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Pyrolytic and Photochemical Wolff Rearrangement of Diazoindanones. Synthesis of 2-Carboalkoxybenzocyclobutenones

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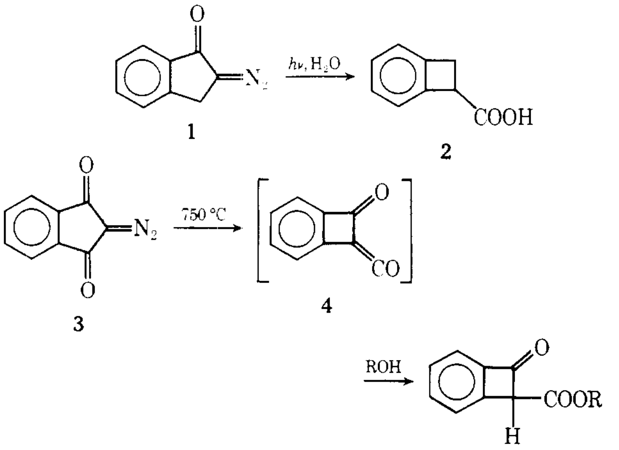
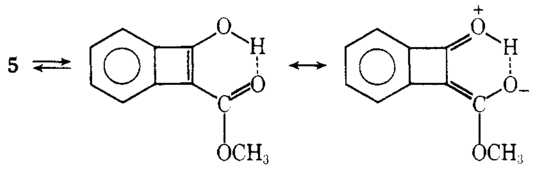
2-Carboalkoxybenzocyclobutenones **5–8** were prepared by the vapor phase pyrolysis of 2-diazo-1,3-indandione (**3**) with alcohols. Similarly the vapor phase pyrolysis of 2-diazo-1-indanone (**1**) with methanol gave methyl benzocyclobutene-1-carboxylate (**24**). These reactions are unusual examples of uncatalyzed thermally induced Wolff rearrangements leading to strained cyclic systems and suggest that the gas phase pyrolysis of cyclic α-diazo ketones may be of use in the synthesis of other strained ring systems. However, the vapor phase pyrolysis of 2-diazo-1,3-indandione (**3**) with water, ammonia, or *tert*-butylamine gave only ring-opened homophthalate derivatives. Ultraviolet irradiation of 2-diazo-1-indanone (**1**) with methanol also yielded methyl benzocyclobutene-1-carboxylate (**24**) as well as 2-methoxy-1-indanone (**26**). In contrast to its pyrolysis, the photolysis of 2-diazo-1,3-indandione (**3**) in methanol gave dimethyl homophthalate (**14**) as the major product.

The ring contraction of diazoindanones has proven to be a useful synthesis of several benzocyclobutene derivatives.[1] For example, the photolysis of aqueous solutions of 2-diazo-1-indanone (**1**) provided an early synthesis of benzocyclobutene-1-carboxylic acid (**2**).[2,3] More recently, Cava and Spangler reported that the gas phase pyrolysis of 2-diazo-1,3-indandione (**3**), under conditions in which the intermediate keto ketene (**4**) could be trapped by methanol, gave 2-carbomethoxybenzocyclobutenone (**5**).[4] The synthesis of **5** from **3** provided the first example of the formation of a strained ring system by an uncatalyzed thermal Wolff rearrangement. We now wish to record the experimental details of this synthetically useful process, to provide examples of other β-keto esters (**6–8**) which can be prepared in this way, to point out some limitations of the process, and to compare the gas phase pyrolysis of diazoindanones **1** and **3** with their solution photochemistry. The β-keto ester **5** is of interest in that its enol tautomer **9** is a benzocyclobutadiene derivative which might be expected to be stabilized not only by intramolecular hydrogen bonding but also by a "push-pull" resonance effect of



1 2 3 4

5, R = CH_3
6, R = $CH(CH_3)_2$
7, R = $C(CH_3)_3$
8, R = $C(CH_3)_2CH{=}CH_2$



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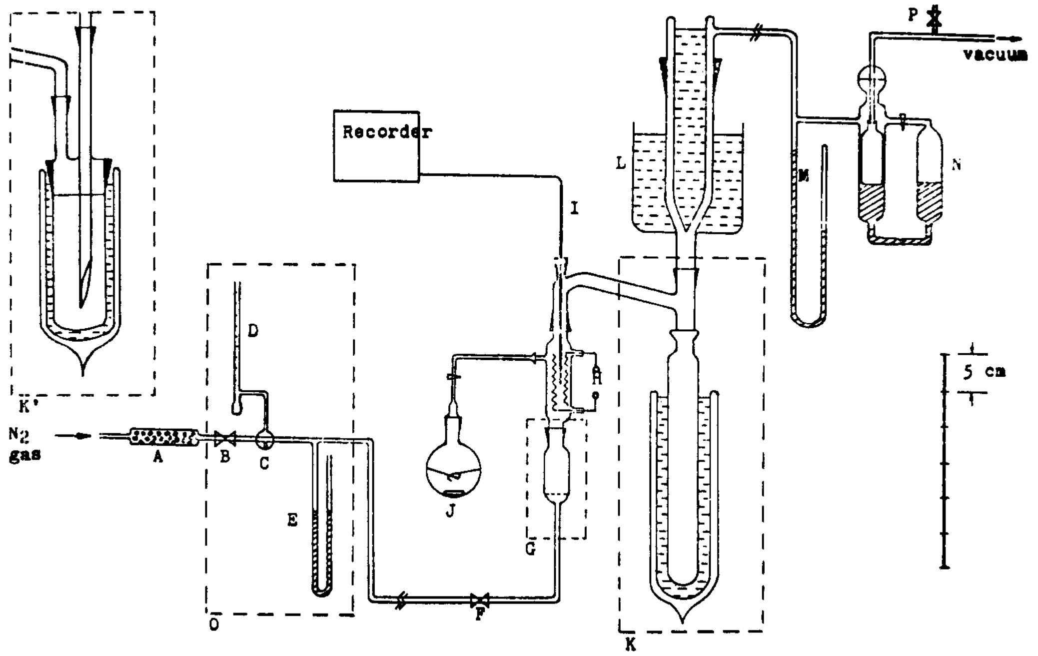


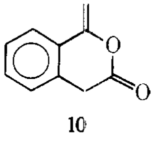
Figure 1. Pyrolysis apparatus.

the hydroxyl and carbomethoxy substituents.[5] The possible existence of enol 9 and the thermal and photochemically induced ring opening reactions of the 2-carboalkoxybenzocyclobutenones 5–8 will be described in a subsequent paper.

Results and Discussion

2-Diazo-1,3-indandione (**3**) was prepared from 1,3-indandione using a modification of the method described by Regitz et al.[6] By using a lower reaction temperature and by purifying the crude product by column chromatography the yield of **3** can be increased from 80–85% as initially reported to 91–95%.[7] 2-Diazo-1-indanone (**1**) was prepared from 2-oximino-1-indanone as described by Cava, Litle, and Napier.[2]

The apparatus (see Figure 1) used for the pyrolysis of diazoindanones **1** and **3** permitted the pyrolysis of a stream of diazoindanone vapor in an inert carrier gas and then allowed the pyrolysate to come immediately into contact with a stream of the vapor of a second reagent capable of reacting with the intermediate keto ketene **4**. In this manner the pyrolysis of 2-diazo-1,3-indandione (**3**) with methanol, 2-propanol, *tert*-butyl alcohol, and 2-methyl-3-buten-2-ol gave the corresponding β-keto esters **5**, **6**, **7**, and **8**, in yields of 50, 42, 30, and 2%, respectively. The efficiency of the reaction appears to be inversely proportional to the size and/or volatility of the alcohol used. The pyrolysis of **3** with 2-methyl-3-buten-2-ol also produced homophthalic anhydride (**10**) in 6% yield and 4-(3-methyl-2-butenyl)homophthalic anhydride (**11**) in 12% yield.



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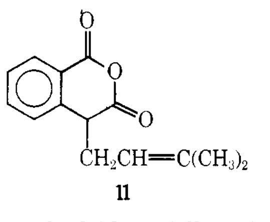

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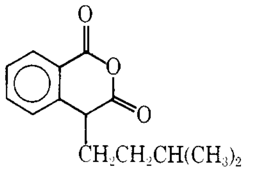
The structure assignment of anhydride **11** follows from its chemical and spectral properties. Thus elemental analysis gave the molecular formula as $C_{14}H_{14}O_3$ in agreement with the molecular ion in the mass spectrum at *m/e* 230. The IR spectrum contains intense bands at 1790 and 1750 cm^{-1}, suggesting that **11** is an anhydride. Weaker bands at 1670 and 840 cm^{-1} indicate the presence of a trisubstituted double bond. The partial NMR spectrum of **11** shows the two methyl groups as three-proton doublets at δ 1.28, the methylene group as a two-proton multiplet at δ 2.5–2.9, the methine proton as a one-proton triplet at δ 4.07 (J = 6.5 Hz), and the vinyl proton as a slightly broadened one-proton triplet at δ 4.88 (J = 8 Hz). Irradiation at δ 2.70 collapsed the triplet at δ 4.07 to a sharp singlet and the triplet at δ 4.88 to a slightly broadened singlet. This NMR behavior is in complete accord with the proposed structure. Hydrogenation of anhydride **11** smoothly yielded the dihydro derivative **12** and hydration of **11** gave the homophthalic acid derivative **13**. The spectral properties of **12** and **13** are also in accord with their proposed structures (see Experimental Section) and serve to further verify the structure of anhydride **11**.



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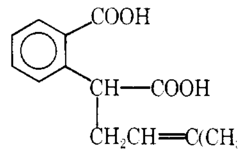

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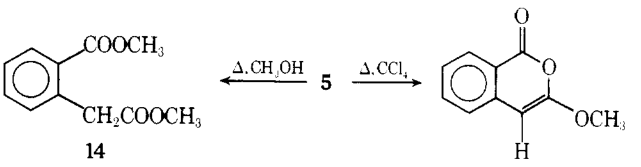
The solid β-keto esters **5** and **7** were readily purified whereas the oily keto esters **6** and **8** could not be obtained free of contaminants. All of the keto esters were fully characterized spectrally. Especially characteristic were the two intense carbonyl absorptions in their IR spectra at 1775–1785 (ketone carbonyl) and 1725–1735 cm^{-1} (ester carbonyl) and the singlet at δ 4.85–4.95 in their NMR spectra due to the methine proton on the four-membered ring. Reaction of keto ester **5** with methanol smoothly produced dimethyl homophthalate (**14**) whereas heating a carbon tetrachloride solution of **5** gave the isomeric 3-methoxyisocoumarin (**15**).[8] Thus the spectroscopic data and their chemical conversions secure the structural assignments for the keto esters **5–8**.



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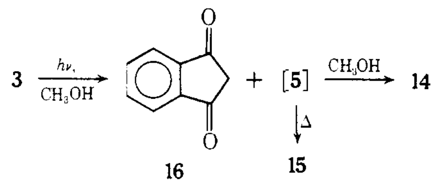
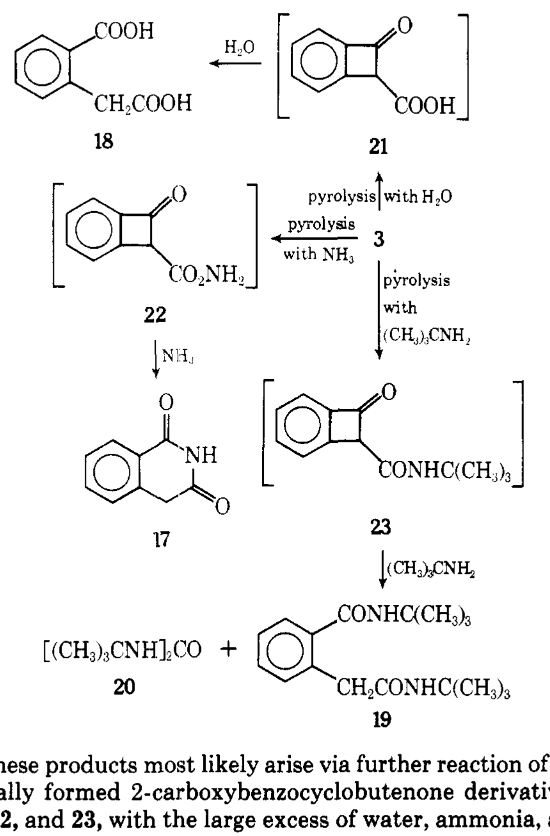
Whereas the gas phase pyrolysis of 2-diazo-1,3-indandione (**3**) with methanol produced synthetically useful yields of 2-carbomethoxybenzocyclobutenone (**5**), the ultraviolet irradiation of a methanol solution of **3**, followed by separation of the products by gas chromatography, gave dimethyl homophthalate (**14**) as the major product (28% yield) with lesser amounts of 1,3-indandione (**16**, 3% yield) and 3-methoxyisocoumarin (**15**, 2% yield). Dimethyl homophthalate (**14**) arises from the further reaction of the initially formed 2-carbomethoxybenzocyclobutenone (**5**) with methanol whereas the 3-methoxyisocoumarin (**15**) arises from the thermal isomerization of **5** in the gas chromatograph. Holt and Wall[9] have reported analogous results. Thus the irradiation of **3** in the presence of water gave homophthalic acid (**18**, 14% yield) and in the presence of aniline gave homophthalic dianilide (76% yield).

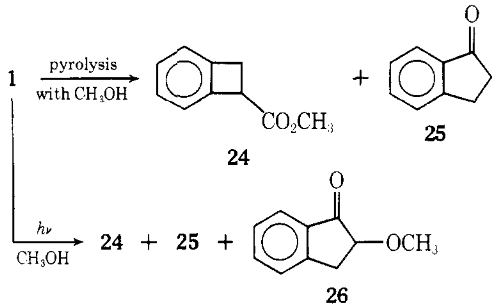


The pyrolysis of the diazoindanone **3** with ammonia, water, or *tert*-butylamine did not produce the desired benzocyclobutenones but instead led to homophthalic acid derivatives. Thus pyrolysis of **3** with ammonia gave homophthalimide (**17**), pyrolysis with water gave homophthalic acid (**18**), and pyrolysis with *tert*-butylamine gave *N,N'*-di-*tert*-butylhomophthalamide (**19**) and *N,N'*-di-*tert*-butylurea (**20**).



These products most likely arise via further reaction of the initially formed 2-carboxybenzocyclobutenone derivatives, **21**, **22**, and **23**, with the large excess of water, ammonia, and *tert*-butylamine which is present in each case. The origin of the *N,N'*-di-*tert*-butylurea (**20**) is not clear. It perhaps arises via the nucleophilic attack of *tert*-butylamine at the amide carbonyl group of intermediate **23**. *N,N'*-Di-*tert*-butyl homophthalamide (**19**) was shown in a separate experiment to be stable toward *tert*-butylamine and thus cannot be the source of the urea **20**.

The pyrolysis of 2-diazo-1-indanone (**1**) with methanol gave methyl benzocyclobutene-1-carboxylate (**24**) in 22% yield and 1-indanone (**25**) in less than 1% yield. The structure of the ester **24** was confirmed by spectral data (see Expermimental Section) and by its hydrolysis to benzocyclobutene-1-carboxylic acid which was shown to be identical with an authentic sample.[2] The pyrolysis of **1** is much less efficient than that of **3** in that **1** does not readily sublime and slowly darkens in the sublimation chamber. DeJongh and Van Fossen[10] have also described a similar pyrolysis of 2-diazo-1-indanone (**1**) with methanol and have reported that 2-methoxy-1-indanone (**26**) was the major pyrolysis product. However, a close examination of their work[11] revealed that the material which these workers thought to be 2-methoxy-1-indanone (**26**) is actually the isomeric methyl benzocyclobutene-1-carboxylate (**24**). In our hands no 2-methoxy-1-indanone (**26**) could be detected in the pyrolysate. However, the photolysis of 2-diazo-1-indanone (**1**) in methanol solution with a low-pressure mercury lamp for 12 h did produce 2-methoxy-1-indanone (**26**) as the major product in 50% yield as well as methyl benzocyclobutene-1-carboxylate (**24**) and 1-indanone (**25**), both in 15% yield. Irradiation under identical conditions for a longer period (26 h) resulted in a substantial change in product distribution: **26**, 34% yield; **24**, 21% yield; **25**, 2% yield. In a separate experiment, irradiation of a cyclohexane solution of pure 2-methoxy-1-indanone (**26**) for 16 h gave a 66% yield of 1-indanone (**25**) and an ether-insoluble tar. Thus the primary photoproducts from 2-diazo-1-indanone (**1**) appear to be methyl benzocyclobutene-1-carboxylate (**24**) and 2-methoxy-1-indanone (**26**). The former is photochemically stable and survives further irradiation whereas the latter photochemically decomposes to 1-indanone (**25**), via a Norrish type II process with the expulsion of formaldehyde.[12] The 1-indanone (**25**) is likewise unstable to extended irradiation, its yield from diazo ketone **1** being 15% after 12 h of irradiation but only 2% after 26 h. Horner, Kirmse and Muth have also described the irradiation of 2-diazo-1-indanone (**1**) using similar conditions but reported only the formation of methyl benzocyclobutene-1-carboxylate (**24**) in 29% yield.[3]



Thus both the pyrolysis and photolysis of 2-diazo-1-indanone (**1**) with methanol gave methyl benzocyclobutene-1-carboxylate (**24**) in about 20% yield. However, the thermally produced ester **24** was more easily purified than photochemically produced **24**. In contrast, the photochemical instability of the keto ester **5** makes its photochemical preparation impossible whereas it can be prepared by the pyrolysis of **3**.

These vapor phase pyrolyses of diazoindanones **1** and **3** to give carboalkoxybenzocyclobutenes **24** and **5–8** are unusual examples of uncatalyzed, thermally induced Wolff rearrangements leading to strained cyclic systems. Although the ultraviolet irradiation of α-diazo ketones to give strained cyclic systems is well known,[13] we are aware of no other uncatalyzed, thermally induced decompositions of α-diazo ketones to strained cyclic systems. The gas phase pyrolysis of α-diazo ketones should be useful in the synthesis of other strained but photochemically unstable systems. However, in the present instance the vapor phase pyrolytic Wolff rearrangement was limited to the synthesis of esters of low molecular weight alcohols. Pyrolysis with higher molecular weight alcohols gave low yields of the β-keto esters; pyrolysis with ammonia; *tert*-butylamine, or water did not give the desired amides **22** and **23** or the keto acid **21** but instead gave ring-opened homophthalate derivatives. These pyrolyses also provide examples of the parallel between the electron impact and thermally induced fragmentation of organic molecules[14] in that the mass spectral decomposition of diazo ketones **1** and **3** is best described as also proceeding via a Wolff rearrangement.[15]

Experimental Section

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. All microvacuum distillations or sublimations were carried out using a Model K-548250 short path distillation apparatus, Kontes Glass Co., Vineland, N.J. IR spectra were determined with a Perkin-Elmer Model 137 or Model 621 spectrometer. NMR spectra were determined with a Varian Model A-60 or HA-100 spectrometer in CCl_4 with Me_4Si as an internal standard unless otherwise specified. Mass spectra were determined at 70 eV with a Hitachi Perkin-Elmer Model RMU-6E mass spectrometer. Elemental analyses were determined with a Perkin-Elmer Model 240 instrument at the University of Idaho and by Midwest Microlab, Inc., Indianapolis, Ind. A Hewlett-Packard Model 700 gas chromatograph equipped with a flame ionization detector and an Aerograph Autoprep A-700 gas chromatograph were used for gas chromatography. The columns used will be designated as column A, 10% SE-30 on 80/100 mesh Chromosorb W/AW-DMCS, 10 ft × 0.25 in.; column B, 10% SE-52 on 80/100 mesh Chromosorb W/AW-DMCS, 10 ft × 0.25 in.; column C, 5% HI-EFF 3B on 80/100 mesh Chromosorb W/AW-DMCS, 6 ft × 0.25 in.

2-Diazo-1,3-indandione (3). A modification of the method of Regitz et al.[6] was used for the preparation of **3**. Thus, to a 1-L beaker, equipped with a thermometer and a magnetic stirrer, was added 1,3-indandione (**16**, 50 g, 0.343 mol) in 300 mL of absolute ethanol followed by cooling to −15 °C in a dry ice–acetone bath. To the mixture was then added triethylamine (45 g, 0.445 mol) in portions while keeping the temperature of the mixture below −5 °C. After an additional 15 min of stirring, tosyl azide[16] (110 g, 0.559 mol) was added over a period of 1 h while maintaining the temperature below −10 °C. The resulting dark red mixture was then stirred for 30 min at below −10 °C, allowed to warm to room temperature by removing the cold bath, and stirred for 1 h at room temperature. The mixture was then cooled with a dry ice–acetone bath to −25 °C and was then rapidly filtered. The resulting dark red crystals were then washed four times with 100-mL portions of cold (−10 to −20 °C) 95% ethanol. The brownish-red crystals thus obtained were then dissolved in 1 L of acetone and this solution was eluted through a 5 × 9 cm column of acid alumina. Evaporation of the acetone on a rotary evaporator gave yellow crystals which were crystallized from hot acetone to give 55 g (91%) of 2-diazo-1,3-indandione (**3**), mp 146–148 °C (lit.[7] mp 149°C).

Pyrolysis Apparatus. A diagram of the pyrolysis apparatus is shown in Figure 1. Nitrogen gas was dried by passage through tower A filled with molecular sieves. The flow rate of the nitrogen carrier gas from the cylinder was controlled by means of needle valve B and was measured with three-way stopcock C open to bubble flowmeter D. After obtaining the desired flow rate, stopcock C was turned to isolate bubble flowmeter D and to allow the carrier gas to enter the pyrolysis system. Needle valve F was adjusted so as to maintain the pressure gauge E at atmospheric pressure. Reactant sublimation chamber G contained a porous glass disk upon which the reactant was placed and was heated by an oil bath. The pyrolysis chamber H contained a coiled nichrome wire heated by a variable transformer. Two kinds of coiled nichrome wire were used. (1) Single strand coil: B. S. gauge 16 nichrome wire was close wound on a 0.6 × 3 cm o.d. glass tube. After being stretched to 5 cm, the coiled wire was sealed inside the pyrolysis chamber with leads extending through the glass wall. The resistance of the installed coil was 0.6 Ω. (2) Multiple strand coil:[17] B. S. gauge 26 nichrome wire was close wound on a $\frac{3}{32}$ in. × 36 cm steel bar. Two turns of the coil were pulled out every 5 cm and a loop twisted in the stretched out portion. In this way the wire was shaped into seven 5-cm coils, each separated by a twisted loop and with hooks at the ends. These strands of coil were stretched by hanging each loop from a glass hook inside the pyrolysis chamber H and by hanging the two ends to leads extending through the glass wall. The resistance of the installed coil was 54 Ω. The pyrolysis temperature was determined with a Chromel-Alumel thermocouple I placed in the center of the pyrolysis chamber H and connected to a 20- or 50-mV strip chart recorder. The diazoindanones **1** and **3** were optimally decomposed at 370–385 °C with the multiple strand wire and at 680 °C with the single strand wire. The trapping reagent was placed in flask J and was introduced as a vapor just above the pyrolysis chamber by warming flask J with a heating mantle and stirring the contents magnetically. Cold trap K or K′ was placed under cold finger L to collect the trapping reagent and pyrolysate that dripped off the cold finger L. The pressure of the system was regulated with a manostat N and was determined with a McLeod gauge or manometer M.

Pyrolysis of 2-Diazo-1,3-indandione (3) with Methanol. The apparatus described in the previous section, except without the carrier gas flow measuring device O and with the single strand coil in the pyrolysis chamber H, was used. In a typical experiment, the sublimation chamber G was charged with **3** (5 g, 29 mmol) and flask J was charged with 500 mL of methanol. The entire system was flushed with nitrogen and then the methanol was cooled in a dry ice–acetone bath. The pressure of the system was then reduced to the minimum obtainable (2.3 mm). Nitrogen was then admitted by opening needle valve F until the system pressure increased to 10 mm. Vacuum release valve P was opened to the atmosphere until the pressure of the system reached 25 mm and then the stopcock in manostat regulator N was closed and valve P was closed so that the regulator maintained the system at a constant 25 mm. The dry ice–acetone bath was then removed from flask J and cold trap K and cold finger L were cooled with dry ice–acetone. Flask J was heated to maintain a stream of methanol vapor from flask J to cold finger L. The nichrome wire was then heated to 680 °C and sublimation chamber G was also heated to achieve a slow sublimation of diazoindanone **3**. Pyrolysis was allowed to proceed for 2 h until all the methanol had distilled from flask J. All the heaters were then turned off and the apparatus was allowed to warm to room temperature under a nitrogen atmosphere before disassembly. Unsublimed diazo ketone (**3**, 1.1 g) was recovered from sublimation chamber G and 0.16 g of tar was removed from the walls of the pyrolysis chamber H. The side arm leading to the cold finger and the cold finger itself were rinsed with ca. 200 mL of methylene chloride and this was combined with the solution in cold trap K. Solvent removal with a rotary evaporator below 35 °C gave a brown oil which crystallized upon standing at −15 °C. The crystalline or oily product was sublimed at an oil bath temperature up to 78 °C (0.4 mm) to give slightly yellow crystals of keto ester **5**. This product was contaminated with a trace of dimethyl homophthalate (**14**) and 3-methoxyisocoumarin (**15**)[8] as determined by NMR. Successive recrystallization from anhydrous ether at −78 °C under nitrogen gave colorless crystals of **5** (2.0 g, 51%): mp 56–57 °C; NMR δ 3.68 (s, 3 H), 4.94 (s, 1 H), and 7.28–7.67 (m, 4 H); IR (KBr) 2995, 1780, 1735, 1640, 1580, 1460, 1425, 1345, 1325, 1290, 1235, 1195, 1164, 1145, 1087, 1025, 937, 922, 870, 845, and 730 cm^{-1}; mass spectrum *m/e* (rel intensity) 176 (7), 148 (57), 133 (100), 105 (18), 89 (48), 88 (9), 77 (18), 63 (29), 62 (15), 51 (11), 50 (8), 39 (20).

Anal. Calcd for $C_{10}H_8O_3$: C, 68.16; H, 4.58. Found: C, 68.10; H, 4.63.

When a solution of **5** (151 mg) in carbon tetrachloride (1.34 g) was heated at 95 °C under a nitrogen atmosphere for 12 h, the NMR of the solution indicated that **5** had completely isomerized to 3-methoxyisocoumarin (**15**).[8] Preparative gas chromatography (column A at 208 °C) gave pure **15**: mp 70–71 °C (lit.[8] mp 69–70 °C); NMR δ 3.96 (s, 3 H), 5.49 (s, 1 H), and 7.10–7.73 (m, 4 H); IR (KBr) 3075, 3000, 2940, 1720, 1640, 1602, 1560, 1483, 1432, 1368, 1330, 1313, 1247, 1220, 1197, 1173, 1037, 1004, 948, 890, 873, 795, 780, and 743 cm^{-1}; mass spectrum *m/e* (rel intensity) 176 (33), 148 (43), 133 (100), 105 (15), 89 (29), 88 (8), 77 (13), 63 (16), 62 (10), and 51 (6). When an equimolar solution of **5** (62.8 mg, 0.36 mmol) and methanol in carbon tetrachloride solution was refluxed for ca. 30 min, the NMR of the resulting solution was identical with that of dimethyl homophthalate (**14**). Preparative gas chromatography (column C at 192 °C) gave pure dimethyl homophthalate (**14**), identical in gas chromatography retention time, infrared, and mass spectra with an authentic sample of **14** prepared by the esterification of homophthalic acid.

Pyrolysis of 2-Diazo-1,3-indandione (3) with 2-Propanol. The pyrolysis of **3** with 2-propanol was carried out as described in the previous section except with the addition of the nitrogen flow measuring device O. Thus diazo ketone **3** (5.4 g, 31.4 mmol) was pyrolyzed at 680 °C while 340 mL of 2-propanol was distilled from flask J to cold trap K, with 100 mL/min of nitrogen flow, a system pressure of 24 mm, and a 2-h reaction time. After pyrolysis, 0.37 g of tar was formed in the pyrolysis chamber H and 0.5 g of unsublimed **3** was recovered from the sublimation chamber G. After rinsing the side arm and cold finger, removal of the combined solvents on a rotary evaporator gave a brown oil which could not be crystallized. This oil was stirred with 300 mL of petroleum ether (bp 30–60 °C) and filtered to remove an insoluble tar. After evaporation of the petroleum ether, the resulting yellow oil was distilled at an oil bath temperature up to 77 °C (0.4 mm) to give 2.43 g (43%) of yellow, liquid 2-carboisopropoxybenzocyclobutenone (**6**). Gas chromatography[18] (column A at 208 °C) indicated that the product **6** was contaminated with a small amount of an unknown compound; this contaminant could not be removed. The purity of **6** was estimated as >97% by NMR. Impure **6** showed the following properties: NMR δ 1.20 (d, 6 H, $J = 6$ Hz), 4.53–5.29 (m with strong s at 4.86, 2 H), and 7.22–7.68 (m, 4 H); IR (film) 3040, 1785, 1730, 1640, 1590, 1465, 1375, 1290, 1195, 1145, 1107, 992, 933, 913, and 758 cm^{-1}; mass spectrum *m/e* (rel intensity) 204 (14), 162 (56), 145 (5), 134 (100), 118 (4), 105 (27), 89 (12), 77 (8), and 63 (11).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.7; H, 5.89. Found: C, 70.0; H, 6.07.

Pyrolysis of 2-Diazo-1,3-indandione (3) with *tert*-Butyl Alcohol. The pyrolyses of **3** with *tert*-butyl alcohol were carried out as described above except that cold trap K′ was used in place of K. Thus, in a typical run, **3** (5.0 g, 28.8 mmol) was pyrolyzed in 2 h at 680 °C while 465 mL of *tert*-butyl alcohol was distilled from flask J; a 100 mL/min nitrogen flow and a 25-mm pressure were maintained. Workup as before gave 0.4 g of recovered diazo ketone **3**, 0.2 g of tar from the pyrolysis chamber, and a viscous, brown pyrolysate. Vacuum distillation of the pyrolysate at an oil bath temperature up to 84 °C (0.5 mm) gave 1.8 g (31%) of a yellow oil which gave white crystals upon washing with a small portion of pentane. Three recrystallizations from ether at −78 °C and one from cold ether–petroleum ether (bp 30–60 °C) (1:2 v/v) gave 2-carbo-*tert*-butoxybenzocyclobutenone (**7**): mp 56–57 °C; NMR δ 1.45 (s, 9 H), 4.86 (s, 1 H), and 7.25–7.67 (m, 4 H); IR (melted film) 3020, 1780, 1730, 1595, 1470, 1370, 1290, 1250, 1207, 1160, 1140, 1090, 980, 935, 887, and 760 cm^{-1}; mass spectrum *m/e* (rel intensity) 218 (1), 162 (54), 145 (37), 134 (98), 118 (12), 105 (25), 90 (15), 89 (40), 77 (8), 63 (27), 57 (100), and 41 (79).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.55; H, 6.43. Found: C, 72.12; H, 6.35.

Pyrolysis of 2-Diazo-1,3-indandione (3) with 2-Methyl-3-buten-2-ol. The pyrolyses of **3** with 2-methyl-3-buten-2-ol were carried out with the apparatus shown in Figure 1 using the multiple strand coil in the pyrolysis chamber H. In a typical run, **3** (8.1 g, 47.1 mmol) was pyrolyzed at 370 °C during 1 h while 60 mL of 2-methyl-3-buten-2-ol was distilled; a 100 mL/min nitrogen flow and a 25-mm pressure were maintained. After pyrolysis, 2.9 g of tar was found in the pyrolysis chamber H and all of **3** was consumed. The viscous, brown pyrolysate, obtained as before, was vacuum distilled at 0.25 mm. The first fraction was collected at an oil bath temperature of 80–100 °C to give 0.36 g of a clear oil containing mostly keto ester **8**; the second fraction was collected at 100–134 °C to give 2.45 g of a yellow oil. The second fraction, in ca. 3 mL of carbon tetrachloride, gave white crystals upon standing at −12 °C overnight. The crystals were filtered and washed with additional carbon tetrachloride to give 0.44 g (5.8%) of homophthalic anhydride (**10**), mp 140–145 °C. The IR, NMR, and mass spectrum were identical with those of an authentic sample. The filtrate and washings were combined and the solvent was then removed at 20 °C with a rotary evaporator. The resulting yellow oil was then taken up in 3 mL of ether followed by cooling in a dry ice–acetone bath. After white crystals appeared, the ether solution was diluted with 20 mL of pentane and was then stored at −12 °C for 2 h. Filtration and air drying gave 4-(3-methyl-2-butenyl)homophthalic anhydride (**11**, 1.3 g, 12%), mp 60–63 °C. Recrystallization from ether at −78 °C gave analytically pure **11**: mp 63–65 °C; NMR δ 1.28 (d, $J = 1$ Hz, 3 H), 1.60 (d, $J = 1$ Hz, 3 H), 2.50–2.90 (m, 2 H), 4.07 (t, $J = 6.5$ Hz, 1 H, irradiation at 2.70 collapsed this triplet to a singlet at 4.07), 4.88 (t, $J = 8$ Hz, 1 H, irradiation at 2.70 collapsed this triplet to a singlet at 4.88), and 7.26–8.15 (m, 4 H); IR (KBr) 2970, 2925, 1790, 1750, 1670, 1610, 1490, 1465, 1383, 1320, 1290, 1200, 1050, 1020, 840, 785, and 755 cm^{-1}; mass spectrum *m/e* (rel intensity) 230 (5), 212 (2), 162 (53), 134 (39), 118 (6), 105 (7), 90 (9), 89 (9), 77 (10), 69 (100), 63 (10), and 41 (94).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.06; H, 6.09. Found: C, 72.95; H, 6.05.

The first fraction failed to crystallize from carbon tetrachloride solution upon standing at −12 °C. Gas chromatography (column B at 253 °C) showed a single peak with a retention time identical with that of **11** because of thermal isomerization in the gas chromatograph. Integration of the NMR spectrum indicated that this fraction contained 92% (2% yield) of keto ester **8** and 8% of acid anhydride **11**. Impure **8** showed the following properties: NMR (minus peaks due to **11**) δ 1.50 (s, 6 H), 4.83–5.30 (m with strong s at 4.88, 3 H), 5.78–6.31 (q, centered at 6.04, 1 H), and 7.29–7.70 (m, 4 H); IR (film) 2975, 1775, 1725, 1585, 1465, 1290, 1195, 1120, 927, and 755 cm^{-1}; mass spectrum *m/e* (rel intensity) 218 (1), 163 (7), 162 (54), 146 (5), 145 (37), 135 (9), 134 (98), 118 (12), 105 (25), 90 (15), 89 (40), 88 (5), 87 (3), 78 (5), 77 (8), 63 (27), 62 (9), 58 (5), 57 (100), 56 (20), 55 (10), 51 (8), 50 (8), 41 (79), 39 (39).

4-(3-Methylbutyl)homophthalic Anhydride (12). A 100-mL Brown[2] hydrogenation flask[19] equipped with a magnetic stirrer was charged with 0.5 g of Darco K-B carbon black[19] and 2 mL of a 0.05 M solution of chloroplatinic acid in 2-propanol and then was connected to a Brown[2] valve, a Brown[2] bubbler, and a buret. To the flask, with vigorous stirring, was added four 5-mL portions of a 0.1 M solution of sodium borohydride in absolute ethanol; then 1.5 mL of concentrated hydrochloric acid was added through a rubber septum by means of a hypodermic syringe. To this mixture was then added a solution of anhydride **11** (920 mg, 4 mmol) in 10 mL of 2-propanol through the rubber septum. Then 5.2 mL of a 0.1 M solution of sodium borohydride in absolute ethanol was added to the flask via the buret over a period of 4 h. At the end of the reaction time, the resulting mixture was filtered and the solvent was removed by a rotary evaporator. The resulting oil was dissolved in ca. 100 mL of ether and the solution was dried over magnesium sulfate. Filtration and evaporation of the solvent followed by distillation with an oil bath temperature up to 178 °C (0.1 mm) gave 4-(3-methylbutyl)homophthalic anhydride (**12**, 840 mg, 87%). The fraction separately collected at an oil bath temperature of 120–140 °C was used for the characterization of **12**: NMR δ 0.63–2.85 (m with strong d at 0.83, $J = 5$ Hz, 11 H), 4.02 (t, $J = 6$ Hz, 1 H), and 7.20–8.21 (m, 4 H); IR (film) 2950, 1795, 1750, 1600, 1455, 1383, 1365, 1285, 1165, 1050, 1015, and 750 cm^{-1}; mass spectrum *m/e* (rel intensity) 232 (6), 188 (17), 162 (26), 145 (27), 131 (100), 117 (16), 115 (17), 103 (17), and 77 (20).

ω-(3-Methyl-2-butenyl)homophthalic Acid (13). A solution of 4-(3-methyl-2-butenyl)homophthalic anhydride (**11**, 810 mg, 3.5 mmol) in aqueous dioxane was stirred for 12 h at room temperature. The solvent was removed on a rotary evaporator and the residue was extracted with ether. Drying (magnesium sulfate) and removed of the ether gave ω-(3-methyl-2-butenyl)homophthalic acid (**13**, 750 mg, 91%), mp 129–131 °C, which was recrystallized once from carbon tetrachloride: mp 132–134 °C; NMR (Me_2SO-d_6) δ 1.49 (d, $J = 1$ Hz, 3 H), 1.59 (d, $J = 1$ Hz, 3 H), 2.43–2.59 (m, 2 H, including some undeuterated Me_2SO-d_6), 4.59 (t, $J = 8$ Hz, 1 H), 4.86–5.20 (m, 1 H), and 7.18–8.00 (m, 4 H); IR (KBr) 3500–2300, 1685, 1600, 1573, 1490, 1405, 1304, 1270, 1220, 1145, 1080, 992, 805, 750, and 730 cm^{-1}; mass spectrum *m/e* (rel intensity) 248 (5), 230 (9), 202 (21), 180 (7), 162 (42), 134 (40), 128 (6), 115 (10), 69 (100), 63 (6), and 41 (59).

Pyrolysis of 2-Diazo-1,3-indandione (3) with Ammonia. The apparatus described in Figure 1, except with a flow regulator and anhydrous ammonia tank in place of flask J and with the multiple strand wire, was used. The flow rate of ammonia was regulated with a disk flow regulator (Model 2403 M2, The Matheson Co., Inc., East Rutherford, N.J.) and was measured with a rotameter. An extra liquid nitrogen cold trap was installed just before the vacuum pump. Thus, **3** (9.6 g, 55.8 mmol) was pyrolyzed at 370 °C in 1 h with a 500 mL/min flow of ammonia and a system pressure of 25 mm. After pyrolysis, 5.8 g of tar was removed from the pyrolysis chamber H and all of **3** was consumed. The pyrolysate was rinsed from the glassware with ca. 200 mL of acetone. After evaporation of the acetone on a rotary evaporator, the crude pyrolysate was sublimed at an oil bath temperature up to 190 °C (2.5 mm) to give yellow crystals. Washing these with a small portion of acetone and air drying gave homophthalimide (**17**, 0.87 g, 9.9%), mp 236–238 °C (lit.[20] mp 233 °C). The IR, mass spectrum, melting point, and mixture melting point were identical with those of an authentic sample of homophthalimide (**17**) prepared from homophthalic acid and aqueous ammonia.[20]

Pyrolysis of 2-Diazo-1,3-indandione (3) with *tert*-Butylamine. The procedure used was identical with that described for the pyrolysis of **3** with 2-methyl-3-buten-2-ol. Thus diazo ketone **3** (8.4 g, 48.4 mmol) was pyrolyzed at 385 °C during 1 h while 80 mL of *tert*-butylamine was distilled from flask J to cold trap K; a 100 mL/min nitrogen flow and a pressure of 25 mm were maintained. After the pyrolysis 5.9 g of tar was left inside the pyrolysis chamber H and all of **3** was consumed. After solvent removal the dark brown pyrolysate was vacuum distilled at 173 °C (0.15 mm) to give a yellow distillate which crystallized on the cold finger. Fractional crystallization of the distillate from ether gave *N,N′*-di-*tert*-butylurea (**20**, 0.79 g, 9.6%), mp 190–234 °C. One recrystallization from carbon tetrachloride gave pure **20**: mp (sealed tube) 251–254 °C (lit.[21] mp 245 °C); NMR ($CDCl_3$–Me_2SO-d_6, 1:1 v/v) δ 1.23 (s, 18 H) and 5.45 (s, 2 H); IR (KBr) 3340, 2955, 2918, 1627, 1595, 1547, 1470, 1442, 1382, 1357, 1287, 1227, 1200, and 632 cm^{-1}; mass spectrum *m/e* (rel intensity) 172 (4), 157 (7), 101 (2), 71 (3), 61 (7), 58 (100), 57 (13), and 41 (10).

The ether-soluble filtrate remaining after the removal of **20** was taken to dryness on a rotary evaporator. The resulting solid was dissolved in ca. 6 mL of acetone followed by the dropwise addition of water until the solution turned milky. The final mixture was then stored overnight at −12 °C. Filtration followed by drying the resulting crystals at 20 °C gave *N,N'*-di-*tert*-butylhomophthalamide (**19**, 1.43 g, 10.3%), mp 137–141 °C. The properties of **19** obtained here were identical with those of a sample of **19** prepared from homophthalic acid (**18**) and *tert*-butylamine (see below).

***N,N'*-Di-*tert*-butylhomophthalamide (19).** A mixture of **18** (18 g, 0.11 mol) and *tert*-butylamine (250 mL) in 100 mL of water was heated on a steam bath to dryness and then in an oil bath for 1 h at 230 °C. The resulting brownish-yellow cake was dissolved in 200 mL of ether and the resulting solution was washed with 200 mL of 20% aqueous sodium carbonate. The aqueous layer was then extracted once with 100 mL of ether. The ether layers were combined, washed once with 50 mL of water, and dried (magnesium sulfate). Removal of the solvent on a rotary evaporator gave 6.9 g of a yellow oil which crystallized upon standing at room temperature. The crystals were sublimed at an oil bath temperature up to 190 °C (0.15 mm) to give **19** (4.8 g, 15%), mp 141–142 °C, after washing with a small amount of ether. Two recrystallizations from aqueous acetone gave pure **19**: mp 144–145 °C; NMR δ 1.30 (s, 9 H), 1.45 (s, 9 H), 2.81 (s, 2 H), 6.56–7.54 (m, 4 H), 8.30 (s, 1 H), and 9.14 (s, 1 H); IR (KBr) 1479, 1454, 1408, 1390, 1360, 1319, 1259, 1222, 927, 886, 778, 746, 737, and 696 cm^{-1}; mass spectrum *m/e* (rel intensity) 290 (3), 218 (15), 217 (6), 191 (100), 176 (28), 162 (42), 148 (7), 145 (8), 136 (21), 135 (41), 134 (26), 133 (17), 119 (70), 118 (34), 116 (14), 91 (14), 90 (16), 89 (15), 58 (17), 57 (36).

Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.33; H, 8.97; N, 9.66. Found: C, 70.38; H, 9.06; N, 9.66.

Stirring either a solution of **19** (105 mg) in *tert*-butylamine (5 mL) or a solution of **19** (70 mg) in *tert*-butylamine (6 mL) and water (4 mL) resulted in the complete recovery of **19** as shown by gas chromatography (column B at 248 °C) and NMR (in Me_2SO-d_6). In particular, no NMR signals corresponding to those of *N,N'*-di-*tert*-butylurea (**20**) could be detected.

Pyrolysis of 2-Diazo-1,3-indandione (3) with Water. The pyrolysis of **3** (2.0 g, 11.6 mmol) with water (400 mL) was carried out in the same manner as described for the pyrolysis of diazoindanone (**3**) with methanol. The resulting aqueous pyrolysate was extracted twice with 300-mL portions of methylene chloride and finally once with 200 mL of ether. The extracts were combined and dried (magnesium sulfate). Evaporation of the solvent on a rotary evaporatory gave homophthalic acid (**18**, 1.1 g, 35%), mp 185–186 °C, identical with an authentic sample in melting point and NMR spectrum.

Pyrolysis of 2-Diazo-1-indanone (1)^2 with Methanol. The pyrolysis of **1** (3.0 g, 17.4 mmol) with methanol (50 mL) was carried out in the manner described for the pyrolysis of 2-diazo-1,3-indandione (**3**) with 2-methyl-3-buten-2-ol. After pyrolysis 2.0 g of darkened **1** was left in the sublimation chamber and no tar was found in the pyrolysis chamber. Solvent removal gave **24** (0.69 g, 22%) as a yellow oil. The spectral properties of **24** obtained here were identical with those of a sample of **24** obtained from the photolysis of **1** in methanol (see below). Gas chromatography (column B at 250 °C) showed that this material also contained ca. 3% of 1-indanone (**25**). Ketone **25** was isolated by preparative gas chromatography and was identified by comparison of its GC retention time, IR, and mass spectrum with those of an authentic sample.

Photolysis of 2-Diazo-1-indanone (1) with Methanol. The procedure of Horner, Kirmse, and Muth^3 was followed. Thus, **1**^{2} (13 g, 82 mmol) and methanol (1.3 L) were placed in a quartz vessel. The resulting solution was flushed with nitrogen and was then irradiated for 12 h with a Rayonet photochemical reactor equipped with RPR-2537 lamps (The Southern New England Ultraviolet Co., Middletown, Conn.). After evaporation of the solvent the resulting oil was distilled at 83–107 °C (1.2 mm) to give 10.5 g of a yellow oil. Gas chromatography (column C at 168 °C) and subsequent isolation showed that the product was a mixture of methyl benzocyclobutene-1-carboxylate (**24**, 18%, 15% yield), 1-indanone (**25**, 18%, 15% yield), and 2-methoxy-1-indanone (**26**, 64%, 50% yield). A similar experiment using **1** (10 g, 60 mmol) in methanol (1 L) gave 4.7 g of a yellow distillate after 26 h of irradiation; this distillate consisted of **24** (62%, 21% yield), **25** (4%, 2% yield), and **26** (34%, 15% yield). 1-Indanone (**25**) was isolated by preparative gas chromatography using the conditions above and was identified by comparison of its GC retention time, IR, and mass spectrum with those of an authentic sample. Attempts to obtain pure **24** by fractional distillation were unsuccessful and **24** was also purified by preparative gas chromatography (column C at 168 °C): NMR δ 3.40 (apparent d, distance between peaks 4 Hz, 2 H), 3.64 (s, 3 H), 4.18 (apparent t, distance between peaks 4.5 Hz, 1 H), and 6.90–7.32 (m, 4 H); IR (film) 2947, 1735, 1458, 1436, 1360, 1307, 1270, 1207, 1167, 1090, 1027, 761, and 728 cm^{-1}; mass spectrum *m/e* (rel intensity) 162 (73), 161 (19), 131 (97), 119 (32), 103 (100), 102 (39), 91 (36), 77 (57), and 51 (33).

Acid hydrolysis^3 of **24** (256 mg, 1.5 mmol) in 1 mL of concentrated hydrochloric acid at 100 °C for 2 h and recrystallization of the resulting crude acid from petroleum ether (bp 30–60 °C) gave benzocyclobutene-1-carboxylic acid (**2**, 180 mg, 77%), mp 73–74 °C (lit.^{2} mp 76.5 °C), identical with an authentic sample:^{2} NMR δ 3.44 (unsymmetrical d, distance between peaks 4 Hz, 2 H), 4.27 (apparent t, distance between peaks 4.5 Hz, 1 H), 6.97–7.32 (m, 4 H), and 12.5 (s, 1 H); IR (KBr) 3350–2170, 1712–1680, 1453, 1412, 1305, 1230, 1128, 1002, 930, 900, 798, 750, and 718 cm^{-1}; mass spectrum *m/e* (rel intensity) 148 (89), 147 (43), 131 (17), 130 (9), 120 (45), 119 (100), 105 (26), 104 (35), 103 (72), 102 (52), 92 (18), 91 (96), 78 (12), 77 (82), 76 (21), 75 (17), 74 (18), 65 (17), 63 (25), 62 (12), 52 (12), 51 (60), and 50 (37).

Pure **26** could be obtained by three fractional distillations of the photolysate with an 18-cm Vigreux column at 94–104 °C (1.2 mm): NMR δ 2.67–3.69 (m, 2 H), 3.60 (s, 3 H), 3.86–4.10 (apparent q, 1 H), and 7.22–7.84 (m, 4 H); IR (film) 2917, 2814, 1712, 1599, 1452, 1313, 1290, 1264, 1200, 1140, 1114, 1083, 1020, 1002, 879, 753, and 709 cm^{-1}; mass spectrum *m/e* (rel intensity) 162 (5), 161 (4), 132 (100), 131 (22), 119 (19), 103 (15), 91 (52), and 77 (13). The dinitrophenylhydrazone of **26**, after recrystallization from dioxane, melted at 254.5–256.5 °C (lit.^{22} mp 253.5 °C).

Photolysis of 2-Diazo-1,3-indandione (3) with Methanol. A Pyrex photochemical reaction vessel equipped with a 450-W Hanovia mercury immersion lamp (see Catalog 600, Ace Glass Inc., Vineland, N.J., stock no. 6515-04, 6515-36, and 6517-05) was charged with **3** (810 mg, 4.7 mmol) and 190 mL of methanol. The resulting solution was flushed with nitrogen and was then irradiated for 2.5 h at 25–30 °C. The dark brown solution was evaporated to 10 mL on a rotary evaporator and 40 mL of cyclohexane was added. A dark brown, insoluble gum was removed by filtration and was washed with additional cyclohexane. The filtrate and washings were combined, the volume was reduced to about 40 mL, and additional insoluble material was removed by filtration. The filtrate was then treated twice with activated charcoal. Solvent removal and vacuum distillation at 2 mm gave 338 mg of a yellow oil. Gas chromatography (a 20 ft × 0.375 in. column packed with 30% SE-30 on 45/60 mesh Chromosorb W at 182 °C) showed that the product consisted of three major volatile components present in the ratio 6/81/12. Isolation by preparative gas chromatography and comparison of the IR spectra and GC retention times of the isolated materials with those of authentic samples showed that these three materials were 1,3-indandione (**16**), dimethyl homophthalate (**14**), and 3-methoxyisocoumarin (**15**),^{8} respectively. The yield of the major product, dimethyl homophthalate (**14**), was determined to be 29% by gas chromatography.

Photolysis of 2-Methoxy-1-indanone (26). Irradiation of a solution of **26** (140 mg, 0.86 mmol) in cyclohexane (4 mL) and under nitrogen with a low-pressure mercury lamp (Model PCQ-X1, Ultraviolet Products Inc., San Gabriel, Calif.) and using a quartz vessel gave 22 mg of an ether-insoluble tar, which was not characterized, and 95 mg of an ether-soluble yellow oil. The yellow oil was shown by GC (column B at 226 °C) to be ca. 80% (66% yield) of 1-indanone (**25**) but was not characterized further.

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Registry No.—**1**, 1775-23-1; **2**, 14381-41-0; **3**, 1807-49-4; **5**, 17539-22-9; **6**, 61665-48-3; **7**, 61665-49-4; **8**, 61665-50-7; **10**, 703-59-3; **11**, 61665-51-8; **12**, 61665-52-9; **13**, 61665-53-0; **15**, 4090-69-1; **16**, 606-23-5; **17**, 4456-77-3; **18**, 89-51-0; **19**, 61665-54-1; **20**, 5336-24-3; **24**, 35095-07-9; **26**, 1579-18-6; methanol, 67-56-1; 2-propanol, 67-63-0; *tert*-butyl alcohol, 75-65-0; 2-methyl-3-buten-2-ol, 115-18-4; *tert*-butylamine, 75-64-9; ammonia, 7664-41-7; water, 7732-18-5.

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Synthesis and Structures of Dilactones Related to Anemonin

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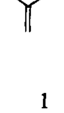
Reduction of anemonin (**2**) with H_2 over Pd/C gave tetrahydroanemonin (**3**) as reported in the literature, and reduction of anemonin with sodium borohydride in methanol gave keto ester **13** and dilactone **14**. However, reduction of anemonin (**2**) with sodium amalgam gave a compound with the properties of isotetrahydroanemonin which was assigned structure **6** in the literature. Spectroscopic evidence and single crystal x-ray analysis showed that isotetrahydroanemonin had structure **15** [2-oxa-3-oxo(*r*-1,*c*-5)bicyclo[3.3.0]octa-6-spiro[*t*-1′-oxa-2′-oxocyclopentane]] and not **6**. In addition, both the trans and cis di-α-methylenebutyrolactones **4a** and **4b** (1,7-dioxadispiro[4.0.4.2]dodeca-3,9-dimethylene-2,8-dione) have been prepared by reaction of cyclobutane-1,2-dione with α-(bromomethyl)acrylate and zinc. The structure of the cis compound **4b** was established by single crystal x-ray techniques. Isotetrahydroanemonin (**15**) crystallized in space group $P2_1/c$ with a = 7.258 (4), b = 5.821 (1), and c = 22.285 (2) Å, β = 85.63 (1)°, and four molecules per unit cell. The structure was solved by direct methods and refined to an R factor of 0.061 on 1340 observed reflections. The di-α-methylene-γ-butyrolactone **4b** also crystallized in space group $P2_1/c$ with a = 11.300 (5), b = 7.915 (2), c = 11.903 (5) Å, β = 92.14 (5)°, and four molecules per unit cell. This structure was also solved by direct methods and refined to an R factor of 0.081 on 1545 independent reflections. The angle strain energy in lactones **4b** and **15** has been estimated using the Westheimer approach. A comparison of these strain energies with the strain energy in other lactones whose crystal structures have been published revealed the effect of ring fusion on the strain energy of these lactones. These comparisons indicated that the order of strain energy for both γ-butyrolactones and α-methylene-γ-butyrolactones was trans fused (to a six-membered ring) > cis fused ≃ spiro fused.

The isolation of anticancer drugs from natural sources has established a number of novel chemical templates which are valuable leads in the design of related synthetic antitumor agents. These compounds include a number of sesquiterpene lactones which have significant cytotoxic and antitumor activity. The biological activity of this class appears to be related to the presence of one or more highly electrophilic groups in the molecule including predominantly epoxides and conjugated carbonyl systems with the α-methylene-γ-butyrolactone group (**1**) appearing to play an especially important role.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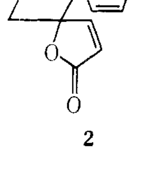
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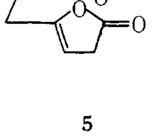
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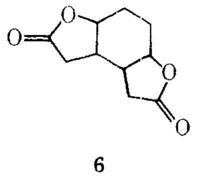
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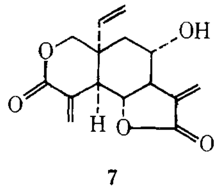
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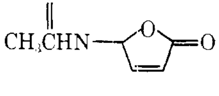
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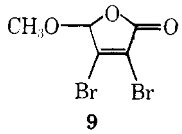
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During the course of our studies aimed at the synthesis of potential tumor inhibitors containing the α-methylene-γ-butyrolactone moiety, we have explored the synthesis of several compounds related to anemonin (**2**).[2] Anemonin, which has received considerable attention in the literature, was an attractive synthetic intermediate based on the presence of two lactone rings in a fixed configuration which could potentially be modified to give an interesting series of related dilactones. For example, reduction of anemonin to tetrahydroanemonin (**3**)[3,4] followed by bis-α-methylenation was envisioned as a route to the bislactone **4a** (Scheme I). Other reported reduction products, including dihydroanemonin (**5**)[2,5,6] and isotetrahydroanemonin (**6**),[5-7] were promising precursors to open-chain dilactones and fused ring dilactones. For example, compound **6** was seen as a potential precursor to a close analogue of the tumor inhibitor vernolepin (**7**).[8] In addition the reported cytotoxic and antitumor activity of