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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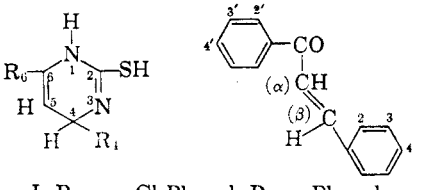
In order to facilitate continued studies[1] on the potential anticancer activity of mercaptopyrimidines,[2] we have prepared and characterized five new mono- and dichloro-derivatives (formulas I–V) of 1,4-dihydro-4,6-diphenyl-2-pyrimidinethiol, and one new dichlorochalcone (X). Such dihydropyrimidinethiols 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).

m.p. the same. The total yield was thus 10.2 g. (41%). A sample recrystallized from ethanol for analysis melted at 169–170° (colorless needles).

Anal. Calcd. for $C_{16}H_{13}ClN_2S$: C, 63.88: H, 4.36: Cl, 11.79. Found: C, 64.11: H, 4.40: Cl, 11.40.

6-p-Chlorophenyl-1,4-dihydro-4-phenyl-2-pyrimidinethiol[9] (IV). From 17.8 g. of 4'-chlorochalcone (IX, m.p. 94–96°, reported[10] m.p. 96°) by a procedure similar to that used for I there was obtained 5.6 g. (25%) of crude product, m.p. 212–216°. A sample recrystallized from ethanol was obtained as colorless needles, m.p. 218–220°.

Anal. Calcd. for $C_{16}H_{13}ClN_2S$: C, 63.88: H, 4.36: Cl, 11.79. Found: C, 64.08: H, 4.37: Cl, 11.81.

4-o-Chlorophenyl-6-p-chlorophenyl-1,4-dihydro-2-pyrimidinethiol (V). From 20.0 g. of recrystallized 2,4'-dichlorochalcone (X, m.p. 85–86°) by similar procedure (20 hr. reflux time) there was obtained 7.2 g. (30%) of crude V, m.p. 206–208°. The analytic sample, colorless needles, melted at 207–209°.

Anal. Calcd. for $C_{16}H_{12}Cl_2N_2S$: C, 57.32: H, 3.61: Cl, 21.15. Found: C, 57.64: H, 3.76: Cl, 20.67.

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(9) It is of interest that the isomeric phenylchlorophenyldihydropyrimidine-thiols III and IV might in principle be interconverted by an allylic rearrangement, or 1,3 prototropic shift. However, no such interconversion has been noted under the conditions thus far employed.

(10) C. F. H. Allen and G. F. Frame, *Can. J. Res.*, **6**, 605 (1932).

Some Urea and Picrate Derivatives of Pyridoxamine

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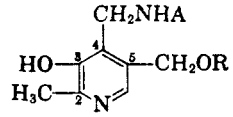
In order to facilitate continued studies[1] on cancer chemotherapy, we have synthesized pyridoxurea hydrochloride[2] (formula II), a derivative of the well known vitamin pyridoxamine (I), in which the primary amino group is replaced by a ureido group. Pyridoxamine free base when briefly heated with equimolar amounts of potassium cyanate and dilute hydrochloric acid reacted to form the desired urea. This product could conveniently be isolated only by conversion to its monopicrate (II.HPic). The picrate, being presumably too toxic for therapeutic use, was converted in the usual manner to the corresponding monohydrochloride (II.HCl), a colorless, stable crystalline solid.

Attempted regeneration of the picrate with an anhydrous solution[3] of hydrogen chloride in acetic acid caused simultaneous acetylation of the primary alcohol group, giving the urea 5-*O*-acetate monohydrochloride (III.HCl).

In order to facilitate characterization of the urea picrate, the previously unreported pyridoxamine monopicrate (I.HPic) was prepared and characterized. Although pyridoxamine free base (I) and the corresponding dipicrate (I.2HPic) have been reported previously,[4,5] it appears that the first detailed and explicit account of their preparation is that now given.



I. R = A = H
II. R = H, A = —$CONH_2$
III. R = —$COCH_3$, A = —$CONH_2$

Numerous attempts to prepare the thiourea analog of II, using various suitable reagents, have led to no useful result. To obtain this derivative it might be necessary to introduce temporary protective groups to prevent possible interference by the phenolic or primary alcohol functional groups.

Biological tests of the various compounds described below against the Ehrlich ascites tumor in Swiss-Webster mice, and other chemotherapeutic tests, are now in progress and will be reported elsewhere.

EXPERIMENTAL

All melting and boiling points have been corrected Melting points were determined with a *Monoscop* micro hotstage. Microanalyses by the Micro-Tech Laboratories, Skokie, Ill.

4-Aminomethyl-3-hydroxy-2-methyl-5-pyridinemethanol (pyridoxamine free base). To a solution of 2.02 g. of sodium bicarbonate in 20 ml. of water was added 2.41 g. of pyridoxamine dihydrochloride, with stirring. The resulting clear solution on standing overnight deposited a crystalline precipitate, which was collected, washed with water, and dried, giving 1.4 g. (83%) of colorless, flaky lumps, very difficult to pulverize. Under the microscope, colorless needles were visible.

This material was recrystallized from absolute ethanol (35 ml./g.; filter hot), giving 0.9 g. of colorless crystals, m.p. 190–191°, reported[4] m.p. 193.5°. The crystals become discolored on prolonged exposure to air and light.

4-Aminomethyl-3-hydroxy-2-methyl-5-pyridinemethanol picrate (pyridoxamine monopicrate). To 168 mg. of pyridoxamine free base in 10 ml. of boiling absolute ethanol was

(1) For previous publication, see G. E. McCasland, Erwin Blanz, Jr., and Arthur Furst, *J. Org. Chem.*, **23**, 1570 (1958).

(2) *Pyridoxurea* is here used as a trivial name for the derivative of pyridoxamine in which a ureido group has replaced the amino group.

(3) This reagent is most conveniently prepared by adding acetic anhydride to concentrated hydrochloric acid. See ref. 1.

(4) S. A. Harris, D. Heyl, and K. Folkers, *J. Am. Chem. Soc.*, **66**, 2088 (1944).

(5) E. E. Snell, *J. Am. Chem. Soc.*, **67**, 194 (1945).