Synthesis of 1-(*N*-Acetylpiperidino)-4-aryl Semicarbazides as Possible Anticonvulsants

R. S. Misra (1), C. Dwivedi, S. S. Parmar and S. P. Singh

Department of Physiology, University of North Dakota, School of Medicine, Grand Forks, North Dakota 58202

Received December 19, 1977

Six 1-(*N*-acetylpiperidino)-4-aryl semicarbazides were synthesized from ethyl-*N*-piperidinoacetate which on treatment with hydrazine hydrate was converted into *N*-piperidinoacethydrazide. The resulting hydrazide on treatment with the appropriate arylisocyanates formed 1-(*N*-acetylpiperidino)-4-aryl semicarbazides. Amongst these piperidinosemicarbazides, three compound possessed low anticonvulsant activity and provided 20-40% protection against pentylenetetrazol-induced convulsions in mice. All piperidino semicarbazides (0.1 m*M*) possessed antihemolytic activity (13-35%) and caused 40-72% inhibition of monoamine oxidase activity of rat brain homogenates at a final concentration of 0.3 m*M*.

J. Heterocyclic Chem., 15, 681 (1978)

A series of hydrazine derivatives (2), semicarbazides and thiosemicarbazides (2,3) were found to inhibit monoamine oxidase. Earlier studies have reported synthesis of some thiosemicarbazides which were found to inhibit monoamine oxidase, stabilize red cell membrane and possess anticonvulsant activity (4-8). In the present study, some 1-(*N*-acetylpiperidino)-4-aryl semicarbazides have been synthesized and evaluated for their anticonvulsant, monoamine oxidase inhibitory and membrane stabilizing properties.

Reaction of ethylchloroacetate with piperidine gave ethyl-*N*-piperidinoacetate (9) which on treatment with hydrazine hydrate resulted in the formation of *N*-piperidinoacethydrazide (10). The hydrazide, on reaction with suitable aryl isocyanates yielded the corresponding 1-(*N*-acetylpiperidino)-4-aryl semicarbazides (**1-6**).

These substituted semicarbazides (100 mg./kg., ip) were tested for their anticonvulsant activity against pentylenetetrazol-induced seizures in albino mice (4). Only three compounds, 1-(*N*-acetylpiperidino)-4-(2-methylphenyl) semicarbazide (**4**), 1-(*N*-acetylpiperidino)-4-(4-methylphenyl) semicarbazide (**6**) and 1-(*N*-acetylpiperidino)-4-(3-chlorophenyl) semicarbazide (**3**) exhibited anticonvulsant activity and the degree of protection ranged from 20-40%. Maximum protection was observed with **3**. All piperidino semicarbazides inhibited oxidative deamination of kynuramine at a final concentration of 0.3 m*M* using rat brain homogenate as the source of monoamine oxidase. The degree of inhibition of monoamine oxidase ranged from 38-72% where maximum inhibition was afforded by 1-(*N*-acetylpiperidino)-4-(4-methylphenyl) semicarbazide (**6**). These compounds were also tested for their membrane stabilizing property and showed protection against hypoosmotic hemolysis of red blood cells of dogs at a final concentration of 0.1 m*M*. The minimum protection of 13% and the maximum protection of 35% was observed with 1-(*N*-acetylpiperidino)-4-(2-chlorophenyl) semicarbazide (**2**) and 1-(*N*-acetylpiperidino)-4-(4-methylphenyl) semicarbazides (**6**), respectively. The ED_{50} values for antihemolytic activity of these piperidino semicarbazides ranged from 0.19-0.38 m*M*.

EXPERIMENTAL

All piperidino semicarbazides were analyzed for their carbon, hydrogen and nitrogen contents. Melting points were taken in open capillary tubes with an immersion thermometer and are corrected. The infra red spectra of these semicarbazides showed characteristic bands for -C=O ($\sim$ 1690 cm^{-1}) and -NH ($\sim$ 3250 cm^{-1}).

Ethyl-*N*-piperidinoacetate.

A solution of ethylchloroacetate (0.15 mole) in 100 ml. of dry benzene was added slowly to a solution of piperidine (0.3 mole) in 150 ml. of dry benzene with constant stirring. After the addition of ethylchloroacetate, the reaction mixture was refluxed for 1 hour on a steam bath. The resulting mixture was filtered and the precipitate was washed several times with dry ether. The filtrate on concentration under reduced pressure yielded ethyl-*N*-piperdinoacetate which was distilled at 215°. Its hydrochloride melted at 130° (reported m.p. 130-131°) (9).

N-Piperidinoacethydrazide.

A solution of ethyl-*N*-piperidinoacetate (0.1 mole) and hydrazine hydrate (0.2 mole; 99-100%) in 100 ml. of absolute ethanol was refluxed on a steam bath for 8 hours. The reaction mixture was distilled under reduced pressure and the fraction boiling at 180°/25 mm was collected, (reported b.p. 130°/2 mm) (10). This compound on crystallization with cyclohexane melted at 38-40°.

1-(*N*-Acetylpiperidino)-4-aryl semicarbazides **1-6**.

Equimolar quantities of *N*-piperidinoacethydrazide (0.005 mole) and the appropriate arylisocyanates (0.005 mole) in 20 ml. of dry benzene were refluxed on a steam bath for 2 hours. Excess of benzene was removed by distillation under reduced pressure and the solid mass thus obtained was filtered, washed with ether and recrystallized from ethanol. The physical constants of piperidino semicarbazides are recorded in Table I.

Anticonvulsant activity.

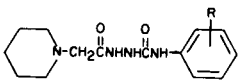
The anticonvulsant activity of piperidino semicarbazides was determined in albino mice (4). All compounds were injected intraperitoneally at a dose of 100 mg./kg. to evaluate their ability to provide protection against convulsions induced by the subcutaneous administration of pentylenetetrazol (90 mg./kg.).

Monoamine oxidase activity.

Monoamine oxidase activity of rat brain homogenate was determined by spectrophotofluorometric method as described earlier

Table I

1-(*N*-Acetylpiperidino)-4-aryl Semicarbazides



Compound No.	R	M.p. °C	Yield %	Molecular Formula	Analysis % Calcd. C	H	N	Found C	H	N
1	H	151	76	$C_{14}H_{20}N_4O_2$	60.87	7.25	20.29	61.06	7.14	20.46
2	2-Cl	165	58	$C_{14}H_{19}ClN_4O_2$	54.10	6.12	18.02	53.90	6.24	17.82
3	3-Cl	188	65	$C_{14}H_{19}ClN_4O_2$	54.10	6.12	18.02	54.38	6.04	18.20
4	2-CH_3	125	56	$C_{15}H_{22}N_4O_2$	62.07	7.58	19.31	62.36	7.42	19.46
5	3-CH_3	166	70	$C_{15}H_{22}N_4O_2$	62.07	7.58	19.31	61.86	7.64	19.20
6	4-CH_3	155	82	$C_{15}H_{22}N_4O_2$	62.07	7.58	19.31	62.29	7.36	19.52

(4) using kynuramine as the substrate. Various piperidino semicarbazides were used at a final concentration of 0.3 m*M*.

Hypoosmotic hemolysis.

The earlier reported procedure was used for the assay of hypoosmotic hemolysis using fresh blood of healthy dogs. The antihemolytic property of piperidino semicarbazides was determined at a final concentration of 0.1 m*M*.

Acknowledgment.

This investigation was supported in part by the United States Public Health Service Grant 7-R01-DA01893-01 and NIH Grant 5 T01 HL-05930-03. Grateful acknowledgment is made to the Northwest Area Foundation, Saint Paul, Minnesota for providing a Hill Professorship to S. S. Parmar.

REFERENCES AND NOTES

(1) Present address: Bio-organic Laboratory, Michigan Cancer Foundation, Meyer L. Prentis Cancer Center, Detroit, Michigan 48201.

(2) J. H. Biel, A. Horita and A. E. Drukker, "Psychopharmacological Agents", Vol. I, M. Gordon, Ed., Academic Press, New York, N. Y., 1960, p. 359 and 414.

(3) L. A. Carter, *J. Med. Chem.*, **10**, 925 (1967).

(4) C. Dwivedi, R. D. Harbison, B. Ali and S. S. Parmar, *J. Pharm. Sci.*, **63**, 1124 (1974).

(5) B. Ali, R. Kumar, S. S. Parmar, C. Dwivedi and R. D. Harbison, *ibid.*, **64**, 1329 (1975).

(6) S. P. Singh, R. S. Misra, S. S. Parmar and S. J. Brumleve, *ibid.*, **64**, 1245 (1975).

(7) S. P. Singh, B. Ali, T. K. Auyong, S. S. Parmar and B. DeBoer, *ibid.*, **65**, 391 (1976).

(8) A. Chaudhari, S. Kumar, S. P. Singh, S. S. Parmar and V. I. Stenberg, *ibid.*, **65**, 758 (1976).

(9) W. V. Drake and S. M. McElvain, *J. Am. Chem. Soc.*, **56**, 697 (1934).

(10) M. Pesson and M. S. Dupin, *Bull. Soc. Chim. (France)*, 250 (1962).