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THE CONVERSION OF CYCLOALKANONES TO ACETYCYCLOALKANES

by

GORDON W. WEBB

B.S. University of Idaho, 1964

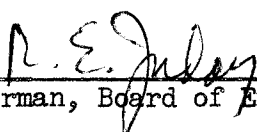
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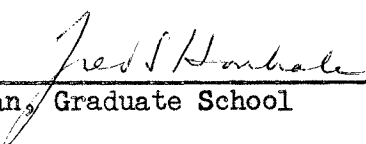
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UNIVERSITY OF MONTANA

1966

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Chairman, Board of Examiners


Dean, Graduate School

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I wish to express my appreciation for the inspiration and guidance given me by Professor Richard E. Juday during this investigation.

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Introduction

The purpose of this investigation was to discover a more efficient method of converting cycloalkanones to acetylcycloalkanes. The syntheses developed in this project were used to prepare steroid analogs lacking ring D, but were unsuccessful for the preparation of progestogen analogs lacking ring C.

Cycloalkanones are usually the first synthetic products obtained in preparing polycyclic structures from simpler starting materials because the annelation procedure commonly involves the use of aldol or Dieckmann condensations. These products, which are analogs of androgens or estrogens, must be converted to acetylcycloalkanones to make progesterone analogs, or to ketals if cortical analogs are desired. Relatively few of these progestogen analogs have been prepared.

It appears that the structural requirements for biological activity for progestogens are quite exacting compared with estrogens, but that the requirements for hormone antagonistic activity are less critical.

Hormone and hormone antagonist activity have some control on the growth of cancerous tumors.¹ The exact mechanism by which a steroid effects cancer growth is not known.

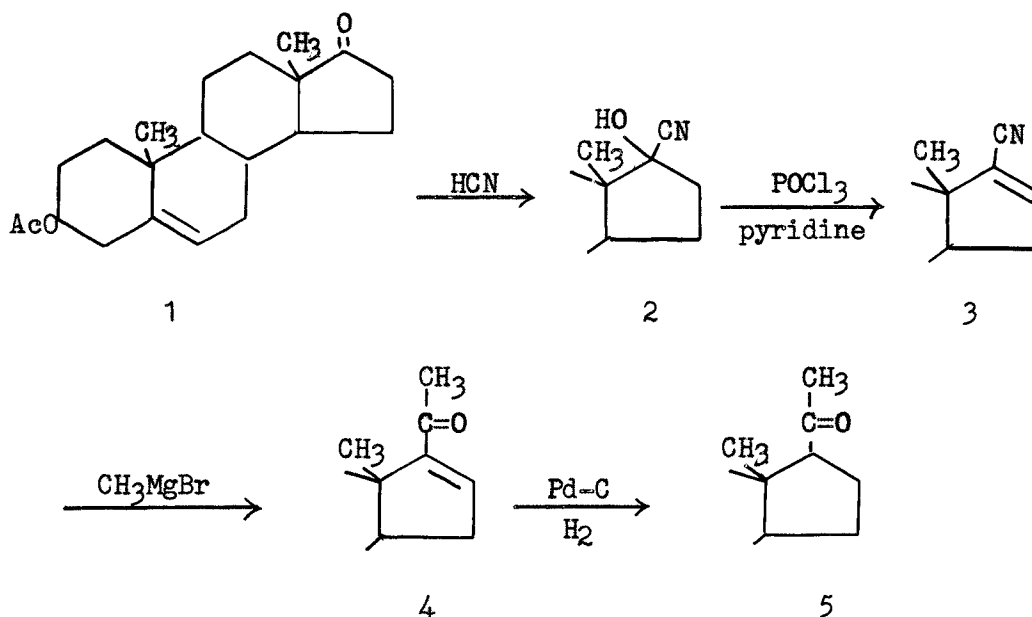
Methods by which a steroid could affect cancer growth are as follows: (1) by specific properties unique to that steroid; (2) by inhibition of pituitary function; (3) by specific anabolic function (i.e., retention of a specific element such as sodium which might influence tumor growth); (4) by affecting the activity

of other steroids; (5) by acting through metabolic products; or (6) by producing specific effects on the tumor unrelated to endocrine activity.

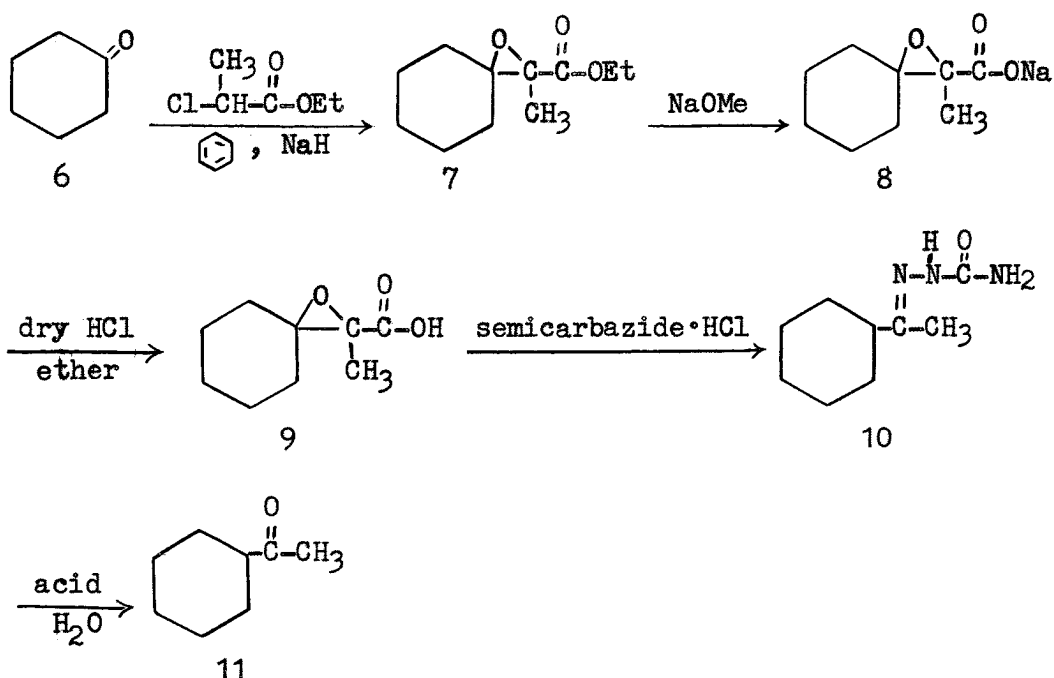
Of the three forms of antagonistic activity, physiological antagonism, competitive antagonism, and chemical antagonism, only the first two forms have been found to involve steroids. In physiological antagonism, the effects of one steroid cancel the effects of another steroid. In competitive antagonism one steroid undergoes a similar reaction to another steroid at an active site physically blocking the other steroid from that site. It thus prevents the other steroid from affecting the tumor.

History

Several methods have been developed for introducing the desired acetyl side chain on a cycloalkanone. One method² involved the addition of hydrocyanic acid to the cycloalkanone (1) to form a cyanohydrin (2). The cyanohydrin (2) was dehydrated with phosphorous oxychloride in pyridine to form 3. Compound 3 was then reacted with a methyl Grignard reagent to form an unsaturated ketone (4), which might be reduced to the desired product (5).

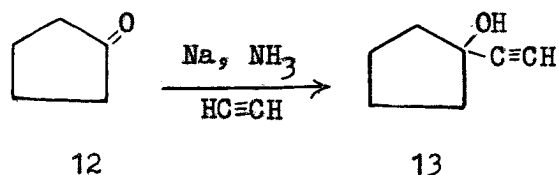


A second method used the Darzen synthesis.³ The cyclic ketone (6) was condensed with ethyl 2-chloropropanoate to form the glycidic ester (7). This ester was hydrolyzed to form the salt (8) which was treated with hydrogen chloride to form the acid (9). Finally, using a hydrazine derivative, such as semicarbazide, to break the epoxide ring and decarboxylate the acid, the semicarbazone (10) was formed. The final product (11) was obtained by acid hydrolysis of the semicarbazone.



Another method involved the ethynylation of a cycloalkanone to form the ethynyl carbinol. Depending on conditions, the ethynyl carbinol might be converted to a ketol, an unsaturated ketone or the dioxolan derivative of the ketone.

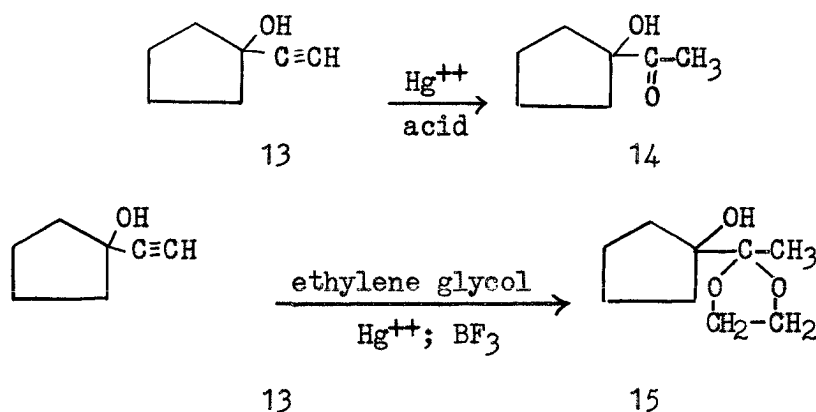
The ethynylation was traditionally run in ammonia using sodium or lithium to form the acetylide.⁴ The ketone (12) was then added, and the product (13) obtained after hydrolysis.



Other methods were developed using the same basic method but changing the solvent and the base. Using ether and potassium hydroxide,⁵ 1-ethynylcyclohexanol was obtained in 60% yield. The same product was formed with sodium and DMSO⁶ (dimethylsulfoxide) in 70% yield. Sodium with acetylene⁷ under five to ten atmospheres

pressure resulted in similar yields, but with a much shorter reaction time. Lithium acetylide-ethylenediamine complex⁸ was used in a variety of solvents with generally good results. The mono Grignard derivative⁹ of acetylene in THF (tetrahydrofuran) solutions has also been used with good results.

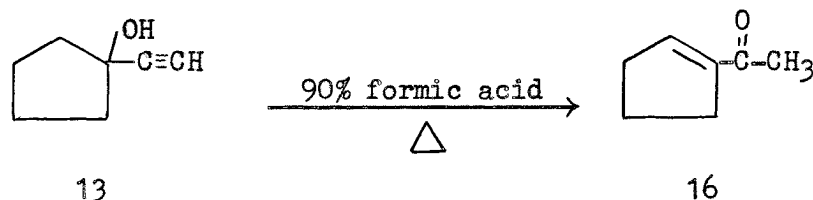
The mercury ion catalyzed hydration of the ethynyl carbinol in an acid medium gave the ketol (14). The reaction with a boron trifluoride and mercury(II) oxide catalyst in dry ethylene glycol gave the dioxolan derivative (15).



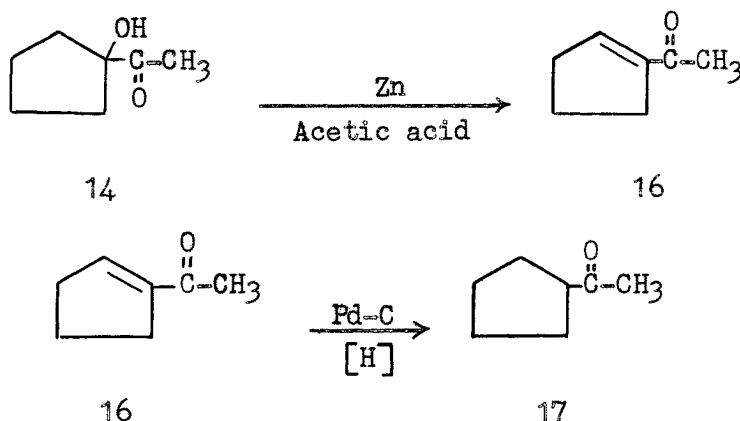
The mercury ion catalyzed hydration was run in sulfuric acid,¹¹ but the yields were frequently low. The reaction was also run in a water-methanol solvent using boron trifluoride and mercury ion as the catalyst.¹² An acid ion-exchange resin (Dowex 50) was impregnated with mercury(II) sulfate; methanol and water were used as the solvent.¹⁰ Many other acids were tried; and it was found that acids which would speed reduction of mercury salts will also hydrolyze the acetylene linkage most rapidly.¹³

The reaction which forms the ethylene dioxy ketone derivatives was found to form ketals with simple alcohols, but in lower yields.¹⁴

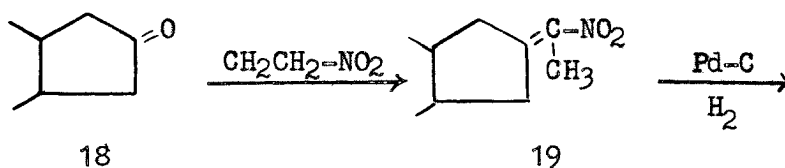
By hydrating the acetylene linkage of 13 in hot 90% formic acid or in 90% acetic acid in the presence of the acid form of Dowex 50,¹⁶ dehydration of the hydroxyl group on the cyclic system also occurs to give the unsaturated ketone (16).

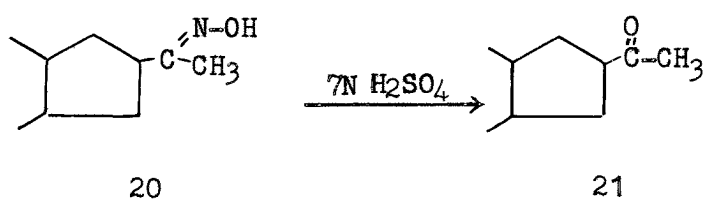


The saturated ketone (17) might also be obtained by reducing the ketol (14) with zinc and acetic acid¹⁷ and by catalytically hydrogenating the unsaturated ketone (16).¹⁸



Another possible method that has been used with aldehydes¹⁹ but not with cycloalkanones would be to convert the cycloalkanone to an unsaturated nitro compound (19). Reduction of 19 to the oxime (20) followed by acid hydrolysis would give the desired product (21).



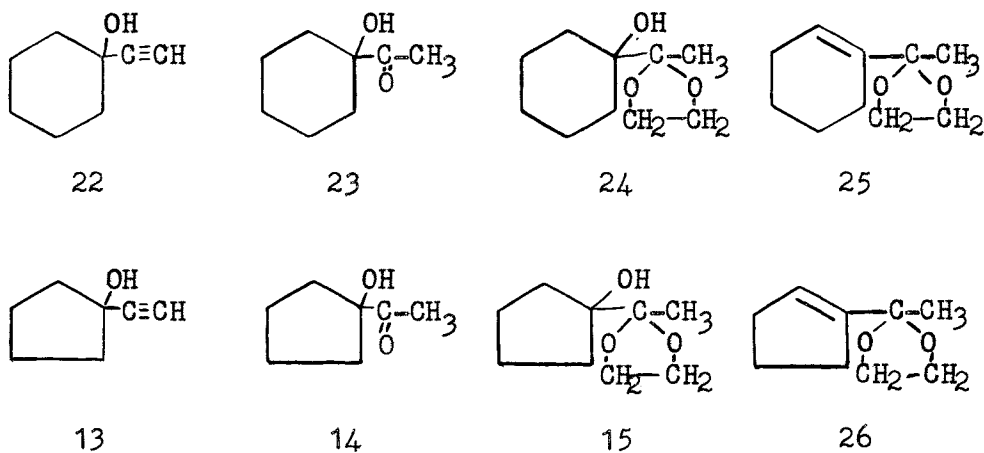


Discussion

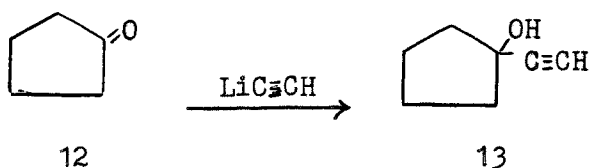
The research program was initiated on the model compounds: cyclopentanone (12) and 1-ethynylcyclohexanol (22). Of the methods previously outlined, the first method which involved five steps, was not attempted. The first step was an equilibrium reaction, and the subsequent steps, although they did work satisfactorily for steroids, did not look promising for general application.

The last method was unsuccessful with cyclopentanone, which failed to react with nitroethane under all conditions attempted.²⁰

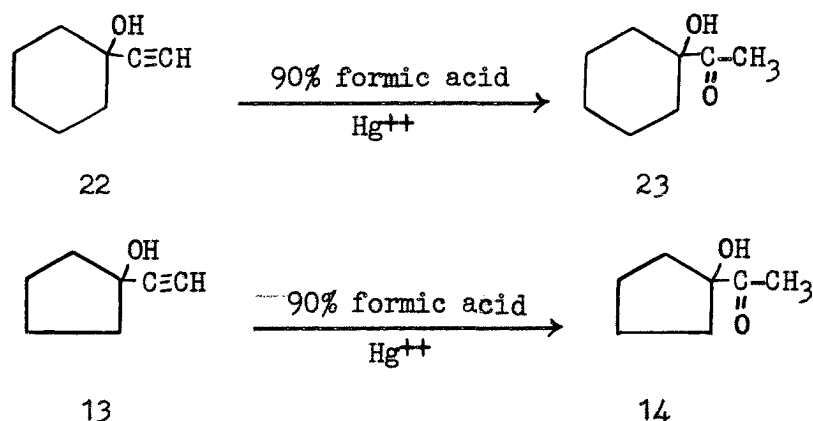
The Darzen's synthesis was tried but gave rather poor results. The decarboxylation of the epoxy acid in particular gave poor yields. Attempts to improve the yield by use of dimethylhydrazine instead of semicarbazide were unsuccessful. Therefore, the study of the ethynylation and subsequent reactions have been employed resulting in the preparation of 23, 24, 25, 13, 14, 15, and 26.



The lithium acetylide-ethylenediamine complex reacted with cyclopentanone (12) to give 52% of 1-ethynylcyclopentanol, (13).

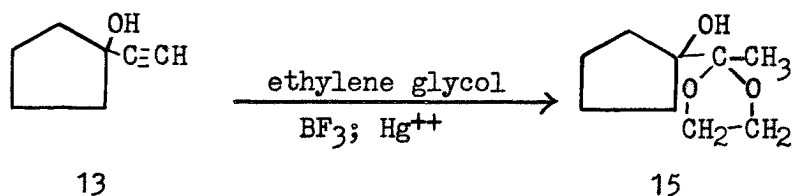
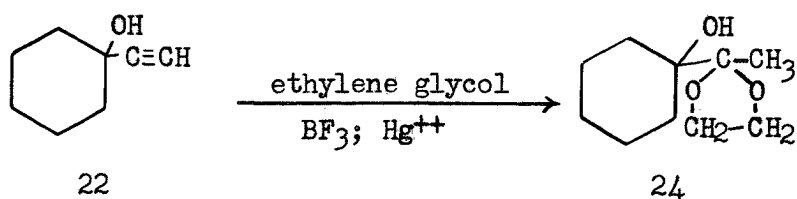


The combined hydration-dehydration, using hot 90% formic acid when used in conjunction with cyclopentanone rings, resulted in poor yields. In general, it was found that the reaction in cold formic acid with a mercury formate catalyst gave excellent result without dehydrating the hydroxyl group. Previously published methods reported more severe conditions which resulted in lower yields. Compounds 22 and 13 were reacted in an acid medium to form the desired ketones, 23 and 14. It was found that 90% formic acid with a small amount of catalyst would produce the ketones, 23 and 14, in 74% and 72% yields, respectively.



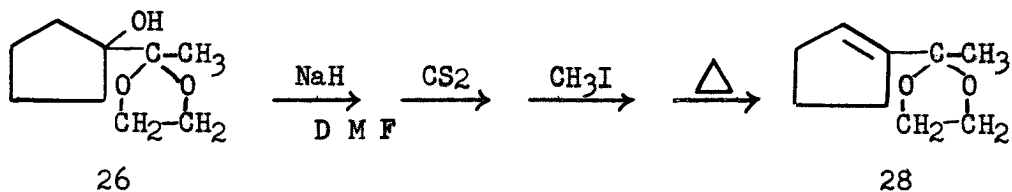
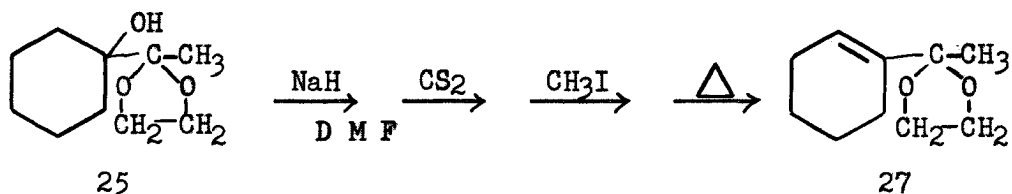
If a larger amount of mercury catalyst was used, the separation of the mercury from the product was impossible with the methods attempted.

Compounds 22 and 13 also reacted with ethylene glycol to form the ethylene dioxy derivative of the ketones, 24 and 15. This reaction, which was run in dry ethylene glycol using a boron trifluoride and mercury oxide catalyst, gave yields of about 72% with both compounds.



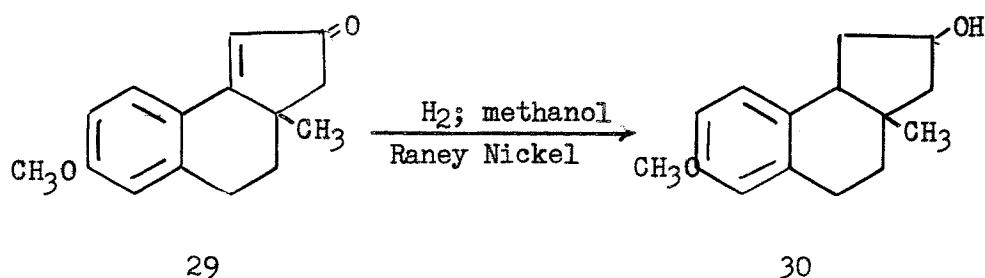
Since attempts to dehydrate the ethynylcyclopentanol with an acid catalyst were unsuccessful, the dehydration was attempted on the dioxolan derivative.

Since the ketal compounds are sensitive to acid, it was necessary to use non-acidic dehydrating agents. The reaction was attempted with dimethylsulfoxide, potassium pyrosulfate, phosphorous oxide, ester pyrolysis, and the Tchugaeff reaction. All reactions except the Tchugaeff were unsuccessful. The usual Tchugaeff procedure employing toluene, was unsuccessful, however, a modified procedure using DMF as solvent worked well in a much shorter time than is usually required.



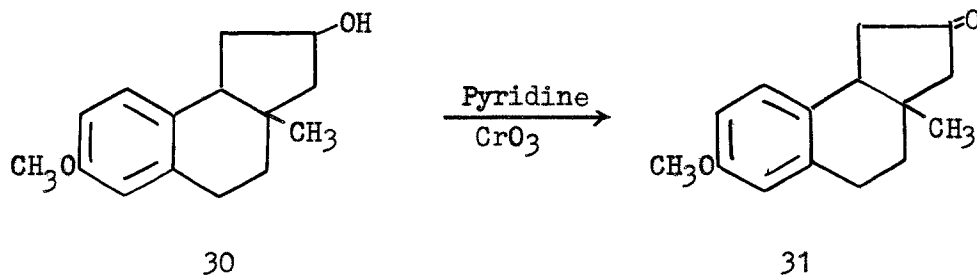
However, it was necessary to utilize silica gel column chromatography to separate the desired products from the sulfur compounds produced. Although a little of 28 was actually isolated the yields were so low that this approach was discontinued.

Compound 29,²¹ which was prepared by a method of Kaiser, was hydrogenated at atmospheric pressure, using Raney Nickel catalyst at room temperature, producing 30.

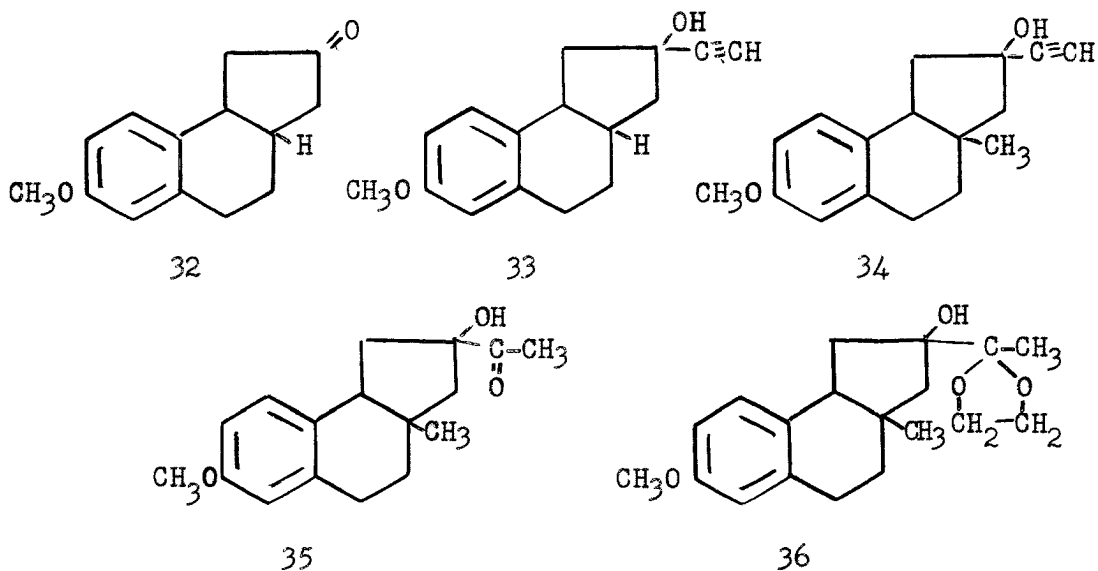


Selective reduction of the double bond, of 30 and not the ketone, was attempted with a palladium and charcoal catalyst. Thin layer chromatography of the product showed three spots which were attributed to 30, 31, and probably the hydrogenolysis product.

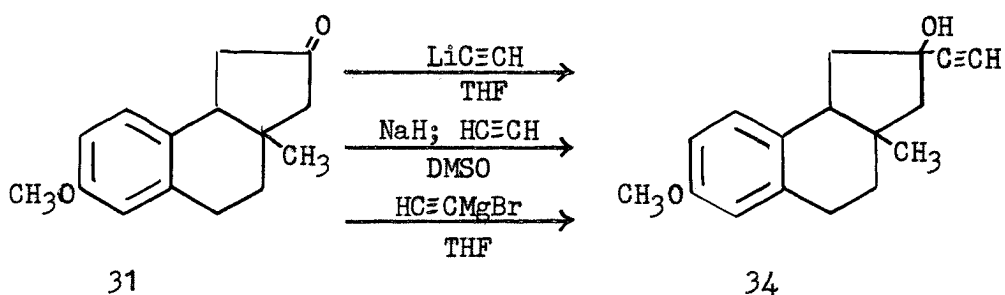
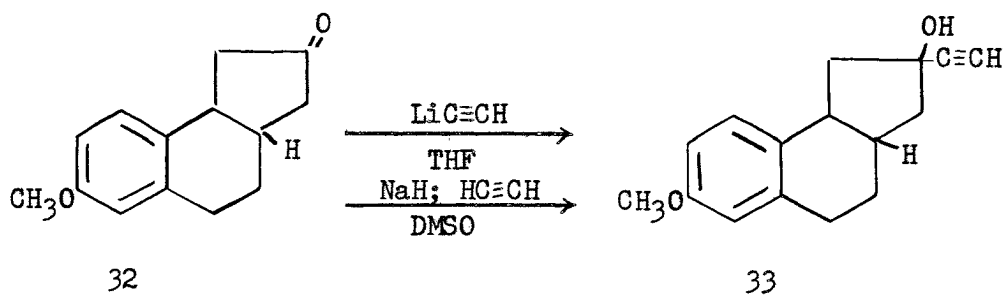
The oxidation of 30 to the saturated ketone, 31, was accomplished with a chromic oxide pyridine mixture.



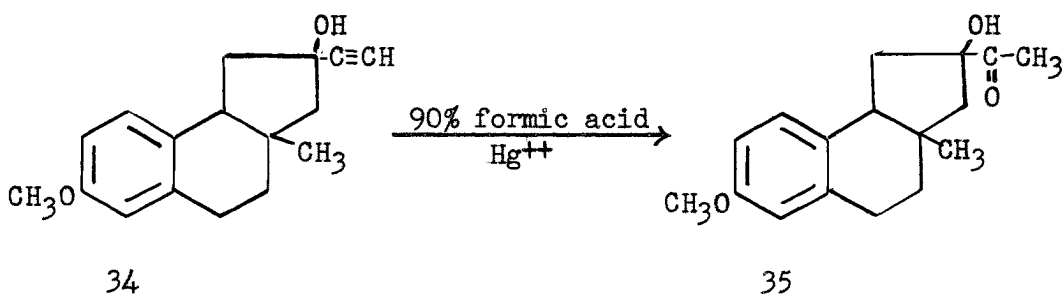
Compounds mentioned on page 8, were used as models for the synthesis of compounds 33, 34, 35, and 36 from 31 and 32.



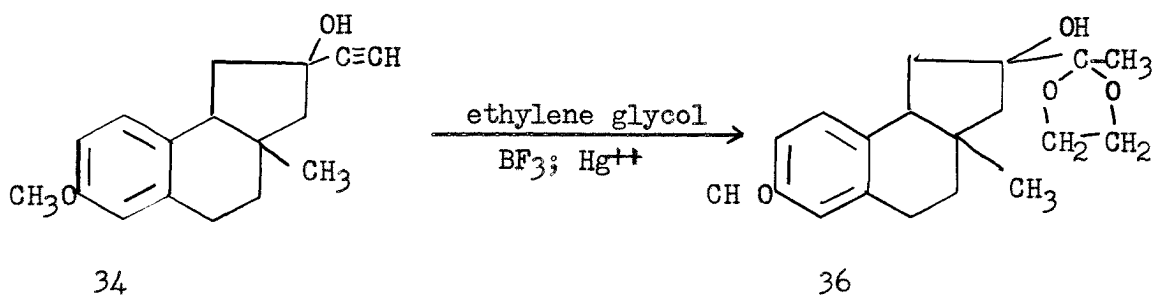
Although the ethynylation of cyclopentanone was fairly successful with lithium acetylide-ethylene-diamine complex when the ethynylation was attempted with 31 and 32, the yields of 34 were only about 50%, and none of 33 was obtained. The reaction was very slow and did not go to completion even after 24 hours. This necessitated the separation of the product from the unreacted starting material, which was difficult. Sodium hydride in DMSO reacted with acetylene to form sodium acetylide which were reacted with compounds 31 and 32 to form 48% of 33 and 34. The mono Grignard of acetylene also reacted with 31 to give 34 in yields of about 90%. The improved results with the Grignard reagent are probably due to its being a weaker base than the sodium or lithium acetylide. The latter are strong bases which, instead of adding to the carbonyl group, can cause condensation reactions.



Compound 34 was hydrated in formic acid with a mercury formate catalyst to give 35 in about 70% yield. It was convenient to separate the ketone as the semicarbazide from trace amounts of an unknown impurity.



Compound 34 also reacted with dry ethylene glycol, using mercury oxide-boron trifluoride as the catalysts to produce 72% of 36.



The stereochemistry of the compounds produced has not yet been determined. Reduction of 29 can give rise to 2 ring isomers—cis and trans, but apparently only one was obtained whether the reduction was accomplished by sodium, ammonia and alcohol, or by catalytic hydrogenation. Analysis of 31 and 33 by TLC and NMR indicated that only one of the two possible isomers was present in each case

Experimental

1-Ethynylcyclopentanol (13). A stirred solution of lithium acetylide-ethylenediamine complex (42 g., 0.47 mole) in dry benzene (200 ml.) and THF (250 ml.) was cooled to 0°C. Acetylene, purified by passing it through two dry ice traps, was passed over the solution until the solution was saturated. Cyclopentanone (50 g., 0.6 mole) was added to the solution dropwise which was then allowed to warm to room temperature and stirred for two hours under an argon atmosphere. Water and hydrochloric acid were added until the precipitate of lithium hydroxide dissolved. The benzene layer was washed with water until the washings were neutral. The benzene solution was evaporated and the residue distilled in vacuo. The yield was 34 g. (52%) of 13, distilling at 72-75°C (15 mm.); 74-76°C (20 mm.) lit.;¹⁰ n_D^{23} 1.4642; n_D^{20} 1.4650 lit.¹⁰ The infrared spectra showed bands at 3.05 μ and 15.35 μ (-C \equiv C-H) and also at 2.95 μ (-O-H).

1-Acetylcyclohexanol (23). Mercury formate (0.1 g.) was added to a solution of 1-ethynylcyclohexanol (22) (24.8 g., 0.2 mole) in 90% formic acid (60 ml.). After the mixture was stirred for twelve hours at room temperature, water was added and the mixture was extracted twice with benzene. The combined benzene extracts were washed with water until the washings were neutral. The benzene was evaporated and the residue distilled in vacuo. The yield was 18.1 g. (75%) of 23 distilling at 90-105°C. (15 mm.); 92-94°C. (22 mm.) lit.¹⁰ The infrared spectra showed bands at 2.8 μ and 2.85 μ (-O-H) and also at 5.9 μ (C=O).

1-Acetylcyclopentanol (14). Mercury formate (0.25 g.)

catalyst was added to a stirred mixture of 1-ethynylcyclopentanol (13) (10 g., 0.092 mole) in 90% formic acid (30 ml.). The product, 14, was obtained using the general procedure described. The yield was 8.2 g. (72%) of 14, distilling at 73-78°C. (15 mm.); 72-74°C. (11 mm.); lit.;¹⁰ n_D^{23} 1.5214; n_D^{20} 1.5220 lit.¹⁰ The infrared spectra showed bands at 2.9 μ (-O-H) and 5.86 μ (C=O).

2-1'-Hydroxycyclohexyl-2-methyl-1:3-dioxolan (24). The

mixture of mercury oxide (0.5 g.) covered with boron trifluoride-ether complex (1 ml.) as a catalyst and dry ethylene glycol (10 g., 0.15 mole) was warmed until the mixture of mercury oxide precipitate dissolved. The solution was cooled to -5°C and stirred while a solution of 1-ethynylcyclohexanol (22) (40 g., 0.32 mole) in ethylene glycol (30 g., 0.45 mole) was added dropwise. The mixture was maintained at -5°C for two hours and then allowed to warm to room temperature and stirred for an additional twelve hours. Potassium carbonate (2 g.) and water were added, and the mixture was extracted twice with benzene. The benzene extract was washed with water until the washings were neutral. The benzene extract was dried with magnesium sulfate and evaporated. The solid residue, 24, was recrystallized from cyclohexane to give a white solid; m.p. 55°C. The yield was 46.4 g. (79%). The infrared spectra showed a peak at 2.8 μ (-O-H).

2-1'-Hydroxycyclopentanol-2-methyl-1:3-dioxolan (15).

A solution of 1-ethynylcyclopentanol, (13), (16.5 g., 0.15 mole)

in ethylene glycol (10 g., 0.15 mole) was added dropwise to the mercury oxide (0.5 g.) covered with boron trifluoride-ether complex (1 ml.) and ethylene glycol (5 g., 0.078 mole). The product, 15, was obtained by the same general method outlined above for 24. The yield was 15.1 g. (64%) distilling at 72-75°C (15 mm.); 69-70° (1 mm.) lit.; n_D^{23} 1.4690; n_D^{20} 1.4695 lit.¹⁰ The infrared spectra showed a peak at 2.86 μ (-O-H).

2-1'-Cyclohexenyl-2-methyl-1;3-dioxolan (25). Sodium hydride (0.6 g., 0.025 mole) was slowly added to a stirred mixture of 2-1'-hydroxycyclohexyl-2-methyl-1;3-dioxolan (24) (5 g., 0.027 mole) and DMF (20 ml.). The mixture was stirred for one hour at room temperature under an argon atmosphere. Carbon disulfide (3 g., 0.04 mole) was added slowly with stirring while the temperature rose and then dropped back to room temperature. The solution was then cooled with an ice bath to 2°C, and methyl iodide (6.5 g., 0.045 mole) was added. The mixture was allowed to warm to room temperature and was stirred for one-half an hour. Water was added and the mixture was extracted twice with ether. The ether extract was washed with water until the washings were neutral. The ether was evaporated and the residue distilled in vacuo. There was an obvious evolution of gas near the boiling point. The yield was 4.4 g. (96%) of 25, distilling at 88-115°C (15 mm.). No analysis was obtained due to a sulfur impurity. The infrared spectra showed a peak at 6.01 μ (C=C)

2-1'-Cyclopentenyl-2-methyl-1;3-dioxolan (26). The product,

26, was obtained using the general procedure described for 25. The sodium hydride (1.5 g., 0.062 mole) in DMF (20 ml.) was combined with 2-1'-hydroxycyclopentyl-2-methyl-1:3-dioxolan (15) (3 g., 0.017 mole). Then carbon disulfide (10 g., 0.16 mole) and ethyl iodide (7.5 g., 0.047 mole) are added respectively. The yield was 2.5 g. (80%) of 26, distilling at 72-78°C (15 mm.). The product was purified by chromatography over silica gel with cyclohexane as elutant. The sulfur impurity moved down the column more rapidly than the product. The infrared spectra showed a peak at 6.02μ (C=C).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.91; H, 9.15.

1,3,-3a,4,5,9b-Hexahydro-2-ethynyl-7-methoxy-2H-benz [e]-inden-2-ol (33). A mixture of sodium hydride (1 g., 0.04 mole); DMSO (25 ml.) was heated under an argon atmosphere until the reaction was complete as indicated by the disappearance of the gray color of the sodium hydride. The mixture was then cooled to 0°C and acetylene gas, purified by passing through two dry ice traps, was passed over the mixture until the reaction was completed as judged by the exothermic character of the reaction. A solution of 1,3,-3a,4,5,9b-hexahydro-7-methoxy-2H-benz [e]inden-2-one (32) (4 g., 0.018 mole) in dioxane was added and the mixture stirred for 24 hrs. at room temperature. Water was added and the solution extracted with benzene.

The benzene extract was washed with water until the washings were neutral. The benzene was evaporated and the residue distilled in vacuo. The yield was 2 g. (48%) of 33, distilling at 150-155°C

(0.1 mm.). The product was purified by recrystallization from 1:1 cyclohexane-benzene solution, giving a white solid; m.p. 85°C. The infrared spectra showed peaks at 2.8 μ (-O-H) and 3.02 μ and 14.8 μ (-C \equiv C-H).

Anal. Calcd. for C₁₆H₁₈O₂: C, 79.34, H, 7.43. Found: C, 79.15; H, 7.34.

1,3,-3a,4,5,9b-Hexahydro-3a-methyl-7-methoxy-2H-benz[e]-inden-2-ol (30). The compound, 3,-3a,4,5-tetrahydro-3a-methyl-7-methoxy-2H-benz[e]inden-2-one (29) (20 g., 0.088 mole), was hydrogenated over Raney Nickel in methanol (100 ml.) at room temperature for four hours absorbing 2 moles of hydrogen gas. The product was obtained by filtering and then evaporated and distilled in vacuo. The yield was 18.5 g. (92%), distilling at 136-140°C (0.1 mm.). The infrared spectra showed peaks at 2.76 μ and 2.95 μ (-O-H).

Anal Calcd. for C₁₅H₂₀O₂: C, 77.58; H, 8.62. Found: C, 77.38; H, 8.49.

1,3,-3a,4,5,9b-Hexahydro-3a-methyl-7-methoxy-2H-benz[e]-inden-2-one (31). Compound, 1,3,-3a,4,5,9b-hexahydro-3a-methyl-7-methoxy-2H-benz[e]inden-2-ol (30) (18.5 g., 0.085 mole), was added to a mixture of chromic oxide (18.5 g., 0.19 mole) and pyridine (400 ml.) and stirred at room temperature for eight hours. The mixture was cooled to 5°C and water and benzene were added. The mixture was filtered and the precipitate was washed with benzene. The combined benzene extracts were washed with hydrochloric acid

until the odor of pyridine was removed; then washed with water until the washings were neutral. The benzene was evaporated and the residue distilled in vacuo. The yield was 15.2 g. (82%), distilling at 150-155°C (0.1 mm.). The product 31 was recrystallized from a 1:4 water-methanol, giving a white solid; m.p. 50°C. The infrared spectra showed a peak at 5.73μ (C=O).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.26, H, 7.82. Found: C, 78.42; H, 8.09.

1,3,3a,4,5,9b-Hexahydro-2-ethynyl-3a-methyl-7-methoxy-2H-benz[e]inden-2-one (34).

Method 1. The compound (31) 1,3,3a,4,5,9b-hexahydro-3a-methyl-7-methoxy-2H-benz[e]inden-2-one (4 g., 0.0175 mole) dissolved in dioxane was added dropwise to a stirred mixture of THF (57 ml.) and lithium acetylide-ethylenediamine complex (6 g., 0.066 mole) over which acetylene gas, purified by passing through two dry ice traps, had been passed until the solvent has been saturated. The mixture was stirred for 24 hours under an argon atmosphere. Water and benzene were added to the mixture. The benzene layer was separated and the water extracted once more with benzene. The benzene extracts were combined and washed with water until neutral. The benzene was evaporated and the residue distilled in vacuo. The yield was 3 g. (70%) of 34, distilling at 141-155°C (0.1 mm.). It was necessary to remove the unreacted starting material as the semicarbazone. After separating the starting material, 31 was recrystallized from 1:1 benzene-cyclohexane mixture and gave 1.6 g. (37%) of 34.

Method 2. DMSO (25 ml.) and sodium hydride (1 g., 0.04 mole) reacted as described in the procedure for 33. Acetylene gas, purified by passing through two dry ice traps, was passed over the solution followed by 31 (3.2 g., 0.014 mole). The yield of 34 was 1.6 g. (45%), distilling at 150-155°C (0.1 mm.) and recrystallized from 1:1 benzene-cyclohexane.

Method 3. Powdered magnesium (5.6 g., 0.23 mole) was slowly added with cooling and stirring to a mixture of ethyl bromide (28 g., 0.26 mole) and ether (50 ml.) under an argon atmosphere. The ethyl magnesium bromide was added dropwise with constant cooling to a saturated solution of acetylene, purified through two dry ice traps, in THF (200 ml.) cooled to 0°C. After the ethyl magnesium bromide had all reacted, compound 31 (11.5 g., 0.05 mole) was added and the mixture stirred at room temperature over night. Water was added and the mixture extracted with benzene. The benzene extract was washed until neutral with water. The benzene was evaporated and the residue distilled in vacuo. The yield was 12.6 g. (98%) of the 34, distilling at 152-155°C (0.1 mm.). The product was recrystallized from 1:1 benzene-cyclohexane, giving a white solid; m.p. 98°C. The infrared spectra showed peaks at 2.9μ (-O-H) and 3.01μ and 15.3μ (-C≡C-H).

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.68; H, 7.81. Found: C, 79.69; H, 7.75.

1,3,3a,4,5,9b-Hexahydro-2-acetyl-3a-methyl-7-methoxy-2H-benz[e]inden-2-ol (35). Mercury formate (0.1 g.) catalyst was added with stirring to a solution of formic acid (100 ml.) and

1,3,-3a,4,5,9b-hexahydro-2-ethynyl-3a-methyl-7-methoxy-2H-benz[e]-inden-2-ol (34). After the mixture was stirred for twelve hours at room temperature, water was added and the mixture extracted with benzene. The benzene extract was washed with water until the washings were neutral. The benzene was evaporated and the residue distilled in vacuo. The yield was 2.3 g. (72%) of 35, distilling at 162-168°C (0.1 mm.). The product was purified by conversion to the semicarbazone followed by hydrolysis. The overall yield was 1.8 g. (51%). The infrared spectra showed peaks at 2.85μ (-O-H) and 5.78μ (C=O).

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.40; H, 8.05. Found: C, 74.33; H, 8.07.

2-(1',3',-3a',4',5',9b'-Hexahydro-3a'-methyl-7'-methoxy-2H-benz[e]inden-2-ol)-2-methyl-1:3-dioxolan (36). A mixture of mercury oxide (0.1 g.) and boron trifluoride-ether complex (0.5 ml.) in ethylene glycol (5 g., 0.08 mole) was heated and stirred until the mercury precipitate dissolved. This solution was cooled to -5°C and then a solution of 1,3,-3a,4,5,9b-hexahydro-2-ethynyl-3a-methyl-7-methoxy-2H-benz[e]inden-2-ol (34) (4.1 g., 0.016 mole) in ethylene glycol (20 g., 0.314 mole) was added dropwise with constant stirring. Stirring was continuous for two hours at -5°C and then for 12 hours at room temperature. Potassium carbonate (3 g.) and water were added to the mixture which was then extracted with benzene. The benzene extract was washed with water until neutral and the benzene evaporated. The residue was distilled in vacuo to give 3.7 g. (73%) of 36, distilling at 169-177°C (0.1 mm.). The product was re-

crystallized from a 7:3 methanol-water to give white crystals; m.p. 99°C. The infrared spectra of 36 showed a peak at 2.77 μ (-O-H).

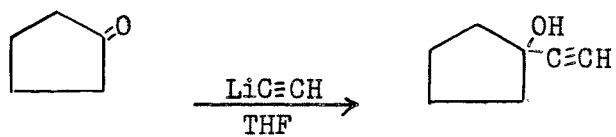
Anal. Calcd. for C₁₉H₂₆O₄: C, 71.65; H, 8.24. Found: C, 71.59; H, 8.12.

Summary

The purpose of this investigation was to improve the method of converting cycloalkanones to acetyl cycloalkanes. This would also serve as a method for preparation of various steroid analogs.

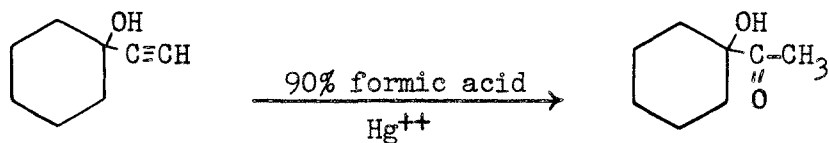
13 was prepared by condensing cyclopentanone with lithium acetylide. Then 22 and 13 were hydrated using formic acid and a mercury(II) formate catalyst to give 23 and 14 respectively. Compounds 22 and 13 also reacted with ethylene glycol using mercury(II) oxide and boron trifluoride catalyst to produce the ketals, 24 and 15 respectively. Ketals 24 and 15 were then dehydrated by the Tchugaeff reaction to produce the dehydrated ketals 25 and 26, respectively.

The unsaturated ketone, 29, was hydrogenated and then oxidized with pyridine and chromic oxide to saturated ketone, 31. Compounds 31 and 32 were condensed with acetylene by several different methods to produce 33 and 34. The Grignard method was the most successful. Compound 34 was hydrated by the method used for 23 to give 35. The ketal, 36, was also produced by the method used to prepare 24.



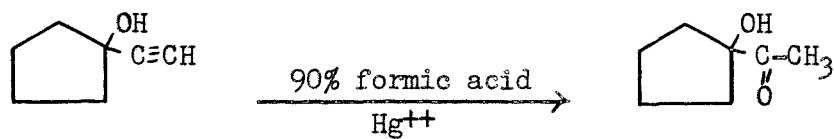
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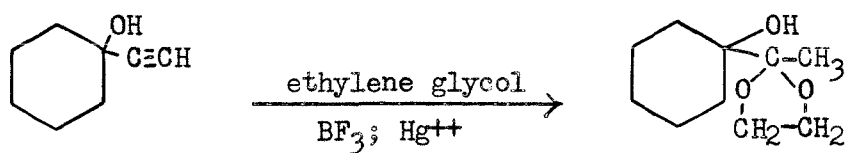
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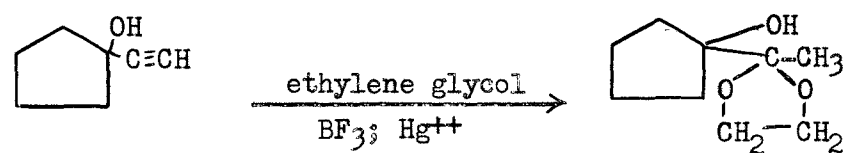
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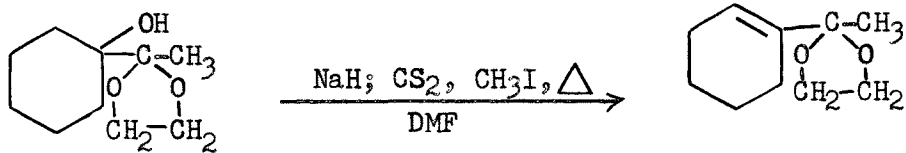
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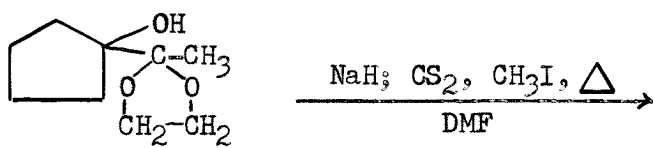
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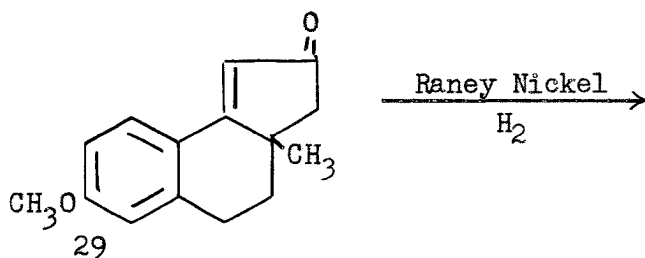
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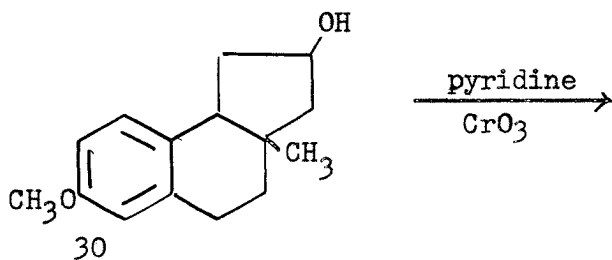
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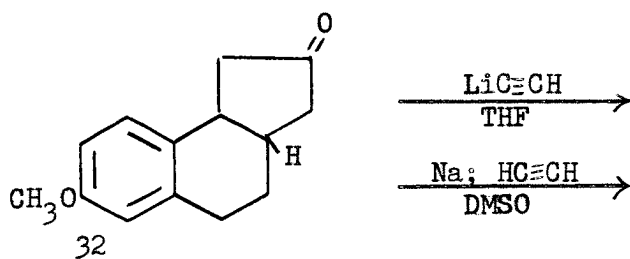
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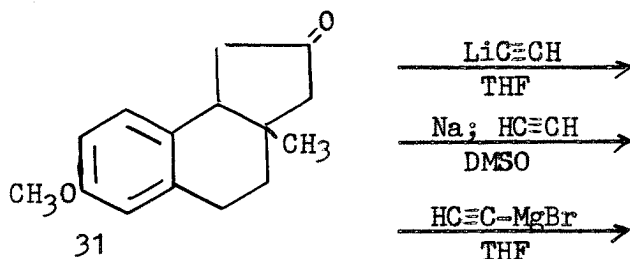
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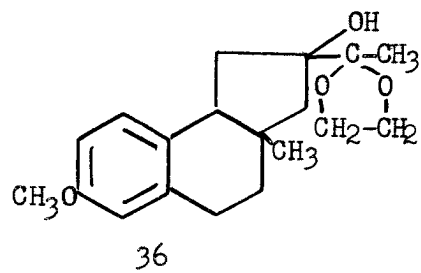
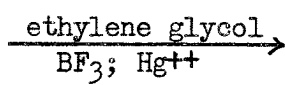
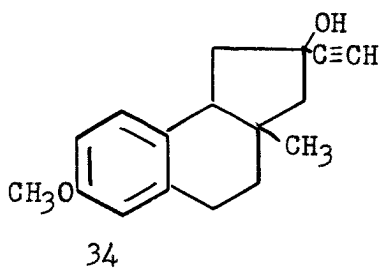
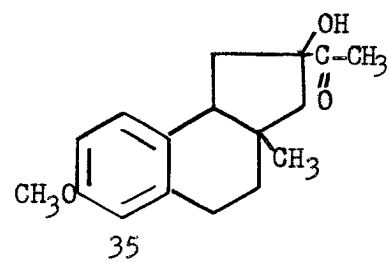
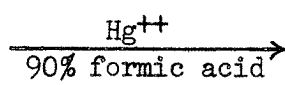
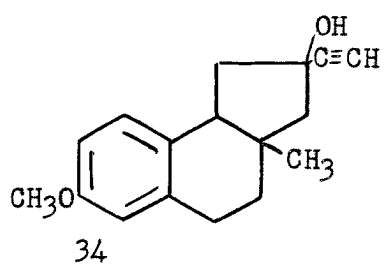
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