Tetrahedron Letters No.8, pp. 387-389, 1964. Pergamon Press Ltd.
Printed in Great Britain.

A SIMPLE SYNTHESIS OF EQUILIN

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(Received 18 December 1963)

A synthesis of equilin by a multi-stage process, including microbiological dehydrogenation as the last step has been described recently (1).

We wish to report now a relatively simple and completely chemical synthesis of this hormone starting with the easily available (2) compound I.

The dienone I was converted into the enol diacetate II in a yield of 56%. This was achieved by refluxing a solution of I (10 g.) in acetic anhydride (200 ml.),acetyl chloride (80 ml.) and pyridine (2.8 ml.) overnight in a nitrogen atmosphere. The product crystallized from methanol as pale yellow needles m.p. 116-120°C. [U.V. λ_{max} 302 (ε=17,620), 315(ε=20,400), 328(ε=14,900) mμ; I.R. 1733 cm^{-1}].

The enol acetate II (1.4 g.) was heated under reflux with sodium bicarbonate (2.8 g.) in dry methanol (40 ml.) for five minutes and the solution was then poured into 270 ml. of 1% acetic acid. The crude product isolated by extraction with ethyl acetate was mainly the acetoxy dienone IIIa contaminated with a small amount of the corresponding hydroxy compound IIIb. Compound IIIb was purified by crystallization from chloroform-hexane to a melting point of 212-214°C [U.V. λ_{max} 239 mμ (ε=15,800); I.R. 3600, 3430, 1727, 1660, 1622 cm^{-1}].

The dienone IIIa was purified by passing the crude product in benzene solution through a column of Woelm Alumina (Act. III). It was obtained as a foam homogeneous in thin layer chromatography in a yield of 62%

[U.V. λ_{max} 236 mμ (ε=12,620); I.R. 1727, 1660, 1620 cm^{-1}].

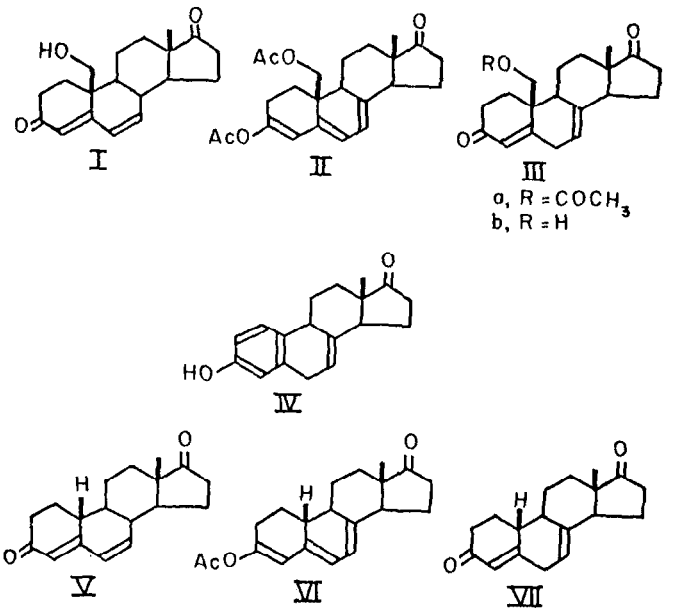
Compound IIIa (0.46 g.) was treated with 1.2 moles of dichlorodicyano-p-benzoquinone in dry dioxane (30 ml.) at reflux temperature for seventeen hours. The crude product was hydrolyzed with 4% methanolic sodium hydroxide. From the reaction mixture equilin was isolated by chromatography on silica gel and on alumina, followed by recrystallization from ethyl acetate. The equilin (IV) thus obtained was identical with an authentic sample by melting point (234-235°C), mixed melting point and infrared spectrum.

The original mixture of IIIa and IIIb when exposed to the action of the spores of Nocardia restrictus poisoned by an 0.325% solution of potassium cyanide gave equilin in a yield of 20%. The equilin was isolated as described and was identical with an authentic sample. Experiments to increase the yield in this process are under way.

It is of some interest that our simple method of deconjugation by hydrolysis of the enol acetate may be also used for the conversion of the 19-nordienone V (1,2) to the dienone VII. Since VII has been converted to equilin by a microbiological method, this constitutes a simplification of Djerassi's synthesis (1).

A solution of dienone V (2.2 g.) in acetic anhydride (44 ml.), acetyl chloride (17.6 ml.) and pyridine (1.76 ml.) was refluxed for 2.25 hours. The solvent was removed under reduced pressure and the residue was crystallized from methanol to give pale yellow needles of the enol acetate VI (yield 58.5%) m.p. 175-8° [U.V. λ_{max} 299(ε=15,830), 311(ε=19,504), 325 (ε=13,990) mμ; I.R. 1722 cm^{-1}].

Compound VI (0.289 g.) was heated under reflux with sodium bicarbonate (0.479 g.) in dry methanol (55 ml.) for ten minutes after which time the reaction mixture was poured into 77 ml. of 10% acetic acid. Extraction with ethyl acetate gave the crude dienone VII (yield 77.6%, based on ultraviolet spectrum). Trituration with ether, followed by crystalliz-



ation from acetone-hexane gave dienone VII m.p. 149-151°, [U.V. ν_{max} 237 mμ ε=14,300; I.R. ν_{max} 1727, 1660, 1625 cm^{-1}].

Acknowledgment:

The authors are very grateful to Dr. C. Vezina for carrying out the microbiological transformations. They also wish to acknowledge the technical assistance of Miss J. Mitchell and Mr. R. Guthrie during this work.

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