

O-PHENYLATION OF 6-AMINO-5-NITROSO-1,3-DIMETHYLURACIL  
WITH DIPHENYLIODONIUM CHLORIDE. A NEW ROUTE TO LUMAZINES<sup>1</sup>

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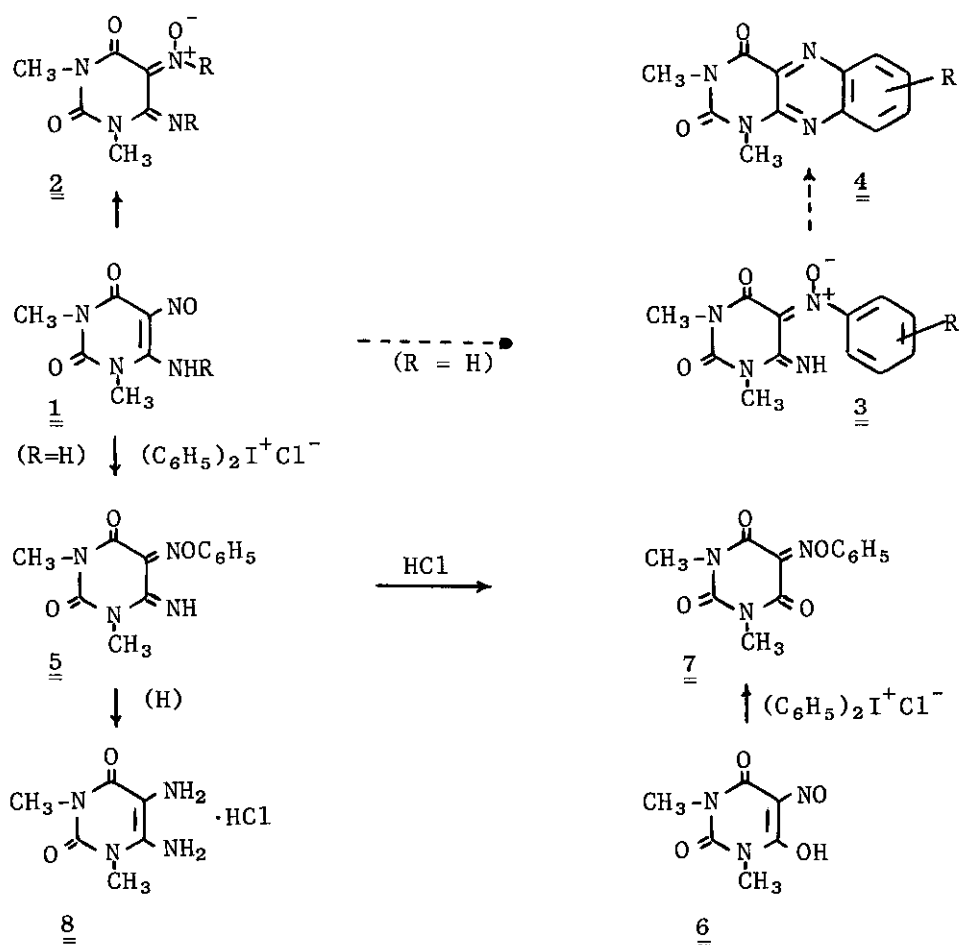
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Treatment of 6-amino-5-nitroso-1,3-dimethyluracil (1, R = H) with diphenyliodonium chloride resulted in O-phenylation to give a quantitative yield of 6-imino-5-phenoxy-1,3-dimethyluracil (5), whose structure was established by both spectral and chemical means. Reaction of 5 with 1-morpholino-1-cyclohexene gave 1,3-dimethyl-2,4(1H,3H)-cyclohexa(g)pteridinedione (9), while reaction with 1-morpholino-1-butene gave 6-ethyl-1,3-dimethylumazine (10).

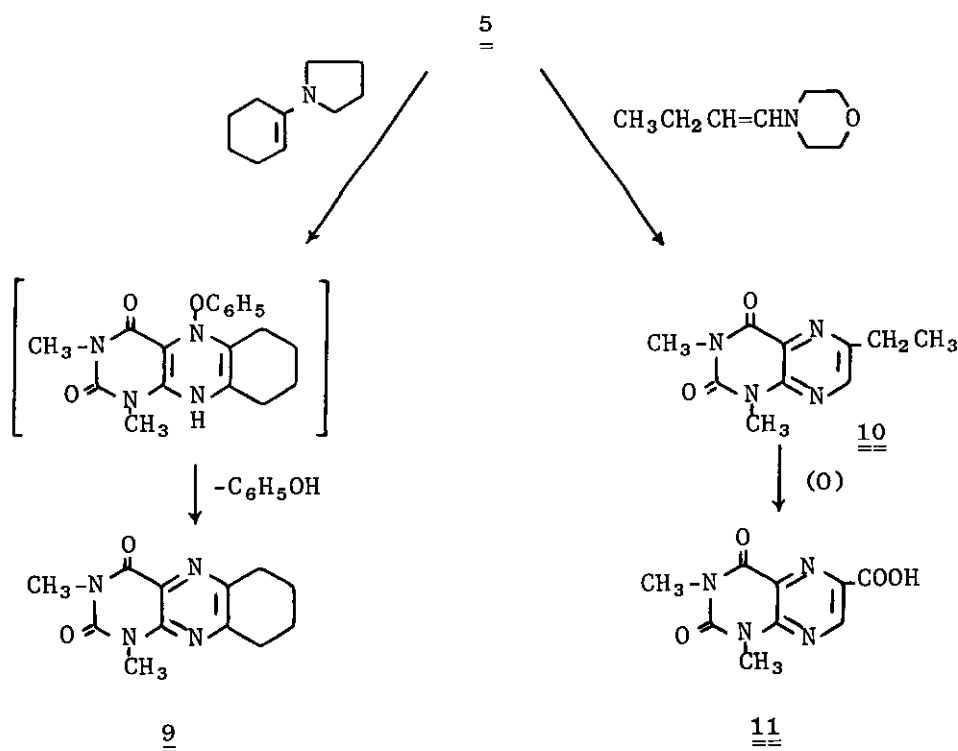
Alkylation of 6-alkylamino-5-nitroso-1,3-dimethyluracil (1, R = alkyl) is known to take place on the nitrogen atom of the 5-nitroso grouping to give nitrones of type 2.<sup>2,3</sup> Although the corresponding N-aryl nitrones (3) have apparently never been described, they are attractive potential intermediates for the preparation of alloxazines (4) via an intramolecular cycloaddition-dehydration process analogous in principle to the known synthesis of isoalloxazines from 6-anilino-5-nitrosouracils.<sup>4</sup>

Treatment of 6-amino-5-nitroso-1,3-dimethyluracil (1, R = H) with diphenyliodonium chloride (or tetrafluoroborate) in isopropanol in the presence of triethylamine resulted in rapid discharge of the deep pink color of the starting material and the separation of colorless needles. That the product was the result of arylation on oxygen to give 6-imino-5-phenoxyimino-1,3-dimethyluracil (5) rather than arylation on nitrogen to give the anticipated nitrone 3 (R = H) was evident not only from spectral data (see Experimental) but also from the following chemical observations. Thus, heating 5 for

15 minutes in 6N hydrochloric acid resulted in quantitative conversion to 5-phenoxyimino-1,3-dimethylbarbituric acid (7), which was obtained independently by reaction of 1,3-dimethylvioluric acid (6) with diphenyliodonium chloride in the presence of triethylamine. Hydrogenation of an aqueous suspension of 5 in the presence of catalytic amounts of  $\text{PtO}_2$  and hydrochloric acid gave 5,6-diamino-1,3-dimethyluracil (8) (64%).



The O-aryloxime derivative 5 represents an unusual 1,4-diazabutadiene<sup>5</sup> which should be capable of serving as a precursor to pteridines by cycloaddition with acetylenes (or acetylene equivalents) followed by aromatization by loss of phenol. Preliminary experiments have verified this prediction. Thus, reaction of 5 with 1-pyrrolidino-1-cyclohexene in refluxing toluene gave 1,3-dimethyl-2,4(1H,3H)-cyclohexa(g)pteridinedione (9) (74%), identical in every respect with an authentic sample.<sup>6</sup> Of even greater interest



was the observation that treatment of 5 with 1-morpholino-1-butene in refluxing toluene gave exclusively 6-ethyl-1,3-dimethylumazine (10), whose structure was confirmed by potassium permanganate

oxidation to the known 1,3-dimethyluracine-6-carboxylic acid (11). The regiospecificity of this cycloaddition reaction is consistent with major contributions to the structure of 5 from canonical forms 5a and 5b.



Unfortunately, attempts to extend the diphenyliodonium chloride O-arylation reaction to other 6-amino-5-nitrosopyrimidines failed, and we assume that this reaction is restricted to 5-nitrosopyrimidine derivatives with insulated bond arrangements such as are found in 1 and 6.

#### EXPERIMENTAL SECTION

6-Imino-5-phenoxyimino-1,3-dimethyluracil (5): To a boiling suspension of 6-amino-5-nitroso-1,3-dimethyluracil (0.92 g, 5 mmol) and diphenyliodonium chloride (1.60 g, 5 mmol) in isopropanol (25 mL) was added triethylamine (0.6 g, 6 mmol) with magnetic stirring. After 10 minutes of heating, the reaction mixture was cooled and the colorless needles of 5 were collected by filtration and washed with small amounts of isopropanol and ether; yield 1.25 g (96%), mp 181-183°C. The product is photosensitive and is best stored in a brown bottle. Identical results were obtained when the reactants were stirred for two days at room temperature, or when diphenyliodonium tetrafluoroborate was used rather than the chloride. Nmr (CF<sub>3</sub>COOH) δ 7.60 (s, 5H), 3.95 (s, 3H), 3.75 (s, 3H). Ir (KBr) 3370, 3100, 3060, 2940, 1720, 1670 cm<sup>-1</sup>. M/e (70 eV) 260, 231, 157, 105, 97, 93 (C<sub>6</sub>H<sub>5</sub>O<sup>+</sup>), 77.

Anal. Calcd for C<sub>12</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>: C, 55.39; H, 4.62; N, 21.53.  
Found: C, 55.19; H, 4.47; N, 21.53.

5-Phenoxyimino-1,3-dimethylbarbituric Acid (7): Method A. A suspension of 6-imino-5-phenoxyimino-1,3-dimethyluracil (5) (0.260 g) in 6 N HCl (20 mL) was heated under reflux for 15 minutes and then cooled. The bright yellow precipitate which had separated was collected by filtration and dried; yield 0.260 g (100%), mp 196-197°. The product is best stored in a brown bottle. Nmr (CF<sub>3</sub>COOH)  $\delta$  7.50 (s, 5H), 3.84 (s, 3H), 3.60 (s, 3H). Ir (KBr) 3060, 2940, 1740, 1680 cm<sup>-1</sup>. m/e 261, 231, 157, 125, 105, 97, 77.

Anal. Calcd for C<sub>12</sub>H<sub>11</sub>N<sub>3</sub>O<sub>4</sub>: C, 55.17; H, 4.21; N, 16.09. Found: C, 55.12; H, 4.14; N, 16.33.

Method B: To a suspension of 1,3-dimethylvioluric acid monohydrate (1.02 g, 5 mmol) and diphenyliodonium chloride (1.60 g, 5 mmol) in isopropanol (25 mL) was added triethylamine (0.6 g, 6 mmol), and the mixture was heated under reflux for 10 minutes. It was then cooled and the yellow precipitate collected by filtration and washed with ether; yield 1.30 g (99.5%). The product was identical in every respect with the compound prepared by Method A.

Reduction of 5 to 5,6-Diamino-1,3-dimethyluracil Hydrochloride (8): A suspension of 1.0 g of 5 in 80 mL of water containing 2 drops of concentrated hydrochloric acid was shaken under 60 p.s.i of hydrogen in the presence of PtO<sub>2</sub> catalyst for 3 hours. The resulting colorless solution was filtered, 20 ml of concentrated hydrochloric acid was added to the filtrate, and the solution was evaporated to dryness under reduced pressure. Trituration of the residue with ethanol/ether, filtration and recrystallization of the crude product from methanol gave 0.5 g (63%) of 5,6-diamino-1,3-dimethyluracil hydrochloride, mp 306-308° dec. (lit.<sup>7</sup> mp 305-308° dec.). The product was identical in every respect with an authentic sample of 8.

1,3-Dimethyl-2,4(1H,3H)-cyclohexa(g)pteridinedione (9): A mixture of 6-imino-5-phenoxyimino-1,3-dimethyluracil (1.3 g, 5 mmol) and 1-pyrrolidino-1-cyclohexene (0.90 g, 6 mmol) in toluene (30 mL) was heated under reflux, protected from light, for 1 hour. The resulting dark red solution was evaporated to dryness under reduced pressure

and the residue was triturated with water. Filtration and recrystallization of the collected solid from ethanol gave colorless platelets of 9; yield 0.91 g (74%), mp 185° (lit.<sup>6</sup> mp 185°). The product was identical in every respect with an authentic sample of 9.

6-Ethyl-1,3-dimethylumazine (10): A suspension of 6-imino-5-phenoxyimino-1,3-dimethyluracil (1.04 g, 4 mmol) in a mixture of toluene (25 mL) and 1-morpholino-1-butene (1.41 g, 10 mmol) was heated under reflux for 1 hour while protected from light with a wrapping of aluminum foil. The solvent was removed by evaporation under reduced pressure and 20 mL of 1 N hydrochloric acid was added to the oily residue. Extraction with ether (3 x 20 mL) and evaporation of the combined ether extracts gave the crude product which was chromatographed on Baker silica gel. Elution with chloroform (400 mL), evaporation, and recrystallization of the residue from ethyl acetate/petroleum ether (60-70°) gave 10 as glistening pale yellow plates; yield 0.32 g (36%), mp 139-141°. Nmr (CDCl<sub>3</sub>) δ 8.55 (s, 1H), 3.80 (s, 3H), 3.55 (s, 3H), 3.03 (q, 2H, J = 8Hz), 1.36 (t, 3H, J = 8Hz). Ir (KBr) 2950, 2870, 1705, 1660, 1535 cm<sup>-1</sup>.

Anal. Calcd for C<sub>10</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>: C, 54.49; H, 5.46; N, 25.46.  
Found: C, 54.32; H, 5.67; N, 25.28.

Oxidation of 10 to 1,3-Dimethylumazine-6-carboxylic Acid (11): A mixture of 6-ethyl-1,3-dimethylumazine (0.044 g, 0.2 mmol) and potassium permanganate (0.050 g) in water (3 mL) was heated over a steam bath for 15 minutes, the precipitated MnO<sub>2</sub> removed by filtration, and the filtrate added to 1 mL of concentrated hydrochloric acid. Evaporation to dryness and recrystallization of the residue from 1 N hydrochloric acid gave 11 as colorless crystals; yield 0.022 g (45%), mp 248-250° (lit.<sup>8</sup> mp 249-250°).

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