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

G. E. MCCASLAND, ERWIN BLANZ, JR., AND ARTHUR FURST

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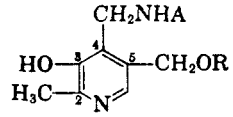
In order to facilitate continued studies[1] on cancer chemotherapy, we have synthesized pyridoxurea hydrochloride[2] (formula II), a derivative of the well known vitamin pyridoxamine (I), in which the primary amino group is replaced by a ureido group. Pyridoxamine free base when briefly heated with equimolar 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).

added a solution of 229 mg. of picric acid[6] in 3.0 ml. of hot absolute ethanol. After cooling, the yellow crystalline product was collected by filtration, washed, and dried (weight 335 mg.).

The material was recrystallized from absolute ethanol (150 ml./g.). After one or two days, there were obtained sheaves of yellow needles, dry weight 221 mg. (56%) m.p. 177–181° (gradually turns to dark viscous liquid).

Anal. Calcd. for $C_{14}H_{15}N_5O_9$: C, 42.32; H, 3.81. Found: C, 41.97; H, 3.66.

4-Aminomethyl-3-hydroxy-2-methyl-5-pyridinemethanol dipicrate (pyridoxamine dipicrate). (A) To pyridoxamine free base (84 mg.) in 6 ml. of boiling ethanol was added a solution of 229 mg. of picric acid[6] in 5 ml. of hot ethanol. The yellow precipitate was collected, washed, dried, and recrystallized from absolute ethanol (220 ml./g.), giving 139 mg. (44%) of glistening yellow leaflets, m.p. 189–192° (gradually changes to dark liquid). The reported[5] (capillary) melting point is 201° (dec.).

This picrate when recrystallized from water separates in the form of long yellow needles.

(B) In an attempted preparation of pyridoxamine thiourea picrate, a solution of 964 mg. of pyridoxamine dihydrochloride, 583 mg. of anhydrous potassium thiocyanate, and 336 mg. of sodium bicarbonate, in 5.0 ml. of water was boiled 10 min. A solution of 1.01 g. of picric acid[6] in 20 ml. of boiling water was then added. The yellow crystals which separated on cooling were collected, washed, and dried (weight 1.3 g.). The material was recrystallized from water (57 ml./g.), giving 1.15 g. (dry weight) of long yellow needles, consisting of starting material dipicrate. The melting behavior was identical with that of the product in Part A (above).

Anal. Calcd. for $C_{20}H_{19}N_8O_{16}$: C, 38.34; H, 2.90; N, 17.88. Found: C, 38.23; H, 2.71; N, 17.56.

3-Hydroxy-2-methyl-4-ureidomethyl-5-pyridinemethanol picrate (pyridoxurea monopicrate). To 336 mg. of pyridoxamine free base was successively added 162 mg. of potassium cyanate, 5.0 ml. of water, and 0.33 ml. of 6*M* hydrochloric acid, with stirring. The resulting mixture was heated to boiling, giving a clear solution, which was boiled under reflux for an additional 10 min.

A 458 mg. portion of crystalline picric acid[6] was added all at once, and the mixture boiled for 5 min. On cooling, there separated yellow crystals, which were collected by filtration, washed with two 5-ml. portions of water, and dried, giving 750 mg. (85%) of crude product.

For analysis, a portion of this material was recrystallized from absolute ethanol (175 ml./g.). After 24 hr. a good recovery was obtained of long yellow needles, m.p. 198–203° (dec.). (It was later found that 50% ethanol, 37 ml./g., is a more convenient crystallizing solvent.).

Anal. Calcd. for $C_{15}H_{16}N_6O_{10}$: C, 40.91; H, 3.66; N, 19.09. Found: C, 41.05; H, 3.41; N, 18.59.

From the mother liquors on standing there separated yellow prisms, which have not yet been characterized.

3-Hydroxy-2-methyl-4-ureidomethyl-5-pyridinemethanol hydrochloride (pyridoxurea monohydrochloride). A 1.55-g. portion of the urea picrate was dissolved in 10.0 ml. of 6*M* hydrochloric acid, and the solution extracted twice with 25 ml. portions of benzene. The acidic aqueous phase was separated, and vacuum distilled to dryness. The residue was recrystallized from 1:1 absolute ethanol–methanol, and dried, giving 560 mg. (64%) of colorless needles, m.p. 205–208° (dec.).

Anal. Calcd. for $C_9H_{14}ClN_3O_3$: C, 43.64; H, 5.70; Found: C, 43.62; H, 5.87.

5-Acetoxymethyl-3-hydroxy-2-methyl-4-ureidomethylpyridine hydrochloride (pyridoxurea 5-O-acetate monohydrochloride). To 440 mg. of the above urea picrate there was added 2.05 ml. of a 2.44*M* solution of hydrogen chloride[3] in glacial acetic acid, with stirring. Within a few minutes the yellow crystals changed into a nearly colorless oil. The mixture was allowed to stand for 24 hr., and 5.0 ml. of benzene was then added, with stirring.

After 30 min. the yellowish crystals were removed by filtration and washed repeatedly with additional 5 ml. portions of benzene until colorless. The crude vacuum-dried (over sodium hydroxide) product weighed 2.5 mg. and melted with decomposition at 190–210°.

To the product in 5.4 ml. of boiling absolute ethanol (slight residue) was added sufficient water (5–10 drops) to give a clear (yellow) solution. On cooling there was obtained 86 mg., dry weight (30%), of flat colorless needles, m.p. 200–208 (dec.).

For analysis this material was again recrystallized, from 95% ethanol, giving sheaves of colorless needles, m.p. 203–206° (dec.).

Anal. Calcd. for $C_{11}H_{16}ClN_3O_4$: C, 45.60; H, 5.57; N, 14.50. Found: C, 45.50; H, 5.42; N, 14.40.

A sample when tested for phenolic hydroxyl with ferric chloride gave an immediate deep red brown color (positive test). A control test on pyridoxamine dihydrochloride gave a similar color. An additional control test on 3-amino-5-aminomethyl-4-ethoxymethyl-2-methylpyridine[7] (which has no phenolic group) did not give any color.

The infrared spectrum (determined with a Perkin-Elmer Model 21 Recording Spectrophotometer, using a potassium bromide pellet) showed a strong absorption maximum at 1730 cm.$^{-1}$. This peak presumably represents the stretching vibration of the ester carbonyl group,[8] and is missing in the spectrum of the nonacetylated urea hydrochloride (II.HCl). A comparison spectrum on pyridoxamine dihydrochloride itself likewise had no absorption maximum in this region.

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(6) The commercial picric acid used presumably contains up to 10% of added water; it is unfortunate that the manufacturers seldom, if ever, specify on the label the added water content of this reagent.

(7) S. A. Harris and K. Folkers, *J. Am. Chem. Soc.*, 61, 1245 (1939).

(8) Although acylation of a urea primary amino group is sometimes possible, we believe that the strongly acidic conditions here used would prevent amine acylation, and at the same time would favor esterification. Under strongly acidic conditions acyl groups, even if originally attached to nitrogen, tend to migrate to oxygen.

Some Sulfones of the Anthraquinone Series

ERWIN KLINGSBERG

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Anthraquinonyl sulfones are usually prepared by oxidation of the corresponding thioethers, which are obtainable from haloanthraquinones, either di-