due yielded 79 g. (87%) of an almost colorless liquid, b. p. 106° (2 mm.); $n^{20}D$ 1.5700.

Anal. Calcd. for $C_{10}H_{12}OS$: C, 66.63; H, 6.71. Found: C, 66.83; H, 6.99.

The ketone was also prepared by an alternate procedure. Ninety grams (0.65 mole) of ethylthioglycolyl chloride, prepared in 90% yield from ethylthioglycolic acid[9] and thionyl chloride, was dissolved in 400 ml. of dry benzene. To the cooled solution was added with stirring 93.3 g. (0.7 mole) of anhydrous aluminum chloride in small portions. After the addition was complete (two hours) the mixture was stirred for two hours. About 300 ml. of cold dilute hydrochloric acid was added with stirring. The benzene layer was removed, dried and distilled. The product consisted of 75 g. (64%) of a pale yellow liquid, b. p. 104° (1.5 mm.); $n^{20}D$ 1.5700.

5-Ethylthiomethyl-5-phenylhydantoin.—The method of Bucherer was employed.[6] To a solution of 36 g. (0.2 mole) of α-ethylthioacetophenone in 600 ml. of 70% ethanol was added 18 g. of potassium cyanide and 56 g. of ammonium carbonate. The flask, fitted with a large bore air condenser, was heated on a water-bath at 55–60° for eight hours. The solution was evaporated to about 300 ml. on a steam-bath and then acidified with cold dilute hydrochloric acid. An oil precipitated which quickly solidified. The cooled mixture was filtered and the residue washed with cold water. The product was purified by dissolving in 5% sodium hydroxide solution, extracting three times with small portions of ether to remove unreacted ketone and reprecipitating with hydrochloric acid. After recrystallization from dilute ethanol the product weighed 34.5 g. (69%); m. p. 196°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64. Found: C, 57.71; H, 5.82.

5-Ethylsulfonylmethyl-5-phenylhydantoin.—To a mixture of 12.5 g. (0.05 mole) of 5-ethylthiomethyl-5-phenylhydantoin in 100 ml. of glacial acetic acid and 25 ml. of acetic anhydride was added 25 ml. of 30% hydrogen peroxide. A clear solution was formed after a few minutes when the heat of reaction had raised the temperature several degrees. When the temperature has increased to 70°, the flask was immersed in ice water for a short time in order to keep the temperature below 80°. After about one hour the solution was poured into two volumes of cold water. A white solid precipitated which was filtered off and recrystallized from alcohol. The yield of pure product was 9.3 g. (74%), m. p. 240°.

Anal. Calcd. for $C_{12}H_{14}N_2O_4S$: N, 9.93. Found: N, 10.06.

(9) Ramberg, *Ber.*, **40**, 2588 (1907).

Summary

A number of α-R-thioacetophenones have been prepared and converted to the corresponding hydantoins which, in general, possess definite anticonvulsant activity.

Oxidation of 5-R-thiomethyl-5-phenylhydantoins to 5-R-sulfonylmethyl-5-phenylhydantoins usually resulted in decreased activity.

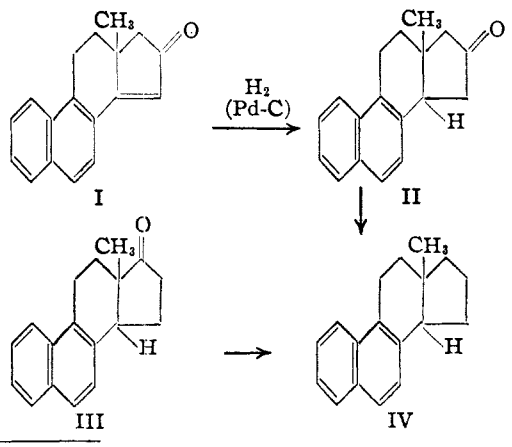
DETROIT, MICHIGAN RECEIVED JULY 18, 1946

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTY OF THE UNIVERSITY OF WISCONSIN]

cis and *trans dl*-Equilenane

BY A. L. WILDS, LLOYD W. BECK AND THOMAS L. JOHNSON

Recently[1] a method was described leading to the synthesis of the unsaturated ketone I having the carbon skeleton of the female sex hormone equilenin, but with the keto group in the 16- rather than the 17-position and lacking the 3-hydroxyl group.[2] By selective reduction using palladium on charcoal as the catalyst it was possible to hydrogenate I to 16-equilenone (II).[1]



Since only one of the two possible racemic mixtures corresponding to II could be isolated, it was of interest to determine its stereochemical configuration for rings C and D, relative to the isomeric 17-equilenones (III).

The synthesis of the *cis* and *trans* isomers of 17-equilenone has been described by Bachmann and Wilds,[3] using the general method employed for the synthesis of equilenin.[4] Each of the 17-equilenones has now been reduced to the corresponding *cis* and *trans* isomers of the parent hydrocarbon equilenane (IV),[5] and these have been compared with the hydrocarbon obtained by reduction of the 16-equilenone isomer. Clemmensen reduction of 16-equilenone gave a solid which was purified through the picrate and by repeated recrystallization to the equilenane (IV) having a melting point of 87.5–89.5°. Wolff–Kishner reduction of the semicarbazone was less satisfactory. The hydrocarbon formed a crystalline picrate and *s*-trinitrobenzene complex.

Clemmensen reduction of α-17-equilenone gave a liquid hydrocarbon which could not be crystallized, but could be converted into crystalline

(1) Wilds and Beck, THIS JOURNAL, **66**, 1688 (1944).

(2) The successful extension of this method to the related compounds having the 3-hydroxyl group (by Warren J. Close) and also with ring B hydroaromatic (by Thomas L. Johnson) will be reported shortly.

(3) Bachmann and Wilds, *ibid.*, **62**, 2084 (1940); this paper may also be referred to for the nomenclature of these compounds.

(4) Bachmann, Cole and Wilds, *ibid.*, **62**, 824 (1940).

(5) The first reduction experiments on the 17-equilenones were carried out by one of us (A. L. W.) in Dr. Bachmann's laboratory in 1939.

derivatives with picric acid and trinitrobenzene. These differed in melting point from the corresponding derivatives of the hydrocarbon from 16-equilenone and gave significant melting point depressions with these samples.

The Clemmensen reduction of β-17-equilenone was incomplete, but a crystalline hydrocarbon could be isolated. The Wolff–Kishner reduction was more satisfactory in this case and by repeated recrystallization and purification through the picrate, the melting point of the hydrocarbon was raised to 86–86.5°. This sample gave no melting point depression with the hydrocarbon from 16-equilenone and gave a crystalline picrate and trinitrobenzene derivative which were identical in melting points and mixed melting points with the derivatives from the other hydrocarbon sample. The melting points of the samples from the three ketones are summarized in Table I.

TABLE I

COMPARISON OF MELTING POINTS (COR.)

Hydrocarbon	M. p., °C.	M. p., °C. Picrate	M. p., °C. Trinitrobenzene complex
α-Equilenane (probably *cis*)	Liquid	100.5–101	113.5–115
β-Equilenane (probably *trans*)	86–86.5	107.5–108.5	120–121.5
Equilenane from 16-equilenone	87.5–89.5	107.5–108.5	120–121.5

One of the stereoisomers of equilenane has been described by Marker and Rohrmann.[6] This hydrocarbon, m. p. 73–75°, is presumably the optically active form corresponding to one of the hydrocarbons reported here, since it was prepared starting with material isolated from the carbinol fraction of pregnant mares' urine.[7]

Thus, the comparison of reduction products of the ketones shows that the 16-equilenone isomer obtained by hydrogenation of I has the same stereochemical configuration at the C:D ring juncture as β-17-equilenone. In regard to its configuration relative to equilenin, there has as yet been no direct stereochemical correlation between the *dl*-17-equilenones (desoxyequilenins) and equilenin itself.[8] Indeed, there is no rigorous evidence for the configuration of the latter, although by analogy with the sterols and bile acids, equilenin (and estrone) is presumed to have the *trans* C:D ring juncture. However, several independent approaches based upon analogy indicate that *dl*-equilenin and β-17-equilenone probably have similar configurations.[9]

(6) Marker and Rohrmann, THIS JOURNAL, **61**, 3314 (1939).

(7) Nenitzescu and Cioranescu [*Ber.*, **75**, 1765 (1942)] have reported the synthesis of a hydrocarbon $C_{18}H_{30}$, for which the structure of an equilenane was considered to be the most probable. As no solid derivatives were reported for this oily hydrocarbon, a comparison with the present authentic samples cannot be made.

(8) Recently Prelog and Führer [*Helv. Chim. Acta*, **28**, 583 (1945)] reported the isolation of one of the optically active forms of 17-equilenone (*d*-3-desoxyequilenin) from pregnant mares' urine, and this was shown to have the same configuration as *d*-equilenin. Consequently the resolution of the *dl*-17-equilenones and comparison with this optically active isomer would complete the correlation of the two *dl* series.

Experimental[10]

Reduction of 16-Equilenone (probably *trans*). (a) **Clemmensen Reduction.**—A mixture of 15 g. of amalgamated zinc, 30 cc. of hydrochloric acid, 5 cc. of acetic acid, 6 cc. of toluene and 1.48 g. of 16-equilenone[1] (m. p. 166–168°) was refluxed vigorously for thirty hours, during which time an additional 24 cc. of hydrochloric acid was added. The oil which was isolated by extraction was evaporatively distilled at 165–185° (0.1 mm.) yielding 1.30 g. of a pale yellow oil which solidified when scratched. Recrystallization from methanol gave (in two crops) 0.96 g. (69%) of hydrocarbon, m. p. 81–85.5°. The compound was purified further by conversion to the picrate (recrystallized to the constant m. p. 107.5–108.5°) and subsequent regeneration of the hydrocarbon followed by additional recrystallizations from methanol. The purest sample of the β-equilenane from 16-equilenone crystallized as colorless blades with the m. p. 87.5–89.5°.

Anal. Calcd. for $C_{18}H_{20}$: C, 91.5; H, 8.5. Found: C, 91.5; H, 8.5.

In one run the reduction was incomplete as indicated by the melting point of the crude product (60–150°) and it was necessary to give the material a second reduction treatment.

The **picrate** was obtained in 83% yield (m. p. 105–108°) from 0.20 g. of the hydrocarbon and 0.30 g. of picric acid in absolute alcohol. The complex tended to dissociate upon recrystallization unless picric acid was added to the alcoholic solution. The purest sample crystallized as bright orange-red blades, m. p. 107.5–108.5°.

Anal. Calcd. for $C_{18}H_{20}\cdot C_6H_3O_7N_3$: C, 61.9; H, 5.0. Found: C, 62.3; H, 5.1.

The **trinitrobenzene complex** was obtained in 80% yield from the hydrocarbon and *s*-trinitrobenzene in absolute alcohol. It was more stable than the picrate and crystallized from methanol as yellow blades, m. p. 120–121.5°. A mixed m. p. with trinitrobenzene showed a depression to 113–119°.

Anal. Calcd. for $C_{18}H_{20}\cdot C_6H_3O_6N_3$: C, 64.1; H, 5.2. Found: C, 64.2; H, 5.1.

(b) **Wolff–Kishner Reduction.**—The **semicarbazone of 16-equilenone** was prepared in 90% yield by refluxing a solution of 83 mg. of the ketone and 83 mg. of semicarbazide hydrochloride in 0.4 cc. of pyridine and 8 cc. of absolute alcohol for one and one-half hours. The product was recrystallized from 35 cc. of boiling *n*-butyl alcohol to give fine colorless leaflets, m. p. 251.5–253° (dec.).

Anal. Calcd. for $C_{19}H_{21}ON_3$: C, 74.2; H, 6.9. Found: C, 74.4; H, 7.0.

A suspension of 115 mg. of the semicarbazone in a solution of 0.3 g. of sodium in 5 cc. of absolute alcohol was heated in a sealed tube at 180° for twelve hours. After cooling, the product was extracted with benzene and washed with dilute acid. Evaporative distillation of the

(9) These two ketones are the higher melting isomers in their series and there is a similar correspondence in the melting points for all of the crystalline intermediates leading to the ketones in the two series.[4,4] The recent experiments of Birch, Jaeger and Robinson [*J. Chem. Soc.*, 582 (1945)] provide further analogy. Using the methylanilinomethylene group to protect the 16-position, they reported that angular methylation of norequilenin methyl ether gave *dl*-isoequilenin methyl ether as the only isomer which could be isolated. Similar methylation of the desoxy analog gave β-17-equilenone as the only isomer, indicating a similar configuration for these ketones and, therefore, also for *dl*-equilenin and α-17-equilenone. They also reported that methylation of the corresponding derivative of 1-hydrindanone gave only the *cis* 8-methyl-1-hydrindanone, indicating that the α- and iso-series are *cis* and the β-equilenone and equilenin series are *trans*, provided the analogy holds.

(10) All melting points are corrected.

oily product (89 mg.) and recrystallization from methanol gave 19 mg. (22%) of impure material, m. p. 80–82.5°. Further crops were oily and difficult to purify even through the derivatives.

Reduction of β-17-Equilenone (probably *trans*). (a) **Clemmensen Reduction.**—Reduction of 298 mg. of β-17-equilenone (m. p. 190–192° vac., prepared by the procedure of Bachmann and Wilds)[3] was carried out as described for 16-equilenone. After evaporative distillation at 160–185° (0.1 mm.) the product crystallized only partially and contained a small amount of high-melting material (probably the result of incomplete reduction). This was removed by dissolving the product in petroleum ether (b. p. 30–60°) at room temperature and filtering. The petroleum ether soluble portion was converted to the picrate and recrystallized to give 30 mg., m. p. 104–107.5°. The hydrocarbon obtained by decomposing the picrate melted at 76–83°. Further recrystallizations afforded a few mg. of the hydrocarbon, m. p. 85.5–86.5°. A mixture with the hydrocarbon from 16-equilenone melted at 85.5–88°.

(b) **Wolff-Kishner Reduction.**—The **semicarbazone of β-17-equilenone** was prepared in 94% yield as described for 16-equilenone, except with refluxing for three hours. The analytical sample was recrystallized from pyridine–alcohol as fine colorless needles, m. p. 256.5–257.5° (dec.).

Anal. Calcd. for $C_{19}H_{21}ON_3$: C, 74.2; H, 6.9. Found: C, 74.2; H, 6.9.

Reduction of 160 mg. of the semicarbazone was carried out as described for the 16-equilenone derivative, except the time of heating was twenty-one hours. Crystallization of the oily product (119 mg.) from methanol gave 65 mg. (53%) of colorless crystals, m. p. 73–80°. The purest sample of β-equilenane from β-17-equilenone, obtained by repeated recrystallization and purification through the picrate, melted at 86–86.5°. A mixture with the hydrocarbon obtained from 16-equilenone (m. p. 87.5–89.5°) melted at 86.5–88.5°.

The picrate, m. p. 107.5–108.5°, and the trinitrobenzene complex, m. p. 120–121.5°, gave no depression in melting point when mixed with the corresponding derivative of the hydrocarbon from 16-equilenone.

Reduction of α-17-Equilenone (probably *cis*).—α-17-Equilenone was prepared by the procedures of Bachmann and Wilds,[3] with essentially the same results reported. The product of the Arndt–Eistert reaction, the dimethyl ester of the α-isomer of 2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrenepropionic acid, however, was obtained as a lower melting polymorphic modification, m. p. 71–73.5° (reported,[3] m. p. 98–99°). Upon cyclization and decarboxylation this afforded α-17-equilenone, m. p. 100–102° (reported,[3] 100–101°). The semicarbazone was prepared in alcohol–pyridine solution and recrystallized from *n*-butyl alcohol, m. p. 264–266.5° (dec.).

Anal. Calcd. for $C_{19}H_{21}ON_3$: C, 74.2; H, 6.9. Found: C, 74.5; H, 7.1.

Clemmensen reduction of 709 mg. of α-17-equilenone, as described for 16-equilenone, afforded 660 mg. of colorless oil after evaporative distillation at 160–180° (0.1 mm.) This was converted to the trinitrobenzene derivative in absolute alcohol, giving 830 mg., m. p. 110–112.5°, and 200 mg., m. p. 106–109°, for a total yield of 81%. Regeneration of the hydrocarbon from a pure sample of the derivative (m. p. 113.5–115°) by passing a benzene solution through a column of alumina, gave a colorless viscous oil which failed to crystallize. Adsorption of the hydrocarbon on alumina and fractional elution also failed to result in a crystalline sample of α-equilenane.

The **picrate of α-equilenane** was formed in methanol solution using an excess of picric acid. Purification was difficult due to the tendency of the complex to dissociate. The analytical sample was obtained as orange blades from methanol, m. p. 100.5–101°. A mixture with the picrate of β-equilenane (from 16-equilenone) gave a depression in m. p. to 93–100°.

Anal. Calcd. for $C_{18}H_{20}\cdot C_6H_3O_7N_3$: C, 61.9; H, 5.0. Found: C, 62.3; H, 5.1.

The **trinitrobenzene complex of α-equilenane** crystallized well from methanol as fine yellow needles, m. p. 113.5–115°. A mixture with the derivative from β-equilenane was depressed to 104–109°.

Anal. Calcd. for $C_{18}H_{20}\cdot C_6H_3O_6N_3$: C, 64.1; H, 5.2. Found: C, 64.2; H, 5.1.

Summary

The *cis* and *trans* forms of *dl*-equilenane have been prepared by reduction of the two forms of 17-equilenone. By comparison with the hydrocarbon obtained from 16-equilenone the latter ketone has been shown to belong to the β-series, which probably has the same C:D ring configuration as equilenin.

MADISON 6, WISCONSIN RECEIVED JUNE 12, 1946

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO.]

Dihydrostreptomycin[1]

BY QUENTIN R. BARTZ, JOHN CONTROULIS, HARRY M. CROOKS, JR., AND MILDRED C. REBSTOCK

Streptomycin has been found to be a strong base with an empirical formula $C_{21}H_{37-9}N_7O_{12}$.[2] Of its component parts streptidine, 1,3-biguanido-2,4,5,6-tetrahydroxycyclohexane[3a,3b,4,5] and N-methyl *l*-glucosamine[6] have been characterized and identified. A third degradation product, maltol, has been isolated[7] and presumably is derived from the remaining six-carbon portion of the molecule. This missing portion combined with the N-methyl *l*-glucosamine constitutes the degradation product designated "streptobiosamine."[8]

The presence of a carbonyl function has been demonstrated in streptomycin[8] and its location assigned to the streptobiosamine portion of the molecule. Since the formation of maltol occurs in alkaline solution a base-catalyzed cleavage of a carbonyl compound appears likely and the carbonyl function may tentatively be assigned to

(1) Presented before the Division of Medicinal Chemistry at Chicago, Illinois, September, 1946.

(2) Peck, Brink, Kuehl, Flynn, Walti and Folkers, THIS JOURNAL, **67**, 1866–1867 (1945).

(3) (a) Carter, Clark, Dickman, Loo, Meek, Skell, Strong, Alberi, Bartz, Binkley, Crooks, Hooper and Rebstock, *Science*, **103**, 53, 4 (1946); (b) Carter, Clark, Dickman, Loo, Skell and Strong, *ibid.*, **103**, 540 (1946).

(4) Fried, Boyack and Wintersteiner, *J. Biol. Chem.*, **162**, 391–392 (1946).

(5) Peck, Hoffhine, Peel, Graber, Holly, Mozingo and Folkers, THIS JOURNAL, **68**, 776–781 (1946).

(6) Kuehl, Flynn, Holly, Mozingo and Folkers, *ibid.*, **68**, 536 (1946).

(7) Schenk and Spielman, *ibid.*, **67**, 2276–2277 (1945).

(8) Brink, Kuehl and Folkers, *Science*, **102**, 506–507 (1945).