Angularly Substituted Octahydrophenathrenes. I. The Synthesis of Hexahydrofluorenone Intermediates

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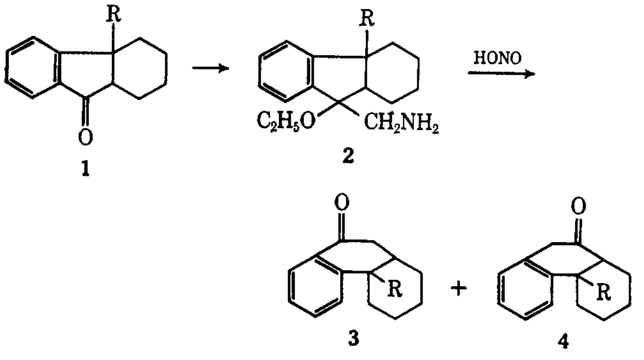
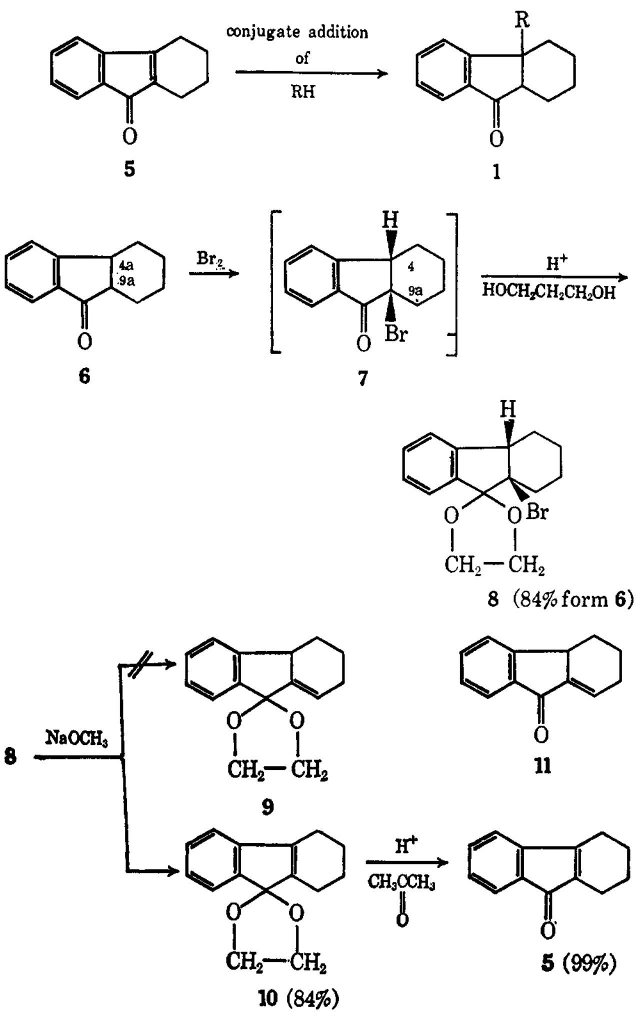
An improved procedure for the preparation of 1,2,3,4-tetrahydrofluoren-9-one (5), which affords the ketone free of double-bond position isomers, is described. The reactions of 5 with hydrogen cyanide, with anions derived from *t*-butyl malonate, malononitrile, and ethyl cyanoacetate, and with organocopper derivatives have been shown to provide high yields of a new class of angularly substituted hexahydrofluoren-9-ones of type 1. These compounds are of interest as intermediates for the preparation of angularly substituted octahydrophenanthrenes and the morphinan ring system.

The reaction sequence shown in Scheme I, which has been described[3] for the case where R = H, offers an attractive synthetic procedure for the preparation of angularly substituted octahydrophenathrenes (**3** and **4**) and derivatives of the morphinan[4] and isomorphinan ring systems. The ultimate success of this proposed synthetic route to such compounds is, however, contingent upon the evolution of a convenient synthesis of the new class of angularly substituted hexahydrofluoronenones of type **1**. In this regard, 1,2,3,4-tetrahydrofluoren-9-one (**5**) has proved to be a useful precursor to a variety of such angularly substituted ketones, as shown at the top of Scheme II, and the synthesis of **5** and a study of its reactions with nucleophilic reagents constitute the subject of this report.

SCHEME I



SCHEME II



Preparation of 1,2,3,4-Tetrahydrofluoren-9-one (5).—The desired ketone **5** was prepared by a new procedure from **6** as shown in Scheme II. This sequence of reactions is preferable to direct dehydrohalogenation of **7**,[5] since the latter process gives a mixture containing approximately 40% **11** and 55% **5**. Bromo ketal **8** was obtained in 84% yield from **6** and was assigned the *cis* relative configuration at carbon atoms C-4a and C-9a based on the configuration previously established for **7**.[5] The facile E2 elimination of hydrogen bromide from **8** to give only **10** is consistent with the *cis* configuration assigned to **8**, and was expected from both kinetic[6] and thermodynamic considerations. The absence of **9** as a product of dehydrohalogenation of **8** was demonstrated, since no vinyl hydrogen was observed in the nmr spectrum of the crude reaction product. Conversion of ketal **10** to **5** was accomplished in essentially quantitative yield, and without any isomerization of the double

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[1] From the Ph.D. Thesis of L. J. Czuba, The University of Minnesota, 1967.

[2] Financial assistance is gratefully acknowledged for a Sinclair Oil Co. Fellowship (1965–1966) and for summer fellowships or assistantships from the Du Pont Co., the Sun Oil Co., and the Smith Kline and French Laboratories. Part of this work was also supported (1966–1967) by the National Science Foundation (GP-6169X).

[3] W. E. Parham and L. J. Czuba, *J. Amer. Chem. Soc.*, **90**, 4030 (1968).

[4] Derivatives of type **1** in which R = CH_2COOH (**22**) are particularly attractive as intermediates for the synthesis of morphinans and isomorphinans [*cf.* J. Hellerbach, O. Schnider, H Besendorf, and B. Pellmont, "Synthetic Analgesics, Part II(a), Morphinans," Pergamon Press, London, 1966, for a review of procedures for the preparation of morphinan and isomorphan systems].

[5] H. O. House, V. Paragmian, R. S. Ro, and D. J. Wluka, *J. Amer. Chem. Soc.*, **82**, 1457 (1960).

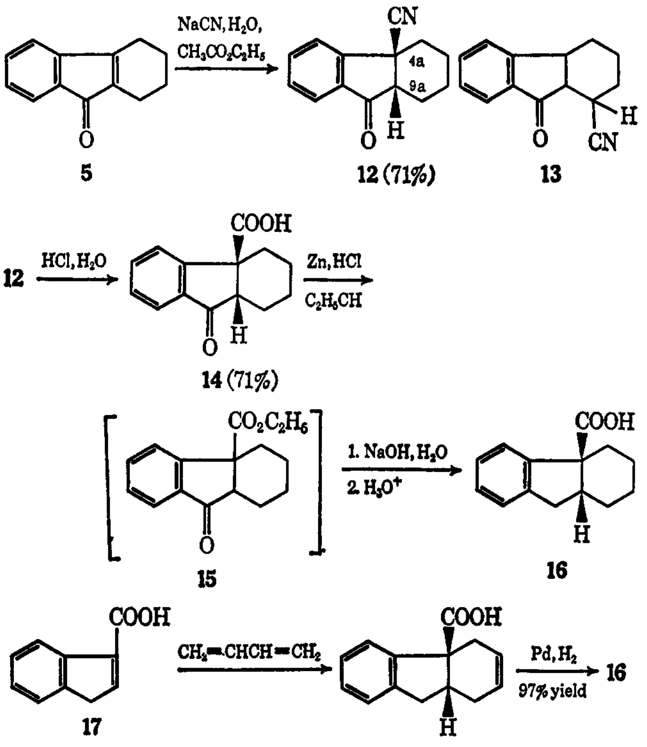
[6] C. H. DePuy, G. F. Morris, J. S. Smith, and R. J. Smat, *ibid.*, **87**, 2421 (1965).

bond, by ketal interchange using dry acetone and *p*-toluenesulfonic acid. The nmr spectrum of the ketone **5** showed no vinyl hydrogen which excluded the presence of isomer **11**.

Conjugate Addition Reactions.—While conjugate addition reactions to give quaternary carbon atoms do not generally proceed in high yields,[7] geometric considerations together with several recently reported synthesis[7d–h] of this type suggested that such reactions should proceed satisfactorily with the unsaturated ketone **5**. This conclusion was confirmed by studies of the reaction of **5** with hydrogen cyanide, with derivatives of malonic acid and malononitrile, and with organocopper compounds.

1. **With Hydrogen Cyanide.**—The reaction of **5** with hydrogen cyanide, generated *in situ* by the method of Koelsch,[8] afforded a crystalline product in 71% yield which was subsequently shown to be 1,2,3,4,4a,9a-hexahydro-9-oxofluorene-4a-carbonitrile (**12**) as shown in Scheme III. Spectral data (uv, ir, and nmr) for this product were consistent with the assigned structure **12**; however, these data did not exclude structure **13**, which could form from **11** derived by isomerization of **5** under the conditions of the reaction. The structure of the nitrile **12**, and the derived acid **14**, were confirmed by the independent synthesis of **16**, as shown in Scheme III.

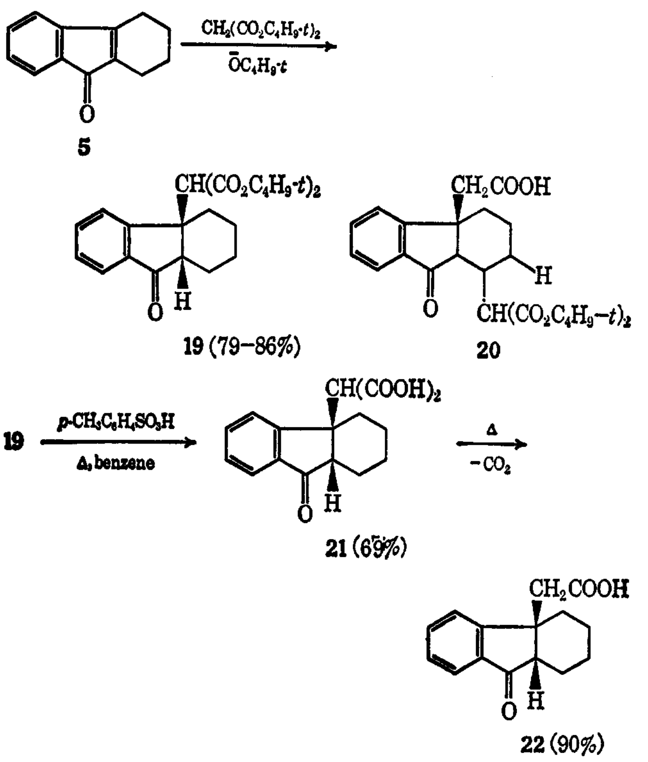
SCHEME III



The stereochemistry of the two angularly substituted hexahydrofluorenones (**12** and **14**) is dependent upon the relative thermodynamic stabilities of the two diastereomers in each case, since enolization of the ketone functions could result in epimerization at C-9a. The isolation of a single diastereomer in high yield in both cases, under conditions where enolization of the ketone function is expected, established a thermodynamic preference for one diastereomer in each case. House[5] and coworkers have shown that the diastereomer of **6** with the *cis* relative configuration at the bridging carbon atoms C-4a and C-9a is considerably more stable than the *trans* isomer (*cis*:*trans* ratio is 86:14 at equilibrium). On this basis **12** and **14** are tentatively assigned *cis* relative configurations at C-4a and C-9a.

2. **With Di-*t*-butyl Malonate.**—The Michael adduct **19** was prepared in 79–86% yield by reaction of **5** with di-*t*-butyl malonate in *t*-butyl alcohol containing a catalylic amount of potassium *t*-butoxide (Scheme IV).

SCHEME IV



The crude product contained **5**, di-*t*-butyl malonate and the Michael adduct **19** (79–86% yield of **19** by nmr); however, attempts to isolate **19** pure by crystallization or column chromatography were unsuccessful. The nmr spectrum of the crude product did, however, exclude the possible presence of the isomeric adduct **20**, which could have formed by isomerization of **5** to **11** prior to the Michael addition reaction. The nmr spectrum of **19** showed methine hydrogen adjacent to the ester functions only as a sharp singlet. Methine hydrogen in **20** would appear as a doublet due to splitting by hydrogen β to the ester function.

Treatment of crude **19** with a small amount of *p*-toluenesulfonic acid in boiling benzene gave the dibasic acid **21** in 69% yield as a white crystalline powder, melting at 160–161° with gas evolution. The ir spectrum of the product was consistent with that

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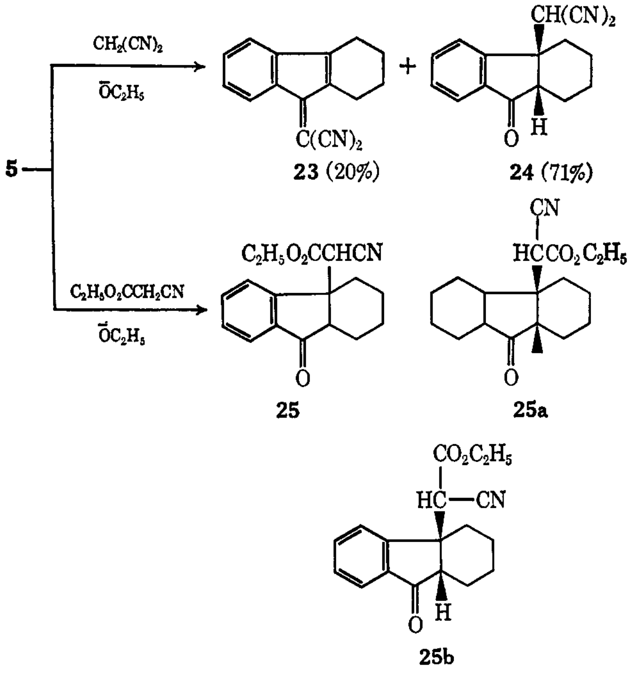
(7) (a) S. Patai and Z. Rapport in "The Chemistry of Alkenes," S. Patai Ed., Interscience Publishers, New York, N. Y., 1964, pp 469, 483, 504; (b) E. D. Bergman, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959). (c) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 694; (d) C. F. Koelsch, *J. Org. Chem.*, **25**, 2088 (1960); (e) E. Campaigne, G. F. Bulenko, W. E. Kreighbaum, and D. R. Maulding, *J. Org. Chem.*, **27**, 4428 (1962); (f) K. Jori, M. Matsui, and Y. Sumiki, *Agr. Biol. Chem.* (Tokyo), **28**, 241 (1964); *Chem. Abstr.*, **61**, 9539 (1965); (g) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, **89**, 1483 (1967); (h) J. A. Marshall and H. Roebke, *J. Org. Chem.*, **33**, 840 (1968).

(8) C. F. Koelsch, private communication.

expected for a dibasic acid, and the composition was in reasonable agreement (±0.4%). The dibasic acid **20** was hygroscopic, and attempts to remove the last traces of water were accompanied by decarboxylation (see Experimental Section). It was surprising, in view of previous reports,[9] that the dibasic acid did not decarboxylate under the conditions of its formation; fusion of **21** at 170–180° gave 1,2,3,4,4a,9a-hexahydro-9-oxofluorene-4a-ylacetic acid (**22**) in 90% yield. The angularly substituted hexahydrofluorenones **19–22** are tentatively assigned the *cis* configurations for reasons analogous to those described above for **12** and **14.**

3. With Malononitrile and Ethyl Cyanoacetate.—The products of reaction of **5** with malononitrile in ethanol containing sodium methoxide were 1,2,3,4-tetrahydrofluoren-9-ylidinemalononitrile (**23**, 20% yield) and 1,2,3,4,4a,9a-hexahydro-9-oxofluoren-4a-ylmalononitrile (**24**, 71% yield) as shown in Scheme V.

SCHEME V



The assignment of structures **23** and **24** were made on the basis of composition and spectral data; the tentative stereochemical assignment by analogy to that discussed for **12, 14,** and **19–22.** The nmr spectrum of **24** showed a sharp singlet at τ 5.62 due to the methine proton in the angular malononitrile function.

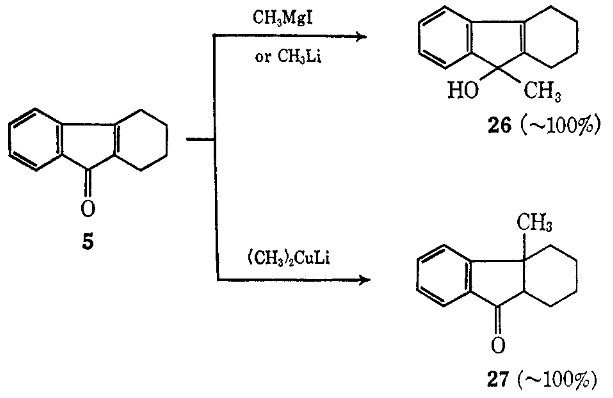
The composition of the product mixture was not changed appreciably when reaction times of 30 min to 2 hr at 25° were employed; however, when the reaction time was increased to 20 hr a more complex mixture was obtained and the amount of **23** increased (35% yield) while the amount of **24** decreased (34% yield). Thus adduct **24** is formed rapidly and is converted into other products after prolonged reaction times. Ylidenemalononitrile **23** was shown not to be a precursor of **24** by its recovery unchanged after treatment with malononitrile in ethanol containing sodium ethoxide.

Similarly, the reaction of **5** with ethyl cyanoacetate gave a mixture containing ethyl 1,2,3,4,4a,9a-hexahydro-9-oxofluoren-4a-ylcyanoacetate (**25**) in 66% yield (by nmr). The 1,4 adduct was obtained pure by distillation, and nmr spectral data of the crude and pure product showed hydrogen α to nitrile only as a sharp singlet (τ 5.94). This observation was consistent for angular substitution but inconsistent for position isomers related to **20.** The nmr spectrum of **25** indicated that it was a mixture of diastereomers with two nonequivalent ester groups (see Experimental Section). On the basis of the rationale offered for the stereochemistry of other angularly substituted hexahydrofluorenones discussed above, it seems reasonable that **25** is a mixture which is epimeric with respect to the asymmetric center in the angular substituent, and that the relative configurations at C-4a and C-9a are *cis* as shown in **25a** and **25b.**

4. With Organometallics.—Studies of the reaction of **5** with methylmagnesium iodide, methyllithium, and derivatives of methylcopper suggests that either exclusive 1,2 addition or exclusive 1,4 addition of organometallic reagents can be achieved. Thus reaction of **5** with methylmagnesium iodide in ether gave an 81% isolated yield of the 1,2-addition product **26.** Alcohol **26** was also obtained (98% yield) by reaction of **5** with methyllithium in ether. The nmr spectrum of the crude products obtained from both of these reactions showed a single methyl hydrogen atom absorption at τ 8.62 which confirmed the absence of any 1,4-addition product **27** (singlet, τ 8.56).

By contrast, the reaction of **5** with lithium dimethyl copper, which is readily prepared from methyllithium and cuprous iodide, gave a 95% isolated yield of 4a-methyl-1,2,3,4,4a,9a-hexahydrofluoren-9-one (**27**) (Scheme VI). The nmr spectrum of the crude product showed only angular methyl absorption at τ 8.56 and the complete absence of absorption at τ 8.62 required if **26** were present. The ir spectrum of the crude product supported the conclusion that this reaction gave exclusively the 1,4-addition product.

SCHEME VI



The reaction of **5** with the complex[10] derived from tetrakis[iodo(tri-*n*-butylphosphine)copper(I)][11] and methyllithium gave, exclusively, the 1,4-addition product **27**; however in this case ketone **27** (82% yield) was difficult to separate from tri-*n*-butylphosphine. The use of these copper reagents for conjugate addition

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(9) D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Amer. Chem. Soc.* **66,** 1286 (1944).

(10) H. O. House, W. L. Repress, and G. M. Whitesides, *J. Org. Chem.* **31,** 3128 (1966).

(11) G. B. Kaufman and L. A. Teter, *Inorg. Syn.* **7,** 9 (1963).

reactions were recently described by House, Repress, and Whitesides,[10] and their application in reactions with **5** offers an exceptionally promising route for the syntheses of angular alkyl-substituted hexahydrofluoren-9-ones of type **1**.

It is interesting to note that the reaction of **5** with methylmagnesium iodide in tetrahydrofuran containing cupric acetate[12,13] gave a mixture of **27** (34%) and **26** (56%), and reaction of **5** with methylmagnesium iodide in ether containing cupric acetate gave the alcohol **26** in 78% yield with no evidence of 1,4 addition. The high selectivity of the organocopper reagents in their reactions with **5**, which afford only 1,4 adduct **27**, is surprising in view of the failure of the copper-catalyzed Grignard reactions to give predominant 1,4 addition. House and coworkers[10] have proposed that the enhancement of the 1,4 addition of Grignard reagents in the presence of catalytic amounts of copper salts occurs becuase the reaction rates for both the formation of organocopper intermediate and the subsequent reaction of this intermediate with the substrate, in a conjugate manner, are much faster than 1,2 addition of the Grignard reagent to the substrate. In the present case, the rate of 1,2 addition of the Grignard reagent to **5** may be fast enough to compete with the rate of formation of the copper intermediate or, alternatively, the rate of 1,4 addition of organocopper reagent to **5** may be of the same order of magnitude as the rate of 1,2 addition of Grignard reagents to **5**.

Experimental Section

Melting points were determined on a calibrated Fisher-Johns hot stage. All melting points were corrected and boiling points were not corrected. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60 spectrometer using 1–2% tetramethylsilane as an internal standard. Mass spectra were obtained by Mr. A. Swanson and his assistant(s) at the University of Minnesota on a Hitachi–Perkin-Elmer RMU-6D mass spectrometer.

9a-Bromo-1,2,3,4,4a,9a-hexahydrofluoren-9-one Ethylene Ketal (8).—Crude bromo ketone **7** (lit.[5] 87% yield, mp 58–59°), obtained from bromine (30.4 g, 0.19 mol) and **6** (35.5 g, 0.019 mol), was treated with a mixture of *p*-toluenesulfonic acid (1.0 g), ethylene glycol (15 ml), and benzene (300 ml). The resulting solution was heated at the reflux temperature for 48 hr during which time 7 ml of water–glycol was separated with a Dean–Stark trap. The resulting mixture was washed with brine and dried (Na_2SO_4). The brown oil (55 g), obtained subsequent to removal of solvent, was crystallized from methanol to give 34.3 g (58.7% yield, mp 94–95°) of **8**. The brown oil, obtained by concentration of the mother liquor, was retreated with *p*-toluenesulfonic acid, and ethylene glycol in benzene as described above. There was obtained an additional 14.91 g (25.6%, mp 94–95°) of **8** (total yield 84.3%). The product melted at 94.5–95.5° after recrystallization from methanol; nmr (32% in $CDCl_3$) showed τ 2.55–3.07 (m, 4, C_6H_4), 5.51–6.12 (m, 4, ketal CH_2), 6.32–6.52 (m, 1, benzylic CH), 7.77–9.23 (m, 7.9, CH_2).

Anal. Calcd for $C_{15}H_{17}BrO_2$: C, 58.26; H, 5.54; Br, 25.85. Found: C, 58.00; H, 5.72; Br, 26.04.

1,2,3,4-Tetrahydrofluoren-9-one Ethylene Ketal (10).—Sodium methoxide powder (27 g, 0.50 mol) was added in one portion to a well-stirred solution of bromo ketal **8** (66.7 g, 0.197 ml) in dimethyl sulfoxide (300 ml) under a dry nitrogen atmosphere. After 30 min the temperature rose to 60° and stirring was continued with no external temperature control for 3 hr. The mixture was diluted with ice–water (700 ml) and then was extracted with three 150-ml portions of ether, and the ether extract was dried and concentrated to give 43.7 g (97% yield) of crude **10** as oily orange crystals. This material was crystallized from methanol to give 37.9 g (84% yield of which 4% was recovered from mother liquor) of **10** (mp 71.5–72°): uv (95% EtOH); λ_{max} mμ (log ϵ) 219 (4.49), 225 (4.45), 277 (3.68); nmr (20% in CCl_4) τ 2.74–3.28 (m, 4, C_6H_4), 5.87–6.14 (m, 4.1, ketal CH_2), 7.60–8.07 (m, 4, allylic CH_2), 8.07–8.48 (m, 4, CH_2).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.21; H, 7.05.

1,2,3,4-Tetrahydrofluoren-9-one (5).—A solution of ketal **10** (35.64 g, 0.156 mol), *p*-toluenesulfonic acid (1.0 g), and dry acetone (200 ml) was heated to reflux with stirring for 15 min. The mixture was then aged for 30 min at room temperature, poured into water (500 ml), and the resulting mixture was extracted with three 125-ml portions of petroleum ether (bp 30–68°). The organic extract was washed successively with aqueous sodium bicarbonate and with brine and was then dried (Na_2SO_4) and concentrated. The crude ketone (28.6 g, 99% yield, yellow crystals, mp 39.5–40.5°) was recrystallized from *n*-pentane to give bright yellow crystals of pure **5** (mp 41–42°, lit.[5] mp 41.5–42.5°): ir (CCl_4) 1705 cm^{-1} (C=O); uv (95% EtOH) λ_{max} mμ (log ϵ) 236 (4.06), 243 (4.67); nmr (20% CCl_4) τ 2.58–3.30 (m, 4, C_6H_4), 7.50–8.03 (m, 4, allylic CH_2), 8.03–8.43 (m, 4, CH_2).

Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 85.08; H, 6.85.

Reaction of 5 with Hydrogen Cyanide.—The following is an adaptation of an unpublished procedure by Professor C. F. Koelsch (University of Minnesota). A mixture of ketone **5** (2.00 g, 10.9 mmol), sodium cyanide (0.69 g, 14 mmol), ethyl acetate (1.8 g, 20 mmol), water (6 ml) and 95% ethanol (9 ml) was heated at the reflux temperature for 1.5 hr and was then poured into cold water (100 ml). The mixture was extracted with four 50-ml portions of ether and the ether extract was then washed with saturated sodium bicarbonate and was dried (Na_2SO_4) and concentrated. The crude light yellow oily solid (2.26 g, 99% yield) was recrystallized from ethanol–water to give 1.62 g (71% yield, mp 74.6–75.3°) of **1,2,3,4,4a,9a-hexahydro-9-oxofluorene-4a-carbonitrile (12)**: ir (CCl_4), 1720 (C=O), 2250 cm^{-1} w (C≡N); uv (95% EtOH) λ_{max} mμ (log ϵ) 244 (4.09), 283 (3.24), 288 (3.24); nmr (25% in $CDCl_3$) τ 2.10–2.63 (m, 4, C_6H_4), 6.79–7.02 (m, 1, bridgehead CH), 7.35–9.19 (m, 8.8, CH_2).

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.31; H, 6.18; N, 6.49.

1,2,3,4,4a,9a-Hexahydro-9-oxofluorene-4a-carboxylic Acid (14).—A mixture of **12** (1.16 g, 5.5 mmol) and concentrated hydrochloric acid (30 ml) was heated on a steam bath for 16 hr. The resulting mixture was diluted with water (150 ml) and extracted with three 50-ml portions of ether. The ether extract was washed with water and with brine, and was then dried (Na_2SO_4) and concentrated to give an oil which crystallized on standing to give light tan prisms (1.23 g, 97% yield, mp 121–126°). The crude acid was recrystallized from benzene–petroleum ether (bp 60–68°) to give **14** as a white powder (0.90 g, 71% yield, mp 136.4–136.6°): ir (halocarbon–Nujol) 1690 and 1712 cm^{-1} (C=O); uv (95% EtOH) λ_{max} mμ (log ϵ) 242 (4.04), 290 (3.32); nmr (14% in $CDCl_3$) τ −2.00 (s, 1, acid OH), 2.16–2.78 (m, 4, C_6H_4), 6.57–6.78 (s, 1, bridgehead H), 7.29–9.06 (m, 7.9, CH_2).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.07; H, 6.24.

2,3,4,4a-*cis*-9,9a-*cis*-Hexahydro-1H-fluorene-4a-carboxylic Acid (16). 1. From 14.—A mixture of granulated zinc metal (0.75 g), mercuric chloride (0.08 g), water (2 ml), and two drops of concentrated hydrochloric acid was stirred for 5 min and the solution was decanted from the zinc amalgam. Water (1 ml), concentrated hydrochloric acid (3 ml), and a solution of keto acid **14** (293 mg, 1.27 mmol) in 95% alcohol (10 ml) was added to the zinc amalgam and the mixture was stirred and heated at the reflux temperature for 24 hr. Additional hydrochloric acid (after 6 hr, 2 ml, and after 12 hr, 2 ml) was added during the reflux period. The mixture was diluted with water (100 ml) and the organic material was extracted with two 40-ml portions of ether. The ether extract was washed with water

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[12] M. S. Karasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice Hall, Inc., New York, N. Y., 1954, p 219.

[13] House and coworkers (see ref 10) have proposed that the enhancement of 1,4 addition by cupric acetate in tetrahydrofuran relative to ether is due to the low solubility of cupric acetate in ether.

and was dried (Na_2SO_4) and concentrated. The crude product contained appreciable unconverted **14** and was reduced again exactly as described above. Chromatography of the crude yellow oil, thus obtained, on 100–200 mesh silica (20 g) gave as the first fraction by elution with chloroform slightly impure ester (**15**, ir and nmr identical with those of authentic **15**, see below; but showing impurity bands at 1265 and 1220 cm^{-1} and sharp bands near the methyl triplet at τ 8.78 and small peaks at τ 3.57 and 6.34). A mixture of the slightly impure ester (157 mg) and 10% ethanolic potassium hydroxide (25 ml) was heated at the reflux temperature, and the cooled mixture was extracted with ether. The basic solution was acidified (concentrated HCl) at 0° and the dry oil (71.8 mg) obtained was chromatographed on 100–200 mesh silica gel (20 g). Acid **16** (57 mg) was eluted with 300 ml of chloroform and was recrystallized from ethanol–water to give pure **16** (47 mg, mp and mmp 107.5–108°). The ir spectrum of the product was identical with that obtained from **16**.

2. From 17.—Acid **18**[14] (22.6 g) was reduced with hydrogen (4 atm) in a Parr apparatus using 95% ethanol (250 ml) as solvent and 10% palladium on carbon powder (0.5 g) as catalyst. The yield of **16** (22.08 g from ethanol–water, mp 108.6–109.5°) was 97%: ir (Nujol) 1695 cm^{-1} (C═O); nmr (25% in $CDCl_3$), τ −2.13 (s, 1, acid OH), 2.53–3.00 (m, 4, C_6H_4), 6.80–8.83 (m, 11, benzylic CH_2, bridgehead CH and CH_2).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.47; H, 7.41.

Acid **16** (3.00 g, 0.014 mol) was further characterized by esterification (with ethanol and sulfuric acid) to ester **15** [3.11 g, 92% yield, bp 98–102° (0.15 mm), $n^{28}D$ 1.5259]: ir (neat) 1720 cm^{-1} (C═O); nmr (32% in $CDCl_3$) τ 2.63–3.04 (m, 4, C_6H_4), 5.88 (q, $J = 7$ Hz, 2, OCH_2), 6.81–7.47 (m, 3, benzlic CH_2 and bridgehead CH), 7.60–8.98 (t, $J = 7$ Hz, CH_3 superimposed on a m, CH_2, total wt 11).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.33; H, 8.44.

Reaction of 5 with Di-*t*-butyl Malonate. 1,2,3,4,4a,9a-Hexahydro-9-oxofluoren-4a-ylmalonic Acid (21).—A mixture of **5** (2.00 g, 0.011 mol), di-*t*-butyl malonate[15] (3.0 g, 0.014 mol), and potassium *t*-butoxide (from 0.10 g, 0.0025 g-atom of potassium) and anhydrous *t*-butyl alcohol was heated with stirring at 60° under a dry nitrogen atmosphere for 3 hr, and was then aged for 16 hr at room temperature. The resulting mixture was treated with acetic acid (0.3 ml) and poured into cold water (100 ml). The aqueous mixture was extracted with four 50-ml portions of petroleum ether (bp 30–60°) and the ether extract was washed with cold water and with brine and was dried (Na_2SO_4) and concentrated. An nmr spectrum of the crude product showed $CH(CO_2R)$ only as a singlet (τ 6.30) and analysis of the peak area (*i.e.*, area of the singlet at τ 6.30 relative to that of the multiplet at τ 2.23–2.85 due to the aromatic protons) suggest 86% conversion into **19**. The crude product was chromatographed on 100–200 mesh silica gel (100 g) and the column was eluted with chloroform to give a mixed fraction of **5** and di-*t*-butyl malonate (0.49 g), a mixed fraction of **19** and di-*t*-butyl malonate (2.04 g), and a fraction of slightly impure **19** (2.33 g). The composition of the fractions was determined by tlc on Stahl silica gel G, developed with benzene. Attempts to crystallize pure samples of **19** were unsuccessful: nmr (32% in CCl_4) showed τ 2.27–2.86 (m, 4, C_6H_4), 6.30 [s, 1, $CH(CO_2R)_2$], 6.61–6.85 [m, 1, C(═O)CH], and 7.40–9.20, (two singlets at τ 8.58 and 8.83 due to nonequivalent *t*-butyl groups superimposed on the multiplet due to CH_2, total 26).

An impure sample of ester (4.68 g, containing 79% of **19**) was dissolved in benzene (100 ml) and the mixture was heated at the reflux temperature with continuous water separation for 30 min to ensure dryness. Dry *p*-toluenesulfonic acid was added and the mixture was heated at the reflux temperature for 2 hr. The cooled mixture was diluted with water (50 ml) and with ether (100 ml) and the organic phase was separated, washed with water (50 ml) and with brine (50 ml) and was dried ($NaSO_4$) and concentrated. The yellow solid (2.94 g), thus obtained, was suspended in boiling benzene (75 ml) and the mixture was cooled and filtered. The white crystalline powder residue was recrystallized from ethanol to give **21** as white crystals which melted at 160–161° with gas evolution: ir (halocarbon–Nujol) 1730, 1710, 1680, 1655 cm^{-1} (C═O).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 67.05; H, 5.42.

The analytical sample had been dried for a short period under vacuum at 100°. This sample was shown to be hydroscopic (by ir) and attempts to remove the last trace of water under vacuum at 60° were unsuccessful. Longer periods of drying at 100° were accompanied by slow decarboxylation and a gradual rise in the carbon content of the residue.

1,2,3,4,4a,9a-Hexahydro-9-oxofluoren-4a-ylacetic Acid (22).—The dibasic acid **21** (1.91 g, 6.63 mm) was heated for 10 min (until gas evolution ceased) at 170–180° under nitrogen. The resulting glassy product was recrystallized from benzene–petroleum ether (bp 60–68°) to give **22** as white crystals (1.46 g, 90% yield, mp 77–81°). Recrystallization of the product produced no change in melting point. The product was ground to a fine powder and was heated under vacuum for 24 hr at 56° and for 48 hr at 80° with only small weight loss, to give pure **22** as a white crystalline powder: mp 102–102.5°; ir (halocarbon–Nujol) 1723 and 1673 cm^{-1} (C═O); uv (95% EtOH) λ_{max} mμ (log ε) 245 (4.06), 291 (3.36); nmr (32% in $CDCl_3$) τ −1.30 (s, 1, acid OH), 2.23–2.88, 4, C_6H_4), 6.89–7.24 (AB, q, $J_{AB} =$ 15 Hz, τ_A 7.07, τ_B 7.17, superimposed on m at τ 6.89–7.24, due to angular CH_2 and proton at C-9a, total wt 3).

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.60, H, 6.69.

The product described above which melted at 77–81° appears to be **22** with 0.166 mol of benzene of crystallization (nmr shows singlet at τ 2.72 superimposed on the multiplet due to C_6H_4 at τ 2.22–2.88, total wt 5).

Anal. Calcd for $C_{15}H_{16}O_3 \cdot 0.166C_6H_6$: C, 74.68; H, 6.66. Found: C, 74.89; H, 6.96.

An attempt to remove the *t*-butyl groups from **19** by reaction in acetic acid and acetic anhydride containing two drops of 85% phosphoric acid at 130° for 2 hr gave acid **22** (20% yield) and a product assumed to be the enol acetate of **22** (16% yield). The two products were separated by a column chromatography and the latter showed: mp 145.2–145.6°; ir (nujol) 1660 m, 1695 s, 1755 cm^{-1} s (C═O); nmr (14% in $CDCl_3$) τ −1.71 (s, 1, acid OH), 2.53–3.10 (m, 4, C_6H_4), 6.96–9.23 (ABQ, J_{AB} = 14 Hz, τ_A 7.14, τ_B 7.47 and s, 7.73 and all superimposed on m, angular CH_2 and CH_3CO superimposed on CH_2); mass spectrum *m/e* (relative intensity) 286 (18, M^+, calcd 286.3 for $C_{17}H_{18}O_4$), 43 (3, CH_3CO), 226 (22, loss of H_2O and CH_3CO), 244 (100, loss of CH_3CO), metastable peak centered on *m/e* 209.3 which corresponds to the 244 → 226 fragmentation.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.35; H, 6.62.

Reaction of 5 with Malononitrile.—A solution of ketone **5** (2.00 g, 0.0109 mol) and malononitrile (1.98 g, 0.030 mol) in absolute ethanol (15 ml) was added to a solution of sodium ethoxide prepared from sodium (0.07 g, 0.003 g-atom) and absolute ethanol. The red solution was allowed to stir for 30 min at room temperature under an atmosphere of dry nitrogen and was then diluted with cold 10% aqueous sodium chloride (100 ml). The mixture was extracted with four 50-ml portions of ethyl acetate and the organic extract was washed with brine (100 ml), dried (Na_2SO_4) and was concentrated. The oily solid residue (3.12 g) was chromatographed on 100–200 mesh silica gel (80 g) and chloroform was used as eluent. The deep red solid, which was eluted first was 1,2,3,4-tetrahydrofluoren-9-ylidenomalononitrile (**23**, 500 mg, 20% yield, mp 207–209° dec). The melting point of a sample of **23** obtained by sublimation of this product, 90° (0.2 mm), was 208–209.5° dec: ir (Nujol), 2240 cm^{-1} (CN); uv (95% EtOH) λ_{max} mμ (log ε) 251 (4.29), 290 (4.24), 353 (4.03); nmr (7% in $CDCl_3$) τ 1.88–2.06 (m, 1, C_6H), 2.57–3.12 (m, 3, C_6H_3), 7.18–7.70 (m, 4, allylic CH_2), 8.07–8.33 (m, 4, CH_2).

Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.86; H, 5.56; N, 12.08.

The second component obtained from the chromatography was recrystallized from benzene–petroleum ether (bp 60–68°) and was 1,2,3,4,4a,9a-hexahydro-9-oxofluoren-4a-ylmalononitrile (**24**, 1.8 g, 70% yield, mp 122–124°). A sample of **24** was purified further by sublimation of this product at 90° (0.05 mm): mp 126–127°; ir (Nujol) 2250 (C≡N), 1703 cm^{-1} (C═O); uv (95% EtOH) λ_{max} mμ (log ε) 243 (4.11), 203 (3.26), 289

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[14] E. F. Godefroi and L. H. Simanyl, *J. Org. Chem.*, **28**, 1112 (1963).

[15] G. S. Fonken and W. S. Johnson, *J. Amer. Chem. Soc.*, **74**, 831 (1952).

(3.26); nmr (25% in $CDCl_3$) τ 2.04–2.68 (m, 4, C_6H_4), 5.62 (s, 1, angular CH), 7.05–7.29 (m, 1, bridgehead **H**), 7.61–9.14 (m, 9, CH_2).

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.59; H, 5.70; N, 11.15.

Reaction of 5 with Ethyl Cyanoacetate.—The reaction of **5** (200 **g**, 0.0109 mol) with ethyl cyanoacetate was carried out for 18 hr at 60° essentially as described above for the reaction with malononitrile. The mixture was treated with acetic acid (0.5 ml) and the crude oil (3.45) obtained after processing as described above was chromatographed on 80 g of 100–200 mesh silica gel. The first compound removed from the column with chloroform was recovered **5** (0.49 g, 25% crude recovery). The second product eluted was shown to be **25** contaminated with ethyl cyanoacetate (tlc). Analysis of this mixture by nmr showed it to be 74.5% **25,** which corresponds to an over-all yield of 66% of **ethyl 1,2,3,4,4a,9a-hexahydro-9-oxofluoren-4a-ylcyanoacetate** from **5.** The Michael adduct was obtained pure by short-path distillation: bp 175–180° (0.7 mm); $n^{27}\text{D}$ 1.5462; ir (neat) 2240 (C≡N), 1735 (C=O), and 1712 cm^{-1} (C=O); nmr (25% in $CDCl_3$) τ 2.10–2.75 (m, 4, C_6H_4), angular CH superimposed on two nonequivalent ester CH_2's (s, τ 5.94 superimposed on *q*, J = 7 Hz, 5.96 and q, J = 7 Hz, 6.03, total wt 3), 6.74–7.01 (m, 1, bridgehead **H**), 7.43–9.15 (t, J = 7 Hz, 8.94 and t, J = 7 Hz, 8.99 superimposed on m, CH_2, total wt ~11).

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44: N, 4.71. Found: C, 72.52; H, 6.29; N, 4.80.

Reaction of 5 with methylmagnesium iodide in ether was carried out in a conventional manner to give the crude 1,2 adduct (**9-methyl-1,2,3,4-tetrahydrofluoren-9-ol, 26**), 97% yield (2.10 g, mp 101–122°). An nmr spectrum of this crude product confirmed the absence of **27.** The crude alcohol was recrystallized from ethanol–water to give pure **26:** white needles, 1.75 g; 81% yield; mp 142–143°; ir (Nujol) 3305 (OH) cm^{-1}; uv (95% EtOH) λ_{max} mμ (log ϵ) 272 (3.83), 276 sh (3.85); nmr (19% in $CDCl_3$) τ 2.58–3.13 (m, 4, C_6H_4), 7.60–7.95 (m, 4, allylic CH_2), 8.08 but varied with concentration (s, 1, OH), 8.13–8.38 (m, 4, CH_2), 8.62 (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.72; H, 7.80.

Reaction of 5 with methyllithium[16] in ether gave 2.15 g (98% yield) of **26** (mp 141–143°).

Reaction of 5 with Lithium Dimethylcopper.—A solution of methyllithium[16] in ether (1.4 *M*, 34 ml, 0.048 mol) was added dropwise, with stirring, under dry nitrogen to a slurry of cuprous iodide (4.76 g, 0.025 mol) in anhydrous ether at 0°. The solution was aged for 30 min and the ketone **5** (2.00 g, 0.0109 mol) in anhydrous ether (40 ml) was then added dropwise. The resulting mixture was aged for 30 min at 0° and was then poured into cold 20% ammonium chloride (100 ml) with vigorous mixing. The dry faintly yellow oil (2.21 g, 100% yield) obtained from the organic extract was essentially pure **4a-methyl-1,2,3,4,4a,9a-hexahydrofluoren-9-one** (**27**); spectral analysis (ir and nmr) confirmed the absence of any alcohol (**26**). Short-path distillation of this crude product gave pure **27** (2.08 g, 95% yield): bp 94–98° (0.2 mm); $n^{26}\text{D}$ 1.5580; ir (neat) 1715 (CO) cm^{-1}; uv (95% EtOH) λ_{max} mμ (log ϵ) 245 (4.03), 290 (3.35); nmr (32% in CCl_4) τ 2.29–2.90 (m, 4, C_6H_4), 7.62–9.03 (s, 8.56, CH_3, superimposed upon m, CH_2, total wt 12).

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.84; H, 8.14.

The **2,4-dintrophenylhydrazone of 27** (82% yield) was recrystallized from ethanol–ethyl acetate and obtained as bright red needles melting at 209–210.6°.

Anal. Calcd for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.19; H, 5.54; N, 14.50.

Ketone 27 was also obtained by reaction of **5** with the complex of methyllithium and tetrakis[iodo(tri-*n*-butylphosphine)copper-(I)]. The reaction was carried out as described for similar reactions by House, *et al.*[10] The crude product contained no alcohol **26** (nmr), and a mixture of **27** and tri-*n*-butylphosphine was obtained by distillation. The mixture thus obtained was treated in ether with excess methyl iodide to precipitate methyl tri-*n*-butyl-phosphonium iodide. Distillation of the residual oil gave 1.79 g (82% yield) of 27, bp 103–106° (0.7–0.6 mm), $n^{25}\text{D}$ 1.5585, which still contained a trace of tri-*n*-butylphosphine.

Registry No.—**5,** 634-19-5; **8,** 19459-37-1; **10,** 19462-82-9; **12,** 19459-38-2; **14,** 19459-39-3; **15,** 19459-40-6; **16,** 19459-41-7; **21,** 19459-42-8; **22,** 19459-43-9; **22** (enol acetate), 19459-44-0; **23,** 19462-83-0; **24,** 19459-45-1; **25,** 19459-46-2; **26,** 19462-84-1; **27,** 19462-85-2; **27** (2,4-dinitrophenylhydrazone), 19462-86-3.

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[16] Obtained from the Foote Mineral Co.

The Synthesis of 4-Bromophenanthrene[1]

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Two routes by which 4-bromophenanthrene (1) has been synthesized are described in detail. In one 4-phenanthrenecarboxylic acid (2) is treated with mercuric acetate in N-methylpyrrolidone at 100°. The resulting solution is treated with pyridinium hydrobromide perbromide (or with bromine) to give 1 in 55% yield. The second route involves conversion of diphenic acid (3) in seven steps to 1 in 11% over-all yield.

The objective of the work herein described was to develop a good synthesis for 4-bromophenanthrene (1). This compound was desired for use in the contemplated synthesis of helicenes by the route developed in this laboratory.[2] Since further synthetic work in this area

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[2] M. S. Newman and D. Lednicer, *J. Amer. Chem. Soc.*, **78,** 4765 (1956).