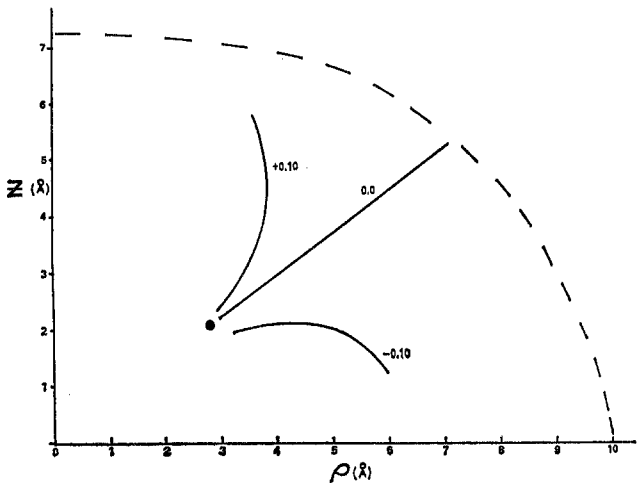


Figure 1.—The +0.10-, 0.00-, and −0.10-ppm isoshielding lines about a phenyl ring. Z is the axis perpendicular to the phenyl nuclear plane and passing through the center of the ring, and ρ is the axis perpendicular to Z and passing through the center of the phenyl ring. The dotted line represents the maximum possible distance of the α protons of sodium ω-phenyloctanoate from the center of the phenyl ring. The origin is at the center of the phenyl ring. The point on the graph represents the distance of closest approach of the α protons to the phenyl ring.

trations listed in Table I are considerably lower than 0.8 *M;* the DSS internal reference constituted no more than 1% by weight of the D_2O solutions used (Table I). The downfield shift of the phenyl protons of ω-phenyloctanoic acid sodium salt (Table I) upon dilution is opposite to that expected if DSS complexed with the carboxylate salt. All of these considerations suggest that the chemical shifts listed in Table I are real and do not reflect a perturbation of the DSS resonance position.

Experimental Section

Proton magnetic resonance spectra were obtained on a Jeolco C-60H nmr spectrometer operating at 60 MHz with an ambient probe temperature of approximately 29°. Tetramethylsilane (TMS) was used as an internal reference in carbon tetrachloride solutions and sodium 4,4-dimethyl 4-silapentane-1-sulfonate (DSS) was used as an internal reference in D_2O solutions. Chemical shifts were found to be reproducible to within ±0.02 ppm. Chemical shifts were estimated by first-order analyses and are believed to be accurate to <0.1 ppm. The D_2O solutions were 0.2 *M* in NaCl. The listed pD values are the readings obtained directly from the pH meter.

Materials.—Solvents and internal reference compounds were obtained from Nuclear Magnetic Resonance Specialties, Inc. Propionic acid (Baker Analyzed reagent), 4-phenylbutyric acid (Eastman), and ω-phenyloctanoic acid (Pfaltz and Bauer) were used without further purification. Octanoic acid (Matheson Coleman and Bell) was distilled under reduced pressure, bp 83–85° (0.25 mm).

Registry No.—4-Phenylbutyric acid sodium salt, 1716-12-7; sodium ω-phenyloctanoate, 24867-14-9.

Acknowledgment.—We gratefully acknowledge support by grants from the Research Corporation and the Miami University Research Committee.

An Efficient Synthesis of Selected Indenones

M. BRAWNER FLOYD AND GEORGE R. ALLEN, JR.

Process and Preparations Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York 10965

Received September 18, 1969

An efficient, apparently general synthesis of 2-alkylindenones is described. This procedure is dependent on the Friedel–Crafts acylation of α-alkyl-β-aryl-β-chloropropionyl chlorides (**5**) to furnish 2-alkyl-3-chloroindanones (**6**), dehydrochlorination of which affords the 2-alkylindenones (**7**). The method is also applicable to the preparation of indenone **7a**. The requisite acid chlorides **5** are prepared by the action of thionyl chloride on β-arylhydracrylic acids **4**, the esters of which are available conveniently by application of the Reformatsky procedure to the appropriate benzaldehyde **1** and α-bromo ester **2**. Selected examples of the reaction of the indenone system with electrophilic and nucleophilic reagents are presented. Isomerization of the alkylindenone system into the 2-alkylideneindanone system was noted to a small extent under certain conditions.

In the course of another investigation, we required a procedure for the synthesis of 2-alkylindenones. Several methods for their preparation have been reported, but none appeared to be uniformly general. Among the potential procedures, dehydrobromination of 2-alkyl-2-bromoindanones, available by bromination of the corresponding 2-alkylindanones, has been studied most extensively. Despite the apparent general nature of this sequence for the preparation of 2-methylindenones,[1] its applicability to the synthesis of higher homologs is questionable. Thus, dehydrobromination of 2-ethyl-2-bromoindanone affords a mixture of 2-ethylindenone and 2-ethylideneindanone, the latter predominating.[2] Yet, treatment of 2-bromo-2-butylindanone with dimethylamine is reported to give 2-butyl-3-dimethylaminoindanone, apparently *via* Michael addition of the amine onto the intermediate 2-butylindenone.[1a] Cyclization of *cis*-cinnamic acids is a second procedure that has been studied.[3] This method appears limited in that the *trans* isomer results from most syntheses, and conversion into the required *cis* isomer is not uniformly successful.[2,4]

Two additional methods for the preparation of 2-alkylindenones have received limited attention. Vilsmeier–Haack formylation of an acetophenone is reported to give a 3-amino-1-chloroindene, which was converted into a 2-methylindenone in two stages.[5] The general utility of this procedure has not been ascer-

(1) (a) S. Allisson, J. Büchi, and W. Michaelis, *Helv. Chim. Acta*, **49**, 891 (1966); (b) J. G. Topliss and L. M. Konzelman, *J. Pharm. Sci.*, **57**, 737 (1968).

(2) H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, *J. Amer. Chem. Soc.*, **82**, 1452 (1960).

(3) (a) R. Stoermer and G. Voht, *Justus Liebigs Ann. Chem.*, **409**, 36 (1915); (b) S. Goszczynski and E. Salwinska, *Zesz. Nauk. Politech. Slask., Chem.*, **24**, 235 (1964); *Chem. Abstr.*, **63**, 11415e (1965).

(4) H. O. House and J. K. Larson, *J. Org. Chem.*, **33**, 448 (1968).

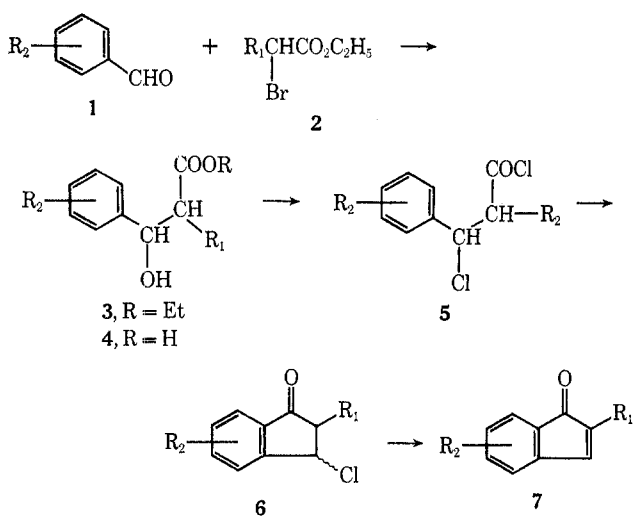
(5) K. Bodendorf and R. Mayer, *Chem. Ber.*, **98**, 3565 (1965).

tained. Secondly, bromination of β-(indanon-2-yl)-propionic acid with N-bromosuccinimide (NBS) and subsequent dehydrobromination is reported to afford 15% β-(indenon-2-yl)propionic acid and 36% lactone of β-(2-hydroxyindanon-2-yl)propionic acid.[2] It is uncertain whether the latter product results from lactonization of the former product or of an alkylideneindanone derivative or is merely the product of intramolecular displacement of halide from an initial 2-bromoindanone. In this connection, NBS bromination of indanone is reported to be nonspecific, although dehydrobromination of the mixed bromides does constitute a synthesis of indenone.[6]

Finally, two other methods for the preparation of the parent substance which could serve for the synthesis of 2-alkyl derivatives should be noted. The earlier procedure is based on the hydrolysis of the condensation product derived from indene and *p*-nitrosodimethylaniline but suffers from low yield.[7] The second method, which is dependent on pyrolysis of 2-acetoxyindanone, requires special equipment and proceeds in only 8% overall yield from indanone.[6]

These reports suggested that dehydrohalogenation of a 2-alkyl-3-haloindanone might offer the greatest potential for a general 2-alkylindenone synthesis. Accordingly, we have investigated an alternative preparation of the former substances and their dehydrohalogenation to give indenones. In contrast to the previous studies,[2,6] the present approach to the required 3-haloindanones was predicated on an intramolecular Friedel–Crafts acylation of an appropriate β-aryl-β-chloropropionyl chloride **5** (see Scheme I).

SCHEME I



The α-alkyl-β-arylhydracrylic esters (**3**), which generally were prepared in good yield by a Reformatsky condensation of the appropriate benzaldehyde (**1**) and α-bromo ester (**2**), proved to be suitable precursors for this purpose. Alkaline hydrolysis of esters **3** gave the hydracrylic acids **4**. However, α,β-diphenylhydracrylic acid was prepared directly from phenylacetic acid and benzaldehyde by the Ivanov procedure,[8] inasmuch as a Reformatsky condensation of ethyl α-bromophenylacetate with benzaldehyde failed to give the required ester. No effort was made to purify the hydracrylic acids **4** because, with the exception of **4a**, they are known to be diastereomeric mixtures,[8,9] and each diastereomer would serve the present purpose. Treatment of the acids **4** with thionyl chloride in the presence of a catalytic amount of dimethylformamide[10] afforded the requisite β-aryl-β-chloropropionyl chlorides **5**.

Acylation of these substances in methylene chloride was effected with aluminum chloride at 25–40° for 10–180 min; the resulting 3-haloindanones **6** were converted into the desired indenones **7** by treatment with pyridine at 70–90°. In the instance of indenone **7a**, this dehydrohalogenation was effected with collidine in ether at room temperature.[6] The more vigorous conditions failed, apparently as a result of the instability of **7a**. The efficiency of the present indenone synthesis is indicated by the generally good overall yield of **7** and by the fact that intermediates **4**–**6** were utilized without purification. In general, the recorded yields were realized in the initial preparation, and no effort was made to ascertain optimum conditions. Moreover, the present procedure is not restricted to the preparation of 2-alkylindenones, as demonstrated by the preparation of indenone **7a**. However, application of this method to the preparation of 2-phenylindenone from α,β-diphenylhydracrylic acid[8] failed. It may be noted that the conversion of the acid halides **5** into the haloindanones **6** is subject to the usual substituent effects.[11] Thus, halide **5g** afforded 71% 5-methoxyindenone **7g** and 13% 7-methoxyindenone **7h**, after dehydrochlorination of the intermediate 2-alkyl-3-chloroindanones.

Because we required a 5-hydroxyindenone for our concurrent study, the preparation of this system from 5-methoxyindenone **7g** was studied intensively. The results further reflect the susceptibility of the indenone system to electrophilic[6] and nucleophilic[1] attack. Thus, ether cleavage of **7g** with aluminum chloride in toluene is accompanied by alkylation of the solvent to furnish indanone **12**, characterized as an aryloxyacetic acid. This result illustrates the susceptibility of the indenone system to attack by the electrophilic aluminum chloride, yielding carbonium ion **10** which alkylates the solvent (see Scheme II). Attempted ether cleavage of **7g** by sodium iodide–hydrogen bromide in acetic acid gave 2-ethyl-5-hydroxyindanone (**11**) presumably by reduction of the 3-iodo compound. This result is indicative of the sensitivity of the indenone system to nucleophilic attack. The latter property is also evident in the alkylation of hydroxyindenone **8** (prepared as described below) with chloroacetic acid; the only isolable product was the dimeric substance **9**.

Finally, treatment of 2-butylindenone (**7e**) with dimethylamine gave 73% indanone **13**. The hydrochloride of **13** has properties in excellent accord with those reported for that derived by reaction of dimethyl-

(6) C. S. Marvel and C. W. Hinman, *J. Amer. Chem. Soc.*, **76**, 5435 (1954).

(7) R. Stoermer and E. Asbrand, *Chem. Ber.*, **64**, 2796 (1931).

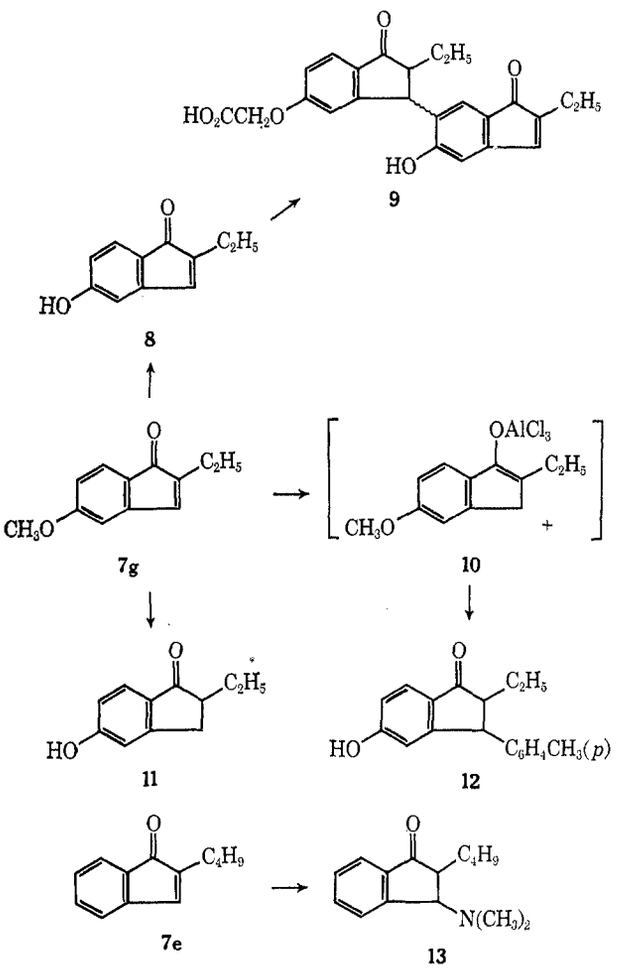
(8) (a) D. Ivanov and N. Nicoloff, *Bull. Soc. Chim.*, **51**, 1325 (1932); (b) H. E. Zimmerman and M. D. Traxler, *J. Amer. Chem. Soc.*, **79**, 1920 (1957).

(9) L. Canonica and F. Pelizzoni, *Gazz. Chim. Ital.*, **84**, 553 (1954); *Chem. Abstr.*, **50**, 879*g* (1956).

(10) H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).

(11) (a) W. S. Johnson, *Org. React.*, **2**, 125 (1944); (b) V. Askam and W. H. Linnell, *J. Chem. Soc.*, 2435 (1954).

SCHEME II

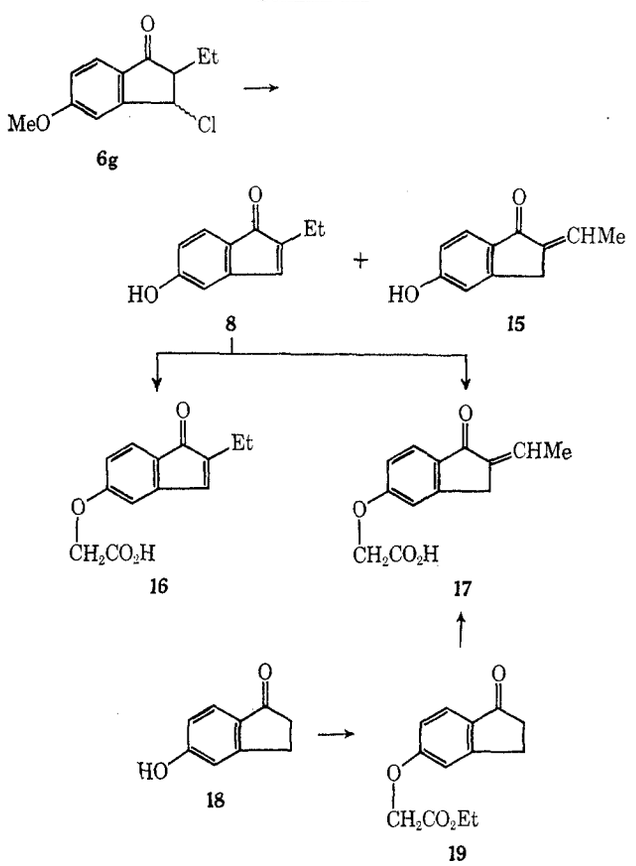


amine with 2-bromo-2-butylindanone.[1a] These results suggest that the latter preparation of **13** indeed proceeds *via* an indenone intermediate and that the dehydrobromination of 2-alkyl-2-bromoindanones may constitute a 2-alkylindenone synthesis of greater potential than indicated by the work of House and his coworkers.[2]

Normal formation of carbonyl derivatives was observed, but in the instance of indenone **7a**, unusual reactivity of the derivative was noted. On reaction with semicarbazide hydrochloride, **7a** furnished a product possessing a melting point of 236–245° in reasonable agreement with the recorded.[7] However, recrystallization of this material from dilute methanol was accompanied by a sharp drop in the melting point to 208–212°. Consideration of the combustion analysis and the mass spectrum of the resulting material indicated it to be a mixture of the semicarbazones of **7a** and 3-methoxyindanone. In particular, the mass spectrum was characterized by ions at *m/e* 219 and 187; however, the absence of a metastable ion for the 219 to 187 transition suggested that the *m/e* 187 ion was a molecular ion. Indeed, tlc of this material indicated it to be a mixture of two substances; however, the limited solubility of these materials precluded their separation by chromatographic techniques. This result is unique in that it represents an example of the Michael addition of a nucleophile to a ketonic derivative of an α,β-unsaturated ketone.

Finally, we would indicate two instances of the isomerization of an alkylindenone into an alkylideneindanone. These isomerizations are noteworthy because House and his collaborators[2] failed to effect detectable isomerization of 2-ethylindenone into 2-ethylideneindanone with γ-collidine at 175°. The first such isomerization was encountered in the preparation of 2-ethyl-5-hydroxyindenone (**8**), which eventually was effected by the action of aluminum chloride on 2-ethyl-5-methoxyindenone (**7g**) or 3-chloro-2-ethyl-5-methoxyindanone (**6g**) in tetrachloroethane. This synthesis of **8** also afforded 2% ethylidene derivative **15** (see Scheme III). Treatment of the sodium salt of **8** with

SCHEME III



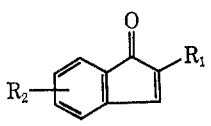
sodium bromoacetate in diglyme results in a similar isomerization. The alkylated material, which was isolated in low yield, consisted of an approximately 13:1 mixture of the ethylindenone **16** and the ethylideneindanone **17**. The latter substance was identical with that prepared independently from 5-hydroxyindanone (**18**). Alkylation of **18** with ethyl chloroacetate gave the oxyacetic ester **19**, which on treatment with base and acetaldehyde afforded the ethylidene derivative **17**.

Physical Properties.—As noted previously,[2,6] the infrared spectra of the various indenones **7** are characterized by sharp carbonyl stretching bands at approximately 5.85 μ and C=C stretching bands at 6.25 μ. The ultraviolet spectrum of indenone (**7a**) is characterized by intense absorption maxima at 233 and 238 mμ in addition to the long wavelength (318 mμ) maximum previously reported (see Table I).[6] A 2-alkyl substituent results in a bathochromic shift of 2–5 mμ in the short wavelength maxima. Further substitution

by a 6-alkyl group causes an additional bathochromic shift in these maxima. The position and intensity of the 318-mμ maximum in the spectrum of **7a** is largely unaffected by alkyl groups in the 2 and 6 positions. In the instance of the 5-oxygenated indenones **7g–i** and **8**, resonance interaction of the 5 substituent with the carbonyl group causes a bathochromic shift of each maximum and a coalescence of the two lower maxima. In the absence of an oxygen function at C-6, the intensity of the short wavelength maximum is diminished and that of the longer absorption is enhanced. However, the presence of an additional methoxy group at C-6 largely negates these effects on the extinction coefficients. A 7-methoxy substituent causes a red shift of 47 mμ in the long wavelength absorption, but the position of the short maximum is unaffected, although a coalescence of the two maxima of the parent substance is observed. The effect of this substituent on the extinction coefficients parallels that of a 5-methoxy group.

TABLE I

ULTRAVIOLET SPECTRA OF INDENONE AND SUBSTITUTED INDENONES



Compd	R_1	R_2	λ_{max}, mμ (ε)		
7a	H	H	233 (36900)	238 (37400)	318 (1820)
7b	Me	H	238 (38600)	243 (43600)	317 (1370)
7c	Et	H	235 (40000)	242 (46100)	318 (1270)
7d	*i*-Pr	H	236 (40600)	242 (47100)	318 (1200)
7e	Bu	H	235 (39100)	241 (42800)	320 (1120)
7f	Et	6-*i*-Pr	240 (38400)	245 (41600)	316 (4100)
7g	Et	5-MeO	218 (12800)	260 (30500)	332 (3950)
8	Et	5-HO	218 (11300)	260 (26300)	333 (3300)
7i	Me	5,6-MeO		261 (38600)	330 (2040)
7h	Et	7-MeO	235 (32400)		365 (4140)

The nmr spectrum of indenone (**7a**) shows two single-proton doublets (J = 5.5 Hz) at δ 7.52 and 5.83, which are ascribed to C-3 and C-2, respectively. The C-3 resonance of the 5- and 7-methoxy derivatives of 2-ethylindenone is apparent at δ 6.90. This resonance appears as a sharp triplet (J = 2.0 Hz) in the spectrum of the latter substance as a result of allylic coupling with the methylene portion of the alkyl substituent. Comparison of the C-3 resonance with that seen in the spectrum of the 5-methoxy derivative suggests that the C-3 proton may also be subject to long range coupling with C-7 ($J_{3,7} \cong 1$ Hz). However, this coupling is only weakly evident in the spectrum of 5,6-dimethoxy-2-methylindenone (**7i**). The spectra of the remaining indenones are not particularly informative because the C-3 resonance is obscured by the aryl proton resonances.

Experimental Section

General.—All melting points and boiling points are uncorrected. The melting points were determined in open capillary tubes on a Mel-Temp apparatus. In the instance of that compound melting below ambient temperature, a vessel containing a sample of the substance was inserted in a cooling bath; the temperature of the bath was allowed to equilibrate with ambient temperature, and the melting range of the substance was recorded by a thermometer immersed in the sample. Infrared spectra were determined in pressed KBr disks on a Perkin-Elmer Model 21 spectrophotometer, and the ultraviolet spectra were measured in methanol solution with a Cary Model 11 recording spectrophotometer. Nmr spectra were determined in deuteriochloroform, except where noted otherwise, on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. The mass spectrum was determined on a AEI MS-9 spectrometer. All evaporations were carried out at reduced pressure. The petroleum ether used was that fraction boiling at 30–60°.

Preparation of the Ethyl α-Alkyl-β-arylhydracrylates (3).—The general procedure described previously[12] was used for the preparation of these esters, the characterization of which is given in Table II. In one experiment, attempted distillation of crude ethyl β-(3,4-dimethoxyphenyl)-α-methylhydracrylate (**3h**) gave **ethyl 3,4-dimethoxy-α-methylcinnamate** (50%): bp 165–167° (0.85 mm); n^{25}D 1.5687; uv max 231, 290, 308 mμ (ε 14,800, 16,200, 15,700); ir 5.85, 6.12, 6.23, 8.02 μ.

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.86; H, 7.14.

In a second experiment the crude ester obtained by removal of the extraction solvent partially crystallized. This mixture was triturated with ether and filtered to give white crystals of **ethyl β-(3,4-dimethoxyphenyl)-α-methylhydracrylate (3h)**. This material was recrystallized from ether–petroleum ether to give white crystals, mp 95–97°. This substance most likely is a pure diastereomer and its characterization is given in Table II. For the preparation of indenone **7i**, the crude diastereomeric mixture was used. The absence of cinnamate esters in the products of Table I was indicated by their ir (no strong absorption at 6.24 μ) and uv spectra.

Preparation of the Indenones (7).—The following experiments illustrate the general procedure. A solution of 12.6 g (50.0 mmol) of ethyl α-ethyl-β-(3-methoxyphenyl)hydracrylate (**3g**) and 8.42 g (150 mmol) of potassium hydroxide in 140 ml of methanol and 20 ml of water was allowed to stand at room temperature for 16 hr. The bulk of the solvent was evaporated, and the resulting white mass was treated successively with 100 ml of water, 50 ml of cracked ice, 120 ml of 10:1 ether–hexane, and 60 ml of 4 *N* HCl. The phases were separated, and the aqueous phase was extracted with additional ether. The combined organic extracts were washed with water, dried, and evaporated at room temperature to give 11.3 g (100%) of α-ethyl-β-(3-methoxyphenyl)hydracrylic acid as a colorless syrup. This mixture of diastereoisomers was used for the subsequent stages without attempted purification; the ir and uv spectra of this product indicated no formation of the corresponding cinnamic acid.

A stirred solution of 12.5 ml (20.6 g, 0.173 mol) of thionyl chloride and 0.15 g (2.0 mmol) of dimethylformamide in 40 ml of methylene chloride was added to a solution of 16.14 g (0.072 mol) of the above hydracrylic acid in 60 ml of methylene chloride over 30 min. The reaction mixture was stirred an additional 30 min at room temperature and then heated at reflux for 15 min. Evaporation at room temperature gave crude β-chloro-α-ethyl-β-(3-methoxyphenyl)propionyl chloride. In the absence of dimethylformamide catalysis, the acid derived from ester **3d** was only partially converted into the corresponding β-chloropropionyl chloride.

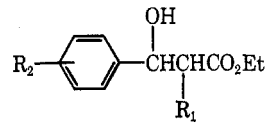
In a pilot experiment the above acid chloride was converted into an amide by treating an ether solution of the compound with anhydrous ammonia at 0° for 1 min. After treatment with water and washing with saturated $NaHCO_3$, the ether solution was dried and evaporated. The crude chloroamide was recrystallized from hexane–ethyl acetate giving white needles: mp 130–132°; uv max 278 mμ (ε 2200); ir 2.98, 3.15, 3.42, 6.04, 6.25 μ.

Anal. Calcd for $C_{12}H_{16}ClNO_2$: C, 59.62; H, 6.67; Cl, 14.67; N, 5.80. Found: C, 59.36; H, 6.79; Cl, 14.57; N, 5.87.

To a stirred solution of the above β-chloro acid chloride in 150 ml of methylene chloride was added 19.3 g (0.080 mol) of anhydrous aluminum chloride powder at room temperature. After the vigorous initial reaction had subsided the dark brown solution was allowed to stand at room temperature for 10 min. The reaction mixture was treated with ice, and the product was extracted with ether. The extract was washed with water and saturated $NaHCO_3$, dried, and evaporated. The resulting crude 3-chloro-2-ethyl-5-methoxyindanone (13.68 g; λ_{max} 266, 287 mμ; precipitate with alcoholic silver nitrate) was dissolved in 50 ml of pyridine and stirred at 70° for 30 min. Treatment of the cooled reaction mixture with ether gave a precipitate. The mix-

(12) R. L. Shriner, *Org. React.*, **1**, 1 (1942).

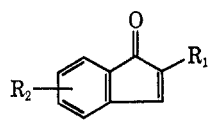
TABLE II
ETHYL α-ALKYL-β-ARYLHYDRACRYLATES



Compd	R_1	R_2	Yield, %	Bp (mm), °C	$n^{25}D$	Molecular formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
3a	H	H	90	99 (0.15)[a]	1.5085	$C_{11}H_{14}O_3$	68.02	7.27	67.89	7.22
3b	Me	H	75	109–110 (0.50)[b]	1.5007	$C_{12}H_{16}O_3$	69.21	7.74	69.09	7.50
3c	Et	H	66	120–122 (0.20)[c]	1.4991[c]	$C_{13}H_{18}O_3$	70.24	8.16	70.45	8.11
3d	*i*-Pr	H	70	110 (0.15)[d]	1.4996	$C_{14}H_{20}O_3$	71.16	8.53	70.95	8.33
3e	Bu	H	79	122 (0.25)	1.4914	$C_{15}H_{22}O_3$	71.97	8.86	71.87	8.74
3f	Et	4-*i*-Pr	65	127–128 (0.55)	1.4964	$C_{16}H_{24}O_3$	72.69	9.15	72.57	9.00
3g	Et	3-MeO	66	148–150 (0.35)	1.5060	$C_{14}H_{20}O_4$	66.64	7.99	66.64	7.93
3h	Me	3,4-MeO	30	Mp 95–97		$C_{14}H_{20}O_5$	62.67	7.51	62.86	7.40

[a] Described previously without characterization by V. N. Andrievskii, *J. Russ. Phys. Chem. Soc.*, **40**, 1635 (1908). [b] Described without characterization by G. Dain, *ibid.*, **28**, 593 (1896). [c] Lit.[9] bp 143–144° (3 mm), $n^{25}D$ 1.525. [d] Lit.[9] bp 132° (3 mm).

TABLE III
INDENONES



Compd	R_1	R_2	Yield, %[a]	Recrystn solvent	Bp (mm), °C	Mp, °C	$n^{25}D$	Molecular formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
7a	H	H	49		75–77 (1.5)[b]		1.5985[b]	C_9H_8O	83.10	4.66	82.87	4.75
7b	Me	H	71	Ether–pet ether		45–47[c]		$C_{10}H_8O$	83.31	5.59	82.99	5.56
7c	Et	H	53		74.5–75.0 (0.25)[d]	9–10	1.5716	$C_{11}H_{10}O$	83.51	6.37	83.15	6.37
7d	*i*-Pr	H	62		84–86 (1.10)		1.5582	$C_{12}H_{12}O$[e]				
7e	Bu	H	81	Pet ether	96–100 (0.65)	35–36		$C_{13}H_{14}O$	83.83	7.58	83.83	7.51
7f	Et	6-*i*-Pr	69		96–99 (0.15)		1.5522	$C_{14}G_{16}O$	83.96	8.05	84.11	8.03
7g	Et	5-MeO	71	Pet ether		37–38		$C_{12}H_{12}O_2$	76.57	6.43	76.35	6.39
7h	Et	7-MeO	13	Pet ether		46–47		$C_{12}H_{12}O_2$	76.57	6.43	76.36	6.44
7i	Me	5,6-MeO	46	Ether–pet ether		84–85[f]		$C_{12}H_{12}O_3$	70.57	5.92	70.36	5.85

[a] Based on material of analytical purity obtained from the corresponding ethyl β-aryl-α-substitued hydracrylate (Table II). [b] Lit.[6] bp 61–63° (0.9 mm), $n^{20}D$ 1.5981; lit.[7] bp 69–70° (0.35 mm). [c] Lit.[3a] mp 47.0–47.5°. [d] H. O. House and D. J. Reif, *J. Amer. Chem. Soc.*, **79**, 6491 (1957), bp 140–150° (10 mm). [e] Satisfactory combustion analyses were unobtainable because of instability and so the physical constants may be in doubt. See Table IV for characterization as the semicarbazone. [f] Lit.[1a] mp 85–86°.

ture was treated with 2 *N* HCl and the organic phase was washed successively with water, saturated $NaHCO_3$, and water. The ether solution was dried and evaporated to give 11.52 g (85%) of a mixture of **2-ethyl-5-methoxyindenone** (**7g**) and **2-ethyl-7-methoxyindenone** (**7h**). These substances could not be separated by distillation under reduced pressure.

A 1-g sample was subjected to column chromatography on diatomaceous silica using the system heptane–methoxyethanol (1:1).[13] The fraction eluted at peak hold-back volume 2.5 (Vm/Vs = 1.83) was evaporated to give 833 mg of **2-ethyl-5-methoxyindenone** (**7g**) as yellow crystals. The fraction eluted at peak hold-back volume 3.1 was evaporated to give 152 mg of **2-ethyl-7-methoxyindenone** (**7h**) as yellow crystals. The characterization of these substances is given in Table III.

Since the above experiments demonstrated the feasibility of the present synthetic approach for the preparation of indenones, the intermediates required for the preparation of **7a–f** and **7i** were not purified prior to their further use.

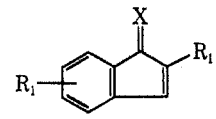
2-Ethyl-5-hydroxy-3-*p*-tolylindan-1-one (**12**).—To a stirred solution of β-chloro-α-ethyl-β-(3-methoxyphenyl)propionyl chloride [prepared by the above procedure from 6.77 g (30 mmol) of hydracrylic acid **4g**] in 60 ml of dry methylene chloride at 0° was added 10 g (75 mmol) of aluminum chloride over 1 min. Following the addition, the reaction mixture was stirred for 15 min. The solvent was evaporated at room temperature, and the resulting red residue was treated with 75 ml of toluene. The mixture was refluxed with stirring for 3 min and poured onto 300 ml of cracked ice. The product was extracted with ether, and the extract was washed successively with 2 *N* HCl and water. Acidic material was extracted into 1.2 *N* NaOH and retrieved by acidification with 4 *N* HCl and ether extraction. The extract was washed with water, dried, and evaporated to give a gum which crystallized on hexane trituration. Recrystallization from isopropyl alcohol–hexane gave 1.75 g of white crystals: mp 146–148°; concentration of the mother liquor and further crystallization gave a total yield of 2.60 g (31%); uv max 222, 271, 297 (sh) mμ (ε 16,900, 11,100, 8500); ir 3.08, 3.38, 5.95, 6.29 μ. An aryloxyacetic acid derivative was prepared and recrystallized from acetone–hexane: mp 161.5–163°; uv max 220, 268, 295 mμ (ε 22,500, 14,900, 9600); ir 5.75, 5.87 μ; nmr δ 7.70 (d, 1, *J* = 7.0 Hz, C-7), 7.14 (s, 4, H of *p*-tolyl ring), 7.08 (m, 1, C-6), 6.61 (broad s, 1, C-4), 4.73 (s, 2, $-OCH_2-$), 4.20 (d, 1, *J* = 5.0 Hz, C-3), 2.50 (m, 1, C-2), 2.26 (s, 3, aryl CH_3), 1.70 (m, 2, 2, CH_2CH_3), 1.17 (t, 3, *J* = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 74.15; H, 6.26.

Reaction of 2-Ethyl-5-methoxyindenone (**7g**) **with Sodium Iodide–Hydrogen Bromide in Acetic Acid.**—A mixture of 0.47 g (2.5 mmol) of 2-ethyl-5-methoxyindenone (**7g**) and 1.50 g (10 mmol) of sodium iodide in 10 ml of 15% HBr in acetic acid was heated at reflux for 17 hr under argon. The dark reaction mixture was treated with water and extracted with ether. The extract was washed successively with water, 10% sodium thiosulfate solution, and water. The aqueous phase from a partition of the extract with 1.2 *N* NaOH was acidified with 4 *N* HCl and extracted with ether. The washed and dried extract was evaporated to give 0.25 g of crude phenolic material. Crystallization from benzene–hexane gave 107 mg (24%) of yellow-brown crys-

(13) For a complete description of this technique as developed by Mr. C. Pidacks of these laboratories, see M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

TABLE IV
INDENONE DERIVATIVES



Indenone	R_1	R_2	X[a]	Mp, °C[b]	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
7b	Me	H	S	189–191[c]	$C_{11}H_{11}N_3O$	65.67	5.51	20.88	65.65	5.79	20.53
7c	Et	H	S	183–185[d]	$C_{12}H_{13}N_3O$	66.95	6.09	19.52	66.97	6.11	19.80
7c	Et	H	DNP	247–248 dec[e,f]							
7d	*i*-Pr	H	S	171–173	$C_{13}H_{15}N_3O$	68.10	6.59	18 33	68.11	6.56	18.26
7e	Bu	H	S	134–136	$C_{14}H_{17}N_3O$	69.11	7.04	17.27	68.70	6.97	17.27
7f	Et	6-*i*-Pr	S	173–175	$C_{15}H_{19}N_3O$	70.00	7.74	16.63	69.88	7.53	16.39
7g	Et	5-MeO	S	162–164	$C_{13}H_{15}N_3O_2$	63.66	6.16	17.13	63.64	6.49	16.84
7h	Et	7-MeO	S	171–173	$C_{13}H_{15}N_3O_2$	63.66	6.16	17.13	63.32	6.13	17.05
7i	Me	5,6-MeO	S	209–211	$C_{13}H_{15}N_3O_3$	59.76	5.79	16.01	60.03	5.83	16.01
7i	Me	5,6-MeO	O	157–159[g]	$C_{12}H_{13}NO_3$			6.39			6.28

[a] S = semicarbazone; DNP = 2,4-dinitrophenylhydrazone; O = oxime. [b] All compound were recrystallized from dilute methanol unless specified otherwise. [c] Lit.[3a] mp 192–193°. [d] Lit.[3a] mp 181°. [e] From acetic acid. [f] H. O. House and D. J. Reif, *J. Amer. Chem. Soc.*, **79**, 6491 (1957), mp 247–248°. [g] Lit.[5] mp 165°.

tals, mp 142–144°. An analytical sample of **2-ethyl-5-hydroxy-1-indanone** was obtained by sublimation at 0.01 mm (bath, 130°): mp 143–145°; uv max 224, 269, 290, 296 mμ (ε 11,300, 10,900, 9350, 9350); ir 2.45, 3.18, 5.98, 6.20, 6.27 μ; nmr (DMSO-d_6) δ 7.51 (d, 1, J = 10 Hz, C-7), 6.90 (s, 1, C-4), 6.84 (m, 1, C-6), 3.04 (d, 1, J = 8 Hz, C-3), 2.78 (d, 1, J = 4 Hz, C-3), 2.50 (m, 1, C-2), 1.67 (m, 2, CH_2), 0.88 (t, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.98; H, 7.15.

Reaction of 2-Ethyl-5-hydroxyindenone with Chloroacetic Acid.—A solution of 2.8 g (16 mmol) of 2-ethyl-5-hydroxyindenone, 1.7 g (18 mmol) of chloroacetic acid, and 1.4 g (35 mmol) of sodium hydroxide in 50 ml of water was heated at *ca.* 100° for 6 hr. During the reaction 0.3 g (3 mmol) of additional chloroacetic acid and 1.5 ml of 2.5 *N* NaOH were added. The reaction mixture was cooled, treated with 15 ml of 4 *N* HCl, and extracted with ether. The extract was washed with water, dried, and evaporated. The red residue was chromatographed on a column of silica gel. Elution with benzene progressively enriched in ether gave impure starting material, (*ca.* 50%) followed by a yellow solid (350 mg) which was recrystallized from acetone–hexane to give **[2-ethyl-3-(2-ethyl-5-hydroxy-1-oxo-6-indenyl)-1-(oxo-5-indenyl)-1-oxo-5-indanyloxy]acetic acid (9)** as an orange powder: mp 142–147°; uv max 222, 265, 295 (sh), 335 mμ (ε 20,300, 40,000, 9100, 2400); ir 2.96, 3.40, 5.75, 6.19 μ; nmr (DMSO-d_6) δ 7.64 (d, 1, J = 8 Hz, C-7), 7.20 (s, 1, C-3′), 7.02 (q, 1, J = 2 and 8 Hz, C-6), 6.97 (s, 1, C-7′), 6.66 (broad s, 2, C-4 and C-4′), 4.73 (s, 2, OCH_2CO), 4.44 (d, 1, J = 4 Hz, C-3), 2.50 (m, 1, C-2), 2.16 (q, 2, J = 7 Hz, CH_2CH_3′), 2.08 (s, 6, acetone), 1.73 (m, 2, CH_2CH_3), 1.10 (t, 3, J = 7 Hz, CH_2CH_3′), 0.97 (t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_{24}H_{22}O_6 \cdot C_3H_6O$: C, 69.81; H, 6.08. Found: 69.80; H, 6.24.

2-Butyl-3-dimethylaminoindanone (13) Hydrochloride.—A solution of 2.05 g (11 mmol) of 2-butylindenone (**7e**) in 100 ml of ethanol that had been saturated with dimethylamine at 0° was heated at reflux for 18 hr. The solvent was removed, and the residue was distributed between ether and 2 *N* hydrochloric acid. The acid solution was chilled and rendered alkaline by addition of KOH pellets. The resulting mixture was extracted with ether, and the dried solution was evaporated to give 1.82 g of liquid. This material was dissolved in ether, and a solution of hydrogen chloride in isopropyl alcohol was added dropwise until precipitation ceased; filtration gave 1.93 g (65%) of the **hydrochloride of 13**: white crystals, mp 140–141° (lit.[1a] mp 136–138°) (recrystallization from isopropyl alcohol–ether failed to alter the melting point); uv max 206, 242, 289 mμ (ε 29,200, 13,000, 1210); ir 3.90, 4.15, 5.80, 6.19, 6.24 μ; nmr δ 13.0 (broad, 1, N^+H), 8.60 (m, 1, C-7), 7.80 (m, 3, aryl H), 5.06 (d, 1, C-3), 3.26 (m, C-2), 2.87 [broad s, $N(CH_3)_2$].

Anal. Calcd for $C_{15}H_{21}NO \cdot HCl$: C, 67.27; H, 8.28; Cl, 13.23; N, 5.23. Found: C, 66.90; H, 8.29; Cl, 13.04; N, 5.19.

Semicarbazones.—These derivatives were prepared by the usual technique[14] and their characterization is given in Table IV. The uv spectra of the semicarbazones of **7b–f** were characterized by maxima at 235–240 mμ (ε 16,600–18,600), 250–252 (14,200–15,800), 288–290 (13,600–14,800), 316–317 (12,800–14,000), and 323–325 (11,700–12,600); for semicarbazone of **7g** uv max 245 mμ (ε 17,600), 290 (18,880), 332 (15,900); for semicarbazone of **7h** uv max 207 mμ (ε 29,000), 239 (15,200), 288 (sh) (15,900), 291 (16,200), 345 (9580); for semicarbazone of **7i** uv max 255 mμ (ε 19,600), 296 (26,400), 328 (14,400), 338 (12,900).

In the instance of indenone **7a**, 500 mg of the ketone gave 470 mg (65%) of yellow crystals: mp 236–245° dec (lit.[7] 240–250° dec) (on recrystallization of the solid from dilute methanol, the melting point dropped to 208–212° dec); mass spectrum (70 eV) *m/e* 219, 204, 187, 161, 145, 144, 120, 115, 90; nmr (DMSO-d_6) δ 10.8 (s, 1, NH), 9.50 (s, 1, NH), 8.0–7.0 (m, 10), 6.85 (broad s, 2, NH_2), 6.54 (broad s, 2, NH_2), 4.96 (m, 1, X H of ABX system), 3.33 (s, 3, OCH_3), 3.00, 2.85 (m, 2, AB H's of ABX system).

Anal. Calcd for $(C_{10}H_9N_3O)_2 \cdot CH_3OH$: C, 62.05; H, 5.46; N, 20.68. Found: C, 62.10; H, 5.50; N, 20.56.

2-Ethyl-5-hydroxyindenone (8).—To a solution of crude 3-chloro-2-ethyl-5-methoxyindan-1-one (18.8 g, 84 mmol) in 250 cc of tetrachloroethane was added 26.7 g (200 mmol) of powdered aluminum chloride over 3 min with stirring. The resulting mixture was stirred and heated at 110° for 20 min and poured onto 300 g of ice and 60 cc of concentrated HCl. The product was extracted with ether, and the extract was washed with half-saturated NaCl. Acidic material was extracted into 0.5 *N* NaOH and recovered by acidification with 4 *N* HCl and ether extraction. The extract was washed with water, dried, and evaporated. The resulting semicrystalline product was chromatographed on 250 g of silica gel and eluted with benzene successively enriched in ether. The total yield of crude product obtained in this way was 87%.

An analytical sample was prepared by column chromatography on diatomaceous silica using a heptane–ethyl acetate–methanol–water (70:30:15:6) system. The fraction eluted at peak hold-back volume 1.1 (Vm/Vs = 2.65) was recrystallized from acetone–hexane to give orange crystals: mp 155–156.5°; uv max 218, 260, 333 mμ (ε 11,300, 26,300, 3300); ir 3.04, 5.92, 6.24 μ; nmr ($CDCl_3$–DMSO-d_6) δ 8.90 (broad s, 1, OH), 7.16 (q, 1, J = 2 and 6 Hz, C-7), 6.91 (broad s, 1, C-3), 6.49 (d, 1, J = 2 Hz, C-4), 6.46 (q, 1, J = 2 and 6 Hz, C-6), 2.24 (q, 2, J = 7 Hz, CH_2), 1.10 (t, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.51; H, 5.86.

The fraction eluted at peak hold-back volume 3.9 yielded **2-ethylidine-5-hydroxyindan-1-one (15)** as off-white crystals on evaporation and recrystallization from acetone–hexane: mp

(14) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 1000.

219–222°; uv max 245, 265, 290, 315 mμ (ε 10,100, 10,100, 12,000 16,000); ir 2.93, 3.25, 5.93, 6.10, 6.23, 6.35 μ; nmr (DMSO-d_6) 7.57 (d, 1, J = 8 Hz, C-7), 6.89 (d, 1, J = 2 Hz, C-4), 6.85 (q, 1, J = 2 and 8 Hz, C-6), 6.63 (q, 1, J = 7 Hz, CH_3CH), 3.56 (broad s, 2, CH_2), 1.90 (d, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.96; H, 6.07.

Similar treatment of indenone methyl ether **7g** afforded crude **8** from which **15** was isolated as above in low yield.

Alkylation of 2-Ethyl-5-hydroxyindenone (8) with Bromoacetic Acid.—Sodium bromoacetate was prepared by treating 1.39 g (10.0 mmol) of bromoacetic acid with 4 ml of 2.5 *M* sodium hydroxide and removing the solvent. The sodium salt of 2-ethyl-5-hydroxyindenone (**8**) was prepared similarly from 0.88 g (5.0 mmol) of **8** and 2 ml of 2.5 *M* sodium hydroxide. A solution of the sodium phenolate in 30 ml of diglyme was added over 2 hr to a stirred and heated (steam bath) suspension of the sodium bromoacetate in 30 ml of diglyme. The mixture was allowed to stand at room temperature for approximately 16 hr and was then heated at 130° for 15 min. The cooled mixture was treated with 40 ml of saturated sodium bicarbonate solution and extracted with three 40-ml portions of ether. The aqueous phase was acidified with 4 *N* HCl and extracted with ether. These ethereal extracts were washed with saline, dried, and evaporated. Evaporation (final pressure ~0.5 mm) gave 700 mg of yellow crystals. This material was recrystallized from methanol to give 113 mg (10%) of **(2-ethylindenon-5-yl)oxyacetic acid (16)** as yellow crystals, mp 164–166°. An additional recrystallization from methanol gave yellow crystals: mp 167–169°; uv max 218, 258, 300 mμ (ε 8700, 22,600, 2400); ir 3.43, 5.75, 5.87, 6.18 μ; (DMSO-d_6) δ 7.27 (d, 1, J = 8 Hz, C-7), 7.21 (s, 1, C-3), 6.73 (d, 1, J = 2 Hz, C-4), 6.59 (q, 1, $J_{4,6}$ = 2 Hz, $J_{6,7}$ = 8 Hz, C-6), 4.72 (s, 2, OCH_2), 2.20 (q, 2, J = 7 Hz, CH_2CH_3), 1.08 (t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.13; H, 5.42.

The combined methanol filtrates were concentrated and cooled to give 125 mg of solid, mp 158–163°. Tlc in an ethyl acetate–heptane–acetic acid (50:5:2) system revealed two substances. This material was subjected to column chromatography on diatomaceous silica using a heptane–methanol system. The fraction eluted at peak hold-back volume 9.5 (Vm/Vs = 2.48)was evaporated to give 33 mg (13% total) of **16**, mp 169–171°.

The fraction eluted at peak hold-back volume **15** was evaporated to give a residue that was recrystallized from methanol to give 20 mg (1%) of **(2-ethylideneindanon-5-yl)oxyacetic acid (17)** as white crystals, mp 179–182°. This material was identical in all respects with that described below.

Ethyl (Indanon-5-yl)oxyacetate (19).[15]—To a stirred, ice-cooled solution of 20.0 g (0.135 mol) of 5-hydroxyindanone (**18**)[16] in 65 ml of dimethylformamide was added in small increments 6.40 g (0.16 mol) of a 60.2% sodium hydride in mineral oil dispersion; stirring was continued for 60 min after completion of the addition. Ethyl chloroacetate (18.4 g, 0.15 mol) was added, and stirring was continued for 2 hr. The solution was poured into ice water and extracted with ether. The dried solution was evaporated to give an oil that was triturated with heptane. The resulting solid was crystallized from ethyl acetate–heptane to give 13.50 g (43%) of crystals: mp 61.5–63.0°; uv max 221, 264, 287, 293 mμ (ε 14,600, 14,500, 9150, 8800); ir 5.71, 5.88, 6.19, 6.28 μ.

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.94; H, 6.28.

(2-Ethylideneindanon-5-yl)oxyacetic Acid (17).—A solution of 9.00 g (39.6 mmol) of ethyl (indanon-5-yl)oxyacetate (**19**) and 2.16 g (40.5 mmol) of sodium methoxide in 60 ml of methanol was stirred for 10 min, at which time a solid separated. A solution of 3.10 g (70 mmol) of acetaldehyde in 5 ml of methanol was added dropwise, and the mixture was stirred at ambient temperature for 1 hr and then poured into water. The aqueous solution was extracted with ether and then acidified with HCl. This solution was extracted with ether, and the dried extracts were evaporated to give a solid that was recrystallized from methanol to give 3.50 g (39%) of solid, mp 182–184°. The sample was further purified by partition with ether and saturated $NaHCO_3$, evaporation of the ether phase, and recrystallization from methanol: mp 179–182°; uv max 238, 285, 308 mμ (ε 9300, 16,600, 17,700); ir 3.50, 4.00, 5.73, 5.92, 6.15, 6.26 μ; nmr (DMSO-d_6) δ 7.66 (d, 1, J = 9 Hz, C-7), 7.08 (d, 1, J = 2 Hz, C-4), 7.00 (dd, 1, $J_{4,6}$ = 2 Hz, $J_{6,7}$ = 9 Hz, C-6), 6.70 (q, 1, J = 7 Hz, CH_3CH), 4.82 (s, 2, OCH_2), 3.58 (s, 2, 3-CH_2), 1.86 (d, 3, J = 7 Hz, $CHCH_3$).

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 66.91; H, 5.40.

Registry No.—**3a**, 5764-85-2; **3b**, 24744-96-5; **3c**, 24744-97-6; **3d**, 24744-98-7; **3e**, 24744-99-8; **3f**, 24745-00-4; **3g**, 24745-01-5; **3h**, 24745-02-6; **7a**, 480-90-0; **7b**, 5728-95-0; semicarbazone of **7b**, 24741-67-1; **7c**, 24741-68-2; semicarbazone of **7c**, 24741-69-3; **7d**, 24799-55-1; semicarbazone of **7d**, 24741-70-6; **7e**, 24741-71-7; semicarbazone of **7e**, 24741-72-8; **7f**, 24741-73-9; semicarbazone of **7f**, 24741-74-0; **7g**, 24741-75-1; semicarbazone of **7g**, 24741-76-2; **7h**, 24741-77-3; semicarbazone of **7h**, 24741-78-4; **7i**, 4900-43-0; semicarbazone of **7i**, 24741-80-8; oxime of **7i**, 4900-48-5; **8**, 24741-82-0; **9**, 24741-83-1; **12**, 24741-84-2; hydrochloride of **13**, 24741-85-3; **15**, 24741-86-4; **16**, 24741-87-5; **17**, 24741-88-6; **19**, 24741-89-7; ethyl 3,4-dimethoxy-α-methylcinnamate, 5415-49-6; 2-ethyl-5-hydroxy-1-indanone, 24741-91-1; aryloxyacetic acid derivative of **12**, 24766-63-0.

Acknowledgment.—We are indebted to Messrs. L. M. Brancone, W. Fulmor, and C. Pidacks, and their associates for the microanalyses, spectral data, and liquid-liquid partition column chromatography, respectively.

(15) This experiment was performed by Dr. R. M. Sheeley.

(16) W. A. Johnson, J. M. Anderson, and W. E. Shelberg, *J. Amer. Chem. Soc.*, **66**, 218 (1944), and references cited therein.