# Pristimerin. Spectroscopic Properties of the Dienone–Phenol-Type Rearrangement Products and Other Derivatives[1]

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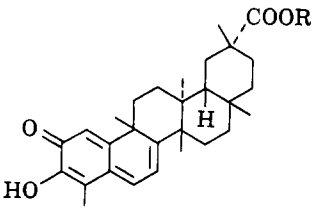
The dienone–phenol-type system in the unique quinonoid triterpene, pristimerin, gives rise to three isomers upon treatment with acid. Structures have already been proposed for these rearrangement products, but closer inspection of their spectroscopic properties indicates that the structure of the second isomer should be revised. These aspects are discussed together with mass spectrometric and other spectroscopic properties of pristimerin derivatives. The so-called reductive acetates of pristimerin and celastrol are still not fully characterized and this point is also discussed.

The early chemical studies on pristimerin and celastrol by Gisvold,[4] Fieser and Jones,[2] Kamat, Fernandes, and Bhatnagar,[5] Seshadri, Mhaskar, Kulkarni, and Shah,[6] and ourselves[7] clarified the nature of its chromophore[8]; subsequent work resulted in determination of the full structure **1**,[3] which has recently been confirmed by Johnson and co-workers.[9] Besides its antibacterial activity,[10] pristimerin possesses notable antitumor properties,[11] but the high toxicity prevents it being used as a cancerostatic agent.




**1**, pristimerin (R = Me)
celastrol (R = H)

The starting material (celastrol) was extracted from *Celastrus strigillosus* Nakai and *Tripterygium Regelii* Sprague et Takeda collected in central Japan, the former being found to be an especially suitable source.

Owing to the presence of the extended dienone system, pristimerin gives rise to three isomers upon treatment with acid. Thus, when pristimerin (**1**) was refluxed for 20 hr. in 2 *N* sulfuric acid under nitrogen,[12] a black solid precipitated, which after recrystallization from methanol gave isopristimerin-I (**2**) in 10% yield. Evaporation of the mother liquor from the black precipitate and acetylation of the residue yielded the second isomer, diacetylisopristimerin-II (**4**), which was identical with the Thiele acetate[12] obtained earlier by treatment of pristimerin with acetic anhydride and sulfuric acid. A third isomer, the styrenoid isopristimerin-III (**8**),[9] was obtained by boiling pristimerin in methanol and dilute sulfuric acid for 20 min.[8]; acetylation of the mother liquor also gave diacetylisopristimerin-II (**4**).

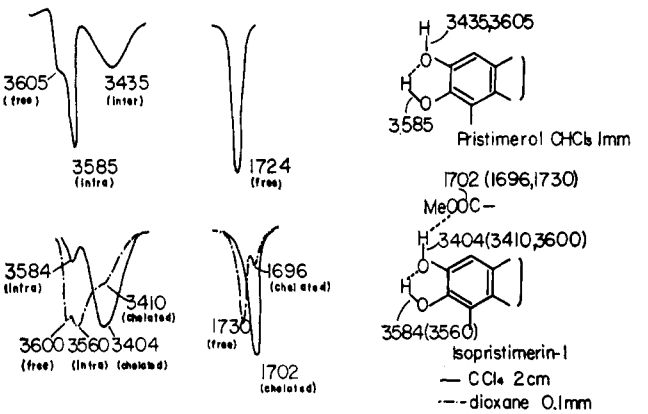



Figure 1.—The hydroxyl and carbonyl bands of pristimerol (upper trace) and isopristimerin-I (lower trace).

**Isopristimerin-I.**—The 8,14-seco structure had been assigned to this isomer to account for the unusually low-frequency infrared absorption of the ester group.[3] A more detailed discussion of the infrared and other spectroscopic properties is given below. The methoxycarbonyl group of pristimerin and derivatives, excepting isopristimerin-I[8] which absorbs at 1694 cm.$^{-1}$ ($CHCl_3$), absorbs in the usual infrared region of 1730 cm.$^{-1}$. The following studies show that this exceptional behavior of isopristimerin-I is caused by a unique intramolecular hydrogen bonding between the ester group and the hydroxyl group of the naphthalene diol moiety. Dihydropristimerin (pristimerol,[7] two hydroxyl groups instead of the two methoxyl groups in structure **10**), which was measured for comparison, had the following infrared bands in $CHCl_3$ (Figure 1): 1724 (ester), 3435 (intermolecular hydrogen-bonded OH), 3585 (intramolecular hydrogen-bonded OH), and 3605 cm.$^{-1}$ (free OH). When measured at different concentrations, the intensity of the 3585-cm.$^{-1}$ band remained constant but those of the 3435- and 3605-cm.$^{-1}$ bands were concentration dependent and the relative intensities mutually interchanged.

(1) It is a great pleasure that we are able to submit this paper to the issue of this journal dedicated to Professor Fieser, since he himself has carried out preliminary chemical studies on this unique quinonoid triterpene[2] and, moreover, it was during the stay of K. N. in Professor Fieser's laboratory (1950–1952) that this work had started. The contents of this paper have been partly reported as a short communication.[3]

(2) L. F. Fieser and R. N. Jones, *J. Am. Pharm. Assoc.*, **31**, 315 (1942).

(3) R. Harada, H. Kakisawa, S. Kobayashi, M. Musya, K. Nakanishi, and Y. Takahashi, *Tetrahedron Letters*, 603 (1962).

(4) O. Gisvold, *J. Am. Pharm. Assoc.*, **28**, 449 (1939); **29**, 12 (1940); **31**, 529 (1942).

(5) V. N. Kamat, F. Fernandes, and S. S. Bhatnagar, *J. Sci. Ind. Res.*, **14C**, 1 (1955).

(6) S. Seshadri, V. V. Mhaskar, A. B. Kulkarni, and R. C. Shah, *ibid.*, **17B**, 111 (1958).

(7) K. Nakanishi, H. Kakisawa, and Y. Hirata, *J. Am. Chem. Soc.*, **77**, 3169, 6729 (erratum) (1955); *Bull. Chem. Soc. Japan*, **29**, 7 (1956).

(8) P. K. Grant, A. W. Johnson, P. F. Juby, and T. J. King, *J. Chem. Soc.*, 549 (1960).

(9) A. W. Johnson, P. F. Juby, T. J. King, and S. W. Tam, *ibid.*, 2884 (1963).

(10) S. S. Bhatnagar and P. V. Divekar, Indian Patent 40968 (1951).

(11) S. Horii, T. Noguchi, Y. Matsui, Y. Watanabe, and M. Goto, *Shoyakugaku Zasshi*, **14**, 91 (1960).

(12) P. K. Grant and A. W. Johnson, *J. Chem. Soc.*, 4079 (1957).

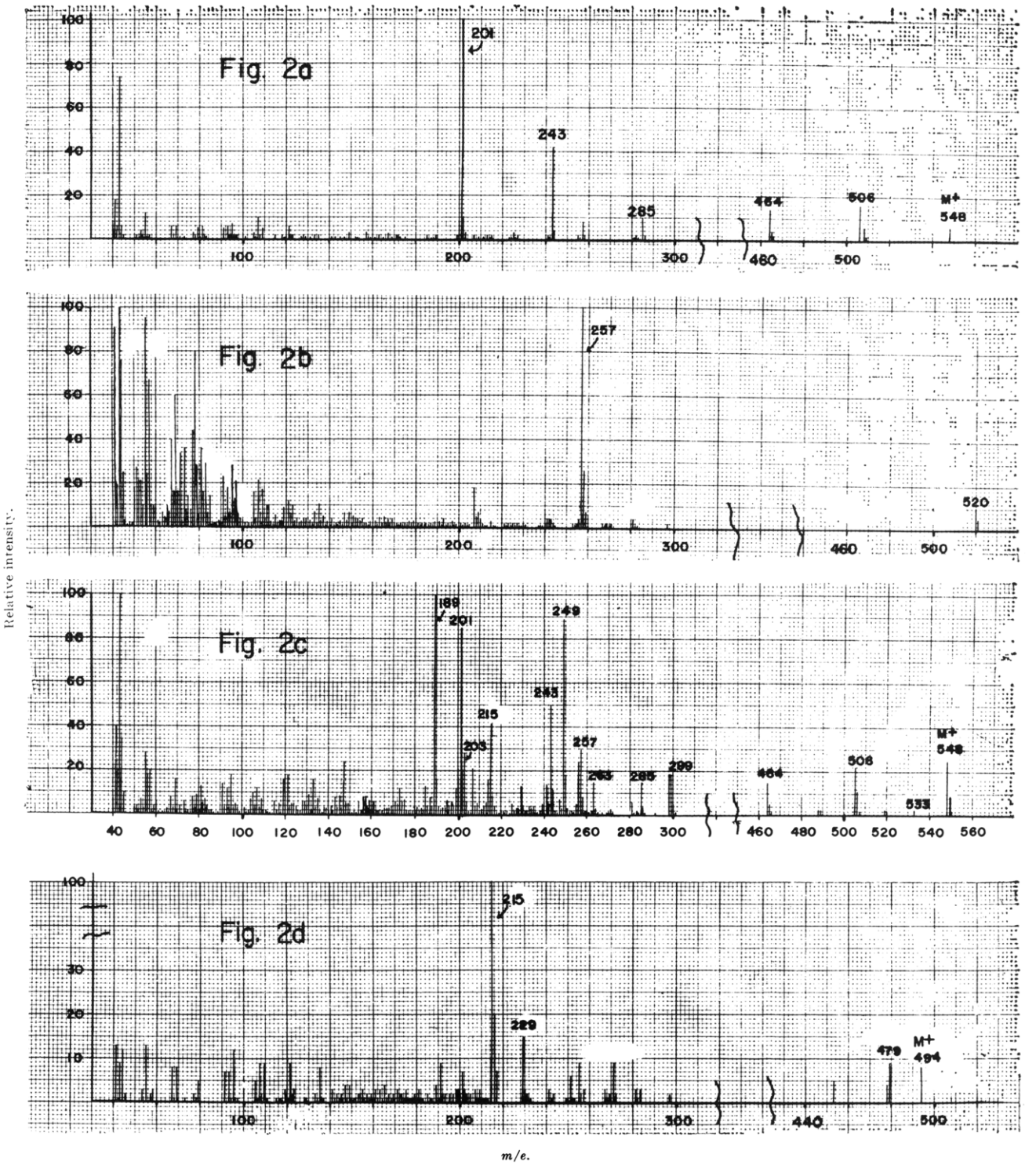
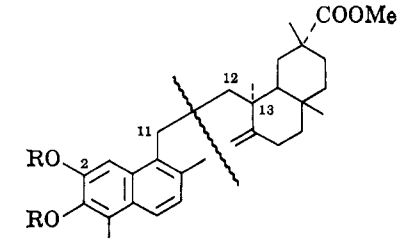


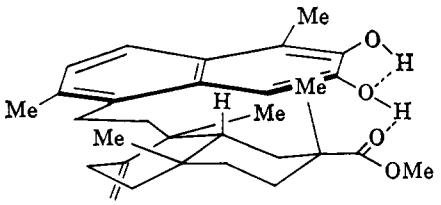

Figure 2.—Mass spectra of pristimerin derivatives: a, isopristimerin-I diacetate (**3**); b, isopristimerin-I (**2**); c, diacetyl isopristimerin-II (**4**); d, dimethylpristimerol (**10**).

In contrast, the intensities of the two OH bands at 3404 and 3584 cm.$^{-1}$ in the $CCl_4$ spectrum of isopristimerin-I were concentration independent, and the ester band was still found at the low wave number of 1702 cm.$^{-1}$ in a dilute solution (2-cm. cell). This suggested that the 1702- and 3404-cm.$^{-1}$ bands were involved in chelation and that the 3584-cm.$^{-1}$ band was due to the intramolecular hydrogen bonding, OH · · · OH. This was confirmed by measurement in dioxane, in which the carbonyl–hydroxyl chelation was mostly cleaved causing the 1702- and 3404-cm.$^{-1}$ peaks to shift to 1730 and 3600 (or 3560) cm.$^{-1}$, respectively (Figure 1). The weak shoulders at 1696 and 3410 cm.$^{-1}$ are due to residual chelation. The ester peak appears at 1732 cm.$^{-1}$ ($CHCl_3$) in diacetyl isopristimerin-I (**3**) in which the two hydroxyls are masked.

The effect of this chelation is also manifested in the n.m.r. spectrum. Namely, the two hydroxyl groups of isopristimerin-I absorb at 6.05 and 8.87 p.p.m., and the ester methyl signal appears at the somewhat low-field position of 3.83 p.p.m., whereas with the diacetate **3** this signal is shifted to the more normal position of 3.67 p.p.m. Further, the other methyl signals appear at 1.12, 1.12, 1.42 (aliph.), 2.45, and 2.55 p.p.m.




**2**, isopristimerin-I (R = H)
**3**, diacetyl isopristimerin-I (R = Ac)




**2a**, isopristimerin-I

(arom.) in the free diol **2**, and at 1.12, 1.14, 1.18 (aliph.), 2.31, 2.37, 2.47, and 2.48 p.p.m. (arom. and acetoxyl) in the acetate **3**. The peak which is shifted from 1.42 (diol) to 1.18 p.p.m. (acetate) can be assigned to the C-20 Me group because in the chelated form of isopristimerin-I (**2a**) it lies in a region subject to the paramagnetic effect of the naphthalene nucleus.

The mass spectra of secotriterpenes have not been studied in detail, but it can be expected that the most vulnerable place in the molecule will be the carbon chain between the two bicyclic nuclei. The only example available[13] was β-onocerin; main fragmentation occurred as expected by breaking the molecule exactly in half.

The breakdown pattern of isopristimerin-I diacetate (**3**) now is straightforward: in the upper mass range the stepwise loss of two 42 mass units (ketene), a feature characteristic for phenol acetates, is observed. Cleavage occurs principally at the 11,12 bond owing to benzylic activation and the resulting fragment (*m/e* 285) again suffers the loss of first one and then two molecules of ketene (Figure 2a). The mass spectrum of isopristimerin-I (**2**) itself, however, was most unexpected (Figure 2b); peaks corresponding to the calculated molecular ion (*m/e* 464) and the C-11–C-12 cleavage product (*m/e* 201) were absent and, instead, intense peaks at *m/e* 520 (10% of base peak) and 257 (base peak), both 56 mass units too high, were present. Changing the solvent for recrystallization from methanol to ether was without any effect. The occurrence of ions (other than isotopes) with a mass higher than that of the parent molecule has been reported only in very rare instances. Nitriles for example exhibit M + 1 and M + 41 peaks of very low abundance.[14] In the case of the indole alkaloid voacamine[15] and vinblastine,[16] peaks have been observed at M + 14 and at M + 14 and M + 28, respectively, and have been interpreted as being due to the intermolecular transfer of methyl group(s) from the methoxycarbonyl group to the nitrogen atom(s) followed by a Hofmann-type elimination. Since phenols are known to lose CO readily,[17] the +56

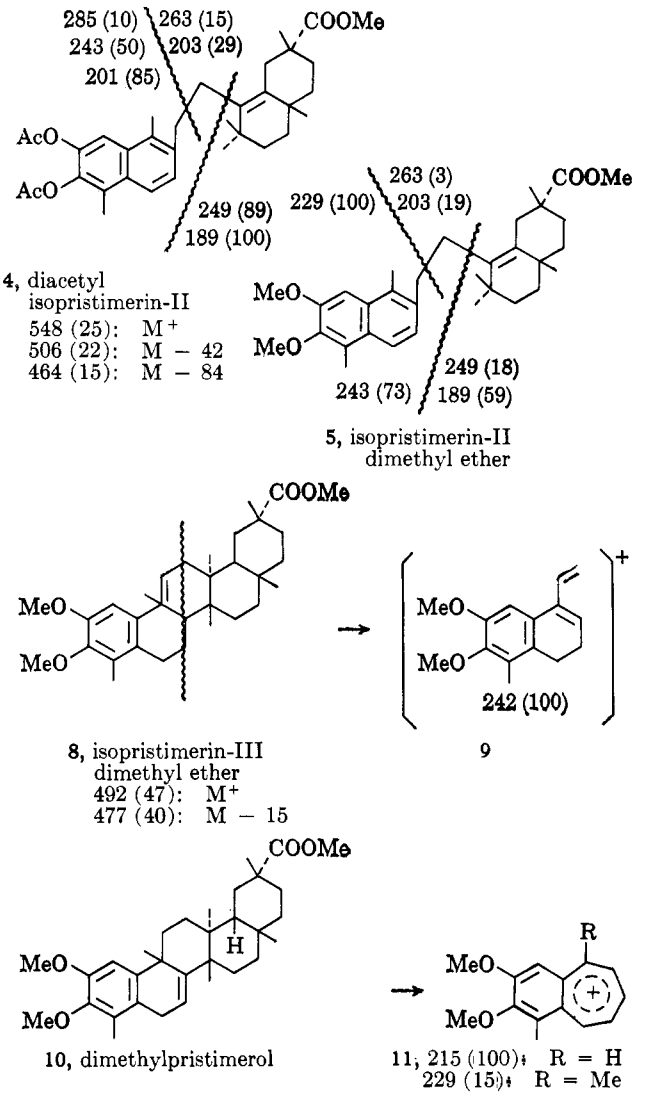
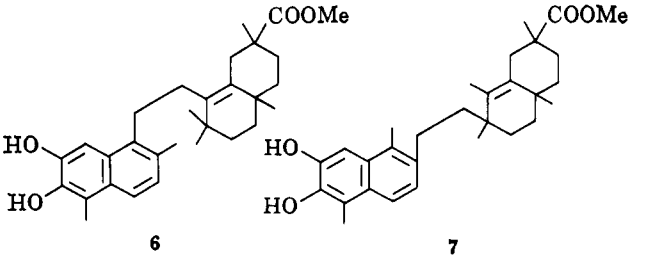



Figure 3.—Mass spectrometric fragmentation of the rearrangement products. The figures in parentheses represent the relative abundances of the fragments (base peak taken as 100).

peaks in the present case might originate in the intermolecular transfer of $C_2O_2$ from the naphthalene diol system.[18]

**Isopristimerin-II.**—Fragmentations of diacetyl isopristimerin-II (**4**) and isopristimerin-II dimethyl ether (**5**) are characterized by two modes of fragmentation (Figure 2c and Figure 3). The fragments containing rings D and E decompose further by the loss of the elements of methyl formate (60 mass units). Two other structures may be considered for this isomer on mechanistic grounds, *i.e.*, **6**[3] and **7**. However, structure **6** is incompatible with the observation that the




**6** **7**

(13) Unpublished results, Stanford University.
(14) F. W. McLafferty, *Anal. Chem.*, **34**, 26 (1962).
(15) G. Büchi, R. E. Manning, and S. A. Monti, *J. Am. Chem. Soc.*, **85**, 1893 (1963).
(16) P. Bommer, W. McMurray, and K. Biemann, *ibid.*, **86**, 1439 (1964).
(17) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, p. 167.

(18) The authors are indebted to a referee for pointing out this possibility. This point is being re-investigated and will be reported in a forthcoming publication.

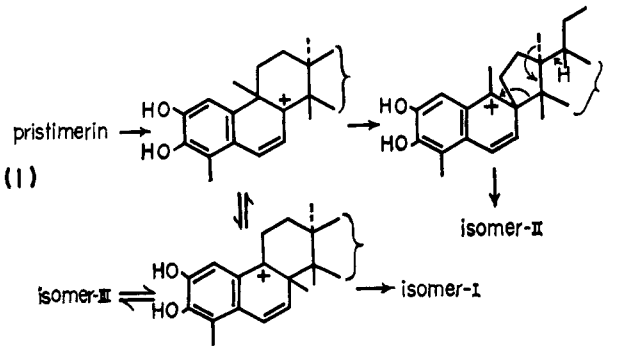



Figure 4.—Acid rearrangements of pristimerin.

infrared absorption of the ester group in isopristimerin-II is at the usual position of 1730 cm.$^{-1}$ ($CCl_4$); namely, it cannot be explained why the intramolecular hydrogen bond present in the closely related isopristimerin-I (**2**) could not be formed in the present case. In structure **7**, approach of the methoxycarbonyl group to the hydroxyl group to form an intramolecular hydrogen bond is indeed sterically hindered. However, the methyl signals in the n.m.r. spectrum of the diacetate appear at 3.42 (COOMe), 2.29, 2.27 (OAc), 2.44, 2.44 (arom.), 1.37, 1.25, 1.20, and 1.07 p.p.m.; accordingly, the vinyl methyl group would have to be assigned to the high-field peak at 1.37 p.p.m. which is incompatible with structure **7**. In contrast to structures **6** and **7** the mentioned 1730-cm.$^{-1}$ infrared peak and the chemical shifts of n.m.r. peaks can both be satisfactorily explained by structures **4** and **5**. Namely, the methoxycarbonyl group cannot form a hydrogen bond to the oxygen function at C-2 (hence the usual position for infrared ester absorptions), and the 1.37-p.p.m. peak can now be assigned to one of the saturated methyl groups. Cleavage of the C-12–C-13 bond, *i.e.*, position adjacent to the C-13–C-18 double bond, is unlikely but it can be rationalized by a shift of the double bond to C-18.

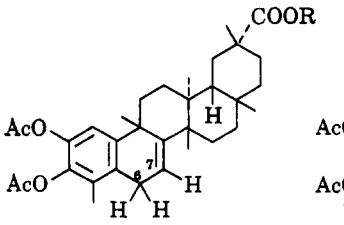
**Isopristimerin-III.**—The main fragmentation of isopristimerin-III dimethyl ether[9] (**8**) corresponds formally to a retro Diels–Alder decomposition to the stable cation **9** as indicated in Figure 3. An analogous behavior has been observed with $\Delta^{9,11}$-oleanenes.[19] The charge is retained with the aromatic portion.

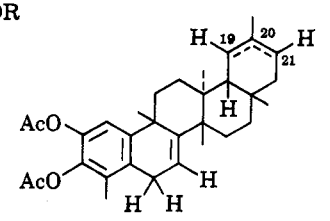
Because the treatment of isopristimerin-I and -III with boiling acetic anhydride and a trace of sulfuric acid merely resulted in straightforward acetylation, whereas under the same conditions pristimerin afforded the acetate of isomer-II (Thiele acetate),[12] it is clear that the two isomers I and III are not intermediates in the formation of isopristimerin-II. However, Johnson and co-workers have shown[9] that, by use of the stronger acid, perchloric acid, isopristimerin-III can be converted into isopristimerin-II. The formation of the three isomers can thus be represented as shown in Figure 4.

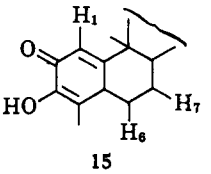
**Other Derivatives.**—The mass spectrum of dimethylpristimerol (**10**)[3,7] has its base peak at *m/e* 215 and this fragment is best formulated as the benztropylium ion **11** (R = H); it is accompanied by a fragment of lesser abundance, *m/e* 229, probably **11** (R = $CH_3$) (Figure 2d and Figure 3).

(19) H. Budzikiewicz, J. M. Wilson, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 3688 (1963); H. Budzikiewicz, J. I. Brauman, and C. Djerassi, *Tetrahedron*, in press.

The n.m.r. and other spectroscopic data allow one to assign structure **12** to diacetyldihydropristimerin,[6] the product obtained by acetylating pristimerol[7] immediately after its preparation from pristimerin (by reduction with $NaBH_4$–ethanol or with $PtO_2$–ethanol): $\nu^{KBr}$ 1775, 1732 cm.$^{-1}$; $\delta$ 3.52 (COOMe), 2.23, 2.20 (OAc), 2.05 (arom. Me), 1.39, 1.24, 1.13, 1.07, 0.60 p.p.m. (other Me) (see also Table I). However, the structure of the so-called reductive acetate of pristimerin[7,12] is still not clear; this was prepared by acetylation in the presence of zinc dust or catalytic hydrogenation ($PtO_2$–$Ac_2O$) followed by direct acetylation (addition of pyridine).[7] As summarized in Table I, the spectroscopic data of these two derivatives differ only slightly, the most clear difference being the integrated intensities of the n.m.r. peaks at 3.21 and 3.60 p.p.m. and the chemical shifts of the aromatic methyl groups. Likewise, structure **13** can be assigned to diacetyldihydrocelastrol: $\nu^{CHCl_3}$ 1767, 1700 cm.$^{-1}$; $\delta$ 2.27, 2.27 (OAc), 2.05 (arom. Me), 1.37, 1.25, 1.13, 1.10, 0.70 p.p.m. (other Me) (see also Table I). However, the structure of celastrol reductive acetate, although undoubtedly closely related to **13**, is also not clear.




H-1, 6.53 p.p.m. (d, 1.5 c.p.s.)
H-6, 7.01 (q, 7 and 1.5 c.p.s.)
H-7, 6.34 (d, 7 c.p.s.)

Oxidative decarboxylation of diacetyldihydrocelastrol (**13**) with lead tetraacetate gave rise to a crystalline mixture, m.p. 161–163°; structure **14** (mixture of 19-ene and 20-ene) can be assigned to it on the basis of the n.m.r. spectrum which showed a new low-field signal at 1.70 p.p.m. (olefinic Me, split into a doublet). The four methyl groups attached to saturated carbon atoms appeared in the range of 0.62 to 1.43 p.p.m., three of them being split into doublets, while the benzylic methylene had its peak at 3.13 p.p.m. (broad) and the olefin protons at C-19 and C-21 resonated at 5.20 and 5.55 p.p.m., respectively. The formation of an olefinic methyl group upon decarboxylation provides further support for placing the –COOR group at C-20 rather than at C-17.[3] The decarboxylation of celastrol reductive acetate also gave a nor compound,[3] m.p. 221°, having spectroscopic properties closely related to **14**, but again the n.m.r. peak at 3.52 p.p.m. (benzylic proton at C-6) had an integrated intensity corresponding to only one proton; this is also a mixture of the 19-ene and 20-ene (n.m.r. signals of olefin-H at 5.13 and 5.78 p.p.m.). Thus, although structures **13** and

TABLE I

DIFFERENCE IN SPECTROSCOPIC PROPERTIES BETWEEN DIACETYLDIHYDROPRISTIMERIN (12) AND PRISTIMERIN REDUCTIVE ACETATE ($C_{34}H_{46}O_6$), AND BETWEEN DIACETYLDIHYDROCELASTROL (13) AND CELASTROL REDUCTIVE ACETATE ($C_{33}H_{44}O_6$)

| Compd. | Ultraviolet, $\lambda_{max}$, mμ (log ε) | Infrared in $CHCl_3$, cm.$^{-1}$ | N.m.r. in $CDCl_3$, p.p.m. |
|---|---|---|---|
| Pristimerin | | | |
| Diacetyldihydro- (12), m.p. 164–165° | 266 (2.92)<br>274 (2.92)<br>248[a] | Differ in absorption in 900–700 region | 2.05, arom. Me<br>3.21 (2H), $CH_2$ at C-6<br>5.82 (1H), C-7 H<br>6.96 (1H), arom. H |
| Reductive acetate, m.p. 252° | 266 (2.78)<br>275 (2.67) | | 1.77, arom. Me<br>3.60 (1H)<br>5.87 (1H)<br>7.18 (1H), arom. H |
| Celastrol | | | |
| Diacetyldihydro- (13), m.p. 211–212° | 266 (2.75)<br>275 (2.75)<br>254[a] | Weak peak at 1070 | 3.10 (2H), $CH_2$ at C-6<br>5.55 (1H), C-7H<br>7.00 (1H), arom. H |
| Reductive acetate, m.p. 244–246° | 268 (2.67)<br>277 (2.56) | Weak peak at 1125 | 3.61 (1H)<br>5.85 (1H)<br>7.10 (1H), arom. H |

[a] $\lambda_{min}$.

**14**, respectively, had previously been assigned to celastrol reductive acetate and its decarboxylated product,[3] these structures should be reassigned to diacetyldihydrocelastrol and its nor compound, and the structures of the reductive acetates of pristimerin and celastrol still remain obscure.

Finally, it is interesting to note that the n.m.r. spectrum of pristimerin shows long-range coupling[20] between the C-1 and C-6 protons ($J$ = 1.5 c.p.s., see **15**).

## Experimental

The mass spectra were measured using a CEC 21-1030 mass spectrometer at an ionization energy of 70 e.v. The n.m.r. spectra were measured with a Varian A-60 model employing TMS as internal reference. Preparations of most of the compounds dealt with in this paper have been described previously (see respective literature quoted) and accordingly the Experimental part only describes those requiring special comments.

**Extraction of Celastrol.**—Roots of *Celastrus strigillosus* Nakai were collected at Kashi Spa, Fukushima Prefecture. The orange-red root barks from 60 kg. of the root were peeled off, dried completely in a current of dry air at a temperature of less than 100°, and ground to 20 mesh to give 7 kg. of orange powder. The powder was extracted repeatedly for about a month with *n*-hexane and the extracts were concentrated *in vacuo* when a red sirup was obtained. This was dissolved in ether, the ether solution was filtered, and the ether was evaporated to the extent that addition of a small amount of petroleum ether gave flocculent precipitates. After the precipitates were filtered, the filtrate was treated with an additional amount of petroleum ether and left overnight to afford crude crystals of celastrol. Repeated recrystallization from ether–petroleum ether finally gave 90 g. of celastrol, m.p. 204–205°, as red cubes. There seemed to be little seasonal variation in the yield.

The root barks of *Tripterygium regelii* Sprague et Takeda were also employed but the extract gave a large amount of noncrystallizable sirup and the yield of celastrol was less.

**Isopristimerin-I (2) and Diacetylisopristimerin-II (4).**—Pristimerin (1 g.) was refluxed for 21 hr. in 60 ml. of 2 *N* sulfuric acid. The resulting black solid was crushed and washed with a small amount of methanol and recrystallized from methanol to give 100 mg. of isopristimerin-I, m.p. 206° (lit.[12] m.p. 207–208°). The methanol-soluble part of the black solid and the mother liquor were combined and taken to dryness, and the residual paste was acetylated with acetic anhydride and pyridine when 200 mg. of diacetylisopristimerin-II, m.p. 160° (lit.[12] Thiele acetate, m.p. 160–161°), was obtained.

**Attempted Isomerization of Isopristimerin-I.**—Isopristimerin-I (30 mg.) was dissolved in 4 ml. of boiling acetic anhydride and treated with a drop of concentrated sulfuric acid. After 10 min. the pale yellow solution was poured into ice–water and extracted with ether, and the extract was evaporated after being washed with water and saturated sodium bicarbonate solution. The residue was chromatographed on alumina and eluted with ether to afford colorless needles, identified as diacetylisopristimerin-I (**3**), m.p. 172–173°.

**Diacetyldihydropristimerin (12) and Diacetyldihydrocelastrol (13).**—A solution of 100 mg. of pristimerin in 4 ml. of ethanol was treated with a small amount of sodium borohydride, and the excess reagent was decomposed with acetic acid. Addition of hot water to the boiling alcoholic solution yielded 100 mg. of dihydropristimerin (pristimerol),[7] m.p. 241°. The crystals were immediately acetylated with acetic anhydride (2 ml.) and pyridine (1 ml.) overnight at room temperature. The reaction mixture was poured into ice–water and filtered, and the precipitates were recrystallized from aqueous methanol to give 40 mg. of colorless plates of diacetyldihydropristimerin, m.p. 164–165°.

*Anal.* Calcd. for $C_{34}H_{46}O_6$: C, 74.15; H, 8.42. Found: C, 74.03; H, 8.21.

Diacetyldihydrocelastrol was prepared in a similar manner by acetylating freshly prepared dihydrocelastrol; however, since the product was contaminated with the acid anhydride (infrared bands at 1810 and 1750 cm.$^{-1}$), it was boiled in methanol for 1.5 hr. From 1 g. of celastrol there was obtained 900 mg. of diacetyldihydrocelastrol, m.p. 211–212° (from methanol).

*Anal.* Calcd. for $C_{33}H_{44}O_6$: C, 73.85; H, 8.26. Found: C, 73.81; H, 8.07.

**Decarboxylation of Diacetyldihydrocelastrol.**—The procedure given in ref. 21 was followed. Diacetyldihydrocelastrol (500 mg.) and 400 mg. of freshly prepared lead tetraacetate (1 mole equiv.) were refluxed for 5 hr. in 50 ml. of dry benzene under nitrogen. The reaction mixture was poured into a solution of ferrous sulfate and extracted with ether, the ether layer was washed in turn with water, sodium bicarbonate, and water, and dried by passing through anhydrous sodium sulfate, and the ether was evaporated. The residue was dissolved in chloroform and chromatographed through silica gel to give the crude decarboxylated product **14**, which was recrystallized from aqueous ethanol, m.p. 161–163°.

*Anal.* Calcd. for $C_{32}H_{42}O_4$: C, 78.33; H, 8.63. Found: C, 78.00; H, 8.29.

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# Regeneration of Steroid Alcohols from Their Methyl Ethers*,[1]

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A mixture of boron trifluoride etherate and acetic anhydride at 0° or below has been found to cleave different types of steroidal methyl ethers. Allylic and homoallylic ethers give the corresponding acetates in yields of over 90%. Completely saturated ethers give the acetate with retention of configuration as the main substitution product, but the epimeric acetate and elimination products are also obtained.

In work on the chemistry of natural products, it is often necessary to protect aliphatic hydroxyl groups before attacking other sensitive centers of the molecule. Esterification of the hydroxyl group is not always useful, since it may not give any protection even under mild alkaline conditions. Methylation does give the necessary protection under alkaline and mild acidic conditions, but there is no simple way to demethylate and regain the hydroxyl group from the methoxyl. The methods available at present[2] either use too drastic conditions, which might break up sensitive parts of the molecule, or may not lead to the desired alcohol.

Following the recent use[3] of boron trifluoride etherate and acetic anhydride at room temperature to cleave a steroid 18,20-epoxide to the 18,20-diacetate, we tried those reagents at 0° to cleave different types of steroid methyl ethers. The progress of the reaction was followed by isolating the total reaction product at intervals and scanning its p.m.r. spectra to see whether the signal due to the methoxyl group had disappeared. (The methyl ethers were prepared in high yields from the corresponding alcohols by using potassium metal and methyl iodide.[4])

It was found that cholesteryl methyl ether gave, after 15 hr. at 0°, cholesteryl acetate in about 93% yield, but, with 4-cholesten-7$\beta$-ol methyl ether, it took 50 hr. at 0° to complete the reaction. The extended time for the latter was not unexpected since the double bond assists in the cleavage of the ethers in both cases, and there is evidence[5] which might mean that the participation of the $\Delta^4$ bond in the departure of a 7$\beta$-equatorial group is less than that of the $\Delta^5$ bond in the departure of a 3$\beta$-equatorial group.

When the reaction was tried on an allylic ether, 4-cholesten-3$\beta$-ol methyl ether, it was observed that a large amount of 3,5-cholestadiene was obtained. As this was ascertained to be due to the elimination of the initially formed allylic acetate under the acidic conditions of the reaction, we found out the minimum conditions under which 4-cholesten-3$\beta$-ol acetate survives the reagents. Under these conditions, *i.e.*, −18° for 3 min., 4-cholesten-3$\beta$-ol methyl ether gave 4-cholesten-3$\beta$-ol acetate in about 90% yield.

Methyl ethers whose cleavage had no such assistance from $\pi$ electrons gave both the epimeric acetates and elimination products. Thus, cholestanyl methyl ether gave cholestanyl acetate (33%), cholestan-3$\alpha$-ol acetate (25%), and 2-cholestene (25%). Similarly from cholestan-3$\alpha$-ol methyl ether, we obtained cholestan-3$\alpha$-ol acetate (14%), cholestanyl acetate (8%), and 2-cholestene (50%).

That both boron trifluoride etherate and acetic anhydride are necessary for this cleavage and that the products, once formed, generally do not undergo further changes has been shown by treating cholestanyl methyl ether with (i) acetic anhydride alone and (ii) with boron trifluoride etherate and benzene, and also by treating cholesteryl and cholestanyl acetates with boron trifluoride etherate and acetic anhydride, and recovering in each case only the starting materials.

The cleavage thus appears to involve the initial formation of an oxonium ion by the addition of boron trifluoride etherate to the ether oxygen and cleavage of the carbon–oxygen bond from (a) the secondary carbon to give the elimination and epimeric products and (b) from the methoxy methyl to give the product with retention of configuration by the nucleophilic attack of the acetate moiety of the acetic anhydride. The boron trifluoride complex of the steroid is subsequently replaced by the acetylium moiety of the acetic anhydride. It is interesting to note that the acetate with retention of configuration predominates in both the cases. The larger amount of elimination with cholestan-3$\alpha$-ol methyl ether is easily explicable as the axial methoxyl group is very favorably set for acid-catalyzed eliminations. When the allylic and homoallylic ethers are cleaved from the steroid nucleus, the double bond assists[6] in stabilizing the carbonium ion and gives the more stable equatorial acetate. Under the acidic conditions, even if a 3,5-cyclopropane-6$\beta$-ol acetate is formed, it will be readily rearranged into the $\Delta^5$-3$\beta$-ol acetate.[6,7] These equatorial ethers, when cleaved from the methoxy

* To Professor Louis F. Fieser.

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