Identity of Hibalactone and Savinin

By Mitsuo Masumura and F. Shigeo Okumura

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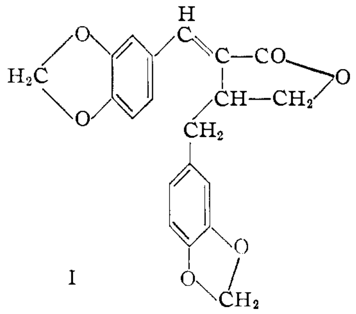
One of us has reported[1] that hibalactone (I), $C_{20}H_{16}O_6$, m.p. 146–146.5°, $[\alpha]^{23}D$ −87° (chloroform), isolated from young leaves of chyabohiba, nikohiba or *Chamaecyparis obtusa* (Cupressiacenae),[2] has the structure shown in Cmpd. I. This structure was established by the production of piperonylic acid, piperonal and oxalic acid either by permanganate oxidation or ozonolysis, by hydrogenation (Raney nickel or sodium amalgam) to (+)-isohinokinin[3] (major product) and (−)-hinokinin[3] (minor product) by spectroscopic evidence pointing to an α,β-unsaturated lactone structure, and by studies of the hydrolysis, nitration and bromination products of I.



I

Independently of these studies on hibalactone, the structure of savinin, m.p. 146.2–147.3°, $[\alpha]^{22}D$ −88° (chloroform), isolated from the dried needles of *Juniperous sabina*, was reported by Schrecker and Hartwell,[4] and we found, quite unexpectedly, that its structure coincides with that of hibalactone. A comparison of the properties of these two substances and their derivatives is given in Table I.

Table I

Comparison of Savinin and Hibalactone

	Savinin, λ_{max}^{EtOH} 334, 293, 237			Hibalactone, λ_{max}^{EtOH} 333, 292, 237		
	M.p., °C.	$[\alpha]^tD$	t, °C.	M.p., °C.	$[\alpha]^tD$	t, °C.
Pure	146.2–147.3	− 88°[a]	22	146–146.5	− 87°[a]	23
Dibromide				181–182	−108[c]	28.5
Tetrabromide				238–239		
Dinitro deriv.				247–248	+157[d]	28.5
Mononitro deriv.				164–165	+143[c]	29
Lactonic acid	108	+ 64[b]	20	107		
Dihydro derivs.	116.3–116.7	+107[a]	21	116–117	+106[e]	19
Isodihydro deriv.				63–64	− 33[a]	19

[a] Chloroform. [b] Ethanol. [c] Benzene. [d] Pyridine. [e] Acetone.

A sample of savinin kindly provided by Dr. Schrecker gave no depression of m.p. when mixed with I, and the infrared spectra[5] of the two substances in chloroform solution showed no significant differences. Therefore, it is concluded that savinin and hibalactone are identical.

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[1] M. Masumura, *J. Chem. Soc. Japan*, in press. Presented in part at the 7th General Meeting of the Chemical Society of Japan, Tokyo, April 4, 1954.

[2] "Chyabohiba" is a garden kind of *Chamaecyparis obtusa* and "nikohiba" is a garden kind of *Chamaecyparis pisifera*.

[3] S. Keimatsu and T. Ishiguro, *J. Pharm. Soc. Japan*, **56**, 103, 901 (1936).

[4] A. W. Schrecker and J. L. Hartwell, This Journal, **76**, 4896 (1954).

[5] Kindly determined by S. M. Aronovic, Department of Chemistry, University of Wisconsin, on a Baird Associates, Inc., Spectrophotometer.

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Transformation of D-Allose to 1,6-Anhydro-β-D-allopyranose in Acid Solution[1,2]

By James W. Pratt and Nelson K. Richtmyer

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It has been recognized for some time that when sugars having the *altro* or *ido* configuration are heated in dilute aqueous acid an equilibrium is established in which a considerable part of the carbohydrate is present in the form of a monomeric non-reducing anhydride.[3] More recently the *gulo* configuration[2,3a] has been added to the list, and in addition it has been established that D-glucose is converted to levoglucosan (1,6-anhydro-β-D-glucopyranose) to a very limited extent under these conditions.[4]

We have extended the study of this reaction to include the *allo* configuration and now wish to report that when D-allose (I) is heated in dilute aqueous acid an equilibrium is established in which 1,6-anhydro-β-D-allopyranose (II) is present to the extent of approximately 14%. Isolation and crystallization of the anhydride were readily accomplished and the new compound melts at 179–180° and shows $[\alpha]^{20}D$ −76° in water.

In order to establish the structure of the new anhydride, we first oxidized with periodate in the usual manner. The consumption of two molar equivalents of oxidant and the liberation of one molar equivalent of acid were unequivocal evidence of the presence in the anhydride of three contiguous secondary hydroxyl groups. The resulting dialdehyde was oxidized further with bromine, and the sodium salt of the dibasic acid III condensed with *p*-phenylphenacyl bromide. A crystalline diester was obtained whose physical constants, including a mixed melting point, were in agreement with those reported for the compound obtained similarly from levoglucosan.[2] Since the structure of levoglucosan is well established, our new anhydride must have the analogous structure of 1,6-anhydro-β-D-allopyranose.

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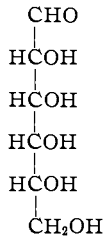
[1] Presented in part before the Division of Carbohydrate Chemistry at the New York Meeting of the American Chemical Society, September 17, 1954; see Abstracts of Papers, page 22D.

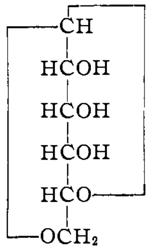
[2] For the preceding paper on anhydro sugars, see L. C. Stewart and N. K. Richtmyer, This Journal, **77**, 1021 (1955).

[3] (a) L. C. Stewart and N. K. Richtmyer, *ibid.*, **77**, 424 (1955); (b) J. W. Pratt, N. K. Richtmyer and C. S. Hudson, *ibid.*, **75**, 4503 (1953).

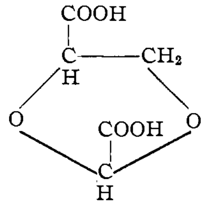
[4] A. Thompson, K. Anno, M. L. Wolfrom and M. Inatome, *ibid.*, **76**, 1309 (1954); L. D. Ough and R. G. Rohwer, Abstracts of Papers, New York Meeting of the American Chemical Society, Sept. 12–17, 1954, page 16D.



I



II



III

Experimental

D-Allose (I).—A solution of 100 g. of D-ribose in 700 ml. of water was cooled to about 3° and to this was added a solution of 43.5 g. of sodium cyanide in 300 ml. of water, also cooled to about 3°. The reaction flask, still immersed in an ice-bath, was allowed to stand in the refrigerator at 5° for 24 hours. At this time the solution exhibited no reducing activity toward Fehling solution. The clear, pale-yellow solution was heated on the steam-bath for 2 hours, and then boiled gently for an additional 6 hours to hydrolyze the nitriles and expel ammonia. The solution, while still hot, was passed through a column of Amberlite IR-120 cation-exchange resin in the calcium cycle (prepared by washing the resin with 10% aqueous calcium chloride and then thoroughly with water). The sodium salts of D-allonic and D-altronic acids were thus converted to calcium salts, and upon concentration of the solution *in vacuo* calcium D-altronate hemiheptahydrate was obtained in a yield of 70.4 g. (43.6%). Calcium was removed from the mother liquor by passing it through Amberlite IR-120-H, and the eluate was concentrated *in vacuo* to a thick sirup from which crystalline D-allonolactone was obtained by the usual procedures. From several runs an average of 31.4% of once-recrystallized D-allonolactone was obtained. Additional calcium D-altronate and D-allonolactone were obtained by reworking the mother liquors. The over-all yields (average of seven runs) were 47% of calcium D-altronate and 34% of D-allonolactone.

D-Allonolactone was reduced with sodium amalgam in the presence of sodium hydrogen oxalate[5,6] to yield 71% of D-allose. This sugar showed $[\alpha]^{20}\mathrm{D}$ $+1.4°$ (2.75 min.) → $+14.4°$ (final, 2.5 hr.) in water (c 6.4), in excellent agreement with the values $-0.2°$ → $+14.4°$ reported by Phelps and Bates.[7]

1,6-Anhydro-β-D-allopyranose (II).—In a preliminary experiment a solution of 0.449 g. of D-allose was dissolved in 0.2 *N* hydrochloric acid and the volume adjusted to 25 ml. This solution showed $\alpha^{20}\mathrm{D}$ $+0.53°$ in a 2-dm. tube. The flask was immersed in a steam-bath for 12 hours. Observations of the rotation made at regular intervals showed a decrease to a constant value of $+0.11°$. Estimation of reducing sugar by the Hanes[8] modification of the Hagedorn and Jensen[9] ferricyanide procedure showed a drop in reducing activity to 81% of the original value. From this value, the specific rotations of the sugar and of its anhydride, and the final observed rotation, it appears that 13% of the sugar was converted to the anhydride. With a correction for the 6% which has disappeared, this means that the equilibrium mixture contains 14% anhydride and 86% sugar. It must be noted that these calculations assume no optically active material other than D-allose and its anhydride. This process was repeated with 40.5 g. of D-allose in 250 ml. of 0.2 *N* hydrochloric acid. The solution was filtered with carbon and passed through Duolite A-4 anion-exchange resin. The deionized solution was concentrated under reduced pressure and the sirup taken up in 200 ml. of absolute alcohol. From this solution 31.7 g. of D-allose was recovered. The mother liquor was concentrated in a stream of air, the sirup taken up in water, and its solution heated for two hours on the steam-bath with barium hydroxide. Excess barium hydroxide was removed by the addition of solid carbon dioxide. The solution was decolorized and filtered, passed through Amberlite IR-120 and Duolite A-4 ion-exchange resins and then concentrated to a sirup under reduced pressure. Taken up in absolute ethanol the material crystallized, yielding 3.8 g. of clear, water-white prisms which on further recrystallization melted at 178.5–180° and showed $[\alpha]^{20}\mathrm{D}$ $-75.8°$ in water (c 0.6).

Anal. Calcd. for $C_6H_{10}O_5$: C, 44.44; H, 6.22. Found: C, 44.28; H, 6.20.

Tri-*O*-acetyl-1,6-anhydro-β-D-allopyranose.—To a solution of 0.85 g. of 1,6-anhydro-β-D-allose in 20 ml. of dry pyridine was added, dropwise, 10 ml. of acetic anhydride. The reaction mixture was allowed to stand at room temperature for 24 hours and then poured over cracked ice and solid sodium bicarbonate. The resulting solution was extracted with chloroform and the washed and dried chloroform extract was concentrated to dryness in a stream of air. The crystalline residue was dissolved in a mixture of ether (15 ml.) and chloroform (5 ml.) from which, by the addition of 10 ml. of pentane, the crystalline solid was obtained in the form of extremely thin, dentelated platelets which melted at 88–89° and showed $[\alpha]^{20}\mathrm{D}$ $-70.8°$ in chloroform (c 1).

Anal. Calcd. for $C_{12}H_{16}O_8$: C, 50.00; H, 5.60; CH_3CO, 44.8. Found: C, 49.86; H, 5.61; CH_3CO, 43.4.

1,6-Anhydro-tri-*O*-*p*-tolylsulfonyl-β-D-allopyranose.—To a solution of 107 mg. of 1,6-anhydro-β-D-allose in 5 ml. of dry pyridine was added 0.9 g. (7 molar equivalents) of *p*-toluenesulfonyl chloride. The mixture was allowed to stand at room temperature for five days and then poured in a thin stream into a mixture of water and ice. The product, which crystallized readily, was filtered, washed with water and partially dried. It was then dissolved in 6 ml. of warm acetone, filtered and caused to crystallize by the cautious addition of water. The white, needle-like crystals were filtered and dried in air to yield 0.35 g. (85%) of material which melted at 157–158° and showed $[\alpha]^{20}\mathrm{D}$ $-35.0°$ in chloroform (c 0.9).

Anal. Calcd. for $C_{27}H_{28}O_{11}S_3$: C, 51.91; H, 4.52; S, 15.40. Found: C, 51.98; H, 4.80; S, 15.18.

Oxidation of 1,6-Anhydro-β-D-allopyranose with Sodium Metaperiodate.—To a solution of 0.1180 g. of the anhydride II in about 18 ml. of water was added 5.0 ml. of 0.48 *M* sodium metaperiodate solution, and the mixture was placed in the dark at 20° for 24 hours. Water was added to make the volume exactly 25 ml. and the rotation observed to be $[\alpha]^{20}\mathrm{D}$ $-14.2°$ (calculated as the expected dialdehyde), in good agreement with the values reported for levoglucosan and other 1,6-anhydro-β-D-hexopyranoses.[10] The anhydride consumed two molar equivalents of periodate and yielded one molar equivalent of acid (presumably formic) and no formaldehyde.

To a solution of 0.6 g. of the anhydride in 30 ml. of water was added 30 ml. of 0.48 *M* sodium metaperiodate solution. After 18 hours at room temperature in the dark the solution was freed of iodate and periodate by adding 3.5 g. of barium chloride dihydrate and neutralizing with a saturated barium hydroxide solution. To the filtered solution was added barium carbonate in excess and 1 ml. of bromine. The solution was kept at room temperature in the dark for 18 hours, and then was filtered, aerated to expel excess bromine, freed of bromide by shaking with silver carbonate, filtered, deionized by passage through IR-120-H, made slightly alkaline to phenolphthalein by the addition of a hot solution of strontium hydroxide, and concentrated to dryness under reduced pressure. The washed and filtered strontium salt weighed 0.3 g., showed $[\alpha]^{20}\mathrm{D}$ $+26.0°$ in water (c 0.4), and a 22.3% loss of weight on heating at 100° *in vacuo* for four hours. Corrected for the loss in weight the rotation becomes $[\alpha]^{20}\mathrm{D}$ $+33.4°$ which is not too far from the value $+36.8°$ reported for the strontium salt monohydrate obtained from 1,6-anhydro-β-D-altropyranose.[11]

Di-(*p*-phenylphenacyl) 4-D-*glycero*-1,3-Dioxolane-2,4-*cis*-dicarboxylate.—To an aqueous solution of strontium salt calculated on the basis of rotation to contain 1.56 meq. of carboxylate was added the stoichiometric amount of sodium

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[5] H. S. Isbell, J. V. Karabinos, H. L. Frush, N. B. Holt, A. Schwebel and T. T. Galkowski, *J. Research Natl. Bur. Standards*, **48**, 163 (1952).

[6] J. W. Pratt, N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **75**, 4505 (1953) (footnote 20).

[7] F. P. Phelps and F. J. Bates, *ibid.*, **56**, 1250 (1934).

[8] C. S. Hanes, *Biochem. J.*, **23**, 99 (1929).

[9] H. C. Hagedorn and B. N. Jensen, *Biochem. Z.*, **135**, 46 (1923).

[10] See reference 2, footnote 3.

[11] N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **62**, 961 (1940).

carbonate. The precipitated strontium carbonate was removed by filtration and the solution containing the sodium salt concentrated to a glass under reduced pressure. The glass was dissolved in 4 ml. of hot water, and 429 mg. of *p*-phenylphenacyl bromide and 8 ml. of ethanol were added. Although some precipitation occurred, this offered no difficulty as it was readily apparent that the character of the solid changed during the ensuing 2-hour refluxing. The mixture was allowed to cool to room temperature and filtered, yielding 0.5 g. of crude ester which after 2 recrystallizations from 40 parts of 1:1 ethanol–acetone melted at 145.5–147.5° with no depression on admixture with the ester prepared similarly by Stewart and Richtmyer from 1,6-anhydro-β-D-gulopyranose.[2]

Acknowledgment.—The authors wish to thank Mr. John T. Sipes of this Laboratory for his help in reducing D-allonolactone with sodium amalgam; and Dr. William C. Alford and his associates of the Institutes' microanalytical laboratory for carrying out the microanalyses.

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Decomposition of Quaternary Ammonium Salts. IV. Methyl Ketones

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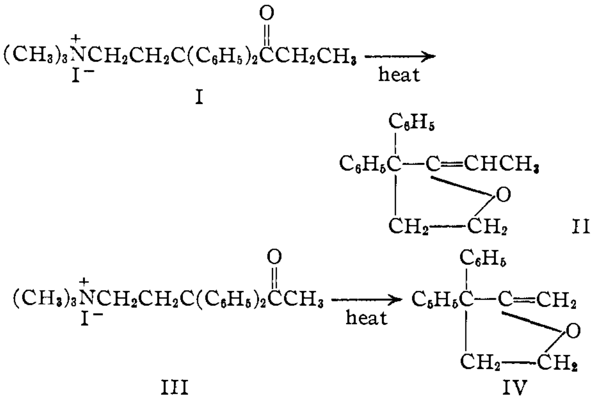
Although the decomposition of quaternary salts of the methadone (I) type to give ethylidenetetrahydrofurans[2,3] has been reported, only ethyl ketones were mentioned. This paper deals with the product obtained from the pyrolysis of the quaternary salt of a methyl ketone, 5-dimethylamino-3,3-diphenyl-2-pentanone (III). Since the product from this reaction was a liquid and all of those reported for the ethyl ketones were solids, it was felt that the reaction might not be analogous. Subsequent reactions, however, substantiate the similarity of these decompositions. The oil decolorizes bromine readily and forms adducts with hydroxylamine and 2,4-dinitrophenylhydrazine to give a product analogous to those reported[2,3] for the ethylidenetetrahydrofurans. The methylidenetetrahydrofuran (IV) gave benzophenone on chromic oxide oxidation.



Experimental

5-Dimethylamino-3,3-diphenyl-2-pentanone.—This compound was prepared according to procedures previously described.[4]

5-Dimethylamino-3,3-diphenyl-2-pentanone Oxalate.—This derivative was prepared by the addition of an excess of oxalic acid to a solution of the ketone in absolute alcohol. Upon the addition of ether the crude product, melting at 160–162°, precipitated. After several recrystallizations it melted at 163.0–163.5°.

Anal. Calcd. for $C_{19}H_{23}ON \cdot C_2H_2O_4$: C, 67.90; H, 6.79; N, 3.77. Found: C, 67.88; H, 6.92; N, 3.73, 3.76.

5-Dimethylamino-3,3-diphenyl-2-pentanonemethiodide.—An excess of methyl iodide was added to a solution of the ketone in absolute alcohol. Upon the addition of ether, an oil separated which crystallized with cooling and scratching. The solid melted at 144–148°, and after repeated crystallization from alcohol and ether melted at 151.5–152°.

Anal. Calcd. for $C_{20}H_{26}ONI$: C, 56.74; H, 6.19; N, 3.32. Found: C, 56.65; H, 6.36; N, 3.26.

Pyrolysis of 5-Dimethylamino-3,3-diphenyl-2-pentanonemethiodide.—In a 50-ml. distilling flask equipped with a receiver and thermometer there was placed 23 g. of the methiodide III. The system was evacuated to 13 mm. and the flask heated gently with a free flame. The solid melted, and in the course of about 15 minutes 8.7 g. of viscous liquid distilled at about 190°. A second fraction weighing 2.2 g. was distilled at 205–270° (13 mm.). A tarry residue remained in the flask. These distillates darkened upon standing.

The viscous liquids obtained above were treated with benzene and a small amount of white solid was filtered from each. The benzene filtrates were extracted with 5% hydrochloric acid, washed with water, and redistilled. The first fraction distilled at 188–192° (12 mm.), and weighed 7.4 g. The second fraction distilled at 195–203° (16 mm.).

Upon standing overnight in an ice-bath, a few tenths of a gram of a white solid separated from the second fraction. After recrystallization from petroleum ether and sublimation under vacuum it melted at 75–78°. It was not investigated further. The remainder of fraction 2 was shown to be the same as fraction one by the preparation of the derivative with 2,4-dinitrophenylhydrazine.

The oil obtained did not react with potassium permanganate in acetone except on long standing, but reacted rapidly with bromine in carbon tetrachloride at ice temperature, with the evolution of hydrogen bromide.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.84. Found: C, 86.26; H, 6.90.

Reactions of Pyrolysis Product of III. (a) With Hydroxylamine.—This reaction was run in the usual manner.[2] After several recrystallizations from alcohol the product melted at 168–170.5°, and after drying in the Abderhalden apparatus at 56° for 2 hours, melted at 171–172°.

Anal. Calcd. for $C_{17}H_{19}O_2N$: C, 75.80; H, 7.11; N, 5.20. Found: C, 75.94, 75.83; H, 6.93, 7.03; N, 5.20, 5.24.

(b) **With 2,4-Dinitrophenylhydrazine.**—This reaction was run in the usual way. The product was a finely divided, bright yellow powder. After several recrystallizations from benzene and petroleum ether it melted at 194.0–194.5° dec. This derivative was unstable and difficult to purify.

Anal. Calcd. for $C_{23}H_{22}O_5N_4$: C, 63.58; H, 5.11; N, 12.90. Found: C, 63.96, 64.11; H, 5.12, 5.28; N, 12.72, 12.75.

(c) **Oxidation with Chromic Oxide.**—One gram of the oil was oxidized with 5 g. of chromic oxide in glacial acetic acid. From this, a neutral oil was obtained which formed a semicarbazone melting at 163–166°. Its melting point was not depressed by the addition of an authentic sample of benzophenone semicarbazone.

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(2) N. R. Easton, S. J. Nelson, V. B. Fish and P. N. Craig, THIS JOURNAL, **75**, 3751 (1953).

(3) N. R. Easton and V. B. Fish, *ibid.*, **76**, 2836 (1954).

(4) D. J. Dupre, J. Elks, B. A. Nems, K. N. Speyer and R. A. Evans, *J. Chem. Soc.*, 500 (1949).