References and Notes

(1) (a) D. A. Evans, G. C. Andrews, and B. Buckwalter, *J. Am. Chem. Soc.*, **96**, 5560 (1974); (b) W. C. Still and T. L. Macdonald, *ibid.*, **96**, 5561 (1974); (c) W. C. Still, *Tetrahedron Lett.*, 2115 (1976).
(2) The site of attachment of the trimethylsilyl group was not investigated in these compounds, but has been tentatively assigned by analogy with the cyclohexanone → **4a** conversion.
(3) (a) D. Abenhaim, E. Henry-Basch, and P. Freon, *Bull. Soc. Chim. Fr.*, 4038 (1969); (b) D. Abenhaim, *C. R. Acad. Sci., Ser. C*, **267**, 1426 (1968); (c) H. Felkin and C. Frajerman, *Tetrahedron Lett.*, 1045 (1970); (d) D. Abenhaim, *J. Organomet. Chem.*, **92**, 275 (1975).
(4) Similar behavior has been noted previously with other allyllithiums: V. Rautenstrauch, *Helv. Chim. Acta*, **57**, 496 (1974).
(5) A number of mechanisms have been proposed to explain this rearrangement and are summarized in ref. 4.
(6) Cf. P. M. Atlani, J. F. Biellmann, S. Dube, and J. J. Vicens, *Tetrahedron Lett.*, 2665 (1974); W. H. Glaze, J. E. Hanicak, J. Chaudhuri, M. L. Moore, and D. P. Duncan, *J. Organomet. Chem.*, **51**, 13 (1973).
(7) (a) J. A. Katzenellenbogen and R. S. Lenox, *J. Org. Chem.*, **38**, 326 (1973); (b) R. B. Bates and W. A. Beavers, *J. Am. Chem. Soc.*, **96**, 5001 (1974); (c) G. A. Taylor and P. E. Rakita, *J. Organomet. Chem.*, **78**, 281 (1974); (d) W. D. Korte, K. Cripe, and R. Cooke, *J. Org. Chem.*, **39**, 1168 (1974); (e) G. Linstrumelle and D. Michelot, *J. Chem. Soc., Chem. Commun.*, 561 (1975); T. E. Stanberry, M. J. Darmon, H. A. Fry, and R. S. Lenox, *J. Org. Chem.*, **41**, 2052 (1976); ref 4.
(8) C. J. Upton and P. Beak, *J. Org. Chem.*, **40**, 1094 (1975).
(9) H. Ahlbrecht and J. Eichler, *Synthesis*, 672 (1974); M. Julia, A. Schouteeten, and M. Baillarge, *Tetrahedron Lett.*, 3433 (1974); P. Savignac, P. Coutrot, and Y. Leroux, *C. R. Acad. Sci., Ser. C*, **279**, 609 (1974).
(10) J. F. Biellmann and J. B. Ducep, *Tetrahedron Lett.*, 5629 (1968); K. Oshima, H. Takahashi, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **95**, 2693 (1973); P. L. Stotter and R. E. Hornish, *ibid.*, **95**, 4444 (1973); S. Torii, H. Tanaka, and Y. Tomotaki, *Chem. Lett.*, 1541 (1974); ref 6.
(11) R. Kow and M. W. Rathke, *J. Am. Chem. Soc.*, **95**, 2715 (1973).
(12) Anions derived from allylic dithianes [D. Seebach, *Synthesis*, 17 (1969)] and allylic sulfoxides [D. A. Evans, G. C. Andrews, T. T. Fujimoto, and D. Wells, *Tetrahedron Lett.*, 1385 (1973)] give large proportions of α-attack on reaction with ketones. Anions of α,β-unsaturated carbonyl compounds give very high selectivity for α-addition to aldehydes and ketones as well as to alkyl halides and protonating agents; cf., inter alia, H. O. House, "Modern Synthetic Reactions", 2d ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 9; M. W. Rathke and D. Sullivan, *Tetrahedron Lett.*, 4249 (1972); J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *ibid.*, 2433 (1973); S. A. G. de Graaf, P. E. R. Oosterhoff, and A. van der Gen, *ibid.*, 1653 (1974).
(13) Simple stabilized allylic anions frequently undergo exclusive γ-attack on benzophenone: R. H. DeWolfe, D. E. Johnson, R. I. Wagner, and W. G. Young, *J. Am. Chem. Soc.*, **79**, 4798 (1957); D. Seebach, *Synthesis*, 17 (1969); E. J. Corey and D. E. Cane, *J. Org. Chem.*, **34**, 3053 (1969); D. Seyferth, G. J. Murphy, and R. A. Woodruff, *J. Am. Chem. Soc.*, **96**, 5011 (1974); D. Seebach and D. Enders, *Angew. Chem., Int. Ed. Engl.*, **14**, 15 (1975).
(14) S. Kohama and S. Fukukawa, *Nippon Kagaku Zasshi*, **81**, 170 (1960); *Chem. Abstr.*, **56**, 496e (1962).

Phenylcinnamalones. 3. Basic Hydrolysis of Phenylcinnamalone[1]

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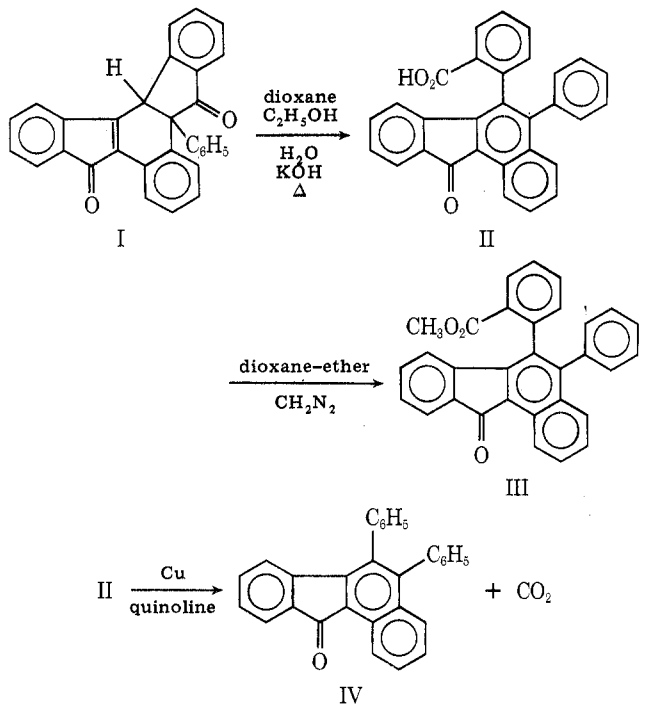
Previous publications in this series have dealt with the preparation and characterization of I,[4] the scope of the preparative reaction,[5] the synthesis of analogues of I,[5] and the nature of some of the potential reaction intermediates.[5] The one-step synthesis of such complicated ring systems utilizing simple starting materials and easily attainable reaction conditions is unusual. Further, we have found that simple single-step reactions allow the conversion of I into a number of compounds also possessing complex ring systems. In this report, we would like to describe the hydrolysis of I to II, the characterization of II, the conversion of II to III, and the decarboxylation of II to IV (see Scheme I).

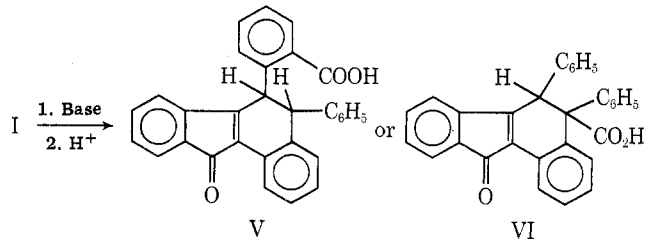
Scheme I



Results and Discussion

It has been found that phenylcinnamalone (I) can be converted to an orange-colored acid (II) by the action of ethanolic potassium hydroxide. Investigation has shown this acid to be of molecular formula $C_{30}H_{18}O_3$. Infrared and proton magnetic resonance (^{1}H NMR) spectral data indicated that the molecular structure of II is that of 6-(*o*-carboxyphenyl)-5-phenyl-11*H*-benzo[*a*]fluoren-11-one (II). ^{1}H NMR spectra of II and its methyl ester (III) reveal it to be a monobasic acid. The spectrum of the acid in Me_2SO-d_6 shows no peak whose chemical shift can be rationalized as resulting from resonance of a carboxyl proton. However, examination of a spectrum of II taken at 120 °C, using protic dimethylformamide (DMF) as the solvent, reveals a singlet, due to the resonance of one proton, at δ 10.03. The spectrum of the methyl ester in Me_2SO-d_6 displays a singlet at δ 3.40. Integration indicates it to be the result of resonance of three protons. The chemical shift of this peak is consistent with those due to resonance of the methyl protons of known carbomethoxy groups.[6] No indication of dibasicity was revealed by the spectra. Neutralization equivalents also confirm monobasicity.

Simple hydrolysis of phenylcinnamalone (I) to form a monobasic acid might be expected to proceed via cleavage of one of the bonds adjacent to one of the two carbonyl groups. Cleavage involving the indanone carbonyl group would result in a monobasic acid (V or VI). Cleavage of the indone grouping



would most likely result in colorless products, a fact not consistent with the observed product. Neither V nor VI agree with the parent peak of the mass spectrum of II. This peak appears at *m/e* 426, as opposed to the expected value of 428 for either V or VI.

Thus, dehydrogenation concurrent with the hydrolysis is

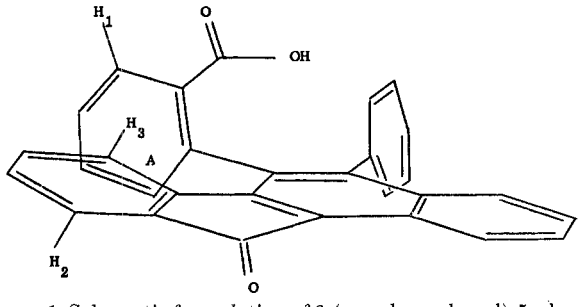


Figure 1. Schematic formulation of 6-(*o*-carboxyphenyl)-5-phenyl-11*H*-benzo[*a*]fluoren-11-one (II) showing relationships of protons and functional groups.

indicated. Simple dehydrogenation of structure VI is not likely. However, dehydrogenation of V could proceed to the completely unsaturated ring system of II. Examination of molecular models of V and II reveals that considerable strain would be relieved by this process.

Additional convincing evidence for structure II (see Figure 1) is supplied by the ^{1}H NMR spectra of II and its methyl ester (III). A well-resolved multiplet appears in both spectra centered at δ 9.03. This chemical shift is not atypical of resonance due to an aromatic proton (H_1, Figure 1) deshielded by the carbonyl group of an ortho carboxyl or carbomethoxy group.[6] Integrations are consistent with resonance due to one proton. A second well-resolved multiplet is centered at δ 7.82 in both spectra. Integration indicates it to be the result of resonance of one proton. Assignment of this multiplet as due to the resonance of an aromatic proton (H_2, Figure 1) deshielded by an ortho ketone carbonyl group is also consistent with the spectra of known compounds.[6]

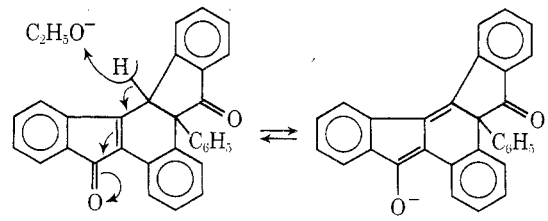
Besides an intense complex multiplet centered at δ 7.15, which is undoubtedly due to resonance of the bulk of the aromatic protons, a third well-resolved multiplet, centered at δ 5.75, appears in the spectra of both II and III. Integration is consistent with one proton.

Examination of a framework molecular model of structure II reveals that the planes of the two unfused aromatic rings are best situated perpendicular to the plane of the benzofluorene ring system. This configuration places the aromatic proton H_3 (Figure 1) directly in the positive ^{1}H NMR shielding zone of the aromatic ring A. By analogy to the argument for the similar situation encountered in the elucidation of the structure of 14b,14c-dihydro-5a-phenyl-10-(*α*-phenyl-*trans*-cinnamoxy)benz[*a*]indeno[2,1-*c*]fluoren-5-one,[5] this proton may be assigned as being responsible for the multiplet at δ 5.75.

Conclusive evidence for structure II is supplied by the decarboxylation of II. The decarboxylation product of II should be IV.

Brand and Stephan[7] prepared IV via another route, and McNelis[8] provided ultraviolet and infrared spectral data using a sample of IV prepared by the same route. These data are in excellent agreement with our data.

Subjection of I to strong enthanolic base immediately produces a dark blue solution. This phenomenon might be ascribed to an enolate anion (VII). Formation of VII can be envisioned as proceeding via abstraction of the methine proton of I. Reflux of the dark blue solution changes its color from blue to green. This color change could be due to formation of a second ion (VIII), via cleavage at the indanone carbonyl group. Acidification of the green solution destroys the color and precipitates II. Thus, upon acidification, VIII would have to lose a molecule of hydrogen in order to produce II. The fact that redissolution of II in strong ethanolic potassium hydroxide does not produce a green solution indicates that dehydrogenation may be the final step in the formation of II. Thus, regeneration of VIII is prevented.



The framework molecular models of structure II show considerable nonbonded interaction, which would probably prevent free rotation of the unfused phenyl rings. Therefore, II should possess total molecular asymmetry. Since the precursor, I, exists as an enantiomorphic pair of isomers, II should represent a racemic form. Resolution of II was not attempted.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 237 spectrophotometer. ^{1}H NMR spectra were taken on a Varian A-60A spectrometer. Melting points were taken on a Reichert polarizing hot stage. Mass spectra were obtained from Morgan and Schaeffer, Montreal, Canada. Elemental analysis were done by Galbraith Laboratories, Knoxville, Tenn.

Phenylcinnamalone (I) was prepared as reported previously.[4,5]

Basic Hydrolysis of Phenylcinnamalone (I). Formation of 6-(*o*-Carboxyphenyl)-5-phenyl-11*H*-benzo[*a*]fluoren-11-one (II). Four grams (0.010 mol) of I was dissolved in 50 ml of 1,4-dioxane. To this solution was added a solution of 5 g of potassium hydroxide in 100 ml of 95% ethanol. A deep blue color immediately developed. The mixture was refluxed for 30 min. The cooled solution was dark green in color. It was added to 500 ml of water. Acidification with concentrated HCl eliminated the green color and an orange solid separated. The orange solid, after recrystallization from glacial acetic acid (4 g, 92%), had mp 312–313 °C. Anal. Calcd for $C_{30}H_{18}O_3 \cdot H_2O$: C, 81.08; H, 4.50. Found: C, 81.08; H, 4.60. ^{1}H NMR: δ[9a] 5.85 m (1), 7.35 m (14), 8.05 m (1), 9.10 d (1), the solvent was Me_2SO-d_6; 5.80 m (1), 7.15, 9.03, m (1), 10.03 broad (1), the solvent was protic DMF; the temperature was 120 °C. Mass spectrum: principal peaks *m/e* 426 (P), 409, 408, 407, 380, 379, 352, 351, 350, 305, 276. Isotopic analysis.[9b] Calcd for $C_{30}H_{18}O_3$: P, 100; (P + 1), 32.81; (P + 2), 5.80. Found: P, 100; (P + 1), 32.5; (P + 2), 5.7.

Preparation of 6-(*o*-Carbomethoxyphenyl)-5-phenyl-11*H*-benzo[*a*]fluoren-11-one (III). One gram (0.0023 mol) of II was dissolved in 50 ml of 1,4-dioxane. This solution was added to a freshly prepared ether solution of diazomethane. The mixture was allowed to stand for 30 min. The excess diazomethane was destroyed with glacial acetic acid. The solvent was removed by distillation. The residue was crystallized from 1,4-dioxane to yield 0.9 g (86%) of orange product, mp 209–211 °C. Anal. Calcd for $C_{31}H_{20}O_3 \cdot H_2O$: C, 81.22; H, 4.80. Found: C, 81.10; H, 5.01. ^{1}H NMR: δ 3.28 s (3), 5.75 m (1), 7.35 m (14), 7.82 m (1), 9.03 m (1); the solvent was Me_2SO-d_6; the temperature was 120 °C.

Preparation of 5,6-Diphenyl-11*H*-benzo[*a*]fluoren-11-one (IV). Two grams (0.0045 mol) of II was heated with 10 ml of quinoline and 0.5 g of barium copper chromite catalyst or copper–bronze powder at 230–240 °C for 24 h. At the end of this time, the reaction mixture was cooled and poured into 100 ml of 10% aqueous HCl. The solid was filtered, dried, and extracted in a Soxhlet extractor with ether for 6 h. The ether solution was dried ($MgSO_4$). On removal of the ether, 1.4 g (81%) of product was obtained, which when recrystallized from glacial acetic acid melted at 239–241 °C. The infrared and ultraviolet spectra of this material were identical with those obtained by McNelis.[8]

Registry No.—I, 18585-55-2; II, 59803-45-1; III, 59796-79-1; IV, 4949-68-2.

References and Notes

(1) Research performed in part under the auspices of the Research Corporation.
(2) (a) Brookhaven National Laboratory; (b) Clarkson College of Technology; (c) Carnegie-Mellon University; (d) California State University, Fullerton.
(3) Taken in part from the dissertations submitted by Drs. Brown, Donaruma,

Kropf, and Stansfield in partial fulfillment of the requirements for the Ph.D degree.
(4) A. L. Bednowitz, W. C. Hamilton, R. G. Brown, L. G. Donaruma, P. L. Southwick, R. A. Kropf, and R. E. Stansfield, *J. Am. Chem. Soc.*, **90**, 291 (1968).
(5) A. L. Bednowitz, R. G. Brown, L. G. Donaruma, W. C. Hamilton, R. A. Kropf, P. L. Southwick, and R. E. Stansfield, *J. Org. Chem.*, **39**, 3537 (1974).
(6) D. W. Mathieson, "Nuclear Magnetic Resonance for Organic Chemists", Academic Press, New York, N.Y., 1967, pp 166, 184.
(7) K. Brand and H. W. Stephan, *Chem. Ber.*, **72**, 2168 (1939).
(8) E. McNelis, *J. Org. Chem.*, **30**, 4326 (1965).
(9) (a) ^{1}H NMR: first number is chemical shift; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, the numbers in parentheses are relative intensities. (b) Isotopic analysis: P = parent peak, (P + 1) = parent peak + 1, (P + 2) = parent peak + 2; numbers are relative intensities.

Reduction of 6-Ketones of the Morphine Series with Formamidinesulfinic Acid. Stereoselectivity Opposite to That of Hydride Reductions

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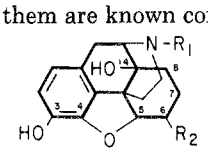
We have previously reported that formamidinesulfinic acid in aqueous alkaline solution reduces N-substituted noroxymorphone derivatives such as naltrexone (**1**) and naloxone (**3**) to the corresponding 6β-hydroxy epimers (**2** and **4**), with no detectable amount of the corresponding 6α epimers.[1] The stereochemistry of these products was the opposite of that obtained in the corresponding hydride reductions.[2]

It was then necessary to examine whether this reagent also reduces other ketones of the morphine series, especially those lacking the hydroxyl at C-14 present in **1** and **3**, and whether such reduction generally yields compounds with the 6β-hydroxy configuration. We therefore reduced a selected number of such ketones with formamidinesulfinic acid, in order to answer these questions and also to obtain reference samples of possible metabolites. Some of these 6β-hydroxy compounds had not been accessible before by a stereoselective reduction procedure; several of them are known compounds obtained



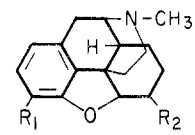
Compound	R_1	R_2
1	CH_2-cyclopropyl	=O
2	CH_2-cyclopropyl	β-OH[a]
3	CH_2-CH=CH_2	=O
4	CH_2-CH=CH_2	β-OH
5	CH_2-cyclobutyl	=O
6	CH_2-cyclobutyl	β-OH
7	CH_3	=O
8	CH_3	β-OH

[a] β-OH refers to the beta configuration

Table I. Partial Characterization of Reduction Products

Registry no.	Compd reduced	Reduction product	Yield, %	Mass spectrum, *m/e* (M)	Ref
16676-33-8	**5**	**6**	72	357	4
76-41-5	**7**	**8**	60	303	5
466-99-9	**9**	**10**	40	287	17
125-29-1	**11**	**12**	63	301	17, 18, 19

previously by more involved reaction sequences. We now report that 17-cyclobutylmethyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one (**5**), 17-methyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one (**7**), 17-methyl-4,5α-epoxy-3-hydroxymorphinan-6-one (**9**), and 17-methyl-4,5α-epoxy-3-methoxymorphinan-6-one (**11**) were reduced to their respective 6β-hydroxy derivatives in the yields shown in Table I. The reduction products were free of 6α-hydroxy epimers; they were isolated in pure form, and characterized by mass spectral and ^{1}H NMR data.[1,3]



Compound	R_1	R_2
9	OH	=O
10	OH	β-OH[a]
11	OCH_3	=O
12	OCH_3	β-OH

[a] β-OH refers to the beta configuration

Compound **6** had not been reported previously.[4] The pharmacology of **8** has been described earlier by Seki et al., who obtained this compound by a separation of 6-hydroxy epimers resulting from a Meerwein–Ponndorf–Verley reduction of 14-hydroxydihydrocodeinone (the 3-methyl ether of **7**), and further demethylation.[5] Weiss and Daum have reported a sodium borohydride reduction of **7**, to yield only the 6α epimer of **8**; however, these authors have indicated that no systematic search was made for the possible presence of 6β epimer, some of which might have been formed by the borohydride reduction.[6] A catalytic reduction of the 3-methyl ether of **7** has been shown to yield both 6-hydroxy epimers, with the 6β epimer as the minor product.[7]

In the present study the reduction products **8** and **10** could not be precipitated from an aqueous alkaline reaction mixture as in the isolation of the products **2**, **4**, and **6**; hence these compounds were extracted from the aqueous reaction mixture, after adjusting to pH 9–10, with a mixture of chloroform–ethanol (2:1). The phenolic compounds dissolve in aqueous NaOH solution and are thus amenable to reduction with formamidinesulfinic acid in aqueous alkaline solution.[1] This method presents a marked advantage over the Meerwein–Ponndorf–Verley reduction, which requires appreciable solubility of the substrates in common organic solvents.[8] Dihydrocodeinone (**11**) was reduced by formamidinesulfinic acid in aqueous ethanol, because of its limited solubility in water.