[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Synthesis of Merimines. 7-Chloro-6-methylmerimine and Related Analogs[1]

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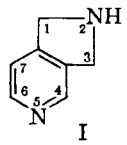
The synthesis and chemistry of several simply substituted 2,3-dihydro-1H-pyrrolo[3,4-c]pyridines, more commonly referred to as merimines, is described. The most interesting members of this series are 7-chloro-6-methylmerimine and its ethyl and 6-demethyl homologues. These compounds had tranquilizing activity in experimental animals.

Preliminary screening in these laboratories indicated that interesting central nervous system activity might be found among compounds containing the 2,3-dihydro-1H-pyrrolo[3,4-c]pyridine or "merimine"[2] heterocyclic ring system (I).



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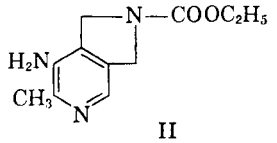
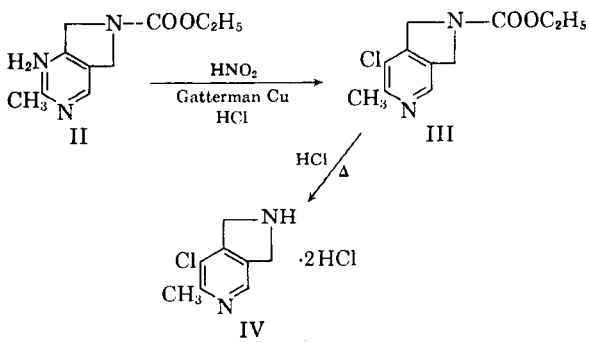


II

The chemistry of a number of merimine derivatives has been reported recently by Wright, Webb, and Smith[3] and by Wright.[4] These authors pointed out that when the 2-position in 7-amino-6-methylmerimine was blocked by a carbethoxy or a benzoyl group, etc., the primary amine in the 7-position could be diazotized and a variety of 2,7-disubstituted 6-methylmerimines could be prepared by standard procedures. In our hands, however, when the compound shown—*i.e.*, 7-amino-2-carbethoxy-6-methylmerimine (II) was subjected to a Sandmeyer reaction using cuprous chloride—it was not possible to obtain the expected 2-carbethoxy-7-chloro-6-methylmerimine (III). However, when the diazotization was carried out in 7.5*N* hydrochloric acid and the diazonium salt was then decomposed in the presence of either electrolytic or Gatterman copper, the desired 7-chloro compound was obtained in yields ranging from 20–60%.



II III IV

In later experiments it was found that copper sulfate or cupric chloride could also be used successfully in this preparation.

Hydrolysis of the 2-carbethoxy blocking group in warm, concentrated hydrochloric acid for forty-eight hours, then gave 7-chloro-6-methylmerimine (IV) as its dihydrochloride, in better than 80% yield.

Fluorine was also introduced into the 7-position of 6-methylmerimine by decomposition of the corresponding diazoniumfluoroborate salt followed by hydrolysis of the 2-carbethoxy group.

On pharmacological evaluation in three animal species, *i.e.*, mice, dogs, and monkeys, 7-chloro-6-methylmerimine showed tranquilizing activity similar to but less than that of reserpine.[5] The 7-bromo and 7-iodo analogs which were available from other work,[2] and the 7-fluoro analog exhibited similar activity. The 7-fluoro derivative however, was only about one-half as active as the chloro compound. In all cases tested, merimines acylated in the 2-position were devoid of tranquilizing activity.

To extend our study to the effect of the alkyl substituent in the 6-position of the merimines in this series, the 6-ethyl and 6-demethyl analogs of IV were prepared for comparison. The synthesis of the 6-ethyl compound proceeded without difficulty as outlined below.

Ethyl propionyl pyruvate (V) was condensed with cyanoacetamide in ethanol at 60° to give 4-carbethoxy-3-cyano-6-ethyl-2(1H)pyridone (VI)[6] in 37% yield. Nitration of this with fuming nitric acid in acetic anhydride solution gave VII in 49% yield.

Treatment of the nitropyridone VII with phosphorus pentachloride in chlorobenzene solution gave the 2-chloro compound VIII (59%) which was hydrogenated using freshly prepared palladium on charcoal in acid solution, and then treated with alkali to give the lactam, 7-amino-6-ethyl-1-ketomerimine (IX), directly in 58% yield. This was

(1) Presented in part at the 136th Meeting of the American Chemical Society in Atlantic City, N. J., September 1959.

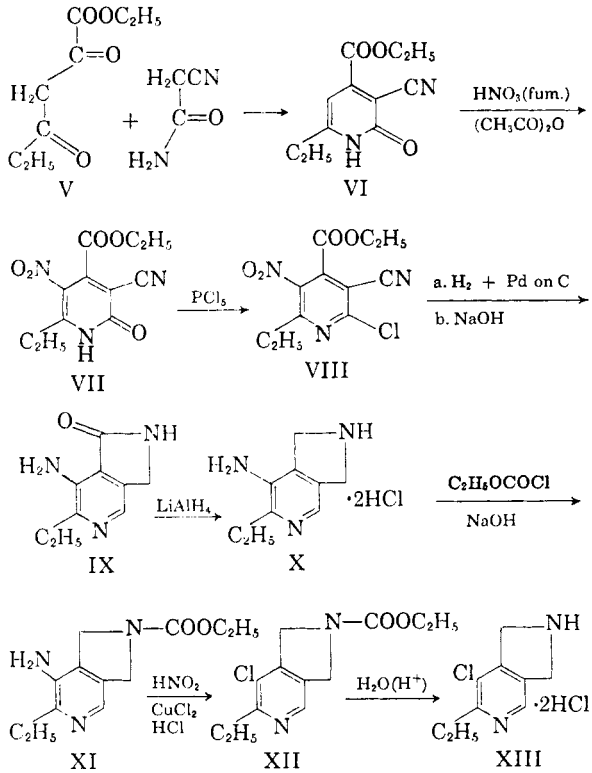
(2) The trivial name "merimine" was assigned to this heterocyclic system by S. Gabriel and J. Colman, *Ber.*, **35**, 2832 (1902), who were the first investigators to prepare the parent compound.

(3) W. B. Wright, Jr., J. S. Webb, and J. M. Smith, Jr., *J. Am. Chem. Soc.*, **79**, 2199 (1957).

(4) W. B. Wright, Jr., *J. Org. Chem.*, **24**, 1016 (1959).

(5) The pharmacological data was obtained from Drs. W. D. Gray, L. Kanegis, and A. C. Osterberg of the Experimental Pharmacology Department, Pearl River Laboratories.

(6) A. Tracy and R. Elderfield, *J. Org. Chem.*, **6**, 72 (1941).



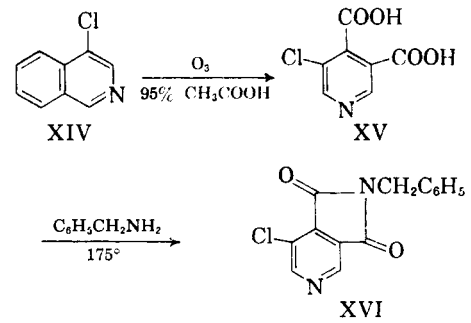
reduced with lithium aluminum hydride in tetrahydrofuran to give the desired key intermediate, 7-amino-6-ethylmerimine (X), which was isolated as its dihydrochloride in 30% yield.

The remaining steps of this synthesis are essentially the same as those previously shown for 7-chloro - 6 - methylmerimine itself. The aminoethylmerimine X was carboethoxylated in the 2-position to give XI in 66% yield. This was then diazotized and treated with cupric chloride under very carefully controlled conditions to give XII in 63% yield. Hydrolysis of XII in concentrated hydrochloric acid for forty-eight hours as before gave the desired ethyl analog, 7-chloro-6-ethylmerimine (XIII), which was isolated as its dihydrochloride in 65% yield.

For the synthesis of 7-chloromerimine (XXIV), the approach used for the preparation of XIII was not completely applicable, because of the difficulty of obtaining the desired 4-carbethoxy-3-cyano-2-pyridone starting material.

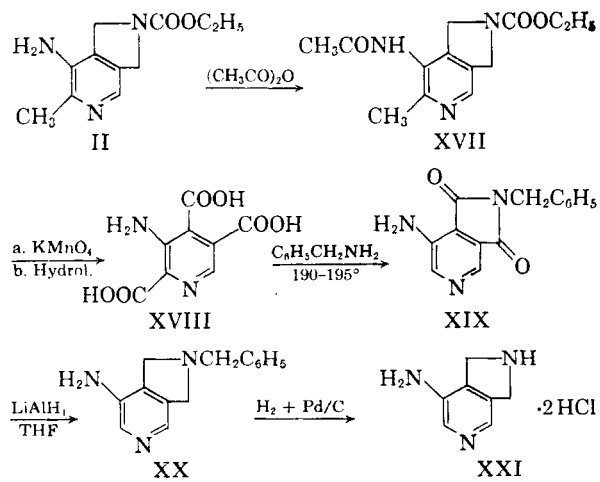
In an alternate approach, 4-chloroisoquinoline (XIV) was prepared and oxidized using ozone in 95% acetic acid solution[7] to give 5-chloro-cinchomeronic acid (XV) in low yield. This was fused with benzylamine to give the corresponding 5-chloro-*N*-benzylcinchomeronimide (XVI) in 55% yield after cystallization from methanol.

It was anticipated from model experiments that Compound XVI could be reduced and debenzylated to the desired chloromerimine without undue difficulty. However, in all cases tried, the chlorine atom was lost before final reduction was achieved, probably because of activation by the neighboring carbonyl group.



The approach to this synthesis which was ultimately successful involved introduction of the chlorine atom in the penultimate step—that is after all reductive procedures had been completed. 7-Amino-2-carbethoxy-6-methylmerimine (II) was acylated to the corresponding 7-acetylaminomerimine (XVII), which was then oxidized by alkaline potassium permanganate and hydrolyzed to 3-aminoberberonic acid (XVIII) in about 30% yield.

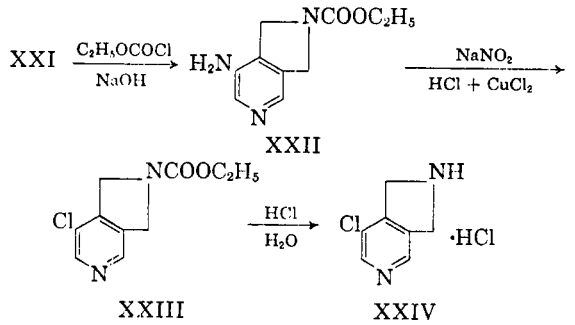
Condensation of XVIII with benzylamine at 190–195° resulted in the formation of 5-amino-*N*-benzylcinchomeronimide XIX, with concurrent decarboylation in the 2-position, in over 80% yield. This imide was reduced smoothly with lithium aluminum hydride in tetrahydrofuran to 7-amino-2-benzylmerimine (XX). Hydrogenolysis of the benzyl group in the 2-position was carried out with freshly prepared palladium catalyst in ethanol to give a 96% yield of 7-aminomerimine (XXI), which was isolated as its dihydrochloride. The yield of merimine obtained was lowered considerably (to 24%) when commercial 10% palladium on charcoal catalyst was used in this hydrogenation.



The procedure for the conversion of 7-aminomerimine (XXI) to the chloro derivative was similar to that utilized in the synthesis of 7-chloro-6-ethylmerimine (XIII).

(7) A. F. Lindenstruth and C. A. Vanderwerf, *J. Am. Chem Soc.*, 71, 3020 (1949).

Thus, 7-amino-2-carbethoxymerimine (XXII) was obtained in 60–85% yields by carbethoxylation of XXI by the usual Schotten-Baumann procedure. Diazotization of the carbethoxy derivative in the presence of cupric chloride gave a 66% yield of 2-carbethoxy-7-chloromerimine (XXIII). When this derivative was hydrolyzed in concentrated hydrochloric acid, a 76% yield of 7-chloromerimine (XXIV) was obtained as its monohydrochloride.



On pharmacological evaluation in experimental animals, 7-chloro-6-ethylmerimine (XIII) was less than one-half as active as 7-chloro-6-methylmerimine (IV) as a tranquilizing agent and 7-chloromerimine (XXIV) was even less active (approximately 25%). It appears, therefore, that in this particular series the desired maximum activity is found in the parent compound, namely 7-chloro-6-methylmerimine dihydrochloride (IV). Clinical testing of IV, however, showed it to be devoid of tranquilizing activity in humans.

EXPERIMENTAL[8]

2-Carbethoxy-6-methyl-7-chloromerimine (III). A solution of 24.0 g. (0.1 mole) of 2-carbethoxy-6-methyl-7-aminomerimine monohydrate[2] in 120 ml. of concd. hydrochloric acid and 75 ml. of water was cooled in a Dry Ice-2-ethoxyethanol bath to −20°. A solution of 11.5 g. of sodum nitrite in 35 ml. of water was then added with good stirring over a 20-min. period. Stirring was continued for an additional 5 min. after which 25 g. of Gattermann copper[9] was added gradually in small portions. A copious evolution of nitrogen and nitrogen dioxide was noticed. The temperature was maintained at −3° or below during addition of the copper. It was then allowed to rise to room temperature over a 1-hr. period and the mixture was filtered. The solid on the funnel was washed with a small volume of water, and the filtrate and the washings were combined and adjusted to 250 ml. with water. A part of this solution (75 ml.) was diluted with an equal volume of water, saturated with hydrogen sulfide, and filtered. The filtrate was cooled in an ice-bath, made basic with 45 ml. of 10*N* sodium hydroxide and then extracted thoroughly with ether (5 × 150 ml.). The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield 2.1 g. (29%) of a dull white solid melting at 94–96°.

Anal. Calcd. for $C_{11}H_{13}N_2O_2Cl$: C, 55.0; H, 5.40; H, 11.7; Cl, 14.8. Found: C, 54.8; H, 5.56; N, 11.9; Cl, 14.8.

6-Methyl-7-chloromerimine dihydrochloride (IV). A solution of 1.2 g. (0.0050 mole) of 2-carbethoxy-6-methyl-7-chloromerimine monohydrate in 10 ml. of concd. hydrochloric acid was refluxed for 30 hr. The solution was then diluted with an equal volume of water, treated with activated carbon, filtered and the filtrate was evaporated to dryness *in vacuo*. The light yellow cake was triturated with 10 ml. of cold, dry ethanol and filtered off. The insoluble solid was washed with an additional 5 ml. of cold ethanol, and the solid was air dried; yield, 1.0 g. (83%), m.p. 275–280° dec.

Recrystallization from a mixture of 1 ml. of water and 5 ml. of saturated ethanolic hydrogen chloride gave a product melting at 276–281° dec. after drying for 4 hr. at 63°.

Anal. Calcd. for $C_8H_{11}N_2Cl_3$: C, 39.8; H, 4.56; N, 11.6; Cl, 44.0. Found: C, 39.9; H, 4.77; N, 11.7; Cl, 43.9.

2-Carbethoxy-6-methyl-7-fluoromerimine. A warm solution of 12 g. of 2-carbethoxy-6-methyl-7-aminomerimine monohydrate in 200 ml. of ethanol was treated with 100 ml. of cold fluoboric acid. A precipitate settled out readily. The mixture was chilled to −10°, treated rapidly with 25 ml. of butylnitrite and stirred at −5° to −10° for 2.5 hr. The resulting pink mixture was then diluted with 100 ml. of reagent grade ether (also maintained at −10°) and the white precipitate which separated was rapidly filtered off on a pre-Dry Ice chilled funnel, washed with cold ether and heptane, and then suspended in 200 ml. of cold heptane. The suspension was allowed to warm and, as the temperature rose, decomposition of the solid with evolution of gas (nitrogen and boron trifluoride) was observed. After the mixture had reached room temperature, it was heated on the steam-cone for a short time and the solvent was decanted from the brown gum which had settled out. The gum was taken up in 20 ml. of water, placed in a separatory funnel, covered with 100 ml. of ether, and a saturated solution of sodium carbonate was then added until the aqueous layer was distinctly alkaline. The mixture was shaken and the ether layer was separated. The aqueous portion was then saturated with solid sodium carbonate and exhaustively extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and evaporated to about 25 ml. to precipitate a light yellow solid. This was filtered off and washed with 20 ml. of ether. The ether filtrate and the washings were combined and evaporated to yield 5.1 g. (46%) of a tan solid melting at 60–61°. A sample of this material recrystallized from an ether–petroleum ether (b.p. 60–70°) mixture melted at 61–62°.

Anal. Calcd. for $C_{11}H_{13}FN_2O_2$: C, 59.0; H, 5.80; N, 12.5; F, 8.47. Found: C, 59.1; H, 5.98; N, 12.7; F, 8.34.

6-Methyl-7-fluoromerimine. A solution of 1.12 g. of 2-carbethoxy-6-methyl-7-fluoromerimine in 10 ml. of concd. hydrochloric acid was refluxed for 60 hr. The dark-brown mixture was diluted with an equal volume of water, warmed, treated with activated charcoal, and filtered. The light yellow filtrate on evaporation to dryness *in vacuo* gave a light yellow solid. This was slurried with 10 ml. of dry ethanol, filtered off, and air dried. The product weighed 0.85 g. (76%) and melted at 255–262° dec.

Anal. Calcd. for $C_8H_{11}Cl_2FN_2$: C, 42.7; H, 4.90; N, 12.5; Cl, 31.6; F, 8.45. Found: C, 42.7; H, 5.05; N, 12.8; Cl, 31.4; F, 7.99.

4-Carbethoxy-3-cyano-6-ethyl-5-nitro-2(1H)pyridone (VII). Yellow fuming nitric acid, 49.0 g. (1.05 mole), was added dropwise to a slurry of 4-carbethoxy-3-cyano-6-ethyl-2(1H)pyridone,[5] 119 g. (0.540 mole), in 290 ml. of acetic anhydride. The temperature during addition was kept below 50°. The reaction was stirred, without cooling, until the temperature dropped to 30°. The reaction mixture was then drowned in ice and the product was filtered off and recrystallized from 800 ml. of hot alcohol. The product, 70.0 g. (49%), melted at 195–197° with slight decomposition above 190°.

Anal. Calcd. for $C_{11}H_{11}N_3O_5$: C, 49.8; H, 4.18; N, 15.9. Found: C, 50.2; H, 4.44; N, 15.9.

4-Carbethoxy-2-chloro-3-cyano-6-ethyl-5-nitropyridine (VIII). A solution of 4-carbethoxy-3-cyano-6-ethyl-5-nitro-2(1H)-pyridone, 20 g. (0.075 mole), 22 g. (0.11 mole), of

(8) All melting points are uncorrected. The ultraviolet spectra were determined in 0.1*N* hydrochloric acid.

(9) L. Gattermann, *Ber.*, 23, 1218 (1890).

phosphorus pentachloride and 170 ml. of chlorobenzene was refluxed for 3 hr. The chlorobenzene and phosphorus oxychloride was evaporated off on the steam bath *in vacuo* and 200 ml. of benzene was added to the residue. The benzene solution was washed four times with water and dried over potassium carbonate. The drying agent was filtered off and the benzene was concentrated *in vacuo* on the steam bath. The residue was dissolved in 125 ml. of hot ethanol and the solution was cooled to crystallize the product, yield 11.0 g. (59%); m.p. 70–71.5°.

Anal. Calcd. for $C_{11}H_{10}ClN_3O_4$: C, 46.5; H, 3.52; N, 14.8; Cl, 12.5. Found: C, 46.6; H, 3.59; N, 14.6; Cl, 12.7.

7-Amino-6-ethyl-1-ketomerimine (IX). In a 1-l. hydrogenation flask equipped with two dropping funnels were placed 150 ml. of water, 2 ml. of concd. hydrochloric acid, 4.5 g. of activated charcoal, 22.8 ml. (0.00400 mole) of palladium chloride solution, and 150 ml. of methanol. In the two funnels were placed separately, solutions of 20.5 g. (0.0720 mole) of the 4-carbethoxy-2-chloro-3-cyano-6-ethyl-5-nitropyridine in 60 ml. of glacial acetic acid at 30°, and 17 ml. of concd. hydrochloric acid in 42 ml. of water.

The apparatus was then sealed and purged. The catalyst was prepared by shaking a mixture of palladium chloride and activated carbon in the presence of hydrogen at −40° and then the hydrochloric acid solution was added to the catalyst. The acetic acid solution of the chloro compound was then added dropwise over a 2-hr. period at 42–45°. The total uptake of hydrogen at 34° was 9710 ml. (theory 10,910 ml.). The mixture was filtered and the filtrate was chilled to −15°; when 0.50 g. of a yellow crystalline solid separated. This was filtered off and the mother liquor was evaporated to one quarter volume at room temperature. The residue from this was made basic to *p*H 8–9 with 9% sodium hydroxide at 0° to 5°, when a heavy yellow precipitate formed which was filtered off, washed with 20 ml. of ice water and dried at 50–55° to a constant weight. The solid weighed 7.4 g. (58%) and melted at 181–183°. A 1-g. sample on two recrystallizations from water gave 0.80 g. of a crystalline solid melting at 180°. λ_{max} 256, 350 mμ; log ε 3.747, 3.936.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.0; H, 6.20; N, 23.7. Found: C, 61.3; H, 6.30; N, 23.5.

7-Amino-6-ethylmerimine dihydrochloride (X). *Method A.* To a solution of 4.0 g. (0.11 mole) of lithium aluminum hydride in 200 ml. of tetrahydrofuran under nitrogen at 40–50° was added slowly a second solution of 1.8 g. (0.010 mole) of the γ-lactam of 3-amino-5-aminomethyl-2-ethylisonicotinic acid in 350 ml. of tetrahydrofuran. The resulting mixture was refluxed at 65° for 7 hr. and allowed to stand overnight at room temperature. The excess of lithium aluminum hydride was destroyed using a mixture of 8 ml. of water in 100 ml. of tetrahydrofuran. The solution was filtered and acidified with 10 ml. of concd. hydrochloric acid. On chilling, a solid product precipitated. This was purified by dissolving it in a minimum amount of water, acidifying with alcoholic hydrochloric acid and reprecipitation using a mixture of alcohol and ether. After four such treatments, 0.60 g. (27%) of product was obtained; m.p. 300° dec. λ_{max} 255, 315 mμ; log ε 3.818, 3.869.

Anal. Calcd. for $C_9H_{13}N_3.2HCl$: C, 45.8; H, 6.41; N, 17.8; Cl, 30.0. Found: C, 45.8; H, 6.35; N, 17.6; Cl, 29.8.

Method B. A 0.50-g. (0.0028 mole) sample of the γ-lactam of 3-amino-5-aminomethyl-2-ethylisonicotinic acid was dissolved in about 30 ml. of alcohol and acidified with alcoholic hydrochloric acid. The monohydrochloride which crystallized was filtered off, washed with ether, and air dried; wt. 0.53 g. This product was mixed with 5.5 ml. of 45% hydriodic acid and 25 mg. of red phosphorus in a sealed tube and heated at 180° for 4 hr. After cooling, the insoluble merimine was filtered off and redissolved in 10 ml. of 2*N* hydrochloric acid. After removal of the solvent by evaporation, the solid residue was recrystallized from alcoholic hydrochloric acid containing a few drops of water to give 0.12 g. (21%) of product.

Anal. Calcd. for $C_9H_{13}N_3.2HCl$: C, 45.8; H, 6.41; N, 17.8. Found: C, 45.7; H, 6.57; N, 18.1.

7-Amino-2-carbethoxy-6-ethylmerimine (XI). A well stirred solution of 1.53 g. (0.00650 mole) of 7-amino-6-ethylmerimine dihydrochloride in a mixture of 8 ml. of water and 3.86 ml. of 5*N* sodium hydroxide was cooled to 5° and 0.71 g. (0.0065 mole) of ethyl chlorocarbonate was added dropwise while keeping the temperature below 10°. A white precipitate formed rapidly. An additional 15 ml. of water was added and the mixture was allowed to come to room temperature and stirred for an additional 30 min. The solid precipitate was filtered off and recrystallized from 50% ethanol to give 1.00 g. (65.6%) of the desired product as a monohydrate, m.p. 158–161° dec.

Anal. Calcd. for $C_{12}H_{17}N_3O_2 \cdot H_2O$: C, 56.8; H, 7.56; N, 16.6. Found: C, 55.7; H, 7.78; N, 16.4.

Prolonged drying *in vacuo* at room temperature gave the anhydrous material, m.p. 154–156° dec.

Anal. Calcd. for $C_{12}N_{17}N_3O_2$: C, 61.2; H, 7.24; N, 17.9. Found: C, 60.6; H, 7.40; N, 17.6.

In neither case was a satisfactory carbon analysis obtained; however, the ultraviolet spectrum for the compound was similar to that of the methyl homolog. λ_{max} 237.5, 308 mμ; log ε 3.956, 3.921. 7-Amino-2-carbethoxy-6-methylmerimine·H_2O, λ_{max} 237.5, 308 mμ; log ε 3.970, 3.911.

2-Carbethoxy-7-chloro-6-ethylmerimine (XII). To a solution of 0.78 g. (0.0033 mole) of 7-amino-2-carbethoxy-6-ethylmerimine monohydrate in 5.8 ml. of concd. hydrochloric acid was added 0.64 g. (0.0038 mole) of cupric chloride dihydrate and the mixture was stirred until a clear solution resulted. After cooling to −10°, a second solution of 0.40 g. (0.0058 mole) of sodium nitrite in 0.58 ml. of water was added slowly beneath the surface with stirring. The temperature was then allowed to rise to 8° and the mixture was diluted with 7.25 ml. of water, made basic with 8.30 ml. of concd. ammonium hydroxide and again cooled for 1–1.5 hr. The resulting precipitate was filtered off and recrystallized (activated carbon) from 50% ethanol to yield 0.52 g. (63%) of product melting at 65–66.5°. After prolonged drying *in vacuo* at room temperature a satisfactory analysis was obtained. λ_{max} 275 mμ; log ε 3.884.

Anal. Calcd. for $C_{12}H_{15}N_3ClO_2$: C, 56.6; H, 5.93; N, 11.0; Cl, 13.9. Found: C, 56.4; H, 6.18; N, 11.1; Cl, 14.1.

7-Chloro-6-ethylmerimine dihydrochloride (XIII). A solution of 0.408 g. (0.00160 mole) of 2-carbethoxy-7-chloro-6-ethylmerimine in 4 ml. of concd. hydrochloric acid was refluxed on the steam bath for 48 hr. The resulting light yellow solution was diluted with 4 ml. of water and evaporated *in vacuo* to a yellow oil. The oil was triturated with 1.2 ml. of absolute ethanol, 0.40 ml. of alcoholic hydrochloric acid, and 1.0 ml. of ether. The resulting crystals were filtered off and washed with ether. Recrystallization of these from a minimum of water (activated carbon) and addition of a 5:1 ratio of alcoholic hydrochloric acid followed by chilling for several hours gave white plates; yield, 0.271 g. (64.5%), m.p. 203–216° dec. The sample was dried *in vacuo* at room temperature for 3 hr. λ_{max} 221, 276 mμ; log ε 3.613, 3.768.

Anal. Calcd. for $C_9H_{13}N_2Cl_3O$: C, 39.5; H, 5.54; N, 9.95; Cl, 38.9. Found: C, 39.5; H, 5.54; N, 10.2; Cl, 38.6.

4-Chloroisoquinoline (XIV). To a suspension of 38.0 g. (0.265 mole) of 4-aminoisoquinoline[10] in 212 ml. of concd. hydrochloric acid was added a solution of 132 g. (0.529 mole) of copper sulfate pentahydrate in 212 ml. of water. The resulting green solution was chilled to −2° in a Dry Ice–2-ethoxyethanol bath and a solution of 36.5 g. (0.529 mole) of sodium nitrite in 175 ml. of water was added dropwise with constant stirring. The temperature was maintained at −2 to −4° during the addition. The mixture was allowed to come to room temperature with stirring and was then heated to 60° until evolution of gas ceased. The mix-

(10) J. J. Craig and W. E. Cass, *J. Am. Chem. Soc.*, 64, 783 (1942).

ture was then diluted with 600 ml. of water and hydrogen sulfide was passed through the suspension until all of the copper was precipitated (about 2 hr.). The mixture was filtered and the filtrate was reduced to 600 ml. *in vacuo* and made basic with 350 ml. of 10*N* sodium hydroxide. This solution was extracted with five 300-ml. portions of ether and the ether extracts were dried over anhydrous magnesium sulfate and evaporated to yield 23 g. of oil. Vacuum distillation of this oil gave a fraction boiling at 100–104° (1–1.5 mm.), which weighed 18.9 g.; yield (43.6%); m.p. 28.5–29.5°.

Anal. Calcd. for C_9H_6ClN: C, 66.1; H, 3.69; Cl, 21.7; N, 8.57. Found: C, 66.4; H, 3.79; Cl, 21.6; N, 8.51.

5-Chlorocinchomeronic acid (XV). A solution containing 4.1 g. (0.025 mole) of 4-chloroisoquinoline, 35 ml. of glacial acetic acid, and 3.5 ml. of water was ozonized at room temperature for 18 hr. intermittently on a Welsbach ozonizer. The reaction warmed up slightly (about 35–40°) initially, and a small amount of solid appeared after 10 hr. of ozonization. At the end of the reaction period, the mixture was filtered and the solid removed was air dried to constant weight; wt. 0.4 g. (8%) m.p. 230–232° (dec., eff.). The solid gave a positive Beilstein flame test indicating the presence of halogen in the product.

Recrystallization of 100 mg. of this material from 5 ml. of hot water gave 52 mg. of a colorless product, m.p. 240–242° (dec., eff.). λ_{max} 280 mμ; log ϵ 3.613.

Anal. Calcd. for $C_7H_4ClNO_4$: C, 41.7; H, 1.98; N, 6.95; Cl, 17.7. Found: C, 41.7; H, 2.14; N, 7.01; Cl, 17.7.

N-Benzyl-5-chlorocinchomeronimide (XVI). A mixture of 2.0 g. (0.010 mole) of 5-chlorocinchomeronic acid, 1.1 g. (0.010 mole) of benzylamine and 1 ml. of water was gradually heated to 175°. The mixture was evacuated partially and heating was continued for 30 min. at 174°. The cooled residue was triturated with about 10 ml. of ether and filtered off. The product weighed 2.0 g. (73%) and melted at 127°. One crystallization from 50 ml. of methanol, gave 1.5 g. (55%) of material melting at 128–129°. λ_{max} 305 mμ; log ϵ 3.605.

Anal. Calcd. for $C_{14}H_9O_2N_2Cl$: C, 61.7; H, 3.30; N, 10.3; Cl, 13.0. Found: C, 61.8; H, 3.70; N, 10.0; Cl, 13.0.

Reduction by lithium aluminum hydride of N-benzyl-5-chlorocinchomeronimide (2-benzylmerimine dihydrochloride). To a solution of 2.0 g. (0.053 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether chilled to 0° was added 1.0 g. (0.0037 mole) of powdered XVI. The mixture was stirred at 0° for 24 hr. The excess of lithium aluminum hydride was then destroyed with 4 ml. of water in 100 ml. of ethanol and the mixture filtered and washed with an additional 100 ml. of ethanol.

On acidifying the filtrate with alcoholic hydrochloric acid and adding 200 ml. of ether, a yellow solid precipitated. After recrystallization from ethanol, alcoholic hydrochloric acid, and ether, 0.20 g. of material was obtained (yield 19%); m.p. 238–243° dec.; 2-benzylmerimine, m.p. 247° dec. Preparation of the free base yielded a solid which gave a negative Beilstein flame test for halogen and a negative chlorine test on sodium fusion; λ_{max} 259 mμ agrees with an authentic sample of 2-benzylmerimine.

Anal. Calcd. for $C_{14}H_{14}N_2 \cdot 2HCl \cdot H_2O$: C, 55.8; H, 6.03; N, 9.32; Cl, 23.58. Found: C, 56.1; H, 6.43; N, 9.41; Cl, 24.5.

From the reductions of this imide in refluxing ether with 2.5, 3.5, and 5 moles equivalent of lithium aluminum hydride only 2-benzylmerimine was isolated.

2-Benzyl-7-chloro-1(or 3)-ketomerimine. To a solution of 1.36 g. (0.00500 mole) of XVI in 31.0 ml. of glacial acetic acid was added 1.95 g. (0.0165 g. at.) of mossy tin. The mixture was heated to 100° with stirring and 2.0 ml. of concd. hydrochloric acid was added dropwise, causing the solution to turn yellow. After 10 min., an additional 1.9 ml. of concd. hydrochloric acid was added and the mixture was kept at 100° with stirring for 50 min. and then refluxed for 10 min. The solution was evaporated to dryness *in vacuo* and the residue was triturated with 58 ml. of ethanol. The alcohol extract was made basic with concentrated ammonia to give a white precipitate. This was filtered off, leaving an orange solution which was again evaporated to dryness. The solid residue was triturated with 30 ml. of ethanol and the remaining salt filtered off. On evaporation of the ethanol extract to dryness, a brown solid was obtained which was insoluble in water and gave a positive Beilstein flame test. Recrystallization from ethanol-water gave 0.94 g. (72.8%) of product, m.p. 112–116° clear.

Anal. Calcd. for $C_{14}H_{11}N_2ClO$: C, 65.0; H, 4.28; N, 10.8; Cl, 13.7. Found: C, 65.0; H, 4.68; N, 11.1; Cl, 13.8.

The ultraviolet spectrum showed no maximum. The infrared spectrum (infra-cord) showed only one band at 5.91 μ, whereas the starting material showed bands at 5.58 and at 5.80 μ (Nujol).

Reduction by lithium aluminum hydride of 2-benzyl-7-chloro-1(or 3)-ketomerimine (2-benzylmerimine dihydrochloride). A solution of 0.517 g. (0.00200 mole) of 2-benzyl-7-chloro-1(or 3)-ketomerimine in 175 ml. of anhydrous ether was added slowly to 0.379 g. (0.0100 mole) of lithium aluminum hydride in 25 ml. of anhydrous ether. The resulting mixture was refluxed for 3 hr. and allowed to stand overnight at room temperature. The excess lithium aluminum hydride was destroyed with water and the mixture was filtered and removed solids were washed with 50 ml. of ethanol. Acidification of the filtrate with alcoholic hydrochloric acid gave an oil which on crystallization from a minimum amount of ethanol containing 2 drops of alcoholic hydrochloric acid gave 0.017 g. (3.0%) of product, m.p. 220–237° dec. λ_{max} 259 mμ; log ϵ 3.596. An authentic sample of 2-benzylmerimine, m.p. 247° dec., gave λ_{max} 259 mμ and log ϵ 3.654.

7-Acetamido-2-carbethoxy-6-methylmerimine (XVII). A mixture of 12.0 g. (0.050 mole) of 7-amino-2-carbethoxy-6-methylmerimine monohydrate and 50 ml. of acetic anhydride was heated on a steam-bath for 45 min. The resultant yellow solution was cooled and diluted with 500 ml. of ether and chilled in an ice bath to give 10.3 g. of white solid melting at 193–196° dec. The filtrate on standing for a few hours gave an additional 2.1 g. of a product melting at 201–206° dec. The second filtrate was evaporated to dryness *in vacuo* and the residue was triturated with 50 ml. of ether to yield 0.7 g. of a white solid decomposing at 198–200°. The pooled product weighed 13.0 g. (99%). A 1.0-g. sample on recrystallization from butanol-ether gave 0.8 g. of crystalline compound melting at 197–199° dec.

Anal. Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.3; H, 6.45; N, 16.0. Found: C, 59.3; H, 6.47; N, 17.1.[11]

3-Aminopyridine-2,4,5-tricarboxylic acid (XVIII) (*3-aminoberonic acid*). To a suspension of 26.3 g. (0.100 mole) of XVII in 150 ml. of water was added a warm solution of 125 g. (0.799 mole) of potassium permanganate in 3.13 l. of water. The mixture was refluxed for 6.5 hr. and 30.0 ml. of glacial acetic acid was added. The mixture continued to be heated until all of the potassium permanganate color had discharged. The manganese dioxide was then filtered off and the clear yellow filtrate was treated with activated carbon and evaporated *in vacuo* to dryness. Since attempts to crystallize this product failed, it was used as a crude intermediate; yield, 26.3 g.

A 7.85-g. (0.03 mole) sample of the crude acid was heated with 45 ml. of concd. hydrochloric acid on a steam bath for 20 hr. The yellow crystalline product which precipitated when the acid mixture was chilled was filtered off and washed with 10 ml. of ice water; yield, 1.8 g. (26.5% overall), m.p. 215–217° (dec., eff.). The product gave a blood red color with ferrous sulfate.[12]

Recrystallization of 100 mg. of this product from 5 ml.

(11) A satisfactory nitrogen analysis was not obtained.

(12) This color reaction is characteristic of pyridine-α-carboxylic acids.

of water gave an analytically pure sample; yield 62.0 mg., m.p. 215–217° (dec., eff.); λ_{max} 372.5 mμ, log ε 3.788.

Anal. Calcd. for $C_8H_6N_2O_6 \cdot 1^1/_2H_2O$: C, 37.5; H, 3.58; N, 11.1. Found: C, 37.2; H, 3.34; N, 10.9.

5-Amino-N-benzylcinchomeronimide (XIX). A well integrated mixture of 2.62 g. (0.0100 mole) of 3-aminoberberonic acid and 1.07 g. (0.0100 mole) of benzylamine was heated gradually in a 25 ml. round bottom flask to 190°. The yellow solid changed to a brown melt and gave off a gas. The reaction mixture was stirred mechanically and maintained at the stated reaction temperature for 0.5 hr. until the evolution of gas had ceased. The flask was then allowed to cool to room temperature and the contents were crystallized from 100 ml. of hot methanol. A light yellow product weighing 2.1 g. (83%); m.p. 161–165° was realized from the crystallization. A twice recrystallized sample, on drying at 108°, melted at 168–169°; λ_{max} 275 and 400 mμ; log ε 3.863, 3.818.

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.5; H, 4.35; N, 16.6. Found: C, 66.4; H, 4.55; N, 16.4.

7-Amino-2-benzylmerimine dihydrochloride (XX). To a suspension of 1.2 g. (0.032 mole) of lithium aluminum hydride in 60 ml. of anhydrous tetrahydrofuran was added slowly a solution of 0.80 g. (0.0032 mole) of *N*-benzyl-5-aminocinchomeronimide in 100 ml. of tetrahydrofuran. An orange brown solution resulted which was refluxed for 6 hr. and allowed to stand at room temperature overnight. The excess of lithium aluminum hydride was decomposed by adding 2 ml. of water to the stirred mixture. The precipitate was then filtered off and the filtrate was dried over anhydrous magnesium sulfate and acidified with 4 ml. of alcoholic hydrochloric acid. The precipitate which formed was filtered off and washed with ethanol; yield 0.36 g. (35.7%) m.p. 254–264°, dec.

Two recrystallizations from ethanol and alcoholic hydrochloric acid gave an analytical sample in 80% recovery which was dried at 60° for 3 hr., m.p. 265–268° dec. λ_{max} 257, 320 mμ; log ε 3.914, 3.724.

Anal. Calcd. for $C_{14}H_{15}N_3.2HCl \cdot H_2O$: C, 53.2; H, 6.06; N, 13.3; Cl, 22.2. Found: C, 53.1; H, 6.35; N, 13.1; Cl, 22.3.

7-Aminomerimine dihydrochloride (XXI). To a solution of 1.0 g. (0.0032 mole) of 7-amino-*N*-benzylmerimine in 50 ml. of ethanol was added 1.1 g. of freshly prepared 10% palladium on charcoal.[13] The reaction mixture was hydrogenated at 30 lbs. for 6 hr. The catalyst was filtered off, washed with water and the filtrate was evaporated to dryness; yield, 0.50 g. (75.5%); m.p. >300°, dec., (darkens >200°).

Three crystallizations from water and alcoholic hydrochloric acid gave a colorless sample; yield 25%, m.p. >300°, dec. λ_{max} 256, 316.5 mμ; log ε 3.886, 3.696.

Anal. Calcd. for $C_7H_9N_3 \cdot 2HCl$: C, 40.4; H, 5.33; N, 20.5; Cl, 33.6. Found: C, 40.4; H, 5.58; N, 20.5; Cl, 33.4.

(13) The catalyst was prepared by hydrogenating for 1 hr. a mixture of 1.0 g. of activated carbon, 0.10 g. of palladium chloride, and 30 ml. of 1.0 sodium acetate solution. The catalyst was filtered and washed with water and alcohol.

7-Amino-2-carbethoxymerimine (XXII). A stirred solution of 1.0 g. (0.0050 mole) of 7-aminomerimine dihydrochloride in 6.1 ml. of water and 3.0 ml. of 5*N* sodium hydroxide was chilled to 5°. To this was added a 0.55-g. (0.0050 mole) sample of ethylchlorocarbonate dropwise, maintaining the temperature below 10°. The mixture was allowed to come to room temperature with stirring, kept there for 0.5 hr. and the resulting white product was filtered off; yield 0.85 g. (85%); m.p. 182–183° dec.

Recrystallization from 10 ml. of 50% ethanol gave 0.56 g. (66%) recovery of product, m.p. 182–183° dec. λ_{max} 240, 309 mμ; log ε 3.720, 3.429.

Anal. Calcd. for $C_{10}H_{13}N_3O_2$: C, 58.0; H, 6.33; N, 20.3. Found: C, 57.8; H, 6.62; N, 20.6.

2-Carbethoxy-7-chloromerimine (XXIII). To a stirred solution of 1.0 g. (0.0050 mole) of 7-amino-2-carbethoxymerimine in 8.8 ml. of concd. hydrochloric acid was added 0.97 g. (0.0058 mole) of cupric chloride dihydrate and the mixture was chilled to −10°. A solution of 0.61 g. (0.0088 mole) of sodium nitrite in 0.90 ml. of water was added dropwise beneath the surface, never allowing the temperature to rise over −5°. The mixture was allowed to come to room temperature and was diluted with 10 ml. of water and heated to boiling. Hydrogen sulfide was passed into the boiling mixture and the precipitated cupric sulfide was filtered off. The clear yellow filtrate was made basic with 15 ml. of concd. ammonium hydroxide and, after chilling, the gray precipitate was filtered off. This product on recrystallization from 17 ml. of 50% ethanol (activated charcoal) yielded 0.73 g. (66.4%) of material; m.p. 92.5–94° clear. One more recrystallization gave an analytical sample in 67% recovery, m.p. 92.5–93.5° clear. λ_{max} 267.5 mμ; log ε 3.626.

Anal. Calcd. for $C_{10}H_{11}N_2O_2Cl \cdot {}^1/_4H_2O$: C, 52.0; H, 5.24; N, 12.2; Cl, 15.4. Found: C, 52.0; H, 4.84; N, 12.1; Cl, 15.4.

7-Chloromerimine monohydrochloride (XXIV). A solution of 0.23 g. (0.0010 mole) of 2-carbethoxy-7-chloromerimine, in 2.5 ml. of concd. hydrochloric acid was heated over steam for 48 hr. The resulting yellow solution was diluted with 3.0 ml. of water and evaporated to dryness under reduced pressure. The residue, an oil, was triturated with 3.0 ml. of ether to yield 0.21 g. (100%) of a light yellow solid, m.p. 240–271° dec. Recrystallization of 100 mg. of this from a mixture of 2 ml. of ethanol, 6 drops of water, and 0.5 ml. of alcoholic hydrochloric acid gave a white crystalline product; yield, 28 mg.; m.p. 245–267° (dec., eff.). λ_{max} 269 mμ; log ε 3.634.

Anal. Calcd. for $C_7H_7N_2Cl \cdot HCl$: C, 43.9; H, 4.22; N, 14.7; Cl, 37.4; ionic Cl, 18.6. Found: C, 43.5; H, 4.48; N, 14.8; Cl, 37.4; ionic Cl, 18.7.

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