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5-alkyl-6-cyclopentyl derivatives of 345678-hexahydro-2-naphthalenones

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5-ALKYL-6-CYCLOPENTYL DERIVATIVES OF 3,4,5,6,7,8-HEXAHYDRO-2-NAPHTHALENONES

by

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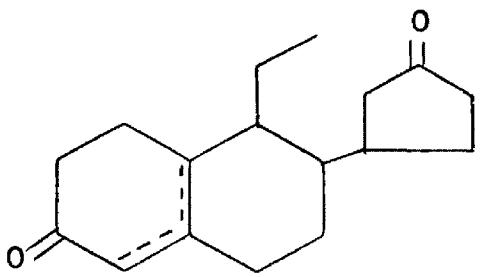
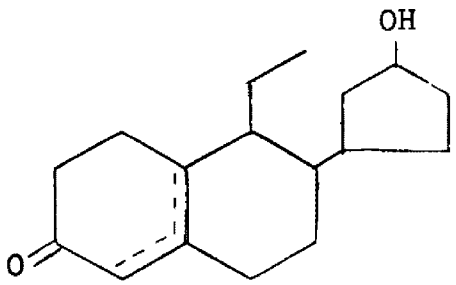
I. INTRODUCTION

The purpose of this research was to synthesize I and II as possible cancer chemotherapeutic agents. These compounds will be tested for steroid hormone activity, hormone antagonist activity, and antitumor activity to hormone dependent cancers. Such compounds would also be of interest in obtaining more information concerning the relationship between structure and biological activity of steroid analogs lacking ring C.



I



II

The realization of the hormone dependence of certain cancers led to the synthesis of many natural and synthetic steroids with biological activity. Naturally occurring androgens and estrogens have caused remissions in patients with cancer of the breast or prostate, and this led to the study of related steroids for their effects on experimental tumor and human cancer.[1] Certain hormones can be of great significance in the maintenance of four neoplasms--those of the breast, the prostate, the thyroid gland, and the lymphomas.[2]

Potential synthetic estrogens have been made containing phenyl,

hydronaphthalene, and hydrophenanthrene nuclei.[3] The effect of the estrogens in the control of mammary cancer is probably due to inhibition of the pituitary.[4] Androgens, in addition to inhibiting the pituitary, also have an antagonistic effect toward estrogens in controlling the growth of mammary cancer. It was this antiestrogenic effect that first led to the investigation of the androgens as possible cancer chemotherapeutic agents.

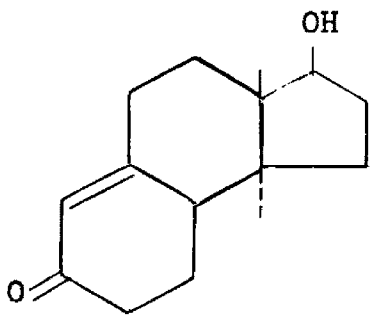
Generally associated with the antitumor effect of the estrogen or androgen were certain toxic effects, eg., virilization, or feminization, depending on the hormone used, and fluid retention.[5] It was hoped that related compounds could be found possessing the desired antitumor effects, but dissociated from the undesirable androgenic or estrogenic activity of the steroid.

The compound Δ^4-testololactone, which represents a variation on the steroid nucleus, was found to be hormonally inactive, but capable of modifying the course of breast cancer.[6] Other examples of compounds producing temporary remission are dihydrotestosterone, 17α-methyltestosterone, methylandrostenediol, 17α-vinyltestosterone, 19-nortestosterone, and the halogenated compound, 9α-fluoro-11β-hydroxy-17α-methyltestosterone.[7]

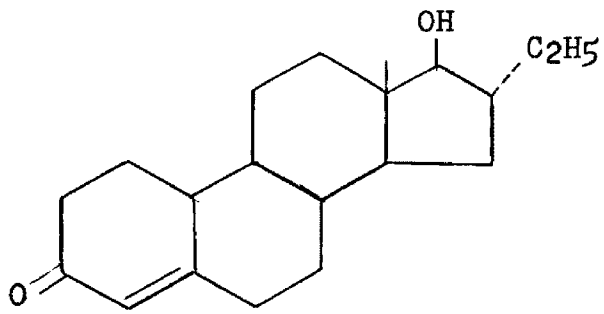
The introduction of the 2α-methyl group into dihydrotestosterone and similar compounds leads to a very potent androgenic, anabolic, and anti-breast-tumor agent.[8] The substitution of fluorine in the 2α-position results only in the reduction of the primary hormone activity, retaining the other effects, even though fluorine is much closer in size to the original hydrogen than the methyl group. This illustrates

the variation of biological activity with structure, for this is a compound with practically the same shape and size as active androgens, yet it shows low primary hormonal activity while retaining secondary characteristics.

Another example of the relationship between structure and biological activity was compound III.[9] It was found to have androgenic and progestational activity. It is structurally related to 17∝-ethyl-19-nortestosterone IV, having a "thickness" equivalent that may be a contributory factor toward the biological activity of the steroids.



III

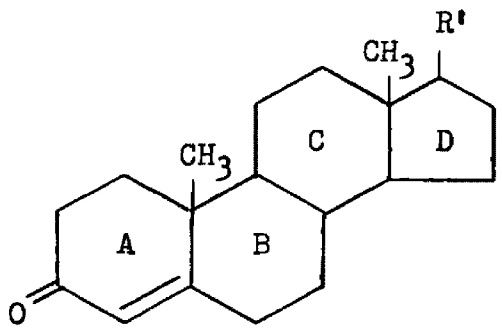


IV

Since relatively less work has been done on androgen analogs than with estrogen analogs, investigation of several synthetic analogs of androgens was undertaken in the hope that a modification of the structure, while retaining somewhat the same molecular shape and size, would result in increased anticancer activity and a decrease in undesirable side effects. Accordingly, 5-alkyl-6-cyclopentyl derivatives I and II of androgen analogs lacking ring C were synthesized.

II. ANDROGEN ANALOGS LACKING RING C

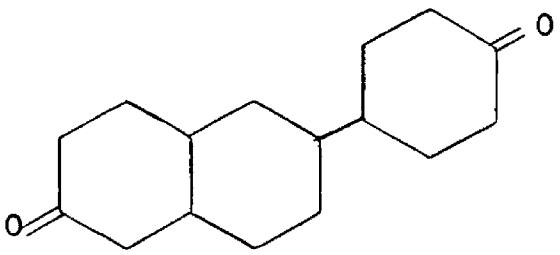
Androgenic hormones have the basic structure V, consisting of rings A,B,C, and D with angular methyls at C - 10 and C - 13. R' is generally an hydroxyl or a carbonyl group, and there is an α,β-unsaturated ketone at C - 3.[10]



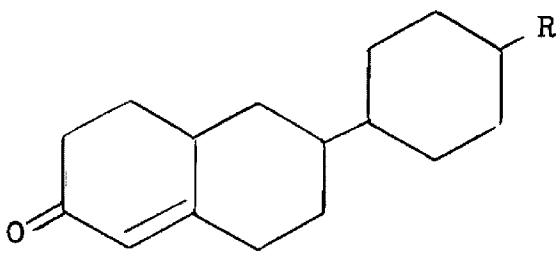
V

Steroid analogs lacking ring C have previously been studied primarily with a six membered ring D. Wilds and Shunk[11] found VI containing part of the testosterone skeleton to be feebly androgenic. They had also synthesized analogs of progesterone and deoxycorticosterone VIIa,b,[12] with no angular methyl groups, and with a six membered ring D. Beginning with bicyclohexyl derivatives the third ring A had been added using an improved Robinson-Mannich base procedure for the synthesis of α,β-unsaturated cyclic ketones. It was felt that these isomers did not correspond to the proper configuration for

highest activity. Wilds and co-workers[13] later synthesized several other analogs of testosterone VIIIa,b, lacking ring C, using basically the same procedure. Some of these analogs appeared to be weakly androgenic.

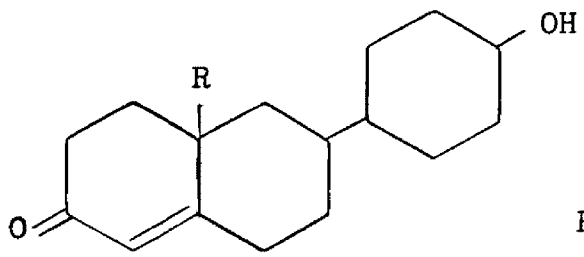


VI

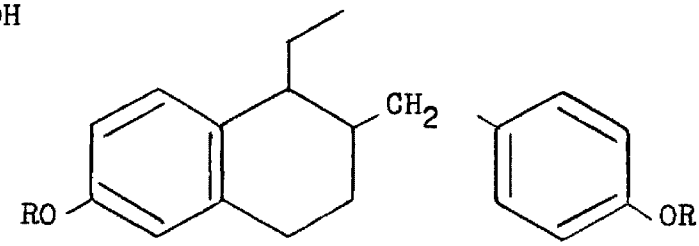


VIIa R = $COCH_3$
b R = $COCH_2OCOCH_3$

Other analogs lacking ring C had been prepared beginning with rings A and B, using derivatives of ∝-tetralone as starting materials. Derivatives of 1-ethyl-2-benzylnaphthalene IXa,b,[14] showed some activity at the 1 mg. level.



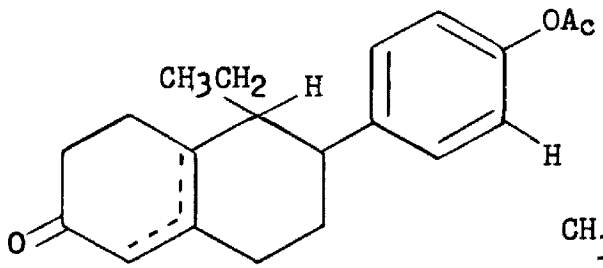
VIIIa R = H
b R = CH_3



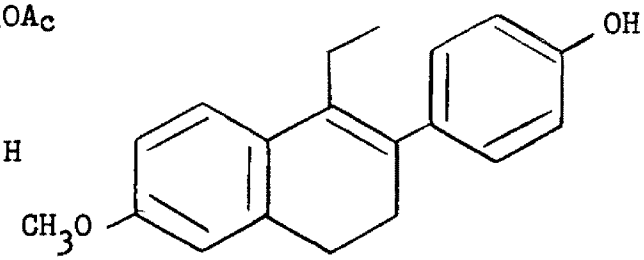
IXa R = CH_3
b R = H

In order to study the effect on biological activity of varying the C - 5 alkyl substitutent and the C - 6 substituted ring a number of

4-oxocyclohexenyl-2-(p-hydroxyphenyl) derivatives of 2-naphthalenone were prepared. The two compounds that showed some biological activity, X and XI, possessed ethyl groups next to the phenol ring. Corresponding compounds lacking the ethyl group were inactive. Compound X was found to be slightly estrogenic, XI antiestrogenic. It was suggested that such a group may be essential for activity. Its function may be to change the shape of the molecule by twisting the adjacent ring so it no longer lies in the general plane of the rest of the molecule.



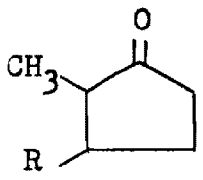
X



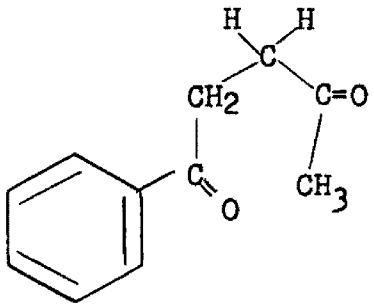
XI

Thus far emphasis has been on compounds with a six membered ring D. Several analogs with a five membered ring D have been prepared. Koebner and Robinson[16] prepared substituted cyclopentanones XII with R = phenyl, β-naphthyl, 6-methoxy-2-naphthyl, or halogenated derivatives. They used Borsche's method of obtaining the five membered ring by condensing ethyl phenacyl bromide with the sodio derivative of ethyl proprionylacetate, and by hydrolysis with alcoholic sodium hydroxide obtaining the substituted cyclopentenone. By selective hydrogenation this can be reduced to the substituted cyclopentanone. These compounds

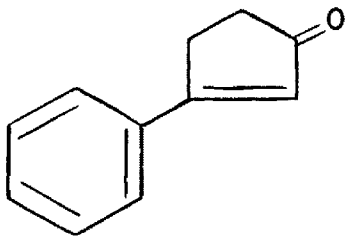
were not tested for biological activity; the authors intended them for modifications of x-norequilenin in the methyl ether series.



XII

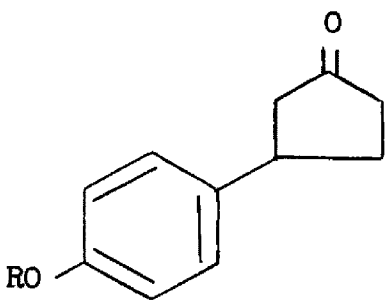


XIII



XIV

Wilds[17] cyclized 1,4 diketones of type XIII to cyclopentanone derivatives XIV. Wilds and Johnson[18] also synthesized 3-(p-hydroxyphenyl) -cyclopentanone-1 XVa and related compound XVb.



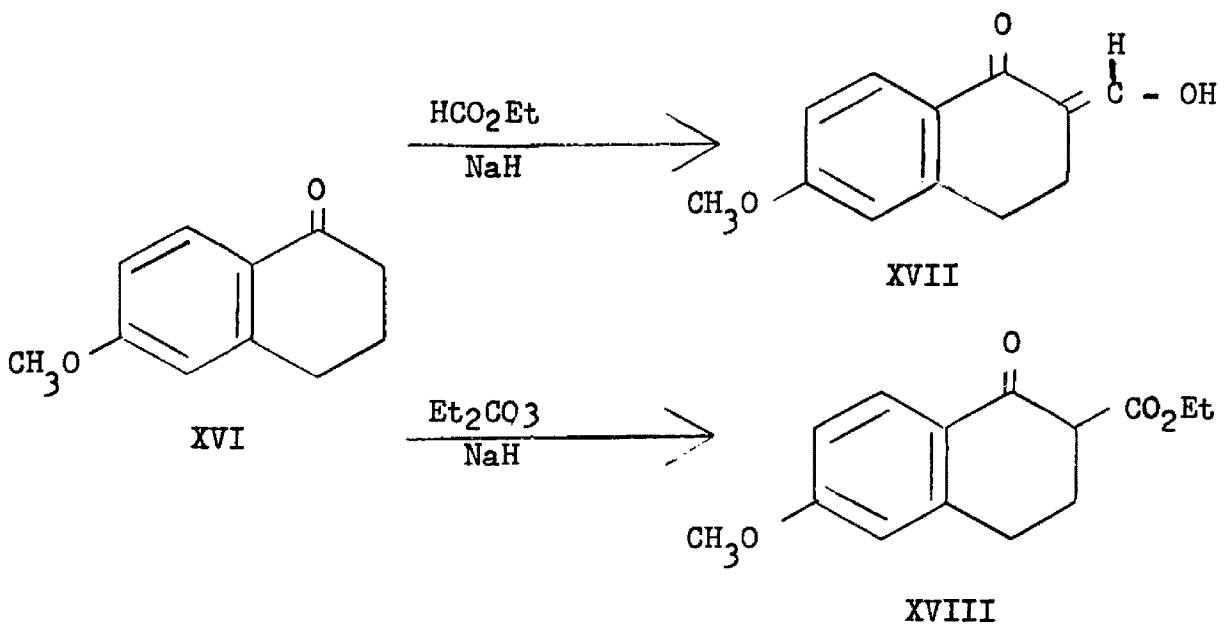
XVa R = H

b R = CH_3

Since analogs with a six membered ring D had shown promise, derivatives with a five membered ring D, more closely related to the androgen structure, might show biological activity.

III. SYNTHESIS OF ANDROGEN ANALOGS WITH FIVE MEMBERED RING D

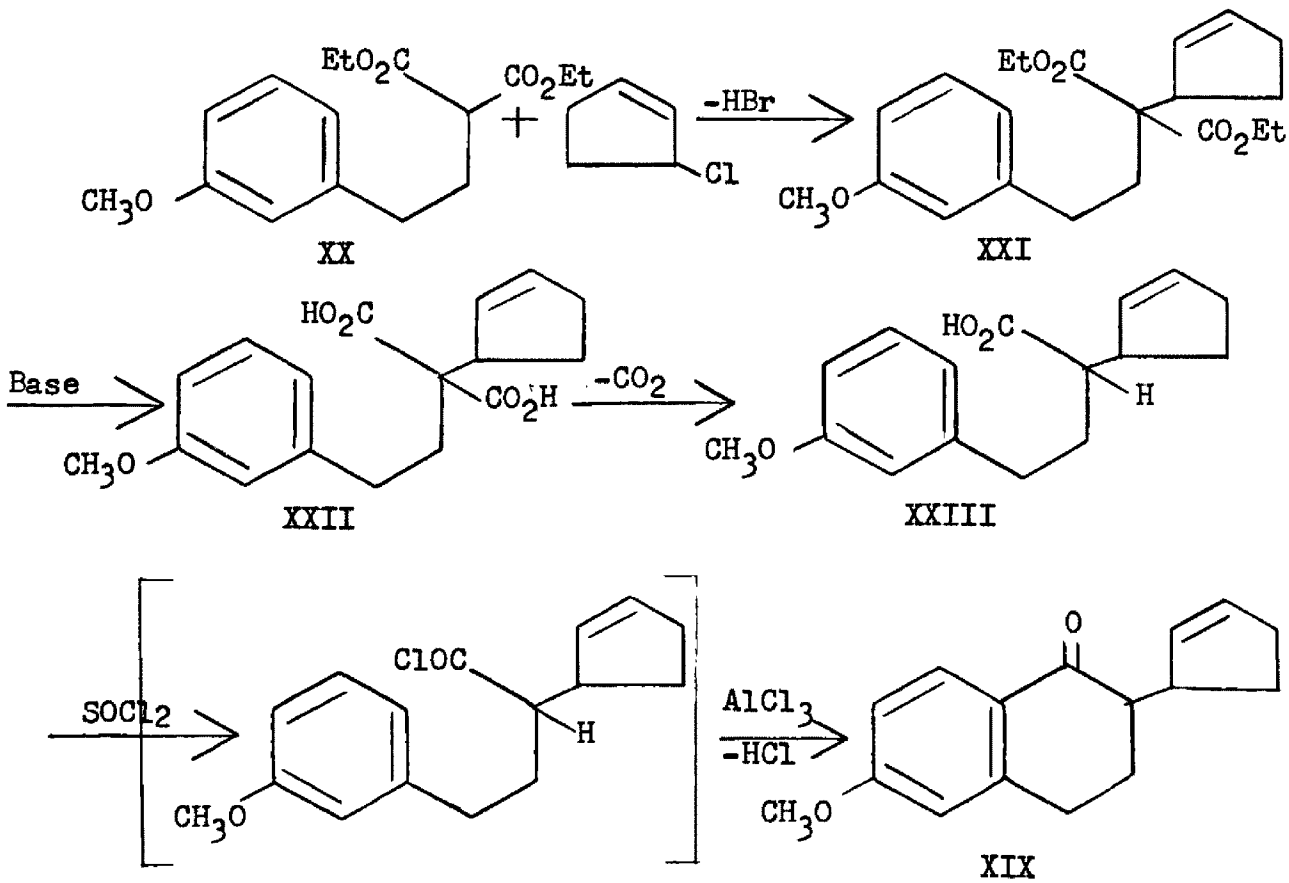
In the synthesis of I and II (see outline on p. 41) it was decided to use 6-methoxytetralone XVI as the simplest starting material. Since a cyclopentenyl group was desired at the two position, the β-keto aldehyde XVII and the β-keto ester XVIII were prepared as intermediates. This was necessary in order to activate the carbon of the ketone. With no activation, alkylation of XVI resulted in the decomposition of cyclopentenyl bromide and the desired product 2-(Δ^2-cyclopentenyl)-1,2,3,4-tetrahydro-6-methoxynaphthalenone XIX was not obtained.



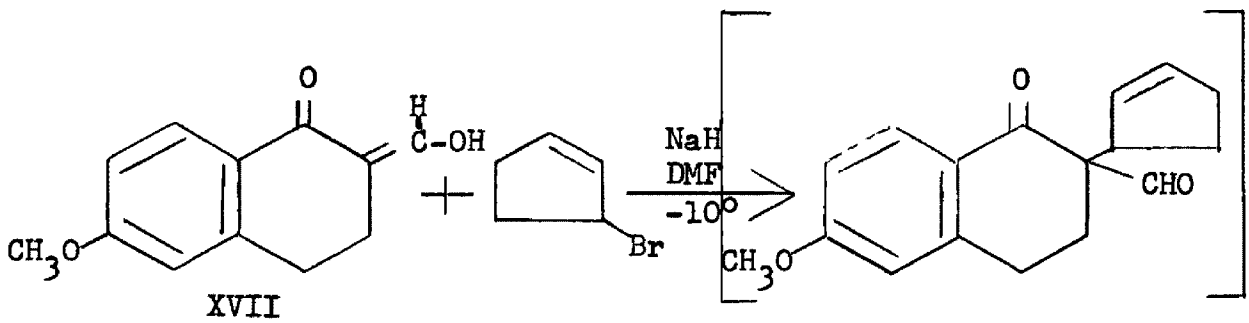
The hydroxymethylene group was obtained at the two position by condensation of XVI with ethyl formate using sodium hydride in benzene.[19] The β-keto ester XVIII was prepared by condensation of XVI with ethyl

carbonate with sodium hydride in ether and a small amount of dimethylformamide. The hydroxymethylene group could be easily removed later by refluxing in alcoholic sodium hydroxide. This was also sufficient to hydrolyze the ester to an acid. Decarboxylation of the acid was accomplished by acidification with dilute hydrochloric acid. The β-keto aldehyde XVII was found to be preferable since the product could be isolated directly and recrystallized from a benzene-cyclohexane mixture. Ninety per cent yields were consistently obtained, and the product was free from starting material.

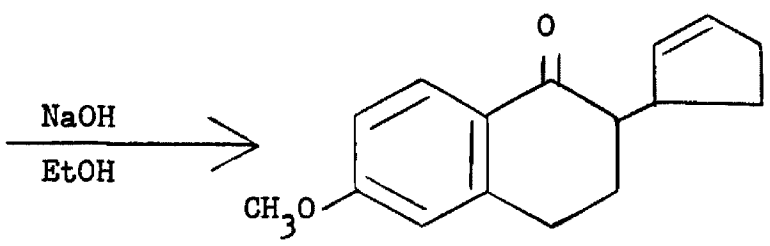
The compound XIX had previously been prepared[20] using the malonic ester synthesis:



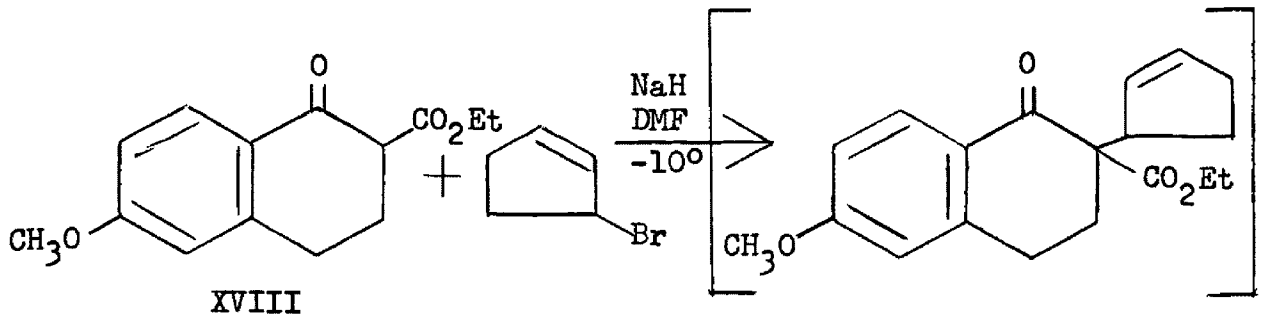
The compound XX was condensed with freshly distilled Δ^2-cyclopentenyl chloride with potassium in dry toluene. The ester XXI was then hydrolyzed to XXII by refluxing with alcoholic potassium hydroxide for twenty-four hours, and decarboxylated with the loss of 1 mole of carbon dioxide to obtain XXIII. Treatment of XXIII with thionyl chloride, followed by ring closure, gave XIX in 21 per cent yield. Buchta and co-workers[20] had also considered the preparation of XIX through XVI by the formation of the methyl glyoxalate of XVI, followed by decarbonylation to the methyl ester, alkylation with Δ^2-cyclopentenyl chloride, and hydrolysis and decarboxylation to XIX. When alkylation of the potassio derivative of the methyl ester of XVI in toluene was attempted, first using cyclopentyl chloride, decomposition occurred. After this failure, alkylation with Δ^2-cyclopentenyl bromide was not even attempted.



XVII



XIX



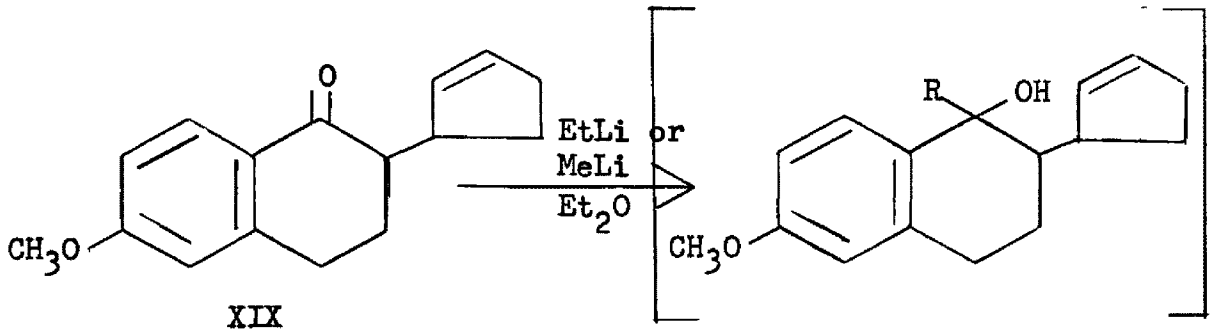
XVIII

XIX

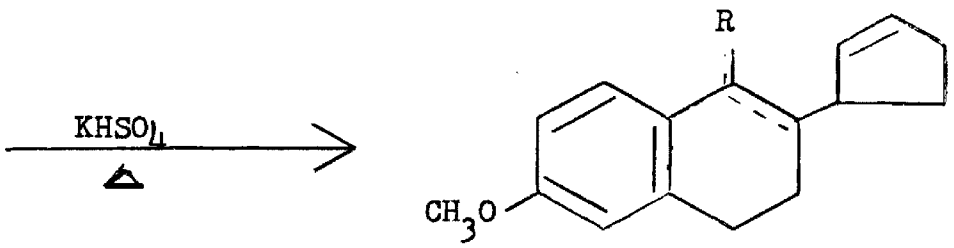
Yields of 70-80 per cent of XIX were obtained by preparing the sodio derivative of XVII or XVIII with sodium hydride in dimethylformamide. With the addition of freshly distilled Δ^2-cyclopentenyl bromide at -10°, alkylation occurred rapidly, accompanied by a 25° temperature increase. Other solvents, such as ether, resulted in decompositon of the Δ^2-cyclopentenyl bromide. The mixture of Δ^2-cyclopentenyl bromide and the sodio derivative of XVII or XVIII was stirred for a few minutes and the product was isolated and refluxed in alcoholic sodium hydroxide under an argon atmosphere to decarbonylate the aldehyde. Longer reflux time was necessary to hydrolyze the ester group to the acid. The acid was decarboxylated with dilute hydrochloric acid. The product XIX provided the basis for derivatives of androgen analogs containing rings A, B and D.

The ethyl or methyl derivative of XIX was prepared by the addition of ethyl or methyl lithium to the carbonyl group, followed by dehydration of the tertiary alcohol with potassium bisulfate to form

2-(Δ^2-cyclopentenyl)-1-ethyl-3,4-dihydro-6-methoxynaphthalene XXIVa or 2-(Δ^2-cyclopentenyl)-3,4-dihydro-6-methoxy-1-methylnaphthalene XXIVb.



XIX

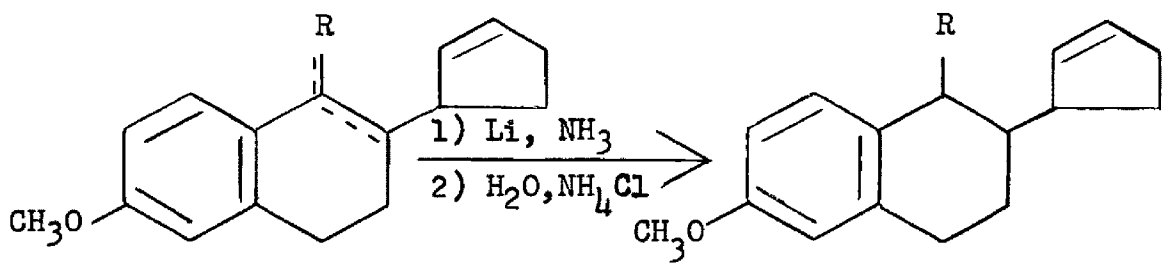


XXIVa R = Et

b R = Me

The alkyl lithium was prepared by the addition of ethyl bromide or methyl iodide to lithium suspended in ether.[21] A small amount of sodium (.1 g.)[22] was dissolved in lithium and the lithium mixture was dispersed in mineral oil. The mineral oil was removed by washing with cyclohexane, and the lithium transferred to the flask with dry ether. A solution of XIX in ether was then added slowly to the alkyl lithium. Even with a large excess of ethyl lithium roughly one third of XIX was recovered due to the formation of the enolate. It was necessary to repeat the treatment with ethyl lithium for XXIVa. This was not necessary with methyl lithium as little starting material was recovered.

The double bond conjugated with the aromatic ring was selectively reduced with lithium in liquid ammonia using water as the proton source to obtain 2-(Δ^2-cyclopentenyl)-1-ethyl-1,2,3,4-tetrahydro-6-methoxy-naphthalene XXVa or 2-(Δ^2-cyclopentenyl)-1,2,3,4-tetrahydro-6-methoxy-1-methylnaphthalene XXVb.



XXIVa R = Et
b R = Me

XXVa R = Et
b R = Me

Alkali metals with ammonia and a proton source have been used for the reduction of a variety of groups, including phenol ethers, unsaturated ketones, and double bonds conjugated with aryl nuclei.[23] This system has no effect on isolated double bonds. The reducing power of the system depends on the alkali metal, lithium being the strongest, and on the nature of the proton source.[24] In general, the stronger the acid, the weaker the reducing power of the proton source. Thus tertiary butyl, isopropyl, or ethyl alcohols with sodium easily reduce phenyl ethers to enol ethers. While methanol and water fail in this reaction they will reduce the conjugated double bond. Generally, ammonium

chloride has been used as a proton source for the reduction of conjugated double bonds, but it is inconvenient because it causes the reaction mixture to become very thick. It was found that water, followed by ammonium chloride, gave excellent results without causing any mechanical problem.

If the aromatic ether is easily reduced, it is often advantageous to use sodium as it gives fewer by-products due to hydrogenolysis. If sodium is used it is necessary to use redistilled ammonia as colloidal iron particles often found in commercial ammonia catalyze the reaction between sodium and alcohol and decrease the amount of reduction.[25] The corresponding reaction between lithium and alcohol is less strongly catalyzed, being unaffected up to 25 ppm. This explains the reported advantage of lithium[26] when ammonia is used without distillation. For reduction of compounds like XXIVa and XXIVb, lithium is often used because it is unnecessary to redistill the ammonia.

The order of addition to the ammonia of the alkali metal, alcohol, and compound to be reduced also has an effect on the reduction. If the alcohol is initially present it serves to reduce the basicity of the reaction medium and suppresses rearrangement, in addition to hydrogenolysis.[27]

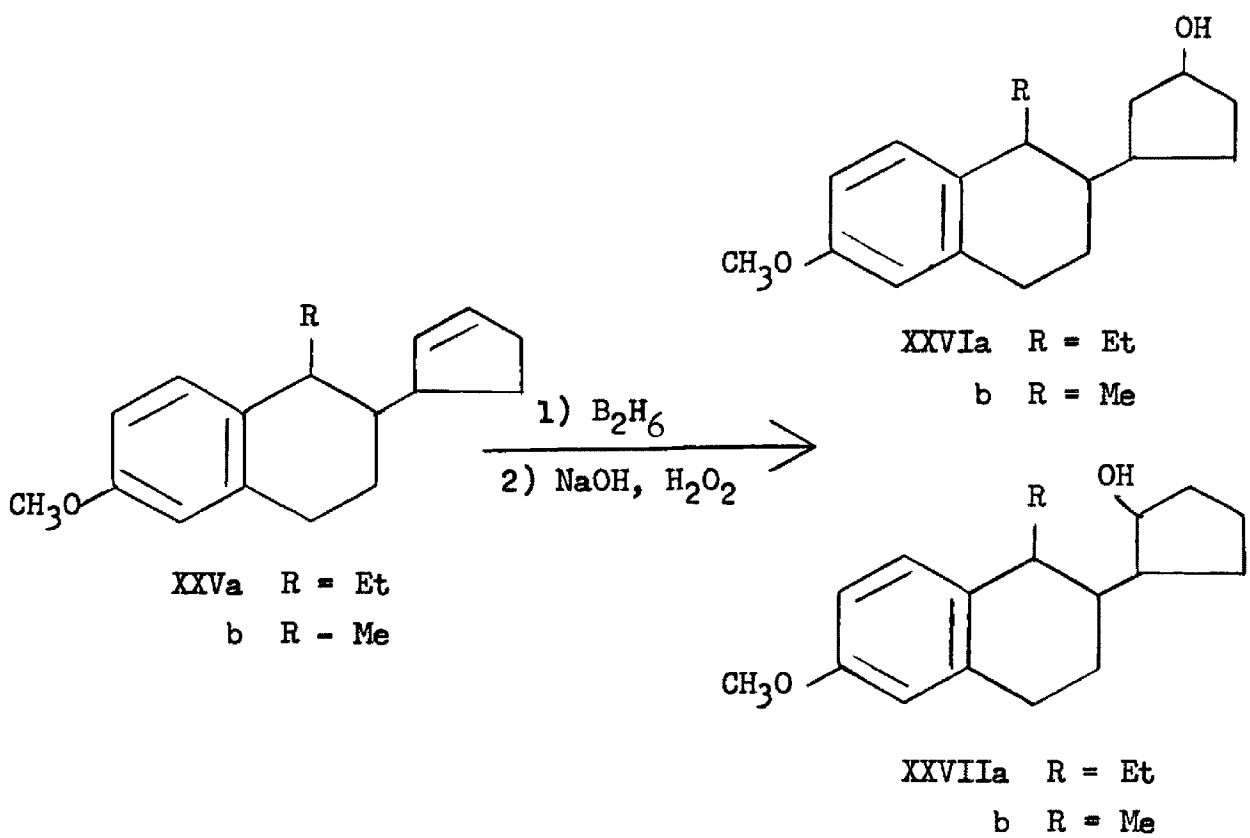
Optimum conditions for the reduction were found to be the rapid addition of lithium to liquid ammonia at -40°, followed by the rapid addition of XXIVa or XXIVb dissolved in a small amount of benzene, alternating this with the co-solvent, ether. Morpholine was also tried as co-solvent but gave poor results. Water, diluted with dioxane, was used as the proton source, followed by ammonium chloride. The product

XXVa or XXVb was chromatographed on silica gel H with benzene to remove some highly colored material.

The ethylenic compounds XXIVa and XXIVb are actually mixtures of two isomers as the double bond can be located in two different positions. The n.m.r. spectra showed that approximately one half of XXIVa contained one ethylenic proton. This would represent the isomer with the external double bond. In the reduction with lithium, addition of lithium to the double bond would be trans due to the repulsion between lithium atoms.[28] When the double bond is reduced the trans isomer would be expected, i.e., the ethyl group trans to the cyclopentenyl group. For the internal double bond only the trans isomer could be obtained. For the external double bond reduction with lithium can result in either the trans isomer or the cis isomer, though the trans isomer would be expected.[29] Thin layer chromatography showed only one isomer. To determine if this was the trans isomer, the results of a lithium reduction of XXIVa were compared to a catalytic reduction[30] which would give both the cis and trans isomer. Since hydrogenation also reduces the cyclopentenyl double bond, XXVa of the lithium reduction was catalytically reduced in order to obtain identical samples for comparison, i.e., 2-cyclopentyl-1-ethyl-1,2,3,4-tetrahydro-6-methoxynaphthalene. Thin layer chromatography showed two isomers for the catalytic reduction, the trans isomer with the ethyl group and cyclopentenyl group trans to each other, and the cis isomer where the two groups are cis. The one isomer from the lithium reduction corresponded to the slower moving of the two (cis and trans) isomers. Since the trans isomer would be more planar, and thus slower on the thin layer, it was assumed that the

lithium reduction gave the trans isomer. This was also supported by the n.m.r. spectra which had shown that approximately one half of XXIVa had one ethylenic proton, representing the isomer with the double bond external to the ring. Since the reduction of XXIVa produced only one isomer, the isomer obtained must be identical to the one obtained when the double bond is located internally, i.e., the trans isomer.

Hydroboration of the cyclopentenyl group, followed by alkaline oxidation, gave two isomeric alcohols, the ethyl or methyl derivatives of 3-(1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol XXVIa,b and the ethyl or methyl derivatives of 2-(1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol XXVIIa,b.



XXVa R = Et
b R = Me

XXVIa R = Et
b R = Me

XXVIIa R = Et
b R = Me

The hydroboration method of Brown and Rao[31] was used. The diborane evolved is quantitative as is the reaction between diborane and the olefin, and there are no other products.[32] The product actually contained four isomers: the two position isomers XXVI and XXVII, and for each of these two epimers, the hydroxyl group cis and trans to the naphthalene nucleus. Since XXVI was the isomer desired an attempt was made to exert a directive influence on the hydroboration. Accordingly, trimethylethylene was first hydroborated to form disiamylborane, which possesses large steric requirements due to the two highly branched organic groups attached to the boron atom.[33] The disiamylborane then reacted with the unsaturated compound XXVa. There was no indication of any directive effect. Approximately the same mixture of isomers was obtained as shown by thin layer chromatography and gas liquid chromatography. In this directive attempt the diborane was generated in situ by the addition of a diglyme solution of iodine to a diglyme solution of sodium borohydride and the unsaturated compound.[34] There was no particular advantage in terms of yield.

$$2NaBH_4 + I_2 \longrightarrow 2NaI + B_2H_6 + H_2$$

Brown and Zweifel[35] state that in general, the hydroboration can be regarded as the cis addition of the elements of water to the less hindered side. The addition of diborane to the double bond is visualized as a four centered cubic transition state, with oxygen in the oxidation placed at precisely the same position occupied by boron in the organoborane.[36]

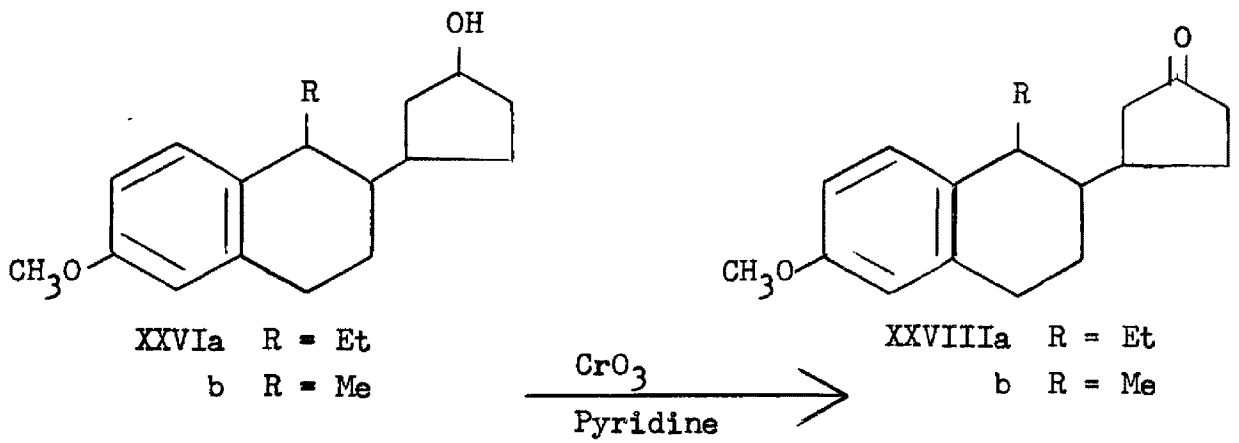
In order to study the relative amounts of the 2-cyclopentanol

and 3-cyclopentanol isomers, XXVIa and XXVIIa, and the cis and trans epimers of each, the mixture was compared to a sample of the pure isomer XXVIa using gas liquid chromatography. The pure isomer XXVIa had been obtained by oxidation of the isomeric alcohol mixture to a mixture of ketonic isomers, and isolation of 1-ethyl-1,2,3,4-tetrahydro-6-methoxy-2-(3-oxocyclopentyl)-naphthalene XXVIIIa through the bisulfite derivative. The compound XXVIIIa was reduced with sodium borohydride to XXVIa. The isomeric mixture of alcohols XXVIa and XXVIIa showed four distinct peaks representing the two position isomers and the cis and trans epimers of each. It was assumed the two larger peaks were the trans isomer since diborane generally approaches from the less hindered side. The 3-cyclopentanol isomer XXVIa showed two peaks due to the cis and trans epimers. The sodium borohydride reduction was evidently not strictly stereospecific. The isomers were identified by chromatographing the 3-cyclopentanol isomer XXVIa with the isomeric mixture XXVIa and XXVIIa. The larger of the peaks of XXVIa corresponded to the trans epimer of XXVIa of the isomeric mixture. The 3-cyclopentanol isomer XXVIa consisted of 71 per cent of the trans epimer and 29 per cent of the cis epimer. The isomeric mixture consisted of 33 per cent of the trans epimer and 11 per cent of the cis epimer of XXVIa, and 40 per cent of the trans epimer and 16 per cent of the cis epimer of XXVIIa. The results indicated that the formation of XXVIa and XXVIIa was approximately one to one, and there was no directive effect.

The sodium borohydride reduction of XXVIIIc, where R = H, was stereospecific giving 100 per cent of the trans epimer.[37] Raney Nickel hydrogenation of XXVIIIc also gave 100 per cent of the trans epimer.[38]

The sodium borohydride probably approaches from the cis side, evidently less hindered, to give the trans epimer.[39] Hydroboration though with diborane gives a mixture of the cis and trans epimers. The presence of the cis epimer where R = Et may be due to front shielding by the ethyl group.

The first step in the separation of the isomers XXVIa and XXVIIa was the chromic acid-pyridine oxidation of the alcohols to the ketone. Tertiary butyl alcohol was tried in place of the pyridine, but the infrared spectra showed incomplete oxidation. Brown[40] had mentioned the oxidation of alcohols directly to ketones after oxidation of the organoborane. The alcohol is dissolved in ether and converted without isolation into the corresponding ketone. If the ketone is subject to epimerization this method offers an advantage.[41] A trial attempt on a modal compound proved unsuccessful.



XXVIa R = Et
b R = Me

XXVIIIa R = Et
b R = Me

XXVIIa R = Et
b R = Me

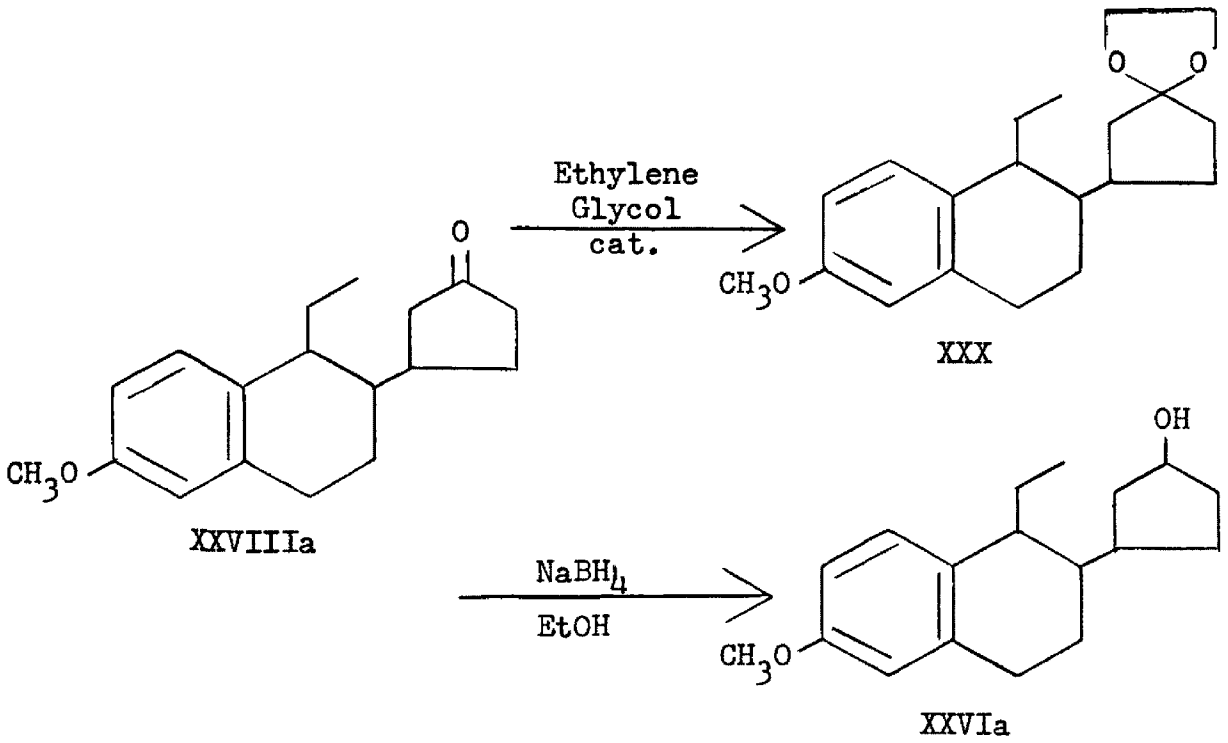
XXIXa R = Et
b R = Me

The separation of the ketone isomers XXVIIIa and XXIXa proved the most difficult and generally resulted in a mixture of the two isomers with XXVIIIa predominating. The semicarbazone of XXVIIIa was prepared and the ketone isomer XXVIIIa isolated by hydrolysis. Attempts to repeat this resulted in a small amount of an oily solid and incomplete separation of the isomers. An attempt to prepare the bisulfite derivative of XXVIIIa was unsuccessful giving only a small amount of XXVIIIa on hydrolysis.

Of the methods tried, the 2,4-dinitrophenylhydrazone removed non-ketonic material but did not separate the isomers. The ethyl group may be a source of steric hindrance, as the methyl derivative XXVIIIb could be separated by the formation of the bisulfite derivative.

The synthesis of the methyl analog of I and II has progressed only to the separation of the isomer XXVIIIb.

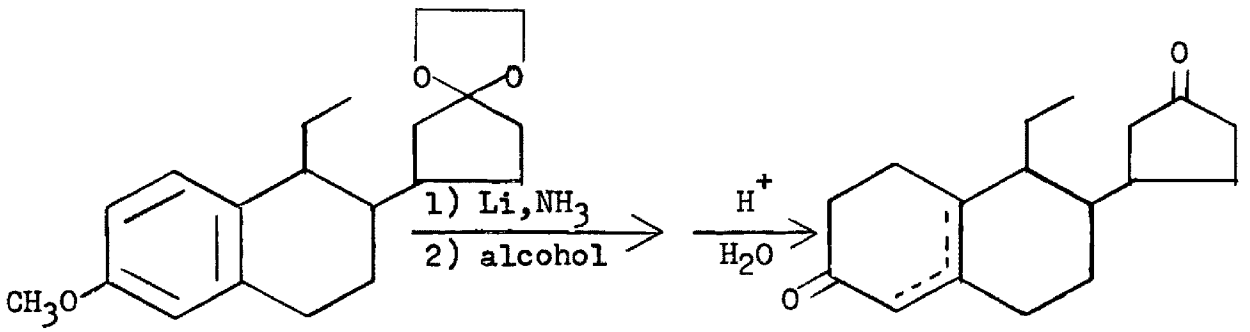
The 3-oxocyclopentyl isomer of the ethyl derivative XXVIIIa was treated in two ways to determine the effect of a carbonyl group and an hydroxyl group on the final compound submitted for bioassay. First, the carbonyl group of XXVIIIa was protected by formation of the ethylene ketal, and this compound XXX was reduced to the unsaturated ketone I. Second, the ketone XXVIIIa was reduced with sodium borohydride to the alcohol XXVIa and this was reduced to the unsaturated ketone II in a method similar to the reduction of XXX.



The ethylene ketal XXX was prepared in nearly quantitative yields by refluxing XXVIIIa with ethylene glycol and p-toluenesulfonic acid. The alcohol XXVIa was prepared by the reduction of XXVIIIa with sodium borohydride in ethanol following Brown's[42] procedure. As the separation of the ketone isomers XXVIIIa and XXIXa was not entirely complete, a minor amount of XXVIIa was also formed. The compound obtained from the reduction XXVIa was shown by gas liquid chromatography to consist of both the cis and trans epimers with the trans epimer in approximately the same proportion as the diborane reaction, 71 per cent of the trans epimer and 29 per cent of the cis epimer.

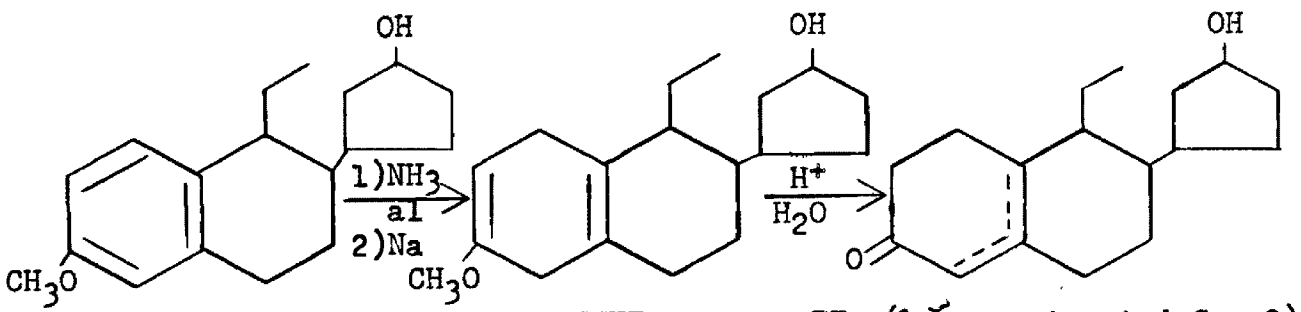
The standard Birch reduction of the anisole ring of both compounds XXX and XXVIa was accomplished using the method of Dryden[25] with some modifications. In both cases redistilled ammonia was used, and the

proton source was isopropyl alcohol. For the reduction of XXX lithium was used as the alkali metal, and the alcohol was added last, whereas for XXVIa sodium was used and added with the alcohol initially present. The co-solvents differed also, morpholine being used for the reduction of XXX, ether for the reduction of XXVIa.



XXX

Ia (β,γ-unsaturated C = O)
b (α,β-unsaturated C = O)

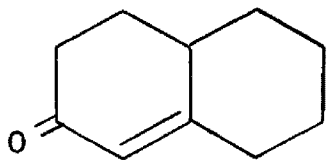


XXVIa XXXI

IIa (β,γ-unsaturated C = O)
b (α,β-unsaturated C = O)

In the reduction of XXX a low boiling forerun indicated that some cleavage of the methoxy group may have occurred. For reasons previously discussed, sodium, instead of lithium, was used in the later reduction of XXVIa with the alkali metal initially present. The enol ether XXX was hydrolyzed with 88 per cent formic acid to I, and then refluxed in dioxane and hydrochloric acid for 30 min. in order to shift the double bond to the conjugated position Ib. The ultraviolet

extinction coefficient value of 3800 indicated that conjugation with the carbonyl was not particularly favored. Assuming an extinction coefficient value of 14,000 for the conjugated isomer Ib, based on an extinction coefficient value of 14,000 for the conjugated unsaturated octalone XXXII[13], the isomeric mixture Ia and Ib contains approximately 27 per cent of Ib. A value of 14,000 seemed reasonable for when this value was assumed as the maximum for II with the ethyl group replaced by H, the n.m.r. spectra, ultraviolet spectra, and gas chromatogram all coincided in the calculation of the percentage of the conjugated isomer.[43]



XXXII

In the reduction of the anisole ring of XXVIa there was no low boiling forerun, but a very high boiling residue was obtained. This may be due to condensation products. The product XXXI was shaken with dilute acetic acid to hydrolyze the enol ether to the unsaturated ketone II. The infrared spectra showed incomplete hydrolysis. When XXXI was shaken with about 53 per cent acetic acid the unsaturated ketone II was obtained. The ultraviolet coefficient value of 3537 indicated that the product contained approximately 26 per cent of the conjugated isomer IIb. In order to further shift the double bond to the conjugated isomer IIb the isomeric mixture was refluxed in dioxane

and 6M hydrochloric acid for 1.5 hrs. The infrared spectra showed only a small shift to the conjugated isomer IIb, and the ultraviolet extinction coefficient value of 3920 indicated that the shift was very slight, only 28 per cent of IIb was indicated.

When the ethyl group of II is replaced by an H atom and treated in a similar manner the enol ether was hydrolyzed by dilute acetic acid immediately to the β,γ-unsaturated ketone. Refluxing this unsaturated ketone in a similar manner with dioxane and hydrochloric acid gave the conjugated ketone in a high percentage.[44] Conversion from 41 per cent to 90 per cent of the α,β-unsaturated ketone occurred in 1.5 hr. The compound II was converted only from 26 per cent to 28 per cent of the α,β-unsaturated ketone in the same length of time. The explanation may be that steric interactions due to the ethyl group are absent when the ethyl group is replaced by a hydrogen atom. The conjugated ketone is more puckered than the non-conjugated, the non-conjugated isomer having a more planar molecule. Possibly when II rearranges to the conjugated isomer IIb there is steric interference of the ethyl group with other groups present.

The fraction of the isomeric mixture IIa and IIb distilling at 137-140° (0.1 mm.) was sent for bioassay.

IV. EXPERIMENTAL[a]

2-Hydroxymethylene-6-methoxytetralone XVII. - Sodium hydride[b] (17 g., 0.375 mole) was added to a cold mixture of 6-methoxytetralone XVI (30 g., 0.17 mole), ethyl formate (50 ml., 0.625 mole), and 300 ml. of dry benzene, and stirred at room temperature under an argon atmosphere for 4 hr. After the reaction was complete, the mixture was cooled in an ice bath and ice water added. The water layer was separated and was acidified with 30 ml. of concentrated hydrochloric acid and ice. The tan precipitate was collected and washed with water and sodium bicarbonate solution until neutral. The crude product was dissolved in benzene, filtered, and recovered from the benzene solution through the addition of cyclohexane.
Yield: pale yellow crystals, 33 g. (90%) m.p. 66-68, lit.[45] m.p. 68-69.

Ethyl ester of 6-methoxy-1-keto-1,2,3,4-tetrahydro-2-naphthoic acid XVIII. - A mixture of sodium hydride (11.2 g., 0.25 mole), 6-methoxytetralone XVI (35.2 g., 0.20 mole), ethyl carbonate (29 ml., 0.24 mole), and 200 ml. of dry ether was heated to reflux and 24 ml. of dry dimethylformamide added. After refluxing gently for 3 hr., the

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a) Melting points are uncorrected. Microanalysis by Galbraith Microanalytical Laboratories. Ultraviolet spectra were taken in 95% ethanol (Beckmann DU) and infrared spectra in carbon tetrachloride, unless otherwise indicated (Beckmann IR5). The n.m.r. spectra were run and interpreted by Dr. Donald P. Hollis of Varian Associates. The gas liquid chromatograms were run by Dr. R. Geer of M.S.U., Bozeman, Montana.

b) The sodium hydride used throughout was a 53% suspension in mineral oil. Prior to use it was washed with dry benzene.

mixture was cooled, and ice water and benzene added. The water layer was acidified with hydrochloric acid and extracted with benzene. After washing the combined benzene layers with water until neutral, the solvent was evaporated in vacuo and the product distilled.
Yield: yellow oil, 39 g. (79%). B.P. 159-166° (0.1 mm.).
Anal. Calc. for $C_{14}H_{16}O_4$: C, 67.74; H, 6.45. Found: C, 67.40; H, 6.76.

Cyclopentene. - Polyphosphoric acid (26 g. of phosphorous pentoxide and 18 g. of syrupy phosphoric acid) was added to cyclopentanol (78 ml., 0.86 mole) and the mixture distilled, keeping the temperature below 55°. The product was dried over calcium chloride and redistilled. The product was refrigerated until used.
Yield: colorless liquid, 50 g. (85%). B.P. 43-44° (76 mm.), lit.[46] B.P. 44°.

Δ^2-Cyclopentenyl bromide.[47] - N-Bromosuccinimide (21 g.) was mixed with 16 ml. of cyclopentene, 25 ml. of carbon tetrachloride, and 1 g. of benzoyl peroxide and the mixture refluxed using a 150 watt floodlamp as the source of heat. A marked drop in the reflux line indicated complete reaction after about 25 min. with a high temperature near 75°. The flask was immediately cooled in cold water and the mixture filtered. The solid was washed with petroleum ether. The product was distilled under vacuum using a cold water condenser with the receiving flask imbedded in ice. Distillation range, 25-40°. The reaction time can be controlled by the amount of carbon tetrachloride used as solvent; decreasing the amount of carbon tetrachloride decreases the reaction time considerably. The product was very unstable,

especially to moisture, and must be used immediately. Thus yields were not determined.

2-(Δ^2-Cyclopentenyl)-1,2,3,4-tetrahydro-6-methoxynaphthalenone XIX. - Freshly distilled Δ^2-cyclopentenyl bromide (approximately 16 g., 0.109 mole) was added to a mixture of 2-hydroxymethylene-6-methoxytetralone XVII (12 g., 0.059 mole), or the ethyl ester of 6-methoxy-1-keto-1,2,3,4-tetrahydro-2-naphthoic acid XVIII (15 g., 0.061 mole), 75 ml. of dimethylformamide, and sodium hydride (3.7 g., 0.082 mole) at -10°. Alkylation occurred immediately as shown by a temperature increase of 25°, and a color change: yellow if the reaction was complete, purple if there was insufficient bromide. After stirring 15 min. at room temperature, the flask was cooled, and water and benzene added. The product was extracted with benzene and the solvent evaporated. If XVII was used the oil obtained was refluxed 30 min. with 25 ml. of 95% ethanol and 20 ml. of 20% sodium hydroxide. For the ester XVIII 30 ml. of ethanol and 30 ml. of sodium hydroxide were used, and the reflux time was increased to 45 min., and then the mixture was poured into 35 ml. of 6 N hydrochloric acid to decarboxylate the acid. For both the alkylation and the hydrolysis an argon atmosphere was used. For every two alkylations, the products were combined and fractionated to remove the low boiling forerun consisting primarily of tetralone. The infrared spectra showed a band at approximately 13.9μ characteristic of the cyclopentenyl group.

Yield: yellow liquid, 11 g. (78%). B.P. 140-160° (0.1 mm.), lit.[48] B.P. 174-178° (1.3-1.5 mm.).

2-(Δ^2-Cyclopentenyl)-1-ethyl-3,4-dihydro-6-methoxynaphthalene XXIVa[c]. - Lithium (2.1 g., 0.29 mole) was melted in a test tube containing 1-2 ml. of mineral oil and sodium (0.1 g.)[22] was added and dissolved in the lithium. The metal was cooled and transferred to a 50 ml. flask containing about 35 ml. of heavy mineral oil, remelted, and stirred at high speed until the metal was dispersed into fine particles. After cooling, the oil was separated and the metal washed with cyclohexane. The metal was then transferred to a 3-necked flask with 50 ml. of dry ether. Ethyl bromide (0.5 ml.) was added to initiate the reaction and when the temperature of the mixture stopped rising it was cooled to -10° (argon atmosphere). Ethyl bromide (11.5 ml., 0.15 mole) dissolved in 11.5 ml. of dry ether was added slowly through an addition funnel. After the addition was completed, 2-(Δ^2-cyclopentenyl)-1,2,3,4-tetrahydro-6-methoxynaphthalenone XIX (17.6 g., 0.073 mole) dissolved in dry benzene was slowly added while keeping the temperature around 10°. The mixture was stirred at room temperature for 15 min., ice water added, and the product extracted with benzene. The tertiary alcohol was not isolated but immediately dehydrated under vacuum by heating with potassium bisulfate (1.0 g., 0.007 mole) in an oil bath at 110° until bubbling ceased. Benzene was then added and the mixture filtered. The oil remaining after evaporation of the benzene was distilled at 130-150° (0.1 mm.). The infrared spectra showed a band at 5.95μ (α,β-unsaturated C = O) indicating that about one

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c) This product is a mixture of two isomers due to different locations of the double bond, i.e., either internal or external to the ring.

third of the starting material was unreacted, and the above procedure was repeated using one half quantities.

Yield: yellow liquid, 17.8 g. (96%). B.P. 144-154° (0.1 mm.).

Anal. Calc. for $C_{17}H_{20}O$: C, 85.04; H, 8.66. Found: C, 85.31; H, 8.84.

2-(Δ^2-Cyclopentenyl)-3,4-dihydro-6-methoxy-1-methylnaphthalene XXIVb[d]. - Compound XXIVb was prepared using the same general procedure outlined for XXIVa. Lithium (11 g., 0.16 mole), methyl iodide (48 ml., 0.078 mole), and 2-(Δ^2-cyclopentenyl)-1,2,3,4-tetrahydro-6-methoxynaphthalenone XIX (9.5 g., 0.039 mole) were reacted as described for XXIVa. It was not necessary to repeat the reaction as the infrared spectra indicated only a small amount of starting material. The product was chromatographed to remove colored impurities. A thin layer chromatogram showed two spots indicating two isomers.

Yield: colorless liquid, 8.6 g. (92%). B.P. 135-143° (0.1 mm.).

2-(Δ^2-Cyclopentenyl)-1-ethyl-1,2,3,4-tetrahydro-6-methoxynaphthalene XXVa. - A benzene solution of 2-(Δ^2-cyclopentenyl)-1-ethyl-3,4-dihydro-6-methoxynaphthalene XXIVa (17.8 g., 0.070 mole) was added alternately with 84 ml. of ether to a solution of lithium (4.2 g., 0.060 mole) in 300 ml. of liquid ammonia at -40°. The mixture was stirred for 10 min. (argon atmosphere) and water (15 ml., 0.83 mole) diluted with 16 ml. of dioxane, was added slowly, discharging the blue-black color of the lithium in a few minutes. Ammonium chloride

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[d] This product is a mixture of two isomers with the double bond located either internal or external to the ring.

(23 g., 0.43 mole) was then added in three portions. The ammonia was evaporated, water added, and the product extracted with benzene. The benzene layer was washed with water until neutral, and after evaporation of the benzene the product was distilled. The product was purified by chromatographing on silica gel H with benzene. A thin layer chromatogram of the product indicated only one isomer.

Yield: colorless liquid, 14.5 g. (81%). B.P. 124-134° (0.1 mm.).

2-(Δ^2-Cyclopentenyl)-1,2,3,4-tetrahydro-6-methoxy-1-methylnaphthalene XXVb. - The same general procedure for XXVa was followed. A benzene solution of 2-(Δ^2-cyclopentenyl)-3,4-dihydro-6-methoxy-1-methylnaphthalene XXIVb (8.6 g., 0.036 mole) was added alternately with 42 ml. of ether to lithium (2.1 g., 0.30 mole) in 150 ml. of ammonia. After stirring 10 min., water (8 ml., 0.44 mole) and dioxane (8 ml.) were added, followed by ammonium chloride (12 g., 0.22 mole). The thin layer chromatogram of this product showed only one spot indicating only one isomer.

Yield: colorless liquid, 8.1 g. (93%). B.P. 126-140° (0.1 mm.).

2-Cyclopentyl-1-ethyl-1,2,3,4-tetrahydro-6-methoxynaphthalene.[49]-1. Hydrogenation of 2-(Δ^2-cyclopentenyl)-1-ethyl-3,4-dihydro-6-methoxynaphthalene XXIVa: Hydrogenation of XXIVa (1.0 g., 0.004 mole) in 25 ml. of ethanol with 0.3 g. of 5% palladium-charcoal catalyst resulted in the absorbtion of about 204 ml. of hydrogen. The mixture was filtered, the filtrate evaporated, and the product distilled. The thin layer chromatogram showed two spots indicating the cis and trans isomers.

Yield: a liquid. B.P. 129° (0.01 mm.). n^{20} 1.5463.

2. Hydrogenation of 2-(Δ^2-cyclopentenyl)-1-ethyl-1,2,3,4-tetrahydro-6-methoxynaphthalene XXVa: Hydrogenation of XXVa (0.9 g., 0.004 mole) in ethanol using 0.3 g. of 5% palladium-charcoal catalyst resulted in the absorbtion of about 107 ml. of hydrogen. The mixture was filtered, the filtrate evaporated, and the product distilled. The thin layer chromatogram of the product showed only one spot indicating only one isomer, and this spot corresponded to the slower moving of the two isomers obtained in the hydrogenation above of XXIVa.

Yield: a liquid, 0.7 g. (77%). B.P. 117-127° (0.01 mm.).

Anal. Calc. for $C_{18}H_{26}O$: C, 83.72; H, 10.07. Found: C, 83.91; H, 10.16.

3-(1-Ethyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol XXVIa and 2-(1-ethyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol XXVIIa.[e] -

1. Diborane Method:

Using the method of Brown and Rao[31] diborane was generated using 9 g. (0.063 mole) of boron trifluoride etherate and 1.4 g. (0.037 mole) of sodium borohydride in an argon atmosphere. The diborane was passed into a 3-necked flask containing 2-(Δ^2-cyclopentenyl)-1-ethyl-1,2,3,4-tetrahydro-6-methoxynaphthalene XXVa (10.7 g., 0.042 mole) and 60 ml. of dry ether at 0°. After stirring at room temperature for 3.5 hr. the mixture was cooled to -10°, and 23 ml. of 12% sodium hydroxide slowly added followed by 35 ml. of 30% hydrogen peroxide, added slowly at first and then rapidly as the reaction ceases. After stirring 10 min. water was added and the product extracted with benzene. After evapora-

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[e] This product is a mixture of four isomers due to the epimers of the two position isomers.

tion of the solvent the product was distilled. The infrared spectra showed an hydroxyl band at 2.9μ.

Yield: colorless liquid, 11.0 g. (96%). B.P. 135-155° (0.1 mm.).

Anal. Calc. for $C_{18}H_{26}O_2$: C, 78.83; H, 9.49. Found: C, 78.79; H, 9.65.

2. Disiamylborane Method:[50]

Diborane was generated in situ by the addition of iodine (15.2 g., 0.060 mole) in 60 ml. of diglyme to a solution of trimethylethylene (12.6 ml., 0.120 mole) and sodium borohydride (4.6 g., 0.120 mole) in 70 ml. of diglyme at -10°. After stirring 1 hr. at room temperature the solution was cooled to 0° and 2-(Δ^2-cyclopentenyl)-1-ethyl-1,2,3,4-tetrahydro-6-methoxynaphthalene XXVa (15.6 g., 0.037 mole) in 10 ml. of diglyme was added slowly. After stirring 2 hr. at room temperature the compound was oxidized as in the diborane method (1) using 40 ml. of 12% sodium hydroxide and 60 ml. of 30% hydrogen peroxide. The reaction mixture was stirred 4 hr. at room temperature and worked up as in the diborane method (1). The infrared spectra of the product showed an hydroxyl band at 2.9μ. Gas liquid chromatography showed four peaks: two large peaks for the trans isomers (73%), and two smaller peaks for the cis isomers (27%).

Yield: colorless liquid, 9.3 g. (91%). B.P. 140-160° (0.1 mm.).

3-(1,2,3,4-Tetrahydro-6-methoxy-1-methyl-2-naphthyl)-cyclopentanol XXVIb and 2-(1,2,3,4-tetrahydro-6-methoxy-1-methyl-2-naphthyl)-cyclopentanol XXVIIb .[f] - Diborane was generated in a separate flask by the slow addition of iodine (8.3 g., 0.32 mole) in

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[f] This product is a mixture of four isomers due to the epimers of the two position isomers.

45 ml. of diglyme to sodium borohydride (2.5 g., 0.065 mole) in 60 ml. of diglyme in an argon atmosphere. The diborane was passed into a solution of 2-(Δ^2-cyclopentenyl)-1,2,3,4-tetrahydro-6-methoxy-1-methylnaphthalene XXVb (15.7 g., 0.065 mole) in 90 ml. of dry ether, and proceeding as in XXVIa, stirred 1 hr. at room temperature, cooled, and 36 ml. of 10% potassium carbonate and 15.5 ml. of 30% hydrogen peroxide added. After stirring overnight at room temperature the product was isolated as before for XXVIa. The infrared spectra of the product showed an hydroxyl band at 2.9μ. The low boiling forerun showed no band at 2.9μ(OH), but had a carbonyl band at 5.8μ. This may have been due to a poor alkylation in the preparation of XIX due to impurities in the ester XVIII. The infrared spectra of both fractions in carbon disulfide showed no band at 13.9μ characteristic of the cyclopentenyl group.

Yield: colorless liquid, 6.3 g. (37%). B.P. 160-180° (0.1 mm.).

1-Ethyl-1,2,3,4-tetrahydro-6-methoxy-2-(3-oxocyclopentyl)-naphthalene XXVIIIa and 1-ethyl-1,2,3,4-tetrahydro-6-methoxy-2-(2-oxocyclopentyl)-naphthalene XXIXa. - To chromic acid (11.2 g., 0.112 mole) in 224 ml. of pyridine was added a pyridine solution of 3-(1-ethyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol XXVIa and 2-(1-ethyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol XXVIIa (11.2 g., 0.041 mole). It was found necessary to keep the reaction mixture cool to prevent a temperature rise which caused the mixture to thicken. After stirring 2 hr. at room temperature, water and benzene were added and the mixture filtered. The filtrate was extracted with benzene and the benzene layer was washed with dilute

hydrochloric acid until there was no odor of pyridine, and washed with water until the benzene layer was neutral. The product was then distilled. The infrared spectra of the product showed a carbonyl band at 5.75μ. The thin layer chromatogram of the product showed two ketone spots. When tertiary butyl alcohol was tried as a solvent the infrared spectra showed an hydroxyl band at 2.9μ indicating incomplete oxidation. Yield: yellow liquid, 10.1 g. (91%). B.P. 150-158° (0.1 mm.).

1,2,3,4-Tetrahydro-6-methoxy-1-methyl-2-(3-oxocyclopentyl)-naphthalene XXVIIIb and 1,2,3,4-tetrahydro-6-methoxy-1-methyl-2-(2-oxocyclopentyl)-naphthalene XXIXb. - The same procedure was followed as for XXVIIIa and XXIXa. Chromic acid (6.3 g., 0.062 mole), 3-(1,2,3,4-tetrahydro-6-methoxy-1-methyl-2-naphthyl)-cyclopentanol XXVIb and 2-(1,2,3,4-tetrahydro-6-methoxy-1-methyl-2-naphthyl)-cyclopentanol XXVIIb (6.3 g. 0.024 mole), and 115 ml. of pyridine were stirred together 8 hr. keeping the temperature below 25°. The infrared spectra showed a carbonyl band at 5.75μ. The thin layer chromatogram of the product showed three ketone spots. The one traveling very fast was evidently a contaminent.
Yield: yellow liquid, 5.0 g. (80%). B.P. 140-150° (0.1 mm.).

Isolation of the isomer 1-ethyl-1,2,3,4-tetrahydro-6-methoxy-2-(3-oxocyclopentyl)-naphthalene XXVIIIa. - The mixture of ketone isomers XXVIIIa and XXIXa (5.6 g., 0.021 mole) was dissolved in 23 ml. of methanol and added to semicarbazide hydrochloride (6 g., 0.054 mole), 20 ml. of water and 9 ml. of pyridine, and stirred overnight at room temperature. The precipitate was filtered, washed with a mixture of

petroleum ether and diethyl ether, and dried at room temperature. The semicarbazone (4.3 g.) was hydrolyzed by refluxing 30 min. in 8.1 ml. of pyruvic acid, 81 ml. of glacial acetic acid, and 41 ml. of water. The thin layer chromatogram showed only one ketone spot. Later attempts to form the semicarbazone resulted in an oily solid and incomplete separation.

Yield: yellow liquid, 3.8 g. (67% of original isomer mixture).

Anal. Calc. for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82. Found: C, 79.11; H, 8.77.

Isolation of the isomer 1-ethyl-1,2,3,4-tetrahydro-6-methoxy-2-(3-oxocyclopentyl)-naphthalene XXVIIIa. - The mixture of ketone isomers XXVIIIa and XXIXa (8.4 g., 0.035 mole) was dissolved in 24 ml. of ether and stirred 48 hr. at room temperature with sodium metabisulfite (45 g., 0.237 mole), 65 ml. of water, and 20 ml. of methanol. The precipitate was collected and washed with petroleum ether. The bisulfite was hydrolyzed by heating with 10 ml. of benzene and 35 ml. of 88% formic acid for 15 min., followed by 30 ml. of 20% hydrochloric acid. Less than 1 g. of product XXVIIIa was obtained. The thin layer chromatogram of the product showed one ketone spot. The filtrate of the above reaction was extracted with benzene and the oil recovered was distilled; 5.9 g. of the ketone isomers XXVIIIa and XXIXa was recovered. The thin layer chromatogram showed two ketone spots indicating the separation was incomplete.

Isolation of the isomer 1,2,3,4-tetrahydro-6-methoxy-1-methyl-2-(3-oxocyclopentyl)-naphthalene XXVIIIb. - The ketone mixture XXVIIIb and XXIXb (5 g., 0.019 mole) was stirred with sodium metabisulfite

(24 g., 0.126 mole), 32 ml. of water, 10 ml. of methanol, and 12 ml. of ether for 16 hr. The product was isolated as for XXVIIIa. The bisulfite was hydrolyzed by refluxing with 40 ml. of 88% formic acid, 25 ml. of benzene, and 55 ml. of 20% hydrochloric acid for 15 min., and isolated as in XXVIIIa. The thin layer chromatogram showed two ketone spots, one very faint, indicating a minor amount of the other isomer. Yield: yellow liquid, 1.9 g. (38%). B.P. 140-170° (0.1 mm.).

Anal. Calc. for $C_{17}H_{22}O_2$: C, 79.11; H, 8.53. Found: C, 80.03; H, 9.32.

2,4-Dinotrophenylhydrazone of 1-ethyl-1,2,3,4-tetrahydro-6-methoxy-2-(3-oxocyclopentyl)-naphthalene XXVIIIa and 1-ethyl-1,2,3,4-tetrahydro-6-methoxy-2-(2-oxocyclopentyl)-naphthalene XXIXa. - An ethanol solution (220 ml.) of the ketone isomers XXVIIIa and XXIXa (10.1 g., 0.037 mole) was mixed with 2,4-dinitrophenylhydrazine (14 g., 0.071 mole) in 80 ml. of 85% phosphoric acid, and the mixture stirred 15 min. The orange precipitate was collected, washed with ethanol, and dried at room temperature. The 2,4-dinitrophenylhydrazone was hydrolyzed by refluxing 4 hr. in 50 ml. pyruvic acid, 300 ml. glacial acetic acid, and about 15 ml. of water. The product was extracted with benzene, the benzene evaporated, and the product distilled. The thin layer chromatogram of the product showed two ketone spots, the first larger and darker, indicating a mixture of the two ketone isomers XXVIIIa and XXIXa was obtained, XXVIIIa predominating. This procedure did not give complete separation of the isomers, but served to remove non-ketonic material.

Yield: yellow liquid, 7.2 g. (71.3% of the original isomer mixture).

1-Ethyl-1,2,3,4-tetrahydro-6-methoxy-2-(3-oxocyclopentyl)-naphthalene ethylene ketal XXX. - A mixture of ethylene glycol (5 ml., 0.09 mole), 1-ethyl-1,2,3,4-tetrahydro-6-methoxy-2-(3-oxocyclopentyl)-naphthalene XXVIIIa (5.3 g., 0.019 mole), and 0.25 g. of p-toluenesulfonic acid was refluxed 4 hr. in 175 ml. dry benzene using a water separator. The mixture was distilled and the distillate was poured into a solution of sodium bicarbonate, and extracted with benzene. After evaporation of the benzene the product was distilled. The infrared spectra showed no carbonyl band at 5.75μ (C = O).
Yield: yellow liquid, 6.0 g. (98%). B.P. 125-140° (0.1 mm.).
Anal. Calc. for $C_{20}H_{28}O_3$: C, 75.95; H, 8.86. Found: C, 76.07; H, 9.12.

3-(1-Ethyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol XXVIa. - A mixture of sodium borohydride (1.4 g., 0.037 mole) and 1-ethyl-1,2,3,4-tetrahydro-6-methoxy-2-(3-oxocyclopentyl)-naphthalene XXVIIIa (4 g., 0.015 mole) was refluxed for 1 hr. in 100 ml. of ethanol. The solution was acidified through the addition of 3 N hydrochloric acid, water was added, and the product was extracted with benzene. The infrared spectra showed an hydroxyl band at 2.9μ (OH). The thin layer chromatogram showed one spot, indicating one alcohol isomer only. The gas liquid chromatogram showed two peaks representing 71% of the trans epimer and 29% of the cis epimer.
Yield: yellow liquid, 4.0 g. (99%). B.P. 135-155° (0.1 mm.).
Anal. Calc. for $C_{18}H_{26}O_2$: C, 78.83; H, 9.49. Found: C, 78.79; H, 9.65.

5-Ethyl-3,4,5,6,7,8-hexahydro-6-(3-hydroxycyclopentyl)-2-(1H)-naphthalenone IIa and 5-ethyl-4,4a,5,6,7,8-hexahydro-6-(3-hydroxycyclopentyl)

-2(3H)-naphthalenone IIb. - Following the procedure of Dryden,[25] 3-(1-ethyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)-cyclopentanol XXVIa[g] (8.8 g., 0.033 mole) was dissolved in 82 ml. of ether and added to 280 ml. of redistilled ammonia at -40°, followed by isopropyl alcohol (82 ml., 1.07 mole). Sodium (3.4 g., 0.15 mole) was added and the mixture stirred until a color change from blue-black to white indicated complete reaction. The ammonia was evaporated, the solution warmed to room temperature, water added, and the product extracted with ether. The ether layer was shaken with 40 ml. of 4% acetic acid, allowed to stand for 2 hr., washed until neutral, and the ether evaporated. The product distilled from 158-180° (0.1 mm.). The infrared spectra showed the enol ether doublet at 5.9μ and 6.0μ. The enol ether was hydrolyzed to the unsaturated ketone by dissolving the enol ether in 53% acetic acid and allowing it to stand for 2 hr. Yield: colorless liquid, 4.2 g. (50%). B.P. 163-170° (0.1 mm.); λmax. 240mμ (ϵ3537); λmax. 5.8μ (ketone C =O), 5.95μ (α,β-unsaturated C = O), 2.9μ (OH).

Approximately 26% of the conjugated isomer IIb was present. To shift the double bond to the conjugated position the mixture of isomers IIa and IIb was refluxed 30 min. in an argon atmosphere with 30 ml. of dioxane and 5 ml. of 6 M hydrochloric acid. The product was extracted with benzene, the benzene evaporated, and the product distilled. Approximately 28% of the conjugated isomer IIb was present. The thin

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g) The product contained a small amount of the other isomer 2-cyclopentanol XXVIIa.

layer chromatogram of the product showed two ketone spots. One of these, the slower travelling ketone, was much darker and smaller, evidently the conjugated isomer. A sample of this product was submitted for bioassay.

Yield: colorless liquid, 1.9 g. (23%). B.P. 137-140° (0.1 mm.). λmax. 240 mμ (ϵ 3930); λmax. 5.8μ (ketone C = O), 5.95μ (α, β-unsaturated C = O), 2.9μ (OH).

Anal. Calc. for $C_{17}H_{26}O_2$: C, 79.86; H, 9.92. Found: C, 80.77; H, 10.50.

5-Ethyl-3,4,5,6,7,8-hexahydro-6-(3-oxocyclopentyl)-2(1H)-naphthalenone Ia and 5-ethyl-4,4a,5,6,7,8-hexahydro-6-(3-oxocyclopentyl)-2(3H)-naphthalenone Ib. - To lithium (3.0 g., 0.43 mole) in 150 ml. of redistilled ammonia at -40°, was added 1-ethyl-1,2,3,4-tetrahydro-6-methoxy-2-(3-oxocyclopentyl)-naphthalene ethylene ketal XXX (6 g., 0.019 mole) dissolved in 60 ml. of morpholine. The mixture was stirred 5 min. at -35°, cooled to -40°, and isopropyl alcohol (40 ml., 0.52 mole) was added. The solution was warmed to -30° and 30 ml. more of isopropyl alcohol was added. The ammonia was evaporated and the enol ether treated as in IIa and IIb.

Yield: colorless liquid, 5.1 g. (99%). B.P. 98-128°.

A small amount of forerun may have been due to cleavage of the methoxy group. A solution of the product and 25 ml. of 88% formic acid was allowed to stand for 45 min. at room temperature. The residue was refluxed 30 min. with 30 ml. of dioxane and 5.7 ml. of 1.5 M hydrochloric acid to shift the double bond to the conjugated isomer Ib. The product was extracted with benzene, the benzene evaporated, and the

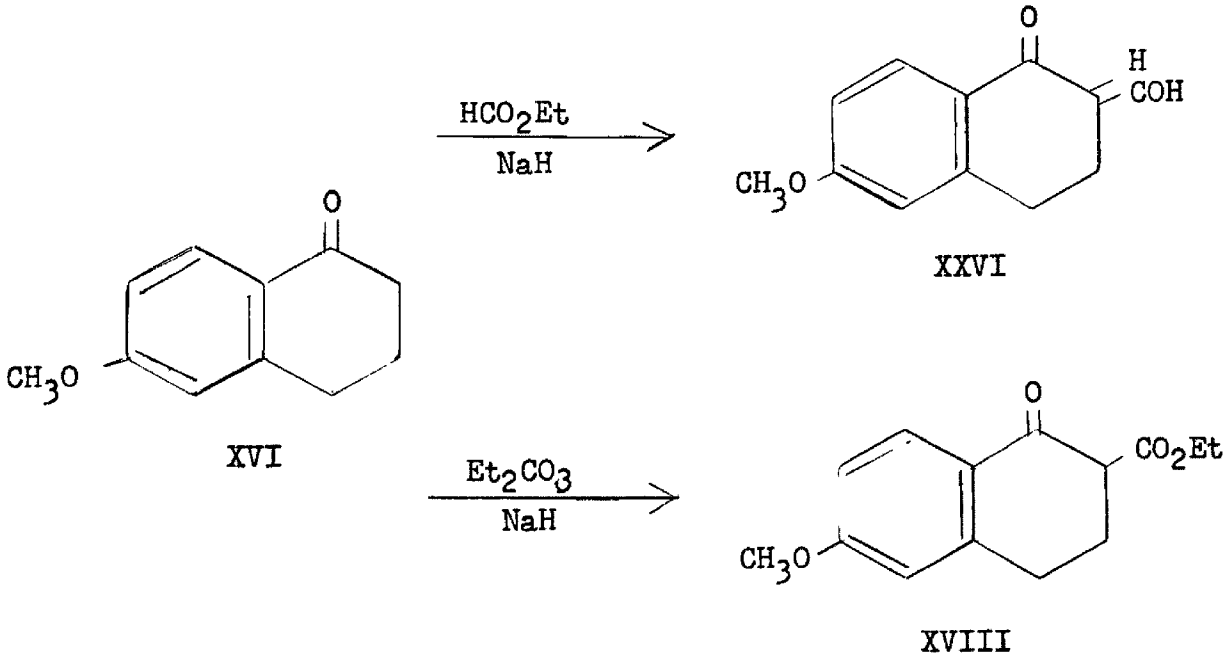
product distilled. Approximately 27% of the conjugated isomer Ib was present. The thin layer chromatogram of the product showed two ketone spots, and the principal isomer Ia was the slower moving.

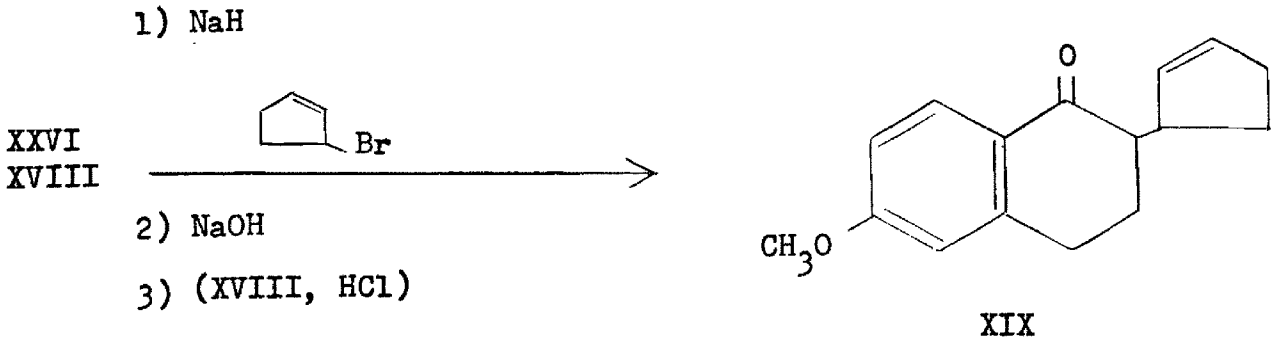
Yield: colorless liquid, 3.5 g. (71%). B.P. 130-158° (0.1 mm.). λmax. 240 mμ (ϵ 3800); λmax. 5.75μ (ketone C = O), 5.95μ (α,β-unsaturated C = O). The fraction distilling at 155-160° (0.1 mm.) was sent for bioassay.

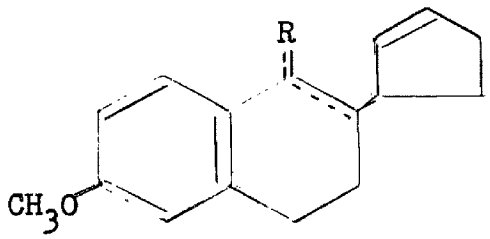
Anal. Calc. for $C_{17}H_{24}O_2$: C, 79.41; H, 8.82. Found: C, 79.11; H, 8.77.

V. SUMMARY

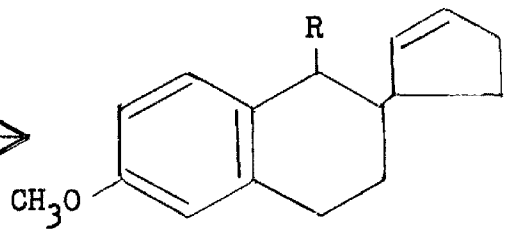
The unsaturated ketone II obtained by the synthesis illustrated below has been sent for bioassay as a potential cancer inhibitor. When the analogous synthesis of the methyl derivative is completed this will also be bioassayed. It will be of interest to compare the biological activity of II where R = H, Me, or Et. Each represents a modification of the alkyl group at carbon five.



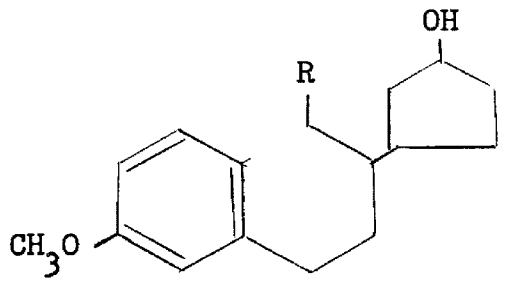


XIX → (1) EtLi or MeLi; (2) $KHSO_4$, △ → 

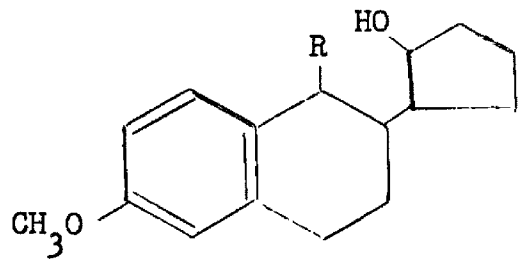
XXIVa R = Et
b R = Me

XXIVa,b → (1) Li, NH_3; (2) H_2O, NH_4Cl → 

XXVa R = Et
b R = Me



XXVIa R = Et
b R = Me

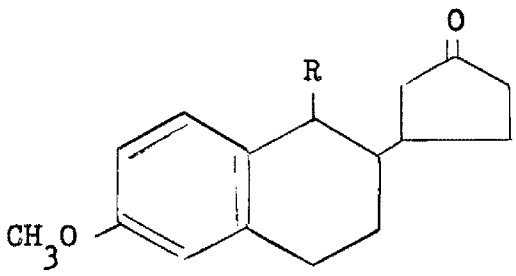
XXVa,b → (1) B_2H_6; (2) NaOH, H_2O_2 → 

XXVIIa R = Et
b R = Me

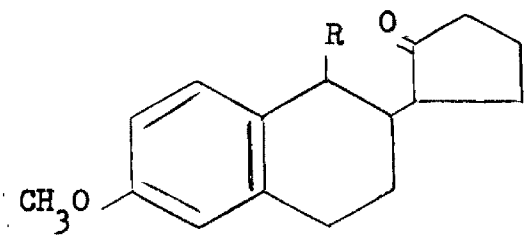
XXVIa,b

XXVIIa,b

CrO_3 / Pyridine

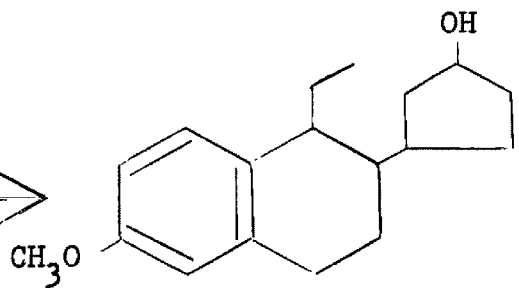


XXVIIIa R = Et
b R = Me
c R = H



XXIXa R = Et
b R = Me

1) Separation of isomers
2) $NaBH_4$ EtOH

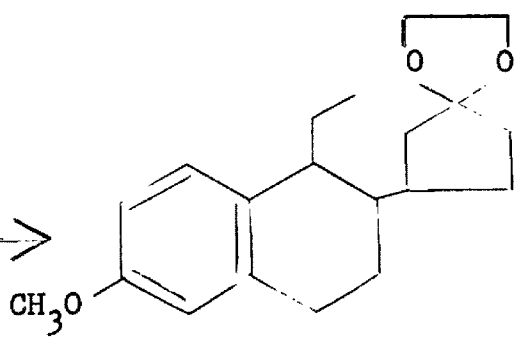


XXVIa

XXVIIIa,b

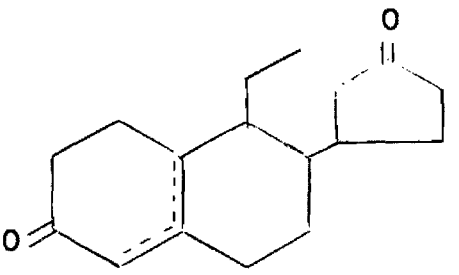
XXIXa,b

1) Separation of isomers
2) Ethylene Glycol catalyst



XXX

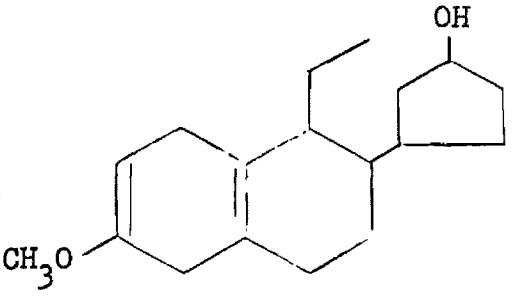
XXX → (1) Li, NH_3 (2) Isopropyl alcohol → (H^+, H_2O) →



Ia (β,γ-unsaturated C=O)

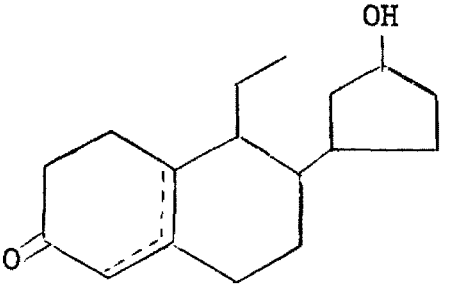
b (α,β-unsaturated C=O)

XXVIa → (1) NH_3 isopropyl alcohol (2) Na →



XXXI

XXXI → (H^+, H_2O) →



IIa (β,γ-unsaturated C=O)

b (α,β-unsaturated C=O)

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