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The Synthesis of 10-methyl-3, 4-benzpyrene and 8,10-dimethyl-3, 4-benzpyrene

Jules Adelfang

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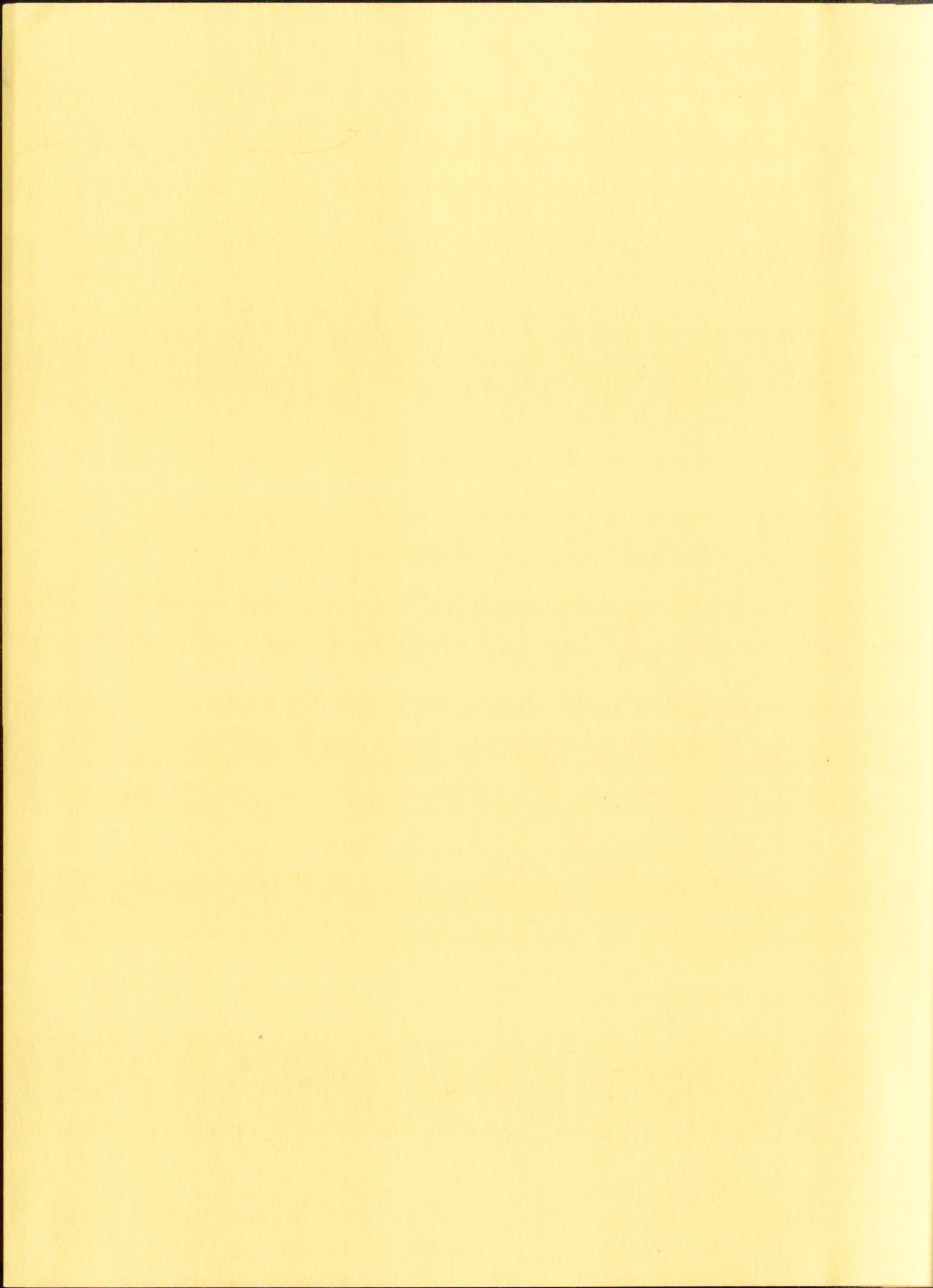
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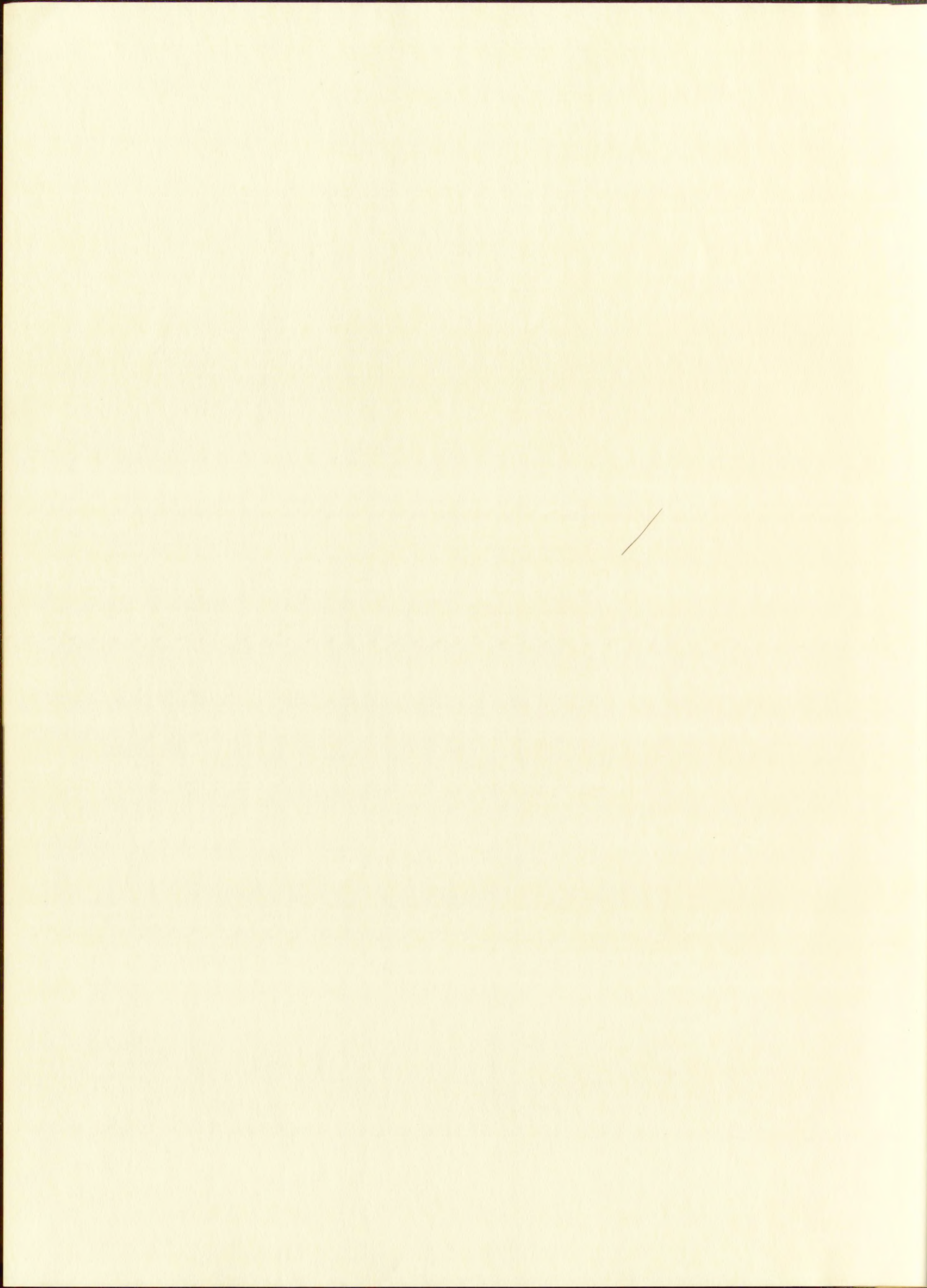


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THE SYNTHESIS OF 10-METHYL-3,4-BENZOPYRENE
AND 8,10-DIMETHYL-3,4-BENZOPYRENE

By
Jules Adelfang

A Thesis
In Partial Fulfillment of the
Requirements for the Degree of
Master of Science in Chemistry

The University of New Mexico

1954

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ACKNOWLEDGMENTS

The writer wishes to express his gratitude to Dr. G. H. Daub for suggesting the original problem and for advice and encouragement during the course of the work.

The financial aid provided by the National Cancer Institute of the United States Public Health Service was greatly appreciated.

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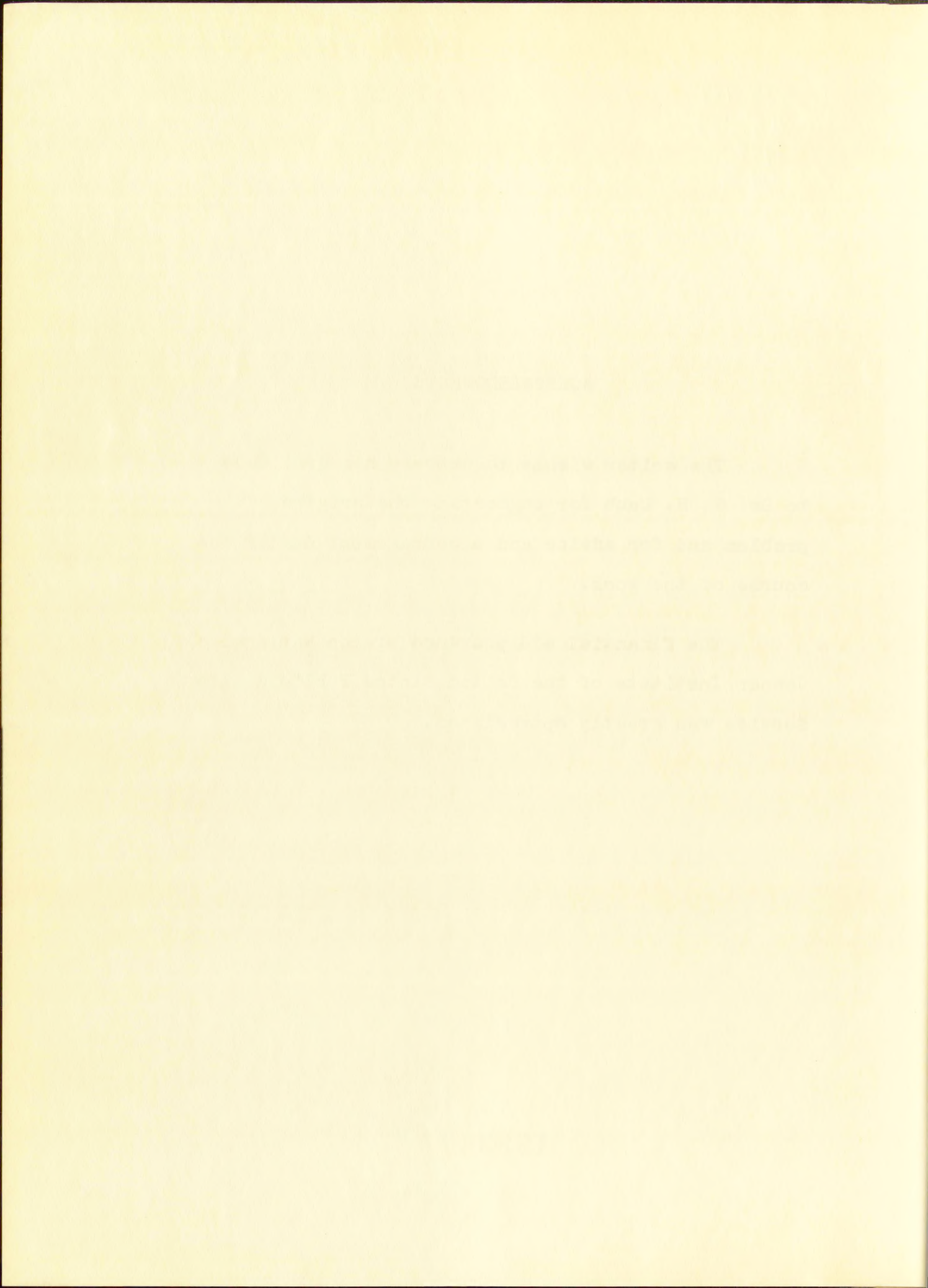
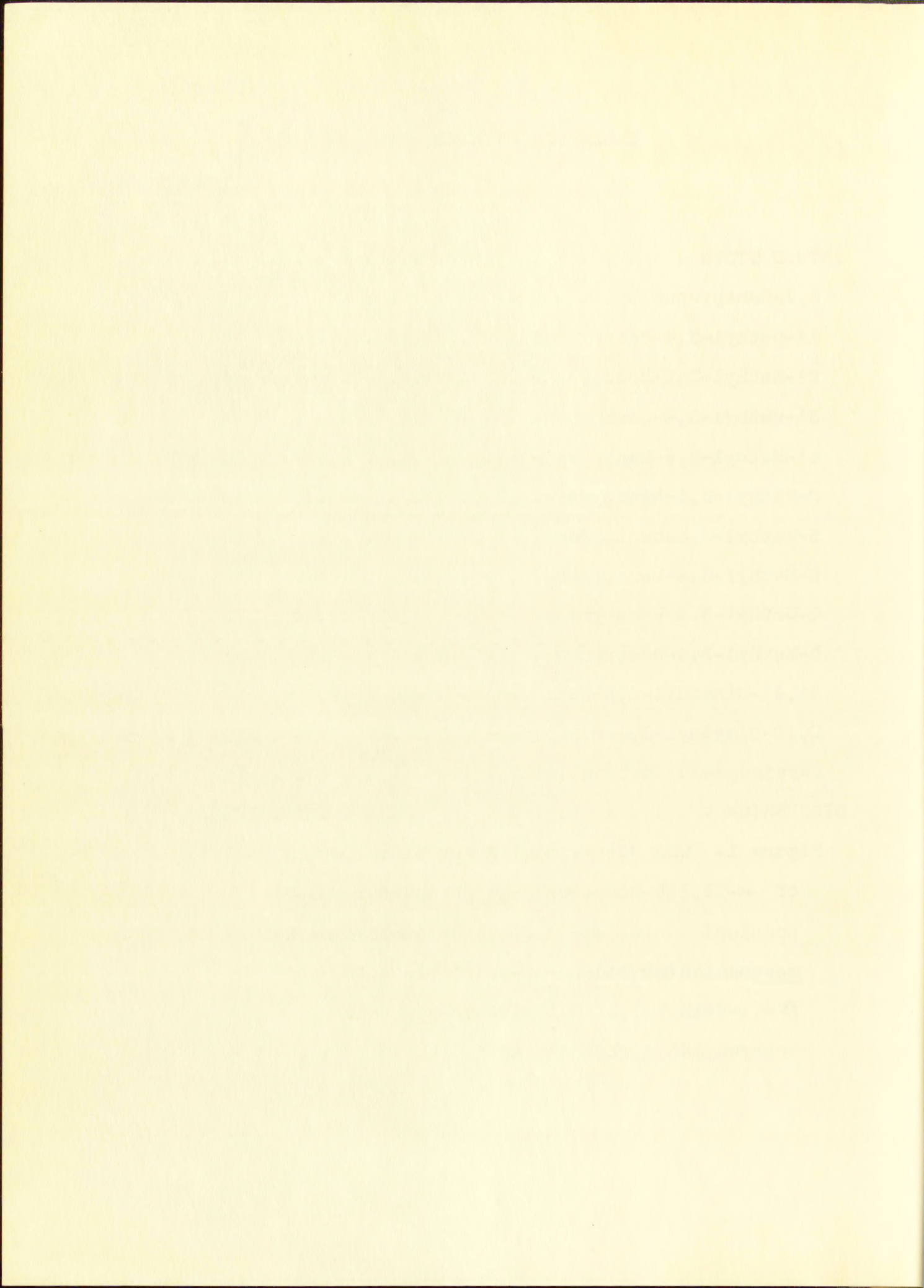
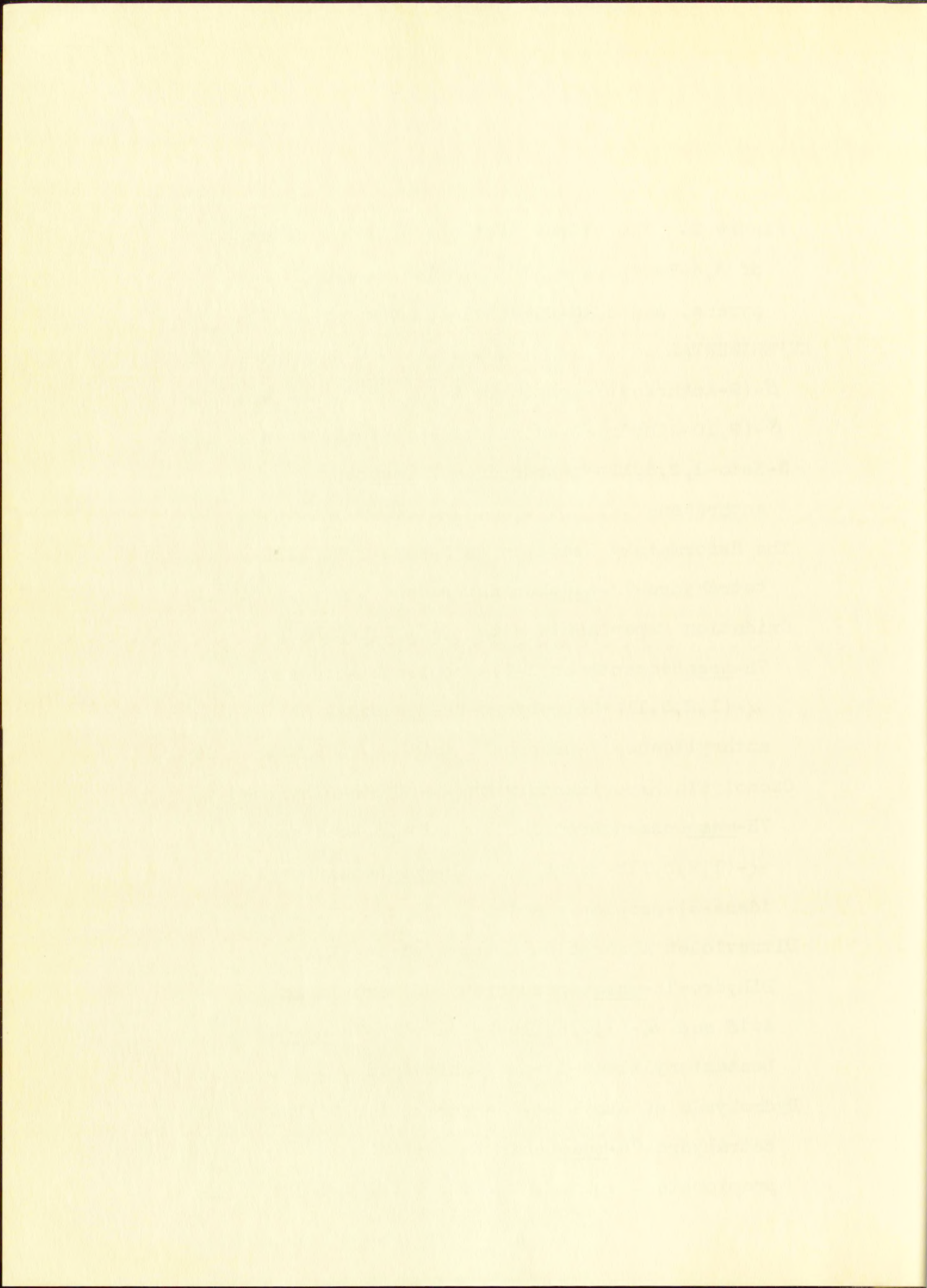


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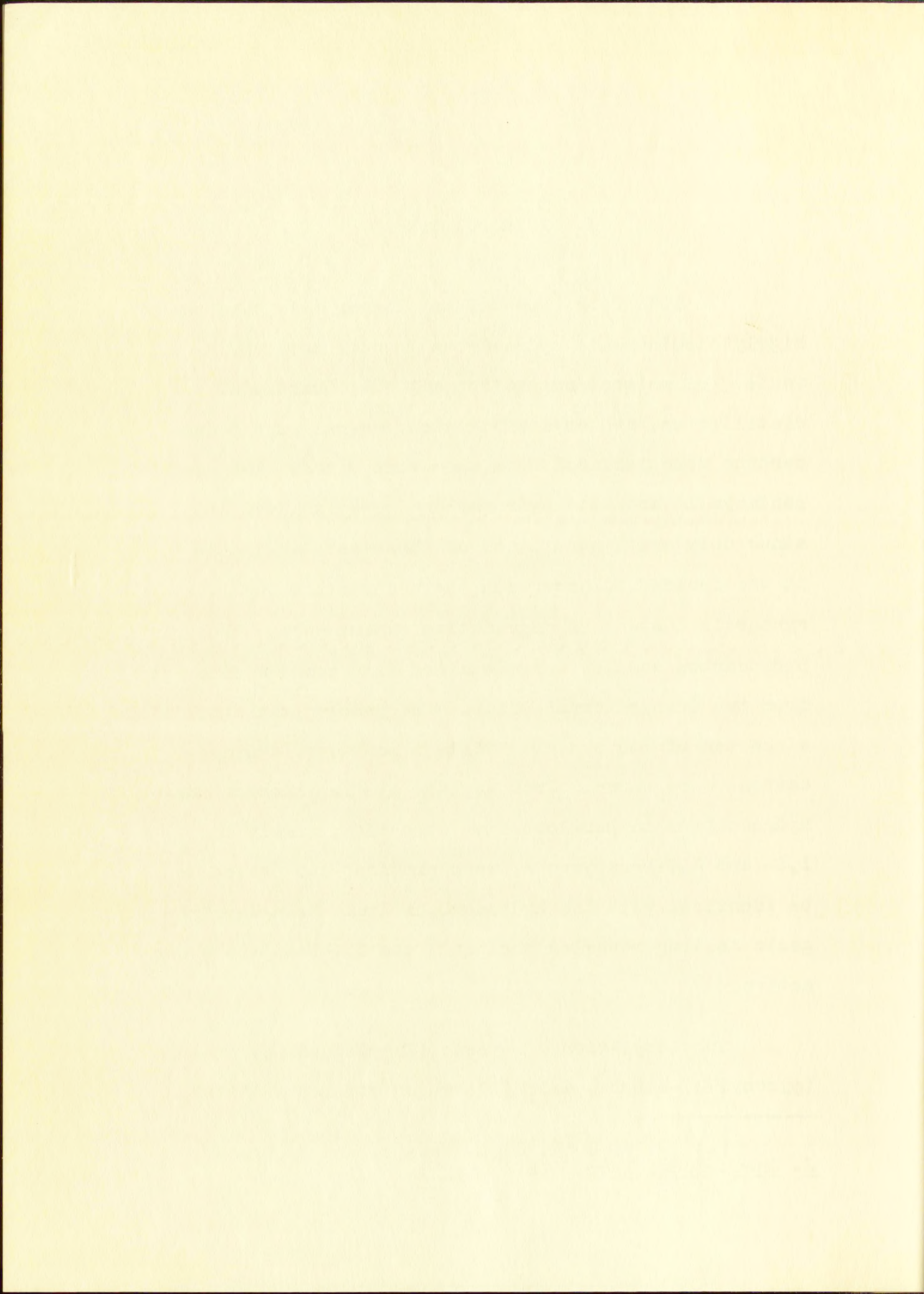


I. INTRODUCTION

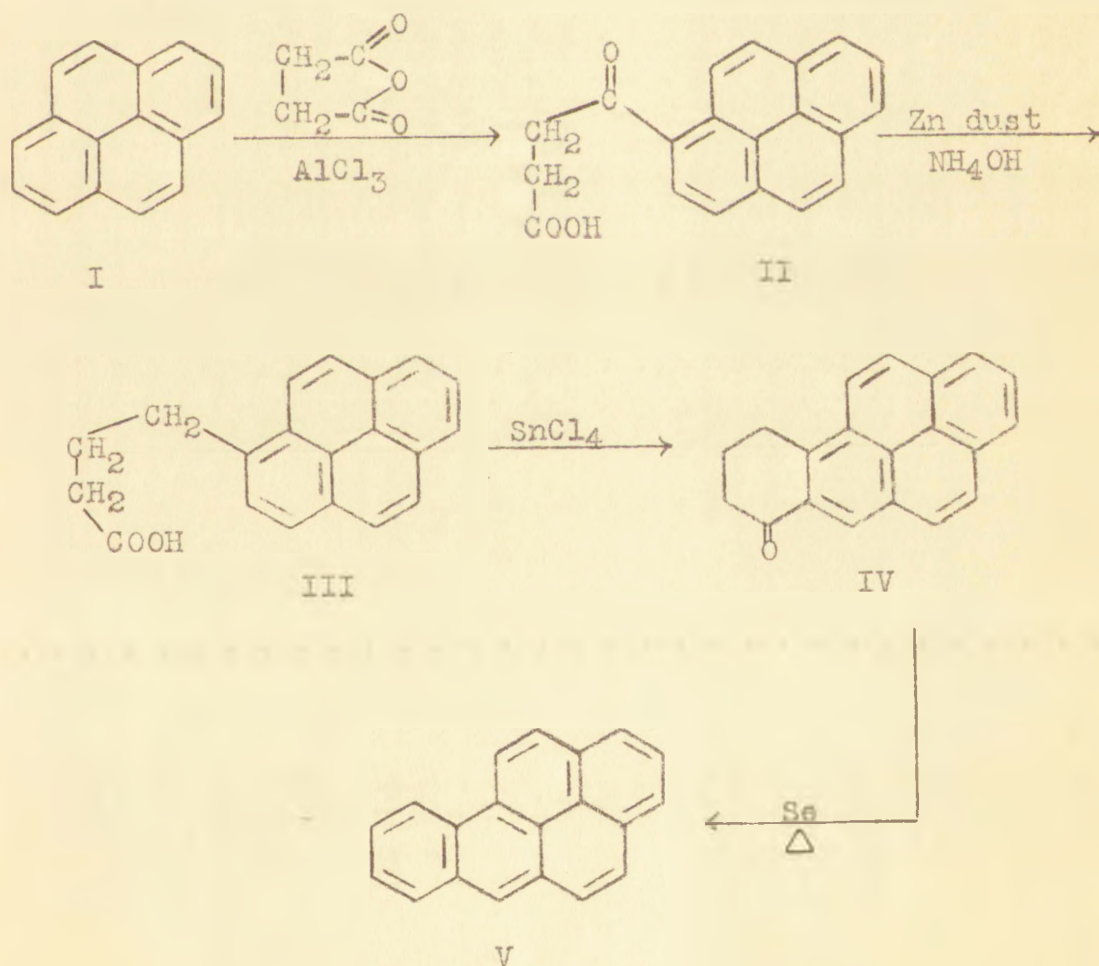
In 1933 Cook, Hewett, and Hieger (1) found a highly carcinogenic hydrocarbon in coal tar. By a variety of solvent extraction methods, fractional distillation, and crystallization several pure hydrocarbons were isolated from the crude pitch. Two new pentacyclic aromatic hydrocarbons were isolated and since only small quantities of these were available it was decided to ascertain their structures by synthesis instead of degradative experiments. The hydrocarbon samples were obtained with great difficulty from two tons of crude pitch. The problem was simplified since ten of the possible fifteen pentacyclic hydrocarbons were known. From certain similarities of these hydrocarbons to perylene its isomerides, namely the 1,2- and 3,4-benzpyrenes, were prepared and proved to be identical with the hydrocarbons isolated. Carcinogenic testing revealed that only the 3,4-benzpyrene was active.

Succinoylation of pyrene (I) yielded γ -keto- γ -(pyrenyl-3)-butyric acid (II) which offered a suitable

(1) J. W. Cook, C. L. Hewett, and I. Hieger, J. Chem. Soc., 1933, 395.



synthetic route to 3,4-benzpyrene (V). The sodium salt of II was reduced to γ -(pyrenyl-3)-butyric acid (III) with zinc dust and ammonia. Ring closure of III was accomplished with stannic chloride yielding 4'-keto-1',2',3',4'-tetrahydro-3,4-benzpyrene (IV) which upon dehydrogenation at 320-340° with selenium afforded 3,4-benzpyrene in 2.9% over-all yield from pyrene (I). Yields were improved when the ketone was reduced prior to dehydrogenation.





Modifications of the succinic anhydride synthesis by Winterstein (2), Fieser (3), and Bachmann (4) improved the yields from pyrene. Attempts to relate structural details to carcinogenicity led to the synthesis of some of the methyl-3,4-benzpyrenes.

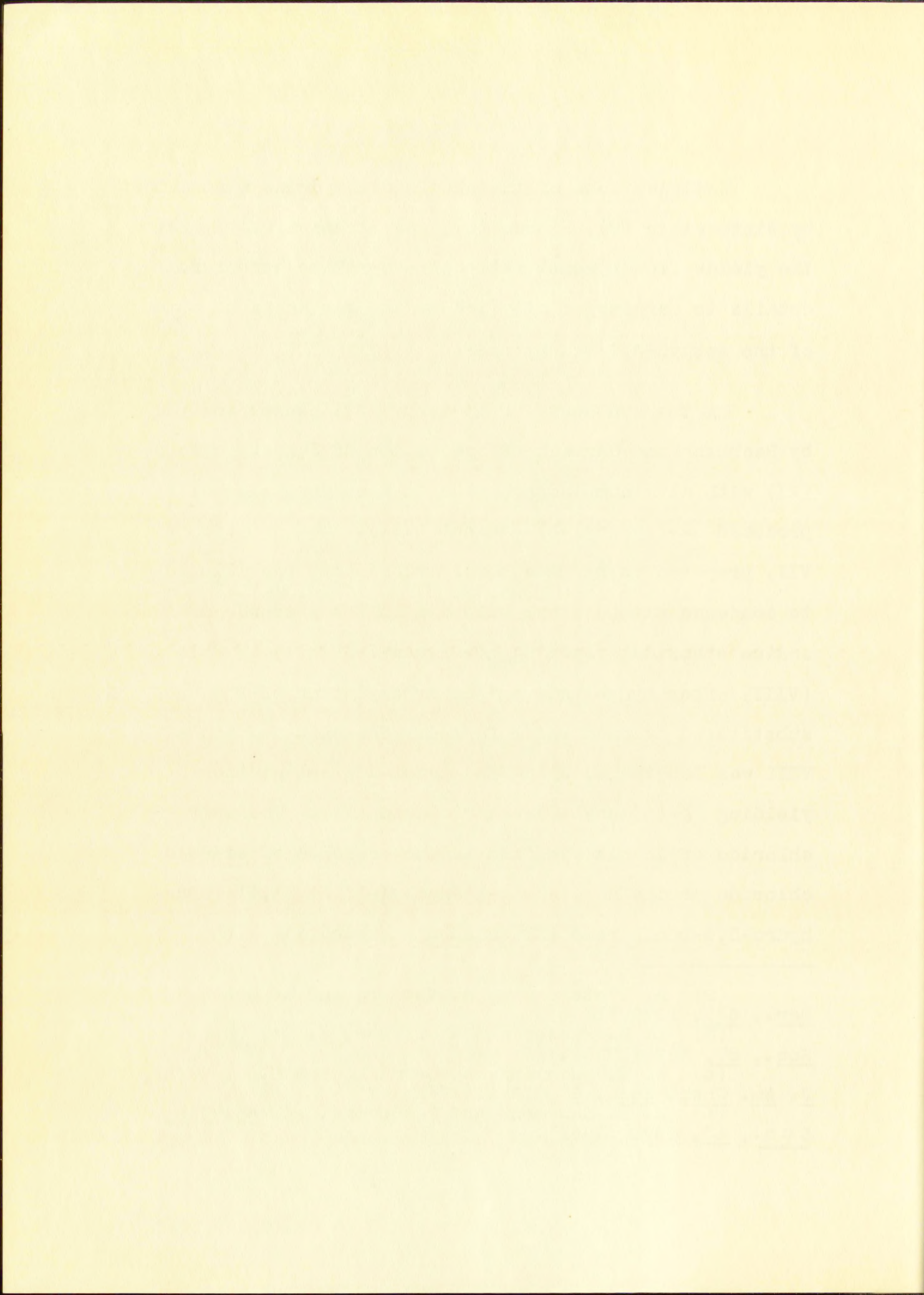
In the synthesis of 1'-methyl-3,4-benzpyrene (XI) by Bachmann and Carmack (5) reduction of 3-acetylpyrene (VI) with aluminum isopropoxide in isopropyl alcohol produced α -(pyrenyl-3)-ethanol (VII). The bromide of VII, prepared using phosphorus tribromide, was allowed to condense with diethyl malonate in the presence of sodium ethoxide, yielding β -(pyrenyl-3)-butyric acid (VIII) after hydrolysis and decarboxylation of the substituted malonic ester formed. The carbon chain of VIII was lengthened using the Arndt-Eistert synthesis yielding γ -(pyrenyl-3)-valeric acid (IX). The acid chloride of IX was cyclized in the presence of stannic chloride producing 4'-keto-1'-methyl-1',2',3',4'-tetrahydro-3,4-benzpyrene (X) which upon reduction with

(2) A. Winterstein, H. Vetter, and K. Schon, Ber., 68B, 1079 (1935).

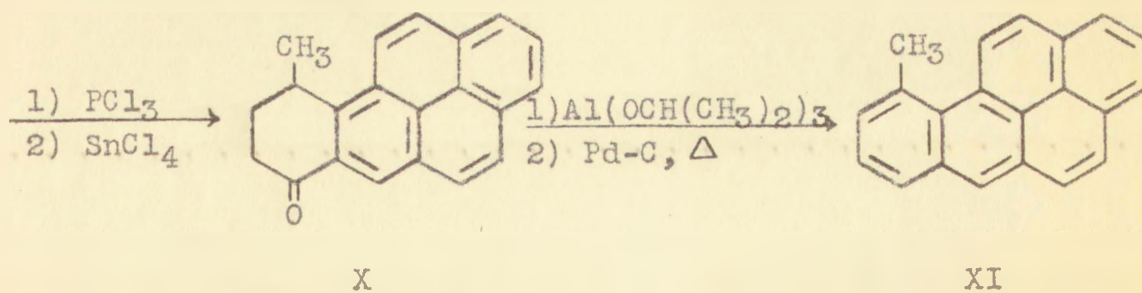
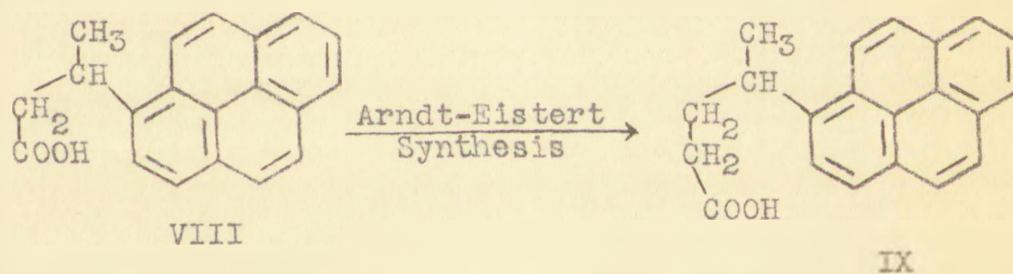
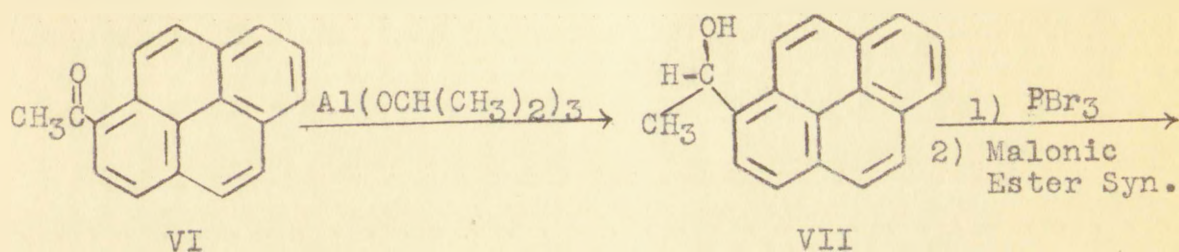
(3) L. F. Fieser and M. Fieser, J. Am. Chem. Soc., 57, 782 (1935).

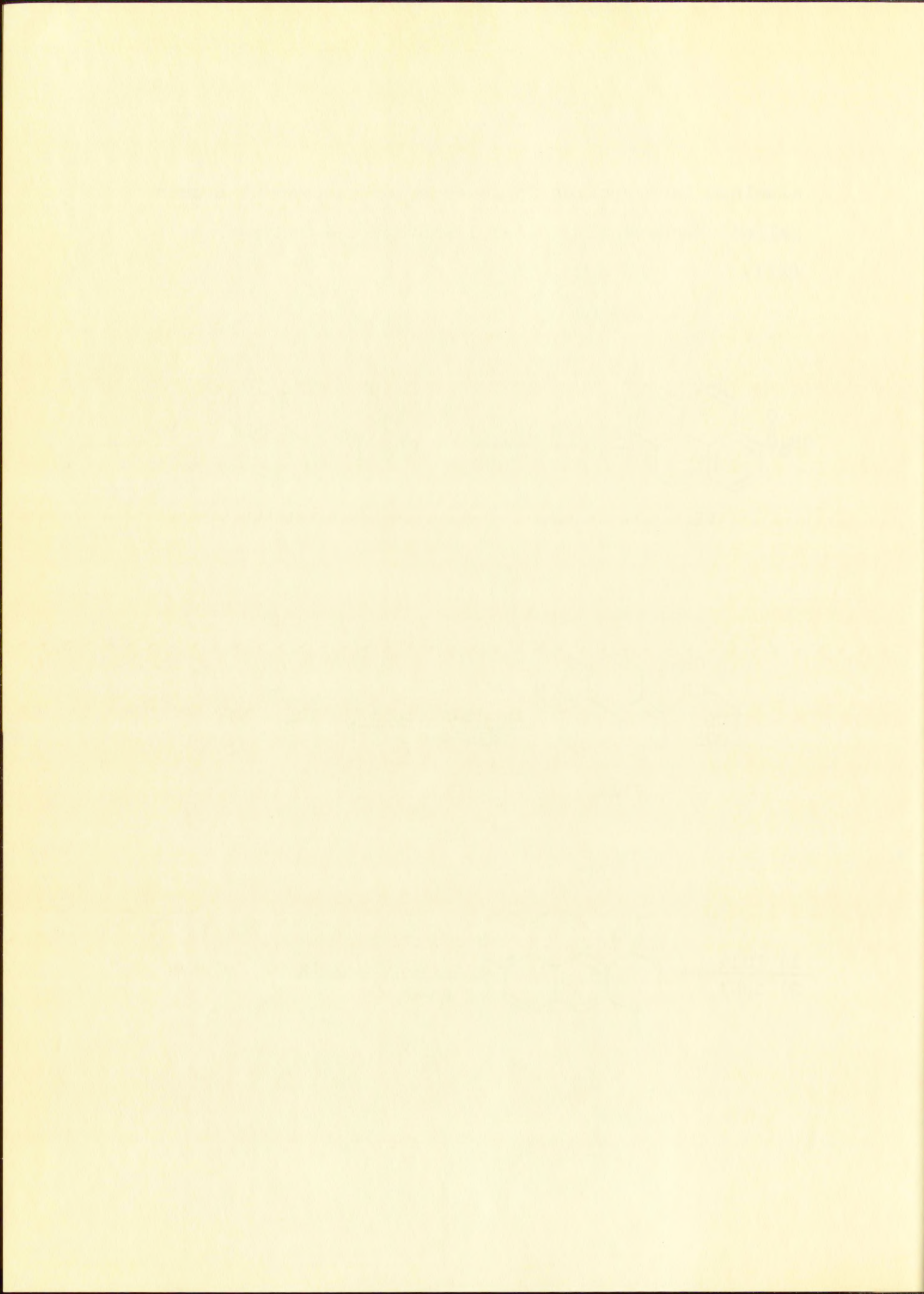
(4) W. E. Bachmann, M. Carmack, and S. R. Safir, J. Am. Chem. Soc., 63, 1682 (1941).

(5) W. E. Bachmann and M. Carmack, J. Am. Chem. Soc., 63, 2494 (1941).

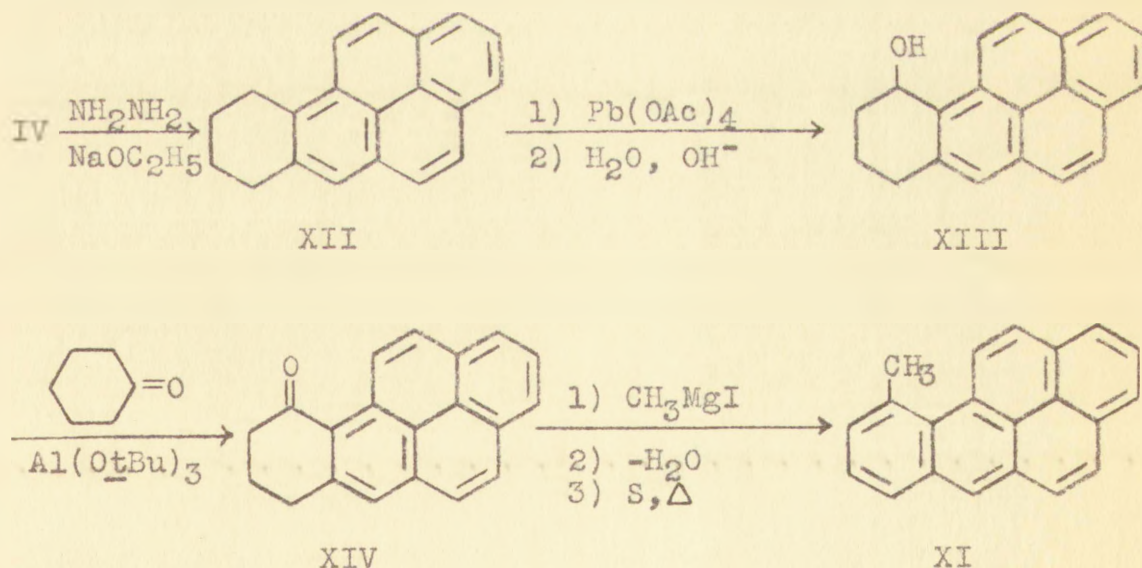


aluminum isopropoxide followed by dehydrogenation over palladium-charcoal yielded 1'-methyl-3,4-benzpyrene (XI).





In 1945 Kon and Roe (6) prepared 1'-methyl-3,4-benzpyrene (XI) from 4'-keto-1',2',3',4'-tetrahydro-3,4-benzpyrene (IV) (p. 2). Reduction of IV with hydrazine and sodium ethoxide (Wolff-Kishner method) gave 1',2',3',4'-tetrahydro-3,4-benzpyrene (XII). Oxidation of XII with lead tetraacetate and hydrolysis of the resulting acetate ester yielded 1'-hydroxy-1',2',3',4'-tetrahydro-3,4-benzpyrene (XIII). Oppenauer oxidation of XIII followed by reaction of the resulting ketone, 1'-keto-1',2',3',4'-tetrahydro-3,4-benzpyrene (XIV), with methylmagnesium iodide yielded a carbinol which was easily dehydrated and dehydrogenated with sulfur to 1'-methyl-3,4-benzpyrene (XI).

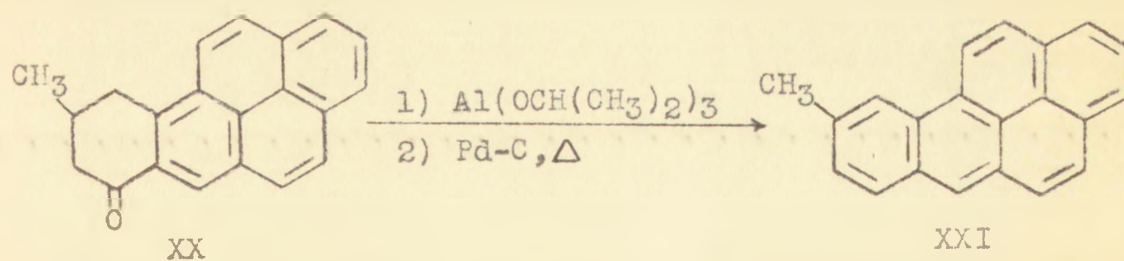
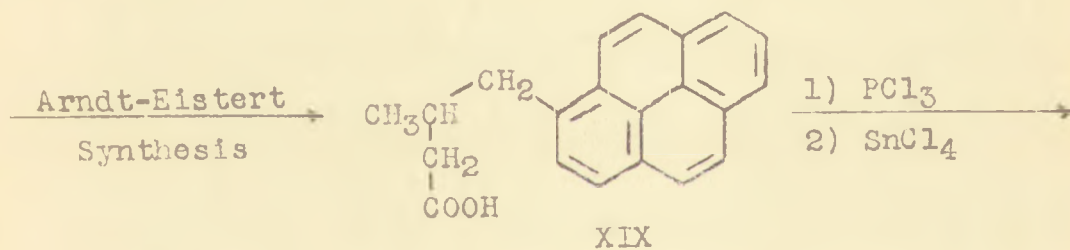
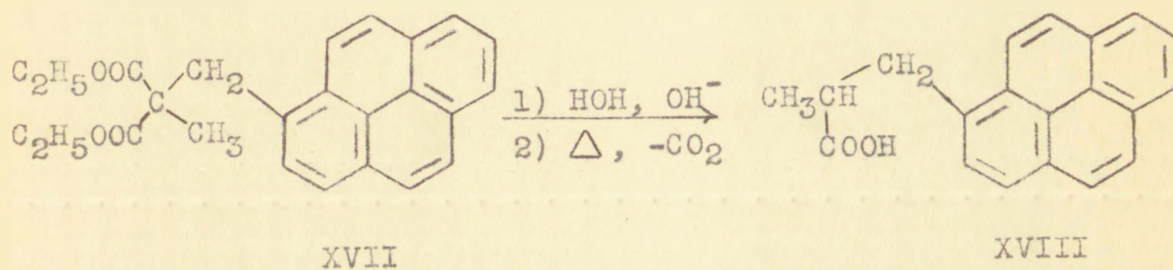
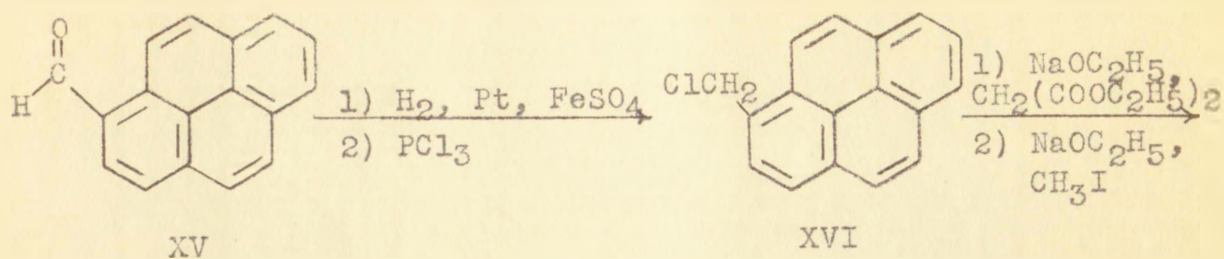


(6) G. A. R. Kon and E. M. F. Roe, J. Chem. Soc., 1945, 143.

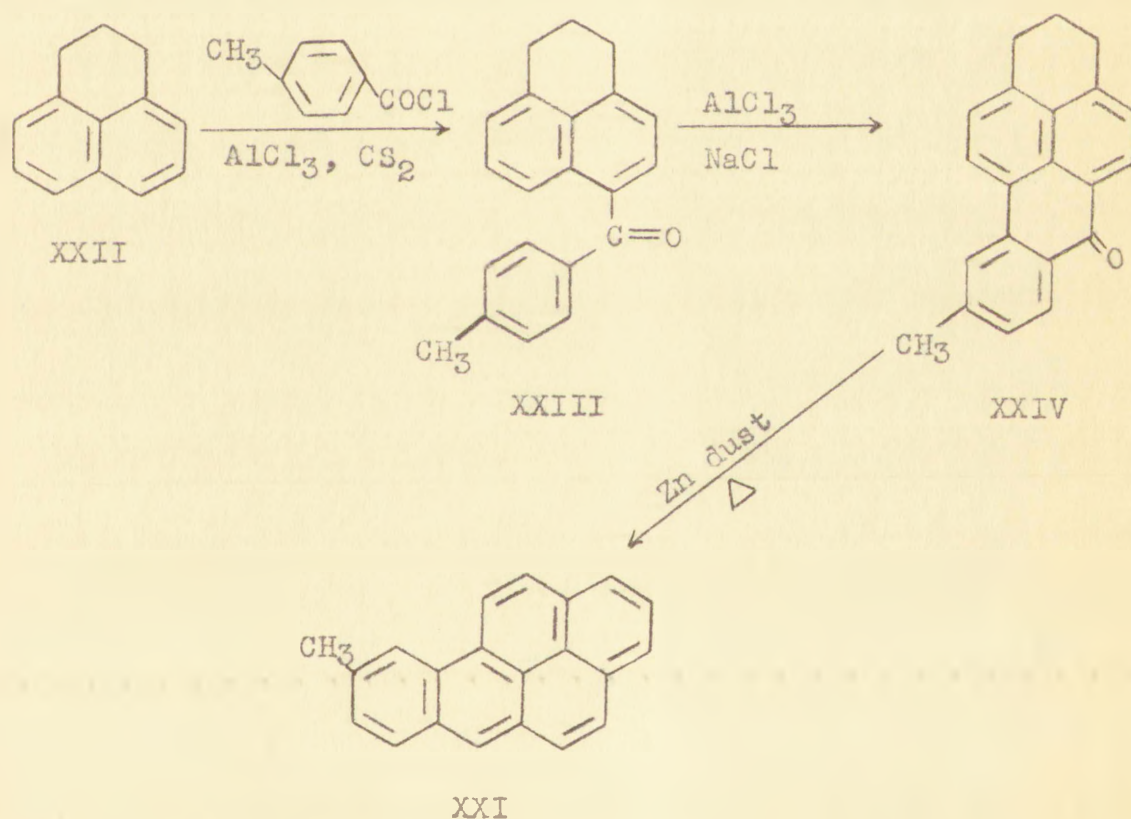


In 1941 Bachmann and Carmack (5) also prepared 2'-methyl-3,4-benzpyrene (XXI) starting with pyrene-3-aldehyde (XV). The aldehyde XV was reduced with hydrogen in the presence of platinum and ferrous sulfate and the resulting carbinol was treated with phosphorus trichloride yielding pyrenyl-3-methyl chloride (XVI). The chloride XVI was allowed to condense with malonic ester in the presence of sodium ethoxide and treatment of the resulting substituted malonic ester with methyl iodide and sodium ethoxide yielded ethyl α -carbethoxy- α -methyl- β -(pyrenyl-3)-propionate (XVII). Hydrolysis followed by decarboxylation of XVII yielded α -methyl- β -(pyrenyl-3)-propionic acid (XVIII). The carbon chain of the acid XVIII was lengthened using the Arndt-Eistert synthesis producing β -methyl- γ -(pyrenyl-3)-butyric acid (XIX). Cyclization of the acid chloride of XIX with stannic chloride yielded 4'-keto-2'-methyl-1',2',3',4'-tetrahydro-3,4-benzpyrene (XX) which upon reduction with aluminum isopropoxide and then dehydration and dehydrogenation over palladium-charcoal gave 2'-methyl-3,4-benzpyrene (XXI).

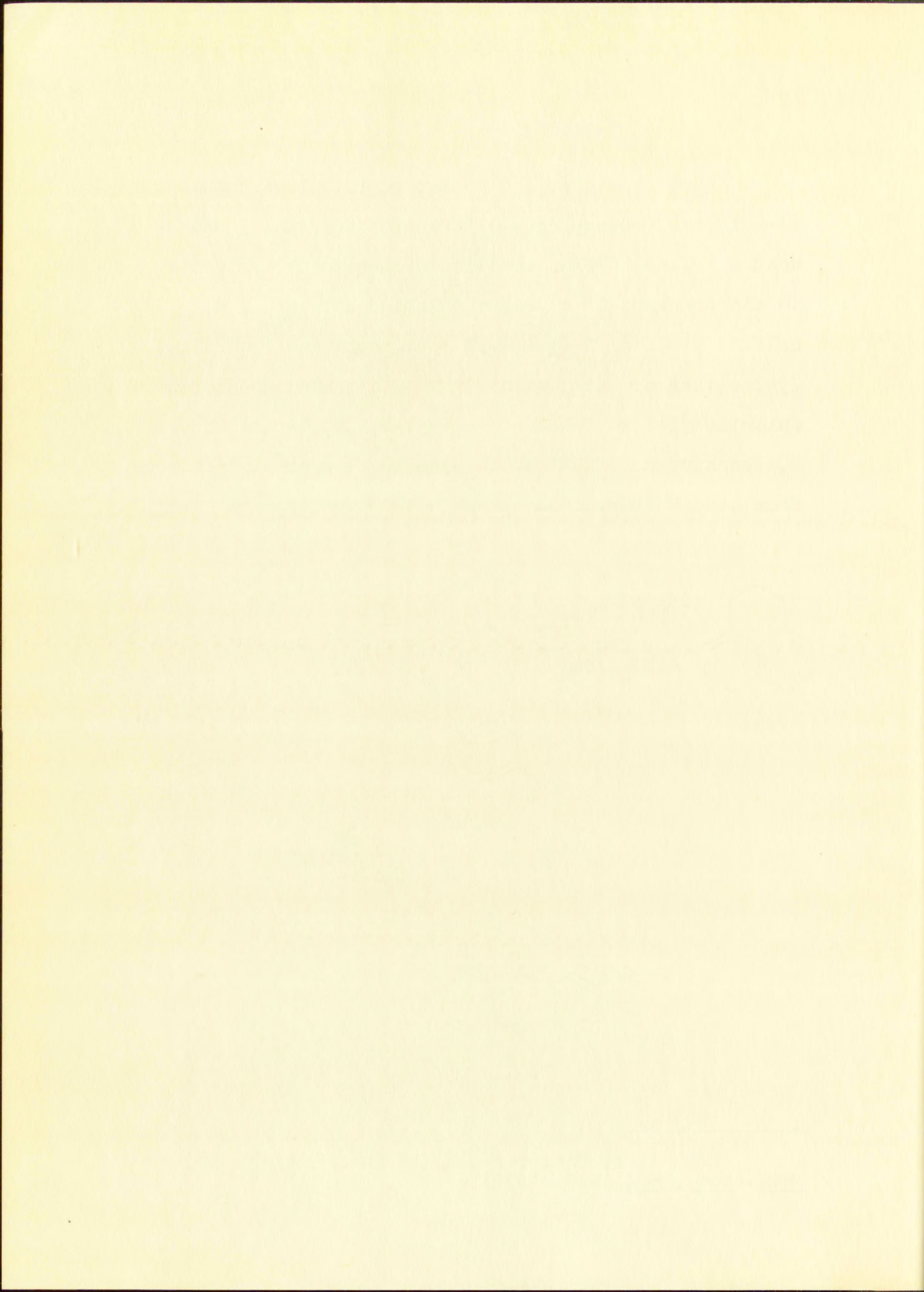




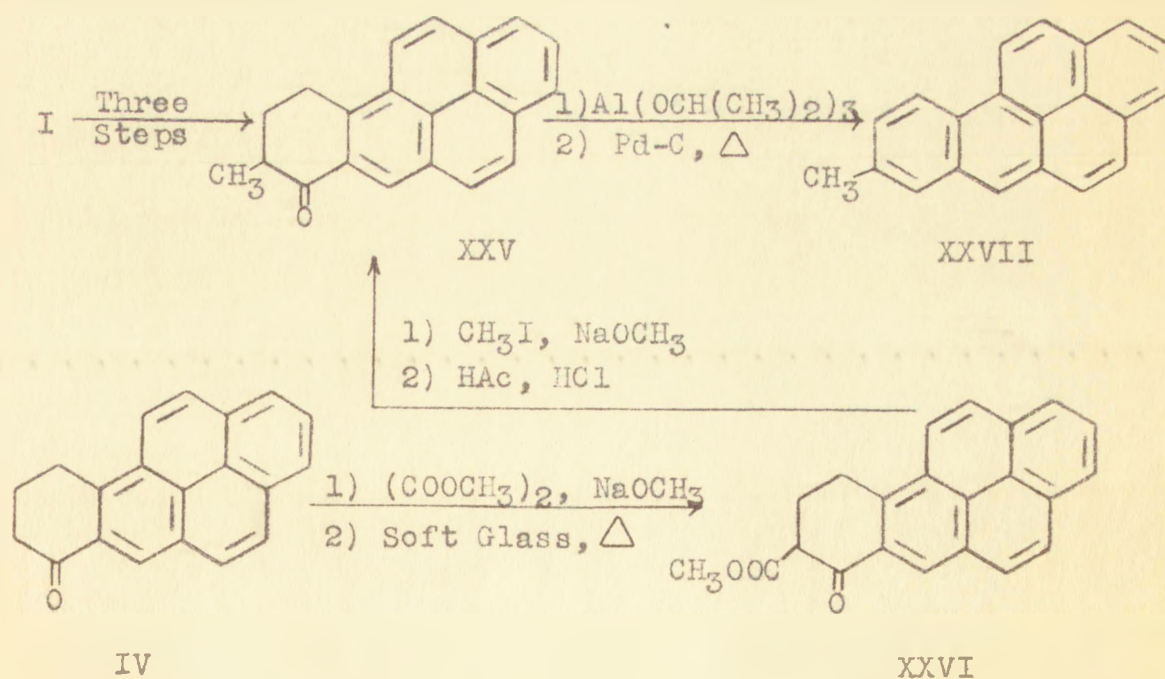
Earlier Fieser and Hershberg (7) also synthesized 2'-methyl-3,4-benzpyrene. Perinaphthane (XXII) underwent a Friedel-Crafts reaction with *p*-toluyl chloride in the presence of aluminum chloride and carbon disulfide yielding 3-(*p*-toluyl)-perinaphthane (XXIII). Cyclization of XXIII with aluminum chloride and sodium chloride yielded 5-keto-2'-methyl-5,8,9,10-tetrahydro-3,4-benzpyrene (XXIV) which upon subsequent distillation from zinc dust produced 2'-methyl-3,4-benzpyrene (XXI).

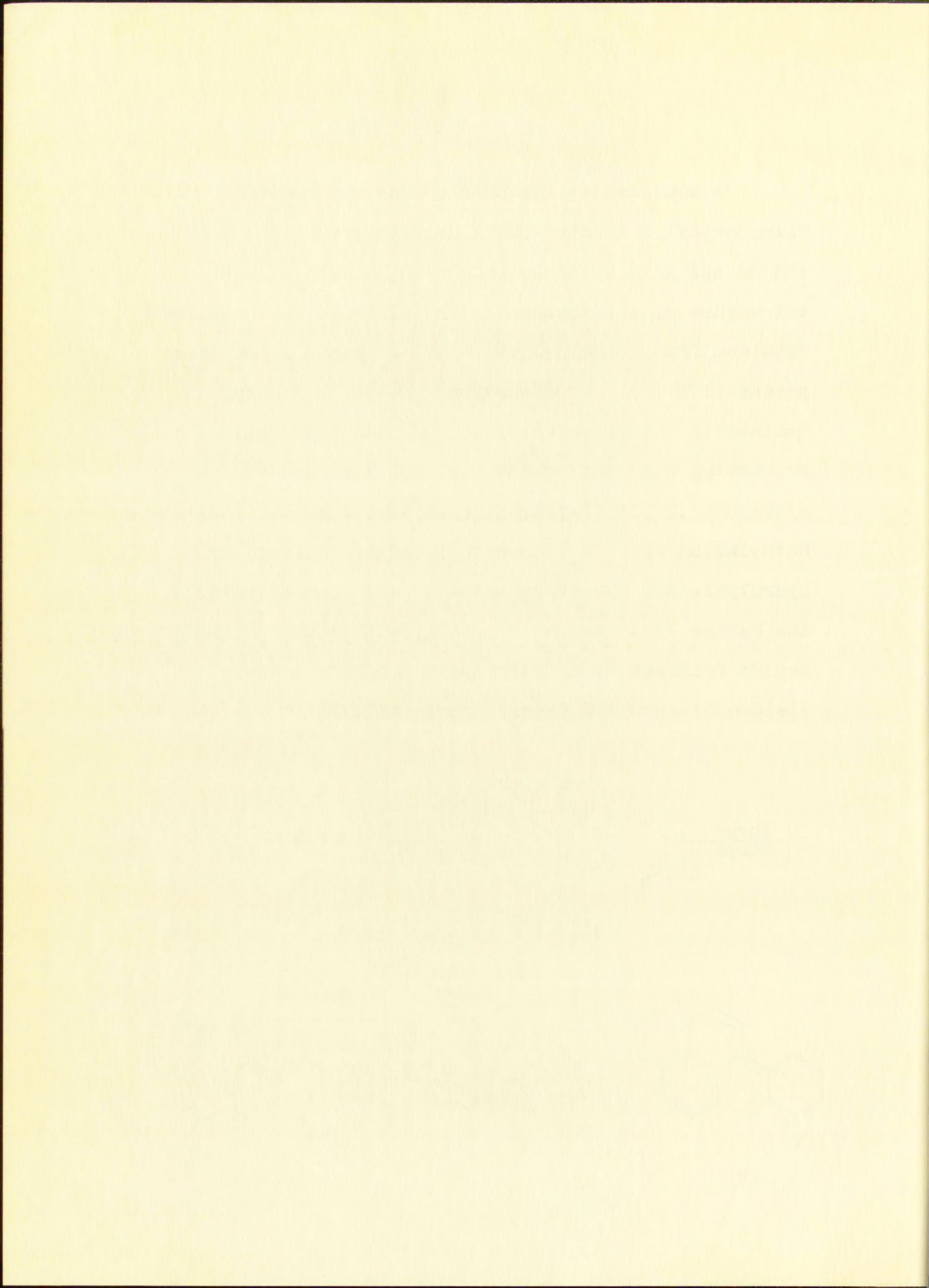


(7) L. F. Fieser and E. B. Hershberg, J. Am. Chem. Soc., 60, 1658 (1938).

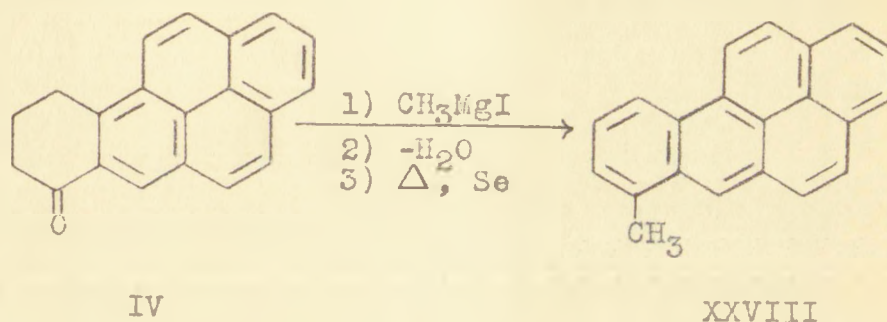


A modified succinic anhydride synthesis (2, 5) using methyl succinic anhydride and pyrene (I) (p. 2) led to the ketone, 4'-keto-3'-methyl-1',2',3',4'-tetrahydro-3,4-benzpyrene (XXV). This ketone was also obtained from 4'-keto-1',2',3',4'-tetrahydro-3,4-benzpyrene (IV) (5). Condensation of IV with dimethyl oxalate in the presence of sodium methoxide followed by heating with soft glass yielded 3'-carbomethoxy-4'-keto-1',2',3',4'-tetrahydro-3,4-benzpyrene (XXVI). Methylation of XXVI with methyl iodide followed by hydrolysis and decarboxylation of the product gave the ketone XXV. Reduction of XXV with aluminum isopropoxide followed by dehydration and dehydrogenation yielded 3'-methyl-3,4-benzpyrene (XXVII).





The reaction of 4'-keto-1',2',3',4'-tetrahydro-3,4-benzpyrene (IV) with methylmagnesium iodide followed by dehydration and dehydrogenation with selenium yielded 4'-methyl-3,4-benzpyrene (XXVIII) (3).

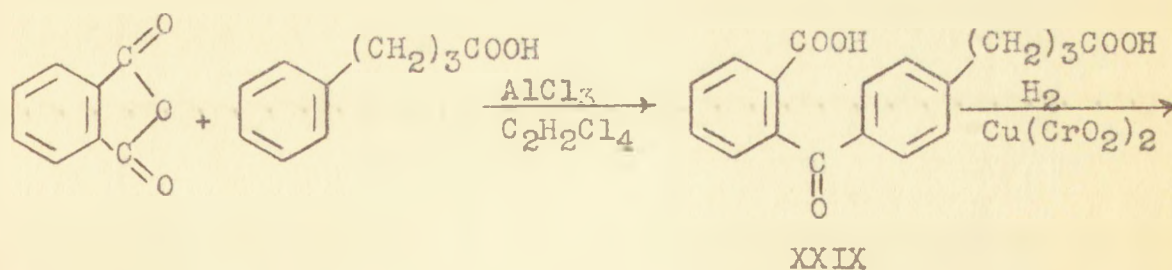


The initial step in the synthesis of 2-methyl-3,4-benzpyrene (XXXVIII) reported by Fieser and Heymann (8) was the condensation of phthalic anhydride with γ -phenylbutyric acid in the presence of aluminum chloride and tetrachloroethane yielding 4-(γ -carboxypropyl)-benzophenone-2'-carboxylic acid (XXIX). Hydrogenation of XXIX over a copper chromite catalyst produced 4-(γ -carboxypropyl)-diphenylmethane-2'-carboxylic acid (XXX) which upon cyclization in the presence of anhydrous hydrogen fluoride yielded 2-(γ -carboxypropyl)-anthrone-9 (XXXI). Reduction of XXXI with zinc and ammonia gave γ -(2-anthranyl)-butyric acid

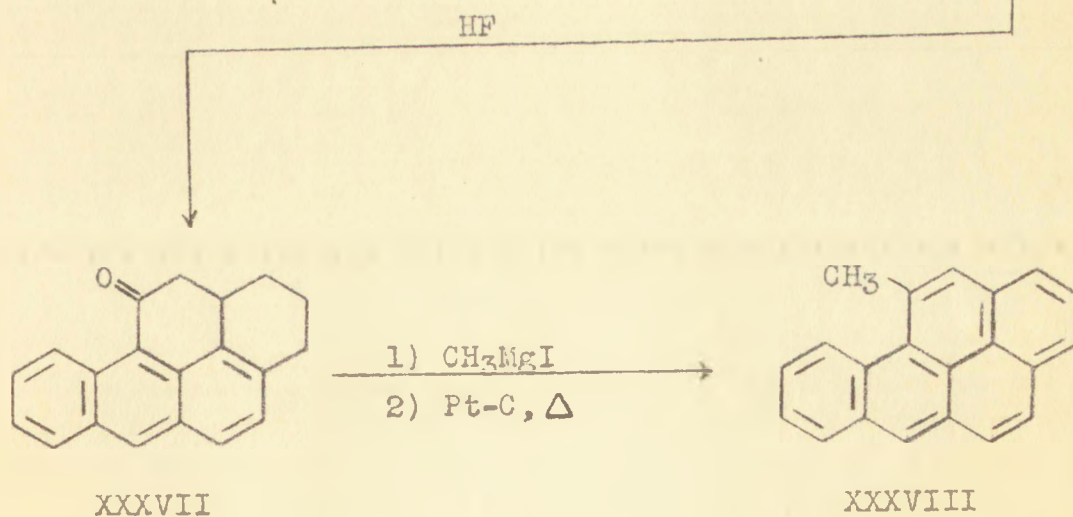
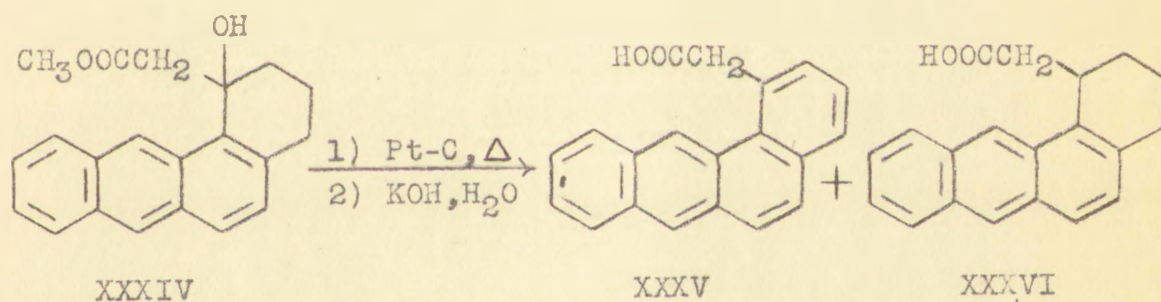
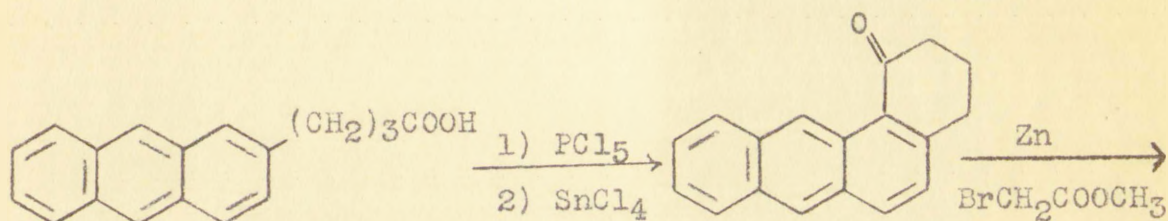
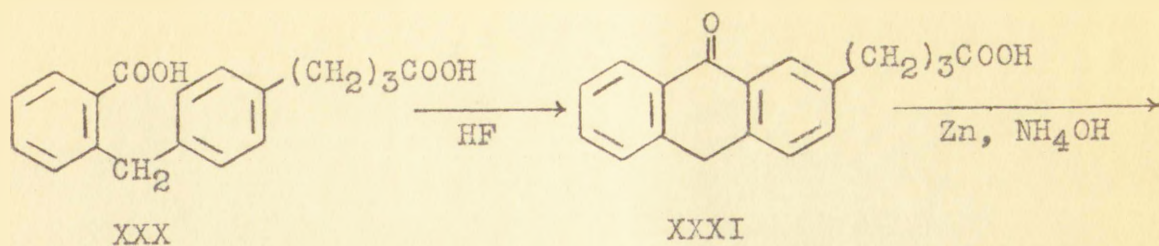
(8) L. F. Fieser and H. Heymann, J. Am. Chem. Soc., 63, 2333 (1941).

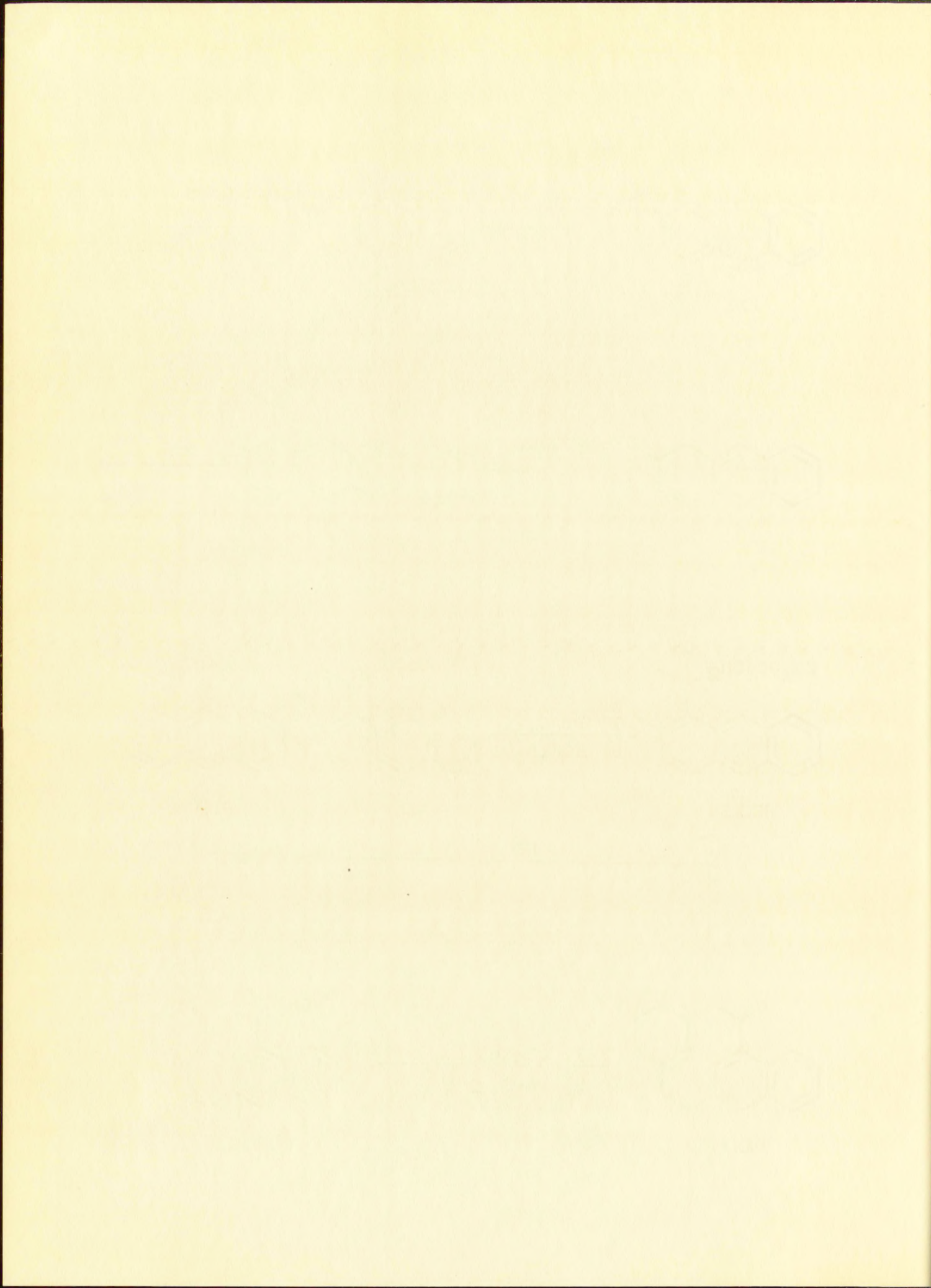


(XXXII). The acid chloride of XXXII cyclized in the presence of stannic chloride to 1'-keto-1',2',3',4'-tetrahydro-1,2-benzanthracene (XXXIII). A Reformatsky reaction with XXXIII and methyl bromoacetate yielded methyl (1'-hydroxy-1',2',3',4'-tetrahydro-1,2-benzanthrenyl-1')-acetate (XXXIV). The ester XXXIV was heated over platinum-charcoal causing dehydration and disproportionation. The resulting mixture of esters was hydrolyzed with potassium hydroxide yielding (1,2-benzanthrenyl-1')-acetic acid (XXXV) and (1',2',3',4'-tetrahydro-1,2-benzanthrenyl-1')-acetic acid (XXXVI). Cyclization of XXXVI with anhydrous hydrogen fluoride yielded 2-keto-1,2,8,9,10,10a-hexahydro-3,4-benzpyrene (XXXVII). The ketone XXXVII was methylated with methylmagnesium iodide and the resulting carbinol was dehydrated and dehydrogenated over platinum-charcoal yielding 2-methyl-3,4-benzpyrene (XXXVIII).









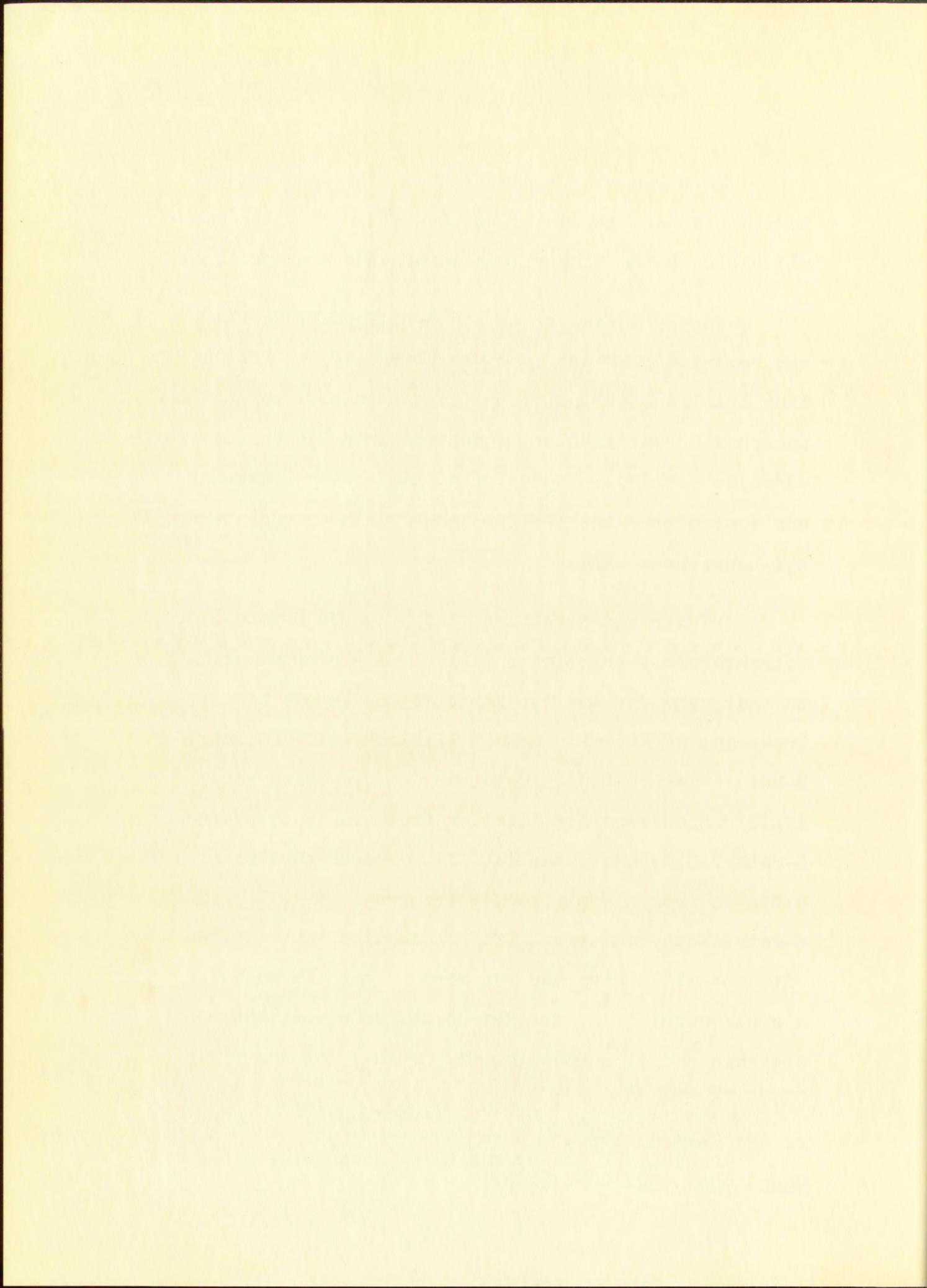
More recently a new synthesis of 2-methyl-3,4-benzpyrene has been described by Patton (9); the overall yields being higher than those obtained by Fieser.

The synthesis of 5-methyl-3,4-benzpyrene (XL) was reported by Fieser and Hershberg (10) in 1938 . They treated 3,4-benzpyrene (V) with methyl formanilide and phosphorus oxychloride and obtained 3,4-benzpyrene-5-aldehyde (XXXIX). Reduction of XXXIX with hydrazine and sodium ethoxide (Wolff-Kishner method) gave 5-methyl-3,4-benzpyrene (XL).

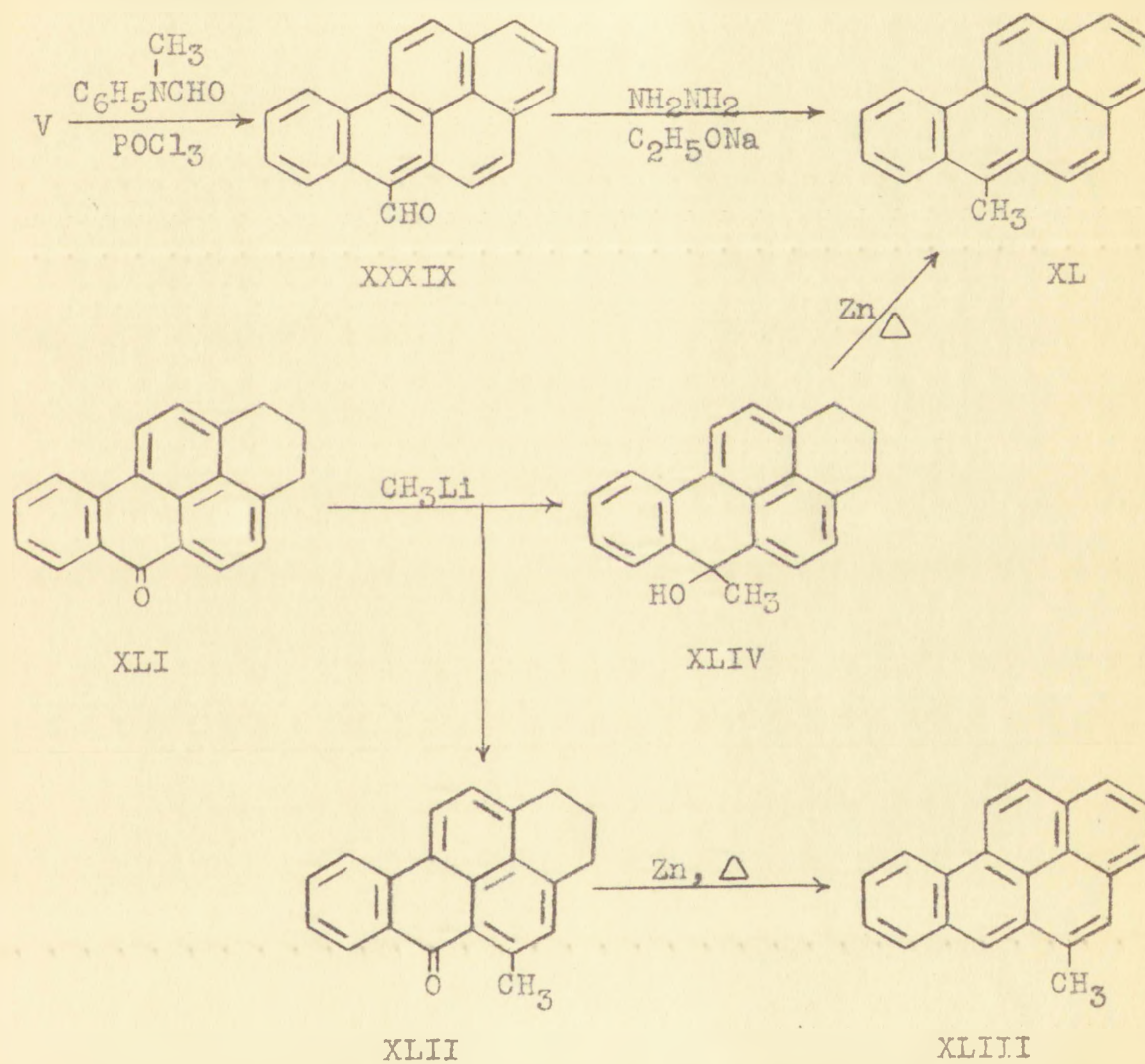
Fieser and Hershberg (10) prepared 5-keto-5,8,9,10-tetrahydro-3,4-benzpyrene (XLI) by a procedure similar to that used for the synthesis of the ketone XXIV. Treatment of XLI with methyl lithium yielded mainly 5-keto-6-methyl-5,8,9,10-tetrahydro-3,4-benzpyrene (XLII) which upon distillation from zinc dust produced 6-methyl-3,4-benzpyrene (XLIII). The properties of XLIII differed from 4'-methyl-3,4-benzpyrene (XXVIII) and 5-methyl-3,4-benzpyrene (XL) indicating that the reaction with methyl lithium had occurred in the six position. A small quantity of the ketone XLI underwent the normal Grignard addition reaction with methyl lithium giving

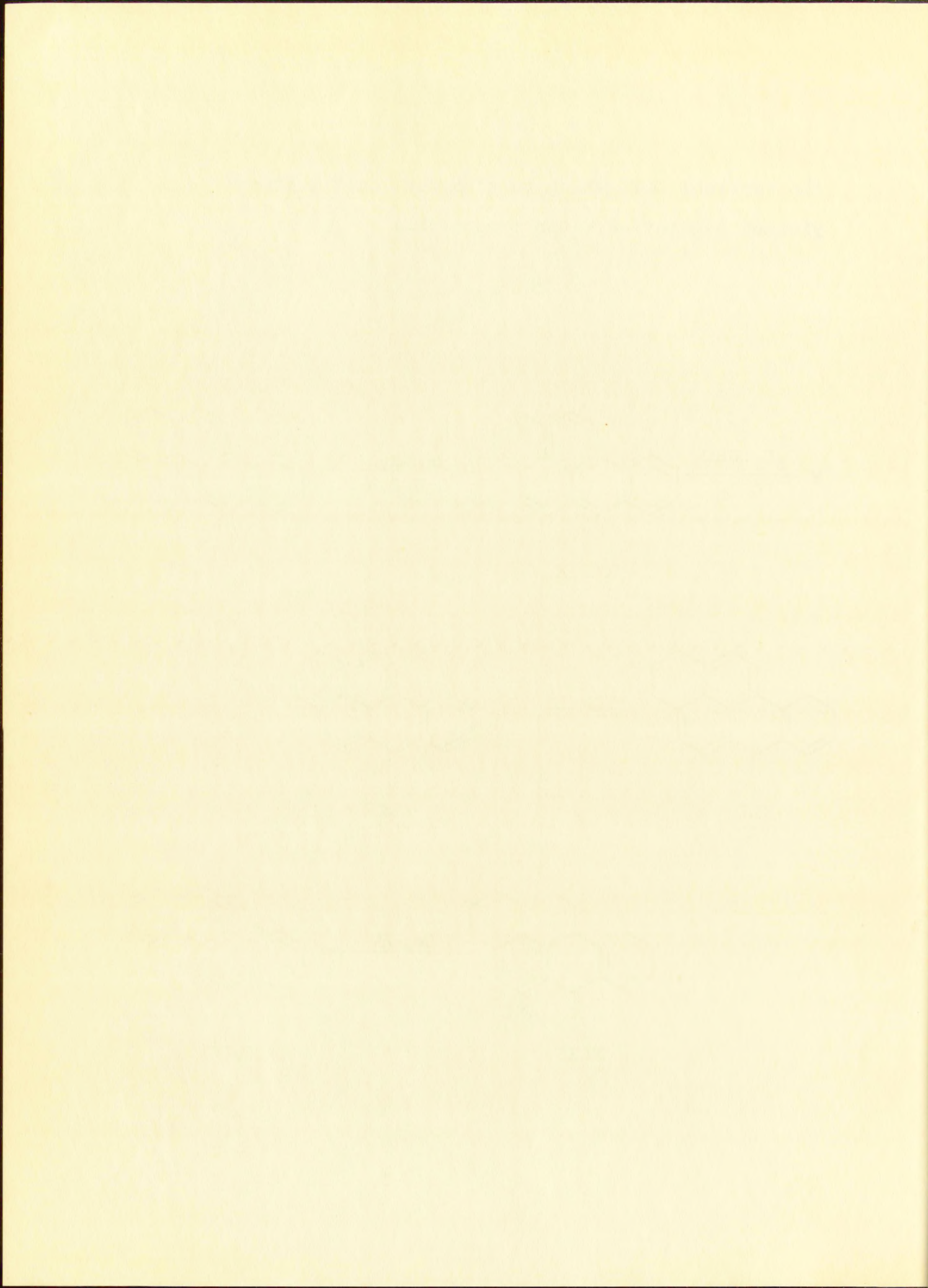
(9) J. W. Patton, "Masters Thesis," University of New Mexico, 1954.

(10) L. F. Fieser and E. B. Hershberg, J. Am. Chem. Soc., 60, 2542 (1938).



the carbinol XLVI which on zinc dust distillation yielded 5-methyl-3,4-benzpyrene (XL).



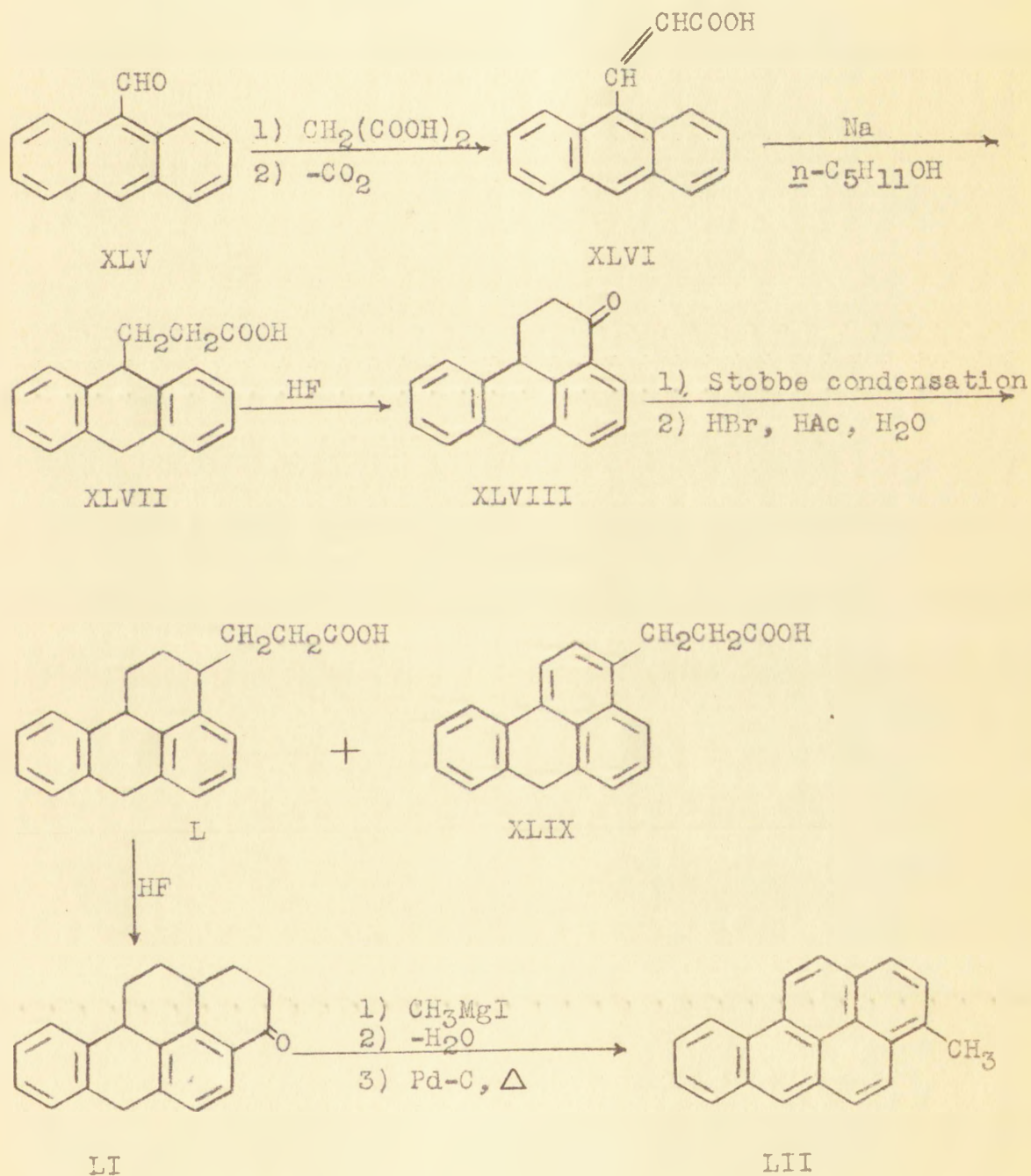


The synthesis of 8-methyl-3,4-benzpyrene (LII) by Cook, Ludwiczak, and Schoental (11) started with the condensation of 9-anthraldehyde (XLV) with malonic acid yielding β -(9-anthranyl)-acrylic acid (XLVI) upon decarboxylation. Reduction of XLVI with sodium and *n*-amyl alcohol yielded β -(9,10-dihydro-9-anthranyl)-propionic acid (XLVII). The acid XLVII has been synthesized by an improved method which will be discussed later (page 21). Cyclization of XLVII with anhydrous hydrogen fluoride yielded 3-keto-1,2,3,11b-tetrahydro-7H-mesobenzanthracene (XLVIII). The ketone underwent a Stobbe condensation with diethyl succinate and decarboxylation of the resulting half ester with a mixture of hydrobromic acid and acetic acid caused disproportionation producing β -(7H-mesobenzanthrenyl-3)-propionic acid (XLIX) and β -(1,2,3,11b-tetrahydro-7H-mesobenzanthrenyl-3)-propionic acid (L). Reduction of XLIX with sodium and *n*-amyl alcohol yielded L. Cyclization of the acid L with anhydrous hydrogen fluoride yielded 8-keto-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (LI). Treatment of LI with methylmagnesium iodide followed by dehydration and dehydrogenation of the product over palladium-charcoal yielded 8-methyl-3,4-benzpyrene (LII). Modifications of the

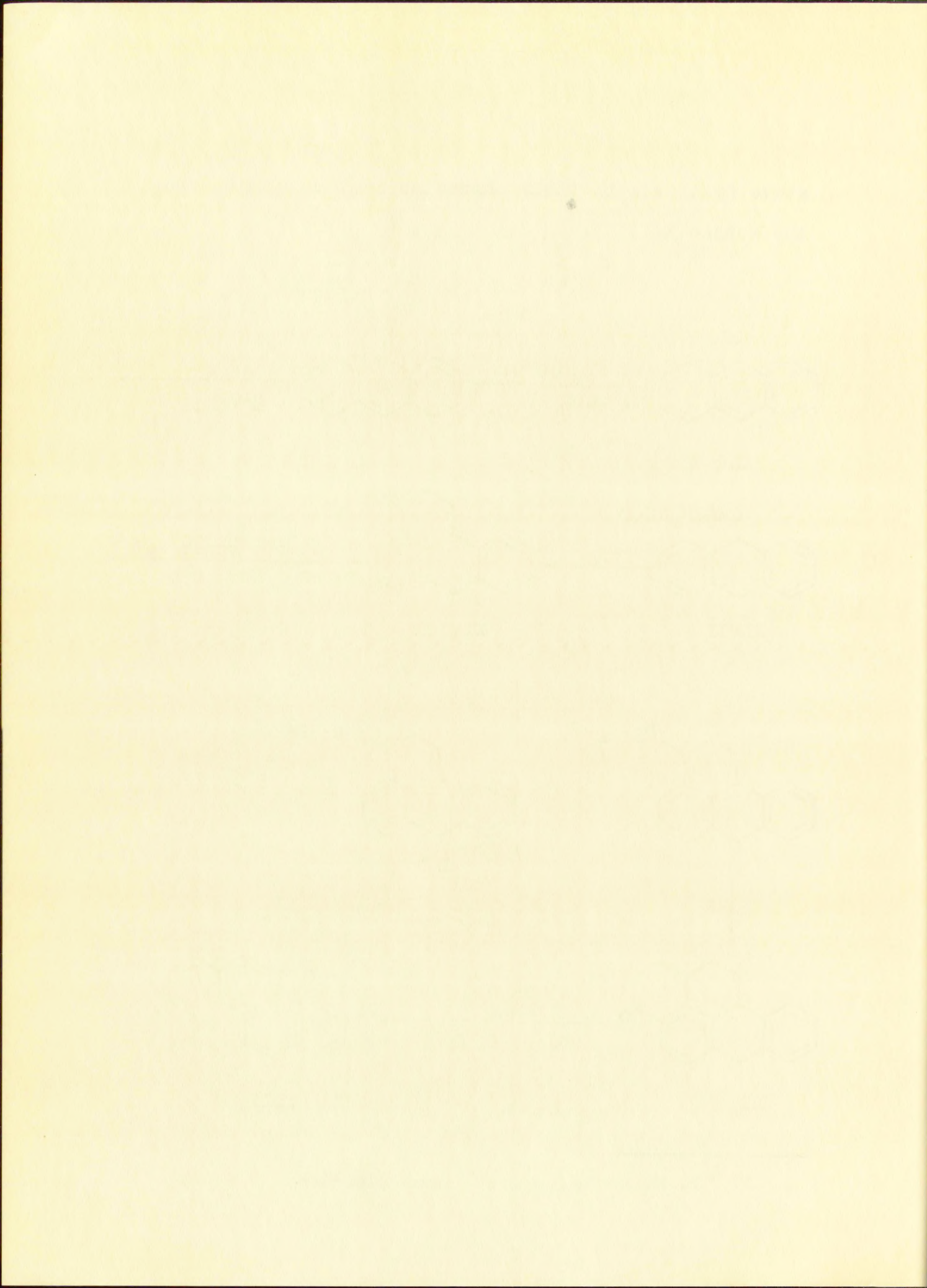
(11) J. W. Cook, R. S. Ludwiczak, and R. Schoental, J. Chem. Soc., 1950, 1112.



above synthesis by Doyle* have improved the yields from the ketone XLVIII.

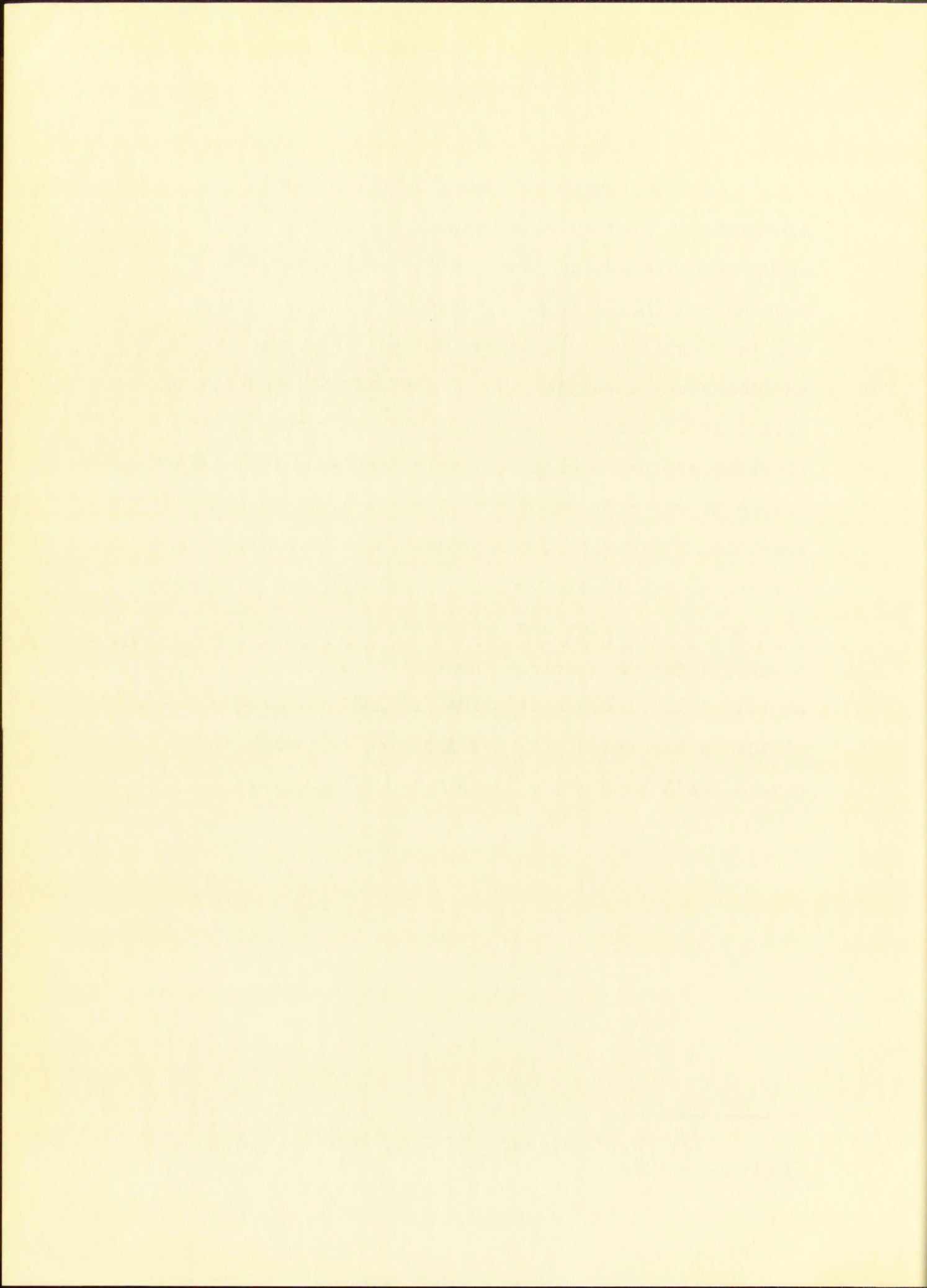


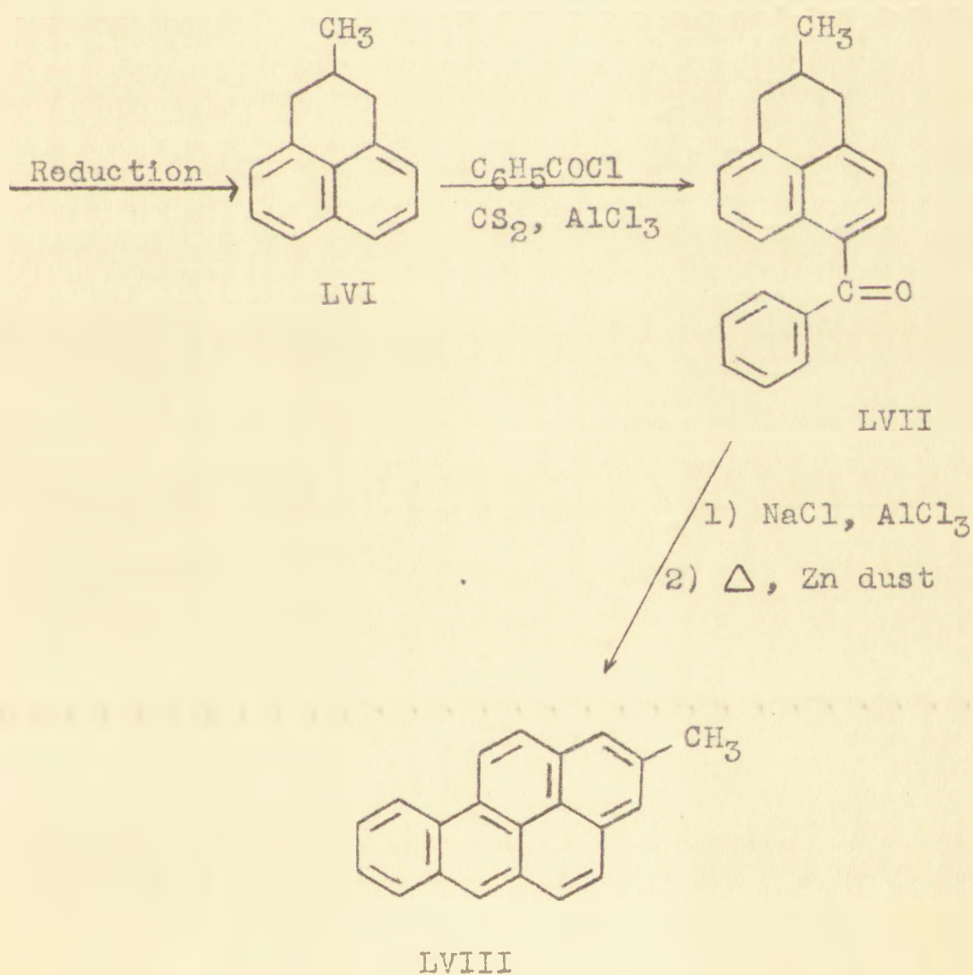
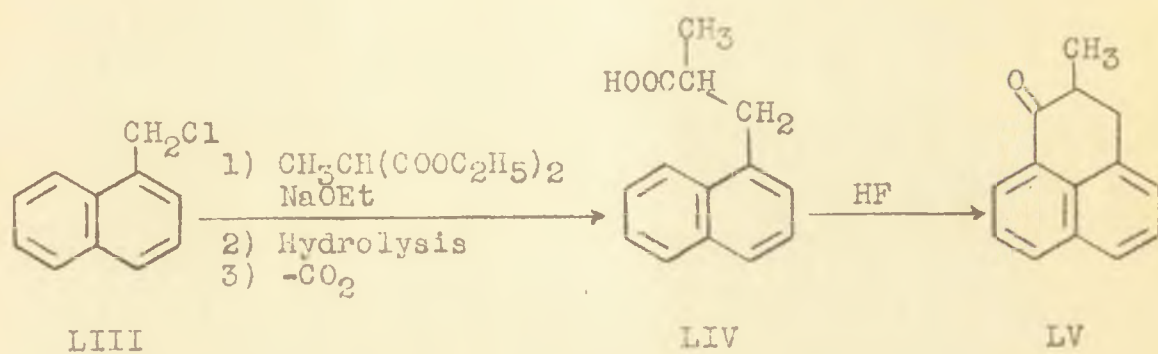
*C. W. Doyle, private communication.



In 1940 Fieser and Novello (12) reported the synthesis of 9-methyl-3,4-benzpyrene (LVIII). Diethyl methylmalonate was condensed with 1-chloromethyl-naphthalene (LIII) in the presence of sodium ethoxide and the resulting substituted malonic ester was hydrolyzed and decarboxylated yielding β -(naphthyl-1)-isobutyric acid (LIV). Cyclization of LIV with anhydrous hydrogen fluoride yielded 8-methylperinaphthan-7-one (LV). The ketone LV was reduced by the Clemmensen method and the resulting hydrocarbon, 8-methylperinaphthane (LVI), was allowed to react with benzoyl chloride in the presence of aluminum chloride and carbon disulfide producing 3-benzoyl-8-methylperinaphthane (LVII). Cyclization of LVII with aluminum chloride and sodium chloride yielded a tar which upon distillation from zinc dust gave a small quantity of 9-methyl-3,4-benzpyrene (LVIII).

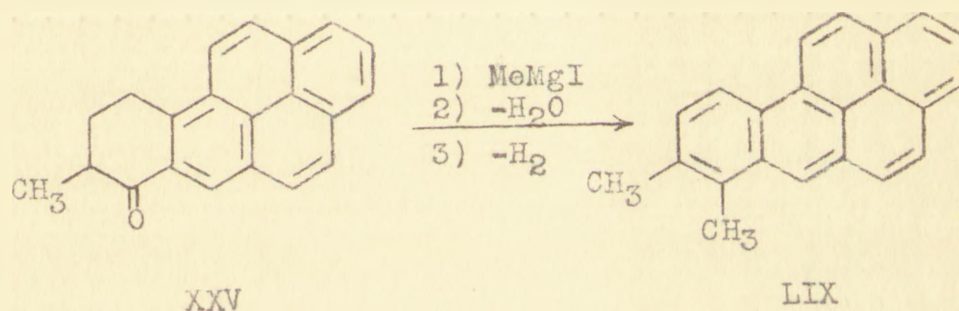
(12) L. F. Fieser and F. C. Novello, J. Am. Chem. Soc., 62, 1855 (1940).



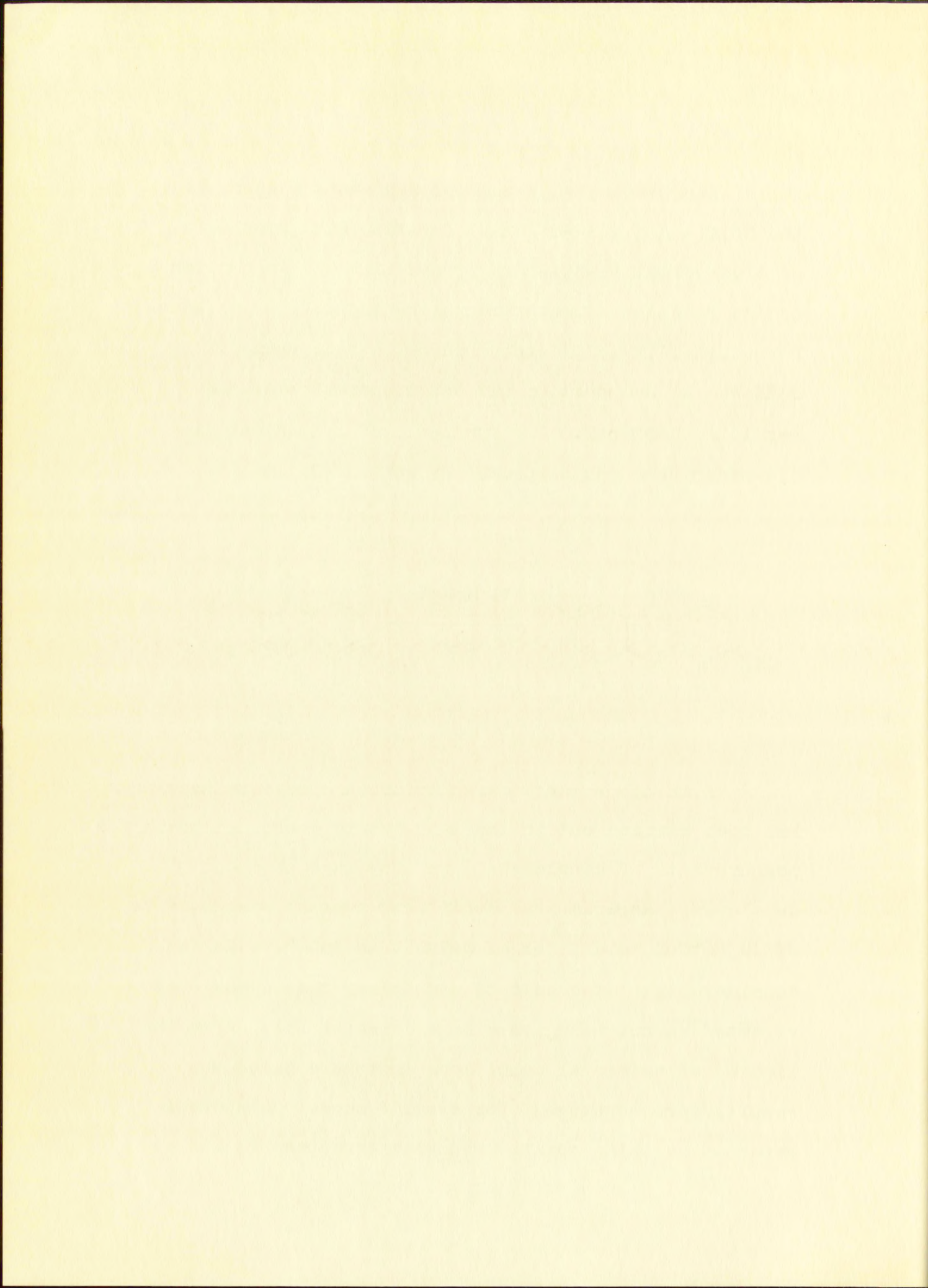




Two dimethyl-3,4-benzpyrenes are known, namely the 3',4'- and 2,10-dimethyl derivatives. Synthesis of 3',4'-dimethyl-3,4-benzpyrene (LIX) was accomplished by the reaction of methylmagnesium iodide with 4'-keto-3'-methyl-1',2',3',4'-tetrahydro-3,4-benzpyrene (XXV) followed by dehydration and dehydrogenation of the resulting carbinol. The synthesis of 2,10-dimethyl-3,4-benzpyrene was completed by Patton (9) in 1954.



Although a large quantity of carcinogenic testing has been carried out in the last twenty years, standardized measurements of carcinogenic potency have not been developed. Experimental conditions such as dosage, site of injection, and types of animals tested have varied considerably. It should be made clear that a compound reported as not being carcinogenic means only under the limited experimental conditions that were tried the results were negative. For example certain compounds reported as being negative in mice have been found to



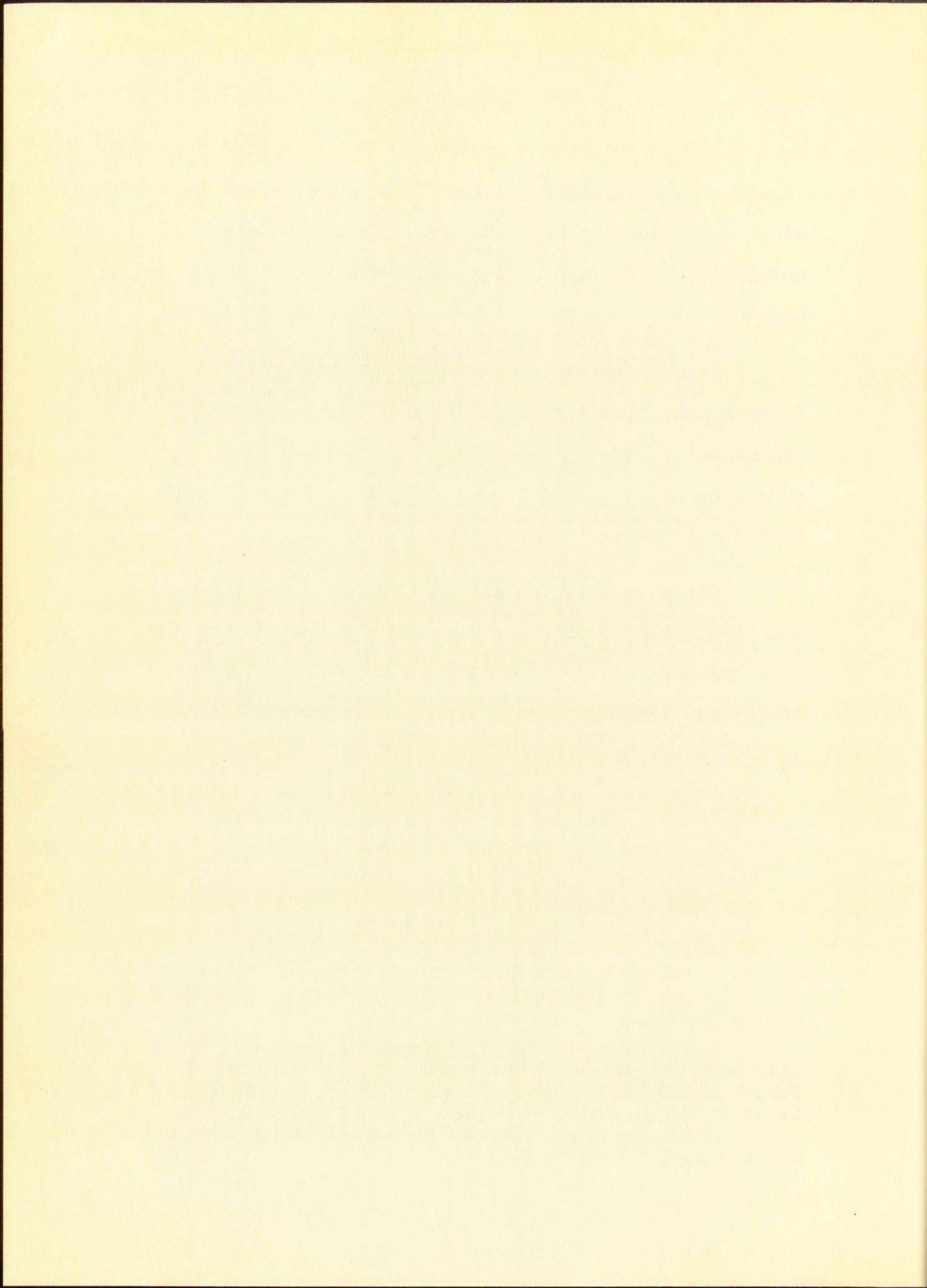
induce tumors in other species (13). However, it is of value to mention here the compounds of the mono-methyl-3,4-benzpyrene series that have been tested and indicate qualitatively the results obtained.

In a large scale experiment with the parent hydrocarbon, 3,4-benzpyrene (14), of 2278 rats administered 0.2 to 4 mg. of the hydrocarbon by subcutaneous injection in paraffin 1369 of the animals developed tumors.

Other results indicate that the 2'- and 3'-methyl-3,4-benzpyrenes are inactive and the 4'- and 6-methyl derivatives show only slight activity; while the 5- and 9-methyl-3,4-benzpyrenes are about as active as the parent hydrocarbon (8).

(13) J. L. Hartwell, "Survey of Compounds Which Have Been Tested for Carcinogenic Activity," P. H. S. Pub. No. 149, U. S. Gov. Printing Office, Washington, D.C., 1951, p. 1.

(14) W. F. Dunning and M. R. Curtis, Am. J. Cancer, 38, 516 (1940).



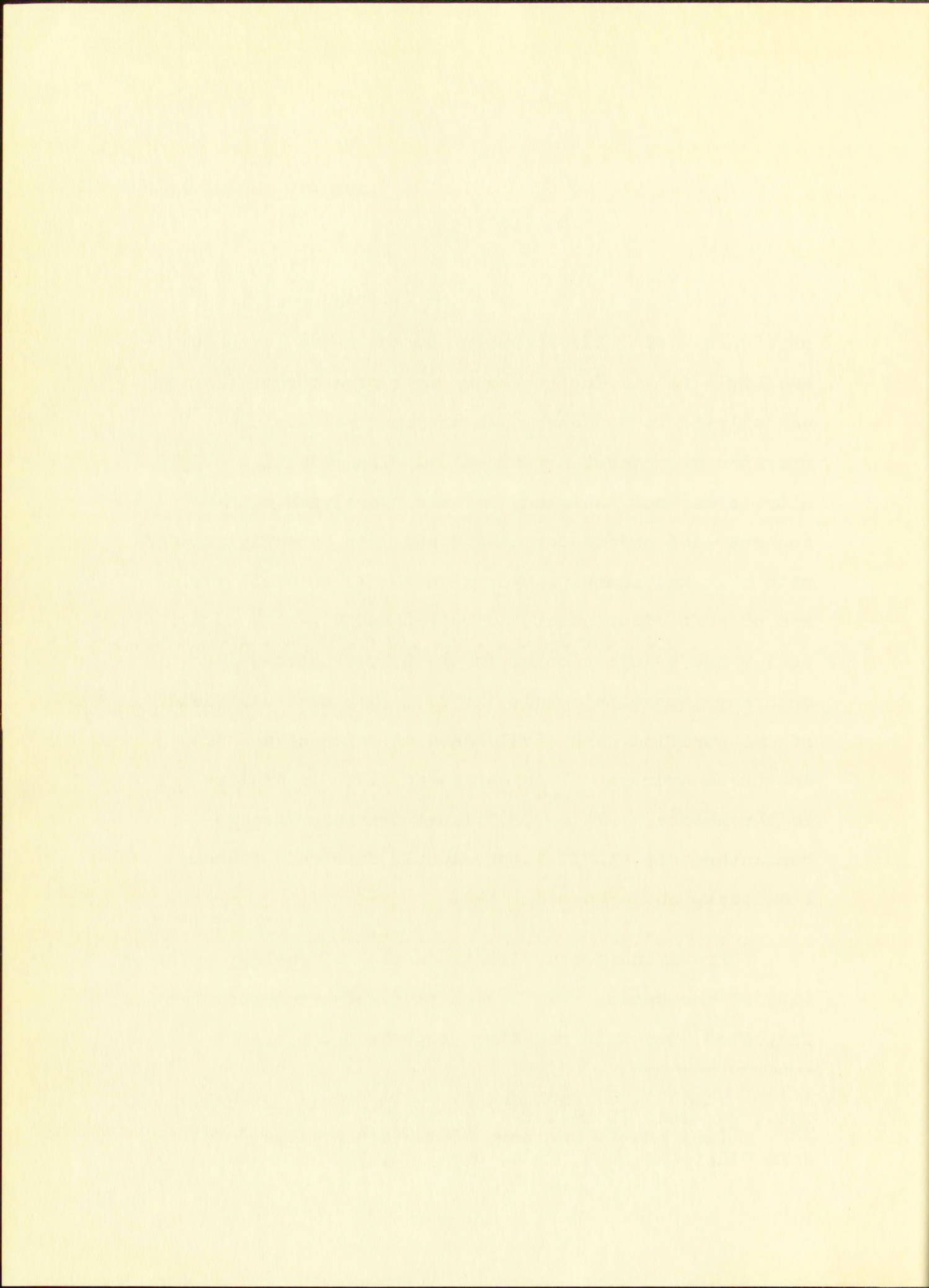
DISCUSSION

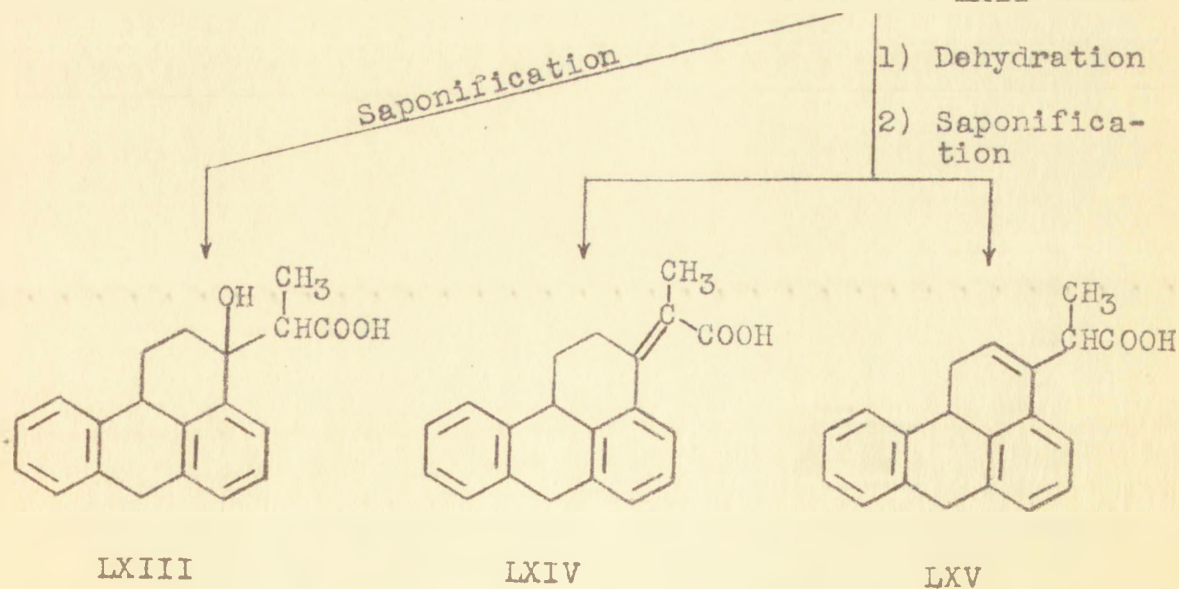
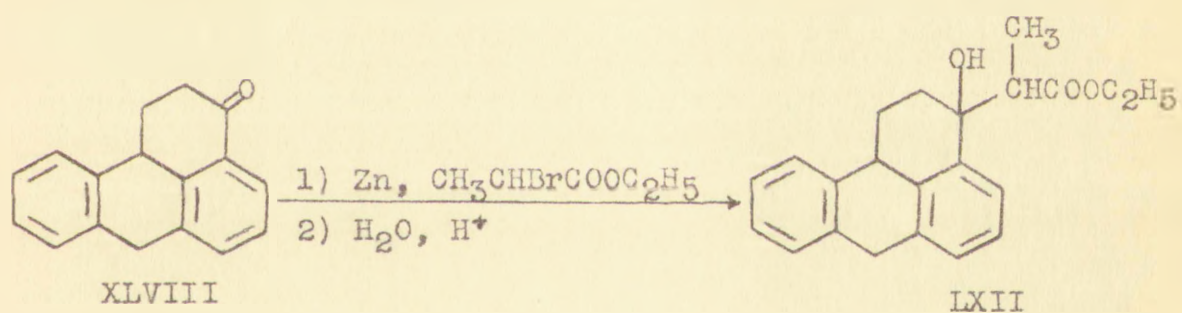
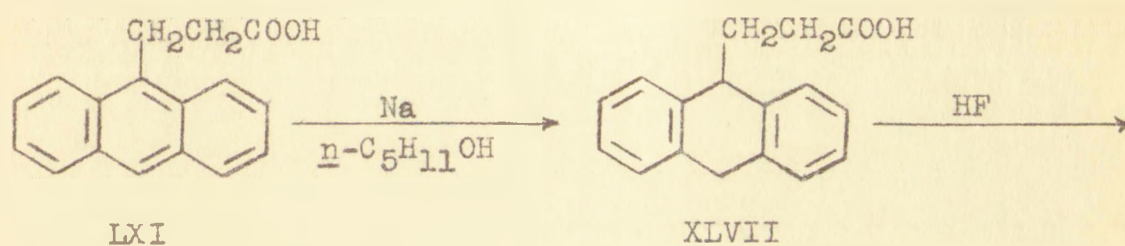
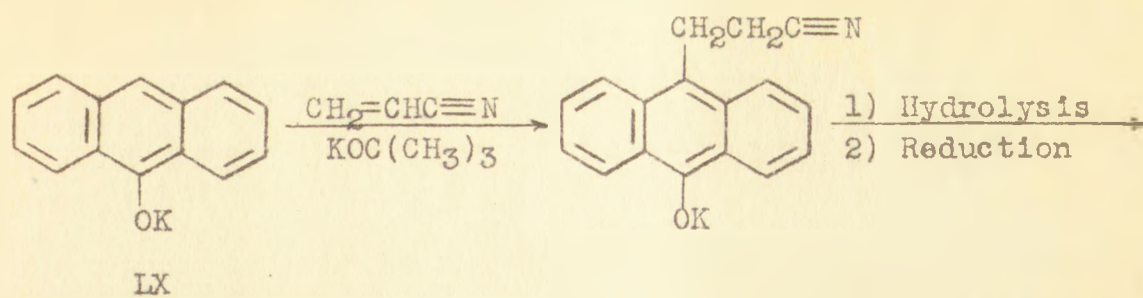
Anthrone was converted to β -(9-anthranyl)-propionic acid (LXI) according to the method of Daub and Doyle (15). The potassium salt of anthrone (LX) was allowed to condense with acrylonitrile in the presence of potassium *t*-butoxide. The resulting oily nitrile was not isolated, but was hydrolyzed with concentrated hydrochloric acid and then directly reduced with zinc and ammonium hydroxide to LXI in 87.5% yield and of sufficient purity to be reduced directly with sodium and *n*-amyl alcohol to β -(9,10-dihydro-9-anthranyl)-propionic acid (XLVII). The over-all yield of the purified acid XLVII based on anthrone was 60%. Anhydrous hydrogen fluoride caused XLVII to cyclize to the ketone, 3-keto-1,2,3,11b-tetrahydro-7H-meso-benzanthracene (XLVIII), previously reported by Cook, Ludwiczak, and Schoental (11).

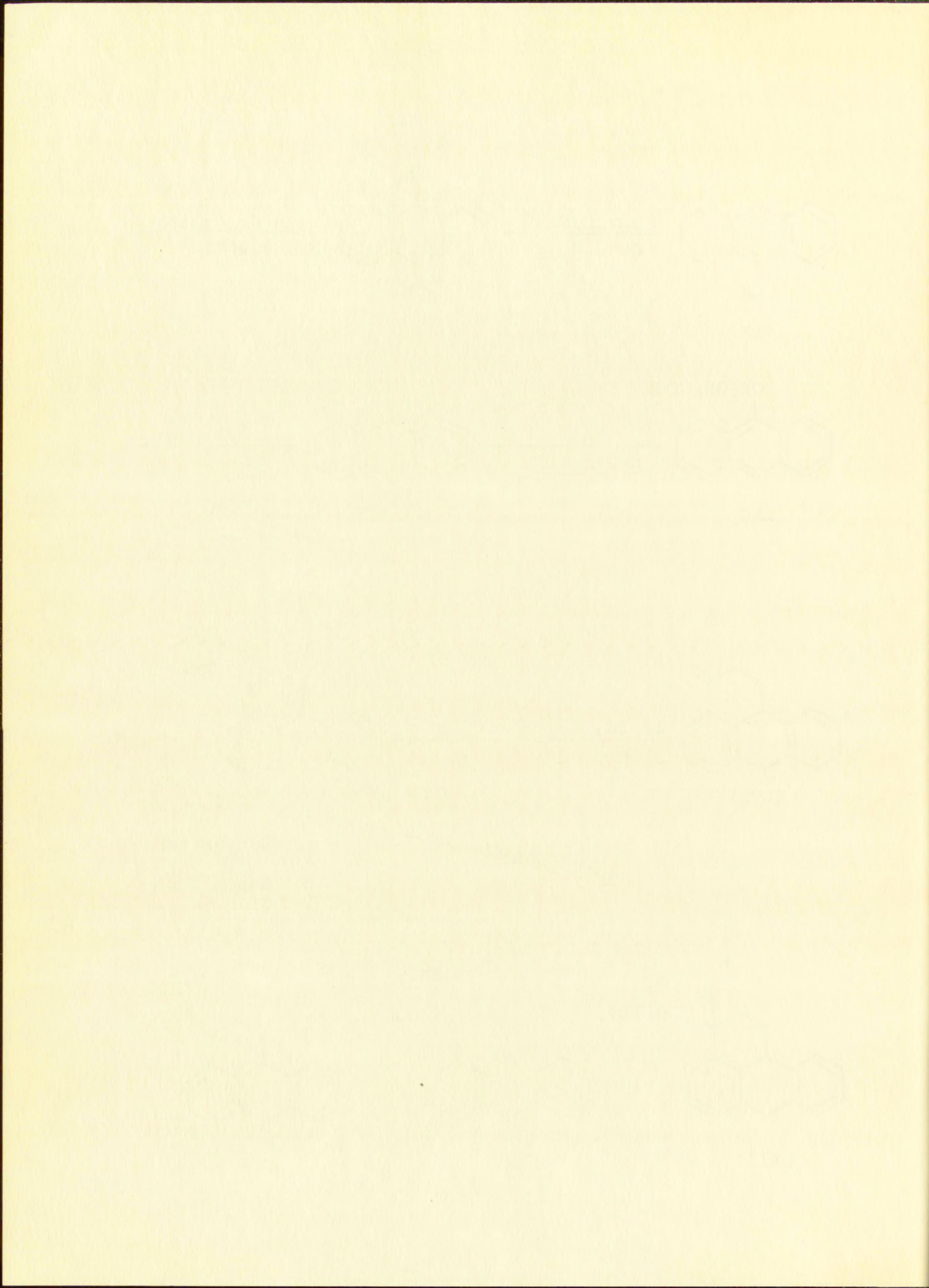
Preliminary experiments on the Reformatsky reaction (16) of the ketone XLVIII with ethyl α -bromopropionate indicated that this reaction progressed comparatively

(15) G. H. Daub and W. C. Doyle, J. Am. Chem. Soc., 74, 4449 (1952).

(16) R. L. Shriner, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942. p. 1.







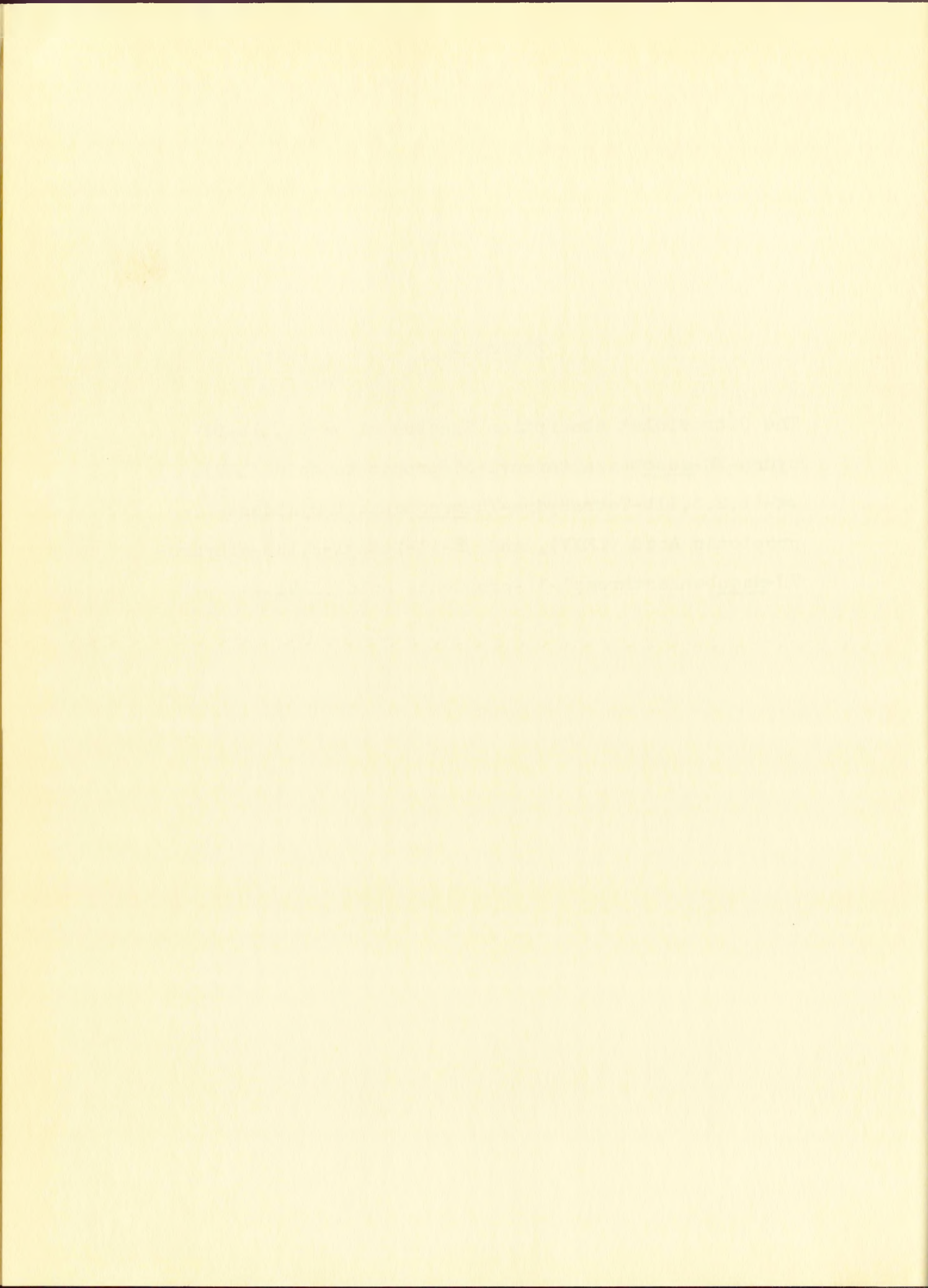
slowly. Since the ketone was insoluble in ether, it was easily recovered from reaction mixtures. To facilitate reaction and increase yields, only pure ketone samples were used and the zinc was activated by amalgamation and protected from air oxidation prior to introduction into the reaction mixture. Direct alkaline hydrolysis of the ethyl α -(3-hydroxy-1,2,3,11b-tetrahydro-7H-mesobenzanthrenyl-3)-propionate (LXII) obtained from the Reformatsky reaction yielded only a small quantity of the corresponding hydroxy acid LXIII and this approach was discarded.* When the hydroxy ester LXII was dehydrated in the presence of anhydrous formic acid and then hydrolyzed with dilute alkali, α -(1,11b-dihydro-7H-mesobenzanthrenyl-3)-propionic acid (LXV) was isolated in 77% over-all yield from the ketone XLVII. Another acid, probably α -(1,2,3,11b-tetrahydro-7H-mesobenzanthrylidene-3)-propionic acid (LXIV), was also isolated but in small quantities (less than 2% yield). Attempts to prove the position of the double bonds in the two isomeric unsaturated acids by oxidation experiments with potassium permanganate or ozonolysis failed to give identifiable products.

The ultraviolet absorption spectra of the two unsaturated acids were measured and comparison of the curves (Fig. 1) with that of the known β -(1-methyl-

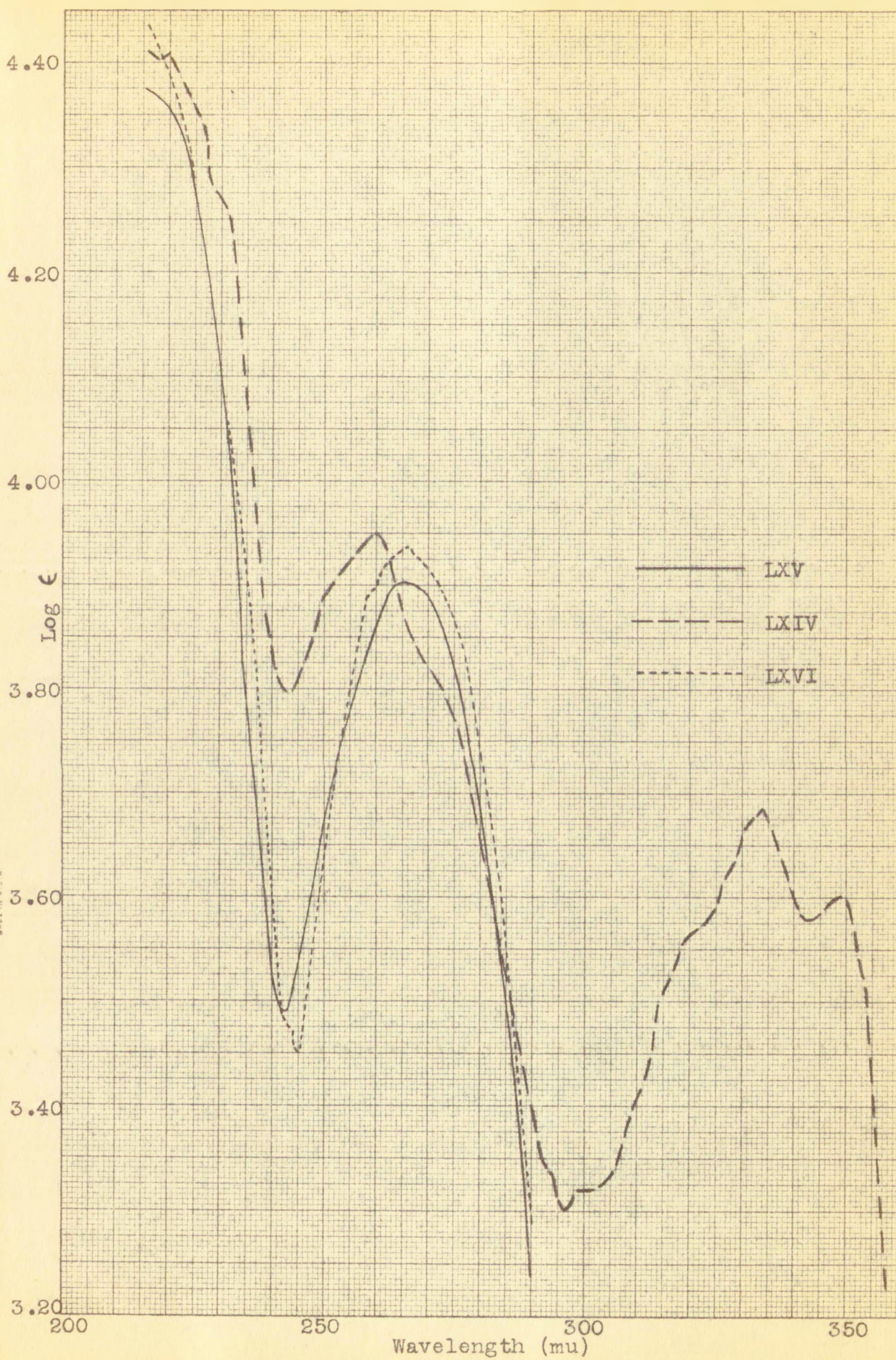


Figure 1

The Ultraviolet Absorption Spectra of α -(1,11b-Dihydro-7H-mesobenzanthrenyl-3)-propionic Acid (LXV), α -(1,2,3,11b-Tetrahydro-7H-mesobenzanthrylidene-3)-propionic Acid (LXIV), and β -(1-Methyl-1,11b-dihydro-7H-mesobenzanthrenyl-3)-propionic Acid (LXVI).

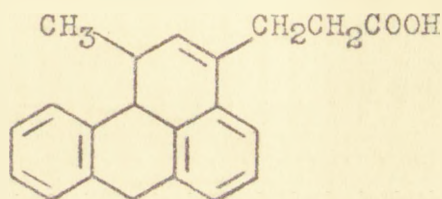


357-14 KEUFFEL & ESSER CO.
Millimeter, 5 mm. line spaced, cm. lines heavy.
MADE IN U.S.A.





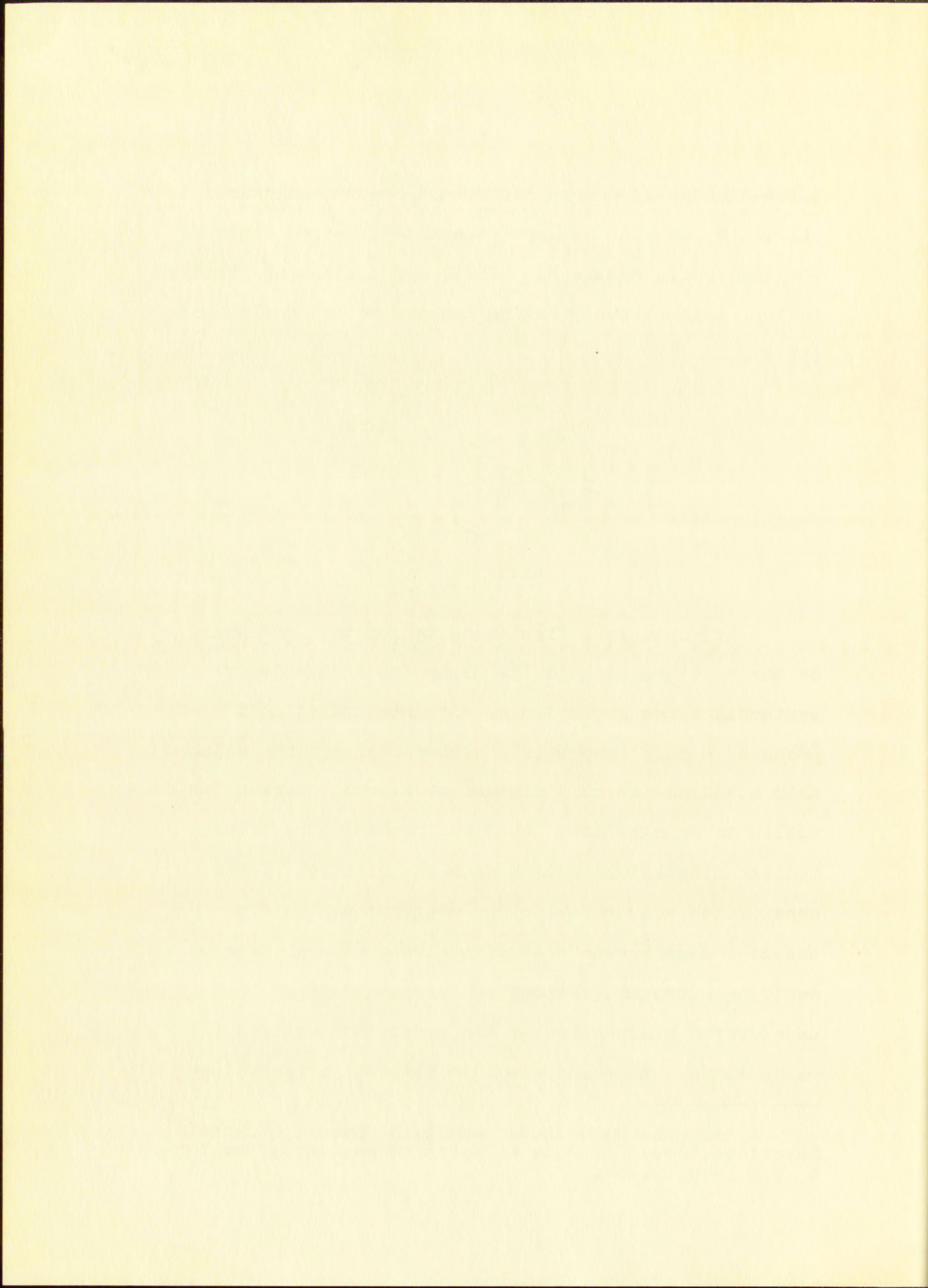
1,11b-dihydro-7H-mesobenzanthrenyl-3)-propionic acid (LXVI) (9) showed the more abundant isomer to contain the endocyclic double bond (LXV) and the isomer obtained in low yield probably having the exocyclic double bond (LXIV).



LXVI

Attempts were first made to lengthen the chain of the unsaturated acid LXV using the Arndt-Eistert synthesis since reduction of the unsaturated acid produces a third asymmetric carbon atom and the reduced acid LXVII was an oily mixture of stereoisomers which failed to crystallize. What was probably the intermediate diazoketone formed from the reaction of the unsaturated acid chloride and diazomethane gave a positive diazoketone test with strong mineral acid by evolving nitrogen. Attempted rearrangement of the unsaturated diazoketone by the prescribed methods (17) using silver oxide and absolute methanol or ammonium

(17) W. E. Bachmann and W. S. Struve, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 38.



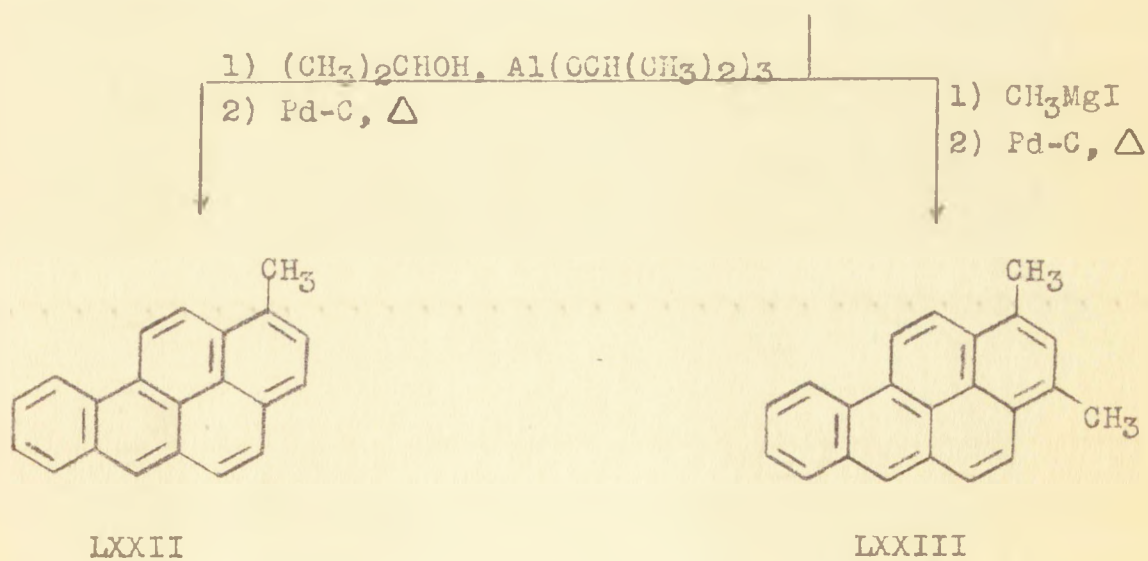
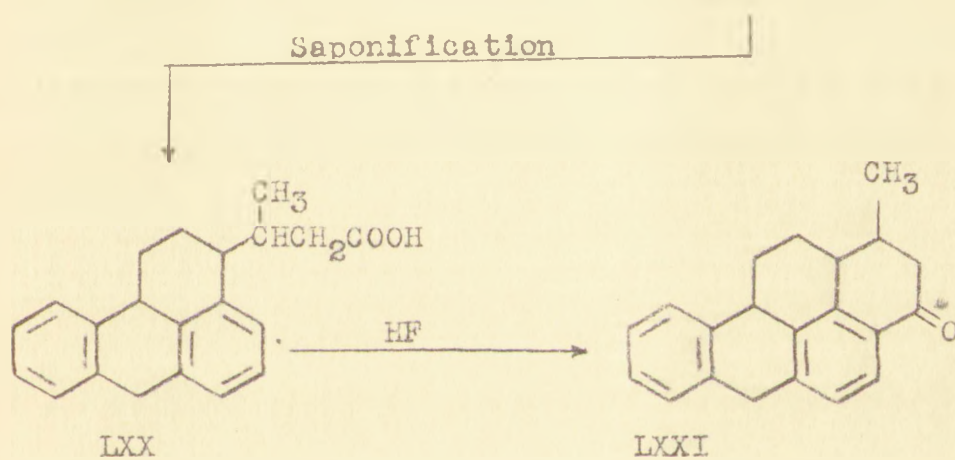
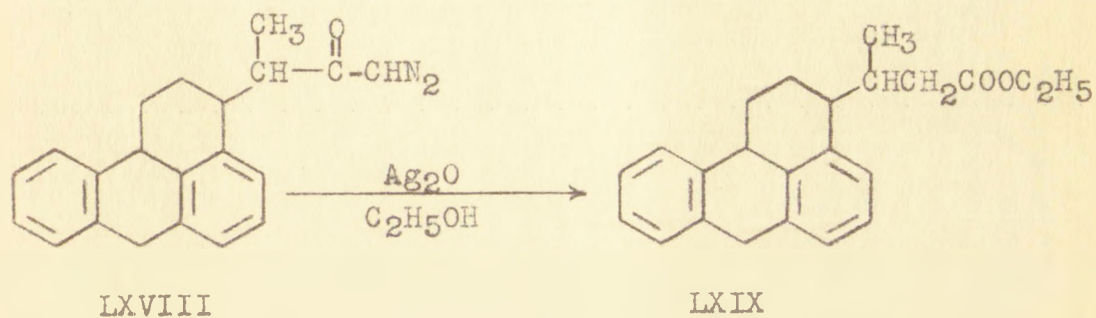
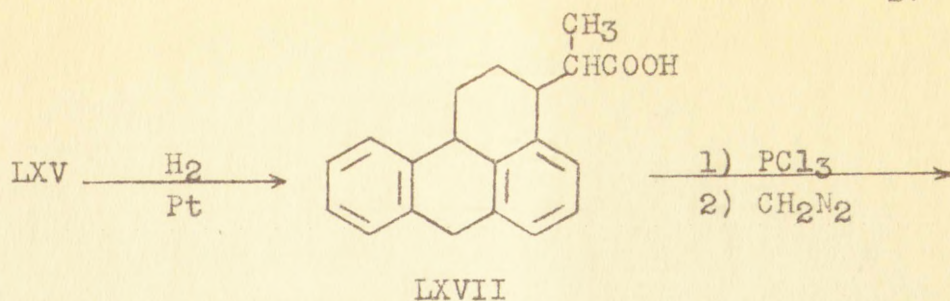
hydroxide failed. The rearrangement using 95% ethanol and silver oxide (18), suggested for compounds containing an α -methyl group, evolved nitrogen but hydrolysis of the ethyl ester obtained gave a mixture of tarry acidic material which could not be resolved. High temperature rearrangement at 170-190° using benzyl alcohol and quinoline or γ -collidine (19), followed by hydrolysis of the resulting benzyl ester also yielded intractable acidic material.

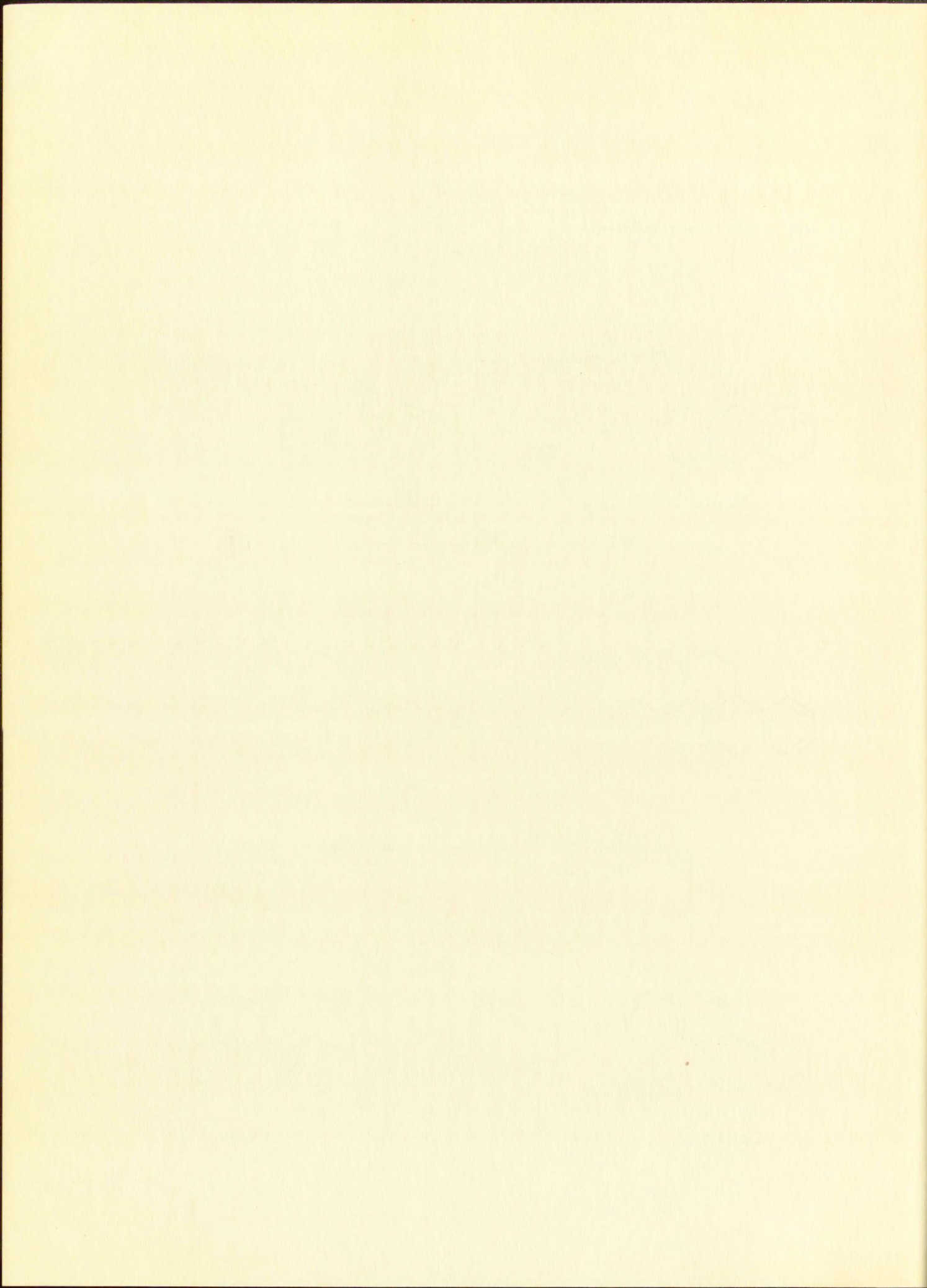
Catalytic hydrogenation of the unsaturated acid LXV over Adam's catalyst at atmospheric pressure yielded α -(1,2,3,11b-tetrahydro-7H-mesobenzanthrenyl-3)-propionic acid (LXVII) as a highly viscous oil. The acid chloride of LXVII prepared from the acid with phosphorus trichloride, was allowed to react with an excess of diazomethane and the resulting diazoketone LXVIII was rearranged in the presence of ethanol and silver oxide. Alkaline hydrolysis of the ethyl ester LXIX formed in the rearrangement gave β -(1,2,3,11b-tetrahydro-7H-mesobenzanthrenyl-3)-butyric acid (LXX) in an over-all yield of 78% from the unsaturated acid LXV. The basic hydrolysis of the ethyl ester LXIX was

(18) M. S. Newman and A. S. Hussey, J. Am. Chem. Soc., 69, 3023 (1947).

(19) A. L. Wilds and A. L. Meader, J. Org. Chem., 13, 763 (1948).







complete in one hour, indicating that the hindering α -methyl group was not present in the acid LXX and the Arndt-Eistert synthesis had been successful. Complete saponification of the unsaturated ester from the Reformatsky reaction in which an α -methyl group was present required thirty-two hours.

Cyclization of the acid LXX with anhydrous hydrogen fluoride afforded 8-keto-10-methyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (LXXI) as a mixture of stereoisomers in 82% yield.

Preparation of 10-methyl-3,4-benzpyrene (LXXII) was accomplished by reduction of the ketone LXXI, with aluminum isopropoxide in isopropyl alcohol, to 8-hydroxy-10-methyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene which was directly dehydrated and dehydrogenated over palladium-charcoal at 280-315°. The hydrocarbon LXXII was obtained in a 46% over-all yield from the ketone LXXI and formed a dark purple picrate derivative.

Reaction of the ketone LXXI with methylmagnesium iodide gave 8-hydroxy-8,10-dimethyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene which was dehydrated and dehydrogenated over a palladium-charcoal catalyst at 300-325°, affording 8,10-dimethyl-3,4-benzpyrene (LXXIII) in 37% over-all yield. The hydrocarbon LXXIII formed a



dark brown picrate derivative which could not be obtained analytically pure due to the very low solubility of the parent hydrocarbon.

The ultraviolet absorption curves for 10-methyl-3,4-benzpyrene (LXXII) and 8,10-dimethyl-3,4-benzpyrene (LXXIII), shown in Figure 2 with the curve for 3,4-benzpyrene (20), substantiate the presence of the parent ring system in these new hydrocarbons.

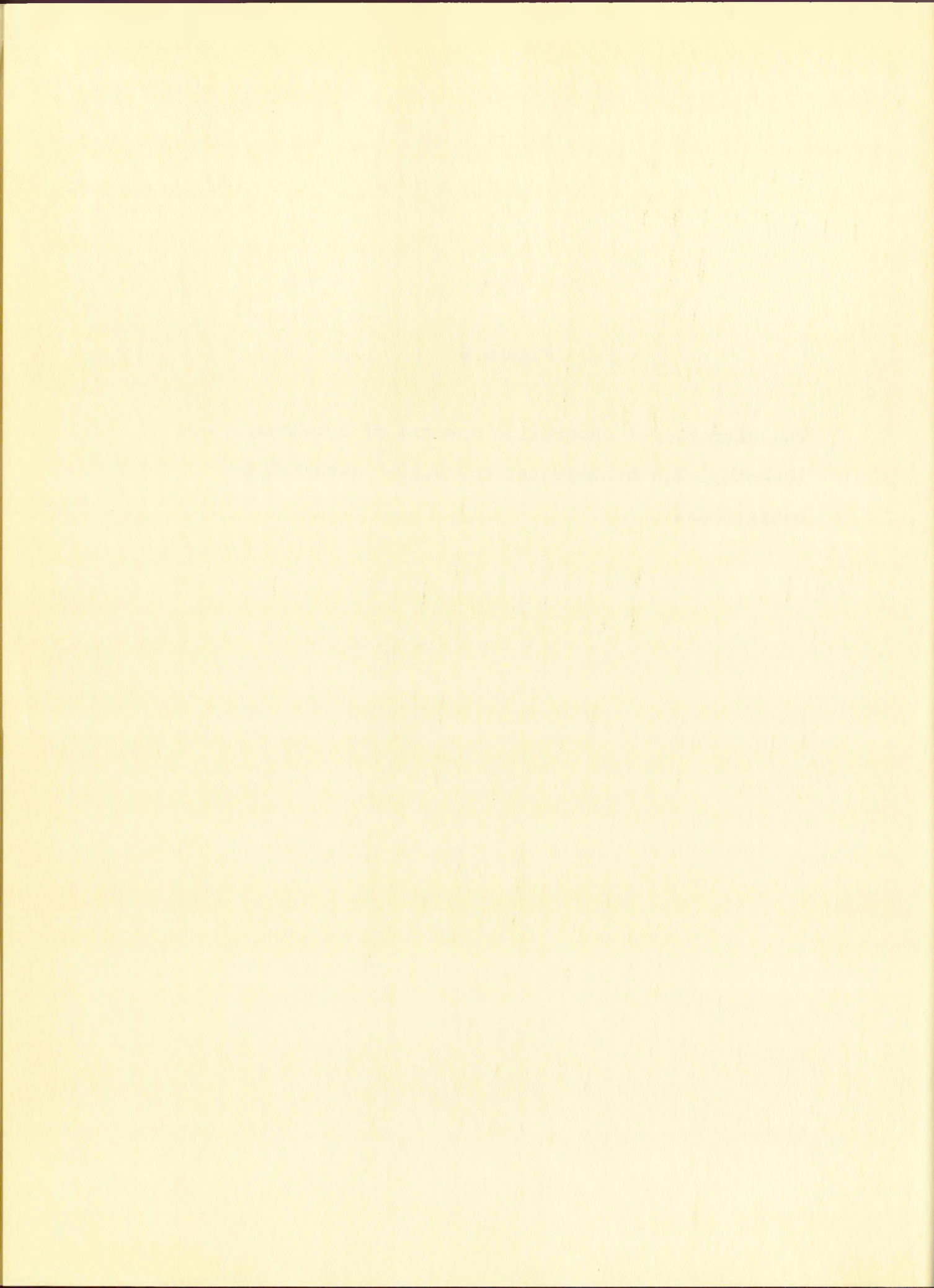
Samples of the hydrocarbons are being tested for carcinogenic activity at Northwestern University Medical School.

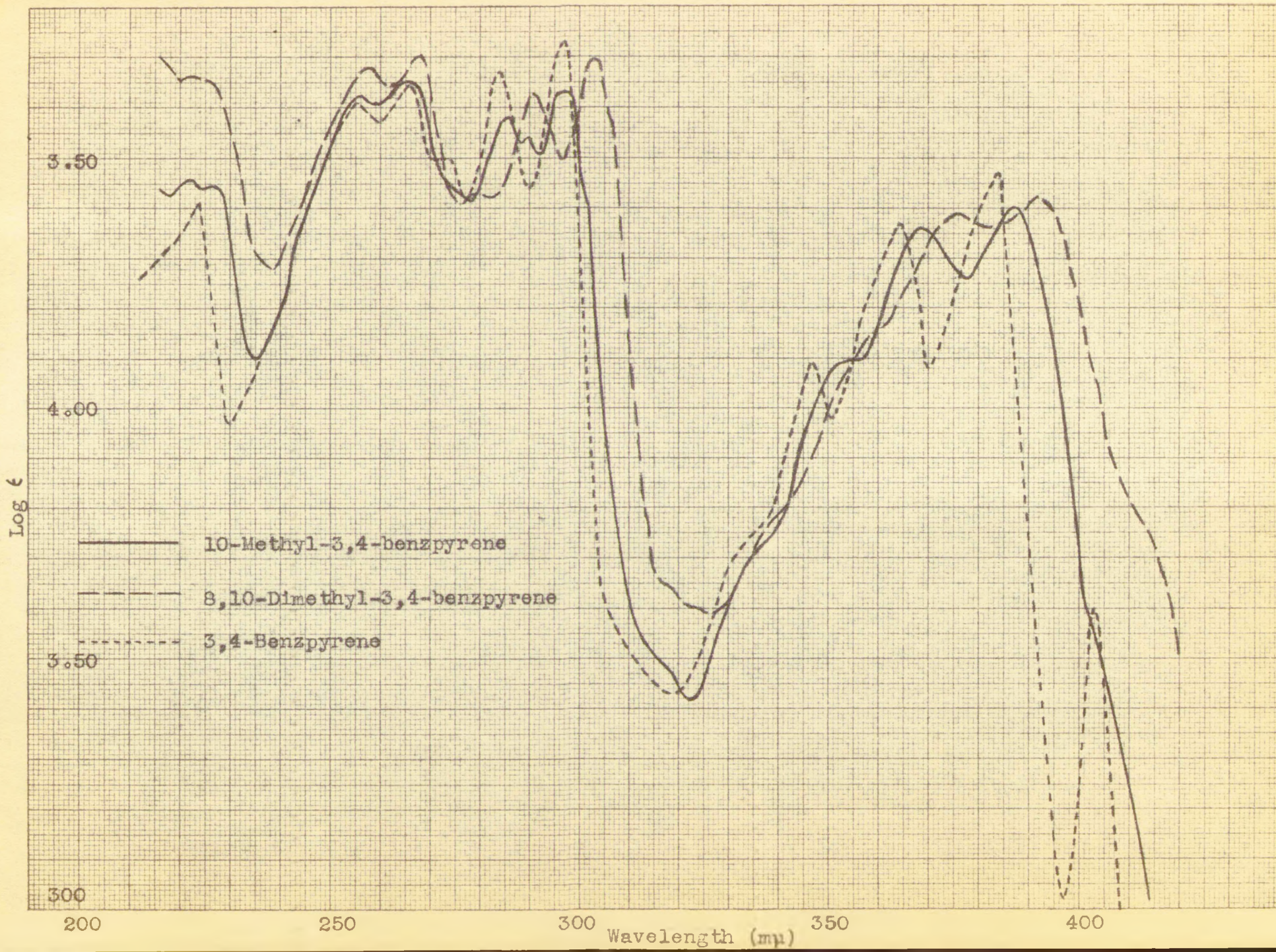
(20) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, No. 554.

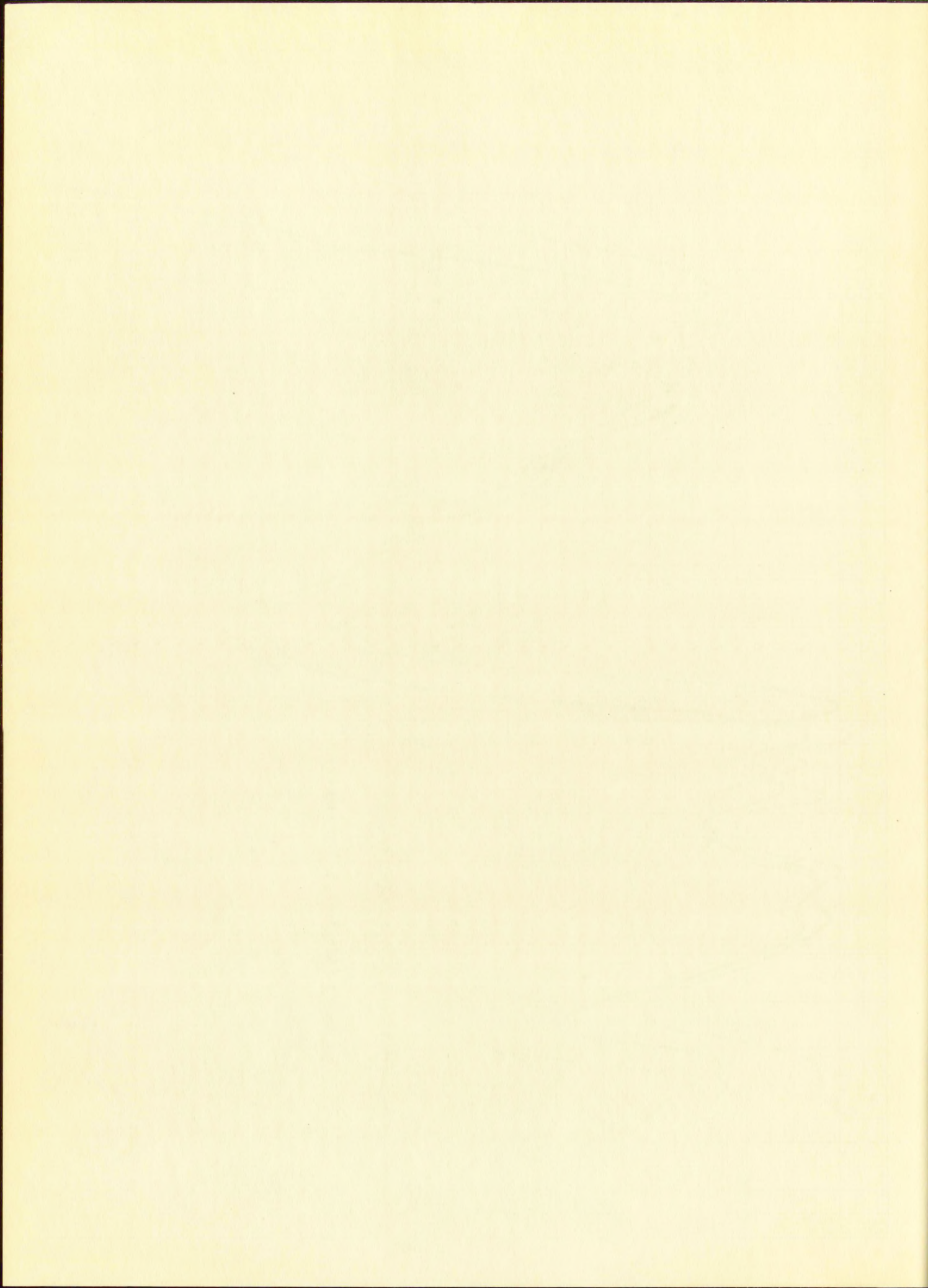


Figure 2

The Ultraviolet Absorption Spectra of 3,4-Benzpyrene,
10-Methyl-3,4-benzpyrene, and 8,10-Dimethyl-3,4-
benzpyrene.





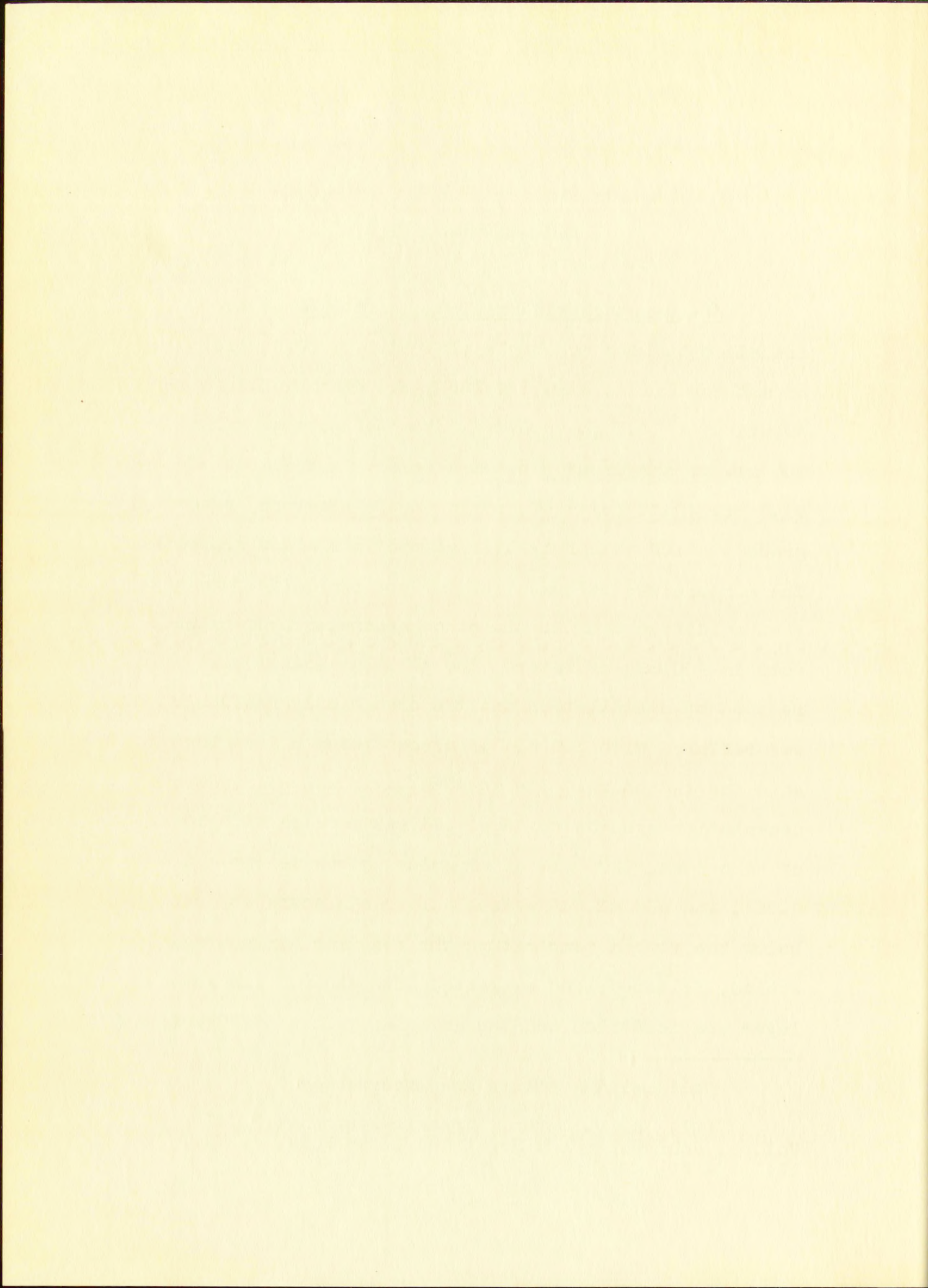


EXPERIMENTAL*

β -(9-Anthranyl)-propionic Acid (LXI). As described by Daub and Doyle (15) 58.3 g. (0.3 mole) of anthrone (21), m.p. 154-155^o, was dissolved in a solution of 14.7 g. (0.375 g. atom) of potassium in 600 ml. of anhydrous t-butyl alcohol. A solution of 21.9 ml. (0.33 mole) of acrylonitrile (Eastman, practical grade) in 100 ml. of t-butyl alcohol was added dropwise. The mixture was refluxed for two and one-half hours and then acidified with 33 ml. of concentrated hydrochloric acid in 400 ml. of water. The t-butyl alcohol was removed by distillation and the orange oily residue was refluxed with 300 ml. of concentrated hydrochloric acid for two hours. The aqueous layer was removed by decantation and the residual oil was reduced with 100 g. of zinc dust, 1080 ml. of ammonium hydroxide (sp. g. 0.90), and 480 ml. of water. After six hours at just below the reflux temperature the reaction mixture was cooled, filtered, and extracted with ether. The aqueous layer was acidified and the granular yellow β -(9-anthranyl)-

*All melting points are uncorrected.

(21) K. H. Meyer, "Organic Syntheses," Col. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 60.



propionic acid (LXI) was collected, washed with water, and dried. The crude acid weighed 66.5 g. (87.5% yield), m.p. 189-193°.

β -(9,10-Dihydro-9-anthranyl)-propionic Acid

(XLVII). The reduction of 66.5 g. (0.27 mole) of LXI, m.p. 189-193°, was carried out in 1650 ml. of boiling *n*-amyl alcohol by the addition of 55 g. (2.4 g. atoms) of sodium metal over a period of five hours. After removal of the alcohol by steam distillation, the alkaline solution was filtered through glass wool and the sodium salt of XLVII allowed to crystallize. The salt was collected on glass wool, dissolved in hot water, and the solution acidified giving 54 g. of a tan granular solid (m.p. 135-138°). Acidification of the mother liquor, from the crystallization of the sodium salt, followed by crystallization of the precipitated acid from ethyl acetate afforded an additional 9 g. of XLVII, m.p. 134-140°. Recrystallization of the total crude acid from ethyl acetate gave 51 g. (76% yield) of β -(9,10-dihydro-9-anthranyl)-propionic acid (XLVII) as almost colorless prisms, m.p. 138-140°, reported m.p. 139-140° (11).

3-Keto-1,2,3,11b-tetrahydro-7H-mesobenzanthracene

(XLVIII). Cyclization of 62.5 g. (0.252 mole) of XLVII



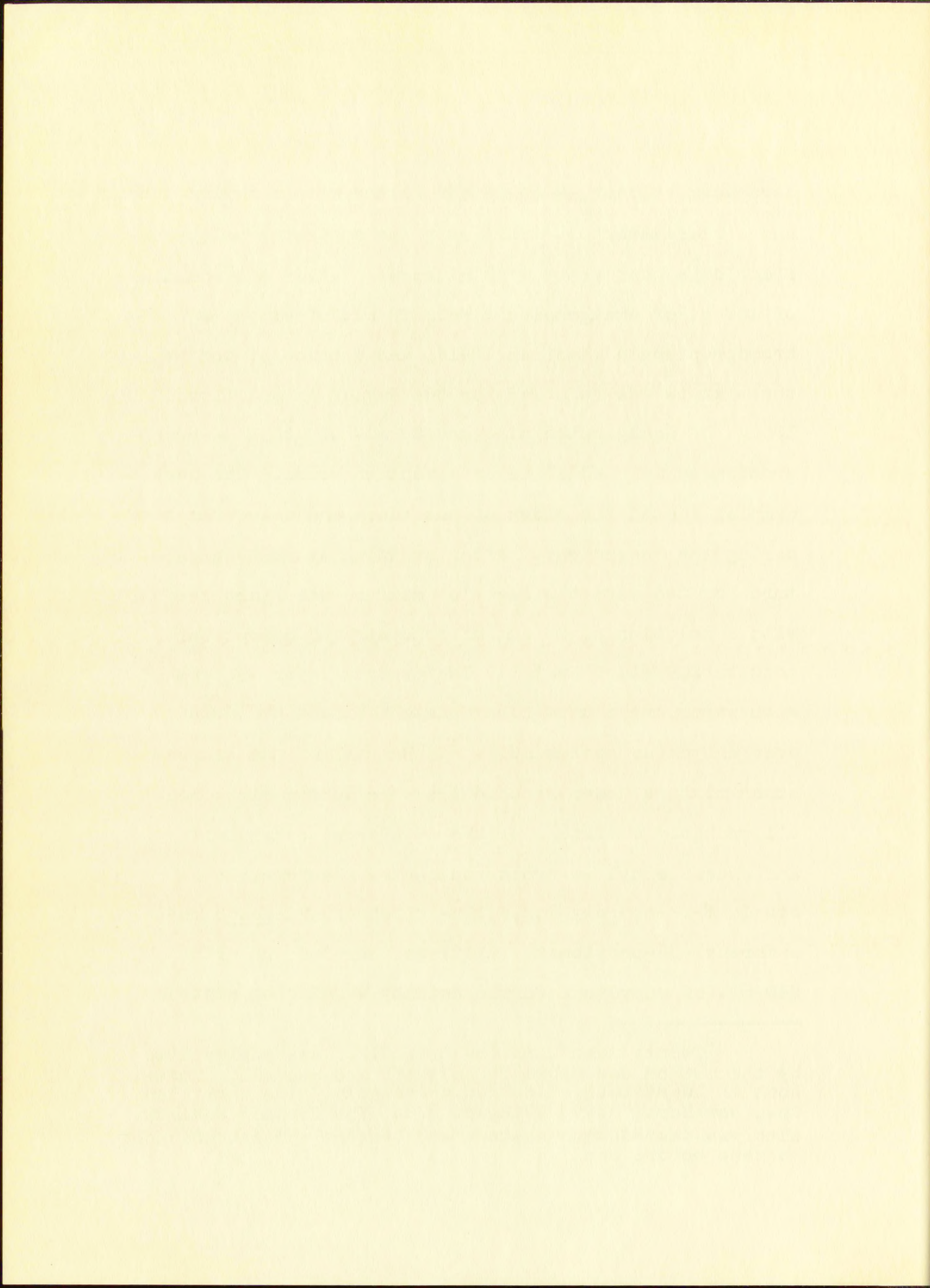
with 440 ml. of anhydrous hydrogen fluoride was carried out in a polyethylene beaker. After standing for two hours the excess hydrogen fluoride was removed with a stream of nitrogen and the reaction mixture was poured on crushed ice. The crude ketone was taken up in benzene and washed with water. Several extractions with aqueous sodium bicarbonate solution yielded no uncyclized acid. After drying over anhydrous sodium sulfate the benzene solution was passed through an alumina column (length 25 cm., diameter 23 mm.). The benzene elutions were concentrated to 100 ml. and upon addition of an equal volume of petroleum ether (b.p. 70-90°) 3-keto-1,2,3,11b-tetrahydro-7H-mesobenzanthracene (XLVIII) crystallized as bright yellow needles, m.p. 129.5-130.5°, reported m.p. 131-132°, 51.6 g. (87% yield). On standing for several months samples of the ketone became discolored and could be purified by recrystallization from 95% alcohol with good recovery.

The Reformatsky Reaction on 3-Keto-1,2,3,11b-tetrahydro-7H-mesobenzanthracene (XLVIII). Forty grams (0.17 mole) of the ketone XLVIII was dissolved in an anhydrous mixture of 600 ml. of C.P. benzene and 600 ml. of C.P. ether in a two liter three necked flask equipped with ground glass joints, fitted with a mercury sealed



Hershberg stirrer, a condenser fitted with a drying tube, and a glass stopper. Initially the apparatus had been flame dried and swept with nitrogen. After the addition of 100 g. of amalgamated zinc*, 28 ml. of ethyl α -bromopropionate (Eastman 1041), and a trace of iodine, the mixture was refluxed for two days. An additional 100 g. of amalgamated zinc and 28 ml. of ethyl α -bromopropionate were added after seventeen hours. The dark complex coated the sides of the flask and caked the zinc during the second day. After standing at room temperature for two days the reaction mixture was hydrolyzed with a solution of 20 ml. of concentrated hydrochloric acid in 200 ml. of water. The organic layer was washed with water and sodium bicarbonate solution and dried over anhydrous sodium sulfate. Removal of the benzene-ether mixture under reduced pressure left a light red oil probably a mixture of the β -hydroxy ester LXII and excess ethyl α -bromopropionate. Dehydration of ethyl β -(3-hydroxy-1,2,3,11b-tetrahydro-7H-mesobenzanthrenyl-3)-propionate (LXII) was carried out with 240 ml. of anhydrous formic acid by warming on a steam

*Twenty mesh zinc (Baker's C.P.) was amalgamated by the method described by Kolthoff and Sandell, "Textbook of Quantitative Inorganic Analysis," The Macmillan Co., New York, N.Y., 1948, p. 598. The freshly amalgamated zinc was washed with acetone and benzene and stored under benzene before use.



bath for fifteen minutes. The formic acid was removed under reduced pressure and the remaining oil was refluxed for thirty-two hours with 56 g. of sodium hydroxide in 1400 ml. of water. The alkaline solution was filtered, extracted with a mixture of ether and benzene, and acidified yielding 46.5 g. (96% yield) of crude acidic material as a pink granular solid, m.p. 143-148°. The benzene-ether extracts gave 0.75 g. of recovered crude ketone. Two crystallizations of the crude acid from ethyl acetate afforded 28.0 g. of α -(1,11b-dihydro-7H-mesobenzanthrenyl-3)-propionic acid (LXV), m.p. 151.5-153°. An additional 9.5 g. of the acid LXV, m.p. 148-153°, was obtained from the mother liquors to make the total yield 37.5 g. (77%). Repeated crystallization from ethyl acetate gave an analytical sample as almost colorless crystals, m.p. 151.5-153°.

Anal. Calculated for $C_{20}H_{18}O_2$: C, 82.74; H, 6.25; neutral equivalent, 290. Found: C, 82.34; H, 6.20; neutral equivalent, 287.

The methyl ester of LXV was prepared with diazomethane. Crystallization from methanol gave methyl α -(1,11b-dihydro-7H-mesobenzanthrenyl-3)-propionate as colorless needles, m.p. 91.5-92.5°.

Anal. Calculated for $C_{21}H_{20}O_2$: C, 82.85;



H, 6.62. Found: C, 83.09; H, 6.54.

The mother liquors from the isolation of the acid LXV afforded a second acid (0.65 g.), probably α -(1,2,3,11b-tetrahydro-7H-mesobenzanthrylidene-3)-propionic acid (LXIV), m.p. 173-176°. An analytical sample was obtained, by repeated recrystallization from ethyl acetate, as hard irregular pellets, m.p. 177-178.5°.

Anal. Calculated for $C_{20}H_{18}O_2$: C, 82.74; H, 6.25; neutral equivalent, 290. Found: C, 82.50; H, 6.07; neutral equivalent, 288.

Oxidation Experiments with α -(1,11b-Dihydro-7H-mesobenzanthrenyl-3)-propionic Acid (LXV) and α -(1,2,3,11b-Tetrahydro-7H-mesobenzanthrylidene-3)-propionic Acid (LXIV). To a solution of 1.07 g. (0.0037 mole) of α -(1,11b-dihydro-7H-mesobenzanthrenyl-3)-propionic acid (LXV) in 110 ml. of 0.05 N sodium hydroxide which was cooled to 0° and covered with a layer of 25 ml. of benzene, a solution of 1.1 g. (0.007 mole) of potassium permanganate in 125 ml. of water was added over a period of three-quarters of an hour with stirring. After three hours at 0° the solution was filtered and the layers were separated. Acidification of the aqueous layer yielded intractable acidic material. The benzene layer did not contain any neutral material.

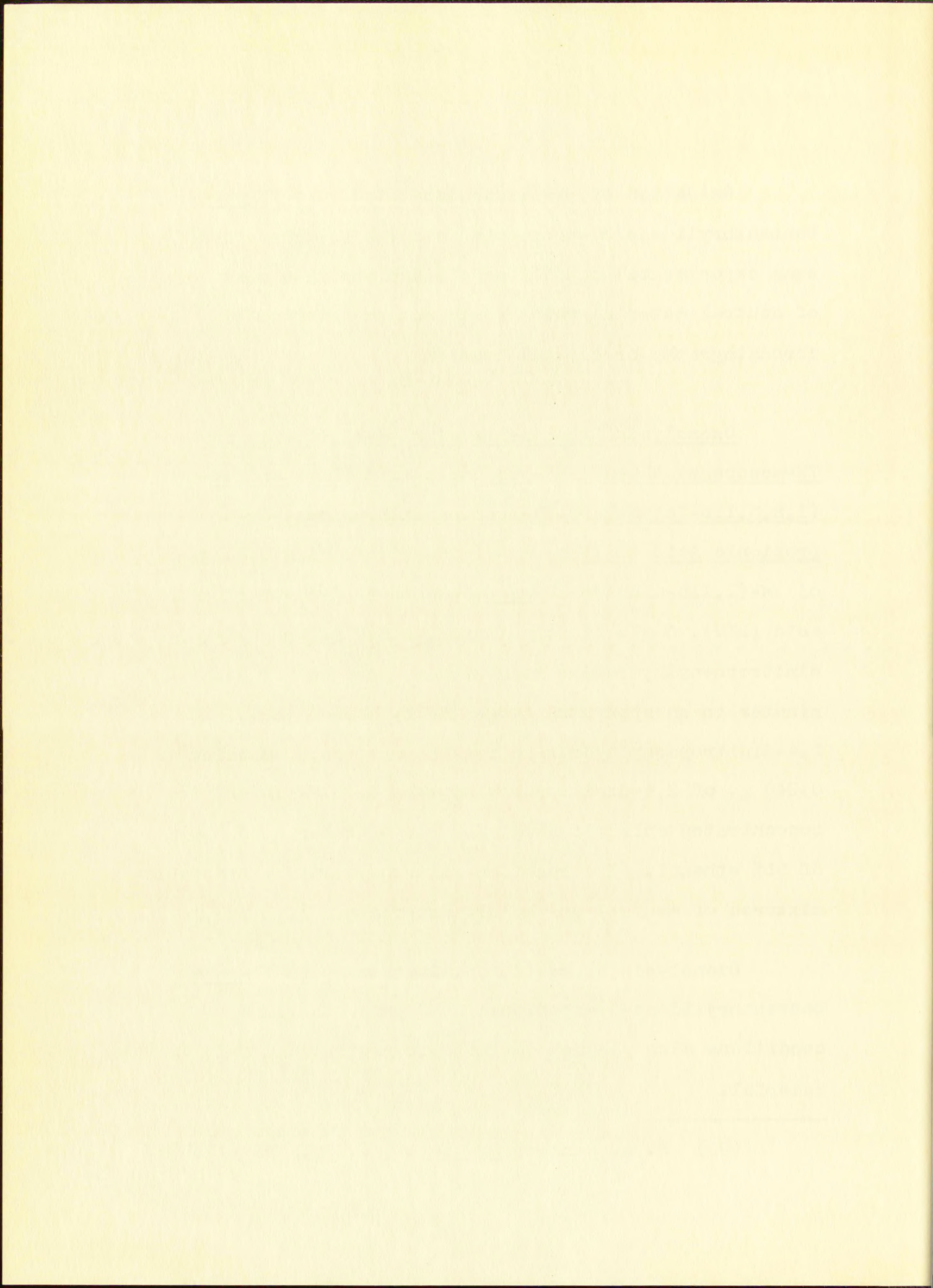


Oxidation of α -(1,2,3,11b-tetrahydro-7H-meso-benzanthrylidene-3)-propionic acid (LXIV) under the same experimental conditions yielded mostly a mixture of neutral material which could not be resolved by chromatography or crystallization.

Ozonolysis Experiments with α -(1,11b-Dihydro-7H-mesobenzanthrenyl-3)-propionic Acid (LXV) and α -(1,2,3,11b-Tetrahydro-7H-mesobenzanthrylidene-3)-propionic Acid (LXIV). A solution containing 0.15 g. of α -(1,11b-dihydro-7H-mesobenzanthrenyl-3)-propionic acid (LXV), 5 ml. of 95% ethanol, and 9 ml. of 2,4-dinitrophenylhydrazine reagent was ozonized for eight minutes in an apparatus suggested by Bonner (22). The 2,4-dinitrophenylhydrazine reagent was prepared using 0.240 g. of 2,4-dinitrophenylhydrazine, 1.2 ml. of concentrated sulfuric acid, 1.8 ml. of water, and 6.0 ml. of 95% ethanol. The reaction mixture yielded intractable mixtures of neutral and acidic materials.

Ozonolysis of α -(1,2,3,11b-tetrahydro-7H-meso-benzanthrylidene-3)-propionic acid under the same conditions also yielded intractable neutral and acidic material.

(22) W. A. Bonner, J. Chem. Ed., 30, 452 (1953).



Ultraviolet Absorption Spectra of α -(1,11b-Dihydro-7H-mesobenzanthrenyl-3)-propionic Acid (LXV) and α -(1,2,3,11b-Tetrahydro-7H-mesobenzanthrylidene-3)-propionic Acid (LXIV). The ultraviolet absorption spectra of the acids LXV and LXIV (see Fig. 1, p. 24) in 95% ethanol were measured with a Model DU Beckman spectrophotometer. Maxima and ($\log \epsilon$) values are: α -(1,11b-dihydro-7H-mesobenzanthrenyl-3)-propionic acid (LXV), 265 m μ (3.90); α -(1,2,3,11b-tetrahydro-7H-mesobenzanthrylidene-3)-propionic acid (LXIV), 259 m μ (3.95), 334 m μ (3.68), and 349 m μ (3.60).

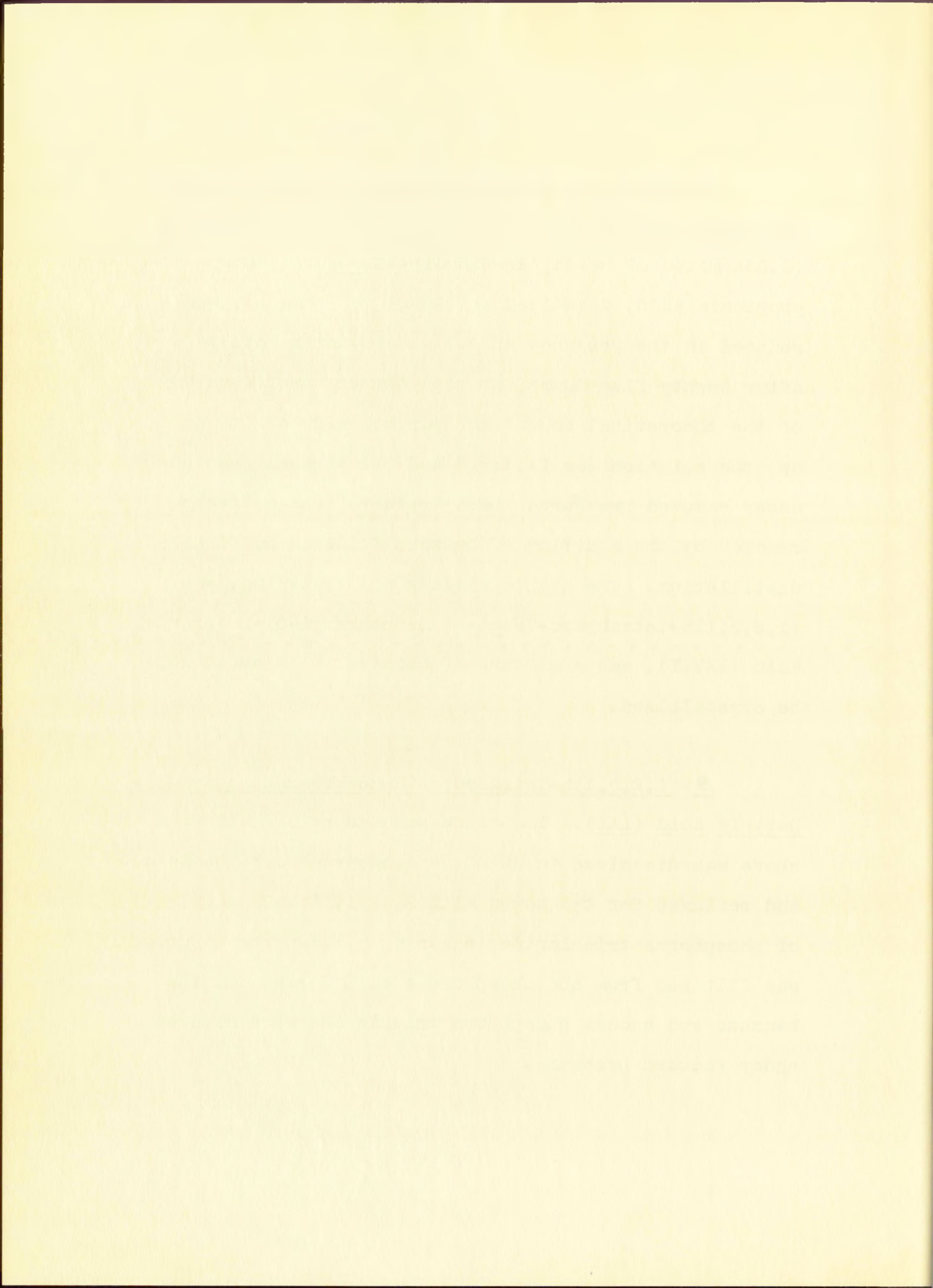
Hydrolysis of Ethyl α -(3-Hydroxy-1,2,3,11b-tetrahydro-7H-mesobenzanthrenyl-3)-propionate (LXII). In an early experiment alkaline hydrolysis of the crude oil obtained from the Reformatsky reaction yielded about 70% of the starting ketone XLVIII and a small quantity of the hydroxy acid LXIII. Trituration of the darkly colored crude acid with ether and crystallization from ethyl acetate using norit yielded needles of α -(3-hydroxy-1,2,3,11b-tetrahydro-7H-meso-benzanthrenyl-3)-propionic acid (LXIII), m.p. 188-188.5 $^{\circ}$.

Neutral equivalent: Calculated for C₂₀H₂₀O₃, 308. Found: 304.



α -(1,2,3,11b-Tetrahydro-7H-mesobenzanthrenyl-3)-propionic Acid (LXVII). At atmospheric pressure, 10.15 g. (0.035 mole) of α -(1,11b-dihydro-7H-mesobenzanthrenyl-3)-propionic acid, dissolved in 125 ml. of ethanol, was reduced in the presence of 0.1 g. of Adam's catalyst. After twenty-five hours, at room temperature, when 90% of the theoretical amount of hydrogen had been taken up, the solution was filtered and the ethanol removed under reduced pressure. Last traces of ethanol were removed by the addition of benzene followed by further distillation. The highly viscous oil remaining, α -(1,2,3,11b-tetrahydro-7H-mesobenzanthrenyl-3)-propionic acid (LXVII), was a mixture of isomers which could not be crystallized.

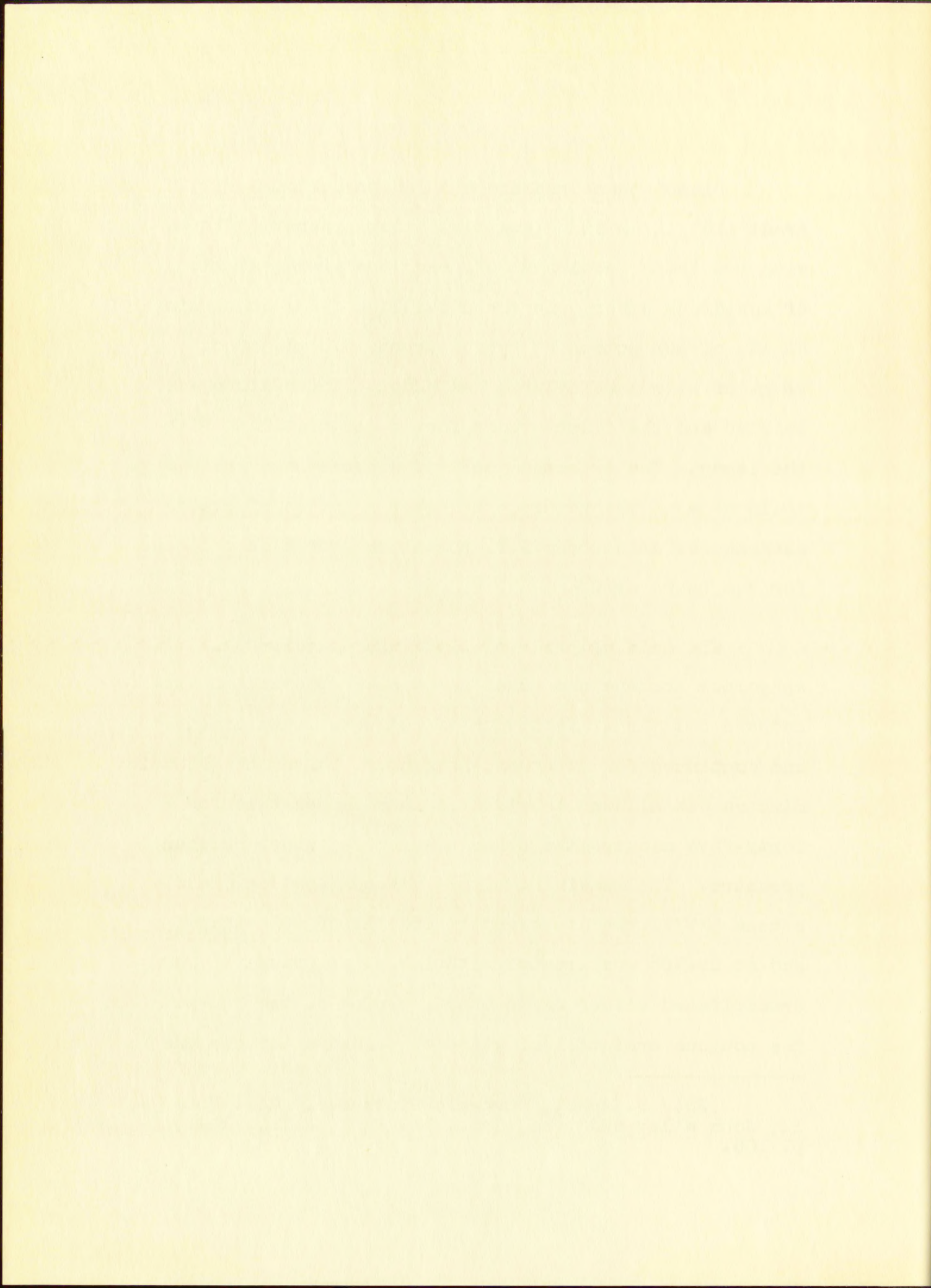
β -(1,2,3,11b-Tetrahydro-7H-mesobenzanthrenyl-3)-butyric Acid (LXX). The crude reduced acid LXVII from above was dissolved in 85 ml. of anhydrous C.P. benzene and refluxed for two hours with 2.2 ml. (0.025 mole) of phosphorus trichloride (Baker's, C.P.). The solution was filtered from the phosphorous acid formed and the benzene and excess phosphorus trichloride were removed under reduced pressure.



Diazomethane was prepared as described by Arndt (23) in an all glass distilling apparatus fitted with two traps, cooled to 0° , each containing 45 ml. of anhydrous ether. To the distilling flask containing 80 ml. of 50% potassium hydroxide and 270 ml. of ether, 25 g. of nitrosomethylurea was added. The mixture was swirled and the diazomethane formed was distilled with the ether. The expected yield of diazomethane was 6.5 g. (0.15 mole). Before use, the ether solution of diazomethane was dried over C.P. potassium hydroxide pellets for two hours at 0° .

The acid chloride of LXVII was dissolved in C.P. anhydrous benzene and added dropwise to the cold diazomethane solution. Evolution of nitrogen began immediately and continued for about one-half hour. After the reaction mixture was allowed to stand at room temperature for forty-five minutes the ether was removed under reduced pressure. The remaining highly viscous, yellow diazoketone LXVIII was dissolved in 150 ml. of 95% ethanol and at $65-70^{\circ}$ was treated with 1.5 g. of freshly precipitated silver oxide over a period of two hours. The copious evolution of nitrogen ceased after one and

(23) F. Arndt, "Organic Syntheses," Col. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 165.



three-quarter hours. The resulting ethanol solution of ethyl β -(1,2,3,11b-tetrahydro-7H-mesobenzanthrenyl-3)-butyrate (LXIX) was treated with norit and passed through an alumina column. The ethanol was removed under reduced pressure and the red oily ester was refluxed for one hour with 175 ml. of 5% sodium hydroxide solution. After one-half hour the insoluble sodium salt precipitated as a gummy mass. The salt was dissolved in hot water and acidification yielded a red oil which was taken up in ether and treated with norit. The ether solution was dried over anhydrous sodium sulfate and removal of the solvent yielded 8.4 g. (78% yield from LXV) of β -(1,2,3,11b-tetrahydro-7H-mesobenzanthrenyl-3)-butyric acid (LXX) as a light red oil.

8-Keto-10-methyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (LXXI). Cyclization of 2.6 g. (0.0090 mole) of crude β -(1,2,3,11b-tetrahydro-7H-mesobenzanthrenyl-3)-butyric acid (LXX) was accomplished with 30 ml. of anhydrous hydrogen fluoride. Chromatographing through an alumina column and concentration of the benzene eluents yielded 2.0 g. (82%) of 8-keto-10-methyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (LXXI) as a light yellow oil. Trituration of this oil with ether gave a solid which was crystallized from



methanol giving the ketone LXXI as a mixture of isomers, m.p. 140-155°.

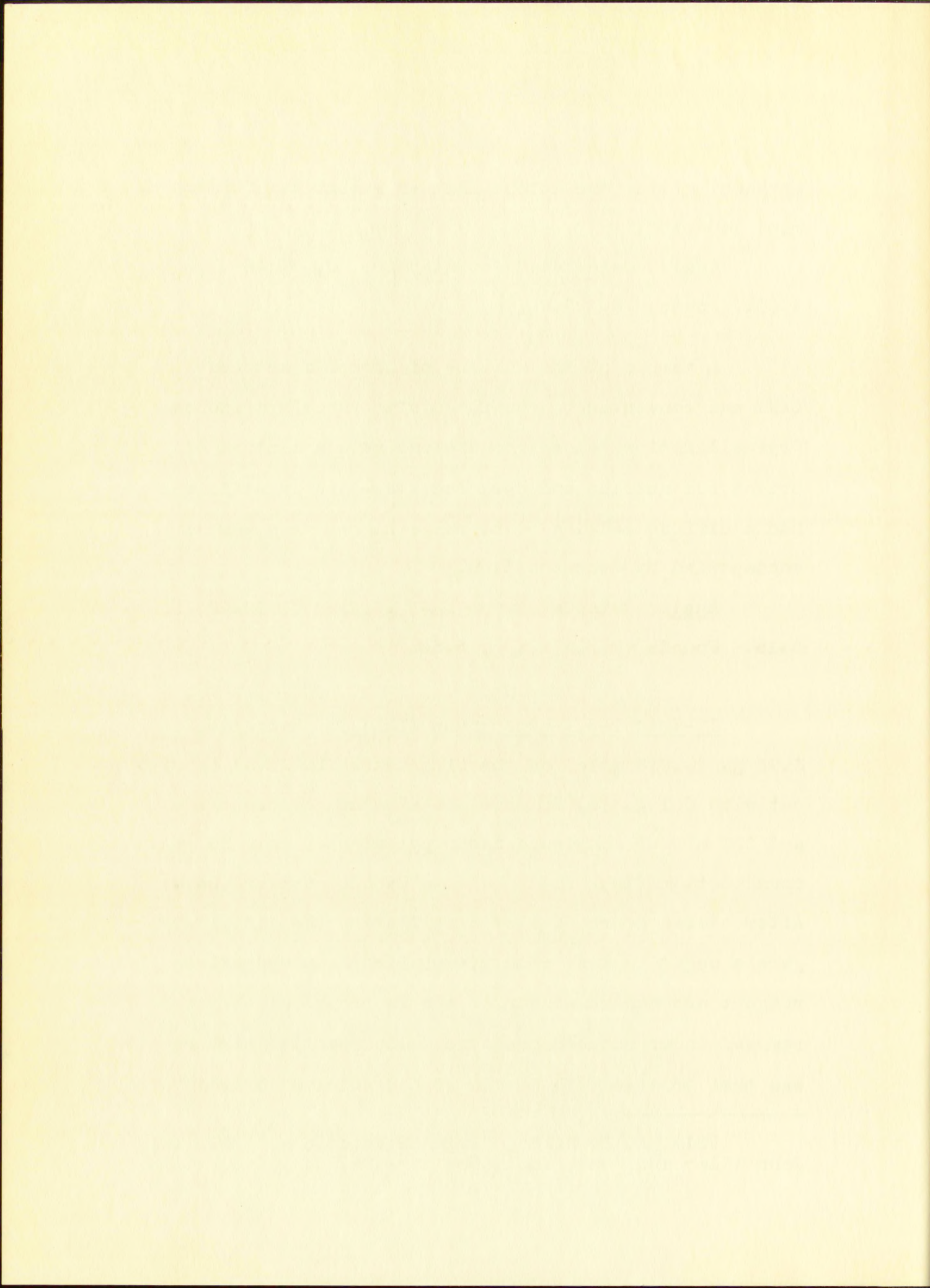
Anal. Calculated for $C_{21}H_{20}O$: C, 87.45; H, 6.99. Found: C, 87.28; H, 7.01.

A sample of the mixture of isomeric ketones LXXI was converted to the 2,4-dinitrophenylhydrazones. Crystallization twice from acetone gave a mixture of bright red needles and dark red star-like crystals which had a diffuse melting point range higher than 220° accompanied by decomposition.

Anal. Calculated for $C_{27}H_{24}O_4N_4$: C, 69.22; H, 5.16. Found: C, 69.22; H, 5.35.

10-Methyl-3,4-benzpyrene (LXXII). Reduction of 3.75 g. (0.013 mole) of the oily ketone LXXI was carried out with 6.1 g. (0.038 mole) of aluminum isopropoxide and 150 ml. of anhydrous isopropyl alcohol in a 250 ml. round bottom flask fitted with a Hahn condenser (24). After eleven hours of slow distillation the distillate gave a negative test with 2,4-dinitrophenylhydrazine reagent and the remainder of the isopropyl alcohol was removed under reduced pressure. The reaction mixture was then treated with 20 ml. of concentrated hydrochloric

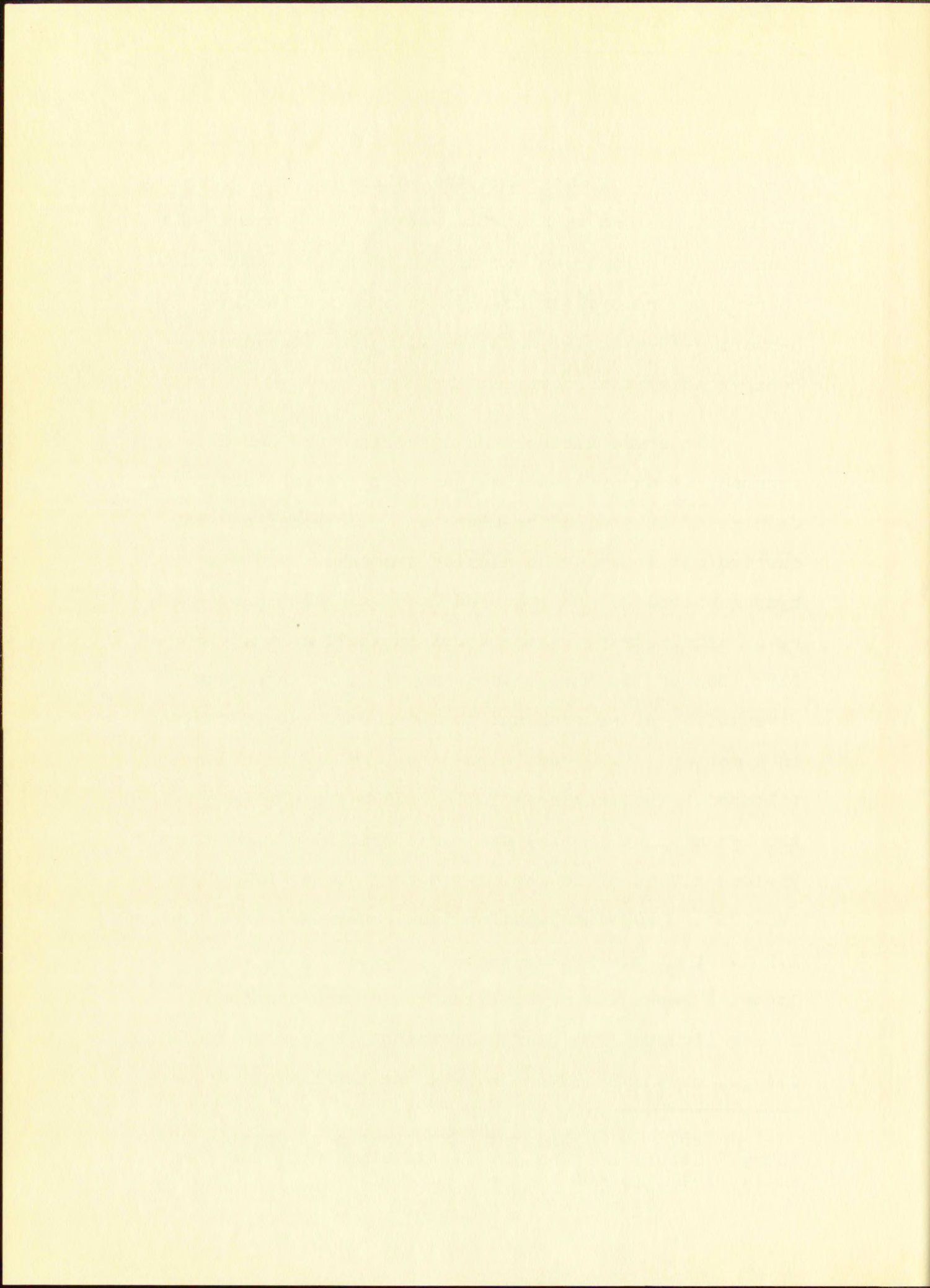
(24) A. L. Wilds, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N.Y., 1944, p. 178.



acid in 80 ml. of water and the yellow oil was taken up in benzene and washed with water. The benzene solution was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure leaving 8-hydroxy-10-methyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene as a viscous oil.

The crude alcohol was dehydrated and dehydrogenated, in an apparatus suggested by Fieser (25), over 0.38 g. of 10% palladium-charcoal. The reaction was carried out in a carbon dioxide atmosphere and the hydrogen evolved was measured in a gas buret protected by an alkali trap. After about one-half hour at 280-315°, 55% of the theoretical amount of hydrogen was given off. After cooling, the hard cake was pulverized in a mortar, dissolved in benzene, and the solution filtered. The benzene solution was twice chromatographed through alumina (Merck) and concentration of the eluents yielded 1.7 g. of 10-methyl-3,4-benzpyrene (LXXII), m.p. 170-175°. Recrystallization from benzene-ethanol yielded 1.2 g. of minute yellow needles, m.p. 177-178°. Chromatography and crystallization of the combined mother liquors from benzene-methanol yielded an additional 0.4 g., m.p. 178-178.5°, making the total yield of

(25) L. F. Fieser, "Experiments in Organic Chemistry," Second Edition, D. C. Heath and Co., New York, N. Y., 1941, p. 462.



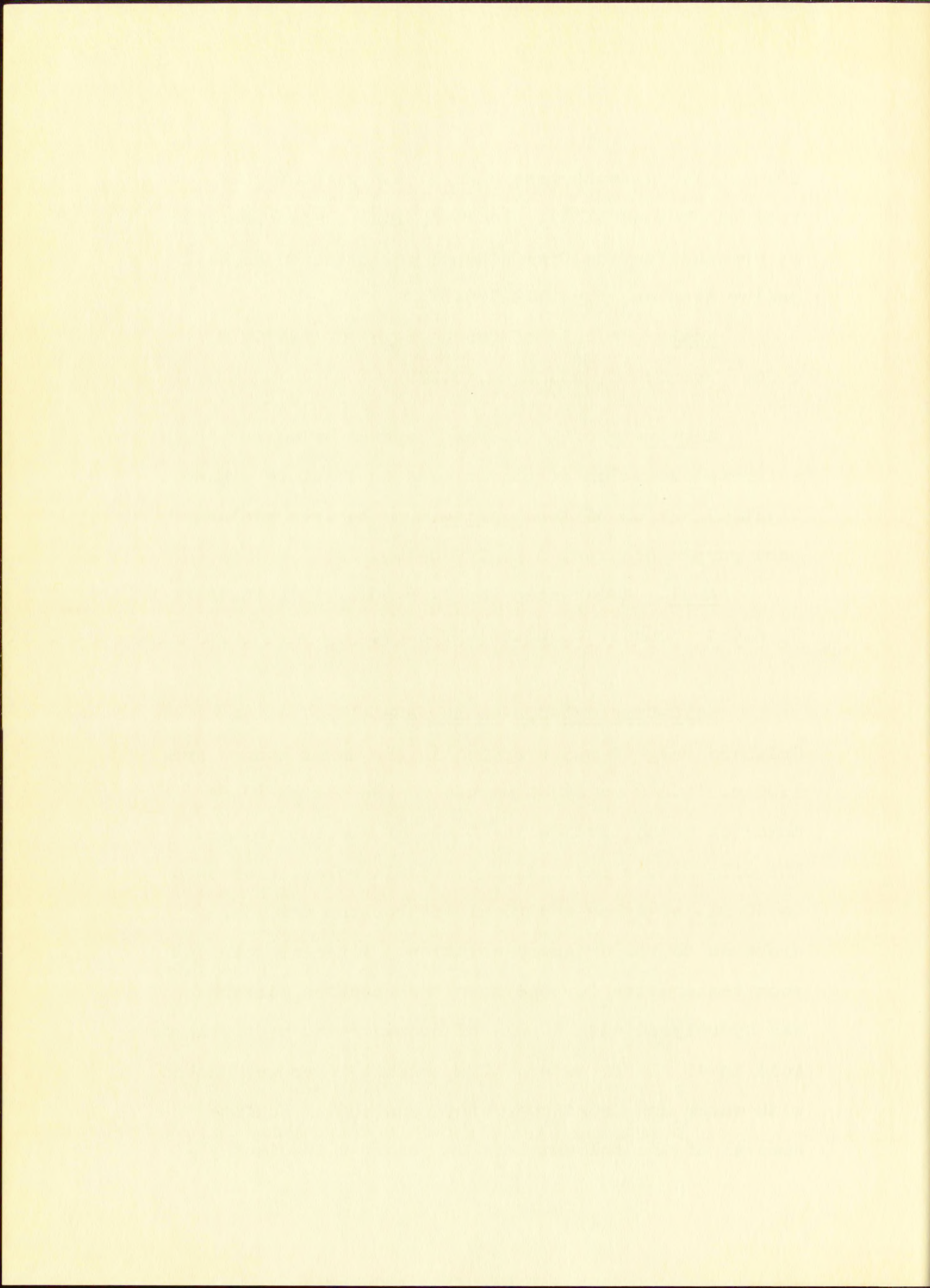
10-methyl-3,4-benzpyrene (LXXII) 1.6 g. (46% yield from the ketone LXXI). An analytical sample prepared by crystallization from ethanol was obtained as small yellow needles, m.p. 178-178.5°.

Anal. Calculated for $C_{21}H_{14}$: C, 94.70; H, 5.30. Found: C, 94.75; H, 5.23.

A picrate of LXXII was prepared using a saturated solution of picric acid in absolute ethanol. Crystallization of the picrate from benzene yielded dark purple needles, m.p. 179.5-180.5°.

Anal. Calculated for $C_{27}H_{17}O_7N_3$: C, 65.45; H, 3.46. Found: C, 65.41; H, 3.09.

8,10-Dimethyl-3,4-benzpyrene (LXXIII). A Grignard reagent was prepared in the usual manner from 1.02 g. (0.042 mole) of magnesium and 6.4 g. (0.045 mole) of methyl iodide in 40 ml. of absolute ether. The oily ketone LXXI, 4.05 g. (0.014 mole), dissolved in 30 ml. of ether and 20 ml. of benzene was added dropwise to the Grignard solution. After standing at room temperature for one hour the reaction mixture was hydrolyzed with 10 ml. of concentrated hydrochloric acid in 40 ml. of water. The organic layer was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent left 8-hydroxy-8,10-dimethyl-

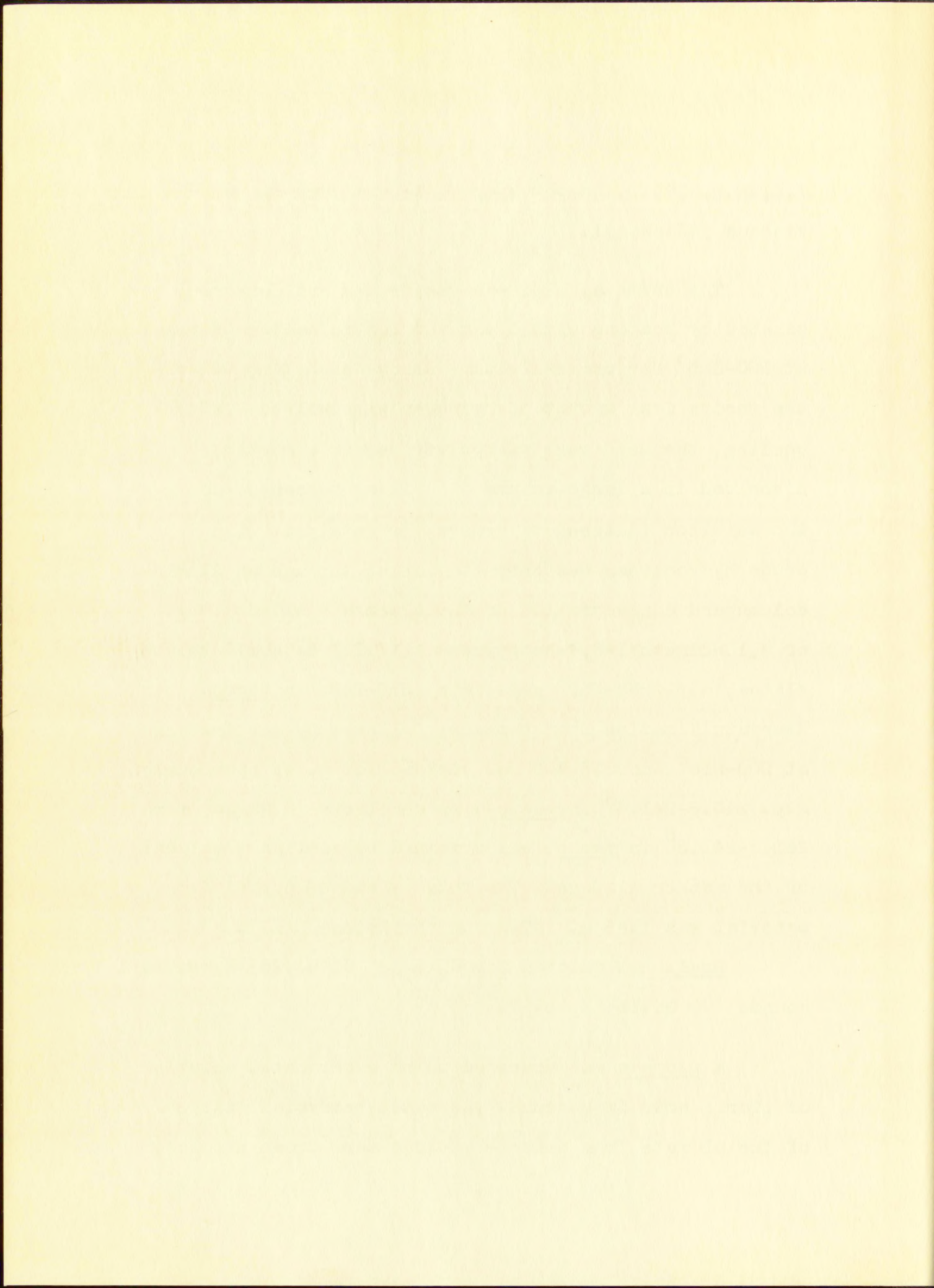


1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene as a viscous yellow oil.

The crude alcohol was dehydrated and dehydrogenated by heating with 0.4 g. of 10% palladium-charcoal at 300-325° for one-half hour during which time 60% of the theoretical amount of hydrogen was evolved. After cooling, the hard cake was pulverized in a mortar, dissolved in a large volume of boiling benzene, and the solution filtered to remove the catalyst. The crude hydrocarbon was chromatographed through an alumina column and concentration of the eluents yielded 1.8 g. of 8,10-dimethyl-3,4-benzpyrene (LXXIII) as small yellow plates, m.p. 235-238° dec., m.p. 238-240° in vacuo. Recrystallization from benzene followed by sublimation at 200-210° and 0.5-1.0 mm. yielded 1.2 g. of hydrocarbon, m.p. 240.5-241.5° in vacuo. An additional 0.25 g., m.p. 240.5-241.5° in vacuo, was obtained by similar treatment of the mother liquors. The total yield of purified material was 1.45 g. (37% from the ketone LXXI).

Anal. Calculated for $C_{22}H_{16}$: C, 94.25; H, 5.75.
Found: C, 94.15; H, 5.67.

A picrate was prepared using a saturated solution of picric acid in benzene. Repeated recrystallization of the picrate from benzene yielded dark brown needles,



m.p. 202.5-203.5°. Analysis did not give the expected values due to contamination of the picrate samples with the highly insoluble hydrocarbon.

Ultraviolet Absorption Spectra of 10-Methyl-3,4-benzpyrene (LXXII) and 8,10-Dimethyl-3,4-benzpyrene (LXXIII). The ultraviolet absorption spectra of 10-methyl- and 8,10-dimethyl-3,4-benzpyrene (see Fig. 2, p. 30) in 95% ethanol were measured with a Model DU Beckman spectrophotometer. Maxima and ($\log \epsilon$) values are: 10-methyl-3,4-benzpyrene (LXXII), 256 m μ (4.62), 266 m μ (4.69), 286 m μ (4.58), 297 m μ (4.64), 369 m μ (4.36), and 387 m μ (4.40); 8,10-dimethyl-3,4-benzpyrene (LXXIII), 257 m μ (4.68), 268 m μ (4.70), 290 m μ (4.62), 304 m μ (4.69), 376 m μ (4.39), and 392 m μ (4.42).

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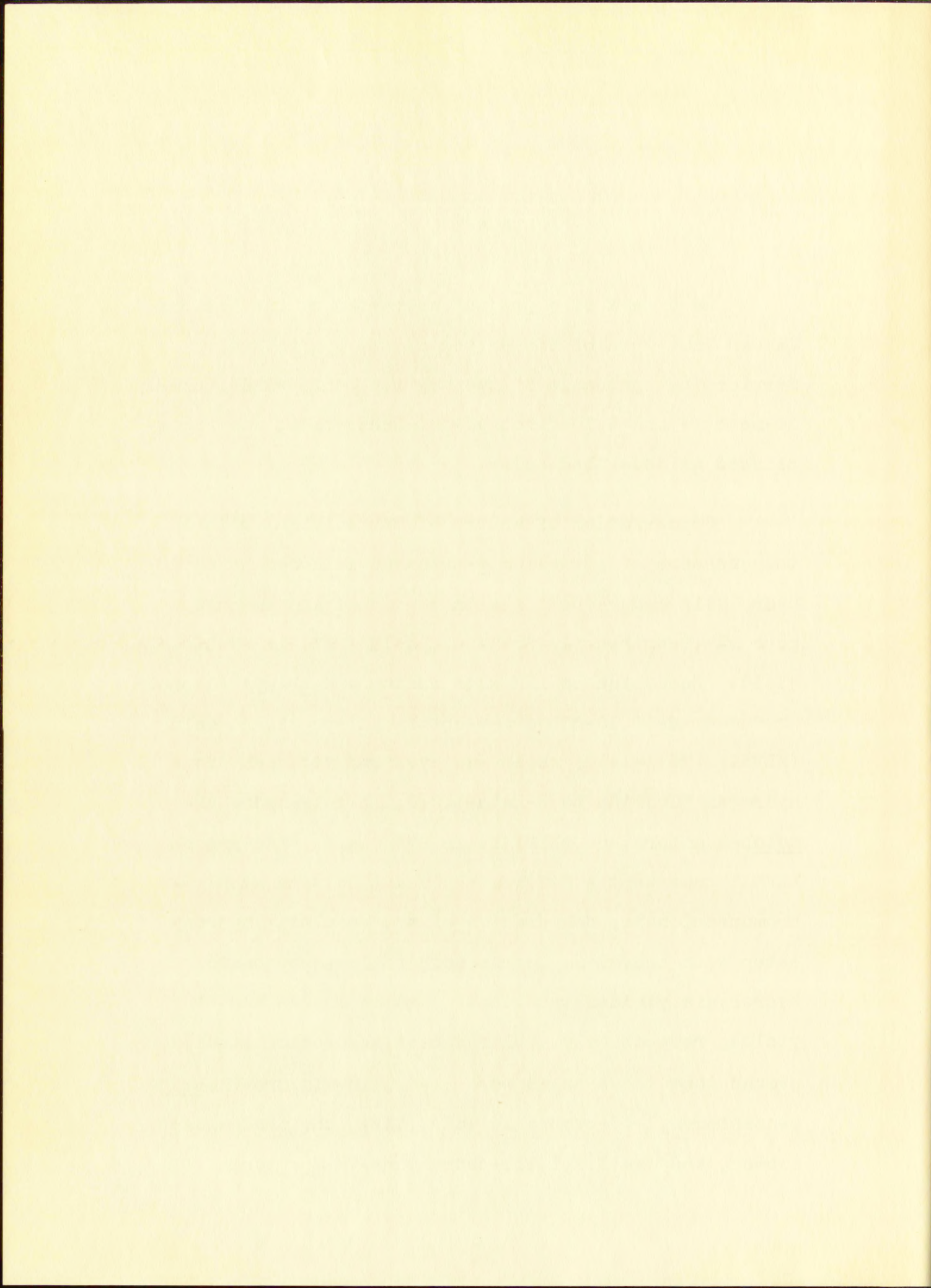
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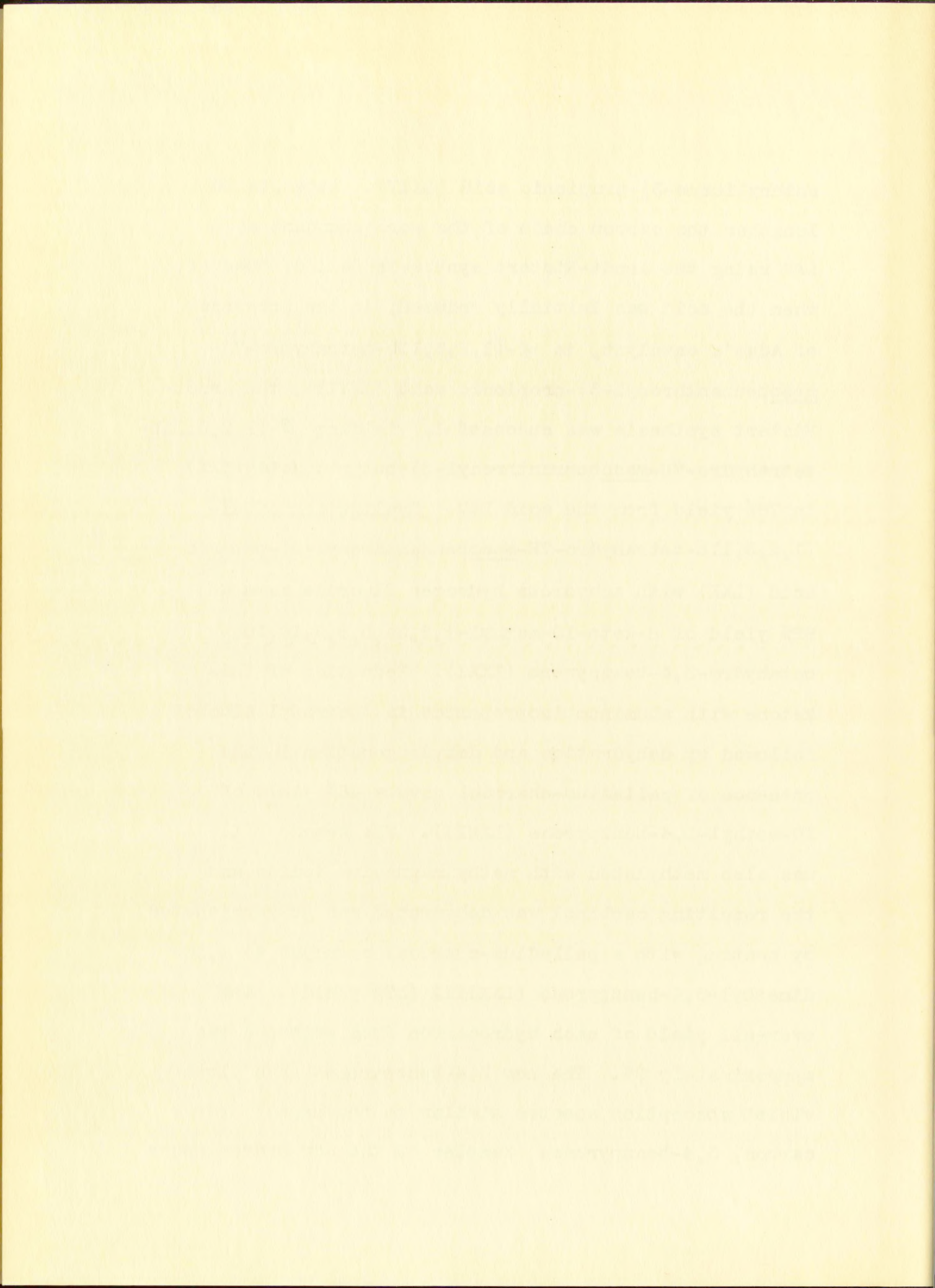
SUMMARY

As a part of a project supported by the National Cancer Institute of the United States Public Health Service the synthesis of two new 3,4-benzpyrenes, namely 10-methyl- and 8,10-dimethyl-3,4-benzpyrene, was accomplished as described below.

Condensation of anthrone with acrylonitrile in the presence of potassium t-butoxide followed by acid hydrolysis and reduction with zinc dust and ammonia gave β -(9-anthranyl)-propionic acid (LXI) in 87.5% yield. Reduction of LXI with sodium and n-amyl alcohol produced β -(9,10-dihydro-9-anthranyl)-propionic acid (XLVII) (76% yield) which was cyclized with anhydrous hydrogen fluoride to 3-keto-1,2,3,11b-tetrahydro-7H-mesobenzanthracene (XLVIII) in 87% yield. The ketone XLVIII underwent a Reformatsky reaction with ethyl α -bromopropionate; dehydration of the resulting hydroxy ester with anhydrous formic acid followed by basic hydrolysis yielded two isomeric acids in 77% and 2% yields, respectively. Ultraviolet absorption studies proved that these acids were α -(1,11b-dihydro-7H-meso-benzanthrenyl-3)-propionic acid (LXV), the predominant isomer, and α -(1,2,3,11b-tetrahydro-7H-mesobenz-



anthrylidene-3)-propionic acid (LXIV). Attempts to lengthen the carbon chain of the more abundant acid LXV using the Arndt-Eistert synthesis failed; however, when the acid was initially reduced, in the presence of Adam's catalyst, to α -(1,2,3,11b-tetrahydro-7H-mesobenzanthrenyl-3)-propionic acid (LXVII), the Arndt-Eistert synthesis was successful, yielding β -(1,2,3,11b-tetrahydro-7H-mesobenzanthrenyl-3)-butyric acid (LXX) in 78% yield from the acid LXV. Cyclization of β -(1,2,3,11b-tetrahydro-7H-mesobenzanthrenyl-3)-butyric acid (LXX) with anhydrous hydrogen fluoride gave an 82% yield of 8-keto-10-methyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (LXXI). Reduction of this ketone with aluminum isopropoxide in isopropyl alcohol followed by dehydration and dehydrogenation in the presence of palladium-charcoal gave a 46% yield of 10-methyl-3,4-benzpyrene (LXXII). The ketone LXXI was also methylated with methylmagnesium iodide and the resulting carbinol was dehydrated and dehydrogenated by heating with a palladium-charcoal catalyst to 8,10-dimethyl-3,4-benzpyrene (LXXIII) (37% yield). The over-all yield of each hydrocarbon from anthrone was approximately 9%. The new 3,4-benzpyrenes gave ultra-violet absorption spectra similar to the parent hydrocarbon, 3,4-benzpyrene. Samples of the new hydrocarbons



have been sent to the Northwestern University Medical School where their carcinogenic activity will be measured.



BIBLIOGRAPHY

- (23) F. Arndt, "Organic Syntheses," Col. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 165.
- (5) W. E. Bachmann and M. Carmack, J. Am. Chem. Soc., 63, 2494 (1941).
- (4) W. E. Bachmann, M. Carmack, and S. R. Safir, J. Am. Chem. Soc., 63, 1682 (1941).
- (17) W. E. Bachmann and W. S. Struve, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 38.
- (22) W. A. Bonner, J. Chem. Ed., 30, 452 (1953).
- (1) J. W. Cook, C. L. Hewett, and I. Hieger, J. Chem. Soc., 1933, 395.
- (11) J. W. Cook, R. S. Ludwiczak, and R. Schoental, J. Chem. Soc., 1950, 1112.
- (15) G. H. Daub and W. C. Doyle, J. Am. Chem. Soc., 74, 4449 (1952).
- (14) W. F. Dunning and M. R. Curtis, Am. J. Cancer, 38, 516 (1940).
- (25) L. F. Fieser, "Experiments in Organic Chemistry," Second Edition, D. C. Heath and Co., New York, N. Y., 1941, p. 462.
- (3) L. F. Fieser and M. Fieser, J. Am. Chem. Soc., 57, 782 (1935).
- (7) L. F. Fieser and E. B. Hershberg, J. Am. Chem. Soc., 60, 1658 (1938).
- (10) L. F. Fieser and E. B. Hershberg, J. Am. Chem. Soc., 60, 2542 (1938).
- (8) L. F. Fieser and H. Heymann, J. Am. Chem. Soc., 63, 2333 (1941).



(12) L. F. Fieser and F. C. Novello, J. Am. Chem. Soc., 62, 1855 (1940).

(20) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, No. 554.

(13) J. L. Hartwell, "Survey of Compounds Which Have Been Tested for Carcinogenic Activity," P. H. S. Pub. No. 149, U. S. Gov. Printing Office, Washington, D. C., 1951, p. 1.

(6) G. A. R. Kon and E. M. F. Roe, J. Chem. Soc., 1945, 143.

(21) K. H. Meyer, "Organic Syntheses," Col. Vol. I, John Wiley and Sons, Inc., New York, N. Y. 1941, p. 60.

(18) M. S. Newman and A. S. Hussey, J. Am. Chem. Soc., 69, 3023 (1947).

(9) J. W. Patton, "Masters Thesis," University of New Mexico, 1954.

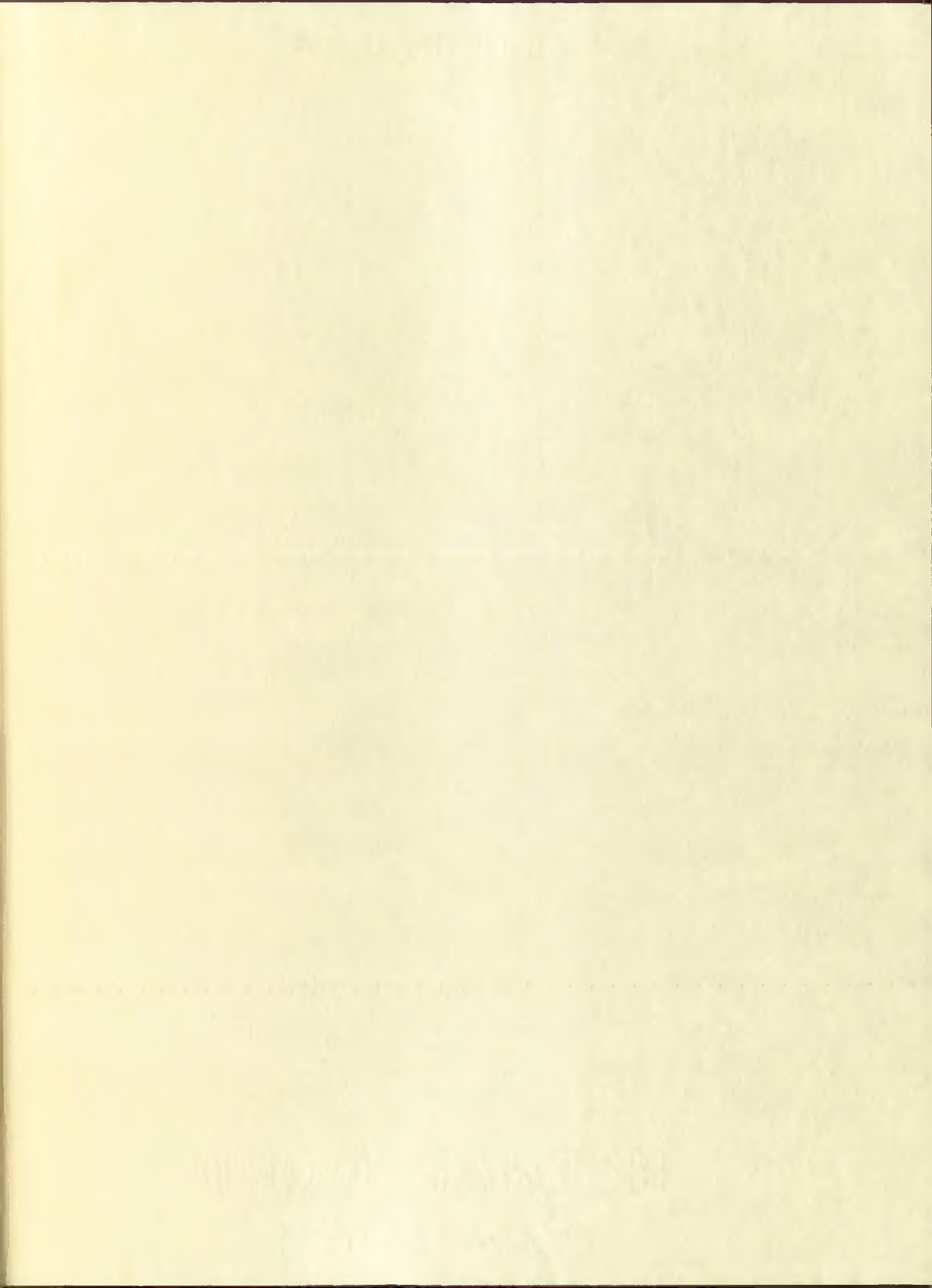
(16) R. L. Shriner, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 1.

(24) A. L. Wilds, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 178.

(19) A. L. Wilds and A. L. Meader, J. Org. Chem., 13, 763 (1948).

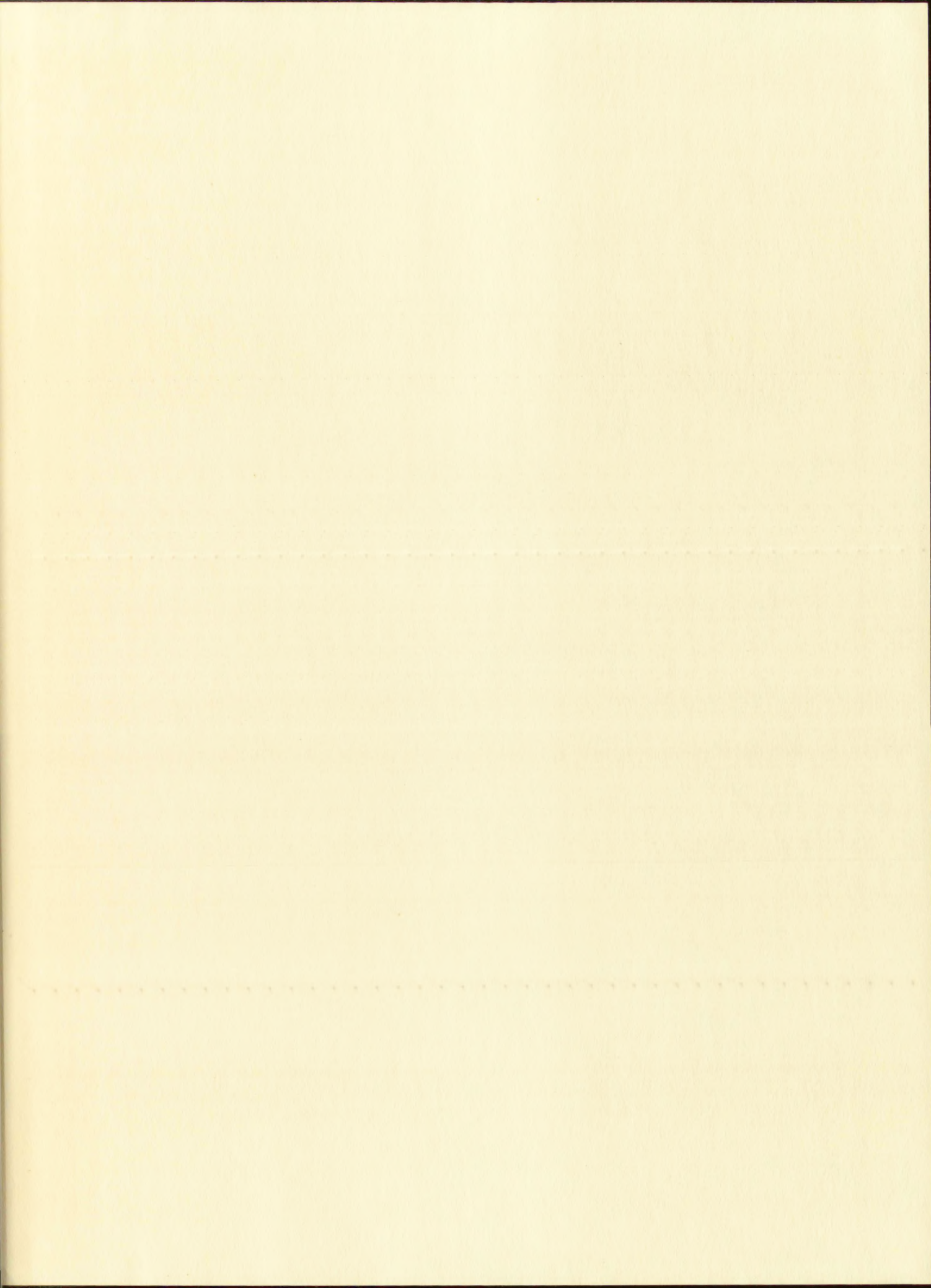
(2) A. Winterstein, H. Vetter, and K. Schon, Ber., 68B, 1079 (1935).

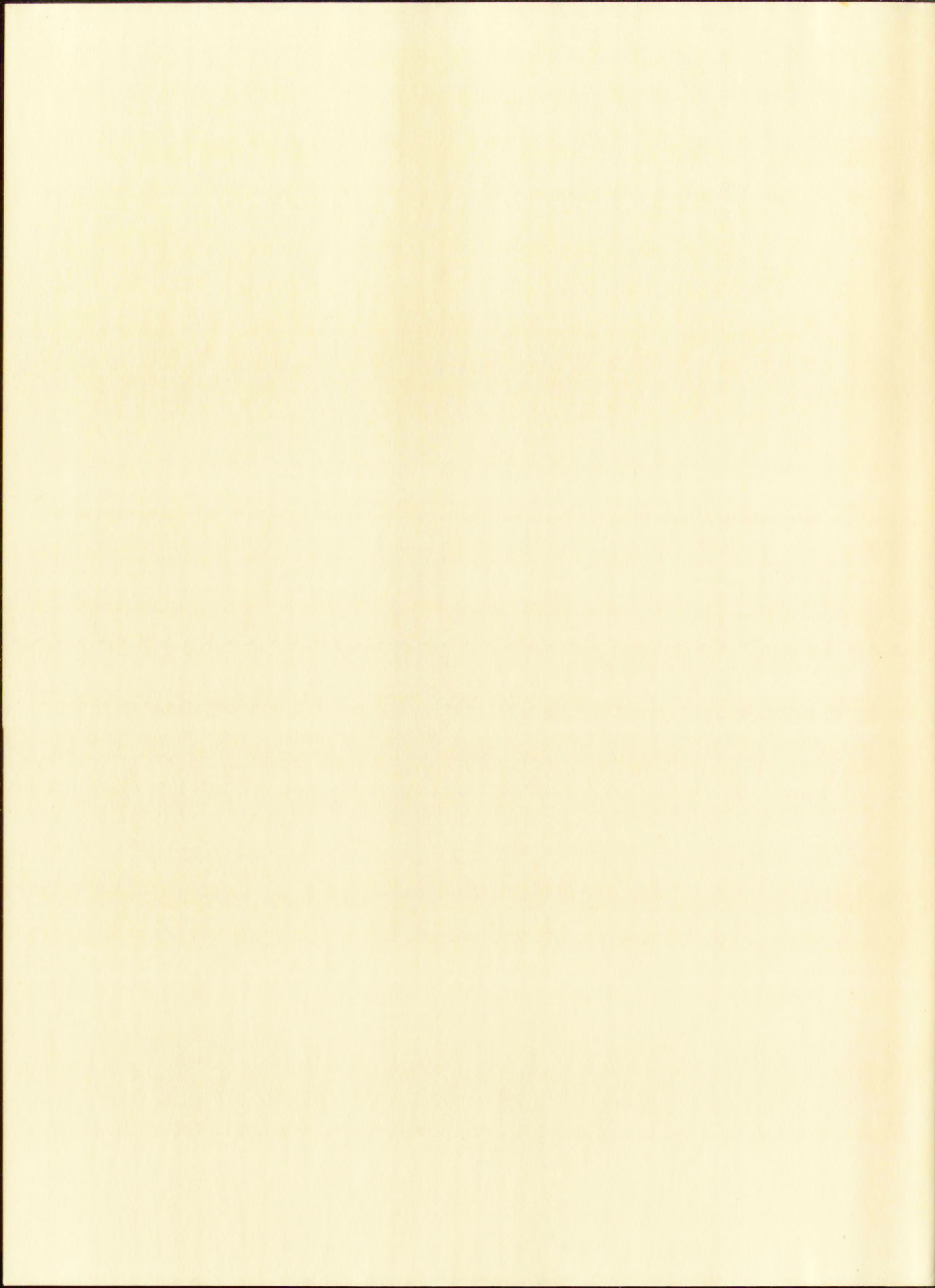




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