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

AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. XX. A SECOND SYNTHESIS.[1]

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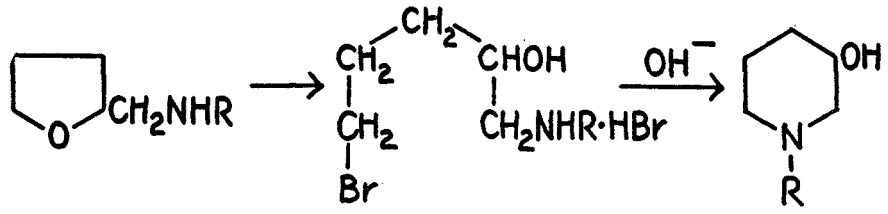
One of the few methods described in the literature for the synthesis of a 3-hydroxypiperidine is that of Paul and Tchelitcheff (1). When a tetrahydrofurfurylamine (I) is treated with hydrogen bromide ring opening to a bromohydrin hydrobromide (II) takes place. Liberation of the free base causes spontaneous cyclization to a 1-substituted-3-hydroxypiperidine (III). This attractive method starting with furfural has now been found to be adaptable to the synthesis of the Hydrangea alkaloid, a 2-substituted 3-hydroxypiperidine.



I II III

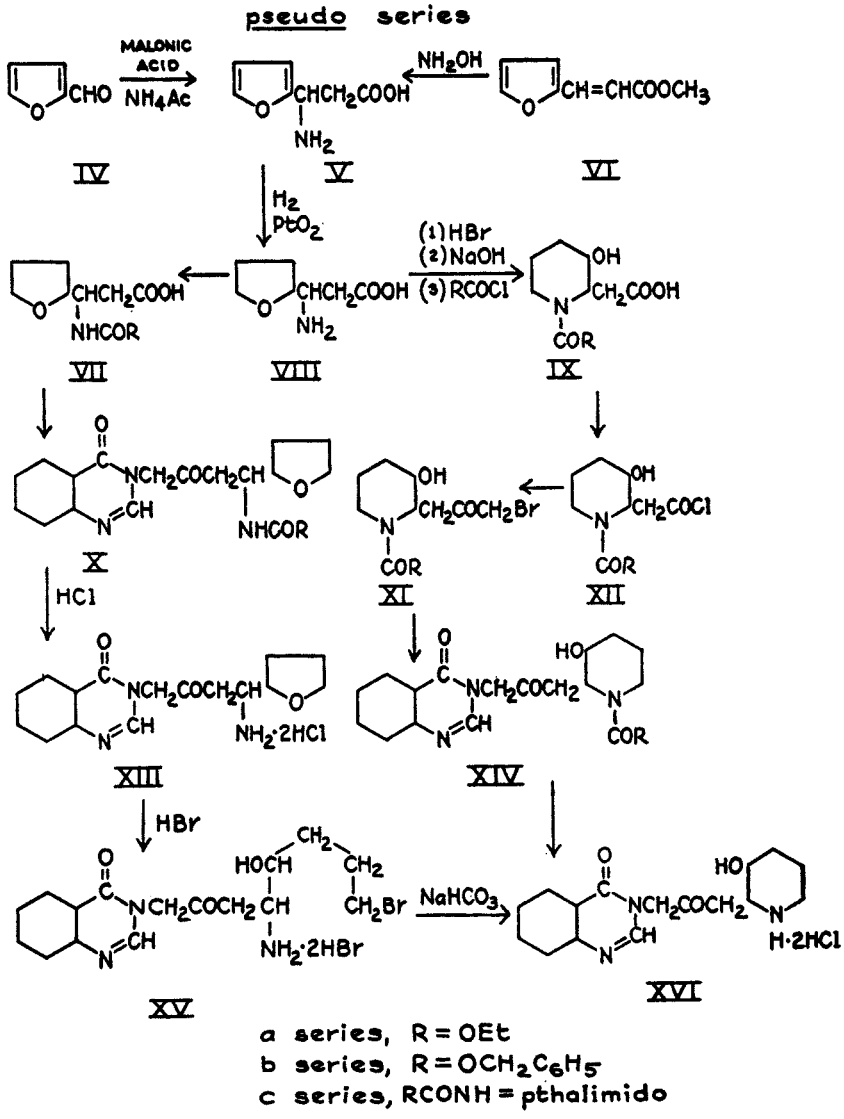
Posner (2) has prepared β-furyl-β-alanine (V) in 20% yield by treatment of ethyl β-furylacrylate with hydroxylamine. By suitable modifications the yield has been raised to 54%. Unfortunately the yields rapidly diminished as the size run was progressively increased over 50 g. When larger quantities were needed another method was sought which would be adaptable to a large scale. Direct condensation of ammonia, furfural, and malonic acid failed to give any β-furyl-β-alanine (V), a process used for β-aminohydrocinnamic acid (3). Replacement of the ammonia with ammonium acetate (4) gave V in 25% yield.

Reduction of the furan ring proceeded in quantitative yield. One of two possible racemates (VIII) could be crystallized at this point, but with some loss. Better over-all yields were obtained without purification. The tetrahydrofuran ring was opened to a bromohydrin with 48% hydrobromic acid at 100°, then cyclized with 10% sodium hydroxide to 3-hydroxypiperidine-2-acetic acid. This amino acid was best isolated by carbethoxylation to IXa which was isolated as an oil in 70% over-all yield from VIII.[2]

[1] Papers XX and XXI of this series were presented at the Fourth Summer Seminar on Natural Products, University of New Brunswick, Canada, August, 1952. These papers were also part of a lecture presented April 27–May 9, 1952 at the following universities: Illinois, Iowa, Michigan, Northwestern, Notre Dame, and Wisconsin.

[2] It is interesting to note that Paul and Tchelitcheff (1) state that this sequence will not succeed with tetrahydrofurfurylamine, but that the amine must be secondary.

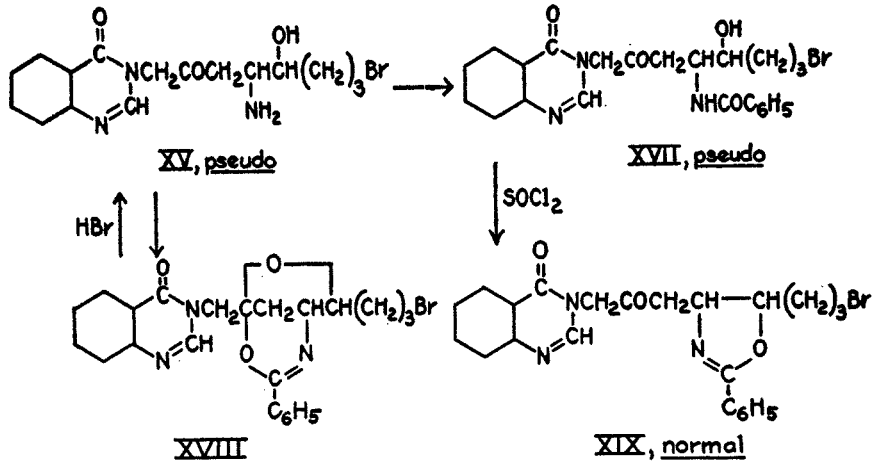
In order to lengthen the side chain to γ-bromoacetonyl *via* the acid chloride, it was thought necessary to block the hydroxyl group by acetylation before acid chloride formation. However, numerous attempts to acetylate the hydroxyl group, including several hours boiling with acetyl chloride, failed to introduce



any appreciable O-acetyl and the products were completely bicarbonate-soluble showing no lactone formation. The inertness of an ethanolamine type of hydroxyl has been described in the literature many times. Since the hydroxyl group was so inert to an acid chloride, it was considered possible to make the hydroxy acid chloride (XIIa) without blocking the hydroxyl group. This was

indeed found to be the case. The acid chloride was converted to the bromoketone (XIa) in the usual fashion with diazomethane and hydrogen bromide. Condensation with 4-quinazolone and hydrolysis gave crystalline XVI, in 6% over-all yield from IXa. This compound was geometrically isomeric to the Hydrangea alkaloid, was inactive as an antimalarial, and is designated as the *dl-pseudo*-alkaloid.

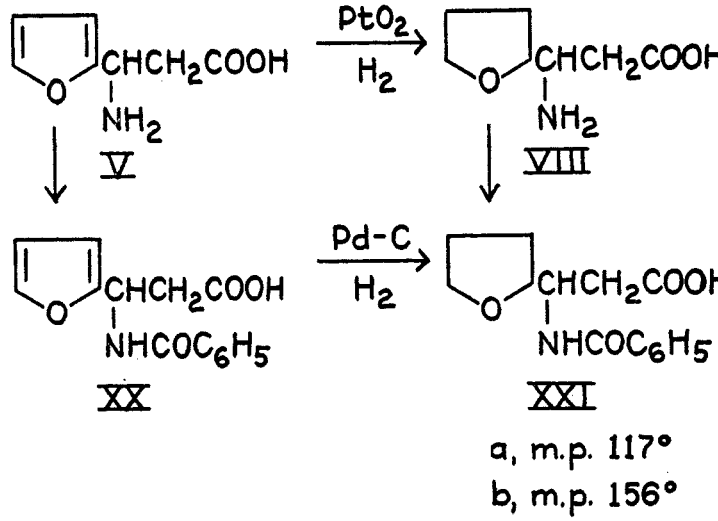
A second route to XVI was also investigated. The amino group of VIII was blocked by carbethoxylation, carbobenzoxylation, or phthalation (VII). The carboxyl group was built up to the bromomethyl ketone in the usual fashion from the acid chloride. Condensation with 4-quinazolone to X and hydrolysis gave the same amino ketone dihydrochloride (XIII) by use of all three blocking groups. The best over-all yield was obtained with the carbobenzoxy blocking group. When heated one hour with 48% hydrobromic acid at 100°, XIII formed the crystalline bromohydrin hydrobromide (XV) in 75% yield. Cyclization with aqueous sodium bicarbonate afforded the alkaloid isomer (XVI) in 76% yield identical with that obtained *via* IXa.



A study of the inversion of the configuration of the *dl-pseudo*-alkaloid or one of its precursors to the *normal* alkaloid configuration was undertaken. Ethanolamines such as threonine and 2-aminocyclohexanol have been inverted by the sequence XV (*pseudo*) → XVII → XIX $\xrightarrow{HCl}$ XV (*normal*) (5, 6). It was unsuccessful in this series since benzoylation of XV did not give XVII, but a product with the loss of an additional molecule of water which could have been either XVIII or XIX. Hydrolysis of the benzoylation product gave *pseudo* XV with unchanged configuration. Thus the benzoylation product could not have been XIX which usually forms by break of the C—OH bond with inversion. It is probable that the benzoylation product had the ketal structure XVIII which would not effect the C—O bond at position 5 of the side chain. It is also possible that XIX could represent the benzoylation product if O-benzoylation proceeded first followed by ring closure on the amine. An attempt to replace the hydroxyl group of XV dihydrobromide with chlorine by the use of thionyl chloride gave only

XV dihydrochloride. Introduction of pyridine into the reaction mixture as a catalyst did not give any isolatable products. Similar results were obtained with thionyl chloride and the *dl-pseudo*-alkaloid (XVI).

Since inversion studies were unsuccessful it was necessary to reinvestigate the isomer-determining step in the synthesis of the *pseudo*-alkaloid to see if it could be modified to give predominately the *normal* racemate. The isomer determining step was the hydrogenation of β-furyl-β-alanine (V) to the tetrahydro derivative (VIII) since further transformations to the *pseudo*-alkaloid do not break any bond attached to an asymmetric carbon. Benzoylation of VIII yielded the N-benzoyl derivative (XXIa), m.p. 117°. However, reversal of these reactions, that is benzoylation to XX followed by hydrogenation gave predominately the XXIb isomer, m.p. 156°, in a ratio of at least 7–3.

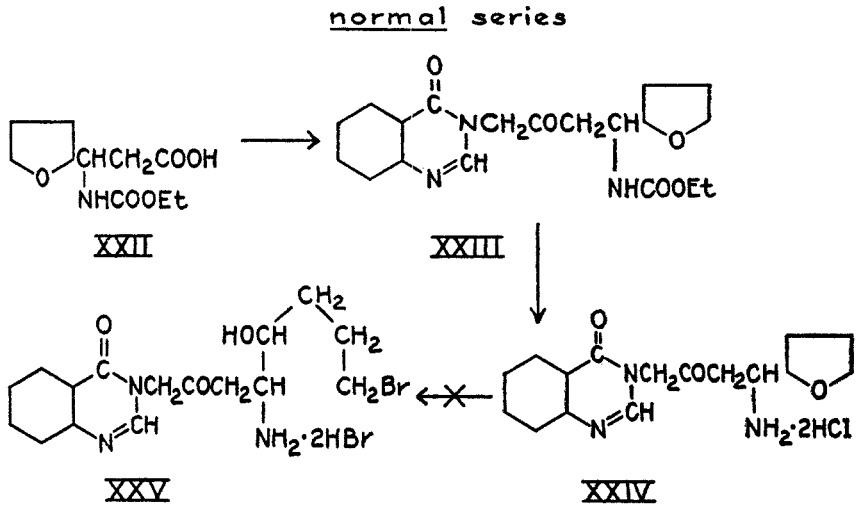


The build up of the alkaloid side chain from XXIb directly with the benzoyl blocking group was not tried since the acid chloride formed poorly. This was avoided by hydrochloric acid hydrolysis followed by carbethoxylation to XXII. The oily acid was converted to the acid chloride, diazoketone, and bromoketone in the usual manner. Condensation with 4-quinazolone gave crystalline XXIII, m.p. 127°, which was isomeric to the *pseudo*-isomer, Xa, m.p. 131°. Hydrochloric acid hydrolysis of XXIII gave XXIV in 55% yield. When XXIV was treated with 48% hydrobromic acid for one hour at 100°, the conditions used satisfactorily for the *pseudo*-isomer (XIII), the dihydrobromide of XXIV was recovered, there was some carbonization, and no appreciable amount of the bromohydrin (XXV) was formed. As the reaction time was increased, there was more carbonization and XXV still could not be isolated.

When *normal*-β-benzamido-β-tetrahydrofurylpropionic acid (XXIa) was treated with 48% hydrobromic acid at 100° for three hours none of the easily isolatable bromolactone hydrobromide (XXVI) was obtained although the N-benzoyl group was completely removed. Three hours at 125° gave 29% of

XXVI. A maximum yield of XXVI was obtained after 24 hours at 100°. After this time the yield began to decrease. Thus, there is a tremendous difference in rate of ring opening of the *pseudo* racemate, which requires one hour at 100°, compared to the *normal* racemate. This apparently carries over to XXIV and XIII also. When XXIV was treated with 48% hydrobromic acid at 100° for 24 hours, complete carbonization took place.

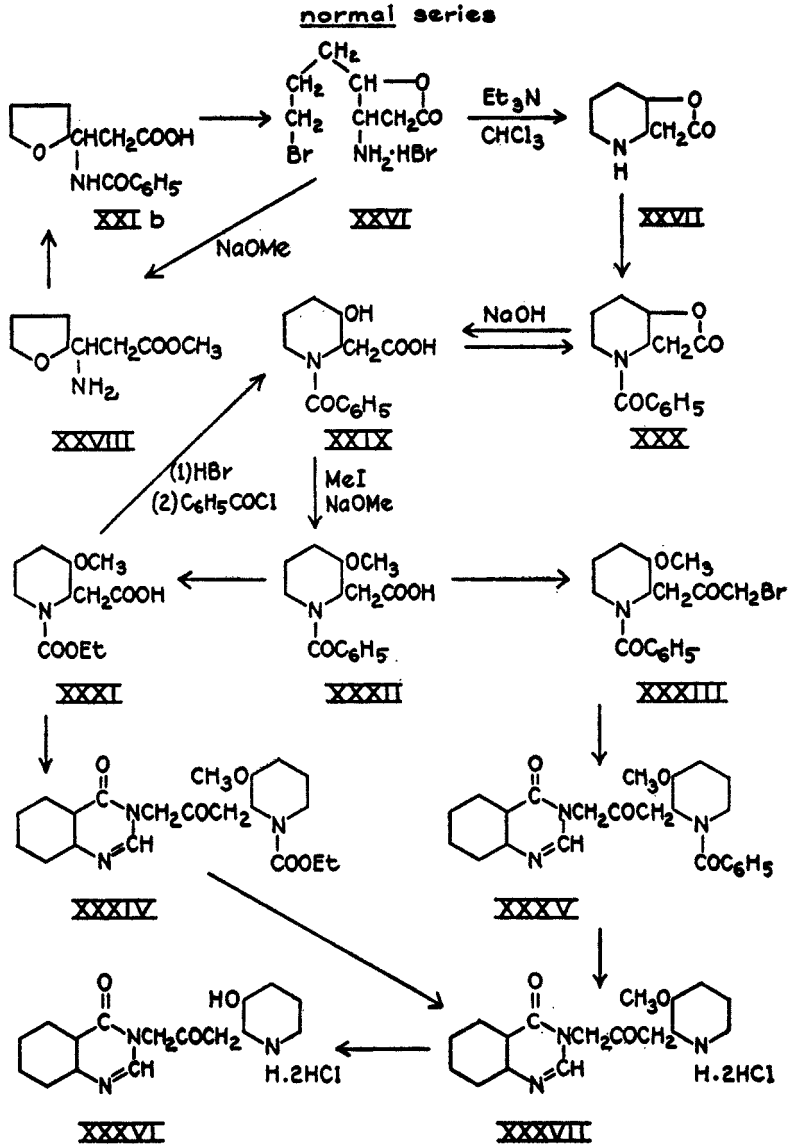
A study of the rate of ring closure of the bromolactone (XXVI) to the piperidine lactone and/or one of its related lactone-opened products was made. In methanol ring closure was complete with sodium methoxide at 25° in 30 minutes as evidenced by Mohr titration of the bromide liberated. With triethylamine the ring closure was much slower since reaction was 63% complete in eight hours and 72% in 15 hours. With aqueous sodium bicarbonate the ring closure was too slow to be practical.



The sodium methoxide ring closure product would have been expected to be methyl 3-hydroxypiperidine-2-acetate. However, benzoylation or carbobenzoxylation followed by alkaline hydrolysis did not give XXIX, but instead gave XXIb and β-carbobenzoxyamino-β-tetrahydrofurylpropionic acid, respectively, characterized as their anilides. It is apparent that methanolic sodium methoxide *trans*-esterifies the bromolactone (XXVI) to methyl 3-amino-4-hydroxy-7-bromoheptanoate. The bromine then reacts much more rapidly with the hydroxyl group than the amino group thus cyclizing back to XXVIII.

Ring closure of XXVI with triethylamine in chloroform gave the unstable piperidinelactone (XXVII), characterized as its stable crystalline hydrochloride and N-benzoyl derivatives (XXX). In this reaction the hydroxyl group is blocked and ring closure to a piperidine is the only way in which the elements of hydrogen bromide can be eliminated. The yield of benzoyl lactone (XXX) was considerably increased to 62–65% if the chloroform solution of XXVII and triethylamine was treated directly with benzoyl chloride. The lactone ring was readily opened with alkali to the hydroxy acid (XXIX) in 95–98% yield. This

hydroxy acid was readily ring closed back to the crystalline lactone (XXX) by such reagents as acetic acid, dilute hydrochloric acid, acetyl chloride, acetic anhydride, ethyl chlorocarbonate, and triethylamine, thionyl chloride, or phenyl



isocyanate. This ease of ring closure contrasts sharply with the stability of the *pseudo*-hydroxy acid, IX. This establishes the *normal* series as *cis* and the *pseudo* series as *trans*.

Hydrobromic acid hydrolysis of 1-carbethoxy-3-methoxypiperidine-2-acetic acid (XXXI), the intermediate used in the first synthesis of the Hydrangea

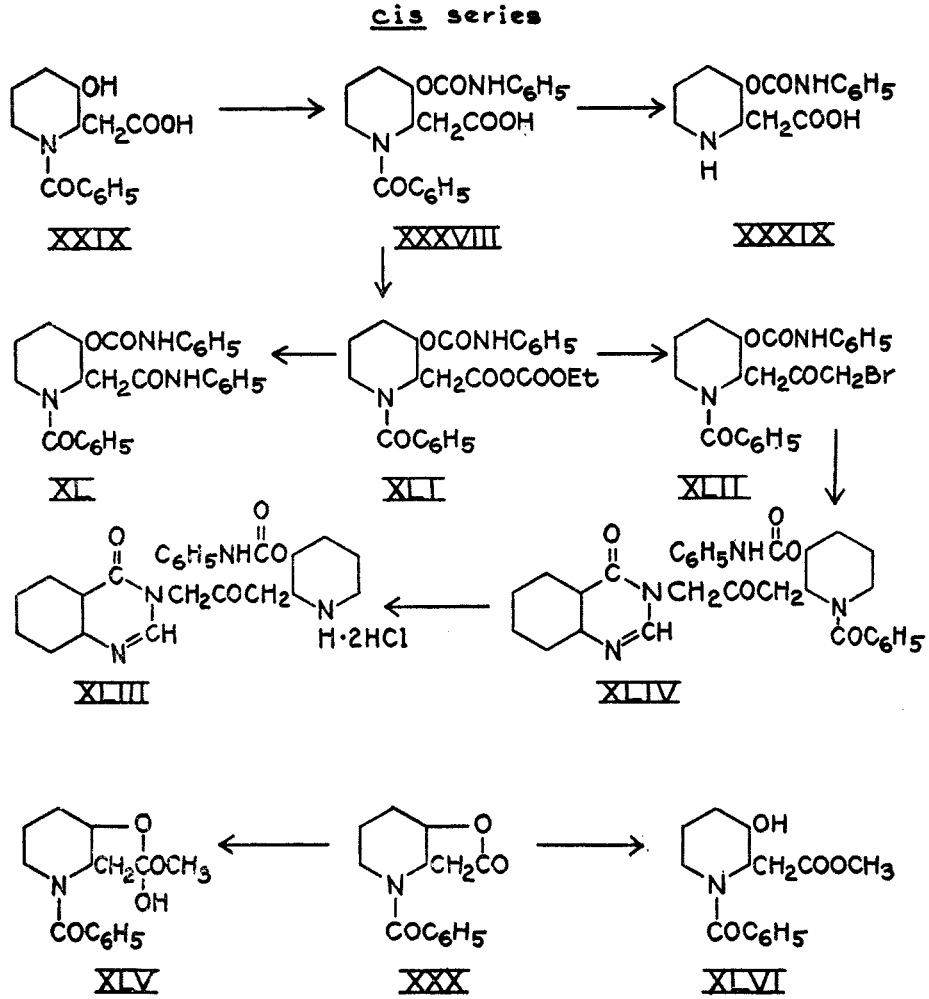
alkaloid (7), followed by benzoylation gave 1-benzoyl-3-hydroxypiperidine-2-acetic acid (XXIX) identical with that obtained from XXX, thus establishing the *normal* alkaloid as having the *cis*-configuration and simultaneously proving XXX to have the correct configuration for synthesis of the alkaloid. Thus the supposition that this whole series of compounds starting with N-benzoyl-β-furyl-β-alanine (XX) have the correct stereochemical configuration related to the alkaloid is completely validated.

Methylation of the dry disodium salt of 1-benzoyl-3-hydroxypiperidine-2-acetic acid (XXIX) to the methyl ether (XXXII) with methyl iodide proceeded in 43% yield and 18% of the lactone (XXX) was recovered by treatment of the mixture with acetic anhydride so that the bicarbonate-soluble methoxy acid (XXXII) could be separated from the bicarbonate-soluble hydroxy acid (XXIX) by conversion of the latter to the bicarbonate-insoluble lactone (XXX). Hydrochloric acid removal of the benzoyl group of XXXII, followed by carbethoxylation gave the oily 1-carbethoxy-3-methoxypiperidine-2-acetic acid (XXXI), an intermediate in the first synthesis of the *dl*-alkaloid (7). The side chain was lengthened to γ-bromoacetonyl, then condensed with sodio-4-quinazolone to the crystalline carbethoxy quinazolone (XXXIV), identical with that obtained in the first synthesis of the *dl*-alkaloid (7). The synthesis is completed by a two-stage hydrolysis to the *dl*-alkaloid (XXXVI).

Since in this method the N-benzoyl group was changed to N-carbethoxy with some losses, use of XXXII directly to XXXVII was investigated. Chain lengthening to the oily bromoketone (XXXIII) proceeded in 86% yield. Condensation with 4-quinazolone gave 85% of the N-benzoyl quinazolone (XXXV) as a gum which had a maximum purity of 55% as shown by u.v. analysis, calculating to a real yield of 47%. Hydrolysis with 6 *N* hydrochloric acid removed the N-benzoyl blocking group, but did not give the *dl*-alkaloid methyl ether (XXXVII), as shown by comparative I.R. spectra with XXXVII obtained in the first synthesis of the *dl*-alkaloid (7), and the failure to obtain the *dl*-alkaloid on further hydrolysis.

Two other blocking groups for the hydroxyl of XXIX were investigated prior to the methylation reaction to XXXII. Due to the ease with which the hydroxy acid (XXIX) lactonizes to XXX, the choice of a reagent for acylation is not simple since all acylating agents are also dehydrating agents. For example, when XXIX was treated with phenyl isocyanate in chloroform, rapid formation of diphenylurea took place with concurrent cyclization back to the lactone (XXX). This could theoretically be avoided by reaction on the sodium salt or the methyl ester (XLVI). The lactone (XXX) rapidly reacted with methanolic sodium methoxide to give what appeared to be the methyl ester (XLVI). This compound, treated with *p*-bromophenyl isocyanate, gave a non-crystalline *p*-bromophenylurethan. However, mild alkaline hydrolysis did not give the expected bromo derivative of XXXVIII, but led to the hydroxy acid (XXIX). These results could be explained on the basis that methanolysis of the lactone (XXX) does not give the normal ester (XLVI) but an ortho ester (XLV), which would form a phenylurethan, but would hydrolyze to the hydroxy acid (XXIX). That a

normal phenylurethan was not formed was further indicated by the stability of XXXVIII to the conditions of the hydrolysis.



If an O-acylation reaction is run on the sodium salt of XXIX to avoid lactonization, the acylating agent cannot evolve any acidic by-product such as acetic or hydrochloric acid which would neutralize the sodium salt and allow lactonization. Two of the few reagents which satisfy these rigorous specifications are isocyanates which give no by-products and isopropenyl acetate which gives the neutral acetone as a by-product.

Treatment of the dry mono sodium salt of XXIX with phenyl isocyanate in pyridine gave the phenylurethan (XXXVIII) in 36–44% yield. The yield of the acid chloride of XXVIII necessary for formation of the bromo ketone (XLII) was poor. Yields of 16–36% of anilide (XL) were obtained under a variety of conditions and considerable quantities of unchanged acid were always recovered.

In contrast, the yield of *p*-chloroanilide *via* the mixed anhydride (XLI) (8) was 92%. Since a mixed anhydride of this type had not been previously reacted with diazomethane to give a diazoketone, the reaction was tried with the mixed anhydride from phthalyl glycine (8) and found to proceed satisfactorily. The mixed anhydride (XLI) was reacted with diazomethane, then with hydrobromic acid to give the crude bromo ketone (XLII) in quantitative yield. This was condensed with 4-quinazolone in the usual fashion to give XLIV in 92% yield as a crude gum which could not be crystallized. A four-hour hydrolysis with boiling 6 *N* hydrochloric acid removed the benzoyl group, but not the phenylurethan blocking group, giving the crystalline dihydrochloride (XLIII) in 21% yield. This compound was further characterized as its N-carbamyl derivative. The surprising stability of the carbanilino group was further demonstrated by a four-hour boiling, 6 *N* hydrochloric acid hydrolysis of the carbanilino acid (XXXVIII) which gave the amino acid (XXXIX) in 70% yield.

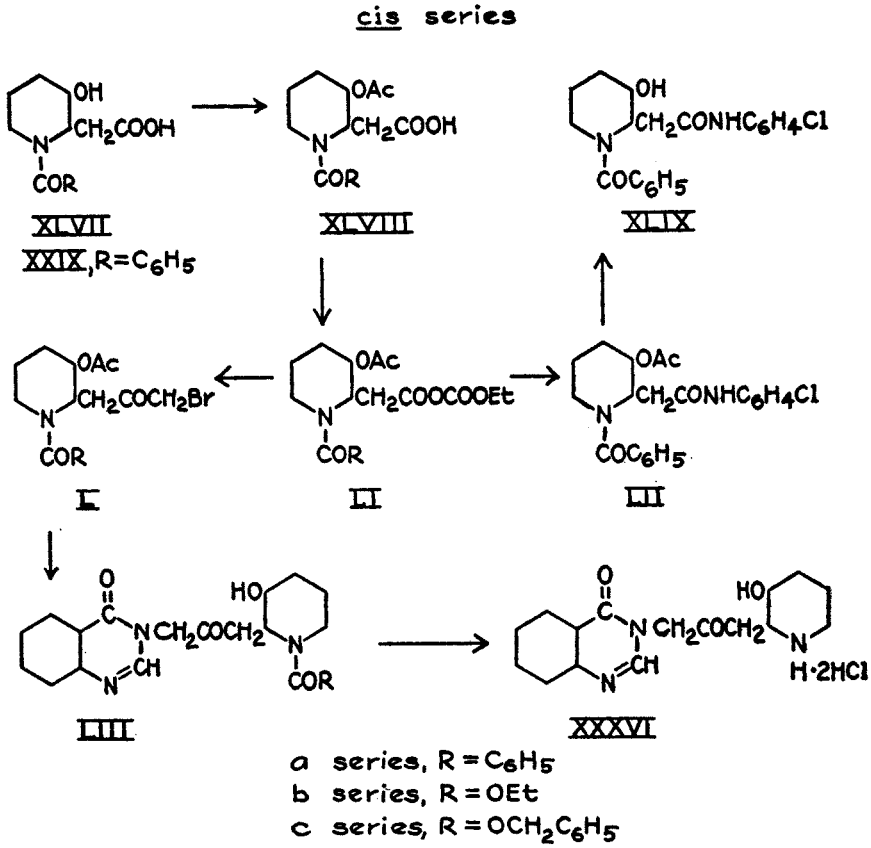
A model compound, N-benzoyl-O-carbanilinoethanolamine, was then subjected to hydrolysis studies. Hydrochloric acid failed to cause hydrolysis due to insolubility. The use of a diluent would cause complications for comparative purposes. However, boiling 48% hydrobromic acid caused hydrolysis of both blocking groups in 20 minutes, aniline being isolated in 93% yield as the tribromo derivative. When the O-carbanilino derivative of the alkaloid (XLIII) was subjected to hydrolysis with boiling 48% hydrobromic acid for 20 minutes, it was recovered unchanged. When the hydrolysis time was increased to one hour, only about 30% of XLIII was recovered, but the remainder suffered further hydrolytic cleavage since the mixture contained less than 5% yield of *dl*-alkaloid by assay. When XLIII was refluxed in 1:1 hydriodic acid (*d*,1.5) and acetic acid for over two hours, 72% was recovered unchanged.

It became obvious at this time that a more easily removable O-blocking group should be employed. Treatment of the dry mono sodium salt of XXIX with isopropenyl acetate in hot pyridine gave the crystalline O-acetyl derivative (XLVIIIa) in about 45% yield. This compound formed a *p*-chloranilide (LII) in 69% yield *via* the mixed anhydride (LIa). The mixed anhydride gave the bromoacetonyl compound (La) in the usual fashion as an oil in quantitative yield. Condensation with 4-quinazolone proceeded to LIIIa in 41% yield as a crude gum; it is probable that the O-acetyl group is lost under the conditions of the condensation as shown by the ease of deacetylation of LII to XLIX by methanolic sodium methoxide. When LIIIa was subjected to hydrolysis with boiling 6 *N* hydrochloric acid, almost complete disruption of the side chain took place; the only isolatable product was 4-quinazolone hydrochloride in 28% yield and less than 5% *dl*-alkaloid was formed as shown by assay.

Since the alkaloid is very stable to boiling acid (9) it is obvious that the N-benzoyl derivative is unstable to acid and that the N-benzoylated side chain decomposes at a faster rate than the N-benzoyl group is removed. To overcome this difficulty two alternatives were possible:

(*a*) A more easily removable N-blocking group such as carbethoxy or carbobenzoxy should be employed.

(*b*) A more stable O-blocking group than acetyl, but less stable than carbanilino should be used such as O-methyl which was employed in the first synthesis of the alkaloid (7).

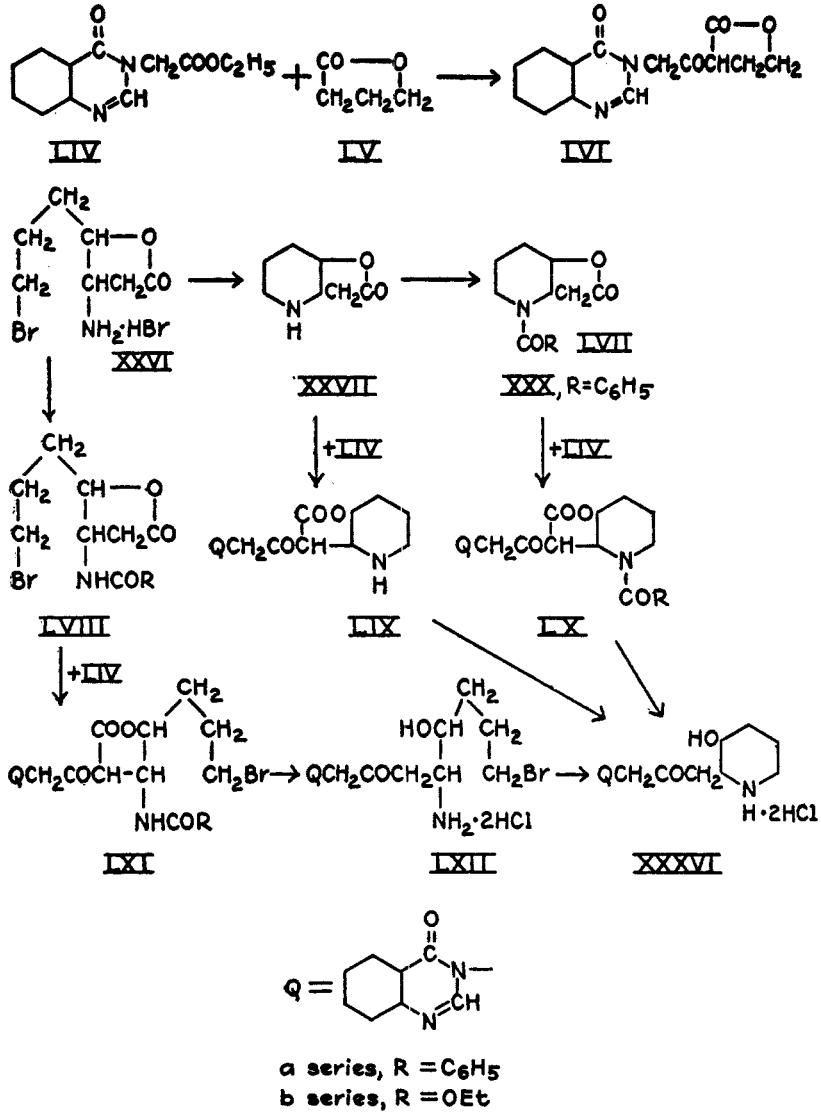


Alternative (*a*) was first investigated. All of the intermediates, XLVII–LIII (b and c) were oils. None of the *dl*-alkaloid (XXXVI) was obtained by removal of the carbobenzoxy group of LIIIc catalytically nor was any obtained when the carbethoxy derivative (LIIIb) was subjected to a five-minute hydrolysis with boiling 48% hydrobromic acid. Thus, it appeared that alternative (*b*) was the only solution to the blocking group problem which had to be solved to complete the synthesis. This has been described earlier in this publication for the sake of continuity rather than chronology.

Two other of the many ways investigated for the potential synthesis of the *dl*-alkaloid bear mentioning.

It has been shown in a previous publication (10) that Claisen condensation of ethyl 4-quinazolone-3-acetate (LIV) and another ester would not take place, but that LIV suffered self condensation. Since it is well known that an activated methylene group in a ring is much more active than the same activated methyl-

ene in an open chain compound (compare cyclohexanone and 3-hexanone), it was considered possible that a lactone might Claisen condense with LIV. This has indeed been found to be the case with butyrolactone, condensation rapidly taking place with sodium methoxide in benzene containing some ethanol to give

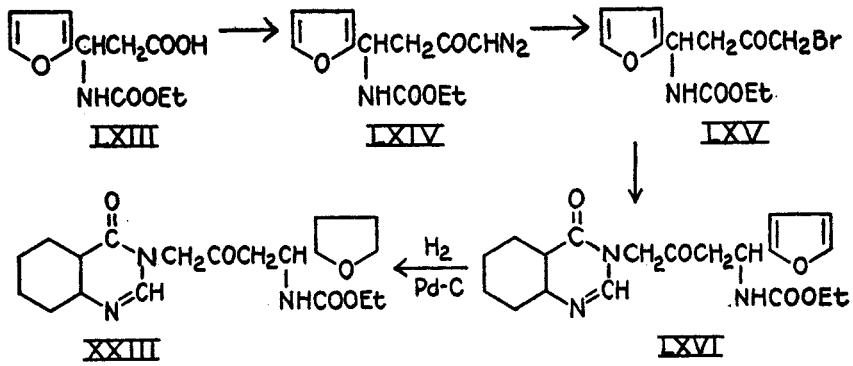


a 25% yield of LVI. However, 3-hydroxypiperidine-2-acetic acid lactone (XXVII) and its acyl derivative (LVII) are rapidly converted to the methyl esters with sodium methoxide. Thus these ordinary conditions (10) of Claisen condensation could not be used. It was then found that sodium *tert*-butoxide in boiling benzene could be substituted for sodium methoxide in the Claisen condensation to the model compound (LVI) in the same yield. When these condi-

tions were applied to XXX, the intermediate LX could not be isolated. Hydrolysis of the crude reaction mixture and separation from 4-quinazolone-3-acetic acid by extraction from alkaline solution gave a maximum yield of 3-alkyl-4-quinazolone (XXXVI?) of 0.5% as shown by u.v. analysis. Similar results were obtained with LVIIb. Construction of a model of LVII showed that the blocking group greatly hindered the active methylene. The hot benzene procedure could not be used for the unblocked piperidine lactone (XXVII) since it polymerized at this temperature. Claisen condensation with XXVII at 25° by use of sodium or lithium *tert*-butoxide followed by hydrolysis of the intermediate LIX gave about an 0.7% over-all yield of *dl*-alkaloid (XXXVI) as determined by assay.

Acylation of the bromolactone hydrobromide (XXVI) in the presence of aqueous sodium bicarbonate gave crystalline carbethoxy and benzoyl derivatives, LVIII. However, attempted Claisen condensation with LIV and sodium methoxide in boiling benzene gave a maximum of less than 1% yield of LXII after hydrolysis as shown by u.v. analysis.

An active hydrogen determination on 1-benzoyl-3-hydroxypiperidine-2-acetic acid lactone (XXX) surprisingly showed 0.85 active hydrogen. This would indicate that a carbanion of XXX is formed on the α-position. Attempts to effect acylation of XXX by treatment with a Grignard reagent, then with ethyl 4-quinazolone-3-acetate or phthalimidoacetyl chloride gave none of the expected β-keto lactones of type LX since no carbon dioxide was evolved on acid hydrolysis of the reaction mixture.



Carbethoxylation of β-furyl-β-alanine gave LXIII in 71% yield. The acid chloride which formed in quantitative yield was reacted with diazomethane to give 58% of the crystalline diazoketone (LXIV). Treatment with hydrobromic acid in alcohol gave 92% of the crystalline bromo ketone (LXV), which condensed with 4-quinazolone in 82% yield to LXVI, an over-all yield of 47% from LXIII. The use of N-benzoyl-β-furyl-β-alanine was much less satisfactory giving an over-all yield of 1.6% of the benzoyl derivative corresponding to LXVI.

Hydrogenation studies for conversion of the furyl quinazolone (LXVI) to the tetrahydrofuran (XXIII) showed that there was not selective absorption of two moles of hydrogen with a palladium-charcoal catalyst, but reduction

stopped at three moles. The u.v. spectra of the oily reduction showed that the 1,2-double bond of the 4-quinazolone ring had also reduced. This was surprising since hydrogenation of certain β-ketoalkyl-4-quinazolones with a benzyl ester in the side chain was successfully selective (10). However, the benzyl esters hydrogenated much more rapidly than the furan ring, thus giving selectivity. Attempts to remove two hydrogens from the 1,2-position to reform 4-quinazolones with iodine in alcohol, formic acid at 100°, or potassium dichromate in acetic acid (at 25° or 100°) led to no change as shown by the u.v. spectra remaining the same. Compound XXIII was subsequently prepared by a different method which has been described earlier in this publication.

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

EXPERIMENTAL

Methyl β-furylacrylate. To a mixture of 50 g. of β-furylacrylic acid (Winthrop), 44 cc. of methanol, and 110 cc. of carbon tetrachloride was added 3.7 cc. of acetyl chloride with swirling. After being refluxed for 4 hours on the steam-bath, the mixture was evaporated to dryness *in vacuo* and the residue distilled in a modified Claisen flask; yield, 43.3 g. (79%) of a colorless oil, b.p. 113–115° (15 mm.), which solidified in the receiver, m.p. 29°.

Ordinary Fischer esterification leads to cleavage of the furan ring (11). This method is a modification of one recently described for sensitive acids (12). A m.p. of 27° and b.p. of 112° (15 mm.) have been recorded for this ester prepared another way (13).

β-Furyl-β-alanine (V). (*A*). To a hot solution of 78 g. of hydroxylamine hydrochloride in 600 cc. of methanol was added 63 g. of sodium methoxide in 300 cc. of methanol. The mixture was cooled and filtered from salt. After the addition of 43 g. of methyl β-furylacrylate the solution was refluxed for 21 hours, then evaporated to dryness *in vacuo* (bath 50–55°). The residue was dissolved in 350 cc. of water and heated on the steam-bath until gas evolution was essentially complete (about 30 minutes). The solution was evaporated to dryness *in vacuo* (bath 50–55°). Trituration of the residue with absolute alcohol gave 30.6 g. of product, m.p. 205–207° dec., which contained 24% salt (real yield 23.6 g.–54%). The carbamyl derivative, prepared by heating an aqueous solution with potassium cyanate, melted at 170°.

In some runs where the evaporations were done directly on the steam-bath, the residue suddenly decomposed vigorously with complete charring. At the lower bath temperature, this difficulty was not encountered. Posner (2) recorded m.p. 205° for the amino acid prepared in 20% yield and m.p. 170° for the carbamyl derivative.

(*B*). A mixture of 15.1 cc. of furfural, 20 g. of malonic acid, 30 g. of ammonium acetate, and 40 cc. of absolute alcohol was refluxed on the steam-bath for 18 hours, then kept at 3° overnight. The mixture containing a gummy solid was diluted with 75 cc. of absolute alcohol, slurried with 20 g. of Celite, and filtered. The filter cake was washed with acetone until no further color was removed. The cake was stirred at 75–85° with 400 cc. of water for ten minutes and filtered hot through Celite. The combined brown filtrate and washings were stirred with 2 g. of Norit at 75–85° for ten minutes and again filtered. The combined water-white filtrate and washings were evaporated to dryness *in vacuo*. Trituration of the residue with absolute alcohol gave 7.3 g. (25%) of white crystals, m.p. 200–201° dec. This reaction has been run on a 10 kg.-scale in the same yield.

pseudo-β-Tetrahydrofuryl-β-alanine (VIII). A mixture of 12.5 g. of V (containing 27% salt), 150 cc. of water, and 100 mg. of platinum oxide was shaken with hydrogen at 2–3 atm. overnight during which time 2 mole-equivalents of hydrogen were absorbed and the

reduction stopped. The filtered solution was evaporated to dryness *in vacuo*, and the residue was extracted with hot absolute alcohol and filtered from salt (3.4 g.). Evaporation of the filtrate *in vacuo* gave 9.5 g. (102%) of residue which crystallized from absolute alcohol on standing; yield, 5.4 g. (57%), m.p. 148–150°. No satisfactory solvent was found for recrystallization. A sample was triturated with hot absolute alcohol giving white crystals, m.p. 173–174° dec., which were partially hydrated.

Anal. Calc'd for $C_7H_{13}NO_3 \cdot \frac{1}{2}H_2O$: C, 49.8; H, 8.38; N, 8.32.
Found: C, 49.1; H, 8.52; N, 8.25.

The *N-benzoyl derivative* (XXIa), prepared with benzoyl chloride and aqueous alkali, formed white crystals from ethyl acetate, m.p. 116–117°.

Anal. Calc'd for $C_{14}H_{17}NO_4$: N, 5.32. Found: N, 5.17.

trans-1-Carbethoxy-3-hydroxypiperidine-2-acetic acid (IXa). A solution of 6.1 g. of crude VIII in 57 cc. of 48% hydrobromic acid was heated on the steam-bath for one hour, then evaporated to dryness *in vacuo*. The residue was dissolved in 72 cc. of water, 50 cc. of 10% sodium hydroxide was added, and the solution was heated on the steam-bath for one hour. The solution was cooled to 5° in an ice-bath and a solution of 5.6 cc. of ethyl chlorocarbonate in 31 cc. of toluene was added dropwise with stirring over a period of 30 minutes. After being stirred 15 minutes more, the mixture was treated with 42 cc. of 10% sodium hydroxide, then dropwise with 5.6 cc. of ethyl chlorocarbonate in 31 cc. of toluene as before. The mixture was stirred an additional 45 minutes in the ice-bath. The alkaline layer was separated, acidified, saturated with salt, and extracted with 3 50-cc. portions of chloroform. Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo*; yield, 6.2 g. (70%) of a viscous oil.

Anal. Calc'd for $C_{10}H_{17}NO_5$: C, 51.9; H, 7.43; N, 6.06.
Found: C, 52.2; H, 7.55; N, 6.02.

trans-1-Carbethoxy-2-(γ-bromoacetonyl)-3-hydroxypiperidine (XIa). To a solution of 6.2 g. of IXa in 31 cc. of acetyl chloride was added 7.4 g. of phosphorus pentachloride. The solution was allowed to stand 20 minutes, then evaporated to dryness *in vacuo* (bath 45–50°) and the evaporation repeated with 52 cc. of toluene. The residual acid chloride (XIIa), dissolved in 42 cc. of benzene, was added dropwise with swirling to an ice-cooled, dried, ethereal solution of diazomethane (from 15.5 g. of nitrosomethylurea). After 10 minutes in the ice-bath and 16 hours at room temperature, the solution was cooled in an ice-bath and treated with 9.6 cc. of acetic acid, then with 30 cc. of 30% hydrogen bromide in acetic acid. Five minutes later the solution was washed twice each with water, excess aqueous sodium bicarbonate, and water. Evaporation *in vacuo* gave 5.6 g. (68%) of crude product as an oil.

The intermediate acid chloride (XIIa), prepared as above, was treated with aniline in toluene. The *anilide of IXa* was obtained as a viscous oil in 42% yield which did not crystallize.

Anal. Calc'd for $C_{16}H_{22}N_2O_4$: N, 9.15. Found: N, 9.41.

pseudo-β-Tetrahydrofuryl-β-carbobenzoxyaminopropionic acid (VIIb). An aqueous solution (110 cc.) of VIIIb obtained after hydrogenation of 6.9 g. of β-furyl-β-alanine (V) was treated with 23 g. of sodium hydroxide and cooled in an ice-bath. To the stirred solution was added 37 cc. of 70% benzyl chlorocarbonate at 7–9° over a period of 30 minutes. The mixture was stirred in the ice-bath for an additional 45 minutes. An insoluble sodium salt separated. After dilution to about 1 l. with water, the mixture was washed with ethyl acetate, acidified, and extracted with ethyl acetate. The latter was back extracted with aqueous sodium bicarbonate. (The product is not pure without this step.) Acidification gave an oil which was extracted with chloroform. The combined extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo*; yield, 4.8 g. (38% based on V) of a colorless gum.

Anal. Calc'd for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.53; N, 4.74.
Found: C, 61.7; H, 7.01; N, 4.64.

Similarly, treatment of an aqueous solution of VIII with ethyl chlorocarbonate in

toluene as described for IXa gave 47% of *pseudo-β-tetrahydrofuryl-β-carbethoxyamino-propionic acid* (VIIa) as a colorless gum.

Anal. Calc'd for $C_{10}H_{17}NO_5$: N, 6.06. Found: N, 5.72.

pseudo-β-Tetrahydrofuryl-β-phthalimidopropionic acid (VIIc). A mixture of 9.3 g. of crude VIII and 8.7 g. of phthalic anhydride was heated at 180° for 30 minutes when gas evolution ceased. An ethyl acetate solution of the residue was extracted with excess aqueous sodium bicarbonate. Acidification gave an oil which was extracted with chloroform. The combined extracts were dried with magnesium sulfate, clarified with Norit, and evaporated to dryness *in vacuo*; yield, 9.6 g. (57%) of an amber gum.

Anal. Calc'd for $C_{15}H_{15}NO_5$: N, 4.84. Found: N, 4.04.

pseudo-1-Bromo-4-carbethoxyamino-4-tetrahydrofuryl-2-butanone. Conversion of 3.5 g. of VIIa to the acid chloride and treatment with diazomethane and hydrogen bromide as described for XIa gave 1.7 g. (36%) of product as an oil.

Similarly, *pseudo-1-bromo-4-carbobenzoxyamino-4-tetrahydrofuryl-2-butanone* was obtained in 63% yield as an oil and *pseudo-1-bromo-4-phthalimido-4-tetrahydrofuryl-2-butanone* in 73% yield as an oil.

pseudo-3-(β-Keto-δ-carbethoxyamino-δ-tetrahydrofurylbutyl)-4-quinazolone (Xa). To a solution of 0.71 g. of 4-quinazolone in 5 cc. of 1 *N* sodium methoxide in methanol was added a solution of 1.6 g. of *pseudo*-1-bromo-4-carbethoxyamino-4-tetrahydrofuryl-2-butanone in 17 cc. of methanol. After one hour the solution was diluted with 67 cc. of iced water and 27 cc. of 10% sodium hydroxide. A gum separated which was extracted with chloroform. The combined extracts were evaporated *in vacuo* leaving 470 mg. of residue which was crystallized from benzene-heptane; yield, 170 mg. (12%), m.p. 121–131°. Recrystallization of a similar preparation from benzene gave white crystals, m.p. 130–131°.

Anal. Calc'd for $C_{19}H_{23}N_3O_5$: C, 61.1; H, 6.23; N, 11.3.
Found: C, 61.1; H, 6.64; N, 11.0.

Similarly, Xb and Xc were prepared in 70% and 42% yields, respectively as crude gums which could not be crystallized.

pseudo-3-(β-Keto-δ-amino-δ-tetrahydrofurylbutyl)-4-quinazolone dihydrochloride (XIII). (*A*). A mixture of 4 g. of crude Xc and 40 cc. of 6 *N* hydrochloric acid was refluxed for 4 hours, decanted from some insoluble tar, and evaporated to dryness *in vacuo*. Trituration of the residue with absolute alcoholic hydrogen chloride gave a white solid which was collected and washed with 1:1 absolute alcohol-acetone; yield, 0.91 g. (27%), m.p. 200–202° dec. The over-all yield from V was 4.6%. A similar preparation, m.p. 205–206° dec., was analyzed.

Anal. Calc'd for $C_{16}H_{19}N_3O_2 \cdot 2HCl \cdot H_2O$: C, 49.1; H, 5.97; N, 10.7; NH_2-N, 4.10.
Found: C, 48.7; H, 6.29; N, 10.9; NH_2-N, 3.06.

(*B*). A mixture of 3.0 g. of Xb and 30 cc. of 6 *N* hydrochloric acid was refluxed for 30 minutes, then worked up as in *A*; yield, 0.73 g. (29%), m.p. 200–202° dec. The over-all yield from V was 4.8%.

(*C*). A mixture of 150 mg. of Xa, m.p. 121–131°, and 2 cc. of 6 *N* hydrochloric acid was treated as in *A*; yield, 50 mg. (33%) of crystalline product. The over-all yield from V was 0.7%.

pseudo-3-(2-Keto-4-amino-5-hydroxy-8-bromoöctyl)-4-quinazolone dihydrobromide (XV). A solution of 3.1 g. of XIII in 31 cc. of 48% hydrobromic acid was heated in a steam-bath for one hour during which time the product began to crystallize. The well-cooled mixture was diluted with an equal volume of acetone. The product was collected and washed with acetone; yield, 3.35 g. (75%), m.p. 243–245°. A similar preparation, m.p. 244–245°, was analyzed.

Anal. Calc'd for $C_{16}H_{20}BrN_3O_3 \cdot 2HBr$: N, 7.72; Br, 44.2.
Found: N, 7.39; Br, 44.9.

trans-3-[β-Keto-γ-(3-hydroxy-2-piperidyl)propyl]-4-quinazolone dihydrochloride (XVI). (*A*). By condensation of 5.6 g. of crude XIa with 4-quinazolone as described for Xa there was obtained 5.1 g. (75%) of *XIVa* which could not be crystallized. This material was

refluxed with 51 cc. of 6 *N* hydrochloric acid for 4 hours, then the solution was evaporated to dryness *in vacuo*. Trituration of the residue with absolute alcohol gave 1.45 g. (21%) of white crystals, m.p. 224–226° dec.

Anal. Calc'd for $C_{16}H_{19}N_3O_3 \cdot 2HCl$: C, 51.3; H, 5.68; N, 11.2; NH_2-N, 0.0.

Found: C, 51.8; H, 6.10; N, 11.2; NH_2-N, 0.0.

This compound exhibited no antimalarial activity at 100 times the dosage required for the Hydrangea alkaloid. The N-carbamyl derivative, formed with potassium cyanate, separated as white crystals from water, m.p. 193–194°.

(*B*). A mixture of 230 mg. of XV, 5 cc. of water, 10 cc. of chloroform, and 210 mg. of sodium bicarbonate was stirred about 18 hours. The aqueous layer was extracted with 5 5-cc. portions of 1:4 butanol-chloroform. The combined organic solutions, dried with magnesium sulfate, were concentrated to a small volume *in vacuo* (bath 35–40°). An excess of absolute alcoholic hydrogen chloride was added and the solution was evaporated to dryness *in vacuo*. Trituration of the solid with saturated absolute alcoholic hydrogen chloride gave white crystals, m.p. 219–221° dec.; yield, 120 mg. (76%). The N-carbamyl derivative melted at 187–188° dec. and a mixture with preparation *A* gave no depression in the m.p.

Benzoylation of pseudo-3-(2-keto-4-amino-5-hydroxy-8-bromoöctyl)-4-quinazolone (XV). A mixture of 1.0 g. of XV dihydrobromide, 30 cc. of chloroform, 25 cc. of water containing 3.7 g. of anhydrous sodium carbonate, and 0.75 cc. of benzoyl chloride was stirred for 1½ hours. The organic layer was washed twice with 1 *N* hydrochloric acid, dried with magnesium sulfate, and evaporated to dryness *in vacuo*. Trituration with benzene gave 225 mg. (25%) of a hydrochloride, m.p. 210–212° dec. Recrystallization from methanol-water afforded white crystals of the free base of *pseudo* XV or *pseudo* XIX, m.p. 153–154°.

Anal. Calc'd for $C_{23}H_{22}BrN_3O_3$: C, 59.0; H, 4.70; N, 8.96.

Found: C, 59.5; H, 5.38; N, 8.92.

normal-β-Benzamido-β-tetrahydrofurylpropionic acid (XXIa). A mixture of 30 g. of XX (2), 150 cc. of Methyl Cellosolve, and 5 g. of 10% palladium-charcoal catalyst was shaken with hydrogen at 2–3 atm. at 80° until reduction stopped (one hour). Two mole-equivalents of hydrogen were absorbed. The filtered solution was evaporated to dryness *in vacuo*. The slightly solvent wet residue (32.8 g.; 107%), m.p. 128–138°, was used without further purification for conversion to XXVI. Several recrystallizations from water gave white crystals, m.p. 155–156°.

Anal. Calc'd for $C_{14}H_{17}NO_4$: C, 63.9; H, 6.50; N, 5.32.

Found: C, 64.0; H, 6.60; N, 5.16.

Reprecipitation of the crude product from an alkaline solution with acid gave an 85% recovery, m.p. 141–148°.

At 25° the reduction is much slower. Raney nickel or palladium-charcoal with an aqueous solution of the sodium salt of XX may also be employed at 25–80°.

To a mixture of 500 mg. of XXIa and 2.2 cc. of acetyl chloride was added 0.15 cc. of thionyl chloride, solution being complete after five minutes shaking. After an additional five minutes volatile matter was removed *in vacuo* (bath 0°). The residual acid chloride, dissolved in 3 cc. of toluene by the addition of a few drops of acetone, was treated with 0.54 cc. of aniline. The mixture of anilide and aniline hydrochloride was collected and washed with toluene, then water. The yield of anilide was 355 mg. (55%), m.p. 192–196°. Recrystallization from aqueous Methyl Cellosolve gave white crystals, m.p. 201–202°.

Anal. Calc'd for $C_{20}H_{22}N_2O_3$: C, 71.0; H, 6.51; N, 8.28.

Found: C, 70.7; H, 6.86; N, 8.06.

By ordinary procedures at 25° or above no crystalline anilide could be obtained.

normal-β-Carbethoxyamino-β-tetrahydrofurylpropionic acid (XXII). A mixture of 7.8 g. of XXIa (m.p. 141–148°) and 78 cc. of 6 *N* hydrochloric acid was refluxed for three hours, cooled, and filtered from benzoic acid. The filtrate was evaporated to dryness *in vacuo*. The residual amino acid hydrochloride was dissolved in 50 cc. of water and 58 cc. of 10% sodium hydroxide, then treated twice with 5 cc. of ethyl chlorocarbonate in 25 cc.

of toluene as described for IXa; yield, 3.4 g. (50%) of a viscous oil. This was characterized as the *anilide* as described for the anilide of XXIa; yield, 74%, m.p. 127–130° (from toluene-heptane). Recrystallization from toluene gave white crystals, m.p. 135–136°.

Anal. Calc'd for $C_{16}H_{22}N_2O_4$: C, 62.7; H, 7.24; N, 9.15.
Found: C, 62.5; H, 7.28; N, 9.52.

normal-β-Carbobenzoxyamino-β-tetrahydrofurylpropionic acid and anilide. Hydrolysis of 11.9 g. of XXIa (m.p. 141–147°) as in the preceding experiment followed by carbobenzoxylation as described for VIIb gave 7.8 g. (58%) of a gum.

Anal. Calc'd for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.48; N, 4.74.
Found: C, 61.5; H, 6.46; N, 4.41.

The *anilide*, prepared as described for the anilide of XXIa in 50% yield, m.p. 140–145°, was recrystallized from dilute methanol: white crystals, m.p. 145–146°.

Anal. Calc'd for $C_{21}H_{24}N_2O_4$: C, 68.4; H, 6.52; N, 7.61.
Found: C, 68.0; H, 6.73; N, 7.43.

normal-3-(β-Keto-δ-carbethoxyamino-δ-tetrahydrofurylbutyl)-4-quinazolone (XXIII). By conversion of 13 g. of XXII to the acid chloride with thionyl chloride in acetyl chloride (see XXII anilide), then treatment with diazomethane and hydrogen bromide as described for XIa, there was obtained 6.0 g. (56%) of crude *normal*-1-bromo-4-carbethoxyamino-4-tetrahydrofuryl-2-butanone as an oil. This was condensed with 4-quinazolone as described for Xa; yield, 1.65 g. (22%), m.p. 119–124°. Recrystallization from benzene-heptane gave white crystals, m.p. 125–127°. Admixture with the *pseudo* isomer, Xa, (m.p. 131°) gave a 15° depression in m.p.

Anal. Calc'd for $C_{19}H_{23}N_3O_5$: C, 61.1; H, 6.21; N, 11.3.
Found: C, 60.7; H, 6.22; N, 11.1.

normal-3-(β-Keto-δ-amino-δ-tetrahydrofurylbutyl)-4-quinazolone dihydrochloride (XXIV). A mixture of 400 mg. of XXIII and 8 cc. of 6 *N* hydrochloric acid was refluxed for 3½ hours when the solid had dissolved. The solution was decanted from some insoluble tar, then evaporated to dryness *in vacuo*. The residue was dissolved in absolute alcohol and the evaporation repeated. Trituration with acetone gave 260 mg. (65%) of product, m.p. 168–173° dec. The analysis agreed with 16–18% ammonium chloride present or a real yield of 56%.

Anal. Calc'd for $C_{16}H_{19}N_3O_3 \cdot 2HCl$: C, 51.3; H, 5.65; N, 11.2.
Found: C, 43.0; H, 4.45; N, 13.5; ash, 2.0.

Attempts to open the tetrahydrofuran ring with 48% hydrobromic acid to XXV were unsuccessful. After one hour at 100°, the starting material hydrobromide, m.p. 168–169° dec, was obtained. As the length of time increased the amount of carbonization was increased. After 24 hours almost complete carbonization resulted.

normal-3-Amino-4-hydroxy-7-bromoheptanolactone hydrobromide (XXVI). A solution of the crude XXIb from 30 g. of XX in 300 cc. of 48% hydrobromic acid was heated in a steam-bath for 24 hours under a condenser. The cooled solution was filtered from benzoic acid and evaporated thoroughly to dryness *in vacuo*. The cooled semi-solid residue was stirred with 300 cc. of acetone until the gum had all disintegrated to a solid or dissolved, but no longer (about 20 minutes). After standing overnight at 3° the mixture was filtered and the product washed with acetone; yield, 15.2 g. (44% based on XX), m.p. 177–180°. For analysis a sample was thoroughly leached with acetone giving white crystals, m.p. 182–184°.

Anal. Calc'd for $C_7H_{12}BrNO_2 \cdot HBr$: C, 27.7; H, 4.29; N, 4.62.
Found: C, 28.1; H, 4.64; N, 4.51.

Changes in the hydrolysis conditions gave the following yields: (a) 15 hr., 125° (0%); (b) 3 hr., 100° (0%); (c) 8 hr., 100° (28%); (d) 15 hr., 100° (40%); (e) 24 hr., 100° (44–46%); (f) 40 hr., 100° (24%); (g) 3 hr., 125° (29%).

With pure XXIb for 24 hours at 100°, the yield was 60%. The losses in purification of XXIb made the over-all yield better when no purification of the intermediate was attempted.

Sodium methoxide ring closure of XXVI. To a solution of 2.0 g. of XXVI in 50 cc. of methanol was added 20 cc. of 1 *N* sodium methoxide. After one hour at room temperature the solution was evaporated to dryness *in vacuo* (bath 35°). The residue of XXVIII and salts was dissolved in 30 cc. of chloroform and 15 cc. of saturated aqueous sodium bicarbonate. Cooled in an ice-bath, the mixture was treated with 4.5 cc. of 70% benzyl chlorocarbonate and stirred for 45 minutes. The separated chloroform layer was evaporated to dryness *in vacuo*. The residue was refluxed with 150 cc. of alcohol and 56 cc. of 10% sodium hydroxide for 30 minutes, then concentrated *in vacuo* to remove alcohol. The mixture was washed three times with chloroform. Acidification of the aqueous layer gave an oil which was extracted with chloroform. The combined dried extracts gave 0.50 g. (26%) of *normal*-β-carbobenzoxyamino-β-tetrahydrofurylpropionic acid as a gum. This gave a 50% yield of anilide, m.p. 142–143°, undepressed when mixed with an authentic sample.

Similarly, benzoylation gave 0.92 g. (49%) of *normal*-methyl β-benzamido-β-tetrahydrofuryl propionate which was saponified and converted to the anilide, m.p. and mixture m.p. 185–186°.

cis-3-Hydroxypiperidine-2-acetic acid lactone (XXVII) *and salts.* A solution of 1.87 g. of XXVI in 62 cc. of chloroform and 4.4 cc. of triethylamine was allowed to stand in a stoppered flask for 24 hours, then evaporated to dryness *in vacuo* (bath 35°). The residue was dissolved in 60 cc. of chloroform and washed with 37 cc. of saturated aqueous sodium bicarbonate. The latter was extracted twice with chloroform. The combined organic extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo* (bath 35°). The residue rapidly crystallized to a waxy solid; yield, 0.88 g. (101%). The lactone can be recrystallized from hot heptane with considerable loss due to polymerization: white crystals, m.p. 94–95°, resolidifies and does not remelt up to 250°.

Anal. Calc'd for $C_7H_{11}NO_2$: C, 59.5; H, 7.80; N, 9.93.
Found: C, 58.8; H, 8.12; N, 9.89.

The *hydrochloride* formed white crystals, m.p. 217–218° dec., when an acetone solution of the free base was treated with a slight excess of absolute alcoholic hydrogen chloride.

Anal. Calc'd for $C_7H_{11}NO_2 \cdot HCl$: C, 47.1; H, 6.72; N, 7.84.
Found: C, 47.0; H, 7.14; N, 7.76.

The *hydrobromide* salt was prepared by adding a slight excess of 30% hydrogen bromide in acetic acid to a chloroform solution of the base. The solid was collected and washed with ether: white crystals, m.p. 207–208° dec.

Anal. Calc'd for $C_7H_{11}NO_2 \cdot HBr$: N, 6.31. Found: N, 6.52.

cis-1-Benzoyl-3-hydroxypiperidine-2-acetic acid lactone (XXX). (*A*). To a solution of 4.0 g. of crude XXVII base in 40 cc. of chloroform and 16 cc. of triethylamine was added 5 cc. of benzoyl chloride with cooling. After two hours at room temperature, the mixture was washed with 80 cc. of 1 *N* hydrochloric acid, then twice with excess aqueous sodium bicarbonate. The dried chloroform solution was evaporated to dryness *in vacuo*. The crude oil (8.5 g.) was crystallized from 25 cc. of ethyl acetate by the addition of 35 cc. of heptane; yield, 2.6 g. (37%) of white crystals, m.p. 99–101°.

Anal. Calc'd for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.12; N, 5.71.
Found: C, 68.3; H, 6.47; N, 5.64.

(*B*). To a solution of 1.00 g. of XXVII hydrochloride and 4.1 cc. of triethylamine in 8.5 cc. of chloroform was added 1.04 cc. of benzoyl chloride. After two hours the solution was worked up as in *A*; yield, 0.65 g. (46%), m.p. 99–101°. The use of the equivalent quantity of tributylamine afforded only a 23% yield.

(*C*). A reaction mixture identical with *B* was refluxed on the steam-bath for one hour; yield, 0.86 g. (61%), m.p. 97–101°. Increasing the time to two hours or doubling the amount of benzoyl chloride gave the same yield.

(*D*). A solution of 8.0 g. of bromo lactone hydrobromide (XXVI) and 19 cc. of triethylamine in 260 cc. of chloroform was allowed to stand in a stoppered flask for 18–24 hours. Then 4.8 cc. of benzoyl chloride was added and the solution was refluxed for one hour. Work-up as in *A* except that the bicarbonate washings were omitted afforded 3.9 g. (61%)

of product, m.p. 99–101°, which gave no depression when mixed with preparation *A*. In numerous runs the yields were consistently 61–65%. In some cases it was necessary to filter the hot ethyl acetate solution during recrystallization to remove triethylamine hydrochloride.

cis-1-Benzoyl-3-hydroxypiperidine-2-acetic acid (XXIX). (*A*). A mixture of 10.2 g. of XXX and 51 cc. of 10% sodium hydroxide was shaken until solution was complete (5 minutes), then filtered, acidified slowly with 12 *N* hydrochloric acid and cooled. The product was collected and washed with 16 cc. of ice-water in portions; yield, 10.7 g. (98%), m.p. 157–158° (slight dec.). Recrystallization from ethyl acetate gave white crystals of unchanged m.p.

Anal. Calc'd for $C_{14}H_{17}NO_4$: C, 63.9; H, 6.51; N, 5.32.

Found: C, 63.3; H, 6.79; N, 5.20.

(*B*). A solution of 2.0 g. of XXXI (7) in 8.7 cc. of 48% hydrobromic acid was refluxed for one hour, then evaporated to dryness *in vacuo*. The residue was treated with 2 1-cc. portions of benzoyl chloride and excess 1 *N* sodium hydroxide. The product was isolated by chloroform extraction and crystallization from ethyl acetate as white crystals, m.p. 153–154° (slight dec.). A mixture with preparation *A* gave no depression in m.p.

Anal. Calc'd for $C_{14}H_{17}NO_4$: C, 63.9; H, 6.51; N, 5.32.

Found: C, 63.7; H, 6.33; N, 5.35.

cis-1-Benzoyl-3-methoxypiperidine-2-acetic acid (XXXII). A solution of 4.0 g. of XXIX in 30 cc. of 1 *N* sodium methoxide was evaporated to dryness *in vacuo*. The residue was baked on the steam-bath *in vacuo* for one hour, leaving a white crystalline residue. The di-sodium salt was refluxed in 25 cc. of acetone and 5.6 cc. of methyl iodide for one hour. After the addition of 5.6 cc. more of methyl iodide the mixture was refluxed on the steam-bath for 16 hours. The mixture was evaporated to dryness *in vacuo*. The residue was heated on the steam-bath with 40 cc. of 10% sodium hydroxide until the oil dissolved (10 minutes). The solution, acidified and saturated with salt, was extracted with 80 cc. of chloroform. The dried extract was evaporated to dryness *in vacuo* leaving 4.0 g. of a mixture of XXIX and XXXII. This material was heated on the steam-bath with 40 cc. of acetic anhydride for one hour, then the hot solution was treated cautiously with 40 cc. of water and heated an additional 15 minutes on the steam-bath. The solution was evaporated to dryness *in vacuo*. A solution of the residue in 40 cc. of ethyl acetate was extracted with excess aqueous sodium bicarbonate. These extracts were acidified, saturated with salt, and extracted twice with chloroform. The combined dried chloroform solutions were evaporated to dryness *in vacuo*. Trituration of the solid residue with ethyl acetate gave 1.8 g. (43%) of XXXII, m.p. 147–149°. A mixture with starting material melted at 130–131°. Recrystallization from ethyl acetate gave white crystals, m.p. 149–150°.

Anal. Calc'd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.91; N, 5.05; CH_3O, 11.2.

Found: C, 64.7; H, 7.05; N, 5.18; CH_3O, 9.69.

The ethyl acetate solution of neutral material was dried with magnesium sulfate and evaporated to dryness *in vacuo*. Crystallization from ethyl acetate-heptane gave 0.70 g. (18%) of lactone (XXX), m.p. 99–101°. The yield of XXXII was 52% corrected for lactone recovered.

Methyl sulfate instead of methyl iodide gave a 25% yield of XXXII and 28% of XXX.

cis-1-Carbethoxy-3-methoxypiperidine-2-acetic acid (XXXI). A solution of 10 g. of XXXII in 100 cc. of 6 *N* hydrochloric acid was refluxed for one hour, cooled, filtered from benzoic acid, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 25 cc. of water and the evaporation repeated. The crystalline hydrochloride was carbethoxylated with ethyl chlorocarbonate as described for IXa, except that a third treatment was made; yield, 8.1 g. (91%) of an almost colorless viscous oil (7).

Anal. Calc'd for $C_{11}H_{19}NO_5$: C, 53.9; H, 7.75; N, 5.71.

Found: C, 53.6; H, 8.12; N, 5.71.

cis-3-[β-Keto-γ-(1-carbethoxy-3-methoxy-2-piperidyl)propyl]-4-quinazolone (XXIV). Conversion of 800 mg. of XXXI to 1-carbethoxy-2-(γ-bromoacetonyl)-3-methoxypiperidine as

previously described (7) proceeded in 84% yield (880 mg.). This was condensed with 4-quinazolone as usual (7) to give 520 mg. (49%) of crystals, m.p. 133–134°, which gave no depression with an authentic sample (7).

Methyl cis-1-benzoyl-3-hydroxypiperidine-2-acetate (XLV?). A solution of 1.25 g. of XXX and 0.33 cc. of 1 *N* sodium methoxide in 12.5 cc. of methanol was allowed to stand for 27 hours in a stoppered flask. The solution was evaporated to dryness *in vacuo*. The residue, dissolved in chloroform, was washed with excess sodium bicarbonate solution. The organic layer was dried with magnesium sulfate and evaporated to dryness *in vacuo*; yield, 1.38 g. (98%) of an oil which was not pure.

Anal. Calc'd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.86; N, 5.05.

Found: C, 64.0; H, 7.01; N, 4.90.

This compound was completely saponified with 10% sodium hydroxide at room temperature in 15 minutes. Acidification gave the corresponding acid, XXIX, in good yields. An attempt to methylate the hydroxyl group with methyl iodide and silver oxide in acetone at 25° resulted in XXIX after saponification.

A solution of 510 mg. of XLV and 550 mg. of *p*-bromophenyl isocyanate in 10 cc. of toluene was heated on the steam-bath under a condenser for 20 hours. The solution was stirred 4 hours with water. The bis-*p*-bromophenylurea was removed by filtration. The separated toluene layer was evaporated to dryness *in vacuo* leaving 0.85 g. (97%) of a *p*-bromophenylurethan as a viscous oil.

Anal. Calc'd for $C_{22}H_{23}BrN_2O_5$: Br, 16.8. Found: Br, 17.4.

The urethan was dissolved in excess 5% sodium hydroxide in 50% alcohol. After 17 hours the reaction mixture gave XXIX in the bicarbonate-soluble fraction, identified by mixture m.p. Similar results were obtained with phenyl isocyanate. When XXVIII was hydrolyzed under these conditions it was recovered unchanged.

cis-1-Benzoyl-3-carbanilinoxypiperidine-2-acetic acid (XXXVIII). A solution of 4.5 g. of XXIX in 17.1 cc. of 1 *N* sodium methoxide was evaporated to dryness *in vacuo* and the residue was baked *in vacuo* on the steam-bath for 25 minutes. The residual sodium salt was dissolved in 45 cc. of reagent pyridine. After the addition of 5.8 cc. of phenyl isocyanate, the solution was heated on the steam-bath under a condenser protected from moisture for 7 hours, then evaporated to dryness *in vacuo*. The residue was partitioned between 135 cc. of ethyl acetate and 100 cc. of saturated aqueous sodium bicarbonate. After removal of the diphenylurea by filtration, the layers were separated and the aqueous phase acidified. The gum was extracted with 2 100-cc. portions of chloroform. An equal volume of acetone was added to dissolve the crystals which began to separate. Dried with magnesium sulfate, the solution was evaporated to dryness *in vacuo*. Crystallization of the residue from chloroform-heptane gave 2.67 g. (41%) of product, m.p. 171–173° dec. Recrystallization of a sample from ethyl acetate-heptane gave white crystals, m.p. 174–175°.

Anal. Calc'd for $C_{21}H_{22}N_2O_5$: C, 66.0; H, 5.81; N, 7.33.

Found: C, 66.0; H, 5.89; N, 7.31.

cis-1-Benzoyl-3-carbanilinoxypiperidine-2-acetanilide (XL). (*A*). A mixture of 300 mg. of XXXVIII, 2 cc. of acetyl chloride, and 180 mg. of phosphorus pentachloride was shaken for 30 minutes when solution was essentially complete. The solution was evaporated to dryness *in vacuo* (bath 45–50°) and the evaporation was repeated with 2 cc. of toluene. The residual acid chloride, dissolved in 5 cc. of acetone, was treated with 0.22 cc. of aniline. After ten minutes the mixture was evaporated *in vacuo*. Partition of the residue between 5 cc. of ethyl acetate and excess aqueous sodium bicarbonate gave 60 mg. (17%) of crude anilide, m.p. 215–216°, at the interphase. Acidification of the bicarbonate layer gave 190 mg. (63%) of unchanged acid, m.p. 162–170°. Recrystallization of the anilide from dilute methanol afforded white crystals, m.p. 257–259°.

Anal. Calc'd for $C_{27}H_{27}N_3O_4$: C, 70.9; H, 5.91; N, 9.19.

Found: C, 70.6; H, 6.08; N, 8.90.

Increase in the length of reaction time did not increase the yield. Four runs with ether (containing 0.5% of pyridine) and thionyl chloride for varying lengths of time gave 15–36% yields of anilide and considerable amounts of acid were recovered in each case.

(*B*). To a solution of 300 mg. of XXXVIII and 0.11 cc. of triethylamine in 2 cc. of chloroform cooled in an ice-bath was added 0.076 cc. of ethyl chlorocarbonate. After ten minutes at 0°, the solution of mixed anhydride (XLI) was treated with 0.072 cc. of aniline (8). After 20 minutes without cooling, during which time carbon dioxide evolution was complete, the mixture was diluted with 4 cc. of chloroform and excess aqueous bicarbonate. The anilide was collected and washed with water, then methanol; yield, 260 mg. (72%), m.p. 257–259°, which gave no depression in m.p. when mixed with preparation *A*. An additional 20% of anilide was isolated from the filtrate.

1-Phthalimido-3-bromoacetone from phthalylglycine via the mixed anhydride. To a solution of 5 g. of phthalylglycine in 30 cc. of chloroform and 3.36 cc. of triethylamine cooled to 0° was added 2.35 cc. of ethyl chlorocarbonate (8). After 10 minutes at 0° the mixture was filtered from triethylamine hydrochloride (only 15%). The filtrate was added portionwise with ice-cooling and swirling to a dried methylene chloride solution of diazomethane (from 7 g. of nitrosomethylurea) (14). After 17 hours at room temperature the solution was stirred with 5.9 cc. of 48% hydrobromic acid with ice-cooling for one hour. An excess of aqueous sodium bicarbonate was added. The organic solution, dried with magnesium sulfate, was evaporated to dryness *in vacuo*. Recrystallization from benzene-petroleum ether gave 3.3 g. (48%) of product, m.p. 127–128°; lit. (15) m.p. 146°.

The bromo ketone was characterized by condensation with 4-quinazolone to give a 46% yield of 3-(β-keto-γ-phthalimidopropyl)-4-quinazolone, m.p. 261–262°, identical with that previously described (16).

The yield of bromo ketone could probably be considerably increased by doubling the amount of diazomethane. In the above run more triethylamine hydrochloride was expected to be insoluble.

cis-1-Benzoyl-2-(γ-bromoacetonyl)-3-carbanilinoxypiperidine (XLII). By conversion of 3.45 g. of XXXVIII to the mixed anhydride XLI, (see XL), reaction with a methylene chloride solution of diazomethane (from 5 g. of nitrosomethylurea) for 18 hours packed in an ice-bath while the ice melted, then reaction with 3.7 cc. of 48% hydrobromic acid as in the preceding experiment, there was formed 4.2 g. (100%) of crude product as a gum. The insoluble triethylamine hydrochloride was not removed by filtration.

cis-3-[β-Keto-γ-(3-carbanilinoxy-2-piperidyl)propyl]-4-quinazolone dihydrochloride (XLIII). Condensation of 4.2 g. of crude XLII with 1.19 g. of 4-quinazolone as described for Xa gave 4.4 g. (92%) of XLIV which could not be crystallized. A mixture of 1.8 g. of XLIV and 18 cc. of 6 *N* hydrochloric acid was refluxed for 4 hours, decanted from some tar, cooled, and filtered from benzoic acid. The filtrate was evaporated to dryness *in vacuo* and the evaporation repeated with absolute alcohol. Crystallization from saturated absolute alcoholic hydrogen chloride gave 0.36 g. (21%) of product as white crystals, m.p. 234–235° dec. This compound has u.v. spectra typical of a 3-alkyl-4-quinazolone (17).

Anal. Calc'd for $C_{23}H_{24}N_4O_4 \cdot 2HCl \cdot H_2O$: C, 54.0; H, 5.57; N, 10.6.

Found: C, 54.2; H, 6.03; N, 10.7, 10.6.

The *N-carbamyl* derivative immediately separated when an aqueous solution of the dihydrochloride was treated with potassium cyanate: white crystals, m.p. 226–227° dec.

Anal. Calc'd for $C_{24}H_{25}N_5O_5 \cdot \frac{1}{2}H_2O$: C, 61.2; H, 5.60.

Found: C, 61.2; H, 5.69.

cis-3-Carbanilinoxypiperidine-2-acetic acid (XXXIX). A mixture of 200 mg. of XXXVIII and 5 cc. of 6 *N* hydrochloric acid was refluxed for 4 hours, solution taking place in about 30 minutes. The cooled solution was filtered from benzoic acid and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in 5 cc. of water and neutralized with sodium bicarbonate. The product was collected and washed with water; yield, 100 mg. (69%) of white crystals, m.p. 198–200°. This compound is insoluble in all common solvents including water and aqueous sodium bicarbonate, but is readily soluble in aqueous sodium hydroxide or alcoholic hydrochloric acid showing its amino acid properties.

Hydrolysis of N-benzoyl-O-carbanilinoethanolamine. A mixture of 2.0 g. of this urethan (18) and 20 cc. of 48% hydrobromic acid was refluxed for 20 minutes. Solution took place

at the b.p. and carbon dioxide evolution was complete after the reflux period. The solution was cooled and filtered from benzoic acid (73%) which was washed with 10 cc. of water. To the combined filtrate and washings was added 1.2 cc. of bromine. Ten minutes later the tribromaniline, m.p. 117–119°, was collected; yield, 2.24 g. (93%).

cis-1-Benzoyl-3-acetoxypiperidine-2-acetic acid (XLVIIIa). A solution of 5.1 g. of XXIX in 19.4 cc. of 1 *N* sodium methoxide was evaporated to a dry powder *in vacuo*. To a hot solution of the residual sodium salt in 51 cc. of pyridine was added 9 cc. of isopropenyl acetate. After being heated on the steam-bath under a condenser protected from moisture for 24 hours, the solution was evaporated to dryness *in vacuo*. The residue was dissolved in 100 cc. of saturated aqueous sodium bicarbonate and 100 cc. of ethyl acetate. The separated aqueous layer was acidified, saturated with salt, and extracted with 3 100-cc. portions of chloroform. The combined dried extracts were evaporated to dryness *in vacuo*. Crystallization from ethyl acetate gave 1.57 g. (27%) of product, m.p. 159–161°. The filtrate was evaporated to dryness *in vacuo* and treated with acetic anhydride as described for XXXII to give an additional 15% of product, m.p. 159–160°. A mixture of either fraction with XXX gave a 20° depression. Recrystallization from 30% alcohol gave white crystals, m.p. 162–163°.

Anal. Calc'd for $C_{16}H_{19}NO_5$: C, 62.9; H, 6.23; N, 4.59; OAc, 14.1.

Found: C, 62.7; H, 6.58; N, 4.76; OAc, 14.7.

The combined ethyl acetate solutions of neutral material gave 14% of lactone (XXX), m.p. 99–101°.

cis-1-Benzoyl-3-acetoxypiperidine-2-acet-p-chloranilide (LII). From 200 mg. of XLVIIIa by conversion to the mixed anhydride (LIa) and reaction with *p*-chloraniline as described for XL there was formed 185 mg. (69%) of white crystals from toluene, m.p. 135–137°.

Anal. Calc'd for $C_{22}H_{23}ClN_2O_4$: C, 63.7; H, 5.55; N, 6.76; Cl, 8.57; OAc, 10.4.

Found: C, 64.0; H, 5.64; N, 6.81; Cl, 8.46; OAc, 10.3.

cis-1-Benzoyl-3-hydroxypiperidine-2-acet-p-chloranilide (XLIX). A solution of 200 mg. of LII in 10 cc. of methanol and 0.5 cc. of 1 *N* sodium methoxide was refluxed for ten minutes, acidified with acetic acid, then evaporated to dryness *in vacuo*. The residue was partitioned between 10 cc. of water and 10 cc. of chloroform. The extract was dried with magnesium sulfate and evaporated to dryness *in vacuo*. Trituration of the residue with 3 cc. of toluene gave 135 mg. (72%) of product, m.p. 180–182°. Recrystallization from ethyl acetate-heptane afforded white crystals, m.p. 185–186°.

Anal. Calc'd for $C_{20}H_{21}ClN_2O_3$: C, 64.4; H, 5.69; N, 7.52; Cl, 9.53.

Found: C, 63.8; H, 6.02; N, 7.31; Cl, 9.75.

α-(4-Quinazolone-3-acetyl)butyrolactone (LVI). (*A*). To a solution of 5 g. of ethyl 4-quinazolone-3-acetate (17) and 2.1 cc. of butyrolactone in 43 cc. of benzene and 3 cc. of absolute alcohol was added 1.3 g. of sodium methoxide. The solution was refluxed for 5 minutes when the sodio derivative separated as a paste. After standing 10 minutes longer, the mixture was acidified with 2.6 cc. of acetic acid, washed with water, and evaporated to dryness *in vacuo*. Crystallization from methanol gave 1.4 g. (25%) of product, m.p. 146–148°. Recrystallization from toluene afforded white crystals, m.p. 150–151°, which gave a red ferric chloride test.

Anal. Calc'd for $C_{14}H_{12}N_2O_4$: C, 62.0; H, 4.43; N, 10.3.

Found: C, 61.7; H, 4.73; N, 10.1.

When a solution of the keto ester in ethyl acetate was shaken with 10% aqueous cupric acetate, a blue copper derivative separated which was collected and washed with water, then alcohol. This compound, m.p. 250–254°, is insoluble in all common solvents. The keto ester can be recovered by shaking the copper derivative with chloroform and 1 *N* hydrochloric acid until the chloroform was no longer green, then evaporation of the organic solution.

Anal. Calc'd for $C_{28}H_{22}CuN_4O_8$: C, 55.4; H, 3.63; N, 9.24.

Found: C, 54.9; H, 3.49; N, 8.95.

(*B*). A solution of 685 mg. of sodium hydride in *tert*-butyl alcohol was evaporated to dryness *in vacuo*. To the residual solid sodium *tert*-butoxide was added a warm solution of 5.0 g. of ethyl 4-quinazolone-3-acetate, 1.8 cc. of butyrolactone, and 4.8 cc. of *tert*-butyl

alcohol in 43 cc. of benzene. The solution was refluxed for 3 hours and worked up as in *A*; yield, 1.4 g. (25%), m.p. and mixture m.p. with preparation *A*, 146–148°.

When this reaction mixture was stirred at 25° for 22 hours, protected from moisture, the yield was only 4%. The substitution of the equivalent quantity of 3-hydroxypiperidine-2-acetic acid lactone (XXVII) in this procedure at room temperature followed by a 30-minute hydrolysis with 6 *N* hydrochloric acid gave only 0.7% of *dl*-alkaloid (XXXVI), as shown by assay.

(*C*). The use of phenyl 4-quinazolone-3-acetate (10) in preparation *B* with the amount of sodium doubled gave a 4% yield.

(*D*). The use of lithium *tert*-butoxide in *B* afforded a 16% yield.

(*E*). The use of phenyl 4-quinazolone-3-acetate and 2 equivalents of lithium amide in dry dioxane gave 30% (by weight) of an unidentified by-product, m.p. >360°. The same substance was obtained in 58% (by weight) when the butyrolactone was omitted.

normal-3-Carbethoxyamino-4-hydroxy-7-bromoheptanolactone (LVIIIb). To a stirred mixture of 1.00 g. of XXVI in 14 cc. of chloroform and 14 cc. of saturated aqueous sodium bicarbonate cooled in an ice-bath was added 0.35 cc. of ethyl chlorocarbonate. After 15 minutes an additional 14 cc. of saturated aqueous sodium bicarbonate and 0.35 cc. of ethyl chlorocarbonate was added. The layers were stirred 15 minutes longer, then separated. The chloroform solution, washed with 1 *N* hydrochloric acid and dried with magnesium sulfate, was evaporated *in vacuo*; yield, 0.92 g. (95%) of an oil which solidified to a low-melting solid on standing.

Anal. Calc'd for $C_{10}H_{16}BrNO_4$: C, 40.8; H, 5.49; N, 4.76.
Found: C, 41.0; H, 5.78; N, 4.70.

When only one treatment with ethyl chlorocarbonate was employed, the yield dropped to 57%.

Similarly, treatment of 1.00 g. of XXVI with 0.3 cc. of benzoyl chloride in one portion gave 0.92 g. (81%) of *normal-3-benzamido-4-hydroxy-7-bromoheptanolactone* (LVIIIa) as a white solid, m.p. 99–107°. No suitable solvent for recrystallization could be found.

Anal. Calc'd for $C_{14}H_{16}BrNO_3$: C, 51.5; H, 4.96; N, 4.29.
Found: C, 51.4; H, 5.07; N, 4.31.

N-Carbethoxy-β-furyl-β-alanine (LXIII). Carbethoxylation of 9 g. of β-furyl-β-alanine with ethyl chlorocarbonate as described for Xa gave a crude product which was crystallized from benzene-heptane; yield, 9.5 g. (71%), m.p. 109–111°. Recrystallization from the same solvents gave white crystals, m.p. 112–113°.

Anal. Calc'd for $C_{10}H_{13}NO_5$: C, 52.9; H, 5.78; N, 6.16.
Found: C, 53.0; H, 6.40; N, 6.31.

This acid was converted to the acid chloride with phosphorus pentachloride in acetyl chloride and the intermediate acid chloride was reacted with aniline; yield, 97% of *anilide*, m.p. 147–149°. Recrystallization from dilute methanol gave white crystals, m.p. 167–168°.

Anal. Calc'd for $C_{16}H_{18}N_2O_4$: N, 9.27. Found: N, 9.40.

1-Diazo-4-carbethoxyamino-4-furyl-2-butanone (LXIV). To a mixture of 5.0 g. of LXIII and 25 cc. of acetyl chloride was added 5.2 g. of phosphorus pentachloride. Solution was complete in a few minutes with shaking. After 20 minutes the solution was evaporated to dryness *in vacuo* (bath 45–50°) and the evaporation repeated with 38 cc. of toluene. The residual acid chloride, dissolved in 38 cc. of benzene (an aliquot gave a 92% yield of anilide), was added dropwise with swirling and ice-cooling to a dried ethereal solution of diazomethane (from 12.8 g. of nitrosomethylurea). After about 45 minutes at room temperature crystals began to separate and gas evolution was complete after 4 hours. The excess diazomethane was destroyed by the addition of 8 cc. of acetic acid. Filtration gave 2.0 g. of product, m.p. 93° dec. From the filtrate was isolated an additional 1.2 g., m.p. 91–93° dec. by crystallization from benzene-heptane; total yield, 3.2 g. (58%). Recrystallization of a sample from methanol gave yellow crystals, m.p. 93–94° dec.

Anal. Calc'd for $C_{11}H_{13}N_3O_4$: C, 52.6; H, 5.22; N, 16.7.
Found: C, 52.9; H, 5.31; N, 16.8.

1-Bromo-4-carbethoxyamino-4-furyl-2-butanone (LXV). To a suspension of 500 mg. of

LXIV in 2.5 cc. of absolute alcohol was added 0.19 cc. of 48% hydrobromic acid. Vigorous evolution of nitrogen took place and when solution was almost complete, the product began to separate. The mixture was warmed briefly to 50° to complete the reaction, then cooled and diluted with several volumes of water; yield, 550 mg. (92%), m.p. 91–92°. Recrystallization from methanol gave white crystals, m.p. 92–93°. After standing for one year the analytical sample had completely carbonized.

Anal. Calc'd for $C_{11}H_{14}BrNO_4$: C, 43.4; H, 4.65; N, 4.61.
Found: C, 43.8; H, 4.91; N, 4.75.

3-(β-Keto-δ-carbethoxyamino-δ-furylbutyl)-4-quinazolone (XLVI). A solution of 500 mg. of XLV in 5 cc. of methanol was added to a solution of 265 mg. of 4-quinazolone in 1.6 cc. of 1 *N* sodium methoxide. After five minutes crystals began to separate and at the end of one hour the mixture was filtered and the product washed with methanol; yield, 495 mg. (82%), m.p. 210–212°. Recrystallization from absolute alcohol gave white crystals, m.p. 212–213°.

Anal. Calc'd for $C_{19}H_{19}N_3O_5$: C, 61.8; H, 5.20; N, 11.4.
Found: C, 61.8; H, 5.39; N, 11.2.

3-(β-Keto-δ-benzamido-δ-furylbutyl)-4-quinazolone. Conversion of XX to 1-bromo-4-benzamido-4-furyl-2-butanone and condensation with 4-quinazolone as described for Xa gave 1.6% over-all yield of product, m.p. 214–216°, from ethyl acetate. None of the intermediates could be obtained crystalline. Recrystallization from methanol gave nearly white crystals, m.p. 218–219°, which were not quite pure.

Anal. Calc'd for $C_{23}H_{19}N_3O_4$: C, 68.8; H, 4.74; N, 10.5.
Found: C, 68.2; H, 5.56; N, 10.0.

SUMMARY

The *trans* isomer of the Hydrangea alkaloid has been synthesized in two ways from β-furyl-β-alanine, the first *via trans*-1-carbethoxy-3-hydroxypiperidine-2-acetic acid and the second *via* hydrobromic acid ring opening of 3-(β-keto-δ-amino-δ-tetrahydrofurylbutyl)-4-quinazolone to a bromohydrin followed by ring closure.

A second synthesis of the Hydrangea alkaloid has been described starting with N-benzoyl-β-furyl-β-alanine and proceeding through the key intermediate, *cis*-1-benzoyl-3-hydroxypiperidine-2-acetic acid.

The Hydrangea alkaloid has been established to have the *cis* configuration in the piperidine ring by comparison of the ease of ring closure of derivatives of *cis*- and *trans*-3-hydroxypiperidine-2-acetic acid to a lactone and conversion of the *cis*-isomer to the Hydrangea alkaloid.

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