Equal mixtures of the two fractions melted at 202–203°. The base obtained from A melted at 116–118°; that from B melted at 75–77°.

(a) Fraction A.—α,α-Diphenyl-1-methyl-2-piperidineethanol was synthesized unequivocally from 1-methyl-2-phenacylpiperidine and phenylmagnesium bromide (method I). The base, m.p. 118–120° (from 95% ethanol), was identical with the base obtained from A. The hydrochloride (1C, Table I), m.p. 236–238° dec., was identical with A.[24] Subsequently, this compound was prepared in good yields (75–80%) by the methylation of α,α-diphenyl-2-piperidineethanol with formaldehyde and formic acid in dilute aqueous solution.[12] This method has been developed as a good procedure for preparing certain disubstituted 1-methyl-2-piperidine-ethanols (see method O).[25]

(b) Fraction B.—A solution of α,α-diphenyl-2-piperidineethanol (0.1 mole) and formalin (0.2 mole) in methanol or ethanol was refluxed for several hours, followed by evaporation of the solvent and recrystallization of the residue from aqueous acetone. The product was a white, crystalline solid, m.p. 77–79°. This was identical with the base obtained from fraction B. The hydrochloride, m.p. 224–226° dec., was identical with B.

(24) The decomposition point of the pure salt usually occurred in the range 230-240°, depending on the rate of heating.

(25) R. B. Burtner and J. M. Brown, THIS JOURNAL, **69**, 630 (1947), described a similar procedure carried out under pressure.

A solution of the base, m.p. 77–79°, in 5% hydrochloric acid was slowly distilled. Formaldehyde evolved, was collected in the aqueous distillate and was identified as its 2,4-dinitrophenylhydrazone, m.p. 163.5–165°.[26] A mixture with authentic formaldehyde 2,4-dinitrophenylhydrazone melted at 164–166°.

Based on the method of synthesis, the analytical data (compound 1B, Table I) and the fact that the compound upon degradation evolved formaldehyde, the structure 3,3-diphenyloctahydropyrid[1,2-c]oxazine (III, R = H; R′ = R² = phenyl) was assigned to this new compound. In addition, the infrared spectra of type II and type IV 2-piperidine-ethanols exhibited a characteristic absorption band at 3300 cm.⁻¹, which was attributed to the tertiary hydroxyl group present. This absorption was absent in type III oxazines.

Finally, it was found that 3,3-diphenyloctahydropyrid-[1,2-c]oxazine, when refluxed with excess 25% formic acid, was reduced to α,α-diphenyl-1-methyl-2-piperidine-ethanol. This reaction has been developed as a general method (method P) for the preparation of type IV compounds (R = H).

(26) A similar procedure was used by W. J. Burke, *ibid.*, **71**, 609 (1949). See also W. J. Burke, R. P. Smith and C. Weatherbee, *ibid.*, **74**, 602 (1952).

CINCINNATI, OHIO

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Mannich Reactions of Pyrimidines. II. 2-Methylmercapto-4-methyl-6-hydroxypyrimidine and 2-Thio-6-methyluracil[1,2]

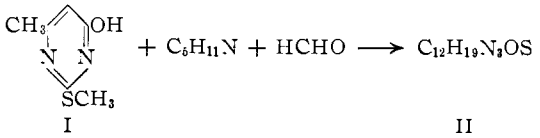
BY H. R. SNYDER, HAROLD M. FOSTER[3] AND GUSTAV A. NUSSBERGER

RECEIVED DECEMBER 31, 1953

2-Methylmercapto-4-methyl-6-hydroxypyrimidine and 2-thio-6-methyluracil react with piperidine and formaldehyde to yield monopiperidylmethyl derivatives. That condensation in both cases had occurred at the same position of the pyrimidine was shown by desulfurization of both Mannich bases to the same piperidylmethyl derivative of 4-methyl-6-hydroxypyrimidine. Catalytic hydrogenation of the desulfurized Mannich base yielded 2-methylbutyramide, proving the presence of the piperidylmethyl group at the 5-position of the pyrimidine nucleus. A preliminary study of the reactivity of the 5-piperidylmethyl derivative of 4-methyl-6-hydroxypyrimidine as an alkylating agent is reported.

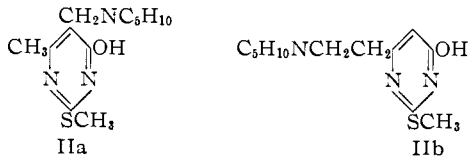
In the first paper in this series[1] the reactivity in the Mannich process of the 2-methyl group of 2,6-dimethyl-4-hydroxypyrimidine, a methylpyrimidine which has but a single ring-activating substituent, was reported. 2-Methylmercapto-4-methyl-6-hydroxypyrimidine (I) contains but a single, strongly ring-activating substituent, the hydroxyl group. The methylmercapto group would be expected to activate the nucleus to some extent. However, since the methylmercapto group cannot tautomerize its effect should be much less pronounced than that of a hydroxyl, thio or amino group.[4] It was felt that it would be of interest to study the reactivity of I in the Mannich reaction and to elucidate the structure of any Mannich bases which might be isolated. It was hoped that this study would help to evaluate the effect of the methylmercapto group as a ring-activating substituent.

An attempt to condense I with dimethylamine hydrochloride and formaldehyde met with failure. However, 2-methylmercapto-4-methyl-6-hydroxypyrimidine (I) was successfully condensed with piperidine and formaldehyde in ethanol solution to yield a Mannich base having the composition calculated for $C_{12}H_{19}N_3OS$ (II). This composition corresponds to a monopiperidylmethyl derivative of I. The Mannich base II could conceivably



I II

have one of two structures IIa or IIb. Structure IIa, 2-methylmercapto-4-methyl-5-(1-piperidyl-



IIa IIb

methyl)-6-hydroxypyrimidine, is given support by the report of Poetsch and Behrend[5] of a nuclear hydroxymethylation of I.

It appeared that the best approach for deciding between structures IIa and IIb would be cleavage

(1) For Paper I in this series, see H. R. Snyder and H. M. Foster, THIS JOURNAL, **76**, 118 (1954).

(2) Grateful acknowledgment is made of the partial support of this research by a grant (G135) from the National Science Foundation 1954.

(3) National Science Foundation Fellow, September, 1952, to July, 1953.

(4) B. Lythgoe, *Quart. Revs.*, **3**, 181 (1949).

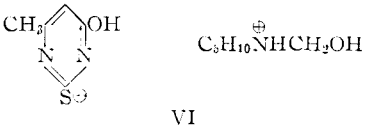
(5) G. Poetsch and R. Behrend, *Ann.*, **448**, 89 (1926).

of the carbon to nitrogen bond of the Mannich base with hydrogen and comparison of the derived pyrimidine with a sample of properly substituted pyrimidine prepared by ring closure. Before any attempt at catalytic hydrogenation could be performed, it was necessary to remove the sulfur from the molecule. Therefore, a desulfurization of II by Raney nickel catalyst was developed.

Brown[6] has reported the desulfurization of several pyrimidines containing thio substituents with a Raney nickel catalyst especially prepared for this type of reaction. Desulfurization of II was effected with the catalyst prepared as described by Brown only in poor yield. It was possible to desulfurize II in yields of about 60% when an extremely reactive catalyst, Raney nickel C described by Hurd and Rudner,[7] was used. The desulfurized Mannich base III, when pure, melts at 167–168° and has the composition calculated for $C_{11}H_{17}N_3O$, corresponding to a monopiperidylmethyl derivative of 4-methyl-6-hydroxypyrimidine.

Because of the difficulty involved in cleaving the methylmercapto group with Raney nickel catalyst, a study of the desulfurization of I was undertaken to determine the optimum conditions for the reaction. In the course of this study, the desulfurization of 2-thio-6-methyluracil (IV) was also achieved. Whereas the desulfurization of I was accomplished, at best, in yields of about 25%, IV was desulfurized in yields of better than 90%. Thus, it was felt advisable to study the Mannich reaction of 2-thio-6-methyluracil (IV) with piperidine and formaldehyde, for if the same type of condensation could be effected with the thiouracil (IV) as with the methylmercaptopyrimidine (II), the desulfurized Mannich base could be obtained more readily.

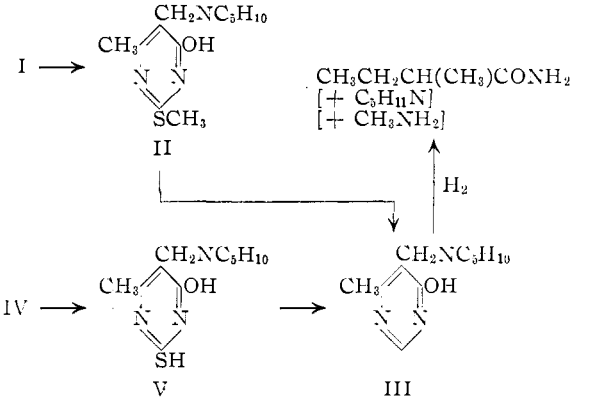
2-Thio-6-methyluracil (IV) reacted with piperidine and formaldehyde in 95% ethanol solution to yield a new compound V, m.p. 187–189° dec., which when dried in vacuum at 55° for 10 hours had the composition calculated for $C_{11}H_{19}N_3O_2S$. This composition corresponds to the hydrate of a monopiperidylmethyl derivative of 2-thio-6-methyluracil. Evidence that this material is really a Mannich base and not a salt such as VI, is given by the fact that when V is dried in vacuum at 100° for about 5.5 hours a stable hemihydrate VII is formed. The hemihydrate also melted at 187–189°



VI

dec. Better evidence, however, is that desulfurization of V with the Raney nickel catalyst of Brown[6] gave the previously described desulfurized Mannich base III in yields of about 80%. Thus both 2-methylmercapto-4-methyl-6-hydroxypyrimidine (I) and 2-thio-6-methyluracil (IV) undergo the Mannich condensation with piperidine and formaldehyde at the same position. Reasons to believe that the condensation occurred at the 5-position of the pyrimidine nucleus are found in the work of Poetsch and Behrend[5] who achieved a nuclear hydroxymethylation of IV. The structure of the hydroxymethyl derivative was established as 2-thio-4-methyl-5-hydroxymethyl-6-hydroxypyrimidine by reduction (tin and hydrochloric acid) to the known 2-thio-5,6-dimethyluracil. However, the condensation of IV with *p*-(dimethylamino)-benzaldehyde is reported to involve the methyl group, yielding the substituted styryl derivative,[8] so the possibility of participation of the methyl group in the Mannich reaction cannot be ignored.

When a sample of the desulfurized Mannich base III was hydrogenated over Raney nickel catalyst[9] at 2000 p.s.i. and 145°, a small quantity of solid material identified as 2-methylbutyramide, by comparison with an authentic sample, was isolated. The formation of the amide clearly indicates that the pyrimidine nucleus was cleaved during the hydrogenation. Reductive cleavage of a pyrimidine nucleus has been previously observed.[1] The isolation of 2-methylbutyramide is ample proof that the pyrimidine nucleus was substituted at the 5-position. Thus the structure of III is indicated as 4-methyl-5-(1-piperidylmethyl)-6-hydroxypyrimidine. From this it follows that the structure of the Mannich base II is 2-methylmercapto-4-methyl-5-(1-piperidylmethyl)-6-hydroxypyrimidine (IIa), and that of V, 2-thio-4-methyl-5-(1-piperidylmethyl)-6-hydroxypyrimidine.



It appears likely that the carbon to nitrogen bond of the Mannich base is cleaved first, followed by rupture of the pyrimidine nucleus. The cleavage of benzyl (or allyl) type bases such as III is well known.[10,11] However, the ease of cleavage of the pyrimidine nucleus was unexpected.

It is of interest to note that Monti and Franchi[12] have described a reaction of 2-thio-6-methyluracil (IV) with piperidine and formaldehyde in concentrated hydrochloric acid. The product VIII which they isolated appeared to be entirely different from that V described in this report. The base VIII is reported to melt at 303–304° to form a viscous red oil; it is insoluble in common organic solvents. Compound V melts at 187–189° to form a viscous

(6) D. J. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950).
(7) C. D. Hurd and B. Rudner, THIS JOURNAL, **73**, 5158 (1951).
(8) D. M. Brown and W. C. J. Ross, *J. Chem. Soc.*, 1715 (1948).
(9) Gilman Paint and Varnish Company, Chattanooga, Tenn.
(10) W. T. Caldwell and T. R. Thompson, THIS JOURNAL, **61**, 765, 2354 (1939).
(11) W. B. Wheatley and L. C. Cheney, *ibid.*, **74**, 2940 (1952).
(12) L. Monti and G. Franchi, *Gazz. chim. ital.*, **79**, 447 (1949).

yellow oil; it can be recrystallized easily from 95% ethanol. The procedure of Monti and Franchi was repeated and a solid material, which corresponded in properties to the description given by these workers, was obtained. It gave no evidence of forming a stable hydrate; the air-dried material, from water solution, melted at 304–305° to a viscous red oil. Thus the base described by Monti and Franchi must be different from that obtained in the present work. Monti and Franchi have formulated their product VIII as 2-thio-4-methyl-5-(1-piperidylmethyl)-6-hydroxypyrimidine without any supporting evidence. It now appears that this substance VIII has a different structure. Further study of this question is in progress in this Laboratory.

The Mannich base III was converted into the benzylmercapto derivative by treatment with methyl iodide and cleavage of the crude methiodide with a basic solution of benzyl mercaptan in methanol. It appears that the methiodide of III may be an even more reactive alkylating agent than quaternary salts derived from benzylamine. The methiodide of III was cleaved with benzyl mercaptan under conditions which probably would not affect quaternary salts derived from benzylamine.[13]

Experimental[14]

Mannich Reaction of 2-Methylmercapto-4-methyl-6-hydroxypyridine (I) with Piperidine and Formaldehyde.—A mixture of 31.2 g. of I,[15] 25 ml. of commercial 40% formalin, 2.4 ml. of glacial acetic acid, 20.4 g. of piperidine (pract.) and 400 ml. of commercial absolute ethanol was heated under reflux. Within a short time all the reactants had dissolved and a clear solution had formed. When the solution had been heated for 2 hr. sufficient product had separated from solution to cause severe bumping. Heating was discontinued and the solution was permitted to cool slowly. The crude product was collected and washed with a few milliliters of cold ethanol. The yield of crude product, identified as 2-methylmercapto-4-methyl-5-(1-piperidylmethyl)-6-hydroxypyrimidine (IIa), m.p. 199–200°, was nearly quantitative. An analytical sample was prepared by recrystallization from 95% ethanol, m.p. 201–203°.

Anal. Calcd. for $C_{12}H_{19}N_3OS$: C, 56.88; H, 7.65; N, 16.58. Found: C, 56.86; H, 7.47; N, 16.63.

The Mannich base II is readily soluble in both acids and bases and can be recovered unchanged by neutralization.

Attempted Mannich Reaction of 2-Methylmercapto-4-methyl-6-hydroxypyrimidine (I) with Dimethylamine Hydrochloride and Formaldehyde.—A mixture of 15.6 g. of the pyrimidine (I), 4.5 g. of paraformaldehyde, 12.2 g. of dimethylamine hydrochloride and 50 ml. of commercial absolute ethanol was heated under reflux for about an hour. An additional 1.5-g. portion of paraformaldehyde and 50 ml. of ethanol were added and the mixture was heated under reflux for an additional 5-hr. period. The clear solution was permitted to cool slowly when gradual precipitation of solid occurred. The solid was collected and was washed with a few milliliters of cold ethanol. The recovery of crude solid, m.p. 215–217°, was 12.4 g.; it was identified as the unchanged reagent I by mixed melting point.

Treatment of 2-Methylmercapto-4-methyl-5-(1-piperidylmethyl)-6-hydroxypyrimidine (IIa) with Sodium Amalgam.—To a slurry of 5.17 g. of II in 50 ml. of water, 77 g. of 3% sodium amalgam was added portionwise with stirring. The mixture was heated for several hours and was then set aside. The cooled reaction mixture was extracted with five 25-ml. portions of ether. The ether extracts were dried over magnesium sulfate and the solution was evaporated to dryness. There was no residue. The aqueous layer was decanted from the mercury and was neutralized with acetic acid. The solid which precipitated was filtered off and the filtrate was evaporated to dryness on the steam-bath. The residue proved to be sodium acetate. The solid which had precipitated on neutralization melted at 195–198°. After a recrystallization from 95% ethanol the material melted at 198–199° and the melting point was not depressed by admixture with a pure sample of II. Thus the precipitate is identified as unchanged reagent.

Desulfurization of 2-Methylmercapto-4-methyl-5-(1-piperidylmethyl)-6-hydroxypyrimidine (IIa).—To a slurry of 10.5 g. of II, 125 ml. of water and 7.5 ml. of concentrated aqueous ammonia, which had been heated on the steam-bath, 30 g. (wet paste) of specially prepared Raney nickel catalyst[6] was added as rapidly as possible. The reaction mixture was heated under reflux for 1.5 hr. When the catalyst had settled, the hot solution was filtered and the catalyst was washed with 100 ml. of boiling 95% ethanol. The combined filtrate and washings were evaporated to dryness on the steam-bath. The solid residue was extracted with 100 ml. of boiling ethanol. The extract was evaporated to dryness and the residue was extracted with boiling acetone. When the acetone extract was concentrated and refrigerated a solid product separated from solution. The yield of crude product, identified as 4-methyl-5-(1-piperidylmethyl)-6-hydroxypyrimidine (III), m.p. 156–161°, was 0.85 g. or 10%. After several recrystallizations from acetone the pure base melted at 167–168°. The material is too soluble in ethanol and methanol to be recrystallized from these solvents.

Anal. Calcd. for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.85; H, 8.31; N, 20.44.

In another experiment, a mixture of 20 g. of II, 500 ml. of distilled water and 20 ml. of concentrated aqueous ammonia was heated on the steam-bath. To the hot slurry, 100 g. (wet paste) of Raney nickel C[7] was added as rapidly as possible. The reaction mixture was heated under reflux for about 2 hr. (This reaction is best carried out in a 2-l. flask because of the severe foaming.) The reaction mixture was permitted to stand until the catalyst had settled, when the clear solution was filtered. The catalyst was washed with two 125-ml. portions of hot water. The combined filtrate and washings were evaporated to dryness on the steam-bath. The residue was recrystallized from acetone. The total yield of crude desulfurized Mannich base III, m.p. 162–165.5°, was 10 g. or 61.1%.

Desulfurization of 2-Methylmercapto-4-methyl-6-hydroxypyrimidine (I).—To a stirred mixture of 30 g. of I and 1 l. of 95% ethanol, 300 g. (wet paste) of Raney nickel catalyst was added rapidly. The reaction mixture was heated under reflux for about 4 hr., and was permitted to stand for about 12 hr. The catalyst was carefully filtered by gravity and was washed with two 100-ml. portions of boiling ethanol. The combined filtrate and washings were treated with hydrogen sulfide to precipitate the dissolved nickel. A treatment with Darco removed the final traces of colored impurities. The solution was acidified (*p*H 4) with hydrochloric acid and was concentrated on the steam-bath. When most of the solvent had been removed, sufficient sodium bicarbonate was added to raise the *p*H to about 8, and the solution was evaporated to dryness. The residue was extracted exhaustively with acetone (250 ml.) and the extract was concentrated to a volume of about 100 ml. and refrigerated. The crude product was recrystallized from methyl ethyl ketone. The total yield of fairly pure 4-methyl-6-hydroxypyrimidine, m.p. 148–149° (reported[16] 149–150°), was 5.3 g. or 25.1%. An analytical sample, m.p. 148–149°, was prepared by vacuum sublimation.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.63; H, 5.46; N, 25.57.

2-Thio-6-methyluracil (IV).—The procedure of Wheeler and McFarland[17] was modified as follows. A mixture of 75.8 g. of thiourea, 130 g. of commercial ethyl acetoacetate, 120 g. of commercial sodium methoxide and 900 ml. of

(13) H. R. Snyder and J. C. Speck, THIS JOURNAL, **61**, 669, 2895 (1939).

(14) All melting points are corrected. Microanalyses were performed by Mr. J. Nemeth, Mrs. E. Fett, Mrs. K. Pih and Mrs. L. Chang. The infrared spectra were obtained by Miss Helen P. Miklas and Mrs. R. Hill.

(15) H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **29**, 486 (1903).

(16) S. Gabriel and J. Colman, *Ber.*, **36**, 3383 (1903).

(17) H. L. Wheeler and D. F. McFarland, *Am. Chem. J.*, **42**, 101 (1909).

methanol was heated gently on the steam-bath and was permitted to evaporate to dryness over a period of 8–9 hr. The residue was dissolved in a liter of hot distilled water and the solution was treated with a few grams of Darco and was filtered. The hot filtrate was carefully treated with 120 ml. of glacial acetic acid. The thiouracil precipitated rapidly and was collected. The solid filter cake was suspended in a boiling solution of 1 l. of distilled water and 20 ml. of glacial acetic acid. The slurry was stirred to break up lumps of the thiouracil and was then refrigerated. The product was collected and was washed with about 200 ml. of cold water in portions. The solid was permitted to drain (suction) for several hours and was then dried in an oven at 70°; yield 98–100 g. or 69–70%.

Desulfurization of 2-Thio-6-methyluracil (IV).—To a hot solution of 10 g. of IV in 200 ml. of distilled water and 20 ml. of concentrated aqueous ammonia, 45 g. (wet paste) of Raney nickel catalyst[6] was added as rapidly as possible. About 30 ml. of distilled water was used to wash all the catalyst into the reaction vessel. The mixture was heated under reflux for about 1.5 hr. The catalyst was permitted to settle, when the clear solution was decanted and filtered by gravity. The catalyst was washed with two 75-ml. portions of hot distilled water. The combined filtrate and washings were evaporated to dryness on the steam-bath. The yield of crude 4-methyl-6-hydroxypyrimidine, m.p. 136–142°, was 7.0–7.2 g. or 91–93%.

Mannich Reaction of 2-Thio-6-methyluracil (IV) with Piperidine and Formaldehyde.—A mixture of 14.2 g. of IV, 9.35 g. of piperidine (pract.), 8.5 ml. of commercial 40% formalin, 1.0 ml. of glacial acetic acid and 250 ml. of 95% ethanol was heated under reflux. When the mixture had been heated for 2 hr. an additional 2-ml. portion of formalin, 2 ml. of piperidine and 50 ml. of 95% ethanol were added. After an additional 3-hr. heating period a clear solution was formed (yellow colored) and heating was discontinued. The solution was concentrated to about half its original volume. When the solution was cooled and the sides of the container were scratched with a glass rod, a solid precipitated. It was collected and was washed with a few milliliters of cold ethanol. The product was dried in an oven at 70°. The yield of crude solid, the hydrate of 2-thio-4-methyl-5-(1-piperidylmethyl)-6-hydroxypyrimidine, m.p. 185–187°, was 16 g. or 62.3%. After one recrystallization from 95% ethanol the melting point was 187.5–189°. An analytical sample was prepared by recrystallization from 95% ethanol; the sample was dried at 55° (1 mm.) for 10 hr.

Anal. Calcd. for $C_{11}H_{17}N_3OS \cdot H_2O$: C, 51.34; H, 7.44; N, 16.33. Found: C, 51.33; H, 7.60; N, 16.22.

If the sample is dried at 100° (1 mm.) for 5.5 hr. a stable hemihydrate is formed. The hemihydrate also melted at 187.5–189°.

Anal. Calcd. for $C_{11}H_{17}N_3Os \cdot {}^1/_2H_2O$: C, 53.20; H, 7.31; N, 16.92. Found: C, 53.10; H, 7.25; N, 16.57.

Desulfurization of 2-Thio-4-methyl-5-(1-piperidylmethyl)-6-hydroxypyrimidine (V).—To a hot solution of 3.1 g. of the hydrate of V in 70 ml. of distilled water and 3 ml. of concentrated aqueous ammonia, 10 g. (wet paste) of Raney nickel catalyst[6] was added as rapidly as possible. The mixture was heated under reflux for 2 hr. The suspension was filtered and the nickel was washed with 25 ml. of boiling 95% ethanol. The combined filtrate and washings were treated with Hiflo Super-cel, filtered, and evaporated to dryness on the steam-bath. The yield of crude solid, m.p. 155–159°, was 2.1 g. or 83%. After several recrystallizations from acetone the compound melted at 167–168°. This material did not depress the melting point of the desulfurized Mannich base III derived from 2-methylmercapto-4-methyl-6-hydroxypyrimidine, and thus is identified.

Catalytic Hydrogenation of 4-Methyl-5-(1-piperidylmethyl)-6-hydroxypyrimidine (III).—A solution of 2.07 g. of III in 50 ml. of reagent grade methanol to which 10 drops of concentrated hydrochloric acid was added was hydrogenated over Raney nickel catalyst[9] (*ca.* 6 g. of wet paste) at 2000 p.s.i. and 140–150° for several hours. The solution was filtered free of catalyst and the catalyst was thoroughly washed with boiling methanol. The combined filtrate and washings were concentrated to about half the original volume on the steam-bath and the concentrate was evaporated at room temperature under an air steam. The oily residue was extracted with two 25-ml. portions of boiling ether. The combined ether extracts were dried over potassium carbonate and the ether was removed. The crude solid residue (*ca.* 100 mg.) melted at 95–100°. The material was purified to some extent by vacuum sublimation (m.p. 106–108°). A mixture of this compound and an authentic sample of *n*-valeramide melted at about 80°. A better purification of the hydrogenation product was effected by recrystallization from acetone–cyclohexane solution. The pure material, m.p. 111–112°, did not depress the melting point of an authentic sample of 2-methylbutyramide and the infrared spectra of the two samples were identical. Thus the hydrogenation product is proved to be 2-methylbutyramide.

Conversion of 4-Methyl-5-(1-piperidylmethyl)-6-hydroxypyrimidine (III) into 4-Methyl-5-benzylmercaptomethyl-6-hydroxypyrimidine.—A mixture of 0.65 g. of III and 10 ml. of reagent grade acetone was heated on the steam-bath for a few minutes and was then permitted to cool to room temperature. To the cooled solution, a slight excess of methyl iodide (0.5 g.) was added. The mixture was shaken intermittently and was permitted to stand at room temperature. After 0.5 hr. the Mannich base had completely dissolved and the acetone had become cloudy. The reaction mixture was placed in the refrigerator. The acetone was decanted from the thick oil which had separated and the oil was dissolved in about 10 ml. of methanol. To the methanolic solution, 0.4 g. of benzyl mercaptan and 0.18 g. of potassium hydroxide were added. The mixture was warmed to dissolve the base. Methanol was added to bring the volume of the solution to about 20 ml. The solution was boiled gently on the steam-bath and was permitted to concentrate to a volume of about 10 ml. The remainder of the solvent was removed at room temperature under an air stream. The residue, a gummy oil, was extracted with about 15 ml. of boiling benzene. The benzene extract was cooled, when 0.2 g. (25.9% of theory based on the quantity of III used) of crude 4-methyl-5-benzylmercaptomethyl-6-hydroxypyrimidine, m.p. 161–163°, separated from solution and was collected. After recrystallization from acetone the pure solid melted at 167–168°. A mixture of this compound and III melted at 135°.

Anal. Calcd. for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.38. Found: C, 63.32; H, 5.79; N, 11.61.

URBANA, ILLINOIS