1.42 mmoles) in methanol (5 ml.) containing anhydrous 95% hydrazine (0.05 ml.) was refluxed for 4 hr., and the mixture was allowed to stand at room temperature overnight. The pure solid was collected by filtration, washed with methanol (4 ml.), and dried *in vacuo* over phosphorus pentoxide; yield, 200 mg. (74%). This compound decomposed rapidly without melting above 200°. The sample was recrystallized from N,N-dimethylformamide–ethanol. λ_{max} mμ ($\epsilon \times 10^{-3}$) at pH 1: 270 (4.44), 372 (7.35). $\bar{\nu}_{max}$ cm.$^{-1}$: 3400 and 3260 (NH); 3080 (aromatic CH); 2980, 2945, 2860, and 2820 (aliphatic CH); 1625 (NH); 1555 and 1485 (C=C, C=N).

Anal. Calcd. for $C_7H_9N_7$: C, 43.95; H, 4.72; N, 51.25. Found: C, 43.90; H, 4.92; N, 51.32.

From the combined filtrate and wash, 50 mg. of VIIIb slightly contaminated with VI, was recovered.

5-Amino-3-methylpyrimido[5,4-*e*]-*as*-triazine (VIIIa).—Solid ethyl *N*-(4-amino-6-chloro-5-pyrimidinyl)acetimidate (2.0 g., 9.3 mmoles)[6] was added to a solution of sodium dihydrogen phosphate hydrate (1.35 g.) and disodium hydrogen phosphate (1.35 g.) in methanol (10 ml.) and water (25 ml.) containing 95% hydrazine (0.42 ml.). The mixture was heated at 80° for 2 hr. and the resulting solution was allowed to stand at room temperature overnight. The dark crystals that deposited were collected by filtration, washed with water (5 ml.), and dried *in vacuo* over phosphorus pentoxide; yield, 500 mg. This solid was recrystallized from ethanol (50 ml.) to yield 350 mg. (23%) of product in two crops, m.p. 277–280° dec. λ_{max} mμ ($\epsilon \times 10^{-3}$) at pH 1: 245 (8.25), 350 (8.40), 358 (sh) (8.25); at pH 7: 252 (13.6), 280 (sh) (2.56), 372 (5.88). $\bar{\nu}_{max}$ cm.$^{-1}$: 3290 and 3100 (broad) (NH); 1655 (NH); 1575 and 1510 (C=C, C=N); 1445, 1350, and 1220 (strong unassigned bands).

Anal. Calcd. for $C_6H_6N_6$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.18; H, 3.95; N, 51.90.

5-Amino-3-ethylpyrimido[5,4-*e*]-*as*-triazine (VIIIb) was prepared by a similar process from 2.0 g. of ethyl *N*-(4-amino-6-chloro-5-pyrimidinyl)propionimidate[6]; yield, 500 mg. (32%); m.p. 223–225° dec. λ_{max} mμ ($\epsilon \times 10^{-3}$) at pH 1: 246 (8.34), 350 (8.34), 359 (sh) (8.17); at pH 7: 253 (13.65), 371 (5.90). $\bar{\nu}_{max}$ cm.$^{-1}$: 3290 and 3100 (NH); 2975, 2940, and 2880 (aliphatic CH); 1650 (NH); 1570 and 1510 (C=C, C=N).

Anal. Calcd. for $C_7H_8N_6$: C, 47.72; H, 4.55; N, 47.72. Found: C, 47.60; H, 4.61; N, 47.98.

5-Benzylamino-3-ethylpyrimido[5,4-*e*]-*as*-triazine (X).—A solution of 5-amino-3-ethylpyrimido[5,4-*e*]-*as*-triazine (1.0 g., 5.7 mmoles) in propanol (20 ml.) containing benzylamine (3.0 ml.) was refluxed for 5 hr. and evaporated to a small volume *in vacuo*. After this residue was washed on a funnel with water (60 ml.) to remove an insoluble dark oil, the remaining solid was dried *in vacuo* over phosphorus pentoxide to yield 1.28 g. (82%), m.p. 143–145° dec. For analysis a sample was recrystallized from petroleum ether (85–105°); m.p. 153–154° dec. λ_{max} mμ ($\epsilon \times 10^{-3}$) at pH 1: 223 (15.6), 254 (5.85), 362 (sh) (12.1), 369 (12.3); at pH 7: 224 (17.9), 257 (9.75), 385 (8.35). $\bar{\nu}_{max}$ cm.$^{-1}$: 3190 (NH); 2950 and 2910 (aliphatic CH); 1600, 1585 (sh), 1560, and 1500 (C=C, C=N).

Anal. Calcd. for $C_{14}H_{14}N_6$: C, 63.18; H, 5.27; N, 31.55. Found: C, 63.22; H, 5.21; N, 31.68.

3-Methylpyrimido[5,4-*e*]-*as*-triazin-5(6H)-one (XIa).—A suspension of 5-amino-3-methylpyrimido[5,4-*e*]-*as*-triazine (250 mg., 1.54 mmoles) in 1.07 *N* sodium hydroxide (1.65 ml.) was stirred at room temperature for 3 hr. The resulting solution was neutralized with 1.03 *N* hydrochloric acid (1.71 ml.) and evaporated to dryness *in vacuo*. This residue was extracted with two 25-ml. portions of acetone, and the combined extracts were evaporated to yield 190 mg. (75%). Recrystallization of this solid from tetrahydrofuran–petroleum ether (85–105°) gave the analytical sample; m.p. 199–200° solidifies and remelts at 213–215 dec. λ_{max} mμ ($\epsilon \times 10^{-3}$) at pH 1: 236 (8.7), 264 (5.36), 336 (5.28). At pH 7: 249 (12.4), 355 (3.73); at pH 13 : 251 (15.7), 278 (sh) (2.96), 372 (4.66). $\bar{\nu}_{max}$ cm.$^{-1}$: 3200 (NH); 2900–2500 (acidic H); 1750, 1735, and 1710 (C=O); 1610, 1595, 1540, and 1520 (C=C, C=N).

Anal. Calcd. for $C_6H_5N_5O$: C, 44.20; H, 3.07; N, 42.90. Found: C, 44.30; H, 3.03; N, 42.79.

3-Ethylpyrimido[5,4-*e*]-*as*-triazin-5(6H)-one (XIb) was prepared by a similar process from 500 mg. of 5-amino-3-ethylpyrimido[5,4-*e*]-*as*-triazine: yield, 340 mg. (68%) m.p. 183–185° dec. A second recrystallization from tetrahydrofuran–petroleum ether gave the analytical sample; m.p., 185–188° dec. λ_{max} mμ ($\epsilon \times 10^{-3}$) at pH 1: 237 (8.70), 265 (5.65), 338 (6.05); at pH 7: 250 (12.7), 360 (3.80); at pH 13: 250 (12.2), 280 (sh) (3.4), 373 (4.68). $\bar{\nu}_{max}$ cm.$^{-1}$: 3200 and 3150 (NH); 2980 (aliphatic CH); 2900–2500 (acidic H); 1730 and 1700 (C=O); 1610 (sh), 1600, 1540, and 1520 (C=C, C=N).

Anal. Calcd. for $C_7H_7N_5O$: C, 47.40; H, 3.95; N, 39.50. Found: C, 47.00; H, 3.78; N, 39.39.

Acknowledgment.—The authors are indebted to Dr. W. J. Barrett and the members of the Analytical Section of Southern Research Institute who performed the spectral and most of the analytical determinations reported, and to Dr. W. C. Coburn and Mrs. M. C. Thorpe for their helpful discussion of the infrared and proton magnetic spectra. Some of the analyses were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tennessee.

Aromaticity in Heterocyclic Systems. I. The Synthesis and Structure of Certain 4,6-Dihydroxyimidazo[4,5-*c*]pyridines[1]

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The synthesis of the imidazo[4,5-*c*]pyridine ring has been accomplished for the first time from imidazole intermediates. 4,6-Dihydroxyimidazo[4,5-*c*]pyridine and related 2-substituted derivatives have been prepared for the first time from the requisite 4-imidazoleacetamide-5-carboxylic acid ester. 4,6-Dihydroxyimidazo[4,5-*c*]-pyridine (I) has been shown by n.m.r. to exist as the diketo form Ia. This accounts for the ease of pyridine ring cleavage of the 4,6-dihydroxy compounds in the presence of hot acid or base. Evidence is considered which supports the existence of the more aromatic enol form Ic present as the anion in dilute base.

Although the synthesis of 4-aminoimidazo[4,5-*c*]-pyridine (3-deazaadenine) and 4-hydroxyimidazo[4,5-*c*]pyridine (3-deazahypoxanthine) previously has been reported,[3] other purine analogs such as 4,6-dihydroxyimidazo[4,5-*c*]pyridine (I), the xanthine analog, and 2,4,6-trihydroxyimidazo[4,5-*c*]pyridine (II), the analog of uric acid, have not been recorded previously. Pre-

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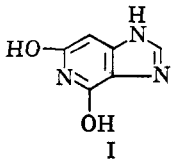
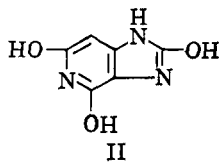
(2) In part from the Master's theses of Claude V. Greco and Calvin G. Beames, Jr., New Mexico Highlands University, 1953 and 1955.

(3) C. A. Salemink and G. M. Van der Want, *Rec. trav. chim.*, **68**, 1013 (1949).



I



II

vious syntheses of the imidazo[4,5-*c*]pyridine ring[4-10] have all proceeded from the appropriate 3,4-diaminopyridine which was then ring closed by various means to give the requisite imidazo[4,5-*c*]pyridine.

It seemed of theoretical interest to investigate the possibility of an alternative synthesis which would involve a substituted imidazole that could then be ring closed to form the pyridine portion of the molecule.

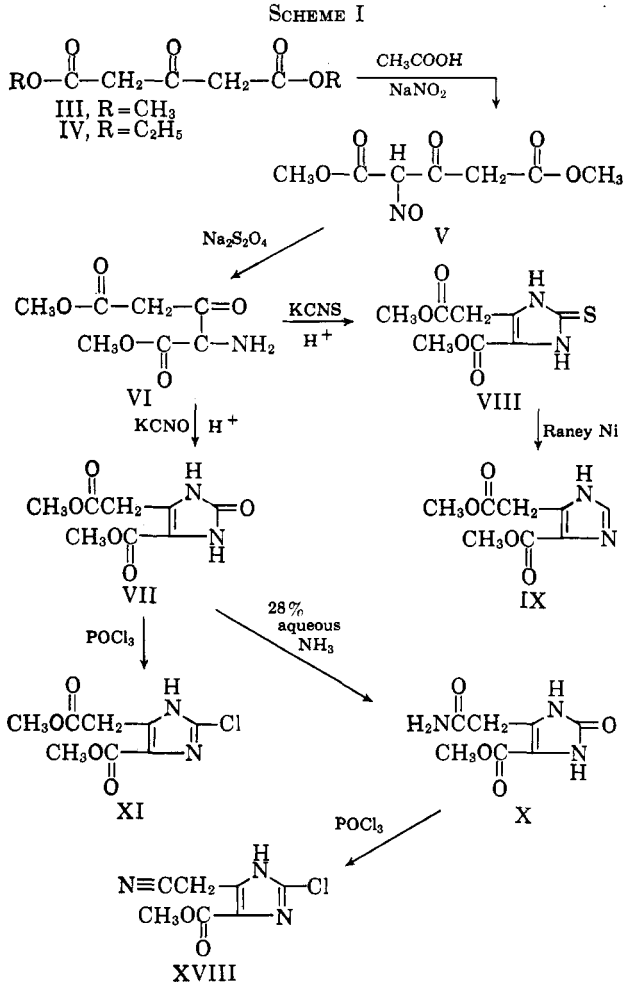
The synthesis of a number of previously unknown required derivatives of imidazole were accordingly investigated. The commercial availability of methyl acetonedicarboxylate (III)[11] and improvement in the synthesis of ethyl acetonedicarboxylate (IV)[12] provided a ready source of starting material for the present work. Methyl acetonedicarboxylate (III) was nitrosated with sodium nitrite in glacial acetic acid after a modified procedure of Pechmann[13] for the diethyl ester to yield dimethyl-2-nitroso-3-ketoglutarate (V) which was reduced with sodium hydrosulfite to the amino derivative VI. When VI was treated with potassium cyanate in the presence of sulfuric acid, 4-acetic acid-2-imidazolone-5-carboxylic acid dimethyl ester (VII) was readily obtained. Potassium thiocyanate in the presence of acid ring closed VI to 4-acetic acid-2-imidazolethione-5-carboxylic acid dimethyl ester (VIII). Treatment of 4-acetic acid-2-imidazolone-5-carboxylic acid dimethyl ester (VII) and phosphorus oxychloride provided 4-acetic acid-2-chloroimidazole-5-carboxylic acid dimethyl ester (XI).

When 4-acetic acid-2-imidazolone-5-carboxylic acid dimethyl ester (VII) was treated with aqueous ammonia heated on the steam bath, a monoamide, 4-acetamide-2-imidazolone-5-carboxylic acid methyl ester (X), was readily prepared. 4-Acetic acid-2-imidazolethione-5-carboxylic acid dimethyl ester (VIII) and hot aqueous ammonia provided 4-acetamide-2-imidazolethione-5-carboxylic acid methyl ester (XII). Treatment of XII with Raney nickel in refluxing ethanol gave 4-imidazoleacetamide-5-carboxylic acid methyl ester (XIII).

The assignment of structure for compounds X, XVI, and XIII as derivatives of 4-imidazoleacetamide-5-carboxylic acid methyl ester was made on the basis of n.m.r. studies.

Examination of Table I reveals that in trifluoroacetic acid, the methyl groups of imidazole-4,5-di-

SCHEME I



carboxylic acid dimethyl ester (XVII)[14] appear at 4.12 δ. Treatment of 4-acetic acid-2-imidazolethione-5-carboxylic acid dimethyl ester (VIII) with Raney nickel gave 4-acetic acid-2-imidazole-5-carboxylic acid dimethyl ester (IX). In compound IX the methyl group of the aliphatic ester appears at 3.94 δ, and the aromatic methyl ester shows a sharp singlet at 4.12 δ.

The n.m.r. spectrum of XIII reveals that the sharp singlet at 3.94 δ has disappeared, while the singlet at 4.12 ϱ remains. Thus, the structure of XIII must be 4-imidazoleacetamide-5-carboxylic acid methyl ester. Since XIII was prepared from XII, it follows that the structure of XII is 4-acetamide-2-imidazolethione-5-carboxylic acid methyl ester. Inspection of Table I shows that similar structural assignment can be made with the 2-chloroimidazole derivatives. Since XVI was prepared by the treatment of XI with ammonia, the structure of XVI must be 4-acetamide-2-chloroimidazole-5-carboxylic acid methyl ester. Treatment of X with phosphorus oxychloride gave 4-acetonitrile-2-chloroimidazole-5-carboxylic acid methyl ester (XVIII). Since the n.m.r. of XVIII shows the sharp singlet at 4.12 δ due to the methyl group of the aromatic ester, it follows that the structure of X is 4-acetamide-2-imidazolone-5-carboxylic acid methyl ester. Thus, in all cases the aliphatic ester reacted to give the corresponding amide. This might be expected, due to the known greater reactivity of aliphatic esters over aromatic esters.

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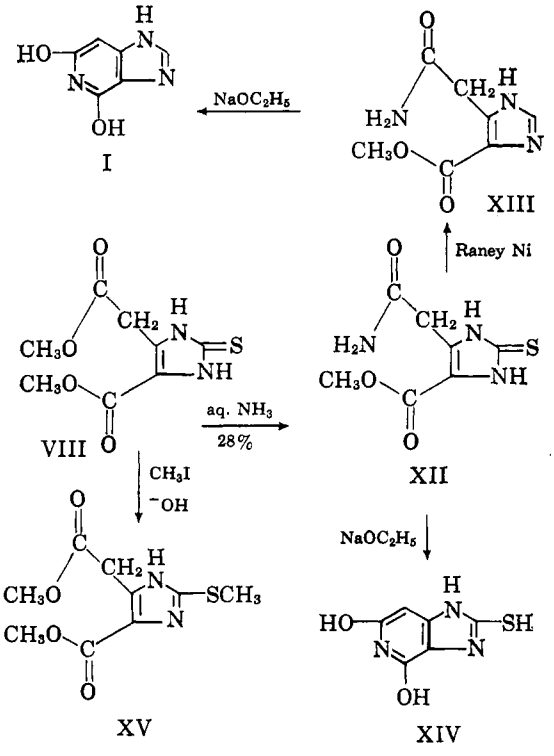
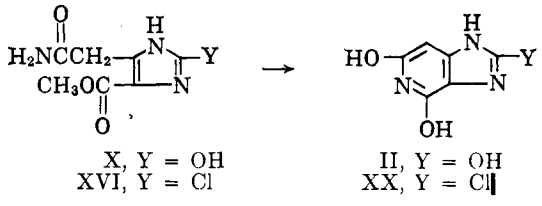
SCHEME II



Strong supporting evidence for this structural assignment of XIII is found in the infrared spectra. Compound IX exhibits two sharp bands in the carbonyl region, 1740 cm.$^{-1}$ (alkyl ester) and 1710 cm.$^{-1}$ (aryl ester). The corresponding monoamide XIII exhibits the same sharp band at 1710 cm.$^{-1}$ (aryl ester), but the band at 1740 cm.$^{-1}$ has been replaced by amide carbonyl absorption at 1680 cm.$^{-1}$.

Attempts to cyclize X, XII, XIII, XVI, and XVIII to a derivative of imidazo[4,5-*c*]pyridine were made using refluxing methanolic hydrogen chloride, concentrated sulfuric acid, refluxing 2 *N* sodium hydroxide, concentrated hydrochloric acid, and refluxing formamide. No cyclized product could be isolated from these reactions. It is now known that, due to the general instability of the 4,6-dihydroxyimidazo[4,5-*c*]pyridine ring, the desired compounds, if formed, would have had little chance of surviving under these conditions. In an effort to vary this approach, 4-acetamide-2-chloroimidazole-5-carboxamide (XIX) was prepared from 4-acetic acid-2-chloroimidazole-5-carboxylic acid dimethyl ester (XI) and ethanolic ammonia at 150°. Attempts to ring close XIX by various means were likewise unrewarding.

The synthesis of 4,6-dihydroxyimidazo[4,5-*c*]pyridine (I) was finally accomplished from XIII by employing sodium ethoxide in refluxing absolute ethanol. The preparation of 4-acetamide-2-chloroimidazole-5-carboxylic acid methyl ester (XVI) was accomplished from XI and aqueous ammonia. Ring closure of XVI with sodium ethoxide in absolute ethanol gave 2-chloro-4,6-dihydroxyimidazo[4,5-*c*]pyridine (XX). 4,6-Dihydroxyimidazo[4,5-*c*]pyridine-2-thiol (XIV) was similarly prepared from the amide ester XII. The uric acid analog, 2,4,6-trihydroxyimidazo[4,5-*c*]pyridine (II), was obtained from X by boiling aqueous sodium carbonate which was found to be a superior reagent for this specific ring closure.



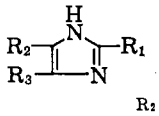
X, Y = OH
XVI, Y = Cl

II, Y = OH
XX, Y = Cl

A general study of the action of refluxing *N* sulfuric acid on the various 4,6-dihydroxyimidazo[4,5-*c*]pyridines revealed that 50% decomposition occurred in 90 minutes with the 2-chloro derivative (XX), in 135 minutes with 4,6-dihydroxyimidazo[4,5-*c*]pyridine (I). Refluxing 0.01 *N* sodium hydroxide hydrolyzed XX and I 50% in 10 minutes as judged by the loss of ultraviolet absorption at 316 and 310 mμ, respectively. The compounds 2,4,6-trihydroxyimidazo[4,5-*c*]pyridine (II) and 4,6-dihydroxyimidazo[4,5-*c*]pyridine-2-thiol (XIV) also decomposed under similar conditions at a slightly slower rate. Although detailed studies were not made to identify the degradation products, in most instances general absorption in the 250-mμ region, typical of imidazole derivatives, was noted. With 4,6-dihydroxyimidazo[4,5-*c*]pyridine (I) the ultraviolet absorption spectra of the acidic and basic degradation products were identical to that of 4-imidazoleacetamide-5-carboxylic acid, prepared by the action of refluxing 2 *N* sodium hydroxide on the ester XIII. Since the corresponding purines, xanthine and uric acid, are essentially unchanged by these conditions, further structural studies of these imidazo[4,5-*c*]pyridines were initiated.

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF CERTAIN IMIDAZOLE DERIVATIVES[a]



Compound	R_1	R_2	R_3
IX	H (8.85)	CH_2—C(=O)—OCH_3 (4.39) (3.94)	C(=O)—OCH_3 (4.12)
XI	Cl	CH_2—C(=O)—OCH_3 (4.38) (3.94)	C(=O)—OCH_3 (4.12)
XIII	H (8.80)	CH_2—C(=O)—NH_2 (4.38)	C(=O)—OCH_3 (4.12)
XV	SCH_3 (2.85)	CH_2—C(=O)—OCH_3 (4.30) (3.90)	C(=O)—OCH_3 (4.10)
XVI	Cl	CH_2—C(=O)—NH_2 (4.36)	C(=O)—OCH_3 (4.11)
XVII	H (8.97)	C(=O)—OCH_3 (4.12)	C(=O)—OCH_3 (4.12)
XVIII	Cl	CH_2—C≡N (4.43)	C(=O)—OCH_3 (4.12)

[a] N.m.r. spectra run in trifluoroacetic acid with tetramethylsilane as an external standard. Values expressed as p.p.m. δ. All spectra appeared as sharp singlets.

Inspection of I reveals that 4,6-dihydroxyimidazo[4,5-*c*]pyridine could well exist in the diketo form Ia or the monoketo form Ib. Examination of the n.m.r. spectrum of 4,6-dihydroxyimidazo[4,5-*c*]pyridine in trifluoroacetic acid revealed a sharp singlet at 9.1 δ (proton at position 2), another singlet at 4.5 δ which integrated for two protons, and finally a broad absorption at 10.1 δ attributed to NH at position 5 since the proton in the imidazole ring is known to exchange in trifluoroacetic acid. Such a spectrum is consistent only with structure Ia where the singlet at 4.5 δ is due to the CH_2 grouping in position 7. Similarly, 2-chloro-4,6-dihydroxyimidazo[4,5-*c*]pyridine (XX) in trifluoroacetic acid showed one proton (NH) at 10.15 δ and a singlet (2 protons) at 4.5 δ. Inspection of the ultraviolet absorption spectra of I and XX revealed that the trifluoroacetic acid, employed as a solvent, had not altered the compounds by hydrolysis. 2-Chloro-4,6-dihydroxyimidazo[4,5-*c*]pyridine (XX) was also examined in deuterated dimethyl sulfoxide in the n.m.r. Absorption appeared at 10.8 δ (1 proton, NH) and a singlet at 3.9 δ (2 protons), which again is strong support for the diketo structure. The structure Ia explains the ready hydrolysis of the pyridine ring since this system is simply a cyclic imide. It is of interest that no evidence of the structure Ib could be detected by n.m.r. Structure Ib might be expected since this tautomer would give the system stability due to increased aromaticity. Inspection of the ultraviolet absorption of the 4,6-dihydroxyimidazo[4,5-*c*]pyridines (Table III) reveals some interesting facts. The absorption maxima of these compounds at pH 1, as compared to the uncyclized imidazoles (Table II), are approximately in the range one might expect for a conjugated cyclic imide. However, at pH 11 in each case the absorption maxima of the 4,6-dihydroxyimidazo[4,5-*c*]pyridines undergo a bathochromic shift of approximately 20–45 mμ. It would thus appear that in a basic solution the anion which is formed has more aromatic character than the unionized species. Thus, it is quite possible that the proton is removed from position 7 to give an anion of type Ic or Id, which would afford greater aromaticity to the system and better conjugation with the imidazole ring. An n.m.r. study of 2-chloro-4,6-dihydroxyimidazo[4,5-*c*]pyridine (XX) in deuterium oxide in the presence of sodium peroxide revealed no strong absorption. Thus, there is rapid exchange with the hydrogens at position 7, which is additional evidence for the existence of an anion such as Ic.

Ia I Ib

Ic Id

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF CERTAIN IMIDAZOLES IN AQUEOUS SOLUTION AT pH 1

Compound	R_1	R_2	R_3	λ_{max}, mμ	ϵ	λ_{min}, mμ	ϵ
VII	OH	$CH_2CO_2CH_3$	CO_2CH_3	269	10,280	229	1720
VIII	SH	$CH_2CO_2CH_3$	CO_2CH_3	257	12,180	275	9200
				284	9,940	223	3910
X	OH	CH_2CONH_2	CO_2CH_3	270	10,540	227	1392
XI	Cl	$CH_2CO_2CH_3$	CO_2CH_3	244	7,670		
XII	SH	CH_2CONH_2	CO_2CH_3	257	13,800	223	3880
				285	10,750		
XIII	H	CH_2CONH_2	CO_2CH_3	226	10,200		
XV	SCH_3	$CH_2CO_2CH_3$	CO_2CH_3	263	12,450		
XVI	Cl	CH_2CONH_2	CO_2CH_3	244	9,800		
XVIII	Cl	$CH_2C{\equiv}N$	CO_2CH_3	247	12,550		

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA OF SOME 4,6-DIHYDROXYIMIDAZO[4,5-*c*]PYRIDINES

		pH 1		pH 11	
Compound	R	λ_{max}, mμ	ϵ	λ_{max}, mμ	ϵ
I	H	242	5,440	262	8,300
		290	6,030	308	7,860
II	OH	302	7,700	278	10,700
				321	7,540
XIV	SH	259	12,800	242	19,400
		309	8,760	320	7,330
XX	Cl	271	7,060	265	5,380
				316	8,170

Experimental[15]

4-Acetic Acid-2-imidazolone-5-carboxylic Acid Dimethyl Ester (VII).—To 128 g. of methyl acetonedicarboxylate[11] and 160 ml. of glacial acetic acid was added, with stirring, a solution of 43.2 g. of sodium nitrite dissolved in 64 ml. of water. The sodium nitrite solution was added at such a rate that the temperature remained between 25–35°. After addition of all the sodium nitrite solution, the mixture was stirred an additional 30 min.; then 600 ml. of water was added, and the solution was stirred for an additional hour. The mixture was transferred to a 4-l. beaker, and 800 ml. of water was added. To this solution was added 384 g. of sodium hydrosulfite, and the solution was stirred until all the solid had dissolved. The mixture was then adjusted to pH 4 by the addition of dilute sulfuric acid, and to this solution was added, in small portions, 200 g. of potassium cyanate. During this process the solution was stirred and cooled in an ice bath. After addition was complete, the solution was allowed to stand for 20 min. and then was heated to 70° on a steam bath. The solution was cooled overnight, and the light yellow crystals were filtered to yield 31.25 g. of crude material, m.p. 208–218°. The yellow solid was recrystallized from methanol and melted at 228–230°.

Anal. Calcd. for $C_8H_{10}N_2O_5$: C, 44.9; H, 4.7; N, 13.2. Found: C, 44.5; H, 4.9; N, 13.5.

4-Acetic Acid-2-imidazolone-5-carboxylic Acid Diethyl Ester.—This compound was similarly prepared from ethyl acetonedicarboxylate[12] in an over-all yield of 38%. The product was recrystallized from hot water to give white needles, m.p. 186–187°.

Anal. Calcd. for $C_{10}H_{14}N_2O_5$: C, 49.6; H, 5.8; N, 11.6. Found: C, 49.6; H, 5.9; N, 11.6.

4-Acetic Acid-2-imidazolethione-5-carboxylic Acid Dimethyl Ester (VIII).—This compound was prepared by the same procedure employed for the synthesis of 4-acetic acid-2-imidazolone-5-carboxylic acid dimethyl ester (VII) except that 184 g. of potas-

(15) All melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus.

sium thiocyanate was used instead of 200 g. of potassium cyanate. No cooling in an ice bath was necessary for this addition. After the yellow solution was heated to 70°, charcoal was added, and the solution was filtered and cooled to yield 32.0 g. of a yellow solid, m.p. 220–222°, which was recrystallized from water to raise the melting point to 222°.

Anal. Calcd. for $C_9H_{11}N_2O_4S$: C, 44.3; H, 4.9; N, 11.5. Found: C, 44.1; H, 5.2; N, 11.6.

4-Acetic Acid-2-imidazolethione-5-carboxylic Acid Diethyl Ester.—This compound was similarly prepared from ethyl acetonedicarboxylate[12] to give a product, m.p. 163–164°, after recrystallization from water.

Anal. Calcd. for $C_{10}H_{14}N_2O_4S$: C, 46.5; H, 5.4. Found: C, 46.7; H, 5.8.

4-Acetic Acid-2-imidazole-5-carboxylic Acid Dimethyl Ester (IX).—To 500 ml. of absolute methanol was added 30 g. of 4-acetic acid-2-imidazolethione-5-carboxylic acid dimethyl ester (VIII) and 60 g. of wet Raney nickel. The mixture was heated to vigorous reflux for 12 hr. The solution was then filtered, the nickel was washed with hot methanol, and the washings were added to the filtrate. The methanol was then removed under reduced pressure, and the yellow residue was recrystallized from water to yield 13.0 g., m.p. 163–178°. A second recrystallization from water raised the melting point to 178–180°.

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 48.5; H, 5.0; N, 14.2. Found: C, 48.8; H, 5.2; N, 14.4.

4-Acetic Acid-2-imidazole-5-carboxylic Acid Diethyl Ester.—This compound was prepared in a similar fashion. Recrystallization of the product from hot water gave white needles, m.p. 130–131°.

Anal. Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.1; H, 6.2; N, 12.8. Found: C, 52.7; H, 6.6; N, 12.8.

4-Acetamide-2-imidazolone-5-carboxylic Acid Methyl Ester (X).—To 100 ml. of boiling 28% ammonium hydroxide was added 6.0 g. of the diester (VII) in small portions. After addition was complete, the solution was boiled for 10 min. on the steam bath, filtered, and cooled in an ice bath. The dark solution was then acidified with dilute sulfuric acid and cooled overnight. The crystals were filtered to yield 4.0 g. (73%) of crude product, m.p. 290–295° dec., which was recrystallized from water to give a pure product, m.p. 299–301° dec.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.8; H, 4.6; N, 21.4. Found: C, 42.3; H, 4.6; N, 21.2.

4-Acetamide-2-imidazolone-5-carboxylic Acid Ethyl Ester.—This compound was similarly prepared. The product was recrystallized from water and melted at 278–279°.

Anal. Calcd. for $C_8H_{11}N_3O_4$: C, 45.1; H, 5.2. Found: C, 45.1; H, 5.4.

4-Acetic Acid-2-chloroimidazole-5-carboxylic Acid Dimethyl Ester (XI).—Dry 4-acetic acid-2-imidazolone-5-carboxylic acid dimethyl ester (VII, 5 g.) was added to 75 ml. of phosphorus oxychloride. The solution was refluxed for 3.5 hr., and the excess phosphorus oxychloride was removed under reduced pressure using a water bath as the source of heat. The residue was poured, with vigorous stirring, onto crushed ice, and the mixture, while still cold, was adjusted to pH 5 with 28% ammonium hydroxide. The solution was allowed to stand 30 min. at room temperature and then was extracted with ether in a continuous extractor for 30 hr. Distillation of the ethereal solution left 3.9 g. (72%) of yellow solid, which was recrystallized from benzene to yield white crystals, m.p. 137°.

Anal. Calcd. for $C_8H_9ClN_2O_4$: C, 41.3; H, 3.9; N, 12.0. Found: C, 41.9; H, 4.0; N, 12.2.

4-Acetamide-2-chloroimidazole-5-carboxamide (XIX).—4-Acetic acid-2-chloroimidazole-5-carboxylic acid dimethyl ester (XI, 2 g.) was added to 150 ml. of ethanol which had been saturated with ammonia at 0°. The reaction mixture was heated in a steel vessel at 150° for 6 hr. The alcoholic solution was cooled and evaporated to dryness on the steam bath, and a small amount of cold water was added to dissolve the inorganic salts. The aqueous solution was filtered, and the product was recrystallized from water to yield 0.424 g. The solid was recrystallized twice from water using decolorizing charcoal and gave a product melting at 275° dec.

Anal. Calcd. for $C_6H_7ClN_4O_2$: C, 35.6; H, 3.4; N, 27.7. Found: C, 35.6; H, 3.6; N, 27.9.

4-Acetic Acid-2-methylthioimidazole-5-carboxylic Acid Dimethyl Ester (XV).—To 100 ml. of water was added 3 g. of VIII and just enough potassium hydroxide to effect solution. Methyl iodide (1.0 g.) was added, and the solution was stirred vigorously at 20° for 1 hr. The pH of the solution at the end of this period was 8. The solution was cooled overnight and filtered to yield 2.6 g. of white solid, m.p. 102–105°, which was recrystallized from water to give needles, m.p. 107°.

Anal. Calcd. for $C_9H_{12}N_2O_4S$: C, 44.3; H, 4.9; N, 11.5. Found: C, 44.1; H, 5.2; N, 11.6.

4-Acetamide-2-imidazolethione-5-carboxylic Acid Methyl Ester (XII).—4-Acetic acid-2-imidazolethione-5-carboxylic acid dimethyl ester (VIII, 20 g.) was added in small portions to 300 ml. of boiling 28% ammonium hydroxide on a steam bath. After each addition the flask and contents were shaken to effect solution. After addition was complete, the dark solution was boiled an additional 5 min. and then filtered and cooled. The solution was acidified to pH 3 with dilute sulfuric acid and cooled overnight, and the light tan crystals were filtered and washed with water to yield 15.7 g. (84%). The compound was recrystallized from water to give a melting point of 233° dec.

Anal. Calcd. for $C_7H_9N_3O_3S$: C, 39.1; H, 4.2; N, 19.5. Found: C, 39.1; H, 4.1; N, 19.5.

4-Acetamide-2-imidazolethione-5-carboxylic Acid Ethyl Ester.—This compound was similarly prepared from 4-acetic acid-2-imidazolethione-5-carboxylic acid diethyl ester and was recrystallized from water to give a melting point of 235–236°.

Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.9; H, 4.8; N, 18.3. Found: C, 42.3; H, 5.2; N, 18.4.

4-Acetonitrile-2-chloroimidazole-5-carboxylic Acid Methyl Ester (XVIII).—To 4.0 g. of 4-acetamide-2-imidazolone-5-carboxylic acid methyl ester (X) was added 75 ml. of phosphorus oxychloride. This mixture was refluxed for 2.5 hr., and then the volume of the solution was reduced to 35 ml. under reduced pressure. The dark liquid was poured slowly with stirring onto crushed ice, and the cold, aqueous solution was adjusted to pH 5 with 28% aqueous ammonia and extracted with ether. The ethereal solution was then washed with a small amount of water and dried over sodium sulfate, and the ether was distilled to leave a yellow viscous residue. The crude product was recrystallized from benzene to yield 1.6 g. (40%) of pure white crystals, m.p. 137°.

Anal. Calcd. for $C_7H_6ClN_3O_2$: C, 42.0; H, 3.0; N, 21.0. Found: C, 42.3; H, 2.7; N, 20.6.

4-Imidazoleacetamide-5-carboxylic Acid Methyl Ester[(XIII).—4-Acetamide-2-imidazolethione-5-carboxylic acid methyl ester (XII, 4 g.) and 15 g. of Raney nickel catalyst were added to 100 ml. of absolute ethanol. The mixture was refluxed for 2 hr.; then the Raney nickel was filtered, and the alcoholic filtrate was evaporated to dryness on a steam bath. The light grey residue was easily recrystallized from water to yield 1.48 g. of pure white solid (44%), m.p. 242–244°.

Anal. Calcd. for $C_7H_9N_3O_3$: C, 45.9; H, 5.0; N, 22.9. Found: C, 46.2; H, 5.0; N, 22.9.

4-Imidazoleacetamide-5-carboxylic Acid Ethyl Ester.—This compound was similarly prepared from 4-acetamide-2-imidazolethione-5-carboxylic acid ethyl ester to give white crystals (75% yield), m.p. 206° dec.

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.7; H, 5.6; N, 21.4. Found: C, 48.5; H, 5.3; N, 20.8.

2,4,6-Trihydroxyimidazo[4,5-c]pyridine (II). Method 1.—To 35 ml. of boiling 10% sodium carbonate solution was added 3.5 g. of 4-acetamide-2-imidazolone-5-carboxylic acid methyl ester (m.p. 278–279°). The solution was refluxed for 5 min., and the reaction mixture was treated with charcoal and filtered. The hot filtrate was neutralized (pH 3) with concentrated hydrochloric acid, which precipitated the desired product. The solution was filtered while hot, and the product was suspended in boiling distilled water and filtered. The product was washed three times with distilled water and dried in a vessel open to the atmosphere. The yield of cyclized material was 0.592 g. (22.2%), m.p. > 300°.

Anal. Calcd. for $C_6H_5N_3O_3 \cdot H_2O$: C, 38.9; H, 3.8; N, 22.7. Found: C, 39.5; H, 3.9; N, 23.0.

A sample was dried in an oven at 130°.

Anal. Calcd. for $C_6H_5N_3O_3$: C, 43.1; H, 3.0; N, 25.2. Found: C, 42.9; H, 3.5; N, 24.8.

Method 2.—When 4-acetamide-2-imidazolone-5-carboxylic acid methyl ester (X, 4.0 g.) was employed as in method 1, a white solid (1.6 g., 47%), m.p. > 300°, was obtained. This product was washed with ethanol and recrystallized from glacial acetic acid. The compound thus obtained was shown by ultraviolet absorption spectra to be identical to that prepared by method 1.

4,6-Dihydroxyimidazo[4,5-c]pyridine-2-thiol (XIV).—Sodium (4.5 g.) was dissolved in 180 ml. of absolute ethanol, and then 6.0 g. of 4-acetamide-2-imidazolethione-5-carboxylic acid methyl ester (XII) was added. The solution was refluxed for 15 min. on a steam bath, and then the pH was adjusted to 6 with glacial acetic acid. The mixture was stirred for 30 min. and cooled. The light green solid was filtered, suspended in 75 ml. of distilled water, and stirred an additional 30 min. The crude material was filtered and washed well first with distilled water and then with ethanol. The light green solid was dried at 60° to yield 5.3 g., m.p. > 300°.

Anal. Calcd. for $C_6H_5N_3O_2S \cdot H_2O$: C, 35.8; H, 3.5; N, 20.9. Found: C, 36.0; H, 4.6; N, 20.5.

A sample was dried at 130°.

Anal. Calcd. for $C_6H_5N_3O_2S$: C, 39.3; H, 2.7; N, 22.9. Found: C, 39.3; H, 3.0; N, 22.7.

4,6-Dihydroxyimidazo[4,5-c]pyridine (I).—4-Imidazoleacetamide-5-carboxylic acid methyl ester (XIII, 10.0 g.) was added to 7.5 g. of sodium dissolved in 300 ml. of absolute ethanol. The solution was refluxed on a steam bath for 30 min. and then acidified with glacial acetic acid. The mixture was stirred for 30 min., cooled, and filtered, and the light tan material was suspended in 100 ml. of water, stirred for 30 min., and again filtered. The cyclized product was dried to yield 7.5 g. (91%), m.p. > 300°, and a small sample was recrystallized from glacial acetic acid and dried at 130° for analysis.

Anal. Calcd. for $C_6H_4N_3O_2$: C, 47.7; H, 3.3; N, 27.8. Found: C, 47.6; H, 3.4; N, 28.0.

4-Acetamide-2-chloroimidazole-5-carboxylic Acid Methyl Ester (XVI).—4-Acetic acid-2-chloroimidazole-5-carboxylic acid dimethyl ester (XI, 10 g.) was treated with aqueous ammonia as for the synthesis of XII and X. The solid was recrystallized from methanol–water to give 8.0 g. of product, m.p. 235–237° dec.

Anal. Calcd. for $C_7H_8ClN_3O_3$: C, 38.7; H, 3.7; N, 19.3. Found: C, 38.6; H, 3.3; N, 19.0.

2-Chloro-4,6-dihydroxyimidazo[4,5-c]pyridine (XX).—4-Acetamide-2-chloroimidazole-5-carboxylic acid methyl ester (XVI, 10.0 g.) was added to 7.5 g. of sodium dissolved in 300 ml. of absolute ethanol. This solution was refluxed on a steam bath for 30 min. and then transferred to an erlenmeyer flask. The pH of the solution was adjusted to 6 with glacial acetic acid, and the mixture was stirred for 30 min. and cooled. The light yellow material was filtered, suspended in 100 ml. of distilled water, and stirred for 30 min. The cyclized product was filtered and dried to yield 5.5 g. of light pink solid (65%), m.p. > 300°. A small sample was recrystallized from glacial acetic acid for analysis.

Anal. Calcd. for $C_6H_4ClN_3O_2$: H, 2.2; N, 22.6. Found: H, 2.5; N, 22.7.

4-Imidazoleacetamide-5-carboxylic Acid.—To 50 ml. of 2 *N* sodium hydroxide was added 2 g. of 4-imidazoleacetamide-5-carboxylic acid methyl ester (XIII). The solution was gently refluxed for 45 min. and then acidified with glacial acetic acid and placed in the refrigerator for 12 hr. The crude brown crystals which were filtered weighed 1.2 g. (70.6%). The crude product was reprecipitated from hot dilute sodium hydroxide (30 ml.) with acetic acid, and the white crystals obtained melted at 240° dec. The compound was dried over phosphorus pentoxide at 110° for analysis.

Anal. Calcd. for $C_6H_7N_3O_2$: C, 42.6; H, 4.1; N, 24.8; neut. equiv., 169. Found: C, 42.4; H, 3.9; N, 24.9; neut. equiv., 168.

The Conversion of 3-Aminoalkylidene-2,4-pyrandiones into 4-Pyridones

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Dehydroacetic acid reacts rapidly with primary amines in warm aqueous dimethylformamide to give aminoethylidenepyrandiones. These compounds can be converted into N-substituted 4-pyridones. Proof of structure of the intermediate compounds and the mechanistic pathway of the dehydroacetic acid–pyridone conversion are discussed.

The conversion of dehydroacetic acid (I) into 2,6-dimethyl-4-pyridinol by the action of aqueous ammonia was first described by Haitinger in 1885.[1] When methylamine was used, 1,2,6-trimethyl-4-pyridone was formed in 94% yield.[2]

Two mechanisms have been proposed for the reaction of ammonia with I. The simpler route, as suggested by Brody and Ruby,[3] involves attack by ammonia at the 6-position followed by opening of the pyrone ring and recyclization with the loss of water and carbon dioxide. A more complicated mechanism was proposed earlier by Feist.[4] He postulated that ammonia condensed first with the carbonyl group in the side chain with elimination of water. This step is analogous to the reaction of ammonia with ethyl acetoacetate.[5] The pyrone ring would then be opened (presumably by attack of water) and subsequently closed to the pyridone system. The isolation of 3-(1-iminoethyl)-4-hydroxy-6-methyl-2-pyrone and its conversion into 2,6-dimethyl-4-pyridinol[6a,b] would lend support to the latter theory.

We have synthesized several N-substituted 4-pyridones (Table III) using dehydro acids and primary amines as starting materials. The rearrangement of the intermediate compounds (Table II) was studied in detail. Phenethylamine and dehydroacetic acid were heated in 50% aqueous dimethylformamide for 30 minutes. A nonbasic compound, whose analysis indicated condensation with loss of one molecule of water, was obtained in 70% yield. A minor product, isolated in 5% yield, was shown to be 1-phenethyl-2,6-dimethyl-4-pyridone (IV) by an unequivocal synthesis in which 2,6-dimethyl-4-pyrone (V) was used as starting material.[7,8]

The ultraviolet spectrum of the major product shows maxima at 237 and 314 mμ while the pyridone IV has a single maximum at 266 mμ. The course of the

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