tetrafluoro-1-propene (III, Ar = C_6H_5), b.p. 147–149° (30 mm.). n_D^{30} 1.5180; d_{30}^{30} 1.235; MR calcd., 65.10; MR found, 65.30.

Anal. Calcd. for $C_{15}H_{10}F_4$: C, 67.7; H, 3.8. Found: C, 67.5; H, 4.2.

Oxidation of III (Ar = C_6H_5) with chromic anhydride in boiling acetic acid gave benzophenone (identified as its dinitrophenylhydrazone, m.p. 236–238°).

p-Chlorophenyl pentafluoroethyl ketone. This ketone was prepared by the above described procedure using 288 g. of *p*-chlorobromobenzene, 36.4 g. of magnesium and 82 g. of pentafluoropropionic acid. Yield, 54.9 g. (42%), b.p. 186–188°.

Anal. Calcd. for $C_9H_4ClF_5O$: C, 41.8; H, 1.6. Found: C, 41.6; H, 1.7. The *dinitrophenylhydrazone* melts at 180–182° (from methanol).

Anal. Calcd. for $C_{15}H_8ClF_5N_4O_4$: C, 41.1; H, 1.8. Found: C, 41.0; H, 2.1.

(p-Chlorophenyl)pentafluoroethyl-carbinol. Reduction of the foregoing ketone (25.9 g.) with lithium aluminum hydride (3.0 g.) as described above, afforded 20.3 g. (78%) of the carbinol, b.p. 115–125° (30 mm.). It solidified and was recrystallized from petroleum ether (40–60°); m.p. 41–42°.

Anal. Calcd. for $C_9H_6ClF_5O$: C, 41.5; H, 2.3. Found: C, 40.8; H, 2.6.

1,1-Di(p-chlorophenyl)-2,2,3,3,3-pentafluoropropane (I, Ar = *p*-C_6H_4Cl). A solution of 19.7 g. (0.075 mole) of (*p*-chlorophenyl)pentafluoroethylcarbinol and 5 ml. of chlorobenzene was added to a mixture of 11 ml. of chlorobenzene, 37 ml. of 95% sulfuric acid and 3.7 ml. of 60% oleum, in the manner described before. After the usual procedure, 22 g. (83%) of the propane was obtained, b.p. 148–152° (5–6 mm.), m.p. 46–50° (from methanol). An analytical sample was obtained by recrystallization from petroleum ether (40–60°), b.p. 52–53°.

Anal. Calcd. for $C_{15}H_9Cl_2F_5$: C, 50.7; H, 2.5. Found: C, 51.0; H, 2.8.

The same compound was obtained in 48% yield by refluxing for 250 hr. 7.4 g. of di-(*p*-chlorophenyl)pentafluoroethylcarbinol[6] with 2 g. of red phosphorus and 0.8 g. of iodine in 20 ml. of glacial acetic acid and 0.5 ml. of water.

Alkaline alcoholysis of 1,1-di-(p-chlorophenyl)-2,2,3,3,3-pentafluoropropane (I, Ar = *p*-C_6H_4Cl). (a). A mixture of 14.2 g. (0.04 mole) of I (Ar = *p*-C_6H_4Cl) and 24.2 ml. of 1.65*M* sodium methoxide was refluxed for 2 hr., cooled, and filtered. The white precipitate of sodium fluoride weighed 1.55 g. Titration of the filtrate showed that 4% of the sodium methoxide had not reacted. After removal of the solvent, the residue was distilled under reduced pressure to yield 10.2 g. (76%) of 1,1-di-(*p*-chlorophenyl)-2,3,3,3-tetrafluoro-1-propene (III, Ar = *p*-C_6H_4Cl), b.p. 130–132° (4 mm.). It solidified slowly and was recrystallized from methanol or petroleum ether; m.p. 40–41°.

Anal. Calcd. for $C_{15}H_8Cl_2F_4$: C, 53.8; H, 2.4. Found: C, 53.9; H, 2.2.

Oxidation with chromic anhydride in hot acetic acid yielded 4,4'-dichlorobenzophenone, m.p. and mixed m.p. with an authentic sample 146–147°.

(b) The same operation was repeated, using a five-fold excess of sodium methoxide solution and a reflux period of 4 hr. Thus, 6.9 g. (50%) of the well crystallized 1,1-di-(*p*-chlorophenyl)-2-methoxy-3,3,3-trifluoro-1-propene (IV, Ar = *p*-C_6H_4Cl) was obtained; m.p. 58–59° (from petroleum ether).

Anal. Calcd. for $C_{16}H_{11}Cl_2F_3O$: C, 55.3; H, 3.2; F, 16.4; OCH_3, 8.9. Found: C, 55.3; H, 2.9; F, 16.8; OCH_3, 9.0.

(c) A mixture of 6.7 g. (0.02 mole) of di-(*p*-chlorophenyl)-2,3,3,3-tetrafluoro-1-propene (III, Ar = *p*-C_6H_4Cl) and 30.4 ml. of 1.65*N* sodium methoxide solution was refluxed for 2 hr. After cooling, the solution was filtered from sodium fluoride (0.80 g.); titration of the filtrate showed that 38% of the sodium methoxide employed had reacted. Upon dilution with water, 1,1-di-(*p*-chlorophenyl)-2-methoxy-3,3,3-trifluoro-1-propene (IV, Ar = *p*-C_6H_4Cl) precipitated; it solidified quickly and was recrystallized from methanol. Yield, 5.9 g. (85%), m.p. 56–58°.

Oxidation of IV (Ar = *p*-C_6H_4Cl) by chromic anhydride in hot acetic acid yielded 4,4'-dichlorobenzophenone. It may be noted that I (Ar = *p*-C_6H_4Cl) is refractory to this treatment and is recovered unchanged.

1,1-Di(p-chlorophenyl)-2,2,3,3,4,4,4-heptafluorobutane (II). A quantity of 10.5 g. (0.025 mole) of di-(*p*-chlorophenyl)-heptafluoropropylcarbinol[6] was reduced with red phosphorus and iodine in aqueous acetic acid as described above. Thus, 6.6 g. (65%) of II was obtained; b.p. 155–160° (4 mm.). The distillate solidified on standing and was recrystallized from methanol; m.p. 58–59°.

Anal. Calcd. for $C_{16}H_9Cl_2F_7$: C, 47.4; H, 2.2. Found: C, 47.0; H, 2.5.

Alkaline alcoholysis of II. When 2.1 g. of II was refluxed for 2 hr. with 3 ml. of 1.65*N* sodium methoxide solution, 0.12 g. (58% of theory) of sodium fluoride was obtained and 33% of the methoxide had not reacted. The oily product which was precipitated by addition of water, was refluxed again for 4 hr. with 10 ml. of 1.65*N* sodium methoxide solution; the solvent was evaporated after neutralization and the residue extracted with ether and fractionated. The fraction (0.7 g.), boiling at 172–175° (5 mm.), n_D^{30} 1.5312, was mainly the methoxy olefin V.

Anal. Calcd. for $C_{17}H_{10}Cl_2F_5O$: C, 51.5; H, 2.5; F, 24.0. Found: C, 51.2; H, 2.6; F, 25.8.

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Pteridines. XXI. A One-Step Synthesis of 4-Aminopteridines[1,2]

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A facile synthesis of 2-substituted adenines has recently been described[3] which involves the isomerization of an amidine salt of isonitrosomalononitrile (I) in an appropriate basic solvent to a 2-substituted 4,6-diamino-5-nitrosopyrimidine (II), followed by reduction to III, formylation to IV and dehydration to V in a single operation by treatment with a mixture of formamide, formic acid, and sodium hydrosulfite. The conversion of I to V may be carried out in one step by employing formamide as the solvent for the initial isomerization of I to II. Since 4,5-diaminopyrimidines (III) may be converted to pteridines by reaction with α-diketones,[4] it was apparent that the above reaction sequence leading to purines might be adapted to the synthesis of pteridines by employing a solvent for the isomerization which could not react

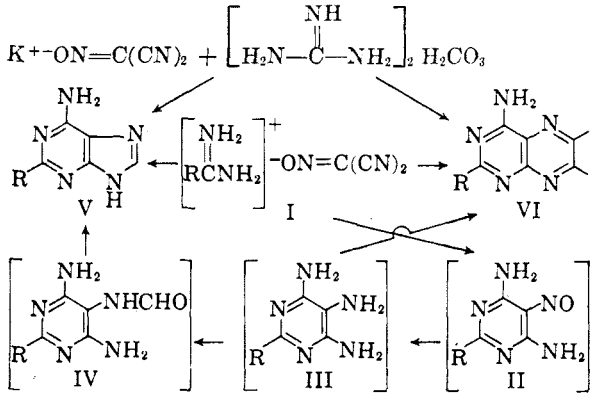
(1) This investigation was supported by a research grant (C-2551) to Princeton University from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) For the previous paper in this series, see E. C. Taylor, O. Vogl and P. K. Loeffler, *J. Am. Chem. Soc.*, **81**, 2479 (1959).

(3) E. C. Taylor, O. Vogl, and C. C. Cheng, *J. Am. Chem. Soc.*, **81**, 2442 (1959).

(4) A. Albert, *Quart. Rev.*, **6**, 197 (1952).

with any subsequent intermediates, and by adding an α-diketone to the reaction mixture after III had been formed. In accordance with this expectation, it has been found that 4-aminopteridines (VI) may conveniently be prepared by heating amidine salts of isonitrosomalononitrile (I) in an appropriate solvent until isomerization to II is complete,



adding water and sodium hydrosulfite (thus giving III), and finally adding an α-diketone. The pteridines thus formed generally crystallize directly from the reaction mixture and are chromatographically pure (see Table I) without further purification except as indicated in the Experimental. Prior formation of the amidine salt I is not necessary in every instance. Thus, 2,4-diaminopteridines (VI. R = $-NH_2$) may be prepared directly from guanidine carbonate and the potassium salt of isonitrosomalononitrile by a reaction sequence analogous to the previously described one-step synthesis of 2,6-diaminopurine (V. R = $-NH_2$).[3]

TABLE I

R_f VALUES, DESCENDING METHOD (22°)[a]

Pteridine	4% Sodium citrate	3% NH_4Cl	*n*-BuOH/5*N* HOAc (2:1)	*n*-PrOH/1% NH_4OH (2:1)
2,4-Diamino-6,7-dimethyl-	0.25	0.54	0.43	0.65
2,4-Diamino-6,7-diphenyl-	0.08	0.17	0.73	0.88
2,4-Diamino-	0.27	0.54	0.28	0.51
2,4-Diamino-5,7-dihydroxypyrimido(5,4-g)-	0.23	~0	~0	~0
4-Amino-2,6,7-triphenyl-	~0		0.88	~1

[a] All spots are fluorescent.

EXPERIMENTAL[5]

2,4-Diamino-6,7-dimethylpteridine. A mixture of 1.0 g. of the potassium salt of isonitrosomalononitrile and 1.1 g. of guanidine carbonate in 10 ml. of ethylene glycol was warmed gently for 3 min. to give a clear, deep red solution. The mixture was diluted with 10 ml. of water, 0.6 g. of sodium hydrosulfite dihydrate added, and the mixture heated on a water bath for 20 min. until a clear, light yellow solution resulted. It was acidified to *p*H 6 with hydrochloric acid, 1 ml. of biacetyl was added, and the mixture was warmed on a water bath for 15 min. Dilution with 20 ml. of ethanol and chilling yielded 1.07 g. (75%) of a yellow crystalline solid which was identical with an authentic sample of 2,4-diamino-6,7-dimethylpteridine formed by the method of Mallette, Taylor, and Cain.[6]

2,4-Diamino-6,7-diphenylpteridine. A mixture of 1.5 g. of the potassium salt of isonitrosomalononitrile, 1.5 g. of guanidine carbonate and 12 ml. of ethylene glycol was heated for 3 min. and then reduced with 1.0 g. of sodium hydrosulfite dihydrate as described above. To the alkaline solution was added 2.2 g. of benzil dissolved in a mixture of 10 ml. of ethyl methyl ketone and 5 ml. of ethanol, and the mixture was heated under reflux for 1 hr. Filtration yielded a small amount of impurity, and the filtrate was chilled to give 1.02 g. (29%) of a yellow crystalline solid which was identical with an authentic sample of 2,4-diamino-6,7-diphenylpteridine.[6]

2,4-Diaminopteridine. A mixture of 3 g. of the potassium salt of isonitrosomalononitrile, 3.3 g. of guanidine carbonate and 20 ml. of ethylene glycol was heated for a few minutes and then reduced with 1.8 g. of sodium hydrosulfite dihydrate, as described above. The light yellow solution was acidified to *p*H 3 with hydrochloric acid and then treated with a solution of 7.5 g. of glyoxal bisulfite in 50 ml. of water. After 40 min. of stirring at 110°, the reaction mixture was allowed to stand at room temperature overnight, made alkaline with ammonium hydroxide, acidified again with glacial acetic acid and filtered. The collected light yellow solid (3.55 g., 97%) was purified by sublimation at 240°/0.05 mm. The product was shown to be 2,4-diaminopteridine by comparison with an authentic sample.[6]

2,4-Diamino-5,7-dihydroxypyrimido(5,4-g)pteridine. A mixture of 2.0 g. of the potassium salt of isonitrosomalononitrile and 2.2 g. of guanidine carbonate was isomerized and then reduced as described above. To the light yellow reduction solution was added 20 ml. of 1*N* hydrochloric acid followed by 2.0 g. of alloxan. The reaction mixture immediately became deep purple, but on shaking it gradually turned orange with the simultaneous separation of an orange solid. The reaction mixture was adjusted to *p*H 9 with potassium hydroxide, heated at 110° for 10 min., reacidified to *p*H 6 with hydrochloric acid and chilled to give 2.8 g. (76%) of an orange solid, m.p. >350°. The product was shown to be identical with an authentic sample of 2,4-diamino-5,7-dihydroxypyrimido(5,4-g.)pteridine prepared by the method of Taylor, Cain, and Loux.[7]

4-Amino-2,6,7-triphenylpteridine. A mixture of 2.0 g. of the benzamidine salt of isonitrosomalononitrile[3] and 10 ml. of 2-picoline was heated at 135° for 30 min. The reaction mixture was diluted with 20 ml. of water and the bluish green suspension was evaporated to dryness under reduced pressure. The residue was treated with 25 ml. of water, heated to 90–100° and treated portionwise with 1.6 g. of sodium hydrosulfite dihydrate. The resulting light brownish-yellow solution was stirred for 20 min., treated with 2 g. of benzil dissolved in a mixture of 15 ml. of ethyl methyl ketone and 15 ml. of ethanol and heated under reflux for 2 hr. Cooling of the reaction mixture yielded a yellow solid which was recrystallized from aqueous ethanol to give 1.9 g. (54.5%) of light yellow, fluffy needles, m.p. 255°.

(5) We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J.

(6) F. M. Mallette, E. C. Taylor, and C. K. Cain, *J. Am. Chem. Soc.*, **69**, 1814 (1947).

(7) E. C. Taylor, C. K. Cain, and H. M. Loux, *J. Am. Chem. Soc.*, **76**, 1874 (1954).

λ_{max}^{EtOH} 290, 377 mμ; log ε 4.53, 4.23.

Anal. Calcd. for $C_{24}H_{17}N_5$: C, 76.8; H, 4.6; N, 18.7. Found: C, 76.7; H, 4.4; N, 19.0.

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Phenyl and Chlorophenyl Derivatives of 1,4-Dihydro-2-pyrimidinethiol

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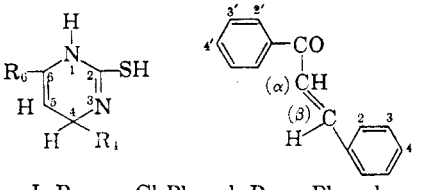
In order to facilitate continued studies[1] on the potential anticancer activity of mercaptopyrimidines,[2] we have prepared and characterized five new mono- and dichloro-derivatives (formulas I–V) of 1,4-dihydro-4,6-diphenyl-2-pyrimidinethiol, and one new dichlorochalcone (X). Such dihydropyrimidinethiols are conveniently prepared by the general procedures of Mathes *et al.*[3,4] and of Robbins,[5] the latter being suitable for derivatives such as I with no substituent on nitrogen. The needed mono and dichloro chalcone intermediates were prepared by alkaline condensation of appropriate acetophenone and benzaldehyde derivatives.

The effect of these five new thiols (and of eighteen similar but previously known thiols) on the mean survival time of Webster-Swiss mice inoculated with the Ehrlich ascites tumor is now being examined, and the results will be reported elsewhere. In previously reported tests[1] in our laboratory on thirty other dihydropyrimidinethiols, marginal activity was found in several cases.

These compounds are of interest not only because of their structural similarity to the well known antileukemic agent, 6-mercaptopurine, but also because of the recent finding[6] that dihydropyrimidines may be intermediates in the catabolism of pyrimidines.



I. R_4 = *o*-Cl-Phenyl, R_6 = Phenyl
II. R_4 = *m*-Cl-Phenyl, R_6 = Phenyl
III. R_4 = *p*-Cl-Phenyl, R_6 = Phenyl
IV. R_4 = Phenyl, R_6 = p-Cl-Phenyl
V. R_4 = *o*-Cl-Phenyl, R_6 = p-Cl-Phenyl
VI. 2-Chloro
VII. 3-Chloro
VIII. 4-Chloro
IX. 4′-Chloro
X. 2,4′-Dichloro

EXPERIMENTAL

All melting and boiling points have been corrected. Melting points were determined with a *Monoscop* micro hot stage. Microanalyses by the Micro-Tech Laboratories, Skokie, Ill., and by Weiler and Strauss, Oxford, England.

2,4′-Dichlorochalcone (X). To a solution of 5.7 g. of sodium hydroxide in 60 ml. of methanol at 25° was added gradually with stirring a solution of 18 g. of *o*-chlorobenzaldehyde and 20 g. of *p*-chloroacetophenone in 100 ml. of methanol. The precipitate which separated almost immediately was collected by filtration, washed with ice cold methanol, and dried, giving 32 g. (90%) of crude product, m.p. not determined. A sample recrystallized from ethanol for analysis (pale yellow needles) melted sharply at 85–86°.

Anal. Calcd. for $C_{15}H_{10}Cl_2O$: C, 65.00; H, 3.64: Cl, 25.59. Found: C, 64.54; H, 3.58: Cl, 26.00.

4-o-Chlorophenyl-1,4-dihydro-6-phenyl-2-pyrimidinethiol (I). To 36.4 g. of 2-chlorochalcone (VI, m.p. 46–52°, reported[7] m.p. 50–52°) was added 15.2 g. of anhydrous ammonium thiocyanate, 80 ml. of anhydrous commercial xylene (isomer mixture) and 15 ml. of cyclohexanol, and the mixture boiled under reflux until (24 hr.) the formation of water had almost ceased. The liberated water was collected and measured by means of a Stark and Dean trap. After cooling, the liquid phase was decanted from the crystalline residue of unreacted ammonium thiocyanate, and vacuum distilled. The viscous, syrupy residue was stirred with 100 ml. of acetone, and the mixture chilled overnight. The crystalline product which separated was collected by filtration, and dried, giving 14.0 g. (31%) of material melting at 182–184°. A sample recrystallized for analysis (colorless needles) melted at 184–184.5°.

Anal. Calcd. for $C_{16}H_{13}ClN_2S$: C, 63.88: H, 4.36; Cl, 11.79, Found: C, 63.81: H, 4.45; Cl, 11.47.

The infrared spectra were recorded for this compound and for the other pyrimidinethiols described below. The spectra were very complex, and showed only slight changes from one isomer, or analog, to another.

4-m-Chlorophenyl-1,4-dihydro-6-phenyl-2-pyrimidinethiol (II). From 16.0 g. of 3-chlorochalcone (VII, m.p. 74–76°, reported[8] m.p. 75°) by a similar procedure (reflux time 40 hr.) there was obtained 7.2 g. (36%) of crude II, m.p. 196–199°. A sample recrystallized from ethanol (colorless needles) melted at 202–204°.

Anal. Calcd. for $C_{16}H_{13}ClN_2S$: C, 63.88: H, 4.36: Cl, 11.79. Found: C, 64.11: H, 4.43: Cl, 11.82.

4-p-Chlorophenyl-1,4-dihydro-6-phenyl-2-pyrimidinethiol (III). From 20.2 g. of 4-chlorochalcone (VIII, m.p. 113–115°, reported[8] m.p. 114.5°) by a similar procedure (reflux time 20 hr.) there was obtained 6.2 g. of III.

In order to improve the yield, the syrupy residue obtained by evaporation of the mother liquor was recycled with additional ammonium thiocyanate (7.6 g.), xylene and cyclohexanol, giving 4.0 g. of additional crude product,

(1) For reports of previous tests, see A. Furst, W. Cutting, and Hudi Gross, *Proc. Am. Assn. Cancer Res.*, Vol. 2, April, 1956.

(2) For anticancer studies on certain 2- and 6-pyrimidinethiols (not dihydro) see: (a) A. di Marco and M. Gaetani, *Estratto da Tumori*, **42**, 531 (1956); (b) E. J. Modest and H. N. Schlein, *Abstracts of Papers*, April 1955 Meeting American Chemical Society, page 7-M; (c) J. F. Holland *et al. Cancer Research*, **18**, 776 (1958).

(3) R. A. Mathes, *J. Am. Chem. Soc.*, **75**, 1747 (1953).

(4) R. A. Mathes, F. Stewart, and F. Swedish, *J. Am. Chem. Soc.*, **70**, 1452 (1948). (*Note:* The " . . . 4,6,6-trimethylpyrimidines" mentioned in this publication should apparently have been designated ". . . 1,4-*dihydro*-4,4,6-trimethylpyrimidines."

(5) T. E. Robbins, U. S. Patent **2,539,480**, January 30, 1951.

(6) R. M. Fink, R. E. Cline, and H. M. Koch, *Federation Proc.*, Vol. **13**, March, 1954.

(7) C. L. Bickel, *J. Am. Chem. Soc.*, **68**, 865 (1946).

(8) J. F. J. Dippy and R. H. Lewis, *Rec. trav. chim.*, **56**, 1000 (1937).