Synthesis of 5-Halo-6-methylcinchomeronic Acids

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New 5-halo-cinchomeronic acids which are structurally related to pyridoxine have been synthesized. These compounds are potential vitamin B_6 antagonists.

IN A CONTINUING SEARCH for antagonists of vitamin B_6 which may be useful as chemotherapeutic agents in tuberculosis or as nonspecific inhibitors of pyridoxine-dependent enzymes, a series of 5-halo derivatives of cinchomeronic acid [3,4-pyridinedicarboxylic acid (I)] were synthesized. These compounds are also useful intermediates for the preparation of substituted nicotinic acids or analogs of pyridoxine (1). An example is the 5-amino-6-methyl derivative II (2–5).

The amino acid II was easily converted by Sandmeyer type reactions to the chloro (III) and bromo (IV) acids in good yields. The iodo acid (V) was obtained by reaction of the diazonium chloride with aqueous potassium iodide. Attempts to prepare the corresponding fluoro acid by the Schiemann reaction, or by diazotization of II in the presence of hydrofluoric acid, were unsuccessful.

The 6-methylcinchomeronic acid VI had previously been prepared by permanganate oxidation (6) of 3-methylisoquinoline and by basic hydrolysis (7) of ethyl 3-cyano-6-methylisonicotinate. We now find that VI is more conveniently prepared from 4-carbomethoxy-3-cyano-6-methyl-2-pyridone (3) by the reaction route VIII → IX → VII → VI. On treatment of the pyridone VIII with phosphorus pentachloride the desired chloro intermediate IX was obtained in good yield. The chloro-diacid VII had previously been prepared by Ryder and Elderfield (8) from the corresponding 3-cyano-4-carboxamide. We find that acidic hydrolysis of the 3-cyano-4-carbomethoxy intermediate IX is equally convenient. Catalytic hydrogenolysis of VII removes the halogen, giving the desired 6-methylcinchomeronic acid VI.

In the course of this work the previously unreported 3-cyano-2,5-dichloro-4-ethoxymethyl-6-methylpyridine (XI) was prepared and characterized.

Biological testing of these compounds is in progress; results will be reported elsewhere.

EXPERIMENTAL

All melting points have been corrected and were measured on a Monoscop or Nalge-Axelrod micro hot stage. Microanalyses by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were recorded with an Infracord recording infrared spectrometer, using potassium bromide pellets.

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5-Chloro-6-methylcinchomeronic Acid Monohydrate (III).—To a well-stirred mixture of 2.15 Gm. of the finely powdered amine (3) (II, m.p. 248°) with 6.0 ml. of 12 *M* hydrochloric acid, kept at from −5 to 0°, was added dropwise over a 10-minute period a solution of 0.9 Gm. of sodium nitrite in 2.5 ml. of water. The mixture became viscous at first but later thinned out. A solution of 0.99 Gm. of cuprous chloride in 1.5 ml. of 12 *M* hydrochloric acid was then added (caution: foaming), and the mixture was allowed to warm to 25°. After heating to 70° for a brief period, the solution was placed in the refrigerator to cool. The white precipitate was collected, washed with water, and dried, giving 1.73 Gm. (74%) of crude product, m.p. 239° dec. A portion of this material was recrystallized from water, giving yellow needles, m.p. 250° with dec. The melting point is dependent on rate of heating.

Anal.—Calcd. for $C_8H_6ClNO_4 \cdot H_2O$: C, 41.14; H, 3.45; Cl, 15.18; N, 6.00; neut. equiv. 117. Found: C, 41.40; H, 3.59; Cl, 15.54; N, 6.00; neut. equiv. 119.

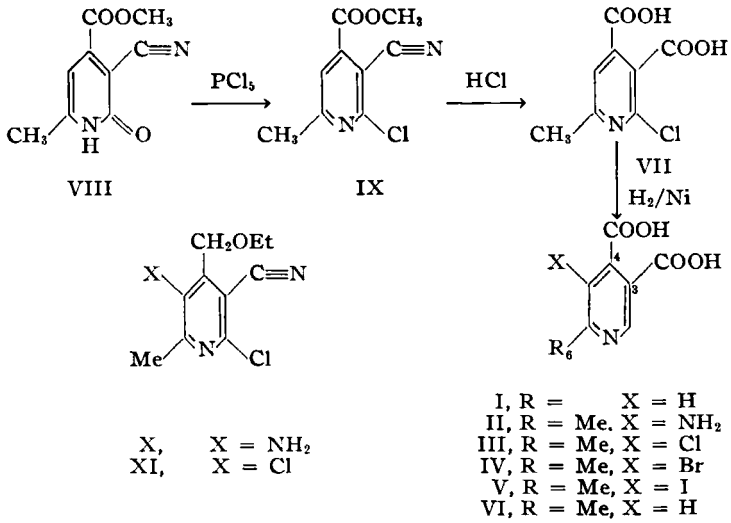
5-Bromo-6-methylcinchomeronic Acid Monohydrate (IV).—The amine (3) (2.15 Gm.) was treated in the manner described above for the chloro analog, but using 8.8 *M* hydrobromic acid, in volumes of 6.0 and 3.0 ml. After final brief heating to 100° and refrigeration, 1.3 Gm. (50%) of the crude product, m.p. 231° dec., was obtained. A portion recrystallized from water gave colorless needles, m.p. 250° with dec. The melting point is almost the same as for the chloro analog and is dependent on rate of heating.

Anal.—Calcd. for $C_8H_6BrNO_4 \cdot H_2O$: C, 34.55; H, 2.90; Br, 28.75; N, 5.04; neut. equiv. 139. Found: C, 34.60; H, 3.02; Br, 28.67; N, 5.11; neut. equiv. 140.

5-Iodo-6-methylcinchomeronic Acid Monohydrate (V).—The amine (3) (2.15 Gm.) was diazotized in the manner described for the chloro analog but using 2.5 ml. of water as solvent for the sodium nitrite. A solution of 1.61 Gm. of potassium iodide in 2.0 ml. of water was added dropwise, to the still cold solution followed by 5.0 ml. additional ice-cold water. The mixture was then allowed to warm to 25°, kept 24 hours, and finally heated to 90–100° for 1 hour. After cooling for several days, the precipitate was collected, washed successively with sodium bisulfite solution and water, and dried, giving 1.51 Gm. (47%) colored crude product, m.p. 240° with dec. A portion recrystallized from water gave tan crystals, melting point unchanged.

Anal.—Calcd. for $C_8H_6INO_4 \cdot H_2O$: C, 29.55; H, 2.48; I, 39.03; N, 4.31. Found: C, 29.81; H, 2.52; I, 39.27; N, 4.24.

The infrared spectra of the chloro, bromo, and iodo acids (III, IV, and V) were very similar, except for small variations in the fingerprint region. The spectra showed O—H stretching absorption at 3500, O—H bending at 1290 and 1263, and carbonyl C=O stretching at 1700 cm.$^{-1}$



I, R = X = H
II, R = Me, X = NH_2
III, R = Me, X = Cl
IV, R = Me, X = Br
V, R = Me, X = I
VI, R = Me, X = H

X, X = NH_2
XI, X = Cl

Methyl 2-Chloro-3-cyano-6-methylisonicotinate (IX).—One-hundred milliliters of phosphorus oxychloride was added to a mixture of 25 Gm. of the pyridone (3) (VIII, m.p. 233°) and 29 Gm. of phosphorus pentachloride. The mixture was heated (anhydrous conditions) at 75–100° for 90 minutes. Phosphorus oxychloride was removed by evaporation *in vacuo*. The dark brown residue was crushed and poured into 100 ml. of ice water. After brief stirring, the product was collected, washed with water, and dried, giving 25.6 Gm. of crude product, m.p. 112–115°. This material was recrystallized from ligroin (1500 ml.), giving 18.5 Gm. (66%) of yellow needles, m.p. 115–116°. A sample recrystallized for analysis melted sharply at 118.5°.

Anal.—Calcd. for $C_9H_7ClN_2O_2$: C, 51.33; H, 3.35; Cl, 16.83; N, 13.30. Found: C, 51.53; H, 3.32; Cl, 16.60; N, 12.97.

2-Chloro-6-methylcinchomeronic Acid (VII).—One-hundred milliliters of 6 *M* hydrochloric acid was added to 10 Gm. of the cyano-ester (IX). The mixture was heated at 90–100° for 5 hours, then cooled. A 2.5-Gm. quantity of yellow crystals was obtained after refrigeration, m.p. 205° dec. The filtrate was evaporated *in vacuo*, giving a yellow residue. The combined crystals and residue were recrystallized from water, giving 4.59 Gm. (45%) of yellow crystals, m.p. 205° with dec. [reported (8) m.p. 205°].

The infrared spectrum showed strong absorption at 2860, 1700, 1290, 1260, and 690 $cm.^{-1}$

6-Methylcinchomeronic Acid (VI).—A 4.0-Gm. portion of the chloro acid (VII) and 2.3 Gm. of sodium hydroxide were dissolved in 75 ml. of water. The mixture was hydrogenated with Raney nickel catalyst at 3 Atm./25° until theoretical hydrogen uptake was reached (about 4 hours). The mixture was filtered and the filtrate adjusted to pH 3 with 16 *M* nitric acid (about 2.7 ml.). The solution was concentrated *in vacuo* to 20 ml., and refrigerated until crystallization was complete, giving 1.3 Gm. (39%) of colorless product, m.p. 240° dec. A sample was recrystallized from water for analysis, giving colorless crystals, m.p. 250° with dec. (reported (7) m.p. 249–251° dec.).

Anal.—Calcd. for $C_8H_7NO_4$: C, 53.04; H, 3.90; N, 7.73; neut. equiv. 90.5. Found: C, 52.54; H, 3.80; N, 7.54; neut. equiv. 90.0.

The infrared spectrum showed strong absorption at 2450, 1700, 1400, 1260, 1060, 892, and 808 $cm.^{-1}$

3-Cyano-2,5-dichloro-4-ethoxymethyl-6-methylpyridine (XI).—A 2.0-Gm. portion of the monochloro-amine (9)(X) was stirred with 5.0 ml. of 12 *M* hydrochloric acid. A clear solution was at first obtained, but the hydrochloride salt soon precipitated. The mixture was treated with sodium nitrite (0.80 Gm.) and cuprous chloride (0.88 Gm.) in the manner described for the chloro compound (III). After final brief heating to 40°, and refrigeration, 1.3 Gm. (63%) of product was obtained, m.p. 50°. A sample recrystallized from ethanol for analysis melted at 52–53°.

Anal.—Calcd. for $C_{10}H_{10}Cl_2N_2O$: C, 49.00; H, 4.11; Cl, 28.93; N, 11.43. Found: C, 48.86; H, 4.19; Cl, 29.07; N, 11.30.

The infrared spectrum showed strong absorption at 2950, 2300, 1590, 1410, 1240, 1160, 1090, 845, 775, and 665 $cm.^{-1}$

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