TABLE I

Compd	Test system[a]	Dose, mg/kg	Cures[b]
Amodiaquine	M	40	0
	M	160	3
	M	640	5
1	M	20	0
	M	40	1
	M	80	2
	M	160	4
	M	640	5
	C	80	0
	C	160	0
	C	320	1
2	M	20*	0
	M	40	1
	M	160	4
	M	640	5
	C	80	0
	C	160	0
	C	320	1
3	M	20*	0
	M	40*	0
	M	80	0
	M	160	2
	M	320	2
	M	640	4
	C	80	0
	C	160	0
	C	320	0

[a] Compounds screened against *P. berghei* in mice (M) by Dr. L. Rane; see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). A test system against blood-induced *P. gallinaceum* infection in white Leghorn cockerel chicks (C) has also been employed. Details of this chick screen will appear in a forthcoming publication from Dr. Rane's laboratory. [b] Number of animals out of five surviving to 60 days postinfection in mice or 30 days postinfection in chick. When mean survival time increase is 100% greater than normal survival time of the untreated infected test animals (7.0 ± 0.5 days in mice and 3.5 ± 0.5 days in chickens) the compound is defined as "active." Compounds were all classed as "active" except at those doses designated with an asterisk.

mole of methyl 6-methoxy-7-fluoro-4(1H)-quinolone-2-carboxylate[10] and 140 ml of 10% (w/w) aqueous NaOH solution was refluxed for 1.5 hr, filtered hot, cooled to ice-bath temperatures, and neutralized with 6 *N* HCl. The acid was thoroughly dried *in vacuo*, powdered, and added in small portions to 180 ml of boiling Ph_2O over a 70-min period. The cooled mixture was diluted with 2 l. of 30–60° petroleum ether and filtered to isolate the quinolone. This was converted directly to the corresponding 4-chloro compound by refluxing for 3 hr with 60 ml of $POCl_3$. Excess $POCl_3$ was removed by vacuum distillation and the remaining solution was added cautiously to 500 g of chopped ice. Neutralization (NH_4OH), filtration, and washing (H_2O) gave 20 g (59% based on methyl 6-methoxy-7-fluoro-4(1H)-quinolone-2-carboxylate) of 4-chloro-6-methoxy-7-fluoroquinoline. An analytical sample was prepared by double vacuum sublimation, mp 153–154°. The nmr spectrum (DMSO-d_6) revealed an *o*-F to proton coupling (H_8–F) at δ 7.92 ppm of 12 Hz, and a *m*-F to proton coupling (H_5–F) at 7.61 ppm of 9 Hz clearly ruling out the 5-fluoro-6-methoxy possibility. *Anal.* ($C_{10}H_7ClFNO$) C, N,N.

6-Methoxy-7-chloro-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline (1).—A solution of 5.9 g (0.025 mole) of *p*-acetamido-α-diethylamino-*o*-cresol[4] and 13 ml of 6 *N* HCl was refluxed for 1 hr and then neutralized with 50% NaOH to pH 6. An equimolar quantity of 4,7-dichloro-6-methoxyquinoline[11] and 25 ml of DMF[12] was then added. The mixture was heated at 90° for 24 hr before being cooled and diluted with H_2O. After filtration the solution was made slightly basic with NaOH and the precipitated solid was collected and taken up in $CHCl_3$. The $CHCl_3$ phase was washed (dilute aqueous NaOH, H_2O), dried ($MgSO_4$), and evaporated to dryness. The solid residue was recrystallized from MeOH (charcoal) to yield 4.5 g (47%) of yellow crystals. Several more recrystallizations from MeOH produced analytical material, mp 236–245° dec. *Anal.* ($C_{21}H_{24}ClN_3O_2$) C, H, N.

Compound **2**.—Application of the above procedure to 4-chloro-6-methoxy-7-fluoroquinoline gave the aminoquinoline as a light tan solid in 64% yield. After three recrystallizations from MeOH, analytical material was obtained, dec pt 246–247°, but no formation of a liquid phase up to 315°. *Anal.* ($C_{21}H_{24}FN_3O_2$) C, H, N.

6-Methoxy-7-trifluoromethyl-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline (3).—The amination of 4-chloro-6-methoxy-7-trifluoromethylquinoline as described above gave a 74% yield of the desired aminoquinoline as pale yellow needles, mp 218–224° dec. *Anal.* ($C_{22}H_{24}F_3N_3O_2$) C, H, N.

(10) In ref 7, a mixture of the 6-methoxy-7-fluoro- and the 5-fluoro-6-methoxyquinolinates was prepared. These isomers could not be separated, and a mixture was therefore employed for the synthetic sequence described above. An nmr analysis (*vide infra*) on the final 4-chloroquinoline obtained by the sequence showed that the isolated material was pure 4-chloro-6-methoxy-7-fluoroquinoline.

(11) H. R. Snyder, H. E. Freier, P. Kovacic, and E. M. Van Heyningen, *J. Am. Chem. Soc.*, **69**, 371 (1947).

(12) A larger quantity of DMF or higher reaction temperatures should be avoided because dimethylamination of the 4-Cl can occur under these conditions see: N. D. Heindel and P. D. Kennewell, *Chem. Commun.*, 38 (1969).

Arylglyoxal N,N-Disubstituted Hydrazones with Antiviral and Antifungal Activity

E. MASSARANI, D. NARDI, R. POZZI, AND L. DEGEN

Research Division, Recordati s.a.s., Milan, Italy

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In continuation of our study of aromatic glyoxals as antiviral agents, we prepared a series of N,N-disubstituted hydrazones of *para*-substituted phenylglyoxals. All compounds were subjected to the usual pharmacological screening, as well as to antiviral, antibacterial, and antifungal activity tests. The acute toxicity of the compounds was determined intraperitoneally in mice. The results are listed in Table I.

No activity was observed when the compounds were tested for smooth-muscle relaxing activity and for coronary vasodilator activity. Compounds **3**, **5**, **7**, and **26** showed anticonvulsant activity at doses of $0.2LD_{50}$ in electroshock, intraperitoneally in mice. In tests for antiinflammatory activity on the rat's formalin paw edema, **1**, **2**, **8**, **10**, **13**, **14**, **26**, **29**, **30**, **36**, **37**, **39**, and **41** were active intraperitoneally at 100–200 mg/kg.

All compounds were also tested in embryonated eggs infected with A-PR8 virus and vaccinia virus. Compounds **15** and **39** were active against A-PR8 virus, and **15** was also active against vaccinia virus (Table II).

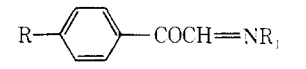
The two active compounds are derivatives of diphenyl, which emphasizes the importance of this supporting moiety for antiviral activity.[1,2]

No compound showed antibacterial activity nor was any active against *Candida albicans*. Some product were active against *Trichophyton mentagrophytes*, gypseum type (2538) (Table III), namely N,N-dimethyl- and N,N-diethylhydrazones of 4-chloro-, 4-nitro-, 4-phenoxy-, and 4-phenylphenglyoxals; among the cyclic

(1) G. Cavallini and E. Massarani, *J. Med. Chem.*, **1**, 365 (1959).
(2) G. Cavallini, *ibid.*, **7**, 255 (1964).

TABLE I

para-SUBSTITUTED PHENYLGLYOXAL N,N-DISUBSTITUTED HYDRAZONES



No.	R	NR_1	Method	Recryst solvent[f]	Mp, °C	Yield, %	Formula	Analyses	LD_{50}, mg/kg ip
1	CH_3	$N(CH_3)_2$	A	E–W	55–57	56	$C_{11}H_{14}N_2O$	C, H, N	350
2	CH_3O	$N(CH_3)_2$	A	L	69–71	78	$C_{11}H_{14}N_2O_2$	C, H, N	560
3	Cl	$N(CH_3)_2$	A	E–W	67–68	82	$C_{10}H_{11}ClN_2O$	C, H, N, Cl	350[i]
4	NO_2	$N(CH_3)_2$	B	E–W	138–140	67	$C_{10}H_{11}N_3O_3$	C, H, N	500[i]
5	C_6H_5O	$N(CH_3)_2$	A	H	47–48	69	$C_{16}H_{16}N_2O_2$	C, H, N	750[i]
6	C_6H_5S	$N(CH_3)_2$	A	H	73–74	70	$C_{16}H_{16}N_2OS$	C, H, N	1300[i]
7	Cl	$N(C_2H_5)_2$	A	P	45–46	29	$C_{12}H_{15}ClN_2O$	C, H, N, Cl	300
8	NO_2	$N(C_2H_5)_2$	A	E–W	89–90	37	$C_{12}H_{15}N_3O_3$	C, H, N	400[i]
9	C_6H_5	$N(C_2H_5)_2$	A	L	44–45	18	$C_{18}H_{20}N_2O$	C, H, N	1300
10	H	N-Pyrrolidino	A	L	71–72	77	$C_{12}H_{14}N_2O$	C, H, N	400
11	CH_3	N-Pyrrolidino	A	L	84–85	88	$C_{13}H_{16}N_2O$	C, H, N	420[i]
12	CH_3O	N-Pyrrolidino	A	E–W	82–83	64	$C_{13}H_{16}N_2O_2$	C, H, N	750[i]
13	Cl	N-Pyrrolidino	A	L	88–89	76	$C_{12}H_{13}ClN_2O$	C, H, N, Cl	500[i]
14	NO_2	N-Pyrrolidino	B	E–W	124–125	51	$C_{12}H_{13}N_3O_3$	C, H, N	500
15	C_6H_5	N-Pyrrolidino	A	E–W	118–119	73	$C_{18}H_{18}N_2O$	C, H, N	>3000
16	C_6H_5O	N-Pyrrolidino	A	L	104–105	71	$C_{18}H_{18}N_2O_2$	C, H, N	3000
17	C_6H_5S	N-Pyrrolidino	A	L	110–111	84	$C_{18}H_{18}N_2OS$	C, H, N	>3000
18	H	N-Piperidino	A	H	38–39	63	$C_{13}H_{16}N_2O$	C, H, N	500
19	CH_3	N-Piperidino	B	E–W	71	72	$C_{14}H_{18}N_2O$	C, H, N	500[i]
20	CH_3O	N-Piperidino	B	E–W	65–66	63	$C_{14}H_{18}N_2O_2$	C, H, N	1200
21	Cl	N-Piperidino	B	E–W	76–77	66	$C_{13}H_{15}ClN_2O$	C, H, N, Cl	750[i]
22	NO_2	N-Piperidino	D	E	127–128	50	$C_{13}H_{15}N_3O_3$	C, H, N	3000
23	C_6H_5	N-Piperidino	D[c]	E	113–114	58	$C_{18}H_{20}N_2O$	C, H, N	2400
24	C_6H_5O	N-Piperidino	C	L	72–73	44	$C_{18}H_{20}N_2O_2$	C, H, N	>3000
25	C_6H_5S	N-Piperidino	B[b]	E–W	64–66	68	$C_{18}H_{20}N_2OS$	C, H, N	2000
26	H	N-Morpholino	A	L	61–62	71	$C_{12}H_{14}N_2O_2$	C, H, N	750[i]
27	CH_3	N-Morpholino	C	L	80–82	35	$C_{12}H_{16}N_2O_2$	C, H, N	850[i]
28	CH_3O	N-Morpholino	D	E	110–111	63	$C_{13}H_{16}N_2O_3$	C, H, N	1000
29	Cl	N-Morpholino	B	E–W	87–88	40	$C_{12}H_{13}ClN_2O_2$	C, H, N, Cl	400[i]
30	NO_2	N-Morpholino	D	E	136–137	54	$C_{12}H_{13}N_3O_4$	C, H, N	800
31	C_6H_5	N-Morpholino	D	E	157	65	$C_{18}H_{18}N_2O_2$	C, H, N	3000
32	C_6H_5O	N-Morpholino	C	L	72–73	48	$C_{18}H_{18}N_2O_3$	C, H, N	1000
33	C_6H_5S	N-Morpholino	D[b]	C	117–118	32	$C_{18}H_{18}N_2O_2S$	C, H, N	>3000
34	H	N′-Methyl-N-piperazino	A[c]	E	213–214	51	$C_{13}H_{17}N_3O\cdot HCl$	C, H, N, Cl	270[j]
35	CH_3	N′-Methyl-N-piperazino	A[d,e]	H	62–64	63	$C_{14}H_{19}N_3O$	C, H, N	400[j]
				E	208–210[g]		$C_{14}H_{19}N_3O\cdot HCl$	C, H, N, Cl	
36	CH_3O	N′-Methyl-N-piperazino	A[d,e]	L	73–75	69	$C_{14}H_{19}N_3O_2$	C, H, N	
				E	224–225		$C_{14}H_{19}N_3O_2\cdot HCl$	C, H, N, Cl	500[i,k]
37	Cl	N′-Methyl-N-piperazino	A[d,e]	L	67–69	73	$C_{13}H_{16}ClN_3O$	C, H, N, Cl	
				E	225–226		$C_{13}H_{16}ClN_3O\cdot HCl$	C, H, N, Cl	300[j]
38	NO_2	N′-Methyl-N-piperazino	A[d,e]	L	120–122	75	$C_{13}H_{16}N_4O_3$	C, H, N	
				E	232–233		$C_{13}H_{16}N_4O_3\cdot HCl$	C, H, N, Cl	250[k]
39	C_6H_5	N′-Methyl-N-piperazino	D[d]	L	107–108	58	$C_{18}H_{21}N_3O$	C, H, N	800
40	C_6H_5O	N′-Methyl-N-piperazino	C[c,e]	E	198–200	49	$C_{19}H_{21}N_3O_2\cdot HCl$	C, H, N, Cl	300[k]
41	C_6H_5S	N′-Methyl-N-piperazino	C[d,e]		86–87	56	$C_{19}H_{21}N_3OS$	C, H, N	
				E	190		$C_{19}H_{21}N_3OS\cdot HCl$	C, H, N, Cl	350[k]

[a] The reaction was carried out at 80°. [b] The reaction was carried out at 80° for 1 hr. [c] The Et_2O solution of the base was acidified with anhydrous HCl to give the HCl salt. [d] An EtOH solution of the base was acidified with anhydrous HCl to give the HCl salt. [e] A double amount of NaOAc was used. [f] E, EtOH; W, H_2O; L, ligroin; H, hexane; P, petroleum ether (bp 60–70°); C, cyclohexane. [g] The product sublimes above 140°, then melts at 208–210°. [h] Clonic convulsions. [i] Reduction of spontaneous motor activity. [j] Thrill. [k] Tonic convulsions. [l] Hypnosis.

TABLE II

ANTIVIRAL ACTIVITY OF *para*-SUBSTITUTED PHENYLGLYOXAL N,N-DISUBSTITUTED HYDRAZONES

	Embryonated eggs		
	MTD,[a]	Virucidal activity[b]	
No.	μmoles/egg	A-PR8	Vaccinia
15	5	3	0[c]
39	20	>2	1

[a] Maximal tolerated dose. [b] The numbers represent the difference between log EID_{95} (egg infective dose) of controls and log EID_{95} of treated. [c] 0 = no effect.

TABLE III

MINIMAL INHIBITORY CONCENTRATION OF *para*-SUBSTITUTED PHENYLGLYOXAL N,N-DISUBSTITUTED HYDRAZONES AGAINST *T. mentagrophytes*

No.	MIC, μg/ml
3	20
5	40
7	40
8	80
9	1.25
24	80

disubstituted hydrazones, only one derivative (**24**) was active.

Compound **9**, was most active *in vitro* but inactive when tested topically in the guinea pig according to the method of Arnold, *et al.*[3]

Experimental Section[4]

Preparation of *para*-Substituted Phenylglyoxal N,N-Disubstituted Hydrazones. Method A.—A mixture of 0.01 mole of α-ketoaldehyde, 0.011 mole of N,N-disubstituted hydrazine hydrochloride, and 0.011 mole of NaOAc in 10 ml of AcOH was stirred for 2 hr at 20–25°. Then a 20% aqueous Na_2CO_3 was added to alkalinity. Some products precipitated as solids, other as thick oils which solidified on standing. The solids were collected and crystallized. Compounds **7, 9,** and **34** did not solidify and were extracted into Et_2O. After drying, the solvent was evaporated and the residue was crystallized.

Method B.—The N,N-disubstituted hydrazine hydrochloride (0.01 mole) and 0.01 mole of NaOAc were added at 20° to a solution of 0.01 mole of α-ketoaldehyde in 20 ml of EtOH, and the mixture was stirred for 24 hr at 20°. When the products crystallized, they were collected, washed (H_2O), and recrystallized. If no crystallization took place, H_2O was added to cloudiness, and the solution was filtered with charcoal and cooled. The separate crystals were collected and recrystallized.

Method C.—The N,N-disubstituted hydrazine hydrochloride (0.01 mole) and 0.01 mole of NaOAc were added at 20° to a solution of 0.01 mole of α-ketoaldehyde in 20 ml of EtOH, and the mixture was stirred for 24 hr at 20°. The mixture was filtered and the solvent was evaporated to dryness *in vacuo* at 20°. Compounds **24, 27,** and **32** were crystallized, while **40** and **41** were dissolved in Et_2O and the extracts were washed with aqueous NaOAc. After drying (Na_2SO_4), the solvents were evaporated and the residues were crystallized.

Method D.—A solution of 0.01 mole of α-ketoaldehyde and 0.01 mole of N,N-disubstituted hydrazine in 20 ml of EtOH was stirred at 25° for 4 hr. After cooling the crystals were collected and recrystallized.

Pharmacological Methods.—For all tests NMRI albino mice (18–20 g) and Wistar albino rats (200–250 g) were used. For *T. mentagrophytes* infection, Pirbright guinea pigs (250–300 g) were used.

Acute Toxicity.—LD_{50} values were determined in mice intraperitoneally, and the mortality over 48 hr was recorded. The animals were also observed for behavior and objective symptoms according to the Irwin scheme.[5]

Other Tests.—All compounds were screened also for their antispasmodic activity *in vitro* following the methods described by Setnikar and Tirone[6] and for their coronary vasodilator activity on the isolated rabbit heart following the method of Setnikar, *et al.*[7]

Antimicrobial and antifungal activity, antiviral activity, anticonvulsant activity, and antiinflammatory activity were determined according to the methods previously described.[8]

Acknowledgments.—We wish to thank Miss B. Olgiati for microanalytical data and Miss M. J. Magistretti for pharmacological screening of these compounds.

(3) H. Arnold, L. Degen, J. Potel, and R. Rebling, *Arzneimittel-Forsch.*, **14**, 68 (1964).

(4) Melting points are uncorrected and were determined on a Kofler micro hot stage. Where analyses are indicated only by symbols of elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

(5) This scheme was discussed informally by S. Irwin at a Gordon Research Conference, New London, N. H., 1959.

(6) I. Setnikar and P. Tirone, *Arzneimittel-Forsch.*, **16**, 1146 (1966).

(7) I. Setnikar, W. Murmann, and M. T. Ravasi, *Arch. Intern. Pharmacodyn.*, **131**, 187 (1961).

(8) E. Massarani, D. Nardi, L. Degen, and M. J. Magistretti, *J. Med. Chem.*, **9**, 617 (1966).

Synthesis and Antimicrobial Activity of Some Thenoyl Amides

M. LIKAR, P. SCHAUER,

Institute of Microbiology, University of Ljubljana, Ljubljana, Yugoslavia

M. JAPELJ, M. GLOBOKAR, M. OKLOBDŽIJA, A. POVŠE, AND V. ŠUNJIĆ[1]

Research-Development Institute, Krka, Pharmaceutical and Chemical Works, Novo Mesto, Yugoslavia

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Antitrichomonal activity of 2-(2-thenoylamino)-5-nitrothiazole[2] has often been ascribed to the nitrothiazole moiety[3a] in accord with the same activity of related heterocyclic compounds,[3b] especially 5-nitroimidazoles.[4] A variety of derivatives of thiophene-2-carboxylic acid have also been found to have some antimicrobial effects.[5] We have now synthesized a number of amides of thiophene-2-carboxylic acid with various aromatic and heteroaromatic amines (Table I) in order to examine their biological properties.

Results of Microbiological Assays.—Thenoyl amides have been tested for their antimicrobial effectiveness according to standard techniques as described elsewhere.[6] A number of pathogenic and saprophytic bacteria, fungi, and viruses were used as test organism and the results are presented in Table II.

None of the compounds were active against *Shigella flexneri, Haemophilus influenzae, Staphylococcus aureus, Streptococcus viridans, Streptococcus pyogenes, Listeria monocytogenes, Pasteurella pseudotuberculosis, Corynebacterium diphtheriae, Bacillus anthracis, Diplococcus pneumoniae, Salmonella typhi, Microsporum canis,* and *Trichophyton interdigitale.*

Some of the compounds (**1, 4, 13**) markedly reduced the titers of influenza A_2 virus grown in allantoic fluids of embryonated eggs. The most active substances were **1** and **13** which reduced the hemagglutinins of influenza A_2 virus in allantoic fluids 20-fold. Compound **12** at 0.00406 *M* protected all the mice infected with $100LD_{50}$ dose of pseudorabies virus. A number of compounds protected 30–60% of mice infected with $100LD_{50}$ dose of Semliki forest virus (arbovirus group A), *i.e.*, **3, 4, 8,** and **11.**

(1) Correspondence should be addressed to this author.

(2) (a) Innothera and N. D. Xuong, French Patent 1,306.603 (Oct. 19, 1962); *Chem. Abstr.*, **58**, 12569c (1963); (b) N. D. Xuong and N. P. Buu Hoi, *Compt. Rend.*, **253**, 3115 (1961); (c) D. Xuong and F. Lajdela, *Bull. Soc. Chim. France*, 1591 (1955).

(3) (a) D. H. Henry, *J. Med. Chem.*, **12**, 303 (1969). (b) G. G. Ehrhart and H. Rushig, "Arzneimittel, Entwicklung, Wirkung, Darstellung," Bd. 2, Verlag Chemie Gmbh, 1968, pp 1314–1319.

(4) (a) C. Cosar, C. Crisan, R. Horclois, R. M. Jacob, J. Robert, S. Tchetcheff, and R. Vaupre, *Arzneimittel-Forsch.*, **16**, 23 (1966); (b) F. Kajfež, V. Šunjić, D. Kolbah, T. Fajdiga, and M. Oklobdžija, *J. Med. Chem.*, **11**, 167 (1968); (c) V. Šunjić, D. Kolbah, F. Kajfež, and N. Blažević, *ibid.*, **11**, 1264 (1968).

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