

**Cinchomeronic Acids from Oxidations of Merimines and
(2,3-Dihydropyrrolo[3,4-c]pyridines) and Reactions of these Acids**

Shreekrishna M. Gadekar and Jean L. Frederick*

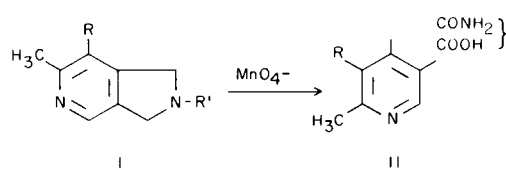
Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamide Company

The syntheses of 5-halo-6-methylcinchomeronic acids as potentially useful antitubercular agents and nonspecific inhibitors of pyridoxine-dependent enzymes were recently reported by Gottwald, McCasland and Furst (1). This report was of particular interest to us because some of these acids were also obtained by the selective oxidation of merimines (2).

It has been shown (3) that when 7-acetamido-2-carboethoxy-6-methylmerimine (Ia) is oxidized with an excess of potassium permanganate a complete oxidation of the dihydropyrrolo portion as well as the methyl group in the 6 position occurs to give 3-aminopyridine-2,4,5-tricarboxylic acid (VI). We would now like to describe selective oxidations of Ia and other substituted merimines (3,4) and some of the transformations of the products of oxidations.

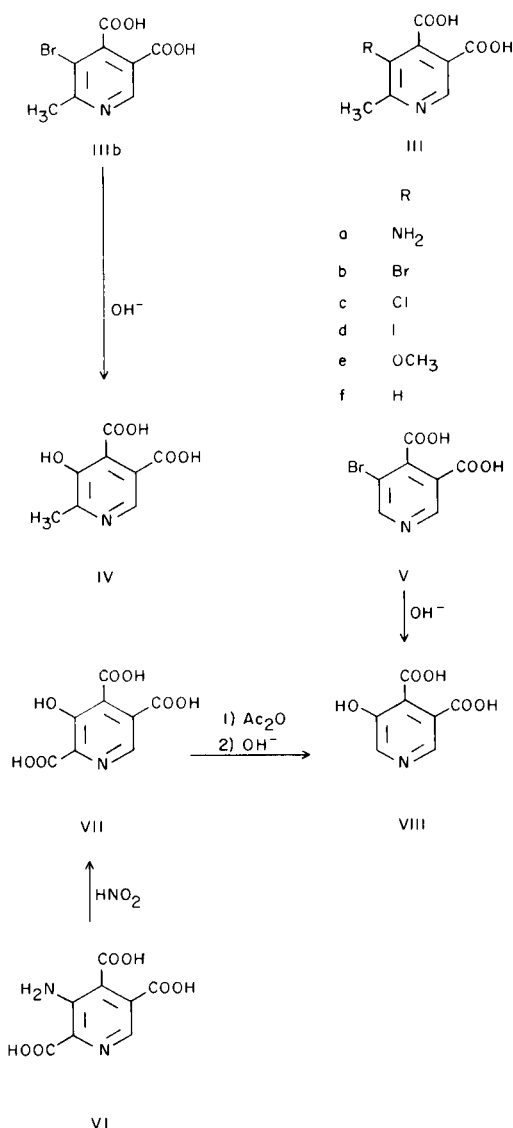
Oxidation of Ia with potassium permanganate (1:2.66 mole ratio) followed by hydrolysis of the residue with concentrated hydrochloric acid afforded 5-amino-6-methylcinchomeronic acid IIIa as a monohydrate (5).

If the reaction mixture is worked up prior to the acid hydrolysis, it is possible to isolate the intermediate



| R' | R | R |
|------------------------------------|----------------------|------|
| a COOC ₂ H ₅ | CH ₃ CONH | a Br |
| b H | Br | b Cl |
| c H | Cl | |
| d H | I | |
| e H | OCH ₃ | |
| f COOC ₂ H ₅ | H | |

↓ H⁺



cinchomeronic acid. Two such acids namely, 5-bromo-6-methyl (IIa) and 5-chloro-6-methyl (3 or 4)-cinchomeronic acid (IIb) were isolated from the oxidations of the corresponding halomerimines. Acid hydrolyses of IIa and IIb afforded the cinchomeronic acids IIIb and IIIc respectively. The overall yields of the cinchomeronic

*Present address: Carter-Wallace, Inc., Cranbury, New Jersey 08512.

acids however were better when the cinchomeronic acids were not isolated. This is believed to be due to the difficulty in the isolation of the cinchomeronic acids which are fairly soluble in the reaction medium. The cinchomeronic acids III_d-III_f were obtained by oxidations of the appropriate merimines. The formation of cinchomeronic and cinchomeronic acids by the oxidations of the merimines thus indicates the instability of the dihydropyrrolo moiety and to the relative stability of the methyl group in the 6 position and of the pyridine ring itself in this system to the action of permanganate. The oxidation of the methyl ether of pyridoxine has been reported (6) to give analogous results.

The transformations III_b→IV and VI→VIII were investigated mainly because of the importance of the resultant pyridine acids as intermediates in the syntheses of pyridoxine (7) and its analogs (8). Consequently, 5-hydroxy-6-methylcinchomeronic acid (IV) "Itiba Acid" which has been prepared by several other procedures (9), was obtained in 80% yield by treating 5-bromo-6-methylcinchomeronic acid (III_b) with sodium hydroxide in the presence of Gattermann copper (3). The reaction proceeded also without the copper but in greatly reduced yield. Application of this method to 5-bromocinchomeronic acid (10) (V) resulted in the formation of the hydroxy acid (VIII) in almost a quantitative yield. Alternately VIII can also be prepared from VII. Thus treatment of VI with nitrous acid afforded VII. This acid gave a positive ferrous sulfate test (red color) indicative of the pyridine α -carboxyl group. The acid was decarboxylated with loss of the α -carboxyl group when refluxed with acetic anhydride. The residual product was then hydrolyzed with alkali to give VII. The overall yield of it from VI was only 14%.

EXPERIMENTAL (11)

5-Amino-6-methylcinchomeronic Acid Hydrate (III_a).

To a 4% aqueous solution of 4.2 g. of potassium permanganate was added 2.6 g. (0.010 mole) of 7-acetamide-2-carbethoxy-6-methylmerimine. The mixture was stirred and heated on a steam bath for 2 hours. The mixture was filtered and the cake was washed with hot water. The combined filtrate was evaporated *in vacuo* to a syrup. The syrup was heated on a steam bath with 10 ml. of concentrated hydrochloric acid for 6 hours and cooled whereupon a crystalline solid separated out. This was filtered off and recrystallized from hot water to give 0.9 g. of a light yellow solid melting at 242-243° dec. (Lit. (5) m.p. 241-242° dec.); λ max. 340 μ ., $\log \epsilon$ 3.800. An additional 0.2 g. of the same material was obtained by evaporating the filtrate from the hydrolysis to dryness and recrystallizing the residue from water; combined yield 1.1 g., (51%).

5-Bromo-6-methyl(3 or 4)-cinchomeronic Acid Hydrate (II_a).

A solution of 5.72 g. (0.0200 mole) of 5-bromo-6-methylmerimine dihydrochloride in 100 ml. of water was adjusted to pH 8 with sodium hydroxide and then oxidized with a 4% aqueous solution of 8.4 g. (0.053 mole) of potassium permanganate at 50°. The warm mixture was filtered and the manganese dioxide was

washed with wto 20 ml. portions of warm water. The pooled filtrates were adjusted to pH 8 and then was evaporated to about 60 ml. Acidification of the filtrate to the congo red with hydrochloric acid gave 2.25 g. (50%) solid, melting at 230-231° dec. An analytical sample was prepared by precipitating the cinchomeronic acid from alkaline solution with sulfur dioxide and washing it with hot ethanol; m.p. 238-239° dec.

Anal. Calcd. for $C_8H_7BrN_2O_3 \cdot H_2O$: C, 34.7; H, 3.27; N, 10.1; Br, 28.8. Found: C, 35.1; H, 3.32; N, 10.1; Br, 29.4.

5-Bromo-6-methylcinchomeronic Acid Hydrate (III_b).

Method A.

A solution of 0.277 g. (0.00100 mole) of II_a in 10 ml. of 1 N hydrochloric acid was refluxed for 6 hours. The yellow solution was evaporated *in vacuo* to a solid which, on trituration with 5 ml. of cold water, yielded 0.26 g. (94%) of the acid. It was recrystallized from hot water; m.p. 247-248° dec; eff. λ max 286 μ ; $\log \epsilon$ 3.784.

Anal. Calcd. for $C_8H_6BrNO_4 \cdot H_2O$: C, 34.5, H, 2.88; N, 5.03; Br, 28.8. Found: C, 34.5; H, 3.07; N, 5.02; Br, 28.5.

Method B.

Oxidation of 14.3 g. (0.0500 mole) of 5-bromo-6-methylmerimine dihydrochloride was carried out as in II_a. However, the intermediate cinchomeronic acid was not isolated, but the residue, on hydrolysis with 25 ml. of 5 N hydrochloric acid for 2 hours, afforded 8.2 g. (63%) of the acid melting at 247-248° dec. eff.

5-Chloro-6-methyl(3 or 4)-cinchomeronic Acid (II_b).

Oxidation of 12 g. (0.050 mole) of 7-chloro-6-methylmerimine dihydrochloride, (1c) as outlined in II_a gave this acid in 49% yield, melting at 275-277° dec.

Anal. Calcd. for $C_8H_7ClN_2O_3$: C, 44.8; H, 3.26; N, 13.1; Cl, 16.5. Found: C, 44.8; H, 3.44; N, 13.3; Cl, 16.6.

5-Chloro-6-methylcinchomeronic Acid Hydrate (III_c).

Method A.

Hydrolysis of 0.214 g. (0.00100 mole) of II_b with 10 ml. of 6 N hydrochloric acid for 6 hours gave 0.2 g. (86%) of the acid melting at 248-250° dec., λ max 282 μ ; $\log \epsilon$ 3.797.

Anal. Calcd. for $C_8H_6ClNO_4 \cdot H_2O$: C, 41.2; H, 3.4; N, 6.02; Cl, 15.3. Found: C, 41.5; H, 3.4; N, 6.34; Cl, 15.5.

Method B.

The yield of acid from the oxidation of 24.1 g. (0.100 mole) of 5-chloro-6-methylmerimine dihydrochloride as described in III_b, Method B, was 68%; m.p. 248-251° dec.

5-Iodo-6-methylcinchomeronic Acid Hydrate (III_d).

By the general procedure outlined in III_b, Method B, 16.6 g. (0.0500 mole) of 7-iodo-6-methylmerimine dihydrochloride was oxidized to give 12.5 g. (81%) of the iodo acid melting at 241-246° dec. eff; λ max 299 μ ; $\log \epsilon$ 3.550.

Anal. Calcd. for $C_8H_6INO_4 \cdot H_2O$: C, 29.6; H, 2.48; N, 4.31; I, 39.1. Found: C, 29.3; H, 2.64; N, 4.25; I, 39.1.

5-Methoxy-6-methylcinchomeronic Acid (III_e).

The yield of this acid from the oxidation of 3.4 g. (0.014 mole) of 7-methoxy-6-methylmerimine dihydrochloride was 34%; m.p. 214-215° dec; (Lit. (12) m.p. 213-215°).

6-Methylcinchomeronic Acid (III_f).

When 5.1 g. (0.025 mole) of 2-carbethoxy-6-methylmerimine was oxidized, the yield of III_f was 3.0 g. (66%); m.p. 249-253° dec; (Lit. (1) m.p. 250° dec.).

5-Hydroxy-6-methylcinchomeronic Acid (IV).

Method A.

A mixture of 1.0 g. (0.0038 mole) of 5-bromo-6-methylcinchomeronic acid (IIIb), 0.50 g. (0.0079 g. atom) of Gattermann copper, and 20 ml. of 10 N sodium hydroxide was heated in an autoclave at 175° for 4 hours. The reaction mixture was filtered to remove copper, and the filtrate was acidified to pH 3 with concentrated hydrochloric acid to produce 0.3 g. of a solid melting at 260-261° dec. An additional 0.3 g. of the same product was obtained by evaporating the filtrate to dryness, extracting the residue with ethanol and acetone, evaporating the extracts to dryness, and recrystallizing the solid from water; total yield 0.6 g. (80%). Another recrystallization of this from water gave analytically pure product melting at 265-270° dec.; (Lit. (5) m.p. 258-259°); λ max 302.5 μ , $\log \epsilon$ 3.825 (13). The results of the ferric chloride test (OH group) were positive; but the Beilstein flame test for halogen was negative.

Anal. Calcd. for $C_8H_7NO_5$: C, 48.8; H, 3.58; N, 7.12; Found: C, 48.6; H, 3.76; N, 7.10.

Method B.

A solution of 1.0 g. (0.0038 mole) of the bromo acid (IIIb) in 20 ml. of 10 N sodium hydroxide was heated in the pressure vessel under the same conditions of time and temperature as Method A but without the copper. However, only 0.25 g. (33%) of the hydroxy acid having the same physical properties (m.p., U.V. absorption) was obtained from this preparation.

5-Hydroxycinchomeronic Acid (VIII).

A mixture of 10 g. (0.035 mole) of 5-bromocinchomeronic acid, (V) 2.5 g. (0.039 g. atom) of Gattermann copper and 150 ml. of 10 N sodium hydroxide was heated in an autoclave at 150° for 4 hours. The reaction mixture was filtered, and the filtrate was acidified with concentrated hydrochloric acid to produce 7.8 g. (98%) of a white solid melting at 255-258° dec. The results of the ferric chloride and the Beilstein flame tests of this material were the same as for the 6-methyl acid (IV). An analytical sample was prepared by one recrystallization from water of the solid obtained; m.p. 254-258° dec.; λ max 298 μ , $\log \epsilon$ 3.714; (Lit. (10) m.p. 243-244°, 237-238°, and 240-245° (8a)).

Anal. Calcd. for $C_7H_5NO_5 \cdot 2H_2O$: C, 38.4; H, 4.14; N, 6.39; Found: C, 38.5; H, 4.37; N, 6.36.

3-Hydroxypyridine-2,4,5-tricarboxylic Acid Dihydrate (VII).

A suspension of 5.24 g. (0.020 mole) of VI in 80 ml. of 4 N hydrochloric acid was treated at 70° with 4.15 g. (0.060 mole) of solid sodium nitrite during one half hour. The bright yellow solution was heated at 70° for an additional one half hour and cooled, when two batches of solids were obtained weighing 1.95 g. and 1.6 g., and melting at 195-200° and 200-205° dec., respectively. These were combined, recrystallized from a minimum amount of hot water to give a sample melting at 198-199° dec.; λ max 280 μ , $\log \epsilon$ 3.718.

Anal. Calcd. for $C_8H_5NO_7 \cdot 0.5H_2O$: C, 40.7; H, 2.54; N, 5.94; Found: C, 40.7; H, 2.60; N, 6.66 (14).

The compound gave positive ferrous sulfate and ferric chloride tests indicating the presence of pyridine α -carboxy and phenolic hydroxyl groups, respectively.

Conversion of VI to VIII.

In this experiment the same quantity of VI was converted to

VII. However, it was not isolated. Instead the mixture was evaporated to dryness *in vacuo*. The resulting residue was treated with 50 ml. of acetic anhydride and the mixture was refluxed for 4 hours. The dark solution was re-evaporated to dryness, and the contents were digested with 100 ml. of 3 N sodium hydroxide. The alkaline solution was reduced to a 25-ml. volume under diminished pressure, and then acidified to pH 2 with hydrochloric acid, whereupon 0.75 g. of a light tan solid was obtained. Recrystallization of this material from hot water afforded 0.5 g. (14%) of a crystalline solid melting at 253-255° dec.; (Lit. (10) m.p. 237-238°). This solid gave a negative ferrous sulfate (loss of α -carboxyl group) and a positive ferric chloride test (phenolic OH), λ max 298, μ $\log \epsilon$ 3.804.

Anal. Calcd. for $C_7H_5NO_5 \cdot H_2O$: C, 40.2; H, 3.51; N, 6.97; Found: C, 40.2; H, 3.95; N, 6.64.

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