133. *Quinamine. Part I.*

By T. A. Henry, K. S. Kirby, and G. E. Shaw.

Quinamine, $C_{19}H_{24}O_2N_2$, is a minor alkaloid of cinchona bark, isolated and characterised by Hesse in 1872. The cinchona alkaloids of known constitution can all be represented by the general formula, $Q–CH(OH)–Q'$, where Q is quinolyl or 6-methoxyquinolyl and Q' is 3-vinyl- or 3-ethyl-quinuclidyl. Quinamine conforms with this general formula. It contains the central carbinol group and is unique among cinchona alkaloids so far known, in that the 3-vinylquinuclidyl nucleus can be isolated intact in the form of 3-vinylquinuclidylcarboxylic acid on oxidation by chromic acid. The principal divergence from the usual type is that Q is not quinolyl or a quinolyl derivative but a heterocyclic nucleus, $C_9H_6(OH)(NH)$, the nature of which is still under investigation.

QUINAMINE, $C_{19}H_{24}O_2N_2$, is a minor cinchona alkaloid, which has not been investigated since the period 1872—1881, when some attention was devoted to its chemistry by its discoverer, Hesse (*Ber.*, 1872, **5**, 265; 1877, **10**, 2152; *Annalen*, 1873, **166**, 217; 1879, **199**, 333; 1881, **207**, 288) and by de Vrij (*Pharm. J.*, 1874, **4**, 609), Howard (*ibid.*, 1875, **5**, 1), and Oudemans (*Annalen*, 1879, **197**, 48). The little that is known about quinamine is mainly due to Hesse (*loc. cit.*), who crystallised the base, prepared a series of salts and investigated the action upon it of acids and acetic anhydride. The latter reagent converted it into acetyl*apo*quinamine, which is amorphous but on hydrolysis furnished a well-defined, crystalline substance, *apo*quinamine, $C_{19}H_{22}ON_2$, differing from quinamine by the elements of a molecule of water. *apo*Quinamine was also formed when quinamine was treated with acids, but depending on the experimental conditions, might then be accom-

panied by two isomerides of quinamine, quinamidine and quinamicine, and a brown amorphous substance, *proto*quinamicine, to which a formula, $C_{17}H_{20}O_2N_2$, was assigned in spite of lack of evidence of its homogeneity. Quinamidine was described as crystalline, m. p. 93°, $[\alpha]_D + 4\cdot5°$ ($c = 2$; alcohol) and yielding crystalline salts, of which the hydrochloride, B,HCl,H$_2$O, was optically inactive.

The material used in the present investigation was prepared by one of us (G. E. S.) during his tenure of office as Quinologist to the Government of Bengal. Apart from the higher melting point, 185—186°, as against 172° found by Hesse for quinamine, and other minor differences, the observations of the earlier workers have been confirmed.

The natural cinchona alkaloids of known constitution may all be represented by the general formula Q–CH(OH)–Q′, where Q is quinolyl or 6-methoxyquinolyl, and Q′ is 3-vinyl- or 3-ethyl-quinuclidyl. In the scission products of oxidation of these alkaloids, Q is generally represented by cinchoninic or 6-methoxycinchoninic acid, whereas the quinuclidine nucleus suffers disruption and is represented by fragments, of which the largest is meroquinine (I). Quinamine has now been treated with various oxidising agents and in no case has a quinoline derivative, or a probable fragment of quinoline, been isolated from the reaction products, and it seems clear that quinamine differs from the cinchona alkaloids so far investigated in not possessing a quinoline nucleus.

When oxidised by chromic acid in presence of sulphuric acid, quinamine yields an acid, $C_{10}H_{15}O_2N$, which is best isolated as its *copper salt*, $(C_{10}H_{14}O_2N)_2Cu,H_2O$. This acid contains an ethylenic linkage, and on decarboxylation yields a base, $C_9H_{15}N$, which forms a picrate, m. p. 143—146°, and on catalytic hydrogenation is converted into 3-ethylquinuclidine, $C_9H_{17}N$. The identity of the latter was established by a mixed melting point determination of its picrate with that of 3-ethylquinuclidine, synthesised for the purpose by Prelog's process from ββ′-dichlorodiethyl ether as a starting point (Hanousek and Prelog, *Coll. Czech. Chem. Comm.*, 1932, **4**, 259; Prelog, Šostarič, and Guštak, *Annalen*, 1940, **545**, 251).

Assuming that the quinuclidine nucleus is attached, as is usual in the cinchona alkaloids, at position 8, *via* the central carbinol group, to the rest of the quinamine molecule, the acid, $C_{10}H_{15}O_2N$, must be 3-*vinylquinuclidine*-8-*carboxylic acid*, and quinamine must be represented by the partial formula (II).

(I.) (II.) (III.)
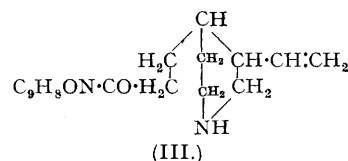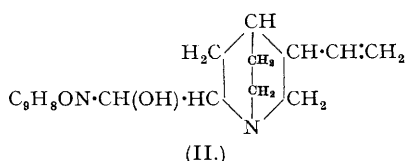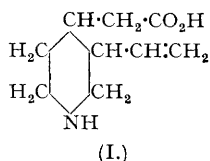
Königs showed that when meroquinine (I) is heated with hydrochloric acid and mercuric chloride, 4-methyl-3-ethylpyridine is produced (*Ber.*, 1894, **27**, 1502). When this process is applied to the acid, $C_{10}H_{15}O_2N$, the product is a base, C_7H_9N, yielding a picrate, having m. p. 127—130°, not depressed by admixture with 3-ethylpyridine picrate.

When the sodium salt of the acid is heated with soda-lime, a base is produced yielding a picrate, m. p. 126—128°, giving analytical results indicating a formula $C_7H_7N,C_6H_3O_7N_3$, which is that of 3-vinylpyridine. The latter has been described by Iddles (*J. Amer. Chem. Soc.*, 1937, **55**, 1945) as yielding a picrate, m. p. 143—144°, and this has been confirmed with a specimen prepared in these laboratories by Iddles's process. The base, regenerated from the picrate of m. p. 126—128°, on catalytic hydrogenation, absorbed more than the quantity of hydrogen necessary to saturate one ethylenic linkage and yielded a picrate, m. p. 127—130°, not depressed on admixture with 3-ethylpyridine picrate. It seems clear therefore that the picrate, m. p. 126—128°, is that of a mixture of bases including one which is hydrogenated to 3-ethylpyridine. The picrate of the latter may also be a component of the picrate, m. p. 126—128°, since on repeated crystallisation of the latter, without change of m. p., it ceases to show depression of m. p. on admixture with 3-ethylpyridine picrate.

The 3-ethylpyridine required for the foregoing comparisons was made by reduction of the hydrazone of 3-acetylpyridine, prepared by the method of Strong and McElvain (*J. Amer. Chem. Soc.*, 1933, **55**, 816).

Quinamine resembles the other cinchona alkaloids in being convertible by prolonged boiling in dilute acetic acid into an isomeric quinicine (quinatoxine), which Hesse named quinamicine. It is represented by the partial formula (III) and yields well-crystallised derivatives of which the *picrate*, 2 : 4-*dinitrophenylhydrazone*, and *oxime* have now been prepared.

On catalytic hydrogenation quinamine yields, by saturation of the vinyl side chain of the quinuclidine nucleus, *dihydroquinamine*. This is similarly convertible into a quinicine, which like these substances in general, is amorphous, but was characterised by the preparation of the crystalline *dihydroquinamicine oxime*.

On catalytic hydrogenation, *apo*quinamine yields rapidly and easily *dihydro*apoquinamine, and much more slowly *tetrahydro*apoquinamine. When subjected to prolonged boiling in dilute acetic acid it is converted into quinamicine, being apparently first hydrated to quinamine.

Though Zerewitinoff determinations indicate the presence of only two replaceable hydrogen atoms in quinamine, there is evidence that it contains three. In the formation from it of acetyl*apo*quinamine, $C_{19}H_{22}ON_2$·CO·CH$_3$, the central carbinol group (see II) is acetylated and a second hydroxyl, in the undetermined heterocyclic residue, C_9H_8ON, is eliminated as water. The third replaceable hydrogen is present in an imino-group in the C_9H_8ON residue, since a nitrosoquinamine, giving the Liebermann reaction, has been

prepared. In this nitroso-derivative only one of the two hydroxyl groups can be acylated, presumably that in the central ·CH(OH)· group. With *apo*quinamine, experimental evidence can only be provided for one replaceable hydrogen atom, while Zerewitinoff determinations indicate the presence of two.

In applying the Herzig–Meyer process for the estimation of methylimino-groups to quinamine, the results are about one-sixth of that required for one NMe group.

These various anomalies seem to be associated with the second heterocyclic nucleus, C_9H_8ON, and it is hoped that the investigation now in progress for the determination of the nature of this group will provide an explanation.

Chopra and David (*Indian J. Med. Res.*, 1927—8, **15**, 343), in their investigation of the pharmacological action of quinamine, noted that *in vitro* it was about as toxic to *Paramœcium caudatum* as cinchonine, and that a 2% solution produced anæsthesia of the rabbit cornea lasting about 30 minutes. Dr. Marshall, of the Wellcome Tropical Medical Laboratories, has tested quinamine and *apo*quinamine in malaria in chicks and canaries and finds that neither alkaloid exhibits antimalarial action.

Little is known about the pharmacological action of the minor cinchona alkaloids. They occur in " quinoidine," which consists of the brown, amorphous residue left after the extraction in quinine factories of the useful components of the total alkaloids of cinchona bark. Quinoidine has been used as a cheap antimalarial drug (Waters, *Indian Med. Gaz.*, 1913, **48**, 89; MacGilchrist, *Indian J. Med. Res.*, 1915, **3**, 1) but the results of preliminary fractionation experiments in these laboratories indicate that such antimalarial properties as it may possess may be due to small quantities of the known cinchona alkaloids remaining in it. Such of its other components as have been isolated and examined in recent years, *e.g.*, *epi*quinine and *epi*quinidine (Thron and Dirscherl, *Annalen*, 1935, **521**, 48) and now quinamine, have all been found inactive in bird malaria.

EXPERIMENTAL.

In the following account the combustion results are for substances dried at 120° in a vacuum unless stated otherwise and were obtained by micro-analysis; the m. p.'s are corrected, and the specific rotations are for M/40 solutions in water for the salts, or N/10-sulphuric acid for the bases, unless otherwise conditions are given.

Quinamine.—The alkaloid, isolated by Hesse's method (*loc. cit.*) from quinine sulphate mother-liquors derived from the total alkaloids of *Cinchona ledgeriana*, was finally freed from traces of cinchonine by repeated crystallisation from boiling benzene. It formed colourless, anhydrous needles, m. p. 185—186°, $[\alpha]_D + 116°$ or 104° ($c = 0.5$; alcohol). Hesse (1881, *loc. cit.*) found m. p. 172° and $[\alpha]_D + 104.5°$ ($c = 2.0$; alcohol) (Found: C, 73.0; H, 7.9; N, 9.1; MeO, nil; NMe, 1.63. Calc. for $C_{19}H_{24}O_2N_2$: C, 73.0; H, 7.7; N, 8.9; NMe, 9.3%). The value for NMe is too low to suggest the presence of a normal methylimino-group and its source is still under investigation. Zerewitinoff determinations indicated the existence of two replaceable hydrogen atoms. On hydrogenation in alcohol in presence of palladised barium sulphate, 0.1991 g. absorbed 14.32 c.c. (N.T.P.) (Calc. for one ethylenic linkage: 14.24 c.c.).

The hydrochloride, B, HCl, H_2O, has m. p. 166—167°, $[\alpha]_D + 102.8°$. Hesse gives $+ 100°$ ($c = 2$; water) or $+ 118.1°$ ($c = 2$; alcohol). The hydriodide, B, HI, has m. p. 224°, $[\alpha]_D + 84.82°$ ($c = 0.5$; alcohol) (Found: C, 52.0; H, 5.4; N, 6.5; I, 29.0. Calc. for $C_{19}H_{24}O_2N_2$,HI: C, 51.9; H, 5.7; N, 6.4; I, 28.8%). The nitrate melts at 186—188° and has $[\alpha]_D + 94.9°$. Oudemans (*loc. cit.*) records $+ 96.8°$ ($c = 0.997$; water). The *picrate* crystallises from boiling water in small yellow needles, m. p. 175—176°, $[\alpha]_D + 90.0°$ (M/40; acetone) (Found: C, 55.5; H, 5.05; N, 13.35. $C_{19}H_{24}O_2N_2,C_6H_3O_7N_3$ requires C, 55.4; H, 5.04; N, 12.9%).

Quinamine (1 g.) in acetic acid (10%; 2.5 c.c.) was added to sodium nitrite (1 g.) in water (10 c.c.), and the solution after standing overnight was added to a mixture of ammonia solution and light petroleum and shaken vigorously. The petroleum layer was separated, dried, and left to evaporate. The residue, showing no tendency to crystallise, was converted into the picrate, and the salt crystallised from methyl alcohol (1 c.c.) by addition of benzene (10 c.c.). *Nitrosoquinamine picrate* forms transparent, yellow leaflets, m. p. 161° after softening at 156° [Found: C, 52.3; H, 4.6; N, 14.2. $C_{19}H_{23}O_2N_2(NO),C_6H_3O_7N_3$ requires C, 52.6; H, 4.6; N, 14.7%]. To the nitroso-derivative (1 g.) in ether (5 c.c.), acetic anhydride (5 c.c.) and pyridine (2 drops) were added, and the mixture left overnight and refluxed for 1 hour next day. Sodium carbonate solution was then added, the reaction product extracted with ether, and the ethereal solution evaporated to low bulk; *nitrosoacetylquinamine* crystallised out in small, yellow cubes, m.'p. 140°. It gave a positive Liebermann reaction, and after crystallisation from ether had m. p. 137—141°, $[\alpha]_D + 282.7°$ ($c = 0.81$, N/10-H_2SO_4) (Found: C, 65.5; H, 6.7; N, 10.9. $C_{19}H_{22}O_3N_3 \cdot CO \cdot CH_3$ requires C, 65.7; H, 6.6; N, 10.9%).

On treatment with methyl iodide (8 c.c.), quinamine (2 g.) is converted into a *monomethiodide*, which after recrystallisation from alcohol (1 g. in 10 c.c.) forms short, colourless rods, m. p. 250—251°, $[\alpha]_D + 114.2°$ (Found: C, 53.2; H, 6.0; N, 6.5; NMe, 6.6; I, 28.6. $C_{19}H_{24}O_2N_2,CH_3I$ requires C, 52.8; H, 6.0; N, 6.2; NMe, 6.4; I, 27.9%). The *monomethochloride*, prepared from the methiodide, melts at 237—240°, $[\alpha]_D + 111.9°$ (Found: C, 66.2; H, 7.5; N, 8.0; NMe, 8.9; Cl, 9.8. $C_{19}H_{24}O_2N_2,CH_3Cl$ requires C, 66.2; H, 7.5; N, 7.7; NMe, 8.0; Cl, 9.8%).

Dihydroquinamine was prepared by hydrogenation of quinamine in N-sulphuric acid in presence of Adams's platinic oxide catalyst. It crystallises from boiling benzene (1 in 5) in colourless needles, m. p. 184—185°, $[\alpha]_D + 119.8°$ (Found: C, 72.5; H, 8.3; N, 9.0. $C_{19}H_{26}O_2N_2$ requires C, 72.5; H, 8.3; N, 8.9%). The *picrate* crystallises from boiling water in orange-coloured rods, m. p. 176—178° (Found: C, 55.6; H, 5.1; N, 12.9. $C_{19}H_{26}O_2N_2,C_6H_3O_7N_3$ requires C, 55.2; H, 5.4; N, 12.9%).

Dihydroquinamine (8.4 g.), mixed with acetone (12 c.c.) and methyl iodide (12 c.c.) and left overnight, deposited the *monomethiodide* (10 g.) which, after recrystallisation four times from dry alcohol (1 in 3), formed short, colourless rods and melted constantly at 219—225° (Found: C, 52.6; H, 6.8; N, 6.2; NMe, 5.4; I, 28.3. $C_{19}H_{26}O_2N_2,CH_3I$ requires C, 52.6; H, 6.4; N, 6.1; NMe, 6.5; I, 27.8%).

apoQuinamine.—Quinamine (12 g.) was refluxed for 4 hours in benzene (100 c.c.) containing acetyl chloride (20 c.c.), and the mixture shaken with sodium carbonate solution until the aqueous layer remained alkaline. The benzene extract was dried, the solvent removed, and the pale brown residue of acetyl*apo*quinamine, which could not be induced to crystallise, was converted into the *picrate*; this was at first red but on crystallisation from methyl alcohol formed yellow needles, m. p. 143—145° (Found: C, 57.9; H, 4.9; N, 12.5. $C_{19}H_{21}ON_2 \cdot CO \cdot CH_3,C_6H_3O_7N_3$ requires C, 57.3; H, 4.8; N, 12.4%).

Acetyl*apo*quinamine (3 g.) in alcohol (15 c.c.) containing potassium hydroxide (1.5 g.) in water (1 c.c.) was boiled for one hour, the alcohol removed, water added, and the base extracted by ether. A solution of this crude base in dilute acetic acid was shaken with ether to remove impurities, then made alkaline and the *apo*quinamine extracted

with ether and crystallised from alcohol. It formed cream-coloured plates, m. p. 115—117° (Hesse, 1881, *loc. cit.*, gives m. p. 114°), and is optically inactive in alcohol, but has $[a]_D$ — 32·9° (M/40; N/10-H_2SO_4). The *hydriodide*, prepared by addition of potassium iodide solution to the base dissolved in dilute acetic acid, was crystallised from boiling, dry alcohol and finally from boiling water. It had m. p. 207—209° (Found : C, 54·1; H, 5·4; N, 6·9; I, 30·0. $C_{19}H_{22}ON_2$,HI requires C, 54·0; H, 5·5; N, 6·6; I, 29·9%). The *picrate* crystallised from methyl alcohol in orange-coloured needles, m. p. 172—174° $[a]_D$ — 0·93° (M/40; acetone) (Found : C, 57·5; H, 4·6; N, 13·5. $C_{19}H_{22}ON_2,C_6H_3O_7N_3$ requires C, 57·3; H, 4·8; N, 13·4%).

Benzoyl*apo*quinamine, prepared from quinamine like the acetyl derivative, was amorphous but yielded a crystalline *picrate*, m. p. 191—193° (Found : C, 61·45; H, 4·6; N, 11·6. $C_{19}H_{21}ON_2$·CO·$C_6H_5,C_6H_3O_7N_3$ requires C, 61·2; H, 4·6; N, 11·2%).

To *apo*quinamine (1 g.) in acetone (5 c.c.), methyl iodide (3 c.c.) was added, and the mixture left overnight. Some crystals separated, and when the glass surface near them was scratched, the solution became semi-solid. The *methiodide* (1·35 g.) was recrystallised from alcohol until of constant m. p. 219—220° (Found : C, 55·1; H, 6·0; N, 7·1; I, 29·1; NMe, 5·8. $C_{19}H_{22}ON_2$,CH_3I requires C, 55·0; H, 5·8; N, 6·4; I, 29·1; NMe, 6·65%).

Hydrogenation of *apo*quinamine in solution in alcohol, in presence of palladised barium sulphate or Adams's platinic oxide, takes place in two stages, one molecule of hydrogen being absorbed within a few minutes, and a second in the course of several hours. From an operation stopped at the end of the first stage, the base was isolated and converted into *dihydroapoquinamine picrate*, which, after two recrystallisations from methyl alcohol, formed orange needles, m. p. 179—181° (Found : C, 57·1; H, 5·2; N, 13·42. $C_{19}H_{24}ON_2,C_6H_3O_7N_3$ requires C, 57·1; H, 5·2; N, 13·32%). Dihydro*apo*quinamine was also prepared from dihydroquinamine by the process described for *apo*quinamine from quinamine. The acetyldihydro*apo*quinamine obtained was amorphous but yielded a crystalline *picrate*, m. p. 148—150° (Found : N, 12·1. $C_{21}H_{26}O_2N_2,C_6H_3O_7N_3$ requires N. 12·3%). The acetyl derivative on hydrolysis yielded *dihydro*apo*quinamine* base, m. p. 124—126°, $[a]_D$ — 5·42° (Found : C, 76·9; H, 8·0; N, 9·5. $C_{19}H_{24}ON_2$ requires C, 77·0; H, 8·2; N, 9·45%). From solutions in which hydrogenation was allowed to proceed to completion, *tetrahydro*apo*quinamine picrate* was prepared in similar fashion. It crystallised from methyl alcohol in yellow needles, m. p. 175—177° (Found : C, 56·8; H, 5·5; N, 13·4. $C_{19}H_{26}ON_2,C_6H_3O_7N_3$ requires C, 56·9; H, 5·4; N, 13·3%).

When a solution of *apo*quinamine in dilute acetic acid was subjected to prolonged ebullition, the expected *apo*quinamicine was not formed but quinamicine (see below) was isolated as the picrate, m. p. 201—203°, and as the 2 : 4-dinitrophenylhydrazone, m. p. 235—239°.

Quinamicine.—Quinamine (2 g.) was heated for 50 hours in acetic acid (20 c.c.; 10%). Ammonia solution was added, and the precipitate collected, washed, dried, dissolved in alcohol, and the solution taken to dryness. The brown residue could not be induced to crystallise as base, acid tartrate, or acid oxalate, but the *picrate* was prepared, by adding picric acid solution to a solution of the acid tartrate, and was recrystallised from boiling water from which it separated in yellow platelets, m. p. 203—205°, $[a]_D$ — 17·46° (M/40; acetone) (Found : C, 55·5; H, 5·15; N, 12·8. $C_{19}H_{24}O_2N_2,C_6H_3O_7N_3$ requires C, 55·4; H, 5·0; N, 12·9%). Quinamicine, unlike most quinicines, gives no coloration with Bachstez's reagent (*Arch. exp. Path. Pharm.*, 1932, **164**, 314). The base (0·6 g.) in alcohol (3 c.c.) was mixed with 2 : 4-dinitrophenylhydrazine (0·55 g.) dissolved in warm alcohol (5 c.c.) with the aid of sulphuric acid (0·1 c.c.), and the mixture left for 3 hours. The precipitate formed was collected, exposed to moist ammonia vapour for 48 hours, and then crystallised from nitrobenzene (0·65 g. in 8 c.c.) as dark red needles of *quinamicine 2 : 4-dinitrophenylhydrazone*, m. p. 239—240° (Found : C, 60·8; H, 5·8; N, 16·8. $C_{19}H_{24}ON_2,C_6H_4O_4N_4$ requires C, 60·9; H, 5·7; N, 17·1%).

Crude quinamicine, prepared from quinamine (12 g.), was dissolved in alcohol (60 c.c.) containing hydroxylamine hydrochloride (4 g.) and potassium hydroxide (3·25 g.) in water (3 c.c.), and the solution refluxed for 5 hours. The alcohol was distilled off at reduced pressure, water added to the residue, and the yellowish product filtered out; more was recovered by passing carbon dioxide through the filtrate. The *oxime* was recrystallised from methyl alcohol to constant m. p. 217—220°, and then had $[a]_D$ + 82·2° (Found : C, 69·7; H, 7·8; N, 12·9. $C_{19}H_{25}O_2N_3$ requires C, 69·7; H, 7·7; N, 12·9%).

On standing with methyl iodide (7 c.c.) and alcohol (3 c.c.), quinamicine (3·5 g.) produced after 3 days a white precipitate of *N-methylquinamicine methiodide*, which after 5 recrystallisations from alcohol, had m. p. 275—276°, $[a]_D$ — 39·8° (c = 0·364; alcohol) (Found : C, 53·9; H, 6·1; N, 6·0; NMe, 12·0; I, 27·7. $C_{19}H_{23}O_2N_2$·CH_3,CH_3I requires C, 53·8; H, 6·2; N, 6·0; 2NMe, 12·4; I, 27·1%). Quinamicine reacts with benzoyl chloride but neither with this nor any of the other usual acylating agents could a well-defined, crystalline acyl derivative be obtained.

Dihydroquinamicine oxime was prepared from dihydroquinamine, by the processes used for quinamicine oxime. It crystallised from methyl alcohol in colourless needles, m. p. 225—227° (Found : C, 69·4; H, 8·6; N, 12·7. $C_{19}H_{27}O_2N_3$ requires C, 69·3; H, 8·3; N, 12·8%).

Oxidation of Quinamine with Chromic Acid.—Quinamine (40 g.) was dissolved in water (600 c.c.) containing sulphuric acid (50 g.). To this, chromic acid (150 g.), dissolved in sulphuric acid (190 g.) diluted with water (600 c.c.), was added gradually during 6 hours with constant stirring, the temperature being kept below 50°. Stirring was continued for 24 hours, after which a slight excess of chromic acid remained. On steam-distillation, a distillate containing acetic acid (3·84 g.) was obtained, and on rendering the residue alkaline, ammonia (1·06 g.) was collected. The reaction mixture was then poured into a solution of barium hydroxide (800 g.), and the now faintly acid solution, after filtration, was evaporated in a vacuum to about 70 c.c. When copper sulphate was added to this concentrate there was gradually deposited a blue precipitate the quantity of which could be increased by further concentration. The *copper* salt is soluble in alcohol, acetone, or chloroform and sparingly soluble in water. It can be recrystallised from chloroform (1 g. in 18 c.c.) or from boiling water (1 g. in 250 c.c.). The crystals are dark blue, decompose from about 278°, and suffer no loss on drying at 120° in a vacuum (Found : C, 54·3; H, 7·1; N, 6·5; Cu, 14·6. $C_{20}H_{30}O_5N_2Cu$ requires C, 54·3; H, 6·8; N, 6·3; Cu, 14·4%). The acid is best recovered by passing hydrogen sulphide through a filtered solution of the copper salt (3 g.) in chloroform (100 c.c.). The filtrate from the copper sulphide on concentration to 5 c.c. deposits colourless, deliquescent needles of the acid, which after three recrystallisations from chloroform melts constantly at 206—208°, and has $[a]_D$ + 57·9° (c = 0·52; chloroform) (Found : C, 66·1; H, 8·3; N, 7·6. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3; N, 7·7%). From this result it appears that the copper salt is a monohydrate, the water of crystallisation not being lost at 120° in a vacuum. The acid is soluble in water, alcohol, acetone, or chloroform but insoluble in dry ether, benzene, or light petroleum. On hydrogenation in presence of palladised barium sulphate, 0·1186 g. absorbed 14·2 c.c. of hydrogen at N.T.P. (Calc. for one ethylenic linkage : 14·7 c.c.).

The acid has the composition and characters of a 3-*vinylquinuclidinecarboxylic acid*, as the results of the following further experiments show.

On treatment with diazomethane, the acid (5 g.) yields a brown oil, which on distillation gives a product, b. p. 100—150°/15 mm., chiefly at 145—147°/15 mm., from which a *picrate*, crystallising from water in yellow needles, m. p. 143—146°, was obtained (Found : C, 48·9; H, 5·1; N, 15·4. $C_9H_{15}N,C_6H_3O_7N_3$ requires C, 49·2; H, 4·9; N, 15·3%). The base (0·0563 g.) regenerated from this picrate, on hydrogenation in presence of Adams's platinic oxide catalyst, absorbed 10·2 c.c. of hydrogen (N.T.P.) (Calc. for $C_9H_{15}N$ with one ethylenic linkage : 9·2 c.c.). The picrate from this hydro-

genated product had m. p. 151—153° and showed no depression of m. p. on admixture with a specimen of 3-ethyl-quinuclidine picrate synthesised for comparison, by Prelog's process (*loc. cit.*).

The acid (1 g.), mixed with copper-bronze powder (1 g.), was heated in a distilling flask immersed in an oil-bath at 200°. The small amount of yellow oil, which distilled, was dissolved in ether and treated with picric acid in the same solvent. The resulting picrate, recrystallised from water, had m. p. 141—144° and showed no depression of m. p. when mixed with the picrate, m. p. 143—146°, resulting from decarboxylation of the methyl ester (p. 527). Like the latter, the base regenerated from it can be hydrogenated in presence of platinic oxide catalyst and the resulting base gives a picrate, m. p. 151—153°, undepressed on admixture with 3-ethylquinuclidine picrate.

The acid (1 g.), dissolved in water (4 c.c.) with hydrochloric acid (2 c.c.) and mercuric chloride (6·1 g.), was heated for 9 hours at 250° in a sealed tube (cf. Königs, *loc. cit.*). The solution was made alkaline, and steam-distilled, the distillate being collected in dilute hydrochloric acid (10%; 10 c.c.) and evaporated to 20 c.c. It was then made alkaline, saturated with sodium chloride, and extracted with ether, which on removal, left a residue, and this on distillation yielded a pale yellow liquid (0·15 g.), b. p. 145—150°. To this, hydrochloric acid (0·5 c.c.; 10%) was added, and the solution evaporated in a vacuous desiccator, leaving a sticky, crystalline mass, m. p. 90—105°. This was dissolved in water (5 c.c.), the acidity reduced with sodium carbonate, and picric acid (0·3 g.) in water (30 c.c.) added. On standing, the precipitate first formed crystallised as pale yellow needles, m. p. 126—128° (Found : C, 46·6; H, 3·5; N, 17·1. Calc. for $C_7H_9N,C_6H_3O_7N_3$: C, 46·4; H, 3·6; N, 16·7%). This picrate has the composition and properties of 3-ethyl-pyridine picrate, m. p. 127—129°, and a mixture of the two substances showed no depression of m. p.

The sodium salt of the acid (0·4 g.) was heated with soda-lime (4 g.) and the distillate of brown oil, with some water, was dissolved in ether, the solution dried, and picric acid (0·3 g.) in ether (20 c.c.) added. A picrate (0·1 g.) crystallised out as yellowish-brown leaflets, and after recrystallisation twice from alcohol had m. p. 126—128° (Found : C, 46·7; H, 3·5; N, 16·3. $C_7H_7N,C_6H_3O_7N_3$ requires C, 46·7; H, 3·2; N, 16·8. Calc. for $C_7H_9N,C_6H_3O_7N_3$: C, 46·4; H, 3·6; N, 16·7%). Depression of melting point is shown when this picrate is mixed with that of either 3-vinylpyridine or 3-ethylpyridine, but after repeated crystallisation, though it still melts at 126—128°, it ceases to show depression of m. p. on admixture with 3-ethylpyridine picrate. The base (0·0705 g.) regenerated from the picrate, on hydrogenation in acetic acid, absorbed 18·1 c.c. (N.T.P.) of hydrogen (Calc. for one ethylenic linkage : 15·0 c.c.). The hydrogenated base gave a picrate, m. p. 127—130°, undepressed on admixture with 3-ethylpyridine picrate.

3-*Ethylpyridine.*—3-Acetylpyridine (2 g.) was refluxed with hydrazine hydrate (95%; 2·5 c.c.) for 24 hours, and the resulting dark brown liquid left overnight in a vacuous desiccator to solidify. It was then transferred to a solution of sodium ethoxide in dry alcohol (sodium, 1·3 g.; alcohol, 25 c.c.), and the mixture heated at 190° in a sealed tube for 8 hours. Water (20 c.c.) was added, the solution acidified with hydrochloric acid, concentrated under reduced pressure to 15 c.c., then made alkaline by the addition of solid sodium carbonate, and the liberated base extracted with ether. The ethereal extract was dried over anhydrous sodium sulphate, the solvent removed, and the residue distilled as a colourless oily liquid, b. p. 160—165° (1·5 g.). The picrate, prepared in the usual manner and crystallised from alcohol, had m. p. 127—129° The b. p. recorded for 3-ethylpyridine is 162—165°/762 mm. and the m. p. of the picrate 128—130°.