	4	1	4						
		0·78	5		5		3	1	0	2	0	2	0	2						
		0·52	5		5		5		0		0		0							
		0·35	4		2		0		0		0		0							

N = Narcotised D = Dead

after administration of the drug, with free access to food (diet 41B) and water. At the end of this period LD 50 estimates were made according to the method of Bliss[10].

Subacute Toxicity

Twenty mice were given 170 mg. (approximately equivalent to half the LD 50) of methylpentynyl carbamate per kg. of body weight, orally as a suspension in 5 per cent gum acacia solution 5 days a week for 19 weeks. Ten mice were kept as controls. The animals had free access to their usual diet and water, and their weights were recorded at the beginning of the experiment and once every week thereafter. Any deaths or untoward symptoms during the experiment were noted. At the end of the experiment a sample of blood was taken from each of the

TABLE VI

ANTICONVULSANT ACTIVITY OF METHYLPENTYNYL CARBAMATE AND METHYLPENTYNOL

Compound	Dose mg./kg.	Number of mice	Number convulsing	Number protected	Per cent protection
Aloxidone	225	49	10	39	79·6
	150	47	16	13	66·0
	100	50	32	18	36·0
Methylpentynol	100	50	8	42	84·0
	67	50	15	35	70·0
	44	50	21	29	58·0
Methylpentynyl carbamate ..	100	50	1	49	98·0
	67	50	5	45	90·0
	44	50	20	30	60·0

survivors which were then killed and post-mortem examinations made. Histological preparations were made of the liver, kidney, and spleen of several animals in each group.

Narcotic Activity

Varying doses of methylpentynyl carbamate and other esters were administered orally to groups of mice, which were then kept at a temperature of 37° and examined 30 minutes, 1 hour and then hourly for 6 hours, after administration. The abolition of the righting reflex for at least 30 seconds was taken as the criterion of narcosis. The doses given were in accordance with one of two series of four geometric dose levels: 1·17, 0·78, 0·52 and 0·35 g./kg., or 1·14, 0·76, 0·56 and 0·34 g./kg. of body weight. Where a preliminary test indicated a very low order of activity, only the top dose was given, and occasionally also lower doses (e.g., 0·23 g./kg.) were given.

Anticonvulsant Activity

Comparative experiments were done with methylpentynyl carbamate and methylpentynol, 100, 67 and 44 mg./kg., and aloxidone, 225, 150 and 100 mg./kg. of body weight. All doses were administered orally as a suspension in 5 per cent gum acacia solution. Two hours later all the mice were given an intravenous injection (caudal vein) of leptazol (0·2 ml. of a 0·6 per cent solution per 20 g. of body weight). This dose of leptazol produced 100 per cent response in animals which received no premedication. The criterion of positive response was the characteristic tonic

extension of the hind leg. The median protective dose (ED 50) was estimated graphically.

Analgesic Activity

The method of Woolfe and Macdonald[11] was used with minor modifications. Methylpentynyl carbamate was injected intravenously at 50 mg./kg. body weight.

TABLE VII

EFFECT OF BEMEGRIDE ON MICE NARCOTISED WITH METHYLPENTYNOL AND METHYLPENTYNYL CARBAMATE

Test No.	Drugs and Doses (Those in parentheses refer to bemegride) 10 mice/dose (intraperitoneal)		Number narcotised						
			½	1	1½	2	2½	3	3½ hrs after injection
3	Methylpentynol alone	700 mg./kg.	10	10	10	10	9	9	8
	Methylpentynyl carbamate alone	350 ,,	10	10	9	7	4	3	1
	Methylpentynol + bemegride	(40) ,,	10	↓10	9	7	5	5	3
	Methylpentynyl carbamate + bemegride	(40) ,,	10	↓0	0	0	0	0	0
4	Methylpentynol alone	600 ,,	10	10	10	10	10	—	6
	Methylpentynyl carbamate alone	400 ,,	10	10	10	10	10	—	10
	Methylpentynol + bemegride	(50) ,,	10	↓4	1	0	0	—	0
	Methylpentynyl carbamate + bemegride	(50) ,,	10	↓1	1	0	0	—	0

↓ = injection of bemegride

Effect on Blood Pressure and Respiration

The animals used were rabbits and cats, the former being anaesthetised with ether and pentobarbitone, and the latter with ether and chloralose. Methylpentynyl carbamate was injected into the cannulated femoral vein in doses of 0·1 to 10·0 mg. in aqueous solution.

Bemegride as Antagonist to Methylpentynol and its Carbamate

The method and experimental details of Frey, Hushahn and Soehring[12] were followed closely. Solutions were made up in Tyrode-Ringer solution with the exception of methylpentynyl carbamate which was administered as a suspension in 5 per cent gum acacia solution. The doses were kept as low as consistent with a high degree of narcosis, and paying due regard to toxicity. Two series of experiments were carried out, in which the drugs were given intraperitoneally and orally respectively. In all cases the bemegride was given intravenously in aqueous solution approximately 20 to 30 minutes after narcosis was complete, as judged by abolition of the righting reflex. Animals which were not narcotised were not given bemegride. In some cases the mice were examined after 24 and 72 hours. The doses of both methylpentynol and the carbamate were all greater than those normally used, the purpose being to establish whether any significant degree of antagonism could be demonstrated.

RESULTS

Acute Toxicity (Table II)

The median lethal dose of methylpentynyl carbamate was estimated at 337 mg./kg. body weight, the corresponding value for methylpentynol

itself being 810 mg./kg. The carbamate is therefore approximately 2·6 times as toxic as methylpentynol.

Subacute Toxicity

The graphical results of the weekly average weights of test and control animals are shown in Figure 1. There was no significant difference between the rate of growth per week in the two groups as shown by treating the results statistically using a '*t*' test. There were four deaths among the twenty test mice, and one death among the ten controls before the end of the experiment (20 and 10 per cent respectively). These deaths were almost exclusively due to subcutaneous abscesses from an unknown cause, generally in the thoracic area. Post-mortem examination of the remaining animals showed no gross pathological changes, and the histological preparations revealed no consistent abnormalities which could be related to the administration of the drug. The red blood corpuscles and the leucocytes were within normal limits, but the average haemoglobin level of the test group was 17·2 per cent greater than that of the controls (137·9 compared with 117·7 per cent—Sahli method). See Table III.

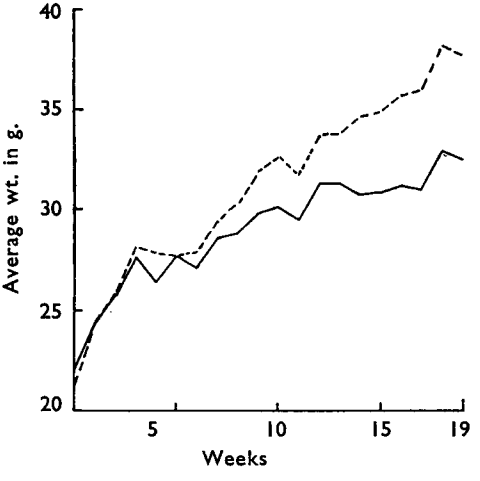

FIG. 1. Average growth curves for mice receiving 170 mg./kg. methylpentynyl carbamate per day (——) and controls (- - -).

Narcotic Activity

The results are shown in Table IV. The number dead and narcotised at each dose level is shown. The results show that methylpentynyl carbamate is at least twice as active as methylpentynol. Both substances act quickly, but the duration of action of the carbamate is greater, at equiactive doses. Table V shows that none of the other esters of methylpentynol possess any appreciable narcotic activity. The carbamates of most of the homologues of methylpentynol show significant activity.

Anticonvulsant Activity

Table VI shows the results of a comparison of the anticonvulsant activity of methylpentynyl carbamate with that of methylpentynol and aloxidone. The ED 50 estimates (obtained graphically) are as follows: aloxidone, 123, methylpentynol, 38, methylpentynyl carbamate, 39 mg./kg.

Analgesic Activity

Methylpentynyl carbamate had no activity.

Effect on Blood Pressure and Respiration

Methylpentynyl carbamate had no effect on the blood pressure or respiration of the animals at the doses used.

Antagonism of Bemegride (Table VII)

These results show that bemegride given intraperitoneally has a significant arousal action on mice narcotised with high doses of methylpentynol or its carbamate. There were no deaths in this series of experiments but the animals were only observed up to 3½ hours after the first injection. Some preliminary experiments have been performed in which the drugs were administered orally. The results so far appear similar to those obtained in the first series, but they have not been so consistent.

It seems clear from the present results that bemegride cannot be regarded as a specific barbiturate antagonist.

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References

1. E.P., 740,990.
2. E.P., 761,817.
3. McLamore, P'an and Bavley, *J. org. Chem.*, 1955, **20**, 1379.
4. Choppin and Rogers, *J. Amer. chem. Soc.*, 1948, **70**, 2967.
5. E.P., 772,721.
6. Heilmann, Glenat and Gaudemaris, *Bull. Soc. chim.*, 1952, 284.
7. Keil, Muschaweck and Rademacher, *Arzneimit.-Forsch.*, 1954, **4**, 477.
8. Blohm and Becker, *Chem. Rev.*, 1952, **51**, 471.
9. Young and Webb, *J. Amer. chem. Soc.*, 1951, **73**, 780.
10. Bliss, *Quart. J. Pharm. Pharmacol.*, 1938, **11**, 192.
11. Woolfe and Macdonald, *J. Pharmacol.*, 1944, **80**, 300.
12. Frey, Hushahn and Soehring, *Arzneimit.-Forsch.*, 1956, **10**, 583.
13. Langecker, Schumann and Junkmann, *Arch. exp. Path. Pharmak.*, 1953, **219**, 130.