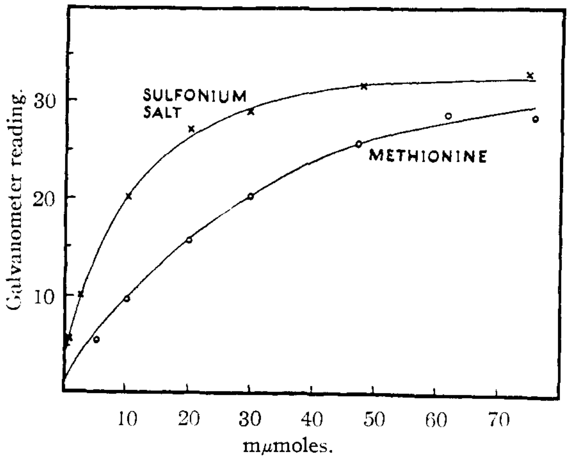


Fig. 2.—Growth response of *E. coli* (Texas) to L-methionine and L-methioninemethylsulfonium iodide.

the presence of the methylsulfonium derivative of methionine in cabbage juice, an intermediate, a sulfonium derivative of methionine which is probably S-adenosylmethionine, has been reported to be involved in the biological transfer of the methyl group of methionine to certain other products containing biologically active labile methyl groups.[13] However, since some organisms requiring methionine do not respond to its methylsulfonium derivative,[6] and since it has been found to be inactive in the biosynthesis of creatine by liver homogenates which can synthesize creatine from methionine,[11] no universal role can be attributed to the compound. By the action of certain organisms upon the methylsulfonium derivative of methionine, dimethyl sulfide is released.[14] In the present investigation, homoserine was identified as a product of decomposition of the methylsulfonium derivative heated in aqueous solution. A characteristic odor of dimethyl sulfide was also obtained under these conditions.

It is interesting that the occurrence and heat-lability of the methylsulfonium derivative parallels closely the occurrence and heat-lability of vitamin U, an unidentified factor in cabbage and other vegetable juices which is reported to reduce the incidence of histamine-induced ulcers in guinea pigs and to be beneficial in treatment of peptic ulcers in human beings.[15]

(13) G. L. Cantoni, This Journal, **74**, 2942 (1952).

(14) F. Challenger and Y. C. Lin, *Rec. trav. chim.*, **69**, 334 (1950).

(15) G. Cheney, *Stanford Med. Bull.*, **6**, 334 (1948); **8**, 144 (1950).

Austin 12, Texas

[Contribution from the Noyes Chemical Laboratory, University of Illinois]

Mannich Reactions of Pyrimidines. I. 2,6-Dimethyl-4-hydroxypyrimidine[1]

By H. R. Snyder and Harold M. Foster[2]

Received August 10, 1953

2,6-Dimethyl-4-hydroxypyrimidine reacts with formaldehyde and piperidine to yield bis-(1-piperidylmethyl) and tris-(1-piperidylmethyl) derivatives. A similar condensation was observed with morpholine in place of piperidine, but not with dimethylamine. The structure of the bis-(1-piperidylmethyl) derivative was established as 2-bis-(1-piperidylmethyl)-methyl-4-methyl-6-hydroxypyrimidine by reductive cleavage of the pyrimidine ring to yield *n*-butyramide, and by hydrogenolysis of the carbon to nitrogen bond of the Mannich base to yield 2-isopropyl-4-methyl-6-hydroxypyrimidine. Products of the reactions of the bis-(1-piperidylmethyl) Mannich base with methyl iodide and with acetic anhydride are described. Evidence for the formulation of the tris-(1-piperidylmethyl) derivative as 2-bis-(1-piperidylmethyl)-methyl-4-(1-piperidyl-2-ethyl)-6-hydroxypyrimidine is given. An improved procedure for the synthesis of 2,6-dimethyl-4-hydroxypyrimidine is described.

Numerous aldol type condensations in the pyrimidine series involving either methyl substituents or the nucleus have been observed. In general, simple methylpyrimidines undergo reaction at the methyl group,[3] whereas methylpyrimidines which have any combination of two or more hydroxy, thio, or amino substituents undergo nuclear condensation.[4-8] 4 - Methyl - 6 - hydroxypyrimidine[9] and 2-hydroxy-4,6-dimethylpyrimidine,[10] two methylpyrimidines which have but a single ring-activating substituent, react with aromatic aldehydes to yield styryl derivatives.

In the present work, the reactivity of 2,6-dimethyl-4-hydroxypyrimidine (I) in the Mannich reaction was studied. This pyrimidine yielded no solid products when treated with formaldehyde and dimethylamine under a variety of conditions. On the other hand, 2,6-dimethyl-4-hydroxypyrimidine reacted with piperidine and formaldehyde in benzene–ethanol solution to yield two Mannich bases. The material which was isolated in the greater amount has the composition calculated for $C_{18}H_{30}N_4O$, and proved to be a bis-(1-piperidylmethyl) derivative (II) of I. The other base has the composition calculated for $C_{24}H_{41}N_5O$, and is a tris-(1-piperidylmethyl) derivative (III) of I. When 0.05 mole of I was treated with approximately 0.1 mole each of piperidine and formaldehyde, II was isolated in yields of about 40%. When the reaction was scaled up to twice this size, the yield of II fell to about 25%; III was isolated in yields of

---

(1) Abstracted in part from the Thesis submitted by H. M. Foster to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy, October, 1953.

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

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

(4) W. Kircher, *Ann.*, **385**, 293 (1911).

(5) K. Schmedes, *ibid.*, **441**, 192 (1925).

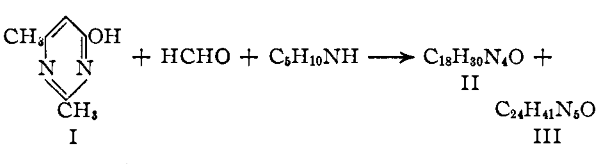
(6) G. Poetsch and R. Behrend, *ibid.*, **448**, 89 (1926).

(7) T. B. Johnson and A. Litzinger, This Journal, **58**, 1940 (1936).

(8) M. Ohta, *J. Pharm. Soc. Japan*, **67**, 175 (1947), *C. A.*, **45**, 9545^6 (1951).

(9) D. M. Brown and W. C. J. Ross, *J. Chem. Soc.*, 1715 (1948).

(10) O. Stark, *Ber.*, **42**, 699 (1909); O. Stark and M. Bögeman, *ibid.*, **3**, 1126 (1910).

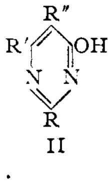


$I + HCHO + C_5H_{10}NH \longrightarrow C_{18}H_{30}N_4O + C_{24}H_{41}N_5O$

II III

about 10%. Piperidine and formaldehyde reacted with I in glacial acetic acid and in isoamyl alcohol to give II in yields of about 12.5%. A bis-(1-morpholinomethyl) derivative was isolated in yields of about 35% when I was treated with morpholine and formaldehyde in benzene–ethanol solution.

The bis-(1-piperidylmethyl) derivative II could conceivably have any one of five structures (IIa, IIb, IIc, IId or IIe). The method proposed for deciding among these possibilities was cleavage of the carbon to nitrogen bond by hydrogen (either directly or indirectly) and comparison of the derived alkylpyrimidine with a sample of the properly constituted pyrimidine prepared by ring closure. Attempts were made to cleave the bond by catalytic hydrogenation, by quaternization of the Mannich base and subsequent cleavage of the quaternary salt, and by acetolysis of the Mannich base, followed by conversion of the expected acetoxymethyl derivative to the halide and hydrogenolysis.



II

a, $R = R' = -CH_2CH_2NC_5H_{10}$, $R'' = -H$

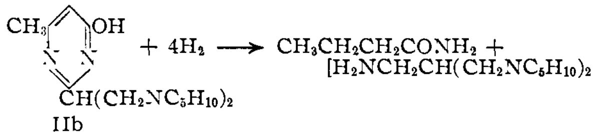
b, $R = -CH(CH_2NC_5H_{10})_2$, $R' = -CH_3$, $R'' = -H$

c, $R = -CH_3$, $R' = -CH(CH_2NC_5H_{10})_2$, $R'' = -H$

d, $R = -CH_2CH_2NC_5H_{10}$, $R' = -CH_3$, $R'' = -CH_2NC_5H_{10}$

e, $R = -CH_3$, $R' = -CH_2CH_2NC_5H_{10}$, $R'' = -CH_2NC_5H_{10}$

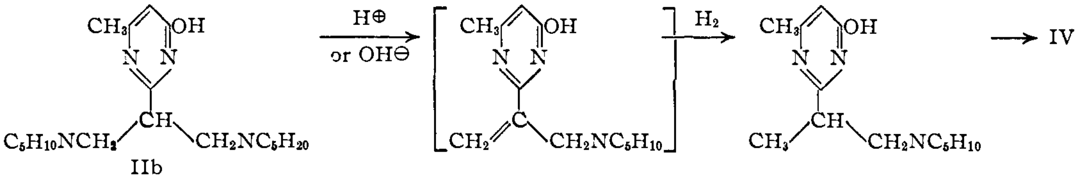
A sample of II in methanol solution was subjected to catalytic hydrogenation over Raney nickel catalyst at 1500 p.s.i. and 150°. A solid material, m.p. 110–112°, having the composition calculated for C_4H_9NO was isolated. This compound proved to be *n*-butyramide. These observations indicate that the pyrimidine ring was cleaved. Of the structural possibilities noted for the bis-(1-piperidylmethyl) derivative, only structure IIb, 2-bis-(1-piperidylmethyl)-methyl-4-methyl-6-hydroxypyrimidine, could be cleaved to yield *n*-butyramide.



$IIb + 4H_2 \longrightarrow CH_3CH_2CH_2CONH_2 + [H_2NCH_2CH(CH_2NC_5H_{10})_2]$

In another experiment a solution of the Mannich base II in methanol solution saturated with potassium carbonate was hydrogenated over Raney nickel catalyst at 2000 p.s.i. and 150–200°. The reduction product, isolated as the hydrochloride, m.p. 238–240° (dec. and subl.), had the composition calculated for $C_8H_{13}N_2OCl$. This material was proved to be 2-isopropyl-4-methyl-6-hydroxypyrimidine hydrochloride by comparison with an authentic sample. This same reaction course was observed when a solution of the Mannich base II in methanol containing several drops of concentrated hydrochloric acid was hydrogenated. Thus the bis-(1-piperidylmethyl)-derivative of 2,6-dimethyl-4-hydroxypyrimidine is clearly established as 2-bis-(1-piperidylmethyl)-methyl-4-methyl-6-hydroxypyrimidine (IIb).

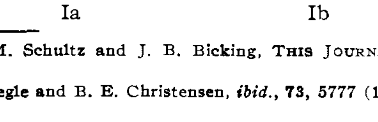
The observed cleavage of the pyrimidine ring does not appear to be a hydrolytic scission followed by reduction. A sample of II in wet methanol containing a trace of sodium hydroxide was heated to 150° in an autoclave for several hours. About 35% of unchanged II was recovered; there was no evidence of ring opening. This cleavage does not appear to be a general reaction of hydroxypyrimidines. Several attempts to effect reductive cleavage of I met with failure. Moreover, 2-isopropyl-4-methyl-6-hydroxypyrimidine (IV), once formed, is also stable to catalytic hydrogenation. The amine cleavage, which is catalyzed by acid or base, probably involves amine elimination with rapid or simultaneous hydrogenation of the vinyl intermediate. Repetition of this sequence would lead to the formation of IV.



IIb

Schultz and Bicking[11] have observed a similar hydrogenolysis of Mannich bases derived from phenylacetone.

The course of the reaction between I and formaldehyde and piperidine was unexpected. Siegle and Christensen[12] note that 4-methylquinazoline reacts with dimethylamine hydrochloride and formaldehyde to yield a Mannich base, whereas 2-methylquinazoline, under the same conditions, does not condense. Thus the hydroxyl group in the 4-position of the pyrimidine ring has a profound effect on the reactivity of the 2-methyl group. Actually this carbon to oxygen bond has a great deal of double bond character. The infrared spectrum of I (strong absorption at 1660 cm.$^{-1}$ and absorption over a broad range in the 3 μ region characteristic of bonded –NH, –OH or salt structure) indicates that a better representation of the structure is given by formula Ia, although resonance structures such as Ib make important contributions to the true state of the molecule. Such an interpretation



Ia Ib

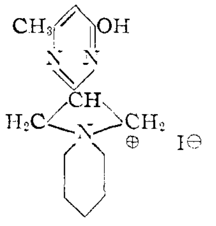
---

[11] E. M. Schultz and J. B. Bicking, This Journal, **75**, 1128 (1953).

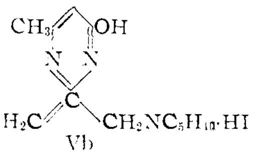
[12] J. Siegle and B. E. Christensen, *ibid.*, **73**, 5777 (1951).

of the structure would help to explain the observed chemical reactivity of the 2-methyl group. This methyl group would be activated not only by a $(-\text{C}{=}\text{N}-)$ group but also by a $(-\overset{\oplus}{\text{N}}\text{H}{=})$ group.

2-Bis-(1-piperidylmethyl)-methyl-4-methyl-6-hydroxypyrimidine (IIb) reacted with an excess of methyl iodide in cold ethanol solution to yield a compound, m.p. 210–211.5°, which has the composition calculated for $C_{13}H_{20}N_3OI$. This material gave an immediate precipitate, insoluble in dilute nitric acid, when treated with silver nitrate. Iodine was liberated rapidly when the compound was treated with aqueous hypochlorite. When an aqueous solution of this material was treated with sodium carbonate, immediate decomposition to a red oil took place. The infrared spectrum of this substance shows a very sharp absorption maximum at 2650 cm.$^{-1}$ which is characteristic of a salt and is probably the best evidence that the compound does, indeed, contain ionic iodine. The properties suggest that the best formulation for this compound is 2-(4-methyl-6-hydroxy-2-pyrimidyl)-4-azaspiro[3,5]nonane iodide (Va). Structure Vb seems unlikely because of the absence of an absorption maximum in the infrared spectrum at 900 cm.$^{-1}$ which would be expected if the compound did contain a terminal vinyl group. Other azetidinium compounds are well known[13] and are surprisingly stable. Gibbs and Marvel[14] have shown that -γdialkylaminopropyl bromides spontaneously undergo intramolecular cyclization to yield crystalline N,N-dialkylazetidinium bromides. Mannich and Baumgarten[15] have made an extensive study of azetidinium halide formation.

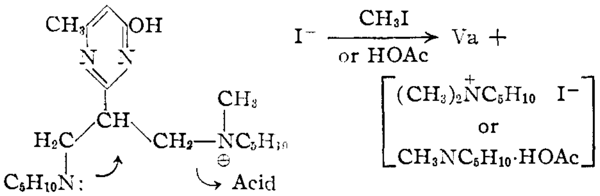


Va



Vb

If the reaction between II and methyl iodide was carried out under different conditions, it was possible to isolate what appeared to be the monomethiodide of the Mannich base. This material was extremely soluble in most common solvents and was quite hygroscopic. Treatment of this material with acetic acid converted it into V. The formation of V appears to be an example of the reaction of a quaternary salt with a tertiary amine. This type of reaction is well known. For example, Geissman and Armen[16] have noted that gramine methiodide reacts with gramine in the presence of excess methyl iodide to yield tetramethylammonium iodide and 3,3′-bis-(indolylmethyl)-dimethylammonium iodide. An extensive investigation of this reaction has been conducted in this Laboratory.[17] Moreover, Gibson and Mann[18] have converted tetrakisdimethylaminomethylmethane into azetidinium iodides by pyrolysis of monoquaternary iodides derived from it; a tertiary amine was eliminated during the reaction. Thus, it appears likely that the monomethiodide VI is converted to Va in the presence of an acidic catalyst (methyl iodide is an acid in the Lewis sense).



VI

The observed instability of V in the presence of a base as weak as sodium carbonate is perhaps surprising. Several stable azetidinium hydroxides have been prepared and characterized.[15] These materials do undergo ring cleavage when heated. The course of the reaction appears to depend very much on the nature of the azetidinium ring.[13] The extreme instability of V toward base can probably be ascribed to the presence of a fairly acidic hydrogen (activated by a —C=N— group as discussed above) at the 2-position of the azaspiro ring. Inasmuch as this hydrogen is on the carbon beta with respect to the azetidinium nitrogen, a rapid elimination reaction to form the vinyl compound would be expected. Polymerization of this vinyl intermediate would account for the formation of the red oil observed. (Other attempts to prepare vinyl pyrimidines have led to the formation of polymers.[19])

The reaction of 2-bis-(1-piperidylmethyl)-methyl-4-methyl-6-hydroxypyrimidine (IIb) with acetic anhydride led to the formation of an anomalous product. On the basis of previous observations on the acetolysis of Mannich bases, the expected product should be a diacetoxyl derivative. For example, Bruson and MacMullen[20] treated 2,4,6-tris-(dimethylaminomethyl)-phenol with acetic anhydride to obtain 2,4,6-tris-(acetoxymethyl)-phenyl acetate. Geissman and Armen[16] have prepared N-acetyl-3-acetoxymethylindole by reaction of gramine with acetic anhydride. In the present experiment there was definite evidence of cleavage of the Mannich base. The expected N-acetylpiperidine was isolated from the reaction mixture in fair yield. The other product isolated was a crystalline solid which decomposed without melting at about 250°. This material has the composition calculated for $C_8H_8N_2O$ and thus differs in composition from II by the elements of two molecules of piperidine. The compound is probably polymeric.

The structure of the tris-(1-piperidylmethyl) derivative III of 2,6-dimethyl-4-hydroxypyrimidine has not been established. Preliminary hydrogenation experiments indicate that two of the piperidyl-

---

[13] S. A. Ballard and D. S. Melstrom in R. C. Elderfield, "Heterocyclic Compounds," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 91–97.

[14] C. F. Gibbs and C. S. Marvel, THIS JOURNAL, **56**, 725 (1934).

[15] C. Mannich and G. Baumgarten, *Ber.*, **70**, 210 (1937).

[16] T. A. Geissman and A. Armen, THIS JOURNAL, **74**, 3916 (1952).

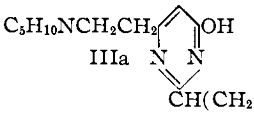
[17] E. R. Lovejoy, Thesis, Doctor of Philosophy, Univ. of Ill., 1953.

[18] G. M. Gibson and F. G. Mann, *J. Chem. Soc.*, 175 (1942).

[19] C. C. Price and J. Zomlefer, *J. Org. Chem.*, **14**, 210 (1949).

[20] H. A. Bruson and C. W. MacMullen, THIS JOURNAL, **63**, 270 (1941).

methyl groups are equivalent whereas the third is different. Hydrogenation of a sample of III over copper chromite catalyst at 2600 p.s.i. and 165° yielded a small quantity of solid material, m.p. 184–185°, which has the composition calculated for $C_{14}H_{23}N_3O$. This composition corresponds to III except that two piperidine groups have been replaced by hydrogen. Since reductive cleavage of piperidylmethyl groups attached to the 2-methyl group of a hydroxypyrimidine has already been described, it appears likely that III contains the 2-bis-(1-piperidylmethyl)-methyl unit found in II. Thus, the best formulation for III appears to be 2-bis-(1-piperidylmethyl)-methyl-4-(1-piperidyl-2-ethyl)-6-hydroxypyrimidine (IIIa).



IIIa

Experimental[21]

2,6-Dimethyl-4-hydroxypyrimidine (I).—The investigation of the Mannich reaction of 2,6-dimethyl-4-hydroxypyrimidine (I) was severely hampered because of the difficulty involved in obtaining sufficient hydroxypyrimidine. Pinner's[22] synthesis of this compound is slow and does not give good yields. The procedure of Pinner and that of Donleavy and Kise[23] for the preparation of 6-methyluracil were consolidated and modified as follows. Forty-seven and one-half grams of crude acetamidine hydrochloride was stirred into a mixture of 65 g. of commercial ethyl acetoacetate and 15 ml. of commercial absolute ethanol in a 4-in. crystallizing dish. The reagents were mixed thoroughly and 20 g. of sodium hydroxide and 10 ml. of commercial absolute ethanol were added. The reaction mixture was stirred from time to time to facilitate the dissolution of the sodium hydroxide. After the reaction mixture had stood for about a day all the sodium hydroxide appeared to have dissolved. The dish was loosely covered with a watch glass and was placed in a vacuum desiccator over sulfuric acid. The desiccator was carefully evacuated (water pump). The still moist reaction product which had stood overnight under reduced pressure was broken up with a spatula, the sulfuric acid was replaced with a fresh portion of the same desiccant, and the desiccator was evacuated for an additional period of 24 hr. The dry residue was mixed with 20 g. of sodium carbonate and 20 g. of sodium bicarbonate and the mixture was thoroughly ground in a mortar. The ground mass was exhaustively extracted (Soxhlet) with benzene (600 ml.). When the benzene extract cooled, about 30 g. of the pyrimidine separated from the solution. Additional product was obtained by concentrating and cooling the mother liquors. The total yield of crude product, m.p. 190–194° (reported[22] 192°), was 45–48 g. (72.5–74.4% of theory). After one recrystallization from ethanol the product melted at 195.5–196.5°.

The hydrochloride, prepared by saturating an alcoholic solution of the pyrimidine with hydrogen chloride, sublimed at 270–280° without melting. An analytical sample was prepared by vacuum sublimation.

Anal. Calcd. for $C_6H_9N_2OCl$: C, 44.87; H, 5.65; N, 17.45. Found: C, 45.05; H, 5.48; N, 17.65.

2-Isopropyl-4-methyl-6-hydroxypyrimidine (IV).—Crude 2-methylpropionamidine hydrochloride[24] (7.55 g.) was condensed with redistilled commercial ethyl acetoacetate (8.05 g.) by the procedure described for the preparation of I. The dry reaction mixture was extracted with a boiling solution of 50 ml. of ethanol and 50 ml. of benzene. The insoluble portion was separated by filtration and the filtrate was concentrated to a volume of about 30 ml. When the concentrate was refrigerated, a solid separated. The solid was collected and was washed with a few milliliters of cold acetone. Glistening white needles of 2-isopropyl-4-methyl-6-hydroxypyrimidine (IV) (2.6 g., 29.6% of theory), m.p. 170–172° (reported[22] 173°), remained. An additional gram of product was obtained by reworking the mother liquors. The total yield was 38.3% of theory.

The hydrochloride, prepared by saturating an alcoholic solution of the pyrimidine with hydrogen chloride, melted at 237–240° with decomposition and sublimation. An analytical sample, m.p. 240–241° (dec. and subl.), was prepared by vacuum sublimation.

Anal. Calcd. for $C_8H_{13}N_2OCl$: C, 50.93; H, 6.94; N, 14.85. Found: C, 51.08; H, 7.08; N, 14.93.

Mannich Reactions of 2,6-Dimethyl-4-hydroxypyrimidine (I). (a) With Piperidine and Formaldehyde in Benzene–Ethanol Solution.—A mixture of 6.2 g. of I, 9.35 g. of piperidine (Matheson practical), 3.0 g. of paraformaldehyde, 1.5 ml. of glacial acetic acid, 50 ml. of thiophene-free benzene and 50 ml. of commercial absolute ethanol was heated under reflux for a period of three to four days. The appearance of a deep yellow color in the reaction mixture seemed to indicate completion of the reaction. The solution was concentrated to a volume of about 50 ml. on the steam-bath and the concentrate was poured into a solution of 75 ml. of water and 4 g. of sodium carbonate. This mixture was permitted to stand under an air stream for about a day. The system was next extracted with 50 ml. of benzene and then with four 25-ml. portions of benzene. The benzene extracts were combined and dried over potassium carbonate. The dry benzene solution was concentrated to a volume of about 75 ml. on the steam-bath. The remainder of the solvent was removed under an air stream at room temperature. The residue was triturated with acetone and the solid material was collected and washed with a few milliliters of cold acetone. The initial yield of crude product was 3 to 5 g. When the acetone filtrate and washings were set aside and permitted to evaporate slowly, additional product separated and was collected. The total yield of crude product, identified as 2-bis-(1-piperidylmethyl)-methyl-4-methyl-6-hydroxypyrimidine (IIb), m.p. 160–164°, was 5.4–6.5 g. (34.0–41% of theory). After several recrystallizations from ethanol the Mannich base melted at 172–174°. The compound is easily soluble in hot ethanol, methanol, benzene and chloroform; it is difficultly soluble in hot acetone and hot water. An analytical sample was prepared by recrystallization from reagent grade acetone.

Anal. Calcd. for $C_{18}H_{30}N_4O$: C, 67.86; H, 9.50; N, 17.61. Found: C, 67.82; H, 9.58; N, 17.76.

When the reaction was scaled up to one-tenth molar quantity of I, the yield of II was 7–8 g. (22–25% of theory). However, a second Mannich base was recovered from the acetone washings. This compound, a tris-(1-piperidylmethyl) derivative III of I, was isolated in yields of 3–4 g. (7.2–9.6% of theory), m.p. 134–140°. This compound was purified by thoroughly washing it with water and then recrystallizing it several times from acetone. The pure base melted at 147–148°. It is too soluble in even cold benzene, ethanol, methanol or chloroform to permit recrystallization from these solvents. An analytical sample was prepared by recrystallization from reagent grade acetone.

Anal. Calcd. for $C_{24}H_{41}N_5O$: C, 69.35; H, 9.94; N, 16.85. Found: C, 69.33; H, 9.75; N, 16.65.

(b) With Piperidine and Formaldehyde in Glacial Acetic Acid.—To a cooled solution of 6.2 g. of I in 100 ml. of reagent grade glacial acetic acid, 9.35 g. of redistilled piperidine was carefully added. When the mixture had cooled, 3.3 g. of paraformaldehyde was added. The mixture was heated under reflux for 1.5 hr. and was then permitted to cool slowly. About 80 ml. of acetic acid was removed under reduced pressure (45–50° at 50 mm.). The oily residue was permitted to stand overnight and was then dissolved in 100 ml. of ether. The ether solution was treated with saturated sodium carbonate solution until the evolution of carbon dioxide ceased. The two-phase system was extracted with four 100-ml. portions of acetone. The acetone extracts were combined and dried over magnesium sulfate. The dried extract was evaporated under an air

---

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

(22) A. Pinner, *Ber.*, **22**, 1612 (1889).

(23) J. J. Donleavy and M. A. Kise, "Organic Syntheses," Coll. Vol. 2, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 422.

(24) N. S. Drozdov and A. F. Bekhli, *J. Gen. Chem. U.S.S.R.*, **14**, 280 (1944), *C. A.*, **39**, 3785 (1945).

stream at room temperature. An oily, gummy residue remained. This residue was dissolved in acetone and the solvent was permitted to evaporate slowly. Solid material gradually separated from solution. The total yield of crude product, identified as IIb, m.p. 158–162°, was 2.0 g. (12.5% of theory). After several recrystallizations from ethanol the melting point of the pure base was 172–174°. This product did not depress the melting point of the material prepared by procedure a.

In another experiment the reaction mixture was heated under reflux for 24 hr. and was worked up as described above. No solid product could be isolated from this reaction.

(c) **With Piperidine and Formaldehyde in Isoamyl Alcohol.**—A mixture of 4.98 g. of I, 6.8 g. of piperidine (Matheson practical), 2.4 g. of paraformaldehyde, 4.8 g. of glacial acetic acid and 50 ml. of isoamyl alcohol was heated under reflux for 6.5 hr. The cooled reaction mixture was poured into 50 ml. of water. Sufficient hydrochloric acid was added to make the mixture acidic to congo paper. The isoamyl alcohol layer was separated mechanically and the water layer was extracted with two 25-ml. portions of ether. The combined ether extracts and isoamyl alcohol layer were extracted with 20 ml. of water; this extract was added to the acid solution. The acidic aqueous solution was poured into a stirred two-phase system composed of concentrated sodium hydroxide solution (10 g. of base in 20 ml. of water) and 50 ml. of benzene. The benzene layer was separated and the aqueous layer was extracted with an additional 50-ml. portion of benzene. The aqueous layer was saturated with sodium bicarbonate and the saturated solution was extracted with two 50-ml. portions of boiling benzene. Finally the aqueous solution was extracted with 50 ml. of boiling acetone. When all the extracts were combined a lower aqueous phase appeared; this was discarded. The organic layer was dried over potassium carbonate. The dried solution was evaporated to dryness under an air stream at room temperature. The residue was triturated with a few milliliters of acetone and the solid residue was collected. The initial yield of crude product, m.p. 161–165°, was 1.3 g. An additional 0.3 g. of product was obtained from the mother liquors. This yield corresponds to 12.5% of theory. After recrystallization from methyl ethyl ketone the product melted at 172–174°, and the melting point was not depressed by mixture with a sample of the Mannich base IIb prepared by procedure a.

(d) **With Morpholine and Formaldehyde in Benzene–Ethanol Solution.**—Morpholine (Eastman Kodak Co. practical) and formaldehyde (paraformaldehyde) were condensed with I by the method described in part a. The yield of crude product, which by analogy with the condensation of piperidine and formaldehyde with I is assigned the structure 2-bis-(1-morpholinomethyl)-methyl-4-methyl-6-hydroxypyrimidine, m.p. 156–160°, was 35% of theory. After several recrystallizations from acetone the melting point of the pure base was 163–164°. The properties of this compound are very similar to those of II. An analytical sample was prepared by recrystallization from reagent grade acetone.

Anal. Calcd. for $C_{16}H_{26}N_4O_3$: C, 59.60; H, 8.13; N, 17.38. Found: C, 59.57; H, 8.36; N, 17.37.

Catalytic Hydrogenation of 2-Bis-(1-piperidylmethyl)-methyl-4-methyl-6-hydroxypyrimidine (IIb). (a) **In Methanol Solution.**—A solution of 1.59 g. of IIb dissolved in 50 ml. of methanol was hydrogenated over Raney nickel catalyst[25] (*ca.* 3 g. wet paste) at 150° and 1500 p.s.i. for 6.5 hr. The reaction mixture was filtered free of nickel catalyst and the catalyst was washed thoroughly with boiling methanol. The combined washings and filtrate were evaporated under an air stream at room temperature. The oily residue was placed in a desiccator over sulfuric acid and the desiccator was evacuated continuously with a water pump. The now solid residue was found to be far too soluble in acetone, methanol or ethanol to be recrystallized from these solvents. An inadequate recrystallization could be effected from ether. After several recrystallizations from ether, the compound melted at 109–111°. An analytical sample was prepared by vacuum sublimation, m.p. 110–112°.

Anal. Calcd. for C_4H_9NO: C, 55.14; H, 10.41; N, 16.08. Found: C, 55.00; H, 10.20; N, 16.00.

This compound did not depress the melting point of an authentic sample of *n*-butyramide and the infrared spectra of the two samples were identical. Thus this hydrogenation product is proved to be *n*-butyramide. The yield of amide was about 0.35 g. (47.5% of theory).

(b) **In Methanol Solution Saturated with Potassium Carbonate.**—A solution of 3.18 g. of IIb in 50 ml. of methanol, saturated with potassium carbonate, was hydrogenated over Raney nickel catalyst[25] (1 tsp. wet paste) at 2000 p.s.i. and 150–200° for about 5 hr. The catalyst was removed by filtration and was thoroughly washed with boiling methanol. The combined filtrate and washings were treated with gaseous hydrogen chloride until the solution was strongly acidic. The solution was evaporated at room temperature under an air stream. When most of the methanol had been removed about 75 ml. of acetone was added. After this solution had stood for several hours a solid material separated from solution and was collected. Additional material was obtained by concentration of the mother liquors. The solid was recrystallized from ethanol when it melted at 230–235° (dec. and subl.). Further purification was effected by vacuum sublimation. The sublimed material melted at 238–240° (dec. and subl.). This material did not depress the melting point of an authentic sample of 2-isopropyl-4-methyl-6-hydroxypyrimidine hydrochloride (IV·HCl) and the infrared spectra of the two samples were identical. The yield of hydrochloride was about a gram (53% of theory).

(c) **In Methanol Solution Containing Hydrochloric Acid.**—A solution of 1.59 g. of IIb in 50 ml. of methanol containing 10 drops of concentrated hydrochloric acid was hydrogenated over Raney nickel catalyst[25] (1 tsp. wet paste) at 2000 p.s.i. and 135–140°. The catalyst was removed by filtration and was thoroughly washed with boiling methanol. The combined filtrate and washings were evaporated under an air stream at room temperature. The residue was extracted with two 50-ml. portions of boiling ether and the ether was carefully evaporated on the steam-bath. The residue melted at 168–170° and did not depress the melting point of an authentic sample of 2-isopropyl-4-methyl-6-hydroxypyrimidine (IV). The melting point of the residue was depressed about 30° on admixture with a sample of the Mannich base IIb. The yield of crude product was nearly theoretical.

Attempted Hydrolytic Cleavage of 2-Bis-(1-piperidylmethyl)-methyl-4-methyl-6-hydroxypyrimidine (IIb).—A solution of 2.0 g. of IIb in a mixture of 95 ml. of methanol and 5 ml. of distilled water which contained one-half of a pellet of sodium hydroxide was heated in an autoclave at 150° for about 4 hr. Most of the solvent was removed on the steam-bath; the remainder was evaporated at room temperature under an air stream. Acetone was added to the oily residue and the solvent was permitted to evaporate slowly. The solid which separated from solution was collected. After several recrystallizations from acetone the compound melted at 169–171° and the melting point was not depressed on mixture with a fresh sample of IIb. The recovery of unchanged IIb was 700 mg. (35%). A large amount of tarry material also was formed.

Attempted Reductive Cleavage of 2,6-Dimethyl-4-hydroxypyrimidine (I).—A solution of 4.96 g. of I in 1200 ml. of methanol was treated with hydrogen over Raney nickel catalyst[25] (*ca.* 5 g. wet paste) at 1700 p.s.i. and 150° for 4 hr. The reaction mixture was filtered free of catalyst and the catalyst was washed with boiling methanol. The filtrate was acidified with concentrated hydrochloric acid and the solvent was removed on the steam-bath. The residue was recrystallized from 95% methanol. The solid sublimed at 270–280° without melting. Comparison of the infrared spectrum of this material with the infrared spectrum of an authentic sample of 2,6-dimethyl-4-hydroxypyrimidine hydrochloride proved their identity.

In another experiment, 2.48 g. of I in 50 ml. of methanol was hydrogenated over Raney nickel catalyst[25] at 2000 p.s.i. and 150°. Unreacted I (as the hydrochloride) was recovered from this reaction also.

Reaction of 2-Bis-(1-piperidylmethyl)-methyl-4-methyl-6-hydroxypyrimidine (IIb) with Methyl Iodide.—A solution of 3.18 g. of IIb in 30 ml. of commercial absolute ethanol was cooled to about 8°. To the cooled slurry which formed, 2.84 g. of methyl iodide, also cooled to 8°, was added. The reaction mixture was swirled gently for a few minutes and was then placed in the refrigerator. After the mixture had stood in the cold for two weeks, the Mannich base had completely dissolved and crystals of a new compound had appeared. The solvent was removed under an air stream at

---

[25] Gilman Paint and Varnish Company, Chattanooga, Tennessee.

room temperature. The residue was triturated with about 15 ml. of methanol and 25 ml. of ether. The solid was collected and was washed with a few milliliters of ether. The yield of crude solid, formulated as 2-(4-methyl-6-hydroxy-2-pyrimidyl)-4-azaspiro[3,5]nonane iodide (Va), m.p. 206–208°, was 2.35 g. (63.7% of theory). After several recrystallizations from methanol the salt melted at 210–211.5°. An analytical sample was prepared by recrystallization from reagent grade methanol.

Anal. Calcd. for $C_{13}H_{20}N_3OI$: C, 43.22; H, 5.58; N, 11.63. Found: C, 43.28; H, 5.63; N, 11.55.

This compound gave an immediate precipitate, insoluble in dilute nitric acid, when treated with silver nitrate. When treated with aqueous hypohalite, the material liberated iodine at once. When an aqueous solution of the material was allowed to react with sodium carbonate, no basic material could be extracted into benzene. A red color rapidly developed in the aqueous solution and finally a gummy red oil separated from solution.

In another experiment, a solution of 1.59 g. of IIb in 10 ml. of commercial absolute ethanol was cooled in a Dry Ice–acetone-bath. To the slurry which formed, 2.13 g. of cold methyl iodide was added slowly with swirling. The reaction mixture was shaken vigorously for a few minutes and was then set aside in a cold chest at −55°. After the mixture had stood for a week, the solid was collected rapidly and was washed with a few milliliters of cold ether. The recovery of crude solid, m.p. 164–165°, was 1.45 g. After recrystallization from ethanol the material melted at 168–169° and did not depress the melting point of a fresh sample of the Mannich base IIb.

It was possible to isolate what appeared to be a monomethiodide of IIb by operating under slightly different conditions. To a freshly prepared slurry of 1.59 g. of IIb and 16 ml. of commercial absolute ethanol, 2.84 g. of methyl iodide, cooled to 8°, was added slowly with swirling. The reaction mixture was set aside in the refrigerator. As soon as the Mannich base IIb had dissolved completely (*ca.* two days) the solvent was removed under an air stream at room temperature. The residue, an oil, was transferred to a desiccator over sulfuric acid and the desiccator was evacuated continuously with a water pump. After a drying period of about 12 hr. the product had partially solidified. The material was dissolved in a few milliliters of methanol and the methanol was removed at room temperature. Again an oil remained. The oil was triturated with a few milliliters of cold ether and was returned to the desiccator which was evacuated for an additional 12-hr. period. The "methiodide" had solidified, and appeared to be completely dry. The yield of extremely hygroscopic crude material was 2.3 g. (theoretical yield based on a monomethiodide). The methiodide could not be recrystallized from ethanol. The compound readily dissolved in cold acetic acid with the liberation of heat. About three to four volumes of dry ether were added to the solution whereupon a gummy solid precipitated. The solid was triturated with a few milliliters of cold ether and it was recrystallized easily from methanol. After a second recrystallization the compound melted at 210–211.5° and was identical with the previously described salt (Va).

Reaction of 2-Bis-(1-piperidylmethyl)-methyl-4-methyl-6-hydroxypyrimidine (IIb) with Acetic Anhydride.—A mixture of 10 g. of IIb and 5 g. of anhydrous sodium acetate in 50 ml. of purified acetic anhydride was heated under reflux for 4 hr. The cooled reaction mixture was poured onto a mixture of 80 g. of sodium carbonate and 300 g. of ice. The reaction flask was washed with 50 ml. of water and 50 ml. of ether. The washings were poured onto the ice also. When all the acetic anhydride had been decomposed, the aqueous mixture was extracted with 100 ml. of benzene and then with eight 25-ml. portions of benzene. The benzene extracts were combined and dried over potassium carbonate. The dry extract was decolorized by two treatments with activated alumina. The solution was concentrated to a volume of about 175 ml. on the steam-bath and the remainder of the solvent was removed under an air stream at room temperature. A partially crystalline, oily mixture remained. The mixture was treated with about 30 ml. of alcohol and the alcohol was evaporated under an air stream at room temperature. This procedure was repeated several times. The solid was collected and was washed with a few milliliters of cold ethanol. The yield of crude solid, which differed in composition from the Mannich base IIb by the elements of two molecules of piperidine, dec. about 250°, was 0.40 g. (8.6% of theory). An analytical sample was prepared by several recrystallizations from redistilled methyl ethyl ketone.

Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.97; H, 5.17; N, 19.19.

The filtrate was freed of ethanol and the oily residue was distilled under vacuum. The portion boiling 40–50° at 0.4 mm. was collected. The oil, which was identified as N-acetylpiperidine (infrared spectrum), was redistilled; the portion distilling at 43–46° at 0.5 mm. was 2.4 g. (28.5% of theory). An analytical sample was prepared by an additional vacuum distillation.

Anal. Calcd. for $C_7H_{13}NO$: N, 11.01. Found: N, 10.88.

The pot residue was dissolved in ethanol. When this extract was concentrated and refrigerated an additional 0.33 g. of the solid compound ($C_8H_8N_2O$) was recovered. The total yield of this compound (0.73 g.) corresponds to 15.7% of theory.

Catalytic Hydrogenation of the Tris-(1-piperidylmethyl) Derivative III of 2,6-Dimethyl-4-hydroxypyrimidine.—A solution of 1.0 g. of the Mannich base dissolved in 50 ml. of commercial absolute ethanol was subjected to catalytic hydrogenation over copper chromite catalyst at 2600 p.s.i. and 165° for about 4 hr. The reaction mixture was filtered free of catalyst and the catalyst was washed with boiling ethanol. The washings and filtrate were combined and evaporated to dryness. The residue was dissolved in a minimum of hot water and the solution was treated with hydrogen sulfide. The precipitated sulfides were filtered, and the filtrate was evaporated to dryness on the steam-bath. The residue was extracted with ethanol and acetone. The combined extracts were concentrated and refrigerated when a small quantity (*ca.* 50 mg.) of crystalline material, m.p. 180–184°, separated from solution and was collected. An analytical sample, m.p. 184–185°, was prepared by recrystallization from reagent grade acetone.

Anal. Calcd. for $C_{14}H_{23}N_3O$: C, 67.43; H, 9.30; N, 16.85. Found: C, 67.43; H, 9.25; N, 16.86.

URBANA, ILLINOIS