filtered, and acidified, giving 45–48 g. (71–76%) of product, m. p. 172–174° without recrystallization (reported[10] m. p. 176°).

Reduction of the potassium salt of 5-methoxy-2-nitro-α-toluic acid in water with Raney nickel and hydrogen at 30 lb. pressure gave the corresponding amino acid, m. p. 122–124° decomp., which was distilled under reduced pressure and analyzed in the form of the resulting lactam, **5-methoxyoxindole,** slightly pink needles from alcohol, m. p. 152–154°.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.3; H, 5.5. Found: C, 66.2; H, 5.5.

Boiling the nitro acid with alcoholic hydrogen chloride gave **ethyl 5-methoxy-2-nitro-α-toluate** in a yield of 55%; the ester boiled at 185° at 1 mm. and formed pale yellow needles from alcohol, m. p. 57–59°.

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.2; H, 5.5. Found: C, 55.0; H, 5.5.

When the nitro ester was reduced in alcohol with Raney nickel and hydrogen at 30 lb. pressure, it yielded ethyl 2-amino-5-methoxy-α-toluate, an oil which was converted into 5-methoxyoxindole when it was heated. The amino ester was analyzed in the form of its **acetyl derivative,** colorless needles from alcohol, m. p. 104–105°.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.2; H, 6.8. Found: C, 62.0; H, 7.2.

A solution obtained by hydrogenating 9.6 g. of the nitro ester in 50 ml. of alcohol was filtered, concentrated under reduced pressure to a volume of 25 ml. and treated at 25° with 15 ml. of a 20% solution of glyoxal (obtained by the action of nitric acid on paraldehyde[12]). The mixture soon solidified when it was scratched or seeded; the product, **glyoxal bis-[2-(carbethoxymethyl)-4-methoxyanil],** crystallized from alcohol in the form of yellow needles (7.3 g., 88%), m. p. 108–109°.

Anal. Calcd. for $C_{24}H_{28}N_2O_6$: C, 65.4; H, 6.4. Found: C, 65.5; H, 6.4.

Seven grams of the anil was added to a solution of 1 g. of sodium in 20 ml. of dry alcohol. The mixture was boiled for five minutes, then acidified with 3 ml. of acetic acid and filtered. Most of the anil was converted into a black insoluble material, but from the filtrate there was isolated ethyl quininate which weighed 0.3 g. after it had been distilled and crystallized, and melted at 65–67° alone or mixed with an authentic sample. The action of pyridine, piperidine, or potassium carbonate in hot quinoline on the anil yielded no ethyl quininate.

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(12) Behrend and Kölln, *Ann.*, **416**, 230 (1918).

Summary

Kulisch's quinoline synthesis can be used for the preparation of ethyl quininate. The starting material is *m*-cresol, and the intermediate steps, involving nitrosation, oxidation and methylation to 3-methyl-4-nitroanisole, then condensation with ethyl oxalate, oxidation, esterification and reduction to ethyl 2-amino-5-methoxy-α-toluate, can be carried out with good yields. The final step. condensation with glyoxal, however, gives the desired substance in very small amount.

MINNEAPOLIS, MINNESOTA RECEIVED AUGUST 28, 1944

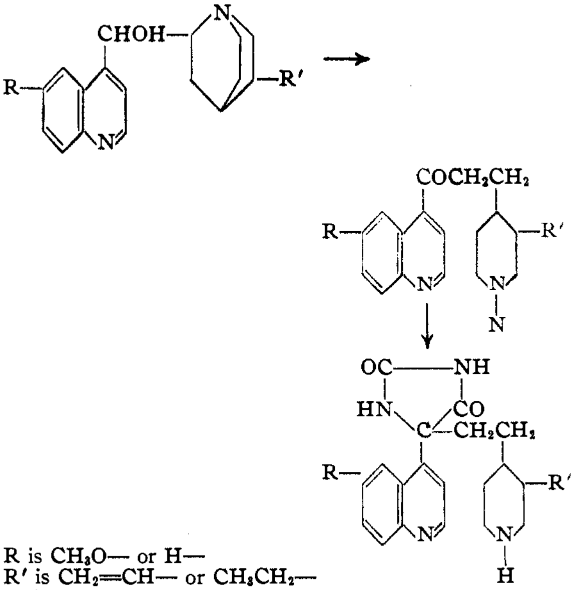
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Preparation of 5-Substituted Hydantoins Related to Certain Cinchona Alkaloids[1]

BY ROBERT LAMBERT McKEE[2] WITH HENRY R. HENZE

For several years past, a considerable amount of effort in this Laboratory has been directed toward the production of synthetic compounds having usefulness as anticonvulsants. To date the most satisfactory substances have been 5,5-disubstituted hydantoins; the latter have been prepared from ketones containing at least one cyclic (usually phenyl) substituent. In order to broaden our investigation, it was decided to prepare samples of 5-substituted hydantoins in which the different groups should be derived from nitrogen heterocycles related to certain cinchona alkaloids.

Molecular rearrangement of certain of the cinchona alkaloids to form ketones has been recognized for a long time; thus, quinine and its isomer quinidine have been converted to the same product, quinotoxine[3] (I). Likewise, both cinchonidine and cinchonine yield cinchotoxine (II). Moreover, the dihydro derivatives[4] of these four cinchona bases undergo the same "hydramine



R is CH_3O— or H—
R′ is $CH_2{=}CH$— or CH_3CH_2—

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(1) From the Ph.D. dissertation of R. L. McKee, June, 1943.

(2) Research Assistant, University of Texas Research Institute, Fall Semester, 1942–1943. Present address: Department of Chemistry, University of North Carolina.

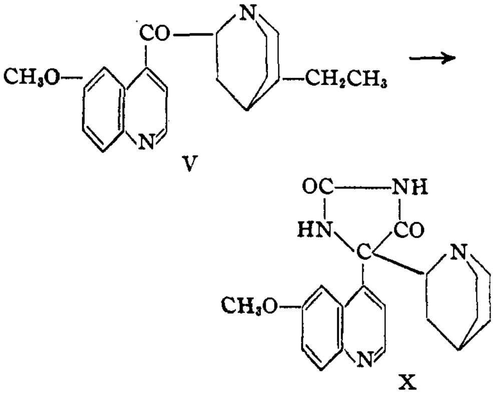
(3) (a) Pasteur, *Compt. rend.*, **37**, 111 (1853); (b) Biddle, THIS JOURNAL, **38**, 906 (1916).

(4) Reduction of the vinyl group in the cinchona bases has been accomplished by Paul and Cottin [*Bull. soc. chim.*, [5] **7**, 370 (1940)] through use of Raney nickel at a hydrogen pressure of 70–100 m and at room temperature.

fission"[5] to produce two, analogous hydrotoxines,[6] (III and IV).

In this investigation, quinotoxine (I), cinchotoxine (II), hydroquinotoxine (III) and hydrocinchotoxine (IV) have been converted into 5,5-disubstituted hydantoins by interaction with potassium cyanide and ammonium carbonate.

The structure of these hydantoins derived from toxines suggested that it would be of very considerable interest to prepare from hydroquinone (V) a related 5,5-disubstituted hydantoin derivative



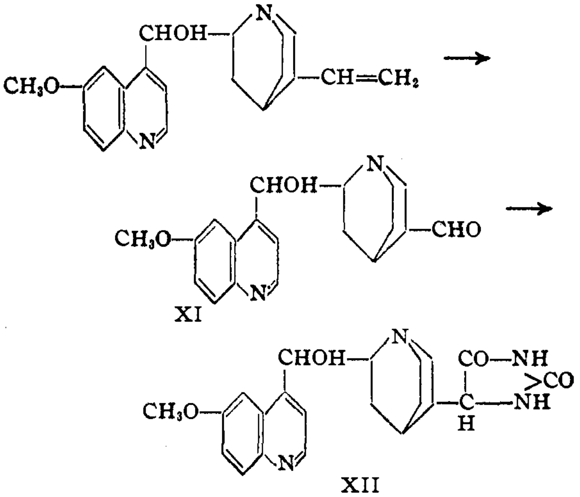
V

X

A hydantoin (X) thus related to hydroquinine, through alteration of the secondary alcohol group, would warrant testing to ascertain whether it possessed pharmacological activity, for no publication of the previous synthesis of a hydantoin containing a quinuclidyl substituent has been noted in the literature. However, none of the methods at present recorded in the chemical literature can be judged to be wholly suitable for conversion of quinine to quininone[7] or of hydroquinine into hydroquininone. These facts caused us to consider oxidation of quinine to the ketone by adaptation of other methods, such as that of Oppenauer[8] (through use of aluminum *t*-butoxide), or of Riley and co-workers[9] (using freshly prepared selenium dioxide[10]). Hence, quinine was treated at 80° in benzene–acetone solution with a three-fold excess of aluminum *t*-butoxide for twenty-four hours, but the alkaloid was recovered unchanged from such treatment. In another attempt, quinine and six molecular equivalents of *p*-benzoquinone[11] were dissolved in benzene and heated with aluminum *t*-butoxide for twelve hours, but 90% of the quinine was regained unaltered. Next, hydroquinine in xylene solution was heated with selenium dioxide and was converted into hydroquinone in about 45% yield. Although this yield is somewhat better than that reported for other oxidation procedures, nevertheless this method is not well-suited to large scale preparations. And our experience suggested that oxidation of quinine by selenium oxide would be unsatisfactory.

From hydroquinone (V) there was obtained, through conversion of its carbonyl group into the hydantoin heterocycle, an example (X) of a novel type of 5,5-disubstituted hydantoin in which the substituents are, respectively, the 4-(6-methoxyquinolyl) and 4-(3-ethylquinuclidyl) groupings.

The hydantoins thus far described have been prepared from ketones derived from certain cinchona alkaloids through oxidation of the secondary alcoholic group and also, in most cases, through conversion of the quinuclidyl group into a piperidylethyl grouping. It was thought to be of interest to attempt to prepare a hydantoin from quinine in such a manner that the secondary alcoholic grouping, with whose existence the antimalarial activity of quinine appears to be very closely related, should remain unaltered and, in addition, that the quinuclidine nucleus should not be cleaved. Thus it was visualized that quinine might be subjected to ozonolysis, with cleavage of the vinyl group to yield the aldehyde radical, in production of quininal (XI), and subsequently the latter might be converted into a mono-substituted hydantoin (XII). If these conversions could be carried out successfully, the structure of the resulting hydantoin would seem to warrant testing for possible antimalarial activity.



XI

XII

Experimental

Quinotoxine (I) was prepared[6] by refluxing a solution of 30 g. of quinine in 400 cc. of 7% acetic acid solution for forty hours; the yield of quinotoxine, as a brown oil, was 28 g. (practically quantitative conversion of the non-recovered quinine).

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(5) Gilman, "Organic Chemistry," Second Edition, John Wiley and Sons, Inc., New York, N. Y., 1943, Vol. II, p. 1205.

(6) The best method for effecting this conversion of RCHOH—R' to $RCOCH_2CH_2R''$ appears to involve heating of a solution of the alkaloid in 7% acetic acid; v. Miller, Rhode and Fussenegger, *Ber.*, **33**, 3228 (1900).

(7) Rabe and Kubiga, *Ann.*, **364**, 346 (1909); Rabe and Kindler, *Ber.*, **51**, 466 (1918).

(8) Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).

(9) Riley, Morley and Friend, *J. Chem. Soc.*, 1875 (1932).

(10) Astin, Newman and Riley, *ibid.*, 391 (1933).

(11) Adkins and Cox [THIS JOURNAL, **60**, 1151 (1938)] have shown that *p*-benzoquinone possesses a much higher oxidation potential than does acetone.

Cinchotoxine (II) was prepared in very nearly the same manner[12] by refluxing a solution of 15 g. of cinchonine in 200 cc. of 7% acetic acid for seven hours; 14 g. of a brown, uncrystallizable oil, was obtained.

Hydroquinine was secured through hydrogenation at room temperature of 15 g. of anhydrous quinine in 75 cc. of ethyl acetate in the presence of 2 g. of Raney nickel under a hydrogen pressure of about 80 cm. of mercury; the reduction was complete in about twenty minutes. A quantitative yield (15 g.) was obtained of base melting[13] at 170–172°.

Hydrocinchonidine was similarly synthesized using 2 g. of Raney nickel, and 15 g. of anhydrous cinchonidine dissolved in 230 cc. of methanol: reduction was complete in fifteen minutes. After recrystallization there remained 14 g. of hydrocinchonidine which melted[14] at 229–230°.

Hydroquinotoxine (III).—As in the preparation of quinotoxine, 15 g. of hydroquinine was dissolved in 200 cc. of 7% acetic acid and the solution was refluxed for thirty-six hours; 14 g. of thick, brown oil resulted.

Hydrocinchotoxine (IV), (12.5 g. of brown, viscous oil) was obtained similarly from 14 g. of hydrocinchonidine.

Hydroquininone (V) was prepared initially in poor yield by the oxidation of hydroquinine by means of chromic acid. In an attempt to improve the yield, 15 g. of hydroquinine was dissolved in 300 cc. of xylene, and 2.8 g. of freshly prepared selenium dioxide was added slowly, over a period of four hours, to the boiling, well-stirred solution; the heating was continued for thirteen hours. Upon chilling the solution there separated 7 g. of material which proved to be unreacted hydroquinine. The xylene solution was extracted with dilute hydrochloric acid, and to this extract was added a slight excess of sodium hydroxide solution. Gummy material separated, was dried *in vacuo* over sulfuric acid, and dissolved in the least amount of boiling benzene. On chilling this solution, an additional 1 g. of hydroquinine was recovered. Concentration of the benzene filtrate, and addition of low-boiling petroleum ether resulted in precipitation of 3.2 g. (45% yield based on the unrecovered hydroquinine) of hydroquininone. Recrystallization from benzene yielded crystalline material melting[15] at 95–97°.

Preparation of 5-[4-(6-Methoxyquinolyl)]-5-{β-[4-(3-vinylpiperidyl)]ethyl}hydantoin (VI).—In the first attempt to produce this hydantoin, 10 g. of quinotoxine (I), 4 g. of potassium cyanide and 12 g. of ammonium carbonate were dissolved in 150 cc. of 50% alcohol and warmed at 58–60° for twelve hours; at the end of this period it was found that practically all of the quinotoxine could be recovered, apparently unchanged.

Next, the same quantities of the reactants were placed, together with 100 cc. of 95% alcohol, in a glass-lined, monel-metal bomb; the latter was then heated at 110° for twelve hours. Upon opening the container, it was noticed that the potassium cyanide had not dissolved completely in the solvent used, and that a thick, black tar, insoluble in alcohol, acids or alkalies, was present on the bottom of the liner. From this attempt, 1.5 g. of I was recovered.

Finally, 15 g. (0.046 mole) of I, 10 g. (0.15 mole) of potassium cyanide and 33 g. (0.30 mole) of ammonium carbonate were dissolved in 125 cc. of 95% alcohol and sufficient water (10 cc.) was added to bring about complete solution of the cyanide. This mixture was heated in the glass-lined bomb at 110° for twelve hours. The reaction solution was concentrated on a steam-bath to remove excess ammonium salts; then was diluted with water, made strongly alkaline with sodium hydroxide solution, and was extracted with ether to remove unreacted I, of which 3 g. was thus recovered. Despite repeated treatment with norit, the extracted solution remained dark brown in color; enough concentrated hydrochloric acid was added to render the solution strongly acidic, and the mixture was heated to boiling for fifteen minutes to ensure ring closure of any hydantoic acid present. Dilute alkali was then added cautiously until amphoteric material precipitated. The latter appeared to imbibe solvent and, after filtration, shrank, at the same time expressing brownish colored liquid.

It was not found to be suitable to crystallize the product from any available organic solvent; each such attempt invariably resulted in the separation of the material as a gum. The most satisfactory preparation resulted from reprecipitation of the hydantoin, by addition of dilute hydrochloric acid, from a dilute solution of its sodium salt. After filtration, the precipitate was dried, in a desiccator and eventually at 110°, and was ground to a light, buff-colored powder which melted with decomposition at 154–159° (cor.). The yield was 5.1 g. of VI (or 34% of the theoretical amount based on unrecovered ketone).

Anal. Calcd. for $C_{22}H_{26}N_4O_3 \cdot {}^1/_2H_2O$: C, 69.50; H, 6.75; N, 13.89. Found: C, 65.49; H, 6.90; N, 13.69.

No water of hydration is lost on heating the product to 130° under a pressure of 3 mm. The hydantoin is soluble in acetone, dioxane, ethyl alcohol, methanol, dilute solutions of acid and alkali, and is insoluble in water, benzene and ether. An aqueous 2% solution of potassium permanganate is decolorized by addition of this hydantoin.

Sulfur dioxide was passed into a suspension of VI in water until solution was complete; addition of a saturated aqueous solution of picric acid caused precipitation of a solid. All attempts to purify this picrate by crystallization invariably resulted in the formation of a yellow-brown, gummy mass. Consequently, the derivative was washed extensively with distilled water, dried in a desiccator, and finally at 110°. The **picrate** melted with decomposition at 144–148° (cor.).

Anal. Calcd. for $C_{28}H_{29}N_7O_{10}$: C, 54.02; H, 4.69; N, 15.75. Found: C, 53.81; H, 4.75; N, 15.60.

Preparation of 5-[4-(6-Methoxyquinolyl)]-5-{β-[4-(3-ethylpiperidyl)]ethyl}hydantoin (VII).—To a solution of 15 g. (0.046 mole) of hydroquinotoxine in 100 cc. of 95% alcohol was added 10 g. (0.15 mole) of potassium cyanide, 33 g. (0.30 mole) of ammonium carbonate and just sufficient water (10 cc.) to cause complete solution of the cyanide. The mixture was heated in a closed container at 110° for twelve hours. There was recovered from the reaction mixture 2.1 g. of unaltered III, and 7.9 g. (51% yield) of a light-brown powder, which melted with decomposition at 144–147° (cor.).

Anal. Calcd. for $C_{22}H_{28}N_4O_3$: C, 66.64; H, 7.12; N, 14.13. Found: C, 66.49; H, 6.94; N, 13.86.

In contrast to VI, an aqueous 2% potassium permanganate solution is not decolorized by addition of VII. The latter has qualitatively the same solubilities as those listed for the vinyl analog, VI. The isoelectric point of VII was found to lie at a *p*H value of 5.3. From VII a **picrate** was formed and was found to melt with decomposition at 137–142° (cor.).

Anal. Calcd. for $C_{28}H_{31}N_7O_{10}$: C, 53.75; H, 4.98; N, 15.68. Found: C, 53.25; H, 4.79; N, 15.31.

Preparation of 5-(4-Quinolyl)-5-{β-[4-(3-vinylpiperidyl)]ethyl}hydantoin (VIII).—In 100 cc. of 95% alcohol was dissolved 14 g. (0.047 mole) of cinchotoxine, and to this solution was added 10 g. (0.15 mole) of potassium cyanide dissolved in 12 cc. of water, and 30 g. (0.30 mole) of ammonium carbonate. This mixture was heated in a bomb at 110° for twelve hours; then the alcohol and excess cyanide was removed by evaporation. The unreacted ketone was recovered through ether extraction, and the hydantoin was precipitated from solution, by exact neutralization with acid, filtered off, washed thoroughly with water, and dried at 110°. Thus prepared the hydantoin weighed 6 g. (35% yield), and melted with decomposition at 190–195° (cor.). The hydantoin when added to an aqueous 2% solution of potassium permanganate caused decolorization of the latter.

Anal. Calcd. for $C_{21}H_{24}N_4O_2$: C, 69.20; H, 6.63; N, 15.37. Found: C, 68.88; H, 6.68; N, 15.03.

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(12) v. Miller and Rhode, *Ber.*, **28**, 1058 (1895).

(13) Hesse [*Ann.*, **241**, 257 (1887)] reported m. p. 172°.

(14) Hesse, *ibid.*, **214**, 4 (1882); m. p. 230°.

(15) Kaufmann and Huber [*Ber.*, **46**, 2922 (1913)] reported m. p. 98°.

A **picrate** was obtained and melted at 133–137° (cor.) (dec.).

Anal. Calcd. for $C_{27}H_{27}N_7O_9$: C, 54.63; H, 4.59; N, 16.52. Found: C, 54.24; H, 4.62; N, 16.30.

Preparation of 5-(4-Quinolyl)-5-{β-[4-(3-ethylpiperidyl)]ethyl}hydantoin (IX).—From 11 g. (0.037 mole) of hydrocinchotoxine, 10 g. (0.15 mole) of potassium cyanide dissolved in 9 cc. of water, 33 g. (0.30 mole) of ammonium carbonate and 100 cc. of alcohol; there was obtained, after heating at 110° for twelve hours, 3.2 g. (23% yield) of hydantoin as a buff, microcrystalline powder melting with decomposition at 185–191° (cor.).

Anal. Calcd. for $C_{21}H_{26}N_4O_2$: C, 68.83; H, 7.15; N, 15.29. Found: C, 68.51; H, 7.21; N, 15.01.

The **picrate** of IX melted with decomposition at 127–129° (cor.).

Anal. Calcd. for $C_{27}H_{29}N_7O_9$: C, 54.45; H, 4.91; N, 16.47. Found: C, 54.01; H, 4.96; N, 16.35.

Preparation of 5-[4-(6-Methoxyquinolyl)]-5-[4-(3-ethylquinuclidyl)]hydantoin (X).—In the usual manner, X was obtained from interaction of 6.0 g. (0.019 mole) of hydroquinone, 4.5 g. (0.07 mole) of potassium cyanide in 10 cc. of water, 13 g. (0.11 mole) of ammonium carbonate and 100 cc. of alcohol by heating at 110° for twelve hours. Thus was prepared 3.5 g. (48% yield) of light brown powder melting at 166–169° (cor.) (dec.).

Anal. Calcd. for $C_{22}H_{26}N_4O_3$: C, 66.98; H, 6.64; N, 14.20. Found: C, 66.69; H, 6.49; N, 14.06.

The **picrate** of X, a light yellow, rather amorphous solid, melted at 155° (cor.) (dec.).

Anal. Calcd. for $C_{28}H_{29}N_7O_{10}$: C, 53.93; H, 4.69; N, 15.73. Found: C, 53.58; H, 4.77; N, 15.55.

Preparation of 5-[3-(9-Hydroxy-6′-methoxy)-rubanyl]-hydantoin (XII). A. **Ozonolysis**[16] **of Quinine.**—Through a solution made by dissolving 5 g. of quinine in 65 cc. of chloroform and maintained at 0° was bubbled a stream of oxygen containing ozone, produced at a rate of 0.046 g. per hour. After about seven hours a light-brown gum began to appear, and continued to increase in amount until, at the end of fifteen hours, ozone was detectable in the effluent gas. The solvent was removed, by heating under diminished pressure, and the light-brown, powdery residue was suspended in water and stirred for twenty-four hours; during this period the evolution of formaldehyde was evident. The liquid portion was made alkaline by addition of ammonium hydroxide and was decanted from the gummy material. After washing with water, the gum was thoroughly dried *in vacuo* and then dissolved in 800 cc. of boiling benzene. Upon chilling this solution, the product separated as a finely divided, slight yellow powder, melting[17] at 155–158°; the yield was 3.2 g. (64%) of quininal [XI].

B. **Production of the Hydantoin** (XII).—A mixture of 50 cc. of 95% alcohol, 4 g. of potassium cyanide, and just enough water to cause solution of the salt, was placed in a glass-lined container together with 4.3 g. of quininal (XI) and 11 g. of ammonium carbonate; the mixture was heated at 95° for twelve hours. After cooling and opening the container, the reaction solution was neutralized by addition of hydrochloric acid, causing separation of a characteristic, slimy precipitate. The latter was filtered off, dissolved in alcohol, and reprecipitated by addition of water. After filtration, and being dried, the final product (XII) weighed 2.4 g. (46% yield) and melted at 214–220°; additional attempts at purification did not alter or raise this temperature range.

By the customary combustion procedure, the analytical results for carbon in this hydantoin were about 2–3% too low, those for hydrogen were uniformly satisfactory, but for nitrogen, also, were about 2% low. This experience, however, is rather typical of that of analysts of the cinchona bases.[18] As a result of using a mixture of copper oxide and manganese dioxide as the combustion tube filling, by placing a small crystal of potassium chlorate with the sample in the micro-Dumas tube, and by using intensive heating during the combustion the following results were obtained.

Anal. Calcd. for $C_{21}H_{24}N_4O_4$: C, 63.63; H, 6.10; N, 14.13. Found: C, 62.77, 62.79, 62.86; H, 6.01, 6.06, 6.13; N, 13.61, 13.69.

Through the courtesy of Parke, Davis and Company of Detroit, Michigan, to whom we express our appreciation, a preliminary testing for possible pharmacological activity has been made for two of these disubstituted hydantoins. That derived from quinotoxine, namely, VI, showed neither analgesic nor hypnotic effect when administered at 0.15 mg./kg., and no anticonvulsant activity when given to mice via stomach tube at a dosage of 62 mg./kg.; likewise, no antimalarial activity was found in a dosage twenty-five times higher than the therapeutic dose of quinine against avian malaria. Similarly, testing of the "quininal-hydantoin" (XII) showed the M. L. D. to be 0.25 mg./kg. without analgesic or hypnotic effect, and no anticonvulsant activity when 30 mg./kg. was administered by stomach tube; nor was antimalarial activity against *Plasmodium cathemerium* in canaries found at a level of five times the dosage of quinine.

Summary

1. Selenium dioxide has been employed in the oxidation of hydroquinine to hydroquininone.

2. Hydroquininone has been converted into a new type of 5,5-disubstituted hydantoin, namely, that containing quinolyl and quinuclidyl groups.

3. Quinotoxine, hydroquinotoxine, cinchotoxine and hydrocinchotoxine have been converted into derivatives of 5-quinolyl-5-piperidylethylhydantoin.

4. From quininal has been prepared a 5-substituted hydantoin containing the 9-hydroxyrubanyl structure characteristic of the cinchona alkaloids possessing useful antimalarial activity.

5. The hydantoins prepared from quininal and hydroquininone, respectively, have been tested elsewhere and found to be devoid of antimalarial, analgesic, anticonvulsant and hypnotic activity.

AUSTIN, TEXAS RECEIVED AUGUST 21, 1944

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[16] Seekles, *Rec. trav. chim.*, **42**, 69 (1923).

[17] Seekles, ref. 16, reported m. p. 155–160°

[18] Seekles, ref. 16, found it necessary to take into account the residual carbon in the weighing boat, in the case of quininal and cinchoninal analyses, in order to approximate the theoretical percentages of carbon.