The Reaction of 2,4-Diamino-6-piperidinopyrimidine 3-Oxide with Acid Anhydrides

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2,4-Diamino-6-piperidinopyrimidine 3-oxide reacts preferentially with acid anhydrides at the 4-amino group. The structures of amide products are readily assigned by the position of the 5-H.

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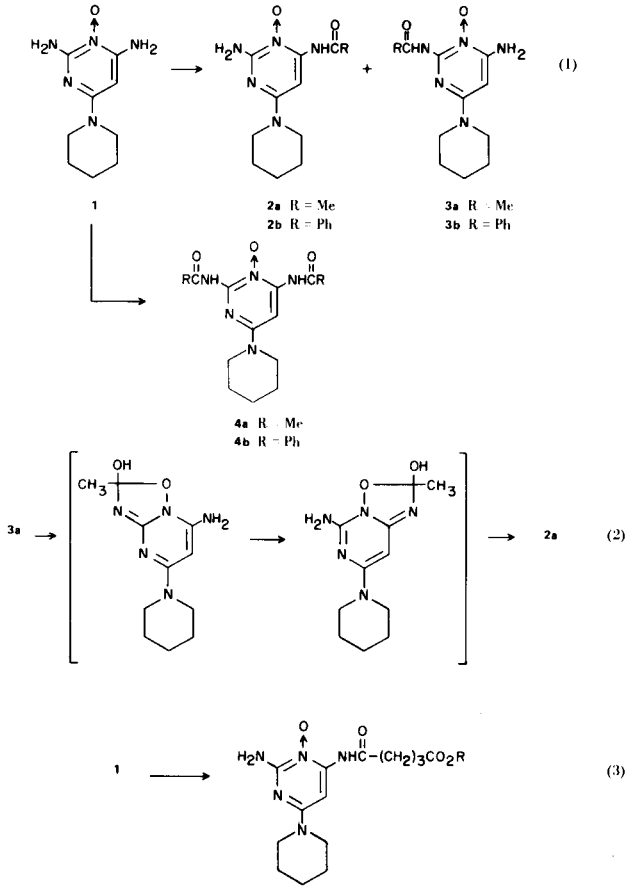
The synthesis (1) and biological activity (2) of a series of *N*-oxides have been reported. Minoxidil (2,4-diamino-6-piperidinopyrimidine 3-oxide) is the parent compound in this series. The reactions of 2,4-diamino-6-piperidinopyrimidine 3-oxide **1** with acetic, benzoic and glutaric anhydride have been examined. This study reveals a dramatic difference in nucleophilic reactivity between the two amino functions of this pyrimidine *N*-oxide.

Acetic anhydride reacts with an equivalent amount of 2,4-diamino-6-piperidinopyrimidine 3-oxide to give monoacetamides **2a** and **3a** in a ratio of 26:1 in an overall isolated yield of 82%. The 5-H in the nmr is quite predictive of structure. In compounds **1**, **2a** and **3a** the 5-H appears at chemical shifts of 5.38, 7.07 and 5.57, respectively.

When compound **3a** is dissolved in DMSO, it gradually converts to the 4-acetamido compound, **2a**. This reaction very likely proceeds *via* *N*-oxide participation (equation 2). Excess acetic anhydride readily forms the 2,4-diacetamide **4a**. The 5-H appears in the nmr at δ 7.35.



Benzoic anhydride also preferentially reacts with the 4-amino group of pyrimidine **1** to give amides **2b** and **3b** in a 16:1 ratio. The protons at C-5 appear at δ 7.30 and 5.55 in **2b** and **3b**, respectively. The 5-H of dibenzamide **4b** has a chemical shift of 7.52.

Glutaric anhydride reacted quite selectively with the 4 amino group of pyrimidine **1** to produce a single glutaramide **5a**. The structure of the methyl ester of this amide was unambiguously assigned by x-ray analysis (3). The 5-H appears at δ 7.07 in the nmr. This dramatic downfield shift of the 5-H relative to the 5-H of pyrimidine **1** is the basis of structure assignment for acetamides and benzamides **2** and **3**.

EXPERIMENTAL

Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60A spectrophotometer and chemical shifts (δ) are in ppm relative to internal trimethylsilane.

(2-Amino-4-acetamido)- and (4-Amino-2-acetamido)-6-piperidinopyrimidine 3-Oxide (**2a** and **3a**).

A solution of 2.44 g. (0.024 mole) of acetic anhydride in 30 ml. of methylene chloride was added to a refluxing suspension of 5.00 g. (0.024 mole) of 2,4-diamino-6-piperidinopyrimidine 3-oxide in 300 ml. of methylene chloride. After 10 minutes, the mixture was partitioned with aqueous sodium bicarbonate. The organic phase was dried over sodium sulfate, concentrated and chromatographed on silica gel with 8% methanol/1% ammonium hydroxide in methylene chloride to yield 4.77 g. (79%) of amide **2a** and 0.17 g. (3%) of amide **3a**. Crystallization from methylene chloride gave pure **2a** and **3a**, m.p. 204-205° and 153.0-153.5°, respectively; nmr (deuteriochloroform): δ 7.07 (C-5 proton of **2a**) and 5.57 (C-5 proton of **3a**).

Anal. Calcd. for $C_{11}H_{17}N_5O_2$: C, 52.57; H, 6.82; N, 27.87. Found (**2**): C, 52.90; H, 6.97; N, 27.59.

2,4-Diacetamido-6-piperidinopyrimidine 3-Oxide (**4a**).

A mixture of 1.00 g. (0.0048 mole) of 2,4-diamino-6-piperidinopyrimidine 3-oxide and 10 ml. of acetic anhydride was stirred at 25° for 30 minutes. The mixture was partitioned between methylene chloride and water. The organic layer was dried and concentrated. The residue was crystallized from methylene chloride/methanol to yield 0.98 g. (70%) of diacetamide **4a**, m.p. 217-217.5°; nmr (deuteriochloroform): δ 7.35 (C-5 proton).

Anal. Calcd. for $C_{13}H_{19}N_3O_3$: C, 53.23; H, 6.53; N, 23.88. Found: C, 53.52; H, 6.81; N, 23.82.

(2-Amino-4-benzamido)-, (4-Amino-2-benzamido)-, and (2,4-Dibenzamido)-6-piperidinopyrimidine 3-Oxide (**2b**, **3b**, and **4b**).

A suspension of 5.00 g. (0.024 mole) of 2,4-diamino-6-piperidino pyrimidine 3-oxide in 700 ml. of methylene chloride was reacted at reflux with 5.41 g. (0.024 mole) of benzoic anhydride for 2 hours. The mixture was partitioned with aqueous sodium bicarbonate. The organic phase was dried and concentrated. The residue was chromatographed on silica gel with 8% methanol in methylene chloride to yield 5.28 g. of benzamide **2b** (m.p. 218-219°), 0.33 g. benzamide **3b** (m.p. 161-162.5°), and 0.73 g. of dibenzamide **4b** (m.p. 200-201°). All were recrystallized from methylene chloride/cyclohexane; nmr (deuteriochloroform): δ 7.30 (C-5 proton of **2b**), 5.55 (C-5 proton of **3b**), and 7.52 (C-5 proton of **4b**).

Methyl *N*(2-Amino-6-piperidino-4-pyrimidinyl)glutaramate 3-Oxide.

A mixture of 2.00 g. (0.0096 mole) of 2,4-diamino-6-piperidinopyrimidine 3-oxide and 1.09 g. (0.0010 mole) of glutaric anhydride were refluxed in 150 ml. of acetone for 2 hours. The white crystalline residue (2.12 g.) was refluxed in 0.001*M* hydrochloric acid/methanol for 1.5 hours. The mixture was concentrated and partitioned between methylene chloride and aqueous potassium carbonate. The organic phase was dried, concentrated, and chromatographed on RP-2® silica gel with 5% methanol/0.5% ammonium hydroxide in methylene chloride. The product was crystallized from hot acetonitrile to yield 1.8 g. of glutaramate, m.p. 135-136.5°; nmr (deuteriochloroform): δ 7.07 (C-5 proton).

Anal. Calcd. for $C_{15}H_{23}N_5O_4$: C, 53.40; H, 6.87; N, 20.76. Found: C, 53.51; H, 6.96; N, 21.07.

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