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

AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. XI. SYNTHESIS OF 3-[β-KETO-γ-(3- AND 4-HYDROXYMETHYL-2-PYRROLIDYL)PROPYL]- 4-QUINAZOLONES

B. R. BAKER, ROBERT E. SCHAUB, AND JAMES H. WILLIAMS

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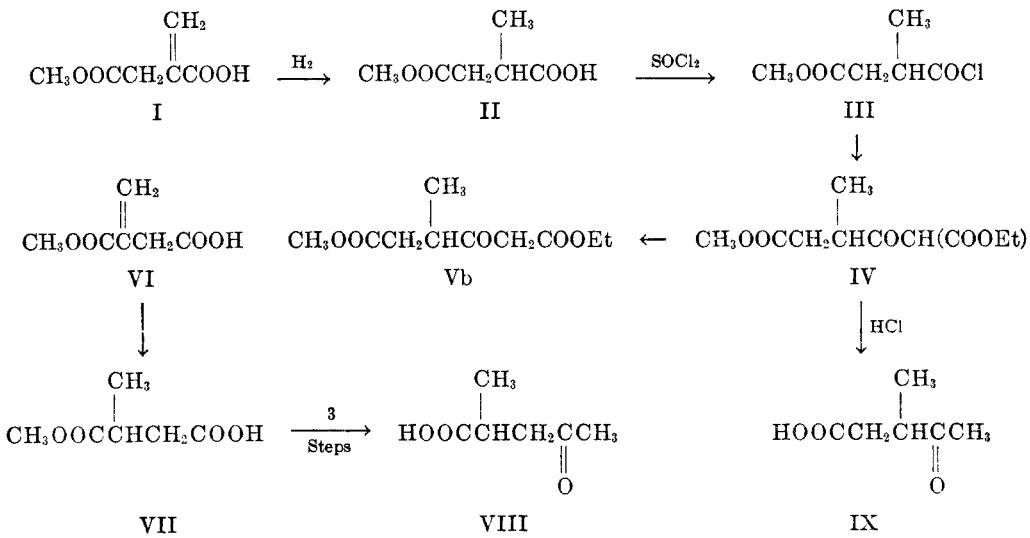
The two possible hydroxymethylpyrrolidine structures (XLV and XLVI) for the Hydrangea alkaloid (1) have now been synthesized *via* the requisite 2-pyrrolidineacetic acids, XLIII. It was found that neither of these two compounds had the alkaloid structure and they were inactive as antimalarials at 500 times the dose required for the alkaloid.

The recent commercial availability of itaconic acid and its esters coupled with the observation that dimethyl itaconate adds methanol to form dimethyl methoxymethylsuccinate (XXVII) (2) made these appear to be attractive starting materials. Some of the key reactions were first established by use of a desoxy series to avoid once again the added complication of an hydroxyl or methoxyl group.

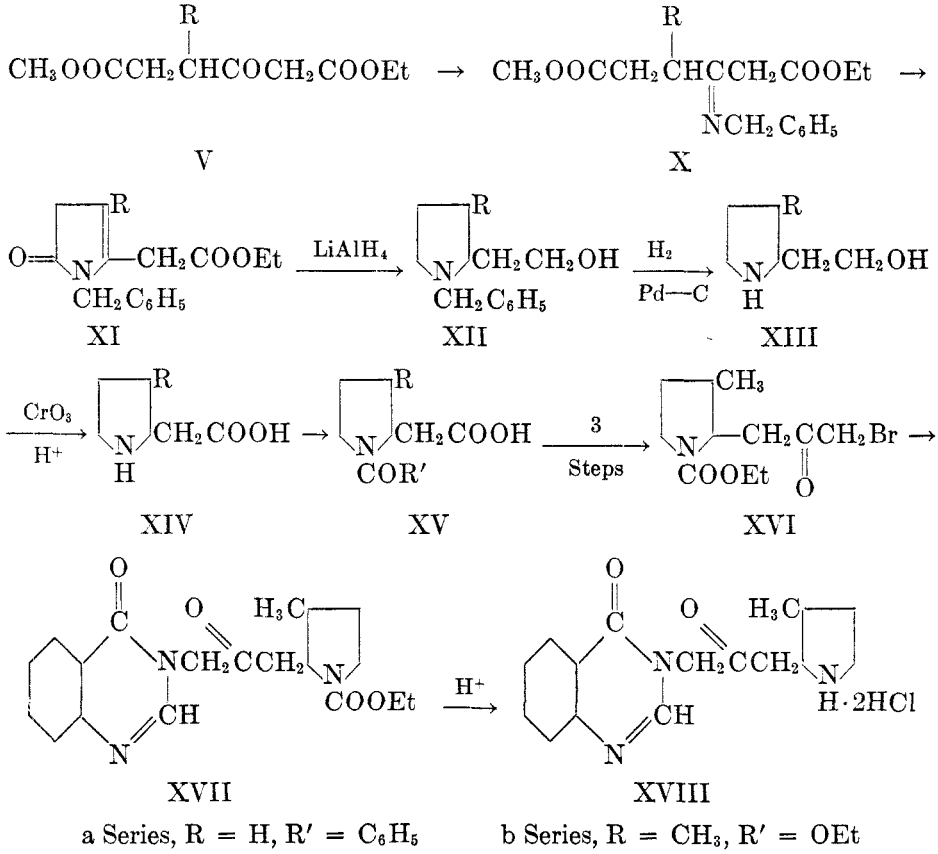
Partial esterification of itaconic acid or ring opening of itaconic anhydride with methanol yields the same crystalline monomethyl ester, presumed to be the (β)-methyl ester, I, by Anschütz and Drugman (3). Hydrogenation of the double bond gave a 97% yield of oily monoester of methylsuccinic acid, II,[1] which was converted to the acid chloride, III, in 95% yield. The latter was characterized as its crystalline methylanilide, m.p. 100–101°. Condensation of the acid chlo-



[1] Partial esterification of methylsuccinic acid, partial hydrolysis of methylsuccinic diester, or reaction of methylsuccinic anhydride with alcohols has been reported to give a mixture of both possible esters (4).

ride with magnesiomalonic ester gave an 85% yield of the keto malonate, IV. Strong acid hydrolysis of the latter resulted in a 72% yield of β-methyllevulinic acid (IX), m.p. 27–30°, thus rigidly confirming the structure previously assigned to the monomethyl ester, I, since the isomeric α-methyl hydrogen itaconate (VI) would yield α-methyllevulinic acid (VIII) by this sequence.[2] Treatment of the keto malonate, IV, with boiling water caused loss of one carbethoxy group with resultant formation of the requisite keto acetate, Vb, necessary for formation of XIb.

The key step for the synthesis of the necessary 2-pyrrolidylethanols would be the lithium aluminum hydride reduction of the pyrrolinone ester, XI. Ruggli and Maeder (6) have described the preparation of the crystalline pyrrolinone ester, XIa. It was considered advisable to try the reduction on this known compound since further processing should lead to a crystalline derivative of pyrrolidyl-2-acetic acid, XVa, which has only one assymetric center and could be readily characterized. These authors treated β-ketoadipic ester, Va, with benzylamine in cold alcohol for 12 hours and isolated the imine, Xa by a high vacuum distilla-



a Series, R = H, R′ = C_6H_5 b Series, R = CH_3, R′ = OEt

[2] β-Methyllevulinic acid has been reported to melt at 31°, whereas α-methyllevulinic acid is an oil melting below 0° (5).

tion. Cyclization to the pyrrolinone, XIa, by a one to two day treatment with 40 volumes of aqueous alcoholic ammonia was reported to give an over-all yield of 85%. Duplication of this procedure gave only a 45% yield which could be increased to 61% if the intermediate imine was not distilled.

A more rapid and convenient procedure has now been devised. The imine, Xa, was prepared in 30 minutes by constant removal of water from the components in boiling benzene. Cyclization was effected by treating this benzene solution with alcoholic sodium ethoxide for ten minutes. The over-all yield was 91% of crystalline material.

Treatment of the pyrrolinone, XIa, with lithium aluminum hydride caused reduction at three sites, the lactam, ester, and pseudo imine double bond with the formation of 1-benzylpyrrolidine-2-ethanol, b.p. 115° (0.1 mm.) in 47% yield. The N-benzyl group was readily removed by hydrogenolysis. The resultant pyrrolidine, XIIIa, was oxidized with chromic acid in dilute sulfuric acid to the amino acid, XIVa, characterized as its benzoyl derivative, XVa.

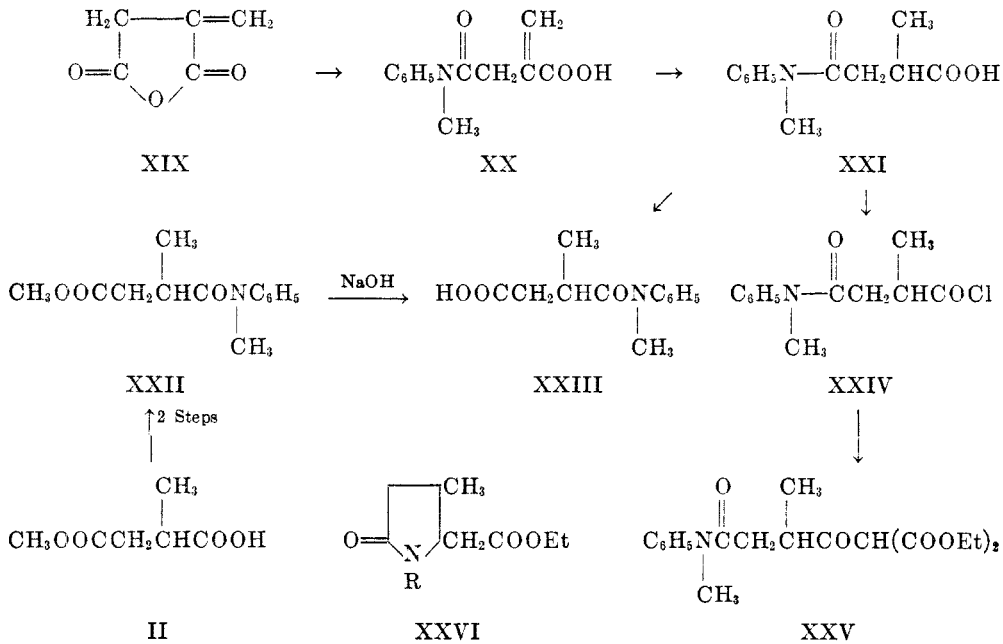
The same sequence of reactions proceeded smoothly from Vb to XVb with R = CH_3. The pyrrolidine acid, XVb, was converted to the bromo ketone, XVI, *via* the acid chloride and diazoketone, then condensed with 4-quinazolone to give the crystalline carbethoxylated 4-quinazolone, XVII, in 76% over-all yield from XVb. Short 48% hydrobromic acid hydrolysis of the latter gave the desired model compound, XVIII, isolated as the dihydrochloride in 80% yield.

Another method for the preparation of the pyrrolidone, XXVI, was also investigated. In this synthesis a β-amino adipic ester was desired which could be cyclized to XXVI rather than form XXVI by the hydrogenation of the pyrrolinone, XI, which takes place with difficulty (6). In addition methanol might be added to the double bond of the ester of XX in order to obtain an intermediate of the methoxymethyl series. Reaction of methylaniline with itaconic anhydride, XIX, rapidly took place to give an 81% yield of a pure anilide, XX, which was hydrogenated to XXI in 92% yield. The structures of the monoanilides, XX and XXI, were proven to be as indicated by the fact that XXI was isomeric with the (α)-monoanilide, XXIII, prepared as indicated from the unequivocal (β)-methyl hydrogen methylsuccinate, II, *via* the acid chloride and ester anilide, XXII.[3] That the (α)-anilide, XXI and (β)-anilide, XXIII, were truly isomeric monoanilides of methylsuccinic acid was shown by conversion to the same dianilide *via* their respective acid chlorides by treatment with methylaniline. These acid chlorides were unstable at 25° and were prepared at 0°.

An unusually facile rearrangement of the (β)-anilide, XXI, to the (α)-anilide, XXIII, was observed at 100°. In 30 minutes about one-half of the (β)-anilide, m.p. 78°, was rearranged to the (α)-anilide, m.p. 161°. However, the (β)-anilide was stable at room temperature as the solid or in solution. If precautions were observed in concentration of solutions of the (β)-anilide (XXI), no difficulty was

[3] A second structure proof for the monomethylanilide of itaconic acid, m.p. 116–118°, was obtained by conversion of (β)-methyl hydrogen itaconate, I, to the acid chloride, XXXVI, and methylanilide which on saponification gave the isomeric N-methyl itacon-(α)-anilic acid, m.p. 124–125°.

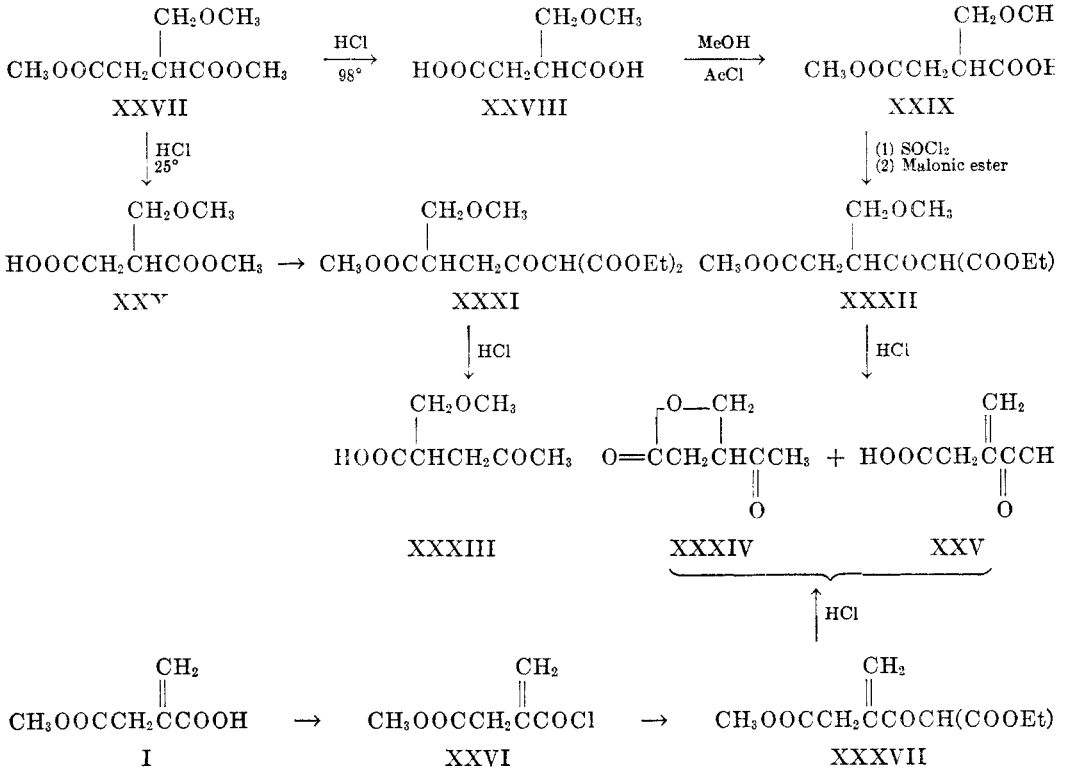
experienced in preparation of this compound. This approach was abandoned when it was found that the acid chloride, XXIV, failed to condense with magnesiomalonic ester under the usual conditions to give any of the keto malonate, XXV.



Condensation of (β)-methyl hydrogen itaconate (I) with magnesiomalonic ester *via* its acid chloride, XXXVI, gave the methylene keto malonate, XXXVII. This compound rapidly reacted with methanol in the presence of a catalytic amount of sodium methoxide with disappearance of the double bond. Instead of the desired methoxy keto malonate, XXXII, being formed, a more complex, unidentified product, b.p. 200° (1 mm.) was formed.

Hot acid hydrolysis of the methylene keto malonate, XXXVII, gave a mixture of β-methylenelevulinic acid, XXXV, and its lactonized derivative, β-acetobutyrolactone, XXXIV, which were converted to their respective 2,4-dinitrophenylhydrazones and readily separated on the basis of the insolubility of the lactone 2,4-dinitrophenylhydrazone in aqueous sodium bicarbonate. The ratio of lactone to acid was 65–25 and was duplicatable within 2%. This lactone can form only when the methylene group is β- to the carboxyl group again confirming the structures assigned. When a mixture of the monoesters of methoxymethylsuccinic acid, XXIX and XXX, were converted to a mixture of the keto malonates, XXXI and XXXII, then hydrolyzed under the identical conditions used for XXXVII, three 2,4-dinitrophenylhydrazones were obtained, namely those of α-methoxymethyllevulinic acid (XXXIII), β-methylenelevulinic acid (XXXV), and β-acetobutyrolactone (XXXIV). Methanol was quantitatively eliminated under these conditions with the methoxyl group β to a ketone group, a phenom-

enon observed previously with other β-methoxyketones (7). The β-acetobutyrolactone 2,4-dinitrophenylhydrazone was again readily separated by virtue of its insolubility in aqueous sodium bicarbonate. The percent of lactone isolated



was then used to determine the percent of the keto malonate, XXXII, in the mixture, based on the assumption that 65% of the crude 2,4-dinitrophenylhydrazone should be formed from pure XXXII.

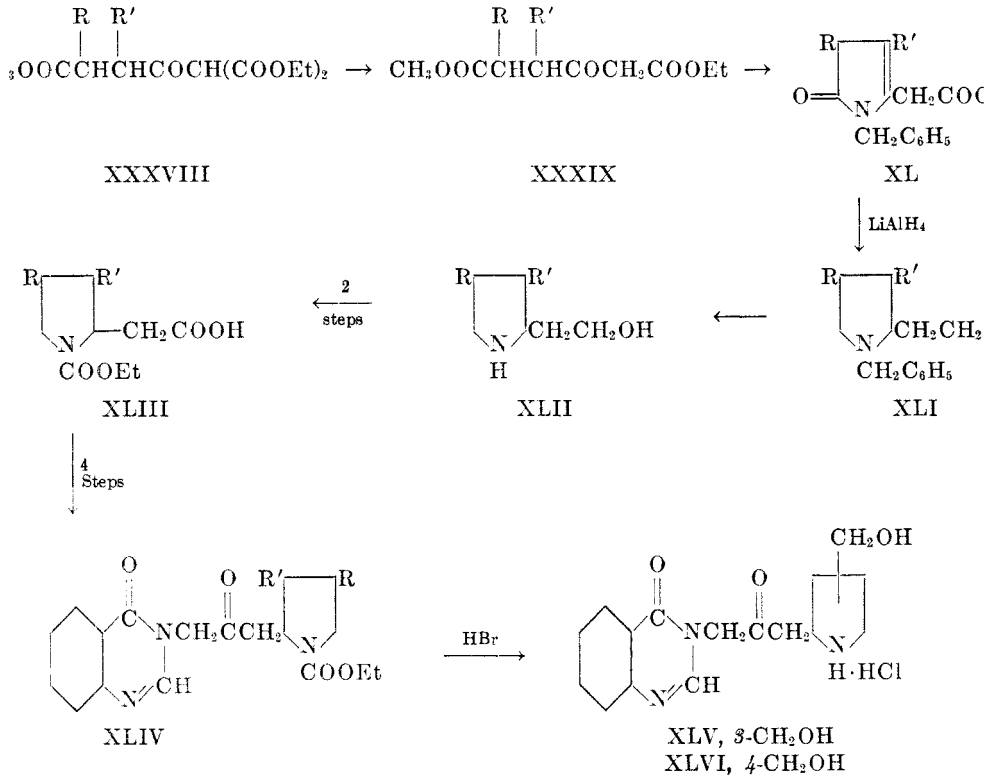
When dimethyl methoxymethylsuccinate was treated with one equivalent of alkali at room temperature, the monoester fraction isolated was found to assay 12% (β)-ester (XXIX) and 88% (α)-ester (XXX) (by difference). Treatment of methoxymethylsuccinic acid, XXVIII, with acetyl chloride gave a 99% yield of anhydride which was opened up to a monoester mixture in 96% yield that assayed 49%(β)-ester (XXIX) and 51% (α)-ester (XXX).

Palomaa, Lehtimäki, and Valkola (8) have reported the relative rates of esterification of a series of methoxy acids, $CH_3O(CH_2)_nCOOH$, where n was 1–8, as well as the rates of acid hydrolysis of their esters. They observed that when n = 3 the rate of esterification was 2.5 times that of n = 2 while the ratio of the rate of acid hydrolysis of the respective esters was 2.8 to 1. Inspection of the structure of methoxymethylsuccinic acid (XXVIII) shows that n = 2 for the (α)-carboxyl and n = 3 for the (β)-carboxyl. The influence of the carboxyl groups should cancel out. However, the methoxymethyl group should, in addition, sterically hinder

the reactions of the (α)-carboxyl more than the (β)-carboxyl, thus making the ratio even more favorable towards selectivity. When methoxymethylsuccinic acid (XXVIII) was partially esterified by short boiling in methanol with acetyl chloride as a catalyst, the monoester fraction, obtained in 43% yield, was found to assay 97% (β)-ester (XXIX) and only 3% (α)-ester (XXX). This method was then developed on a preparative scale for the keto malonate, XXXII.

On the other hand when dimethyl methoxymethylsuccinate (XXVII) was treated with 6 *N* hydrochloric acid at room temperature for three hours, the monoester fraction, obtained in 67% yield, assayed only 3–5% (β)-ester (XXIX) and 97–95% (α)-ester (XXX). In this case the 2,4-dinitrophenylhydrazone of α-methoxymethyllevulinic acid (XXXIII) could be isolated pure from the bicarbonate-soluble fraction.

The pure keto malonates, XXXVIII, were hydrolyzed to the respective keto acetates, XXXIX, by boiling water. Reaction of the keto acetates with ben-



a Series, R = H; R′ = —CH_2OCH_3
b Series, R = —CH_2OCH_3; R′ = H

zylamine proceeded rapidly in one hour with XXXIXb, but required three hours for elimination of water from XXIXa due to the steric hindrance caused by the methoxymethyl group adjacent to the ketone. Cyclization of the imine to XLa with boiling methanolic sodium methoxide caused considerable tar formation,

but prodeeded satisfactorily when cyclized four hours at 25°. In the case of cyclization to XLb, the methanolic sodium methoxide caused almost complete disruption of the molecule, but aqueous-alcoholic ammonia was very satisfactory.

The pyrrolinones, XL, were respectively converted to the carbethoxypyrrolidyl 4-quinazolones, XLIV, in the same manner as described in the desoxy series for preparation of XVII. In both cases XLIV was obtained crystalline, XLIVa, m.p. 94–96° and XLIVb, m.p. 100–102°, and on admixture gave a large depression in the m.p. Five-minute hydrolysis with boiling 48% hydrobromic acid resulted in formation of the final hydroxymethylpyrrolidine isomers of the alkaloid, XLV and XLVI.

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EXPERIMENTAL

(β)-Methyl hydrogen itaconate (I). *(A)*. A mixture of 100 g. of itaconic acid and 200 cc. of acetyl chloride was refluxed on the steam-bath for one hour, solution being complete in 50 minutes. The solution was evaporated to dryness *in vacuo* (bath 70–80°) and the evaporation repeated with two 120-cc. portions of toluene. The residual anhydride solidified on cooling. It was heated on the steam-bath under reflux with 35 cc. of methanol for one hour. Dilution with 200 cc. of benzene and 300 cc. of heptane followed by cooling gave 81.5 g. (73%) of product, m.p. 67–70°.

Anschütz and Drugman have recorded m.p. 67° (3).

(B). To a mixture of 100 g. of itaconic acid and 100 cc. of methanol was added 2 cc. of acetyl chloride with shaking. The mixture was refluxed on the steam-bath for 20 minutes, solution taking place at the boiling point. The excess methanol was immediately evaporated *in vacuo*. The residue was recrystallized from 200 cc. of benzene by the addition of 300 cc. of heptane and chilling to 0°; yield, 93 g. (84%), m.p. 66–68° which gave no depression when mixed with preparation *A*.

(β)-Methyl hydrogen methylsuccinate (II). A solution of 100 g. of I in 100 cc. of methanol was added to a suspension of 2 g. of 10% palladium-charcoal catalyst in 10 cc. of Methyl Cellosolve and shaken with hydrogen at 2–3 atm. until hydrogenation was complete (90 minutes). The filtered solution was evaporated to dryness *in vacuo* leaving a quantitative yield of an oil.

3-Carbomethoxyisobutyryl chloride (III). To 32.5 g. of the above II was added 23 cc. of reagent ether (containing 0.5% pyridine) and 23 cc. of thionyl chloride. The solution was refluxed gently on the steam-bath until gas evolution was essentially complete (15 minutes). Distillation gave 34.9 g. (95%) of a colorless oil, b.p. 84–87° (11 mm.). Treatment of a sample in benzene with methylaniline gave a 91% yield of the N-methylanilide (XXII), m.p. 91–97°. Recrystallization from benzene-heptane afforded white crystals, m.p. 100–101°.

Anal. Calc'd for $C_{13}H_{17}NO_3$: C, 66.3; H, 7.28; N, 5.96.

Found: C, 66.2; H, 7.63; N, 6.18.

Ethyl (3-carbomethoxyisobutyryl)malonate (IV). To the vortex of a stirred solution of 80 g. of magnesium methoxide dimethanolate, and 165 cc. of ethyl malonate in 480 cc. of benzene was added a solution of 87.7 g. of 3-carbomethoxyisobutyryl chloride (III) in 330 cc. of toluene over a period of 40 minutes. The temperature was maintained at 25–30° by immersion of the flask in a cold tap-water bath. After being stirred an additional 15 minutes, the solution was acidified with 57 cc. of acetic acid and washed with 400 cc. of 3 *N* hydrochloric acid, then water. The solvent was removed *in vacuo* and the residue distilled to give 131 g. (86%) of colorless oil, b.p. 123° (0.1 mm.), which gave a red ferric chloride test.

Anal. Calc'd for $C_{13}H_{20}O_7$: C, 54.2; H, 7.00.
Found: C, 54.5; H, 7.17.

A mixture of 5.3 g. of this keto malonate and 25 cc. of 6 *N* hydrochloric acid was refluxed for 35 minutes when carbon dioxide evolution was complete. The solvent was removed *in vacuo* and the residue distilled to give 1.8 g. (72%) of β-methyllevulinic acid (IX), b.p. 95° (0.1 mm.), m.p. 27–30°.[2]

Ethyl (3-carbomethoxyisobutyryl)acetate (Vb). A mixture of 128 g. of the above keto malonate, IV, and 600 cc. of water was refluxed vigorously for three hours, during which carbon dioxide was evolved. The cooled mixture was extracted with two 50-cc. portions of carbon tetrachloride. The solvent was removed *in vacuo* and the residue distilled from a modified Claisen flask. After a forerun, b.p. 54° (0.1 mm.), the product was obtained as a colorless oil, b.p. 98–102° (0.1 mm.), which gave a red ferric chloride test; yield, 60.7 g. (63%). There was a residue of 16 g. (13%) of starting material which was added to the next batch.

Anal. Calc'd for $C_{10}H_{16}O_5$: C, 55.2; H, 7.47.
Found: C, 55.2; H, 7.74.

The *2,4-dinitrophenylhydrazone* formed orange-yellow needles from alcohol, m.p. 92–93°.

Anal. Calc'd for $C_{16}H_{20}N_4O_8$: C, 48.4; H, 5.08.
Found: C, 48.4; H, 5.16.

Ethyl 1-benzyl-5-oxo-2-pyrroline-2-acetate (XIa). Ethyl 3-keto-5-carbomethoxyvalerate (Va), b.p. 102–105° (0.1 mm.), was obtained in 40% yield from methyl succinyl chloride as described for Vb. A solution of 10 g. of Va and 6.1 cc. of benzylamine in 30 cc. of benzene was refluxed under a constant water separator for 30 minutes when the separation of water (0.9 cc.) was complete. Then 31 cc. of absolute alcohol followed by 3.1 g. of sodium methoxide was added. The solution was refluxed for ten minutes, acidified with 4 cc. of acetic acid, washed twice with water, and evaporated to dryness *in vacuo*; yield, 11.8 g. (91%) of an orange oil which rapidly solidified on cooling to nearly white crystals, m.p. 63–70°.

Ruggli and Maeder (6) record m.p. 79°.

Similarly, *ethyl 1-benzyl-3-methyl-5-oxo-2-pyrroline-2-acetate* (XIb), was obtained as an orange oil in 87–91% yield except that imine (Xb) formation required two hours.

Anal. Calc'd for $C_{16}H_{19}NO_3$: C, 70.2; H, 7.02; N, 5.13.
Found: C, 69.6; H, 7.01; N, 5.54.

1-Benzylpyrrolidine-2-ethanol (XIIa). To a refluxing solution of 13 g. of lithium aluminum hydride in 130 cc. of ether was added with shaking a solution of 35.3 g. of XIa in 35 cc. of warm benzene diluted with 130 cc. of reagent ether at such a rate that the solution refluxed briskly (ten minutes). The mixture was refluxed for 30 minutes during which time the initial spongy solid which had separated became granular. The excess hydride was decomposed by the dropwise addition of 40 cc. of ethyl acetate, then 20 cc. of water was added dropwise with ice-cooling to control the vigorous boiling. After the addition of 180 cc. of 10% sodium hydroxide, the mixture was shaken until the aqueous phase became a sludge. The ether was decanted and the sludge extracted with two 100-cc. portions of benzene. The combined organic solutions, dried with magnesium sulfate, were evaporated *in vacuo*. Distillation gave 13 g. (47%) of a colorless oil, b.p. 112–115° (0.05 mm.)

Anal. Calc'd for $C_{13}H_{19}NO$: N, 6.83. Found: N, 6.60.

In the same manner reduction of 85.5 g. of XIb with 21 g. of lithium aluminum hydride gave 40.6 g. (59%) of *1-benzyl-3-methylpyrrolidyl-2-ethanol* (XIIb) as a colorless oil, b.p. 125–135° (0.2 mm.), but mainly at 132°.

Anal. Calc'd for $C_{14}H_{21}NO$: N, 6.38. Found: N, 6.02.

2-Pyrrolidineethanol (XIIIa). A solution of 12 g. of XIIa in 75 cc. of acetic acid was shaken with hydrogen at 2–3 atm. in the presence of 2 g. of 10% palladium-charcoal for five hours when hydrogenation (77%) stopped. After the addition of 6 cc. of 12 *N* hydrochloric acid, the filtered solution was evaporated to dryness *in vacuo*. The residue was dissolved in 12 cc. of water, saturated with potassium carbonate until heavier than chloroform, then extracted with three 50-cc. portions of chloroform. The combined extracts,

dried with magnesium sulfate, were evaporated *in vacuo* (bath 35°). Distillation of the residue in a modified Claisen flask gave 3.2 g. (48%) of a colorless oil, b.p. 105–106° (16mm.).

Hess (9) recorded b.p. 80° (0.04 mm.) for this compound prepared in a different manner.

Similarly, hydrogenation of 40.6 g. of XIIb gave 14.9 g. (62%) of *3-methylpyrrolidine-2-ethanol* (XIIIb) as a colorless oil, b.p. 100–113° (10 mm.), but mainly at 103°.

2-Pyrrolidineacetic acid (XIVa) *and its 1-benzoyl derivative* (XVa). To a solution of 8.4 cc. of 96% sulfuric acid and 5.2 g. of chromic anhydride in 100 cc. of water was added a solution of 3.0 g. of XIIIa in 65 cc. of water. After 23 hours at room temperature a hot solution of 62 g. of barium hydroxide hydrate in 170 cc. of water was added. The mixture was digested on the steam-bath for ten minutes, then filtered and the barium salts washed with two 40-cc. portions of 1% barium hydroxide. The filtrate was treated with Dry Ice and the barium carbonate was removed. The filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 50 cc. of hot absolute alcohol, filtered, and again evaporated to dryness *in vacuo*. A solution of the residue in 10 cc. of absolute alcohol was diluted with 50 cc. of acetone and 50 cc. of ether. After five hours at 0°, the amino acid was removed and washed with acetone; yield, 1.0 g. (30%) of hydroscopic crystals, m.p. 145–148° with partial melting at 105°. This amino acid (0.95 g.) was characterized by benzoylation by the procedure described for 1-benzoylpiperidine-2-acetic acid (10); yield, 1.32 g. (77%), m.p. 133–134°. Recrystallization from benzene gave white crystals, m.p. 134–134.5°.

Anal. Calc'd for $C_{13}H_{15}NO_3$: C, 66.8; H, 6.48; N, 6.02.

Found: C, 66.6; H, 6.55; N, 6.38.

The filtrate from the 1 g. of amino acid was evaporated *in vacuo* and the 2.1 g. of residue benzoylated to give an additional 1.15 g., m.p. 133–135°. Thus, the yield of amino acid was 64%.

3-Methylpyrrolidine-2-acetic acid (XIVb). Oxidation of 14.9 g. of XIIIb as described for XIIIa gave 12.5 g. (76%) of product as a light yellow gum which could not be crystallized.

1-Carbethoxy-3-methylpyrrolidine-2-acetic acid (XVb). To a stirred solution of 12.5 g. of XIVb in 124 cc. of 5% sodium hydroxide cooled in an ice-bath was added over a period of 20 minutes a solution of 8.3 cc. of ethyl chlorocarbonate in 33 cc. of toluene. After being stirred ten minutes more, 62 cc. of 10% sodium hydroxide was added followed by the dropwise addition of 8.3 cc. of ethyl chlorocarbonate in 33 cc. of toluene over a period of 15 minutes. After being stirred in the ice-bath for one hour, the layers were separated and the aqueous layer acidified. The oil was isolated by two chloroform extractions; yield, 11.5 g. (61%) of a colorless oil which was nearly pure.

Anal. Calc'd for $C_{10}H_{17}NO_4$: C, 55.8; H, 7.90; N, 6.51.

Found: C, 55.1; H, 8.21; N, 6.43.

3-[β-Keto-γ-(1-carbethoxy-3-methyl-2-pyrrolidyl)propyl]-4-quinazolone (XVII). From 5.6 g. of XVb by conversion to the acid chloride, treatment with diazomethane, then with hydrogen bromide as described for 1-carbethoxy-4-methylpyrrolidine-2-acetic acid (11) there was obtained 7.4 g. (97%) of 1-carbethoxy-2-(γ-bromoacetonyl)-3-methylpyrrolidine. This bromoketone, dissolved in 74 cc. of methanol, was added to a solution of 2.3 g. of 4-quinazolone in 24 cc. of 1 *N* methanolic sodium methoxide. After one hour the solution was diluted with 320 cc. of ice-water and 128 cc. of 10% sodium hydroxide. The product was collected and washed with water; yield, 6.3 g. (78%), m.p. 145–148°. Recrystallization of a sample from benzene-heptane gave white crystals, m.p. 149–150°.

Anal. Calc'd for $C_{19}H_{23}N_3O_4$: C, 63.9; H, 6.45; N, 11.8.

Found: C, 63.5; H, 7.02; N, 12.0.

3-[β-Keto-γ-(3-methyl-2-pyrrolidyl)propyl]-4-quinazolone dihydrochloride (XVIII). A solution of 3.0 g. of XVII in 30 cc. of 48% hydrobromic acid was refluxed for ten minutes when carbon dioxide evolution was complete, then evaporated to dryness *in vacuo*. The residue was twice dissolved in 25 cc. of 6 *N* hydrochloric acid and evaporated to dryness *in vacuo*. Trituration with absolute alcoholic hydrogen chloride gave 2.4 g. (80%) of white crystals, m.p. 237° dec. Recrystallization from methanol by addition of absolute alcoholic hydrogen chloride did not raise the m.p.

Anal. Calc'd for $C_{16}H_{19}N_3O_2 \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 52.4; H, 6.01; N, 11.5; Cl, 19.4.
Found: C, 52.4; H, 6.12; N, 11.7; Cl, 19.3.

The *dihydrochloride* was also obtained in 60% yield, m.p. 236° dec., from XVII by seven hours refluxing with 6 *N* hydrochloric acid.

N-Methyl itacon-(β)-anilic acid (XX). To a solution of itaconic anhydride, prepared from 100 g. of itaconic acid, in 300 cc. of toluene was added 100 cc. of methylaniline. The temperature rose from 40° to 80°. When the temperature began to drop, the solution was diluted with 100 cc. of heptane and cooled to 20°. The product was collected and washed with 200 cc. of 3:1 toluene-heptane in portions; yield, 138 g. (81%) of white crystals, m.p. 116–118°. The m.p. was unchanged when a sample was recrystallized from benzene.

Anal. Calc'd for $C_{12}H_{13}NO_3$: C, 65.7; H, 5.97; N, 6.38.
Found: C, 65.6; H, 6.28; N, 6.51.

When a 20-g. sample of this material was fractionally precipitated from an alkaline solution, the m.p. of all the fractions was 116–118°, thus showing the homogeneity of the anilide.

N-Methyl methylsuccin-(β)-anilic acid (XXI). A solution of 75 g. of XX in 150 cc. of alcohol was shaken with hydrogen at 2–3 atm. in the presence of 0.2 g. of platinum oxide. Reduction was complete in 75 minutes and was slightly exothermic. The filtered solution was evaporated to dryness *in vacuo* (bath 30–40°). The viscous oil readily solidified when triturated with petroleum ether; yield, 69.2 g. (92%), m.p. 76–78°. Recrystallization of a sample from benzene-petroleum ether gave white crystals, m.p. 77–78°.

Anal. Calc'd for $C_{12}H_{15}NO_3$: N, 6.33. Found: N, 6.58.

N-Methyl methylsuccin-(α)-anilic acid (XXIII). A mixture of 500 mg. of the corresponding methyl ester, XXII, and 3.2 cc. of 10% sodium hydroxide was heated on the steam-bath for two minutes with mixing when solution was complete. The cooled solution was acidified yielding 460 mg. (98%) of product, m.p. 155–156°. Recrystallization from ethyl acetate gave white crystals, m.p. 161–161.5°.

Anal. Calc'd for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.78; N, 6.33.
Found: C, 65.4; H, 7.19; N, 6.51.

(β)-Methyl itaconyl chloride (XXXVI). From 100 g. of (β)-methyl hydrogen itaconate (I) by reaction with thionyl chloride as described for III was obtained 97 g. (85%) of a yellow oil, b.p. 92–97° (11 mm.). When a sample of the acid chloride was dissolved in dilute acetone and the solution evaporated to dryness *in vacuo*, (β)-methyl hydrogen itaconate was recovered and identified by mixed m.p., showing that no rearrangement of the double bond had taken place.

(β)-Methyl N-methyl itaconanilate. To a solution of 5 g. of the acid chloride, XXXVI, in 25 cc. of acetone cooled in an ice-bath was added 7.8 cc. of methylaniline. After one minute the solution was treated with 78 cc. of 1 *N* hydrochloric acid, diluted to 250 cc. with water, and cooled in an ice-bath; yield, 6 g. (84%) of white crystals, m.p. 78–79°. Recrystallization of a sample from heptane did not change the m.p.

Anal. Calc'd for $C_{13}H_{15}NO_3$: C, 66.8; H, 6.50; N, 6.01.
Found: C, 67.0; H, 6.57; N, 6.17.

N-Methyl itacon-(α)-anilic acid. Saponification of the preceding methyl ester as described for XXIII gave 75% of product, m.p. 124–125°. Recrystallization from benzene afforded white crystals, m.p. 124–125°.

Anal. Calc'd for $C_{12}H_{13}NO_3$: C, 65.7; H, 5.97; N, 6.38.
Found: C, 65.2; H, 6.18; N, 6.42.

A mixture with (β)-anilic acid, XX, (m.p. 118°), melted at 97–105°.

N,N'-Dimethyl methylsuccinanilide. (*A*). To 500 mg. of XX cooled in an ice-bath was added 0.5 cc. of reagent ether (containing 0.5% pyridine), 0.5 cc. of chloroform, and 0.18 cc. of thionyl chloride. After being shaken for ten minutes in the ice-bath, the acid had dissolved and two layers were present. The solvent was removed *in vacuo* (bath 0°). The residual acid chloride was dissolved in 5 cc. of benzene and 0.5 cc. of acetone and treated with 0.5 cc. of methylaniline. The product was isolated in the usual manner; yield, 510 mg.

(73%), m.p. 130–138°. Recrystallization from benzene-heptane gave white crystals, m.p. 139–140°.

Anal. Calc'd for $C_{19}H_{22}N_2O_2$: C, 73.6; H, 7.17; N, 9.03.
Found: C, 73.6; H, 7.20; N, 9.27.

When a similar preparation of acid chloride was dissolved in 1 cc. of acetone and treated with water, the (β)-anilic acid, XX, was recovered, showing that no rearrangement had taken place.

(*B*). From 500 mg. of the (α)-anilic acid, XXIII, there was obtained 500 mg. (73%) of crude dianilide as in *A*. Recrystallization from benzene-heptane gave white crystals, m.p. and mixed m.p. with preparation *A*, 139–140°.

When either acid chloride was added to magnesiomalonic ester in the usual manner, the crude products gave no ferric chloride test, showing no keto malonate, XXV, was formed.

Rearrangement of N-methyl methylsuccin-(β)-anilic acid (XXI) *to N-methyl methylsuccin-(α)-anilic acid* (XXIII). The (β)-anilic acid, XXI, (75 g., m.p. 76–78°) was heated on the steam-bath for 30 minutes, during which the mixture partially solidified. The mixture now melted at 80–125°. Fractional crystallization from ethyl acetate gave 28.2 g. (37%) of (α)-anilic acid, XXIII, m.p., and mixed m.p. 160–161°. Additional (α)-anilic acid was in the filtrates.

Ethyl (2-methylene-3-carbomethoxypropionyl)malonate (XXXVII). By condensation of 93 g. of (β)-methyl itaconyl chloride (XXXVI) with 178 cc. of ethyl malonate and 85 g. of magnesium methoxide as described for IV there was obtained 100 g. (60%) of a colorless oil, b.p. 147° (0.1 mm.) which gave a red ferric chloride test.

Anal. Calc'd for $C_{13}H_{18}O_7$: C, 54.5; H, 6.82.
Found: C, 54.6; H, 6.69.

This compound reacted exothermically with methanol in the presence of a catalytic amount of sodium methoxide and in 25 minutes the unsaturation had completely disappeared as determined by a catalytic reduction method which was standardized by use of XXXVII. Instead of the expected methoxymethyl keto malonate, XXXII, the product formed distilled at about 200° (1 mm.) and was not identified. It may have been formed by cleavage to dimethyl itaconate and ethyl malonate followed by Michael addition.

Attempts to add methanol to XXXVII in the presence of sulfuric acid for eight days at 25° resulted in 78% recovery of unchanged starting material.

2,4-Dinitrophenylhydrazones of β-methylenelevulinic acid (XXXV) *and β-acetobutyrolactone* (XXXIV). A mixture of 1.70 g. of XXXVII and 17 cc. of 6 *N* hydrochloric acid was refluxed vigorously for 15 minutes when gas evolution was essentially complete, solution taking place in eight minutes. The hot solution was diluted with 17 cc. of water and 1.3 g. of 2,4-dinitrophenylhydrazine was added. The products rapidly separated and after ten minutes were collected; yield, 1.70 g. (89%), m.p. 168–171°.

A mixture of 0.80 g. of crude product and about 15 cc. of half-saturated aqueous sodium bicarbonate was shaken for 30 minutes. The insoluble lactone was collected and washed with water; yield, 0.52 g. (65% recovery), m.p. 183–185°. Recrystallization from Methyl Cellosolve gave orange needles, m.p. 191–192°.

Anal. Calc'd for $C_{12}H_{12}N_4O_6$: C, 46.7; H, 3.95; N, 18.2.
Found: C, 47.0; H, 4.09; N, 18.2.

The combined orange bicarbonate solution and washings were acidified to give 0.20 g. (25% recovery) of acid, m.p. 210–211° dec. Recrystallization from dilute alcohol gave orange-yellow crystals, m.p. 211–212° dec.

Anal. Calc'd for $C_{12}H_{12}N_4O_6$: C, 46.7; H, 3.95; N, 18.2.
Found: C, 46.4; H, 4.26; N, 18.2.

The *methyl ester*, prepared by Freudenberg esterification, formed orange crystals from methanol, m.p. 136–137°.

Anal. Calc'd for $C_{13}H_{14}N_4O_6$: C, 48.4; H, 4.38; N, 17.4.
Found: C, 48.6; H, 4.45; N, 17.6.

When the length of the hydrolysis of XXXVII was increased to 40 minutes, the yield of mixed 2,4-dinitrophenylhydrazones was decreased to 75%. However, the ratio of lactone to acid was unchanged.

Dimethyl methoxymethylsuccinate (XXVII). A solution of 400 g. of dimethyl itaconate and 11.8 g. of sodium methoxide in 1300 cc. of methanol was allowed to stand four days in a stoppered flask. After acidification of the solution with 16 cc. of acetic acid, most of the methanol was removed *in vacuo*. The residue was diluted with water and the oil was extracted with chloroform. Evaporation of the extracts *in vacuo* and distillation of the residue through a Widmer column gave 60 g. (15%) of starting material, b.p. 93–94° (10 mm.) and 381 g. (79%) of product as a colorless oil, b.p. 116–118° (10 mm.).

Michael and Wiener (2) have recorded b.p. 80° (1.5 mm.).

Methoxymethylsuccinic acid (XXVIII). A solution of 396 g. of XXVII in 1200 cc. of 6 *N* hydrochloric acid was immersed in a steam-bath in an open flask for two hours, the temperature rising to 98°. The solution was distilled to dryness *in vacuo*. The residual oil was crystallized from 900 cc. of toluene and 75 cc. of acetone by chilling at 0° for two hours; yield, 246 g. (76%), m.p. 92–100°. This material was sufficiently pure for the next step.

Alkaline hydrolysis by the procedure of Michael and Wiener (2) afforded a 58% yield, m.p. 99–102°, but was difficultly adaptable to a large scale due to the high water solubility of the product. These authors recorded m.p. 102–103°.

(β)-Methyl hydrogen methoxymethylsuccinate (XXIX). To a mixture of 20 g. of methoxymethylsuccinic acid (XXVIII) and 20 cc. of methanol was added 0.3 cc. of acetyl chloride with shaking. The solution was refluxed on a steam-bath for 20 minutes, then the solvent was immediately removed *in vacuo* and the residue distilled. After a forerun of 10.2 g. (43%) of dimethyl ester, XXVII, b.p. 63–66° (0.6 mm.), the product distilled at 113–116° (0.1 mm.) as a colorless oil; yield, 9.6 g. (44%).

Anal. Calc'd for $C_7H_{12}O_5$: C, 47.7; H, 6.83; CH_3O, 35.2.

Found: C, 47.5; H, 7.12; CH_3O, 36.1.

On a larger scale the yield was 204 g. (63%), b.p. 123–135° (0.5–1.0 mm.), and 25% of the dimethyl ester was obtained in the forerun.

An attempt to prepare this compound by addition of methanol to the double bond of (β)-methyl hydrogen itaconate (I) in methanol in the presence of 1.1 moles of sodium methoxide was unsuccessful since 98% of the unsaturation, as determined by hydrogenation of an aliquot, was still present after four days at 25°.

Ethyl (2-methoxymethyl-3-carbomethoxypropionyl)malonate (XXXII). A mixture of 7.3 g. of XXIX, 3.3 cc. of reagent ether (containing 0.5% pyridine), and 4.4 cc. of thionyl chloride was refluxed gently on the steam-bath for 12 minutes when gas evolution was complete. Volatile material was removed *in vacuo* (bath 35°) and the evaporation repeated after the addition of 30 cc. of benzene. The residual acid chloride, dissolved in 30 cc. of toluene, was condensed with 20 cc. of ethyl malonate and 9.2 g. of magnesium methoxide in 40 cc. of toluene as described for IV: yield, 48% of a colorless oil, b.p. 142–143° (0.1 mm.), n_D^{19} 1.4505.

Anal. Calc'd for $C_{14}H_{22}O_8$: C, 52.8; H, 6.92.

Found: C, 52.4; H, 7.09.

This keto ester was hydrolyzed to β-acetobutyrolactone (XXXIV) and β-methylenelevulinic acid (XXXV) as described for XXXVII. The crude 2,4-dinitrophenylhydrazone mixture was isolated in 84% yield, m.p. 162–167°. Treatment with aqueous sodium bicarbonate gave a 68% recovery of lactone 2,4-dinitrophenylhydrazone, m.p. 185–187°, and 25% recovery of somewhat impure acid 2,4-dinitrophenylhydrazone, m.p. 196–198° dec. Mixtures with these same products obtained from XXXVII gave no depression in m.p. Thus, the original monomethyl ester from which the malonate was prepared was estimated to be at least 97% of (β)-methyl ester, XXIX.

(α)-Methyl hydrogen methoxymethylsuccinate (XXX). To 80.5 g. of the dimethyl ester, XXVII, was added 480 cc. of 6 *N* hydrochloric acid. The mixture was shaken for about five minutes when solution was complete, then it was allowed to stand for three hours. The solution was partially neutralized with 100 g. of anhydrous potassium carbonate. Just

sufficient water was added to dissolve the potassium chloride, then the solution was extracted with three 150-cc. portions of chloroform. Distillation gave a forerun of 15.7 g. (20%) of unchanged diester and the product distilled at 130–132° (0.3 mm.) as a colorless oil; yield, 35.2 g. (47%).

Anal. Calc'd for $C_7H_{12}O_5$: C, 47.7; H, 6.83.
Found: C, 47.8; H, 7.17.

Ethyl (3-carbomethoxy-4-methoxybutyryl)malonate (XXXI). From the above ester, XXX, by conversion to the acid chloride and condensation with magnesiomalonic ester as described for XXXII was obtained an 82% yield of product as a colorless oil, b.p. 148° (0.2 mm.).

Anal. Calc'd for $C_{14}H_{22}O_8$: C, 52.8; H, 6.92.
Found: C, 52.8; H, 7.36.

For proof of structure and assay, a mixture of 1.00 g. of this keto malonate and 10 cc. of 6 *N* hydrochloric acid was refluxed for 15 minutes when gas evolution was essentially complete. Solution took place in six minutes. The hot solution, diluted with 10 cc. of water, was shaken with 0.70 g. of 2,4-dinitrophenylhydrazine. A red gum separated. The aqueous solution was decanted and was combined with a water rinse. On standing the aqueous solution deposited yellow crystals.

The red gum was dissolved in 15 cc. of hot alcohol and poured into a mixture of 100 cc. of water and 15 cc. of saturated aqueous sodium bicarbonate. The turbid solution was allowed to stand until clear. The solid (170 mg.) was collected and was mostly 2,4-dinitrophenylhydrazine. The solid was suspended in 10 cc. of hot alcohol and 1 cc. of 12 *N* hydrochloric acid was added to dissolve the hydrazine. The mixture was cooled, and the yellow lactone (XXXIV) 2,4-dinitrophenylhydrazone was collected and washed with alcohol. This compound is very insoluble in alcohol; yield, 25 mg., m.p. 180–187°, indicating that there was 4% (β)-ester and 96% (α)-ester in the original monoester fraction.

The sodium bicarbonate solution was acidified and combined with the original aqueous decantate. The 2,4-dinitrophenylhydrazone of α-methoxymethyllevulinic acid (XXXIII) was collected; yield, 710 mg. (66%), m.p. 125–127°. Recrystallization from toluene-heptane gave orange crystals, m.p. 129–130°.

Anal. Calc'd for $C_{13}H_{16}N_4O_7$: C, 45.8; H, 4.74; N, 16.5; CH_3O, 9.12.
Found: C, 45.6; H, 4.79; N, 16.6; CH_3O, 9.04.

Preparation of monoesters (XXIX and XXX) *by alkaline hydrolysis of dimethyl methoxymethylsuccinate* (XXVII). To a stirred solution of 40.7 g. of XXVII in 85 cc. of methanol was added dropwise 86 cc. of 10% sodium hydroxide over a period of ten minutes. The solution was allowed to stand about 15 hours. After dilution with an equal volume of water, the solution was extracted with two 50-cc. portions of chloroform. Evaporation of the extracts gave 5 g. (12%) of unchanged diester. The aqueous layer was acidified with 28 cc. of 12 *N* hydrochloric acid and extracted with three 100-cc. portions of chloroform. Distillation gave 22.7 g. (60%) of monoester as a colorless oil, b.p. 118–120° (0.2 mm.).

Anal. Calc'd for $C_7H_{12}O_5$: C, 47.7; H, 6.83.
Found: C, 47.0; H, 6.96.

The monoester (17.7 g.) was converted to a mixture of keto malonates, XXXI and XXXII in 77% yield, as described for XXXII. Hydrolysis assay showed the original monoester contained 12% (β)-ester (XXIX) and 88% (α)-ester (XXX) by difference. Thus, acid hydrolysis of XXVII is more selective than basic hydrolysis.

Methoxymethylsuccinic anhydride. A mixture of 20 g. of methoxymethylsuccinic acid (XXVIII) and 20 cc. of acetyl chloride was refluxed gently on the steam-bath until gas evolution was complete (13 minutes). Distillation gave 17.5 g. (99%) of a colorless oil, b.p. 110° (0.1 mm.).

The anhydride was converted to a mixture of the monoesters, XXIX and XXX, by heating on the steam-bath under a condenser with 5.3 cc. of methanol for 45 minutes. Distillation gave 20.6 g. (96%) of a colorless oil, b.p. 127–128° (0.15 mm.).

The monoesters were converted to the keto malonates, XXXI and XXXII, as before. Hydrolysis assay showed that the original monoester contained 49% (β)-ester, XXIX, and 51% (α)-ester (by difference).

Ethyl (2-methoxymethyl-3-carbomethoxypropionyl)acetate (XXXIXa). (*A*). A mixture of 36 g. of XXXII and 180 cc. of water was refluxed for one hour when carbon dioxide evolution became slow. The cooled mixture was extracted with two 50-cc. portions of carbon tetrachloride. Fractional distillation gave, after a forerun of b.p. 43–75° (0.1 mm.), the product as a colorless oil, b.p. 115–125°, mainly at 120° (0.2 mm.); yield, 14.7 g. (53%).

Anal. Calc'd for $C_{11}H_{18}O_6$: C, 53.7; H, 7.33.

Found: C, 53.9; H, 7.23.

Distillation of the residue gave 8.6 g. (24%) of unchanged starting material, b. p. 143° (0.2 mm.).

(*B*). The synthesis of this compound on a preparative scale was developed which eliminated isolation of the intermediates and gave an over-all yield of 36% of XXIXa with recovery of 25% of the dimethyl methoxymethylsuccinate (XXVII). When all of the intermediates were isolated as in method *A*, the over-all yield was 22% with the same % recovery of XXVII.

To a boiling solution of 310 g. of methoxymethylsuccinic acid (XXVIII) in 310 cc. of methanol was added 5 cc. of acetyl chloride. The solution was refluxed for 20 minutes, then immediately evaporated to dryness *in vacuo*. The residue was dissolved in 200 cc. of toluene and the evaporation repeated. To the crude monoester (336 g.), containing some diester and some diacid, was added 110 cc. of reagent ether (containing 0.5% pyridine) and 145 cc. of thionyl chloride. The solution was refluxed gently on the steam-bath for 45 minutes when gas evolution was complete. The acid chloride was isolated and condensed with 430 cc. of ethyl malonate and 210 g. of magnesium methoxide as described for IV. The crude product was distilled at 0.2 mm. up to a pot temperature of 130°. The distillate of ethyl malonate and XXVII was redistilled through a Widmer column and 90 g. (25%) of XXVII was recovered, b.p. 110–116° (9 mm.). The residue of the first distillation consisting of crude XXXII weighed 316 g. (52%) and was used without further purification. It assayed 97% by the hydrolytic method.

A mixture of 315 g. of crude keto malonate, XXXII, and 1570 cc. of water was refluxed one hour, then worked up as in *A* to give 111 g. (46%) of ketoacetate, XXXIXa, b.p. 125–130° (0.3 mm.) and 108 g. (33%) of keto malonate, XXXII, b.p. 137–147° (0.3 mm.). When 180 g. of recovered, distilled, keto malonate was retreated with boiling water for 90 minutes, 76 g. (54%) of ketoacetate was obtained and 58 g. (32%) of keto malonate was recovered.

Ethyl (3-carbomethoxy-4-methoxybutyryl)acetate (XXXIXb). (*A*). A mixture of 55.5 g. of XXXI and 280 cc. of water was refluxed vigorously for 90 minutes, then worked up as described for XXXIXa; yield, 24.5 g. (57%) of a colorless oil, b.p. 117–122° (0.1 mm.) which gave a red ferric chloride test and 10.4 g. of starting material was recovered.

Anal. Calc'd for $C_{11}H_{18}O_6$: C, 53.7; H, 7.33.

Found: C, 53.3; H, 7.53.

(*B*). A preparative procedure was devised which gave a considerable increase in yield when the intermediates were not isolated. A solution of 212 g. of XXVII in 630 cc. of 3 *N* hydrochloric acid was allowed to stand three hours. The monoester, XXX, was isolated as previously described. Unchanged diester (53.4 g., 25%) was distilled at 91–105° (0.2 mm.). The residual crude monoester was used without further purification; yield, 98 g. (50%). It was converted to the crude keto malonate, XXXI, in the same manner as described for the isomer keto malonate, XXXII, under XXXIXa; yield, 157 g. (89%). Hydrolytic assay showed the presence of 5% of the isomeric XXXII. The 156 g. was decarbethoxylated as in part *A* to give 58.3 g. (49%) of product, b.p. 117–122° (0.1 mm.), and 37.8 g. of keto malonate was recovered.

Ethyl 1-benzyl-4-methoxymethyl-5-oxo-2-pyrroline-2-acetate (XLb). A solution of 58.3 g.

of XXXIXb and 29 cc. of benzylamine in 140 cc. of benzene was refluxed for one hour under constant water separation when reaction was complete. Evaporation *in vacuo* gave 79 g. (99%) of imine as a yellow oil which gave a negative ferric chloride test.

A solution of 15 g. of this imine in 300 cc. of 28% ammonia water and 300 cc. of absolute alcohol was allowed to stand for four hours. The solution was concentrated to about one-half the volume *in vacuo* when it became turbid. Diluted with an equal volume of water and acidified with acetic acid, the mixture was extracted twice with chloroform. Evaporation of the combined extracts *in vacuo* gave a yellow oil; yield, 11.3 g. (84%).

Anal. Calc'd for $C_{17}H_{21}NO_4$: C, 67.4; H, 6.98; N, 4.62.
Found: C, 67.6; H, 7.26; N, 5.07.

Similarly, 65 g. of the intermediate imine gave 54 g. (91%) of yellow oil. When the cyclization was carried out as described for XIb, the product was a dark brown oil which gave no XLIb on lithium aluminum hydride reduction.

Ethyl 1-benzyl-3-methoxymethyl-5-oxo-2-pyrroline-2-acetate (XLa). From 47.5 g. of XXXIXa by treatment with benzylamine, then sodium methoxide as described for XIb, except that the cyclization was carried out at 25° for two hours, there was obtained 53 g. (90%) of product as an orange oil.

1-Benzyl-4-methoxymethylpyrrolidine-2-ethanol (XLIb). By reduction of 10.8 g. of XLb with 2.5 g. of lithium aluminum hydride as described for XIIa there was obtained 6.5 g. (73%) of a light yellow oil, b.p. 143–145° (0.1 mm.).

Anal. Calc'd for $C_{15}H_{23}NO_2$: N, 5.36. Found: N, 5.36.

1-Benzyl-3-methoxymethylpyrrolidine-2-ethanol (XLIa). Treatment of XLa with lithium aluminum hydride as described for XIIa, except that the reaction was carried out two hours at the b.p., gave a 41% yield of product as a light yellow oil, b.p. 138–140° (0.05 mm.).

Anal. Calc'd for $C_{15}H_{23}NO_2$: N, 5.36. Found: N, 5.76.

4-Methoxymethylpyrrolidine-2-ethanol (XLIIb). Catalytic reduction of 31.3 g. of XLIb as described for XIIIa, except that acidification with hydrochloric acid was omitted and 4:1 chloroform-butanol was used for extraction, gave 12.8 g. (66%) of a colorless oil, b.p. 140–142° (10 mm.).

Similarly, *3-methoxymethylpyrrolidine-2-ethanol* (XLIIa) was obtained as a colorless oil in 52–73% yield, b.p. 133–136° (10 mm.).

Anal. Calc'd for $C_8H_{17}NO_2$: N, 8.80; CH_3O, 19.5.
Found: N, 8.36; CH_3O, 20.9.

1-Carbethoxy-4-methoxymethylpyrrolidine-2-acetic acid (XLIIIb). Oxidation of 12.4 g. of XLIIb as described for XIVa gave 11.2 g. (82%) of a nearly colorless oily amino acid which was carbethoxylated according to XVb to 12.4 g. (79%) of product as a colorless oil.

Anal. Calc'd for $C_{11}H_{19}NO_5$: C, 53.8; H, 7.75; N, 5.72.
Found: C, 53.8; H, 8.62; N, 5.78.

Similarly, oxidation of XLIIa resulted in an 84% yield of amino acid which was carbethoxylated to *1-carbethoxy-3-methoxymethylpyrrolidyl-2-acetic acid* (XLIIIa), a colorless oil, in 77% yield.

Anal. Calc'd for $C_{11}H_{19}NO_5$: C, 53.8; H, 7.75; N, 5.72.
Found: C, 54.5; H, 8.44; N, 6.04.

3-[β-Keto-γ-(1-carbethoxy-4-methoxymethyl-2-pyrrolidyl)propyl]-4-quinazolone (XLIVb). A 92% yield of 1-carbethoxy-2-(γ-bromoacetonyl)-4-methoxymethylpyrrolidine was obtained from XLIIIb as described for 1-benzoyl-2-(γ-bromoacetonyl)piperidine (10). Condensation with 4-quinazolone (10) gave 4.3 g. (49%) of crystalline product (from benzene-heptane), m.p. 94–96°. Recrystallization from the same solvents afforded white crystals, m.p. 100–102°.

Anal. Calc'd for $C_{20}H_{25}N_3O_5$: C, 62.0; H, 6.46; N, 10.8.
Found: C, 61.7; H, 6.89; N, 11.0.

Similarly, an 88% yield of bromoketone was obtained from XLIIIa, which in turn gave a 54% yield of *3-[β-keto-γ-(1-carbethoxy-3-methoxymethyl-2-pyrrolidyl)propyl]-4-quinazolone*

(XLIVa), m.p. 91–93°. Recrystallization from benzene-heptane afforded white crystals, m.p. 94–96°. Admixture with isomeric XLIVb gave a 20° depression in m.p.

Anal. Calc'd for $C_{20}H_{25}N_3O_5$: C, 62.0; H, 6.46; N, 10.8.

Found: C, 62.3; H, 6.89; N, 10.8.

3-[β-Keto-γ-(4-hydroxymethyl-2-pyrrolidyl)propyl]-4-quinazolone dihydrochloride (XLVI). By hydrolysis of 2.0 g. of XLIVb with 20 cc. 48% hydrobromic acid at the b.p. for five minutes there was obtained 1.5 g. (78%) of product, m.p. 225° dec., as described for XVIII. Recrystallization gave white crystals, m.p. 228° dec.

Anal. Calc'd for $C_{16}H_{19}N_3O_3 \cdot 2HCl \cdot H_2O$: C, 49.1; H, 5.98; N, 10.7.

Found: C, 48.7; H, 6.14; N, 11.0.

3-[β-Keto-γ-(3-hydroxymethyl-2-pyrrolidyl)propyl]-4-quinazolone dihydrochloride (XLV). Hydrolysis of 2.0 g. of XLIVa with 20 cc. of 48% hydrobromic acid as described for XVIII, gave 1.2 g. (62%) of white crystals, m.p. 230° dec. Recrystallization did not change the m.p.

Anal. Calc'd for $C_{16}H_{19}N_3O_3 \cdot 2HCl$: C, 51.3; H, 5.65; N, 11.4; Cl, 18.9; NH_2, 0.0.

Found: C, 50.7; H, 5.90; N, 11.4; Cl, 19.3; NH_2, 0.0.

The *carbamyl derivative*, formed in water with potassium cyanate, melted at 185–187°.

SUMMARY

1. Lithium aluminum hydride reduction of ethyl 1-benzyl-5-oxo-2-pyrroline-2-acetate and its 3- or 4-alkyl substituted derivatives occurred at three sites with formation of the corresponding alkyl derivatives of 1-benzylpyrrolidine-2-ethanol.

2. Two structural isomers of the Hydrangea alkaloid, 3-[β-keto-γ-(3- and 4-hydroxymethyl-2-pyrrolidyl)propyl]-4-quinazolone, have been synthesized from itaconic acid *via* the isomeric monomethyl esters of methoxymethylsuccinic acid and 1-carbethoxy-3(and 4)-methoxymethyl-2-pyrrolidineacetic acid.

PEARL RIVER, N. Y.

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