after washing and drying left 2.12 g (94%) of oil, which from ir and nmr evidence appeared to be a mixture of ketones **5** and **14**. A solution of 2.02 g of this mixture of ketones in 20 ml of ether was reduced with $LiAlH_4$ in the usual way to give 1.91 g (93%) of a solid showing hydroxyl but not carbonyl absorption in the ir. To 1.79 g of this solid was added 3.5 ml of bis(trimethylsilyl)-acetamide,[18] and the mixture was allowed to stand for 19 hr. The product was extracted into pentane, washed with water, and dried. There was recovered 2.22 g (82%) of a liquid showing no hydroxyl absorption in the ir. Vpc on column E gave a partial separation of these ethers into three components in the ratios 1:2:1. The third component was collected and shown to be homogeneous on reinjection. Hydrolysis of this ether in 2 *M* aqueous HCl followed by Jones oxidation[14] of the alcohol **15b** gave a single ketone (**5**). This was purified by vpc on column B and was identical with the photoproduct described above.

Registry No.—**1**, 33777-32-1; **3**, 33777-33-2; **5**, 33890-38-9; **12c**, 33780-85-7; **13e**, 14926-88-6.

Acknowledgments.—It is a pleasure to thank Mr. S. T. Bella for microanalyses, Miss Luz Catan for technical assistance, and Mr. Peter Ziegler for 220-MHz nmr spectra.

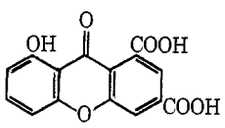
Synthesis of a Hydroxyxanthone Dicarboxylic Acid, Cassiaxanthone. Reactions of γ-Resorcylic Acid with Phenols

T. ARUNACHALAM, MARJORIE ANCHEL,* AND M. S. R. NAIR

The New York Botanical Garden, Bronx, New York 10458

Received August 27, 1971

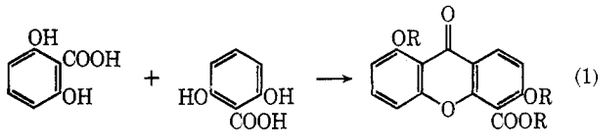
Cassiaxanthone (**1**)[1] and cassiolin (pinselin)[2] (**4h**) are, to our knowledge, the only xanthones from *Cassia*



1

species so far reported. It is interesting that these both have a carboxylic acid function on the xanthone nucleus. None of the other xanthones isolated from higher plants are of this type.[3]

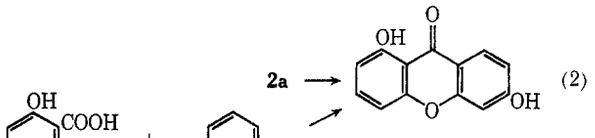
In the course of investigating possible routes to the synthesis of cassiaxanthone, γ-resorcylic acid was condensed with a number of phenols, using either polyphosphoric acid (PPA)[4] or $POCl_3$ and $ZnCl_2$.[5] These reactions generally afforded, besides or instead of the expected xanthone, a mixture of other products. We have examined this mixture and found that the main components are (a) 1,6-dihydroxyxanthone-5-carboxylic acid (**2a**) resulting from self-condensation (eq 1); (b) 1,6-dihydroxyxanthone resulting from self-condensation and subsequent decarboxylation or from condensation of γ-resorcylic acid with resorcinol resulting



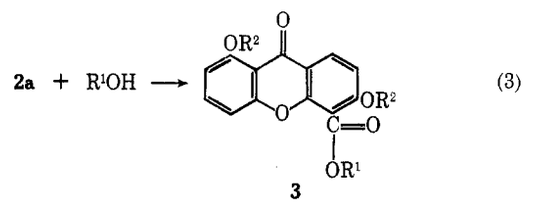
(1)

2a, R = H
b, R = Me

from decarboxylation (eq 2); (c) esters of **2a** (**3a**, **3c**, **3e**) (eq 3); and (d) polymeric products.



(2)



(3)

3

Compd	R^1	R^2
a	Phenyl	H
b	Phenyl	Me
c	3,5-Methylphenyl	H
d	3,5-Methylphenyl	Me
e	Ethyl	H
f	Ethyl	Me

The proportion of the various products obtained is shown in Table I. Most of the crude product (see last column), not accounted for in other columns, was an insoluble material which remained at the origin of a thin layer chromatogram, and is probably polymeric.

It is apparent that the temperature, the reagent, and the nature of the participating phenol all influence the results.

Attempted condensation of γ-resorcylic acid with phenol at lower temperatures yielded only a small amount of the expected product, 1-hydroxyxanthone. The two main products were the result of self-condensation of γ-resorcylic acid. One was 1,6-dihydroxyxanthone-5-carboxylic acid. The second was a compound of mp 196–197°. Preliminary examination suggested that this might be 1,8-dihydroxyxanthone formed by condensation ortho to both hydroxyl groups of resorcinol.[6] This possibility was ruled out by nmr spectrum which showed a peak at δ 8.41 for a proton peri to the xanthone carbonyl.

Clues to the structure of the compound were afforded by its ir spectrum and that of its methylation product, and by its mass spectrum. In the ir spectrum of the methylated product, in contrast to that of the parent compound, there was a peak at 1760 cm^{-1} suggesting the presence of a phenyl ester grouping, the carbonyl

(1) M. S. R. Nair, T. C. McMorris, and M. Anchel, *Phytochem.*, **9**, 1153 (1970).

(2) C. E. Moppett, *J. Chem. Soc. D*, 423 (1971).

(3) J. Carpenter, H. O. Locksley, and F. Scheinmann, *Phytochem.*, **8**, 2013 (1969).

(4) F. Uhlig and H. R. Snyder, *Advan. Org. Chem.*, **1**, 35 (1960).

(5) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 880.

(6) Analytical values for C, H, and O were in good agreement. The R_f was higher than that of 1,6-dihydroxyxanthone. Comparison of the melting point and uv spectrum with those reported in the literature[7-10] for samples prepared by a different method did not permit an unequivocal conclusion as to identity.

(7) A. Baeyer, *Justus Liebigs Ann. Chem.*, **372**, 80 (1910).

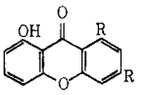
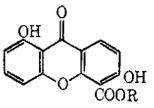
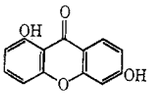
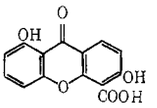
(8) D. L. Dreyer, Ph.D. Thesis, University of Washington, 1960. University Microfilms, Inc., Ann Arbor, Mich.

(9) P. Yates and G. H. Stout, *J. Amer. Chem. Soc.*, **80**, 1691 (1958).

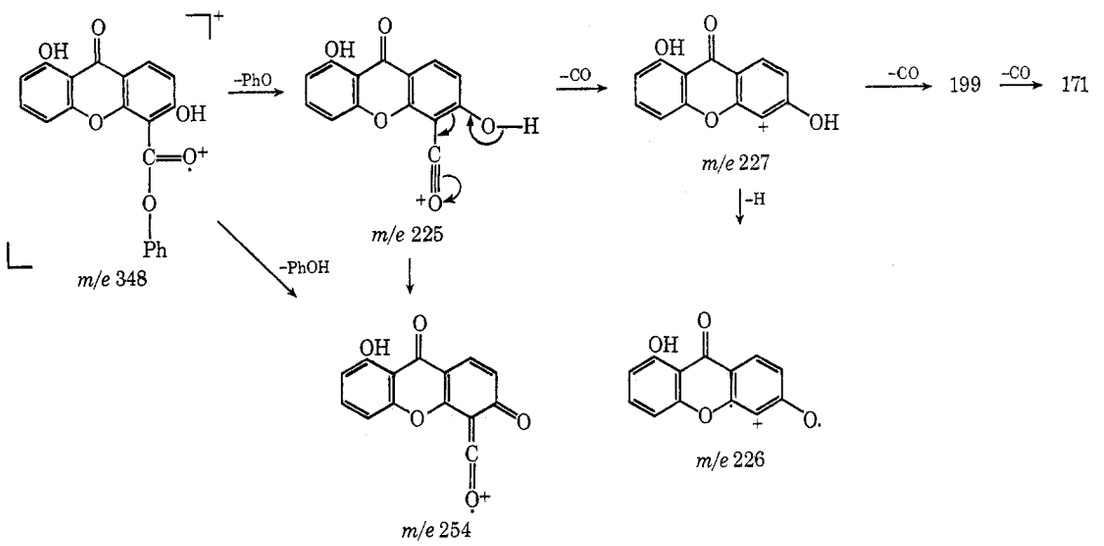
(10) O. R. Gottlieb, M. Taveira Magalhaes, M. Ottoni da Silva Pereira, A. A. Lins Mesquita, D. de Barros Correa, and G. G. De Oliveira, *Tetrahedron*, **24**, 1601 (1968).

TABLE I

YIELD OF PRODUCTS (g) FROM CONDENSATION OF γ-RESORCYLIC ACID (0.01 *M*, 1.54 g) WITH PHENOLS (0.01 *M*)

Phenol	Reagent (A, $POCl_3$–$ZnCl_2$; B, PPA)	Temp (°C), time (hr)	 R	g	 R	g	 g	 g	Wt of crude product, g
Phenol	A	30, 160	H	0.02	Ph	0.12	Trace	0.45	0.9
Phenol	A	60–80, 2	H	0.024	Ph	0.29	Trace	0.25	1.3
Phenol	A	100–110, 2							1.2
Xylenol	A	60–80, 2	Me	0.19	3,5-Dimethylphenyl	0.23	Trace	Trace	2.4
Resorcinol	A	60–80, 2					0.73		1.2
γ-Resorcylic acid	A	30, 160						1.85	2.2
γ-Resorcylic acid	A	60–80, 2					Trace	1.56	1.9
γ-Resorcylic acid	A	100–110, 2					Trace	Trace	1.6
Phenol	B	140, 4	H	0.035	Ph	Trace	0.23	Trace	0.64
Phenol	B	100, 5	H	0.025	Ph	0.015	0.175	0.035	0.52
Phenol	B	75, 5	H	0.02	Ph	0.155	0.065	0.110	0.45
Phenol	B	40, 5	H	0.01	Ph	Trace	Trace	0.155	0.34
Resorcinol	B	140, 4					0.75		1.2
γ-Resorcylic acid	B	140, 4					0.6	Trace	0.95
γ-Resorcylic acid	B	40, 7					0.04	0.8	0.98
Xylenol	B	140, 4	Me	0.85			0.115		1.3

SCHEME I



group of which was bonded to hydroxyl in the parent compound. The mass spectrum, M^+ 348, suggested that the compound might be **3a**, the phenyl ester of **2a**. The fragmentation pattern, peaks at *m/e* 348, 255, 254, 227, 226, 199, 171, and 94 was interpreted as shown in Scheme I. In confirmation of this formulation, hydrolysis yielded **2a** and phenol.

An analogous by-product in the reaction of γ-resorcylic acid with 3,5-dimethylphenol was **3c**. With resorcylic acid itself, besides the free acid **2a** and a polymeric product, a very small amount of the ethyl ester (**3e**) was obtained, presumably formed during the working up procedure which involved extraction with ethanol and chloroform.[11] The corresponding methylated products of **3a**, **3c**, and **3e** in each instance revealed the ester peak, not present in the ir spectrum of the parent compound.

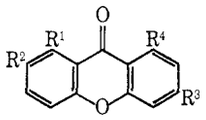
In general, at lower temperatures, larger proportions of **2a** or **3** were obtained, while at higher temperatures the product was mostly polymer or 1,6-dihydroxyxanthone. Evidently, high temperature favors decarboxylation either of the γ-resorcylic acid itself or of **2a**. When γ-resorcylic acid alone is subjected to condensing conditions, the main product at low temperature is **2a**, while at high temperatures it is polymer.

For the synthesis of cassiaxanthone, γ-resorcylic acid was condensed with 3,5-dimethylphenol. The reaction proceeded smoothly under the usual conditions[4,5] to give 1-hydroxy-6,8-dimethylxanthone (**4a**). The structure of this compound was confirmed by analysis and by spectral data. The uv absorption spectrum, max 232, 251, 286, 302, 358 nm, is typical of hydroxyxanthones[12] and resembles very closely that of 1-hydroxyxanthone itself.[13] The ir showed a peak at 1642 cm^{-1} for chelated

(11) The same product may well have been formed in the other reactions, but, since it has the same R_f as **2a** and **2b**, it could have gone undetected.

(12) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Macmillan, New York, N. Y., 1964, p 158.

(13) A. A. Lins Mesquita, D. DeBarros Correa, O. R. Gottlieb, and M. Taveira Magalhaes, *Anal. Chim. Acta*, **42**, 311 (1968).



4

Compd	R^1	R^2	R^3	R^4
a	OH	H	Me	Me
b	OMe	H	Me	Me
c	OMe	H	COHO	Me
d	OMe	H	COOH	COOH
e	OMe	H	COOMe	Me
f	OMe	H	COOMe	COOMe
g	OH	H	COOH	Me
h	COOMe	OH	Me	OH

carbonyl and the nmr showed signals at δ 2.35 and 2.77 for six methyl protons.

For oxidation, **4a** was converted to the methyl ether (**4b**). With $KMnO_4$ under suitable conditions, this afforded a mixture of the mono- and diacids (**4c** and **4d**) in good yield. Owing to poor solubility, the acid mixture could not be separated. Hence, it was esterified. The resulting mixture, separated by preparative tlc, yielded the mono- and diesters (**4e** and **4f**) in about equal amounts. The uv spectra of the esters showed the expected xanthone maxima. Both showed ester peaks in the ir at 1730 cm^{-1} and carbonyl absorption at 1675 and 1670 cm^{-1}, respectively. In the nmr, **4e** showed signals at δ 2.93 for three protons of the C_8 methyl group, 3.97 for three protons of the ester methyl group, and at 4.02 for three protons of the methoxyl carbon. The diester, **4f**, showed a signal at 3.98 for six protons of the methyl ester groups and at 4.05 for three methoxyl protons. It was identical in all respects (melting point, uv, ir, and R_f on tlc) with the completely methylated product prepared from cassiaxanthone.

Alkaline hydrolysis of **4e** and **4f** yielded the corresponding acids, **4c** and **4d**, in good yield. Treatment of **4e** and **4f** with HBr yielded the hydroxy acid **4g** and the hydroxy diacid **1** (cassiaxanthone), respectively. The synthetic product was identical with natural cassiaxanthone in all respects.

Experimental Section[14]

The following represent typical procedures. Data for the new compounds are reported at the end.

Condensation of γ-Resorcylic Acid with Phenols.—The reactions were carried out with either PPA or $POCl_3$–$ZnCl_2$ at a number of different temperatures.

Procedure A.—To a mixture of γ-resorcylic acid (1.54 g, 0.01 *M*), phenol (0.94 g, 0.01 *M*), and freshly fused and powdered anhydrous $ZnCl_2$ (4.5 g) was added $POCl_3$ (10.5 ml). The mixture was heated around 70° with stirring for 2 hr and then poured into crushed ice. The orange red solid (1.3 g) was dissolved in a minimum volume of 1:1 chloroform–ethanol and chromatographed over silica gel (40 g). Elution with benzene–Skelly-B gave 1-hydroxyxanthone: mp 148–149° (40 mg); uv max 229, 250, 279, 295, 335, 362 nm [lit. mp 147–148°;[15] uv max 230, 250, 282, 298 (sh), 362 nm[13]]. Elution with benzene followed by benzene–chloroform yielded **3a**, mp 196–197° (290 mg). The chloroform fraction furnished traces of 1,6-dihydroxyxanthone: mp 248°; uv max 229, 247, 265, 304, 352 nm (lit. mp 242–243°,[13] 248–250°;[8] uv max 231, 252, 265, 306, 353 nm[13]). Finally, elution with 25% methanol–chloroform yielded **2a**, mp 228–230° (250 mg).

When the reaction was carried out at higher temperatures, mostly polymeric product was obtained.

Procedure B.—A powdered mixture of 0.01 *M* γ-resorcylic acid (1.54 g) and phenol (0.94 g) was added to PPA (freshly prepared from 5 ml of H_3PO_4 and 8 g of P_2O_5), heated with stirring around 75° for 5 hr, and then poured into crushed ice. The brownish yellow solid (450 mg) was taken up in a minimum volume of ethanol–chloroform and chromatographed over silica gel (20 g). Elution with benzene gave 1-hydroxyxanthone (20 mg) and the benzene–chloroform fraction gave **3a** (155 mg). Further elution with chloroform yielded 1,6-dihydroxyxanthone (65 mg), and the chloroform–methanol (5:1) fraction furnished **2a** (110 mg).

Methylation.—Methylation of hydroxyxanthones, including **3a**, was carried out by refluxing with $(CH_3)_2SO_4$ and anhydrous K_2CO_3 in acetone for 12–15 hr. The methylated products were crystallized from ethanol or aqueous ethanol.

Hydrolysis.—On hydrolysis with 10% NaOH at room temperature, **3a** (45 mg) yielded **2a** (20 mg) and phenol (7 mg). Similarly, hydrolysis of **3c** (60 mg) furnished **2a** (30 mg) and 3,5-dimethylphenol (10 mg).

1,6-Dihydroxyxanthone-5-carboxylic Acid (2a).—**2a** was obtained as pale yellow crystals from acetone: mp 228–230°; uv max 225 nm (ε 17,000), 245 (sh) (18,300), 256 (20,000), 295 (8500), 310 (9500), and 355 (10,700); in 10% NaOH, uv max 240 (ε 21,000), 265 (19,000), 375 (15,500) nm; ir max 3500–2800 (bonded OH), 1675 (chelated COOH), 1647 (chelated C=O), 1608, 1481 (aromatic C=C), 1266, 1235, 1075, 1060 (=COC–), 813, 792, 715, 678 cm^{-1}; nmr (acetone-d_6 and DMSO-d_6) δ 6.77 (d, 1, J = 8.5 Hz, C_2 H), 6.93 (d, 1, J = 8.5 Hz, C_4 H), 7.03 (d, 1, J = 9 Hz, C_7 H), 7.58 (t, 1, J = 8.5 Hz, C_3 H), 8.18 (d, 1, J = 9 Hz, C_8 H).

Anal. Calcd for $C_{14}H_8O_6$: C, 61.77; H, 2.96; O, 35.27; mol wt, 272. Found: C, 61.58; H, 3.06; O, 35.46; mol wt, 273 (by depression of vapor pressure).

1,6-Dimethoxyxanthone-5-carboxylic Acid Methyl Ester (2b).—**2b** was obtained as white crystals from aqueous ethanol: mp 160°; uv max 225 nm (ε 34,000), 245 (sh) (29,000), 290 (19,000), 341 (13,400); ir max 1740 (ester C=O), 1665 (xanthone C=O), 1623, 1600, 1480 (aromatic C=C), 1290, 1272, 1242, 1105, 1071 (=COC–), 797 704, 684 cm^{-1}; nmr δ 3.97 (s, 3, $COOCH_3$), 4.02 (s, 6, Ar OCH_3), 6.79 (d, 1, J = 8.5 Hz, C_2 H), 6.97 (d, 2, J = 8.5 Hz, C_4 H and C_7 H), 7.57 (t, 1, J = 8.5 Hz, C_3 H), 8.35 (d, 1, J = 9 Hz, C_8 H).

Anal. Calcd for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49; O, 30.55. Found: C, 65.07; H, 4.56; O, 30.10.

1,6-Dihydroxyxanthone-5-carboxylic Acid Phenyl Ester (3a).—**3a** was obtained as pale yellow crystals from ethanol: mp 196–197°; uv max 225 nm (ε 27,800), 252 (28,000), 295 (11,700), 303 (11,750), 355 (10,600); ir max 3300–2700, 1653, 1613, 1600, 1587, 1481, 1261, 1235, 1072, 1058, 810, 788, 760, 750, 730, 718, 678 cm^{-1}; nmr δ 6.83 (d, 1, J = 9 Hz, C_2 H), 7.58 (t, 1, J = 8.5 Hz, C_3 H), 6.9–7.5 (m, 7, Ar H), 8.35 (d, 1, J = 9 Hz, C_8 H), 12.02 (s, 1, OH), 12.41 (s, 1, OH).

Anal. Calcd for $C_{20}H_{12}O_6$: C, 68.96; H, 3.47; O, 27.56; mol wt, 348. Found: C, 68.55; H, 3.44; O, 28.02; mol wt, 348 (by mass spectrum), 339 (by depression of vapor pressure).

The diacetate had mp 203–205°; nmr (DMSO-d_6) δ 2.33 (s, 3), 2.37 (s, 3), (2, $OCOCH_3$).

1,6-Dimethoxyxanthone-5-carboxylic Acid Phenyl Ester (3b).—**3b** was obtained as white crystals from aqueous ethanol: mp 208–210°; uv max 224 nm (ε 35,800), 245 (30,000), 290 (16,800), 342 (11,200); ir max 1760 (COOPh), 1667 (xanthone C=O), 1626, 1600, 1481 (aromatic C=C), 1290, 1275, 1242, 1108, 1067, 795, 747, 687 cm^{-1}; nmr δ 4.03 (s, 6, Ar OCH_3), 6.81 (d, 1, J = 9 Hz, C_2 H), 7.58 (t, 1, J = 8.5 Hz, C_3 H), 8.4 (d, 1, J = 9 Hz, C_8 H), 6.9–7.45 (m, 7, Ar H).

Anal. Calcd for $C_{22}H_{16}O_6$: C, 70.21; H, 4.29; O, 25.51; mol wt, 376. Found: C, 70.20; H, 4.25; O, 25.60; mol wt, 384 (by depression of vapor pressure).

1,6-Dihydroxyxanthone-5-carboxylic Acid 3,5-Dimethylphenyl Ester (3c).—**3c** was obtained as crystals from ethanol: mp 185–186°; uv max 225 nm (ε 27,400), 252, (27,500), 295 (12,200), 303 (12,450), 355 (11,800); ir max 1672 (chelated ester C=O), 1653 (xanthone C=O), 1613, 1580, 1480 (aromatic), 1238, 1075, 810, 762, 676 cm^{-1}; nmr δ 2.4 (s, 6, Ar CH_3), 6.76 (d, 1, J =

(14) All uv spectra were taken in ethanol on a Cary Model 11 spectrophotometer. The ir spectra were taken in KBr pellets on a Perkin-Elmer Model 21 spectrometer. The nmr spectra were recorded on a Varian A-60A spectrometer, using $CDCl_3$ as solvent (unless otherwise stated) and TMS as internal standard. The melting points were determined on a Kofler hot stage and are uncorrected.

(15) R. P. Mull and F. F. Nord, *Arch. Biochem.*, **4**, 419 (1944).

8.5 Hz, C_2 H), 6.8–7.1 (m, 5, Ar H), 7.53 (t, 1, J = 8.5 Hz, C_3 H), 8.35 (d, 1, J = 9 Hz, C_8 H), 12.05 (s, 1, OH), 12.38 (s, 1, OH).

Anal. Calcd for $C_{22}H_{16}O_6$: C, 70.21; H, 4.29; O, 25.51. Found: C, 70.20; H, 4.38; O, 25.57.

1,6-Dimethoxyxanthone-5-carboxylic Acid 3,5-Dimethylphenyl Ester (3d).—**3d** was obtained as crystals from aqueous ethanol: mp 235–236°; uv max 222 nm (ε 36,000), 245 (30,500), 290 (17,000), 341 (11,500); ir max 1754 (ester C=O), 1669 (xanthone C=O), 1623, 1605, 1480, 1290, 1274, 1242, 1103, 1072, 797, 681 cm^{-1}; nmr δ 2.37 (s, 6, Ar CH_3), 4.02 (s, 6, Ar OCH_3), 6.81 (d, 1, J = 9 Hz, C_2 H), 6.85–7.25 (m, 5, Ar H), 7.6 (t, 1, J = 8.5 Hz, C_3 H), 8.39 (d, 1, J = 9 Hz, C_8 H).

Anal. Calcd for $C_{24}H_{20}O_6$: C, 71.28; H, 4.99; O, 23.74. Found: C, 71.31; H, 5.05; O, 23.85.

1,6-Dihydroxyxanthone-5-carboxylic Acid Ethyl Ester (3e).—**3e** was obtained as crystals from ethanol: mp 160°; uv max 225 nm (ε 23,500), 243 (sh) (24,600), 254 (26,800), 295 (10,200), 304 (9800), 355 (9600); ir max 1660–1650 (chelated C=O), 1605, 1587, 1481, 1242, 1078, 1040, 812, 766, 678 cm^{-1}; nmr δ 1.53 (t, 3, J = 7 Hz, $COOCH_2CH_3$), 4.53 (q, 2, J = 7 Hz, $COOCH_2CH_3$), 6.6–7 (m, 3, C_2 H, C_4 H, and C_7 H), 7.52 (t, 1, J = 8.5 Hz, C_3 H), 8.26 (d, 1, J = 9 Hz, C_8 H), 12.4 (s, 2, OH).

Anal. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03; O, 31.97. Found: C, 63.74; H, 4.00; O, 32.19.

1,6-Dimethoxyxanthone-5-carboxylic Acid Ethyl Ester (3f).—**3f** was obtained as crystals from 1:1 ethyl acetate–petroleum ether (bp 60–70°): mp 187°; uv max 227 nm (ε 30,500), 245 (sh), (24,200), 290 (16,500), 341 (11,000); ir max 1737 (ester C=O), 1670, (xanthone C=O), 1626, 1605, 1575, 1481 (aromatic C=C), 1290, 1274, 1242, 1105, 1075, 1020, 793, 684 cm^{-1}; nmr δ 1.45 (t, 3, J = 7 Hz, $COOCH_2CH_3$), 3.98 (s, 3, Ar OCH_3), 4.02 (s, 3, Ar OCH_3), 4.53 (q, 2, J = 7 Hz, $COOCH_2CH_3$), 6.8 (d, 1, J = 8.5 Hz, C_2 H), 6.98 (d, 2, J = 9 Hz, C_4 H and C_7 H), 7.58 (t, 1, J = 8.5 Hz, C_3 H), 8.36 (d, 1, J = 9 Hz, C_8 H).

Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91; O, 29.24. Found: C, 65.81; H, 4.63; O, 29.83.

1-Hydroxy-6,8-dimethylxanthone (4a).—**4a** was obtained as light yellow crystals from ethanol: mp 179°; uv max 232 nm (ε 25,600) 251 (22,250), 286 (8400), 302 (8050), 358 (4400); ir max 1642, 1618, 1600, 1563, 1481, 1271, 1239, 1062, 901, 840, 780, 672 cm^{-1}; nmr δ 2.35 (s, 3, C_6 Me), 2.77 (s, 3, C_8 Me), 7.45 (t, 1, J = 8.5 Hz, C_3 H), 12.88 (s, 1, OH), 6.6–7.0 (m, 4).

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03; O, 19.98. Found: C, 74.61; H, 4.90; O, 20.35.

The acetate (Ac_2O, NaOAc, reflux) had mp 205°; nmr (DMSO-d_6) 2.46 (s, C_6 H) 2.48 (s, C_3 H).

1-Methoxy-6,8-dimethylxanthone (4b).—A mixture of **4a** (1.3 g), $(CH_3)_2SO_4$ (2 ml), and anhydrous K_2CO_3 (5 g) in acetone (100 ml) was refluxed for 12 hr, during which time the yellow color of the solution disappeared. The solvent was removed *in vacuo* and ice water was added to the residue. The white solid, filtered off and crystallized from ethanol, gave **4b** (1.1 g) as white crystals: mp 156°; uv max 240 nm (ε 39,000), 282 (12,700), 295 (11,550), 343 (7,600); ir max 1660, 1621, 1600, 1478, 1258, 1095, 1081, 1055, 952, 880, 841, 811, 777, 670 cm^{-1}; nmr δ 2.33 (s, 3, C_6 Me), 2.82 (s, 3, C_8 Me), 3.93 (s, 3, OCH_3), 6.63 (d, 1, J = 8.5 Hz, C_2 H), 6.74 (d, 2, J = 1.5 Hz, C_5 H), 6.82 (d, 1, J = 8.5 Hz, C_4 H), 6.89 (d, 1, J = 1.5 Hz, C_7 H), 7.38 (t, 1, J = 8.5 Hz, C_3 H).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55; O, 18.88. Found: C, 75.38; H, 5.48; O, 19.06.

A 130-mg sample of **4b**, heated in 3 ml of HBr at 110–120° for 5 hr, gave a quantitative yield of **4a**.

Oxidation of 1-Methoxy-6,8-dimethylxanthone.—Of the various reagents and conditions used to oxidize the CH_3 groups to COOH, only the following gave good yields:

To a refluxing solution of 4b (4.33 g) in *tert*-butyl alcohol (160 ml) and water (80 ml) was added a solution of 17 g of $KMnO_4$ in 170 ml of water dropwise, with stirring, over a period of 3–4 hr. The refluxing and stirring were continued until the purple color completely disappeared (4–5 hr). The mixture was cooled, acidified with 10% sulfuric acid, refluxed again for 20 min, cooled, and treated with $NaHSO_3$ to remove MnO_2. The pale yellow solid remaining was stirred with a saturated solution of $NaHCO_3$. The bicarbonate extract, acidified with concentrated HCl, yielded a mixture of acids (2.75 g).

For separation of the components, the mixture was esterified (10 ml of $(CH_3)_2SO_4$ and 12 g of anhydrous K_2CO_3 in 200 ml of acetone, refluxed 15 hr). The crude ester (2.9 g) showed two main spots on tlc. It was separated by preparative tlc (silica gel, Merck PF 254 (containing $CaSO_4$) using 1% methanol in chloroform as developer.

1-Methoxy-6-carbomethoxy-8-methylxanthone (4e).—The ester fraction with the higher R_f value (0.55) furnished **4e** (750 mg) as fluffy white crystals from ethanol: mp 183°; uv max 235 nm (ε 25,150), 245 (sh, 23,300), 255 (24,400), 285 (5780), 310 (8380), 355 (5030); ir max 1730, 1675, 1613, 1572, 1486, 1242, 1099, 1058, 1000, 970, 927, 885, 817, 772, 727, 679 cm^{-1}; nmr δ 2.93 (s, 3, C_8 Me), 3.97 (s, 3, $COOCH_3$), 4.02 (s, 3, Ar OCH_3), 6.77 (d, 1, J = 8.5 Hz, C_2 H), 6.99 (d, 1, J = 8.5 Hz, C_4 H), 7.58 (t, 1, J = 8.5 Hz, C_3 H), 7.7 (d, 1, J = 1.5 Hz, C_5 H), 7.88 (d, 1, J = 1.5 Hz, C_7 H).

Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73; O, 26.82. Found: C, 66.92; H, 5.08; O, 27.74.

This compound apparently is difficult to free of solvent. About 9% ethanol would account for the analytical results.

1-Methoxy-6,8-dicarbomethoxyxanthone (4f).—The ester fraction with the lower R_f value (0.25) yielded 1.05 g of **4f** as white crystals from ethanol: mp 239–240°; uv max 235 nm (ε 22,800), 260 (23,180), 286 (5700), 298 (5890), 310 (7130), 356 (5030); ir max 1730, 1670, 1608, 1570, 1477, 1235, 1092, 1080, 1018, 813, 775, 767, 760, 725, 722, 667 cm^{-1}; nmr δ 3.98 (s, 6, $CO-OCH_3$), 4.05 (s, 3, Ar OCH_3), 6.82 (d, 1, J = 8.5 Hz, C_2 H), 7.05 (d, 1, J = 8.5 Hz, C_4 H), 7.63 (t, 2, J = 8.5 Hz, C_3 H), 7.88 (d, 2, J = 1.5 Hz, C_5 H), 8.14 (d, 1, J = 1.5 Hz, C_7 H). This compound was identical in all respects (melting point, uv, ir, nmr, tlc) with that obtained by refluxing natural cassiaxanthone with $(CH_3)_2SO_4$ and anhydrous K_2CO_3 in acetone.

Anal. Calcd for $C_{18}H_{14}O_7$: C, 63.16; H, 4.12; O, 32.72. Found: C, 63.07; H, 4.02; O, 32.70.

When pyridine was used instead of *tert*-butyl alcohol as solvent, the yield of both mono- and diester was decreased.

1-Methoxy-8-methylxanthone-6-carboxylic Acid (4c).—Hydrolysis of **4e** (60 mg) with aqueous NaOH furnished the acid **4c** (35 mg) as white crystals from ethanol: mp 302–305°; uv max 235 nm (ε 25,700), 252 (25,250), 286 (6900), 309 (8500), 355 (5360); ir max 3300–2800, 1725, 1647, 1625, 1608, 1570, 1480, 1278, 1180, 1092, 1082, 1053, 946, 882, 815, 784, 750, 713, 670 cm^{-1}.

Anal. Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26; O, 28.14. Found: C, 66.93; H, 4.29; O, 28.27.

1-Methoxyxanthone-6,8-dicarboxylic Acid Cassiaxanthone Methyl Ether (4d).—Hydrolysis of **4f** (60 mg) with aqueous NaOH yielded the acid **4d** (30 mg) as crystals from acetic acid: mp 285–290° dec; uv max 235 nm (ε 23,700) 256 (22,900), 286 (5800), 308 (5900), 355 (5100); ir max 3250–2800, 1730, 1660, 1613, 1575, 1484, 1275, 1090, 1080, 880, 817, 774, 730, 670 cm^{-1}.

Anal. Calcd for $C_{16}H_{10}O_7$: C, 61.15; H, 3.21; O, 35.64. Found: C, 60.01, H, 3.38; O, 36.65.

The compound apparently holds solvent, even when dried *in vacuo* at 80°.

Anal. Calcd for $C_{16}H_{10}O_7 \cdot 0.25C_2H_4O_2$: C, 60.20; H, 3.37; O, 36.43.

1-Hydroxy-8-methylxanthone-6-carboxylic Acid (4g).—A mixture of **4e** (60 mg) and HBr (47–49%, 5 ml) was heated at 110–120° with stirring for 5 hr, cooled, and diluted with water. Yellow crystals from alcohol were obtained: 45 mg; mp 312–315°; uv max 235 nm (ε 26,650), 261 (28,350), 291 (6750), 316 (9500), 370 (5800); $uv_{max}^{EtOH-NaOH}$ 239 nm (ε 33,350), 268 (23,250) 314 (11,600), 322 (12,300), 400 (7560); ir max 3300–2800, 1710, 1653, 1613, 1565, 1475, 1235, 1212, 1058, 890, 817, 772, 767, 723, 682, 666 cm^{-1}.

Anal. Calcd for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73; O, 29.60. Found: C, 66.52; H, 3.76; O, 29.24.

1-Hydroxyxanthone-6,8-dicarboxylic Acid (1) (Cassiaxanthone).—The diester **4f** (60 mg) was heated with 2 ml of HBr at 110–120° for 5 hr, cooled, and diluted with H_2O. The product, a yellow solid, was crystallized from acetic acid, yielding 40 mg of cassiaxanthone as pale yellow crystals: mp 330–333°; uv max 235 nm (ε 27,100) 262 (28,500), 290 (7500), 314 (8000) (the peak at 314 nm was originally reported in error as being at 300 nm[1]); ir max 1704, 1653 (reported in error as 1635[1]), 1613, 1575, 1471, 1265, 1220, 1050, 995, 890, 813, 763, 730, 695, 672 cm^{-1}. The synthetic sample was identical in all respects (melting point, uv, ir) with that obtained from *Cassia reticulata*.

Anal. Calcd for $C_{15}H_8O_7$: C, 60.01; H, 2.69; O, 37.31. Found: C, 59.74; H, 2.71; O, 37.13.

Registry No.—**1**, 28917-02-4; **2a**, 33780-61-9; **2b**, 33777-15-0; **3a**, 33777-16-1; **3b**, 33777-17-2; **3c**, 33777-18-3; **3d**, 33777-19-4; **3e**, 33777-20-7; **3f**, 33777-21-8; **4a**, 33777-22-9; **4a** acetate, 33777-23-0; **4b**, 33777-24-1; **4c**, 33777-25-2; **4d**, 33777-26-3; **4e**, 33780-62-0; **4f**, 33780-63-1; **4g**, 33780-64-2.

Acknowledgments.—This work was supported by NIH Grants Al-00226 and FR 5 S01 RRO5621. The authors also wish to thank Dr. T. C. McMorris for helpful discussions.

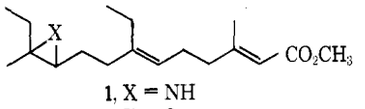
Synthesis of Imino Derivatives of *Cecropia* Juvenile Hormone[1]

R. J. ANDERSON, C. A. HENRICK,* AND J. B. SIDDALL

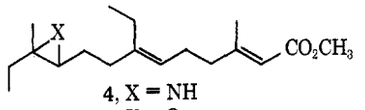
Chemistry Research Laboratory, Zoecon Corporation, Palo Alto, California 94304

Received August 23, 1971

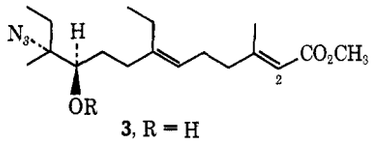
In connection with our studies of the effects of the juvenile hormones[2] of *Hyalophora cecropia* on insect metamorphosis, we were encouraged to devise an efficient synthesis for the imino analog **1**, particularly in view of a report[3a] of the preparation of **1**, by an undetailed method,[3b] and of its interesting biological properties.



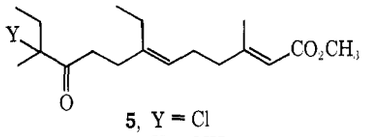
1, X = NH
2, X = O



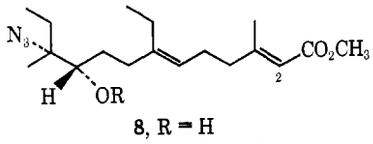
4, X = NH
11, X = O



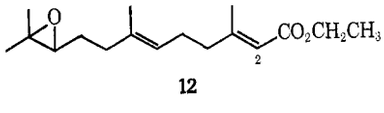
3, R = H
9, R = SO_2CH_3



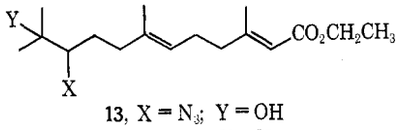
5, Y = Cl
6, Y = NH_2
7, Y = N_3



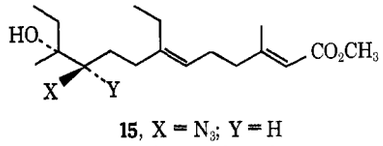
8, R = H
10, R = SO_2CH_3



12



13, X = N_3; Y = OH
14, X = OH; Y = N_3



15, X = N_3; Y = H
16, X = H; Y = N_3

Initial attempts to prepare **1** from the racemic Röller juvenile hormone **2** *via* opening of the epoxide ring with either azide ion or with hydrazoic acid under a variety of conditions failed, although a later variation (see below) did allow the preparation of **1** by this method but in poor yield. In this connection it was found that treatment of **2** with excess lithium azide in dimethoxyethane–acetic acid at 25° for 24 hr failed to give any of the required azido alcohol **3** (*cf.* 3b).

An efficient synthesis of the racemic imino C_{18} juvenile hormone (JH) analogs **1** and **4** was developed starting with the available chloro ketone **5**.[4] Since initial attempts to convert **5** to the amino ketone **6** were unsuccessful, we prepared the corresponding azido ketone **7** from the chloro ketone **5** in 90% yield using sodium azide in dimethylformamide (100° for 3 hr). Reduction of **7** with 1 equiv of sodium borohydride in methanol gave a mixture of the diastereoisomeric azido alcohols **3** and **8** (ratio 3:2), which was separated by thin layer chromatography in an overall combined yield of 65% from **5**. Each pure alcohol was separately converted into its corresponding azido mesylate using methanesulfonyl chloride in triethylamine–pentane[5] (yield 80–85% after purification *via* preparative tlc). The final conversion of the azido mesylates **9** and **10** into the aziridines **1** and **4**, respectively, was best carried out by reduction using hydrazine hydrate and Raney nickel in ethanol.[6] Preparative tlc of the reduction products gave **1** (62% yield) and **4** (55% yield) in high purity. Use of an alternative reduction system, cobaltous bromide–dipyridyl–sodium borohydride,[7] also gave the aziridines, but some selective saturation[8] of the α,β-unsaturated ester double bond also occurred. The two aziridines **1** and **4** could be differentiated by glc and by the different chemical shift of the C-11 methyl in their nmr spectra.

The diastereoisomeric azido alcohols **3** and **8**, and thus the aziridines derived from them, were assigned their stereochemistry on the basis of the correlations with the synthetic trans,trans,cis hormone **2** and the all-trans isomer **11**, respectively,[4] providing also an alternative synthesis of the imino JH analogs. These correlations were established using an epoxide opening

(1) Contribution No. 5 from the Research Laboratory of Zoecon Corp. This work was presented in part at the XXIII International Congress of Pure and Applied Chemistry, Boston, Mass., July 1971.

(2) H. Röller, K. H. Dahm, C. C. Sweeley, and B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, **6**, 179 (1967); A. S. Meyer, H. A. Schneidermann, E. Hanzmann, and J. H. Ko, *Proc. Nat. Acad. Sci. U. S.*, **60**, 853 (1968).

(3) (a) Report by Dr. E. J. Corey at the International Conference on Juvenile Hormones, Basel, Switzerland, Oct 1970; (b) L. M. Riddiford, A. M. Ajami, E. J. Corey, H. Yamamoto, and J. E. Anderson, *J. Amer. Chem. Soc.*, **93**, 1815 (1971).

(4) P. Loew, J. B. Siddall, V. L. Spain, and L. Werthemann, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1462, 1824 (1970).

(5) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

(6) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 5288 (1963); K. Ponsold, *Chem. Ber.*, **97**, 3524 (1964).

(7) K. Ponsold, *J. Prakt. Chem.*, **36**, 148 (1967).

(8) T. Satoh, J. Nanba, and S. Suzuki, *Chem. Pharm. Bull.*, **19**, 817 (1971).