Hydrolysis of Pyrimidine N-Oxides to Give Isoxazole Derivatives

TETSUZO KATO, HIROSHI YAMANAKA, AND NAKO YASUDA

Pharmaceutical Institute, Tohoku University School of Medicine, Kita-4, Sendai, Japan

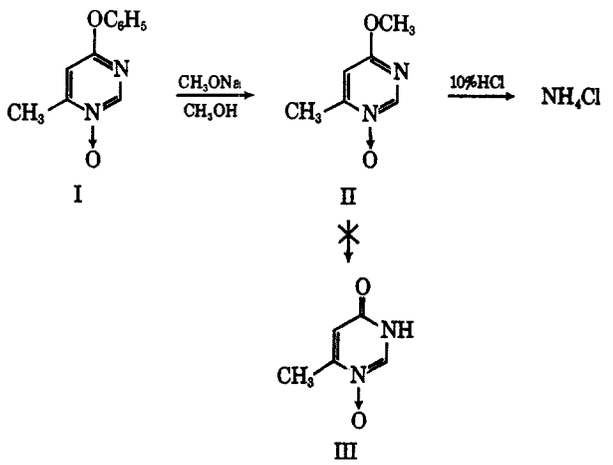
Received May 31, 1967

Refluxing of 4-phenylpyrimidine 1-oxide (IV) in an excess of 10% hydrochloric acid gives 5-phenylisoxazole (V) in good yield. When V is treated with methanolic sodium hydroxide, benzoylacetonitrile (VI) is obtained in 85% yield. Similarly, 4,6-dimethylpyrimidine 1-oxide (VII) and 6-methyl-4-phenylpyrimidine 1-oxide (VIII) are hydrolyzed in an acidic medium to give 3,5-dimethylisoxazole (IX) and 3-methyl-5-phenylisoxazole (X), respectively. However, 4-methoxy-6-methylpyrimidine 1-oxide (II) does not afford the isoxazole derivative; instead, decomposition occurs to give ammonia, acetone, and formic acid.

It has been shown that pyrimidine N-oxides are relatively stable toward alkaline hydrolysis but unstable toward acidic hydrolysis. For instance,[1] 4-phenoxy-6-methylpyrimidine 1-oxide (I) reacts readily with nucleophilic reagents such as sodium methoxide to give the 4-methoxy derivative (II) in good yield, but treatment of 4-methoxy-6-methylpyrimidine 1-oxide (II) with 10% hydrochloric acid does not afford 6-methyl-4-pyrimidone 1-oxide (III); instead decomposition occurs to give ammonium chloride.

In the present paper we report the acidic hydrolysis of several pyrimidine N-oxide homologs, which was found to induce ring contraction to isoxazole derivatives (Chart I).

CHART I

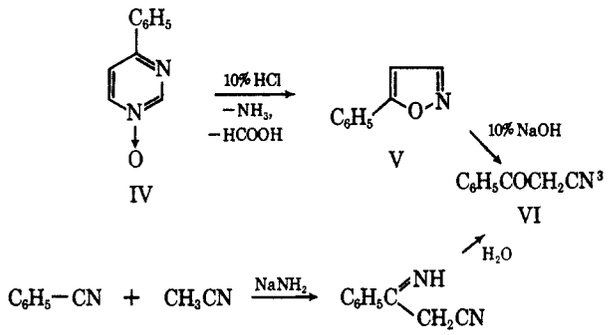


Refluxing of 4-phenylpyrimidine 1-oxide (IV) in an excess of 10% hydrochloric acid afforded a colorless oil, bp 131° (17 mm), C_9H_7ON (V), in 80% yield, together with ammonium chloride and formic acid. This oil has been unambiguously characterized as 5-phenylisoxazole (V) on the basis of elemental analysis and infrared and nmr data.

Quilico[2] has reported that 5-alkyl- or -arylisoxazole reacts with alkali to give the ring-opened product, acylacetonitrile. According to the Italian worker, treatment of V with methanolic sodium hydroxide gave colorless leaves, mp 80.5–81.5°, C_9H_7ON (VI), in 85% yield. The infrared spectrum of this compound exhibited characteristic nitrile and carbonyl peaks at 2273 and 1695 cm^{-1}, respectively.

The data described above suggested that the product VI was benzoylacetonitrile. This was conclusively proved by a mixture melting point test with an authentic sample of VI prepared from benzonitrile and acetonitrile according to the method of Dornow, *et al.*[3] (Chart II).

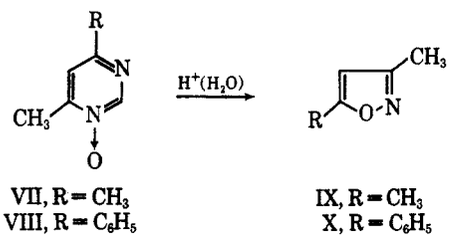
CHART II



Similarly, 4,6-dimethylpyrimidine 1-oxide (VII) and 6-methyl-4-phenylpyrimidine 1-oxide (VIII) were hydrolyzed in an acidic medium to give 3,5-dimethylisoxazole (IX) and 3-methyl-5-phenylisoxazole (X), respectively. However, as described above 4-methoxy-6-methylpyrimidine 1-oxide (II) was transformed into ammonia, acetone, and formic acid.

On the other hand, alkaline hydrolysis of IV gave mainly the starting material together with a small amount of benzoylacetonitrile (VI) (Chart III).

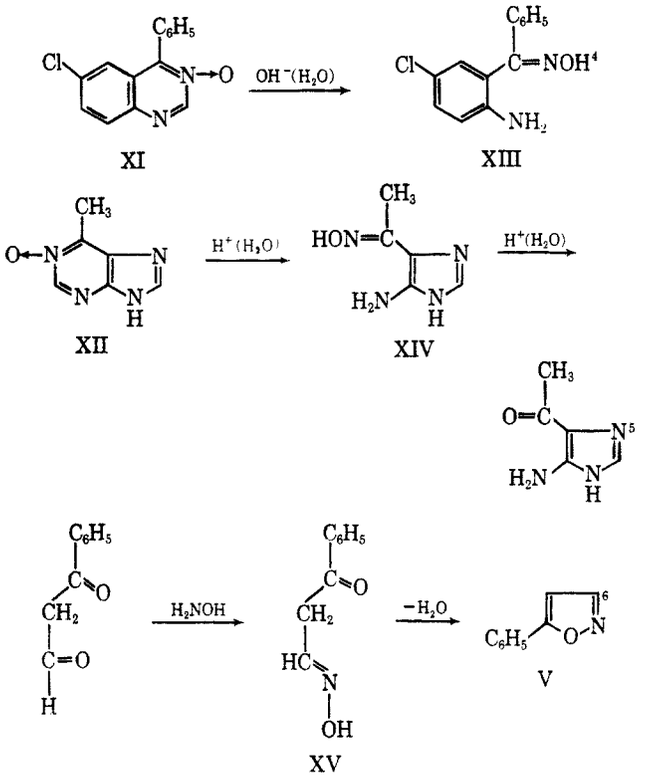
CHART III



Concerning this ring rearrangement reaction, Sternbach[4] and Stevens[5] reported that hydrolysis of 6-chloro-4-phenylquinazoline 3-oxide (XI) and purine N-oxide (XII) afforded the ring-opened products (XIII and XIV) as shown in Chart IV. Both reactions show that position 2 of the pyrimidine ring is active toward nucleophiles and that the next stage might well involve fission at this position. On the other hand, Claisen[6] reported the synthesis of 5-phenylisoxazole (V) from benzoylacetaldehyde oxime (XV).

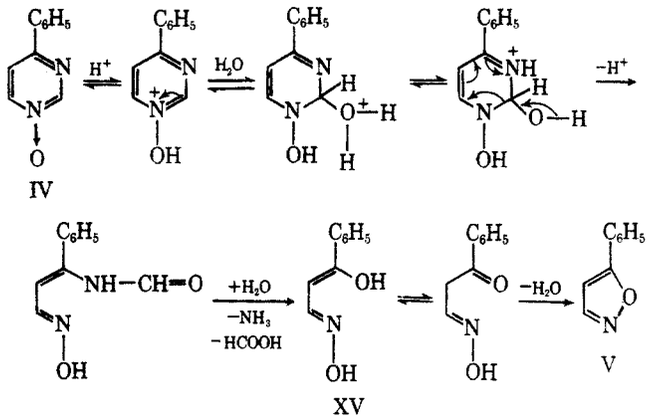
(1) H. Yamanaka, *Chem. Pharm. Bull.* (Tokyo), **7**, 505 (1959).
(2) A. Quilico, *Atti Accad. Naz. Lincei, Rend. Classe Sci. Fis., Mat. Nat.*, **15**, 357 (1953); *Chem. Abstr.*, **49**, 6228 (1955).
(3) A. Dornow and K. Peterlein, *Ber.*, **82**, 254 (1949).
(4) L. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).
(5) M. Stevens, H. Smith, and G. Brown, *J. Am. Chem. Soc.*, **81**, 1734 (1959).
(6) L. Claisen, *Ber.*, **24**, 131, 134, (1891).

CHART IV



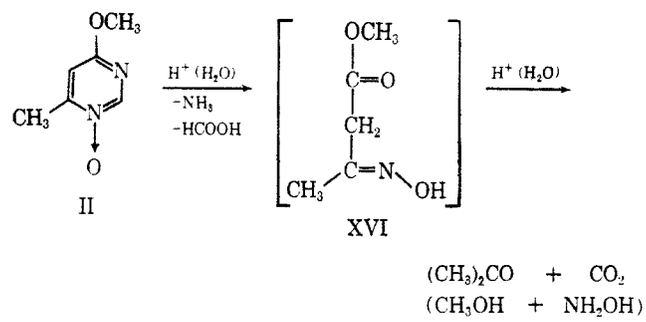
A likely pathway of this reaction based on these observations is shown in Chart V.

CHART V



This mechanism also accounts for the reason that 4-methoxy-6-methylpyrimidine 1-oxide (II) affords neither the 4-hydroxy derivative (III) nor the isoxazole derivative. As shown in Chart VI, the intermediate of this reaction would be methyl acetoacetate oxime (XVI), which decomposes easily upon acidic hydrolysis giving acetone, methanol, carbon dioxide, and hydroxylamine.

CHART VI



Experimental Section

Hydrolysis of 4-Phenylpyrimidine 1-Oxide (IV).[7] **A. With 10% Hydrochloric Acid.**—4-Phenylpyrimidine 1-oxide (IV) (1.5 g) was added to 15 ml of 10% hydrochloric acid. The reaction mixture was refluxed for 5 hr, during which time an oil separated. After neutralization with sodium carbonate, the oil was extracted with ether. The ether layer was dried over potassium carbonate, filtered, and concentrated. The residue was distilled under reduced pressure to give a colorless oil: bp 131° (17 mm); yield, 1 g (80%).

Anal. Calcd for C_9H_7ON (V): C, 74.47; H, 4.86; N, 9.65. Found: C, 74.81; H, 5.00; N, 9.26.

Infrared and ultraviolet data are, respectively, λ_{max}^{liq} 3145, 3067, 1681, and 763 cm^{-1} and λ_{max}^{EtOH} 262 mμ (log ϵ 4.30). The nmr spectrum ($CDCl_3$) showed peaks at 1.75 (1 H, isoxazole ring proton, doublet, J = 3.5 cps), 3.53 (1 H, isoxazole ring proton, doublet, J = 3.5 cps), and 2.1–2.7 ppm (5 H, benzene ring proton, multiplet).

From the ether-insoluble fraction, 0.2 g (13%) of IV was recovered.

To a part of the ether-insoluble layer, 40% sodium hydroxide was added to evolve gas, which was identified as ammonia by its odor and the Nessler reagent. Formic acid was identified by acidification of a part of the water-insoluble layer with hydrochloric acid, and the subsequent addition of tin metal. When reduction was completed, chromotropic acid–sulfuric acid was added and warmed, and blue coloration appeared.

B. With Alkali.—A solution of 4-phenylpyrimidine 1-oxide (IV) (1.57 g), sodium hydroxide (0.46 g), and 50% methanol (10 ml) was refluxed. After 7 hr, the reaction mixture was neutralized (pH 7–8) with dilute hydrochloric acid, and was concentrated under reduced pressure. The residue was washed with ether and then with chloroform. The chloroform washing was purified by passing it through an alumina column, and was concentrated to give a crystalline residue, later purified by recrystallization from benzene–petroleum ether (bp 60–80°) to yield 1.25 g (80%) of the starting material (IV), mp 150–151°. The ether washing was dried (anhydrous sodium sulfate), filtered, and condensed to give a pale brown crystalline solid, which was purified by recrystallization from petroleum ether giving colorless leaves: mp 80–81° (undepressed on admixture with an authentic sample[8] of benzoylacetonitrile (VI)); yield, 0.1 g (8%).

Anal. Calcd for C_9H_7ON (VI): C, 74.47; H, 4.86; N, 9.65. Found: C, 74.40; H, 4.93; N, 9.41.

Infrared data gave λ_{max}^{KBr} 2273 (CN st) and 1695 cm^{-1} (CO st).

Hydrolysis of 5-Phenylisoxazole (V) with Alkali.—A mixture of V (0.6 g), sodium hydroxide (0.2 g), and 50% methanol (10 ml) was heated in a water bath. After 3 hr, the reaction mixture was condensed under reduced pressure to give a residue, to which 10% hydrochloric acid (5 ml) was added and extracted with ether. The ether layer was dried (anhydrous sodium sulfate), filtered, and evaporated to give a white crystalline substance. Recrystallization from petroleum ether gave colorless leaves: mp 80.5–81.5° (undepressed on admixture with an authentic sample[8] of benzoylacetonitrile (VI)); yield, 0.51 g (85%).

Hydrolysis of 4,6-Dimethylpyrimidine 1-Oxide[6] (VII) with Sulfuric Acid.—4,6-Dimethylpyrimidine 1-oxide (VII) (2.5 g) was dissolved in 20% sulfuric acid (30 ml), and the solution was refluxed for 7 hr. After being neutralized with sodium carbonate, the solution was extracted with ether and then with chloroform. The ether layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give an oil, which was purified by distillation to afford a colorless oil, bp 141°, whose infrared spectrum was identical in every respect with that of an authentic sample[9] of 3,5-dimethylisoxazole (IX); yield, 1.3 g (67%). From the chloroform extract 0.3 g (12%) of starting N-oxide (VII) was recovered.

(7) T. Kato, H. Yamanaka, and T. Shibata, Yakugaku Zasshi, **87**, No. 9 (1967) in press.

(8) R. Hunt, J. McOmie, and E. Sayer, *J. Chem. Soc.*, 525 (1959).

(9) G. Morgan and H. Burges, *ibid.*, **119**, 697 (1921).

Hydrolysis of 6-Methyl-4-phenylpyrimidine 1-Oxide (VIII)[10] with Sulfuric Acid.—A solution of 6-methyl-4-phenylpyrimidine 1-oxide (VIII) (1.9 g) in 30% sulfuric acid (15 ml) was refluxed for 7 hr. In a fashion similar to the above, the reaction mixture was treated with ether and chloroform. From the ether fraction 0.5 g (30%) of 3-methyl-5-phenylisoxazole (X)[11] was obtained, bp 152° (19 mm), mp 67–68° (lit. 67–68°). From the chloroform extract, 1.1 g (58%) of the starting material (VIII) was recovered.

Hydrolysis of 6-Methyl-4-methoxypyrimidine 1-Oxide (II)[12] with Hydrochloric Acid.—A solution of II (1.4 g) in 10% hydrochloric acid (20 ml) was refluxed for 1 hr, during which time carbon dioxide was identified as barium carbonate by passing the gas evolved from the top of the refluxing condenser to a barium hydroxide solution.

A part of the reaction mixture was treated with tin, and then chromotropic acid–sulfuric acid was added, and on warming in a water bath blue coloration appeared (formic acid positive).

Another part of the reaction mixture was distilled, and 2,4-dinitrophenylhydrazine was added to the distillate, giving orange crystals. Recrystallization from methanol afforded orange leaves, mp 128° (undepressed on admixture with an authentic sample of acetone 2,4-dinitrophenylhydrazone). The residue was identified as ammonium chloride.

Registry No.—IV, 14161-40-1; V, 1006-67-3; VII, 14161-42-3; VIII, 14161-43-4.

Acknowledgment.—We wish to express our sincere appreciation to Miss. A. Sato, N. Nanjo, R. Oikawa, and Y. Tadano of the Analytical Laboratories, of this institute, for the microanalyses and infrared and nmr spectral measurements.

(10) H. Bredereck, R. Gompper, and H. Herlinger, *Chem. Ber.*, **91**, 2832 (1958).
(11) L. Claisen, *ibid.*, **59**, 194 (1926).
(12) E. Ochiai and H. Yamanaka, *Pharm. Bull.* (Tokyo) **3**, 173 (1955).

Synthesis of 5-Hydroxyalkylpyrimidines from Lactones. III. 5-Dihydroxycyclopentylpyrimidines[1]

JOHN D. FISSEKIS AND BARBARA MARKERT CREEGAN

Division of Biological Chemistry, Sloan-Kettering Division, Graduate School of Medical Sciences, Cornell University Medical College, New York, New York 10021

Received May 3, 1967

Syntheses of several 5-(*trans*-2′,3′-dihydroxycyclopentyl)pyrimidines, including those of uracil and cytosine, are described. From the α-hydroxymethylene(*trans*-2-hydroxy-3-methoxycyclopentyl)acetic acid γ-*cis*-lactone, 4-hydroxy-5-(*trans*-2′-hydroxy-3-methoxycyclopentyl)-2-mercaptopyrimidine (**13**), 2,4-dihydroxy-5-(*trans*-2′,3′-dihydroxycyclopentyl)pyrimidine (**14**), and 2,4-dihydroxy-5-(*trans*-2′,3′-dihydroxycyclopentyl)-3-methylpyrimidine (**15**) were prepared. The cytosine analog 4-amino-2-hydroxy-5-(*trans*-2′,3′-dihydroxycyclopentyl)pyrimidine (**19**) was synthesized from **14** *via* acetylation and thiation of the 4 position. Evidence is presented that intramolecular hydrogen bonding occurs in 5-hydroxyalkyluracils.

The ultraviolet spectral shifts in the high alkaline region (pH 12–14) have been proposed as evidence for significant intramolecular hydrogen bonding in pyrimidine derivatives. However, a study of such shifts in 5-(2-hydroxyethyl)uracil (**29**)[2] and of 5-(2-hydroxycyclopentyl)uracil (**31**)[3] has raised certain questions regarding this interpretation. Such changes in the spectrum of N-1-glycosylpyrimidines[4,5] were regarded to involve primarily, a C′-2 hydroxyl to C-2 carbonyl hydrogen bond which is broken by ionization of the sugar alcohol at pH 12–14. By analogy it was postulated[6] that 5-hydroxyalkylpyrimidines such as 5-hydroxymethyluracil and the pseudouridine C isomer have a hydrogen bond between the 5-hydroxyalkyl side chain or the 5′-hydroxymethyl group of the 5-ribosyl moiety and the C-4 carbonyl. A ratio, at pH 12, of the absorption at 280 mμ to that at 260 mμ of 1.8 or higher was proposed[6] as the criterion for the presence of the latter hydrogen bond. Compounds such as 5-methoxy-, ethoxy-, and *n*-butoxymethyluracil[7] still show the high ratio proposed as characteristic of the presence of the hydrogen bond whereas 2′-O-methylpseudouridine[8] shows a low ratio. In the former three the hydrogen bond is blocked, although in the latter the 5′-hydroxymethyl group is still available for hydrogen-bond formation. Both the A_S (β-ribopyranosyl) and A_F (α-ribopyranosyl) isomers of pseudouridine are capable of forming a hydrogen bond between the C-4 carbonyl and the C′-3 hydroxyl; yet they show $A_{280}:A_{260}$ ratios of 2.1[9] and 1.4.[6] No interpretation has been offered for that difference.

The recent results of Asbun and Binkley[10] are of interest. The high ratio (*ca.* 2.22) exhibited by the 5-β-D-xylofuranosyluracil (xylo analog of pseudouridine C) is in agreement with the proposed hydrogen-bond theory. The low ratios (1.46 and 1.68) shown by the other two analogs, *i.e.*, 5-α-D-arabinitol- and 5-α-D-ribitoluracil are more difficult to interpret. In these compounds, regardless of the anomeric configuration of the C-5,C′-1 bond, there are several possibilities of hydrogen bonding to the C-4 carbonyl. Also the electromeric effect of the side chain should be similar to that of the CH_2OH in 5-hydroxymethyluracil as both these compounds are substituted derivatives of the latter. Of course, extensive intramolecular bonding among the hydroxyls might restrict the side chain to a conformation prohibiting any bonding to the C-4 carbonyl.

(1) This investigation was supported in part by funds from the Maude K. Irving Memorial Grant for Cancer Research from the American Cancer Society and National Cancer Institute, National Institutes of Health, U. S. Public Health Service Research Grant No. CA 08748.
(2) J. D. Fissekis, A. Myles, and G. B. Brown, *J. Org. Chem.*, **29**, 2670 (1964).
(3) J. D. Fissekis and B. A. Markert, *ibid.*, **31**, 2945 (1966).
(4) J. J. Fox, L. F. Cavalieri, and N. Chang, *J. Am. Chem. Soc.*, **75**, 4315 (1953).
(5) J. J. Fox, J. F. Codington, N. Chang Yung, L. Kaplan, and J. O. Lampen, *ibid.*, **80**, 5155 (1958).
(6) R. W. Chambers, V. Kurkov, and R. Shapiro, *Biochemistry*, **2**, 1192 (1963).
(7) R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959).
(8) R. H. Hall, *Biochemistry*, **3**, 876 (1964).
(9) R. W. Chambers, *Progr. Nucleic Acid Res. Mol. Biol.*, **5**, 377 (1966).
(10) W. Asbun and S. B. Binkley, *J. Org. Chem.*, **31**, 2215 (1966).