[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF LIBERAL ARTS, TEMPLE UNIVERSITY]

The Synthesis and Reactions of Some Imidazo[1,2-a]pyrimidines[1]

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RECEIVED JUNE 29, 1959

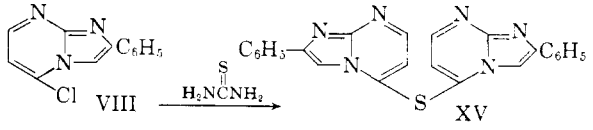
A number of new imidazo[1,2-a]pyrimidines have been prepared in which the 5-position is substituted by hydroxy, chloro and mercapto groups. Comparisons show that replacement of hydrogen by methyl in the 7-position greatly alters the chemical properties of these compounds.

Numerous studies have been made of condensed pyrimidine systems as antagonists of naturally occurring purines. Although many variations of the purine nucleus have been described, relatively little has been reported concerning derivatives of the imidazo[1,2-a]pyrimidines.[2-5] The present paper deals with the preparation and investigation of some imidazo[1,2-a]pyrimidines.

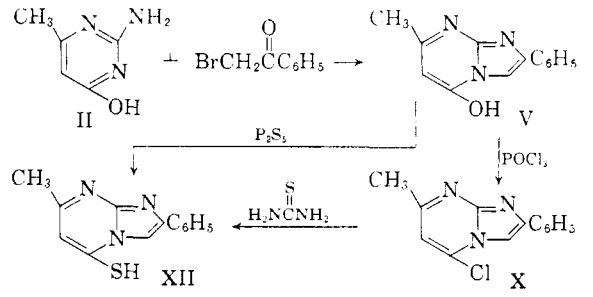
Although the general method[2,4,5] employed to prepare these compounds involved condensation of equimolar quantities of the corresponding 2-aminopyrimidines and phenacyl bromides in alcohol, the reaction was found to proceed more readily using dimethylformamide as solvent and an excess of the pyrimidine. Usually the product precipitated out of the reaction mixture either upon cooling or upon the addition of cold water.

Isocytosine (I) and 2-amino-4-hydroxy-6-methylpyrimidine (II) were condensed with several phenacyl bromides to give the corresponding 5-hydroxyimidazo[1,2-a]pyrimidines (III–VI,XVI). Isocytosine (I) was also condensed successfully with chloroacetone, but the reaction did not proceed readily and 2,7-dimethyl-5-hydroxyimidazo[1,2-a]-pyrimidine (VII) was isolated and purified only with difficulty.

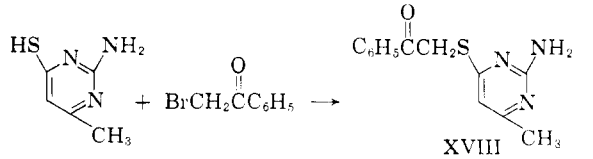
The derivatives obtained from the two series of pyrimidines exhibited a number of marked differences in their physical and chemical properties. The infrared spectra of the 5-hydroxyimidazo-[1,2-a]pyrimidines (III,IV) obtained from isocytosine(I) gave strong carbonyl absorptions, indicating predominance of the keto form (Fig. 1). They were generally more soluble in organic solvents and lower melting than the corresponding hydroxy compounds obtained from 2-amino-4-hydroxy-6-methylpyrimidine (II). Treatment of the 5-hydroxyimidazo[1,2-a]pyrimidines with phosphorus oxychloride gave acid-insoluble, high melting chloro compounds (VIII,IX). An attempt to prepare 2-phenyl-5-chloroimidazo[1,2-a]pyrimidine (VIII) by reaction of phenacyl bromide with 2-amino-4-chloropyrimidine gave only unreacted starting material (*cf.* ref. 5). The action of thiourea on VIII and IX gave alkali-insoluble bis-(5-imidazo[1,2-a]pyrimidyl) sulfides (XIV,XV)[6] which were very high melting and extremely insoluble in organic solvents. Attempts to prepare a mercaptan from 2-*p*-bromophenyl-5-hydroxyimidazo-[1,2-a]pyrimidine (IV) using phosphorus pentasulfide in pyridine or in tetralin gave products which could not be purified.



The infrared spectra of the 5-hydroxy-7-methylimidazo[1,2-a]pyrimidines (V, VI, VII, XVI) obtained from 2-amino-4-hydroxy-6-methylpyrimidine (II) showed moderate carbonyl absorption.



These reacted with phosphorus oxychloride to give acid-soluble chloro derivatives(X, XI) which then reacted with thiourea to give the corresponding alkali-soluble mercaptans (XII, XIII). 2-Phenyl-5 - mercapto - 7 - methylimidazo(1,2 - a)pyrimidine (XII) was also prepared directly rom 2-phenyl - 5 - hydroxy - 7 - methylimidazo(1,2 - a)-pyrimidine (V) by reaction with phosphorus pentasulfide in tetralin. An attempt to prepare XII a third way by the condensation of phenacyl bromide with 2-amino-4-mercapto-6-methylpyrimidine gave instead 2-amino-6-methyl-4-(phenacylthio)-pyrimidine (XVIII).



All of the hydroxyimidazo(1,2-a)pyrimidines, even those containing no halogen, gave a bright green flame when heated on a copper wire.[7]

Since ring closure can take place at either the 1- or 3-nitrogen in the pyrimidine ring to form two different compounds, an investigation was under-

(1) Taken from a part of the thesis submitted by Stanley C. Bell to the Temple University Graduate Council in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) E. Ochiai and K. Yanai, *J. Pharm. Soc. Japan*, **59**, 18 (1939).

(3) A. de Cat and A. van Dormael, *Bull. soc. chim. Belges*, **59**, 573 (1950).

(4) Ng. Ph. Buu-Hoi and Ng. Dat. Xuong, *Compt. rend.*, **243**, 2090 (1956).

(5) T. Matsukawa and S. Ban, *J. Pharm. Soc. Japan*, **71**, 760 (1951).

(6) *Cf.* H. Schmitt and M. Polonovski, *Bull. soc. chim.*, **17**, 417, 616 (1950).

(7) See R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 3rd Edition, 1948, p. 55.

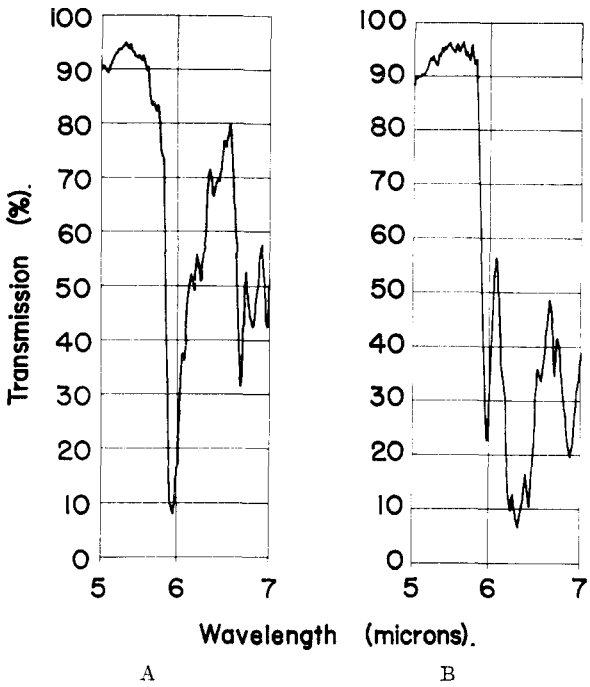
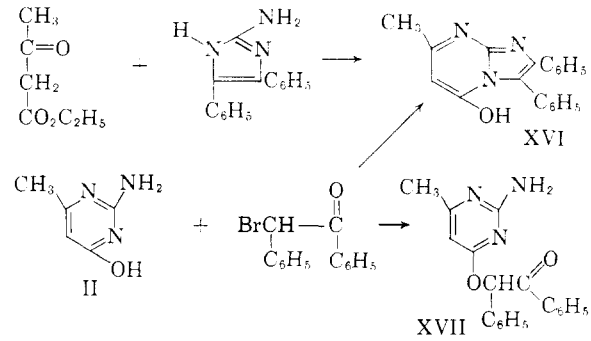


Fig. 1.—A (left), 2-phenyl-5-hydroxyimidazo[1,2-a]pyrimidine; B (right), 2-phenyl-5-hydroxy-7-methylimidazo [1,2-a]pyrimidine. The relative intensities are of such a nature that the presence of a methyl group seems to enhance the relative hetero ring absorption whereas the absence of a methyl group seems to enhance the relative carbonyl absorption.

taken in order to establish the correct structure of the product. Matsukawa and Ban[5] reported that the condensation of 2-amino-4-hydroxy-6-methylpyrimidine (II) with *p*-nitrophenacyl bromide gave 2-*p*-nitrophenyl-5-methyl-7-hydroxyimidazo(1,2-a)-pyrimidine. Other evidence in the literature[8,8a] indicates that similar ring closure results in the formation of 5-hydroxyimidazo(1,2-a)pyrimidines. In an attempt to establish the correct structure, a related compound, 2,3-diphenyl-5-hydroxy-7-methylimidazo(1,2-a)pyrimidine (XVI), was prepared by two routes. De Cat and van Dormael[3] have previously synthesized this compound from the condensation of ethyl acetoacetate and 2-amino-4,5-diphenylimidazole. The main product[9] from the condensation of 2-amino-4-hydroxy-6-methylpyrimidine (II) with 2-bromo-2-phenyl-



acetophenone was compared by mixed melting point and ultraviolet spectrum with the compound prepared by de Cat and found to be the same. It is probable, therefore, that ring closure takes place in the other examples similarly to give the 5-hydroxyimidazo(1,2-a)pyrimidines.

Experimental[10]

2-Phenyl-5-hydroxy-7-methylimidazo(1,2-a)pyrimidine (V).—A mixture of 31.2 g. of 2-amino-4-hydroxy-6-methylpyrimidine (0.25 mole), 20 g. of phenacyl bromide (0.1 mole) and 300 ml. of dimethylformamide, heated on a steam-bath for 1.25 hours with stirring, formed a clear solution. Upon cooling there was obtained 13 g. (61%) of product, m.p. 310–312° dec. Recrystallization from dimethylformamide and then methoxyethanol gave a pure sample, m.p. 315–317° dec.; λ_{max}^{Nujol} 5.98(m), 6.25(s), 6.32(s), 6.45(s).

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.50; H, 4.76; N, 18.89.

2-*p*-Chlorophenyl-5-hydroxy-7-methylimidazo(1,2-a)pyrimidine (VI) was made in the same way as the above compound (56% yield) and recrystallized from 2-methoxyethanol, m.p. 362–364°; λ_{max}^{Nujol} 5.92(m), 6.02(m), 6.23(s), 6.33(s), 6.42(s).

Anal. Calcd. for $C_{13}H_{10}ClN_3O$: C, 60.12; H, 3.88; N, 16.18. Found: C, 60.23; H, 3.89; N, 16.67.

2,7-Dimethyl-5-hydroxyimidazo(1,2-a)pyrimidine (VII) was made in a similar way as the above compound and recrystallized from water, m.p. 275–277°.

Anal. Calcd. for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.75. Found: C, 59.25; H, 6.05; N, 26.25.

2-Phenyl-5-chloro-7-methylimidazo(1,2-a)pyrimidine (X).—A mixture of 3.0 g. of 2-phenyl-5-hydroxy-7-methylimidazo(1,2-a)pyrimidine (V) and 50 ml. of phosphorus oxychloride after refluxing for three hours formed a clear red solution. The phosphorus oxychloride was removed *in vacuo* and the residue dissolved in water. Addition of dilute ammonium hydroxide and filtration of the resultant solid gave a theoretical yield of product. Upon recrystallization from ethyl acetate and then cyclohexane it was obtained as colorless needles, m.p. 173–174°.

Anal. Calcd. for $C_{13}H_{10}ClN_3$: C, 64.07; H, 4.14; N, 17.24. Found: C, 64.31; H, 4.20; N, 17.25.

2-*p*-Chlorophenyl-5-chloro-7-methylimidazo(1,2-a)pyrimidine (XI) was made in the same way as the above compound (72% yield) and recrystallized from isopropyl alcohol, m.p. 185–186.5°.

Anal. Calcd. for $C_{13}H_9Cl_2N_3$: C, 56.13; H, 3.26; N, 15.11. Found: C, 56.44; H, 3.32; N, 15.20.

2-Phenyl-5-mercapto-7-methylimidazo (1,2-a) pyrimidine (XII). Method A.—A mixture of 0.5 g. of 2-phenyl-5-chloro-7-methylimidazo(1,2-a)pyrimidine (X), 0.5 g. of thiourea and 25 ml. of absolute ethanol, upon refluxing for two hours, formed a yellow solution. After cooling, there was collected 0.4 g. (80%) of yellow precipitate, m.p. 253–255° dec. Recrystallization from absolute ethanol gave pale yellow needles, m.p. 255–256° dec.

(8) M. A. Prokof'ev, E. G. Antonovich and Yu P. Shvachkin, *Doklady Akad. Nauk S.S.S.R.*, **87**, 783 (1952); *C. A.*, **48**, 169f (1954). M. A. Prokof'ev and Yu P. Shvachkin, *Zhur. Obshchei Khim.*, **24**, 1046 (1954); *C. A.*, **49**, 9661b (1955); M. A. Prokof'ev, Z. A. Shabrova and E. G. Antonovich, *ibid.*, **25**, 397 (1955); *C. A.*, **49**, 9660c (1955); E. G. Antonovich and M. A. Prokof'ev, *Vestnik Moskov. Univ.*, **10**, No. 3, *Ser. Fiz-Mat. i Estestven Nauk*, **No. 2**, 57 (1955); *C. A.*, **49**, 10972e (1955); M. A. Prokof'ev and Yu P. Shvachkin, *Zhur. Obshchei Khim.*, **25**, 975 (1955); *C. A.*, **50**, 3458 (1956); *Chem. U.S.S.R.*, **25**, 939 (1955), English translation; Yu P. Shvachkin and M. A. Prokof'ev, *ibid.*, **26**, 3416 (1956); *C. A.*, **51**, 9628e (1957).

(8a) After the submission of this paper, there appeared a paper by C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, **24** 779 (1959), discussing the structure of this and related heterocyclic ring systems based on the interpretation of ultraviolet absorption spectra.

(9) Simultaneously a small amount of an alkali-insoluble substance (XVII) was formed, the analysis of which indicated that it was an ether, 2-amino-6-methyl-4-(α-phenylphenacyloxy)-pyrimidine (XVII).

(10) All melting points were taken on a metal block and are uncorrected. Infrared values are given comparing the relative absorptions in the 5–7 μ region of the 2-phenyl-5-hydroxyimidazo(1,2-a)pyrimidines.

Anal. Calcd. for $C_{13}H_{11}N_3S$: C, 64.70; H, 4.59; N, 17.41. Found: C, 64.51; H, 4.90; N, 17.20.

Method B.—One gram of 2-phenyl-5-hydroxy-7-methylimidazo(1,2-a)pyrimidine (V) was treated with phosphorus pentasulfide in tetralin according to the procedure of Cheng and Robins[11] to give 0.85 g. of crude product, m.p. 243–244° dec. Recrystallization from an alcohol–water mixture gave yellow needles, m.p. 253–255° dec., which did not produce a depression in a mixed m.p. with a sample from method A.

2-*p*-Chlorophenyl-5-mercapto-7-methylimidazo(1,2-a)-pyrimidine (XIII) was made in the same way as the above compound (90% yield) and recrystallized from ethanol, m.p. 283–285°.

Anal. Calcd. for $C_{13}H_{10}ClN_3S$: C, 56.62; H, 3.66; N, 15.24. Found: C, 56.92; H, 3.75; N, 15.18.

2-Amino-6-methyl-4-(phenacyltbio)-pyrimidine (XVIII).—An attempt to prepare 2-phenyl-5-mercapto-7-methylimidazo(1,2-a)pyrimidine(XII) in a third way by treating 1.55 g. of 2-amino-4-mercapto-6-methylpyrimidine[12] with phenacyl bromide in dimethylformamide gave instead 1.1 g. of the sulfide. Several recrystallizations from isopropy alcohol gave long white needles, m.p. 151–153°.

Anal. Calcd. for $C_{13}H_{13}N_3OS$: C, 60.21; H, 5.05; N, 16.21. Found: C, 60.39; H, 5.10; N, 16.21.

2-*p*-Bromophenyl-5-hydroxyimidazo(1,2-a)pyrimidine (IV).—A mixture of 11.0 g. of isocytosine (0.1 mole), 11.0 g. of *p*-bromophenacyl bromide (0.04 mole) and 150 ml. of dimethylformamide was refluxed for 0.75 hour, the product precipitated by addition of 250 ml. of cold water and filtered. Purification was accomplished by dissolving the crude solid in 500 ml. of hot 0.3 *N* sodium hydroxide, filtering from insoluble impurities and precipitating the product with dilute acetic acid. There was obtained 7.9 g. (68%) of white solid, m.p. 302–304° dec. Recrystallization from 2-methoxyethanol gave colorless needles, m.p. 303–305° dec.; λ_{max}^{Nujol} 5.95(s), 6.18(w), 6.22(w), 6.29(w).

Anal. Calcd. for $C_{12}H_8BrN_3O$: C, 49.68; H, 2.78; N, 14.49. Found: C, 50.15; H, 2.84; N, 14.74.

2-Phenyl-5-hydroxyimidazo(1,2-a)pyrimidine (III) was made in the same way as the above compound (27% yield) and recrystallized from water–alcohol, m.p. 271–273°; λ_{max}^{Nujol} 5.95(s), 6.19(w), 6.25(w), 6.39(vw).

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.63; H, 4.50; N, 20.60.

2-*p*-Bromophenyl-5-chloroimidazo(1,2-a)pyrimidine (IX).—Two grams of 2-*p*-bromophenyl-5-hydroxyimidazo-(1,2-a) pyrimidine (IV) was refluxed in 50 ml. of phosphorus oxychloride for three hours, the excess phosphorus oxychloride removed *in vacuo* and the viscous residue treated with ice-cold water. The resultant solid was filtered, washed with dilute sodium hydroxide solution and then water giving a theoretical yield of impure product. Several recrystallizations from 2-methoxyethanol gave an analytically pure sample, m.p. 320° dec.

Anal. Calcd. for $C_{12}H_7BrClN_3$: C, 46.71; H, 2.29; N, 13.62. Found: C, 46.97; H, 2.56; N, 13.66.

2-Phenyl-5-chloroimidazo(1,2-a)pyrimidine (VIII) was made in the same way as the above compound (91% yield) and recrystallized from 2-methoxyethanol, m.p. 261–262°.

Anal. Calcd. for $C_{12}H_8ClN_3$: C, 62.75; H, 3.51; N, 18.30. Found: C, 63.13; H, 3.59; N, 18.74.

Bis-(2-*p*-bromophenyl-5-imidazo(1,2-a)pyrimidyl) Sulfide (XIV).—A suspension of 0.5 g. of 2-*p*-bromophenyl-5-chloroimidazo(1,2-a)pyrimidine (IX) in a solution of 0.5 g. of thiourea and 200 ml. of alcohol was refluxed for 14 hours. There was filtered off 0.35 g. (74%) of a yellow alkali-insoluble product, m.p. > 380°. This compound was very insoluble in the common organic solvents and could only be recrystallized from a large volume of dimethylformamide.

Anal. Calcd. for $C_{24}H_{14}Br_2N_6S$: C, 49.84; H, 2.44; N, 14.53. Found: C, 49.87; H, 2.53; N, 14.26.

Bis-(2-phenyl-5-imidazo(1,2-a)pyrimidyl) sulfide (XV) was prepared in a way similar to that used for obtaining the above (XIV) compound, m.p. 319–321° dec.

Anal. Calcd. for $C_{24}H_{16}N_6S$: C, 68.55; H, 3.84; N, 19.99. Found: C, 68.61; H, 3.97; N, 19.81.

2,3-Diphenyl-5-hydroxy-7-methylimidazo(1,2-a)pyrimidine (XVI). Method A.—The condensation of 2-amino-4,5-diphenylimidazole with ethyl acetoacetate according to the procedure of de Cat and van Dormael[3] was modified as follows: A solution of 0.4 g. of the amine, 1.5 ml. of the ester and 5 ml. of glacial acetic acid was refluxed for 2 hours and, upon cooling, 0.15 g. of colorless crystals was obtained, m.p. 293–295° dec. (lit.[3] 309°); ultraviolet absorption; $\lambda_{max}^{C_2H_5OH}$ 210,240, 314 mμ.

Method B.—A mixture of 2.75 of 2-bromo-2-phenylacetophenone, 3.2 g. of 2-amino-4-hydroxy-6-methylpyrimidine and 50 ml. of dimethylformamide was heated on the steam-bath for two hours after which the solvent was removed *in vacuo* and the residue triturated with acetone. Evaporation of the acetone and washing with ethanol left 1.3 g. of colorless solid, m.p. 173–185°. This solid was treated with dilute sodium hydroxide and the solution filtered from insoluble material, m.p. 192–194°. Acidification of the alkaline filtrate gave a high melting solid which was recrystallized from ethanol, m.p. 295–297°; λ_{max}^{Nujol} 5.96(m), 6.02(w), 6.15(s) 6.28(s), 6.32(s); ultraviolet absorption; $\lambda_{max}^{C_2H_5OH}$ 210, 240 (20,000), 313 mμ.

Anal. Calcd. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02. Found: C, 75.42; H, 5.10.

A mixed melting point with the product from method A gave no depression and the ultraviolet absorption spectra were the same.

2-Amino-6-methyl-4-(α-phenylphenacycloxy)-pyrimidine (XVII).—The alkali-insoluble fraction from method B was recrystallized from ethanol, m.p. 193–195°. The analysis indicated that it is an oxide.

Anal. Calcd. for $C_{19}H_{17}N_3O_2$: C, 71.45; H, 5.37; N, 13.16. Found: C, 71.13; H, 5.46; N, 13.16.

Acknowledgment.—The authors wish to thank K. B. Streeter and staff of Merck Sharp and Dohme Research Laboratories for the elemental analyses and Eli Lilly & Co. for pharmacological tests in which no significant activity was found. They also thank Temple University for a Grant-in-Aid, and Dr. E. Howard, Jr., and H. White for the infrared analyses.

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(11) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **23**, 196 (1958).

(12) S. Gabriel and J. Coleman, *Ber.*, **32**, 2926 (1899).