[CONTRIBUTION FROM NATIONAL RESEARCH INSTITUTE OF CHEMISTRY, ACADEMIA SINICA]

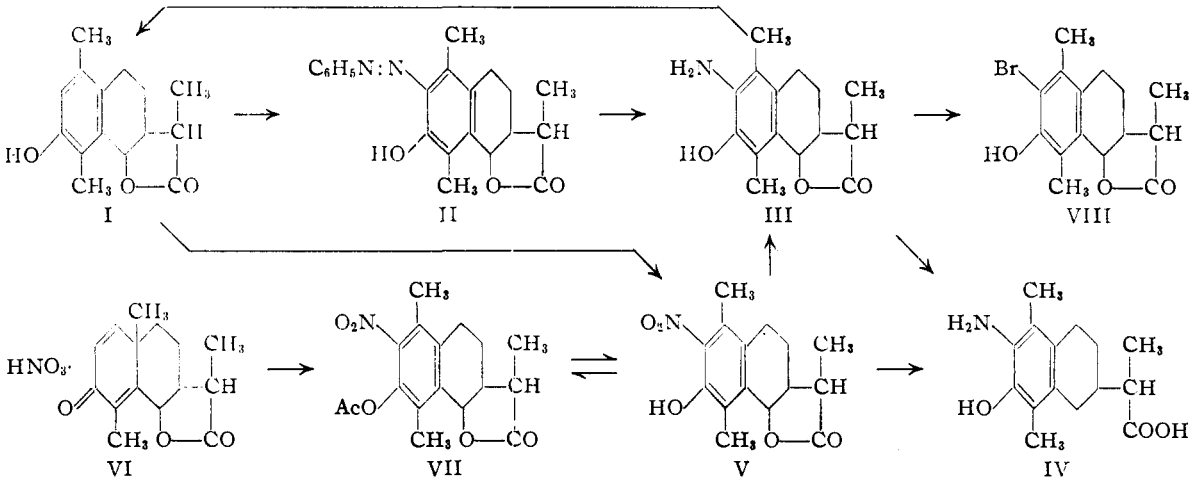
Studies in the Santonin Series. III.[1,2,3] The Introduction of Nitrogen into the Desmotroposantonin Molecule

BY HUANG-MINLON[4] AND SHAO-CHI CHENG

Some time ago E. Wedekind[5] studied the introduction of nitrogen in the form of a salt-forming group into the desmotroposantonin molecule (I), with a view to obtain basic derivatives resembling the alkaloids and to determine pharmacologically the possible variation of the physiological properties of santonin. He attempted to transform benzene-azo-*d*-β-desmotroposantonin (II),[6] prepared from *d*-β-desmotroposantonin (I),[7] into aminodesmotroposantonin (III) by reduction with stannous chloride and hydrochloric acid. However, he obtained not the desired product but an amino acid melting at 206°, which as he recognized arose from benzene-azo-desmotroposantonin through the simultaneous reduction of the lactone ring. The product, therefore, according to him is an aminodesmotroposantonous acid (IV). He further reported that the attempt to employ nitrodesmotroposantonin (V) as the starting material for the preparation of aminodesmotroposantonin had likewise a negative result, and therefore emphasized in his report that in general the preparation of such a substance, on account of the sensitiveness toward reducing agents, would be difficult.

After we had found the interesting rearrangement and isomerization of santonin and desmotroposantonin[2] as well as of its bromination products[3] we wished to ascertain whether or not nitrogen containing derivatives of santonin and desmotroposantonin could give similar reactions. We started with the preparation of nitrodesmotroposantonins (V). The nitro derivative of *d*-β-desmotroposantonin had already been prepared by Andreocci,[8] but under the conditions briefly described by him the nitration did not proceed uniformly. Nitric acid, even in the cold, produces a small amount of the desired nitrodesmotroposantonin and a product melting at 250°, which is perhaps identical with the so-called hydroxynitrodesmotroposantonin obtained by Andreocci[8] by the nitration of *d*-β-desmotroposantonin at room temperatures.

When the nitration is carried out in glacial acetic acid solution and under the controlled conditions described in the experimental part a much better yield of the nitrodesmotroposantonins was obtained. We have prepared up to the present only two of them: the dextro-rotatory nitro-*d*-β-desmotroposantonin, melting at 191–192°, from



d-β-desmotroposantonin, and the new levo-rotatory nitro-*l*-α-desmotroposantonin, melting at 216°, from *l*-α-desmotroposantonin. The nitro compound melting at 216° can also be prepared by treatment of the addition product of santonin and nitric acid (VI)[9] with acetic anhydride and a drop of concentrated sulfuric acid, followed by

(1) This work was done in 1943; publication was delayed because it was impossible to make the stipulated analyses of the new compounds in China during wartime. The analytical data supplied here were performed by Margaret Racich Reese, Chemical Laboratories, Harvard University, to whom the authors are greatly indebted.

(2) Huang-Minlon, Lo and Chu, THIS JOURNAL, **65**, 1780 (1943).

(3) Huang-Minlon, Lo and Chu, *ibid.*, **66**, 1954 (1944).

(4) Present address: Department of Chemistry, Harvard University, Cambridge, Mass.

(5) Wedekind, *Z. physiol. Chem.*, **43**, 240 (1904).

(6) Wedekind and Schmidt, *Ber.*, **36**, 1386 (1903).

(7) For nomenclature of desmotroposantonins and desmotroposantonous acids see Reference 2.

(8) Andreocci, *Atti Acad. Lincei*, [5] **5**, II, 311 (1897); *Chem. Centr.*, **68**, I, 165 (1897); Bargellini and Daconto, *Gazz. chim. ital.*, **38**, II, 42 (1908).

(9) Andreocci, *Atti Acad. Lincei*, [5] **5**, II, 310 (1896); Wedekind and Koch, *Ber.*, **38**, 425 (1905).

saponification of the resulting acetate (VII) which melts at 230–231°. Compound VII has been proved to be identical with the acetylation product of nitro-*l*-α-desmotroposantonin, melting at 230–231°. The mechanism of the reaction is similar to that of the transformation of santonin into *l*-α-desmotroposantonin.[2] But it is more interesting in this case since, in addition to the aromatization of the first ring the rearrangement of the angular methyl group, an indirect nitration has taken place.

The nitrodesmotroposantonins (V), unlike the desmotroposantonins[2] and bromodesmotroposantonins,[3] are not so readily transformable into each other. They remain unchanged after treatment with sulfuric acid and decompose readily on alkali fusion. On reduction under mild conditions with zinc dust and ammonium chloride in alcoholic solutions both of the nitrodesmotroposantonins give the corresponding, previously unknown, aminodesmotroposantonins (III): the dextro-rotatory amino-*d*-β-desmotroposantonin, melting at 197–198°, and the levo-rotatory amino-*l*-α-desmotroposantonin, melting at 170°. Both of the amino compounds are soluble in alcohol but not in water and sodium carbonate solution, and they form water-soluble hydrochlorides. From the aqueous solution of their salts the corresponding aminodesmotroposantonins can be precipitated by the addition of sodium carbonate solution.

The constitution of amino-*d*-β-desmotroposantonin was established by the fact that by the Sandmeyer reaction it is transformed into the already known bromo-*d*-β-desmotroposantonin (VIII).[3] Besides, it is reconverted into *d*-β-desmotroposantonin (I) on diazotization and replacement of the diazo group with hydrogen. These transformations further demonstrate that amino-*d*-β-desmotroposantonin and of course nitro-*d*-β-desmotroposantonin, in respect to the three asymmetric carbon atoms in the lactone ring, must have the same configuration as their parent substance, *d*-β-desmotroposantonin.

Owing to the scarcity of material amino-*l*-α-desmotroposantonin has not yet been converted into compounds of known constitution. We believe, however, that there should be little doubt about this conversion because the *l*-α-isomer is obtained by the same methods and under exactly the same experimental conditions, from *l*-α-desmotroposantonin, as those under which amino-*d*-β-desmotroposantonin is formed from *d*-β-desmotroposantonin. Its levo-rotatory character, as well as its conversion to a dextro-rotatory amino acid which will be discussed later, further illustrates that it retains the configuration of *l*-α-desmotroposantonin with regard to the lactone ring. As in the case of the nitrodesmotroposantonins, the attempt to convert the aminodesmotroposantonins by acid or alkali into their respective stereoisomers gave negative results.

By reduction with zinc dust and acetic acid amino-*d*-β-desmotroposantonin and amino-*l*-α-desmotroposantonin are converted into the corresponding aminodesmotroposantonous acids (IV) melting at 190 and 197°, respectively. These aminodesmotroposantonous acids, like desmotroposantonous acids, show directions of specific rotation opposite to those of their respective parent substances so that they are denoted as amino-*l*-β-desmotroposantonous and amino-*d*-α-desmotroposantonous acid.

Both of these amino acids can also be obtained directly from the appropriate nitrodesmotroposantonin (V), but our amino-*l*-β-desmotroposantonous acid is not identical with that obtained by Wedekind, although he also used *d*-β-desmotroposantonin as the starting material. Our acid and its hydrochloride are levorotatory and it forms an unstable hydrochloride in opposition to the properties of Wedekind's acid; furthermore, the melting point of our acid is lower than and depressed by admixture of Wedekind's acid.

We believe that our compound is the true amino-*l*-β-desmotroposantonous acid because all known desmotroposantonous acids and their substitution products show a direction of specific rotation opposite to that of their parent compounds. The specific rotation reported by Wedekind is that of the hydrochloride rather than that of the free amino compound, but we do not believe that a change of sign of rotation accompanies salt formation in this case since all the hydrochlorides of the amino compounds of the santonin series show the same direction of rotation as the free amino compounds.[10]

Owing to lack of specific information exact repetition of Wedekind's work was not feasible, but on treatment of benzene-azo-*d*-β-desmotroposantonin with stannous chloride we did obtain an amino acid melting at 206° and not identical with amino-*l*-β- and amino-*d*-α-desmotroposantonous acid, which probably is the same product that Wedekind had. Unfortunately lack of material prevented further characterization of the 206°-acid. Contrary to his findings, however, we also isolated amino-*d*-β-desmotroposantonin from the reduction mixture.

Experimental

Nitro-*d*-β-desmotroposantonin (V).—A suspension of ground *d*-β-desmotroposantonin (10 g.) in glacial acetic acid (100 cc.) was cooled to 6–7°. A 10% solution of concentrated nitric acid in glacial acetic acid (40 cc.) was added dropwise from a buret to the stirred suspension in eighty minutes. Stirring was continued for ten more minutes after complete addition; the mixture was poured into ice-water and filtered. Recrystallization of the separated solid from alcohol gave nitro-*d*-β-desmotroposantonin (8 g.) as yellow prisms, m. p. 191–192°, $[\alpha]^{24}D$ +119.5° (*c*, 0.4% in alcohol).

Anal. Calcd. for $C_{15}H_{17}O_6N$: C, 61.88; H, 5.88. Found: C, 62.19; H, 5.79.

(10) Examples for the generalization concerning the sign of rotation are: amino-*d*-β-desmotroposantonin and *d*-hydrochloride, amino-*l*-α-desmotroposantonin and *l*-hydrochloride (see text), *l*-aminohyposantonin and *d*-aminohyposantonous acid hydrochloride [Asahina and Momose, *Ber.*, **71**, 1425 (1938)].

Amino-*d*-β-desmotroposantonin (III).—Nitro-*d*-β-desmotroposantonin (8 g.) and ammonium chloride (1.5 g.) were dissolved in dilute alcohol (600 cc. of alcohol in 300 cc. of water) and heated to 62–67°, when zinc dust (1.5 g.) was added slowly. The reaction mixture was kept at this temperature for one hour. The filtrate on cooling precipitated long thin plates (2.85 g.), m. p. 195–196°. The mother liquid, after distillation of the major part of the alcohol, gave a second crop (0.88 g.). The combined precipitate was then recrystallized from alcohol; amino-*d*-β-desmotroposantonin was obtained as plates, m. p. 197–198°, $[\alpha]^{23}D$ +113.8°, (*c*, 0.44% in alcohol).

Anal. Calcd. for $C_{15}H_{19}O_3N$: C, 68.95; H, 7.31. Found: C, 69.24; H, 7.03.

It gave the hydrochloride as long prisms by dissolving in a small amount of hot 5% hydrochloric acid and cooling; m. p. 265–267° (dec.), $[\alpha]^{25}D$ +66.4° (*c*, 0.34% in alcohol).

Anal. Calcd. for $C_{15}H_{20}O_3NCl$: Cl, 11.92. Found: Cl, 11.47.

Amino-*l*-β-desmotroposantonous Acid (IV).—(a) Nitro-*d*-β-desmotroposantonin (10 g.), zinc dust (37 g.) and 70% acetic acid (300 cc.) were refluxed for ten hours. The filtrate was diluted with 4–5 times its volume of water, when a white precipitate settled out. Dissolution of the separated solid in sodium carbonate solution followed by acidification of the filtrate gave the product in a purer state. The purified solid was then recrystallized from alcohol; amino-*l*-β-desmotroposantonous acid (1.44 g.) separated as plates, m. p. 190°, $[\alpha]^{25}D$ −56.3°, (*c*, 0.8% in alcohol). (b) Amino-*d*-β-desmotroposantonin (1 g.), zinc dust (5 g.) and 70% acetic acid (43 cc.) were treated as described in (a); m. p. 189–190°, not depressed by admixture with the product obtained from nitro-*d*-β-desmotroposantonin.

Anal. Calcd. for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.03. Found: C, 68.38; H, 8.10.

The hydrochloride was prepared by dissolving the amino acid in small amount of hot alcohol and followed by addition of concentrated hydrochloric acid; m. p. 245–246°, $[\alpha]^{24}D$ −59.2° (*c*, 0.6% in alcohol). The fact that several determinations gave about the same but lower value for the chloride content may be due to the loss of hydrogen chloride during drying, because the substance reverts to the free base on standing overnight in a vacuum desiccator over potassium hydroxide or on recrystallization from alcohol.

Anal. Calcd. for $C_{15}H_{22}O_3NCl$: Cl, 11.83. Found: Cl, 10.65.

Conversion of Amino-*d*-β-desmotroposantonin into Bromo-*d*-β-desmotroposantonin.—A mixture of copper sulfate (1 g.), copper powder (0.35 g.), sodium bromide (2.5 g.), concentrated sulfuric acid (0.3 cc.) and water (16 cc.) was boiled for three to four hours until the solution had become yellow. Amino-*d*-β-desmotroposantonin (0.4 g.) dissolved in a little water containing three drops of sulfuric acid was diazotized with sodium nitrite (0.12 g.) in the presence of copper sulfate (0.1 g.). The diazotized mixture was then poured into the cuprous bromide solution at 60–70°. After cooling the brown precipitate was filtered and dissolved in alcohol. Narrow thin plates separated overnight. After being decolorized with bone char it was recrystallized from alcohol giving bromo-*d*-β-desmotroposantonin in prismatic needles (0.03 g.), m. p. 209–210°, unchanged by admixture with an authentic specimen of bromo-*d*-β-desmotroposantonin.[3] The product gave a positive Beilstein test. Its racemic compound with bromo-*l*-β-desmotroposantonin[3] was found to be identical with bromo-*dl*-β-desmotroposantonin[3] both in crystal form and in melting point. A mixture of the two showed no melting point depression.

Conversion of Amino-*d*-β-desmotroposantonin into *d*-β-Desmotroposantonin.—Amino-*d*-β-desmotroposantonin (0.2 g.) dissolved in alcohol (10 cc.) containing two drops of concentrated sulfuric acid was diazotized with sodium nitrite (0.06 g.). After standing for twenty minutes in an ice-bath the diazotized compound was decomposed by boiling for twenty minutes in the presence of a small amount of zinc dust. Dilution of its filtrate with water gave a yellow precipitate (0.1 g.) which was then dissolved in alcohol and decolorized with bone char. Concentration and cooling of the decolorized filtrate yielded *d*-β-desmotroposantonin in prisms, m. p. 259–260°, unchanged by admixture with an authentic specimen of *d*-β-desmotroposantonin. The product gave with *l*-β-desmotroposantonin a racemic compound that was identical with *dl*-β-desmotroposantonin.[2]

Nitro-*l*-α-desmotroposantonin (V).—(*a*) This was obtained from *l*-α-desmotroposantonin (10 g.) by the same procedure as described in the nitration of *d*-β-desmotroposantonin. It crystallized from alcohol as yellow prisms (7.8 g.), m. p. 216–217°, $[\alpha]^{25}D$ −105°, (*c*, 0.4% in alcohol).

Anal. Calcd. for $C_{15}H_{17}O_5N$: C, 61.88; H, 5.88. Found: C, 62.20; H, 5.46.

(*b*) Santonin (2 g.) was dissolved in concentrated nitric acid while warm. Upon cooling there separated the addition compound of santonin and nitric acid of m. p. 140–142°, which after filtration and drying over potassium hydroxide in the desiccator was added with water cooling to acetic anhydride (8 cc.) containing a drop of concentrated sulfuric acid. The reaction mixture was heated on a water-bath for about ten minutes. Dilution with water gave the acetate (VII) at first as an oil and then as a semisolid which, after recrystallization from chloroform–alcohol, melted at 230–231°, unchanged by admixture with the acetylation product of nitro-*l*-α-desmotroposantonin.

For saponification the product was refluxed with a 10% postassium hydroxide solution for half an hour when it dissolved rapidly to form a deep red solution. Acidification of the resulting reaction mixture gave the nitro compound in prisms, m. p. 215–216°. This was shown to be identical with the product obtained from (a) in crystal form, solubility and melting point. A mixture of the two showed no melting point depression. It was reconverted into the acetate of m. p. 230–231° on being refluxed with acetic anhydride for half an hour.

Amino-*l*-α-desmotroposantonin (III).—On reduction under the same conditions as those described in the reduction of nitro-*d*-β-desmotroposantonin, nitro-*l*-α-desmotroposantonin (1 g.) gave amino-*l*-α-desmotroposantonin as prisms (0.41 g.), m. p. 170°, $[\alpha]^{25}D$ −157.5° (*c*, 0.4% in alcohol).

Anal. Calcd. for $C_{15}H_{19}O_3N$: C, 68.95; H, 7.31. Found: C, 69.34; H, 7.42.

Amino-*l*-α-desmotroposantonin Hydrochloride.—This hydrochloride (0.13 g.) was obtained from amino-*l*-α-desmotroposantonin (0.15 g.) by the same procedure as that described for the preparation of amino-*d*-β-desmotroposantonin hydrochloride. It crystallized from 5% hydrochloric acid solution as plates, m. p. 273–274°, $[\alpha]^{25}D$ −125°, (*c*, 0.4% in alcohol).

Amino-*d*-α-desmotroposantonous Acid (IV).—This was obtained from either nitro-*l*-α-desmotroposantonin or amino-*l*-α-desmotroposantonin. The procedures were exactly the same as those described in the preparation of amino-*l*-β-desmotroposantonous acid. It crystallized from alcohol as prisms, m. p. 197°, $[\alpha]^{25}D$ +76.2° (*c*, 0.4% in alcohol); yield, 0.12 g. from 1 g. of nitro-*l*-α-desmotroposantonin.

Anal. Calcd. for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.03. Found: C, 68.29; H, 8.05.

Amino-*d*-β-desmotroposantonin and the Amino Acid of m. p. 206° from Benzene-azo-desmotroposantonin.—A hot solution of benzene-azo-desmotroposantonin (0.6 g.) in glacial acetic acid (110 cc.) was added to a solution of stannous chloride (4 g.) in boiling concentrated hydrochloric acid (20 cc.). After dilution with water the reaction mixture was treated with hydrogen sulfide. The filtrate was evaporated at first on a water-bath and then distilled under vacuum until a white precipitate separated.

Treatment with sodium carbonate solution separated the precipitate into a soluble and an insoluble portion. The latter on recrystallization from alcohol gave amino-*d*-*β*-desmotroposantonin in plates, m. p. 196–197°, unchanged by admixture with an authentic specimen of amino-*d*-*β*-desmotroposantonin. Acidification of the sodium carbonate soluble portion followed by recrystallization of the separated solid from alcohol gave a product in prismatic needles, m. p. 205–206°, depressed to 170° by admixture with amino-*l*-*β*-desmotroposantonous acid and to 176° by admixture with amino-*d*-*α*-desmotroposantonous acid. Its hydrochloride crystallized from dilute hydrochloric acid in plates.

Summary

1. Amino-*d*-*β*- and amino-*l*-*α*-desmotroposantonin have been prepared from the corresponding nitro compounds, the former also from benzeneazo-*α*-*β*-desmotroposantonin.

2. The corresponding aminosantonous acids were prepared from the aminodesmotroposantonins.

3. The constitution and configuration of the new compounds are discussed.

CAMBRIDGE, MASS. RECEIVED JUNE 16, 1947

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

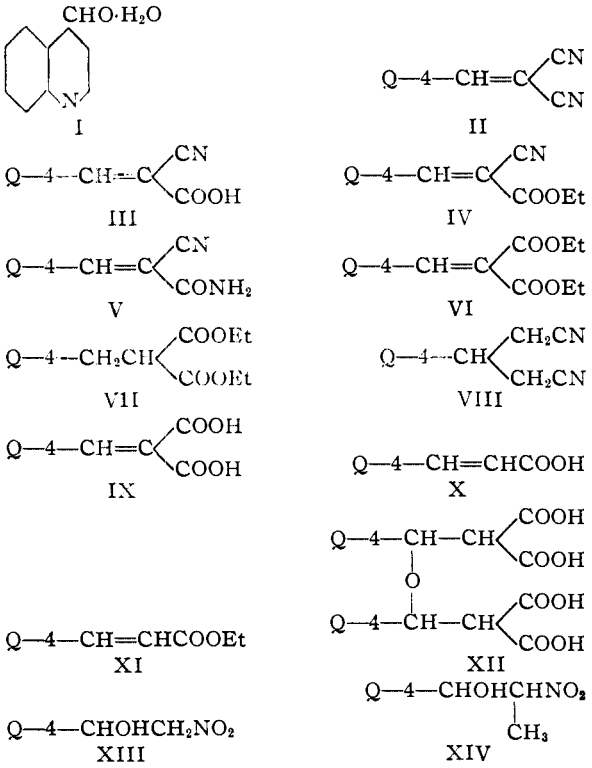
Cinchoninaldehyde and Reactive Methylene Compounds. IV[1]

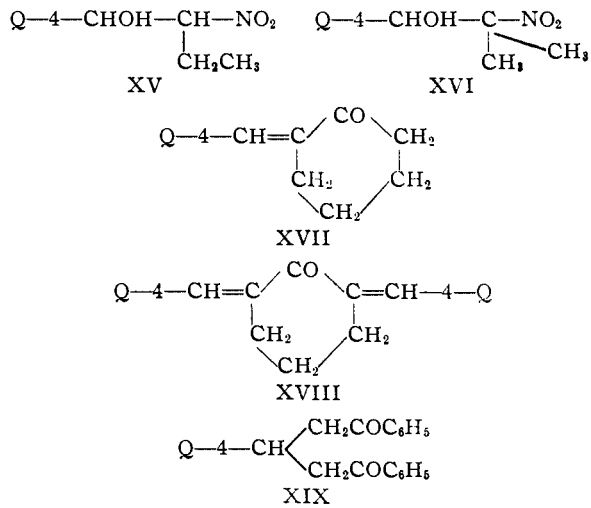
BY ARTHUR P. PHILLIPS

This paper reports the reaction of cinchoninaldehyde (I)[2] with a variety of malonic acid type compounds, with several of the lower nitroalkanes, and with cyclohexanone.

Cinchoninaldehyde (I) reacted so rapidly with one equivalent of malononitrile that no catalyst was used and a nearly theoretical yield of II was obtained. Use of two molecular equivalents of malononitrile in this reaction, in an attempt to obtain the "2 to 1" type of condensation product, gave only II though in poorer yield.

CHART OF COMPOUNDS





Cyanoacetic acid, cyanoacetic ester, cyanoacetamide, malonic ester and malonic acid, when condensed with I in alcohol, aqueous or aqueous alcohol solution, with diethylamine (or piperidine) catalyst gave excellent yields of the products: III, IV, V, VI, IX.

When cyanoacetic ester was condensed with I by means of sodium ethylate in ethanol, acidification of the reaction mixture gave only the corresponding acid, III. Hydrolysis had resulted presumably as a consequence of using the aldehyde hydrate. Esterification of this acid by the Fischer method produced the same substance, IV, obtained earlier by combination of the reactants in the presence of diethylamine.

The malonic ester product was obtained in poorer yield (60%) and no sharp boiling point was observed. Since the base showed no tendency to crystallize, this product was purified as its hydrochloride.

When the condensation with malonic acid was varied by the use of pyridine as solvent with a little piperidine as catalyst, excellent yields of quinolyl-4-acrylic acid (X) resulted rapidly and

(1) For paper III of this series see THIS JOURNAL, **69**, 865 (1947).

(2) For the method of preparation of I see reference (4).