

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure and Reactions of Malonyl- $\alpha$ -aminopyridine. IBY H. R. SNYDER AND MICHAEL M. ROBISON<sup>1</sup>

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Malonyl- $\alpha$ -aminopyridine reacts with phosphorus oxychloride to form 2-chloro-4H-pyrido[1,2-a]pyrimidin-4-one. It also undergoes coupling with diazonium salts to form products which are readily solvolyzed by the lower alcohols and amines to form mesoxalamic acid derivatives. Methylmalonyl- $\alpha$ -aminopyridine also reacts with diazonium salts, but the direct coupling products are not stable even at room temperature; they undergo hydrolysis and decarboxylation to form pyruvamide derivatives.

Since the discovery of malonyl- $\alpha$ -aminopyridine (I) by Chichibabin<sup>2,3</sup> the effects of substituents in the pyridine ring on the formation of compounds of this type have been studied by several investigators,<sup>4</sup> but except for the reduction<sup>5</sup> of the ring system little attention appears to have been given to the chemistry of the substance (I).

Chichibabin demonstrated in his original investigation<sup>2</sup> that while the bicyclic compounds are easily formed from aminopyridine and malonic ester or a monosubstituted malonic ester, the reaction fails when a disubstituted malonic ester is employed. Indeed, subsequent investigations<sup>6</sup> showed that no cyclic compound results from the reaction of 2-aminopyridine even with diethylmalonyl dichloride, but that an acyclic diamide

is formed instead. A mechanism involving the enol form of malonic ester (or of malonyl dichloride) was proposed<sup>6</sup> to explain these observations, but no evidence was presented in support of the hypothesis. The above limitations of the cyclization, the extremely high decomposition points of the compounds, and their small solubilities in non-polar solvents are rather surprising in view of the structures assigned (Ia); indeed it seems likely that these phenomena might better be explained on the basis either of enolic forms (such as Ib and Ic) or of completely aromatic zwitterions (such as Id and Ie). Accordingly, a general investigation of the spectra and chemistry of these substances has been undertaken.

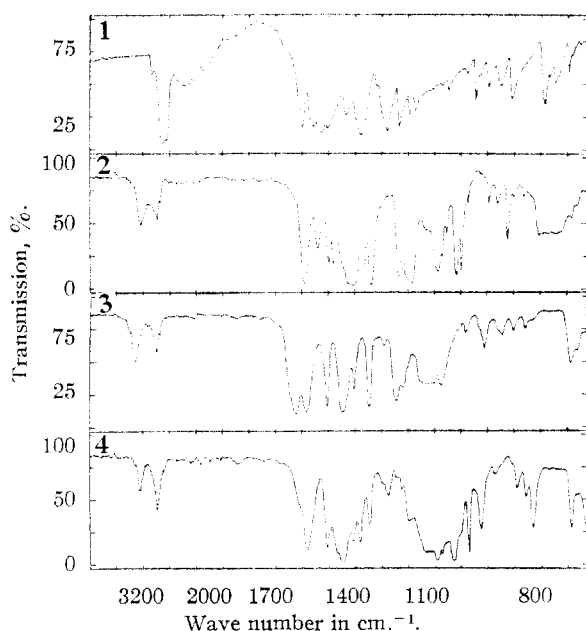
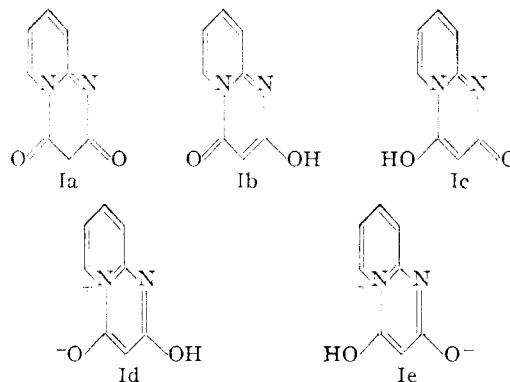
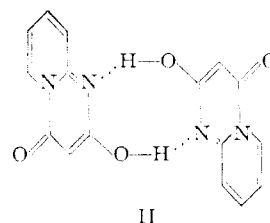


Fig. 1.—Curve 1, malonyl- $\alpha$ -aminopyridine, Nujol mull, Nujol blank; curve 2, methyl N-( $\alpha$ -pyridyl)-mesoxalamate phenylhydrazone, chloroform solution 5%, chloroform blank; curve 3, methyl malonanilate, chloroform solution 3.5%, chloroform blank; curve 4, ethyl glyoxylate phenylhydrazone, chloroform solution 7%, chloroform blank.



It was expected that the existence of structures such as Ib–Ie would be indicated by the characteristic hydroxyl absorption in the infrared spectrum. However, the absorption curve (curve 1, Fig. 1) of malonylaminopyridine does not contain the expected hydroxyl band (3300–3600  $\text{cm}^{-1}$ ). Nevertheless, the substance reacts smoothly with phosphorus oxychloride to give a product (III) having a chlorine atom instead of one of the oxygen and one of the hydrogen atoms of the original compound (I). The apparent replacement of a hydroxyl group that is not revealed in the infrared absorption, together with evidence for hydrogen bonding (absorption at 2000–2800  $\text{cm}^{-1}$ ) that can be added from the infrared curve (curve 1, Fig. 1), suggests that dimeric structures such as II



(1) Allied Chemical and Dye Corporation Fellow, 1951–1952.

(2) A. E. Chichibabin, *Ber.*, **57**, 1168 (1924).

(3) A. E. Chichibabin, *J. Russ. Phys. Chem. Soc.*, **57**, 399 (1926).

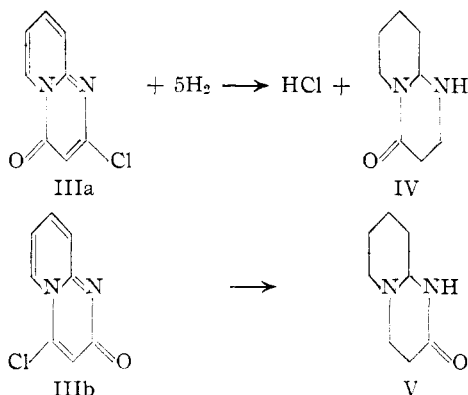
(4) N. F. Kucherova, V. F. Kucherov and D. A. Kocheshkov, *J. Gen. Chem. (U.S.S.R.)*, **16**, 1706 (1946), *C. A.*, **41**, 6243a (1947); G. R. Lappin, Q. R. Petersen and C. E. Wheeler, *J. Org. Chem.*, **15**, 377 (1950); C. R. Hauser and M. J. Weiss, *ibid.*, **14**, 453 (1949); G. R. Lappin, *THIS JOURNAL*, **70**, 3348 (1948).

(5) V. Boekelheide and J. Figueras, *ibid.*, **71**, 2587 (1949).

(6) G. B. Crippa and E. Scevola, *Gazz. chim. Ital.*, **67**, 327 (1937).

also should be considered in the representation of malonylaminopyridine. The structure II shown is analogous to that of a dimeric carboxylic acid; it can be written in a number of resonance forms, including those in which the two remaining amide functions are polarized.

The product of the reaction with phosphorus oxychloride might have a chlorine atom in either position 2 (IIIa) or position 4 (IIIb). That the structure IIIa is correct is indicated by the catalytic reduction to a chlorine-free octahydro derivative (IV) which has the properties of a secondary amine. The alternative structure (IIIb) should



have given the tertiary amine V. Furthermore, Adams and Pachter<sup>7a</sup> have previously prepared the octahydro derivative V by hydrogenation of the deschloro compound corresponding to IIIb, and it is not identical with the compound obtained by reduction of III. These investigators carried out a similar reduction<sup>7b</sup> of the deschloro compound corresponding to IIIa and obtained an octahydro derivative (IV) identical with that produced from III. Finally, the ultraviolet absorption spectrum of III is very similar to that of the deschloro analog<sup>7b</sup> of IIIa, and quite different from that of the deschloro compound corresponding to IIIb.

The ultraviolet absorption spectrum of malonyl- $\alpha$ -aminopyridine (Fig. 2, curve 1) is somewhat similar to the spectra of 2-chloro-4H-pyrido[1,2-a]pyrimidin-4-one (IIIa, Fig. 2, curve 2) and of the deschloro analog of IIIb<sup>7b</sup>; however, the differences are sufficiently pronounced as to support the conclusion, gained from the infrared studies, that the formulations Ib and Ic do not provide a complete representation of the structure of malonyl-aminopyridine.

In an attempt to replace a hydroxyl group in I by chlorine by reaction with a mixture of phosphorus oxychloride and phosphorus pentachloride, two new derivatives were obtained. They are considered to be 2,3-dichloro-4H-pyrido[1,2-a]pyrimidin-4-one (VI) and 2-hydroxy-3-chloro-4H-pyrido[1,2-a]pyrimidin-4-one (VII). That neither chlorine atom in the first compound is on the pyridine ring is shown by hydrolysis of the material in acid and isolation of 2-aminopyridine from the mixture. That the chlorine atoms are in the 2- and 3-positions is indicated by the close similarity

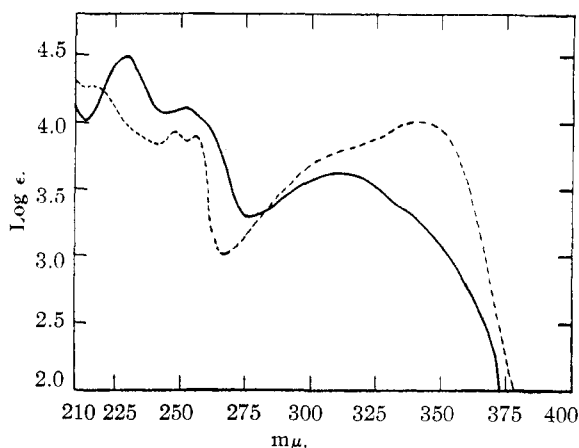
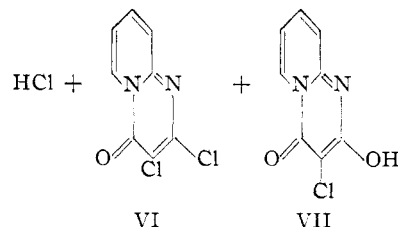
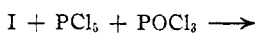


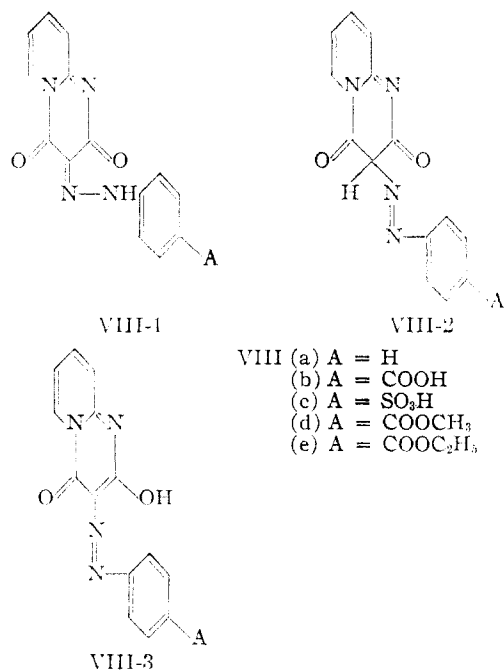
Fig. 2.—2-Chloro-4H-pyrido[1,2-a]pyrimidin-4-one, concentration  $5 \times 10^{-5}$  mole per liter, solvent isopropyl alcohol, broken line, malonyl- $\alpha$ -aminopyridine, concentration  $5 \times 10^{-5}$  mole per liter, solvent water, solid line.

of the ultraviolet spectrum of this compound to that of the 2-chloro compound from the phosphorus oxychloride reaction. It seems probable that in the reaction with phosphorus pentachloride, a chlorine atom is first introduced into the 3-position. In a second reaction carried out over a longer period only the dichloro compound was isolated; hence it appears that the monochloro compound (VII) is an intermediate in the formation of the dichloro derivative (VI).



Consideration of the structures Ib-Ie suggests that malonylaminopyridine may react with diazonium salts. The reaction with several such reagents was tested, and coupling products were obtained in excellent yields. Indeed, it seems probable that only mechanical losses prevented quantitative yields in some cases. The orange to red solids obtained from these reactions are insoluble in most solvents and melt at elevated temperatures with decomposition. The possible structures for these materials are VIII-1, VIII-2 and VIII-3 (and isomers corresponding to structures Ic, d and e). If the malonylaminopyridine residue is enolic in these compounds, only an azo linkage is possible. Spectral and chemical evidence suggests that VIII-3 is the principal structure. Thus, the infrared spectrum of compound VIIIa reveals no NH absorption, and the ultraviolet spectrum of VIIIa is similar to the product (probably 2-chloro-3-phenylazo-4H-pyrido[1,2-a]pyrimidin-4-one) obtained by treatment of VIIIa with phosphorus oxychloride (Fig. 3 curves 1 and 2). However, certain reactions of the substances seem to require the existence of structure VIII-1, or a related

(7) (a) R. Adams and I. J. Pachter, *THIS JOURNAL*, **74**, 4906 (1952); and private communication from the same authors; (b) **74**, in press (1952).



anion formed by addition of a hydroxyl ion, in basic media.

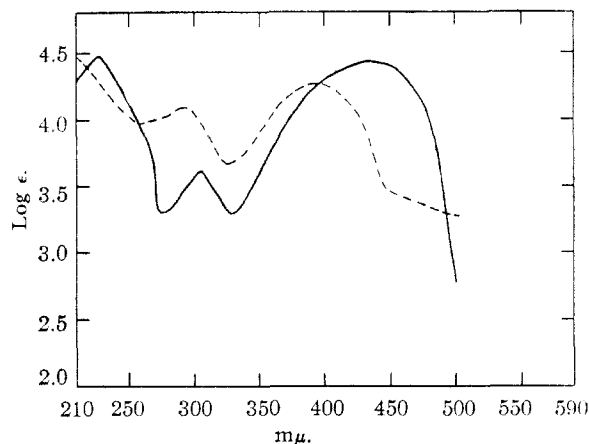
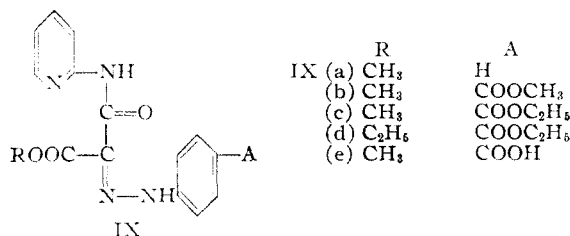
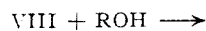


Fig. 3.—Aniline coupling product, concentration  $5 \times 10^{-5}$  mole per liter, solvent isopropyl alcohol, solid line; product from reaction of aniline coupling product with phosphorus oxychloride, concentration  $5 \times 10^{-5}$  mole per liter, solvent isopropyl alcohol, broken line.

Attempted recrystallization of the crude coupling products from methanol or ethanol leads not to their purification, but to the formation of new compounds, in yields which depend on the purity of the original coupling products. The new materials result from ring-opening to form mesoxal-

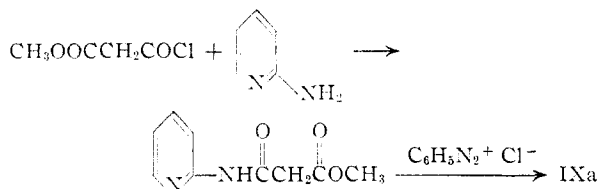


amic acid derivatives (*vide infra*). Their identity was established by independent synthesis and by their infrared spectra.

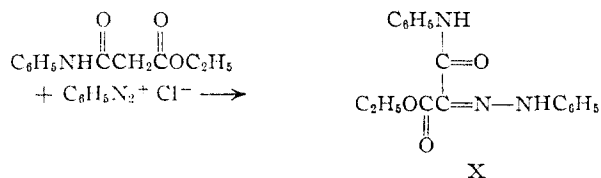
It seemed likely that the ring-opening by the alcohols was brought about by the catalytic action of basic impurities present in the crude products. To test this interpretation a mixture of the pure coupling product VIIIa and methanol containing a trace of potassium hydroxide was boiled until solution was complete (one or two minutes); when the solution was cooled the ester IXa separated. In a parallel experiment in which no potassium hydroxide was added, the coupling product was not dissolved appreciably and was recovered unchanged.

The higher alcohols are much less active than methanol and ethanol in the base-catalyzed cleavage of the diazonium coupling products, and in some cases they fail to react at all. Thus, samples of VIIIe which reacted readily with methanol, after heating for two hours with *n*-amyl alcohol at 100° were only partially solvolyzed, as evidenced by incomplete color change. With branched alcohols no reaction occurred; compound VIIIa containing basic impurities was in fact purified for analysis by recrystallization from isopropyl alcohol.

That the proposed structures (IX) are correct for the alcoholysis products was demonstrated chemically in several ways. First, it was possible to effect transesterification reactions with the compounds. In this manner IXb was converted to IXd. Compound IXb was also reduced catalytically and methyl *p*-aminobenzoate was isolated, as the trinitrobenzene derivative, from the reduction mixture. Compound IXa was also prepared by an independent synthesis as shown

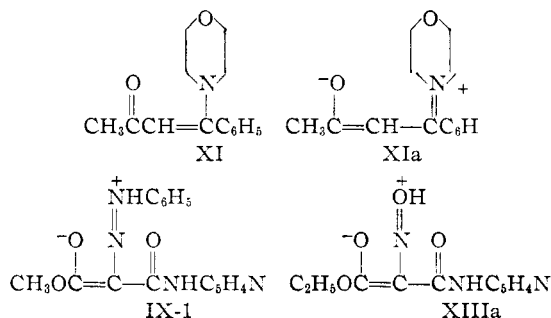


The infrared absorption spectrum of IXa reveals a single carbonyl band at 1686 cm.<sup>-1</sup>, due to both the ester and amide carbonyl groups. That the shifting of the ester band from its usual position near 1730 cm.<sup>-1</sup> is not caused by any interaction of this group with the pyridine ring was shown by the similar characteristics of the spectrum of ethyl mesoxalanilate phenylhydrazone (X) which was prepared from the known ethyl malonanilate by the scheme shown below. In this spectrum a single carbonyl band appeared at 1685 cm.<sup>-1</sup>.

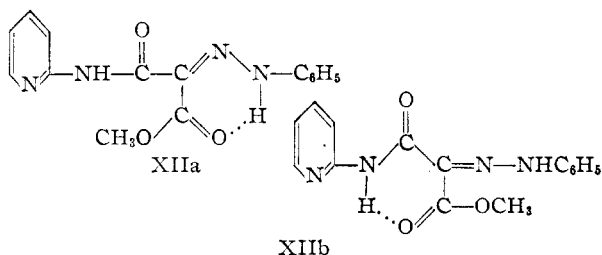


Although shifts of the ester band to a position below 1700 cm.<sup>-1</sup> are not widely known, examples have been reported previously by Rasmussen and

Brattain.<sup>8</sup> These authors found that while the ester band of methyl N,N-dimethylantranilate appeared at a normal position for a conjugated ester (*circa* 1730 cm.<sup>-1</sup>), when "conjugated chelation" may be possible, as in methyl N-methylantranilate, the ester absorption is found at 1685 cm.<sup>-1</sup>. That a nitrogen atom in the  $\beta$ -position of an  $\alpha,\beta$ -unsaturated carbonyl compound may cause such shifts even when chelation is not possible was shown in work<sup>9</sup> with  $\beta$ -amino  $\alpha,\beta$ -unsaturated ketones. Ketone carbonyl absorptions were shifted 30 cm.<sup>-1</sup> from the expected positions in compounds such as XI where no chelation is possible, and larger shifts were observed when the  $\beta$ -amino nitrogen atom carried a hydrogen. It was concluded that contributions from such resonance forms as XIa were responsible for the shifts in the disubstituted compounds and that where chelation was possible its effect was superimposed on the resonance effect.



It is therefore not surprising that a similar shift occurs in compounds of type IX since there are possibilities in these cases both for resonance with forms of type IX-1 and for chelation. It may be noted that in these compounds, however, the  $\alpha,\beta$ -unsaturation is in the form of a C=N rather than a C=C double bond. If chelation alone were responsible, the carbonyl shift could be attributed to either of two possible chelate structures (XIIa or XIIb). To determine which conformation might be responsible, the spectra of methyl malonanilate (Fig. 1, curve 3) and of ethyl glyoxylate phenylhydrazone (Fig. 1, curve 4) were examined. Although in the amide the ester band is shifted slightly to  $1720\text{ cm}^{-1}$ , in the phenylhydrazone the only band which can be attributed to the ester carbonyl is found at  $1680\text{ cm}^{-1}$ .



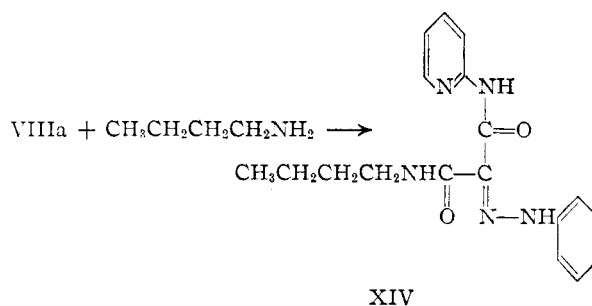
It is interesting to note that the ester absorption band of ethyl N-( $\alpha$ -pyridyl)-isonitrosomalonnate (XIII), which was synthesized by the action of

(8) R. S. Rasmussen and R. R. Brattain, *THIS JOURNAL*, **71**, 1073 (1949).

(9) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank and D. J. Wallace, *ibid.*, **71**, 3337 (1949).

*n*-propyl nitrite<sup>10</sup> on ethyl N-( $\alpha$ -pyridyl)-malonate, showed an ester absorption band at 1734 cm.<sup>-1</sup> as well as an amide absorption at 1700 cm.<sup>-1</sup>. In this case chelation may have been impossible because the oxime hydroxyl was anti to the ester group, or, if resonance forms such as those shown above are responsible, it is seen that XIIIa, which carries a positive charge on oxygen, would probably contribute less to the ground state of the molecule than the corresponding forms with a quaternary nitrogen atom.

By analogy to the alcohololyses it was thought that the lower amines might also cleave the coupling products. This was found to be the case. *n*-Butylamine reacted with VIIIa at reflux temperature to produce the amide XIV. The higher amines, as exemplified by piperidine and aniline, either failed to react or reacted to an inconsequential extent, although VIIIe was refluxed with the former for six hours, and was treated with the latter in a comparable manner.



The coupling products are also easily cleaved by dilute aqueous base on standing at room temperature. Although these solvolyses may proceed at first in a manner analogous to that already mentioned, the decomposition is here more far-reaching, and except under very mild conditions results in disintegration of the molecule with the formation of hydrogen cyanide, which material arises from the methylene carbon and adjacent nitrogen. This hydrolysis will be the subject of a separate communication.

To determine whether monoalkylmalonylamino-pyridines would behave in a fashion similar to that of I, compound XV was subjected to diazonium coupling. It is to be noted that in this case it is impossible for the coupling product to exist in the hydrazone form unless migration of the methyl group takes place. Although coupling occurs readily, the initial product undergoes hydrolysis and decarboxylation. Only a pyruvamide derivative of type XVI could be isolated.

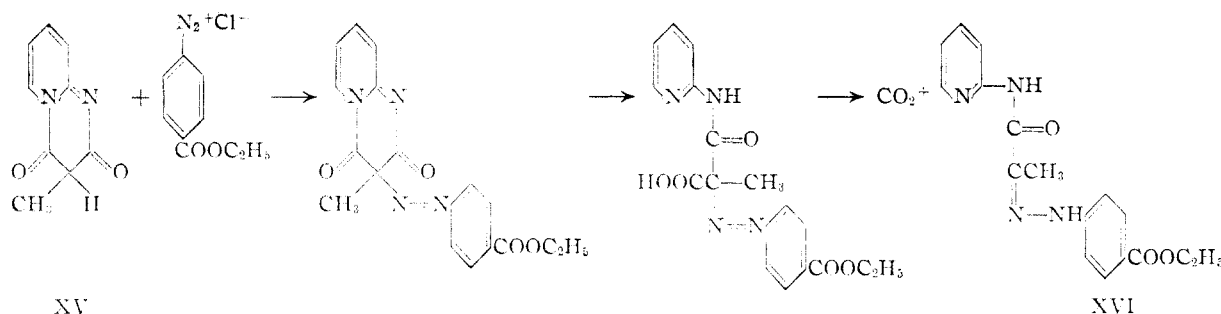
## Experimental<sup>11,12</sup>

**Malonyl- $\alpha$ -aminopyridine.**—This compound was prepared by the method of Chichibabin.<sup>2</sup> Since it was not convenient to recrystallize the large quantities required from water, owing to the small solubility, the purification procedure employed consisted of suspending the crude ethanol-

(10) A. Gero and M. W. Seitchek, private communication, suggested the use of this ester in nitrosations.

(11) All melting points are uncorrected.

(12) Microanalyses by Miss Emily Davis, Mrs. Jean Fortney, Mrs. E. Fett and Mrs. Katherine Pih. Infrared spectra by Miss Elizabeth Petersen and Miss Helen Miklas. Ultraviolet spectra by Mr. Homer Birch.



washed product in distilled water (750 ml. per 100 g.), adding just sufficient sodium hydroxide solution to dissolve all the solid, then stirring in 6 g. of Darco and allowing the mixture to stand overnight at room temperature. The Darco was removed by filtration, and Dry Ice was added to the solution to cause precipitation of nicely crystalline light yellow leaflets. The product was filtered off periodically, washed with water, and air-dried. This material was in all respects identical with that obtained by water recrystallization.

**Methylmalonyl- $\alpha$ -aminopyridine (XV).**—This material was also prepared by the method of Chichibabin<sup>2</sup>; it was purified by the procedure described above.

**2-Chloro-4H-pyrido[1,2-a]pyrimidin-4-one (IIIa).**—Malonylamino-pyridine (5.75 g.) was heated under reflux with 15 g. of phosphorus oxychloride for a period of 45 minutes. Vigorous evolution of hydrogen chloride took place and all of the solid dissolved before the end of the heating period. The mixture was cooled and poured into ice-water, the cold solution filtered and the solid washed with water. The crude product was obtained in 36% yield (2.3 g.). Recrystallization from water (Darco) produced, on slow cooling, white needles, m.p. 155.2–156.2°. The product, unlike the parent compound, was base-insoluble.

*Anal.* Calcd. for  $C_8H_6N_2OCl$ : C, 53.20; H, 2.79; N, 15.51; Cl, 19.63. Found: C, 53.22; H, 2.68; N, 15.58; Cl, 19.83.

In another preparation, on a 0.1 molar scale, the excess phosphorus oxychloride was distilled *in vacuo* and the residue was triturated with 250 ml. of cold water. The suspension was filtered and the filtrate neutralized with solid sodium bicarbonate to yield more product. The two batches were combined and recrystallized from water; yield 9.6 g. (53%) of crude material, m.p. 151–154°.

**Octahydro-4H-pyrido[1,2-a]pyrimidin-4-one (IV).**—The crude chloro compound (4.5 g., m.p. 154.5–155°) was mixed with 200 ml. of absolute alcohol and 200 mg. of platinum oxide and shaken with hydrogen at 3 atmospheres pressure (room temperature) for a period of about 8 hours. After the theoretical amount of hydrogen was absorbed the platinum was filtered off and the yellow solution was evaporated to dryness on a steam-bath. The solid residue of amine hydrochloride was triturated with acetone to remove colored impurities and then dissolved in 15 ml. of concentrated sodium carbonate solution. The brown oil which separated was extracted with chloroform and the extracts were dried over sodium sulfate and treated with alkali-washed Darco at room temperature. Evaporation of the solvent produced an orange oil. This was dissolved in 50 ml. of benzene and the benzene was evaporated to remove traces of water and alcohol. The resulting oil solidified after standing in an ice-box for several days. The solid, which was very soluble in water and organic solvents, was recrystallized by dissolution in boiling absolute ether (Darco) followed by thorough chilling in an ice-box. The resulting hygroscopic white crystals, which had an amine-like odor, melted at 61–61.8°.

*Anal.* Calcd. for  $C_8H_{14}N_2O$ : C, 62.30; H, 9.15; N, 18.17. Found: C, 62.71; H, 9.06; N, 18.08.

The infrared spectrum of the octahydro derivative revealed no absorption band in the 1515–1560  $cm^{-1}$  region (80–83% transmission). Since such an absorption is a very reliable indication of a monosubstituted amide group<sup>13</sup>

its absence provides support for the postulated 4-one structure. The carbonyl absorption band appeared at 1625  $cm^{-1}$ , and that of the amine NH at 3240  $cm^{-1}$ .

When the secondary amine was heated on a steam-bath for one minute with excess phenyl isothiocyanate, the phenylthiourea was formed. The product was washed with cyclohexane and recrystallized from isopropyl alcohol; white crystals, m.p. 174.5–176°.

*Anal.* Calcd. for  $C_{15}H_{19}N_2OS$ : C, 62.25; H, 6.62. Found: C, 62.43; H, 6.84.

**Reaction of I with Phosphorus Pentachloride and Phosphorus Oxychloride.**—This reaction was patterned after the procedure of Wibaut<sup>14</sup> for the preparation of 4-chloropyridine. Phosphorus pentachloride (7.5 g.) and phosphorus oxychloride (7.5 g.) were warmed in a reflux apparatus until the solid dissolved, and then allowed to cool. Compound I (5.75 g.) was added to the partially crystallized mixture, followed by 8 g. more phosphorus oxychloride. The slurry was then heated to 110–120°, at which point reaction set in and hydrogen chloride was evolved. The mixture was heated at this temperature for a period of three hours during which time most of the solid dissolved and the liquid turned reddish-brown. On cooling, the mixture crystallized. The solid was poured into water and the mixture was filtered to yield a yellow solid which was washed with dilute sodium hydroxide solution.

The residue from the alkali washing was recrystallized from isopropyl alcohol (Darco) to produce filaments, m.p. 225.8–226.5°. These crystals of 2,3-dichloro-4H-pyrido[1,2-a]pyrimidin-4-one were insoluble in dilute acid or base and somewhat soluble in water or organic solvents.

*Anal.* Calcd. for  $C_8H_6N_2OCl_2$ : C, 44.68; H, 1.87; N, 13.03. Found: C, 45.09, 44.73; H, 2.04, 1.88; N, 13.24.

The filtrate from the alkali washing procedure was acidified to produce faintly yellow needles. These were soluble in 5% aqueous sodium bicarbonate and insoluble in hydrochloric acid of the same concentration. After several recrystallizations from water they had no melting point, but decomposed slowly at 290° without becoming liquid.

*Anal.* Calcd. for  $C_8H_5N_2O_2Cl$ : C, 48.87; H, 2.56; N, 14.25. Found: C, 48.71; H, 2.66; N, 14.43.

In a second reaction, which was identical with the above except that the mixture was heated for a period of four hours, no product was obtained on acidification of the alkali washings and only the dichloro compound was isolated.

**Hydrolysis of the Dichloro Derivative.**—The pure chlorination product (0.3 g.) was refluxed with 10 ml. of 6 N hydrochloric acid for a period of 18 hours. Part of the resulting colorless liquid was boiled off and to the residue was added, with cooling, sufficient 50% sodium hydroxide solution to effect neutralization. The resulting solution was saturated with sodium carbonate and extracted with ether. The extracts were dried and evaporated on the steam-bath. On drying in a vacuum desiccator, white crystals of 2-aminopyridine formed; m.p. 58.5–60°. On admixture with an authentic sample of the amine, a melting point of 58.5–60° was observed.

**Diazonium Couplings. Procedure I. Non-amphoteric Amines.**<sup>15</sup>—The aromatic amine (0.2 mole) was dissolved or suspended in a mixture of 60 ml. of water and 42 ml. of concentrated hydrochloric acid, which had previously been

(13) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangle, "Infrared Determination of Organic Structures," D. Van Nostrand Co., New York, N. Y., 1949, p. 11.

(14) J. P. Wibaut and F. W. Broekman, *Rec. trav. chim.*, **58**, 885 (1939).

(15) This procedure was patterned after that used by R. P. Linstead and A. B. Wang, *J. Chem. Soc.*, 807 (1937).

cooled to 0°. To this mixture was added dropwise a previously cooled solution of 18 g. (0.225 mole if 100%) of potassium nitrite in 100 ml. of water; addition was continued to the starch-iodide end-point. When the diazotization was complete, 24 g. of solid potassium acetate was added directly to the slurry with stirring. Malonyl- $\alpha$ -aminopyridine (32.4 g., 0.2 mole) was dissolved in a solution of 27 g. of potassium hydroxide in 800 ml. of water which had previously been cooled to 0°, and to this clear solution the diazonium mixture was added *all at once* with vigorous stirring. When the diazotized aminobenzoic esters were used, the mixtures set immediately to semi-solid pastes. After the benzenediazonium chloride reaction the pH was adjusted to about 7 with acetic acid to complete the precipitation of the product. When the other mixtures had been allowed to stand in the ice-bath for about one-half hour, the clay-like precipitates were filtered by suction as rapidly as possible, washed thoroughly with dilute acetic acid, cold water, and then with acetone, and dried in the air. Since the precipitated esters are contaminated by their potassium salts, thorough trituration with the acetic acid is necessary.

**Procedure II, Amphoteric Amines.**—The procedure was similar to the above, except that on a 0.2 molar scale from 30 to 40 g. of potassium acetate was added to the diazonium salt solution. After addition to the malonylaminopyridine, the pH was adjusted to 8, and any solid (unchanged malonylaminopyridine) present in the mixture was filtered off and discarded. The solution was then acidified to congo red with concentrated hydrochloric acid, and the resulting orange precipitate filtered, washed and dried as above.

**Aniline Coupling Product (VIII-a).**—By procedure I an 85% yield of crude product (m.p. 227–229° dec.) was obtained. In the first preparations, in which the mixtures were not acidified after the coupling, the crude VIIIa was obtained in yields of about 50%. Repeated recrystallization of such products from isopropyl alcohol yielded golden-orange plates, m.p. 246–246.4° dec. (block). The decomposition point was found to depend greatly on the rate of heating, as was the case with all of the other direct coupling products.

*Anal.* Calcd. for  $C_{14}H_{10}N_4O_2$ : C, 63.15; H, 3.79; N, 21.04. Found: C, 63.06; H, 3.70; N, 21.04.

**Methyl *p*-Aminobenzoate Coupling Product (VIII-d).**—This compound was obtained in 70% yield (crude product) and was purified for analysis by five recrystallizations from benzene. Large volumes of the solvent were required to dissolve the substance, and the resulting solutions did not deposit crystals until they had been evaporated to about half volume. The pure, golden-brown leaflets melted at 252° dec.

*Anal.* Calcd. for  $C_{16}H_{12}N_4O_4$ : C, 59.25; H, 3.73; N, 17.28. Found: C, 59.64; H, 3.75; N, 17.10.

**Ethyl *p*-Aminobenzoate Coupling Product (VIII-e).**—This compound was obtained as an orange powder. Repeated recrystallization from benzene gave shiny red-orange leaflets, m.p. 249° dec.

*Anal.* Calcd. for  $C_{17}H_{14}N_4O_4$ : C, 60.35; H, 4.17; N, 16.56. Found: C, 60.43; H, 4.09; N, 16.61.

**Sulfanilic Acid Coupling Product (VIII-c).**—The crude substance was obtained as an orange powder in 93% yield. Its purification was effected by dissolution in a minimum amount of dilute ammonium hydroxide and treatment of this solution with Darco at room temperature. After filtration the red liquid was placed in a desiccator with a beaker of concentrated hydrochloric acid and allowed to stand until complete precipitation had taken place. This procedure was repeated four times without use of Darco. The final product was washed repeatedly with water until the filtrate gave no precipitate with silver nitrate solution, then washed with cold alcohol and dried; m.p. 248° dec. (block). A series of direct neutralization equivalents determined in water by use of a pH meter indicated that the material exists as the hemihydrate.

*Anal.* Calcd. for  $C_{14}H_{10}N_4O_5 \cdot \frac{1}{2}H_2O$ : C, 47.32; H, 3.12; N, 15.77; neut. equiv., 355. Found: C, 47.32; H, 3.19; N, 15.95; neut. equiv., 358, 356, 352, 358.

***p*-Aminobenzoic Acid Coupling Product (VIII-b).**—This substance was an orange-red powder, formed in 96% yield (crude). Purification by dissolution in base and reprecipitation was not practicable because rapid hydrolysis of the compound took place in the basic solution. The only ef-

fective recrystallization solvent discovered was pyridine; repeated recrystallizations from this yielded a red material with a strong pyridine odor. Washing with chloroform removed the odor and left an orange powder, m.p. 261.2–262° dec. (block). This substance was not, however, analytically pure, and no method of effecting complete purification was discovered.

**Reaction of VIIIa with Phosphorus Oxychloride.**—Compound VIIIa (2.7 g.) was heated under reflux with 17 g. of phosphorus oxychloride for a period of four hours, during which time hydrogen chloride was evolved and all of the solid dissolved. The mixture was allowed to stand for seven hours more at room temperature and then poured into 300 ml. of water. The resulting precipitate was filtered, washed with water and dried. Extraction with boiling cyclohexane left a large residue of unreacted starting material and produced, on cooling, red, base-insoluble needles. These, after several recrystallizations from cyclohexane (Darco) melted at 177–178.2° without decomposition.

*Anal.* Calcd. for  $C_{14}H_9N_4OCl$ : C, 59.07; H, 3.19; N, 19.68. Found: C, 59.15; H, 3.26; N, 19.85.

**Alcoholyses, General Procedure.**—These reactions were usually carried out by recrystallization, from methanol or ethanol, of a coupling product which had not been trituated with dilute acid. Although the products were in most cases nicely crystalline substances which exhibited sharp, constant melting points, their compositions, as demonstrated by analysis, varied. For example, a sample on which a good analysis had been obtained on further recrystallization might have a content which differed by as much as 1%. It is thought that this phenomenon may be due to cyclization with loss of alcohol.

**Methyl N-( $\alpha$ -Pyridyl)-mesoxalamate Phenylhydrazone (IXa).**—This compound was obtained by recrystallization of VIIIa from methanol. Repeated recrystallizations from this solvent yielded light yellow, hair-like filaments; m.p. 164.8–165.2°.

*Anal.* Calcd. for  $C_{15}H_{14}N_4O_2$ : C, 60.39; H, 4.74; N, 18.78; methoxyl, 10.40. Found: C, 60.86; H, 4.83; N, 18.52; methoxyl (Zeisel), 11.10.

The compound was also obtained by independent synthesis as follows.

**Potassium Methylmalonate.**—This was prepared from dimethyl malonate (Eastman Kodak Co., white label) by the procedure for potassium ethyl malonate,<sup>16,17</sup> in 60% yield.

**Methylmalonyl Chloride.**—This was synthesized by the method of Staudinger<sup>18</sup> in a yield of 55.4%; b.p. 47–50° (5 mm.).

**Methyl N-( $\alpha$ -Pyridyl)-malonamate.**—A solution of 19 g. of the acid chloride in 140 ml. of absolute ether was added to a solution of 13.1 g. of 2-aminopyridine (Eastman Kodak Co., white label) in 350 ml. of absolute ether. The gummy, yellow-white precipitate which formed was shaken with 100 ml. of a saturated sodium carbonate-sodium chloride solution. After all of the solid had dissolved, the water layer was extracted with ether overnight in a continuous extractor. Evaporation of the ether left 15.4 g. (56.4%) of the crude amide as a light red oil. It was not found possible or necessary to crystallize or distill this substance; rather it was used directly in the diazonium coupling.<sup>19</sup>

**Methyl N-( $\alpha$ -Pyridyl)-mesoxalamate Phenylhydrazone.**—The product, obtained in practically quantitative yield, exhibited a melting point of 166–167° after two recrystallizations from methanol, and on admixture with a sample from the first source melted at 166–166.5°. The infrared spectra of the two samples were identical.

Another portion of the crude product from Kruckeberg's procedure after two recrystallizations from absolute ethanol melted at 162.5–164°, and when mixed with the methanolysis product IXa melted at 163.5–164.5°.

**Methyl N-( $\alpha$ -Pyridyl)-mesoxalamate *p*-Carbomethoxyphenylhydrazone (IXb).**—This substance, which was obtained by methanol recrystallization of VIIIc exhibited m.p. 189.5–190°.

(16) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans Green and Company, London, 1948, p. 265.

(17) The methyl ester was saponified in methanol.

(18) H. Staudinger and H. Becker, *Ber.*, **50**, 1019 (1917).

(19) The method devised by F. Kruckeberg, *J. prakt. Chem.*, [2] **49**, 321 (1894), for a diazonium coupling with ethyl cyanoacetate, was used for the coupling.

*Anal.* Calcd. for methoxyl, 17.42. Found: methoxyl (Zeisel), 18.39, 18.09, 18.07.

**Hydrogenation of Compound IXb.**—The substance (1.5 g.) was hydrogenated in 150 ml. of absolute alcohol at 1600 p.s.i. and 100° for three hours with a Raney nickel catalyst. The resulting cloudy yellow solution was evaporated *in vacuo*, the residue extracted with water, and the remaining solid taken up in ether. The solution, after drying, was evaporated to yield leaflets; m.p. 93–104°. Treatment with *sym*-trinitrobenzene in alcohol produced dark orange needles, which after recrystallization from alcohol melted at 113.5–114.2° (reported<sup>20</sup> m.p. 114–114.5°). With an authentic sample of this derivative (m.p. 112.5–114.5°), a mixed melting point of 113.5–114.5° was observed.

**Ethyl N-( $\alpha$ -Pyridyl)-mesoxalamate *p*-Carbethoxyphenylhydrazone (IXd).**—This ester was prepared by ethanol recrystallization of VIIIe; light yellow filaments, m.p. 165–165.5°.

*Anal.* Calcd. for  $C_{19}H_{20}N_4O_5$ : C, 59.37; H, 5.24; N, 14.58; ethoxyl, 23.46. Found: C, 59.12; H, 4.89; N, 14.86; ethoxyl (Zeisel), 22.83, 22.72.

The ester was obtained by a second route from IXb by transesterification. The dimethyl ester was suspended in absolute alcohol which contained a small amount of sodium ethoxide and allowed to stand for three days. The solid obtained by filtration contained sodium ion. Trituration with dilute hydrochloric acid, followed by repeated recrystallization from absolute alcohol produced a material whose melting point was 157–159°. This melting point could not be raised by further recrystallization or by treatment again with ethanolic sodium ethoxide. On admixture with the pure diethyl ester (m.p. 165–165.5°), the melting point was 159–161°. The infrared spectrum of the transesterification product, however, was practically identical with that of the 165° material; there were some differences in sharpness of bands, though not in frequency.

**Methyl N-( $\alpha$ -Pyridyl)-mesoxalamate *p*-Carbethoxyphenylhydrazone (IXc).**—This compound was obtained by repeated recrystallization of VIII-e from methanol; yellow filaments, m.p. 175.2–176°.

*Anal.* Calcd. for  $C_{18}H_{18}N_4O_5$ : C, 58.37; H, 4.90; N, 15.83. Found: C, 58.44; H, 4.97; N, 16.03.

**N-( $\alpha$ -Pyridyl)-N'-*n*-butylmesoxalamide Phenylhydrazone (XIV).**—Product VIIa (2.66 g., 0.01 mole) was suspended in 20 ml. of *n*-butylamine and refluxed on the steam-bath until dissolution was complete. Filtration of the hot red solution, followed by evaporation of excess amine, produced a red oil. This was extracted several times with hot, low-boiling petroleum ether. Cooling the extracts produced an oil, which solidified. This crude product was obtained in 50% yield. Several recrystallizations from low-boiling petroleum ether produced yellow filaments which were quite soluble in all organic solvents; m.p. 110.5–111.5°.

*Anal.* Calcd. for  $C_{18}H_{21}N_5O_2$ : C, 63.70; H, 6.24; N, 20.64. Found: C, 63.79; H, 6.30; N, 20.67.

**N-( $\alpha$ -Pyridyl)-pyruvamide *p*-Carbethoxyphenylhydrazone (XVI).**—This substance was prepared on a 0.01 molar scale by coupling methylmalonyl- $\alpha$ -aminopyridine with diazotized ethyl *p*-aminobenzoate; the procedure ordinarily employed with the unsubstituted malonyl compound was used. There was obtained 2.9 g. (89% on the basis of final product) of yellow-red precipitate. Recrystallization from

cyclohexane yielded a white powder interspersed with large red needles. Repeated recrystallizations from a 1:1 mixture of benzene and cyclohexane produced reddish-brown needles alone. These were dimorphic. On rapid heating, they melted sharply and completely at about 185°; on slow heating, they sintered sharply at this temperature and then melted at 204.5–205°. If the material was caused to melt at 185° and then immediately cooled, it resolidified and did not melt again until 205°.

*Anal.* Calcd. for  $C_{17}H_{18}N_4O_3$ : C, 62.56; H, 5.56; N, 17.17. Found: C, 62.70; H, 5.47; N, 17.14.

**Ethyl Mesoxalanilate Phenylhydrazone.**—Ethyl malonanilate, prepared by the method of Chattaway,<sup>21</sup> was subjected to a diazonium coupling by the method of Kruckeberg.<sup>19</sup> Recrystallization of the precipitate from 95% alcohol produced yellow filaments; m.p. 103.2–103.8°.

*Anal.* Calcd. for  $C_{17}H_{17}N_3O_5$ : C, 65.58; H, 5.51; N, 13.50. Found: C, 65.57; H, 5.58; N, 13.54.

**Ethyl N-( $\alpha$ -Pyridyl)-isonitrosomalonomate (XIII).**—Potassium ethylmalonate<sup>18</sup> was treated with thionyl chloride<sup>18</sup> to produce ethylmalonyl chloride in 40% yield, b.p. 60° (7 mm.) (reported<sup>18</sup> b.p. 63–64° (10 mm.)). The product was then added to 2-aminopyridine by the same procedure as given above for methyl N-( $\alpha$ -pyridyl)-malonomate. The amide, which was obtained as an oil in a yield of 72% (crude), was nitrosated in the following manner.

Ethyl N-( $\alpha$ -pyridyl)-malonomate (4.16 g., 0.02 mole, crude) was dissolved in a mixture of 20 ml. of absolute alcohol and 20 ml. of absolute ether. This solution was mixed with *n*-propyl nitrite<sup>10</sup> (1.78 g., 0.02 mole) and 0.02 mole of sodium ethoxide in 20 ml. of absolute alcohol was added. The mixture turned dark red and became warm. After it had been allowed to stand for about ten minutes, glacial acetic acid was added to pH 7, at which point a heavy precipitate formed; this solid contained inorganic material. It was taken up in a minimum quantity of hot alcohol and reprecipitated by the addition of water, then repeatedly recrystallized from a mixture of 50% benzene and 50% cyclohexane. The pure compound appears as rosettes of white filaments; m.p. 165.8–166° dec.

*Anal.* Calcd. for  $C_{16}H_{17}N_3O_4$ : C, 50.63; H, 4.68; N, 17.71. Found: C, 50.77; H, 4.76; N, 17.51.

**Ethyl Glyoxylate Phenylhydrazone.**—Ethyl glyoxylate hemiacetal<sup>22</sup> (8.8 g.) was treated with a mixture of 6.5 g., of phenylhydrazine and 3.6 g. of glacial acetic acid in 40 ml. of water. The crude phenylhydrazone was produced in 67% yield. One recrystallization from 50% aqueous alcohol produced yellow filaments, m.p. 128.5–130° (reported<sup>22</sup> m.p. 131°, and m.p. 129–130°<sup>23</sup>).

**Methyl Malonanilate.**—This compound was prepared by the method of Chattaway<sup>21</sup> for the corresponding ethyl ester. Several recrystallizations from an ether-petroleum ether mixture produced white plates, m.p. 47–48.5° (reported<sup>18</sup> m.p. 42°).

**Ultraviolet Spectra.**—All spectra were determined<sup>12</sup> by means of a Cary automatic recording spectrophotometer.

**Infrared Spectra.**—All infrared spectra were determined<sup>12</sup> using a Perkin-Elmer model 21 double beam automatic recording spectrophotometer.

#### URBANA, ILLINOIS

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