pale yellow. On dilution and appropriate manipulation, the same lactone (XXII) is obtained from both; it was identical with a previously prepared specimen.[5]

Formation of 1-Phenyl-3-benzoylisobenzofuran (XXIII).—The yield of this substance from the glycol (XXI)[5] has been improved (90%) by modifying the procedure as follows: A mixture of 8 g. of the glycol, 0.3 g. of potassium hydroxide, and 50 ml. of alcohol is refluxed for three hours and worked up as usual.

Formation of *o*-Benzoylbenzoic Acid. A. From the Indone.—A mixture of 1.4 g. of 2,3-diphenylindone, 0.39 g. of sodium amide, and 10 ml. of xylene was refluxed for twelve hours. It was then diluted first with alcohol, then with water, and 1 ml. of 40% sodium hydroxide, and the xylene distilled with steam. The residual alkaline solution was treated with Norite and acidified. After some time, *o*-benzoylbenzoic acid separated in a yield of 50%, and was identified by comparison with an authentic specimen.

B. From 1-Phenyl-3-benzoylisobenzofuran (XXIII).—A mixture of 1.5 g. of the furan, 0.5 g. of potassium hydroxide, and 75 ml. of absolute alcohol was heated in a current of oxygen for five hours. The next day the solvent was removed *in vacuo*, the residue taken up in water, treated with Norite, acidified, and extracted with benzene. The acid was caused to crystallize by the addition of ligroin; the yield was 0.98 g. (93%); it was shown to be *o*-benzoylbenzoic acid by mixed melting point.

Oxidation of Isobenzofurans to 1,2-Aroylbenzenes. A. *o*-Dibenzoylbenzene.—A solution of 0.4 g. of 1,3-diphenylisobenzofuran in 15 ml. of benzene was refluxed for thirty-four hours in a slow current of oxygen. When the fluorescence had disappeared, the solvent was evaporated and the residue recrystallized from methanol. The yield of *o*-dibenzoylbenzene was 0.37 g. (86%); m. p. 145–147°. It was identified by comparison with a sample at hand.

B. *o*-Benzoylbenzil (V).—A solution of 1 g. of 1-phenyl-3-benzoylisobenzofuran in 20 ml. of alcohol was refluxed in a current of air for seven hours, the solvent removed, and the residue crystallized from acetic acid. The yellow crystals (0.55 g.) melted at 96°; a mixed melting point with a stock sample was not depressed.

Summary

1,3-Diphenylisobenzofuran is easily obtained by the action of alcoholic potassium hydroxide upon 2,3-diphenylindone, its epoxide, and *o*-benzoylbenzil. Mechanisms are proposed to account for the reactions.

1,3-Disubstituted isobenzofurans are slowly but completely oxidized by air or oxygen, in refluxing alcoholic solutions, to *o*-diaroylbenzenes.

1-Phenyl-3-benzoylisobenzofuran, in an alkaline alcoholic refluxing solution, is oxidized to *o*-benzoylbenzoic acid. This same acid also results when 2,3-diphenylindone is cleaved by sodium amide in boiling xylene.

ROCHESTER 4, NEW YORK RECEIVED FEBRUARY 2, 1948

[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

Morphine Studies. 2-(2′,3′-Dimethoxyphenyl)-2-(β-ethoxyethyl)-cyclohexanone

BY E. C. HORNING, M. G. HORNING AND E. J. PLATT[1]

One of the chief structural characteristics of morphine and many of its derivatives is the presence of a quaternary carbon, identified in the Gulland–Robinson formula as C-13 of the octahydrophenanthrene system. Methods for the synthesis of octahydrophenanthrenes of this kind are quite limited; few such compounds have been made, and attempted applications of known methods to the synthesis of morphine derivatives have not been successful.

It was recognized by Cook[2] that octahydrophenanthrenes could be obtained from 2-arylcyclohexanones by an apparently general method involving a Reformatsky reaction, followed by dehydration, hydrogenation and cyclization. This method was applied by the English workers to 2-phenylcyclohexanone, and we have used it with 2-(2′,3′-dimethoxyphenyl)-cyclohexanone.[3]

We have been interested in the application of Cook's procedure to the synthesis of certain morphine derivatives, and for this purpose it has first been necessary to investigate the preparation of a dimethoxyarylcyclohexanone containing an appropriately substituted carbon in the 2-position. The reactions employed are indicated on the diagram; the starting material was prepared by the sodamide alkylation of 2,3-dimethoxyphenylacetonitrile with δ-chlorovaleronitrile. Continued study of this reaction has led to the inclusion of certain apparently minor modifications which result in consistent yields of 80–83%. The product, 2-(2′,3′-dimethoxyphenyl)-pimelonitrile, is a dinitrile which can undergo cyclization to a six-membered β-iminonitrile, but which can also be alkylated directly by the sodamide method. This situation apparently arises through the structural factors which affect the cyclization. In the case of pimelonitriles, cyclization does not occur so readily as in the case of adiponitriles, and structural modifications may impose added difficulty in the way of the reaction. In the cyclization of α-(2,3-dimethoxyphenyl)-pimelonitrile (I) with sodium,[3] the cyclizing agent will produce a carbanion by removal of the most acidic hydrogen, which in this case is that associated with the phenylacetonitrile system. If a carbanion of this structure is formed, however, cyclization may follow directly only by addition of a completely substituted carbanion carbon to the nitrile group at the other end of the chain. The effective steric hindrance presented toward this addition is a barrier which in similar cases usually is sufficient to prevent cyclization. It is not known whether

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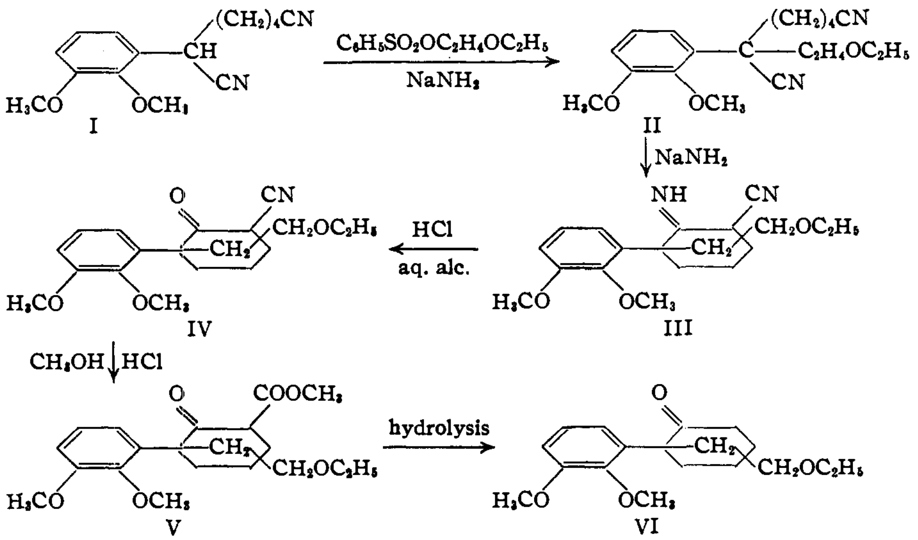
(1) Rohm and Haas Research Assistant.

(2) Cook, Hewett and Lawrence, *J. Chem. Soc.*, 71 (1936).

(3) Horning, Horning and Platt, THIS JOURNAL, 69, 2929 (1947).

the cyclization which occurs here takes place in spite of this steric effect, or whether a partial replacement of one of the α-hydrogens at the other end of the chain leads to cyclization in the other direction; this would also be possible, but it would represent a condition not easily arrived at in the presence of the more acidic hydrogen of the phenylacetonitrile system. These effects, which retard cyclization, are fortunately the same effects which are needed to allow alkylation of I in the desired position. With β-ethoxyethyl benzenesulfonate as the alkylating agent, an 80% yield of 2-(2′,3′-dimethoxyphenyl)-2-(β-ethoxyethyl)-pimelonitrile (II) may be obtained.

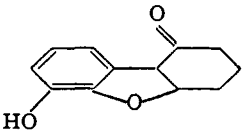


The cyclization of this pimelonitrile (II) can occur in only one fashion, and the structure of the resulting β-iminonitrile is that of III. Sodamide (in boiling benzene) was used as the cyclizing agent; a nitrogen atmosphere must be employed. The iminonitrile was isolated in crystalline form, and was converted into the β-ketonitrile IV in quantitative yield by acid hydrolysis in aqueous ethanol. Treatment of IV with hydrogen chloride in dry methanol gave the β-ketoester V.

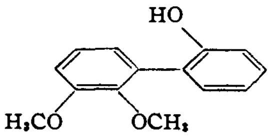
Under appropriate conditions, it might be expected that either III, IV or V would undergo hydrolysis-decarboxylation to yield the desired product, 2-(2′,3′-dimethoxyphenyl)-2-(β-ethoxyethyl)-cyclohexanone (VI). Three methods were investigated; the best proved to lie in the hydrolysis of the β-ketoester (V) with a dilute alcoholic solution of potassium hydroxide, followed by brief heating of the acidified solution to effect decarboxylation. The ketone (VI) was obtained from (V) in 83% yield as a colorless viscous oil.

The removal of the carbomethoxy group of (V) by ester interchange-decarboxylation with ethyl hydrogen adipate, following the general method of Fourneau[4] was also investigated. It was not possible to obtain material of analytical purity by this method, although the reaction apparently proceeded without difficulty. The yield was slightly lower than that obtained by direct hydrolysis-decarboxylation.

The use of a boiling hydrochloric acid–acetic acid mixture for hydrolysis led to an unexpected result. When this hydrolysis method was applied to the iminonitrile (III), with a reflux period of three hours, a crystalline phenolic product was isolated. While demethylation under such circumstances is not unusual, analytical data for the phenol indicated that the β-ethoxyethyl chain was no longer present. The structure of this compound is under investigation; the analytical results correspond to structure VII.



(VII)



(VIII)

The possibility that the product was 2,3-dimethoxy-2′-hydroxybiphenyl (VIII) was excluded both by analysis and by synthesis of (VIII) by dehydrogenation of 2-(2′,3′-dimethoxyphenyl)-cyclohexanone.

Experimental

All melting points are corrected.

α-(2,3-Dimethoxyphenyl)-pimelonitrile (I).—By the introduction of several apparently minor modifications into the procedure described previously,[3] the yield has been raised to 80–83%. After addition of the solvent (toluene), the ammonia was allowed to evaporate, with little or no warming, over several hours. The addition of δ-chlorovaleronitrile was started while the mixture was at room temperature, and was carried out as rapidly as possible. Good stirring and spraying of water on the flask during the addition were necessary to allow continued control of the vigorous exothermic reaction. Under these circumstances, 88.5 g. (0.50 mole) of 2,3-dimethoxyphenylacetonitrile yielded 106.5 g. (83%) of the dinitrile, b. p. 191–199° (0.5–0.7 mm.).

β-Ethoxyethyl Benzenesulfonate.—A mixture of 180 g. of ethylene glycol monoethyl ether, 360 g. of benzenesulfonyl chloride, 200 ml. of water, and 200 ml. of chloroform was stirred in an ice-bath while a solution of 120 g. of sodium hydroxide in 700 ml. of water was added dropwise over one hour. The mixture was then stirred for one hour longer at room temperature. The chloroform layer was separated and washed with 200 ml. of water. After drying over magnesium sulfate the solvent was removed and the residue distilled under reduced pressure. There was obtained 232 g. (50%) of the ester, as a nearly colorless oil, b. p. 136–144° (0.7 mm.).

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[4] Fourneau, *Bull. soc. chim.*, [4] **43**, 859 (1928); Stoll, *Helv. Chim. Acta*, **30**, 1401 (1947).

α-(2,3-Dimethoxyphenyl)-α-(β-ethoxyethyl)-pimelonitrile (II).—Sodamide was prepared from 8.85 g. (0.38 mole) of sodium in approximately 350 ml. of ammonia. With the aid of 40 ml. of dry ether, 89.0 g. (0.35 mole) of α-(2,3-dimethoxyphenyl)-pimelonitrile was added with stirring. After ten minutes, 200 ml. of dry benzene was added, and the mixture was allowed to stand until the ammonia had evaporated. There was then added with good stirring, at a rate compatible with the ensuing vigorous reaction, 97.6 g. (0.42 mole) of β-ethoxyethyl benzenesulfonate. The mixture was heated and stirred for two and one-half hours; methanol (30 ml.) and water (150 ml.) were added to the cooled mixture, and the benzene layer was separated. The aqueous layer was extracted with 100 ml. of benzene and two 50-ml. portions of ethyl acetate. The combined extracts were washed with 100-ml. portions of 5% sodium hydroxide solution, water, 5% hydrochloric acid, water, and saturated sodium bicarbonate solution, and dried over magnesium sulfate. The solvents were removed by distillation and the residue distilled under reduced pressure. The product was collected as a light yellow viscous oil at 210–220° (0.5–0.7 mm.); yield 91.2 g. (80%).

Anal. Calcd. for $C_{19}H_{26}O_3N_2$: C, 69.00; H, 7.87. Found: C, 69.00; H, 7.77.

2-(2′,3′-Dimethoxyphenyl)-2-(β-ethoxyethyl)-6-cyanocyclohexanone Imine (III).—Sodamide was prepared from 4.6 g. (0.20 mole) of sodium. There was added to the sodamide-ammonia mixture 59.0 g. (0.18 mole) of α-(2,3-dimethoxyphenyl)-α-(β-ethoxyethyl)-pimelonitrile in 50 ml. of dry ether, and this was stirred for fifteen minutes. After providing a nitrogen atmosphere, 175 ml. of dry benzene was added and the ammonia was evaporated with slight warming. The mixture was heated under reflux for two and one-half hours, cooled, and treated with methanol (15 ml.) and water (100 ml.). The benzene layer was separated, and the aqueous layer washed with 50 ml. of benzene and four 50-ml. portions of ethyl acetate. The combined extracts were washed with 100-ml. portions of 5% sodium hydroxide solution, water, 2% aqueous acetic acid, and saturated sodium bicarbonate solution, and dried over magnesium sulfate. The solvents were removed by distillation; the product was collected at 191–200° (0.2–0.3 mm.) as a very viscous light-yellow oil; yield, 47.3 g. (80%).

The distillate solidified immediately, but was apparently composed of both oil and solid. Trituration with ether–pentane (2:1) gave 32.5 g. of colorless crystalline material; evaporation of the solvents returned an oil which crystallized in part on standing. The nature of the oily product obtained here has not been determined; it may have been unchanged starting material.

Recrystallization from cyclohexane–ethyl acetate provided an analytical sample, m. p. 116–117°.

Anal. Calcd. for $C_{19}H_{26}O_3N_2$: C, 69.09; H, 7.88; N, 8.48. Found: C, 69.24; H, 7.64; N, 8.54.

2-(2′,3′-Dimethoxyphenyl)-2-(β-ethoxyethyl)-6-cyanocyclohexanone.—A mixture of 3.0 g. of the iminonitrile, 45 ml. of ethanol (95%), 9 ml. of concentrated hydrochloric acid, and 9 ml. of water was heated under reflux for one hour. The solution was diluted with 300 ml. of water, and the product was extracted with five 100-ml. portions of ether. The ethereal extract was washed well with water and with two 30-ml. portions of saturated sodium bicarbonate solution, and dried over magnesium sulfate. Evaporation of the ether gave a crystalline residue of crude, slightly discolored ketonitrile; yield, 3.0 g.; m. p. 97–99°.

A small sample was recrystallized from ether–pentane to give a colorless crystalline product, m. p. 98–99°.

Anal. Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60. Found: C, 69.11; H, 7.74.

2-(2′,3′-Dimethoxyphenyl)-2-(β-ethoxyethyl)-6-carbomethoxycyclohexanone (V).—A solution of 2.00 g. of crude ketonitrile in 25 ml. of methanol was saturated with hydrogen chloride, without cooling. After standing at room temperature for twelve hours, the mixture was poured into 300 ml. of water, and the product extracted with four 50-ml. portions of ether. The ether solution was washed with water and with saturated sodium bicarbonate solution, dried over magnesium sulfate, and evaporated to yield 1.68 g. of crude ketoester. This material was used directly for decarboxylation.

Additional purification by evaporative distillation at 110–130° (0.1 mm.) gave the ketoester as a colorless, viscous oil.

Anal. Calcd. for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 66.49; H, 7.67.

2-(2′,3′-Dimethoxyphenyl)-2-(β-ethoxyethyl)-cyclohexanone (VI).—A solution was prepared from 1.50 g. of potassium hydroxide, 3 ml. of water, and 27 ml. of absolute ethanol. To this was added 2.00 g. of β-ketoester (V), and the mixture was heated under reflux for three hours. It was acidified by the addition of 5 ml. of concentrated hydrochloric acid in 5 ml. of water, and refluxing was continued for fifteen minutes. The solution was diluted with 200 ml. of water and the product extracted with four 60-ml. portions of ether. The combined extracts were washed with two 30-ml. portions of 5% sodium hydroxide solution, and with 30-ml. portions of water and 2% aqueous acetic acid. After drying, the ether was removed and the residue evaporatively distilled at 110–120° (0.07 mm.) to yield 1.40 g. (83%) of the ketone as a colorless, viscous oil.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.69; H, 8.25.

Ester Interchange Method.—A solution of 1.68 g. of crude ketoester (V) in 9.0 ml. of ethyl hydrogen adipate was heated under gentle reflux in an apparatus arranged for sweeping with dry nitrogen. The rate of evolution of carbon dioxide was followed by means of an attached anhydrone–ascarite absorption tube. About forty minutes were required for the collection of 210 mg. (theoretical, 202 mg.) of carbon dioxide.

Hydrolysis of the mixture was carried out by adding 90 ml. of ethanol and a solution of 20 g. of potassium hydroxide in 50 ml. of water. The solution was heated under reflux for two hours, and most of the ethanol was removed by distilling until 90 ml. of distillate was obtained. The residue was diluted with 250 ml. of water and extracted with five 60-ml. portions of ether. The combined ether extracts were washed well with water and with 50 ml. of 2% aqueous acetic acid, and dried over magnesium sulfate. After evaporation of the ether, the remaining oil was evaporatively distilled at 105–110° (0.05 mm.) to provide 0.99 g. of the cyclohexanone as a colorless viscous oil. Material obtained in this way was not of analytical purity (about 0.5% or more from the calcd. values) although it was evidently the same compound as that obtained by hydrolysis-decarboxylation.

Hydrolysis with Hydrochloric Acid-Acetic Acid.—A mixture of 1.00 g. of the iminonitrile (III), 10 ml. of acetic acid, 10 ml. of concentrated hydrochloric acid, and 3 ml. of water was heated under reflux for three hours. After dilution with 100 ml. of water, 30 ml. of saturated sodium bicarbonate solution was added and the mixture was extracted with three 30-ml. portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution, and with four 30-ml. portions of Claisen alkali. The combined Claisen solution was diluted with water and treated with 20 ml. of concentrated hydrochloric acid, followed by saturation with carbon dioxide. After chilling, the crystalline phenol was removed by filtration and air dried. The product, 290 mg., was recrystallized twice from ether–ethyl acetate to give a colorless product, m. p. 134–135°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.56; H, 5.92. Found: C, 70.78; H, 5.71.

In separate experiments, it was established that a noncrystalline fraction, insoluble in sodium bicarbonate solution, which was isolated as a reaction product after a reflux period of twenty minutes, had a composition by analysis indicating that one nitrogen atom had been lost, and that the β-ethoxyethyl chain was largely intact. A reflux period of six hours resulted in a lowered yield of phenolic product.

2,3-Dimethoxy-2-hydroxybiphenyl.—A mixture of 500 mg. of 2-(2',3'-dimethoxyphenyl)-cyclohexanone, 5 ml. of triethylbenzene, and 1.0 g. of 5% palladium–charcoal catalyst[5] was heated under reflux for one hour. The warm solution was filtered and the catalyst washed with warm benzene. The organic solution was extracted with one 25-ml. and one 15-ml. portion of Claisen alkali. The Claisen solution was washed with benzene, and the benzene added to the organic solvents. The combined organic solution was extracted with three 15-ml. portions of Claisen alkali, and the combined Claisen solution was washed with 40 ml. of pentane. The alkaline solution was diluted with 100 ml. of water. A 40-ml. portion of concentrated hydrochloric acid was added and neutralization was completed with carbon dioxide (Dry Ice). After chilling, the crystalline product was removed by filtration and air dried. The yield of phenol, m. p. 102–104°, was 225 mg. Recrystallization from cyclohexane gave a colorless sample, m. p. 103–104.5°.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.22; H, 6.07.

Acknowledgment.—The authors are indebted to Miss Sarah H. Miles for carrying out the analyses reported here.

Summary

The synthesis of 2-(2',3'-dimethoxyphenyl)-2-(β-ethoxyethyl)-cyclohexanone is described.

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[5] "Organic Syntheses," 26, 77 (1946).

[CONTRIBUTION FROM THE KERCKHOFF LABORATORIES OF BIOLOGY OF THE CALIFORNIA INSTITUTE OF TECHNOLOGY AND THE EMERGENCY RUBBER PROJECT, BUREAU OF PLANT INDUSTRY, U. S. DEPARTMENT OF AGRICULTURE]

Chemical Investigation in Guayule. II. The Structure of Partheniol, A Sesquiterpene Alcohol from Guayule

BY A. J. HAAGEN-SMIT AND C. T. O. FONG[1]

In studies conducted in this Laboratory on the constituents of guayule, *Parthenium argentatum, Gray*, it was found that cold alcohol extracted from the plant a cinnamate of an optically active sesquiterpene alcohol previously isolated by Alexander.[2] The yield of the alcohol from the plant was approximately 0.03%. Later, the same ester was obtained by chromatographic adsorption of guayule extracts on silicic acid. Further studies showed that guayule resin obtained from Mexico as a by-product of guayule rubber refining would serve as a convenient source of this alcohol, yielding as much as 0.3% of the desired substance.

The physical constants of this alcohol and its cinnamate are listed below and are compared with those given by Alexander[2] and by Walter.[3]

Parthenyl cinnamate: empirical formula, $C_{24}H_{30}O_2$,[4,2] $C_{24}H_{32}O_2$[3]; m. p. 125–126°[4,2,3]; molecular weight by saponification of ester, 355[4], 354.[3]

Partheniol: empirical formula, $C_{15}H_{24}O$,[4,2] $C_{15}H_{26}O$[3]; m. p. 127–128°,[4,2] 131°[3]; mol. wt. 215,[4] 222[2]; $[\alpha]^{26}\text{D}$ 116.5° ($CHCl_3$, *c* 1.29%),[4] $[\alpha]^{24}\text{D}$ + 88.7° ($CHCl_3$, *c* 1.566%)[3]; parthenyl *p*-phenylazobenzoate, m. p. 162.5–164°[4]; parthenyl 3,5-dinitrobenzoate, m. p. 143–144°.[4]

Our data for the alcohol are in agreement with those of Alexander and the empirical formula $C_{15}H_{24}O$ for the alcohol was substantiated throughout this work. Also the melting point of partheniol repeatedly recrystallized from different solvents agrees with that of Alexander. The chromatographic separation of the phenylazobenzoate showed only traces of compounds other than the partheniol derivative. The presence of isomeric forms of partheniol might explain the melting point of 131° found by Walter[3] since we have observed that heating partheniol with alcoholic potassium hydroxide resulted in a raise of melting point to 132–132.5°. Similar observations were made in preparing a maleic anhydride addition compound.

Catalytic hydrogenation of the alcohol indicated the presence of two double bonds. The absorption spectrum of partheniol, together with the failure of partheniol to form an adduct with maleic anhydride or to be reduced by sodium in alcohol, indicates that the two double bonds are not conjugated.

The relative ease of dehydration with potassium bisulfate confirms the presence of an alcoholic hydroxyl group and indicates that the hydroxyl group is probably tertiary. The failure of esterification with phthalic anhydride under conditions described by Ruzicka, *et al.*,[5] as well as the failure to form a xanthate indicated that partheniol is a tertiary alcohol.[6]

Dehydration of partheniol with potassium bisulfate resulted in the formation of a mixture of isomeric hydrocarbons, $C_{15}H_{22}$, which we shall call dehydroparthenene.[7] These hydrocarbons contain three double bonds, which physical and chemical methods show are not conjugated.

Dehydrogenation of dehydroparthenene with sulfur gave blue S-guaiazulene which was identified by its 1,3,5-trinitrobenzene addition product, its picrate and its trinitrotoluene addition prod-

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[1] Present address, Lederle Research Laboratories, Pearl River, N. Y.

[2] Alexander, *Ber.*, 44, 2320 (1911).

[3] Walter, THIS JOURNAL, 66, 419 (1944).

[4] Data of Haagen-Smit and Fong.

[5] Ruzicka, Pontalti and Balas, *Helv. Chim. Acta*, 6, 858 (1923).

[6] Feigl, "Spot Tests," Nordemann Publishing Co., New York, N. Y., 1937, p. 251.

[7] Conforming to sesquiterpene nomenclature: parthenene is $C_{15}H_{24}$.