Cyclohexenone-4-acetic Acid Derivatives from the Addition of Diazoacetic Ester to β,γ-Unsaturated Ketals[1]

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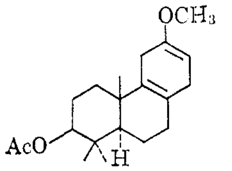
The addition of ethyl diazoacetate to various β,γ-unsaturated ketals varying in the degree of substitution of the double bond has been investigated. Satisfactory yields of cyclopropane derivatives were obtained in the monocyclic cases that have been examined. The reaction failed in bicyclic systems in which the double bond was present at the ring fusion. Ketal cleavage and ring opening of the cyclopropanes that were successfully prepared yielded cyclohexenone-4-acetic acid derivatives, which are of interest as synthetic intermediates.

Various terpenoids of current interest, *e.g.*, kaurene, phyllocladene, gibberellic acid, etc., contain a substituted bicyclo[3.2.1]octane system as a prominent structural feature. Several solutions to the synthetic problem presented by this arrangement have been published.[3] The present work was undertaken with a view toward incorporation of the elements of the bridged system, after construction of the polycyclic nucleus was complete, by introduction of a functionalized angular substituent followed by directionally controlled cyclization. The preparation of intermediates of type **4** was of interest in this connection.

As an approach to the synthesis of compound **4** it appeared that addition of diazoacetic ester to the unsaturated ketal **2** would afford a cyclopropane derivative **3** which on hydrolysis to the corresponding ketone could undergo base-catalyzed cleavage to the desired product. This procedure represents an extension of the methods employed by Birch[4] and by Winstein[5] for angular alkylation through the use of carbenoid reagents.



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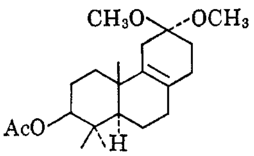

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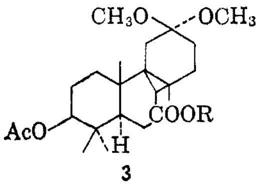

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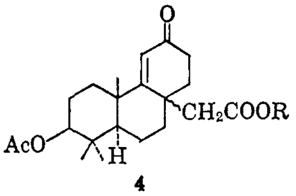

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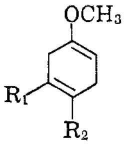
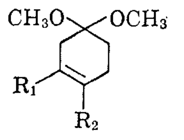
The dihydro anisole derivative (**1**), obtained as described in the Experimental Section, was accordingly treated with methanol and *p*-toluenesulfonic acid,[4] under which conditions ketal (**2**) was produced in good yield. However, the reaction of this substance with diazoacetic ester in the presence of copper–bronze powder[6] under a variety of conditions led only to recovery of starting material. We were, therefore, prompted to undertake an examination of the reaction sequence in simpler model compounds.

Dihydroanisoles **5a**, **b**, and **c** were prepared by Birch reduction of the appropriate anisoles and were smoothly converted into the ketals **6a**, **b**, and **c** by reaction with methanol and *p*-toluenesulfonic acid.[4] The products obtained in this way were then treated with diazoacetic ester and copper–bronze powder without solvent at temperatures ranging from 120 to 135°.

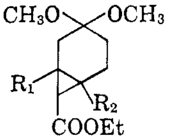
Material derived from **6a** proved to be thermally unstable and, although a pure sample of **7a** could be isolated by vapor chromatography, some elimination of methanol occurred and afforded an additional peak which appeared from nmr analysis to consist of a mixture of enol-ethers (**10**). It is of interest to note that the molecular ion of mass 228 is not observed in the mass spectrum of **7a**, but instead an ion, *m/e* 197, appears corresponding to the loss of a methoxyl group.[7]



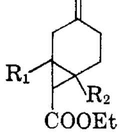
5a, $R_1 = R_2 = H$
b, $R_1 = H; R_2 = CH_3$
c, $R_1 = R_2 = CH_3$



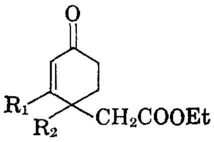
6a, $R_1 = R_2 = H$
b, $R_1 = H; R_2 = CH_3$
c, $R_1 = R_2 = CH_3$



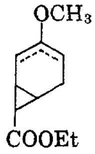
7a, $R_1 = R_2 = H$
b, $R_1 = H; R_2 = CH_3$
c, $R_1 = R_2 = CH_3$



8a, $R_1 = R_2 = H$
b, $R_1 = H; R_2 = CH_3$
c, $R_1 = R_2 = CH_3$



9a, $R_1 = R_2 = H$
b, $R_1 = H; R_2 = CH_3$
c, $R_1 = R_2 = CH_3$



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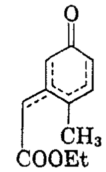

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Cleavage of the ketal function in **7a** by exchange with acetone afforded keto ester **8a**, which was further transformed into the cyclohexenone **9a** by the action of *p*-

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[1] Support of this work by the Robert A. Welch Foundation is gratefully acknowledged.

[2] Department of Chemistry, Texas A & M University, College Station, Texas 77843.

[3] See for example (a) R. B. Turner and K. H. Gänshirt, *Tetrahedron Lett.*, 231 (1961); (b) R. A. Bell, R. E. Ireland, and R. A. Partyka, *J. Org. Chem.*, **27**, 3741 (1962); (c) S. Masamune, *J. Amer. Chem. Soc.*, **86**, 288 (1964); *ibid.*, **86**, 289 (1964); (d) G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *ibid.*, **87**, 1148 (1965).

[4] A. J. Birch, J. M. Brown, and G. S. R. Subba Rao, *J. Chem. Soc.*, 3309 (1964).

[5] T. Hanafusa, L. Birladeanu, and S. Winstein, *J. Amer. Chem. Soc.*, **87**, 3510 (1965).

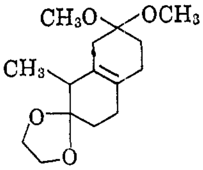
[6] S. Akiyoshi and T. Matsuda, *ibid.*, **77**, 2476 (1955).

[7] We are indebted to Professor J. L. Franklin of this department for the mass spectral data.

toluenesulfonic acid in refluxing benzene. The over-all yield in the latter two steps was 88%, and the structure of the final product (**9a**) was established by palladium-catalyzed dehydrogenation and hydrolysis to *p*-hydroxyphenylacetic acid, identical in all respects with an authentic sample.

Cleavage of ketal ester **7b** similarly afforded keto ester **8b**, which, however, furnished a mixture of products on acid-catalyzed ring opening. On the basis of the assumption that in this case acid treatment can result in competitive cleavage to yield substances of type **11**, sodium acetate in ethanol was substituted for the *p*-toluenesulfonic acid, and **9b** was thus obtained cleanly and in good yield. The acid-catalyzed procedure permitted conversion of the dimethyl derivative **7c** into **9c**, which was obtained in an over-all yield of 63% from the starting β,γ-unsaturated ketal (**6c**).

The question of the behavior of bicyclic systems in the reaction scheme was next explored. Ketals **12** and **13** were prepared by procedures described in the Experimental Section, and the reaction of these substances and of Δ^9-octalin (**14**)[8] with diazoacetic ester and copper–bronze were examined. Only in the case of **14** was any evidence of reaction obtained. In this instance 17% of a product was isolated by vapor chromatography, which possessed spectral properties (nmr) compatible with those expected for the cyclopropane derivative **15**. The photolytic and uncatalyzed thermal reactions of diazoacetic ester with Δ^9-octalin were also attempted, but no recognizable products could be obtained. It would appear, therefore, that direct application of this method to bicyclic systems containing a double bond at the ring fusion is, for practical purposes, precluded.



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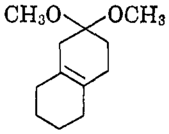

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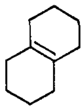

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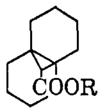

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Experimental Section[9]

Preparation of Dihydroanisole (1).—A 1.0-g sample of 1,1,12-trimethyl-2-hydroxy-6-methoxy-1,2,3,4,9,12-hexahydrophenanthrene[10] in 30 ml of acetic acid was shaken with 500 mg of 10% palladium-on-charcoal in an atmosphere of hydrogen until the uptake of hydrogen ceased. The catalyst was removed by filtration, and the filtrate was diluted with water and extracted with ether. The organic phase was then washed successively with water, diluted sodium hydroxide solution, water, and a saturated solution of sodium chloride. After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure, and the product was crystallized from ether–petroleum ether (bp 30–60°) to yield 650 mg: mp 110–110.5°; $\lambda_{\max}^{CS_2}$ 2.79 μ.

Anal. Calcd for $C_{13}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 79.00; H, 9.54.

Birch reduction of the product (1.49 g) obtained in the previous paragraph was carried out in a mixture of 100 ml of absolute ether and 300 ml of dry liquid ammonia containing 24 ml of ethanol. Lithium metal was added in small pieces to this solution at a rate which permitted maintenance of a blue color for a period of 45 min. The ammonia was then allowed to evaporate under a nitrogen atmosphere. Ice water and ether were added, and the product was isolated by ether extraction. After the usual washing and drying operations, the solvent was removed, and the product was crystallized from ether–petroleum ether to yield 1.16 g: mp 142–143°; $\lambda_{\max}^{CH_2Cl_2}$ 2.81, 5.90, 6.01, 9.70 μ.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.39; H, 10.22.

Acetylation of this material with acetic anhydride and pyridine afforded the corresponding acetate (1) (77% yield): mp 152–153°; $\lambda_{\max}^{CH_2Cl_2}$ 5.80, 5.90, 6.01, 9.71 μ.

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.37; H, 9.46.

Preparation of Acetoxy Ketal 2.—To a solution of 206 mg of compound 1 in 8 ml of anhydrous ether were added 0.2 ml of methanol and a catalytic amount of *p*-toluenesulfonic acid. The solution was maintained at 0° for 2 hr and was then heated under reflux for 30 min. At the end of this time the reaction mixture was poured into cold, dilute sodium bicarbonate solution, and the ether phase was washed with water and saturated sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was removed, and the residue was crystallized from ether–petroleum ether. The yield of compound 2 was 165 mg: mp 120–121°; $\lambda_{\max}^{CH_2Cl_2}$ 5.80, 8.94, 9.50, 9.70 μ.

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.95; H, 9.70.

Preparation of Ketal 6a.—A solution of 100 g of anisole in a mixture of 100 ml of anhydrous ether, 200 ml of absolute ethanol, and 550 ml of liquid ammonia was treated with small pieces of lithium metal added at a rate sufficient to maintain a blue color for a period of 45 min. The excess lithium was then destroyed by addition of ammonium chloride, and the ammonia was then allowed to evaporate. Addition of 1.5 l. of cold water followed by thorough extraction with ether furnished an ethereal solution which was washed, and dried over anhydrous sodium sulfate.

The ether solution (800 ml) was then treated with 125 ml of anhydrous methanol and several crystals of *p*-toluenesulfonic acid. The reaction mixture was allowed to stand at room temperature for 8 hr and was finally heated under reflux in a nitrogen atmosphere for 8 hr. At the end of this time the solution was cooled, washed with sodium bicarbonate solution, water, and saturated sodium chloride. After drying over anhydrous sodium sulfate, the solvent was removed by careful distillation through a Vigreaux column. The crude product was purified by preparative vapor chromatography yielding 93.4 g of compound **6a**. The analytical sample was obtained by resubmitting a portion of this material to vapor chromatography. The nmr spectrum of the material taken in carbon tetrachloride showed a two-hydrogen multiplet centered at 5.53 (tetramethylsilane standard), a six-hydrogen singlet at 3.11 and a broad six-hydrogen multiplet in the 1.5–2.2-ppm region.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.52; H, 9.87.

Preparation of Ketal 6b.—A 60.0-g sample of *p*-methylanisole was reduced with lithium by the procedure of the previous experiment. The crude dihydro derivative was then treated with methanol in the presence of *p*-toluenesulfonic acid as described above, and the product was purified by distillation through a spinning-band column to yield 40.0 g, bp 82–84° (21 mm).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.23; H, 10.15.

Preparation of Ketal 6c.—This substance was prepared from 3,4-dimethylanisole by the previously described procedure. A 26.0-g sample of starting anisole afforded 25.5 g of 4,4-dimethoxy-1,2-dimethylcyclohexene, bp 70–71° (7 mm).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.67; H, 10.64.

Preparation of 4,4-Dimethoxynorcarane-7-carboxylic Acid Ethyl Ester (7a).—The unsaturated ketal (**6a**), 6.7 g, was heated to 120–130° in an oil bath, and a mixture of 13.5 g of ethyl diazoacetate and a further 6.7-g sample of ketal (**6a**) was added dropwise over a period of 7 hr in the presence of copper and bronze powders in a 1:1 ratio. Filtration and distillation of the crude reaction product afforded 9.9 g of material, bp 95–105° (0.06 mm). Vapor chromatography (column temperature, 200°) afforded the sample for analysis with nmr characteristics compatible with structure **7a**.

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[8] W. P. Campbell and G. C. Harris, *J. Amer. Chem. Soc.*, **63**, 2721 (1941).

[9] Infrared and nmr spectra were taken routinely on all products.

[10] J. D. Tauber, Ph.D. Thesis, Rice University, 1967.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.63; H, 8.75.

There was obtained in addition a second peak which proved to be a mixture of unsaturated isomers (**10**). It was subsequently established that elimination of methanol occurred during chromatography.[11]

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.34; H, 8.20.

Preparation of 4-Ketonorcarane-7-carboxylic Acid Ethyl Ester (8a).—A solution of 6.0 g of compound **7a** in 300 ml of acetone was treated with 1.0 g of *p*-toluenesulfonic acid monohydrate, and the mixture was allowed to stand at room temperature for 18 hr. At the end of this time cold, dilute sodium bicarbonate solution was added, and the product was isolated by ether extraction. After the usual washing and drying operations, the solvent was removed affording 6.02 g of crude material which was shown to contain 75% of compound **8a** by vapor chromatography. A chromatographically pure sample ($\lambda_{\max}^{\text{film}}$ 5.78, 5.83 μ) was analyzed.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.97; H, 7.77.

The 2,4-dinitrophenylhydrazone, prepared as a derivative, melted at 129–132° (95% ethanol).

Anal. Calcd for $C_{16}H_{18}N_4O_6$: C, 53.04; H, 5.01; N, 15.46. Found: C, 53.01; H, 5.03; N, 15.50.

Preparation of Conjugated Keto Ester 9a.—A solution of 3.7 g of keto ester (**8a**) in 125 ml of dry benzene was heated under reflux for 8 hr in the presence of a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was then cooled, washed successively with dilute sodium bicarbonate solution, water, and saturated sodium chloride, and finally dried over anhydrous magnesium sulfate. Removal of the solvent followed by vapor chromatography of the residual oil furnished a 90% yield of **9a**, $\lambda_{\max}^{\text{film}}$ 5.78, 5.92 μ.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.92; H, 7.61.

Conversion of Compound 9a into *p*-Hydroxyphenylacetic Acid.—A 300-mg sample of (**9a**) was dissolved in 1 ml of xylene and 300 mg of 10% palladium on charcoal was added. The mixture was heated in an oil bath (180°) for 5 hr, and was then cooled, diluted with ether, and filtered. Extraction with dilute sodium hydroxide and acidification furnished 55 mg of phenolic material, which was hydrolyzed by treatment with 1.5 ml of 10% potassium hydroxide solution for 50 min at reflux temperature. Routine work-up afforded 27 mg of crystalline material, which was purified by sublimation and recrystallization from ether–petroleum ether. The product melted at 153–154.5° and was identified as *p*-hydroxyphenylacetic acid by direct comparison with an authentic sample.

Preparation of 4,4-Dimethoxy-1-methylnorcarane-7-carboxylic Acid Ethyl Ester (7b).—The unsaturated ketal (**6b**), 14.8 g, was heated to 120°, and was treated by dropwise addition with 11.4 g of ethyl diazoacetate in the presence of copper bronze powder. Distillation of the resulting dark oil afforded 4.7 g of starting material (**6b**) and 10.7 g of product **7b**, bp 78–79° (0.007 mm).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.31; H, 8.90.

Preparation of 4,4-Dimethoxy-1,2-dimethylnorcarane-7-carboxylic Acid Ethyl Ester (7c).—Unsaturated ketal (**6c**), 11.5 g, was treated with 16.7 g of ethyl diazoacetate at 125–135° by the procedure of the previous experiment. Distillation furnished 2.3 g of starting material and 10.2 g of ester **7c**, bp 76–96° (0.02–0.05 mm). The analytical sample was prepared by vapor chromatography.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.62; H, 9.25.

Preparation of Compound 8b.—Ketal ester **7b**, 6.33 g, was cleaved by exchange with acetone according to the procedure described for the preparation of keto ester (**8a**). The product was purified by vapor chromatography: yield 84%; $\lambda_{\max}^{\text{film}}$ 5.78, 5.82 μ.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.00; H, 8.16.

Preparation of Keto Ester 8c.—Cleavage of 1.8 g of ketal ester **7c** was carried out by the procedure described above. The product was isolated by vapor chromatography, but since some attendant decomposition occurred, the exact yield could not be determined. A pure sample absorbed in the infrared at 5.78 and 5.81 mμ.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.86; H, 8.41.

Preparation of Compound 9b.—A solution of 1.0 g of keto ester (**8b**) in 40 ml of absolute ethanol containing a catalytic amount of sodium acetate was heated under reflux (nitrogen atmosphere) for 5 hr. The reaction mixture was then diluted with water and extracted with ether. After standard washing and drying procedures, the solvent was removed, and the residue was subjected to vapor chromatography: yield 87%; $\lambda_{\max}^{\text{film}}$ 5.78, 5.92 μ.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 66.61; H, 7.92.

The dinitrophenylhydrazone prepared as a derivative melted at 116–117.5° (95% ethanol).

Anal. Calcd for $C_{17}H_{20}N_4O_6$: C, 54.25; H, 5.36; N, 14.89. Found: C, 54.07; H, 5.52; N, 15.09.

Preparation of Conjugated Keto Ester 9c.—A 1.37-g sample of crude keto ester **8c** was dissolved in 50 ml of dry ethanol and a trace of *p*-toluenesulfonic acid was added. The solution was heated under reflux in a nitrogen atmosphere for 3 hr at the end of which time the bulk of the solvent was evaporated under reduced pressure. Routine washing and drying furnished crude material which was purified by vapor chromatography: yield 63%; $\lambda_{\max}^{\text{film}}$ 5.78, 5.99 μ.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.41; H, 8.66.

The 2,4-dinitrophenylhydrazone prepared as a derivative melted at 119.5–120° (95% ethanol).

Anal. Calcd for $C_{18}H_{22}N_4O_6$: C, 55.38; H, 5.68; N, 14.35. Found: C, 55.21; H, 5.91; N, 14.42.

Preparation of Ketal 12.—A solution of 44.4 g of 1-methyl-7-methoxy-2-tetralone[12] in 500 ml of dry benzene and 100 ml of ethylene glycol containing a small amount of *p*-toluenesulfonic acid was heated to reflux temperature under a water separator for a period of 6 hr. The product, isolated in the customary way, crystallized after removal of the solvent. The analytical sample was prepared by sublimation at 65° (0.004 mm), followed by recrystallization from ether–petroleum ether, and had mp 73.5–74°.

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.89; H, 7.69.

A 1.0-g sample of this ketal in 120 ml of liquid ammonia, 60 ml of absolute ether, and 20 ml of dry ethanol was treated with small pieces of lithium added at a rate sufficient to maintain a blue color for 45 min. Evaporation of the ammonia, addition of water, and extraction with ether furnished a dihydro derivative as a crude oil which resisted all attempts at crystallization, $\lambda_{\max}^{\text{film}}$ 5.87, 5.96 μ. The material was hence treated directly with methanol and *p*-toluenesulfonic acid in ether as described for preparation of acetoxy ketal **2**. Distillation of the crude product afforded 1.08 g of ketal **12**, bp 98–111° (0.01 mm).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.03; H, 8.97.

Registry No.—**1**, 16831-46-2; free base of **1** (mp 110–110.5°), 10064-10-5; $C_{18}H_{28}O_2$ (mp 142–143°), 16831-66-6; **2**, 16831-47-3; **6a**, 16831-48-4; **6b**, 16831-49-5; **6c**, 16831-50-8; **7a**, 16831-51-9; **7b**, 16831-52-0; **7c**, 16831-53-1; **8a**, 16831-54-2; **8a** 2,4-dinitrophenylhydrazone, 16831-55-3; **8b**, 16831-56-4; **8c**, 16831-57-5; **9a**, 16831-58-6; **9b**, 16831-59-7; **9b** 2,4-dinitrophenylhydrazone, 16831-60-0; **9c**, 16831-61-1; **9c** 2,4-dinitrophenylhydrazone, 16831-62-2; **12**, 16831-63-3; diazoacetic ester, 623-74-5; $C_{14}H_{18}O_3$ (mp 73.5–74°), 16831-64-4.

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(11) A. Serini and H. Koster, *Ber.*, **71**, 1766 (1938).

(12) M. E. Kuehne, *J. Amer. Chem. Soc.*, **83**, 1492 (1961).