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SOME NEW DERIVATIVES OF UREA SHOWING ANTICONVULSANT AND ANXIOLYTIC PROPERTIES

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Two new urea derivatives N-carbanoylindane-2-carboxamide(2a) and 1,2,3,4-tetrahydro-2-naphthoyl urea (2 b) have been prepared by the condensation of the appropriate acid chlorides with urea. On pharmacological screening, it was found that these compounds exhibited marked anticonvulsant activity and a low order of tranquillizing activity. Parallel tests on phenobarbitone are also described.

INTRODUCTION

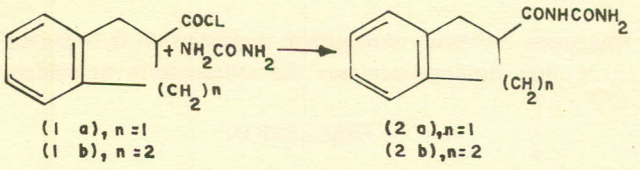
Phenyl acetylurea was found to be active against all types of major epilepsy, it was especially useful in the treatment of psychomotor seizures [1,2]. Despite its serious toxic effects it is still employed in patients whose seizures are impossible to control with other recognised anticonvulsants [3]. Recently some new derivatives of urea have shown considerable variety of biological activities, such as antiviral antineoplastic, C.N.S. depressant and hypoglycaemic [4-6]. Rasmussen *et al.* [7] also reported a new class of ureas derivatives having anticonvulsant, sedative and hypnotic properties.

Previous work has indicated that urea derivative may be considered as an open model of the barbiturate less one carbon atom and the presence of ureide group is important for anticonvulsant activity. The influence of flexibility of drug molecules on their biological action has been comprehensively discussed by Williams [8]. Recently Qazi *et al.* [9] compared the anticonvulsant activity of comparatively rigid barbiturates structures with that of more flexible 'ring opened' ureas structures. It was, therefore, thought worthwhile to synthesize some new derivatives of urea and to evaluate them for their anticonvulsant and anxiolytic properties.

MATERIALS AND METHODS

N-carbamoylindane-2-carboxamide (2 a) was obtained by the following two methods: (1). By condensing indane-2-carbonyl chloride with excess of urea in dry benzene. (2). It was also obtained in good yield as a cleaved product by the cleavage of indane-2-spirobarbituric acid [10].

1,2,3,4-Tetrahydro-2-naphthoyl urea (2 b) was prepared by the condensation of urea with 1,2,3,4-tetrahydro-2-naphthoyl chloride (1 b) in dry benzene.



The structures of all the compounds were checked by IR spectra recorded on Perkin-Elmer 237 spectrophotometer (Nujol mulls); UV spectra were run on a Unicam SP 800 spectrophotometer using solutions in spectroscopic ethanol. NMR spectra were determined on a Varian HA-100 spectometer using tetramethylsilane as an internal standard. Mass spectra were produced by the Physico-Chemical Measurement Unit, Harwell.

Indane-2-carbonyl Chloride (1 a).

Indane-2-carboxylic acid (16.2g, 0.1 mol) in dry benzene (85 ml) was added in over 1hr to a well-stirred solution of freshly distilled thionyl chloride (23.8g, 0.2 mol) in dry benzene (30 ml). Stirring was continued for 4 hr at 75-85°. The excess of thionyl chloride and benzene were evaporated under reduced pressure, the residue was recrystallised from ethanol to afford colourless needles, m.p.37° (lit., m.p. 35-30°) [11].

N-Carbamoylindane-2-carboxamide (2 a)

Procedure (1). The above carbonyl chloride (1 a) (9g, 0.05 mol) in dry benzene (30 ml) was added dropwise in over 0.5 hr to a well-stirred solution of urea (6g, 0.1 mol) in dry benzene (20 ml) and stirring was continued for 0.5hr at 60°. A further quantity of urea (3g, 0.05 mol) was added and the mixture was heated under reflux for 3hr. After cooling the

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solid was removed by filteration, washed with petroleum ether (b.p.60-80°) twice and recrystallised from ethanol to yield colourless crystals (8.4g,80%) m.p.223-224°. ν_{max} 3400, 3350, 3225, (NH), 1720, 1675 and 1625 (CONH)cm^{-1}, λ_{max} 247, 260, 267 and 273 nm (log ϵ 2.44, 2.63, 2.83 and 3.12), τ(CF_3COOH)2.8(4H,s,aromatic) 6.63 (5H, m, CH_2 CH CH_2) Found: C, 64.70; H, 5.95; N, 13.75 and M^+204.$C_{11}H_{12}N_2O_2$ requires; C,64.69; H,5.92; N,13.72 % and M^+204.

Procedure (2). Diethyl indane2,2-dicarboxylate (4g, 0.015 mol) in absolute ethanol (20 ml) was added dropwise over 0.5hr to a solution of sodium (0.7 g, 0.03 mol) and urea (2g,0.033 mol) in absolute ethanol (35 ml). The mixture was heated under reflux for 6hr. After cooling the mixture was acidified to give a crystalline solid,2g, 64.5%) m.p. 222-223° (ethanol). The colourless solid was shown to be identical with the above compound (2 a), (m.p., mixed m.p., IR, UV and NMR.

1,2,3,4-Tetrahydro-2-naphthoyl Chloride (1 b).

This compound (1 b) was prepared by the same procedure as mentioned for (1 a) from the corresponding acid. The excess of thionyl chloride and benzene were evaporated under reduced pressure, the residue distilled to afford (1 b) in good yield, b.p. 196-200° (100 mm).

1,2,3,4-Tetrahydro-2-naphthoyl Urea (2 b).

This compound was obtained by the same procedure as described for (2 a) above to give colourless crystals in good yield (76 %) m.p. 244-246° (ethanol), ν_{max} 3392, 3318, 3242 (NH), 1717, 1682, 1620 (CONH)cm^{-1}, λ_{max} 209 and 278 nm (log ϵ 3.9, 3.3) τ (CF_3COOH) 2.85 (4H, aromatic) 6.0 (1H, tCH_2 CH CO) 7.6-8.2 (4H, m,CH_2–CH CO CH_2) 8.4 (2H, m, CH CH_2CH_2) (Found; C, 65.9; H, 6.3; N, 12.8 and M^+218.$C_{12}H_{14}N_2O_2$ requires; C, 66.01; H, 6.42; N, 12.84 % and M^+218). Alkaline hydrolysis gave a known compound, 1,2,3,4-tetrahydro-2-naphthoic acid, m.p. 100° (lit, 99°) [12].

PHARMACOLOGICAL RESULTS

Albino mice of either sex of CFLP-ICI strainI) weighing 18-22 g and rats weighing 200-210 g were taken from a randomly bred stock in our laboratories. The mice were distributed into groups of ten. All compounds were dissolved or suspended in arachis oil and administered intraperitoneally while control groups received equal volume of injection vehicle. All experiments were performed under constant environmental conditions of temperature 26 + 2° and relative humidity.

ANTICONVULSANT ACTIVITY

Anticonvulsant study was carried out on a group of mice, which received leptazol (100 mg/kg) dissolved in saline vehicle at intervals of one or two hr, after the administration of test compounds while the control group was given leptazol alone. The anticonvulsant activity of the compounds was assessed by their ability to inhibit leptazol induced convulsions. The results obtained were then quantified using a seizure severity score [13].

Table 1. Anticonvulsant activity of 2a and 2b compared to phenobarbitone.

Drug	Time after administration (hr)	% reduction in group seizure score
Phenobarbitone (10 mg/kg i.p.)	1	70 %
	2	33.6 %
Compound 2 a (350 mg/kg i.p.)	1	75.2 %
	2	65.8 %
Compound 2b (350 mg/kg i.p.)	1	78.8 %
	2	70.2 %

The anticonvulsant activity of compounds 2a and 2b were significantly less than phenobarbitone, even though only a small amount of the latter was used. On the contrary their activity was relatively persistent in duration and changed marginally after 2 hr (Table 1). This might be due to a slower rate of metabolism resulting from enzyme inhibition. This mechanism might partly explain why phenyl acetylurea appears to be an effective medicament when it is given in combination with other anticonvulsant drugs to help to maintain the concentration of them in the tissues.

SPONTANEOUS LOCOMOTOR ACTIVITY (S.L.A.)

This was measured by means of Capacitance Electrodes fitted to cages (G. Washington Ltd., Model Aa 100-2) each containing ten mice. The mice were allowed to get accustomed to the new surroundings prior to the administration of test compound or arachis oil vehicle. The activity was recorded in cumulative unit counts for a period of 1 hr and expressed as percentage changes relative to the appropriate control group. Both compounds 2a, 2b and phenobarbitone showed a reduction in locomotor activities and none caused loss of righting reflexes at the dose employed. (Table 2).

DEPRESSANT ACTIVITY

This was determined by means of Conditioned Avoid-

ance Apparatus (Ugo Basile Condtioner T 501), where male rats were trained two days prior to the administration of drugs. The integrated delay time for individual animals was determined in response to a total of 70 electric stimuli.

Table 2. Depressant and locomotor activities of 2a, 2b and compared to phenobarbitone.

Drug	Integrated delay times (min) to 70 electric stimuli	% reduction in group S.L.A. in mice
Vehicle (i.p.)	3.9	–
Phenobarbitone (10 mg/kg i.p.)	8.4	35.2
2a (350 mg/kg i.p.)	8.0	36.4
(100 mg/kg i.p.)	4.0	20.1
2b (350 mg/kg i.p.)	8.1	34.5
(100 mg/kg i.p.)	4.6	21.5

Compounds 2a and 2b showed almost the same degree of sedation as shown by phenobarbitone but at a much higher dose. At a lower dose this effect is less significant in these compounds. Experimentally these compounds exhibited weak anxiolytic activity (Table 2).

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