Midwest Research Institute

Pyrimidines. XIX. Pyrimido[4,5-*e*]dihydro-1,3-oxazines and Related Compounds (1)

Darrell E. O'Brien, Louis T. Weinstock, Robert H. Springer and C. C. Cheng

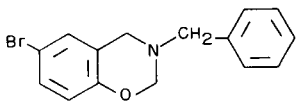
A number of 2-substituted 4,5-dihydroxy-6-(substituted aminomethyl)pyrimidines (VIII) were prepared from the corresponding 2-substituted 4,5-dihydroxypyrimidines (VII) by a new pyrimidine Mannich reaction. The structure of VIII was proved by an independent synthesis. Further study of this reaction led to the synthesis of a new class of compounds: the pyrimido[4,5-*e*]dihydro-1,3-oxazines (VI).

Urbañski and co-workers (2) reported that some benzo- and napthodihydro-1,3-oxazines (*e.g.*, compounds I-III) inhibited the growth of Crocker sarcoma in mice. This anticancer activity has also been discovered in *in vitro* experiments (3). In an extension of their study, these workers reported that a number of dihydro-1,3-oxazines and nitrotetrahydro-1,3-oxazines (IV) are active against the solid forms of Ehrlich ascites carcinoma and amytyl ascites sarcoma (4). Kuehne and Konopka provided substantial evidence for the antineoplastic effect of dihydro-1,3-oxazine derivatives by synthesizing and testing a variety of mono- and bis-dihydro-1,3-oxazines (5) as well as steroidal dihydro-1,3-oxazines (*e.g.*, V) (6) and found that many were active against adenocarcinoma E0771 tumors in mice.

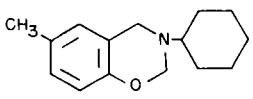
On the basis of this information, synthesis of certain derivatives possessing the dihydro-1,3-oxazine moiety should be investigated in order to gain a better understanding with regard to the relationship between structure and biological activity. Incorporation of this moiety into certain biologically important ring systems may provide some useful information for cancer chemotherapeutic studies. Synthesis of pyrimido[4,5-*e*]dihydro-1,3-oxazines (VI), therefore, has been initiated.

The benzodihydro-1,3-oxazines and related compounds were prepared by the treatment of phenolic derivatives with two equivalents of formaldehyde and one equivalent of primary amine according to the method of Burke *et al.*, (7). This reaction can be visualized as being carried out in two steps: a Mannich reaction followed by a cyclization of the resulting intermediate with a second molecule of formaldehyde.

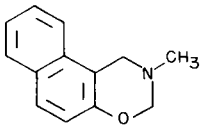
In a preliminary communication from our laboratory (8), a new pyrimidine Mannich reaction of 5-hydroxyuracil (9) (VIIa) with formaldehyde and piperidine was reported. In order to ascertain whether this Mannich reaction is of a general type for 4,5-dihydroxypyrimidines, several compounds in this series (VII) were prepared and examined. Among these, the 2-methyl- (9b,10) (VIIb), 2-phenyl- (VIIc), and 2-unsubstituted (9b,11) (VIId) derivatives



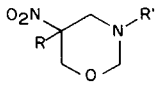
I



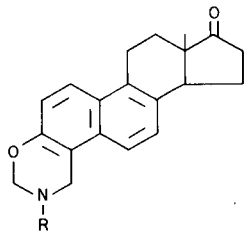
II



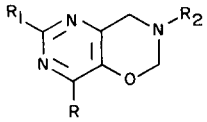
III



IV



V

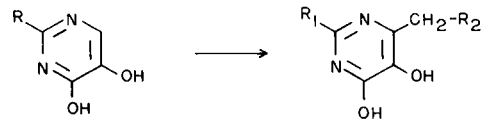


VI

were found to readily undergo the new Mannich reaction to give the corresponding 6-(*N*-substituted aminomethyl)pyrimidines (12) (VIII). This reaction probably involves an electrophilic attack at the 6-position of the pyrimidine ring system. Since the Mannich reaction involves the replacement of active hydrogen atoms with substituted aminomethyl groups (13), the tautomeric keto form (IX) of 4,5-dihydroxypyrimidines (14) is perhaps responsible for achieving the present Mannich reaction. The postulation is further substantiated by the observation that 5-methoxyuracil (17) (X) did not react under the same Mannich reaction conditions. In a parallel case, 4,5-dihydroxypyrimidines were reported to undergo diazonium coupling (18) and nitrosation (19) reactions at the 6-position, yet none of these reactions could take place with 5-methoxyuracil (X).

The structure of Mannich products VIII was proved by the following unambiguous synthesis: self-condensation of ethyl tetrahydropyran-2-yloxyacetate (XI) by sodium, according to the procedure of Davoll and Laney (16), gave the acetoacetic ester intermediate XII. Reaction of XII with benzamidine hydrochloride (20) yielded 2-phenyl-4-hydroxy-5-(tetrahydropyran-2-yloxy)-6-(tetrahydropyran-2-yloxymethyl)pyrimidine (XIII), which was hydrolyzed in acid to give 2-phenyl-4,5-dihydroxy-6-(hydroxymethyl)pyrimidine (XIV). Chlorination of XIV with thionyl chloride followed by treating the resulting product XV with piperidine gave 2-phenyl-4,5-dihydroxy-6-(piperidinomethyl)pyrimidine (XVI). This product was found to be identical (melting point, ultraviolet and infrared absorption, and chromatographic comparison) with that prepared by the Mannich condensation of 2-phenyl-4,5-dihydroxypyrimidine (VIIc) with formaldehyde and piperidine.

The desired pyrimido[4,5-*e*]dihydro-1,3-oxazines (VI, R = OH) were prepared by the reaction of a 4,5-dihydroxypyrimidine, formaldehyde and a primary amine in the ratio of 1:2:1, respectively. Although the product gave a positive ferric chloride test (21), nuclear magnetic resonance spectrum of the products ruled out the possibility of an alterna-



VIIa, R = OH

b, R = CH_3

c, R = C_6H_5

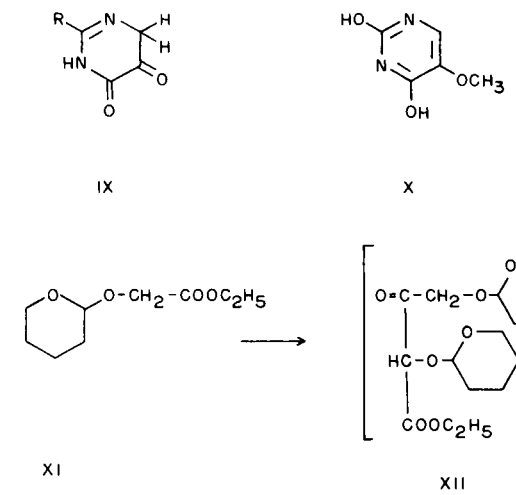
d, R = H

VIIIa, R_1 = H, R_2 = $C_5H_{10}N$

b, R_1 = CH_3, R_2 = $C_5H_{10}N$

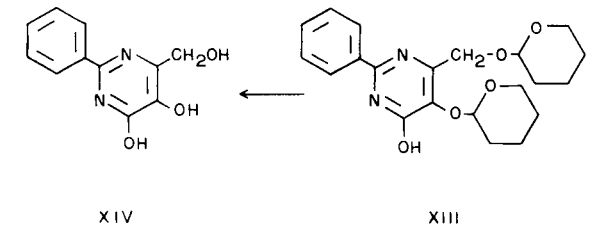
c, R_1 = OH, R_2 = $(CH_3)_2N$

d, R_1 = OH, R_2 = $C_5H_{10}N$

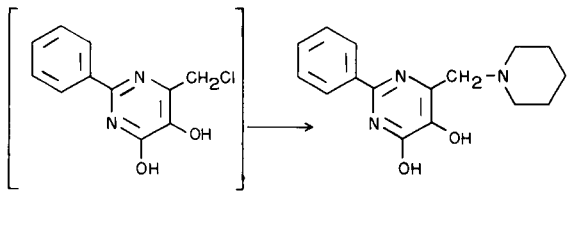


IX X

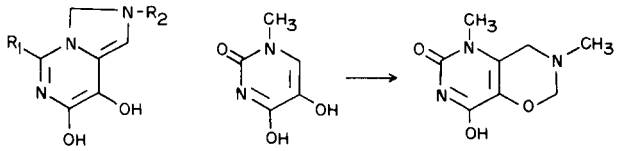
XI XII



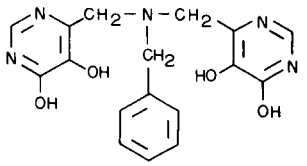
XIV XIII



XV XVI



XVII XVIII XIX



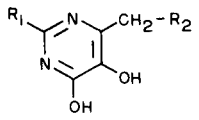
tive structure XVII, which could conceivably be formed by cyclization through the ring nitrogen atom rather than the oxygen atom at the 5-hydroxyl group. The structural assignment was further substantiated by the fact that 1-methyl-5-hydroxyuracil (22) (XVIII) underwent the same reaction with formaldehyde and methylamine to yield 3,5-dimethyl-6-oxo-8-hydroxy-3,4,5,6-tetrahydro-2*H*-pyrimido-[4,5-*e*]-1,3-oxazine (XIX). In this case, cyclization through N-1 of the pyrimidine ring is not feasible.

Preparation of dihydro-1,3-oxazines has been extended to include other 4,5-dihydroxypyrimidines and different primary amines. The desired pyrimido-[4,5-*e*]dihydro-1,3-oxazines (VI, R = OH) with the 6-phenyl, 6-methyl and 6-hydroxy substituents were successfully isolated. During the course of this study it was found that higher yields of VI were obtained when methanol was used as the reaction solvent. Attempted preparation of the 6-unsubstituted analogs from 4,5-dihydroxypyrimidine, formaldehyde and primary amines failed to yield the desired products. When benzylamine was used, for example, the product was found to be *N,N*-bis(4,5-dihydroxy-6-pyrimidinylmethyl)benzylamine (XX).

5-Hydroxypyrimidine, prepared by the method of Chesterfield, McOmie and Tute (17), did not undergo the new Mannich condensation at the 4-position with

TABLE I

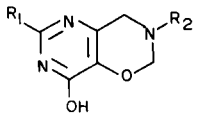
2-Substituted 4,5-Dihydroxy-6-(disubstituted aminomethyl)pyrimidines



					Analyses						Ultraviolet absorption			
					Calcd., %			Found, %			*p*H 1		*p*H 11	
R_1	R_2	Recrystn. solvents	Yield, %	M.p., °C	C	H	N	C	H	N	λ max (mμ)	ε	λ max (mμ)	ε
H	$C_5H_{10}N$	Methanol	52	194-195	57.4	7.22	20.1	57.1	6.90	19.7	240 276	6,060 7,530	269 sh 293	8,150 8,770
CH_3	$C_5H_{10}N$	Ethyl acetate	65	184-185	59.2	7.67	18.8	59.1	7.45	18.6	270	12,080	264 298	9,350 10,250
OH	$(CH_3)_2N$	Methanol	45	180-182	45.4	5.99	22.7	45.4	6.25	22.4	282	7,000	239 310	5,700 5,400
OH	$C_5H_{10}N$	Methanol	57	210-211	53.3	6.72	18.7	53.1	7.08	18.8	283	6,100	241 310	6,100 5,600
C_6H_5	$C_5H_{10}N$	Methanol	70	214-217	67.4	6.72	14.7	67.5	6.62	14.7	271 295	11,000 13,200	229 304	12,300 14,300

TABLE II

3,6-Disubstituted 3,4-Dihydro-8-hydroxy-2*H*-pyrimido[4,5-*e*]-1,3-oxazines



					Analyses						Ultraviolet absorption			
					Calcd., %			Found, %			*p*H 1		*p*H 11	
R_1	R_2	Recrystn. Solvents	Yield, %	M.p., °C	C	H	N	C	H	N	λ max (mμ)	ε	λ max (mμ)	ε
CH_3	CH_3	Ethyl acetate	61	200-202	53.0	6.12	23.2	52.7	6.00	22.9	244 273	7,100 8,700	295	11,400
CH_3	$CH_2C_6H_5$	Methanol	59	199-200	65.4	5.87	16.3	65.5	5.69	16.4	243 276	6,700 8,000	295	11,500
CH_3	C_6H_{11}	Methanol	64	166-167	62.6	7.69	16.9	62.3	7.70	16.8	249 sh 272	7,000 8,500	295	10,400
OH	CH_3	Water	46	218-219 dec.	45.9	4.95	22.9	45.7	5.00	22.8	276	14,300	240 301	8,700 11,500
OH	$CH_2C_6H_5$	Methanol	67	211-213	60.3	5.06	16.2	60.5	4.98	16.2	278	10,300	243 306	7,500 9,100
C_6H_5	CH_3	Ethanol	33	197-199	64.2	5.39	17.3	64.2	5.17	17.2	297	13,000	231 306	9,600 13,600
C_6H_5	$CH_2C_6H_5$	Ethanol	50	187-189	71.6	5.36	13.2	71.7	5.20	13.0	298	13,100	231 305	10,500 13,400

either piperidine or benzylamine and formaldehyde. Previous investigators also reported the failure of these 5-hydroxypyrimidines to couple with diazotized *p*-nitroaniline (17).

Biological evaluation (23) indicated that none of the pyrimido[4,5-*e*]dihydro-1,3-oxazines (VI) demonstrated activity against leukemia L-1210 in BDF_1 mice or Walker 256 (intramuscular) in noninbred albino rats. Borderline activity against Walker 256 has been noted with 2-substituted-4-hydroxy-5-benzyloxypyrimidines.

EXPERIMENTAL (24)

2-Phenyl-4-hydroxy-5-benzyloxypyrimidine.

A solution of benzyl benzyloxyacetate (10) (128 g., 0.5 mole) and ethyl formate (37.0 g., 0.5 mole) was added dropwise to a well stirred suspension of finely cut sodium (11.5 g., 0.5 g.-atom) in 200 ml. of anhydrous ether. The resulting mixture was allowed to stir at room temperature until all the sodium had reacted. The reaction mixture was then evaporated to dryness *in vacuo* to yield an orange residue.

A solution of benzamidine in ethanol [prepared from a solution of benzamidine hydrochloride (78.2 g., 0.5 mole) in 200 ml. of absolute ethanol that had been neutralized with a solution of sodium (11.5 g., 0.5 g.-atom) in 200 ml. of absolute ethanol] was added to the aforementioned orange residue. The mixture was refluxed with stirring for 8 hours. It was then cooled and added to 200 ml. of water. The *p*H of the resulting solution was adjusted to 5 with concentrated hydrochloric acid. The mixture was chilled, the yellow precipitate separated by filtration, washed with water, and finally dried at 80° to give 69.5 g. (50% yield) of product, m.p. 205-210°.

A small sample was recrystallized from a large volume of ethyl acetate to yield an analytically pure sample, m.p. 218-221°; λ max (*p*H 1), 245 (ε, 12,800), 228 mμ (ε, 16,200); λ max (*p*H 11), 228 (ε, 16,400), 285 mμ (ε, 12,500).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.4; H, 5.06; N, 10.1. Found: C, 73.2; H, 5.07; N, 10.2.

2-Phenyl-4,5-dihydroxypyrimidine (VIIIc).

A solution of 2-phenyl-4-hydroxy-5-benzyloxypyrimidine (50 g., 0.18 mole) in 1,500 ml. of 6 *N* hydrochloric acid was refluxed for 1 hour. The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in 500 ml. of water. The solution was carefully neutralized with solid sodium bicarbonate, then chilled. The precipitated solid was filtered, washed with ether, and air dried to give 27.8 g. (80% yield) of crude product, m.p. 205-210°. Recrystallization from water yielded an analytically pure sample, m.p. 212-215°; λ max (*p*H 1), 243 (ε, 10,000), 287 mμ (ε, 11,900); λ max (*p*H 11), 230 (ε, 9,800), 315 mμ (ε, 13,700).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.9; H, 4.28; N, 14.9. Found: C, 63.8; H, 4.05; N, 14.7.

General Preparation of 2-Substituted 4,5-Dihydroxy-6-(dialkylaminomethyl)pyrimidine (VIII).

A suspension of a secondary amine (0.025 mole), 35% aqueous formaldehyde (2.15 g., 0.025 mole) and 2-substituted 4,5-dihydroxypyrimidine (0.025 mole) in 250 ml. of water was stirred at 0-5° for 3 hours. At the end of this time most of the solid dissolved and a small amount of insoluble material was separated by filtration and discarded. The filtrate was evaporated to dryness at 40-50° under reduced pressure. The resulting residue was purified by recrystallization from the appropriate solvent listed in Table I.

2-Phenyl-4-hydroxy-5-(tetrahydropyran-2-yloxy)-6-(tetrahydropyran-2-yloxymethyl)pyrimidine (XIII).

Finely cut sodium (2.9 g., 0.125 g.-atom) was added to a solution of ethyl tetrahydropyran-2-yloxyacetate (47.0 g., 0.25 mole) in 500 ml. of anhydrous ether. The mixture was stirred at room temperature for 2 days. At the end of this period all the sodium had reacted and an orange salt precipitated. It was evaporated to dryness to yield an orange residue.

A solution of benzamidine in ethanolic sodium ethoxide [prepared from a solution of benzamidine hydrochloride (19.6 g., 0.125 mole) in 200 ml. of absolute ethanol and a solution of sodium (5.74 g., 0.25 g.-atom) in 200 ml. of absolute ethanol] was added to the orange residue. The resulting mixture was refluxed with stirring for 8 hours and then evaporated to dryness under reduced pressure. The red residue was dissolved in 300 ml. of water and the resulting solution was extracted with 2 x 250 ml. of ether. The *p*H of the remaining aqueous layer was then adjusted to 5 by the addition of glacial acetic acid. The mixture was chilled overnight, the solid separated by filtration, washed with ether then air dried to give 13.5 g. (28% yield) of crude product, m.p. 137-139°. Recrystallization from a minimum amount of anhydrous methanol gave an analytically pure sample, m.p. 150-151°; λ max (ethanol), 245 (ε, 14,300), 301 mμ (ε, 16,200).

Anal. Calcd. for $C_{21}H_{28}N_2O_5$: C, 65.2; H, 6.78; N, 7.25. Found: C, 65.2; H, 7.02; N, 7.37.

2-Thio-5-(tetrahydropyran-2-yloxy)-4-hydroxy-6-(tetrahydropyran-2-yloxymethyl)pyrimidine.

A solution of thiourea (9.5 g., 0.125 mole) in 250 ml. of ethanol was added to the orange residue (prepared according to the method described in the preceding section), and the resulting mixture was refluxed for 3 hours. At the end of this time the mixture was evaporated to dryness *in vacuo*, and the dark brown residue dissolved in 200 ml. of water. The aqueous solution was extracted with 2 x 250 ml. of ether. The remaining aqueous layer was then adjusted to *p*H 5 by means of glacial acetic acid, then chilled. The resulting tan colored solid product was collected by filtration, washed with ether and air dried to give 21.4 g. (50% yield), m.p. 139-141°. Recrystallization from a minimum amount of anhydrous methanol yielded an analytically pure sample, m.p. 158-160°; λ max (ethanol), 279 mμ (ε, 19,900).

Anal. Calcd. for $C_{15}H_{22}N_2O_5S$: C, 52.6; H, 6.46; N, 8.18. Found: C, 52.4; H, 6.50; N, 7.95.

2-Phenyl-4,5-dihydroxy-6-hydroxymethylpyrimidine (XIV).

A suspension of 15 g. of XIII in 150 ml. of 3 *N* hydrochloric acid was stirred at room temperature for 6 hours, during which time a complete solution was formed. The solution was decolorized with charcoal and filtered. The light yellow filtrate was adjusted to *p*H 5 by the slow addition of sodium bicarbonate. The resulting tan solid was separated by filtration, washed with cold water, and dried at 80°. The product, m.p. 210-212°, weighed 7.0 g. (83% yield). Further recrystallization from water did not change the melting point; λ max (*p*H 1), 244 (ε, 11,400); 272 mμ (ε, 13,700); λ max (*p*H 11), 227 (ε, 11,300), 309 mμ (ε, 15,100).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.5; H, 4.62; N, 12.8. Found: C, 60.6; H, 4.66; N, 13.0.

2-Thio-4,5-dihydroxy-6-hydroxymethylpyrimidine.

A mixture of 20 g. of 2-thio-5-(tetrahydropyran-2-yloxy)-4-hydroxy-6-(tetrahydropyran-2-yloxymethyl)pyrimidine in 250 ml. of 3 *N* hydrochloric acid was stirred for 3 hours. The solid was collected by filtration, washed with water, methanol, ether, then air dried to give 8.8 g. (86% yield) of product, m.p. 265-266° dec. Recrystallization from water gave an analytically pure sample, m.p. 268-269° dec; λ max (*p*H 1), 223 (ε, 11,300), 283 mμ (ε, 17,400); λ max (*p*H 11), 240 (ε, 10,100), 283 mμ (ε, 12,700).

Anal. Calcd. for $C_5H_6N_2O_3S$: C, 34.5; H, 3.47; N, 16.1. Found: C, 34.7; H, 3.48; N, 16.4.

2-Phenyl-4,5-dihydroxy-6-(piperidinomethyl)pyrimidine (XVI).

A suspension of 2 g. of XIV in 200 ml. of thionyl chloride was refluxed on a steam bath while the solid slowly dissolved. After 2 hours the solution was evaporated under reduced pressure to a yellow solid. The residual trace of thionyl chloride was removed by dissolving the solid in 200 ml. of anhydrous acetone and once again evaporating to dryness. The crude 2-phenyl-4,5-dihydroxy-6-(chloromethyl)-pyrimidine was dissolved in 200 ml. of anhydrous acetone containing 5 g. of piperidine and the mixture was heated on a steam bath for 1 hour. The precipitated piperidine hydrochloride was separated by filtration. Evaporation of the yellow filtrate followed by trituration of the resulting yellow paste with ether gave a yellow solid, which, after recrystallization from ethanol gave 0.75 g. (29% overall yield) of the desired product, m.p. 212-214°. The ultraviolet and infrared absorption spectra of this product were identical with those of the compound VIIIe prepared by the aforementioned Mannich reaction. A mixture melting point determination showed no depression. Both products gave identical Rf values in 5% ammonium carbonate (0.73) and 7:3 methanol-water (0.72) paper chromatograms.

General Preparation of 3,6-Disubstituted 3,4-Dihydro-8-hydroxy-2*H*-pyrimido[4,5-*e*]-1,3-oxazines (VI).

To a solution of 35% formaldehyde (8.6 g., 0.1 mole) in 250 ml. of methanol was added a primary amine (0.05 mole) and a 4,5-dihydroxypyrimidine (0.05 mole). The mixture was refluxed on the steam bath for 2 hours. The resulting solution was refrigerated overnight and the precipitated product collected by filtration. The recrystallization solvents and analytical data are listed in Table II.

3,5-Dimethyl-6-oxo-8-hydroxy-3,4,5,6-tetrahydro-2*H*-pyrimido[4,5-*e*]-1,3-oxazine (XIX).

A mixture of 35% formaldehyde (8.6 g., 0.1 mole), 40% aqueous methylamine (3.9 g., 0.05 mole) and 1-methyl-5-hydroxyuracil (22) (7.1 g., 0.05 mole) in 250 ml. of methanol was refluxed on the steam bath for 2 hours. The resulting solution was then treated with decolorizing carbon and filtered. The filtrate was chilled and the resulting precipitate collected by filtration. Recrystallization of the solid from methanol gave 4.6 g. (47% yield) of analytically pure product, m.p. 208-210° dec.; λ max (*p*H 1), 286 mμ (ε, 7,400); λ max (*p*H 11), 236 (ε, 6,100), 293 mμ (ε, 4,700).

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.7; H, 5.62; N, 21.3. Found: C, 48.7; H, 5.86; N, 21.0.

3-Benzyl-5-methyl-6-oxo-3,4,5,6-tetrahydro-8-hydroxy-2*H*-pyrimido-[4,5-*e*]-1,3-oxazine.

The compound, m.p. 195-197° dec., was prepared in 68% yield from benzylamine, formaldehyde and 1-methyl-5-hydroxyuracil (22) in a similar manner as for the preparation of the preceding analog; λ max (*p*H 1), 270 mμ (ε, 7,900); λ max (*p*H 11), 233 (ε, 6,800), 288 mμ (ε, 4,900).

Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.6; H, 5.54; N, 15.4. Found: C, 61.7; H, 5.41; N, 15.1.

N,*N*-Bis(4,5-dihydroxy-6-pyrimidinylmethyl)benzylamine (XX).

To 125 ml. of ethanol was added 4.3 g. (0.05 mole) of 35% aqueous formaldehyde, 2.68 g. (0.025 mole) of benzylamine and 5.6 g. (0.05 mole) of 4,5-dihydroxypyrimidine. The suspension was brought to reflux. After a short time the reactants formed a complete solution which was followed by precipitation of a solid. At the end of 4 hours reflux the reaction mixture was immediately filtered and the off-white solid was washed with ethanol to yield 4.0 g. (45% yield) of analytically pure XX; λ max (*p*H 1), 242 (ε, 13,700), 277 mμ (ε, 15,700); λ max (*p*H 11), 292 mμ (ε, 18,950).

Anal. Calcd. for $C_{17}H_{17}N_5O_4$: C, 57.5; H, 4.82; N, 19.7. Found: C, 57.7; H, 5.08; N, 20.0.

Acknowledgment.

The authors wish to express their appreciation to Mrs. Margaret L. Rounds, Mr. John R. Gravatt and Mr. Leland R. Lewis for the analytical and instrumental measurements.

REFERENCES

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service, Contract PH-43-65-94.

(2) T. Urbański, C. Radzikowski, Z. Ledóchowski, and W. Czarnocki, *Nature*, 178, 1351 (1956).

(3a) S. Slopek, H. Mordarska, T. Urbański, and D. Gürne, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, 6, 361 (1958); (b) A. Leonardi, *Bull. Soc. Ital. Biol. Speriment*, 35, 796 (1959).

(4a) T. Urbański, D. Gürne, S. Ślopek, H. Mordarska and M. Mordarski, *Nature*, 187, 426 (1960); (b) J. B. Chylińska, E. Grochowski, M. Mordarski, and T. Urbański, *Unio. Intern. Contra Cancrum*, 20, 118 (1964), and references cited therein.

(5) M. E. Kuehne and E. A. Konopka, *J. Med. Pharm. Chem.*, 5, 257 (1962).

(6) M. E. Kuehne, E. A. Konopka, and B. F. Lambert, *ibid.*, 5, 281 (1962).

(7a) W. J. Burke, *J. Am. Chem. Soc.*, 71, 609 (1949); (b) W. J. Burke and C. Weatherbee, *ibid.*, 72, 4691 (1950); (c) W. J. Burke, R. P. Smith, and C. Weatherbee, *ibid.*, 74, 602 (1952); (d) W. J. Burke and C. W. Stephens, *ibid.*, 74, 1518 (1952); (e) W. J. Burke, M. J. Kolbezen, and C. W. Stephens, *ibid.*, 74, 3601 (1952); (f) W. J. Burke and R. J. Reynolds, *ibid.*, 76, 1291 (1954); (g) W. J. Burke, K. C. Murdock, and G. Ec, *ibid.*, 76, 1677 (1954).

(8) D. E. O'Brien, R. H. Springer, and C. C. Cheng, *J. Heterocyclic Chem.*, 3, 115 (1966).

(9a) D. Davidson and O. Baudisch, *Ber.*, 58, 1685 (1925); (b) P. Chang and K. C. Chiang, *Acta Chemica Sinica* (Peking), 22, 557 (1956); (c) S. Y. Wang, *J. Am. Chem. Soc.*, 81, 3786 (1959).

(10) J. H. Chesterfield, D. T. Hurst, J. F. W. McOmie, and M. S. Tute, *J. Chem. Soc.*, 1001 (1964).

(11) J. F. W. McOmie and A. B. Turner, *ibid.*, 5590 (1963).

(12) Under similar reaction conditions, 2-amino-4,5-dihydroxypyrimidine (VII, R = NH_2) yielded a yellow resinous substance. The desired Mannich product could not be isolated when the reaction was carried out using either excess formaldehyde, under different *p*H, or at different reaction temperatures. Failure of this reaction may be attributed to polymerization in addition to Schiff base formation between formaldehyde and the 2-amino function on the pyrimidine ring.

(13) For a general review of Mannich reaction, *cf.* H. Hellmann and G. Opitz, "α-Aminoalkylierung - Darstellung und Eigenschaften der Kondensations-produkte H-acider Stoffe mit Carbonylverbindungen und Aminen", Verlag Chemie, GmbH, 1960.

(14) Ultraviolet spectra studies of pyrimidines have shown that 2- and 4(6)-hydroxypyrimidines exist mainly or entirely in the pyrimidone form (15). The 5-hydroxy group in general, exists as such (16). For convenience of nomenclature, tautomerizable hydroxy groups substituted in the pyrimidine ring system in this paper are shown as the *enol* rather than the *keto* form.

(15a) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 1004 (1951); (b) P. V. Boarland and J. F. W. McOmie, *ibid.*, 3716, 3722 (1952); (c) D. J. Brown, E. Hoerger, and S. F. Mason, *ibid.*, 211 (1955).

(16) J. Davoll and D. H. Laney, *ibid.*, 2124 (1956).

(17) J. H. Chesterfield, J. F. W. McOmie and M. S. Tute, *ibid.*, 4590 (1960).

(18) M. T. Bogart and D. Davidson, *Proc. Nat. Acad. Sci.*, 18, 215 (1932).

(19) D. Davidson and M. T. Bogart, *ibid.*, 18, 490 (1932).

(20) A. W. Dox, *Org. Syn.*, Coll. Vol. I, 6 (1941). The melting point for anhydrous benzamidine hydrochloride is 168-169°, whereas the dihydrate was reported to melt at 70-73°.

(21) Oxazine ring systems are known to be readily cleaved by Lewis acids. For comparison, 3-benzyl-6-bromo-3,4-dihydro-4*H*-benzo-1,3-oxazine (I), prepared according to the procedure of Kuehne and Konopka (5), also gave a positive ferric chloride test.

(22) Z. Budešinsky, J. Přikryl and E. Svátek, *Coll. Czech. Chem. Commun.*, 29, 2980 (1965).

(23) Biological testing work was carried out by contract screeners of CCNSC of the National Cancer Institute.

(24) All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrophotometer.

Received November 19, 1966 Kansas City, Missouri 64110