addition of ether as in the preparation of the D isomer[1] and recrystallization from ethanol gave a 36% yield of 11.)

Acknowledgment. This investigation was supported by the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, through Contract NO1-CM-43762. The authors are indebted to Mrs. Anne D. Brazier for biological computations and to Mr. Marion C. Kirk for specific rotations.

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1-(Dichloroacetyl)-1,2,3,4-tetrahydro-6-quinolinol Esters. New Potent Antiamebic Agents

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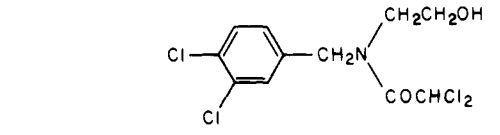
A series of 1-(dichloroacetyl)-1,2,3,4-tetrahydro-6-quinolinols and certain *O*-acyl derivatives thereof have been prepared and shown to be potent antiamebic agents in the *Entamoeba criceti* infected hamster model. Compounds were compared with etichlordifene and diloxamide and one of them, 1-(dichloroacetyl)-6-(2-furoyloxy)-1,2,3,4-tetrahydroquinoline (**4**), was selected for human trial.

The first dichloroacetamide antiamebic agent to receive extensive animal testing and clinical trial was chlorbetamide[1] (I; Mantomide®). Later additions to this clinically effective class of compounds were teclozan[2] (II; Falmonox®), etichlordifene[3] (III; Kitnos®), and diloxamide[4] (IV; Furamide®). We now describe a new class of dichloroacetamide, 1-(dichloroacetyl)-1,2,3,4-tetrahydro-6-quinolinol, derivatives (V), several of which are more potent than any of the above reference drugs when screened against an *Entamoeba criceti* model in hamsters.



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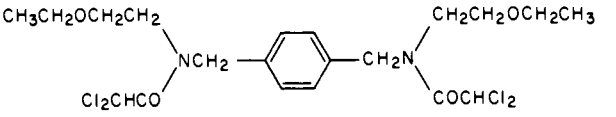

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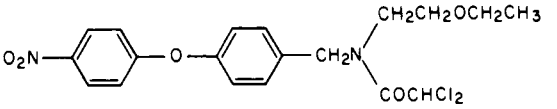

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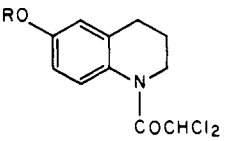
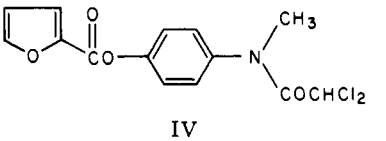


V



IV

Chemistry. Compounds **2** through **13** of Table I were prepared from the free phenol **1**, which in turn was prepared by direct dichloroacetylation of the known[5] 1,2,-3,4-tetrahydro-6-quinolinol. The halogenated phenols **8** and **9** were prepared by direct interaction of **1** with sulfuryl chloride and elemental bromine, respectively, and were determined to be the 5-halo isomers by inspection of their NMR spectra. Esterification of the phenolic amides was accomplished using the appropriate acyl chloride and triethylamine in an appropriate solvent.

Screening. Young adult female Sprague–Dawley hamsters weighing 100–120 g and harboring trophozoites of the naturally occurring *Entamoeba criceti* in the cecum and colon were used in the studies. The animals had a rate of spontaneous infection with *E. criceti* of nearly 100% in the breeding colony. Examinations for infectivity were made in ten randomly chosen animals weekly, and in no

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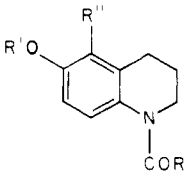
Table I. 1-(Haloacyl)-1,2,3,4-tetrahydro-6-quinolinol Derivatives



compd[a]	R	R'	R''	mp, °C	ED_{50} ± SE,[f]
1	$CHCl_2$	H	H	136.0–136.5	1.20 ± 0.13
2	$CHCl_2$	C_6H_5CO	H	119.0–119.5	0.20 ± 0.03
3	$CHCl_2$	$(C_4H_3S)CO$[b]	H	109.0–110.5	0.16 ± 0.02
4	$CHCl_2$	$(C_4H_3O)CO$[c]	H	150.5–151.0	0.20 ± 0.03
5	$CHCl_2$	$CH_3(CH_2)_2CO$	H	107–108	0.75 ± 0.16
6	$CHCl_2$	$CH_3(CH_2)_{14}CO$	H	84–86	1.75 ± 0.21
7	$CHCl_2$	CH_3NHCO	H	113–117	5.7[d]
8	$CHCl_2$	H	Cl	189.5–192.5	0.50 ± 0.09
9	$CHCl_2$	H	Br	207–210	0.56 ± 0.10
10	$CHCl_2$	$(C_4H_3S)CO$[b]	Cl	131–134	0.22 ± 0.04
11	$CHCl_2$	$(C_4H_3O)CO$[c]	Cl	132–133	0.21 ± 0.03
12	$CHCl_2$	$(C_4H_3S)CO$[b]	Br	149–150	1.24 ± 0.29
13	$CHCl_2$	$(C_4H_3O)CO$[c]	Br	159–161	0.39 ± 0.06
14	CH_2Cl	H	H	146.5–150.0	2.0[d]
15	CCl_3	H	H	153–155	3.0 ± 0.4
III					0.38 ± 0.04[e]
IV					>3.2

[a] C, H, N; analyses were within ±0.4% of theory for all new compounds. [b] 2-Thiophenecarbonyl. [c] 2-Furancarbonyl. [d] AED_{50}. [e] This value was obtained in a side by side four dose level comparison with compound 4 (quinfamide) in which the latter demonstrated a value of 0.27 ± 0.03. [f] (mg/kg)/day po for 3 days.

instance were animals used if the rate of infection fell below 90%. Drugs were suspended in 1.0 mL of 10% gelatin and were administered by intragastric gavage in two 0.5-mL aliquots, once in the morning and once in the afternoon, on 3 consecutive days. Groups of five animals each received test drugs at three twofold drug levels per test. On the day following the last dose, the animals were sacrificed using ether, and scrapings from the wall of the cecum were suspended in saline and examined microscopically under low-power (43×) magnification. The absence of trophozoites in a preparation resulted in a "cleared" score for that animal. If all five animals were cleared at the lowest dose tested, additional tests at lower doses were performed.

Results and Discussion

Esterification of the phenol 1 generally produced agents of higher potency than the parent. Likewise, halogenation of the aromatic portion of 1 resulted in compounds with enhanced activity, but their esters 10–13 showed no advantage over the respective unhalogenated analogues.

In an effort to differentiate compounds 2–4, the effect of a single dose of each of these on spontaneous *E. criceti* infections in hamsters was examined. The single dose ED_{50} values ± SE (mg/kg po) for these three compounds (2–4) were 1.60 ± 0.22, 4.8 ± 1.1, and 0.75 ± 0.09, respectively. Because of the single-dose efficacy and low toxicity of 4 (no deaths in rats or hamsters after acute administration of 10 g/kg po), this compound was selected for field trial and is currently undergoing testing in humans.

Experimental Section

Melting points were taken in capillary tubes and are uncorrected. NMR spectra were recorded using a Varian HA 100 spectrometer. Elemental analyses were performed by Instranal Laboratories, Rensselaer, N.Y.

1-(Dichloroacetyl)-1,2,3,4-tetrahydro-6-quinolinol (1). To a stirred mixture of 14.9 g (0.1 mol) of 1,2,3,4-tetrahydro-6-quinolinol[5] and 250 mL of dry ethylene dichloride was added dropwise 16.2 g (0.11 mol) of dichloroacetyl chloride. The mixture was heated (steam bath) for 14 h and then volatile materials were removed under vacuum. The residue was dissolved in chloroform and the solution was again stripped of solvent in vacuo. The residual powder was slurried at ambient temperature with a mixture of 100 mL of *n*-hexane and 10 mL of isopropyl alcohol. After filtration of the slurry, the residual solid was crystallized twice from chloroform–*n*-hexane and dried at 60 °C (0.1 mm) to give 10.5 g of product, mp 136.0–136.5 °C. Anal. ($C_{11}H_{11}NO_2Cl_2$) C, H, N.

5-Chloro-1-(dichloroacetyl)-1,2,3,4-tetrahydro-6-quinolinol (8). To a stirred solution of 32 g (0.132 mol) of 1 in 400 mL of hot benzene was added rapidly 17.7 g (0.132 mol) of sulfuryl chloride. After the initial exothermic reaction subsided, the mixture was stirred and refluxed for 1 h and filtered hot to give 21.8 g of product of mp 189.0–191.5 °C. Recrystallization of this material from acetonitrile gave 19.4 g: mp 189.5–192.5 °C; NMR δ 7.50, 6.76 (J = 8 Hz; aromatic hydrogens, ortho coupled). Anal. ($C_{11}H_{10}NO_2Cl_3$) C, H, N.

5-Bromo-1-(dichloroacetyl)-1,2,3,4-tetrahydro-6-quinolinol (9). A solution of 4.0 g (0.025 g-atom) of bromine in 50 mL of chloroform was added over 1 h to a stirred mixture of 6.15 g (0.024 mol) of 1 and 2 g of powdered calcium carbonate in 100 mL of chloroform. The reaction mixture was maintained at −5 °C during the addition and for 1.5 h longer, at which time all of the bromine color was dispelled. The mixture was transferred to a separatory funnel along with an additional 600 mL of chloroform, and the whole was washed twice with 10% aqueous sodium bicarbonate solution and then with water. The chloroform solution was dried over sodium sulfate and stripped. The remaining material was crystallized twice from acetonitrile to yield 2.3 g of product; mp 207–210 °C; NMR δ 7.35, 6.87 (J = 8 Hz; aromatic hydrogens, ortho coupled). Anal. ($C_{11}H_{10}NO_2BrCl_2$) C, H, N.

1-(Dichloroacetyl)-6-(2-furoyloxy)-1,2,3,4-tetrahydroquinoline (4). The following procedure is typical of the acylation technique used to produce the esters of Table I. A solution of 11.0 g (0.042 mol) of 1 in 200 mL of chloroform and 6.3 mL of triethylamine was stirred and chilled in ice while 5.8 g (0.044 mol) of 2-furoyl chloride in 15 mL of chloroform was added dropwise. After 1 h, the ice bath was removed and stirring was continued for 3 h. The mixture was poured into ice and water containing 4 mL of acetic acid. The chloroform layer was separated and washed successively with water, 10% aqueous sodium bicarbonate, and again with water. The organic solution was dried (sodium sulfate), decolorized with charcoal, and concentrated under vacuum. The residual solid was crystallized first from methanol and then from ethyl acetate to give 13.1 g of product, mp 150.5–151.0 °C. Anal. ($C_{16}H_{13}NO_4Cl_2$) C, H, N.

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Book Reviews

Organophosphorus Chemistry. Volume 9. Specialist Periodical Reports. By S. Trippett, Senior Reporter. The Chemical Society, Burlington House, London. 1978. ix + 288 pp. 14.5 × 22.5 cm. $48.00.

This year's volume of this continuing series, covering publications appearing between July 1976 and June 1977, lacks a chapter on "Photochemical, Radical, and Deoxygenation Reactions". In other respects, it is similar to last year's report, with its many virtues and minor defects.

University of Massachusetts **Bernard Miller**

Metal Toxicity in Mammals. Volume 1. Physiologic and Chemical Basis for Metal Toxicity. Edited by T. D. Luckey and B. Venugopal. **Volume 2. Chemical Toxicity of Metals and Metalloids.** Edited by B. Venugopal and T. D. Luckey. Plenum Press, New York. Vol 1: 1977. x + 238 pp. 16 × 23.5 cm. $27.50. Vol 2: 1978. 16 × 23.5 cm. x + 409 pp. $35.00.

This two-volume treatise provides biologists and physical scientists with an understanding of the chemical toxicity of metals, metalloids, and their inorganic compounds. Volume 1 offers introducing and background information about metals and their salts in mammalian nutrition, physiology, and toxicology and summarizes the chemical toxicity of all nonradioactive metals. This volume also explores the role of metals in carcinogenicity teratogenecity, including the phenomenon of surface carcinogenesis. The second volume focuses on the toxic effects of inorganic salts, and discuses the chemical toxicity and metabolism of radioactive metals. In addition, there are chapters which deal with comparative toxicity of metals by interspecies, routes of administration, as well as a discussion of metal toxicity in groups 1–8 in the periodic table. A summary of the toxicity of all metals by groups, periods, modes of administration, and species is given in a summary chapter. An appendix, a glossary, a list of pertinent source materials and references, and a subject index is provided in each volume.

These volumes provide easy access to the toxicological effect of metals and should be valuable to medicinal chemists, as well as to toxicologists, pharmacologists, and other biological scientists.

Staff Review

Metal Ions in Biological Systems. Volume 7. Iron in Model and Natural Compounds. Edited by Helmut Sigel. Marcel Dekker, New York, N.Y. 1978. xvii + 417 pp. 15.5 × 23.5 cm. $39.50.

Like previous volumes in this series, this volume contains recent review chapters on various aspects of its principal topic, "iron in model and natural compounds". Three chapters deal with small-molecule iron compounds, covering "Prebiotic Coordination Chemistry", the "Biological Significance of Low Molecular Weight Iron(III) Complexes", and "Synthetic Analogs of the Oxygen-Binding Hemoproteins". Four more chapters cover macromolecular topics such as "Iron–Sulfur Proteins and their Synthetic Analogs", "Catalases and Iron Complexes with Catalase-Like Properties", "Monooxygenase Hemoproteins", and "Mechanisms for the Modulation of Hemoglobin Oxygenation". Finally, there are two chapters dealing with iron in living systems, covering the "Storage and Transport of Iron" and "Human Iron Metabolism".

Each of the chapters is full of tabular data, well illustrated, and thoroughly referenced. In reviewing them it is interesting to note the extent to which "models" have (or have not) approached the biological realities; the iron–sulfur proteins and cytochromes P-450 are particularly interesting cases in point. Several of the chapters on coordination chemistry and metabolism of iron will be valuable to medicinal chemists concerned with the therapy of iron deficiency and/or iron overload. They may also provide valuable background for contemplating the therapeutic uses of transition metal derivatives of other compounds, such as L-dihydroxyphenylalanine or antiinflammatory agents, which have shown recent successes.

In conclusion, Dr. Sigel and his collaborating authors have produced a fine addition to a highly worthwhile series.

University of Kansas **Robert P. Hanzlik**

Synthetic Methods of Organic Chemistry. Volume 32. Edited by W. Theilheimer. (1978 Yearbook mit deutschem Registerschlussel). S. Karger AG, Basel 1978. xvi + 593 pp. 16 × 23 cm. $267.00.

New methods for the synthesis of organic compounds and improvements of known methods are being recorded continuously in this classic reference source. This is the second volume of the seventh series. New references to material in the preceding series have been included in the text. The index is cumulative for volumes 31 and 32 and also contains additional and revised entries to previous volumes. The formula index of functional combinations has been expanded to include pertinent items from all previous volumes, as well as nomenclature which had been discontinued in the later volumes. Most of the references in this volume are to papers published between 1975 and 1977. It is inconceivable that any library that serves the needs of organic chemists can be without this most valuable reference source, even at the stagering price of this volume.

Staff Review

Aromatic and Heteroaromatic Chemistry. Volume 6. Specialist Periodical Reports. Edited by H. Suschitzky and O. Meth-Cohn, Senior Reporters. The Chemical Society, Burlington House, London. 1978. xii + 326 pp. 14 × 22 cm. $56.00.

Those who are familiar with this series of "Specialist Periodical Reports" will find a pleasant surprise in this latest volume. The new senior reporters have recast the format so that it parallels that of the "Saturated Heterocyclic Chemistry" series. Thus, there are chapters concerned with all of the expected ring sizes, except for the six-membered homocycles which are to be covered in the next volume. Electrophilic and nucleophilic substitution reactions and substitutions by free radicals, carbenes, and nitrenes are covered in three chapters. The report is completed with three chapters on porphyrins and other naturally occuring aromatic compounds. While these last chapters are of particular interest to medicinal chemists, almost everyone will also find a topic of interest elsewhere in the report. The new format makes it easier to locate that topic via the table of contents.