Reduction of the Amidine C=N Bond of 7-Aminofurazano(3,4-\(d\))-
pyrimidines with Sodium Borohydride

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(Received May 26, 1975)

Reduction of 5-phenyl-7-substituted aminofurazano (3,4-\(d\)) pyrimidines with sodium borohydride was undertaken. In a sharp contrast with the cases of amino, alkylamino and tosylamino derivatives, the presence of acetyl group on the C-aromatic function results in the smooth reduction of the amidine C=N bond to give 7-acetamido-6,7-dihydro derivative. The presence of benzoyl group led to the formation of 6,7-dihydro derivative accompanied with loss of benzamide. Analogously, reduction of 5-phenyl-7-ethylthiofurfurazano (3,4-\(d\)) pyrimidine gave the 6,7-dihydro derivative.

Our previous works have well documented the versatility of 7-aminofurazano(3,4-\(d\))-pyrimidines as an intermediate for the synthesis of various fused pyrimidines, which originates mainly from the extraordinary ease with which nucleophilic attack occurs at position 7.

This paper describes further observations on the unusual chemical properties of this system. We found that occurrence of the reduction of 5-phenyl-7-substituted furazano(3,4-\(d\))-pyrimidines with sodium borohydride at a C=N double bond in their pyrimidine ring markedly influenced by the natures of substituents at position 7. It is particularly noticeable that the presence of a 7-acetamido function results in the smooth reduction of the amidine C=N bond to give the corresponding stable 6,7-dihydro derivative. The present results provide an interesting example of borohydride reduction of the amidine C=N bond which has a highly \(\pi\)-deficient carbon.

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\begin{align*}
\text{I} & : R = \text{NH}_2 \\
\text{II} & : R = \text{N(CH}_3)_2 \\
\text{III} & : R = \text{NCOCH}_3 \\
\text{IV} & : R = \text{SC}_2\text{H}_5
\end{align*}
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Chart

1) Location: 492-36, Mitahora, Gifu.
3) Physical data also suggest the unusual \(\pi\)-deficiency of the pyrimidine ring, particularly at position 7. Using as input the precise bond lengths found for 7-aminofurazano (3,4-\(d\))pyrimidine by the X-ray crystallographic study, molecular orbital (MO) calculation was carried out. The calculation indicates a low charge density (0.511) at position 7 (cf. reference 1 d). 5-Phenyl-7-dimethylaminofurfurazano(3,4-\(d\))pyrimidine (Ib) reveals the presence of two nonequivalent methyl signals in the nuclear magnetic resonance (NMR) spectrum at room temperature. The temperature-dependent NMR experiment proved a high rotational energy-barrier around the C-aromatic-N bond (H = 21.4 kcal/mole), which may reflect the great contribution of the \(\pi\)-deficient pyrimidine-\(\pi\)-excessive furazane structure to the resonance hybrid.
The reduction of 5-phenyl-7-amino[3,4-d]furanizano(3,4-d)pyrimidines (Ia—e) with sodium borohydride was carried out in tetrahydrofuran at room temperature.

Upon subjection of 7-amino and 7-pyrrolidino derivatives (Ia, b) to the reductive conditions, no formation of 6,7-dihydro compounds was observed and the starting materials were recovered. In the case of N-acetyl derivative (Ic), however, the reduction led to the formation of 6,7-dihydro-7-acyl[3,4-d]furanizano(3,4-d)pyrimidine (II) in 70% yield.

Proof of the 6,7-dihydro structure rests upon satisfactory microanalytical results and consonant spectral data. In the infrared (IR) spectrum of II, an acetyl C=O bond is observed at a noticeably lower frequency (1660 cm⁻¹) than that of Ic (1705 cm⁻¹). Its nuclear magnetic resonance (NMR) spectrum reveals a quartet signal at 6.70 δ (1H, J₁=2 Hz, J₂=8 Hz, coalesced to a singlet by deuterium exchange) attributed to the C₇-proton. If the product adopts an alternate 4,7-dihydro structure, the signal of the C₇–H must be observed as a doublet, because long range coupling between the C₇–H and the H₄–H expected to be very weak. The dihydro derivative, II, was identical in every respect with a sample obtained upon irradiation of Ic in ethanol.

On the other hand, N-benzoyl derivative (Id) suffered the reduction in a different fashion to afford 5-phenyl-6,7-dihydrofuranizano(3,4-d)pyrimidine (III) in 60% yield. Benzamide was also isolated from the reaction mixture. The NMR spectrum of III shows a doublet signal at 4.98 δ (2H, J=2 Hz), which coalesces to a sharp signal upon addition of D₂O. The ultraviolet (UV) spectrum of III, n max\(\mu\) (log ε): 240 (4.50), 302 (4.05), is similar to that of II, n max\(\mu\) (log ε): 242 (4.08), 292 (3.95).

The reduction of 5-phenyl-7-ethylthiophuranizano(3,4-d)pyrimidine (IV) (see experimental part) with sodium borohydride also resulted in the formation of III in 55% yield, accompanied with loss of ethylmercaptan.

In the case of N-tosyl derivative (Ie), the sodium borohydride reduction led only to smooth conversion into its sodium salt, which is soluble in water and recovers Ie after acidification.

Above observations can be rationalized as follows: The presence of an acetylamo group could increase a-deficiency at the 7-position, comparing with the cases of amino and pyrrolidino groups. Thus the borohydride reduction occurs smoothly to give the corresponding 6,7-reduced product (II). The benzamido and ethylthio groups appear to be better leaving group than the acetylamido group. These groups, therefore, can be easily displaced by a hydride ion probably prior to the reduction of the C₇=N₆ bond. The presence of the tosyl group, which is more electron-attracting than benzoyl and acetyl groups, on the C₇-amino function prevents the reduction presumably by the formation of N-anion compensating electron deficiency at the carbon of the amidine bond.

Experimental

All melting points are uncorrected. IR spectra were run on a Hitachi-215 spectrophotometer. NMR spectra were recorded at 60 MHz with a Hitachi R-20B using tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

Preparation of 5-Phenyl-7-substituted-furanizano(3,4-d)pyrimidines (Ia—e)---a 5-Phenyl-7-amino[3,4-d]furanizano(3,4-d)pyrimidine (Ia), mp 230—232°, was prepared by lead tetraacetate oxidation of 2-phenyl-4,6-diamino-5-nitro[3,4-d]pyrimidine (cf. reference 2a).

b) 5-Phenyl-7-pyrrolidino[3,4-d]pyrimidine (Ib): Ia (1 g) was shaken with pyrrolidine (5 ml) at room temperature. The reaction mixture became clear with evolution of ammonia and then deposited a pale yellow product. The product was recrystallized from ethanol to give Ib, mp 221—223°, in 90% yield. Anal. Calcd. for C₁₁H₁₂O₂N₄: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.82; H, 4.96; N, 26.18. IR v max cm⁻¹: no NH bond. NMR (CDCl₃) δ: 2.40 (4H, m, pyrrolidine ring protons), 4.32 (4H, m, pyrrolidine ring protons). BF₃ salt, mp 290° (decomp.) (from MeOH).

c) 5-Phenyl-7-acetamidofuranizano(3,4-d)pyrimidine (Ic), mp 193°, was obtained by acetylation with pyridine—aetic anhydride (cf. reference 2a).

d) 5-Phenyl-7-benzamidofuranizano(3,4-d)pyrimidine (Id), mp 185°, was obtained by benzoylation with pyridine—benzoyl chloride (cf. reference 2a).

e) 5-Phenyl-7-(p-toluenesulfonamido)furanizano(3,4-d)pyrimidine (Ie): A mixture of Ia (1 g) and p-
toluenesulfonyl chloride (1 g) in pyridine (10 ml) was allowed to stand at room temperature for about 7 hr. After addition of water, the reaction mixture deposited a crystalline mass, which was recrystallized from ethanol to give Ie, 210°—211°, as pale yellow crystals in 58% yield. Anal. Calcd. for C₁₇H₁₆O₂N₅: C, 55.59; H, 3.57; N, 19.07. Found: C, 56.11; H, 3.78; N, 18.85.

f) 5-Phenyl-7-ethylthiofuranbazo(3,4-d)pyrimidine (IV): A suspension of Ia in 5% hydrochloric acid was stirred at 80°—90° for 4 hr. The insoluble product was collected, washed well with H₂O and recrystallized from ethanol to give 5-phenyl-7(6H)-furanazano(3,4-d)pyrimidinone, mp 223°—224°, as pale yellow crystals in 75% yield. Anal. Calcd. for C₁₅H₁₂O₂N₇: C, 56.07; H, 2.82; N, 26.10. Found: C, 56.22; H, 3.04; N, 26.08. IR (max) cm⁻¹: 3150 (NH), 1710 (C=O). Acetate: mp 215° (from acetone–ether), IR (max) cm⁻¹: 3250 (NH), 1730 (acetyl C=O). A mixture of 5-phenyl-7(6H)-furanazo(3,4-d)pyrimidinone (1 g) and P₂S₅ (2 g) in pyridine (50 ml) was refluxed for 1 hr. After evaporation of pyridine as sufficient as possible, the residue was washed well with boiling H₂O and recrystallized from benzene to give 5-phenyl-7-mercaptofuranazano(3,4-d)pyrimidine, mp 191°—194°, as red crystals in about 90% yield. Anal. Calcd. for C₁₅H₁₂O₂N₅S: C, 52.18; H, 2.63; N, 24.34. Found: C, 52.32; H, 2.85; N, 24.31. To a solution of 7-mercapto compound (1 g) in CH₂Cl₂ (40 ml) was added excess triethyloxonium tetrafluoroborate. After being stirred at room temperature for 40 hr, the reaction mixture was concentrated under reduced pressure. The residue was extracted with CHCl₃. The CHCl₃ solution washed with H₂O and dried over anhyd. Na₂SO₄. After evaporation of the solvent, the resulting oily residue was submitted to silica gel chromatography (solvent: CHCl₃) to separate IV, mp 163°, as yellow crystals in 70% yield. Anal. Calcd. for C₁₅H₁₂O₂N₅: C, 55.18; H, 3.90; N, 21.70. Found: C, 55.53; H, 3.93; N, 21.89. NMR (CDCl₃) δ: 1.60 (3H, t, -CH₂CH₃), 3.56 (2H, q, -CH₂CH₂), 7.53, 8.55 (5H, m, aromatic protons).

Reduction of 5-Phenyl-7-acetamidofuranazano(3,4-d)pyrimidine (Ic) with Sodium Borohydride—To a suspension of Ic (1 g) in tetrahydrofuran (30 ml) NaBH₄ (0.17 g) was added in portions with stirring. The reaction mixture was stirred at room temperature for 24 hr. To the resulting red-brown solution 80% acetic acid was added in ice cooling in order to decompose excess NaBH₄. Removal of the solvent from the mixture under reduced pressure left an oily residue, which was solidified spontaneously by addition of H₂O. The solid mass thus obtained was recrystallized from ethanol to give II, mp 265°, as colorless crystals in 50% yield. Anal. Calcd. for C₁₅H₁₄O₂N₅: C, 56.06; H, 4.20; N, 27.23. Found: C, 56.16; H, 4.20; N, 27.16. IR (max) cm⁻¹: 3300 (NH), 1650 (NH₂). NMR (dimethyl sulfoxide (DMSO)-d₄) δ: 1.77 (3H, s, CH₂CO–), 6.70 (1H, q, C₂-H), 7.1 = 2 Hz, 7.8 = 8 Hz), 7.44, 7.90 (5H, m, aromatic protons), 9.20 (2H, broad, two NH). UV (max) mμ (log ε): 242 (4.08), 292 (3.95).

Reduction of 5-Phenyl-7-benzamidofuranazano(3,4-d)pyrimidine (Id) with Sodium Borohydride—To a solution of Id (1 g) in tetrahydrofuran (50 ml) was added sodium borohydride (0.15 g) in portions. The reaction mixture was stirred at room temperature for 24 hr. After addition of 80% acetic acid to decompose excess hydride, the reaction mixture was concentrated under reduced pressure. The residue was extracted with boiling ethanol and then the ethanol solution was evaporated to dryness. The crystalline mass thus obtained was dissolved in CHCl₃ and chromatographed over silica gel to separate III, mp 235°, as colorless crystals, and benzamide in 60% and 15% yields respectively. Anal. Calcd. for C₁₅H₁₄O₂N₅: C, 59.99; H, 4.03; N, 27.99. Found: C, 60.13; H, 4.03; N, 27.84. IR (max) cm⁻¹: 3320, 3300 (sh.) (NH). NMR (DMSO-d₄) δ: 4.88 (2H, d, C₂-H₂), 7.60, 8.00 (5H, m, aromatic protons), 8.75 (1H, broad, NH). UV (max) mμ (log ε): 242 (4.65), 302 (4.05). Benzamide was identical in every respect with an authentic sample.

Similarly sodium borohydride reduction of (IV) resulted in the formation of III in 55% yield.