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

AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. VIII. ATTEMPTED SYNTHESIS OF 3-[β-KETO-γ-(4-HYDROXY-2-PIPERIDYL)PROPYL]-4-QUINAZOLONE BY THE DIKETONE APPROACH

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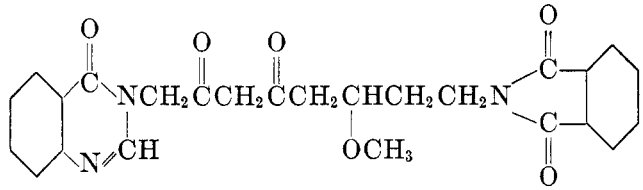
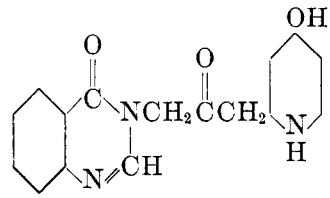
One of the approaches (1) used for the synthesis of 3-[β-keto-γ-(2-piperidyl)-propyl]-4-quinazolone involved diketones of type I, but without the methoxyl



I

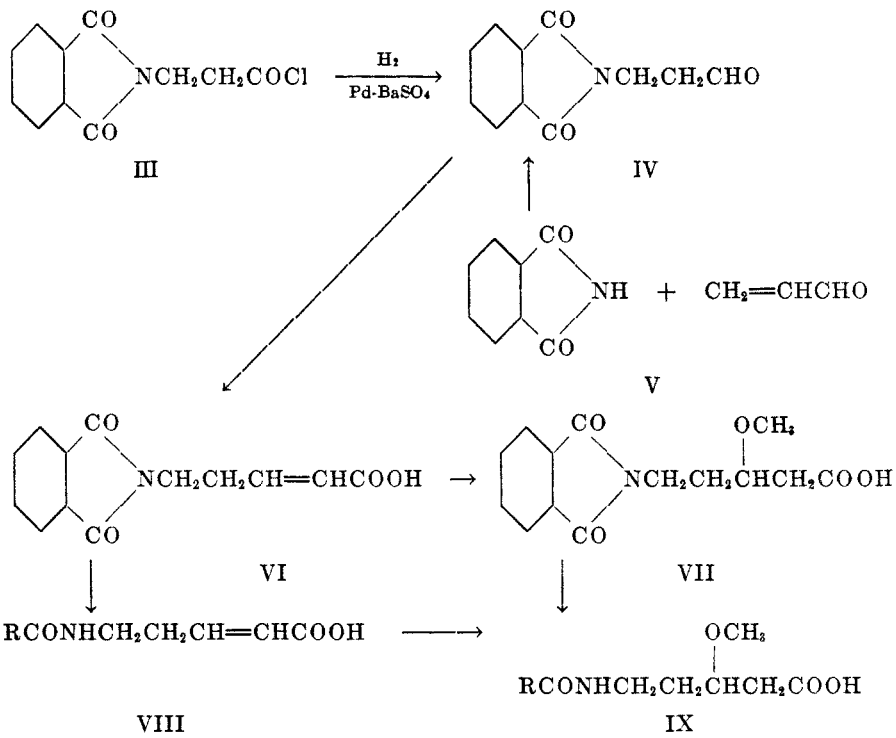


II

group. This approach was also used successfully for the 5-hydroxypiperidyl isomer of II (2). The synthesis of the appropriate diketone, I, and the unsuccessful attempts to convert I to II are now described.

5-Phthalimido-2-pentenoic acid (VI) was first made by Rosenmund reduction of 3-phthalimidopropionyl chloride (III) to the easily polmerized aldehyde, IV, followed by condensation with malonic acid. The over-all yield was 21–32% depending, in part, how long the reduction required. It was then observed that phthalimide rapidly added to the double bond of acrolein in the presence of methanolic Triton B.[1] However, during the attempt to isolate the aldehyde, IV, most of the material had polymerized and only a 19% yield of crude 5-phthalimido-2-pentenoic acid (VI) could be isolated after condensation with malonic acid. The phthalimide-acrolein condensation could also be carried out in pyridine, the solvent necessary for the malonic acid condensation so that the aldehyde would not have to be isolated. It was found empirically that the acrolein condensation was best carried on for exactly 30 minutes at 28–30°. Treatment with malonic acid and piperidine then gave 54–62% of the crude pentenoic

[1] Moe and Warner (3) have since described this addition reaction using sodium ethoxide as a catalyst and record a yield of 26% of crude aldehyde.

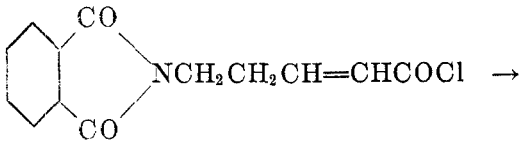


acid, VI, or 40–43% purified. The requisite methoxyl group was introduced by esterification of VI, addition of methanol in the presence of a sodium methoxide catalyst, and acid hydrolysis to VII. The phthalyl group was readily removed from VII by treatment of an aqueous solution of its sodium salt with hydrazine. An alternate blocking group (IX) was then introduced under Schotten-Bauman conditions using benzoyl chloride, ethyl chlorocarbonate, benzyl chlorocarbonate, or benzenesulfonyl chloride. All these compounds (IX) were oils, characterized as their respective anilides. Alternately, the N-blocking group could be removed from VI, a new one introduced (VIII) and then methanol could be added to the double bond. The N-benzoyl derivative, IX, was best made in this way.

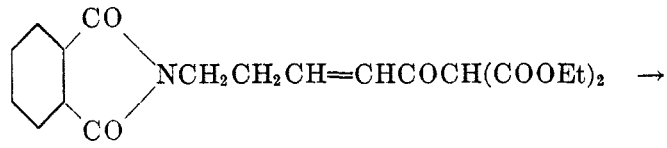
Condensation of the acid chloride of 5-phthalimido-2-pentenoic acid (X) with magnesiomalonic ester[2] to the keto malonate, XI, proceeded in good yield.

[2] After a number of magnesio malonic ester condensations with various acid chlorides had been run employing preformed magnesium methoxide, it was observed that the yield of magnesium methoxide after drying at 100° *in vacuo* was 170% based on magnesium. Analysis showed two methanols of crystallization. It can be readily seen that if the molecular weight is incorrectly assumed to 86 instead of 150, one mole of this alkoxide would be present in only slight excess over that necessary to combine with one mole of malonic ester. However, using the corrected molecular weight, it was observed that at least two moles of malonic ester were necessary to dissolve one mole of the alkoxide, indicating that a 1:1 compound, the expected methoxymagnesiomalonic ester (6) does not form. These results do not agree with the data described for preformed magnesium ethoxide (6).

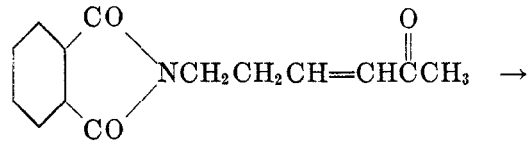
Mild acid hydrolysis led to the unsaturated ketone, XII, in 87% yield as a crude



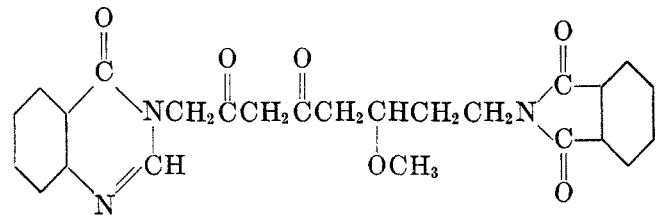
X



XI



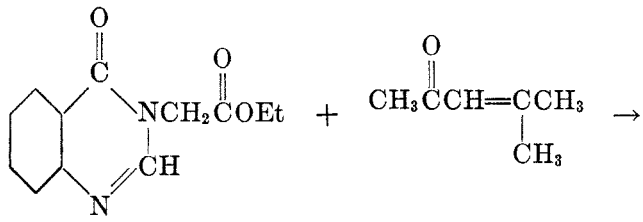
XII

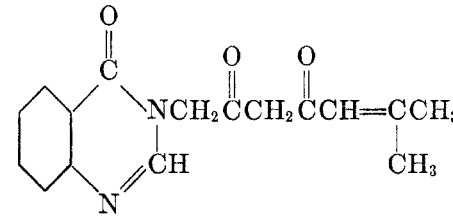


I

oil which gave a 42% yield of a crystalline 2,4-dinitrophenylhydrazone. Attempts to Claisen condense this ketone with ethyl 4-quinazolone-3-acetate to I in benzene containing some methanol were unpromising. A 10% yield of a copper derivative, m.p. 165–185° dec., was obtained which analyzed poorly. Methoxyl analysis indicated about 80% of the product had added methanol across the double bond. The m.p. of pure I, obtained in a manner described later, was 218°. Condensation of ethyl 4-quinazolone-3-acetate with the more stable mesityl oxide in the presence of sodium methoxide gave 19–25% of XIV, isolated as the crystalline copper salt. However, under these same conditions the relatively unstable *n*-butylidene acetone or 4-hydroxy-2-heptanone gave products from which no diketone could be isolated.

It was next considered possible that a β-methoxy ketone such as XVII would be more stable than the α,β-unsaturated ketone, XII, towards Claisen condensation. These acid sensitive ketones were made by condensation of 5-phthalimido or 5-benzamido-3-methoxyvaleric acid (XV) as the acid chloride with benzyl magnesiomalonate to XVI followed by hydrogenolysis of the benzyl esters and decarboxylation to the desired ketones, XVII (4). Attempted acid





XIV

hydrolysis of the ethyl ester of XVIb led to extensive decomposition and acid hydrolysis of the corresponding phthalimido ethyl ester gave what appeared to be a mixture of XVIIa and XII. The two ketones, XVII, obtained by the

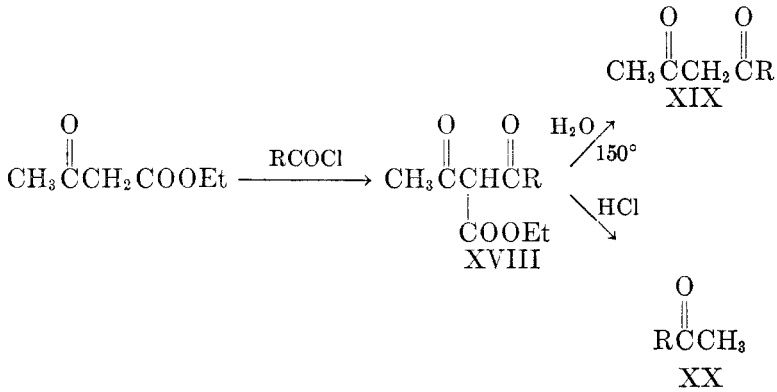
XV XVI

XVII

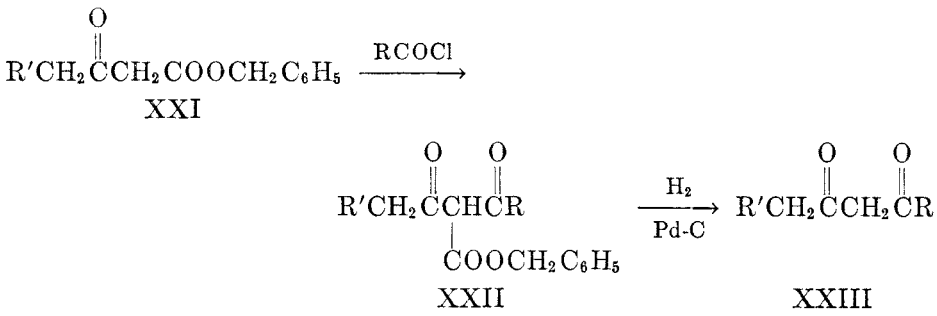
a series, RN = phthalimido
b series, RN = benzamido

benzyl ester method were isolated as analytically pure oils with the methoxyl intact. However, when these ketones were converted to their 2,4-dinitrophenylhydrazones, methanol was eliminated with the formation of the derivatives of the unsaturated ketones, XII. Some thirty attempts to Claisen condense either of these two ketones to diketones of type I with the methyl, ethyl, phenyl, or benzyl esters of 4-quinazolone-3-acetic acid using sodium methoxide, sodium hydride, sodium *tert*-butoxide, lithium methoxide, calcium methoxide, magnesium methoxide, aluminum *tert*-butoxide, or lithium amide in such solvents as ether, benzene, *tert*-butyl alcohol, methanol-benzene, and *tert*-butyl alcohol-benzene gave tarry products which gave at best a faint ferric chloride test, but from which no copper derivatives could be isolated. The lack of success was probably due to the instability of the products rather than inertness of the methyl ketone since ethyl 4-quinazolone-3-acetate readily self-condenses to an easily isolatable product if no methyl ketone is present.

Bouveault (5) prepared 1,3-diketones (XIX) by C-acylation of acetoacetic ester to XVIII followed by water hydrolysis at 150°. Hydrochloric acid, on the other hand, first cleaved the aceto group from XVIII and the product isolated was a methyl ketone, XX, rather than a diketone. Duplication of Bouveault's



water hydrolysis procedure in the R = *n*-propyl series led mainly to acidic cleavage products, the yield of *n*-butyrylacetone being only 9–12% from XVIII and acid hydrolysis, as expected, gave no diketone. These difficulties have now been circumvented by use of the benzyl ester. Acylation of the sodio derivative of benzyl acetoacetate (XXIa) with *n*-butyryl chloride followed by hydrogenol-



a series, R′ = H
b series, R′ = phthalimido
c series, R′ = 4-quinazolone-3

ysis and mild decarboxylation led to a 60% over-all yield of *n*-butyrylacetone isolated as the copper salt or in 49% yield by use of the magnesio derivative.[3] Acylation of benzyl magnesio acetoacetate with 5-benzamidovaleryl chloride or 3-methoxy-5-benzamidovaleryl chloride gave 39% and 31% of the respective diketones, XXIIIa.

[3] Similarly the use of ethyl benzyl magnesiomalonate led to γ-substituted acetoacetic ethyl esters. *n*-Butyryl chloride gave a 56% yield of ethyl *n*-butyrylacetate and 5-benzamidovaleric acid, *via* the acid chloride, gave an over-all yield of 38% of ethyl (5-benzamidovaleryl)acetate.

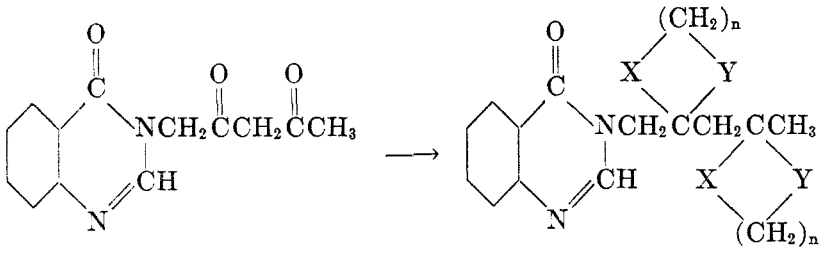
A study of the acylation of benzyl (4-quinazolone-3-acetyl)acetate (XXIc) revealed that this ester reacted with magnesium methoxide in toluene sluggishly. Addition of 5-benzamidovaleryl chloride led to a 60% recovery of starting ester and a disappointing 1% yield of diketone, XXIIIc (R = benzamidobutyl), after hydrogenolysis and decarboxylation. Acylation of the sodio derivative suspended in toluene with *n*-butyryl chloride gave a 2.5% yield of diketone and 50% of the benzyl ester was recovered unchanged whereas in acetone the yield was 12%. When the sodio derivative suspended in Diethyl Carbitol was acylated with 5-phthalimidovaleryl chloride, an 11% yield of diketone was obtained isolated as the copper salt and no unchanged benzyl ester was recovered. The inference from this experiment was that O-acylation predominated over C-acylation.[4] This was verified by treating the acylation mixture with potassium carbonate (7) at 50° prior to hydrogenolysis which raised the yield of diketone to 19%. Application of these conditions to 3-methoxy-5-phthalimidovaleryl chloride gave only a 2.4% yield of diketone, 0% with potassium carbonate at 50° and 3.1% with potassium carbonate at 25°. A study of fourteen other sets of acylation conditions involving the lithium, sodium, or magnesium derivatives of XXIc in dioxane, acetone, toluene, tetraethyleneglycol dimethyl ether, ether, Diethyl Cellosolve, and Diethyl Carbitol revealed that the latter solvent with the lithium salt gave the maximum yield, 6.2%, of 3-(2,4-diketo-6-methoxy-8-phthalimidoöctyl)-4-quinazolone (I).

No diketone could be obtained when the 3-methoxy-5-aminovaleric group was blocked on the nitrogen with carbethoxy, benzoyl, N-benzylbenzenesulfonyl, or toluenesulfonyl. In these cases 36–67% of the benzyl ester, XXIc, was recovered unchanged. Since the above reaction to I proceeded, unfortunately, only with the phthalimido group, a study was made of possible ways to remove this blocking group. Acid hydrolysis led to tars leaving as the only alternative hydrazinolysis. As expected, the carbonyls reacted with hydrazine preferentially to the phthalimido group, since no phthalhydrazide could be isolated with one mole-equivalent of hydrazine, but readily formed with two moles of hydrazine. The product obtained in the second case was probably an aminopyrazole. Thus, it was necessary to try to find a suitable blocking group for the ketones before hydrazinolysis.

Since 4-quinazolone-3-acetylacetone (XXIV) was readily available (1), the conversion of this compound to diketals (XXV) was extensively investigated. Surprisingly, it was found that only one ketone group could be blocked when the reaction was run to completion, the other being inert. Ethylene glycol, propylene glycol, and mercaptoethanol all gave the same results. It seemed that only one of the ketones reacted predominately since crystalline products were isolated in two cases.

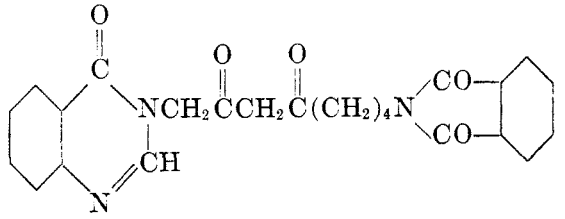
Although one of the ketone groups was inert to ketal formation, it was not

[4] Attempted acylation of sodio or magnesio benzyl γ-phthalimidoacetoacetate or (3-methoxy-5-phthalimidovaleryl)acetate gave no C-acylation product showing that the difficulty was not due to the basic 4-quinazolone group, but was possibly due to any group substituted in the γ-position of the acetoacetate.

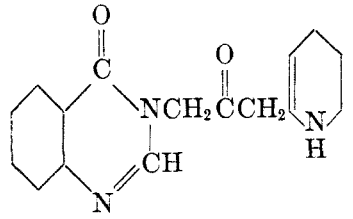


XXIV XXV

inert to hydrazine. When XXVI was converted to the ketal then treated with one mole of hydrazine, no phthalhydrazide could be isolated, but a hydrazone was obtained. Treatment with a second mole of hydrazine then removed the



XXVI



XXVII

phthalyl group as phthalhydrazide, but the remainder of the molecule was presumably converted to a pyrazole since none of the known XXVII (2) could be isolated.

Work on this diketone approach was postponed when a subsequent method was found satisfactory (8).

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EXPERIMENTAL

5-Phthalimido-2-pentenoic acid (VI). (*A*). Through a stirred and refluxed mixture of 81 g. of β-phthalimidopropionyl chloride (9), 500 cc. of xylene, 7 g. of 5% palladium-barium sulfate, and 0.7 cc. of quinoline-sulfur poison solution (10) was passed hydrogen at a rate of about 200 bubbles per minute. Elimination of hydrogen chloride (10) was essentially complete in five hours. The mixture was filtered through Celite. One-quarter of this solution was

evaporated to dryness *in vacuo*. To a crude solid aldehyde (IV) (11.5 g.) was added 10.3 g. of malonic acid, 16.5 cc. of reagent pyridine, and 0.4 cc. of piperidine. The mixture was heated at 50° for 2½ hours, then poured into dilute hydrochloric acid. The solid was collected and extracted with half-saturated aqueous sodium bicarbonate containing a drop of Aerosol OT. The filtered solution gave, on acidification, 4.0 g. (19%) of crude product, m.p. 180–183°. Recrystallization from alcohol afforded white crystals, m.p. 198–200°.

Anal. Calc'd for $C_{13}H_{11}NO_4$: C, 63.7; H, 4.52; N, 5.72.
Found: C, 63.6; H, 4.44; N, 5.86.

(*B*). To a stirred mixture of 400 g. of technical phthalimide (40 mesh), 800 cc. of reagent pyridine, and 200 cc. of acrolein was added 16 cc. of 38% trimethylbenzylammonium hydroxide. The temperature was maintained at 28–30° by occasional ice-cooling. The phthalimide dissolved in ten minutes. Exactly 30 minutes after the Triton B had been added 400 g. of malonic acid and 16 cc. of piperidine were added. An ice-bath was immediately applied. The temperature rose to 55° and carbon dioxide was evolved. When the temperature dropped to 50°, the ice-bath was removed. The mixture was stirred until the malonic acid dissolved, then it was allowed to stand 15–20 hours. The solution was added cautiously to a stirred solution of 360 g. of anhydrous sodium carbonate in 7 l. of water. The mixture was filtered through Celite to remove some insoluble gum. The filtrate was added to a vigorously stirred mixture of 3200 cc. of 6 *N* hydrochloric acid and 1200 cc. of toluene in a thin stream over a period of about five minutes. After being stirred ten minutes more, the mixture was filtered and the solid washed with water and toluene. The crude product melted at 175–185°. The moist cake was heated to boiling with 1200 cc. of alcohol with stirring, then cooled to 5°. The product was collected and washed with two 250-cc. portions of ice-cold alcohol; yield, 277 g. (43%), m.p. 198–200°. A sample recrystallized from alcohol formed white prisms, m.p. and mixed m.p. with preparation *A*, 200–201°.

Anal. Calc'd for $C_{13}H_{11}NO_4$: C, 63.7; H, 4.52; N, 5.72.
Found: C, 64.0; H, 4.73; N, 5.88.

Methyl 5-phthalimido-2-pentenoate. To a mixture of 100 g. of VI and 500 cc. of methanol was added dropwise with shaking 50 cc. of acetyl chloride. The mixture came to a boil and was then refluxed for 40 minutes, solution being complete in ten minutes. The solution was diluted with 500 cc. of benzene and 2 l. of water. The separated organic layer, washed with aqueous sodium bicarbonate and water, was evaporated to dryness *in vacuo;* yield, 103 g. (97%), m.p. 88–90°. Recrystallization of a sample from methanol gave white crystals, m.p. 90–92°.

Anal. Calc'd for $C_{14}H_{13}NO_4$: C, 64.8; H, 5.06; N, 5.40.
Found: C, 64.4; H, 4.87; N, 5.41.

3-Methoxy-5-phthalimidovaleric acid (VII). To a mixture of 103 g. of methyl 5-phthalimido-2-pentenoate and 450 cc. of methanol was added 3.3 g. of sodium methoxide. The solution was refluxed one hour, then acidified with 6.6 cc. of acetic acid and evaporated to a paste *in vacuo*. The residue was refluxed with 250 cc. of acetic acid and 250 cc. of 6 *N* hydrochloric acid for 40 minutes, concentrated to a syrup *in vacuo*, and portioned between 200 cc. of water and 300 cc. of ethyl acetate. The aqueous layer was extracted again with 300 cc. of ethyl acetate. Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo*. The residue was recrystallized by solution in 600 cc. of boiling benzene, addition of 300 cc. of heptane, and slow cooling to 0°; yield, 83 g. (75%), m.p. 115–118°. Recrystallization of a sample from benzene-petroleum ether gave white crystals, m.p. 119–121°.

Anal. Calc'd for $C_{14}H_{15}NO_5$: N, 5.06. Found: N, 5.07.

The *anilide*, prepared *via* the acid chloride, formed white crystals from dilute alcohol, m.p. 132–133°.

Anal. Calc'd for $C_{20}H_{20}N_2O_4$: C, 68.2; H, 5.73; N, 7.95; CH_3O, 8.82.
Found: C, 68.0; H, 5.58; N, 7.84; CH_3O, 8.60.

5-Benzamido-2-pentenoic acid (VIII, R = C_6H_5). A mixture of 88 g. of 5-phthalimido-2-pentenoic acid (VI), 440 cc. of water, and 20.2 g. of anhydrous sodium carbonate was heated on the steam-bath with stirring until solution was complete and the temperature reached

85°. Then 18 cc. of 100% hydrazine hydrate was added. The mixture was heated *exactly* ten minutes, acidified with 62 cc. of 12 *N* hydrochloric acid, and heated ten minutes more. The mixture was cooled to 25° and filtered from phthalhydrazide. The combined filtrate and washings were cooled in an ice-bath to 5° with stirring. An ice-cold solution of 40.5 g. of sodium hydroxide in 200 cc. of water was added. When the temperature returned to 10°, 41 cc. of benzoyl chloride was added in one portion. After being stirred in the ice-bath 20 minutes, the mixture was treated again with an ice-cold solution of 17.5 g. of sodium hydroxide in 88 cc. of water followed by 41 cc. of benzoyl chloride. The mixture was stirred 30 minutes in the ice-bath, then 30 minutes more with the ice-bath removed. The solution was clarified by filtration through Celite. The filtrate was covered with 350 cc. of ethyl acetate and acidified with 65 cc. of 12 *N* hydrochloric acid with vigorous stirring, then kept at 3° for 15 hours. The white crystals were washed with water and ethyl acetate; yield, 43.5 g. (56%), m.p. 165–168°. Recrystallization of a sample from 20% alcohol raised the m.p. to 167–169°.

Anal. Calc'd for $C_{12}H_{13}NO_3$: C, 65.7; H, 5.98; N, 6.38.
Found: C, 65.4; H, 6.06; N, 6.58.

The *anilide* was prepared in 89% yield *via* the acid chloride and formed white crystals from Methyl Cellosolve-water, m.p. 229–231°.

Anal. Calc'd for $C_{18}H_{18}N_2O_2$: C, 73.5; H, 6.14; N, 9.55.
Found: C, 73.1; H, 6.55; N, 9.94.

The structure of the acid was demonstrated by hydrogenation in alcohol in the presence of platinum oxide. One mole-equivalent of hydrogen was rapidly absorbed and the hydrogenation stopped. A 95% yield of 5-benzamidovaleric acid, m.p. 98–100°, was obtained and was identified by mixed m.p. with the same compound prepared by oxidation of benzoylpiperidine as described by Schotten (11) who recorded m.p. 105°.

5-Carbobenzoxyamino-2-pentenoic acid. To 5-amino-2-pentenoic acid hydrochloride in water prepared from 100 g. of 5-phthalimido-2-pentenoic acid (VI) as in the preceding experiment and cooled in an ice-bath to 5° was added with stirring a cold solution of 60 g. of sodium hydroxide in 300 cc. of water. When the temperature returned to 7°, 125 cc. of 70% benzyl chlorocarbonate was added over a period of seven minutes. The mixture was stirred an additional 50 minutes in the ice-bath, then washed with ethyl acetate and acidified. The white solid was washed with water; yield, 101 g. (99%), m.p. 131–137°. Recrystallization from ethyl acetate raised the m.p. to 139–141°.

Anal. Calc'd for $C_{13}H_{15}NO_4$: C, 62.7; H, 6.07; N, 5.63.
Found: C, 62.7; H, 6.31; N, 5.74.

The *anilide* was prepared in 88% yield, m.p. 151–153°, *via* the acid chloride. Recrystallization from benzene gave white crystals, m.p. 159–161°.

Anal. Calc'd for $C_{19}H_{20}N_2O_3$: C, 70.5; H, 6.18.
Found: C, 70.3; H, 6.71.

Methyl 5-benzamido-2-pentenoate. This compound was prepared in 85% yield, m.p. 81–84°, by Freudenberg esterification of 5-benzamido-2-pentenoic acid as described for the esterification of VI. Recrystallization from benzene-heptane gave white leaflets, m.p. 86–87°.

Anal. Calc'd for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.48; N, 6.01.
Found: C, 66.7; H, 6.90; N, 6.29.

Similarly, *methyl 5-carbobenzoxyamino-2-pentenoate*, was prepared in 84% yield as a low melting solid.

3-Methoxy-5-benzamidovaleric acid (IX, R = C_6H_5). A solution of 68 g. of methyl 5-benzamido-2-pentenoate and 3.2 g. of sodium methoxide in 280 cc. of methanol was refluxed two hours. After the addition of 170 cc. of 10% aqueous sodium hydroxide, the solution was refluxed 30 minutes, acidified with 40 cc. of acetic acid, and evaporated nearly to dryness *in vacuo*. To the residue was added 160 cc. of water and 30 cc. of 12 *N* hydrochloric acid. The solution was saturated with salt and extracted with two 150-cc. portions of chloroform. Evaporation of the combined dried extracts *in vacuo* gave 73 g. (99%) of a thick oil.

A sample formed an *anilide*, *via* the acid chloride, in 97% yield, m.p. 145–147°. Recrystallization from benzene-heptane gave white crystals, m.p. 148–150°.

Anal. Calc'd for $C_{19}H_{22}N_2O_3$: C, 69.8; H, 6.75; N, 8.59; CH_3O, 9.50.
Found: C, 69.8; H, 7.17; N, 8.76; CH_3O, 9.92.

This compound could also be prepared from VII in 69% yield as described for 3-methoxy-5-carbobenzoxyaminovaleric acid. However, the crystalline anilide was obtained in only 25% yield.

3-Methoxy-5-carbobenzoxyaminovaleric acid. (*A*). A solution of 69.5 g. of VII in 290 cc. of water containing 12.9 g. of anhydrous sodium carbonate was treated with 11.6 cc. of 100% hydrazine hydrate, then carbobenzoxylated with 71 cc. of benzyl chlorocarbonate as described for the conversion of VI to 5-carbobenzoxyamino-2-pentenoic acid. The oil which separated from the acidified aqueous solution was isolated by ethyl acetate extraction; yield, 59.5 g. (91%).

The *anilide* was obtained in 53% yield, m.p. 101–103°, *via* the unstable acid chloride (8). Recrystallization from benzene gave white crystals, m.p. 102–104°.

Anal. Calc'd for $C_{26}H_{24}N_2O_4$: C, 67.4; H, 6.80; N, 7.87.
Found: C, 67.4; H, 6.50; N, 8.18.

(*B*). A solution of 89 g. of methyl 5-carbobenzoxyamino-2-pentenoate and 2.8 g. of sodium methoxide in 400 cc. of methanol was refluxed one hour, treated with 200 cc. of 10% aqueous sodium hydroxide, and refluxed 30 minutes more. The solution was acidified with 50 cc. of 12 *N* hydrochloric acid, then concentrated to turbidity *in vacuo*. The oil was isolated by chloroform extraction; yield, 85 g. (89%). The *anilide* formed in 62% yield, m.p. 99–103°, and gave no depression when mixed with the anilide of preparation *A*.

3-Methoxy-5-carbethoxyaminovaleric acid. From 50 g. of VII according to method *A* for 3-methoxy-5-carbobenzoxyaminovaleric acid using 23 cc. of ethyl chlorocarbonate there was obtained 30 g. (76%) of an oil. The *anilide* formed in 50% yield, m.p. 89–91°, *via* the acid chloride. Recrystallization from benzene-petroleum ether gave white crystals, m.p. 91–92°.

Anal. Calc'd for $C_{15}H_{22}N_2O_4$: C, 61.3; H, 7.48; N, 9.52.
Found: C, 61.5; H, 7.79; N, 9.92.

Similarly, *3-methoxy-5-benzenesulfonamidovaleric acid* was prepared as in oil in 61% yield.

Anal. Calc'd for $C_{12}H_{17}NO_5S$: C, 50.0; H, 5.90; N, 4.87; S, 11.1.
Found: C, 49.6; H, 5.89; N, 4.83; S, 11.1.

The *anilide* was obtained as a gum which could not be crystallized. It was soluble in 10% aqeuous sodium hydroxide but insoluble in aqueous sodium bicarbonate.

N-Benzyl 3-methoxy-5-benzenesulfonamidovaleric acid. A mixture of 3.0 g. of 3-methoxy-5-benzenesulfonamidovaleric acid, 9.3 cc. of 10% aqueous sodium hydroxide, and 1.4 cc. of benzyl chloride was refluxed for seven hours, cooled, washed with benzene, and acidified. The oil was extracted with chloroform; yield, 3.4 g. (86%).

Anal. Calc'd for $C_{19}H_{23}NO_5S$: N, 3.72. Found: N, 3.52.

The *anilide* was obtained in near quantitative yield as a gum insoluble in 10% sodium hydroxide.

5-Phthalimidovaleric acid. (*A*). A solution of 5.8 g. of sodium methoxide, 41 cc. of ethyl malonate, and 29 g. of γ-bromopropylphthalimide in 145 cc. of absolute alcohol was refluxed six hours, diluted to 1 l. with water, acidified, and extracted twice with carbon tetrachloride. The solvent was removed *in vacuo* and the residue was heated with 87 cc. of 48% hydrobromic acid in a modified Claisen flask (bath 140–150°). After 20 minutes solution was almost complete and no more ethyl bromide distilled. The excess hydrobromic acid was removed at 15 mm. (bath 120–130°). The residual malonic acid solidified. The bath was raised to 180–190°. Decarboxylation was complete in 15 minutes. The cooled residue was portioned between ethyl acetate and water. The organic layer was extracted with aqueous sodium bicarbonate. Acidification gave 13.5 g. (51%) of white crystals, m.p. 118–120°.

The procedure is a simplification of that described by Gabriel (12) who recorded m.p. 117° and a yield of 40%.

(*B*). A mixture of 50 g. of 5-phthalimido-2-pentenoic acid (VI), 200 cc. of Methyl Cellosolve, and 0.3 g. of platinum oxide was shaken with hydrogen at 2–3 atm. until reduction was complete (one hour). The mixture was filtered through Celite after the addition of

Norit. The filtrate was evaporated to dryness *in vacuo* leaving 50 g. (99%) of product, m.p. 115–118°, and identical with preparation *A*.

5-Carbobenzoxyaminovaleric acid. By hydrazinolysis of 50 g. of 5-phthalimidovaleric acid and carbobenzoxylation as described for the conversion of VI to 5-carbobenzoxyamino-2-pentenoic acid there was obtained, after recrystallization from toluene, 42 g. (82%) of white crystals, m.p. 106–108°. The m.p. was unchanged on recrystallization.

Anal. Calc'd for $C_{13}H_{17}NO_4$: C, 62.2; H, 6.83; N, 5.57.
Found: C, 62.4; H, 7.07; N, 5.88.

The *anilide* formed in 91% yield, m.p. 123–125°, *via* the acid chloride. Recrystallization from benzene-petroleum ether resulted in white crystals, m.p. 125–126°.

Anal. Calc'd for $C_{19}H_{22}N_2O_3$: C, 69.9; H, 6.75; N, 8.59.
Found: C, 70.2; H, 7.19; N, 8.63.

3-Bromo-5-benzamidovaleric acid. A mixture of 2.0 g. of 5-benzamido-2-pentenoic acid and 5 cc. of 30% hydrogen bromide in acetic acid in a stoppered flask was occasionally shaken for four days when solution was complete. Dilution with water gave 2.1 g. (78%) of product, m.p. 126–128°. Recrystallization from ethyl acetate-heptane afforded white crystals, m.p. 128–130°.

Anal. Calc'd for $C_{12}H_{14}BrNO_3$: C, 48.0; H, 4.69; N, 4.66; Br, 26.7.
Found: C, 48.0; H, 5.02; N, 5.09; Br, 26.4.

Attempts to prepare 3-phenoxy-5-benzamidovaleric acid from this acid as the sodium salt or methyl ester with sodium phenoxide gave 5-benzamido-2-pentenoic acid as the product. An attempt to add phenol to the double bond of methyl 5-benzamido-2-pentenoate in methanol resulted in 3-methoxy-5-benzamidovaleric acid (identified as the anilide) after hydrolysis. 5-Benzamido-2-pentenoic acid was recovered unchanged when treated with phenol in alkaline solution.

Ethyl (5-phthalimido-2-pentenoyl)malonate (XI). A mixture of 30 g. of 5-phthalimido-2-pentenoic acid (VI), 30 cc. of reagent ether (containing 0.5% pyridine), and 60 cc. of thionyl chloride was shaken until solution was complete (15 minutes), then allowed to stand ten minutes. Volatile material was removed *in vacuo* (bath 60°) and the evaporation repeated with 180 cc. of benzene. The residual acid chloride, dissolved in 250 cc. of warm benzene, was added dropwise to a vigorously stirred solution of 73 cc. of ethyl malonate and 37 g. of magnesium methoxide dimethanolate[2] in 220 cc. of benzene over a period of 30 minutes. The solution was acidified with 25 cc. of acetic acid and washed with 3 *N* hydrochloric acid, then with water. The residue obtained on evaporation of the solution to dryness *in vacuo* was dissolved in 480 cc. of alcohol, treated with 220 cc. of 10% aqueous cupric acetate, and cooled in an ice-bath. The product was removed and washed with 60% alcohol; yield, 44 g. (85%), m.p. 189–192°. Recrystallization of a sample of the *copper derivative* from absolute alcohol afforded blue crystals, m.p. 192–194°.

Anal. Calc'd for $C_{40}H_{40}CuN_2O_{14}$: N, 3.35. Found: N, 3.39.

The *free keto ester* was obtained as an oil in 99% recovery by shaking the copper derivative with chloroform and dilute hydrochloric acid and evaporating the dried chloroform solution *in vacuo*.

Similarly, 10 g. of 5-benzamido-2-pentenoic acid gave 2.6 g. (48%) of the *copper derivative* of *ethyl (5-benzamido-2-pentenoyl)malonate*, m.p. 162–164°. Recrystallization from ethyl acetate-heptane gave green crystals, m.p. 181–183°.

Anal. Calc'd for $C_{38}H_{44}CuN_2O_{12}$: C, 58.1; H, 5.61; N, 3.57; Cu, 8.15.
Found: C, 58.1; H, 6.03; N, 3.86; Cu, 8.13.

The *free keto ester* was recovered as an oil.

Ethyl (3-methoxy-5-phthalimidovaleryl)malonate. A solution of 2.5 g. of 3-methoxy-5-phthalimidovaleric acid in 2.5 cc. of reagent ether (containing 0.5% pyridine) and 2.5 cc. of thionyl chloride was allowed to stand ten minutes, then worked up and condensed with ethyl magnesiomalonate as described above for XI; yield, 3.15 g. (78%) of the *copper derivative*, m.p. 119–123°. Recrystallization from alcohol gave green needles, m.p. 121–123°.

Anal. Calc'd for $C_{42}H_{48}CuN_2O_{16}$: N, 3.11. Found: N, 2.96.

The *free keto ester* was obtained as an oil in 95% recovery with chloroform and excess dilute hydrochloric acid.

1-Phthalimido-3-hexen-5-one (XII). (*A*). A mixture of 1.1 g. of ethyl (3-methoxy-5-phthalimidovaleryl)malonate, 2.5 cc. of alcohol, and 5 cc. of 3 *N* hydrochloric acid was refluxed for 2½ hours, then diluted with several volumes of water and extracted with ethyl acetate. The extract, washed with aqueous sodium bicarbonate and water, was evaporated to dryness *in vacuo;* yield, 0.60 g. (98%) of an oil which contained about 60% of a mixture of XII and XVIIa. The 0.60 g. of oil was converted to the *2,4-dinitrophenylhydrazone of XII;* yield, 0.60 g. (60%), m.p. 188–198° dec. Recrystallization from toluene-alcohol gave red crystals, m.p. 198–201° dec.

Anal. Calc'd for $C_{21}H_{21}N_5O_7$: C, 55.3; H, 4.66; N, 15.4; CH_3O, 6.82.
Calc'd for $C_{20}H_{27}N_5O_6$: C, 56.7; H, 4.04; N, 16.5; CH_3O, 0.0.
Found: C, 57.0; H, 4.75; N, 16.5; CH_3O, 0.0.

(*B*). Hydrolysis of 2.45 g. of XI as described in *A* gave 1.35 g. (87%) of an oil which in turn gave a 42% yield of a *2,4-dinitrophenylhydrazone,* m.p. 188–190° dec. Recrystallization from toluene-alcohol afforded red crystals, m.p. and mixed m.p. with preparation *A*, 198–201° dec.

Hydrolysis of ethyl (5-benzamido-2-pentenoyl)malonate in a similar fashion or with boiling 9:1 ethylene glycol-water gave oils from which no crystalline 2,4-dinitrophenylhydrazone could be isolated.

3-(2,4-Diketo-6-methyl-5-heptenyl)-4-quinazolone (XIV). Condensation of 2.8 g. of ethyl 4-quinazolone-3-acetate with 1.2 cc. of mesityl oxide as described for acetone (1) gave 0.61 g. (19%) of the *copper derivative,* m.p. 229–232° dec.

Anal. Calc'd for $C_{32}H_{30}CuN_4O_6$: C, 61.0; H, 4.76; N, 8.90; ash, 12.7.
Found: C, 59.9; H, 4.96; N, 9.30; ash, 12.6.

n-Butylidene acetone or 4-hydroxy-2-heptanone under the same conditions resulted in crude products which gave no ferric chloride test and no copper derivative.

Dibenzyl malonate. (*A*). A mixture of 500 g. of malonic acid, 1140 cc. of toluene, 1140 cc. of benzyl alcohol, and 4.1 cc. of 96% sulfuric acid was refluxed under a constant water separator until no more water (180 cc.) was removed which required 75 minutes. The cooled solution was washed with aqueous sodium bicarbonate and water, then dried with magnesium sulfate. The filtrate had a total volume of 3.08 l. Of this, 92 cc. was removed and distilled; yield, 35.8 g., b.p. 188° (0.2 mm.). Thus, the total yield was 1300 g. (95%) and was used directly in the toluene solution.

Backer and Solkema (13) prepared this compound in 52% yield, b.p. 187° (1.2 mm.) by heating the reactants without solvent at 120° for two hours.

(*B*). A mixture of 76 cc. of ethyl malonate, 110 cc. of benzyl alcohol, and 1.8 g. of sodium methoxide was gradually distilled up to a bath temperature of 185° over a period of two hours when no more alcohol distilled. The residue was washed with aqueous sodium bicarbonate and water, then distilled; yield, 62 g. (44%), b.p. 193–196° (1 mm.).

Phenyl 4-quinazolone-3-acetate. A mixture of 5.2 g. of sodium hydride and 160 cc. of *tert*-butyl alcohol was refluxed for 75 minutes when all of the hydride had reacted. After the addition of 31.7 g. of 4-quinazolone, the mixture was refluxed on the steam-bath for 15 minutes during which the 4-quinazolone dissolved and its sodio derivative separated. Treated with 40.6 g. of phenyl chloroacetate, the mixture was refluxed for 50 minutes when it was neutral. The mixture, diluted with 700 cc. of water, was extracted with 300 cc. of benzene and the latter washed with 3% sodium hydroxide and water. Evaporation *in vacuo* gave a brown semi-solid which was dissolved in 125 cc. of acetone and treated with 70 cc. of saturated absolute alcoholic hydrogen chloride. After several hours the hydrochloride was collected and washed with acetone: white solid, m.p. 205–213° dec.

The hydrochloride was suspended in water and 1:1 ethyl acetate-benzene. Excess saturated aqueous sodium bicarbonate was added and the mixture shaken until solution was complete. The separated organic layer was washed with water and evaporated to near

dryness *in vacuo*. Trituration with heptane gave 16 g. (26%) of product, m.p. 122–126°. Recrystallization of a sample from methanol afforded white crystals, m.p. 122–124°.

Anal. Calc'd for $C_{16}H_{13}N_2O_3$: C, 68.2; H, 4.63; N, 9.96.
Found: C, 68.6; H, 4.91; N, 10.1.

If solid sodium methoxide was used in place of sodium hydride, the only product which could be isolated was 20% of methyl 4-quinazolone-3-acetate, whereas with sodium hydroxide no ester was obtained. No phenyl ester could be isolated when 4-quinazolone-3-acetyl chloride hydrochloride was treated with phenol in pyridine or chloroform containing excess dimethylaniline.

Benzyl 4-quinazolone-3-acetate. A mixture of 25 g. of ethyl 4-quinazolone-3-acetate (18), 75 cc. of toluene, and 15 cc. of benzyl alcohol in a modified Claisen flask was distilled until anhydrous. After the addition of 0.40 g. of sodium methoxide the mixture was distilled until the vapor temperature rose from 70 to 110° which required 30 minutes. After acidification with 0.8 cc. of acetic acid, the mixture was evaporated to dryness *in vacuo* and recrystallized from methanol; yield, 21.5 g. (67%), m.p. 111–113°. Further recrystallization of a sample afforded white crystals, m.p. 114–115°.

Anal. Calc'd for $C_{17}H_{14}N_2O_3$: C, 69.3; H, 4.79; N, 9.52.
Found: C, 69.6; H, 5.03; N, 9.75.

Benzyl (3-methoxy-5-benzamidovaleryl)malonate (XVIb). A mixture of 11.5 g. of 3-methoxy-5-benzamidovaleric acid in 11.5 cc. of reagent ether (containing 0.5% pyridine) and 11.5 cc. of thionyl chloride was shaken until solution was complete (ten minutes), then allowed to stand ten minutes more. Volatile material was removed *in vacuo* (bath 40°) and the evaporation repeated with 50 cc. of benzene. The residual acid chloride, dissolved in 50 cc. of toluene and 10 cc. of acetone, was added dropwise to a vigorously stirred solution of 13.6 g. of magnesium methoxide in 100 cc. of 43.5% dibenzyl malonate in toluene, and 30 cc. of toluene over a period of 20 minutes, then stirred ten minutes longer. The mixture was acidified with 9.5 cc. of acetic acid and 85 cc. of 3 *N* hydrochloric acid was added. The separated organic layer was washed with water and evaporated to dryness *in vacuo*. The residue, dissolved in 120 cc. of ethyl acetate and 120 cc. of heptane, was stirred with 120 cc. of 10% cupric acetate for about 15 hours. The *copper salt* was collected and washed with 1:1 ethyl acetate-heptane and water; yield, 12.3 g. (50%), m.p. 143–146°. Recrystallization of a sample from ethyl acetate-heptane gave blue-green crystals, m.p. 145–147°.

Anal. Calc'd for $C_{60}H_{60}CuN_2O_{14}$: C, 65.9; H, 5.49; N, 2.56; Cu, 5.85; ash, 7.32.
Found: C, 66.2; H, 5.84; N, 2.88; Cu, 5.85; ash, 7.27.

The *free keto ester* was recovered quantitatively, by use of ethyl acetate and excess dilute hydrochloric acid, as an oil which gave a red ferric chloride test.

Similarly, 8.4 g. of 3-methoxy-5-phthalimidovaleric acid gave 10.6 g. (64%) of *benzyl (3-methoxy-5-phthalimidovaleryl)malonate* (XVIa) as an oil *via* the *green copper salt*, m.p. 109–111°.

Anal. Calc'd for $C_{62}H_{58}CuN_2O_{16}$: C, 64.6; H, 5.04; N, 2.44.
Found: C, 64.3; H, 5.39; N, 2.46.

From 5 g. of 5-phthalimido-2-pentenoic acid (VI) was obtained 5 g. (45%) of the *copper derivative* of *benzyl (5-phthalimido-2-pentenoyl)malonate*, m.p. 162–165°.

Anal. Calc'd for $C_{60}H_{50}CuN_2O_{14}$: C, 66.4; H, 4.61; N, 2.58.
Found: C, 66.0; H, 4.99; N, 2.66.

1-Phthalimido-3-methoxy-5-hexanone (XVIIa). A solution of 10.6 g. of XVIa in 30 cc. of ethyl acetate was shaken with Norit, filtered, washed with 20 cc. of ethyl acetate, and the filtrate added to a suspension of 1.5 g. of 10% palladium-charcoal in 30 cc. of acetic acid. The mixture was shaken with hydrogen at 2–3 atm. for two hours when hydrogenation was complete. The catalyst was removed by filtration through Celite and the filtrate refluxed on the steam-bath until carbon dioxide evolution was complete (45 minutes). The solution, washed with water, aqueous sodium bicarbonate, and water, was evaporated to dryness *in vacuo* leaving 5.0 g. (93%) of a colorless oil.

Anal. Calc'd for $C_{15}H_{17}NO_4$: C, 65.4; H, 6.19; N, 5.09; CH_3O, 11.3.
Found: C, 64.6; H, 6.55; N, 4.87; CH_3O, 11.1.

When a solution of this methoxy ketone in alcohol was converted to the 2,4-dinitrophenylhydrazone in the usual manner an orange solution formed at the b.p. which changed to red in one minute. A 97% yield of the *2,4-dinitrophenylhydrazone of XII*, m.p. and mixed m.p. 192–197°, was obtained. Thus methanol is eliminated during the preparation of this derivative.

Similarly, hydrogenolysis of 35.8 g. of XVIb gave 13.7 g. (80%) of *1-benzamido-3-methoxy-5-hexanone* (XVIIb) as a nearly colorless oil.

Anal. Calc'd for $C_{14}H_{19}NO_3$: C, 67.4; H, 7.63; N, 5.62; CH_3O, 12.4.
Found: C, 67.0; H, 8.00; N, 5.43; CH_3O, 12.0.

When the methoxy ketone was converted to the 2,4-dinitrophenylhydrazone in the usual manner the methoxyl group was again eliminated as methanol and the derivative of 1-benzamido-3-hexen-5-one was formed. Recrystallization from benzene-heptane gave orange crystals, m.p. 185–188°.

Anal. Calc'd for $C_{19}H_{19}N_5O_5$: C, 57.4; H, 4.78; N, 17.6; CH_3O, 0.0.
Found: C, 57.5; H, 5.06; N, 17.6; CH_3O, 0.0.

1-Phthalimido-3-methoxy-5-hexanone ethylene ketal. Attempts to convert XVIIa to XVIIb *via* 1-amino-3-methoxy-5-hexanone were unsuccessful. Strong acid hydrolysis to remove the phthalyl group (1) led to disruption of the molecule. When XVIIa was treated with one mole of hydrazine, no phthalhydrazide was obtained, whereas with two moles a good yield was obtained indicating that the ketone group reacted first. The ketone was then blocked as follows:

To a solution of 2.00 g. of XVIIa in 10 cc. of benzene was added 0.54 cc. of a solution of 40 mg. of *p*-toluenesulfonic acid in 10 cc. of ethylene glycol. The solution was refluxed under a constant water separator for two hours when reaction was complete. The solution, washed with aqueous sodium bicarbonate and water, was evaporated *in vacuo* leaving 2.12 g. (92%) of product as an oil.

Anal. Calc'd for $C_{17}H_{21}NO_5$: C, 63.9; H, 6.59; N, 4.39.
Found: C, 63.9; H, 6.62; N, 4.36.

With one mole of hydrazine in boiling alcohol a maximum of 0.43 mole of phthalhydrazide was formed indicating that the keto group suffered hydrazinolysis at about the same rate as the phthalyl group. Thus the phthalyl group could not be removed selectively.

The ketal using propylene glycol was prepared in a similar manner in 92% yield as an oil.

Anal. Calc'd for $C_{18}H_{23}NO_5$: N, 4.21. Found: N, 4.48.

With one mole-equivalent of hydrazine this ketal formed a maximum of 9.4% of phthalhydrazide indicating that this ketone blocking group was not as stable towards hydrazinolysis.

Ethyl α,γ-bis-(4-quinazolone-3)acetoacetate. To a solution of 3.15 g. of ethyl 4-quinazolone-3-acetate (18) in 20 cc. of benzene and 2.4 cc. of absolute alcohol was added 0.82 g. of sodium methoxide. The mixture was refluxed one hour during which a thick paste was formed. Acidified with 1.7 cc. of acetic acid and shaken with water, the mixture was filtered from some solid (0.6 g., m.p. >250°) and the filtrate separated. The benzene solution was evaporated *in vacuo*. Crystallization from 5 cc. of alcohol gave 1.4 g. (56%) of solid, m.p. 193–196°. Recrystallization from alcohol resulted in white crystals, m.p. 202–204°.

Anal. Calc'd for $C_{22}H_{18}N_4O_6$: N, 13.7. Found: N, 13.4.

This compound formed a *blue-green copper salt*, m.p. 236–239° dec., from dilute alcohol. It was insoluble in all common solvents.

1,3-Bis-(4-quinazolone-3)acetone. A solution of 1.00 g. of the preceding keto ester in 20 cc. of 6 *N* hydrochloric acid was refluxed for 20 minutes when gas evolution was complete. After ten minutes a white solid had separated. The hydrochloride salt was removed from the ice-cold solution by filtration and digested with 15 cc. of pyridine on the steam-bath for 20 minutes. Diluted with water, the mixture was filtered and the solid washed with

aqueous pyridine; yield, 0.50 g. (60%), m.p. 309–311° dec. No solvent for recrystallization could be found.

Anal. Calc'd for $C_{19}H_{14}N_4O_3$: C, 65.9; H, 4.04; N, 16.2.
Found: C, 65.8; H, 4.46; N, 16.2.

Benzyl acetoacetate. A mixture of 75 cc. of benzyl alcohol (20% excess) and 75 cc. of ethyl acetoacetate was heated in a modified Claisen flask (bath 160–170°) for 30 minutes, distillation of alcohol being essentially complete in 20 minutes. Distillation gave 76 g. (67%) of product, b.p. 156–159° (10 mm.). The forerun was retreated as above and an additional 24 g. (total 89%) of benzyl ester was obtained.

This procedure is a modification of that described by Arndt (14) who recorded a quantitative yield using a 2–1 excess of keto ester; he described b.p. 162–167° (15 mm.). Duplication of his procedure gave a 65% yield.

n-Butyrylacetone. A mixture of 17.5 cc. (30% excess) of benzyl acetoacetate, 8.6 g. of magnesium methoxide, and 75 cc. of toluene was stirred for about ten minutes when solution was complete. Then 7.8 g. of *n*-butyryl chloride in 25 cc. of toluene was added dropwise over a period of ten minutes with vigorous stirring. After being stirred an additional ten minutes, the mixture was acidified with 9 cc. of acetic acid, then washed with dilute hydrochloric acid and water. The residue remaining after evaporation to dryness *in vacuo* was dissolved in 75 cc. of ethyl acetate and treated with Norit. The filtrate was added to a suspension of 3 g. of 10% palladium-charcoal in 20 cc. of acetic acid and shaken with hydrogen at 2–3 atm. Reduction was complete in 20 minutes. The filtered solution was refluxed 40 minutes when carbon dioxide evolution was complete. The solution was washed thoroughly with excess sodium bicarbonate, then twice with water. Distillation from a modified Claisen flask gave 4.9 g. (49%) of product as a colorless oil, b.p. 170–175°, which formed a *blue copper salt*, m.p. 163–165°. The forerun contained some diketone.

Weygand and Baumgertel (15) have recorded b.p. 175° and m.p. 164–165° for the copper salt.

Treatment of the sodio derivative of benzyl acetoacetate, prepared from the keto ester and sodium hydride in benzene, with an excess of *n*-butyryl chloride gave a 60% yield of the *copper derivative* of *n*-butyrylacetone, m.p. 160–162.°

Similarly, the acid chloride from 4.6 g. of 5-benzamidovaleric acid was condensed with the magnesio derivative to give 2.4 g. (39%) of the *copper salt of 8-benzamido-2,4-octanedione*, m.p. 209–210°. Recrystallization from Methyl Cellosolve-water gave blue crystals, m.p. 215–216°.

Anal. Calc'd for $C_{30}H_{36}CuN_2O_6$: N, 4.79. Found: N, 4.93.

The *free diketone* was obtained as white crystals, m.p. 72–73° in 87% recovery by decomposition with chloroform and dilute hydrochloric acid, then recrystallization from benzene-heptane. This compound gave a red ferric chloride test.

Anal. Calc'd for $C_{15}H_{19}NO_3$: C, 68.8; H, 7.33; N, 5.37.
Found: C, 69.1; H, 7.59; N, 5.40.

6-Methoxy-8-benzamido-2,4-octanedione. 3-Methoxy-5-benzamidovaleric acid (3.6 g.) was converted to the diketone as in the previous experiment. The *copper salt* formed blue crystals, m.p. 168–170°; yield, 1.4 g. (31%).

Anal. Calc'd for $C_{32}H_{40}CuN_2O_8$: C, 59.7; H, 6.27; N, 4.34; CH_3O, 9.63.
Found: C, 59.6; H, 6.45; N, 4.07; CH_3O, 8.15.

The copper salt was decomposed, the *free diketone* being obtained as a white solid, m.p. 75–76°.

Ethyl benzyl malonate. A mixture of 90 cc. of benzyl alcohol, 262 cc. of ethyl malonate (2:1 ratio), 180 cc. of toluene, and 3.1 g. of sodium methoxide was distilled through a Vigreux column until the vapors reached 95° which required 25 minutes. The residue was acidified with 5 cc. of acetic acid and portioned between ethyl acetate and water. The organic layer, dried with sodium sulfate, was evaporated *in vacuo* and the residue distilled through a Vigreux column. After a forerun, b.p. 70–115° (1 mm.), the product distilled at 138–139° (1 mm.); yield, 125 g. (66%).

Anal. Calc'd for $C_{12}H_{14}O_4$: C, 64.9; H, 6.34.
Found: C, 65.0; H, 6.73.

With only a 30% excess of ethyl malonate the yield was 45% while with a 1:1 ratio the yield was 35%. This compound has been mentioned in the patent literature (16) as being prepared from benzyl acetate and ethyl oxalate; b.p. 145° (4 mm.).

Ethyl n-butyrylacetate. To a vigorously stirred solution of 20 cc. (22.2 g.) of ethyl benzyl malonate and 8.6 g. of magnesium methoxide in 75 cc. of toluene was added dropwise over a period of 20 minutes a solution of 11.5 cc. of *n*-butyryl chloride in 25 cc. of toluene. The reaction mixture was worked up as described for *n*-butyrylacetone using 3 g. of 10% palladium-charcoal in the reduction; yield, 8.8 g. (56%) of a colorless oil, b.p. 88–90° (10 mm.) which gave a deep red ferric chloride test. The *copper derivative* formed blue crystals, m.p. 123–124°.

Abromovitch and Hauser (17) have recorded b.p. 94–95° (15 mm.) for this keto ester prepared another way and m.p. 124–125° for the copper salt.

Ethyl (5-benzamidovaleryl)acetate. The acid chloride from 13.8 g. of 5-benzamidovaleric acid was condensed with 43 cc. of ethyl benzyl malonate as in the preceding experiment. The product, isolated *via* its *copper salt*, m.p. 174–176° dec., was obtained as a colorless oil in 38% yield which solidified to white crystals, m.p. 45°.

Anal. Calc'd for $C_{16}H_{21}NO_4$: C, 65.9; H, 7.28; N, 4.82.
Found: C, 66.0; H, 7.44; N, 4.95.

4-Quinazolone-3-acetyl chloride hydrochloride. A mixture of 7 g. of pulverized 4-quinazolone-3-acetic acid (18), 35 cc. of reagent ether (containing 0.5% pyridine), and 35 cc. of thionyl chloride was shaken for 30 minutes. The acid rapidly dissolved and the product separated. The mixture was diluted with reagent ether and filtered. The product, washed with ether, was dried *in vacuo;* yield, 8.3 g. (94%), m.p. 230° dec.

This acid chloride was characterized as the *anilide* by treating a suspension in cold acetone with aniline; yield, 62%, m.p. 237–239°. Recrystallization from alcohol gave white crystals, m.p. 243–245°.

Anal. Calc'd for $C_{16}H_{13}N_3O_3$: C, 68.8; H, 4.68; N, 15.1.
Found: C, 68.7; H, 5.08; N, 15.4.

Benzyl (4-quinazolone-3-acetyl)malonate. A mixture of 1550 cc. of 42.2% dibenzyl malonate in toluene, 193 g. of magnesium methoxide, and 500 cc. of toluene was stirred until solution was essentially complete (ten minutes), then cooled in an ice-bath. When the temperature dropped to 8°, 193 g. of 4-quinazolone-3-acetyl chloride hydrochloride was added. The mixture was stirred vigorously for one hour in the ice-bath, then one hour with the ice-bath removed. The mixture was acidified with 390 cc. of acetic acid, diluted with 1200 cc. of water, and stirred until solution of the salts was complete. The organic layer was separated, washed with 1 l. of water, stirred with 700 cc. of 10% aqueous cupric acetate for five minutes, and diluted with 800 cc. of heptane. The copper salt was collected and washed with 1:1 ethyl acetate-heptane. The moist cake was stirred with 750 cc. of water, 400 cc. of chloroform, and 135 cc. of 12 *N* hydrochloric acid until solution was complete and the organic layer was no longer green. The aqueous layer was extracted once more with 100 cc. of chloroform. The combined extracts were evaporated to dryness *in vacuo* to give 155 g. (44%) of a yellow oil.

The intermdiate *copper salt,* on recrystallization from ethyl acetate, formed light green needles, m.p. 210–211° dec.

Anal. Calc'd for $C_{54}H_{42}CuN_4O_{12}$: C, 64.7; H, 4.23; N, 5.59; Cu, 6.35.
Found: C, 64.6; H, 4.67; N, 5.80; Cu, 6.72.

Similarly, *ethyl (4-quinazolone-3-acetyl)malonate* was obtained in 49% yield as an oil by use of ethyl magnesiomalonate. The copper derivative formed blue crystals, m.p. 224° dec.

Anal. Calc'd for $C_{34}H_{36}CuN_4O_{12}$: C, 53.3; H, 4.73; N, 7.32; Cu, 9.61.
Found: C, 53.4; H, 5.00; N, 7.66; Cu, 9.47.

Benzyl phthalimidoacetylmalonate. Addition of the acid chloride from 40 g. of phthalimidoacetic acid (19) in 160 cc. of toluene to a stirred solution of 240 cc. of 46.3% dibenzyl malo-

nate in toluene, 70 cc. of toluene, and 58 g. of magnesium methoxide gave an oil as described for XVIb. The oil, dissolved in 400 cc. of ethyl acetate, was shaken with 250 cc. of 10% cupric acetate. The *copper salt*, m.p. 226–230°, was collected and washed with ethyl acetate, then methanol. A sample was recrystallized from Methyl Cellosolve to give blue-green crystals, m.p. 228–230°.

Anal. Calc'd for $C_{54}H_{40}CuN_2O_{14}$: N, 2.79. Found: N, 3.04.

The remainder of the wet copper salt was decomposed with 150 cc. of chloroform and 120 cc. of 4 *N* hydrochloric acid to give 72 g. (78%) of a solid which formed white crystals from methanol, m.p. 111–113°.

Anal. Calc'd for $C_{27}H_{21}NO_7$: C, 68.8; H, 4.49; N, 2.97.
Found: C, 69.3; H, 4.53; N, 2.99.

Benzyl (4-quinazolone-3-acetyl)acetate. (*A*). A mixture of 158 g. of benzyl (4-quinazolone-3-acetyl)malonate and 790 cc. of water was refluxed vigorously for one hour when gas evolution became slow. The mixture was diluted with 790 cc. of alcohol and cooled to 3°; yield, 75 g. (65%), m.p. 124–130°. A mixture with preparation *B* gave no depression.

Similarly, *ethyl (4-quinazolone-3-acetyl)acetate* was prepared from ethyl (4-quinazolone-3-acetyl)malonate in 49% yield, m.p. 122–125°. Recrystallization from water gave white crystals, m.p. 123–125°, which gave a red ferric chloride test.

Anal. Calc'd for $C_{14}H_{14}N_2O_4$: C, 61.3; H, 5.14; N, 10.2.
Found: C, 61.3; H, 5.67; N, 10.3.

Attempts to prepare this compound by alkylation of sodio 4-quinazolone with ethyl γ-bromo- or γ-chloro-acetoacetate did not give any of the desired product although reaction was vigorous.

(*B*). Trans-esterification of ethyl (4-quinazolone-3-acetyl)acetate with benzyl alcohol as described for benzyl 4-quinazolone-3-acetate proceeded in 39% yield, m.p. 124–127°. Recrystallization from methanol gave white crystals, m.p. 134–136°, which gave a red ferric chloride test.

Anal. Calc'd for $C_{19}H_{16}N_2O_4$: C, 67.9; H, 4.79; N, 8.33.
Found: C, 68.2; H, 5.31; N, 8.61.

The *copper derivative* formed in 81% yield as blue-green crystals, m.p. 214° dec., when an ethyl acetate solution of the keto ester was shaken with aqueous cupric acetate.

Anal. Calc'd for $C_{38}H_{30}CuN_4O_8$: Cu, 8.77; N, 7.63.
Found: Cu, 8.41; N, 7.42.

Benzyl γ-phthalimidoacetoacetate. A mixture of 71 g. of benzyl phthalimidoacetyl malonate and 355 cc. of water was refluxed 30 minutes when gas evolution became slow. On cooling the oil solidified; yield 50 g. (97%), m.p. 80–83°. Recrystallization from alcohol afforded white crystals, m.p. 87–87.5°, which gave an orange-red ferric chloride test.

Anal. Calc'd for $C_{19}H_{15}NO_5$: C, 66.7; H, 4.48; N, 4.15.
Found: C, 67.1; H, 4.79; N, 4.20.

Benzyl (3-methoxy-5-phthalimidovaleryl)acetate. A mixture of 12.2 g. of benzyl (3-methoxy-5-phthalimidovaleryl)malonate, 60 cc. of water, and 30 cc. of dioxane was refluxed for two hours, then diluted with several volumes of water and extracted with ethyl acetate. The extract was washed with water, then diluted with two volumes of heptane, and stirred with 45 cc. of 10% cupric acetate for 20 hours. The *copper derivative* was collected; yield, 5.6 g. (56%), m.p. 94–96° dec. It seemed solvated and could not be recrystallized. The copper derivative (5.5 g.) was decomposed with chloroform and dilute hydrochloric acid in the usual manner. The keto ester was obtained as a light yellow oil with 90% recovery.

Anal. Calc'd for $C_{23}H_{23}NO_6$: C, 67.3; H, 5.67; N, 3.41; CH_3O, 7.57.
Found: C, 67.5; H, 6.14; N, 3.26; CH_3O, 7.72.

3-(2,4-Diketo-8-phthalimidoöctyl)-4-quinazolone. A mixture of 290 mg. of sodium hydride and 40 cc. of *tert*-butyl alcohol was refluxed ten minutes when solution was complete. To the solution was added 4.0 g. of benzyl (4-quinazolone-3-acetyl)acetate (XXIc). The mixture was refluxed on the steam-bath for 20 minutes during which the sodio derivative sepa-

rated as the keto ester dissolved. The mixture was evaporated to dryness *in vacuo*. The keto benzyl ester, XXIc, can be recovered in 85% yield at this point showing that little or no decomposition or alcoholysis took place during the preparation.

The dry sodio derivative was suspended in 40 cc. of Diethyl Carbitol and shaken with a solution of 3.2 g. of 5-phthalimidovaleryl chloride in 30 cc. of Diethyl Carbitol for 20 minutes when solution was complete. The solution was divided in half and treated as follows:

(*A*). One-half of the acylation mixture was diluted with several volumes of water and extracted with ethyl acetate. The combined extracts were evaporated to dryness *in vacuo*. No unchanged XXIc could be recovered at this point showing near complete acylation. The residue, dissolved in 25 cc. of acetic acid, was shaken with 0.5 g. of Norit for ten minutes and filtered. The combined filtrate and washings were added to 1 g. of 10% palladium-charcoal and shaken with hydrogen at atmospheric pressure until reduction was complete (2½ hours). The mixture was filtered through Celite and the combined filtrate and washings were refluxed ten minutes when carbon dioxide evolution was complete. The solution was evaporated to dryness *in vacuo*, the residue dissolved in 20 cc. of ethyl acetate and shaken with 10 cc. of 10% cupric acetate. The *copper derivative* was collected and washed with ethyl acetate, then methanol; yield, 0.30 g. (11%), m.p. 228° dec. A mixture with this same copper salt prepared by a Claisen condensation (1) gave no depression in m.p.

(*B*). The other half of the acylation mixture was stirred with 4 g. of anhydrous potassium carbonate in a 50°-bath for four hours, then worked up as in part *A;* yield, 530 mg. (19%), m.p. 229° dec.

Treatment with potassium carbonate at 100° for four hours gave a yield of 4.7% while at 25° for 20 hours the yield was 15%. When the acylation was carried out in acetone instead of Diethyl Carbitol as in *A*, no copper salt was obtained.

Acylation of the sodio derivative from 2 g. of XXIc in acetone with *n*-butyryl chloride and work up as in *A* gave 0.23 g. (12%) of the *copper derivative* of *3-(2,4-diketoheptyl)-4-quinazolone*, m.p. 252° dec., whereas acylation in toluene gave a 2.5% yield of copper derivative and 50% of the ester was recovered unchanged.

Anal. Calc'd for $C_{30}H_{30}CuN_4O_6$: Cu, 10.5; N, 9.23.

Found: Cu, 10.4; N, 9.18.

3-(2,4-Diketo-6-methoxy-8-phthalimidoöctyl)-4-quinazolone. The sodio derivative of XXIc was acylated with 3-methoxy-5-phthalimidovaleryl chloride according to procedure *A* of the previous experiment; yield, 2.4% of the *copper derivative* as blue crystals, m.p. 218° dec.

Anal. Calc'd for $C_{56}H_{44}CuN_6O_{12}$: N, 8.55; Cu, 6.47.

Found: N, 8.07; Cu, 6.47.

By acylation of the sodio derivative in toluene, absolute ether, or Diethyl Cellosolve no copper derivative of the diketone could be isolated, whereas in purified dioxane the yield was 4.6%. The best yield obtained, 6.2%, was by use of the lithium salt of XXIc, prepared with lithium methoxide as described in procedure *A*. When lithium carbonate was added after acylation as in procedure *B*, no diketone was obtained after 90 minutes at 50° or 20 hours at 25°. Decomposition of the copper salt with chloroform and 1 *N* hydrochloric acid gave a 90% recovery of *free diketone*, m.p. 105–108°.

When the sodio derivative of benzyl γ-phthalimidoacetoacetate was prepared and acylated with 3-methoxy-5-phthalimidovaleryl chloride according to method *A*, no copper salt of a diketone could be isolated. Similar results were obtained in three attempts to acylate the magnesio derivative of benzyl (3-methoxy-5-phthalimidovaleryl)acetate.

Monoethylene ketal of 4-quinazolone-3-acetylacetone. A mixture of 3.0 g. of the diketone, XXIV, 2.3 cc. of ethylene glycol, 30 cc. of benzene, 30 cc. of butanol, and 2.35 g. of *p*-toluenesulfonic acid was refluxed under a constant water separator for one hour when water separation was complete. If only a catalytic amount (7 mg.) of the sulfonic acid was used, no water separation occurred. The reaction mixture was washed twice with water, then with two 10-cc. portions of ice-cold 3% alkali when a negative ferric chloride test was obtained. The organic layer was washed with water until neutral, then evaporated *in vacuo;* yield, 2.14 g. of a semi-solid. Nitrogen analysis of the crude product indicated only a monoketal

had formed. It was purified by recrystallization from benzene-heptane to give white crystals, m.p. 85–87°.

Anal. Calc'd for $C_{17}H_{20}N_2O_5$: N, 8.46.

Calc'd for $C_{15}H_{16}N_2O_4$: N, 9.71. Found: N, 9.61.

The *monopropylene ketal of 4-quinazolone-3-acetylacetone* formed in the same yield and was obtained as an oil.

Anal. Calc'd for $C_{16}H_{18}N_2O_4$: N, 9.28. Found: N, 9.21.

Similarly, β-mercaptoethanol gave a 75% yield of crude product which was predominately a monoketal.

Anal. Calc'd for $C_{17}H_{20}N_2O_3S_2$: S, 17.6.

Calc'd for $C_{15}H_{16}N_2O_3S$: S, 10.5. Found: S, 11.6, 11.2.

Recrystallization of 1.0 g. of crude product gave 0.80 g. of pure product, m.p. 113–115°, indicating that one of the two possible monoketals predominated.

Anal. Calc'd for $C_{15}H_{16}N_2O_3S$: C, 59.2; H, 5.27; N, 9.21.

Found: C, 58.9; H, 5.45; N, 9.17.

Ethylene ketal of 3-(2,4-diketo-8-phthalimidoöctyl)-4-quinazolone. A mixture of 1.0 g. of diketone, 0.39 cc. of ethylene glycol, 0.45 g. of *p*-toluenesulfonic acid, 10 cc. of benzene, and 10 cc. of butanol was refluxed under a constant water separator for one hour when reaction was complete. The alkali-insoluble fraction consisted of 1.13 g. of an oil.

A solution of 840 mg. of the ketal in 10 cc. of alcohol was refluxed with 0.79 cc. of 10% hydrazine hydrate in alcohol for 30 minutes. After acidification with 0.32 cc. of 12 *N* hydrochloric acid, the solution was refluxed 15 minutes, then allowed to stand 15 hours at 3°. No phthalhydrazide separated.

SUMMARY

The acid sensitive 1-phthalimido- and 1-benzamido-3-methoxy-5-hexanones have been synthesized from the corresponding derivatives of 3-methoxy-5-aminovaleric acid by use of dibenzylmalonate. Twenty-five attempts to Claisen condense either of these two ketones with three different esters of 4-quinazolone-3-acetic acid failed to yield any of the expected diketones.

3-(2,4-Diketo-6-methoxy-8-phthalimidoöctyl)-4-quinazolone has been obtained in a maximum of 6.2% yield by the acylation of benzyl (4-quinazolone-3-acetyl) acetate with 3-methoxy-5-phthalimidovaleryl chloride. The phthalyl group could not be removed from this diketone without side reactions.

Benzyl acetoacetate and ethyl benzyl malonate have been found to be useful reagents for the synthesis of 2,4-diones and γ-alkyl-β-keto esters, respectively.

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