Formation of Thiazoles, Thiazines, and Thiadiazines from 1-Phthalazine Thiosemicarbazides as Potential Anticonvulsants

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Abstract □ 3-Substituted-4-oxothiazolin-2-yl-(1-phthalazinyl)hydrazones, 3-substituted-4-oxo-5,6-dihydro-1,3-thiazin-2-yl-(1-phthalazinyl)hydrazones, and 2-substituted-amino-5-oxo-4-(1-phthalazinyl)-6-hydro-1,3,4-thiadiazines were prepared and tested for their anticonvulsant activity. Some compounds showed weak to moderate anticonvulsant activity.

Keyphrases □ Anticonvulsants, potential—thiazoles, thiazines, and thiadiazines formed from 1-phthalazine thiosemicarbazides, synthesis and evaluation for activity □ Thiazoles—synthesis from 1-phthalazine thiosemicarbazides, evaluation for anticonvulsant activity □ Thiazines—synthesis from 1-phthalazine thiosemicarbazides, evaluation for anticonvulsant activity □ Thiadiazines—synthesis from 1-phthalazine thiosemicarbazides, evaluation for anticonvulsant activity

Various pharmacological properties have been shown to be associated with thiazolidone derivatives. These properties include anticonvulsant (1–4), anesthetic (5), and hypnotic (6) activities. Anticonvulsant activity also has been reported for compounds having a hydrazino or hydrazine moiety (1, 7). These observations prompted the synthesis of 3-substituted-4-oxothiazolin-2-yl-(1-phthalazinyl)hydrazones (II and III), 3-substituted-4-oxo-5,6-dihydro-1,3-thiazin-2-yl-(1-phthalazinyl)hydrazones (IV), and 2-substituted-amino-5-oxo-4-(1-phthalazinyl)-6-hydro-1,3,4-thiadiazines (V) for evaluation of their anticonvulsant activity.

EXPERIMENTAL[1]

The synthetic routes are illustrated in Scheme I.

4-Substituted-1-(1-phthalazinyl)thiosemicarbazides (I)—A solution of the appropriate isothiocyanate (0.01 mole) in ethanol (10 ml) was mixed with a solution of 1-hydrazinophthalazine hydrochloride (0.01 mole) and sodium bicarbonate (1.1 g) in ethanol (10 ml). The mixture was refluxed for 30 min, treated with sufficient hot water to dissolve the inorganic salts, and set aside overnight, after which the thiosemicarbazide was separated as crystals.

3-Substituted -4- oxothiazolin-2-yl-(1-phthalazinyl)hydrazones (II)—*Method A*—A solution of I (0.01 mole) and ethyl bromoacetate (0.01 mole) in ethanol (25 ml) was refluxed for 2 hr. The solvent was removed under reduced pressure, and the residue was dissolved in water and neutralized with sodium carbonate solution. The crude product obtained was recrystallized from the proper solvent.

Method B—To a mixture of sodium ethoxide (0.01 mole) and I (0.01 mole) in absolute ethanol (25 ml) was added dropwise, with stirring, ethyl bromoacetate (0.01 mole) in absolute ethanol (5 ml). The reaction mixture was refluxed for 1 hr and concentrated. The crude product obtained was purified by recrystallization from the proper solvent.

Compounds obtained by this method were identical with those prepared following Method A as confirmed by their melting points, mixed melting points, IR spectra, and TLC analysis (Table I).

3 - Substituted-4-oxo-5-methylthiazolin-2-yl-(1-phthalazinyl)-hydrazones (III)—This series of compounds was prepared following Method A, using ethyl 2-bromopropionate in place of ethyl bromoacetate (Table I).

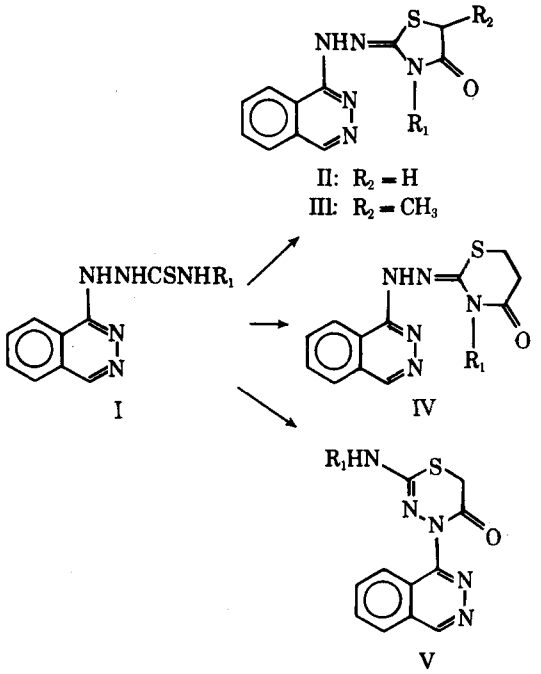
3-Substituted-4-oxo-5,6-dihydro -1,3- thiazin-2-yl-(1-phthalazinyl)hydrazones (IV)—A solution of I (0.01 mole) and ethyl 3-bromopropionate (0.01 mole) in ethanol (25 ml) was refluxed for 2 hr and then concentrated and allowed to crystallize. The crude crystals were purified by recrystallization from the appropriate solvent (Table II).

2-Substituted-amino-5-oxo -4- (1-phthalazinyl)-6-hydro-1,3,4-thiadiazines (V)—A mixture of I (0.01 mole) and ethyl bromoacetate (0.01 mole) in concentrated hydrochloric acid (25 ml) was refluxed for 1 hr. The precipitate formed after cooling was filtered and recrystallized from absolute ethanol–ether (Table III).

RESULTS AND DISCUSSION

Chemistry—The synthesis of some 4-substituted-1-(1-phthalazinyl)thiosemicarbazides (I) was reported previously. It was accomplished through the reaction between hydralazine and the appropriate isothiocyanate in ethanol.

Cyclization of thiosemicarbazides with α-halo carbonyl compounds was a subject of controversy. It was reported (9) that condensation of a thiosemicarbazide with an α-halo carbonyl compound may result in the formation of one or more five- or six-membered heterocyclic isomers. The hydrogen-ion concentration of the medium, the type of substituent present, and temperature favor the formation of specific structural isomers (10). Cyclization of a thiosemicarbazide with phenacyl bromide (11) or chloroacetone (9) might produce a thiazole, a thiazoline, or a thiadiazine. With phenacyl bromide, the stable ring was the thiadiazine, while with chloroacetone, the thiazoline was more stable (12). On the other hand, thiosemicarbazides in the presence of sodium ethoxide reacted with



Scheme I

[1] Melting points were determined in open glass capillaries and are uncorrected. IR spectra were taken as Nujol mulls with a Beckman IR 4210 spectrophotometer. Microanalyses were performed at the Microanalytical Unit, Faculty of Science, University of Cairo, Cairo, Egypt.

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Table I—3-Substituted-4-oxothiazolin-2-yl-(1-phthalazinyl)hydrazones

Compound	R_1	R_2	Yield, %	Melting Point	Formula[a]	Analysis, % Calc.	Found
IIa	C_2H_5	H	65	273–275°	$C_{13}H_{13}N_5OS$	C 54.4	54.6
						H 4.5	4.4
						N 24.4	24.2
IIb	CH_2=$CHCH_2$	H	62	270–271°	$C_{14}H_{13}N_5OS$	C 56.2	56.6
						H 4.4	4.4
						N 23.4	23.2
IIc	$CH_3(CH_2)_3$	H	70	273–274°	$C_{15}H_{17}N_5OS$	C 57.1	57.4
						H 5.4	5.5
						N 22.2	22.6
IId	C_6H_{11}	H	72	128–130°	$C_{17}H_{19}N_5OS$	C 59.8	60.0
						H 5.6	5.8
						N 20.5	20.8
IIe	C_6H_5	H	68	195–197°	$C_{17}H_{13}N_5OS$	N 20.9	20.5
IIf	$C_6H_5CH_2$	H	76	132–133°	$C_{18}H_{15}N_5OS$	C 61.9	62.1
						H 4.3	4.5
						N 20.1	20.5
IIIa	C_2H_5	CH_3	66	150–151°	$C_{14}H_{15}N_5OS$	C 55.8	56.0
						H 5.0	5.0
						N 23.3	23.5
IIIb	CH_2=$CHCH_2$	CH_3	60	130–131°	$C_{15}H_{15}N_5OS$	C 57.5	57.2
						H 4.8	5.0
						N 22.4	22.5
IIId	C_6H_{11}	CH_3	78	222–224°	$C_{18}H_{21}N_5OS$	C 60.8	60.5
						H 5.9	6.3
						N 19.7	19.9
IIIe	C_6H_5	CH_3	72	230–232°	$C_{18}H_{15}N_5OS$	C 61.9	62.2
						H 4.3	4.5
						N 20.1	20.3
IIIf	$C_6H_5CH_2$	CH_3	80	147–149°	$C_{19}H_{17}N_5OS$	C 62.8	62.5
						H 4.7	4.9
						N 19.3	19.6

[a] The IR spectra of these compounds showed a carbonyl band at 1670–1740 cm^{-1} and an NH group at 3200–3400 cm^{-1}.

Table II—3-Substituted-4-oxo-5,6-dihydro-1,3-thiazin-2-yl-(1-phthalazinyl)hydrazones

Compound	R_1	Yield, %	Melting Point	Formula[a]	Analysis, % Calc.	Found
IVa	C_2H_5	72	>260°	$C_{14}H_{15}N_5OS$	C 55.8	55.6
					H 5.0	4.8
					N 23.3	23.1
IVb	CH_2=$CHCH_2$	70	197–198°	$C_{15}H_{15}N_5OS$	C 57.5	57.3
					H 4.8	4.9
					N 22.4	22.8
IVc	$CH_3(CH_2)_3$	74	170–172°	$C_{16}H_{19}N_5OS$	C 58.4	58.1
					H 5.8	6.1
					N 21.3	21.6
IVd	C_6H_{11}	78	207–208°	$C_{18}H_{21}N_5OS$	C 60.8	61.2
					H 5.9	5.5
					N 19.7	20.1
IVe	C_6H_5	68	>265°	$C_{18}H_{15}N_5OS$	C 61.9	61.5
					H 4.3	4.1
					N 20.1	19.9
IVf	$C_6H_5CH_2$	75	166–168°	$C_{19}H_{17}N_5OS$	C 62.8	63.1
					H 4.7	5.0
					N 19.3	19.5

[a] The IR spectra of these compounds showed a carbonyl band at 1630–1750 cm^{-1} and an NH group at 3220–3320 cm^{-1}.

Table III—2-Substituted-amino-5-oxo-4-(1-phthalazinyl)-6-hydro-1,3,4-thiadiazines

Compound	R_1	Yield, %	Melting Point	Formula	Analysis, % Calc.	Found
Va	C_2H_5	60	219–220°	$C_{13}H_{14}ClN_5OS$	C 48.2	48.2
					H 4.3	3.9
					N 21.6	21.3
Vf	$C_6H_5CH_2$	70	262–263°	$C_{18}H_{16}ClN_5OS$	N 18.2	18.4

α-halo acids or esters to give thiazole derivatives (13, 14). Refluxing the formed 2,3-dihydrothiazole derivatives with concentrated hydrochloric acid resulted in the formation of a six-membered ring to give the hydrochloride of 2-amino-5-methyl-1,3,4-thiadiazine (10).

Pharmacology—The anticonvulsant activity of some representative compounds of series II–V was determined (15). Mice of both sexes (15–20 g) were divided into groups of 10, with the group weights kept as near as possible. The test compounds were suspended in aqueous carboxymethylcellulose (1% w/v) and injected intraperitoneally. Four hours after this administration, the mice were injected subcutaneously with 90 mg of pentylenetetrazol/kg. This dose produced convulsions in all untreated mice during the 1st hr following injection and caused 70% mortality during the 24-hr period.

The occurrence of seizures was observed for 60 min. An episode of

Table IV—Anticonvulsant Activity of Thiazole, Thiazine, and Thiadiazine Derivatives of 1-Phthalazine

Compound	Anticonvulsant Activity, % protection[a]	Pentylenetetrazol, % mortality[b]
IId[c]	70	20
IIf	20	50
IIIa	10	90
IIIf	40	50
IVa	30	60
IVb[c]	0	100
IVd	20	70
IVe	30	50
IVf[c]	10	90
Va	50	30

[a] Anticonvulsant activity was determined at doses of 1.0 mmole/kg, equivalent to 200 mg of meprobamate/kg, as described under *Experimental*. Meprobamate (200 mg/kg) and phenobarbital sodium (80 mg/kg) were used as standard anticonvulsants; they exerted 90–100 and 100% protection, respectively, against pentylenetetrazol-induced convulsions in mice under similar conditions. [b] Represents mortality over 24 hr in each group of animals administered pentylenetetrazol at 90 mg/kg. [c] Compounds IId, IVb, and IVf were used in doses equivalent to 50 mg of meprobamate/kg. Their corresponding LD_{50} ($\pm SD$) values were 135 ± 19, 202 ± 7, and 137 ± 12 mg/kg, respectively.

clonic spasm that persisted for a minimum of 5 sec after administration of pentylenetetrazol was considered a threshold convulsion. Transient intermittent jerks and tremors were not counted. Animals devoid of threshold convulsions over 60 min were considered protected. The number of animals protected in each group was recorded, and the anticonvulsant activity of the test compounds was represented as percent protection. The mice then were observed for 24 hr, and the mortality rate in each group was recorded (Table IV). The LD_{50} of some compounds was determined by the graphical method of Miller and Tainter (16).

The data presented in Table IV show that the compounds possess weak to moderate anticonvulsant activity and that the doses required for demonstration of anticonvulsant activity are very close to their corresponding toxic doses.

REFERENCES

(1) A. K. Dimri and S. S. Parmar, *J. Heterocycl. Chem.*, **15,** 335 (1978).

(2) H. D. Troutman and L. M. Long, *J. Am. Chem. Soc.*, **70,** 3436 (1948).

(3) C. Dwinedi, T. K. Gupta, and S. S. Parmar, *J. Med. Chem.*, **15,** 553 (1972).

(4) S. P. Singh, B. Ali, T. K. Auyong, S. S. Parmar, and B. DeBoer, *J. Pharm. Sci.*, **65,** 391 (1976).

(5) A. R. Surrey, *J. Am. Chem. Soc.*, **71,** 3354 (1949).

(6) W. J. Doran and H. A. Shonle, *J. Org. Chem.*, **3,** 193 (1938).

(7) S. P. Singh, T. K. Auyong, and S. S. Parmar, *J. Pharm. Sci.*, **63,** 960 (1974).

(8) A. I. El-Sebai, M. Ragab, R. Soliman, and M. Gabr, *Pharmazie*, **31,** 436 (1976).

(9) R. C. Elderfield, "Heterocyclic Compounds," vol. 7, Wiley, New York, N.Y., 1961, p. 826.

(10) E. Campaigne and T. P. Selby, *J. Heterocycl. Chem.*, **15,** 401 (1978).

(11) P. K. Bose, *Q. J. Indian Chem. Soc.*, **1,** 51 (1924). *Ibid.*, **2,** 95 (1925).

(12) H. Beyer, *Q. Rep. Sulfur Chem.*, **1970,** 177.

(13) F. J. Wilson and R. Burns, *J. Chem. Soc.*, **1922,** 870.

(14) J. Melean and F. J. Wilson, *ibid.*, **1937,** 556.

(15) A. K. Chaturvedi, J. P. Barthwal, S. S. Parmar, and V. I. Stenberg, *J. Pharm. Sci.*, **64,** 454 (1975).

(16) L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.*, **57,** 261 (1944).

Quantitative Determination of Pilocarpine, Isopilocarpine, Pilocarpic Acid, and Isopilocarpic Acid in Clinical Ophthalmic Pilocarpine Formulations by Reversed-Phase Liquid Chromatography

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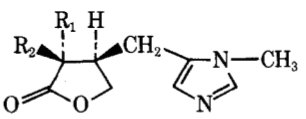
Abstract □ A rapid and convenient reversed-phase high-performance liquid chromatographic procedure for the quantitative determination of pilocarpine and its degradation products was used to analyze 10 clinical ophthalmic pilocarpine formulations.

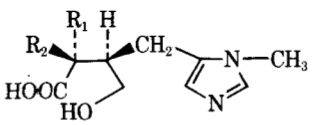
Keyphrases □ Pilocarpine—reversed-phase high-performance liquid chromatographic analysis with isopilocarpine, pilocarpic acid, and isopilocarpic acid in ophthalmic pilocarpine formulations □ High-performance liquid chromatography, reversed phase—analysis, pilocarpine, isopilocarpine, pilocarpic acid, and isopilocarpic acid in ophthalmic pilocarpine formulations

(+)-Pilocarpine {(2*S*,3*R*)-2-ethyl-3-[(1-methyl-5-imidazolyl)methyl]-4-butanolide} is an imidazole alkaloid for which a stereoselective synthesis was reported recently (1). It is used frequently in ophthalmology to relieve intraocular pressure, specifically glaucoma. For this purpose, buffered, stabilized, isotonic aqueous solutions of pilocarpine hydrochloride or nitrate usually are used (2).

In an aqueous medium, pilocarpine (I) can hydrolyze to



I: R_1 = H, R_2 = C_2H_5
II: R_1 = C_2H_5, R_2 = H



III: R_1 = H, R_2 = C_2H_5
IV: R_1 = C_2H_5, R_2 = H

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