AN ABSTRACT OF THE THESIS OF

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Title The Synthesis of Amino Alcohols Derived from Pyrimidines

Abstract Approved _____
Major Professor

This work was undertaken as a continuation of the problem of synthesizing pyrimidine amino alcohols in the 2,4 and 5 positions. This laboratory has reported the synthesis of a series of pyrimidine amino alcohols in the 5-position which were made by coupling amines with 5-acetyl-4-methyl-2-phenylpyrimidine by means of the Mannich reaction.

A homologous series of amino alcohols may be prepared by coupling amines with bromomethyl ketones of pyrimidines. The bromomethyl ketones are usually made either by direct bromination of the acetyl derivative or by the Arndt-Eistert synthesis. The latter method is usually preferable because it utilizes the more common acid derivative and entails less separation and characterization problems.

In this laboratory, 5-methyl-6-oxo-2-phenyl-4-pyrimidinecarboxylic acid was prepared and converted with phosphorous pentachloride to 6-chloro-5-methyl-2-phenyl-4-pyrimidine acid chloride in good yield. By treating this acid chloride with diazomethane and reacting the intermediate diazo ketone with concentrated hydrobromic acid, 4-bromoacetyl-6-chloro-5-methyl-2-phenylpyrimidine was prepared. The desired amino alcohols, 4-(2-diethylamino-1-hydroxyethyl)- and 4-(2-di-n-propylamino-1-hydroxyethyl)-6-chloro-5-methyl-2-phenylpyrimidine

hydrochloride were prepared by condensing this bromoacetyl pyrimidine with the appropriate amine followed by catalytic reduction of the amino ketone.

4-Methyl-2-phenyl-5-pyrimidinecarboxylic acid was prepared according to the directions of Mitter and Bardhan. Preliminary attempts to convert this acid to the bromoacetyl derivative by means of the Arndt-Eistert synthesis were unsuccessful. For this reason, a study of the direct bromination of 5-acetyl-4-methyl-2-phenyl-pyrimidine was undertaken. Bromination in chloroform at room temperature gave over a 90 percent yield of crude bromination product. Analysis and solubility characteristics indicated this to be the hydrobromide salt of the bromo derivative.

Initial tests indicated that this bromo derivative was probably an isomeric mixture. One constituent, representing approximately 60 percent of the mixture, was isolated in the pure state as the free base by a procedure which was based upon the insolubility of this compound in petroleum ether. The structure of this compound was found to be 5-acetyl-4-bromomethyl-2-phenylpyrimidine by oxidation studies. Oxidation with sodium hypobromite gave an acid which still retained one bromine atom. When this bromo acid was oxidized with potassium permanganate, a dicarboxylic acid was obtained which analysis indicated to be 2-phenyl-4, 5-pyrimidinedicarboxylic acid.

The 5-acetyl-4-bromomethyl-2-phenylpyrimidine condensed readily with amines (dimethylamine, diethylamine, morpholine). By catalytic reduction of these products, compounds of the type 4-dialkylamino-methyl-5-(1'-hydroxyethyl)-2-phenylpyrimidine hydrochloride have been prepared.

THE SYNTHESIS OF AMINO ALCOHOLS DERIVED FROM PYRIMIDINES

by

RAY ALLEN CLARKE

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APPROVED:

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THE SYNTHESIS OF AMINO ALCOHOLS DERIVED FROM PYRIMIDINES

INTRODUCTION

This work was undertaken as a continuation of the problem of synthesizing pyrimidine amino alcohols with the amino alcohol substituent in the 2, 4 and 5 positions. These compounds were desired for purposes of documentation in the antimalarial program.

This laboratory had previously prepared a series of amino alcohols with this substituent in the 5 position. These were made by coupling the acetyl derivative of the pyrimidine with various amines by means of the Mannich reaction. This gives a product which is homologous to those prepared by bromination procedures.

In this work major emphasis was given to the preparation of derivatives with the desired substituent in the 4 position. The details of this work constitute Part One of the thesis.

Part Two of the thesis deals with the study of the direct bromination of 5-acetyl-4-methyl-2-phenylpyrimidine in an attempt to prepare the lower homolog of those amino alcohols which were recently reported by this laboratory.

PART ONE

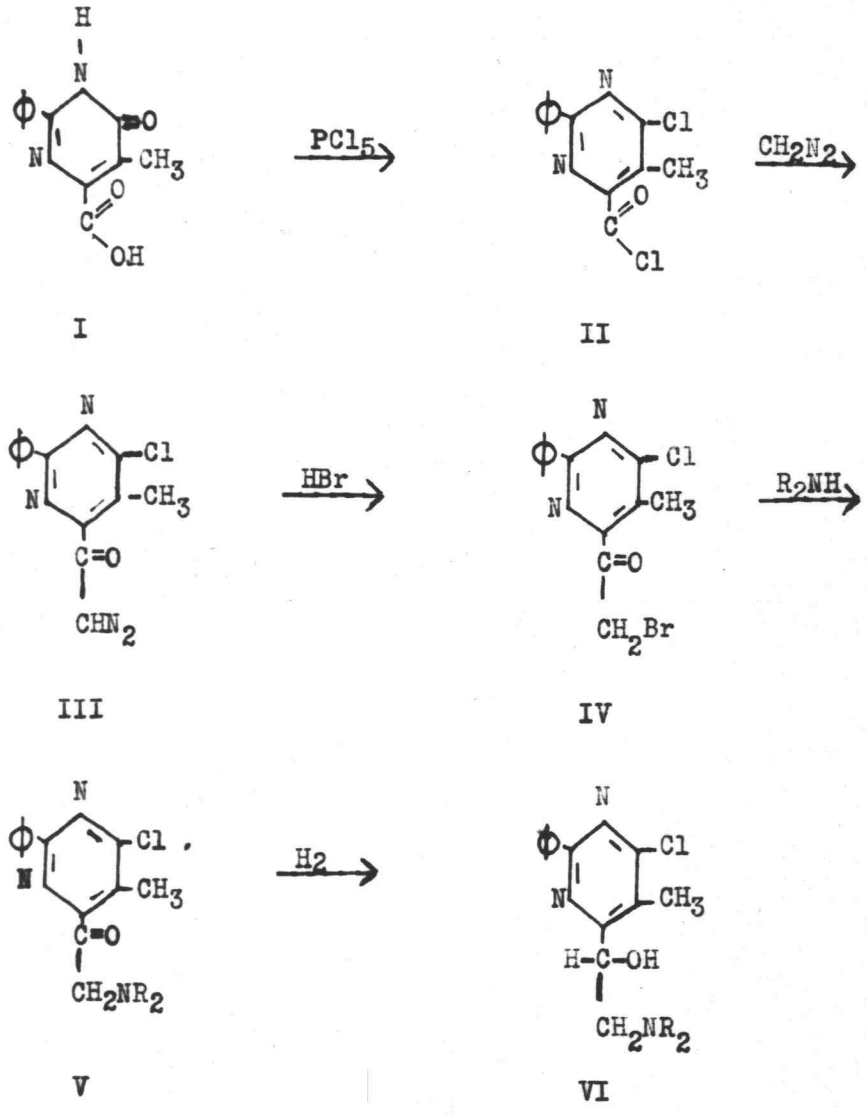
For purposes of documentation it became desirable to prepare a series of pyrimidine compounds with amino alcohol substituents in 2, 4 and 5 positions. This laboratory had previously synthesized (1) a number of compounds with the desired substituent in the 5 position. These were prepared by the application of the Mannich reaction to various 5-acetyl pyrimidines.

The usual methods for the preparation of such compounds involve the Mannich reaction on the acetyl derivative or the coupling of the bromomethyl ketone with the desired amine. The bromomethyl ketones are prepared either by direct bromination of the acetyl derivative or by means of the Arndt-Eistert synthesis. Whenever possible this latter method is preferable since it utilizes the acid rather than the less common acetyl derivative of the desired nucleus. Furthermore there is less possibility of brominating other positions in the molecule and hence entails fewer separation and characterization problems.

Several 4-pyrimidinecarboxylic acid derivatives have been reported. Diethyloxalacetate has been condensed with both benzamindine (3) and p-nitrobenzamidine (4). T. B. Johnson (2) has prepared 2-ethylmercapto-5-methyl-6-oxo-4-pyrimidinecarboxylic acid from sodio diethyloxalpropionate and pseudoethylthiourea.

In this laboratory, 5-methyl-6-oxo-2-phenyl-4-pyrimidinecarboxylic acid (I) was prepared (See Figure 1) in 50 to 60 percent yield from sodio diethyloxalpropionate and benzamidine. This

Figure I


H
N
O
CH3
C
O
OH
PCl5
N
Cl
CH3
C
O
Cl
CH2N2
I
II
N
Cl
CH3
C=O
CHN2
HBr
N
Cl
CH3
C=O
CH2Br
R2NH
III
IV
N
Cl
CH3
C=O
CH2NR2
H2
N
Cl
CH3
H-C-OH
CH2NR2
V
VI

reaction was found to proceed quite rapidly at 35 to 40°C. and the yield of acid obtained after allowing the reaction to proceed for one hour was not increased by a more prolonged reaction time, as was apparently the case with pseudoethylthiourea. The desired acid was obtained directly in contrast to the intermediates obtained by Pinner (3) and Rappeport (4).

By heating the acid with an excess of phosphorous pentachloride at 130°, it was converted to the acid chloride (II) in a good yield. At the same time, the oxygen on the pyrimidine ring was replaced by a chlorine atom.

The acid chloride reacted very rapidly with diazomethane in a benzene solution to form the intermediate diazo ketone (III) which was then readily converted to the chloromethyl ketone or bromomethyl ketone (IV) by concentrated aqueous hydrochloric or hydrobromic acids. The yield was 85 to 90 percent based on the acid chloride.

The condensation of the bromomethyl ketone (one mole) with amines (two moles) was carried out in a dry benzene-ether solution. Because of the greater reactivity of the bromomethyl ketone, it was used in preference to the chloromethyl ketone in the condensation reaction. The reaction appeared to be quite rapid as indicated by the almost immediate formation of crystalline amine hydrobromide which in some cases was obtained in nearly quantitative yields. After 15 to 30 minutes, the amine hydrobromide was removed by filtration. The condensate was isolated by precipitating it as the hydrochloride from the benzene-ether solution and purified by

recrystallization. The chlorine on the pyrimidine ring could conceivably also react with amines. Analysis of the condensate, however, indicated that bromine had been removed and not chlorine under the conditions used.

The amino ketone (V) appears to be rather unstable as the free base, as prolonged standing and evaporation of the solvent caused a decreased yield of product. It was apparently quite stable, however, as the hydrochloride salt.

The amino ketones were reduced at room temperature to the amino alcohol (VI) with 30 to 40 pounds hydrogen pressure using platinum oxide or palladized charcoal catalyst. The amino alcohols were isolated as the hydrochloride salts and purified by the usual recrystallization techniques.

EXPERIMENTAL

5-Methyl-6-oxo-2-phenyl-4-pyrimidinecarboxylic acid.--An aqueous solution of sodio-diethyloxalpropionate was prepared according to the directions of Johnson and Mackenzie (2) by reacting one-half molar quantities of ethyl oxalate and ethyl propionate in dry benzene (500 cc.) in the presence of sodium (0.5 mole). To the aqueous solution (500 cc.) was added 34.8 g. (0.22 moles) of benzamidine hydrochloride and a solution containing 21 g. (0.445 moles, assuming 85 percent purity) of sodium hydroxide. The mixture was allowed to stand for one hour. A small amount of solid material was filtered off. The filtrate was acidified with concentrated hydrochloric acid causing a precipitate to form. After cooling in the refrigerator the white- to tan-colored solid was filtered off by suction, washed with water, and dried. The yield of acid was 27 g. (53 percent). This acid was purified for analysis by dissolving in dilute alkali, decolorizing with charcoal, and reprecipitating with hydrochloric acid. The acid melted at 274° with decomposition.

Analysis calculated for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.35; N, 12.18; neutral equivalent, 230. Found: C, 62.35; H, 4.24; N, 12.29; neutral equivalent, 228.

6-Chloro-5-methyl-2-phenylpyrimidine-4-acid chloride.--Sixteen grams (0.07 mole) of 6-keto-5-methyl-2-phenyl-4-pyrimidinecarboxylic acid and 87.5 g. (0.42 mole) of phosphorous pentachloride were mixed and heated in an oil bath at 130° for one hour. The mixture cooled to a solid mass and the acid chloride was extracted from the excess PCl_5 by warm dry ether. By partial evaporation and cooling

of the ether, the acid chloride crystallized and was removed by filtration. The yield of very nearly pure acid chloride was 16 g. (86 percent). This was recrystallized from 50 cc. heptane obtaining 13.5 g. of product, m.p. 99-101°.

Analysis calculated for $C_{12}H_8Cl_2N_2O$: C, 54.0; H, 3.00; N, 10.49; Cl, 26.6. Found: C, 53.5; H, 3.36; N, 10.53; Cl, 26.4.

4-Bromoacetyl-6-chloro-5-methyl-2-phenylpyrimidine.--A solution of 6-chloro-5-methyl-2-phenylpyrimidine-4-acid chloride (12 g., 0.045 moles) in 60 cc. of dry benzene was added dropwise with stirring to 200 cc. of a cold benzene solution of diazomethane (0.135 moles). The reaction appeared to take place rapidly as evidenced by the vigorous evolution of nitrogen. The solution was allowed to warm up to room temperature and after standing for about one hour, the benzene was evaporated under reduced pressure. The solid residue was suspended in ether and 25 cc. of 48 percent hydrobromic acid was slowly added with stirring. The bromomethyl ketone precipitated and nitrogen was evolved. The crude product (13.0 g.) was removed by filtration. Some additional material was obtained by evaporation of the ether. This residue and crude product were combined and recrystallized from heptane obtaining 12.6 g. (86 percent yield) of slightly yellow needles. For analysis a portion of this product was decolorized with charcoal and twice recrystallized from heptane (m.p. 139-141°).

Analysis calculated for $C_{13}H_{10}BrClN_2O$: C, 47.93; H, 3.08; total halogen, 35.4. Found: C, 48.38; H, 3.39; total halogen, 35.4.

4-Chloroacetyl-6-chloro-5-methyl-2-phenylpyrimidine.--The chloromethyl ketone was prepared in a manner similar to the bromomethyl ketone. From 4.00 g. of the acid chloride was obtained 3.48 g. of the crystalline chloromethyl ketone, m.p. 155-156° C. This was purified for analysis by recrystallization from heptane.

Analysis calculated for $C_{13}H_{10}Cl_2N_2O$: N, 9.96; Cl, 25.2. Found: N, 10.02; Cl, 24.8.

4-(2-Diethylamino-1-oxyethyl-)6-chloro-5-methyl-2-phenylpyrimidine hydrochloride.--4-Bromacetyl-6-chloro-5-methyl-2-phenylpyrimidine (2.00 g., 0.00615 moles) was dissolved in 20 cc. dry benzene and 1.26 cc. (0.0123 moles) of diethylamine were added dropwise. The formation of crystalline diethylamine hydrobromide was very rapid. After standing for 15 minutes, the mixture was diluted with dry ether and the crystalline solid (0.82 g.) was filtered off by suction and washed with dry ether.

Dry hydrogen chloride was passed into the filtrate to precipitate the condensate as the hydrochloride. The solid was filtered off by suction and washed with dry ether. The weight of crude product was 2.15 g. This material was purified by three recrystallizations from isopropanol obtaining 0.61 g. of crystalline product, m.p. 170-178° C,to red liquid.

Analysis calculated for $C_{17}H_{21}Cl_2N_3O$: N, 11.86; total Cl, 20.0; ionizable Cl, 10.0. Found: N, 12.10; total Cl, 20.0; ionizable Cl, 9.84.

4-(2-Diethylamino-1-hydroxyethyl-)6-chloro-5-methyl-2-phenylpyrimidine hydrochloride.--The amino ketone (0.50 g.) was dissolved

in 20 cc. of methanol and reduced in a low pressure hydrogenation apparatus at 34 pounds pressure using 30 mg. of platinum oxide catalyst. After about two hours the catalyst was removed by filtration and the solvent evaporated. The residue was taken up in 10 cc. of warm isopropanol and upon cooling deposited 0.29 g. of white solid. This product partially melted at 160°, resolidified and finally melted at 170-172°.

Analysis calculated for $C_{17}H_{23}Cl_2N_3O$: N, 11.80; total Cl, 19.9; ionizable Cl, 9.82. Found: N, 12.15; total Cl, 19.5; ionizable Cl, 9.95.

4-(2-Di-n-propylamino-1-oxyethyl)-6-chloro-5-methyl-2-phenylpyrimidine hydrochloride.--The condensation of the bromomethyl ketone with di-n-propyl amine was carried out in the same manner as that with diethylamine. From 2.00 g. (0.00615 moles) of the bromomethyl ketone, 1.85 g. of crude amino ketone hydrochloride was obtained. This was recrystallized twice from a minimum amount of isopropanol to obtain 0.85 g. of product, m.p. 170 - 178° to red liquid.

Analysis calculated for $C_{19}H_{25}Cl_2N_3O$: N, 11.00; total Cl, 18.6; ionizable Cl, 9.28. Found: N, 11.06; total Cl, 18.3; ionizable Cl, 9.45.

4-(2-Di-n-propylamino-1-hydroxyethyl)-6-chloro-5-methyl-2-phenylpyrimidine hydrochloride.--The reduction to the di-n-propyl amino alcohol was carried out in the same way as that given for the preparation of the diethylamino alcohol. This amino alcohol crystallized very slowly with low recovery from a minimum of isopropanol.

From 0.50 g. of the amino ketone was obtained 0.20 g. of solid product, m. p. 180-181°.

Analysis calculated for $C_{19}H_{27}Cl_2N_3O$: N, 10.94; total Cl, 18.5; ionizable Cl, 9.23. Found: N, 11.33; total Cl, 18.3; ionizable Cl, 9.18.

SUMMARY

4-Bromo (and chloro) acetyl-6-chloro-5-methyl-2-phenyl-pyrimidine were prepared by application of the Arndt-Eistert synthesis to the acid chloride from 5-methyl-6-oxo-2-phenyl-4-pyrimidinecarboxylic acid.

The amino alcohols, 4-(2-diethylamino-1-hydroxyethyl)- and 4-(2-di-n-propylamino-1-hydroxyethyl)-6-chloro-5-methyl-2-phenylpyrimidine hydrochloride, were prepared by coupling the bromoacetyl pyrimidine with the appropriate secondary amine and subsequent reduction of the amino ketones.

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PART TWO

An amino alcohol substituent in the 5 position of the pyrimidine nucleus has recently been reported in the literature (1). A series of these compounds were prepared by coupling various secondary amines with 5-acetyl-4-methyl-2-phenylpyrimidine by means of the Mannich reaction. Since this procedure gives one type of an amino alcohol, the coupling of amino alcohols by amines with bromomethyl ketones was investigated.

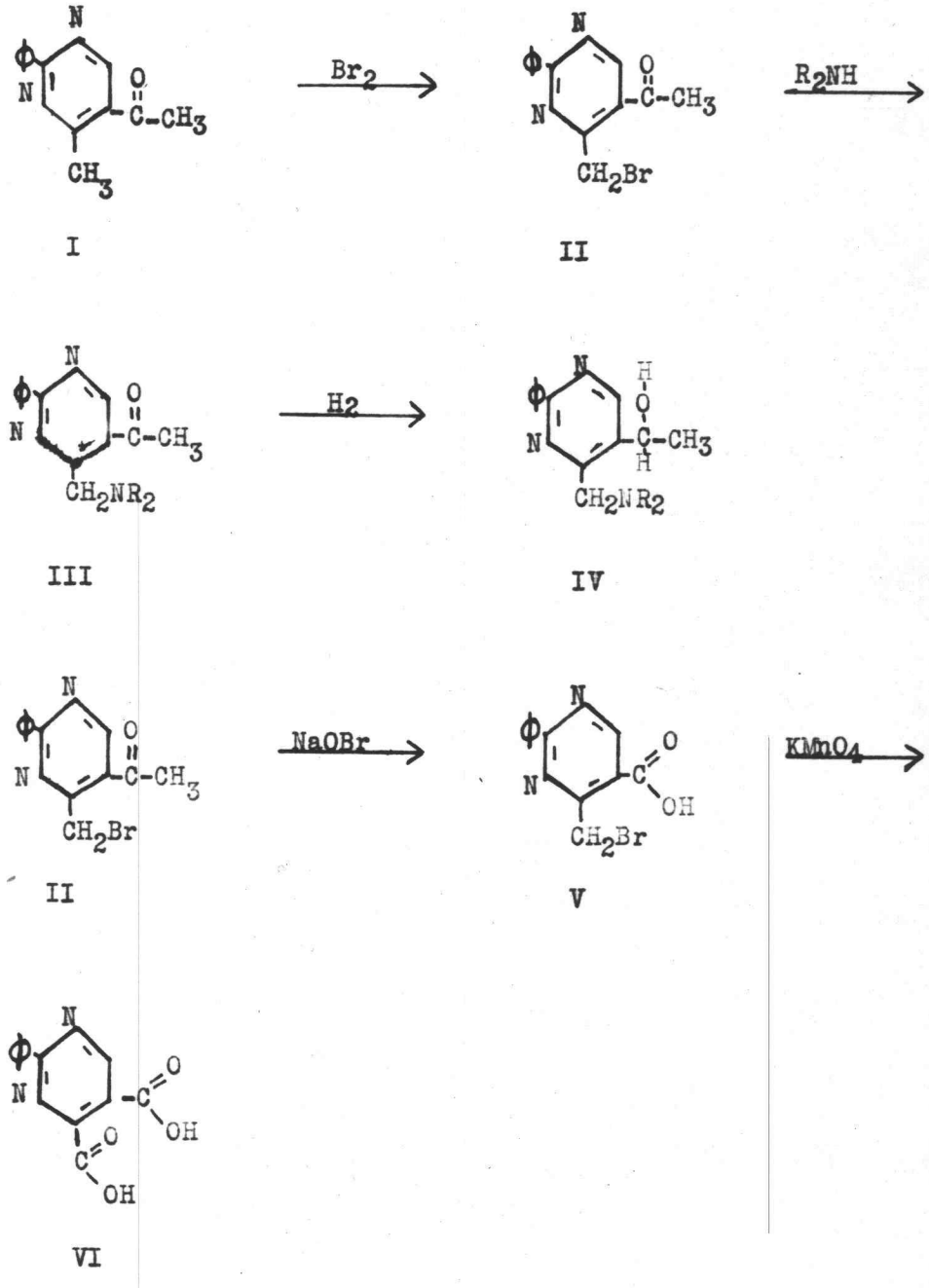
The bromomethyl ketones are usually prepared either by direct bromination of the acetyl derivative or by the Arndt-Eistert synthesis. Whenever possible this latter method is preferable since it utilizes the acid rather then the less common acetyl derivatives of the desired nucleus.

4-Methyl-2-phenyl-5-pyrimidinecarboxylic acid was prepared according to directions of Mitter and Bardhan (2). Preliminary attempts to convert the acid to the bromomethyl ketone by means of the Arndt-Eistert synthesis were unsuccessful.

For this reason, the direct bromination of the easily prepared 5-acetyl-4-methyl-2-phenylpyrimidine (I) was studied. Bromination in chloroform solution at room temperature gave over a 90 percent yield of crude bromination product. Analysis and solubility characteristics indicated the crude product to be the hydrobromide salt of the bromo derivative.

It was very evident from initial tests that this brominated derivative was probably an isomeric mixture. The crude product loses

Figure I



the ionizable bromine atom very readily. Shaking the material with chloroform containing a small amount of water converted it to the free base. Evaporation of the chloroform and extraction of the residue with petroleum ether divided the material into two fractions. The petroleum ether insoluble fraction, representing approximately 60 percent of the crude material, appears to be homogeneous, containing one atom of bromine, and recrystallizes nicely from high boiling ligroin. The petroleum ether soluble fraction which does not appear to be homogeneous, judging from its melting point and low bromine content, has not been completely investigated.

By dissolving the crude bromination product in hot isopropanol and cooling, a crystalline product was obtained which corresponds to the petroleum ether insoluble fraction. This isolation procedure appears to be easier than that described above.

The structure of this compound was established to be 5-acetyl-4-bromomethyl-2-phenylpyrimidine (II) on the basis of oxidation studies. Sodium hypobromite oxidized the compound to an acid (V) which still retained one bromine atom. The same procedure using 5-acetyl-4-methyl-2-phenylpyrimidine gave a product which was identical with 4-methyl-2-phenyl-5-pyrimidinecarboxylic acid. Potassium permanganate oxidation of the bromo acid gave a dicarboxylic acid which analysis indicated to be 2-phenyl-4, 5-dicarboxylic acid (VI).

The 5-acetyl-4-bromomethyl-2-phenylpyrimidine coupled readily with amines in a benzene-ether solution. The condensate (III) was isolated as the hydrochloride and purified by recrystallization. The

ketone was reduced to the alcohol (IV) at 30 to 40 pounds pressure of hydrogen using platinum oxide catalyst.

The 5-acetyl-4-morpholinomethyl-2-phenylpyrimidine hydrochloride was oxidized with sodium hypobromite to the 5-carboxy-4-morpholinomethyl-2-phenylpyrimidine hydrochloride which confirmed the position of the amino substituent.

EXPERIMENTAL

Bromination of 5-acetyl-4-methyl-2-phenylpyrimidine.--Eleven and one-half grams (0.054 moles) of 5-acetyl-4-methyl-2-phenylpyrimidine were dissolved in 75 cc. chloroform. Two and eight-tenths milliliters (0.054 moles) of bromine in 15 ml. chloroform were added to the solution of the acetyl pyrimidine. The solution was then placed in a quartz beaker, fitted with a cover and exposed to ultraviolet light. After one- and one-fourth hours the bromine color had disappeared and the solution was diluted with an equal volume of dry ether to precipitate a white to light yellow solid, 18.5 g. (92 percent yield).

Analysis of crude mixture calculated for $C_{13}H_{12}Br_2N_2O$: Br total, 43.0; ionizable, 21.5. Found: Br total, 44.5; ionizable, 21.3.

Separation and purification of 5-acetyl-4-bromomethyl-2-phenylpyrimidine.--Hydrogen bromide was removed from the crude bromine containing mixture (10 g.) by shaking it in a separatory funnel with 35 cc. of chloroform and 5 cc. of water. The chloroform was removed from the extract by distillation under reduced pressure leaving 7.5 g. of a white solid.

This solid was placed in a soxhlet thimble and extracted in a soxhlet apparatus with petroleum ether (boiling range, 35-65°C). The insoluble material (4.10 g.) left in the thimble was the crude 5-acetyl-4-bromomethyl-2-phenylpyrimidine. As an alternate purification procedure 0.50 g. of the crude bromination product was

dissolved in 15 cc. of hot isopropanol. Upon cooling, crystals (0.23 g.) deposited which were identical with petroleum ether insoluble fraction. The pure material (m.p. 168-170°) was obtained as white needles by several recrystallizations from ligroin (boiling range 97-140°).

Analysis calculated for $C_{13}H_{11}BrN_2O$: Br, 27.5; C, 53.61; H, 3.81. Found: Br, 27.4; C, 53.23; H, 4.16.

4-Bromomethyl-2-phenylpyrimidine-5-carboxylic acid.--5-Acetyl-4-bromomethyl-2-phenylpyrimidine (1.00 g., 0.00344 moles) was dissolved in 20 cc. of warm dioxane. A sodium hypobromite solution was prepared by adding a solution of 1.30 g. (0.0275 moles, assuming 85 percent purity) of sodium hydroxide in 10 cc. water to 0.71 cc. (0.0138 moles) of bromine. The sodium hypobromite was then added to the dioxane solution. The temperature immediately rose to 60° and the solution became reddish brown in color. After about two minutes, the solution was cooled and diluted with 50 cc. of cold water. A small amount (0.23 g.) of starting material precipitated and was removed by filtration. The aqueous solution was extracted with ether to remove bromoform and was then treated with an aqueous sodium bisulfite solution, until a negative starch-potassium iodide test was obtained, to reduce excess sodium hypobromite. Acidification with nitric acid precipitated a solid. This was filtered off by suction and washed with water. The yield of the crude acid was 0.48 g. (62 percent).

Analysis calculated for $C_{12}H_9BrN_2O_2$: Br, 27.3; neutral equivalent, 293. Found: Br, 25.6; neutral equivalent, 290.

2-Phenylpyrimidine-4, 5-dicarboxylic acid.--The crude 4-bromomethyl-2-phenyl-5-pyrimidinecarboxylic acid (0.66 g., 0.00225 moles) was dissolved in an equivalent molar amount of dilute sodium hydroxide solution. A solution of 1.19 g. (0.075 moles) of potassium permanganate in 60 cc. of water was added and the resulting solution was refluxed one and one-half hours. After cooling to room temperature, the excess permanganate was reduced with sulfur dioxide and the manganese dioxide was removed by centrifuging. The supernatant liquid was evaporated to a volume of 25 cc. and the hot solution was acidified with nitric acid. The dicarboxylic acid gradually crystallized on cooling and was removed by filtration and washed with water. The weight of product was 0.32 g. This acid was purified for analysis by one recrystallization from hot water. It melted (capillary tube) at 279-281° with decomposition.

Analysis calculated for $C_{12}H_8N_2O_4$: N, 11.47; neutral equivalent, 122. Found: N, 11.36; neutral equivalent, 123.

5-Acetyl-4-dimethylaminomethyl-2-phenylpyrimidine hydrochloride.--5-Acetyl-4-bromomethyl-2-phenylpyrimidine (0.30 g., 0.00103 moles) was dissolved in 5 cc. warm benzene. One milliliter of a 30 percent solution of dimethylamine in benzene was added. The formation of dimethylamine hydrobromide was very rapid. After standing for 15 minutes, the dimethylamine hydrobromide was filtered off and the filtrate was evaporated to dryness under reduced pressure to remove the excess dimethylamine. The residue was taken up in dry ether and dry hydrogen chloride was passed in to precipitate the

condensate as the hydrochloride. The white solid was removed by filtration and washed with dry ether. This solid, 0.24 g., was recrystallized once from absolute ethanol to obtain a white crystalline product, 0.19 g., m.p. 236° with decomposition.

Analysis calculated for $C_{15}H_{18}ClN_3O$: C, 61.75; H, 6.18; N, 14.40; Cl, 12.17. Found: C, 61.97; H, 6.50; N, 14.30; Cl, 12.05.

4-Dimethylaminomethyl-5-(1'-hydroxyethyl)-2-phenylpyrimidine hydrochloride.--5-Acetyl-4-dimethylaminomethyl-2-phenylpyrimidine hydrochloride (2.00 g.) was dissolved in 100 cc. methanol and reduced with hydrogen at 30 pounds pressure using platinum oxide catalyst (50 mg.). After shaking for a few hours, the catalyst was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in 75 cc. hot absolute ethanol, and diluted with 75 cc. dry ether. A crystalline product formed on standing and was removed by filtration. This product (1.50 g.) melted at 236-237°.

Analysis calculated for $C_{15}H_{20}ClN_3O$: C, 61.33, H, 6.81; N, 14.31; Cl, 12.08. Found: C, 61.36; H, 7.11; N, 14.35, Cl, 12.0.

A mixed melting point determination of the reduced and unreduced dimethylamine derivatives indicated that they were not identical compounds, m.p. 220-225° with decomposition.

5-Acetyl-4-morpholinomethyl-2-phenylpyrimidine hydrochloride.--5-Acetyl-4-bromomethyl-2-phenylpyrimidine (0.30 g., 0.00103 moles) was dissolved in 5 cc. of warm benzene and 0.18 cc. (0.00206 moles) of morpholine were added. A white crystalline precipitate

formed almost immediately. After about five minutes, dry ether was added to the mixture and the solid (0.15 g.) was filtered off by suction and washed with dry ether. Dry hydrogen chloride was passed into the filtrate to precipitate the condensate as a white solid. This was filtered off by suction and washed with dry ether. This solid (0.33 g.) was recrystallized from 3 N hydrochloric acid to obtain 0.29 g. of fine white needles. This solid starts to decompose at 213° and finally melts with decomposition at 220°.

Analysis calculated for $C_{17}H_{20}ClN_3O_2$: N, 12.60; Cl, 10.63. Found: N, 12.51; Cl, 10.40.

5-(1'Hydroxyethyl)-4-morpholinomethyl-2-phenylpyrimidine hydrochloride.--As the acetylmorpholinomethylpyrimidine was only slightly soluble in ethanol or methanol, it was first converted to the free base and then reduced in the usual manner. Two and one-half grams of 5-acetyl-4-morpholinomethyl-2-phenylpyrimidine were converted to the free base with 5 percent sodium bicarbonate, extracted with ether and the ether evaporated. The solid residue was dissolved in 50 cc. methanol and reduced overnight at 35 pounds pressure using 50 mg. platinum oxide catalyst. The catalyst was filtered off and the solvent evaporated. The syrupy residue was taken up in dry ether and dry hydrogen chloride was passed in to precipitate the condensate as the hydrochloride. The solid was removed by filtration and dissolved in 50 cc. hot absolute ethanol. The alcohol solution was diluted with an equal volume of dry ether and the solution was allowed to stand. The crystals which gradually formed were filtered off by suction. This solid (1.40 g.) was recrystallized

again in a similar manner obtaining 1.06 g. of white crystals, m.p. 230-232° softening and darkening at about 220°.

Analysis calculated for $C_{17}H_{22}ClN_3O_2$: C, 60.80; H, 6.56; N, 12.52; Cl, 10.57. Found: C, 60.87; H, 6.76; N, 12.22; Cl, 10.50.

5-Acetyl-4-diethylaminomethyl-2-phenylpyrimidine hydrochloride. This condensation with diethylamine was carried out in a manner similar to that with morpholine. From one gram (0.00344 moles) of 5-acetyl-4-bromomethyl-2-phenylpyrmidine and 0.71 cc.(000688 moles) of diethylamine was obtained 1.04 g. (95 percent yield) of product. This solid was recrystallized twice from absolute ethanol to obtain 0.51 g. of white crystals, m.p. 215-220° with decomposition.

Analysis calculated for $C_{17}H_{22}ClN_3O$: N, 13.15; Cl, 11.10. Found: N, 13.10; Cl, 11.02.

4-Diethylaminomethyl-5-(1'-hydroxyethyl)-2-phenylpyrimidine hydrochloride.--5-Acetyl-4-diethylaminomethyl-2-phenylpyrimidine hydrochloride (2.50 g.) was dissolved in 50 cc. methanol and shaken for six hours under thirty pounds pressure of hydrogen using 50 mg. of platinum oxide catalyst. The catalyst was then filtered off and the methanol evaporated. The residue was dissolved in 20 cc. hot absolute ethanol and diluted with 40 cc. dry ether. The crystalline solid (1.85 g.) which formed on standing was removed and recrystallized again in a similar manner obtaining 1.78 g. of crystalline product, m.p. 185-187°.

Analysis calculated for $C_{17}H_{24}ClN_3O$: C, 63.45; H, 7.47; N, 13.07; Cl, 11.03. Found: C, 63.75; H, 7.69; N, 13.19; Cl, 10.95.

5-Carboxy-4-morpholinomethyl-2-phenylpyrimidine hydrochloride. 5-Acetyl-4-morpholinomethyl-2-phenylpyrimidine hydrochloride (0.50 g., 0.0015 moles) was suspended in 5 cc. of dioxane. A sodium hypobromite solution was prepared by adding a solution of 0.636 g. of sodium hydroxide in 10 cc. of water to 0.31 cc. (0.006 moles) of bromine. The sodium hypobromite solution was added to the dioxane suspension. The reaction was exothermic, and the solution became dark red in color. After standing for 15 minutes the solution was diluted with 40 cc. water and extracted with ether. The excess sodium hypobromite was reduced by adding a few drops of a saturated sodium bisulfite solution and the solution was then acidified with concentrated hydrochloric acid. A fine crystalline solid gradually formed on standing. This was removed by filtration yielding 0.24 g. of a tan-colored solid. Two-tenths grams of this material was recrystallized from isopropanol containing dry hydrogen chloride to yield 0.13 g. of product.

Analysis calculated for $C_{16}H_{18}ClN_3O_3$: N, 12.52; Cl, 10.58; neutral equivalent, 168. Found: N, 12.92; Cl, 10.34; neutral equivalent, 173.

SUMMARY

Bromination of 5-acetyl-4-methyl-2-phenylpyrimidine gave 5-acetyl-4-bromomethyl-2-phenylpyrimidine as one of the bromination products. Its structure was established by oxidation to 4-bromomethyl-2-phenyl-5-pyrimidinecarboxylic acid and to 2-phenyl-4,5-pyrimidinedicarboxylic acid.

By the coupling of 5-acetyl-4-bromomethyl-2-phenylpyrimidine with various secondary amines (dimethylamine, diethylamine, morpholine) followed by catalytic reduction, compounds of the type 4-dialkylaminomethyl-5-(1-hydroxyethyl)-2-phenylpyrimidine have been prepared.

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