[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Pyrimidine. III. Study of the Bromination of 5-Acetyl-4-methyl-2-phenylpyrimidine[1]

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An amino alcohol substituent in the 5-position of the pyrimidine nucleus has recently been reported in the literature.[2] 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 amino alcohol, the preparation of amino alcohols by reaction of amines with bromomethyl ketones was investigated.

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

4-Methyl-2-phenyl-5-pyrimidinecarboxylic acid was prepared according to the directions of Mitter and Bardham.[3] Preliminary attempts to convert the acid to the bromomethyl ketone by means of the diazomethane synthesis were unsuccessful.

For this reason, the direct bromination of the easily prepared 5-acetyl-4-methyl-2-phenylpyrimidine (Fig. 1, I) was studied. Bromination in chloroform solution at room temperature gave over a 90% yield of crude bromination product. Analysis and solubility characteristics indicated the crude product to be the hydrobromide salt of the bromo derivative.

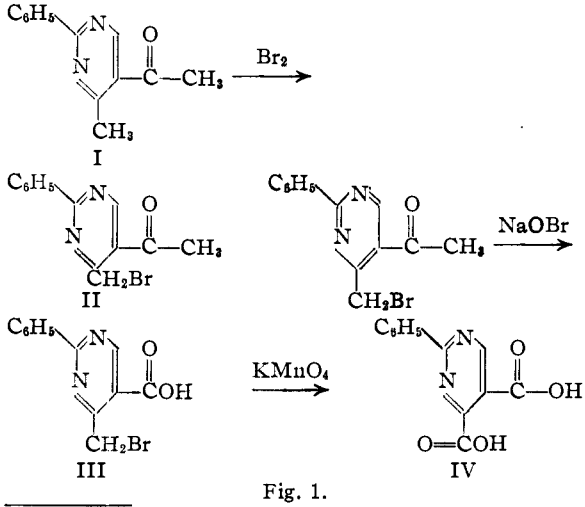

Fig. 1.

It was very evident from initial tests that this brominated derivative was probably an isomeric mixture. The crude product loses the ionizable bromine atom very readily. Shaking the material with chloroform containing a small amount of water converted it to the free base.

The principal product of the bromination was a petroleum ether insoluble compound. 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 (III) 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 the 2-phenyl-4,5-dicarboxylic acid (IV).

The 5-acetyl-4-bromomethyl-2-phenylpyrimidine reacted readily with amines in a benzene–ether solution. The 5-acetyl-4-morpholinomethyl-2-phenylpyrimidine hydrochloride was oxidized with sodium hypobromite to the 5-carboxyl-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 mole) of 5-acetyl-4-methyl-2-phenylpyrimidine was dissolved in 75 ml. of chloroform. Two and eight-tenths milliliters (0.054 mole) of bromine in 15 ml. of chloroform was added to the solution of the acetylpyrimidine. 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% yield).

Anal. of crude mixture. Calcd. 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 ml. of chloroform and 5 ml. 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, 36–65°). 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 ml. of hot isopropyl alcohol. Upon cooling, crystals (0.23 g.) deposited which were identical with petroleum ether insoluble fractions. The pure material (m. p. 168–170°) was obtained as white needles by several recrystallizations from ligroin (boiling range 97–140°).

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(2) Bruce Graham, A. M. Griffith, C. S. Pease and B. E. Christensen, THIS JOURNAL, **67**, 1294 (1945).

(3) P. G. Mitter and J. C. Bardham, *J. Chem. Soc.*, **123**, 2179 (1923).

Anal. Calcd. 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-bromo-methyl-2-phenylpyrimidine (1.00 g., 0.00344 mole) was dissolved in 20 ml. of warm dioxane. A sodium hypobromite solution was prepared by adding a solution of 1.30 g. (0.0275 mole, assuming 85% purity) of sodium hydroxide in 10 ml. water to 0.71 ml. (0.0138 mole) 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 ml. of cold water. A small amount (0.25 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 by suction and washed with water. The yield of the crude acid was 0.48 g. (62%).

Anal. Calcd. 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 mole) was dissolved in an equivalent molar amount of dilute sodium hydroxide solution. A solution of 1.19 g. (0.075 mole) of potassium permanganate in 60 ml. of water was added and the resulting solution was refluxed for 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 ml. 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.

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

Directions for Reaction of Amines with 5-Acetyl-4-bromomethyl-2-phenylpyrimidine.—Three-tenths gram (0.00103 mole) of 5-acetyl-4-bromomethyl-2-phenyl-pyrimidine was dissolved in 5 ml. of warm benzene. To this solution was added 0.00206 mole of the free base. Usually after a few minutes the hydrobromide of the free base (*i. e.*, morpholine hydrobromide) formed. Dry ether was then added to the mixture and the solid removed by filtration and washed with dry ether. Dry hydrogen chloride was passed into the filtrate to precipitate the product as a white solid. This was removed by filtration and washed with dry ether.

5-Acetyl-4-dimethylaminomethyl-2-phenylpyrimidine Hydrochloride.—The product was purified by recrystallization from absolute ethanol to obtain a white crystalline product, 63% yield, m. p. 236° with decomposition:

Anal. Calcd. 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.

5-Acetyl-4-morpholinomethyl-2-phenylpyrimidine Hydrochloride.—The product was purified by recrystallization from 3 *N* hydrochloric acid. The yield was 84% of fine white needles which started to decompose at 213° and finally melted with decomposition at 220°.

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

5-Acetyl-4-diethylaminomethyl-2-phenylpyrimidine Hydrochloride.—The yield of crude product was 95%. This was purified by recrystallization (twice) with absolute ethanol resulting in white crystals, m. p. 215–220° with decomposition.

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

Directions for the Reduction of the Amino Ketones.—Two to two and one-half grams of the amino ketone hydrochloride was dissolved in 100 ml. 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.

4-Dimethylaminomethyl-5-(1-hydroxyethyl)-2-phenylpyrimidine Hydrochloride.—The residue from the reduction was dissolved in 75 ml. of hot absolute ethanol, and diluted with equal volume of dry ether. The crystalline product which formed on standing was removed by filtration. This product melted at 236–237°; yield was 75%.

Anal. Calcd. 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, 14.36; Cl, 12.0.

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

5-(1-Hydroxyethyl)-4-morpholinomethyl-2-phenylpyrimidine Hydrochloride.—Since the acetylmorpholinomethylphenylpyrimidine was only slightly soluble in ethanol or methanol it was first converted to the free base. Two and one-half grams of 5-acetyl-4-morpholinomethyl-2-phenylpyrimidine hydrochloride was converted to the free base with 5% sodium bicarbonate, extracted with ether and the ether evaporated. The residue was reduced in the usual manner. The reduction product (a sirupy residue) was dissolved in dry ether and dry hydrogen chloride was added to precipitate the product as the hydrochloride. The solid was removed by filtration and dissolved in 50 ml. of hot absolute ethanol. The alcohol solution was diluted with an equal volume of dry ether and the solution allowed to stand. The crystals which gradually formed were removed. This solid was recrystallized again in a similar manner to give 42% yield of white crystals, m. p. 230–232°, softening and darkening at about 220°.

Anal. Calcd. 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.

4-Diethylaminomethyl-5-(1-hydroxyethyl)-2-phenylpyrimidine Hydrochloride.—The residue from the reduction was dissolved in 20 ml. of hot absolute ethanol and diluted with 40 ml. of dry ether. The crystalline solid which formed on standing was removed and recrystallized again in a similar manner to give 71% yield of a crystalline product, m. p. 185–187°.

Anal. Calcd. 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 mole) was suspended in 5 ml. of dioxane. A sodium hypobromite solution was prepared by adding a solution of 0.636 g. of sodium hydroxide in 10 ml. of water to 0.31 ml. (0.006 mole) 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 fifteen minutes the solution was diluted with 40 ml. of 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 gram of this material was recrystallized from isopropyl alcohol containing dry hydrogen chloride to yield 0.13 g. of product.

Anal. Calcd. 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-phenyl-

pyrimidine 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-pyrimidine-carboxylic acid and 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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[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

Condensation of Some Tertiary Octyl Alcohols with Benzene

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Previous communications[2] from this Laboratory have reported the condensation of eight of the seventeen possible tertiary octyl alcohols with benzene in the presence of aluminum chloride. The purpose of this investigation was to condense the remaining tertiary octyl alcohols with benzene and to determine the boiling points, refractive indices and surface tensions of the resulting octylbenzenes. To this end, the alcohols shown in Table I were prepared.[3] Of these, 3,4-dimethyl-3-hexanol has not been reported previously. This alcohol was synthesized successfully from 3-methyl-2-pentanone and ethyl Grignard reagent and from 3-methyl-4-hexanone and methyl Grignard reagent. Attempts to prepare it from butanone and secondary butyl Grignard reagent failed, the product being contaminated with large amounts of homomesityl oxide, which boils at approximately the same temperature as the desired alcohol.[4]

In general the condensations of the alcohols with benzene were carried out as described previously.[2c,5] The products were distilled under diminished pressure, traces of octyl chloride were removed from the octylbenzene fraction by refluxing with alcoholic potassium hydroxide or alcoholic silver nitrate, and the octylbenzene fraction was carefully distilled through a Fenske-type column.

Our results agree with previous observations from this Laboratory[2b,5] that branching on the β-carbon atom of the alcohol results in a decreased yield of the octylbenzene (see Table II). The alcohols without branching on the β-carbon atom, namely, 3-methyl-3-heptanol, 4-methyl-4-heptanol, 3-ethyl-3-hexanol and 2,4-dimethyl-4-hexanol gave their respective octylbenzenes in yields of 19 to 31%. These hydrocarbons possess closely related physical properties and the determined molecular refractions are within 0.1 unit of the theoretical value. Because of the large yields of pure hydrocarbons with practically constant boiling points and indices of refraction, the accuracy with which the physical constants of these compounds were determined is greater than for the other four octylbenzenes.

Those alcohols with branching on one β-carbon atom, 2,3-dimethyl-3-hexanol, 3,4-dimethyl-3-hexanol, and 2-methyl-3-ethyl-3-pentanol fall into a second group. The crude octylbenzene fraction obtained from these is more complex than that obtained from the alcohols in the first group. Fractionation gave only a few grams (5 to 9%) of ma-

TABLE I

TERTIARY OCTYL ALCOHOLS

	Carbonyl cpd.	Grignard	B. p., °C. (mm.)	$n^{20}D$
3-Methyl-3-heptanol	MeCOEt	BuMgBr[a]	158 (742) 63–64 (13)	1.4270 (22°)
4-Methyl-4-heptanol	$MeCO_2Et$	PrMgBr[b]	62–63 (12)	1.4258
3-Ethyl-3-hexanol	$PrCO_2H$ PrCOCl	EtMgBr[c] EtMgBr[d]	153–155 (748) 64–65 (14)	1.4326
2,3-Dimethyl-3-hexanol	*i*-PrCOMe	PrMgBr[e]	155.5–157.5 (748) 54–56 (13)	1.4332
2,4-Dimethyl-4-hexanol	MeCOEt *i*-BuCOMe	*i*-BuMgBr[f] EtMgBr[g]	54.5 (13) 60–62 (16)	1.4278
3,4-Dimethyl-3-hexanol	See Experimental		150–152 (740) 58 (11)	1.4350
2-Methyl-3-ethyl-3-pentanol	*i*-$PrCO_2H$ *i*-PrCOCl	EtMgBr[c] EtMgBr[d]	156–157 (748) 53 (10)	1.4372
2,3,4-Trimethyl-3-pentanol	$(i\text{-Pr})_2CO$	MeMgBr[h]	146–147 (740) 53–54 (13)	1.4342

[a] Whitmore and Badertscher, THIS JOURNAL, **55**, 1559 (1933). [b] Halse, *J. prakt. Chem.*, **89**, 453 (1914). [c] Ref. 14. [d] E. R. Breining, Master's Thesis, Michigan State College, 1938. [e] Clarke, THIS JOURNAL, **33**, 528 (1911). [f] Meyer and Tuot, *Compt. rend.*, **196**, 1232 (1933). [g] Clarke, THIS JOURNAL, **30**, 1147 (1908). [h] Whitmore and Laughlin, *ibid.*, **54**, 4392 (1932).

(1) Present location: (a) Flint Junior College, Flint, Michigan; (b) Pigments Division, du Pont Company, Newport, Del.; (c) Wyeth, Inc., Mason, Mich.; (d) Ethyl Corporation, Baton Rouge, La.

(2) (a) Huston and Guile, THIS JOURNAL, **61**, 69 (1939); (b) Huston, Guile, Sculati and Watson, *J. Org. Chem.*, **6**, 252 (1941); (c) Huston and Krantz, *ibid.*, **13**, 63 (1948).

(3) The condensation of 2,3,3-trimethyl-2-pentanol is now being reinvestigated along with the condensation of 2,2,3-trimethyl-3-pentanol.

(4) Grignard and Fluchaire, *Ann. chim.*, **9**, 27 (1927), have shown that butanone yields homomesityl oxide when treated with bromo- or iodo-magnesium butoxides. Since appreciable quantities of 2-butanol were recovered in our work, the bromo-magnesium alkoxide of this alcohol was probably responsible for the condensation.

(5) Huston, Fox and Binder, *J. Org. Chem.*, **3**, 251 (1938).