

Synthesis of New Mercaptotriazoles with Potential Antibilharzial Activity

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Abstract □ Several 3-mercaptoptriazoles with the 8-hydroxyquinoline moiety in the 5-position were prepared and tested for antiparasitic activity. Preliminary biological tests on experimentally infected mice with *Schistosoma mansoni* worms revealed that the new compounds possess potent schistosomicidal activity.

Keyphrases □ Antibilharzial agents—mercaptoptriazoles, synthesis, screening, *Schistosoma mansoni*, structure-activity relationships □ Mercaptoptriazoles—antibilharzial activity, synthesis, screening, *Schistosoma mansoni*, structure-activity relationships □ Structure-activity relationships—mercaptoptriazoles, antibilharzial activity, synthesis, screening, *Schistosoma mansoni* □ *Schistosoma mansoni*—treatment with mercaptoptriazoles, synthesis, screening in mice, structure-activity relationships

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).

BACKGROUND

A novel schistosomicide of apparent clinical utility is 1-(5-nitro-2-thiazolyl)-2-imidazolidinone (niridazole). This compound showed considerable efficacy against *Schistosoma mansoni* and *S. haematobium* via oral administration (5), but three types of side effects were encountered: frequent ECG changes; neuropsychic effects, and transitory spermatogenesis impairment (6).

A new entry in bilharzial chemotherapy is 1,2,3,4-tetrahydro-2-[(1-methylethylamino)methyl]-7-nitro-6-quinoline methanol (oxamniquine). It has potent schistosomicidal activity against *S. mansoni* by causing worms to shift from the mesenteric veins to the liver where they are destroyed (7).

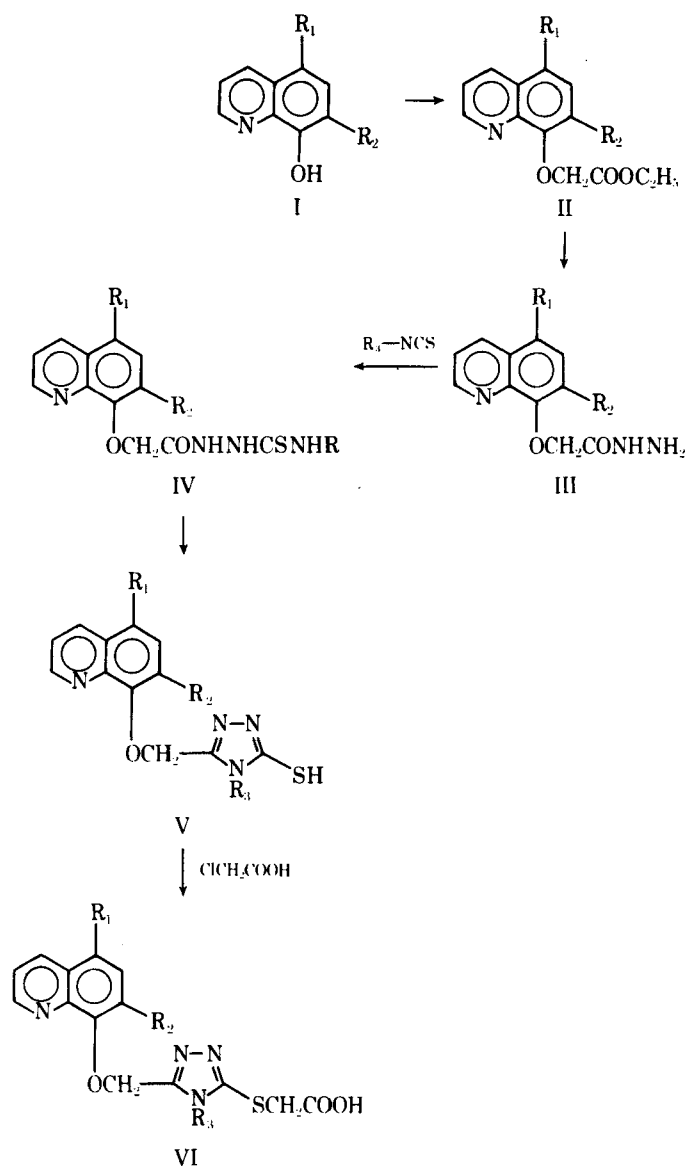
Recently, interest has been focused on the pharmacology of 1-phenyl-1,2,4-triazoles and 4-phenyl-1,2,4-triazoles (8), which showed diverse biological activities. Furthermore, 1,4-disubstituted thiosemicarbazides (the precursors for cyclized triazole synthesis) possess a broad spectrum of biological activities (9, 10).

These observations prompted the synthesis of several 3-mercaptoptriazoles having the substituted 8-hydroxyquinoline moiety in the 5-position. Incorporation of the potent antiparasitic drug iodochlorhydroxyquin or diiodohydroxyquin in the 3-mercaptoptriazole ring produced compounds with potential schistosomicidal activity and no undesirable or toxic effects.

CHEMISTRY

The various substituted 1,2,4(4*H*)-triazoles were synthesized by reactions outlined in Scheme I. Conversion of the 8-hydroxyquinoline derivative (I) to the corresponding ethyl 8-quinolinoxyacetate (II) was carried out to synthesize 8-quinolinoxyacetic acid hydrazide (III) through refluxing in ethanol with 99–100% hydrazine hydrate.

Substituted thiosemicarbazides (IV, Table I), prepared by the reaction of III with the appropriate isothiocyanate, were cyclized to the corresponding mercaptoptriazoles (V, Table II) in 2*N* NaOH. Condensation



of the substituted triazoles with chloroacetic acid produced substituted triazole-3-mercaptoacetic acids (VI, Table III). All compounds were characterized by their sharp melting points, elemental analyses, and IR spectra.

EXPERIMENTAL¹

Ethyl 8-Quinolinoxyacetate (IIa): Method A—To a solution of 8-hydroxyquinoline (0.1 mole) in absolute ethanol (60 ml) was added

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

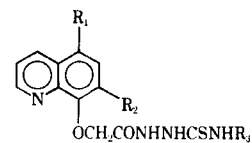


Table I—1-(8-Quinolinoxyacetyl)-4-Substituted Thiosemicarbazides

Compound	R ₃	R ₁	R ₂	Yield, %	Melting Point	Formula	Analysis, %	
							Calc.	Found
IVa	C ₂ H ₅	H	H	65	198°	C ₁₄ H ₁₆ N ₄ O ₂ S	C 55.3 H 5.3 N 18.4	55.4 5.5 18.6
IVb	CH ₂ =CHCH ₂	H	H	68	129°	C ₁₅ H ₁₆ N ₄ O ₂ S	C 57.0 H 5.1 N 17.7	57.0 5.1 17.9
IVc	CH ₃ (CH ₂) ₃	H	H	66	194°	C ₁₆ H ₂₀ N ₄ O ₂ S	C 58.2 H 6.1 N 17.0	58.0 6.0 17.1
IVd	C ₆ H ₁₁	H	H	70	150°	C ₁₈ H ₂₂ N ₄ O ₂ S	C 60.3 H 6.1 N 15.6	60.5 6.1 15.8
IVe	C ₆ H ₅	H	H	75	234°	C ₁₈ H ₁₆ N ₄ O ₂ S	C 61.4 H 4.5 N 15.9	61.6 4.5 15.9
IVf	C ₆ H ₅ CH ₂	H	H	78	169°	C ₁₉ H ₁₈ N ₄ O ₂ S	C 62.3 H 4.9 N 15.3	62.6 5.0 15.0
IVg	CH ₂ =CHCH ₂	Cl	I	70	177°	C ₁₅ H ₁₄ ClIN ₄ O ₂ S	C 37.8 H 2.9 N 11.8	38.0 3.1 11.5
IVh	CH ₃ (CH ₂) ₃	Cl	I	68	172°	C ₁₆ H ₁₈ ClIN ₄ O ₂ S	C 39.0 H 3.7 N 11.4	39.4 4.0 11.5
IVi	C ₆ H ₁₁	Cl	I	62	169°	C ₁₈ H ₂₀ ClIN ₄ O ₂ S	C 41.7 H 3.9 N 10.8	41.9 4.1 11.1
IVj	C ₆ H ₅	Cl	I	70	165°	C ₁₈ H ₁₄ ClIN ₄ O ₂ S	C 42.1 H 2.7 N 10.9	42.4 3.0 11.0
IVk	C ₆ H ₅ CH ₂	Cl	I	75	106°	C ₁₉ H ₁₆ ClIN ₄ O ₂ S	C 43.3 H 3.0 N 10.6	43.5 3.3 11.0
IVl	<i>m</i> -CH ₃ C ₆ H ₄	Cl	I	66	160°	C ₁₉ H ₁₆ ClIN ₄ O ₂ S	C 43.3 H 3.0 N 10.6	43.4 3.1 10.9
IVm	C ₂ H ₅	I	I	64	196°	C ₁₄ H ₁₄ I ₂ N ₄ O ₂ S	C 30.2 H 2.5 I 45.7	30.6 2.8 46.0
IVn	CH ₂ =CHCH ₂	I	I	68	183°	C ₁₅ H ₁₄ I ₂ N ₄ O ₂ S	C 31.7 H 2.5 I 44.7	31.9 2.7 44.9
IVo	CH ₃ (CH ₂) ₃	I	I	60	194°	C ₁₆ H ₁₈ I ₂ N ₄ O ₂ S	C 32.9 H 3.1 I 43.5	33.1 3.3 43.6
IVp	C ₆ H ₁₁	I	I	72	190°	C ₁₈ H ₂₀ I ₂ N ₄ O ₂ S	C 35.4 H 3.3 I 41.6	35.8 3.5 42.0
IVq	C ₆ H ₅	I	I	75	185°	C ₁₈ H ₁₄ I ₂ N ₄ O ₂ S	C 35.8 H 2.3 I 42.1	36.1 2.6 42.2
IVr	C ₆ H ₅ CH ₂	I	I	78	180°	C ₁₉ H ₁₆ I ₂ N ₄ O ₂ S	C 36.9 H 2.6 I 41.1	37.2 3.0 41.5

sodium ethoxide (0.1 mole of sodium in 20 ml of absolute ethanol) followed by ethyl chloroacetate (0.1 mole). The reaction mixture was refluxed under anhydrous conditions for 3 hr and filtered. The filtrate was poured over 100 ml of ice-cold water. The separated ester was extracted with ether and dried over anhydrous magnesium sulfate. Excess ether was removed by distillation, and the remaining crude ester was used to prepare the corresponding hydrazide.

Ethyl 8-(5-Chloro-7-iodo)-quinolinoxyacetate (IIb): Method B—Equimolar quantities of iodochlorohydroxyquin (Ib, R₁ = Cl, R₂ = I) (0.1 mole), ethyl chloroacetate (0.1 mole), and potassium carbonate (0.12 mole) in absolute ethanol (100 ml) were refluxed for 3 hr. The reaction mixture was filtered, and the filtrate was concentrated and allowed to cool. The crude ester was collected and recrystallized from ethanol as yellow needles, mp 168°, in an 80% yield.

Anal.—Calc. for C₁₃H₁₁ClINO₂: C, 39.8; H, 2.8; N, 3.6. Found: C, 39.6; H, 2.7; N, 3.9.

Ethyl 8-(5,7-Diiodo)-quinolinoxyacetate (IIc)—Method B produced yellow needles, mp 195°, in an 84% yield.

Anal.—Calc. for C₁₃H₁₁I₂NO₂: C, 32.3; H, 2.3; I, 52.6. Found: C, 32.0; H, 2.3; I, 52.4.

8-Quinolinoxyacetic Acid Hydrazides (IIIa–IIIc)—To a solution of 0.1 mole of IIa–IIc in absolute ethanol (50 ml) was added 7 g of 99–100% hydrazine hydrate, and the mixture was refluxed for 2 hr. The crude hydrazide, which separated on cooling, was collected by filtration and recrystallized from ethanol. Compound IIIa was obtained as white needles, mp 71°, in a 60% yield.

Anal.—Calc. for C₁₁H₁₁N₃O₂: C, 60.8; H, 5.1; N, 19.4. Found: C, 60.6; H, 5.2; N, 19.4.

Compound IIIb was obtained as yellow needles, mp 178°, in a 65% yield.

Anal.—Calc. for C₁₁H₉ClIN₃O₂: C, 35.0; H, 2.4; N, 11.1. Found: C, 34.8; H, 2.5; N, 11.0.

Compound IIIc was obtained as yellow needles, mp 186°, in a 68% yield.

Anal.—Calc. for C₁₁H₉I₂N₃O₂: C, 28.1; H, 1.9; I, 54.2. Found: C, 28.0; H, 2.0; I, 54.5.

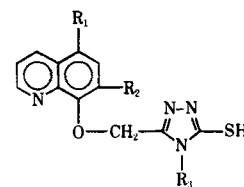


Table II—5-(8-Quinolinoxymethyl)-4-Substituted-3-mercapto-1,2,4(4H)-triazoles

Compound	R ₃	R ₁	R ₂	Yield, %	Melting Point	Formula	Analysis, %		
							Calc.	Found	
Va	C ₂ H ₅	H	H	68	180°	C ₁₄ H ₁₄ N ₄ OS	C 58.7	58.8	
							H 4.9	5.2	
							N 19.6	20.0	
Vb	CH ₂ =CHCH ₂	H	H	66	208°	C ₁₅ H ₁₄ N ₄ OS	C 60.4	60.8	
							H 4.7	5.0	
							N 18.8	18.6	
Vc	CH ₃ (CH ₂) ₃	H	H	71	162°	C ₁₆ H ₁₈ N ₄ OS	C 61.1	61.3	
							H 5.7	5.7	
							N 17.8	17.8	
Vd	C ₆ H ₁₁	H	H	75	175°	C ₁₈ H ₂₀ N ₄ OS	C 63.5	63.5	
							H 5.9	6.0	
							N 16.5	16.5	
Ve	C ₆ H ₅	H	H	78	182°	C ₁₈ H ₁₄ N ₄ OS	C 64.7	64.9	
							H 4.2	4.4	
							N 16.8	17.1	
Vf	C ₆ H ₅ CH ₂	H	H	73	145°	C ₁₉ H ₁₆ N ₄ OS	C 65.5	65.6	
							H 4.6	4.5	
							N 16.1	15.8	
Vg	CH ₂ =CHCH ₂	Cl	I	65	185°	C ₁₅ H ₁₂ ClIN ₄ OS	C 39.3	39.5	
							H 2.6	2.7	
							N 12.2	12.5	
Vh	CH ₃ (CH ₂) ₃	Cl	I	67	168°	C ₁₆ H ₁₆ ClIN ₄ OS	C 40.5	40.8	
							H 3.4	3.3	
							N 11.8	12.1	
Vi	C ₆ H ₁₁	Cl	I	72	138°	C ₁₈ H ₁₈ ClIN ₄ OS	C 43.2	43.3	
							H 3.6	3.4	
							N 11.2	11.1	
Vj	C ₆ H ₅	Cl	I	78	182°	C ₁₈ H ₁₂ ClIN ₄ OS	C 43.7	44.1	
							H 2.4	2.6	
							N 11.3	11.0	
Vk	C ₆ H ₅ CH ₂	Cl	I	70	120°	C ₁₉ H ₁₄ ClIN ₄ OS	C 44.8	45.1	
							H 2.8	2.4	
							N 11.0	11.0	
Vi	<i>m</i> -CH ₃ C ₆ H ₄	Cl	I	66	170°	C ₁₉ H ₁₄ ClIN ₄ OS	C 44.8	44.7	
							H 2.8	3.1	
							N 11.0	11.2	
Vm	C ₂ H ₅	I	I	60	172°	C ₁₄ H ₁₂ I ₂ N ₄ OS	C 31.2	31.0	
							H 2.2	2.5	
							I 47.2	47.5	
Vn	CH ₂ =CHCH ₂	I	I	64	142°	C ₁₅ H ₁₂ I ₂ N ₄ OS	C 32.7	32.9	
							H 2.2	2.4	
							I 46.2	46.4	
Vo	CH ₃ (CH ₂) ₃	I	I	72	150°	C ₁₆ H ₁₆ I ₂ N ₄ OS	C 33.9	34.1	
							H 2.8	3.0	
							I 44.9	45.3	
Vp	C ₆ H ₁₁	I	I	77	154°	C ₁₈ H ₁₈ I ₂ N ₄ OS	C 36.5	36.7	
							H 3.0	3.2	
							I 42.9	43.1	
Vq	C ₆ H ₅	I	I	68	168°	C ₁₈ H ₁₄ I ₂ N ₄ OS	C 36.7	36.8	
							H 2.4	2.4	
							I 43.2	43.2	
Vr	C ₆ H ₅ CH ₂	I	I	70	134°	C ₁₉ H ₁₄ I ₂ N ₄ OS	C 38.0	38.1	
							H 2.3	2.5	
							I 42.3	42.0	

1-(8-Quinolinoxymethyl)-4-Substituted Thiosemicarbazides (IV)—Equimolar quantities of IIIa–IIIc (0.02 mole) and the appropriate isothiocyanate (0.02 mole) were mixed in dry benzene, and the mixture was refluxed on a steam bath for 2 hr. Excess benzene was removed by distillation. The separated solid was collected by filtration, washed with cold ethanol–water, dried, and recrystallized from ethanol. The various substituted thiosemicarbazides (Table I) were characterized by their sharp melting points and elemental analyses.

5-(8-Quinolinoxymethyl)-4-Substituted-3-mercapto-1,2,4(4H)-triazoles (V)—A solution of 1-(8-quinolinoxymethyl)-4-substituted thiosemicarbazide (0.01 mole) in 2 *N* NaOH (20 ml) was refluxed for 2–3 hr. After cooling, the mixture was filtered; the filtrate was acidified with dilute hydrochloric acid until complete precipitation occurred (11, 12). The separated solid was collected by filtration, washed with water, dried, and recrystallized from ethanol. Various substituted mercaptotriazoles were characterized by their sharp melting points and elemental analyses

(Table II).

5-(8-Quinolinoxymethyl)-4-Substituted-1,2,4(4H)-triazole-3-mercaptoacetic Acids (VI)—A mixture of the appropriate substituted mercaptotriazole (0.005 mole), chloroacetic acid (0.005 mole), and sodium hydroxide (0.01 mole) in ethanol (20 ml) was refluxed for 3 hr. The mixture was cooled and acidified with dilute hydrochloric acid. The solid mass, which separated, was collected and recrystallized from ethanol (Table III).

Antibilharzial Activity—Swiss albino mice were infected with 100 cercariae of *S. mansoni* by the tail immersion technique (13). Eight weeks after infection, the animals were divided into six groups: a control group and a group for each of the new drugs to be tested (Vb, Vd, Vg, Vi, and hycanthone as a standard).

The drugs were given orally as a single 100-mg/kg dose. 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 3rd day on five

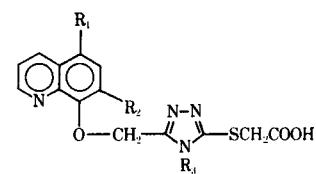


Table III—5-(8-Quinolinoxymethyl)-4-Substituted-1,2,4(4H)-triazole-3-mercaptoacetic Acids

Compound	R ₃	R ₁	R ₂	Yield, %	Melting Point	Formula	Analysis, %	
							Calc.	Found
VI _d	C ₆ H ₁₁	H	H	70	226°	C ₂₀ H ₂₂ N ₄ O ₃ S	C 60.3 H 5.5 N 14.1	60.3 5.6 14.1
VI _e	C ₆ H ₅	H	H	80	196°	C ₂₀ H ₁₆ N ₄ O ₃ S	C 61.2 H 4.1 N 14.3	61.4 4.1 14.5
VI _f	C ₆ H ₅ CH ₂	H	H	78	145°	C ₂₁ H ₁₈ N ₄ O ₃ S	C 62.1 H 4.4 N 13.8	62.1 4.4 14.1
VI _g	CH ₂ =CHCH ₂	Cl	I	75	180°	C ₁₇ H ₁₄ ClIN ₄ O ₃ S	C 39.5 H 2.7 N 10.8	39.1 3.0 11.0
VI _h	CH ₃ (CH ₂) ₃	Cl	I	72	164°	C ₁₈ H ₁₈ ClIN ₄ O ₃ S	C 40.6 H 3.4 N 10.5	41.0 3.5 10.5
VI _i	C ₆ H ₁₁	Cl	I	68	168°	C ₂₀ H ₂₀ ClIN ₄ O ₃ S	C 43.0 H 3.6 N 10.0	43.2 3.8 9.8
VI _j	C ₆ H ₅	Cl	I	85	172°	C ₂₀ H ₁₄ ClIN ₄ O ₃ S	C 43.4 H 2.5 N 10.1	43.6 3.0 10.5
VI _k	C ₆ H ₅ CH ₂	Cl	I	82	166°	C ₂₁ H ₁₆ ClIN ₄ O ₃ S	C 44.5 H 2.9 N 10.0	44.7 3.3 10.2
VI _m	C ₂ H ₅	I	I	75	168°	C ₁₆ H ₁₄ I ₂ N ₄ O ₃ S	C 32.2 H 2.3 I 44.6	32.5 2.6 45.0
VI _o	CH ₃ (CH ₂) ₃	I	I	77	175°	C ₁₈ H ₁₈ I ₂ N ₄ O ₃ S	C 34.6 H 2.9 I 40.7	34.9 3.2 41.1
VI _p	C ₆ H ₁₁	I	I	73	180°	C ₂₀ H ₂₀ I ₂ N ₄ O ₃ S	C 36.9 H 3.1 I 39.1	37.2 3.5 38.8
VI _q	C ₆ H ₅	I	I	78	200°	C ₂₀ H ₁₄ I ₂ N ₄ O ₃ S	C 37.3 H 2.2 I 39.4	37.6 2.5 39.0
VI _r	C ₆ H ₅ CH ₂	I	I	70	190°	C ₂₁ H ₁₆ I ₂ N ₄ O ₃ S	C 38.3 H 2.4 I 38.6	38.1 2.8 39.0

Table IV—Oogram Findings in the Liver and Small Intestine of Infected Mice Treated with Experimental Compounds

Compound	Liver			Intestine		
	Total Immature Eggs, %	Mature Eggs, %	Dead Eggs, %	Total Immature Eggs, %	Mature Eggs, %	Dead Eggs, %
Control	76	18	6	70	28	2
Hycanthone	—	—	—	0	48	52
V _b	0	70	30	0	68	32
V _d	0	86	14	18	74	8
V _g	10	70	12	20	60	20
V _i	15	70	15	20	56	24

animals from each group.

Table IV shows the average oogram pattern in the liver and intestine during the period of maximum drug effect, which was usually at the end of the 1st week, compared with hycanthone (14).

Effect on *Toxocara canis* Larvae—Swiss albino mice were infected with 1000 larvated *T. canis* eggs by intragastric tube. Compound Vg was given as a single 100-mg/kg po dose to a group of the infected animals and

Table V—Average Larval Counts in the Brain of Mice Infected with *T. canis* Larvae

Duration of Autopsy, days	Average Larval Count	
	Control Mice	Treated Mice
7	33	20
15	41	27

a second group served as controls. Table V shows the larval counts in the brain of the treated group compared with the control group.

RESULTS AND DISCUSSION

The efficiency of a new antischistosomal drug was assessed in experimental infection by the oogram changes, which were said to be caused by loss of schistosoma worm muscle tone, drug action on the parasite reproductive organs, and death of the worms (15).

Deviation of the oogram picture from normal was considered when there was an absence of any immature stages or when the number of mature ova exceeded 50% (15).

Results obtained with Vb, Vd, Vg, and Vi showed marked deviation of the oogram picture from normal, indicating their potent antibilharzial effect. Furthermore, Vb and Vd eliminated all immature stages, demonstrating a powerful effect on the worm reproductive organs.

Compound Vg reduced the number of *T. canis* larvae in the brains of mice experimentally infected with visceral larva migrans.

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Kinetics of Digestive Enzyme Stability in Solid State I: Application of Weibull Distribution Function to Solid-State Enzyme Inactivation

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Abstract □ The Weibull distribution function was applied to solid-state enzyme inactivation. On Weibull probability paper (within a narrow range), the plots of the accumulated inactivation ratio of each enzyme versus time regressed to a straight line. The parameters m and k , which correspond to the type and rate of the inactivation, were characteristic of each enzyme. The effect of temperature and parameter reproducibility are discussed.

Keyphrases □ Weibull distribution function—application to solid-state enzyme inactivation studies □ Enzyme kinetics—application of Weibull distribution to inactivation studies □ Enzyme inactivation—kinetics, application of Weibull distribution to solid-state studies

Stability is important for drug quality assurance, and reports on drug stability in solid dosage forms have been published (1, 2). The essential requirement in stability studies is the selection of rate equations, which have been determined in practical systems by trial and error.

Some investigations using enzymes in the solid state failed because there was an inherent difficulty in fitting common rate equations to experimental data. Enzyme stability is complicated and is readily affected by factors such as temperature, humidity, and coexisting substances.

This paper¹ describes application of the Weibull distribution function to solid-state enzyme inactivation. The Weibull distribution originally was applied to stability predictions of other solid drugs (3, 4).

THEORETICAL

Efforts have been made to interpret the shelflife of enzymes in solids

and solutions and to describe mathematically the inactivation profile with meaningful parameters. Although equations possibly could be derived from empirical treatment of the process, *e.g.*, pseudo-first-order kinetics, no suitable function has been found. Therefore, shelflives rarely have been mentioned in solid-state enzyme inactivation studies.

A general function, applicable to all inactivation curves, was derived by Weibull (5) and discussed in detail (6–8). A concise survey also was reported (9). When applied to enzyme inactivation rate data in the solid state, the Weibull distribution expresses the accumulated inactivation ratio, α , of the enzyme activity at time, t , by:

$$\alpha = 1 - \exp[-(t)^{m/k}] \quad (\text{Eq. 1})$$

where the scale parameter, k , defines the time scale of the process and the shape parameter, m , characterizes the curve as an exponential function. The relationship between m and curve shape was discussed previously (8, 9).

Graphical representation of the data according to the Weibull distribution and the practical aspects of linearizing experimental data were reported (6, 7). Equation 1 may be rearranged:

$$\ln \ln (1/1 - \alpha) = \ln k + m \ln t \quad (\text{Eq. 2})$$

From Eq. 2, a linear relation is obtained from a $\ln \ln$ plot of $\ln (1/1 - \alpha)$ versus t . The shape parameter, m , is obtained from the slope, and k is obtained from the ordinate value at $t = 1$.

The theoretical correlation between Eq. 2 and chemical kinetics was discussed in detail (4). The equation expressing chemical kinetics varies according to the inactivation mechanism. However, within a narrow range, it is possible to express them by:

$$\frac{d\alpha}{dt} = K g(a, \alpha, P_i) \quad (\text{Eq. 3})$$

where K is the rate constant, a is the initial enzyme activity, and P_i is the parameter independent of time, t . The integrated form of Eq. 3 is:

$$f(a, \alpha, P_i) = Kt \quad (\text{Eq. 4})$$

Equations 2 and 4 can be correlated by assuming that logarithms of Eq. 4 are expressed approximately as a linear function of Eq. 2:

$$\ln f(a, \alpha, P_i) = \ln K + \ln t \approx A_0 + A_1 \ln \ln (1/1 - \alpha) \quad (\text{Eq. 5})$$

$$\ln \ln (1/1 - \alpha) \approx 1/A_1 (\ln K - A_0) + 1/A_1 \ln t \quad (\text{Eq. 6})$$

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