Functionalization of Substituted 2(1*H*)- and 4(1*H*)-Pyridones. III. The Preparation of Substituted 6-Vinyl-1,2-dihydro-2-oxo- and 1,4-Dihydro-4-oxo-3-pyridinecarboxylic Acids Through the Chemistry of Pyridone Dianions

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The synthesis of various substituted 6-vinyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic acids from the dianions of 1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile and the corresponding 3-*t*-butyl ester is reported. The dianions were generated with LDA in THF at low temperature and reacted with various carbonyl substrates. Several conditions for the dehydration and hydrolysis of these adducts to the vinyl pyridone acids are discussed. Employing the conditions used for the 2-pyridone analogs, a series of substituted 6-vinyl-1,4-dihydro-4-oxo-3-pyridinecarboxylic acids was prepared through the new dianion of 1,4-dihydro-6-methyl-4-oxo-3-pyridinecarboxylic acid, *t*-butyl ester.

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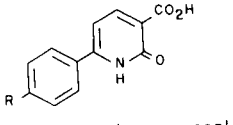
As part of our search for new side chains for various penicillin and cephalosporin nuclei, we discovered that the substituted 1,2-dihydro-2-oxo-6-phenyl-3-pyridinecarboxylic acids (**1**) conferred excellent broad spectrum activity, especially against Pseudomonas species, to the β-lactams to which they were appended [1]. With this chemical lead in hand, we decided to explore the synthesis of the vinyl analogs **2**, where a substituted vinyl group replaces the phenyl moiety as the 6-substituent on the pyridone ring, with the hope of improving the antibacterial activity and pharmacokinetics bestowed by the pyridone class of side chains. We also desired to develop a synthesis the 6-vinyl-4-pyridone analogs **3** [2].

Most of the vinyl pyridones that have been previously reported were prepared by total synthesis (eq 1) through the condensation of cyanoacetamide with the appropriately substituted formyl vinyl ketones [3]. This method is limited to the availability of the substituted vinyl ketone. For our purposes a more general method was desired utilizing a common precursor if possible. The first such method for the synthesis of vinyl pyridones was provided by Hauser [4] who prepared the dianion **5** from the cyano pyridone **4** by use of potassium amide in liquid ammonia and reported its condensation with a few alkyl halides and carbonyl derivatives, the latter giving the vinyl cyano pyridones **2a** upon dehydration of the corresponding aldol type adducts.



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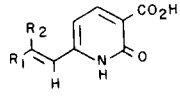

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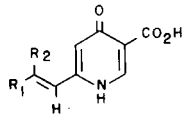

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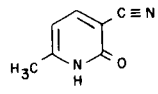


4

We have already utilized Hauser's conditions to functionalize the C_6-methyl group of the cyano pyridone **4** and have found that in certain cases the reaction was sluggish and gave incomplete conversion [5]. Furthermore, the handling of potassium and liquid ammonia proved burdensome for the preparation of a wide variety of compounds. Another difficulty encountered involved the elimination of water from the aldol products to give vinyl pyridones. Our preliminary investigations showed that the method reported by Hauser [4b] for a few derivatives was not at all general. Finally, Hauser [4b] clearly demonstrated that in liquid ammonia the potassium derived dianion **5** gave exclusive 1,4-addition to conjugated enones forming products of type **6**. To obtain vinyl pyridones of type **2** we would require a predominance of 1,2-addition to the conjugated enones.

One other approach to the synthesis of vinyl pyridones **2** was provided by Beak [6] who utilized the lithium dianion of the masked pyridone **7**. Low overall yields and the protection-deprotection steps made this approach less attractive.

For the synthesis of the 6-vinyl-4-pyridone analogs **3**, only a tedious multistep route has been reported which yielded the 1-alkyl derivatives [7].

In this paper, we describe a very workable synthesis of a broad series of 1,2-dihydro-2-oxo-6-vinyl-3-pyridinecarboxylic acids through some new applications of the dianion chemistry of the 1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile **4** and the corresponding *t*-butyl ester **10**. We also report the extension of this methodology to the synthesis of the isomeric vinyl 4-pyridones **3** through the pre-

Table 1

The Synthesis of Substituted 6-Vinyl-1,2-dihydro-2-oxo- and 1,4-Dihydro-4-oxo-3-pyridinecarboxylic Acids **2** and **3** *via* the Dianions **5**, **11** and **15**

			Aldol type Adducts **8**, **12**, or **16**,			Vinyl Pyridones **2**, or **3**,	
Entry	Starting Pyridone	Starting Carbonyl Substrate	R_1 = R_2 =	(Yield %) [a]	Dehydration Conditions [b]	R_1 = R_2 =	(Yield %) [a]
1	**4**	benzaldehyde	**8**, phenyl, H-	(85)	48% HBr:AcOH	**2**, phenyl, H-	(70)
2	**4**	acetaldehyde	**8**, methyl, H-	(60) [c]	48% HBr:AcOH	**2**, methyl H-	(<25) [d]
3	**4**	4-pyridinecarboxaldehyde	**8**, 4-pyridyl, H-	(92) [e]	48% HBr:AcOH	**2**, 4-pyridyl, H-	(58)
4	**4**	3-pyridinecarboxaldehyde	**8**, 3-pyridyl, H-	(79)	48% Hbr:AcOH	**2**, 3-pyridyl, H-	(97)
5	**4**	2-pyridinecarboxaldehyde	**8**, 2-pyridyl, H-	(81)	48% HBr:AcOH	**2**, 2-pyridyl, H-	(60)
6	**4**	cinnamaldehye	**8**, 2-phenylethenyl, H-	(67)	48% HBr: AcOH	**2**, 2-phenylethenyl, H-	(93)
7	**4**	2-thiophenecarboxaldehyde	**8**, 2-thienyl, H-	(70)	48% HBr:AcOH [f]	**2**, 2-thienyl, H-	(76)
8	**4**	6-methylpyridine-2-carboxaldehyde	**8**, 6-methyl-2-pyridyl, H-	(64)	48% HBr:AcOH	**2**, 6-methyl-2-pyridyl, H-	(46)
9	**4**	3-chloro-3-(4'-methoxyphenylpropenal	**8**, 2-chloro-2-(4'-methoxyphenyl)ethenyl, H-	(77)	48% HBr:AcOH [f]	**2**, 4-methoxyphenylethynyl, H-	(71)
10	**4**	4-dimethylaminobenzaldehyde	**8**, 4-dimethylaminophenyl H-	(78)	48% HBr:AcOH	**2**, 4-dimethylaminophenyl, H-	(87) [g]
11	**4**	4-methylthiobenzaldehyde	**8**, 4-methylthiophenyl H-	(64)	48% HBr:AcOH [f]	**2**, 4-methylthiophenyl, H-	(75)
12	**4**	4-methoxybenzaldehyde	**8**, 4-methoxyphenyl, H-	(71)	48% HBr:AcOH [f]	**2**, 4-methoxyphenyl, H-	(53)
13	**4**	2-methoxybenzaldehyde	**8**, 2-methoxyphenyl, H-	(81)	48% HBr:AcOH [f]	**2**, 2-methoxyphenyl, H-	(69)
14	**4**	furfuraldehyde	**8**, 2-furyl, H-	(30)	— [h]	—	
15	**4**	4-phenyl-3-buten-2-one	**8**, 2-phenylethenyl, methyl	(83)	— [h]	—	
16	**4**	cyclohexanone	**8**, pentyl	(45)	— [h]	—	
17	**4**	2-acetylpyridine	**8**, pyridyl, methyl	(69)	— [h]	—	
18	**4**	di-2-pyridyl ketone	**8**, 2-pyridyl, 2-pyridyl	(88)	— [h]	—	
19	**4**	benzophenone	**8**, phenyl, phenyl	(88)	acetic anhydride: sulfuric acid [f]	**2**, phenyl, phenyl	(89)
20	**10**	furfuraldehyde	**12**, furyl, H-	(77)	methyltriphenoxyphosphonium iodide [i]	**2**, 2-furyl, H-	(95) [i]
21	**10**	benzaldehyde	**12**, phenyl, H-	(83)	thionyl chloride: pyridine, THF	**2**, phenyl, H-	(95) [j]
22	**10**	acetaldehyde	**12**, methyl, H-	(95)	thionyl chloride: pyridine, THF	**2**, methyl, H-	(95) [j]
23	**10**	benzophenone	**12**, phenyl, phenyl	(66)	acetic anhydride: sulfuric acid	**2**, phenyl, phenyl	(93) [j]
24	**14**	benzaldehyde	**16**, phenyl, H-	(95)	acetic anhydride: sulfuric acid thionyl chloride: pyridine	**3**, phenyl, H-	(15) (70)
25	**14**	acetaldehyde	**16**, methyl, H-	(36)	thionyl chloride: pyridine	**3**, methyl, H-	(5)
26	**14**	benzophenone	**16**,	— [k]	—	—	
27	**14**	acetophenone	**16**,	— [k]	—	—	

Table 1, continued

Entry	Starting Pyridone	Starting Carbonyl Substrate	Aldol type Adducts **8**, **12**, or **16**, R_1 = R_2 =	(Yield %) [a]	Dehydration Conditions [b]	Vinyl Pyridones **2**, or **3**, R_1 = R_2 =	(Yield %) [a]
28	**14**	furfuraldehyde	**16**, 2-furyl, H-	(96)	acetic anhydride: acetic acid	**3**, 2-furyl,	(99)
					methyl triphenoxy-phosphonium iodide [i]	H-	(58)
29	**14**	2-pyridinecarboxaldehyde	**16**, 2-pyridyl, H-	(96)	acetic anhydride: acetic acid	**3**, 2-pyridyl	(90)
					acetic anhydride: sulfuric acid	H-	(58)
30	**14**	3-thiophenecarbox-aldehyde	**16**, 3-thienyl, H-	(80)	acetic anhydride: acetic acid	**3**, 3-thienyl, H-	(80)
31	**14**	3,4,5-trimethoxybenz-aldehyde	**16**, 3,4,5-trimethoxy-phenyl, H-	(88)	acetic anhydride: acetic acid	**3**, 3,4,5-trimethoxy-phenyl, H-	(90)

[a] All yields reported are for isolated materials unless otherwise indicated. [b] Dehydration reactions were performed at reflux. [c] This product was crude and dehydrated without purification. [d] This product was identified by spectral properties but resisted purification to analytical material. It was spectrally equivalent to the material obtained in Entry 22 which was analytical. [e] Analyzed as the HCl salt. [f] Dehydration was performed at room temperature to give the cyano pyridone **2a** which was hydrolyzed in a second step with sodium hydroxide. The yield is for the combined two steps. [g] A *trans-cis* mixture was obtained which could not be separated. The *trans* isomer was predominant >70%. [h] All dehydration conditions gave a mixture of products, or no reaction at all. [i] Reaction was run at 50°. The *t*-butyl ester was removed with TFA. Yield is for both steps combined. [j] Products obtained were identical to those obtained from **4**. [k] No reaction was obtained.

viously unknown dianion **15**.

Results and Discussion.

The Dianion **5**.

Our approaches to the synthesis of the vinyl pyridones **2** are shown in Scheme 1. The first method utilized the 6-methyl cyano pyridone **4** [8] which was converted to the dianion **5** with two equivalents of lithium diisopropylamide (LDA) in THF at 0°. The sparingly soluble nitrile **4** formed a reddish brown solution upon addition to the LDA. After several minutes a reddish brown precipitate formed, which was assumed to be the dilithium salt **5** of **4** as evidenced by the 98% deuterium incorporation at the C_6-methyl when the anion mixture was quenched with deuterium oxide. Other bases used to generate the dianion **5** included *n*-butyl and *t*-butyl lithium in ether or THF. As might be expected, in addition to some formation of the dianion **5**, these latter reagents attacked the 3-cyano group even at −78°. Neither of the amine bases, lithium dicyclohexyl amide or lithium hexamethyldisilazide, proved better than LDA. Alkoxide bases were not sufficiently strong to effect formation of the dianion under any conditions although removal of the NH proton by these reagents was complete. The dianion **5** was then treated with various aldehydes and ketones at ~0° to give aldol type adducts **8** in very good yields. While the purity of the carbonyl substrate was vital, the rate of addition and the temperature range of the reaction (−15 to +15°) were not important variables. Reactions were typically complete in 1-5 hours, but for convenience were usually stirred overnight (Table I). The condensations with aldehydes were faster and gave better yields than with the ketones. Even aldehydes and ketones with enolizable hydrogens (entries 2, 15, 16 and 17) gave good yields, although condensation of the dianion **5** with acetone was never accomplished.

As we had desired, and contrary to the results of Hauser using liquid ammonia [4b], the lithium dianion **5** in THF gave exlcusive 1,2-addition to the α,β-unsaturated aldehydes and ketones (entries 6, 9, and 15).

The conversion of the adducts **8** to the vinyl pyridones **2** required both the elimination of water and the hydrolysis of the nitrile, which we hoped could be accomplished in one step. Despite the formation of a favorably cross conjugated vinyl pyridone product **2**, the elimination of water from the aldol type adducts **8** proved difficult under many of the conditions examined. Treatment of the adducts **8** with any base, hydroxide, ethoxide, or LDA, gave a retro reaction yielding the cyano pyridone **4**, and various amounts of the starting aldehyde along with its Cannizzaro products, forcing us to employ acidic elimination conditions.

When acetic anhydride and sulfuric acid were employed, Hauser's conditions [4b], elimination was often incomplete or was accompanied by some decyanation to contaminate the vinyl pyridone products, except for entries 1 and 19 which eliminated smoothly under these conditions [9]. Other methods examined were phosphoryl chloride: pyridine, sulfuric acid, and thionyl chloride; pyridine or

Table 2

IR, H-NMR, and Melting Points for the 6-Vinyl-1,2-dihydro-2-oxo- and 1,4-Dihydro-4-oxo-3-pyridinecarboxylic Acids **2** and **3** Prepared by Dehydration Procedures A-D

Compound Number [a]	Melting Point, °C (Crystallized from)	IR cm^{-1} [b]	H-NMR δ [c]
2-1 [d]	240-248 (DMA/water)	1740, 1650, 1620	8.35 (d, J = 8 Hz, 1H, C_4H), 7.85 (d, J = 17 Hz, 0.75H, *trans* vinyl), 7.4 (m, 5H, Ar), 7.1 (d, J = 17 Hz, 0.75H, *trans* vinyl), 7.0 (d, J = 8 Hz, 0.75H, C_5H), 6.9 (d, J = 6 Hz, 0.25H, *cis* vinyl), 6.45 (d, J = 6 Hz, 0.25H, *cis* vinyl), 6.25 (d, J = 9 Hz, 0.25H C_5H)
2-2 [e]	256-257 (DMA/water)	1750, 1630, 1595	8.3 (d, J = 8 Hz, 1H, C_4H), 7.0 (d, J = 18 Hz, 1H, vinyl), 6.8 (d, J = 8 Hz, 1H, C_5H), 6.4 (m, 1H, vinyl), 1.9 (d, J = 9 Hz, 3H, CH_3)
2-3 [f]	296 (DMF/*i*-PrOH/hexane)	1730, 1640, 1610	8.7 (m, 2H, Ar), 8.35 (d, J = 8 Hz, 1H, C_4H), 7.8 (d, J = 17 Hz, vinyl), 7.7 (d, 2H, Ar), 7.4 (d, J = 17 Hz, 1H, vinyl), 7.0 (d, J = 8 Hz, 1H, C_5H)
2-4	276-279 (AcOH)	1720, 1610, 1590	9.1 (s, 1H, Ar), 8.9 (d, 1H, Ar), 8.75 (d, 1H, Ar), 8.45 (d, J = 8 Hz, 1H, C_4H), 8.0 (d, J = 17 Hz, 1H, vinyl), 7.5 (d, J = 17 Hz, 1H, vinyl), 7.1 (d, J = 8 Hz, 1H, C_5H)
2-5	291-292 (DMA/water)	1750, 1640, 1590	8.6 (d, 1H, Ar), 8.35 (d, J = 8 Hz, 1H, C_4H), 7.8 (d, J = 17 Hz, 1H, vinyl), 7.8 (m, 1H, Ar), 7.5 (d, 1H, Ar), 7.5 (d, J = 17 Hz, 1H, vinyl), 7.35 (m, 1H, Ar), 7.1 (d, J = 8 Hz, 1H, C_5H)
2-6	233-236 (AcOH)	1735, 1645, 1615	8.3 (d, J = 8 Hz, 1H, pyridone), 8.25 (d, J = 8 Hz, 1H, pyridone), 6.2-7.8 (complex, 10H, Ar and vinyl)
2-7	316-317 (DMF/MeOH)	1750, 1640, 1610	8.13 (d, J = 7 Hz, 1H, C_4H), 8.05 (d, J = 16 Hz, 1H, vinyl), 7.7 (d, 1H, Ar), 7.4 (d, 1H, Ar), 7.15 (m, 1H, Ar), 7.0 (d, J = 7 Hz, 1H, C_5H), 6.85 (d, J = 16 Hz, 1H, vinyl)
2-8	295-296 (AcOH)	1740, 1640	8.35 (d, J = 8 Hz, 1H, C_4H), 7.85 (d, J = 16 Hz, 1H, vinyl), 7.7 (m, 2H, Ar), 7.3 (d, J = 16 Hz, 1H, vinyl), 7.3 (m, 1H, Ar), 7.1 (d, J = 8 Hz, 1H, C_5H)
2-9	285-287 (DMA/water)	2190, 1740, 1650, 1610, 1600	8.3 (d, J = 8 Hz, 1H, C_4H), 7.45 (d, J = 9 Hz, 2H, Ar), 7.1 (d, J = 18 Hz, 1H, vinyl), 7.0 (d, J = 8 Hz, 1H, C_5H), 6.9 (d, J = 9 Hz, 2H, Ar), 6.8 (d, J = 18 Hz, 1H, vinyl), 3.8 (s, 3H, OCH_3)
2-10 [g]	>300 (DMA/water)	1740, 1650, 1610, 1590	8.25 (d, J = 8 Hz, 1H, C_4H), 7.75 (d, J = 17 Hz, 0.75H, *trans* vinyl), 7.45 (d, J = 9 Hz, 1H, Ar), 7.35 (d, J = 9 Hz, 1H, Ar), 6.95 (d, J = 8 Hz, 0.75H, C_5H), 6.85 (d, J = 17 Hz, 0.75H, *trans* vinyl), 6.75 (d, J = 9 Hz, 2H, Ar), 6.6 (d, J = 7 Hz, 0.25H, *cis* vinyl), 6.35 (d, J = 7 Hz, 0.25H, *cis* vinyl), 6.15 (d, J = 8 Hz, 0.25H, C_5H), 3.0 (d, 6H, $(CH_3)_2N$)
2-11	>300 (DMA/water)	1730, 1620, 818	8.2 (d, J = 8 Hz, 1H, C_4H), 7.7 (d, J = 16 Hz, 1H, vinyl), 7.4 (q, 4H, Ar), 7.1 (d, J = 16 Hz, 1H, vinyl), 6.9 (d, J = 8 Hz, 1H, C_5H)
2-12	>300 (DMA/water)	1740, 1625, 1600	8.3 (d, J = 8 Hz, 1H, C_4H), 7.8 (d, J = 17 Hz, 1H, vinyl), 7.55 (d, J = 9 Hz, 2H, Ar), 7.05 (d, J = 9 Hz, 2H, Ar), 6.99 (d, J = 17 Hz, 1H, vinyl), 6.95 (d, J = 8 Hz, 1H, C_5H), 3.8 (s, 3H, OCH_3)
2-13	251-253 (DMA/water)	1720, 1620, 760	8.35 (d, J = 7 Hz, 1H, C_4H), 7.95 (d, J = 17 Hz, 1H, vinyl), 7.6 (m, 1H, Ar), 7.35 (m, 1H, Ar), 7.2 (d, J = 17 Hz, 1H, vinyl), 7.1 (m, 2H, Ar), 7.0 (d, J = 7 Hz, 1H, C_5H), 3.9 (s, 3H, OCH_3)
3-24	>300 (DMA/water)	1700, 1650, 1625	8.55 (s, 1H, C_2H), 7.5 (m, 6H), 7.2 (d, J = 18 Hz, 1H, vinyl), 7.05 (s, 1H, C_5H)
3-28	295-298 (AcOH)	1740	8.3 (s, 1H, C_2H), 7.65 (m, 1H, Ar), 7.4 (d, J = 15 Hz, 1H, vinyl), 6.6 (m, 4H)
3-29	293-295 (AcOH)	1705, 1650, 1622	9.1 (s, 1H, C_2H), 8.8-8.3 (m, 3H), 8.1-7.9 (m, 3H), 7.7 (s, 1H, C_5H) [h]
3-30	>300 (AcOH)	1710, 1640, 1620	8.55 (s, 1H, C_2H), 7.7 (m, 4H), 7.05 (d, J = 15 Hz, 1H, vinyl), 7.0 (s, 1H, C_5H) [h]
3-31	303-305 (AcOH)	1710, 1650, 1620, 1585	9.0 (s, 1H, C_2H), 7.75 (d, J = 16 Hz, 1H, vinyl), 7.1 (m, 3H, Ar and vinyl), 4.05 (2s, 9H, 3-OCH_3) [h]

[a] All physical constants were obtained on analytical material. [b] All ir spectra were obtained using potassium bromide pellets. [c] All nmr spectra were obtained using DMSO-d_6 unless otherwise indicated. [d] *Trans:cis* ratio was 3:1. In Entry 21 **2**-1 was formed in a 4:1 *trans:cis* ratio [e] The identical product was obtained from Entry 22 of Table 1 [f] Analyzed as the hydrobromide salt. [g] A *trans:cis* ratio of 3:1 was obtained. [h] TFA solvent was employed.

triethylamine, none of which gave satisfactory dehydration. A two step elimination sequence involving hydroxyl acetylation followed by treatment with potassium *t*-butoxide gave some of the desired alkene, but acetylation yields were usually below 40%. Dehydration was finally effected in good yields with concomitant hydrolysis of the nitrile by using 48% hydrogen bromide in acetic acid at reflux. Under these conditions, the *trans* olefins were predominantly obtained in all cases based on the coupling constants in the proton nmr. In those cases (entries 7, 9, 11, 12, and 13) where these reaction conditions proved too harsh, dehydration was effected cleanly with 48% hydrogen bromide in acetic acid at room temperature giving the vinyl nitriles **2a**. Subsequent hydrolysis with 10-20% sodium hydroxide in dioxane or water-glycol mixtures gave the vinyl pyridone acids **2**.

The tertiary aldol type adducts **8** (entries 15, 16, 17, and 18) could not be dehydrated with 48% hydrogen bromide in acetic acid even after reflux for 30 hours. None of the other methods mentioned above gave any vinyl pyridone either. Mild work up of these dehydration reactions sometimes produced small amounts (~5-15%) of the bromide or acetate implying that under these elimination conditions a tertiary carbonium ion was formed but did not eliminate a proton. The benzophenone adduct (entry 19) was dehydrated within minutes, however, using either acetic anhydride:sulfuric acid or hydrogen bromide in acetic acid at 100°. These results impose a rather unexpected limitation on the synthesis of highly substituted vinyl pyridones using this method.

Table 3

Analytical Results for the Substituted 6-Vinyl-1,2-dihydro-2-oxo- and 1,4-Dihydro-4-oxo-3-pyridine Carboxylic Acids **2** and **3**

Compound	Molecular Formula	Analysis % Calcd./Found C	H	N
2-1	$C_{14}H_{11}NO_3$ [a]	69.70	4.60	5.81
		70.04	4.57	5.66
2-2	$C_9H_9NO_3$ [a]	60.30	5.03	7.82
		59.94	5.41	7.60
2-3	$C_{13}H_{11}ClN_2O_3$ [b]	56.03	3.95	10.05
		55.81	4.31	10.05
2-4	$C_{13}H_{10}N_2O_3$	64.46	4.16	11.57
		64.60	4.20	11.65
2-5	$C_{13}H_{10}N_2O_3$	64.46	4.16	11.57
		64.72	4.20	11.73
2-6	$C_{16}H_{13}NO_3$	71.90	4.90	5.24
		71.81	5.30	5.54
2-7	$C_{12}H_9NO_3S$	58.30	3.64	5.67
		58.55	3.55	5.78
2-8	$C_{14}H_{12}N_2O_3$	65.51	4.72	10.93
		56.28	4.68	10.74
2-9	$C_{17}H_{13}NO_4$	69.14	4.44	4.74
		69.11	4.73	4.91
2-10	$C_{16}H_{16}N_2O_3$	67.59	5.67	9.85
		67.28	5.40	9.87
2-11	$C_{15}H_{13}NO_3S$	62.67	4.53	4..87
		62.93	4.64	4.84
2-12	$C_{12}H_{13}NO_4$	66.41	4.83	5.16
		65.99	5.04	5.33
2-13	$C_{15}H_{13}NO_4$	66.41	4.83	5.16
		66.10	4.92	5.36
2-20	$C_{12}H_9NO_4$]c]	62.34	3.89	6.06
		61.97	3.88	6.24
3-24	$C_{14}H_{11}NO_3$ [c]	69.74	4.56	5.81
		69.51	4.30	5.52
3-28	$C_{12}H_9NO_4$ [c]	62.34	3.89	6.06
		62.60	4.04	6.37
3-29	$C_{13}H_{10}N_2O_3$	64.46	4.13	11.57
		64.33	4.07	11.81
3-30	$C_{12}H_9NO_3S$ [c]	58.31	3.64	5.67
		57.96	3.35	5.60
3-31	$C_{17}H_{17}NO_6$	61.65	5.14	4.23
		61.33	5.13	4.10

[a] Was also analytical as the imidazolide derivative. [b] Was analyzed as the hydrochloride salt. [c] Was also analytical as the ethyl ester.

One vinyl pyridone of particular interest to us was the furan derivative **2**, (R_1 = 2-furyl, R_2 = H, entries 14 and 20). Employing the dianion **5** with furfuraldehyde gave poor yields of the adduct **8** (entry 14) and elimination using acidic reagents gave severe decomposition. Using methyltriphenoxyphosphonium iodide [12], the vinyl cyanopyridone **2a** could be obtained (31%) but the nitrile still could not be hydrolyzed without furan decomposition. In order to circumvent this hydrolysis problem, and to explore the importance of the cyano group in the stability of the dianion **5**, we decided to examine the dianion chemistry of the 1,2-dihydro-6-methyl-2-oxo-3-pyridinecarboxylic acid, *t*-butyl ester (**10**).

The Dianion **11**.

The *t*-butyl ester **10** was chosen after preliminary experiments indicated that the trianion of the pyridone acid **9** could not be readily prepared, probably due to the very poor solubility of the lithium carboxylate salt. No deuterium incorporation was ever seen in these experiments. The preparation of the *t*-butyl ester **10** and its chemistry with potassium amide in liquid ammonia has been reported [5]. For this work we developed a new synthesis of **10** (Scheme 1) from the carboxylic acid **9** by treating **9** with 1,1'-carbonyldiimidazole followed by reaction with *t*-butoxide in *t*-butyl alcohol. When the *t*-butyl ester **10** was

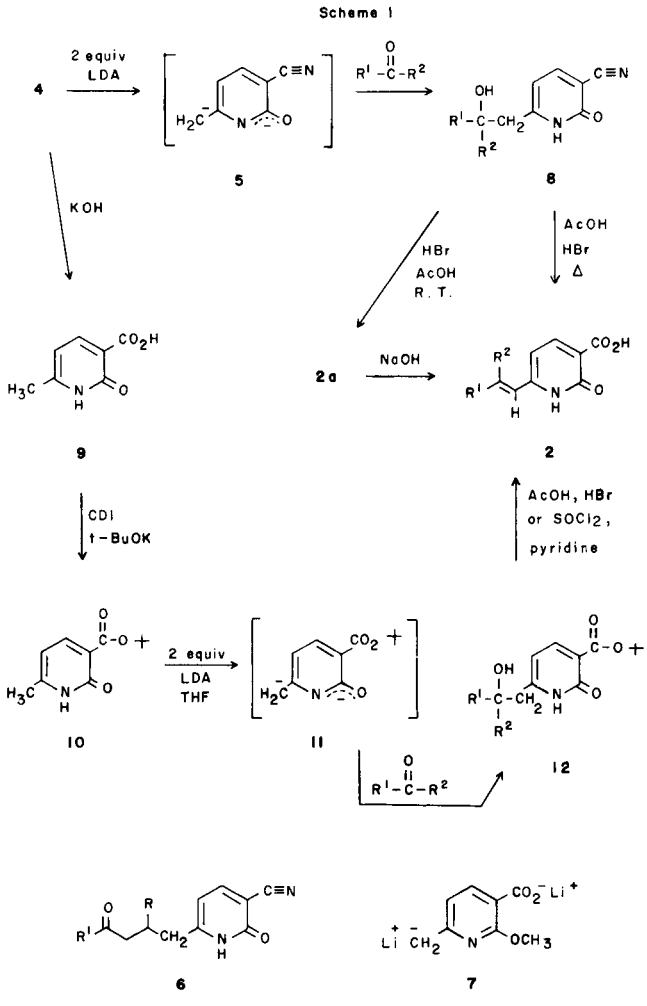
2a

treated with two equivalents of LDA at −30° for 1 hour, a dark green solution of the dianion **11** was obtained, which reacted cleanly with aldehydes to give the adducts **12**. Dehydration of these adducts to the vinyl pyridones **2** was accomplished with 48% hydrogen bromide in acetic acid, as above, or with refluxing thionyl chloride:pyridine in THF. For the special case of the furyl vinyl pyridone **2** (R_1 = furyl), dehydration with methyltriphenoxyphosphonium iodide [12] followed by treatment with TFA gave **2** (entry 20) in excellent overall yield. In one case, in the dehydration of the *t*-butyl ester/acetaldehyde adduct **12** (R_1 = CH_3, R_2 = H), the secondary halide **17** was obtained in moderate yield using thionyl chloride:pyridine with a mild nonaqueous workup. This halide when returned to the reaction conditions eventually converted to the vinyl pyridone **2**.

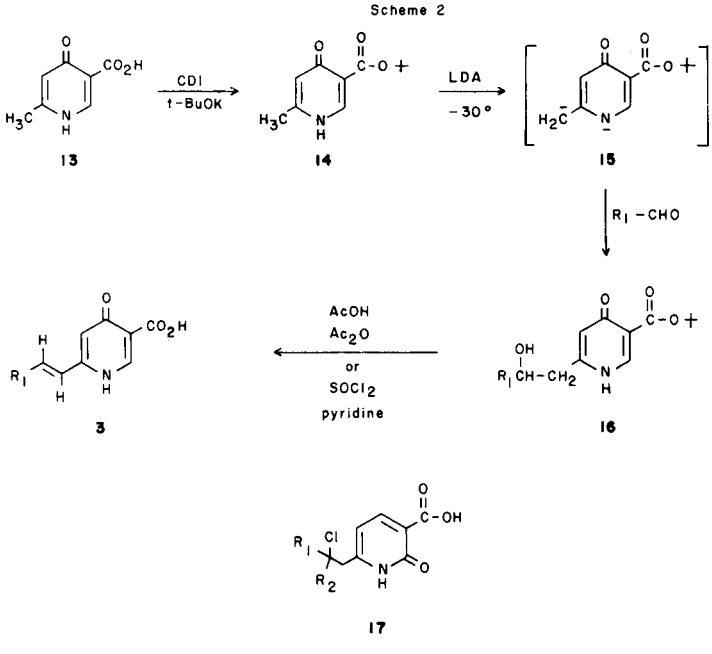
In forming the dianion **11** more careful temperature control was required than in preparing **5**. At −10° to 0° the dianion **11** slowly began to self condense with the *t*-butyl ester. Below −50°, no appreciable dianion formation took place.

Hauser [4a] has speculated that the 3-cyano group in **4** may be replaceable with other electron withdrawing func-

Scheme 1



Scheme 2



tionalities. His attempts to perform the reaction using the 3-carboxamide, **4** (C≡N replaced by $CONH_2$), failed. Our results with the dianion of the *t*-butyl ester **10** demonstrate that electron deficient groups other than the cyano group do indeed facilitate the formation and stabilization of the negative charge at C_6 in these pyridones relative to those bearing no such groups [10].

The 4-Pyridone Dianion **15**.

Using the dianion formation of the 6-methyl-2-pyridone carboxylic acid, *t*-butyl ester **10** as a guide, we prepared the 4-pyridone analog **14** and explored its possible dianion formation. The 4-pyridone carboxylic acid **13** [11] was converted to the *t*-butyl ester in 92% yield in the same manner as was its 2-pyridone isomer (Scheme 2). The dianion of the *t*-butyl ester **14** was prepared using LDA in THF at −30°. This dianion was much less stable than either of the 2-pyridone dianions **5** or **11**, forming only between −35° to −25° and decomposing to polymeric materials at −20° in a few hours. Quenching the dianion with deuterium oxide at −30° gave 80% yield of recovered **14** with 90% deuterium incorporation. The same experiment, done after warming the dianion from −30° to 0° for 1 hour gave only 25% recovery of the ester with 83% deuterium incorporation. At temperatures below −40°, little dianion could be prepared (10% incorporation). This difference in stability may be due to the movement of the 2-oxygen atom to the 4-position from which it can no longer share in the same resonance forms as drawn for **5** and **11** where the close proximity to the oxygen and nitrogen atoms might lend added stability.

Not only was the 4-pyridone dianion different in stability, but its reactivity was also unlike that of the 2-pyridone dianions. The reaction of **15** with aldehydes was slightly more sluggish and the yields lower than those obtained with **5** or **11**. More significant was its reaction with ketones (entries 26 and 27, Table I). Even though the color of the dianion disappeared upon addition of ketones, quenching with water at *p*H 7.5, after the reaction had been brought to room temperature overnight, gave recovered starting materials in 30-50% yield, the remainder being polymeric materials. No sign of the product was observed. The dianion itself under the identical conditions without ketone present gave only polymer. These data suggest that some ketone adduct **16** was formed during the reaction, and that the retro reaction occurs upon quenching or warming to room temperature. When the quench was performed at *p*H 2-4, some product was obtained (~10%) contaminated with starting materials. The same retro reaction in the 2-pyridone series required much more vigorous conditions (~1*N* sodium hydroxide at 100°). Also contrary to dianions **5** and **11** the dianion **15** could not be formed at all using potassium amide in liquid ammonia.

The formation of the 6-vinyl-4-pyridones **3** from the

aldol adducts **16** was subject to the same problems experienced with the 2-pyridones. The dehydration of the adducts **16** was most readily accomplished under mild conditions using acetic anhydride in acetic acid at reflux for 16 hours. These conditions were sufficiently acidic to remove the *t*-butyl ester but did not have any adverse effect on other acid labile groups (entry 28). These elimination conditions when employed with the 2-pyridone adducts **8** or **12** did not give complete reaction. Dehydration with thionyl chloride:pyridine or hydrogen bromide:AcOH was also possible with the adducts **16**, but gave lesser yields.

Conclusion.

Our results have demonstrated that the pyridone dianions **5** and **11** may be prepared without the use of potassium amide and liquid ammonia, and are excellent precursors to a wide variety of 6-vinyl-2-pyridonecarboxylic acids **2**. We have also delineated the optimum conditions for the dehydration and hydrolysis of the aldol type adducts **8** and have shown that the tertiary adducts are especially resistent to dehydration limiting the synthesis to the preparation of mono substituted vinyl pyridones. Finally, this general synthesis has been extended through the new dianion **15**, to the preparation of the 6-vinyl-4-pyridones **3**. These pyridone acids, when coupled to β-lactam nuclei, gave semi-synthetic antibiotics of excellent activity. These results will soon be reported elsewhere.

EXPERIMENTAL

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 (pmr) spectra were recorded on a Varian EM-390 or Bruker WH-90 instrument. The Bruker WH-90 was modified with a Nicolet Technology Corporation B-NC12 data acquisition system. Chemical shifts are reported as δ values in ppm 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. Tetrahydrofuran (THF) was dried and distilled from sodium aluminum-hydride just prior to use. *In vacuo* refers to 0.2-1.5 mm. Solutions were dried using magnesium sulfate and concentrated on a rotary evaporator at 30-45° at pressures of 10-20 mm. Charcoal refers to activated "Darco" G-60. Carbonyl substrates were commercially available with the exception of 3-chloro-3-(4-methoxyphenyl)-propenal [14] and 4-(methylthio)benzaldehyde [15] which were prepared just prior to use. Diisopropylamine was obtained from Aldrich and was dried over 4A sieves. *n*-Butyllithium was from Foote Chemical Company and its activity was determined by titration [13]. All moisture sensitive reactions were performed under dry nitrogen.

1,2-Dihydro-6-methyl-2-oxo-3-pyridinecarboxylic Acid (**9**).

To 134 g (1.00 mole) of the cyano pyridone **4** [8] was added 500 ml of 20% sodium hydroxide. The reaction was taken to 140° in a bomb for 24 hours. The solution obtained was brought to *p*H 8.5 with concentrated hydrochloric acid and was extracted twice with dichloromethane. The water layer was acidified to *p*H 3.0 and the solids filtered. Drying *in vacuo* yielded 130 g (85%) of **9**, mp 230-232°; ir (potassium bromide): 3200-2600, 1700, 1610, 1465 cm^{-1}; nmr (DMSO-d_6): δ 14.7 (s, 1H, CO_2H), 13.3 (s, 1H, N*H*), 8.3 (d, J = 8 Hz, 1H, pyridone-C_4H), 6.65 (d, J = 8 Hz, 1H, pyridone-C_5H), 2.4 (s, 3H, CH_3).

Anal. Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.58; N, 9.15. Found: C, 54.69; H, 4.59; N, 9.11.

1,2-Dihydro-6-methyl-2-oxo-3-pyridinecarboxylic Acid, *t*-Butyl Ester (**10**).

To 80.0 g (0.523 mole) of the pyridone acid **9**, in 500 ml of DMF (dried over 4A sieves) was added 105 g (1.25 equivalents) of 1,1'-carbonyldiimidazole. The mixture was heated at 55° with overhead stirring. After 2.5 hours the solids were filtered and washed with dry THF and dried overnight *in vacuo*. The dry imidazolide (106 g, ~100% yield) was treated, without purification, with 2.5 ℓ of *t*-butyl alcohol and 58.99 g (1.0 theoretical equivalent) of potassium *t*-butoxide. The mixture was heated to 70° for 3.5 hours. It was concentrated, and acidified to *p*H 5 with concurrent extraction into dichloromethane. The dichloromethane was concentrated and the solids washed with copious amounts of water. Drying gave 104 g (96%) of the *t*-butyl ester **10**, identical with the previously reported material [5].

Preparation and Condensation of the Dianion **5**. A General Procedure. Synthesis of 1,2-Dihydro-6-[2-hydroxy-2-(2-pyridinyl)ethyl]-2-oxo-3-pyridinecarbonitrile (**8**-5).

A solution of 425 ml (3.0 mmoles) of diisopropylamine in 3.6 ℓ of THF was cooled in ice and treated with 1.8 ℓ (1.0 equivalent, 1.65 *N*, heptane) of *n*-butyllithium. After 15 minutes, 181.1 g (1.35 moles) of the solid nitrile **4** was added in portions, all dissolved, then another solid appeared. After stirring for 2 hours at 0°, the suspension was treated dropwise with a solution of 130 ml (1.35 moles) of 2-pyridinecarboxaldehyde (distilled) in 260 ml of THF. The mixture was kept at 0° for 2 hours, then allowed to stir at room temperature overnight. The solvent was removed *in vacuo*, the residue taken up in water and washed twice with ether, and then petroleum ether. The aqueous solution was then adjusted to *p*H 4.5 with dilute hydrochoric acid. The solid was collected and washed with 2-propanol then ether to give 179.4 g (81%) of **8**-5, mp 190-191° dec; ir (potassium bromide): 2220, 1650, 1610, 1570 cm^{-1}; nmr (DMSO-d_6): δ 8.45 (d, 1H, pyridine), 7.9 (d, J = 8 Hz, 1H, C_4H), 7.8 (m, 1H, pyridine), 7.45 (d, 1H, pyridine), 7.2 (t, 1H, pyridine), 6.2 (d, J = 8 Hz, 1H, C_5H), 5.7 (d, 1H, O*H*), 4.9 (m, 1H, C*H*), 3.0 (m, 2H, CH_2).

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.27; H, 4.60: N, 17.42. Found: C, 64.27; H, 4.60; N, 17.37.

Preparation and Condensation of the Dianion **11**. A General Procedure. Synthesis of 1,2-Dihydro-6-(2-hydroxypropyl)-2-oxo-3-pyridinecarboxylic Acid, *t*-Butyl Ester (**12**-22).

To 6.73 ml (48.0 mmoles) of diisopropylamine in 50 ml of THF was added 30.8 ml (1.05 equivalents, 1.65 *N*, heptane) of *n*-butyllithium over 20 minutes at 0°. The mixture was cooled to −40° and 5.02 g (24.0 mmoles) of the 2-pyridone *t*-butyl ester **10** in 40 ml of THF was added keeping the temperature below −30°. The mixture was stirred for 2.5 hours at −30° and 1.47 ml (1.1 equivalents) of acetaldehyde was added. The reaction was stirred for 2 hours and brought to 0° in 1 hour, when it was poured into saturated aqueous ammonium chloride and ice. The product was extracted into dichloromethane, dried, and concentrated to a red oil which was purified by column chromatography to give 5.81 g (95%) of **12**-22 as an oil; ir (neat): 3400, 1722, 1640, 1605 cm^{-1}; nmr (DMSO-d_6): δ 11.7 (s, 1H, N*H*), 7.85 (d, J = 8 Hz, 1H, C_4H), 6.05 (d, J = 8 Hz, 1H, C_5H), 4.75 (s, 1H, O*H*), 3.9 (m, 1H, C*H*), 2.5 (m, 2H, CH_2), 1.45 (s, 9H, C_4H_9), 1.05 (d, J = 5 Hz, 3H, CH_3).

Anal. Calcd. for $C_{13}H_{18}NO_4$: C, 61.66; H, 7.11; N, 5.53. Found: C, 61.39; H, 6.84; N, 5.30.

1,4-Dihydro-6-methyl-4-oxo-3-pyridinecarboxylic Acid, *t*-Butyl Ester (**14**).

Using the procedure employed for the 2-pyridone *t*-butyl ester **10**, 48.0 g (0.313 mole) of the 4-pyridone acid **13** [11] was converted to 58.8 g (92%) of the imidazolide in 1.0 ℓ of THF and 350 ml of *N,N*-dimethylacetamide. Treatment of the imidazolide with 35.0 g (0.30 mole) of potassium *t*-butoxide gave 55.6 g (92%) of **14**, mp 166-167°; ir (potassium bromide): 3440, 1720, 1650 cm^{-1}; nmr (deuteriochloroform): δ 11.2 (s, 1H, N*H*), 8.6 (s, 1H, C_2H), 6.6 (s, 1H, C_5H), 2.45 (s, 3H, CH_3), 1.55 (s, 9H, C_4H_9).

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.09; H, 7.18; N, 6.70. Found: C, 62.79; H, 6.99; N, 6.54.

Preparation and Condensation of the Dianion **15**. A General Procedure. Synthesis of 6-[2-(2-Furanyl)-2-hydroxyethyl]-1,4-dihydro-4-oxo-3-pyridinecarboxylic Acid *t*-Butyl Ester (**16**-28).

To 10.72 ml (76.4 mmoles) of diisopropylamine in 100 ml of THF at 0°, was added 51 ml of *n*-butyllithium (1.65 *N*, heptane) over 20 minutes. When addition was complete the mixture was cooled to −35° and 8.0 g (38 mmoles) of the *t*-butyl ester **14** in 350 ml of THF was added at such a rate that the temperature did not exceed −30°. After 2.5 hours at −35°, 3.49 ml (1.1 equivalents) of furfuraldehyde (distilled) was added over 3 minutes. The reaction was brought to −20° over 2 hours and was poured directly into a mixture of ice, aqueous ammonium chloride, and dichloromethane. The dichloromethane was extracted twice with water, dried, and concentrated to a white solid which was triturated with ether and filtered to give 11.2 g (96%) of **16**-28: mp 142-144°; ir (potassium bromide): 3220, 1710, 1650, 1610 cm^{-1}; nmr (deuteriochloroform): δ 8.05 (s, 1H, C_2H), 7.5 (d, J = 2 Hz, 1H, Ar), 6.3 (m, 3H, Ar), 4.8 (t, J = 6 Hz, 1H, C*H*), 2.9 (m, 2H, CH_2), 1.5 (s, 9H, C_4H_9).

Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.95; H, 6.23; N, 4.59. Found: C, 62.95; H, 6.22; N, 4.58.

Dehydration and Hydrolysis of the Adducts **8**, **12**, and **16** to the Vinyl Pyridones **2** and **3**. Four General Procedures Indicated in Table 1.

Procedure A. 48% Hydrobromic Acid: Acetic Acid.

The aldol type adduct **8**, **12**, or **16** was added to a mixture of acetic acid (2.3 ml/mmole) and 48% hydrobromic acid (1 ml/mmole) and the reaction was heated at reflux overnight. The mixture was concentrated *in vacuo* and the products suspended in water. The *p*H was adjusted to 12 with 50% sodium hydroxide causing solution to occur. The *p*H was then taken to 5 with concentrated hydrochloric acid and the solids filtered and purified by crystallization if necessary.

Procedure B. Dehydration-Hydrolysis.

Dehydration was performed as above at room temperature giving **2a**. The isolated solids were hydrolyzed with 10-20% sodium hydroxide in water, 20% aqueous dioxane, or 20% ethylene glycol at reflux overnight.

Procedure C. Thionyl Chloride-Pyridine.

The aldol type adduct **12** or **16** was added to dry THF (15-30 ml/mmole) and pyridine (1.0 equivalent). At reflux, thionyl chloride (1.5 equivalents) was added and the mixture stirred overnight. The mixture was concentrated *in vacuo* and the residue triturated with ether. The solids were isolated by filtration and column purified or recrystallized if necessary.

Procedure D. Acetic Anhydride-Acetic Acid.

The aldol type adduct **12** or **16** was added to a mixture of acetic anhydride (5 ml/mmole) and acetic acid (3 ml/mmole). The reaction mixture was refluxed for 24 hours, concentrated to 50% volume, and the solids filtered. The alkene obtained was further purified as necessary.

6-(2,2-Diphenylethenyl)-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**2**-19,23).

Using the general procedure of Hauser [4b], 6.75 g (19.6 mmoles) of **8**-19 was dehydrated to 6.21 g of cyano pyridone **2a** (R_1 and R_2 = Ph). To this solid was added 20% sodium hydroxide and the mixture refluxed for 40 hours. The *p*H was brought to 3.5 with concentrated hydrochloric acid and the solids isolated and dried to give 5.5 g of **2**-19, mp 220-230° dec; ir (potassium bromide): 3440, 1740, 1620 cm^{-1}; nmr (DMSO-d_6): δ 13.3 (s, 1H, O*H*), 8.1 (d, J = 8 Hz, 1H, C_4H), 7.5 (m, 10H, Ar), 7.1 (s, 1H, vinyl), 6.95 (d, J = 8 Hz, 1H, C_5H).

In similar fashion [4b], 28.0 g (83.5 mmoles) of the *t*-butyl ester **12**-23 was converted to 21.25 g of **2**-23 identical to the material described above.

6-[2-(2-Furanyl)ethenyl]-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**2**-20).

To 305 mg (1.0 mole) of the alcohol **12**-20 was added 5 ml of HMPA and 0.90 g (2.0 equivalents) of methyltriphenoxyphosphonium iodide. The mixture was stirred for 1.5 hours at 50°. The solution was taken up in dichloromethane and extracted with water four times. Concentration gave an oil, which was diluted with water to give a yellow solid which was filtered and dried. The solid was treated directly at 0° with 5.0 ml of TFA and 0.5 ml of dimethoxybenzene. After 3.5 hours, the mixture was brought to 25°, concentrated, and the residual oil was added to hexane:ether (1:2) giving 219 mg of **2**-20 as fine yellow needles, mp 280-283° dec; ir (potassium bromide): 3300-2800, 1750, 1620, 1550 cm^{-1}; nmr (DMSO-d_6): δ 8.25 (d, J = 8 Hz, 1H, C_4H), 7.7 (m, 2H), 6.8 (m, 4H).

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