BASE-CATALYZED RING CONTRACTION OF 6-IMINO-5-PHENOXYIMINO-1,3-DIMETHYLURACIL TO 4,5-DIIMINO-1,3-DIMETHYLIMIDAZOLIDIN-2(1H)-ONE. A NEW SYNTHESIS OF IMIDAZOPYRAZINES[1]

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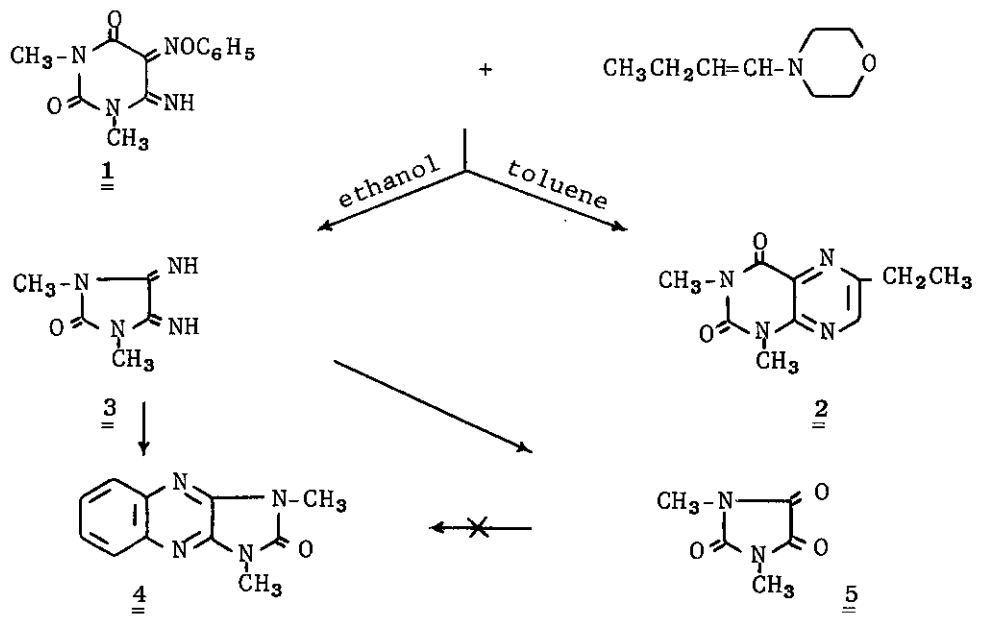
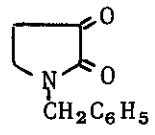
Treatment of 6-imino-5-phenoxyimino-1,3-dimethyluracil either with morpholine or with aqueous base resulted in smooth ring contraction to give 4,5-diimino-1,3-dimethylimidazolidin-2(1H)-one (3). Condensation of 3 with o-phenylenediamine, 2,3-diaminopyridine, 5,6-diamino-1,3-dimethyluracil, and 2,4,5,6-tetraaminopyrimidine gave the condensed imidazopyrazine derivatives 4, 8, 9, and 10 respectively.

In the accompanying paper[2] we have described the reaction of 6-amino-5-nitroso-1,3-diaminouracil with diphenyliodonium chloride, which led to O- rather than to N-arylation to give 6-imino-5-phenoxyimino-1,3-dimethyluracil (1) in almost quantitative yield. During our investigation of the chemical properties of the latter 1,4-diazabutadiene derivative, we found that reaction with 1-morpholino-1-butene in refluxing toluene gave 6-ethyl-1,3-dimethyllumazine (2), but that the use of ethanol rather than xylene as the reaction medium resulted in facile ring contraction of 1 to 4,5-diimino-1,3-dimethylimidazolidin-2(1H)-one (3). That this ring contraction probably involved the reaction of 1 with morpholine, present as a minor contaminant in the starting enamine, was readily confirmed by the observation that 1 was smoothly converted to 3 in refluxing ethanol containing a trace of added morpholine. Conversion of 1 to 3 could also be smoothly effected with 1 N aqueous sodium hydroxide at room temperature, and is thus analogous to the reported base-catalyzed rearrangement of 6-amino-5-nitroso-1,3-dimethyluracil to 3.[3] Such benzylic acid-type ring contractions have other precedents in pyrimidine chemistry.[4]

Treatment of 3 with o-phenylenediamine in glacial acetic acid resulted in an exothermic reaction and the formation of 1,3-dimethylimidazo(4,5-b)quinoxalin-2(1H)-one (4). The ease of this latter conversion should be contrasted with the failure of all attempts to condense o-phenylenediamine with 1,3-dimethylparabanic acid (5). The unreactivity of 5 with o-phenylenediamine is reminiscent of the



recently reported failure by Schneller and Sun[5] to condense N-benzylpyrrolidin-2,3-dione (6) with various diamines; only spiro compounds of type 7 were obtained. The enhanced reactivity of imines as compared with their parent ketones in condensation reactions with active methylene compounds is well known,[6] and it would now appear that carbonyl-type reactivity of cyclic amides can also be substantially



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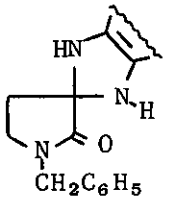

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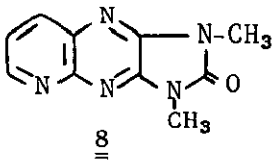
enhanced by conversion to the corresponding imines (cyclic amidines). This observation has interesting synthetic consequences in various areas of heterocyclic synthesis which are under investigation.

We have found that 3 condensed smoothly in glacial acetic acid with 2,3-diaminopyridine, 5,6-diamino-1,3-diaminouracil, and 2,4,5,6-tetraaminopyrimidine to give 1,3-dimethylimidazo(4,5-b)pyrido(3,2-e)pyrazin-2(1H)-one (8), 1,3,6,8-tetramethylimidazo(4,5-b)pyrimido(5,4-e)pyrazin-2,5,7(1H,6H,8H)-trione (9), and 1,3-dimethyl-5,7-diamino-imidazo(4,5-b)pyrimido(5,4-e)pyrazin-2(1H)-one (10) respectively. It is of particular interest that Russupteridine-yellow$_{IV}$, isolated from mushrooms of the genus Russula, has recently been shown to be an



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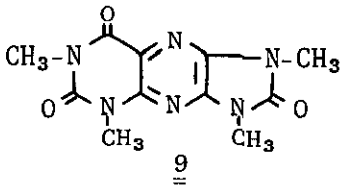

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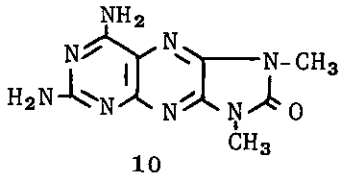

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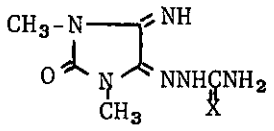
imidazo(4,5-b)pyrimido(5,4-e)pyrazine;[7] the above condensation reaction (e.g., 3 → 9) would appear to constitute a facile route to these new naturally-occurring 6,7-diaminolumazine derivatives. However, an attempt to extend this condensation to the use of aliphatic diamines was not successful. Heating 3 and diaminomaleonitrile (DAMN) in hot acetic acid led only to extensive decomposition of the latter, while the use of a catalytic amount of acetic acid in aqueous ethanol (conditions successfully employed by Popp[8] for the condensation of DAMN with isatin) led only to hydrolysis of 3 to give 1,3-dimethylparabanic acid (5) in quantitative yield.

Reaction of 3 with thiosemicarbazide and with semicarbazide in hot acetic acid gave the thiosemicarbazone 11 and the semicarbazone 12 respectively, but attempts to effect cyclization of the latter derivatives to fused 1,2,4-triazines, either with aqueous ammonia[9] or with alkali,[10] were unsuccessful.



11, X = S
12, X = O

EXPERIMENTAL SECTION

4,5-Diimino-1,3-dimethylimidazolidin-2(1H)-one (3): A mixture of 6-imino-5-phenoxyimino-1,3-dimethyluracil[2] (1) (0.52 g, 2 mmol) and 1-morpholino-1-butene (0.30 g, 2.1 mmol) in ethanol (15 mL) was heated under reflux for 30 minutes. The resulting red solution was evaporated under reduced pressure to about 5 mL, cooled, and the colorless needles which had separated were collected by filtration and washed with petroleum ether; yield 0.224 g (80%), mp 200° (lit.[3] mp 202-204°). The same compound was obtained in comparable yield by heating 1 with a trace of morpholine in ethanol, or by stirring at room temperature for 2 hours with 5% sodium hydroxide, followed by acidification, extraction with chloroform, and evaporation of the dried chloroform extracts. Nmr (DMSO-d_6) δ 11.40 (br s, 2H), 2.96 (s,6H). Ir (KBr) 3260, 2940, 1725, and 1640 cm^{-1}.

Hydrolysis of 3 with hydrochloric acid in aqueous ethanol gave 1,3-dimethylparabanic acid, mp 152° (lit.[11] mp 152-153°) in 90% yield.

1,3-Dimethylimidazo(4,5-b)quinoxalin-2(1H)-one (4): To a solution of 4,5-diimino-1,3-dimethylimidazolidin-2(1H)-one (0.63 g, 4.5 mmol) in glacial acetic acid (20 mL) was added o-phenylenediamine (0.5 g, 4.6 mmol). An immediate exothermic reaction ensued with the separation of a colorless solid. The reaction mixture was warmed over a steam bath for 1 hour, cooled, and filtered to give 0.68 g of colorless needles. Concentration of the filtrate gave an additional 0.23 g for a total yield of 0.91 g (95%), mp 224°. Recrystallization from acetic acid did not raise the melting point. Nmr ($CDCl_3$) δ 8.08-7.8 (m,2H), 7.75-7.5 (m,2H), 3.54 (s,6H). IR (KBr) 3040, 2900, 1730, 1640, 1600 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.68; H, 4.67; N, 26.17. Found: C, 61.46; H, 4.49; N, 26.07.

1,3-Dimethylimidazo(4,5-b)pyrido(3,2-e)pyrazin-2(1H)-one (8): To a solution of 2,3-diaminopyridine (0.436 g, 4 mmol) in glacial acetic acid (8 mL) was added 4,5-diimino-1,3-dimethylimidazolidin-2(1H)-one (0.56 g, 4 mmol). A slightly exothermic reaction ensued. The mixture was then heated under reflux for 30 minutes, cooled, basified by the addition of excess aqueous sodium bicarbonate, and the yellow solid which had separated was collected by filtration and recrystallized from ethanol; yield 0.49 g (71%), mp 217-218°. Nmr (DMSO-d_6) δ 8.77 (dd, 1H, $J_{\alpha,\beta}$= 4.5 Hz, $J_{\alpha,\gamma}$= 1.8 Hz, H_α), 8.30 (dd, 1H, $J_{\beta,\gamma}$= 8Hz, $J_{\alpha,\gamma}$= 1.8 Hz, H_γ), 7.60 (dd, 1H, $J_{\alpha,\beta}$= 4.5Hz, $J_{\beta,\gamma}$= 8Hz, H_β), 3.42 (s,3H), 3.40 (s,3H). Ir (KBr) 3040, 2940, 1730, 1600 cm^{-1}.

Anal. Calcd for $C_{10}H_9N_5O$: C, 55.81; H, 4.19; N, 32.56. Found: C, 55.65; H, 3.99; N, 32.42.

1,3,6,8-Tetramethylimidazo(4,5-b)pyrimido(5,4-e)pyrazin-2,5,7(1H,-6H,8H)-trione (9): To a solution of 5,6-diamino-1,3-dimethyluracil (0.68 g, 4 mmol) in acetic acid (10 mL) was added 4,5-diimino-1,3-dimethylimidazolidin-2(1H)-one (0.56 g, 4 mmol). A slightly exothermic reaction took place with the formation of a deep red color. The reaction mixture was heated under reflux for 1 hour and the excess acetic acid removed by evaporation under reduced pressure. Recrystallization of the residue from ethanol gave 0.82 g (74%) of yellow crystals

of 9, mp 280-281°. Nmr (CF_3COOH) δ 3.44 (s,3H), 3.20 (s,6H), 3.14 (s,3H). Ir (KBr) 2940, 1740, 1690, 1650, 1615, 1595 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_6O_3$: C, 47.83; H, 4.35; N, 30.44. Found: C, 47.57; H, 4.26; N, 30.66.

1,3-Dimethyl-5,7-diaminoimidazo(4,5-b)pyrimido(5,4-e)pyrazin-2(1H)-one (10): A mixture of 2,4,5,6-tetraaminopyrimidine hydrochloride (1.06 g, 6 mmol) and 4,5-diimino-1,3-dimethylimidazolidin-2(1H)-one (0.84 g, 6 mmol) in acetic acid (10 mL) was heated under reflux for 40 minutes, cooled, and the yellow precipitate collected by filtration, washed with ethanol followed by ether and then dried; yield 1.30 g (90%). The analytical sample of 10, mp > 300° was prepared by dissolution of the crude product in a small amount of 88-90% formic acid, filtration, and precipitation by addition of dilute ammonium hydroxide. Nmr (CF_3COOH) δ 8.25 (s,1H,1/2 H_2O of hydration), 3.70 (s,6H). Ir (KBr) 3460, 3380, 2950, 1750, 1640 cm^{-1}.

Anal. Calcd for $C_9H_{10}N_8O \cdot 1/2\ H_2O$: C, 42.35; H, 4.31; N, 43.92. Found: C, 42.32; H, 4.03; N, 43.97.

4,5-Diimino-1,3-dimethylimidazolidin-2(1H)-one 4-thiosemicarbazone (11): A mixture of 4,5-diimino-1,3-dimethylimidazolidin-2(1H)-one (0.42 g, 3 mmol) and thiosemicarbazide (0.273 g, 3 mmol) in glacial acetic acid (5 mL) was heated over a steam bath for 30 minutes, cooled, and the shiny yellow crystals which had separated were collected by filtration, washed with ethanol followed by ether and dried; yield 0.49 g (83%), mp 288-290° dec. Nmr (DMSO-d_6) δ 8.30 (br s, 2H), 7.80 (s,2H), 2.90 (s,3H), 2.84 (s,3H). Ir (KBr) 3400, 3260, 3200, 3140, 2930, 1740, 1635, 1600, 1500 cm^{-1}.

Anal. Calcd for $C_6H_{10}N_6SO$: C, 33.64; H, 4.67; N, 39.25; S, 14.95. Found: C, 33.47; H, 4.38; N, 38.96; S, 15.16.

4,5-Diimino-1,3-dimethylimidazolidin-2(1H)-one 4-semicarbazone (12) was prepared in the same manner as described above from 3 and semicarbazide hydrochloride in acetic acid solution, and was obtained as colorless crystals, mp 228-230° dec. in 67% yield. Nmr (DMSO-d_6) δ

9.40 (br s, 1H), 7.40 (br s, 1H), 6.6 (br s, 2H), 2.95 (s,3H), 2.91 (s,3H). Ir (KBr) 3460, 3300-2600, 1740, 1600, 1580 cm^{-1}.

Anal. Calcd for $C_6H_{10}N_6O_2$: C, 36.36; H, 5.05; N, 42.42. Found: C, 36.60; H, 4.83; N, 42.20.

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