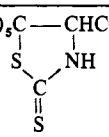
Table I *(Continued)*

Class	Compd[a]	Structure[b]	MIC, μg/ml[c,d] H-7	MIC, μg/ml[c,d] H-25	Solvent[e]
	58		–	–	MT*
Miscellaneous	59[f]	$CH_3C(O)SMe$	–	–	MT
	60	$CH_3C(S)OEt$	–	–	MT
	61	p-$C_7H_7SO_2S^-K^+$	–	–	W

[a]Compds were prepared and suitably characterized (except for 19) in our laboratories by methods published elsewhere, except where other sources are indicated. [b]C_5H_4N = pyridyl; $C_{10}H_7$ = naphthyl; p-C_7H_7 = p-tolyl. [c]MIC = Minimum inhibitory concn. Numerals indicate the lowest concn in μg/ml that resulted in complete inhibition of growth during a 7-day incubation period. A numeral preceded by the letter "p" indicates that inhibition was partial at the concn indicated;— means no inhibition was evident after 7 days of incubation. General methods and strains H-7 and H-25 were as described in ref 2, 4a, and 4c. [d]The highest concn tested was 20 μg/ml except for **28** and **57** where it was 15 and 7.5 μg/ml, respectively. [e]Compds dissolved in dioxane (D) or MeOH (M) were dild with a 0.04% aqueous soln of Tween 80 (T) or water (W) so that the following final concns in the medium were not exceeded: M, 0.25%; T, 0.008%. W = soln in H_2O. An asterisk indicates that the compd did not dissolve completely. Hot solvent was used to dissolve **1**, **10**, **14**, **30**, **40**, **43**, **45–48**, **52**, and **57**. [f]Commercial sample. [g]NaOH added to effect soln. [h]Efforts to purify **19**, described in ref 4d, were unsuccessful, and the assay had to be done with crude **19**. [i]The samples **20** (in MT), **31** (in 0.01 *N* NaOH), **35** (in W), 55 (in DT), and **37** (in the medium) were sterilized in an autoclave; some destruction of the compd may have resulted. [j]Compd kindly provided by Dr. J. D. Buckman, Buckman Laboratories, Inc., Memphis, Tenn. [k]Compd **54** was dissolved in alcoholic NaOH, which then was brought as near neutrality as possible (using AcOH) without causing pptn.

moiety. Among the disulfides **18–31**, only **18–21** and **31** showed much activity. Compds **19** and **20** might be expected to produce hydrodisulfides. Acyl disulfides with structures resembling **18–20** previously were reported to be active.[4c] The activity of **21** is of interest since the corresponding thiol **4** was virtually inactive. The activity of **31** may result from decomposition to 2-(*n*-decylamino)ethanethiol (MIC 7.5–10 μg/ml).[4a]

Certain dithiocarbamates, trithiopercarbamates, and thiuram disulfides have proved promising as inhibitors of *H. capsulatum*.§ However, the dithiocarbamates **32–37** were inactive or nearly so, as were the trithiopercarbamate **38** and the thiuram-type structures **39** and **40**. Perhaps the significance is that relative simplicity is the keynote, so that bulky or polar types of molecules exemplified by **32–40** are unsatisfactory because of poor transport through membranes or because of adsorption at improper sites.

The thiocyanates **41–43**, the first we have examined, show quite promising activity and appear to provide a lead that should be pursued.

The thiolsulfonates **44–46** and the sulfones **47–55** (a major class we have not tested heretofore) showed little (**44**, **49**, and **51**) or no activity. The thiazolidine **56** showed reasonable promise, but inactivity of the variations **57** and **58** make further work in this area unattractive; moreover, even **56** was unpromising *in vivo*.#

S compds with low molecular weight usually have given the best results.[4a,c] The simple thiol and thion esters **59** and **60** therefore were logical for trial; neither was active. The thiosulfonate salt **61** was of interest because of the activity of methyl methanethiolsulfonate,[4a] but in common with the thiolsulfonates **44–46** no useful lead developed.

References

(1) L. Field, W. S. Hanley, and I. McVeigh, *J. Med. Chem.*, 14, 995 (1971) (paper 9).
(2) I. McVeigh and Z. Evans, *Mycopathol. Mycol. Appl.*, 35, 313 (1968).
(3) J. D. Buckman, B. S. Johnson, and L. Field, *Can. J. Microbiol.*, 12, 1263 (1966).
(4) (a) I. McVeigh, Z. Evans, L. Field, and W. S. Hanley, *Mycopathol. Mycol. Appl.*, 37, 349 (1969); (b) I. McVeigh, L. Field, and W. S. Hanley, "Proceedings of the Second National Conference on Histoplasmosis," Atlanta, Ga., 1969, Charles C. Thomas, Springfield, Ill. (in press); (c) L. Field, W. S. Hanley, I. McVeigh, and Z. Evans, *J. Med. Chem.*, 14, 202 (1971); (d) L. Field, W. S. Hanley, and I. McVeigh, *J. Org. Chem.*, 36, 2735 (1971).

§For examples and leading references, see ref 2.

#There was no prolongation of the life of mice exposed to X-rays and then infected with *H. capsulatum* before treatment with **56**. We are indebted for this test to Drs. R. S. Gordee and W. B. Lacefield of Eli Lilly and Co.; it was performed essentially by methods described in ref 1 and 4c.

Quinoxaline Studies. 20.[1†] Potential Antimalarials. Synthesis of *anti*- and *syn*-*N,N*-Dialkylaminomethyl 2-Quinoxalinyl Ketoximes

Henry R. Moreno, John E. Oatis, Jr., and Harry P. Schultz*

Department of Chemistry, University of Miami, Coral Gables, Florida 33124.

Received September 23, 1971

Unlike many quinolinemethanols,[2] quinoxalinemethanols were demonstrated[3,4] to possess no useful antimalarial activity. It was hoped, however, that aminomethyl 2-quinoxalinyl ketoximes, possessing as they do the seemingly requisite OH and amine functions, would display antimalarial activity. The purpose of this paper is to report the synthesis of a series of *N,N*-dialkylaminomethyl 2-quinoxalinyl ketoximes for testing as antimalarials; neither oximes nor intermediates, unfortunately, had significant antimalarial activity (Table I).[5,‡]

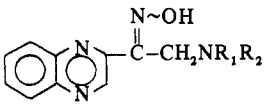
Chloromethyl 2-quinoxalinyl ketone (**1**)[3] was chosen as the starting material for this investigation. Because of previous demonstration[3] of the instability of the corresponding aminomethyl 2-quinoxalinyl ketones, the sequence **1**, chloromethyl 2-quinoxalinyl ketoxime (**2**), and aminomethyl 2-quinoxalinyl ketoxime (**3**) was dictated as the only reasonable course to the objective described in this paper.

2-Chloroacetylquinoxaline formed **2**, a single oxime (nmr), which decomposed when subjected to a variety of Beckmann rearrangement reagents. Examination of Dreiding

†Contribution No. 892 from the Army Research Program on Malaria, supported by the U.S. Army Medical Research and Development Command *via* Contract DADA 17-67-7064.

‡The authors thank the staff of the Division of Medicinal Chemistry, Walter Reed Army Institute of Research, for transmitting the test results provided by Dr. L. Rane, University of Miami.

Table I. *anti/syn-N,N*-Dialkylaminomethyl 2-Quinoxalinyl Ketoximes[a-e]



No.	Compound $R_1 = R_2 =$	Formula	Method of preparation	Recryst solvent	Yield, %	% *anti*-aminomethyl	Mp, C°	Antimalarial activity, life span increase, days, mouse 640 mg/kg
1	Me	$C_{12}H_{14}N_4O$	See Experimental	C_6H_6–ligroin (3:2; 250 ml/g)	49	52	162–167 dec	0.8
2	Et	$C_{14}H_{18}N_4O$	D	EtOH–H_2O (1:1; 20 ml/g)	54	53	145–145.5	0.4
3	*n*-Bu	$C_{18}H_{26}N_4O$	C	2-Propanol–H_2O (10:3; 16 ml/g)	14	60	83.5–84.5	0.7
4	*n*-Pe	$C_{20}H_{30}N_4O$	C	C_6H_6–ligroin (1:10; 20 ml/g)	5	Not executed	76–77	Not tested
5	*N*-Pyrrolidyl	$C_{14}H_{16}N_4O$	D	C_6H_6–ligroin (2:3; 100 ml/g)	66	50	160–163, followed by 187–189	0.2

[a]Uv spectra; average λ_{max} nm (ϵ) 211 (16,000), 244 (22,400), 327 (7100), and in addition for **2**, 322 (9400). [b]H-nmr (1 and 4 excepted); average δ ppm ($CDCl_3$); anti isomers 3.80 (s, 2 H, CH_2), 7.98 (m, 4 H, arom), 9.39 (s, 1 H, heterocyclic); syn isomers 4.29 (s, 2 H, CH_2), 7.98 (m, 4 H, arom), 9.69 (s, 1 H, heterocyclic); also present, complex peaks of alkyl substituents. [c]H-nmr (1); δ ppm (DMSO-d_6); anti 2.18 (2.13) (s, 6 H, $N(CH_3)_2$), 7.95 (m, 4 H, arom), 9.25 (s, 1 H, heterocyclic); syn 2.13 (2.18) (s, 6 H, $N(CH_3)_2$), 7.95 (m, 4 H, arom), 9.04 (s, 1 H, heterocyclic); CH_2 obscured by H_2O. [d]All anal were for C, H, and N; values were within ±0.4% of the theoretical values. [e]Average life span of control mice infected with *Plasmodium berghei*, 6.2 days.

models of **2** as well as analogy with the known stereochemistry of the corresponding ω-chloroacetophenone oxime,[6,§] justifies regarding **2** as being the *syn*-chloromethyl 2-quinoxalinyl ketoxime. The tertiary aminoketoximes prepared from **2** and secondary amines were mixtures of about equal parts of the *syn*-and *anti*-ketoximes, contrary to the reported[8] stereospecificity of similar reactions.

Assignment of syn and anti structures to the compounds described in this paper was based upon the general nmr method established by Karabatsos and coworkers;[9] the farthest downfield of the 2 CH_2 singlets (relative to TMS) indicated the syn relationship# between NOH and CH_2Z groups (Table I).

Experimental Section**

syn-Chloromethyl **2-Quinoxalinyl Ketoxime (2).** A soln of 2.07 g of 2-chloroacetylquinoxaline,[3] 1.5 g of $H_2NOH \cdot HCl$, 20 ml of THF, and 20 ml of 95% EtOH was heated at 60° with stirring for 30 min, then dild with H_2O to give 2.17 g (97%) of product, mp 195–196° dec. A sample was purified for analysis by recrystn (75%) from EtOH–H_2O (2:1; 20 ml/g); mp 194.5–195° dec, pmr (DMSO) δ (ppm) 4.89 (s, 2 H, CH_2), 8.10 (m, 4 H, aromatic), 9.52 (s, 1 H, heterocyclic), 13.16 (s, 1 H, OH), OH removed by exchange with D_2O, λ_{max} 211 nm (ϵ 14,400), 249 (19,500), 321 (5700), 330 (6200). *Anal.* ($C_{10}H_8ClN_3O$) C, H, Cl, N.

anti/syn-N,N-**Dimethylaminomethyl 2-Quinoxalinyl Ketoxime.** To a stirred suspension of 2.22 g of *syn*-chloromethyl 2-quinoxalinyl ketoxime in 50 ml of $CHCl_3$ was added 16 ml of a 25% H_2O soln of Me_2NH. After 5 min the H_2O layer was sepd and discarded, the $CHCl_3$ soln was then extd with 1 *N* HCl and H_2O. The acidic ext was washed with $CHCl_3$, treated with decolorizing C and Filter-Aid, and filtered. The filtrate was made basic (pH ~ 8; $KHCO_3$) to give 1.94 g (84%) of product; mp 171–173° dec, see Table I.

anti/syn-N,N-**Dialkylaminomethyl 2-Quinoxalinyl Ketoxime. Method C.** A soln of 0.01 mole each of *syn*-chloromethyl 2-quinoxalinyl ketoxime, secondary amine, and Et_3N in 20 ml of C_6H_6 stood at 24° for 72 hr. The solvent was removed and the residual oil was washed with H_2O, followed by soln in the minimum of 1 *N* HCl or 95% EtOH. After clarification with decolorizing C and Filter-Aid, the crude product was recovered either by removal of the EtOH or pptn from the aqueous phase ($KHCO_3$), followed by recrystn.

anti/syn-N,N-**Dialkylaminomethyl 2-Quinoxalinyl Ketoximes. Method D.** To a stirred suspension or soln of 0.01 mole of the *syn*-α-halomethyl ketoxime in 20 ml of C_6H_6 at 24° was added a 6- to 8-fold excess of the desired secondary amine. After stirring for 2 hr, the reaction mixt was extd with 1 *N* HCl and H_2O. The aqueous ext was treated with decolorizing C and Filter-Aid, and filtered; solid K_2CO_3 was added to the filtrate (pH ~ 9) to ppt the product.

§These authors referred to their products, however, as the *syn*-phenyl chloromethyl ketoxime and *syn*-phenyl bromomethyl ketoxime, upon isolating chloro- and bromoacetanilide, respectively, from their Beckmann rearrangement products, believing as they did at that early date that the Beckmann rearrangement involved a cis, rather than the later proven trans, migration. *Cf.* ref 7.

#The unequivocal E-Z system used to designate the sterochemistry of unsymmetrical oximes (ref 10) is confusing to apply in this study, hence is not used, because the E-Z nomenclature of this series varies, even though the stereochemistry of the oxime remains fixed. Of the methyl 2-quinoxalinyl ketoximes the *syn*-methyl ketoxime is E, 2-quinoxalinyl is fiducial; *syn*-chloromethyl ketoxime is Z, chloromethyl is fiducial; and the *syn*-dimethylaminomethyl ketoxime is E.

**Spectra were recorded as follows: uv, Bausch and Lomb 505 or Jasco ORD/UV-5, in 95% ethanol, except where noted differently; H-nmr, Hitachi Perkin-Elmer R-20, 60 MHz, 34°, referred to TMS, the δ values for multiplets were taken at the center of gravity. Melting points, determined on a Thomas-Hoover apparatus, were uncorrected. Elemental analyses were performed by P C R, Inc., Gainesville, Florida.

References

(1) D. Gracian and H. P. Schultz, *J. Org. Chem.*, 36, 3989 (1971) (paper 19).
(2) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Monograph No. 9, U.S. Government Printing Office, Washington, D.C., 1953.
(3) H. R. Moreno and H. P. Schultz, *J. Med. Chem.*, 13, 119 (1970).
(4) H. R. Moreno and H. P. Schultz, *ibid.*, 13, 1005 (1970).
(5) T. S. Osdene, P. B. Russell, and L. Rane, *ibid.*, 10, 431 (1967).
(6) H. P. Korton and R. Scholl, *Chem. Ber.*, 34, 1901 (1901).
(7) L. G. Donaruma and W. Z. Heldt, *Org. React.*, 11, 70 (1960).
(8) H. P. Fischer and C. A. Grob, *Helv. Chim. Acta*, 45, 2528 (1962).
(9) G. J. Karabatsos and C. E. Osborne, *Tetrahedron*, 24, 3361 (1968), previous papers in the series, and references cited therein.
(10) E. L. Eliel, *J. Chem. Educ.*, 48, 163 (1971).