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Synthesis of Some Imidazo[1,2-*c*][1,2,3]triazolo[4,5-*e*]pyrimidines

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Synopsis. The reaction of 7-amino[1,2,3]triazolo-[4,5-*d*]pyrimidine (**1a**) with chloroacetaldehyde gave imidazo-[1,2-*c*][1,2,3]triazolo[4,5-*e*]pyrimidine (**2a**) which underwent facile ring opening in dilute hydrochloric acid. The methyl derivatives (**2b,c,d**) were similarly made from the appropriate triazolopyrimidine (**1b,c,d**) and chloroacetaldehyde.

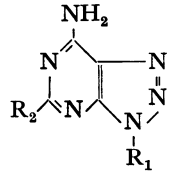
The isolation and structural elucidation of the fluorescent imidazo[1,2-*a*]purines from baker's yeast ^{Phe}t-RNA[1] and *T. utilis* ^{Phe}t-RNA[2] has aroused considerable interest in the chemistry and biology of fused tricyclic compounds derived from the common base residues of nucleic acids. At about the same time, Kost and his co-workers reported that the reaction of 9-methyladenine with chloroacetaldehyde gave fluorescent 3-methylimidazo[2,1-*i*]purine.[3] The ribonucleoside and ribonucleotides of imidazo[2,1-*i*]purine have been synthesized and their activities in several enzymatic systems reported.[4] It has also been shown that two fluorescent substances derived from N^6-(3-methyl-2-butenyl)adenosine, a clinically useful antileukemic agent, were members of the imidazo[2,1-*i*]purine series.[5] This finding prompted us to investigate the synthesis of analogous ring systems with a view to possible biological activities. In the present paper, we describe the synthesis of certain imidazo[1,2-*c*]-[1,2,3]triazolo[4,5-*e*]pyrimidines.

Treatment of 7-amino[1,2,3]triazolo[4,5-*d*]pyrimidine (**1a**)[6] with chloroacetaldehyde in aqueous ethanol in the presence of sodium acetate gave the fluorescent imidazo[1,2-*c*][1,2,3]triazolo[4,5-*e*]pyrimidine (**2a**) in moderate yield. The ^{1}H NMR spectrum of **2a** in TFA exhibited a pair of doublets at δ 8.25 and 8.62 (J= 2.0 Hz) representing protons at the 7- and 8-position, and a singlet at δ 9.77 for 5-H. Similarly, the condensation of 7-amino-5-methyl[1,2,3]triazolo[4,5-*d*]pyrimidine (**1b**)[7] with chloroacetaldehyde gave 5-methylimidazo[1,2-*c*][1,2,3]triazolo[4,5-*e*]pyrimidine (**2b**). This compound showed UV spectra very similar to those of **2a**; also a singlet at δ 3.82 and a pair of doublets at δ 8.28 and 8.42 (J=2.0 Hz) in its ^{1}H NMR spectrum.

When **2a** was treated with dilute hydrochloric acid, its fluorescence disappeared and a ring-opened product, 4-amino-5-(2-imidazolyl)-1,2,3-triazole (**3**) was obtained. The same compound was formed also, but more slowly, when **2a** was boiled in water. The structure of **3** was derived from elemental analysis, UV spectra, and a ^{1}H NMR spectrum exhibiting a sharp singlet at δ 7.48 for both 4- and 5-H of the imidazole ring. This ring opening took place most probably by nucleophilic addition of water at the 5,4-double bond. Therefore, a compound such as **2b**, with a blocking methyl group[8] at the site of potential addition, is expected to resist ring opening. In fact, no ring opening was detected when **2b** was treated with hydrochloric acid as above.

3-Methyl-(**2c**) and 3,5-dimethyl-imidazotriazolopyrimidines(**2d**) were made similarly from 3-methyl- and 3,5-dimethyl-7-aminotriazolopyrimidine(**2c** or **d**) respectively.

We also investigated the reaction of **1a** with bromoacetone. Under a variety of conditions, the reaction gave 7-acetonylamino[1,2,3]triazolo[4,5-*d*]pyrimidine(**4a**) as a main product; several minor products were formed, but no imidazotriazolopyrimidine was detected. The structure of **4a** was confirmed by elemental analysis and by UV spectra which were very similar to those of **1a**. Its ^{1}H NMR spectrum showed singlets at δ 2.63(CH_3), δ 5.93(CH_2), and δ 8.80 (the aromatic proton of the pyrimidine ring). The reaction of **1b** with bromoacetone took place in a similar manner to give the 5-methyl compound(**4b**) without any imidazotriazolopyrimidine.



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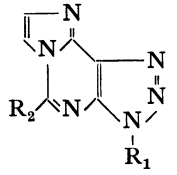

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	a	b	c	d
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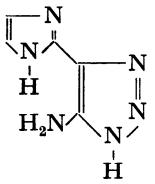
R_2	H	CH_3	H	CH_3



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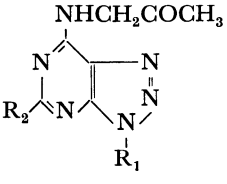

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Experimental

The elemental analyses were done by the Analytical Section, Meijo University, Nagoya. The pK_a values were determined by a spectroscopic method and the UV spectra on a JASCO UVIDEC-1 spectrophotometer. The ^{1}H NMR spectra were determined on a JEOL JNM-MH-60 NMR spectrometer in TFA with TMS as an internal standard.

Imidazo[1,2-c][1,2,3]triazolo[4,5-e]pyrimidine (2a). One gram of **1a**, chloroacetaldehyde (0.50 g,) and NaOAc (1.0 g) were heated in 50% aq EtOH (200 ml) under reflux for 2 h. The solution was evaporated to dryness and the residue was chromatographed on a Florisil column (4×40 cm) by gradient elution using 0—1% ammonia (1.0 l). The fluorescent fractions were combined, concentrated to *ca.* 50 ml under reducted pressure, treated with charcoal, and chilled to give colorless needles (1.10 g) of **3a**; mp>300 °C (Found: C,

38.67; H, 3.55; N, 44.87%. Calcd for $C_6H_4N_6$–1.5H_2O: C, 38.50; H, 3.74; N, 44.92%); ^{1}H NMR: δ 8.25(d, J=2.0 Hz, 1), 8.62(d, J=2.0 Hz, 1), and 9.77(s, 1); pK_a 2.46±0.03; λ_{max} (log ε) at pH 0.44: 214(4.35), 270(sh, 3.83), 282(3.88); at pH 5.0: 219(4.32), 235(sh, 4.19), 284(3.82).

*5-Methylimidazo[1,2-c][1,2,3]triazolo[4,5-e]pyrimidine (**2b**).* A solution of **1b**[7] (2.5 g), chloroacetaldehyde (2.0 g), and NaOAc (4 g) were refluxed in 50% aq EtOH (400 ml) for 4 h. Evaporation under reduced pressure and subsequent crystallization from water gave colorless needles (2.0 g) of **2b**; mp>300 °C (Found: C, 48.09; H, 3.27; N, 48.55%. Calcd for $C_7H_6N_6$: C, 48.27; H, 3.45; N. 48.26%); ^{1}HNMR: δ 3.82(s, 3), 8.28(d, J=2.0 Hz, 1), and 8.42(d, J=2.0 Hz, 1); pK_a 2.57±0.02; λ_{max} (log ε) at pH 0.44: 212(4.38), 270(sh, 3.85), 279(3.90); at pH 5.0: 217(4.31), 240(sh, 3.97), 285(3.87).

*4-Amino-5-(2-imidazolyl)-1,2,3-triazole (**3**).* A solution of **2a** (270 mg) in 1M-HCl (20 ml) was kept at 20 °C for 10 h. Evaporation to dryness under reduced pressure and crystallization from EtOH gave colorless needles (145 mg) of **3** as hydrochloride; mp>300 °C (Found: C, 32.45; H, 3.66; N, 44.99%. Calcd for $C_5H_6N_6$–HCl: C, 32.17; H, 3.75; N, 45.04%); ^{1}HNMR: δ 7.48(s); pK_a 8.30±0.03, 5.24±0.03, and −1.39±0.05; λ_{max} (log ε) at H_0 −3.0: 251 (4.05), 295(sh, 3.41); at pH 2.0: 243(3.86), 278(4.10); at pH 6.5: 243(3.87), 277(4.08); at pH 10.5: 215(3.81), 273(4.15).

*3-Methylimidazo[1,2-c][1,2,3]triazolo[4,5-e]pyrimidine (**2c**) and the 3,5-Dimethyl Derivative (**2d**).* 7-Amino-3-methyltriazolopyrimidine[9] (1.0 g), chloroacetaldehyde (2 g) and NaOAc (2 g) were heated in water (300 ml) at 60 °C for 5 h. Evaporation under reduced pressure to *ca.* 20 ml gave a solid which was crystallized from MeOH to give colorless needles (0.45 g) of **2c**. The analytical sample was prepared by sublimation at 160 °C/1 Torr; mp 282—283 °C(decomp) (Found: C, 48.57; H, 3.27; N, 47.82%. Calcd for $C_7H_6N_6$: C, 48.27; H, 3.47; N, 48.26%); ^{1}H NMR: δ 4.67(s, 3), 8.25(d, J=2.0 Hz, 1), 8.60(d, J=2.0 Hz, 1), and 9.70(s, 1); pK_a 2.47±0.01; λ_{max} (log ε) at pH 0.44: 219.5(4.38), 263(3.74), 281(3.73); at pH 5.0: 229(4.35), 260(3.60), 298(3.50).

4-Amino-6-chloro-2-methyl-5-nitropyrimidine[10] and 30% methanolic methylamine under reflux gave *the 6-methylamino analogue* in 90% yield; mp 242—243.5 °C (from MeOH) (Found: C, 39.29; H, 4.82; N, 38.23%. Calcd for $C_6H_9N_5O_2$: C, 39.34; H, 4.92; N, 38.25%). The nitropyrimidine (2.0 g) was hydrogenated over Pd/C in 0.5M-HCl (50 ml), and subsequently treated with $NaNO_2$ to give *7-amino-3,5-dimethyl[1,2,3]triazolo[4,5-d]pyrimidine* (**1d**) (1.35 g; colorless needles when recrystallized from water); mp>300 °C (Found: C, 44.13; H, 4.95; N, 51.46%. Calcd for $C_6H_8N_6$: C, 43.89; H, 4.29; N, 51.19%). This compound was treated with chloroacetaldehyde as in the foregoing reaction to give **2d** (95% yield); mp 221—222 °C (sublimed at 160 °C/1 Torr) (Found: C, 51.23; H, 3.91; N, 44.35%. Calcd for $C_8H_8N_6$: C, 51.04; H, 4.29; N, 44.66%); ^{1}H NMR: δ 3.27(s, 3), 4.58(s, 3), 8.20(d, J=2.0 Hz, 1). and 8.37(d, J=2,0 Hz, 1); pK_a 2.65±0.01; λ_{max} (log ε) at pH 0.44: 219(4.41), 268.5 (3.79), 281(3.81); at pH 5.0: 219(4.35), 266.5(3.60), 295.5 (3.65).

*7-Acetonylamino[1,2,3]triazolo[4,5-d]pyrimidine (**4a**) and Its I5-Methyl Derivative(**4b**).* A solution of **1a** (1.0 g) and bromoacetone (2.5 g) in 50% aq EtOH (300 ml) was refluxed for 2 h. Evaporation under reduced pressure and subsequent crystallization from water gave colorless needles (0.50 g) of **4a**; mp> 300 °C (Found: C, 43.63; H, 4.03; N, 43.87%. Calcd for $C_7H_8N_6O$: C, 43.74; H, 4.20; N, 43.73%); ^{1}H NMR: δ 2.63(s, 3), 5.93(s, 2), and 8.80(s, 1), pK_a 2.42±0.01; λ_{max} (log ε) at pH 0.44: 205(4.27), 264(4.09); at pH 4.5: 214 (4.07), 279(4.06).

The 5-methyl derivative (**4b**) was similarly obtained from **1b** in 56% yield; mp>300 °C (Found: C, 46.32; H, 4.85; N, 40.62%. Calcd for $C_8H_{10}N_6O$: C, 46.59; H, 4.90; N, 40.76%); pK_a 3.08±0.02; λ_{max} (log ε) at pH 0.83: 205(4.30), 264(4.10); at pH 5.5: 215(4.22), 277(4.06); ^{1}H NMR: δ 5.82(s, 3), 2.88(s, 3), and 5.87(s, 2).

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