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AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. VI. A SECOND SYNTHESIS OF 3-[β-KETO-γ-(2-PIPERIDYL)-PROPYL]-4-QUINAZOLONE

B. R. BAKER, MERLE V. QUERRY, ROBERT E. SCHAUB, AND JAMES H. WILLIAMS

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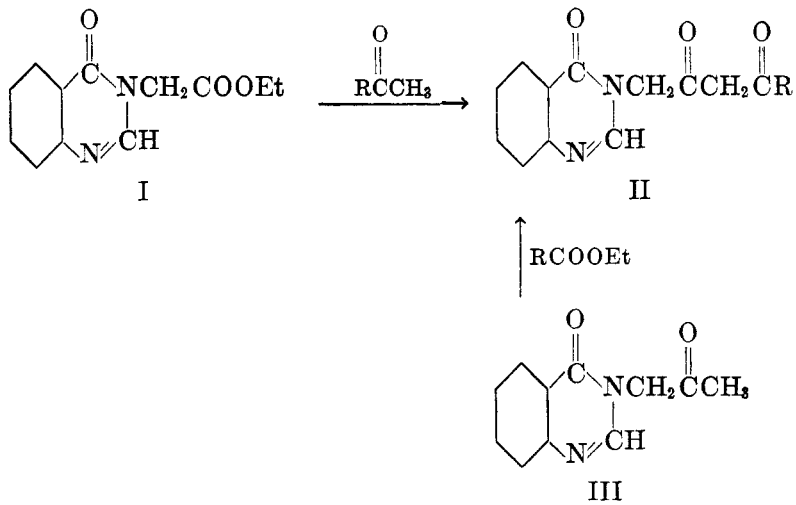
A synthesis of 3-[β-keto-γ-(2-piperidyl)propyl]-4-quinazolone (XI) was described in an earlier publication (1). This compound was the first of some sixty 3-alkyl-4-quinazolones (2) tested to show antimalarial activity, being about 1% as active as the Hydrangea alkaloid or about equal to quinine.[1] Since this compound also duplicated all of the reactions of the natural alkaloid except those due to the hydroxyl function (3), a second type of synthesis was devised which would be applicable to the introduction of an hydroxyl group on certain positions of the piperidine moiety.

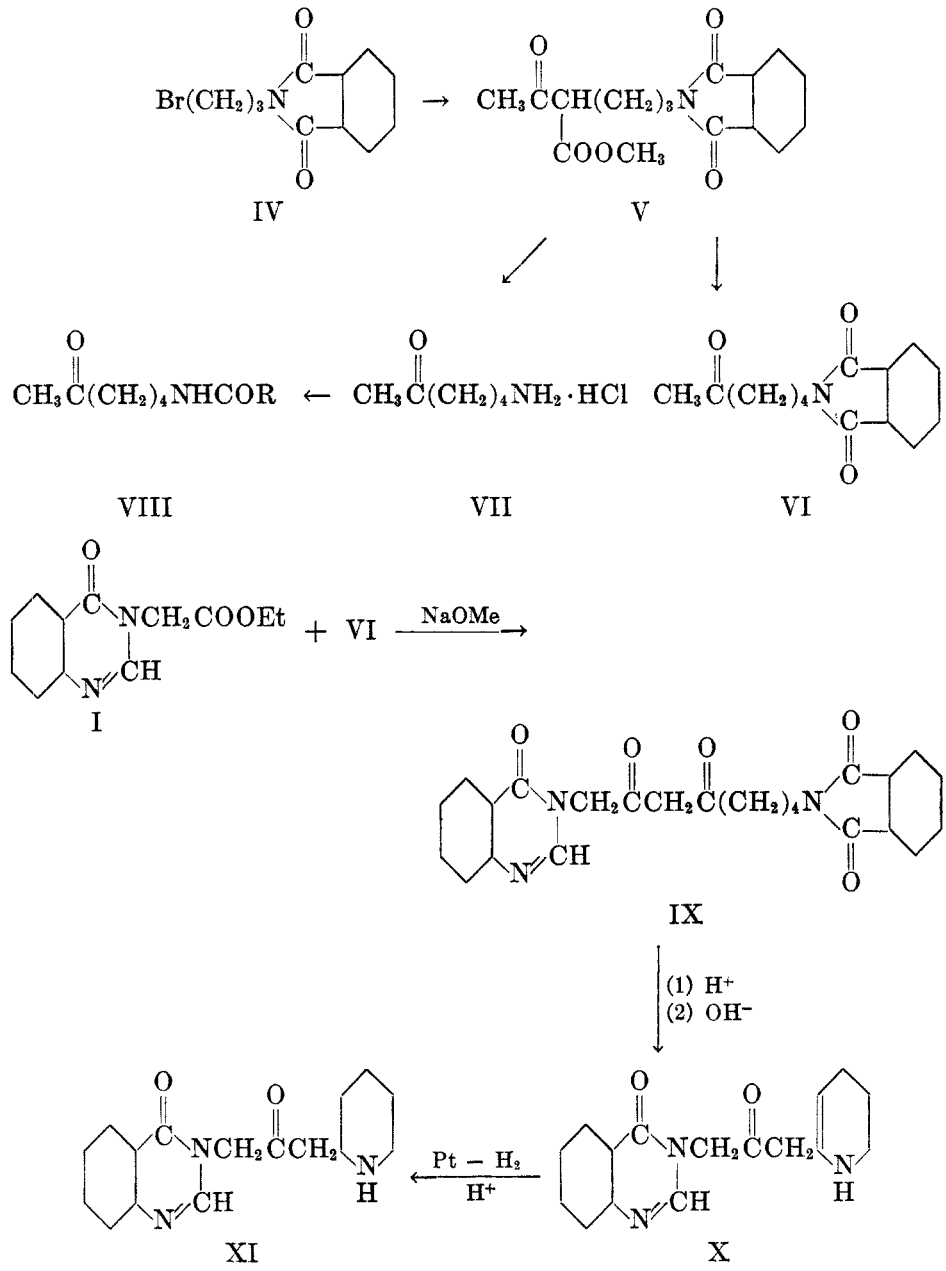
The key reaction (4) was cyclization of a properly substituted δ-aminoketone to a tetrahydropyridine (X), followed by hydrogenation of the resultant double bond. The necessary diketone, IX, was obtained by an ester-ketone Claisen condensation. Attempted Claisen condensation between 3-acetonyl-4-quinazo-



lone (III) with ethyl acetate in the presence of sodium methoxide failed to give any of the diketone, II. However, Claisen condensation of ethyl 4-quinazolone-3-acetate (I) with acetone or methyl ethyl ketone in the presence of sodium methoxide gave II in 52 and 32% yields, respectively.

The appropriately substituted methyl ketone, VI, was readily obtained by alkylation of methyl acetoacetate with γ-bromopropylphthalimide (IV) fol-

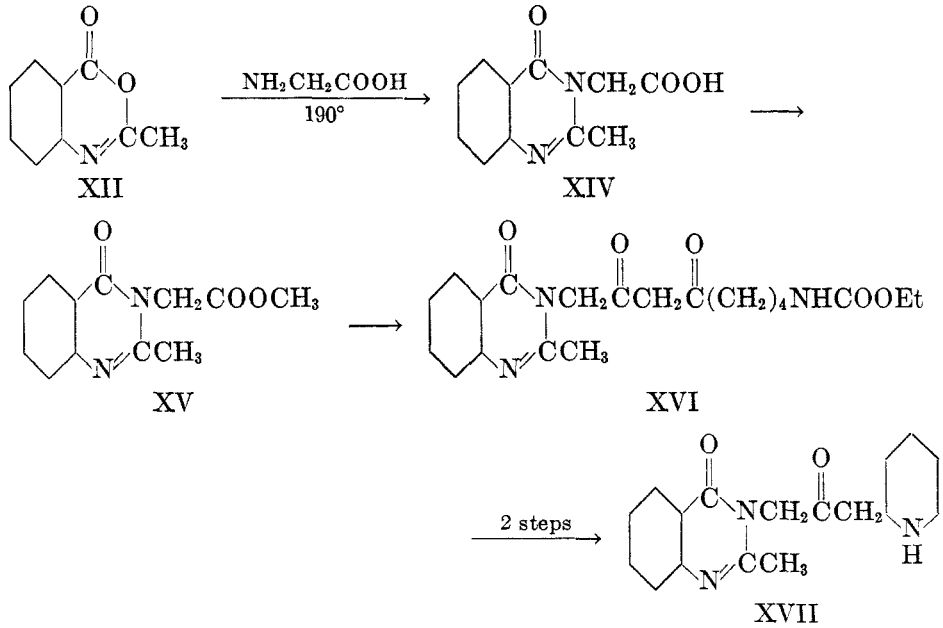
[1] The biological data will be presented elsewhere by Dr. Reginald Hewitt and coworkers of these laboratories.



lowed by mild acid decarbomethoxylation. Claisen condensation with ethyl 4-quinazolone-3-acetate (I) gave the diketone, IX, in 10–17% yield, isolated as the copper salt, under the best conditions found. Acid hydrolysis of the phthalyl group proceeded slowly and after basification, the tetrahydropyridine derivative, X, was isolated in 29% yield. Although the double bond of 2-alkyl-1,4,5,6-

tetrahydropyridines has been reported to reduce with ease (4, 5), X was resistant to hydrogenation at room temperature in the presence of Raney nickel or platinum oxide catalysts. Determination of the u.v. spectra of X in 0.1 *N* sodium hydroxide showed that there was eight times the usual absorption at 312 mμ which completely obscured the 302 and 315 mμ peaks and distorted the 267 mμ peak characteristic of 3-alkyl-4-quinazolones (2). However, in 0.1 *N* hydrochloric acid the 312 mμ peak nearly disappeared. These results indicate that X free base has a strong resonating system in the side chain which must involve the double bond and hence make it resistant to hydrogenation. Since, in contrast, the amine salt formed in acid solution seems to destroy this resonance, it might be expected that the double bond would hydrogenate normally under these conditions. This has been found to be the case using Adams catalyst, the desired compound, XI, being obtained which was identical with that described previously (1).

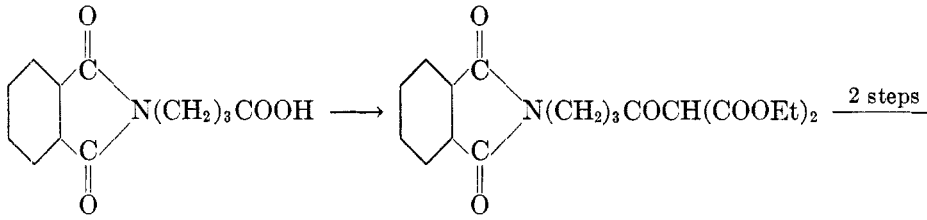
The use of several other N-blocking groups (VIII) for the methyl ketone, VII, were investigated since the phthalyl group gave poor yields. Strong acid hydrolysis of the keto ester, V, led to removal of the phthalyl group as well as decarbomethoxylation. The resultant amino ketone hydrochloride, VII, was then treated with one of three acid chlorides by the Schotten-Baumen procedure, namely ethyl chlorocarbonate, benzyl chlorocarbonate, and benzoyl chloride. The resultant ketones were characterized as their 2,4-dinitrophenylhydrazones. All three ketones gave better yields in the Claisen condensation than VI. The three blocking groups were removed from the diketones by hydrochloric acid hydrolysis. The carbethoxy group could be efficiently removed by hydrobromic acid hydrolysis also. The carbethoxy blocking group was found to



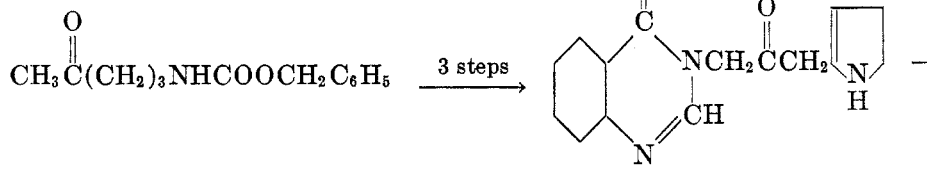
give the best over-all yield (20%) from VIII to X whereas the phthalyl gave 4%, benzoyl 14%, and carbobenzoxy 10%.

The diketone synthesis was also applicable to preparation of a 2-methyl-4-quinazolone homolog, XVII. Acetanthranil (XII) reacted with glycine at 190° to form 2-methyl-4-quinazolone-3-acetic acid (XIV) in 60% yield. Claisen condensation of the corresponding ester, XV, with 1-carbethoxyamino-5-hexanone (VIII, R = OEt) gave the diketone, XVI, which was hydrolyzed, cyclized, and reduced to XVII. This compound was found to be inactive as an antimalarial at the dosage tested,[1] indicating that a 2-methyl substituent on the 4-quinazolone moiety of the Hydrangea alkaloid might also reduce the activity.

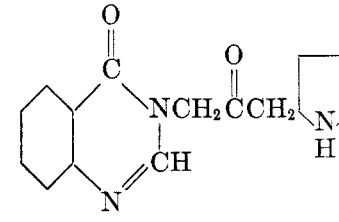
Application of the diketone synthesis for preparation of a pyrrolidine analog (XXII) was investigated. 4-Phthalimidobutyric acid (XVIII) (6) was converted to the acid chloride and condensed with magnesiomalonic ester. The keto malonate on strong acid hydrolysis was converted to 1-amino-4-pentanone, then carbobenzoxylated to XX. The phthalyl derivative of the amino ketone was also employed.



XVIII XIX



XX XXI



XXII

The dihydropyrrole, XXI, had u.v. spectra identical with X. No crystalline derivatives of XXII could be isolated after hydrogenation in acid solution.

Acknowledgement. The authors are grateful to Miss E. Sherman for the literature searches, Messrs. W. McEwen, J. Polleto, and L. Binovi for large scale

preparation of some of the intermediates, and Mr. L. Brancone and his staff for the microanalyses and u.v. data.

EXPERIMENTAL

1-Phthalimido-5-hexanone (VI). To a solution of 12 g. of sodium methoxide and 48 cc. of methyl acetoacetate in 300 cc. of methanol was added 60 g. of γ-bromopropylphthalimide. After being refluxed for 18 hours the solution was concentrated *in vacuo* until solid began to separate. The mixture, diluted with about three volumes of water and acidified with acetic acid, was extracted with chloroform. The combined extracts were evaporated *in vacuo*. The residual crude keto ester (V) was refluxed with 100 cc. of methanol and 250 cc. of 3 *N* hydrochloric acid for 3½ hours when gas evolution became slow. The mixture was diluted to about 1 l. with water and the oil extracted with ethyl acetate. The extract, washed successively with water, aqueous sodium bicarbonate, and water, was evaporated to dryness *in vacuo* leaving 45 g. (82%) of crude product as an oil.

The *semicarbazone* formed in 53% yield, m.p. 148–152°. Recrystallization from methanol gave white crystals, m.p. 152–154°.

Anal. Calc'd for $C_{15}H_{18}N_4O_3$: C, 59.6; H, 6.00; N, 18.5.
Found: C, 59.7; H, 6.40; N, 18.4.

The *2,4-dinitrophenylhydrazone* formed in 77% yield, m.p. 140–142°. Recrystallization from Methyl Cellosolve gave orange-yellow crystals, m.p. 158–160°.

Anal. Calc'd for $C_{20}H_{19}N_5O_6$: C, 56.5; H, 4.52; N, 16.5.
Found: C, 56.2; H, 4.74; N, 16.9.

The above crude ketone was used in the Claisen condensation without purification. The pure ketone could be obtained by preparation of the insoluble sodium bisulfite derivative in 50% alcohol. The solid ketone was recovered in 29% yield and formed white crystals from ether-petroleum ether, m.p. 66–68°.

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Anal. Calc'd for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.17; N, 5.72.
Found: C, 68.7; H, 6.24; N, 5.86.

1-Carbethoxyamino-5-hexanone (VIII, R = OEt). The crude condensation product, V, from 60 g. of γ-bromopropylphthalimide obtained in the same manner as described in the previous experiment was refluxed with 600 cc. of 6 *N* hydrochloric acid for nine hours. The cooled solution was filtered from phthalic acid and evaporated to dryness *in vacuo*. The residual crude 1-amino-5-hexanone hydrochloride (VII) (27.1 g.) was dissolved in 162 cc. of water and cooled to 5° in an ice-bath. The stirred solution was treated with an ice-cold solution of 20.3 g. of sodium hydroxide in 124 cc. of water. Then 23 cc. of ethyl chlorocarbonate was added dropwise over a period of 20 minutes maintaining the temperature at 5–9°. After being stirred 35 minutes longer in the ice-bath, the mixture was extracted twice with benzene and the combined extracts washed with water. Evaporation *in vacuo* gave 23.6 g. (56%) of an oil.

The *2,4-dinitrophenylhydrazone* was prepared in 62% yield, m.p. 123–125°. Recrystallization from methanol gave yellow crystals, m.p. 128–129°.

Anal. Calc'd for $C_{15}H_{21}N_5O_6$: C, 49.1; H, 5.71; N, 19.1.
Found: C, 49.5; H, 6.20; N, 19.0.

1-Carbobenzoxyamino-5-hexanone (VIII, R = $C_6H_5CH_2O$). The crude 1-amino-5-hexanone hydrochloride (VII, 23.4 g.) from 57 g. of γ-bromopropylphthalimide (IV) was treated with 39 cc. of 70% benzyl chlorocarbonate as described in the preceding experiment. The crude product still contained some acid chloride which was removed by stirring with 10% sodium hydroxide for 30 minutes; yield, 35.8 g. (68%) of an oil which in turn gave a 57% yield of *2,4-dinitrophenylhydrazone*, m.p. 103–106°. Recrystallization from methanol afforded orange-yellow crystals, m.p. 106–108°.

Anal. Calc'd for $C_{20}H_{23}N_5O_6$: C, 56.0; H, 5.42; N, 16.3.
Found: C, 56.0; H, 5.83; N, 16.4.

Similarly, 24.2 g. of VII (from 57 g. of IV) with benzoyl chloride at 20–25° gave 26 g. (75%) of *1-benzamido-5-hexanone* which solidified on standing (7).

By treatment of 27.8 g. of 1-amino-5-hexanone hydrochloride with 19 cc. of benzenesulfonyl chloride in the same manner there was obtained 17.1 g. (37%) of *1-benzenesulfonamide-5-hexanone* which gave in turn a 45% yield of *2,4-dinitrophenylhydrazone* as yellow-orange crystals from benzene-heptane, m.p. 116–117°.

Anal. Calc'd for $C_{18}H_{21}N_5O_6S$: C, 49.6; H, 4.83; N, 16.1.

Found: C, 49.9; H, 5.00; N, 16.5.

3-(β,δ-Diketoamyl)-4-quinazolone (II, R = CH_3). To a solution of 46.4 g. of ethyl 4-quinazolone-3-acetate (I) (8), 40 cc. of reagent acetone, and 24 cc. of absolute ethanol in 400 cc. of benzene was added 12 g. of sodium methoxide. The solution was heated to boiling when a gelatinous sodio derivative separated. After standing for 15 minutes more, the mixture was acidified with 24 cc. of acetic acid, diluted with water, and shaken until the solid dissolved. The separated benzene layer was washed with water, then concentrated *in vacuo* until solid began to separate. Warmed until solution took place, the mixture was diluted with about two volumes of heptane and chilled; yield, 25.4 g. (52%), m.p. 120–124°. Recrystallization of a sample from alcohol gave white crystals, m.p. 130–130.5°, which gave a red ferric chloride test.

Anal. Calc'd for $C_{13}H_{12}N_2O_3$: C, 63.8; H, 4.97; N, 11.5.

Found: C, 63.5; H, 4.99; N, 11.6.

The diketone formed a *blue copper derivative* from dilute alcohol, m.p. 260° dec.

Similarly, *3-(β,δ-Diketohexyl)-4-quinazolone* (II, R = Et) was prepared in 32% yield from methyl ethyl ketone. The product was isolated as its *blue-green copper derivative*, m.p. 225–227° dec., which could not be recrystallized and was not quite pure.

Anal. Calc'd for $C_{28}H_{26}CuN_4O_6$: C, 58.3; H, 4.58; N, 9.72.

Found: C, 57.5; H, 4.82; N, 10.6.

3-(2,4-Diketo-8-phthalimidoöctyl)-4-quinazolone (IX). To a warm solution of 49 g. of crude 1-phthalimido-5-hexanone (VI), 33.3 g. of ethyl 4-quinazolone-3-acetate (I), and 29 cc. of absolute alcohol in 490 cc. of benzene was added 9.8 g. of sodium methoxide. The solution was refluxed for one hour, acidified with 18 cc. of acetic acid, washed twice with water, and evaporated to dryness *in vacuo*. The oily residue was dissolved in ethyl acetate and shaken with 300 cc. of 10% aqueous cupric acetate for five minutes. The *copper derivative* was collected and washed with ethyl acetate and water; yield, 7.2 g. (11%) of a blue-green solid, m.p. 235° dec. For analysis a sample was leached with hot alcohol since this compound was insoluble in all common solvents.

Anal. Calc'd for $C_{48}H_{40}CuN_6O_{10}$: N, 9.10; Cu, 6.88.

Found: N, 8.86; Cu, 6.74.

In other runs the yield varied from 10 to 17%.

3-(2,4-Diketo-8-carbethoxyaminoöctyl)-4-quinazolone. By condensation of 17 g. of ethyl 4-quinazolone-3-acetate (I) with 18.6 g. of 1-carbethoxyamino-5-hexanone as in the preceding experiment there was obtained an oil which gave a red ferric chloride test. This oil was dissolved in 160 cc. of alcohol and treated with 120 cc. of 10% aqueous cupric acetate. The *copper derivative* was collected and washed with 50% alcohol; yield, 9.5 g. (32%), of blue crystals, m.p. 208–210° dec.

Anal. Calc'd for $C_{38}H_{44}CuN_6O_{10}$: Cu, 7.92; N, 10.4.

Found: Cu, 8.49; N, 10.4.

3-(2,4-Diketo-8-carbobenzoxyaminoöctyl)-4-quinazolone. Condensation of 5.0 g. of 1-carbobenzoxyamino-5-hexanone with 3.4 g. of ethyl 4-quinazolone-3-acetate (I) as in the preceding experiment gave 1.15 g. (17%) of a *copper derivative*, m.p. 178–182°, suitable for the next step. Recrystallization from Methyl Cellosolve-water afforded blue crystals, m.p. 184–185°, which were still not pure.

Anal. Calc'd for $C_{48}H_{48}CuN_6O_{10}$: Cu, 6.85; N, 9.04.

Found: Cu, 7.94; N, 10.5.

3-(2,4-Diketo-8-benzamidoöctyl)-4-quinazolone. Treatment of 13 g. of crude 1-benzamido-

5-hexanone with 13.7 g. of ethyl 4-quinazolone-3-acetate (I) in the same manner as described for IX gave a solid on evaporation of the benzene solution. Trituration with ethyl acetate resulted in 7.1 g. (30%) of product, m.p. 122–124°. White crystals, m.p. 125–127°, were obtained by recrystallization of a sample from alcohol-water. This diketone gave a red ferric chloride test.

Anal. Calc'd for $C_{23}H_{21}N_3O_4$: N, 10.4. Found: N, 10.6.

The *copper salt* separated as blue crystals, m.p. 227–229° dec., when an alcoholic solution of the diketone was treated with 10% aqueous cupric acetate.

Anal. Calc'd for $C_{46}H_{40}CuN_6O_8$: N, 9.69; Cu, 7.37.

Found: N, 9.29; Cu, 7.51.

3-[β-Keto-γ-(1,4,5,6-tetrahydro-2-pyridyl)propyl]-4-quinazolone (X). (*A*). A mixture of 5 g. of the copper derivative of IX and 100 cc. of 6 *N* hydrochloric acid was refluxed four hours, then cooled and filtered from insoluble material. The filtrate was concentrated *in vacuo* until phthalic acid began to separate. The filtered solution was evaporated to dryness *in vacuo*. An aqueous solution of the residue was poured into excess ammonia water and extracted with chloroform. Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo*. Trituration of the residue with ethyl acetate gave 0.88 g. (29%) of product, m.p. 167–170°. Recrystallization from alcohol afforded white crystals, m.p. 176–178°.

Anal. Calc'd for $C_{16}H_{17}N_3O_2$: C, 67.8; H, 6.06; N, 14.9.

Found: C, 67.5; H, 5.75; N, 15.2.

Longer or shorter reflux periods led to a decrease in yield. The yield was no better if the free diketone, IX, was isolated from the copper salt first, then hydrolyzed. Use of alcohol to increase solubility gave a 9% yield.

(*B*). A solution of 1.0 g. of the copper derivative of 3-(2,4-diketo-8-carbobenzoxyaminooctyl)-4-quinazolone in 10 cc. of 6 *N* hydrochloric acid was refluxed for 15 minutes when carbon dioxide evolution was essentially complete. The solution was poured onto ice and excess ammonia water, then worked up by chloroform extraction as in part *A*; yield, 0.42 g. (69%), m.p. 168–170°.

(*C*). A solution of 1.8 g. of the copper derivative of 3-(2,4-diketo-8-carbethoxyaminooctyl)-4-quinazolone in 20 cc. of 6 *N* hydrochloric acid was refluxed 35 minutes, then worked up as in *B*; yield, 0.49 g. (36%), m.p. 171–175°. The yield might have been increased by a longer reflux period.

(*D*). A solution of 1.0 g. of the copper derivative of 3-(2,4-diketo-8-carbethoxyaminooctyl)-4-quinazolone in 10 cc. of 48 % hydrobromic acid was refluxed for five minutes when gas evolution was complete. The reaction mixture was worked up as in *B;* yield, 0.44 g. (63%), m.p. 168–171°.

(*E*). A mixture of 7 g. of 3-(2,4-diketo-8-benzamidoöctyl)-4-quinazolone and 70 cc. of 6 *N* hydrochloric acid was refluxed four hours, cooled, filtered from benzoic acid, and worked up as in *A*; yield, 2.3 g. (44%), m.p. 167–170°.

3-[β-Keto-γ-(2-piperidyl)propyl]-4-quinazolone (XI) *and dihydrochloride.* A solution of 0.72 g. of X in 50 cc. of methanol and 0.5 cc. of 12 *N* hydrochloric acid was shaken with hydrogen at 1 atm. in the presence of 0.1 g. of platinum oxide until one mole-equivalent of hydrogen was absorbed. The filtered solution was evaporated to dryness *in vacuo* and the residue triturated with absolute alcohol to give 0.60 g. (66%) of a dihydrochloride, m.p. 212–214°. The free base was obtained by solution in a small amount of water, basification with potassium carbonate, and extraction with chloroform. Evaporation of the combined dried extracts *in vacuo* and crystallization from chloroform-petroleum ether gave white crystals of the free base, m.p. 138–140°.

Anal. Calc'd for $C_{16}H_{19}N_3O_2$: C, 67.3; H, 6.70; N, 14.7.

Found: C, 67.7; H, 6.94; N, 15.0.

When the dihydrochloride of XI, prepared *via* the piperidine-2-acetic acid method (1), was converted to the free base in the same manner, white crystals, m.p. 140–142°, were obtained which gave no depression in m.p. on admixture with the preceding compound.

Anal. Found: N, 14.4.

3-[β-Keto-γ-(1-benzenesulfonyl-2-piperidyl)propyl]-4-quinazolone. To a solution of 210 mg. of XI·dihydrochloride in 2.6 cc. of water was added successively 1.4 cc. of 10% sodium hydroxide, 0.15 cc. of benzenesulfonyl chloride, and 2 cc. of chloroform. The mixture was shaken for 30 minutes, then acidified with 6 cc. of 1 *N* hydrochloric acid, and extracted twice with chloroform. The combined extracts were evaporated *in vacuo* and the residue crystallized by solution in 3.5 cc. of hot absolute alcohol and addition of 2 cc. of water; yield, 195 mg. (78%), m.p. 165–166°. Recrystallization from Methyl Cellosolve-water gave white blades, m.p. 166–167°.

Anal. Calc'd for $C_{22}H_{33}N_3O_4S$: C, 62.2; H, 5.46; N, 9.88.

Found: C, 62.2; H, 5.63; N, 9.61.

2-Methyl-4-quinazolone. A mixture of 8 g. of acetanthranil (XII) (9) and 4.3 g. of ammonium acetate in a test tube was placed in a bath at 130°. When the inside temperature reached 115°, reaction took place with the evolution of water and acetic acid, formation of a solid, and a rise in temperature to 140°. The mixture was heated at 170–180° (bath) for five minutes, then 8 cc. of Methyl Cellosolve was added followed by dilution with water to about 30 cc. The crude product was recrystallized from dilute alcohol to give 4.7 g. (59%) of nearly white crystals, m.p. 234–236°.

The best yield found in the literature is 36% formed by reaction of anthranilamide hydrochloride and acetic anhydride at 200° to give a product, m.p. 239–241° (10).

2-Methyl-4-quinazolone-3-acetic acid (XIV). In a 1-l. flask equipped with a stirrer, a thermometer reaching into the reaction mixture, a downward condenser, and a Glas-col heating mantle was placed 73.5 g. of acetanthranil (XII) (9), 147 cc. of Diethyl Carbitol, and 34 g. of glycine. The mixture was vigorously stirred and brought to an inside temperature of 180° when reaction took place as evidenced by solution of the glycine, evolution of water, and separation of the product. The stirred mixture was distilled until 20 cc. of distillate was obtained (about ten minutes), then cooled to 80°, diluted with 370 cc. of alcohol, and cooled in an ice-bath. The product was removed, washed twice each with alcohol, water, and alcohol, then dried on the steam-bath; yield, 60 g. (60%), m.p. 258–261° dec.

In a smaller run no diluent was used. The initial reaction was vigorous with the temperature rising spontaneously from 160° to 210°. The yield was 67% (3.6 g.), m.p. 261° dec. Recrystallization of a sample from 50% aqueous Methyl Cellosolve gave white crystals, m.p. 263° dec. This compound was readily soluble in aqueous sodium bicarbonate or 1 *N* hydrochloric acid.

Anal. Calc'd for $C_{11}H_{10}N_2O_3$: C, 60.6; H, 4.62; N, 12.8.

Found: C, 60.3; H, 4.68; N, 12.5.

Methyl 2-methyl-4-quinazolone-3-acetate (XV). To a swirled mixture of 60 g. of XIV and 330 cc. of methanol was added dropwise 33 cc. of acetyl chloride. The solution was refluxed for 30 minutes, then concentrated *in vacuo* (bath 50°) to about one-half the volume when the hydrochloride salt began to separate. The mixture was poured into 1 l. of ice-water and basified with ammonia water. The product was removed by two extractions with chloroform and evaporation of the extracts *in vacuo*. The residue was recrystallized from benzene-heptane; yield, 28.4 g. (45%), m.p. 110–112°. Recrystallization from the same solvents gave white crystals, m.p. 114–115°.

Anal. Calc'd for $C_{12}H_{12}N_2O_3$: C, 62.1; H, 5.22; N, 12.1.

Found: C, 62.3; H, 5.61; N, 12.5.

2-Methyl-3-(2,4-diketo-8-carbethoxyaminoöctyl)-4-quinazolone (XVI). Condensation of 5.8 g. of XV with 7 g. of 1-carbethoxyamino-5-hexanone as described for IX gave 2.2 g. (21%) of blue crystals of the copper derivative, m.p. 201–202° dec.

Anal. Calc'd for $C_{40}H_{48}CuN_6O_{10}$: Cu, 7.60; N, 10.0.

Found: Cu, 7.97; N, 10.6.

2-Methyl-3-[β-keto-γ-(1,4,5,6-tetrahydro-2-pyridyl)propyl]-4-quinazolone. By hydrolysis of 2.1 g. of the copper salt of XVI with 21 cc. of 48% hydrobromic acid according to procedure

D used for X was obtained 1.25 g. (84%) of product, m.p. 193–195°. Recrystallization from alcohol gave white crystals, m.p. 198–198.5°.

Anal. Calc'd for $C_{17}H_{19}N_3O_2$: C, 68.7; H, 6.44; N, 14.1.
Found: C, 68.9; H, 6.89; N, 14.3.

2-Methyl-3-[β-keto-γ-(2-piperidyl)propyl]-4-quinazolone (XVII) *dihydrochloride*. A solution of 1.25 g. of the preceding compound in 25 cc. of 6 *N* hydrochloric acid was shaken with Norit for ten minutes, filtered, and the Norit washed with 25 cc. of 6 *N* hydrochloric acid. The filtrate was shaken with hydrogen at atmospheric pressure in the presence of 100 mg. of platinum oxide catalyst until one molecular equivalent of hydrogen was absorbed. The reduction required two hours after a 45-minute induction period. The filtered solution was evaporated to dryness *in vacuo*. The residue was crystallized by solution in saturated absolute alcoholic hydrogen chloride by addition of ether to turbidity; yield, 0.70 g. (45%), m.p. 110–113°, with gas evolution at 125°. A sample of this hydrated material was recrystallized from absolute alcohol-ether to give hygroscopic white crystals, m.p. 187–189° dec. with shrinking at 160°.

Anal. Calc'd for $C_{17}H_{21}N_3O_2 \cdot 2HCl$: C, 52.3; H, 6.46; N, 10.8.
Found: C, 52.8; H, 6.58; N, 10.6.

Ethyl (4-phthalimidobutyryl)malonate (XIX). A mixture of 81.5 g. of 4-phthalimidobutyric acid (6), 81 cc. of reagent ether (containing 0.5% pyridine), and 81 cc. of thionyl chloride was allowed to react for 20 minutes with shaking until solution took place. Solvent was removed *in vacuo* (bath 60°). The evaporation was twice repeated after addition of benzene. The residual acid chloride, dissolved in 200 cc. of benzene, was added dropwise to a stirred solution of 192 cc. of ethyl malonate and 106 g. of magnesium methoxide in 640 cc. of benzene over a period of 35 minutes. After being stirred ten minutes longer, the solution was acidified with 35 cc. of acetic acid, then washed with dilute hydrochloric acid and finally water. The solvent was removed *in vacuo* and the residue dissolved in 700 cc. of alcohol. Addition of 700 cc. of 10% aqueous cupric acetate gave 126 g. (89%) of the *copper derivative*, m.p. 183–186°. Recrystallization of a sample from absolute alcohol afforded blue crystals, m.p. 190–191°.

Anal. Calc'd for $C_{38}H_{40}CuN_2O_{14}$: C, 56.2; H, 4.97; N, 3.45; Cu, 7.83.
Found: C, 55.9; H, 5.02; N, 3.47; Cu, 7.68.

If the magnesiomalonic ester ratio to acid chloride was reduced to 1.1–1 the yield dropped to 49%. The free keto ester was recovered in quantitative yield as an oil by shaking the copper derivative with chloroform and excess dilute hydrochloric acid until the organic layer was no longer blue, followed by evaporation of the dried organic solution *in vacuo*.

1-Phthalimido-4-pentanone. A mixture of 120 g. of the keto malonate, XIX, 360 cc. of alcohol, and 600 cc. of 3 *N* hydrochloric acid was refluxed for three hours when gas evolution was essentially complete. Work-up of the reaction mixture as described for VI gave 58 g. (78%) of product as an oil. The *2,4-dinitrophenylhydrazone* formed in 64% yield; m.p. 228–229°. Recrystallization from toluene gave orange crystals, m.p. 230°.

Anal. Calc'd for $C_{19}H_{17}N_5O_6$: C, 55.6; H, 4.18; N, 17.0.
Found: C, 55.5; H, 4.36; N, 17.4.

This ketone could also be prepared from β-bromoethylphthalimide and acetoacetic ester as described for VI, but the yield and quality were too poor to be of use. The *semicarbazone* was recrystallized from Methyl Cellosolve-ether, m.p. 190–192°.

Anal. Calc'd for $C_{14}H_{16}N_4O_3$: C, 58.3; H, 5.58; N, 19.4.
Found: C, 58.3; H, 5.50; N, 18.9.

1-Carbobenzoxyamino-4-pentanone (XX). A mixture of 40 g. of the keto malonate, XIX, and 400 cc. of 6 *N* hydrochloric acid was refluxed for three hours, gas evolution and solution being complete in two hours. The mixture was processed as described for VIII (R = $OCH_2C_6H_5$), to give 26.1 g. (103%) of crude product as an oil. The *2,4-dinitrophenylhydrazone* formed in 41% yield, m.p. 132–134°, which gave yellow crystals, m.p. 134–135, when recrystallized from methanol.

Anal. Calc'd for $C_{19}H_{21}N_5O_6$: C, 54.9; H, 5.08; N, 16.9.
Found: C, 55.2; H, 5.29; N, 16.9.

3-(2,4-Diketo-7-carbobenzoxyaminoheptyl)-4-quinazolone. By Claisen condensation of 5 g. of the above crude ketone (XX) with 3.6 g. of ethyl 4-quinazolone-3-acetate as described for IX there was obtained 1.2 g. (17%) of the copper derivative, m.p. 182–184° dec. The compound was not quite pure and no suitable solvent for recrystallization could be found.

Anal. Calc'd for $C_{46}H_{44}CuN_6O_{10}$: Cu, 7.07; N, 9.29.

Found: Cu, 7.31; N, 9.99, 9.97.

The free diketone was recovered as an oil in 80% yield by use of the chloroform-1 *N* hydrochloric acid procedure.

3-(2,4-Diketo-7-phthalimidoheptyl)-4-quinazolone. Claisen condensation of 1-phthalimido-4-pentanone with ethyl 4-quinazolone-3-acetate as described for IX gave 19–25% of the desired product isolated as the *copper derivative*, m.p. 232–235° dec.

Anal. Calc'd for $C_{46}H_{36}CuN_6O_{10}$: Cu, 7.08; N, 9.36.

Found: Cu, 6.90; N, 8.57.

3-[β-Keto-γ-(4,5-dihydropyrrolyl)propyl]-4-quinazolone (XXI). (*A*). A mixture of 0.89 g. of 3-(2,4-diketo-7-carbobenzoxyaminoheptyl)-4-quinazolone and 9 cc. of 6 *N* hydrochloric acid was refluxed for 15 minutes then worked up as described for X, procedure *B*; yield, 0.20 g. (35%), m.p. 203–208°. Recrystallization from toluene gave white crystals, m.p. 207–208°.

Anal. Calc'd for $C_{15}H_{15}N_3O_2$: C, 66.8; H, 5.79; N, 15.6.

Found: C, 66.4; H, 6.17; N, 15.3.

(*B*). A mixture of 1.0 g. of the copper derivative of 3-(2,4-diketo-7-phthalimidoheptyl)-4-quinazolone and 30 cc. of 6 *N* hydrochloric acid was refluxed for 2½ hours, then worked up as described for X, procedure *A*; yield, 0.25 g. (42%), m.p. 189–194°.

SUMMARY

A second synthesis of 3-[β-keto-γ-(2-piperidyl)propyl]-4-quinazolone, *via* 3-(2,4-diketo-8-acylaminoöctyl)-4-quinazolones, has been described. This method has been shown to be adaptable to the synthesis of an homolog with a methyl group on the 2 position of the 4-quinazolone nucleus.

PEARL RIVER, N. Y.

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