Synthesis of a Novel Heterocyclic System: 2-Oxo-1,3-Dioxolo[4,5-*c*]pyridine-6-carboxylic Acid, Phenylmethyl Ester

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The synthesis of heterobicyclic carbonate **4** and its conversions to the mixed carbonate **5** and carbamate **6** are described.

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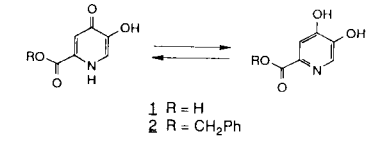
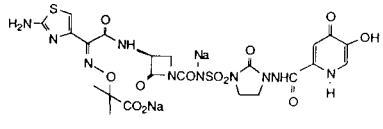
Comenamic acid **1** and related dihydroxypyridines have been employed for the preparation of physiologically active compounds [1-5]. In the synthesis of monobactams, combination of the pyridone moiety with the sulfonylaminocarbonyl activating group produced the highly potent antibiotic pirazmonam SQ 83,360 (**3**) [1,2]. The presence of two additional active hydrogen atoms in acid **1** makes the amidation reaction *via* an activated unprotected acid quite problematic. During a search for appropriate protecting groups for pyridone **2** [2] we prepared derivatives of the new heterocyclic system 2-oxo-1,3-dioxolo[4,5-*c*]pyridine-6-carboxylic acid. Synthesis of this bicyclic carbonate is reported in this paper.



1 R = H
2 R = CH_2Ph



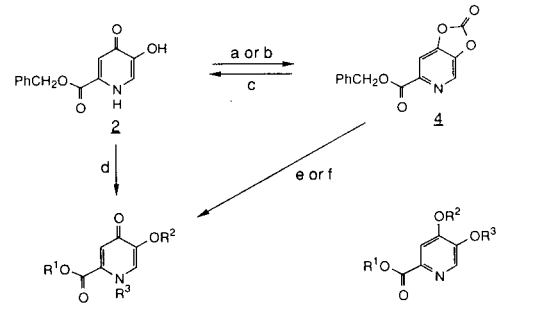
3 SQ 83,360

Figure 1

Cyclic carbonates of catechols are well known and a few methods for their preparation are available [6-13]. To our knowledge, the corresponding carbonates derived from pyridine heterocycles are not described in the literature. Prototropic tautomerism of hydroxypridines has been studied extensively [14-16]. Unlike catechol, 5-hydroxy 4-pyridones possess an additional reaction site due to the ambident nucleophilic nature of the nitrogen atom and the oxygen atom at C-4. Acylation reactions of 4-pyridones form both *N*- and *O*-acylated products [17-19].

The synthesis and chemical reactions of cyclic carbonate **4** are given in Figure 2. The reaction of 5-hydroxy-4-pyridone **2** with trichloroacetylchloroformate (diphosgene) in the presence of diazabicycloundecene in dichloromethane formed 2-oxo-1,3-dioxolo[4,5-*c*]pyridine-6-carboxylic acid, phenylmethyl ester **4** in 75% yield (58% recrystallized). In an alternate preparation, the extremely toxic diphosgene was replaced by carbonyldiimidazole. Acylation of **2** with carbonyldiimidazole in the presence of diazabicycloundecene in dichloromethane produced compound **4** in 94% yield (70% recrystallized) [20]. The cyclic carbonate **4** is a crystalline solid, mp 149-150° dec. The carbonyl absorption in the ir (chloroform) spectrum at 1871 cm^{-1} is consistent with the assigned structure and indicated its high reactivity.

Autocatalysis by the pyridine moiety as well as protonation of the ring nitrogen atom should enhance the reactivity of the carbonate function in **4** towards nucleophiles. Exposure of carbonate **4** to water regenerated pyridone **2**. The reaction of **4** to water regenerated pyridone **2**. The reaction of **4** with methanol furnished the mixed carbonate **5** in 70% yield. Substance **5** produced in this manner was identical to the product obtained by the reaction of 5-hydroxy-4-pyridone **2** with methyl chloroformate. Cyclic carbonate **4** was stable to hot *t*-butyl alcohol. Reaction of **4** with piperidine gave urethane **6** in 79% yield [21].



5 $R^1 = CH_2Ph$, $R^2 = CO_2CH_3$, $R^3 = H$
6 $R^1 = CH_2Ph$, R^2 = CON⟨⟩, $R^3 = H$
7 $R^1 = CH_2Ph$, $R^2 = CO_2CH_3$, $R^3 = H$
8 $R^1 = CH_2Ph$, R^2 = CON⟨⟩, $R^3 = H$

a. Trichloroacetylchloroformate (diphosgene), diazabicycloundecene (DBU), dichloromethane (DCM), -78°.
b. Carbonyldiimidazole, DBU, DCM, -78°.
c. Water, room temperature.
d. Methylchloroformate, DBU, DCM, -78°.
e. Methanol, DCM, 0°.
f. Piperidine, DCM, 0°.

Figure 2

The assignments of structures **5** and **6** are tentative. A comparison of the chemical shifts of the C-4 carbon atom of cyclic carbonate **4** with those of compounds **5** and **6** lends support to these assignments. The chemical shift

data for the most deshielded (next to oxygen) carbons in compounds **4** to **6** is summarized in Table 1. In cyclic carbonate **4** the C-4 and C-5 carbons are part of the aromatic pyridine ring. The chemical shift of C-4 (150.4 ppm) is close (144.6 ppm) to that of the similarly substituted C-5 carbon. In products **5** and **6** the C-4 carbonyl and the ester carbonyl resonances appeared very close to each other at 162.3/163.4 and 161.9/162.6, ppm, respectively. Therefore the pyridone (doubly vinylogous amide) structures **5** and **6** are more likely than the corresponding isomeric forms **7** and **8**.

Table 1

CMR Spectra (ppm)

Compound	C-4	C-5	C-6	C-7
4 [a]	150.4	144.6	163.2	149.6
5 [b]	162.3 [c]	141.5	163.4 [c]	152.5
6 [b]	161.9 [c]	141.2	162.6 [c]	151.6

[a] In deuteriochloroform. [b] In deuteriodimethyl sulphoxide in the presence of a few drops of trifluoroacetic acid. [c] Chemical shift values may be interchanged.

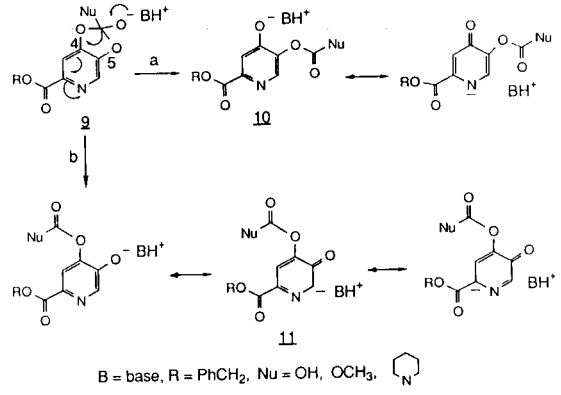


Figure 3

The predominant formation of compounds **5** and **6** is probably due to the better stabilisation of the incipient negative charge on the oxygen atom at C-4 developed during collapse of the tetrahedral intermediate **9** (Figure 3, path a) compared to stabilization of the transition state leading to **11**. The C-4 oxyanion acts as a better leaving group than the C-5 oxyanion.

In summary we have described two methods for the synthesis of 2-oxo-1,3-dioxolo[4,5-*c*]pyridine-6-carboxylic acid, phenylmethyl ester (**4**) which should be generally applicable to this ring system.

EXPERIMENTAL

The ir spectra were measured on a Mattson Sirius 100 FT spectrometer. The nmr spectra were recorded on a Jeol FX-270 spectrometer. The ms spectra were obtained using a Finnigan TSQ-4600 spectrometer.

2-Oxo-1,3-dioxolo[4,5-*c*]pyridine-6-carboxlylic Acid, Phenylmethyl Ester (**4**).

Compound **4** was prepared by two methods.

Method-A.

A solution of pyridone **2** (0.5 g, 2.0 mmoles) and diazabicycloundecene (0.33 ml, 2.1 mmoles) in 5 ml dichloromethane was cooled to −78°. A solution of diphosgene (0.46 *M* in dichloromethane, 4.75 ml, 2.2 mmoles) was added dropwise over 5 minutes. A precipitate formed. After 0.5 hours, additional diazabicycloundecene (0.33 ml, 2.1 mmoles) was introduced and the solution was stirred for 0.5 hours at −78° and then allowed to warm to 0°. The mixture was poured into 60 ml *p*H 3 buffer (0.2 molar aqueous sodium dihydrogenphosphate acidified with phosphoric acid). The mixture was filtered and the organic layer was washed with water, dried (sodium sulfate) and evaporated under vacuum to yield 0.41 g (76%) of crude solid **4**. The material (0.105 g) was recrystallized from ethyl acetate-hexane to give 0.081 g (58%) of crystalline **4**, mp 147-149° dec; ir (chloroform): ν C=O, 1871, 1717 cm^{-1}; pmr (deuteriochloroform): δ 5.48 (s, 2, CH_2), 7.3-7.5 (m, 5, Ph), 8.1 (s, 1, H-3), 8.7 ppm (s, 1, H-5); cmr (deuteriochloroform): δ, 67.0, 108.0, 128.2, 128.4, 130.8, 135.6, 144.0, 144.6, 149.6, 150.4, 163.2 ppm; ms: (CI) M + H 272.

Anal. Calcd. for $C_{14}H_9NO_5$: C, 61.99; H, 3.34; N, 5.17. Found: C, 61.91; H, 3.35; N, 5.19.

Method-B.

Carbonyldiimidazole (0.4 g, 2.24 mmoles) was added to a solution of pyridone **2** (0.5 g, 2.0 mmoles) and diazabicycloundecene (0.64 ml, 4.29 mmoles) in 4 ml of dicholoromethane chilled to −78°. After 0.5 hour the mixture was poured into 60 ml of dichloromethane and 60 ml of *p*H 3 buffer (0.3 molar sodium dihydrogenphosphate solution acidified with phosphoric acid) cooled in an ice bath. The organic phase was washed with 60 ml of cold *p*H 3 buffer, 60 ml of cold water and then dried over magnesium sulfate. The solution was filtered and the filtrate was evaporated under vacuum to give 0.51 g (94%) of crude **5**. The product was recrystallized from dichloromethane-hexane to furnish 0.21 g (39%) of crystalline **4**, mp 149-150° dec, (second crop of **4** was isolated from mother liquor, 0.173 g, (31%), mp 140-145°); ir and pmr were identical to the spectra of compound prepared by Method-A.

Anal. Calcd. for $C_{14}H_9NO_5$: C, 61.99; H, 3.34; N, 5.17. Found: C, 61.89; H, 2.91; N, 5.02.

5-[(Methoxycarbonyl)oxy]-1,4 dihydro-4-oxo-2-pyridonecarboxylic Acid, Phenylmethyl Ester (**5**).

The mixed carbonate **5** was prepared by two methods.

Method-A.

A solution of pyridone **2** (0.5 g, 2.0 mmoles) and diazabicyloundecene (0.37 ml, 2.7 mmoles) in 5 ml of dichloromethane was cooled to −78°. A solution of methylchloroformate (0.17 ml, 2.2 mmoles) in 5 ml dichloromethane was added dropwise over 5 minutes. After 0.5 hour, additional diazabicycloundecene (0.33 ml, 2.2 mmoles) was added and then the reaction mixture was poured into 50 ml of *p*H 3 buffer (0.2 molar sodium dihydrogenphosphate acidified with phosphoric acid). The mixture was filtered and the organic layer was washed with *p*H 3.0 buffer and water. The solution was dried (magnesium sulfate) and the sol-

vent was evaporated under vacuum to give 0.41 g (68%) of mixed carbonate **5**. The product was recrystallized from acetonitrile: mp 168-169° dec; ir (potassium bromide): ν, C=O, 1780, 1723 cm^{-1}; pmr (dimethyl sulfoxide-d_6 + trifluoroacetic acid): δ 3.8 (s, 3, OCH_3), 5.39 (s, 2, CH_2), 7.4-7.5 (m, 6, Ph + CH), 8.3 ppm (s, 1, CH); cmr (dimethyl sulfoxide-d_6 + trifluoroacetic acid): δ 55.8, 67.3, 116.6, 128.3, 128.5, 135.5, 138.0, 140.5, 141.5, 152.5, 162.3, 163.4 ppm; ms: (CI) M + H = 304; [21].

Anal. Calcd. for $C_{15}H_{13}NO_6$: C, 59.40; H, 4.32; N, 4.62. Found: C, 59.55; H, 4.26; N, 4.83.

Method-B.

A solution of bicyclic carbonate **4** (0.25 g, 1.02 mmoles) in 2 ml of dichloromethane was cooled in an ice bath. Absolute methanol (0.5 ml) was added and the mixture was warmed to ambient temperature. The solvent was removed under vacuum and the residue was triturated with ether. The material was filtered, washed with ether and dried under vacuum to give 0.216 g (~70%) of the mixed carbonate **5**, mp 158-162° dec; the pmr, cmr and ir spectra of this compound were identical to the spectra of compound prepared by method-A.

5-[(Piperidylcarbonyl)oxy]-1,4-dihydro-4-oxo-2-pyridonecarboxylic Acid, Phenylmethyl Ester (**6**).

Piperidine (0.25 ml, 2.5 mmoles) was added to a solution of cyclic carbonate **4** (0.25 g, 0.92 mmoles) in 2 ml dichloromethane at ice bath temperature. After 0.5 hour the mixture was diluted with 6 ml dichloromethane and washed with *p*H 3 buffer (0.2 molar sodium dihydrogenphosphate acidified with phosphoric acid) and water. The organic phase was dried (magnesium sulfate) and evaporated under vacuum to furnish 0.28 g crude **6**. The material was triturated with ether, filtered and dried under vacuum to afford 0.25 g (74%) of urethane **6**, mp 202-204° dec; ir (potassium bromide): ν, C=O, 1725, 1630 cm^{-1}; pmr (dimethyl sulfoxide-d_6 + trifluoroacetic acid): δ 1.6 (br s, 6, 3, CH_2), 3.4 (br s, 2, NCH_2), 3.6 (br s, 2, NCH_2), 5.4 (s, 2, OCH_2), 7.3-7.6 (m, 6, Ph and CH), 8.3 ppm (s, 1, CH); cmr (dimethyl sulfoxide-d_6 + trifluoroacetic acid): δ 23.6, 25.1, 44.9, 45.3, 67.4, 115.4, 128.3, 128.4, 128.5, 135.4, 139.7, 140.5, 141.2, 151.6, 161.9, 162.6 ppm; ms: (CI) M + H = 357, M − H = 355; [21].

Anal. Calcd. for $C_{19}H_{20}N_2O_5$: C, 64.03; H, 5.66; N, 7.86. Found: C, 63.96; H, 5.53; N, 7.73.

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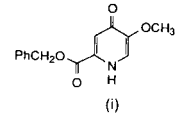
[20] Alkylation of pyridone **2** with methyl iodide (diazabicycloundecene, dichloromethane) formed 5-methoxy pyridone (i) in ~50% yield. The structural assignment was based on cmr; the C-4 carbonyl was observed at 162 ppm.



(i)

[21] The product contained a minor impurity which is assumed to be the corresponding (less stable) C-4-isomer.