Summary

1. 9,11-Dimethylbenz[*a*]anthracene and 8,9,11-trimethylbenz[*a*]anthracene have been prepared by an improved synthesis for benz[*a*]anthracene derivatives.

EVANSTON, ILLINOIS RECEIVED AUGUST 15, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Carcinogenic Hydrocarbons. 3,5-Dimethylcholanthrene[1]

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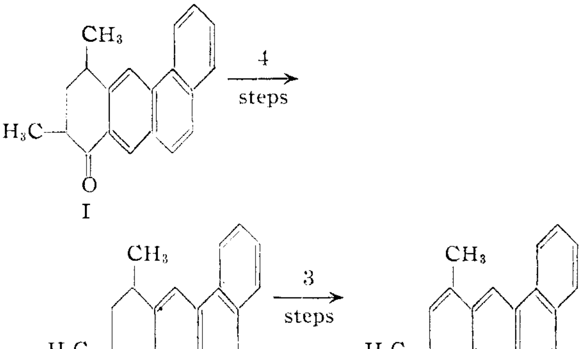
Since the preparation of methylcholanthrene from desoxycholic acid,[4] and from cholic acid[5] by a series of reactions whose types are known to occur in the animal body, it has been a natural speculation[6] that some tumors may be caused by carcinogenic agents produced by an abnormal metabolism of sterols or bile acids. The formation of substituted cholanthrenes from steroids requires a ring closure between the steroid side chain and ring C of the nucleus. The residue of the side chain will then occupy the 5 position in cholanthrene, and the C-20 methyl group of the steroid will be at the 3 position of cholanthrene (present system of numbering[7]). To date, 3,5-dialkylcholanthrenes have not been prepared and tested for carcinogenic activity. The biological reasons for desiring such information are obvious.

The first member of this series, 3,5-dimethylcholanthrene (III), has been prepared by general methods already recorded in the literature[8] for the preparation of substituted cholanthrenes. The starting material was 8-keto-9,11-dimethyl-8,9,10,11-tetrahydrobenz[a]anthracene (I).[9] By means of a Reformatsky reaction followed by dehydration, hydrogenation, and saponification, the ketone (I) was transformed into 9,11-dimethyl-8,9,10,11-tetrahydrobenz[a]anthryl-8-acetic acid (II). Cyclization of this acid by the action of stannic chloride upon the acid chloride produced a viscous liquid ketone which after reduction and dehydrogenation gave 3,5-dimethylcholanthrene. The action of liquid hydrogen fluoride upon the acid gave two products, one of which was an acetone-soluble viscous liquid, and the other (35%) was an acetone-insoluble substance crystallizing in bright yellow needles with a melting point of 267–270°. The physical properties and analysis of this substance conform well with those expected for 1-keto-3,5-dimethylcholanthrene. It is evident that extensive dehydrogenation has occurred, presumably by hydrogen transfer during the cyclization, although the low hydrogen content found in the acid indicates the possibility that dehydrogenation occurred in an earlier step. At the time this experimental work was performed, the extent of the dehydrogenation was not suspected, and both the non-crystalline and the crystalline cyclization products were combined, after reduction of the keto group, and carried through to 3,5-dimethylcholanthrene which was obtained in fair yield from the mixture.

The reduction of the ketonic material was accomplished by the Martin modification of the Clemmensen reduction.[10] The reduction products from both the solid and the oily ketone were combined. Two methods were used for aromatization of this material: (1) the Linstead liquid phase method[11] which gave pure 3,5-dimethylcholanthrene (III) but in poor yield, and (2) the heating of the crude tetrahydro hydrocarbon with palladium–charcoal at 300°. This last method was distinctly superior, giving the 3,5-dimethylcholanthrene (III) in a 51% yield.



From ethanol or ethanol–acetone 3,5-dimethylcholanthrene crystallized as orange-yellow needles melting at 183–184°, but from acetone alone, it crystallized either as diamond-shaped plates or

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(1) From the Ph. D. Theses by Michael A. Kubico, 1943, and John G. Burr, Jr., 1947.

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(4) H. Wieland and E. Dane, *Z. physiol. Chem.*, **219**, 240 (1933).

(5) L. F. Fieser and M. S. Newman, THIS JOURNAL, **57**, 961 (1935).

(6) J. W. Cook and G. A. D. Haslewood, *Chemistry and Industry*, **52**, 758 (1933); *J. Chem. Soc.*, 428 (1934).

(7) A. M. Patterson and L. T. Capell, "The Ring Index," Reinhold Publishing Corp., New York, N. Y., 1940, p. 437.

(8) (a) J. W. Cook and G. A. D. Haslewood, *J. Chem. Soc.*, 767 (1935); (b) E. Bergman and O. Blum-Bergmann, THIS JOURNAL, **59**, 1573 (1937); (c) W. E. Bachmann, *J. Org. Chem.*, **3**, 434 (1938); (d) W. E. Bachmann and J. M. Chemerda, *ibid.*, **6**, 50 (1941).

(9) B. Riegel and J. G. Burr, Jr., THIS JOURNAL, **70**, 1070 (1948).

(10) E. L. Martin, *ibid.*, **58**, 1438 (1936).

(11) R. P. Linstead, A. F. Millidge, S. L. S. Thomas and A. L. Walpole, *J. Chem. Soc.*, 1146 (1937).

stout rods all having the same melting point alone or admixed. An acetone or alcohol solution of the hydrocarbon has a strong violet fluorescence. When 3,5-dimethylcholanthrene is dissolved in concentrated sulfuric acid, a rose colored solution with a yellow fluorescence is formed. The hydrocarbon was characterized[12] by means of its ultraviolet absorption spectrum. The curve for this exhibits the maxima characteristic of the benz[*a*]-anthracene system which show a bathochromic shift of 30–40 Å. units when compared to positions of the maxima of cholanthrene (Table I). The same shift has been observed for the two methyl groups in 3,11- and 4,11-dimethylcholanthrene (Table I).

TABLE I

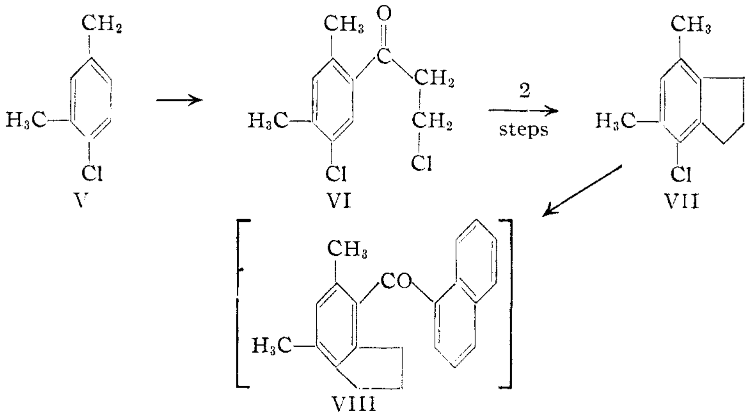
MAXIMA IN THE ULTRAVIOLET ABSORPTION SPECTRA OF CHOLANTHRENES (λ IN Å. UNITS) AND CORRESPONDING INTENSITIES (LOG E_M); SOLVENT, ETHANOL

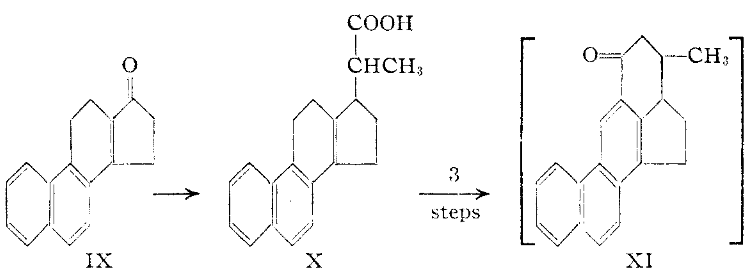
Cholanthrene and dimethyl derivatives	A	B	C	D	E	F
Cholanthrene[a]	2615	2740	2845	2950	3280	3420
	4.6	4.6	4.8	4.9	3.6	3.8
4,11-Dimethyl[12]	2635	2780	2882	2985	3310	3445
	4.64	4.63	4.78	4.82	3.69	3.80
3,11-Dimethyl[12]	2610	2768	2868	2983	3255	3430
	4.65	4.65	4.89	4.98	3.69	3.85
3,5-Dimethyl	2650	2770	2880	3000	3300	3460
	4.60	4.55	4.81	4.94	3.63	3.80

[a] L. F. Fieser and E. B. Hershberg, THIS JOURNAL, **60**, 940 (1938).

The method which has been most widely used for the preparation of substituted cholanthrenes is the Elbs pyrolysis of the appropriately substituted naphthoylhydrindenes.[13] In spite of the fact that pyrolysis of the ketone (VIII) could yield two possible isomers, caused by ring closure to either the *o*-methyl group or the *o*-methylene group, several efforts were made to prepare this substance with the aim of pyrolyzing it to 3,5-dimethylcholanthrene (III). By the chlorination of xylene,[14] 4-chloro-1,3-dimethylbenzene (V) was prepared. A Friedel–Crafts condensation of this compound with *β*-chloropropionyl chloride should produce theoretically three different isomeric chlorodimethyl-*β*-chloropropiophenones. Two of these possible isomers, *i. e.*, where substitution has taken place at the 5 or 6 positions of the 4-chloro-1,3-dimethylbenzene (V), would give the same and desired hydrindene (VII) after cyclization and Clemmensen reduction of the chlorodimethylhydrindones. One of these isomers, tentatively assigned the structure written as VI, was obtained as a sharp melting crystalline product. It gave a high yield (94%) of chlorodimethylhydrindone on ring closure with concentrated sulfuric acid. The chlorine atom in VII proved so highly hindered that a negligible yield of VIII was obtained by condensation of the lithium derivative with *α*-naphthonitrile. Attempts to exchange the chlorine atom in 4-chloro-5,7-dimethylhydrindene (VII) for a cyano group and then condense the resulting 4-cyano-5,7-dimethylhydrindene with *α*-naphthylmagnesium bromide were likewise fruitless.

An alternative path was sought in the reaction of 3′-keto-3,4-dihydro-1,2-cyclopentenophenanthrene (IX) with ethyl *α*-bromopropionate. It was planned to extend the side chain of the resulting acid (X) by the Arndt–Eistert procedure and then by aromatization and cyclization to arrive at the ketone (XI). 3,5-Dimethylcholanthrene could be derived from this ketone (XI) by an obvious series of reactions. However, the reaction of the ketone (IX) with ethyl *α*-bromopropionate gave a product which could not be characterized either as the ester or as the free acid.





Several other synthetic schemes were also explored but with less success than those described. Samples of 3,5-dimethylcholanthrene have been submitted to Dr. M. J. Shear, National Cancer Institute, and Dr. A. M. Seligman, for biological testing.

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[12] L. F. Fieser and D. M. Bowen, THIS JOURNAL, **62**, 2103 (1940).

[13] L. F. Fieser and A. M. Seligman, *ibid.*, **58**, 2482 (1936).

[14] O. Jacobsen, *Ber.*, **18**, 1761 (1885).

Experimental[15]

9,11-Dimethyl-8,9,10,11-tetrahydrobenz[*a*]anthryl-8-acetic Acid (II).—On warming a mixture of 2.0 g. of 8-keto - 9,11 - dimethyl - 8,9,10,11 - tetrahydrobenz[*a*]-anthracene,[9] 3 ml. of ethyl α-bromoacetate, 0.2 g. of iodine, 4.0 g. of 20-mesh zinc (thoroughly cleaned and dried), 20 ml. of dry ether and 20 ml. of dry benzene, a brisk spontaneous reaction set in. When the reaction subsided (fifteen minutes), the solution was refluxed for three hours, and hydrolyzed with dilute hydrochloric acid. The aqueous layer was extracted three times with ether, then the combined organic solutions were dried and concentrated. The deep red residue was warmed gently *in vacuo* and dissolved in a mixture of 30 ml. of dry alcohol and 20 ml. of dry benzene containing some anhydrous sodium sulfate. Dry hydrogen chloride was passed into the solution (chilled in an ice-bath) for one-half hour. The chloro compound was recovered by diluting the solution with water and extracting with ether. The ether solution was washed with dilute potassium carbonate solution, dried, and the solvent was removed. Dehydrohalogenation was effected by distilling the dark residue under two microns pressure at a bath temperature of 140–190°. The distillation was carried out very slowly to minimize a persistent tendency to bump. The light amber viscous distillate weighed 2.43 g. (98%). On one larger run, the distillation was stopped when 14.0 g. (78%) of the unsaturated ester had distilled during a period of one-hundred forty-four hours at 10^{-4} mm. (bath at 115–120°). In this case the still residue was a dark stiff glass which weighed 5.46 g. (31%).

The unsaturated ester (2.43 g., 0.0071 mole) was hydrogenated in absolute ethanol, using 0.34 g. of platinum oxide. During one and three-quarters hours, it absorbed 136 ml. of hydrogen at 27° (78% of the theoretical). This same hydrogen uptake was observed in a number of runs which varied in size. The saturated ester was obtained as a viscous yellow liquid. It was saponified in a nitrogen atmosphere with alcoholic potassium hydroxide. The alkaline solution was diluted with water, extracted with ether and acidified. The acid (II) precipitated as light yellow flakes and crystals which weighed 2.04 g. (87%) after filtering and air-drying. In other runs, yields as high as 95% were observed, based on the dimethyl ketone (I). A portion of the acid was crystallized once from ethanol, then from methanol, and was obtained as colorless needles which melted at 192.5–194°.

Anal. Calcd. for $C_{22}H_{22}O_2$: C, 83.0; H, 6.96. Found: C, 83.3; H, 6.30.

1-Keto-3,5-dimethylcholanthrene.—The acid (II), 11.36 g. (including 3.06 g. of non-crystalline material), was cyclized by dissolving it in about 150 g. of anhydrous liquid hydrogen fluoride contained in a copper beaker surrounded by an ice-bath. After evaporation of the hydrogen fluoride, the residue was washed with water and with a solution of potassium carbonate, then triturated with acetone. The resulting solid was suspended in boiling benzene which was cooled slightly and diluted with ether. The solid product (yellow-brown crystals) was separated by filtration and crystallized twice from chloroform and twice from benzene. It was very difficultly soluble in both solvents, as well as acetone. The ketone forms brilliant yellow needles melting at 267–270°, and it gives a precipitate when heated with alcoholic 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_{22}H_{16}O$: C, 89.2; H, 5.40. Found: C, 89.6; H, 5.57.

The **oxime** crystallized from chloroform as fluffy yellow needles which darkened at 245° and decomposed without melting at 254–258°.

Anal. Calcd. for $C_{22}H_{17}ON$: N, 4.50. Found: N, 4.42.

A total of 4.7 g. of this solid ketone was obtained. The acetone-soluble fraction composed 8.75 g. of a stiff red-brown oil. This was considered to be the tetrahydro ketone.

The solid ketone (3.5 g.), and the oily ketone (8.75 g.) were dissolved separately in 34-ml. portions of glacial acetic acid. To each of these solutions was added 50 ml. of toluene, 34 ml. of water, 200 ml. of concentrated hydrochloric acid, and 65 g. of amalgamated mossy zinc. The solutions were refluxed for forty-eight hours; 150 ml. of concentrated hydrochloric acid was added in 50-ml. portions at twelve-hour intervals. From each of these experiments, when worked up, was obtained a deep red gum. During the work-up, 1.3 g. of acidic material was recovered, presumably uncyclized (II). The products were combined, giving 10.1 g. of hydrocarbon.

3,5-Dimethylcholanthrene (III). A.—A 2-g. sample of the above product was dissolved in 50 ml. of *p*-cymene (terpene-free), 0.15 g. of 5% palladium–charcoal added and the solution heated to brisk boiling in a stream of carbon dioxide. The gases were collected in a nitrometer. In all, 202 ml. of inert gas (uncorrected for blank) were obtained during several days. The product recovered from this solution was an amber viscous substance (1.46 g.) which could not be made to crystallize. It was distilled under 4 microns pressure (bath at 140–170°). The 0.90 g. of light orange distillate (a viscous liquid) was crystallized from ethanol–benzene, giving 0.30 g. of orange-yellow needles, m. p. 170–173°. 3,5-Dimethylcholanthrene, after three crystallizations from ethanol–acetone, formed pale orange-yellow needles melting at 183–184°.

Anal. Calcd. for $C_{22}H_{18}$: C, 93.6; H, 6.45. Found: C, 93.4; H, 6.49.

B. Another sample of the Clemmensen product, 10.1 g., was heated with 1.50 g. of 5% palladium–charcoal at 300–310° for forty minutes. A brisk evolution of gas occurred at 285–310°. The cooled melt was repeatedly extracted with benzene; and the benzene solution, after filtering, was concentrated. The solution was diluted with an equal volume of ethanol, decolorized, and filtered. The filtrate gave 2.2 g. of yellow-brown plates, m. p. 175–179°. The mother liquors were evaporated to dryness and the residue triturated with boiling ethanol. An additional 2.7 g. of crystalline hydrocarbon was thus obtained. The ethanol solution deposited 0.5 g. of hydrocarbon, making a total yield of 5.5 g. (51%). The crude hydrocarbon was decolorized in acetone solution, then a benzene solution of it passed through alumina. The material recovered from the eluate was crystallized from acetone. A total of 3.28 g. of shining yellow-brown plates was obtained, which melted at 179–181°. A mixture of this material with the needle form of the hydrocarbon showed no depression of the melting point; it crystallized from ethanol as needles.

3,5-Dimethylcholanthrene forms a **picrate**, m. p. 179–180°, which dissociates when recrystallized from ethanol.

Anal. Calcd. for $C_{22}H_{18}\cdot C_6H_3N_3O_7$: N, 8.22. Found: N, 8.22.

The **trinitrobenzene derivative** forms massive dull red needles from ethanol, which melt at 189–190°.

Anal. Calcd. for $C_{22}H_{18}\cdot C_6H_3N_3O_6$: N, 8.48. Found: N, 8.24.

The **trinitrofluorenone derivative** crystallizes as blue microneedles, melting at 252–255°.

A Beckmann spectrophotometer was used for observation of the ultraviolet spectrum. The hydrocarbon, weighed on a microbalance, was dissolved in absolute ethanol, and the solution diluted accurately to a concentration of 0.0025 mg./ml.

β-(α-Naphthoyl)-propionic Acid.—The intermediate used for the preparation of compound (IX) was 1-keto-1,2,3,4-tetrahydrophenanthrene. Several methods were investigated for the preparation of this intermediate because it is a laborious task. One of the possible starting materials for its synthesis is β-(α-naphthoyl)-propionic acid. The following new method for the preparation of this starting material was explored. A benzene solution of di-α-naphthylcadmium (prepared by the general method

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[15] All melting points were taken on a Fischer–Johns apparatus. Microanalyses are by Patricia Craig and Nelda Mold, Northwestern University.

of Cason and Prout[16] from 20.7 g. of α-bromonaphthalene and 9.7 g. of anhydrous cadmium chloride) reacted with 16.5 g. of carbomethoxypropionyl chloride. The crude ester isolated from this reaction was a pale yellow oil boiling at 184–188° (1 mm.). It was saponified with alcoholic potassium hydroxide, giving 10.2 g. (45%) of the free acid which after one crystallization from dilute ethanol melted at 133–134° (lit.[17] 132–133°).

This acid was also prepared by the customary[17] acylation of naphthalene with succinic anhydride, using tetrachloroethane as solvent in place of nitrobenzene.

Reaction between 3′-Keto-3,4-dihydro-1,2-cyclopentenophenanthrene (IX)[18] and Ethyl α-Bromopropionate.—A mixture of 2.20 g. of the ketone (X) (m. p. 214–216°), 2.09 g. of ethyl α-bromopropionate, 5 g. of thoroughly cleaned and dried 20-mesh zinc, 0.10 g. of iodine, 70 ml. of benzene, and 30 ml. of toluene was refluxed for four and one-half hours. The iodine color faded immediately, and the pale yellow solution became orange as the reaction progressed. Two additions of 2.5 g. of zinc were made at forty-five minute intervals, and 1.90 g. of bromoester was added after one and one-half hours. The neutral material isolated from this reaction was distilled in high vacuum; and the distillate, after numerous fruitless attempts at crystallization, was saponified with alcoholic potassium hydroxide. The acidic material so obtained was 2.52 g. (93%) of a very viscous liquid, which could not be made to crystallize. Only a small fraction of it was volatile in a high vacuum. When this reaction was carried out in ether-benzene solution, the ketone (IX) was recovered almost quantitatively.

Chloro-*m*-dimethyl-β-chloropropiophenone (VI).—Aluminum chloride, 72 g., was added in portions to a solution of 36 g. of β-chloropropionyl chloride and 40 g. of 4-chloro-1,3-dimethylbenzene[14] (b. p. 187–194° (760 mm.)) in 145 ml. of carbon disulfide. The addition required two to three hours. Stirring was continued overnight, and the reaction then heated briefly to 45°. The mixture was hydrolyzed, and the solvent layer after drying was distilled (keeping the temperature below 60°). The residue crystallized on chilling; it weighed 67.5 g. Trituration of this solid with methanol gave 20.7 g. of slightly yellow solid, m. p. 84–87°, suitable for cyclization. Seven crystallizations of this solid from petroleum ether produced the β-chloroketone (VI) with a melting point of 93–93.5°.

Anal. Calcd. for $C_{11}H_{12}OCl_2$: C, 57.1; H, 5.24. Found: C, 57.2; H, 5.32.

***x*-Chloro-*m*-dimethylhydrindone.**—A solution of 19 g. of the crude crystalline β-chloroketone (VI) in 50 ml. of benzene was slowly run into 150 ml. of concentrated sulfuric acid at 105–120°, with rapid stirring. The mixture was stirred for twenty minutes, then poured onto cracked ice. The precipitated solid, 15 g. (93.5%), when recrystallized once from methanol melted at 110–111°.

The non-crystalline substance recovered from the methanol washings above was cyclized separately. An additional 8 g. of hydrindone was so obtained.

Anal. Calcd. for $C_{11}H_{11}OCl$: C, 67.8; H, 5.70. Found: C, 67.8; H, 5.77.

4-Chloro-5,7-dimethylhydrindene (VII).—The chlorohydrindone, 10 g., was reduced by the Martin modification of the Clemmensen procedure.[10] The hydrindene was isolated as a colorless liquid, 8.67 g. (94%), which boiled at 126–129° (12 mm.); d^{26} 1.116; n^{19}_{D} 1.5549.

Anal. Calcd. for $C_{11}H_{13}Cl$: C, 73.1; H, 7.25. Found: C, 73.0; H, 7.15.

Attempts to Condense the Hydrindene (VII) with α-Naphthonitrile.—A mixture of 3.77 g. of the hydrindene (VII), 30 ml. of absolute ether and 0.32 g. of lithium metal cut into tiny pieces was refluxed and stirred in a nitrogen atmosphere for twenty-four hours. Although some of the lithium remained unreacted, 3.19 g. of α-naphthonitrile dissolved in 40 ml. of dry benzene was added and reflux with stirring continued for three hours. The material obtained from hydrolysis of the reaction mixture was refluxed with alcoholic hydrochloric acid, then distilled under reduced pressure. A large amount of the hydrindene (VII) was recovered and a very small amount of high boiling material. When di-*n*-butyl ether was used as the solvent for this reaction, 2.0 g. of the hydrindene required nineteen hours to react with 0.19 g. of lithium metal. However, treatment of the solution with 1.69 g. of the nitrile resulted in almost quantitative recovery of both starting materials.

Summary

1. 3,5-Dimethylcholanthrene has been prepared from 8-keto-9,11-dimethyl-8,9,10,11-tetrahydrobenz[a]anthracene and characterized by means of its ultraviolet spectrum. This dimethylcholanthrene has a second methyl group in the same position that would be occupied by the steroid side chain.

2. Attempts to prepare 3-naphthoyl-5,7-dimethylhydrindene, with the intention of pyrolyzing this ketone to 3,5-dimethylcholanthrene, were unsuccessful. Apparently the two *ortho* groups offer too much hindrance for the preparation of the ketone.

3. The Reformatsky reaction of 3′-keto-3,4-dihydro-1,2-cyclopentenophenanthrene with ethyl α-bromopropionate gave a product which could not be characterized.

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[16] J. Cason and F. S. Prout, THIS JOURNAL, **66**, 46 (1944).

[17] L. F. Fieser and M. A. Peters, *ibid.*, **54**, 4347 (1932).

[18] Prepared by the method of W. S. Johnson and J. W. Petersen, *ibid.*, **67**, 1366 (1945).