Tetrahedron Letters No. 14, pp. 603-607, 1962. Pergamon Press Ltd. Printed in Great Britain.

STRUCTURE OF PRISTIMERIN, A QUINONOID TRITERPENE

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(Received 25 April 1962; in revised form 15 May 1962)

PRISTIMERIN,[1] $C_{30}H_{40}O_4$, is the methyl ester of celastrol.[2] Since the isolation of celastrol (tripterine)[3] a number of chemical studies have been carried out[4] because of its antibiotic properties and conspicuous orange colour. Investigations on pristimerin were resumed here when it was found that the roots of Tripterygium regelii Sprague et Takeda, and especially Celastrus strigillosus Nakai were suitable sources for celastrol. The following chemical and NMR evidences allow the recently proposed structure I[5] to be extended to the full expression II.

Information on the carbocyclic skeleton, especially C, D and E rings, was gained from selenium dehydrogenation of the ester anhydride III[5] (permanganate oxidation product of pristimerin). The minute amount of product, in the form of its trinitrobenzolate, m.p. 140-148°, absorbed at 260, 282,

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291, 303.5, 322, 330, 337.5, 345 and 353 mμ, these maxima[6] being identical with those reported for 1,2,6-trialkylphenanthrene.[7] This evidence coupled with the production of an alkylpicene by zinc-dust distillation[2] supports its pentacyclic skeleton.

The fact that the NMR[8] methyl peaks of all derivatives of pristimerin appeared as singlets suggested the oleanane type ring E. For example, the spectrum of dimethyl pristimerol (IV) showed in CCl_4: nine methyl singlets at 9.41, 8.92, 8.85, 8.77, 8.66 (C-Me), 7.85 (Ar-Me), 6.52 (COOMe), 6.26, 6.06 (Ar-OMe); an allylic methylene at 6.87 (broad); a vinyl proton at 4.27 (broad) and an aromatic proton singlet at 3.35. The 6.87 peak is absent in oxodimethylpristimerol (V),[5] and the 4.27 and 7.85 peaks are shifted lower to 3.87 (singlet) and 7.40, respectively. The shift of the 7.85 singlet in IV to 7.40 in V indicates an aromatic methyl group in a peri-position (C_4) to the C_6-C=O.

Treatment of pristimerin with 2N H_2SO_4 in nitrogen gave the naphthalenoid compounds, isopristimerin-I[9] (VII) m.p. 207-208°, and -II (IX) m.p. 70-75°, the latter being found to be identical with the hydrolysis product[5] of the so-called Thiele acetate (X).[9] These are formulated as shown for the following reasons. The NMR spectrum of VII in $CDCl_3$ showed: an AB type quartet[10] at 2.48 and 2.94 (J=8.2 cps) superimposed on a singlet at 2.95 (aromatic ortho protons and isolated proton); two aromatic methyl singlets

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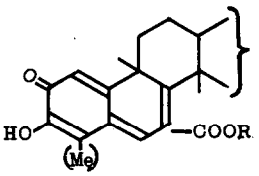
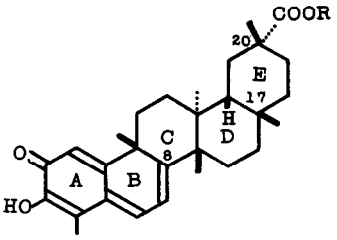
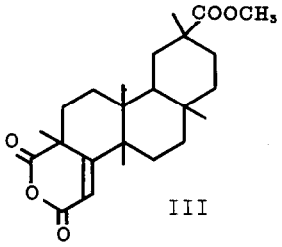


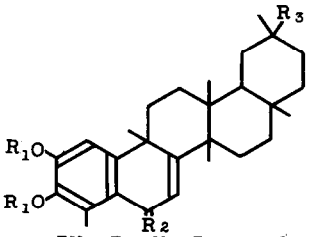
I Celastrol,R:H
Pristimerin,R:Me



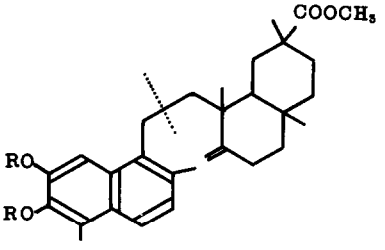
II Celastrol,R:H
Pristimerin,R:Me



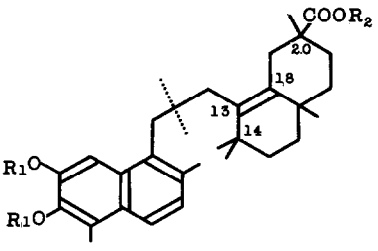
III



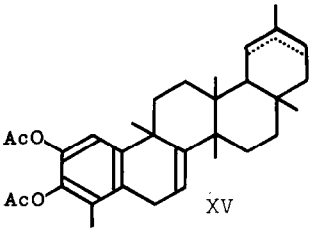
IV R_1:Me,R_2:H_2,R_3:COOMe
V R_1:Me,R_2:O, R_3:COOMe
VI R_1:Ac,R_2:H_2,R_3:COOH
XVI R_1:Ac,R_2:H_2,R_3:CH_2OAc



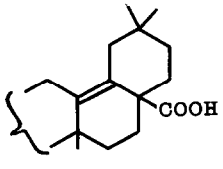
VII Isopristimerin-I,R:H
VIII R:Ac



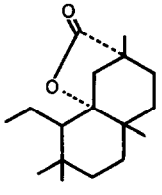
IX Isopristimerin-II,R_1:H,R_2:Me
X Thiele acetate,R_1:Ac,R_2:Me
XI R_1:R_2:Me
XII R_1:Me,R_2:H



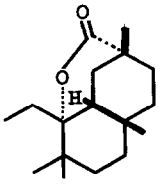
XV



XIIa



XIII



XIV

at 7.47 and 7.56; and a two-proton doublet at 4.95 and 5.09 due to the terminal methylene group. The aromatic substitution pattern is supported by clear I.R. peaks at 893 and 815 cm^{-1} (KBr). The I.R. in CCl_4 showed bands at 3584 (medium), 3400 (strong, broad) and 1702 cm^{-1}; intramolecular hydrogen bonding is associated with all three of them since concentration variation did not affect their relative intensities, whereas in dioxane they were shifted to higher frequencies, i.e. to 3600, 3560 and 1730 cm^{-1}. The ester band is also at the normal position of 1732 cm^{-1} (CCl_4) in the acetate (VIII) where the phenolic hydroxyls are masked by acetyl groups, and in all other derivatives of pristimerin. These I.R. and NMR data can only be accounted for by cleaving bond C_8-C_{14} as shown in VII so that an intramolecular bond can be formed between the ester group and one of the hydroxyl groups. The NMR spectra of isopristimerin-II diacetate (X) and dimethyl ether (XI) were also in full accord with the structures shown, which are both easily derivable from pristimerin by initial protonation on the carbonyl group. The mass spectrometric data also unambiguously support the structures shown. For example, the only conspicuous peaks in the spectrum of isopristimerin-I diacetate (VIII) were at m/e 285, 243 and 201 (base peak), corresponding to cleavage between C_{11}-C_{12} accompanied by deacetylation (-42, -84). Isopristimerin-II diacetate (X) similarly gave the 285, 243 and 201 peaks, but also showed peaks a and b originating from the D/E rings and stabilized by the ring D double bond:

(a) 263, 203: 203=263-60 ($-COOCH_3$, -H)
(b) 249, 189 (base peak): 263-14 (CH_2), 203-14.

The position of the methoxycarbonyl group will be discussed next. The NMR spectrum of the reductive triacetate (XVI), $C_{35}H_{48}O_6$, m.p. 103-106°, obtained by lithium aluminium hydride reduction of pristimerin followed by acetylation, showed an AB type quartet at 6.19 and 6.37 (J=10.5 cps) due to a hindered primary hydroxyl, and this indicated that the methoxycarbonyl

was attached to a quaternary carbon atom. Of the possible positions for the attachment only C_{17} and C_{20} have to be considered on the basis of the structure of isopristimerin-I and -II (VII and IX). Several data all suggested the C_{20}-position: (i) The acid XII was recovered unchanged after being kept at 160° for 1 hr in vacuo; thus it could not be the β,γ-unsaturated acid XIIa; (ii) treatment of the acid XII with hydrogen chloride afforded two lactones, $C_{31}H_{42}O_4$, m.p. 229-230°, I.R. max (KBr) 1780 cm^{-1} (XIII), and m.p. 149-150°, I.R. max (CCl_4) 1732 cm^{-1} (XIV), which arise from addition of the carboxyl group to C_{18} and C_{13}, respectively. If structure XIIa were correct the δ-lactone could only be formed by attachment of the carboxyl at positions C_{12}, C_{14}, or C_{20} after appropriate 1,2-migrations. However, the NMR spectrum, which showed the four saturated methyl peaks as singlets at 8.95, 8.89, 8.85 and 8.81 (in CCl_4) was fully consistent with structure XIV and also excluded other possibilities; (iii) treatment of celastrol reductive acetate (VI), $C_{33}H_{44}O_6$, m.p. 244-246°, with lead tetraacetate[11] afforded a decarboxylated nor-compound, $C_{32}H_{42}O_4$, m.p. 221°. This is represented as XV on the basis of the NMR spectrum (in CCl_4) which showed a new low-field methyl singlet at 8.42 (C_{20}-methyl) and a broad signal at 4.87 (C_{21}-proton). Decarboxylation of a C_{17}-carboxyl would not give an allylic methyl group.

The stereochemistry at ring junctures is derived from logical biogenetic transformations from a β-amyrin type precursor, and it is interesting to note that pristimerin is a triterpene in a most advanced oxidative stage. The C_{20}-COOR is regarded as being α in view of the formation of lactones XIII and XIV. The chemical correlation with known triterpenes is being attempted.

Acknowledgements - The authors are indebted to Professor C. Djerassi and Dr. H. Budzikiewicz, Stanford University, for measurement of the mass spectra. We are also grateful to Colonel S.S. Bhatnagar, St. Xaviers College, Bombay, for providing us material used in the early stage, and to Dr. K. Nukada, Tokyo Kogyo Shikenjo, for use of the NMR instrument. The work was supported by grant No. GA MNS 60183 from the Rockefeller Foundation.

[11] G. Büchi, R.E. Erickson and N. Wakabayashi, J. Amer. Chem. Soc. 83, 927 (1961).