DERIVATIVES OF ACETAMIDE AND BENZAMIDE AS HYPNOTICS

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It has been known since 1910[1] that certain dialkyl-arylacetamides possess sedative, hypnotic and antipyretic properties, and Lumière and Perrin[2] later described the hypnotic activity of phenylacetamides in dogs. Trialkylacetamides have been reported to possess spasmolytic[3] and hypnotic[4] properties, but none of the compounds described appears to have found its way into clinical use.

Our interest in 3-methylpentynol, and in hypnotics in general, led us to reinvestigate and extend earlier work in this connection, in the hope of discovering a compound with hypnotic properties intermediate between those of methylpentynol and the barbiturates, but without the disadvantages of the latter.

Although a number of active compounds were found, none was sufficiently outstanding to justify its introduction to clinical use. Nevertheless, in addition to the preparation of a number of new compounds, we have attempted a correlation of their hypnotic activity and chemical constitution within the group of acetamide derivatives.

Benzamide[5] has also been reported to possess hypnotic properties and a number of derivatives have been examined, but without discovering any which was of practical interest.

Narcotic Effect

The criterion of narcotic activity adopted was the abolition of the righting reflex in mice. Screening tests were carried out at four geometric dose levels, 1·14, 0·77, 0·52 and 0·35 g./kg. on groups of five female mice (Schofield strain), with methylpentynol as the reference compound in all cases, and observations were made at half an hour, 1 hour, and then hourly intervals up to 6 hours after oral administration of the appropriate dose in suspension in 5 per cent acacia solution. The doses chosen were such that on the top dose all the animals treated with methylpentynol invariably showed abolition of the righting reflex, whereas on the lowest dose only rarely did more than one animal show a positive response. Only in those in which the narcotic activity of the compound was similar or greater than that of methylpentynol, was a more detailed examination made using a larger number of animals, except when it appeared necessary to assist correlation of narcotic activity with

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chemical constitution. An estimate of the median narcotic dose (ND50) was made as described by Marshall and Vallance[6], when required.

Toxicity

Determinations of acute oral toxicity (LD50) were made only when narcotic activity indicated possible clinical value. Indications of gross toxicity were obtained in many cases during narcotic screening tests. Appropriate compounds were administered orally to female mice (Schofield strain) under the conditions specified by Marshall and Vallance[6] and the LD50 estimates were made as described by Bliss[7].

Preparation of chemical compounds

Aliphatic Derivatives of Acetamide

The alkyl acetamides were prepared by the action of alkyl halides on acetonitrile in the presence of sodamide in liquid ammonia[8], and subsequent hydrolysis of the nitrile with 85 per cent sulphuric acid. In the case of the ethyl and *n*-propyl derivatives, mixtures of the di- and tri-alkyl acetonitriles (with a trace of the monoalkyl acetonitrile) were obtained and were separated by fractionation, but *n*-butyl-bromide gave only the corresponding tri-alkyl derivative. Tri-chloroacetamide, *N*-ethyl and *NN*-diethyltrichloroacetamide were all prepared from trichloroacetyl chloride by reaction with ammonia or the appropriate amine. Siccatamide B was prepared from the acid, via the acid chloride.

Derivatives of Phenylacetamide

All the compounds of the phenylacetamide series have been prepared from the corresponding nitrile by hydrolysis. Nitriles with an α-hydrogen atom or an α-methyl group can be hydrolysed by 90 per cent (w/w) sulphuric acid, but sulphonation occurred with *o*- and *p*-tolyl-dimethyl-acetonitrile, and a modified procedure was adopted in these cases. The higher homologues are found to be very resistant to hydrolysis and require heating with 10 per cent potassium hydroxide in amyl alcohol for up to 48 hours. Unfortunately, under these conditions a varying amount of non-volatile material, possibly a polymer, is formed, which may increase the difficulty of purifying the amide. In the case of diallyl-phenylacetamide so much of the material was formed that none of the desired product could be isolated.

Symmetrical di-alkyl phenylacetonitriles were prepared by the reaction of the theoretical quantity of sodamide with phenylacetonitrile in ether and the subsequent addition of the appropriate alkyl halide. Unalkylated and monoalkylated nitriles were separated by reaction with acrylonitrile to give high-boiling fractions, which were easily separated by distillation.

In all the derivatives prepared containing two different alkyl groups, one of these was either methyl or ethyl. Bulk quantities of phenyl-ethyl-acetonitrile and phenyl-methyl-aceto-nitrile were prepared by the alkylation of phenyl cyanacetic ester followed by hydrolysis and decarboxylation. The second alkyl group was then introduced by the action of the alkyl halide on the sodio-derivative in ether. This reaction failed with

hydratroponitrile and *tert.*-butyl chloride;. The following are typical examples:

Phenyl-αα-diethylacetonitrile. 31·5 g (0·81 mole) of sodamide and 750 ml. of dry benzene were heated to boiling point and, after removal of the source of heat, 90 g. (0·77 mole) of phenylacetonitrile was added at a rate sufficient to maintain gentle boiling. After refluxing for a further half-hour the dark red solution was cooled and 90 g. (0·825 mole) of ethyl bromide was added dropwise during about 2 hours and the whole left to stand overnight. After addition of a further 31·5 g. of sodamide the mixture was refluxed for 12 hours and then reacted as above with a further 90 g. of ethyl bromide. After cooling to room temperature, 200 ml. of water was added and the whole was extracted with benzene and once with ether. The combined extracts were washed with 2N-hydrochloric acid, 2N-sodium carbonate and water, and dried over anhydrous magnesium sulphate. Removal of the solvent left 70 g. of a crude product which contained unchanged material together with mono- and diethyl derivatives. 65 g. (1·23 moles) of acrylonitrile was added together with a few drops of sodium ethoxide in ethanol. The temperature was kept below 30° by cooling and, when the reaction had subsided a further small amount of catalyst was added until no further substantial rise in temperature occurred. After standing overnight 30 ml. of water was added, the base was neutralised with acetic acid, and the mixture was extracted with ethylene dichloride. The extracts were washed with water and dried over anhydrous magnesium sulphate. After removal of the solvent the residue was fractionally distilled and 55 g. of phenyl-αα-diethylacetonitrile, b.p. 137 to 139°/21 mm., was obtained. The high-boiling residue consisted of condensation products of acrylontrile with the other nitriles originally present.

Phenyl-αα-diethylacetamide (*Compound* 437). 65 g. (0·376 mole) of the above nitrile was added to a hot solution of 30 g. (0·535 mole) of potassium hydroxide in 300 ml. of technical amyl alcohol, and the mixture refluxed for 24 hours, cooled, and poured into an equal volume of water. After ether extraction the organic layer was washed free from alkali with water, and dried over anhydrous magnesium sulphate. After removal of the solvent the residue gave on fractional distillation, a forerun of 19·2 g. (largely unchanged nitrile) and phenyl-αα-diethylacetamide; yield 33·9 g. (70 per cent on nitrile hydrolysed), m.p. 51 to 52° ex cyclohexane, *lit.* 53°. Found: C, 75·40; H, 8·82; N, 7·15. $C_{12}H_{17}ON$ requires C, 75·35; H, 8·96; N, 7·32 per cent.

From the alkaline liquors 9·7 g. (19·4 per cent on reacted nitrile) of phenyl-αα-diethylacetic acid was obtained on acidification.

Hydratroponitrile. · $C_6H_5{\cdot}CH(CH_3)CN$ 23 g. of sodium were dissolved in 350 ml. of dry ethanol and cooled to about 70°, and 189 g. (1 mole) of ethylphenylcyanacetate were added, followed by 145 g. (1·01 mole) of methyl iodide dropwise to maintain gentle boiling. Refluxing was continued for 2 hours, 10 ml. of water was added, most of the ethanol was distilled off, and the residue was poured into water and extracted with ether. The ether extract was washed with water, dried over

anhydrous magnesium sulphate and the solvent was removed. Fractional distillation of the residue yielded 96 g. (73·6 per cent) of hydratroponitrile, b.p. 108°/10 mm. (*cf.* Newman and Closson[10], Goerner and Workman[9]). Hydratroponitrile was alkylated to give the unsymmetrical phenyl-αα-dialkylacetonitriles, as described for phenyl-αα-diethylacetonitrile above.

α-Phenyl-αγ-dimethylvaleramide. $C_6H_5{\cdot}C(R,R'){\cdot}CONH_2$·(R = Me; R′ = *iso*-Bu) 9·27 g. (0·05 mole) of α-phenyl-αγ-dimethylvaleronitrile was mixed with 35 g. of 90 per cent (w/w) sulphuric acid, heated to 100° and concentrated sulphuric acid added dropwise until all the oil dissolved. Heating was continued for a further 15 hours, and the mixture cooled and poured into water. The product was extracted with ether, washed with aqueous sodium carbonate and water, and dried (magnesium sulphate). After removal of the ether, the residual oil was fractionated. Yield, 6·2 g. (61·5 per cent), b.p. 182°/8 mm. Found: C, 76·05; H, 9·13; N, 6·70. $C_{13}H_{19}ON$ requires C, 76·05; H, 9·33; N, 6·82 per cent. The product was a viscous liquid. The above method gave better results than the alkaline hydrolysis described for phenyl-αα-diethylacetonitrile.

Diphenylacetamide. Diphenylacetonitrile (4 g.) prepared by Shapiro's method[11] was hydrolysed by Anschutz and Romig's method[12]. Yield, 2·2 g. (50 per cent), m.p. 167 to 168° (*lit.* 166°).

Nuclear substituted phenylacetamides. *o*- and *p*-Methyl benzyl chlorides were prepared from the respective xylenes, and *o*-, *m*-, and *p*-chlorobenzyl chlorides were prepared from the corresponding chlorotoluenes, by an adaptation of the method of Kharasch and Brown[13]. The corresponding acetonitriles were then prepared by known methods, and the subsequent alkylation was carried out as described for phenyl-αα-diethylacetonitrile. The hydrolysis of the chloro-compounds was carried out by the method described above, but *o*-tolyl-dimethylacetonitrile was attacked vigorously by 90 per cent sulphuric acid with the formation of water soluble products, presumably sulphonic acids. This nitrile was hydrolysed by refluxing with 20 per cent potassium hydroxide in ethanol for 7 hours. The *p*-isomer was hydrolysed by warming with 75 per cent (w/w) sulphuric acid for 25 minutes.

Derivatives of Benzylacetamide

Haller and Bauer[14] found that benzylacetamide derivatives with both the α-hydrogen atoms replaced by alkyl groups may be prepared by the action of sodamide on the corresponding ω-di-alkyl benzylacetophenones in xylene. The latter were obtained by benzylation of ketones prepared by the Friedel-Crafts reaction with acid chlorides and benzene. The splitting reaction did not occur in the expected way with the di-propyl and the methyl propyl derivatives. The preparation of mono-alkyl benzyl acetophenones by the catalytic reduction of the analogous chalcones failed because, with all the catalysts tried, the carbonyl group was reduced rather than the double bond.

α-Benzyl-isobutyrophenone. This compound was prepared by Haller and Bauer's method[14]. Yield, 15 per cent, b.p. 176 to 177°/7 mm. (*lit.* 180 to 185°/11 mm.).

αα-Dimethyl-hydrocinnamic amide. (Benzyldimethylacetamide). This compound was prepared by Haller and Bauer's method[14]. Yield, 33·6 per cent, m.p. 65° ex light petroleum (*lit.* 62 to 63°).

TABLE I

NEW CHEMICAL COMPOUNDS

Nitriles	B.p.	Yield per cent (ex corresponding phenylaceto-nitrile)
Phenyl-αα-methyl*iso*propylacetonitrile ..	123°/15 mm.	59·5
Phenyl-αα-ethyl-*n*-propylacetonitrile ..	122–130°/12 mm.	73·0
Phenyl-αα-di-*n*-propylacetonitrile	98°/1·3 mm.	41·0
o-Chlorophenyl-αα-dimethylacetonitrile ..	80–81°/0·2 mm.	12·0
m-Chlorophenyl-αα-dimethylacetonitrile	134–135°/20 mm.	22·5
p-Chlorophenyl-αα-dimethylacetonitrile ..	122–127°/7 mm.	by-product
p-Chlorophenyl-αα-diethylacetonitrile ..	149–150°/10 mm. (m.p. 38·5°)	32·4

Amides	Yield per cent (ex Nitriles)	M.p.	Found per cent	Calc. per cent
Phenyl-αα-methyl-*n*-propylacetamide ($C_{12}H_{17}NO$)		b.p. 127°/0·09 mm.	C 75·1 H 9·06 N 7·35	75·35 8·96 7·32
Phenyl-αα-methyl*iso*propylacetamide		53–54° (b.p. 132°/0·5 mm.)	C 75·8 H 8·82 N 7·15	
Phenyl-αα-methyl*sec.*-butylacetamide ($C_{13}H_{19}NO$)	<30	b.p. 136°/0·5 mm.	C 76·11 H 9·61 N 6·29	76·05 9·33 6·82
Phenyl-αα-methyl*iso*butylacetamide ..	61	b.p. 182°/8 mm.	C 76·05 H 9·13 N 6·7	
Phenyl-αα-ethyl-*n*-propylacetamide ($C_{13}H_{19}NO$)		54–56° (b.p. 136°/0·5 mm.)	C 75·99 H 9·15 N 6·6	76·05 9·33 6·82
Phenyl-αα-ethylallylacetamide ($C_{13}H_{17}NO$)	<10	b.p. 142–144°/0·5 mm.	C 77·03 H 8·57 N 6·9	76·81 8·43 6·89
o-Chlorophenyl-αα-dimethylacetamide ($C_{10}H_{12}ONCl$)	55	84–85°	C 61·2 H 6·09 N 7·25	60·7 6·07 7·1
m-Chlorophenyl-αα-dimethyl-acetamide	37	121·5–123°	C 61·0 H 6·5 N 7·1	
p-Chlorophenyl-αα-dimethylacetamide	<20	123–124°	C 60·9 H 6·38 N 6·8	
p-Chlorophenyl-αα-diethylacetamide ($C_{12}H_{16}ONCl$)	<20	107–108°	C 63·7 H 7·1 N 6·2	63·9 7·15 6·2
*Phenyl-αα-diethyl-N-allylacetamide ($C_{16}H_{21}ON$)	46 (exchloride)	74°	C 77·9 H 9·0 N 5·7	77·8 9·15 6·1
*α-t-Butyl-αγγ-trimethylvaleramide (Siccatamide B) ($C_{13}H_{25}ON$) ..		131°	C 72·9 H 12·72 N 6·8	72·3 12·64 7·1

*These compounds were prepared via the acid chloride with allylamine and ammonia respectively.

TABLE II

BIOLOGICAL RESULTS

No.	Compound	Narcotic activity relative to methylpentynol	Toxicity relative to methylpentynol
Aliphatic Amides			
460	Acetamide	Inactive at 1·14 g./kg.	
420	Trichloroacetamide	Inactive	
422	*N*-ethyl-trichloroacetamide	Less active	
430	*NN*-Diethyl-trichloroacetamide	Inactive	
431	Diethylacetamide	Similar	More toxic
432	Triethylacetamide	Similar	Much more toxic
439	Di-*n*-propylacetamide	Similar	More toxic
443	Tri-*n*-propylacetamide	Less active	
456	Tri-*iso*-propylacetamide	Inactive	
446	Tri-*n*-butylacetamide	Inactive	
536	α-*t*-Butyl-αγγ-trimethylvaleramide (Siccatic acid B amide)	Less active	Similar
Derivatives of Phenylacetamide			
445	Hydratropamide	Less active	Less toxic
429	Phenyl-αα-dimethylacetamide	Less active	
452	Phenyl-α-ethylacetamide	Similar	Similar
457	Phenyl-αα-methyl-ethylacetamide	Similar	Much more toxic
497	Phenyl-αα-methyl-*n*-propylacetamide	Less active	Similar
459	Phenyl-αα-methyl-*iso*-propylacetamide	Similar	More toxic
437	Phenyl-αα-diethylacetamide	ca. twice as active	More toxic
509	Phenyl-α-*n*-butylacetamide	Inactive	
471	Phenyl-αα-methyl-*n*-butylacetamide	Inactive	
508	Phenyl-αα-methyl-*iso*-butylacetamide	Less active	
462	Phenyl-αα-methyl-*sec.*-butylacetamide	Less active	
455	Phenyl-αα-ethyl-*n*-propylacetamide	Similar	Less toxic
461	Phenyl-αα-ethyl-*iso*-propylacetamide	Less active	Similar
469	Phenyl-α-*n*-amylacetamide	Less active	More toxic
444	Phenyl-αα-di-*n*-propylacetamide	Less active	Less toxic
447	Diphenylacetamide	Inactive	
454	Phenyl-αα-allylacetamide	Less active	
492	Phenyl-αα-ethylallylacetamide	Less active	Less toxic
420	*p*-Tolyldimethylacetamide	Inactive	
563	*o*-Tolyldimethylacetamide	Similar	Much more toxic
518	*p*-Chlorophenyldimethylacetamide	Similar (c.f. 429)	Less toxic
643	*m*-Chlorophenyldimethylacetamide	Similar	Less toxic
644	*o*-Chlorophenyldimethylacetamide	Appreciably greater	Much more toxic
529	*p*-Chlorophenyldiethylacetamide	Similar (c.f. 437)	Similar
540	*N*-Allylphenyldiethylacetamide	Inactive	Convulsant
Derivatives of Benzylacetamide			
510	Benzyl-αα-dimethylacetamide	Less active	Similar
517	Benzyl-αα-methylethylacetamide	Inactive	
Derivatives of Benzamide			
458	Benzamide	Less active	Less toxic
467	*N*-Methyl-benzamide	Less active	Similar
466	*N*-Ethyl-benzamide	Less active	Similar
468	*NN*-Diethyl-benzamide	Less active	Similar
500	*p*-Toluamide	Inactive	
499	*m*-Toluamide	Less active	Similar
498	*p*-Nitrobenzamide	Inactive	Less toxic
463	Salicylamide	Less active	
464	*o*-Methoxy-benzamide	Less active	Similar
465	*N*-Acetyl-salicylamide	Less active	Less toxic
472	Phthalimide	Inactive	
513	Phthalic diamide	Inactive	
Derivatives of Hydroxyacetamide			
438	α-Hydroxy-*iso*-butyramide	Inactive	
451	Atrolactinamide	Similar	

The only other compound prepared satisfactorily by this method was α-methyl-α-ethyl-hydrocinnamic amide (benzylmethyl-ethylacetamide), an oil b.p. 183 to 184°/6 mm.

Derivatives of Benzamide

Benzamide and its *N*-alkyl derivatives were prepared from benzoyl chloride, and *p*-nitrobenzamide was also prepared from the acid chloride. *m*- and *p*-Toluamide were prepared from the corresponding nitriles by

hydrolysis with 90 vol. hydrogen peroxide in warm dilute alkali[15]. The nitriles were obtained by a Sandmeyer reaction from the amines. Salicylamide, *o*-methoxy benzamide and *N*-acetyl salicylamide were also prepared by known methods.

α-Hydroxyacetamides

α-Hydroxy-isobutyramide. This compound (m.p. 93 to 94°) was obtained in low yield by refluxing a solution of the ethyl ester in ammonia (0·880) for 65 hours, followed by evaporation and crystallisation from acetone. Ciamician and Silber[16] gave m.p. 96°.

Atrolactinamide. This compound (m.p. 99 to 100°) was obtained from acetophenone cyanhydrin by Staudinger and Ruzicka's method[17].

New Chemical Compounds

So far as we can ascertain, the compounds in Table I have not been described hitherto in the literature.

Our findings with regard to *p*-tolyl-dimethylacetamide, prepared by hydrolysis of the corresponding nitrile, agree with those of Lambert and others[18] who report m.p. 143 to 144° for the compound obtained by catalytic reduction (Raney nickel) of the hydroxamic acid, whereas Rupe and Burgin[19] give m.p. 119°, and Wallach[20] gives m.p. 123 to 124°. Our synthesis from *p*-tolyl-acetonitrile gave a product m.p. 142°. Found: C, 74·3; H, 8·36; N, 8·0; Calc. for $C_{11}H_{15}ON$: C, 74·53; H, 8·5; N, 7·9 per cent. The intermediate *p*-tolyl-dimethylacetonitrile had b.p. 72 to 73°/0·3 mm. (Lambert and others[18] give 122 to 123°/12 mm. and Wallach[20] gives 247 to 248°).

Discussion

The criterion of activity was a narcotic effect greater than that of methylpentynol, and a better therapeutic index. Di- and triethylacetamides are the only compounds in the aliphatic group that are more active than methylpentynol, and they are much more toxic. (Table II).

The most interesting compounds belong to the αα-disubstituted phenylacetamide group, of which the most active are phenyl-αα-diethylacetamide (compound 437), phenyl-αα-ethyl-*n*-propylacetamide (455) and *o*-chlorophenyl-αα-dimethylacetamide (644). Compound 437 seemed most worthy of further investigation, since it appeared to be twice as active as methylpentynol. The results are shown in Table III. The acute oral toxicity (LD50) was found to be 489 mg./kg. (limits 422 to 567 mg./kg., cf. Bliss[7]), compared with 760 to 860 mg./kg. for methylpentynol[6], Table IV.

Optimal activity within the phenylacetamide group occurs when the α-carbon atom is substituted by two alkyl radicals. The αα-diethy-compound (437) and the α-ethyl-α-*n*-propyl compounds are the most active, whilst the isomeric α-methyl-α-butylacetamides are all less active. Maximal activity seems to reside in compounds containing *n*-alkyl groups with the total number of carbon atoms 4 or 5.

Phenyldimethylacetamide (429) and *p*-tolyldimethylacetamide (420) are inactive, whereas the corresponding *o*-tolyl compound (563) is more

TABLE III

COMPARATIVE NARCOTIC ACTIVITY OF PHENYLDIETHYLACETAMIDE AND METHYLPENTYNOL

Experiment	Compound	No. of mice	Route	Dose g./kg.	Time after injection (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
I	Methylpentynol	5	Oral	1·14	5		5		5		3	2	0	5	0	5	0	5
				0·77	5		5		5		5		5		5		5	
				0·52	5		5		5		4		4		4		3	
	Phenyldiethyl-acetamide (437)	5	Oral	1·14	1	4	0	5	0	5	0	5	0	5	0	5	0	5
				0·77	3	2	3	2	2	3	1	4	1	4	1	4	1	4
				0·52	5		5		5		5		5		5		5	
				0·35	5		5		5		5		5		5		5	
II	Methylpentynol	5	Oral	1·14	5		5		5		5		3	2	2	3	1	4
				0·77	5		5		5		5		5		5		5	
				0·523	4		5		5		2		3		1		1	
				0·348	1		1		1		0		1		0		0	
	Phenyldiethyl-acetamide (437)	5	Oral	0·523	5		5		5		4	1	3	2	3	2	2	3
				0·348	5		5		5		5		5		3	1	3	1
				0·233	3		5		3		1		2		2		1	
				0·155	2		2		1		0		1		0		0	

* N = Narcotised. † D = Dead.

active than methylpentynol. It was also shown that *o*-chlorophenyldimethylacetamide (644) was more active than the *m*- and *p*-isomerides (Table V), and all the isomerides were more active than compound 429. Nevertheless, similar substitution in the phenyl group of compound 437 resulted in a reduction in activity.

It would therefore appear that the level of narcotic effect may be largely a question of molecular weight, apart from the demonstrated influence of the orientation of the phenyl-substituents, and it might be of interest to test this by the preparation of compounds with other phenyl-substituents.

TABLE IV

ACUTE ORAL TOXICITY OF PHENYLDIETHYLACETAMIDE (437)

Dose mg./kg.	No. of mice	Deaths (5 days)
1200	18	18
800	18	15
533	18	10
356	18	3
237	18	2
158	14	0

LD50 = 489 mg./kg.
Fiducial limits = 422–567 mg./kg. (cf. Bliss[7]).
The acute oral toxicity of methylpentynol was found to be 760–860 mg./kg.[6]

TABLE V

COMPARATIVE NARCOTIC ACTIVITY OF THE ISOMERIC CHLOROPHENYLDIMETHYLACETAMIDES

Compound	No. of mice	Route	Dose g./kg.	Time after injection (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
518 *p*-Chlorophenyldimethyl-acetamide	10	Oral	0·506	0		1		4		6		6		9		8	2
			0·338	0		0		1		2		4		4		5	
643 *m*-Chlorophenyl-dimethylacetamide	10	Oral	0·506	1		4		9		9		9		9		9	
			0·338	0		1		4		4		4		4		3	
644 *o*-Chlorophenyldimethyl-acetamide	10	Oral	0·506	8		8		9		10		10		4	6	1	8
			0·338	6		6		8		8		8		5	4	4	5
Methylpentynol	10	Oral	0·506	2		6		7		8		7		8		8	1
			0·338	0		1		1		1		1		0		0	

*N = Narcotised. †D = Dead.

SUMMARY

1. A series of derivatives of acetamide and benzamide has been synthesised and examined for narcotic activity, in comparison with methylpentynol.

2. Of the alkylacetamides only di- and triethylacetamides are more active and they are also more toxic.

3. The most interesting compounds belong to the group of aryldialkylacetamides. Phenyldiethylacetamide (compound 437) is approximately twice as active as methylpentynol, but also more toxic.

4. *ortho*-Substitution in the phenyl radical considerably enhances the narcotic activity compared with that of the *m*- and *p*-isomerides, but increases the acute toxicity at the same time.

5. A *p*-chlorine substituent increases the activity of phenyl-dimethylacetamide (429), but depresses that of compound 437.

6. Variation in narcotic activity, apart from the demonstrated effect of orientation of the phenyl-substituents, may possibly be correlated to some extent with molecular weight.

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