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SYNTHESIS OF 2-AMINO-6-PHENYL-4(3H)-PYRIMIDINONE-1-OXIDE

Wendell Wierenga*, Harvey I. Skulnick,
Robert L. Dow, and Constance G. Chidester

Experimental Chemistry Research,
Physical and Analytical Chemistry Research,
The Upjohn Company
Kalamazoo, Michigan 49001

Introduction of a 2,4-dichlorophenoxy group at the 4-position of 2-amino-6-phenylpyrimidine allowed a regioselective oxidation to the N_1-oxide. The resultant pyrimidine oxide, derived from m-chloroperoxybenzoic acid treatment, was converted to the pyrimidinone by acidic hydrolysis. The structure was unambiguously determined by x-ray crystallographic analysis.

We have recently described the synthesis and preliminary antiviral/interferon inducing activities of a series of 2-amino-5-halo-6-aryl-4(3H)-pyrimidinones.[1,2] Our interest in these compounds extended to possible metabolites as potential bioactive analogs. The demonstration that one of several metabolites from rat appeared to be an N-oxide[3] prompted our attempt to synthesize one of the putative metabolites.

Direct oxidation of pyrimidines to N-oxides with percarboxylic acids or hydrogen peroxide is a well known process.[4] However, certain 2-aminopyrimidines prove unreactive when treated with these oxidants.[5-7] For example, 2,6-diamino-4(3H)-pyrimidinone undergoes ring-carbon oxidation followed by rearrangement to 6-amino-s-triazine-2,4(1H,3H)-dione.[5a,6] When we treated 2-amino-6-phenyl-4(3H)-pyrimidinone (1) with a variety of oxidants (H_2O_2, CH_3CO_3H, $PhCO_3H$, $(PhCO_2)_2O$) the only product isolated was the rather labile 5-hydroxypyrimidone, 7.[14] Since the nature of the pyrimidine ring substituents appears to exert significant control over the site-selectivity of oxidation,[5b,7] we chose to convert 1 to the corresponding 2-amino-4-(2,4-dichlorophenoxy) pyrimidine and examine its oxidation. This specific choice was based on an earlier finding by Ursprung and Anthony that the corresponding 6-methylpyrimidine afforded the N_1-oxide.[9] In fact, earlier work[10] had demonstrated that oxidation of 2-ethoxyquinoxaline afforded 3-ethoxyquinoxaline-1-oxide, the first demonstration of preference for the *nitrogen more remote from the alkoxy* group.

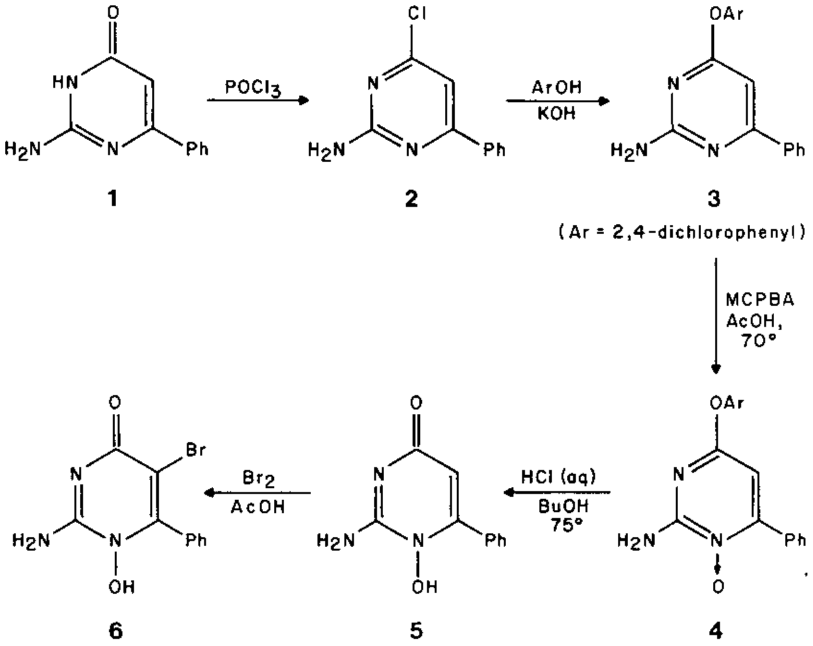
2-Amino-6-phenyl-4(3H)-pyrimidinone (1) was converted to the 4-chloropyrimidine, 2,[13,16] and subsequently treated with 2,4-dichlorophenol and potassium hydroxide to give crystalline 3 in 77% isolated yield. Oxidation of the 4-aryloxypyrimidine was examined under several conditions and ultimately proceeded best with m-chloroperoxybenzoic acid in acetic acid at elevated temperatures. This procedure gave only one N-oxide (4; 44% yield). After attempted hydrolysis of the aryloxy group with aqueous sodium hydroxide (165°)[9] gave the pyrimidinone in only 36% yield, we found that acid hydrolysis in butanol proceeded smoothly at 75° to afford 5 in 90% yield. Lastly, bromination in acetic acid gave the desired 6 in 80% yield.[2]

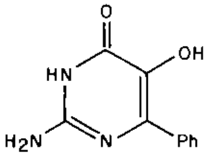
The question of site of oxidation was as yet undetermined. The N-oxide derived from the oxidation of 4-ethoxy-6-phenylpyrimidine, as reported by Kato, et al.,[11] was presumed to be the N_1-oxide. While cognizance of this and the previously cited work[15] strongly suggests isomer 4, direct evidence was lacking. Examination of the relevant ^{13}C-nmr spectra of 2-6 and related pyrimidines (see Experimental) failed to unambiguously support one particular regioisomer.[13]

The structure of 6 was ultimately derived from a single crystal x-ray study. The details are given in the experimental section. Final atomic parameters and standard deviations are listed in Table I. Figure 1 shows bond distances, angles and numbering. Hydrogen distances and angles are not shown, but all bond lengths were in the range 0.77(3)Å (for the water hydrogen) to 0.95(3)Å. Table II lists the complicated hydrogen bonding scheme; the hydroxyl and water oxygens act as both donors and acceptors; the carbonyl oxygen accepts two hydrogens and the NH_2 nitrogen donates both hydrogens.

A least-squares plane was calculated through the pyrimidine ring atoms and substituents, excluding the phenyl group, O(1), and hydrogens. O(1) is 0.09Å out of this plane, and C(7) is 0.14Å out on the opposite side of the plane.

Theissen, Levy and Flaig[21] in their neutron diffraction study of hydroxyurea (8 in figure 2) observed similar bond lengths (the hydrogen-bonding scheme is also similar). In hydroxyurea, the N-OH, C=O, and C-NH_2 bond distances were 1.390(1)Å, 1.255(1)Å and 1.328(1)Å. These values are in good agreement with N-OH, C=O, and C-NH_2 distances of 1.394(1)Å, 1.259(1)Å, and 1.319(1)Å in 6 (figure 2). Theissen, Levy and Flaig[21] also reported the structure of 3-hydroxyxanthine (9 in





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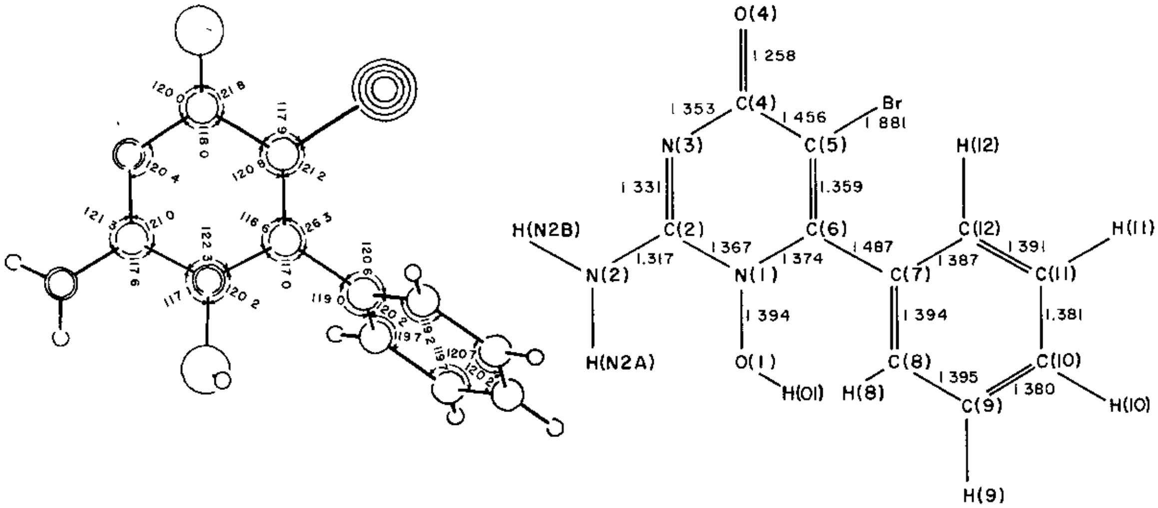
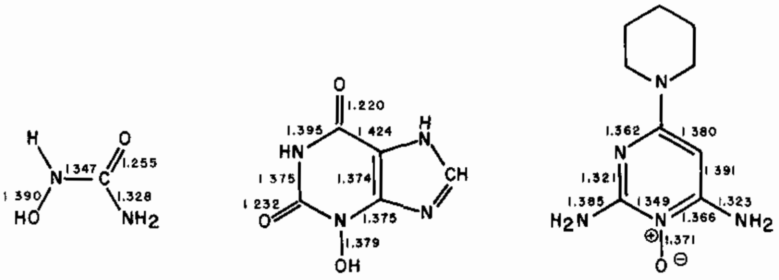


Figure 1

Numbering and bond distances and angles for 6. Standard deviations are 0.002-0.004Å for bond lengths and 0.1-0.2° for bond angles.



8
hydroxyurea

9
3-hydroxyxanthine

10
minoxidil

Figure 2

Table I

Final atomic coordinates and anisotropic thermal parameters of heavier atoms (x 10^4) for 6. Final hydrogen coordinates (x 10^3).

The form of the anisotropic temperature factors is $\exp(-B_{11}h^2-B_{22}k^2-B_{33}l^2-B_{12}hk-B_{13}hl-B_{23}kl)$.

	X	Y	Z	B11	B22	B33	B12	B13	B23
BR	3593 (1)	8023 (1)	4631 (1)	3 (1)	117 (1)	16 (1)	14 (1)	-1 (1)	-3 (1)
N(1)	4155 (1)	2385 (4)	3167 (2)	3 (1)	74 (9)	10 (1)	-0 (2)	-3 (1)	-4 (5)
O(1)	4093 (1)	1052 (4)	2220 (1)	4 (1)	80 (7)	9 (1)	-5 (2)	-2 (1)	-10 (4)
C(2)	4489 (1)	1685 (5)	3920 (2)	2 (1)	103(11)	13 (1)	-3 (2)	-1 (1)	18 (5)
N(2)	4731 (1)	-166 (5)	3686 (2)	4 (1)	129(10)	16 (1)	19 (2)	-6 (1)	-22 (5)
N(3)	4566 (1)	2839 (4)	4853 (2)	2 (1)	114 (9)	12 (1)	8 (2)	-2 (1)	1 (5)
C(4)	4326 (1)	4790 (5)	5061 (2)	2 (1)	125(11)	12 (1)	-0 (2)	1 (1)	10 (6)
O(4)	4418 (1)	5943 (4)	5919 (1)	3 (1)	149 (8)	12 (1)	11 (2)	-5 (1)	-28 (4)
C(5)	3953 (1)	5445 (5)	4287 (2)	2 (1)	75(10)	17 (1)	8 (2)	1 (1)	8 (6)
C(6)	3863 (1)	4188 (5)	3360 (2)	2 (1)	68(10)	14 (1)	-0 (2)	0 (1)	19 (5)
C(7)	3471 (1)	4530 (5)	2553 (2)	2 (1)	107(11)	12 (1)	6 (2)	-1 (1)	-8 (6)
C(8)	3129 (1)	2847 (6)	2477 (2)	3 (1)	113(11)	18 (2)	-1 (2)	-2 (1)	22 (6)
C(9)	2757 (1)	3150 (6)	1730 (2)	3 (1)	137(12)	27 (2)	-3 (3)	-2 (1)	-10 (7)
C(10)	2735 (1)	5094 (6)	1058 (2)	3 (1)	170(12)	21 (2)	12 (3)	-3 (1)	2 (7)
C(11)	3076 (1)	6756 (6)	1136 (2)	6 (1)	114(12)	25 (2)	11 (3)	-7 (1)	41 (7)
C(12)	3447 (1)	6488 (5)	1881 (2)	4 (1)	103(12)	24 (2)	-11 (3)	-4 (1)	11 (6)
O(S)	0	1015 (6)	2500	8 (1)	114(11)	22 (2)	0	-12 (1)	0

	X	Y	Z
H(O1)	418 (1)	196 (6)	176 (3)
H(N2A)	467 (1)	-102 (6)	314 (3)
H(N2B)	492 (1)	-73 (6)	412 (2)
H(8)	315 (1)	154 (6)	291 (3)
H(9)	253 (1)	199 (6)	170 (3)

	X	Y	Z
H(10)	249 (1)	528 (6)	57 (2)
H(11)	306 (1)	806 (6)	66 (3)
H(12)	368 (1)	753 (6)	193 (3)
H(OS)	-13 (1)	25 (5)	206 (2)

Table II

Hydrogen bond parameters and standard deviations for 6.

D-H----A	D-A,(Å)	H-A,(Å)	DHA angle (°)	Symmetry of Acceptor
O(1)-H(O1)----O(4)	2.579(3)	1.76(3)	122(2)	x, 1-6, z-1/2
N(2)-H(N2B)----N(3)	3.060(3)	2.26(3)	169(2)	1-x, -y, 1-z
N(2)-H(N2A)----O(S)	2.769(4)	2.13(3)	133(2)	1/2-x, y±1/2, 1/2-z
N(2)-H(N2A)----O(1)	2.616(3)	2.31(3)	102(2)	internal, fixed by geometry of molecule
O(S)-H(OS)----O(4)	2.746(2)	1.99(3)	164(2)	x±1/2, 1/2-y, z±1/2

figure 2) by x-ray diffraction and found the N-OH bond length for a hydrogen bonded hydroxyl oxygen to be 1.379(1) Å.

It is interesting to compare bond lengths around the pyrimidine ring in 6 with ring distances found in minoxidil (Loniten®) hemi-hydrochloride,[22] which has different substituents (10 in figure 2). Evidently electron density in the pyrimidine ring of minoxidil is much more delocalized. C-C bond lengths in the minoxidil ring are 1.391(2) Å and 1.380(2) Å; in contrast, the C-C bonds for 6 (see figure 1) are 1.456(3) Å and 1.359(3) Å, much more like single and double bonds.

Experimental:

2-Amino-4-(2',4'-dichlorophenoxy)-6-phenylpyrimidine (3). To 70.0 g (0.34 mole) of 2 under N_2 was added 272.2 g (1.67 mole) of 2,4-dichlorophenol and 21.3 g (0.38 mole) of potassium hydroxide. After stirring at 85° for 36 h the mixture was added to 2,500 ml of 2N KOH. After cooling, the resulting solid was taken up in 1500 ml of ethyl acetate (EtOAc). The organic solution was washed with 2 x 300 ml of H_2O, dried over Na_2SO_4, and concentrated to a gray solid. Recrystallization from acetone/hexane afforded 86.5 g (77%) of 3, mp 147.5-148.5°. Calc'd for $C_{16}H_{11}N_3OCl_2$: C, 57.85, H, 3.34, N, 12.65; Found: C, 57.93, H, 3.34, N, 12.61. ^{1}H-nmr (DMSO): 8.0-7.8 (m, 2H), 7.55-7.35 (m, 4H), 7.3-7.15 (m, 2H), 6.65 (s, 1H), 5.1 (2H, br. s); ^{13}C-nmr (DMSO): 169.96 (C_4), 166.44 (C_6), 163.32 (C_2), 91.35 (C_5).[12]

2-Amino-4-(2',4'-dichlorophenoxy)-6-phenylpyrimidine-1-oxide, (4). To 8.3 g (25 mmole) of 3 in 50 ml of acetic acid was added 12.9 g (75 mmole) of m-chloroperoxybenzoic acid and stirred for 100 h at 70°. The soln was cooled, concentrated in vacuo, taken up in methylene chloride and washed with satd aqueous sodium bicarbonate. The organic phase was separated, dried over Na_2SO_4, concentrated, and chromatographed on silica gel (600 g) with 2.5% 2-propanol/chloroform followed by 5% to remove the higher R_f materials. The only ferric chloride positive band (Tlc $R_f = 0.15$ with 5% methanol/chloroform) was then removed with 5% methanol/chloroform to give 3.84 g (44%) of 4. Recrystallization from acetone gave mp 216.5-217.5°. Calc'd for $C_{16}H_{12}N_{30}Cl_2$: C, 55.15, H, 3.48, N, 12.07, Cl, 20.36; Found: C, 55.08, H, 3.06, N, 11.87, Cl, 20.57. ^{1}H-nmr (DMSO): 8.3-8.0 (m, 2H), 7.85-7.70 (d, 1H), 7.65-7.4 (m, 5H), 6.90 (s, 1H), 6.75 (s, 2H). ^{13}C-nmr (DMSO): 157.14 (C4), 154.71 (C2), 153.46 (C6), 94.92 (C5).

2-Amino-1-hydroxy-6-phenyl-4-pyrimidinone (5). In 100 ml of n-butanol was added 150 ml of concentrated hydrochloric acid and 6.96 g (20 mmol) of 4. After stirring at 75° for 48 h (clear soln), the mixture was cooled and N_2 was bubbled through for 45 min. The soln was then concentrated and the resulting solid was slurried with H_2O (100 ml), filtered, washed with 8 x 50 ml of acetone, and dried in vacuo at 75°. The white solid (3.62 g, 90%) gave a mp 130-131° (dec). Calc'd for $C_{10}H_9N_3O_2$ HCl H_2O: C, 48.26, H, 4.23, N, 10.89; Found: C, 47.99, H, 4.46, N, 16.70.

2-Amino-5-bromo-1-hydroxy-6-phenyl-4-pyrimidinone (6). To 3.44 g (17 mmole) of 5 in 100 ml of acetic acid (heterogeneous) was added 4.1 g (25.5 mmole) of bromine dropwise with stirring. After stirring at room temperature for 2.5 h (homogeneous), the soln was concentrated in vacuo and the resulting yellow solid triturated with H_2O (75 ml). The solid was filtered and dried in vacuo at 70° to yield 3.85 g (80%), mp 209.5-210° (dec). Calc'd for $C_{10}H_8N_3O_2Br$: C, 42.57, H, 2.86, N, 14.89, Br, 28.33; Found: C, 42.20, H, 3.23, N, 14.84, Br, 27.48. ^{13}C-nmr (DMSO): 166.44 (C_6), 163.57 (C_4), 153.52 (C_1), 101.91 (C_5).

X-Ray Study of 6. Crystal data for 6 ($C_{10}H_8N_3O_2Br.1/2(H_2O)$) were: monoclinic; space group C2/c; Z = 8; a = 29.700(6) Å; b = 5.682(2) Å; c = 12.348(2) Å; β = 94.20(2) Å; D calc = 1.86 g cm^{-3}; μ (CuK) = 50.4 cm^{-1}; 1779 reflections (1649 reflections with intensities greater than 3 standard deviations). All $h\ k\ l$ reflections with $h + k$ odd and all $h\ o\ l$ reflections with l odd were systematically absent.

Intensity data for all reflections with 2 $\theta < 138°$ were collected using the step-scan technique[17] at low temperature (about -155°C) on a Syntex PL diffractometer controlled by a Harris computer using graphite monochromatized CuKα radiation (λ = 1.5418 Å). The data were corrected for systematic errors, including absorption.[18] The usual Lorentz correction was made along with a polarization correction appropriate for a monochromator with 50% perfect character. Standard deviations in observed intensities were approximated by the function $\sigma^2(I) = \sigma^2$ counting statistics + $(0.044I)^2$, where the coefficient of I was calculated from intensities of ten reflections monitored throughout the data collection, considering deviations in intensities which were not explained by counting statistics.[17]

The structure was solved by direct methods and refined (including coordinates and anisotropic thermal parameters of heavier atoms and hydrogen coordinates) by multiple matrix crystallographic least squares minimizing the function $\Sigma\omega(|F_o|^2-|F_c|^2)^2$ where weights ω were taken as the reciprocals of the variances $\sigma^2(F_o^2)$. The water oxygen is located in a special position, on a two-fold axis. One water hydrogen is related to the other by the two-fold axis, so the water molecule is not disordered, but is half-populated in the unit cell. Atomic form factors are from "International Tables for X-ray Crystallography,"[19] except for hydrogen form factors which are taken from Stewart, Davidson and Simpson.[20] The final agreement index $R[R = \Sigma||F_o|-|F_c||/\Sigma|F_o|]$ was 0.027, and the standard deviation of fit was 3.0. All calculations were carried out on an IBM

370 computer using the CRYM system of crystallographic programs written by David J. Duchamp, The Upjohn Company, Kalamazoo, Michigan.

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