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Substituted Benzopyranopyridine and Pyrimidine Ring Syntheses by the Ternary Condensation of Ethyl Cyanoacetate, Salicylaldehyde, and Certain Aldehydes in the Presence of Ammonium Acetate

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Various 1-substituted benzopyranopyridines were readily prepared by the condensation of ethyl cyanoacetate and salicylaldehyde (or 3-methoxysalicylaldehyde) with aliphatic aldehydes (propion, *n*-butyl, *n*- and isovaleraldehyde) in the presence of ammonium acetate. On the other hand, condensation with aromatic aldehydes such as benzaldehyde and *o*-, *m*-, or *p*-substituted benzaldehydes gave 2-aryl-benzopyranopyrimidines.

In a previous paper,[1] the synthesis of 2- or 1,2-disubstituted benzopyranopyridines by the condensation of ethyl cyanoacetate, salicylaldehyde, and ketones in the presence of ammonium acetate has been reported.

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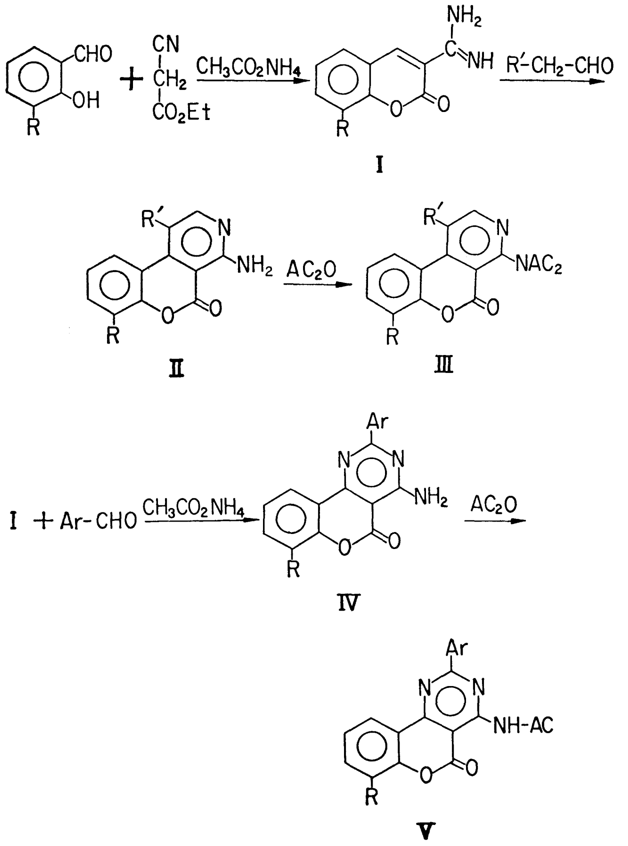
[1] A. Sakurai, H. Midorikawa, and Y. Hashimoto, This Bulletin, **43**, 2925 (1970).

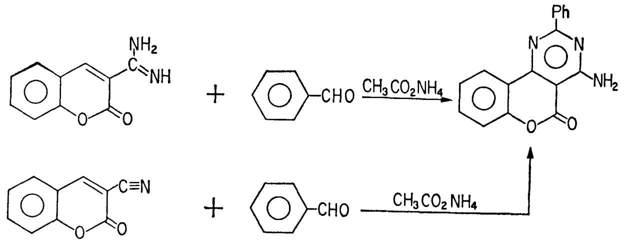
The present paper will deal with the syntheses of 1-alkylbenzopyranopyridines (from aliphatic aldehyde) and 2-arylbenzopyranopyrimidines (from aromatic aldehyde) by the reaction of ethyl cyanoacetate and salicylaldehyde or 3-methoxysalicylaldehyde with various aldehydes in the presence of ammonium acetate.

The reaction of ethyl cyanoacetate and salicylaldehyde or 3-methoxysalicylaldehyde with aliphatic aldehydes was carried out by refluxing a mixture of the ester, salicylaldehyde, aliphatic aldehyde, and ammonium acetate (molar ratio 1:1:1:1-1.5) in ethanol. In this case, the condensation of the amino group of 3-amidinocoumarin[1] (I) with the carbonyl group of the aldehyde, cyclization between the methylene group adjacent to the aldehyde carbonyl and the 4-position of the coumarin ring, and subsequent dehydrogenation took place to form 1-alkyl-4-amino-5-oxo-[1]-benzopyrano[3,4-*c*]pyridines (II).

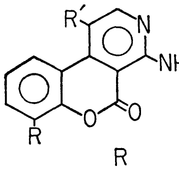


Scheme 1

However, when isobutyraldehyde was employed as the aldehyde reactant, the corresponding product of the type II was not obtained. The NMR spectrum (in CF_3CO_2H) of IIa (from propionaldehyde) showed only a methyl singlet at 2.9 ppm, while IIb (from *n*-butyraldehyde) showed a methyl triplet at 1.55 ppm and a methylene quartet at 3.35 ppm in a higher field than the aromatic-ring region. These facts indicated that the methylene group adjacent to the aldehyde carbonyl was involved in this cyclization. On the other hand, the condensation with aromatic aldehydes (benzaldehyde or its derivatives) gave 2-aryl-4-amino-5-oxo-[1]benzopyrano[4,3-*d*]pyrimidines (IV). In this case, 1 mol each of ethyl cyanoacetate, salicylaldehyde, and benzaldehyde (or its derivatives) reacted with 2 mol of ammonia to give IV, with the elimination of 1 mol of ethanol and 2 mol each of water and hydrogen. The compound IVa was also obtained by the condensation of 3-amidinocoumarin or 3-cyanocoumarin with benzaldehyde in the presence of ammonium acetate



Scheme 2



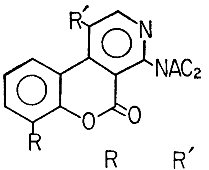
II

Table 1

1-Alkyl-4-amino-5-oxo-[1]benzopyrano[3,4-C]pyridine (II)

						Calcd,%			Found,%	
	R	R'	MP,°C	Yield,%	Formula	C	H	N	C	H	N

	R	R'	MP,°C	Yield,%	Formula	Calcd,% C	Calcd,% H	Calcd,% N	Found,% C	Found,% H	Found,% N
IIa	H	CH_3	221-222	34	$C_{13}H_{10}O_2N_2$	69.01	4.46	12.38	68.93	4.66	12.36
b	H	C_2H_5	207-209	19	$C_{14}H_{12}O_2N_2$	69.99	5.03	11.66	69.92	5.07	11.66
c	H	n-C_3H_7	186-187	20	$C_{15}H_{14}O_2N_2$	70.85	5.55	11.02	70.32	5.57	10.80
d	H	i-C_3H_7	176-177	5	$C_{15}H_{14}O_2N_2$	70.85	5.55	11.02	70.87	5.41	11.16
e	H	n-C_4H_9	173-174	20	$C_{16}H_{16}O_2N_2$	71.62	6.01	10.44	71.74	5.93	10.42
f	OCH_3	CH_3	212-215	35	$C_{14}H_{12}O_3N_2$	65.62	4.72	10.93	65.37	4.50	10.96
g	OCH_3	C_2H_5	214-215	19	$C_{15}H_{14}O_3N_2$	66.65	5.22	10.37	66.40	5.24	10.30
h	OCH_3	n-C_3H_7	200-202	20	$C_{16}H_{16}O_3N_2$	67.59	5.67	9.85	67.57	5.69	9.71
i	OCH_3	i-C_3H_7	211-212	12	$C_{16}H_{16}O_3N_2$	67.59	5.67	9.85	67.10	5.64	9.78
j	OCH_3	n-C_4H_9	181-182	19	$C_{17}H_{18}O_3N_2$	68.44	6.08	9.39	68.29	6.03	9.29



III

Table 2
1-Alkyl-4, 4-diacetamino-5-oxo-[1] benzopyrano [3,4-C] pyridine (III)

	R	R′	MP,°C	Yield,%	Formula	Calcd,% C	Calcd,% H	Calcd,% N	Found,% C	Found,% H	Found,% N
IIIa	H	CH_3	176–179	55	$C_{17}H_{14}O_4N_2$	65.80	4.55	9.03	65.50	4.64	9.21
b	H	C_2H_5	132–135	86	$C_{18}H_{16}O_4N_2$	66.66	4.97	8.64	66.96	5.02	8.86
c	H	n-C_3H_7	104–108	88	$C_{19}H_{18}O_4N_2$	67.44	5.36	8.28	67.66	5.28	8.42
d	OCH_3	CH_3	228–230	45	$C_{18}H_{16}O_5N_2$	63.52	4.74	8.23	63.40	4.69	8.37
e	OCH_3	C_2H_5	177–180	89	$C_{19}H_{18}O_5N_2$	64.40	5.12	7.91	64.48	5.33	8.05
f	OCH_3	n-C_3H_7	160–163	90	$C_{20}H_{20}O_5N_2$	65.21	5.47	7.61	65.54	5.52	7.92

TABLE 3. INFRARED SPECTRAL DATA FOR THE COMPOUNDS II

	ν NH_2	ν C=O	δ NH_2	Aromatic ring	δ CH
IIa	3430, 3270, 3150	1700	1625	1610, 1590, 1570, 1545	760
b	3420, 3260, 3130	1690	1620	1610, 1590, 1565, 1540	755, 745
c	3410, 3270, 3130	1700	1625	1610, 1590, 1570, 1545	765, 750
d	3420, 3260, 3120	1720	1630	1610, 1590, 1565, 1545	765, 750
e	3410, 3260, 3120	1700	1630	1610, 1570, 1550	770
f	3420, 3270, 3140	1695	1620	1610, 1590, 1570, 1550	780
g	3410, 3260, 3130	1700	1625	1610, 1590, 1570, 1550	785
h	3410, 3260, 3140	1695	1620	1610, 1570, 1545	785
i	3400, 3260, 3150	1695	1620	1610, 1590, 1565, 1540	780
j	3410, 3260, 3140	1700	1625	1610, 1590, 1570, 1550	785

TABLE 4. INFRARED SPECTRAL DATA[a] FOR THE COMPOUNDS III

	ν O-C=O	ν N-C=O	Aromatic ring	δ CH
IIIa	1725	1700,	1610, 1590, 1575, 1540	770
b	1735	1715, 1700	1600, 1590, 1570, 1540	770
c	1735	1720, 1695	1610, 1590, 1570, 1540	770
d	1725	1705	1610, 1590, 1575, 1545	785
e	1730	1685	1610, 1590, 1570, 1540	790, 785
f	1725	1695, 1680	1610, 1580, 1570, 1540	785

a) All spectra were taken in potassium bromide disks; cm^{-1}

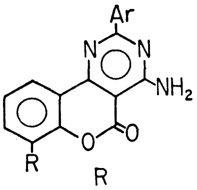
(Scheme 2).

The infrared spectra of IV revealed slightly lower shifted absorption bands for a primary amino group at about 3400 and 3300 cm^{-1} and at about 1700 cm^{-1} for a coumarin-type carbonyl group. This shows the presence of intramolecular $C=O\cdots H_2N$ bonding, as is shown in the compounds obtained by condensation with ketones.[1] When heated with acetic anhydride in pyridine, type IV compounds were converted to their corresponding monoacetylated derivatives (V). On

TABLE 5. NMR SPECTRAL DATA[a] FOR THE COMPOUNDS II AND III

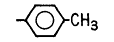
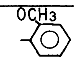
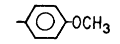
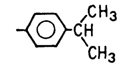
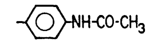
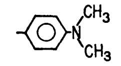
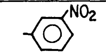
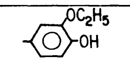
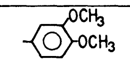
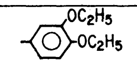
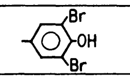
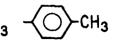
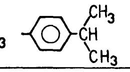
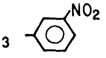
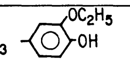
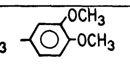
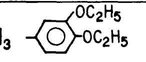
	CH_3	OCH_3	CH_2	$-\overset{\vert}{C}H-$	Ring -CH=
IIa	2.9 (s, 3H)				7.5–8.2 (m, 4H), 8.6–8.8(m, 5H)
b	1.55(t, 3H)		3.35(q, 2H)		7.5–8.8 (m, 5H)
c	1.2 (t, 3H)		1.9 (sx, 2H), 3.25 (t, 2H),		7.5–8.8 (m, 5H)
g	1.5 (t, 3H)	4.1 (s, 3H)	3.3 (q, 2H)		7.5–7.7, 8.0–8.3 (m, 2H each)
h	1.2 (t, 3H)	4.12(s, 3H)	1.95(sx, 2H), 3.25(t, 2H)		7.5–7.7, 8.0–8.3 (m, 2H each)
i	1.5 (d, 6H)	4.1 (s, 3H)		3.7–4.3(m, 1H)	7.4–7.8, 7.9–8.4 (m, 2H each)
IIIb	1.6 (t, 3H)	2.7 (s, 3H each)	3.5 (q, 2H)		7.5–8.1, 8.4–8.8 (m, 5H)
	2.4, 2.7 (s, 3H each)				

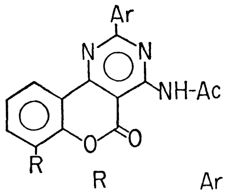
a) Parts per million downfield from tetramethylsilane in CF_3CO_2H; s=singlet, d=doublet, t=triplet, q=quartet, sx=sextet, m=multiplet the other hand, type II compounds gave diacetylated derivatives (III) under the same reaction conditions. In the infrared spectra of III, carbonyl stretching bands shifted to frequencies higher by from 20 to 30 cm^{-1} than those of the compounds II. However, the carbonyl bands of V appeared in the region nearly the same as or slightly lower than those of the compounds IV, and the imino stretching band always appeared at 3250 cm^{-1}. These data, therefore, can reasonably be explained by the presence of intramolecular hydrogen bonding in the compounds II and IV.



IV

Table 6
2-Aryl-4-amino-5-oxo-[1]benzopyrano[4,3-d]pyrimidine (IV)

	R	Ar	MP, °C	Yield, %	Formula	Calcd, %			Found, %		
						C	H	N	C	H	N
IVa	H	Ph	266-268	20	$C_{17}H_{11}O_2N_3$	70.58	3.83	14.53	70.33	4.01	14.47
b	H		277-280	13	$C_{18}H_{13}O_2N_3$	71.27	4.32	13.86	71.06	4.10	13.68
c	H		211-213	8	$C_{18}H_{13}O_3N_3$	67.70	4.11	13.16	67.81	4.04	13.34
d	H		262-264	11	$C_{18}H_{13}O_3N_3$	67.70	4.11	13.16	67.77	4.12	13.11
e	H		229-231	17	$C_{20}H_{17}O_2N_3$	72.49	5.17	12.68	72.36	4.98	12.56
f	H		318-321	17	$C_{19}H_{14}O_3N_4$ $1\frac{1}{2}H_2O$	61.12	4.55	15.01	61.34	4.40	15.20
g	H		254-256	6	$C_{19}H_{16}O_2N_4$	68.66	4.85	16.86	68.42	4.51	16.89
h	H		254-257	25	$C_{17}H_{10}O_4N_4$	61.08	3.02	16.76	61.82	3.27	16.62
i	H		225-228	10	$C_{19}H_{15}O_4N_3$	65.32	4.33	12.03	65.14	4.27	11.98
j	H		247-248	12	$C_{19}H_{15}O_4N_3$	65.32	4.33	12.03	65.47	4.23	12.29
k	H		185-186	13	$C_{21}H_{19}O_4N_3$	66.83	5.07	11.14	66.80	4.55	11.18
l	H		322-324	13	$C_{17}H_9O_3N_3Br_2$	44.09	1.96	9.07	44.18	2.19	8.96
m	OCH_3	Ph	283-284	20	$C_{18}H_{13}O_3N_3$	67.70	4.11	13.16	67.43	3.97	13.06
n	OCH_3		263-265	15	$C_{19}H_{15}O_3N_3$	68.46	4.54	12.61	68.07	4.55	12.35
o	OCH_3		234-236	15	$C_{21}H_{19}O_3N_3$	69.79	5.30	11.63	69.50	5.11	11.48
p	OCH_3		300-303	40	$C_{18}H_{12}O_5N_4$	59.34	3.32	15.38	59.30	3.24	15.83
q	OCH_3		327-330	12	$C_{20}H_{17}O_5N_3$	63.32	4.52	11.08	62.52	4.24	11.59
r	OCH_3		251-253	28	$C_{20}H_{17}O_5N_3$	63.32	4.52	11.08	63.06	4.38	11.30
s	OCH_3		222-225	26	$C_{22}H_{21}O_5N_3$	64.85	5.20	10.31	64.91	5.17	10.46



V

Table 7
2-Aryl-4-acetamino-5-oxo-[1]benzopyrano [4,3-d] pyrimidine (V)

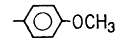
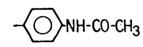
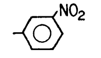
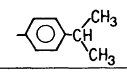
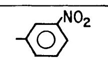
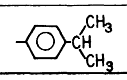
	R	Ar	MP,°C	Yield,%	Formula	Calcd,% C	Calcd,% H	Calcd,% N	Found,% C	Found,% H	Found,% N
Va	H	Ph	252-253	87	$C_{19}H_{13}O_3N_3$	68.87	3.96	12.68	68.80	3 48	12.78
b	H		257-260	88	$C_{20}H_{15}O_4N_3$	66.47	4.18	11.63	66.44	4 23	11.53
c	H		330-332	77	$C_{21}H_{16}O_4N_4$	64.94	4.15	14.43	64.22	4.51	14.48
d	H		260-263	88	$C_{19}H_{12}O_5N_4$	60.64	3 21	14.89	59.95	3.45	15.05
e	H		235-237	89	$C_{22}H_{19}O_3N_3$	70.76	5.13	11.25	70.79	4.99	11.45
f	OCH_3	Ph	267-268	70	$C_{20}H_{15}O_4N_3$	66.47	4.18	11.63	66.19	4.45	11.75
g	OCH_3		303-305	89	$C_{20}H_{14}O_6N_4$	59.11	3.47	13.79	58.69	3.71	13.85
h	OCH_3		238-239	91	$C_{23}H_{21}O_4N_3$	68.47	5.25	10.42	68.94	5.21	10.60

TABLE 8. INFRARED SPECTRAL DATA[a)] FOR THE COMPOUNDS IV

	ν NH_2	ν C=O	δ NH_2	Aromatic ring	δ CH
IVa	3480, 3360	1705	1630	1615, 1595, 1555, 1535	765, 700
b	3430, 3330	1695	1630	1615, 1605, 1580, 1550, 1540	825, 770
c	3400, 3260	1710		1615, 1600, 1555, 1540	770, 765
d	3430, 3330	1695	1625	1615, 1600, 1580, 1540	830, 775
e	3430, 3330	1695	1625	1610, 1575, 1550, 1535	825, 775, 770
f	3420, 3290, 3200	1710, 1680	1640	1615, 1600, 1550, 1530	825, 775
g	3420, 3345	1700	1625	1615, 1600, 1565, 1545	820, 775
h	3450, 3340	1705	1625	1610, 1600, 1555, 1545	770, 750, 710
i	3470, 3410, 3290	1690	1625	1615, 1605, 1555, 1540, 1520	825, 765
j	3420, 3290	1705	1630	1615, 1605, 1590, 1555, 1540	820, 770
k	3420, 3300	1700	1630	1615, 1605, 1585, 1555, 1540	815, 770
l	3480, 3380	1705	1625	1610, 1590, 1560, 1535,	770
m	3510, 3370	1700		1615, 1595, 1555, 1535	785, 740
n	3450, 3340	1715	1630	1615, 1565, 1540	825, 795
o	3470, 3350	1715	1620	1610, 1565, 1555, 1535	830, 800
p	3430, 3350	1715	1620	1610, 1565, 1555, 1535	790, 750
q	3460, 3330	1695	1630	1615, 1605, 1570, 1540	790, 735
r	3420, 3290	1705	1635	1600, 1570, 1540, 1525	795
s	3430, 3310	1700	1625	1615, 1600, 1585, 1565, 1535	790

a) All spectra were taken in potassium bromide disks; cm^{-1}

TABLE 9. INFRARED SPECTRAL DATA FOR THE COMPOUNDS V

	ν NH	ν O-C=O, NH-C=O	Aromatic ring	δ CH
Va	3250	1700, 1685	1610, 1600, 1590, 1570, 1550	765, 700
b	3250	1680	1610, 1600, 1590, 1570, 1545, 1520	825, 780
c	3360, 3250	1700, 1680	1615, 1600, 1580, 1550, 1530	830, 775
d	3250	1700, 1690	1610, 1590, 1575, 1550, 1535	830, 780, 770
f	3250	1695, 1685	1615, 1605, 1590, 1580, 1555	795, 750
g	3250	1690	1610, 1590, 1580, 1555, 1530	805, 745, 705

TABLE 10. NMR SPECTRAL DATA[a)] FOR THE COMPOUNDS IV AND V

	CH_3	OCH_3	CH_2	$-\overset{\vert}{C}H-$	Ring -CH=	NH
IVa					7.55–8.9(m, 10H)	9.75(br, 1H)
c		4.4 (s, 3H)			7.2–8.3, 8.7–8.9(m, 9H)	9.48(br, 1H)
d		4.05(s, 3H)			7.15–8.7(m, 9H)	9.6 (br, 1H)
e	1.35(d, 6H)			2.75–3.4(m, 1H)	7.5–8.8(m, 8H)	8.5, 9.6(s, 1H each)
f	2.52(s, 3H)				7.6–8.8(m, 9H)	9.3, 9.7(s, 1H each)
g	3.6 (s, 6H)				7.6–8.1, 8.5–8.8(m,9H)	9.8 (br, 1H)
j		4.12(d, 6H)			7.2–8.8(m, 8H)	9.65(br, 1H)
k	1.55(t, 6H)	4.4 (q, 4H)			7.1–8.8(m, 8H)	9.6 (br, 1H)
m		4.1 (s, 3H)			7.4–8.3(m, 8H)	8.45, 9.5(br, 1H each)
o	1.35(d, 6H)	4.1 (s, 3H)		2.7–3.4(m, 1H)	7.4–7.8, 8–8.4(m, 7H)	8.45, 9.6(br, 1H each)
r		4.1 (s, 9H)			7.2–8.2(m, 6H)	8.6, 9,6(br, 1H each)
s	1.6 (t, 6H)	4.15(s, 3H)	4.45(q, 4H)		7.1–8.7(m, 7H)	9.65(br, 1H)
Va	2.73(s, 3H, CO–CH_3)				7.5–8.95(m, 9H)	12.22(br, 1H)
e	1.4(d, 6H)2.7 (s, 3H, CO–CH_3)			2.8–3.4(m, 1H)	7.5–9(m, 8H)	12.25(br, 1H)
f	2.74(s, 3H, CO–CH_3)	4.17(s, 3H)			7.6–8.6(m, 8H)	12.27(br, 1H)
h	1.4(d, 6H) 2.7(s, 3H, CO–CH_3)	4.1 (s, 3H)		2.8–3.4(m, 1H)	7.5–8.6(m, 7H)	12.2 (br, 1H)

a) Parts per million downfield from tetramethylsilane in CF_3CO_2H; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad

Experimental

All the melting points are uncorrected. The infrared spectra were determined by means of potassium bromide disks. The NMR spectra were determined in trifluoroacetic acid at 60 Mc, using tetramethylsilane as the internal standard. The chemical shifts are reported as parts per million downfield from TMS.

Reaction of Ethyl Cyanoacetate and Salicylaldehyde or 3-Methoxysalicylaldehyde with Aldehydes. A mixture of ethyl cyanoacetate (0.03 mol), salicylaldehyde or 3-methoxysalicylaldehyde (0.03 mol), aldehyde (0.03 mol), and ammonium acetate (0.04 mol) in ethanol (10 m*l*) was refluxed for 0.5—1.5 hr. A pale yellow crystalline matter precipitated out during the reaction. The experimental results and spectral data are summarized in Tables 1,3,5,6,8, and 10.

Reaction of 3-Amidinocoumarin (1) and Benzaldehyde. A mixture of 1 (2.82 g), benzaldehyde (1.59 g), and ammonium acetate (1.54 g) in ethanol (5 m*l*) was refluxed for 0.5 hr. A crystalline precipitate was formed during the reaction; this was collected, and washed with ethanol and then with water. Recrystallization from pyridine afforded 0.9 g of pale yellow crystals; mp 265—267°C. By their infrared spectra and the results of elemental analyses, this compound was identified with IVa.

Reaction of 3-Cyanocoumarin and Benzaldehyde. A mixture of 3-cyanocoumarin (2.55 g), benzaldehyde (1.59 g), and ammonium acetate (1.54 g) in pyridine (5 m*l*) was heated for 1 hr. The pale yellow crystals which precipitated were then recrystallized from pyridine to give 0.8 g of almost white crystals; mp 262—264°C. This compound was proved to be identical with IVa by a study of their infrared spectra.

Reaction of the II and IV Compounds and Acetic Anhydride. To a solution of II or IV (0.001 mol) dissolved in pyridine (3—5 m*l*), acetic anhydride (5—8 m*l*) was added, the mixture was then refluxed for 2—4 hr. After standing overnight at room temperature, the crystalline precipitate thus formed was washed with dilute methanol. The experimental results and spectral data are summarized in Tables 2,4,7,9, and 10.

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