Stereoselective Synthesis for *cis*-β-Acetoxystyrene[1]

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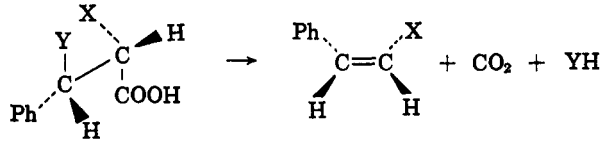
The synthesis of *cis*-β-acetoxystyrene (I) is patterned after the classical preparation of *cis*-β-bromostyrene (II) from *trans*-cinnamic acid dibromide (III). *trans*-β-Phenylglycidic acid (VII) reacts with *p*-toluenesulfonic acid yielding the *erythro*-α-ol-β-tosyloxy derivative (VIII). Subsequent acetylation followed by *trans* decarboxylation and β-elimination of tosylate affords I. Infrared and n.m.r. data for the β-acetoxystyrene isomers is discussed and compared with data in the β-bromostyrene series.

Prior to the recent work of House and Kramar[3] there had been few studies dealing with the separation and investigation of pure *cis*- and *trans*-enol acetates.[4] Further, the only syntheses available entail esterification of the enol form of an aldehyde or ketone.[3,4] When both *cis* and *trans* isomers are able to be formed, this method yields a mixture in which *trans* predominates. Because of their close boiling points, gas–liquid chromatography is employed to separate the geometrical isomers.[3]

As a prerequisite to a study of enol acetates relative to an investigation of steric requirements for cholinergic activity,[5] we initiated a program which would enable us to prepare geometrically pure isomers of the general structure Ar–CH=CH–OAc where Ar may contain a nitrogen function. β-Acetoxystyrene, where Ar = phenyl, was employed in our initial investigations since this system is not complicated by a basic nitrogen atom. In this communication we report a stereoselective synthesis for the thermodynamically less stable *cis* isomer I. We anticipate that this scheme will be generally applicable to the synthesis of aromatic *cis*-enol acetates.

Our synthesis is patterned after Grovenstein's[6] classical preparation of *cis*-β-bromostyrene (II),[6,7] which was obtained through *trans* decarboxylation and β-elimination of bromide from the sodium salt of *trans*-cinnamic acid dibromide (III). Introduction of an acetoxy group in place of bromide on the carbon α to the carboxyl group of III and utilization of an even better leaving group (tosyloxy) on the β-carbon affords compound IV, which under analogous elimination conditions should yield *cis*-β-acetoxystyrene.

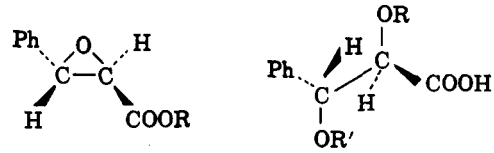


III, X = Y = Br
IV, X = OAc; Y = OTs

I, X = OAc
II, X = Br

While *trans*-cinnamic acid dibromide (III) is readily prepared by *trans* addition of bromine to *trans*-cinnamic acid,[6] a new approach is necessary for the synthesis of IV. Ethyl *trans*-β-phenylglycidate (V)[8] served as the starting material and is readily prepared by Darzens condensation of benzaldehyde with ethyl chloroacetate. This condensation yields a mixture of *cis* and *trans* isomers. Hydrolysis and conversion to the sodium salt followed by fractional crystallization from aqueous ethanol affords pure sodium *trans*-β-phenylglycidate (VI) as the less soluble isomer.[9] The *trans* configuration was confirmed by n.m.r. data which was in agreement with the results of Tung, Speziale, and Frazier.[10] The sodium salt was readily converted to the free acid VII through treatment with dilute hydrochloric acid.[9] Utilization of our experimental procedure affords pure *trans*-β-phenylglycidic acid in 77% yield.

Treatment of β-phenylglycidic acid (VII) with *p*-toluenesulfonic acid in ether yields compound VIII, believed to have the *erythro* configuration. Assignment



V, R = C_2H_5
VI, R = Na
VII, R = H

(only one enantiomorph shown)
VIII, R = H; R′ = Ts
IX, R = Ac; R′ = Ts

of this structure is in accord with the results of addition of *p*-toluenesulfonic acid to methyl *cis*-β-phenylglycidate in which attack of the tosyloxy group occurred at the carbon α to the aromatic ring and epoxide opening occurred with inversion of configuration.[11] In addition, under the conditions of the elimination, only this isomer could eventually yield *cis*-β-acetoxystyrene (I). The corresponding *threo* compound would yield the *trans* isomer. Stereoselective formation of *cis*-β-acetoxystyrene from the *threo* isomer would require a less likely double inversion.

Since some openings of benzylic epoxides with various Brønsted acids in nonpolar media have been shown to occur with retention of configuration,[10,12] independent evidence for the configuration of the β-tosyloxy-α-hydroxy acid VIII is desirable. Thus far our attempts to prepare stable derivatives of compound VIII which could subsequently be compared to derivatives of the

(1) Portions of this work were supported by a grant from the Abbott Laboratories, North Chicago, Ill. This work was presented at the 148th National Meeting of the American Chemical Society, Medicinal Chemistry Section, Chicago, Ill., Sept. 1964.

(2) Support by a grant from the Iowa Cancer Society is gratefully acknowledged.

(3) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

(4) P. Z. Bedoukian, *J. Am. Chem. Soc.*, **67**, 1430 (1945).

(5) For a discussion of stereochemical requirements for muscarinic and nicotinic acti ity, see C. J. Cavallito and A. P. Gray, "Progress in Drug Research," Vol. 2, Birkhaeuser Verlag, Basel and Stuttgart, 1960.

(6) E. Grovenstein, Jr., and D. E. Lee, *J. Am. Chem. Soc.*, **75**, 2639 (1953).

(7) S. J. Cristol and W. P. Norris, *ibid.*, **75**, 2645 (1953).

(8) L. Field and C. G. Carlile, *J. Org. Chem.*, **26**, 3170 (1961).

(9) H. O. House, J. W. Blaker, and D. A. Madden, *J. Am. Chem. Soc.*, **80**, 6386 (1958).

(10) C. C. Tung, A. J. Speziale, and H. W. Frazier, *J. Org. Chem.*, **28**, 1514 (1963).

(11) R. P. Linstead, L. N. Owen, and R. F. Webb, *J. Chem. Soc.*, 1218 (1953).

(12) H. H. Wasserman and N. E. Aubrey, *J. Am. Chem. Soc.*, **78**, 1726 (1956); J. Boeseken, *Rec. trav. chim.*, **41**, 199 (1922); R. Kuhn and F. Ebel, *Ber.*, **58**, 919 (1925); D. Y. Curtin, A. Bradley, and Y. G. Hendrickson, *J. Am. Chem. Soc*, **78**, 4064 (1956); C. C. Tung and A. J. Speziale, *J. Org. Chem.*, **28**, 2009 (1963); H. O. House, *ibid.*, **21**, 1306 (1956).

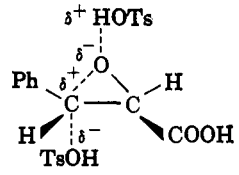


Figure 1.

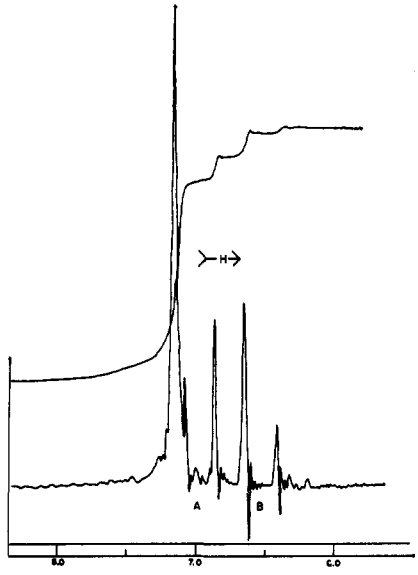


Figure 2.—The n.m.r. spectrum of *trans*-β-bromostyrene in carbon tetrachloride.

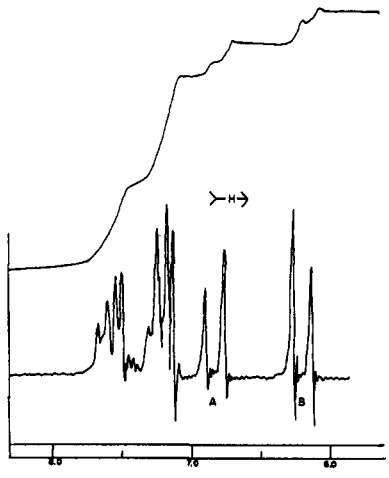


Figure 3.—The n.m.r. spectrum of *cis*-β-bromostyrene in carbon tetrachloride.

known *erythro* or *threo* diols[13] have been unsuccessful. This is largely due to the instability of the β-tosyloxy-α-carboxy system which readily decomposes under relatively mild conditions.

Selective formation of the *erythro* tosylate can be rationalized in terms of the intermediate shown in Figure 1. Such an intermediate would be favored over a pure carbonium-ion type in nonpolar solvents.[14] For this reaction to be successful the starting materials as well as the ether solvent must be absolutely dry. Breaking of the bond between epoxide oxygen and the carbon α to the aromatic ring is probably favored, since a positive charge on that carbon could be stabilized through resonance with the aromatic ring.

Reaction of VIII with acetic anhydride in pyridine at room temperature afforded *cis*-β-acetoxystyrene directly. Exclusive formation of the *cis* isomer was shown by gas–liquid chromatography of the distilled oil. The retention time for this compound was identical with the first major peak resulting from chromatography of the distilled mixture of *cis*- and *trans*-β-acetoxystyrene. The mixture was prepared by direct acetylation of phenylacetaldehyde.[4,15]

Attempts to isolate sufficient quantities of the β-tosyloxy-α-acetoxy intermediate IX for characterization failed although small amounts of a compound whose infrared spectra was in agreement with structure IX was obtained in some experiments when the reaction was run under very mild conditions (0–5°, 30 min.). Even under such mild conditions relatively good yields of the enol ester were isolated. If acetic anhydride was omitted, the reaction mixture afforded phenylacetaldehyde. Phenylacetaldehyde production increased with the duration of the reaction, but, even with only a 15-min. reaction period and at a temperature of 0–5°, a 20% yield was obtained. While we believe acetylation probably took place prior to decarboxylative elimination, these data do not exclude the possibility that the reverse is true and that acetylation of the enol occurred prior to the establishment of equilibrium between the enol and aldehyde. This is conceivable since studies with the enol of α-phenylpropionaldehyde indicate that ketonization of such enols is relatively slow.[16]

The gas–liquid chromatography data indicates that the enol acetate has the *cis* configuration and is in agreement with the results of House and Kramar[3] who have previously experienced elution of the *cis* enol ester prior to the *trans* isomer. Further proof for the *cis* structure was obtained from infrared spectroscopy. In the 10–14-μ region the infrared spectrum for pure *cis*-β-acetoxystyrene (I) was different from that for the mixture of enol acetates prepared by the direct method of acetylation. The pure *cis* isomer exhibited a much stronger absorption band at 12.74 μ and only very weak absorption at 10.72 and 13.32 μ. The mixture gives strong absorption at the latter two wave lengths because of the presence of the *trans* isomer. A similar out-of-plane bending[17] absorption pattern has been observed by Grovenstein[6] in the bromostyrene series.

Comparison of the n.m.r. spectrum in the acetoxystyrene series with the spectrum in the bromostyrene series provides us with the opportunity to note some expected similarities as well as some interesting differences. In the bromostyrene series (Figure 2, *trans*; Figure 3, *cis*)[18] J_{AB} for the vinyl protons of the *trans* isomer is 13.5 c.p.s. and for the *cis* isomer is 8.0 c.p.s. Similarly, in the acetoxystyrene series (Figure 4, *cis*; Figure 5, mixture of *cis* and *trans*) J_{AX} for the vinyl protons of the *trans* isomer is 13.5 c.p.s. and for the *cis* isomer is 7.5 c.p.s. Also, the vinyl protons in the *cis*

(13) W. Rigby, *J. Chem. Soc.*, 2452 (1956); E. Erlenmeyer, *Ber.*, **39**, 788 (1906); R. Fittig and R. Ruer, *Ann.*, **268**, 27 (189); J. Boeseken and C. DeGraaff, *Rec. trav. chim.*, **41**, 199 (1922); C. N. Riber, *Ber.*, **41**, 2413 (1908).

(14) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956); see p. 660.

(15) A modification of the general method utilized in ref. 4 was employed. To minimize the amount of polymerization no acid catalyst was used. Even with this modification only a 16% yield of enol acetate could be isolated.

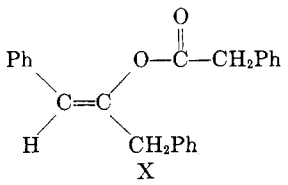
(16) V. J. Shiner, Jr., and B. Martin, *J. Am. Chem. Soc.*, **84**, 4824 (1962).

(17) L. Crombie, *Quart. Rev.* (London), **6**, 101 (1952).

(18) We thank Dr. Grovenstein for a sample of pure *cis*-β-bromostyrene. *trans*-β-Bromostyrene was purchased from Eastman Kodak Co.

compounds always appear further upfield relative to their respective *trans* isomers.

Vinyl protons on a carbon α to an aromatic ring generally occur further downfield because of the deshielding effect of the ring.[19] In the bromostyrene series the resonances of these protons are found at δ 6.94 (*trans*) and 6.84 (*cis*), while the resonances of the protons β to the aromatic ring are found at δ 6.55 (*trans*) and 6.20 (*cis*). The observation by Buckles and Cooper[20] that the single vinyl proton in 1-phenyl-2-benzyl-2-phenylacetoxyethylene (X) appears as a

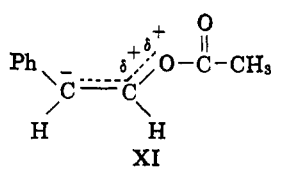


X

(stereochemistry unknown)

single line at δ 5.83 prompted us to label the doublet which is furthest upfield in the acetoxystyrene series to resonance of the proton β to the acetoxy group (α to the phenyl ring). In the acetoxystyrene series, then, the protons α to the phenyl ring are assigned to the doublet at δ 6.27 (*trans*) and 5.56 (*cis*) while the protons β to the phenyl ring are assigned to the doublet at δ 7.80 (*trans*) and 7.36 (*cis*). This assignment is similar to what has been observed for vinyl acetate[21] and other β-alkylvinyl esters.[3] To confirm this interpretation partially (methylene) deuterated phenylacetaldehyde was prepared and converted to the mixture of *cis*- and *trans*-β-acetoxystyrene. The n.m.r. integration for the *trans* vinyl protons showed a decrease in absorption at δ 6.27 in comparison to the absorption at 7.80.[22]

These data indicate that the acetoxy group is not only capable of shielding a vinyl proton β to it, but is also able to overcome the opposing deshielding effect of the aromatic ring. It is also apparent that the acetoxy group causes a deshielding of vinyl protons attached to the same carbon atom thereby enabling them to absorb radiofrequency energy considerably further downfield. A probable explanation for this observation lies in the importance of the resonance structure XI which apparently is a very important contributor to the electronic character of the molecule.[3,23]



XI

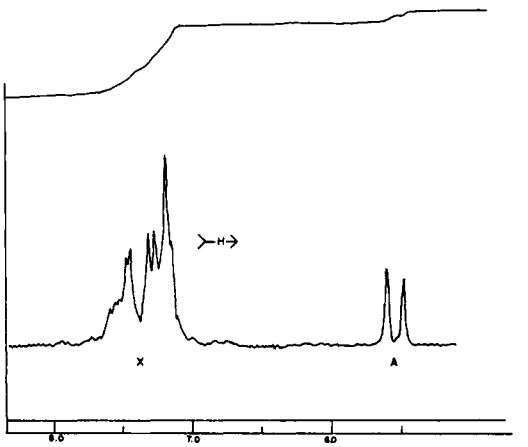


Figure 4.—The n.m.r. spectrum of *cis*-β-acetoxystyrene in carbon tetrachloride.

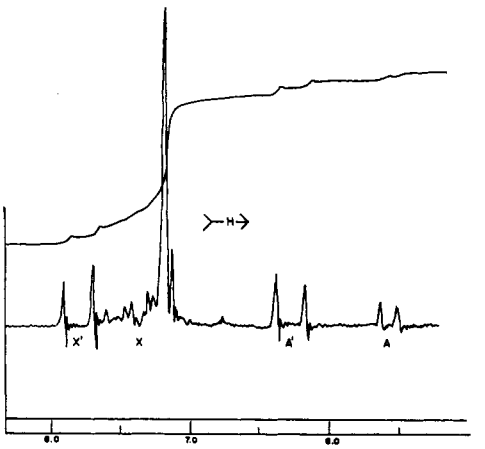


Figure 5.—The n.m.r. spectrum of a mixture of *cis*- and *trans*-β-acetoxystyrene in carbon tetrachloride.

Experimental[24]

***trans*-β-Phenylglycidic Acid (VII).**[9]—Sodium β-phenylglycidate (28.0 g., 0.15 mole) was dissolved in 280 ml. of water and cooled to 0°. To this solution was added 30 ml. of dilute hydrochloric acid (10%) dropwise and with stirring over a 15-min. period. The stirring was continued for an additional 15 min. and the reaction mixture was filtered affording 19.0 g. (77%) of white, crystalline *trans*-β-phenylglycidic acid: m.p. 85° dec., lit. m.p. 85° dec.

***erythro*-α-Hydroxy-β-phenyl-β-toluene-*p*-sulfonyloxypropionic Acid (VIII).**—To a suspension of 15.0 g. (0.091 mole) of *trans*-β-phenylglycidic acid in 250 ml. of ether in a 500-ml., three-necked flask was added 16.7 g. (0.097 mole) of anhydrous *p*-toluenesulfonic acid. The reaction mixture was stirred and heated under reflux for 1 hr. and then stirred for an additional hour at room temperature. A small amount (2.5 g.) of *p*-toluenesulfonic acid separated from the mixture and was filtered. The filtrate was concentrated under reduced pressure to 250 ml. Upon cooling, the concentrated filtrate afforded 10.0 g. (32.6%) of white solid, m.p. 80–81°, which turned green on prolonged exposure to the atmosphere and light. The infrared spectrum (Nujol) showed absorption bands at 2.9 (OH), 5.78 (C=O), 3.8–4.0 (COOH), 6.25, and 6.7 μ (aromatic). The characteristic epoxy bands at 11 and 12 μ were absent.[25]

(19) D. Y. Curtin, H. Gruen, and B. A. Shoulders, *Chem. Ind.* (London), 1205 (1958); L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," The Macmillan Co., New York, N. Y., 1959, pp. 18, 115, 125.

(20) We wish to thank Dr. Buckles for showing us his paper prior to its publication: R. E. Buckles and J. A. Cooper, *J. Org. Chem.*, **30**, 1588 (1965).

(21) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "Varian High Resolution NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962, spectrum no. 65.

(22) From the n.m.r. analysis it appears as though 25 ± 5% of the enol ester was deuterated at the carbon α to the aromatic ring.

(23) J. Feeny, A. Ledwith, and L. H. Sutcliffe, *J. Chem. Soc.*, 2021 (1962).

(24) All melting points are corrected and were taken with a Thomas-Hoover melting point apparatus. Infrared spectra were taken with a Beckman IR-5A spectrophotometer. Gas chromatography experiments were run with an F and M Model 500 gas chromatograph equipped with a flame-ionization detector. N.m.r. data was obtained with the Varian A-60. Elemental analyses were run by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.; Clark Microanalytical Laboratory, Urbana, Ill.; and the Chemistry Department, University of Iowa, Iowa City, Iowa.

(25) A. J. Speziale and H. W. Frazier, *J. Org. Chem.*, **26**, 3176 (1961); E. D. Bergmann, S. Yaroslavsky, and H. Weiler-Feilchenfeld, *J. Am. Chem. Soc.*, **81**, 2775 (1959).

Anal. Calcd. for $C_{16}H_{16}O_6S$: C, 57.15; H, 4.76; S, 9.52. Found: C, 57.18; H, 5.00; S, 9.44.

***cis*-β-Acetoxystyrene (I).**—*erythro*-α-Hydroxy-β-phenyl-β-toluene-*p*-sulfonyloxypropionic acid (3.5 g., 0.01 mole), acetic anhydride (1.0 g., 0.01 mole), and 10 ml. of anhydrous pyridine were mixed at 10° and allowed to stand at room temperature for 4 hr. The reaction mixture was poured onto 6 ml. of 10% hydrochloric acid and 200 g. of ice and was extracted with two 200-ml. portions of ether. The ether layer was washed with two 200-ml. portions of 5% hydrochloric acid and with 200 ml. of water. Final washing with two 200-ml. portions of 5% sodium bicarbonate solution and 200 ml. of water afforded a yellow ether solution which was dried over anhydrous sodium sulfate. Filtration followed by removal of the solvent under reduced pressure afforded 1.3 g. (78%) of yellow oil. Distillation, b.p. 86–87° (2.0 mm.), yielded a colorless oil which analyzed for *cis*-β-acetoxystrene: ν^{film} 5.7 (C=O), 6.05 (C=C), 6.28, and 6.7 μ (aromatic). Gas chromatography on a 10% silicone gum rubber (SE-30) on Chromosorb W (80–100 mesh) 4 ft. × 0.25 in. column with the column temperature 100°, detector temperature 230°, injection port temperature 300°, inlet pressure of 60 p.s.i., and carrier gas (He) flow rate of 75 ml./min. gave a retention time of 8.5 min.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 73.79; H, 6.19. Found: C, 73.48; H, 6.20.

***cis*- and *trans*-β-Acetoxystyrene.**[4]—A mixture of 48.0 g. (0.40 mole) of phenylacetaldehyde[26] and 102 g. (1.00 mole) of acetic anhydride was heated in an oil bath to reflux, allowing the distillate boiling at 118° to escape. After a reaction period of 3 hr. the oil bath temperature was increased in order to remove most of the acetic anhydride. The residue was washed several times with water and finally with 5% sodium carbonate solution. The crude oil was distilled employing an 18-in. Vigreux column, affording 9.8 g. (16%) of colorless liquid, b.p. 86–87° (2.0 mm.). Gas chromatography (same conditions as above for *cis*-β-acetoxystyrene) gave retention times for three peaks of 2,[27] 8.5 (*cis*), and 10.2 min. (*trans*).

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 73.79; H, 6.19. Found: C, 73.36; H, 6.11.

α-Deuterated *cis*- and *trans*-β-Acetoxystyrene.—A mixture of 6 g. (0.05 mole) of phenylacetaldehyde, 60 ml. of deuterium oxide, and 10 mg. of anhydrous sodium carbonate was shaken at 30° in a stoppered flask for 4 days. The reaction mixture was extracted with anhydrous ether (250 ml.) and dried over anhydrous sodium sulfate. Filtration followed by removal of ether under reduced pressure afforded a yellow oil. Distillation, b.p. 65–67° (0.45 mm.), afforded 2.09 g. of colorless liquid. The enol acetate was prepared from this methylene-deuterated phenylacetaldehyde by the method described above.

(26) Aldrich Chemical Co., Milwaukee, Wis.

(27) A trace of phenylacetaldehyde distils with the mixture. G.l.c. indicates that *trans* predominates over *cis* by 61%.

On the Bromopyrenes[1]

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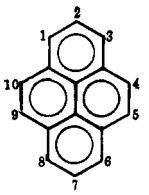
Treatment of 1-bromopyrene with potassium amide in liquid ammonia gave a mixture of 1-amino- and 2-aminopyrene. Sandmeyer reaction with the latter amine gave 2-bromopyrene in low yield. Bromination of 1,2,3,6,7,8-hexahydropyrene gave the 4-bromo derivative which was dehydrogenated with *o*-chloranil to 4-bromopyrene.

Despite the interest generated in polynuclear aromatic hydrocarbons in recent years as the result of advances in the theories of π-electron systems, relatively little progress has been made in the chemistry of these compounds, especially with respect to the introduction of substituents at relatively unreactive sites in the parent hydrocarbon. An important case in point is that of pyrene (I). The isomeric tritiated



I

pyrenes were required for our studies of the rates of acid- and base-catalyzed isotope exchange in aromatic hydrocarbons[3]; the labeled hydrocarbons are generally readily available from the corresponding bromides but only 1-bromopyrene is described in the literature.[4]

1-Substituted pyrenes are readily available by direct electrophilic substitution. The usual approach to substituents in the 2- and 4-positions of pyrene follows the lines of the early work of Vollmann[5] who started with the carboxylic acids. Synthesis of the acids themselves, however, often involves unpredictable yields and tedious separation of isomers.[6] Furthermore, this approach is cumbersome for the introduction of halogens in that the acid is converted to the amine which must then be converted to the halide by the Sandmeyer reaction or a variation thereof, a reaction which often goes in low yield with polynuclear aromatic amines.

In an effort to circumvent some of these difficulties, two additional approaches to the problem have been employed: (a) use of partially hydrogenated pyrene to effect specific directivity in bromination, followed by dehydrogenation and (b) use of *cine* substitution *via* a 1,2-dehydropyrene intermediate to convert 1-bromopyrene to a mixture of 1- and 2-aminopyrene, separation of the amines and conversion to the halide. Neither of these approaches is without precedent in polynuclear aromatic compounds, though neither has to our knowledge been employed in the pyrene series. Method a, for example, has been used to prepare 3-bromofluoranthene from 1,2,3,10b-tetrahydrofluoranthene in excellent yield.[7] An analogous approach has also been reported recently in the synthesis of the

(1) This research was supported in part by The Directorate of Chemical Sciences, Air Force Office of Scientific Research, Grant No. M4 (965) 62/64-554.

(2) National Science Foundation Predoctoral Fellow, 1960–1963; Eastman Kodak Science Award in Chemistry, 1962.

(3) A. Streitwieser, Jr., and R. G. Lawler, *J. Am. Chem. Soc.*, **85**, 2854 (1963); A. Streitwieser, Jr., and I. Schwager, unpublished results.

(4) G. Lock, *Ber.*, **70**, 926 (1937).

(5) H. Vollmann, H. Becker, N. Corell, and H. Streeck, *Ann.*, **531**, 1 (1937).

(6) A. Berg, *Acta Chem. Scand.*, **10**, 1362 (1956).

(7) R. Tobler, T. Holbro, P. Sutler, and W. Kern, *Helv. Chim. Acta*, **24**, 100E (1941).