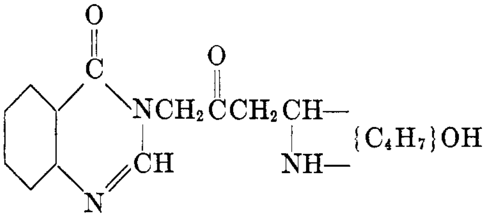
[Contribution from the Lederle Laboratories Division American Cyanamid Co.]

AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. VII. 3-[β-KETO-γ-(5-HYDROXY-2-PIPERIDYL)PROPYL]-4-QUINAZOLONE, AN ISOMER

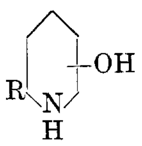
B. R. BAKER, MERLE V. QUERRY, RALPH POLLIKOFF, ROBERT E. SCHAUB, and JAMES H. WILLIAMS

Received September 27, 1951

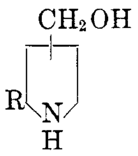
Degradation of the Hydrangea alkaloid (1) led to the partial structure I. Since the alkaloid has no C-methyl group and no double bond there are five major possible structures for the C_5 remainder of the side chain, II–VI. The diketone synthesis (2) has now been successfully applied for the synthesis of the 5-hydroxypiperidine structure (IV). This compound was not the Hydrangea alkaloid since it was inactive as an antimalarial at five hundred times the dose required for the alkaloid.



I



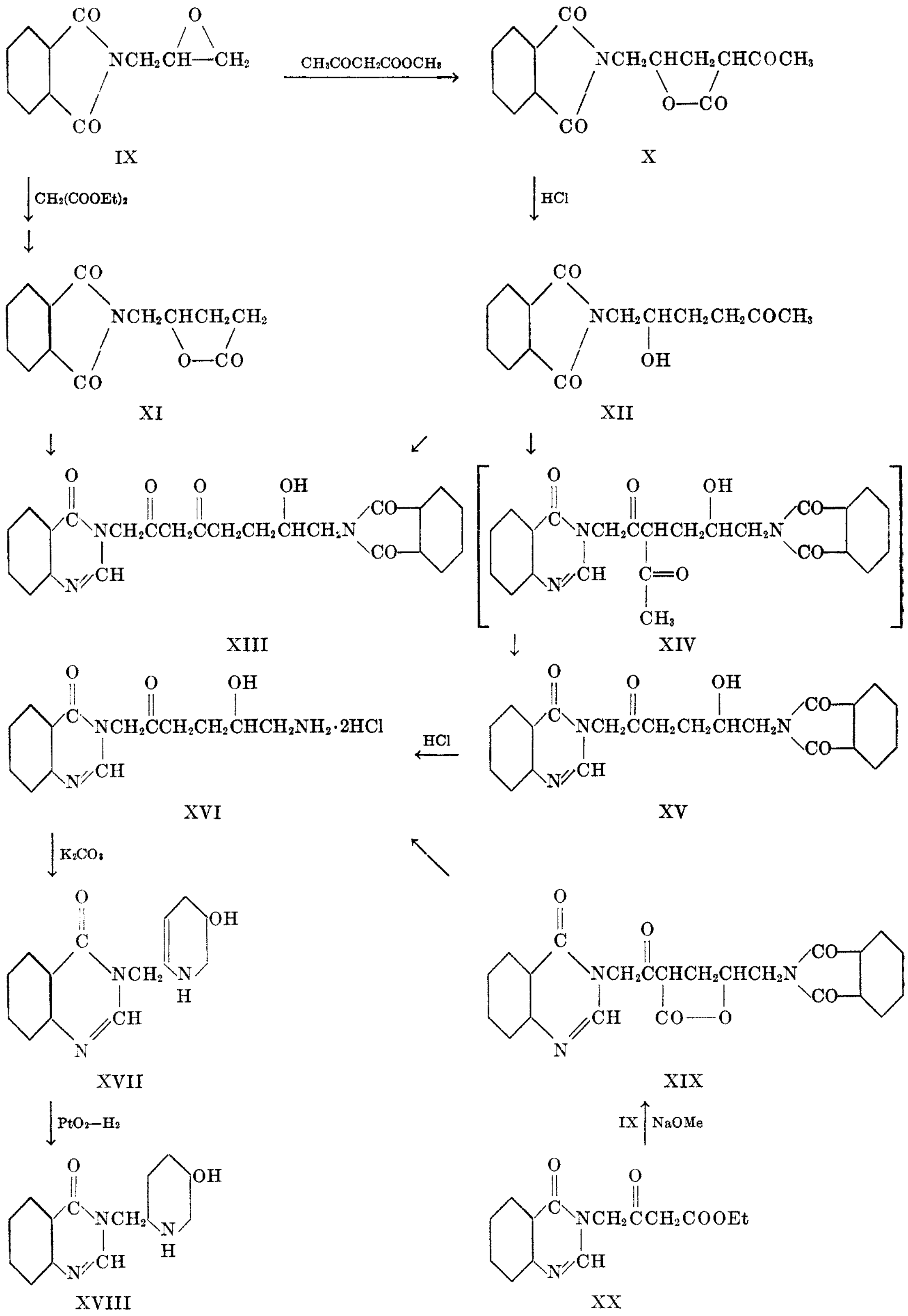
II, *3*-OH
III, *4*-OH
IV, *5*-OH



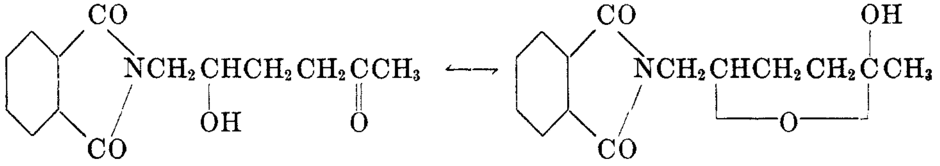
V, *3*-CH_2OH
VI, *4*-CH_2OH

Condensation of epoxypropylphthalimide (IX) with methyl acetoacetate resulted in the keto lactone, X, isolated as the copper derivative. Mild hydrolysis formed the crystalline hydroxy ketone, XII. Claisen condensation of the latter with ethyl 4-quinazolone-3-acetate did not lead to the expected diketone, XIII, but gave a product which had lost the elements of C_2H_2O. The most logical explanation seemed to be that the methylene group of the hydroxy ketone, XII, rather than the methyl group, condensed with the ester to form XIV which could be cleaved to the ketone, XV, by the alcohol present in the reaction mixture. Hydrolysis of the imide, XV, gave an amino ketone hydrochloride (XVI) which immediately cyclized to XVII when treated with aqueous potassium carbonate. The double bond was readily hydrogenated in neutral solution in the presence of Adams' catalyst. The crystalline product, XVIII, was a mixture of *cis* and *trans* isomers.

The structure of the anomalous Claisen condensation to XV was proven by an unequivocal synthesis of the amino ketone, XVI, by condensation of epoxypropylphthalimide (IX) with ethyl (4-quinazolone-3-acetyl)acetate (XX) to the lactone, XIX, followed by hydrolysis and decarboxylation. The two amino ketone hydrochlorides (XVI) were identical as were the cyclization products (XVII).


IX
CH₃COCH₂COOCH₃
X
CH₂(COOEt)₂
HCl
XI
XII
XIII
XIV
HCl
XVI
XV
K₂CO₃
XVII
XIX
PtO₂—H₂
IX
NaOMe
XVIII
XX

The anomalous Claisen condensation on the methylene group adjacent to the ketone, rather than on the methyl group, is entirely unexpected in view of the classical work of Morgan and his co-workers (3). They demonstrated that only the methyl group took part in the reaction and that a dimethylene ketone failed to react to any appreciable extent. Since the Claisen condensation proceeds normally with XII when the hydroxyl group is not present (2), the anomalous reaction is most probably due to the position of the hydroxyl group which is favorable for furanoside formation (XXI). A study of various conditions for the Claisen condensation led either to no reaction or to the abnormal ketone, XV, and an attempted Claisen condensation between γ-phthalimidomethylbutyrolactone (XI) and 3-acetonyl-4-quinazolone to form the diketone, XIII, did not take place.



XII

XXI

The difficulty caused by the hydroxyl group should be circumventable by blocking the hydroxyl group as a methyl ether. Allylphthalimide (XXII) condensed rapidly with mercuric acetate in methanol to XXIII (4). The latter on treatment with potassium iodide was converted to the iodomercury intermediate which with iodine gave N-(2-methoxy-3-iodopropyl)phthalimide (XXIV). It was not necessary to isolate the intermediates and allylphthalimide (XXII) could be converted to XXIV in the same reaction mixture in 70–75% over-all yield.[1] The iodo compound (XXIV) was condensed with acetoacetic ester and on mild acid hydrolysis the crude ketone, XXV, was obtained. This contained considerable non-ketonic material and the ketone was purified *via* its sodium bisulfite addition compound with quantitative recovery of the ketone present.

Attempts to Claisen condense the phthalimido ketone, XXV, with ethyl 4-quinazolone-3-acetate were unpromising. However, when the phthalyl group was replaced with a benzoyl blocking group (XXVI), the Claisen condensation to the diketone, XXVII, isolated as the copper salt, proceeded smoothly. Hydrochloric acid hydrolysis and ring closure by basification resulted in the demethylated product, XXVIII, in 15% yield. The best conditions found after considerable study was 9 *N* sulfuric acid hydrolysis, ring closure, and demethylation with 48% hydrobromic acid giving 45–56% yields of XXVIII. Hydrogenation of the double bond in 6 *N* hydrochloric acid solution led to the desired compound, V, in 50–55% yield.

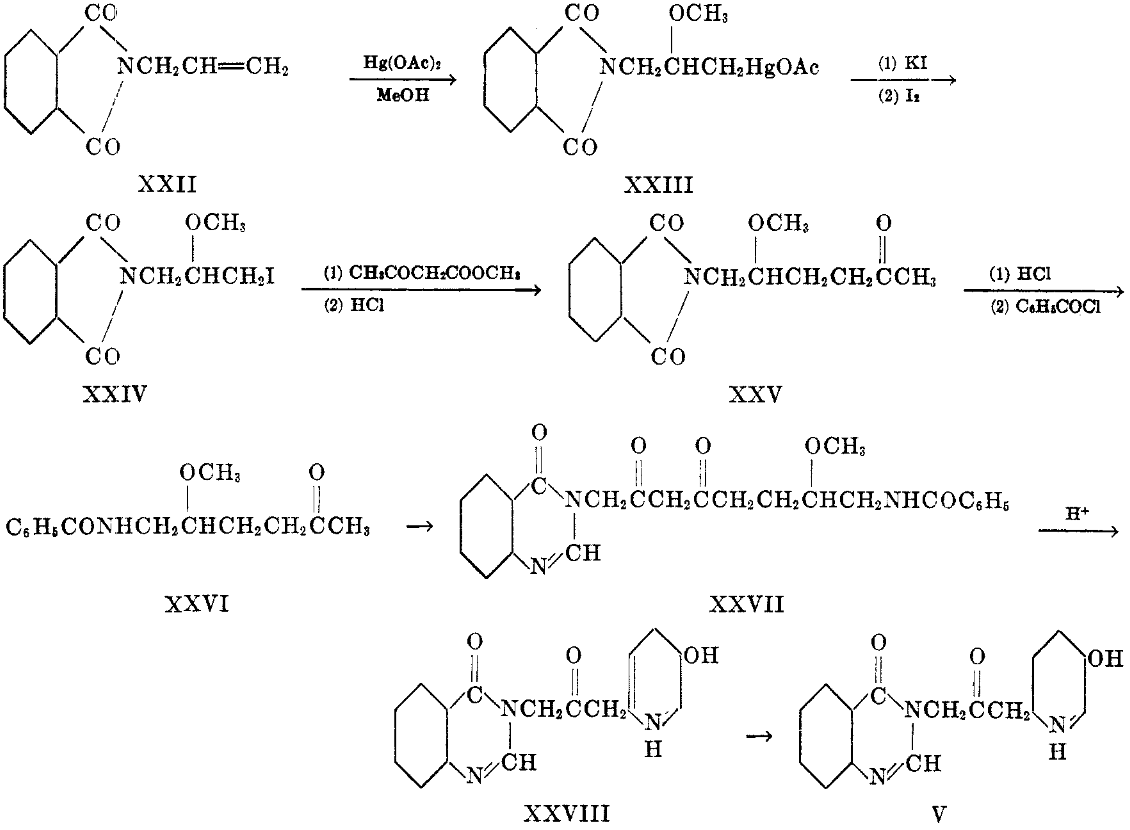
The piperideine, XXVIII, had the same u.v. spectra as the corresponding desoxy compound (2) and again there was no hydrogen absorbed on attempted

---

[1] Pearson, Sigal, and Krug (6) have since described the preparation of this compound from allylphthalimide, but not without isolation of the intermediates.

catalytic reduction in neutral solution. The ease of reduction of a similar compound without the carbonyl group, XVII, indicates that the ketone is also part of the stable resonating system in neutral solution (2).

Since there are three possible sites of hydrogenation in the piperideine, XXVIII, namely: the double bond, the carbonyl, and the 1,2-position of the 4-quinazolone nucleus, it was necessary to prove the structure of the product.



(a) The u.v. spectra in 0.1 *N* acid and base were that of a typical 3-alkyl-4-quinazolone (5), proving that the piperideine double bond had been reduced and the 1,2-position of the 4-quinazolone had not.

(b) The ketone group was still present as shown by ammonia evolution when heated with dilute base (5).

Acknowledgement. The authors are grateful to Mr. L. Brancone and staff for the microanalyses and u.v. data and to Miss E. Sherman for certain literature searches.

EXPERIMENTAL

1-Aceto-5-phthalimido-4-valerolactone (X). To 211 g. of crude epoxyprophylphthalimide, obtained in 96% yield, m.p. 80–85° (7), was added a solution of 74 g. of sodium methoxide and 137 cc. of methyl acetoacetate in 1050 cc. of methanol. The mixture was refluxed for 2½ hours after solution took place (15 minutes). The solution was acidified with 100 cc. of acetic acid, diluted with 4 l. of water, and extracted with ethyl acetate. The extract was washed with water, then stirred with 2 l. of 10% aqueous cupric acetate for 30 minutes. The green copper derivative was collected and washed with alcohol until the washings were colorless; yield, 113 g. (34%). The use of purified epoxypropylphthalimide (7) gave the same yield. When the reaction was run at 25° for 16 hours the yield was also the same. The yield could be raised to 41% by using *tert*-butyl alcohol at the b.p. instead of methanol. A preparation, m.p. 278° dec., was analyzed.

Anal. Calc'd for $C_{30}H_{24}CuN_2O_{10}$: C, 56.7; H, 3.81; N, 4.41; Cu, 9.88.

Found: C, 56.8; H, 4.38; N, 4.44; Cu, 9.49.

A mixture of 113 g. of the copper derivative, 270 cc. of 4 *N* hydrochloric acid, 90 cc. of alcohol, 150 cc. of ethyl acetate, and 150 cc. of benzene was shaken until solution was complete, then diluted with 500 cc. of water and the organic layer separated. The aqueous phase was extracted once more with ethyl acetate. The combined extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo* giving 101 g. (99% recovery) of lactone suitable for the next step. Recrystallization of a sample from benzene-heptane gave white crystals, m.p. 108–110°, which gave a negative ferric chloride test.

Anal. Calc'd for $C_{15}H_{13}NO_5$: C, 62.7; H, 4.57; N, 4.87.

Found: C, 63.0; H, 4.88; N, 5.05.

1-Phthalimido-2-hydroxy-5-hexanone (XII). A mixture of 17 g. of the lactone, X, 85 cc. of 3 *N* hydrochloric acid, and 42 cc. of alcohol was refluxed for 30 minutes when gas evolution was essentially complete. The solution was diluted to about 500 cc. with water and extracted with ethyl acetate. The extract, washed with water, was evaporated to dryness *in vacuo* and the residue recrystallized from benzene-heptane; yield, 8.2 g. (53%), m.p. 95–99°. Further recrystallization from benzene-heptane gave white rosettes, m.p. 102–103°.

Anal. Calc'd for $C_{14}H_{15}NO_4$: C, 64.3; H, 5.78; N, 5.37.

Found: C, 64.2; H, 6.34; N, 5.29.

2-Carboxy-5-phthalimido-4-valerolactone. A mixture of 10 g. of 2-carbethoxy-5-phthalimido-4-valerolactone (8), 25 cc. of alcohol, and 50 cc. of 3 *N* hydrochloric acid was refluxed for 35 minutes. There was no appreciable carbon dioxide evolution. The solution was concentrated *in vacuo* to about 25 cc. and the oil extracted with ethyl acetate. The extract was back extracted with aqueous sodium bicarbonate, and the latter extract was added to the original aqueous solution and acidified if necessary. The mixture was concentrated *in vacuo* to remove dissolved ethyl acetate, then it was cooled in an ice-bath. The oil gradually solidified on rubbing; yield, 3.9 g. (40%) of white crystals, m.p. 171–172° dec. The m.p. was not raised after recrystallization from absolute alcohol-heptane.

Anal. Calc'd for $C_{14}H_{11}NO_6$: C, 58.2; H, 3.84; N, 4.84.

Found: C, 58.2; H, 4.53; N, 4.95.

From the ethyl acetate solution of neutral material was recovered 2.6 g. (26%) of starting material.

5-Phthalimido-4-valerolactone (XI). 2-Carboxy-5-phthalimido-4-valerolactone (3.5 g.) was heated in a bath at 180–190° for ten minutes when carbon dioxide evolution was complete. To the still hot melt was added about 20 cc. of alcohol. The product rapidly crystallized; yield, 2.9 g. (97%), m.p. 158–161°. Recrystallization from alcohol gave white crystals, m.p. 161–164°.

Anal. Calc'd for $C_{13}H_{11}NO_4$: C, 63.7; H, 4.52; N, 5.72.

Found: C, 63.6; H, 4.95; N, 5.59.

3-(2-Keto-5-hydroxy-6-phthalimidohexyl)-4-quinazolone (XV). (*A*). To a solution of 6.1 g. of the hydroxy ketone, XII, and 6.4 g. of ethyl 4-quinazolone-3-acetate (2) in 61 cc. of benzene and 4.9 cc. of absolute alcohol was added 1.7 g. of sodium methoxide. The solution was refluxed for 45 minutes, acidified with 3.4 cc. of acetic acid, cooled to 25°, and shaken with 25 cc. of 6 *N* hydrochloric acid. The crude hydrochloride of XV was collected and washed successively with benzene, 6 *N* hydrochloric acid, and ethyl acetate; yield, 7 g. (68%), m.p.

192–195° dec. with shrinking at 155°. This material was suitable for the next step, but could not be further purified.

A number of runs under various conditions were made, but only slight ferric chloride tests were obtained and no copper derivative could be isolated, indicating no diketone, XIII, had been formed.

(*B*). A solution of 1.0 g. of XII and 1.1 g. of ethyl 4-quinazolone-3-acetate in 4 cc. of 1 *N* methanolic sodium methoxide was refluxed for one hour. The red-brown solution was acidified with acetic acid and on standing deposited 0.55 g. (35%) of XV, m.p. 215–217°. Recrystallization from Methyl Cellosolve gave white crystals, m.p. 224–225°.

Anal. Calc'd for $C_{22}H_{19}N_3O_5$: C, 65.2; H, 4.73; N, 10.4.

Found: C, 64.9; H, 4.97; N, 10.1.

2-(4-Quinazolone-3-acetyl)-5-phthalimido-4-valerolactone (XIX). To a warm solution of 500 mg. of ethyl γ-(4-quinazolone-3-)acetoacetate (XX) (9) in 3.15 cc. of methanol and 1.85 cc. of 1 *N* methanolic sodium methoxide was added 420 mg. of epoxypropylphthalimide (7). After being refluxed for one hour, the solution was acidified with acetic acid, diluted with 15 cc. of water, and shaken with 5 cc. of ethyl acetate. The product gradually separated from the two-phase system; yield, 150 mg. (19%), m.p. 206–208°. Recrystallization from Methyl Cellosolve-water gave hydrated crystals, m.p. 209–210° with sintering at 201°.

Anal. Calc'd for $C_{23}H_{17}N_3O_6 \cdot \frac{1}{2}H_2O$: C, 62.7; H, 4.12; N, 9.55.

Found: C, 62.5, 62.3; H, 4.48, 4.33; N, 10.0.

3-(2-Keto-5-hydroxy-6-aminohexyl)-4-quinazolone dihydrochloride (XVI). (*A*). A mixture of 26.4 g. of crude XV hydrochloride (prepared by method *A*) and 264 cc. of 6 *N* hydrochloric acid was refluxed for four hours, cooled, filtered from phthalic acid, and evaporated to dryness *in vacuo*. Trituration with absolute alcoholic hydrogen chloride gave 14.4 g. (71%) of product, m.p. 190–194° dec. No suitable solvents for recrystallization could be found. A similar preparation, m.p. 195–198° dec., was analyzed.

Anal. Calc'd for $C_{14}H_{17}N_3O_3 \cdot 2HCl$: C, 48.2; H, 5.51; N, 12.1; Cl, 20.4.

Found (corr. for 1.1% ash): C, 48.1; H, 6.13; N, 12.1, 12.3; Cl, 20.5.

(*B*). A solution of 440 mg. of the lactone, XIX, in 8.8 cc. of 6 *N* hydrochloric acid was refluxed for four hours and worked up as in part *A*; yield, 250 mg. (70%), m.p. and mixed m.p. with preparation *A*, 197–198° dec.

3-(5-Hydroxy-1,4,5,6-tetrahydro-2-pyridylmethyl)-4-quinazolone (XVII). To a solution of 14.2 g. of the preceding dihydrochloride, XVI, (prepared by method *A*) in 28 cc. of water was added 140 cc. of chloroform followed by potassium carbonate until potassium chloride began to separate. The chloroform layer was separated and the aqueous phase extracted with three 70-cc. portions of chloroform. The combined extracts were warmed to about 50°, dried with magnesium sulfate, and then evaporated to dryness *in vacuo*. The solid residue was heated to boiling with 150 cc. of ethyl acetate. The mixture was cooled in an ice-bath. The product was removed by filtration and washed with ethyl acetate; yield, 8.6 g. (78%), m.p. 171–172°. Recrystallization from alcohol-ethyl acetate gave white crystals, m.p. 172–174°.

Anal. Calc'd for $C_{14}H_{15}N_3O_2$: C, 65.3; H, 5.87; N, 16.3.

Found: C, 65.5; H, 5.97; N, 16.2, 16.3.

The *dihydrochloride* was prepared by solution in absolute alcohol and addition of alcoholic hydrogen chloride followed by acetone to turbidity: white prisms, m.p. 213–214° dec.

Anal. Calc'd for $C_{14}H_{15}N_3O_2 \cdot 2HCl$: C, 50.8; H, 5.18; N, 12.7; Cl, 21.5.

Found: C, 50.8; H, 5.66; N, 12.7; Cl, 21.1.

The *dipicrate* formed yellow crystals from alcohol, m.p. 214° dec.

Cyclization of 240 mg. of XVI, prepared by method *B*, in the same manner gave 140 mg. (81%) of product, m.p. 169–171°. There was no depression in m.p. on admixture with the preceding free base.

3-(5-Hydroxy-2-piperidylmethyl)-4-quinazolone (XVIII) *and dihydrochloride.* A mixture of 2.0 g. of XVII and 50 cc. of methanol was shaken with hydrogen at atmospheric pressure in the presence of 100 mg. of platinum oxide. One mole-equivalent of hydrogen was absorbed in 30 minutes and the reduction became slow. The filtered solution was evaporated to dryness *in vacuo*. The residue was crystallized as the dihydrochloride by solution in hot absolute alcoholic hydrogen chloride and addition of acetone to incipient turbidity; yield, 1.95 g. (78%), m.p. 173–175° dec. Recrystallization from methanol by the addition of alcoholic hydrogen chloride gave white crystals, m.p. 175–177° dec.

Anal. Calc'd for $C_{14}H_{17}N_3O_2 \cdot 2HCl \cdot H_2O$: C, 47.9; H, 6.06; N, 12.0.
Found: C, 47.4; H, 6.31; N, 12.2.

The *dihydrochloride* was converted to the *free base* by the method used for conversion of XVI to XVII. Crystallization from benzene-heptane gave a 67% conversion to white crystals, m.p. 120–132°, which are probably a mixture of *cis* and *trans* isomers.

Anal. Calc'd for $C_{14}H_{17}N_3O_2$: C, 64.8; H, 6.63; N, 16.2.
Found: C, 64.6; H, 6.84; N, 16.3.

Allylphthalimide (XXII). A mixture of 200 g. of potassium phthalimide, 1 l. of absolute alcohol, and 102 cc. of allyl bromide was refluxed and stirred for 18 hours, diluted with about 1.5 l. of water, extracted twice with chloroform, and the combined extracts evaporated *in vacuo*. The residue was dissolved in benzene at room temperature, filtered from phthalimide, and again evaporated to dryness *in vacuo;* yield, 174 g. (87%) of crude product, m.p. 59–60° (lit. 70°), suitable for the next step.

2-Methoxy-3-phthalimidopropylmercuric acetate (XXIII). To a solution of 5 g. of allylphthalimide in 50 cc. of methanol was added 7.7 g. of mercuric acetate. The mixture was refluxed for ten minutes when a sample did not give a red color on addition of excess aqueous sodium hydroxide. The cooled solution deposited 9.6 g. (84%) of product, m.p. 129–132°.

Carrari and Mori (4) record a m.p. of 139–140° and yield of 60%.

2-Methoxy-3-phthalimidopropylmercuric iodide. A solution of 9.6 g. of allylphthalimide in 96 cc. of methanol was refluxed with 15.7 g. of mercuric acetate for ten minutes, then treated with a warm solution of 9 g. of potassium iodide in 90 cc. of methanol. A white solid separated. The cooled mixture was filtered and the solid washed with methanol; yield, 20.4 g. (76%), m.p. 150–154°. Recrystallization from chloroform-absolute alcohol gave white crystals, m.p. 154–156°.

Anal. Calc'd for $C_{12}H_{12}HgINO_3$: C, 26.3; H, 2.21; N, 2.56.
Found: C, 26.8; H, 2.56; N, 2.47.

Pearson, Sigal, and Krug (6) have recorded m.p. 159–160° (corr.).

2-Methoxy-3-phthalimidopropyl iodide (XXIV). To a solution of 174 g. of allylphthalimide (XXII) in 1740 cc. of methanol in a 5-l. flask was added 285 g. of mercuric acetate. The solution was refluxed and stirred on the steam-bath for ten minutes, then treated with a solution of 156 g. of potassium iodide in 310 cc. of water. After the mixture was refluxed ten minutes more, 256 g. of iodine was added and the mixture refluxed an additional 15 minutes during which the iodomercury compound, XXIII, dissolved and mercuric iodide separated. The latter was dissolved by the addition of 178 g. of potassium iodide in 1260 cc. of water. Sodium bisulfite was added in small portions until the iodine color had bleached. During this time part of the product crystallized. The mixture was diluted to 5 l. with water and cooled to 25°. The solid was collected and washed with water containing a little potassium iodide. Recrystallization of the wet cake from 1 l. of alcohol gave 243 g. (75%) of product, m.p. 105–107°. Further recrystallization of a sample from alcohol afforded white crystals, m.p. 107–108°.

Anal. Calc'd for $C_{12}H_{13}INO_3$: C, 41.7; H, 3.51; N, 4.06; CH_3O, 8.98.
Found: C, 41.9; H, 3.85; N, 3.93; CH_3O, 8.64.

Pearson, Sigal, and Krug (6) recorded m.p. 108–109° (corr.).

1-Phthalimido-2-methoxy-5-hexanone (XXV). To a solution of 47 g. of sodium methoxide and 165 cc. of methyl acetoacetate in 465 cc. of *tert*-butyl alcohol was added 243 g. of XXIV. The solution was refluxed on a steam-bath for 42 hours, then it was acidified with 47 cc. of acetic acid and evaporated to dryness *in vacuo*. The residue was refluxed with 550 cc. of alcohol and 550 cc. of 3 *N* hydrochloric acid for three hours when carbon dioxide evolution was essentially complete. The mixture was concentrated to about one-half *in vacuo*, diluted with an equal volume of water, and extracted with about 750 cc. of ethyl acetate. The extract, washed with aqueous sodium bicarbonate and dried with magnesium sulfate, was evaporated to dryness *in vacuo* leaving 184 g. of an oil. An aliquot gave a 30% yield of *2,4-dinitrophenylhydrazone*, m.p. 175–177°.

To a hot solution of the crude ketone in 215 cc. of absolute alcohol was added a solution of 70 g. of sodium bisulfite in 215 cc. of water. The mixture was heated five minutes, then stirred for three hours without heating during which time the addition compound separated. The mixture was diluted with 530 cc. of absolute alcohol and 1600 cc. of ethyl acetate and allowed to stand at 3° for about 15 hours. The solid was collected and washed with ethyl acetate. The addition compound was decomposed by shaking with 330 cc. of water, 210 cc. of 12 *N* hydrochloric acid, and 530 cc. of chloroform until solution was complete. The separated aqueous solution was extracted once more with chloroform. Evaporation of the combined extracts *in vacuo* gave 54.6 g. (28%) of pure ketone which solidified on standing (m.p. about 40°). The recovery was 99% of the ketone present and it now gave a 98% yield of *2,4-dinitrophenylhydrazone*, m.p. 179–180°. Recrystallization of a similar preparation from benzene gave orange crystals, m.p. 180.5—181°.

Anal. Calc'd for $C_{21}H_{21}N_5O_7$: N, 15.4; CH_3O, 6.82.
Found: N, 15.1; CH_3O, 7.10.

1-Benzamido-2-methoxy-5-hexanone (XXVI). A mixture of 41 g. of purified phthalimidoketone, XXV, and 410 cc. of 6 *N* hydrochloric acid was refluxed for three hours, then processed as described for 1-benzamido-5-hexanone (2); yield, 26.1 g. (70%) of an oil which gave a 58% yield of *2,4-dinitrophenylhydrazone*, m.p. 130–134°. Recrystallization from alcohol afforded yellow crystals, m.p. 132–134°.

Anal. Calc'd for $C_{20}H_{23}N_5O_6$: C, 56.0; H, 5.43; N, 16.3.
Found: C, 56.4; H, 5.73; N, 16.3.

3-(2,4-Diketo-7-methoxy-8-benzamidoöctyl)-4-quinazolone (XXVII). Claisen condensation of 11 g. of 1-benzamido-2-methoxy-5-hexanone (XXVI) with 12 g. of ethyl 4-quinazolone-3-acetate as described for 3-(2,4-diketo-8-phthalimidoöctyl)-4-quinazolone (2) gave 27–38% yields of diketone isolated as the *blue copper derivative*, m. p. 218–220° dec. No suitable solvent for recrystallization could be found.

Anal. Calc'd for $C_{48}H_{48}CuN_6O_{10}$: N, 9.00; Cu, 6.85.
Found: N, 8.83; Cu, 6.29.

A sample of the copper derivative was dissolved in warm 1 *N* hydrochloric acid, then cooled. The hydrochloride of the copper-free diketone was collected; white crystals, m.p. 178–180° dec.

Anal. Calc'd for $C_{24}H_{25}N_3O_5 \cdot HCl$: C, 61.2; H, 5.57; N, 8.92.
Found: C, 61.6; H, 5.95; N, 9.12.

The *free base* was isolated from the copper derivative by chloroform extraction from a suspension in 1 *N* hydrochloric acid in 89% recovery after recrystallization from benzene-heptane: white crystals, m.p. 113–116°, which give a red ferric chloride test.

3-[β-Keto-γ-(5-hydroxy-1,4,5,6-tetrahydro-2-pyridyl)propyl]-4-quinazolone (XXVIII). A solution of 12.2 g. of the copper derivative of XXVII in 47 cc. of water and 15.6 cc. of 96% sulfuric acid was refluxed for two hours, cooled, and poured into excess ice and 63 cc. of 15 *N* ammonium hydroxide. The mixture was extracted three times with equal volumes of chloroform. The combined extracts were warmed on the steam-bath and sufficient Methyl Cellosolve was added to dissolve the solid XXVIII which had separated. The dried solution was evaporated *in vacuo*. The residue (10.2 g.) was refluxed with 51 cc. of 48% hydrobromic acid for 20 minutes, then poured into ice and 51 cc. of 15 *N* ammonium hydroxide. The solid was removed and the filtrate extracted twice with equal volumes of chloroform. The solid was added to the chloroform and heated to boiling. Sufficient Methyl Cellosolve was added to dissolve the solid. The hot solution was dried with magnesium sulfate and evaporated to dryness *in vacuo*. Trituration of the residue with ethyl acetate gave 4.4 g. (56%) of product, m.p. 219–223°. Recrystallization of a sample from alcohol afforded white needles, m.p. 229–230°.

Anal. Calc'd for $C_{16}H_{17}N_3O_3$: C, 64.2; H, 5.73; N, 14.0; CH_3O, 0.0.

Found: C, 64.0; H, 6.06; N, 14.0; CH_3O, 0.0.

Seven sets of conditions, including initial hydrobromic acid hydrolysis, were tried but all gave less yield (18–31%) than the above procedure.

3-[β-Keto-γ-(5-hydroxy-2-piperidyl)propyl]-4-quinazolone (V) *dihydrochloride.* By hydrogenation of XXVIII in 6 *N* hydrochloric acid by the procedure described for the preparation of 2-methyl-3-[β-keto-γ-(2-piperidyl)propyl]-4-quinazolone (2) there was obtained a 54% yield of *dihydrochloride*, m.p. 220–222° dec. Recrystallization from methanol by the addition of absolute alcoholic hydrogen chloride gave white crystals, m.p. 225–227° dec.

Anal. Calc'd for $C_{16}H_{19}N_3O_3 \cdot 2HCl$: C, 51.3; H, 5.65; N, 11.2.

Found: C, 51.0; H, 6.17; N, 11.4.

The *free base*, m.p. 130–133°, was obtained in 92% recovery by extraction of an alkaline solution with chloroform (2) and trituration of the residue with ethyl acetate.

SUMMARY

The synthesis of an isomer of the Hydrangea alkaloid, 3-[β-keto-γ-(5-hydroxy-2-piperidyl)propyl]-4-quinazolone, *via* the key intermediate 3-(2,4-diketo-7-methoxy-8-benzamidoöctyl)-4-quinazolone has been described.

Claisen condensation with 1-phthalimido-2-hydroxy-5-hexanone has been unexpectedly found to take place on the methylene group rather than the methyl group.

PEARL RIVER, N.Y.

REFERENCES

(1) HUTCHINGS, GORDON, ABLONDI, WOLF, AND WILLIAMS, *J. Org. Chem.*, **17**, Paper III of this series.

(2) BAKER, QUERRY, SCHAUB, AND WILLIAMS, *J. Org. Chem.*, **17**, Paper VI of this series.

(3) MORGAN AND CO-WORKERS, *J. Chem. Soc.*, **125**, 740, 756, 760, 1271 (1924); **127**, 2619, 2620 (1925); *Ber.*, **58**, 333 (1925).

(4) CARRARI AND MORI, *Gazz. chim. ital.*, **73**, 113 (1943).

(5) BAKER, QUERRY, KADISH, AND WILLIAMS, *J. Org. Chem.*, **17**, Paper IV of this series.

(6) PEARSON, SIGAL, AND KRUG, *J. Org. Chem.*, **15**, 1048 (1950).

(7) TITUS, CRAIG, GOLUMBIC, MIGHTON, WEMPEN, AND ELDERFIELD, *J. Org. Chem.*, **13**, 50 (1948).

(8) DEY, *J. Chem. Soc.*, 1166 (1937).

(9) BAKER, SCHAUB, QUERRY, AND WILLIAMS, *J. Org. Chem.*, **17**, Paper VIII of this series.