[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE[1]]

Amino Alcohols Derived from Pyrimidines

BY BRUCE GRAHAM, A. M. GRIFFITH, C. S. PEASE AND B. E. CHRISTENSEN

The physiological properties of the amino alcohols have aroused considerable interest. Compounds with a phenanthrene,[2] carbazole,[3] quinoline,[4] dibenzofuran,[5] nucleus, for example, have recently been synthesized for this reason.

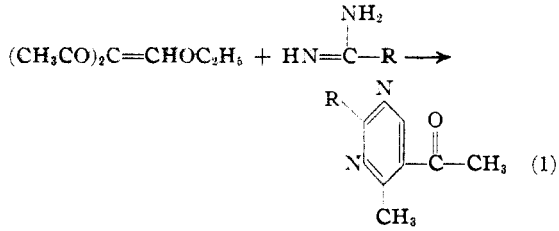
Such synthesis centers around the acetyl derivative of the nucleus which is converted to the amino ketone by bromination procedures or by means of the Mannich reaction.

At the suggestion of Dr. Lyndon Small, this Laboratory undertook the preparation of amino alcohols with a pyrimidine nucleus.

5-Acetyl-4-methyl-2-phenylpyrimidine was prepared from ethoxymethyleneacetylacetone and benzamidine according to the directions of Mitter and Bardhan.[6]

Since guanidine and acetamidine were also found to condense with ethoxymethyleneacetylacetone, it was possible to prepare two additional acetylpyrimidines for intermediates.

Amino alcohols prepared from these substituted pyrimidines are described in this paper. These were obtained by the reduction of the amino ketones which were produced by the Mannich reaction. The reactions are indicated in (1), (2), (3), below



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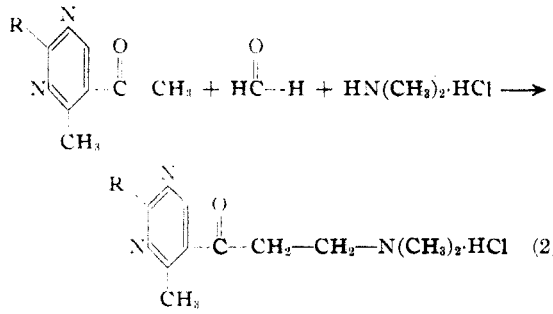

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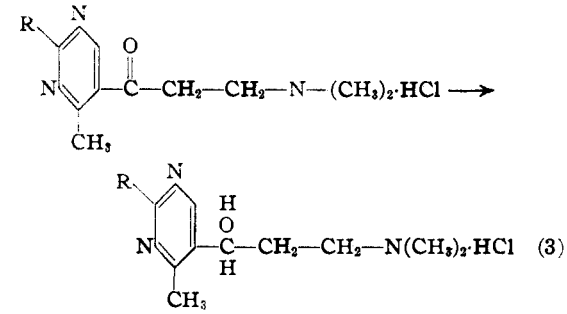

(3)

Experimental

5-Acetyl-2,4-dimethylpyrimidine.—Forty-three grams of acetamidine hydrochloride (0.45 mole) was dissolved in absolute alcohol and added to an alcoholic solution of sodium ethoxide (10.4 g. of sodium (0.45 mole) in 300 ml. of absolute alcohol). Seventy-two grams of ethoxymethyleneacetylacetone (0.46 mole) was 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 was obtained in this way. This was distilled at reduced pressure; yield 43 g. (63%); b. p. 62–64° at 3 mm. The melting point was 23°. It was soluble in water.

Anal. Calcd. $C_8H_{10}N_2O$: N, 18.66. Found: N, 18.56.

The picrate of this compound was prepared from an ethereal solution of the acetylpyrimidine and an 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°.

5-Acetyl-2-amino-4-methylpyrimidine.—Eighteen and four-tenths grams (0.19 mole) of guanidine hydrochloride was dissolved in 200 ml. of absolute ethanol, and 4.4 g. of sodium in 200 ml. of absolute alcohol (0.19 mole sodium ethoxide) was added to the guanidine solution. A white precipitate formed. Thirty grams (0.192 mole) of ethoxymethyleneacetylacetone in 100 ml. of absolute alcohol was 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 g. (80%) of very light yellow crystals. The melting point in a sealed tube was 227° uncor. It sublimes above 150°. *Anal.* Calcd. for $C_7H_9N_3O$: C, 55.61; H, 6.00; N, 27.80. Found: C, 55.74; H, 6.16; 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 had a melting point of 195°.

2-Acetamino-5-acetyl-4-methylpyrimidine.—Six grams (0.04 mole) of 5-acetyl-2-amino-4-methylpyrimidine was refluxed for two minutes in 30 ml. of acetic anhydride. It was then cooled and poured into 250 ml. of water and allowed to stand for ten minutes. The solution was neutralized with dilute sodium hydroxide, cooled and filtered, and the precipitate was washed with water. The yield was 3 g. (39%) of white powder with a melting point of 152–153°. *Anal.* Calcd. for $C_9H_{11}N_3O_2$: C, 55.94; H, 5.74; N, 21.74. Found: C, 55.74; H, 5.90; N, 21.80.

5-(3-Dimethylamino-1-oxopropyl)-4-methyl-2-phenylpyrimidine. Forty-two and four-tenths grams (0.2 mole) of

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(2) Van de Kamp and Mosettig, THIS JOURNAL, **58**, 1568 (1936).

(3) Ruberg and Small, *ibid.*, **63**, 736 (1941).

(4) King and Work, *J. Chem. Soc.*, 401–404 (1942).

(5) Mosettig and Robinson, THIS JOURNAL, **57**, 2186 (1935).

(6) Mitter and Bardhan, *J. Chem. Soc.*, **123**, 2179 (1923).

the 5-acetyl-4-methyl-2-phenylpyrimidine was refluxed for four hours under nitrogen in 200 ml. of absolute alcohol with 18 g. of dimethylamine hydrochloride (0.21 mole) and 6 g. of paraformaldehyde; then 3 g. of paraformaldehyde was added, and refluxing 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 g. (20%) of white crystals with a melting point of 188°. *Anal.* Calcd. for $C_{16}H_{20}ClN_3O$: C, 62.84, H, 6.59; N, 13.74; Cl, 11.60. Found: C, 62.64; H, 6.40; N, 13.58; Cl, 11.60.

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

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 mg. of platinum oxide required four hours. The reduction was continued for fifteen hours with no further pressure drop. The catalyst was then removed and the methanol distilled at reduced pressures. The resulting sirup, 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 2 g. (40%) of fine, short needles melting at 176°. Some impure product was obtained by careful evaporation of the mother liquor. *Anal.* Calcd. for $C_{16}H_{22}ClN_3O$: C, 62.43; H, 7.21; N, 13.65; Cl, 11.52. Found: C, 62.39; H, 7.52; N, 13.68; Cl, 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°.

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 g. (0.05 mole) of diethylamine hydrochloride and 1.5 g. of paraformaldehyde were refluxed under nitrogen for three and a half hours in 50 ml. of absolute alcohol; then 0.75 g. 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 g. (21%) of white, needle-like crystals with a melting point of 125°. *Anal.* Calcd. for $C_{18}H_{24}ClN_3O$: 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°.

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 was reduced in 50 ml. of ethanol with 50 mg. 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 twenty-four hours. This gave a yield of 1.5 g. (60%) of a crystalline product with a melting point of 150°. *Anal.* Calcd. for $C_{18}H_{26}ClN_3O$: 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 g. (0.1 mole) of dimethylamine hydrochloride and 3 g. of paraformaldehyde in 35 ml. of absolute ethanol were refluxed for three quarters of an 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 the minimum amount of absolute ethanol. The yield was 7.0 g. (29%) of white granular crystals with a melting point of 148°. *Anal.* Calcd. for $C_{11}H_{18}ClN_3O$: C, 54.20; H, 7.44; N, 17.24; Cl, 14.55. Found: C, 54.24; H, 7.53; N, 17.21; Cl, 14.57.

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

5-(3-Dimethylamino-1-hydroxy-*n*-propyl)-2,4-dimethylpyrimidine.—The reduction of 7 g. (0.029 mole) of the amino ketone hydrochloride 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 sirup which would not crystallize from the usual solvents.

This sirup 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 was 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°. *Anal.* Calcd. for $C_{11}H_{19}N_3O$: 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°.

2-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 g. (0.1 mole) of dimethylamine hydrochloride and 3 g. of paraformaldehyde were refluxed for three hours under nitrogen in 300 ml. of absolute ethanol. One gram of paraformaldehyde and 0.5 g. of dimethylamine 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 13.5 g. (54%) of white solid with a melting point of 208–210°. *Anal.* Calcd. for $C_{10}H_{17}ClN_4O$; 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 sodium picrate, after recrystallization from ethanol, melted at 170–172°.

2-Amino-5-(3-dimethylamino-1-hydroxy-*n*-propyl)-4-methylpyrimidine Hydrochloride.—Two grams (0.008 mole) of the amino ketone hydrochloride in 100 ml. of methanol with 100 mg. of platinum oxide was reduced ten 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°, finally melting at 204–206°. *Anal.* Calcd. for $C_{10}H_{19}ClN_4O$: 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°.

Summary

5-Acetyl-2-amino-4-methylpyrimidine and 5-acetyl-2,4-dimethylpyrimidine have been prepared.

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 $CHOHCH_2CH_2NR_2$ (—NR_2 = dimethylamino, diethylamino) is located at the five position.

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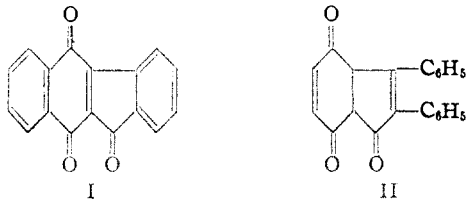
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

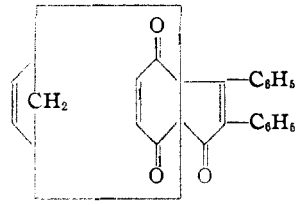
1-Keto-2,3-diphenylindene-4,7-quinone[1]

BY C. F. KOELSCH AND E. J. PRILL

Certain properties of 9-keto-2,3-benzofluorene-1,4-quinone (I)[2] indicated that it would be interesting to study a simpler substance in which a quinoid and a ketocyclopentene ring were fused together. The present paper reports the results of such a study, the compound prepared and studied being 1-keto-2,3-diphenylindene-4,7-quinone (II).



I II



III

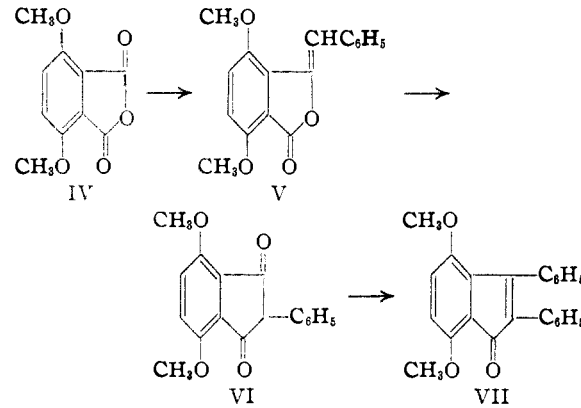
The solid quinone is a yellow crystalline substance, probably a polymer, but in acetic acid or benzene it forms a red solution that becomes purple when it is warmed. Cryoscopic determinations in benzene showed that the solution contains the monomeric quinone; the monomeric nature of the quinone in solution is also indicated by the formation of 4,7-dihydroxy-2,3-diphenylindone by reaction with benzohydroquinone. In benzene the quinone reacts with cyclopentadiene almost immediately, forming a crystalline adduct, presumably III, since it is yellow and not red as are compounds containing a cyclic crossed conjugated system.

In acetic acid, the quinone has a normal oxidation–reduction potential of 0.835 v. Comparison of this value with that reported previously[3] for benzoquinone in acetic acid (0.650 v.), and with that determined in the present research for I (0.623 v.), indicates that fusion of a cyclopentenone ring with a quinone nucleus raises the oxidation potential of the latter by 0.185 v. This increase is nearly independent of the substituents attached to the 2,3-positions of the cyclopentenone ring, for the difference between the oxidation potentials of I and II (0.212 v.) is approximately equal to the usual lowering (0.224 v.)[4] caused by fusion of a benzene ring with a quinone nucleus.

Experimental

The quinone II was obtained through the hydroquinone XIII, from 4,7-dimethoxy-2,3-diphenylindone (VII). This in turn was obtained in three ways.

The first route to VII involved the reactions



IV V VI VII

2,3-Dicyanohydroquinone was obtained in 66% yield from 20 g. of quinone and in 50% yield from 100 g. of quinone by the method of Thiele and Meisenheimer,[5] and in 55% yield from 33 g. of quinone by the method of Helferich.[6] The latter preparation is of some interest in view of reports[7] of the complete failure of this relatively inexpensive procedure. From the sodium salt of the hydroquinone and methyl sulfate in water, a 29% yield of 3,6-dimethoxyphthalonitrile was obtained. But when the methylation was carried out in dry xylene using excess methyl sulfate, the excess being subsequently destroyed by boiling for one hour with sodium hydroxide, there was obtained 62.5% of 3,6-dimethoxyphthalonitrile and 24% of 3,6-dimethoxyphthalic anhydride. The nitrile was best hydrolyzed by boiling 20 g. of it with 50 g. of potassium hydroxide in 100 ml. of butyl alcohol and 25 ml. of water for five hours, a yield of 77% of sublimed 3,6-dimethoxyphthalic anhydride (IV), m. p. 261–263° (reported[7a] 259–261°) being obtained.

A mixture of 9.7 g. of 3,6-dimethoxyphthalic anhydride, 9 g. of phenylacetic acid, and 0.5 g. of potassium acetate was heated in an oil-bath at 215–220° for two hours.

(1) From the Ph.D. Thesis of E. J. Prill, July, 1941.

(2) Koelsch, THIS JOURNAL, **67**, 159 (1945).

(3) Conant and Chow, *ibid.*, **55**, 3745 (1933). This figure was checked in the present investigation.

(4) Conant and Fieser, *ibid.*, **46**, 1864 (1924); Fieser and Dietz, *ibid.*, **53**, 1132 (1931). The figure is an average between the one obtained in water (0.229) and the one obtained in alcohol (0.218).

(5) Thiele and Meisenheimer, *Ber.*, **33**, 675 (1900).

(6) Helferich, *ibid.*, **54**, 155 (1921).

(7) (a) Graves and Adams, THIS JOURNAL, **45**, 2439 (1923); (b) Allen and Wilson, *ibid.*, **63**, 1756 (1941).