eluate (B), Table I, *in vacuo* to a dry sirup and acetylation of this sirup resulted in the isolation of a colorless sirup rotating +93.4° (c, 2 in chloroform). This acetate, dissolved in ethanol, crystallized overnight at 25°. The total yield of pure octaacetyl-6-[α-D-glucopyranosyl]-β-D-glucose, $[\alpha]^{25}$D +98.0° (c, 2 in chloroform), m. p. 143°, was 9.2 g. or 77%.

Crystallization of 6-[α-D-Glucopyranosyl]-D-glucose.—Six grams of (IV), $[\alpha]^{25}$°D +98.0° in chloroform, was deacetylated catalytically with barium methylate at 0°. The barium was precipitated with 0.5 N sulfuric acid and removed by filtration as barium sulfate. A colorless solution, *p*H 7.0, resulted. Concentrated *in vacuo* to a sirup and taken up in ethanol the deacetylated material crystallized during several days as long prisms. Recrystallized under similar conditions the sugar was separated by filtration, washed and dried to constant weight at 98°. The dry crystalline substance melted at 120° and had an equilibrium $[\alpha]^{25}$D value (c, 1.2 in water) of +120° mutarotating downwards. Its M_{Cu} value (c, 1) was 97%; yield, 2.3 g.

Anal. Calcd. as $C_{12}H_{22}O_{11}$: C, 42.1; H, 6.43. Found: C, 41.9; H, 6.66.

Acknowledgment.—The authors are indebted to Dr. N. N. Hellman for the X-ray photographs, Mr. C. H. Van Etten and Mrs. M. B. Wiele for the microanalyses, to Dr. L. J. Wickerham for the distillers' yeast, *Saccharomyces cerevisiae* (NRRL 567), and to Mr. R. W. Haines for the photomicrographs.

Summary

1. Waxy corn starch was exhaustively hydrolyzed with enzymes and the fermentable sugars removed by fermentation.

2. A disaccharide, apparently the anomalous unit, was isolated from the unfermentable residue in the form of three crystalline derivatives.

3. The three derivatives were shown to be interconvertible.

4. The structure of the disaccharide was proved to be 6-[α-D-glucopyranosyl]-D-glucose through its octaacetyl derivative (IV) which is identical with octaacetyl-6-[α-D-glucopyranosyl]-β-D-glucose isolated from dextran hydrolyzates and identified by periodate analyses of the methyl glycoside of the disaccharide.

5. In a second similar experiment the hydrolyzate was not fermented. The principal products, D-glucose and isomaltose, were separated by sorption and desorption on carbon–Celite columns.

6. The preparative procedure for 6-[α-D-glucopyranosyl]-D-glucose from starch has been simplified. The new disaccharide has been isolated for the first time as a crystalline substance.

PEORIA 5, ILLINOIS RECEIVED SEPTEMBER 16, 1948

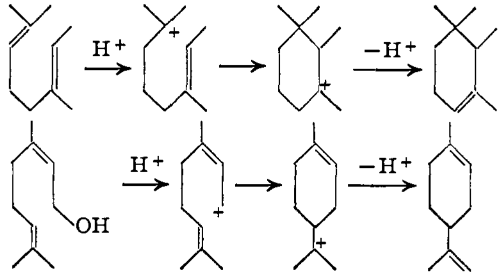
[CONTRIBUTION FROM THE STERLING CHEMICAL LABORATORY OF YALE UNIVERSITY]

A New Synthesis of the Cyclopentane Ring with Notes on the Biological Origin of Terpenes and Sterols[1,2]

BY PHILIP G. STEVENS[3] AND SAMUEL C. SPALDING, JR.[4]

The great rarity in nature of monocyclic cyclopentanes stands in sharp contrast to the abundance of cyclohexanes. This is particularly noticeable in the terpene field in which, thus far, no authentic case of the occurrence of a monocyclic cyclopentane terpenoid, sesqui, or diterpenoid is known to exist.[5] Indeed the only cyclopentane rings in this field are those in which the five-membered ring is fused[6] to another larger ring such as in the azulenoids, in perhaps a few complex pentacyclic triterpenes, and in the partially isoprenic steroids.

In the case of the terpenes, sesqui-terpenes, and their derivatives, the mode of formation in nature is considered to involve a cyclization of an acyclic dienic[7] precursor, in the manner typified either by the formation in the presence of acids of cyclomethylgeraniolene from methylgeraniolene, or by the formation of dipentene from geraniol.[8] In each of these ring formations, a carbonium ion appears to be formed first, which then adds to a double bond—a mechanism similar to that proposed by Whitmore for the polymerization of isobutene[9]



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[1] Presented before the Organic Division of the American Chemical Society at Atlantic City, N. J., April 15, 1947.

[2] From a dissertation submitted in partial fulfillment for the degree of Doctor of Philosophy by Samuel C. Spalding, Jr., in 1947 to Yale University.

[3] Present address: The General Aniline and Film Corporation, New York, N. Y.

[4] Present address: The Devoe and Raynolds Company, Inc., Louisville, Ky.

[5] The structures advanced for lanceol (Bradfield, Francis, Penfold and Simonsen, *J. Chem. Soc.*, 1619 (1936) and for nepatalic acid (McElvain, Bright and Johnson, THIS JOURNAL, **63**, 1558 (1941); McElvain, Walters and Bright, *ibid.*, **64**, 1828 (1942)) are too uncertain for these substances to be considered as exceptions to this statement; and the cyclopentyl ketone of Naves (*Helv. Chim. Acta*, **27**, 51 (1944)) is not a terpenoid. In any case it is probably a degradation product of fenchene. The cyclopentyl terpenoid isolated by Schmidt (*Ber.*, **80**, 528 (1947)) from Spanish eucalyptus oil (yield only 0.005%) may be an artifact.

[6] Bridged ring terpenes like camphene, etc., are considered to be cyclohexanes, not cyclopentanes.

[7] Or trienic, etc.

[8] Compare Butz, Butz and Geddes, *J. Org. Chem.*, **5**, 179 (1940).

[9] Compare Bloomfield, *J. Chem. Soc.*, 289 (1943).

These cyclic compounds formed thus are termed primary ring compounds, as distinguished from those formed by fission or rearrangement from other ring compounds. In every case a six-membered ring is formed from the acyclic diene, although from the standpoint of ring strain, it might be expected that cyclopentanes would arise concurrently with cyclohexanes.[10,11]

The most important class of cyclopentanes with fused rings is that of the steroids. The biological origin of these substances is still obscure, but the suggestion has been made by Robinson[12] that the triterpene squalene could, on cyclization, accommodate the sterol skeleton. A more plausible scheme has been advanced by Bryant[13] in which the tetraterpene carotene is the sterol precursor. In this latter case, the five-membered ring is represented as formed at the central tail-to-tail isoprenoid section of the molecule. It seemed worthwhile, therefore, to try to prepare cyclopentanes from suitably selected acyclic dienes, and thus in a way test Bryant's hypothesis, because, even though today it is thought by some that the sterol skeleton is built up from C_2 or other small units, it has not been shown that these C_2 units are not first condensed to a carotenoid, which is then converted to a sterol.

The first attempts to form specially a cyclopentane ring from a simple diene in the presence of acids was made by Bedoukian[14] with dimethallyl, but without success in spite of the diene's close similarity to geraniolene; the only cyclic product isolated was 2,2,5,5-tetramethyltetrahydrofuran. It was clear that it would be necessary to use a diene more closely akin to the central tail-to-tail section of the carotene molecule.

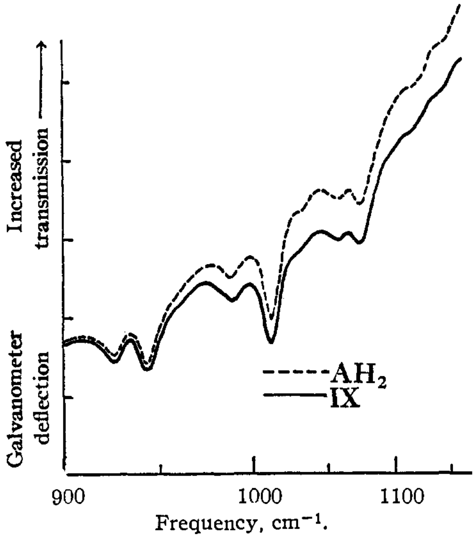
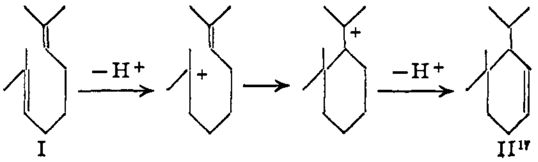


Fig. 1.

Since simple dienes with terminal isopropylidene groups have not as yet been cyclized[15,16] it was deemed advisable to see if such groups would interfere with cyclization because of some steric effect. To this end, 2,8-dimethylnonadiene-2,7 (I), which should yield the easily-formed six-membered ring, was treated with phosphoric acid. As expected, the product formed was cyclic, and almost certainly must be 1,1-dimethyl-2-isopropylcyclohexene (II), since its infrared absorption spectrum shows in the region of 1365–1385 cm.$^{-1}$ a well-defined doublet characteristic of an isopropyl group. Furthermore the molecular parachor indicates both the isopropyl and *gem*-methyl groups.



I II[17]

The diene which most closely resembles the tail-to-tail section of carotene, and which might then be expected to form a five-membered ring is 2,7-dimethyloctadiene-2,6 (III). On treatment with phosphoric acid it was found to cyclize readily, forming however a mixture of products.

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[10] Zonis (*J. Gen. Chem. U. S. S. R.*, **9**, 2191 (1939)) reported the formation of 3,3-dimethylcyclopentadiene (b. p. 108–111°) from 5-methyl-5-hydroxy-1,3-hexadiene, but this exception to the above statement requires confirmation. From the above boiling point, it would appear that Zonis may have obtained dihydrotoluene. Compare Alder and Windemuth (*Ann.*, **543**, 28 (1940)), and footnote 16.

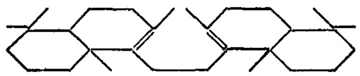
[11] Cyclopentane ring closure involving an aromatic ring (compare Bogert and Davidson, THIS JOURNAL, **56**, 185 (1934)) can occur, but these closures are not considered here as germane to the terpene and allied fields.

[12] Robinson, *J. Soc. Chem. Ind.*, **53**, 1062 (1934).

[13] Bryant, *ibid.*, **54**, 907 (1935).

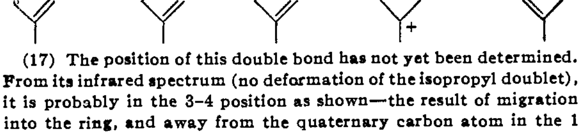
[14] Bedoukian, Dissertation, McGill University, 1941.

[15] The closest approach is the cyclization of methylgeranic acid, the structure of the products from which are still undetermined (Tiffeneau, *Compt. rend.*, **146**, 1155 (1908)). Petrov and Sanin, (*J. Gen. Chem.* (*U. S. S R.*), **9**, 2129 (1939)) probably cyclized 2,7-dimethyloctadiene-2,6, (III), but did not realize it. Heilbron, Kamm and Owens (*J. Soc. Chem.*, 1630 (1926) attempted to cyclize squalene completely, but failed to achieve the final ring closure to a pentacyclic compound. Since in all probability their final product had the structure



it can be seen that direct ring closure to either a six- or five-membered ring is equally hindered, because both ring closures would generate two adjacent quaternary carbon atoms. This failure to cyclize suggests that structures with two such adjacent quaternary carbon atoms attributed by Ruzicka, Goldberg and Hofmann (*Helv. Chim. Acta*, **20**, 324 (1937)) to compounds like the saponin oleanolic acid and similar substances are incorrect as far as the position of one of the methyl groups goes.

[16] The triene 2,5-dimethylhexatriene, corresponding to the diene dimethallyl has been cyclized by Zal'kind (*C. A.*, **17**, 3477 (1923)) to dihydro-*p*-xylene (compare ref. 8). This ring closure can be explained as follows



[17] The position of this double bond has not yet been determined. From its infrared spectrum (no deformation of the isopropyl doublet), it is probably in the 3–4 position as shown—the result of migration into the ring, and away from the quaternary carbon atom in the 1 position. Compare Linstead and Elliott (*J. Soc. Chem.*, 660 (1938)).

TABLE I

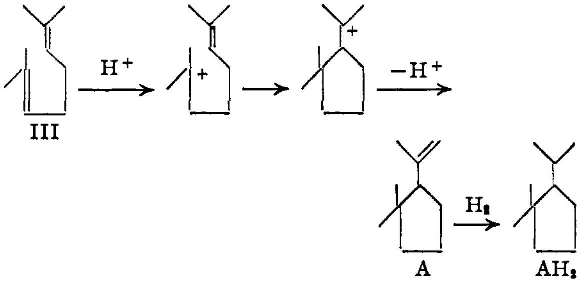
Compound	A	AH_2	IX	B	BH_2a	BH_2b
B. p. °(757 mm.)[a]	150.9	163.0	163.0	161.1[b]	166.5	167.0
B. p. °(36 mm.)	60.5	70.2	70.2	68.2	74.9	75.5
n^{25}_D	1.4410	1.4377	1.4377	1.4479	1.4390	1.4420
d^{25}_4	0.7948	0.7959	0.7959	0.8107	0.8006	0.8079
M_D	45.93	46.29	46.29	45.67	46.08	45.93
M_D (calcd.)	45.75	46.22	46.22	45.71	46.18	46.18

[a] Modified Cottrell apparatus—mercury completely in vapor. [b] 758 mm.

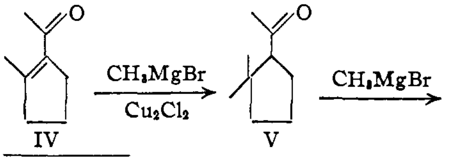
Separation of these by careful distillation at 36 mm. yielded three distinct substances with the boiling points: A, 60.5°; B, 68.2°; C, 72.0°.

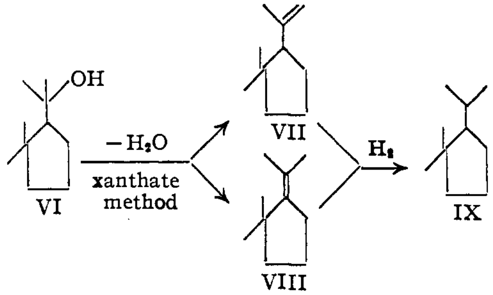
The relative amounts of A, B and C varies with the experimental conditions. When the cyclization is carried out with phosphoric acid slowly under a fractionating column, taking off the low-boiling material progressively, the relative amounts of A, B and C are approximately 31, 4 and 65%, respectively. If, however, cyclization takes place during the dehydration of the glycol used to prepare the diene, so that the cyclization treatment is not prolonged, the yields are about 74, 23 and 3%. It can be seen therefore that A is very likely the first cyclic product formed, and that B and C are formed from A.[18]

Compound A.—As a determination of the structure of A by ozone or permanganate degradation was unsuccessful, it was clear that proof of its structure could be had only by an independent synthesis. Rather than attempt a synthesis of A, that of the reduction product AH_2 was undertaken. In the belief that AH_2 was 1,1 - dimethyl - 2 - isopropylcyclopentane, this hitherto unknown substance was prepared by an unequivocal synthesis. The two substances were found to have identical physical constants and, in addition, identical infrared absorption spectra. There can be no doubt but that AH_2 has the above structure. The position of the double bond in A is still uncertain. From the strongly deformed isopropyl doublet of the infrared spectrum, it is probably in the exocyclic position as shown.



The synthesis of AH_2 was carried out as follows





The formation of the hitherto unknown saturated ketone V from IV is an interesting variant of the work of Kharasch and Tawney[19] with 1,4 addition occurring practically exclusively. The dehydration of VI by the Chugaev[20] xanthate method assured the retention of the original carbon skeleton. In Table I are the physical properties of compounds A, AH_2, IX, B, BH_2a and BH_2b.

It has now been established[21] that the peaks and valleys in the infrared spectrum are finger prints of a compound's structure, and that each peak, etc., is to be considered a physical constant just as definite and important for identification purposes as any other physical constant such as the boiling point or refractive index. Although four different physical constants of AH_2 and IX had already been found to be identical, it was desirable to compare many more constants. Ac-

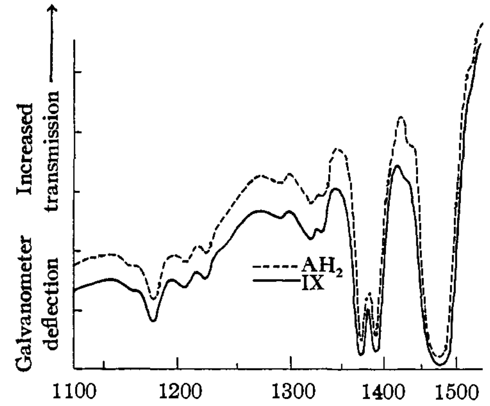


Fig. 2.

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[18] No cyclic ether was found at any time, contrary to the reports of Michiels (*Bull. soc. chim. Belg.*, **27**, 25 (1912)).

[19] Kharasch and Tawney, THIS JOURNAL, **63**, 2308 (1941).

[20] Chugaev, *Ber.*, **32**, 3332 (1899).

[21] R. B. Barnes, Liddel and Williams, *Ind. Eng. Chem., Anal. Ed.*, **15**, 659 (1943); Symposium, *Trans. Faraday Soc.*, **41**, 171 (1945).

cordingly qualitative infrared spectrograms of the two compounds were made[22]; a critical region thereof—between wave-frequencies 910 and 1500 cm.$^{-1}$—is reproduced below. It can be seen that the peaks and valleys of each spectrogram exactly coincide, and the same can be said throughout the entire region examined from 775 to 4000 cm.$^{-1}$. Clearly AH_2 and IX are the same substance.

Compounds B and C.—From analyses and the number of double bonds, B is also cyclic. Lack of time prevented elucidation of its structure; it is possible that it and C (d^{24}_4 0.8289, n^{25}_{D} 1.4623) are isomers of cyclodihydromyrcene, formed as the result of molecular rearrangements.

Conclusions

The formation of 1,1-dimethyl-2-isopropenylcyclopentane from 2,7-dimethyloctadiene-2,6 has now clearly demonstrated that cyclopentane ring formation occurs without difficulty, as long as the acyclic diene is properly constituted so that cyclohexane ring formation is difficult, either because of steric factors, or because migration of the double bonds (or a rearrangement of the initially formed carbonium ion) to positions favorable for cyclohexane formation involves too much energy. It further demonstrates that Bryant's hypothesis for sterol formation from carotene is not untenable, on formal grounds at least. It should also be pointed out that only those dienes with isoprenic tail-to-tail unions have structures which do not allow the above-mentioned ease of migration of the double bond or rearrangement of the carbonium ion. An intimate biological relationship between the absence of tail-to-tail unions in acyclic mono-, sesqui- and diterpenoids, and the rarity of cyclopentanes seems inescapable.

Thanks are due to Professor Werner Bergmann for help and suggestions in the latter part of this work, and to the Stamford Research Laboratories of the American Cyanamid Company through whose courtesy the infrared measurements cited in this paper were obtained.

Experimental

2,8-Dimethylnonadiene-2,7, I.—47.8 g. of 2,8-dimethylnonadiol-2,8 (prepared from 1,5-dimagnesiumdibromopentane and acetone[23]) dissolved in 100 ml. of acetic acid was treated with hydrogen bromide in the cold, whereupon a reddish oil separated. The reaction mixture was poured into water, extracted with low-boiling petroleum ether, the ether washed with water, and evaporated *in vacuo*. The heavy straw-colored dibromide remaining was refluxed in a nitrogen atmosphere with 60 g. of pyridine for three hours. The diene solution, after cooling, was treated with water, and was extracted with dilute sulfuric acid, with aqueous potassium carbonate, water, then dried and distilled, b. p. 94° (36 mm.), 187° (755 mm.), n^{25}_{D} 1.4458, d^{25}_4 0.7717, M_{D} calcd. 52.06; found 52.60.

1,1-Dimethyl-2-isopropylcyclohexene, II.—Equal parts of the diene and 85% phosphoric acid were refluxed gently at 36 mm. under a four-foot Podbielniak-type spiral column. The head temperature slowly fell from 94 to 86°, and the whole of the volatile material was taken off at this temperature; yield 85%. On redistillation, the new material boiled sharply at 86.7° (36 mm.), n^{25}_{D} 1.4570, d^{25}_4 0.8260. *Anal.* Calcd. for $C_{11}H_{20}$: C, 86.8; H, 13.2. Found: C, 86.7; H, 13.3. 62.9 mg. absorbed 10.05 ml. of hydrogen at 296.7°K. and 750.6 mm., equivalent to 0.99 double bond. Parachor calcd.: 423.0[24]; found 424.

2,7-Dimethyloctadiene-2,6, III.—Twenty grams of 2,7-dimethyloctadiol-2,7 (prepared from ethyl adipate and methylmagnesium chloride according to the method of Zelinskii[25]) was slowly distilled with a crystal of iodine, dehydration occurring readily. The yield of diene after careful fractionation was 78%, b. p. 78° (36 mm.), 168° (760 mm.), n^{25}_{D} 1.4450, d^{25}_4 0.7704, M_{D} calcd. 47.44; found 47.76.[26]

1,1-Dimethyl-2-isopropenylcyclopentane, A.—Twenty grams of diene was refluxed with 10 ml. of 85% phosphoric acid under a fractionating column. The head temperature soon fell to 60° at 36 mm. As three different substances were found to be formed, the cyclization was repeated with the diene prepared from 680 g. of crude glycol. Due to traces of dilute sulfuric acid therein, the diene was found, after refluxing with iodine, to have already cyclized to a large extent. Using a 100-plate $^3/_4$" Stedman column, separation of the products at 36 mm. was very sharp:

Fraction	B. p., °C.	%	
1	60.5	49.2	Compound A
2	67.0	9.5	Acyclic diene
3	68.2	15.7	Compound B
4	72.0	1.8	Compound C
5	78.0	24.3	Acyclic diene, III

Fraction 2, (d^{25}_4 0.7611, n^{25}_{D} 1.4310) from its hydrogen absorption had 1.82 double bonds—hence is essentially open-chained and must be an isomer of the original diene. Fraction 5 was the original diene. Fractions 1, 3 and 4 represented the cyclic products. The boiling point of fraction 1 (compound A) on refractionation through the Stedman column did not change. *Anal.* Calcd. for $C_{10}H_{18}$: C, 86.9; H, 13.1. Found: C, 86.8; H, 12.7. 53.23 mg. absorbed at 298.1°K. and 746 mm.; 9.00 ml. of hydrogen, equal to 0.94 double bond. Perbenzoic acid titration showed 1.02 double bonds.

Fraction 5 (60 ml.) was refluxed with 10 ml. of 85% phosphoric acid under the Podbielniak-type column, yielding the following fractions at 36 mm.:

Fraction	B. p., °C.	%	
6	60.5	30.9	Compound A
7	68.2	4.4	Compound B
8	72.0	64.7	Compound C

1,1-Dimethyl-2-isopropylcyclopentane, AH_2.—Twenty ml. of A was hydrogenated using Adams platinum catalyst. The reduced product boiled sharply at 70.2° (36 mm.). *Anal.* Calcd. for $C_{10}H_{20}$: C, 85.6; H, 14.4. Found: C, 86.0; H, 14.5.

Compound B.—61.69 mg. of B absorbed 10.60 ml. of hydrogen at 296.6°K. and 732.2 mm., equivalent to 0.94 double bond. *Anal.* Calcd. for $C_{10}H_{18}$: C, 86.9; H, 13.1. Found: C, 86.9; H, 13.3.

Compound BH_2.—Ten ml. of B was hydrogenated; the product on distillation yielded two cuts, *a* and *b*. *Anal.* Calcd. for $C_{10}H_{20}$: C, 85.6; H, 14.4. Found for *a:* C, 85.9, 14.6; for *b*: C, 85.8; H, 14.5.

Synthesis of **1,1-Dimethyl-2-isopropylcyclopentane IX. 1. 1,1 - Dimethyl - 2 - acetylcyclopentane, V.**—Thirteen grams of 1-acetyl-2-methylcyclopentene-1 (prepared ac-

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[22] No attempt was made to obtain quantitative spectrograms, and the two curves are drawn one below the other merely to facilitate comparison. Any change in the difference in amount of transmission at the peaks and valleys of the two spectra can be attributed to the qualitative nature of these spectra.

[23] von Braun and Sobecki, *Ber.*, **44**, 1923 (1911).

[24] Using the atomic values of Mumford and Phillips, *J. Chem. Soc.*, 2112 (1929).

[25] Zelinskii, *J. Russ. Phys.-Chem. Soc.*, **38**, 931 (1906).

[26] Henne and Chanan (THIS JOURNAL, **66**, 394 (1944)) reported b. p. 168° (760 mm.), n^{20}_{D} 1.4478, d^{20}_4 0.7755, M_{D} found 47.71.

cording to Haworth[27] or Zelinskii[28]) dissolved in 300 ml. of ether was added slowly to a stirred mixture of methylmagnesium bromide (3.1 g. of Mg in 200 ml. of ether) and 1 g. of freshly prepared cuprous chloride, so that no refluxing occurred. After twelve hours, the reaction products were treated with dilute sulfuric acid, the ether layer separated and distilled, yielding 9 ml. of saturated ketone, b. p. 86.8° (36 mm.), which was then purified through the semicarbazone, m. p. 172.5° (from 50% ethanol). *Anal.* Calcd. for $C_{10}H_{19}N_3O$: C, 60.9; H, 9.7; N, 21.3. Found: C, 60.9; H, 9.8; N, 21.3.[29] Regeneration by steam distillation from oxalic acid yielded the pure ketone with the boiling point unchanged.

2. **Dimethyl-2,2-dimethylcyclopentyl Carbinol, VI.**—16.8 g. of the above ketone was added slowly to 0.22 mole of methylmagnesium bromide solution so that no refluxing occurred. After twelve hours stirring, the products were treated with aqueous ammonium chloride, extracted with ether, and dried over anhydrous potassium carbonate. The material was then distilled directly therefrom at 0.5 mm., the bath temperature never exceeding 50°. The yield of crude carbinol was 90% or 16.8 g., d^{25}_4 0.9045, n^{25}_D 1.4580. *Anal.* Calcd. for $C_{10}H_{20}O$: C, 76.8; H, 12.9. Found: C, 78.1; H, 13.4.

3. **1,1-Dimethyl-2-isopropenyl- and -isopropylidenecyclopentane, VII and VIII.**—Thirty-one grams of biphenyl dissolved in dimethylcellosolve was treated with 3 g. of sliced sodium.[29] After the sodium biphenyl had been completely formed, the solution was drawn off into a dropping funnel, and added to 16.8 g. of the above carbinol, dissolved in 100 ml. of decalin, until a permanent color persisted.[31] Seventeen ml. of carbon disulfide was then added, followed two hours later by 16 ml. of methyl iodide. After standing overnight, the reaction products were distilled at 760 mm., until biphenyl began to distil over. The decomposition of the xanthate occurred readily, and was complete by the time the temperature reached 100°. The product was then distilled approximately 5 ml. of unsaturated material passing at about 152°, and 10 ml. at 165°; yield 80%.

4. **1,1-Dimethyl-2-isopropylcyclopentane, IX.**—The mixture of unsaturated products above was reduced in ethanol with Adams platinum catalyst. Unfortunately the reduction proceeded with great difficulty, and much material was lost by manipulations. Finally, the unreduced material was removed from the reduced by extraction with a 1:1 mixture of concentrated sulfuric acid and acetic anhydride. Thus one gram of completely saturated material was obtained (no color with tetranitromethane). On distillation, it had identical physical properties with AH_2. *Anal.* Calcd. for $C_{10}H_{20}$: C, 85.6; H, 14.4. Found: C, 84.9; H, 14.5.

Summary

1. 2,7-Dimethyloctadiene-2,6 undergoes ring closure in the presence of phosphoric acid to 1,1-dimethyl-2-isopropenylcyclopentane.

2. A possible biological relationship between rarity in the terpene field of tail-to-tail isoprenic unions and of cyclopentanes has been suggested.

New York, N. Y.
Louisville, Ky.

Received May 21, 1948

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[27] Haworth, *J. Chem. Soc.*, 1249 (1913).

[28] Zelinskii and Tarassowa, *Ann.*, **508**, 141 (1934).

[29] Thanks are due to Mr. James Fang of the Yale Graduate School for this analysis.

[30] Scott, Walker and Hinsley, This Journal, **58**, 2442 (1936).

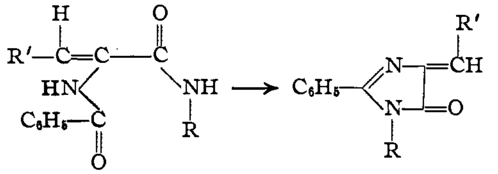
[31] Stevens and Deans, *Can. J. Research*, **17B**, 290 (1939).

[Contribution from the Division of Medicinal Chemistry, The Squibb Institute for Medical Research

Analogs of Aspergillic Acid. III. Synthesis of Cyclic Hydroxamic Acids with a Five-membered Ring[1]

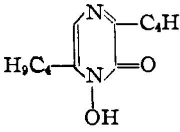
By Elliott Shaw and Jean McDowell

Erlenmeyer[2] and Mohr and Geis[3] have observed the facile cyclization of certain α-acylamino amides to 5-imidazolones. For example, α-benzoylaminocinnamamide (I, R = H, R′ = C_6H_5) forms the imidazolone (II, R = H, R′ = C_6H_5) when heated a few minutes in aqueous alkali.[2]



(I) (II)

Similar changes have now been studied in the hydroxamic acid series and the goal of preparing II, R = OH, has been achieved by an acid cyclization of the open acid (V) to VII. This acid is a five-membered ring analog of the antibiotic, aspergillic acid (III).



(III)

As the starting point of this synthesis, the reaction of the azlactone, 2-phenyl-4-benzylidene-5-oxazolone (IV), with methanolic hydroxylamine was undertaken. The course of the reaction was found to be dependent on the dryness of the methanolic hydroxylamine employed. When prepared from hydroxylamine hydrochloride and methanolic potassium hydroxide, methanolic hydroxylamine also contains the water of neutralization. Addition of the oxazolone (IV) to methanolic hydroxylamine prepared in this way resulted in gradual precipitation, over a period of several days, of the cyclic hydroxamic acid (VII) in low yields. If, however, methanolic sodium methylate was used to liberate hydroxylamine from its hydrochloride, the reaction of the resultant anhydrous solution with the oxazolone (IV) did not lead directly to the cyclic hydroxamic acid (VII). The initial product separating from the reaction mixture was identified as the β-hydroxylamino hydroxamic acid (VI) arising from both addition to the double bond and cleavage of the oxazolone ring. From the mother liquor of this material, the hydroxamic acid (V) was obtained.

Although the desired cyclic acid (VII) had been obtained in a single step from the oxazolone (IV)

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[1] For the previous paper in this series see Lott and Shaw, This Journal, **71**, 70 (1949).

[2] Erlenmeyer, *Ber.*, **33**, 2036 (1900).

[3] Mohr and Geis, *ibid.*, **41**, 798 (1908).