Indian Journal of Chemistry
Vol. 24B, August 1985, pp. 840-844

Synthesis of 10,11-Dihydrodibenz[*b*,*f*][1,4]oxazepine Derivatives as Potential Anticonvulsant & Psychotropic Agents†

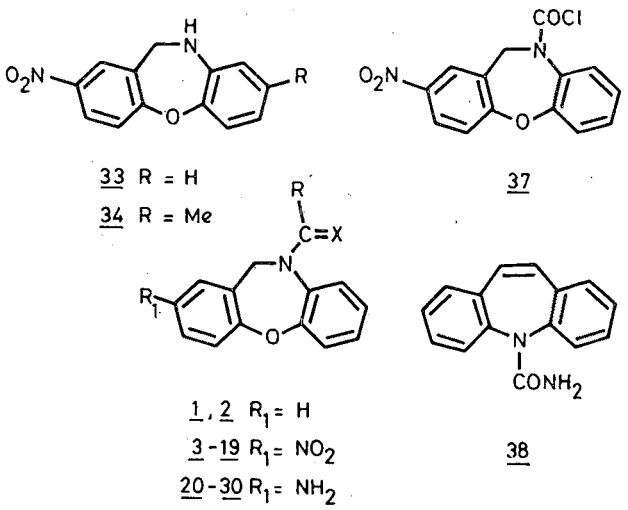
K NAGARAJAN, J DAVID* & G A BHAT
Hindustan CIBA-GEIGY Ltd, Research Centre, Bombay 400 063

Received 10 *December* 1984; *accepted* 31 *January* 1985

Several acyl, carbamoyl and thiocarbamoyl derivatives of 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine, most of them carrying either a nitro or amino group at position-2 have been synthesized as analogues of carbamazepine (**38**) and evaluated as anticonvulsants associated with potential neuroleptic activity. Among these, 10,11-dihydro-2-nitrodibenz[*b*,*f*][1,4]oxazepine-10-carboxylic acid hydrazide (**11**) and 2-amino-10-dimethylcarbamoyl-dibenz[*b*,*f*][1,4]oxazepine (**04**) have moderate activity in the electroshock test but are inactive against chemoshock. 10,11-Dihydro-10-thiocarbamoyldibenz[*b*,*f*][1,4]oxazepine (**2**) is active against electroshock as well as against strychnine-induced seizures, has some analgesic activity and also exhibits neuroleptic properties, but the overall profile of **2** does not present any advantages over the well known drug, carbamazepine (**38**).

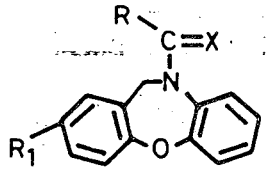
The management of behavioural disorders with the anticonvulsant drug, carbamazepine (**38**)[1] constitutes a new departure in psychoactive pharmacotherapy and its psychotropic properties have been demonstrated in epileptic patients[2]. Improvement in mentation and neurophysiological functioning in epileptic patients, a major reason for selecting carbamazepine over other agents with comparable efficacy, seems to derive at least in part from a pharmacologic factor emanating from the tricyclic molecular configuration of the drug[3,4]. During the course of our extensive studies on condensed heterotricycles that led to the development of the safe and effective nitrodibenz[*b*,*f*][1,4]oxazepine antidepressant, Sintamil[5-7], we had available to us an easy method for the synthesis of 10,11-dihydro-2-nitrodibenz[*b*,*f*][1,4]oxazepine (**33**)[8]. This prompted us to transform **33** into various acyl, carbamoyl and thiocarbamoyl derivatives for an anticonvulsant screening programme which aimed at discovering molecules iith carbamazepine-like properties with better psychotropic effects if possible. It may be pointed out in this context that 10-carbamoyl-10, 11-dihydrodibenz[*b*,*f*][1,4]oxazepine (**1**) has been reported to have anticonvulsant properties, as also the des-nitro derivative of the acetyl semicarbazide **11** which additionally has prostaglandin antagonistic properties, while the diethylaminoethyl urea of 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine has low antiinflammatory activity. 3-Chloro-10-carbamoyl-10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine has been tried in the clinic for anticonvulsant activity[7].

The thiourea (**2**) was prepared from 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine[9] and thiocyanic acid, and **1** by the use of cyanic acid. A similar reaction on **33** gave **3**. Compounds **4-8** were obtained from **33** and appropriate isocyanates. Transformation of **33** to the chlorocarbonyl derivative (**37**) and further exposure to dimethylamine and hydrazine gave **9** and **10** respectively, the latter being acetylated to **11**. Compound (**12**) resulted from the action of ethanol on **37**. Acylation of **33** with acyl halides/or anhydrides gave **13-15**, **15** being further transformed to the aminoacyl derivatives **16-18**. The action of methyl isothiocyanate on **33** produced the thiourea (**19**). Amines **21-29** were obtained by catalytic hydrogenation of the respective nitro derivatives. **33** as well as its 8-methyl derivative (**34**) (prepared by the procedure used for **33**) were catalytically reduced to amines (**35**) and (**36**), respectively. The reaction of **35** with cyanic acid afforded both **20** and **30**. Compounds **31** and **32** have been reported earlier. Physical data for



†Contribution No. 733 from Research Centre.

Table 1—N-Acyl-, Carbamoyl and Thiocarbamoyl-10,11-dihydrodibenz[*b*,*f*][1,4]oxazepines

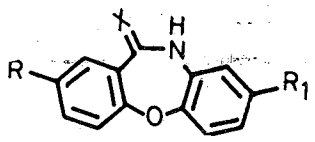


[X=S for **2** and **19** and O for the rest, R_1=H for **1**,**2**: NO_2 for **3**-**19**: NH_2 for **20**-**29**: and $NHCONH_2$ for **30**]

Compd	R	Mol. formula*	Crystallised from†	m.p.‡ °C	Antielectroshock mg/kg p.o.		% protection following		% inhibition AcOH writhing at
					ED_{50}	ED_{100}	Metrazol at 30 mg/kg i.p.	Strychnine at 30 mg/kg i.p.	100 mg/kg p.o.
1	NH_2	$C_{14}H_{12}N_2O_2$	H	162-64	70.5±14.4	200[a,b–c]	50	25	—
2	NH_2	$C_{14}H_{12}N_2OS$	H	188-90	130±22	500[a,c]	Ø	50	87 (ED_{50}; 47)
3	NH_2	$C_{14}H_{11}N_3O_4$	D+B	213-15	—	Ø 500	Ø	Ø	62
4	NHMe	$C_{15}H_{13}N_3O_4$	B	204-5	>300	500[a,c]	25	Ø	69
5	NHEt	$C_{16}H_{15}N_3O_4$	B	145-46		>500[a,c]	Ø	Ø	59
6	NHPr(n)	$C_{17}H_{17}N_3O_4$	B	135-38		Ø 500[c]	Ø	Ø	58
7	NHC_6H_{11}	$C_{20}H_{21}N_3O_4$	B+G	182-83	—	Ø 500	25	25	16
8	NHPh	$C_{20}H_{15}N_3O_4$	B	215-16		Ø 500	50	Ø	16
9	NMe_2	$C_{16}H_{15}N_3O_4$	H	145-46	>100	250[b]	Ø	Ø	—
10	$NHNH_2$	$C_{14}H_{12}N_4O_4$	C+H	201-2	81±17	250	50	25	—
11	NHNHAc	$C_{16}H_{14}N_4O_5$	F	207-8	—	50[b]	Ø	Ø	—
12	OEt	$C_{16}H_{14}N_2O_5$	B+G	166-67	—	Ø 500[b]	25	Ø	47
13	CH_3	$C_{15}H_{12}N_2N_4$	D	182-83	—	Ø 500[c]	25	Ø	38
14	CF_3	$C_{15}H_9F_3N_2O_4$	D	181-82		Ø 500	Ø	Ø	
15	CH_2Cl	$C_{15}H_{11}ClN_2O_4$	D	172-73		Ø 500	25	Ø	28
16	morpholino-methyl	$C_{19}H_{19}N_3O_5$	D	165-66		Ø 500[b,c]	Ø	Ø	—
17	CH_2NEt_2	$C_{19}H_{21}N_3O_4$	E+G	130-31		500	—	—	—
18	4-methyl-piperazino-methyl	$C_{20}H_{22}N_4O_4$	A	166-67		Ø 500[b]	25	Ø	38
19	NHMe	$C_{15}H_{13}N_3O_3S$	A+B	268-69		Ø 500			63
20	NH_2	$C_{14}H_{13}N_3O_2$	D	209-10					
21 (HCl)	NHMe	$C_{15}H_{16}ClN_3O_2$	D	245-46(d)	500	>500[a,b,c]	Ø	Ø	73
22	NHC_6H_{11}	$C_{20}H_{23}N_3O_2$	B	159-60	200	250[b]	25	Ø	40
23 (HCl)	NHPh	$C_{20}H_{20}N_3O_3Cl$	D+E	180-83(d)	73±10.9	250[c]	50	Ø	71
24	NMe_2	$C_{16}H_{17}N_3O_2$	E+G	147-48	28.5±9.7	100[a,b,c]	Ø	Ø	—
25	$NHNH_2$	$C_{14}H_{14}N_4O_2$	D	160-61		250[a,c]	Ø	Ø	—
26 (HCl)	OEt	$C_{16}H_{17}ClN_2O_3$	D+E	225-28(d)	53±11.2	>100[a,c]	Ø	Ø	64
27	CH_3	$C_{15}H_{14}N_2O_2$	D+E	119-20(d)	48±54	100[a,c]	25	Ø	69
28	CF_3	$C_{15}H_{11}F_3N_2O_2$	E+G	146-47	68±4.4	>250	Ø	Ø	52
29	CH_2NEt_2	$C_{19}H_{23}N_3O_2.\frac{1}{2}H_2O$	E+G	82-83	<250	500[b]	50	25	85
30	NH_2	$C_{15}H_{14}N_4O_3$	H	250-51(d)	—	Ø 500[c]	Ø	Ø	71

*All new compounds had C, H, N values within ±0.4% of the calculated values.
†Solvents for crystallisation: A-acetone; B-benzene; C-chloroform; D-ethanol; E-ether; F-ethyl acetate; G-hexane; H-methanol.
‡All the mething points are uncorrected.
[a](a) Alaxia; (b) Loxic convulsions and tremors; (c) sedation; (Ø) no effect at indicated dose.

Table 2—Some Dibenzoxazepinones and 10,11-Dihydrodibenzoxazepines



[X = O for **31**, **32**; H_2 for **33-36**; R = NH_2 for **31**, **32**, **35**, **36**; NO_2 for **33**, **34**; R_1 = H for **31**, **33**, **35**; Me for **32**, **34**, **36**]

Compd	Mol. formula*	Crystallised from†	m.p.‡ °C	Antielectroshock[δ] mg/kg p.o.		% Protection following		% Inhibition AcOH writhing at 100 mg/kg p.o.
				ED_{50}	ED_{100}	Metrazol at 30 mg/kg i.p.	Strychnine at 30 mg/kg i.p.	
31				50	100	—	—	—
32				100	250[c]	—	—	ED_{50}: 4 p.o.
33					Ø 500	Ø	Ø	—
34	$C_{14}H_{12}N_2O_3$	B+G	137-38					
35	$C_{13}H_{12}N_2O$	E+G	145-46		500**[a,c]	Ø	Ø	59
36	$C_{14}H_{14}N_2O$	D	127-28		Ø 500[a,c]	25	25	63

*All the new compounds had C, H, N values within 0.4% of the calculated values.
†Solvents for crystallisation: B-benzene; E-ether; D-ethanol; G-hexane.
‡All melting points are incorrected.
δ(a) Ataxia; (b) toxic convlusions and tremors; (c) sedation; (Ø) no effect at indicated dose.
**At 100mg/kg p.o., 50% mice showed loss of righting reflex and there was marked activity(++++) at 5 mg/kg p.o. in the DOPA response potentiation test and antagonism of reserpine induced hypothermia (ED_{50} = 4.1 mg/kg p.o.) showing antidepressant type of activity.

compounds **1-30** are given in Table 1 and for **34-36** in Table 2.

Biological evaluation

Compounds were administered orally (p.o.) in 0.2% agar suspension or parenterally (i.p.) to CF male mice (n = 6/dose) for evaluation of anticonvulsant activity. Protection against electroshock seizures (Test 1) was routinely done at graded doses upto 500 mg/kg p.o. and 125 mg/kg i.p. ED_{100} and/or ED_{50} doses were determined one hour post-dose and used for comparison[10]. Protection against chemoshock convulsions induced by pentylenetetrazole (Metrazol), 150 mg/kg i.p. (Test 2) and strychnine, 2.5 mg/kg i.p. (Test 3) was examined after a test dose of 30 mg/kg i.p., and inhibition of acetic acid induced writhing (Test 4) was determined as % inhibition[10]. Selected compounds were also tested in mice for potential psychotropic properties and for evidence of amphetamine antagonism (Test 5) and catatonia (Test 6)[11], for inhibition of perifornical rage in cats (Test 7)[12] and for DOPA response potentiation in mice (Test 8)[13]. Test 5 to 7 are commonly used for the detection of potential neuroleptic activity and Test 8 for the detection of antidepressant activity[10,13]. Results of Tests 1-4 for compounds (**1-30**) are recorded in Table 1 and for compounds (**31-36**) in Table 2. Table 3 compares compound (**2**) with carbamazepine in Tests 1-8.

Table 3—ED_{50} (mg/kg) Values for **2** and **38** in Tests 1-8

Test		**2**	**38**
Antielectroshock	(p.o.)	130±22	11±1.2
Antimetrazol	(i.p.)	Ø 30	17.3±3.8
Antistrychnine	(i.p.)	30 (approx)	17±4.1
Inhibition AcOH writhing	(p.o.)	47	5
Antiamphetamine	(i.p.)	<30	<30
Catatonia	(p.o.)	500	Ø 500
Inhibition of perifornical rage in cat	(p.o.)	100	60
DOPA test	(p.o.)	Ø 25	Ø 25

It is seen from Table 1 that acetylsemicarbazide (**11**) is highly potent against electroshock seizures but is inactive against chemoshock convulsions. Moreover even at 50 mg/kg p.o. it produced dyspnoea. Many of the other 11-substituted-2-nitro-10,11-dihydrodibenz[*b*,*f*][1,4]oxazepines have low anticonvulsant activity in Test 1, while the 2-amino derivatives tended to be more active. Table 2 shows that without an acyl substituent at position-10, both 2-nitro and 2-amino derivatives are inactive, whereas two 2-aminodibenzoxazepinones (**31**) and (**32**)[14] have moderate antielectroshock activity. The most active compound in this study, **24**, was 1/5 as active as

carbamazepine in Test 1, had no appreciable activity in Tests 5-8 and further produced ataxia and toxic convulsions and tremors at 100 mg/kg p.o. Urea (**1**) was 1/6 as active as **38** in Test 1, but offered some protection against chemoshocks (Tests 2, 3). However, ataxia and toxic convulsions were seen at 200 mg/kg p.o. Only the thiourea (**2**) showed catatonia and frog-like jumping behaviour in the CNS profile (a property of neuroleptics) and hence it was tested exhaustively. Its performance in Tests 1-8 were compared with that of carbamazepine (**38**) (Table 3). Compounds (**2**) and (**38**) were characterized by activity against seizures induced in mice, activity in some neuroleptic test systems and absence of activity in the DOPA response system. Compound (**2**) was twelve times weaker in the antielectroshock test; unlike **38**, **2** produced catatonia in mice and is $1\frac{1}{2}$ times weaker in inhibition of electrically induced aggression in cats, a property characterizing neuroleptics. Although **2** was well-tolerated in the mouse ($LD_{50} > 300$ mg/kg p.o. versus 3600 mg for **38**), it was inferior to **38** in the tests designed for our specific objective and was hence not pursued further. The methylthiourea (**19**) had no antielectroshock activity which was a disincentive to synthesis and evaluation of higher homologues. **35** was characterized by marked activity in the DOPA response potentiation test and antagonism of reserpine-induced hypothermia, tests in which **38** was not active.

Experimental Procedure

10,11-Dihydro-8-methyl-2-nitrodibenz[bf]-[1,4]oxazepine (**34**)

This was prepared by the procedure reported for **33**[8] as follows: 2-Chloro-5-nitrobenzaldehyde (37 g, 0.2 mol) was condensed with 2-amino-*p*-cresol (24.6 g, 0.2 mol) in warm ethanol (200 ml) to afford the schiff base (54 g), m.p. 175-76° (from EtOH) (Found: C, 57.7; H, 3.9; N, 9.3. $C_{14}H_{11}CN_2O_3$ requires C, 57.8; H, 3.9; N, 9.3%).

Schiff base (5.8 g, 20 mmol) and sodium hydride (50% suspension in mineral oil, 1 g, 22 mmol) were heated together in DMF (15 ml) for 15 min. The solution was poured in water and the product recovered by extraction with ethyl acetate to afford 8-methyl-2-nitrodibenz[*b,f*][1,4]oxazepine (2.6 g), m.p. 159-60° (from EtOH) (Found: C, 66.2; H, 4.3; N, 10.6. $C_{14}H_{10}N_2O_3$ requires C, 66.1; H, 4.0; N, 11.0%).

Reduction of a solution of above (3.2 g) in dioxane (10 ml) and methanol (20 ml) with sodium borohydride (0.9 g) during $1\frac{1}{2}$ hr and dilution with water gave after crystallisation from benzene-hexane, **34** (2.8 g), m.p. 137-38° (Found: C, 65.5; H, 4.7; N, 10.5. $C_{14}H_{12}N_2O_3$ requires C, 65.6; H, 4.7; N, 10.9%).

10,11-Dihydro-10-thiocarbamoyldibenz[b,f]-[1,4]oxazepine (**2**)

10,11-Dihydrodibenz[*b,f*][1,4]oxazepine (0.8 g, 4 mmol) was dissolved in dil HCl (4 ml of 1.026 *N*) and treated with potassium thiocyanate (0.4 g, 4 mmol). The solution was heated overnight. The precipitate was filtered off and crystallised from methanol to give **2** (0.5 g).

10-Carbamoyl-10,11-dihydro-2-nitrodibenz[b,f]-[1,4]oxazepine (**3**)

A solution of **33** (2.5 g, 10 mmol) in acetic acid (2 ml) was heated with potassium cyanate (0.9 g, 11 mmol) on a water-bath for 3 hr and poured into water to give **3** (1 g) (from EtOH-benzene).

Similar treatment of the dihydrochloride of **35** (6 g) with potassium cyanate (3.4 g) in water (50 ml) gave a precipitate which was filtered off and washed with a little dil. HCl. Crystallisation from methanol gave the bis-carbamoyl derivative (**30**) (1.8 g). Neutralization of the filtrate with sodium hydroxide gave the monocarbamoyl derivative considered tentatively to be **20** which was purified by crystallisation from ethanol (2.2 g).

10-Alkyl(cycloalkyl, aryl)carbamoyl-10,11-dihydro-2-nitrodibenz[b,f][1,4]oxazepines (**4-8**)

A solution of **33** (0.97 g, 4 mmol) and methyl isocyanate (0.23 g, 4 mmol) in benzene (50 ml) was heated under reflux for 24 hr and then evaporated to give crude methylcarbamoyl derivative (**4**). Crystallisation from benzene afforded pure **4** (0.8 g). Derivatives **5-8** were made similarly from the appropriate isocyanates.

10,11-Dihydro-2-nitrodibenz[b,f][1,4]oxazepine-10-carboxylic acid chloride (**37**)

To a solution of phosgene (1.5 g, 15 mmol) in toluene (30 ml) at 5-10° was added with stirring, the amine **33** (2.7 g, 11 mmol) and triethylamine (1.1 g) in a mixture of ether (10 ml) and methylene chloride (10 ml). After 1 hr, the product was crystallized from benzene to give **37** (2.5 g), m.p. 185-86° (Found: C, 55.4; H, 3.4; N, 9.6. $C_{14}H_9ClN_2O_4$ requires C, 55.2; H, 3.0; N, 9.2%).

10,11-Dihydro-10-dimethylcarbamoyl-2-nitrodibenz-[b,f][1,4]oxazepine (**9**)

A solution of **37** (0.4 g) in a 1:1 mixture of ether-methylene chloride (50 ml) was stirred at 10° for 1 hr with 40% aq. dimethylamine (0.2 g) and left overnight. Evaporation afforded **9** (0.3 g) which was crystallised from methanol.

10,11-Dihydro-2-nitrodibenz[b,f][1,4]oxazepine-10-carboxylic acid hydrazide (**10**)

37 (1.21 g) was treated with hydrazine hydrate (0.6 g) as above to give **10** (0.8 g), which upon warming with

acetic anhydride (2.5 ml) on the water-bath for 10-15 min afforded the acetyl derivative (**11**).

10-*Acetyl*-10,11-*dihydro*-2-*nitrodibenz*[*b,f*]-[1,4]*oxazepine* (**13**)

33 (2 g) and acetic anhydride (2.5 ml) were heated together on a water-bath for 3 hr and poured into water to give **13** (1.9 g). Trifluoracetyl derivative (**14**) was prepared similarly.

10-*Chloracetyl*-10,11-*dihydro*-2-*nitrodibenz*[*b,f*]-[1,4]*oxazepine* (**15**)

A solution of **33** (2.9 g, 12 mmol) in benzene (100 ml) containing chloracetyl chloride (1.15 g, 12 mmol) and triethylamine (1.95 g) was heated under reflux for 5 hr, filtered and the filtrate evaporated *in vacuo*. The residue was crystallised from ethanol to give **15** (2.1 g).

Similar reaction of **33** (2.4 g, 10 mmol) with ethyl chloroformate (1.5 g, 14 mmol), but without using triethylamine gave **12** (1.9 g).

10,11-*Dihydro*-10-(*morpholinoacetyl*)-2-*nitrodibenz*-[*b,f*][1,4]*oxazepine* (**16**)

A solution of **15** (1.9 g, 6 mmol) and morpholine (0.7 g, 8 mmol) in benzene (50 ml) was heated under reflux for 20 hr and filtered. Evaporation of the filtrate and crystallization from ethanol afforded **16** (1.3 g).

Aminoacyl derivatives (**17**) and (**18**) were prepared similarly.

10,11-*Dihydro*-10-*methylthiocarbamoyl*-2-*nitro-dibenz*[*b,f*][1,4]*oxazepine* (**19**)

A solution of **33** (1 g, 4 mmol) and methyl isothiocyanate (0.4 g, 5.5 mmol) in benzene (20 ml) was heated under reflux for 48 hr and evaporated. The product was crystallised from acetone-benzene to afford **19** (0.6 g).

2-*Amino*-10-*alkyl*(*cycloalkyl, aryl*)*carbamoyl- and* 2-*amino*-10-*acyl*(*aminoacyl*)-10,11-*dihydrodibenz*-[*b,f*][1,4]*oxazepines* (**21-29**)

The general procedure is exemplified for **21**. A solution of **4** (4 g) in methanol (200 ml) was shaken with hydrogen at 1 atmospheric pressure and room temperature in the presence of platinum catalyst (from 100 mg PtO_2) during 17 hr when uptake of 3 mol of hydrogen was complete. The mixture was filtered and the filtrate evaporated. The residue was converted into the hydrochloride salt which was crystallised from ethanol to afford **21** HCl (2.9 g). **23** and **26** were similarly characterized as hydrochlorides, while **22**, **24**, **25** and **27-29** were crystalline solids by themselves.

2-Amino-10,11-dihydrodibenz[*b,f*][1,4]oxazepines (**35**) and (**36**) carrying no substituent at position-10 were similarly prepared from **33** and **34** respectively.

References

1 Kuhn R, *Epileptic seizures—Behaviour-pain*, edited by W Birkmayer (Hans Huber, Vienna) 1976 p 268.

2 Murray W J & Kier L B, *Medicinal chemistry: Anticonvulsants*, Vol. 15 edited by J A Vida (Academic Press, New York) 1977 p 577.

3 Gagneux A R, *Epilepitic seizures—Behaviour-pain*, edited by W Birkmayer (Hans Huber, Vienna) 1976 p 120.

4 Troupin A S, *Recent advances in epilepsy*, edited by T A Pedley & B S Meldrum (Churchill Livingstone, Edinburgh) 1983 p 47.

5 Kaiser C & Setler P E, *Burger's medicinal chemistry*, Part III edited by M E Wolff (Wiley, New York) 1979 p 997.

6 von Voigtlander P F, *Annual reports in medicinal chemistry*, Vol. 11, edited by F H Clarke (Acedmic Press, New York) 1976 p 3.

7 Nagarajan K, *Studies in organic chemistry—New trends in heterocyclic chemistry*, edited by R B Mitra, N R Ayyangar, V N Gogte, R M Acheson & N Cromwell (Elsevier, New York) 1974 p 317.

8 Nagarajan K, Venkateswarlu A, Kulkarni C L & Shah R K, *Indian J Chem*, **12** (1974) 227.

9 Hunziker F, Kuenzel F, Schindler O & Schmutz J, *Helv Chim Acta*, **47** (1964) 1163.

10 David J & Grewal R S, *Indian J exptl Biol*, **12** (1974) 225.

11 Merpurgo C, *Arzneimittel Forsch*, **11** (1971) 1727.

12 Koella W P, Levin P & Baltzer V, *Epileptic seizures—Behaviour-pain*, edited by W Birkmayer (Hans Huber, Vienna) 1976 p 32.

13 Nagarajan K, David J & Shah R K, *J mednl Chem*, **19** (1976) 508.

14 Nagarajan K, Venkateswarlu A, Kulkarni C L, Goud A N & Shah R K, *Indian J Chem*, **12** (1974) 236.