8.6 g. of pyridine hydrochloride was heated at 185–195° for three hours. After cooling it was poured into water, extracted repeatedly with ether, the ethereal layer washed with dilute hydrochloric acid, water and dried. Evaporation of the solvent gave 0.54 g. (82%) of the naphthol which after recrystallization from methylcyclohexane melted at 169–171°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 71.81; H, 7.74. Found: C, 71.69; H, 7.86.

6-Methoxy-2-methyl-2-carbomethoxy-1-keto-1,2,3,4-tetrahydronaphthalene.—This compound was prepared according to the procedure of Bachmann and Thomas.[4] Recrystallization from petroleum ether (55–75°) gave needles, m. p. 91.5–92°.

6-Methoxy-2-methyl-2-carbomethoxy-1-ethyl-1-hydroxy-1,2,3,4-tetrahydronaphthalene.—Ten and three-tenths grams of the above ketone was treated with 40 cc. of ethylmagnesium bromide solution as described for the 7-methoxy compound. Evaporation of the solvent gave 9.8 g. (87%) of product. A sample washed once with anhydrous ether melted at 100.5–101°.

6-Methoxy-2-methyl-2-carbomethoxy-1-ethylidene-1,2,3,4-tetrahydronaphthalene.—Dehydration of 5 g. of the carbinol with 20 cc. of 85% formic acid gave, after working up as described above, 3.7 g. (80%) of the unsaturated ester as an oil; b. p. 135–140° (0.08 mm.).

6-Methoxy-2-methyl-2-carboxy-1-ethylidene-1,2,3,4-tetrahydronaphthalene.—The above ester (3.32 g.) was refluxed for twelve hours with 30 cc. of 15% methanolic potassium hydroxide. The alcohol was distilled and the solid residue taken up in water. The solution was extracted once with ether to remove a small amount of neutral material, and then acidified with 5% hydrochloric acid. After standing overnight in the ice box there was obtained 2.63 g. (84%) of material; m. p. 109–114° (dec.). Recrystallization from dilute methanol gave material melting at 113–115° (dec.); yield, 2.2 g.

6-Methoxy-2-methyl-2-carboxy-1-ethyl-1,2,3,4-tetrahydronaphthalene.—One gram of the unsaturated acid in 40 cc. of 95% ethyl alcohol was hydrogenated over palladium charcoal at room temperature and atmospheric pressure. Removal of the solvent gave an oil which crystallized on cooling and scratching. Recrystallization from methanol gave 0.6 g. of material, m. p. 131–132°.

6-Hydroxy-2-methyl-2-carboxy-1-ethyl-1,2,3,4-tetrahydronaphthalene.—A mixture of 0.53 g. of the above ether and 6 g. of pyridine hydrochloride was heated in an oil-bath for three hours at 185–195°. After cooling it was poured into water and extracted repeatedly with ether. The ethereal layer was washed with dilute hydrochloric acid, then water, and dried. Removal of the ether gave an oil which crystallized on cooling and scratching; yield 0.3 g. (60%). Recrystallization from methylcyclohexane gave the compound, m. p. 150.5–152°.

Summary

1. Two analogs of bisdehydrodoisynolic acid containing the naphthalene ring system have been prepared.

2. Preliminary tests indicate that these compounds are estrogenically inactive in doses up to 100 γ.

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The Alkaloids of Lycopodium Species. IX. *Lycopodium Annotinum* Var. *Acrifolium*, Fern. and the Structure of Annotinine[1]

BY RICHARD H. F. MANSKE AND LÉO MARION

A previous examination of *Lycopodium annotinum* L.[2] has yielded eight alkaloids, the chief of which was a new one named annotinine. This alkaloid seemed to be one of the large group of Lycopodium alkaloids which would be more amenable to chemical study because of functional groups in the molecule. It was therefore desirable to obtain larger quantities of annotinine and for this purpose a second lot of a plant presumed to be *L. annotinum* L. was worked up. The authors are greatly indebted to Professor P. L'Ecuyer, Laval University, who generously placed this material at their disposal. It was collected in the vicinity of Duchesnay, Que.

Chemical examination soon disclosed, however, that the two lots of plants were definitely distinct and evinced differences that could not be accounted for by accidental variations in isolation procedure. Indeed the distinction was so marked as to suggest taxonomic differences and accordingly Mr. C. A. Weatherby of the Gray Herbarium, Harvard University, was consulted. He reported that the plant in question was *Lycopodium annotinum* var. *acrifolium* Fern., thus confirming the differences of kind. Although the plants are not too readily recognizable they are more distinct, taxonomically, than for instance *L. flabelliforme* and *L. complanatum* which are both given specific rank. The presence of lycopodine which occurs in this plant calls for no comment; its absence would definitely arouse interest. The occurrence of annotinine, which is the chief alkaloid, indicates an affinity with the type species but the absence of alkaloids L6, L8, L9, L11 and L12, all found in the type and the presence of five new ones, indicates that this affinity can be only remote. Even obscurine (L6) which has been found in *L. flabelliforme*[3] and *L. obscurum*[4] was either absent or present only in doubtful traces. In view of such marked differences between the type and the variety; in view also of the fact that the variety possesses morphological characteristics by means of which it can be differentiated from the type by a relatively experienced observer,

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[1] Published as National Research Council Bull. No. 1529.

[2] R. H. F. Manske and L. Marion, *Can. J. Research*, **B21**, 92 (1943).

[3] (a) R. H. F. Manske and L. Marion, *ibid.*, **B20**, 87 (1942); (b) *ibid.*, **B22**, 1 (1944).

[4] R. H. F. Manske and L. Marion, *ibid.*, **B22**, 53 (1944).

it is suggested that the variety be raised to specific rank. It would then become *Lycopodium acrifolium* (Fern.) N. Comb. The plant has been described by Fernald.[5]

The five new alkaloids are acrifoline (L27) ($C_{16}H_{21}O_2N$), L28 ($C_{17}H_{27}O_2N$), L29 ($C_{16}H_{23}O_2N$), L30 ($C_{16}H_{25}O_2N$) and L31 ($C_{20}H_{29}O_4N$). They were all isolated and characterized as their perchlorates. The free bases L27 and L30 were obtained crystalline but the others have not yet been crystallized. In addition to the above there were obtained a number of perchlorates which were obviously mixtures as well as a not inappreciable fraction of basic material from which no crystalline derivatives could be obtained.

The lack of functional groups in most of the Lycopodium alkaloids renders their degradation to simpler compounds of constitutional value peculiarly difficult. The lactonic group of annotinine however seemed to offer possibilities of attack if for no other reason than that mild oxidation in aqueous solutions could be attempted. Annotinine was converted by the action of ethanolic potassium hydroxide to annotinine hydrate, $C_{16}H_{23}O_4N$, which could not be reconverted to the parent base, but which on oxidation with permanganate gave only a small amount of a compound which appears to be $C_{16}H_{21}O_4N$.

When, however, annotinine is suspended in water and oxidized by the slow addition of potassium permanganate, it is converted into a new base, $C_{16}H_{19}O_4N$, which contains the lactone ring intact. There appear to be two carbonyl groups in this product because Clemmensen reduction of it yields a saturated base, $C_{16}H_{23}O_2N$, which however is not identical with alkaloid L29 of the same empirical formula.

Annotinine is not reducible catalytically although under sufficiently drastic conditions it undergoes hydrogenolysis yielding two bases, containing less carbon and no oxygen, which have not yet been further investigated. The Clemmensen reaction applied to annotinine to reduce a possible carbonyl oxygen gave unexpected results. The strong hydrochloric acid present under the conditions of the experiment added to the molecule yielding a compound, $C_{16}H_{22}O_3NCl$, which is still a base and which is not reduced by amalgamated zinc in acid solution. In fact, heating the alkaloid with strong hydrochloric acid or with hydrobromic acid readily yields addition compounds which form sparingly soluble salts. The hydrogen chloride addition compound is obviously related closely to annotinine hydrate and seems to be a chlorohydrin because on treatment with alcoholic alkali, it can be converted into the hydrate. Furthermore, it can be dechlorinated by reduction with chromous chloride to yield an unsaturated base, $C_{16}H_{21}O_2N$, which is sensitive to air and easily reduced catalytically to the same base, $C_{16}H_{23}O_2N$, obtained from the Clemmensen reduction of the oxidation product of annotinine. The chromous chloride reduction is anomalous since not only is the chlorine replaced by hydrogen, which process should lead to $C_{16}H_{23}O_3N$, but a molecule of water is lost. The foregoing reactions of annotinine may be represented as follows

$$\begin{tikzcd}
C_{16}H_{21}O_3N \arrow[rr, "HCl"] \arrow[dr, "KOH"] \arrow[dd, "KMnO_4"'] & & C_{16}H_{22}O_3NCl \arrow[dl, "KOH"'] \arrow[dd, "CrCl_2"] \arrow[rddd, dashed, "KMnO_4"] & \\
& C_{16}H_{23}O_4N \arrow[d, "KMnO_4"] & & \\
C_{16}H_{19}O_4N \arrow[dr, "Zn + Hg"] & C_{16}H_{21}O_4N & C_{16}H_{21}O_2N \arrow[dl, "H_2 + PtO_2"'] & \\
& C_{16}H_{23}O_2N & & C_{16}H_{22}O_4NCl
\end{tikzcd}$$

Until further evidence is available, a satisfactory interpretation of these results is that annotinine contains an ether bridge and the hydrate is then a dihydroxy- compound. The hydrogen chloride addition product is a chlorohydrin which on reduction with chromous chloride yields an alcohol which dehydrates easily. On this basis the oxidation product, $C_{16}H_{19}O_4N$, would be the diketone, corresponding to the glycol which must be disecondary, and then its Clemmensen reduction would be understandable. Owing to the fact that it is colorless and quite stable, it is probably neither a 1,2- nor a 1,3-diketone and therefore the ether bridge in the alkaloid is part of a five or six membered ring. That the hydrate is not a 1,2-diol is indicated by the impossibility of oxidizing it with periodic acid. The points not clarified by such an explanation are the ease with which alkali should open such a large ring and the fact that only the halogen acids succeed in doing so.

Experimental

The crude alkaloid from 67 kg. of dried plant material was obtained by the procedure previously outlined.[3a] When worked up for annotinine[2] there was obtained a total of 60 g. of pure base not contaminated with obscurine.

Acrifoline (L27).—The combined mother liquors from which the annotinine had been obtained was largely freed of solvent and the residue dissolved in acetone and treated with aqueous perchloric acid until just acid to congo red. Ethyl acetate was added until the incipient turbidity just disappeared on mixing. The perchlorate which then separated was filtered off and washed with acetone–ethyl acetate. The free base was regenerated from this salt and in order to remove some annotinine it was heated for an hour in methanol solution with some strong aqueous potassium hydroxide. This treatment hydrolyzed the lactonic ring of annotinine and subsequent dilution with water and removal of the methanol yielded an oily base which crystallized readily from ether. After one recrystallization from ether or from a large volume of hexane acrifoline consisted of fine colorless needles melting sharply at 97°.[6] Yield was 10 g.

Anal. Found: C, 73.52, 73.50; H, 8.59, 8.95; N, 5.50, 5.53. Calcd. for $C_{16}H_{23}O_2N$: C, 73.56; H, 8.81; N, 5.36.

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[5] M. L. Fernald, *Rhodora*, **17**, 123 (1915).

[6] All melting points are corrected.

The perchlorate was prepared from the pure base and recrystallized from acetone–ethyl acetate. It consisted of stout prisms melting at 266° when placed in the bath at 250°.

Anal. Found: C, 53.13, 53.29; H, 6.90, 6.73; N, 3.91, 3.74. Calcd. for $C_{16}H_{23}O_2N \cdot HClO_4$: C, 53.11; H, 6.64; N, 3.87.

The aqueous alkaline solution from which acrifoline had been removed was rendered acid to congo red with hydrochloric acid, boiled for a short time, filtered to remove a little amorphous material and basified with excess ammonia. During the course of several days about 3 g. of annotinine hydrate separated. It was identical with a specimen prepared as described below.

Annotinine Hydrate.—A solution of annotinine (2 g.) in hot ethanol (30 cc.) was treated with potassium hydroxide (2 g.) in ethanol (20 cc.) and the mixture heated under reflux until a test portion yielded a clear solution on dilution with water (two hours). The ethanol was evaporated on the steam-bath, the last traces being removed by repeated additions of water. The clear aqueous solution was acidified with sulfuric acid and heated on the steam-bath to lactonize the free carboxyl and after cooling it was basified with excess ammonia. The base which slowly separated in stout needles was recrystallized from methanol by adding ether to the concentrated solution. The yield of hydrate was virtually quantitative if the aqueous ammoniacal solution was extracted with ether. The annotinine hydrate thus obtained consisted of stout colorless prisms melting sharply at 228°. In admixture with annotinine it was completely liquid at 195°.

Anal. Calcd. for $C_{16}H_{23}O_4N$: C, 65.53; H, 7.85; N, 4.78. Found: C, 65.23, 65.43; H, 7.77, 7.99; N, 4.76.

Lycopodine.—The solvents were removed under reduced pressure from the mother liquors from which the crude perchlorate of alkaloid L27 had been obtained. Water was added, the remaining solvents boiled out and the hot solution filtered. In the course of several weeks some resin and a mixture of perchlorates were deposited. The separated material was recrystallized several times from hot water and then converted to free base. The latter when recrystallized from hexane melted either alone or admixed with lycopodine at 116°. The total yield was *ca.* 3.0 g.

Alkaloid L28.—The total mother liquors from which the above-mentioned alkaloids had been isolated were basified, the free bases recovered and these were distilled at a low pressure, yielding the following fractions: (a) b. p. up to 138° (1.5 mm.); (b) b. p. 138–152° (1.5 mm.); (c) b. p. 150–163° (1.0 mm.); (d) b. p. 163–180° (1.0 mm.); (e) b. p. 180–230° (1.0 mm.), and (f) residue.

Fraction (a) yielded chiefly lycopodine isolated as its perchlorate. The perchlorate of fraction (b) together with the acetone-soluble perchlorate from fraction (a) was recrystallized several times from acetone–ethyl acetate and the regenerated bases again distilled. There was obtained a fraction (g) b. p. 125° (2 mm.) and then a fraction (h) b. p. 150° (2 mm.) together with a very small intermediate fraction. The perchlorate from fraction (g) was easily recrystallized to the constant melting point of 211° from acetone–ethyl acetate. The perchlorate of alkaloid L28 thus obtained consisted of slender prisms readily soluble in acetone, but the free base could not be made to crystallize. The yield was *ca.* 0.5 g.

Anal. Found: C, 53.64, 53.92; H, 7.48, 7.58; N, 3.81, 3.72. Calcd. for $C_{17}H_{27}O_2N \cdot HClO_4$: C, 54.04; H, 7.42; N, 3.71.

Alkaloid L30.—The distilled base obtained in fraction (h) crystallized in the receiver. When recrystallized twice from ether–hexane, alkaloid L30 was obtained in nacreous plates melting sharply at 178°; yield *ca.* 2.0 g.

Anal. Found: C, 73.44, 73.15; H, 9.39, 9.54; N, 5.35, 5.32. Calcd. for $C_{16}H_{25}O_2N$: C, 73.00; H, 9.50; N, 5.32.

The perchlorate was moderately soluble in hot acetone and was recrystallized by adding ethyl acetate to its concentrated solution in acetone. It melted sharply although with extensive decomposition at 311° when placed in the bath at 280°.

Anal. Found: C, 52.82, 53.07; H, 6.85, 7.09; N, 3.52, 3.69. Calcd. for $C_{16}H_{25}O_2N \cdot HClO_4$: C, 52.82; H, 7.15; N, 3.85.

Alkaloid L29.—Fraction (c), b. p. 150–163° (1.0 mm.), obtained as described under alkaloid L28, was converted to perchlorate and crystallized from acetone–ethyl acetate. The first crop of crystals melted at 273°—the mother liquor yielded a small amount of alkaloid L30 perchlorate—and when recrystallized from the same solvents consisted of short prisms melting sharply at 274°.

Anal. Found: C, 53.32, 53.03, 53.51; H, 6.65, 6.90, 6.88; N, 3.78, 3.64. Calcd. for $C_{16}H_{23}O_2N \cdot HClO_4$: C, 53.11; H, 6.64; N, 3.87.

The free base could not be crystallized.

Alkaloid L31.—The chloroform extract (c)[3a] obtained by extracting the aqueous hydrochloric acid solution of the total bases contains in addition to a large amount of non-basic resin a small amount of alkaloids which were obtained by extracting the evaporated extract repeatedly with water and filtering the cooled extract. The latter was then extracted with ether, basified with ammonia and again extracted with ether. The bases in the last extract were converted to perchlorates in acetone–ethyl acetate. The sparingly soluble salt which separated proved to be the perchlorate of lycopodine. The more soluble fraction in the filtrate was recrystallized several times from hot water. The free base was regenerated but it could not be crystallized. It was again converted to the perchlorate in hot methanol and the salt crystallized readily on cooling in colorless plates melting at 132° with some previous sintering. *In vacuo* (15 mm.) it lost 3.17% of its weight in five hours at 100°. The theoretical loss for one molecule of water of crystallization is 4.02%. The anhydrous salt on which the analyses were conducted melted sharply at 217°.

Anal. Found: C, 53.90, 53.99; H, 7.06, 6.85; N, 3.02, 3.09. Calcd. for $C_{20}H_{29}O_4N \cdot HClO_4$: C, 53.64; H, 6.71; N, 3.13.

The other fractions could not be made to yield crystalline derivatives although nearly 10 g. of such material remained. The non-volatilized residue did yield several crystals which may be obscurine but their identification is quite uncertain.

Oxidation of Annotinine.—A suspension of very finely ground annotinine (1.0 g.) in water (75 cc.) was treated with small portions of potassium permanganate until the color of the latter was permanent and remained so for two days. The excess oxidant was destroyed by heating the mixture with a little methanol. After cooling, the brown suspension was extracted repeatedly with ether. The residue from the combined extract (1.0 g.) melted at 234° either before or after recrystallization from hot chloroform–methanol. The recrystallized base consisted of brilliant stout prisms.

Anal. Calcd. for $C_{16}H_{19}O_4N$: C, 66.44; H, 6.57; N, 4.84. Found: C, 66.68; H, 6.78; N, 4.79, 4.68.

Reduction of Oxidized Annotinine.—A suspension of the oxidation products (2 g.) in 10% hydrochloric acid (25 cc.) was boiled for six hours with an excess of amalgamated zinc during which time it gradually dissolved. The filtered solution was basified with excess ammonia and extracted with ether. The colorless resinous residue was converted into its perchlorate which when recrystallized from acetone–ethyl acetate yielded colorless stout prisms melting at 277°. The regenerated base was recrystallized from hexane to yield colorless rectangular plates melting sharply at 109°.

Anal. Calcd. for $C_{16}H_{23}O_2N$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.47, 73.41; H, 9.05, 8.70; N, 5.35, 5.46.

Addition of Hydrogen Chloride to Annotinine.—Annotinine was boiled for two hours with twenty times its weight of 10% hydrochloric acid. On cooling, the hydrochloride of the hydrogen chloride addition product crystallized for the greater part. The mixture was basified with excess ammonia and the liberated base extracted with ether. The perchlorate was prepared from the residue from the ether extract and recrystallized to colorless stout prisms from acetone–ethyl acetate which melted at 278°.

Anal. Calcd. for $C_{16}H_{22}O_3NCl \cdot HClO_4$: C, 46.60; H, 5.58; N, 3.40. Found: C, 46.80; H, 6.20; N, 3.68.

The free base regenerated from the perchlorate and recrystallized from ether–hexane formed colorless stout plates melting sharply at 190°.

Anal. Calcd. for $C_{16}H_{22}O_3NCl$: C, 61.64; H, 7.07; N, 4.50. Found: C, 61.53, 61.71; H, 7.53, 7.48; N, 4.48, 4.86.

The hydrogen bromide addition product was prepared by heating annotinine (2 g.) with 20% hydrobromic acid (30 cc.) for two hours. The base dissolved readily in the cold but in thirty minutes the sparingly soluble salt of the addition product began to crystallize from the boiling solution. The salt was filtered from the cooled mixture and washed with a little water. The free base was regenerated by shaking the salt with aqueous ammonia and ether. It crystallized with great facility from ether in brilliant stout prisms melting not quite sharply at 209° when placed in the bath at 190° and rapidly heated. When slowly heated from room temperature it melted indefinitely with decomposition at 202–205°.

Anal. Calcd. for $C_{16}H_{22}O_3NBr$: C, 54.56; H, 6.25; N, 3.98. Found: C, 54.06, 54.03; H, 6.33, 6.24; N, 3.59, 3.54.

Oxidation of the Hydrogen Chloride Adduct.—When this material was oxidized as described under the oxidation of annotinine there was obtained a small amount of a substance only sparingly soluble in methanol from which it was recrystallized twice. It then consisted of colorless prisms which melted not quite sharply at 288°.

Anal. Calcd. for $C_{16}H_{20}O_4NCl$: C, 59.00; H, 6.14; N, 4.30. Found: C, 58.62, 58.93; H, 6.24, 6.21; N, 4.55.

A more soluble fraction consisted of unchanged starting material.

Reduction of the Hydrogen Chloride Adduct.—The adduct of annotinine and hydrogen chloride was prepared by boiling the base (2.75 g.) with concentrated hydrochloric acid (10 cc.) and the resulting mixture of crystallized salt and solution was heated in an atmosphere of nitrogen for two hours with a solution of chromous chloride prepared from chromic chloride hydrate (20 g.) and an excess of metallic zinc. The cooled and diluted mixture was basified with excess ammonia and exhausted with ether. The base which crystallized from the somewhat concentrated ether extract was recrystallized again from dry ether. It consisted of stout colorless prisms melting sharply at 132° to a yellow to brown melt. It was free of halogen and when slightly impure became colored on exposure to air.

Anal. Calcd. for $C_{16}H_{21}O_2N$: C, 74.13; H, 8.11; N, 5.41. Found: C, 74.09, 74.42; H, 7.94, 8.13; N, 5.61.

A small portion of this base was reduced catalytically in methanol in the presence of platinum oxide. It was isolated in the usual way and recrystallized from ether–hexane, to yield colorless triangular prisms with pyramidal terminations melting at 109°. In admixture with the base obtained by the Clemmensen reduction of the oxidation product of annotinine as described above, it also melted sharply at 109°.

Anal. Calcd. for $C_{16}H_{23}O_2N$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.59, 73.46; H, 8.85, 8.86; N, 5.36, 5.51.

The perchlorate of the above catalytically reduced base was recrystallized twice from hot methanol in which it is only moderately soluble and obtained in colorless rhombic plates melting at 282°.

Oxidation of Annotinine Hydrate.—An aqueous alkaline solution of the hydrate was treated with potassium permanganate in small portions until the purple color remained for two hours. The filtered and acidified solution was evaporated to dryness *in vacuo* and the residue extracted with acetone. The acetone was evaporated and the residue dissolved in water and treated with calcium chloride and ammonia to precipitate the oxalic acid. The filtered solution after acidification was again evaporated to dryness *in vacuo* and the residue once more extracted with acetone. The residue from the last extract was extracted with ethyl acetate and the residue from the latter distilled. The fraction obtained at 230–250° (1 mm.) was recrystallized twice from acetone and once from a large volume of ethyl acetate. The almost colorless stout polyhedra thus obtained melted at 290°.

Anal. Found: C, 66.07, 65.73; H, 6.94, 7.08; N, 4.98. Calcd. for $C_{16}H_{21}O_2N$: C, 65.98; H, 7.22; N, 4.81.

Summary

1. Seven alkaloids, including lycopodine and annotinine have been isolated from *Lycopodium annotinum*, var. *acrifolium* Fernald. The two bases named above are also present in the type species, *L. annotinum* L., but the other five are new and are not present in the type. The remaining six alkaloids present in the type are absent from the variety. Such differences are indicative of differences greater than varietal and it is suggested that specific rank be given to the plant.

2. The new alkaloids are acrifoline (L27) ($C_{16}H_{21}O_2N$), alkaloid L28 ($C_{17}H_{27}O_2N$), alkaloid L29 ($C_{16}H_{23}O_2N$), alkaloid L30 ($C_{16}H_{25}O_2N$) and alkaloid L31 ($C_{20}H_{29}O_4N$).

3. Preliminary work on the structure of annotinine has indicated that in addition to the lactone grouping, the third indifferent oxygen is present in a five or six membered ether bridge.

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