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.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

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

RICHARD BALTZLY, LINDA WRIGHT SHEEHAN, AND ALAN STONE

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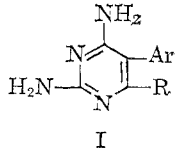
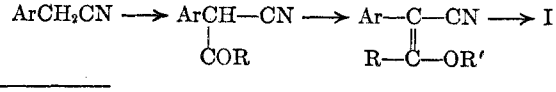
The preparation of 2,4-diamino-6-alkyl-5-[3′,4′-difluorophenyl- and 3′-chloro-4′-fluorophenyl]pyrimidines is described. The route followed involved the chloromethylation of *o*-difluorobenzene and *o*-chlorofluorobenzene and orientation of the product in the latter case.

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:

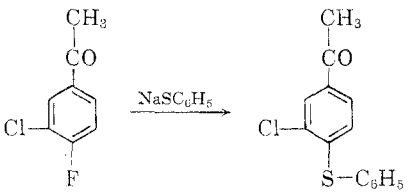


No difficulty was anticipated in following this route except for possible lability of fluorine on aryl during the first and last steps which require strongly alkaline conditions. The necessary starting materials, however, were not readily accessible and it was necessary to prepare them from available 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).

The Friedel-Crafts reaction on *o*-chlorofluorobenzene gave an acceptable yield of a solid ketone and careful examination of mother-liquors (through formation of the semicarbazone) afforded no evidence of the presence of isomers. A portion of this ketone reacted with sodium thiophenolate to give the diphenyl sulfide II the analyses of whose phenylhydrazone and semicarbazone demonstrate that fluorine rather than chlorine had been displaced. Since halogen *para* to the carbonyl ought to be somewhat activated, we consider this transformation to be evidence that acetylation had taken place *para* to the fluorine.




II

The Willgerodt reaction of 3-chloro-4-fluoroacetophenone (with morpholine and sulfur) gave a most intractable mixture from which (after hydrolysis) only a very small quantity (around 2%) of an acid melting at 53° could be isolated.

The originally preferred approach having failed, recourse was had to the chloromethylation reaction. Since the acid melting at 53° must be the 3-chloro-4-fluorophenyl acetic acid a means of identifying isomers would be available if necessary. While no example of the use of this reaction on *ortho*-dihalogenobenzenes was found, the original paper of Stephen, Short, and Gladding,[3] which describes the chloromethylation of *o*- and *p*-nitrotoluenes under rather drastic conditions, suggested that suitable conditions could be found in this case also. Such indeed proved to be the case. When dissolved in equal parts of sulfuric and acetic acids in the presence of chloromethyl ether and heated on the steam-bath chlorofluorobenzyl chloride was obtained in 12–33% yield depending on the time of heating. When a portion of the acetic acid was replaced by acetic anhydride the yield was raised to about 50%.

This chloromethyl derivative was smoothly converted to a liquid nitrile and a portion of this was hydrolyzed (under acid conditions) to a single chlorofluorophenyl acetic acid, identical with that obtained previously from 3-chloro-4-fluoroacetophenone.

This method of chloromethylation gave similar yields from *o*-difluorobenzene from which only one isomer would be expected. Further operations by the projected route led smoothly to 2,4-diamino-5-[3′-chloro-4′-fluorophenyl]-6-methylpyrimidine, 2,4-diamino-5-[3′,4′-difluorophenyl]-6-methyl and 6-ethylpyrimidines. In tests against transplantable tumors in mice, all three compounds showed no more than trace activity at best.

(3) H. Stephen, W. F. Short, and G. Gladding, *J. Chem. Soc.*, **117**, 510 (1920); *cf.* S. Nishida, *Repts. Sci. Research Inst. (Japan)*, **25**, 399 (1949).

## EXPERIMENTAL

*3-Chloro-4-fluoroacetophenone.* In 100 cc. of carbon bisulfide was dissolved 40 g. (0.3 mole) of *o*-chlorofluorobenzene. To this was added 45 g. of aluminum chloride and gradual addition of acetyl chloride (30 g. = 0.32 mole) was begun, with stirring. When about half of the acetyl chloride had been added there were definite signs of reaction (warming and evolution of hydrogen chloride). The solution was warmed to gentle reflux and the rest of the acetyl chloride was added gradually. After refluxing for 2 hr. the reaction mixture (now in two layers) was allowed to stand overnight. It was then refluxed 2 hr. longer. The upper layer was decanted and the two layers were hydrolyzed separately with ice and hydrochloric acid. The lower layer, taken into ether, dried over calcium chloride, and evaporated contained 30 g. of oil (A). The upper layer, after similar treatment, was found to contain 13 g. of oil (B).

Fraction A was distilled at 7 mm. pressure. After a fore-run (3 g.) boiling around 50° there was obtained a main fraction (19 g.) boiling at 100°. This material solidified and melted about 30°. After two crystallizations from pentane there was obtained 10.5 g. of flat prisms melting at 41–42°.

*Anal.* Calcd. for $C_8H_6ClFO$: C, 55.7; H, 3.5. Found: C, 55.9; H, 3.9. This ketone forms a phenylhydrazone, m.p., 116–119°.

*Anal.* Calcd. for $C_{14}H_{12}ClFN_2$: C, 64.0; H, 4.6. Found: C, 63.9; H, 4.2. The semicarbazone melts at 212–213.5°.

*Anal.* Calcd. for $C_9H_9ClFN_3O$: C, 47.1; H, 4.0. Found: C, 47.2; H, 3.7. Both the phenylhydrazone and semicarbazone melted somewhat irregularly, apparently with decomposition.

Fraction B together with the fore-run of A was distilled at atmospheric pressure, 10 g. of *o*-chlorofluorobenzene being recovered. From the residue of this distillation and from the mother liquors from crystallization of the crystalline ketone, phenylhydrazones and semicarbazones were prepared. The melting points of these indicated presence of not more than traces of isomeric ketone.

*3-Chloro-4-phenylmercaptoacetophenone.* To 10 cc. of absolute ethanol was added 2.2 g. (0.02 mole) of thiophenol and 1 g. of the crystalline 3-chloro-4-fluoroacetophenone. The solution was heated to gentle reflux and 0.6 g. (0.11 mole) of solid sodium methoxide was added. The solution was refluxed 4.5 hr., cooled, diluted with water, and partitioned between ether and dilute sodium hydroxide solution. The ethereal layer was washed again with alkali, then with water, and dried over calcium chloride. Evaporation of solvent left a pale-colored oil that did not crystallize. It was distilled at 20–30 $\mu$ pressure. The highest-boiling fraction (furnace temperature, 100–117°) was dissolved in ether and shaken with sodium sulfide solution and alkali (to remove traces of diphenyl disulfide). On evaporation of the ether, 1 g. of oil remained. This could not be crystallized; it was dissolved in alcohol and 1 g. of phenylhydrazine and 1 cc. of acetic acid were added. After warming for an hour, cooling and diluting with water a yellow oil separated and subsequently solidified. It was recrystallized from aqueous alcohol forming pale yellow diamond-shaped plates. Since these appeared to be solvated they were recrystallized again from ether-hexane mixture, m.p., 112°.

*Anal.* Calcd. for $C_{20}H_{17}ClN_2S$: C, 68.1; H, 4.9. Calcd. for $C_{20}H_{17}FN_2S$: C, 71.4; H, 5.1. Found: C, 67.9; H, 4.9.

Another portion of this ketone was converted to the semicarbazone (0.6 g. from 0.5 g. of oily ketone). Colorless crystals from alcohol, m.p., 203°.

*Anal.* Calcd. for $C_{15}H_{14}ClN_3OS$: C, 56.3; H, 4.4. Calcd. for $C_{15}H_{14}FN_3OS$: C, 59.4; H, 4.7. Found: C, 56.5; H, 4.9.

*Willgerodt reaction with 3-chloro-4-fluoroacetophenone.* The ketone (8.5 g. 0.05 mole), 2.5 g. of sulfur and 7 g. of morpholine were heated to reflux for 9.5 hr.; 20 cc. of alcohol was added and the mixture was allowed to stand overnight. Attempts to obtain a crystalline thioamide being unsuccessful, the entire material was subjected to hydrolysis with 1:1:2 sulfuric acid–water–acetic acid. The hydrolysate contained much tarry material insoluble in benzene, ether, acid, and alkali. By extraction of the ether-benzene layers with sodium carbonate solution and acidification there was obtained a small amount of organic acid. This was distilled at 20–40 $\mu$ pressure and the distillate was crystallized twice from ether-hexane mixture, m.p., 51–53°.

*3-Chloro-4-fluorobenzyl chloride.* In 70 cc. of glacial acetic acid was dissolved 26 g. (0.2 mole) of *o*-chlorofluorobenzene. To this was added 70 cc. of concd. sulfuric acid, 35 cc. of chloromethyl ether, and 30 cc. of acetic anhydride. The reaction mixture was heated under a reflux condenser for 18 hr. on the steam bath. At the start there was some evolution of gas but at no time was there condensation in the condenser. The reaction mixture was poured onto ice and partitioned between ether and water. The ethereal layer was washed three times with water, once with sodium carbonate solution, and once again with water. After drying over calcium chloride and evaporation of the ether the residue was distilled *in vacuo*. There was a small fore-run followed by a main fraction of 18 g. boiling at 86–93° at 7 mm. This corresponds to a 50% yield. When the acetic anhydride was omitted the conversion was 33% after 18 hr. heating and 12–15% after 3.5 hr.

From the distillation residues was obtained a solid that melted at 85–87° after crystallization from pentane.

*Anal.* Calcd. for $C_{13}H_8Cl_2F_2$: C, 57.2; H, 3.0. Found: C, 56.9; H, 2.8. This is presumably 3,3′-dichloro-4,4′-difluorodiphenylmethane. It was obviously not the only higher-boiling component of the distillation residues.

*3-Chloro-4-fluorophenylacetonitrile.* Thirty-four grams of crude chlorofluorobenzylchloride was refluxed 5 hr. with 20 g. of potassium cyanide in 120 cc. of methanol. The solvent was boiled off and the product was taken into ether, washed until neutral, dried over calcium chloride, and distilled at 7 mm. pressure. There was obtained 17 g. of oil boiling from 130–134°.

A 1-g. portion of this nitrile was hydrolyzed in a mixture of 5 cc. each of sulfuric acid, water and acetic acid (22 hr. on the steam-bath). The hydrolysis mixture was cooled, diluted, and partitioned between ether and water. Extraction of the ethereal layer with sodium carbonate solution followed by acidification gave a low-melting organic acid. This was recrystallized from hexane, needles, m.p., 55–56°. There was no depression of melting point when mixed with the 53° melting acid obtained from the Willgerodt procedure.

*Anal.* Calcd. for $C_8H_6ClFO_2$: C, 50.9; H, 3.2. Found: C, 51.1; H, 2.9.

*3,4-Difluorophenylacetonitrile.* The chloromethylation of *o*-difluorobenzene was conducted essentially as described for *o*-chlorofluorobenzene and with yields of 42–45%. Omission of the acetic anhydride resulted in 25–30% yields. The 3,4-difluorobenzyl chloride boiled at 76–80° at 15 mm. pressure. It was not possible to isolate a crystalline tetrafluorodiphenylmethane from the distillation residues.

The difluorobenzyl chloride was converted to the nitrile which boils at 110–120° at 13 mm. A 1-g. portion was hydrolyzed to the acid (3,4-difluorophenylacetic acid) which melted at 40–42° after crystallization from hexane.

*Anal.* Calcd. for $C_8H_6F_2O_2$: C, 55.8; H, 3.5. Found: C, 55.7; H, 3.4.

*α-Aryl-β-hydroxycrotononitriles*[4] (*α-aryl-α-acyl-acetonitriles*). The dihalogenophenylacetonitriles were condensed with ethyl acetate or ethyl propionate (*ca.* 3 eq.) and sodium ethoxide (1.5 eq.) in absolute alcohol at reflux for 6 hr. essentially as described by Russell and Hitchings.[1] The ketonitriles were obtained fairly pure through solution in alkali followed by acidification and were crystallized from ether-hexane mixture and from methanol for analysis.

*α-[3-Chloro-4-fluorophenyl]-β-hydroxycrotononitrile* was obtained in 72% yield, as colorless needles, m.p., 136°, from methanol.

*Anal.* Calcd. for $C_{10}H_7ClFNO$: C, 56.8; H, 3.4 Found: C, 56.8; H, 3.4.

*α-[3,4-Difluorophenyl]-β-hydroxycrotononitrile* was obtained as colorless prisms from methanol, m.p., 137–138°, yield, 80%.

*Anal.* Calcd. for $C_{10}H_7F_2NO$: C, 61.6; H, 3.6. Found: C, 61.4; H, 3.4. The ultraviolet absorption spectrum in 95% ethanol showed: λmax., 265 mμ ($\epsilon$ max., 13,500); λ min., 235 mμ ($\epsilon$ min., 4,400).[4]

*α-[3,4-Difluorophenyl]-β-hydroxy-Δ-α-pentenonitrile* formed colorless prisms from aqueous methanol, m.p. 67–69°; yield, 71%.

*Anal.* Calcd. for $C_{11}H_9F_2NO$: C, 63.2; H, 4.3. Found: C, 63.3; H, 4.6.

*2,4-Diamino-6-alkyl-5-[dihalogenophenyl]pyrimidines.* The hydroxycrotononitriles were methylated (to the enol ethers) with excess diazomethane in ether and the enol ethers, without isolation, were condensed with guanidine in absolute ethanol at reflux for 2–3 hr. The pyrimidines were purified by recrystallization from alcohol.

*2,4-Diamino-5-[3′-chloro-4′-fluorophenyl]-6-methylpyrimidine* formed colorless needles, m.p., 290–291°.

*Anal.* Calcd. for $C_{11}H_{10}ClFN_4$: C, 52.4; H, 4.0. Found: C, 52.1; H, 4.3.

*2,4-Diamino-5-[3′,4′-difluorophenyl]-6-methylpyrimidine* formed colorless platelets, m.p., 280–281°.

*Anal.* Calcd. for $C_{11}H_{10}F_2N_4$: C, 56.0; H, 4.3; N, 23.8. Found: C, 56.2; H, 4.2; N (Kjeldahl), 23.8.

*2,4-Diamino-5-[3′,4′-difluorophenyl]-6-ethylpyrimidine* formed colorless plates, m.p., 245–247°.

*Anal.* Calcd. for $C_{12}H_{12}F_2N_4$: C, 57.6; H, 4.8. Found: C, 57.4; H, 4.7.

*Acknowledgment.* The authors wish to express their gratitude to Dr. S. W. Blackman and Mr. Charles Marr for the micro-analyses here recorded.

TUCKAHOE, N. Y.

(4) For evidence that these compounds are predominantly enolic, *cf.* P. B. Russell and J. Mentha, *J. Am. Chem. Soc.*, **77**, 4245 (1955).