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BEIRUT, LEBANON

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY]

Synthesis of Some Functionally Substituted Benzocyclanones[1]

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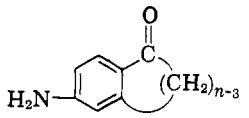
The synthesis of a group of indanones, tetralones, benzosuberones, and benzocyclooctanones is described. The compounds have various functional groups (amino, hydroxyl, carboxyl, fluoro, and derivatives) on the aromatic ring in the position *para* to the ketone group.

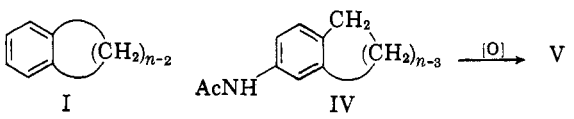
For studies concerning Hammett sigma constants a series of compounds VI was desired. The amines were selected as the first goal, since the amino



VIa. $n=6$
b. $n=5$
c. $n=7$
d. $n=8$

group is easily convertible to various other groups that were required. This paper describes only the synthesis of these and related compounds; the theoretical studies will form the subject of a later paper.

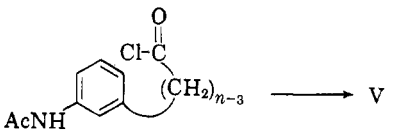
A synthesis was desired which would be general and which could be extended to various homologs. Because of the more ready accessibility of starting materials, the $n = 6$ case was investigated first. There appeared to be two general synthetic routes which might be pursued. The first of these involved as a key step the introduction of the ketonic oxygen into the saturated side chain. The oxidation



would be expected to occur at the desired methylene, rather than at the one *meta* to the amido group, since the intermediate radical or carbonium ion formed in the rate-determining step of the oxidation would be better stabilized.[2]

A synthetic scheme based on this step is attractive in general since it can begin with hydrocarbons (I), which are accessible without undue difficulty, even for the medium rings.

An alternative synthetic scheme would place a Friedel-Crafts ring-closure step near the end of the synthesis. A disadvantage in this case is the poor



yield anticipated in the cyclization step when a medium ring is closed.[3]

The first scheme appeared to offer the most promise and was undertaken initially. Compounds IVa and IVb are known, and their oxidation was studied. The reaction proceeded to give Va and Vb in yields of 57 and 74%, respectively. It was established (see below) that the oxidation took place at the *para* position as predicted. However, for the amide with $n = 7$, by the same procedure, no yield of the desired ketone could be obtained. Under the conditions which gave good results in the five- and six-membered rings, no oxidation occurred and the starting material was recovered. Under more strenuous conditions the starting material was not recovered, but none of the desired product could be isolated.

The alternative synthetic scheme, involving a Friedel-Crafts cyclization to yield the bicyclic amino ketones, was therefore undertaken. The method for synthesis of the benzosuberone derivative is outlined on the flow sheet. Nitration of γ-benzoylbutyric acid and reduction of the nitro group furnished the amino keto acid (XVIII). Acetylation of the amino group and hydrogenolysis of the ketonic oxygen gave the amido acid (XIX), which was cyclized to the amidobenzosuberone (Vc) both with polyphosphoric acid[4] and by treatment of the acid chloride with aluminum chloride in nitrobenzene.

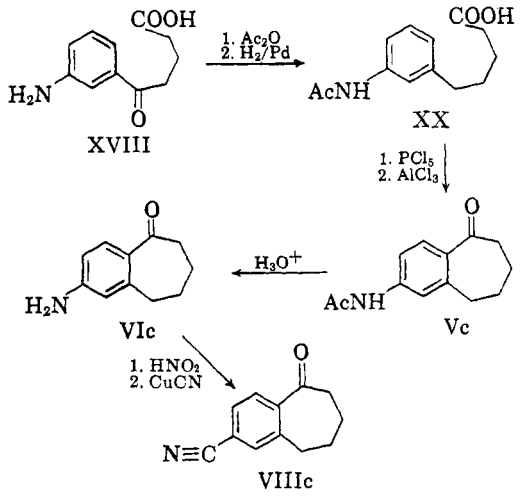
This synthetic sequence was repeated beginning with β-benzoylpropionic acid, which led to the amino tetralone (VIa). The compound obtained in this way was identical with the sample prepared by the oxidation of IVa. This proves that the Friedel-

(1) This research was supported by the Office of Ordnance Research, U. S. Army, under Contracts No. DA-20-018-ORD-14652 and No. DA-20-018-ORD-22743.

(2) K. B. Wiberg and R. J. Evans, *Tetrahedron*, **8**, 313 (1960).

(3) R. Huisgen and W. Rapp, *Ber.*, **85**, 826 (1952).

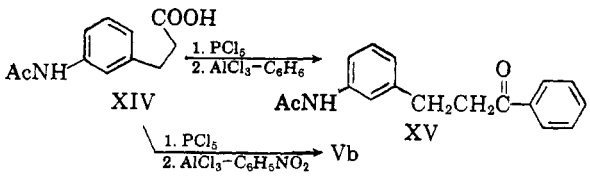
(4) R. C. Gilmore, Jr., and W. J. Horton, *J. Am. Chem. Soc.*, **73**, 1411 (1951).



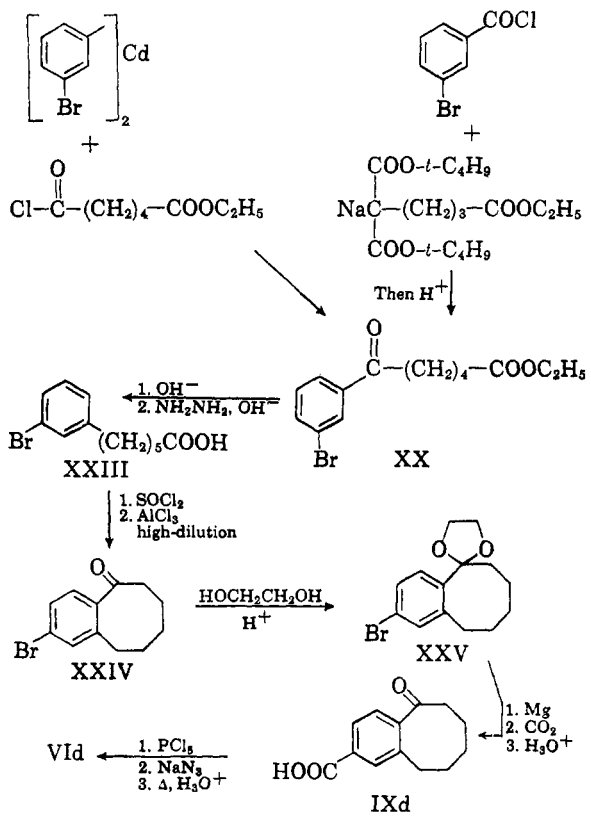
Crafts ring-closure of the amino acid occurs at the position *para* to the amido group, rather than *ortho*, and that the oxidation of IVa takes place at the methylene *para* to the amido group, since only by both of these reactions following the designated courses can such an identity occur. Also, it may be noted that the ultraviolet spectrum of the compound is similar to that of *p*-aminoacetophenone, but different from those of the *ortho* and *meta* isomers.[5]

This synthetic scheme was also repeated beginning with β-(*m*-acetamidophenyl)propionic acid, which similarly led to the aminoindanone (VIb). The identity of the compounds prepared by the two synthetic routes again proved the structure of the compound.

Originally the Friedel-Crafts ring closure of the amido acid XIV was attempted in benzene. The product isolated proved to be, surprisingly, a ketone (XVI) resulting from an intermolecular reaction between the acid chloride and the benzene solvent. In nitrobenzene however, the desired cyclization occurred.



The synthetic approach to the smaller rings by cyclization was not extended successfully to the eight-membered ring. To obtain reasonable yields in the Friedel-Crafts cyclization to benzocyclooctanones, it is in general[6] necessary to employ high dilution. Nitrobenzene is not a suitable solvent for this purpose because of its high boiling point. Carbon disulfide was unsuitable as the solvent because the solubility of the acid chloride was too low. A solvent mixture of carbon disulfide and nitrobenzene was tried but was not successful. A rather roundabout synthesis was therefore devised, the basic modification of which was to have the aromatic ring substituted with a group other than the amide which would give the desired solubility characteristics, be *ortho-para* directing, and be convertible to an amino group at a later stage. A bromine atom seemed to have the desired characteristics, and a synthesis using this substituent was designed and is outlined on the flow sheet. δ-(*m*-Bromobenzoyl)valeric acid (XXI) was prepared in two ways, either *via* the reaction of the cadmium reagent[7] from the mono-Grignard of *m*-dibromobenzene with the half ester acid chloride of adipic acid, or from the acylation with *m*-bromobenzoyl chloride of the ester (XXII) prepared from the reaction of ethyl γ-bromobutyrate with di-*t*-butyl malonate, followed by treatment of the product with acid.



The resulting ester (XX) was hydrolyzed to the corresponding acid (XXI), which was reduced by the Wolff-Kishner method[8] to the bromo acid (XXIII). This acid was converted to the acid chloride, and the latter was cyclized in 61% yield in a high dilution apparatus[9] using aluminum chloride in carbon disulfide. Bromo ketone XXIV was then

(5) P. Grammaticakis, *Bull. soc. chim. France*, 93 (1953).

(6) R. Huisgen and V. Vossius, *Monatsh. fur Chemie*, **88**, 517 (1957).

(7) J. Cason and F. S. Prout, *Org. Syntheses*, Coll. Vol. III, 601 (1955).

(8) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(9) N. L. Allinger, M. Nakazaki, and V. Zalkow, *J. Am. Chem. Soc.*, **81**, 4074 (1959).

converted to the ethylene ketal, and the Grignard reagent was prepared. The Grignard was formed with considerable difficulty under ordinary conditions, but when the reaction was carried out in tetrahydrofuran using ethyl bromide for entrainment, the preparation and carbonation of the Grignard gave the desired acid (IXd) in 59% yield. Conversion of this acid to the corresponding amine (VId) was carried out by the Curtius method,[10] treating the acid chloride with sodium azide to give the acid azide followed by thermal decomposition of the latter in refluxing benzene. The resulting isocyanate gave the amine upon acid hydrolysis in a yield of 60%.

From each of the amino ketones (VI), the corresponding diazonium salt was prepared and treated with various reagents to give a number of compounds. Thus with water the phenols were obtained, and with fluoroboric acid followed by pyrolysis,[11] the fluorides were obtained. The carboxylic acid with $n = 8$ has already been described. The smaller homologs were prepared by first treating the corresponding diazonium salts with cuprous cyanide to give the nitrile. Except for the indanone derivative (VIIIb), these nitriles could be hydrolyzed to the acids without difficulty. The indanone nitrile (VIIIb) gave polymeric material on hydrolysis. It was found that the nitrile could be converted to the corresponding amide in 73% yield with hydrogen peroxide and alkali, and hydrolysis of the amide to the acid proceeded satisfactorily.

EXPERIMENTAL

6-Acetamido-1-tetralone (Va). 6-Acetyltetralin[12] was converted to the oxime,[13] m.p. 104–105° (lit.[13] m.p. 105–106°). Rearrangement of the oxime[14] furnished the amide (IVa), m.p. 106–106.5° (lit.[14] m.p. 107°). To a solution of 28.9 g. of IVa in 70 ml. of acetic acid and 20 ml. acetic anhydride was added a solution of 20 g. of chromium trioxide in 15 ml. of water and 60 ml. of acetic acid, while the solution was kept below 10° by external cooling. After stirring overnight, the solution was poured into 1 l. of ice water and filtered. The product was washed with water and recrystallized from aqueous alcohol to yield 17.2 g. (57%) of the ketone (Va), m.p. 124–125°. A sample recrystallized for analysis had m.p. 124.5–125°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.44. Found: C, 70.95; H, 6.66.

6-Amino-1-tetralone (VIa). A mixture of 22.3 g. of keto amide (Va) and 150 ml. of 6*N* hydrochloric acid was heated under reflux for 2 hr., cooled, and made basic. The product was collected, washed with water, and crystallized from aqueous alcohol to give 16.0 g. (90.5%). The product, m.p. 129–130°, was recrystallized to give m.p. 129.5–130°.

Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.50; H, 6.88. Found: C, 74.28; H, 6.76.

6-Hydroxy-1-tetralone (VIIa). To 5.0 g. of amine (VIa) in 50 ml. of 6*N* hydrochloric acid cooled to 0–5°, was added dropwise a solution of 2.5 g. of sodium nitrite in 25 ml. of water. The resulting solution was poured with stirring into 150 ml. of boiling 20% sulfuric acid. Heating was continued for 2 min.; the mixture was then cooled and extracted with ether. The ether solution was decolorized with charcoal, filtered, and the ether was distilled. The crude product was recrystallized from water to give 2.0 g. (40%) of the phenol, m.p. 151–153°. After recrystallization a sample had m.p. 154–154.5°.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.04; H, 6.22. Found: C, 73.82; H, 6.21.

6-Cyano-1-tetralone (VIIIa). The procedure used was adapted from that given in *Organic Syntheses*.[15] To a solution of 10 g. of hydrated copper sulfate and 2.7 g. of sodium chloride in 50 ml. of hot water was added a solution of 2.1 g. of sodium bisulfite and 1.0 g. of sodium hydroxide in 25 ml. of water with stirring. The mixture was allowed to cool to room temperature, the cuprous chloride was washed by decantation and then was suspended in 25 ml. of water. A solution of 7 g. of potassium cyanide in 20 ml. of water was added with stirring and the mixture was cooled to 0–5°. The amine (VIa), 4.64 g., was dissolved in a solution of 7 ml. of concd. hydrochloric acid in 10 ml. of water. A solution of 2.1 g. of sodium nitrite in 5 ml. of water was added dropwise to the amine solution keeping the temperature below 5°. After the addition was complete the solution was neutralized with solid sodium carbonate. Ten milliliters of toluene was poured onto the surface of the cooled cuprous cyanide solution and the diazonium salt solution was then added slowly keeping the temperature at 5° by the addition of ice. The mixture was allowed to warm to room temperature and then was heated at 50° for 1 hr. The solution was cooled and filtered. The product was washed with water and recrystallized from aqueous alcohol to give 3.26 g. (63%) of nitrile, m.p. 133–134°.

Anal. Calcd. for $C_{11}H_9NO$: C, 77.16; H, 5.30; N, 8.18. Found: C, 77.12; H, 5.50; N, 8.22.

6-Carboxy-1-tetralone (IXa). A mixture of 6.84 g. of nitrile (VIIIa) and 70 ml. of 6*N* hydrochloric acid was refluxed overnight and then cooled. The product was filtered, washed with water, and recrystallized from aqueous ethanol to give 5.86 g. (76%) of acid, m.p. 219–20°. A sample recrystallized further gave m.p. 220–221°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.45; H, 5.30. Found: C, 69.47; H, 5.27.

6-Fluoro-1-tetralone (Xa). To a solution of 6.45 g. of amine (VIa) in 9 ml. of hydrochloric acid and 6 ml. of water was added a solution of 2.9 g. of sodium nitrite in 4 ml. of water, maintaining the temperature below 5°. Then 8 g. of 48% fluoroboric acid was added and the solution was allowed to stand at 0° for 30 min. After cooling the solution to −30°, the salt was collected and washed in turn with 10 ml. of cold methanol and 10 ml. of cold ether. After drying, the yield of fluoroborate salt was 7.56 g., m.p. 58–61° dec. The dry salt was added to 100 ml. of benzene and the solution was heated slowly to boiling. The solution was heated under reflux for 1 hr. after the initial evolution of gas ceased. The hot solution was then decanted from the insoluble tar. The cooled solution was washed with water, dilute sodium hydroxide solution, and water. After drying the solution over magnesium sulfate, the benzene was evaporated and the residue was distilled through a Vigreux column to yield 3.67 g. (56%) of product, b.p. 136–140° (10 mm.), n_D^{25} 1.5450. A sample redistilled for analysis had b.p. 105° (3 mm.), n_D^{25} 1.5454.

Anal. Calcd. for $C_{10}H_9FO$: C, 73.14; H, 5.53; F, 11.57. Found: C, 73.10; H, 5.76; F, 11.69.

3-m-Acetamidobenzoylpropionic acid (XII). β-Benzoyl-

(10) P. A. S. Smith, *Org. Reactions*, Vol. III, 387 (1946).

(11) B. L. Zenitz and W. H. Hartung, *J. Org. Chem.*, 11, 444 (1946).

(12) M. S. Newman and H. V. Zahm, *J. Am. Chem. Soc.*, 65, 1097 (1943).

(13) K. Schofield, T. Swain, and R. S. Theobald, *J. Chem. Soc.*, 2399 (1949).

(14) N. McLeish and N. Campbell, *J. Chem. Soc.*, 1103 (1937).

(15) H. T. Clarke and R. R. Read, *Org. Syntheses*, Coll. Vol. I, 514 (1948).

propionic acid was prepared according to *Organic Syntheses*[16] and was nitrated to yield the *m*-nitro derivative, m.p. 162–164° (reported[17] m.p. 162–164°). The nitro acid was reduced to the corresponding amino acid with hydrogen and palladium in methanol, m.p. 128–130° (reported[17] m.p. 131–132°). To 11.0 g. of the amino acid in 25 ml. of water was added 25 ml. of acetic anhydride, and the mixture was warmed on a steam bath for 1 hr. The solution was cooled and filtered. The amide was washed well with water and recrystallized from aqueous alcohol to give 11.3 g. (84%) of product, m.p. 172–174°. A sample recrystallized for analysis had m.p. 173–174°.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.25; H, 5.57. Found: C, 61.29; H, 5.60.

4-m-Acetamidophenylbutyric acid (XIII). A solution of 11.0 g. of XII and 0.5 g. of 10% palladium on carbon in 75 ml. of acetic acid was hydrogenated at 65°. After 12 hr. the theoretical amount of hydrogen had been taken up, the solution was cooled and filtered, and the acetic acid was distilled under vacuum. The residue was crystallized from aqueous alcohol to give 9.5 g. (91%) of product, m.p. 119–120°.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.13; H, 6.83. Found: C, 64.98; H, 7.02.

Friedel-Crafts cyclization of XIII. Compound XIII, 2.2 g., was converted to the acid chloride by allowing it to react with 2.1 g. of phosphorus pentachloride in 10 ml. of nitrobenzene at 80° for 2 hr. The solution was diluted with an additional 50 ml. of nitrobenzene, and the resulting solution was added dropwise during 2 hr. to a stirred mixture of 4.0 g. of anhydrous aluminum chloride in 50 ml. of nitrobenzene at room temperature. Stirring was continued for an additional 3 hr., and the cooled mixture was then hydrolyzed with 25 ml. of water and 25 ml. of 10% hydrochloric acid. The solvent was removed by steam distillation and the aqueous phase was extracted with chloroform. The aqueous phase was then made basic with dilute sodium hydroxide and was again extracted with chloroform. Evaporation of the solvent from the latter chloroform extracts yielded 1.0 g. (62%) of VIa, m.p. 128–130°. Mixed melting point of this material with a sample prepared from the oxidation of Va showed no depression.

5-Acetamido-1-indanone (Vb). The general synthesis was patterned after that described for the preparation of Va. Beginning with 5-acetylindane (IIb),[18] the oxime was prepared,[19] m.p. 110–112° (lit.[19] m.p. 114°) and rearranged as described previously to give 5-acetamidoindane (IVb), m.p. 105–106°, (lit.[13] m.p. 105–106°). The oxidation of IVb was carried out as described for the synthesis of Va. From 70 g. of IVb there was obtained 55 g. (74%) of product, m.p. 169–170° after recrystallization from aqueous alcohol. For analysis a sample was recrystallized, m.p. 170.5–171°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.81; H, 5.86; N, 7.40. Found: C, 69.68; H, 5.98; N, 7.19.

5-Amino-1-indanone (VIb). Hydrolysis of amide Vb with 6*N* hydrochloric acid resulted in the formation of an insoluble very high melting material. By refluxing 15.1 g. of Vb with 200 ml. of 2*N* hydrochloric acid for 1 hr., however, 8.0 g. (73%) of VIb, m.p. 186–186.5° was obtained. Recrystallization from aqueous alcohol gave a sample, m.p. 186.5–187°.

Anal. Calcd. for C_9H_9NO: C, 73.43; H, 6.17. Found: C, 73.25; H, 6.33.

5-Hydroxy-1-indanone (VIIb). Using the procedure described for the preparation of the homolog (VIIa), from 4.42 g. of VIb was obtained 2.51 g. (57%) of VIIb, m.p. 180–181° from aqueous ethanol (reported[20] m.p. 182°).

5-Cyano-1-indanone (VIIIb). The synthesis was carried out as described for preparation of the homolog (VIIIa); from 8.84 g. of amine VIb, there was obtained 6.10 g. (65%) of VIIIb, m.p. 130–131° from aqueous alcohol. Further recrystallization gave a sample with m.p. 131.5–132°.

Anal. Calcd. for $C_{10}H_7NO$: C, 76.40; H, 4.49; N, 8.91. Found: C, 76.27; H, 4.45; N, 8.84.

Attempted hydrolysis of 5-cyano-1-indanone (VIIIb). When compound VIIIb was heated under reflux in 6*N* hydrochloric acid or in 50% sulfuric acid, there resulted a base-insoluble material which did not melt below 300°.

5-Carboxamido-1-indanone. The procedure was adapted from *Organic Syntheses.*[21] To 4.72 g. of nitrile VIIIb were added 15 ml. of 30% hydrogen peroxide and 10 ml. of 25% potassium hydroxide. The mixture was stirred for 1 hr., the temperature being kept below 50° with external cooling. The solution was then stirred and maintained at 50° for 2 hr. and was cooled. The crystals were collected and recrystallized from aqueous ethanol to yield 3.84 g. (73%) of amide, m.p. 203–205°. A small sample recrystallized gave m.p. 204.5–205°.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.55; H, 5.18; N, 8.00. Found: C, 68.34; H, 5.33; N, 7.96.

5-Carboxy-1-indanone (IXb). A sample of the crude amide obtained from 4.72 g. of nitrile VIIIb was heated under reflux with 75 ml. of 4*N* hydrochloric acid for 2 hr., then cooled, and filtered. Recrystallization of the solid from aqueous alcohol gave 2.69 g. (51%) of acid IXb, m.p. 270° dec. Further recrystallization gave a sample with m.p. 272–273° dec.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.17; H, 4.58. Found: C, 68.26; H, 4.65.

5-Fluoro-1-indanone (Xb). This compound was prepared in a manner similar to that described for the preparation of Xa except that the fluoroborate salt was decomposed in toluene rather than in benzene. From 5.89 g. of amine VIb, there was obtained 8.10 g. of fluoroborate salt, m.p. 85–87° dec. After decomposition of the salt and distillation of the toluene, there remained 2.3 g. of an oily solid. This material was washed with ether and the ether extracts were combined and distilled to yield 0.88 g. (15%) of Xb, b.p. 100–115° (18 mm.), n_D^{25} 1.5482. Redistillation of combined samples of the compound gave 1.4 g. of liquid, b.p. 113–114° (10 mm.), 1.5499.

Anal. Calcd. for C_9H_7FO: C, 71.97; H, 4.70. Found: C, 72.04; H, 4.89.

Friedel-Crafts reaction of 3-m-acetamidophenylpropionic acid (XIV). To 1.0 g. of amido acid XIV[22] and 1.00 g. of phosphorus pentachloride was added 20 ml. of dry benzene. The mixture was allowed to stand at room temperature for 2 hr. and was then diluted with 30 ml. of dry benzene. Two grams of anhydrous aluminum chloride was then added portionwise with external cooling. The reaction was then stirred at 0° for 0.5 hr. and at room temperature for 3 hr. Hydrolysis of the mixture with water and hydrochloric acid, separation of the benzene phase, and evaporation of the solvent yielded 0.7 g. (52%) of a solid compound (XV), m.p. 132–133°, after recrystallization from aqueous alcohol.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.37; H, 6.41; mol. wt., 267. Found: C, 76.34; H, 6.22; mol. wt. (Rast) 275.

Repetition of the procedure using nitrobenzene as solvent gave 0.5 g. (35%) of amino ketone, m.p. 185–187°. The mixture melting point of the compound with VIb from the chromic acid oxidation showed no depression.

7-Acetylbenzocycloheptane oxime (IIIc). 4-Benzoylbutyric

(16) L. F. Somerville and C. F. H. Allen, *Org. Syntheses*, Coll. Vol. II, J. Wiley and Sons, Inc., New York, 1943, p. 81.

(17) E. L. Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

(18) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **62**, 49 (1940).

(19) J. von Braun, G. Kirschbaum, and H. Schuhman, *Ber.*, **53**, 1155 (1920).

(20) C. K. Ingold and H. A. Piggott, *J. Chem. Soc.*, **123**, 1469 (1923).

(21) C. R. Noller, *Org. Syntheses*, Coll. Vol. II, 586 (1943).

(22) A. K. De, *J. Ind. Chem. Soc.*, **5**, 29 (1928).

acid[23] was reduced to 5-phenylvaleric acid,[24] which was converted to the acid chloride and cyclized[24] with aluminum chloride to 1-benzosuberone (XVI). The ketone was reduced[8] to benzocycloheptane, b.p. 78–82° (3 mm.), n_D^{30} 1.5382 (reported,[25] b.p. 101° (15 mm.), n_D^{16} 1.5495). The preparation of 7-acetylbenzocycloheptane (IIc) was carried out by the procedure described for the preparation of the smaller homolog IIa. From 73.0 g. of Ic, there was obtained 86 g. (91%) of product, b.p. 139–143° (2 mm.), reported[25] b.p. 180° (22 mm.). From 85 g. of ketone IIc there was obtained 86 g. (92%) of oxime, m.p. 89–91° from aqueous alcohol. Further recrystallization gave a sample with m.p. 90.5–91°.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.10; H, 8.45; N, 6.70.

7-Acetamidobenzocycloheptane (IVc). The amide was prepared from the oxime (IIIc) as described for the smaller homolog (IVa). From 13.0 g. of IIIc there was obtained 9.5 g. (73%) of amide, m.p. 113–114° from aqueous alcohol. Recrystallization of a small sample gave m.p. 115.5–116°.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.45; H, 8.36; N, 7.07.

Attempted oxidation of 7-acetamidobenzocycloheptane (IVc). To 2.0 g. of IVc in 50 ml. of acetic acid and 10 ml. of acetic anhydride at 0–10° was added a solution of 1.5 g. of chromium trioxide in 10 ml. of acetic acid and 5 ml. of water, keeping the temperature below 10° with external cooling. The mixture was stirred overnight at room temperature and was diluted with 1 l. of water. Extraction with ether yielded 1 g. of starting material.

The procedure was repeated, but the final mixture was heated at 50° overnight. Again the starting material was recovered.

The reaction was then carried out at 95° and again the starting material was recovered.

The reaction was also carried out in pyridine and was also carried out as described earlier at 50° with the addition of 0.1 g. of benzoyl peroxide, but no product was obtained in either case.

4-m-Nitrobenzoylbutyric acid (XVII). To a stirred mixture of 50 ml. of fuming nitric acid (sp. gr. = 1.5) and 25 ml. of concd. sulfuric acid cooled to −10 to 0°, was added in portions 25.0 g. of 4-benzoylbutyric acid.[23] The mixture was stirred at −5° for an additional 0.5 hr. and was then poured into 1 l. of ice water. The product was collected, washed free of acid, and recrystallized from chloroform-hexane to yield 12.0 g. (39%) of product, m.p. 137–138°. Further recrystallization gave m.p. 138.5–139°.

Anal. Calcd. for $C_{11}H_{11}NO_5$: C, 55.69; H, 4.68. Found: C, 55.57; H, 4.50.

4-m-Aminobenzoylbutyric acid (XVIII). The nitro acid (XVII) (23.7 g.) was hydrogenated in the presence of 0.1 g. of 10% palladium on charcoal in 50 ml. of methanol until the theoretical amount of hydrogen had been taken up. The product, crystallized from aqueous alcohol, yielded 18.5 g. (89%), m.p. 125–126°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.74; H, 6.32. Found: C, 63.60; H, 5.98.

4-m-Acetamidobenzoylbutyric acid (XIX). Acetylation of 18.0 g. of amino acid (XVIII) by the procedure described earlier for the preparation of XII gave 17.5 g. (80%) of amide, m.p. 172–174° from aqueous alcohol. Recrystallization raised the melting point to 173–174°.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.63; H, 6.07. Found: C, 62.46; H, 5.81.

5-m-Acetamidophenylvaleric acid (XX). Amido acid (XIX), 17.0 g. was hydrogenolyzed by the procedure described for the synthesis of XIII. The product, obtained as before and recrystallized from aqueous alcohol, yielded 15.0 g. (95%), m.p. 138–139°.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.35; H, 7.29; N, 5.95. Found: C, 66.21; H, 7.41; N, 5.98.

7-Amino-1-benzosuberone (VIc). The ring closure of the acid chloride from XX was carried out as described for Va. After steam distillation of the solvent, the aqueous phase was extracted with chloroform. The aqueous phase was then made basic and again extracted with chloroform. The combined chloroform extracts were dried. The solvent was evaporated and the residue was heated under reflux with 80 ml. of 6*N* hydrochloric acid for 2 hr. The cooled solution was made basic, the amine was collected and recrystallized from aqueous alcohol to give 1.7 g. (39%) of compound, m.p. 113–114°.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.39; H, 7.48. Found: C, 75.39; H, 7.24.

7-Acetamido-1-benzosuberone (Vc). Thirty grams of phosphorus pentoxide and 20 ml. of phosphoric acid were mixed, and after the initial reaction had subsided the mixture was digested on a steam bath for 2 hr. The acid (XX), 5.88 g., was added, the resulting mixture was heated for an additional 2 hr. with stirring and was then poured onto 100 g. of ice. The product was collected, washed with water, 5% carbonate solution and water to yield 3.18 g. (58%) of product, m.p. 115–116° from aqueous alcohol. A small sample was recrystallized to give m.p. 116.5–117°.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.85; H, 6.96; N, 6.45. Found: C, 71.65; H, 6.98; N, 6.53.

A small sample of this amide was hydrolyzed with 6*N* hydrochloric acid and gave the amine, m.p. 112–113°. The mixture melting point with the amine obtained from the Friedel-Crafts reaction was undepressed.

7-Hydroxy-1-benzosuberone (VIIc). This phenol was prepared by the method described earlier for the preparation of VIIa. From 2.63 g. of amine there was obtained 1.75 g. (66%) of phenol, m.p. 162–163° from aqueous alcohol. Recrystallization raised the m.p. to 162.5–163°.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.87. Found: C, 75.18; H, 6.73.

7-Cyano-1-benzosuberone (VIIIc). The nitrile was prepared from 5.26 g. of amine (VIc) by the method described earlier for the preparation of VIIIa. Recrystallization from aqueous alcohol gave 2.86 g. (51%) of nitrile, m.p. 60–61°. The analytical sample had m.p. 61–62°.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.80; H, 5.99; N, 7.56. Found: C, 77.64; H, 6.20; N, 7.78.

7-Carboxy-1-benzosuberone (IXc). A mixture of 2.97 g. of nitrile (VIIIc) and 50 ml. of 6*N* hydrochloric acid was heated under reflux overnight. The solution was cooled, the product was collected and recrystallized from aqueous alcohol to yield 2.94 g. (90%) of acid m.p. 177–178°. A sample recrystallized further gave 178–179°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.93. Found: C, 70.30; H, 5.92.

7-Fluoro-1-benzosuberone (Xc). From 3.50 g. of amine (VIc), following the procedure outlined for the preparation of Xa, there was obtained 5.00 g. of fluoroborate salt, m.p. 85–87° dec. Decomposition of this salt in toluene gave 2.99 g. (64%) of fluoro ketone, b.p. 131–135° (5 mm.). Redistillation gave 1.94 g. of product b.p. 125° (3 mm.), n_D^{25} 1.5420.

Anal. Calcd. for $C_{11}H_{11}FO$: C, 74.13; H, 6.22. Found: C, 74.33; H, 6.28.

5-m-Bromobenzoylvaleric acid (XXI). To a mixture of 10.0 g. of magnesium in 150 ml. of ether was added dropwise 94.4 g. of *m*-dibromobenzene.[26] After the addition was complete the mixture was heated under reflux for 1 hr. The solution was cooled and 46.0 g. of anhydrous cadmium chloride was added in portions.[7] The mixture was stirred and heated for 3 hr. after which time the Gilman test was negative. One hundred milliliters of ether was then removed

(23) L. F. Somerville and C. F. H. Allen, *Org. Syntheses*, Coll. Vol. II, 82 (1943).

(24) G. O. Aspinall and W. Baker, *J. Chem. Soc.*, 743 (1950).

(25) P. Cagniant, *Compt. rend.*, **226**, 1623 (1948).

(26) J. L. Hartwell, *Org. Syntheses*, Coll. Vol. III, 185 (1955).

by distillation, 300 ml. of benzene was added, and an additional 200 ml. of solvent was distilled. An additional 300 ml. of benzene was then added to the solution, followed by the dropwise addition of 57.8 g. of 5-carbethoxyvaleroyl chloride. The solution was heated under reflux overnight, cooled, and hydrolyzed with 250 ml. of water followed by 100 ml. of 6*N* hydrochloric acid. The organic layer was separated, dried over magnesium sulfate, and the solvent was evaporated. The crude residue was dissolved in 500 ml. of absolute ethanol, 25 ml. of sulfuric acid was added and the solution was heated under reflux overnight. Three hundred milliliters of solvent was distilled and the cooled residue was poured into 500 ml. of water. The mixture was extracted with ether, and the ether extracts were washed and dried. The ether was evaporated and the residue was distilled. The product boiled at 171–176° (0.9 mm.), yield 46.6 g. (50%). The refractive index of the various fractions of product was variable, and hence this material was hydrolyzed directly to the acid. To 46.0 g. of ester was added 100 ml. of ethanol and 200 ml. of 10% sodium hydroxide solution. The mixture was heated under reflux for 2 hr., cooled, acidified, and filtered. The crude product was crystallized from ether-pentane and yielded 34.4 g. (41% over-all) of XXI, m.p. 72–73°. A sample recrystallized for analysis had m.p. 73.5–74°.

Anal. Calcd. for $C_{12}H_{13}BrO_3$: C, 50.55; H, 4.59. Found: C, 50.54; H, 4.70.

1,1-Dicarbo-t-butoxy-4-carbethoxybutane (XXII). All apparatus was washed with dilute base, rinsed with water, and dried before use. To a solution of 13.7 g. of potassium in 400 ml. of *t*-butyl alcohol was added 68.5 g. of *t*-butyl[27] malonate followed by 68.3 g. of ethyl 4-bromobutyrate.[28] The mixture was stirred at room temperature overnight, the alcohol was removed by distillation, and the residue was diluted with 500 ml. of water. The mixture was extracted with ether, the ether layer was separated, dried over magnesium sulfate, and the ether was evaporated. The residue was distilled through a short Vigreux column. The fractions boiling at 123–128° (0.5 mm.) were collected to yield 47.2 g. (45%), n_D^{25} 1.4312. A center cut was used for analysis.

Anal. Calcd. for $C_{17}H_{30}O_6$: C, 61.80; H, 9.15. Found: C, 62.10; H, 9.10.

m-Bromobenzoylvaleric acid (XXI). To a solution of 4.9 g. of sodium hydride (49%) dispersion in mineral oil in 200 ml. of ether was added 30.0 g. of triester XXII in 50 ml. of ether. The mixture was heated under reflux with stirring for 24 hr., after which time 21.0 g. of *m*-bromobenzoyl chloride in 50 ml. of ether was added. The resulting solution was heated under reflux overnight, cooled, and hydrolyzed with 100 ml. of water. The ether layer was separated and washed with saturated sodium bicarbonate solution and with water. After evaporation of the ether, decarboxylation was carried out by heating the residue in 75 ml. of benzene under reflux overnight with 1 g. of *p*-toluenesulfonic acid. The cooled solution was washed with 10% sodium carbonate, water, dried over magnesium sulfate, and distilled to give 9.6 g. of crude ethyl *m*-bromobenzoylvalerate, b.p. 170–180° (1 mm.). The crude ester was heated under reflux in a solution of 50 ml. of ethanol and 100 ml. of 10% sodium hydroxide. The cooled solution was extracted with ether. The aqueous phase was then acidified and filtered. The solid was recrystallized from ether-pentane and gave 6.8 g. (40%) of XXI, m.p. 74–75°. Mixed melting point with the sample prepared by the cadmium reaction was undepressed.

6-m-Bromophenylhexanoic acid (XXIII). To a solution of 20 g. of potassium hydroxide in 150 ml. of diethylene glycol was added 26.0 g. of acid (XXI), followed by 20 ml. of 85% hydrazine hydrate, and the mixture was heated under reflux for 2 hr. Material was then removed by distillation until the bath temperature reached 190° and the solution was maintained at 190° for 5 hr. The cooled solution was poured onto 500 g. of ice, and 50 ml. of hydrochloric acid was added. The product was extracted with ether. The extracts were dried; the solvent was evaporated and the product was distilled through a short column, b.p. 158–161° (0.4 mm.), n_D^{26} 1.5391, to yield 14.8 g. (60%). The sample solidified upon standing and melted at about 30°.

Anal. Calcd. for $C_{12}H_{15}BrO_2$: C, 53.14; H, 5.58. Found: C, 53.02; H, 5.61.

8-Bromo-1-benzocyclooctanone (XXIV). To 14.6 g. of acid (XXIII) was added 12 ml. of thionyl chloride, and the mixture was warmed on the steam bath for 2 hr. The excess thionyl chloride was removed under vacuum and the remaining acid chloride was diluted with 500 ml. of carbon disulfide. This solution was added dropwise during 29 hr. to a stirred mixture of 24 g. of aluminum chloride in 1200 ml. of refluxing carbon disulfide in a high dilution apparatus.[9] Stirring and heating were continued for 2 hr. after the addition was complete, and the solvent was then distilled. To the residue were added 1.5 l. of water and 50 ml. of hydrochloric acid. The product was then steam distilled, the distillate was extracted with ether, and the extracts were dried over magnesium sulfate. The ether was evaporated, and the residue was distilled to give 8.3 g. (61%) of XXIV, b.p. 128–131° (0.6 mm.), n_D^{26} 1.5915.

Anal. Calcd. for $C_{12}H_{13}BrO$: C, 56.94; H, 5.18; Br, 31.58. Found: C, 57.19; H, 5.23; Br, 31.03.

8-Bromo-1-benzocyclooctanone ethylene ketal (XXV). A mixture of 8.1 g. of ketone XXIV, 3.1 g. of ethylene glycol and 0.5 g. of *p*-toluenesulfonic acid in 75 ml. of benzene was heated under reflux for 48 hr. using a water separator. The cooled solution was washed with 10% sodium carbonate and water, dried over potassium carbonate, and distilled to yield 8.0 g. of (84%) of ketal, b.p. 135–140° (0.7 mm.). An analytical sample was taken from a center cut, n_D^{25} 1.5696.

Anal. Calcd. for $C_{14}H_{17}BrO_2$: C, 56.57; H, 5.77. Found: C, 56.41; H, 5.68.

8-Carboxy-1-benzocyclooctanone (IXd). A solution of 6.0 g. of ethyl bromide and 7.80 g. of ketal XXV in 50 ml. of tetrahydrofuran was added dropwise to a suspension of 3.65 g. of magnesium in 25 ml. of refluxing tetrahydrofuran. Heating and stirring was continued for 2 hr. after the addition was complete. The cooled mixture was then poured onto 200 g. of powdered Dry Ice. The resulting mixture was allowed to warm to room temperature with occasional stirring and was then hydrolyzed by the addition of 25 ml. of water followed by 25 ml. of 6*N* hydrochloric acid. The solution was warmed until the tetrahydrofuran had distilled and then was cooled and the product was filtered. The crude acid was dissolved in 100 ml. of 10% sodium hydroxide and the solution was extracted with ether. The aqueous phase was reacidified and filtered. Recrystallization of the product from aqueous alcohol gave 3.38 g. (59%) of product, m.p. 160–162°. A sample recrystallized gave m.p. 162–163°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.53; H, 6.47. Found: C, 71.53; H, 6.54.

8-Amino-1-benzocyclooctanone (VId). A mixture of 5.45 g. of acid IXd and 5.62 g. of phosphorus pentachloride in 20 ml. of benzene was heated under reflux for 2 hr. The solvent was evaporated, the acid chloride was taken up in 75 ml. of dry acetone and the solution was cooled to 0°. A solution of 3.25 g. of sodium azide in 10 ml. of water was added all at once and the mixture was stirred at room temperature for 1 hr. The solution was then poured into 150 ml. of water. The resulting oil solidified upon scratching and the solid was collected. The yield of dry azide was 5.2 g., m.p. 58–63° dec. The azide was decomposed by heating under reflux in 25 ml. of benzene for 3 hr. Seventy-five milliliters of 6*N* hydrochloric acid was then added, the benzene was removed by steam distillation, and the mixture was heated under reflux for 2 hr. The cooled aqueous solution was decanted

(27) A. L. McCloskey and G. S. Fonken, *Org. Syntheses*, Vol. **34**, 26 (1954).

(28) A. W. D. Avison and A. L. Morrison, *J. Chem. Soc.*, 1469 (1950).

from the residual tar. The residue was heated under reflux overnight with an additional 25 ml. of concd. hydrochloric acid. The combined acid solutions were made basic and extracted with ether. The ether extracts were washed, dried, and the ether was evaporated. The residue was crystallized from benzene–petroleum ether (b.p. 60–90°) and gave 2.85 g. (60%) of amine, m.p. 126–128°. The analytical sample had m.p. 129–129.5°.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.14; H, 8.00; N, 7.40. Found: C, 76.00; H, 8.16; N, 7.46.

8-Hydroxy-1-benzocyclooctanone (VIId). A solution of 0.5 g. of sodium nitrite in 3 ml. of water was added dropwise to a solution of 0.95 g. of amine (VId) in 5 ml. of water and 2 ml. of concd. hydrochloric acid at 0°. The resulting diazonium salt solution was then added to a stirred solution of 8 ml. of sulfuric acid and 12 ml. of water at 90–100°. The solution was stirred for 2 min., cooled, and extracted with ether. The ether solution was washed with water, dried over magnesium sulfate, and the ether was evaporated. The product was recrystallized from ether-pentane to yield 0.2 g. (21%), m.p. 136.5–138.5°. Further recrystallization gave a sample with m.p. 138.5–139.5°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.30; H, 7.41.

8-Fluoro-1-benzocyclooctanone (Xd). To a solution of 2.37 g. of amine (VId) in 4 ml. of hydrochloric acid and 6 g. of ice was added a solution of 1.05 g. of sodium nitrite in 4 ml. of water, keeping the temperature below 5°. With continued cooling and stirring 3.0 ml. of 48% fluoroboric acid was then added. The mixture was stirred at 0° for 0.5 hr., cooled to −10°, and filtered. The fluoroborate salt was washed with 5 ml. of cold methanol and with cold ether, then was dried. There was obtained 3.04 g. of salt, m.p. 82–85° dec. The dry salt was decomposed by refluxing in 50 ml. of toluene for 1 hr. The toluene solution was washed with dilute sodium hydroxide and water, and then dried. The solvent was removed and the residue was distilled to yield 1.4 g. (59%) of product, b.p. 93–94° (0.4 mm.), n_D^{22} 1.5424.

Anal. Calcd. for $C_{12}H_{13}FO$: C, 74.98; H, 6.82; F, 9.89. Found: C, 74.68; H, 6.99; F, 9.74.

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[CONTRIBUTION FROM THE EVANS CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

The Syntheses of 1′-Fluoro- and 1′-Fluoro-10-methyl-1,2-benzanthracene[1]

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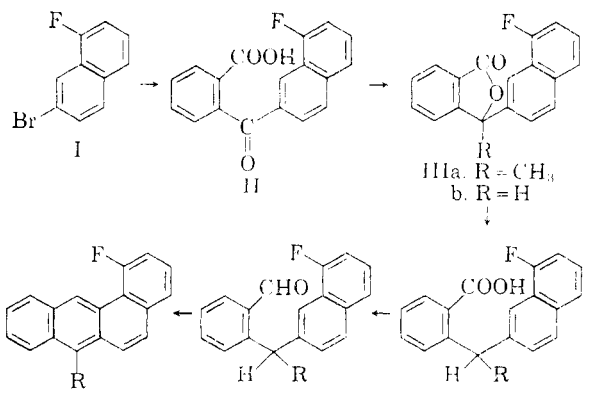
The syntheses of 1′-fluoro-1,2-benzanthracene, VIb, and 1′-fluoro-10-methyl-1,2-benzanthracene, VIa, were accomplished in good yield by a new method involving cyclization of *o*-(8-fluoro-2-naphthylmethyl)benzaldehyde, Vb, and of *o*-[1-(8-fluoro-2-naphthyl)ethyl]benzaldehyde, Va, respectively, by heating with polyphosphoric acid. An attempt to synthesize 1′-fluoro-9,10-dimethyl-1,2-benzanthracene by a similar cyclization of *o*-[1-(8-fluoro-2-naphthyl)ethyl]acetophenone failed, undoubtedly because of steric factors.

The reasons for the synthesis of monofluoro methyl-1,2-benzanthracenes have been stated.[2] In this paper the synthesis of 1′-fluoro-1,2-benzanthracene, VIb, and of 1′-fluoro-10-methyl-1,2-benzanthracene, VIa, as outlined in the chart below are described.



VIa. (R = CH_3). Va. (R = CH_3). IVa. (R = CH_3).
b. (R = H). b. (R = H). b. (R = H).

(1) This work was supported by a grant from the National Institutes of Health.

(2) M. S. Newman, D. MacDowell, and S. Swaminathan, *J. Org. Chem.*, **24**, 509 (1959).

The required 7-bromo-1-fluoronaphthalene, I, was prepared in three steps (44% overall yield) from 7-bromo-1-methylnaphthalene[3] by (1) oxidation to 7-bromo-1-naphthoic acid[4] using aqueous potassium dichromate[5] at 235°; (2) conversion of this acid to 7-bromo-1-naphthylamine (not isolated) by the Schmidt reaction;[6] and (3) replacement of the amino group by fluorine by the Rutherford modification[7] (hexafluorophosphoric acid) of the Schiemann reaction. Some modifications and improvement in the synthesis of 7-bromo-1-methylnaphthalene[3] were effected, the main one being in the use of chloranil for the dehydrogenation of 7-bromo-1-methyl-3,4-dihydronaphthalene to 7-bromo-1-methylnaphthalene.

(3) L. F. Fieser and A. M. Seligman, *J. Am. Chem. Soc.*, 60, 170 (1938).

(4) H. Goldstein and H. A. Fischer, *Helv. Chim. Acta*, 21, 1921 (1938).

(5) M. S. Newman and H. Boden, *J. Org. Chem.*, **26**, 1759 (1961). See ref. 4 in this paper for information concerning this oxidation.

(6) H. Wolff in Organic Reactions, John Wiley and Sons, Inc., New York, N. Y., 1946, Vol. III, p. 307.

(7) We are greatly indebted to Dr. K. Rutherford, Essex College, Windsor, Canada, for information about this method soon to be published.