gave color distinguishable in the CD spectrometer, but warming to room temperature yielded only a yellow solution with no detectable CD absorption. On reducing the temperature of a solution containing **12** to −187°, the spectrum amplitude increased but no position changes were noticed.

Registry No.—**1**, 25630-12-0; **2**, 25630-11-9; **3**, 25558-52-5; **4**, 25630-13-1; **5**, 25558-53-6; **6**, 25554-40-9; **7**, 25554-41-0; **8**, 25554-42-1; **9**, 25554-43-2; **10**, 25554-44-3; **12**, 1912-59-0; **13**, 25554-46-5; **14**, 25554-47-6; **15**, 25554-48-7; **16**, 25554-49-8; **17**, 25554-50-1; **18**, 25554-51-2; **19**, 25554-52-3; **20**, 25554-53-4.

Azacoumarins[1]

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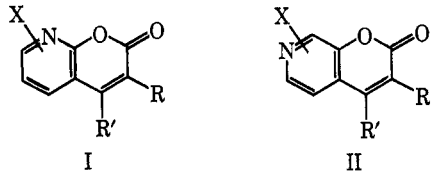
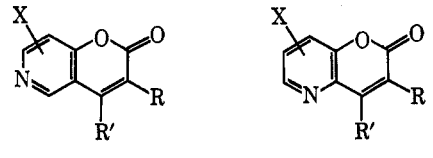
Eighteen azacoumarins were prepared by condensation of appropriate esters, acids, or anhydrides with *o*-hydroxypyridine aldehydes or ketones. This constitutes examples of all four possible types (I, II, III, and IV) of azacoumarins with N replacing CH of the benzene ring. Two 8-azaflavones and a number of intermediates and by-products are also reported.

Part A

Coumarins in which a CH group is replaced by a nitrogen can be called "azacoumarins." In a broad sense this could include the 2*H*-1,4-benzoxazin-2-ones[2] and 2*H*-1,3-benzoxazin-2-ones.[3] However, this paper comprises only those azacoumarins in which the nitrogen replaces a CH of the benzene ring (I, II, III, and IV). The literature contains only two references



I II



III IV

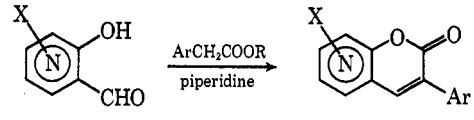
to 2*H*-pyranopyridin-2-ones,[4,5] both of which are of the [2,3-*b*] type, I. One of these[5] gives no information on the synthesis. Robinson and Watt[4] report the synthesis of 7-hydroxy-5-methyl-2*H*-pyrano[2,3-*b*]-pyridin-2-one (I, R and R′ = H; X = 7-OH, 5-CH_3) by the Pechmann synthesis from 2,6-dihydroxy-4-methylpyridine[6] and malic acid. This procedure was confirmed by our synthesis of the corresponding desmethyl analog **7**. However, in general, the Pechmann synthesis does not seem to work on monohydroxypyridines, doubtless because of the protonation of the pyridine ring by the strong acid used. The Kostanecki–Robinson modification of the Perkin reaction or the Knoevenagel reaction were found to be more generally applicable methods and examples of all four types of these azacoumarins were prepared. Types II, III, and IV appear to constitute new classes of compounds.

(1) Presented in part at the Great Lakes Regional Meeting of the American Chemical Society, Fargo, N. D., June 18–19, 1970.
(2) R. B. Moffett, *J. Med. Chem.*, **9**, 475 (1966).
(3) R. L. McKee, *Chem. Heterocycl. Compounds*, **17**, 351 (1962).
(4) R. Robinson and J. S. Watt, *J. Chem. Soc.*, 1536 (1934).
(5) K. v. Auwers, *J. Prakt. Chem.*, **150**, 166 (1938).
(6) Many 2- and 4-hydroxypyridines are known to exist in the pyridone form. However, in this article the pyridol nomenclature will be used since it is the hydroxy form that reacts in our syntheses.

Of the requisite pyridinol aldehydes or ketones only pyridoxal was available. 3-Hydroxy-2- (and -4-) pyridinecarboxaldehydes were prepared by the method of Heinert and Martell[7] and 3-acetyl-4-hydroxy-2,6-dimethylpyridine was made as described by Ziegler, Herbst, and Kappe.[8] 3-Acetyl-2-hydroxy-6- (and -4,6-di-) methylpyridines were prepared from the corresponding 3-nitriles by treatment with methyllithium in yields of 47–61%, respectively. Since this work was done the 4,6-dimethyl compound (**20**) has been reported by Bonsall and Hill[9] who prepared it by condensation of acetylacetone with acetoacetamide.

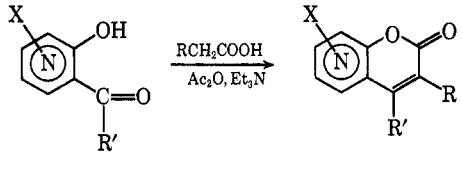
In general the Knoevenagel reaction (Scheme I) was

SCHEME I



used with the pyridol aldehydes employing an arylacetic ester and piperidine. Scheme I was not applicable with the pyridol ketones and so the Perkin reaction (Scheme II) was used.

SCHEME II

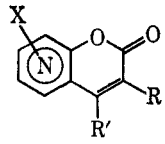


In the one case where a direct comparison was made, 3-phenyl-2*H*-pyrano[3,2-*b*]pyridin-2-one (**17**), about the same yield was obtained by both methods. Table I lists the azacoumarins prepared and their melting points.

An attempt was made to prepare the 4-hydroxy-8-azacoumarin **22** by condensation of the acetylpyridol **20** with diethyl carbonate in the presence of NaH.[10]

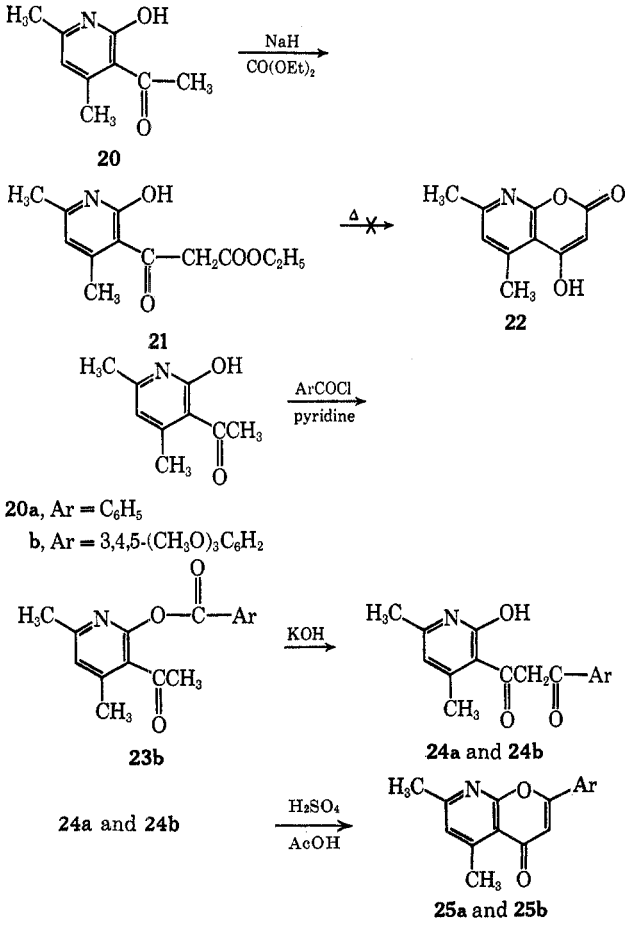
(7) D. Heinert and A. E. Martell, *J. Amer. Chem. Soc.*, **81**, 3933 (1959).
(8) E. Ziegler, I. Herbst, and Th. Kappe, *Monatsh. Chem.*, **100**, 132 (1969).
(9) C. Bonsall and J. Hill, *J. Chem. Soc. C*, 1836 (1967).
(10) Method described for 4-hydroxycoumarin: British Patent 705,316 (1954).

TABLE I



No.	Position of aza N	X	R	R′	Method of prepn[a]	Yield,[b] %	Mp, °C[c]
1	8	7-CH_3	*p*-BrC_6H_4	CH_3	B	65	226.5–228
2	8	7-CH_3	*m*-$CH_3OC_6H_4$	CH_3	B	56	158.5–159.5
3	8	5,7-Di-CH_3	C_6H_5	CH_3	B	49	163–164.5
4	8	5,7-Di-CH_3	*p*-FC_6H_4	CH_3	B	35	194.5–196
5	8	5,7-Di-CH_3	3,4,5-$(CH_3O)_3C_6H_2$	CH_3	B	38	225.5–227.5
6	8	5,7-Di-CH_3	3-Pyridyl	CH_3	B	17	180–180.5
7	8	7-OH	H	H	C	8	293–297 dec
8	7	H	*p*-$CH_3OC_6H_4$	H	B	83	217.5–219.5
9	7	H	2-Pyridyl	H	A	49	150–152
10	7	5-CH_2OH, 8-CH_3	4-Pyridyl	H	A	44	188–197
11	7	5-CH_2OH, 8-CH_3	*p*-$NO_2C_6H_4$	H	A	26	233.5–235
12	6	5,7-Di-CH_3	C_6H_5	CH_3	B	36	166–168
13	6	5,7-Di-CH_3	*m*-$CH_3C_6H_4$	CH_3	B	24	125–126
14	6	5,7-Di-CH_3	*p*-ClC_6H_4	CH_3	B	49	206.5–208
15	5	H	H	H	D[d]	26	107.5–108.5
16	5	H	COOH	H	...[e]	68	192–193 dec
17	5	H	C_6H_5	H	A and B	12	156–157.5
18	5	H	4-Pyridyl	H	A	79	252–254
19	5	H	*p*-$NO_2C_6H_4$	H	A	86	243.5–244.5

[a] A = Knoevenagel reaction (Scheme I); B = Kostanecki–Robinson modification of the Perkin reaction (Scheme II); C = Pechmann synthesis;[4] D = Perkin reaction. [b] The yield is based on the pyridol aldehyde or ketone and is reported for material melting not less than 2° below the highest melting point obtained. [c] Elemental analyses and ir and uv spectra were obtained on all azacoumarins and nmr on selected examples. All were in accord with the proposed structures. Data are given in the Experimental Section for an example of each type of azacoumarin (compd no. 1, 10, 12, and 15). [d] Obtained both by the Perkin reaction (Ac_2O + KOAc) and along with 16 by heating (3-hydroxy-2-pyridyl)methylenemalonic acid, which was prepared from 3-hydroxypicolinaldehyde and malonic acid. [e] Prepared by heating (3-hydroxy-2-pyridyl)methylenemalonic acid with polyphosphoric acid.



However, the ring did not close, probably owing to the pyridone structure[6] of the intermediate, and only the β-keto ester **21** was isolated. The same acetylpyridol **20** was utilized in the preparation of two azaflavones (**25a** and **25b**).

Since completion of this work, the preparation of compounds **24a** and **25a** by slightly different methods have been reported by Bonsall and Hill.[9] Our melting points agree with theirs. All the compounds reported herein have been widely screened for biological activity but only minimal activity was found.

Part B

Experimental Section[11]

3-Acetyl-2-hydroxy-4,6-dimethylpyridine[9] (20).—Methyllithium was prepared from 21.0 g (3.0 g-atoms) of Li and 142.5 g (1.5 mol) of MeBr in 900 ml of Et_2O. To this was added with vigorous stirring under N_2 a suspension of 74.0 g (0.5 mol) of 3-cyano-2-hydroxy-4,6-dimethylpyridine in 900 ml of THF. Most of the ether was distilled through a fractionating column (to bp 60°) and then the solution was stirred under reflux for 2.5 hr. After cooling, the mixture was poured into ice water, acidified with HCl, and allowed to stand at room temperature for 1 hr. The solution was neutralized to pH 7–8 with NaOH and continuously extracted with Et_2O for 40 hr. Evaporation of the extract gave 76.4 g of orange colored solid. Recrystallization from 1.5 l. of

(11) Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. Nmr spectra were determined with a Varian A-60 spectrometer, ir spectra were on Nujol mulls, and uv spectra were in EtOH.

EtOH yielded 50.0 g (61%) of yellow solid, mp 215–216°. An additional 5 g, mp 209–210°, was obtained from the filtrate. A sample recrystallized from benzene gave mp 216–218°.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.54; H, 6.71; N, 8.48; O, 19.37. Found: C, 65.57; H, 6.31; N, 8.73; O, 19.32.

3-Acetyl-2-hydroxy-6-methylpyridine.—By a similar procedure this was prepared from 47 g (6.7 g-atoms) of Li, 320 g (3.36 mol) of MeBr, 2.1 l. of Et_2O, 150 g (1.12 mol) of 3-cyano-2-hydroxy-6-methylpyridine, and 3.4 l. of THF. The product was recrystallized twice from EtOH (with Darco G-60 treatment) yielding 78.3 g (47%) of light yellow crystals, mp 202–207°. A sample recrystallized for analysis had mp 208.5–209.5°.

Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.71; H, 6.09; N, 8.98.

3-(*p*-Bromophenyl)-4,7-dimethyl-2*H*-pyrano[2,3-*b*]pyridin-2-one (1) (Example of Method B).—A solution of 7.5 g (0.05 mol) of 3-acetyl-2-hydroxy-6-methylpyridine, 15 g (0.07 mol) of *p*-bromphenylacetic acid, and 7 ml (0.05 mol) of Et_3N in 31.5 ml (0.35 mol) of Ac_2O was stirred under N_2 under reflux for 6 hr. After cooling the crystal containing mixture was poured into water and adjusted to pH 8 with NH_4OH. The solid was collected, washed with water, and boiled with EtOH. After cooling the solid was collected and dried giving 11.77 g of light brown crystals. Recrystallization from 100 ml of ethylene glycol monomethyl ether (filtered hot) yielded 10.6 g (64.6%) of tan crystals, mp 226.5–228°. Principal spectral bands: uv 222, 236, 274, and 317 mμ; ir C=CH at 3075, C=O/C=N at 1710, C=C at 1616, 1597, 1588, 1553, and 1487, C—H/C—O at 1145 and 1075, arom at 817 cm^{-1}; nmr (in $CDCl_3$) two Me singlets (integrating 3 each) at δ 2.33 and 2.67, and aromatic multiplets (integrating 6) between δ 7 and 8.

Anal. Calcd for $C_{16}H_{12}BrNO_2$: C, 58.20; H, 3.66; Br, 24.20; N, 4.24. Found: C, 58.26; H, 3.65; Br, 24.11; N, 4.21.

3-(*m*-Methoxyphenyl)-4,7-dimethyl-2*H*-pyrano[2,3-*b*]pyridin-2-one (2).—By a similar procedure this was prepared from 7.5 g (0.05 mol) of 3-acetyl-2-hydroxy-6-methylpyridine, 16.6 g (0.1 mol) of *m*-methoxyphenylacetic acid, 31.5 ml (0.35 mol) of Ac_2O, and 7 ml (0.05 mol) of Et_3N. The crude solid was recrystallized from 150 ml of EtOH (with Darco G-60 treatment) yielding 7.75 g (55.5%) of light tan solid, mp 158–160°. A sample recrystallized again from EtOH had mp 158.5–159.5°.

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.38; N, 4.98. Found: C, 72.53; H, 5.42; N, 4.98.

4,5,7-Trimethyl-3-phenyl-2*H*-pyrano[2,3-*b*]pyridin-2-one (3).—By a similar procedure this was prepared from 8.3 g (0.05 mol) of 3-acetyl-2-hydroxy-4,6-dimethylpyridine, 13.6 g (0.1 mol) of phenylacetic acid, 28.2 ml (0.3 mol) of Ac_2O, and 14 ml (0.1 mol) of Et_3N. The mixture was stirred under reflux for 22 hr and then the solvent was distilled, under N_2, from a bath at 190° during 2 hr. The crude solid was sublimed at 0.01 mm from a bath at 190° giving 6.9 g of light tan solid. This was recrystallized from 120 ml of EtOH yielding 6.53 g (49%) of white crystals, mp 163–164.5°.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.76; H, 5.53; N, 5.30.

3-(*p*-Fluorophenyl)-4,5,7-trimethyl-2*H*-pyrano[2,3-*b*]pyridin-2-one (4).—By a similar procedure this was prepared from 5.54 g (0.033 mol) of 3-acetyl-2-hydroxy-4,6-dimethylpyridine, 18.8 ml (0.2 mol) of Ac_2O, and 4.7 ml (0.33 mol) of Et_3N. The mixture was heated under reflux, under N_2, for 10 hr. The crude product was recrystallized from EtOH (with Darco G-60 treatment) yielding 3.28 g (35%) of light tan crystals, mp 194.5–196°.

Anal. Calcd for $C_{17}H_{14}FNO_2$: C, 72.07; H, 4.98; F, 6.71; N, 4.94. Found: C, 71.93; H, 4.59; F, 6.68; N, 4.85.

3-(3,4,5-Trimethoxyphenyl)-4,5,7-trimethyl-2*H*-pyrano[2,3-*b*]-pyridin-2-one (5).—By a similar procedure this was prepared from 16.6 g (0.1 mol) of 3-acetyl-2-hydroxy-4,6-dimethylpyridine, 27.2 g (0.12 mol) of 3,4,5-trimethoxyphenylacetic acid, 56.4 ml (0.6 mol) of Ac_2O, and 28 ml (0.2 mol) of Et_3N. After heating under reflux for 19 hr the solvent was distilled from a bath at 175° during 2 hr. The crude product was recrystallized twice from EtOH yielding 13.35 g (38%) of tan crystals, mp 225.5–227.5°.

Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.62; H, 6.33; N, 4.10.

4,5,7-Trimethyl-3-(3-pyridyl)-2*H*-pyrano[2,3-*b*]pyridin-2-one (6).—By a similar procedure this was prepared from 16.6 g (0.1 mol) of 3-acetyl-2-hydroxy-4,6-dimethylpyridine, 14.6 g (0.12 mol) of 3-pyridylacetic acid, 56.4 ml (0.6 mol) of Ac_2O, and 28 ml (0.2 mol) of Et_3N. After heating under reflux for 24 hr the solvent was distilled from a bath at 200° during 2 hr. The crude gummy product was boiled with 400 ml of EtOH, filtered, and evaporated to dryness. The resulting gum was sublimed at 0.01 mm from a bath up to 250°. After removing a little white solid the product sublimed as a partly crystalline solid. This was recrystallized from 2-propanol yielding 4.55 g (17%) of yellow solid, mp 170–180°. A sample recrystallized from EtOH gave mp 180–180.5° after sintering at 173.5–175°.

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.09; H, 5.36; N, 10.79.

3-(*p*-Methoxyphenyl)-2*H*-pyrano[2,3-*c*]pyridin-2-one (8).—By a similar procedure this was prepared from 1.23 g (0.01 mol) of 3-hydroxyisonicotinaldehyde,[7] 3.32 g (0.02 mol) of *p*-methoxyphenylacetic acid, 10 ml of Ac_2O, and 1.4 ml (0.01 mol) of Et_3N. The solution was heated under reflux for 5 hr. The crude product boiled with EtOH, cooled, collected, and dried giving 2.1 g (83%) of tan crystals, mp 217.5–219°. Recrystallization from 25 ml of ethylene glycol monomethyl ether gave 2.0 g of light tan crystals, mp 217.5–219.5°.

Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.29; H, 4.34; N, 5.42.

4,5,7-Trimethyl-3-phenyl-2*H*-pyrano[3,2-*c*]pyridin-2-one (12).—By a similar procedure this was prepared from 5.0 g (0.03 mol) of 3-acetyl-4-hydroxy-2,6-dimethylpyridine,[8] 8.15 g (0.06 mol) of phenylacetic acid, 17 ml (0.16 mol) of Ac_2O, and 5 ml (0.36 mol) of Et_3N. The solution was stirred under reflux for 8 hr. The crude product was crystallized from 2-propanol and recrystallized from EtOH (with Darco G-60 treatment) yielding 2.9 g (36.4%) of nearly white crystals, mp 166–168°. Principal spectral bands: uv 206, 234, and 302 mμ; ir C=O at 1720, C=C/C=N at 1595, 1540, and 1495, C–O, C–N at 1180, 1090, and 985, arom at 735 and 710 cm^{-1}; nmr (in $CDCl_3$) three Me singlets (integrating 3 each) δ 2.40, 2.57, and 2.90, 8-H singlet (integrating 1) at δ 6.99, and aromatic multiplet (integrating 5) centered at δ 7.4.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.69; H, 5.69; N, 5.35.

4,5,7-Trimethyl-3-(*m*-tolyl)-2*H*-pyrano[3,2-*c*]pyridin-2-one (13).—By a similar procedure this was prepared from 8.0 g (0.048 mol) of 3-acetyl-4-hydroxy-2,6-dimethylpyridine,[8] 14.5 g (0.96 mol) of *m*-tolylacetic acid, 27 ml (0.256 mol) of Ac_2O, and 8 ml (0.058 mol) of Et_3N. The solution was stirred under N_2 under reflux for 8 hr. The crude product was crystallized from 2-propanol and recrystallized from MeOH (with Darco G-60 treatment) yielding 3.2 g (23.8%) of nearly white crystals, mp 125–126° (with sintering at 121–122°).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.14; N, 5.02. Found: C, 77.63; H, 6.43; N, 5.27.

3-(*p*-Chlorophenyl)-4,5,7-trimethyl-2*H*-pyrano[3,2-*c*]pyridin-2-one (14).—By a similar procedure this was prepared from 7.5 g (0.045 mol) of 3-acetyl-4-hydroxy-2,6-dimethylpyridine,[8] 15.3 g (0.09 mol) of *p*-chlorophenylacetic acid, 25 ml (0.24 mol) of Ac_2O, and 7.5 ml (0.054 mol) of Et_3N. The solution was heated under reflux, under N_2, for 8 hr. The crude product was boiled with 150 ml of 2-propanol and cooled, and the solid was collected giving 6.6 g (49%) of light brown solid, mp 202–206°. Recrystallization from EtOH (with Darco G-60 treatment) yielded 4.65 g of nearly white crystals, mp 206.5–208°.

Anal. Calcd for $C_{17}H_{14}ClNO_2$: C, 68.12; H, 4.71; Cl, 11.83; N, 4.67. Found: C, 68.02; H, 4.80; Cl, 11.87; N, 4.76.

3-Phenyl-2*H*-pyrano[3,2-*b*]pyridin-2-one (17) (Method B).—By a similar procedure this was prepared from 1.23 g (0.01 mol) of 3-hydroxypicolinaldehyde,[7] 2.72 g (0.02 mol) of phenylacetic acid, 10 ml of Ac_2O, and 1.4 ml (0.01 mol) of Et_3N. The product was extracted with Et_2O from the weakly basified aq mixture, containing much tar, washed (H_2O and satd NaCl), and dried (Na_2SO_4). After removal of the ether the gummy product was sublimed at 0.015 mm from a bath up to 194° and then crystallized from 2-propanol yielding 0.26 g (12%) of pink crystals, mp 152.5–154.5°. The infrared spectrum was identical with that of material prepared by method A (below).

3-Phenyl-2*H*-pyrano[3,2-*b*]pyridin-2-one (17) (Method A).—A solution of 1.23 g (0.01 mol) of 3-hydroxypicolinaldehyde,[7] 1.65 g (0.011 mol) of methyl phenylacetate, and 1 ml of piperidine in 25 ml of abs EtOH was heated under reflux for 4 hr. After filtration and evaporation, the dark tar was sublimed at 0.01 mm from a bath up to 193°. The sublimate was recrystallized from 2-propanol (with Darco G-60 treatment) yielding 0.27 g (12%) of white crystals, mp 156–157°. A sample for analysis was recrystallized again from 2-propanol, mp 156–157.5°.

Anal. Calcd for $C_{14}H_9NO_2$: C, 75.32; H, 4.06; N, 6.28. Found: C, 75.09; H, 4.02; N, 6.24.

3-(*p*-Nitrophenyl)-2*H*-pyrano[3,2-*b*]pyridin-2-one (19).—A solution of 1.23 g (0.01 mol) of 3-hydroxypicolinaldehyde,[7] 2.3 g (0.011 mol) of ethyl *p*-nitrophenylacetate, and 1 ml of piperidine in 25 ml of abs EtOH was heated under reflux for 0.5 hr. After cooling the resulting crystalline solid was collected, washed (EtOH), and dried giving 2.3 g (86%) of light tan crystals, mp 243–244°. Recrystallization from ethylene glycol monomethyl ether gave 2.15 g of fluffy cream colored needles, mp 243.5–244.5°.

Anal. Calcd for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.00; N, 10.43. Found: C, 62.33; H, 2.99; N, 10.52.

3-(4-Pyridyl)-2*H*-pyrano[3,2-*b*]pyridin-2-one (18).—A solution of 12.3 g (0.1 mol) of 3-hydroxypicolinaldehyde,[7] 15.1 g (0.1 mol) of methyl 4-pyridylacetate, and 5.8 ml of piperidine in 125 ml of abs EtOH was heated under reflux for 1 hr. After cooling the resulting crystalline solid was collected, washed (EtOH), and dried, giving 17.7 g (79%) of light brown solid, mp 245–252°. This was recrystallized from 140 ml of DMF yielding 16.6 g of brown crystals, mp 249–253°. A sample for analysis was sublimed at 0.05 mm from a bath up to 187° and recrystallized from DMF giving white needles, mp 252–254°.

Anal. Calcd for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.59; N, 12.50. Found: C, 69.87; H, 3.57; N, 12.36.

3-(2-Pyridyl)-2*H*-pyrano[2,3-*c*]pyridin-2-one (9).—A solution of 1.23 g (0.01 mol) of 3-hydroxyisonicotinaldehyde,[7] 1.66 g (0.011 mol) of methyl 2-pyridylacetate, and 0.3 ml of piperidine in 25 ml of abs EtOH was heated, under N_2, under reflux for 2 hr. The mixture was dissolved in more EtOH, treated with Darco G-60 at bp, filtered, and cooled, yielding 1.1 g (49%) of pink crystals, mp 150–152°.

Anal. Calcd for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.59; N, 12.50. Found: C, 69.36; H, 3.26; N, 12.39.

5-(Hydroxymethyl)-8-methyl-3-(4-pyridyl)-2*H*-pyrano[2,3-*c*]-pyridin-2-one (10).—A solution of 20.36 g (0.1 mol) of pyridoxal hydrochloride, 15.1 g (0.1 mol) of methyl 4-pyridylacetate, and 15.8 ml of piperidine, in 120 ml of abs EtOH was heated under reflux for 2 hr. After filtration the solution was evaporated *in vacuo* and the residue was shaken with water giving 13.5 g of pink solid, mp 187–192°. This was recrystallized from 160 ml of EtOH yielding 11.9 g (44.5%) of pink crystals, mp 188–197°. A sample dissolved in hot water and separated (still at bp) as fluffy needles, mp 192–197°. The infrared spectra indicated dimorphic forms. Principal spectral bands: uv 240, 295, and 346 mμ; ir OH at 3180, C=CH at 3070, C=O at 1728, C=C/C=N at 1628, 1542, and 1600, C–N/C–O at 1230, 1144, 1079, and 102 cm^{-1}; nmr (in deuterated DMSO) Me singlet at 2.57, CH_2 doublet centered at 4.82, OH broad triplet centered at 5.65, and vinyl and aromatic multiplets between δ 7 and 9.

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44; O, 17.89. Found: C, 66.91; H, 4.63; N, 10.23; O, 17.82.

5-(Hydroxymethyl)-8-methyl-3-(*p*-nitrophenyl)-2*H*-pyrano-[2,3-*c*]pyridin-2-one (11).—A solution of 10.4 g (0.05 mol) of pyridoxal hydrochloride, 11.5 g (0.055 mol) of ethyl *p*-nitrophenylacetate, and 9.9 ml (0.1 mol) of piperidine in 30 ml of abs EtOH was heated under reflux for 2 hr. The dark solution was cooled and poured into water. The resulting orange-brown solid was dissolved in 100-ml of ethylene glycol monomethyl ether, treated with Darco G-60, filtered, diluted with 150 ml of ethanol, and cooled, yielding 4.1 g (26%) of cream colored fluffy needles, mp 233.5–235°.

Anal. Calcd for $C_{16}H_{12}N_2O_5$: C, 61.53; H, 3.87; N, 8.97. Found: C, 61.22; H, 3.75; N, 8.82.

2*H*-Pyrano[3,2-*b*]pyridin-2-one (15).—A mixture of 1.23 g (0.01 mol) of 3-hydroxypicolinaldehyde,[7] 1 g (0.01 mol) of KOAc, and 4 ml (0.04 mol) of Ac_2O was heated under reflux for 2 hr. The dark mixture was distilled *in vacuo* in a short path apparatus. The distillate in EtOH was mixed with 2 g of $NaHCO_3$ and evaporated to dryness. The residue was sublimed at 0.02 mm from a bath up to 150°. The sublimate was recrystallized from EtOH yielding 0.39 g (26%) of white crystalline solid, mp 107.5–108.5°. Principal spectral bands: uv 230, 251, 257, 261, 308, 314, 328, and 335 mμ; ir C=CH at 3070, C=O at 1765 and 1725, C=C/C=N at 1655, 1610, 1583, and 1558, C—N/C—O at 1207, 1165, 1084, and arom at 792; nmr (in $CDCl_3$) showed only vinyl and aromatic multiplets between δ 6.5 and 8.7.

Anal. Calcd for $C_8H_5NO_2$: C, 65.30; H, 3.42; N, 9.52. Found: C, 65.19; H, 3.36; N, 9.79.

This same azacoumarin was obtained by twice subliming a sample of [(3-hydroxy-2-pyridyl)methylene]malonic acid (below) at 0.01 mm from a bath up to 200°. It was recrystallized from EtOH, mp 107.5–108.5°.

[(3-Hydroxy-2-pyridyl)methylene]malonic Acid.—A solution of 1.23 g (0.01 mol) of 3-hydroxypicolinaldehyde[7] and 1.56 g (0.015 mol) of malonic acid in 25 ml of abs EtOH was heated under reflux with stirring for 2 hr. Solid separated during the first 5 min. After cooling, the solid was collected and dried giving 0.94 g (54.4%) of yellow-tan crystals, mp 174.5–175.5° dec. A sample for analysis was dissolved in DMSO at room temp, filtered, and diluted with methanol giving yellow-tan solid melting with decomposition between 163° and 179.5° depending on the rate of heating.

Anal. Calcd for $C_9H_7NO_5$: C, 51.68; H, 3.37; N, 6.70. Found: C, 51.50; H, 3.38; N, 6.64.

2-Oxo-2*H*-pyrano[3,2-*b*]pyridine-3-carboxylic Acid (16).—A mixture of 5.1 g (0.03 mol) of [(3-hydroxy-2-pyridyl)methyl)-methylene]malonic acid and 20 g of polyphosphoric acid was heated with stirring in a bath at 125–130° for 20 min. After cooling the mixture was well mixed with 100 ml of H_2O and the resulting solid was collected, washed (H_2O), and dried yielding 3.77 g (68%) of white solid, mp 192–193° dec.

Anal. Calcd for $C_9H_5NO_4$: C, 56.55; H, 2.64; N, 7.33; equiv wt, 191.1. Found: C, 56.42; H, 2.68; N, 7.32. equiv wt, 189.

7-Hydroxy-2*H*-pyrano[2,3-*b*]pyridin-2-one (7).—To 23.6 g (0.16 mol) of 2,6-dihydroxypyridine hydrochloride was cautiously added 70 ml of conc H_2SO_4. After the evolution of HCl had ceased 22 g (0.164 mol) of malic acid was added and the solution was heated with stirring under N_2 on a steam bath for 5.75 hr. After cooling the solution was poured into 300 ml of ice water and allowed to stand at 0–5° for 3 days. The resulting crystalline solid was collected, washed (ice water), and dried giving 6.1 g of light brown solid. This was sublimed at 0.01 mm from a bath up to 262° giving 4 g of solid, mp 280–290° dec. This was recrystallized from 70% aq EtOH and then from ethylene glycol monomethyl ether (with Darco G-60 treatment) yielding 2 g (7.7%) of nearly white solid, mp 293–297° dec.

Anal. Calcd for $C_8H_5NO_3$: C, 58.90; H, 3.09; N, 8.59. Found: C, 58.69; H, 3.01; N, 8.51.

Ethyl β-(2-Hydroxy-4,6-dimethyl-3-pyridine)-β-oxopropionate (21).—To a warm mixture of 2.4 g (0.1 mol) of NaH (4.5 g of 54% suspension in mineral oil), 11.8 g (0.1 mol) of diethyl carbonate, and 60 ml of toluene was slowly added with stirring 8.3 g (0.05 mol) of 3-acetyl-2-hydroxy-4,6-dimethylpyridine. Solvent was slowly distilled through a short column to bp 109°. After cooling, water was added. The aqueous layer was washed with ether and acidified (pH 6) with AcOH. The resulting solid was collected, washed (H_2O), and dried giving 4.83 g of tan crystals, mp 127–129°. This was recrystallized from 40 ml of abs EtOH (with Darco G-60 treatment) yielding 4.05 g (34%) of light yellow crystals, mp 132–133°. Ir, uv, and nmr spectra confirm the proposed structure.

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.67; H, 6.35; N, 5.91.

3-Acetyl-4,6-dimethyl-2-pyridyl 3,4,5-Trimethoxybenzoate (23b).—To a suspension of 82.5 g (0.5 mol) of 3-acetyl-2-hydroxy-4,6-dimethylpyridine in 500 ml of dry pyridine was slowly added during 25 min 138 g (0.6 mol) of 3,4-trimethoxybenzoyl chloride. After heating on a steam bath for 15 min and standing overnight the mixture was poured into ice water and extracted with ether. The ether solution was washed (cold dil NaOH and H_2O) and dried (Na_2SO_4), evaporated, and crystallized from 2-propanol giving 102.7 g (68%) of solid, mp 82–91°. This was recrystallized from 2-propanol yielding 86 g (48%) of yellow crystals, mp 85–88°. A sample recrystallized again from 2-propanol (with Darco G-60 treatment) had mp 87–90°.

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.37; H, 5.95; N, 4.16.

1-(2-Hydroxy-4,6-dimethyl-3-pyridyl)-3-(3,4,5-trimethoxyphenyl)propane-1,3-dione (24b).—To a solution of 21.7 g (0.06 mol) of the above ester (**23b**) in 150 ml of pyridine was slowly added with stirring 9 g of powdered 85% KOH. The mixture, containing gummy solid was placed on a mechanical shaker and shaken overnight. Most of the pyridine was distilled, under reduced pressure, and the residue was mixed with ice water and adjusted to pH 6.5 with AcOH. The resulting fluffy yellow solid was collected, washed (H_2O), and dried giving 12.9 g solid, mp 181–183°. This was recrystallized from a mixture of

700 ml of ethanol and 300 ml of methanol yielding 12.2 g (61%) of yellow crystals, mp 183.5–185°.

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.32; H, 5.75; N, 3.92.

2-(3,4,5-Trimethoxyphenyl-5,7-dimethyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (25b).—To a suspension of 7 g (0.0195 mol) of the above dione (**24b**) in 105 ml of AcOH was added with stirring 2.6 ml of concd H_2SO_4. After heating on a steam bath for 45 min the solution was cooled, poured into ice water, and neutralized with NaOH. The resulting solid was collected, washed (H_2O), and dried giving 6.73 g (100%) of solid, mp 203–206°. Recrystallization from 175 ml of benzene yielded 4.49 g of light yellow crystals, mp 204–206°.

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.47; H, 5.69; N, 3.98.

1-(2-Hydroxy-4,6-dimethyl-3-pyridyl)-3-phenylpropane-1,3-dione[9] (24a).—This was prepared by a process similar to that used for **24b** above. The intermediate 3-acetyl-4,6-dimethyl-2-pyridylbenzoate was distilled, bp 150° (0.05 mm), but was not highly pure. The dione **24a** was obtained in a 62% yield (mp 199–210°) from 3-acetyl-2-hydroxy-4,6-dimethylpyridine on neutralization of the basic solution. After recrystallization of 8.84 g from ethylene glycol monomethyl ether and then from a large volume of methanol 4.6 g of fluffy needles was recovered, mp 220–227° (Bonsall and Hill[9] report mp 220–226°).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.38; H, 5.82; N, 5.40.

5,7-Dimethyl-2-phenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one[9] (25a).—This was prepared by a process similar to that used for **25b** above. A yield of 72.5% of yellow-tan crystals after recrystallization from EtOH, mp 182.5–184.5° (Bonsall and Hill[9] report mp 182–184°).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.58. Found: C, 76.57; H, 5.29; N, 5.88.

Registry No.—1, 25957-01-1; 2, 25957-02-2; 3, 25957-03-3; 4, 25957-04-4; 5, 25957-05-5; 6, 25957-06-6; 7, 25957-07-7; 8, 25957-08-8; 9, 25957-09-9; 10, 25957-10-2; 11, 25957-11-3; 12, 25957-12-4; 13, 25957-13-5; 14, 25957-14-6; 15, 25957-15-7; 16, 25957-16-8; 17, 25957-17-9; 18, 25957-18-0; 19, 25957-19-1; 20, 25957-20-4; 21, 25957-21-5; 23b, 25957-22-6; 24a, 25957-24-8; 24b, 25957-25-9; 25b, 25957-26-0; 3-acetyl-2-hydroxy-6-methylpyridine, 25957-23-7; [(3-hydroxy-2-pyridyl)methylene]malonic acid, 25957-27-1.

Dianions Derived from Glutarimide, 3,5-Morpholinedione, and 3,5-Thiomorpholinedione as Useful New Synthetic Intermediates[1]

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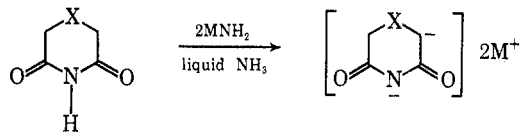
Glutarimide, 3,5-morpholinedione, and 3,5-thiomorpholinedione were converted to their respective dianions by means of slightly more than 2 mol equiv of sodium amide in liquid ammonia. Reactions of the dianions derived from glutarimide and 3,5-morpholinedione with alkyl halides and carbonyl compounds afforded α-substituted derivatives of the parent heterocycles. The dianion of 3,5-thiomorpholinedione gave a similar monosubstituted derivative on treatment with methyl benzoate but underwent a dicondensation reaction with benzophenone and polyalkylation with *n*-butyl bromide. Satisfactory monoalkylation at the α carbon of 3,5-thiomorpholinedione was accomplished when lithium amide was used to generate the dianion. Synthetically useful yields were obtained in a majority of the reactions of these new dianions.

Part A

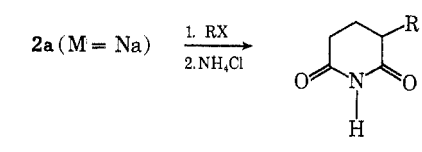
Conventional methods for introduction of substituents at one or both of the α carbons of glutarimide (**1a**), 3,5-morpholinedione (**1b**), and 3,5-thiomorpholinedione (**1c**) involve cyclization of appropriately substituted glutaric, diglycolic, and thiodiglycolic acid derivatives, respectively.[3] Such procedures require the preparation of a number of intermediates, with each member of a series requiring the synthesis of a separate acyclic precursor.

In the present study we have found that dianion **2a–c**,[4] prepared from **1a–c** by means of 2.3–2.4 mol equiv of alkali amide in liquid ammonia, can serve as convenient intermediates for the synthesis of a number of α-substituted derivatives of **1a–c** by virtue of their regiospecific reactions with electrophilic reagents.



1a, X = $-CH_2-$ **2a**, X = $-CH_2-$
b, X = $-O-$ **b**, X = $-O-$
c, X = $-S-$ **c**, X = $-S-$

Results with the Glutarimide Dianion (2a).—Alkylations of dianion **2a** (M = Na) with a series of primary halides produced monlsubstituted glutarimides of type **3** (Table I). Structural assignments for these compounds were based on nmr spectra (see Experimental Section), and acid-catalyzed hydrolysis to the appropriate 2-alkylglutaric acids in 80–90% yield.



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(2) Abstracted from the Ph.D. Thesis of T. G. R., Virginia Polytechnic Institute, Aug 1968.

(3) For examples of such a synthetic procedure as applied to glutarimide derivatives, see (a) T. Kametani, W. Taub, and D. Ginsburg, *Bull. Chem. Soc. Jap.*, **31**, 357 (1958). (b) T. Y. Yu and M. Y. Huang, *Hua Hsueh Hsueh Pao*, **25**, 146 (1959); *Chem. Abstr.*, **54**, 4564*i* (1960). (c) For examples of the synthesis of substituted 3,5-morpholinediones, see F. A. Baron and C. A. Vanderwerf, *J. Med. Chem.*, **10**, 276 (1967). (d) See G. S. Skinner and R. M. MacNair, *J. Org. Chem.*, **25**, 1164 (1960), and references cited therein for examples of the synthesis of substituted 3,5-thiomorpholinediones.

(4) See C. R. Hauser and D. R. Bryant, *J. Amer. Chem. Soc.*, **83**, 3468 (1961), and R. F. C. Brown, *Aust. J. Chem.*, **17**, 154 (1964), for what appear to be the only previous reports of dianions derived from cyclic imides.