Pyrimidines. 54.[1] Ring Transformation of 5-(2-Carbamoylvinyl)uracil Derivatives to 5-Carbamoylpyridin-2-ones

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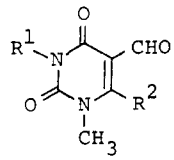
Reaction of 5-formyluracil derivatives **1** with (carbamoylmethylene)triphenylphosphorane led to the formation of both the corresponding (*Z*)- and (*E*)-5-(2-carbamoylvinyl)uracil derivatives **2** and **3**. Upon treatment of the *Z* isomers **2** with ethanolic sodium ethoxide, a mononuclear heterocyclic rearrangement occurred easily to give 3-(ethoxycarbamoyl)pyridin-6-ones (**4**) and 3-(*N*-substituted carbamoyl)pyridin-6-ones (**5**). Under the analogous conditions, the *E* isomers **3** were converted into **4** and **5** together with 3-(*N*-substituted carbamoyl)-1-methylpyridin-6-ones (**6**). Addition of water to the reaction mixture accelerated the conversion of **3** into **6**. Conceivable reaction sequences for the present pyrimidine-to-pyridine transformations are discussed.

Ring transformations in the uracil ring system by reaction with various ambident nucleophiles have been well documented.[2] We have now investigated the reaction of 5-(2-carbamoylvinyl)uracil derivatives. This paper described new ring transformation of uracil into pyridine ring system.

Synthesis of 5-(2-Carbamoylvinyl)uracil Derivatives 2 and 3. Reaction of 5-formyl-1,3-dimethyluracil (**1a**)



1a, $R^1=CH_3$, $R^2=H$

1b, $R^1=C_2H_5$, $R^2=H$

1c, $R^1=R^2=CH_3$

with (carbamoylmethylene)triphenylphosphorane in dry acetonitrile gave a mixture of (*Z*)-5-(2-carbamoylvinyl)-1,3-dimethyluracil (**2a**) and its *E* isomer (**3a**) in 31% and 69% yield, respectively. The assignment of the geometry of the isomer mainly rests upon NMR and UV spectra. The vinyl protons of *Z* isomer **2a** appeared as two doublets (J = 13.0 Hz) at 5.88 and 6.61 ppm. Those of *E* isomer **3a** appeared as two doublets (J = 16.0 Hz) at 6.95 and 7.24 ppm.[3] Analogous Wittig reaction of 3-ethyl-5-formyl-1-methyluracil (**1b**) and 5-formyl-1,3,6-trimethyluracil (**1c**)[4] afforded the corresponding 5-carbamoylvinyl derivatives (**2b** 30% and **3b** 68%) and (**2c** 29% and **3c** 61%). The predominant formation of the *E* isomer **3** squares with the usual Wittig reaction.[5]

Rearrangement of *Z* Isomers 2. Refluxing of *Z* isomer **2a** in ethanolic sodium ethoxide for 2 h followed by neutralization of the reaction mixture furnished 3-(ethoxycarbonyl)pyridin-6-one (**4a**)[6] and 3-(*N*-methylcarbamoyl)pyridin-6-one (**5a**) in 84% and 10% yield, respectively (see Table I). The latter product (**5a**) was also obtained by the reaction of **4a** with methylamine. Heating of 3-ethyl derivative **2b** in ethanolic sodium ethoxide formed **4a** and the corresponding *N*-(ethylcarbamoyl)-pyridine (**5b**) in 82% and 12% yield, respectively. This result indicates that the *N*-alkyl group of **5a** originates from the 3-alkyl group of the uracil. Analogous treatment of 1,3,6-trimethyl derivative **2c** with sodium ethoxide afforded 3-(ethoxycarbonyl)-2-methylpyridin-6-one (**4b**), as a sole product, in 85% yield. The corresponding pyridin-6-one derivative was not detected in the reaction mixture (TLC or ^{1}H NMR).

Table I. Mononuclear Heterocyclic Rearrangement of 5-(2-Carbamoylvinyl)uracil Derivatives 2 and 3

starting compd	reaction time, h	prod (yield, %)		
		4	5	6
2a	2	**4a** (84)	**5a** (10)	
2b	2	**4a** (82)	**5b** (12)	
2c	2	**4b** (85)		
3a	24	**4a** (59)	**5a** (24)	**6a** (16)
	12 (+H_2O)	**4a** (28)	**5a** (16)	**6a** (51)
	1 (in aq NaOH)		**5a** (11)	**6a** (83)
	3 (+C_2H_5SH)	**4a** (65)	**5a** (19)	
3b	24	**4a** (63)	**5b** (10)	**6b** (9)
3c	24	**4b** (66)	**5b** (19)	

The suggested reaction sequence for the formation of **4** and **5** is outlined in Scheme I. An initial nucleophilic attack of the terminal amino group in the side chain on the 6-position of the uracil could produce an allophanoylpyridone intermediate (A), which is converted into **4** by subsequent attack of ethoxide anion on the carbonyl group corresponding to the 4-position of uracil (path a). A solvolytic (path b) or thermal cleavage of the urea moiety of the intermediate A results in the formation of **5**.

Rearrangement of *E* Isomers 3. Treatment of **3a** with ethanolic sodium ethoxide for 24 h gave **4a**, **5a**, and 1-methyl-3-(*N*-methylcarbamoyl)pyridin-6-one (**6a**) in 59%, 24%, and 16% yield, respectively (see Table I). The unexpected product **6a** was identified by comparison of its spectral data with those of an authentic sample prepared by the methylation of **5a**. Disappearance of starting material required a long reaction time in contrast to that of the *Z* isomer **2a**. In order to determine the source of the 1-methyl group of **6a**, the reaction of **3b** possessing different substituent at 1- and 3-positions with ethanolic sodium ethoxide was carried out. The reaction of **3b** afforded **4a**, **5b**, and 3-(*N*-ethylcarbamoyl)-1-methylpyridin-6-one (**6b**) in 63%, 10%, and 9% yield, respectively. This result clearly shows that the N_1-substituent

(1) For part 53, see: Hirota, K.; Banno, K.; Yamada, Y.; Senda, S. *J. Chem. Soc., Perkin Trans. 1*, in press.

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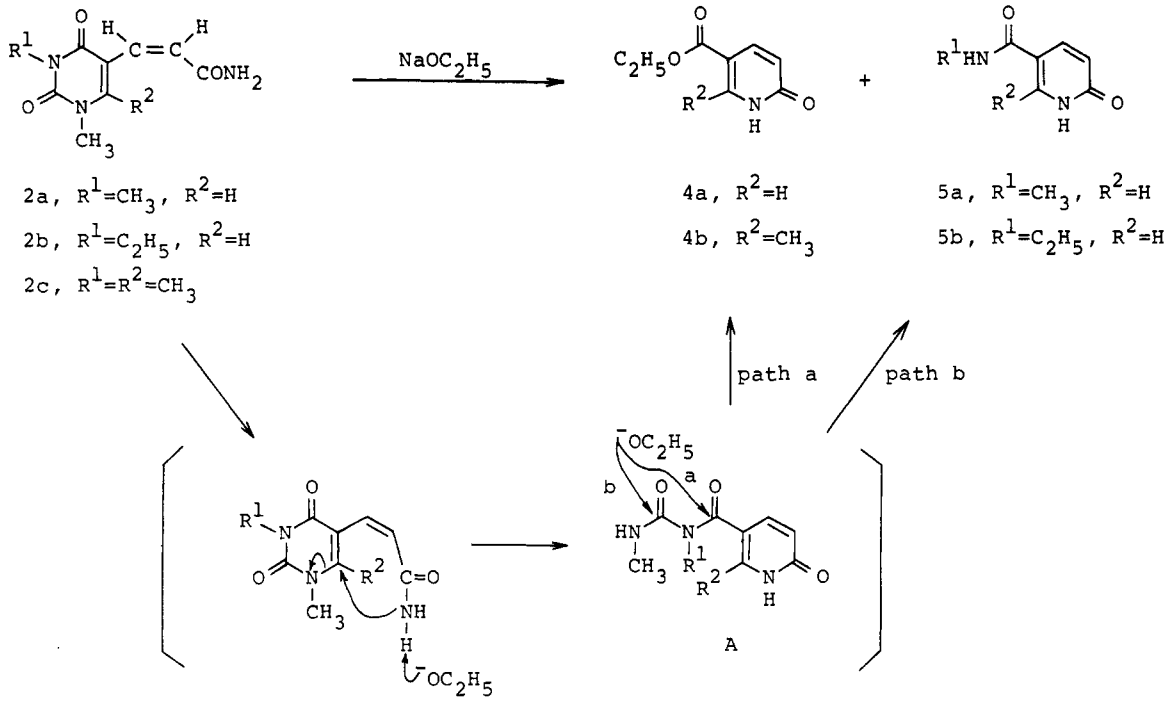
0022-3263/85/1950-1512$01.50/0

Scheme I



of **6** originates from 1-substituent of the parent uracils (**3**). Addition of catalytic amount of water to the reaction mixture increased the yield (51%) of **6a**. This fact indicates that the presence of water in the reaction mixture facilitates the conversion of **3a** into **6a**. Thus, treatment of **3a** with aqueous sodium hydroxide for 1 h proceeded easily to give **6a** (83%) along with **5a** (11%). Treatment of 1,3,6-trimethyl derivative **3c** with ethanolic sodium ethoxide gave **4b** and 2-methyl-3-(*N*-methylcarbamoyl)-pyridin-6-one (**5c**) in 66% and 19% yield, respectively.

To obtain some insight into the mechanisms of these reactions the effect of the addition of thiols to the reaction mixture was investigated because thiols are excellent nucleophiles for addition to the 5,6-double bond of uracils.[7] Thus, reaction of **3a** with ethanethiol in ethanolic sodium ethoxide for 3 h smoothly converted into **4a** (65%) and **5a** (19%). Formation of hydrolysis product **6a** was not detected. The addition of ethanethiol is presumed to accelerate the $E \rightarrow Z$ interconversion, paralleling the reduction in the reaction time and the increase of the yield of **4a**. From the above results, sequences for the formation of **4**, **5**, and **6** from the *E* isomer **3** are outlined in Scheme II. Reaction of the *E* isomer with ethoxide anion or ethanethiolate anion could produce a Michael adduct B, which isomerizes to the *Z* isomer **2**. The *Z* isomer **2** thus formed could undergo the mononuclear heterocyclic rearrangement[8] to give the final products **4** and **5** as described in Scheme I. On the other hand, hydrolysis of **3** at the 2-position could produce open-chain tautomers C and D. Cyclization of D to **6** can be explained in terms of an intramolecular nucleophilic attack of the methylamino group on the carbamoyl group (originated from the side chain at the 5-position) with loss of ammonia (path a). Nucleophilic attack of the amido group (path b), which occurs to some extent, leads to the formation of **5**.

Experimental Section

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Laboratory of our university. Proton magnetic resonance spectra (60 MHz) were recorded on a Hitachi Perkin-Elmer R-20B spectrometer, with tetramethylsilane (Me_4Si) as an internal reference. Carbon magnetic resonance spectra (25 MHz) were determined with a JEOL JNM-FX-100 Fourier Transform spectrometer with Me_4Si as an internal reference. Chemical shifts are reported in parts per million (δ), the *J* values are given in hertz, and signals are quoted as s (singlet), d (doublet), dd (double doublet), dq (double quartet), t (triplet), q (quartet), m (multiplet), or br (broad); *J* values are first order. Infrared spectra were taken on a Hitachi 215 instrument as KBr pellets. Mass spectra were obtained in a JEOL JMS-D300 machine operating at 70 eV. Ultraviolet spectra were obtained from ethanol on a Hitachi 323 spectrophotometer. Column chromatography was carried out on silica gel (Wakogel C-300).

5-Formyl-1,3-dimethyluracil (1a). To a mixture of uracil (44.8 g, 0.4 mol) in 20% NaOH solution (192 mL) was added dropwise dimethyl sulfate (110 g, 0.88 mol) below 40 °C. The mixture was extracted with chloroform. The extract was dried with $MgSO_4$, and the solvent was removed under reduced pressure to give crude product (54 g, 96%). Recrystallization from ethanol gave pure 1,3-dimethyluracil, mp 124–125 °C (lit.[9] mp 123–124 °C). Phosphorus oxychloride (11.5 g, 0.075 mol) was dissolved in dry dimethylformamide (DMF) (40 mL) below 5 °C and 1,3-dimethyluracil (7 g, 0.05 mol) was added thereto. The mixture was heated at 80–90 °C for 1 h. The solvent was removed under reduced pressure, and the residue was dissolved in cold water. The resulting precipitate was collected by filtration and recrystallized from ligroin to give analytically pure 1a:[10] 6.04 g (72%); mp 122–124 °C; ^1H NMR ($CDCl_3$) δ 3.37 (3 H, s), 3.53 (3 H, s), 8.09 (1 H, s), 10.01 (1 H, s); mass spectrum, *m/e* 168 (M^+). Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.26; H, 4.80; N, 16.48.

3-Ethyl-5-formyl-1-methyluracil (1b). To a mixture of 1-methyluracil[11] (3.78 g, 0.03 mol) in 20% NaOH solution (6.7 mL) was added dropwise diethyl sulfate (4.62 g, 0.03 mol) at 50–60

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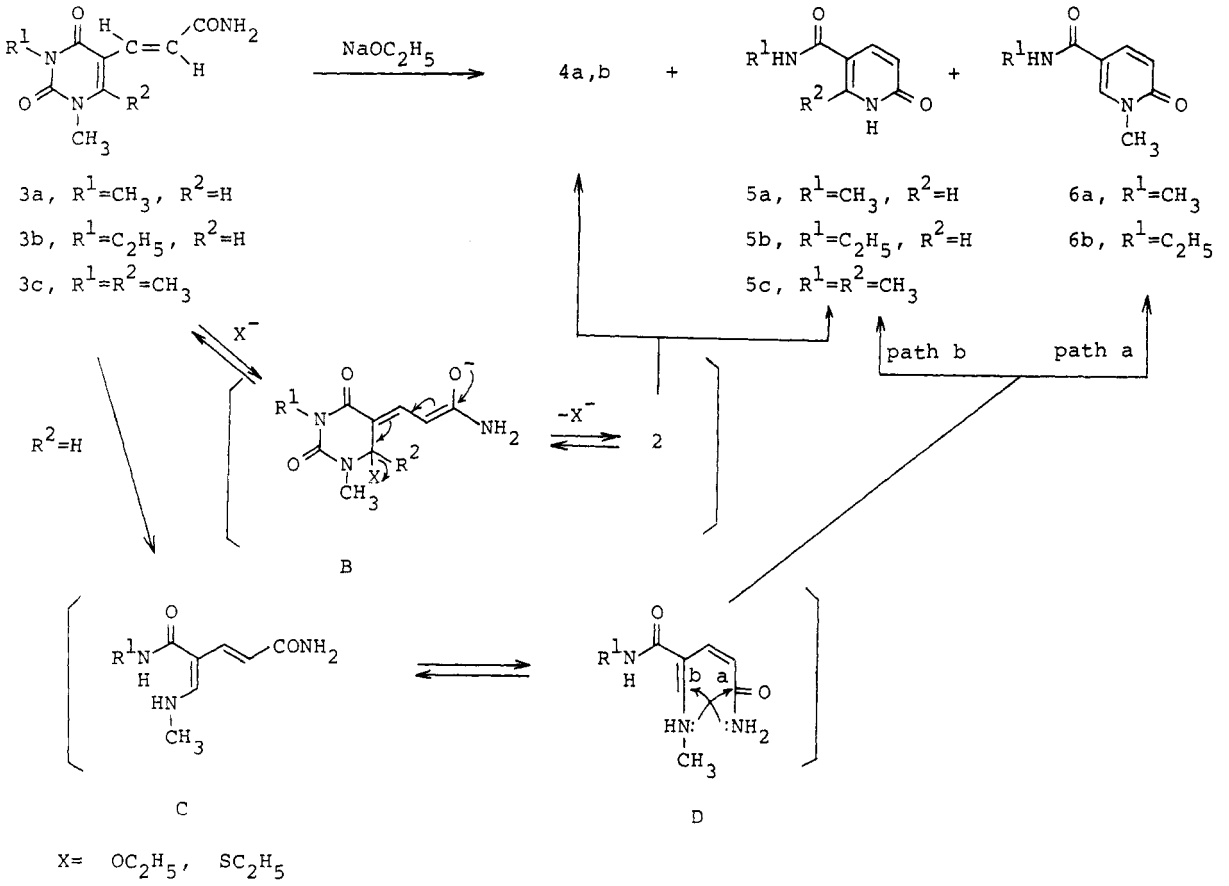
Scheme II



°C. The mixture was neutralized with diethyl sulfate and extracted with chloroform. The extract was dried with $MgSO_4$ and evaporated off in vacuo to give 3-ethyl-1-methyluracil:[12] 2.6 g (56%); mp 42–45 °C. Phosphorus oxychloride (2.3 g, 0.015 mol) was dissolved in dry DMF (13 mL) below 5 °C and 3-ethyl-1-methyluracil (2.55 g, 0.014 mol) was added thereto. The mixture was heated at 80–90 °C for 1 h. The solvent was removed under reduced pressure, and the residue was dissolved in cold water. The resulting precipitate was collected by filtration and recrystallized from ligroin to give **1b**: 1.50 g (59%); mp 133–134 °C; ^1H NMR ($CDCl_3$) δ 1.24 (3 H, t, J = 7.5 Hz), 3.54 (3 H, s), 4.03 (2 H, q, J = 7.5 Hz), 8.06 (1 H, s), 9.95 (1 H, s); mass spectrum, m/e 182 (M^+). Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: 52.51; H, 5.56; N, 15.34.

(*Z*)-5-(2-Carbamoylvinyl)-1,3-dimethyluracil (2a) and (*E*)-5-(2-Carbamoylvinyl)-1,3-dimethyluracil (3a). A mixture of **1a** (2.52 g, 0.015 mol) and (carbamoylmethylene)triphenylphosphorane (9 g, 0.028 mol) in dry acetonitrile (50 mL) was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform–methanol (30:1). Elution of the first fraction gave triphenylphosphine oxide, which was identical with an authentic sample. The second fraction gave **2a**, which was recrystallized from benzene: 1.019 g (31%); mp 183–184 °C; ^1H NMR (Me_2SO-d_6) δ 3.19 (3 H, s), 3.34 (3 H, s), 5.88 (1 H, d, J = 13 Hz), 6.61 (1 H, d, J = 13 Hz), 7.00 (1 H, br), 7.56 (1 H, br), 9.22 (1 H, s); ^{13}C NMR (Me_2SO-d_6) δ 27.67 (q), 37.09 (q), 106.36 (s), 121.04 (d), 129.82 (d), 146.78 (d), 150.59 (s), 162.23 (s), 167.55 (s); IR ν_{max} 3400, 3200 cm^{-1}; UV λ_{max} 294 (ϵ 9690), 252 nm (9460); mass spectrum, m/e 209 (M^+). Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.40; H, 5.27; N, 19.88.

The third fraction gave **3a**, which was recrystallized from methanol: 2.224 g (69%); mp 236–237 °C; ^1H NMR (Me_2SO-d_6) δ 3.24 (3 H, s), 3.39 (3 H, s), 6.90 (1 H, br), 6.95 (1 H, d, J = 16 Hz), 7.24 (1 H, d, J = 16 Hz), 7.32 (1 H, br), 7.99 (1 H, s); ^{13}C NMR (Me_2SO-d_6) δ 27.50 (q), 36.68 (q), 107.12 (s), 120.81 (d), 132.74 (d), 146.55 (d), 150.35 (s), 161.23 (s), 167.38 (s); IR ν_{max} 3400, 3200 cm^{-1}; UV λ_{max} 301 (ϵ 15800), 270 nm (11100); mass spectrum, m/e 209 (M^+). Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.44; H, 5.27; N, 19.93.

(*Z*)-5-(2-Carbamoylvinyl)-3-ethyl-1-methyluracil (2b) and (*E*)-5-(2-Carbamoylvinyl)-3-ethyl-1-methyluracil (3b). A mixture of **1b** (2.73 g, 0.015 mol) and (carbamoylmethylene)triphenylphosphorane (9 g, 0.028 mol) in dry acetonitrile (50 mL) was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform–methanol (30:1). Elution of the first fraction gave triphenylphosphine oxide, which was identical with an authentic sample. Elution of the second fraction gave **2b**, which was recrystallized from benzene: 0.849 g (30%); mp 186–188 °C; ^1H NMR (Me_2SO-d_6) δ 1.11 (3 H, t, J = 7 Hz), 3.36 (3 H, s), 3.89 (2 H, q, J = 7 Hz), 5.91 (1 H, d, J = 13 Hz), 6.65 (1 H, d, J = 13 Hz), 7.03 (1 H, br), 7.60 (1 H, br), 9.24 (1 H, s); IR ν_{max} 3420, 3340 cm^{-1}; UV λ_{max} 295 (ϵ 9060), 253 nm (8540); mass spectrum, m/e 223 (M^+). Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.95; H, 5.95; N, 18.83.

Elution of the third fraction gave **3b**, which was recrystallized from ethanol: 1.508 g (68%); mp 255–256 °C; ^1H NMR (Me_2SO-d_6) δ 1.12 (3 H, t, J = 7 Hz), 3.34 (3 H, s), 3.90 (2 H, q, J = 7 Hz), 6.93 (1 H, d, J = 16 Hz), 6.95 (1 H, br), 7.20 (1 H, d, J = 16 Hz), 7.50 (1 H, br), 8.13 (1 H, s); IR ν_{max} 3450, 3350 cm^{-1}; UV λ_{max} 302 (ϵ 17900), 271 nm (12600); mass spectrum, m/e 223 (M^+). Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.99; H, 6.00; N, 18.96.

(*Z*)-5-(2-Carbamoylvinyl)-1,3,6-trimethyluracil (2c) and (*E*)-5-(2-Carbamoylvinyl)-1,3,6-trimethyluracil (3c). A mixture of **1c**[4] (2.73 g, 0.015 mol) and (carbamoylmethylene)-triphenylphosphorane (9 g, 0.028 mol) in dry acetonitrile (50 mL) was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform–methanol (30:1). Elution of the first fraction gave triphenylphosphine oxide, which was identical with an authentic sample. Elution of the second fraction gave **2c**, which was recrystallized from benzene: 0.978 g (29%); mp 195 °C; ^1H NMR (Me_2SO-d_6) δ 2.17 (3 H, s), 3.18 (3 H, s), 3.37

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(3 H, s), 6.06 (1 H, d, J = 12 Hz), 6.49 (1 H, d, J = 12 Hz), 6.93 (1 H, br), 7.35 (1 H, br); IR ν_{max} 3420, 3160 cm^{-1}; UV λ_{max} 281 nm (ϵ 10100); mass spectrum, m/z 223 (M^+). Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.83; H, 5.84; N, 18.89.

Elution of the third fraction gave **3c**, which was recrystallized from ethanol: 2.028 g (61%); mp 298 °C; ^1H NMR (Me_2SO-d_6) δ 2.44 (3 H, s), 3.22 (3 H, s), 3.43 (3 H, s), 6.95 (1 H, br), 7.01 (1 H, d, J = 16 Hz), 7.38 (1 H, d, J = 16 Hz), 7.50 (1 H, br); IR ν_{max} 3430, 3330, 3220 cm^{-1}; UV λ_{max} 303 (ϵ 11700), 275 nm (7600); mass spectrum, m/e 223 (M^+). Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.59; H, 5.94; N, 18.67.

Reaction of 2a with Sodium Ethoxide. A mixture of **2a** (0.454 g, 0.0022 mol) in ethanolic sodium ethoxide [prepared from Na (0.1 g) in dry ethanol (55 mL)] was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was dissolved in cold water (10 mL). The solution was acidified with concentrated HCl and the water was removed under reduced pressure. The residue was chromatographed on a silica gel column eluting with ethyl acetate. Elution of the faster fraction gave **4a**,[10] which was recrystallized from ligroin: 0.304 g (84%); mp 149–150 °C (lit.[7] mp 145–146 °C); ^1H NMR ($CDCl_3$) δ 1.35 (3 H, t, J = 7.5 Hz), 4.33 (2 H, q, J = 7.5 Hz), 6.58 (1 H, d, J = 9.5 Hz), 8.02 (1 H, dd, J = 9.5, 3 Hz), 8.23 (1 H, d, J = 3 Hz), 13.25 (1 H, br); UV λ_{max} 286 (ϵ 5900), 257 nm (17000), λ_{max} (0.1 N HCl) 283 (ϵ 5900), 229 nm (16800), λ_{max} (0.1 N NaOH) 276 nm (ϵ 18900); mass spectrum, m/e 167 (M^+). Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43, N, 8.38. Found: C, 57.37; H, 5.38; N, 8.54.

Elution of the slower fraction gave **5a**, which was recrystallized from ethanol: 0.033 g (10%); mp 254–255 °C; ^1H NMR (Me_2SO-d_6) δ 2.72 (3 H, d, J = 4.5 Hz), 6.35 (1 H, d, J = 9.5 Hz), 7.85 (1 H, dd, J = 9.5, 3 Hz), 7.94 (1 H, d, J = 3 Hz), 8.18 (1 H, br), 11.86 (1 H, br); IR ν_{max} 3350, 3280 cm^{-1}; UV λ_{max} 292 (ϵ 7200), 252 nm (19700), λ_{max} (0.1 N HCl) 292 (ϵ 5400), 252 nm (14600), λ_{max} (0.1 N NaOH) 264 nm (ϵ 17400); mass spectrum, m/z 152 (M^+). Anal. Calcd for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.31; H, 5.28; N, 18.12.

Alternative Preparation of 4a. A mixture of 6-hydroxynicotinic acid[13] (10 g) in 10% ethanolic hydrochloride (200 mL) was refluxed for 30 min. The solvent was removed under reduced pressure and the residue was acidified with saturated $NaHCO_3$ solution. The solution was extracted with chloroform and the extract was dried with $MgSO_4$. The solvent was removed under reduced pressure to give **4a**, which was identical with the product prepared above.

Alternative Preparation of 5a. A mixture of **4a** (5 g) in 40% methylamine solution (50 mL) was stirred for 5 days at room temperature. The resulting precipitate was collected by filtration to give **5a**, which was identical with the product prepared above.

Reaction of 2b with Sodium Ethoxide. A mixture of **2b** (0.446 g, 0.002 mol) in ethanolic sodium ethoxide [prepared from Na (0.092 g) in dry ethanol (50 mL)] was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was dissolved in cold water (10 mL). The solution was acidified with concentrated HCl and the water was removed under reduced pressure. The residue was chromatographed on a silica gel column eluting ethyl acetate. Elution of the faster fraction gave **4a**, which was identical with the authentic sample prepared above, 0.274 g (82%).

Elution of the slower fraction gave **5b**, which was recrystallized from ethanol: 0.04 g (12%); mp 200–202 °C; ^1H NMR (Me_2SO-d_6) δ 1.08 (3 H, t, J = 7.5 Hz), 3.25 (2 H, dq, J = 7.5, 3 Hz), 6.35 (1 H, d, J = 9.5 Hz), 7.87 (1 H, dd, J = 9.5, 3 Hz), 7.97 (1 H, d, J = 3 Hz); IR ν_{max} 3320 cm^{-1}; UV λ_{max} 292 (ϵ 7200), 252 nm (19700); mass spectrum, m/e 167 ($M^+ + 1$). Anal. Calcd for $C_9H_{11}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.57; H, 6.05; N, 16.68.

Reaction of 2c with Sodium Ethoxide. A mixture of **2c** (0.446 g, 0.002 mol) in ethanolic sodium ethoxide [prepared from Na (0.092 g) in dry ethanol (55 mL)] was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was dissolved in cold water (10 mL). The solution was acidified with Amberlite CG-120 and the water was removed under reduced pressure. The residue was recrystallized from ethanol to give analytically pure 3-(ethoxycarbonyl)-2-methylpyridin-6-one (**4b**): 0.308 g (85%); mp 222 °C; ^1H NMR (Me_2SO-d_6) δ 1.28 (3 H, t, J = 7 Hz), 2.54 (3 H, s), 4.22 (2 H, q, J = 7 Hz), 6.23 (1 H, J = 10 Hz), 7.85 (1 H, d, J = 10 Hz), 12.03 (1 H, br); UV λ_{max} 294 (ϵ 6200), 260 nm (13200), λ_{max} (0.1 N HCl) 294 (ϵ 5700), 259 nm (11900), λ_{max} (0.1 N NaOH) 284 nm (ϵ 17300); mass spectrum, m/e 181 (M^+). Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.67; H, 6.21; N, 7.71.

Reaction of 3a with Sodium Ethoxide. A mixture of **3a** (0.454 g, 0.0022 mol) in ethanolic sodium ethoxide [prepared from Na (0.0092 g) in dry ethanol (35 mL)] was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in cold water (10 mL). The solution was acidified with 10% HCl and the water was removed under reduced pressure. The residue was chromatographed on a silica gel column eluting ethyl acetate. Elution of the first fraction gave **4a**, which was identical with the authentic sample prepared above: 0.214 g (59%).

Elution of a second fraction gave 1-methyl-3-(*N*-methylcarbamoyl)pyridin-6-one (**6a**): 0.093 g (16%); mp 192 °C; ^1H NMR (Me_2SO-d_6) δ 2.70 (3 H, d, J = 4 Hz), 3.42 (3 H, s), 6.29 (1 H, d, J = 9.5 Hz), 7.73 (1 H, dd, J = 9.5, 3 Hz), 8,03 (1 H, br), 8.18 (1 H, d, J = 3 Hz); UV λ_{max} 296 (ϵ 5200), 254 nm (14900), λ_{max} (0.1 N HCl) 296 (ϵ 5100), 254 nm (14700), λ_{max} (0.1 N NaOH) 296 (ϵ 5300), 255 nm (15700); mass spectrum, m/e 166 (M^+). Anal. Calcd for $C_9H_{11}N_2O_2$: C, 57.82; H, 6.07; N, 16,86. Found: C, 57.57; H, 6.05; N, 16.68.

Elution of the third fraction gave **5a**, which was identical with the authentic sample prepared above, 0.081 g (24%).

Alternative Preparation of 6a. A mixture of **5a** (1.52 g), methyl iodide (2 mL), and sodium hydroxide (0.6 g) in nitromethane (20 mL) was stirred for 5 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting ethyl acetate to give **6a**, which was identical with the product prepared above.

Reaction of 3a with Sodium Ethoxide in the Presence of Water. A mixture of **3a** (0.418 g, 0.002 mol) and water (0.09 g) in ethanolic sodium ethoxide [prepared from Na (0.092 g) in dry ethanol (50 mL)] was refluxed for 12 h. The solvent was removed under reduced pressure and the residue was dissolved in cold water (10 mL). The solution was acidified with 10% HCl. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting ethyl acetate. Elution of the first fraction gave **4a**, which was identical with the authentic sample prepared above, 0.092 g (28%).

Elution of the second fraction gave **6a**, which was identical with the authentic sample prepared above, 0.168 g (51%).

Elution of the third fraction gave **5a**, which was identical with the authentic sample prepared above, 0.047 g (16%).

Reaction of 3a with Aqueous Sodium Hydroxide. A mixture of **3a** (0.42 g, 0.002 mL) and sodium hydroxide (0.16 g, 0.004 mol) in water (40 mL) was refluxed for 1 h. The water was removed under reduced pressure and the residue was dissolved in cold water (10 mL). The solution was acidified with concentrated HCl and the water was removed under reduced pressure. The residue was chromatographed on a silica gel column eluting ethyl acetate. Elution of the first fraction gave **6a**, which was identical with the authentic sample prepared above, 0.276 g (83%).

Elution of the second fraction gave **5a**, which was identical with the authentic sample prepared above, 0.033 g (11%).

Reaction of 3a with Sodium Ethoxide in the Presence of Ethanethiol. A mixture of **3a** (0.42 g, 0.002 mol) and ethanethiol (0.50 g, 0.008 mol) in ethanolic sodium ethoxide [prepared from Na (0.10 g) in dry ethanol (50 mL)] was refluxed for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in cold water (10 mL). The solution was acidified with 10% HCl and the water was removed under reduced pressure. The residue was chromatographed on a silica gel column eluting ethyl acetate. Elution of the first fraction gave **4a**, which was identical with the authentic sample prepared above, 0.220 g (65%).

Elution of the second fraction gave **6a**, which was identical with the authentic sample prepared above, 0.060 g (19%).

Reaction of 3b with Sodium Ethoxide. A mixture of **3b** (0.446 g, 0.002 mol) in ethanolic sodium ethoxide [prepared from Na (0.092 g) in dry ethanol (50 mL)] was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was

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dissolved in cold water (10 mL). The solution was acidified with 10% HCl and the water was removed under reduced pressure. The residue was chromatographed on a silica gel column eluting ethyl acetate. Elution of the first fraction gave **4a**, which was identical with the authentic sample prepared above, 0.21 g (63%).

Elution of the second fraction gave 3-(*N*-ethylcarbamoyl)-1-methylpyridin-6-one (**6b**), which was recrystallized from ethyl acetate: 0.034 g (9%); mp 159 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.11 (3 H, t, J = 7 Hz), 3.49 (2 H, dq, J = 7, 2 Hz), 6.40 (1 H, d, J = 9.5 Hz), 7.87 (1 H, dd, J = 9.5, 3 Hz), 8.15 (1 H, br), 8.33 (1 H, d, J = 3 Hz); IR ν_{max} 3310 cm^{-1}; UV λ_{max} 296 (ϵ 5400), 229 nm (15 100), λ_{max} (0.1 N HCl) 296 (ϵ 5400), 229 nm (14 800), λ_{max} (0.1 N NaOH) 296 (ϵ 5500), 230 nm (15 700); mass spectrum, m/e 180 (M^+). Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.99; H, 6.80; N, 15.61.

Elution of the third fraction gave **5b**, which was identical with the product prepared above, 0.053 g (16%).

Reaction of 3c with Sodium Ethoxide. A mixture of **3c** (0.446 g, 0.002 mol) in ethanolic sodium ethoxide [prepared from Na (0.092 g) in dry ethanol (55 mL)] was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in cold water (10 mL). The water was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting ethyl acetate. Elution of the first fraction gave **4b**, which was identical with the product prepared above, 0.240 g (66%).

Elution of the second fraction gave 2-methyl-3-(*N*-methylcarbamoyl)pyridin-6-one (**5c**): 0.063 g (19%); mp 255 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.37 (3 H, s), 2.71 (3 H, d, J = 4.5 Hz), 6.19 (1 H, d, J = 9.5 Hz), 7.56 (1 H, d, J = 9.5 Hz), 8.03 (1 H, br), 11.78 (1 H, br); IR ν_{max} 3400, 3300 cm^{-1}; UV λ_{max} 300 (ϵ 7100), 246 nm (10 700), λ_{max} (0.1 N HCl) 297 (ϵ 6700), 246 nm (9800), λ_{max} (0.1 N NaOH) 288 (ϵ 7700), 258 nm; mass spectrum, m/e 166 (M^+). Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.92; H, 6.12; N, 16.90.

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Registry No. **1a**, 4869-46-9; **1b**, 80981-21-1; **1c**, 23941-84-6; **2a**, 95387-35-2; **2b**, 95387-36-3; **2c**, 95387-37-4; **3a**, 95387-38-5; **3b**, 95387-39-6; **3c**, 95387-40-9; **4a**, 18617-50-0; **4b**, 3424-43-9; **5a**, 1007-18-7; **5b**, 95387-41-0; **5c**, 95387-42-1; **6a**, 62415-66-1; **6b**, 62415-68-3; $NH_2C(O)CH{=}PPh_3$, 38821-11-3; uracil, 66-22-8; 1-methyluracil, 615-77-0; 1,3-dimethyluracil, 874-14-6; 3-ethyl-1-methyluracil, 59495-24-8; 6-hydroxynicotinic acid, 5006-66-6.

Synthetic Applications of 2-Cyano-1,2,3,6-tetrahydropyridines. 2.[1] Synthesis of Isodasycarpidone and Related Systems, the Ervitsine Skeleton, and Its Benzo Analogue[2]

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The synthesis of isodasycarpidone (**8a**), *N*-demethylisodasycarpidone (**9a**), and their epi derivatives **8b** and **9b** is described. The condensation of an appropriate 2-cyano-1,2,3,6-tetrahydropyridine with indole and the conjugate addition of diethylcopper(I)–magnesium bromide to the resulting α,β-unsaturated esters constitute the key steps of this synthesis. A similar condensation from methyl 2-cyano-1-methyl-1,2,3,6-tetrahydropyridine-4-acetate (**11**) and indolylmagnesium iodide or (*m*-methoxyphenyl)magnesium bromide, followed by catalytic hydrogenation, hydrolysis, and PPA cyclization establishes synthetic routes to the tetracyclic framework (**16**) of the indole alkaloid ervitsine and its benzo analogue **19**.

2-Cyano-1,2,3,6-tetrahydropyridines are useful synthetic intermediates since they have proven to be synthons for 2,5-dihydropyridinium salts.[3] These compounds are easily accesible from the corresponding pyridinium salts by reductive cyanation by means of sodium borohydride in the presence of a large excess of cyanide ions.[4] They are able to react with Grignard reagents to give 2-substituted-1,2,3,6-tetrahydropyridines[5,6] or with activated aromatic rings such as indole itself[1] as Grignard reagent[1,6] or as alkali metal salt,[7] to give 3-(tetrahydro-2-pyridyl)indole systems. In this way, 2-cyano-1,2,3,6-tetrahydropyridines bearing a functionalized carbon substituent at the C-4 position have been elaborated to deethyldasycarpidone.[1] On the other hand, 2-cyano-1,2,3,6-tetrahydropyridines having an indol-3-ylethyl substituent at the nitrogen atom can be cyclized to the indolo[2,3-*a*]quinolizine skeleton,[8] whereas catalytic hydrogenation of the carbon–carbon double bond of 4-(indolylmethyl)-2-cyano-1,2,3,6-tetrahydropyridines followed by acid cyclization led to bridged polycyclic systems related to indole alkaloids.[9]

In this paper we wish to further illustrate some synthetic applications of 2-cyano-1,2,3,6-tetrahydropyridines: (a) The α,β-unsaturated ester moiety of methyl 2-(3-indolyl)tetrahydropyridine-4-carboxylates **3** and **4**, prepared from appropriate 2-cyano-1,2,3,6-tetrahydropyridines, allows the introduction of an ethyl substituent by means of conjugate addition of diethylcopper(I)–magnesium bromide. By this route we report efficient syntheses of isodasycarpidone (**8a**), *N*-demethylisodasycarpidone (**9a**), and their epiderivatives **8b** and **9b**, respectively. (b) We also describe the preparation of a 2-cyano-1,2,3,6-tetrahydropyridine (**11**), having a C-4 (alkoxycarbonyl)methyl substituent, and its condensation

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(2) Presented in part at the 19th Reuniôn Bienal de la Real Sociedad Española de Quimica, Santander, Spain, 1982, and at the 3rd European Symposium on Organic Chemistry, Canterbury, England, 1983.

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