divalent ionic species are associated below this dielectric constant value. The decreasing solubility with increasing nonpolarity suggests increasing association of the calcium and oxalate moieties as a partially dissociated ion-pair. These ion-pairs would be strongly associated at lower dielectric constants, resulting in diminished solubility, with the association decreasing in strength as the dielectric constant of the medium increased.

Since the data were available, the Born theory (13) could be tested for validity in predicting the average ion radius once solubilities had been determined in two solvents of varying dielectric constants. These calculations were given previously (11) and are summarized here. In Fig. 3, $\log S_1/S_2$ for calcium oxalate is plotted *versus* the reciprocal of the difference in dielectric constants in the ethanol–water mixtures.

A straight-line relationship is observed at water concentrations of 60% (v/v) to pure water. The slope of this line has a value of 53. From this slope, an average ion radius of 2.27 Å was calculated.

The theoretical ionic radius for calcium and oxalate could be obtained from ionic radii and water numbers. The calcium ion possesses a water number of 8–12, and the oxalate ion has a water number of 2. The radius for the oxalate anion was about 2.4 Å. For calcium with a water number of 8, indicating a monolayer of water dipoles, the average ion radius was also 2.4 Å. With a water number of 12, a bimolecular layer of water dipoles is present and the radius was 3.6 Å.

The good agreement of the average ion radius from theoretical consideration of 2.4 Å and the experimentally determined value of 2.27 Å supports the use of the Born expression and suggests that the calcium ion in these binary systems possesses a water number of 8.

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Pyrrole, Furan, and Thiophene Oxamates as Potential Antiallergy Agents

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Received July 28, 1977, from the *Department of Medicinal Chemistry, School of Pharmacy, University of Georgia, Athens, GA 30602.* Accepted for publication September 8, 1977.

Abstract □ Nine heterocyclic oxamic acid derivatives were synthesized and tested in the rat passive cutaneous anaphylactic assay as potential antiallergy agents. Some compounds also were tested for their effects on cholesterol–lipoprotein levels and for diuretic, antidiabetic, and antifertility activities in rats.

Keyphrases □ Heterocyclic oxamates, various—synthesized, evaluated as antiallergy agents □ Oxamates, various heterocyclic—synthesized, evaluated as antiallergy agents □ Antiallergy agents, potential—various heterocyclic oxamates evaluated □ Structure–activity relationships—various heterocyclic oxamates evaluated as antiallergy agents

Some years ago, several heterocyclic oxamates (II*a*–II*i*, Table I) were synthesized (Scheme I) as possible precursors for various indole isosteres. Although these efforts proved unsuccessful, routine screening[1] of these new compounds in the rat passive cutaneous anaphylaxis (PCA) assay as potential antiallergy agents (1–3) showed some significant activity (*viz.*, II*a*, Table II) (4). Subsequently, the activity (parenterally) was shown to reside in the free acid (5). Antiallergic activity associated with novel oxamic acids was noted recently (6–13), and Sellstedt *et al.* (14) described structure–activity relationships between the oxamates and cromolyn sodium, "the only compound on the market that prophylactically inhibits the liberation of the mediators of allergic reactions initiated by antibody-antigen interactions" (14).

In addition to the evaluation for antiallergic activity, pharmacological test data were obtained for diuretic activity in fasted rats (II*a*–II*c*, II*e*–II*i*, and III) (15) and antidiabetic activity in rats (II*b*, II*c*, II*e*, II*h*, and III) (16). No significant activity was observed. In an antifertility test (17), II*h* administered subcutaneously to three female rats (10 mg/day) prevented conception in all animals, and the compound was considered active by the criteria of this test. In the modified procedure of Tinsho *et al.* (18) for effect on cholesterol–lipoprotein levels in rats, II*a* lowered both serum cholesterol (T/C = 0.67) and serum lipoprotein (T/C = 0.63) fractions significantly at 50 mg/kg po. However, II*a* was inactive in preventing experimental thrombosis.

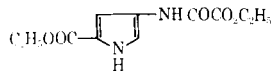
EXPERIMENTAL[2]

The amino-substituted heterocycles, I*a*–I*f*, were prepared by the procedure of Gewald and coworkers (19–21). 2-Amino-5-ethoxycarbon-

[1] From The Upjohn Co.'s biological evaluation program.

[2] Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. NMR spectra were determined on a Hitachi Perkin-Elmer R 20A high-resolution NMR spectrometer, using tetramethylsilane as the internal reference. IR spectra were determined on a Perkin-Elmer 237B grating spectrophotometer, using the potassium bromide technique. UV spectra were determined in methanol solution with a Perkin-Elmer 202 UV–visible spectrophotometer. Elemental analyses were determined by Atlantic Microlab, Atlanta, Ga. TLC was performed on Eastman chromatogram sheets, type 6060 (silica gel).

Table I—Oxamic Acid Derivatives

Compound	X	R_1	R_2	R_3	R_4	Yield[a], %	Melting Point	Formula	Analysis, % Calc.	Found
II*a*	NH	CH_3	CH_3	CN	C_2H_5	66.1	132–133°	$C_{11}H_{13}N_3O_3$	C 56.17	56.27
									H 5.53	5.67
									N 17.87	17.74
II*b*	O	CH_3	CH_3	CN	H	22.5[b]	172–173°	$C_9H_8N_2O_4$	C 51.92	52.13
									H 3.85	4.09
									N 13.46	13.25
II*c*	O	CH_3	CH_3	CN	C_2H_5	50[c]	97–100°	$C_{11}H_{12}N_2O_4$	C 55.93	56.06
									H 5.08	5.18
									N 11.86	11.93
II*d*	S	CH_3	CH_3	CN	C_2H_5	71.4	85–87°	$C_{11}H_{12}N_2O_3S$	C 52.37	52.13
									H 4.79	4.77
									N 11.10	11.15
									S 12.71	12.93
II*e*	S	H	C_6H_5	$COOC_2H_5$	C_2H_5	70.6	102–105°	$C_{17}H_{17}NO_5S$	C 58.79	58.66
									H 4.90	5.04
									N 4.03	4.06
II*f*	S	CH_3	CH_3	$COOC_2H_5$	C_2H_5	81.6	87–89°	$C_{13}H_{17}NO_5S$	C 52.17	52.31
									H 5.69	5.85
									N 4.68	4.86
II*g*	S	$COOC_2H_5$	H	H	C_2H_5	44.1	140–142°	$C_{11}H_{13}NO_5S$	C 48.71	48.72
									H 4.80	4.99
									N 5.17	5.25
									S 11.81	11.86
II*h*	O	$COOC_2H_5$	H	H	C_2H_5	50.7	127–129°	$C_{11}H_{13}NO_6$	C 51.76	51.73
									H 5.09	5.17
									N 5.49	5.61
II*i*						32.8	183–185°	$C_{11}H_{14}N_2O_5$	C 51.97	52.04
									H 5.51	5.73
									N 11.02	11.15

[a] All compounds were recrystallized from 95% ethanol, unless indicated otherwise. [b] Methanol. [c] Ethyl acetate–ligroin.

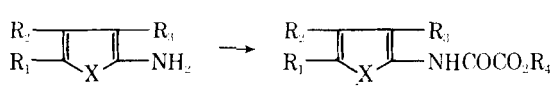
Table II—Inhibition of Rat Passive Cutaneous Anaphylactic Reaction[a]

Compound	Inhibition[b], % 50 mg/kg iv	10 mg/kg iv	1 mg/kg iv
II*a*	100	90	54
II*b*	63	63	25
II*c*	38	—	—
II*d*[c]	—	—	—
II*e*	0	—	—
II*f*	0	—	—
II*g*	0	—	—
II*i*	12	—	—
III	0	—	—

[a] Data were collected in the laboratory of Dr. H. G. Johnson, The Upjohn Co. [b] Ethyl 2-cyanophenyloxamate (14) exhibited 53% inhibition at 200 mg/kg ip. [c] See Ref. 6.

ylthiophene (I*g*) was prepared by the method of Sy and deMalleray (22). 2-Amino-5-ethoxycarbonylfuran (I*h*) (23) was prepared by Raney nickel reduction of ethyl 5-nitrofuroate (24). 2-Ethoxycarbonyl-4-aminopyrrole (I*i*) was prepared by Raney nickel reduction of 2-ethoxycarbonyl-4-nitropyrrole (25).

Ethyl (3-Cyano-4,5-dimethyl-2-pyrrolyl)oxamate (II*a*)—The procedure for the synthesis of II*a* is given as representative for II*c*–II*i*. To 10 g (0.074 mole) of 2-amino-3-cyano-4,5-dimethylpyrrole (I*a*), dissolved in 300 ml of ethyl acetate[3], 7.59 g of triethylamine was added. To this solution, at about 0°, 10.24 g of ethyl oxalyl chloride in 25 ml of ethyl acetate was added slowly with stirring. A yellow precipitate formed immediately, and the reaction mixture was stirred for about 2 hr in an ice bath and for 1 hr at room temperature. The triethylamine hydrochloride was removed by filtration, and the filtrate was stored for about 16 hr. Evaporation of the solvent *in vacuo* gave a reddish solid, mp 100–120°. Recrystallization from 95% ethanol gave 11.5 g of bright-yellow product, mp 132–133°.



I*a*–I*i* II*a*–II*i*

Scheme I

[3] Ether or tetrahydrofuran also may be utilized.

3-Cyano-4,5-dimethylfuryloxamic Acid (II*b*)—2-Amino-4,5-dimethyl-3-cyanofuran (I*b*) (6.8 g, 0.05 mole) was dissolved in 100 ml of anhydrous ether and 6 ml of triethylamine. This solution was treated cautiously by the dropwise addition of 7.6 g (0.06 mole) of oxalyl chloride in 80 ml of ether. The reaction mixture was stirred for 2 hr and then allowed to stand overnight at room temperature. A yellowish solid was removed from the ether solution by filtration. This solid was suspended in water to remove triethylamine hydrochloride, and the insoluble residue was collected and dried. After recrystallization from dimethylformamide–water, this material (4.3 g) melted at 263–264° and proved to be the *N,N'*-bis(3-cyano-4,5-dimethyl-2-furyl)oximide (III).

Anal.—Calc. for $C_{16}H_{14}N_4O_4$: C, 58.90; H, 4.29; N, 17.18. Found: C, 59.13; H, 4.31; N, 17.34.

The ether filtrate from the above was removed *in vacuo*, and the residue was washed with water, collected, and air dried. After recrystallization from methanol, this material (2.3 g, 22.5%) melted at 172–173°; NMR (dimethyl sulfoxide-d_6): δ 2.0 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 6.45 (broad, 1H, NHCO), and 11.65 (broad, 1H, COOH) (see Table I for analyses).

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Synthesis of *as*-Triazines as Potential Antiviral Agents

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Received July 7, 1977, from the *Department of Chemistry, Georgia State University, Atlanta, GA 30303.* Accepted for publication September 2, 1977.

Abstract □ Four acenaphtho[1,2-*e*]-*as*-triazines and 11 5,6-diaryl-*as*-triazines, all substituted with an aliphatic or aromatic amino function in the 3-position, were synthesized. Two acenaphthotriazines were active against vesicular stomatitis virus in tissue culture.

Keyphrases □ *as*-Triazines, various substituted—synthesized, antiviral activity evaluated □ Antiviral activity—various substituted *as*-triazines evaluated □ Structure–activity relationships—various substituted *as*-triazines evaluated for antiviral activity

The broad spectrum antiviral activity of the 5*H*-*as*-triazino[5,6-*b*]indoles (1–3), as well as reports of antiviral activity of other *as*-triazines (4–6), prompted preparation of a series of related analogs for evaluation as potential antiviral agents. This effort consisted of the synthesis of two series, one containing a coplanar ring system and the other containing a similar number of aromatic rings but not in a coplanar arrangement.

The first series, 9-substituted acenaphtho[1,2-*e*]-*as*-triazines (Table I), is modeled after the 5-alkyl-*as*-triazino[5,6-*b*]indoles in that a hydrophobic moiety (the acenaphtho ring) is substituted for the alkylindolo ring. The resulting compounds contain a planar aromatic surface, similar to that of the *as*-triazinoindoles, but lacking the steric factors contributed by the alkyl group, which can rotate above and below the plane of the fused rings.The second series of compounds, 3-substituted 5,6-diaryl-*as*-triazines (Table II), was prepared to determine the necessity of the planar fused rings in antiviral activity by building a system that could not attain a coplanar configuration. All compounds (Tables I and II) were substituted with alkyl or aryl amino side chains, which have been demonstrated to be efficacious in antiviral triazines (2, 3).

RESULTS AND DISCUSSION

The synthetic pathways utilized in the preparation of I–XX are similar and consist of the acid- or base-catalyzed condensation of either thiosemicarbazide or semicarbazide hydrochloride with acenaphthoquinone or the appropriately substituted benzil. Products of the thiosemicarbazide–quinone condensation could be treated directly with the desired alkyl or aryl amine to produce the corresponding derivatives, II–V. However, the 5,6-diaryl-*as*-triazin-3(2*H*)-ones do not react with the amines, necessitating their conversion to the corresponding 3-chloro derivatives by reaction with phosphoryl chloride. The enhanced reactivity of 3-chloro-5,6-diaryl-*as*-triazines allowed their facile conversion to X–XX.

Compounds III–V, X–XV, and XVII–XX were subjected to both *in vitro* and *in vivo* antiviral activity screens as described under *Experimental.* A tissue culture evaluation of III and IV indicated activity when the compounds were exposed to cells challenged with vesicular stomatitis virus, a single-stranded RNA rabies-like virus, as determined by the dye retention assay. The activity of IV against vesicular stomatitis virus (active at 25 μg/ml of culture medium) was greater than that of III (active at 50 μg/ml); however, IV also exhibited a greater toxicity (50 μg/ml) to cell cultures than did III (toxic at 250 μg/ml). Other compounds failed to demonstrate any significant *in vitro* activity against vesicular stomatitis virus.

All compounds were judged inactive when tested *in vitro* (under similar conditions) against the following viruses: respiratory syncytial, parainfluenza-3, herpes simplex, rhinovirus-14, shipping fever (bovine parainfluenza-3), and Newcastle disease.

The *in vivo* antiviral evaluation system consisted of an encephalomyocarditis virus-in-mouse screen in which activity is determined by a prolongation of survival time in the treated animals. None of the compounds demonstrated activity.

Because several related 3,5-diamino-*as*-triazines (7) have exhibited antimalarial activity, X–XX also were evaluated for *in vivo* antimalarial activity in mice infected with *Plasmodium berghei* by the method of Osdene *et al.* (8). None of the compounds showed any significant activity in the malaria screen.

EXPERIMENTAL[1]

All melting points were obtained using an oil bath melting-point apparatus and are uncorrected. Satisfactory IR spectra were obtained, and the expected PMR spectra were obtained in deuterochloroform (tetramethylsilane standard).

Acenaphtho[1,2-*e*]-*as*-triazine-9(8*H*)-thione (I)—Attempts to prepare this compound by the method reported for the corresponding

[1] Elemental analyses were determined by Atlantic Microlab, Atlanta, Ga.