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Central muscle relaxant properties of 2,6-dimethylphenethylurea and related compounds

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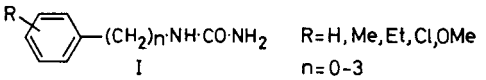
Twenty-eight phenylalkylureas with alkyl, hydroxy, methoxy or chloro-substituents in the aryl ring have been synthesized and tested for central depressant and muscle relaxant properties. In this series, the dimethylphenethylureas with at least one *ortho*-methyl group show unexpectedly selective muscle relaxant activity. 2,6-Dimethylphenethylurea inhibits polysynaptic reflexes more readily than monosynaptic ones, but also depresses muscle contractions by an action independent of its effect on interneuronal transmission. It is a weak anticonvulsant, suppresses rage episodes in "fighting" mice, and has no selective blocking action on conditioned responses. It thus has a pharmacological profile resembling those of mephenesin and meprobamate, but distinct from either, and differing still more from those of phenobarbitone, chlordiazepoxide or chlorpromazine. However, tolerance to its action develops readily.

Urea derivatives have long been known to possess central depressant properties (see review by Wheeler, 1963). De Beer, Buck, Hjort and their co-workers (1934, 1935, 1937) found that the fairly widespread hypnotic activity of aryl, alkyl and mixed aryl alkyl ureas correlated tolerably well with some of their physical properties. The range of compounds included in their broad survey was restricted by the need for moderate water solubility, since the compounds were administered intraperitoneally, and no quantitative assessment was made of the dose required to produce actions other than hypnosis or death. Depression of motor activity, ataxia and loss of righting reflex are frequently seen on oral administration of aralkylureas to mice. The pinnal reflex is often abolished at a dose much lower than that required to abolish the corneal reflex, suggesting a mephenesin-like muscle-relaxant action (Goodsell, Toman, & others, 1954).

This paper describes some aralkylureas with one or more ring substituents (I), which show selective depressant effects of this kind. More detailed pharmacological results



I

are given for 2,6-dimethylphenethylurea (cpd 16), one of the more interesting of these compounds as a potentially useful sedative and muscle relaxant (Green & Willey, 1967).

CHEMISTRY

o-, *m*- and *p*-Methylphenethylurea (*o*-, *m*- and *p*-tolylethylurea; compounds 4–6) were supplied by Smith Kline & French Laboratories, Philadelphia. The other compounds were synthesized by conventional methods. The unsubstituted aralkylureas

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(cpds 1–3), and 2,4-dimethylbenzylurea (cpd 8) (Hinrichsen, 1889), 3,5-dimethylbenzylurea (cpd 12) (Landau, 1892), 2,5- and 3,4-dimethylbenzylurea (cpds 9, 11) (Trivedi & Trivedi, 1958), 2,4- and 3,4-dimethoxyphenethylurea (cpds 22, 23) (Buck, 1934), 3,4,5-trimethoxyphenethylurea (cpd 25) (Jansen, 1931), 2,6-xylylurea (cpd 7) (Dahlbom & Österberg, 1955), β-hydroxyphenethylurea (cpd 28) (Mannich & Thiele, 1915) and *p*-hydroxyphenethylurea (cpd 27) (Cloetta & Wünsche, 1923) have been described previously. Analytical data and melting points for the new ureas are given in Table 1.

Table 1. *Substituted aralkylureas*

Compound				m.p. °C	Required (%)			Found (%)		
No.	R	n	Empirical formula	(uncorrected)	C	H	N	C	H	N
10	2,6-Me_2	1	$C_{10}H_{14}N_2O$	240 (dec.)	67·4	7·9	15·7	67·6	8·0	15·6
13	2,3-Me_2	2	$C_{11}H_{16}N_2O$	141–2	68·7	8·4	14·6	68·6	8·4	14·4
14	2,4-Me_2	2	$C_{11}H_{16}N_2O$	129	68·7	8·4	14·6	68·6	8·35	14·5
15	2,5-Me_2	2	$C_{11}H_{16}N_2O$	133–5	68·7	8·4	14·6	68·65	8·4	14·3
16	2,6-Me_2	2	$C_{11}H_{16}N_2O$	173–4	68·7	8·4	14·6	68·4	8·4	14·7
17	3,4-Me_2	2	$C_{11}H_{16}N_2O$	121–3	68·7	8·4	14·6	68·7	8·2	14·7
18	3,5-Me_2	2	$C_{11}H_{16}N_2O$	141–2	68·7	8·4	14·6	68·3	8·5	14·4
20	2,4-Cl_2	2	$C_9H_{10}Cl_2N_2O$	174	46·4	4·3	12·0	46·4	4·2	11·8
21	2,6-Cl_2	2	$C_9H_{10}Cl_2N_2O$	165	46·4	4·3	12·0	46·5	4·4	11·8
19	2,6-Et_2	2	$C_{13}H_{20}N_2O$	145–6	70·9	9·15	12·7	70·95	9·0	12·65
24	2,4,6-Me_3	2	$C_{12}H_{18}N_2O$	205 (dec.)	69·9	8·8	13·6	69·9	8·8	13·4
26	2,6-Me_2	3	$C_{12}H_{18}N_2O$	154	69·9	8·8	13·6	69·8	8·8	13·55

All the ureas were obtained by heating the appropriate aralkylamine salt with aqueous sodium cyanate solutions (Kehm & Whitehead, 1963; Green & Willey, 1967). 2,4- 2,5- and 3,4-Dimethylbenzylamine were available commercially (Koch-Light Laboratories Ltd.); 2,6-dimethylbenzylamine was obtained by reduction of 2,6-dimethylbenzonitrile with lithium aluminium hydride (Herr, Enkoji & Dailey, 1957) and 3,5-dimethylbenzylamine from α-bromomesitylene (Aldrich Chemical Co. Inc.) with hexamine (Galat & Elion, 1939). The substituted phenethylamines were synthesized by one of two methods: (a) treatment of an arylmagnesium halide with ethylene oxide to give a phenethyl alcohol, which with hydrogen bromide gave the phenethyl bromide (Cagniant, Jecko & Cagniant, 1960), which was converted into the amine by the Gabriel reaction with potassium phthalimide followed by hydrazinolysis (Sheehan & Bolhofer, 1950); or b) by treatment of a benzyl halide with an alkali cyanide to give the corresponding phenylacetonitrile which was then reduced with lithium aluminium hydride (Benington, Morin & Clark, 1960). 2,6-Xylylpropylamine was likewise obtained from 2,6-dimethylphenethyl bromide by conversion into the nitrile and subsequent reduction.

PHARMACOLOGY

Methods

General. Unless otherwise stated, drugs were suspended in 0·5% gum tragacanth (w/v) and administered orally. Only 2,6-dimethylphenethylurea (cpd 16) was studied in all the tests, but other compounds were given for comparison in most tests, and all the compounds (listed in Table 2) were examined for their effects in conscious mice.

Dose-range studies. Drugs were given in a volume of 10 ml/kg to groups of 3 mice

(weight range 16–24 g) at doses spaced in geometric progression (dose ratio = 2). Each mouse was placed in a separate plastic beaker and observed for motor stimulation or depression, ataxia and loss of pinnal, corneal and righting reflexes. The effects were maximal usually within 5 min to 1 h. The dose producing a particular effect in 50% of the mice at the time of maximum activity (ED50) was calculated using the method of moving averages (Weil, 1952). A rough estimate of the LD50 was made from the number of mice dying up to 24 h after administration of the drug.

Anticonvulsant activity. At various times after administration of the drug, seizures were induced in groups of 5 mice by intravenous leptazol (56 mg/kg), intravenous strychnine hydrochloride (0·63 mg/kg), or an electroshock (25 mA, 50 Hz for 0·18 s) applied through Spiegal corneal electrodes, using the apparatus and technique described by Swinyard (1949) and by Woodbury & Davenport (1952). These chemical or electrical stimuli were just sufficient to induce tonic extensor spasms in the hind legs of 99% of the mice. The ED50 was estimated as the dose of drug required to prevent these tonic seizures in half the mice.

Effect on locomotor activity in mice (after Dews, 1953). Four groups of 5 mice per "light" box were used at each dose of drug. Control groups given the tragacanth suspension, but no drug, were tested at the same time to obviate errors due to spontaneous diurnal variation in the activity. The mice were placed in the boxes immediately after being given the drug and the total numbers of interruptions of the light beam every 15 min were integrated for each set of 4 boxes and recorded by a print-out device.

Effect on fighting behaviour in mice (Tedeschi, Tedeschi & others, 1959). Fighting behaviour in mice was produced by exposing pairs to a mild electric foot shock in an enclosed space. Ten pairs were used at each dose of drug. At various times after the drug, the number of rage episodes (i.e. periods when the mice stood on their hind legs and sparred) was recorded during a 3 min exposure to the electroshock. The ED50 was calculated as the dose of drug required to prevent 5 of the 10 pairs of mice from exhibiting more than 3 rage episodes in 3 min.

Effect on conditioned avoidance responses in rats (after Cook & Weidley, 1957). Rats were trained to escape from a box with an electrified grid floor by jumping into a small elevated side chamber, and to associate the shock with a buzzer. With further training, some rats learned to jump into the side chamber as soon as they were placed on the grid, without waiting for either buzzer (conditioned response) or shock (unconditioned response). This effect is denoted as the secondary conditioned response, and only rats which had learned this response were used in the drug tests. Drugs were given in a volume of 2 ml/kg to groups of 8 rats. Estimates were then made of the dose of drug required to suppress each type of response in half the rats at various times after drug administration.

Other behavioural studies. Compound 16 was given orally to conscious dogs or squirrel monkeys, which were then observed for behavioural changes and loss of reflexes.

Effect on reflexes in the anaesthetized cat. Cats anaesthetized with chloralose (80–100 mg/kg, i.v.) were used. Flexor contractions of the left tibialis anterior muscle were elicited by stimulating the central end of the severed ipsilateral tibial nerve with single rectangular pulses of 0·5 ms duration at a strength about 10V. In some experiments, contractions were also elicited by applying 1 ms pulses through electrodes placed directly on the muscle. Each flexor contraction was recorded alternately with a contraction of the right quadriceps femoris muscle, elicited by tapping the patellar tendon.

RESULTS

Dose-range studies. Table 2 summarizes the dose range studies in mice for 28 aralkylureas. Phenobarbitone, chlorpromazine, chlordiazepoxide, meprobamate and mephenesin are included for comparison.

Table 2. *Toxicity and CNS depressant properties of aralkylureas*

No.	Compound R	n	ED50 (g/kg) for Loss of pinnal reflex	Loss of corneal reflex	Motor depression	Ataxia	Loss of righting reflex	Approx. LD50 (g/kg)
1	H	1	0·2	1·4	0·06	0·1	0·6	0·6
2	H	2	0·45	1·1	0·1	0·4	1·1	2·5
3	H	3	1·6	3·2	1	1·5	2·3	>3
4	2-Me	2	0·4	0·6	0·07	0·2	0·6	1·5
5	3-Me	2	0·4	0·9	0·07	0·2	0·9	1·5
6	4-Me	2	0·6	1·8	0·2	0·9	1·4	>1·5
7	2,6-Me_2	0	2·2	>3·2	1	1	>3·2	>3
8	2,4-Me_2	1	2·5	>3·2	0·1	1·4	>3·2	>3
9	2,5-Me_2	1	1	>3·2	0·4	0·7	>3·2	>3
10	2,6-Me_2	1	1	>3·2	0·15	0·9	>3·2	>3
11	3,4-Me_2	1	1	>3·2	0·2	1·4	>3·2	>3
12	3,5-Me_2	1	1·5	>3·2	0·1	1·0	>3·2	>3
13	2,3-Me_2	2	0·1	0·45	0·05	0·22	0·6	1·2
14	2,4-Me_2	2	0·12	0·6	0·06	0·15	0·7	1·5
15	2,5-Me_2	2	0·2	0·6	0·07	0·15	0·7	2·3
16	2,6-Me_2	2	0·1	0·6	0·06	0·2	0·3	1·5
17	3,4-Me_2	2	0·5	2	0·25	0·6	3	3
18	3,5-Me_2	2	0·7	1·5	0·06	0·9	1·1	>1·5
19	2,6-Et_2	2	0·6	>3·2	0·05	0·5	1·5	>3
20	2,4-Cl_2	2	0·25	0·9	0·07	0·4	1·1	>3
21	2,6-Cl_2	2	0·02	0·07	0·005	0·15	0·08	0·1
22	2,4-$(OMe)_2$	2	2	>3·2	0·7	2	>3·2	>3
23	3,4-$(OMe)_2$	2	1	>3·2	0·15	1	>3·2	>3
24	2,4,6-Me_3	2	2	>3·2	0·7	3	>3·2	>3
25	3,4,5-$(OMe)_3$	2	3	>3·2	0·35	>3·2	>3·2	>3
26	2,6-Me_2	3	0·3	>3·2	0·1	0·2	0·9	>3
27	4-OH	2	2	>3·2	0·6	>3·2	>3·2	>3
28	C_6H_5·CH(OH)·CH_2·NH·CO·NH_2		>3·2	>3·2	0·6	>3·2	>3·2	>3
	Chlordiazepoxide		0·5	1·5	0·1	0·1	3	3
	Meprobamate		0·2	0·45	0·1	0·15	0·7	1
	Mephenesin		0·1	0·6	0·1	0·1	0·7	2·5
	Chlorpromazine		0·05	0·1	0·002	0·05	2	>2
	Phenobarbitone		0·07	0·2	0·04	0·08	0·15	0·3

Table 3. *Anticonvulsant activity of* 2,6-*dimethylphenethylurea and other central and spinal depressants*

Drug	Time after oral administration (h)	ED50 (mg/kg) against Electro-shock	Leptazol	Strychnine
2,6-Dimethylphenethylurea ..	0·5	300	300	600
Mephenesin	0·25	250	250	700
Meprobamate	1	140	50	300
Chlordiazepoxide	1	30	5	40
Phenobarbitone	3	15	5	40
Chlorpromazine	1	200	300	>300

Comparative studies with 2,6-*dimethylphenethylurea.* In Table 3, the ability of 2,6-dimethylphenethylurea (cpd 16) to prevent convulsions induced by electroshock, leptazol or strychnine is compared with that of a variety of other central or spinal

depressants. The anticonvulsant action of mephenesin and, to a lesser extent, of 2,6-dimethylphenethylurea is more transient than that of the other drugs, and these two compounds were consequently tested at shorter times after administration.

Potency of these short-acting drugs as depressants of locomotor activity in the "light" box was determined from the dose required to halve the number of counts in the period 15–30 min after injection of the drug. Under these conditions the ED50 for 2,6-dimethylphenethylurea was 150 mg/kg compared with 300, 400, 100 and 200 mg/kg for meprobamate, mephenesin, 2,6-diethylphenethylurea (cpd 19) and 2,6-xylylpropylurea (cpd 26) respectively.

Potency as antagonists of rage episodes in 'fighting' mice was assessed at the time of maximum activity, namely 15 min after administration of 2,6-dimethylphenethylurea or mephenesin, or 1 h after the other drugs tested. ED50 values were 150, 100, 30 and 10 mg/kg respectively for 2,6-dimethylphenethylurea, meprobamate, chlorpromazine and chlordiazepoxide. Mephenesin failed to suppress rage episodes in half the mice at non-prostrating doses.

2,6-Dimethylphenethylurea has little selectivity in blocking conditioned reflexes in rats. The secondary conditioned response was lost in half the rats at about 200 mg/kg while both the conditioned and unconditioned responses were lost at about 400 mg/kg. Similar values were obtained for meprobamate. In contrast, chlorpromazine blocked the conditioned responses at much lower doses than the unconditioned response, ED50 values being about 5 and 15 mg/kg for the secondary conditioned response and the conditioned response, and $>$ 30 mg/kg for the unconditioned response.

In male squirrel monkeys, oral administration of 50 mg/kg of 2,6-dimethylphenethylurea caused pronounced depression of motor activity lasting about 5 h, accompanied by ataxia and weakening of the corneal, myotatic and grasping reflexes. At 12·5 mg/kg there was still some depression, but this was much less marked than at the higher dose.

In conscious female dogs (beagles), 100 or 200 mg/kg orally of 2,6-dimethylphenethylurea caused ataxia and abolition or weakening of the flexor, extensor, placing, extensor postural thrust and righting reflexes. However, the knee jerk reflex was unaffected. Male dogs showed an essentially similar pattern of effects but the drug was less active.

In mice, rats and dogs, there is a fairly rapid development of tolerance and a second dose of 2,6-dimethylphenethylurea 24 h after the first generally produced less effect.

Simultaneous recording of both the flexor and patellar reflexes in anaesthetized cats showed that 2,6-dimethylphenethylurea suppressed the polysynaptic flexor reflex more than the monosynaptic patellar reflex. However, as shown in Fig. 1, the differentiation between mono- and poly-synaptic reflexes was much less sharp than with mephenesin, which had no effect on the patellar reflex in doses producing at least 50% inhibition of the flexor reflex.

Besides its inhibitory action on interneuronal transmission, 2,6-dimethylphenethylurea also has a direct depressant effect on the muscles themselves. A dose of 20 mg/kg intravenously reduced the contractions of the tibialis muscle in response to direct stimulation, or to stimulation of the peroneal nerve leading to the muscle, by up to 40%. This direct depressant effect renders the results obtained in experiments such as that shown in Fig. 1 liable to misinterpretation. A clear differentiation between the various effects of 2,6-dimethylphenethylurea was brought out in an anaesthetized cat given a large dose (200 mg/kg) orally. In this cat, the patellar reflex was reduced

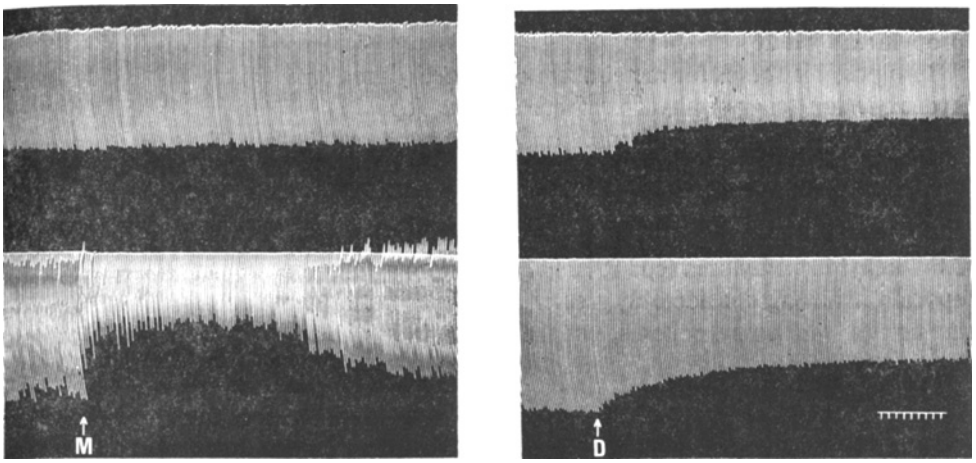

FIG. 1. Effect of mephenesin and 2,6-dimethylphenethylurea on patellar and flexor reflexes. Cat anaesthetized with chloralose (80 mg/kg) and injected intravenously at M with mephenesin (20 mg/kg), and after 90 min, at D, with 2,6-dimethylphenethylurea (10 mg/kg). Upper panels —patellar reflex, lower panels—flexor reflex. Single stimuli (10V, 0·5 ms) at 15 s intervals. Time 1 min.

within 10 min to 60% of normal, at which level it remained for a further 4 h. The flexor reflex declined more slowly, taking 30 min to drop to 50% of normal, but it then continued to fall, disappearing completely after about 3 h. The contractions of the tibialis muscle in response to direct stimulation fell to about 35% of normal in 1 h, but remained at this level for a further 3 h. At this time, similar responses were elicited by stimulation of the peroneal nerve, showing the absence of neuromuscular block.

DISCUSSION

In view of the small number of animals used in the dose range studies, no significance should be placed on minor differences in activity. Nevertheless, several clear-cut qualitative structure-activity relations emerge from the results in Table 2. If a high ratio ED50 (corneal reflex)/ED50 (pinnal reflex) coupled with a low ED50 for the pinnal reflex relative to the LD50 is used as a criterion of selective muscle relaxant potency (Goodsell & others, 1954), the dimethylphenethylureas (cpds 13–16) containing at least one methyl group in the *ortho*-position stand out clearly. The dimethylbenzylureas (cpds 8–12), 3,4- and 3,5-dimethylphenethylurea (cpds 17, 18) and 2,6-xylylurea (cpd 7) are much less active, as are the monomethylphenethylureas (cpds 4–6) and phenethylurea itself (cpd 2). Addition of a third methyl group to give 2,4,6-trimethylphenethylurea (cpd 24) also results in a tenfold fall in activity. The di- or tri-methoxy-compounds (cpds 22, 23, 25) likewise have only low activity. 2,4-Dichlorophenethylurea (cpd 20) is about half as active as the corresponding dimethyl compound (cpd 14), but 2,6-dichlorophenethylurea (cpd 21) is exceptional in being both appreciably more active and much more toxic than the 2,6-dimethyl compound (cpd 16). Replacement of the two methyl groups in positions 2 and 6 by ethyl groups to give 2,6-diethylphenethylurea (cpd 19) leads to a large rise in ED50 for abolition of both pinnal and corneal reflexes, but to no change in ED50 for motor depression. In the "light" box experiments, this compound was slightly more active as a depressant than the corresponding dimethyl compound. A similar change in

activity profile occurs when the methylene chain is lengthened to give 2,6-xylylpropylurea (cpd 26).

Two possible routes for metabolism of phenethylurea (cpd 2) are ring or side-chain hydroxylation to give *p*-hydroxyphenethylurea (cpd 27) or β-hydroxyphenethylurea (cpd 28), both of which are almost inactive. If such metabolism occurred, this might account for the short duration of the activity displayed by many of the compounds.

The activity profile for 2,6-dimethylphenethylurea (cpd 16) in these dose-range experiments thus lies somewhere between those for meprobamate and mephenesin. 2,6-Diethylphenethylurea (cpd 19) and 2,6-xylylpropylurea (cpd 26) resemble chlordiazepoxide in having considerably greater potency as motor depressants than in depressing corneal and pinnal reflexes, but they differ from chlordiazepoxide in not causing ataxia so readily.

From this group of compounds, 2,6-dimethylphenethylurea was chosen for investigation in more detail. It has only weak anticonvulsant activity and in this respect it closely resembles mephenesin, and differs from meprobamate, which is moderately active against leptazol. As a motor depressant in the "light" box, it is slightly more active then either meprobamate or mephenesin and differs from phenobarbitone which depresses motor activity only at doses high enough to cause almost complete prostration. Tedeschi & others (1959) have shown that a distinctive feature of meprobamate is its ability to suppress rage episodes in "fighting" mice at a lower dose than is required to depress motor activity or to prevent electrically-induced convulsions. Although 2,6-dimethylphenethylurea, unlike mephenesin, will also suppress these rage episodes, the ratio ED50 (motor depression)/ED50 (rage episodes) is appreciably less than for meprobamate (1 instead of 3). Like meprobamate, and in contrast to chlorpromazine, 2,6-dimethylphenethylurea displays little selectivity in suppressing conditioned responses in rats.

In both conscious dogs and anaesthetized cats, 2,6-dimethylphenethylurea inhibits polysynaptic reflexes more readily than the patellar reflex, which is usually regarded as monosynaptic. However, it is less selective in this respect than is mephenesin, and it also has a depressant effect on the muscle contractions independent of its depressant effect on interneuronal transmission.

Thus, 2,6-dimethylphenethylurea has an activity profile resembling those of mephenesin and meprobamate, but distinct from either, and differing still more from those of phenobarbitone, chlordiazepoxide and chlorpromazine.

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