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Basic dihydromorphanthridinones with anticonvulsant activity

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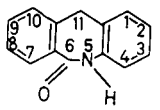
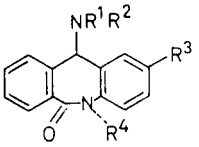
Some 11-alkylamino-5,6-dihydro-6-oxomorphanthridines and related compounds have been prepared and screened for anticonvulsant activity. One of the more active compounds, 11-dimethylamino-5,6-dihydro-6-oxomorphanthridine (ICI 45,337) was selected for further study and taken to clinical trial in epileptic patients.

There is currently considerable interest in drugs with tricylic structures as anti-depressants (Stewart, Charest & Herr, 1963; Boissier, Simon & others, 1965, among others) and as anticonvulsants (Theobald & Kunz, 1963; Davis, Winthrop & others, 1964). One such tricyclic structure (I) was chosen for investigation and a series of novel basic dihydromorphanthridinones prepared and examined for their effects on the central nervous system.

Structural requirements for anti-epileptic activity have been reviewed extensively (Spinks & Waring, 1962). Most of the currently useful drugs are weakly acidic (barbiturates, hydantoins) or chemically neutral (primidone, succinimides) and the presence of one or more –CO·NH– linkages in the molecule is considered by many writers to be associated with anticonvulsant activity. The dihydromorphanthridinones (II) described in this investigation may be regarded as cyclic amides but they are also bases and are thus unlike the drugs at present in use for the treatment of epilepsy.



I



II

CHEMISTRY EXPERIMENTAL

Compounds in which the amide nitrogen atom was unsubstituted (II; R^4=H) were prepared by reaction of 11-chloro-5,6-dihydro-6-oxomorphanthridine with the appropriate amine either alone (Methods A and B) or in dimethylformamide (Method C).

Compounds in which the amide nitrogen atom was substituted (II; R^4=alkyl)

were not available by this route. 11-Chloro-5,6-dihydro-5-methyl-6-oxomorphanthridine failed to react with diethylamine at reflux temperature. The 5-alkyl compounds were, however, conveniently obtained by reaction of the sodium derivative of the 11-dialkylamino-5,6-dihydro-6-oxomorphanthridine with the appropriate alkyl halide in dimethylformamide solution (Method D).

Method A

11-Chloro-5,6-dihydro-6-oxomorphanthridine was added gradually to ten times its weight of the appropriate amine, with stirring and cooling. When the exothermic reaction was over, the mixture was heated under reflux for 30 min and then cooled and filtered. The filtrate was distilled to remove the excess of amine, the residue stirred with water, and the mixture filtered. The solid residue of crude product was then crystallized, usually from methanol or aqueous methanol.

Method B

11-Chloro-5,6-dihydro-6-oxomorphanthridine (0·01 mol) was added gradually to the amine (0·06 mol) with stirring and cooling. When the exothermic reaction was over, the mixture was heated at 90–95° for 15 min. The mixture was cooled, diluted with water and the solid collected by filtration. The crude solid product was dissolved in cold 3N hydrochloric acid, the solution filtered, and the filtrate made alkaline with ammonia solution. The precipitated solid was collected by filtration and crystallized from methanol or aqueous methanol.

Method C

11-Chloro-5,6-dihydro-6-oxomorphanthridine, dissolved in five times its weight of dimethylformamide, was mixed with three times its weight of the amine (40% aqueous solution), and the mixture heated at 90–100° for 30 min. The mixture was cooled and filtered, and the crude solid product dissolved in ice-cold 3N hydrochloric acid. The solution was filtered, and the filtrate made alkaline with ammonia solution. The precipitated solid was filtered, washed with water, and crystallized from methanol or aqueous methanol.

Method D

Sodium hydride (0·01 mol; 50% dispersion in oil) was added in portions to a stirred, cooled solution of the appropriate 11-dialkylamino-5,6-dihydro-6-oxomorphanthridine (0·01 mol) in dry dimethylformamide (20 ml), the temperature being kept between 0 and 10°. The mixture was allowed to warm to 20° and then the appropriate alkyl halide (0·01 mol) added gradually to the solution of the sodium derivative, the temperature being allowed to rise to about 40°. The mixture was finally heated at 50–60° for 1 h to complete the reaction. The mixture was cooled, poured into ice water and the precipitated solid collected by filtration and washed with water. After washing with light petroleum (b.p. 40–60°), the product was crystallized from methanol, aqueous methanol or light petroleum (b.p. 60–80°).

11-Diethylamino-5,6-dihydro-6-oxomorphanthridine hydrochloride was prepared by adding ethereal hydrogen chloride to a solution of the base in methanol. The precipitated hydrochloride was collected by filtration and crystallized from methanol; m.p. 166° (decomp.). (Found: C, 65·2; H, 7·3; N, 7·9. $C_{18}H_{20}N_2O,HCl,CH_3OH$ requires C, 65·4; H, 7·2; N, 8·0). When the hydrochloride was prepared in acetone with ethereal hydrogen chloride, and the product crystallized from methanol/ether, it

was obtained as a monohydrate, m.p. 172° (decomp.). (Found: C, 64·4; H, 6·7; N, 8·0. $C_{18}H_{20}N_2O,HCl,H_2O$ requires C, 64·6; H, 6·9; N, 8·4).

11-*Chloro*-5,6-*dihydro*-6-*oxomorphanthridine*. A mixture of 5,6-dihydro-11-hydroxy-6-oxomorphanthridine (11 g), chloroform (50 ml) and thionyl chloride (6 g) was heated under reflux for 30 min and then cooled and filtered. The solid residue was recrystallized from benzene to give 11-*chloro*-5,6-*dihydro*-6-*oxomorphanthridine*, m.p. 226° (decomp.) (Found: C, 69·3; H, 4·0; N, 5·3. $C_{14}H_{10}ClNO$ requires C, 69·0; H, 4·1; N, 5·7%).

2-*Bromo*-5,6-*dihydro*-6,11-*dioxomorphanthridine*. A mixture of 5,6-dihydro-6,11-dioxomorphanthridine (10 g), acetic acid (250 ml) and bromine (2·5 ml, 8 g) was heated under reflux on a steam bath for 4 h. The solution was cooled, and the crystals collected by filtration and recrystallized from acetic acid to give 2-*bromo*-5,6-*dihydro*-6,11-*dioxomorphanthridine* (8 g), m.p. 308–310°. (Found: C, 55·7; H, 2·7; N, 4·3. $C_{14}H_8BrNO_2$ requires C, 55·6; H, 2·7; N, 4·6%.)

2-*Bromo*-5,6-*dihydro*-11-*hydroxy*-6-*oxomorphanthridine*. Sodium borohydride (3 g) was added in portions to a stirred, cooled suspension of 2-bromo-5,6-dihydro-6,11 dioxomorphanthridine (8 g) in ethanol (200 ml), the temperature being kept at 10–15°. The mixture was stirred at room temperature for 18 h, diluted with water (200 ml), acidified with dilute hydrochloric acid and filtered. The solid 2-*bromo*-5,6-*dihydro*-11-*hydroxy*-6-*oxomorphanthridine*, m.p. 270–272°, was used directly without further purification.

2-*Bromo*-11-*dimethylamino*-5,6-*dihydro*-6-*oxomorphanthridine*. Thionyl chloride (1·5 ml) was added gradually to a solution of 2-bromo-5,6-dihydro-11-hydroxy-6-oxomorphanthridine (2 g) in dry dimethylformamide (25 ml) at 60°. When the exothermic reaction was over, the solution was cooled to 20°, and dimethylamine (12·5 ml of a 40% solution) cautiously added. The mixture was heated at 90° for 30 min, cooled, poured into water and filtered. The solid residue was suspended in water (200 ml), and the mixture acidified with 20% hydrochloric acid and filtered. The filtrate was made alkaline with ammonia solution and filtered. The solid residue was recrystallized from methanol to give 2-*bromo*-11-*dimethylamino*-5,6-*dihydro*-6-*oxomorphanthridine*, m.p. 216–217°.

2-*Chloro*-5,6-*dihydro*-11-*hydroxy*-6-*oxomorphanthridine*. Sodium borohydride (2 g) was added in portions to a stirred, cooled suspension of 2-chloro-5,6-dihydro-6,11-dioxomorphanthridine (8 g) in methanol (200 ml), the temperature being kept at 0–5°. The mixture was stirred for 1 h, diluted with water (200 ml), acidified with dilute hydrochloric acid and filtered. The solid (7 g) was recrystallized from aqueous dimethylformamide to give 2-*chloro*-5,6-*dihydro*-11-*hydroxy*-6-*oxomorphanthridine*, m.p. 268–270°. (Found: C, 64·1; H, 3·9; N, 5·5. $C_{14}H_{10}ClNO_2$ requires C, 64·6; H, 3·9; N, 5·4).

2-*Chloro*-11-*dimethylamino*-5,6-*dihydro*-6-*oxomorphanthridine*. This compound was prepared in exactly the same way as the 2-bromo-analogue, starting from 2-chloro-5,6-dihydro-11-hydroxy-6-oxomorphanthridine, but without isolation of the intermediate 11-chloro-compound.

5,6-*Dihydro*-11-*hydroxy*-5-*methyl*-6-*oxomorphanthridine*. Sodium borohydride (4 g) was added in portions to a stirred, cooled suspension of 5,6-dihydro-5-methyl-6,11-dioxomorphanthridine (Drukker & Judd, 1965) (10 g) in methanol (200 ml), the temperature being kept below 10°. The mixture was stirred for 1 h at 10–15°, diluted with water (150 ml), acidified with dilute hydrochloric acid and filtered. The solid

(9·5 g) had m.p. 198–200° and the m.p. of a sample was unchanged after crystallization from methanol. (Found: C, 75·1; H, 5·6; N, 5·8. $C_{15}H_{13}NO_2$ requires C, 75·3; H, 5·5; N, 5·85%).

11-*Chloro*-5,6-*dihydro*-5-*methyl*-6-*oxomorphanthridine*. A mixture of 5,6-dihydro-11-hydroxy-5-methyl-6-oxomorphanthridine (2·3 g), thionyl chloride (2·4 ml) and chloroform (A.R.) was heated under reflux on a steam bath for 30 min. The solvent was removed by distillation under reduced pressure, and the residue recrystallized from benzene to give 11-*chloro*-5,6-*dihydro*-5-*methyl*-6-*oxomorphanthridine*, m.p. 164–165°. (Found: C, 71·1; H, 4·4; N, 5·5. $C_{15}H_{12}ClNO$ requires C, 69·9; H, 4·7; N, 5·4%.)

5,6-*Dihydro*-6-*oxo*-11-*succinimidomorphanthridine* (cpd 31). Sodium hydride (0·8 g, 50% dispersion in oil) was added to a stirred, cooled solution of succinimide (1·7g) in dry dimethylformamide (20 ml), the temperature being kept below 15°. After stirring for 30 min, 11-chloro-5,6-dihydro-6-oxomorphanthridine (4 g) was added, and the temperature allowed to rise to 28°. The mixture was poured into ice-water (50 ml), and the precipitate collected by filtration. The solid product was crystallized from a large volume of ethanol to give 5,6-*dihydro*-6-*oxo*-11-*succinimidomorphanthridine*, m.p. 279–280°. (Found: C, 70·4; H, 4·6; N, 8·8. $C_{18}H_{14}N_2O_3$ requires C, 70·6; H, 4·6; N, 9·15%.)

5,6-*Dihydro*-6-*oxo*-11-*phthalimidomorphanthridine* (cpd 32). This compound was obtained in a similar manner from potassium phthalimide (1·8 g), suspended in dimethylformamide (20 ml), and 11-chloro-5,6-dihydro-6-oxomorphanthridine (2·4 g). The mixture was heated at 100° for 30 min and then poured into water. The product was crystallized from ethanol to give 5,6-*dihydro*-6-*oxo*-11-*phthalimidomorphanthridine*, m.p. 244–5°. (Found: C, 74·3; H, 4·0; N, 7·8. $C_{22}H_{14}N_2O_3$ requires C, 74·6; H, 4·0; N, 7·9%.)

11-N-*Ethylacetamido*-5,6-*dihydro*-6-*oxomorphanthridine* (cpd 33). Acetic anhydride (1 ml) was added to a suspension of 11-ethylamino-5,6-dihydro-6-oxomorphanthridine (0·2 g) in dry pyridine (5 ml) and the mixture heated on a steam bath for 3 min. After cooling, the mixture was diluted with water, filtered, and the solid residue washed with cold dilute hydrochloric acid. The insoluble residue was crystallized from aqueous methanol to give 11-N-*ethylacetamido*-5,6-*dihydro*-6-*oxomorphanthridine*, m.p. 221–2°. (Found: C, 73·3; H, 6·0; N, 9·7. $C_{18}H_{18}N_2O_2$ requires C, 73·45; H, 6·2; N, 9·5%.)

PHARMACOLOGY EXPERIMENTAL

Methods and materials

General. Specific pathogen-free (SPF) male and female mice of the Alderley Park strain, weighing 19–21 g and (SPF) male and female rats, 95–125 g, were used. Compounds were dissolved or suspended by ball-milling for at least 24 h in an inert dispersing agent containing per litre:—Lissapol NX 1 g, Lissapol C 1 g, Dispersol OG 1 g, and adjusted to pH 7. For parenteral injection the basic dihydromorphanthridinones were given as solutions of the hydrochlorides. Unless otherwise stated, doses of the drugs were given by stomach tube in a dose volume of 25 ml/kg body weight for mice and 5 ml/kg body weight for rats. Where comparisons are made between treated and control animals it should be understood that the control animals received an equal volume of the vehicle alone by the same route.

Mouse maximal electroshock method. Seizures were induced in mice by the application of an electrical current from a constant current stimulator through aural clip electrodes. The animals received a single shock of 0·33 s duration and an intensity of 20 mA. This current stuns the animals immediately and subsequently produces tonic extension of the hind limbs. Pretreatment with anticonvulsant drugs prevents the tonic extension following electroshock. Pretreatment times were 1 or 2 h. The number of animals in a group which fail to show tonic extension is a measure of the protection afforded by the drug. For purposes of comparison, the anticonvulsant activity of the various drugs was expressed as the dose which prevented tonic extension in 50% of a group of animals (Median Effective Dose — ED50). The confidence limits for the estimate of the ED50 were determined by logit analysis or by the method of Litchfield & Wilcoxon (1949).

Duration of action in mice. Groups of 10 mice received a dose equivalent to twice the oral ED50. The proportion of animals protected was determined at intervals of ½, 1, 2, 4, 6, 8, 12 and 24 h after dosing.

Prevention of supramaximal leptazol seizures. Groups of 10 mice received 160 mg/kg of leptazol intraperitoneally. In unprotected animals this dose of leptazol produced clonic convulsions and tonic hind limb extension, and killed most of the animals within 30 min. Drugs were given orally 1 or 2 h before injection of leptazol and ED50 values were calculated from the numbers of animals in which the hind leg tonic extension component of the normal seizure was prevented. The protective dose (PD50) was also calculated from the number of animals alive 30 min after injection of leptazol.

Rat low current electroshock test. Anticonvulsant activity was measured using the method of Bogue & Carrington (1953). In this test, the energy, in mWs, necessary to elicit hindlimb tonic extensor spasm was measured. Animals received a low current of 7·5 mA which was applied for not more than 10 s by means of aural clip-on electrodes, moistened with saline. Groups of 8–10 rats were used for the estimation of ED50 values; for less active compounds the percentage of animals protected at a particular dose is recorded.

Ataxia in mice. Three parameters measuring different aspects of drug-induced coordination were measured. These were the ability of mice to remain on a rotating 12 inch diameter roller rotating at a surface speed of 50 cm/min; the ability to remain on a 0·9 cm diameter rod rotating at 2 rev/min; and the ability to remain on, or walk to the edge of the underside of a horizontal 0·78 cm mesh. The assessment of performance was based on the length of time that the animal was able to remain on the obstacle. The neurotoxic dose was derived from the mean of the doses producing a significant degree of motor incoordination in each of the several tests.

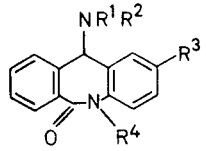
Acute toxicity. Median lethal doses were determined after administration of single oral doses to groups of 2–20 mice. The number of survivors seven days later was determined by inspection and median lethal doses (LD50) with 95% confidence limits were calculated from the proportion of animals surviving using standard methods of logit analysis.

RESULTS

Structure activity relations

Compounds are referred to by order number in Tables 2 (a), (b) and (c).

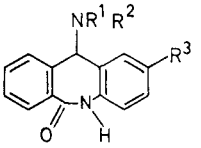
Table 1.



No.	R^1	R^2	R^3	R^4	M.p. °C	Found (%) C	H	N	Formula	Required (%) C	H	N	Method
1	Me	Me	H	H	208–9	76·4	6·6	11·0	$C_{16}H_{16}N_2O$	76·2	6·6	11·1	C
2	Et	Et	H	H	157–8	77·1	7·6	10·1	$C_{18}H_{20}N_2O$	77·1	7·2	10·0	A
3	Pr^i	Pr^i	H	H	192	77·6	7·9	9·1	$C_{20}H_{24}N_2O$	77·9	7·8	9·1	A
4	Pr^n	Pr^n	H	H	154–6	77·7	7·7	9·0	$C_{20}H_{24}N_2O$	77·9	7·8	9·1	A
5	Me	$CH_2{\cdot}CH_2OH$	H	H	167–8	71·6	6·4	9·9	$C_{17}H_{18}N_2O_2$	72·3	6·4	9·9	B
6	H	Et	H	H	178–9	76·3	6·3	10·9	$C_{16}H_{16}N_2O$	76·2	6·4	11·1	C
7	H	$CH_2{\cdot}CH_2OH$	H	H	134–5	71·3	6·1	10·4	$C_{16}H_{16}N_2O_2$	71·6	6·0	10·4	B
8	H	Pr^n	H	H	140–1	75·5	6·7	10·4	$C_{17}H_{18}N_2O$	76·7	6·8	10·5	A
9	H	$[CH_2]_3{\cdot}NMe_2$	H	H	156–7	73·7	7·5	13·3	$C_{19}H_{23}N_3O$	73·75	7·5	13·6	B
10	Me	Me	Cl	H	206–7	67·1	5·8	9·9	$C_{16}H_{15}ClN_2O$	67·0	5·2	9·8	C
11	Me	Me	Br	H	216–7	57·9	4·7	8·2	$C_{16}H_{15}BrN_2O$	58·0	4·5	8·5	C
12	Et	Et	Cl	H	174–5	68·4	6·2	8·7	$C_{18}H_{19}ClN_2O$	68·7	6·0	8·9	C
13		$-[CH_2]_4-$	H	H	193–4	77·4	6·6	10·0	$C_{18}H_{18}N_2O$	77·7	6·5	10·1	B
14		$-[CH_2]_5-$	H	H	205	78·1	6·9	9·5	$C_{19}H_{20}N_2O$	78·05	6·9	9·6	B
15		$-[CH_2]_6-$	H	H	175–6	78·6	7·3	9·3	$C_{20}H_{22}N_2O$	78·4	7·2	9·1	B
16		$-[CH_2]_2{\cdot}O{\cdot}[CH_2]_2-$	H	H	208	73·4	6·0	9·4	$C_{18}H_{18}N_2O_2$	73·45	6·2	9·5	B
17		$-[CH_2]_2{\cdot}N{\cdot}[CH_2]_2-$ CO·O·Et	H	H	223–4	69·3	6·3	11·4	$C_{21}H_{23}N_3O_3$	69·0	6·3	11·5	B
18	H	Ph	H	H	213–4	79·8	5·6	9·4	$C_{20}H_{16}N_2O$	80·0	5·4	9·3	B
19	Me	Me	H	Me	160–1	76·8	6·8	10·6	$C_{17}H_{18}N_2O$	76·7	6·8	10·5	D
20	Me	Me	H	Et	126–7	76·8	7·3	9·9	$C_{18}H_{20}N_2O$	77·1	7·2	10·0	D
21	Me	Me	H	Pr^n	107–8	77·4	7·6	9·4	$C_{19}H_{22}N_2O$	77·5	7·5	9·5	D
22	Me	Me	H	$CH_2{\cdot}CH:CH_2$	114–6	77·8	7·0	9·5	$C_{19}H_{20}N_2O$	78·05	6·9	9·6	D
23	Me	Me	H	Bu^n	107–8	78·0	7·9	9·1	$C_{20}H_{24}N_2O$	77·9	7·8	9·1	D
24	Me	Me	H	$CH_2{\cdot}Ph$	136–7	80·7	6·2	8·1	$C_{23}H_{22}N_2O$	80·7	6·5	8·2	D
25	Me	Me	H	CO·O·Et	99–100	70·2	6·4	8·7	$C_{19}H_{20}N_2O_3$	70·35	6·2	8·6	D
26	Me	Me	H	$CH_2{\cdot}CO{\cdot}NH_2$	249–50	69·6	6·4	13·7	$C_{16}H_{19}N_3O_2$	69·9	6·2	13·6	D
27		$-[CH_2]_5-$	H	Me	142–3	78·6	7·1	9·2	$C_{20}H_{22}N_2O$	78·4	7·2	9·2	D
28		$-[CH_2]_5-$	H	Et	119–20	78·4	7·5	8·9	$C_{21}H_{24}N_2O$	78·8	7·5	8·8	D
29		$-[CH_2]_5-$	H	$CH_2{\cdot}CH:CH_2$	111–2	80·0	7·0	8·5	$C_{22}H_{24}N_2O$	79·5	7·2	8·4	D
30		$-[CH_2]_5-$	H	Pr^n	116–7	79·4	7·7	8·3	$C_{22}H_{26}N_2O$	79·1	7·8	8·4	D

Compound 9 was recrystallized from ethyl acetate; cpds 29 and 30 from light petroleum (b.p. 60–80°C).

Table 2 (a). *Pharmacological activity of some substituted dihydromorphanthridinones. Doses are expressed as mg base/kg given by stomach tube*



Compound No.	Structure R¹	R²	R³	Electroshock test ED50	Leptazol test ED50	Leptazol test PD50	Acute lethal dose LD50
I (ICI 45,337)	Me	Me	H	42	38	100	1400
2	Et	Et	H	60	25	50–100	2680
3	Pr^i	Pr^i	H	NA at 250*	25–50	200	2000
4	Pr^n	Pr^n	H	118	50–100	50–100	
5	Me	$CH_2 \cdot CH_2OH$	H	160			
6	H	Et	H	44			
7	H	$CH_2 \cdot CH_2OH$	H	NA at 250	>200	>200	>2000
8	H	Pr^n	H	NA at 250	25	50	
9	H	$[CH_2]_3 \cdot NMe_2$	H	NA at 250			
10	Me	Me	Cl	34	100	100–200	
11	Me	Me	Br	49	50	50	
12	Et	Et	Cl	63	50–100	50–100	
13	$-[CH_2]_4-$		H	NA at 250			
14	$-[CH_2]_5-$		H	50†			
15	$-[CH_2]_6-$		H	NA at 250		>2000	
16	$-[CH_2]_2 \cdot O \cdot [CH_2]_2-$		H	NA at 250	>200	>200	
17	$-[CH_2]_2 \cdot N \cdot [CH_2]_2-$ $CO \cdot OEt$		H	NA at 250	200	200	
18	H	Ph	H	NA at 250	50	100	
31	$-CO \cdot [CH_2]_2 \cdot CO-$		H	NA at 250	200	>200	
32	$-CO \cdot C_6H_4 \cdot CO-$		H	NA at 250	200	>200	>2000
33	Et	$CO \cdot Me$	H	NA at 250			

* Not active at this dose.
† Convulsions produced at this dose.

Table 2 (a) summarizes the activity of those dihydromorphanthridinones which were unsubstituted in the position 5 (II; R^4=H).

Among the most active compounds in this class were those in which the basic substituent at the position 11 was a lower dialkylamino-group (e.g. II; R^1=R^2=Me; R^3=R^4=H; ICI 45,337, cpd 1), a monoalkylamino-group (e.g. R^1=H; R^2=Et; R^3=R^4=H; cpd 6), or a piperidino-group (R^1R^2=$-[CH_2]_5-$; R^3=R^4=H; cpd 14). In the series of dialkylamino derivatives, activity decreased in the order of dimethyl, diethyl, di-n-propyl and di-isopropyl substitution. The monoethylamino-compound (cpd 6) was highly active in the electroshock test but the hydroxyethylamino-compound (cpd 7) was inactive at 250 mg/kg. Acetylation of the monoethylamino-compound (to give cpd 33) also resulted in complete loss of activity. Substitution of a halogen atom at position 2 (R^3=Hal) gave compounds with the same order of activity as cpd 1 in the electroshock test but with less activity against leptazol-induced seizures.

The effect of substitution of the amide nitrogen atom at position 5 was studied by choosing two of the most active members of the unsubstituted series, viz., the 11-dimethylamino-compound (cpd 1) and the 11-piperidino-compound (cpd 14), and

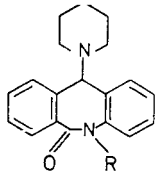
Table 2 (b). *Anticonvulsant activity of some 5-alkyl-11-dimethylamino-5,6-dihydro-6-oxomorphanthridines*

No.	R	Dose mg/kg	Electroshock test no. of mice protected
19	Me	80	10/10
		40	0/10
20	Et	100	5/5
		50	1/5
21	Pr^n	100	0/5
22	$CH_2{\cdot}CH:CH_2$	100	2/5
23	Bu^n	100	1/5
24	$CH_2{\cdot}Ph$	100	2/5
25	$CO{\cdot}O{\cdot}Et$	100	1/5
26	$CH_2{\cdot}CO{\cdot}NH_2$	100	3/5

varying the alkyl substituent at position 5 in these two structures. The effect of this substitution on anticonvulsant activity is shown in Tables 2 (b) and (c). In general, alkylation at position 5 in cpd 1 (II; $R^1=R^2=Me$; $R^3=H$) caused a diminution of activity especially with the larger alkyl groups. Alkylation at position 5 in cpd 14 ($R^1R^2=-[CH_2]_5-$; $R^3=H$) however had less effect on activity, and anticonvulsant properties in this group were in general maintained. The 5-alkyl derivatives of the 11-piperidino-dihydromorphanthridinones were generally more active than those of the analogous 11-dimethylamino-series (which includes cpd 1), but the compounds in this group all had higher acute oral toxicities. Table 2 (c) shows that in each case the ratio between the anticonvulsant and toxic doses was lower than that of cpd 1.

The dimethylamino- and diethylamino-dihydromorphanthridinones unsubstituted

Table 2 (c). *Anticonvulsant activity and toxicity of some 5-alkyl-11-piperidino-5,6-dihydro-6-oxomorphanthridines. Compounds were given orally, 1h pre-treatment*



No.	R	Electroshock test, ED50 mg/kg (approx.)	Acute oral toxicity LD50 mg/kg	$\frac{LD50}{ED50}$
27	Me	8	60	7·5
28	Et	8	110	14
29	$CH_2CH:CH_2$	22	100	4·5
30	Pr^n	60	300	5

Table 3. *Central nervous system activity of compound* 1 (*ICI* 45337) *and some standard anticonvulsants in mice. Doses are expressed as mg/kg orally and* 95% *confidence limits are given in parentheses.*

Compound	Pre-treatment time (h)	Electroshock test ED50	Leptazol test ED50		Potentiation of hexobarbitone sleeping time	Neurotoxic dose (NTD)	Acute toxicity LD50	Therapeutic ratio	
			Inhibition of tonic extension	Protection from lethal effect				LD50/ ED50	NTD/ ED50
Cpd 1 (ICI 45,337) ..	1	25 (23–28·5)	38	110		140	1400 (1100–1700)	56	5·6
	2	47 (42–53)			250	87		30	1·9
Primidone ..	2	8 (4·9–12·9)		70	46	250	770 (560–1060)	96	31
Phenobarbitone ..	2	13·4 (12·1–14·9)	5	11	43	30	250 (230–280)	19	2·2
Phenytoin ..	2	6·2 (5·2–7·4)			100	90	270 (230–310)	44	15
Phensuximide	2	330 (276·6–393·8)	100	100		183	1513 ± 61†	8·3	1
Ethosuximide		183 ± 5·2 2070 mg/kg†	381	401 (1 h)			1530 ± 40†		

†Data from Chen, Weston & Bratton, Jr. (1963).

in the 5-position (cpds 1 and 2) were selected for extended study, and finally 11-dimethylamino-5,6-dihydro-6-oxomorphanthridine (cpd 1, ICI 45,337) was chosen on the basis of its activity and stability for chronic toxicity studies, and tested in man.

Pharmacological activity of 11-*dimethylamino*-5,6-*dihydro*-6-*oxomorphanthridine.* Table 3 summarizes the pharmacological properties of 11-dimethylamino-5,6-dihydro-6-oxomorphanthridine (cpd 1, ICI 45,337) and some anticonvulsants of clinical importance. The activity of cpd 1 is less than that of phenobarbitone, phenytoin and primidone but greater than that of phensuximide. The acute lethal dose is greater than that of any of these compounds and the calculation of a 'therapeutic ratio' shows that cpd 1 is superior to phenobarbitone in this respect (Table 3). The therapeutic ratio based on the dose producing the first signs of motor impairment and the anticonvulsant dose measured at 2 h is slightly lower than that for phenobarbitone but better than that for phenobarbitone when based on the activity at 1 h. Cpd 1 potentiated hexobarbitone sleeping time only at the relatively high dose of 250 mg/kg whereas the other compounds were active at doses in the range of 40–100 mg/kg.

The observed differences in anticonvulsant ED50 at 1 and 2 h suggested that cpd 1 was quickly absorbed and showed peak activity earlier than the other compounds.

Table 4. *Duration of action of compound* 1 (*ICI* 45,337) *and other anticonvulsants in mice. Groups of* 10 *animals received a dose equivalent to twice the oral ED*50 (*measured after* 2 *h pretreatment*). *The proportion of animals protected was determined at various intervals after dosing.*

Compound	Dose mg/kg	No. of animals protected/10 at the stated number of hours after dosing							
		½	1	2	4	6	8	12	24
Cpd 1 (ICI 45,337)	92	10	10	10	9	6	2	0	0
Primidone	16	0	3	7	8	9	8	0	0
Phenobarbitone	26·8	9	9	10	10	10	9	3	0
Phenytoin	12·4	0	4	6	8	8	7	2	0

Table 5. *Pharmacological activity of compound* 1 (*ICI* 45,337) *and some standard anticonvulsants in rats.* Effective doses are expressed as mg/kg orally fiducial limits ($P = 0{\cdot}05$) in parentheses

Compounds	Low-current electroshock test ED50	Acute oral toxicity LD50 mg/kg
Oral dosing		
Cpd 1 (ICI 45,337)	28 (25–32)	2000
Primidone	2·9 (2·5–3·4)	1000
Phenobarbitone	8·1 (6·1–11)	
Phenytoin	39·5 (29–53)	2000
Intravenous dosing		
Cpd 1 (ICI 45,337)	5·6	

The duration of action of cpd 1 and other anticonvulsants is shown in Table 4. Groups of 10 animals were given a dose equivalent to twice the ED50 and were challenged with electroshock at intervals after dosing. Cpd 1 gave maximal protection within half an hour, and maintained more than 50% protection for 6–8 h. In the same test phenobarbitone gave rapid protection and a duration of action of 8–12 h. Primidone and phenytoin gave maximum protection at 4–6 h which persisted for more than 8 h.

Anticonvulsant activity in rats. Cpd 1 was more active than phenytoin in this test but less active than phenobarbitone or primidone (Table 5). The intravenous ED50 of cpd 1 was about 1/5 of the oral ED50.

Ataxia. The mean doses of compounds producing significant incoordination are shown in Table 3. At 1 h after dosing cpd 1 produced less ataxia than at 2 h, whereas the greatest anticonvulsant effect is observed at 1 h.

Potentiation of hexobarbitone-induced and ethanol-induced narcosis. The extension of hexobarbitone sleeping time is an index of potential sedative effects of compounds which do not themselves produce hypnosis. The dose of cpd 1 required to double the sleeping time of mice treated with hexobarbitone was 250 mg/kg which is 10 times the anticonvulsant dose (Table 3). With primidone, phenobarbitone and phenytoin the effective doses in this test were 5·7, 3·2 and 16 times the anticonvulsant doses respectively.

In the ethanol potentiation test cpd 1 doubled the sleeping time of ethanol-treated mice at a dose of 250 mg/kg.

DISCUSSION

11-Dimethylamino-5,6-dihydro-6-oxomorphanthridine (cpd 1, ICI 45,337) shows anticonvulsant activity in a number of laboratory tests which detect clinically useful anticonvulsants. It is more active in antagonizing convulsions produced by electrical stimulation than chemically induced convulsions. The therapeutic ratio calculated for cpd 1 from the acute lethal and effective doses is higher than that of phenobarbitone. The ratio of neurotoxic to effective doses of cpd 1 at the time of peak activity is also greater than that of phenobarbitone.

In view of its potentially useful therapeutic ratio and low acute and chronic toxicity (Baker, 1966: personal communication), cpd 1 was taken to clinical trial (Grant, 1966: personal communication).

The patients used in this study were refractory cases of mixed epilepsies, and were

already receiving phenobarbitone, phenytoin or primidone and in most cases one or two other anticonvulsants. Under these conditions cpd 1 did not produce any anticonvulsant effect over and above that produced by the existing treatment. The early appearance of drug-induced rashes in a high proportion of patients precluded the possibility of investigating the anticonvulsant activity of cpd 1 alone. No symptoms of sedation or nausea were observed at doses up to 2 g/day.

It is known that some anticonvulsants, particularly phenobarbitone, induce hepatic microsomal metabolizing enzymes (see review by Conney & Burns, 1963). Metabolic studies (Platt, 1966: personal communication) showed that cpd 1 also stimulated the formation of hepatic microsomal metabolizing enzymes producing a similar pattern of enzyme induction to that caused by phenobarbitone. It is therefore probable that cpd 1 was being given to patients in whom metabolizing enzymes had been induced and who were capable of inactivating it more rapidly than patients who had not previously received phenobarbitone.

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