ture steam distilled to remove unreacted V, freed of manganese dioxide and the solution acidified to give 16.2 g. (55%) of VI, m. p. 190–193°. A portion of this product was recrystallized from toluene to give VI, m. p. 192–193.5°.

Anal. Calcd. for $C_8H_7O_3F$ (170): C, 56.5; H, 4.2. Found: C, 56.7; H, 4.2.

2-Fluoro-4-methoxybenzoyl Chloride (VII).[7]—VI (29.9 g.) was refluxed with 40 ml. of thionyl chloride for ten hours[8] and the reaction mixture fractionally distilled to give 32 g. (97%) of VII, b. p. 120–122° (3 mm.), m. p. 37–40°.

2-Fluoro-4-methoxybenzyl Chloride (VIII).[7]—A solution of 30.8 g. of VII in 300 ml. of absolute ether was reduced with 200 ml. of 0.5 *M* lithium aluminum hydride.[9] When the reduction had been completed, 10 ml. of water was added, the mixture poured into a slurry of ice in dilute sulfuric acid, the ethereal phase collected, the aqueous phase repeatedly extracted with ether, the ethereal extracts combined, washed with water until neutral, dried and the solvent removed to give 30 g. of crude 2-fluoro-4-methoxybenzyl alcohol. This latter product was taken up in 25 ml. of thionyl chloride, the solution allowed to stand overnight and then warmed at 90° for one hour. The excess thionyl chloride was removed by distillation *in vacuo* and the residue fractionally distilled to give 23 g. (81%) of VIII, b. p. 110–112° (7 mm.), d. 1.22.

Anal. Calcd. for C_8H_8OFCl (174.5): C, 55.0; H, 4 6. Found: C, 55.1; H, 4.6.

Diethyl α-Acetamido-α-(2-fluoro-4-methoxybenzyl)-malonate (IX).—To a solution of 3.1 g. of sodium and 30 g. of diethyl acetamidomalonate in 250 ml. of absolute ethanol was added 21.8 g. of VIII, the mixture refluxed for four hours,[10,11] the sodium chloride removed and 600 ml. of water added to the filtrate. The crystalline product was collected, washed with 30% aqueous ethanol and then with water to give 36.8 g. (85%) of IX, m. p. 118–120°. A portion of this product was recrystallized from absolute ethanol to give IX, m. p. 120–121.5°.

Anal. Calcd. for $C_{17}H_{22}O_6NF$ (355): C, 57.5; H, 6.2; N, 3.9. Found: C, 57.6; H, 6.3; N, 3.9.

N-Acetyl-2-fluoro-4-methoxy-DL-phenylalanine (X).—IX (35.5 g.) was refluxed for six hours with 175 ml. of 2.5 *M* sodium hydroxide, 95 ml. of 5 *M* hydrochloric acid added and the mixture refluxed for an additional two hours[10,11] to give, after standing at 4° overnight, 15.8 g. (62%) of X, m. p. 162–170° which was then recrystallized from ethanol to give 13.7 g. of X, m. p. 169.5–171.5°.

Anal. Calcd. for $C_{12}H_{14}O_4NF$ (255): C, 56.5; H, 5.5; N, 5.5. Found: C, 56.5; H, 5.5; N, 5.6.

2-Fluoro-4-methoxy-DL-phenylalanine (XI).—X (1.0 g.) was refluxed with 40 ml. of 3 *M* hydrochloric acid for seven hours, the hydrolysate concentrated *in vacuo*, the residue taken up in 20 ml. of water, an excess of ammonium hydroxide added, the excess expelled by boiling, and 15 ml. of ethanol added to the cold solution to give 0.53 g. (63%) of XI, long needles, dec. point 218–226°. Recrystallization of this latter product from 50% aqueous ethanol gave XI, dec. point 217–221°.

Anal. Calcd. for $C_{10}H_{12}O_3NF$ (213): C, 56.3; H, 5.7; N, 6.6. Found: C, 56.4; H, 5.8; N, 6.6.

2-Fluoro-DL-tyrosine (XII).—A solution of 1.4 g. of X in 20 ml. of aqueous hydrobromic acid was refluxed for seven hours, the excess hydrogen bromide removed by distillation *in vacuo*, and the residue crystallized from aqueous ammonia to give 0.87 g. (80%) of XII, dec. point 280–285°, which was recrystallized from water to give XII, dec. point 280–285°.

Anal. Calcd. for $C_9H_{10}O_3NF$ (199): C, 54.3; H, 5.1; N, 7.0. Found: C, 54.2; H, 5.0; N, 7.1.

Ultraviolet Spectra and Ionization Constants.—The methods used have been described previously.[12]

Summary

The synthesis of 2-fluoro-DL-tyrosine and 2-fluoro-4-methoxy-DL-phenylalanine has been described and their ultraviolet absorption spectra determined.

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(7) VII was prepared with the intent to reduce it to 2-fluoro-4-methoxybenzaldehyde. Difficulties encountered in this reduction led to the procedure described. It is clear that the benzoic acid could have been reduced directly to the alcohol.

(8) B. Helferich and W. Schaefer, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 147.

(9) R. Nystrom and W. Brown, THIS JOURNAL, **69**, 1197 (1947).

(10) N. Albertson and S. Archer, *ibid.*, **67**, 308 (1945).

(11) H. Snyder, J. Shekleton and C. Lewis, *ibid.*, **67**, 310 (1945).

(12) J. C. Nevenzel, W. Shelberg and C. Niemann, *ibid.*, **71**, 3024 (1949).

PASADENA 4, CALIFORNIA RECEIVED AUGUST 23, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

Some Reactions of *cis*-3,5-Dibromocyclopentene

BY EVANS B. REID AND JOHN F. YOST[1]

A survey of the literature reveals that 3,5-dihalocyclopentenes have been virtually neglected as intermediates in the synthesis of substituted cyclopentenes. This paper reports several studies, mainly carried out on the *cis*-dibromide, directed toward the synthesis of 3,5-dialkylcyclopentenes, and especially 3,5-di-*s*-butylcyclopentene, which is the ring system reported to be present in the two plant hormones, auxins a and b.[2] Although attempts to effect substitution of both bromine atoms failed, *cis*-3,5-dibromocyclopentene proved very efficient for the introduction of the cyclopentadienyl unit by means of alkylation and Barbier-type[3] reactions.

Despite the fact that Grignard reagents have been shown to react with 3-halocyclopentenes[4,5,6] in the normal Brooks–Humphrey fashion,[7] our efforts to extend this type of reaction to either *cis*- or *trans*-3,5-dibromocyclopentene were without success. Although many attempts were made under various conditions and with different Grignard reagents, deep polymerization inevitably resulted, and no monoalkyl or dialkyl product

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(1) From the doctoral dissertation of John F. Yost, The Johns Hopkins University.

(2) Kögl, Erxleben, Michaelis and Visser, *Z. physiol. Chem.*, **235**, 181 (1935).

(3) Barbier, *Compt. rend.*, **128**, 110 (1899).

(4) Braun, Kamp and Kopp, *Ber.*, **70B**, 1750 (1937).

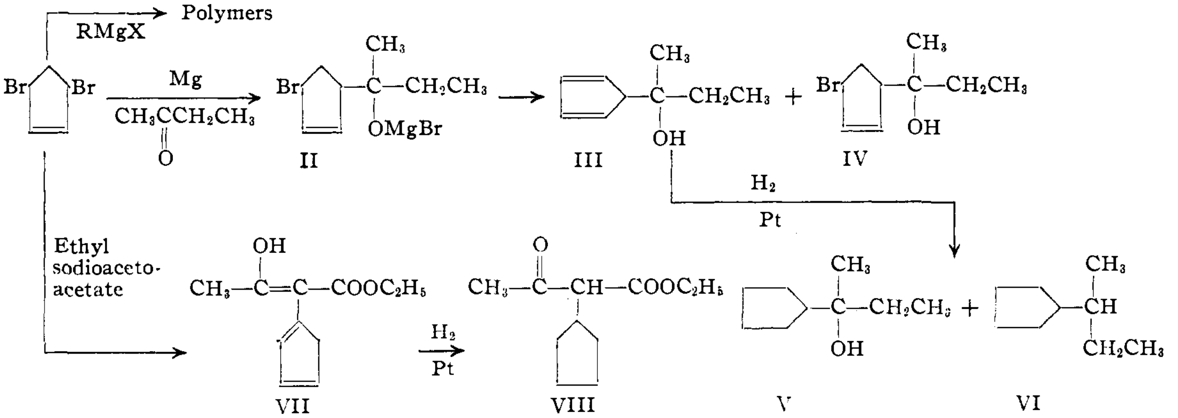
(5) Braun and Reitz-Kopp, *ibid.*, **74B**, 1105 (1941).

(6) Crane, Boord and Henne, THIS JOURNAL, **67**, 1237 (1945).

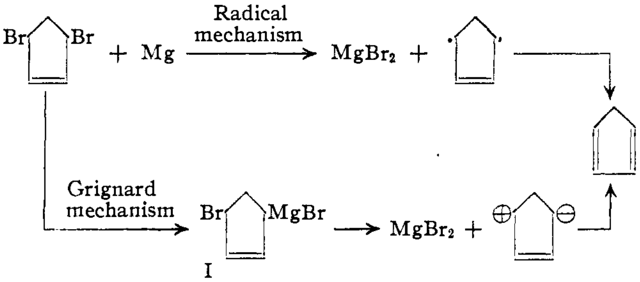
(7) Brooks and Humphrey, *ibid.*, **40**, 822 (1918).

could be isolated. The use of cuprous chloride has been reported[8] in overcoming the inertia of *n*-butylacetylenemagnesium bromide toward allyl bromide, and in the present instance it was thought that this catalyst might exert a directive influence. However, it merely intensified the vigor of reaction and increased the amount of polymeric products formed. It is apparent, therefore, that a two-step reaction between the dihalide and Grignard reagents is blocked by the presence of the second bromine atom, whose strong electron attraction prevents stabilizing resonance of the necessary intermediate ion. And since simultaneous reaction of both bromine atoms would necessitate a great amount of activation energy and, further, would involve an intermediate dicarbonium ion, in which resonance of the allyl type[9] would be impossible, polymerization takes place. Our observations roughly parallel those of Macallum and Whitby,[10] who attempted the same type of reaction with 1,4-dibromo-2,3-dimethyl-2-butene, and obtained polymers.

Since allylmagnesium bromide has been obtained in very high yield,[11] experiments were directed toward the formation of the dimagnesium derivative of *cis*-3,5-dibromocyclopentene. The results were somewhat unexpected, for although normal Grignard formation appeared to take place, its presence could not be demonstrated after the magnesium was consumed. The product was cyclopentadiene, and its direct formation appears to find an analogy in the open-chain series, for Khitrick[12] has reported that 1,3-butadiene results from interaction of magnesium with 1,4-dibromo-2-butene in ethereal solution.



Either of two mechanisms may be invoked to rationalize the formation of cyclopentadiene. The reaction may involve no intermediate Grignard reagent, but proceed through radicals, the hydrocarbon resulting from appropriate electronic shifts within the radical. On the other hand a true Grignard reagent might form, and this, by ionization to $MgBr^+$ and Br^- followed by suitable electronic displacements within the organic moiety, could give rise to cyclopentadiene. These hypotheses are illustrated



To test this point we utilized the Barbier reaction, and found that when magnesium was allowed to interact with *cis*-3,5-dibromocyclopentene in the presence of butanone, no cyclopentadiene was formed, but ethylmethylfulvenol (III), was obtained in high yield.

The second mechanism, therefore, applies in the case of the Barbier reaction, and it seems safe to assume that the formation of cyclopentadiene from the dibromide and magnesium also involves the monomagnesium derivative (I). The rate of elimination of magnesium bromide from this bromo-Grignard reagent must be sufficiently slow to permit normal addition to carbonyl groups, provided the latter are immediately available for reaction. The bromo-Grignard addition complex (II), which is thus formed, then generates the fulvenol (III), and magnesium bromide, but this step must be comparatively slow since considerable unreacted Grignard addition complex was present at the time of quenching. Also, fractional distillation of the product yielded the fulvenol contaminated with a trace of halogen compound, and left a small amount of high-boiling residue which contained halogen. This residue, in all

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[8] Danehy, Killian and Nieuwland, *ibid.*, **58**, 611 (1936).

[9] Fieser and Fieser, "Organic Chemistry," Heath and Co., Boston, Mass., 1944, p. 648.

[10] Macallum and Whitby, *Trans. Roy. Soc. Canada*, **22**, 33 (1928).

[11] Gilman and McGlumphy, *Bull. soc. chim.*, **43**, 1322 (1928).

[12] Khitrick, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 2098 (1940).

probability, was the ethylmethylbromocyclopentenecarbinol (IV), since it tended to lose hydrogen bromide on heating, and on keeping for several months developed the typical and pronounced odor of ethylmethylfulvenol. Catalytic reduction of the fulvenol yielded ethylmethylfulvanol (V), and some secondary butylcyclopentane (VI), together with a small amount of hydrogen bromide. These reactions appear in the formula chart.

Finally, *cis*-3,5-dibromocyclopentene was investigated as an alkylating agent, since alkylation of two molecules of ethyl acetoacetate by one of the dibromide should furnish a compound that would be transformable to 3,5-dialkylcyclopentenes. The product, however, contained only one acetoacetate residue. It was a strongly enolic oil with a permanent pale yellow color. Its structure, therefore, is ethyl α-(1-cyclopentadienyl)-acetoacetate (VII). Reduction with Adams catalyst formed the known, colorless, ethyl α-cyclopentylacetoacetate (VIII).[13]

Since it has been shown[10] that 1,4-dibromo-2,3-dimethyl-2-butene does not undergo dehydrohalogenation on treatment with sodium ethoxide, but forms a di-ether instead, it follows that the first step in the reaction of ethyl sodioacetoacetate (a weaker base than alkoxide) with *cis*-3,5-dibromocyclopentene must be monoalkylation. The resulting bromo compound then loses bromide ions and protons to the basic environment, and this dehydrohalogenation is too facile to permit of a second alkylation. Of interest is the fact that our over-all yield of ethyl α-cyclopentylacetoacetate is identical with that reported[13] for direct alkylation with bromocyclopentane.

Acknowledgment.—One of the authors (J. F. Y.) wishes to express his appreciation of a grant-in-aid from the Hynson, Westcott and Dunning Fund in the pursuance of this research.

Experimental

Cyclopentadiene.—Pure material, b. p. 40–41°, was obtained by thermal depolymerization of commercial dicyclopentadiene according to the method of Schultze.[14]

cis- **and** *trans*-**3,5-Dibromocyclopentene.**—Improved yields of the *trans* form were obtained by modifying the method of Blomquist and Mayes.[15] One mole of freshly prepared cyclopentadiene and 50 ml. of ligroin were placed in a 1-liter flask equipped with dropping funnel, stirrer, calcium chloride tube, and provision for a nitrogen atmosphere. The mixture was rapidly stirred and maintained at −40 ± 5°, by a bath of toluene–acetone–Dry Ice, during the two hours required for the dropwise addition of a mole of bromine in 100 ml. of ice-cold ligroin. The solvent was decanted and the white crystals, m. p. 45–46°, were used immediately. The yield of product was 214 g., or 95%. The material was strongly lachrymatory, and while it was stable under nitrogen, exposure to air for a few minutes caused the crystals to become green, finally forming a black liquid.

The *cis* analog proved, in our hands, easier to obtain free of both solvent and hydrogen bromide. It was therefore used for most of the experiments, and was prepared by the method of Blomquist and Mayes.[15] Immediately after the addition of bromine, the mixture was washed with dilute sodium thiosulfate solution. After separation, 75 ml. of benzene was added to the organic layer, which was then fractionally distilled through a short column in an atmosphere of nitrogen. Pure *cis*-3,5-dibromocyclopentene, b. p. 54–57° at 2 mm., was obtained in 65% yield. The product was water-white, but rapidly turned green and then black on exposure to air.

Grignard Reagents and 3,5-Dibromocyclopentene.—Numerous reactions were carried out using *cis*, *trans*, and mixtures of *cis* and *trans* dibromide. These were allowed to interact, under nitrogen, with *s*-butylmagnesium bromide and iodide, and with *n*-propylmagnesium bromide and iodide. In absolute diethyl ether exothermic reactions were noted in all cases, with the formation of soft brown to black tars which had strong terpenoid odors. Steam distillation produced minute amounts of low-boiling material. Decreasing the reaction temperature resulted in less tar formation and recovery of larger amounts of starting materials. In absolute diisopropyl ether the reaction was weakly exothermic. Addition of catalytic amounts of cuprous chloride[8] caused a vigorous reaction, with increased tar formation.

cis-**3,5-Dibromocyclopentene and Magnesium.**—One mole of magnesium turnings was placed in a 2-liter flask equipped with stirrer, reflux condenser, dropping funnel, and means for provision of a nitrogen atmosphere. Fifty milliliters of absolute diethyl ether and a crystal of iodine were added, after which, with vigorous stirring, 0.5 mole of pure *cis*-3,5-dibromocyclopentene in 200 ml. of absolute ether was added dropwise over a forty-five-minute period. The reaction was very vigorous. At first a grayish compound formed on the surface of the magnesium, but this was immediately replaced by a clear brown solution. As the reaction progressed a slate-colored lower layer formed, which was not dissolved by the further addition of 200 ml. of ether. Examination of the ether layer showed it to contain cyclopentadiene. The Baeyer test was positive, as was the Wieland and Stenzl test[16] for cyclopentadiene. A sample immediately discharged the color of bromine without hydrogen bromide elimination, and evaporation of the ether left a small amount of lachrymatory oil which rapidly turned green and then black in air. With maleic anhydride the known cyclopentadiene–maleic anhydride adduct[17] was obtained. It had m. p. 163–164°, either alone or admixed with authentic material.

Hydrolysis of the lower layer gave a feeble reaction, and examination of the product showed it to be highly ethereal, but containing about 3% of cyclopentadiene. This estimate was based on the amount of maleic anhydride–cyclopentadiene adduct formed.

In other experiments, *cis*-3,5-dibromocyclopentene was allowed to react to *completion* with magnesium. Ketones were then added to the reaction mixture, but no fulvenols were produced, even after long periods of heating and stirring. In each case cyclopentadiene and unchanged ketone were obtained.

The Reaction of *cis*-**3,5-Dibromocyclopentene with Magnesium and Butanone.**—One mole of magnesium turnings, 3.0 moles of freshly distilled butanone, 300 ml. of absolute ethyl ether, and a crystal of iodine were placed in a two-liter flask equipped as previously described. Under a nitrogen atmosphere, 0.5 mole of freshly prepared dibromide in 300 ml. of absolute ether was introduced dropwise. The reaction was slow, and the addition of a few ml. of a reacting mixture of the dibromide and magnesium in ether had no accelerating effect. The mixture was refluxed for two hours, during which a considerable amount of white amorphous material separated. After standing overnight, spontaneous refluxing was engendered merely by stirring. This exothermic period continued for three and one-half hours. After refluxing for an additional six hours most of the magnesium had reacted.

The ether layer was decanted from the lower semi-solid mass, and treated with 10% aqueous ammonium chloride.

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[13] Burschkies and Scholl, *Arch. Pharm.*, **281**, 328 (1943).

[14] Schultze, THIS JOURNAL, **56**, 1552 (1934).

[15] Blomquist and Mayes, *J. Org. Chem.*, **10**, 134 (1945).

[16] Wieland and Stenzl, *Ann.*, **360**, 309 (1908).

[17] Dedusenko, *Bull. Acad. Sci.* (*U. S. S. R.*), 59 (1936).

An exothermic reaction occurred. After drying with anhydrous sodium sulfate the ethereal solution was distilled under nitrogen. Thirty-five grams of pale yellow liquid was collected, b. p. 60–67° at 30 mm. Similar treatment of the lower layer yielded 40 g. of light yellow oil with the same boiling range and refractive index. They were combined and fractionated through a Vigreux column. Sixty-five grams (94.2%) of nearly colorless oil was obtained, b. p. 82–85° at 45 mm., n^{27}_D 1.4506, d^{27}_4 0.8965. A small amount of water was observed to form during each distillation, and the product gave positive Beilstein and Baeyer tests. A small dark residue remained after the first distillations. On heating a portion of this residue, fumes of hydrogen bromide were evolved. Another portion on being stored for three months had developed the characteristic odor of ethylmethylfulvenol. Calculated *MR* for ethylmethylfulvenol, 43.53; found 44.7.

Difficulty was experienced in effecting complete reduction. For each 10 g. of fulvenol in 10 ml. of absolute ethanol a total of 2 g. of Adams catalyst was used, 0.5 g. being added to the charge at the end of each twelve-hour period. One-half gram of ferric chloride was added with the last increment of catalyst. Approximately 0.16 mole of hydrogen was absorbed; theory requires 0.145. The product, about 8 g. of oil, gave negative Beilstein and Baeyer tests. The *p*H of the aqueous washings was 1.0, and titration of an aliquot of this with standard sodium hydroxide showed the presence of 0.008 equivalent of halide ion per 10 g. of original oil. The oil, after drying over anhydrous sodium sulfate, was distilled. A small fraction, b. p. 153–155° was obtained, which corresponds[18] to the reported b. p. of *s*-butylcyclopentane. The main fraction was collected at 163–167° (80%). Refractionation of this gave pure ethylmethylfulvanol, b. p. 167°; n^{20}_D 1.4266.

Anal. Calcd. for $C_9H_{18}O$: C, 76.0; H, 12.75. Found: C, 75.86; H, 12.81.

Action of Ethyl Sodioacetoacetate on *cis*-3,5-Dibromocyclopentene.—In the previously described apparatus was placed 1.0 mole of sodium shot and 200 ml. of absolute ether. One mole of ethyl acetoacetate in 200 ml. of absolute ether was introduced, under nitrogen, during a four-hour period. Absolute ether (200 ml.), was again added, and the curd-like mass was allowed to stand overnight. One-half mole of freshly prepared *cis*-3,5-dibromocyclopentene, b. p. 56–58° at 2 mm., in 200 ml. of absolute ether was added dropwise. No observable reaction occurred, and the mixture was allowed to stand overnight. Most of the ether was then removed by distillation, and it was noticed during this operation that the curd-like particles were slowly replaced by crystalline material. After refluxing for two hours, it was again allowed to stand overnight. After addition of water the *p*H of the mixture was 9.0. This was adjusted to 7.0 with dilute hydrochloric acid, and the ether layer was washed once with water and dried over anhydrous sodium sulfate. Upon fractional distillation under nitrogen at 5 mm., 68 g. (70% yield) of pale yellow oil was collected, b. p. 108–109°. A negligible amount of high-boiling residue remained, and no definite fraction could be obtained from it. The oil reacted with bromine, liberating hydrogen bromide, and gave a strong enol (ferric chloride) test. A Beilstein test was feebly positive. It had n^{27}_D 1.4970. *MR* calculated for ethyl α-(1-cyclopentadienyl)-acetoacetate, 53.0; found 51.2.

Reduction was effected at 40 p. s. i. g.: twenty-four grams (0.123 mole) in 25 ml. of absolute ethanol was treated with 0.5 g. of Adams catalyst. Hydrogen was absorbed rapidly at first, but the rate became progressively slower. In a twelve-hour period 0.214 mole was taken up, as compared with 0.226 mole required by theory. After removal of the catalyst, the product was fractionated through a short column under nitrogen. The main fraction, 21.5 g., had b. p. 118–120° at 12 mm. The yield of colorless material was 90%. It was free of halogen, and slowly gave the ferric chloride enol test. Upon refractionation it had b. p. 120° at 12 mm., and was pure ethyl α-cyclopentylacetoacetate.[13]

Anal. Calcd. $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.90; H, 8.96.

Summary

1. *cis*- and *trans*-3,5-dibromocyclopentene do not react with Grignard reagents in the normal fashion, but yield polymeric products.

2. *cis*-3,5-Dibromocyclopentene does not form a dimagnesium derivative, but is dehydrobrominated to cyclopentadiene.

3. *cis*-3,5-Dibromocyclopentene forms a monomagnesium derivative, since the Barbier reaction with butanone forms ethylmethylfulvenol.

4. A mechanism is proposed for the formation of cyclopentadiene from *cis*-3,5-dibromocyclopentene and magnesium.

5. *cis*-3,5-Dibromocyclopentene monoalkylates ethyl sodioacetoacetate, introducing the cyclopentadienyl group on the methylene carbon atom.

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[18] Willstätter, *Ber.*, **46**, 525 (1913).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Studies on the Mechanism of Chugaev and Acetate Thermal Decompositions. I. *cis*- and *trans*-2-Phenylcyclohexanol

BY ELLIOT R. ALEXANDER AND ANTON MUDRAK

The conversion of an alcohol to an olefin by the thermal decomposition of a xanthate prepared from it is called the Chugaev reaction. The formation of olefins from the pyrolysis of carboxylic esters appears to be a related transformation. The unusual feature of these reactions is that they usually avoid the rearrangements which are frequently encountered in the dehydration of certain alcohols by other methods. Thus, pinacolyl alcohol (I) leads to *t*-butylethylene (II) by a Chugaev dehydration[1] (Equation 1) and pure 2-alkyl-1,3-butadienes (IV) have been obtained from the pyrolysis of the corresponding 2-alkyl-3-acetoxy-1-butenes (III)[2] (Equation 2). Dehydration of the alcohols by other methods led to products in which rearrangement had occurred.

Little is known of the actual mechanism of these reactions, and since they are thermal decompositions, the possibility of free radical processes must be considered. It has been suggested, however, that the transformations are initiated by the intramolecular hydrogen bonding of a sulfur

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[1] Fomin and Sochanski, *Ber.*, **46**, 244 (1913).

[2] Marvel and Williams, THIS JOURNAL, **70**, 3842 (1948).