Ring Transformation of Pyrimidines to Pyridines. Synthesis of 4-Alkylaminopyridin-2-ones by Alkaline Hydrolysis of 6-(2-Dimethylaminovinyl)uracils [1,2]

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Alkaline hydrolysis of 1,3-disubstituted 6-(2-dimethylaminovinyl)uracils **2** induced a novel ring transformation giving 4-alkylaminopyridin-2-ones **3** *via* ring-opening and ring-closure processes. The 4-methylamino-3-nitropyridin-2-one (**3a**) thus obtained was employed for the synthesis of 3-deazahypoxanthine derivative **8**. 4-Alkylamino-3-cyanopyridin-2-ones **11**, ricinine analogs, were also prepared by the reaction of 4-chloro-3-cyano-1-methylpyridin-2-one (**10**) with amines.

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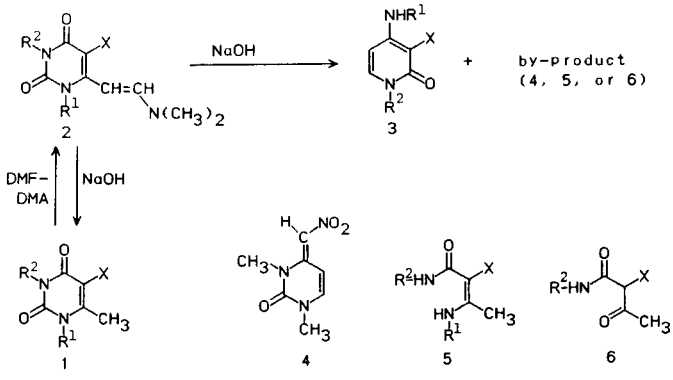
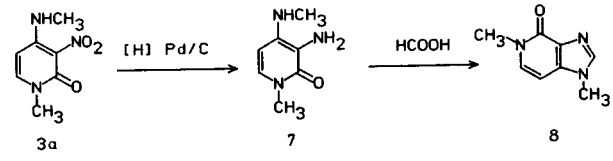
Various ring transformations have been extensively investigated and efficiently utilized as a prominent tool for the synthesis of heterocycles [3]. The presence of an appropriate side chain on the heterocyclic ring frequently made possible the ring transformation into other heterocyclic ring systems [4-6]. We have also reported the ring transformation of uracil derivatives, possessing a terminal amino side chain at the 5-position, into pyrazole [7] and pyridine [8] ring systems. During our study on the reactivity of 5-nitrouracils possessing a dimethylaminovinyl group as a side chain at the 6-position [9], we found a novel type of ring transformation of uracils into pyridin-2-ones. The present reaction is applicable as a method for the facile synthesis of 3-substituted 4-alkylamino(or anilino)pyridin-2-ones **3**.

6-(2-Dimethylaminovinyl)uracils **2**, employed here as starting materials, were prepared by the condensation of 5-nitro- (**1a-c** and **1k-m**), 5-cyano- (**1d-g**), 5-formyl- (**1h**), and 5-unsubstituted- (**1i,j**) 6-methyluracils and dimethylformamide dimethylacetal (DMF-DMA) according to the method described previously [9]. The stereochemistry of the vinyl moiety at the 6-position of **2** was deduced to adopt a *trans* orientation from the coupling constant in the NMR spectrum (see Table 3).



Scheme 1

Treatment of 1,3-dimethyl-6-(2-dimethylaminovinyl)-5-nitrouracil (**2a**) in 10% aqueous sodium hydroxide at 90° resulted in the formation of 1-methyl-4-methylamino-3-nitropyridine-2-one (**3a**) and 1,3-dimethyl-4(3*H*)-*exo*-nitromethylenepyrimidin-2(1*H*)-one (**4**) in 62% and 14% yields, respectively. The structures of **3a** and **4** were confirmed on the basis of their microanalytical results, spectral data, and chemical conversions. The ^{1}H nmr spectrum of **4** showed the presence of three olefinic protons (see Table 1) and its ^{13}C nmr spectrum exhibited signals assignable to four olefinic carbons and a carbonyl carbon at 98.1 (d), 112.4 (d), 140.1 (d), 145.4 (s), and 150.0 (s) ppm, although the stereochemistry of the exomethylene moiety has not been determined yet. The 3-nitropyridin-2-one (**3a**) was converted into 1,9-dimethyl-3-deazahypoxanthine (**8**) in two steps: catalytic reduction of **3a** on palladium charcoal gave the 3-aminopyridin-2-one **7**, which was derived to the 3-deazahypoxanthine **8** in 34% yield upon treatment with formic acid [10].



Scheme 2

Analogous hydrolysis of various 1,3-disubstituted 6-(2-dimethylaminovinyl)uracil derivatives **2b-i** caused the ring transformation giving predominantly the corresponding pyridin-2-ones **3b-i**. Open-chain products such as methacrylamide derivatives **5a,b** and acetamide derivatives **6a,b** were obtained as by-products. In these reaction, however, the ring transformation products corresponding to **4** were not isolated.

Table 1

Alkaline Hydrolysis Products **1** and **3-6** of 6-(2-Dimethylaminovinyl)uracils **2**

Starting Compound	Product No.	R^1	R^2	X	Yield %	Mp °C (Recrystallization solvent)	^{1}H NMR δ (J in Hz)	Molecular formula	Analysis % Calcd./Found C	H	N
2a	**3a**	CH_3	CH_3	NO_2	62	168-169 (AcOEt)	6.04, 7.78 (each 1H, d, 8.0) [a]	$C_7H_9N_3O_3H_2O$	41.79 42.11	5.51 5.37	20.89 21.09
	4	–	–	–	14	259-260 (MeOH)	6.87 (1H, d, 1.0) 7.00 (1H, dd, 8.5, 1.0), 7.75 (1H, d, 8.5) [b]	$C_7H_9N_3O_3$	45.90 45.90	4.95 4.96	22.94 22.75
2b	**3b**	CH_3	H	NO_2	26	177-178 (AcOEt)	5.93, 7.42 (each 1H, d, 8.0) [b]	$C_{12}H_{17}N_3O_3$	57.35 57.29	6.82 6.77	16.73 16.76
	5a	CH_3	H	NO_2	10	192-194 (AcOEt)	2.47 (3H, s), 3.12 (3H, d, 5.0) [b]	$C_{11}H_{13}N_3O_3$	54.75 54.77	7.94 7.98	17.42 17.15
2c	**3c**	CH_3	p-$NO_2C_6H_4$	NO_2	21	274-275 [c] (MeOH)	6.23, 7.72 (each 1H, d, 8.0) [a]	$C_{12}H_{10}N_4O_5$	49.66 49.77	3.47 3.54	19.31 19.18
2d	**3d**	CH_3	CH_3	CN	79	243-244 (MeOH)	5.92, 7.69 (each 1H, d, 8.0) [a]	$C_8H_9N_3O$	58.86 58.64	5.56 5.40	25.75 25.56
	6a	–	CH_3	CN	19	100 (H_2O)	2.29 (3H, s), 2.91 (3H, d, 5.0) [b]	$C_6H_8N_3O_2$	51.42 51.35	5.75 5.75	19.99 19.82
2e	**3e**	C_6H_5	CH_3	CN	79	173-174 (AcOEt)	5.87, 7.69 (each 1H, d, 7.5) [a]	$C_{13}H_{11}N_3O$	69.32 69.17	4.92 4.91	18.66 18.32
2f	**3f**	CH_3	C_2H_5	CN	54	178-179 (AcOEt)	5.83, 7.34 (each 1H, d, 8.0) [b]	$C_9H_{11}N_3O$	61.00 60.99	6.26 6.37	23.72 23.76
	6b	–	C_2H_5	CN	39	92 (ligroin)	2.31 (3H, s) [b]	$C_7H_{10}N_2O_2$	54.53 54.48	6.54 6.53	18.17 18.06
2g	**3g**	$CH_2C_6H_5$	CH_3	CN	35	209-210 (EtOH)	5.89, 7.64 (each 1H, d, 8.0) [a]	$C_{14}H_{13}N_3O$	70.27 70.43	5.48 5.40	17.56 17.63
	5b	$CH_2C_6H_5$	CH_3	CN	20	161-162 (benzene)	2.25 (3H, s), 2.86 (3H, d, 5.0) [b]	$C_{13}H_{15}N_3O$	68.10 68.55	6.59 6.51	18.33 18.14
2h	**3h**	CH_3	CH_3	CHO	9	147-148 (ligroin)	5.82, 7.33 (each 1H, d, 8.0) 10.24 (1H, s) [b]	$C_8H_{10}N_2O_2$	57.82 58.00	6.07 6.07	16.86 16.86
2i	**3i**	C_6H_5	CH_3	H	56	239-240 (EtOH)	5.78 (1H, d, 2.5) 5.97 (1H, dd, 7.0. 2.5), 7.49 (1H, d, 7.0) [a]	$C_{12}H_{12}N_2O$	71.98 71.71	6.04 6.04	13.99 13.81
2j	**1j**	CH_3	CH_3	H	86						
2k	**1k**	CH_3	H	NO_2	90						
2l	**1l**	H	CH_3	NO_2	95						
2m	**1m**	H	H	NO_2	94						

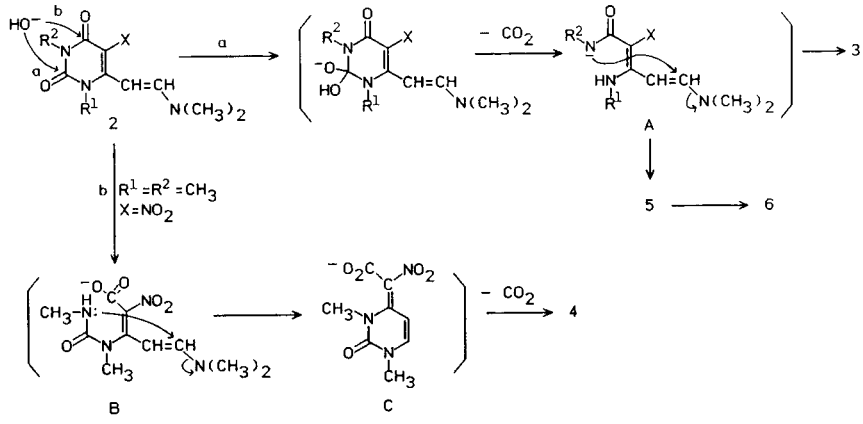
[a] In DMSO-d_6. [b] In deuteriochloroform. [c] Decomposition point.

When 5-unsubstituted 1,3-dimethyluracil **2j** and 1- and/or 3-unsubstituted 5-nitrouracils **2k-m** were treated with 10% aqueous sodium hydroxide, the corresponding 6-methyluracils **1j-m** were obtained in high yields without occurrence of any ring transformation. The results thus obtained are summarized in Table 1.

The substituents on the uracil ring play a significant role for determining whether the ring transformation takes place or not: (1) the presence of electron withdrawing groups such as a nitro or a cyano group at the 5-position facilitates the ring transformation into the pyridin-2-ones **3a-g**, (2) alkaline hydrolysis of the N_1-phenyl compounds **2e** and **2i** gives the pyridin-2-ones **3e** and **3i** in good yields. The smooth ring transformation of **2i** not possessing an electron withdrawing group at the 5-position shows remarkable effects of N_1-phenyl substituent on this type of the reaction, (3) the N_1 and/or N_3 unsubstituted uracils **2k-m** undergo only hydrolysis of the dimethylaminovinyl residue to give 6-methyluracils **1k-m**.

The tentative reaction sequence for the hydrolysis of **2** is outlined in Scheme 3.

The conversion of **2** into **3**, **5**, and **6** could involve initial attack of hydroxide ion at the C_2-position, followed by decarboxylation leading to an open-chain intermediate A.



Scheme 3

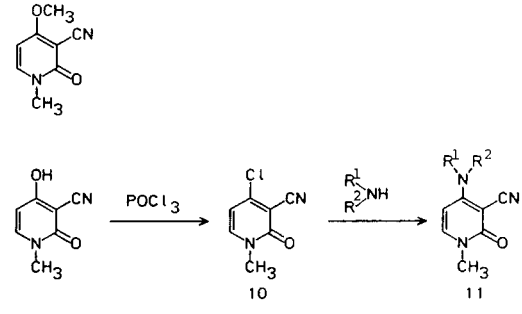
Subsequent recyclization of A accompanied by elimination of dimethylamine results in the formation of **3**. Further hydrolysis of A gives rise to **5** and **6**.

Electron withdrawing substitutents at C_5 and the phenyl group at N_1 are of importance to facilitate initial attack of hydroxide ion and subsequent steps leading to the ring transformation product. Our previous works [11-14] demonstrated that the substitution of a phenyl group at the N_1-position of uracil derivatives causes the smooth cleavage of the 1-6 bond as a result of the attack of nucleophiles at the C_6-position. Analogously when hydroxide ion attacks at the C_2-position, the N_1-phenyl group could also accelerate the fission of the 1-2 bond. Ionization of **2k-m**, which possess dissociable proton, with sodium hydroxide prevents the attack of hydroxide ion at the C_2-position and as a consequence the ring transformation does not take place.

Strong evidence supporting the above reaction sequence was obtained by the isolation of the key intermediate **9** [A ($R^1 = R^2 = Me$, X = CN) in Scheme 3, 13%] along with **3d** (46%) upon treatment of **2d** with 10% aqueous sodium hydroxide at 90° for 10 minutes. The intermediate **9** was readily converted into **3d** in a quantitative yield under the conditions for the ring transformation.

As to mechanism for the formation of **4**, an initial step is an attack of hydroxide ion at the C_4-position rather than at the C_2-position. The resulting intermediate **B** could undergo recyclization to the pyrimidine **C**, whose decarboxylation gives **4**.

3-Cyano-1-methyl-4-methylaminopyridin-2-one (**3d**), obtained above by the ring transformation of **2d**, is structurally similar to ricinine (3-cyano-4-methoxy-1-methylpyridin-2-one) [15,16] which is a toxic alkaloid from *Ricinus communis L.* Systematic synthesis of 4-substituted amino analogs of ricinine was carried out with purpose of the conclusive structure elucidation of the ring transformation products **3** and the evaluation of the biological activity of **3**. The reaction of ricininic acid [16] with phosphorus oxychloride under reflux afforded the 4-chloropyridin-2-one **10** in high yield. Subsequent amination of **10** with methylamine and benzylamine led to the formation of 4-methylamino- and 4-benzylamino-3-cyanopyridin-2-ones, which were identical with the products **3d** and **3g** obtained previously by ring transformation of **2d** and **2g**, respectively. Similarly 3-cyano-1-methyl-4-(substituted amino)-pyridin-2-ones **11a-h** were prepared by reaction of **10** with various amines (Table 2).



Scheme 4

Evaluation of the pyridin-2-ones **3a-i** and **11a-h**, prepared in the present study, for antimicrobial activity and coccidiostatic activity is now in progress.

EXPERIMENTAL

Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. Infrared (ir) spectra were recorded with a Hitachi Model 215 spectrometer using potassium bromide pellets. Ultra-violet (uv) spectra were obtained from ethanol on a Hitachi 323 spectrophotometer. Proton nuclear magnetic resonance (H^1 nmr) spectra were determined with a Hitachi Perkin-Elmer R-20B (60-MHz) instrument with tetrametylsilane as internal standard. Chemical shifts are reported in parts per million (δ) and signals are quoted as a s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); and J values are first order. ^{13}C nmr spectra were determined with a JEOL JNM-GX270 Fourier transform spectometer operating at 67.80 MHz, with tetramethylsilane as internal standard. Mass spectra (ms) were taken on a JEOL JMS-D300 machine operating at 70 eV.

Table 2

4-Alkylamino (or Anilino)-3-cyano-1-methylpyridin-2-ones **3d**, **3g**, and **11a-h**

Compound No.	R^1	R^2	Yield %	Mp °C (Recrystallization solvent)	Molecular formula	Analysis % Calcd./Found C	H	N
3d	CH_3	CH_3	79	[a]				
3g	$CH_2C_6H_5$	CH_3	60	[a]				
11a	C_2H_5	H	67	185-186 (EtOH)	$C_9H_{11}N_3O$	61.00 61.02	6.26 6.09	23.72 23.58
11b	C_3H_7	H	60	132-133 (AcOEt)	$C_{10}H_{13}N_3O$	62.80 62.80	6.85 6.45	21.98 22.22
11c	C_4H_9	H	74	110-111 (benzene)	$C_{11}H_{15}N_3O$	64.36 64.38	7.37 7.31	20.47 20.37
11d	i-C_4H_9	H	41	129-131 (AcOEt)	$C_{11}H_{15}N_3O$	64.36 64.57	7.37 7.48	20.47 20.64
11e	C_6H_5	H	81	173-174 (EtOH)	$C_{13}H_{11}N_3O$	69.32 69.60	4.92 4.95	18.66 18.81
11f	$CH_2CH=CH_2$	H	80	119-120 (benzene)	$C_{10}H_{11}N_3O$	63.47 63.72	5.87 5.72	22.21 22.39
11g	H	H	77	163-164 (EtOH)	$C_{13}H_{17}N_3O$	67.50 67.25	7.41 7.17	18.17 18.07
11h	CH_3	CH_3	75	167-168 (EtOH)	$C_9H_{11}N_3O$	61.00 60.83	6.26 6.02	23.72 23.44

[a] See Table 1.

Table 3

Formation of 6-(2-Dimethylaminovinyl)uracils **2**

Compound No.	R^1	R^2	X	Mp °C (Recrystallization solvent)	Yield %	Molecular formula	^{1}H NMR, δ, 6-vinyl proton (J in Hz)	Analysis % Calcd./Found C	H	N
2c	CH_3	p-$NO_2C_6H_5$	NO_2	242-243 (MeOH)	79 [a]	$C_{15}H_{15}N_5O_6$	4.95, 7.25 (11.5)	49.86 49.70	4.18 4.14	19.37 19.16
2d	CH_3	CH_3	CN	207-208 (EtOH)	97	$C_{11}H_{14}N_4O_2$	4.68, 8.13 (13.0)	56.40 56.47	6.02 6.07	23.92 23.93
2e	C_6H_5	CH_3	CN	242-243 (EtOH)	85	$C_{16}H_{16}N_4O_2$	4.13, 8.05 (13.0)	64.86 64.66	5.44 5.42	18.91 18.64
2f	CH_3	C_2H_5	CN	196-197 (MeOH)	30	$C_{12}H_{16}N_4O_2$	4.69, 8.06 (13.0)	58.05 58.29	6.50 6.55	22.57 22.80
2g	$CH_2C_6H_5$	CH_3	CN	163-164 (AcOEt)	86	$C_{17}H_{16}N_4O_2$	4.63, 8.07 (13.0)	65.79 65.76	5.85 5.80	18.05 18.13
2h	CH_3	CH_3	CHO	156-157 (ligroin)	82	$C_{11}H_{13}N_3O_3$	5.10, 7.52 (11.5)	55.68 55.81	6.37 6.38	17.71 17.99
2i	C_6H_5	CH_3	H	228-229 (EtOH)	89	$C_{15}H_{17}N_3O_2$	3.92, 7.02 (13.0)	66.40 66.23	6.32 6.33	15.49 15.25
2j	CH_3	CH_3	H	201-202 (AcOEt)	71	$C_{10}H_{15}N_3O_2$	4.63, 7.05 (13.0)	57.40 57.49	7.23 7.24	20.08 19.86
2k	CH_3	H	NO_2	230-231 (dec) (MeOH)	56	$C_9H_{12}N_4O_4$	4.69, 7.06 (13.0)	45.00 45.20	5.04 4.82	23.33 23.11
2l	H	CH_3	NO_2	268-269 (dec) (acetone)	88	$C_9H_{12}N_4O_4$	5.38, 8.22 (13.0)	45.00 45.20	5.04 5.10	23.33 23.06
2m	H	H	NO_2	>300 (DMF)	98	$C_8H_{10}N_4O_4$	5.42, 8.17 (13.0)	42.48 42.71	4.46 4.51	24.77 24.50

[a] The reaction was carried out at room temperature.

Starting Materials **1a-h** and **2a,b**.

5-Nitrouracils **1a-c** and **1k-m** [17], 5-cyanouracils **1d-g** [18], 5-formyl-1,3-dimethyluracil **1h** [19], and 1,3-dimethyl- **2a** or 3-cyclohexyl-1-methyl- **2b** 6-(2-dimethylamino)-5-nitrouracil [9] were prepard according to the procedure reported.

General Procedure for the Preparation of 6-(2-Dimethylaminovinyl)uracil Derivatives **2c-m**.

A mixture of the 6-methyluracil **1** (20 mmoles) and DMF-DMA (2.86 g, 24 mmoles) in dry DMF was refluxed until **1** was not detected by tlc (for about 0.3-2 hours. The solution was evaporated under reduced pressure and the residue was triturated with ether or water to give the crude products. Recrystallization from an appropriate solvent gave pure **2** (Table 3).

General Procedure for the Reaction of 6-(2-Dimethylaminovinyl)uracils **2a-m** in Aqueous Solution of Sodium Hydroxide.

A suspension of **2** (1.0 g) in 10% aqueous sodium hydroxide (50 ml) was heated at 90° until **2** was completely dissolved, and then the heating was continued for further 10 minutes. Upon cooling to room temperature the resulting precipitate was filtered off and recrystallized from an appropriate solvent to give pyridin-2-one **3**. If no precipitate forms, the reaction solution was extracted with chloroform. The extract was dried over magnesium sulfate and evaporated under reduced pressure to give **3** or **1j**. The mother solution was acidified with acetic acid to give the 6-methyluracils **1k-m** or the by-products **4**, **5**, or **6** (see Table 1).

Additional spectral data of 1-methyl-4-methylamino-3-nitro-pyridin-2-one (**3a**) and 1,3-dimethyl-4(3*H*)-*exo*-nitromethylenepyrimidin-2(3*H*)-one (**4**). Compound **3a** had uv (ethanol): λ max 242 nm (log ε 4.1), 340 (3.9); ir (potassium bromide): 3280 cm^{-1} (NH), 1640 (C=O). Compound **4** had ^{13}C nmr (deuteriochloroform): δ 31.9 (q, 36.2), 37.8 (q, 36.2), 98.1 (d, 71.4), 112.4 (d, 70.5), 140.1 (d, 68.5), 145.4 (s), and 150.0 (s) ppm; ms: 183 (M^+), 137 ($M^+ - HNO_2$); uv (ethanol): λ max 275 nm (log ε 3.6), 285 (3.5), 384 (4.5); ir (potassium bromide): 1685 cm^{-1} (C=O).

1,9-Dimethyl-3-deazahypoxanthine (**8**).

To a solution of **2a** (1.0 g) in ethanol (150 ml) was added 0.2 g of palladium on charcoal and the mixture was shaken under an hydrogen stream (1 atmosphere) at room temperature. After hydrogen absorption had ceased, the solution was filtered to remove the catalyst. The filtrate was evaporated to dryness under reduced pressure to give the crude 3-aminopyrimidin-2-one **7**; ^1H nmr (deuteriochloroform): δ 2.90 (3H, s, NHMe), 3.40 (2H, br, NH_2), 3.54 (3H, s, NMe), 5.91 (1H, d, J = 8.0 Hz, C_5-H), 6.91 (1H, d, J = 8.0 Hz, C_6-H). The amino compound **7** was treated with refluxing formic acid (1 ml) for 1 hour. Excess formic acid was removed under reduced pressure. The residue was dissolved in ethanol and the solution was treated with calcium carbonate (300 mg), filtered, and concentrated to dryness under reduced pressure. The residue was triturated with ether to give the crude product **8**. Recrystallization from ethyl acetate gave 150 mg (34%) of colorless needles, mp 188-189°; ^1H nmr (DMSO-d_6): δ 3.66 and 3.80 (each 3H, each s, each N-Me), 6.45 and 7.30 (each 1H, each d, J = 7.0 Hz, C_2-H and C_3-H), 7.78 (1H, s, C_8-H).

Anal. Calcd. for $C_8H_9N_3O$: C, 58.88; H, 5.56; N, 25.74. Found: C, 58.89; H, 5.58; N, 25.79.

Isolation of 2-Cyano-5-dimethylamino-*N*-methyl-3-methylamino-2,4-pentadienamide (**9**).

A suspension of 5-cyano-6-(2-dimethylaminovinyl)-1,3-dimethyluracil (**2d**) (1.0 g) in 10% aqueous sodium hydroxide (50 ml) was heated at 90° for 10 minutes. Insoluble starting material was immediately removed by filtration while the reaction solution was hot. Upon cooling the filtrate to room temperature the resulting precipitate was filtered off and recrystallized from ethanol to give 3-cyano-1-methyl-4-methylaminopyridin-2-one (**3d**) (46%), which was identical with the pyridin-2-one **3d** obtained above (see Table 1). The mother liquor was acidified with acetic acid to give the crude product. Recrystallization from ethyl acetate gave 115 mg (13%) of the pentadienamide **9**, mp 170-172°; ^1H nmr (deuteriochloroform): δ 2.83 (3H, d, 5 Hz, NHMe), 2.95 (3H, d, 6 Hz, NHMe), 2.98 (6H, s, NMe_2), 4.51 (1H, d, 13 Hz, CH=), 5.77 and 10.35 (each 1H, br, NH x 2), 7.50 (1H, d, 13 Hz, CH=).

Anal. Calcd. for $C_{10}H_{16}N_4O$: C, 57.67; H, 7.74; N, 26.90. Found: C, 57.66; H, 7.80; N, 26.85.

Conversion of the Pentadienamide **9** into the Pyridin-2-one **3d**.

A solution of **9** (70 mg) in 10% aqueous sodium hydroxide (3 ml) was heated at 90° for 20 minutes. Upon cooling the resulting precipitate was filtered to give the pyridine-2-one **3d** quantitatively.

4-Chloro-3-cyano-1-methylpyridin-2(1*H*)-one (**10**).

A mixture of ricininic acid [16] (1.0 g, 6.5 mmoles) in phosphorus oxychloride (50 ml) was refluxed for 9 hours. Excess phosphorus oxychloride was removed by evaporation under reduced pressure and ice was added to the residue. The resulting precipitate was collected by filtration and recrystallized from benzene to give 0.96 g (86%) of colorless needles, mp 164-165°; ir (potassium bromide): 2225 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.63 (3H, s, NMe), 6.43 (1H, d, J = 7.8 Hz, C_5-H), 7.8 (1H, d, J = 7.8 Hz, C_6-H).

Anal. Calcd. for $C_7H_5ClN_2O_2$: C, 49.90; H, 2.99; N, 16.63. Found: C, 50.11; H, 2.98; N, 16.93.

4-Alkylamino- (or Anilino)-3-cyano-1-methylpyridin-2(1*H*)-ones **3d**, **3g**, and **11a-f**.

A solution of **10** (1.0 g, 5.9 mmoles) and amines (1 ml) in methanol (20 ml) was refluxed for 30 minutes. Methanol was removed by evaporation under reduced pressure and the residue was triturated with a small amount of water. The resulting precipitate was collected by filtration and recrystallized from an appropriate solvent (see Table 2).

REFERENCES AND NOTES

[1] This paper is part **61** of a series entitled "Pyrimidines". For part **60**: see, K. Hirota, Y. Kitade, T. Tomishi, Y. Maki, and E. De Clercq, *J. Chem. Soc., Perkin Trans. 1*, in press (1988).

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