SYNTHESIS AND ANTICONVULSANT ACTIVITY OF SOME NEW N-[*p*-(SUBSTITUTED BENZAMIDO) BENZOYL] HYDRAZONES

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ABSTRACT

A series of N-[*p*-(substituted benzamido) benzoyl] hydrazones was synthesized by refluxing N-[*p*-(substituted benzamido) benzoyl] hydrazines with various araldehydes in ethanol in the presence of a few drops of glacial acetic acid. Some of these compounds when screened for anticonvulsant activity provided protection against pentylenetetrazole-induced convulsions in mice.

INTRODUCTION

HYDRAZINE derivatives[1] have been found to be potent inhibitors of MAO enzyme and inhibitors of this enzyme have displayed pronounced anticonvulsant activity. Various substituted phenyl hydrazone derivatives have also shown an appreciable anticonvulsant activity[2–4]. Furthermore, the presence of 3,4,5-trimethoxybenzene nucleus in reserpine[5] was shown to be responsible for CNS depressant and hypotensive properties. These findings led us to synthesise the title hydrazones with a view to assessing their anticonvulsant activity.

Substituted benzoyl chloride was allowed to react with ethyl *p*-aminobenzoate to give ethyl *p*-(substituted benzamido) benzoate which, on reaction with hydrazine hydrate, yielded N-[*p*-(substituted benzamido) benzoyl] hydrazines. The latter on being refluxed with various araldehydes afforded the title hydrazones.

EXPERIMENTAL

All melting points were taken in open capillaries and are uncorrected. The purity of the compounds was checked by T.L.C. on silica gel-G using iodine vapours as visualising agent. The IR spectra were recorded on perkin-Elmer infracord spectrometer. The PMR spectra were taken on varian EM-360 spectrometer using TMS as an internal reference.

Ethyl p-aminobenzoate (I)

Ethyl *p*-aminobenzoate was prepared by esterification of *p*-aminobenzoic acid by the method reported earlier[6].

Ethyl p-(R-substituted benzamido) benzoates (II)

To a solution of ethyl *p*-aminobenzoate (0.02 mole) in anhydrous tetrahydrofuran (30 ml) was slowly added substituted benzoyl chloride (0.03 mole) slowly in small portions with shaking, the temperature of the mixture being maintained at 0–10°C. The resulting mixture was stirred for one hour and allowed to stand overnight in a fridge. The solvent was removed by distillation under reduced pressure. The solid residue filtered and washed with 5% hydrochloric acid and 5% sodium carbonate and then with water. The product was recrystallised from benzene-petroleum ether and characterised by I.R. (KBr) spectral bands at 1680 cm^{-1} (N–$\overset{O}{\overset{\|}{C}}$ str.), 1710–1720 cm^{-1} ($COOC_2H_5$ str.) and 3350 cm^{-1} (–NH str.). The esters thus prepared are as follows:

(a) 4 = 4-Chloro, m.p. 180°C, yield – 73%. Found: C, 62.78; H, 4.47 and N, 4.35%. $C_{16}H_{14}NO_3Cl$ requires C, 63.26; H, 4.61 and N, 4.61%.

(b) R = 4-Methoxy, m.p. 175°C, yield – 70%. Found: C, 68.53; H, 5.32 and N, 4.92%. $C_{17}H_{17}NO_4$ requires C, 68.22; H, 5.68 and N, 4.68%. PMR (DMSO-d_6) δ: 1.24 (t, 3H, $COOCH_2CH_3$), 3.75 (s, 3H, OCH_3), 4.29 (q, 2H, $COOCH_2CH_3$), 7.26–7.88 (m, 8H, aromatic), 10.32 (b, 1H, $\overset{O}{\overset{\|}{C}}$–NH).

(c) R = 3,4,5-Trimethoxy, m.p. 113°C (Lit[7] 114°C), yield – 65%. Found: N, 4.23%, $C_{19}H_{21}NO_4$ requires N, 3.89%.

N-[p-(R-substituted benzamido)benzoyl] hydrazines (III)

A mixture of II (0.02 mole) and hydrazine hydrate (0.02 mole) in absolute ethanol (25 cc) was refluxed on a steambath for 16 hr. The excess ethanol was distilled off and the solid that separated on cooling was filtered, dried and recrystallised from ethanol The IR (KBr) spectra of the products showed peaks at

1680–1700 cm^{-1} (N–$\overset{O}{\overset{\|}{C}}$ str.) and 3360–3380 cm^{-1} (CONH NH_2 str.). The hydrazines thus prepared are as follows:

(I) R = 4-Chloro, m.p. 160 C, yield–68%. Found: C, 57.62; H, 4.47 and N, 14.27%. $C_{14}H_{12}N_3O_2Cl$ requires C, 58.03; H, 4.14 and N, 14.50%.

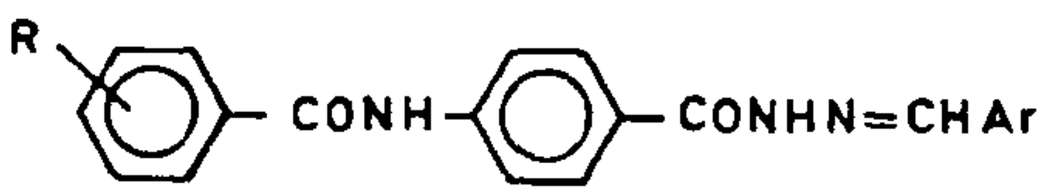
(II) R = 4-Methoxy, m.p. 140°C, yield – 65%. Found: C, 62.73; H, 5.43 and N, 14.49%. $C_{15}H_{15}N_3O_3$ requires C, 63.15; H, 5.26 and N, 14.73%. PMR (DMSO-D_6) δ: 3.72 (s, 3H, OCH_3), 4.38 (b, 2H, $CONHNH_2$), 7.25–7.80 (m, 8H, aromatic), 9.87 (b, 1H, $CONHNH_2$), 10.46 (b, 1H, CONH).

(III) R = 3,4,5-Trimethoxy, m.p. 198°C [Lit[8] 202°C]. Found: N, 11.82%. $C_{17}H_{19}N_3O_5$ requires N, 12.17%.

N-(p-substituted benzamido) benzoyl] hydrazones (IV)

A mixture of III (0.002 mole), an appropriate aldehyde (0.02 mole), ethanol (15 ml) and a few drops of glacial acetic acid was refluxed on a steam bath for 4 to 5 hr. Excess ethanol was distilled off. The solid mass thus obtained was washed with water and recrystallised from ethanol (table 1).

Table 1 *N-[p-Substituted benzamido)benzoyl]hydrazones*



S. No.	R	AR	M.P. °C	Molecular formula	% Nitrogen Found	% Nitrogen Calcd.
1.	4-Chloro	2-Hydroxyphenyl	153	$C_{21}H_{16}N_3O_3Cl$	10.94	10 67
2*.	"	4-Methoxyphenyl	162	$C_{22}H_{18}N_3O_3Cl$	9 97	10.30
3.	"	4-Hydroxy-3-methoxyphenyl	108	$C_{22}H_{18}N_3O_4Cl$	9.64	9.92
4.	4-Methoxy	Styryl	165	$C_{24}H_{21}N_3O_3$	10.21	10.52
5.	"	2-Nitrophenyl	158	$C_{22}H_{18}N_4O_5$	13.12	13 39
6.	"	Furyl	166	$C_{20}H_{17}N_3O_4$	11.19	11 57
7*.	3,4,5-Trimethoxy	4-Methoxyphenyl	110	$C_{25}H_{25}N_3O_6$	8.74	9.07
8.	"	4-N,N-Dimethylaminophenyl	205	$C_{26}H_{28}N_4O_5$	11.43	11.76
9.	"	Furyl	152	$C_{22}H_{21}N_3O_6$	9 62	9.93
10.*	4-Chloro	3,4-Dimethoxyphenyl	157	$C_{23}H_{20}N_3O_4Cl$	9.32	9 60
11.	"	4-Tolyl	159	$C_{22}H_{18}N_3O_2Cl$	10.41	10.72
12.	"	4-N,N-Dimethylaminophenyl	154	$C_{23}H_{21}N_4O_2Cl$	13.04	13.37
13.	4-Methoxy	4-Hydroxy-3-methoxyphenyl	155	$C_{23}H_{21}N_3O_5$	10.32	10.02
14.	"	2-Hydroxyphenyl	205–208	$C_{22}H_{19}N_3O_4$	10.45	10.79
15.	"	3,4-Dimethoxyphenyl	153	$C_{24}H_{23}N_3O_5$	9 32	9 69
16*.	3,4,5-Trimethoxy	4-Tolyl	140	$C_{25}H_{25}N_3O_5$	9.72	9.39
17.	"	2-Nitrophenyl	85	$C_{24}H_{22}N_4O_7$	11.73	11.71
18.	"	Styryl	181	$C_{26}H_{25}N_3O_5$	8.74	9 15
19.	4-Chloro	Furyl	168	$C_{19}H_{14}N_3O_3Cl$	11.16	11.42
20.	"	3-Nitrophenyl	95	$C_{21}H_{15}N_4O_4Cl$	12.87	13.25
21.	"	Styryl	170	$C_{23}H_{18}N_3O_2Cl$	10.13	10 40
22*.	4-Methoxy	4-Methoxyphenyl	118	$C_{23}H_{21}N_3O_4$	13 06	13.42
23.	"	4-N,N-Dimethylaminophenyl	190	$C_{24}H_{24}N_4O_3$	13.12	13.46
24.	"	4-Tolyl	137	$C_{23}H_{21}N_3O_3$	10.43	10 85
25.	3,4,5-Trimethoxy	2-Hydroxyphenyl	186	$C_{24}H_{23}N_3O_6$	9.12	9.35
26*.	"	4-Hydroxy-3-methoxyphenyl	210	$C_{25}H_{25}N_3O_7$	8.48	8.76
27.	"	3,4-Dimethoxyphenyl	189	$C_{26}H_{27}N_3O_7$	8 21	8.52

* Showed I R. (KBr) spectral bands at 1650–1670 cm^{-1} (C=NH str), 1680–1710 cm^{-1} (N–$\overset{O}{\overset{\|}{C}}$–str), 2900 cm^{-1} (CH_2 str), 3200–3300 cm^{-1} (–NH str.).

Satisfactory analysis for C and H were obtained

Compounds No. 2, 8, 10, 17, 21, 22, 24, 25, 27 afforded 0, 40, 20, 20, 0, 0, 0, 20, 20% protection respectively against pentylenetetrazole-induced seizures in mice where as diazepam afforded 100% protection.

BIO ASSAY

(1) *ALD_{50} and gross behavioural effects*

ALD_{50} was determined following the method of Horn[9]. Different doses of compounds including 1/5th of ALD_{50} were administered i.p. in groups of animals, which were then observed for 6 hr and 24 hr for any effect on gross behaviour[10].

(2) *Anticonvulsant activity*

Anticonvulsant activity was determined by the method of Swinyard *et al*[11]. The compounds were tested against pentylenetetrazole-induced seizures in albino mice of either sex weighing between 15–20 g. Groups of 5 mice, pretreated with 1/5th ALD_{50} dose of compounds i.p. were injected pentylenetetrazole (80 mg/kg) subcutaneously after one hour. Animals were observed for a period of 60 min for the occurrence of clonic convulsions. Animals not exhibiting threshold convulsions during this period of observations were considered protected. The number of animals protected in each group was recorded and the anticonvulsant activity of the compounds expressed in terms of percentage protection.

RESULTS AND DISCUSSION

The approximate LD_{50} values of the compounds ranged from 562 to 1000 mg/kg. The maximum value was exhibited by compounds no. 2, 17 and 22. However, the compounds No. 8, 10, 21, 24, 25, 27 exhibited ALD_{50} (mg/kg) values as 681, 825, 681, 562, 825, 681 respectively. The ALD_{50} value of diazepam was found to be 121 mg/kg.

The depressant feature was common among these compounds with the exception of no. 21. The compounds reduced the rate of respiration in mice and decreased in reactivity to body and limbs. Loss of righting reflux and ataxia were observed in experimental animals. Reactivity towards sound and touch was also decreased. The compounds (vide footnote table 1) exhibited anticonvulsant activity ranging from 20 to 40% which was considerably less than that of diazepam. The compounds having R = 3,4,5-trimethoxy and Ar = 3,4-dimethoxyphenyl showed moderate activity. Compounds having R = *p*-OCH_3 or Cl and Ar = *p*-tolyl, styryl and *p*-methoxy phenyl were inactive. The maximum protection (40%) was exhibited by the compound 8 having R = 3,4,5-trimethoxy and Ar = *p*-N,N-dimethylaminophenyl. It appears therefore, that the presence of 3,4,5-trimethoxyphenyl moiety in these compounds is essential for conferring the anticonvulsant activity on them.

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