[CONTRIBUTION FROM THE CHEMICAL AND BIOLOGICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. XXII.[1] SYNTHESIS BY THE PYRIDINE APPROACH. I

B. R. BAKER AND FRANCIS J. McEVOY

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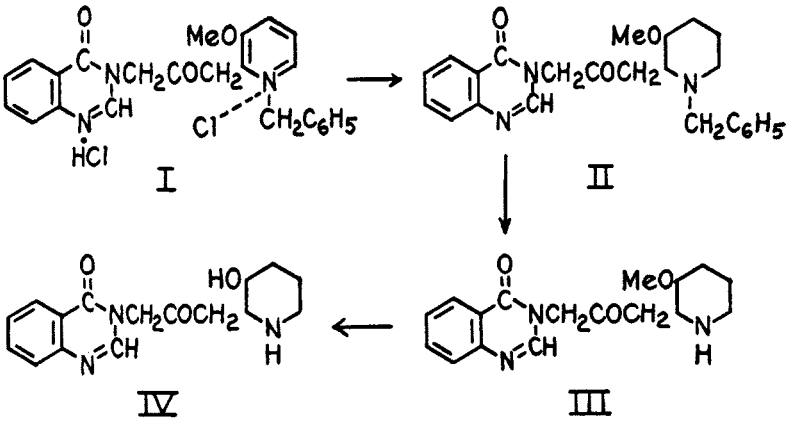
One of the possible approaches to the synthesis of the Hydrangea alkaloid (IV) would involve build-up of the side-chain through a properly substituted pyridine. Such an intermediate would be 3-[β-keto-γ-(1-benzyl-3-methoxy-2-pyridinium) propyl]-4-quinazolone chloride (I). A group on the 1-position of the pyridine ring would serve two useful functions; (a) it would activate an adjacent group on the 2-position towards condensation reactions useful for the synthesis of I and (b) it would allow preferential reduction of the pyridine ring over the ketone function (1) for formation of II. The benzyl group was selected since it should be possible to effect its removal by catalytic hydrogenolysis with formation of the Hydrangea alkaloid methyl ether (III), a previously synthesized intermediate (2). In this paper is described the synthesis of the key compound, I, along with some novel reactions of pyridinium compounds.

In the approaches to the synthesis of the Hydrangea alkaloid (IV) and related compounds used in the past (3–6), it was found both advisable and fruitful to study the key reactions without the presence of the hydroxyl function in order to avoid secondary complications while unknown sequences of reactions were being studied. The study of this current pyridine approach was attacked in the same fashion.

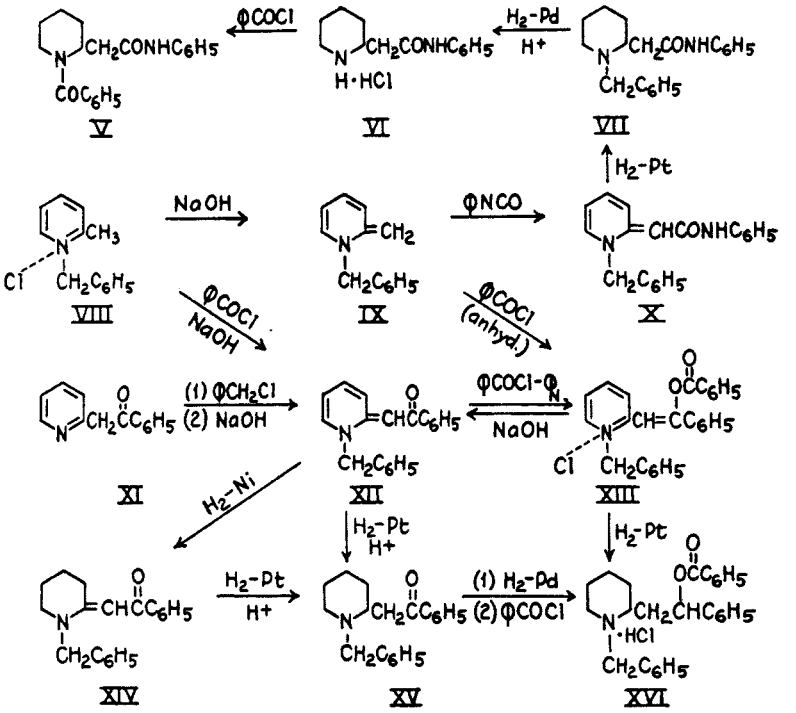
Schneider, Gaertner, and Jordan (7) described the reaction of 1-alkylpicolinium halides such as 1-benzyl-2-picolinium chloride (VIII) with aqueous base to give the unstable and highly reactive methylene base, IX. A solution of this base in ether was found to react immediately with phenyl isocyanate to give 1-benzyl-1, 2-dihydro-2-pyridylideneacetanilide (X) or with phenyl isothiocyanate to give the corresponding thioanilide. Attempts to duplicate their procedure for preparation of X by ether extraction of the methylene base failed to give any desired product although a 63 % yield of 1-benzyl-1,2-dihydropyridylidenethioacetanilide could be obtained. It has now been found that the use of methylene chloride for extraction of the methylene base, IX, allowed the formation of the desired anilide, X, in 47 % yield. Subsequently, it was observed that a simple addition of aqueous alkali to a stirred mixture of 1-benzylpicolinium chloride (VIII) in water and phenyl isocyanate in methylene chloride at 5° gave a yield of 58 % of X.

Catalytic reduction of the anilide, X, in the presence of platinium oxide proceeded smoothly to give 1-benzyl-2-piperidineacetanilide (VII) in quantitative yield. The N-benzyl group was removed by hydrogenolysis of the hydrochloride of VII in dilute acetic acid. The product was characterized as its N-benzoyl

[1] Some of the material in this paper was presented at the New Jersey meeting-in-miniature, Jan. 25, 1954. For Paper XXI of this series see Baker, McEvoy, Schaub, Joseph and Williams, *J. Org. Chem.*, **18**, 178 (1953).



derivative (V), identical with an authentic sample (5). The over-all yield of V from the pyridylacetanilide, X, was 54% for the three steps. Since the anilide VI should be easily hydrolyzed to piperidine-2-acetic acid, this sequence establishes a new route to these compounds which have previously been useful as intermediates for the synthesis of Hydrangea alkaloid (2, 8). However, the general method *via* piperidine-2-acetic acids suffers from the disadvantage that the subsequent use of diazomethane limits the size of the runs which can be made.



Mumm (9) recorded that methylene bases of type IX would also add an acid chloride to give, presumably, 1-alkyl-2-(β-ketoalkyl) pyridinium halides. He gave no experimental details, no description or mention of any of the products obtained and stated that these results would be reported in a subsequent publication. A search of the literature failed to reveal any such type compound or publication. It has now been found that when a methylene chloride solution of the 1-benzyl methylene base, IX, was treated with benzoyl chloride a salt was isolated which was not 1-benzyl-2-phenacylpyridinium chloride, but its O-benzoyl derivative, XIII. When an aqueous solution of XIII was made basic with sodium hydroxide, orange crystals of 1-benzyl-1,2-dihydro-2-pyridylideneacetophenone (XII) rapidly separated with concurrent hydrolysis of the O-benzoyl group. This unsaturated ketone (XII) was synthesized unequivocally by quaternization of 2-phenacylpyridine (10)[2] with benzyl chloride followed by treatment with aqueous sodium hydroxide.

Since the CH_2 group of the methylene base, IX, appeared to be similar to an NH_2 group towards acylating agents, it was considered possible that VIII could be converted directly to the desired pyridylidene ketone, XII, by a Schotten-Baumen procedure in aqueous solution. This was indeed found to be the case and XII was readily obtained in 71% yield. Treatment of XII with benzoyl chloride in methylene chloride containing 1 mole of pyridine rapidly gave the O-benzoyl pyridinium chloride (XIII) in 85% yield. Similarly, XII gave an O-*p*-nitrobenzoyl derivative.

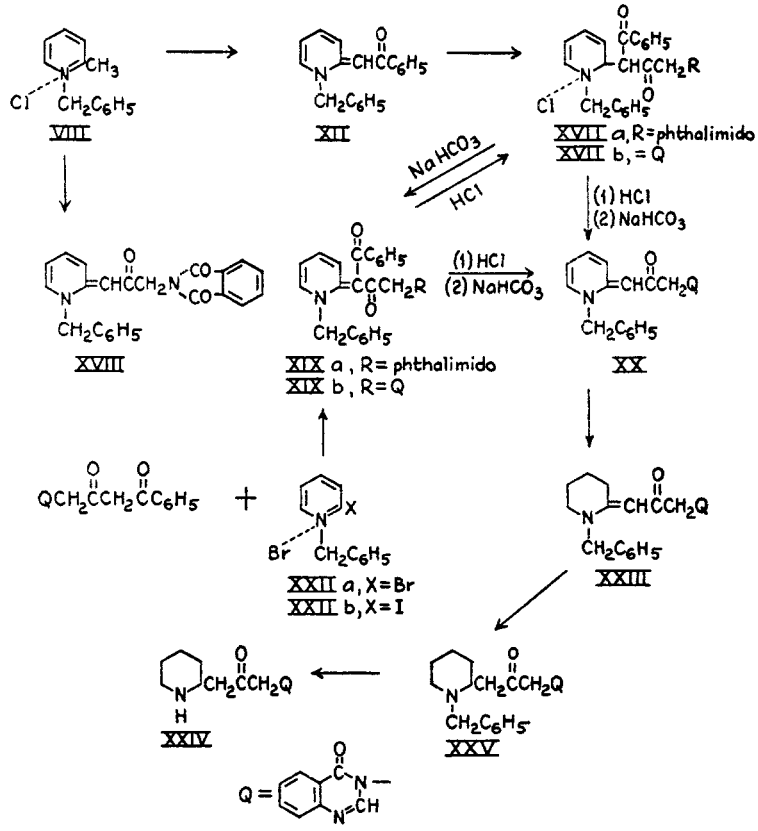
To complete this model series of reactions it would be necessary to saturate the pyridine ring to piperidine and remove the N-benzyl group by hydrogenolysis. When XII was shaken with hydrogen in alcohol in the presence of a platinum catalyst, two moles of hydrogen were rapidly absorbed and a third and fourth mole more slowly with an unsharp, though definite break at two moles. With Raney nickel the two mole break was much sharper. When XII was dissolved in alcoholic hydrochloric acid, forming 1-benzyl-2-phenacylpyridinium chloride, then hydrogenated in the presence of a platinum catalyst, there was a sharp break at a three mole uptake of hydrogen and a quantitative yield of 1-benzyl-2-phenacylpiperidine hydrochloride (XV) was obtained which contained less than 1% of XII hydrochloride as shown by u.v. analysis. Work up of a Raney nickel catalyzed reduction of XII after a two mole uptake gave the piperidylideneketone, XIV, in 60% yield as light yellow crystals with the typical u.v. spectra expected for the N—C=C—C=O system. Further reduction of XIV in dilute acid in the presence of platinum consumed one mole of hydrogen to give a quantitative yield of the saturated ketone, XV.

The next step was the removal of N-benzyl group by hydrogenolysis in the presence of a palladium-charcoal catalyst. The product, isolated by benzoylation, was not the expected 1-benzoyl-2-phenacylpiperidine, but was 1-benzyl-2-(β-benzoyloxy-β-phenylethyl) piperidine hydrochloride (XVI) formed by reduction of the ketone to hydroxyl (instead of hydrogenolysis of the N-benzyl group)

[2] We are indebted to Dr. James M. Smith of the Calco Chemical Division, American Cyanamid Co. for a sample of this compound.

followed by O-benzoylation. Only one of the two possible racemates was obtained crystalline. Hydrogenation of the O-benzoyl pyridinium chloride, XIII, was found to be a superior method for preparation of XVI and, incidently, offered an alternate structure proof for XVI. The fact that the ketone group was reduced prior to the N-benzyl was not surprising since the ketone group is activated by the adjacent phenyl group. In the proposed synthesis of the Hydrangea alkaloid, the phenyl group would be replaced by the non-activating 4-quinazolone-3-methyl group.

With the partial success of this model series attention then was directed towards a sequence for synthesis of the desoxy derivative (XXIV) of the Hydran-



gea alkaloid. Direct acylation of 1-benzyl-2-picolinium chloride (VIII) in aqueous base or the methylene base (IX) in inert solvents with 4-quinazolone-3-acetyl chloride (11) gave none of the desired product, XX. Phthalimidoacetyl chloride reacted with VIII in basic solution as described for XII to give a 5% yield of the pyridylidene ketone, XVIII.[3] Variation of the usual conditions of the Schotten-Baumen reaction as employed for XII gave less or no yield.

[3] 2-Phenyl-7-chloroquinoline-4-carbonyl chloride, 2-chloro-6-nitrohippuryl chloride, dimethylcarbamyl chloride or diphenylcarbamyl chloride failed to give any acylated methylene base when reacted with VIII.

Although aromatic acid chlorides such as benzoyl chloride and *p*-nitrobenzoyl chloride reacted with XII to give enol benzoates (XIII), it was considered possible that aliphatic acid chlorides such as phthalimidoacetyl chloride might give a C-acylation product. There indeed was obtained a true C-acylation product, since it could be converted to the methylene base, XIXa, without loss of the acyl group and gave a red ferric chloride test[4] as expected for a 1,3-diketone in contrast to XIII. 4-Quinazolone-3-acetyl chloride also gave the desired diketone as the crystalline pyridinium chloride (XVIIb), m.p. 206°, in 65% yield which formed a methylene base (XIXb), m.p. 220°, and gave a red ferric chloride test.[5] When XVIIb was refluxed in 6 *N* hydrochloric acid, cleavage of either one of the two acyl groups took place. The mixture of cleavage products was readily separated by conversion to the free bases, since the key intermediate, XX, obtained in 50% yield, was very insoluble in methanol. From the mother liquor there was isolated 31% of the other possible cleavage product, XII.[6]

Another method for the synthesis of the diketone, XIXb, was found which is more adaptable to the synthesis of 3-methoxy derivatives necessary for the Hydrangea alkaloid. Claisen condensation of ethyl 4-quinazolone-3-acetate (4, 12) with acetophenone in benzene in the presence of sodium methoxide gave the diketone, XXI, in 68% yield. When the dry sodium salt of XXI was reacted with 1-benzyl-2-iodopyridinium bromide (XXIIb) in boiling benzene for 1 hour, a 70% yield of the pyridylidene diketone, XIXb, was obtained. 1-Benzyl-2-bromopyridinium bromide (XXIIa) could also be used but the yield was lower (58%). This condensation reaction was rather specific as to the solvent employed, since no product was obtained in methanol, *tert*-butyl alcohol or Diethyl Carbitol.[7] Triethylamine and the free diketone (XXI)[6] could be used in place of the sodium salt of XXI but the yield (46%) and quality of XIXb were inferior.

Reduction studies to convert XX to the desoxy alkaloid, XXIV, were not pursued since simultaneous work on the alkaloid synthesis had arrived at 3-[β-keto-γ-(1-benzyl-3-methoxy-1,2-dihydro-2-pyridylidene)propyl]-4-quinazolone (XXX).

A suitable starting material for the preparation of the key intermediate, I, in the proposed synthesis of the Hydrangea alkaloid (IV) was the commercially available 3-pyridol, which could be iodinated to 2-iodo-3-pyridol (XXVII) (13). Methylation of XXVII with dimethyl sulfate gave less than 20% yield of 2-iodo-3-methoxypyridine (XXVIII) due to the competing reaction of quaterniza-

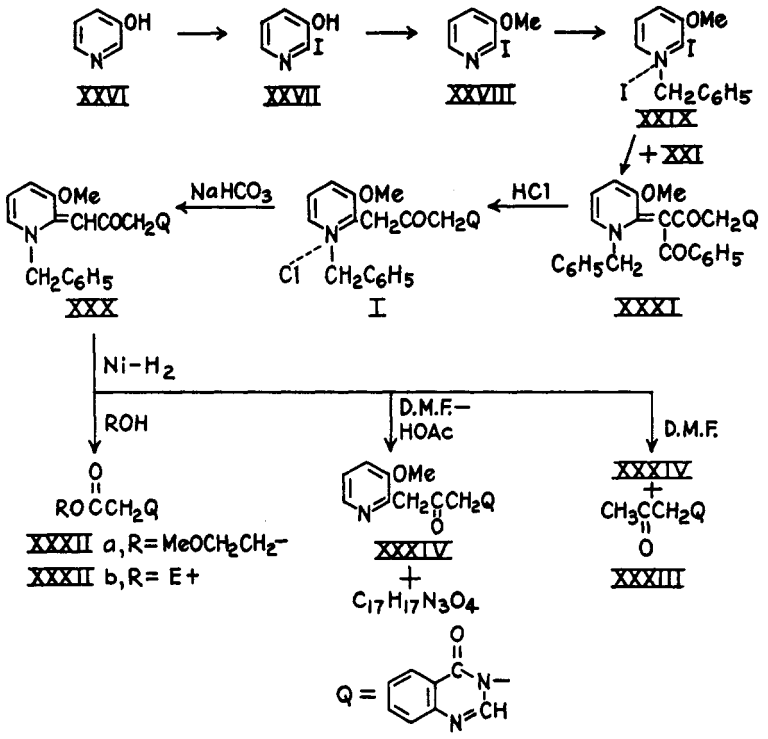
[4] It should be noted that XIXa cannot enolize as such in order to give a ferric chloride test, but that this acidic reagent allows addition of hydrogen chloride with resultant formation of the enolizable XVIIa.

[5] The C-acylation of XII is not general for aliphatic acid chlorides since phenylacetyl chloride gave an O-acylated product. It would appear that C-acylation is general at least for acid chlorides of the type >N CH_2COCl.

[6] Brooker and White (18) have observed that compounds such as 1-ethyl-2-methylmercaptoquinolinium *p*-toluenesulfonate condensed with acetylacetone in alcohol in the presence of one equivalent of triethylamine to form 1-ethyl-2-diacetylmethylene-1,2-dihydroquinoline. The latter lost one acetyl group on acid hydrolysis to form 1-ethyl-1,2-dihydro-2-quinolylideneacetone.

[7] Trade name for the diethyl ether of diethylene glycol.

tion. However, methylation by pyrolysis of the trimethylphenylammonium salt of XXVII in dimethylformamide, a modification of the procedure described by Rodionow (14) for the methylation of morphine to codeine, gave a 58% yield



of XXVIII isolated as the hydrochloride. Quaternization of the free base at 52° with benzyl iodide smoothly formed 1-benzyl-2-iodo-3-methoxypyridinium iodide (XXIX) in 88% yield. Condensation of this quaternary salt with the sodium salt of 3-(β,δ-diketo-δ-phenylbutyl)-4-quinazolone (XXI) in benzene gave 53% of the pyridylidene diketone, XXXI.[8,9] Cleavage of the C-benzoyl group as benzoic acid proceeded smoothly in boiling 6 *N* hydrochloric acid to

[8] Although 2-iodo-3-pyridol (XXVII) and benzyl bromide readily formed a quaternary salt, the latter failed to condense with the sodium salt of XXI. This result might be expected since the salt has a free phenolic group. 2-Iodo-3-pyridol acetate and benzoate also reacted with benzyl iodide to give quaternary salts. However, these failed to condense with the sodium salt of XXI but were recovered unchanged. This is probably due to steric interaction as can readily be shown by molecular models.

[9] 2-Bromo-3-ethoxypyridine (15)[10] also quaternerized with benzyl iodide, then reacted smoothly with the sodium salt of XXI to give the desired pyridylidene diketone corresponding to XXXI. However, the method of preparation of 2-bromo-3-ethoxypyridine (15) was not considered as useful as the present method of synthesis of 2-iodo-3-methoxypyridine (XXVIII) since the former suffered from two low yields and one strongly acidic sealed tube reaction unsuitable for a preparative scale.

[10] We wish to thank Dr. James M. Smith of the Calco Chemical Division, American Cyanamid Co. for a sample of this material prepared according to ref. (15).

form the key pyridinium chloride, I, in 76–80% yield. The free base (XXX) was readily prepared by addition of sodium bicarbonate to an aqueous solution of I.

Previously, 1-benzyl-1,2-dihydro-2-pyridylideneacetophenone (XII) was smoothly reduced to XV. Thus, no difficulty was anticipated in reduction of the pyridine ring of XXX to give II. Unfortunately, this goal was not achieved due to some unforeseen abnormal cleavage reactions of XXX during an intensive study involving over twenty reductions.

A number of attempts to hydrogenate the pyridinium chloride, I, in the presence of Adams catalyst or Raney nickel failed since I failed to consume hydrogen. Reduction of XXX in an hydroxylic solvent such as ethanol or Methyl Cellosolve[11] in the presence of Raney nickel caused cleavage to the ethyl and methoxyethyl esters of 4-quinazolone-3-acetic acid (XXXII), respectively. This cleavage took place in the absence of catalyst merely by solution in the solvent. The other fragment was presumably a methylene base which decomposed rapidly by air oxidation, but under reductive conditions formed the more stable 2-methyl-3-methoxypiperidine. Small amounts of a base, m.p. 160°, were also separated which later proved to be the hydrogenolysis product, XXXIV.

Since an hydroxylic solvent caused cleavage, a non-hydroxylic solvent was tried with Raney nickel as catalyst. The only one found in which the methylene base, XXX, was sufficiently soluble for reduction was dimethylformamide. In this case the first attack was hydrogenolysis of the N-benzyl group followed by attack of the ketone group. The pyridyl ketone, XXXIV, could be isolated in low yield as well as a small amount of 3-acetonyl-4-quinazolone (XXXIII), another cleavage product. When acetic acid was added to the dimethylformamide, the yield of the pyridyl ketone, XXXIV, was higher as might be anticipated. In addition a small quantity of higher-melting by-product, $C_{17}H_{17}N_3O_4$, was obtained which, from ultraviolet and infrared data appeared to be a salt of 4-quinazolone-3-acetic acid and a C_7H_9NO base which has a $C{=}N^{\oplus}$ linkage.

Since the desoxy methylene base, XII, is easily hydrogenated without cleavage, it is apparent that the 3-methoxyl group makes the functional system of XXXI susceptible to cleavage at either the carbon bearing the ketone group or at the 2-position of the pyridine ring. Thus, to solve this problem of the incompatability of functional groups in this system it would be necessary to operate without the ketone group since the methoxyl (or hydroxyl) group is essential for the synthesis of the Hydrangea alkaloid (IV). Such a compound would be 2-(β-hydroxypropyl)-3-methoxypyridine where the hydroxyl can be oxidized to a ketone after hydrogenation of the ring. Of necessity the quinazolone ring must be introduced after the oxidation since 3-(β-hydroxypropyl)-4-quinazolone could not be oxidized to 3-acetonyl-4-quinazolone (12). The use of this concept has led to a successful synthesis of the Hydrangea alkaloid (IV) by the pyridine approach as described in the accompanying paper XXIII of this series.

Acknowledgment. The authors wish to thank L. Brancone and his staff for the microanalysis, W. Fulmor and staff for the spectrophotometric data and W. McEwen and staff for large scale preparation of some intermediates.

[11] Trade name for the monomethyl ether of ethylene glycol.

EXPERIMENTAL

1-Benzyl-2-picolinium chloride (VIII). A mixture of 42 cc. of α-picoline and 55 cc. of benzyl chloride was heated on the steam-bath for 4 hours. After 15 minutes a lower layer separated which gradually increased until the upper layer disappeared in 3½ hours. The thick oil was dissolved in 250 cc. of water and washed with 3 50-cc. portions of chloroform. Evaporation of the aqueous solution to dryness *in vacuo* left 73 g. (77%) of product as an amber gum.

Walther and Weinhagen (16) record that this salt is amorphous but give no experimental details of its preparation.

1-Benzyl-1,2-dihydro-2-pyridylideneacetanilide (X). (*A*). To a solution of 2.0 g. of VIII in 12 cc. of water was added 10 cc. of methylene chloride. The air was displaced by an inert atmosphere, then the mixture was basified with 10 cc. of 25% sodium hydroxide and shaken vigorously. The methylene chloride solution of IX was separated into an air-free flask, quickly dried with magnesium sulfate, and treated with 1 cc. of phenyl isocyanate. After 3 minutes the solution was concentrated to about ⅓ volume and cooled to −10°. The product was collected and washed with ether; yield, 1.3 g., m.p. 191–192°. When 10 g. of VIII was employed, the yield dropped to 33%.

Schneider, Gaertner, and Jordan (7) used ether to extract the methylene base (IX) and obtained the product, m.p. 192°, in unspecified yield. No product could be obtained by the use of ether extraction, although phenyl isothiocyanate gave a 63% yield of 1-benzyl-1,2-dihydro-2-pyridylidenethioacetanilide, m.p. 188° dec. The methylene chloride procedure above (without drying) gave a 76% yield of the thioanilide, m.p. 184–185° dec.

(*B*). To a stirred solution of 13 g. of VIII in 47 cc. of water and 125 cc. of methylene chloride cooled to 5° in an ice-bath was added 6.5 cc. of phenyl isocyanate followed by the dropwise addition of 76 cc. of 25% sodium hydroxide at such a rate that the temperature remained at 5° (7 minutes). The product rapidly separated. After being stirred an additional 30 minutes in the ice-bath, the mixture was filtered. The product was washed with water, then ether; yield, 10.4 g. (58%) of yellow crystals, m.p. 191–192°.

1-Benzoylpiperidine-2-acetanilide (V). A suspension of 4.0 g. of X and 0.2 g. of platinum oxide in 200 cc. of absolute alcohol was shaken with hydrogen at 1 atm. until reduction was complete (100% absorbed in 40 minutes). During the reduction the solid dissolved to give a colorless solution. The mixture was filtered through Celite. Evaporation of the combined filtrate and washings to dryness *in vacuo* gave 4.0 g. (98%) of VII as a nearly colorless gum which could not be crystallized.

A solution of 1.00 g. of VII in 75 cc. of acetic acid, 25 cc. of water, and 0.5 cc. of 12 *N* hydrochloric acid was shaken with hydrogen at 1 atm. in the presence of 0.3 g. of 10% palladium-charcoal until reduction stopped (78% in 2 hours). The filtered solution was evaporated to dryness *in vacuo*; yield, 0.89 g. (102%) of VI as a gum which did not crystallize.

A stirred solution of 0.84 g. of VI in 15 cc. of chloroform and 16 cc. of saturated aqueous sodium bicarbonate was treated with 0.35 cc. of benzoyl chloride. After being stirred for 1½ hours, the layers were separated. The chloroform layer was washed with water and twice with 1 *N* hydrochloric acid, then dried with magnesium sulfate and evaporated to dryness *in vacuo*. Crystallization from ethyl acetate-heptane gave 0.58 g. (56%) of V, m.p. 138–140°, identical with an authentic sample (5). The over-all yield of V from X was 54%.

Benzoylation of VI with triethylamine and benzoyl chloride in chloroform at room temperature gave V in only 37% yield.

1-Benzyl-1,2-dihydro-2-pyridylideneacetophenone (XII). (*A*). To a vigorously stirred solution of 5.85 g. of VIII in 24 cc. of water and 50 cc. of methylene chloride in a nitrogen atmosphere was added 4.7 cc. of benzoyl chloride. Then 36 cc. of 25% sodium hydroxide was added over 5 minutes. After being stirred ½ hour, the mixture became dark blue and most of the methylene chloride had evaporated. The dark solid (5.8 g.) was collected and washed with water. Recrystallization from benzene-heptane gave 2.7 g. of product, m.p.

158–160°, and 2.6 g., m.p. 149–153°, was isolated from the filtrate; total 5.3 g. (71%). Several recrystallizations from benzene afforded golden crystals, m.p. 161–162°, $\lambda_{max.}^{alc.}$ 255 (ε 15,300), 340 (ε 12,800), 422 mμ (ε 27,400); $\lambda_{max.}^{0.1NHCl}$ 260 mμ (ε 27,000) (broad).

Anal. Calc'd for $C_{20}H_{17}NO$: C, 83.6; H, 5.92; N, 4.88.

Found:[12] C, 82.5; H, 6.26; N, 4.85.

To a hot suspension of 40 g. of XII in 500 cc. of absolute alcohol was added 7.5 cc. (1 mole) of 96% sulfuric acid. The remaining insoluble crystals changed from yellow to white. The mixture was cooled to 0° and filtered; yield, 51.8 g. (96%) of *1-benzyl-2-phenacylpyridinium acid sulfate*, m.p. 231° dec. Recrystallization from absolute alcohol gave white crystals, m.p. 236° dec.

Anal. Calc'd for $C_{20}H_{17}NO \cdot H_2SO_4$: C, 62.3; H, 4.94; N, 3.64.

Found: C, 62.3; H, 5.10; N, 3.35.

(*B*). For preparative purposes toluene was substituted for methylene chloride in method *A*. The crude product was purified by solution in dilute hydrochloric acid, clarification with Norit, and neutralization with sodium bicarbonate; yield, 55–60%.

(*C*). A solution of 300 mg. of XIII in water was made basic with excess 10% sodium hydroxide. The product was collected and washed with water; yield, 125 mg. of orange crystals, m.p. 163–164°. Recrystallization from dilute methanol gave golden crystals, m.p. 163–164°, which gave no depression in m.p. when mixed with preparation *A*.

Anal. Found:[12] C, 82.1; H, 6.33; N, 5.01.

(*D*). A mixture of 0.50 g. of 2-phenacylpyridine[3] and 0.32 cc. of benzyl chloride was heated on the steam-bath for 4 hours. Crystallization from acetone gave 0.22 g. of crude 1-benzyl-2-phenacylpyridinium chloride, m.p. 92–94°. A solution of 0.20 g. of this salt in 20 cc. of water was basified with 0.6 cc. of 10% sodium hydroxide. The golden crystals were collected and washed with water; yield, 70 mg. (11%), m.p. 160–161°. A mixture with preparation *A* gave no depression in m.p.

α-Benzoyloxy-β-(1-benzyl-2-pyridyl)styrene chloride (XIII). (*A*). To a solution of 2.0 g. of XII in 20 cc. of methylene chloride was added 0.30 cc. of pyridine and 0.90 cc. of benzoyl chloride. The temperature rose from 30 to 37° and within 5 minutes the product rapidly separated. After 1 hour the mixture was filtered and the solid was washed with methylene chloride; yield, 2.68 g. (85%) of white crystals, m.p. 192–193°. Recrystallization from water afforded white crystals, m.p. 194–195°, which gave a negative ferric chloride test, $\lambda_{max.}^{0.1NHCl}$ 235 (ε 53,200) (broad), 322 (ε 32,700), 335 mμ (ε 31,700) (inflect.). The compound showed ester absorption at 5.78 and 8.09 μ, OH absorption (from H_2O) at 3.00 μ and C=C at 6.08 μ in the infrared.

Anal. Calc'd for $C_{27}H_{21}ClNO_2 \cdot H_2O$: C, 72.7; H, 5.43; N, 3.15.

Found: C, 71.8; H, 5.32; N, 3.33.

Without the pyridine the yield was only 40% after 20 hours. The yield was 52% after 18 hours when triethylamine was used in place of pyridine.

(*B*). To a dried methylene chloride solution of IX (prepared from 5.8 g. of VIII) in an inert atmosphere was added 3.3 cc. of benzoyl chloride. After 16 hours the solution was evaporated to dryness *in vacuo*. Crystallization of the residue from 75 cc. of acetone and 6 cc. of absolute alcohol gave 2.0 g. (17%) of product, m.p. 188–189°. Recrystallization by solution in water and addition of 12 *N* hydrochloric acid gave white crystals of unchanged m.p. Admixture with preparation *A* gave no depression in m.p.

Anal. Calc'd for $C_{20}H_{18}ClNO_2 \cdot H_2O$: C, 72.7; H, 5.43; N, 3.15.

Found: C, 73.2; H, 5.58; N, 3.34.

α-p-Nitrobenzoyloxy-β-(1-benzyl-2-pyridyl)styrene chloride. Reaction of 2.0 g. of XII with 1.3 g. of *p*-nitrobenzoyl chloride as described for XIII (procedure *A*) gave 2.35 g. (72%) of product, m.p. 189–190° dec. Recrystallization from 50% methanol afforded pale yellow crystals, m.p. 195–196° dec., $\lambda_{max.}^{0.1NHCl,H_2O}$ 260 (ε 42,000), 318 mμ (ε 25,500); $\lambda_{max.}^{Nujol}$ 5.68, 8.07 μ (ester OC=O), 6.05 μ (C=C).

[12] Most of these keto methylene bases appeared to be somewhat hydrated.

Anal. Calc'd for $C_{27}H_{21}ClN_2O_4$: C, 68.6; H, 4.23; N, 5.93.
Found: C, 68.4; H, 4.53; N, 5.87.

This compound gave a negative ferric chloride test. Treatment with aqueous sodium bicarbonate at 100° for 15 minutes gave 65% of *p*-nitrobenzoic acid and 61% of XII.

α-(1-Benzyl-1,2-dihydro-2-pyridylidene)-2-acetofuran. By reaction of 29 g. of VIII with 26 cc. of furoyl chloride as described for XII (procedure *A*) there was obtained 6.1 g. (16.5%) of crude product, m.p. 76–78°. Recrystallization from 50% methanol gave yellow crystals, m.p. 88–89°, which developed brown spots on standing overnight in a sealed tube. When exposed to air a black tar is formed within 1 day. A freshly recrystallized sample was converted to *1-benzyl-2-furacylpyridinium hydrogen sulfate* by solution in absolute alcohol and addition of 1 mole of 96% sulfuric acid. White crystals, m.p. 206–207°, separated immediately. This salt was stable to air.

Anal. Calc'd for $C_{18}H_{15}NO_2 \cdot H_2SO_4$: C, 57.6; H, 4.53; N, 3.73.
Found: C, 57.8; H, 5.12; N, 3.63.

1-Methyl-1,2-dihydro-2-quinolylideneacetophenone. By reaction of 4.9 g. of quinaldine methiodide (17) with 3.65 cc. of benzoyl chloride as described for XII (Procedure *A*) there was obtained 1.7 g. (38%) of brown crystals, m.p. 108–111°. Recrystallization from toluene gave golden needles, m.p. 110–111°.

Anal. Calc'd for $C_{18}H_{15}NO$: C, 82.8; H, 5.75; N, 5.36.
Found: C, 83.0; H, 5.95; N, 5.43.

1-Benzyl-2-piperidylideneacetophenone (XIV). A mixture of 5.0 g. of XII, 100 cc. of absolute alcohol, and ¼ teaspoon of Raney nickel was shaken with hydrogen at 2–3 atm. until exactly 2.2 mole-equivalents were absorbed (42 minutes). The filtered solution was evaporated to dryness *in vacuo*. Crystallization from 25 cc. of methanol gave 3.0 g. (60%) of yellow crystals, m.p. 134–135°. Recrystallization from the same solvent afforded yellow crystals, m.p. 136–137°; $\lambda_{max.}^{alc.}$ 242 (ε 10,600), 340 mμ (ε 26,700); $\lambda_{max.}^{0.1NHCl}$ 250 mμ (ε 5700).

Anal. Calc'd for $C_{20}H_{21}NO$: C, 82.4; H, 7.22; N, 4.81.
Found: C, 82.1; H, 7.40; N, 5.07.

1-Benzyl-2-phenacylpiperidine hydrochloride (IV). (*A*). A mixture of 25 g. of XII, 100 cc. of absolute alcohol, 9.0 cc. of 12 *N* hydrochloric acid, and 200 mg. of platinum oxide was shaken with hydrogen at 2–3 atm. until exactly 3.3 mole-equivalents were absorbed. The filtered solution was evaporated to dryness *in vacuo* leaving 29.7 g. (99%) of nearly colorless gum which could not be crystallized but contained less than 1% of XII and XIV as shown by u.v. analysis.

Anal. Calc'd for $C_{20}H_{23}NO \cdot HCl$: C, 72.9; H, 7.29; N, 4.25.
Found: C, 72.2; H, 7.46; N, 4.13.

Although there is a definite break at 3.0–3.3 mole-equivalents of hydrogen, about 5 mole-equivalents eventually will be absorbed if the reduction is allowed to continue, probably by reduction of the carbonyl to methylene.

(*B*). A solution of 1.00 g. of XIV in 65 cc. of methanol containing 0.67 cc. of 12 *N* hydrochloric acid was shaken with hydrogen in 1 atm. in the presence of 100 mg. of platinum oxide until exactly 1.2 equivalents were absorbed (4 minutes). The filtered solution was evaporated to dryness *in vacuo* leaving a quantitative yield of product as a colorless gum which contained about 1% of XIV as shown by u.v. analysis.

1-Benzyl-2-(β-benzoyloxy-β-phenylethyl)piperidine hydrochloride (XVI). (*A*). A solution of 3.1 g. of XV in 100 cc. of 75% acetic acid was shaken with hydrogen at 1 atm. in the presence of 0.5 g. of 10% palladium-charcoal catalyst until 1.06 mole-equivalents of hydrogen were absorbed (40 minutes). There was a sharp break in the rate of reduction at 1 mole-equivalent. The filtered solution was evaporated to dryness *in vacuo*. The residue (3.0 g.) was dissolved in 15 cc. of chloroform. After the addition of 1.33 cc. of benzoyl chloride and a solution of 1.9 g. of anhydrous sodium carbonate in 15 cc. of water, the mixture was stirred for 1 hour. The chloroform layer was separated and evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate and washed with three 25-cc. portions of 1 *N* hydrochloric acid. Dried with magnesium sulfate, the ethyl acetate solution was evaporated

to dryness *in vacuo*. Crystallization of the residue (3.3 g.) from 20 cc. of ethyl acetate gave 0.91 g. (24%) of product, m.p. 185–189°. For analysis a sample was dissolved in absolute alcohol, the solution was evaporated to dryness *in vacuo* and the glassy residue was crystallized from ethyl acetate to give white crystals, m.p. 193–194°.

Anal. Calc'd for $C_{22}H_{28}NO_2 \cdot HCl$: C, 74.4; H, 6.88; N, 3.21; Cl, 8.15.

Found: H_2O, 0.6 (K. Fischer).

Found (corr. for H_2O): C, 73.8; H, 7.17; N, 3.15; Cl, 8.29.

The other possible racemate did not crystallize. It is interesting to note that XVI, a hydrochloride, is more soluble in wet ethyl acetate, than in water.

(*B*). A mixture of 3.0 g. of XIII, 50 cc. of absolute alcohol, and 0.1 g. of platinum oxide was shaken with hydrogen at 1 atm. until 4.2 mole-equivalents were absorbed (1 hour). The filtered solution was evaporated to dryness *in vacuo*. Crystallization of the residue from 35 cc. of ethyl acetate gave 1.10 g. (36%) of product, m.p. 185–188°, which gave no depression in m.p. when mixed with preparation *A*. Method *B* is the one of choice for preparative purposes.

α-(1-Benzyl-1,2-dihydro-2-pyridylidene)-γ-phthalimidoacetone (XVIII). To a stirred solution of 5.2 g. of VIII in 20 cc. of water cooled in an ice-salt bath to 5° was added a cold solution of 8.0 g. of phthalimidoacetyl chloride in 50 cc. of methylene chloride. Then 31 cc. of 25% sodium hydroxide was added dropwise over a period of 5 minutes. Crystals rapidly began to separate. After being stirred an additional 15 minutes in the cooling bath, the mixture was filtered and the product washed thoroughly with water; yield, 0.70 g. (5.4%), m.p. 210–220°. Several recrystallizations from Methyl Cellosolve-methanol gave yellow crystals of constant m.p. 220–221°, $\lambda_{max.}^{Nujol}$ 5.68, 5.85 (C=O of phthalyl), 6.12 μ (conj. C=O).

Anal. Calc'd for $C_{22}H_{18}N_2O_3$: C, 74.6; H, 4.86; N, 7.57.

Found:[12] C, 72.3; H, 5.48; N, 7.33.

The above conditions gave the best yields out of some 20 variants of time, temperature, basicity and solvents that were tried.[3]

2-Iodopyridine. By refluxing 35 g. of 2-bromopyridine (20) with 175 cc. of hydriodic acid (*sp. gr.* 1.7, containing some free iodine) for 6 hours as described (21) there was obtained 51% of product, b.p. 100–103° (15 mm.) and 4 g. (11%) of lower boiling 2-bromopyridine was recovered. A yield of 35% and b.p. 93–95° (13 mm.) has been recorded (21).

1-Benzyl-2-bromopyridinium bromide (XXIIa). A mixture of 2.5 g. of 2-bromopyridine (20) and 2.0 cc. of benzyl bromide was heated on the steam-bath for 3 hours. Trituration of the cooled reaction mixture with acetone gave 4.53 g. (87%) of white crystals, m.p. 156–157°, unchanged on recrystallization from absolute alcohol.

Anal. Calc'd for $C_{12}H_{11}Br_2N$: C, 43.8; H, 3.34; N, 4.26.

Found: C, 43.6; H, 3.59; N, 4.16.

1-Benzyl-2-iodopyridinium bromide (XXIIb). A mixture of 20.1 g. of 2-iodopyridine and 22.6 cc. of benzyl bromide was heated on the steam-bath for 4 hours. The resultant cake was triturated with acetone. The product was collected and washed with acetone until the odor of benzyl bromide was completely removed; yield, 32.2 g. (90%) of white crystals, m.p. 153–154° dec., unchanged on recrystallization from absolute alcohol.

Anal. Calc'd for $C_{12}H_{11}BrIN$: C, 38.3; H, 2.93; N, 3.72.

Found: C, 38.1; H, 3.34; N, 3.80.

3-(β,δ-Diketo-δ-phenylbutyl)-4-quinazolone (XXI). To a warm solution of 23 g. of ethyl 4-quinazolone-3-acetate (4) in 197 cc. of benzene was added successively 13.1 cc. of acetophenone, 12 cc. of absolute ethanol, and 6.0 g. of sodium methoxide (12). The solution was refluxed for 1 hour, then acidified with 6 cc. of acetic acid and shaken with 100 cc. of water. On standing the heterogeneous system deposited crystals which were collected and washed with water and benzene; yield, 21.0 g. (68%), m.p. 155–156°. Recrystallization from benzene gave white crystals, m.p. 158–159°, which gave a red ferric chloride test.

Anal. Calc'd for $C_{18}H_{14}N_2O_3$: C, 70.6; H, 4.58; N, 9.15.

Found: C, 70.2; H, 4.65; N, 9.07.

3-[β-Keto-γ-benzoyl-γ-(1-benzyl-1,2-dihydro-2-pyridylidene)propyl]-4-quinazolone (XIXb) *and salts.* (*A*). To a solution of 78 g. of XII in 615 cc. of methylene chloride and 44 cc. of pyridine was added 71 g. of 4-quinazolone-3-acetyl chloride hydrochloride (11). The stoppered solution was allowed to stand 6 days. During this time white crystals of XVIIb separated. The product was collected and washed successively with methylene chloride and absolute alcohol; yield, 90.3 g. (65%), m.p. 205–206°. A similar preparation of this monohydrochloride was recrystallized from absolute alcohol to give white crystals of unchanged m.p. The dihydrochloride formed in solution with alcoholic hydrogen chloride was soluble. The lack of color of the hydrochloride shows that the hydrogen chloride had added to the pyridylidene ring to give a pyridinium salt. This compound gave a red ferric chloride test.

Anal. Calc'd for $C_{30}H_{24}ClN_3O_3 \cdot H_2O$: C, 68.2; H, 4.97; N, 7.96; H_2O, 3.41.
Found: C, 68.2; H, 5.16; N, 7.92; H_2O, 2.05 (K. Fischer).

When the above reaction was allowed to proceed for 24 hours, the yield was 24% and after 64 hours, 45%. With triethylamine in place of pyridine, the yield was 19% after 65 hours. When the reaction was run in boiling methylene chloride for 24 hours, the yield was 40%, but only 12% in boiling chloroform.

A mixture of 3.15 g. of XVIIb, 50 cc. of chloroform, and 50 cc. of saturated aqueous sodium bicarbonate was shaken until solution was complete. The separated chloroform layer was dried with magnesium sulfate and evaporated to dryness *in vacuo*. The glassy yellow residue was heated on the steam-bath with 25 cc. of toluene when it rapidly crystallized; yield, 2.88 g. (98%) of yellow crystals of XIXb, m.p. 219–220° dec. Recrystallization from 33% alcohol did not change the m.p.

Anal. Calc'd for $C_{30}H_{23}N_3O_3 \cdot H_2O$:[12] C, 73.5; H, 5.15; N, 8.56.
Found: C, 74.0; H, 5.27; N, 8.73.

(*B*). A solution of 2.8 g. of XXI in 9.2 cc. of 1 *N* methanolic sodium methoxide was evaporated to dryness *in vacuo*. The residue was suspended in 50 cc. of benzene and the evaporation was repeated. A suspension of the dry sodium salt and 2.5 g. of XXIIa in 70 cc. of benzene was refluxed with vigorous stirring for 1 hour. The mixture was evaporated to dryness *in vacuo*. The residue was dissolved in a mixture of 90 cc. of chloroform and 70 cc. of 3% sodium hydroxide. The separated chloroform layer was washed with 70 cc. of 3% sodium hydroxide, dried with magnesium sulfate, and evaporated to dryness *in vacuo*. Digestion of the residue with warm toluene caused crystallization of the gum; yield, 2.1 g. (58%) of XIXb, m.p. 211–212° dec. A mixture with preparation *A* melted at 215–216° dec.

Similarly, condensation of XXI with XXIIb proceeded in 70% yield. An attempt to use acetylacetone[6] in place of XXI failed.

(*C*). *Hydrobromide.* To a hot filtered solution of 350 mg. of XVIIb base in 6 cc. of absolute alcohol was added 0.082 cc. of 48% hydrobromic acid. Cooling gave 390 mg. (95%) of nearly colorless crystals, m.p. 203–204° dec.

Anal. Calc'd for $C_{30}H_{24}BrN_3O_3 \cdot H_2O$: C, 62.9; H, 4.58; N, 7.35; H_2O, 3.14.
Found: C, 62.4; H, 4.91; N, 7.23; H_2O, 2.21.

(*D*). *Bisulfate.* To a hot filtered solution of 300 mg. of XVIIb base in 6 cc. of absolute alcohol was added 0.35 cc. of 96% sulfuric acid. The solution became colorless and on chilling deposited 340 mg. (94%) of white crystals, m.p. 204–205°.

Anal. Calc'd for $C_{30}H_{24}N_3O_3 \cdot HSO_4$: C, 63.0; H, 4.38; N, 7.36.
Found: C, 61.9; H, 4.87; N, 7.07; H_2O, 0.56.
Found (corr. for H_2O): C, 62.3; H, 4.84; N, 7.12.

3-[β-Keto-γ-(1-benzyl-1,2-dihydro-2-pyridylidene)propyl]-4-quinazolone (XX). A solution of 90.3 g. of XVIIb hydrochloride in 900 cc. of 6 *N* hydrochloric acid was refluxed 4 hours, cooled, filtered from benzoic acid (48%), and evaporated to dryness *in vacuo*. The residue was dissolved in 350 cc. of methanol and neutralized with excess (~50 cc.) of triethylamine. After chilling in an ice-bath, the mixture was filtered and the product washed with methanol; yield, 34.1 g. (50%), m.p. 197–199° dec. No suitable solvent for recrystallization could be found. For analysis a sample was dissolved in 1 *N* hydrochloric acid, the solu-

tion was clarified with Norit, then neutralized with aqueous sodium bicarbonate. The bright yellow crystals, m.p. 198–200° dec., were washed well with water; $\lambda_{max.}^{0.1NHCl}$ 267 mμ (ε 12,900); $\lambda_{max.}^{H_2O,0.1NNaOH}$ 270 (ε 10,200), 305 (ε 12,400), 315 (ε 12,000), 385 mμ (ε 20,100); $\lambda_{max.}^{Nujol}$ 5.94 μ (amide CO), 6.08 μ (conj. ketone CO), 6.20 μ (C=N).

Anal. Calc'd for $C_{23}H_{19}N_3O_2$: C, 74.8; H, 5.15; N, 11.4.

Found: C, 74.5; H, 5.31; N, 11.2.

By dilution of the original methanol mother liquor with water a 31% yield of XII, m.p. and mixture m.p. 162–163°, was obtained.

The *bisulfate salt* of XX was prepared by solution of 300 mg. of base in 10 cc. of 1 *N* hydrochloric acid, addition of 2.0 cc. of 1 *N* sulfuric acid, and evaporation to dryness *in vacuo*. The colorless glass changed to white crystals by trituration with hot methyl ethyl ketone. The m.p. of 185–187° dec. was unchanged after recrystallization of the salt from absolute alcohol.

Anal. Calc'd for $C_{23}H_{19}N_3O_2 \cdot H_2SO_4$: C, 59.1; H, 4.54.

Found: C, 58.7; H, 5.05.

1-Benzyl-2-bromo-3-ethoxypyridinium iodide. To 520 mg. of the free base of 2-bromo-3-ethoxypyridine hydrobromide (15)[10] was added 1.7 g. of benzyl iodide. The mixture was heated in a bath at 52° for 2 hours. The resulting crystalline mass was triturated with ether; yield, 720 mg. (75%) of pale yellow crystals, m.p. 134–141° dec., suitable for the next step. At 100° there was considerable resinification.

If the quaterization was attempted with benzyl bromide by fusion at 100° or in boiling benzene, a benzene-insoluble red gum was obtained. The red gum was dissolved in water and converted to the insoluble iodide salt by addition of saturated aqueous potassium iodide. A yellow crystalline product, m.p. 138–142°, was obtained in yields varying from 0–35%. Recrystallization from absolute alcohol gave yellow crystals, m.p. 160–162° dec.

Anal. Calc'd for $C_{14}H_{15}BrINO$: C, 40.0; H, 3.57; N, 3.81.

Found: C, 37.8; H, 3.69; N, 3.04.

The low combustion values are due to a partial exchange of the 2-bromo for iodine, also described later for 2-chloro-3-acyloxypyridines quaternized with benzyl iodide.

2-Iodo-3-methoxypyridine hydrochloride (XXVIII). To a solution of 9.5 g. of sodium methoxide and 38.8 g. of 2-iodo-3-pyridol [prepared (13) in 67% yield, m.p. 190–192° dec.] in 50 cc. of methanol was added a solution of 33.4 g. of trimethylphenylammonium chloride in 40 cc. of methanol. The salt was removed by filtration and the combined filtrate and washings were evaporated to dryness *in vacuo*. The residue was dissolved in 30 cc. of dimethylformamide, concentrated *in vacuo* to remove the last of the methanol, and then an additional 210 cc. of dimethylformamide was added. The solution was refluxed for 1 hour, cooled, and filtered. It was acidified with 190 cc. of saturated absolute alcoholic hydrogen chloride, and the solution was evaporated to dryness *in vacuo*. Trituration of the residue with 100 cc. of acetone gave 28 g. (58%) of hydrochloride salt, m.p. 154–155° dec.

A sample of the salt was converted to the *free base* by shaking with chloroform and excess aqueous sodium bicarbonate until solution was complete. The chloroform solution was evaporated to dryness *in vacuo*. Trituration of the residue with heptane gave white crystals, m.p. 55–56°. Recrystallization from heptane raised the m.p. to 56–57°.

Anal. Calc'd for C_6H_6INO: C, 30.6; H, 2.55; N, 5.97.

Found: C, 30.8; H, 2.93; N, 5.85.

1-Benzyl-2-iodo-3-methoxypyridinium iodide (XXIX). The crude free base from 21 g. of XXVIII hydrochloride and 47 g. of benzyl iodide was heated in a bath at 52° for 2 hours. The resultant cake of crystals was stirred with 50 cc. of benzene until the lumps disintegrated. The product was collected and washed with acetone until free of benzyl iodide; yield, 30.6 g. (88%), m.p. 168–169° dec. Recrystallization from methanol gave yellow crystals, m.p. 175–176° dec.

Anal. Calc'd for $C_{13}H_{13}I_2NO$: C, 34.4; H, 2.87; N, 3.09.

Found: C, 34.2; H, 3.06; N, 2.97.

1-Benzyl-2-iodo-3-hydroxypyridinium bromide. A mixture of 5.0 g. of 2-iodo-3-pyridol (13) and 8.1 cc. of benzyl bromide was heated on the steam-bath for 25 minutes, then cooled and triturated with 20 cc. of acetone. The product was collected and washed with acetone until the benzyl bromide was completely removed; yield, 6.6 g. (75%) of white crystals, m.p. 159–160° dec. Recrystallization from water raised the m.p. to 160–161° dec.

Anal. Calc'd for $C_{12}H_{11}BrINO$: C, 36.7; H, 2.81; N, 3.57.

Found: C, 36.3; H, 3.35; N, 3.59.

2-Iodo-3-benzoyloxypyridine. To a refluxing solution of 3.2 g. of 2-iodo-3-pyridol (13) and 2.6 cc. of triethylamine in 80 cc. of benzene was added dropwise 1.9 cc. of benzoyl chloride (3 minutes). The solution was refluxed for 30 minutes, then cooled and filtered. The filtrate was washed with two 30-cc. portions of 3% sodium hydroxide, dried with magnesium sulfate, and evaporated to dryness *in vacuo*. Trituration of the residue with heptane afforded 4.1 g. (87%) of white crystals, m.p. 89–90°. Recrystallization of a similar preparation from heptane gave white crystals, m.p. 90–91°.

Anal. Calc'd for $C_{12}H_8INO_2$: C, 44.3; H, 2.46; N, 4.31.

Found: C, 44.4; H, 2.79; N, 4.42.

1-Benzyl-2-iodo-3-benzoyloxypyridinium iodide. A mixture of 4.1 g. of 2-iodo-3-benzoyloxypyridine and 8.0 g. of benzyl iodide was heated in a bath at 52° for 18 hours. Trituration of the crystalline mass with benzene gave 6.5 g. (93%) of yellow crystals, m.p. 148–149° dec. The m.p. was unchanged after recrystallization from absolute alcohol.

Anal. Calc'd for $C_{19}H_{15}I_2NO_2$: C, 42.0; H, 2.76; N, 2.58.

Found: C, 42.1; H, 3.13; N, 2.51.

Chlorination of 3-pyridol to 2-chloro-3-pyridol (13) gave no product unless the temperature was maintained at 75–80°. The reaction mixture was processed as soon as it was no longer exothermic; yield, 22%, m.p. 166–167°. Benzoylation as described for 2-iodo-3-pyridol above gave 56% of 2-chloro-3-benzoyloxypyridine, m.p. 53–55°. Quaternization with benzyl iodide gave a 65% yield of the title compound, arising by halogen interchange at the 2-position. Attempted quaternizations with benzyl chloride at 52–135° gave none of desired quaternary salt.

1-Benzyl-2-iodo-3-acetoxypyridinium iodide. To a solution of 2.5 g. of 2-iodo-3-pyridol and 2.1 cc. of triethylamine in 50 cc. of benzene was added 0.89 cc. of acetyl chloride. After 15 minutes the triethylamine hydrochloride was removed by filtration. Evaporation of the filtrate to dryness *in vacuo* left 3.2 g. of crude 2-iodo-3-acetoxypyridine as an oil. A mixture of 2.7 g. of this compound and 6.7 g. of benzyl iodide was heated at 52° for 2½ hours. Trituration with ether gave a crystalline salt which was collected by filtration, washed well with ether, then 10 cc. of methanol; yield, 4.1 g. (83%) of yellow crystals, m.p. 148–149° dec. Recrystallization from methanol gave yellow crystals, m.p. 153–154° dec.

Anal. Calc'd for $C_{14}H_{13}I_2NO_2$: C, 34.9; H, 2.70; N, 2.91.

Found: C, 34.5; H, 3.09; N, 3.30.

Reaction of 2-chloro-3-acetoxypyridine, prepared from 2-chloro-3-pyridol as described above for the 2-iodo derivative, with benzyl iodide led to the title compound by interchange of the 2-chloro group by iodo.

3-[β-Keto-γ-benzoyl-γ-(1-benzyl-3-ethoxy-1,2-dihydro-2-pyridylidene)propyl]-4-quinazolone. By condensation of the sodium salt from 368 mg. of XXI with 420 mg. of 1-benzyl-2-bromo-3-ethoxypyridinium iodide as described for XVIIb there was obtained 420 mg. (79%) of product, m.p. 210–215° dec. Since no suitable solvent for recrystallization could be found, the compound was characterized by hydrolysis as follows.

3-[β-Keto-γ-(1-benzyl-3-ethoxy-1,2-dihydro-2-pyridylidene)propyl]-4-quinazolone. A solution of 275 mg. of the preceding compound in 10 cc. of 6 *N* hydrochloric acid was refluxed for 4 hours, cooled, and filtered from benzoic acid. The filtrate was evaporated to dryness *in vacuo*. Crystallization of the residue from 5 cc. of absolute alcohol gave 175 mg. (68%) of *hydrochloride salt* as white crystals, m.p. 178–179° dec. The free base was obtained by addition of aqueous sodium bicarbonate to an aqueous solution of the hydrochloride:

yellow crystals, m.p. 193–194° dec.; $\lambda_{max.}^{0.1N HCl}$ 275 (ε 8600), 295 mμ (ε 11,500); $\lambda_{max.}^{H_2O}$ 265 (ε 8680), 274 (ε 9100), 298 (ε 10,500), 400 mμ (ε 4600). The compound appeared to decompose rapidly in basic solution.

Anal. Calc'd for $C_{25}H_{22}N_3O_3$: C, 72.6; H, 5.57; N, 10.2.

Found: C, 72.3; H, 5.81; N, 9.92.

3-[β-Keto-γ-benzoyl-γ-(1-benzyl-3-methoxy-1,2-dihydro-2-pyridylidene)propyl]-4-quinazolone (XXXI). The dry sodium salt from 15 g. of XXI, 18.5 g. of 1-benzyl-2-iodo-3-methoxypyridinium iodide (XXIX), and 750 cc. of benzene was refluxed and stirred for 21 hours. The mixture was evaporated to dryness *in vacuo*. The residue was shaken with 550 cc. of chloroform and 370 cc. of 3% sodium hydroxide until no more solid appeared to dissolve. This solid (5.4 g.) was collected and treated separately as described below.

The separated chloroform solution, washed with another 370 cc. of 3% sodium hydroxide and dried with magnesium sulfate, was evaporated to dryness *in vacuo*. Trituration of the residue with 100 cc. of toluene caused crystallization. The product was collected by filtration of the cooled mixture; yield, 6.5 g. (32%) of yellow crystals, m.p. 228–230° dec.

The 5.4 g. of above solid, a mixture of XXIX and XXXI•HI, was suspended in 50 cc. of absolute alcohol and 4 cc. of triethylamine, and refluxed for two hours. During this time the solid changed over to bright yellow crystals. The product was collected on a filter and washed with absolute alcohol; yield, 4.2 g., m.p. 243–245° dec. A mixture of the two fractions melted at 234–235° dec. The total yield was 10.7 g. (53%). Since no suitable solvent for recrystallization could be found, the compound was characterized by hydrolysis to XXX.

Attempts to condense XXIX with sodio or triethylammonium acetylacetone or sodio benzoylacetone under similar conditions failed to give the desired compounds. Similarly, attempts to condense the sodium salt of XXI with 1-benzyl-2-iodo-3-hydroxypyridinium iodide O-acetate or O-benzoate were unfruitful and the quaternary salts were recovered unchanged.

3-[β-Keto-γ-(1-benzyl-3-methoxy-1,2-dihydro-2-pyridylidene)propyl]-4-quinazolone (XXX). A solution of 16.1 g. of XXXI in 161 cc. of 6 *N* hydrochloric acid was refluxed for 4 hours, then cooled and filtered. The filtrate was evaporated to dryness *in vacuo*. Trituration of the residue with 50 cc. of hot absolute alcohol caused crystallization. The pyridinium chloride (I) was collected on a filter and washed with absolute alcohol, then acetone; yield, 12.0 g. (80%), m.p. 197–198° dec. A similar preparation was recrystallized from absolute alcohol forming white crystals of unchanged m.p.; $\lambda_{max.}^{0.1N HCl}$ 265 (ε 7240) (inflect.), 278 (ε 8380), 297 mμ (ε 12,600); $\lambda_{max.}^{H_2O}$ 265 (ε 8750), 275 (ε 8850), 300 mμ (ε 12,600); $\lambda_{max.}^{0.1N NaOH}$ 267 (ε 8670), 276 (ε 9410), 297 (ε 9380), 400 mμ (ε 9880). The compound was unstable to 0.1 *N* sodium hydroxide and appeared to be cleaved rapidly. The above alkaline u.v. spectrum was determined in less than 1 minute on a Cary recording spectrophotometer. After 4 minutes the maxima were 267 (ε 8190), 276 (ε 9030), 297 (ε 10,000), and 400 mμ (ε 2640). After ten minutes the 400 mμ peak had completely disappeared.

Anal. Calc'd for $C_{24}H_{23}Cl_2N_3O_3 \cdot \frac{1}{2}H_2O$: C, 59.9; H, 4.99; N, 8.73.

Found: C, 59.7; H, 5.42; N, 8.44.

When 1.5 g. of the dihydrochloride was converted to the *free base*, XXX, as described for XVIIb, 1.23 g. (97%) of yellow crystals, m.p. 199–200° dec., were obtained.

Anal. Calc'd for $C_{24}H_{21}N_3O_3 \cdot \frac{1}{2}H_2O$:[12] C, 70.6; H, 5.40; N, 10.3.

Found: C, 70.8; H, 5.40; N, 10.5.

Hydrogenation of 3-[β-keto-γ-(1-benzyl-3-methoxy-1,2-dihydro-2-pyridylidene)propyl]-4-quinazolone (XXX). (*A*). *In Methyl Cellosolve with Raney nickel.* A solution of 2.0 g. of XXX in 100 cc. of Methyl Cellosolve was shaken with hydrogen at 1 atm. in the presence of ¼ teaspoon of Raney nickel. A total of 1.25 mole-equivalents of hydrogen was absorbed in 2 hours and reduction ceased. The bright orange color of XXX disappeared with about 1.15 mole-equivalent of hydrogen uptake. The filtered solution was evaporated to dryness *in vacuo* leaving 1.3 g. of a gum. This gum was extracted with 30 cc. of hot water, decanted, and the solution was cooled to give 60 mg. of a product, m.p. 157–158°. This compound had the u.v. of a typical 3-alkyl-4-quinazolone with pyridine unsaturation in the side-chain (12).

Since the u.v. data showed this was a cleavage product, it was not further investigated until procedure *C* and was identified as XXXIV.

The aqueous filtrate was evaporated to dryness *in vacuo* and the residue (0.9 g.) solidified. Recrystallization from alcohol gave white crystals, m.p. 81–82°. The compound had a u.v. spectrum typical of a saturated-3-alkyl-4-quinazolone with apparent molecular weight of 245 ± 24. The IR spectrum showed the quinazolone C=O at 5.96 μ and ester absorption at 5.70 μ with a companion band at 8.20 μ.

Anal. Calc'd for $C_{12}H_{14}N_2O_4$(262): C, 59.6; H, 5.34; N, 10.7.
Found: C, 60.0; H, 5.66; N, 11.1.

The spectroscopic and combustion data indicated that this compound was the methoxyethyl ester of 4-quinazolone-3-acetic acid (XXXIIa) which was verified by comparison with the authentic sample prepared as follows:

A mixture of 1.00 g. of 4-quinazolone-3-acetyl chloride hydrochloride (11) and 25 cc. of Methyl Cellosolve was heated on the steam-bath for 20 minutes, solution being complete in 5 minutes. The solution was evaporated to dryness *in vacuo* and the residue was dissolved in 10 cc. of water. Neutralization to *p*H 8 with sodium bicarbonate and cooling gave 0.27 g. (27%) of XXXIIa, m.p. 80–81°, which gave no depression in m.p. when mixed with the above cleavage product. No attempt was made to isolate additional material.

The same cleavage of XXX to XXXIIa was effected by simply warming a solution of XXX in Methyl Cellosolve.

(*B*). *Hydrogenation in absolute ethanol with Raney nickel.* A mixture of 500 mg. of XXX, 50 cc. of absolute alcohol and ¼ teaspoon of Raney nickel was shaken with hydrogen at 1 atm. until 2.2 mole-equivalents of hydrogen were absorbed (83 minutes). The filtered solution was evaporated to dryness *in vacuo* leaving 180 mg. of a gum. Crystallization from 2 cc. of absolute alcohol gave 15 mg. of a solid, m.p. 157–158°. This material was identical, as shown by mixture m.p., with the 158° material described in preparation *A*.

To the filtrate from the 15 mg. was added 2 cc. of saturated absolute alcoholic hydrogen chloride. The white crystals were collected and washed with a small amount of absolute alcohol, then acetone; yield, 160 mg., m.p. 202–205° dec. Recrystallization from absolute alcohol gave white crystals, m.p. 204–205° dec. This compound showed a u.v. spectrum typical of a saturated-3-alkyl-4-quinazolone with an apparent molecular weight of 260 ± 26. The I.R. spectrum showed ester carbonyl absorption at 5.70 and 8.20 μ, quinazolone C=O at 5.98 μ, and C=NH$^+$ at 5.90 μ.

Anal. Calc'd for $C_{12}H_{12}N_2O_3 \cdot HCl$(268.5): C, 53.7; H, 4.88; N, 10.4.
Found: C, 54.3; H, 5.08; N, 10.4.

The spectral and analytical data indicated that this compound was ethyl 4-quinazolone-3-acetate hydrochloride which was verified by comparison with the hydrochloride prepared from an authentic sample of the ester (12).

(*C*). *In dimethylformamide-acetic acid with Raney nickel.* A solution of 1.57 g. of XXX in 70 cc. of dimethylformamide and 7 cc. of acetic acid was shaken with hydrogen at 1 atm. in the presence of ½ teaspoon of Raney nickel (washed with dimethylformamide) for 16 hours. During this time hydrogenation stopped at 1.85 mole-equivalent uptake. The filtered solution was evaporated to dryness *in vacuo* leaving 1.10 g. of a gum. Crystallization from 10 cc. of absolute alcohol gave 300 mg. of white crystals, m.p. 150–152° (turbid). Two recrystallizations from absolute alcohol gave white crystals, m.p. 199–200°, $\lambda_{max.}^{0.1HCl}$ 292 mμ (ϵ 14,000), $\lambda_{max.}^{H_2O,0.1NNaOH}$ 267 (inflection), 275 (ϵ 12,700), 302 (ϵ 3830), 313 mμ (ϵ 2520). The extinctions are much higher at 292 and 275 mμ than ordinary 3-alkyl-4-quinazolones and thus show conjugated unsaturation in the quinazolone side chain.

Anal. Calc'd for $C_{17}H_{17}N_3O_4 \cdot \frac{1}{2}H_2O$: C, 60.7; H, 5.40; N, 12.5; H_2O, 2.67.
Found: C, 60.5; H, 5.01; N, 12.7; H_2O, 2.86 (Fischer).

The compound gave a green color with ferric chloride. The I.R. spectrum indicated a salt between a strong C_7H_8NO base having a C=N$^\oplus$ group and 4-quinazolone-3-acetic acid since it had N$^\oplus$ absorption at 4.25 and 4.87 μ, C=N$^\oplus$ at 5.74 μ, C=O (of the 4-quinazolone) at 5.93 μ, C=N (of the 4-quinazolone) at 6.15 μ and ionized COO$^-$ at 6.37 and 7.05 μ.

By evaporation of the mother liquors from the recrystallization of the 300 mg. was obtained 180 mg. of solid, m.p. 152–153°. Recrystallization from 10% alcohol gave white crystals, m.p. 159–160°. A mixture with the product, m.p. 157–158°, isolated in procedure *A* gave no depression in m.p. This compound had u.v. peaks in 0.1 *N* sodium hydroxide at 268, 277, 302 and 313 mμ. The 277 mμ peak was higher in extinction than the shoulder usually observed at that point for a typical saturated-3-alkyl-4-quinazolone (22). In 0.1 *N* HCl the 277 mμ peak was shifted to 292 mμ with considerable increase in extinction. By analysis of the 302 mμ peak, the molecular weight was estimated to be >260, the exact amount greater not known due to the raising of the 302 mμ peak by the abnormal peak at 277 mμ. Combustion data agreed with an empirical formula of $C_{17}H_{15}N_3O_3$ (M.W. 309) or $C_{11}H_{10}N_2O_2$ (M.W. 202). The latter empirical formula was eliminated since the M.W. by u.v. analysis was >260. The infrared spectrum showed the quinazolone C=O at 5.92 μ and carbonyl absorption at 5.72 μ which was a ketone since the companion band for an ester at 8.2 μ was absent. These properties all agree with the hydrogenolysis product, 3-[β-keto-γ-(3-methoxy-2-pyridyl)propyl]-4-quinazolone (XXXIV), since the 277 mμ peak in the u.v. spectrum and the 292 mμ peak in acid correspond exactly to those of 2-methyl-3-methoxypyridine (23),

Anal. Calc'd for $C_{17}H_{15}N_3O_3$: C, 66.0; H, 4.85; N, 13.6.

Found: C, 65.7; H, 4.88; N, 13.8.

Other points of the I.R. spectrum showing that this compound contained a 2-alkyl-3-methoxypyridine residue were found by comparison with the spectrum of 2-(β-hydroxypropyl)-3-methoxypyridine (23). Both had the aromatic ether C—O—C absorption doublet at 7.77–7.82 and 9.77–9.82 μ, aromatic pyridine absorption at 12.45–12.47 μ and substituted pyridine C=N doublet at 6.25 and 6.30 μ.

The only structure which can be written for a 3-alkyl-4-quinazolone with empirical formula $C_{11}H_{10}N_2O_2$ contaning a ketone in the side chain is 3-acetonyl-4-quinazolone, m.p. 164° (12). A mixture with an authentic sample melted at 130–150°.

(*D*). ***In dimethylformamide with Raney nickel.*** Reduction of 1.00 g. of XXX in 50 cc. of dimethylformamide as described in procedure *C* gave 1.5 mole-equivalent hydrogen uptake. Evaporation to dryness *in vacuo* left 710 mg. of a gum which had a u.v. spectrum characteristic of 3-substituted-4-quinazolone with pyridine unsaturation in the side chain. Extraction with hot water gave on cooling 135 mg. of XXXIV, which had an I.R. spectrum identical with that described in procedure *C*.

In a similar run 10 mg. of 3-acetonyl-4-quinazolone (12) was isolated by direct crystallization from methanol and identified by mixture m.p.

SUMMARY

Several methods of preparation, as well as a number of reactions, of some unusual keto methylene bases have been investigated during attempts to synthesize 3-[β-keto-γ-(3-hydroxy-2-piperidyl) propyl]-4-quinazolone (IV), the Hydrangea alkaloid.

PEARL RIVER, NEW YORK

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