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The Preparation of Some Merimine Derivatives¹

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The preparation and properties of a number of derivatives of 6-methylmerimine have been described.

The compound 2,3-dihydro-1H-pyrrolo[3,4-c]-pyridine was prepared by Gabriel and Colman,² in 1902, by the hydrogen iodide and phosphorus reduction of the γ -lactam of 3-aminomethylisonicotinic acid and was named merimine. The only other compounds of this bicyclic ring structure known in the literature are the imides and lactams derived from substituted pyridinecarboxylic acids.

7-Amino-6-methylmerimine (I) was prepared by the lithium aluminum hydride reduction of the γ -lactam of 3-amino-5-aminomethyl-2-methylisonicotinic acid (II).³ Compound I was used as the basic raw material in the preparation of the series of compounds outlined in Chart I.

When compound I was treated with nitrous acid, dark tars were obtained. When the 2-position was blocked by a carbethoxy (III) or a benzoyl (IV) group, the primary amino group was easily diazotized and a variety of 2,7-disubstituted derivatives (V-X) could be obtained by standard procedures. Hydrolysis with either acid or alkali resulted in the 7-substituted-6-methylmerimines (XI-XV). These merimines, unsubstituted in the 2-position, are strong bases which absorb carbon dioxide on standing. They are best stored as the high melting dihydrochlorides.

When 7-methoxy-6-methylmerimine (XI) was heated with 48% hydrobromic acid, 7-hydroxy-6-methylmerimine (XII) dihydrobromide was obtained. Catalytic reduction converted 7-bromo-6-methylmerimine dihydrochloride (XIV) to 6-methylmerimine dihydrochloride (XV). 2-Benzoyl-7-iodo-6-methylmerimine (XVI) and 2-benzoyl-7-bromo-6-methylmerimine (XVII) were not prepared easily by diazotization of IV, but were obtained in excellent yield by the Schotten-Baumann reaction on XIII and XIV.

Typical reactions of merimines unsubstituted in the 2-position are illustrated with 7-methoxy-6-methylmerimine (XI) in Chart II. The 2-guanyl (XVIII) and 2-imidazolyl (XIX) derivatives were prepared by reaction with thiuronium salts, 2-carbamyl derivatives (XXI) by reaction with potassium cyanate, and 2-dialkylsulfamyl derivatives (XX) by reaction with dialkylsulfamyl chlorides. When XI was treated with acetic anhydride, the 2-acetyl derivative XXII was formed and this was converted easily to the methiodide XXIII. The 2-*p*-acetylsulfanyl derivative XXIV was prepared and was hydrolyzed to the unacetylated derivative XXV.

Similar derivatives were prepared from other 2-

unsubstituted merimines and additional examples are described in the Experimental section.

Experimental

7-Amino-6-methylmerimine Dihydrochloride (I).—A solution of 2.0 g. of lithium aluminum hydride in 100 ml. of tetrahydrofuran was stirred under nitrogen at a temperature of 45–50° while a solution of 1.0 g. of the γ -lactam of 3-amino-5-aminomethyl-2-methylisonicotinic acid (II) in 200 ml. of tetrahydrofuran was added. The reaction mixture was heated at 60–65° for seven hours and then allowed to stand at room temperature overnight. A solution of 4 ml. of water in 50 ml. of tetrahydrofuran was added and the insoluble portion was filtered off and washed with ethanol. The filtrate was acidified with concentrated hydrochloric acid and the precipitate which separated was filtered and oven-dried. The yield was 0.77 g. of brown powder. This powder was dissolved in 10 ml. of water and treated with activated charcoal. The solution was concentrated to dryness and then diluted with 1 ml. of concentrated hydrochloric acid and 10 ml. of ethanol. The precipitate was filtered and washed with ethanol. The product was dissolved once more in 1.5 ml. of water and then diluted with 0.4 ml. of concentrated hydrochloric acid. The precipitate which separated was filtered, washed with ethanol and dried. The yield of 7-amino-6-methylmerimine dihydrochloride was 0.21 g. (15%).

Anal. Calcd. for C₈H₁₃Cl₂N₃: C, 43.3; H, 5.90; Cl, 32.0; N, 18.9. Found: C, 43.1; H, 5.86; Cl, 31.7; N, 18.9.

7-Amino-6-methylmerimine.—A mixture of 4.55 g. of the dihydrochloride, 2.16 g. of sodium methylate and 20 ml. of absolute ethanol was stirred under nitrogen for 2 hours at room temperature. The mixture was heated to the boil and filtered. The filtrate was concentrated *in vacuo* until heavy precipitation occurred and then diluted with ether. The mixture was filtered and the cake was washed with ether and dried. Two grams of 7-amino-6-methylmerimine (67%), m.p. 167–169°, was obtained.

Anal. Calcd. for C₈H₁₁N₃: C, 64.4; H, 7.43; N, 28.2. Found: C, 64.3; H, 7.47; N, 28.1.

7-Amino-2-carbethoxy-6-methylmerimine (III).—A solution of 448 g. of 7-amino-6-methylmerimine dihydrochloride in 2,500 ml. of water and 800 ml. of 5 *N* sodium hydroxide was cooled to 10° and 194 ml. of ethyl chloroformate and 400 ml. of 5 *N* sodium hydroxide were added simultaneously over a 15-minute period while allowing the temperature to rise to 20°. The reaction mixture was stirred for 1.5 hours longer and then filtered. The cake was washed with ice-water and then recrystallized from ethanol. A 65% yield of 7-amino-2-carbethoxy-6-methylmerimine monohydrate, m.p. 182–183°, was obtained.

Anal. Calcd. for C₁₁H₁₇N₃O₃: C, 55.2; H, 7.16; N, 17.6. Found: C, 55.2; H, 6.85; N, 17.9.

7-Amino-2-benzoyl-6-methylmerimine (IV).—A solution of 280 g. of 7-amino-6-methylmerimine dihydrochloride and 150 g. of sodium hydroxide in 2,400 ml. of water was adjusted to 33° and 165 g. of benzoyl chloride was added over a 40-minute period at 30–35°. The mixture was stirred for two hours longer at this temperature and the insoluble product was filtered, washed with water and dried at 50°. Recrystallization from ethanol resulted in a 61% yield of 7-amino-2-benzoyl-6-methylmerimine, m.p. 202–203°.

Anal. Calcd. for C₁₈H₁₆N₃O: C, 71.1; H, 5.97; N, 16.6. Found: C, 71.0; H, 5.98; N, 16.5.

2-Carbethoxy-7-hydroxy-6-methylmerimine Hydrochloride (V).—A mixture of 95.5 g. of 7-amino-2-carbethoxy-6-methylmerimine monohydrate, 320 ml. of 5 *N* hydrochloric

(1) Presented in part at the 126th Meeting of the American Chemical Society in New York City, September, 1954.

(2) S. Gabriel and J. Colman, *Ber.*, **35**, 2832 (1902).

(3) L. Velluz and G. Amiard, *Bull. soc. chim.*, **14**, 136 (1947).

tassium iodide in 500 ml. of water. The mixture was warmed over a 4-hour period to 25–30° and then filtered to remove some brown insoluble material. The filtrate was treated with sodium bicarbonate and filtered to remove the precipitate. This was washed with water, dried and recrystallized twice from ethanol. The yield of 2-carbethoxy-7-iodo-6-methylmerimine, m.p. 130–131°, was 34%.

Anal. Calcd. for $C_{11}H_{13}IN_2O_2$: C, 39.8; H, 3.95; I, 38.2. Found: C, 39.8; H, 3.86; I, 38.0.

7-Bromo-2-carbethoxy-6-methylmerimine (VII).—A solution of 2.9 g. of sodium nitrite in 30 ml. of water was added over a 5-minute period at –1 to –4° to a mixture of 9.56 g. of 7-amino-2-carbethoxy-6-methylmerimine monohydrate, 15 ml. of 48% HBr and 150 ml. of water. The reaction mixture was held at this temperature for 20 minutes and then poured into a solution of 7 g. of cuprous bromide in 25 ml. of 48% HBr and 15 ml. of water. The dark brown foamy mixture was left at room temperature overnight and then warmed to 60° and filtered. The filtrate was treated with activated carbon and then with hydrogen sulfide gas. After filtration, the light colored filtrate was treated with sodium bicarbonate. An oil separated and gradually solidified. The precipitate was filtered off and washed with water. The yield of 7-bromo-2-carbethoxy-6-methylmerimine was 3.2 g. (28%). After recrystallization from ether the melting point was 93–94°.

Anal. Calcd. for $C_{11}H_{13}BrN_2O_2$: C, 46.4; H, 4.60; Br, 28.0. Found: C, 46.4; H, 4.02; Br, 27.7.

A purer product, m.p. 99–101°, was prepared by treating 7-bromo-6-methylmerimine (XIV) with ethyl chloroformate in aqueous alkali; yield 78%. Found: C, 46.6; H, 4.62; Br, 27.9.

2-Carbethoxy-6-methylmerimine Hydrochloride (VIII).—A solution of 2.17 g. of sodium nitrite in 10 ml. of water was added over a 10-minute period to a solution of 7.17 g. of 7-amino-2-carbethoxy-6-methylmerimine monohydrate and 24 ml. of 5 *N* hydrochloric acid in 200 ml. of water while holding the temperature at 0 to –5°. The reaction mixture was stirred for 5 minutes longer and 19.8 g. of 50% hypophosphorous acid was then added. The temperature was allowed to rise to 22° over a 7-hour period and sodium bicarbonate was then added until foaming no longer occurred. The solution was concentrated to a low volume, extracted with ether, and the ether layer was dried over sodium sulfate. On addition of hydrogen chloride 2-carbethoxy-6-methylmerimine hydrochloride separated. On recrystallization from alcohol and ether, 3.3 g. (45%), m.p. 219–220° dec., was obtained.

The same compound, m.p. 221–223° dec., was obtained in 67% yield by treating 6-methylmerimine dihydrochloride with ethyl chloroformate in aqueous alkali.

Anal. Calcd. for $C_{11}H_{13}ClN_2O_2$: C, 54.4; H, 6.25; N, 11.5. Found: C, 54.3; H, 6.40; N, 11.7.

2-Benzoyl-7-methoxy-6-methylmerimine (IX).—A mixture of 101 g. of 7-amino-2-benzoyl-6-methylmerimine, 4 liters of methanol and 166 ml. of concentrated hydrochloric acid was heated to 48° and a solution of 56 g. of sodium nitrite in 160 ml. of water was added over a 1-hour period at 48–59°. The reaction mixture was held for one hour longer at this temperature and then partially concentrated. The mixture was diluted with water, neutralized with sodium carbonate to a pH of about 8, and then concentrated further to remove all methanol. The precipitate which separated was filtered off and then dissolved in water adjusted to pH 3 with hydrochloric acid. The solution was treated with activated carbon and clarified and the filtrate was adjusted with sodium carbonate to pH 5.2. The product was filtered off and recrystallized first from ethanol and then from a mixture of ethanol and isopropyl acetate. The yield of 2-benzoyl-7-methoxy-6-methylmerimine, m.p. 149–151°, was 38%.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.6; H, 6.01; N, 10.4. Found: C, 71.6; H, 5.95; N, 10.6.

2-Benzoyl-7-hydroxy-6-methylmerimine Hydrochloride (X).—A mixture of 76 g. of 7-amino-2-benzoyl-6-methylmerimine, 3,500 ml. of water and 240 ml. of 5 *N* hydrochloric acid was cooled to 0 to –5° and a solution of 21 g. of sodium nitrite in 100 ml. of water was added over a 30-minute period at this temperature. The reaction mixture was allowed to gradually warm over a two hour period to 28°. The mixture was adjusted with 5 *N* sodium hydroxide

to a pH of about 3 and then concentrated *in vacuo* until heavy precipitation occurred. The precipitate was filtered off and washed with acetone. On recrystallization from ethanol, 2-benzoyl-7-hydroxy-6-methylmerimine hydrochloride, m.p. 228–230°, was obtained in 59% yield.

Anal. Calcd. for $C_{15}H_{15}ClN_2O_2$: C, 62.0; H, 5.20; Cl, 12.2; N, 9.64. Found: C, 61.7; H, 5.26; Cl, 12.4; N, 9.93.

7-Methoxy-6-methylmerimine Dihydrochloride (XI).—A mixture of 295 g. of 2-benzoyl-7-methoxy-6-methylmerimine, 1,100 ml. of 5 *N* sodium hydroxide and 1,800 ml. of ethanol was heated on the steam-bath for three hours, cooled, neutralized with 475 ml. of concentrated hydrochloric acid, concentrated to remove the ethanol and then further acidified with a mixture of 200 ml. of concentrated HCl and 400 ml. of water. The precipitated benzoic acid was filtered off and the filtrate was then treated with 530 ml. of 5 *N* sodium hydroxide and concentrated to remove as much water as possible. The residue was boiled with 400 ml. of ethanol, filtered hot and the salt cake washed with 300 ml. of ethanol. The filtrate was concentrated to a thick mush. This was dissolved in 500 ml. of water and the solution was treated with activated carbon and then acidified with 210 ml. of concentrated hydrochloric acid and further diluted with 500 ml. of ethanol. The crystalline product was filtered, washed with ethanol and dried. The yield of 7-methoxy-6-methylmerimine dihydrochloride, m.p. about 290° dec., was 65%. On concentration of the filtrate, an additional 25% was obtained.

Anal. Calcd. for $C_9H_{14}Cl_2N_2O$: C, 45.6; H, 5.95; Cl, 29.9; N, 11.8. Found: C, 45.5; H, 5.73; Cl, 29.7; N, 11.9.

7-Methoxy-6-methylmerimine Base.—A mixture of 166 g. of the dihydrochloride, 75.5 g. of sodium methylate and 1,500 ml. of ethanol was refluxed under nitrogen for three hours. The reaction mixture was filtered hot to remove the salt and the filtrate was concentrated to an oil. The 7-methoxy-6-methylmerimine was distilled at 125–130° (2 mm.), yield 76%. On cooling, it solidified as white crystals which melted at 57–59°.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.8; H, 7.37; N, 17.1. Found: C, 65.6; H, 7.23; N, 17.2.

7-Hydroxy-6-methylmerimine Dihydrochloride (XII).
A. By Acid Hydrolysis.—A mixture of 10 g. of 2-benzoyl-7-hydroxy-6-methylmerimine hydrochloride and 80 ml. of 5 *N* hydrochloric acid was heated on the steam-bath for five hours. The reaction mixture was cooled and the benzoic acid was filtered off. The filtrate was treated with activated carbon and then concentrated until solidification occurred. The product was filtered, washed with alcohol and dried at 60°. The yield of 7-hydroxy-6-methylmerimine dihydrochloride, m.p. above 290°, was 91%.

Anal. Calcd. for $C_9H_{12}Cl_2N_2O$: C, 43.1; H, 5.42; Cl, 31.8; N, 12.6. Found: C, 42.9; H, 5.49; Cl, 31.8; N, 12.8.

B. By Alkaline Hydrolysis.—The same product was isolated in 68% yield by the alkaline hydrolysis of 2-carbethoxy-7-hydroxy-6-methylmerimine monohydrochloride.

C. From 7-Methoxy-6-methylmerimine.—When 7-methoxy-6-methylmerimine was heated on the steam-bath with 48% hydrobromic acid for 16 hours a 70% yield of 7-hydroxy-6-methylmerimine dihydrobromide, m.p. above 290°, was isolated.

Anal. Calcd. for $C_9H_{12}Br_2N_2O$: Br, 51.2; N, 8.98. Found: Br, 51.8; N, 8.89; CH_3O , 0.0.

7-Bromo-6-methylmerimine Dihydrochloride (XIV).
A. Alkaline Hydrolysis of 7-Bromo-2-carbethoxy-6-methylmerimine.—A mixture of 86 g. of 7-bromo-2-carbethoxy-6-methylmerimine, 267 ml. of 4.5 *N* sodium hydroxide and 333 ml. of ethanol was heated on the steam-bath for 2.5 hours. The reaction mixture was cooled and the precipitate was filtered off. The filtrate was acidified with 125 ml. of concentrated hydrochloric acid and clarified with activated charcoal. The solution was concentrated to dryness and the solid residue was washed into a filter with ethanol. The cake was mixed with 26.4 g. of sodium methylate and 500 ml. of ethanol and the mixture was stirred at room temperature for one hour and heated at reflux for 30 min. and then filtered to remove the salt. The filtrate was cooled and HCl gas was passed through to precipitate 7-bromo-6-methylmerimine dihydrochloride as a light tan powder;

yield 72 g. (84%). Recrystallization from 85% ethanol resulted in an almost white powder which decomposed about 275°.

Anal. Calcd. for $C_8H_{11}BrCl_2N_2$: C, 33.6; H, 3.88; Br, 27.9; Cl, 24.8; N, 9.80. Found: C, 33.6; H, 3.88; Br, 27.7; Cl, 24.6; N, 9.90.

B. Acid Hydrolysis of 7-Bromo-2-carbethoxy-6-methylmerimine.—A mixture of 113 g. of 7-bromo-2-carbethoxy-6-methylmerimine and 500 ml. of concentrated hydrochloric acid was heated on the steam-bath for 30 hours and then concentrated to dryness *in vacuo*. The light brown residue was washed onto a filter with ethanol and then recrystallized from 85% ethanol. A 67% yield of 7-bromo-6-methylmerimine dihydrochloride was obtained as almost white crystals which decomposed about 275°.

7-Iodo-6-methylmerimine Dihydrochloride (XIII).—Alkaline hydrolysis of 2-carbethoxy-7-iodo-6-methylmerimine as described above resulted in a 28% yield of 7-iodo-6-methylmerimine dihydrochloride, m.p. 257° dec. Recrystallization was from aqueous acetone.

Anal. Calcd. for $C_8H_{11}Cl_2IN_2$: C, 28.9; H, 3.33; Cl, 21.3. Found: C, 29.2; H, 3.52; Cl, 21.0.

6-Methylmerimine Dihydrochloride (XV). **A. From 2-Carbethoxy-6-methylmerimine Hydrochloride.**—A 76% yield of 6-methylmerimine dihydrochloride, m.p. 280° dec., was obtained by the acid hydrolysis of 2-carbethoxy-6-methylmerimine. A 30% yield of pure product was obtained by alkaline hydrolysis of the same compound.

Anal. Calcd. for $C_8H_{11}Cl_2N_2$: C, 46.4; H, 5.84; Cl, 34.3; N, 13.5. Found: C, 46.2; H, 5.96; Cl, 34.1; N, 13.6.

B. From 7-Bromo-6-methylmerimine Dihydrochloride.—A mixture of 5.72 g. of 7-bromo-6-methylmerimine dihydrochloride, 50 ml. of water and 1.0 g. of palladium-on-carbon catalyst was reduced in a Parr shaker. One molar equivalent of hydrogen was absorbed in 15 min. The reaction mixture was filtered and concentrated to dryness. Alcoholic HCl was added and the mixture was again concentrated to dryness. The white crystals were washed into a filter with alcohol and dried at 60°; crude yield 92%. Analysis indicated a mixed hydrochloride hydrobromide salt of 6-methylmerimine.

The above product was dissolved in 5 *N* NaOH and the base was extracted with ether. The extract was treated with HCl gas and the 6-methylmerimine dihydrochloride so obtained did not depress the melting point of the product prepared by method A.

2-Benzoyl-7-iodo-6-methylmerimine (XVI).—The Schotten-Baumann reaction of benzoyl chloride and 7-iodo-6-methylmerimine dihydrochloride yielded 2-benzoyl-7-iodo-6-methylmerimine as white crystals which melted at 193–195° dec.

Anal. Calcd. for $C_{15}H_{13}IN_2O$: C, 49.5; H, 3.60; I, 34.9; N, 7.70. Found: C, 49.9; H, 3.58; I, 34.8; N, 7.62.

2-Benzoyl-7-bromo-6-methylmerimine (XVII).—The Schotten-Baumann reaction of benzoyl chloride and 7-bromo-6-methylmerimine dihydrochloride yielded 2-benzoyl-7-bromo-6-methylmerimine as white crystals which melted at 174–176°.

Anal. Calcd. for $C_{15}H_{13}BrN_2O$: C, 56.8; H, 4.13; Br, 25.2; N, 8.84. Found: C, 56.9; H, 3.65; Br, 25.6; N, 8.91.

2-Guanyl-7-methoxy-6-methylmerimine Hydrobromide (XVIII).—A solution of 1.7 g. of 7-methoxy-6-methylmerimine and 1.85 g. of S-ethylthiuronium bromide in 10 ml. of ethanol was allowed to stand at room temperature for 2 hours and then heated on the steam-bath for 1 hour. The mixture was cooled and filtered and then recrystallized from dilute ethanol. An 87% yield of 2-guanyl-7-methoxy-6-methylmerimine hydrobromide was obtained. This material darkened about 260° but was of indefinite melting point.

Anal. Calcd. for $C_{10}H_{15}BrN_4O$: C, 41.9; H, 5.27; Br, 27.8; N, 19.5. Found: C, 41.8; H, 5.10; Br, 27.9; N, 19.7.

7-Amino-2-guanyl-6-methylmerimine Hydrobromide.—This compound was prepared as above from 7-amino-6-methylmerimine and S-ethylthiuronium bromide. A white product of indefinite melting point was obtained after two recrystallizations from water.

Anal. Calcd. for $C_9H_{14}BrN_5$: C, 39.7; H, 5.18; Br, 29.4; N, 25.7. Found: C, 39.4; H, 4.74; Br, 28.9; N, 25.5.

2-(2-Imidazolyl)-7-methoxy-6-methylmerimine Hydroiodide (XIX).—This compound was prepared as above from 7-methoxy-6-methylmerimine and 2-methylmercaptoimidazole hydroiodide. The yield of 2-(2-imidazolyl)-7-methoxy-6-methylmerimine hydroiodide was 89%.

Anal. Calcd. for $C_{12}H_{17}IN_4O$: C, 40.0; H, 4.76; I, 35.2; N, 15.5. Found: C, 39.7; H, 4.70; I, 34.9; N, 15.7.

2-Dimethylsulfamyl-7-methoxy-6-methylmerimine (XX).—A solution of 2.37 g. of 7-methoxy-6-methylmerimine dihydrochloride in 20 ml. of 1 *N* sodium hydroxide was treated with 1.08 ml. of dimethylsulfamyl chloride. After one hour, 10 ml. of 1 *N* sodium hydroxide was added and the precipitate which separated was filtered and recrystallized from aqueous ethanol. The yield of 2-dimethylsulfamyl-7-methoxy-6-methylmerimine, m.p. 100–103°, was 33%.

Anal. Calcd. for $C_{11}H_{17}N_3O_3S$: C, 48.7; H, 6.32; N, 15.5; S, 11.8. Found: C, 48.6; H, 6.23; N, 15.3; S, 12.1.

2-Dimethylsulfamyl-7-hydroxy-6-methylmerimine.—This compound was prepared as above from 7-hydroxy-6-methylmerimine dihydrochloride and dimethylsulfamyl chloride. Recrystallization from ethanol resulted in a 33% yield of white powder of indefinite melting point.

Anal. Calcd. for $C_{10}H_{15}N_3O_3S$: C, 46.7; H, 5.88; N, 16.3; S, 12.4. Found: C, 46.4; H, 5.80; N, 16.4; S, 12.4.

2-Diethylsulfamyl-7-hydroxy-6-methylmerimine.—A 22% yield of 2-diethylsulfamyl-7-hydroxy-6-methylmerimine, m.p. 195–197°, was obtained when 7-hydroxy-6-methylmerimine dihydrochloride and diethylsulfamyl chloride were allowed to react as above.

Anal. Calcd. for $C_{12}H_{19}N_3O_3S$: C, 50.5; H, 6.71; N, 14.7; S, 11.2. Found: C, 50.2; H, 6.73; N, 14.8; S, 10.9.

2-Carbamyl-7-methoxy-6-methylmerimine (XXI).—A mixture of 32.8 g. of 7-methoxy-6-methylmerimine, 200 ml. of 1 *N* hydrochloric acid and 16.2 g. of potassium cyanate was allowed to stand overnight at room temperature and was then heated on the steam-bath for 30 minutes. The solution was treated with activated carbon and cooled. The precipitate was filtered, washed with water, and then dried at 100°. The yield of 2-carbamyl-7-methoxy-6-methylmerimine, m.p. 233° dec., was 40 g. (97%).

Anal. Calcd. for $C_{10}H_{13}N_3O_2$: C, 58.0; H, 6.32; N, 20.3. Found: C, 58.1; H, 6.18; N, 20.4.

The following compounds were prepared by essentially the same procedure:

7-Amino-2-carbamyl-6-methylmerimine: yield 95%, m.p. 275° dec. *Anal.* Calcd. for $C_9H_{12}N_4O$: C, 56.2; H, 6.29; N, 29.2. Found: C, 56.3; H, 6.30; N, 29.0.

2-Carbamyl-7-hydroxy-6-methylmerimine: yield 82%, m.p. above 275°. *Anal.* Calcd. for $C_9H_{11}N_3O_2$: C, 56.0; H, 5.74; N, 21.8. Found: C, 56.0; H, 5.74; N, 21.8.

7-Bromo-2-carbamyl-6-methylmerimine: yield 58%, m.p. 243–244°. *Anal.* Calcd. for $C_9H_{10}BrN_3O$: C, 42.2; H, 3.94; Br, 31.2; N, 16.4. Found: C, 42.0; H, 3.57; Br, 31.2; N, 16.3.

2-Carbamyl-7-iodo-6-methylmerimine: yield 56%, m.p. 232–234° dec. *Anal.* Calcd. for $C_9H_{10}IN_3O$: C, 35.7; H, 3.34; I, 41.9; N, 13.9. Found: C, 35.6; H, 3.18; I, 41.9; N, 13.7.

2-Acetyl-7-methoxy-6-methylmerimine (XXII).—A mixture of 49.3 g. of 7-methoxy-6-methylmerimine and 150 ml. of acetic anhydride was heated on the steam-bath for 90 min. and then concentrated to a dark oil. Ether was added and a precipitate separated and was filtered off. After recrystallization from ethanol, the yield of 2-acetyl-7-methoxy-6-methylmerimine, m.p. 115–116°, was 35 g. (70%).

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.1; H, 6.84; N, 13.6. Found: C, 64.0; H, 6.89; N, 13.7.

The following were prepared by the same general procedure:

7-Acetoxy-2-acetyl-6-methylmerimine: yield 26%, m.p. 143–144°. *Anal.* Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.5; H, 6.02; N, 12.0. Found: C, 61.3; H, 5.74; N, 12.3.

7-Acetamido-2-acetyl-6-methylmerimine: yield 71%, m.p. 226–228°. *Anal.* Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.8; H, 6.48; N, 18.0. Found: C, 61.5; H, 6.48; N, 17.9.

2-Acetyl-7-methoxy-6-methylmerimine Methiodide (XXIII).—A mixture of 2.06 g. of 2-acetyl-7-methoxy-6-

methylmerimine, 1.87 ml. of methyl iodide and 15 ml. of ethanol was allowed to stand at room temperature for 5 days and was then heated at reflux for 90 min. The solution was concentrated and then diluted with ether. The precipitate which separated was filtered off and recrystallized from ethanol. The yield of 2-acetyl-7-methoxy-6-methylmerimine methiodide, m.p. 175–177°, was 89%.

Anal. Calcd. for $C_{12}H_{17}IN_2O_2$: C, 41.4; H, 4.92; I, 36.5; N, 8.05. Found: C, 41.4; H, 4.71; I, 36.5; N, 8.27.

The following were prepared by the same general procedure:

7-Acetoxy-2-acetyl-6-methylmerimine methiodide: yield 61%, m.p. 222–224°. *Anal.* Calcd. for $C_{13}H_{17}IN_2O_3$: C, 41.5; H, 4.56; I, 33.8; N, 7.45. Found: C, 41.4; H, 4.53; I, 33.6; N, 7.55.

7-Acetamido-2-acetyl-6-methylmerimine methiodide: yield 41%, m.p. 198–199°. *Anal.* Calcd. for $C_{13}H_{18}IN_2O_2$: C, 41.6; H, 4.84; I, 33.8; N, 11.2. Found: C, 41.7; H, 4.88; I, 32.9; N, 11.0.

2-Carboethoxy-6-methylmerimine methiodide: yield 54%, m.p. 183–185°. *Anal.* Calcd. for $C_{12}H_{17}IN_2O_2$: C, 41.4; H, 4.92; I, 36.5; N, 8.05. Found: C, 41.1; H, 4.62; I, 36.4; N, 7.78.

2-(*p*-Acetylsulfanilyl)-7-methoxy-6-methylmerimine (XXIV).—A mixture of 1.18 g. of 7-methoxy-6-methylmerimine dihydrochloride, 1.23 g. of *p*-acetylsulfanilyl chloride and 30 ml. of 1 *N* sodium hydroxide was allowed to react at 30–35° for one hour and then heated on the steam-bath for two hours. The precipitate was filtered hot, washed with water, dried and then recrystallized from ethanol. The yield of 2-(*p*-acetylsulfanilyl)-7-methoxy-6-methylmerimine, m.p. 212–213°, was 0.7 g. (44%).

Anal. Calcd. for $C_{17}H_{19}N_3O_4S$: C, 56.5; H, 5.30; N, 11.6; S, 8.85. Found: C, 56.7; H, 5.14; N, 11.4; S, 8.85.

The following compounds were prepared by the same general procedure:

2-(*p*-Acetylsulfanilyl)-7-hydroxy-6-methylmerimine: yield 35%, m.p. above 250°. *Anal.* Calcd. for $C_{16}H_{17}N_3O_4S$: C, 55.3; H, 4.93; N, 12.1; S, 9.23. Found: C, 55.2; H, 4.93; N, 11.9; S, 9.03.

2-(*p*-Acetylsulfanilyl)-7-amino-6-methylmerimine hemihydrate: yield 75%, m.p. above 280°. *Anal.* Calcd. for $C_{16}H_{18}N_4O_3S \cdot 0.5H_2O$: C, 54.1; H, 5.38; N, 15.8; S, 9.02. Found: C, 54.4; H, 5.05; N, 15.7; S, 8.85.

7-Methoxy-6-methyl-2-(*p*-sulfanilyl)-merimine (XXV).—A mixture of 1.08 g. of the above acetyl derivative, 20 ml. of ethanol and 5 ml. of 5 *N* sodium hydroxide was heated on the steam-bath for one hour. The reaction mixture was concentrated and diluted with water and the precipitate was filtered. On recrystallization from ethanol, 0.55 g. (58%) of 7-methoxy-6-methyl-2-(*p*-sulfanilyl)-merimine, m.p. 204–205°, was obtained.

Anal. Calcd. for $C_{16}H_{17}N_2O_3S$: C, 56.4; H, 5.37; N, 13.2; S, 10.0. Found: C, 56.4; H, 5.11; N, 13.5; S, 9.60.

7-Amino-6-methyl-2-(*p*-sulfanilyl)-merimine.—This compound was prepared as above from 2-(*p*-acetylsulfanilyl)-7-amino-6-methylmerimine. The yield was 80%, m.p. 217° dec.

Anal. Calcd. for $C_{14}H_{16}N_4O_2S$: C, 55.2; H, 5.30; N, 18.4; S, 10.5. Found: C, 55.0; H, 5.32; N, 18.6; S, 10.9.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Alkaloid Studies. XVII.¹ The Structure of the Cactus Alkaloid Pilocereine²

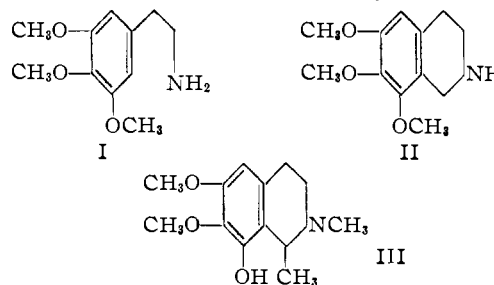
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In contrast to the hitherto known cactus alkaloids which are based on a β -phenylethylamine or tetrahydroisoquinoline skeleton, pilocereine consists of two tetrahydroisoquinoline nuclei fused by an ether linkage. Its exact structure (XIIIa) was elucidated by diaryl ether cleavage of pilocereine methyl and ethyl ether with potassium in liquid ammonia and identification of all of the cleavage products. Attention is called to the presence of the 1-isobutyl substituent, which appears to be unique in alkaloid chemistry, and to certain side reactions in the potassium-ammonia cleavage of diaryl ethers.

The most remarkable chemical feature of the hitherto studied cactus alkaloids⁴ is the simplicity of the various structures which are all based on β -phenylethylamine or 1,2,3,4-tetrahydroisoquinoline. Mescaline (I) and anhalinine (II) can be offered as two examples which also illustrate their close biogenetic origin⁵ and even the most compli-

cated cactus alkaloid, pelletine (III) contains only thirteen carbon atoms and one nitrogen atom.



Consequently, it was of particular interest to elucidate the structure of pilocereine, an alkaloid found^{6–8} in various giant cacti and possessing the unusually high (at least for a cactus alkaloid)

(6) G. Heyl, *Arch. Pharm.*, **239**, 451 (1901). Heyl did not obtain the alkaloid in crystalline form, but he did arrive at the correct empirical formula (*cf. ref. 9*).

(7) C. Djerassi, N. Frick and L. E. Celler, *THIS JOURNAL*, **75**, 3632 (1953).

(8) C. Djerassi, C. R. Smith, S. P. Marfey, R. N. McDonald, A. J. Lemin, S. K. Figdor and H. Estrada, *ibid.*, **76**, 3215 (1954).

(1) Paper XVI, C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney and S. C. Pakrashi, *THIS JOURNAL*, **79**, 1217 (1957).

(2) Our initial studies in this field were supported by a grant-in-aid from the American Heart Association, Inc. Subsequently, financial assistance was provided by the National Heart Institute of the U. S. Public Health Service (Grant No. H-2040).

(3) (a) Postdoctorate Research Fellow, 1953–1954; (b) Postdoctorate Research Fellow, 1955–1956; (c) Predoctorate Research Fellow, 1955–1956.

(4) For recent reviews see L. Reti in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Vol. VI, Springer, Vienna, 1950, pp. 242–289, and L. Reti in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. IV, Academic Press, Inc., New York, N. Y., 1954, pp. 7–28.

(5) It is now generally accepted that 1,2,3,4-tetrahydroisoquinolines are formed in the plant from substituted β -phenylethylamines and an appropriate amino acid or equivalent (α -keto acid, aldehyde, etc.), the latter providing carbon atom 1 and any substituent attached to it. For pertinent review see R. Robinson, "The Structural Relations of Natural Products," Oxford University Press, 1955.