Flavonoids. I. Synthesis of 2,2-Dialkyl-Δ^3-isoflavenes from Coumarins[1]

C. E. COOK, ROBERT C. CORLEY, AND MONROE E. WALL

The Natural Products Laboratory, Research Triangle Institute, Durham, North Carolina 27702

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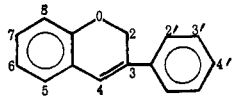
The preparation of a series of 2,2-dialkyl-Δ^3-isoflavenes [3-aryl-1(2H)-benzopyrans] has been carried out by reaction of Grignard reagents with coumarins. The required coumarins were synthesized by the following route: arylacetonitrile → α-aryl-β-ketonitrile → α-aryl-β-keto ester → 7-hydroxycoumarin. Acylation of arylacetonitriles occurred in good yield in dimethyl sulfoxide, and liquid hydrogen fluoride gave excellent yields of coumarins when used as solvent for the von Pechmann reaction.

The synthesis of Δ^3-isoflavenes (1) [3-aryl-1(2H)-benzopyrans][2] is of interest because of the biological activity of compounds in this series.[3] Although synthetic routes involving isoflavone intermediates are known[4-6] these often leave much to be desired from the viewpoint of yield and suitability for large-scale synthesis.



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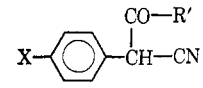
It appeared to us that the Δ^3-isoflavene structure might be readily obtained from coumarins (6) in which the 4-alkyl-(aryl)-Δ^3-3-aryl system was already formed and only the 2-substituents need be introduced. This report deals with the introduction of the 2,2-dialkyl group by reaction of coumarins with Grignard reagents. The compounds thus prepared constitute a new series, since previously reported Δ^3-isoflavenes have carried only a single substituent at carbon 2.

Synthesis of Coumarin Intermediates.—The coumarins required for this scheme were prepared by the route shown in Chart I. An arylacetonitrile (2) was converted to its sodium salt by treatment with the sodium salt of dimethyl sulfoxide.[7] Addition of an ester resulted in acylation to yield a β-ketonitrile **3** which was converted to the corresponding ethyl imidate hydrochloride (not isolated) and then to the ethyl ester **4** by successive treatment with ethanolic hydrogen chloride and water.[8] The acylation of arylacetonitriles has generally been accomplished previously by use of a sodium alkoxide in alcohol or an inert solvent. The present method is recommended by its simplicity, rapidity, and the generally good yields obtained (Table I). Although Price and Whiting have recently reported that more complex reactions than simple deprotonation occur when phenylacetonitrile reacts with the sodium salt of dimethyl sulfoxide,[9] our results show that useful reactions are possible in spite of this complicating feature. Reaction of *p*-methoxyphenylacetonitrile (2, X = OCH_3) with both aryl and alkyl esters gave yields ranging from 62 to 84%. Use of *p*-chlorophenylacetonitrile gave a poor yield (11%), whereas the acylation of the corresponding *p*-fluoro

TABLE I

PREPARATION OF β-KETONITRILES



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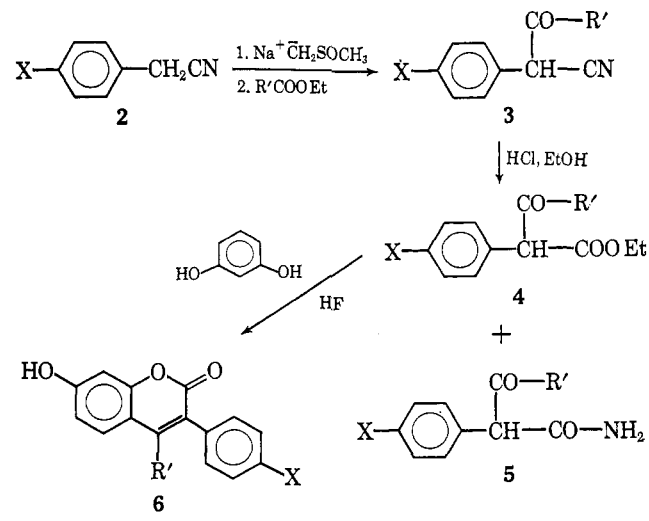
Compd. 3	X	R′	% yield	M.p., °C.
a	OCH_3	CH_3	80	80–81[a]
b	OCH_3	C_2H_5	81	100–104[b]
c	OCH_3	n-C_3H_7	84	71–73[c]
d	OCH_3	n-C_4H_9	62	50–53[d]
e	OCH_3	C_6H_5	83	85–88[e]
f	OCH_3	3-C_5H_4N	72	155–156[f]
g	OCH_3	p-$CH_3OC_6H_4$	..	Oil[g]
h	F	CH_3	54	85–88[h]
i	Cl	CH_3	11	123–125[i]

[a] Lit.[11] m.p. 80–81°. [b] Lit.[11] m.p. 88°. [c] Lit.[11] m.p. 71°. [d] Lit.[11] m.p. 52–53°. [e] *Anal.* Calcd. for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.24; H, 5.12; N, 5.86. [f] *Anal.* Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.48; H, 4.69; N, 11.30. [g] Used without further purification. [h] P. B. Russell and G. H. Hutchings [*J. Am. Chem. Soc.*, **73**, 3763 (1951)] reported m.p. 89–90°. [i] A. Hunger, J. Kebrle, A. Rosi, and K. Hoffmann [*Helv. Chim. Acta*, **43**, 1046 (1960)] reported m.p. 123–126°.

CHART I



(1) (a) Abstracted in part from work done by R. C. Corley in partial fulfillment of the requirements for the Ph.D. degree at North Carolina State University at Raleigh. (b) Portions of this work have been reported at the 147th National Meeting of the American Chemical Society, New York, N. Y., April 1964; Abstracts, p. 23M. (c) This research was carried out under Contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

(2) In accordance with common usage, compounds in this paper are named as derivatives of the isoflavan nucleus, with the numbering shown in **1**.

(3) For a discussion of the uterotropic activity of Δ^3-isoflavenes and a general review on these compounds, see ref. 4.

(4) R. A. Micheli, A. N. Booth, A. L. Livingston, and E. M. Bickoff, *J. Med. Chem.*, **5**, 321 (1962).

(5) R. B. Bradbury and D. E. White, *J. Chem. Soc.*, 871 (1953).

(6) W. Lawson, *ibid.*, 4448 (1954).

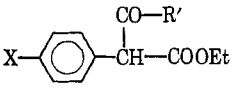
(7) E. J. Corey and M. Chaykowski, *J. Am. Chem. Soc.*, **84**, 866 (1962).

(8) F. V. Wessely, E. Kerschbaum, A. Kleedorfer, F. Prillinger, and E. Zajic, *Monatsh.*, **73**, 143 (1941).

(9) G. G. Price and M. C. Whiting, *Chem. Ind.* (London), 775 (1963).

TABLE II

PREPARATION OF β-KETO ESTERS



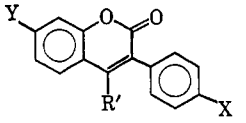
4

Compd. 4	X	R′	% yield	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
a	OCH_3	CH_3	81	63–65[a]					
b	OCH_3	C_2H_5	100	98–100[b]					
c	OCH_3	n-C_3H_7	90	35–39[c]					
d	OCH_3	n-C_4H_9	86	Oil[d]					
e	OCH_3	C_6H_5	82	81–83	$C_{18}H_{18}O_4$	72.46	6.08	72.50	6.13
f	OCH_3	3-C_5H_4N	15	70–71	$C_{17}H_{17}NO_4$[e]	68.21	5.73	68.28	5.73
g	OCH_3	p-$CH_3OC_6H_4$	48	82–83	$C_{19}H_{20}O_5$	69.50	6.14	69.15	6.61
h	F	CH_3	84	Oil[d]					

[a] Lit.[8] m.p. 78°. [b] Lit.[8] m.p. 97°. [c] Lit.[8] m.p. 38–39°. [d] Used without further purification. Infrared spectra supported the assigned structure, as did subsequent reactions. [e] *Anal.* Calcd.: N, 4.68. Found: N, 4.87.

TABLE III

SYNTHESIS OF COUMARINS



6

Compd. 6	X	Y	R′	Method[a]	% yield[b]	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
a	OCH_3	OH	CH_3	A	63	216–228		...	...	...	...
				B	66	224–236					
				D	89	233–234[c]					
b	OCH_3	OH	C_2H_5	A	42	160–209		...	...	...	...
				C	24	206–210					
				D	93	216–218[d]					
c	OCH_3	OH	n-C_3H_7	D	81	201–202[e]					
d	OCH_3	OH	n-C_4H_9	D	70	199–200	$C_{20}H_{20}O_4$	74.05	6.22	73.76	6.15
e	OCH_3	OH	C_6H_5	D	60	256–258	$C_{22}H_{16}O_4$	76.73	4.68	77.00	4.75
f	OCH_3	OH	p-$CH_3OC_6H_4$	D	19	272–273	$C_{23}H_{18}O_5$	73.79	4.85	74.15	5.11
g	OCH_3	OH	3-C_5H_4N	D	90	299–301	$C_{21}H_{15}NO_4$	73.03	4.38	73.19	4.40[f]
h	F	OH	CH_3	D	74	236–238	$C_{16}H_{11}FO_3$	71.10	4.10	71.09	4.46
i	OCH_3	OCH_3	CH_3	[g]	85	145–146					
j	OH	OH	CH_3	[h]	95	311–313	$C_{16}H_{12}O_4$	71.63	4.51	71.46	4.66
k	OH	OH	C_2H_5	[h]	96	316–320[i]					

[a] Method A: resorcinol plus β-ketonitrile in sulfuric acid. Method B: resorcinol plus β-ketonitrile in hydrogen fluoride. Method C: resorcinol plus β-keto ester in polyphosphoric acid. Method D: Resorcinol plus β-keto ester in hydrogen fluoride. [b] Per cent yield of material with given melting points. [c] Lit.[11] m.p. 235°. [d] Lit.[11] m.p. 215°. [e] Lit.[11] m.p. 200°. [f] *Anal.* Calcd.: N, 4.06. Found: N, 4.11. [g] Prepared by reaction of **6a** with methyl iodide and potassium carbonate in dimethyl sulfoxide. P. L. Sawhney and T. R. Seshadri, [*J. Sci. Ind. Res.* (India), **B13**, 316 (1954)] reported m.p. 144–145°. [h] Made by the method of ref. 11 (demethylation of corresponding ether). [i] Lit.[4] m.p. 317° (see footnote 34b of ref. 4).

compound proceeded in a yield of 54%[10] (see Table I).

During the preparation of some of the β-keto esters (Table II), higher melting, nitrogen-containing by-products were obtained. These were shown to be the β-ketoamides **5** by analysis and by basic hydrolysis. Thus, **5** (R′ = p-methoxyphenyl, X = methoxy) on hydrolysis with 1 *N* potassium hydroxide yielded ammonia and anisic acid (identified by comparison with an authentic sample).

Preparation of Coumarins by a Modified von Pechmann Reaction.—Mentzer and co-workers have reported obtaining a series of 3-(4-methoxyphenyl)-4-alkyl-7-hydroxycoumarins, where the alkyl group was methyl, ethyl, or *n*-propyl, by reaction of the appropriate β-ketonitrile or β-keto ester with resorcinol in sulfuric acid (the von Pechmann reaction). No yields were reported.[11] Repetition of Mentzer's work gave the desired coumarins **6a** and **6b** (4-methyl and 4-ethyl, see Chart I and Table III), but the yields were rather low and the coumarins were contaminated with impurities which were difficult to remove by recrystallization. Koo reported high yields of 4-methyl-7-hydroxycoumarin by use of polyphosphoric acid in the von Pechmann reaction,[12] but application of this to the α-aryl-β-keto esters gave discouraging results.

In contrast, when a mixture of resorcinol and ethyl α-(p-methoxyphenyl)-β-ketovalerate (**4b**) was treated with hydrogen fluoride, a novel reagent for the von Pechmann reaction, a 93% yield of the corresponding

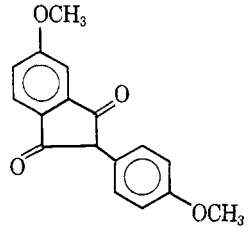
(10) The benzyne mechanism suggested (ref. 7) for the reaction of chlorobenzene with the sodium salt of dimethyl sulfoxide under similar conditions may explain the poor yield obtained with p-chlorophenylacetonitrile and the better yield with the less reactive p-fluoro analog.

(11) G. Mentzer, P. Gley, D. Molho, and D. Billet, *Bull. soc. chim. France*, [5] **13**, 271 (1946).

(12) J. Koo, *Chem. Ind.* (London), 445 (1955).

coumarin **6b** was obtained by stirring the resulting solution overnight. This method was then applied to a series of β-keto esters with the results shown in Table III. As can be seen from the table, quite good yields of coumarins were obtained in most cases. Impurities were usually easily removed by recrystallization. The same coumarins could also be obtained from β-ketonitriles and resorcinol in hydrogen fluoride followed by acid hydrolysis, but the reaction was not as clean.[13]

The low yield (19%) from ethyl α,β-bis(*p*-methoxyphenyl)-β-ketopropionate (**4g**) and the moderate yield (60%) from ethyl α-(*p*-methoxyphenyl)-β-phenyl-β-ketopropionate (**4e**) cannot be explained on steric grounds, since the analogous β-(3-pyridyl) compound **4f** gave a 90% yield. The tarry nature of the by-products precluded identification. The possibility of intramolecular condensation of the β-keto ester to indandione **7** was eliminated by an 84% recovery of keto ester **4g** after treatment with hydrogen fluoride alone.



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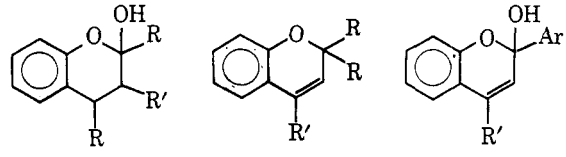
Reaction of Coumarins with Grignard Reagents.—It has been reported that 3-substituted coumarins react with Grignard reagents by a combination of 1,2 and 1,4 addition to yield 2,3,4-trisubstituted chromanols (**8**) while 4-alkylcoumarins yield 2,2,4-trisubstituted Δ^3-chromenes (**9**). However, with limited amounts of phenyl Grignard reagents, monoaddition may occur to yield chromenols (**10**).[14] (See Chart II.) No

CHART II

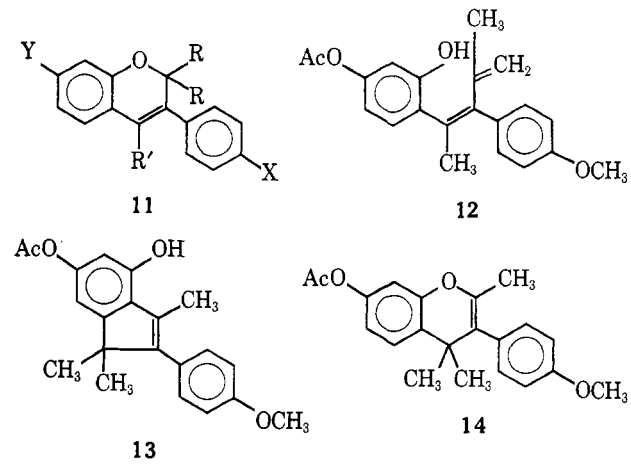


8 **9** **10**

reports could be found concerning the reaction of Grignard reagents with 3-aryl-4-alkyl- or -arylcoumarins, although Adams and Baker did report the synthesis of 2,2-dimethyl-Δ^3-chromenes from methyl Grignard reagent and 3,4-cyclohexenocoumarins.[15]

When coumarin **6a** was refluxed with methyl Grignard reagent in ether–benzene solution and resulting material was acetylated, white crystals, m.p. 153–155°, were obtained. Analytical data agreed with the formula $C_{21}H_{22}O_4$, which is in accord with the isoflavene structure **11a** (Chart III and Table IV). The infrared spectrum showed no hydroxyl absorption. This elimi-

CHART III



11 **12** **13** **14**

nates the possibility of structures such as the partially acetylated diene **12** or the partially acetylated indene **13** which could have arisen by ring opening followed by recyclization. The lack of a vinyl ether band in the 1650–1700-cm.$^{-1}$ region of the infrared spectrum was evidence against a 2,4,4-trimethyl-Δ^2-isoflavene structure (**14**), which could have arisen by a combination of 1,2 and 1,4 addition of the Grignard reagent to the coumarin.

The ultraviolet spectrum (maxima at 225, 271, and 308 mμ) was in substantial agreement with that reported for the 2-monoalkyl-Δ^3-isoflavenes, but not with that of a Δ^2-isoflavene, which had no maximum in the region above 300 mμ.[5] Finally, a simple n.m.r. spectrum was obtained which was in complete accord with the Δ^3-isoflavene structure. Four sharp singlets and a multiplet were observed (ratio 6:3:3:3:7). The singlet at 81 c.p.s. (60 Mc., internal tetramethylsilane standard) was assigned to the *gem*-dimethyl group, while the peaks at 104, 136, and 230 c.p.s. were assigned, respectively, to the 4-methyl, acetyl, and methoxyl protons. The aromatic multiplet appeared at 395–435 c.p.s.[16] Thus we conclude that the Δ^3-isoflavene structure **11** must be assigned to the Grignard product from coumarin **6a** and the analogs prepared later.

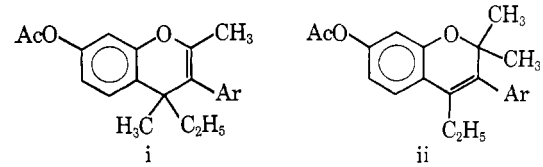
Since the starting coumarins were almost insoluble in benzene, the solvent mixture for the Grignard reaction was changed to tetrahydrofuran–ether. An improved yield resulted. Only a small decrease in yield was observed in going from methyl to ethyl to *n*-butyl Grignard reagents, but both phenyl Grignard reagent and phenyllithium gave quite poor results.

(13) It has recently been reported [L. L. Woods and J. Sapp, *Chem. Abstr.*, **62**, 6454 (1965)] that α-aryl-β-ketonitriles react with phenols in trifluoroacetic acid to yield isoflavones. In our hands resorcinol and ketonitrile **3a** in trifluoroacetic acid yielded only coumarin **6a**, as shown by direct comparison with genuine samples of **6a** and 2-methyl-4′-methoxy-7-hydroxyisoflavone.

(14) S. Wawzonek, "Heterocyclic Compounds," Vol. 2, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 204–207.

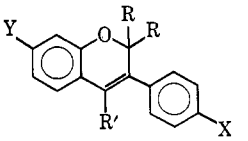
(15) R. Adams and B. Baker, *J. Am. Chem. Soc.*, **62**, 2405 (1940).

(16) While this n.m.r. spectrum alone would not distinguish between the 2,2,4- and 2,4,4-trimethyl structures **11a** and **14**, the n.m.r. spectra of other analogs definitely excluded this possibility. All compounds assigned the 2,2-dimethyl-Δ^3-isoflavene structure showed a single peak for the two methyl groups. N.m.r. would be expected to distinguish clearly between the methyl groups of, for example, i, whereas ii would be expected to give a single *gem*-dimethyl peak.



i ii

TABLE IV



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Compd. 11	R′	R	X	Y	% yield	M.p., °C.	Formula	—Calcd., %— C	H	—Found, %— C	H	Ultraviolet,[a] λ_{max}, mμ (ε)
a	CH_3	CH_3	OCH_3	OAc	76[b]	153–155	$C_{21}H_{22}O_4$	74.53	6.55	74.46	6.56	271 (11,400), 308 (9700)
b	CH_3	C_2H_5	OCH_3	OAc	48	92.5–93.5[c]	$C_{23}H_{26}O_4$	75.38	7.15	75.34	7.20	274 (8700), 312 (9000)
c	CH_3	n-C_4H_9	OCH_3	OAc	50	64.5–65.5	$C_{27}H_{34}O_4$	76.74	8.11	76.50	8.18	274 (8700), 312 (9000)
d	CH_3	CH_3	OAc	OAc	*d*	181–184	$C_{22}H_{22}O_5$	72.11	6.05	72.44	6.13	270 (9600), 308 (8700)
e	CH_3	CH_3	OCH_3	OCH_3	94[e]	137–139	$C_{23}H_{22}O_3$	77.39	7.14	77.09	7.00	279 (13,800), 307 (12,500)
f	CH_3	CH_3	F	OAc	74	143–145	$C_{20}H_{19}FO_3$	73.59	5.83	73.29	6.05	269(9100), 309 (8500)
g	C_2H_5	CH_3	OCH_3	OAc	66	124–126	$C_{22}H_{24}O_4$	74.99	6.86	75.05	7.01	270 (11,900), 307 (9400)
h	C_2H_5	CH_3	OCH_3	OH	*f*	150–152	$C_{20}H_{22}O_3$	77.39	7.14	77.18	7.29	277 (11,700), 306 (10,200)
i	C_2H_5	CH_3	OAc	OAc	54[d]	174–176	$C_{23}H_{24}O_5$	72.61	6.36	72.84	6.11	270 (9700), 309 (8100)
j	n-C_3H_7	CH_3	OCH_3	OAc	65	103–105	$C_{23}H_{26}O_4$	75.38	7.15	75.53	7.27	270 (10,900), 307 (8900)
k	n-C_4H_9	CH_3	OCH_3	OAc	77	60.5–62	$C_{24}H_{28}O_4$	75.76	7.42	75.89	7.45	271 (10,900), 308 (8600)
l	C_6H_5	CH_3	OCH_3	OAc	71	158–159	$C_{26}H_{24}O_4$	77.98	6.04	78.03	6.07	284 (10,200), 310 (10,100)
m	p-$CH_3OC_6H_4$	CH_3	OCH_3	OAc	55	138–140	$C_{27}H_{26}O_5$	75.33	6.09	75.08	6.33	284 (10,600), 308 (10,300)

[a] Determined in methanol solution. All compounds had high absorption around 220 mμ (ε ~30,000). [b] Unless otherwise stated, yields were obtained by the general procedure given in the Experimental Section (tetrahydrofuran–ether solvent). [c] Rapid crystallization gave needles, m.p. 92.5–93.5°. If the needles were allowed to stand in contact with solution or, if crystallization was slow, prisms, m.p. 80–82°, were obtained. [d] See Experimental Section for method. [e] Reaction was carried out in benzene–ether. [f] Isolated by elimination of the acetylation step.

Although the ultraviolet spectra of various products resembled those of the dialkylisoflavenes, no pure compounds could be obtained in these cases from the complex reaction mixtures. Even in the 2,2,4-trimethyl derivative the steric constraints are considerable, with the result that the aryl ring must be twisted so that it is not coplanar with the benzopyran ring system. The steric factors involved in the formation of a 2,2-diphenyl analog would be expected to be formidable.

Little difficulty was experienced in extending the reaction to coumarins having varied substituents in the 4-position, and a list of isoflavenes prepared is given in Table IV. Since the synthetic sequence led easily to 4′-methoxy, 4′-halogeno, etc., analogs, it was felt desirable to prepare the 4′,7-dihydroxy (or diacetoxy) analogs of some of the structures. Attempts to do this by acidic cleavage of methoxyl groups attached to the isoflavene nucleus led to an interesting rearrangement, which is discussed in the following paper.[17] Attempts to prepare the 4′,7-dihydroxy derivatives by direct Grignard reaction on the 4′,7-dihydroxycoumarins failed owing to the extreme insolubility of the coumarin–magnesium complex in tetrahydrofuran.

The use of readily cleaved hydroxyl-protecting groups was then investigated. On occasion the tetrahydropyranyl group has been used to protect a phenolic OH.[18] Reaction of the dihydroxycoumarin **6j** with dihydropyran was hampered by solubility problems, and use of dimethylformamide as a cosolvent was necessary, but a crude bis(tetrahydropyranyl) derivative was obtained. When this was refluxed with methyl Grignard reagent in benzene, protecting groups removed and the hydroxyls acetylated, a mixture of two products was obtained. Separation by chromatography gave A, m.p. 181–184°, and B, m.p. 177–180°. A was shown to be the desired isoflavene **11d** by ultraviolet (λ_{max} 270, 308 mμ) and n.m.r. spectra and analysis. B had a single ultraviolet maximum at 271 mμ, the empirical formula C_4H_4O, and a very strong aryl acetate infrared band. It was identified as an indene derivative.[17]

On a large scale the excess dihydropyran and its polymerization products proved hard to remove and a more suitable protective group was sought. The trimethylsilyl group, which has had limited use as a phenol protecting group,[19] appeared to have precisely the properties we needed. The required protecting groups were readily attached to coumarin **6k** by the method described by Waiss.[20] Successive treatment of the

(17) Paper II: C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **30**, 4120 (1965).

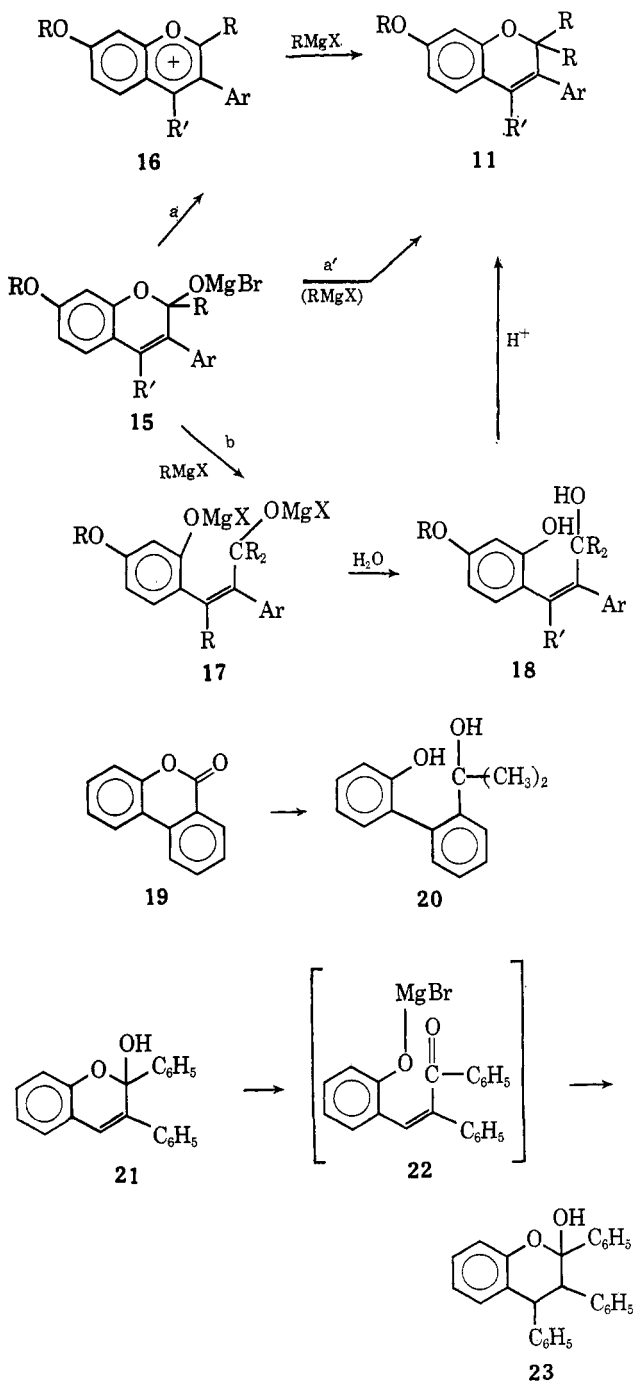
(18) (a) W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.*, **70**, 4187 (1948); (b) B. Iselin and R. Schwyzer, *Helv. Chim. Acta*, **39**, 57 (1956).

(19) J. L. Speier, *J. Am. Chem. Soc.*, **74**, 1003 (1952).

(20) A. C. Waiss, Jr., R. E. Lundin, and D. J. Stern, *Tetrahedron Letters*, 513 (1964).

resulting bis(trimethylsilyl) ether with Grignard reagent, hydrochloric acid, and acetic anhydride gave the desired isoflavene **11i** in 54% over-all yield. As expected, the trimethylsilyl groups were cleaved by merely shaking an ether solution of the intermediate silyl ether with concentrated hydrochloric acid.

CHART IV



In the usual work-up of the Grignard products, it was found that colored by-products could be most readily removed by extracting an ether solution of the crude product with small amounts of concentrated hydrochloric acid (which presumably removed substances convertible to pyrylium salts). The question arose as to whether closure of the heterocyclic ring was not also taking place at the same time. Two possible products (**11** and **18**) could be obtained initially from the Grignard reaction (Chart IV). Path a involves intermediate formation of a pyrylium compound (**16**) which yields heterocycle **11** directly, path a′ involves some sort of direct displacement to yield **11**, and path b involves either a displacement of (complexed) phenoxide or formation and reaction of a ketone to yield the open-chain intermediate **18** which must be cyclized in a second (acid-catalyzed) step to **11**.

Adams and Baker[21] isolated a ring-opened compound (**20**) analogous to **18** in the reaction of benzocoumarin **19** with methyl Grignard reagent. On the other hand, Shriner and Sharp[22] produced evidence that no ring opening occurred in the reaction of coumarin itself with methyl Grignard reagent to yield 2,2-dimethyl-Δ^3-chromene. Geissman and Baumgartner[23] found that 2,3-diphenyl-Δ^3-chromen-2-ol (**21**) gave 2,3,4-diphenylchromanol (**23**) and suggested the intermediacy of ketone **22**. Thus, it was necessary to decide between path a (or a′) and path b for the present case.

The product from the above Grignard reaction (preparation of **11i**) after treatment with ammonium chloride was readily soluble in carbon tetrachloride and had $\nu_{max}^{CCl_4}$ 3580, 3540, and 3300 cm.$^{-1}$ (hydrogen-bonded hydroxyl); $A_{305}/A_{280} = 0.45$ (peak at 280 mμ, shoulder at 305 mμ). After treatment with hydrochloric acid it was no longer soluble in carbon tetrachloride and had $\nu_{max}^{CH_2Cl_2}$ 3575 cm.$^{-1}$ (free phenolic hydroxyl); $A_{305}/A_{280} = 0.80$ (peaks at 305 and 280 mμ; the ratio is about that of the isoflavene diacetate **11i**). Compound **18** might be expected to lack the long wave length ultraviolet absorption of **11**, since steric repulsions would tend to prevent coplanarity of the aryl groups with the double bond[24] when the restricting influence of ring formation is missing. The increase in long wave length absorbance upon acid treatment thus suggests ring closure and indicates that path b predominates. The infrared data also support the theory that both ring closure and cleavage of the trimethylsilyl groups occurred upon acid treatment.

Experimental Section[25]

General Procedure for Synthesis of β-Ketonitriles 3.—All apparatus was dried overnight. The reaction was carried out under a nitrogen atmosphere in a three-neck flask fitted with thermometer, mechanical stirrer, gas-inlet tube, and addition funnel protected by a Drierite drying tube.

A solution of the sodium salt of dimethyl sulfoxide was prepared according to the procedure of Corey and Chaykowski.[7] Sodium hydride (0.7 mole as a 50% suspension in oil) was added all at once to 385 ml. of dimethyl sulfoxide and the suspension was stirred and heated at 70–75° until bubbling had ceased, which was usually around 75 min. The solution was cooled (ice bath) and stirred while *p*-methoxyphenylacetonitrile (0.68 mole) was added as rapidly as possible while maintaining the

(21) R. Adams and B. R. Baker, *J. Am. Chem. Soc.*, **62**, 2208 (1940).
(22) R. L. Shriner and A. G. Sharp, *J. Org. Chem.*, **4**, 575 (1939).
(23) T. A. Geissman and E. Baumgartner, *J. Am. Chem. Soc.*, **65**, 2135 (1943).
(24) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p. 389 ff.
(25) Melting points were taken in capillary tubes (oil bath) and are uncorrected. Ultraviolet spectra were run in methanol on a Bausch and Lomb Spectronic 505. N.m.r. spectra were recorded in deuteriochloroform on a Varian Model A-60, using tetramethylsilane as an internal standard, by Miss D. Linker of the University of North Carolina at Chapel Hill, Charles Driscoll of Duke University, and Sam Justice of this laboratory. Microanalyses were by Micro Tech Laboratories, Skokie, Ill.

temperature between 20 and 25°. Five minutes after addition was complete, the ester (0.68 mole) was added as rapidly as possible while maintaining the temperature below 20°. After addition was complete, the ice bath was removed, and stirring was continued for 2 hr. at room temperature, at which time the solution was poured into 2 l. of ice–water and extracted with four portions (350 ml. each) of methylene chloride. The water layer was gravity filtered through previously wet filter paper and acidified with 56 ml. of acetic acid. The white precipitate was filtered, triturated with water, filtered, washed thoroughly with water, and dried in a vacuum oven.

General Procedure for Synthesis of β-Keto Esters 4.—According to the procedure of Wessely, *et al.*,[8] the β-ketonitrile was dissolved in absolute ethanol and saturated with anhydrous hydrogen chloride. After standing overnight at room temperature, the solvent was removed *in vacuo* and the oily intermediate imino ester was dissolved in 95% ethanol. (In some cases it was necessary to warm on a steam bath to dissolve the oil.) An equal volume of water was added and the precipitate was filtered off and dried in a vacuum oven.

Synthesis and Degradation of β-Ketoamides 5.—In the synthesis of the keto esters **4e**, **4f**, and **4g**, a minor quantity of β-ketoamide was formed. α-(4-Methoxyphenyl)-β-phenyl-β-ketopropionamide (**5a**), m.p. 194–195°, was separated from ester **4e** by fractional crystallization from ethyl acetate.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61. Found: C, 71.04; H, 5.61.

α,β-Bis(4-methoxyphenyl)-β-ketopropionamide (**5b**), m.p. 172–174°, was separated from ester **4g** by chromatography over Woelm activity III alumina. Ester **4g** was eluted by 3% 2-propanol in benzene, and amide **5b** by 50% methanol in benzene.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73. Found: C, 68.24; H, 5.92.

α-(4-Methoxyphenyl)-β-(3-pyridyl)-β-ketopropionamide (**5c**), m.p. 153–155°, was separated from ester **4f** by fractional crystallization from benzene.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.73; H, 4.84; N, 10.23.

A sample of amide **5b** was refluxed for 1 hr. in 1 *N* potassium hydroxide solution. A strong odor of ammonia was apparent. The solution was made acidic with hydrochloric acid and refluxed for another 3 hr. Cooling resulted in the separation of white needles, m.p. 160–169°, which were recrystallized from methanol. Infrared spectra, melting point (180–182°), and mixture melting point (180–181°) identified the product as anisic acid.

Synthesis of Coumarins 6 from β-Ketonitriles and Resorcinol in Sulfuric Acid (Method A[11]).—Sulfuric acid (17.2 ml.) was placed in a 50-ml. pear-shaped flask equipped with sealed stirrer and thermometer. An intimate mixture of α-(4-methoxyphenyl)-β-ketobutyronitrile (13.0 g., 69 mmoles) and resorcinol (7.6 g., 69 mmoles) was added in small portions with vigorous stirring and cooling to keep the temperature at 3–7°. Addition required 70 min. Stirring was continued at 5–10° for 1.5 hr., 15° for 2 hr., and room temperature for 17 hr. The viscous mixture was poured into a mixture of 120 g. of ice and 120 ml. of water. The yellow tar which separated was washed with a little water and then stirred and heated with 340 ml. of 10% sulfuric acid. When the mixture reached the boiling point, the clear yellow solution was decanted from an orange tar and boiled gently for 2 hr. Chilling followed by filtration yielded 20.4 g. of pale yellow, moist solid. This was boiled with 300 ml. of absolute ethanol. The turbid solution was treated with charcoal, filtered, and diluted with 300 ml. of hot water. This gave 7.9 g. of **3-(4-methoxyphenyl)-4-methyl-7-hydroxycoumarin** (**6a**), m.p. 222–228°. Further hydrolysis and recrystallization of the above orange tar yielded another 4.0 g., m.p. 216–222°, for a total yield of 11.9 g. (63%). Further recrystallization from 85% ethanol raised the melting point to 232–237°.

The result of application of this technique to the synthesis of **3-(4-methoxyphenyl)-4-ethyl-7-hydroxycoumarin** (**6b**) is described in Table I.

General Procedure for Synthesis of Coumarins 6 in Hydrogen Fluoride (Methods B and E, Table IV).—Equimolar quantities of the β-keto ester and resorcinol (method E) were intimately mixed in a polyethylene flask and dissolved in liquid hydrogen fluoride (*ca.* 5 ml./g. of ester). The solution was stirred overnight during which time nearly all of the hydrogen fluoride evaporated. A stream of nitrogen was passed through the flask until a check with litmus paper indicated the absence of acid. At this stage, the product was usually present as a viscous oil which solidified upon addition of water. The solid was then filtered and recrystallized from methanol, acetic acid, or acetonitrile. Occasionally the product did not solidify upon addition of water. In these cases the water was decanted and the oil was taken up in methanol and treated with Norit. Concentration and chilling then gave a crystalline product.

In the cases where a β-ketonitrile was used in place of a β-keto ester, the oil from the hydrogen fluoride cyclization was refluxed in 20% sulfuric acid for 4 hr. (method B). Chilling the solution gave crystalline product.

3-(4-Methoxyphenyl)-4-ethyl-7-hydroxycoumarin (**6b**) **by Method D (Polyphosphoric Acid Catalyst[12]).**—Resorcinol (1.10 g., 10 mmoles) and ethyl α-(4-methoxyphenyl)-β-ketovalerate (2.50 g., 10 mmoles) were intimately mixed and treated with 20 ml. of polyphosphoric acid. The mixture was heated at 80–85° with stirring for 0.5 hr. and poured into 300 ml. of ice–water. A mixture of yellow solid and red gum was obtained. Recrystallization of this from aqueous ethanol gave yellow crystals of **6b** weighing 0.72 g. (24%), m.p. 206–210°.

2,2,4-Trimethyl-4′-methoxy-7-hydroxy-Δ^3-isoflavene (**11a**) **by Grignard Reaction in Benzene–Ether.**—A suspension of 3-(4-methoxyphenyl)-4-methyl-7-hydroxycoumarin (**6a**, 0.70 g., 2.48 mmoles) in benzene (30 ml.) was added rapidly to a cooled 3 *M* solution of methylmagnesium bromide in ether. The resulting solution was refluxed for 26 hr. and worked up with aqueous ammonium chloride. Acetylation (refluxing acetic anhydride for 2 hr.) of the product (0.75 g.) followed by crystallization from 95% ethanol and then methanol gave 0.19 g. of brownish crystals, m.p. 149–154°. Sublimation (125° and 0.01 mm.) gave 150 mg. of white microneedles, m.p. 153–155° (with sublimation). In a second run using larger amounts a yield of 49% was obtained.

General Procedure for the Synthesis of Isoflavenes 11.—All apparatus was dried overnight and the reaction was carried out under a nitrogen atmosphere. The materials were used in a ratio of 8 ml. of dry tetrahydrofuran and 1.33 ml. of 3 *M* methyl magnesium bromide in ether per millimole of coumarin.

To a cooled solution of coumarin in tetrahydrofuran, the Grignard solution was rapidly added. The ice bath was removed and the solution was refluxed for 2 hr. Excess Grignard reagent was decomposed with water followed by concentrated hydrochloric acid. The mixture was filtered and the solid was washed with tetrahydrofuran. The combined organic layers were dried over magnesium sulfate and filtered, and the solvent was removed *in vacuo*. The residual gum was dissolved in ether, washed successively with two portions of concentrated hydrochloric acid, saturated sodium bicarbonate solution, and saturated ammonium sulfate solution, and dried over magnesium sulfate. The ether was removed *in vacuo* and the residual gum was refluxed with acetic anhydride for 3 hr. Excess acetic anhydride was decomposed with methanol and the solvents were removed *in vacuo*. The residual solid was recrystallized from methanol.

2,2,4-Trimethyl-4′,7-diacetoxy-Δ^3-isoflavene (**11d**) **and 1,3,3-Trimethyl-2-(4-acetoxyphenyl)-5,7-diacetoxyindene.**—A solution of 1.40 g. (4.73 mmoles) of 3-(4-hydroxyphenyl)-4-methyl-7-hydroxycoumarin (**6j**) and 5 mg. of *p*-toluenesulfonic acid in 10 ml. of dimethylformamide and 20 ml. of dihydropyran was stirred for 48 hr., poured into 5% sodium bicarbonate solution, and extracted with ether–benzene. The residue from evaporation of the organic layer was stirred with 20 ml. of methanol and filtered. A white powder, 1.50 g., m.p. 159–169°, ν_{max}^{Nujol} 1710 cm.$^{-1}$ (no OH), assumed to be the bistetrahydropyranyl derivative of **6j**, was obtained. Without further purification it was dissolved in 25 ml. of hot benzene and treated with 10 ml. of 3 *M* methylmagnesium bromide in ether. The mixture was refluxed for 20 hr. and worked up, using dilute acetic acid and ether. The residue from the ether solution was allowed to stand overnight with 12 ml. of methanol and 2 ml. of concentrated hydrochloric acid and then was acetylated in refluxing acetic anhydride. The product was crystallized from 8 ml. of methanol to yield a solid which weighed 470 mg. and melted at 155–172°. Chromatography on silica gel (60 g.) using petroleum ether (b.p. 30–60°) and benzene as the eluting solvents gave two pure products (shown by thin layer chromatography) which were recrystallized from methanol. The first substance eluted, **2,2,4-trimethyl-4′-7-diacetoxy-Δ^3-isoflavene** (**11d**, 212 mg., 12%), had m.p. 181–184°. It was identified by analysis, n.m.r., and by its ultraviolet spectrum (Table IV).

The second product, **1,3,3-trimethyl-2-(4-acetoxyphenyl)-5,7-diacetoxyindene** (19 mg., 1%), had m.p. 177–180°, λ_{max}^{MeOH} 271

mμ (ε 16,800). It was identified by analysis, ultraviolet spectrum, and comparison with a sample prepared in a different manner.[17]

Anal. Calcd. for $C_{24}H_{24}O_6$: C, 70.52; H, 5.96. Found: C, 70.57; H, 5.92.

2,2-Dimethyl-4-ethyl-4'7-diacetoxy-Δ³-isoflavene (11i).—Twenty grams (71 mmoles) of 4-ethyl-3-(4-hydroxyphenyl)-7-hydroxycoumarin (**6k**), 100 ml. of pyridine, and 30 ml. of hexamethyldisilazane were heated for 1 hr. under nitrogen in an oil bath at 80°. Evaporation (rotary evaporator connected to vacuum pump) and drying *in vacuo* until the pyridine odor was gone gave the bis(trimethylsilyl) ether of **6k** as an off-white solid, $\nu_{max}^{CCl_4}$ 1720 cm.$^{-1}$. This was dissolved in ether and treated with 3 *M* methylmagnesium bromide in ether at such a rate as to maintain a gentle reflux. The solution was then refluxed for 0.5 hr. and poured into a mixture of 90 g. of ammonium chloride, 100 g. of ice, and 150 ml. of water. Ether extraction was followed by washing the ether solution (total volume 700 ml.) with 30 ml. and two 15-ml. portions of concentrated hydrochloric acid, sodium bicarbonate, and ammonium chloride solutions. The dried (Drierite) solution was evaporated and the residue was refluxed for 2 hr. with 125 ml. of acetic anhydride. The cooled solution was treated with 125 ml. of methanol and allowed to stand overnight. Filtration then separated 16 g. ol white crystals. After two recrystallizations from 2-propanof (35 ml./g.) and two from acetone (10 ml./g.), white crystals weighing 10.85 g. were obtained, m.p. 174–176°. From the mother liquors two more crops were obtained: 2.69 g., m.p. 174–176°; and 1.30 g., m.p. 173–175°. The total yield was 14.84 g. (54%). For characterization see Table IV.

Flavonoids. II. Rearrangement of 2,2-Dimethyl-Δ³-isoflavenes to Indenes[1,2]

C. E. COOK, ROBERT C. CORLEY, AND MONROE E. WALL

Natural Products Laboratory, Research Triangle Institute, Durham, North Carolina 27702

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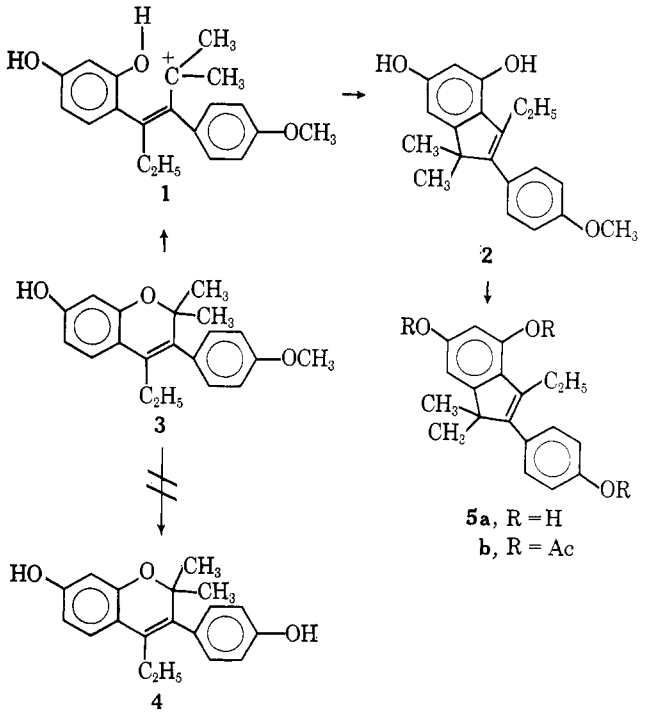
Attempts to demethylate methoxy derivatives of 2,2-dimethyl-Δ³-isoflavenes under acidic conditions (pyridine hydrochloride, aluminum chloride) led to facile rearrangement to the corresponding 7-hydroxyindenes.

In connection with the synthesis of Δ³-isoflavenes,[2] we wished to prepare 4',7-dihydroxy- (or diacetoxy-) 4-ethyl-2,2-dimethyl-Δ³-isoflavene (**4**). An obvious route was by demethylation of the readily obtainable 4'-methoxy-7-hydroxy-4-ethyl-2,2-dimethyl-Δ³-isoflavene (**3**) (see Chart I).[2] Attempts to carry out this reaction under acidic conditions led to an interesting rearrangement which forms the subject of this paper.

CHART I



An attempt by Lawson to demethylate a 2-monoalkyl-Δ³-isoflavene was reported to result in disruption of the molecule, but no details were given.[3] It is apparent that any method which involves attack of a Lewis acid on an ether oxygen should result first in the cleavage of the heterocyclic ring, since the carbonium ion **1** resulting from such cleavage would be highly stabilized by resonance with the aromatic ring. We therefore sought media in which the ring-opened product might be demethylated without further degradation, so that acid-catalyzed ring closure would yield the desired dihydroxy-Δ³-isoflavene.

When isoflavene **3** was fused with pyridine hydrochloride, thin layer chromatography indicated the formation of a more polar compound (probably **2**, compare **6** → **7b**, Chart II) as an intermediate which was gradually converted to the yet more polar final product **5a**. After acetylation, the product was shown by elemental analyses to have the formula $C_{25}H_{26}O_6$. Acetyl analysis showed three hydrolyzable acetyl groups. The n.m.r. spectrum (60 Mc., internal tetramethylsilane standard) suggested the presence of six aromatic protons (area from 405 to 430 c.p.s.), two equivalent methyl groups (singlet at 73 c.p.s.), an ethyl group (triplet centered at 63 c.p.s., J = 7.5 c.p.s.—the methylene quartet was buried under the acetyl resonance), and three acetyl methyl groups (two peaks at 136 and 137 c.p.s.). The presence of three hydrolyzable acetyl groups requires that none of the oxygen functions be involved in a ring, the number of aromatic protons requires a total of six substituents, and the analytical results require the presence of 13 sites of unsaturation. These requirements are met by 1-ethyl-2-(4-acetoxyphenyl)-3,3-dimethyl-5,7-diacetoxyindene (**5b**), obtained by intramolecular rearrangement. The C-4 and C-6 protons appear as a pair of doublets centered at 407 and 416 c.p.s. (J = 2 c.p.s., indicative of *meta* coupling), while the protons of the acetoxyphenyl group appear as a single peak at 424 c.p.s.

(1) (a) Abstracted in part from work done by R. C. Corley in partial fulfillment of the requirements for the Ph.D. degree at North Carolina State University at Raleigh. (b) This work was carried out under Contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

(2) Flavonoids. I: C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **30**, 4114 (1965).

(3) W. Lawson, *J. Chem. Soc.*, 4448 (1954).