CONDENSED *as*-TRIAZINES: SYNTHESIS OF IMIDAZO[4,5-*e*]-*as*-TRIAZINE 1-OXIDES (6-AZAPURINE 6-OXIDES) AS GUANINE AND HYPOXANTHINE ANALOGUES

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Abstract - Imidazo[4,5-*e*]-*as*-triazine 1-oxides (6-azapurine 6-oxides), structurally related to guanine and hypoxanthine, have been prepared. Reaction of 5,6-diamino-3-methylsulfonyl-*as*-triazine 1-oxide(**1**) with hydrazine afforded 5,6-diamino-3-hydrazino-*as*-triazine 1-oxide(**2**) which was then oxidized with mercuric oxide to give 5,6-diamino-*as*-triazine1-oxide(**3**). The 3-methylsulfonyl group of **1** was also replaced with liquid ammonia and methanolic ammonia respectively to give 3-amino (**5**) and 3-methoxy (**6**) derivatives. *as*-Triazine *N*-oxides were then cyclized with triethyl orthoformate (TEOF) to afford the title compounds.

The chemistry of compounds which are structurally related to the naturally occurring purines, e. g., adenine, hypoxanthine, and guanine receives attention daily mainly because such compounds have shown a wide spectrum of chemotherapeutic and biological activities.[1,2] For example, simply replacing the oxygen atom of hypoxanthine with the bioisosteric sulfur has provided an extremely active anticancer agent 6-mercaptopurine (6-MP). 8-Azaguanine, an analogue of guanine in which the C8 carbon has been replaced by a nitrogen atom,

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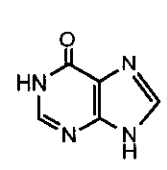
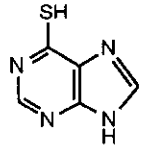
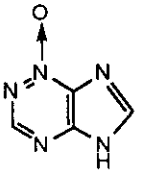
displayed notable carcinostatic effects against murine malignancies.[3] Other examples of the bioisosteric replacement of an enolizable carbonyl with the *N*-oxide group, such as uricytin (uridine analogue),[4] emimycin (pyrimidine analogue),[5,6] and *as*-triazine *N*-oxides (uracil and thymine analogues)[7,8] have also been prepared and shown to exhibit antitumor properties. We have been interested in the preparation of novel nitrogen bicyclic heterocycles derived from *ortho*-diamino-*as*-triazines.[9-12] Recently, we reported the synthesis of 3-aminoimidazo[4,5-*e*]-*as*-triazine[13] and its benzylated analogue.[14] The present report describes the preparation of imidazo[4,5-*e*]-*as*-triazine 1-oxide which is regarded as a bioisosteric isomer of hypoxanthine. The synthesis of 3-amino derivative, a guanine analogue, and 3-methoxy derivative are also described.



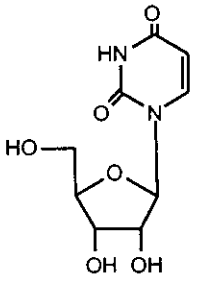
Hypoxanthine



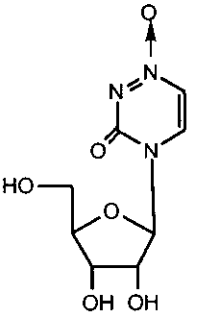
6-MP



6-Azapurine 6-Oxide



Uridine



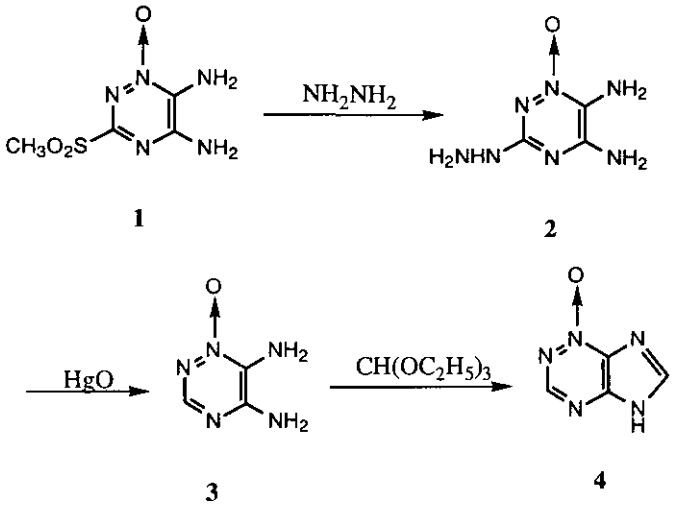
Uricytin

RESULTS AND DISCUSSION

5,6-Diamino-3-methylsulfonyl-*as*-triazine 1-oxide (**1**), prepared from the oxidation of 5,6-diamino-3-methylthio-*as*-triazine with *m*-chloroperbenzoic acid (*m*CPBA),[13] was treated with hydrazine to give 5,6-diamino-3-hydrazino-*as*-triazine 1-oxide (**2**) in 48% yield. Oxidative dehydrazination[15] of **2** with mercuric oxide in ethanol gave 5,6-diamino-*as*-triazine 1-oxide (**3**) which was then cyclized with triethyl orthoformate

to afford imidazo[4,5-*e*]-*as*-triazine 1-oxide (**4**), an isosteric isomer of hypoxanthine and 6-mercaptopurine (Scheme I).

Scheme 1

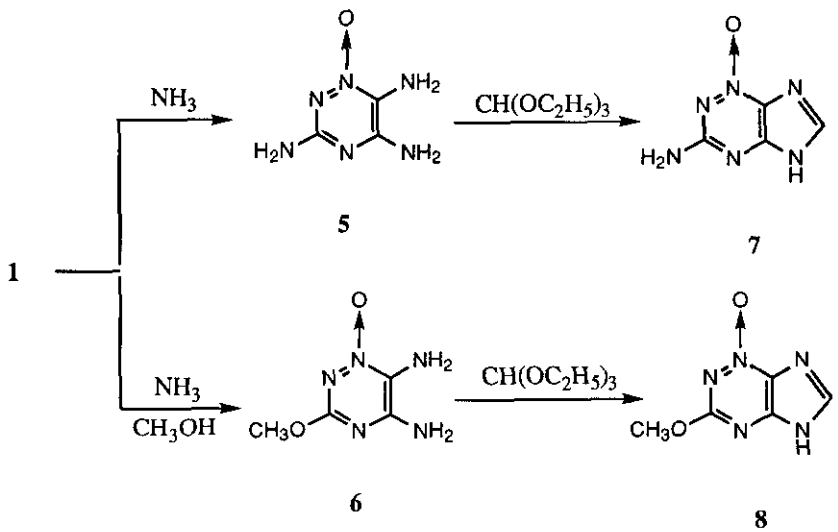


1 **2** **3** **4**

Treatment of **1** with liquid ammonia gave 3,5,6-triamino-*as*-triazine 1-oxide (**5**)[13] in 72% yield. When the reaction was carried out under the same conditions except that methanolic ammonia (saturated at 5 °C) was used instead of liquid ammonia, the desired **5** was not obtained. The ^{1}H nmr spectrum of the sole product isolated showed three singlets at δ 3.72, 6.06 and 7.52 ppm corresponding to 3-OCH_3, 6-NH_2, and 5-NH_2 respectively. The ^{13}C nmr spectrum supported the ^{1}H nmr spectrum in confirming the presence of one methoxy carbon appeared at δ 54.40 ppm and three heteroaromatic carbons at δ 127.29, 152.31, and 158.24 ppm corresponding to C6, C5, and C3 respectively. Elemental analysis was in accord with the molecular formula $C_4H_7N_5O_2$ which, taken together with spectral evidences, suggests a structure of 5,6-diamino-3-methoxy-*as*-triazine 1-oxide (**6**). Ring closure of **6** with triethyl orthoformate (TEOF) under acidic conditions afforded 3-methoxylimidazo[4,5-*e*]-*as*-triazine 1-oxide (**8**) in 48% yield. However, the ring closure of **5** with TEOF under the same reaction conditions was not successful due to the poor solubility of **5** in TEOF. To circumvent this situation, a mixed solvent of TEOF and dimethylformamide in equal volume was used instead of a neat TEOF. The cyclization product thus obtained was a mixture of 3-aminoimidazo[4,5-*e*]-*as*-triazine 1-oxide (**7**) and its 3-formamido derivative [^{1}H nmr: 8.27 (s, 1H, $C_6\underline{H}$), 9.21(s, 1H, $\underline{H}CO$), 10.82 (br s, 1H, C_3-N$\underline{H}$); ms: *m/z* 180(M^+)] which were difficult to be separated and purified. Therefore, the initial product

was treated with methanolic ammonia to cleave the formamide bond and pure **7** was obtained in 50% yield (Scheme 2).

Scheme 2



EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The ultraviolet spectra were determined in 0.1 N HCl (pH 1), methanol and 0.1 N NaOH (pH 13) with a Hitachi-U-2000 spectrophotometer. Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Varian VSR-300S spectrometer. All the samples were dissolved in dimethyl sulfoxide-d_6, and the chemical shifts are expressed in parts per million with respect to tetramethylsilane(TMS) as an internal standard. The progress of reaction was followed by thin layer chromatography(tlc) on silica gel 60 F-254 plates purchased from E. Merck. Mass spectra were determined with a Quattro VG-5022 mass spectrometer in the electron impact(EI) mode. Elemental analyses were preformed by Heraeus CHN-O-Rapid elemental analyzer.

5,6-Diamino-3-hydrazino-as-triazine 1-oxide (**2**). Compound (**1**) (410 mg, 2.0 mmol) was dissolved in 70% ethanol (50 ml). To this solution was added hydrazine hydrate (2.0 ml, 40 mmol), and the mixture was refluxed for 24 h. After this period, the solution was concentrated in vacuo to 25 ml and was cooled to room temperature. The precipitate was collected and crystallized from 30 % ethanol to give **2** (150 mg, 48%), mp >

300 °C; uv: λmax/nm (pH 1) 327 (5900), 234 (12400); (methanol) 328 (5100), 237 (15700); (pH 13) 326 (5600), 232sh (15800); ^{1}H nmr δ 3.90 (br s, 2H, hydrazino NH_2), 5.70 (s, 2H, C6-NH_2), 7.20 (s, 2H, C5-NH_2). ^{13}C nmr δ 125.30 (C-6), 151.60 (C-5), 158.27 (C-3); ms: *m/z* 157 (M^+,100%), 141 (16), 140 (82), 127 (23). Anal. Calcd for $C_3H_7N_7O$: C, 22.93; H, 4.49; N, 62.40. Found: C, 22.66; H, 4.38; N, 62.01.

5,6-Diamino-as-triazine 1-oxide (**3**). Yellow mercuric oxide (1.0 g, 4.6 mmol) was added to a suspension of **2** (157 mg, 1.0 mmol) in absolute ethanol (80 ml). The resulting mixture was refluxed for 24 h, filtered and the filtrate was evaporated. The residue was crystallized from ethanol to give **3** (88 mg , 69%), mp 280-282 °C; uv: λmax/nm (pH 1) 319 (6800), 237 (8300), 216 (12100); (methanol) 320 (8000), 238 (10300), 217 (15400); (pH 13) 316 (6100), 237sh (9100); ^{1}H nmr: δ 6.52(s, 2H, C6-NH_2), 7.42 (s, 2H, C5-NH_2), 7.80 (s, 1H, H3); ^{13}C nmr: δ 131.55 (C-6), 146.83 (C-3), 150.56 (C-5); ms: *m/z* 127 (M^+,89%), 111 (10), 97 (24). Anal. Calcd for $C_3H_5N_5O$: C, 28.34; H, 3.96; N, 55.10. Found: C, 28.11; H, 4.19; N, 54.90.

Imidazo[4,5-e]-as-triazine 1-oxide (**4**). To a well stirred suspension of **3** (127 mg, 1.0 mmol) in triethyl orthoformate (25 ml, 150 mmol) was added concentrated hydrochloric acid (0.3 ml). The mixture was then heated at reflux for 1.5 h, filtered and the filtrate was evaporated in vacuo. The residue was purified by flash column chromatography on silica gel using chloroform : methanol (3:1) as an eluent. The homogeneous fractions were pooled and evaporated. The residue was crystallized from methanol to give **4** (62 mg, 56%), mp 216-218 °C; uv: λmax/nm (pH 1) 307 (8700), 225 (11700); (methanol) 309 (7300), 228 (11700); (pH 13) 316 (6400), 229 (14800); ^{1}H nmr: δ 8.39 (s, 1H, H-3), 8.62(s, 1H, H-6); ^{13}C nmr: δ 138.23 (C-7a), 150.60 (C-6), 152.23 (C-3), 154.79 (C-4a); ms: *m/z* 137(M^+,100%), 121 (7); HRms: *m/z* Calcd for $C_4H_3N_5O$: 137.0338. Found: 137.0330.

3,5,6-Triamino-as-triazine 1-oxide (**5**). A mixture of **1** (400 mg, 1.95 mmol) and liquid ammonia (12 ml) was heated in a steel bomb at 80 °C for 48 h. After the reaction cooled, excess ammonia was vented off and the residual solid was collected by filtration, washed with cold, absolute ethanol, and crystallized from H_2O to give **5** (200 mg, 72 %), mp>300 °C; uv: λmax/nm (pH 1) 332 (7400), 234 (21000); (methanol) 337 (9300), 234 (26700); (pH 13) 321 (9100), 232sh (22400); ^{1}H nmr: δ 5.52(s, 2H, C3-NH_2), 5.80 (s, 2H, C6-NH_2),

7.21(s, 2H, C5-NH_2); ^{13}C nmr: δ 124.93 (C-6), 151.96 (C-5), 156.60 (C-3). Anal. Calcd for $C_3H_6N_6O$: C,25.35; H, 4.26; N, 59.13. Found: C, 25.17; H, 4.43; N, 58.89.

6-Amino-3-methoxy-as-triazine 1-oxide (**6**). A mixture of **1** (205 mg, 1.0 mmol) and methanolic ammonia (30 ml, previously saturated at 0°C) was heated in a steel bomb at 80 °C for 48 h. The excess methanolic ammonia was evaporated to 10 ml. The white precipitate was collected and crystallized from methanol to give **6** (125 mg, 80 %), mp >300 °C; uv: λmax/nm (pH 1) 319 (8700), 226 (14600); (methanol) 322 (8900), 225 (15100); (pH 13) 314 (10600); ^1H nmr: δ 3.72 (s, 3H, OCH_3), 6.06 (s, 2H, C6-NH_2), 7.52 (br s, 2H, C5-NH_2); ^{13}C nmr: δ 54.40 (OCH_3), 127.29 (C-6), 152.31 (C-5),158.24 (C-3); ms: *m/z* 157 (M^+, 100%), 141(10), 140 (23), 127(89). Anal. Calcd for $C_4H_7N_5O_2$: C,30.57; H, 4.49; N, 44.57. Found: C, 30.68; H, 4.52; N, 44.20.

3-Aminoimidazo[4,5-e]-as-triazine 1-oxide (**7**). To a well stirred suspension of **5** (142 mg, 1.0 mmol) in triethyl orthoformate (15 ml, 90 mmol) and dimethylformamide (15 ml) was added concentrated hydrochloric acid (0.3 ml). The mixture was refluxed for 4 h, filtered, and the filtrate was evaporated in vacuo. The residue was dissolved in methanolic ammonia (25 ml) and heated in a glass-lined, stainless steel reaction vessel at 70 °C for 16 h. The excess solvent was evaporated in vacuo and the residue was purified by flash column chromatography on silica gel using chloroform : ethanol (2:1) as an eluent. The homogeneous fractions were pooled and evaporated. The residue was crystallized from ethanol to afford **7** (76 mg, 50%), mp > 300 °C; uv: λmax/nm (pH 1) 359 (8300), 252 (10800), 227 (34000); (mehanol) 362 (8900), 228 (34000), (pH 13) (8000), 302 (6400), 256 (10800), 229sh (30000); ^1H nmr: δ 6.937 (s, 2H, C3-NH_2), 8.194 (s, 1H, H-6) 13.2 (br s, 1H, NH); ^{13}C nmr: δ 131.34 (C-7a), 141.99 (C-6), 151.28 (C-4a), 161.05 (C-3); ms: *m/z* 157 (M^+,100%), 141 (10), 140 (23), 127 (89); HRms: *m/z* Calcd for $C_4H_4N_6O$: 152.0447. Found: 152.0440.

3-Methoxyimidazo[4,5-e]-as-triazine 1-oxide (**8**). The procedure for the preparation of **8** was similar to that for **4** except that the starting heterocycle was **6** (157 mg). The resulting residue was purified by flash column chromatography using chloroform : ethanol (4:1) as an eluent. The homogeneous fractions were pooled and evaporated. Crystallization of the residue from ethanol afforded **8** (80 mg, 48%), mp >300 °C; uv: λmax/nm (pH 1) 327 (9900), 222 (18900); (methanol) 327 (9600), 223 (19300); (pH 13) 338 (7200), 302 (6600),

248sh (6900); ^{1}H nmr: δ 3.957 (s, 3H, OCH_3), 8.479 (s, 1H, H-6); ^{13}C nmr: δ 55.80 (OCH_3), 133.89 (C-7a), 144.61 (C-6), 151.03 (C-4a), 162.98 (C-3); ms: *m/z* 167 (M^+, 100%), 151 (20), 137 (54); HRms: *m/z* Calcd for $C_5H_5N_5O_2$: 167.0443. Found: 167.0457.

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