[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Derived Steroids. I. Cholesteryl Ketones[1]

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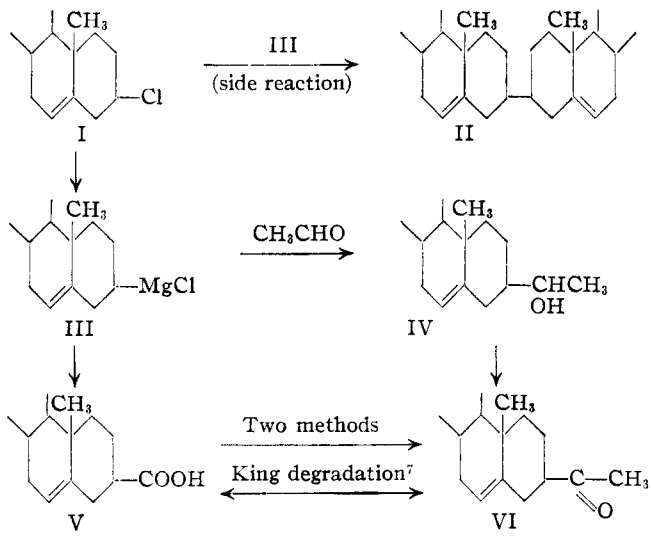
As a model for the preparation of 3-acylsteroids, we have made a study of various methods for preparing methyl cholesteryl ketone, VI. All of the successful methods make use of cholesteryl Grignard reagents. This reagent may be converted into an impure methyl carbinol, IV, which is then oxidized to the ketone or it may be converted into the acid and to the acid chloride which with methyl Grignard or dimethylcadmium yields the ketone.



The preparation of cholesterylmagnesium chloride has been described briefly by Marker.[3] The reaction is carried out in the presence of ethylmagnesium bromide and is very slow in refluxing ethyl ether. Even though the cholesteryl chloride is added slowly over a period of six hours, there is always formed the coupling product, 3-cholesteryl-5-cholestene (biocholesteryl), II. This compound is almost insoluble in ether, and, although it must have been encountered previously, it has not been characterized.[4] We have isolated the compound in yields as high as 12% and have characterized it by physical constants and molecular weight determination. Cholesteryl bromide forms the Grignard reagent more rapidly than does the chloride but offers no advantage as a means of diminishing the production of bicholesteryl.

The reactions of cholesteryl Grignard are quite slow and although it is possible to carbonate it in almost quantitative yield, those reagents which are condensable undergo reaction with the production of large quantities of cholestene.[5] Table I summarizes the Grignard reactions. Cholestene was formed in all of these runs in yields of approximately 50%. In spite of the fact that acetaldehyde probably condenses more rapidly than do the other reagents used, it also reacts more rapidly in the desired way. The products of the acetaldehyde reactions do not crystallize, probably due to the presence of steroisomeric carbinols. The product of the Oppenauer[6] oxidation of the crude carbinol also is difficult to crystallize, but after purification by way of the semicarbazone it crystallizes very well.

Another approach, through the reaction of methylmagnesium bromide or dimethylcadmium on cholesteryl-3-carboxylic acid chloride, has proven to be the best route to the ketone. Although these methods, involving two Grignard reactions, would seem to be longer than the first ones discussed they are actually economical of time since the ketone is produced without an oxidation step and its purity is sufficiently high to allow crystallization without purification by the semicarbazone. An approximately 40% yield of crystalline ketone may be obtained by use of the magnesium or 82% by use of the cadmium reagents.

Diethylcadmium furnishes the ethyl ketone to about the same extent. In early experiments with the cadmium alkyls the reaction was carried out over long periods of time at comparatively low temperature and there resulted high-melting by-products. One of these has been identified as dimethylcholesterylcarbinol by comparison with a sample synthesized from 3-carbomethoxy-5-cholestene and methylmagnesium iodide. Since the color test for methylmagnesium bromide was negative it appears that a large excess of organocadmium reagent is capable of production of tertiary alcohols.

The various methods have thus far produced only one crystalline form of the methyl ketone, m. p. 104–105°; $[\alpha]^{27}D$ − 11°. The assignment of structure is based not only on its method of synthesis but also upon the fact that it has been de-

(1) Presented under the the title "Methyl Cholesteryl Ketone" at the Atlantic City Meeting of the American Chemical Society, April, 1947.

(2) Junior Fellow of the National Institute of Health.

(3) Marker, Oakwood and Crooks, THIS JOURNAL, **58**, 481 (1936); Marker, Kamm, Oakwood and Laucius, *ibid.*, **58**, 1948 (1936).

(4) The white solid (ref. 3) which was removed by filtration and rejected probably was bicholesteryl. The compound obtained by Galinovsky and Bretschneider (*Monatsh.*, **72**, 190 (1938) by the catalytic reduction of cholestenone pinacol may have been it though no physical constants were given.

(5) Carbonization and oxidation (ref. 3) are the only previously studied reactions of this Grignard reagent.

(6) Oppenauer, *Rec. trav. chem.*, **56**, 137 (1937).

TABLE I

Organometallic	Reagent	%Products[a] Ketone	3-Cholesteryl-5-cholestene, II
RMgCl[b]	CH_3CHO	16.3	7
RMgBr	CH_3CHO	12.8	12
RMgBr	CH_3COCl	0.34	
RMgCl	CH_3CN	0	
RMgCl	$CH_3COCOCH_3$	0	3
CH_3MgBr	RCOCl	40	
$(CH_3)_2Cd$	RCOCl	82	
$(C_2H_5)_2Cd$	RCOCl	75	

[a] Cholestene accounts for approximately 50% of each yield except the last three. [b] R is 3-cholesteryl.

graded to cholesteryl-3-carboxylic acid. The degradation was accomplished according to the excellent method discovered by Professor Carroll King of these Laboratories.[7] When heated with iodine and pyridine the ketone was converted into the crude pyridinium iodide in 75% yield and this upon cleavage by alkali gave Marker's acid[8] in 86% yield.

The success experienced recently in the replacement of the *p*-toluenesulfonoxy group through the use of sodiomalonic ester[8] led to attempts to effect similar replacements with potassium cyanide. Such a cyanide would probably yield the methyl ketone by reaction with methyl Grignard. The replacement has not been accomplished, but this reaction is of interest because it produces 3,5-cholestadiene in good yield. Suspensions of equimolar mixtures of cholesteryl tosylate and potassium cyanide in xylene do not react at 80° or 100° during twenty-four hours, but refluxing (139°) for eighteen hours produced the easily isolated diene in 70% yield. The diene is also formed (81%) by fusion of cuprous cyanide and cholesteryl bromide at 130° for four hours, but the product is more difficult to purify.

Experimental[9]

Cholesteryl Chloride, I.—This was prepared according to Diels[10] with the exceptions that enough thionyl chloride was used to take all the cholesterol into solution and the reaction product was poured into water. A quantitative yield of crude product was obtained and this was reduced to 63% by crystallization from four times its weight of acetone, m. p. 96–97°. A quantitative yield of crude product, m. p. 84–92°, was also obtained from the reaction of equal weights of cholesterol and phosphorus oxychloride for eighteen hours at room temperature but the product is difficult to purify.

It is necessary that the cholesteryl chloride used in the preparation of cholesterylmagnesium chloride be very pure; the melting point should be as high as 95–96°. The purification has been accomplished by chromatographic adsorption. A solution of 10 g. of crude cholesteryl chloride, m. p. 85–93°, in 100 ml. of petroleum ether (80–100°) was passed through a column containing 18 × 100 mm. of 80–200 mesh activated alumina and 18 × 50 mm. of Norit. The petroleum ether was evaporated off under vacuum and the cholesteryl chloride crystallized from acetone, m. p. 95–96°. The purified compound was then crystallized from absolute ether at −50° and dried *in vacuo* at 78° for four hours.

Cholesteryl-3-carboxylic Acid, V.—This was prepared in 85% yield, m. p. 210–220°, by a modification of Marker's method[8] in which the Grignard solution made from 12 g. of chloride was poured into a flask containing crushed Dry Ice in absolute ether and allowed to stand overnight before working up. One crystallization from benzene gave 90% of the material, m. p. 222–223°, and 10%, m. p. 225–227°.

Cholesterylmagnesium Chloride and Bromide.—To 0.73 g. (0.03 mole) of powdered magnesium there was added 0.7 g. (0.0064 mole) of ethyl bromide in 10 ml. of absolute ether. When this reaction was complete a solution of 9.2 g. (0.023 mole) of pure cholesteryl chloride in 50 ml. of dry ether was added over a period of three hours, gentle reflux being maintained throughout the addition time and for an additional thirty to thirty-five hours. The volume of the solution was maintained at 50–60 ml. by occasional addition of dry ether. Stirring was not used.

The preparation of the bromo Grignard was similarly carried out with the exception of a shorter refluxing period, fifteen to twenty hours.

3-Cholesteryl-5-cholestene, II.—This was isolated from the early experiments by filtration of the ether extracts of acidified reaction mixtures. The suspended material collects at the interface between the aqueous and ether phases, but is re-suspended upon shaking. In later experiments it was removed from the Grignard preparation by filtration prior to addition of the reactant. It was separated from any unreacted magnesium by extraction with hot benzene in which it is only slightly soluble. It crystallizes from benzene in small colorless plates which melt at 267–269° to a cloudy melt with decomposition, $[\alpha]^{24.5}D$ +30° (6.8 mg. made up to 5 ml. with benzene, α + 0.07°; *l*, 2 dm.).

Anal. Calcd. for $C_{54}H_{90}$: C, 87.73; H, 12.27; mol. wt., 739. Found: C, 87.90; H, 12.39; mol. wt. (Rast), 751.

Methyl Cholesteryl Ketone Semicarbazone.—To the Grignard solution prepared from 0.7 g. (0.006 mole) of ethyl bromide and 9.2 g. (0.023 mole) of cholesteryl chloride in 50 ml. of ether was added 50 ml. of an absolute ether solution of dry acetaldehyde (0.077 mole). The addition was made at 0° over a period of two hours and the mixture was allowed to stand, finally reaching room temperature over a period of four hours. The mixture was then hydrolyzed with 5% hydrochloric acid and extracted with ether. The crude bicholesteryl, 1.2 g., was separated by filtration and then the ether solution was evaporated to an oil which was dried *in vacuo* at 100°.

The oil was oxidized by refluxing for fourteen hours in a mixture of 75 ml. of dry acetone and 150 ml. of benzene containing 10 g. of aluminum *t*-butoxide. Upon working up the product there was obtained about 5 g. of a yellow oil which was heated *in vacuo* at 100° for three hours in order to remove the simple condensation products of acetone.

The resulting ketonic oil was refluxed for one hour with 0.9 g. of semicarbazide hydrochloride and 2 ml. of pyridine in 20 ml. of ethanol. The solvent and pyridine were removed by evaporation and the solid was washed with ether and collected on a filter. It was then boiled with 20 ml. of water and filtered hot to remove biurea. The dried **semicarbazone** weighed 1.74 g., (16.3%), m. p. 215–225°. Crystallized from benzene twice the m. p. is 229–231°, dec.

Anal. Calcd. for $C_{30}H_{51}ON_3$: C, 76.70; H, 10.94; N, 8.95. Found: C, 76.87; H, 10.98; N, 9.02.

Methyl Cholesteryl Ketone, VI.—To 194 mg. of the semicarbazone and 20 ml. of 95% ethanol there was added 1 ml. of concentrated sulfuric acid and the mixture heated under reflux. The suspension became homogeneous and when concentrated to 10 ml. after two hours of heating

(7) King, THIS JOURNAL, **66**, 894, 1612 (1944).

(8) Kaiser and Svarz, *ibid.*, **67**, 1309 (1945).

(9) Microanalyses by Margaret Ledyard and Patricia Craig.

(10) Diels and Blumberg, *Ber.*, **44**, 2847 (1911); Diels and Abderhalden, *ibid.*, **37**, 3102 (1904).

and cooled to 0° the ketone crystallized. This was taken up in ether and washed with potassium carbonate solution then water and the ketone was recovered. Crystallization from 5 ml. of 95% ethanol gave 51 mg. (29.8%) of colorless needles, m. p. 104–105°, $[\alpha]^{27}D$ −11° (67 mg. made up to 2.0 ml. with chloroform, α −0.37; *l*, 1 dm.).

Anal. Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.44; H, 11.76.

Methyl Cholesteryl Ketone (second method).—3-Cholesterylcarboxylic acid, 2.84 g. (0.0069 mole), m. p. 210–220°, was dried for one hour *in vacuo* at 100°. It was then mixed with 2.0 g. (0.0096 mole) of phosphorus pentachloride and the mixture heated *in vacuo* at 100° for an hour. The dark reaction mixture was allowed to stand at room temperature for eighteen hours at the end of which time it was taken up in dry ether and filtered to remove the insoluble residue. The ether solution was then cooled to −10° and to it was added a solution of methylmagnesium iodide prepared from 1.24 ml. (0.02 mole) of methyl iodide and 0.5 g. of magnesium in 10 ml. of ether. The mixture was allowed to stand at −10° for thirty-six hours during which time an oil had settled out. The mixture was then poured into 50 ml. of ice water containing 10 ml. of 10% sulfuric acid. The organic material was then taken up in ether which was dried, filtered, and evaporated to a gum, 0.74 g. The gum was then dissolved in acetone, filtered and crystallized to yield two fractions; 0.138 g., m. p. 107–112°, and 0.280 g., m. p. 98–103°. The latter fraction was recrystallized from acetone to give a product, m. p. 100–103°, which with methylcholesteryl ketone, previously prepared, m. p. 104–105°, gave a mixed m. p. 103–105°.

Methyl Cholesteryl Ketone (third method).—Thionyl chloride was a more suitable reagent than phosphorus pentachloride for the preparation of 3-cholesterylcarboxylic acid chloride. The acid, 1.2 g., was refluxed with 1 ml. of thionyl chloride in 10 ml. of benzene for four hours and allowed to stand overnight. The solvent and excess reagent were then removed *in vacuo* at 100° leaving the crude acid chloride, 96% yield, m. p. 118–120°.

The acid chloride, 0.50 g. (1.15×10^{-3} mole), in 3 ml. of ether was added to 2×10^{-3} mole of dimethylcadmium contained in 5 ml. of ether at 0°. The mixture was refluxed for forty-five minutes and then decomposed by ice water. The product was extracted with ether and washed with 10% hydrochloric acid, saturated sodium bisulfite, 10% potassium hydroxide and then water. Acidification of the alkaline wash afforded 0.10 g. of crude 3-cholesteryl carboxylic acid. The ether solution was dried over sodium sulfate and evaporated to yield 0.39 g. of ketone, m. p. 103–105°, 82% yield.

Variation of this procedure by refluxing the reactants in benzene for two hours[11] led to a product more difficult to purify in 40% yield.

Ethyl Cholesteryl Ketone.—In a manner similar to the third method described above diethylcadmium gave the ethyl ketone, m. p. 133–134°; $[\alpha]^{27}D$ −14 (25.9 mg. made up to 3.61 ml. with chloroform, α −0.10, *l*, 1 dm.).

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.82. Found: C, 84.31; H, 11.77.

The **semicarbazone** of ethyl cholesteryl ketone was prepared in order to determine the amount of ketone in an impure fraction of material prepared as above. By use of the pyridine method previously described, 1.45 g. of ketonic material gave 0.58 g. of semicarbazone, m. p. 224–225°, from benzene–ethanol.

Anal. Calcd. for $C_{31}H_{53}N_3O$: C, 76.93; H, 11.03; N, 8.73. Found: C, 77.24; H, 11.08; N, 8.41.

Degradation of Methyl Cholesteryl Ketone.[7]—Methyl cholesteryl ketone, 65 mg. (1.58×10^{-4} mole) was heated with 1 ml. (1.24×10^{-2} mole) of pyridine and 25 mg. (1×10^{-4} mole) of iodine at 100° for twenty-two hours. The pyridine was then removed *in vacuo* at 100° and the product was extracted with three 1-ml. portions of absolute ether which yielded 26 mg. of starting material. The ether insoluble material was then extracted with three 2-ml. portions of warm methanol. By fractional crystallization of the methanol solution there was obtained 43 mg. of the crude pyridinium iodide of methyl cholesteryl ketone, m. p. 190–192° with prior softening (75% yield based on recovered ketone).

The pyridinium iodide, 20 mg. (3.2×10^{-5} mole) in 5 ml. of ethanol containing 0.2 ml. of 10% potassium hydroxide was then refluxed three hours. The reaction mixture was then poured into water and extracted with ether. The aqueous layer upon acidification with sulfuric acid gave a yellow coagulum, which, after cooling to 0° and filtering, yielded 11.5 mg. (86%) of crude acid. Crystallized from benzene the acid melted at 223–225° and showed no depression with mixtures of 3-cholesteryl carboxylic acid.

3-Carbomethoxy-5-cholestene.—Following the method of Marker,[3] 550 mg. (1.3×10^{-3} mole) of 3-cholesterylcarboxylic acid, V, was converted into 559 mg. of the methyl ester, m. p. 93–103°. One crystallization from methanol or chromatographing a cyclohexane solution on alumina followed by elution with benzene yielded crystals, m. p. 100–101°, $[\alpha]^{27}D$ −16 (53 mg. made up to 2 ml. with chloroform, α −0.42, *l*, 1 dm.). The purified product amounted to 64% of the total ester. The benzene eluate, 33%, melted at 86–90° and this indicates that the 101.5°-melting form of Marker is probably entirely of one configuration.

Dimethylcholesterylcarbinol.—This compound was isolated in about 4% yield from reactions of five-fold excess cadmiumdimethyl (prepared from methyl bromide) with the acid chloride in benzene at 25° for eighteen hours. It was isolated in two ways. Upon adding petroleum ether solutions of the reaction product to ethanol there was obtained as many as three fractions melting variously between 143 and 160°. The filtrate from the third fraction upon evaporation yielded the ketone. When the whole reaction product was absorbed from petroleum ether solution on alumina and eluted with methanol, the ketone was removed first and the carbinol melted as low as 128°. Air-dried crystals from methanol melt about 128° and prolonged drying *in vacuo* at 100° (72 hours) is required to obtain an analytically pure sample, m. p. 159–160°; $[\alpha]^{28}D$ −26 (47.0 mg. made up to 2.0 ml. with chloroform, α −0.62; *l*, 1 dm.).

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 83.96; H, 12.02.

The melting point was not depressed by mixtures with a sample synthesized as follows:

Methylmagnesium iodide was prepared in the usual way from 0.5 g. (2.06×10^{-2} mole) of magnesium powder and 2.28 g. (1.6×10^{-2} mole) of methyl iodide in 8 ml. of ether. To the Grignard solution, 200 mg. of 3-carbomethoxy-5-cholestene in 2 ml. of ether was added. The reaction mixture was allowed to reflux twenty-four hours with stirring under 800 mm. nitrogen pressure. The ether was evaporated and the residue cooled to 0°. This was hydrolyzed by slow addition of 13 ml. of 10% ammonium chloride solution and the mixture was allowed to stand eighteen hours. The solution was transferred to a separatory funnel, and following acidification with sulfuric acid it was extracted twice with ether. The ether extracts were washed once with water, once with saturated sodium bisulfite, and then four times with water; the ether was then dried over anhydrous sodium sulfate for eighteen hours, filtered and evaporated to dryness *in vacuo* yielding crystals; 200 mg., m. p. 129–130°.

Upon drying *in vacuo* at 100° for seventy-two hours a different form of the carbinol results, m. p. 159–160°.

3,5-Cholestadiene.—Cholesteryl-*p*-toluenesulfonate,[12] 5 g. (0.0093 mole), and 1.2 g. of potassium cyanide (0.0185 mole) were dried and suspended in 20 ml. of xylene. The mixture was refluxed for eighteen hours at which time a heavy white precipitate is obtained. The suspension was cooled and extracted by filtration with 200

(11) Cason, THIS JOURNAL, **68**, 2078 (1946).

(12) Wallis, Fernholz and Gephart, *ibid.*, **59**, 137 (1937).

ml. of dry ether. The clear filtrate was evaporated in a dry air stream at 100° and the product crystallized from 100 ml. of acetone to produce 2.4 g. (70%) of 3,5-cholestadiene, m. p. 73–74°. Crystallization from acetone then absolute ethanol raised the m. p. to 76–77°, $[\alpha]^{22.5}D$ −96.5 (109.8 mg. made up to 5 ml. with chloroform, α, −4.24°; l, 2 dm.); γ_{max} (obs.) 236. These values are in agreement with those of the literature, m. p. 78–79°,[13] $[\alpha]^{20}D$ −97.5,[13] γ_{max} (obs.) mμ 235.[14] The diene gives a 20° depression in m. p. when mixed with *i*-cholestadiene[15] and its ultraviolet spectrum is clearly different from that of the *i*-diene.[16]

Isolation of 5-Cholestene.—Separate experiments generally were made to determine the extent of cholestene formation. The product resulting from the reaction of 0.026 mole of diacetyl with a mixture of 0.024 mole of cholesterylmagnesium chloride was treated so as to remove bicholesteryl. Of the remaining 8.3 g. of oil, 2 g. was dissolved in 50 ml. of petroleum ether (30–60°) and passed through a 17 by 1 cm. column packed with Brockman alumina. The eluate, 45 ml., and the first 15 ml. fraction of petroleum ether washings gave upon evaporation 1.26 g. of product, m. p. 80–84°. Crystallized once from acetone the m. p. was 85–87°, $[\alpha]^{24.5}D$ −53.5°. The literature[17] values are 89–90° and −56.3°.

(13) Stavely and Bergmann, *J. Org. Chem.*, **1**, 567 (1937).

(14) Woodward, THIS JOURNAL, **64**, 74 (1942).

(15) Kindly furnished by Professor Byron Riegel.

(16) We are indebted to Professor I. M. Klotz and his associates for determining this spectrum, *cf.* Klotz, *ibid.*, **66**, 88 (1944).

(17) Mauthner, *Monatsh.*, **28**, 1113 (1907).

Acknowledgment.—We are grateful to Professor Byron Riegel for help and encouragement during the course of this work.

Summary

1. Methyl cholesteryl ketone has been prepared by the reaction of cholesteryl Grignard reagents with acetaldehyde followed by oxidation of the impure carbinol and by Grignard alkylation of cholesteryl-3-carboxylic acid chloride. Its semicarbazone is described.

2. The ketone has been degraded back to cholesteryl-3-carboxylic acid.

3. 3-Cholesteryl-5-cholestene has been identified as a by-product of the formation of cholesteryl Grignard reagents.

4. 5-Cholestene is formed in large quantity in the reaction of cholesteryl Grignard reagents with a variety of compounds.

5. 3,5-Cholestadiene is conveniently prepared by the reaction of cholesteryl *p*-toluenesulfonate with potassium cyanide.

6. Ethyl cholesteryl ketone, its semicarbazone, and dimethylcholesterylcarbinol have also been prepared.

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The Cleavage of Benzyl Ethers with Hydrogen

BY ROBERT H. BAKER, KATHRYN HEROLD CORNELL AND MARTIN J. CRON

Recently it has been shown that vinyl ethers and amines which are so substituted as to activate the alkyloxy or alkylamino group may be cleaved by hydrogen prior to saturation of the double bond which carries the activating effect.[1] It was hoped that the remarkable promoting effects of perchloric and sulfuric acids[2] might allow preferential cleavage of unsaturated benzyl ethers, but the results, Table I, were not promising.

Cyclic ethers bearing phenyl groups on the α carbon atom have been found to undergo hydrogenolysis. 2-Phenyltetrahydropyran[3] yields 5-phenylpentanol and since the starting materials are easily available, a convenient synthesis for 5-arylpentanols is indicated. Phenyldioxane and 2,3-diphenyldioxane[4] reacted, respectively, with one and two moles of hydrogen. The 2-(2-phenylethoxy)-ethanol produced from the former of these demonstrated that the ether linkage β to a phenyl group is quite stable under the conditions which will completely cleave a similar group in the α position.

(1) Baker and Weiss, THIS JOURNAL, **66**, 343 (1944); Baker and Schlesinger, *ibid.*, **68**, 2009 (1946).

(2) Karg and Marcus, *Ber.*, **75**, 1850 (1942); Kindler and Kwok, *Ann.*, **554**, 9 (1943).

(3) Paul, *Compt. rend.*, **198**, 1246 (1934).

(4) The aryldioxanes were furnished by Prof. R. K. Summerbell, *cf.* Summerbell and Bauer, THIS JOURNAL, **57**, 2364 (1935).

Two isomeric compounds, m. p. 122 and 174°, to which the structure of *cis* and *trans* 2,5-diphenyldioxane have been tentatively assigned failed to behave in the expected manner.[5] Over palladium–charcoal they showed no reduction in acetic acid; with added hydrochloric acid the reduction was very slow and with added perchloric or sulfuric acids they took up three moles of hydrogen with no diminution of the rate at two moles. This can hardly be due to cleavage of 2-phenylethanol followed by its reduction to ethylbenzene because this would require four moles of hydrogen and repeated values of three would be unexpected. Further evidence against this explanation is seen in the behavior of phenethyl benzyl ether and in the fact that 2-phenylethanol takes up only 4% of one mole of hydrogen in the time and under the conditions required for complete cleavage of the phenyldioxanes.

A liquid described as 2,6-diphenyldioxane was

(5) These compounds were prepared by Aldro Bryan, Ph.D. Thesis, Northwestern University, 1945, by reaction of 2,5-dichlorodioxane with a phenyl Grignard. They were believed to contain no acetal or ketal linkage on the basis of stability to acid hydrolytic conditions. Dibromination followed by hydrolysis and treatment with phenylhydrazine produced the osazone of phenylglyoxal in poor yield. The compound referred to as 2,5-diphenyl-1,4-dioxane, m. p. 147–152°, by Smedley, U. S. Patent 2,414,982; *C. A.*, **41**, 2755 (1947), is in fact the source of these isomers.