Potential Anticancer Compounds. I. Synthesis of Thiodiacetic Acid Hydrazides and Homologs

HANS ZIMMER AND EDWARD SHAHEEN

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The activity of bis(2-chloroethyl) sulfide and of several nitrogen analogs (nitrogen mustards) against certain types of cancer is well established.[1] However, besides a more or less pronounced toxicity, all of these compounds suffer from several unfavorable physiological properties. Therefore, the synthesis of compounds was undertaken which have the structural element $S(CH_2)_n-$ / $S(CH_2)_n-$ of mustard oil but which have instead of the Cl atom the groups $-C(=O)-NHN=R$ (R = aralkylidene) or $-C(=O)-NHNHR$ (R = H or phenyl). It was hoped that these compounds would retain anticancer activity while being less toxic than the mustards. The $-C(=O)-NHN-$ group was chosen to provide the compounds with some hydrophilic solubility. Preliminary tests against three types of experimental tumors in mice, adenocarcinoma (Ca = 755), sarcoma (Sa = 180), and leukemia (L = 1210), however, showed that the compounds exhibit no activity against these tumor systems.

The compounds were prepared by established methods[2] and are compiled in Tables I and II. The corresponding bromosubstituted fatty acid es-

TABLE I

ALKYLIDENE HYDRAZIDES OF THIODIACETIC ACID AND HOMOLOGS

Compound	M.P.	Formula	C		H	
			Calcd.	Found	Calcd.	Found
		$S(CH_2CONHN=R)_2$				
R = C_6H_5CH	169–170	$C_{18}H_{18}N_4O_2S$	61.0	60.3[a]	5.1	5.2
2-ClC_6H_4CH	205–206	$C_{18}H_{16}Cl_2N_4O_2S$	51.1	50.8	3.8	3.7
4-$CH_3OC_6H_4CH$	210–212	$C_{20}H_{22}N_4O_4S$	57.9	58.1	5.3	5.6
$C_6H_5CH=CH-CH$	207–208	$C_{22}H_{22}N_4O_2S$	65.0	64.9	5.5	5.5
4-$(CH_3)_2NC_6H_4CH$	185–186	$C_{22}H_{28}N_6O_2S$	60.0	59.2[a]	6.4	6.0
2-HOC_6H_4CH	222–224	$C_{18}H_{18}N_4O_4S$	56.0	56.0	4.7	4.9
$C_6H_5CCH_3$	182–183	$C_{20}H_{22}N_4O_2S$	62.8	62.8	5.8	5.9
		$S(CH_2CH_2CONHN=R)_2$				
R = C_6H_5CH	204–206	$C_{20}H_{22}N_4O_2S$	62.8	62.6	5.8	5.8
2-ClC_6H_4CH	170–172	$C_{20}H_{20}Cl_2N_4O_2S$	53.2	53.2	4.5	4.6
4-$CH_3OC_6H_4CH$	145	$C_{22}H_{26}N_4O_4S$	59.7	59.7	5.9	5.9
$C_6H_5CH=CH-CH$	237–240	$C_{24}H_{26}N_4O_2S$	66.3	66.1	6.0	6.1
4-$(CH_3)_2NC_6H_4CH$	247–250	$C_{24}H_{32}N_6O_2S$	61.5	61.5	6.9	6.9
2-HOC_6H_4CH	236–238	$C_{20}H_{22}N_4O_4S$	58.0	58.0	5.3	5.5
$C_6H_5CCH_3$	205–207	$C_{22}H_{26}N_4O_2S$	64.4	63.4[a]	6.4	6.6
		$S(CH_2CH_2CH_2CONHN=R)_2$				
R = C_6H_5CH	130–132	$C_{22}H_{26}N_4O_2S$	64.4	63.5[a]	6.4	6.4
2-ClC_6H_4CH	172–175	$C_{22}H_{24}Cl_2N_4O_2S$	55.1	53.7[a]	5.0	4.9
4-$CH_3OC_6H_4CH$	137–138	$C_{24}H_{30}N_4O_4S$	61.2	60.2[a]	6.4	6.2
$C_6H_5CH=CH-CH$	201–203	$C_{26}H_{30}N_4O_2S$	67.5	67.2	6.5	6.4
2-HOC_6H_4CH	193–195	$C_{22}H_{26}N_4O_4S$	59.7	59.8	5.9	6.1
$C_6H_5CCH_3$	151–153	$C_{24}H_{30}N_4O_2S$	65.7	63.7[a]	6.9	6.7
		$S[CH(CH_3)CONHN=R]_2$				
R = C_6H_5CH	223–224	$C_{20}H_{22}N_4O_2S$	62.8	62.5	5.8	5.7
2-ClC_6H_4CH	243–244	$C_{20}H_{20}Cl_2N_4O_2S$	53.2	53.3	4.5	4.5
4-$CH_3OC_6H_4CH$	239–240	$C_{22}H_{26}N_4O_4S$	59.7	59.9	5.9	6.0
$C_6H_5CH=CH-CH$	231–232	$C_{24}H_{26}N_4O_2S$	66.3	66.0	6.0	6.0
4-$(CH_3)_2NC_6H_4CH$	234–235	$C_{24}H_{32}N_6O_2S$	61.5	61.4	6.9	7.1
2-HOC_6H_4CH	225–226	$C_{20}H_{22}N_4O_4S$	58.0	58.2	5.4	5.5
$C_6H_5CCH_3$	212–213	$C_{22}H_{26}N_4O_2S$	64.4	64.2	6.4	6.8

[a] The analysis could not be improved by further recrystallization.

(1) Jesse P. Greenstein, "Biochemistry of Cancer," Academic Press Inc., New York, N. Y., 1954, p. 282.

TABLE II

HYDRAZIDES OF THIODIACETIC ACID AND HOMOLOGS

Compound	M.P.	Formula	C		H	
			Calcd.	Found	Calcd.	Found
		$S(CH_2CONHNHR)_2$				
R = H	117–119[a]	$C_4H_{10}N_4O_2S$	26.9	27.2	5.6	5.6
C_6H_5	212–215	$C_{16}H_{18}N_4O_2S$	58.2	58.2	5.5	5.4
		$S(CH_2CH_2CONHNHR)_2$				
R = H	152–153	$C_6H_{14}N_4O_2S$	34.9	35.0	6.8	6.9
C_6H_5	204–206[b]	$C_{18}H_{22}N_4O_2S$	60.3	59.6	6.2	6.3
		$S(CH_2CH_2CH_2CONHNR)_2$				
R = H	128–131[c]	$C_8H_{18}N_4O_2S$	41.0	41.0	7.7	7.7
C_6H_5	151–153	$C_{20}H_{26}N_4O_2S$	62.1	60.6[de]	6.8	6.6
		$S[CH(CH_3)CONHNR]_2$				
R = H	174–175[b]	$C_6H_{14}N_4O_2S$	34.9	35.8	6.8	7.1
C_6H_5	169–170	$C_{18}H_{22}N_4O_2S$	60.3	62.5[e]	6.2	6.2

[a] Recrystallized from methanol. [b] Recrystallized from methanol/dimethylformanide. [c] W. Reppe, *Ann.*, **596**, 158 (1955), m.p. 130°. [d] Recrystallized from ethanol/dimethylformanide. [e] The analysis could not be improved by further recrystallization.

ters were treated with sodium sulfide in aqueous ethanol. The thiodiacid esters were isolated and, on reaction with excess hydrazine, furnished the corresponding hydrazides. The latter were converted into the aralkylidene hydrazides by the method of Zimmer and George.[3] The hydrazides are characterized by an extremely low solubility in most of the common solvents. They are, however, soluble in *N,N*-dimethylformamide and can be recrystallized from this solvent. They all have rather unsharp melting points and melt with considerable decomposition. Therefore, these derivatives are not well suited for possible identification of carbonyl compounds. In the preparation of the phenylhydrazides,[4] it was found advantageous to use the acids rather than the esters as starting materials.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses are by A. Bernhardt, Microanalytisches Laboratorium im Max-Planck-Institut, Mulheim/Ruhr, Germany.

Materials. Generally, Eastman White Label products or comparable grades were employed without further purification. Ethyl 4-bromobutyrate was obtained from Fluka, A.G., Buchs, Switzerland.

The preparations of the hydrazides were generally performed as follows: To a solution of the corresponding thiodiacid diester (0.05 mole) in 25 ml. absolute methanol, a 30% excess of hydrazine hydrate (85%) was added. After 3 drops of glacial acetic acid had been added as a catalyst, the mixture was refluxed for about 3 hr. After the mixture was cooled, an additional 25 ml. of absolute methanol was added, and the mixture was left overnight for crystallization. An additional crop of compound could be obtained by keeping the mother liquor for a short period in the refrigerator. The compounds were recrystallized from a minimum amount of *N,N*-dimethylformamide (Table II).

3,3′-Thiodipropionic acid, bis(p-dimethylaminobenzylidenehydrazide). To a solution of 2.67 g. (0.015 mole) of 3,3′-thiodipropionic acid dihydrazide in 40 ml. of water, a solution of 5.97 g. (0.04 mole) of *p*-dimethylaminobenzaldehyde in 70 ml. of ethanol was added. After a brief period, crystals began depositing and were collected after about 1 hr. They were washed with ethanol and air-dried. Yield, 5.69 g. (81%), m.p. 247–250°. The analytical sample was recrystallized from *N,N*-dimethylformamide, m.p. 247–250° (dec.). The remaining aralkylidene hydrazides were prepared similarly (Table I).

3,3′-Thiodipropionic acid, bis(phenylhydrazide). To a solution of 6.5 g. phenylhydrazine in 25 ml. tetrahydrofuran, 3.56 g. (0.02 mole) of 3,3′-thiodipropionic acid was added. After being refluxed for 7 hr., the mixture was cooled and the deposited phenylhydrazide was filtered and washed with ether. Yield, 5.02 g. (70%), m.p. 197–200°. The analytical sample was recrystallized from a minimum amount of *N,N*-dimethylformamide, m.p. 204–206°. The remaining phenylhydrazides were prepared similarly (Table II).

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UNIVERSITY OF CINCINNATI
DEPARTMENT OF CHEMISTRY
CINCINNATI 21, OHIO

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A Procedure for Converting Aryl Halides to High Molecular Weight Phenols

THEODORE L. YARBORO[1] AND CLARENCE KARR, JR.

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Authentic specimens of phenols were desired for part of an extensive program on characterizing