Summary

A study of the dehydrogenation of 3-methyl-5-(*p*-methoxyphenyl)-2-cyclohexen-1-one in boiling solvents with a palladium-carbon catalyst has shown that dehydrogenation to the corresponding phenol occurs readily at temperatures from 136 to 252°. Yields of 78-84% may be obtained in *p*-cymene, triethylbenzene and phenyl ether, with a reaction time of two hours. The corresponding *o*-methoxyphenyl-, 2,3-dimethoxyphenyl- and 3,4-dimethoxyphenylphenols were also obtained by the same procedure, in yields of 72, 70 and 86%, respectively.

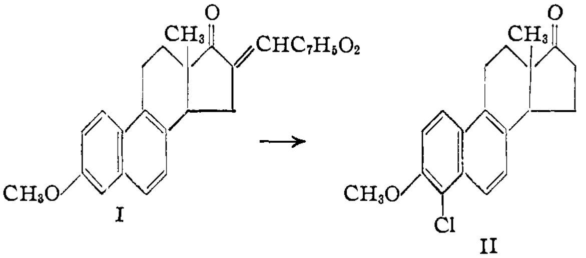
PHILADELPHIA, PENNA. RECEIVED JANUARY 31, 1947

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Introduction of the Angular Methyl Group. III. The Alkoxymethylene Blocking Group[1]

BY WILLIAM S. JOHNSON AND HARVEY POSVIC[2]

In order to introduce the methyl group into the angular position of a polycyclic ketone like decalone-1, VII, it has been found expedient to protect the methylene group (at C-2) with a substituent which can be removed after methylation. In the first paper of this series[3] the use of the benzylidene residue as the blocking group was described. The removal was effected by chlorination of the double bond followed by a series of hydrolytic steps which finally involved the cleavage of an α-benzoyl ketone. Although the method proved to be very successful for the methylation of decalone-1, it promised to present some difficulties in further application because of the uncertainty involved in the direction of cleavage of the intermediate β-diketone. The hydrolysis of 2-benzoyl-6,6-dimethylcyclohexanone, for example, was particularly unfavorable for the preparation of 2,2-dimethylcyclohexanone, VI. Another difficulty was envisaged in the necessity of using a chlorination step. Indeed, Birch, Jaeger and Robinson[4] applying our method to the removal of the piperonylidene group from the isoequilenin derivative I, found that nuclear chlorination occurred giving rise to a chloro ketone, probably II. Although the halogen could probably be removed by reductive methods, an additional operation would be involved.

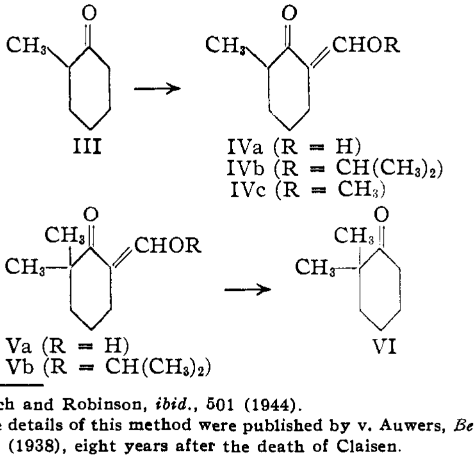


I

II

In an effort to circumvent some of the aforementioned difficulties the use of the easily removable alkoxymethylene residue (=CHOR) as a blocking group has been investigated. While our study was in progress Robinson and his collaborators[4,5] reported on the successful use of the methylanilinomethylene ($=CHNCH_3C_6H_5$) blocking group. In the present work the methylation of four ketones, III, VII, XIIIa and XIIIb was investigated.

2-Methylcyclohexanone, III, was condensed with ethyl formate in the presence of alcohol-free sodium methoxide to give the hydroxymethylene derivative, IVa, in 72% yield. The best of various methods which were tried for effecting O-alkylation was that of Claisen which involved heating the hydroxymethylene derivative with an alkyl halide and potassium carbonate in acetone.[6] When methyl iodide was used the product contained only about 20% of the O-methyl ether IVc, the remainder presumably being C-alkylation product. The proportion of O-alkylation could be greatly increased by using isopropyl iodide. The product thus obtained proved to contain at least 84% of the enol ether IVb, the amount being determined by submitting the mixture to the hydrolytic sequence described below for removing the alkoxymethylene group, and isolating the regenerated 2-methylcyclohexanone as the semicarbazone. Methylation of IVb was effected



III

IVa (R = H)
IVb (R = $CH(CH_3)_2$)
IVc (R = CH_3)

Va (R = H)
Vb (R = $CH(CH_3)_2$)

VI

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[1] For a preliminary announcement of this work see Johnson and Posvic, THIS JOURNAL, **67**, 504 (1945).

[2] du Pont Fellow, 1945-1946. Present address: Cornell University, Ithica, N. Y.

[3] Johnson, THIS JOURNAL, **65**, 1317 (1943).

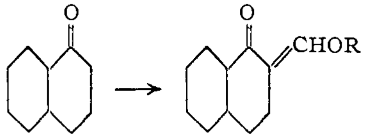
[4] Birch, Jaeger and Robinson, *J. Chem. Soc.*, 582 (1945).

[5] Birch and Robinson, *ibid.*, 501 (1944).

[6] The details of this method were published by v. Auwers, *Ber.*, **71B**, 2082 (1938), eight years after the death of Claisen.

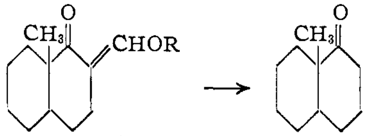
with potassium *t*-butoxide in *t*-butyl alcohol and methyl iodide, and the resulting oil was submitted to hydrolysis with cold dilute alcoholic hydrochloric acid. Any enol ether Vb thus was converted into the *gem*-dimethyl hydroxymethylene ketone Va which was separated by virtue of its solubility in alkali. This substance was found to be hydrolyzed in good yield to 2,2-dimethylcyclohexanone, VI, by aqueous alkali, and yields as high as 87% were obtained from distilled Vb. For the preparation of VI it was found unnecessary to purify any of the intermediate products. Thus from 112 g. of III it was possible to obtain 40 g. (a 32% over-all yield) of VI, representing a substantial improvement over the benzylidene method for the preparation of VI.[3]

When the method was applied to decalone-1, VII, the isopropoxymethylene derivative VIIIb proved to be crystalline and was obtained in 93–98% over-all yield from VII without distillation of the intermediate hydroxymethylene derivative VIIIa. The enol ether VIIIb proved to be more resistant to methylation than IVb; thus when potassium *t*-butoxide or sodium amide was used, the product, after removal of the protecting group, contained some decalone-1. When potassium amide was employed, essentially complete methylation was realized. The cleavage of the methylated enol ether IXb was effected particularly readily by alcoholic ferric chloride solution, and the hydroxymethylene derivative IXa was liberated from the dark ferric chloride complex by hydrochloric acid. The alkaline hydrolysis of IXa gave a mixture of *cis*- and *trans*-9-methyldecalone-1, X, in 43% over-all yield from decalone-1 in a 0.5-mole run, although yields as high as 57% were realized on a small scale. That the product contained little if any decalone-1 was shown by distillation through an efficient column followed by fairly complete separation of the stereoisomers *via* the semicarbazones. Advantage was taken of the differential rate of formation of these derivatives,[3] and by carefully controlled experiments it was possible to show that the mixture contained at least 71% of the *trans*[7] isomer and 20% of the *cis*.[7] Since it was easy to separate the *trans* semicarbazone, this represents the best method known to us for preparing this substance. The benzylidene method, on the other hand, is excellent for preparing the *cis* isomer. The methylanilinomethylene method of Birch and Robinson also appears to favor the formation of the *cis* isomer. The over-all yield of mixture obtained by them was 55%. From the published results, however, it is not possible to determine if their product was free of decalone-1[8]: this would not be revealed by the analytical data. Their product boiled over a six-degree range, and only a partial separation of the semicarbazones was effected.



VII

VIIIa (R = H)
VIIIb (R = CH(CH$_3$)$_2$)

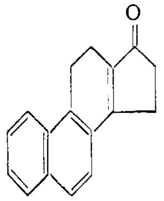


IXa (R = H)
IXb (R = CH(CH$_3$)$_2$)

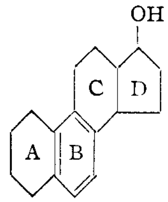
X

Methylation of desoxynorequilenin, XIIIa, by the isopropoxymethylene method gave results similar to those reported for the methylanilinomethylene method,[4] in that only the α-isomer (probably *cis*), of 17-equilenone, XVa, was isolated. The hydroxymethylene derivative and the isopropoxymethylene derivative XIVa were formed in good yields. The methylation step, however, afforded a large proportion of product which was not convertible into alkali-soluble material by acid hydrolysis.

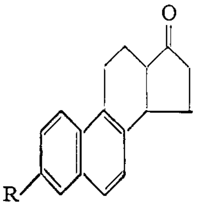
The starting ketone XIIIa was prepared in fair yields by the reduction of the readily available ketone XI[9] over palladium-on-strontium carbonate at 70 atmospheres and 75°. At room temperature the reduction was slower and appreciable amounts of a product, m. p. 127–128°, were isolated. The analysis was compatible with the formula XII, and this structure was supported by



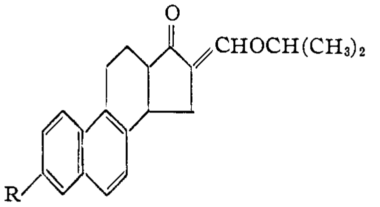
XI



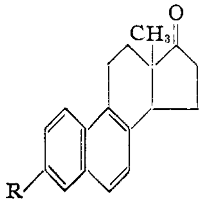
XII



XIIIa (R = H)
XIIIb (R = OCH$_3$)



XIVa (R = H)
XIVb (R = OCH$_3$)



XVa (R = H)
XVb (R = OCH$_3$)

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(7) These are probable configurations.

(8) The possibility of its presence is suggested by the fact that unmethylated material was isolated when the methylanilinomethylene method was applied to XIIIb (ref. 4).

(9) Johnson and Petersen, THIS JOURNAL, **67**, 1366 (1945).

the following facts: it failed to form ketone derivatives, but gave a crystalline benzoate having the appropriate analysis; on exhaustive oxidation with permanganate, benzene-1,2,3,4-tetracarboxylic acid was produced evidently arising from ring B. It was also found possible to obtain XIIIa from XI by electrolytic reduction in aqueous isopropyl alcohol containing ammonium chloride as the supporting electrolyte at the surface of an agitated mercury cathode. The yields, however, were capricious, varying from 0–55%.

The isopropoxymethylene method was also applied to norequilenin methyl ether, XIIIb, which was prepared by the ingenious synthesis of Robinson and his collaborators.[4,10] As in the case of the methylanilinomethylene method,[4] the only homogeneous substance which could be isolated was racemic isoequilenin methyl ether.

Experimental Part[11]

2-Methylcyclohexanone Series

2-Hydroxymethylene-6-methylcyclohexanone (IVa) has been prepared previously by v. Auwers and Krollpfeiffer.[12] Metallic sodium was used as the condensing agent and the yield was 53%. Using sodium methoxide in benzene,[13] we have realized yields of about 70%.

To an ice cold suspension of powdered sodium methoxide[14] (from 46 g. of sodium) in 750 cc. of benzene were added with swirling 112.5 g. of 2-methylcyclohexanone (Eastman Kodak Company grade) and 148 g. of ethyl formate. The system was evacuated and filled with nitrogen, and the mixture was allowed to stand at room temperature overnight. Ice water was added, the aqueous layer was separated, and the benzene solution washed thoroughly with cold dilute sodium hydroxide. All of the aqueous solutions were combined, washed once with ether, and acidified with dilute hydrochloric acid. The resulting oily suspension was saturated with salt and extracted thoroughly with ether. The ether solution was washed with water followed by saturated salt solution, and dried over anhydrous sodium sulfate followed by Drierite. Distillation gave 100.5 g. (or 72% yield) of colorless hydroxymethylene ketone, b. p. 87.5–92.5° (14 mm.). On redistillation it boiled at 76–77° (8 mm.); reported b. p. 79.2–79.4° (10 mm.).[12] It gave an instantaneous deep violet color with alcoholic ferric chloride, and formed a heavy crystalline precipitate with sodium bisulfite solution.

2-Isopropoxymethylene-6-methylcyclohexanone (IVb) was best prepared according to the general method of Claisen.[6] To a stirred suspension of 41.5 g. of freshly ignited and finely powdered potassium carbonate in 150 cc. of acetone (dried over anhydrous potassium carbonate) was added in small portions 28.2 g. of 2-hydroxymethylene-6-methylcyclohexanone prepared as described above. Isopropyl iodide (42.5 g.) was then added, and the mixture was stirred at room temperature. After forty hours the mixture, which was originally granular, had changed to a thick creamy suspension, but still gave an instantaneous color test with ferric chloride. The mixture was then heated under reflux with stirring for twenty-six hours, or until the ferric chloride test developed only slowly. The solvent was removed under reduced pressure with stirring, water was added, and the organic material was taken up in ether where it was washed twice with 5% sodium hydroxide solution, water, and finally saturated salt solution. After drying over anhydrous potassium carbonate, the solution was concentrated, and the residue distilled rapidly through a short Vigreux column; yield 32 g. (or 87%) boiling at 70–75° (0.1 mm.). This product, which contained at least 84% of O-alkylated material (see hydrolysis experiments below), gave a slowly developing violet color with alcoholic ferric chloride. It is a very sensitive compound and will not survive well a slow distillation. On standing in air it gradually becomes viscous, apparently due to oxidation. Even upon analysis of freshly redistilled material, b. p. 68–69° (0.08 mm.), $n^{20}\text{D}$ 1.4877, the carbon values were somewhat low.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 71.88, 71.78; H, 9.99, 9.74.

Methylation of 2-Hydroxymethylene-6-methylcyclohexanone by Claisen's Method.[6]—To a stirred suspension of 14 g. of powdered, ignited potassium carbonate in 125 cc. of dry acetone was added 21 g. of methyl iodide, followed by 14.0 g. of distilled hydroxymethylene ketone. The mixture was allowed to reflux with stirring for fifteen hours. Dry ether (60 cc.) was then added and after standing an hour the mixture was filtered and distilled. The product boiling at 95–110° (12 mm.) amounted to 12.0 g. and gave a slowly developing color with ferric chloride. On redistillation some decomposition occurred, and the product, b. p. 101–110° (11 mm.), gave an immediate color with ferric chloride. Like the isopropyl derivative this substance was sensitive to air (note the low carbon values). The methoxyl determination was about one-fifth of the calculated value suggesting that about four-fifths of the product was C-methylated material.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15; OCH_3, 20.1. Found: C, 69.41, 69.02, 68.94; H, 8.97, 8.94, 9.08; OCH_3, 4.14.

2-Isopropoxymethylene-6,6-dimethylcyclohexanone (Vb).—Freshly distilled enol ether IVb (9.0 g.) was added to an ice-cold solution of 6 g. of potassium in 200 cc. of *t*-butyl alcohol. The system was evacuated and filled with nitrogen, and 23 g. of methyl iodide was added to the clear red solution. After one hour at room temperature the reaction appeared to be complete, as indicated by precipitation of potassium iodide. The solvent was largely removed under reduced pressure, water was added, and the organic material was taken up in ether where it was washed twice with dilute sodium hydroxide solution and then with saturated salt solution. After drying over anhydrous potassium carbonate the solution was distilled giving 3.8 g. (a 39% yield) of material boiling at 82–83° (0.5 mm.). This product gave a slowly developing violet color with ferric chloride, and like the lower homolog appeared to be sensitive to air as indicated by the low carbon analysis.

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.42; H, 10.27. Found: C, 72.58; H, 10.33.

2,2-Dimethylcyclohexanone (VI). (*a*) *From Distilled 2 - Isopropoxymethylene - 6,6 - dimethylcyclohexanone.*—The distilled enol ether (2.5 g.), prepared as described in the preceding experiment, was dissolved in a mixture of 10 cc. of methanol and 0.5 cc. of water. The solution was cooled in ice, and 0.1 cc. of concentrated hydrochloric acid was added. After standing in the cold for one hour, the clear solution was diluted with water, and the oil which separated was taken up in ether and washed with water. The ether solution was then extracted with 5% sodium hydroxide solution. The neutral material remaining after evaporation of the ether amounted to 0.8 g. and since it gave a slowly developing color with ferric chloride, it was retreated with acid, the neutral fraction after the second hydrolysis amounting to 0.3 g., and after the third, 0.1 g. (giving no color with ferric chloride). The combined alkaline solutions were washed once with petroleum ether (to remove ether) and submitted to slow distillation. The distillate was saturated with salt and extracted with ether. From the dried ether solution was obtained 1.41 g. (87.5%

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[10] Robinson, *J. Chem. Soc.*, 1390 (1938); Koebner and Robinson, *ibid.*, 1994 (1938).

[11] All melting points are corrected unless otherwise specified.

[12] v. Auwers and Krollpfeiffer, *Ber.*, **48**, 1226 (1915).

[13] *Cf.* Johnson, Anderson and Shelberg, This Journal, **66**, 218 (1944).

[14] The sodium methoxide was rendered alcohol-free by heating for two hours at 200° under reduced pressure (vacuum pump). After cooling, the product was powdered by shaking.

yield) of crude ketone. The semicarbazone melted at 199–200° (dec.) and after two recrystallizations from ethyl acetate melted sharply at 201.5–202° (dec.). The m. p. was not depressed on admixture with an authentic specimen of 2,2-dimethylcyclohexanone semicarbazone, m. p. 201–202° (dec.).[3] In another run in which undistilled enol ether was used, the final product was converted to the oxime, m. p. 91–92°. After recrystallization from petroleum ether (b. p. 40–60°), the m. p. was 93–93.5°. No depression of the m. p. was observed on admixture with an authentic specimen of 2,2-dimethylcyclohexanone oxime, m. p. 92.5–93°.[3]

(*b*) *Prepared without Purification of the Intermediates*.—One mole (112 g.) of 2-methylcyclohexanone was converted to the hydroxymethylene derivative as already described. Without distillation the crude product (127.5 g.) was treated with 200 g. of powdered, ignited potassium carbonate and 232 g. of isopropyl iodide in 300 cc. of butanone-2. After refluxing and stirring for six hours the mixture gave a slow color test with ferric chloride, and the product was worked up as described above except that it was not distilled. After drying to constant weight over potassium hydroxide in a vacuum desiccator the crude enol ether (146.5 g.) was added to an ice-cold solution of 63 g. of potassium in 1250 cc. of *t*-butyl alcohol in an atmosphere of nitrogen. Methyl iodide (100 cc.) was then added to the dark red solution, and the mixture became warm and began to reflux. After standing for forty-five minutes the mixture was worked up as described above except that the crude methylated enol ether (186 g., containing some *t*-butyl alcohol) was not distilled, but was treated directly with 350 cc. of methanol, 70 cc. of water and 1 cc. of concentrated hydrochloric acid. After standing overnight at room temperature the solvent was removed under reduced pressure, saturated salt solution was added and the oil was extracted with ether. To the ether solution was added the acidic material (11.5 g.) which was liberated from the alkaline washings of the crude methylated enol ether above, and the whole was washed with water and extracted with four 250-cc. portions of 5% sodium hydroxide solution. The combined extracts were washed with petroleum ether and slowly distilled for one hour. The distillate (about 400 cc.) was saturated with salt and extracted with ether. The ether solution was washed with saturated salt solution, dried over Drierite and concentrated, giving 56.5 g. of crude product. Distillation through a 12-inch Vigreux column gave 40.3 g. (32% yield) of 2,2-dimethylcyclohexanone boiling at 168–174°, mostly at 168° (740 mm.). The crude semicarbazone melted at 196–196.5° (dec.), and after recrystallization from ethyl acetate, at 199.6–199.8° (dec.).

When potassium amide was used instead of potassium *t*-butoxide for the methylation, the yield was only about 4%.

2-Hydroxymethylene-6,6-dimethylcyclohexanone (Va) was not isolated from the methylation experiments, but was prepared from 2,2-dimethylcyclohexanone for the purpose of studying the hydrolysis. The *gem*-dimethyl ketone (6.18 g.), prepared as described under procedure (*b*) above and 7.5 g. of ethyl formate in 50 cc. of benzene were added to powdered sodium methoxide[14] prepared from 2.5 g. of sodium. The reaction was carried out and worked up as described above for the lower homolog; yield 6.0 g. (79.5%) of material boiling at 79–80° (11 mm.); $n^{20}\text{D}$ 1.4995. It gave an instantaneous violet color with alcoholic ferric chloride. A satisfactory analysis for carbon could not be obtained perhaps because this substance, like others in the series, was susceptible to air oxidation.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 68.99; H, 9.13.

The crystalline **benzoate**, however, was easily obtained pure. It was prepared in pyridine with benzoyl chloride, and crystallized from petroleum ether (b. p. 60–68°) in the form of colorless fluffy needles, m. p. 61.5–62.5°. It gave a slowly developing color with warm alcoholic ferric chloride, and turned to a dark gum on standing several months.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.49; H, 6.96.

Hydrolysis Experiments.—A control experiment with 2,2-dimethylcyclohexanone (0.170 g.), 0.22 g. of semicarbazide hydrochloride and 0.22 g. of sodium acetate in 11 cc. of water, gave after shaking and standing overnight, 0.229 g. (93% yield) of crude semicarbazone, m. p. 191–193.5° (dec.). This same procedure was used in the isolation of the product of the following hydrolysis experiment.

2-Hydroxymethylene-6,6-dimethylcyclohexanone was dissolved in about 100 volumes of 5% sodium hydroxide, and the solution was distilled slowly. The semicarbazone obtained from the ketone in the distillate amounted to a 75% over-all yield. This corresponds to an 81% yield for the cleavage step.

A similar experiment was performed with 2-hydroxymethylene-6-methylcyclohexanone. The semicarbazone of 2-methylcyclohexanone was isolated in 84–86% over-all yields. Since the conversion of pure ketone to semicarbazone was 88–91%, the yield for the hydrolysis step was about 95%. When freshly distilled hydroxymethylene ketone was used, the yields on hydrolysis proved to be almost quantitative.

2-Isopropoxymethylene-6-methylcyclohexanone (1.105 g.) was dissolved in 5 cc. of methanol, and 2.5 cc. of 5% hydrochloric acid was added. After three hours at room temperature 50 cc. of 5% sodium hydroxide was added and the solution was distilled. The semicarbazone prepared from the ketone in the distillate amounted to 0.734 g. (or 72% over-all yield). This corresponded to an 84% yield for the combined hydrolysis steps.

Decalone Series

2-Isopropoxymethylenedecalone-1 (VIIIb).—To an ice-cold suspension of powdered sodium methoxide[14] (from 4.5 g. of sodium) in 250 cc. of benzene, were added 7.6 g. of decalone-1 (purified *via* the bisulfite addition compound; b. p. 240–241° at 740 mm.) and 15 g. of ethyl formate. The system was evacuated and filled with nitrogen, and the mixture was allowed to stand at room temperature overnight. Ice water was then added, the aqueous layer separated, and the organic layer washed twice with dilute sodium hydroxide. Crystals of the sodio derivative sometimes separated when the alkaline solutions were cooled in ice. The aqueous layer and alkaline extracts were combined, washed once with ether and acidified with hydrochloric acid. The oily hydroxymethylene ketone was taken up in ether where it was washed with saturated salt solution and dried over Drierite. The product obtained on evaporation of the ether was treated with 200 cc. of dry acetone, 14 g. of powdered, ignited potassium carbonate and 17 g. of isopropyl iodide. The mixture was allowed to reflux with stirring for twelve hours, and then the solvent was removed under reduced pressure. Water and ether were added, the ether layer was separated and washed twice with dilute sodium hydroxide followed by saturated salt solution. After drying over anhydrous potassium carbonate the ether was removed leaving 10.3 g. (93% yield) of pale yellow oil which set to a crystalline mass on standing, m. p. 69–73°. Material of this purity was satisfactory for the methylation step. A sample recrystallized twice from petroleum ether (b. p. 40–60°) was obtained as colorless needles, m. p. 77–78°.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.31; H, 9.77.

The pure enol ether has a floral odor, and with alcoholic ferric chloride gives a violet color after five to ten minutes. It can be preserved for some time in an atmosphere of nitrogen, but decomposes in a few days in the presence of air.

Methylation of 2-Isopropoxymethylenedecalone-1.—Potassium amide prepared by dissolving potassium in liquid ammonia, adding ether, and allowing the ammonia to boil off at room temperature is usually obtained as a grayish solid cake. In order to obtain finely divided material which is more satisfactory, the following procedure was used: To 400 cc. of liquid ammonia and 0.1 g. of ferric nitrate in a 1-liter dropping funnel was added 40 g. of potassium in small portions over a period of about five hours. The blue color was allowed to fade before each addition. This solution was added dropwise with vigorous stirring into 1 liter of refluxing ether, the whole system being protected from moisture. It was found expedient to use a liquid ammonia-cooled condenser to prevent excessive escape of ether, but to permit escape of the ammonia. During the addition ether was added to replace that which was lost. Finally the grayish-white suspension was allowed to reflux with a slow stream of nitrogen passing through until no more ammonia could be detected. Material thus prepared is extremely reactive and should not be allowed to come in contact with air or moisture.

The crude 2-isopropoxymethylenedecalone-1 (111.5 g.) prepared (by the procedure described above) from 76 g. (0.5 mole) of decalone-1 was dissolved in 500 cc. of ether, and added slowly with stirring over a period of one hour to the above suspension of potassium amide. The mixture was cooled in an ice-bath during the addition, an atmosphere of nitrogen being maintained throughout the experiment. The orange suspension was stirred at room temperature for one day and then at refluxing temperature for twelve hours. The mixture was cooled (ice-bath) and 100 cc. of methyl iodide was added slowly with stirring over a period of about one hour. Stirring was continued for five hours at room temperature and the color gradually faded to a faint yellow. Water was added, and the ether layer was separated and washed with dilute potassium hydroxide solution followed by water. The ether was evaporated, and to the residue was added an ice-cold solution of 200 g. of ferric chloride hexahydrate in 500 cc. of methanol. The solution, which gradually turned very dark, was allowed to stand in an atmosphere of nitrogen in the cold (ice-bath) for two hours. The ferric chloride complex was then decomposed with 500 cc. of cold 1 to 1 (by volume) hydrochloric acid. The oil was taken up in ether, washed with dilute hydrochloric acid, and then extracted with five 100-cc. portions of 5% potassium hydroxide solution. The combined alkaline solutions were filtered to remove a small amount of ferric hydroxide, washed once with ether, and then distilled slowly. The ketone which steam distilled amounted to 36 g. (43% yield), and consisted almost entirely of a mixture of pure *cis*- and *trans*-9-methyldecalone-1 as shown by the distillation and semicarbazone formation described below.

On distillation of the above ketone through a Fenske column packed with glass helices and rated at 22 theoretical plates, practically no forerun was obtained, and the product distilled at 245–248° (mostly at 247–248°) at 742 mm. The recovery was 29.4 g., the remaining material being retained as hold-up in the column (*cis*- and *trans*-9-methyldecalone-1 boil about 3° apart at 14 mm.[3]).

Fractional distillation of the alkali-insoluble fraction remaining after the ferric chloride hydrolysis showed that it consisted largely of products that were higher boiling than the 9-methyldecalones.

Separation of *cis*- and *trans*-9-Methyldecalone-1 *via* the Semicarbazones.—In order to realize effective separation it was found expedient to carry out the reactions in the cold. Five grams of the distilled ketone mixture described in the preceding experiment was dissolved in 100 cc. of alcohol and cooled in an ice-bath. To this was added a cold, filtered solution of 5 g. of semicarbazide hydrochloride and 5 g. of sodium acetate in 25 cc. of water, and the mixture was allowed to stand in the cold (ice-bath). After thirty minutes fraction (1), 2.3 g., m. p. 216–218° (dec.), was collected; and after two hours fraction (2), 2.5 g., m. p. 216–217° (dec.), was collected. These fractions represented a 71.5% yield of practically pure *trans*-9-methyldecalone-1 semicarbazone. The melting points were not depressed on admixture with an authentic specimen melting at 218–219° (dec.).[3] The filtrate from fraction (2) was boiled under reflux for thirty minutes. On dilution with 100 cc. of water and cooling, the mixture deposited fraction (3), 1.47 g. (22% yield), m. p. 213–218° (dec.). From this mixture there was obtained by recrystallization twice from alcohol, 0.3 g. (a 4.5% yield) of *cis*-9-methyldecalone-1 semicarbazone; m. p. 227–228° dec. (introduced in bath at 220° with slowly rising temperature), not depressed on admixture with an authentic specimen.[3,15]

In another similar experiment in which methanol instead of ethyl alcohol was used as the solvent, it was found possible to isolate the *cis*-isomer in about 20% yield. After thirty minutes in the cold, the first fraction amounted to 4.75 g. (71% yield) of impure semicarbazone, m. p. 207–210°. From the filtrate, after heating twenty minutes, there was obtained on dilution with 25 cc. of water and cooling, 1.3 g. of *cis*-9-methyldecalone-1 semicarbazone, m. p. 225–227° (dec.). A single recrystallization from alcohol gave material melting at about 228–229° (dec.)[15] alone or when mixed with an authentic specimen. A 20° depression was observed in the melting point on admixture with decalone-1 semicarbazone (m. p. 227–228°, dec.).

In experiments conducted at room temperature, the separations were not clean. It was found possible to isolate pure fractions, however, by hydrolysis of the crude derivatives, followed by reformation of the semicarbazones.

Tetracyclic Ketone Series

3′-Keto-1,2,3,4-tetrahydro-1,2-cyclopentenophenanthrene (XIIIa).—3′-Keto-3,4-dihydro-1,2-cyclopentenophenanthrene (XI) was prepared *via* the Stobbe condensation with 1-keto-1,2,3,4-tetrahydrophenanthrene.[9] For the reduction studies material was used which had been sublimed and then recrystallized from isopropyl alcohol; m. p. 220.5–222°. A suspension of 1.0 g. of the ketone and 1.0 g. of a 2% palladium-strontium carbonate catalyst[16] in 50 cc. of isopropyl alcohol was placed in a small bomb and shaken at 75° under a pressure of about 70 atmospheres of hydrogen. The product was isolated as the sparingly soluble semicarbazone. The yields of this derivative upon variation of the reaction time were as follows: in two and one-half hours, 0.65 g. (52%), m. p. 258–259° (dec.); in one hour and forty minutes, 0.76 g. (61%), m. p. 255–256° (dec.); in one hour, 0.81 g. (65%), m. p. 257–258° (dec.) and 0.90 g. (72%), m. p. 258–260° (dec.). When the time was reduced to forty-five minutes some starting material was recovered. Hydrolysis of the crude semicarbazones with boiling 20% hydrochloric acid gave practically quantitative yields of the ketone which after recrystallization from methanol melted at 113–114°. The reported melting points are 111–112°,[17] and 112–113°.[18] The 2,4-dinitrophenylhydrazone had the m. p. 258–259° (dec.) (reported[17] 255–256°). The **semicarbazone** was reformed by warming a pyridine solution of the ketone with semicarbazide hydrochloride. The derivative crystallized as small colorless prisms, m. p. 268–269° (dec.). It turned yellow on exposure to light.

Anal. Calcd. for $C_{18}H_{19}ON_3$: C, 73.69; H, 6.53. Found: C, 73.54; H, 6.68.

3′-Hydroxy-1,2,3,4,5,6,7,8-octahydro-1,2-cyclopentenophenanthrene (XII).—A hydrogenation experiment with 0.20 g. of XI and an equal weight of palladium-strontium

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[15] The melting point of the semicarbazone of *cis*-9-methyldecalone-1 varies considerably with the rate of heating. Melting points as high as 234° have been observed with samples introduced close to 230°. On the other hand, a sample will eventually melt at 220° after being held at this temperature for some time.

[16] *Cf.* Koebner and Robinson (ref. 10). Our catalyst was prepared as follows: Strontium carbonate, freshly precipitated by mixing solutions of pure strontium chloride and potassium carbonate, was separated and washed thoroughly with distilled water by centrifugation. To the moist product was added a solution of palladium chloride (2% of the weight of strontium carbonate) in dilute hydrochloric acid. The sludge was thoroughly mixed, and a few drops of dilute potassium carbonate solution was added. The product was separated and washed thoroughly by centrifugation, and finally dried in an oven at 50°.

[17] Koebner and Robinson, *J. Chem. Soc.*, 566 (1941).

[18] Bachmann, Gregg and Pratt, This Journal, **65**, 2314 (1943).

carbonate catalyst[16] in 25 cc. of isopropyl alcohol was carried out at 70 atmospheres of hydrogen at room temperature for twenty-four hours. The catalyst was removed by filtration, and the solution evaporated in a current of air. The oily residue (0.20 g.) was crystallized from hexane, giving as the first crop 0.08 g. of the crude alcohol XII, m. p. 120–122°. From the mother liquor there was obtained 0.077 g. of crude XIIIa, m. p. 95–105° (108–110° after recrystallization). Recrystallization of the 120–122° material from hexane gave colorless needles, m. p. 127–128°.

Anal. Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.12; H, 8.98.

This substance did not form a semicarbazone or 2,4-dinitrophenylhydrazone, but with benzoyl chloride in pyridine gave a **benzoate**, m. p. 112–113°. Two recrystallizations from hexane gave colorless blades, m. p. 114.4–114.8°.

Anal. Calcd. for $C_{24}H_{26}O_2$: C, 83.20; H, 7.57. Found: C, 83.08; H, 7.64.

A 20-mg. sample of the alcohol was boiled with a solution of 0.30 g. of potassium permanganate in 3 cc. of water for three hours. The mixture was acidified, a slight excess of permanganate was added, and then the whole was bleached with sodium bisulfite. This mixture was extracted six times with ether, and the combined ether solutions were treated with an excess of diazomethane. The ester obtained on evaporation was recrystallized three times from hexane and twice from methanol. The product thus obtained melted at 129.5–130° and showed no depression on admixture with an authentic specimen of tetramethyl benzene-1,2,3,4-tetracarboxylate (m. p. 129–130°).

2′-Isopropoxymethylene-3′-keto-1,2,3,4-tetrahydro-1,2-cyclopentenophenathrene (XIVa).—A solution of 0.287 g. of 3′-keto-1,2,3,4-tetrahydro-1,2-cyclopentenophenanthrene, prepared as described above in 15 cc. of benzene was added to a suspension of powdered sodium methoxide[14] (prepared from 0.5 g. of sodium) in 10 cc. of benzene and 4 cc. of ethyl formate. The mixture was allowed to stand overnight in an atmosphere of nitrogen. The clear yellow solution was treated with ice water, and extracted thoroughly with dilute potassium hydroxide. The combined aqueous solutions were filtered and acidified. This gave 0.30 g. (a 93.5% yield) of pale yellow 2′-hydroxymethylene - 3′ - keto - 1,2,3,4 - tetrahydro - 1,2-cyclopentenophenanthrene, m. p. 133–135° (reported[4] 134°). A solution of this product in 25 cc. of dry acetone was allowed to reflux for one day with 1.0 g. of powdered, ignited potassium carbonate and 1 cc. of isopropyl iodide. The solvent was removed under reduced pressure, water and ether were added, and the ether layer was separated and washed with dilute potassium hydroxide solution. After drying over anhydrous potassium carbonate, the ether was evaporated leaving 0.32 g. of gummy solid. Crystallization from hexane gave 0.23 g. (62% over-all yield) of the enol ether, m. p. 117–118°. Material twice recrystallized (in a nitrogen atmosphere) from hexane was obtained as almost colorless elongated prisms, m. p. 119.8–120°.

Anal. Calcd. for $C_{21}H_{22}O_2$: C, 82.31; H, 7.24. Found: C, 82.37; H, 7.16.

The pure enol ether gave a slowly developing violet color with boiling alcoholic ferric chloride. At room temperature the color appeared only after several hours. Like other enol ethers described in this work, XIVa appears to be sensitive to air. A solution in hexane on exposure to air for a day deposits some high-melting material which was not further investigated.

Methylation of XIVa.—A solution of 0.26 g. of the enol ether XIVa (m. p. 118–119.5°) in 20 cc. of ether was added to an ice-cold suspension of potassium amide (from 0.65 g. of potassium) in ether. The mixture was allowed to stir under nitrogen at ice-bath temperature for one hour. Methyl iodide (6 cc.) was added to the dark red mixture and stirring continued for six hours at room temperature. After standing for twelve hours at room temperature, the mixture was treated with water. The ether layer was washed with dilute potassium hydroxide, then with water and dried in the usual manner. Evaporation gave 0.24 g. of oil which was dissolved in 10 cc. of ether and 5 cc. of methanol. To this was added a solution of 1 g. of ferric chloride hexahydrate in 10 cc. of methanol. The solution was allowed to stand at room temperature under nitrogen for fifteen hours, and then 100 cc. of 5% tartaric acid was added to decompose the dark complex. The product was taken up in ether, washed with dilute tartaric acid, and extracted with 100 cc. of 1% potassium hydroxide solution. (The alkali-insoluble material obtained by evaporation of the ether amounted to 0.175 g. and did not give a color with hot ferric chloride solution.) The alkaline extracts were heated on the steam-bath for four hours and the product which separated was isolated *via* chloroform extraction; yield 0.045 g. of brown solid. On crystallization from methanol some sparingly soluble material melting above 250° was first obtained. From the mother liquors a small amount of crystalline material, m. p. 96–100°, was isolated. After recrystallization from methanol it melted at 100–101°, and showed no depression of the m. p. on admixture with an authentic specimen of α-17-equilenone, XVa, (m. p. 99–102°) prepared by Dr. Jack W. Petersen.

***d,l*-Isoequilenin Methyl Ether (XVb).**—3′-Keto-7-methoxy - 1,2,3,4 - tetrahydro - 1,2 - cyclopentenophenanthrene (XIIIb) was prepared according to the procedures of Robinson and his collaborators[4,10]; m. p. 115–116° (reported, 116–117°). A solution of 52 mg. of this ketone and 5 cc. of ethyl formate in 25 cc. of dry benzene was added to powdered sodium methoxide[14] (from 0.34 g. of sodium). The mixture was treated as described above for the ketone XIIIa, except that the hydroxymethylene ketone was finally isolated *via* chloroform extraction; yield 56 mg. or 97% of solid. This was converted to the enol ether with 2 g. of potassium carbonate, 2 cc. of isopropyl iodide and 25 cc. of acetone according to the procedure described above for the preparation of XIVa. The isopropoxymethylene derivative XIVb was isolated as an oil (68 mg.) which was methylated in ether with potassium amide (from 0.5 g. of potassium) and methyl iodide (5 cc.). The mixture was heated for one-half hour to form the potassio derivative, and then for six hours after the addition of the methyl iodide. The crude methylated enol ether was isolated as described above, and hydrolyzed with 5 cc. of ether and 0.5 g. of ferric chloride hexahydrate in 5 cc. of methanol. After twenty hours at room temperature under nitrogen, the product was worked up as described above. The product obtained on boiling the alkaline extracts for four hours under nitrogen, amounted to 8 mg., m. p. 123–126°. On admixture with an authentic sample of *d,l*-isoequilenin methyl ether[19] (m. p. 129–130°), the m. p. was 125–129.5°.

Summary

A new method has been found for introducing the angular methyl group into polycyclic ketones related to the steroids. The process consists of (1) condensation of the ketone with ethyl formate followed by alkylation of the potassio derivative with isopropyl iodide, (2) methylation of the resulting isopropoxymethylene ketone with a strong base and methyl iodide, (3) removal of the alkoxymethylene blocking group by acid followed by basic hydrolysis.

MADISON, WISCONSIN RECEIVED OCTOBER 22, 1946

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[19] Johnson, Petersen and Gutsche, THIS JOURNAL, **67**, 2274 (1945).