Functionalization of Substituted 2(1*H*)- and 4(1*H*)-Pyridones. 4. Synthesis of Substituted 6-(Aminocarbonyl)-1,2-dihydro-2-oxo- and 6-(Aminocarbonyl)-1,4-dihydro-4-oxo-3-pyridinecarboxylic Acids

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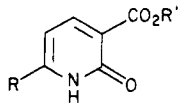
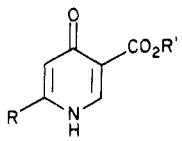
The synthesis of various substituted 6-(aminocarbonyl)-1,2-dihydro-2-oxo-3-pyridinecarboxylic acids from the 5-ethyl and 5-*tert*-butyl 1,6-dihydro-6-oxo-2,5-pyridinedicarboxylates is described. These esters were prepared by ozonolysis and oxidative workup of the corresponding 6-(2,2-diphenylethenyl)-1,2-dihydro-2-oxo-3-pyridinecarboxylates. The structure of the previously reported 2-ethyl 1,6-dihydro-6-oxo-2,5-pyridinecarboxylate was established by an unambiguous synthesis. The 5-ethyl 1,4-dihydro-4-oxo-2,5-pyridinedicarboxylate and some substituted 6-(aminocarbonyl)-1,4-dihydro-4-oxo-3-pyridinecarboxylic acids were also prepared.

As part of our search for new pyridone side chains of type **1** for various penicillin and cephalosporin nuclei,[1] we



	R	R′
1	$C_6H_4SO_2NR_1R_2$, $C_6H_4NHCOR_1$ $C_6H_4CONR_1R_2$	H
2	$CONR_1R_2$	H
4	CO_2H	H
5	$COCH_3$	H
6a	C≡N	t-C_4H_9
b	C≡N	CH_3CH_2
c	$CONH_2$	CH_3CH_2
7a	CO_2H	CH_3CH_2
b	CO_2H	t-C_4H_9
9a	CH_3	CH_3CH_2
b	CH_3	t-C_4H_9
16a	COCl	CH_3CH_2
b	COCl	t-C_4H_9
24	$CH_2COH(Ph_2)$	t-C_4H_9



3	$CONR_1R_2$	H
8	CO_2H	CH_3CH_2

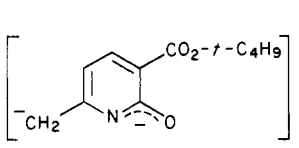
decided to prepare some 6-(aminocarbonyl)-1,2-dihydro-2-oxo-3-pyridinecarboxylic acids to test the effect of placing the amide linkage in **1** directly on the pyridone ring as in **2**. We also desired to examine the activity of the corresponding 4-pyridone analogues **3**.[2]

The obvious precursor to the substituted 6-(aminocarbonyl)-2-pyridones **2** appeared to be some form of the 2-pyridone diacid **4**[3] that would enable us to aminate the 6-carbonyl group regiospecifically. A monoester of **4** has been reported,[3] with the exact position of the ester group unknown. The diester was not known. The diacid **4** was later synthesized by the oxidation of the 6-acetyl-2-pyridone **5**,[4,6] although the 3-carboxyl monoester was not readily obtainable by this route.[5] We have previously reported the synthesis of the 6-cyano- and 6-(aminocarbonyl)-2-pyridone-3-carboxylates (**6**),[6] in which the two carboxyl groups are chemically distinguishable, but in a practical sense, the 6-cyano and the 6-amido functions were not readily transformable in the presence of a 3-carboxylate.[5] None of the corresponding 4-pyridones were known.

In this paper, we describe an unequivocal synthesis of the 3-ethyl and 3-*tert*-butyl 1,2-dihydro-2-oxo- and 1,4-dihydro-4-oxopyridine-3,6-dicarboxylates **7** and **8** and the conversion of these selectively protected acids to the desired amides **2** and **3**. We have also elucidated the structure of the 2-pyridone monoester previously described.[3]

Results and Discussion

Initial attempts to prepare the 2-pyridone monoesters **7a,b** from the 1,2-dihydro-6-methyl-2-oxo-3-pyridinecarboxylates **9a,b** by oxidation of the C_6 methyl with potassium permanganate[7a] or selenium dioxide[7b] were unsuccessful and, in most cases, gave complete destruction of the pyridone ring. To direct the oxidation to C_6, we prepared the dianion **10**,[6,8] but treatment with oxygen[7c] or



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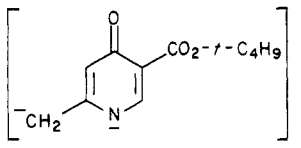

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MoO_5·Py·HMPA[7d] gave only trace amounts of products. The dianion **10** could be oxidatively quenched with either phenyl disulfide or *n*-butyl nitrite[6] (eq 1). The resulting adducts **11** and **12** could not be converted to the 6-aldehyde

(1) Kaltenbronn, J. S.; Haskell, T. H.; Doub, L.; Knoble, J.; DeJohn, D.; Krolls, U.; Jenesel, N.; Huang, G.; Heifetz, C. L.; Fisher, M. W. *J. Antiobiot.* **1979**, *32*, 621. Kaltenbronn, J. S.; Doub, L.; Schweiss, D. U.S. Patent 4 053 470, 1977. Kaltenbronn, J. S.; Haskell, T. H.; Doub, L. U.S. Patent 4 101 661, 1977. Doub, L.; Haskell, T. H.; Mich, T.; Schweiss, D. U.S. Patent 4 315 859, 1982. Nicolaides, E. D.; Woo, P. W. K.; Huang, G. G. U.S. Patent 4 278 681, 1981.

(2) Certain 6-alkyl-1,4-dihydro-4-oxo-3-pyridinecarboxylic acids have been reported as active β-lactam side chains: Isaka, I.; Koda, K.; Murakami, Y. Jpn. Kokai Tokkyo Koho 7 930 197, 1979; *Chem. Abstr.* **1979**, *91*, 57037a.

(3) Uedo, K. *J. Pharm. Soc. Jpn.* **1937**, *56*, 654.

(4) Rateb, L.; Mina, G. A.; Soliman, G. *J. Chem. Soc. C.* **1968**, 2140.

(5) Results obtained in our laboratories.

(6) Showalter, H. D. H.; Domagala, J. M.; Sanchez, J. P. *J. Heterocycl. Chem.* **1981**, *18*, 1609.

(7) (a) Miller, A. D.; Osuch, C.; Goldberg, N. N.; Levine, R. *J. Am. Chem. Soc.* **1956**, *78*, 674. (b) Jerchel, D.; Bauer, E.; Hippchen, H. *Chem. Ber.* **1955**, *88*, 156. (c) Moersch, G. W.; Zwiesler, M. L. *Synthesis* **1971**, 647. (d) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188, and the references therein.

(8) DeJohn, D.; Domagala, J. M.; Kaltenbronn, J. S.; Krolls, U. *J. Heterocycl. Chem.* **1983**, *20*, 1295.

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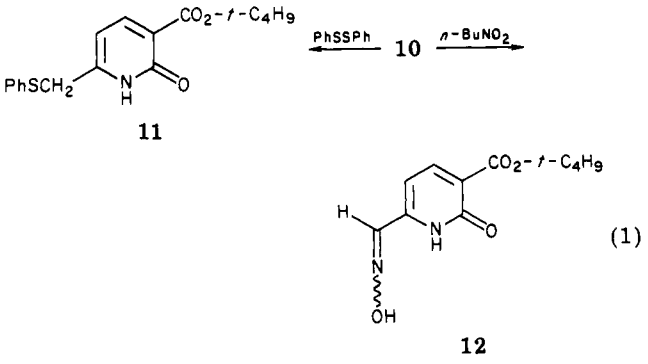


(1)

using general published procedures.[9] Since it was reported that pyridones survive ozonolysis,[4] we decided to subject certain 6-vinylpyridones, obtainable from the dianion **10**,[8] to ozonolysis and oxidative workup with the hope of obtaining the pyridone monoesters **7** (Scheme I).

For convenience in handling, we chose to examine the vinylpyridone **13b**, which was highly crystalline and obtainable in excellent yield from the reaction of the dianion **10** with benzophenone, followed by dehydration of the aldol adduct with $SOCl_2$ and pyridine in THF. After much experimentation, the vinylpyridone **13b** was smoothly oxidized to the 6-acid 3-*tert*-butyl ester **7b** by using excess O_3 in CH_2Cl_2 at −78 °C, followed by overnight stirring with H_2O_2 and AcOH.[10] The only isolated byproduct of this reaction was the diacid **4** obtained by hydrolysis of the *tert*-butyl ester during workup. This problem was easily overcome by conversion of the *tert*-butyl ester **13b** or the acid **13a** to the vinyl ethyl ester **14**. Compound **14** was transformed to the monoester **7a** under identical ozonolysis conditions.

This ozonolysis procedure was general for many vinylpyridones, with **14** giving the best results. Solvent and temperature were important variables in the ozonolysis. The use of CH_2Cl_2 improved yields by 20% over MeOH or THF. At higher temperatures, even −10 °C, the pyridone ring was destroyed.

The oxidation of the ozonide with H_2O_2, although mild and complete, was found to be unnecessary because exposure to oxygen (2–3 days) decomposed the ozonide to **7a,b** in good yields. In fact, quenching the ozonide with reducing agents (CH_3SSCH_3) in an effort to obtain the aldehyde was only partially successful because the isolated 6-aldehyde decomposed gradually to the 6-acid upon exposure to air.

To avoid the interference by the 2-oxygen during acid chloride formation at the C_6 carboxyl, the 6-acid 2-pyridone monoester **7a** was first silylated with excess Me_3SiCl and Et_3N to form **17**. Treatment of **17** with $SOCl_2$ in CH_2Cl_2 produced the 6-acid chloride, which was easily captured by the addition of alcohols to form the 6-esters or by the addition of amines to form the 6-amide 3-esters **15**. The reaction was successful with a variety of amines. Hydrolysis of the 3-ethyl ester in **15** was readily accomplished with 2.1 equiv of 2 M NaOH in EtOH to give the desired substituted 6-(aminocarbonyl)-1,2-dihydro-2-oxo-3-pyridinecarboxylic acids **2** (Table I).

With the technology for preparing and coupling the 5-ethyl or 5-*tert*-butyl 1,6-dihydro-6-oxo-2,5-pyridinedicarboxylates (**7**) established, the corresponding 4-pyridone isomer **8** was prepared in an analogous manner, described in Scheme II, from the 4-pyridone dianion **18**.

The 2-pyridone 3-ethyl ester **7a**, prepared regioselectively by the ozonolysis method, had mp 236–238 °C. The ethyl 1,2-dihydro-2-oxo-3,6-pyridonedicarboxylate reported in the literature[3] had mp 206 °C. To be certain that these esters were indeed two different isomers, the 6-ethyl ester was prepared by an unequivocal route (Scheme III). First, the 3-*tert*-butyl 6-cyano-1,2-dihydro-2-oxopyridinecarboxylate **6a**[6] was subjected to strong base hydrolysis to give the diacid **4**. This diacid **4** was esterified to a monoester, mp 204–206 °C, and the diester **22** using literature conditions. The monoester **21** obtained by the literature procedure was different spectroscopically from the 2-pyridone 3-ethyl ester **7a**. The final proof of the structure of **21** was achieved when 6-carboxylic acid 3-*tert*-butyl ester **7b** was converted to the 6-ethyl 3-*tert*-butyl diester **23** through standard coupling conditions used for amide preparation. Treatment of **23** with TFA in CH_2Cl_2 produced **21**, which was identical spectroscopically with the monoester **21** prepared from **4**.

In conclusion, methods have been developed to selectively protect 1,2-dihydro-2-oxo- and 1,4-dihydro-4-oxo-3,6-pyridinedicarboxylic acids **7** and **8**, as well as coupling these acids to amines to prepare the desired 6-aminocarbonyl derivatives **2** and **3**. In addition, the structure of the previously reported monoester 2-pyridone has been established as the 6-ethyl ester **21**.

Experimental Section

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Digilab FTS-14 or Beckman IR9 grating dispersion instrument. Proton magnetic resonance (^1H NMR) spectra were recorded on a Varian EM-390 or Bruker WH-90 instrument. The Bruker WH-90 was modified with a Nicolet Technology Corp. B-NC12 data acquisition system. Chemical shifts are reported as δ values in parts per million from internal tetramethylsilane. Combustion analyses were performed on a Perkin-Elmer 240 elemental analyzer. Column chromatography was performed with E. Merck silica gel 60, 70–230 mesh ASTM. Ozone was generated with a Welsbach ozonizer using dried oxygen. Tetrahydrofuran (THF) was dried and distilled from sodium aluminum hydride just prior to use. Solutions were dried with $MgSO_4$ and concentrated on a rotary evaporator at 30–45 °C at pressures of 10–20 mm. Carbonyl substrates and amines were commercially available. Diisopropylamine was obtained from Aldrich Chemical Co. and was dried over 4Å sieves. *n*-Butyllithium in heptane was from Foote Chemical Co., and its activity was determined by titration.[11] Thionyl chloride was distilled prior to use. All moisture-sensitive reactions were performed under dry nitrogen.

1,2-Dihydro-6-(2,2-diphenylethenyl)-2-oxo-3-pyridinecarboxylic Acid (13a) and Its *tert*-Butyl Ester 13b. To 20.18 mL (2.0 equiv) of diisopropylamine in 150 mL of dry THF at 0 °C was added 92.5 mL of *n*-BuLi (1.65 M, 2.0 equiv). After 15 min, the mixture was taken to −40 °C, and 15.06 g (72.2 mmol) of the *tert*-butyl ester **9b** in 120 mL of THF was added, keeping the temperature at −35 to −40 °C. After 1.5 h at −40 °C, 13.6 g (74.7 mmol) of benzophenone in 60 mL of THF was added. The mixture was kept at −40 °C for 1 h and brought to 0 °C over 3 h. It was poured over ice and NH_4Cl. The slush was brought to pH 7.0 and extracted with CH_2Cl_2, which was dried and concentrated to give 26.88 g (>99%) of the aldol adduct **24** as a yellow solid: mp 165–166 °C; IR (KBr) 3400, 1730, 1680, 1650 cm^{-1}; NMR (Me_2SO-d_6) δ 11.2 (s, 1 H, NH), 7.7 (d, J = 8 Hz, 1 H, C_4 H), 7.3 (m, 10 H, Ar), 6.2 (s, 1 H, OH), 5.95 (d, J = 8 Hz, 1 H, C_5 H), 3.65 (s, 2 H, CH_2), 1.5 (s, 9 H, C_4 H_9).

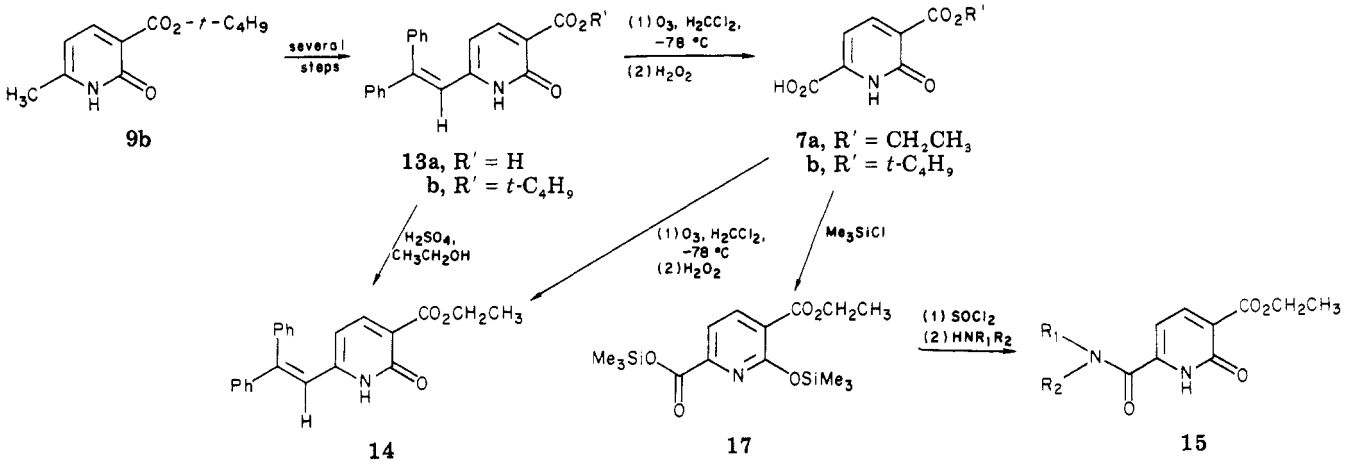
This material was treated with 550 mL of THF and 10.5 mL (1.8 equiv) of pyridine, and then at gentle reflux, 7.3 mL (1.4 equiv) of $SOCl_2$ was added. After 1 h, the mixture was concentrated, and the black solids were recrystallized from 600 mL of acetone to give 12.0 g (45%) of the *tert*-butyl ester **13b** as a yellow solid:

(9) (a) Bakuzis, P.; Backuzis, M. L. F. *J. Org. Chem.* **1977**, *42*, 2362. (b) Drabowicz, J. *Synthesis* **1980**, 125, and the references therein. (c) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 4446.

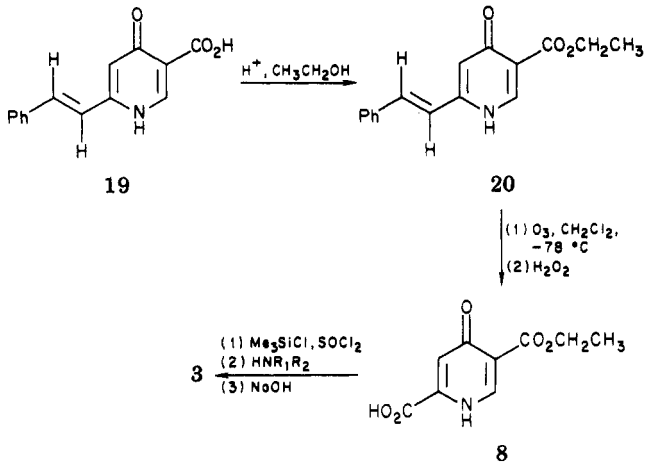
(10) Wilms, H. *Justus Liebigs Ann. Chem.*, **1950**, *567*, 96.

(11) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

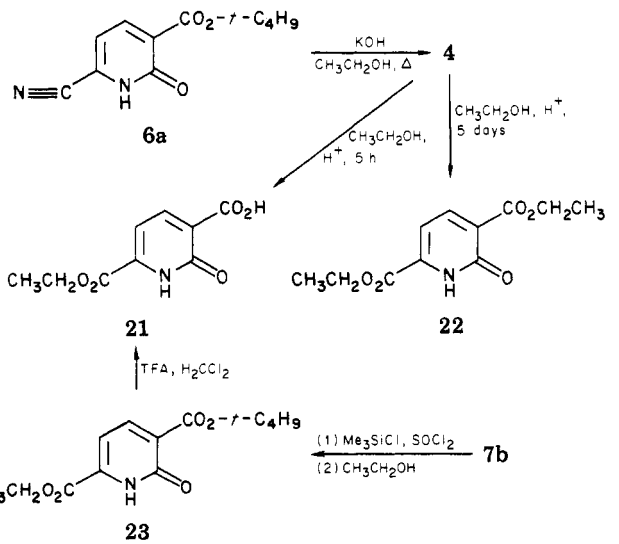
Scheme I



Scheme II



Scheme III



mp 230–231 °C dec; IR (KBr) 1740, 1705, 1660 cm^{-1}; NMR (Me_2SO-d_6) δ 7.55 (d, J = 8 Hz, 1 H, C_4 H) 7.3 (m, 10 H), 6.8 (s, 1 H, vinyl), 5.4 (d, J = 8 Hz, 1 H, C_5 H), 1.45 (s, 9 H, t-C_4H_9). Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.21; H, 6.17; N, 3.75. Found: C, 77.63; H, 5.88; N, 4.18.

The aldol adduct **24** could be dehydrated directly to the acid **13a** (~85%) when a mixture of refluxing H_2SO_4 in Ac_2O was used as reported by Hauser:[12] mp 220–230 °C dec; IR (KBr) 3440, 1740, 1620 cm^{-1}; NMR (Me_2SO-d_6) δ 13.3 (s, 1 H, OH), 8.1 (d, J = 8 Hz, 1 H, C_4 H), 7.5 (m, 10 H, Ar), 7.1 (s, 1 H, vinyl), 6.95 (d, J = 8 Hz, 1 H, C_5 H). Anal. Calcd. for $C_{20}H_{15}NO_3$: C, 75.71; H, 4.73; N, 4.42. Found: C, 75.38; H, 4.72; N, 4.33.

Ethyl 1,2-Dihydro-6-(2,2-diphenylethenyl)-2-oxo-3-pyridinecarboxylate (14). To 13.6 g (35.8 mmol) of the *tert*-butyl ester **13b** in 2.0 L of absolute EtOH was added 2.0 mL of concentrated H_2SO_4, and the mixture was refluxed for 48 h. The mixture was concentrated, and the residue was neutralized with H_2O and dilute $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried and concentrated, and the residue was column purified ($HCCl_3$/hexane/EtOH, 7:2:1) to give 10.5 g (85%) of **14** as a white solid: mp 169–171 °C; IR (KBr) 1735, 1700, 1650 cm^{-1}; NMR (Me_2SO-d_6) δ 11.9 (s, 1 H, NH), 7.65 (d, J = 8 Hz, 1 H, C_4 H), 7.3 (m, 10 H), 6.8 (s, 1 H, vinyl), 5.4 (d, J = 8 Hz, 1 H, C_5 H), 4.1 (q, J = 7 Hz, 2 H, CH_2), 1.2 (t, J = 7 Hz, 3 H, CH_3). Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.52; H, 5.51; N, 4.06. Found: C, 76.12; H, 5.31; N, 4.00.

The identical material, **14**, was obtained in similar fashion from the acid **13a**.

Ethyl 1,4-Dihydro-4-oxo-6-(2-phenylethenyl)-3-pyridinecarboxylate (20). The vinyl 4-pyridone acid **19**[8] (14.01 g, 58.1 mmol) was esterified with EtOH and H_2SO_4 to give 9.42 g (60%) of **20** after column purification ($CHCl_3$/hexane, 3:1): mp 166–167 °C; IR (KBr) 1715, 1650, 1620 cm^{-1}; NMR (Me_2SO-d_6) δ 10.3 (s, 1 H, NH), 8.4 (s, 1 H, pyridone), 7.4 (m, 6 H, Ar and vinyl), 7.1 (d, J = 18 Hz, 1 H, vinyl), 6.7 (s, 1 H, pyridone), 4.2 (q, J = 7 Hz, 2 H, CH_2), 1.2 (t, J = 7 Hz, 3 H, CH_3). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.30; H, 5.58; N, 5.20. Found: C, 71.00; H, 5.64; N, 5.04.

Ozonolysis, a General Procedure. Preparation of 5-Ethyl 1,6-Dihydro-6-oxo-2,5-pyridinedicarboxylate (7a). To 7.8 g (22.7 mmol) of ethyl ester **14** in 500 mL of CH_2Cl_2 was added a stream of O_3 for ~45 min until the mixture turned blue. After 10 min, the O_2 stream was removed, and dry N_2 added for 10 min until the blue color had dissipated. The mixture was taken to 0 °C and placed under vacuum for 30 min to ensure complete O_3 removal. At this temperature, 3.5 mL of 30% H_2O_2, 3.5 mL of AcOH, and 3.0 mL of H_2O were added. After 24 h, the mixture was extracted with 0.5 N NaOH. Subsequent acidification and filtration yielded 3.27 g (68%) of **7a** as a white solid: mp 236–238 °C; IR (KBr) 3440, 2500, 1900, 1740, 1690, 1635 cm^{-1}; NMR (Me_2SO-d_6) δ 8.0 (d, J = 8 Hz, 1 H, C_4 H), 6.9 (d, J = 8 Hz, 1 H, C_5 H), 4.2 (q, J = 7 Hz, 2 H, CH_2), 1.3 (t, J = 7 Hz, 3 H, CH_3). Anal. Calcd for $C_9H_9NO_5$: C, 51.18; H, 4.27; N, 6.64. Found: C, 51.19; H, 4.11; N, 6.35.

5-*tert*-Butyl 1,6-Dihydro-6-oxo-2,5-pyridinedicarboxylate (7b). Compound **13b** (10.0 g, 26.0 mmol) was converted to 2.40 g (37%) of **7b** by the general procedure: white solid; mp >275 °C dec; IR (KBr) 3430, 3100, 2500, 1800, 1730, 1700, 1635 cm^{-1}; NMR (Me_2SO-d_6) δ 14.1 (s, 1 H, OH), 12.9 (s, 1 H, NH), 7.85 (d, J = 8 Hz, 1 H, C_4 H), 6.85 (d, J = 8 Hz, 1 H, C_5 H), 1.5 (s, 9 H, t-C_4H_9). Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.44; N, 5.86. Found: C, 55.23; H, 5.00; N, 5.85.

5-Ethyl 1,4-Dihydro-4-oxo-2,5-pyridinedicarboxylate (8). Compound **20** (4.25 g, 15.8 mmol) was converted into 2.51 g (78%)

(12) Boatman, S.; Harris, T. M.; Hauser, C. R. *J. Org. Chem.* **1965**, *30*, 3593.

Table I. Physical Constants of the Substituted 6-(Aminocarbonyl)-1,2-dihydro-2-oxo- and 6-(Aminocarbonyl)-1,4-dihydro-4-oxo-3-pyridinecarboxylic Acids 2 and 3

no.	R_1 and R_2 in 2 or 3 and in HNR_1R_2	% yield[a] of 2 or 3	mp °C	IR (KBr), cm^{-1}	NMR chem shift,[b] δ (J in hertz)
2a	$R_1 = CH_2CH_3$; $R_2 = H$	83	265-266	3310, 1745, 1670, 1650	11.8 (s, 1 H), 8.9 (t, J = 6, 1 H), 8.3 (d, J = 8, 1 H), 7.15 (d, J = 8, 1 H), 3.3 (m, 2 H), 1.15 (t, J = 7, 3 H)
2b	R_1 =  $R_2 = H$	68	272-275	3450, 1715, 1680, 1650, 1580, 1550	8.45 (m, 3 H, NH and Ar), 8.2 (d, J = 8, 1 H), 7.55 (d, J = 8, 1 H), 7.25 (m, 2 H)
2c	$R_1 = t\text{-}C_4H_9$; $R_2 = H$	70	255-257	3360, 1725, 1680, 1625, 1600, 1550	8.35 (d, J = 7, 1 H), 8.3 (s, 1 H), 7.15 (d, J = 7, 1 H), 1.4 (s, 9 H)
2d	$R_1 = CH_2CH_3$; $R_2 = CH_2CH_3$	84	172-174	1740, 1660, 1630	13.6 (s, 1 H), 8.3 (d, J = 7, 1 H), 6.6 (d, J = 7, 1 H), 3.3 (m, 4 H), 1.15 (m, 6 H)
2e	$R_1 = CH_2CH_2OH$; $R_2 = H$[c]	85	243-245	3420, 1710, 1670, 1630	8.9 (t, J = 5, 1 H), 8.3 (d, J = 7, 1 H), 7.2 (d, J = 7, 1 H), 3.4 (m, 4 H)
2f	$R_1, R_2 = CH_3N(CH_2CH_2)_2$	89	260-262	1640, 1590	8.05 (d, J = 7, 1 H), 7.8 (d, J = 7, 1 H), 3.8 (s, 4 H), 3.0 (s, 4 H), 2.6 (s, 3 H)
3a	$R_1 = CH_2CH_3$; $R_2 = H$	50	277-278	3520, 1735, 1675, 1635	9.1 (t, J = 5, 1 H), 8.4 (s, 1 H), 7.4 (s, 1 H), 3.35 (m, 2 H), 1.15 (t, J = 7, 3 H)
3b	$R_1 = H$; $R_2 = H$	94	>300	3390, 3170, 1720, 1700, 1645, 1610	10.0 (s, 2 H), 8.7 (s, 1 H), 8.5 (s, 1 H), 8.35 (s, 1 H)
3c	$R_1, R_2 = O(CH_2CH_2)_2$	80	215-222	1730, 1645	8.5 (s, 1 H), 7.75 (s, 1 H), 3.55 (br s, 8 H)

[a] All yields are for isolated materials and represent the combined coupling and hydrolysis steps of 7 to 2 or 8 to 3. All acids reported had satisfactory C, H, and N analyses, as did the esters from which they were derived. [b] NMR solvent was Me_2SO. [c] $NH_2CH_2CH_2OCOCH_3$ was the amine employed. Hydrolysis removed the acetyl group. Use of ethanolamine gave a mixture of products.

of 8 by the general procedure: white solid; mp 225–227 °C; IR (KBr) 3440, 3080, 2460, 1745, 1645 cm^{-1}; NMR (Me_2SO-d_6) δ 12.1 (s, 1 H, NH), 8.2 (s, 1 H, pyridone), 6.8 (s, 1 H, pyridone), 4.15 (q, J = 7 Hz, 2 H, CH_2), 1.2 (t, J = 7 Hz, 3 H, CH_3). Anal. Calcd for $C_9H_9NO_5$: C, 51.18; H, 4.27; N, 6.64. Found: C, 50.92; H, 4.24; N, 6.49.

A General Coupling Procedure for the Preparation of the Amides 2 and 3. 6-[(Ethylamino)carbonyl]-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (2a). To 3.00 g (14.2 mmol) of the ethyl ester **7a** in 90 mL of CH_2Cl_2 was added 3.97 mL (2.0 equiv) of Et_3N. After the mixture was rapidly stirred for 20 min, 3.55 mL (2.0 equiv) of Me_3SiCl was added, and the mixture stirred for an additional 1.5 h. To this solution was added 2.07 mL of $SOCl_2$, keeping the mixture at ~20 °C. Acid chloride formation was complete after 1.5 h, and the mixture was quenched at 0 °C with excess $EtNH_2$. The mixture was extracted with H_2O and dilute acid and then dried and concentrated. The residue was column purified ($CHCl_3$/hexane, 8:2) to give 2.71 g (80%) of the ethyl amide **15** ($R_1 = CH_3CH_2$; $R_2 = H$): mp 104–106 °C; IR (KBr) 3360, 1740, 1680, 1640 cm^{-1}; NMR ($CDCl_3$) δ 11.6 (s, 1 H, NH), 8.35 (d, J = 8 Hz, 1 H, C_4 H), 7.85 (m, 2 H, C_5 H and NH), 4.45 (q, J = 7 Hz, 2 H, OCH_2), 3.5 (m, 2 H, $NHCH_2$), 1.4 (m, 6 H, 2 CH_3). This material was dissolved in 20 mL of EtOH, and 2 equiv of 2 N NaOH was added. After 24 h, the product was diluted with 0.1 N NaOH and then extracted with CH_2Cl_2, and the H_2O layer was acidified. The solids were collected and gave 2.19 g (92%) of **2a**. Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.34; H, 4.76; N, 13.33. Found: C, 51.10; H, 4.72; N, 13.07.

All the amides **2** and **3** reported in Table I were prepared in identical fashion. The pyridone NH of these amides usually displayed a weak band at 3280–3400 cm^{-1}. When the 6-carboxamides were monosubstituted ($R_2 = H$), a strong NH band in this area was observed. In the proton NMR, the pyridone proton was very broad and usually appeared from δ 12.0 to 9.55.

1,6-Dihydro-6-oxo-2,5-pyridinedicarboxylic Acid (4). To 660 mg (3.0 mmol) of the nitrile **6a**[6] were added 15 mL of H_2O and 1.2 g (30 mmol) of NaOH. The mixture was refluxed for 48 h, acidified, and extracted with CH_2Cl_2. The CH_2Cl_2 was dried and concentrated. The residue was triturated with H_2O and filtered to give 400 mg (72%) of **4**: mp 304–305 °C (lit.[3] mp 303–305 °C); IR (KBr) 2650, 2520, 1730, 1630 cm^{-1}; NMR (Me_2SO-d_6) δ 13.1 (s, 2 H, OH), 8.40 (d, J = 8 Hz, 1 H, C_4 H), 7.1 (d, J = 8 Hz, 1 H, C_5 H).

2-Ethyl 1,6-Dihydro-6-oxo-2,5-pyridinedicarboxylate (21). The diacid **4** (500 mg, 2.75 mmol) was esterfied with refluxing 3% concentrated H_2SO_4 in EtOH for 5 h. The product was diluted with H_2O, extracted into CH_2Cl_2, and purified by column chromatography ($CHCl_3$/hexane, 9:1) to give 408 mg (70%) of **21**: mp 206–207 °C (lit.[3] mp 204–206 °C); IR (KBr) 3460, 3060, 1740, 1645, 1610 cm^{-1}; NMR (Me_2SO-d_6) δ 8.35 (d, J = 8 Hz, 1 H, C_4 H), 7.2 (d, J = 8 Hz, 1 H, C_5 H), 4.30 (q, J = 7 Hz, 2 H, CH_2), 1.3 (t, J = 7 Hz, 3 H, CH_3). This material was identical in all respects with that prepared from **7b**.

Diethyl 1,6-Dihydro-6-oxo-2,5-pyridinedicarboxylate (22). When the above esterification was run for 5 days, the diethyl ester **22** was obtained as a white solid: mp 198–200 °C; IR (KBr) 1760, 1730, 1700, 1650, 1620; NMR ($DCCl_3$) δ 10.6 (s, 1 H, NH), 8.15 (d, J = 8 Hz, 1 H, C_4 H), 7.15 (d, J = 8 Hz, 1 H, C_5 H), 4.35 (m, 4 H, 2 CH_2), 1.4 (m, 6 H, 2 CH_3). Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.44; N, 5.86. Found: C, 55.60; H, 5.33; N, 6.15.

Authentic Synthesis of 2-Ethyl 1,6-Dihydro-6-oxo-2,5-pyridinedicarboxylate (21) from 7b. To 300 mg of (1.2 mmol) of the *tert*-butyl ester **7b** in 8 mL of CH_2Cl_2 was added 0.35 mL (2 equiv) of Et_3N. After 15 min, 0.31 mL (2 equiv) of Me_3SiCl was added, and the mixture was stirred for 1.5 h. To this solution was added 0.18 mL of $SOCl_2$. After stirring for another 1.5 h, the mixture was added to 50 mL of EtOH. TLC showed only one product. The mixture was concentrated, diluted with CH_2Cl_2, and extracted once with dilute $NaHCO_3$. The organic layer (~30 mL) was dried and treated with 5 mL of TFA for 2 h. After concentration, the oily mixture was added to Et_2O/hexane (3:1), and the solids were filtered to give 61 mg of **21**, whose properties were identical with those described above.

Registry No. 2a, 87762-34-3; **2b**, 87869-32-7; **2c**, 87762-41-2; **2d**, 87762-42-3; **2e**, 87762-43-4; **2f**, 87762-44-5; **3a**, 87762-45-6; **3b**, 87762-46-7; **3c**, 87762-47-8; **4**, 19841-78-2; **6a**, 81450-70-6; **7a**, 87762-31-0; **7b**, 87762-32-1; **8**, 87762-33-2; **9b**, 81450-67-1; **13a**,

87762-26-3; **13b**, 87762-27-4; **14**, 87781-73-5; **15a**, 87762-35-4; **15b**, 87762-36-5; **15c**, 87762-37-6; **15d**, 87762-38-7; **15e**, 87762-39-8; **15f**, 87762-40-1; **19**, 87762-30-9; **20**, 87762-29-6; **21**, 87762-51-4; **22**, 87762-52-5; **24**, 87762-28-5; ethyl 6-[(ethylamino)carbonyl]-1,4-dihydro-4-oxo-3-pyridinecarboxylate, 87762-48-9; ethyl 6-(aminocarbonyl)-1,4-dihydro-4-oxo-3-pyridinecarboxylate, 87762-49-0; ethyl 6-(morpholinocarbonyl)-1,4-dihydro-4-oxo-3-pyridinecarboxylate, 87762-50-3; benzophenone, 119-61-9.

Isoquinoline-*N*-Boranes as Precursors to Substituted Tetrahydroisoquinolines[1]

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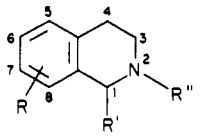
A new approach to the syntheses of 1,2-disubstituted 1,2,3,4-tetrahydroisoquinolines from isoquinoline-*N*-boranes is described. The method is a "one-pot" operation in which substituents are introduced consecutively as electrophiles and nucleophiles with accompanying reduction of the heterocyclic ring. This procedure differs from the classical ones in that both requisite rings are present in the starting material and thus avoids the inefficient cyclizations of phenethylamine derivatives when unactivated substrates would be required. The synthetic utility of this process is demonstrated with several examples including the alkaloids carnegine and hydrohydrastinine.

Since the early 1900s, construction of the 1,2,3,4-tetrahydroisoquinoline ring system **1** has been a popular area

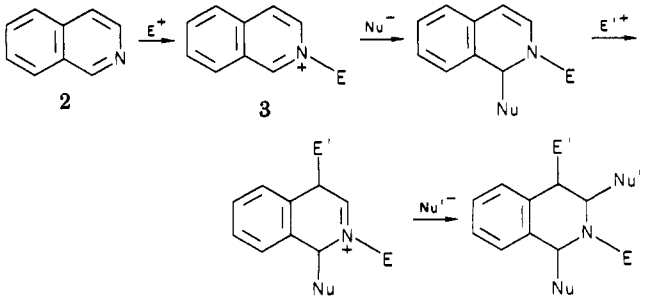


1

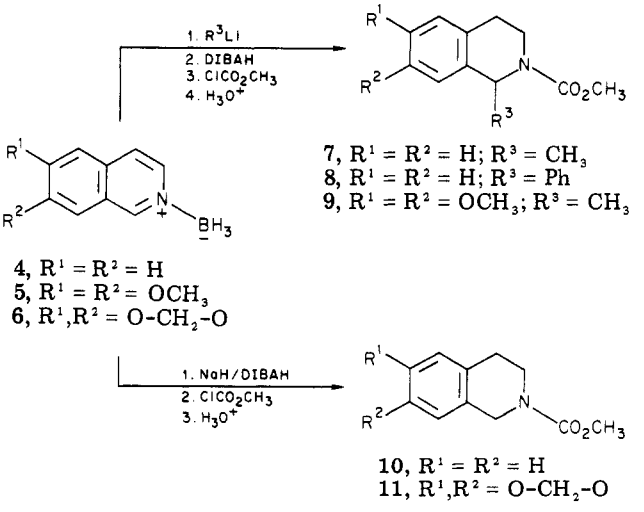
of research in natural products chemistry. Preparative routes to **1** are diverse and include such familiar methods as Pictet-Spengler,[2] Bischler-Napieralski,[3] and other cyclization reactions[4,5] as well as various hydride reductions[6-8] of isoquinolines and isoquinolinium salts. None of these is without limitation, but the most serious is the failure of certain β-phenethylamine derivatives to cyclize efficiently in the absence of electron-donating aromatic substituents para to the site of ring closure. In order to circumvent this problem, we have formulated an alternative approach to the synthesis of **1** based partly on an investigation by Francis et al.[9] and supported by some recent work these laboratories.[10]

Scheme I depicts a general synthetic strategy which would allow a variety of substituted 1,2,3,4-tetrahydroisoquinolines to be synthesized from isoquinoline. The investigation described below demonstrates the validity of this approach to 1,2-disubstituted examples including the alkaloids carnegine and hydrohydrastinine.

Scheme I



Scheme II



7, $R^1 = R^2 = H$; $R^3 = CH_3$
8, $R^1 = R^2 = H$; $R^3 = Ph$
9, $R^1 = R^2 = OCH_3$; $R^3 = CH_3$

4, $R^1 = R^2 = H$
5, $R^1 = R^2 = OCH_3$
6, $R^1, R^2 = O\text{-}CH_2\text{-}O$

10, $R^1 = R^2 = H$
11, $R^1, R^2 = O\text{-}CH_2\text{-}O$

Results and Discussion

The general reaction pathway previously outlined in Scheme I has now been used to synthesize tetrahydroisoquinolines **7**-**11** in 60-70% yields from the corresponding isoquinolines (Scheme II). Amine-boranes **4**-**6**, which correlate with **3** in Scheme I, are air-stable crystalline solids and can be isolated if desired. In practice, **4** was generated quantitatively by addition of 1.0 equiv of BH_3·THF to a tetrahydrofuran solution of freshly distilled **2** at -78 °C

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