544. *The Application of the Hofmann Reaction to the Synthesis of Heterocyclic Compounds. Part VII. Synthesis of Pyridinopyrimidine Derivatives.*

By A. C. McLean and F. S. Spring.

Treatment of quinolinamide with alkaline potassium hypobromite gives 2 : 6-*dihydroxypyridino*(2′ : 3′-4 : 5)*pyrimidine* (VII) together with 2-aminonicotinic acid. Treatment of ethyl 5-cyano-2-methyl*iso*nicotinate with ammonia gives according to the reaction conditions either 6-*methylcinchomeronimide α-imine* (XIV) or a compound $C_8H_9O_2N_3$, into which the imide (XIV) is converted on treatment with water. On reaction with alkaline sodium hypochlorite, these two compounds give 2 : 4-dihydroxy-6-methylcopazoline (XIII), the structure of which follows from its hydrolysis to 5-*amino*-2-*methyl*iso*nicotinic acid*.

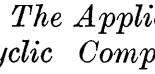
Treatment of cinchomeronamide (I) with two molecular proportions of potassium hypobromite in alkaline solution gives a mixture of 2 : 4-dihydroxycopazoline (II) and 3-amino*iso*nicotinic acid (III) (Blumenfeld, *Monatsh.*, 1895, **16**, 703; Gabriel and Colman, *Ber.*, 1902, **35**, 2831). The reaction is of interest in that it gives only 2 : 4-dihydroxycopazoline and not 2 : 6-dihydroxypyridino(4′ : 3′-4 : 5)pyrimidine (IV). We now report the behaviour of quinolinamide when treated with alkaline hypobromite. With one molecular proportion of the latter, the amide (V) gives a compound, $C_7H_5O_2N_3$, together with 2-aminonicotinic acid (VI). The compound, $C_7H_5O_2N_3$, is a weak acid precipitated by carbon dioxide from its solution in

(I.)

(II.)

(III.)

(IV.)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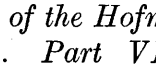
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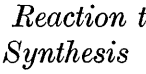
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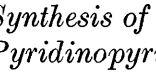
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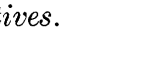
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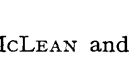
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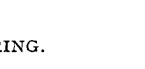
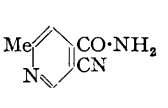

(XI.)

sodium hydroxide; it is either 2 : 6-dihydroxypyridino-(2′ : 3′-4 : 5)- (VII) or -(3′ : 2′-4 : 5)-pyrimidine (VIII). It has been characterised as the former by hydrolysis with alkal which yields 2-aminonicotinic acid (VI), and by hydrolysis with 100% sulphuric acid which yields 2-aminopyridine. Methylation of (VII) using alkali and methyl sulphate gives 2 : 6-*diketo*-1 : 3-*dimethyl*-1 : 2 : 3 : 6-*tetrahydropyridino*(2′ : 3′-4 : 5)*pyrimidine* (IX). Treatment of 2 : 6-dihydroxypyridino(2′ : 3′-4 : 5)pyrimidine with phosphoryl chloride gives 2 : 6-*dichloropyridino*(2′ : 3′-4 : 5)*pyrimidine* (X) which reacts with sodium methoxide to yield the corresponding 2 : 6-*dimethoxy*-derivative (XI).

Reider and Elderfield (*J. Org. Chem.*, 1942, **7**, 286) have described the reaction between 5-cyano-2-methyl*iso*nicotinamide (XII) and alkaline hypochlorite. They obtained a product which does not melt up to 310° and which they formulated without proof as 2 : 4-dihydroxy-6-methylcopazoline (XIII). This reaction has been reinvestigated. The preparation of 5-cyano-2-methyl*iso*nicotinamide has not been successfully repeated. Reider and Elderfield obtained this compound by the action of ice-cold aqueous ammonia upon ethyl 5-cyano-2-methyl*iso*nicotinate. In our hands the reaction gives a compound $C_8H_7ON_3$, which is not identical with

the isomeric 5-cyano-2-methyl*iso*nicotinamide described by Reider and Elderfield, and has been characterised as 6-*methylcinchomeronimide α-imine* (XIV) since on treatment with dilute mineral acid it gives 6-*methylcinchomeronimide* (XV). A similar type of reaction has been reported by Braun and Tcherniac (*Ber.*, 1907, **40**, 2709) who showed that treatment of *o*-cyanobenzamide with ammonia or alkali gives α-iminophthalide (XIX). Both *o*-cyanobenzamide and α-iminophthalide on treatment with alkaline hypochlorite yield 2 : 4-dihydroxyquinazoline (XX). The formation of (XIV) from ethyl 5-cyano-2-methyl*iso*nicotinate probably proceeds by formation of 5-cyano-2-methyl*iso*nicotinamide (XII), followed by intramolecular cyclisation.

The reaction of ethyl 5-cyano-2-methyl*iso*nicotinate with aqueous ammonia appears to be very sensitive to conditions. At room temperature it gives a mixture of (XIV) and a compound $C_8H_9O_2N_3$. The latter appears not to be a hydrate of 5-cyano-2-methyl*iso*nicotinamide (XII)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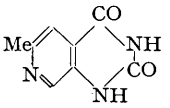
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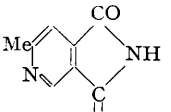
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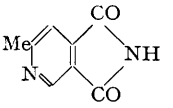
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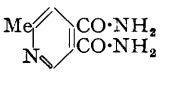
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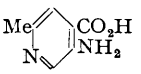
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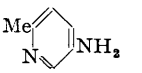
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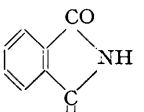
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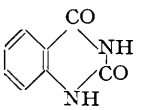
(XX.)

since Reider and Elderfield have shown that the cyano-amide is readily converted into 5-cyano-2-methyl*iso*nicotinic acid by treatment with dilute mineral acid. The compound $C_8H_9O_2N_3$ is recovered unchanged after similar treatment. The compound is also obtained by heating the imide (XIV) with water, and conversely, when sublimed in a vacuum it is converted into (XIV), reactions which appear to suggest that it is a simple hydrate of (XIV). This simple relation is excluded since the compound $C_8H_9O_2N_3$ is recovered unchanged after treatment with dilute mineral acid. The compound is not identical with the isomeric 6-*methylcinchomeronamide* (XVI), which was prepared by reaction of *methyl* 6-*methylcinchomeronate* with ammonia. When sublimed, (XVI) loses ammonia and gives 6-methylcinchomeronimide (XV).

Treatment of either the compound $C_8H_9O_2N_3$ or 6-methylcinchomeronimide α-imine (XIV) with alkaline sodium hypochlorite solution gives 2 : 4-dihydroxy-6-methylcopazoline (XIII). The structure of the last compound was established by hydrolysis with sodium hydroxide, whereupon 5-*amino*-2-*methyl*iso*nicotinic* acid (XVII) was obtained and characterised as its *methyl* ester and by decarboxylation to 5-amino-2-methylpyridine (XVIII).

Experimental.

2 : 6-*Dihydroxypyridino*(2′ : 3′-4 : 5)*pyrimidine* (VII).—Quinolinamide was prepared by saturating a methanolic solution of methyl quinolinate with ammonia at 0°; it separates from aqueous ethanol as needles, m. p. 208—209° (decomp.) (Found : C, 50·9; H, 4·3. Calc. for $C_7H_7O_2N_3$: C, 50·9; H, 4·2%). Engler (*Ber.*, 1894, **27**, 1784) gave m. p. 209° (decomp.) for quinolinamide. Attempted recrystallisation of quinolinamide from hot water leads to considerable decomposition with evolution of ammonia.

Quinolinamide (5 g.) was treated with alkaline potassium hypobromite solution (1 mol., 105 c.c.; prepared as described by Baxter and Spring, *J.*, 1945, 229), and the mixture kept at 0° for 1 hour. Dissolution was complete in a few minutes; ammonia was evolved. The solution was then heated to 80° for 1 hour, cooled, and treated with carbon dioxide. The precipitated solid (1·25 g.) was collected (filtrate *A*) and washed successively with water, alcohol, and ether. It was purified by dissolution in hot glacial acetic acid, from which 2 : 6-*dihydroxypyridino*(2′ : 3′-4 : 5)*pyrimidine* separates as a flocculent powder, slightly soluble in hot water and pyridine but insoluble in the common organic solvents. The compound is soluble in aqueous sodium hydroxide and insoluble in a solution of sodium hydrogen carbonate. For analysis it was sublimed at 170°/10^{-3} mm. and obtained as a colourless powder, m. p. 361° (decomp.) (Found : C, 51·0; H, 3·3; N, 25·8. $C_7H_5O_2N_3$ requires C, 51·5; H, 3·1; N, 25·7%). Light absorption in 0·1N-sodium hydroxide : Max. at 3160 A., $\varepsilon = 5360$.

2-*Aminonicotinic acid* (VI).—(*a*) The filtrate *A* was acidified to approximately pH 5·0 by the addition of dilute hydrochloric acid, and the mixture kept overnight at 0°. The crystalline solid (0·8 g.) was collected and recrystallised twice from water, from which 2-aminonicotinic acid separated as needles, m. p. 306° (decomp.) (Found : C, 52·2; H, 4·5; N, 20·0. Calc. for $C_6H_6O_2N_2$: C, 52·2; H, 4·3; N, 20·3%).

(*b*) 2 : 6-Dihydroxypyridino(2′ : 3′-4 : 5)pyrimidine (0·5 g.) was heated in a sealed tube with aqueous sodium hydroxide (5 c.c.; 14%) for 4 hours at 170°. The cold reaction mixture was saturated with carbon dioxide and filtered. The solution was acidified to pH approximately 5·0 with dilute hydrochloric acid, and the crystalline precipitate (260 mg.) collected and recrystallised from water to yield 2-aminonicotinic

acid as needles, m. p. 306—307° (decomp.) (Found: C, 52·3; H, 4·4; N, 20·0. Calc. for $C_6H_6O_2N_2$: C, 52·2; H, 4·3; N, 20·3%). This is soluble in dilute mineral acids and in cold aqueous sodium hydrogen carbonate with effervescence, and is undepressed in m. p. when mixed with the specimen described above. Phillips (*Ber.*, 1894, **27**, 840) gives m. p. 310° (decomp.) for 2-aminonicotinic acid. The acid was characterised by conversion into its methyl ester by heating a methanolic solution under reflux in the presence of dry hydrogen chloride. Methyl 2-aminonicotinate separates as needles, m. p. 84—85° from water (Found: C, 55·5; H, 5·2; N, 18·6. Calc. for $C_7H_8O_2N_2$: C, 55·3; H, 5·3; N, 18·4%). Kirpal (*Monatsh.*, 1900, **21**, 962) describes the ester as needles (from aqueous alcohol), m. p. 85°.

2-*Aminopyridine*.—(*a*) 2 : 6-Dihydroxypyridino(2′ : 3′-4 : 5)pyrimidine (0·5 g.) was heated at 250—280° with 100% sulphuric acid (5 c.c.) for 25 minutes. The cold mixture was poured on ice and made strongly alkaline by the addition of 30% sodium hydroxide solution, and the mixture extracted with ether. After drying, the extract was evaporated, and the oily residue dissolved in ethanol and treated with an ethanolic solution of picric acid. The solid separating was collected and recrystallised from ethanol to yield 2-aminopyridine picrate (95 mg.) as yellow needles, m. p. 216—217° undepressed when mixed with an authentic specimen (Found: N, 21·8. Calc. for $C_{11}H_9O_7N_5$: N, 21·7%).

(*b*) 2-Aminonicotinic acid [isolated from 2 : 6-dihydroxypyridino(2′ : 3′-4 : 5)pyrimidine] (0·25 g.) was mixed with copper bronze (1·75 g.) and distilled. The distillate crystallised in the receiver and was recrystallised from light petroleum (b. p. 40—60°), from which 2-aminopyridine separated as colourless plates (125 mg.), m. p. 56—57° either alone or when mixed with an authentic specimen.

2 : 6-*Diketo*-1 : 3-*dimethyl*-1 : 2 : 3 : 6-*tetrahydropyridino*(2′ : 3′-4 : 5)*pyrimidine* (IX).—A solution of 2 : 6-dihydroxypyridino(2′ : 3′-4 : 5)pyrimidine (0·5 g.) in 1·75N-sodium hydroxide (20 c.c.) was gradually treated with methyl sulphate (6 g.). The crystalline solid (0·3 g.) which separated was collected and recrystallised from ethanol, from which the 1 : 3-*dimethyl* derivative separates as needles, m. p. 164—165° (Found: C, 56·5; H, 4·6. $C_9H_9O_2N_3$ requires C, 56·5; H, 4·7%).

2 : 6-*Dichloropyridino*(2′ : 3′-4 : 5)*pyrimidine* (X).—2 : 6-Dihydroxypyridino(2′ : 3′-4 : 5)pyrimidine (1 g.) was heated under reflux for 5 hours with phosphoryl chloride (15 c.c.). The excess of phosphoryl chloride was removed under reduced pressure, the residue treated with water (20 c.c.), and the mixture extracted with chloroform. The extract was evaporated, and the brown solid residue sublimed at 120°/5 mm. The colourless sublimate (0·43 g.) was crystallised from light petroleum (b. p. 100—120°), from which 2 : 6-*dichloropyridino*(2′ : 3′-4 : 5)*pyrimidine* separates as colourless needles, m. p. 156—157° (Found: C, 42·2; H, 1·8; N, 20·6; Cl, 35·3. $C_7H_3N_3Cl_2$ requires C, 42·0; H, 1·5; N, 21·0; Cl, 35·5%).

2 : 6-*Dimethoxypyridino*(2′ : 3′-4 : 5)*pyrimidine* (XI).—A solution of 2 : 6-dichloropyridino(2′ : 3′-4 : 5)pyrimidine (0·26 g.) in methanol (10 c.c.) was treated with a solution of sodium methoxide in methanol (from 0·065 g. of sodium and 15 c.c. of methanol), and the mixture heated under reflux for 5 hours. The solution was evaporated to dryness and the residue extracted with boiling benzene. The extract was reduced to small bulk and diluted with light petroleum (b. p. 60—80°), whereupon 2 : 6-*dimethoxypyridino*-(2′ : 3′-4 : 5)*pyrimidine* (0·16 g.) separated; it was recrystallised from water, from which it separates as needles, m. p. 138—139° (Found: C, 56·5; H, 4·6; N, 21·4. $C_9H_9O_2N_3$ requires C, 56·5; H, 4·7; N, 22·0%).

Compound $C_8H_9O_2N_3$.—Ethyl 5-cyano-2-methyl*iso*nicotinate (10 g.) was shaken for 4 hours at room temperature with aqueous ammonia (*d* 0·88; 400 c.c.). The solution was concentrated under reduced pressure to 50 c.c., and a mass of long felted needles (7 g.) separated. These were collected and recrystallised from water, from which the *compound* $C_8H_9O_7N_3$ separates as prisms, m. p. 261—262° (decomp.). For analysis a specimen was dried at 110°/10^{-3} mm. (Found: C, 53·1; H, 5·6; N, 23·6. $C_8H_9O_2N_3$ requires C, 53·6; H, 5·0; N, 23·5%).

2 : 4-*Dihydroxy*-6-*methylcopazoline* (XIII).—A solution of the compound $C_8H_9O_2N_3$ (2 g.) in aqueous potassium hydroxide (30 c.c.; 10%) was treated with a neutral solution of sodium hypochlorite (M.; 12·4 c.c.) and kept at 80° for 30 minutes. The cold solution was acidified with acetic acid, and the voluminous yellow precipitate (1·2 g.) filtered off and washed successively with water, alcohol, and ether. Crystallisation from glacial acetic acid gave 2 : 4-dihydroxy-6-methylcopazoline as small pale yellow needles which slowly decomposed above 300° but did not melt below 360° (Found: C, 54·4; H, 4·5; N, 23·2. Calc. for $C_8H_7O_2N_3$: C, 54·2; H, 4·0; N, 23·7%). It is sparingly soluble in boiling ethanol and boiling pyridine. It is soluble in dilute mineral acids and in sodium hydroxide solution but insoluble in sodium hydrogen carbonate solution.

5-*Amino*-2-*methyliso*nicotinic *acid* (XVII).—A solution of 2 : 4-dihydroxy-6-methylcopazoline (875 mg.) in aqueous sodium hydroxide (5 c.c.; 15%) was heated in an autoclave at 155° for 2 hours, then cooled and saturated with carbon dioxide which did not precipitate any unchanged material. The solution was acidified (Congo-red) with dilute hydrochloric acid, and the solid (500 mg.) collected and crystallised from water, from which 5-*amino*-2-*methyliso*nicotinic *acid* separates as long pale yellow needles (Found: C, 55·7; H, 5·7; N, 18·4. $C_7H_8O_2N_2$ requires C, 55·3; H, 5·3; N, 18·4%). The colour was not removed by charcoal treatment. The amino-acid does not melt but commences to decompose at about 290°. It is soluble in dilute mineral acids and in sodium hydrogen carbonate solution.

Methyl ester. A stream of dry hydrogen chloride was passed through a refluxing solution of the acid (0·5 g.) in methanol (20 c.c.) for 3 hours. The methanol was removed under reduced pressure, and the residue neutralised with sodium hydrogen carbonate solution. The solid (0·42 g.) crystallised from water to yield *methyl* 5-*amino*-2-*methyliso*nicotinate as pale yellow needles, m. p. 150—150·5° (Found: C, 57·8; H, 6·3; N, 16·6. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·0; N, 16·9%).

5-*Amino*-2-*methylpyridine* (XVIII).—An intimate mixture of 5-amino-2-methyl*iso*nicotinic acid (500 mg.) and copper-bronze (2·5 g.) was distilled. The distillate solidified in the receiver. After sublimation of the distillate at 80°/2 mm, followed by crystallisation from benzene–light petroleum (b. p. 60—80°), 5-amino-2-methylpyridine was obtained as plates, m. p. 95—96° (Found: C, 66·1; H, 7·6; N, 25·7. Calc. for $C_6H_8N_2$: C, 66·7; H, 7·4; N, 25·9%). The m. p. was not depressed when it was mixed with a specimen prepared as described by Graf (*J. pr. Chem.*, 1932, **133**, 19).

The picrate separated from ethanol as plates, m. p. 206—207° (decomp.) (Found: C, 42·5; H, 3·2;

Calc. for $C_{12}H_{11}O_7N_5$: C, 42·7; H, 3·3%). A mixture with an authentic specimen, which had m. p. 206—207° (decomp.), was undepressed in m. p. (Graf, *loc. cit.*, gives m. p. 201° for 5-amino-2-methylpyridine picrate).

6-*Methylcinchomeronimide α-Imine* (XIV).—(*a*) Ethyl 5-cyano-2-methyl*iso*nicotinate (3 g.) was stirred at 0° with aqueous ammonia (*d* 0·88; 120 c.c.) for 3 hours. The ester slowly dissolved, and after 1½ hours a flocculent solid (2·1 g.) separated which gradually decomposed between 225° and 260°. It is soluble in hot water and it can be recrystallised from ethanol, pyridine, or dioxan without changing the decomposition behaviour on heating. After recrystallisation from dioxan 6-*methylcinchomeronimide α-imine* separates in prisms (Found: C, 59·8; H, 4·1; N, 25·8. $C_8H_7ON_3$ requires C, 59·6; H, 4·3; N, 26·1%).

(*b*) Ethyl 5-cyano-2-methyl*iso*nicotinate (9 g.) was shaken at room temperature with aqueous ammonia (*d* 0·88; 350 c.c.) for 3 hours. Ammonia was then removed by keeping the solution under reduced pressure for 1 hour at room temperature. A flocculent solid (3·0 g.) separated, and after recrystallisation from ethanol 6-methylcinchomeronimide α-imine was obtained as prisms which decomposed between 225° and 260° (Found: C, 59·8; H, 4·6; N, 25·8%). Evaporation of the filtrate from the imino-imide and crystallisation of the solid residue from water gave the compound $C_8H_9O_2N_3$ (see p. 2584) as prisms (2·9 g.), m. p. 260—261° (decomp.) (Found: C, 53·3; H, 4·6; N, 23·0%).

A solution of 6-methylcinchomeronimide α-imine (0·4 g.) in water (15 c.c.) was heated under reflux for 2 hours. No separation of solid occurred on cooling this solution to room temperature. The solution was evaporated under reduced pressure to 5 c.c. and cooled. The solid (0·38 g.) was collected and crystallised from water, from which the compound $C_8H_9O_2N_3$ separated as prisms, m. p. 260—261° (decomp.), not depressed when mixed with the specimen described above (Found: C, 53·5; H, 5·2; N, 23·4%).

Treatment of 6-methylcinchomeronimide α-imine with alkaline sodium hypochlorite as described above gave 2 : 4-dihydroxy-6-methylcopazoline, crystallising from glacial acetic acid as small pale yellow needles which decompose above 300° (60%) (Found: C, 53·9; H, 4·0%). This was characterised by alkaline hydrolysis, under the conditions previously described, to give 5-amino-2-methyl*iso*nicotinic acid (decomposing about 290°), characterised as its methyl ester, which separated from water as pale yellow needles, m. p. 149·5—150·5° undepressed when mixed with the specimen described above.

6-*Methylcinchomeronimide* (XV).—6-Methylcinchomeronimide α-imine (200 mg.) was dissloved at room temperature in 0·1N-hydrochloric acid (15 c.c.), and the mixture kept at 0° for 3 hours. The solid (100 mg.) was collected and recrystallised from water containing a little dioxan, from which 6-*methylcinchomeronimide* separated as minute prisms, m. p. 276—278° either alone or when mixed with an authentic specimen prepared as described below (Found: C, 59·1; H, 4·3; N, 17·2. $C_8H_6O_2N_2$ requires C, 59·3; H, 3·7; N, 17·3%).

6-*Methylcinchomeronic Acid.*—Ethyl 5-cyano-2-methyl*iso*nicotinate (5·1 g.) was heated under reflux with aqueous sodium hydroxide (28 c.c.; 15%) until evolution of ammonia had ceased (3 hours). The solution was acidified (Congo-red) with 25% nitric acid, the mixture kept for 2 hours at 0°, and the crystalline solid (*A*) (3·2 g.) collected. The filtrate was neutralised with ammonia, and aqueous lead acetate added to the boiling solution. The lead salt was collected, suspended in hot water (20 c.c.), and decomposed with hydrogen sulphide. The mixture was filtered, the filtrate evaporated to dryness, and the crystalline residue (0·65 g.) combined with the solid (*A*) and recrystallised from water, from which 6-*methylcinchomeronic acid* separated as small needles which decompose at 249—251° without melting (Found: C, 52·5; H, 4·2; N, 7·8. $C_8H_7O_4N$ requires C, 53·0; H, 3·9; N, 7·7%).

Methyl ester. Dry hydrogen chloride was passed into a refluxing solution of 6-methylcinchomeronic acid (3·85 g.) in dry methanol (55 c.c.) for 3½ hours. The methanol was evaporated under reduced pressure, and the syrupy residue poured into an excess of aqueous sodium hydrogen carbonate. The voluminous mass (3·3 g.) of felted needles was collected and washed with water. Crystallisation from light petroleum (b. p. 40—60°) gave *methyl* 6-*methylcinchomeronate* as needles, m. p. 68—69° (Found: C, 57·4; H, 5·3; N, 6·5. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%).

6-*Methylcinchomeronamide* (XVI).—A solution of methyl 6-methylcinchomeronate (1·5 g.) in methanol (25 c.c.) was saturated with ammonia at 0° and kept at 0° for 3 days. The solid (1·0 g.) which separated was collected and crystallised from methanol, from which 6-*methylcinchomeronamide* separate as small needles (Found: C, 53·7; H, 5·0; N, 23·1. $C_8H_9O_2N_3$ requires C, 53·6; H, 5·0; N, 23·5%). On rapid heating this melts with decomposition at 215—220°, resolidifies, and again melts at 273—278°; on slow heating gradual evolution of ammonia occurs and only the higher m. p. is observed.

6-*Methylcinchomeronimide* (XV).—6-Methylcinchomeronamide (150 mg.) was heated at 220—225° until the evolution of ammonia had ceased (10 minutes). The product (100 mg.) was sublimed at 190°/5 mm. and was recrystallised from methanol, from which 6-methylcinchomeronimide separated as small needles, m. p. 277—278° (Found: C, 59·6; H, 4·0%).

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