Summary

Quantitative measurements have been made of the binding of sulfanilamide, sulfapyridine, N^1-acetylsulfanilamide, 5-sulfanilamido-3-methylisoxazole, 5-sulfanilamido-5-chloropyridine and N^1-benzoylsulfanilamide, respectively, by crystallized bovine serum albumin. Binding energies have been calculated and have been correlated with the structures of the compounds.

EVANSTON, ILLINOIS RECEIVED NOVEMBER 1, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

The Synthesis of Some Cyclopropane and Spirane Hydrocarbons[1]

BY R. W. SHORTRIDGE, R. A. CRAIG, K. W. GREENLEE, J. M. DERFER AND C. E. BOORD

This paper describes an extension of the Gustavson method[2,3,4] for the synthesis of cyclopropane and its derivatives. Three 1,1-dialkylcyclopropanes have been prepared; two of these compounds are new, and improved physical properties were determined for the third. The method has been applied to the preparation of spiranes containing a cyclopropane ring and provides an easy, straightforward way of producing this type of hydrocarbon in quantity and in a good state of purity. Cleavage of the cyclopropane ring by hydrogen has been investigated.

1,1-Dimethylcyclopropane has been produced from *sym*-dibromoneopentane most recently by Whitmore[5] and his co-workers. Isobutyraldehyde was condensed with formaldehyde in the presence of potassium hydroxide to obtain 2,2-dimethyl-1,3-propanediol which was converted to the corresponding dibromide by the action of phosphorus tribromide; the cyclization was accomplished with zinc in molten acetamide (Hass–McBee[6] procedure). In the present work the intermediates were synthesized by the same series of reactions, but the dibromide was cyclized by zinc in aqueous ethanol. The hydrocarbon was obtained in 96% yield (based on distilled dibromide), and it froze over a 0.4° range; physical properties were determined on a center fraction from the distillation of this product at about 10-plate efficiency.[7]

1,1-Diethylcyclopropane and 1-ethyl-1-butylcyclopropane were prepared by an analogous series of reactions. The yields from the dibromides were 92 and 94%, respectively; as in the case of 1,1-dimethylcyclopropane, the initial product was of high purity.[8] These two compounds have not been described previously.

TABLE I

		B. p., °C. (760 mm.)	F. p., °C.	d^{20}_4	n^{20}_D
1,1-Dimethyl cyclopropane	This work	20.63	−108.96	0.6589	1.3668
	Whitmore[5]	19.9	−108.4 to −107.3	....	....
1,1-Diethylcyclopropane		88.67	−105.91	.7318	1.4042
1-Ethyl-1-butylcyclopropane		140.41	−102.68	.7559	1.4183

Few spiranes have been synthesized. In all reported preparations where closure of the second ring was not the final step, the over-all yields have been no more than a few per cent. Recently spiropentane has been identified as a product from the reaction of pentaerythrityl tetrabromide with zinc[9,10] the yield being in the neighborhood of 25% based on the tetrabromide; this is the highest yield reported for any spirane. We have applied the Gustavson reaction to the preparation of spiro(2.5)octane and 4-methylspiro(2.5)octane. This work provides a general method for the preparation of spiranes containing a cyclopropane ring and is limited only by the availability of cyclic aldehydes which contain the desired configuration and which will undergo the methylol reaction to yield *gem*-dicarbinols. The yields are good.

Spiro(2.5)octane was prepared in the following way: 3-Cyclohexene-1-carboxaldehyde was prepared by condensing acrolein with butadiene (Diels–Alder). The adduct, an unsaturated alde-

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[1] The material in this paper is taken from three sources: (a) From the dissertation submitted by R. W. Shortridge to the Graduate School of the Ohio State University in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in 1943; present address: Midwest Research Institute, Kansas City, Missouri. This portion of the material was presented before the Organic Division at the April, 1944, meeting of the American Chemical Society. (b) From a thesis submitted by R. A. Craig to the Graduate School of The Ohio State University in partial fulfillment of the requirements for the Degree of Master of Science; present address: The Ohio State University. This portion of the material was presented before the Organic Division at the April, 1946, meeting of the American Chemical Society. (c) From the experimental work of the American Petroleum Institute Research Project 45 which is administered by The Ohio State University Research Foundation.

[2] Gustavson, *J. prakt. Chem.*, **36**, 300 (1887).

[3] Gustavson and Popper, *J. prakt. Chem.*, **58**, 458 (1898).

[4] This reaction has been called the Freund reaction on occasion. However, reference to the original literature shows that although Freund (*Monatsh.*, **2**, 642 (1881)) was the first to make cyclopropane itself, he used an extension of the Wurtz reaction, and therefore had no claim to the method of ring closure which employs zinc in the presence of protonic solvent. This method was first reported by Gustavson[2] in 1887 by a paper entitled: "Concerning a New Method of Preparation of Trimethylene." Gustavson and Popper[4] extended this method to the preparation of substituted cyclopropanes.

[5] Whitmore, Popkin, Bernstein and Wilkins, THIS JOURNAL, **63**, 124 (1941).

[6] Hass, McBee, Hinds and Glusenkamp, *Ind. Eng. Chem.*, **28**, 1178 (1936).

[7] All plate ratings given in this paper represent estimates of column efficiency under actual operating conditions.

[8] Using this method, the American Petroleum Institute Research Project No. 45 has prepared four liters of 1,1-dimethylcyclopropane and five liters of 1,1-diethylcyclopropane, both in a state of high purity.

[9] Murray and Stevenson, THIS JOURNAL, **66**, 812 (1944).

[10] Slabey, *ibid.*, **68**, 1335 1(946).

hyde, reacted with formaldehyde to yield 4,4-bis-(hydroxymethyl)-1-cyclohexene which was hydrogenated catalytically to the corresponding saturated diol. Treatment of the diol with phosphorus tribromide gave 1,1-bis-(bromomethyl)-cyclohexane. Cyclization of the dibromide with zinc in ethanol produced spiro(2.5)octane in 91% yield. On distillation at about 25-plate efficiency, 71% of this material had a boiling range of 0.1° and a refractive index range of 0.0007; 51% had a constant boiling point and refractive index. The sample did not absorb bromine from carbon tetrachloride solution, and its time–temperature freezing curve showed it to be of high purity. Physical properties were determined on the constant index material.

4-Methylspiro(2.5)octane was made by the same series of reaction, starting with crotonaldehyde and butadiene. The yield of crude spirane was 89% from the dibromide; distillation at about ten-plate efficiency reduced this yield to 58% having a refractive index range of 0.0002. A good time–temperature freezing curve could not be obtained for this material, even after redistillation at about 25-plate efficiency and fractional crystallization. The physical properties listed were determined on the sample after recrystallization, and the material appeared to freeze over a range of about 5°. Since the ring closure reaction on di-primary halides gives high purity products consistently, it does not seem logical that in this case rearrangement occurred with the formation of an inseparable impurity; it is believed that the cryoscopic behavior can be attributed to a low heat of fusion for this spirane.

TABLE II

	B. p., °C. (760 mm.)	F. p., °C.	$d^{20}{}_4$	$n^{20}{}_4$
Spiro(2.5)octane	125.5	−86.2	0.8282	1.4476
4-Methylspiro(2.5)-octane	149.0	−53.6	.8386	1.4529

The stability of the cyclopropane ring is greatly affected by the nature and position of substituted groups. Willstätter and Bruce[11] found that cyclopropane, itself, is converted to propane at 80° by hydrogen over a nickel catalyst. Both Whitmore[12] and Fuson[13] state that alkyl-substituted cyclopropanes usually undergo ring opening more easily than does the parent substance. Studies on certain alkylcyclopropanes by other workers[14] indicate that temperatures of 150–170° are necessary to effect rupture of the ring.

In the present work hydrogenation studies have been carried out on three compounds containing the cyclopropane ring. No reaction occurred when an attempt was made to treat 1,1-diethylcyclopropane with hydrogen over platinum oxide catalyst at 60° and 40 p. s. i.; likewise, no reaction occurred when a palladium on calcium carbonate catalyst was used under these conditions. When the hydrocarbon was diluted with 60% of its volume of absolute ethanol, absorption of hydrogen did not occur even at 195° and 2400 p. s. i. over nickel on kieselguhr catalyst (Universal Oil Products). Successful hydrogenation of 1,1-diethylcyclopropane was accomplished in the absence of a solvent at 180° and 2000 p. s. i. over the nickel catalyst. Distillation of the hydrogenated product at about 10-plate efficiency gave 20% as headings and tailings (decomposition products and unchanged 1,1-diethylcyclopropane) and 80% of material (3° boiling range) which was identified as 3,3-dimethylpentane by inspection of the distillation curves (b. p. and $n^{20}\text{D}$). The boiling point range may be attributed to the presence of unchanged 1,1-diethylcyclopropane which boils only 2.5° higher than 3,3-dimethylpentane. No evidence was found for the presence of the other possible hydrogenation product, 3-ethylpentane.

Spiro(2.5)octane was hydrogenated successfully in the absence of a solvent over the nickel catalyst at 155° and 1900 p. s. i.; the theoretical amount of hydrogen was absorbed. Distillation of the hydrogenated product at about 25-plate efficiency gave 9% headings and tailings (decomposition products and unchanged spirane) and 91% of material (0.5° boiling range) which was identified as 1,1-dimethylcyclohexane on the basis of the physical properties of a heart cut (b. p. 119.65° (760 mm.), f. p. −34.02°, $d^{20}{}_4$ 0.7809, $n^{20}\text{D}$ 1.4291). No evidence was found for the presence of the other possible hydrogenation product, ethylcyclohexane.

4-Methylspiro(2.5)octane was hydrogenated under the same conditions as spiro(2.5)octane. The single hydrogenation product found was tentatively identified as 1,1,2-trimethylcyclohexane, a new compound, and it had the following physical properties: b. p. 145.2° (760 mm.), f. p. −29.2°, $d^{20}{}_4$ 0.7986, $n^{20}\text{D}$ 1.4385. A good freezing curve could not be obtained for this product, the general contour being the same as that for the original unhydrogenated spirane. 1,1,2-Trimethylcyclohexane, prepared at a later date[15] by a different method, and believed to be of good purity, had physical properties which agreed well with those of the product prepared by the hydrogenation of 4-methylspiro(2.5)octane. It exhibited the same peculiar cryoscopic behavior and was found to have a low heat of fusion and an unusually high freezing point depression on addition of *n*-heptane as impurity. This suggests that the original 4-methylspiro(2.5)octane was of good purity.

These studies indicate that when a *gem*-dialkylcyclopropane, or a spirane containing a cyclo-

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(11) Willstätter and Bruce, *Ber.*, **40**, 4456 (1907).

(12) Whitmore, "Organic Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1947, p. 623.

(13) Fuson, Chapter in Gilman's "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 101.

(14) (a) Kishner, *J. Russ. Phys.-Chem. Soc.*, **44**, 169 (1912); **45**, 987 (1913). (b) Rosanoff, *ibid.*, **48**, 168 (1916). (c) Zelinsky, *Ber.*, **40**, 4743 (1907); **46**, 1466 (1913).

(15) Unpublished data of George L. Evans of this Laboratory.

propane ring, is hydrogenated under the conditions described above, rupture of the cyclopropane ring occurs almost exclusively at the bond opposite the *gem*-disubstituted carbon atom. Thus, hydrogenation under controlled conditions can provide an easy, reliable method for proving the structure of these types of compounds, and in some cases it may prove to be a good preparative reaction for synthesizing *gem*-dimethylcycloalkanes with rings containing more than three carbon atoms. Since ring cleavage requires rather severe conditions (especially in the presence of a solvent), it appears that alkylcyclopropanes can be produced from cyclopropylolefins by preferential hydrogenation of the carbon–carbon double bond.

Experimental

Preparation of 2,2-Dimethyl-1,3-propanediol.—This diol was prepared from isobutyraldehyde and formaldehyde by the procedure of Whitmore and his co-workers,[5] except that stirring of the reaction mixture was maintained during the dropwise addition of the alcohol solution of the reactants. Sodium hydroxide could be substituted for potassium hydroxide with little sacrifice in yield. After a twenty-four hour reflux period the reaction mixture was stripped of alcohol, and the residue was subjected to continuous ether extraction. After removal of the ether, the crude product was distilled from a Claisen flask at atmospheric pressure to obtain a 76% yield of the diol boiling at 176–205°. The bulk of the product was collected at about 200°; it melted at 130°.

Preparation of 1,3-Dibromo-2,2-dimethylpropane.—This compound was prepared from 2,2-dimethyl-1,3-propanediol and phosphorus tribromide by the procedure of Whitmore, *et al.*,[5] except for the following innovation. Phosphorus tribromide was added to the diol at 70°, the rate of addition being such as to maintain the temperature. The reaction is immediate under these conditions and is easily kept under complete control.[16] It was not necessary to stir the reaction mixture, although this is now believed to be advisable for large runs.

The steam distillate, after drying, was fractionated under reduced pressure at 5 to 10-plate efficiency. Based on diol, a 46% yield of good dibromide was obtained. It had the following physical properties: b. p. 68° (9 mm.), n^{20}_{D} 1.5050, d^{20}_{4} 1.6934.

Preparation of 1,1-Dimethylcyclopropane.—The method of cyclization was a modification of that of Gustavson.[2,3] In a 2-liter three-necked flask equipped with a dropping funnel, mercury-sealed stirrer and reflux condenser (connected to a trap surrounded by a Dry Ice–acetone-bath), were placed 900 ml. of 95% ethanol, 90 ml. of distilled water and 628 g. (9.6 moles) of zinc dust; it was necessary to maintain vigorous stirring at all times to prevent caking of the zinc. The mixture was brought to gentle reflux, and 562 g. (2.4 moles) of 1,3-dibromo-2,2-dimethylpropane was added dropwise at this temperature. Heating and stirring were continued for twenty-four hours after the last of the dibromide had been added; the bulk of the hydrocarbon collected in the trap during this period. The remaining 1,1-dimethylcyclopropane (along with some alcohol) was then distilled from the reaction flask and was collected in the trap. The crude product (162 g.) was washed with ice water and dried. The properties and purification of this material have already been described.

Preparation of 2,2-Diethyl-1,3-propanediol.—This compound was prepared from 2-ethylbutyraldehyde (Carbide and Carbon) by the same procedure as was used for the synthesis of 2,2-dimethyl-1,3-propanediol from isobutyraldehyde. Because of the lesser solubility of the resulting diol in water in this case, continuous ether extraction was unnecessary, and the crude product was merely extracted from the reaction mixture with ether. The ether was removed from the extract by distillation, and the residue was distilled from a Claisen flask to give a 91% yield of good product (b. p. 128–132° (12 mm.)). This material was fractionated at about 10-plate efficiency, and the following physical properties were determined on a center fraction: b.p. 131° (13 mm.), m. p. 61.0–61.6°. This compound has not been described previously. *Anal.* Calcd. for $C_7H_{16}O_2$: C, 63.6; H, 12.2. Found: C, 64.0; H, 12.2.

Preparation of 1,3-Dibromo-2,2-diethylpropane.—This dibromide was prepared from the corresponding diol in exactly the same way as 1,3-dibromo-2,2-dimethylpropane was prepared from 2,2-dimethyl-1,3-propanediol. The yield of steam distilled material was 40% (from diol) and was shown to be 90% pure by distillation under reduced pressure at 5 to 10-plate efficiency. The following physical properties were determined on a purified sample: b. p. 97° (10 mm.), m. p. 39.2–40.6°; this compound has not been described previously. *Anal.* Calcd. for $C_7H_{14}Br_2$: Br, 61.9. Found: Br, 62.1.

Preparation of 1,1-Diethylcyclopropane.—The ring closure reaction was carried out in the same way as in the preparation of 1,1-dimethylcyclopropane. Since the dibromide (1,3-dibromo-2,2-diethylpropane) was a solid, it was necessary to heat the dropping funnel in order to use the same technique. The 1,1-diethylcyclopropane was allowed to accumulate in the reaction flask; then the hydrocarbon was distilled from the reaction mixture through a 1.5 × 50 cm. Vigreux column until dilution of the fresh distillate with water did not cause a phase separation. The distillate was washed free of alcohol and was fractionated at about 10-plate efficiency; all of the material distilled at a constant temperature and had a constant refractive index; the total yield was 92% of theory (from dibromide). The physical properties of the distilled hydrocarbon are listed in Table I. This compound has not been described previously. *Anal.* Calcd. for C_7H_{14}: C, 85.6; H, 14.4. Found: C, 85.9; H, 14.2.

Preparation of 2-Ethyl-2-butyl-1,3-propanediol.—This diol was prepared from 2-ethylhexaldehyde (Carbide and Carbon) in the same way 2,2-diethyl-1,3-propanediol was prepared from 2-ethylbutyraldehyde. The crude product distilled at 151–152° (11 mm.) and was obtained in 70% yield. The material was redistilled at about 10-plate efficiency, and the following physical properties were determined on a center cut: b. p. 152° (10 mm.), m. p. 41.4–41.9°. This compound has not been described previously. *Anal.* Calcd. for $C_9H_{20}O_2$: C, 67.4; H, 12.6. Found: C, 67.6; H, 12.5.

Preparation of 1,3-Dibromo-2-ethyl-2-butylpropane.—This dibromide was prepared from the corresponding diol in exactly the same way as 1,3-dibromo-2,2-dimethylpropane was prepared from 2,2-dimethyl-1,3-propanediol. The yield of steam distilled material was 59% (from diol) and was shown to be 80% pure by distillation at about 10-plate efficiency. The following physical properties were determined on a purified sample: b. p. 133° (16 mm.), d^{20}_{4} 1.4400, n^{20}_{D} 1.5018. This compound has not been described previously. *Anal.* Calcd. for $C_9H_{18}Br_2$: Br, 55.9. Found: Br, 56.2.

Preparation of 1-Ethyl-1-butylcyclopropane.—1,3-Dibromo-2-ethyl-2-butylpropane was cyclized in the same way as was 1,3-dibromo-2,2-diethylpropane in the preparation of 1,1-diethylcyclopropane. The crude 1-ethyl-1-butylcyclopropane was fractionated at about 10-plate efficiency, and all of the material distilled at a constant temperature and had a constant refractive index. The yield from the dibromide was 94%. The physical constants of the distilled hydrocarbon are listed in Table I. This compound has not been described previously. *Anal.* Calcd. for C_9H_{18}: C, 85.6; H, 14.4. Found: C, 85.6; H, 14.4.

Preparation of 3-Cyclohexene-1-carboxaldehyde.—The procedure used was patterned after that described by Chayanov.[17] Butadiene (5 moles) was placed in a one-

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[16] At lower temperatures an excess of phosphorus tribromide may accumulate, and a sudden uncontrollable reaction may occur.

[17] N. A Chayanov, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 460 (1938).

liter steel bomb (American Instrument Company type) which contained acrolein (5 moles) and 5 g. of hydroquinone, the bomb and contents having been cooled previously in a Dry Ice chest. The bomb was sealed, placed in a mechanical shaker, and heated as rapidly as possible to 130°. At this temperature reaction appeared to begin, and the temperature quickly rose to 185° without further external heating. After cooling, the crude adduct (543 g.) was distilled at reduced pressure (75 mm.) through a 122 cm. Vigreux column. A center cut with a refractive index range of 0.0004 and a boiling point range of 1.0° represented 74% of the theoretical yield. Physical properties were determined on a heart fraction (values in parentheses are those of Chayanov[17]): b. p. 164° (760 mm.) (163.5–164.5°), f. p. −96.1°, d^{20}_{4} 0.9709 (d^{19}_{4} 0.965), n^{20}_{D} 1.4725 (n^{19}_{D} 1.4725).

When the reaction was run on a larger scale, lower yields were obtained. This may be explained by the fact that rapid heating to reaction temperature is necessary to minimize the formation of by-products; further, the temperature rise from the heat of reaction is greater in larger batches and may cause undesirable side reactions.[18]

Preparation of 4,4-bis-(Hydroxymethyl)-1-cyclohexene.—This diol was prepared from 3-cyclohexene-1-carboxaldehyde by the same procedure as 2,2-dimethyl-1,3-propanediol was prepared from isobutyraldehyde. On evaporation of the ether from the extract a large crop of crystals separated; the uncrystallized residue was distilled to obtain the remainder of the diol (b. p. 128° (3 mm.)). The total yield of diol was 84% of theory (from aldehyde), and, after two crystallizations, it melted sharply at 92.0°. (literature value,[19] 92.5°).

Preparation of 1,1-bis-(Hydroxymethyl)-cyclohexane.—1,1-bis-(Hydroxymethyl)-3-cyclohexene was dissolved in methanol (40 g. per 100 ml.) and placed in a steel bomb with 9% by weight of Raney nickel catalyst. Absorption of hydrogen began at 45° and 1000 p. s. i. The catalyst was removed by filtration, and the solvent was removed by distillation; white crystals melting at 98.5° remained. No further purification was attempted.

Preparation of 1,1-bis-(Bromomethyl)-cyclohexane.—This dibromide was prepared from the corresponding diol in the same way as 1,3-dibromo-2,2-dimethylpropane was prepared from 2,2-dimethyl-1,3-propanediol. After a twelve-hour heating period at 140–150°, the reaction mixture was hydrolyzed and subjected to superheated (150°) steam distillation. The steam distillate was dried and fractionated at 5 to 10-plate efficiency under reduced pressure to obtain a 27% yield (from diol) of purified dibromide. Physical constants determined on a center cut were: b. p. 117° (6 mm.), d^{20}_{4} 1.6302, n^{20}_{D} 1.5390.

Preparation of Spiro(2.5)octane.—1,1-bis-(Bromomethyl)-cyclohexane was cyclized in the same way as was 1,3-dibromo-2,2-dimethylpropane in the preparation of 1,1-dimethylcyclopropane. The hydrocarbon was allowed to accumulate in the reaction mixture and was isolated by distillation from the reaction flask. The crude product (n^{20}_{D} 1.4660) was washed free of alcohol and was obtained in 91% yield from dibromide.

Preparation of 6-Methyl-3-cyclohexene-1-carboxaldehyde.—This compound was prepared from butadiene and crotonaldehyde. The crotonaldehyde was placed in a steel bomb and heated to 150°. The butadiene was placed in a small cylinder connected to the bomb by small bore steel tubing. Nitrogen (pressure 300 p. s. i.) was used to push the butadiene into the reaction bomb in liquid form, the rate of addition being regulated by a valve so that about 7 g. per minute were added. A 46% yield of the desired aldehyde was obtained after distillation at 5 to 10-plate efficiency under reduced pressure. Its physical properties were: b. p. 99° (64 mm.) or 117.8° (760 mm.), d^{20}_{4} 0.9500, n^{20}_{D} 1.4680.

Preparation of 4,4-bis-(Hydroxymethyl)-5-methylcyclohexene.—This compound was prepared from 6-methyl-3-cyclohexene-1-carboxaldehyde by the same procedure as 2,2-dimethyl-1,3-propanediol was prepared from isobutyraldehyde. Purification was attempted by reduced pressure distillation. The distillate (b. p. 134° (6 mm.)) contained substantial amounts of the cyclic aldehyde (from dissociation during distillation); a yield was not calculated. Some pure crystalline diol was separated and melted at 45°. (This value agrees well with that given by French and Gallagher.[19])

Preparation of 1,1-bis-(Hydroxymethyl)-2-methylcyclohexane.—The crude cyclohexenedicarbinol was hydrogenated at 45° in ethanol solution over 10% by weight of Raney nickel. Distillation of the hydrogenated material at low efficiency gave a 51% yield (from original aldehyde) of saturated diol (m. p. 77°.).

Preparation of 1,1-bis-(Bromoethyl)-2-methylcyclohexane.—This compound was prepared from the corresponding diol by the same procedure as 1,1-bis-(bromomethyl)-cyclohexane was prepared from 1,1-bis-(hydroxymethyl)-cyclohexane; the yield of purified dibromide was 28% (from diol), and it had the following physical properties: b. p. 115° (4 mm.), n^{20}_{D} 1.5380.

Preparation of 4-Methylspiro(2.5)octane.—1,1-bis-(Bromomethyl)-2-methylcyclohexane was cyclized in the same way as was 1,1-bis-(bromomethyl)-cyclohexane in the preparation of spiro(2.5)octane. An 89% yield of crude spirane was obtained.

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Summary

1. The synthesis of three *gem*-dialkylcyclopropanes is described; two of these are new compounds; improved physical properties were determined for the third.

2. Spiro(2.5)octane and 4-methylspiro(2.5)octane, both new compounds, have been synthesized in good yield by an extension of the Gustavson reaction. This method appears to be a general one for preparing spiranes containing a cyclopropane ring.

3. Hydrogenation of three of these compounds has been investigated to determine the point of rupture of the cyclopropane ring and the conditions necessary to effect it. Cleavage seems to occur exclusively at the bond opposite to the gem-disubstituted carbon atom. The stability of the cyclopropane ring toward catalytic hydrogenation is discussed.

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[18] It has been observed both here and in other laboratories that in Diels–Alder reactions of this kind (especially when butadiene is involved) an extremely exothermic reaction may occur quite suddenly, thus raising the temperature and pressure to extreme values. This is supposedly due to self-polymerization of the diene and is catalyzed by peroxides; it can be checked by use of peroxide free dienes and/or addition of a strongly reducing substance such as hydroquinone. Other essential precautions are that the reactants should be thoroughly mixed, the reaction vessel (bomb) should not be filled to more than two-thirds of its capacity at room temperature, and the vessel should be connected directly to a blow-out assembly with a discharge line leading to the out-of-doors. Neglect of these precautions caused one bad accident in this Laboratory. The head was blown from a 3-liter bomb containing butadiene and crotonaldehyde; the ensuing gas explosion did much damage and burned one man seriously.

[19] French and Gallagher, THIS JOURNAL, **64**, 1497 (1942).