Oxidation and Solvolysis of Lumi- and Photohecogenin and Their Derivatives

LELAND J. CHINN

Division of Chemical Research, G. D. Searle & Co., Chicago, Illinois 60680

Received October 5, 1966

Oxidation of either lumihecogenin (IIa) or photohecogenin (IIIa) with chromium trioxide in dilute acetic acid gives 14α-hydroxyhecogenone (V). As solvolysis of lumihecogenin acetate (IIb) and photohecogenin acetate (IIIb) in dilute acetic acid affords 12α,14α-dihydroxytigogenin 3-acetate (VIIIa), the mechanism of the oxidation of IIa is considered to be one in which cyclization precedes oxidation to give the β-hydroxycyclohexanone system of V.

Irradiation of hecogenin acetate (I) with ultraviolet light affords two isomeric substances, lumihecogenin acetate (IIa) and photohecogenin acetate (IIIa).[1] In the course of elucidating their structures, Bladon, *et al.*, converted both compounds to 14α-hydroxyhecogenone (V), although in an indirect way.

Lumihecogenin acetate (IIa) was oxidized with chromium trioxide–sulfuric acid in acetone to give 14α-hydroxyhecogenin acetate (IVa). Saponification of IVa gave 14α-hydroxyhecogenin (IVb), which was then oxidized to 14α-hydroxyhecogenone (V).[1]

The conversion of photohecogenin acetate (IIIa) to V involved isomerization of IIIa to 12α-hydroxy-14-dehydrotigogenin acetate (VI). The latter was epoxidized following which the epoxide was reductively cleaved with lithium aluminum hydride. In the process, the ester group at C-3 was removed. Oxidation of the resultant triol with chromium trioxide–sulfuric acid in acetone gave V.[1]

In our study, we found that 14α-hydroxyhecogenone (V) can be obtained directly from either lumihecogenin (IIb) or photohecogenin (IIIb) with chromium trioxide in dilute acetic acid. Although Bladon, *et al.*,[1] were not able to obtain lumihecogenin (IIb) from its acetate IIa, we obtained IIb as a crystalline product by saponifying IIa in a nitrogen atmosphere.

When photohecogenin (IIIb) is oxidized with chromium trioxide in pyridine[2] instead of in acetic acid, oxidation occurs at C-3, and the product is photohecogenone (VII). When the same conditions are applied to photohecogenin acetate (IIIa), only starting material is recovered, thus confirming that C-3 is the sole center which is affected in the chromium trioxide–pyridine oxidation of IIIb. Treatment of photohecogenin acetate (IIIa) with chromium trioxide in dilute acetic acid results in the formation of 14α-hydroxyhocegenin acetate (IVa, see Scheme I).

Our results suggest that acetic acid promotes the opening of the oxetane ring of photohecogenin. Indeed, a solution of photohecogenin acetate (IIIa) in dilute acetic acid, on standing, yields a mixture of products from which 12α,14α-dihydroxytigogenin 3-acetate (VIIIa) can be isolated after chromatography.[3] The latter can be converted to the diacetate (VIIIb). Under the same conditions, lumihecogenin acetate (IIa) solvolyzes to give the same mixture of products. The transformation of IIa to VIIIa is an example of an intramolecular Prins reaction.[4]

As both lumihecogenin acetate (IIa) and photohecogenin acetate (IIIa) yield the same mixture of products on solvolysis, it appears very likely that a common intermediate is involved in the formation of 14α-hydroxyhecogenone (V) from lumihecogenin (IIb) and photohecogenin (IIIb). Although the oxidation of lumihecogenin acetate (IIa) to 14α-hydroxyhecogenin acetate (IVa) has been postulated[1] as proceeding by an initial oxidation of the double bond by chromic acid followed by cyclization of the aldehyde function, our results are more compatible with a mechanism in which cyclization precedes oxidation in the formation of the β-hydroxycyclohexanone system.

Experimental Section[5]

Lumihecogenin (IIb).—A mixture of 500 mg of lumihecogenin acetate (IIa),[1] 5 ml of methanol, and 195 mg of 85% potassium hydroxide pellets was heated under reflux in an atmosphere of nitrogen for 1 hr. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4), and evaporated to dryness to afford a viscous, colorless oil. The oil was crystallized from hexane to afford 329 mg of IIb: mp 152–157°; λ_{max}^{KBr} 2.87, 3.63, 5.82, 10.23, 10.83, 11.10, 11.57 μ; $[\alpha]^{25}D$ −30° (*c* 1, dioxane). The aldehydic proton signal appeared at 568 cps downfield with respect to internal tetramethylsilane when the nmr spectrum was determined in $CDCl_3$ on a Varian A-60 instrument.

Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 75.36; H, 10.16.

Oxidation of Lumihecogenin (IIb).—To a mixture of 242 mg of lumihecogenin (IIb), 3 ml of glacial acetic acid, and 1.5 ml of water, stirred at room temperature, was added a solution of 100 mg of chromium trioxide in 2 drops of water and 2 ml of glacial acetic acid. The reaction mixture was stirred at room temperature for 0.5 hr and then allowed to stand at room temperature for an additional 15 hr, after which it was poured into ice water. The resultant colorless solid was collected, washed well with water, and dried: mp 206–238°, yield 203 mg. Crystallization from ether–hexane afforded 89 mg of 14α-hydroxyhecogenone (V), mp 246–251°. Another crystallization from ether–hexane raised the melting point to 252.5–255° (lit.[1] mp 259–261°); λ_{max}^{KBr} 2.84, 5.86, 10.21, 10.88, 11.12, 11.54 μ.

Anal. Calcd for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found: C, 72.99; H, 8.94.

Oxidation of Photohecogenin (IIIb).—A solution of 371 mg of IIIb,[1] 4 ml of glacial acetic acid, 2 ml of water, and 140 mg of chromium trioxide was allowed to stand at room temperature for 16 hr. The reaction mixture was diluted with ice water. The

(1) P. Bladon, W. McMeekin, and I. A. Williams, *J. Chem. Soc.*, 5727 (1963).

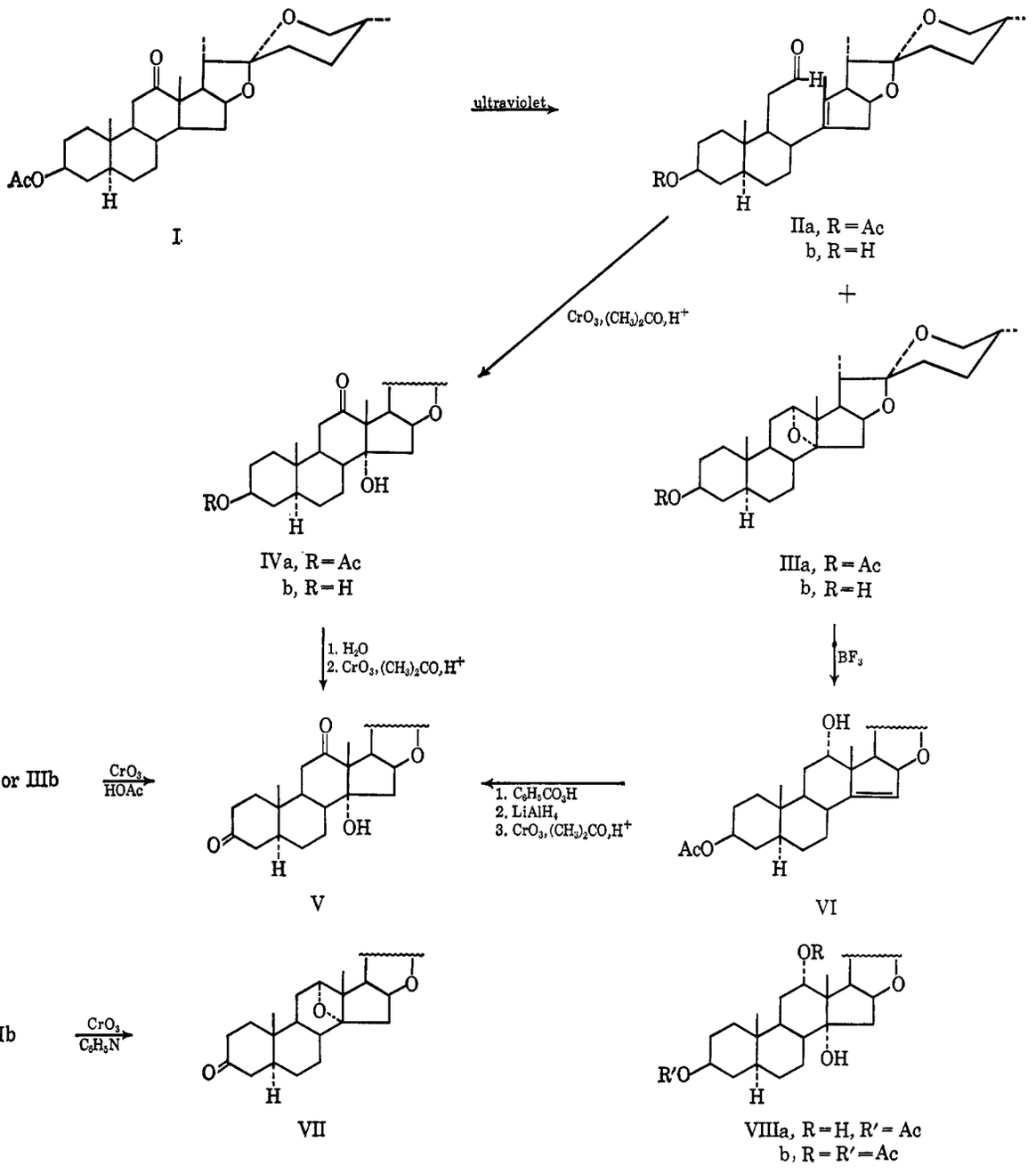
(2) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 425 (1953); J. R. Holum, *J. Org. Chem.*, **26**, 4814 (1961).

(3) On the assumption that the crude product was a mixture of VIIIa and its 12β epimer, we converted it to the 3,12 diacetates. The crude diacetates were then subjected to methanolysis in the presence of triethylamine–triethylammonium acetate buffer with the expectation that 12α,14α-dihydroxytigogenin 3,12-diacetate (VIIIb) would be selectively solvolyzed at the 12 position because of the 1,3-diaxial relationship of the 12α-acetoxy and the 14α-hydroxyl groups; *cf.* S. M. Kupchan, S. P. Eriksen, and M. Friedman, *J. Am. Chem. Soc.*, **88**, 343 (1966). Although the desired solvolysis occurred to some extent, as shown by thin layer chromatography, we were not able to obtain VIIIa from the reaction mixture by direct crystallization.

(4) H. J. Prins, *Chem. Weekbald*, **16**, 1510 (1919); F. Arundale and L. A. Mikeska, *Chem. Rev.*, **51**, 505 (1952); E. E. Smissman, R. A. Schnettler, and P. S. Portoghese, *J. Org. Chem.*, **30**, 797 (1965).

(5) Melting points were determined on a Fisher-Johns melting block and are corrected.

SCHEME I



solid was collected, washed well with water, and dried: yield 225 mg, mp 186–232.5°. Crystallization from ether–hexane gave 68 mg of 14α-hydroxyhecogenone (V), mp 248.5–249.5°. After another crystallization from ether–hexane, it melted at 253–257°. Its infrared spectrum was identical with that of V, mp 252.5–255°, prepared from lumihecogenin (IIb).

Photohecogenone (VII).—To a chilled mixture of 400 mg of chromium trioxide in 4 ml of pyridine was added a solution of 578 mg of photohecogenin (IIIb)[1] in 5 ml of pyridine. The reaction mixture was allowed to stand at room temperature for 14 hr. Then it was diluted with water and cooled to 0°. The resultant solid was collected, washed with water, and dried. It was dissolved in ethyl acetate. The ethyl acetate solution was treated with charcoal and filtered. The filtrate was concentrated to a very small volume, and the residue was diluted with hexane to afford 158 mg of VII, mp 189–192.5°. From the mother liquor a second crop of VII was obtained: mp 179.5–190°, yield 242 mg. The first crop was crystallized from hexane to afford 113 mg of VII: mp 192.5–194°; $[\alpha]^{25}D$ −25° (*c* 1, dioxane); λ_{max}^{KBr} 5.84, 10.18, 10.90, 11.12, 11.57 μ.

Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 76.07; H, 9.52.

Attempted Oxidation of Photohecogenin Acetate (IIIa) with Chromium Trioxide in Pyridine.—To a mixture of 400 mg of chromium trioxide and 4 ml of pyridine, cooled in an ice bath, was added a solution of 445 mg of photohecogenin acetate (IIIa) in 5 ml of pyridine. The reaction mixture was allowed to stand at room temperature for 17 hr. Then it was poured into ice water. The resultant colorless solid was collected, washed well with water, and dried: yield 397 mg, mp 188.5–200.5°. Crystallization from methanol afforded 384 mg of IIIa, mp 201.5–202.5°, undepressed when admixed with the starting material (lit.[1] mp 205–208°). The infrared spectra of the product and the starting material were identical.

Oxidation of Photohecogenin Acetate (IIIa) with Chromium Trioxide in Acetic Acid.—To a mixture of 463 mg of photohecogenin acetate (IIIa),[1] 6 ml of glacial acetic acid, and 2 ml of water, stirred at room temperature, was added a solution of 100 mg of chromium trioxide in 2 drops of water and 2 ml of glacial acetic acid. The reaction mixture was stirred at room temperature for 7 hr and then allowed to stand at room temperature for an additional 15 hr, after which it was diluted with ice water. The resultant, colorless solid was collected, washed with water, and dried. Crystallization from hexane gave 219 mg of

14α-hydroxyhecogenin acetate (IVa): mp 232.5–235°, (lit.[1] mp 231–235°); λ_{max}^{KBr} 2.81, 5.77, 5.84, 8.02, 10.20, 10.90, 11.12, 11.49 μ.

Anal. Calcd for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 71.05; H, 9.13.

Treatment of Photohecogenin Acetate (IIIa) with Dilute Acetic Acid.—A mixture of 454 mg of IIIa,[1] 6 ml of glacial acetic acid, and 2 ml of water was stirred at room temperature for 0.5 hr during which time complete solution was effected. The reaction mixture was allowed to stand at room temperature for an additional 19.5 hr, after which it was poured into ice water. The colorless solid was collected, washed well with water, and dried, mp 207.5–217°. Thin layer chromatography indicated that the product was a mixture of at least two substances. Crystallization from methanol afforded 370 mg of 12α,14α-dihydroxytigogenin 3-acetate (VIIIa): mp 221–225° (lit.[1] mp 219–222.5°); λ_{max}^{KBr} 2.83, 2.88, 5.77, 8.00, 10.18, 10.91, 11.08, 11.52 μ.

Anal. Calcd for $C_{29}H_{46}O_6$: C, 70.98; H, 9.45. Found: C, 71.22; H, 9.41.

Thin layer chromatography indicated that VIIIa (mp 221–225°) was still contaminated with a small amount of a more polar substance. Separation of the contaminant by preparative thin layer chromatography on silica gel with 35% ethyl acetate in benzene as the solvent system gave a pure sample of VIIIa, mp 220–222°.

Treatment of Lumihecogenin Acetate (IIa) with Dilute Acetic Acid.—A mixture of 319 mg of IIa,[1] 6 ml of glacial acetic acid, and 2 ml of water was stirred at room temperature for 20 hr during which time complete solution was effected. The reaction mixture was poured into ice water. The resultant colorless solid was collected, washed with water, and dried, mp 213–219.5°. Thin layer chromatography indicated that the crude product was a mixture having the same composition as that obtained from photohecogenin acetate (IIIa). The infrared spectra of the two mixtures were indistinguishable. Crystallization from methanol gave 190 mg of 12α,14α-dihydroxytigogenin 3-acetate (VIIIa), mp 213–217.5°. Its infrared spectrum was identical with that of VIIIa, mp 221–225°, obtained from photohecogenin acetate (IIIa).

12α,14α-Dihydroxytigogenin 3,12-Diacetate (VIIIb).[1]—A solution of 86 mg of 12α,14α-dihydroxytigogenin 3-acetate (VIIIa), 0.2 ml of pyridine, and 0.2 ml of acetic anhydride was heated on the steam bath for 3 hr. The cooled reaction mixture was poured into ice water. The colorless solid was collected, washed well with water, and dried. Crystallization from methanol gave 45 mg of VIIIb, mp 227–229° (lit.[1] mp 223–225.5°). Admixed with the starting material, it melted at 194–196°.

Anal. Calcd for $C_{31}H_{48}O_7$: C, 69.89; H, 9.08. Found: C, 69.90; H, 9.18.

Registry No.—V, 10075-96-4; VII, 10102-97-3; IVa, 10102-98-4; VIIIa, 10102-99-5; VIIIb, 10075-97-5; IIa, 10075-98-6; IIIa, 10102-96-2.

Experiments Directed toward the Total Synthesis of Terpenes. XI. The Total Synthesis of (±)-Rimuene and (±)-13-*epi*-Rimuene[1a]

ROBERT E. IRELAND[1b] AND LEWIS N. MANDER

Contribution No. 3402 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California, and the Department of Chemistry, The University of Michigan, Ann Arbor, Michigan

Received August 16, 1966

A stereoselective total synthesis of the diterpenoid hydrocarbon rimuene (1) is described. In order to ascertain the configuration about the 13 position of rimuene (1), 13-*epi*-rimuene (16) was synthesized as well and both compounds related to the pimaradiene series of known C-13 configuration.

The diterpenoid hydrocarbon rimuene (1) has in recent years been the subject of intensive structural study by several groups.[2] Initial structural postulates[2a,b] were shown to be untenable by synthetic work in these laboratories,[3] and it was not until the work of Overton[2e] and Corbett[2d] and their respective collaborators that the final answer to this structural problem was provided. The structure 1, on which both groups agree, represents a skeletal rearrangement of the more common tricyclic diterpenoid backbone as found in the pimaradenes 19 and 22*. As such rimuene (1) is structurally more closely related to the mould metabolite rosenenolactone,[4] and indeed may arise by a biogenetic pathway that is similar to the early stages of the proposed rosenonolactone scheme.[5]

Our historical connection[3] with the rimuene problem, as well as our continuing interest in developing synthetic methods for the construction of diterpenoid structural variants, prompted us to undertake a total synthesis of this new structure.

The framework of rimuene molecule 1 is sufficiently different from that of the pimaradienes to require a somewhat different synthetic approach. In particular, the nuclear double bond is far removed from the vinyl group at C-13[6] in rimuene (1). Therefore each of these functional groups will have to be developed independently in contrast to the approach used in the pimaradiene-type syntheses.[3]

Recognizing the lability of the C-13 vinyl group toward common reaction conditions, we chose to introduce the substituents at C-13 in the last stages of the synthesis. A logical functional group that could serve as the root for this branching was a ketone, and hence our consideration was shifted to the tricyclic ketone (2).

The principal remaining synthetic complexity in rimuene skeleton 1 is the arrangement of carbon atoms that make up ring A. Of particular note is *the lack of a C-10[6] angular methyl group*. The fact that the A/B ring fusion is unencumbered by a quaternary carbon at C-10 suggested to us that a suitably substituted

(1) (a) A portion of the work here recorded was reported in preliminary form: see R. E. Ireland and L. N. Mander, *Tetrahedron Letters*, 3453 (1964). Support for this work in the form of a research grant (GM-09067-03) from the Public Health Service is gratefully acknowledged. (b) Alfred P. Sloan Foundation Research Fellow, 1962–1966.

(2) (a) L. H. Briggs, B. F. Cain, and J. K. Wilmhurst, *Chem. Ind.* (London), 599 (1958); (b) L. H. Briggs, B. F. Cain, and R. C. Cambie, *Tetrahedron Letters*, 17 (1959); (c) R. M. Carman, *Australian J. Chem.*, **16**, 225 (1963); (d) R. E. Corbett and S. G. Wylie, *Tetrahedron Letters*, 1903 (1964); (e) J. D. Connolly, R. McCrindle, R. D. H. Murray, and K. H. Overton, *J. Chem. Soc.*, 273 (1966); (f) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965).

(3) R. E. Ireland and P. W. Schiess, *ibid.*, **28**, 6 (1963); R. F. Church and R. E. Ireland, *ibid.*, **28**, 17 (1963).

(4) G. A. Ellestad, B. Green, A. Harris, W. B. Whalley, and H. Smith, *J. Chem. Soc.*, 7246 (1965).

(5) A. J. Birch, R. W. Rickards, H. Smith, A. Harris, and W. B. Whalley, *Proc. Chem. Soc.*, 223 (1958); J. J. Britt and D. Arigoni, *ibid.*, 224 (1958).

(6) Unless specifically indicated by an asterisk following the formula number, all compounds referred to in this report are racemic modifications although only one enantiomer is depicted in the drawings.