[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION,
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AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. III. DEGRADATION

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The isolation of an antimalarial alkaloid from Hydrangea has been described (1). The elemental analysis indicated an empirical formula of $C_{16}H_{19}N_3O_3 \cdot 2HCl$.

Degradation studies were initiated even though only extremely small amounts of the alkaloid were available. The limited supply of the alkaloid made it imperative that maximum use be made of model compounds.[1]

Through the following discussion it will become apparent that many of the postulates could have been decided by straightforward degradation reactions. However, with only a few milligrams of the alkaloid available at any one time, many of these approaches were not feasible. All exploratory reactions were run on 2–3 milligram samples, and because of the difficulty of isolating products or determining the course of a reaction, some of these ended in failures that would have been circumvented had larger samples been employed.

As a descriptive summary of the approach to the problem, the course of the degradation has been more or less described as it evolved under the actual conditions.

Determinations for N-methyl, O-methyl, and C-methyl groupings in the Hydrangea alkaloid were negative as were tests for isolated unactivated double bonds or for amino nitrogen. The alkaloid absorbed ultraviolet light with absorption maxima at 265, 275, 302.5, and 313 mμ in 0.1 *N* sodium hydroxide and at 272.5 mμ with an inflection at 295 mμ in 0.1 *N* hydrochloric acid.

When the alkaloid was subjected to alkaline hydrolysis, there was extensive coloration with marked changes in the ultraviolet absorption spectra. Concomitant with these changes an aromatic amine was formed that could be detected by the method of Bratton and Marshall (2). The rate and extent of amine formation was dependent on the concentration of alkali. One-tenth normal sodium hydroxide for 4 hours at 100° liberated 59% of theory, an amount that could not be further increased by prolonged hydrolysis. Two normal sodium hydroxide under similar conditions liberated 96% of theory. The rate of color formation of the unknown amine with the reagents of the Bratton and Marshall test indicated the amine to be similar to the *o*-aminobenzoic acids. Solvent partition of the compound from acidic and basic solutions revealed the amphoteric nature of the amine. From alkaline hydrolysates of the alkaloid the amine was isolated and characterized as *o*-aminobenzoic acid.

The formation of *o*-aminobenzoic acid on alkaline hydrolysis could have proceeded from a 4-quinazolone nucleus. When a number of model 4-quinazolones were compared on the basis of their absorption of ultraviolet light, it became

[1] All of the model compounds were synthesized by Dr. B. R. Baker and associates. We are indebted to them for their kind cooperation throughout this work.

apparent that the alkaloid was most probably a 4-quinazolone substituted in the 3-position (Table I). The ultraviolet absorption spectra further indicated that the characteristic absorption of the compound in ultraviolet light was due solely to the substituted quinazolone nucleus.

The alkaloid and the model quinazolones were further compared on the basis of their rates of alkaline hydrolysis. Under defined conditions (0.1 *N* NaOH—3 hours at 100°) 3-(γ-piperidinopropyl)-4-quinazolone liberated 35% of the theoretical *o*-amine whereas 2-methyl-3-(γ-piperidinopropyl)-4-quinazolone yielded only 3.5% of the theoretical amount of *o*-aminobenzoic acid. When the possible effects of functional groups adjacent to the quinazolone ring on the rate of hydrolysis of the alkaloid were taken into consideration, it became apparent that the rate of hydrolysis of 3-(γ-piperidinoropyl)-4-quinazolone was not too dissimilar from that of the alkaloid. Substitution in the 2-position definitely stabilized the quinazolone ring to alkaline cleavage. The 2,3-disubstituted model was approximately 10 times as stable as the 3-substituted 4-quinazolone. Thus,

TABLE I

ULTRAVIOLET ABSORPTION OF COMPOUNDS RELATED TO THE HYDRANGEA ALKALOID

COMPOUND	POINTS OF MAXIMA IN 0.1 *N* SODIUM HYDROXIDE, mμ	mμ	ε
Hydrangea alkaloid	265, 275, 302.5, 313	265	8,240
		302.5	4,640
o-Aminobenzoic acid	240, 310		
4-Quinazolone	282, 308		
3-(γ-Piperidinopropyl)-4-quinazolone	267, 273, 302.5, 317	267	8,000
		302.5	4,000
2-Methyl-3-(γ-piperidinopropyl)-4-quinazolone	267, 273, 305, 317	267	8,710
		305	4,355

the hydrolysis characteristics of the models supported the conclusions derived from the ultraviolet absorption data that the alkaloid was a 3-substituted 4-quinazolone.

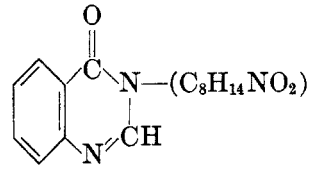
Fragmentary evidence was accumulated suggesting that 4-quinazolone was also formed during the hydrolysis with 0.1 *N* sodium hydroxide. This hypothesis seemed plausible on the basis of the liberation of only 0.6–0.7 mol of *o*-amine, which was indicative that the alkaloid was being hydrolyzed by more than one reaction. The necessary requisite that 4-quinazolone exhibit stability to 0.1 *N* caustic was satisfied.

During the hydrolysis with 0.1 *N* sodium hydroxide, vapors were evolved that were basic in reaction. A quantitative determination for ammonia gave a value of 0.6 mole of ammonia liberated. *o*-Aminobenzoic acid under similar conditions was stable.

On the basis of the known lability of β-aminoketones to alkali and assuming the nitrogen of the 3-position of the quinazolone ring to be the source of ammonia, 3-(γ-ketobutyl)-4-quinazolone was subjected to aklaline hydrolysis. The

compound liberated only slight amounts of *ortho* amine and no detectable amounts of ammonia. The liberation of ammonia by the alkaloid was apparently not due to the presence of a substituted β-aminoketone grouping.

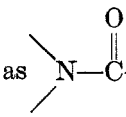
The alkaloid which could be represented as I contained a nitrogen atom and



I

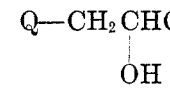
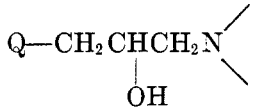
two oxygen atoms that could be associated with functional groups. Cursory examination with ketonic reagents gave negative results. During abortive experiments on attempts to chlorinate the alkaloid, a method was evolved that would yield a crystalline O-acetyl derivative. When the alkaloid was dissolved in glacial acetic acid and reacted with thionyl chloride, a crystalline mono-O-acetyl alkaloid dihydrochloride was formed. Acid hydrolysis of the acetate regenerated the parent alkaloid. The formation of the monoacetoxy compound indicated the presence of a hydroxyl group in the Hydrangea alkaloid.

The free base of the alkaloid reacted with phenyl isothiocyanate to form a derivative that was characterized by its extreme lability to alkaline hydrolysis with the formation of one mole of *o*-amine. In further contrast to the alkaloid the derivative did not discolor on alkaline hydrolysis nor did it liberate but a fraction of the expected quantity of ammonia. The properties of the compound suggested that the side chain was stabilized by the reaction with phenyl isothiocyanate. The product analyzed for one mole of water less than that calculated for a phenylthiourea derivative, suggesting that a cyclization on a reactive functional group had taken place.

Attempts were made to isolate the stabilized side chain. However, work-up of the solution after removal of the anthranilic acid caused extensive coloration. When the solution was reacted with benzoyl chloride, a crystalline dibenzoyl derivative was obtained. The data were interpreted to suggest the following: (a) a secondary amine group was present in the alkaloid, (b) the functional group reacting to effect cyclization was probably ketonic in nature, (c) the proposed ketonic group was not present in the alkaloid as  , and (d) the proposed ketonic group was *alpha* or *beta* to the secondary amine.

With potassium cyanate the intermediate N-carbamyl derivative was obtained. Treatment of this product with ethanolic hydrogen chloride resulted in cyclization of the compound.

Additional structural evidence was obtained from a study of the oxidation of the alkaloid. Because of the small amounts of the alkaloid available, the oxidation characteristics of a number of model 4-quinazolones were first determined.

Several oxidants and conditions were tried but the most promising appeared to be a neutral permanganate oxidation at reflux temperature for 30 minutes. The model experiments indicated that the groupings  or  could be oxidized to yield 3-(carboxymethyl)-4-quinazolone.

When the alkaloid was oxidized similarly to the known compounds, 3-(carboxymethyl)-4-quinazolone was obtained. The most logical interpretation was that the carbon atom *beta* to the quinazolone ring carried an oxygen or nitrogen atom as a substituent. An alternative but less attractive possibility was that in addition the α-position was carbon-substituted which would lead to a substituted malonic acid that would decarboxylate to form 3-(carboxymethyl)-4-quinazolone. However, when 3-(α-methylol-β-hydroxyethyl)-4-quinazolone was oxidized, 4-quinazolone and an unidentified oil were obtained. The inability to obtain 3-(carboxymethyl)-4-quinazolone tentatively ruled against α-substitution. When the alkaloid was oxidized with periodic acid no formaldehyde was formed.

Sublimation of the alkaloid would at times yield a product that would react immediately with phenylhydrazine. The compound could be obtained with ease if the alkaloid was mixed with zinc dust and then sublimed. The sublimate was identified as 3-(β-ketopropyl)-4-quinazolone by analysis, by derivative, and by comparison with an authentic sample.

As no ketonic derivative other than the bicyclic derivative with phenyl isocyanate or potassium cyanate had been formed with the alkaloid, the above data did not establish the presence or absence of a ketonic group in the alkaloid. The possibility of the conversion of a hydroxyl group to a ketonic group by zinc dust distillation was considered. When the model compound, 3-(γ-butylamino-β-hydroxypropyl)-4-quinazolone was distilled under conditions similar to those employed for the alkaloid, unchanged starting material was recovered. This fact was interpreted as presumptive evidence for the presence of a ketonic group β- to the quinazolone ring.

Further indicative evidence for the presence of a ketonic group in the β-position was obtained when it was found that 3-(β-ketopropyl)-4-quinazolone on alkaline hydrolysis formed 0.7 mole of ammonia. The behavior of the degradation product was thus identical to that of the naturally occurring alkaloid.

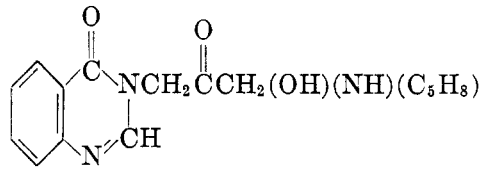
The formation of 3-(β-ketopropyl)-4-quinazolone on zinc dust distillation necessitated the re-examination of the alkaloid for the presence of a ketonic group. It was found that when the alkaloid was refluxed in pyridine-ethanol solution or when the alkaloid was allowed to stand in sodium carbonate solution with hydroxylamine, an oxime was readily formed from which the alkaloid could be regenerated on acid hydrolysis.

When an attempt was made to form the oxime of the O-acetyl alkaloid, a deacetylated compound was obtained. The product analyzed as the alkaloid oxime but melted approximately 80° lower.

The differing oximes were suggestive of the *syn* and *anti* forms of this derivative.

The deacetylation of the alkaloid on oximation was suggestive of an interaction between the hydroxyl group and the ketonic group. However, corroborative or more definitive data were not obtained.

The foregoing data made possible the formulation of the alkaloid as II.



II

The position of the secondary amino group relative to the ketone was investigated. The bicyclic derivative that was formed with phenylisothiocyanate or potassium cyanate required the grouping to be *alpha* or *beta*. In an attempt to determine which of these two possibilities was probable, various model compounds were studied with respect to reaction with potassium cyanate, distillation from zinc dust, and oxidation.

When the model compounds 3-(β-keto-γ-aminopropyl)-4-quinazolone and 3-(β-3-piperidyl-β-ketoethyl)-4-quinazolone were reacted with potassium cyanate, the former compound reacted and cyclized to form the imidazolone while the latter compound formed an N-carbamyl derivative that would not cyclize under the usual conditions. However, the results with the piperidyl compound may be complicated by the point of attachment of the 3-(β-ketoethyl)-4-quinazolone radical to the piperidine ring.

Distillation of 3-(β-keto-γ-aminopropyl)-4-quinazolone from zinc dust resulted in the product being recovered unchanged. The behavior of the compound did not preclude the possibility that a similar compound in which the nitrogen was secondary would yield 3-(β-ketopropyl)-4-quinazolone but it suggested that such compounds would not yield the desired quinazolone acetone.

Oxidation of certain model compounds had earlier established that the grouping $Q—CH_2COCH_2N\begin{matrix}/\\ \\ \backslash\end{matrix}$ would oxidize to form 3-(carboxymethyl)-4-quinazolone.

In order to determine whether the grouping $Q—CH_2COCH_2CO—$, real or potential, would function as an activating group, the compounds 3-(γ-carbethoxy-β-ketopropyl)-4-quinazolone and 3-(β-3-piperidyl-β-ketoethyl)-4-quinazolone were oxidized under conditions similar to those employed for the alkaloid. Both compounds formed 3-(carboxymethyl)-4-quinazolone on oxidation.

The work on the models tended to favor the secondary amine group as being β- to the ketone but did not summarily exclude the possibility of the α-position.

The unknown portion of the alkaloid by the methods of degradation used had invariably ended up as uncharacterizable fragments. A more stable component was visualized if a modification of the ketonic group could be effected.

Microhydrogenation experiments were designed to satisfy several arbitrary

criteria. From experience on the alkaloid and its derivatives and on the model compounds it was reasoned that if the ketonic group only was reduced the ultraviolet absorption of the compound would not be affected. On alkaline hydrolysis the aromatic amine should be liberated with no loss of NH_3 and the solution should not evidence marked decomposition. These standards were adopted to gain as much information as possible from the small amount of compound available as it was not always possible to recover the product.

In a number of experiments using platinum as the catalyst it was not possible to correlate hydrogen uptake with the above mentioned criteria sufficiently to warrant further work.

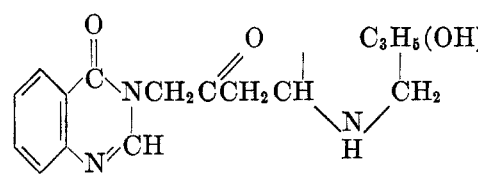
Attention was then directed to the possible hydrogenolysis of the mercaptole of the alkaloid. For model experiments the mercaptole of 3-(β-ketopropyl)-4-quinazolone was prepared. All attempts to effect hydrogenolysis of this compound were unsuccessful and yielded either 3-(β-ketoethyl)-4-quinazolone or 4-quinazolone. The latter compound was a hydrogenolysis product of the former. Efforts to prepare the mercaptole of the alkaloid were singularly ineffective and starting material was recovered.

When the alkaloid was reduced with zinc and hydrochloric acid at room temperature or with zinc amalgam and hydrochloric acid at reflux temperature, an amine was formed that behaved in the Bratton and Marshall test as a *m*- or *p*-amine. When 3-(methyl)-4-quinazolone was treated similarly, an analogous amine was formed. Thus, the formation of the amine was a characteristic of the quinazolone nucleus. Because of the desirability of maintaining the intact quinazolone nucleus so that the reaction could be more easily evaluated, this approach was discontinued.

A further attempt was made to reduce the compound with hydriodic acid and red phosphorus. Under a variety of conditions, the alkaloid appeared to be stable and was recovered unchanged.

Lastly, a number of trials to effect a Beckmann rearrangement of the alkaloid oxime were carried out. Our attempts were without success and the parent alkaloid was recovered.

The reactions and properties of the alkaloid could be ascribed to a compound having structure III.

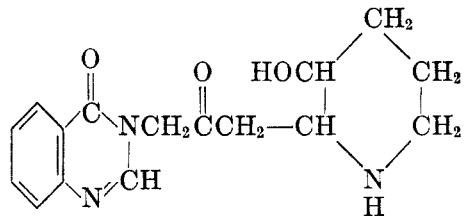


III

Accordingly, the model compound 3-[β-keto-γ-(2-piperidyl)propyl]-4-quinazolone was prepared by Baker and co-workers (3). The compound contains desired spacial arrangement of the various functional groups with the exception of the hydroxyl group and in addition was the desoxy derivative of what was considered to be the more probable structure of the alkaloid.

When the compound was subjected to the so-called typical reactions of the alkaloid which encompassed the formation of anthranilic acid and ammonia on alkaline hydrolysis, the cleavage to yield 3-(β-ketopropyl)-4-quinazolone, and the formation of the N-carbamyl derivative with subsequent cyclization, the compound was found to behave identically to the naturally occurring alkaloid. It seemed quite reasonable to assume, therefore, that the alkaloid contained the groupings in III. It is quite apparent that the information presented does not locate the position of the hydroxyl group, other than the mere suggestion of its spacial proximity to the ketonic group, nor is the size of the ring indicated by the data. However, the probability of the compound being a substituted hydroxypiperidine or a substituted hydroxymethylpyrrolidine was chosen as the more likely possiblity.

The stability of the compound to acid and the lack of formation of formaldehyde on periodate oxidation indicated the alkaloid was most probably 3-[β-keto- γ-(3- or 4-hydroxy-2-piperidyl)propyl]-4-quinazolone or 3-[β-keto-γ-(3- or 4-hydroxymethyl)-2-pyrrolidyl)propyl]-4-quinazolone. The correctness of this postulate was demonstrated when Baker and associates synthesized these compounds (4, 5, 6) and proved the hydrangea alkaloid to be 3-[β-keto-γ-(3-hydroxy-2-piperidyl)propyl]-4-quinazolone (IV).



IV

After the degradation work was completed, a number of papers appeared describing the isolation of antimalarial alkaloids from *Dichroa febrifuga* Lour. Chou, Fu, and Kao (7) reported the isolation of 3 compounds designated as α, β, and γ-dichroine. The empirical formula for each compound was $C_{16}H_{21}N_3O_3$. The α-isomer could be converted to the β- or γ-isomer. The β-dichroine was interconvertible with γ-dichroine. Alkaline permanganate oxidation formed 4-quinazolone and alkaline hydrolysis yielded anthranilic acid, ammonia, and formic acid. The presence of a quinazolone nucleus was thus established.

Kuehl, Spencer, and Folkers (8) isolated two distinct compounds by chromatography of a preparation obtained by the decomposition of an alkaloid oxalate prepared from extracts of similar botanical material. The two products were interconvertible and both analyzed for $C_{16}H_{19}N_3O_3$.

Koepfli, Mead, and Brockman (9, 10) in an extensive study isolated two products from *Dichroa febrifuga* Lour. which were designated as febrifugine and isofebrifugine. Both compounds had the empirical formula $C_{16}H_{19}N_3O_3$.

In a structural study quite distinct from that herein presented, the presence of a 3-substituted 4-quinazolone ring, a ketonic group, a secondary amine, and a

probable hydroxyl group was postulated. In a recent paper Koepfli, Brockman, and Moffat (11) outlined the course of the periodate reaction on febrifugine and from the product obtained and its subsequent reaction with semicarbazide demonstrated that febrifugine has structure IV.

The identity of the Hydrangea alkaloid with the alkaloid isolated from Ch'ang Shan (*Dichroa febrifuga* Lour.) as shown by Ablondi and co-workers (1) makes it certain that the compound with high antimalarial activity isolated by Chou, *et al.*; Kuehl, *et al.*; Koepfli, *et al.*; and Ablondi, *et al.* is identical.

Acknowledgment. The authors are grateful to the late Dr. Y. SubbaRow for his interest in the problem. We are indebted to Mr. Louis Brancone and staff for the microanalyses. Thanks are especially due Mr. William Fulmor for the microhydrogenations and to Mr. John Morton for help on the oxidation of certain model compounds.

EXPERIMENTAL[2]

Ultraviolet absorption. All ultraviolet absorption measurements were made on a Beckman Model DU spectrophotometer.

Test for unsaturation. A sample of 14.9 mg. of the alkaloid was dissolved in 4 ml. of glacial acetic acid containing 2 drops of triethylamine, and 4 ml. of iodine monobromide was added. After 1.5 hours in the dark, 3 ml. of 15% potassium iodide was added and then 10 ml. of water. The solution was then titrated with standard thiosulfate solution. The titration of the blank and the sample were the same indicating the absence of isolated or unactivated unsaturation.

Amino nitrogen. The alkaloid was run in the usual manner for α-amino acid nitrogen except the reaction time was increased to 10 minutes. There was no evolution of nitrogen. Later, the model compound, 3-(β-aminoethyl)-4-quinazolone was run under similar conditions except the reaction time was 3 minutes. There was found 91% of 1 mole of amino nitrogen.

Alkaline hydrolysis. The alkaloid was dissolved in 0.1, 1.0, and 2.0 *N* sodium hydroxide, 1.0 *N* sodium methoxide, and 28% ammonium hydroxide at a concentration of 1.0 mg. per ml., placed in tubes and sealed, and heated at 100° for 4 hours. The amine liberation was measured by the Bratton and Marshall method (2). *p*-Aminobenzoic acid reaches maximum color development in 10 minutes, whereas the unknown at 1.5 hours had developed only 51.5% of the molal color of *p*-aminobenzoic acid and at 19 hours had reached a value of 70.3%. The behavior of the amine thus resembled *o*-aminobenzoic acid. The color developed at 1.5 hours was determined and arbitrarily expressed as *p*-aminobenzoic acid equivalents. The amine formed expressed as per cent of theory based on 1 mole per mole of alkaloid was 59, 87, 96, 25, and 28%, respectively.

The liberated amine was not extractable from alkaline solution or from 1.0 *N* hydrochloric acid by ethyl acetate but was readily extracted at *p*H 2.0.

A typical preparation of the amine is outlined. The alkaloid dihydrochloride (53 mg.) was dissolved in 50 ml. of 0.1 *N* sodium hydroxide and heated on the steam-bath for 3 hours. The brownish colored solution was cooled, adjusted to *p*H 2.0, and extracted with one volume of ethyl acetate. The ethyl acetate extract was washed with one-tenth volume of water and then concentrated to dryness. The residue was dissolved in a small volume of ethanol, treated with a little charcoal to remove pigmented material, and the resulting solution concentrated to dryness in a distillation head. The compound was distilled in a

[2] The melting points were taken on a Fischer micro block. At times only isolated crystals were available so that the recorded melting points should be evaluated only as proving the identity or non-identity of the stated compounds.

high vacuum at 118–120° for 7 hours. The sublimate was crystallized from 0.2 ml. of water; yield 5 mg., m.p. 143–144.5°

Anal. Found: C, 61.06; H, 5.11; N, 10.61.

The compound was soluble in ethyl acetate, ethanol, acetone, and similar solvents but insoluble in petroleum ether. The product exhibited no optical rotation, gave a negative $FeCl_3$ test, and had a marked blue fluorescence in solution. The ultraviolet absorption of the compound was identical to the absorption of anthranilic acid. The unknown in admixture with a sample of anthranilic acid m.p. 144–145° melted at 142.5–143.5°. The theoretical analytical values for *o*-aminobenzoic acid are C, 61.31; H, 5.11; N, 10.23.

Alkaline hydrolysis of model 4-quinazolones. 3-(γ-Piperidinopropyl)-4-quinazolone dihydrochloride and 2-methyl-3-(γ-piperidinopropyl)-4-quinazolone dihydrochloride were dissolved at a concentration of 1 mg. per ml. in 0.1 *N* sodium hydroxide and heated for 3 hours on the steam-bath. The *ortho* amine was determined by the method of Bratton and Marshall. The former compound liberated 0.35 mole of *o*-amine, whereas the latter yielded 0.035 mole.

Possible presence of 4-quinazolone. After removal of the aromatic amine the 0.1 *N* sodium hydroxide hydrolysate contained a compound that absorbed ultraviolet light. The points of minima were not too sharply defined but there were broad maxima from 260–270 mμ and from 300–310 mμ. After precipitation with phosphotungstic acid and decomposition of the resulting phosphotungstate with barium hydroxide, the compound had maxima at 265–275 and 305 mμ. The general shape of the absorption curve was similar to that for 4-quinazolone. The substance was not more definitely characterized.

When 4-quinzaolone was dissolved in 0.1 *N* sodium hydroxide and heated for 4 hours on the steam-bath, no aromatic amine was liberated.

Formation of ammonia on alkaline hydrolysis of the alkaloid. The alkaloid dihydrochloride was dissolved at a concentration of 1 mg. per ml. in 0.1 *N* sodium hydroxide (2–3 mg. samples were used) and the tubes were sealed and heated on the steam-bath for 3 hours. The tubes were cooled, opened, and the ammonia determined by Nesslerization; 1.0 mg. of the alkaloid formed 27.7γ of ammonia. If one of the nitrogen atoms of the alkaloid appears as ammonia, the theory for a 1.0-mg. sample would be 45.5γ. Thus, 0.61 mole of ammonia was liberated on alkaline hydrolysis. In this experiment, 0.62 mole of anthranilic acid was formed.

Under similar conditions *o*-aminobenzoic acid and 3-(γ-piperidinopropyl)-4-quinazolone failed to yield detectable quantities of ammonia.

Alkaline hydrolysis of 3-(γ-ketobutyl)-4-quinazolone. The compound was hydrolyzed at a concentration of 1 mg. per ml. in 0.1 *N* sodium hydroxide in a sealed tube for 3 hours on the steam-bath. Only 0.034 mole of *o*-amine was formed and detectable amounts of ammonia were not liberated. (See paper IV in this series for a complete explanation of the alkaline hydrolysis of this compound.)

Preparation of the mono-O-acetyl derivative of the alkaloid. To 100 mg. of the alkaloid dihydrochloride suspended in 3 ml. of glacial acetic acid was added 2 ml. of thionyl chloride. A reaction at room temperature was observed with a brisk evolution of sulfur dioxide and solution of the alkaloid. After 4 hours, the crystalline mass was thinned with 2 ml. of glacial acetic acid and 2 ml. of ether, and the compound was collected, washed thoroughly with ether, and dried. The compound was recrystallized from ethanol-ethyl ether; yield 82 mg., m.p. 184–188°.

Anal. Calc'd for $C_{18}H_{21}N_3O_4 \cdot 2HCl$: C, 51.9; H, 5.56; N, 10.09; Cl. 17.06; Ionic Cl, 17.06; O-acetyl, 10.33.

Found: C, 51.86; H, 5.89; N, 10.03; Cl, 16.94; Ionic Cl, 17.31; O-acetyl, 12.41.

The compound was converted to the free base by solution in water, addition of sodium carbonate to *p*H 8–9, and extraction with chloroform. After crystallization from chloroform-petroleum ether the base melted at 110°.

Anal. Calc'd for $C_{18}H_{21}N_3O_4$: N, 12.23.

Found: N, 12.20.

When the acetoxy compound was refluxed with ethanol 0.1 *N* with hydrogen chloride, the parent alkaloid was recovered.

Reaction with phenyl isothiocyanate. To 100 mg. of the alkaloid dihydrochloride dissolved in ethanol with the aid of triethylamine was added 0.5 ml. of phenyl isothiocyanate. After standing for 15 hours at 32°, the solution was concentrated to a syrup *in vacuo*. The residue was dissolved in 50 ml. of ethanol, a small amount of ethanolic hydrogen chloride was added, and then 50 ml. of petroleum ether. After chilling, the crystals were collected and recrystallized from ethanol-petroleum ether; yield, 80 mg. The compound exhibited no definite melting point.

Anal. Calc'd for $C_{23}H_{24}N_4O_3S \cdot HCl$: C, 58.4; H, 5.29; N, 11.85; S, 6.78; Cl, 7.51.
Calc'd for $C_{23}H_{22}N_4O_2S \cdot HCl$: C, 60.75; H, 5.96; N, 12.32; S, 7.04; Cl, 7.81.
Found: C, 60.66; H, 5.50; N, 11.97; S, 7.11; Cl, 7.86.

Alkaline hydrolysis of the derivative formed with phenyl iosthiocyanate. The derivative (1.4 mg.) was suspended in 0.5 ml. of ethanol and 0.5 ml. of 0.1 *N* sodium hydroxide was added to effect solution. An *ortho* amine test run immediately gave a value of 0.1 mole of anthranilic acid liberated. If the derivative was dissolved in 25% ethanol containing a small amount of sodium acetate, only 0.0078 mole of anthranilic acid was formed. The extreme lability of the derivative was thus demonstrated.

The derivative (6.1 mg.) was dissolved in 1 ml. of 50% ethanol containing a small amount of sodium acetate. Then 10 ml. of 1.0 *N* sodium hydroxide was added and the tube was sealed and heated on the steam-bath for 5 hours. There was formed 1.04 moles of anthranilic acid as measured by the Bratton and Marshall test. Nesslerization of aliquots of the hydrolysate indicated the presence of 725γ of ammonia or 0.33 mole. If the time of heating was reduced to 30 minutes, at which time the theoretical amount of amine was liberated, slightly less than 0.1 mole of ammonia was formed.

Isolation of the hydrolysis product of the phenyl isothiocyanate derivative. A mixture of 100 mg. of the derivative and 88 ml. of 1.0 *N* sodium hydroxide containing 8 ml. of ethanol was hydrolyzed for 1 hour on the steam-bath. The solution was cooled and 2 ml. of benzoyl chloride was added with constant shaking for 2 hours. The reaction mixture was adjusted to *p*H 8–9 and extracted with two 0.5 volumes of chloroform. The chloroform extracts were combined, dried over magnesium sulfate, and concentrated to dryness. After two crystallizations from ethyl acetate, 43 mg. was obtained that evidenced no sharp melting point but darkened with decomposition up to 230°.

Anal. Calc'd for $C_{29}H_{29}N_3O_4S$: C, 67.57; H, 5.63; N, 8.16; S, 6.22.
Calc'd for $C_{29}H_{27}N_3O_3S$: C, 70.02; H, 5.43; N, 8.45; S, 6.44.
Found: C, 69.82; H, 5.84; N, 8.63; S, 6.93.

Reaction with potassium cyanate. The alkaloid dihydrochloride (30 mg.) and 19.7 mg. of potassium cyanate were dissolved separately in 2 ml. of water and then mixed by filtering into a centrifuge tube. After standing 15 hours at 32°, some crystalline material had separated. After scratching and cooling, additional crystalline material formed. The precipitate was collected and washed twice with ice-water by centrifugation. Yield, 19.6 mg. that melted not sharply at 205–210°.

Anal. Calc'd for $C_{17}H_{20}N_4O_4$: C, 59.30; H, 5.82; N, 16.28.
Found: C, 59.43; H, 6.13; N, 15.95.

Cyclization of the N-carbamyl derivative of the alkaloid. The N-carbamyl derivative (50 mg.) was dissolved in 10 ml. of ethanol 0.1 *N* with hydrogen chloride and refluxed for 1 hour. At the end of 30 minutes, a crystalline precipitate began to separate. The compound was collected by filtration.

Anal. Calc'd for $C_{17}H_{18}N_4O_3 \cdot HCl$: C, 56.27; H, 5.24; N, 15.45; Cl, 9.79.
Found: C, 55.48; H, 5.64; N, 15.72; Cl, 9.56.

Oxidation of model 4-quinazolones. 3-(β-Hydroxyethyl)-4-quinazolone (1 g.) dissolved in the minimum amount of water was added to 200 ml. of a potassium permanganate solution (containing 7 g. of potassium permanganate and 10 g. of magnesium sulfate heptahydrate) and the mixture was refluxed for 30 minutes. The excess permanganate was discharged by the addition of a saturated solution of sodium bisulfite. The manganese dioxide was removed from the hot solution by filtration. The solution was saturated with sodium chloride, ad-

justed to *p*H 8–9, and extracted with an equal volume of ethyl acetate. The aqueous solution was then adjusted to *p*H 2.0–2.5 and extracted 4 times with 0.25 volumes of ethyl acetate. The ethyl acetate extracts were combined, dried, and concentrated to dryness. The residue was crystallized by dissolving in absolute ethanol and adding 20–30 volumes of petroleum ether.

Anal. Calc'd for $C_{10}H_8N_2O_3$: C, 58.8; H, 3.92.
Found: C, 58.64; H, 3.52.

The compound melted at 240–242° and in admixture with an authentic sample of 3-(carboxymethyl)-4-quinazolone showed no depression.

Similarly, 3-(β-butylaminoethyl)-4-quinazolone, 3-(γ-diethylamino-β-hydroxypropyl)-4-quinazolone, and 3-(γ-piperidino-β-hydroxypropyl)-4-quinazolone yielded 3-(carboxymethyl)-4-quinazolone.

Oxidation of the alkaloid. A solution containing 200 mg. of the alkaloid dihydrochloride in 6 ml. of water was added to 20 ml. of the potassium permanganate-magnesium sulfate solution at the reflux temperature. After reacting 30 minutes the mixture was worked-up as described above. There was obtained 18 mg. of a compound melting at 238–240° and exhibiting no depression when melted with an authentic sample of 3-(carboxymethyl)-4-quinazolone.

Anal. Calc'd for $C_{10}H_8N_2O_3$: C, 58.8; H, 3.92; N, 13.70.
Found: C, 58.40; H, 4.36; N, 13.35.

The oxidation product (3 mg.) was dissolved in 3 ml. of methanol 1.0 *N* with hydrogen chloride and the solution was allowed to stand at room temperature for 24 hours. The reaction mixture was concentrated to dryness, the residue was dissolved in water, and the solution was saturated with sodium chloride, adjusted to *p*H 8–9, and extracted with four 0.5 volumes of ethyl acetate. The ethyl acetate extracts were combined, dried, and concentrated to dryness. The residue was crystallized from a mixture of ethyl acetate-petroleum ether; yield 1.6 mg., m.p. 151–151.5°. The methyl ester of an authentic sample of 3-(carboxymethyl)-4-quinazolone was prepared. The compound melted at 151.5–152° and evidenced no depression when melted with the ester of the oxidation product.

Oxidation of 3-(α-methylol-β-hydroxyethyl)-4-quinazolone. A 200-mg. sample of 3-(α-methylol-β-hydroxyethyl)-4-quinazolone was oxidized under conditions identical to those used for the alkaloid. The ethyl acetate extract of the basified reaction mixture yielded 15 mg. of a substance melting at 203–208°.

Anal. Calc'd for $C_8H_6N_2O$: C, 65.8; H, 4.11; N, 19.18.
Found: C, 65.44; H, 4.76; N, 19.32.

The compound was converted to the hydrochloride, m.p. 219–220°, which in admixture with a known sample of 4-quinazolone hydrochloride melting at 221–222° showed no depression. The ultraviolet absorption spectra of the unknown was identical with the absorption spectra of 4-quinazolone.

When the reaction mixture was acidified and extracted with ethyl acetate, an uncharacterizable oil was obtained.

Periodate oxidation of the alkaloid. The alkaloid dihydrochloride (12 mg.) was dissolved in 6 ml. of water and 10 ml. of 0.04 *M* periodic acid was added. After 4 hours the mixture was steam-distilled and 2 volumes were collected. The distillate gave no color with chromotropic acid (12).

The addition of excess dimedon to 10 ml. of the distillate gave no evidence of the formation of a derivative.

Sublimation of the alkaloid from zinc dust. An intimate mixture of 54 mg. of the alkaloid dihydrochloride and 2 g. of zinc dust was distilled at 250° and 1–2 mm. for 3.5 hours. The distillate was dissolved in 6 ml. of hot water and a solution of phenylhydrazine hydrochloride and sodium acetate in 3 ml. of hot water was added. The tube was placed in a water-bath at 80° for 15 minutes. The solution was thoroughly cooled and the crystals collected. After recrystallization from ethanol and water 11.2 mg. was obtained. The melting point varied with the rate of heating ranging from 155–162°.

Anal. Calc'd for $C_{17}H_{16}N_4O$: C, 69.99; H, 5.48; N, 19.18.
Found: C, 69.88; H, 5.80; N, 19.05.

The *phenylhydrazone* of 3-(β-ketopropyl)-4-quinazolone was prepared. The derivative melted at 155–159° and under similar conditions the phenylhydrazone of the zinc dust distillate and a mixture of the two phenylhydrazones melted at 155–159°.

The *free base* of the sublimate was prepared as follows: 39 mg. of the alkaloid was distilled from zinc dust as described above. The sublimate was dissolved in 20 ml. of hot water, adjusted to alkalinity with sodium carbonate, and extracted with 100 ml. of ethyl acetate. The ethyl acetate extract was washed with 0.1 volume of sodium carbonate solution and then two 0.1-volume portions of water. After drying over sodium sulfate, the ethyl acetate extracts were concentrated to dryness. After two crystallizations from ethyl acetate-petroleum ether the compound melted at 159–160° and in admixture with an authentic sample showed no depression.

Sublimation of 3-(γ-butylamino-β-hydroxypropyl)-4-quinazolone from zinc dust. A mixture containing 300 mg. of the compound and 3 g. of zinc dust was distilled as previously described. The compound was isolated as the free base by the same general procedure as noted above and then crystallized twice from ethyl acetate-petroleum ether. The compound did not react with phenylhydrazine. The product melted at 106–107° and showed no depression when melted with an authentic sample of 3-(γ-butylamino-β-hydroxypropyl)-4-quinazolone.

Ammonia liberation by 3-(β-ketopropyl)-4-quinazolone. 3-(β-Ketopropyl)-4-quinazolone was dissolved at a concentration of 1 mg. per ml. in 0.1 *N* sodium hydroxide and heated in a sealed tube on the steam-bath for 3 hours. The amounts of ammonia and aromatic amine formed were 0.71 and 1.06 moles, respectively.

Formation of the oxime of the alkaloid. The alkaloid dihydrochloride (100 mg.) and 100 mg. of hydroxylamine hydrochloride were dissolved in 7.5 ml. of pyridine and 7.5 ml. of absolute ethanol. After refluxing for 5 hours, the solvents were removed *in vacuo*. The residue was dissolved in 35 ml. of water. On adding excess sodium carbonate, the compound crystallized. The product was recrystallized from ethanol-petroleum ether; yield 49 mg., m.p. 232–233°.

Anal. Calc'd for $C_{16}H_{20}N_4O_3$: C, 60.65; H, 6.63; N, 17.68.
Found: C, 59.76; H, 6.55; N, 17.84.

An identical oxime was formed by the following procedure: 20 mg. of the alkaloid dihydrochloride and 20 mg. of hydroxylamine hydrochloride were dissolved in 5 ml. of water, adjusted to alkalinity with sodium carbonate, and allowed to stand at room temperature overnight. After thorough cooling, the precipitate was collected and recrystallized from ethanol-petroleum ether to yield 12 mg. of compound.

Hydrolysis of the oxime. A mixture of 30 mg. of the alkaloid oxime and 5 ml. of 5 *N* hydrochloric acid was heated in a sealed tube at 120° for 1.5 hours. The solution was cooled, adjusted to *p*H 8–9 with sodium carbonate and extracted with 3 volumes of ethyl acetate. The ethyl acetate extract was concentrated to dryness. The residue was converted to the hydrochloride and thrice recrystallized from ethanol-petroleum ether to obtain 22 mg. of a compound that melted at 223–225° and showed no depression when melted with the alkaloid.

Anal. Calc'd for $C_{16}H_{19}N_3O_3 \cdot 2HCl$: C, 51.4; H, 5.09; N, 11.23; Cl, 18.97.
Found: C, 50.94; H, 6.05; N, 11.44; Cl, 18.57.

Biological assay[3] indicated the compound to have the same activity as the original alkaloid.

Formation of the isomeric oxime. The O-acetyl alkaloid dihydrochloride (60 mg.) was dissolved with an equivalent weight of hydroxylamine hydrochloride in 3 ml. of pyridine and 3 ml. of absolute ethanol and the mixture was heated for 2.5 hours on the steam-bath. The solution was concentrated to a thick syrup and then taken up in 10 ml. of water and adjusted to *p*H 8–9 with sodium carbonate. On standing essentially no precipitate formed. This is a

[3] The biological assay was performed by Dr. Reginal Hewitt.

marked contrast to the oxime melting at 232–233°. The solution was extracted with 3 volumes of ethyl acetate. The ethyl acetate extracts were combined, dried, and concentrated to 4 ml. Hot petroleum ether was added to turbidity. The crystals were collected and recrystallized as above; yield 26 mg., m.p. 152–153°.

Anal. Calc'd for $C_{18}H_{23}N_4O_4$: C, 60.1; H, 6.96; N, 15.60; OAc, 11.97.
Found: C, 60.54; H, 6.74; N, 16.97; OAc, 0.81.

The essentially negative value for the O-acetyl content indicated the compound was not the desired O-acetyl alkaloid oxime but rather the isomeric alkaloid oxime.

Acid hydrolysis of the oxime essentially as described for the oxime melting at 232–233° gave a product indistinguishable from the original alkaloid.

Reaction of 3-(β-keto-γ-aminopropyl)-4-quinazolone and 3-(β-3-piperidyl-β-ketoethyl)-4 quinazolone with potassium cyanate. A mixture of 1 g. of 3-(β-keto-γ-aminopropyl)-4-quinazolone dihydrochloride and 0.84 g. of potassium cyanate was dissolved in 30 ml. of water and placed at 30° for 24 hours. The compound was collected and recrystallized from methanol containing a small amount of water. The compound decomposed at 271°.

Anal. Calc'd for $C_{12}H_{12}N_4O_3$: C, 55.42; H, 4.62; N, 21.52.
Calc'd for $C_{12}H_{10}N_4O_2$: C, 59.48; H, 4.13; N, 23.15.
Found: C, 59.54; H, 4.40; N, 22.77.

The compound had cyclized to the desired imidazolone.

A mixture of 156 mg. of 3-(β-3-piperidyl-β-ketoethyl)-4-quinazolone dihydrochloride and 96 mg. of potassium cyanate was dissolved in 10 ml. of water and placed at 30° for 24 hours. The compound was collected and recrystallized from water. There was obtained 98 mg., m.p. 197–199°.

Anal. Calc'd for $C_{16}H_{18}N_4O_3$: C, 61.15; H, 5.73; N, 17.83.
Found: C, 60.85; H, 5.87; N, 18.06.

The compound was suspended in ethanolic hydrogen chloride (0.2 *N*) and refluxed for 1 hour. The compound was collected and recrystallized from absolute ethanol.

Anal. Calc'd for $C_{16}H_{18}O_3N_4 \cdot HCl \cdot H_2O$: C, 52.10; H, 5.69; N, 15.18; Cl, 9.62.
Found: C, 52.29; H, 6.28; N, 14.94; Cl, 10.11.

The compound failed to cyclize and the starting material was recovered as the monohydrochloride monohydrate.

Distillation of 3-(γ-amino-β-ketopropyl)-4-quinazolone from zinc dust. 3-(γ-Amino-β-ketopropyl)-4-quinazolone (200 mg.) was distilled from zinc dust as previously described. After 3 hours at 165–175° the sublimate was collected, dissolved in methanol, and converted to the hydrochloride. The compound was crystallized from methanol-ether; yield 50 mg., m.p. 195–199°.

Anal. Calc'd for $C_{11}H_{11}O_2N_3 \cdot 2HCl$: C, 45.63; H, 4.49; Cl, 24.45.
Found: C, 45.20; H, 4.57; Cl, 24.92.

The compound distills unchanged.

Oxidation of 3-(γ-carbethoxy-β-ketopropyl)-4-quinazolone and 3-(β-3-piperidyl-β-ketoethyl)-4-quinazolone. The above compounds (200- mg. quantities) were oxidized under conditions identical to those described for the oxidation of the alkaloid and yielded, respectively, 58 mg. and 24 mg. of a compound that melted at 237–238° and in admixture with an authentic sample of 3-(carboxymethyl)-4-quinazolone evidenced no depression.

Anal. Calc'd for $C_{10}H_8N_2O_3$: C, 58.8; H, 3.92; N, 13.72.
Found for O_2-product of 3-(γ-carbethoxy-β-ketopropyl)-4-quinazolone: C, 58.36; H, 4.16; N, 14.02.
Found for O_2-product of 3-(β-3-piperidyl-β-ketoethyl)-4-quinazolone: C, 59.2; H, 4.99; N, 13.88.

Microhydrogenation. The alkaloid dihydrochloride was hydrogenated with platinum in acetic acid, methanol-acetic acid, aqueous acetic acid, and in methanol with triethylamine. The following illustrates a typical experiment.

To 17 mg. of the alkaloid dissolved in glacial acetic acid was added 8.5 mg. of platinum oxide. The solution was hydrogenated for 2 hours and 40 minutes at which time 0.92 mole

of hydrogen had been adsorbed. The catalyst was removed, and the solution was diluted with water, adjusted to *p*H 8–9, and extracted with ethyl acetate.

Aliquots of the ethyl acetate extract were used for the determination of the ultraviolet absorption spectra and for alkaline hydrolysis.

The reduced solution absorbed ultraviolet light similarly to an equivalent amount of the original alkaloid.

When hydrolyzed for 3 hours, the brown-colored hydrolysate contained 0.5 mole of anthranilic acid.

In this experiment the decomposition on alkaline hydrolysis was interpreted as evidence that the ketonic group was still intact.

Under the various hydrogenation conditions, the requirement that the adsorption of one mole of hydrogen give a compound with unchanged ultraviolet absorption and that would form an *ortho*-amino amine with no decomposition in alkaline hydrolysis was not realized.

Formation of the mercaptole of 3-(β-ketopropyl)-4-quinazolone. 3-(β-Ketopropyl)-4-quinazolone (0.5 g.) was dissolved in 15 ml. of concentrated hydrochloric acid and the solution cooled in ice. Ethyl mercaptan (0.6 ml.) was added and the cooled solution was shaken at intervals for 15 minutes. Crushed ice was then added and after an additional 15 minutes the product was collected and recrystallized from ethyl acetate; yield 300 mg., m.p. 120–125°.

Anal. Calc'd for $C_{15}H_{20}N_2OS_2 \cdot HCl$: C, 52.3; H, 6.1; N, 8.12; S, 18.6; Cl, 10.03.
Found: C, 52.73; H, 6.57; N, 8.50; S, 19.37; Cl, 10.18.

The compound was converted to the free base and after three recrystallizations from petroleum ether melted at 55–56°.

Hydrogenolysis of the mercaptole of 3-(β-ketopropyl)-4-quinazolone. The modified Raney nickel catalyst (13) was used on both the free base and the hydrochloride of the mercaptole dissolved in absolute or 70% ethanol, methanol, or dioxane for periods ranging from 45 minutes to 15 hours. In all reactions the only identifiable products were 3-(β-ketopropyl)-4-quinazolone and 4-quinazolone, the latter being a hydrogenolysis product of the former. A typical experiment is outlined. To 100 mg. of the mercaptole dissolved in 5 ml. of ethanol was added 3 ml. of catalyst. The mixture was refluxed for 15 hours. The catalyst was removed and extracted several times with hot ethanol. The filtrate and washings were combined and concentrated to dryness. The residue (60 mg.) was extracted with hot petroleum ether. On cooling crystals formed that on recrystallization melted at 151–152° and showed no depression on admixture with a sample of 3-(β-ketopropyl)-4-quinazolone. The petroleum ether-insoluble residue was dissolved in water, adjusted to *p*H 8–9, and extracted three times with equal volumes of ethyl acetate. The ethyl acetate extracts were combined, dried, and concentrated to dryness. The residue was crystallized twice from ethyl acetate to give a compound of m.p. 215–217° that evidenced no depression when melted with a sample of 4-quinazolone, m.p. 216°.

Anal. Calc'd for $C_8H_6N_2O$: C, 65.8; H, 4.11; N, 19.2.
Found: C, 65.45; H, 4.21; N, 19.33.

When 0.5 g. of 3-(β-ketopropyl)-4-quinazolone was treated as above, 234 mg. of starting material (identified by mixed melting point and analysis) and 40 mg. of 4-quinazolone identified similarly were obtained.

Attempted formation of the mercaptole of the alkaloid. The alkaloid was treated with ethyl mercaptan in concentrated hydrochloric acid, in the presence of anhydrous sodium sulfate and freshly fused zinc chloride, and with the latter reagents in the presence of chloroform. From all reactions a compound was recovered that melted at 134–136° and on admixture with the free base of the alkaloid showed no depression.

Chemical reduction of the alkaloid. To 3.9 mg. of the alkaloid dihydrochloride dissolved in 7.8 ml. of 0.5 *N* hydrochloric acid was added excess zinc dust. After 10 minutes the residual zinc was removed. A Bratton and Marshall test indicated the formation of 0.24 mole of an amine that responded in the color test as a *m*- or *p*-amine. The amine was not extractable

from the reduction solution with ethyl acetate but was extracted by ethyl acetate when the aqueous solution was adjusted to *p*H 8–9.

The alkaloid (1.9 mg.) was refluxed in 5 *N* hydrochloric acid in the presence of 1 g. of amalgamated zinc for 30 minutes and 0.35 mole of amine was liberated. The amine behaved similarly to the compound formed in the presence of zinc-hydrochloric acid.

3-Methyl-4-quinazolone was dissolved in 0.5 *N* hydrochloric acid at a concentration of 200γ per ml. and reduced with zinc dust for 10 minutes. A Bratton and Marshall test indicated the formation of 0.3 mole of amine that behaved similarly in the color test to the compound formed from the alkaloid.

Attempted reduction with hydriodic acid and red phosphorus. The alkaloid was refluxed in acetic acid-hydriodic acid or propionic acid-hydriodic acid mixtures for periods up to 4 hours. The following experiment is typical: 20 mg. of the alkaloid was dissolved in 2 ml. of hydriodic acid (sp. gr. 1.5), and 8 ml. of propionic acid. One gram of red phosphorus and a crystal of iodine was added. The solution was refluxed for 4 hours, diluted with water, adjusted to *p*H 8–9, and extracted with ethyl acetate. The ethyl acetate extract was dried and concentrated to dryness. The residue was converted to the hydrochloride and crystallized from methanol-ethanol-petroleum ether; yield 9.1 mg., m.p. 223–225°.

Anal. Calc'd for $C_{16}H_{19}N_3O_3 \cdot 2HCl$: C, 51.4; H, 5.09.

Found: C, 51.2; H, 6.30.

Experiments on the Beckmann rearrangement of the alkaloid oxime. A number of attempts were made to rearrange the oxime of the alkaloid (m.p. 232–233°) using the following conditions: phosphorus pentachloride in ether, thionyl chloride-chloroform, benzenesulfonyl chloride-chloroform, and glacial acetic acid-acetic anhydride-hydrogen chloride. The alkaloid was recovered in all experiments. The following is illustrative.

The alkaloid oxime (150 mg.) was suspended in 21 ml. of chloroform and 9 ml. of thionyl chloride. The reaction was allowed to stand 18 hours at −4° after which time the oxime was in solution. The reaction mixture was concentrated *in vacuo* and the residue dissolved in 10 ml. of 5 *N* hydrochloric acid and refluxed for 5 hours. The free base was isolated as previously described and the product crystallized twice from ethanol-petroleum ether to give 45 mg. of a compound melting at 135–136° and exhibiting no depression when melted with a sample of the free base of the alkaloid.

Anal. Calc'd for $C_{16}H_{20}N_4O_3$: N, 17.72.

Calc'd for $C_{16}H_{19}N_3O_3$: N, 13.95. Found: N, 14.1.

Alkaline hydrolysis of 3-[β-keto-γ-(2-piperidyl)propyl]-4-quinazolone. The compound was dissolved at a concentration of 1 mg. per ml. in 0.1 *N* sodium hydroxide and heated in a sealed tube on the steam-bath for 3 hours. Nesslerization of the cooled hydrolysate indicated the presence of 34.0γ of ammonia nitrogen per ml. or 0.34 mole of ammonia. A Bratton and Marshall test showed the presence of 0.47 mole of anthranilic acid.

Distillation of 3-[β-keto-γ-(2-piperidyl)propyl]-4-quinazolone from zinc dust. A mixture of 0.5 g. of the compound and 5 g. of zinc dust was distilled at 190–200° and 2.5 mm. for 2.5 hours. The distillate was dissolved in 10 ml. of water containing 2 ml. of ethanol, a small amount of hydroxylamine hydrochloride, and enough sodium hydroxide to make the solution 0.1 *N*. After heating 15 minutes on the steam-bath, the solution was acidified with acetic acid. After cooling, the compound was collected and recrystallized from aqueous ethanol to yield 64 mg. of product.

Anal. Calc'd for $C_{11}H_{11}N_3O_2$: C, 60.6; H, 5.05; N, 19.92.

Found: C, 60.12; H, 5.33; N, 19.44.

The compound melted at 212° and when melted with an authentic sample of the oxime of 3-(β-ketopropyl)-4-quinazolone melting at 214° it melted at 213°.

Reaction of 3-[β-keto-γ-(2-piperidyl)propyl]-4-quinazolone with potassium cyanate. A mixture of 0.5 g. of the model compound and 0.34 g. of potassium cyanate was dissolved in 24 ml. of water at room temperature. After 15 hours at 32° the solution was cooled and the product collected and washed thoroughly with cold water; yield 0.4 g., m.p. 193–197°.

Anal. Calc'd for $C_{17}H_{20}N_4O_3$: C, 62.2; H, 6.11; N, 17.10.
Found: C, 62.3; H, 5.62; N, 17.25.

Cyclization of the N-carbamyl derivative of 3-[β-keto-γ-(2-piperidyl)propyl]-4-quinazolone. To 0.36 g. of the derivative dissolved in 12 ml. of ethanol was added 3 ml. of ethanolic hydrogen chloride (1.0 *N*). The mixture was refluxed for 1.5 hours. The solution was cooled and the product collected and washed thoroughly with cold ethanolic hydrogen chloride, yield 157 mg.

Anal. Calc'd for $C_{17}H_{18}N_4O_2 \cdot HCl$: C, 58.8; H, 5.48; N, 16.16; Cl, 10.23.
Found: C, 58.7; H, 6.01; N, 16.29; Cl, 10.03.

SUMMARY

From a study of the Hydrangea alkaloid and various model compounds the partial structure of the alkaloid has been postulated.

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