ethylamine, 2,6-dimethylpyridine, and triethylenediamine) were tried as condensing agents without improvement. The bicyclic triethylenediamine reacted with P,P-bis(1-aziridinyl)phosphinic chloride to produce a white complex of unknown structure which did not react further with primary amines at room temperature.

Preliminary screening in the Walker 256 test system[7] revealed that the compounds prepared possess the following approximate therapeutic indices, LD_{10}/ED_{90} = TI[8]: IIa, 1.2/0.43 = 3; IIb, 12.5/2.7 = 5; IIc, 4.5/1.6 = 3; IIe, 3.8/0.62 = 6. IId is the most toxic compound in this series (LD_{10} = 0.6) and it is inactive against Walker 256. The difference in pharmacological activity between IId and its methyl ether IIe provides for another example of the importance of the so-called "carrier" moiety[9] in biological alkylating agents.

Experimental[10]

P,P-Bis(1-aziridinyl)phosphinic Chloride (Ia).—A solution of 46 g. (0.3 mole) of phosphorus oxychloride in 700 ml. of dry 1,2-dimethoxyethane was cooled to −20° and stirred vigorously under completely anhydrous conditions. A solution of 60.0 g. (0.6 mole) of triethylamine in 470 ml. of 1,2-dimethoxyethane was added during 0.5 hr., followed by a solution of 25.8 g. (0.6 mole) of ethylenimine in 470 ml. of 1,2-dimethoxyethane which was added during 1 hr. After 10 additional min., the precipitated triethylamine hydrochloride was removed by filtration (98% of theory). The filtrate containing the product was used immediately for subsequent reactions.

P,P-Bis(1-aziridinyl)phosphinothioic Chloride (Ib).[5]—This compound was prepared in a similar manner to Ia, using either 1,2-dimethoxyethane or tetrahydrofuran as a solvent. After all of the ethylenimine had been added, the mixture was allowed to warm to room temperature and was stirred overnight. After removal of the amine salt (95% of theory), the filtrate was used directly for further reactions.

P,P-Bis(1-aziridinyl)-N-cyclohexylphosphinic Amide (IIa).—A solution of 29.7 g. (0.30 mole) of cyclohexylamine in 700 ml. of 1,2-dimethoxyethane was added during 2 hr. to a solution of 0.15 mole of Ia in 900 ml. of 1,2-dimethoxyethane which was cooled to 0° and stirred vigorously. After stirring overnight at room temperature, the suspension was filtered to remove the cyclohexylamine hydrochloride (77%) and the filtrate was evaporated *in vacuo*. The residue was dissolved in 200 ml. of hot 1,2-dimethoxyethane, decolorized, cooled slowly, and finally stored in the freezer. The precipitated white, crystalline product weighed 8.3 g. (24%); m.p. 100–102°; ethylenimine assay[11] 96% of theory. ν_{max}^{KBr} 3240, 2930, 1460, 1270, 1190, 1110, 935, and 705 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{20}N_3OP$: C, 52.39; H, 8.79; N, 18.33. Found: C, 52.42; H, 8.72; N, 17.98.

P,P-Bis(1-aziridinyl)-N-cyclohexylphosphinothioic Amide (IIb).[5]—A solution of 17.8 g. (0.18 mole) of cyclohexylamine in 500 ml. of tetrahydrofuran was added during 2.5 hr. to a tetrahydrofuran solution (570 ml.) containing 0.09 mole of Ib which was cooled to 0°and stirred vigorously. After stirring overnight at room temperature, the mixture was filtered to remove the amine hydrochloride (70%). The filtrate was concentrated to dryness in a rotary evaporator, taken up in 400 ml. of benzene, decolorized, filtered, and evaporated to dryness. The residue (60% of theory) was stirred with 300 ml. of warm "Skellysolve B," decanted from a gummy, insoluble residue, then decolorized and cooled slowly to −12°. The precipitated crystalline product was recrystallized by the same procedure, yielding 7.3 g. (33%) of white needles; m.p. 96–97°; ethylenimine assay[11] 99.8% of theory. ν_{max}^{KBr} 3350, 2930, 1420, 1260, 1150, 1100, 930, 892, 828 and 720 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{22}N_3PS$: C, 48.95; H, 8.22; N, 17.13; P, 12.63. Found: C, 48.20; H, 8.28; N, 16.94; P, 12.52.

P,P-Bis(1-aziridinyl)-N-(3-hydroxypropyl)phosphinic Amide (IIc).—This compound was prepared by the same technique used for the corresponding cyclohexyl derivative (IIb). The amine hydrochloride was produced in nearly theoretical yield. Evaporation of the filtrate afforded an oil which was dissolved in benzene and decolorized. Because the solution gave a positive chloride test with alcoholic silver nitrate, it was stirred with anhydrous sodium carbonate for 2 hr. The chloride-free filtrate was evaporated, then dried at 1 mm. pressure. The residue ($n^{25}D$ 1.5028, ethylenimine assay[11] 96%) was dissolved in absolute ethanol, decanted from a small quantity of insoluble oil, decolorized, and evaporated. The final oily product was stripped of volatiles at 10^{-3} mm.; it weighed 21 g. (70%); $n^{25}D$ 1.5030. The product deteriorated slowly when stored in the refrigerator. $\nu_{max}^{CHCl_3}$ 3400, 2999, 1409, 1269, 1170, 1110, 1070, and 940 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{16}N_3O_2P$: C, 40.97; H, 7.86; N, 20.48; P, 15.10. Found: C, 40.76; H, 7.84; N, 19.87; P, 14.46.

P,P-Bis(1-aziridinyl)-N-(3-hydroxypropyl)phosphinothioic Amide (IId).—A solution of 800 ml. of tetrahydrofuran containing 0.126 mole of Ib was added during 2.5 hr. to a solution of 9.4 g. (0.126 mole) of 3-aminopropanol and 25.5 g. (0.252 mole) of triethylamine in 500 ml. of tetrahydrofuran which was cooled to 0° and stirred vigorously. After stirring at room temperature overnight, the mixture contained a semisolid precipitate indicated by infrared spectra to be a mixture of the two amine hydrochlorides. The supernatant solution was evaporated to dryness in a rotary evaporator. The residue was dissolved in 400 ml. of benzene, decolorized, and concentrated to about 150 ml. On standing overnight, the solution deposited large, colorless prisms weighing 6.1 g.; m.p. 75–77°; ethylenimine assay[11] 99.8%. The mother liquor afforded an additional 2.5 g. (31% total yield) of product of the same quality. ν_{max}^{KBr} 3250, 2910, 1425, 1250, 1109, 950, 930, 892, 825, and 738 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{16}N_3OPS$: C, 38.00; H, 7.29; N, 18.99; P, 14.00. Found: C, 38.11; H, 7.07; N, 18.90; P, 13.87.

P,P-Bis(1-aziridinyl)-N-(3-methoxypropyl)phosphinothioic Amide (IIe).—This preparation was carried out exactly as the preceding one, except that 1,2-dimethoxyethane was used as a solvent. After the amine hydrochlorides had been removed, the filtrate was evaporated to dryness and the residue was dissolved in 500 ml. of benzene. It was decolorized and evaporated to dryness again. The residual oil was taken up in 500 ml. of ether, decolorized, and concentrated in a small volume, then boiling "Skellysolve B" was added until the solution became turbid. After cooling to room temperature the suspension was refrigerated overnight. Several crops of colorless plates were obtained in this way. They were combined and recrystallized twice from a mixture of ether and "Skellysolve B," yielding 3.06 g. (10%) of product; m.p. 65–67°; ethylenimine assay[11] 97%. ν_{max}^{KBr} 3260, 2910, 1440, 1260, 1110, 930 and 725 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{18}N_3OPS$: C, 40.84; H, 7.71; N, 17.86. Found: C, 40.39; H, 7.30; N, 17.06.

(7) The compounds are being evaluated by the Cancer Chemotherapy National Service Center, and complete data will be published in a future *Cancer Chemotherapy Screening Data* supplement to *Cancer Research*.

(8) The therapeutic index (TI) is defined as the ratio of the lethal dose producing 10% deaths in non-tumor bearing rats (LD_{10}) to the dose producing a 90% inhibition of tumor weight (ED_{90}). The LD_{10} and ED_{90} are expressed in mg./kg./day and the therapeutic index is determined graphically. Also, consult: H. E. Skipper and L. H. Schmidt, *Cancer Chemotherapy Reports*, **17**, 1 (1962).

(9) L. F. Larionov, "Biological Approaches to Cancer Chemotherapy," R. J. C. Harris, Ed., Academic Press, London, 1961, p. 139.

(10) All starting materials and solvents were carefully purified before use. All reactions and most other manipulations were conducted in a nitrogen atmosphere. Some of the final products were prepared, purified, and analyzed many times before acceptable analytical values could be obtained. Melting points are corrected.

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Thiopegan Derivatives. XXIII. Synthesis of 5H-Thiazolo[3,2-a]quinazolin-5-one and 5H-Thiazolo[2,3-b]quinazolin-5-one Derivatives Containing Phenolic, Alkoxy, and Alkyl Groups

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This paper constitutes an extension and continuation of previous work.[1b] As the incorporation of a hydroxyl

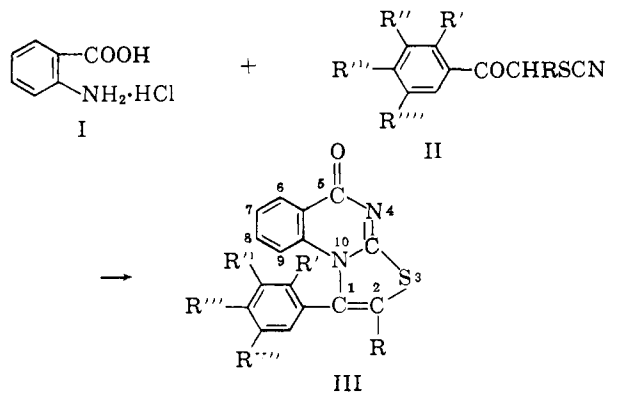
TABLE I

5H-THIAZOLO[3,2-a]QUINAZOLIN-5-ONE DERIVATIVES (III)

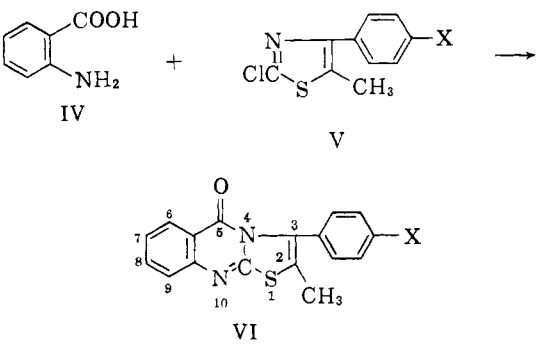
Sl. no.	α or ω-thiocyanato ketone	Product III R	R′	R″	R‴	R⁗	Yield, %	M.p., °C.[a]	Molecular formula	Analyses	Calcd., %	Found, %
1.	-Thiocyanato-3,4-dimethoxyacetophenone	H	H	OCH_3	OCH_3	H	34	275	$C_{18}H_{14}N_2O_3S$	N,	8.3	8.15
										S,	9.46	9.5
2.	-Thiocyanato-*p*-ethylacetophenone	H	H	H	C_2H_5	H	75	213	$C_{18}H_{14}N_2OS$	N,	9.15	9.25
										S,	10.45	10.7
3.	-Thiocyanato-2-hydroxy-5-methoxyacetophenone	H	OH	H	H	OCH_3	41	285	$C_{17}H_{12}N_2O_3S$	N,	8.64	8.30
										C,	62.96	63.00
										H,	3.7	3.65
4.	α-Thiocyanato-*p*-bromopropiophenone	CH_3	H	H	Br	H	35	266	$C_{17}H_{11}BrN_2OS$	N,	7.54	7.22
										Br,	21.54	21.80
5.	α-Thiocyanato-*p*-ethyl propiophenone	CH_3	H	H	C_2H_5	H	59	194	$C_{19}H_{16}N_2OS$	N,	8.75	8.90
										S,	10.0	10.1
6.	α-Thiocyanato-*p*-chloropropiophenone	CH_3	H	H	Cl	H	53	287	$C_{17}H_{11}ClN_2OS$	N,	8.54	8.70
										Cl,	12.15	12.3
7.	α-Thiocyanatopropiophenone	CH_3	H	H	H	H	41	290	$C_{17}H_{12}N_2OS$	N,	9.58	9.40
										S,	10.96	11.3
8.	α-Thiocyanato-*p*-methyl propiophenone	CH_3	H	H	CH_3	H	67	185	$C_{18}H_{14}N_2OS$	S,	10.45	10.92

[a] Recrystallized from 80% ethanol.

group in the benzene ring often enhances antibacterial activity, it was deemed pertinent to synthesize thiazoloquinazoline derivatives containing phenolic hydroxyl groups. Besides, some compounds containing alkyl and alkoxyl groups at different positions of the thiazole ring have been prepared with a view to study the effect of these groups on the biological activity of the resulting compounds. The synthesis was achieved by the general procedure reported previously, involving the condensation of *o*-aminobenzoic acid hydrochloride (I) with the requisite α- or ω-thiocyanatoketone (II), which gives rise to 5H-thiazolo[3,2-a]quinazolin-5-one derivatives (III). The mechanistic details of the reaction intermediates involving the formation of III have already been reported.[1b,2]



A number of 5H-thiazolo[2.3-b]quinazolin-5-one derivatives containing a methyl group in position 2 of the thiazole ring have also been synthesized through the reaction involving the condensation of anthranilic acid with the requisite 2-chlorothiazole.



Experimental

5H-Thiazolo[3,2-a]quinazolin-5-one (III) (**R″ = R‴ = OCH**)$_3$.—ω-Thiocyanato-3,4-dimethoxyacetophenone (4.43 g.) and anthranilic acid hydrochloride (3 g.) were dissolved in hot absolute ethanol (40 ml.) and the mixture was refluxed for 8 hr. The solvent was removed by distillation and the residue was made basic with sodium bicarbonate solution. The solid obtained was collected, washed with water to free it from the adhering alkali, and crystallized from 80% ethanol as fine light yellow needles, m.p. 275°; yield, 2.5 g. (34%). The physical characteristics and the analytical data of the thiazoloquinazoline derivatives prepared by this procedure, are listed in Table I.

5H-Thiazolo[2,3-b]quinazolin-5-one (**VI**) (**X = Br**).—A mixture of anthranilic acid (1.2 g.) and 4-(*p*-bromophenyl)-2-chloro-5-methylthiazole (2.6 g.) was heated in an oil bath at 140–160° for 2 hr. The product was dissolved in ethanol and made basic with sodium bicarbonate solution. The fine solid was washed with water until free from alkali and then crystallized from dilute ethanol (Norit); colorless needles, m.p. 184–185°; yield 1.0 g. (30%). All the compounds listed in Table II were prepared by similar procedures.

In preliminary tests, III (R = R′ = R⁗ = H; R″ = R‴ = OCH_3) has been found to be effective against *Bacillus subtilis*, *Salmonella paratyphi* and *Shigella paradysenteriae* Flexner at a dilution[3] of 1:1000 and is bacteriostatic against *Streptococcus hemolyticus* at 1:5,000; III (R = CH_3, R″ = Cl, R′ = R″ R⁗ = H) showed activity against *St. hemolyticus*, *Micrococcus pyogenes* var. *aureus*, *B. Subtilis*, *S. paratyphi* and *Sh. sonnei* at 1:5,000, and VI (R‴ = C_2H_5) showed bacteriostatic action against *S. paratyphi*, *S. schottmuelleri* and *S. typhi* at 1:1,000.

(1) (a) To whom inquiry regarding this paper should be made at Department of Chemistry, University of Western Ontario, London, Ontario, Canada. (b) H. S. Sachdev, K. S. Dhami, and K. S. Narang, *J. Sci., Ind. Res.* (India) **19C**, **II** (1960).

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(3) All the compounds were tested in water solution, using sulfanilamide as the standard.

TABLE II
5H-THIAZOLO[2,3-b]QUINAZOLIN-5-ONE-DERIVATIVES (VI)

Sl. no.	2-Chloro-5-methylthiazole derivative	(VI): X[a]	Yield, %	M.p., °C.	Molecular formula	Analysis Calcd., %	Analysis Found, %
1.	4-(*p*-Bromo-phenyl)	Br	30	184–58	$C_{17}H_{11}BrN_2OS$	N, 7.54	7.7
						Br, 21.54	Br, 21.7
2.	4-Phenyl	H	43	210	$C_{17}H_{12}N_2OS$	N, 9.58	9.40
						S, 10.96	S, 11.50
						N, 8.54	8.7
3.	4-(*p*-Chloro-phenyl)	Cl	45	145	$C_{17}H_{11}ClN_2OS$	S, 9.81	S, 10.00
4.	4-(*p*-Tolyl)	CH_3	22	172	$C_{18}H_{14}N_2OS$	N, 9.15	9.25
						S, 10.45	10.60
5.	4-(4-Ethylphenyl)	C_2H_5	15	178	$C_{19}H_{16}N_2OS$	N, 8.75	8.90
						S, 10.0	10.2

[a] Recrystallized from dilute ethanol.

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The Synthesis of Halogenated Tuberculostatic Thiocarbanilides

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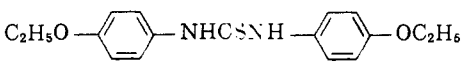
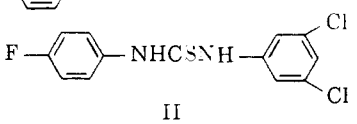
Numerous publications have shown that the class of thiocarbanilides (N,N′-diarylthioureas) bearing alkoxy groups includes very potent antimycobacterial agents.[1] Several such compounds are now in current use in human therapeutics: 4,4′-diethoxythiocarbanilide (I) and 4-butoxy-4′-dimethylaminothiocarbanilide in the treatment of leprosy,[2] and 4,4′-diisoamyloxythiocarbanilide in the treatment of tuberculosis.[3] Further,



I

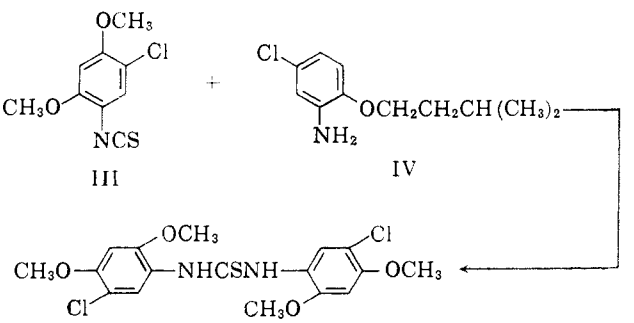


II

several thiocarbanilides bearing halogen substituents, such as 3,5-dichloro-4′-fluorothiocarbanilide (II), have shown considerable fungistatic properties, both experimentally and in clinical practice.[4] It was therefore logical to proceed to the synthesis of thiocarbanilides bearing at the same time halogen and alkoxy substituents, and to investigate their activity with regard both to mycobacteria and to pathogenic fungi.

The synthesis of symmetrical thiocarbanilides was effected by condensation of the appropriate halogenated mono- or dialkoxyaniline with carbon disulfide in the presence of small amounts of sulfur or potassium hydroxide (Hugershof reaction).[5] This reaction was found to be sensitive to steric hindrance, and the presence of bulky substituents *ortho* to the amino group led to yields that were distinctly lower than normally observed; the presence of nitro groups inhibited the reaction, and 2-amino-5-nitroanisole and 4-amino-3-nitroanisole failed to give condensation products under normal experimental conditions. Similar observations had already been made with the nitroanilines,[5] and with 5-nitro-2-aminothiazole.[5]

Unsymmetrical thiocarbanilides (Table I) were obtained from the reaction of the appropriate arylamine and aryl isothiocyanate; the isothiocyanates were prepared by treatment of symmetrical thiocarbanilides (Table II) with acetic anhydride (Werner reaction). The condensation of arylamines with aryl isothiocyanates was also found to be sensitive to steric hindrance; for instance, 5-chloro-2,4-dimethoxyphenyl isothiocyanate (III) reacted with 5-chloro-2-isoamyloxyaniline (IV) to give the symmetrical 5,5′-dichloro-2,4,2′,4′-tetramethoxythiocarbanilide (V), instead of



III IV

V

the expected, sterically more hindered unsymmetrical thiocarbanilide. With the same isothiocyanate, normal condensation products were obtained; however, when the reacting arylamine was not sterically hindered, as in the case of *p*-isoamyloxyaniline, or was less sterically hindered, as with 4-bromo-2-methoxy-5-

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