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A NEW PREPARATION OF CYCLOPENTANONES

by

KENT KAISER

B.A. Montana State University, 1964

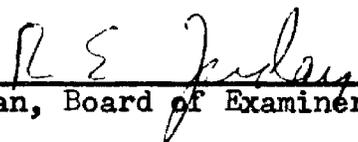
Presented in partial fulfillment of the requirements for the degree of

Master of Science

UNIVERSITY OF MONTANA

1965

Approved by:


Chairman, Board of Examiners


Dean, Graduate School

AUG 20 1965

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ACKNOWLEDGMENTS

I wish to express my gratitude to Professor Richard E. Juday for his guidance throughout this project.

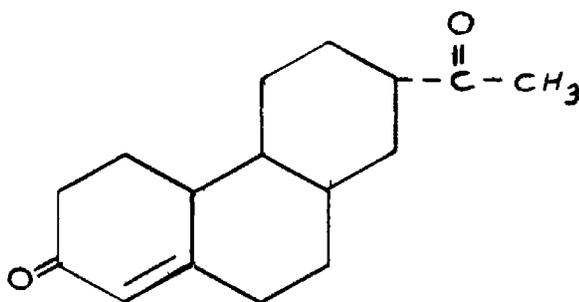
This project was supported by a research grant (CA-05077) from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

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INTRODUCTION

The purpose of this investigation was to find an improved synthesis of compounds containing fused cyclopentenone and cyclopentanone ring systems. This would also serve as important intermediates in the preparation of steroid analogs and as a model synthesis for the preparation of steroids. The final products could then be tested for steroid hormone activity and hormone antagonistic activity. It has been recently established that hormones which control growth are closely related to the cancer problem. Hormonal control of cancer is contingent on two principles. First, cancer cells differ only slightly from normal cells in some respects. Therefore, withdrawal of hormonal support to cells which have a high rate of dependency on hormones for metabolic activity will result in atrophy. This applies equally to the normal as well as the cancerous cell. Secondly, the hormonal function can be operating at normal or even subnormal levels and still sustain the cancer. At present, no satisfactory evidence exists to prove that antitumor effects can be generally dissociated from androgenic or estrogenic activity of the steroid. However, a few compounds have been found that inhibit the action of cancerous growth. In this regard, the phenanthrene derivative,



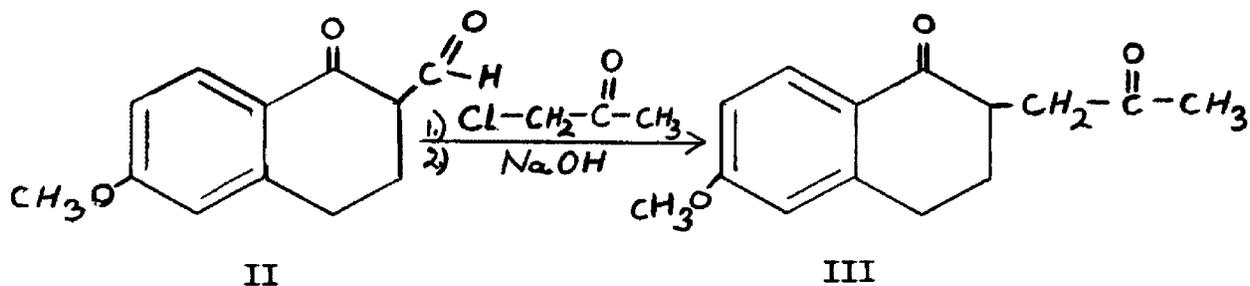
I

I, has been found to inhibit acanthoses and mitotic activation. This compound is of special interest, since it differs from the one to be synthesized only by the contraction of the six membered ring C to a five membered ring.

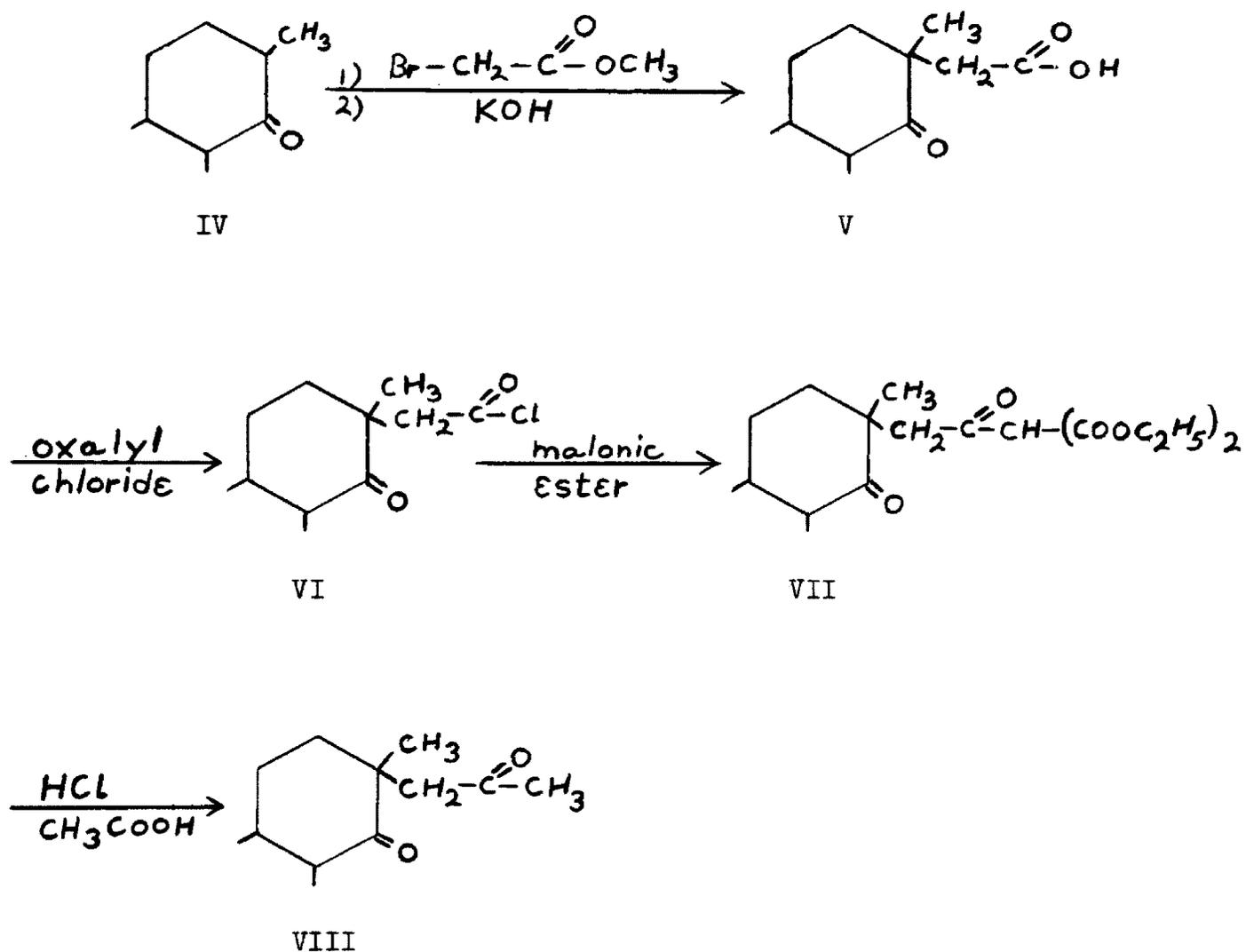
HISTORY

The simplest method of preparing the desired compounds is by the aldol condensation of the corresponding 1,4-diketone. For a number of compounds this is a simple procedure and gives good yields. By starting with a suitably substituted 1,4-diketone, compounds containing angular alkyl groups can also be made by this method. Several routes have been used to prepare the 1,4-diketone.

The oldest method is the preparation of the diketone by the alkylation of a beta ketoester with bromo- or chloroacetone. (1-4). However, the yields were usually low. In our experience, the alkylation of compound II with chloroacetone produced III in about a 30% yield.

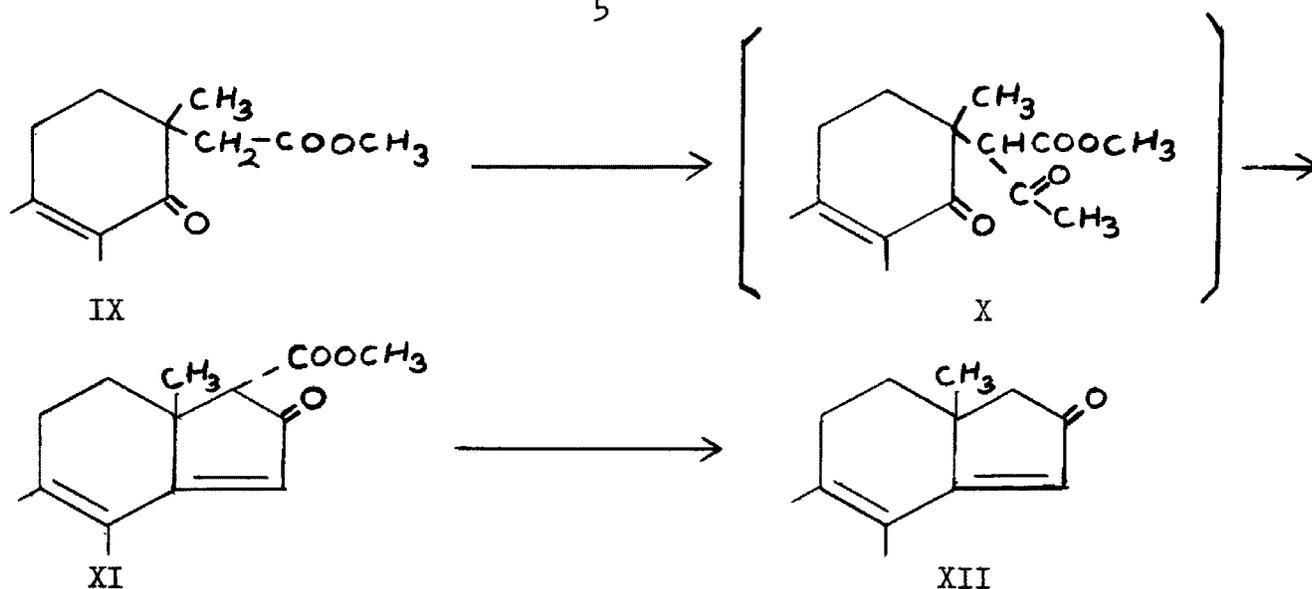


Another method, illustrated by conversion of IV to VIII, was the alkylation of a ketone with bromoacetic acid, chloroacetic acid, or methyl bromoacetate to give a gamma ketoacid or ester. (5-9). The acid was then converted to acid chloride by treatment with thionyl or oxalyl chloride. This was then converted to the methyl ketone by condensing it with sodiomalonic ester followed by hydrolysis and decarboxylation with hydrochloric and acetic acids.

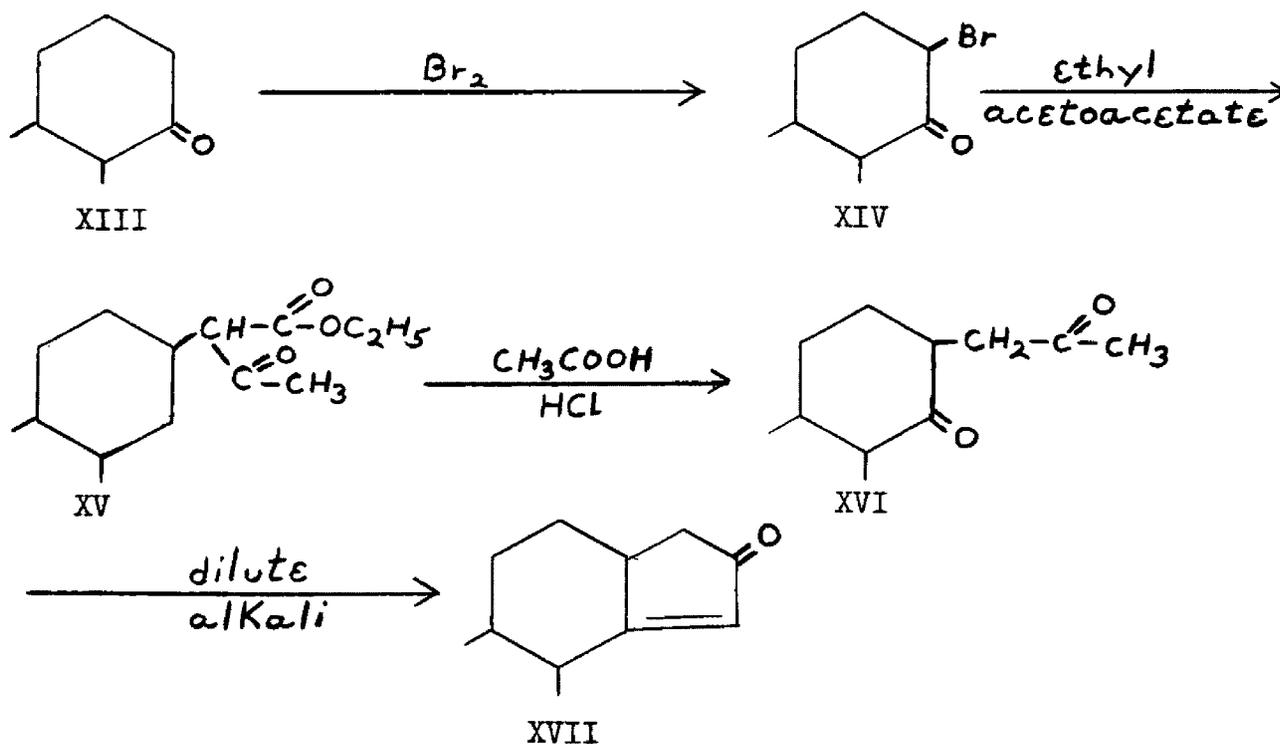


However, the formation of the diketone requires several steps and overall yields of 30-50% were obtained.

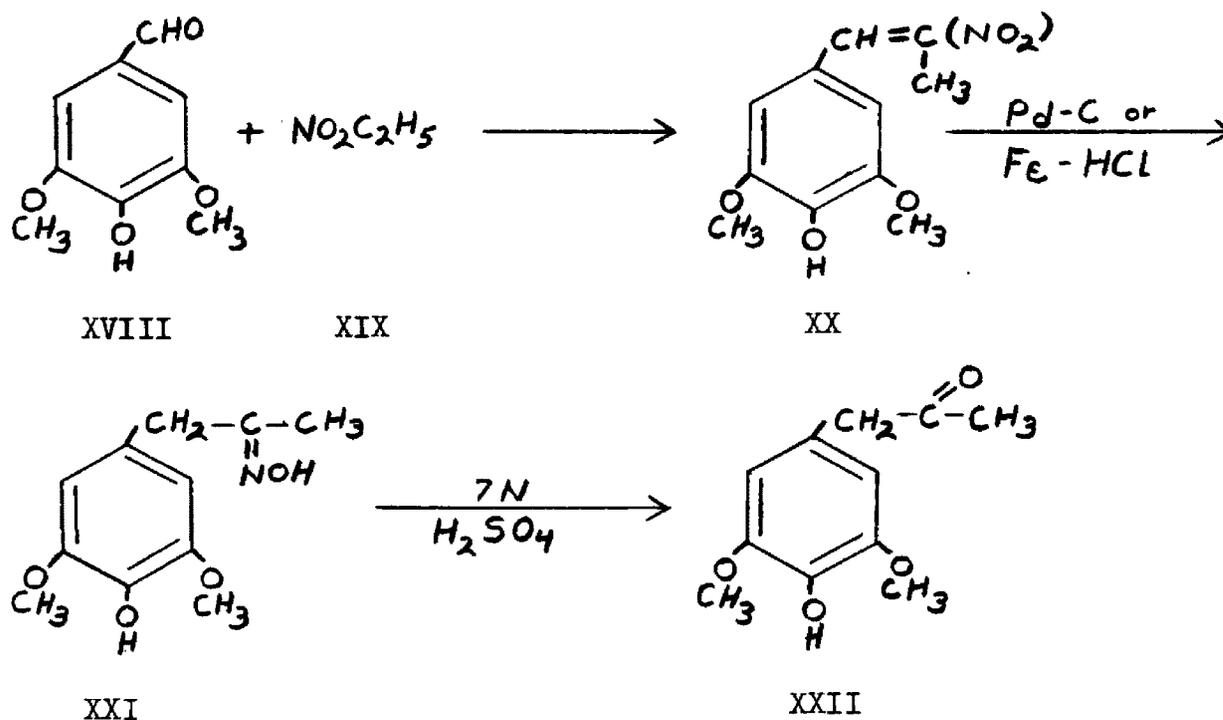
A modification of this synthesis was to make the enolate of IX with triphenylmethylsodium and condense it with phenyl acetate to yield X. (2). This was hydrolyzed with sodium hydroxide and decarboxylated to give directly the cyclic ketone XII in an 11% yield.



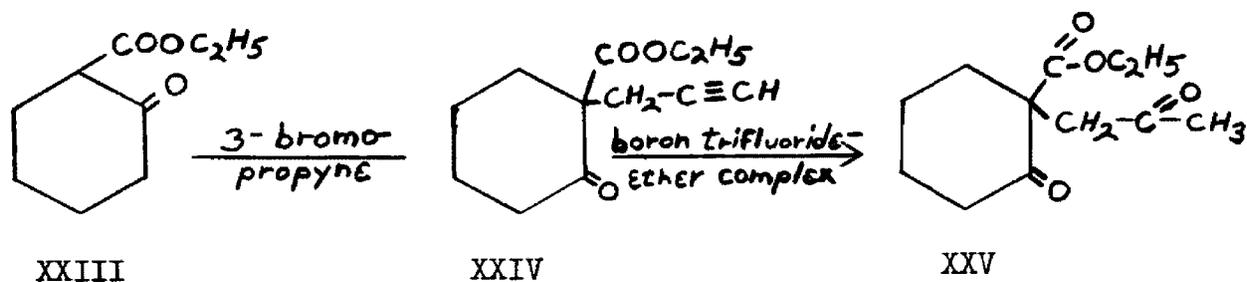
A third method was the reaction of a ketone with bromine yielding an alpha bromoketone. (10). This compound was then reacted with ethyl acetoacetate to produce XV. The ester could either be hydrolyzed with acetic and hydrochloric acids yielding the 1,4-diketone, or hydrolyzed and ring closed all in one step by treatment with dilute potassium hydroxide solution. However, the overall yield was less than 66%.



A fourth method, which was of special interest, was the condensation of an aldehyde with nitroethane. (11). The condensation yielded the unsaturated nitro compound XX which was reduced to the oxime using either palladium on carbon or iron and hydrochloric acid. The oxime was then hydrolyzed to give the ketone XXII in good yields. We hoped that by starting with a beta ketoaldehyde, the corresponding 1,4-diketone would be obtained.



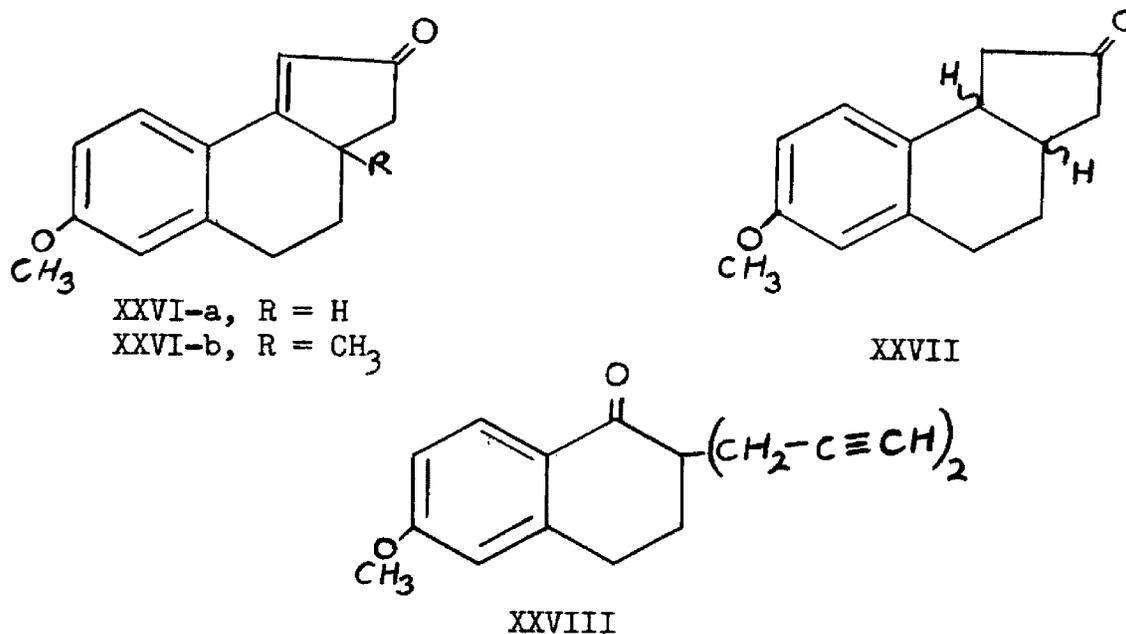
The fifth method consisted of the alkylation of a beta ketoester with 3-bromopropyne followed by hydration to form the ketone. A. M. Islan and R. A. Raphael synthesized XXV by this method. (12).



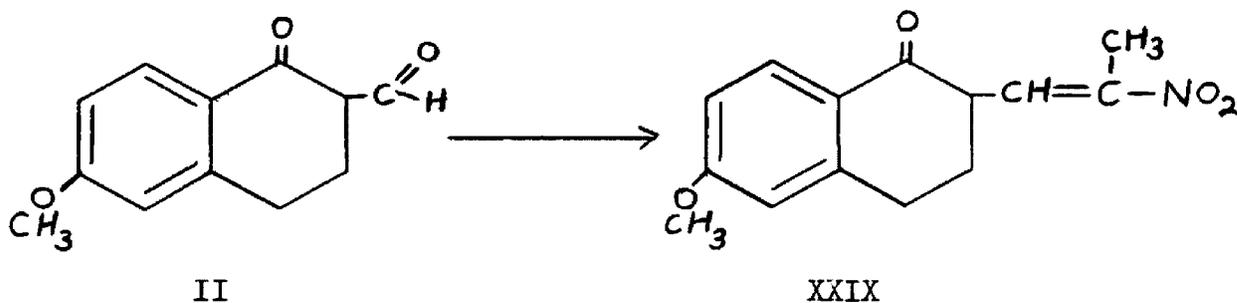
Other methods, which have been used to form 1,4-diketones, are of limited use since the starting materials are not readily available. They include: splitting of 2,5-disubstituted furans (4), reduction of alpha keto acid chlorides (6), and the oxidation of dihydroxy compounds (7).

DISCUSSION

Starting with 6-methoxy- α -tetralone, compounds XXVI, XXVII, and XXVIII have been prepared.



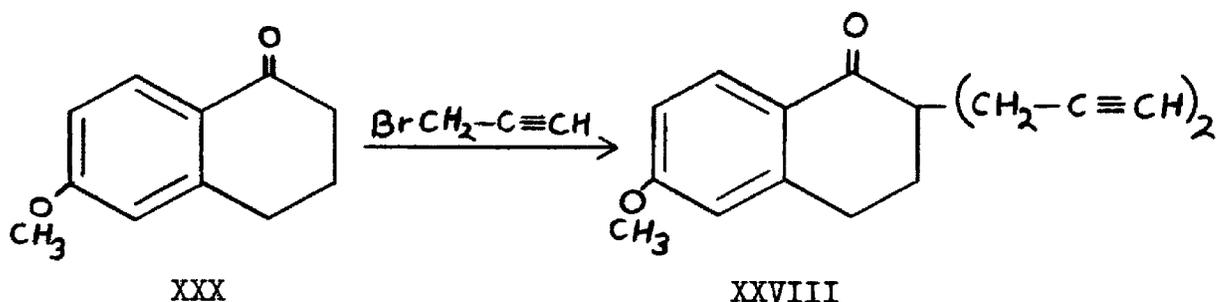
The first attempt to synthesize compound XXVI was by condensing nitroethane with II, as described in the fourth method.



Different solvents and catalysts were used but none resulted in the desired product XXIX. When II was refluxed with nitroethane in chloroform or benzene, it reacted with the morpholine catalyst but did not react with the nitroethane.

Since only 30% yields of III were obtained by alkylation of II with chloroacetone, a better preparation of the 1,4-diketone was needed. Compound XXXI was alkylated with 3-bromopropyne in DMF (dimethyl formamide) using sodium hydride as a catalyst.

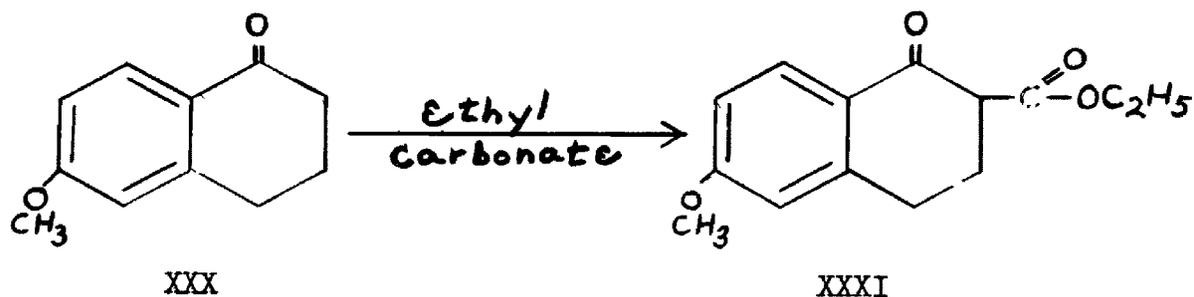
It is difficult to monoalkylate an alpha methylene group of a ketone, as a mixture of starting material and mono- and dialkylated products are obtained. However, if excess alkylating agent is used, dialkylsubstituted products may be obtained. Alkylation of 6-methoxy- α -tetralone with excess 3-bromopropyne yields XXVIII.



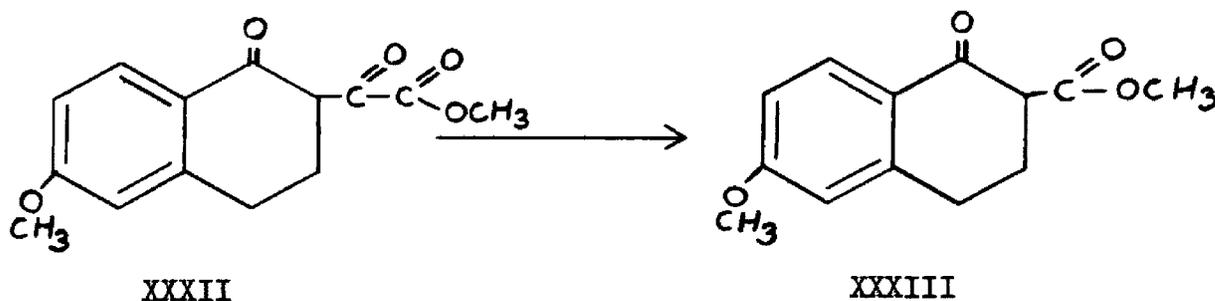
If one wishes to monoalkylate the methylene group, it is necessary to block the position in some way. The blocking group is then removed after alkylation. For this purpose, hydroxymethylene, carbethoxy, and enamine groups have been used.

In this work, hydroxymethylene and carbethoxy groups have been used successfully but the ketone is too hindered to form an enamine. The best yields were obtained with the carbethoxy group, so it was used in most cases.

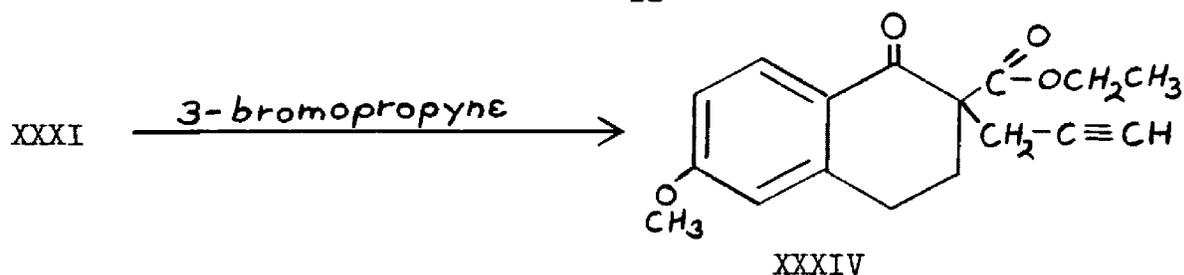
The first step of this synthesis was the condensation of ethyl carbonate with the sodium derivative of the starting material forming the beta ketoester XXXI. Yields of 85-90% were obtained by refluxing ethyl carbonate, compound XXX, and sodium hydride in ether.



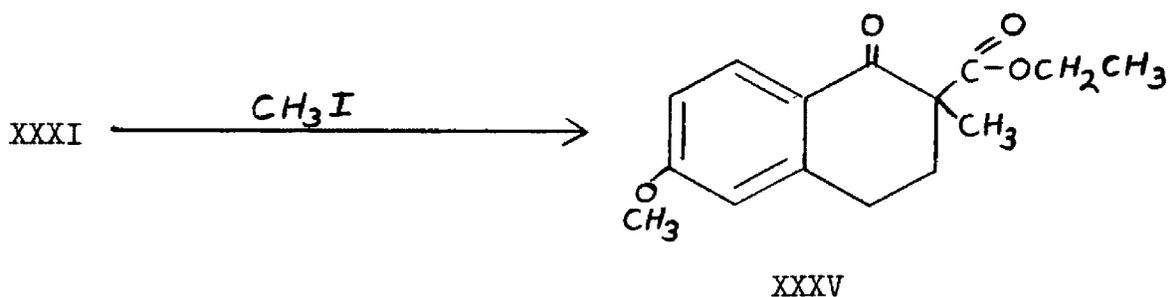
Preparations of beta ketoesters and beta ketoaldehydes have been extensively studied, since they represent one of the most reactive classes of organic compounds. The aldehyde of 6-methoxy- α -tetralone, 2-hydroxy-methylene-6-methoxy- α -tetralone, has been prepared by K. v. Auwers and C. Wiegand. (13). This compound was prepared in the laboratory obtaining yields of 80-85%. However, the beta ketoester XXXI gave better yields and hence was preferred to this synthesis. The methyl ester has generally been prepared by condensation of dimethyl oxalate with the ketone. This gives the glyoxylate XXXII in high yields which is then decarbonylated to form the methyl ester XXXIII. Similar attempts were made using diethyl oxalate, however, the decarbonylation failed to give the yields reported for the methyl ester.



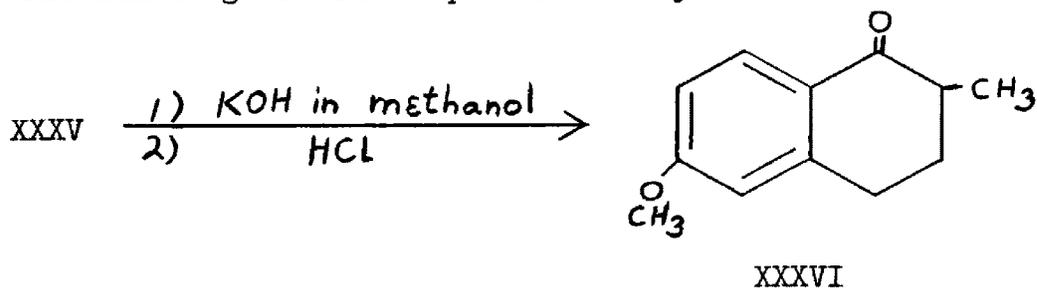
The next step was the alkylation of the beta ketoester XXXI with 3-bromopropyne. The sodium salt of the beta ketoester XXXI was alkylated in DMF at 0°C. Yields of 85-90% of XXXIV were obtained.



In order to introduce the methyl group for the synthesis of XXVI-b, compound XXXI is alkylated with iodomethane to obtain XXXV. When the method described for the 3-bromopropyne alkylation was used, yields of 90% were obtained.

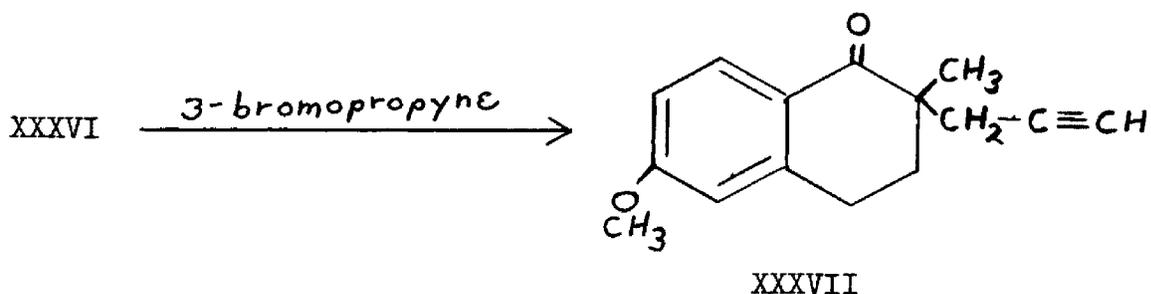


Compound XXXV was then hydrolyzed and decarboxylated by refluxing with sodium hydroxide in aqueous methanol followed by acidification and extraction to give almost quantitative yields of XXXVI.



This compound has been prepared by E. W. Hughes through the hydroxymethylene ketone II. (14). The methyl substituted 6-methoxy- α -tetralone XXXVI was alkylated directly with 3-bromopropyne. Since the compound is no longer a beta ketoester and therefore less reactive, a more polar medium than DMF was necessary to form the sodium salt. The second alpha hydrogen of the ketone was removed by the methylsul-

finylcarbanion, which is the conjugate base of DMSO (dimethyl sulfoxide). The preparation of the methylsulfinylcarbanion is given by E. J. Corey and M. Chaykovsky. (15). The sodium salt of XXXVI was then alkylated with 3-bromopropyne to form XXXVII. After distillation, the yield appeared to be 76-80%. However, the product was not pure since the odor of the DMSO was present.

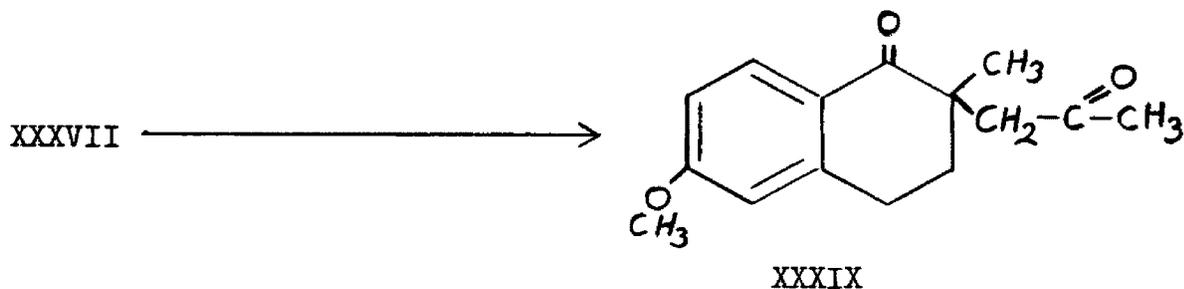
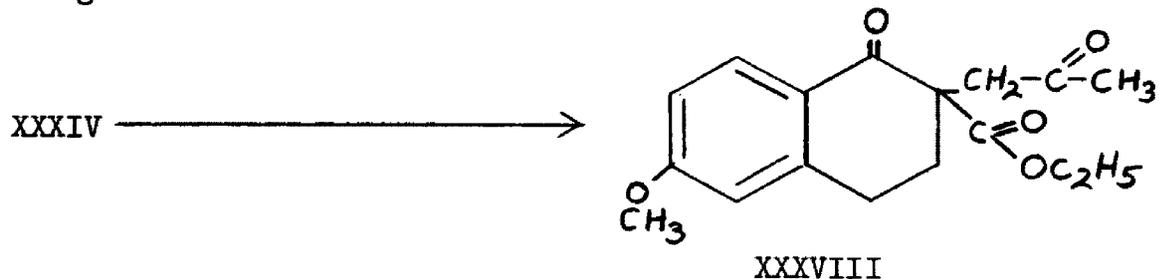


Further investigation is needed to determine whether the solvent was partially alkylated.

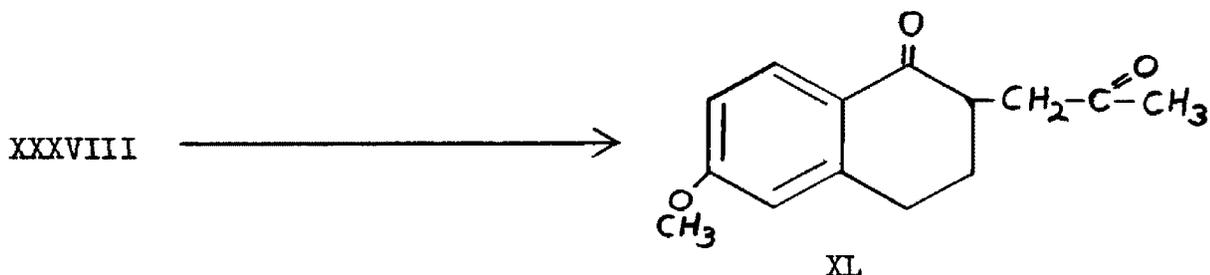
The acetylenic compounds XXXIV and XXXVII were then hydrated to form XXXVIII and XXXIX. Many methods involve the use of mercury salts in the hydration of triple bonds to form carbonyl compounds. Thomas, Cambell, and Hennion used mercury sulfate and sulfuric acid as catalysts. (16). Yields of only 40% were obtained. Higher yields were obtained with a mixture of mercuric oxide, boron trifluoride-ether complex, trichloroacetic acid, and methanol by A. M. Islan and R. A. Raphael. (12).

In this laboratory, the best results for the hydration were achieved by using fifteen milligrams of mercuric oxide as a catalyst, and 88% formic acid as the solvent. Enough formic acid was used so that two moles of water would be present for each mole of acetylene compound. The yields obtained were approximately 85%. They were probably higher since the purity of XXXIV and XXXVII was doubtful and a low

boiling forerun was collected.

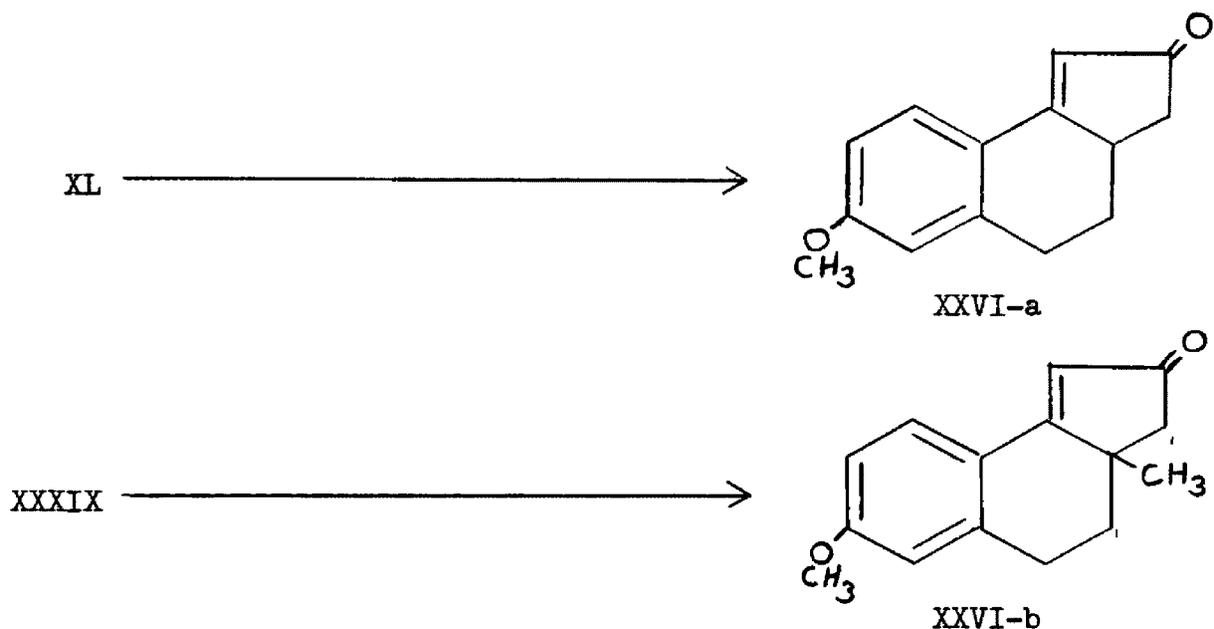


Compound XXXVIII was then hydrolyzed and the acid formed decarboxylated to yield compound XL.



Methods of hydrolysis, which involved refluxing XXXVIII in alcoholic potassium hydroxide, resulted in considerable black residue and low yields. However, hydrolysis at room temperature using equal weights of XXXVIII, potassium hydroxide, and water were more successful. The yields obtained were 65-70%. Acid hydrolysis was not attempted since the formation of a furan ring for a similar compound has been reported by A. L. Wilds. (10).

The diketones, XL and XXXIX, were then ring closed to form XXVI-a and XXVI-b.

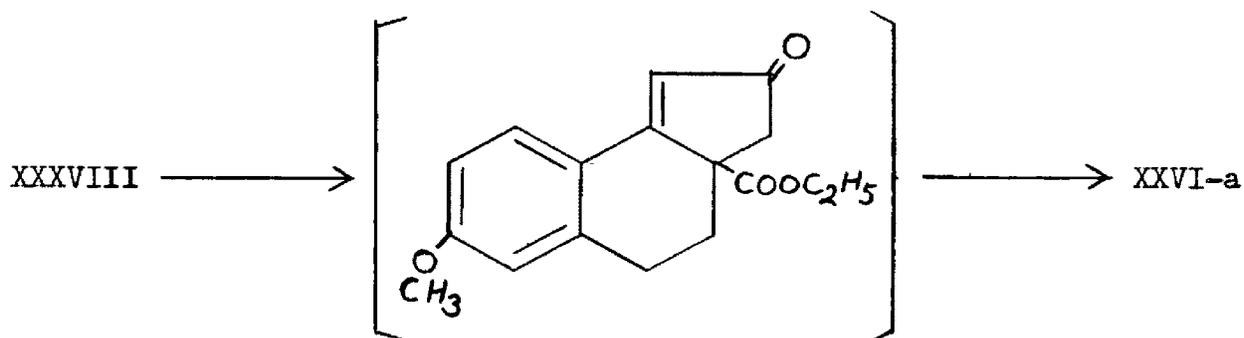


Several methods of ring closure were investigated. Ring closure of 2,5-dodecandione was reported by Heinz Hunsdiecker. (17). This was accomplished by heating a mixture of the diketone, borax, water, and alcohol in a bomb tube at 200°C. Generally, alcoholic potassium hydroxide has been used, however, under the same conditions, compound XL became black even before it had started to reflux and no product was obtained. High temperature reactions were not attempted with borax, and sodium or potassium hydroxide since the methoxy group could be cleaved under these conditions. An attempt was made using barium hydroxide in ethylene glycol, but the product again turned very dark.

Another method tried was refluxing the compound with either sodium hydride or sodamide in various solvents. Refluxing the compound with sodium hydride and DMF failed to ring close the compound. Refluxing in dioxane and sodamide or in benzene and sodium hydride resulted in a 53% yield of the ring closed product. The best results were obtained by using equal molar quantities of diketone XL and tertiary-butyl

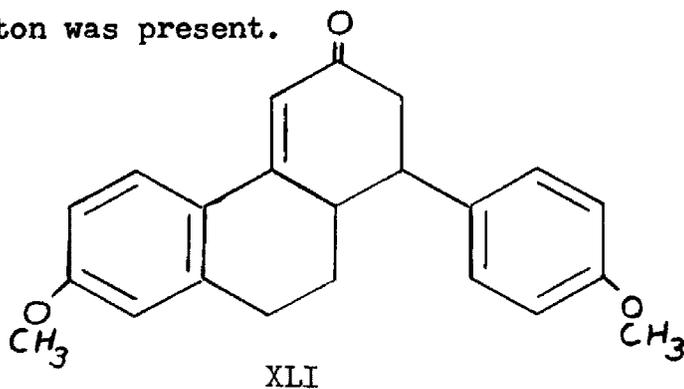
alcohol, and a 10-15% molar excess of sodium hydride. The yields obtained in this manner were 65-70%. It was also found that shortening the reflux time to less than half an hour led to a mixture of starting material and product.

Attempts were also made to ring close XXXVIII directly and then decarboxylate the ester.



This method has been used successfully by A. L. Wilds and T. L. Johnson on a similar compound X, but yields were less than 15%. (2). Compound XXXVIII could not be ring closed by refluxing with sodium hydride and benzene for varying lengths of time.

The location of the double bond in XXVI-a and XXVI-b is as shown. The ultraviolet spectrum of XXVI-a had an absorption maximum of 235 mu, which is comparable to the absorption maximum at 241 mu. for conjugated compound XLI. The NMR (nuclear magnetic resonance) also showed that one ethylenic proton was present.



palladium on charcoal was used, a mixture of XXVII, XLII, and a low boiling forerun were obtained. The low boiling forerun was probably a hydrogenolysis product but was not further identified.

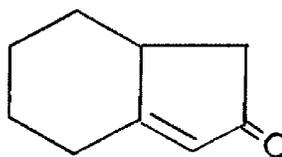


Separation of the two products was achieved by forming the semi-carbazone derivative of the ketone. Reduction attempts with lithium and ammonia also led to the same products. However, hydrogenolysis with Raney Nickel did not result in a low boiling forerun and the yields were almost quantitative. The product, without being isolated, was then oxidized to XXVII in an 80% yield. The oxidation of the alcohol to the ketone was carried out using the chromic acid-pyridine complex. This method has been reported by L. H. Sarett and co-workers to convert secondary alcohols to ketones in yields approaching theoretical. (20).

Catalytic hydrogenation in neutral and acidic medium resulted in only one isomer of XXVII. A. L. Wilds, A. Johnson, and R. E. Sutton reported that both the cis and trans isomers were obtained in neutral hydrogenation of XLIII, and that the ratio of the isomers could be changed by altering pH of the medium. (18). However, R. T. Augustine and A. D. Broom found that catalytic hydrogenation of XLIV in neutral, acidic, and basic medium resulted in only the cis isomer. (21).

Chemical and catalytic reduction also gave the same isomer of XXVII. It was originally thought that the chemical reduction would give the more stable of the two possible isomers, or the trans isomer. Recently, G. Stork and S. D. Darling showed that the energies of the stereoelectronically allowed transition determined the stereochemistry

and not the energies of the reduction products. (22). Further evidence is necessary to establish the stereochemistry of XXVII.



XLIV

EXPERIMENTAL

Ethyl, 1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-naphthalencarboxylate (XXXI). - A stirred solution of 6-methoxy- α -tetralone (XXX) (35.2 g., 0.200 mole), sodium hydride (5.94 g., 0.248 mole), ethyl carbonate (29 ml., 0.238 mole), and dry diethyl ether (200 ml.) were heated to refluxing. DMF (24 ml.) was then added to start the reaction. After refluxing gently for 3-4 hours, the mixture was cooled and ice water and benzene were added. The water layer was then acidified and extracted with benzene. The diethyl ether and benzene layers were combined. After washing until neutral, the aromatic layer was evaporated and the product distilled. A yield of 39.2 g. (79%) of product distilling at 159-169/.1 mm. was obtained.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.74; H, 6.45. Found: C, 67.40; H, 6.76.

Ethyl, 1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-(propynyl-2)-2-naphthalencarboxylate (XXXIV). - A solution of ethyl, 1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-naphthalencarboxylate (XXXI) (20.1 g., .080 mole) and DMF (80 ml.) were cooled to $-9^{\circ}C$. and sodium hydride (4.5 g., .0994 mole) was added slowly. An argon atmosphere was maintained throughout the reaction. The mixture was cooled to $-7^{\circ}C$. and 3-bromopropyne was added dropwise. The mixture was then stirred at -5° to $0^{\circ}C$. for 40 minutes and allowed to warm to room temperature. It was diluted with water and acidified with dilute hydrochloric acid. The benzene layer was then washed with potassium carbonate and water. After drying over magnesium sulfate, the benzene was removed by vacuum evaporation, and

the product was distilled at 159-169/.1 mm.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.32; H, 6.29. Found: C, 71.27; H, 6.30.

Ethyl, 1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-(propanone-2)-2-naphthalencarboxylate (XXXVIII). - A stirred solution of ethyl, 1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-(prophnyl-2)-2-naphthalencarboxylate (XXXIV) (12.8 g., .042 mole) and formic acid (85 ml.) was cooled to 1°C. Then mercuric oxide (15 mg.) dissolved in formic acid (2 ml.) was added slowly until the temperature rise of 2° to 3°C. occurred. After stirring at room temperature for 30 minutes, water and benzene were added. The benzene was washed with sodium bicarbonate and water, dried, and evaporated under vacuum. A yield of 11.3 g. (83%) of product distilling at 154-163/.1 mm. was obtained.

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.10; H, 6.58. Found: C, 68.06; H, 6.70.

1,2,3,4-Tetrahydro-6-methoxy-2-(propanone-2)-naphthalenone-1 (XL). - A solution of ethyl, 1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-(propanone-2)-2-naphthalencarboxylate (XXXVIII) (29.6 g., 0.0974 mole) and methanol (125 ml.) was cooled to 10°C. under an argon atmosphere. Then potassium hydroxide (30.0 g., .455 mole) dissolved in water (30.0 g., 1.67 mole) was added rapidly. After the mixture was stirred at room temperature for an hour, the methanol was evaporated under vacuum. Water and benzene were added and the contents transferred to a separatory funnel. The aqueous layer was drawn off into ice and hydrochloric acid (50 ml., 12 N.). After stirring and allowing time for the precipitate to coagulate, it was filtered and washed with water. The yield

obtained after recrystallization from methanol was 14.3 g. (64%), m.p. 93-95°C.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.41; H, 6.90. Found: C, 72.58; H, 6.95.

3,-3a,4,5-Tetrahydro-7-methoxy-2H-benz[e]inden-2-one (XXVI-a).

- A mixture of sodium hydride (0.46 g., .010 mole), tertiary-butyl alcohol (0.8 ml., .009 mole), and benzene (60 ml.) was heated until the sodium hydride reacted. Then 1,2,3,4-tetrahydro-6-methoxy-2-(propanone-2)-naphthalenone-1 (XL) (2.0 g., .0086 mole) was added and heated to refluxing in an argon atmosphere. After refluxing for 30 minutes, the reaction was cooled and dilute hydrochloric acid was added. The aqueous layer was extracted twice with benzene. After washing until neutral, the solvent was evaporated and the product distilled. A yield of 1.2 g. (68%) of product was obtained after distilling at 145-148/.1 mm. and recrystallization from methanol, m.p. 138-140°C.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.50; H, 6.54. Found: C, 78.26; H, 6.44.

1,3,-3a,4,5,9b-Hexahydro-7-methoxy-2H-benz[e]inden-2-one (XXVII).

3,-3a,4,5-Tetrahydro-7-methoxy-2H-benz[e]inden-2-one (XXVI-a) (11.4 g., .532 mole) was dissolved in dioxane (30 ml.) and stirred with one teaspoon of Raney Nickel and hydrogen at room temperature and atmospheric pressure. It absorbed $1\frac{1}{2}$ moles of hydrogen in 2 hours. The product was obtained by filtering and evaporating the solvent.

Chromic acid (10.3 g., .105 mole) was added to pyridine (202 ml., 2.54 mole) and the mixture cooled to 10°C. The product obtained above

was added. After stirring for eight hours at 20°C., the reaction was cooled and water and benzene were added. The mixture was filtered and the precipitate washed with benzene. The benzene layer was washed with hydrochloric acid until the odor of pyridine was removed. The solvent was washed until neutral and evaporated. A yield of 8.5 g. (74%) of product distilling at 155-160/.1 mm. was obtained; m.p. 63-65°C.

Ethyl, 1,2,3,4-tetrahydro-2-methyl-1-oxo-2-naphthalencarboxylate (XXXV). - The procedure used to make XXXIV was followed. Starting with ethyl, 1,2,3,4-tetrahydro-6-methoxy-1-oxo-2-naphthalencarboxylate (XXXI) (13.4 g., .0540 mole), sodium hydride (2.72 g., .0621 mole), iodomethane (4.5 ml., .0729 mole), and DMF (70 ml.), a yield of 12.8 g. (90%) of product distilling at 150-165/.1 mm. was obtained.

1,2,3,4-Tetrahydro-6-methoxy-2-methyl-naphthalenone-1 (XXXVI). - A mixture of ethyl, 1,2,3,4-tetrahydro-2-methyl-1-oxo-2-naphthalencarboxylate (XXXV) (12.8 g., .049 mole), sodium hydroxide (30 ml. of 20%, .15 mole), and methanol (70 ml.) were refluxed for one hour in an argon atmosphere. The solution was acidified by pouring it into ice and hydrochloric acid. The aqueous layer was extracted with benzene. The benzene layer was washed until neutral, dried, and evaporated under vacuum. A yield of 9.2 g. (98%) of product distilling at 114-115/.1 mm. was obtained. This compound has been prepared by E. W. Hughes through the hydroxymethylene ketone II. (14).

1,2,3,4-Tetrahydro-6-methoxy-2-methyl-2-(propynyl-2)-naphthalenone-1 (XXXVII). - A mixture of sodium hydride (2.4 g., .0519 mole) and DMSO (75 ml.) was heated under an argon atmosphere to 55-60°C. to form the methylsulfinylcarbanion. (15). It was cooled to 20°C. and

1,2,3,4-tetrahydro-6-methoxy-2-methyl-naphthalenone-1 (XXXVI) was added rapidly. After cooling to 10°C., 3-bromopropyne (6.1 g., .0519 mole) was added slowly. The reaction was stirred for 3½ hours at room temperature. Water and dilute hydrochloric acid were added and the aqueous layer was extracted twice with benzene. The benzene layer was filtered, washed with water, and evaporated. A yield of 7.6 g. (80%) of product distilling at 125-132/.1 mm. was obtained. The product was further purified by chromatographic separation on silica gel. However, the odor of DMSO was still present and an analytical sample was not obtained.

1,2,3,4-Tetrahydro-6-methoxy-2-methyl-2-(propanone-2)-naphthalenone-1 (XXXIX). - The procedure used to make XXXVIII was followed. Starting with 1,2,3,4-tetrahydro-6-methoxy-2-methyl-2-(propynyl-2)-naphthalenone-1 (XXXVII) (11.0 g., .0482 mole), formic acid (85 ml.), and mercuric oxide (15 mg.) dissolved in formic acid, a yield of 9.9 g. (84%) of product was obtained. After distilling at 120-140/.1 mm., the smell of DMSO still persisted. Recrystallization from 50/50 water alcohol mixture failed to remove the impurity and therefore no carbon and hydrogen determination was obtained.

3,-3a,4,5-Tetrahydro-3a-methyl-7-methoxy-2H-benz [e]inden-2-one (XXVI-b). - The procedure used to make XXVI-a was followed. Sodium hydride (.70 g., .0156 mole), tertiary-butyl alcohol (1.2 ml., .0130 mole), dry benzene (70 ml.), and 1,2,3,4-tetrahydro-6-methoxy-2-methyl-2-(propanone-2)-naphthalenone-1 (XXXIX). - The product was distilled at 122-175/.1 mm. and solidified upon swirling with pet ether and scratching. The pet ether was decanted off and the residue swirled with cyclohexane, and filtered. A yield of 1.3 g. (41%) was obtained,

m.p. 82-84°C.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.94; H, 7.02. Found: C, 78.80; H, 7.09.

1,2,3,4-Tetrahydro-6-methoxy-2-methyl-2,2-(dipropynyl-2)-naphthalenone-1 (XXVIII). - A mixture of sodium hydride (6.4 g., .142 mole) and DMSO (100 ml.) was heated under argon to 55-60°C. It was cooled to 20°C. and 6-methoxytetralone (XXX) (10.0 g., .0569 mole) was added rapidly. The mixture was cooled to 18°C. and 3-bromopropyne (11.3 ml., .1422 mole) was slowly added. After stirring at room temperature for 2 hours, the mixture became very thick; dry benzene (100 ml.) was added. After stirring an additional 2 hours, water and dilute hydrochloric acid were added. The product was taken up in benzene. The benzene layer was filtered, washed with water, and dried. The solvent was removed by vacuum evaporation and the crude product was recrystallized from methanol to yield 9.0 g. (62%) of product, m.p. 108-119°C.

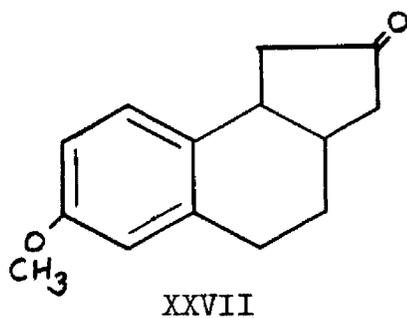
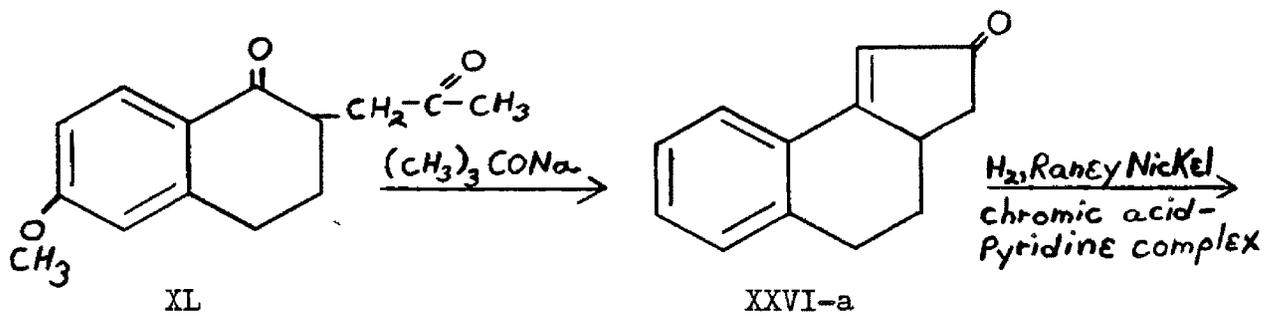
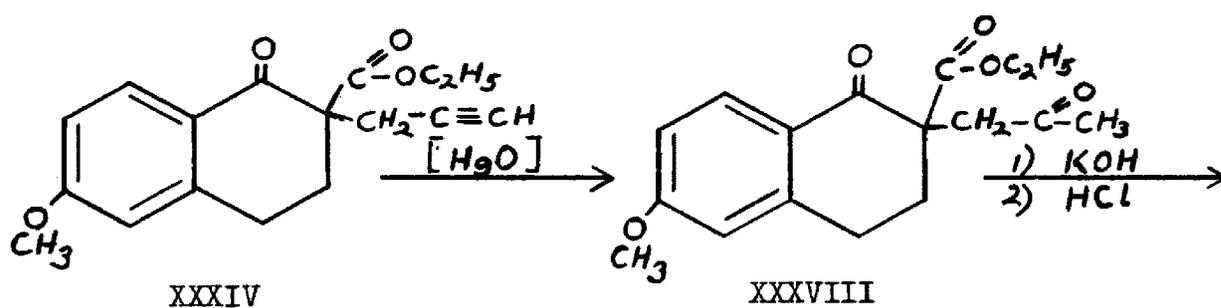
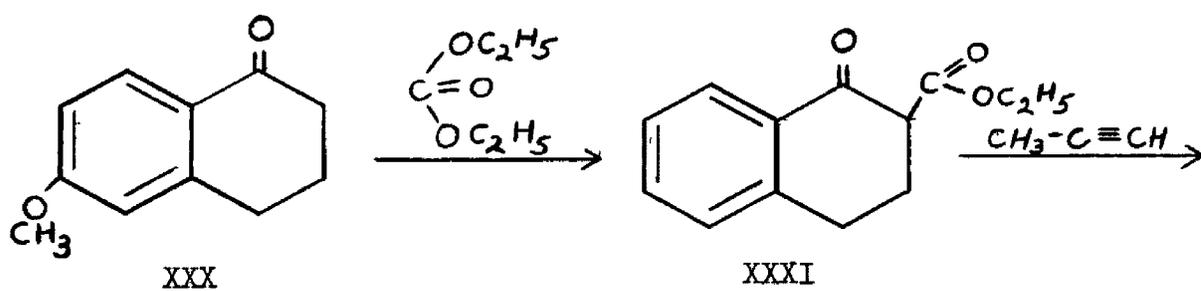
Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.95; H, 6.34. Found: C, 80.68; H, 6.29.

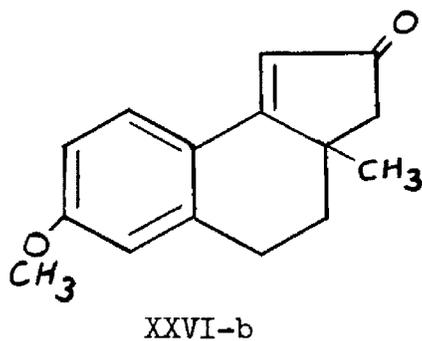
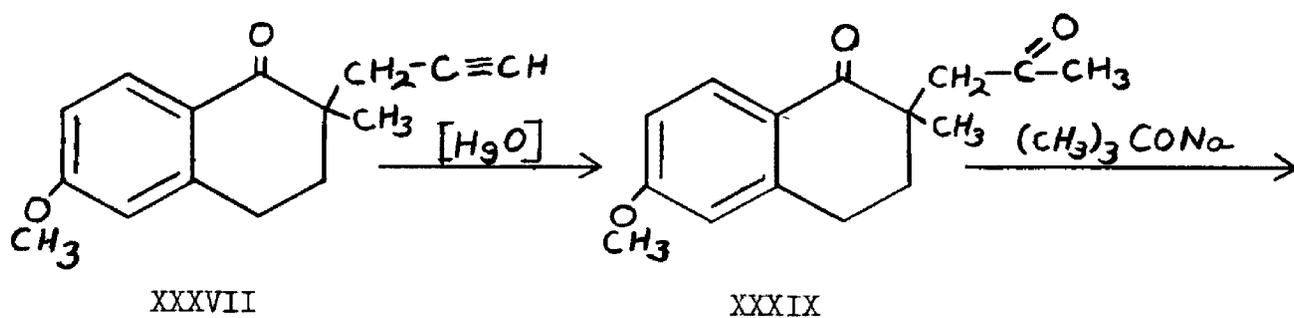
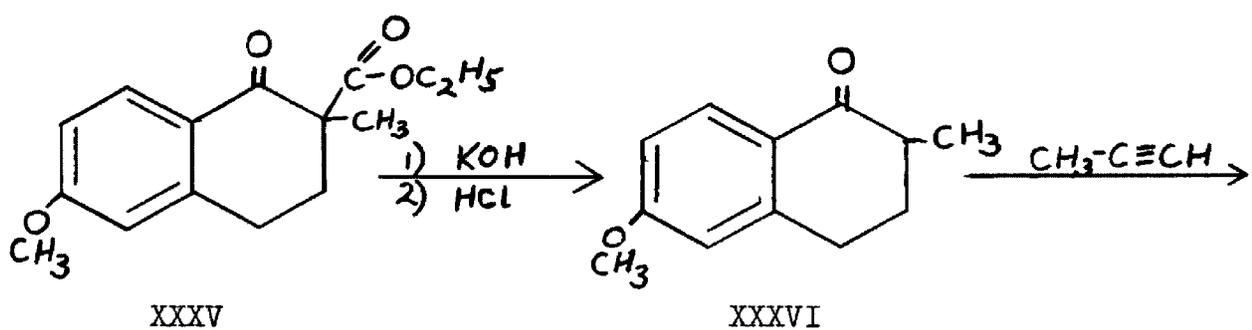
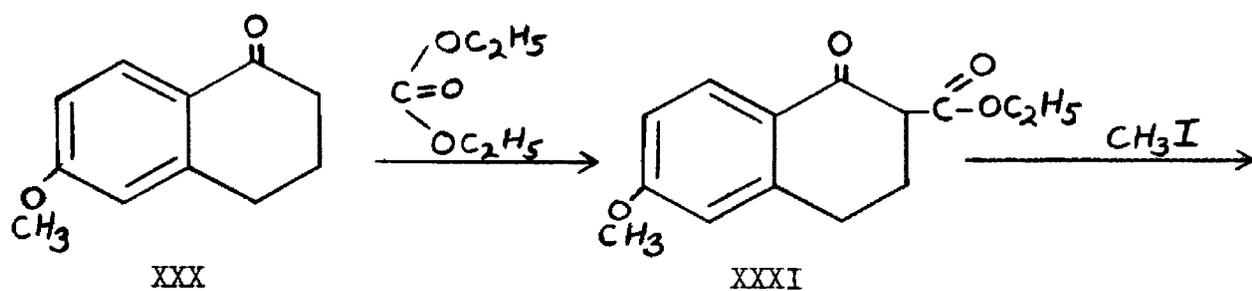
SUMMARY

The purpose of this investigation was to find an improved synthesis of compounds containing fused cyclopentenone and cyclopentanone ring systems. This would also serve as a model synthesis for the preparation of steroids.

The preparation of XXVII started with the condensation of XXX with ethyl carbonate to form XXXI. This was alkylated with 3-bromopropyne and the triple bond hydrated to form XXXVIII. Treatment with alcoholic potassium hydroxide hydrolyzed the ester, and pouring into acid resulted in the decarboxylated product XL. The compound was then refluxed in benzene with sodium tertiary-butoxide, obtaining XXVI-a. The ketone and double bond of XXVI-a were catalytically hydrogenated with Raney Nickel, and the alcohol oxidized with chromic acid-pyridine complex to form XXVII. The stereochemistry of XXVII has not yet been determined.

The synthesis of the angular methyl compound XXVI-b began with the alkylation of XXXI with iodomethane. This was then hydrolyzed and decarboxylated to form XXXVI. Direct alkylation of XXXVI with 3-bromopropyne resulted in XXXVII. The compound XXXVII was then hydrated and ring closed to form XXVI-b.





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