yellow mass containing bubbles. It dissolves readily in methyl or ethyl alcohol, acetone, or chloroform.

Analyses. Calc. for $C_{23}H_{33}O_2N_2Br.H_2O$: H_2O, 3.86. Found: 3.89. Calc. for $C_{23}H_{33}O_2N_2Br$: Br, 17.78. Found: 17.72.

Dihydroquinine Ethyl Bromide.—The components were boiled for 4 hours in a mixture of equal volumes of dry chloroform and dry acetone. Washed with acetone and recrystallized first from water and then from alcohol by adding ether, the salt formed rosets of glistening platelets. When anhydrous it gives $[\alpha]_D^{22.5}$ $-111.1°$ in water $c=1.004$, and when rapidly heated to 185°, then slowly, melts slowly at 188–190° with slight decomposition. It is less soluble in acetone than the optochin derivative.

Analyses. Calc. for $C_{22}H_{31}O_2N_2Br.0.5H_2O$: H_2O, 2.03. Found: 2.06. Calc. for $C_{22}H_{31}O_2N_2Br$: Br, 18.36. Found: 18.31.

Hydrobromocinchonidine.—This substance was prepared as in the case of the hydrobromo compound described in the next paragraph, and to Leger's[19] description we can add only the following data. When rapidly heated to 175°, then slowly, the base discolors somewhat and melts to form a reddish liquid, with decomposition, at 176–177°. $[\alpha]_D^{21.5}$ is $-226.8°$ in dry methyl alcohol; $c=0.1608$.

Analysis. Calc. for $C_{19}H_{23}ON_2Br$: N, 7.47. Found: N, 7.52.

Hydrobromocupreine (or hydrobromo-apoquinine)dihydrobromide.—Ten and a half g. of quinine were heated for 6 hours at 110° in an oil-bath with 60 cc. of hydrobromic acid (sp. gr. 1.49). On cooling and standing for several days the above salt crystallized. Recrystallized from water containing a little hydrobromic acid, the dihydrobromide separated as delicate, tawny, voluminous needles. The yield was 4.5 g. Like solutions of the di-acid dihydrocupreine salts, the very faintly yellow solution in water turns a deeper yellow on neutralization (the reverse of the phenomena observed in the case of the quinicines), and then gives a pale brown color with ferric chloride. The base is precipitated by sodium carbonate, redissolving on adding sodium hydroxide to yield a solution which couples with diazotized sulfanilic acid. The anhydrous salt gives $[\alpha]_D^{21}$ $-161.8°$ in water, $c=1.022$, and softens slightly when heated, sintering at 190–195° and slowly intumescing at 197–203°. It is somewhat soluble in cold absolute alcohol, the solution crystallizing on rubbing.

Analyses. Calc. for $C_{19}H_{23}O_2N_2Br.2HBr.3.5H_2O$: H_2O, 10.23. Found: 10.24. Calc. for $C_{19}H_{23}O_2N_2Br.2HBr$: Br^-, 28.91. Found: 29.20.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

SYNTHESES IN THE CINCHONA SERIES. X. DIHYDROCINCHONICINOL AND THE DIHYDROQUINICINOLS[1]

BY MICHAEL HEIDELBERGER AND WALTER A. JACOBS

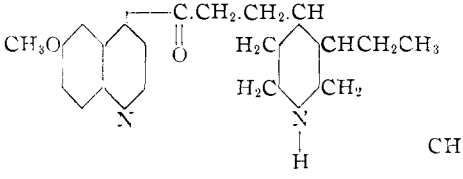
Received July 28, 1921

In the course of the bacteriological study of certain cinchona derivatives undertaken in conjunction with Dr. Martha Wollstein and Dr. Lloyd D. Felton it developed that in general the dihydrogenated alkaloids of the quinicine type (I) were less pneumococcidal than the original alkaloids (II) from which they were derived. While it seemed possible

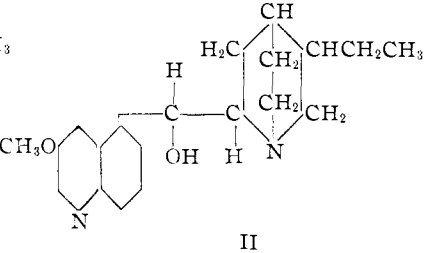
[19] Leger, *Bull. soc. chim.*, [4] **25**, 572 (1919).

[1] Presented at the Annual Meeting of the American Chemical Society, New York, September, 1921.

that this effect was in some way due to the breaking up of the fused quinuclidene nucleus into the simpler piperidine ring, it seemed also possible that the loss of the secondary hydroxyl group might play a part, especially

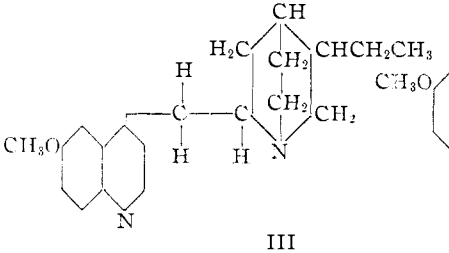


I

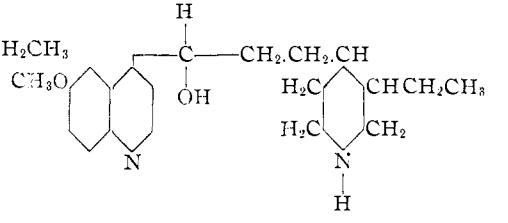


II

as dihydroquinane and its related alkaloids,[2] (III) in which the quinuclidene nucleus is still intact, had previously been found to be less active than the parent alkaloids. It was therefore hoped that the restoration of the secondary alcohol group in the quinicine series would enhance the pneumococcidal power of these alkaloids. While it was found possible to reduce the keto group in the desired sense, the resulting alkaloids (IV) were devoid of marked pneumococcidal power, even when the tertiary character of the piperidine nitrogen atom was restored by methylation or ethylation.



III



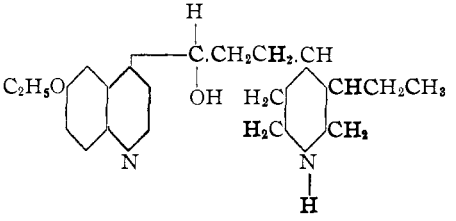
IV

The reduction was accomplished with the aid of palladium black and hydrogen, and we have named the new alkaloids so prepared the dihydrocinchonicinols and dihydroquinicinols, depending on whether the alkoxy group is absent or present. It is obvious that in the reduction of the keto group the central carbon atom is restored to its original condition of asymmetry, so that optical isomers should result. The reduction products proved, as expected, to be mixtures and, depending on the particular case, could be separated into the optical isomers either as the free base or as an appropriate salt. In every case the *d*- compound proved the easier to isolate, and of those investigated, only in the case of N-methyl-dihydroquinicinol, could both the *d*- and *l*- bases be obtained crystalline. Dihydrocinchonicinol was separated into the *d*- and *l*- sulfates; *d*-dihydroquinicinol crystallized, but the *l*- isomer could be isolated only as the

[2] THIS JOURNAL, **42**, 1489 (1920).

dihydrochloride; *d*-N-ethyl-dihydroquinicinol and *d*-O-ethyl-dihydrocupreicinol (V) (corresponding to ethyldihydrocupreine, or optochin), were obtained crystalline, and while in the former case a second dihydrochloride was obtained, no crystalline derivative of *l*-O-ethyl-dihydrocupreicine could be prepared. The mixture of N-benzyl-dihydroquinicinols also failed to yield crystalline derivatives.

d-N-Methyl-dihydroquinicinol and *d*-N-ethyl-dihydroquinicinol were also prepared by alkylation of the parent *d*-dihydroquinicinol, and similar derivatives were also formed from *d*-O-ethyl-dihydrocupreicinol, crystallizing with little difficulty.



V

An interesting consequence of the restoration of the secondary hydroxyl group in the case of the dihydroquinicinols (and O-ethyl-dihydrocupreicinol) was the restoration of the bluish fluorescence of the bases when dissolved in excess nitric or sulfuric acid, thus supporting Kaufmann's statement that the alkoxy group and the secondary hydroxyl are necessary to produce this phenomenon.[3] The dilute acid solutions were also relatively stable to potassium permanganate.

It is hoped soon to study the pharmacological properties of this new series of alkaloids.

Experimental

d- **and** *l*-**Dihydrocinchonicinol Sulfates.**[4]—Fifty g. of air-dry cinchonicine oxalate were dissolved in water and dil. hydrochloric acid, the solution made alkaline with sodium hydroxide, shaken out with ether, and the extract dried for a few moments and concentrated. The residue was taken up in about 100 cc. of water and 14 g. of conc. sulfuric acid and shaken in an atmosphere of hydrogen with the palladium black from 8 cc. of 2% palladious chloride solution, with the addition of 3 cc. of the palladium chloride solution after reduction had commenced, in order to accelerate the reaction. The absorption was 5570 cc. (Calc. for $2H_2$, 5965 cc.). In a later experiment cinchonicine oxalate itself was reduced after dissolving with the aid of an equivalent of sulfuric acid and the absorption found to be slightly greater than that calculated. The solution was diluted, decanted from the palladium, made alkaline with sodium hydroxide, and the base extracted with ether. The ether extract was thoroughly dried, finally over sodium

[3] Kaufmann, *Ber.*, **46**, 1827 (1913).

[4] After most of the work on the quinicinols had been completed it was found that Kaufmann and Huber [*Ber.*, **46**, 2919 (1913)] mention that cinchonicine absorbs 4 atoms of hydrogen, giving yellowish, oily "hydrocinchotoxol" which was not investigated.

hydroxide, concentrated, dissolved in 150 cc. of absolute alcohol and made just barely acid to litmus with conc. sulfuric acid. On seeding with crystals obtained from a portion which was precipitated with dry acetone and allowed to stand for several days, 7.6 g. of the crude *d*-sulfate gradually crystallized. This was recrystallized first from absolute alcohol, then boiled out with a little absolute alcohol, and finally dissolved in the minimum amount of 95% alcohol. Dry acetone was then added to marked turbidity, followed by treatment with bone black and filtering, and again the addition of dry acetone to incipient turbidity. The rotation of the salt which then crystallized was found to have attained a constant value.

d-Dihydrocinchonicinol sulfate forms cream colored, microscopic needles which dissolve readily in water to form a solution with a pale yellow color and are difficultly soluble in absolute alcohol, but somewhat more so in dry methyl alcohol. The anhydrous salt sinters and turns brown at 222°, melting at 223–224° with slow gas evolution, and gives $[\alpha]_D^{29}$ + 63.6° in water; $c = 1.014$.

Analyses. Calc. for $(C_{19}H_{26}ON_2)_2.H_2SO_4.2H_2O$: H_2O, 4.93. Found: 5.23. Calc. for $(C_{19}H_{26}ON_2)_2.H_2SO_4$: C, 65.65; H, 7.84; N, 8.07; $SO^{=}_4$, 13.83. Found: C, 65.35; H, 7.47; N, 8.27; $SO^{=}_4$, 13.98.

The filtrate from the crude *d*-sulfate was treated with dry acetone and stirred until the initial gummy precipitate dissolved with difficulty, the solution bottled, and allowed to stand in the ice-box for about 2 weeks. The drab-colored precipitate, which resembled the first fraction, weighed 9.1 g., but after recrystallization from absolute alcohol only 2.2 g. were recovered, and the product was strongly levorotatory. It was accordingly boiled with a little absolute alcohol, cooled, the colored alcoholic solution poured off, and the residue dissolved in boiling dry methyl alcohol. Dry acetone was then added to incipient turbidity, the solution treated with bone black and rapidly filtered; more dry acetone was added to incipient turbidity and the mixture allowed to stand. The *l*-sulfate separated as rosets of minute, cream colored leaflets which were dried *in vacuo* over sulfuric acid. $[\alpha]_D^{32}$ in water was constant at $-57.3°$; $c = 1.109$. When rapidly heated to 230°, then slowly, the salt melts with preliminary softening at 232–234°, with gas evolution. In properties, as well as in appearance, it greatly resembles its optical isomer.

Analyses. Calc. for $(C_{19}H_{26}ON_2)_2.H_2SO_4$: C, 65.65; H, 7.84; N, 8.07; $SO^{=}_4$, 13.83. Found: C, 65.74; H, 7.87; N, 8.14; $SO^{=}_4$, 14.03.

Neither the *d*- nor *l*- base, liberated from its sulfate, could be made to crystallize.

On addition of more dry acetone to the mother liquors from the *d*- and *l*- sulfates mixtures of the *d*- and *l*- forms were obtained.

Dihydroquinicinol

***d*-Dihydroquinicinol Nitrate.**—Sixty g. of recrystallized quinicine hydrochloride[5] were dissolved in 180 cc. of water and 7.5 cc. of conc. sulfuric acid and reduced with palladium and hydrogen. The absorption was 7655 cc. (Calc. for 2 H_2, 7453 cc.) The filtrate from the palladium was neutralized to litmus with 10% aqueous sodium hydroxide, and care was taken to redissolve the gummy precipitate locally formed by the alkali. To the filtered solution (about 350 cc.), powdered sodium nitrate was added to incipient turbidity and the mixture allowed to stand for several days, with occasional rubbing. The crystalline deposit weighed 28 g. after washing with 5% sodium nitrate solution. Recrystallized first from 25% alcohol, then from absolute alcohol, the nitrate forms faintly yellow rhombs which yield a white powder when ground. It is sparingly soluble in cold water, quite readily on boiling, the solution giving a blue-violet fluorescence with a little nitric or sulfuric acid and also giving the thalleoquinine test.

[5] THIS JOURNAL, **41**, 832 (1919).

When rapidly heated, the air-dry salt melts at 125–135° with effervescence and preliminary softening, but when anhydrous it softens above 90°, begins to melt at 95°, and is completely fluid at 115°. $[\alpha]_D^{27.5}$ of the anhydrous salt is +100.7° in 50% alcohol; $c = 1.063$.

Analyses. Calc. for $C_{20}H_{28}O_2N_2.HNO_3.H_2O$: H_2O, 4.40; C, 58.64; H, 7.64. Found: H_2O, 4.35; C, 58.73; H, 7.68.[6] Calc. for $C_{20}H_{28}O_2N_2.HNO_3$: N, 10.74. Found: 10.92.

d-**Dihydroquinicinol.**—The purified nitrate was converted into the base with alkali and shaken out with ether. After removing the solvent the warm residue was dissolved in a little hot benzene, with which it is miscible only if too much is not used. After cooling to room temperature and seeding with crystals obtained by allowing a test portion in benzene to evaporate spontaneously, the base crystallized rapidly as cream colored rhombs which were washed with a little cold benzene and air dried. It dissolves readily in alcohol, acetone or chloroform and turns gummy under dry ether or toluene, then dissolving with difficulty. It begins to sinter at 68° and is completely fluid at about 80°. $[\alpha]_D^{26}$ of the anhydrous base is + 87.1° in absolute alcohol; $c = 1.045$.

Analyses. Calc. for $C_{20}H_{28}O_2N_2.0.5H_2O$: H_2O, 2.66. Found: 2.34. Calc. for $C_{20}H_{28}O_2N_2$: C, 73.12; H, 8.60; N, 8.53. Found: C, 73.39; H, 8.63; N, 8.33.

d-**Dihydroquinicinol Dihydrochloride.**—An absolute alcoholic solution of the base was acidified to congo red with absolute alcoholic hydrochloric acid. The dihydrochloride gradually separated as rosets of minute needles which dissolve readily in water and rather sparingly in cold absolute alcohol, more easily on boiling. When rapidly heated to 210°, then slowly, the salt melts at 212–214° with gas evolution to form a yellow liquid. $[\alpha]_D^{31}$ is +151.8° in water; $c = 1.096$.

Analysis. Calc. for $C_{20}H_{28}O_2N_2.2HCl$: Cl, 17.67. Found: Cl, 17.54.

l-**Dihydroquinicinol Dihydrochloride.**—In preliminary reduction experiments it was found that on taking up the crude base in absolute alcoholic hydrochloric acid an apparently homogeneous salt crystallized which, on recrystallization from absolute alcohol containing a little hydrochloric acid, finally attained a constant rotation of about +8°. Indeed it was from this salt that it was first found possible to obtain a portion as the *d*- nitrate, thus pointing to the initial isolation of this salt as the best method of separating the optical isomers. On adding more solid sodium nitrate to the filtrate from the first crop of the nitrate until turbid it is not always possible to obtain more of the nitrate free from an oily salt (probably the *l*- nitrate), but unless a considerable amount of the oil is precipitated with the remaining portions of the *d*- nitrate, some of the latter remains in solution, and on subsequent conversion of the filtrate into the dihydrochloride it is impossible to attain maximal levorotation. Accordingly solid sodium nitrate was added to the filtrate from the first crop until considerable oily material separated, and after standing overnight the mixture was treated with bone black, filtered, and the dry base obtained from the filtrate in the usual manner. On dissolving in absolute alcohol containing an excess of dry hydrogen chloride and letting the mixture stand, the *l*-dihydrochloride separated on cooling as rosets of diamond-shaped, glistening platelets which then were repeatedly crystallized from absolute alcohol containing a little absolute alcoholic hydrochloric acid. In this way a maximum $[\alpha]_D$ of −117.7° was finally obtained in water; $c = 0.994$. The salt is very hygroscopic in warm, moist air, and must therefore be filtered in a cold room. It is very soluble in water and rather difficultly so in absolute alcohol, especially in the presence of dry hydrogen chloride. Like the *d*- form it gives the thalleoquinine reaction and fluoresces on adding a suitable acid. The free base was not obtained crystalline. The salt slowly sinters together above 135° and effervesces at 170°.

[6] This analysis refers to a portion recrystallized again from 25% alcohol.

Analyses. Calc. for $C_{20}H_{28}O_2N_2.2HCl$: C, 59.86; H, 7.49; N, 6.98. Found: C, 59.22; H, 7.87; N, 7.67.

Essentially the same results were obtained when dihydroquinicine sulfate[7] was used as the starting material, except that in this case only one molecular equivalent of hydrogen was absorbed.

N-Methyl-dihydroquinicinol

d-N-**Methyl-dihydroquinicinol.**—The crude quinicine base from 113.6 g. of quinidine methiodide[8] was dissolved in 300 cc. of 10% sulfuric acid and reduced with 35 cc. of 2% palladious chloride solution and hydrogen. Approximately 2 molecular equivalents of hydrogen were absorbed. The clear centrifuged liquid and washings were diluted, covered with ether, and made alkaline. The residue from the dried ethereal extract crystallized on cooling, and was recrystallized from 50% alcohol, yielding 33 g. of crude *d*-N-methyl-dihydroquinicinol, or almost as much as if the intermediate quinicine salt[8] had actually been isolated. After 4 recrystallizations from 70% alcohol $[\alpha]_D^{27}$ was constant at +93.9° in absolute alcohol, $c = 1.012$, the yield being 8.3 g. The base forms rhombic crystals which are anhydrous and melt at 165.5–166.0° with slight preliminary softening. It is very readily soluble in chloroform, easily in dry methyl or ethyl alcohol, and sparingly in cold dry acetone or benzene but quite soluble on boiling. Dissolved in conc. sulfuric acid it gives a faint yellow color which deepens and shows a green fluorescence when the solution is warmed on the water-bath. It gives the thalleoquinine test and exhibits a violet-blue fluorescence when dissolved in dil. nitric or sulfuric acid.

Analyses. Calc. for $C_{21}H_{30}O_2N_2$: C, 73.63; H, 8.84; N, 8.19. Found: C, 73.47; H, 8.79; N, 8.34.

d-N-**Methyl-dihydroquinicinol from *d*-Dihydroquinicinol Nitrate.**—A dry acetone solution of *d*-dihydroquinicinol obtained from the nitrate was treated with a slight excess of methyl iodide. Heat was evolved, and when the solution was rubbed the N-methyl hydriodide separated as microscopic rhombs. The collected salt was dissolved in hot water, the solution cooled and treated with an excess of sodium carbonate. The base separated as an oil which soon crystallized on rubbing. After 3 recrystallizations from 70% alcohol $[\alpha]_D^{30}$ was +93.8° in absolute alcohol, $c = 1.002$, the melting point 165.5–166.0°, and the other properties also were identical with those of the base obtained from N-methyl-dihydroquinicine.

d-N-**Methyl-dihydroquinicinol Hydrobromide.**—A solution of the base in a slight excess of 10% aqueous hydrobromic acid was neutralized to litmus and the filtrate treated with solid sodium bromide until just turbid. The hydrobromide separated on chilling the solution and letting it stand. Recrystallized from water, it formed a hard crust of rhombs which were anhydrous, and turned pink and softened on heating, melting at 218–223° with darkening. It is rather sparingly soluble in cold water or absolute alcohol, but dissolves readily on heating. With a little sodium iodide or nitrate the aqueous solution soon deposits minute rosets of the iodide or rhombs of the nitrate. $[\alpha]_D^{24}$ is +80.2° in water; $c = 1.090$.

Analyses. Calc. for $C_{21}H_{30}O_2N_2.HBr$: N, 6.62; Br, 18.88. Found: N, 7.01; Br, 18.95.

d-N-**Methyl-dihydroquinicinol Dihydrochloride.**—This was obtained as in the case of *d*-dihydroquinicinol dihydrochloride. Recrystallized from absolute alcohol with the aid of dry ether it forms rosets of glistening platelets, which are extremely easily soluble in water, readily so in absolute alcohol, and practically insoluble in dry

[7] See preceding paper, THIS JOURNAL, **44,** 1092 (1922).

[8] Ref. 7, p. 1091.

acetone. The salt softens markedly above 140°, gradually melting and evolving gas, and becoming completely fluid at about 190°. $[\alpha]_D^{24}$ is +145.7° in water; $c = 1.078$.

Analyses. Calc. for $C_{21}H_{30}O_2N_2.2HCl$: N, 6.75; Cl, 17.08. Found: N, 6.91; Cl, 16.97.

d-N-**Methyl-dihydroquinicinol Methiodide.**—The oily salt separated from a solution of equimolecular parts of the constituents in chloroform, and soon crystallized. After washing with dry acetone it was recrystallized from water, by seeding the solution while still warm and letting it stand in a warm place until crystallization was almost complete, in order to avoid deposition of a gelatinous form. It forms a crust of faintly yellow rhombs which are very difficultly soluble in cold water or absolute alcohol, but more easily on boiling. When rapidly heated to 220°, then slowly, it begins to soften above this point and melts at 225–227° to a brown, turbid liquid which clears at 228°. $[\alpha]_D^{23.5}$ is +68.7° in water; $c = 1.025$.

Analysis. Calc. for $C_{22}H_{33}O_2N_2I$: I, 26.21. Found: 26.27.

l-N-**Methyl-dihydroquinicinol.**—The mother liquors from the first two recrystallizations of the crude N-methyl dihydroquinicinol were diluted to incipient turbidity and allowed to stand, when they deposited 8.4 g. of the crude *l*- compound with $[\alpha]_D$ −15° in absolute alcohol. After 2 recrystallizations from 60% alcohol 4.2 g. were obtained with $[\alpha]_D^{25.5}$ −24.9° in absolute alcohol, $c = 1.003$, the rotation being unchanged by further recrystallization. The *l*- base forms crusts of minute plates which melt with slight preliminary softening at 136.5–137.5° to a liquid containing crystals, but becoming clear at 144°. It is more soluble in the usual organic solvents than the *d*-isomer, but otherwise greatly resembles this substance.

Analyses. Calc. for $C_{21}H_{28}O_2N_2$: C, 73.63; H, 8.84; N, 8.19. Found: C, 73.78; H, 8.50; N, 8.04.

The mother liquor from which the first crop of crude *l*- base was obtained still contained considerable amounts of base, which investigation showed to be a mixture.

l-N-**Methyl-dihydroquinicinol Dihydrochloride.**—This salt was obtained as in previous cases. Recrystallized from absolute alcohol, with the addition of a drop of absolute alcoholic hydrochloric acid after cooling, it separated as microscopic platelets. It is extremely easily soluble in water, readily so in dry methyl alcohol, sparingly soluble in cold absolute alcohol, and practically insoluble in dry acetone or chloroform. When rapidly heated to 230°, then slowly, it decomposes at 232–235°. The salt thus melts higher and is less soluble in absolute alcohol than the *d*-isomer. $[\alpha]_D^{24}$ is +1.45° in water; $c = 1.034$.

Analyses. Calc. for $C_{21}H_{30}O_2N_2.2HCl$: N, 6.75; Cl, 17.08. Found: N, 7.10; Cl, 17.06.

l-N-**Methyl-dihydroquinicinol Methiodide.**—The salt separated from a chloroform solution of the components. Recrystallized from water, it formed cream colored rosets of thick plates which are sparingly soluble in cold water, readily so in hot, and dissolve very difficultly in boiling absolute alcohol or dry chloroform or acetone. The iodide melts with preliminary browning and softening at about 253–254°, with decomposition. $[\alpha]_D^{23}$ is −50.0° in 50% alcohol; $c = 1.130$.

Analysis. Calc. for $C_{22}H_{33}O_2N_2I$: I, 26.21. Found: 26.42.

N-Ethyl-dihydroquinicinol

d-N-**Ethyl-dihydroquinicinol.**—The crude quinicine from 93.5 g. of quinidine ethyl bromide[9] was reduced as in the case of the N-methyl compound. The crude base

[9] THIS JOURNAL, **44**, 1091 (1922).

obtained from the ether extract was taken up in benzene and seeded with crystals obtained on concentration of a test portion of the crude base in ether. The *d*- base gradually crystallized, 12.8 g. being obtained after washing with a little benzene. Recrystallized twice from 70% alcohol it formed colorless, glistening rhombs which melted constantly at 140–141° and gave a constant $[\alpha]_D^{23}$ of +91.7° in absolute alcohol; $c=1.030$. It is readily soluble in the cold in alcohol, methyl alcohol or chloroform, rather sparingly so in cold dry acetone, and difficultly soluble in cold benzene, but readily on boiling. In its reactions it greatly resembles the N-methyl derivative.

Analyses. Calc. for $C_{22}H_{32}O_2N_2$: C, 74.10; H, 9.05; N, 7.86. Found: C, 74.20; H, 8.88; N, 8.26.

d-N-**Ethyl-dihydroquinicinol from** *d*-**Dihydroquinicinol Nitrate.**—The base obtained from the nitrate was treated in acetone solution with 1.2 mols. of ethyl iodide. After several hours the hydriodide separated on rubbing as minute rosets, and was converted into the base. After 2 crystallizations from 70% alcohol this melted at 140–141° and had attained the maximum $[\alpha]_D^{25}$ of 92.0° in absolute alcohol; $c=1.120$. In analysis and in its properties it also corresponded with the base as obtained directly.

d-N-**Ethyl-dihydroquinicinol Hydrochloride.**—Prepared as usual in absolute alcoholic solution the salt deposited after the addition of dry ether. Recrystallized from dry methyl ethyl ketone it formed minute rhombs which are very easily soluble in water. The solution has an intensely bitter taste. The salt dissolves readily in absolute alcohol, less easily in dry acetone, and sparingly in dry chloroform. When anhydrous, it softens at 130° and melts completely at 135° with slight decomposition. $[\alpha]_D^{20.5}$ in water is +85.4°; $c=1.043$.

Analyses. Calc. for $C_{22}H_{32}O_2N_2.HCl.H_2O$: H_2O, 4.39. Found: 3.63. Calc. for $C_{22}H_{32}O_2N_2.HCl$: N, 7.13; Cl, 9.03. Found: N, 7.55; Cl, 8.97.

d-N-**Ethyl-dihydroquinicinol Dihydrochloride.**—The salt was obtained from absolute alcoholic hydrochloric acid with the aid of dry ether and was crystallized by a repetition of the process as minute platelets which are extremely soluble in water, readily in absolute alcohol, and sparingly so in dry acetone or chloroform; $[\alpha]_D^{23}$ is +142.6° in water; $c=1.002$. It softens at about 150° and becomes semifluid, with the formation of gas bubbles at about 180° if slowly heated further, but if rapidly heated it melts and decomposes at about 250°.

Analysis. Calc. for $C_{22}H_{32}O_2N_2.2HCl$: N, 6.53; Cl, 16.52. Found: N, 6.79; Cl, 16.47.

A portion of the base recovered from the recrystallized salt had not increased in rotation.

d-N-**Ethyl-dihydroquinicinol Methiodide.**—A chloroform solution of the components was evaporated to dryness after one-half hour. The additon of dry acetone caused rapid crystallization. When recrystallized from water, the salt separated, oily at first if allowed to cool too quickly, but formed glistening platelets when the solution was seeded while still warm with crystals of the hydrate. When anhydrous it softens above 80°, melting completely at about 135°; $[\alpha]_D^{21}$ is +62.9° in 50% alcohol; $c=0.962$. It also dissolves readily in absolute alcohol or dry chloroform.

Analyses. Calc. for $C_{23}H_{35}O_2N_2I.2H_2O$: H_2O, 6.74. Found: 6.31. Calc. for $C_{23}H_{35}O_2N_2I$: I, 25.48. Found: 25.90.

l-N-**Ethyl-dihydroquinicinol Dihydrochloride.**—In a preliminary experiment in which N-ethyl dihydroquinicine hydrochloride[10] was used as starting material, the crude base was taken up in hot ligroin and the *d*-base allowed to separate from the warm solvent, cooling resulting in contamination with an oily fraction. The base recovered

[10] THIS JOURNAL, **44**, 1094 (1922).

from the ligroin solution was converted as usual into the dihydrochloride. This was recrystallized from absolute alcohol with the aid of a little dry hydrogen chloride and dry ether, forming slightly brownish rosets which gave $[\alpha]_D^{25}$ −16.7° in water; $c = 1.081$. When rapidly heated to 235°, then slowly, it decomposes at 237–238°. The amount obtained was insufficient for recrystallization to constant rotation. A portion, reconverted into the base, crystallized partially.

The fraction corresponding to the *l*-dihydrochloride in the larger experiment separated very quickly from absolute alcoholic hydrochloric acid on seeding, and was very difficult to filter. After recrystallization from absolute alcohol, to which dry hydrogen chloride was added after cooling, it again separated in very finely divided form, and as the base recovered from the salt showed little tendency to crystallize, further work on this considerable fraction was abandoned.

O-Ethyl-dihydrocupreicinol

d-O-**Ethyl-dihydrocupreicinol Hydrochloride.**—The reduced solution of 20 g. of ethyl-dihydrocupreicine sulfate[11] was centrifuged from the palladium black, neutralized with sodium hydroxide, and treated with solid sodium chloride until just turbid. The salt slowly crystallized. After several days in the ice-box it was filtered off, washed with 10% salt solution, and recrystallized from water, separating as cream colored prisms and needles. Further recrystallization from absolute alcohol yielded practically white plates containing alcohol of crystallization. The yield was 7.2 g. $[\alpha]_D^{26}$ of the dried salt was constant at +81.1° in water, $c = 1.010$, and the melting point was 209–210° with preliminary softening. The salt is sparingly soluble in water or absolute alcohol at 0°, but dissolves more easily in methyl alcohol. An aqueous solution has a weakly bitter taste and a marked anesthetic action on the tip of the tongue. When treated with sodium bromide it soon deposits the bromide as sheaves and rosets of minute needles, and yields a nitrate of somewhat similar appearance with sodium nitrate.

Analyses. Calc. for $C_{21}H_{30}O_2N_2.HCl$: N, 7.40; Cl, 9.36. Found: N, 7.40; Cl, 9.26.

d-O **Ethyl-dihydrocupreicinol.**—An aqueous solution of the salt was made alkaline with sodium carbonate. On letting stand, with occasional rubbing, the base gradually crystallized. When dissolved in alcohol and then well chilled and treated with water until the initial turbidity just redissolved, the base separates on seeding and standing in the ice-box as radiating masses of flat needles. If the recrystallization is attempted at room temperature the crystalline hydrate apparently does not form, and the base comes out oily. When washed with a little chilled 50% alcohol and air dried it comes to equilibrium with 2 molecules of water of crystallization. The hydrate dissolves readily in alcohol or acetone and melts at 59.5–61.5°. When anhydrous the base melts to a semifluid mass at 56–58°, with preliminary sintering and softening, and is completely fluid at 105–110°. $[\alpha]_D^{24.5}$ is +100.2° in absolute alcohol; $c = 1.018$.

Analyses. Calc. for $C_{21}H_{30}O_2N_2.2H_2O$: H_2O, 9.53. Found: 9.48. Calc. for $C_{21}H_{30}O_2N_2$: C, 73.63; H, 8.84; N, 8.19. Found: C, 73.97; H, 8.66; N, 8.67.

d-O-**Ethyl-dihydrocupreicinol Dihydrochloride.**—This was prepared from the monohydrochloride with alcoholic hydrochloric acid and ether. It forms rosets of platelets which are extremely soluble in water and rather sparingly so in absolute alcohol at room temperature but easily on heating. It gelatinizes under dry chloroform and dissolves with difficulty. When rapidly heated to 190°, then slowly, it melts with preliminary softening at 192–194° with gas evolution to a yellow liquid. $[\alpha]_D^{24}$ is +149.2° in water; $c = 1.045$.

[11] THIS JOURNAL, **44**, 1094 (1922).

Analyses. Calc. for $C_{21}H_{30}O_2N_2.2HCl$: N, 6.75; Cl, 17.08. Found: N, 6.96; Cl, 16.96.

Neither the *l*- base nor any of its salts could be obtained crystalline.

d-N-**Methyl**-O-**Ethyl-dihydrocupreicinol.**—*d*-O-Ethyl-dihydrocupreicinol hydrate was treated in dry acetone with an equivalent of methyl iodide. The N-methyl hydriodide which separated as minute rosets and prismatic needles was converted into the base by addition of sodium carbonate to its aqueous solution. Recrystallized from 50% alcohol, it formed rosets of long, narrow, glistening platelets which melted slowly at 136.5–137.0° with slight preliminary softening, giving $[\alpha]_D^{26.5}$ + 88.2° in absolute alcohol, $c = 0.993$, and greatly resembled the corresponding dihydroquinicinol base in properties and reactions, except for a slightly greater solubility in organic solvents.

Analyses. Calc. for $C_{22}H_{32}O_2N_2$: C, 74.10; H, 9.05; N, 7.87. Found: C, 74.16; H, 8.93; N, 8.64.

d-N,O-**Diethyl-dihydrocupreicinol.**—Equimolecular amounts of the base and ethyl iodide were allowed to react in dry acetone, the hydriodide of the diethyl compound separating as sheaves of delicate needles. The base, obtained from the salt as in the preceding case, crystallized on adding a little ether and allowing this to evaporate. It was dissolved in hot 70% alcohol, cooled, and treated with water until just turbid, separating slowly when seeded and aided by the addition of occasional small portions of water as minute, glistening rhombs. The base melts constantly at 110–111° with slight preliminary softening and gives $[\alpha]_D^{29}$ + 87.1° in absolute alcohol; $c = 0.804$. In its properties it resembles the methyl homolog, but is even more easily soluble.

Analyses. Calc. for $C_{23}H_{34}O_2N_2$: C, 74.54; H, 9.25; N, 7.57. Found: C, 74.87; H, 9.46; N, 7.68.

Summary

Cinchona alkaloids of the cinchonicine and quinicine type, reduced with palladium and hydrogen, yield mixtures of stereoisomers of a new type of alkaloids which we have called dihydrochonicinols and dihydroquinicinols. In general the *d*- forms proved easier to isolate. A number of the *d*- bases, one of the *l*- bases, and numerous salts of the *d*- and *l*- forms are described.

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THE AUTOXIDATION OF ETHYL ETHER

BY A. M. CLOVER

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When a glass-stoppered bottle of ordinary ethyl ether is allowed to stand for several months, it is known to acquire oxidizing properties which are usually attributed to hydrogen peroxide or to "ethyl peroxide." When this impure ether is allowed to evaporate in an open vessel, a liquid residue remains which possesses, besides these oxidizing properties, a very pungent odor. The residue completely disappears in time, through evaporation.

Frequent references occur in pharmaceutical literature to explosions[1]

[1] Schär, *Arch. Pharm.*, **225**, 623 (1887). Cleve, *Chem. News*, **63**, 101 (1891); *Pharm. Ztg.*, **34**, 426 (1889). Neander, *Chem. Ztg.*, **26**, 336 (1902).