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

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

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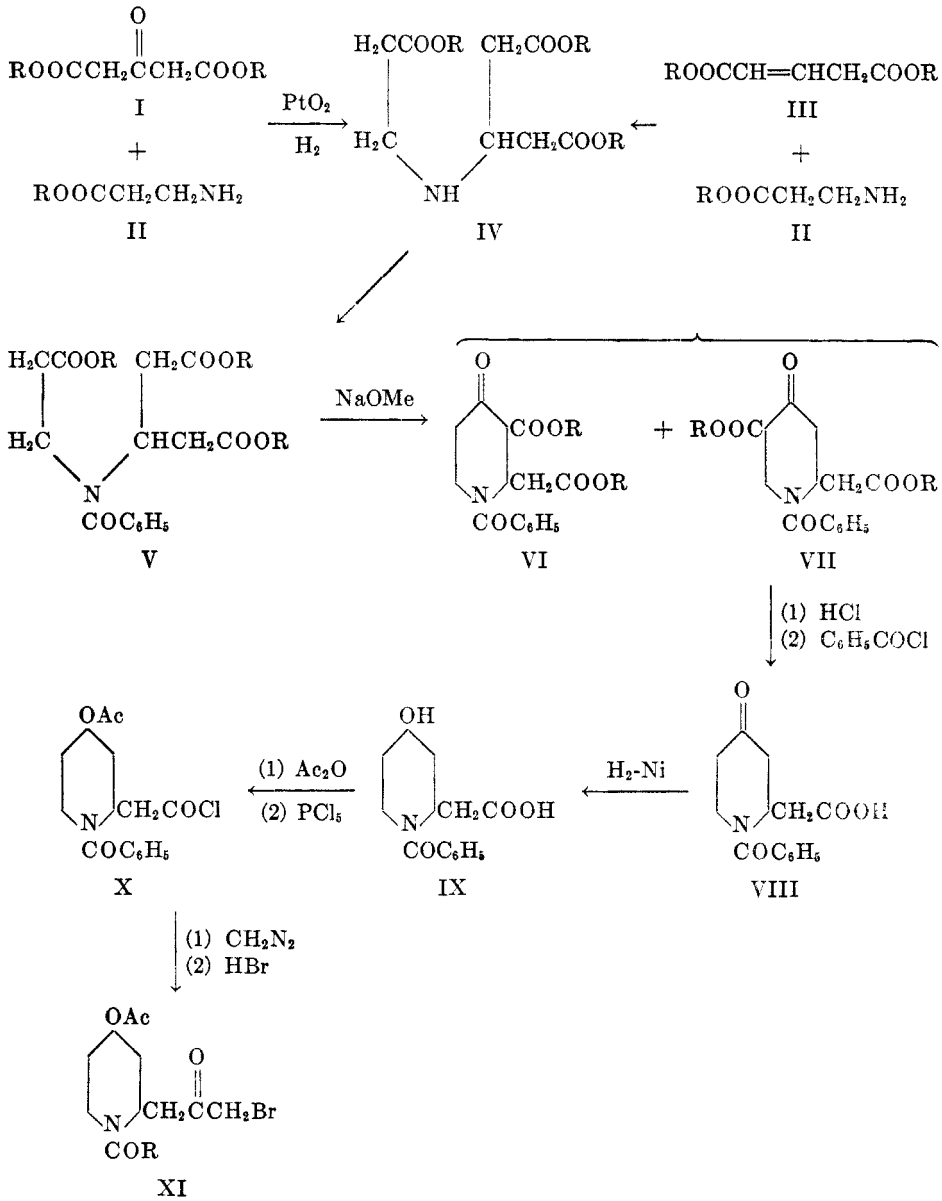
One of the structures considered highly possible for the Hydrangea alkaloid was 3-[β-keto-γ-(4-hydroxy-2-piperidyl) propyl]-4-quinazolone (XXVI) (1). Attempts to synthesize this compound *via* the diketone approach were described in the preceding paper (2). The second type of approach used for these compounds involved 2-piperidineacetic acid as the key intermediate (3). This approach has been found feasible through 4-methoxy-2-piperidineacetic acid.

Of the methods in the literature for preparation of 4-piperidols, the Dieckmann cyclization approach (4, 5) appeared attractive. The requisite amino triester (IV) was obtained by the reductive amination of ethyl acetonedicarboxylate (I) with β-alanine ester (II) in 40–45% yield or by addition of β-alanine ester (II) to methyl glutaconate (III). Benzoylation to V followed by Dieckmann cyclization gave only 38–40% yields of the keto esters, VI and VII. Decarbalkoxylation was accompanied by debenzoylation under acid conditions (4), the benzoyl acid, VIII, being isolated in 8–12% yield after rebenzoylation. Hydrogenation of the carbonyl group at 120° in alkaline solution in the presence of a nickel catalyst gave a mixture of oily 4-piperidol isomers, IX. Acetylation and conversion to the acid chloride, X, allowed isolation of one of the isomers in crystalline form.

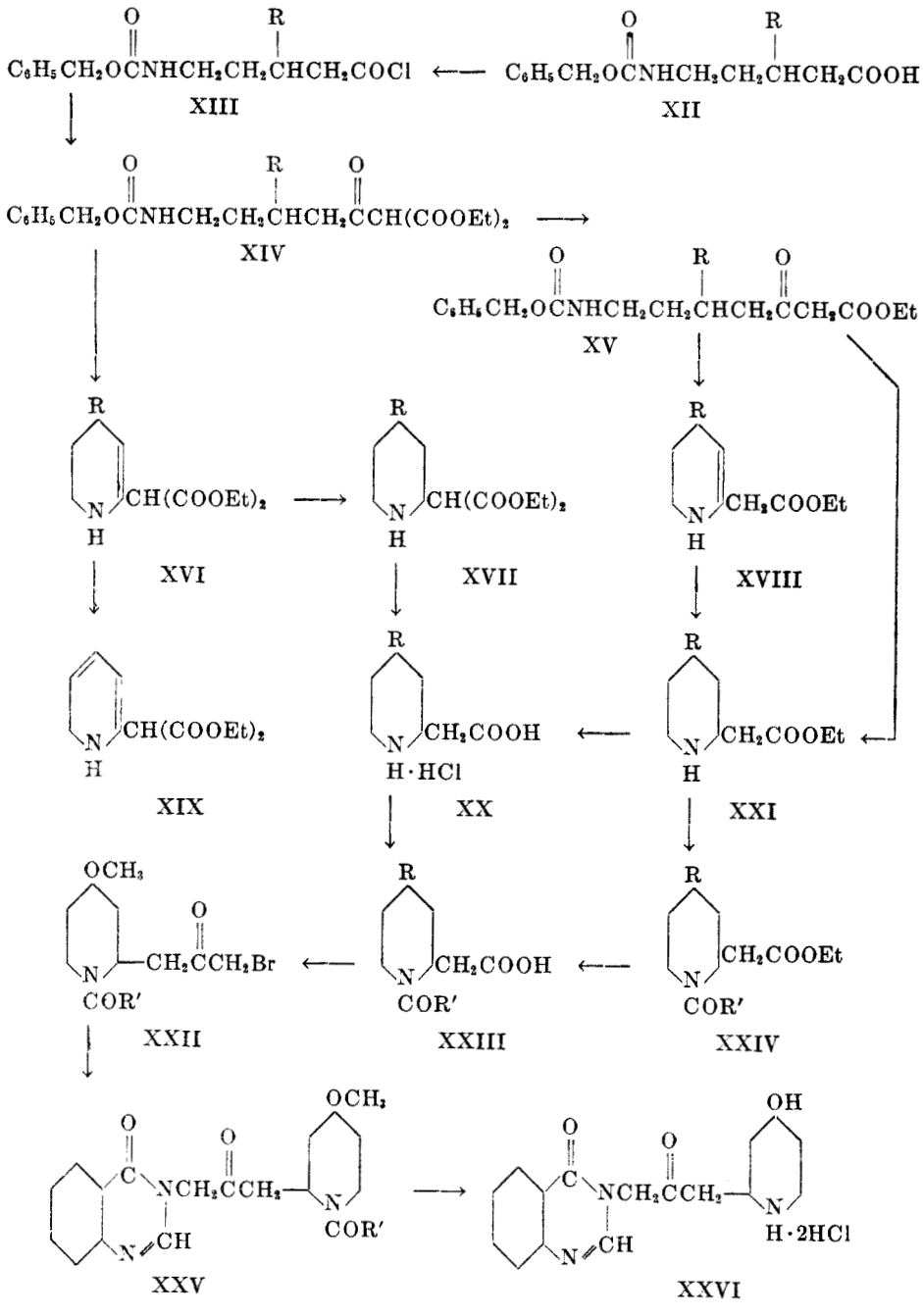
Treatment of the crystalline isomer or the mixed isomers with diazomethane, then with hydrogen bromide gave a negligible yield of bromo ketone, XI. Sufficient material could not be obtained for studying this last reaction due to the consecutive low yields and the fact that larger scale preparation of IV from I gave greatly diminished yields. In some larger runs no triester, IV, could be isolated. The poor conversion of X to XI was subsequently found to be due to the benzoyl blocking group and probably could have been overcome by choice of a different N-blocking group. This point will be discussed later.

The piperidine-2-acetic acids (XX) were then synthesized by a modification of the well known δ-aminoketone cyclization (6–8) followed by hydrogenation. The 5-carbobenzoxyaminovaleric acids (XII) (2) were converted to the ketomalonates, XIV, *via* the acid chlorides, XIII.

The conversion of the ketomalonates (XIV) to the piperidine-2-acetic acids (XX) involved two variables, first, the new modification of the amino ketone ring closure by hydrogenolysis of the carbobenzoxy group, ring closure, and reduction to XVII and, secondly, the influence of the methoxy group (R = CH_3O) on this method. In order to eliminate the second variable and study only the reductive cyclization reaction, the series R = H was investigated since the intermediate XVIIa should be convertable to 1-benzoyl-2-piperidineacetic acid (XXIIIa), a compound characterized in an earlier publication (3).



The ketomalonate, XIVa, was hydrogenated in acetic acid with a 10% palladium-charcoal catalyst, then hydrogenated further without isolation in the presence of platinum oxide. The crude piperidine-2-malonate (XVIIa) was hydrolyzed to XXa, then benzoylated to give a 55% over-all yield of 1-benzoyl-2-piperidineacetic acid (XXIIIa). Thus, the over-all yield for hydrogenolysis of the carbobenzoxy group, ring closure, reduction, and hydrolysis to 2-piperidineacetic acid hydrochloride (XXa) must have been 73% since benzoylation of pure 2-piperidineacetic acid proceeds in 75% yield (3).



a series, R = H
b series, R = OCH_3

When these hydrogenation conditions were applied to the methoxy ketomalonate, **XIV**b, considerably more hydrogen was absorbed and the only products

which could be isolated were derivatives of 2-piperidineacetic acid (XXa), the methoxyl group having been lost by hydrogenolysis. If a mixture of ethyl acetate and acetic acid was used for hydrogenation in order to try to decrease the extent of hydrogenolysis of the methoxyl group, the general method became poor. The yields of benzoyl acid, XXIIIa, from the ketomalonate, XIVa, were unpredictably variable, 0–20%. In many cases, not one, but both carboxyl groups were unexplainably lost during the hydrolysis step XVIIa→XXa. Subsequent studies indicated that the reactions sometimes stopped at the dehydro ester stage, XVIa, since this pure dehydro ester on hydrolysis and benzoylation gave 1-benzamido-5-hexanone with loss of both carboxyls. This point will be discussed later.

Treatment of the ketomalonates, XIV, with boiling water resulted in removal of one carbethoxy group (9) and formation of the ketoacetates, XV. Hydrogenation of XVa in acetic acid-ethyl acetate to XXIa followed by hydrolysis and benzoylation gave a 14–30% yield of 1-benzoyl-2-piperidineacetic acid (XXIIIa). In these cases all of the hydrogen was taken up with use of only the palladium-charcoal catalyst and no additional hydrogen was absorbed by subsequent addition of a platinum oxide catalyst. The yields appeared to be too low and variable to try on the methoxy series.

At this point it seemed that hydrogenation without hydrogenolysis could not be carried out with acid present. Since all of the literature references found on hydrogenolysis of a carbobenzoxy group demanded the presence of either mineral acids or acetic acid, it seemed improbable that the carbobenzoxy group could be removed in neutral solution, a condition which should decrease hydrogenolysis of the methoxyl group. In this laboratory (10) it had been possible to remove a carbobenzoxy blocking group from the amine of certain neutral molecules in neutral solution.

Hydrogenation of the methoxy ketoacetate, XVb, in alcohol with a palladium-charcoal catalyst led to a distillable reduction product which gave low hydrogen values for structure XXIb on combustion, but still contained the 4-methoxy group. Similarly, hydrogenation of XVa gave an oil, b.p. 95° (1 mm.). Since the expected ethyl 2-piperidineacetate should boil about 60° (1 mm.) (11), it seemed probable that the reduction products were intermediate between XV and XXI, namely the dehydropiperidines, XVIII. That these structures were actually obtained was demonstrated as follows:

1. The hydrogen combustion values agreed for structure XVIII and not XXI.

2. The methoxy and desoxy reduction products had essentially the same u.v. spectra in absolute alcohol, a peak at 290 mμ with ϵ values of 9500 and 9300, respectively, which are the same as the values for enolic acetylacetone. The u.v. absorption disappeared in 0.1 *N* alcoholic hydrochloric acid.

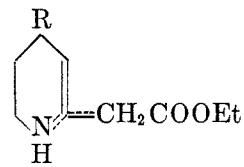
3. Acid hydrolysis of the desoxy reduction product led to rapid decarboxylation. Benzoylation of the hydrolysis product gave a 37% yield of pure 1-benzamido-5-hexanone. This could arise from a compound of structure XVIIIa, but not XXIa which gives 2-piperidineacetic acid on hydrolysis. The methoxy reduction product also evolved carbon dioxide on acid hydrolysis and gave a non-characterizable, alkali-insoluble oil on benzoylation. Similar results were obtained by acid

hydrolysis of the methoxy ketomalonate, XIVa, the β-methoxy ketone linkage being inherently unstable to hot acid.

Hydrogenolysis of the desoxy keto malonate, XIVa, in neutral solution resulted in the dehydropiperidine-2-malonate, XVIa, which absorbed in the u.v. at the same place, 290 mμ, but had twice the ε value, 18,500. Its structure was confirmed by acid hydrolysis and benzoylation to 1-benzamido-5-hexanone in 66% yield.

Hydrogenolysis of the methoxy keto malonate, XIVb, in neutral solution probably gave XVIb, but the elements of methanol were lost on distillation forming a product which appeared to be the dihydropyridine, XIX. This compound had characteristic u.v. spectra different than XVI and XVIII. Two peaks were obtained in absolute alcohol, one at 245 mμ (ε = 7100) and the other at 330 mμ (ε = 7500), whereas in 0.1 *N* alcoholic hydrochloric acid there were peaks at 232, 292, and 330 mμ with about the same order of extinction. This compound was not further characterized.

The u.v. data now offered an explanation why the hydrogenation of the keto esters, XIV and XV, stopped at the dehydro stage, in contrast to normal molecules of this type structure which readily hydrogenate in neutral solution (12), and why hydrogenation proceeded to XVII and XXI, respectively, in acid solution. In neutral solution there is strong resonance or conjugation which resists hydrogenation, but disappears in acid solution to allow the double bond to reduce in a normal fashion. This resonance in neutral solution may be due to the oscillation of the double bond as indicated by the dotted lines in XXVII. One or more of these oscillating structures are eliminated in acid solution.



XXVII

Isolation of these intermediates also clarified why hydrogenolysis of the methoxyl took place. Inspection of formulas XVIb and XVIIIb reveals that they have the allyl alcohol system, C=C—C—O— which is known to undergo hydrogenolysis under certain conditions and that Raney nickel gives the most favorable ratio of hydrogenation to hydrogenolysis (13–15).

When the methoxy dehydropiperidine, XVIIIb, was subjected to hydrogenation in the presence of Raney nickel, no reduction occurred until a temperature of 120° (2000 p.s.i.) was reached. Fractional distillation of the product gave 53% of a main fraction, b.p. 92° (1 mm.) which could be either the desoxy dehydropiperidine, XVIIIa, or the methoxypiperidine, XXIb, or a mixture of both. The u.v. spectrum in absolute alcohol showed the presence of only 2% of XVIIIa. That the remainder was the desired XXIb was shown by acid hydrolysis. No decarboxylation took place and a 58% yield of 1-benzoyl-4-methoxypiperidine-2-acetic acid was obtained, one-fourth of which was a crystalline isomer, m.p.

156°. The yield of crystalline isomer was increased to 76–78% by benzoylation of the ester, XXIb, to XXIVb followed by alkaline hydrolysis. Similarly, the 1-carbethoxy derivative of XXIII was obtained as an oil in 96% yield.

Conversion of the carbethoxy acid to the bromo ketone, XXII, *via* the acid chloride and diazoketone, followed by condensation with 4-quinazolone and hydrobromic acid hydrolysis gave the desired final product, XXVI, m.p. 232–233° dec. This compound was inactive for malaria when assayed at 100 times the dose required for the Hydrangea alkaloid.

When the crystalline benzoyl acid, XXIIIb, was carried through this sequence, low yields of oils were obtained from which none of the final product, XXVI, could be isolated. It is possible that the Dieckmann approach discussed earlier might also have been successful if a carbethoxy, instead of benzoyl blocking group, had been employed.

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EXPERIMENTAL

Ethyl acetonedicarboxylate. The preparation of this compound from citric acid (16) has been considerably simplified in that the free acid was not isolated.

To 200 g. of citric acid in a 2 l. beaker was added 200 cc. of 25% fuming sulfuric acid with manual stirring. After 45 minutes the solution was covered with 400 cc. of benzene, cooled in an ice-bath, and treated with 200 cc. of absolute alcohol with stirring at such a rate that the temperature was 35–45° (about five minutes). The mixture was transferred to a round-bottom flask using a little absolute alcohol as a rinse. The mixture was stirred four hours protected from moisture, then poured on 400 cc. of ice and water. The organic layer was thoroughly washed with aqueous sodium bicarbonate, then once with water. The solvent was removed *in vacuo* and the residue distilled; yield, 78–86 g. (41–45%) of a colorless oil, b.p. 104° (1 mm.).

On a 2-kg. scale the yield was 36.5–36.8%. Without the benzene as a heat exchanger, the temperature could not be effectively controlled and the yields dropped to about 10% on a 2-kg. scale.

n-Butyl β-alanate. A mixture of 50 g. of β-alanine and 250 cc. of *n*-butyl alcohol was treated with hydrogen chloride gas with ice-cooling until 104 g. was absorbed. The mixture was heated on the steam-bath under a condenser with shaking until solution took place (15 minutes), then heating was continued for one hour more. The solution was evaporated to dryness *in vacuo*. The cooled residue was dissolved in ice-water and the solution saturated with potassium carbonate with ice cooling. The mixture was extracted twice with ether. The combined extracts, dried with magnesium sulfate, were evaporated *in vacuo* (bath 35°). Distillation gave 48.2–48.4 g. (59%) of a colorless oil, b.p. 56–57° (1 mm.).

This preparation cannot be interupted after neutralization of the hydrochloride and the product must be used immediately. On a scale three times this size the yield was 0–15%.

The ethyl ester was prepared similarly except that a stream of hydrogen chloride was bubbled through the boiling solution for one hour. The ester was isolated as described by Weigand (18).

Methyl β-alanate hydrochloride. To a solution of 22.5 g. of hydrogen chloride gas in 400 cc. of warm methanol was added 50 g. of β-alanine. Solution took place on swirling. Then 40 cc. of acetyl chloride was added dropwise with swirling at such a rate that the solution refluxed briskly (five minutes). After being refluxed one hour, the solution was evaporated

to dryness *in vacuo*. The hot semi-solid residue was dissolved in *n*-butanol and an equal volume of acetone was added. After 15–20 hours at 3° the mixture was filtered and the product washed with acetone; yield, 46 g. (59%) of white crystals, m.p. 96–100°.

This modified Freudenberg esterification is more satisfactory than the ordinary amino acid esterification procedure with methanol-hydrogen chloride. The latter gave a 42% yield, m.p. 85–90°. However, no product could be isolated by the acetyl chloride procedure when run at ten times the scale described.

Hale and Honan (17) record m.p. 94–95° for methyl β-alanate hydrochloride.

Esters of β-carboxymethylaminoglutaric acid (IV). (*A*). To 100 g. of ethyl acetonedicarboxylate in 200 cc. of absolute alcohol was added 63.4 g. of freshly distilled ethyl β-alanate in 100 cc. of absolute alcohol followed by 200 cc. of acetic acid. After standing 15–20 hours the solution was shaken with hydrogen at 1–3 atm. until 0.65–0.70 mole-equivalents of hydrogen were absorbed (about six hours). The filtered solution was concentrated to a syrup *in vacuo*, water was added and the solution brought to *p*H 8–9 with potassium carbonate. The oil was isolated by chloroform extraction. Distillation gave 84.6 g. (56%) of triethyl ester as a nearly colorless oil, b.p. 165–168° (1 mm.).

Anal. Calc'd for $C_{14}H_{25}NO_6$: C, 55.4; H, 8.27; N, 4.64.
Found: C, 55.4; H, 8.33; N, 4.30.

In other runs the yield was 30–56%. None of the desired product was obtained if the acetic acid was omitted.

Similarly, 23.8 g. of methyl acetonedicarboxylate and 27.2 g. of butyl β-alanate in methanol-acetic acid afforded 22.9 g. (57%) of the dimethylbutyl ester, b.p. 158–161° (1 mm.). Analysis indicated some transesterification of the butyl group had taken place.

Anal. Calc'd for $C_{13}H_{25}NO_6$: C, 55.4; H, 8.27; N, 4.64.
Found: C, 54.0; H, 8.80; N, 4.90.

Also, methyl β-alanate and methyl acetonedicarboxylate gave a 60% yield of the trimethyl ester, b.p. 145–147° (1 mm.).

Anal. Calc'd for $C_{11}H_{19}NO_6$: C, 50.6; H, 7.33; N, 5.37.
Found: C, 50.6; H, 7.17; N, 5.35.

(*B*). The following procedure was devised to avoid isolation of the β-alanine esters.

A mixture of 23.2 g. of methyl β-alanate hydrochloride, 27 cc. of ethyl acetonedicarboxylate, 14 cc. of methanol, 40 cc. of acetic acid, 18 g. of lithium acetate dihydrate, and 200 mg. of platinum oxide was shaken with hydrogen at 2–3 atm. until 0.8 mole-equivalent of hydrogen was absorbed (10–20 hours). Sufficient water to dissolve the lithium salts was added and the solution worked up as in part *A*; yield, 17.4 g. (41%) of the methyldiethyl ester, b.p. 154–156° (1 mm.).

(*C*). A mixture of 20 g. of methyl glutaconate and 21.2 g. of freshly distilled *n*-butyl β-alanate was allowed to stand 24 hours. Distillation gave 19.4 g. (49%) of the dimethylbutyl ester, b.p. 165–168° (1 mm.).

Anal. Calc'd for $C_{13}H_{25}NO_6$: C, 55.4; H, 8.27; N, 4.64.
Found: C, 55.0; H, 8.32; N, 4.77.

(*D*). To a solution of 22.5 g. of methyl β-alanate hydrochloride and 28 g. of methyl glutaconate in 100 cc. of methanol was added with ice-cooling 9.4 g. of sodium methoxide. After standing for 24 hours the mixture was diluted with about 500 cc. of water and the oil isolated by chloroform extraction; yield, 18.3 g. (44%) of the trimethyl ester, b.p. 155–162° (2 mm.).

Ethyl N-(β-carbethoxyethyl)-β-benzamidoglutarate (V). To a solution of 84.5 g. of IV triethyl ester and 80 cc. of tributylamine in 220 cc. of benzene was added 36 cc. of benzoyl chloride (19). After being refluxed for one hour on the steam-bath, the solution was poured into iced hydrochloric acid. The organic layer, washed three times with 6 *N* hydrochloric acid and once each with aqueous sodium bicarbonate and water, was evaporated *in vacuo;* yield, 110.6 g. (98%) of an oil.

Anal. Calc'd for $C_{21}H_{29}NO_7$: C, 62.0; H, 7.11; N, 3.44.
Found: C, 62.4; H, 7.72; N, 3.37.

The mixed esters of IV gave similar yields.

1-Benzoyl-2-carbethoxymethyl-3 (and/or 5)-carbethoxy-4-piperidone (VI and VII). To a solution of 54 g. of V and 10.5 cc. of absolute alcohol in 195 cc. of benzene was added 8.6 g. of sodium methoxide. The solution was refluxed one hour, cooled to 2°, and extracted twice with ice-water. The aqueous extracts were immediately run into iced acetic acid. The oil which separated was extracted with ethyl acetate. The extract, washed with water, excess aqueous sodium bicarbonate, and water, was evaporated to dryness *in vacuo;* yield, 19 g. (40%) of an oil which gave a blue-black ferric chloride test.

Anal. Calc'd for $C_{19}H_{23}NO_6$: N, 3.88. Found: N, 3.62.

In other runs with the triethyl ester or mixed esters, the yields were 38–40%.

1-Benzoyl-4-piperidone-2-acetic acid (VIII). A mixture of 16 g. of the preceding keto ethyl esters and 160 cc. of 6 *N* hydrochloric acid was refluxed four hours when gas evolution was essentially complete. The cooled solution was filtered from benzoic acid and evaporated to dryness *in vacuo.* The residue (7 g.) was dissolved in 126 cc. of 1 *N* sodium hydroxide and stirred with 4.4 cc. of benzoyl chloride for ten minutes with cooling in a 20°-water bath. Then 84 cc. of 1 *N* sodium hydroxide and 4.4 cc. of benzoyl chloride were added and the mixture stirred for 10–20 minutes until all the acid chloride had reacted. The mixture was acidified and filtered from benzoic acid. The filtrate was saturated with salt and extracted three times with ethyl acetate. The combined extracts, dried with magnesium sulfate, were concentrated *in vacuo* to 10–20 cc., then seeded and allowed to stand at 3° overnight; yield, 1.05 g. (9.2%), m.p. 178–185°. Recrystallization from ethyl acetate containing a little methanol gave white crystals, m.p. 190–191°.

Anal. Calc'd for $C_{14}H_{15}NO_4$: C, 64.3; H, 5.78; N, 5.37.
Found: C, 64.0; H, 5.43; N, 5.25.

In five more runs the yields were 8–12%.

The *2,4-dinitrophenylhydrazone* was prepared by the addition of 85 cc. of test solution (120 mg. of 2,4-dinitrophenylhydrazine in 25 cc. of water and 21 cc. of 12 *N* hydrochloric acid diluted with 125 cc. of water) to 50 mg. of the keto acid in 5 cc. of water. After one hour the orange, hydrated solid was collected and dried over phosphorus pentoxide at 1 mm.; m.p. 150° with shrinking at 105°.

Anal. Calc'd for $C_{20}H_{19}N_5O_7$: C, 54.4; H, 4.34; N, 15.9.
Found: C, 54.7; H, 4.78; N, 15.7.

The *semicarbazone* separated from water as white crystals, m.p. 205°, soluble in aqueous sodium bicarbonate.

Anal. Calc'd for $C_{15}H_{18}N_4O_4$: C, 56.6; H, 5.70; N, 17.6.
Found: C, 56.9; H, 5.87; N, 17.5.

1-Benzoyl-4-hydroxypiperidine-2-acetic acid (IX). A solution of 1.00 g. of VIII in 4 cc. of 1 *N* sodium hydroxide and 8 cc. of water was shaken with 1 g. of nickel catalyst (Universal Oil Products) and hydrogen at 900 p.s.i. and 110° for 17 hours. The filtered solution was acidified and concentrated *in vacuo* to about 10 cc., then extracted with 80 cc. of ethyl acetate in three portions. The combined extracts were dried with magnesium sulfate and evaporated to dryness *in vacuo;* yield, 0.60 g. (60%) of a colorless gum which gave a negative ketone test with 2,4-dinitrophenylhydrazine test solution.

1-Benzoyl-4-acetoxypiperidine-2-acetyl chloride. A solution of 0.60 g. of the preceding hydroxy acid, IX, and 6 cc. of acetic anhydride was heated on the steam-bath for one hour. After the addition of 5 cc. of water, the solution was heated ten minutes more, then evaporated *in vacuo.* The residue was dissolved in 15 cc. of warm toluene and the evaporation repeated; yield, 0.70 g. of 1-benzoyl-4-acetoxypiperidine-2-acetic acid.

To the 0.70 g. of 1-benzoyl-4-acetoxypiperidine-2-acetic acid was added 7 cc. of redistilled acetyl chloride and 0.50 g. of phosphorus pentachloride. Solution took place after three minutes of shaking, then crystals began to separate. After five hours the mixture was filtered and the product washed with acetyl chloride; yield, 120 mg., m.p. 130–137°, which was not further purified.

Anal. Calc'd for $C_{16}H_{18}ClNO_4$: C, 59.3; H, 5.62; Cl, 11.0.
Found: C, 59.2; H, 6.05; Cl, 10.4.

When 80 mg. of crystalline acid chloride was treated with diazomethane, then with hydrogen bromide (3), only 8 mg. of oil was obtained in the bromoketone fraction. When the total acid chloride product was treated similarly, a 20% yield of oil was obtained which apparently did not have any bromoketone in it as it failed to give a condensation product with sodio 4-quinazolone.

Ethyl (3-methoxy-5-carbobenzoxyaminovaleryl)malonate (XIVb). A mixture of 25 g. of XII (2), 50 cc. of reagent ether (containing 0.5% pyridine), and 7.1 cc. of thionyl chloride was shaken for five minutes when solution was complete, then allowed to stand ten minutes more. Volatile material was removed *in vacuo* (bath 0°). The residual acid chloride, dissolved in 74 cc. of cold benzene, was added dropwise with stirring over a period of 20 minutes to the vortex of a solution of 48 cc. of ethyl malonate and 27 g. of magnesium methoxide (2) in 265 cc. of benzene. After being stirred an additional 15 minutes, the mixture was acidified with 19 cc. of acetic acid and washed with dilute hydrochloric acid and water. Solvent was removed *in vacuo*. The residue was dissolved in 150 cc. of heptane and 25 cc. of toluene and cooled to 3°. The mixture was extracted with two 50-cc. portions of iced 3% sodium hydroxide (made up by freshly mixing equal volumes of ice, water, and 10% sodium hydroxide). The lowest layer was immediately run into ice and hydrochloric acid. With the first extract three layers were formed, but the middle layer dissolved in the second extract. The organic layer now gave a negative ferric chloride test. The aqueous mixture was extracted twice with ethyl acetate. The combined extracts, washed with aqueous sodium bicarbonate and water, were evaporated to dryness *in vacuo;* yield, 29 g. (77%) of an oil which gave a red ferric chloride test.

Similarly, from 676 g. of XII was obtained 822 g. (71–80%) of product in six runs.

Anal. Calc'd for $C_{21}H_{29}NO_8$: C, 59.5; H, 6.85; N, 3.31.
Found: C, 59.4; H, 6.87; N, 3.58.

Some difficulty was experienced in this preparation in early runs which was subsequently found to be due to the instability of the acid chloride, XIIIb. After two hours at 30° or 24 hours at 3°, no crystalline anilide (2) could be obtained from the acid chloride on treatment with aniline indicating cyclization to a piperidone had taken place (20). This difficulty was avoided by use of a slight excess of thionyl chloride and concentration at 0° as described above.

Ethyl (5-carbobenzoxyaminovaleryl)malonate (XIVa). From 80 g. of XIIa (2) by conversion to the acid chloride and condensation with magnesiomalonic ester as described for XIVb there was obtained 120 g. (95%) of product as an oil which gave a red ferric chloride test and contained 10–15% of ethyl malonate. For analyses a sample was dried at 70° (0.1 mm.) over phosphorus pentoxide.

Anal. Calc'd for $C_{20}H_{27}NO_7$: C, 61.1; H, 6.89; N, 3.57.
Found: C, 60.7; H, 7.33; N, 3.82.

Ethyl (3-methoxy-5-carbobenzoxyaminovaleryl)acetate (XVb). A mixture of 94.5 g. of XIVb and 500 cc. of water was vigorously refluxed for two hours when gas evolution became slow. The insoluble oil was removed from the cooled mixture by extraction with ethyl acetate. The extract was washed with aqueous sodium bicarbonate and water, then dried with magnesium sulfate and evaporated *in vacuo;* yield, 74 g. (94%) of an oil which gave a red ferric chloride test.

Anal. Calc'd for $C_{18}H_{25}NO_6$: C, 61.4; H, 7.11; N, 3.98.
Found: C, 61.4; H, 7.25; N, 4.27.

Ethyl (5-carbobenzoxyaminovaleryl)acetate (XVa). From 144 g. of XIVa as described for XVb there was obtained 110 g. (92%) of product as an oil which gave a red ferric chloride test.

Anal. Calc'd for $C_{17}H_{23}NO_5$: C, 63.5; H, 7.22; N, 4.36.
Found: C, 63.5; H, 7.45; N, 4.44.

1-Benzoyl-2-piperidineacetic acid. (A). A solution of 10.1 g. of the keto malonate, XIVa, in 50 cc. of acetic acid was shaken with 3 g. of Norit for ten minutes, then filtered, and the Norit washed with 25 cc. of acetic acid. After the addition of 3 g. of 10% palladium-char-

coal, the mixture was shaken with hydrogen at 2–3 atm. for six hours when hydrogenation stopped (83 mole-% absorbed). Then 300 mg. of platinum oxide was added and the hydrogenation continued overnight (75 mole-% absorbed). The mixture was filtered through Celite and evaporated to dryness *in vacuo*. The residue was refluxed in 70 cc. of 6 *N* hydrochloric acid for two hours when gas evolution was complete, then evaporated *in vacuo*. The residual crude 2-piperidineacetic acid hydrochloride (XXa) was benzoylated as previously described (3) to give 3.5 g. (55%) of product, m.p. 137–141°. Recrystallization from benzene-heptane gave white crystals, m.p. and mixed m.p. 144–145°.

Anal. Calc'd for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.93; N, 5.67.
Found: C, 68.3; H, 6.98; N, 6.04.

The *anilide* was obtained in the usual manner *via* the thionyl chloride prepared acid chloride in 65% yield, m.p. 140–143°. Recrystallization from dilute methanol gave white crystals, m.p. 142–144°.

Anal. Calc'd for $C_{20}H_{22}N_2O_2$: C, 74.5; H, 6.83; N, 8.69.
Found: C, 74.1; H, 7.31; N, 8.86.

(*B*). A solution of 5.7 g. of keto acetate, XVa, in 25 cc. of ethyl acetate was shaken with 2 g. of Norit for ten minutes, then filtered and the Norit washed with 25 cc. of ethyl acetate. This solution was added to a suspension of 2 g. of 10% palladium-charcoal in 20 cc. of acetic acid and shaken with hydrogen at atmospheric pressure until reduction stopped (80 minutes, 50% of two mole-equivalents absorbed). No additional hydrogen was absorbed after the addition of 50 mg. of platinum oxide. The reduction mixture was worked up as in part *A* to give 14–30% of 1-benzoyl-2-piperidineacetic acid, identified by mixed m.p.

Ethyl 4-methoxy-1,4,5,6-tetrahydro-2-pyridylacetate (XVIIIb). A solution of 20 g. of the keto acetate, XVb, in 75 cc. of absolute alcohol was stirred with 6 g. of Norit for ten minutes, filtered, and the Norit washed with 75 cc. of absolute alcohol. The filtrate, added to a suspension of 5 g. of 10% palladium-charcoal suspended in 45 cc. of Methyl Cellosolve, was shaken with hydrogen at 2–3 atm. for 15–20 hours (100 mole-% absorbed). The filtered solution was evaporated to dryness *in vacuo* and the residue (16.7 g.) dissolved in 50 cc. of cold chloroform. The solution was washed with 28 cc. of ice-cold 10% sodium hydroxide, then dried with magnesium sulfate and evaporated *in vacuo*. Distillation gave 4.8 g. (43%) of a yellow oil, b.p. 110–125° (1 mm.), mainly at 123–125°. Two runs were combined and redistilled in a modified Claisen flask and a portion b.p. 124–126° (1 mm.) was submitted for analysis. The compound was not quite pure.

Anal. Calc'd for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.53; N, 7.03.
Found: C, 59.7; H, 8.34; N, 7.65.

Ethyl 1,4,5,6-tetrahydro-2-pyridyl malonate (XVIa). Reduction of 25 g. of the keto malonate, XIVa, as described in the previous experiment gave 9.9 g. (63%) of a colorless oil, b.p. 143–144° (1 mm.), which was nearly pure.

Anal. Calc'd for $C_{12}H_{19}NO_4$: C, 59.9; H, 7.89; N, 5.80.
Found: C, 59.2; H, 8.10; N, 6.16.

A solution of 1.00 g. of XVIa in 10 cc. of 6 *N* hydrochloric acid was refluxed for 90 minutes when gas evolution was complete. Evaporation *in vacuo* gave 0.77 g. of crystalline 1-amino-5-hexanone hydrochloride which was benzoylated to 1-benzamido-5-hexanone as previously described (21); yield, 0.60 g. (66%), m.p. 74–77°. The *2,4-dinitrophenylhydrazone* formed orange-yellow crystals from methanol, m.p. 127–129°.

Anal. Calc'd for $C_{19}H_{21}N_5O_5$: C, 57.1; H, 5.26; N, 17.6.
Found: C, 57.0; H, 5.71; N, 18.0.

Lipp (22) has recorded m.p. 75–76° for the 1-benzamido-5-hexanone.

Ethyl 1,4,5,6-tetrahydro-2-pyridylacetate (XVIIIa). By hydrogenation of 20 g. of the keto acetate, XVa, as described for XVIIIb there was obtained 5 g. (48%) of a colorless oil, b.p. 96–98° (1 mm.).

Anal. Calc'd for $C_9H_{15}NO_2$: N, 8.28. Found: N, 8.69.

Hydrolysis and benzoylation as in the preceding experiment gave a 37% yield of 1-benzamido-5-hexanone, m.p. 73–75°.

Ethyl 5,6-dihydro-2-pyridylmalonate (XIX). Hydrogenation of 25 g. of XIVb in the same

manner as described for XIVa gave, after two distillations, 6.9 g. (49%) of product, b.p. 153° (1 mm.).

Anal. Calc'd for $C_{12}H_{17}NO_4$: C, 60.3; H, 7.17; N, 5.86; CH_3O, 25.9.
Found: C, 59.5; H, 7.81; N, 5.84; CH_3O, 25.3.

Ethyl 4-methoxy-2-piperidineacetate (XXIVb). A mixture of 30 g. of ethyl 4-methoxy-1,4,5,6-tetrahydro-2-pyridylacetate (XVIIIb), b.p. 110–125° (1 mm.), two teaspoons of Raney nickel catalyst, and 18 cc. of absolute alcohol was shaken with hydrogen at 120° at an initial pressure of 2000 p.s.i. for 2½ hours when reduction became slow (103 mole-%). Distillation gave 24.7 g., b.p. 85–110° (1 mm.), which was redistilled in a modified Claisen flask; yield, 15.9 g. (53%) of a colorless oil, b.p. 85–92° (1 mm.).

Anal. Calc'd for $C_{10}H_{19}NO_3$: N, 6.98. Found: N, 6.91.

1-Benzoyl-4-methoxy-2-piperidineacetic acid (XXIIIb, R′ = C_6H_5). (*A*). A solution of 1.00 g. of XXIVb in 10 cc. of 6 *N* hydrochloric acid was refluxed for 30 minutes. There was *no* gas evolution. The solution was evaporated to dryness *in vacuo* and the residue benzoylated as usual (3). The residue from the chloroform extracts was extracted several times with hot heptane until no more benzoic acid was removed. The nearly colorless gum (0.80 g.) was crystallized from benzene; yield, 200 mg. (15%), m.p. 136–148°. Recrystallization from toluene gave white crystals, m.p. 153–156°.

Anal. Calc'd for $C_{15}H_{19}NO_4$: C, 64.9; H, 6.92; N, 5.06; CH_3O, 11.2.
Found: C, 65.1; H, 7.16; N, 5.01; CH_3O, 9.96.

(*B*). A solution of 2.00 g. of XXIVb in 20 cc. of chloroform, stirred with 1.1 g. of anhydrous sodium carbonate in 15 cc. of water, was treated dropwise with 1.3 cc. of benzoyl chloride. After being stirred for 30 minutes, the layers were separated and the aqueous portion extracted once more with chloroform. The combined extracts were evaporated to dryness *in vacuo*. The residual benzoyl ester, XXIVb, (3.5 g.) was refluxed with 8 cc. of alcohol and 8 cc. of 10% sodium hydroxide for 30 minutes. The clear solution was concentrated *in vacuo* to remove alcohol, then diluted to the original volume with water, and acidified. The oil was removed by two extractions with chloroform. The combined extracts were evaporated *in vacuo* and the residue crystallized from toluene; yield, 2.08 g. (76%), m.p. 153–156°.

The *anilide* was obtained from the thionyl chloride-prepared acid chloride in 59% yield, m.p. 130–136°. Recrystallization from methanol-water gave white crystals, m.p. 133–135°.

Anal. Calc'd for $C_{21}H_{24}N_2O_3$: N, 7.95. Found: N, 8.02.

1-Carbethoxy-4-methoxy-2-piperidineacetic acid (XXIIIb, R′ = OEt). To a stirred solution of 1.00 g. of XXIVb in 10 cc. of chloroform and a solution of 0.53 g. of sodium carbonate in 10 cc. of water cooled in an ice-bath was added 0.53 cc. of ethyl chlorocarbonate. After 15 minutes the mixture was worked up as in the preceding experiment, procedure *B;* yield, 1.17 g. (96%) of a yellow gum.

Anal. Calc'd for $C_{11}H_{19}NO_5$: C, 53.8; H, 7.75; N, 5.71.
Found: C, 53.5; H, 7.95; N, 5.89.

The *anilide* was obtained in 84% yield as an oil which could not be crystallized.

Anal. Calc'd for $C_{17}H_{24}N_2O_4$: N, 8.75. Found: N, 8.78.

1-Carbethoxy-2-(γ-bromoacetonyl)-4-methoxypiperidine (XXII, R′ = OEt). By conversion of 4.2 g. of 1-carbethoxy-4-methoxy-2-piperidineacetic to the acid chloride, diazoketone, and bromoketone as described for 1-benzoyl-2-piperidineacetic acid (3), there was obtained 4.8 g. (87%) of an oil.

3-[β-Keto-γ-(4-hydroxy-2-piperidyl)propyl]-4-quinazolone dihydrochloride (XXVI). By condensation of 2.0 g. of 4-quinazolone in 13.6 cc. of 1 *N* sodium methoxide with 4.8 g. of the preceding bromoketone in the usual manner (3) there was obtained 5.6 g. of an oily base (XXVb, R′ = OEt). This oil in 56 cc. of 48% hydrobromic acid was refluxed for ten minutes. The dark solution was evaporated to dryness *in vacuo* and the residue crystallized from 56 cc. of saturated absolute alcoholic hydrogen chloride; yield, 2.0 g. (36%), m.p. 225–226° dec. Recrystallization from methanol by addition of absolute alcoholic hydrogen chloride gave white crystals, m.p. 232–233° 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; Cl, 18.3.
Found: C, 49.1; H, 5.32; N, 10.9; Cl, 18.2.

The *carbamyl derivative*, prepared with potassium cyanate, formed nearly white crystals from 40% methanol, m.p. 190–191° dec.

Anal. Calc'd for $C_{17}H_{20}N_4O_4 \cdot H_2O$: C, 56.4; H, 6.06; N, 15.5.
Found: C, 56.4, 56.7; H, 5.76, 6.13; N, 16.0.

SUMMARY

A structural isomer of the Hydrangea alkaloid, 3-[β-keto-γ-(4-hydroxy-2-piperidyl) propyl]-4-quinazolone, has been synthesized *via* the key intermediates, 3-methoxy-5-carbobenzoxyaminovaleric acid and 1-carbethoxy-4-methoxy-2-piperidineacetic acid.

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