The Synthesis of Certain 8-Cyano-2,4-disubstituted-imidazo[1,5-*a*]pyrimidines

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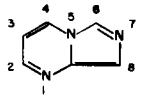
A number of imidazo[1,5-*a*]pyrimidine-8-carboxamides were synthesized by reacting various β-dicarbonyl compounds with 5(4)-aminoimidazole-4(5)carboxamide (AICA, **1**), the non-ribosylated form of AICAR, a key intermediate in the metabolic pathway of purine biosynthesis. Cyclization of **1** with ethylacetoacetate yielded 2-methylimidazo[1,5-*a*]pyrimidin-1*H*-4-one-8-carboxamide (**2**). The treatment of **2** with phosphorus oxychloride gave 4-chloro-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**3**). Various nucleophiles displaced the 4-chloro substituent of **3** under mild conditions. However, the 4-methylthio group of 8-cyano-2-methyl-4-methylthio-imidazo[1,5-*a*]pyrimidine (**8a**) was also displaced under very mild conditions. Even more strangely, the 4-diethylamino group of 8-cyano-4-diethylamino-2-methylimidazo[1,5-*a*]pyrimidine (**5a**) was displaced by ammonia to give 4-amino-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**7**).

In the course of investigating various fused pyrimidine ring systems for potential biological activity as purine antagonists (1-3), we wished to explore the imidazo[1,5-*a*]-pyrimidines (4).



Imidazo[1,5-*a*]pyrimidine

This ring system had not been examined in much depth in the literature, but two synthetic approaches have been reported. Ochiai (5) first synthesized this heterocycle by condensing the unstable 5-amino-2-methylimidazole (obtained *in situ* from the reduction of 5-nitro-2-methylimidazole) with acetylacetone, affording 2,4,6-trimethylimidazo-[1,5-*a*]pyrimidine. Later, Guerret and co-workers (6) improved upon the synthesis by reacting ethyl 4(5)amino-imidazole-5(4)carboxylate (obtained in several steps from ethyl cyanoacetate) with acetylacetone, affording ethyl 2,4-dimethylimidazo[1,5-*a*]pyrimidine-8-carboxylate.

An imidazole nucleotide, 5-amino-β-D-ribofuranosyl-imidazole-4-carboxamide-5′-phosphate (AICAR), has been known for some years to be a key intermediate in the metabolic pathway of purine biosynthesis (7). The non-ribosylated form of this compound, 5(4)aminoimidazole-4(5)carboxamide (AICA, **1**) was found to be a useful intermediate in the synthesis of 8-substituted-imidazo[1,5-*a*]pyrimidines. Shaw (8) first synthesized **1** *via* several steps. However, the recent commerical availability (9) of **1** (as the hydrochloride salt) allowed us to synthesize a number of imidazo[1,5-*a*]pyrimidines in good yield.

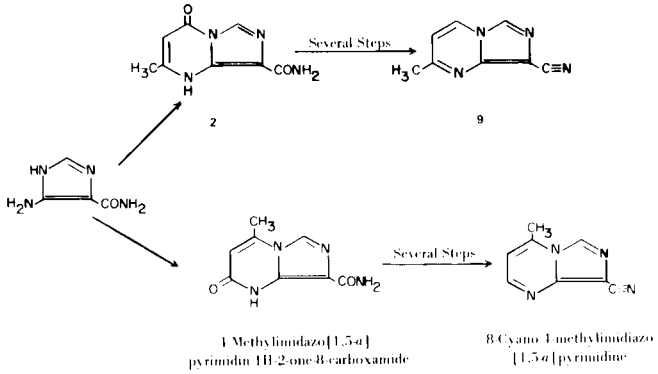
The previous chemistry reported on **1** has been limited to the condensation of this compound with acetic acid to afford 2-methylhypoxanthine (10). The ring closure in this case was through the 4(5)amino and 5(4)carboxamide groups of **1**. We condensed **1** with ethylacetoacetate in analogy to the previously reported methods (5,6), cyclizing through the 4(5)amino group and the imidazole nitrogen, obtaining 2-methylimidazo[1,5-*a*]pyrimidin-1*H*-4-one-8-carboxamide (**2**, Scheme I).

Dehydration of the 8-carboxamide group and chlorination of the 4-keto function occurred upon refluxing **2** with phosphorus oxychloride. Thus, the resultant 4-chloro-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**3**) was expected to be useful from the standpoint of having two reactive functional groups, *e.g.*, the 4-chloro group, which could be displaced by nucleophiles and the 8-cyano group, which could be converted to 8-carboxamidine, 8-thiocarboxamide, and 8-amidrazone groups. A halogen atom in a position adjacent to the bridgehead nitrogen of a fused pyrimidine system was known to be readily displaced by nucleophiles. For example, Makisumi (11) reacted 5-methyl-7-chloro-pyrazolo[1,5-*a*]pyrimidine with sodium methoxide to obtain 7-methoxy-5-methylpyrazolo[1,5-*a*]pyrimidine.

Thus, 4-chloro-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**3**) was converted to 8-cyano-2-methylimidazo[1,5-*a*]-

pyrimidin-1*H*-4-thione (**4**) with thiourea. Also, **3** was converted to 8-cyano-4-ethoxy-2-methylimidazo[1,5-*a*]pyrimidine (**6**) with sodium ethoxide. Additionally, **3** gave various 8-cyano-4-di(mono)alkylamino-2-methylimidazo[1,5-*a*]-pyrimidines (**5a-d**) upon treatment with the corresponding di(mono)alkylamines. Hydrazine also displaced the chlorine atom of **3** to yield 8-cyano-4-hydrazino-2-methylimidazo-[1,5-*a*]pyrimidine (**14**).

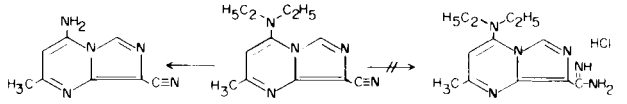
Dethiation of 8-cyano-2-methylimidazo[1,5-*a*]pyrimidine-1*H*-4-thione (**4**) with Raney nickel afforded both 8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**18**) and 2-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide (**19**). The latter compound (**19**) presumably resulted from the alkaline hydrolysis of the former (**18**) under the reaction conditions employed. The pmr spectrum of 3-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**9**) substantiated the structural assignment of 2-methylimidazo[1,5-*a*]pyrimidin-1*H*-4-one-8-carboxamide (**2**). The coupling constant J = 6.7 Hz for the doublets at δ 7.05 and δ 8.70 (measured in parts per million in DMSO-d_6 with DSS (15) as a standard) indicated that the two adjacent protons which were coupled had to have been located at the C_3- and C_4-positions of the ring (6) which favored structure **9**) rather than at the C-2 and C-3 positions of the ring (which would have supported the isomeric structure 8-cyano-4-methylimidazo[1,5-*a*]pyrimidine). Referring to the reaction Scheme I, it can be seen that ethyl acetoacetate must have condensed with AICA to yield **9**, rather than the isomeric 4-methylimidazo[1,5-*a*]-pyrimidin-1*H*-2-one-8-carboxamide (below).



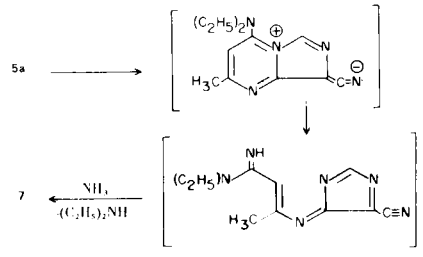
The condensations of ethyl acetoacetate with 3-aminopyrazole and also with 3-amino-1,2,4-triazole, have been reported to have afforded 5-methyl pyrazolo[1,5-*a*]pyrimidin-1*H*-7-one (**12**) and 5-methyl-1,2,4-triazolo[1,5-*a*]-pyrimidin-1*H*-7-one (**13**), respectively. However, since the structures of these bridgehead heterocycles were characterized before the advent of pmr, it has been assumed that the structures were substantiated only on the basis of the reactivity of the chlorinated products (5-methyl-7-chloropyrazolo[1,5-*a*]pyrimidine and 5-methyl-7-chloro-1,2,4-triazolo[1,5-*a*]pyrimidine, respectively.

In fact, the reactivity of all functional groups in the C-4 position (adjacent to the bridgehead nitrogen) appeared to be assisted in this ring system by the electron withdrawal effect of the cyano function in the C-8 position. For example, alkylation of 8-cyano-2-methylimidazo[1,5-*a*]-pyrimidine-1*H*-4-thione (**4**) by methyl iodide had been expected to yield 8-cyano-2-methyl-4-methylthioimidazo-[1,5-*a*]pyrimidine (**8a**), under the mild conditions employed. Instead, however, 8-cyano-4-ethoxy-2-methylimidazo[1,5-*a*]pyrimidine (**6**) was isolated as the sole product. It was presumed that 8-cyano-2-methyl-4-methylthioimidazo[1,5-*a*]pyrimidine (**8a**) was formed initially but that the 4-methylthio group was then easily displaced by a very dilute concentration of ethoxide ion.

Even more surprising was the fact that ammonia displaced the diethylamino group of 8-cyano-4-diethylaminomethylimidazo[1,5-*a*]pyrimidine (**5a**). On the other hand, the 8-cyano group of **5a** was unaffected by ammonia. Witkowski (14) reported that 3-cyano-1-(2,3,5-tri-O-acetyl-β-D-ribofuransyl)-1,2,4-triazole reacted with ammonia in the presence of ammonium chloride to yield 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamidine hydrochloride. Therefore, when 8-cyano-4-diethylamino-2-methylimidazo-[1,5-*a*]pyrimidine (**5a**) was heated at 80° in a bomb in the presence of ammonium chloride, 4-diethylamino-2-methylimidazo[1,5-*a*]pyrimidine-3-carboxamidine hydrochloride was expected to be the product. Instead, however, 4-amino-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**7**) was isolated exclusively.



A possible explanation for this result was that the imidazo[1,5-*a*]pyrimidine ring opened and then recyclized with the resultant loss of diethylamine. Perhaps the resonance stabilized 8-cyanoimidazo[1,5-*a*]pyrimidine ring system (below) with the positive charge density located on the nitrogen accounted for the fact that the 8-cyano function was practically inert (except to certain hydrolysis reactions in the presence of strong acid). On attempting to react the 8-cyano group of **5a** with the various reagents utilized in Witkowski's transformations of various cyano-

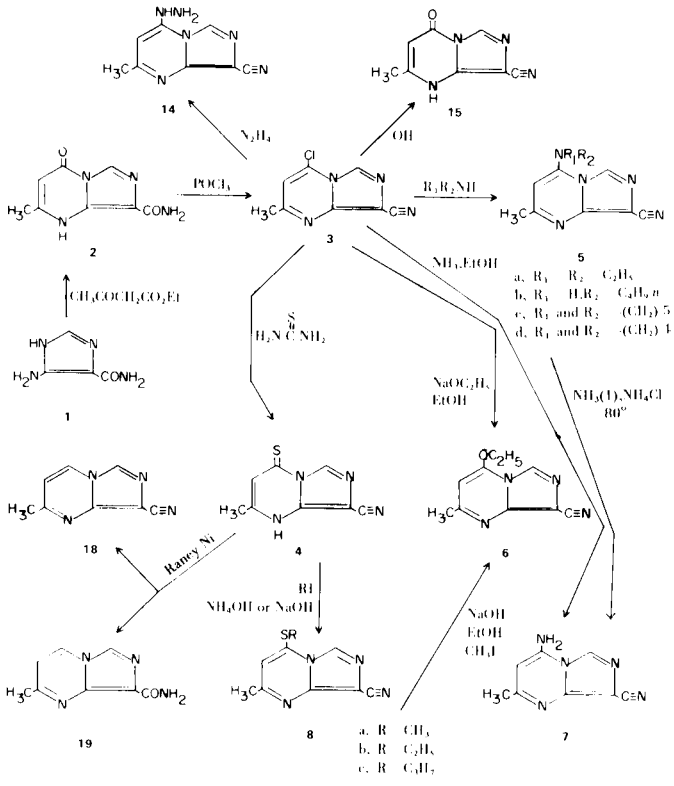


triazoles (14), we only recovered the starting material **5a**.

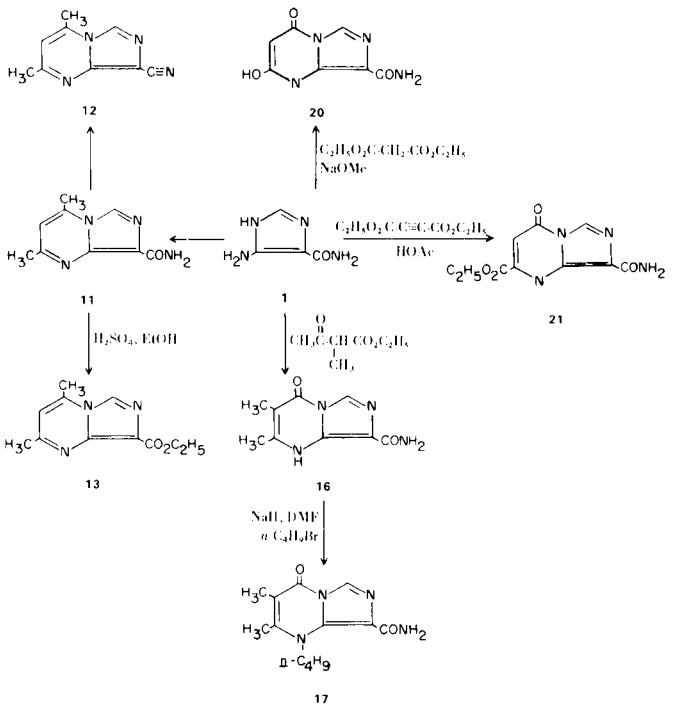
Hydrolysis of the 4-chloro substituent of 4-chloro-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**3**) under mild conditions gave 8-cyano-2-methylimidazo[1,5-*a*]pyrimidin-1*H*-4-one (**15**), without the subsequent hydrolysis of the cyano function.

Condensation of AICA (**1**) with ethyl 2-methylacetoacetate afforded 2,3-dimethylimidazo[1,5-*a*]pyrimidin-1*H*-4-one-8-carboxamide (**16**). Chlorination of **16** with phosphorus oxychloride met with no success. Alkylation on the N-1 position, however, was achieved with *n*-butyl bromide and sodium hydride in dimethylformamide. Thus **16** was alkylated to give 1-*n*-butyl-8-carbamoylimidazo[1,5-*a*]-pyrimidin-2-one (**17**).

Finally, AICA (**1**) was condensed with several other carbonyl reagents. The reaction of **1** with diethylmalonate in the presence of base gave 2-hydroxyimidazo[1,5-*a*]-pyrimidin-1*H*-4-one-8-carboxamide (**20**). Condensation of **1** with diethyl acetylenedicarboxylate afforded ethyl imidazo[1,5-*a*]pyrimidin-1*H*-4-one-8-carboxamide-2-carboxylate (**21**). Also, β-diketones condensed with **1**. Thus, acetylacetone gave 2,4-dimethylimidazo[1,5-*a*]pyrimidine-8-carboxamide (**11**), and dehydration of **11** (with phosphorus oxychloride) gave 8-cyano-2,4-dimethylimidazo-[1,5-*a*]pyrimidine (**12**). The treatment of **12** with sulfuric



SCHEME I



SCHEME II

acid in the presence of ethanol afforded ethyl 2,4-dimethylimidazo[1,5-*a*]pyrimidine-8-carboxylate (**13**). Compound **13** was identical to the product obtained by Guerret (6) formed by the condensation of ethyl 5(4)aminoimidazole-4(5)carboxylate with acetylacetone.

EXPERIMENTAL

Melting points were recorded on a Hoover-Thomas capillary melting point apparatus and were uncorrected. All pmr spectra were recorded on a Hitachi Perkin-Elmer high resolution Model R-20A (60 MHz) instrument. Sodium-2,2-dimethyl-2-silapentane-5-sulfonate (DSS) (15) was used as an internal standard for all pmr spectra run in deuterated dimethylsulfoxide (DMSO-d_6). The ir spectra were recorded in potassium bromide discs with a Perkin-Elmer Model 257 instrument. All uv spectra were recorded in methanol on a Cary 15 instrument. All analyses for C, H, and N were performed by Heterocyclic Chemical Corporation of Harrisonville, Missouri. Pmr assignments were recorded as parts per million (δ).

2-Methylimidazo[1,5-*a*]pyrimidin-1*H*-4-one-8-carboxamide (**2**).

A mixture of 65 g. (0.4 mole) of 5(4)aminoimidazole-4(5)-carboxamide hydrochloride (9) (**1**, AICA), 52 g. (0.4 mole) of ethyl acetoacetate, 34 g. (0.4 mole) of sodium acetate, and 500 ml. of glacial acetic acid was refluxed with stirring for 20 hours. The cooled reaction mixture was filtered. The gray precipitate which was filtered off was washed well with water, then recrystallized from dimethylformamide (1 g. of **2** in *ca.* 200 ml. of hot DMF) to yield 35 g. of the title compound. The acetic acid filtrate was evaporated to yield a residue which was recrystallized to afford an additional 5 g. (total 40 g., 52%), m.p. 307-309° (gray-white

cubettes); pmr (DMSO-d_6): δ 2.30 (s, 3), δ 4.10 (broad band, 3). δ 5.42 (s, 1), and δ 8.02 (s, 1) in ppm; uv λ max (methanol): (log ε max) 225 (4.06), 280 (3.73), 283 sh (3.71) and 340 (4.10) nm.

Anal. Calcd. for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.16. Found: C, 49.68; H, 4.15; N, 29.29.

4-Chloro-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**3**).

A mixture of 35 g. (0.16 mole) of 2-methylimidazo[1,5-*a*]-pyrimidin-1*H*-4-one-8-carboxamide (**2**), 30 ml. of *N,N*-dimethylaniline, and 400 ml. of AR grade phosphorus oxychloride was refluxed with stirring. Refluxing was continued for only 20 minutes once the solids dissolved. Then the dark solution was cooled (externally) rapidly to 40° and the excess phosphorus oxychloride was removed by distillation (rotovac, 40°/15 mm). The residual red oil thus obtained was cautiously poured over 500 g. of chipped ice (stirred manually). The organic material was extracted from this mixture with 3 X 300 ml. portions of chloroform. The chloroform extract was washed once with 300 ml. of 10% aqueous sodium bicarbonate solution. Next, the chloroform solution was dried (anhydrous sodium sulfate) for 2 hours and then quickly poured over 300 g. of Woelm basic alumina (activity grade 1) in a large glass Buchner funnel. The alumina was washed (suction) with a total of *ca.* 4 l. of chloroform. The combined washings were evaporated (rotovac 30°/15 mm) to yield a light orange colored solid. Recrystallization of this solid afforded 16.0 g. (46%) of pale yellow plates, m.p. 211-212°; pmr (DMSO-d_6): δ 2.65 (s, 3), δ 7.45 (s, 1), δ 8.65 (s, 1); uv λ max (methanol): (log ε max) 227 nm (4.40); ir cm^{-1} 2210 (C≡N).

Anal. Calcd. for $C_8H_5N_4Cl$: C, 49.87; H, 2.59; N, 29.09. Found: C, 49.99; H, 2.81; N, 29.31.

8-Cyano-2-methylimidazo[1,5-*a*]pyrimidine-1*H*-4-thione (**4**).

A mixture of 1.93 g. (10 mmoles) of 4-chloro-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**3**), 0.86 g. (12 mmoles) thiourea, and 2 drops of 88% aqueous formic acid in 20 ml. of absolute ethanol was refluxed for 12 hours. Evaporation of the resultant red solution (rotovac) afforded a red solid which was recrystallized from methanol-water yielding 1.8 g. (95%) of **4** as yellow platelets, m.p. 285-287° dec.; pmr (DMSO-d_6): δ 2.42 (s, 3), δ 6.72 (s, 1), δ 8.55 (s, 1), δ 10.5 (broad band, 1); uv λ max (methanol): (log ε max) 222 (4.89), 271 (3.08), 292 sh (2.73), 3.05 sh (2.74), 370 (3.19) nm.

Anal. Calcd. for $C_8H_6N_4S$: C, 50.52; H, 3.15; N, 29.47. Found: C, 50.37; H, 3.20; N, 29.55.

General Procedure:

8-Cyano-4-diethylamino-2-methylimidazo[1,5-*a*]pyrimidine (**5a**).

A solution of 1.93 g. (10 mmoles) of 4-chloro-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**3**) in 25 ml. of absolute ethanol was stirred at room temperature as 1.46 g. (0.02 mole) of diethylamine was slowly added. The resultant mixture was heated to boiling (steam bath) for 10-15 minutes. Then the solution was evaporated (rotovac) and the residual solid which was obtained was mixed with 10 ml. of water (to dissolve water soluble diethylamine hydrochloride). The water insoluble residue was then recrystallized from methanol-water to afford 1.2 g. (52%) of **5** in the form of pale yellow needles, m.p. 115-116°; pmr (DMSO-d_6), δ 1.23 (t, 3), δ 2.52 (s, 3), δ 3.54 (q, 2), δ 6.40 (s, 1), δ 8.24 (s, 1); ir (potassium bromide): 2210 cm^{-1} (C≡N); uv λ max (methanol): (log ε max) 220 (4.21), 225 (3.99), 355 (4.03) nm.

Anal. Calcd. for $C_{12}H_{15}N_5$: C, 62.88; H, 6.55; N, 30.56. Found: C, 62.53; H, 6.70; N, 30.78.

The following members of this series **5b-d** were prepared by an identical procedure and the analytical data and yields are given below.

4-*n*-Butylamino-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**5b**).

This compound was obtained in 44% yield as pale yellow plates, m.p. 154-155° (methanol-water); ir (potassium bromide): 2210 cm^{-1} (C≡N); uv λ max (methanol): (log ε max) 220 (4.08), 255 (4.18), 357 (4.14) nm.

Anal. Calcd. for $C_{12}H_{15}N_5$: C, 62.88; H, 6.55; N, 30.56. Found: C, 63.01; H, 6.72; N, 30.33.

8-Cyano-2-methyl-4-piperidinoimidazo[1,5-*a*]pyrimidine (**5c**).

This compound was obtained in 90% yield as light yellow plates, m.p. 160-161° (methanol-water); ir (potassium bromide): 2205 cm^{-1} (C≡N); uv λ max (methanol): (log ε max) 223 (4.28), 260 (3.92), 3.55 (3.98) nm.

Anal. Calcd. for $C_{13}H_{15}N_5$: C, 64.73; H, 6.22; N, 29.04. Found: C, 65.01; H, 6.17; N, 29.22.

8-Cyano-2-methyl-pyrrolidinoimidazo[1,5-*a*]pyrimidine (**5d**).

This compound was obtained in 93% yield as light yellow plates, m.p. 210-211° (ethanol); ir (potassium bromide): 2210 cm^{-1} (C≡N); uv λ max (methanol): (log ε max) 210 (4.08), 249 (4.07), 285 sh (3.67), 295 sh (3.68), 350 (4.07) nm.

Anal. Calcd. for $C_{12}H_{13}N_5$: C, 63.42; H, 5.77; N, 30.82. Found: C, 63.60; H, 5.80; N, 31.06.

8-Cyano-2-methylimidazo[1,5-*a*]pyrimidin-1*H*-4-one (**15**).

A suspension of 0.963 g. (5 mmoles) of 4-chloro-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**3**) in 5 ml. of 2*N* sodium hydroxide containing 10 ml. of methanol was heated on the steam bath for 5 minutes at *ca.* 50°. The resultant solution was then quickly chilled (ice bath). Then 2*N* hydrochloric acid (cold) was added dropwise to bring the solution to *p*H 5. The mixture deposited a yellowish precipitate which was subsequently filtered, washed with water and sucked dry on the filter plate. The precipitate was recrystallized from DMF-water to afford 0.76 g. (88%) of **15** as yellow plates, m.p. 358° dec., (darkens at 300°); pmr (DMSO-d_6, one drop of sodium deuteroxide added): δ 2.40 (s, 3), δ 2.68 (s, 1), δ 8.25 (s, 1); ir (potassium bromide): 2215 cm^{-1} (C≡N); uv λ max (methanol): (log ε max) at *p*H 7, 230 (4.11), 270 (3.86), 325 (3.92) nm; λ max (methanol): (log ε max) at *p*H 11, 235 (4.19), 280 (3.82), 335 (4.12) nm.

Anal. Calcd. for $C_8H_6N_4O$: C, 55.17; H, 3.44; N, 32.18. Found: C, 54.89; H, 3.40; N, 32.30.

8-Cyano-4-hydrazino-2-methylimidazo[1,5-*a*]pyrimidine (**14**).

A solution of 3.8 g. (20 mmoles) of 4-chloro-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**3**) in 50 ml. of ethanol was cooled to 15° and 5 ml. of 85% hydrazine hydrate was added. The mixture was then stirred for 30 minutes at room temperature during which time a voluminous white solid precipitated. The precipitate was recrystallized from ethanol-water to yield 3.4 g. (85%) of **14** in the form of silky yellow-white needles, m.p. 225-226°; ir (potassium bromide): 2208 cm^{-1} (C≡N); uv λ max (methanol): (log ε max) at *p*H 7, 210 (4.17), 240 (4.29), 280 sh (3.25), 290 sh (3.30), 335 (4.03) nm: λ max (methanol): (log ε max) at *p*H 1, 209 (4.25), 245 sh (3.67), 265 (3.40), 275 sh (3.36), 320 (4.03) nm.

Anal. Calcd. for $C_8H_8N_6$: C, 51.05; H, 4.28; N, 44.66. Found: C, 50.86; H, 4.32; N, 44.80.

8-Cyano-4-ethoxy-2-methylimidazo[1,5-*a*]pyrimidine (**6**).

Method A.

A solution of 400 mg. of 85% potassium hydroxide pellets in

5 ml. of water was prepared. To this solution was added 760 mg. (4 mmoles) of 8-cyano-2-methylimidazo[1,5-*a*]pyrimidine-1*H*-4-thione (**4**) and 1.5 g. of methyl iodide dissolved in 10 ml. of ethanol. The solution was stirred for 5-10 minutes at room temperature. Within a few minutes the solution depositied a white solid which was then filtered. The precipitate was filtered and recrystallized from ethanol to yield 360 mg. (48%) of the title compound **6**, m.p. 198-199°; pmr (DMSO-d_6): δ 2.60 (s, 3), δ 1.54 (t, 3), δ 4.55 (q, 2), δ 6.62 (s, 1), δ 8.35 (s, 1); uv λ max (methanol): (log ε max), 225 (4.74), 272 (3.12), 282 (3.13), 325 (3.27) nm.

Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.98; N, 27.71. Found: C, 59.06; H, 5.07; N, 28.03.

Method B.

A solution of 250 mg. of sodium metal in 20 ml. of ethanol was prepared and cooled to 15°. To this solution was added 1.93 g. (10 mmoles) of 4-chloro-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**3**), and the resultant mixture was stirred. The solution was allowed to come to room temperature and was left to stand at 25° for *ca.* 4 hours. Then the solvent was evaporated (rotovac) and the residue obtained was dissolved in water. This solution was then carefully neutralized with 2*N* hydrochloric acid, whereupon a precipitate was formed. The precipitate was filtered, washed with water, dried by suction (Büchner) and recrystallized from ethanol to yield 1.76 g. (85%) of **6**, m.p. 198-199°. The mixed melting point of samples prepared by methods A and B showed no depression. The spectra (ir, uv, pmr) of samples obtained from either method had identical characteristics.

General Method:

8-Cyano-2-methyl-4-methylthioimidazo[1,5-*a*]pyrimidine (**8a**).

A solution of 950 mg. (5 mmoles) of 8-cyano-2-methylimidazo-[1,5-*a*]pyrimidine-1*H*-4-thione (**4**) in 3 ml. of 17*M* ammonium hydroxide and 5 ml. of water was treated with 760 mg. (5 mmoles) of methyl iodide idssolved in 1 ml. of ethanol. The resultant solution was stirred at 25° for *ca.* 2 hours whereupon a precipitate formed. The precipitate was filtered and washed successively with 10 ml. of water, 5 ml. of cold ethanol and 5 ml. of cold ether. The dried material was then recrystallized from ethanol to afford 500 mg. (43%) of yellow platelets, m.p. 210-212°; ir (potassium bromide): 2210 cm^{-1} (C≡N); uv λ max (methanol): (log ε max) 225 (4.30), 254 (3.62), 285 (3.41), 297 (3.42), 340 (3.45) nm.

Anal. Calcd. for $C_9H_8N_4S$: C, 52.94; H, 3.92; N, 27.45. Found: C, 52.88; H, 3.97; N, 27.38.

8-Cyano-4-ethylthio-2-methylimidazo[1,5-*a*]pyrimidine (**8b**).

This compound was obtained in 43% as yellow prisms, m.p. 168-169° (ethanol); pmr (DMSO-d_6): δ 1.45 (t, 3), δ 2.60 (s, 3), δ 3.40 (q, 2), δ 7.10 (s, 1), δ 8.42 (s, 1).

Anal. Calcd. for $C_{10}H_{10}N_4S$: C, 55.04; H, 4.62; N, 25.68. Found: C, 54.85; H, 4.56; N, 25.43.

8-Cyano-2-methyl-4-*n*-propylthioimidazo[1,5-*a*]pyrimidine (**8c**).

This compound was prepared similarly in 52% as yellow prisms, m.p. 139-141° (ethanol-ether); uv λ max (methanol): (log ε max) 225 (4.32), 253 (3.51), 285 (3.36), 297 (3.37), 340 (3.39) nm.

4-Amino-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**7**).

Method A.

In a pressure bomb were placed 2.3 g. (10 mmoles) of 8-cyano-4-diethylamino-2-methylimidazo[1,5-*a*]pyrimidine (**5a**), 0.6 g. (10 mmoles) of ammonium chloride, and 150 ml. of liquid ammonia. The bomb was sealed and heated at 85° for *ca.* 72 hours. The bomb was cooled and the ammonia was allowed to evaporate (hood). The residual solid thus obtained was suspended in 100 ml. of water, filtered and recrystallized from ethanol, affording 1.1 g. (52%) of lemon yellow needles, m.p. 282-283° dec.; pmr (DMSO-d_6), with 1-2 drops of sodium deuteroxide), δ 2.42 (s, 3), δ 6.1 (s, 1), δ 8.48 (s, 1); uv λ max (methanol): (log ε max) 210 (4.10), 237 (4.18), 384 (3.74) nm.

Anal. Calcd. for $C_8H_7N_3$: C, 55.48; H, 4.07; N, 40.44. Found: C, 55.64; H, 3.98; N, 40.13.

Method B.

A solution of 1.93 g. (10 mmoles) of 4-chloro-8-cyano-2-methylimidazo[1,5-*a*]pyrimidine (**3**) in 200 ml. of ethanol was cooled to 15°. Then ammonia gas was bubbled into the solution at a rapid rate for *ca.* 2 hours. The solution was boiled for 30 minutes to expel excess ammonia. Then the ethanolic solution was evaporated (rotovac) and the residue was recrystallized from ethanol-water to afford 1.76 g. (92%) of **7**, m.p. 282-283°. The analysis of the compound prepared by Method B was identical (within ± 0.4%) and no mixed melting point depression was observed from a mixture of samples. The pmr, ir, and uv of each sample were identical in all respects.

8-Cyano-2-methylimidazo[1,5-*a*]pyrimidine (**18**) and 2-Methylimidazo[1,5-*a*]pyrimidine-8-carboxamide (**19**).

A solution of 2.5 g. (15 mmoles) of 8-cyano-2-methylimidazo-[1,5-*a*]pyrimidine-1*H*-4-thione in 20 ml. of 17*M* ammonium hydroxide was diluted with 200 ml. of water. To this solution was added *ca.* 20 g. of Raney nickel (Grace catalyst #W28) and the mixture was refluxed with mechanical stirring for 1.5 hours. The mixture was filtered hot and the Raney nickel was washed with 150 ml. of boiling ethanol. The washings and filtrate were combined and concentrated to 80 ml., whereupon the solution deposited tan colored solid. The solid was recrystallized from ethanol then from ethyl acetate, affording 1.2 g. (65%) of **19**, m.p. 205-206°, as tan-white plates; ir (potassium bromide): 3410 (NH_2), 1730, (C=O) cm^{-1} (no C≡N band); uv λ max (methanol): (log ε max) 222 (4.49), 227 sh (4.47), 242 sh (3.99), 250 (3.84), 265 (3.76), 276 (3.81), 285 sh (3.73), 340 (3.45) nm.

Anal. Calcd. for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.60; H, 4.61; N, 32.03.

Further evaporation of the remaining 30 ml. of aqueous ethanol filtrate (above) obtained upon washing the Raney nickel, yielded 0.9 g. (26%) of **18**, recrystallized from ethanol-ethyl acetate as yellowish needles, m.p. 227-228°; pmr (DMSO-d_6): δ 2.61 (s, 3), δ 7.05 (d, 1), δ 8.45 (s, 1), δ 8.70 (d, 1): $J_{3,4}$ = 6.7 Hz; ir (potassium bromide): 2210 cm^{-1} (C≡N); uv λ max (methanol): (log ε max) 227 (4.32), 261 sh (3.61), 272 (3.65), 283 (3.61) nm.

Anal. Calcd. for $C_8H_6N_4$: C, 60.75; H, 3.82; N, 35.43. Found: C, 60.93; H, 4.02; N, 35.61.

2,3-Dimethylimidazo[1,5-*a*]pyrimidin-1*H*-4-one-8-carboxamide (**16**).

A mixture of 16.25 g. (0.1 mole) of AICA (**1**) hydrochloride, 14.42 g. (0.1 mole) of ethyl 2-methylacetoacetate (16), 8.21 g. (0.1 mole) of sodium acetate and 300 ml. acetic acid was refluxed for 20 hours. The mixture was cooled and filtered and the precipitate thus obtained was recrystallized from DMF (1 g. of **16** to 30 ml. of boiling DMF) to yield an analytical sample, m.p. *ca.* 354° dec., as white crystals.

Anal. Calcd. for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.29; H, 5.02; N, 27.12.

1-*n*-Butyl-2,3-dimethylimidazo[1,5-*a*]pyrimidin-4-one-8-carboxamide (**17**).

A suspension of 100 mg. of sodium hydride (50% in mineral oil) (17) in 50 ml. of dry DMF was stirred under nitrogen as 206 mg. (1 mmole) of 8-carbamoyl-2,3-dimethylimidazo[1,5-*a*]pyrimidin-4-one (**16**) was added. After stirring the mixture for 10 minutes at 25°, 400 mg. (2.5 mmoles) of *n*-butyl iodide in 5 ml. of DMF was added *via* addition funnel (dropwise over a 5 minute period). The mixture was stirred at 25° for 24 hours and then 2 ml. of water was cautiously added to decompose the excess sodium hydride. The mixture was evaporated (rotovac 40-50°/1 mm) and the residue thus obtained was suspended in water (50 ml.) and filtered. The filtered product was recrystallized from DMF-ethanol to give a tan powder, m.p. 328-330° dec.; pmr (DMSO-d_6): δ 0.95 (m, 3), δ 1.50 (m, 4), δ 2.00 (s, 1), δ 2.30 (s, 1), δ 3.40 (m, 2), δ 7.80 (s, 1), δ 8.45 (m, 2); ir (potassium bromide): 2280, 2920, 3115 cm^{-1}; uv λ max (methanol): (log ε max) at *p*H 7, 275 (4.30), 335 (3.70) nm; at *p*H 11, 283 sh (3.53), 292 (3.62), 355 (4.54) nm.

Anal. Calcd. for $C_{13}H_{18}N_4O_2$: C, 59.54; H, 6.87; N, 21.37. Found: C, 59.30; H, 7.02; N, 21.53.

2-Hydroxyimidazo[1,5-*a*]pyrimidin-1*H*-4-one-8-carboxamide (**20**).

A solution of sodium ethoxide was prepared from 5.4 g. of sodium metal and 400 ml. of absolute ethanol. To this solution was added 16.25 g. (0.1 mole) of AICA (**1**) hydrochloride and 15.5 ml. (16.50 g., 0.1 mole) of diethyl malonate. The mixture was stirred and refluxed for 15 hours under nitrogen. The mixture was cooled and a tan precipitate was filtered. This precipitate was dissolved in water and acidified (acetic acid) to *p*H 5, while the mixture was chilled in an ice bath. This solution was then partially reduced in volume (rotovac) until a white paste formed. The paste was filtered and then purified by reprecipitation from sodium hydroxide solution with dilute hydrochloric acid. A white solid was obtained, 8.5 g. (45%), m.p. 338-340° dec.; pmr (DMSO-d_6): δ 7.60 (s, 1), δ 7.85 (s, 1).

Anal. Calcd. for $C_7H_6N_4O_3$: C, 43.29; H, 3.09; N, 28.86. Found: C, 43.40; H, 3.15; N, 29.06.

Ethyl Imidazo[1,5-*a*]pyrimidin-1*H*-4-one-8-carboxamide-2-carboxylate (**21**).

A mixture of 4.08 g. (25 mmoles) of AICA (**1**) hydrochloride, 3.63 g. (25 mmoles) of diethyl acetylenedicarboxylate (16), 2.05 g. (25 mmoles) of sodium acetate, and 65 ml. of glacial acetic acid was stirred for 7 days at 25° under nitrogen. Then the mixture was filtered and the pricipitate was discarded. The filtrate was evaporated (rotovac, 40°/2 mm) and the resultant oily residue was triturated with ethanol-water (1:1) to yield a yellow solid. The crude product was recrystallized from ethanol-water to afford 2.2 g. (41%) of yellow plates, m.p. 240-242° dec.

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 48.00; H, 4.02; N, 23.29. Found: C, 47.83; H, 3.96; N, 22.45.

2,4-Dimethylimidazo[1,5-*a*]pyrimidine-8-carboxamide (**11a**).

A mixture of 8.13 g. (5 mmoles) of AICA (**1**) hydrochloride, 5.0 g. (5 mmoles) of pentane-2,4-dione (17) (acetylacetone), 2.00 g. (5 mmoles) of sodium hydroxide (pellets) in 25 ml. of water, 2 drops of piperidine, and 100 ml. of ethanol was refluxed with stirring for 3 hours. The mixture was stirred overnight at 25° and then filtered. The filtrate was evaporated (rotovac) to yield a yellow oil. The oil was triturated with ethanol which afforded a yellow solid. Recrystallization of this solid from methanol gave 6.5 g. (73%) of **11a** as a yellow powder, m.p. 305-307° dec.

Anal. Calcd. for $C_8H_9N_3$: C, 65.30; H, 6.12; N, 28.57. Found: C, 65.52; H, 6.31; N, 28.73.

8-Cyano-2,4-dimethylimidazo[1,5-*a*]pyrimidine (**12**).

A suspension of 5.7 g. of 2,4-dimethylimidazo[1,5-*a*]pyrimidine-8-carboxamide (**11a**) in 80 ml. of phosphorus oxychloride was refluxed with stirring for 1 hour. The excess phosphorus oxychloride was distilled off and the red oily residue was carefully poured onto 100 g. of crushed ice with manual stirring. The acidic solution was neutralized with solid sodium bicarbonate and the organic material was extracted with 2 X 50 ml. portions of chloroform. The chloroform extracts were combined, washed with water (separatory funnel) and dried (anhydrous sodium sulfate). The chloroform was evaporated and the solid obtained was recrystallized from acetone in the form of yellow platelets, m.p. 209-210°; pmr (DMSO-d_6): δ 2.60 (s, 3), δ 2.74 (s, 1), δ 6.95 (s, 1), δ 8.50 (s, 1); ir (potassium bromide): 2250 cm^{-1} (C≡N).

Anal. Calcd. for $C_9H_8N_4$: C, 62.77; H, 4.68; N, 32.54. Found: C, 62.52; H, 4.48; N, 32.72.

Ethyl 2,4-Dimethylimidazo[1,5-*a*]pyrimidine-8-carboxylate (**13**).

A solution of 200 mg. (1 mmole) of 8-cyano-2,4-dimethylimidazo[1,5-*a*]pyrimidine (**11**) in 2 ml. of concentrated sulfuric acid (18*M*) was carefully added to 50 ml. of absolute ethanol (ice bath cooling). The resultant solution was then refluxed for *ca.* 5 hours. The solution was cooled and neutralized with aqueous sodium bicarbonate solution and the neutral mixture was evaporated (rotovac, 45°/2 mm). The residue obtained on evaporation of the solvent was then recrystallized from benzene-petroleum ether to afford 240 mg. (95%) of **13** as pale yellow needles, m.p. 147-148° (lit. (6) m.p. 145-146°).

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