charcoal, and evaporated to dryness in the evaporator. The product was taken up in 150 ml. of methanol and cooled for several days in the freezer. The crystals were filtered, washed with acetone and dried, yielding 29.8 g. of crude material, 61%, m.p. 186–189° dec. An analytical sample was prepared from 1:1 methanol ether, m.p. 189–190° dec., lit.,[17] m.p. 193° dec.

Anal. Calcd. for $C_6H_{10}ClNO_2$: C, 44.17; H, 6.12: N, 8.56. Found: C, 43.97; H, 6.29; N, 8.49.

5-Methylproline hydrochloride (V-a). A solution of 16.4 g. (0.1 mole) of Δ′-2-methylpyrroline-5-carboxylic acid hydrochloride in 150 ml. of methanol was made and 50 mg. of platinum oxide was added. The mixture was hydrogenated in the Parr hydrogenator under 3 atm. of pressure for 0.5 hr., at which time the theoretical uptake of hydrogen was completed. The catalyst was filtered off and the solvent evaporated under a stream of air. A quantitative yield of 5-methylproline hydrochloride was obtained, m.p. 184–188°. An analytical sample was obtained from methanol, m.p. 191–192°, lit.,[19] m.p. 186–187°.

Anal. Calcd. for $C_6H_{12}ClNO_2$: C, 43.50; H, 7.25; N, 8.46. Found: C, 43.66; H, 7.27; N, 8.50.

5-Methylproline (VI-a). The free amino acid was obtained from the hydrochloride by passing an aqueous solution through a column of Amberlite IR-45 in the acetate cycle. The effluent was taken to dryness under vacuum and the residue was recrystallized from isopropyl alcohol, m.p. 188–189°.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.81; H, 8.53; N, 10.85. Found: C, 56.22; H, 8.72; N, 10.60.

Δ′-2,3-Dimethylpyrroline-5-carboxylic acid hydrochloride (IV-b). The title compound was prepared from ethyl 2-acetamido-2-carbethoxy-4-methyl-5-oxohexanoate in the same manner as Δ′-2-methylpyrroline-5-carboxylic acid hydrochloride. The yield was 61%, m.p. 148–150°. An analytical sample was prepared from methanol mixed with ether, m.p. 153–154°.

Anal. Calcd. for $C_7H_{12}ClNO_2$: C, 47.32; H, 6.76; N, 7.89. Found: C, 47.45; H, 6.78; N, 8.01.

4,5-Dimethylproline hydrochloride (V-b). This compound was prepared by hydrogenation in the same manner as 5-methylproline hydrochloride. The yield was quantitative, m.p. 128–130°. An analytical sample was prepared from methanol, m.p. 131.5–133.0°.

Anal. Calcd. for $C_7H_{14}ClNO_2$: C, 46.92; H, 8.35; N, 7.80. Found: C, 46.52; H, 8.30; N, 7.90.

4,5-Dimethylproline (VI-b). The method of preparation was the same as for 5-methylproline. An analytical sample was prepared from isopropyl alcohol, m.p. 196.5–197.5°.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.74; H, 9.09; N, 9.79. Found: C, 58.36; H, 8.86; N, 9.33.

Δ′-2-Phenylpyrroline-5-carboxylic acid hydrochloride (IV-c). The title compound was prepared from ethyl 2-acetamido-4-benzoyl-2-carbethoxybutyrate by the same method as Δ′-2-methylpyrroline-5-carboxylic acid hydrochloride. The yield was 55%, m.p. 169–173°. An analytical sample was prepared from a 1:2 methanol-ether mixture, m.p. 172–173°.

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.76; N, 6.29. Found: C, 58.43; H, 5.50; N, 6.20.

5-Phenylproline hydrochloride (V-c). The method of preparation was the same as for 5-methylproline hydrochloride; however, the product crystallized only once after standing in the freezer for 2 years. It could not be recrystallized. The yield was 62% and the product was analyzed without further purification, m.p. 115–117°.

Anal. Calcd. for $C_{11}H_{14}ClNO_2$: C, 58.02; H, 6.15; N, 6.15. Found: C, 58.38; H, 6.37; N, 6.17.

5-Phenylproline (VI-c). The method of preparation was the same as for 5-methylproline. An analytical sample was prepared from isopropyl alcohol, m.p. 213–214°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.10; H, 6.81; N, 7.33. Found: C, 69.57; H, 7.28; N, 7.23.

RIDGEFIELD, N. J.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, TENNESSEE EASTMAN CO., DIVISION OF EASTMAN KODAK CO.]

Addition of 2-Aminopyridines to Methyl Propiolate

GERALD R. LAPPIN

Received September 15, 1960

The reaction of 2-aminopyridine with methyl propiolate gave not only the expected 2H-pyrido[1,2-a]pyrimidin-2-one, but also a noncyclic adduct of one mole of the aminopyridine and two moles of ester, methyl 2-(2-methoxycarbonylvinylimino)-1(2H)-pyridineacrylate. The various methyl-2-aminopyridines reacted similarly to form methyl-2H-pyrido[1,2-a]-pyrimidin-2-ones. Unexpectedly, 6-methyl-2-aminopyridine gave only this type of product. The other methyl-2-aminopyridines gave, in addition, homologs of the 1:2 adduct above noted. A 1:1 adduct, a methyl 2-imino-3(or 4)-methyl-1(2H)-pyridineacrylate, could also be obtained in the reaction with 3-methyl-2-aminopyridine and 4-methyl-2-aminopyridine

The addition of amines to α,β-acetylenic esters has been reported to give β-amino-α,β-ethylenic esters.[1] The addition of 2-aminopyridines to an α,β-acetylenic ester has not been reported. However, this amine adds to methyl acrylate to give not only a noncyclic product derived from the amino tautomer[2] but also a cyclic product derived from the imino tautomer of the aminopyridine.[2,3] It appeared of interest to investigate the effect of the 2-aminopyridine tautomerism on its addition to an α,β-acetylenic ester such as methyl propiolate.

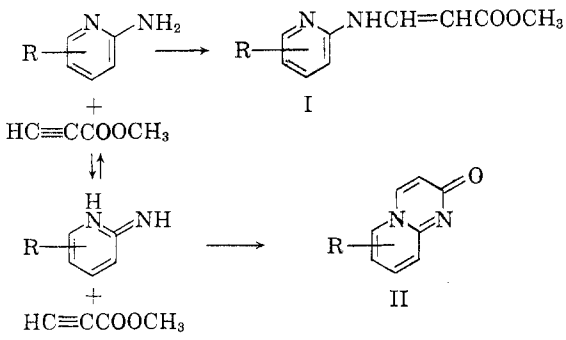
By analogy with the reported reaction with methyl acrylate, the addition of 2-aminopyridine to methyl propiolate might be expected to give two products, methyl 2-(2-pyridylamino)acrylate (I. R = H) and 2H-pyrido[1,2-a]pyrimidin-2-one (II. R = H).

Compounds having both types of structures are known. The acid produced by hydrolysis of I, 2-(2-pyridylamino)acrylic acid, can be prepared by hydrolysis of diethyl (2-pyridylaminomethylene)

(1) C. Moureu and I. Lazennec, *Bull. Soc. Chim.*, **35**, 1190 (1906).

(2) R. Adams and I. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952).

(3) G. R. Lappin, *J. Org. Chem.*, **23**, 1358 (1958).



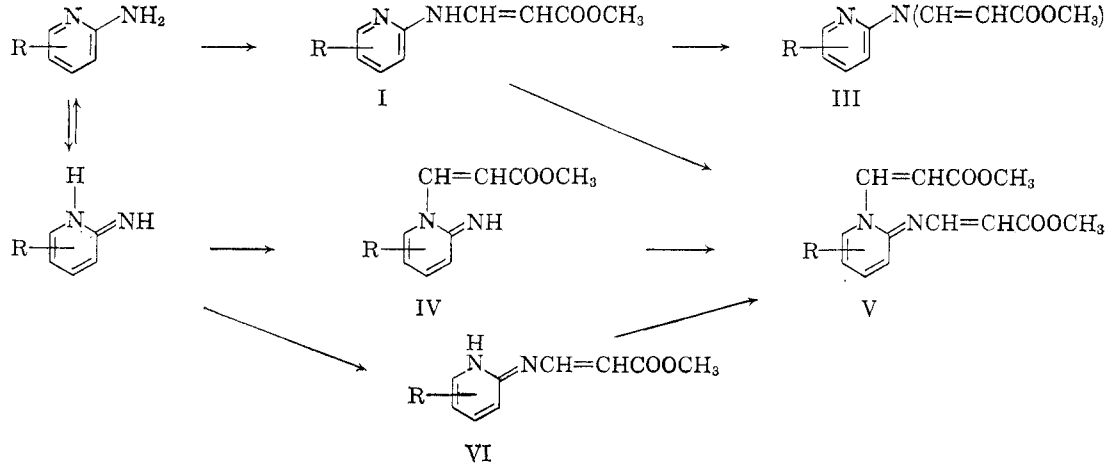
malonate,[4] while II can be prepared by the reaction of 2-aminopyridine with 2-bromoacrylic acid.[2]

When 2-aminopyridine was mixed with methyl propiolate, a violently exothermic reaction occurred. The product was a red tar from which no identifiable substance could be obtained. However, if the reaction was carried out in ether solution at 10–20° using equimolar quantities of the two reactants, a solid product slowly precipitated from the solution. Visual examination of this product showed that it consisted of a mixture of white crystals and orange crystals. These two substances could be cleanly separated by continuous ether extraction. The white, completely insoluble product was shown to be 2H-pyrido[1,2-a]pyrimidin-2-one (II. R = H) by comparison of its infrared spectrum with that of an authentic specimen. The slightly soluble, orange, crystalline product, m.p. 134–135°, had the correct analysis for $C_{13}H_{14}N_2O_4$, an adduct of one mole of 2-aminopyridine with two moles of methyl propiolate. This type of product will hereafter be called a diadduct. The use of an excess of 2-aminopyridine did not alter the nature of the products obtained.

When this reaction was applied to the various methyl-2-aminopyridines, the results were similar. All except 6-methyl-2-aminopyridine gave a mixture of an ether-insoluble, high-melting, colorless product in 7–34% yield and a lower melting yellow or orange product which was slightly ether-soluble in 29–63% yield. Only one product was obtained with 6-methyl-2-aminopyridine, a 77% yield of a high-melting, ether-insoluble, colorless solid. In each case, ether extraction gave a clean separation of the two types of products. All of the high-melting, insoluble products were shown to be methyl - 2H - pyrido[1,2 - a]pyrimidin - 2 - ones (II. R = CH_3) by analysis and comparison of their infrared spectra with that of 2H-pyrido[1,2-a]-pyrimidin-2-one. Because 6-methyl-2-amino-pyridine had previously given only 1,8-naphthyridine derivatives in cyclization reactions[5] and gave no cyclic product with methyl acrylate,[3] the high yield of 5-methyl-2H-pyrido[1,2-a]pyrimidin-2-one was completely unexpected. To further confirm the structure of this product, it was subjected to alkaline hydrolysis. A good yield of 6-methyl-2-aminopyridine was obtained, showing that the compound did indeed have the pyridopyrimidinone structure. The isomeric 1,8-naphthyridin-4-ol would have survived this hydrolysis unchanged.

Analysis of the colored, lower melting products showed that only the one from 5-methyl-2-aminopyridine was a diadduct of the type given by 2-aminopyridine. Both 3-methyl-2-aminopyridine and 4-methyl-2-aminopyridine gave a monoadduct; that is, a 1:1 adduct of the amine and methyl propiolate. These monoadducts, however, could be converted to diadducts by reaction with more methyl propiolate. In the case of 4-methyl-2-aminopyridine, using an excess of methyl propiolate gave a low yield of monoadduct in the insoluble product, but also a higher yield of the more soluble diadduct in the ether solution. Neither 2-aminopyridine nor 5-methyl-2-aminopyridine could be made to give a monoadduct, however. It appears that the type of adduct formed is largely dependent on the relative insolubility of the monoadduct and diadduct of a given 2-aminopyridine in ether.

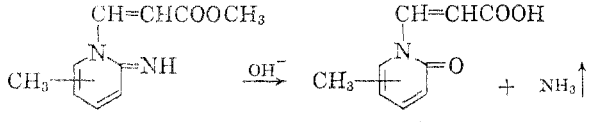
The structures considered for the adducts were



as follows. If the initial attack was at the amino nitrogen, the monoadduct would have the 2-(2-pyridylamino)acrylate structure, I. The addition of the second mole of methyl propiolate could then

(4) G. R. Lappin, *J. Am. Chem. Soc.*, **71**, 3258 (1949).
(5) G. R. Lappin, *J. Am. Chem. Soc.*, **70**, 3348 (1948).

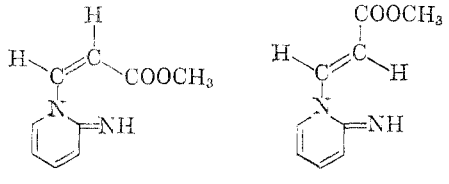
occur either at the amino nitrogen or the ring nitrogen to give either III or V. If the initial attack occurred at the ring nitrogen, the monoadduct would be a 2-imino-1(2H)-pyridineacrylate (IV) and the second mole of methyl propiolate could react only at the imino nitrogen to give a 2-(2-methoxycarbonylvinylimino) - 1(2H) - pyridineacrylate (V). Another, but less likely, structure for the monoadduct is VI, which would also give V as the diadduct. The fact that the monoadducts and diadducts were colored seemed to eliminate I and III from consideration. The structure of the monoadducts was positively established as IV by their easy alkaline hydrolysis to ammonia and a methyl-2-oxo-1(2H) - pyridineacrylic acid (VII). Neither I nor VI could give these products.



VII

With the structure IV established for the monoadduct, the diadduct could only be V.

Attempts to cyclize the monoadduct to II were unsuccessful; therefore, the addition of the 2-aminopyridine to methyl propiolate must not be stereospecific, but must, rather, produce both the *cis* and *trans* monoadduct. The *cis* adduct (IVa) is favorably disposed for ring closure and immediately closes to II. The *trans* adduct (IVb) is not favorably arranged for ring closure and is isolated as either the monoadduct or diadduct.



IVa IVb

The reaction of 2-aminopyridine and the methylaminopyridines has produced two unexpected and, at present, unexplained results. First, 6-methyl-2-aminopyridine gave a good yield of pyridopyrimidinone, although in all previously reported reactions of this compound only noncyclic products or 1,8-naphthyridines have been produced. Second, noncyclic, nonresonance-stabilized, imino-form adducts have been isolated for the first time. Previously reported 2-aminopyridine derivatives substituted on the ring nitrogen have been either a quaternary salt such as 1-methyl-2-aminopyridinium iodide, in which the pyridine ring is in its normal resonance-stabilized form rather than the imino form or a cyclic derivative of the imino form such as II.

EXPERIMENTAL

Addition of 2-aminopyridine to methyl propiolate. To a cold solution of 9.4 g. (0.1 mole) of 2-aminopyridine in 50 ml. of ether, a solution of 8.4 g. (0.1 mole) of methyl propiolate in 10 ml. of ether was added. A solid precipitate appeared after 30 min. and appeared to continue to increase in amount for 48 hr. After this time, the product was collected by filtration and was then extracted with dry ether in a Soxhlet extractor until the effluent from the extraction was colorless. There remained undissolved 3.4 g. (24%) of off-white crystals, m.p. 248–250°. This material was shown to be 2H-pyrido[1,2-a]pyrimidin-2-one (II. R = H) by comparison of its infrared spectrum with that of an authentic specimen.

The ether solution from the extraction was evaporated to dryness to give 8.0 g. (29%) of yellow-orange crystals (V. R = H), m.p. 134–135° after recrystallization from ethyl alcohol.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.5; H, 5.35; N, 10.7. Found: C, 59.8; H, 5.47; N, 10.5.

When this experiment was repeated using 18.8 g. (0.2 mole) of 2-aminopyridine and 8.4 g. (0.1 mole) of methyl propiolate, there was obtained 3.8 g. of II, R = H, and 6.8 g. of V, R = H.

A third experiment carried out in the same manner, except that 9.4 g. (0.1 mole) of 2-aminopyridine and 16.8 g. (0.2 mole) of methyl propiolate were used, gave 2.3 g. of II, R = H, and 10.5 g. of V, R = H.

Addition of 3-methyl-2-aminopyridine to methyl propiolate. To a cold solution of 11.0 g. (0.1 mole) of 3-methyl-2-aminopyridine in 50 ml. of ether, a solution of 8.4 g. (0.1 mole) of methyl propiolate in 10 ml. of ether was added. The reaction was quite exothermic and cooling was required to prevent the solution from boiling. After 24 hr. at 5–10°, the product was collected and extracted with dry ether in a Soxhlet extractor, as in the reaction with 2-aminopyridine. The insoluble, white crystalline product (II. R = 8 — CH_3) m.p. 226–228°, weighed 6.0 g. (37%).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.00; N, 17.5. Found: C, 67.3; H, 5.13; N, 17.2.

By evaporation of the ether solution there was obtained 8.5 g. (44%) of IV, R = 3 — CH_3, as golden yellow crystals, m.p. 114–115°.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.25; N, 14.59. Found: C, 62.1; H, 6.44; N, 14.60.

Addition of 4-methyl-2-aminopyridine to methyl propiolate. To a solution of 11.0 g. (0.1 mole) of 4-methyl-2-aminopyridine in 200 ml. of ether was added 8.4 g. (0.1 mole) of methyl propiolate. After 1 week the product was collected and extracted as before. There was obtained 1.1 g. (7%) of II R = 7 — CH_3; m.p. 255–260° dec.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.00; N, 17.5. Found: C, 67.4; H, 5.12; N, 17.3.

The soluble product (IV. R = 4 —CH_3) was obtained as golden yellow crystals from ethyl alcohol–ether, m.p. 101–102°, weight, 12.0 g. (63%).

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.25; N, 14.59. Found: C, 62.4; H, 6.44; N, 14.38.

When 11.0 g. (0.1 mole) of 4-methyl-2-aminopyridine was treated in exactly the same manner with 16.8 g. (0.2 mole) of methyl propiolate, the insoluble product gave, after extraction, 1.2 g. of the pyridopyrimidinone (II. R = 7 —CH_3) and 5.6 g. of the monoadduct (IV. R = 4 — CH_3). Evaporation of the filtrate from the reaction mixture, followed by recrystallization of the residue from ethyl alcohol, gave 9.1 g. of pinkish buff crystals (V. R = 4 — CH_3) m.p. 140–141°.

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.8; H, 5.80; N, 10.15. Found: C, 60.7; H, 5.63; N, 10.02.

Addition of 5-methyl-2-aminopyridine to methyl propiolate. A solution of 11.0 g. (0.1 mole) of 5-methyl-2-aminopyridine and 8.4 g. (0.1 mole) of methyl propiolate in 50 ml. of ether was held at room temperature for 4 days. The product was collected and extracted as before. There was obtained 2.3 g. (15%) of II, R = 6 — CH_3, m.p. 226–228°.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.00; N, 17.5. Found: C, 67.4; H, 5.05; N, 17.1.

There was also obtained 11.3 g. (41%) of V, R = 5 − CH_3, as yellow crystals, m.p. 152–153°, after recrystallization from alcohol.

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.8; H, 5.80; N, 10.15. Found: C, 61.1; H, 6.10; N, 10.25.

Addition of 6-methyl-2-aminopyridine to methyl propiolate. A solution of 11.0 g. (0.1 mole) of 6-methyl-6-aminopyridine and 8.4 g. (0.1 mole) of methyl propiolate in 50 ml. of dry ether was held at room temperature for 5 days. Filtration of the mixture gave 12.3 g. (77%) of II, R = 5 − CH_3, m.p. 194–195°.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.5; H, 5.00; N, 17.5. Found: C, 67.2; H, 5.21; N, 17.6.

This substance rapidly absorbed water from the air to give a dihydrate which dehydrated to the anhydrous form when heated to about 150°.

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.1; H, 6.10; N, 14.30. Found: C, 55.3; H, 6.05; N, 14.32.

Evaporation of the filtrate from the isolation of the above product gave a red tar, from which was obtained by distillation 1.3 g. of recovered 6-methyl-2-aminopyridine.

Hydrolysis of 5-methyl-2H-pyrido[1,2-a]pyrimidin-2-one (II. R = 5 −CH_3). This substance (4.8 g., 0.03 mole) was refluxed with 10 ml. of 10% aqueous sodum hydroxide for 10 hr. After being cooled, the solution was extracted with ether in a continuous extractor. Evaporation of the extract gave 2.9 g. (88%) of 6-methyl-2-aminopyridine.

Conversion of monoadduct to diadduct by reaction with methyl propiolate. A solution of 1.9 g. (0.10 mole) of the monoadduct (IV) and 1.0 g. (0.12 mole) of methyl propiolate in 25 ml. of chloroform and 25 ml. of dry ether was refluxed for 4 hr. The solution was then evaporated to dryness *in vacuo* and the residue was recrystallized from ethyl alcohol. In this way the following compounds were obtained.

Methyl 2-(2-methoxycarbonylvinylimino)-4-methylpyridineacrylate (V. R = 4 − CH_3). The yield of brick colored crystals m.p. 140–141°, was 2.1 g. (70%). This compound was shown by a mixture melting point to be identical with the product previously obtained from the reaction of 2 moles of methyl propiolate with 1 mole of 4-methyl-2-aminopyridine.

Methyl 2-methoxycarbonylvinylimino)-3-methylpyridineacrylate (V. R = 3 − CH_3). The yield of yellow crystals, m.p. 151–152°, was 1.8 g. (65%).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.8; H, 5.80; N, 10.15. Found: C, 60.6; H, 5.71; N, 9.96.

Hydrolysis of IV. R = 3 − CH_3. Three grams of this adduct was refluxed for 30 min. with 30 ml. of 10% aqueous sodium hydroxide. Ammonia was evolved during this heating. The solution was cooled and acidified with dilute hydrochloric acid to give, after drying in a vacuum oven, 2.1 g. (70%) of 3-methyl-2-oxo-1(2H)-pyridineacrylic acid, m.p. 238–240°.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.4; H, 5.03; N, 7.82. Found: C, 60.3; H, 5.14; N, 7.65.

Hydrolysis of IV. R = 4 − CH_3. This adduct was hydrolyzed as previously described for IV, R = 3 − CH_3, to give a 62% yield of 4-methyl-2-oxo-1(2H)-pyridineacrylic acid, m.p. 229–230°.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.4; H, 5.03; N, 7.82. Found: C, 60.2; H, 5.30; N, 7.68.

KINGSPORT, TENN.

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

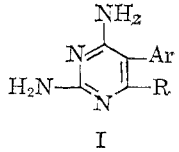
2,4-Diamino-5-[4′-fluoro-3′-halogenophenyl]pyrimidines

RICHARD BALTZLY, LINDA WRIGHT SHEEHAN, AND ALAN STONE

Received December 7, 1960

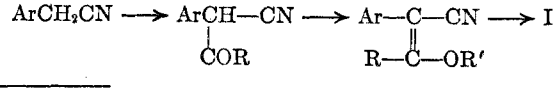
The preparation of 2,4-diamino-6-alkyl-5-[3′,4′-difluorophenyl- and 3′-chloro-4′-fluorophenyl]pyrimidines is described. The route followed involved the chloromethylation of *o*-difluorobenzene and *o*-chlorofluorobenzene and orientation of the product in the latter case.

The 2,4-diamino-6-alkyl-5-[3′,4′-dichlorophenyl] pyrimidines[1] (I. Ar = 3,4-dichlorophenyl; R = alkyl) have appreciable though not spectacular activity against Adenocarcinoma 755 in mice. The corresponding 3′,4′-dibromophenyl derivatives were found to be less active. Hence the synthesis of 3′,4′-difluorophenyl and of chlorofluorophenyl analogs was indicated.



I

The general line of synthesis of this type of pyrimidine is by the route:



No difficulty was anticipated in following this route except for possible lability of fluorine on aryl during the first and last steps which require strongly alkaline conditions. The necessary starting materials, however, were not readily accessible and it was necessary to prepare them from available compounds. Since *o*-chlorofluorobenzene could be purchased, the preparation was worked out starting with it rather than with the still more expensive *o*-difluorobenzene. Substitution into *o*-chlorofluorobenzene could give rise to isomers.[2] Ingold and Vass reported that nitration took place predominantly *para* to the fluorine (ratio *ca.* 4:1). Since it was desired to avoid a mixture of isomers we first attempted a route through a Friedel-Crafts reaction (which is known to be highly selective). It was hoped to convert the expected 3-chloro-4-fluoroacetophenone to 3-chloro-4-fluorophenylacetic acid by the Willgerodt reaction and thence obtain the desired nitrile.

(1) P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951).

(2) C. K. Ingold and C. C. N. Vass, *J. Chem. Soc.*, 417 (1928).