Physical Sciences Section

Pak. j. sci. ind. res., vol. 34, nos. 2-3, February-March 1991

ANTIEPILEPTIC ACTIVITY OF 1, 2, 3, 4-TETRAHYDRO-1-NAPHTHONYL UREA

TARIQ UMER KAZI

5-Mayfield Avenue, Kings Cross, Halifax, HX13XE, United Kingdom

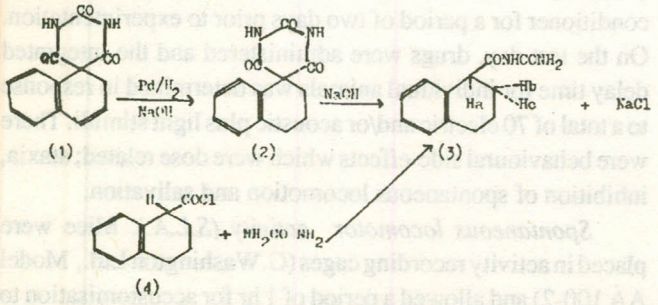
(Received July 7, 1986; revised January 5, 1991)

The synthesis of 1, 2, 3, 4- tetrahydro-1-naphthonyl urea (3) by the condensation of its acid chloride with urea is described. This compound was also obtained as a cleavage product in the synthesis of spiro-1-(1, 2, 3, 4-tetrahydro-naphthyl) -5-barbituric acid (2). Compound (3) gives good protection against leptazol convulsions. Parallel tests on phenobarbitone are also described.

Key words : Antiepileptic drugs, Phenobarbitone, 1, 2, 3, 4-Tetrahydro-1-naphthonyl urea.

Introduction

Antiepileptic therapy has changed only marginally since the introduction of phenobarbitone as an effective and valuable drug nearly 80 years ago. However, phenobarbitone possesses certain disadvantages, such as a sedative effect in adults and behavioural disturbances in children. Tolerance and toxicity in overdose are other problems. In addition, rebound seizures on withdrawal of this type of drug are observed. Like many other drugs used in grand mal therapy, phenobarbitone is a potent enzyme inducer. It is also implicated in drug interactions: for instance it reduces the plasma concentration of tricyclic anti-depressant drugs and in combination wiht other antiepileptic drugs such as phenytoin and sodium valproate it enhances their sedative effects [1,2]. Recent studies in the development of antiepileptic drugs have been directed towards the structural modifications which are considered to reduce their side effects. Thus Heyringen [3] reported that spiro-1-cyclopentane-5-barbituric acid is an excellent antiepileptic drug with a low hypnotic activity. Qazi [4-7] has also reported the preparation of several new antiepileptic drugs and has synthesised spiro-1-(1, 2, 3, 4-tetrahydronaphthyl)-5-barbituric acid (2) in an attempt to develop an alternative series of antiepileptic drugs.



Materials and Methods

The structures of all the compounds were checked by IR spectra recorded on Perkin-Elmer 237 spectrophotometer (Nujal mulls); UV spectra were run on a Unicam SP 800 spectraophotometer using solutions in spectroscopic ethanal. NMR spectra were recorded on a Varian HA-100 spectrometer using tetramethylsilane as an internal standard. Mass spectra were produced by the Physico-Chemical Measurement Unit, Harwell, and microanalyses were performed by the School of Pharmacy, London. 1, 2, 3, 4-Tetrahydro-1-naphthonyl urea (3) was obtained by the following two methods:

(i) By condensing 1, 2, 3, 4-tetrahydro-1-naphthonyl chloride (4) with excess of urea in dry benzene.

(ii) It was also obtained in good yield as a cleaved product by the cleavage of compound (2).

Preparation of 1, 2, 3, 4-tetrahydro-1-naphthonyl chloride (4). (i) 1, 2, 3, 4-Tetrahydro-1-carboxylic acid (17.6gm, 0.1 mol) in dry benzene (100 ml) was added over 1/2 hr. to a well-stirred solution of freshly distilled thionyl chloride (23.8gm, 0.2 mol) in dry benzene (40 ml). Stirring of the mixture was continued for 4 hrs at 70-80°. The excess of thionyl chloride and benzene was distilled under reduced pressure, the residue was fractionally separated under reduced pressure to give compound (4) in good yield, b.p. 200-204° (100 mm Hg).

Preparation of 1, 2, 3, 4-tetrahydro-1-naphthonyl urea (3). 1, 2, 3, 4-tetrahydro-1-naphthonyl chloride (4) (9.7 gm, 0.05 mol) in dry benzene (40 ml) was added drop by drop in 1 hr. to a well stirred solution of urea (6.0 gm, 0.1 mol) in dry benzene (30 ml) and stirring was continued for 1/2 hr. at 60°. A further quantity of urea (3 gm, 0.05 mol) was added and the mixture was heated under reflux for 6 hrs. After cooling for 24 hrs the solid formed was removed by filtration. The solid was washed with petroleum ether (b.p. 60-80°) three times and finally recrystallised from absolute alcohol to yield colourless crystals (8.2 gm, 76%) m.p. 218°. IR υ_{max} 3390, 3315, 3240 (NH), a broad peak centred at 1760 with shoulders at 1680 and 1615 (CONH) cm^{-1} and UV λ_{max} 209 and 282 nm (loge 3.95 and 3.50) and NMR δ(CF_3COOH) 7.15 (4 H,m, Aromatic), 4.1 (IH, t, Ha, J 7 HZ) 2.8 (IH, m, Hb, J 6HZ) 2.82 (IH, m, J 6HZ) 2.5-1.8 (2H, m, $CH\underline{CH_2}$ CH_2(1.5 (2H, m, $CH_2\underline{CH_2}$ $\underline{CH_2}$) Found; 65.78; H, 6.45, N, 12.75% $C_{12}H_{14}N_2O_2$ requires; C, 66.04; H, 6.40; N, 12.80% and m/z 218. Alkaline

hydrolysis of compound (3) gave a known compound, 1, 2, 3, 4-tetrahydro-1-naphthoic acid, m.p. 83° (lit., 84°) [8]. (ii) Preparation of compound (1) and its hydrogenation into compound (2) has been described in earlier unpublished work [9]. During an attempted hydrogeneration of compound (1) in 1% sodium hydroxide solution over palladium/charcoal for 6 hrs at 60° after the filtration of the catalyst, the filtrate was acidified with dilute hydrocholic acid. The mixtur was allowed to stand 48 hrs at 4°, the product was obtained as colourless crystals. The crystals were dissolved in a small quantity of dioxan, leaving behind a small amount of white powder, which was further recrystallised from ethyl alcohol to give a colourless powder m.p. 250° (Found; C, 63.86; H, 4.82; N, 11.22% $C_{13}H_{12}N_2O_3$ requires, C, 63.94; H, 4.91; N, 11.47%). The IR NMR and microanalyses were consistent with compound (2). The above dioxan solution was shaken with diethyl ether to give white crystals. Its TLC gave one spot only. Diethyl ether/benzene (4:8) was used as developing solvent (Rf_{100} = 75), m.p. 218°. The compound was shown to be identical with the above compound (3) (m.p., mixed m.p., IR, UV and NMR).

Pharmacological studies. Albino mice of either sex of CFLP-ICI strain 1, weighing 18 - 22 gm and rats weighing 200-210gm were taken from a randomly bred stock in our laboratories. The mice were distributed into groups of ten. All drugs were finally pulverised with pestle and mortar and were dissolved or suspended in arachis oil and administered intraperitoneally, while control groups received equal volumes of the vehicle also intraperitoneally. All experiments were performed under constant environmental conditions of temperature and relative humidity.

Antiepileptic activity. Antiepileptic study was carried on a group of mice. The mice were injected a single dose of leptozol (100 mg/kg) intraperitoneally. The leptozol was dissolved in saline vehicle. It was administered into the abdominal area remote from prior injections of the test compound/ drugs and at periods of one to two hrs. The control group received leptozol alone. The antiepileptic activity of these drugs was assessed by their ability to inhibit leptozol induced convulsions which were recorded and quantified using the method prescribed by Swinyard *et al.* [10]. The compound (3) and its β isomer 1, 2, 3, 4-tetrahydro-2-napthonyl urea (3-A) were tested for their antileptozol activity and compared with phenobarbitone [5].

The antiepileptic activity of compounds (3 and 3-A) was significally less than phenobarbitone even though the latter was used in small amounts. At lower dosage these compounds gave inadequate protection against leptazol induced convulsions, thus showing a steep dose-response relationship. At the site of injection their absorption is rather slow indicating the rigid ring structure (Table 1). It contributed to their having more persistent and prolong activities which changed only marginally even after 2 hrs, whereas the more flexible ring structure of phenobarbitone had dropped its activity considerably after 2 hrs. Structure activity study shows that receptor sites affinity increases from the direction of monocyclic towards polycyclic rings thus making polycyclic rings more lipobilic and enable such compounds to cross the blood brain barrier. Another factor could be a slow rate of metabolism affected by higher doses of compounds (3 and 3A) used. Compound (3) showed slower oxidation rate during its metabolism than compound (3-A). It may be possible that compounds (3) uride group had experienced electronic hinderance from the adjoining phenyl ring, thus making it less polar and less selective for enzymic attack than its β isomer (3-A). The above observations also indicated that compound (3) had more lipid binding ability than its β isomer. Therefore, compound (3) seemed to be more potent than compound (3-A).

TABLE 1.

Drug	Time after administration (hr)	%reduction in group seizure score
Phenobarbitone (10 mg/kg i.p.)	1	72%
	2	35%
Compound 3 (350 mg/kg i.p.)	1	83%
	2	74%
Compound 3A (350 mg/kg i.p.)	1	77%
	2	70%

+ The antiepileptic activity of compound (2) was carried out by Roche Products Ltd., London

Depressant action in the conditioned avoidance apparatus. Depressant activity was carried by means of Conditioned Avoidance Apparatus (Ugo Basile Conditioner T501), (Milan, Italy). [11]. Male rats were trained to respond to conditioned (acoustic solus light) followed by avoidance - (electric) stimuli in the above automatic avoidance conditioner for a period of two days prior to experimentation. On the test day, drugs were administered and the integrated delay time for individual animals was determined in response to a total of 70 electric and/or acoustic plus light stimuli. There were behavioural side effects which were dose related; ataxia, inhibition of spontaneous locomotion and salivation.

Spontaneous locomotor activity (S.L.A.). Mice were placed in activity recording cages (G.Washington Ltd., Model AA 100-2) and allowed a period of 1 hr for accustomisation to the environment. Animals were then injected with either test compound or arachis oil vehicle and activity was recorded in cumulative unit counts for a period of 1 hr and expressed as percentage changes relative to the appropriate control group. The activities of compounds 3 and 3-A were significantly the

TABLE 2. DEPRESSANT ACTIVITY OF 3 AND 3AAND COMPARED TO PHENOBARBITONE.

Drug	Integrated delay times (min) to 70 electric and/or acoustic plus light stimuli in rats	%reduction in group S.L.A in mice
Vehiscle (i.p.)	3.8	–
Phenobarbitone (10 mg/kg i.p.)	8.2	36.0
(3-) (350 mg/kg i.p.)	7.8	35.0
(100 mg/kg i.p.)	4.0	21.0
(3-A) (350 mg/kg i.p.)	8.0	36.0
(100 mg/kg i.p.)	4.5	21.5

same as phenobarbitone in locomotor activity tests (Table 2) but their doses were much higher. These compounds also exhibited weak depressant activity.

Discussion

Coumpound (3) was obtained in good yield by condensing urea with its corresponding acid chloride. The resulting compound was recrystallised from ethyl alcohol to give a colourless solid (m.p. 218°). The IR spectrum of this compound produced an absorption at 3390, 3315 and 3240 cm^{-1} (NH) and a broad peak at 1720 with shoulders at 1680 and 1615 cm^{-1} (CONH). The NMR and mass spectra were consistent with the above structure. Moreover compound (3) on alkaline hydrolysis yielded a known compound 1, 2, 3, 4-tetrahydro-1-naphthoic acid (m.p. 83°). Compound (3) was also obtained as a cleaved product during the attempted hydrogenation of compound (2) to give a colourless solid, m.p. 218° which was shown to be identical to compound (3) by m.p., mixed m.p. IR and NMR spectra. Thus these findings clearly support the above structure (3). Previous work has indicated that when the spiro heterocyclic ring in anticonvulsant is cleaved, the resultant more flexible open chain compounds such as (3-and 3A) are considerably less active than the parent compounds [12].

References

1. A. Spinks and W. S. Waring, *Progress in Medicinal Chemistry*, G. P. Ellis and G. B. West, (eds) (Butterworth Press, London, 1963), Vol. III, pp. 261.
2. G. R. Brown, *British National Formulary*, (eds), (The British Medical Association and The Pharmaceutical Society of G. Britain, (Pitman Press, 1988), Vol. XV, pp. 431
3. E.M.V. Heyningen, U. S. *Patent*, 2, 621, 183 (1952).
4. T. U. Qazi, V. Askam and R. D. Sewell, Libyan J. Sci., **9**, 79 (1979).
5. T. U. Qazi, Pak. j. sci. ind. res., **26**, 364 (1983).
6. T. U. Qazi, Pak. j. sci. ind. res., **27**, 326 (1984).
7. T. U. Qazi, Pak. j. sci. ind. res., **30**, 687 (1987).
8. R. L. Letsinger and W. J. Vullo, J. Org. Chem., **25**, 844 (1960).
9. T. U Qazi, Ph. D. Thesis, University of Wales, United Kingdom, (1975).
10. E.A. Swinyard, W. C. Brown and L. S. Goodman, J. Pharmacol. Exptl. Therap., **106**, 319 (1952).
11. L. L. Coughenour, J. R. Mclean and R. B. Parker, Pharmacol. Biochem. Behav., **6**, 351 (1977).
12. A. Spinks and W. S. Waring, *Progress in Medicinal Chemistry*, G. P. Ellis and G. B. West (eds) (Butterworth Press, London, 1963)Vol. III,pp. 284.