200° at 2 mm. and 1.0 g. of tarry residue. On redistillation, the 2-phenethyl-pyrazine boiled at 118–121° at 2 mm. A sample of this material was reduced by treatment with sodium in ethanol to 2-phenethylpiperazine, m.p. 101–102° after recrystallization from petroleum ether (b.p. 60–70°) (see Table II).

PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DEPARTMENT, AGRICULTURAL DIVISION, AMERICAN CYANAMID CO.

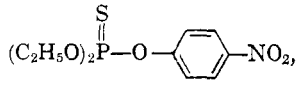
Synthesis of Pyridazinyl-Substituted Phosphorothioate Esters

SHIRLEY DU BREUIL

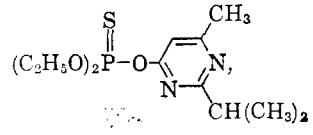
Received January 4, 1960

A series of insecticidally active dialkyl pyridazinyl phosphates and phosphorothioates was prepared by the reaction of the appropriate phosphorochloridate with hydroxypyridazinones.

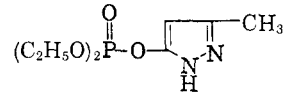
Since the introduction of parathion,



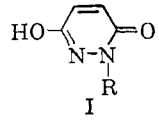
as a potent broad-spectrum insecticide, there have appeared a variety of other phosphate insecticides prepared from compounds containing an acidic or enolizable hydrogen atom. Of particular interest have been derivatives of nitrogen-containing heterocycles such as Diazinon[1] *O,O*-diethyl *O*-(2-isopropyl-6-methyl-4-pyrimidyl) phosphorothioate;[1a]



and Pyrazoxon[1] diethyl 3-methyl-5-pyrazolyl phosphate,[2]

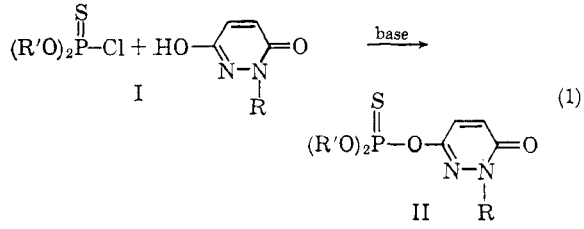


In our laboratories, interest has centered on the derivatives of 6-hydroxy-3(2*H*)-pyridazinone, more commonly known as maleic hydrazide (I, R = H):



I

I(R = H) is a difficultly soluble, high melting monobasic acid which has pK_a 7.6 in 90% ethanol (5.7 in water[3]). Substitution at the (2*H*) position by alkyl or aryl groups does not affect the acidity appreciably, but the solubility in organic solvents is improved. As expected, these compounds react similarly to phenols with *O,O*-dialkyl phosphorochloridothioates (equation 1):



(1)

The products obtained are usually crystalline solids, soluble in organic solvents other than the paraffinic hydrocarbons, and essentially insoluble in water. When R = H, the phosphorothioates are weakly acidic (pK_a 10–11 in 90% ethanol), and they may be recovered in fair yield upon acidification of an alkaline solution.

Generally the *O,O*-dialkyl *O*-pyridazinyl phosphorothioates (II) were prepared according to equation 1, using anhydrous sodium carbonate as the base in *N,N*-dimethylformamide (DMF) or 1-methyl-2-pyrrolidone (NMP). In some cases the preformed sodium salts of I were used, and, in fact, these were preferred for those pyridazinones having pK_a values of 8.5 or higher in 90% ethanol. Reactions conducted in acetone, methyl isobutyl ketone, or toluene were not successful, possibly due to the extreme insolubility of the starting heterocycles. Dioxane and tetrahydrofuran appeared to dissolve small amounts of maleic hydrazide, but the desired products were not isolated from reactions conducted in these solvents. Reactions utilizing *O,O*-dimethyl phosphorochloridothioate (equation 1, R′ = CH_3), were conducted in water with an equivalent of potassium or sodium hydroxide, since in dimethylformamide or 1-methyl-2-pyrrdidone this phosphorochloridothioate reacted preferentially and violently with the solvents. It is possible that higher homologs also reacted with the solvents to some extent, and this competing reaction may account in part for the low yields obtained in many of the preparations.[4]

(1) Registered Trademark of J. R. Geigy A.-G.

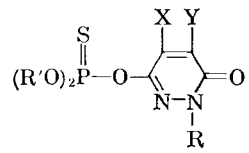
(1)(a) H. Gysin and A. Margot, U. S. Patent **2,754,243**, July 10, 1956 (to J. R. Geigy A.-G.).

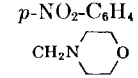
(2) H. Gysin and A. Margot, U. S. Patent **2,754,244**, July 10, 1956 (to J. R. Geigy A.-G.).

(3) A. Albert and J. N. Philips, *J. Chem. Soc.*, 1294 (1956).

TABLE I

O,O-DIALKYL *O*-(1,6-DIHYDRO-6-OXO-3-PYRIDAZINYL) PHOSPHOROTHIOATES

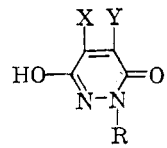


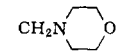
Compound Number	R′	R	X	Y	M.P., or n_D^{25}	Method	Yield, %	Recrystallization Solvents	Calcd. N.E.[a]	Calcd. N	Calcd. P	Found N.E.	Found N	Found P
III	CH_3	H	H	H	71.5–73	C	57	Ether	236.2	11.86	13.11	236.0	11.76	13.05
IV	C_2H_5	H	H	H	90.5–91.5	A, C	[b]	Ether + heptane	264.2	10.60	11.46	265.0	10.54	11.69
V	*n*-C_3H_7	H	H	H	113–114	A	57	Benzene + heptane	292.3	9.59	10.97[c]	292.4	9.60	10.99[c]
VI	*i*-C_3H_7	H	H	H	86.5–87	A	37	Benzene + heptane	292.3	9.59	10.97[c]	281.0	9.54	11.17[c]
VII	C_2H_5	H	CH_3	H	108.5–109.5[d]	B	52	Methanol	278.3	10.05	11.49[c]	271.8	10.04	11.46[c]
VIII	C_2H_5	H	C_6H_5	H	162.5–163.5[d]	A	71[e]	Ethanol	340.5	8.23	9.10	329.5	8.52	9.71
IX	C_2H_5	H	H	C_6H_5	135.5–136.5	A	71[e]	Benzene	340.5	8.23	9.10	342.7	8.79	8.71
X	C_2H_5	H	Cl	H	144–145[d]	A	56[e]	Methanol	298.7	9.38	10,74	301.8	9.45	10.87
XI	C_2H_5	H	H	Cl	91–92	A	56[e]	Benzene + heptane	298.7	9.38	10.74	298.3	9.50	10.84
XII	C_2H_5	H	Br	Br	120–123	A	48	Ethanol	422.1	6.64	6.85	428.9	6.82	7.16
XIII	C_2H_5	CH_3	H	H	n_D^{25} 1.5133	A	68	Methanol[f]		9.46	10.46[g]		9.44	10.54
XIV	*i*-C_3H_7	CH_3	H	H	37–38.5	A	73	Petroleum ether			9.88			10.35
XV	C_2H_5	CH_3	Br	Br	67–68	A	90	Benzene + heptane		6.42	7.10		6.33	7.63
XVI	C_2H_5	CH_2OH	H	H	64–65	[h]	96		294.3	9.52	10.53	302.7	9.77	10.78
XVII	CH_3	C_6H_5	H	H	46.5–47.5	B	63	Ethanol + water		8.97	9.92		9.06	10.17
XVIII	C_2H_5	C_6H_5	H	H	56–57.	A	69	Methanol		8.23	9.10		8.28	9.12
XIX	C_2H_5	C_6H_5	Cl	H	82.5–83	A	85	Ether + heptane		7.48	8.27		7.39	8.67
XX	C_2H_5	C_6H_5	H	Cl	n_D^{25} 1.5753	A	86			7.48	8.27		7.03	8.67
XXI	C_2H_5	*p*-Br-C_6H_4	H	H	67.5–68	A	55	Ether + heptane		6.68	7.39		6.40	7.82
XXII	C_2H_5	*p*-NO_2-C_6H_4	H	H	72–73	A	91	Ethanol		10.91	8.04		10.88	7.90
XXIII	*n*-C_4H_9	*p*-NO_2-C_6H_4	H	H	32–32.5	A	84	Benzene + heptane		9.52	7.02		9.30	7.13
XXIV	C_2H_5		H	H	40–42	A	79	Ether + heptane	373.4	11.26	8.30	382.7	11.77	8.64

[a] Neutral equivalent. [b] In DMF: 42.2%; in NMP: 73.6%; in water: 37.9%. [c] % Sulfur. [d] Higher melting isomers are assigned this structure to conform to XIX and XX, which are derived from intermediates of known configuration based on K. Meier, B. H. Ringier, and J. Druey, *Helv. Chim. Acta*, **37**, 523 (1954). [e] Combined yield; isomers then separated by fractional crystallization. [f] Recrystallization done at −70°. [g] Analysis calculated for monomethanolate. [h] See Experimental section.

TABLE II

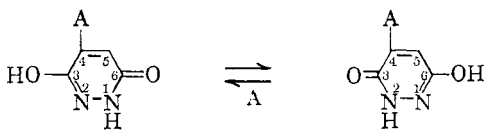
6-HYDROXY-3(2H)-PYRIDAZINONES



Compound Number	R	X	Y	M.P.	Yield %	Neut. Equiv. Calcd.	Neut. Equiv. Found	pK_a
XXV	H	H	H	305.5 dec.[a]	85	112.1	111.3	7.61
XXVI	H	Cl	H	269–272 dec.[b]	84	146.5	147.4	6.38
XXVII	H	Br	Br	325[c]	96	269.9	265.0	6.2
XXVIII	H	CH_2	H	[d]	83	126.1	126.9	8.28
XXIX	H	C_6H_5	H	279–280	99[e]	188.2	200.0	7.6
XXX	CH_3	H	H	213.5–215[f]	79	126.1	125.6	7.76
XXXI	CH_3	Br	Br	226–228	97	283.9	282.2	5.3
XXXII	C_6H_5	H	H	268.5–269[g]	84	188.2	187.5	7.57
XXXIII	C_6H_5	Cl	H	274 dec.[h]	91[i]	222.6	225.7	6.44
XXXIV	C_6H_5	H	Cl	199–200[j]		222.6	223.2	6.85
XXXV	*p*-Br-C_6H_4	H	H	275	84[k]	267.1	275.7	7.65
XXXVI	*p*-NO_2-C_6H_4	H	H	278–283	48.1[l]	233.2	246.8	7.13
XXXVII	CH_2OH	H	H	170 dec.[m]	93.2[n]	142.9	141.9	7.53
XXXVIII		H	H	187–187.5[o]	62	211.2	213.7	8.05

[a] Lit. melting points vary in range 260–310°. [b] R. R. Mizzoni and P. E. Spoerri *J. Am. Chem. Soc.*, **76**, 2201 (1954) reported m.p. 265–268°. [c] P. Ruggli and C. Hartman *Helv. Chim. Acta*, **3**, 506 (1920) reported m.p. 340° dec. [d] Lit. m.p. 286.5–287°. (Footnote *b*.) [e] *Anal.* Calcd. for $C_{10}H_8N_2O_2$: N, 14.89. Found: N, 14.22. [f] K. Eichenberger, A. Staehlin and J. Druey, *Helv. Chim. Acta*, **37**, 837 (1954), reported m.p. 210–211°. [g] J. Druey *et al.*, *Helv. Chim. Acta*, **37**, 510 (1954), reported m.p. 255–256°. [h] Lit. m.p. 255–256° reported by K. Meier *et al.* (Table I, Footnote *d*). [i] The mixture of isomers obtained was separated first in acetic acid, XXXIII being insoluble. Thereafter, each isomer was purified by fractional recrystallization from ethanol and methanol. XXXIV was five times more soluble in these solvents than XXXIII. [j] K. Meier *et al.* (Footnote *h*) reported m.p. 198.5–199°. [k] Recrystallized from acetic acid. [l] See Experimental section for alternate procedure. [m] Sealed tube, immersed in bath at 170°. Formaldehyde was evolved, after which the solid residue melted 301–304° dec. as XXV. [n] See Experimental section for procedure. [o] Prepared according to H. Hellmann and I. Löschmann, *Angew. Chem.*, **67**, 110 (1955) who reported m.p. 183°.

In reactions of *C*-substituted pyridazinones, the replacement of one or the other tautomeric hydrogen atoms in IA



permits the existence of two *O*-acylated isomers. Stefanye and Howard[5] reported the isolation of only one isomer from reactions with benzoyl chloride, but did not specify which. In the present work, both the 4- and 5-substituted isomers were isolated by repeated fractional crystallization when the ring substituent A was chlorine or phenyl. When A was methyl, only one isomer was obtained in pure form (Table I, Compound VII); a lower melting crude fraction was not successfully purified.

The *N*-hydroxymethyl derivative (II, R = CH_2OH, R′ = C_2H_5) could not be prepared *via* the general method because the hydroxymethyl group of the intermediate pyridazinone (I, R = CH_2OH) was cleaved readily by both acid and alkali. However, the desired compound was formed in excellent yield by the action of aqueous formaldehyde on the parent phosphorothioate (II, R = H, R′ = C_2H_5).

Table I shows the compounds of type II which were prepared, along with their physical properties and analyses.

The intermediate 6-hydroxy-3(2*H*)-pyridazinones (I) were prepared by the reaction of the appropriately substituted maleic anhydrides with hydrazine salts in refluxing water. Our work substantiated reports[6,7] that under strongly acidic conditions the six-membered cyclic hydrazide forms almost exclusively, whereas, under other conditions the five membered *N*-aminoimide also results. Thus, phenylhydrazine hydrochloride and maleic anhydride gave I (R = C_6H_5) in 90% yield, whereas phenylhydrazine in acetic acid with maleic anhydride gave only 52%. Use of excess hydrazine salt, longer heating periods, or smaller volumes of water

(4) The analogous reaction of acyl halides with dimethylformamide is a complex one, which has been studied by G. M. Coppinger, *J. Am. Chem. Soc.*, **76**, 1372 (1954) and H. K. Hall, Jr., *J. Am. Chem. Soc.*, **78**, 2717 (1956).

(5) D. Stefanye and W. L. Howard, *J. Org. Chem.*, **19**, 115 (1954).

(6) R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 1873 (1951).

(7) Y. A. Baskakov and N. N. Mel'nikov, *Zhur. Obshcheĭ Khim.*, **24**, 1216 (1954).

did not affect the yields appreciably. In one run using hydrazine sulfate to prepare I (R = H), purification was complicated by the insolubility of the sulfate in water. The crude reaction products often contained a strong organic acid impurity, which was conveniently removed by careful acidification of an aqueous solution of the sodium salt of the pyridazinone. The acid was believed to be fumaric acid formed by hydrolysis of the starting anhydride followed by isomerization of the resulting maleic acid. The yields and physical constants of the intermediates are shown in Table II.

Insecticidal activity. The dialkyl pyridazinyl phosphorothioates (II) were tested for insecticidal activity against the aphid (*Aphis rumicis*), two-spotted spider mite [*Tetranychus telarius* (L.)], large milkweed bug (Oncopeltus *fasciatus* (Dall.)], German cockroach [*Blatella germanica* (L.)], confused flour beetle (*Tribolium confusum* Duv.), and the Southern army worm [*Prodenia eridania* (Cram.)]. In general, the compounds were potent insecticides. For a homologous series, the diethyl esters were more active insecticidally than the corresponding dimethyl esters, followed by the di-isopropyl, di-*n*-propyl, and di-*n*-butyl esters. This is essentially in agreement with observations on a variety of phosphate insecticides.[8]

Usually the compounds having a substituent on the nitrogen atom of the heterocyclic ring were more effective than the unsubstituted derivatives. Substituents on the phenyl ring attached to this nitrogen did not appear to affect the activity to any large extent. On the other hand, substituents other than methyl on the 4- or 5- carbon atom of the heterocyclic ring reduced the activity markedly. Replacement of the carbonyl oxygen in the 6-position with halogen (XLI) gave an active but very unstable compound.

There did not appear to be any comparable relationship between the insecticidal activity of the final phosphorothioate and the pK_a of the intermediate heterocycle, such as the correlation which exists in the parathion series between activity and the acidity of the starting phenol.[9]

Acknowledgments. The biological tests were conducted under the direction of Mr. K. G. Nolan and Dr. E. L. Clark, and the analyses were performed by the staff of the Microanalytical Group under the direction of Dr. J. A. Kuck. The author is indebted to Dr. G. A. Johnson for many helpful discussions and suggestions.

EXPERIMENTAL[10,11]

O,O-Dialkyl phosphorochloridothioates. These intermediates were prepared by chlorination of the appropriate *O,O*-dialkyl hydrogen phosphorodithioates,[12] and were distilled before use.

Maleic anhydrides. Most of these were available commercially. Phenylmaleic anhydride was prepared according to the literature.[13,14] Dibromomaleic anhydride was obtained from the acid as described,[15] but the dibromomaleic acid could not be prepared from mucobromic acid and nitric acid as claimed. Instead, it was obtained from tetrabromothiophene by oxidation.[16]

6-Hydroxy-3(2H)-pyridazinones (I). *General method.* The procedure of Mizzoni and Spoerri[9] was followed. It was convenient to heat the solution of hydrazine salt initially to 95° only. Sufficient heat was generated during addition of the anhydride to cause the mixture to reflux. Pure products were most readily obtained by careful acidification of an aqueous solution of the sodium salt. In a few cases, the products were also recrystallized. The results are shown in Table II.

3,6-Dichloropyridazine (XXXIX). The procedure of Rogers and English[17] gave a 75% yield of material, m.p. 63–69° (lit. m.p. 68–69°).

6-Chloro-3-pyridazinol (XL). The method of Druey *et al.*[18] was modified such that the sodium hydroxide solution was heated first to 95°. Then XXXIX was added portionwise at a rate allowing reaction and dissolution between each addition.[19] Reaction time was decreased to 30 min., after which acidification with concd. hydrochloric acid gave a 95.5% yield, m.p. 144–144.5° (lit. m.p. 138–140°), neut. equiv. 134.5 (theory 130.5). Recrystallization from 10% hydrochloric acid did not affect the melting point, but the neut. equiv. improved to 132.0; pK_a 9.62.

6-Hydroxy-2-(p-nitrophenyl)-3(2H)-pyridazinone (XXXVI). Solid XXXII (30.1 g., 0.16 mole) was added portionwise to 300 ml. of fuming nitric acid (sp. gr. 1.5) at −5 to 0°. After 1 hr. at 0° the clear red solution was poured over crushed ice to give 25.5 g. (68%) of a yellow solid, m.p. 278–283°; neut. equiv. 228.7 (theory 233.2).

6-Hydroxy-2-hydroxymethyl-3(2H)-pyridazinone (XXXVII). Powdered XXV (112.1 g., 1 mole) was added to 37% methanol-free formaldehyde solution (222 g., 2 moles), the temperature rising to 40–50°. The solids dissolved above 70°, and the solution was kept at 70–75° for 1 hr. On cooling the solution, 132.2 g. (93%) of XXVI crystallized.

Anal. Calcd. for $C_5H_6N_2O_3$: CH_2O, 21.1. Found: 21.0.

Salts of 6-hydroxy-3(2H)-pyridazinones. The potassium or sodium salts of I were conveniently prepared by dissolving I in a minimum volume of water containing an equivalent of alkali and precipitating the salt by addition of three to five volumes of acetone or ethanol.

O,O-Dialkyl O-(1,6-dihydro-6-oxo-3-pyridazinyl) phosphorothioates (II). *Method A.* Anhydrous sodium carbonate (0.1 mole) and I (0.1 mole) were suspended in 150 ml. of dimethylformamide. The *O,O*-dialkyl phosphorochloridothioate (0.1 mole) was added all at once and the mixture was

(8) R. L. Metcalf, *Organic Insecticides*, Interscience Publishers, New York, N. Y., 1955, p. 288.

(9) Ref. (7), p. 289 ff.

(10) Many of the phosphorothioates (II) are very toxic to mammals, and due precautions should be exercised during any investigation of their properties.

(11) The melting points were taken in a Hirschberg apparatus, and are uncorrected.

(12) J. H. Fletcher *et al.*, *J. Am. Chem. Soc.*, **72**, 2461 (1950).

(13) E. Baer and M. Kates, *J. Am. Chem. Soc.*, **67**, 1482 (1945).

(14) C. S. Rondestvedt and A. H. Filbey, *J. Org. Chem.*, **19**, 119 (1954).

(15) O. Diels and M. Reinbeck, *Ber.*, **43**, 1271 (1910).

(16) A. Angeli and G. Ciamician, *Ber.*, **74**, 76 (1891).

(17) M. M. Rogers and J. P. English, U. S. Patent **2,671,086**, March 2, 1954 (to American Cyanamid Co.).

(18) J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

(19) This reaction was uncontrollably exothermic when the reactants were mixed at room temperature and then heated to reflux.

allowed to stir at room temperature overnight. A slow rise in temperature to 35–40° usually occurred during the first 2 hr., and a very fine precipitate of sodium chloride could be observed. The mixture was filtered with the aid of Hyflo and solvent was removed from the filtrate *in vacuo*. The viscous residue was treated with 100–200 ml. toluene and filtered again, to recover unchanged I. The toluene solution was washed with 10% sodium carbonate solution until the washings gave no precipitate when acidified. Finally solvent was allowed to evaporate in an air stream, whereupon the product usually crystallized.

Method B. Equimolar quantities of the sodium salt of I and *O,O*-dialkyl phosphorochloridothioate were used. Otherwise the procedure was the same as in Method A.

Method C. Equimolar amounts of potassium hydroxide and I were dissolved in a minimum volume of water. Then a 10% excess of *O,O*-dialkyl phosphorochloridothioate was added and the emulsion was stirred vigorously for 3 to 4 hr. The mixture was treated with an equal volume of toluene and filtered to remove unreacted I. The two-phase filtrate was separated and the aqueous portion was extracted with additional toluene. Evaporation of the organic solution yielded crystalline product. Acidification of the aqueous portion gave additional I.

The compounds (II) prepared are shown in Table I. In most cases it was possible to recover sufficient I from the reaction mixtures to bring the material balance of starting I to 90–95%.

O,O-Diethyl O-(6-chloro-3-pyridazinyl) phosphorothioate (XLI). XLI was obtained in 45% yield from XL by Method C. After recrystallization from heptane-ether, a m.p. 46.5–47.5° was observed.

Anal. Calcd. for $C_8H_{12}ClN_2O_3PS$: P, 10.96 Found: P, 10.56.

XLI changed to a green gum on standing overnight in air, and even samples stored under nitrogen in the dark turned green after several months. The decomposed mixture no longer dissolved completely in ether.

O,O-Diethyl O-[1,6-dihydro-1-(hydroxymethyl)-6-oxo-3-pyridazinyl] phosphorothioate (XVI). IV (31.7 g., 0.12 mole) was added to 37% methanol-free formaldehyde solution (39.0 g., 0.48 mole) to give a thick white paste. Two immiscible liquid layers appeared above 49°, and the mixture was heated at 70–72° for 2 hr. The mixture was cooled and the lower organic layer was separated. The aqueous portion was extracted with ether and the latter combined with the main organic fraction. This was then washed repeatedly with saturated sodium chloride solution and dried. Removal of the solvent *in vacuo* yielded crystalline product, which after extensive drying *in vacuo* over calcium chloride, showed a formaldehyde content of 10.7% (theory 10.2%).

STAMFORD, CONN.

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

The Use of *N,N*-Dimethylformamide in the Carbon Disulfide Ring Closure of 4,5-Diaminopyrimidines[2]

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An improved procedure for the preparation of purine-8-thiols by the reaction of 4,5-diaminopyrimidines with carbon disulfide in *N,N*-dimethylformamide is described. Application of this procedure to 4,5-diaminopyrimidines containing a group in the 6-position susceptible to nucleophilic attack resulted in intramolecular displacement of this group by the intermediate dithiocarbamate anions to give thiazolo[5,4-*d*]pyrimidine-2-thiols.

The general utility of this ring closure for the preparation of other heterocyclic systems is also demonstrated.

It became necessary to prepare some purine-8-thiols (III) as intermediates in the synthesis of hemisulfur mustard derivatives of purines[3] which might prove to be of interest as anticancer agents.

Purine-8-thiols are most commonly prepared form 4,5-diaminopyrimidines by reaction with carbon disulfide in pyridine[4,5] or fusion with thiourea.[6–9] In an effort to improve the preparation of purine-8-thiol (IIIa)[6,7] itself, the reaction of 4,5-diaminopyrimidine (Ia) and carbon disulfide in *N,N*-dimethylformamide was investigated and, indeed, an almost quantitative yield of the purine was obtained in this manner. This marked improvement in yield over that reported in the literature[7] encouraged us to attempt to extend the application of this procedure. A good yield of 9-ethyl-9*H*-purine-8-thiol (IIIb) was obtained from 5-amino-4-ethylaminopyrimidine (Ib),[10] but when the procedure was applied to 4,5-diamino-6-chloropyrimidine (Ic),[11] the expected product—6-chloropurine-8-thiol—was not obtained. Instead, a compound containing no chlorine was isolated in good yield. The same compound resulted when 4,5-diamino-6-

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