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The Cyclization of Ethyl Cyanoacetate and Salicylaldehyde or 3-Methoxysalicylaldehyde with Ketones by Means of Ammonium Acetate

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Various substituted benz[*f*]isoquinolines were readily prepared by the condensation of ethyl cyanoacetate and salicylaldehyde or 3-methoxysalicylaldehyde with aliphatic ketones (acetone, diethyl ketone, methyl pentyl ketone, methyl isopentyl ketone, *etc.*) or aromatic ketones (acetophenone, *o*-hydroxyacetophenone, *m*-nitroacetophenone, propiophenone, *etc.*) in the presence of ammonium acetate. On the other hand, condensation with cyclic ketones such as cyclopentanone and cyclohexanone gave benz[*f*]cyclopent[*c*]isoquinolines and benzo[*k*]phenanthridines respectively.

Previous papers have shown that ethyl cyanoacetate condensed with ketones[1] (aliphatic methyl, aromatic, cyclic, and α,β-unsaturated) or aldehydes[2] (salicyl and 3-methoxysalicyl) in the presence of ammonium acetate to afford substituted pyridones, quinolines (from ketone), and benzo[*h*]quinazolines (from aldehyde).

The present paper will deal with the syntheses of 6-oxabenz[*f*]isoquinoline, 7-oxabenz[*f*]-2,3-dihydro-1*H*-cyclopent[*c*]isoquinoline, and 8-oxa-1,2,3,4-tetrahydrobenzo[*k*]phenanthridine derivatives by the condensation of ethyl cyanoacetate, salicylaldehyde, or 3-methoxysalicylaldehyde, and a variety of ketones in the presence of ammonium acetate.

The reaction of ethyl cyanoacetate and salicylaldehyde or 3-methoxysalicylaldehyde with ketones was carried out by heating a mixture of ester, aldehyde, ketone, and ammonium acetate (molar ratio 1 : 1 : 1 : 1—1.5) in ethanol. In this case (Scheme 1), the dehydration of the amino group of I and the carbonyl group of ketone, cyclization between the methyl or methylene group of the ketone and the 4-position of the coumarin ring, and subsequent dehydrogenation took place to form 2- or 1,2-disubstituted-4-amino-5-oxo-6-oxabenz[*f*]isoquinolines (II).

When salicylaldehyde was heated with ethyl cyanoacetate and ammonium acetate in ethanol for few minutes, a crystalline product was obtained. Its infrared spectrum exhibited no characteristic absorption for a C≡N group. When dissolved in dilute hydrochloric acid, this substance afforded pale yellow needles. This compound was confirmed as the HCl salt of 3-amidinocoumarin (Ia) on the basis of elemental analysis and its infrared spectrum. Furthermore, when heated with ketones and ammonium acetate in ethanol, crude Ia gave compounds of the types II and V. The cyclization reaction in the present study, therefore, can reasonably be explained in terms of a two-step condensation. Ethyl cyanoacetate and salicylaldehyde condensed to give 3-cyanocoumarin, which in turn converts readily to 3-amidinocoumarin. Then, 3-amidinocoumarin condenses with ketones to give heterocyclic compounds of the types II, IV, and V. When 3-methoxysalicylaldehyde was used instead of salicylaldehyde, the condensation afforded the corresponding methoxy derivatives. The structural assignment of these products was based on the infrared and NMR spectra (Tables 3 and 5). For example, the NMR spectrum of IIa (prepared when acetone was employed as the ketone reactant) showed only a methyl singlet at 2.8 ppm corresponding to three protons in a higher field than the aromatic-ring region. This fact indicated that one methyl group of acetone was involved in this cyclization. In the infrared spectra of II, carbonyl and amino stretching bands shifted to slightly lower frequencies because of the presence of intramolecular C=O···H_2N bonding. The structure of the type II was further supported by the fact that the compound obtained by the condensation of 3-amidinocoumarin (Ia) and methyl *n*-propyl ketone in the presence of ammonium acetate was found to be

1) A. Sakurai and H. Midorikawa, This Bulletin, **40**, 1680 (1967).

2) A. Sakurai and H. Midorikawa, *J. Org. Chem.*, **34**, 3612 (1969).

Table 1. 4-Amino-5-oxo-6-oxabenz[*f*]isoquinoline derivatives and related compounds

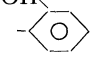
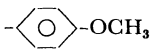
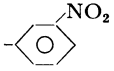
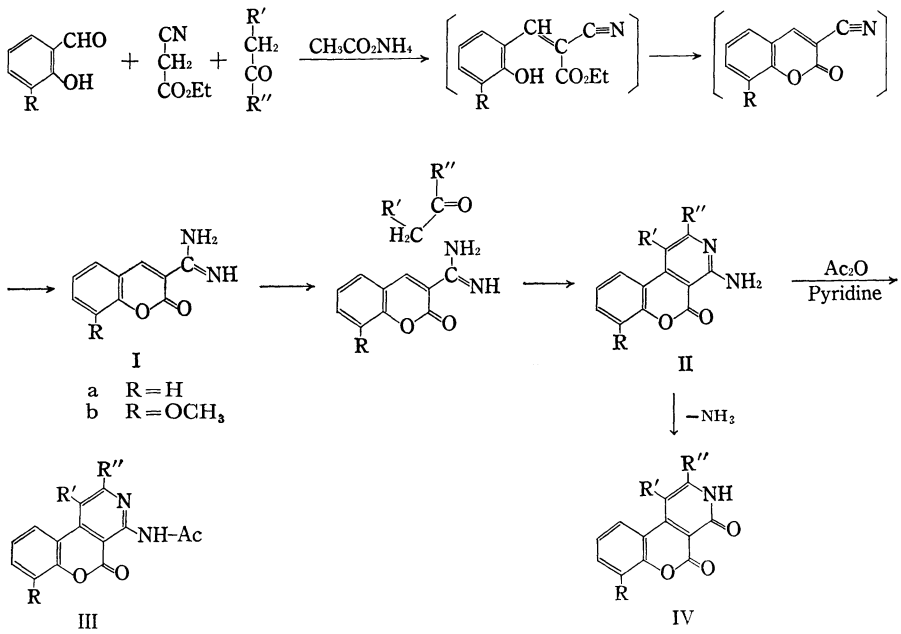
Compd.	R	R′	R″	Mp, °C	Yield, %	Formula	Calcd, %			Found, %		
							C	H	N	C	H	N
IIa	H	H	CH_3	241—242	33	$C_{13}H_{10}O_2N_2$	69.01	4.46	12.38	68.92	4.56	12.44
b	H	H	C_2H_5	171—173	13	$C_{14}H_{12}O_2N_2$	69.99	5.03	11.66	70.02	4.82	11.81
c	H	H	*n*-C_3H_7	173—174	24	$C_{15}H_{14}O_2N_2$	70.85	5.55	11.02	71.22	5.57	10.94
d	H	H	iso-C_3H_7	145—147	18	$C_{15}H_{14}O_2N_2$	70.85	5.55	11.02	70.58	5.34	11.03
e	H	H	*n*-C_4H_9	147—148	22	$C_{16}H_{16}O_2N_2$	71.62	6.01	10.44	71.56	5.89	10.57
f	H	H	*s*-C_4H_9	118—120	9	$C_{16}H_{16}O_2N_2$	71.62	6.01	10.44	71.74	5.89	10.44
g	H	H	iso-C_4H_9	155—156	27	$C_{16}H_{16}O_2N_2$	71.62	6.01	10.44	71.48	5.73	10.51
h	H	H	*n*-C_5H_{11}	143—145	24	$C_{17}H_{18}O_2N_2$	72.32	6.43	9.92	72.16	6.27	10.06
i	H	H	iso-C_5H_{11}	149—151	23	$C_{17}H_{18}O_2N_2$	72.32	6.43	9.92	72.15	6.50	9.73
j	H	H	*n*-C_9H_{19}	103—105	10	$C_{21}H_{26}O_2N_2$	74.52	7.74	8.28	74.12	7.55	8.08
k	OCH_3	H	CH_3	233—234	42	$C_{14}H_{12}O_3N_2$	65.62	4.72	10.93	65.47	4.75	11.00
l	OCH_3	H	C_2H_5	186—189	10	$C_{15}H_{14}O_3N_2$	66.65	5.22	10.37	66.83	5.03	10.47
m	OCH_3	H	*n*-C_3H_7	210—212	23	$C_{16}H_{16}O_3N_2$	67.59	5.67	9.85	67.80	5.58	9.86
n	OCH_3	H	*n*-C_4H_9	182—184	26	$C_{17}H_{18}O_3N_2$	68.44	6.08	9.39	68.51	5.89	9.52
o	OCH_3	H	iso-C_4H_9	195—197	33	$C_{17}H_{18}O_3N_2$	68.44	6.08	9.39	68.31	6.11	9.28
p	OCH_3	H	*n*-C_5H_{11}	174—176	30	$C_{18}H_{20}O_3N_2$	69.21	6.45	8.97	69.00	6.23	9.12
q	OCH_3	H	iso-C_5H_{11}	185—187	26	$C_{18}H_{20}O_3N_2$	69.21	6.45	8.97	69.01	6.08	8.97
r	H	CH_3	CH_3	218—220	7	$C_{14}H_{12}O_2N_2$	69.99	5.03	11.66	70.10	5.17	11.75
s	H	CH_3	C_2H_5	167—169	15	$C_{15}H_{14}O_2N_2$	70.85	5.55	11.02	71.04	5.26	10.91
t	H	CH_3	*n*-C_4H_9	163—166	13	$C_{17}H_{18}O_2N_2$	72.32	6.43	9.92	72.40	6.25	10.05
u	OCH_3	CH_3	CH_3	225—228	8	$C_{15}H_{14}O_3N_2$	66.65	5.22	10.37	66.38	5.06	10.26
v	H	H		300—302	32	$C_{18}H_{12}O_3N_2$	71.04	3.98	9.21	71.00	3.83	9.44
w	H	H		263—266	48	$C_{18}H_{11}O_4N_3$ 1/2 H_2O	63.15	3.51	12.28	62.94	3.71	11.91
x	H	H	$-(CH_2)_2-Ph$	169—171	40	$C_{20}H_{16}O_2N_2$	75.93	5.10	8.86	75.65	4.85	8.90
y	OCH_3	H	$-(CH_2)_2-Ph$	183—185	29	$C_{21}H_{18}O_3N_2$	72.82	5.24	8.09	72.70	5.13	8.20
z	H	CH_3	Ph	242—243	17	$C_{19}H_{14}O_2N_2$	75.48	4.67	9.29	75.22	4.80	9.29
IVa	OCH_3	H	iso-C_4H_9	272—273	7	$C_{17}H_{17}O_4N$	68.21	5.73	4.68	68.01	5.74	4.66
b	H	H	Ph	272—273	38	$C_{18}H_{11}O_3N$	74.73	3.83	4.84	74.33	3.93	4.83
c	OCH_3	H	Ph	303—304	42	$C_{19}H_{13}O_4N$	71.47	4.10	4.39	71.26	4.33	4.55
d	H	H		299—301	35	$C_{19}H_{13}O_4N$	71.47	4.10	4.39	71.27	4.18	4.39
Va	H	$n=1$		249—251	20	$C_{15}H_{12}O_2N_2$	71.41	4.80	11.11	71.73	4.55	11.50
b	H	$n=2$		228—230	18	$C_{16}H_{14}O_2N_2$	72.16	5.30	10.52	72.50	5.39	10.65
c	OCH_3	$n=1$		255—257	30	$C_{16}H_{14}O_3N_2$	68.07	5.00	9.92	68.20	4.97	9.69
d	OCH_3	$n=2$		239—241	21	$C_{17}H_{16}O_3N_2$	68.90	5.44	9.45	68.66	5.34	9.15

Table 2. 4-Acetamino-5-oxo-6-oxabenz[*f*]isoquinoline derivatives and related compounds

Compd.	R	R′	R″	Mp, °C	Yield, %	Formula	Calcd, %			Found, %		
							C	H	N	C	H	N
IIIa	H	H	CH_3	253—255	64	$C_{15}H_{12}O_3N_2$	67.15	4.51	10.44	67.29	4.42	10.58
b	H	H	C_2H_5	200—203	42	$C_{16}H_{14}O_3N_2$	68.07	5.00	9.92	68.39	4.76	10.03
c	H	H	*n*-C_3H_7	216—217	64	$C_{17}H_{16}O_3N_2$	68.90	5.44	9.45	69.14	5.32	9.70
d	H	H	iso-C_3H_7	191—193	69	$C_{17}H_{16}O_3N_2$	68.90	5.44	9.45	69.00	5.33	9.51
e	H	H	*n*-C_4H_9	207—209	87	$C_{18}H_{18}O_3N_2$	69.66	5.85	9.03	69.51	5.76	8.96
f	H	H	*s*-C_4H_9	187—188	60	$C_{18}H_{18}O_3N_2$	69.66	5.85	9.03	69 71	5 85	9.24
g	H	H	iso-C_4H_9	224—226	87	$C_{18}H_{18}O_3N_2$	69.66	5.85	9.03	69.50	5.73	9.04
h	H	H	iso-C_5H_{11}	202—204	72	$C_{19}H_{20}O_3N_2$	70.35	6.22	8.64	69.99	5.99	8.44
i	OCH_3	H	CH_3	273—275	65	$C_{16}H_{14}O_4N_2$	64.42	4.73	9.39	64.29	4.89	9.43
j	OCH_3	H	*n*-C_4H_9	235—237	73	$C_{19}H_{20}O_4N_2$	67.04	5.92	8.23	66.87	5.84	8.22
k	OCH_3	H	*n*-C_5H_{11}	219—221	88	$C_{20}H_{22}O_4N_2$	67.78	6.26	7.91	67.52	6.02	7.97
l	OCH_3	H	iso-C_5H_{11}	229—231	88	$C_{20}H_{22}O_4N_2$	67.78	6.26	7.91	67.53	6.11	8.02
m	H	CH_3	CH_3	210—213	64	$C_{16}H_{14}O_3N_2$	68.07	5.00	9.92	67.93	5.24	9.97
n	H	CH_3	C_2H_5	205—208	70	$C_{17}H_{16}O_3N_2$	68.90	5.44	9.45	68.78	5.42	9.59
o	H	CH_3	*n*-C_4H_9	169—172	65	$C_{19}H_{20}O_3N_2$	70.35	6.22	8.64	70.45	6.30	8.72
p	H	H		231—233	67	$C_{22}H_{16}O_5N_2$	68.03	4.15	7.21	67.79	3.97	7.19
q	H	H		305—307	92	$C_{20}H_{13}O_5N_3$	64.00	3.49	11.20	64.33	3.80	11.60
VIa	H	$n=1$		229—232	74	$C_{17}H_{14}O_3N_2$	69.39	4.80	9.52	69.78	4.78	9.23
b	H	$n=2$		241—242	65	$C_{18}H_{16}O_3N_2$	70.11	5.23	9.09	69.95	5.04	9.17



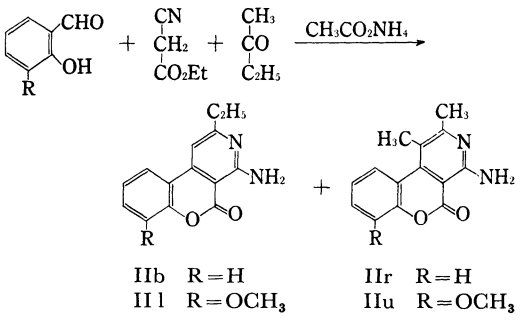
Scheme 1

identical with IIc by a comparison of their melting points and by infrared and elemental analyses.

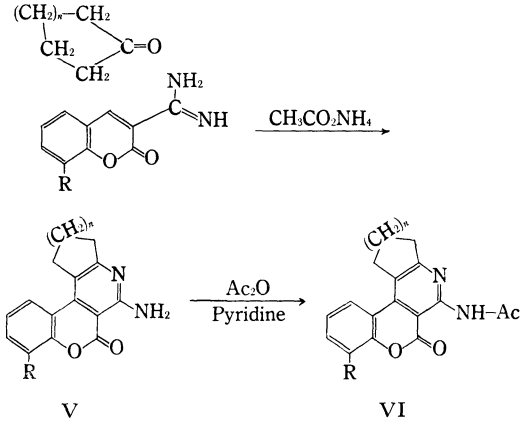
The reaction of ethyl cyanoacetate and 3-methoxysalicylaldehyde with methyl isobutyl ketone gave a mixture of 4-amino-2-isobutyl-7-methoxy-5-oxo-6-oxabenz[*f*]isoquinoline (IIo) as the main product, plus a small ammount of 2-isobutyl-7-methoxy-5-oxo-6-oxabenz[*f*]-1(2*H*)-isoquinolone (IVa). In the infrared spectrum of IVa, the carbonyl band (5-position) shifted to higher frequencies (1750 cm^{-1}) than that of IIo, and a new, strong band appeared at 1640 cm^{-1}. This band was characteristic of a pyridone- or quinolone-type carbonyl. When methyl ethyl ketone was employed as the ketone reactant, two products, melting at 173 and 218°C, were isolated. Their elemental analyses indicated the formula of $C_{14}H_{12}O_2N_2$. NMR spectrum of the former (mp 173°C) exhibited a triplet corresponding to three protons (CH_3) and a quartet corresponding to two protons (CH_2). On the other hand, the latter (mp 218°C) showed only a singlet corresponding to six protons (CH_3). On the basis of these data, it seemed reasonable to assume the two structures of IIb and IIr for them, as is indicated below. The ratio of the formation of IIb to IIr was about 1 : 0.5, while that of IIl to IIu was about 1 : 1 (Scheme 2).

Reaction with ketones such as methyl nonyl ketone or methyl *s*-butyl ketone gave products, but in poor yields. However, methyl *t*-butyl, di-*n*-propyl, diisopropyl, or diisobutyl ketones gave no corresponding compounds of the type II.

Reaction with cyclic ketones (Scheme 3) proceeded much as in the case of the reaction with the straight-chain ketones described above. In



Scheme 2



Scheme 3

Table 3. Infrared spectral data[a] for 4-amino-5-oxo-6-oxabenz[*f*]isoquinoline derivatives and related compounds

	νNH_2	$\nu C{=}O$	δNH_2	Aromatic ring	δCH
IIa	3420, 3265, 3120	1700	1630	1610, 1600, 1585, 1550	755
IIb	3420, 3260, 3120	1700	1630	1610, 1600, 1590, 1560	765
IIc	3420, 3280, 3130	1700	1630	1610, 1600, 1580, 1550	765
IId	3420, 3280, 3150	1705	1630	1615, 1580, 1550	760
IIe	3410, 3270, 3150	1705	1625	1610, 1600, 1580, 1545	760
IIf	3400, 3285, 3160	1710	1630	1615, 1600, 1580, 1550	770
IIg	3400, 3260, 3130	1695	1630	1610, 1600, 1585, 1550	765
IIh	3400, 3260, 3130	1700	1625	1610, 1600, 1580, 1545	775
IIi	3410, 3270, 3140	1690	1630	1610, 1600, 1580, 1550	760
IIj	3410, 3270, 3140	1695	1630	1610, 1600, 1585, 1550	760
IIk	3430, 3265, 3140	1705	1635	1625, 1590	790
III	3410, 3270, 3150	1695	1630	1610, 1585, 1550, 1495	785
IIm	3420, 3270, 3150	1690	1630	1615, 1585, 1550, 1550	790
IIn	3410, 3280, 3150	1725	1635	1615, 1585, 1555	780
IIo	3410, 3270, 3150	1695	1625	1615, 1580, 1550, 1495	785, 780
IIp	3410, 3280, 3145	1700	1630	1610, 1580, 1550	788
IIq	3400, 3260, 3130	1700	1630	1615, 1590, 1555	780
IIr	3500, 3380	1680		1610, 1595, 1585, 1535	765
IIs	3500, 3380	1680		1610, 1590, 1580, 1555, 1535	765
IIt	3400, 3260, 3120	1700	1620	1610, 1590, 1550	765
IIu	3400, 3270, 3140	1685	1620	1605, 1580, 1550	790
IIv	3430, 3300	1705	1630	1615, 1600, 1585, 1550	760, 750
IIw	3440, 3360	1700		1610, 1600, 1580, 1525, 1530, 1350 (νNO_2)	768, 755, 738
IIx	3410, 3270, 3150	1710	1630	1615, 1600, 1585, 1555, 1500	770, 760, 700
IIy	3410, 3280, 3150	1705	1630	1610, 1575, 1550	775, 750, 700
IIz	3410, 3270, 3150	1710	1630	1610, 1590, 1550, 1540	765, 710
IVa		1760, 1655		1610, 1595, 1540, 1490	790
IVb		1760, 1640		1615, 1590, 1540, 1510	755
IVc		1745, 1630		1610, 1590, 1575, 1540, 1505	770, 725, 695
IVd		1740, 1625		1610, 1590, 1575, 1535, 1520	825, 770
Va	3470, 3350	1675		1600, 1590, 1580, 1545	765
Vb	3420, 3260, 3130	1690	1620	1610, 1610, 1550	765
Vc	3400, 3260, 3130	1695	1625	1615, 1565, 1555	785
Vd	3430, 3260, 3130	1685	1620	1610, 1590, 1550	785

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

Table 4. Infrared spectral data[a] for 4-acetamino-5-oxo-6-oxabenz[*f*]isoquinoline derivatives and related compounds

	νNH	Ring C=O, NH-C=O	Aromatic ring	δCH
IIIa	3240	1695, 1665	1610, 1595, 1560, 1525	770
IIIb	3260	1700, 1675	1610, 1595, 1555	780
IIIc	3250	1700, 1665	1615, 1595, 1555, 1520, 1500	775
IIId	3250	1700, 1665	1615, 1590, 1550, 1520	770
IIIe	3250	1695, 1665	1615, 1595, 1555, 1520, 1500	775
IIIf	3250	1700, 1665	1615, 1595, 1550	765
IIIg	3250	1700, 1670	1615, 1595, 1550, 1515	775, 770
IIIh	3260	1700, 1670	1615, 1595, 1555, 1520	775
IIIi	3240	1700, 1670	1620, 1610, 1600, 1565	790
IIIj	3250	1700, 1670	1620, 1610, 1595, 1560, 1520	790
IIIk	3250	1695, 1665	1620, 1610, 1600, 1555, 1525	790
IIIm	3240	1675	1605, 1595, 1565, 1550, 1500	780
IIIn	3250	1675	1605, 1595, 1570, 1550, 1500	775
IIIo	3240	1670	1605, 1595, 1570, 1550, 1500	775
IIIp	3260	1760, (O-Ac) 1700, 1675	1610, 1595, 1550, 1520	770
IIIq	3240	1700, 1670	1610, 1595, 1530, 1520, 1550, 1350 (NO_2)	775
VIa	3230	1670	1605, 1595, 1570, 1550, 1500	765
VIb	3240	1700, 1670	1590, 1570, 1550	770

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

Table 5. NMR spectral data[a] for 4-amino-5-oxo-6-oxabenz[*f*]isoquinoline derivatives and related compounds

	CH_3	OCH_3	CH_2	-CH-	Ring -CH=	NH
IIa	2.8(s, 3H)				7.5—8.5(m, 6H)	8.9—9.7(br, 1H)
IIb	1.55(t, 3H)		3.1(q, 2H)		7.5—8.7(m, 7H)	8.9—9.6(br, 1H)
IIc[b]	1.02(t, 3H)		2.7(t, 2H) 1.8(sx, 2H)		7.0(s, 1H), 7.15—7.5(m, 5H) 7.85—8.1(m, 1H)	
IId[b]	1.35(d, 6H)			2.5—3.3(sp, 1H)	7.0(s, 1H), 7.15—7.7(m, 5H) 7.85—8.1(m, 1H)	
IIe	1.1(t, 3H)		1.4—2.2(m, 4H) 3.1(t, 2H)		7.4—8.4(m, 5H)	8.8—9.7(br, 1H)
IIf	1.13(t, 3H) 1.6(d, 3H)		1.95(qi, 2H)	3.1(sx, 1H)	7.4—8.4(m, 5H)	8.7—9.6(br, 1H) 11.65(br, 1H)
IIg	1.15(d, 6H)		2.9(d, 2H)	2.0—2.5(m, 1H)	7.4—8.4(m, 6H)	8.9—9.7(br, 1H)
IIh[b]	0.9(t, 3H)		1.2—2.0(m, 6H) 2.68(t, 2H)		6.9(s, 1H), 7.0—7.6(m, 5H) 7.75—8.0(m, 1H)	
IIk	2.8(s, 3H)	4.13(s, 3H)			7.5—8.0(m, 5H)	8.8—9.5(br, 1H)
IIl	1.55(t, 3H)	4.1(s, 3H)	3.08(q, 2H)		7.4—8.0(m, 5H)	
IIm	1.2(t, 3H)	4.1(s, 3H)	2.0(sx, 2H) 3.05(t, 2H)		7.3—8.1(m, 4H)	8.7—8.9(br, 1H)
IIo	1.15(d, 6H)	4.1(s, 3H)	2.9(d, 2H)	2.0—2.5(m, 1H)	7.4—8.1(m, 5H)	
IIr	2.8(s, 6H)				7.5—8.0(m, 4H)	8.5(br, 1H) 8.65(br, 1H)
IIs	1.55(t, 3H) 2.87(s, 3H)		3.17(q, 2H)		7.4—8.0(m, 3H), 8.55(d, 1H)	
IIt	1.1(t, 3H) 2.85(s, 3H)		1.4—2.2(br, 4H) 2.7—3.35(br, 2H)		7.4—8.0(m, 3H), 8.55(d, 1H)	
IIu	2.8(s, 6H)	4.1(s, 3H)			7.4—7.7(d, 2H), 8.0—8.2(t, 1H)	
IIw					7.5—9.0(m, 9H)	9.3—9.9(br, 1H)
IIx			3.3(t, 4H)		7.2—8.2(m, 10H)	8.9—9.5(br, 1H)
IIy		4.12(s, 3H)	3.3(t, 4H)		7.1—7.8(m, 9H)	8.9—9.6(br, 1H)
IIz	2.8(s, 3H)				7.5—8.1, 8.5—8.8(m, 9H)	
IVd		4.07(s, 3H)			7.2—8.6(m, 9H)	
Va			2.3—2.9(m, 2H) 3.1—3.9(m, 4H)		7.5—8.9(m, 5H)	10.9(s, 1H)
Vc		4.1(s, 3H)	2.3—2.8(m, 2H) 3.15—3.8(m, 4H)		7.5—7.7(d, 2H), 7.9—8.2(t, 1H)	
Vd		4.13(s, 3H)	1.8—2.3(br, 4H) 2.9—3.5(br, 4H)		7.53(d, 2H), 8.15(t, 1H)	

a) Parts per million downfield from tetramethylsilane in CF_3CO_2H; s=singlet, d=doublet, t=triplet, q=quartet, qi=quintet, sx=sextet, sp=septet, m=multiplet, br=broad. b) In $CDCl_3$ solution.

Table 6. NMR Spectral data[a] for 4-acetamino-5-oxo-6-oxabenz[*f*]isoquinoline derivatives and related compound

	CH_3	NH-CO-CH_3	OCH_3	CH_2	-CH-	Ring -CH=	NH
IIIa	2.98(s, 3H)	2.66(s, 3H)				7.5—8.5(m, 5H)	12.6(br, 1H)
IIIc	1.2(t, 3H)	2.67(s, 3H)		2.05(sx, 2H) 3.23(t, 2H)		7.5—8.5(m, 5H)	12.55(br, 1H)
IIId	1.6(d, 6H)	2.65(s, 3H)			3.5(sp, 1H)	7.4—8.5(m, 5H)	12.5(br, 1H)
IIIf	1.1(t, 3H) 1.6(d, 3H)	2.68(s, 3H)		2.0(qi, 2H)	3.3(sx, 1H)	7.5—8.5(m, 5H)	12.55(br, 1H)
IIIi	2.98(s, 3H)	2.66(s, 3H)	4.13(s, 3H)			7.5—8.0(m, 3H) 8.2(s, 1H)	12.55(br, 1H)
IIIn	1.65(t, 3H) 2.98(s, 3H)	2.67(s, 3H)		3.38(q, 2H)		7.5—8.6(m, 4H)	12.6(br, 1H)
IIIp		2.72(s, 3H) 2.45(O-CO-CH_3, s, 3H)				7.5—8.6(m, 9H)	12.67(br, 1H)
VIa		2.7(s, 3H)		2.3—2.9(m, 2H) 3.3—4.1(m, 4H)		7.2—8.1(m, 4H)	12.75(br, 1H)

a) Parts per million downfield from tetramethylsilane in CF_3CO_2H; s=singlet, d=doublet, t=triplet, q=quartet, qi=quintet, sx=sextet, sp=septet, m=multiplet, br=broad.

this case, cyclization occured between the methylene group adjacent to the carbonyl group of the ketone and the 4-position of the coumarin ring to form 5-amino-6-oxo-7-oxabenz[*f*]-2,3-dihydro-1*H*-cyclopent[*c*]isoquinoline (Va) (from cyclopentanone) and 6-amino-7-oxo-8-oxa-1,2,3,4-tetrahydrobenzo[*k*]phenanthridine (Vb) (from cyclohexanone). These structures were supported by a study of the infrared and NMR spectra (Tables 3 and 5). In addition, a product obtained by the condensation of Ia and cyclohexanone was identified with Vb. Reaction with methyl aryl ketones (Scheme 1) gave 4-amino-2-aryl-5-oxo-6-oxabenz[*f*]isoquinolines (IIv-y). On the other hand, the use of acetophenone or *p*-methoxyacetophenone as the ketone reactant afforded 2-aryl-5-oxo-6-oxabenz[*f*]-1(2*H*)-isoquinolones (IVb-d) as the main product under the same reaction conditions. The infrared spectra of IVb-d have strong bands at about 1750 and 1640 cm^{-1}. The former band shifted to frequencies higher by from 50 to 60 cm^{-1} than those of the compounds II. This fact shows the absence of intramolecular hydrogen bonding in the structure of the type IV, since the latter band (1640 cm^{-1}) can be attributed to the carbonyl group (4-position) of the quinolone type.

The reaction of ethyl cyanoacetate and salicylaldehyde with propiophenone gave 4-amino-1-methyl-5-oxo-2-phenyl-6-oxabenz[*f*]isoquinoline (IIz). The NMR spectrum revealed only a singlet corresponding to three protons (CH_3) in the high field. It is clear that the cyclization occurred between the methylene group of the ketone and the coumarin ring. The acetylation of the compounds of the types II and V, when treated with acetic anhydride in pyridine, afforded monoacetyl derivatives (III) and (VI) respectively (Table 2), while a diacetamino derivative was obtained from IIz under the same reaction conditions as produced those of the compounds III and VI.

Experimental

All the melting points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 521 grating spectrophotometer by means of potassium bromide pellets. The NMR spectra were obtained using a JNM-C-60 spectrometer; the peak positions are reported in δ values (parts per million downfield from tetramethylsilane).

Reaction of Ethyl Cyanoacetate and Salicylaldehyde. To a solution of ethyl cyanoacetate (4.52 g, 0.04 mol) and salicylaldehyde (4.88 g, 0.04 mol) in ethanol (5 m*l*), ammonium acetate (3.08 g, 0.04 mol) was added and heated for several minutes. The resulting crystals were filtered to give 4.8 g of crude 3-amidinocoumarin (Ia). When this crude Ia (3 g) was dissolved in dilute hydrochloric acid and allowed to stand at room temperature, pale yellow needles were formed. Recrystallization from ethanol afforded 1.5 g of 3-amidinocoumarin hydrochloride melting at 264—266°C (dec); ν_{max}^{KBr} 3390 (=NH), 3320, 3200 (NH_2), 1720 (C=O), 1670 (C=N), 1645 (δ NH_2), 1610, 1575, 1535 (ring); NMR {$(CD_3)_2SO$}, 7.4—8.0 (m, 4H, ring), 8.95 (s, 1H, ring), 9.6 ppm (br, 3H, NH_2 and =NH).

Found: C, 53.35; H, 4.01; N, 12.56; Cl, 16.20%. Calcd for $C_{10}H_8O_2N_2 \cdot HCl$: C, 53.46; H, 4.01; N, 12.47; Cl, 15.80%.

Reaction of Ethyl Cyanoacetate and 3-Methoxysalicylaldehyde. To a solution of ethyl cyanoacetate (2.26 g, 0.02 mol) and 3-methoxysalicylaldehyde (3.04 g, 0.02 mol) dissolved in ethanol (7 m*l*), ammonium acetate (1.51 g, 0.02 mol) was added. After the reaction mixture had been heated for several minutes, 3.4 g of 8-methoxy-3-amidinocoumarin (Ib) were obtained. When this crude Ib (1 g) was dissolved in dilute hydrochloric acid and allowed to stand at room temperature, a pale yellow precipitate was formed. It was then recrystallized from ethanol to afford 0.7 g of 8-methoxy-3-amidinocoumarin hydrochloride; mp 250°C (dec.).

Found: C, 51.53; H, 4.54; N, 10.87; Cl, 13.62%. Calcd for $C_{11}H_{10}O_3N_2 \cdot HCl$: C, 51.89; H, 4.32; N, 11.00; Cl, 13.92%.

Reaction of 3-Amidinocoumarin (Ia) and Methyl *n*-Propyl Ketone. A mixture of Ia (2 g), methyl *n*-propyl ketone (1 g), and ammonium acetate (1 g) in ethanol (3 m*l*) was heated for 1 hr. After cooling, the resulting precipitate was collected and recrystallized from ethanol-glacial acetic acid to give 1.1 g of colorless needles, mp 173—174°C, this substance was found to be identical with IIc by the elemental analyses and by a study of the infrared spectral data.

Reaction of 3-Amidinocoumarin (Ia) and Cyclohexanone. A mixture of Ia (2 g), cyclohexanone (1 g), and ammonium acetate (1 g) in ethanol (3 m*l*) was heated for 1 hr. A pale yellow crystalline matter precipitated out during the reaction; this was collected and recrystallized from glacial acetic acid to afford 0.8 g of pale yellow crystals, mp 225—227°C. This substance was proved to be identical with Vb by a study of their infrared spectra and by the results of elemental analyses.

Reaction of Ethyl Cyanoacetate and Salicylaldehyde or 3-Methoxysalicylaldehyde with Ketones. To a mixture of ethyl cyanoacetate (0.01 mol), salicylaldehyde or 3-methoxysalicylaldehyde (0.01 mol), and ketone (0.01 mol) in ethanol (3 m*l*), ammonium acetate (0.01—0.02 mol) was added, and the new mixture was refluxed for 0.5—2 hr. A crystalline compound precipitated out during the reaction or after the reaction mixture had been allowed to stand at room temperature. The experimental results and spectral data are summarized in Tables 1, 3, and 5. The molecular weight, as determined by means of high-resolution mass spectrometry, exhibited the following values: IIa, 226 (calcd for $C_{13}H_{10}O_2N_2$, 226.23), IIb, 240 (calcd for $C_{14}H_{12}O_2N_2$, 240.25), IId, 254 (calcd for $C_{15}H_{14}O_2N_2$, 254.27), IIr, 240 (calcd for $C_{14}H_{12}O_2N_2$, 240.25), IIs, 254 (calcd for $C_{15}H_{14}O_2N_2$, 254.27), Vb, 266 (calcd for $C_{16}H_{14}O_2N_2$, 266.29), IIv, 304 (calcd for $C_{18}H_{12}O_3N_2$, 304.29), IVb, 289 (calcd for $C_{18}H_{11}O_3N$, 289.28), IVd, 319 (calcd for $C_{19}H_{13}O_4N$, 319.3).

Acetylation of the Compounds II and V by Acetic Anhydride in Pyridine. To a solution of II or V (0.001 mol) dissolved in pyridine (2—4 m*l*), acetic anhydride (4—6 m*l*) was added, after which the

mixture was refluxed for 2—4 hr. After being cooled, the deposited precipitate was collected and washed with dilute methanol. The experimental results and spectral data are summarized in Tables 2, 4, and 6.

Acetylation of IIz. Acetic anhydride (7 m*l*) was added to a solution of IIz (0.5 g) dissolved in pyridine (4 m*l*), after which the mixture was refluxed for 4 hr. After cooling, ice water was added to the reaction mixture to afford a crystalline precipitate. The precipitate was collected, washed with cold dilute methanol, and dried. Recrystallization from glacial acetic acid gave 0.6 g of 4,4-diacetylamino-1-methyl-5-oxo-2-phenyl-6-oxabenz[*f*]isoquinoline, mp 205—207°C; ν_{max}^{KBr} 1740 (O–C=O), 1710, 1695 (CH_3–C=O), 1610, 1590, 1560, 1530 (hetero ring and phenyl), 775, 705 (δ CH); NMR (CF_3CO_2H) peaks at 2.35, 2.65 (s, 3H each, CO–CH_3), 3.0 (s, 3H, CH_3), 7.5—8.0 and 8.55—8.8 ppm (m, 9H, ring).

Found: C, 71.51; H, 4.75; N, 7.31%. Calcd for $C_{23}H_{18}O_4N_2$: C, 71.49; H, 4.70; N, 7.25%.

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