TABLE I

Isoflavthione (yield, %)	Ratio (g) isoflavone/P_2S_5	Mp, °C	Color[a]	Infrared data (cm^{-1})	λ_{max}^{MeOH}, mμ (ε)	Formula	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
2a (51)	0.50	189–191	Magenta prisms	1610, 1510, 1440	385 (17,200),[b] 282 (11,200),[b] 355 (10,700)[b,c]	$C_{16}H_{14}OS$	73.79	1.85	8.56	73.32	1.51	8.51
2b (184)	0.38	163–164	Magenta prisms	1570, 1615, 1600, 1510	381 (14,100), 276 (11,500)	$C_{17}H_{16}OS$	66.25	1.32	9.81	66.23	1.35	9.61
2c (85)	0.71	181–185	Purple rods	1760, 1600, 1546, 1505	373 (16,800), 278 (11,900)	$C_{16}H_{13}OS$	67.05	1.75	9.40	67.30	1.81	9.34
2d (38.4)	0.50	93 and 110–112 (dimorphous)	Purple-black rods	1770, 1620, 1602, 1550, 1520	377 (16,300), 285 (12,600)	$C_{16}H_{13}OS$	68.17	5.47	8.69	68.63	5.86	8.58

[a] The color is undoubtedly due to solid-state and association phenomena, for it was imparted only to very concentrated solutions and was unmeasurable in the region 400–600 mμ employing 10^{-3} to 10^{-5} *M* solutions of the isoflavthiones **2** in methanol, benzene, and hexane. [b] Benzene, not methanol, was the solvent. [c] Shoulder.

Synthesis of Potential Antineoplastic Agents. XVIII. Synthesis of New Alkylating Agents[1]

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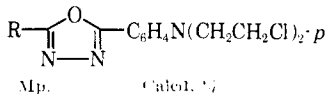
The preparation of a number of potential biological alkylating agents and related compounds is reported.

Experimental Section[3]

2-{*p*-[Bis(2-chloroethyl)amino]phenyl}-5-alkyl-1,3,4-oxadiazole.—Following the procedure of Ainsworth,[4] 2.0 g of *p*-[bis(2-chloroethyl)amino]benzhydrazide[5] was heated to reflux in 15 ml of the appropriate, freshly distilled, triethylorthoalkyl ester. The mixture was refluxed overnight and the excess orthoester was removed *in vacuo*. The oxadiazoles were recrystallized from ethanol–water and are shown in Table I.

TABLE I



R	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H[a]	55	68–70	50.36	4.58	14.69	50.56	4.60	14.62
CH_3	79	122–125	52.01	5.04	14.00	52.11	5.13	13.92
C_2H_5	84	109–113	53.14	5.45	13.37	53.35	5.58	13.12

[a] We should like to thank Dr. D. W. Alwani for assistance with this compound. This compound was inactive[7] against Walker carcinosarcoma.

1,4-Bis[(2-chloroethyl)thio]-2,3,5,6-tetrafluorobenzene. A mixture of 1 g of 1,4-bis[(2-hydroxyethyl)thio]-2,3,5,6-tetrafluorobenzene[6] and 5 ml of $SOCl_2$ was refluxed for 3 hr and the excess $SOCl_2$ was removed *in vacuo* to give 1.3 g of solid, mp 110–116°. Recrystallization from ethanol gave white needles, mp 114–116°.

Anal. Calcd for $C_{10}H_8F_4Cl_2S_2$: C, 35.40; H, 2.37; F, 22.40; Cl, 20.90; S, 18.90. Found: C, 35.30; H, 2.75; F, 22.06; Cl, 20.85; S, 18.90.

This compound was inactive[7] against Walker carcinosarcoma 256.

Diethyl [Bis(2-hydroxyethyl)amino]methylenemalonate.—A mixture of 5.07 g (0.048 mole) of bis(2-hydroxyethyl)amine and 10.5 g (0.048 mole) of diethyl ethoxymethylenemalonate in 60 ml of absolute ethanol was refluxed for 1 hr and the solvent was removed *in vacuo* to give an oil. Distillation gave 9.9 g (74%) of liquid, bp 58–61° (0.8 mm).

Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.09; H, 7.66; N, 4.89.

This compound was inactive[7] against Sarcoma 180 and L1210 lymphoid leukemia.

[Bis(2-hydroxyethyl)amino]methylenemalononitrile.—Using a similar procedure 8.6 g (98%) of solid, mp 86–87° (from ethanol), was obtained.

Anal. Calcd for $C_9H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.86; H, 5.93; N, 23.32.

This compound was inactive[7] against L1210 lymphoid leukemia and S91 Cloudman melanoma and only very slightly (T/C = 61% at 500 mg/kg) active against Sarcoma 180.

Ethyl [Bis(2-chloroethyl)amino]methylenecyanoacetate.—A solution of 0.05 mole of ethyl ethoxymethylenecyanoacetate and bis(2-chloroethyl)amine (from 0.05 mole of its hydrochloride) in benzene was refluxed for 6 hr. Removal of the solvent *in vacuo* gave an oil which was chromatographed on acid-washed alumina and the solid eluted was recrystallized from ethanol to give 4.7 g (36%) of solid, mp 56–59°.

Anal. Calcd for $C_{10}H_{14}Cl_2N_2O_2$: C, 45.30; H, 5.32; N, 10.57; Cl, 26.74. Found: C, 45.31; H, 5.42; N, 10.52; Cl, 26.78.

This compound was inactive[7] against Walker carcinosarcoma 256. The hydroxyethyl analog of this compound[8] was inactive[7] against L1210 lymphoid leukemia and Friend virus leukemia and only slightly active (T/C = 65% at 62 mg/kg) against Heptoma 129. Preliminary attempts to convert this hydroxyethyl compound directly to the chloroethyl compound with $SOCl_2$ failed.

(1) (a) Part XVII: F. D. Popp, F. P. Silver, and D. W. Alwani, *J. Med. Chem.*, **10**, 481 (1967). (b) Supported in part by research grants from the American Cancer Society and from the National Cancer Institute.

(2) Abstracted in part from the M.S. Thesis of F. P. S.

(3) Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points are taken in capillaries and are corrected.

(4) C. Ainsworth, *J. Am. Chem. Soc.*, **77**, 1148 (1955).

(5) R. C. Elderfield and T. K. Liao, *J. Org. Chem.*, **26**, 4996 (1961).

(6) J. Burdon, V. Damodaran, and J. Tatlow, *J. Chem. Soc.*, 763 (1964).

(7) Screening results were supplied by the CCNSC of the National Institutes of Health.

(8) A. A. Santilli, W. F. Bowe, and T. S. Osdene, *J. Med. Chem.*, **7**, 68 (1964).

Synthesis of Potential Antineoplastic Agents. XIX. Some 5-(ω-Chloroacylamino)quinolines and 4- and 5-(ω-Chloroacylamino)isoquinolines[1]

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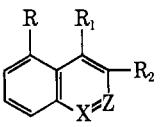
A number of 5-(ω-chloroacylamino)quinolines and 4- and 5-(ω-chloroacylamino)isoquinolines were prepared by reaction of

(1) (a) Part XVIII: F. D. Popp, F. P. Silver, and A. C. Noble, *J. Med. Chem.*, **10**, 986 (1967). (b) Supported in part by research grants from the American Cancer Society and from the National Cancer Institute. (c) A portion of this material is abstracted from the M.S. Thesis of F. P. S., Clarkson College of Technology, 1967.

TABLE I



X	Z	R	R_1	R_2	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
CH	N	$NHCOCH_2Cl$	H	H	290–291	59.87	4.11	12.70	60.14	4.14	13.00
CH	N	$NHCOCH_2CH_2Cl$	H	H	144–145	61.41	4.73	11.94	61.46	4.73	11.71
CH	N	$NHCO(CH_2)_3Cl$	H	H[a]	114–115	62.74	5.27	11.27	62.78	5.39	11.16
CH	N	H	$NHCOCH_2Cl$	H	280–282	59.87	4.11	12.70	60.04	4.14	12.68
CH	N	H	$NHCOCH_2CH_2Cl$	H	134–135	61.41	4.73	11.94	61.60	4.84	12.24
CH	N	H	$NHCO(CH_2)_3Cl$	H	122–123	62.74	5.27	11.27	62.70	5.55	11.10
CH	N	$NHCOCH_2Cl$	H	CH_3[b]	162–165	61.41	4.73	11.94	60.90	4.65	11.68
CH	N	$NHCOCH_2CH_2Cl$	H	CH_3	145–146	62.74	5.27	11.27	62.48	5.05	11.02[c]
CH	N	$NHCO(CH_2)_3Cl$	H	CH_3	143–144	64.00	5.75	10.66	63.69	5.90	10.45
N	CH	$NHCOCH_2CH_2Cl$	H	H[d]	139–140	61.41	4.73	11.94	61.44	4.96	11.92
N	CH	$NHCO(CH_2)_3Cl$	H	H[d]	115–118	62.74	5.27	11.27	62.73	5.20	11.29
N	CH	$NHCO(CH_2)_4Cl$	H	H	139–141	64.00	5.75	10.66	63.81	5.60	10.66

[a] Gave 5-aminoisoquinoline on reaction with $HN(CH_2CH_2OH)_2$. [b] Gave 3-methyl-5-aminoisoquinoline on reaction with $HN(CH_2CH_2OH)_2$. [c] *Anal.* Calcd: Cl, 14.26. Found: Cl, 14.20. [d] Gave 5-aminoquinoline on reaction with $HN(CH_2CH_2OH)_2$.

ω-chloroacyl chlorides with the appropriate aminoheterocycle. It was hoped to convert these to alkylating agents similar to those prepared by Elderfield and LeVon[3] from 8-aminoquinolines but in several preliminary experiments these amides were readily hydrolyzed in reactions with N,N-bis((2-hydroxyethyl)amine and the route was abandoned.

Experimental Section[4]

Preparation of Amides.—The appropriate aminoquinoline or aminoisoquinoline was treated with the appropriate ω-chloroacyl chloride under the conditions of Elderfield and LeVon,[3] the conditions of DiGangi,[5] or more conveniently in CH_2Cl_2 or $CHCl_3$ to give after neutralization the amides listed in Table I.

***p*-N,N-Bis(2-chloroethyl)aminobenzoyl Derivative of 5-Aminoquinoline.**—Use of *p*-[N,N-bis(2-chloroethyl)amino]benzoyl chloride and 5-aminoquinoline in the above sequence gave a 53% yield of solid, mp 169–172°. This compound exhibited no antineoplastic activity against Walker carcinosarcoma 256 at 25 mg/kg.

Anal. Calcd for $C_{20}H_{19}Cl_2N_3O$: C, 61.86; H, 4.93; N, 10.82; Cl, 18.26. Found: C, 61.82; H, 5.00; N, 10.82; Cl, 18.21.

(2) (a) Clarkson College of Technology. (b) University of Miami. (c) To whom inquiries should be addressed at Clarkson College of Technology.

(3) R. C. Elderfield and E. F. LeVon, *J. Org. Chem.*, **25**, 1576 (1960).

(4) Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points are taken in capillaries and are corrected.

(5) F. E. DiGangi, *J. Am. Pharm. Assoc.*, **44**, 136 (1955).

Book Reviews

The Epidemiology of Tropical Diseases. By OSCAR FELSENFELD. Charles C Thomas, Publisher, Springfield, Ill. 1966. xiv + 488 pp. 16.5 × 24 cm. $14.75.

Only an insignificant number of American medicinal scientists and physicians are working in the field of tropical diseases, in spite of the fact that almost 500,000 Americans have been sent into jungles where they lie in foxholes, wade through vector-infested streams, and eat food that would be condemned as unsanitary in their home land. The reason for this apparent lack of interest is, quite simply, money. The U. S. Public Health Service must marshall its funds wisely for the health of the nation, and in the now increasingly rare intervals of "peace," tropical diseases present no major health hazard to most Americans. Most of the pharmaceutical industry sees little financial incentive in producing drugs that the impoverished underdeveloped countries in tropical regions could ill afford. This is a deplorable state of affairs both from a human and scientific point of view. Disregarding our inherent humanitarian impulses to help our fellow men to rid themselves of disease, we appear to be condemned by circumstances and by unwise policies to send wave after wave of our best young males to fight in tropical countries for many years to come. This alone should call for a major public and private effort to sponsor research in tropical diseases. Scientifically, huge unexplored areas lure the medicinal and medical investigator to apply to them experiments in fundamental science and clinical art.

The textbook by Felsenfeld makes a valuable contribution to this neglected field and should be required reading for any committee that toys with plans for research on tropical maladies. It can be read profitably by epidemiologists and by laymen. The infectious process, including routes and vectors of infections, start off the book and lead next to control measures by sanitation and immunization. The next four major sections are devoted to detailed discussions of the epidemiology of bacterial, mycotic, parasitic, rickettsial, and viral diseases encountered in hot, humid belts; some of these infections overlap with conditions prevalent in North America as well. The final section of the book deals with noncommunicable diseases of nutritional and occupational origin, malignancies, dental and cardiovascular disorders, and addiction and mental diseases. Here again the tropics hold no privileged position, and much of what the author has observed there would apply to domestic conditions.

The book is clearly written, well printed, and thoroughly readable. There is an adequate subject index, and at the end of each section a list of references to books, recent monographs, and reviews.

UNIVERSITY OF VIRGINIA ALFRED BURGER
CHARLOTTESVILLE, VIRGINIA

Developmental and Metabolic Control Mechanisms and Neoplasia. A Collection of Papers Presented at the Nineteenth Annual Symposium on Fundamental Cancer Research, 1965, at The University of Texas M. D. Anderson Hospital and Tumor Institute. The Williams and Wilkins Company, Baltimore, Md. 1965. x + 514 pp. 16 × 23.7 cm. $16.00.