of the dissolution medium and the bottom of the vessel, filtered through 0.45-μm membrane, and assayed spectrophotometrically. The volume of the dissolution medium was maintained at 1000 mL by the addition of the appropriate medium and cumulative corrections were made for the previously removed samples in determining the total amount of drug in solution. The results of all the dissolution studies, which were run in duplicate, are shown in Table II.

RESULTS AND DISCUSSION

The data in Table II clearly show the more rapid presence of I, II, or III in either dissolution medium when the corticoid solutions were dispersed on the five silicas used. As a micronized powder, II (samples 19 and 20) dissolved very slowly in either GI medium; after 20 min <60% had dissolved. However, when a solution of II was dispersed on IV, V, or VI, >70% of II was in solution within 5 min (samples 21, 22, and 23) in simulated gastric juice. In simulated intestinal juice, the rate was not as large; within 10 min >68.5% of II had dissolved (samples 26, 27, and 28).

Silicas IV, V, and VI were consistently more efficient in releasing the drug solutions dispersed on them than were VII and VIII. When silicas VII and VIII were used with a solution of II <100% of II had dissolved in the simulated GI media after 120 min (samples 24, 25, 29, and 30).

A comparison of solvent-deposited I with its silica-dispersed solution is also of interest. In every instance the silica-dispersed solutions were superior (samples 3 *versus* 13, 4 *versus* 14, 5 *versus* 15; 8 *versus* 16, 9 *versus* 17, and 10 *versus* 20). Ball-milled samples were not prepared. However, Yang *et al.* (3) reported that after ball-milling prednisone with a 20-fold excess of IV, V, or VI, a maximum of 65% of II had dissolved after 120 min in simulated GI media. Their dissolution studies were conducted at 100 rpm. Narurkar and Jarowski (5) also reported similar slow dissolution rates for I that had been ball-milled with various ratios of IV, V, VI, or VII. When solutions of I or II were dispersed on IV, V, VI, VII, or VIII and their dissolution rates studied at 100 rpm, all but one sample released 83–99% within 120 min. The exception was a solution of II dispersed on VI; only 60% had dissolved in simulated intestinal fluid after 120 min.

Such reduction in dissolution rate resulting from reduced basket speed is of concern since the anticipated superiority in the *in vivo* performance of silica-dispersed solutions over micronized powders is suspect. A preliminary *in vivo* experiment with salicylamide indicates that more rapid oral absorption does occur when the compound is dissolved and dispersed on silica. This data will be published elsewhere.

REFERENCES

(1) "The United States Pharmacopeia," 19th rev., U.S. Pharmacopeial Convention, Rockville, Md., 1975, pp. 398, 404.

(2) T. H. Nguyen, Master's Thesis, St. John's University (1978).

(3) K. Y. Yang, R. Glemza, and C. I. Jarowski, *J. Pharm. Sci.*, **68**, 560 (1979).

(4) "The United States Pharmacopeia," 19th rev., U.S. Pharmacopeial Convention, Rockville, Md., 1975, p. 765.

(5) A. N. Narurkar, Doctoral Thesis, St. John's University (1979).

Synthesis of New 8-(5-Substituted Amino-1,3,4-oxadiazol-2-yl) and 8-(5-Substituted Amino-1,3,4-thiadiazol-2-yl) Methoxyquinolines with Antibilharzial Activity

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Received November 8, 1982, from the **Department of Pharmaceutical Chemistry, Faculty of Pharmacy* and the ‡*Department of Chemistry, Faculty of Science, University of Alexandria, Alexandria, Egypt.* Accepted for publication February 1, 1983. §Present address: College of Pharmacy, University of Florida, J. Hillis Miller Health Center, Gainesville, FL 32610.

Abstract □ Several 5-substituted amino-1,3,4-oxadiazol-2-yl and 5-substituted amino-1,3,4-thiadiazol-2-yl derivatives with different 8-hydroxyquinoline moieties in the 2-position were prepared and tested for their antiparasitic activity. Preliminary biological tests on mice experimentally infested with *Schistosoma mansoni* revealed that the new compounds show moderate schistosomicidal activity.

Keyphrases □ 8-(5-Substituted amino-1,3,4-oxadiazol-2-yl) methoxyquinolines—synthesis, antibilharzial activity against *Schistosoma mansoni* □ 8-(5-Substituted amino-1,3,4-thiadiazol-2-yl) methoxyquinolines—synthesis, antibilharzial activity against *Schistosoma mansoni* □ Antischistosomal agents—synthesis of 8-(5-substituted amino-1,3,4-oxadiazol-2-yl) and 8-(5-substituted amino-1,3,4-thiadiazol-2-yl) methoxyquinolines

The fact that lucanthone (1) and its active metabolite hycanthone (2) were the first metal-free compounds to show clinical activity against bilharziasis initiated the synthesis of a distantly related compound 6-chloro-5-(2-diethylaminoethylamino)-8-methylquinoline. The latter exhibited outstanding activity against experimental schistosomiasis (3, 4). Unfortunately, preclinical toxicity studies indicated wide differences among various species of laboratory animals, precluding early clinical trials of this compound (3). A new entry in bilharzial chemotherapy is 1,2,3,4-tetrahydro-2-[[(1-methylethyl)amino]methyl]-7-nitro-6-quinolinemethanol (oxamniquine). It has potent schistosomicidal activity against *Schistosoma mansoni* by causing worms to shift from the mesenteric veins to the liver, where they are destroyed (5).

In our previous work (6) several 3-mercaptotriazoles with the 8-hydroxyquinoline moiety were prepared by cyclization of their corresponding substituted thiosemicarbazides by the action of hot sodium hydroxide solution. Preliminary biological tests revealed that those mercaptotriazoles showed potent schistosomicidal activity. These observations prompted the synthesis of several 5-substituted amino-1,3,4-oxadiazol-2-yl and 5-substituted amino-1,3,4-thiadiazol-2-yl derivatives with different 8-hydroxyquinoline moieties in the 2-position. Contrary to the mercaptotriazoles, the incorporation of the potent antiparasitic drug iodochlorhydroxyquinoline in the 2-oxadiazole or 2-thiadiazole rings produced compounds with moderate or low schistosomicidal activity.

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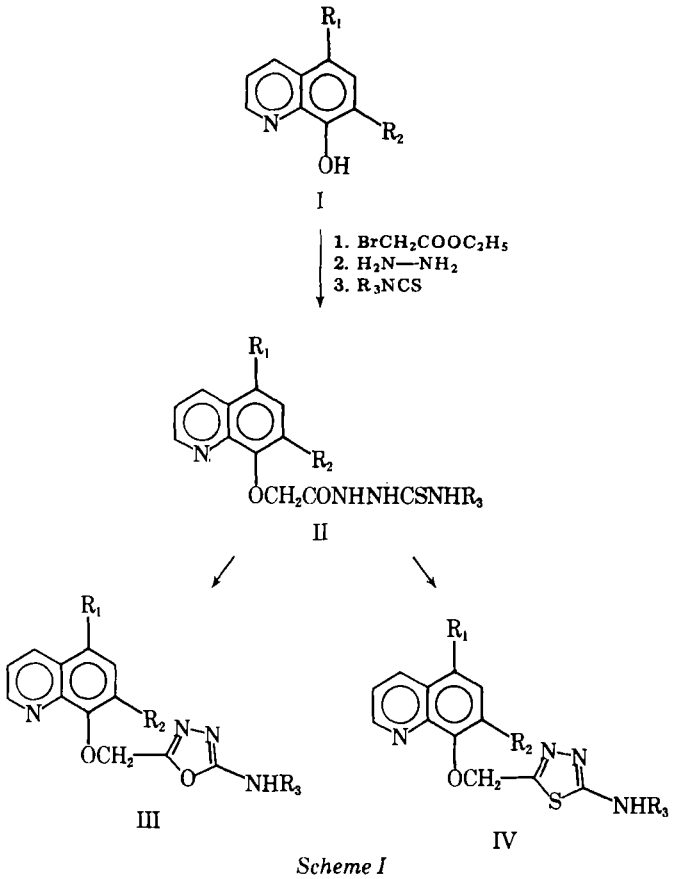

Scheme I

EXPERIMENTAL[1]

The various 1,3,4-oxadiazoles and 1,3,4-thiadiazoles were synthesized by reactions outlined in Scheme I. Conversion of the 8-hydroxyquinoline derivative (I) to the 8-quinolinoxyacetic acid hydrazide was effected by treating the corresponding ethyl ester with 99–100% hydrazine hydrate.

Substituted thiosemicarbazides (II), prepared by the reaction of 8-quinolinoxyacetic acid hydrazide with the appropriate isothiocyanate, were cyclized to the corresponding 8-(5-substituted amino-1,3,4-oxadiazol-2-yl)methoxyquinoline (III) in 4 M NaOH and 5% iodine in potassium iodide solution, and to the corresponding 8-(5-substituted amino-1,3,4-thiadiazol-2-yl)methoxyquinoline (IV) by the action of cold concentrated sulfuric acid (7). All compounds were characterized by their melting points, elemental analysis, and IR and ^{1}H-NMR spectra.

1-(8-Quinolinoxyacetyl)-4-substituted Thiosemicarbazides (II)—Series II compounds were prepared as mentioned previously (6), by refluxing equimolar quantities of 8-quinolinoxyacetic acid hydrazides with the appropriate isothiocyanate in dry benzene.

8-(5-Substituted Amino-1,3,4-oxadiazol-2-yl) Methoxyquinolines (III)—To a suspension of the appropriate 1-(8-quinolinoxyacetyl)-4-substituted thiosemicarbazide (II, 0.01 mol) in water (10 mL) was added a cold solution of sodium hydroxide (4 M, 5 mL) with stirring. When a clear solution was obtained, iodine in potassium iodide solution (5%) was then added in a dropwise manner with stirring until the color of iodine persisted at room temperature. Thereafter, the reaction mixture was heated at reflux on a boiling-water bath, and more iodine solution was carefully added until a permanent tinge of excess iodine remained. After cooling the mixture was poured into ice-cold water, and the precipitated solid was removed by filtration, washed with a dilute solution of sodium thiosulfate and then washed with water, dried, and crystallized from a suitable solvent (Table I).

IIId—^{1}H-NMR ($CDCl_3$): δ 7.2–8.9 (m, ArH), 5.2 (s, 2, OCH_2), and 4.5 ppm (d, N*H*-Ar).

[1] Melting points were determined in open glass capillaries and are uncorrected. IR spectra were determined as Nujol mulls with Beckman IR-4210; ^{1}H-NMR spectra were recorded on a Varian EM-360 60-Hz NMR spectrophotometer in $CDCl_3$ with TMS as internal standard. Microanalyses were performed by the Microanalytical Unit, Faculty of Science, University of Cairo, Cairo, Egypt.

Table I—8-(5-Substituted Amino-1,3,4-oxadiazol-2-yl) Methoxyquinolines (III) and 8-(5-Substituted Amino-1,3,4-thiadiazol-2-yl) Methoxyquinolines (IV) [a]

Compound	R_1	R_2	R_3	Yield, %	Melting Point, °C	Formula
IIIa	H	H	$-CH_2CH=CH_2$	65	154	$C_{15}H_{14}N_4O_2$
IIIb	H	H	$-(CH_2)_3CH_3$	70	175	$C_{16}H_{18}N_4O_2$
IIIc	H	H	$-C_6H_{11}$	68	160	$C_{18}H_{20}N_4O_2$
IIId	H	H	$-C_6H_5$	65	219	$C_{18}H_{14}N_4O_2$
IIIe						
IIIf	H	H	$-C_6H_4$-*p*-CH_3	73	218	$C_{19}H_{16}N_4O_2$
IIIg	Cl	I	$-CH_2CH=CH_2$	70	150	$C_{15}H_{12}ClIN_4O_2$
IIIh	Cl	I	$-(CH_2)_3CH_3$	66	135	$C_{16}H_{16}ClIN_4O_2$
IIIi	Cl	I	$-C_6H_{11}$	70	150	$C_{18}H_{18}ClIN_4O_2$
IIIj	Cl	I	$-C_6H_5$	68	120	$C_{18}H_{12}ClIN_4O_2$
IIIk	Cl	I	$-CH_2C_6H_5$	72	156	$C_{19}H_{14}ClIN_4O_2$
IIIl	Cl	I	$-C_6H_4$-*p*-CH_3	75	170	$C_{19}H_{14}ClIN_4O_2$
IVa	H	H	$-CH_2CH=CH_2$	70	250	$C_{15}H_{14}N_4OS$
IVb	H	H	$-(CH_2)_3CH_3$	68	160	$C_{16}H_{18}N_4OS$
IVc	H	H	$-C_6H_{11}$	73	200	$C_{18}H_{20}N_4OS$
IVd	H	H	$-C_6H_5$	65	225	$C_{18}H_{14}N_4OS$
IVe	H	H	$-CH_2C_6H_5$	66	195	$C_{19}H_{16}N_4OS$
IVf	H	H	$-C_6H_4$-*p*-CH_3	70	208	$C_{19}H_{16}N_4OS$
IVg	Cl	I	$-CH_2CH=CH_2$	65	140	$C_{15}H_{12}ClIN_4OS$
IVh	Cl	I	$-(CH_2)_3CH_3$	70	127	$C_{16}H_{16}ClIN_4OS$
IVi	Cl	I	$-C_6H_{11}$	74	132	$C_{18}H_{18}ClIN_4OS$
IVj	Cl	I	$-C_6H_5$	67	136	$C_{18}H_{12}ClIN_4OS$
IVk	Cl	I	$-CH_2C_6H_5$	70	130	$C_{19}H_{14}ClIN_4OS$
IVl	Cl	I	$-C_6H_4$-*p*-CH_3	72	160	$C_{19}H_{14}ClIN_4OS$

[a] All compounds were recrystallized from ethanol and showed absorption in the IR range at 3200–3095 cm^{-1} (NH). Elemental analyses (C, H, N, and S for all compounds, I for compounds with R_2 = I) were within ±0.4% from theoretical for all of the methoxyquinolines.

IIIh—^{1}H-NMR ($CDCl_3$): δ 7.0–8.2 (m, ArH), 5.2 (s, 2, OCH_2), 4.1 (t, 2, N—CH_2), 1.8 (m, CH_2), 1.4 (m, CH_2), and 1.0 ppm (t, CH_3).

8-(5-Substituted Amino-1,3,4-thiadiazol-2-yl) Methoxyquinolines (IV)—1-(8-Quinolinoxyacetyl)-4-substituted thiosemicarbazide (II, 0.01 mol) was added in small portions to concentrated sulfuric acid (25 mL) with stirring, maintaining the temperature below 0°C during addition for 1 h. The reaction mixture was allowed to stand at room temperature overnight and then warmed to 50°C. It was then cooled and poured onto crushed ice. The solid product was removed by filtration, washed with water, treated with dilute ammonia to remove any sulfonated product, again washed with water, dried, and crystallized from a suitable solvent (Table I). ^{1}H-NMR ($CDCl_3$) for IVf: δ 7.1–9.0 (m, ArH), 5.7 (s, 2, OCH_2), 5.1 (d, N*H*-Ar), and 2.3 ppm (s, Ar-C*H*$_3$).

Antibilharzial Activity—Swiss albino mice were inoculated with 100 cercariae of *S. mansoni* by the tail immersion technique (8). Eight weeks after infestation, the animals were divided into seven groups: an untreated control group, a group for each of the new drugs to be tested (IIId, IIIh, IVf, IVh, and IVj), and hycanthone as a positive control group. The drugs were given orally as a single 100-mg/kg dose in suspension of 1% carboxymethylcellulose. Hycanthone was given as a single injection, 70 mg/kg im in 0.1 mL of distilled water. Oogram studies of the liver and intestine were made every third day on five animals from each group, (3, 6, 9, and 12 d posttreatment). Table II shows the average oogram pattern in the liver and small intestine during the period of maximum drug effect (9 d), which was usually at the end of the first week, compared with hycanthone (9).

RESULTS AND DISCUSSION

The efficiency of a new antischistosomal drug was assessed in experimentally infested mice by the oogram changes, which were said to be caused by loss of schistosoma worm muscle tone, during action on the parasite reproductive organs, and death of the worms (10). Deviation of the oogram picture from normal was considered to be an absence of any immature stages or when the number of mature ova exceeded 50% (10). Results obtained showed small deviation of the oogram picture from normal. Compounds IVf, IVh, and IVj showed moderate activity, while the others showed only mild activity.

Table II—Oogram Findings in Liver and Small Intestine of Infested Mice 9 d After Treatment with Experimental Compounds

Compound	Liver				Small Intestine			
	Mean Eggs/ Mouse (Range)	Total Immature Eggs, %	Mature Eggs, %	Dead Eggs %	Mean Eggs/ Mouse (Range)	Total Immature Eggs, %	Mature Eggs, %	Dead Eggs, %
Control	25–30	76	18	6	27–31	70	28	2
Hycanthone	23–29	—	—	—	25–30	0	48	52
IIId	26–31	35	30	35	28–32	16	34	50
IIIh	28–30	32	38	30	24–30	20	60	20
IVf	25–30	20	40	40	25–31	2	55	43
IVh	27–32	15	47	38	26–30	13	60	27
IVj	26–30	10	42	48	25–32	2	68	30

REFERENCES

(1) W. Kikuth and R. Connert, *Ann. Trop. Med. Parasitol.*, **42**, 256 (1948).

(2) D. Rosi, G. Peruzzotti, E. W. Dennis, D. A. Berberian, H. Freele, and S. Archer, *Nature (London)*, **208**, 1005 (1965).

(3) N. W. Bristow, B. Lessel, H. C. Richards, and G. A. Williams, *Nature (London)*, **216**, 282 (1967).

(4) J. Pellegrino, N. Katz, and J. F. Scherrer, *J. Parasitol.*, **53**, 1225 (1967).

(5) P. Schmidt and M. Wilhelm, *Angew. Chem. Int. Ed.*, **5**, 857 (1966).

(6) R. Soliman and N. A. Hammouda, *J. Pharm. Sci.*, **68**, 1377 (1979).

(7) S. N. Sawhney, J. Singh, and O. P. Bansal, *Ind. J. Chem.*, **13**, 804 (1975).

(8) J. M. Watson and M. Abdel Azim, *Ann. Trop. Med. Parasitol.*, **43**, 41 (1949).

(9) H. F. Farag, M. Youssef, N. A. Hammouda, and H. N. Awadalla, *Egypt. J. Soc. Parasitol.*, **8**, 1 (1978).

(10) J. Pellegrino, C. A. Oliveira, J. Faria, and A. Cunha, *Am. J. Trop Med. Hyg.*, **11**, 201 (1962).

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Synthesis and Anticonvulsant Evaluation of *N*-Aminosuccinimides

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Abstract □ Twelve new *N*-aminosuccinimides were synthesized by the condensation of hydrazines with succinic anhydrides in glacial acetic acid. The compounds were evaluated in the maximal electroshock seizure and subcutaneous pentylenetetrazol seizure threshold tests for anticonvulsant activity and in the rotorod test for neurotoxicity in mice. The lowest dose at which several of the compounds exhibited anticonvulsant activity was 300 mg/kg.

Keyphrases □ *N*-Aminosuccinimides—synthesis, anticonvulsant and neurotoxic potential, mice □ Anticonvulsants—potential, *N*-aminosuccinimides, synthesis, neurotoxicity, mice

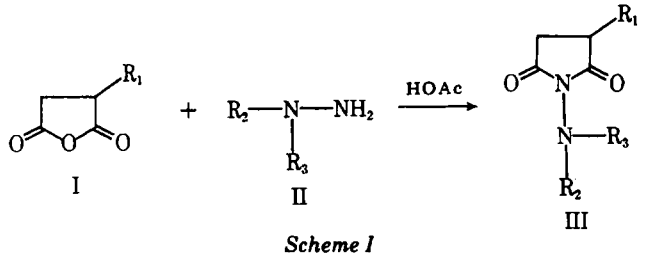
Potential anticonvulsants and hydrazine-derived drugs in general have been a principal interest of ours over several years. Anticonvulsant activity has been found among the 3,5-pyrazolidinediones (1), semicarbazides (2–4), and hydrazino urethans (5, 6). Because of the effectiveness of the succinimides such as phensuximide, methsuximide, and ethosuximide for the treatment of the petit mal condition and the paucity of information (7) concerning *N*-aminosuccinimides, an investigation in this area appeared warranted. A related compound, *N*-amino-3-(*m*-bromophenyl)succinimide, has been shown to possess potent maximal electroshock seizure activity (8). A decrease in spontaneous motor activity by *N*-arylaminosuccinimides has been noted (9).

This paper reports on the synthesis and anticonvulsant activity of a series of *N*-aminosuccinimides. The compounds vary in the nature of the amino nitrogen (alkylated or arylated) and in the α-position of the succinimide ring (unsubstituted, methyl, or phenyl).

RESULTS AND DISCUSSION

The synthesis of the aminosuccinimides (III) was accomplished by treating various succinic anhydrides (I) with substituted hydrazines (II) in glacial acetic acid (Scheme I) (Table I). Others (10) have used a mixture of equal volumes of glacial acetic acid and concentrated sulfuric acid to effect this condensation.

Compounds IIIa–IIIn were tested in the maximal electroshock seizure and subcutaneous pentylenetetrazol seizure threshold tests for anticonvulsant activity and in the rotorod test for neurotoxicity in male mice[1] by reported procedures (2). None of the compounds showed activity at 100 mg/kg in either test. In the maximal electroshock seizure test, IIIc, IIId, IIIf, IIIk, and IIIm exhibited activity at 300 mg/kg at 30 min with no indication of toxicity. One compound, IIIg, showed activity at this same dose at 4 h. In the pentylenetetrazol seizure test, IIIb, IIIl, and IIIm displayed activity at 300 mg/kg at 30 min with no toxicity. Overall, this



Scheme I

[1] No. 1, Carworth Farms.

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