[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Stereochemical Relationships between the Isomers of Equilenin, Desoxyequilenin and 1,2,3,4-Tetrahydrodesoxyequilenin

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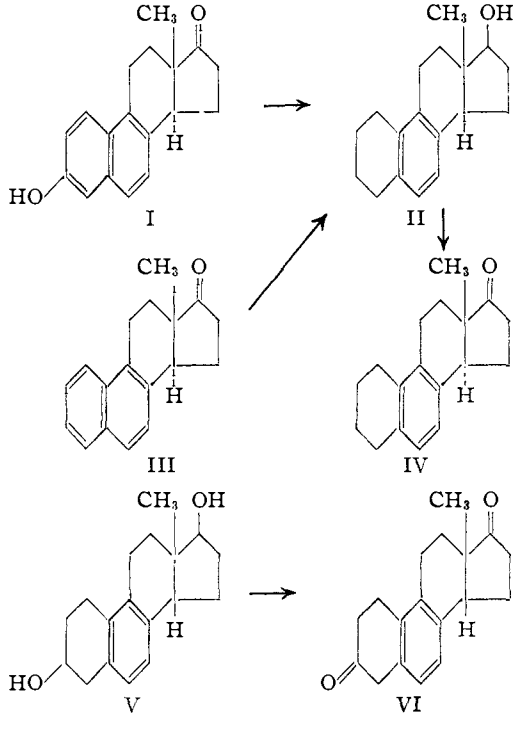
dl-1,2,3,4-Tetrahydrodesoxyequilenin and *dl*-1,2,3,4-tetrahydrodesoxyisoequilenin, which had been obtained previously by total synthesis, were prepared from *dl*-equilenin and *dl*-isoequilenin, respectively. *d*- and *l*-desoxyisoequilenin were obtained by total synthesis. Hydrogenation of *d*-isoequilenin and of *d*-desoxyisoequilenin yielded *d*-1,2,3,4-tetrahydro-17-dihydrodesoxyisoequilenin. Reduction of *d*-isoequilenin afforded also *d*-1,2,3,4-tetrahydro-17-dihydroisoequilenin which was oxidized to *d*-3-keto-1,2,3,4-tetrahydrodesoxyisoequilenin.

When the two racemic forms of the compounds corresponding to desoxyequilenin and desoxyisoequilenin[1] and the two forms of the 1,2,3,4-tetrahydro derivatives[2] were synthesized, their configurational relationships to equilenin were not known with certainty. Accordingly the isomers were distinguished from each other by the prefixes α and β. In the present work it is shown that the α forms correspond to *dl*-isoequilenin and the β forms to *dl*-equilenin. The results have already been of value in the study of the configuration of the C/D ring juncture in the estrogenic hormones.[3,4]



Hydrogenation of *dl*-equilenin (I) in acid solution in the presence of Adams catalyst according to the procedure described for the *d*-isomer[5] resulted in the formation of *dl*-1,2,3,4-tetrahydro-17-dihydrodesoxyequilenin (II) by saturation of the A ring, loss of the 3-hydroxyl group and reduction of the 17-keto group. Oxidation of II by chromic anhydride in acetic acid afforded *dl*-1,2,3,4-tetrahydrodesoxyequilenin (IV), which was identical with the β-form that had been synthesized by Bachmann and Morin.[2] Similarly, *dl*-1,2,3,4-tetrahydrodesoxyisoequilenin, the α form of Bachmann and Morin, was obtained from *dl*-isoequilenin by hydrogenation followed by oxidation.

The formation of different products on reduction of racemic equilenin and racemic isoequilenin showed that no isomerization took place at the C/D ring juncture under the conditions of the hydrogenation. The result showed that the hydrogenation reaction can be used for the correlation of configuration at the C/D ring juncture and added validity to the proof of the relative configuration of natural *d*-desoxyequilenin on the basis of the formation of the same reduction product from it and *d*-equilenin.[6] Independent evidence for this steric relationship was presented recently when *d*-equilenin was converted directly into *d*-desoxyequilenin.[7]

That the β and α forms of the desoxy compound III have the same configuration as the β and α forms of the tetrahydrodesoxy compound IV had been demonstrated by dehydrogenation[2] of the two forms of IV to the two forms of III and by dehydrogenation of two intermediates in their synthesis.[4] Hence Bachmann and Wilds' α-*dl*-17-equilenone is *dl*-desoxyisoequilenin and their β form is *dl*-desoxyequilenin.

Application of the acidic hydrogenation conditions to *d*-isoequilenin and to *d*-desoxyisoequilenin yielded *d*-1,2,3,4-tetrahydro-17-dihydrodesoxyisoequilenin. In the presence of only a small amount of acid *d*-isoequilenin was reduced to *d*-1,2,3,4-tetrahydro-17-dihydroisoequilenin (V) without loss of the 3-OH group. Oxidation of the diol with chromic anhydride in acetic acid afforded *d*-3-keto-1,2,3,4-tetrahydrodesoxyisoequilenin (VI).

d- and *l*-desoxyisoequilenin were prepared by total synthesis. The previously described *dl-cis*-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthreneacetic acid was resolved in the form of its *l*-menthyl ester and each of the enantiomorphs was carried through an Arndt–Eistert synthesis and Dieckmann cyclization according to the procedures described for the racemic mixture.[1] The melting points, rotations and configurations of natural *d*-desoxyequilenin and the three stereoisomers are shown in Table I. Application of the method of molecular rotation differences gives $\Delta_{13} = -707$ and $\Delta_{14} = +133$. The values cal-

(1) W. E. Bachmann and A. L. Wilds, THIS JOURNAL, **62**, 2084 (1940).

(2) W. E. Bachmann and R. D. Morin, *ibid.*, **66**, 553 (1944).

(3) W. E. Bachmann and F. Ramirez, *ibid.*, **72**, 2527 (1950).

(4) W. E. Bachmann and A. S. Dreiding, *ibid.*, **72**, 1323 (1950).

(5) R. E. Marker, O. Kamm, D. M. Jones, E. L. Wittle, T. S. Oakwood and H. M. Crooks, *ibid.*, **59**, 768 (1937); R. E. Marker and E. Rohrmann, *ibid.*, **61**, 3314 (1939); L. Ruzicka, P. Mueller and E. Moergeli, *Helv. Chim. Acta*, **21**, 1394 (1938).

(6) V. Prelog and J. Fuehrer, *Helv. Chim. Acta*, **28**, 583 (1945).

(7) W. E. Bachmann and A. S. Dreiding, THIS JOURNAL, **72**, 1329 (1950).

culated from *d*-equilenin and its stereoisomers were $\Delta_{13} = -615$ and $\Delta_{14} = +167$.[8]

TABLE I

PROPERTIES OF *d*-DESOXYEQUILENIN AND STEREOISOMERS

	Racemate	Active forms
Desoxyequilenin *trans*	M.p. 188–189°	M.p. 160–161° $[\alpha]^{27}D \pm 115°$
Desoxyisoequilenin *cis*	M.p. 101–102°	M.p. 107.5–108.5° $[\alpha]^{27}D \pm 168°$

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Experimental[9]

***dl*-1,2,3,4-Tetrahydrodesoxyequilenin (IV) from *d*-Equilenin.**—A mixture of 75 mg. of *dl*-equilenin,[10] 75 mg. of Adams catalyst, 9 cc. of methanol and 0.35 cc. of concd. hydrochloric acid was shaken under one atmosphere of hydrogen at room temperature for one hour. The filtered solution was evaporated and the product was recrystallized from petroleum ether (b.p. 30–40°) and ether; m.p. 126–128°; yield, 50 mg.

Without further purification a 35-mg. sample of the *dl*-1,2,3,4-tetrahydro-17β-dihydrodesoxyequilenin (II) was oxidized by treating a solution of it in 3.5 cc. of glacial acetic acid with a solution of 40 mg. of chromic anhydride in 1.8 cc. of glacial acetic acid and 0.4 cc. of water for two hours at room temperature. The mixture was diluted with water to 40 cc. and extracted with ether. After being washed exhaustively with 10% sodium hydroxide and then saturated sodium chloride, the solution was concentrated and the residue was crystallized from methanol; yield, 21 mg. of almost colorless crystals of *dl*-1,2,3,4-tetrahydrodesoxyequilenin (IV); m.p. 110–113° alone and when mixed with a sample of the β form of 1,2,3,4-tetrahydro-17-equilenone (m.p. 114–115°).[2]

***dl*-1,2,3,4-Tetrahydrodesoxyisoequilenin from *dl*-Isoequilenin.**—Oxidation of 172 mg. of the product obtained by hydrogenation of *dl*-isoequilenin[10] in the manner described in the previous experiment gave 80 mg. of *dl*-1,2,3,4-tetrahydrodesoxyisoequilenin; m.p. 65–69°, raised to 69.5–70.5° by recrystallization from methanol. It was identical with the α-form of 1,2,3,4-tetrahydro-17-equilenone (m.p. 72–73°).[2]

***d*-1,2,3,4-Tetrahydro-17-dihydrodesoxyisoequilenin.** (a) **From *d*-Isoequilenin.**—A mixture of 600 mg. of *d*-isoequilenin, 800 mg. of Adams catalyst, 110 cc. of methanol and 6 cc. of concd. hydrochloric acid was shaken under an atmosphere of hydrogen at room temperature until no more hydrogen was consumed. The isolated liquid product was heated briefly with excess acetic anhydride in 5 cc. of benzene, the solution was extracted with 2% sodium hydroxide and concentrated, and the residue was crystallized from a small amount of petroleum ether (b.p. 30–60°) and methanol. Recrystallization from aqueous methanol yielded 350 mg. of fine colorless needles, m.p. 79–82°. A solution of these in petroleum ether was filtered to remove a small amount of insoluble material and evaporated. After two recrystallizations from aqueous methanol, the **acetate of *d*-1,2,3,4-tetrahydro-17-dihydrodesoxyisoequilenin** formed colorless, fine, silky needles; m.p. 84°.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.5; H, 8.8. Found: C, 80.9; H, 9.0.

The combined second crops of the last two crystallizations of the acetate (115 mg., m.p. 75–83°) were hydrolyzed in a refluxing solution of 150 mg. of potassium hydroxide in 6 cc. of methanol and 2 cc. of water for four hours. Some of the methanol was removed in a stream of air and replaced by water and the product was extracted into benzene. After removal of the solvent the residue was crystallized from petroleum ether (b.p. 30–60°); m.p. 113–113.5°. Recrystallization from petroleum ether afforded 80 mg. of ***d*-1,2,3,4-tetrahydro-17-dihydrodesoxyisoequilenin** as colorless prisms; m.p. 113.5–114°; $[\alpha]^{28}D$ +39.4° (*c* = 1.49, in chloroform).

Anal. Calcd. for $C_{18}H_{24}O$: C, 84.3; H, 9.4. Found: C, 84.2; H, 9.7.

(b) **From *d*-Desoxyisoequilenin.**—The compound (230 mg.) was hydrogenated as described in the previous experiment and the crude product was recrystallized from petroleum ether (b.p. 30–60°); yield, 190 mg. (80%) of *d*-1,2,3,4-tetrahydro-17-dihydrodesoxyisoequilenin; m.p. 112–113°, identical with the product in (a).

***d*-1,2,3,4-Tetrahydro-17-dihydroisoequilenin (V).**—A mixture of 600 mg. of *d*-isoequilenin, 600 mg. of Adams catalyst, 75 cc. of methanol and 0.5 cc. of concd. hydrochloric acid was shaken under an atmosphere of hydrogen at room temperature for six hours. The catalyst was removed by filtration, the filtrate was concentrated and a solution of the residue in benzene was extracted with 2% sodium hydroxide. The product crystallized from a 4:1 mixture of petroleum ether (b.p. 60–75°) and ether in clusters of colorless prisms; yield, 400 mg.; m.p. 100–115°. After two recrystallizations from ethyl acetate–petroleum ether (b.p. 60–75°) the colorless prisms of ***d*-1,2,3,4-tetrahydro-17-dihydroisoequilenin (V)** had m.p. 149.5–150.5°; yield 100 mg.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.5; H, 8.9. Found: C, 78.6; H, 9.1.

A solution of the combined second crops (260 mg.) in 50 cc. of glacial acetic acid was oxidized by the dropwise addition of a solution of 600 mg. of chromic anhydride in 6 cc. of water and 25 cc. of glacial acetic acid. After standing at room temperature for three hours, the reaction mixture was diluted with water and extracted with ether, and the solution was washed with aqueous alkali and evaporated. A solution of the product in 5 cc. of benzene was filtered through a column of 10 g. of alumina (Merck, according to Brockmann). The column was washed with 125 cc. of benzene and the combined filtrates were concentrated to a viscous liquid. A portion was converted into the **dioxime of *d*-3-keto-1,2,3,4-tetrahydrodesoxyisoequilenin (VI)**, which crystallized from methanol in colorless needles; m.p. 266° dec., with previous softening.

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.5; H, 7.4; N, 9.4. Found: C, 72.6; H, 7.1; N, 9.1.

Reaction of the crude diketone with 2,4-dinitrophenylhydrazine in 50% aqueous sulfuric acid yielded a **mono-2,4-dinitrophenylhydrazone**, which is undoubtedly the 3-derivative; it crystallized from ethyl acetate–ethanol in orange red prisms, m.p. 215–220° dec.

Anal. Calcd. for $C_{24}H_{24}N_4O_5$: N, 12.5. Found: N, 12.5.

Esterification of *dl-cis*-2-Methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthreneacetic Acid with *l*-Menthol.—The powdered *dl-cis*-acid ester (4.5 g., m.p. 133–134°)[1] was added with swirling to a solution of 3.25 cc. of thionyl chloride in 6 cc. of dry benzene at 5°. One drop of pyridine was added and the mixture was allowed to stand at room temperature for forty-five minutes when all the solid had dissolved. The volatile components were removed under reduced pressure at 45°. After 10 cc. of benzene was added and removed in the same way, a solution of the residual acid chloride in 10 cc. of benzene was treated with 3 g. of *l*-menthol in 6 cc. of benzene and 1 drop of pyridine at room temperature for twelve hours, during which time precipitation occurred. Sufficient benzene was added to give a clear solution, which was washed twice with a saturated sodium bicarbonate solution and once with water. Acidification of the sodium bicarbonate extract gave no precipitate indicating that the esterification was complete. After drying, the benzene solution was concentrated and the oily residue dissolved in hot petroleum ether (b.p. 60–75°). On cooling, the ***l*-menthyl ester of *l-cis*-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthreneacetic acid** separated as colorless needles, m.p. 135–152°. Recrystallization from the same solvent raised the melting point to 159–160°; yield, 1.7 g.; $[\alpha]^{26}D$ −178° (in benzene).

Anal. Calcd. for $C_{29}H_{38}O_4$: C, 77.3; H, 8.5. Found: C, 77.2; H, 8.5.

The mother liquor of the above crystallization was concentrated and heated under reduced pressure to remove free menthol. The residue was dissolved in warm 90% aqueous methanol and some of the higher melting diastereoisomer

(8) W. Klyne, *Nature*, **161**, 434 (1938).

(9) Microanalyses by Micro-Tech Laboratories, Skokie, Illinois.

(10) W. E. Bachmann, W. Cole and A. L. Wilds, THIS JOURNAL, **72**, 824 (1940).

was removed by filtration. On cooling, the **l-menthyl ester of d-cis-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrenacetic acid** precipitated. After four recrystallizations it had a melting point of 111–114°, which was not altered by further recrystallizations; $[\alpha]^{27}D$ +77° (in benzene). This product apparently still contained a small amount of the diastereoisomer but purification at this stage did not improve the melting point. Complete removal of the racemic compound was possible at later stages of the synthesis.

Anal. Calcd. for $C_{29}H_{38}O_4$: C, 77.3; H, 8.5. Found: C, 77.4; H, 8.5.

d-Desoxyisoequilenin.—A solution of 4 g. of the higher-melting menthyl ester (m.p. 159–160°), and 50 g. of potassium hydroxide in 80 cc. of methanol and 20 cc. of water was heated on a steam-bath for six hours. After removal of the methanol in a current of air, the residue was dissolved in water, the menthol was extracted with benzene and the **l-cis-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthreneacetic acid** recovered by acidification of the aqueous solution, m.p. 209–210.5°. Without further purification, this diacid was esterified and half hydrolyzed according to the procedure described for the racemate.[1] Crystallization from 60% methanol yielded **l-cis-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthreneacetic acid,** m.p. 113.5–114.5°, $[\alpha]^{29}D$ −173° (in benzene).

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.1; H, 6.4. Found: C, 73.0; H, 6.7.

The Arndt–Eistert reaction was carried out on this acid ester by the method described for the racemate.[1] The resulting **dimethyl ester of l-cis-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrenepropionic acid** was crystallized from methanol, m.p. 122–123°. A solution of 1.4 g. of the dimethyl ester in 60 cc. of anhydrous benzene was added to dry sodium methoxide, prepared from 0.228 g. of sodium, and heated for two hours under an atmosphere of nitrogen so that the solvent distilled slowly. The product was worked up, hydrolyzed and decarboxylated according to the described procedure.[1] The **d-desoxyisoequilenin** was purified by filtration of a benzene solution through a column of activated alumina, and by recrystallization from 90% aqueous methanol; m.p. 107–108°, $[\alpha]^{26}D$ +159° (in chloroform); yield, 0.85 g. (reported,[4,7] m.p. 107.5–108.5°, $[\alpha]^{27}D$ +168)°.

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.4; H, 7.2. Found: C, 86.3; H, 7.6.

l-Desoxyisoequilenin.—The reactions employed in the synthesis of *l*-desoxyisoequilenin from the lower melting menthyl ester (m.p. 111–114°) were the same as those described in the previous experiment for the synthesis of the enantiomorph. The **d-cis-2-methyl-2-carbomethoxy-1,2-3,4-tetrahydrophenanthreneacetic acid** had m.p. 112.5–114.5° after several recrystallizations from 60% aqueous methanol.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.1; H, 6.4. Found: C, 73.0; H, 6.5.

The Arndt–Eistert reaction yielded the **dimethyl ester of d-cis-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrenepropionic acid**; m.p. 122–123°.

Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.1; H, 7.1. Found: C, 74.1; H, 7.1.

The Dieckmann reaction and subsequent hydrolysis and decarboxylation afforded **l-desoxyisoequilenin**; m.p. 107–108°; $[\alpha]^{28}D$ −159° (in chloroform).

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.4; H, 7.2. Found: C, 86.1; H, 7.4.

A hot solution of equal weights of the *d*- and *l*-isomers of desoxyisoequilenin in 90% aqueous methanol deposited colorless plates of *dl*-desoxyisoequilenin; m.p. 100.5–101.5° alone and when mixed with an authentic specimen.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Polycyclic Compounds. I. The Reimer–Tiemann Reaction with 1-Alkyl-2-naphthols

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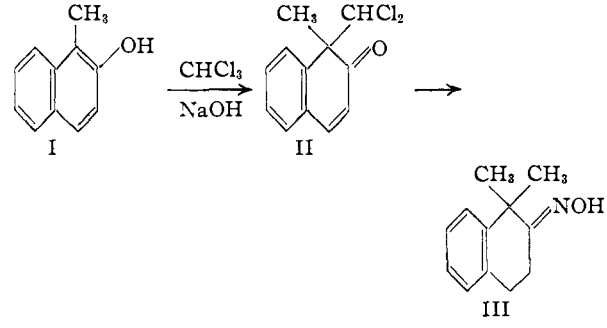
The Reimer–Tiemann reaction with 1-methyl-2-naphthol, 1-allyl-2-naphthol and 1-(3-chloro-2-butenyl)-2-naphthol produced the corresponding 1-alkyl-1-dichloromethyl-2-keto-1,2-dihydronaphthalene in fair yield. All of these bicyclic compounds possess a quaternary carbon atom. An unsuccessful attempt was made to hydrolyze and cyclize the 1-(3-chloro-2-butenyl)-1-dichloromethyl-2-keto-1,2-dihydronaphthalene with 90% sulfuric acid to 2-keto-12-dichloromethyl-2,3,4,12-tetrahydrophenanthrene.

For the past year we have been studying the Reimer–Tiemann reaction with 1-alkyl-2-naphthols in order to develop a method for the synthesis of polycyclic compounds containing a quaternary carbon atom which could be useful in the synthesis of steroids. Recently, the Reimer–Tiemann reaction with 1-methyl-2-naphthol was reported.[2] This prompts us to report our preliminary results with this reaction.

1-Methyl-2-naphthol (I) reacted with chloroform and aqueous sodium hydroxide to form 1-methyl-1-dichloromethyl-2-keto-1,2-dihydronaphthalene (II) in 77% yield. The only other organic material isolated from the reaction proved to be starting material. The structure of II followed from the analysis, from the analogy with the Reimer–Tiemann reaction with alkylphenols,[3] and from its conversion to 1,1-dimethyl-2-tetralone oxime (III).

1-Methyl-1-dichloromethyl-2-keto-1,2-dihydronaphthalene (II) failed to react with hydroxylamine and semicarbazide, but the infrared spectra of a solution of II in carbon tetrachloride indicated the presence of a conjugated carbonyl group (1660



cm.$^{-1}$). No vibrational frequency corresponding to a hydroxyl group (3400–3600 cm.$^{-1}$) was present.[4]

The ultraviolet absorption spectra of II in 95% alcohol has maxima at 239 mμ (ε 11,900) and 314 mμ (ε 9,200). Pyrolysis of II in liquid petrolatum at

(1) Abstracted, in part, from the Ph.D. thesis of William P. Webb.

(2) Bell and Hunter, *J. Chem. Soc.*, 2903 (1950); received December 1, 1950.

(3) v. Auwers and Winternitz, *Ber.*, **35**, 465 (1902).

(4) We are indebted to Dr. Bryce Crawford and Mr. John Lancaster for the infrared spectra.