Four amino alcohols were synthesized from three acetylpyrimidine intermediates. 5-Acetyl-4-methyl-2-phenylpyrimidine, first synthesized in 1923 by Mitter and Bardhan, was used as an intermediate, as were the two following acetylpyrimidines synthesized by the same method in this laboratory: 5-acetyl-2,4-dimethylpyrimidine and 2-amino-5-acetyl-4-methylpyrimidine.

The acetylpyrimidines were converted to 5-(3-di-R-amino-1-hydroxy-n-propyl)-4-methyl-2-R'-pyrimidine hydrochlorides (R = methyl, ethyl; R' = amino, methyl, phenyl) by the Mannich reaction.

These ketones were then reduced to the following amino alcohols by catalytic reduction:

5-(3-dimethylamino-1-hydroxy-n-propyl)-4-methyl-2-phenylpyrimidine hydrochloride,

5-(3-diethylamino-1-hydroxy-n-propyl)-4-methyl-2-phenylpyrimidine hydrochloride,

5-(3-dimethylamino-1-hydroxy-n-propyl)-2,4-dimethylpyrimidine hydrochloride, and

2-amino-5-(3-dimethylamino-1-hydroxy-n-propyl)-4-methylpyrimidine.
AMINO ALCOHOLS
DERIVED FROM PYRIMIDINES

by

BRUCE GRAHAM

A THESIS
submitted to the
OREGON STATE COLLEGE

in partial fulfillment of
the requirements for the
degree of

DOCTOR OF PHILOSOPHY

June 1945
ACKNOWLEDGMENT

The author wishes to express his gratitude to Dr. B. E. Christensen and Dr. C. S. Pease for their efforts in facilitating this research.

He wishes also to thank A. M. Griffith, A. J. Torni-sek and S. C. Fang for their cooperation in analytical procedures.
TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Acetylpyrimidines</td>
<td>4</td>
</tr>
<tr>
<td>Amino Ketones</td>
<td>7</td>
</tr>
<tr>
<td>Amino Alcohols</td>
<td>8</td>
</tr>
<tr>
<td>Experimental</td>
<td>9</td>
</tr>
<tr>
<td>Summary</td>
<td>17</td>
</tr>
<tr>
<td>Bibliography</td>
<td>18</td>
</tr>
<tr>
<td>Appendix (Structural Formulas)</td>
<td>19</td>
</tr>
</tbody>
</table>
AMINO ALCOHOLS DERIVED FROM PYRIMIDINES

INTRODUCTION

The analgesic action of some natural amino alcohols has aroused considerable interest regarding this class of compounds generally. Two of the common natural amino alcohols widely used in analgesia are morphine and its methyl ester, codeine: (2)

![Chemical structure of morphine](image)

Even though morphine was the first organic base to be isolated and characterized as such (Sertürner, 1805), (3) it is today one of the most useful drugs known.

Scientists have long endeavored to produce synthetic drugs with analgesic action comparable to that of the morphine alkaloids but with less toxicity and less tendency toward habit formation. These endeavors have met with some success.

The γ-aminoalcohols, in the form of their benzoates and p-aminobenzoates, find application as local anesthetics, and many such physiologically active compounds have been prepared through the Mannich reaction. (5,6,7,8,9,
The commercial local anesthetic, Turocaine, is made from the alcohol obtained by reduction of the Mannich base from dimethylamine, formaldehyde, and ethyl methyl ketone; the alcohol is converted to the p-aminobenzoate, and the latter is used as the hydrochloride.

\[ (p) \ H_2NOC_6H_4COOCH-CHOH_2N(CH_3)_2-HCl \]

\[ \text{H}_3 \text{CH} \]

Lyndon Small of the Cobb Chemical Laboratory at the University of Virginia is a recognized authority on amino alcohols. He has synthesized many of these compounds and studied their physiological effects. Outstanding among his discoveries have been the amino alcohols derived from carbazole. One of these is 2-(3-diethylamino-1-hydroxy-n-propyl)-9-methylcarbazole, which approaches codeine in analgesic action.

He has synthesized also amino alcohols embodying the phenanthrene nucleus and the dibenzofuran nucleus. One conclusion drawn from his studies is: "--as a working hypothesis, the assumption seems justified that various carbocyclic or heterocyclic nuclei, in themselves indifferent, may be activated by, or serve to carry, groups
conferring the desired type of physiological effect". (19)

Using this working hypothesis as a basis, this laboratory has undertaken the synthesis of heterocyclic compounds in which the activating amino alcohol side chains are attached to various pyrimidine nuclei.
ACETYLPYRIMIDINES

The most promising approach to the preparation of amino alcohols derived from pyrimidines is that involving acetylpyrimidines as intermediates. There are three methods of preparing acetylpyrimidines, and five such compounds are reported in the literature.

1. Acetylbarbituric acid is prepared by refluxing malonic acid and urea in excess acetic anhydride or by heating barbituric acid with acetic anhydride. (1)

\[
\begin{align*}
\text{COOH} & \quad \text{NH}_2 \quad \text{HN CO} \\
\text{CH}_2 & + \quad \text{C} = \text{O} \quad \text{Ac}_2\text{O} \rightarrow \\
\text{COOH} & \quad \text{NH}_2 \quad \text{HN CO}
\end{align*}
\]

2. 5-Acetyl-4-methyl-2-phenylpyrimidine can be prepared by two methods. One which appeared in the German patent literature in 1939 condenses ethyl benzimidate hydrochloride with aminomethyleneacetone. (16)

\[
\begin{align*}
\text{NH}_2\text{HCl} & \quad \text{O} = \text{C} - \text{CH}_3 \quad \text{N} - \text{C} - \text{CH}_3 \\
\text{C}_6\text{H}_5 & + \quad \text{O} = \text{C} - \text{CH}_3 \rightarrow \\
\text{OEt} & \quad \text{H}_2\text{N} - \text{CH} \quad \text{N} = \text{CH}
\end{align*}
\]

The details of this process are not given in the abstract of the patent. (16)

3. The other, a general method, was developed by Mitter and co-workers (17,18). In this synthesis amidine hydrochlorides are condensed with ethoxymethyleneacetone in the presence of sodium ethoxide, as illustrated
in the general equation following:

\[
\begin{array}{c}
\text{NH-HCl} \quad \text{EtO-CH} \\
\text{R-C} \quad \text{O-O-CH}_3 \\
\text{NH}_2 \quad \text{O-O-CH}_3
\end{array}
\]

\[
\begin{array}{c}
\text{NaOEt} \quad \text{Ethanol} \\
\text{N - CH} \\
\text{R-C} \quad \text{O-O-CH}_3 \\
\text{N = C-CH}_3
\end{array}
\]

With analogous reactions employing various intermediates, Mitter prepared the following compounds: 5-acetyl-4-methyl-3-phenylpyrimidine, 5-acetyl-4-methyl-3-p-tolylpyrimidine, 5-acetyl-3-p-anisyl-4-methylpyrimidine, and 5-acetyl-4-methyl-3-(2-naphthyl)-pyrimidine.

In this investigation only the first and third methods were used to prepare the acetylpyrimidine intermediates. The first method was soon discarded because the acetylbarbituric acid did not yield Mannich products with a facility comparable to that of the acetylpyrimidines prepared by the Mitter method.

Of the four acetylpyrimidines prepared by Mitter only the 2-phenyl derivative was employed by this laboratory in synthesizing amino alcohols.

In addition, two new acetylpyrimidines were synthesized from ethoxymethyleneacetyleacetone. Acetamidine hydrochloride condenses with it to yield 5-acetyl-2,4-dimethylpyrimidine. Guanidine hydrochloride, when substituted for the amidines, yields 5-acetyl-2-amino-4-methylpyrimidine. These two new acetylpyrimidines also served as intermediates in the preparation of the amino alcohols.

For purposes of characterization the 5-acetyl-2-
amino-4-methyl pyrimidine was acetylated, to yield 5-acetyl-2-acetyl-amino-4-methylpyrimidine.

The synthesis of the amino alcohols from the acetyl-pyrimidines may be represented by the following general equations:

\[
R\text{-}\overset{0}{\text{O}}\text{-CH}_3 + R_2\text{NH} \cdot \text{HCl} + \text{HCl} \rightarrow R\text{-}\overset{0}{\text{O}}\text{-CH}_2\text{-CH}_2\text{-NR}_2 \cdot \text{HCl}
\]

\[
R\text{-}\overset{0}{\text{O}}\text{-CH}_2\text{-CH}_2\text{-NR}_2 \cdot \text{HCl} + \text{H}_2 \rightarrow R\text{-}\overset{\text{OH}}{\text{O}}\text{-CH}_2\text{-CH}_2\text{-NR}_2 \cdot \text{HCl}
\]

These reactions are discussed more completely in the following two sections.
AMINO KETONES

There are two well-known methods of converting ketones to amino ketones. One is the Mannich reaction:

\[ \text{R-}C\mathbf{\text{O--CH}}_3 \text{+ R}_2\text{NH} \cdot \text{HCl + HC-H } \rightarrow \text{R-}C\mathbf{\text{O--CH}}_2\text{CH}_2\text{-NR}_2 \cdot \text{HCl} \]

The other involves bromination procedure followed by an amination:

\[ \text{R-}C\mathbf{\text{O--CH}}_3 \text{+ Br}_2 \rightarrow \text{R-}C\mathbf{\text{O--CH}}_2\text{Br + HBr} \]
\[ \text{R-}C\mathbf{\text{O--CH}}_2\text{Br + HNR}_2 \rightarrow \text{R-}C\mathbf{\text{O--CH}}_2\text{NR}_2 \cdot \text{HBr} \]

Since the most promising results were obtained by the Mannich reaction in preliminary work, it was used in preference to bromination procedure.

No Mannich reaction involving acetylpyrimidines is described in the chemical literature. However, numerous similar acetyl heterocyclic compounds of nitrogen have been used in Mannich reactions. (4,19,20)

In this laboratory it was found that the acetylpyrimidines, other than acetylbarbituric acid, give workable yields in the Mannich reaction when dimethylamine hydrochloride is used. When diethylamine hydrochloride is used, only the 2-phenyl derivative yields a crystalline product, while the 2-amino and 2-methyl derivatives give syrupy products that make isolation extremely difficult.
AMINO ALCOHOLS

An attempt was made to reduce the amino ketones to amino alcohols using the highly selective aluminum isopropylate, which is specific for the carbonyl group.

\[
3 \text{R}_2=\text{C}=\text{O} + \text{Al(OCH(CH}_3)\text{)_2} \rightarrow (\text{R}_2 \text{CHO})\text{Al} + 3 \text{(CH}_3\text{)_2C}=\text{O} \\
(\text{R}_2\text{CHO})\text{Al} + 3 \text{H}_2\text{O} \rightarrow 3 \text{R}_2\text{CHOH} + \text{Al(OH)}_3
\]

This method was discarded because the prolonged heating caused decomposition and because of the necessity of converting the amino alcohols to free bases in the subsequent isolation.

The amino ketones reduce with varying speeds at 30 to 45 pounds hydrogen pressure using platinum oxide catalyst. The crystalline amino alcohol hydrochlorides can be isolated directly by crystallization procedures, except in one case.
5-Acetyl-3,4-dimethylpyrimidine. Forty-three grams of acetamidine hydrochloride (0.45 mole) were dissolved in absolute alcohol and added to an alcoholic solution of sodium ethoxide (10.4 grams of sodium in 300 ml. of absolute alcohol). Seventy-two grams of ethoxymethyleneacetylacetone were added slowly with shaking. The mixture was refluxed for one hour and the alcohol removed under reduced pressure. The residue was extracted with petroleum ether. The latter proved to be more selective than ethyl ether, making possible the separation of a colored impurity. Fifty grams of crude product were obtained in this way. Distillation of this product at 3 mm. and 62-64°C. yielded 43 grams (65%) of a light oil. The melting point was 23°C. It was soluble in water. Analysis calculated C₈H₁₀N₂O: N, 18.60. Found: N, 18.56.

The picrate of this compound was prepared from an ethereal solution of the acetylpyrimidine and ethereal solution of picric acid. The resulting mixture was allowed to stand twenty-four hours, and the precipitate was then recrystallized from dry ether. The melting point was 120°C.

5-Acetyl-2-amino-4-methylpyrimidine. Eighteen and four-tenths grams (0.19 mole) of guanidine hydrochloride were dissolved in 200 ml. of absolute ethanol, and 4.4
grams of sodium in 200 ml. of absolute alcohol (0.19 mole sodium ethoxide) were added to the guanidine solution. A white precipitate formed. Thirty grams (0.193 mole) of ethoxymethyleneacetylacetone in 100 ml. of absolute alcohol were added with shaking, causing the formation of yellow crystals. The mixture was refluxed gently for one hour, cooled, and filtered. The precipitate was washed with 300 ml. of cold water and then recrystallized from 500 ml. of 75% ethanol. The yield was 23 grams (80%) of very light yellow crystals. The melting point in a sealed tube was 227°C. uncorr. It sublimes above 150°C. Analysis calculated for C7H9N3O: C, 55.61; H, 6.00; N, 27.80. Found: C, 55.74; H, 6.18; N, 27.92.

An alcoholic solution of the acetylpyrimidine, when treated with an alcoholic solution of picric acid, yielded a crystalline product. The picrate on recrystallization from absolute alcohol has a melting point of 195°C.

2-Acetamino-5-acetyl-4-methylpyrimidine. Six grams (0.04 mole) of 2-amino-4-methyl-5-acetylpyrimidine were refluxed for two minutes in 30 ml. of acetic anhydride. They were then cooled and poured into 250 ml. of water and allowed to stand for 10 minutes. The solution was neutralized with dilute sodium hydroxide, cooled and filtered, and the precipitate was washed with water. The yield was 3 grams (39%) of white powder with a melting

5-(3-Dimethylamino-1-oxopropyl)-2-phenyl-4-methylpyrimidine. Forty-two and four-tenths grams (0.2 mole) of the 5-acetyl-4-methyl-2-phenylpyrimidine were refluxed four hours under nitrogen in 200 ml. of absolute alcohol with 18 grams (0.22 mole) of dimethylamine hydrochloride and 6 grams of paraformaldehyde; then 3 grams of paraformaldehyde were added, and refluxing was continued for two hours. The reaction mixture was cooled in a refrigerator and filtered, and the precipitate was washed with successive portions of warm, dry ether until free of unreacted ketone. The Mannich product recrystallized from absolute ethanol yielded 12 grams (20%) of white crystals with a melting point of 188°C. Analysis calculated for C₁₆H₂₀O₁N₃O: C, 62.84; H, 6.59; N, 13.74; O₁, 11.60. Found: C, 62.64; H, 6.40; N, 13.58; O₁, 11.60.

The picrate prepared from aqueous sodium picrate and the salt, after recrystallization from alcohol, melted at 144-146°C.

5-(3-Dimethylamino-1-hydroxy-n-propyl)-4-methyl-2-phenylpyrimidine hydrochloride. The reductions of all ketones were carried out at room temperature and 30-45 pounds pressure. Five grams (0.016 mole) of the corresponding amino ketone hydrochloride in 50 ml. of methanol
with 50 milligrams of platinum oxide required four hours. The reduction was continued for 15 hours with no further pressure drop. The catalyst was then removed and the methanol distilled at reduced pressures. The resulting syrup, after being taken up in 10 ml. of absolute ethanol, crystallized when placed overnight in a refrigerator. The crystals were washed with a small amount of cold alcohol. The yield was 3 grams (40%) of fine, short needles melting at 178°C. Some impure product was obtained by careful evaporation of the mother liquor. Analysis calculated for C₁₆H₂₂O₁₅N₃O: C, 62.43; H, 7.21; N, 13.65; O₁, 11.52. Found: C, 62.39; H, 7.52; N, 13.68; O₁, 11.55.

The picrate, prepared by the addition of aqueous sodium picrate to a solution of the hydrochloride in water, separated as an oil. Recrystallization from ethanol by long cooling gave crystals melting at 135-137°C.

5-(3-Diethyl-1-oxopropyl)-4-methyl-2-phenylpyrimidine hydrochloride. Ten and five-tenths grams (0.05 mole) of 5 acetyl-4-methyl-2-phenylpyrimidine, 5.5 grams (0.05 mole) of diethylamine hydrochloride and 1.5 grams of paraformaldehyde were refluxed under nitrogen for 3.5 hours in 50 ml. of absolute alcohol; then 0.75 gram of paraformaldehyde was added, and the refluxing was continued for another 1.5 hours. The solution was then cooled in a refrigerator and filtered, and the precipitate was washed with ether until free of unreacted ketone. The crude
product recrystallized from absolute alcohol yielded 3.5 grams (21%) of white, needle-like crystals with a melting point of 125°C. Analysis calculated for C_{18}H_{24}ClN_{3}O: C, 64.75; H, 7.25; N, 12.59; Cl, 10.62. Found: C, 64.50; H, 7.32; N, 12.51; Cl, 10.80.

The picrate prepared from the salt and aqueous sodium picrate, after recrystallization from ethanol, melted at 135-137°C.

5-(3-Diethylamino-1-hydroxy-n-propyl)-4-methyl-2-phenylpyrimidine hydrochloride. Two and five-tenths grams (0.0075 mole) of the amino ketone hydrochloride were reduced in 50 ml. of ethanol with 50 milligrams of platinum oxide over a period of two hours. Continuation of the reduction gave no further pressure drop. The catalyst was removed and the solution cooled in a refrigerator for 24 hours. This gave a yield of 1.5 grams (64%) of a crystalline product with a melting point of 150°C. Analysis calculated for C_{18}H_{26}ClN_{3}O: C, 64.36; H, 7.80; N, 12.51; Cl, 10.56. Found: C, 64.17; H, 7.96; N, 12.96; Cl, 10.75.

The picrate made from addition of aqueous sodium picrate to a solution of the hydrochloride was an oil which would not crystallize from alcohol.

5-(3-Dimethylamino-1-oxopropyl)-2,4-dimethylpyrimidine hydrochloride. Fifteen grams (0.1 mole) of 5-acetyl 2,4-dimethylpyrimidine and 8.1 grams (0.1 mole) of dimethylamino hydrochloride and 3 grams of paraformaldehyde
in 35 ml. of absolute ethanol were refluxed for 0.75 hour under nitrogen. The solution was then cooled in a refrigerator and filtered, and the precipitate was washed with absolute ethanol. The crystals were then triturated and washed with warm, dry ether, and the product was recrystallized from a minimum amount of absolute ethanol. The yield was 7.0 grams (29%) of white granular crystals with a melting point of 148°C. Analysis calculated for C_{11}H_{18}O_1N_3O: C, 54.20; H, 7.44; N, 17.24; Cl, 14.55. Found: C, 54.24; H, 7.53; N, 17.31; Cl, 14.57.

The picrate prepared from the salt and aqueous sodium picrate, after recrystallization from ethanol, melted at 148°C.

5-(3-Dimethylamino-1-hydroxy-n-propyl)-2,4-dimethylpyrimidine hydrochloride. The reduction of 7 grams (0.029 mole) of the amino ketone in 40 ml. of ethanol required five hours. The catalyst was removed, but the product failed to crystallize. The solvent was then removed, yielding a syrup which would not crystallize from the usual solvents.

This syrup was dissolved in 10 ml. of water, treated with 10 ml. of 20% sodium hydroxide, then extracted with ether. The product was a brown oil which slowly crystallized upon standing. Two and five-tenths grams of these crystals were dissolved in an excess of petroleum ether and treated several times with charcoal. The petroleum
ether solution was then slowly evaporated at reduced pressure and room temperature until crystals appeared, whereupon it was cooled in a refrigerator. The yield was one gram of large, soft, slightly-yellow crystals with a melting point of 60°C. Analysis calculated for C₁₁H₁₉N₃O: C, 63.12; H, 9.15; N, 20.08. Found: C, 63.30; H, 8.93; N, 20.17.

The picrate made in ethereal solution and recrystallized from alcohol melted at 130-133°C.

3-Amino-5-(-3-Dimethylamino-1-oxopropyl)-4-methylpyrimidine hydrochloride. Fifteen and one-tenth grams (0.1 mole) of 5-acetyl-2-amino-4-methylpyrimidine, 8.1 grams (0.1 mole) of dimethylamine hydrochloride and 3 grams of paraformaldehyde were refluxed for three hours under nitrogen in 300 ml. of absolute ethanol. One gram of paraformaldehyde and 0.5 gram of dimethylamino hydrochloride were added, and refluxing was continued for another hour. The solution was then cooled in a refrigerator, filtered, and washed with a small amount of absolute ethanol, then triturated and washed with warm ether. The crude product was then recrystallized from absolute ethanol. The yield was 53.5 grams (54%) of white solid with a melting point of 208-210°C. Analysis calculated for C₁₀H₁₇O₁N₄Cl: C, 49.08; H, 7.00; N, 22.89; Cl, 14.49. Found: C, 49.02; H, 7.27; N, 22.83; Cl, 14.58.

The picrate prepared from the salt and aqueous sodi-
um picrate, after recrystallization from ethanol, melted at 170-172°C.

2-Amino-5-(3-dimethylamino-1-hydroxy-n-propyl)-4-methylpyrimidine. Two grams (0.008 mole) of the amino ketone hydrochloride in 100 ml. of methanol with 100 milligrams of platinum oxide were reduced 10 hours. The catalyst was removed and the product crystallized by slowly evaporating the methanol under vacuum at room temperature. The crystals were recrystallized from a minimum amount of ethanol. The yield was one gram (50%) of white crystalline material. The crystals undergo a monotropic transformation on the melting point block around 185°C, finally melting at 204-206°C. Analysis calculated for C₆H₁₉ClN₄O: C, 48.67; H, 7.76; N, 22.71; Cl, 14.38. Found: C, 48.40; H, 7.81; N, 22.68; Cl, 14.25.

The picrate prepared from aqueous sodium picrate and the hydrochloride precipitated as yellow needles. The product recrystallized from alcohol melted at 162-164°C.
SUMMARY

5-Acetyl-2-amino-4-methylpyrimidine and 5-acetyl-2,4-dimethylpyrimidine have been prepared by Mitter's method of synthesizing acetylpyrimidines.

By application of the Mannich reaction to 2-R-5-acetyl-4-methylpyrimidines (R = amino, methyl, phenyl) followed by catalytic reduction, pyrimidine amino alcohols have been prepared in which the side chain \( \text{CHOHCH}_2\text{NH}_2 \) \( \text{CHO}_2\text{NR}_2 \) (\( \text{NR}_2 \) = dimethylamino, diethylamino) is located at the 5 position.
BIBLIOGRAPHY


(6) Mannich and Braun, Ber., 55, 1874 (1920).


(8) Mannich and Heilner, Ber., 55, 356 (1922).


(10) Mannich and Hönig, Arch. Pharm., 265, 598 (1927).


(12) Mannich and Lammering, Ber., 55, 3510 (1922).


APPENDIX

STRUCTURAL FORMULAS

Acetylpyrimidines

\[
\begin{align*}
N & : \text{CH} \\
(CH_3)_2 & : \text{CONH} \\
(NH_2) & : \text{C} \\
& : \text{O} \\
\end{align*}
\]
\[ N = \text{O-CH}_3 \]

Amino ketones

\[
\begin{align*}
N & : \text{CH} \\
(CH_3)_2 & : \text{CONH} \\
(NH_2) & : \text{C} \\
& : \text{O} \\
\end{align*}
\]
\[ N = \text{O-CH}_3 \]

Amino alcohols

\[
\begin{align*}
N & : \text{CH} \\
(CH_3)_2 & : \text{CONH} \\
(NH_2) & : \text{C} \\
& : \text{O} \\
\end{align*}
\]
\[ N = \text{O-CH}_3 \]

The compounds described in the "Experimental" section of this paper are represented on this page. The synthesis of all these compounds was originated and developed in this laboratory.