[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. XII. SYNTHESIS OF 3-[β-KETO-γ-(3-HYDROXY-2-PIPERIDYL) PROPYL]-4-QUINAZOLONE, THE ALKALOID

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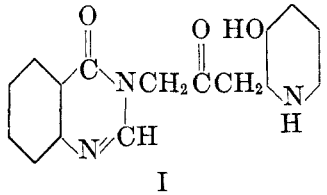
The last major possible structure for the Hydrangea alkaloid (1), 3-[β-keto-γ-(3-hydroxy-2-piperidyl)propyl]-4-quinazolone, I, has now been synthesized *via*



I

3-methoxypiperidine-2-acetic acid and found to be the *dl*-form of the alkaloid.[1, 2]

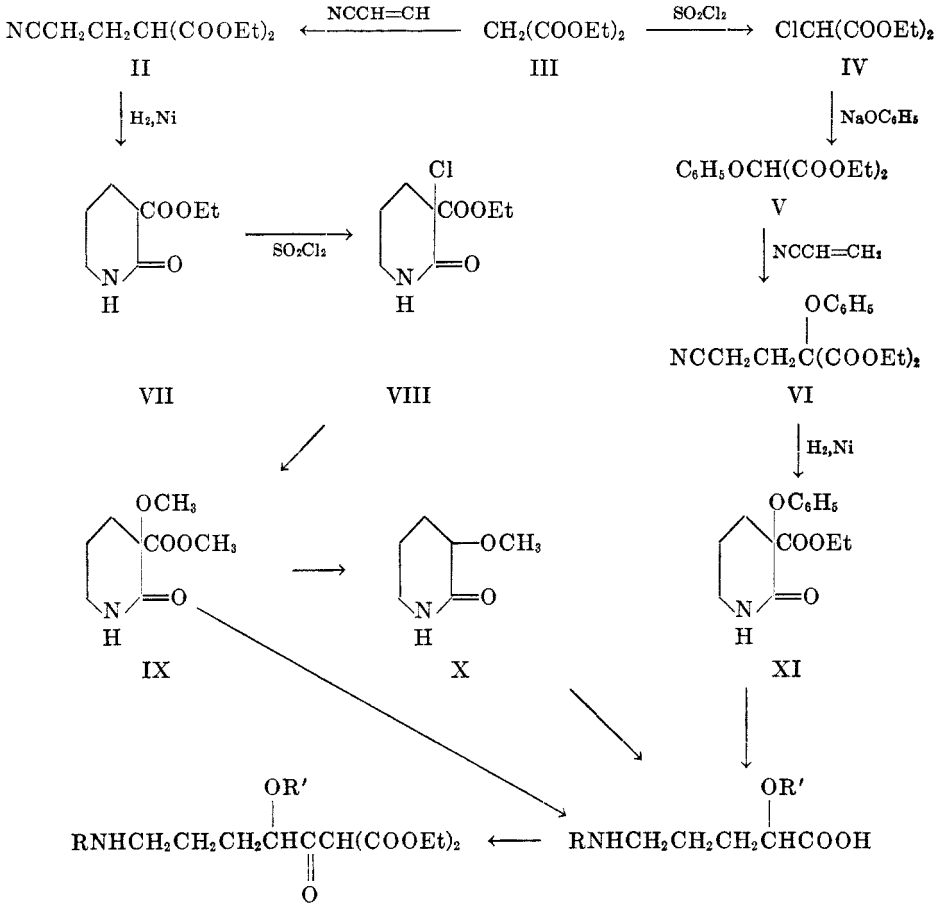
The key type of intermediate necessary for the synthesis of a molecule such as I would be the O, N-derivatives of 2-hydroxy-5-aminovaleric acid. Two different blocking groups on the hydroxyl were investigated, O-methyl and O-phenyl, and three blocking groups on the nitrogen: phthalyl, carbobenzoxy, and carbethoxy.

Ethyl phenoxymalonate (V), prepared by chlorination of ethyl malonate and treatment with sodium phenoxide (4), was condensed with acrylonitrile to give VI in 85% yield. Low pressure catalytic reduction in Diethyl Carbitol at 100° in the presence of Raney nickel caused cyclization to 3-phenoxy-3-carbethoxy-2-piperidone (XI). Hydrolysis and decarboxylation with hot 6 *N* hydrochloric acid resulted in 2-phenoxy-5-aminovaleric acid hydrochloride which was treated with the appropriate acid chloride or anhydride to form XII, XIV, or XVI. The methoxy series was prepared in a somewhat similar method in which some of the steps were reversed. 3-Chloro-3-carbethoxy-2-piperidone (VIII), prepared from ethyl malonate essentially according to the method of Albertson and Fillman (5), when treated with methanolic sodium methoxide formed 3-methoxy-3-carbomethoxy-2-piperidone (IX). This compound, m.p. 80°, could be recrystallized only after distillation. On a larger scale it was found that the losses became progressively higher due to decomposition. This was avoided by hydrolysis and decarboxylation of the crude ester. The resultant 3-methoxy-2-piperidone (X) was distilled more readily. Hydrolysis of either methoxypiperidone (IX or X) to the corresponding 5-aminovaleric acid hydrochloride followed by introduction of the N-blocking group gave XIII or XV.

[1] Koepfli, Brockman, and Moffat (2) have recently proposed this structure for the antimalarial alkaloid, febrifugine, isolated from *Dichroa febrifuga*. Febrifugine and the Hydrangea antimalarial alkaloid have been reported to be identical (3).

[2] The work described in this and the preceding eight papers was presented July 10, 1951 at the University of New Brunswick Summer Seminar on natural products.

The valeric acids (XII–XVI) were only slowly converted to the acid chlorides with thionyl chloride since after one–two hours in boiling ether (containing 0.5%

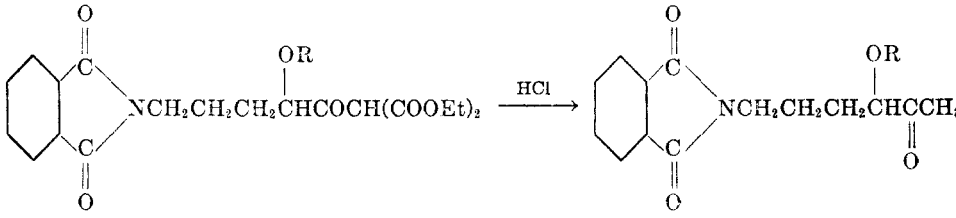


XVII, RNH = phthalimido, R′ = C_6H_5—
XVIII, RNH = phthalimido, R′ = CH_3—
XIX, R = carbobenzoxy, R′ = C_6H_5—
XX, R = carbobenzoxy, R′ = CH_3—
XXI, R = carbethoxy, R′ = C_6H_5—

XII, RNH = phthalimido, R′ = C_6H_5—
XIII, RNH = phthalimido, R′ = CH_3—
XIV, R = carbobenzoxy, R′ = C_6H_5—
XV, R = carbobenzoxy, R′ = CH_3—
XVI, R = carbethoxy, R′ = C_6H_5—

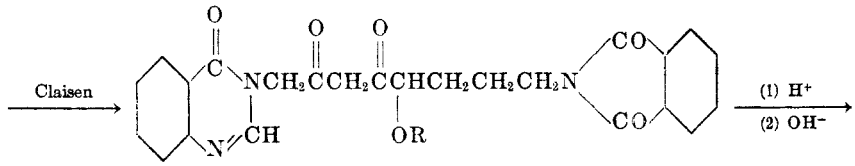
pyridine) the conversion was still incomplete. This contrasts sharply with the corresponding β-methoxyvaleric acid where acid chloride formation was complete in 15 minutes at room temperature (6). The α-alkoxy acid chlorides were condensed with magnesiomalonic ester in the usual manner with formation of the keto malonates, XVII–XXI.

Acid hydrolysis of the phthalimido keto malonates, XVII or XVIII, led to the corresponding phthalimido ketones, XXII, which were Claisen condensed with ethyl 4-quinazolone-3-acetate to the diketones, XXIII, (7). Work on this approach was postponed at this point when the preparation of I *via* the piperidine-2-acetic acid, XXVI, proved successful.



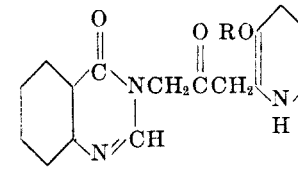
XVII, R = C_6H_5-
XVIII, R = CH_3-

XXII



XXIII

a series, R = C_6H_5-
b series, R = CH_3-

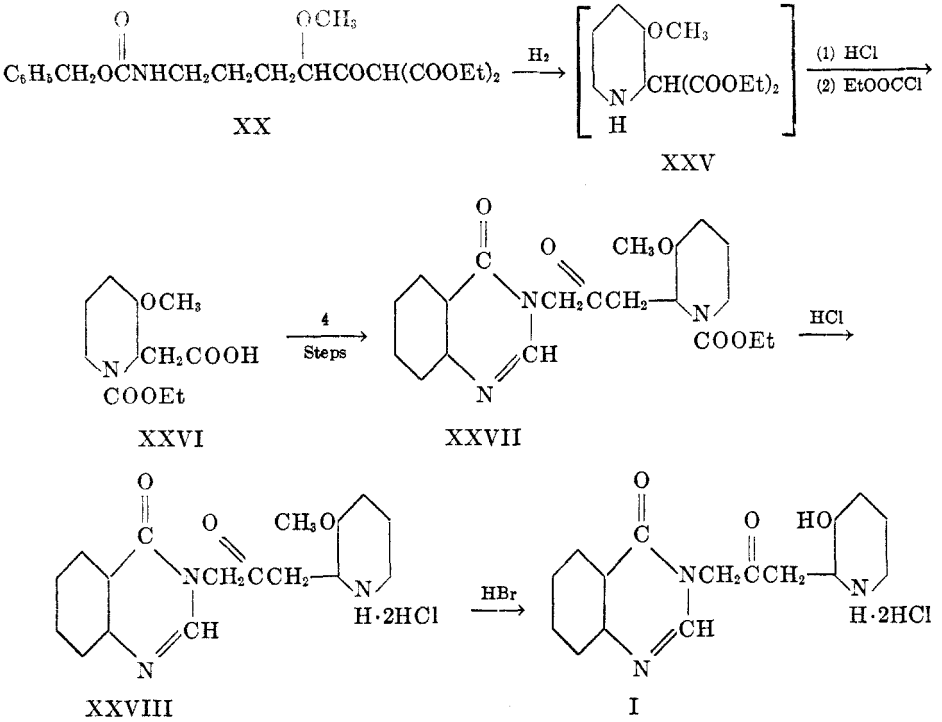


XXIV

Hydrogenation of the carbobenzoxy keto malonate, XX, prepared by the thionyl chloride method, could not be made to take place as usual (8) due to catalyst poisoning by the sulfur compounds. These were not removed by pretreatment with Raney nickel. This difficulty was readily overcome by preparing the acid chloride of XV with phosphorus pentachloride in acetyl chloride. The keto malonate then smoothly hydrogenated to the 2-piperidinemalonic ester, XXV, which was acid-hydrolyzed, then carbethoxylated to the second key intermediate, 1-carbethoxy-3-methoxypiperidine-2-acetic acid (XXVI). Conversion to the acid chloride, diazoketone, and bromoketone followed by condensation with 4-quinazolone gave one isomer of XXVII which readily crystallized, m.p. 138–140°.[3] Direct 48% hydrobromic acid hydrolysis of XXVII to I in the usual manner (8) led to mixtures from which it was difficult to isolate any crystalline

[3] When a phenoxy group was used in place of the methoxy no crystalline product could be isolated at this stage, nor could any crystalline product be obtained after hydrolysis of one or both blocking groups.

products. However, 6 *N* hydrochloric acid gave the methyl ether base, XXVIII, isolated as the dihydrochloride in 35–40% yield under the best conditions found. When this was treated with boiling 48% hydrobromic acid, the *dl*-alkaloid



dihydrochloride, I, could be isolated in 45% yield and was found to be one-half as active an antimalarial as the Hydrangea alkaloid. When this compound was treated with periodate as described by Koepfli, Mead, and Brockman (9) for febrifugine, a compound $C_{16}H_{17}N_3O_3$ was isolated, m.p. 165–167°. This was identical with the compound obtained from the Hydrangea alkaloid as shown by mixed m.p., infrared, and ultraviolet spectra, thus proving the alkaloid to have structure I.

Acknowledgment: The authors are grateful to Miss E. Sherman for the literature searches, Dr. R. Hewitt for the antimalarial assays, W. McEwen and J. Poletto for large scale preparation of some of the early intermediates, and L. Brancone and his staff for the microanalyses and spectra data.

EXPERIMENTAL

Ethyl cyanoethylphenoxymalonate (VI). To 65.7 g. of ethyl phenoxymalonate (4) in 66 cc. of *tert*-butyl alcohol was added 0.6 g. of sodium methoxide and 15.4 cc. of acrylonitrile. The mixture was warmed to 40° when reaction started. In ten minutes the temperature spontaneously reached 69°, then began to drop. At this point the solution was heated on the steam-bath under a condenser for one hour, then acidified with 2 cc. of acetic acid, diluted to about 500 cc. with water, and extracted with two 65-cc. portions of carbon tetrachloride. Distillation gave 67.5 g. (87%) of a nearly colorless oil, b.p. 158° (0.1 mm.).

Anal. Calc'd for $C_{16}H_{19}NO_5$: C, 62.9; H, 6.28; N, 4.58.
Found: C, 62.4; H, 6.66; N, 4.62.

At 35–25° for 16 hours the yield was only 51% and 30% of unchanged malonate was recovered.

3-Phenoxy-3-carbethoxy-2-piperidone (XI). A mixture of 100 g. of VI, 100 cc. of Diethyl Carbitol, and one teaspoon of Raney nickel was shaken with hydrogen at 2–4 atm. and 95–100° in an electrically-heated bottle until reduction was complete (eight hours). The filtered solution was distilled at 10 mm. up to a bath temperature of 145°; yield of residue, 92 g. (106%) which still contained some solvent. For analysis a sample was dried in a high vacuum at 80°.

Anal. Calc'd for $C_{14}H_{17}NO_4$: C, 63.8; H, 6.52; N, 5.32.
Found: C, 63.5; H, 6.92; N, 4.88.

Similarly, 90 g. of ethyl cyanoethylmalonate (II) was reduced at 80–90° (90 minutes). The solvent was removed at 100° *in vacuo* and the hot residue poured into 500 cc. of heptane and cooled at 0° for one hour; yield, 61.2 g. (85%) of 3-carbethoxy-2-piperidone (VII), m.p. 75–78°. Diethyl Cellosolve can also be used as a solvent in which case the yield was 90%.

Albertson and Fillman (5) have described this reduction at 80° and 60 atm. in ethanol. They recorded a yield of 80–93% and m.p. about 75°.

3-Methoxy-3-carbomethoxy-2-piperidone (IX). A solution of 7 g. of sodium methoxide and 20.6 g. of 3-chloro-3-carbethoxy-2-piperidone (VIII) (5) in 100 cc. of methanol was refluxed and stirred on the steam-bath for 90 minutes, acidified with acetic acid, and cooled. The salt was removed and the filtrate evaporated to dryness *in vacuo*. About 20 cc. of water was added and the solution extracted twice with equal volumes of chloroform. The solvent was removed *in vacuo* and the residue (15 g.) distilled. The product was a colorless oil, b.p. 142–150° (0.15 mm.) which soon solidified, m.p. 60–67°; yield, 10.6 g. (57%). Several recrystallizations from benzene-petroleum ether gave white crystals, m.p. 79.5–80°.

Anal. Calc'd for $C_8H_{13}NO_4$: C, 51.3; H, 7.00; N, 7.48.
Found: C, 51.4; H, 7.07; N, 7.66.

In a run ten times the size there was considerable decomposition during the distillation, b.p. 155–160° (1.5 mm.), and the product only partially solidified; yield, 48%.

3-Methoxy-2-piperidone (X). To a solution of 31 g. of crude non-distilled IX in 150 cc. of methanol was added 11.7 g. of potassium hydroxide in 12 cc. of water. The solution was refluxed ten minutes, then acidified with 17.3 cc. of 12 *N* hydrochloric acid with cooling. When the temperature dropped to 20°, the potassium chloride was removed and the filtrate evaporated to dryness *in vacuo* on the steam-bath. The decarboxylation was completed by heating 90 minutes on the steam-bath *in vacuo* or at 140° for eight minutes. Distillation gave 13.8 g. (58% based on VIII) of product, b.p. 112–116° (0.3 mm.), which gradually solidified to a waxy hygroscopic solid. No solvent for recrystallization could be found and although the material was not analytically pure it was satisfactory for the next step.

Anal. Calc'd for $C_6H_{11}NO_2$: C, 55.8; H, 8.59.
Found: C, 54.0; H, 8.93.

The same yield was obtained on a 150-g. scale.

3-Phenoxy-2-piperidone. By hydrolysis of 5 g. of 3-phenoxy-3-carbethoxy-2-piperidone (XI) as described for X there was obtained a solid after decarboxylation at 160°. Recrystallization from benzene-acetone gave 1.6 g. (44%) of a product, m.p. 154°, unchanged by further recrystallization.

Anal. Calc'd for $C_{11}H_{13}NO_2$: C, 69.1; H, 6.87; N, 7.32.
Found: C, 68.9; H, 6.99; N, 7.07.

2-Phenoxy-5-phthalimidovaleric acid (XII). A mixture of 39 g. of 3-carbethoxy-3-phenoxy-2-piperidone (XI) and 128 cc. of 6 *N* hydrochloric acid was refluxed for one hour when carbon dioxide evolution was essentially complete. The solution was evaporated to dryness *in vacuo*. The crude 2-phenoxy-5-aminovaleric acid hydrochloride (35 g.) was heated with 21.6 g. of phthalic anhydride at 190–195° for 50 minutes when water evolution was nearly

complete. The melt, dissolved in ethyl acetate, was washed with water and extracted with excess aqueous sodium bicarbonate. Acidification gave a gum which gradually solidified and was recrystallized from benzene-heptane; yield, 23 g. (48%), m.p. 117–122°. Further recrystallization afforded white crystals, m.p. 122–124°.

Anal. Calc'd for $C_{19}H_{17}NO_5$: C, 67.3; H, 5.06; N, 4.12.
Found: C, 67.7; H, 5.51; N, 4.14.

The *anilide*, prepared in 85% yield, m.p. 119–121°, *via* the acid chloride, was recrystallized from benzene-heptane as white crystals, m.p. 121–123°.

Anal. Calc'd for $C_{25}H_{22}N_2O_4$: C, 72.5; H, 5.31; N, 6.76.
Found: C, 72.1; H, 5.45; N, 7.05.

2-Methoxy-5-phthalimidovaleric acid (XIII). A mixture of 9 g. of distilled 3-methoxy-3-carbomethoxy-2-piperidone (IX, m.p. 60–67°) and 30 cc. of 6 *N* hydrochloric acid was refluxed for one hour, then evaporated to dryness *in vacuo*. The residue was heated with 4.2 g. of anhydrous sodium acetate and 7.6 g. of phthalic anhydride at 190–195° for ten minutes when gas evolution was complete. The cooled mixture was partitioned between ethyl acetate and water. The organic layer was extracted with excess aqueous sodium bicarbonate. Acidification gave an oil which was extracted with ethyl acetate. The extract, washed with water and dried with magnesium sulfate, was evaporated *in vacuo* and the residue crystallized from benzene-heptane; yield, 6.9 g. (49%), m.p. 114–117°. Further recrystallization gave white crystals, m.p. 120–121°.

Anal. Calc'd for $C_{14}H_{15}NO_5$: C, 60.7; H, 5.45; N, 5.05; CH_3O, 11.2.
Found: C, 61.1; H, 5.54; N, 5.04; CH_3O, 10.8.

The *anilide*, prepared in 50% yield, m.p. 110–112°, was further purified by recrystallization from benzene-heptane to give white crystals, m.p. 111–113°.

Anal. Calc'd for $C_{20}H_{20}N_2O_4$: C, 68.2; H, 5.68; N, 7.95.
Found: C, 68.6; H, 5.94; N, 8.15.

2-Phenoxy-5-carbobenzoxyaminovaleric acid (XIV). To a stirred and ice-cooled solution of the crude 2-phenoxy-5-aminovaleric acid hydrochloride from 92 g. of 3-carbethoxy-3-phenoxy-2-piperidone (XI) in 395 cc. of water was added a cold solution of 63 g. of sodium hydroxide in 370 cc. of water. When the temperature returned to 6°, 101 cc. of 70% benzyl chlorocarbonate was added dropwise with stirring at such a rate that the temperature was 7–9° (20 minutes). The mixture was stirred in the ice-bath for an additional 45 minutes, then extracted with ethyl acetate. The bottom layer of the three-layer system was run into dilute hydrochloric acid. Water was added and the middle layer of sodium salt dissolved to give two layers. The lower layer was also run into the dilute acid. The oil was extracted with ethyl acetate. The extract, washed with water, dried with magnesium sulfate, and clarified with Norit, was evaporated to dryness *in vacuo;* yield, 103 g. (90%) of a viscous amber oil.

Similarly, hydrolysis and carbobenzoxylation of 64.2 g. of 3-methoxy-2-piperidone gave 133 g. (96%) of *2-methoxy-5-carbobenzoxyaminovaleric acid* (XV) as an oil which gradually solidified. Recrystallization of a sample from benzene-heptane gave white crystals, m.p. 63–65°.

Anal. Calc'd for $C_{14}H_{19}NO_5$: C, 59.8; H, 6.76; N, 4.98.
Found: C, 59.6; H, 7.02; N, 5.20.

The *anilide* formed white crystals from benzene-heptane, m.p. 78–80°.

Anal. Calc'd for $C_{20}H_{24}N_2O_4$: C, 67.3; H, 6.80; N, 7.87.
Found: C, 67.6; H, 6.82; N, 8.23.

2-Phenoxy-5-carbethoxyaminovaleric acid (XVI). From 94 g. of 3-phenoxy-3-carbethoxy-2-piperidone (XI) by hydrolysis and carbethoxylation with 42 cc. of ethyl chlorocarbonate in 150 cc. of toluene as described for XIV, there was obtained 82 g. (90%) of a viscous oil. It gave an *anilide* as white crystals from benzene-heptane, m.p. 97–98°.

Anal. Calc'd for $C_{20}H_{24}N_2O_4$: C, 67.4; H, 6.74; N, 7.87.
Found: C, 67.6; H, 7.36; N, 8.22.

Ethyl (2-phenoxy-5-phthalimidovaleryl) malonate (XVII). A mixture of 23 g. of 2-phenoxy-5-phthalimidovaleric acid (XII), 46 cc. of reagent ether (containing 0.5% pyridine), and 23

cc. of thionyl chloride was refluxed on the steam-bath for one hour when gas evolution was essentially complete, then evaporated *in vacuo* (bath 50°). The evaporation was repeated after the addition of 80 cc. of benzene. The residual acid chloride was condensed with ethyl magnesiomalonate in toluene in the usual manner (6). The mixture remaining after evaporation of the toluene was distilled at 1 mm. up to a bath temperature of 120°. The oily residue, sufficiently pure for the next step, weighed 28.5 g. (87%) and gave a red ferric chloride test.

Similarly, from 5.9 g. of 2-methoxy-5-phthalimidovaleric acid (XIII) there was obtained 7.1 g. (80%) of *ethyl (2-methoxy-5-phthalimidovaleryl) malonate* (XVIII) as an oil which gave a red ferric chloride test.

Ethyl (2-methoxy-5-carbobenzoxyaminovaleryl)malonate (XX). To a solution of 83 g. of 2-methoxy-5-carbobenzoxyaminovaleric acid (XV) in 200 cc. of acetyl chloride was added 67 g. of phosphorus pentachloride in portions over seven minutes. Hydrogen chloride was evolved and the reaction was slightly exothermic. After standing for 23 minutes more, the solution was evaporated *in vacuo* (bath 50°). After the addition of 200 cc. of toluene, the evaporation was repeated. The residual acid chloride, dissolved in 200 cc. of toluene, was condensed with 140 cc. of ethyl malonate and 66 g. of magnesium methoxide in 300 cc. of toluene as previously described (6). The product was isolated by cold alkaline extraction; yield, 60 g. (48%) of a light brown oil which gave a red ferric chloride test.

Anal. Calc'd for $C_{21}H_{29}NO_8$: C, 59.6; H, 6.86; N, 3.32.
Found: C, 58.9; H, 7.04; N, 3.43.

In subsequent runs the yields were 53–56%.

Similarly, from 101 g. of 2-phenoxy-5-carbobenzoxyaminovaleric acid (XIV) there was obtained 91.8 g. (64%) of *ethyl (2-phenoxy-5-carbobenzoxyaminovaleryl)malonate* (XIX) as an oil which gave a red ferric chloride test.

Anal. Calc'd for $C_{26}H_{31}NO_8$: C, 64.3; H, 6.40; N, 2.88.
Found: C, 63.6; H, 6.50; N, 2.94.

From 40 g. of 2-phenoxy-5-carbethoxyaminovaleric acid (XVI) in the same manner there was obtained 35.2 g. (59%) of *ethyl (2-phenoxy-5-carbethoxyaminovaleryl)malonate* (XXI) as an oil which also gave a red ferric chloride test.

Anal. Calc'd for $C_{21}H_{29}NO_8$: C, 59.6; H, 6.86; N, 3.32.
Found: C, 60.3; H, 7.18; N, 3.62.

1-Phthalimido-4-phenoxy-5-hexanone (XXIIa). A mixture of 18 g. of the keto malonate, XVII, and 180 cc. of 6 *N* hydrochloric acid was refluxed for six hours when gas evolution became slow. The cooled mixture was extracted twice with benzene. The combined extracts, washed with aqueous sodium bicarbonate and water, were evaporated *in vacuo;* yield, 10 g. (80%) of an oil which soon solidified. Recrystallization from methanol gave white crystals, m.p. 97–98°.

Anal. Calc'd for $C_{20}H_{19}NO_4$: C, 71.3; H, 5.64; N, 4.15.
Found: C, 71.5; H, 6.05; N, 4.42.

The *2,4-dinitrophenylhydrazone*, prepared in 91% yield from the crude ketone, formed yellow crystals from Methyl Cellosolve, m.p. 140–141°.

Anal. Calc'd for $C_{26}H_{23}N_5O_7$: C, 60.3; H, 4.45; N, 13.5.
Found: C, 60.0; H, 4.91; N, 13.5.

1-Phthalimido-4-methoxy-5-hexanone (XXIIb). A mixture of 7.1 g. of the keto malonate, XVIII, and 70 cc. of 6 *N* hydrochloric acid was refluxed for two hours, then worked up as in the previous experiment; yield, 2.1 g. (45%) of an oil which gave a negative ferric chloride test. The *2,4-dinitrophenylhydrazone* formed in 31% yield, m.p. 230–235° dec. No solvent for recrystallization could be found.

Anal. Calc'd for $C_{21}H_{20}N_5O_7$: C, 55.4; H, 4.62; N, 15.4.
Found: C, 54.4; H, 4.49; N, 16.1.

3-(2,4-Diketo-5-phenoxy-3-phthalimidooctyl)-4-quinazolone (XXIIIa). To a solution of 2.6 g. of 1-phthalimido-4-phenoxy-5-hexanone (XXIIa) and 2.1 g. of ethyl 4-quinazolone-

3-acetate (11) in 26 cc. of benzene and 1.7 cc. of absolute alcohol was added 0.56 g. of sodium methoxide. The solution was refluxed on the steam-bath for one hour, acidified with 1.2 cc. of acetic acid, diluted with ethyl acetate, washed with water, and evaporated *in vacuo*. The residual oil, which gave a red ferric chloride test, was dissolved in 48 cc. of alcohol and treated with 8 cc. of 10% cupric acetate. The *green copper salt* was collected and washed with 80% alcohol; yield, 1.9 g. (44%), m.p. 140–145° dec.

Anal. Calc'd for $C_{60}H_{48}CuN_6O_{12}$: N, 7.59; Cu, 5.78.

Found: N, 7.75; Cu, 5.43.

1-Carbethoxy-3-methoxypiperidine-2-acetic acid (XXVI). A solution of 25 g. of ethyl (2-methoxy-5-carbobenzoxyaminovaleryl)malonate (XX) in 100 cc. of acetic acid was hydrogenated in the presence of 5 g. of 10% palladium-charcoal and 0.5 g. of platinum oxide, then hydrolyzed as described for ethyl (5-carbobenzoxyaminovaleryl)malonate (8). A total of 53% of two mole-equivalents of hydrogen was absorbed.

The crude 3-methoxy-2-piperidineacetic acid hydrochloride was dissolved in 42 cc. of water and 74 cc. of 10% sodium hydroxide, then cooled in an ice-bath. A solution of 6.2 cc. of ethyl chlorocarbonate in 30 cc. of toluene was added dropwise with stirring over a period of ten minutes at 5–7°. After being stirred 15 minutes more, the mixture was treated with 50 cc. of 10% sodium hydroxide, then dropwise with 6.2 cc. of ethyl chlorocarbonate in 30 cc. of toluene. The solution was stirred one hour more in the ice-bath, then extracted with ethyl acetate. The aqueous layer was acidified and extracted three times with chloroform. Evaporation of the combined extracts *in vacuo* gave 5.3 g. (37%) of an oil.

Anal. Calc'd for $C_{11}H_{19}NO_5$: N, 5.71. Found: N, 6.28.

In larger runs (120 g.) the yield increased to 52–55%.

Similarly, reduction of 45 g. of the phenoxy keto malonate, XIX, gave 7.2 g. (25%) of *1-carbethoxy-3-phenoxypiperidine-2-acetic acid* as an oil.

Anal. Calc'd for $C_{16}H_{21}NO_5$: N, 4.56. Found: N, 4.39.

1-Carbethoxy-2-(γ-bromoacetonyl)-3-methoxypiperidine. By conversion of 5.3 g. of XXVI to the acid chloride, diazoketone, and bromoketone in the usual manner as described for 1-benzoyl-2-piperidineacetic acid (10) except that the diazomethane step was allowed to proceed for 16 hours, there was obtained 5.1 g. (73%) of an oil.

3-[β-Keto-γ-(1-carbethoxy-3-methoxy-2-piperidyl)propyl]-4-quinazolone (XXVII). Condensation of 2.15 g. of 4-quinazolone in 15 cc. of 1 *N* sodium methoxide with 5.1 g. of 1-carbethoxy-2-(γ-bromoacetonyl)-3-methoxypiperidine in 51 cc. of methanol as described for 1-benzoyl-2-(γ-bromoacetonyl)piperidine (10) there was obtained 4.6 g. of a crude base. Crystallization from benzene-heptane gave 2.3 g. (38%) of product, m.p. 137–139°. Recrystallization from the same solvents afforded white crystals, m.p. 138–140°.

Anal. Calc'd for $C_{20}H_{25}N_3O_5$: C, 62.0; H, 6.46; N, 10.9; CH_3O, 16.0.

Found: C, 62.1; H, 6.76; N, 10.9; CH_3O, 16.8.

3-[β-Keto-γ-(3-methoxy-2-piperidyl)propyl]-4-quinazolone dihydrochloride (XXVIII). A solution of 1.00 g. of XXVII in 20 cc. of 6 *N* hydrochloric acid was refluxed for four hours, then evaporated to dryness *in vacuo*. Crystallization from absolute alcoholic hydrogen chloride gave 380 mg. (35%) of a product, m.p. 195–198° dec. with softening at 168°. Recrystallization from methanol by the addition of absolute alcoholic hydrogen chloride afforded white crystals, m.p. 155–159° dec. This compound is hydrated and the extent of hydration may vary.

Anal. Calc'd for $C_{17}H_{21}N_3O_3 \cdot 2HCl \cdot 2H_2O$: C, 48.2; H, 6.42; N, 9.92; CH_3O, 7.32.

Found: C, 48.3; H, 6.41; N, 10.2; CH_3O, 7.54.

The low yield appeared to be due to the acid instability of the starting material rather than the product, since the latter could be recovered in 70% yield when refluxed four hours in 6 *N* hydrochloric acid.

3-[β-Keto-γ-(3-hydroxy-2-piperidyl)propyl]-4-quinazolone dihydrochloride (I). A solution of 125 mg. of XXVIII in 5 cc. of 48% hydrobromic acid was refluxed for 13 minutes, then evaporated to dryness *in vacuo*. The residue was dissolved in 3 cc. of absolute alcohol and

the evaporation repeated. Crystallization from absolute alcohol saturated with hydrogen chloride gave 50 mg. (45%) of white crystals, m.p. 203° dec. Recrystallization from methanol by the addition of absolute alcoholic hydrogen chloride raised the m.p. to 204° dec.

Anal. Calc'd for $C_{16}H_{19}N_3O_3 \cdot 2HCl \cdot H_2O$: C, 49.2; H, 5.93; N, 10.7; CH_3O, 0.0.
Found: C, 49.6; H, 6.24; N, 10.4; CH_3O, 0.4.

This compound was one-half as active an antimalarial as the optically-active Hydrangea alkaloid.

With potassium cyanate in water a *carbamyl derivative*, m.p. 216–217°, was obtained.

Anal. Calc'd for $C_{17}H_{20}N_4O_4 \cdot 1H_2O$: C, 56.3; H, 6.12; N, 15.5.
Found: C, 56.6; H, 5.90; N, 15.7.

Treatment of I with periodate as described by Koepfli, Mead, and Brockman (9) gave white crystals, m.p. 165–167°. Admixture with the periodate oxidation product of the alkaloid, $C_{16}H_{17}N_3O_3$, m.p. 163–165°, gave no depression in m.p. The identity of the two compounds was further demonstrated by their identical infrared and ultraviolet absorption spectra.

SUMMARY

3-[β-Keto-γ-(3-hydroxy-2-piperidyl) propyl]-4-quinazolone (I), synthesized *via* the key intermediates 2-methoxy-5-carbobenzoxyaminovaleric acid and 1-carbethoxy-3-methoxy-2-piperidineacetic acid, has been demonstrated to be the *dl*-form of the Hydrangea antimalarial alkaloid.

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