general acid-catalyzed reaction and suggests that in processes leading to the formation of salts of the dianil of 2-hydroxyglutaconaldehyde, VII–VIII, a generalized 1,6-addition may occur.

Representation of the reaction mechanism as involving the intermediate formation of the anil is based in part on the early studies of de Chalmot[13] who reported that aniline hydrochloride and furfural anil reacted to form the purple compound described by Stenhouse.[2] The work of König, *et al.*,[8,10] is similarly suggestive. In addition to the preparation of the chloride and nitrate salts of VII–VIII from the anil for this study, a variety of similar compounds, unsymmetric anils of 2-hydroxyglutaconaldehyde, have been prepared from substituted-anils of furfural and various aromatic amines in the presence of acid.[14]

Borsche and co-workers[15] have proposed a mechanism for the formation of the substituted dienes in which hydrogen chloride cleaves the furan ring of the anil at the 1- and 5-positions. This is followed by a 1,6-addition of aniline to the intermediate and subsequent 1,6-elimination of hydrogen chloride to give structure I. The mechanism of Borsche, *et al.*, involves the reaction of a vinylic chloride with an amine, whereas the mechanism proposed here invokes reaction of an allylic chloride or α-chloroether. Both of the latter species are notably reactive.

(13) G. de Chalmot, *Ann.*, **271**, 11 (1892).

(14) W. M. Foley, Jr., C. V. Brouillette, G. E. Sanford and H. McKennis, Jr., THIS JOURNAL, in preparation.

(15) W. Borsche, H. Leditschke and K. Lange, *Ber.*, **71B**, 957 (1938).

Experimental

Preparation of 1-Phenylimino-5-phenylamino-2-hydroxypenta-2,4-diene Hydrochloride (Under Anhydrous Conditions).—The anhydrous anil of furfural[13] (5.64 g.) was mixed with 4.23 g. of anhydrous aniline hydrochloride in 30 ml. of anhydrous ethanol under an atmosphere of dry nitrogen. The solvent was removed under diminished pressure. The residue, m.p. 166.5–167.5°, weighed 9.21 g. (93%). Recrystallization from anhydrous ethanol gave a product, m.p. 169° (dec.). Williams and Wilson[16] reported a melting point of 166–167° (dec.). The melting point of this and related compounds varies with the rate of heating. The hydrochloride is hygroscopic and decomposes under the influence of subdued light.

Anal. Calcd. for $C_{17}H_{17}N_2OCl$: C, 67.8; H, 5.64; N, 9.28; Cl, 11.8. Found: C, 67.5; H, 5.7; N, 9.01; Cl, 11.9.

Preparation of the Nitrate.—Aniline nitrate (1.42 g.) and 1.71 g. of the anil of furfural were dissolved in 17 ml. of anhydrous ethanol. The product, 1.91 g. (61%) formed and was removed by filtration and dried under diminished pressure, m.p. 124–126° (dec.). The salt is very hygroscopic and extremely sensitive to light.

Anal. Calcd. for $C_{17}H_{17}N_3O_4$: N, 12.85. Found: N, 12.85.

Preparation of the Acid Sulfate.—The method of Stenhouse[2] was employed. It was found that purification could best be effected by dissolving the compound in warm ethanol (not over 50°) and chilling as soon as possible. The product was dried under diminished pressure. In common with the other salts it is hygroscopic and decomposes in the presence of light.

Acknowledgment.—The authors wish to thank Dr. Carl T. Redemann and Mr. Robert J. Brotherton for the microanalyses, and Mr. Elmer Streed, all of this Laboratory, for determination of the absorption spectra.

(16) G. Williams and C. L. Wilson, *J. Chem. Soc.*, 506 (1942).

PORT HUENEME, CALIFORNIA

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

Ultraviolet Spectra and Structures of the Pyrido[1,2-a]pyrimidones

BY ROGER ADAMS AND IRWIN J. PACHTER

RECEIVED JUNE 16, 1952

The ring nitrogen of 2-aminopyridine adds to acrylic acid, ethyl acrylate and α-bromoacrylic acid; on the other hand, the amino nitrogen adds to ethoxymethylenemalonic ester. These facts were established by determination of the structure of the addition products. Pyrido[1,2-a]pyrimidin-4-one was synthesized and its ultraviolet absorption spectrum compared with that of pyrido[1,2-a]pyridin-2-one. The differences were sufficiently great to permit these spectra to be used as models in a reconsideration of the structures assigned to several pyridopyrimidones reported in the literature.

The chemistry of 2-aminopyridine is complicated by the presence in the molecule of two nitrogen atoms of similar reactivity, and it is frequently difficult to present unequivocal proof of structure of the reaction products of the base. In the present paper the structures of the pyrido[1,2-a]pyrimidones derived from 2-aminopyridine will be considered.

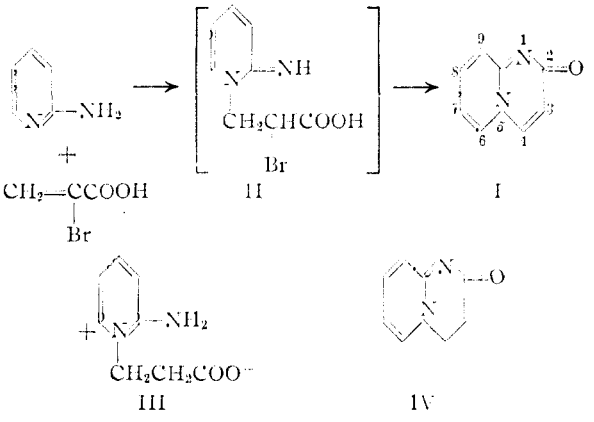
When 2-aminopyridine was heated with α-bromoacrylic acid in chloroform, the hydrobromide of 2H-pyrido[1,2-a]pyrimidin-2-one (I) was obtained in 45% yield. The intermediate II (or its zwitterionic tautomer) was probably formed and then eliminated hydrogen bromide and water. The free base (I) was obtained from the hydrobromide by treatment with either silver oxide or sodium hydroxide. The structure of I was established previously and it was also synthesized by another route.[1]

Acrylic acid and ethyl acrylate reacted with 2-aminopyridine to give the previously characterized compounds[1] III and IV, respectively.

These reactions involved attachment of the ring nitrogen of 2-aminopyridine to the β-carbon atom of acrylic acid, its ethyl ester and its α-bromo derivative. Previously, Lappin[2] described the reactions of several 2-aminopyridine derivatives with ethoxymethylenemalonic ester to give products in which he assumed that the amino nitrogen atom of 2-aminopyridine had become attached to the carbon atom β to the carbethoxy groups. The condensation products derived from certain 6-substituted 2-

(1) R. Adams and I. J. Pachter, THIS JOURNAL, **74**, 4906 (1952).

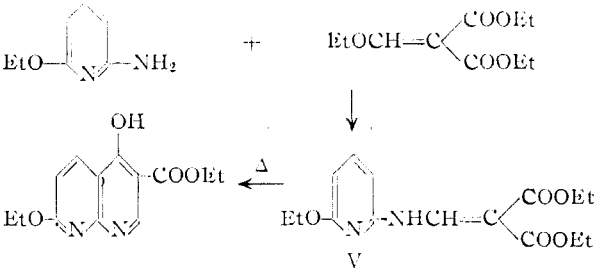
(2) G. R. Lappin, *ibid.*, **70**, 3348 (1948).



II I

III IV

aminopyridines and ethoxymethylenemalonic esters formed naphthyridines upon cyclization; for example



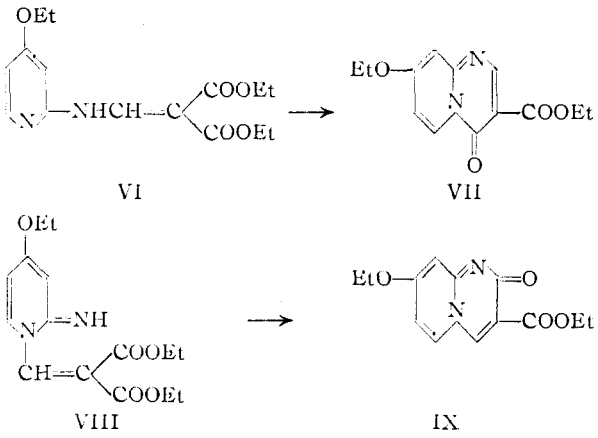
V

2-Aminopyridine derivatives which were not substituted in the 6-position, however, reacted with ethoxymethylenemalonic ester to form intermediates which cyclized to pyrido[1,2-a]pyrimidones rather than to naphthyridines. For example, 2-amino-4-ethoxypyridine reacted with ethoxymethylenemalonic ester to form a compound to which Lappin assigned formula VI and which cyclized in boiling diphenyl ether to give a compound which he believed to be VII.

Lappin assumed that all of the 2-aminopyridines initially reacted in the same way with ethoxymethylenemalonic ester to give intermediates such as V or VI. He suggested that due to steric effects, naphthyridines rather than pyridopyrimidones formed from those intermediates in which the 6-position was substituted, but that pyridopyrimidones such as VII formed preferentially when steric interferences were absent.

Another possible explanation of the differences is that when the ring nitrogen of the 2-aminopyridines is not sterically hindered, it reacts preferentially to give intermediates such as VIII as it does in the reactions between 2-aminopyridine and acrylic acid and its derivatives. These intermediates should cyclize to give pyridopyrimidin-2-ones such as IX. When the ring nitrogen is hindered, however, intermediates such as V are formed which cyclize to give naphthyridines.

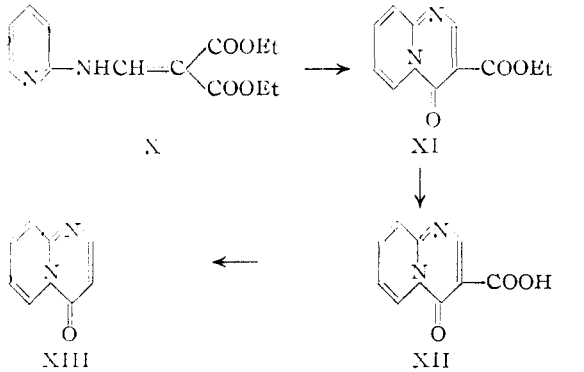
To determine whether the pyridopyrimidones obtained by Lappin's procedure are 2-ones or 4-ones, the reaction of ethoxymethylenemalonic ester with 2-aminopyridine was studied, since in this case hydrolysis and decarboxylation of the cyclized ester would yield either 2H-pyrido[1,2-a]pyrimidin-2-one (I) or the isomeric compound 4H-pyrido[1,2-a]pyrimidin-4-one (XIII). It has been reported by one group of workers[3] that 2-aminopyridine failed to yield a cyclized product when heated with ethoxymethylenemalonic ester, and Lappin[2] found that although he could obtain the intermediate condensation product to which he assigned structure X, attempted cyclization of this substance resulted in the formation of tar. When the cyclization experiment described by Lappin was repeated in this Laboratory, no tar was obtained. Instead, a pyridopyrimidonecarboxylic ester was formed in 94% yield. It is not clear why the cyclization reaction failed in the hands of the previous workers.



VI VII

VIII IX

Lappin[2] reported that pyridopyrimidonecarboxylic esters were degraded to 2-aminopyridines when heated with dilute alkali. It was found in this investigation that hydrolysis with cold alkali followed by acidification with acetic acid yielded the desired acid. Attempted hydrolysis and decarboxylation of the ester by means of dilute or concentrated hydrochloric acid under conditions which proved effective with somewhat related compounds[4] resulted in evolution of acetaldehyde. When the acid was heated above its melting point, gas was evolved and 4H-pyrido[1,2-a]pyrimidin-4-one (XIII), the isomer of I, was produced in 91% yield. Its ultraviolet spectrum and that of the ester from which it was formed are shown in Fig. 1. The formation of XIII rather than I proves that the cyclized ester is ethyl 4-keto-4H-pyrido[1,2-a]-pyrimidine-3-carboxylate (XI) and that the condensation product of ethoxymethylenemalonic es-



X XI

XIII XII

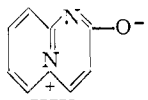
(3) J. T. Adams, C. K. Bradsher, D. S. Breslow, S. T. Amore and C. R. Hauser, THIS JOURNAL, **68**, 1317 (1946).

(4) V. Boekelheide and J. P. Lodge, Jr., *ibid.*, **73**, 3681 (1951).

ter and 2-aminopyridine has the structure shown in X.

It is thus obvious that either the ring nitrogen or amino nitrogen of 2-aminopyridines may react with α,β-unsaturated systems. Decisions without sufficient evidence that it was the ring nitrogen which added to quinone[5] and that it was the amino nitrogen which reacted with certain other α,β-unsaturated carbonyl compounds[6] must be considered uncertain.

Both I and XIII are colorless compounds. Compound XIII, the 4-one, melts at 127°, is moderately soluble in water (about 5 g. per 100 ml. at room temperature) and may be recrystallized from ligroin. Compound I, the 2-one, on the other hand, melts at 250°, is extremely soluble in water (over 80 g. per 100 ml. at room temperature), soluble in ethanol, sparingly soluble in hot chloroform and insoluble in ether and less polar solvents. The properties of I suggest that fully aromatic structures such as XIV contribute largely to its resonance hybrid. Upon catalytic reduction of I and



XIV

XIII, the corresponding perhydro compounds were produced.

With the synthesis and determination of the ultraviolet spectra of I and XIII accomplished, it becomes possible to consider in new light other previously reported pyrido[1,2-a]pyrimidones which have been prepared from 2-aminopyridine.

The formation of a pyrido[1,2-a]pyrimidone from 2-aminopyridine and ethyl acetoacetate was studied by several workers[7-9] who used a variety of reaction conditions. Hauser and Weiss[8] obtained a product which they believed was 4-methyl-2H-pyrido[1,2-a]pyrimidin-2-one (XVI), in about 45% yield. They did not isolate an intermediate reaction product. Khitrik[9] found that 2-acetoacetamidopyridine (XV),[10] which may be obtained by warming 2-aminopyridine with ethyl acetoacetate,[9,11] cyclized to give the same compound in 25% yield when treated with cold sulfuric acid. He also considered this to have structure XVI. Later, Antaki and Petrow[11a] discovered that when ethyl β-aminocrotonate was heated with 2-bromopyridine at 180–200° for several hours, a cyclized compound was obtained in unspecified yield which was identical with that synthesized by previous workers.[7-9] Antaki and Petrow formulated their product as XVII.

From the experimental evidence reported, no definite conclusion can be adduced as to the structure

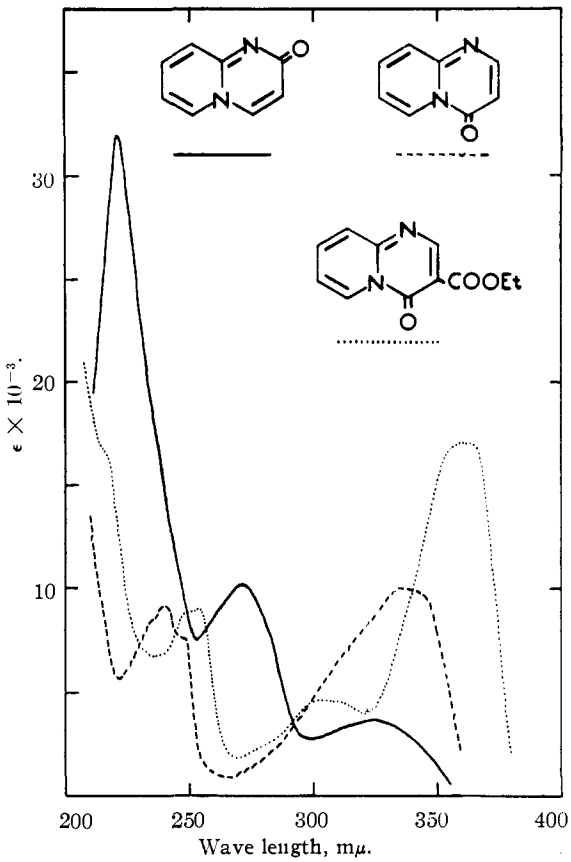
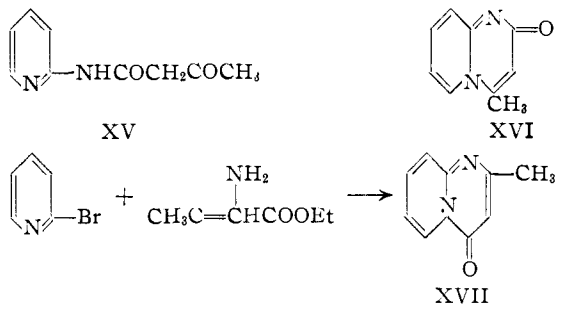


Fig. 1.

of the product since it is not certain in which of these reactions rearrangement occurs. To decide between structures XVI and XVII, the ultraviolet spectrum of the compound (Fig. 2) was compared with those of I and XIII (Fig. 1). The similarity of the spectrum to that of XIII establishes its formula as XVII. Thus XV obviously must rearrange when cyclized by the action of sulfuric acid.



Hauser and Weiss[8] synthesized XVII under mild conditions. A mixture of 2-aminopyridine, ethyl acetoacetate and a few drops of hydrochloric acid was allowed to stand over sulfuric acid in an evacuated desiccator for seven days at room temperature and was then distilled under reduced pressure. The yield obtained by this procedure was almost twice as high as that reported by Khitrik[9] from the action of sulfuric acid on XV. Antaki and Petrow[11a] reported that all attempts to cyclize XV to the pyrimidine base, except by the sulfuric acid procedure described by Khitrik, proved unsuccessful. These

(5) L. Schmid and H. Czerny, *Monatsh.*, **83**, 31 (1952).

(6) C. F. H. Allen, F. W. Spangler and E. R. Webster, *J. Org. Chem.*, **16**, 17 (1951).

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

(8) C. R. Hauser and M. J. Weiss, *J. Org. Chem.*, **14**, 453 (1949).

(9) S. N. Khitrik, *J. Gen. Chem.* (*U.S.S.R.*), **9**, 1109 (1939).

(10) The structure of this compound was proved by the work of Khitrik[9] and C. F. H. Allen, J. VanAllen and C. V. Wilson, THIS JOURNAL, **66**, 1805 (1944).

(11) F. C. Palazzo and A. Tamburini, *Atti accad. Lincei*, **20**, I, 37 (1911) [*C. A.*, **5**, 1586 (1911)].

(11a) H. Antaki and V. Petrow, *J. Chem. Soc.*, 551 (1951).

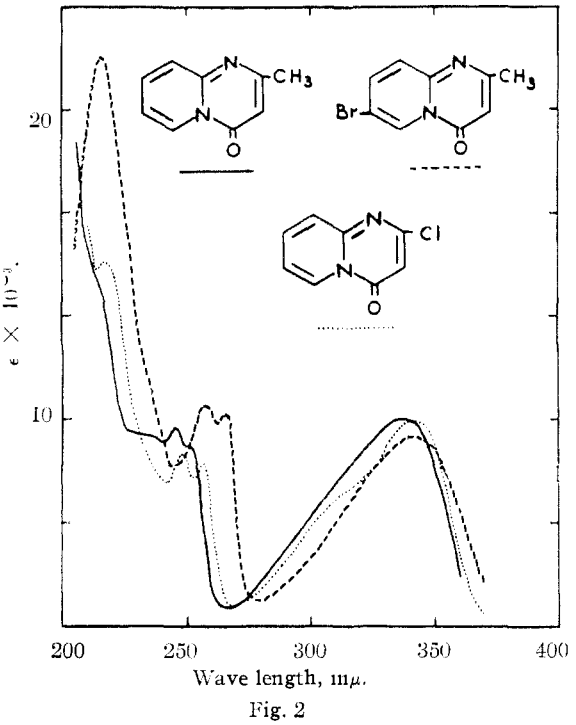
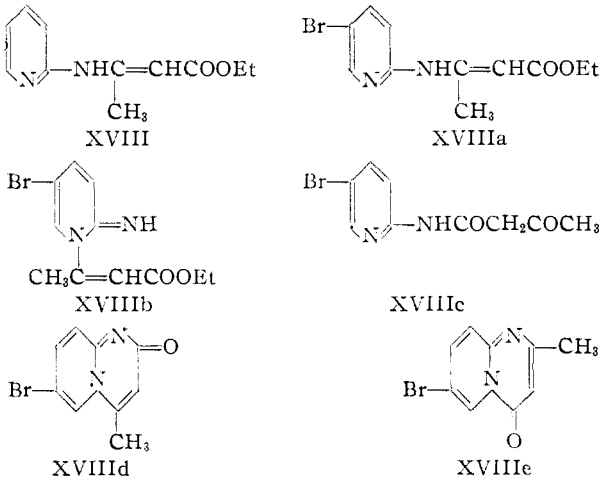


Fig. 2

facts indicate that the reaction of Hauser and Weiss probably did not proceed through the intermediate XV but instead went through XVIII which then cyclized (perhaps during distillation) to give XVII.

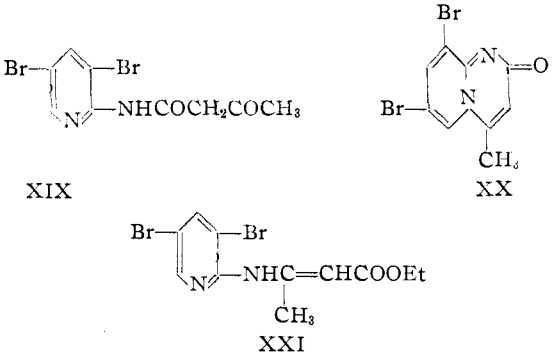
Antaki and Petrow[12] synthesized XVII in good yield by heating 2-aminopyridine with ethyl β-aminocrotonate. It is probable that this reaction also proceeded through XVIII.



A bromo analog of XVIII was actually a product of the reaction between 2-amino-5-bromopyridine and ethyl acetoacetate.[12a,b] Kucherov first assigned structure XVIIIa to the product,[12a] but later decided that structure XVIIIb was correct since cyclization of this ester yielded a compound which was identical with that obtained when the amide XVIIIc was cyclized with sulfuric acid.[12b] Kucherov believed that the cyclized product had structure XVIIId. The ultraviolet absorption spectrum of the cyclized product is shown in Fig. 2. Its spectrum shows it to be 7-bromo-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (XVIIIe) rather than XVIIId. Compound XVIIIc, like compound XV, therefore rearranges when treated with sulfuric acid. The ester obtained by Kucherov should consequently have the formula which he first assigned to it, β-(5-bromo-2-pyridylamino)-crotonate (XVIIIa).

It has been reported[13] that when 2-amino-3,5-dibromopyridine was heated with ethyl acetoacetate the expected compound, 2-acetoacetamido-3,5-dibromopyridine (XIX) was not obtained but that the product, $C_{11}H_{12}Br_2N_2O_2$, formed by loss of one molar equivalent of water, was an ethanol solvate of 7,9-dibromo-4-methyl-2H-pyrido[1,2-a]pyrimidin-2-one (XX). The suggestion was made that "ring closure to form a pyrimidine is facilitated by the bromine atoms, for with the unsubstituted amide, drastic treatment is necessary for cyclization." Other workers[2,14] have since found that when base-weakening halogen atoms were attached to the pyridine ring, ring closure was made more difficult.

A product was synthesized in this Laboratory from 2-amino-3,5-dibromopyridine and ethyl acetoacetate. The previous workers did not report the conditions of their experiment or the melting point of their product, and their formula was based upon a questionable bromine analysis. It is probable, however, that the compound in hand is the same as the one which they obtained. Carbon, hydrogen and nitrogen analyses lend additional support to the proposed empirical formula. To remove ethanol of crystallization suggested by Allen, *et al.*,[13] as existing in the molecule, the compound was dissolved in benzene and passed through a column of alumina, recrystallized several times from ligroin, heated *in vacuo* over phosphorus pentoxide and boiled in an open vessel with diphenyl ether. The original product was recovered in each case. Its ultraviolet spectrum (Fig. 3) bears little similarity to the spectra of the pyrido[1,2-a]pyrimidones described in this paper and shown in Figs. 1, 2 and 4, but resembles the spectra of XVIIIa and X. The evidence indicates that the compound is not an ethanol solvate of XX, but that it is ethyl β-(3,4-dibromo-2-pyridylamino)-crotonate (XXI).



(12) (a) V. F. Kucherov, *J. Gen. Chem.* (*U.S.S.R.*), **20**, 1890 (1950) [*C. A.*, **45**, 2941 (1951)]; (b) V. F. Kucherov, *J. Gen. Chem.* (*U.S.S.R.*), **21**, 1145 (1951) [*C. A.*, **46**, 5043 (1952)].

(13) C. F. H. Allen, J. Van Allen and C. V. Wilson, THIS JOURNAL, **66**, 1808 (1944).

(14) N. F. Kucherova, V. F. Kucherov and K. A. Kocheshkov, *J. Gen. Chem.* (*U.S.S.R.*), **16**, 1706 (1946) [*C. A.*, **41**, 6243 (1947)].

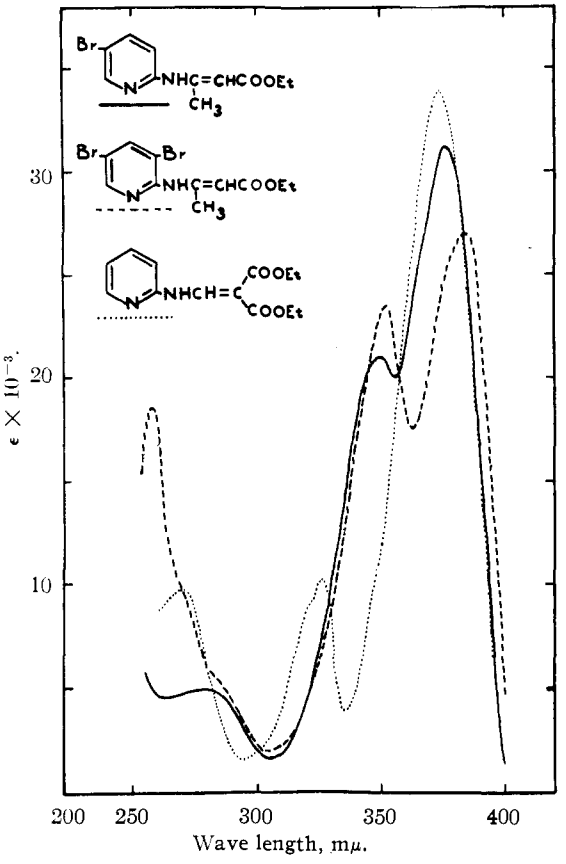
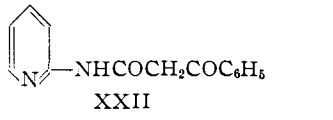
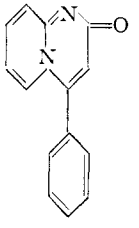


Fig. 3.

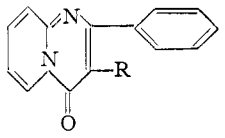
The cyclization of benzoylacetamidopyridine (XXII) by sulfuric acid has been studied.[11,15] It was concluded by Seide[11] that the structure of the product is represented by formula XXIII. However, the finding that acetoacetamidopyridine rearranges on cyclization now requires that structure XXIV also be considered.



XXII



XXIII



XXIV, R = H
XXV, R = Cl
XXVI, R = Br

If formula XXIII is correct, the ultraviolet spectrum of the compound should closely resemble that of I since in XXIII steric effects should inhibit interaction of the phenyl group with the rest of the molecule.[16,17] On the other hand, if XXIV is correct, the spectral pattern of the compound should exhibit marked differences from the spectra of I and XIII as a result of interaction of the phenyl group with the pyridopyrimidone group.

The absorption spectrum of the compound is shown in Fig. 4. Its differences from that of compound I (Fig. 1) indicate that XXIII is not the correct structure and that the compound is probably XXIV. If the compound is XXIV, one might anticipate that introduction of groups into the 3-position of XXIV would sterically inhibit interaction of the phenyl group with the rest of the molecule. The main effect of this inhibition on the spectrum should be a decrease in intensity of the band at 273 mμ since XIII differs from XXIV mainly in the presence of this strong band in the latter.

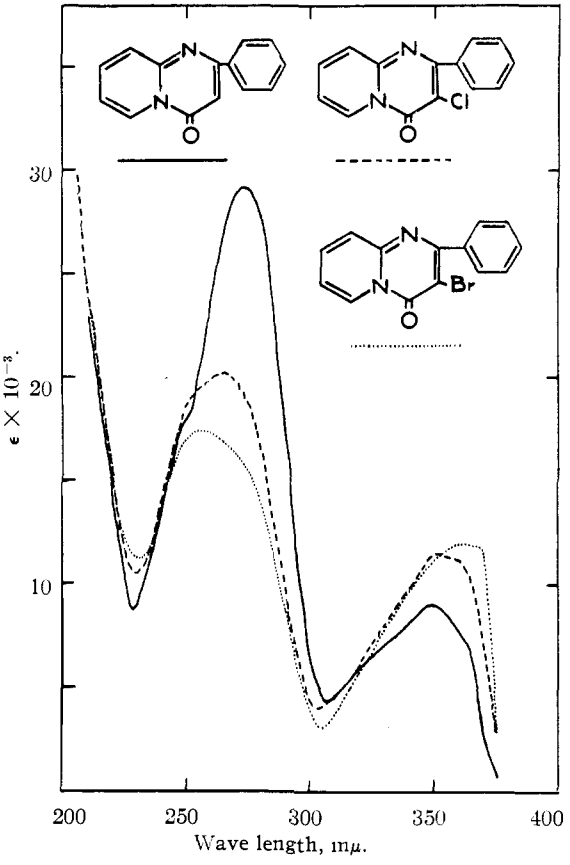


Fig. 4.

Khitrik[9] showed that nitration of XVII occurred at the 3-position. It was assumed that halogenation of these compounds would also give 3-substituted products. Compound XXIV was therefore chlorinated with phosphorus pentachloride[15] and brominated with N-bromosuccinimide to give excellent yields of XXV and XXVI. The spectra of the halogenated compounds are shown in Fig. 4. It may be seen that the main effect of the hindering groups was indeed an attenuation of the band originally at 273 mμ. The result of the introduction of a halogen atom was to make the spectrum of the compound more similar to the spectra of the other pyrido[1,2-a]pyrimidin-4-ones.

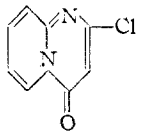
It may be observed that as hydrogen was replaced by chlorine and then by bromine, the wave length of ϵ_{max} dropped from 273 to 265 to 257 mμ. This was apparently due to the fact that the strong band of

(15) O. Seide, *Ber.*, **58**, 352 (1925).
(16) R. N. Jones, *Chem. Revs.*, **32**, 34 (1943).
(17) V. Boekelheide and E. J. Agnello, THIS JOURNAL, **72**, 5005 (1950).

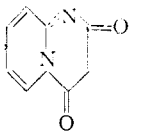
XXIV was actually the sum of two bands, one in the vicinity of 250 mμ present in all pyrido[1,2-a]-pyrimidin-4-ones and one due to the interaction of the two ring systems. As hydrogen was replaced by bulkier groups and the latter band decreased in intensity, the effect of the former became more important and the result was a shift toward shorter wave lengths.

The evidence indicates that cyclization of XXII in sulfuric acid proceeds with rearrangement and that the structure of the cyclized product is XXIV.

Snyder and Robison[18] isolated a chloropyrido-[1,2-a]pyrimidone (XXVII) from the reaction between malonylaminopyridine (XXVIII) and phosphorous oxychloride. The structure of their compound was proved both physically, by comparison of its ultraviolet spectrum[18] (Fig. 2) with that of I and of XIII (Fig. 1), and chemically by the fact that upon catalytic reduction it gave a deschloro compound[18] which was different from that obtained upon reduction of I[1] but identical with that obtained from XIII. It was also found that the reduction product of XXVII had the properties of a secondary amine.[18]

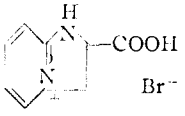


XXVII

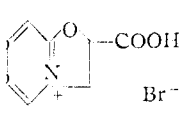


XXVIII

The reaction between 2-aminopyridine and α-bromoacrylic acid in chloroform yielded besides the main product (I) a second product, $C_8H_9BrN_2O_2$, in low yield. When the reaction was effected in the absence of a solvent, this second substance was actually the main product. It is very probable that this substance is 2-carboxy-2,3-dihydroimidazo[1,2-a]pyridinium bromide (XXIX), formed *via* the intermediate II through displacement of bromide ion by the imino group. Such a reaction would be analogous to that which resulted in the formation of XXX from 2-pyridone and α-bromoacrylic acid.[1]



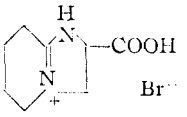
XXIX



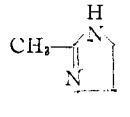
XXX

Treatment of XXIX with silver oxide yielded the free amino acid. Reduction of XXIX with hydrogen and platinum oxide resulted in the uptake of two molar equivalents of hydrogen to give a product which was probably 2-carboxy-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridinium bromide (XXXI). It has been shown previously[19] that salts of dihydroimidazoles such as the bitartrate of XXXII are not reduced by hydrogen and platinum oxide at 100°.

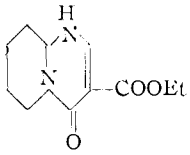
It was observed during the course of this work that the catalytic reduction of XI failed to yield a perhydro compound, though there was no difficulty in introducing four moles of hydrogen into the carbethoxy-free analog (XIII). Hydrogen uptake ceased when three molar equivalents were absorbed. The product was probably XXXIII.



XXXI



XXXII



XXXIII

Acknowledgment.—The authors are indebted to Miss Emily Davis, Mrs. Esther Fett and Mrs. Katherine Pih for the microanalyses, and to Mr. H. J. Birch for the ultraviolet spectra determinations.

Experimental[20]

Reaction of 2-Aminopyridine with α-Bromoacrylic Acid. (A) In the Absence of a Solvent.—A mixture of 8.5 g. of 2-aminopyridine and 0.5 g. of *t*-butylcatechol was melted, stirred and cooled. It was ground with 13.6 g. of α-bromoacrylic acid and the resulting mixture was warmed gently. An exothermic reaction began and ended in about 1 minute. After being heated for 1 hour on a steam-bath, the solid mass was dissolved in boiling 90% ethanol. The solution was concentrated to 60 ml. and placed in a refrigerator for 3 hours. There was obtained 5.2 g. (25%) of prisms of 2H-pyrido[1,2-a]pyrimidin-2-one hydrobromide (hydrobromide of I), m.p. 321–323° (dec.) after darkening near 290°. The compound occasionally crystallized as rods rather than prisms.

Anal. Calcd. for $C_8H_7BrN_2O$: C, 42.31; H, 3.11; N, 12.34. Found: C, 42.57; H, 3.10; N, 12.50.

The mother liquor was concentrated until most of the solvent was removed. It was cooled in the refrigerator for 4 hours and filtered to give 8 g. of crude product. This material was dissolved in boiling absolute ethanol and the solution was filtered to remove a small amount of the hydrobromide of I. The alcoholic solution yielded 6.5 g. (29%) of prisms of 2-carboxy-2,3-dihydroimidazo[1,2-a]pyridinium bromide (XXIX), m.p. 198–201°. A final recrystallization, effected by dissolving the material in absolute ethanol, adding nitromethane and concentrating until crystallization began, raised the m.p. to 203–204°. The compound gave a blue color with ferric chloride and a yellow color with cold aqueous sodium hydroxide.

Anal. Calcd. for $C_8H_9BrN_2O_2$: C, 39.20; H, 3.72. Found: C, 39.06; H, 3.86.

(B) In the Presence of Chloroform.—To 150 ml. of chloroform was added 9.4 g. of 2-aminopyridine, 0.5 g. of *t*-butylcatechol and 15.1 g. of α-bromoacrylic acid. A salt crystallized but dissolved when the mixture was heated. After 24 hours under reflux with stirring, the mixture was cooled and filtered and the solid product was treated as described in (A). There was obtained 10.2 g. (45%) of pure hydrobromide of I, m.p. 321° (dec.), and 2.3 g. of the crude imidazopyridine, m.p. 195–198° The milder reaction conditions apparently favor pyridopyrimidone formation.

A solution of 3.0 g. of the hydrobromide of I in 30 ml. of 10% sodium hydroxide was heated under reflux for 2 hours. The alkaline solution was extracted with ether and the ethereal extract was dried and evaporated to yield 1.1 g. (90%) of 2-aminopyridine.

2H-Pyrido[1,2-a]pyrimidin-2-one (I). (A) From the Hydrobromide of I and Silver Oxide.—To 2.0 g. of the hydrobromide of I in 4 ml. of water, was added 10 ml. of methanol and the silver oxide from 2 g. of silver nitrate. The mixture was macerated in a mortar, filtered and the filtrate was evaporated to dryness. The residue was sublimed at 230° (1 mm.) to give 0.97 g. (76%) of sublimate which, after one recrystallization from chloroform, melted at 249–250°. The same compound was prepared previously by another method.[1]

(B) From the Hydrobromide of I and Sodium Hydroxide.—A solution of 4 g. of the hydrobromide of I in 15 ml. of water was titrated with 10% sodium hydroxide to the phen-

(18) H. R. Snyder and M. M. Robison, THIS JOURNAL, **74**, 4910 (1952).

(19) E. Waser and A. Gratsos, *Helv. Chim. Acta*, **11**, 944 (1928).

(20) All melting points are corrected.

olphthalein end-point. The solution was evaporated to dryness and the residue was extracted with chloroform–ethanol. Concentration of the extract and cooling gave 2.15 g. of the free base. Upon recrystallization from chloroform, there was obtained 1.82 g. (71%) of I, m.p. 248–250°.

Reaction of 2-Carboxy-2,3-dihydroimidazo[1,2-a]pyridinium Bromide (XXIX) with Silver Oxide.—To 1.00 g. of the imidazopyridinium salt in 10 ml. of methanol, was added the silver oxide from 1 g. of silver nitrate. The mixture was ground in a mortar, filtered, and the filtrate carefully treated with dilute hydrochloric acid until no further precipitate of silver chloride separated. After refiltration, evaporation of the filtrate to dryness, and recrystallization of the residue from absolute ethanol–methyl acetate, there was obtained 0.46 g. of prisms of the amino acid, m.p. 261–262° (dec.).

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91. Found: C, 58.64; H, 4.94.

2-Carboxy-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridinium Bromide (XXXI).—A solution of 0.40 g. of the imidazopyridinium salt (XXIX) in 20 ml. of 95% ethanol to which had been added 20 mg. of platinum oxide catalyst was hydrogenated at atmospheric pressure. Removal of the catalyst, evaporation to dryness, and recrystallization of the residue from nitromethane yielded 0.29 g. of the hexahydro compound, m.p. 183–185°.

Anal. Calcd. for $C_8H_{13}BrN_2O_2$: C, 38.57; H, 5.26. Found: C, 38.39; H, 5.27.

Reaction of 2-Aminopyridine with Acrylic Acid.—A mixture of 4.7 g. of 2-aminopyridine, 4 g. of glacial acrylic acid and 0.05 g. of *t*-butylcatechol was heated on a steam-bath for 8 hours. It was then diluted with chloroform, cooled in a refrigerator for several hours and filtered. There was obtained 6.95 g. of 2-imino-1(2H)-pyridinepropionic acid (III) which on recrystallization from 98% ethanol melted at 178° (dec.) and was identical with a sample[1] prepared previously by another route.

Reaction of 2-Aminopyridine with Ethyl Acrylate.—A mixture of 4.7 g. of 2-aminopyridine, 5.5 g. of ethyl acrylate and 0.1 g. of *t*-butylcatechol was heated on a steam-bath for 12 hours. The dark colored oily solid which resulted was stirred with benzene, filtered, dissolved in chloroform and treated with decolorizing carbon. Concentration of the chloroform solution until crystallization commenced, followed by dilution with ligroin, yielded 3.9 g. (53%) of 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one (IV), m.p. 187–188°. Upon admixture with a sample prepared as described previously,[1] the m.p. was not depressed.

Ethyl 4-Keto-4H-pyrido[1,2-a]pyrimidine-3-carboxylate (XI).—To 100 ml. of refluxing diphenyl ether was added 10 g. of diethyl 2-pyridylaminomethylenemalonate (X).[2] The resulting solution was heated under reflux for 10 minutes, cooled and diluted with 500 ml. of petroleum ether (b.p. 30–60°). There crystallized 7.7 g. (94%) of XI, m.p. 110–111°.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62. Found: C, 60.73; H, 4.70.

4-Keto-4H-pyrido[1,2-a]pyrimidine-3-carboxylic Acid (XII).—To 200 ml. of 1% sodium hydroxide solution at 0–5° was added 5.0 g. of ester (XI) with stirring. Stirring was continued at 0–5° until solution was complete (1 hour) and then for 15 minutes longer. To the solution was added 4 ml. of acetic acid. The precipitate which formed was filtered and recrystallized from boiling water to give 2.4 g. (55%) of acid (XII), m.p. 265° (dec.). The original precipitate contained a quantity of inorganic material.

Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.84; H, 3.18. Found: C, 56.84; H, 3.30.

4H-Pyrido[1,2-a]pyrimidin-4-one (XIII).—A tube containing 1.0 g. of the acid (XII) was partially immersed in a 300°-bath. The acid melted and gas was evolved. The product distilled and solidified on the cooler portion of the tube. It was recrystallized from ligroin to yield 0.71 g. (91%) of XIII, m.p. 127°.

Anal. Calcd. for $C_8H_6N_2O$: C, 65.74; H, 4.14. Found: C, 65.69; H, 4.07.

Hydrogenation of 4H-Pyrido[1,2-a]pyrimidin-4-one (XIII).—To a solution of 200 mg. of XIII in 10 ml. of ethanol was added 30 mg. of platinum oxide. Hydrogenation at 1 atm. was complete in 4 hours. Removal of the catalyst and evaporation of the solution to dryness yielded the perhydrogenated product which, upon recrystallization from ether, melted at 57–59°. Upon admixture with a sample, m.p. 58–60°, previously prepared[18] and furnished by Snyder and Robison, the m.p. was 57.5–59.5°.

Ethyl 1,2,6,7,8,9-Hexahydro-4-keto-4H-pyrido[1,2-a]pyrimidine-3-carboxylate (XXXII).—A solution of 0.70 g. of ester (XI) in 15 ml. of absolute ethanol was hydrogenated at 1 atm. using 40 mg. of platinum oxide catalyst. Hydrogen uptake ceased after the absorption of 3 molar equivalents and the product (XXXII) crystallized from solution. It was dissolved by warming and the solution was filtered to remove platinum. The ethanolic solution yielded 0.59 g. of product, m.p. 211–213°.

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.47. Found: C, 58.99; H, 7.14; N, 12.22.

Reaction of 2-Amino-3,5-dibromopyridine with Ethyl Acetoacetate.—A mixture of 2 g. of 2-amino-3,5-dibromopyridine and 4 ml. of ethyl acetoacetate was heated on a steam-bath for 24 hours. On cooling, the mass solidified. It was recrystallized from ligroin and then dissolved in benzene and passed through a short column of alumina to remove colored impurities. The benzene solution was evaporated to dryness and the residue was recrystallized from petroleum ether (b.p. 80–110°) to give 1.2 g. of needles of ethyl β-(3,5-dibromo-2-pyridylamino)-crotonate (XXI), m.p. 110–111°.

Anal. Calcd. for $C_{11}H_{12}Br_2N_2O_2$: C, 36.29; H, 3.32; N, 7.70. Found: C, 36.32; H, 3.32; N, 7.53.

3-Bromo-2-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (XXVI).—A mixture of 1.11 g. of 2-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (XXV),[15] 1.0 g. of N-bromosuccinimide and 100 ml. of carbon tetrachloride was heated under reflux for 30 minutes. Upon cooling, crystallization occurred. The crystals were removed by filtration and washed with water. The filtrate was washed with water and evaporated to dryness to yield a second crop of crystals. The combined solids were recrystallized from ethanol to give 1.42 g. (94%) of long colorless needles, m.p. 174.5–175.5°.

Anal. Calcd. for $C_{14}H_9BrN_2O$: C, 55.83; H, 3.01; N, 9.30. Found: C, 55.94; H, 3.17; N, 9.02.

Ultraviolet spectra were determined with a Cary Automatic Recording Spectrophotometer Model 11, at concentrations of $0.5–1.0 \times 10^{-4}$ molar. With the exception of the spectrum of compound XXVII which was determined in isopropylalcohol,[18] all spectra were determined in 95% ethanol solution.

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