carbon analyses lay between the theoretical values for the monohydrate and the anhydrous base. The chief difficulty in drying was caused by the fact that the base sublimed at temperatures as low as 35° (0.1 mm.). The best analysis was obtained on a sample which had been twice sublimed, twice recrystallized from aqueous ethanol, and sublimed three more times.

Anal. Calcd. for $C_{15}H_{26}N_2$: C, 76.86; H, 11.18; N, 11.96. Found: C, 75.81; H, 11.22; N, 11.60.

***l*-α-Isosparteine Monohydrate.**—The monohydrate was prepared by recrystallizing *l*-α-isosparteine from aqueous ethanol; m. p. 98–115°, $[\alpha]^{30}D$ − 55.8 ± 0.8° (c = 7.216, methanol). Since this would correspond to a rotation of −60.1° in terms of the anhydrous base, it seems likely that Winterfeld and Rauch,[17] who reported $[\alpha]$ −56.2° in methanol, probably experienced partial hydration of their α-isosparteine.

Anal. Calcd. for $C_{15}H_{28}N_2O$: C, 71.38; H, 11.18; N, 11.10. Found: C, 71.57; H, 11.37; N, 10.95.

***l*-α-Isosparteine Dipicrate.**—Prepared in ethanol and recrystallized from aqueous ethanol, the dipicrate formed tiny diamond-shaped plates, m. p. 221° (dec.).

Anal. Calcd. for $C_{27}H_{32}N_8O_{14}$: C, 46.82; H, 4.66; N, 16.18. Found: C, 47.06; H, 4.68; N, 16.15.

The melting point of a mixture of *l*- and *dl*-α-isosparteine dipicrates melted at 213–218° with decomposition. In this behavior, they are similar to the corresponding *l*- and *dl*-sparteine dipicrates.

***l*-α-Isosparteine Bisulfate.**—Prepared by addition of methanolic sulfuric acid to an ethanolic solution of the base, the bisulfate formed tiny rhombic crystals, m. p. 267° (dec.) (reported, 244–245°[17]).

Infrared Spectra.[31]—The crystalline dipicrates of natural *l*-, resolved *l*-, natural *d*- and resolved *d*-sparteine gave identical infrared spectra (as nujol mulls). The spectrum of crystalline synthetic *dl*-sparteine dipicrate (as a nujol mull) was slightly different from the active forms (Fig. 1). In a solvent these minor spectral differences between racemic and active forms disappeared. A suitable solvent for determination of the infrared spectra in solution was difficult to find, but in acetonitrile and in acetone the curves of *d*-, *l*- and *dl*-sparteine dipicrates appeared to be identical. There was considerable absorption due to the solvent and to the picric acid portion of the molecule.

A comparison of synthetic *dl*-sparteine, obtained by purification through the perchlorate, with natural *l*-sparteine, each in chloroform solution, showed the infrared absorption spectra to be identical (Fig. 2, Curves 1 and 2).

The infrared spectra of *dl*-sparteine dipicrate and *dl*-α-isosparteine dipicrate showed minor differences in the absorption curves when the compounds were measured in acetone solution or in the crystalline state. The curves of the free bases, *dl*-sparteine and *dl*-α-isosparteine, in chloroform solution were more satisfactory for differentiation between these compounds (Fig. 2, Curves 1 and 3). The infrared spectrum of freshly sublimed *l*-α-isosparteine in chloroform (Fig. 2, Curve 4) was identical with that of synthetic *dl*-α-isosparteine (Curve 3) except for small differences in the regions of 1110, 1140 and 1640 cm.$^{-1}$. The spectra of the hydrates of these two bases were completely identical and were best represented by Curve 4 of Fig. 2.

(31) The authors are indebted to Mrs. James L. Johnson and Miss Elizabeth M. Petersen for determination of the infrared absorption spectra.

Summary

1. *dl*-Sparteine and *dl*-α-isosparteine have been synthesized by the reductive cyclization of both 1-carbethoxy-4-keto-3-(α-pyridyl)-pyridocoline and diethyl 2,4-di-(α-pyridyl)-glutarate.

2. Methods of separation of *dl*-sparteine and *dl*-α-isosparteine have been described.

3. *dl*-Sparteine has been resolved into its optical antipodes and the identity of the resolved bases with natural *d*- and *l*-sparteine has been established.

URBANA, ILLINOIS RECEIVED AUGUST 12, 1949

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

Epimerization, Dehydrogenation, and Ring Cleavage of Some Steroids and Related Compounds by Palladium. Stereochemistry of the Estrogens

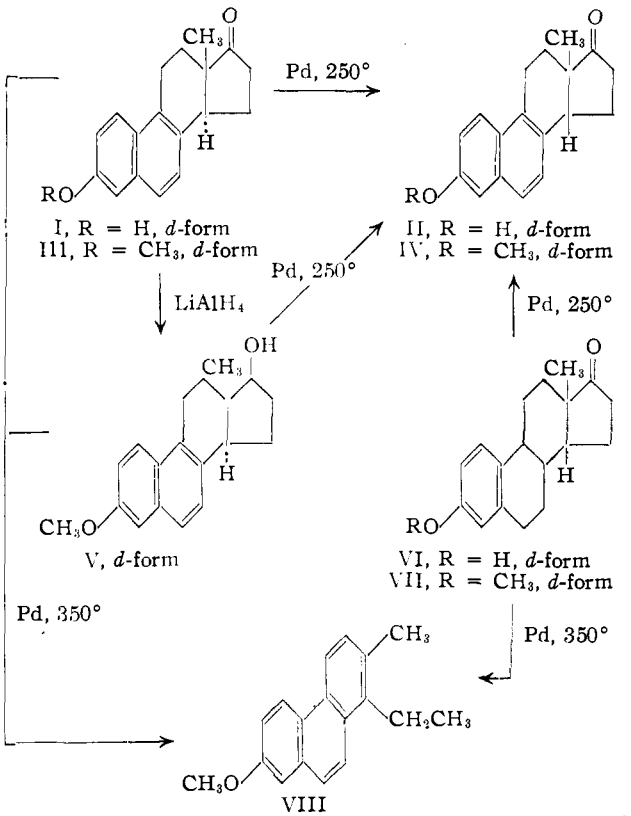
BY W. E. BACHMANN AND ANDRE S. DREIDING[1]

An investigation of the action of 5% palladium-on-charcoal on equilenin, estrone and some related compounds at 250° and at 350° has shown that epimerization at C_{14}, dehydrogenation and even cleavage of the D ring can occur depending on (1) the configuration of the C–D ring juncture, (2) the state of reduction of rings A and B, and (3) the temperature of the reaction. The epimerization can occur without concomitant dehydrogenation. The cleavage reaction takes place only at the higher temperature.

Reactions with 5% Palladium-on-Charcoal at 250°.—When *d*-equilenin (I) or its methyl ether (III) was heated briefly with an equal weight of 5% palladium-on-charcoal at 250° *d*-isoequilenin (II) or its methyl ether (IV), respectively, was obtained in good yield. This represents a convenient method of preparing the diastereoisomer from the natural hormone. The change in the reverse direction could not be brought about. Since the product was a pure diastereoisomer and not a racemic mixture, an inversion of the configuration must have taken place at only one carbon atom and the change may be called an epimerization. The epimerization occurs at C_{14} since *d*-equilenin and *d*-isoequilenin differ in configuration only at that carbon atom.[2]

(1) Alfred H. Lloyd Postdoctoral Fellow in the Horace H. Rackham School of Graduate Studies, 1947–1948.

(2) (a) Hirschmann and Wintersteiner, *J. Biol. Chem.*, **126**, 737 (1938); (b) Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940). This evidence is based on the conclusion that an isomerization at the C–D ring juncture took place during Hirschmann and Wintersteiner's acid-catalyzed conversion of equilin to isoequilin A. The conditions of this experiment could produce an epimerization only at C_{14}. Recently some doubt has been expressed on the configuration of isoequilin A by Heer and Miescher, *Helv. Chim. Acta*, **31**, 1289 (1948). They consider the possibility that the epimerization may have occurred during the dehydrogenation of isoequilin A to *d*-isoequilenin with six times the weight of palladium at 80° for sixteen hours. If this were so then the epimerization could not be located with certainty at C_{14}. This possibility had been excluded



As anticipated, the catalyst converted *dl*-desoxyequilenin (IXa)[3,4] into *dl*-desoxyisoequilenin (Xa). The latter was not affected by the catalyst.

At 250°, the catalyst can also effect the dehydrogenation of rings A and/or B (which, in all the compounds described here, do not carry an angular methyl group) if they are reduced. Rings C and D (which do have an angular methyl group) are not dehydrogenated at 250°, but they may or may not undergo an epimerization, depending on the nature of the C–D ring fusion. Thus *dl*-1,2,-3,4-tetrahydrodesoxyisoequilenin (XIIa)[4,5] experienced only dehydrogenation of ring A and gave *dl*-desoxyisoequilenin (Xa), while *d*-1,2,3,4-tetrahydrodesoxyequilenin (XI) and its racemate (XIa) suffered both epimerization and dehydrogenation and yielded *d*-desoxyisoequilenin (X)[6] and its racemate (Xa), respectively. Dehydrogenation of estrone (VI) has been found to yield *d*-isoequilenin (II)[7] (and not *d*-equilenin), although estrone and *d*-equilenin have the same configuration at C_{13} and C_{14}. The conclusion by Butenandt, Wolff and Karlson[7] that epimerization occurred at C_{14} is entirely in agreement with our results. In confirmation we found that the methyl ether of estrone (VII) gave an 85% yield of the methyl ether of *d*-isoequilenin (IV).

The catalyst is also able to dehydrogenate a C_{17} hydroxyl group to a keto group at 250°. β-Dihydroequilenin methyl ether (V) was prepared by reduction of equilenin methyl ether (III) with lithium aluminum hydride or by methylation of β-dihydroequilenin.[8] The reduction by lithium aluminum hydride represents a new method of preparing the C_{17} dihydro compound in form of its methyl ether and is evidence for the β-orientation of the C_{17} hydroxyl group (CH_3–OH *cis*); it is of interest that the product has the same configuration as the dihydroequilenin obtained by catalytic hydrogenation and predominantly by aluminum isopropoxide reduction.[9] The catalyst oxidized and epimerized the methyl ether of β-dihydroequilenin to *d*-isoequilenin methyl ether (IV). All three effects, *i. e.*, epimerization at C_{14}, dehydrogenation of ring A, and dehydrogenation of the C_{17} hydroxyl group were observed with *d*-1,2,3,4-tetrahydro-β-dihydroequilenin (XIII)[8] which was converted into *d*-desoxyisoequilenin (X) by the action of palladium at 250°.[10]

The epimerizations reported in these experi-

by Hirschmann and Wintersteiner on the basis of the results of Dirscherl and Hanusch, *Z. physiol. Chem.*, **236**, 131 (1935), who obtained *d*-equilenin by dehydrogenation of equilin with twice the weight of palladium under the same conditions. We found that *d*-equilenin was recovered unchanged when treated with an equal weight of 5% palladium-on-charcoal at 80–90° for sixteen hours.

The method of molecular rotation differences [Klyne, *Nature*, **161**, 434 (1948)] has furnished confirmatory evidence for the conclusion that *d*-isoequilenin is the C_{14} epimer of *d*-equilenin.

(3) Bachmann and Wilds, THIS JOURNAL, **62**, 3084 (1940).

(4) Recent work in this Laboratory has shown that the configuration at the C–D ring juncture in β-17-equilenone (IXa)[3] and in β-1,2,3,4-tetrahydro-17-equilenone (XIa)[6] is the same as in equilenin (I). They are therefore called desoxyequilenin (IXa) and 1,2,3,4-tetrahydrodesoxyequilenin (XI and XIa), respectively, in order to indicate the relation to equilenin. It was also demonstrated that the α-forms (X, Xa and XIIa) correspond to isoequilenin (II) and thus are desoxyisoequilenin (X, Xa) and 1,2,3,4-tetrahydrodesoxyisoequilenin (XIIa), respectively. These experiments will be published soon.

(5) Bachmann and Morin, THIS JOURNAL, **66**, 553 (1944).

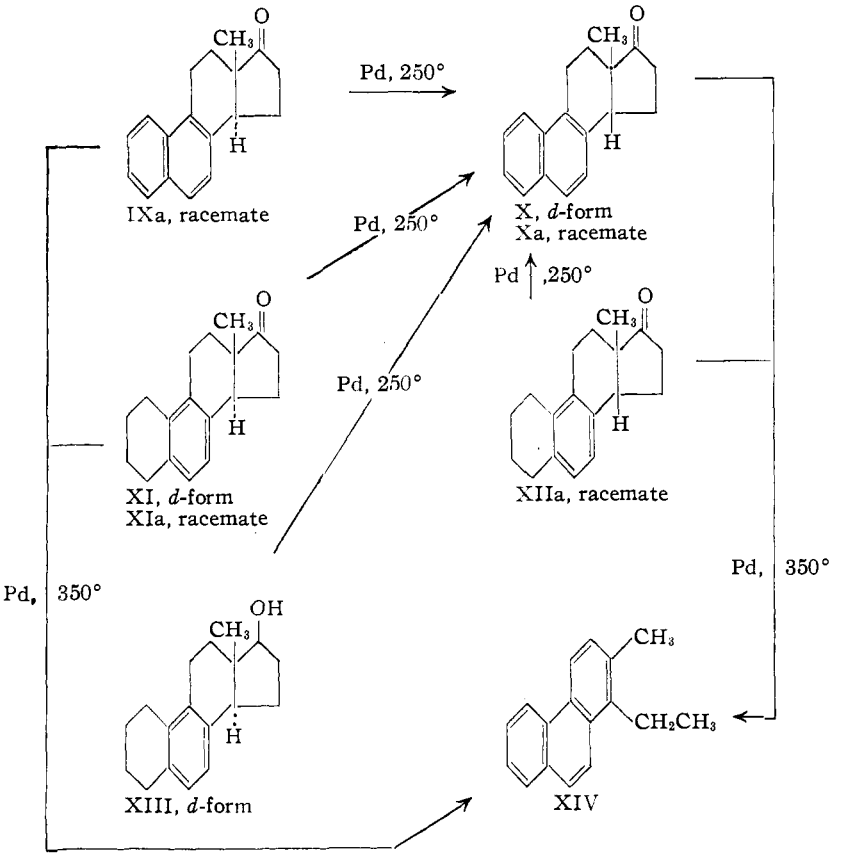
(6) This ketone was recently prepared through total synthesis by Miss E. F. Stephenson in this Laboratory.

(7) Butenandt, Wolff and Karlson, *Ber.*, **74**, 1308 (1941).

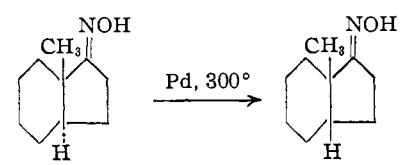
(8) The α-configuration (CH_3–OH *trans*) was originally assigned to this compound by Ruzicka, Mueller and Moergeli, *Helv. Chim. Acta*, **21**, 1394 (1938).

(9) Ott and Murray, Abstracts of the 113th A. C. S. Meeting, Chicago, 1948, used lithium aluminum hydride for the reduction of the C_{17} keto group in estrone and its methyl ether. The experimental details of their work were not available to us. They also obtained the same isomer of estradiol which results from catalytic hydrogenation. These experiments have been interpreted as evidence for the β-orientation of the OH group in natural estradiol by Fieser and Fieser, *Experientia*, **4**, 284 (1948); "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Publishing Corp., New York, N. Y., p. 327.

(10) Marker, Rohrmann, Lawson and Wittle, THIS JOURNAL, **60**, 1901 (1938), considered that the product of the dehydrogenation of dodecahydroequilenin (estranediol) with platinum black was *d*-equilenin. Assuming that the action of platinum is similar to that of palladium, the results of our work suggest that, in addition to the dehydrogenation of rings A and B and of the C_{17} hydroxyl group, epimerization at C_{14} may have occurred and that the product may have been impure *d*-isoequilenin rather than *d*-equilenin. The evidence cited for the *d*-equilenin configuration (m. p. 247° with formation of a red dye, and mixed melting point with *d*-equilenin 250–254°) does not exclude impure *d*-isoequilenin, as it has been described by Hirschmann and Wintersteiner.[2a] In the light of present knowledge it is better to employ the methyl ethers for comparison of equilenin and isoequilenin.



ments are all from a compound of the *normal* series to one of the *iso*-series. The reverse is apparently not possible under the same conditions. This indicates that, at least at 250°, the iso-configuration is the more stable one. We have found that, under similar conditions (5% palladium-on-charcoal at 300°), *trans*-8-methyl-1-hydrindanone in the form of its oxime (XV) is converted to its *cis*-isomer (XVI).[11] If it is assumed that the presence of a



XV, racemate XVI, racemate

naphthalene system fused at the 4,5-position does not change the free energy relationships of the two isomers of 8-methyl-1-hydrindanone, we may conclude that all the epimerizations reported here are from *trans* to *cis*, and that *d*-equilenin and all other normal compounds have the *trans*-configuration at the C–D ring juncture.[12]

It appears that this ease of isomerization from the *trans* to the *cis* series is peculiar to the C–D ring system, for no epimerization could be observed when ring D was open. The dimethyl esters of the *trans*- and *cis-dl*-2-methyl-2-carboxy-1,2,-3,4,5,6,7,8 - octahydro - 1 - phenanthreneacetic acids (XVII and XIX) gave the dimethyl esters of the *trans*- and *cis-dl*-2-methyl-2-carboxy - 1,2,3,4 - tetrahydro - 1-phenanthreneacetic acids (XVIII and XX),[13] respectively, when heated briefly with 5% palladium-on-charcoal at 250°. These results were significant for they made it possible to relate the configurations at the C–D ring juncture of estrone and *d*-equilenin through the marrianolic acids. Marrianolic acid is readily available by mild reactions from estrone[14a,b] and bis-dehydromarrianolic acid from *d*-equilenin.[14c] Dehydrogenation with palladium at 250° of the methyl ether of the dimethyl ester of marrianolic acid (XXI) gave an excellent yield of the methyl ether of the dimethyl ester of bis-dehydromarrianolic acid (XXII). This result is new and independent evidence[15] for the correspondence of the configuration both at C_{13} and C_{14} of estrone (VI) and *d*-equilenin (I).

Reactions with 5% Palladium-on-Charcoal at 350°.—When the temperature of the treatment

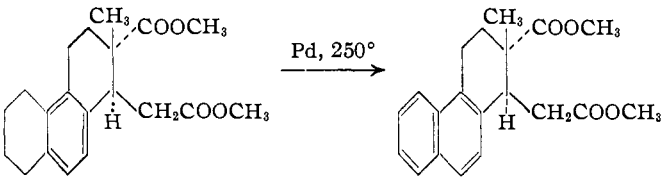
(11) The configurations of the two 8-methyl-1-hydrindanones are known since the *cis*-isomer has been both degraded to [Chuang, Tien and Ma, *Ber.*, **69**, 1494 (1936); Kon, Linstead and Simons, *J. Chem. Soc.*, 814 (1937)] and synthesized from [Bachmann and Kushner, THIS JOURNAL, **65**, 1963 (1943)] *cis*-2-methyl-2-carboxycyclohexaneacetic acid (m. p. 163–164°) the configuration of which has recently been established [see footnote 3 in Bachmann and Dreiding, *J. Org. Chem.*, **13**, 317 (1948)].

(12) For a recent review of the present views concerning the C–D ring configuration see Chapter X (by Turner) in Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Publishing Corp., New York, N. Y., p. 626–627. A critical review of the evidence on which the tentative conclusions there were based will be presented in a forthcoming paper. Further indicative evidence has recently been published by Bachmann and Ramirez, THIS JOURNAL, **71**, 2273 (1949).

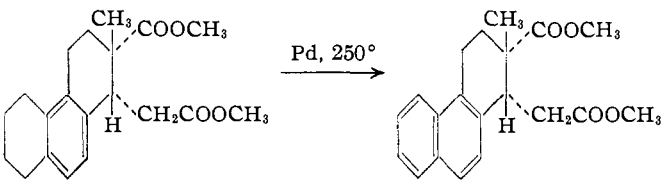
(13) The *trans* configuration is assigned to the esters XVII and XVIII (originally called the β-forms) because they are intermediates in the syntheses of *dl*-1,2,3,4-tetrahydrodesoxyequilenin (XIa)[5] and *dl*-desoxyequilenin (IXa),[3] respectively, which according to the above evidence have the *trans* configuration. Correspondingly, the esters XIX and XX have the *cis* configuration.

(14) (a) Litvan and Robinson, *J. Chem. Soc.*, 1997 (1938); (b) Heer and Miescher, *Helv. Chim. Acta*, **28**, 156 (1945); (c) Heer Billeter and Miescher, *ibid.*, **28**, 991 (1945).

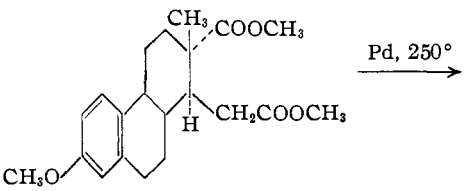
(15) The previously available evidence, which was recently reviewed by Shoppee, *Nature*, **161**, 207 (1948), and by Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Publishing Corp., New York, N. Y., p. 321, consists of the conversion of equilin into equilenin on the one hand and by a long series of reactions into estrone or desoxoestrone on the other hand.



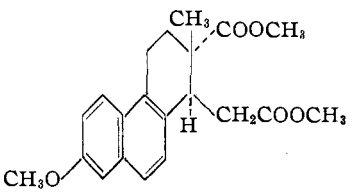
XVII, racemate XVIII, racemate



XIX, racemate XX, racemate



XXI, *d*-form

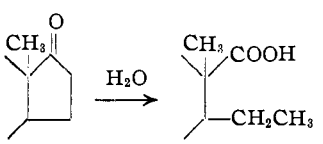


XXII, *d*-form

with an equal weight of the catalyst was 350° for twenty minutes a more drastic change of the steroid molecule occurred. The five-membered D ring was cleaved with loss of a carbon atom (probably C_{17}) and the attached oxygen atom. The six-membered A, B and C rings remained intact but were aromatized to a phenanthrene nucleus, to which a methyl group (formerly the angular methyl group) was attached in the 2-position and an ethyl group (previously part of the D ring) was attached at the 1-position. Thus, *dl*-desoxyisoequilenin (Xa), which remained unaffected at 250°, was converted into 1-ethyl-2-methylphenanthrene (XIV) in good yield at 350°. Similarly *dl*-desoxyequilenin (IXa), *dl*-1,2,3,4-tetrahydrodesoxyequilenin (XIa) and *dl*-1,2,3,4-tetrahydrodesoxyisoequilenin (XIIa) yielded 1-ethyl-2-methylphenanthrene (XIV) at 350°. The optically active members of these series would necessarily yield the same product (XIV).

Under the same conditions the methyl ethers of *d*-equilenin (III), of estrone (VII), and of α-dihydroequilenin (V) gave 7-methoxy-1-ethyl-2-methylphenanthrene (VIII). The latter compound was synthesized from 7-methoxy-1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene and ethylmagnesium iodide, with subsequent dehydration and dehydrogenation. This methoxyphenanthrene derivative (VIII) would also be expected as the product of the dehydrogenation at 350° of the methyl ethers of all the stereoisomers of equilenin and of estrone, as well as of the methyl ethers of equilin, of estradiol and their stereoisomers.

Some light was thrown on the mechanism of the cleavage of ring D by the identification of carbon dioxide as one of the products of the treatment of the methyl ether of equilenin (III) with 5% palladium-on-charcoal at 350°. This could be explained by assuming hydrolytic cleavage of the C_{16}–C_{17} bond by moisture adsorbed on the catalyst (which reacted neutral to moist litmus) to give the methyl ether of bis-dehydrodoisynolic acid, which under the conditions of the experiment would be decarboxylated and dehydrogenated[14b] to 7-methoxy-1-ethyl-2-methylphenanthrene (VIII).



The reactions reported here should prove useful in the diagnosis of the structure and configuration of both natural and synthetic polycyclic compounds.

We are grateful to Parke, Davis and Company for a gift of equilenin and estrone.

Experimental[16]

Reactions with 5% Palladium-on-Charcoal at 250°

General Method (Method a).—Equal weights of the substance to be dehydrogenated (and/or epimerized) and of 5% palladium-on-charcoal catalyst (Wilkens-Anderson Co., Chicago, Illinois) were placed into a test-tube under a nitrogen atmosphere, and the air was excluded by a mercury trap. The tube was inserted one inch into a Wood's metal-bath at 250 ± 5°, as read by a 360° thermometer immersed two inches in the bath, and was kept there for eight minutes. The contents were cooled and leached with benzene (or another solvent when stated). The catalyst was removed by filtration and the colorless filtrate was concentrated in a stream of dry air. The residue was recrystallized as described in the various experiments.

Epimerization of *d*-Equilenin (I).—*d*-Equilenin (1 g.) was subjected to the treatment of method (a), the melt was extracted in this case with acetone, and the hot solution was filtered with suction and concentrated to 15 cc. After the addition of 10 cc. of ethanol, the solution was boiled for a few minutes and allowed to cool slowly. A first crop of 0.7 g. of *d*-isoequilenin and a second crop of 0.15 g. of the same product were isolated. The combined crops were sublimed at 180–200° and 0.01 mm. as large colorless prisms of *d*-isoequilenin (II); m. p. 264–266° (vac.); yield, 83%; optical rotation, $[\alpha]^{26}D$ + 146° (*c* 2.06, in dioxane); [reported,[2b] m. p. 265–266° (vac.); $[\alpha]^{29}D$ + 147°].

No epimerization occurred when a mixture of 0.4 g. of *d*-equilenin, 0.4 g. of 5% palladium-on-charcoal and 25 cc. of ethanol was shaken and heated at 80–90° for sixteen hours in a closed pressure flask. The *d*-equilenin was recovered by removing the catalyst through filtration, concentrating the filtrate on a steam-bath to 15 cc. and allowing to cool. The slightly discolored (red) needles melted

(16) All melting points are corrected. All microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

at 257–258° (vac.); weight, 0.3 g. The mother liquor yielded 0.05 g. of colorless needles of the same melting point. The combined crops were converted to the methyl ether (III); m. p. 196–197° alone and then mixed with an authentic sample.

Epimerization of *d*-Equilenin Methyl Ether (III).—Method (a) was applied to 50 mg. of *d*-equilenin methyl ether (m. p. 196–197°). A crop of 45 mg. (90%) of *d*-isoequilenin methyl ether (IV), m. p. 115–117°, crystallized from methanol. The recrystallized product melted at 118–118.5° alone and when mixed with an authentic sample[2b]; optical rotation, $[\alpha]^{28}D$ + 164° (*c* 0.900, in chloroform[1]).

Derivatives of *dl*-Desoxyequilenin (IXa).—They were prepared from a sample of the ketone which melted at 188–189°.[3] The ***sym*-trinitrobenzene complex** crystallized from ethanol in yellow needles; m. p. 153–154°.

Anal. Calcd. for $C_{24}H_{21}N_3O_7$: C, 62.20; H, 4.57. Found: C, 62.32; H, 4.76.

The **oxime** crystallized from methanol in colorless prismatic needles; m. p. 217–217.5°, with previous softening and partial sublimation at 213°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22. Found: C, 81.33; H, 7.30.

Derivatives of *dl*-Desoxyisoequilenin (Xa).—The ***sym*-trinitrobenzene complex** (prepared from a sample of the ketone,[3] m. p. 101–102°) crystallized from ethanol in fine yellow needles, m. p. 133–134°.

Anal. Calcd. for $C_{24}H_{21}N_3O_7$: C, 62.20; H, 4.57; N, 9.07. Found: C, 61.95; H, 3.98; N, 8.90.

The **oxime** crystallized from methanol in large flat prisms; m. p. 192–193°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22. Found: C, 81.50; H, 6.90.

Epimerization of *dl*-Desoxyequilenin (IXa).—Method (a) was applied to 15 mg. of *dl*-desoxyequilenin (m. p. 188–189°). A crop of 10 mg. of colorless plates of *dl*-desoxyisoequilenin (Xa), m. p. 100–101°, crystallized from methanol. From the mother liquor 6 mg. of the *sym*-trinitrobenzene complex of *dl*-desoxyisoequilenin, m. p. 133–134°, was obtained. A sample of the ketone gave the oxime; m. p. 190–192°. The identities of the products were established by mixed melting points.

When *dl*-desoxyisoequilenin (Xa) was treated in the same manner, it was recovered in 85% yield.

Dehydrogenation and Epimerization of *dl*-1,2,3,4-Tetrahydrodesoxyequilenin (XIa).—Treatment of 100 mg. of the ketone (m. p. 114–115°)[5] as described in method (a) gave 85.6 mg. (86%) of *dl*-desoxyisoequilenin (Xa); m. p. 98–100°; after recrystallization from methanol, m. p. 101–102° alone and when mixed with an authentic sample. The melting points of the derivatives also were not depressed by authentic samples.

Dehydrogenation of *dl*-1,2,3,4-Tetrahydrodesoxyisoequilenin (XIIa).—The reaction was carried out on 53 mg. of the ketone (m. p. 70–71°)[5] according to method (a). Recrystallization of the product from methanol yielded 43 mg. (81%) of *dl*-desoxyisoequilenin (Xa) as fine colorless plates, m. p. 101–102° alone and when mixed with an authentic sample. The derivatives proved identical with authentic samples.

Dehydrogenation and Epimerization of *d*-1,2,3,4-Tetrahydrodesoxyequilenin (XI).—The application of method (a) to 50 mg. of this ketone (m. p. 106–107°)[17] yielded 35 mg. (72%) of colorless crystals from methanol; m. p. 102–104°. After two recrystallizations the *d*-desoxyisoequilenin (X) melted at 107.5–108.5°; optical rotation, $[\alpha]^{27}D$ + 168° (*c* 1.515, in chloroform).

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.11; H, 7.24.

This ketone proved identical with a sample obtained by total synthesis.[6] The ***sym*-trinitrobenzene complex** crystallized from ethanol in yellow needles; m. p. 135.5–136.5°.

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

Anal. Calcd. for $C_{24}H_{21}N_3O_7$: C, 62.20; H, 4.57; N, 9.07. Found: C, 62.24; H, 4.52; N, 8.86.

The **2,4-dinitrophenylhydrazone** crystallized from ethyl acetate in orange-red prisms; m. p. 235–237° dec.

Anal. Calcd. for $C_{24}H_{22}N_4O_4$: C, 66.96; H, 5.15; N, 13.02. Found: C, 66.85; H, 5.64; N, 12.97.

The oxime crystallized in clusters of colorless needles when a dilute solution in petroleum ether (b. p. 60–75°) was concentrated by boiling and allowed to cool; m. p. 153.5–154.5°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.43; H, 7.18; N, 5.50.

Dehydrogenation and Epimerization of the Methyl Ether of Estrone (VII).—The methyl ether of estrone (20 mg.) was treated according to method (a). On recrystallization of the residue from methanol, 17 mg. of *d*-isoequilenin methyl ether (IV) was obtained as glistening colorless plates; m. p. 119–120° alone and when mixed with an authentic sample.

Isomerization of the Oxime of *trans*-8-Methyl-1-hydrindanone (XV)[18] to its *cis*-Form (XVI).—A mixture of 25 mg. of the oxime of *trans*-8-methyl-1-hydrindanone (m. p. 116.5–117.5°) and 25 mg. of 5% palladium-on-charcoal catalyst, sealed in a 10 × 75 mm. Pyrex test-tube, was heated in a Wood's metal-bath at 290–300° for ninety minutes. The product, extracted with ether, had a camphoraceous odor, indicating the presence of some ketone. The whole was converted to the oxime of *cis*-8-methyl-1-hydrindanone which, after isolation by means of ether and purification by evaporative distillation at 50–60° and 0.4 mm., melted at 84–85°; yield 10 mg. (40%). When mixed with an authentic sample of the oxime of *cis*-8-methyl-1-hydrindanone (m. p. 86–87°)[18] it melted at 85–87°, and when mixed with an authentic sample of the oxime of the *trans* form (m. p. 116.5–117.5°) at 72–75°.

β-Dihydroequilenin Methyl Ether (V).—A mixture of 0.2 g. of lithium aluminum hydride (Metal Hydrides, Inc., Beverly, Mass.) and 25 cc. of anhydrous ether was heated to reflux for twenty minutes. The lumps of hydride were crushed and refluxing was continued for thirty minutes. A suspension of 0.1 g. of *d*-equilenin methyl ether (III) (m. p. 196–197°) in 10 cc. of ether was added and the resulting mixture was refluxed for three hours. The excess reducing agent was decomposed by the addition of 5 cc. of 10% sodium hydroxide and the insoluble salts were dissolved with excess hydrochloric acid. The β-dihydroequilenin methyl ether (V) which remained after concentration of the organic layer crystallized from aqueous methanol in colorless plates; m. p. 149–150°; yield, 98 mg. (97%). When *d*-equilenin itself was treated with lithium aluminum hydride under these conditions, it was recovered unchanged.

The same product was obtained when β-dihydroequilenin[8,17,19] [m. p. 255–256° (vac.); reported, 248°] was methylated. A hot solution of 0.1 g. of β-dihydroequilenin in 10 cc. of 2% aqueous sodium hydroxide was treated with 1 cc. of dimethyl sulfate in small portions. The methyl ether of β-dihydroequilenin (V) which precipitated crystallized from aqueous methanol in thin colorless plates; m. p. 144–146°; yield 90 mg. (89%). A portion was recrystallized from petroleum ether containing a little benzene; m. p. 149.5–150.5°.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.70; H, 8.01.

Epimerization and Dehydrogenation of β-Dihydroequilenin Methyl Ether (V).—Method (a) was applied to 60 mg. of the above methyl ether. A crop of 30 mg. of colorless prisms of *d*-isoequilenin methyl ether (IV) crystallized from methanol; m. p. 119–119.5°. From the mother liquor a second crop of 20 mg., m. p. 118–119°, was

(18) Bachmann and Kushner, *ibid.*, **65**, 1963 (1943). The *trans*-8-methyl-1-hydrindanone was used in form of its oxime because this was the only form available in our laboratory at the time.

(19) Marker, Kamm, Oakwood and Tendick, THIS JOURNAL, **59**, 768 (1937).

isolated. The melting point was not depressed by an authentic sample.

Epimerization and Dehydrogenation of *d*-1,2,3,4-Tetrahydrodesoxy-β-dihydroequilenin (XIII).—The reaction was carried out on 0.3 g. of the compound (m. p. 147–148°)[8,17,19] according to method (a). A solution of the crude product in 10 cc. of reagent benzene was adsorbed on a column of 10 g. of activated alumina (Merck, according to Brockmann) and eluted with benzene. Removal of the solvent and crystallization from petroleum ether (b. p. 60–75°) yielded 0.21 g. (72%) of colorless prisms of *d*-desoxyisoequilenin (X); m. p. 107.5–108.5°. The identity of this product was demonstrated by a mixed melting point of a synthetic sample[6] and by the melting points alone and mixed of the *sym*-trinitrobenzene complex (135–136°) and of the 2,4-dinitrophenylhydrazone (234–237° dec.).

Dehydrogenation of the Dimethyl Esters of *trans*- and *cis-dl*-2-Methyl-2-carboxy-1,2,3,4,5,6,7,8-octahydro-1-phenanthreneacetic Acids (XVII and XIX).—The two esters were dehydrogenated in identical manner according to method (a). From the *trans*-form (XVII, m. p. 81.5–82.5°)[5,13] (50 mg.) the dehydrogenated ester (XVIII) was obtained as an oil, in accordance with previous experience.[3] Hydrolysis with one equivalent of alkali yielded *dl-trans*-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydro-1-phenanthreneacetic acid, which crystallized very slowly from ether; yield 20 mg.; m. p. 156–157° alone and when mixed with an authentic sample.[3]

From the *cis*-form (XIX, m. p. 70.5–71.5°)[5,13] (50 mg.) was obtained 40 mg. (81%) of the dimethyl ester of *dl-cis*-2-methyl-2-carboxy-1,2,3,4-tetrahydro-1-phenanthreneacetic acid (XX), which crystallized from methanol in colorless elongated prisms, m. p. 99–100°. After recrystallization it melted at 103–104° alone and when mixed with an authentic sample (m. p. 104.5–105.5°).[3] A portion (30 mg.) on half hydrolysis gave *dl-cis*-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydro-1-phenanthreneacetic acid, which crystallized from aqueous acetone as glistening soft needles; yield 25 mg.; m. p. 130–132° alone and when mixed with an authentic sample (m. p. 133–134°).[3]

Dehydrogenation of the Methyl Ether of the Dimethyl Ester of Marrianolic Acid (XXI).—Estrone methyl ether (VII) was oxidized by potassium hypoiodite as has been described for the benzyl ether[14b] and the product was esterified with diazomethane. The crude diester (XXI) (24 mg.) was treated according to method (a). The residue was crystallized from methanol and yielded a first crop of 16 mg. of the methyl ether of the dimethyl ester of bis-dehydromarrianolic acid (XXII), m. p. 134–135°, and a second crop of 6 mg.; m. p. 130–133°. A sample of the first crop, mixed with an authentic sample of XXII, obtained by oxidation of equilenin methyl ether (III) with potassium hypoiodite and esterification of the product with diazomethane (m. p. 137.5–138.5°),[14c] melted at 135–138.5°.

Reactions with 5% Palladium on Charcoal at 350°

General Method (Method b).—The reactions were carried out in the same manner as in method (a) with the exception that the bath temperature was kept at 350 ± 10° for twenty minutes.

Ring Cleavage and Dehydrogenation of *dl*-Desoxyisoequilenin (Xa).—When method (b) was used on 0.17 g. of the ketone (m. p. 101–102°) evolution of gas was noticeable. A solution of the crude product in 15 cc. of a mixture of four parts of petroleum ether (b. p. 60–75°) and one part of benzene was passed through a column of 6 g. of activated alumina (Merck, according to Brockmann). Elution with 50 cc. of the same solvent mixture and concentration yielded 0.13 g. (87%) of 1-ethyl-2-methylphenanthrene (XIV), m. p. 75–77°. After two recrystallizations from methanol, it appeared as thin feather-like flakes; m. p. 79–80° alone and when mixed with an authentic sample made according to the described procedure.[20]

(20) Haworth, Mavin and Sheldrick, *J. Chem. Soc.*, 460 (1934).

Anal. Calcd. for $C_{17}H_{16}$: C, 92.68; H, 7.32. Found: C, 92.52; H, 7.41.

The ultraviolet absorption spectrum of the product of this reaction was identical with that of the authentic sample of 1-ethyl-2-methylphenanthrene. The picrate (m. p. 135–136°) also proved identical with that derivative of an authentic sample. The ***sym*-trinitrobenzene complex of 1-ethyl-2-methylphenanthrene** crystallized from ethanol in yellow needles, m. p. 152.5–153°, and was identical with the same derivative made from an authentic sample of the hydrocarbon (XIV).

Anal. Calcd. for $C_{23}H_{19}N_3O_6$: C, 63.74; H, 4.42; N, 9.70. Found: C, 63.95; H, 4.34; N, 9.63.

Ring Cleavage and Dehydrogenation of *dl*-Desoxyequilenin (IXa), *dl*-1,2,3,4-Tetrahydrodesoxyequilenin (XIa) and *dl*-1,2,3,4-Tetrahydrodesoxyisoequilenin (XIIa).—The application of method (b) to these three ketones also yielded 1-ethyl-2-methylphenanthrene (XIV). Alternate methods of purification were evaporative distillation at 100–120° (0.02 mm.) and subsequent crystallization from methanol, or regeneration from the *sym*-trinitrobenzene complex (m. p. 152–153°) by reduction with stannous chloride in concentrated hydrochloric acid and ethanol, extraction with ether and crystallization from methanol.

Ring Cleavage and Dehydrogenation of *d*-Equilenin Methyl Ether (III).—The application of method (b) to 0.3 g. of *d*-equilenin methyl ether (m. p. 196–197°) gave 0.26 g. of crystalline brown residue. A solution of this in 10 cc. of 1:1 benzene–petroleum ether (b. p. 60–75°) was passed through a column of 10 g. of activated alumina (Merck, according to Brockman). Elution with 50 cc. of the same solvent mixture, concentration of the eluate and crystallization of the residue from methanol (Norit) yielded 0.17 g. (63%) of 7-methoxy-1-ethyl-2-methylphenanthrene (VIII) as colorless flakes; m. p. 114–115° (softening at 108°). From the mother liquor 0.05 g. of *sym*-trinitrobenzene complex was obtained as yellow needles; m. p. 130.5–131.5°. The picrate (orange blades) melted at 127.5–128.5°. The product of this reaction and its derivatives proved identical with the synthetic samples, prepared as described below.

In another experiment with 0.2 g. of *d*-equilenin methyl ether (III) method (b) was modified to allow a slow stream of nitrogen to pass over the reaction mixture and through a saturated barium hydroxide solution. The carbon dioxide which was evolved during the reaction formed 90 mg. (65%) of barium carbonate. The residue from the benzene extract was crystallized from methanol (Norit) yielding 88 mg. (49%) of almost colorless flakes of 7-methoxy-1-ethyl-2-methylphenanthrene (VIII); m. p. 108–109°.

Ring Cleavage and Dehydrogenation of Estrone Methyl Ether (VII) and of β-Dihydroequilenin Methyl Ether (V).—Method (b) was applied to 40 mg. of estrone methyl ether (m. p. 171–172°) and to 90 mg. of β-dihydroequilenin methyl ether (149–150°). By crystallizing the crude residues from methanol (Norit) 25 mg. (71%) and 54 mg. (86%), respectively, of 7-methoxy-1-ethyl-2-methylphenanthrene (VIII) were isolated; m. p. 108–109°.

7-Methoxy-1-ethyl-2-methylphenanthrene (VIII).—To a solution of the Grignard reagent made from 0.2 g. of magnesium turnings and 0.5 g. of ethyl iodide in 10 cc. of ether was added a solution of 0.4 g. of 7-methoxy-1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene[2b] in 6 cc. of benzene in small portions at room temperature. The reaction mixture was refluxed for a few minutes, the complex was decomposed with ice and the magnesium salts were dissolved with acid. The product obtained from the organic layer after two recrystallizations from petroleum ether (b. p. 60–75°) formed compact clusters of nearly colorless prisms of **7-methoxy-1-ethyl-2-methyl-3,4-dihydrophenanthrene**; m. p. 108.5–109.5; yield 0.43 g. (96%).

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.50; H, 8.03.

The dehydrogenation of 0.4 g. of the above compound was carried out by heating it with 0.3 g. of 5% palladium-

on-charcoal at 250° for five minutes. The product was taken up in benzene and the catalyst was removed by filtration. The filtrate was concentrated and the residue crystallized from methanol. A fine network of colorless flakes of **7-methoxy-1-ethyl-2-methylphenanthrene (VIII)** was obtained; m. p. 114.5–115.5°; yield 0.34 g. (92%).

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.08; H, 7.30.

The ***sym*-trinitrobenzene complex** crystallized from ethanol in yellow needles; m. p. 130.5–131.5°.

Anal. Calcd. for $C_{24}H_{21}N_3O_7$: C, 62.20; H, 4.57; N, 9.07. Found: C, 62.60; H, 4.50; N, 8.82.

The **picrate** was obtained from ethanol in long orange blades; m. p. 128–129°.

Anal. Calcd. for $C_{24}H_{21}N_3O_8$: C, 60.12; H, 4.42. Found: C, 60.68; H, 4.52.

A sample of 0.08 g. of VIII was refluxed with 3 cc. of glacial acetic acid and 2 cc. of 48% hydrobromic acid under an atmosphere of nitrogen for twenty hours. After dilution with water, the product was extracted with benzene, washed with sodium bicarbonate solution and dissolved in hot sodium hydroxide. Impurities were removed by treating the hot solution with Norit and filtering while hot. On acidification of the filtrate, 0.07 g. of the crude phenanthrol precipitated; m. p. 160–163°. After recrystallization from xylene and sublimation *in vacuo*, the colorless prisms of 7-hydroxy-1-ethyl-2-methylphenanthrene melted at 166–167° (reported,[14b] 166–167° for the product obtained from bis-dehydrodoisynolic acid).

Summary

The action of 5% palladium-on-charcoal catalyst on some steroids and related compounds at 250° and at 350° was investigated.

The action at 250° results in three effects, depending on the compounds: (1) When the C–D ring juncture has the *trans*-configuration epimerization takes place at C_{14}. When the C–D ring configuration is *cis*, and when ring D is open in compounds of both configurations, no epimerization is observed. (2) When ring A (and/or B) is alicyclic it is aromatized. (3) A C_{17} hydroxyl group is dehydrogenated to a keto group.

At 350°, rings A, B and C are dehydrogenated and a cleavage of ring D occurs with loss of a carbon atom as carbon dioxide in such a manner that a 1-ethyl-2-methylphenanthrene structure results.

The methyl ether of β-dihydroequilenin was prepared by lithium aluminum hydride reduction of the methyl ether of *d*-equilenin. 7-Methoxyl-1-ethyl-2-methylphenanthrene was synthesized from 7-methoxy-1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene.

New evidence is cited for the correspondence of the configuration at C_{13} and at C_{14} of estrone and *d*-equilenin and for the assignment of the *trans*-configuration to the C/D ring juncture in these hormones as well as in the other *normal* compounds.

ANN ARBOR, MICHIGAN RECEIVED JULY 14, 1949

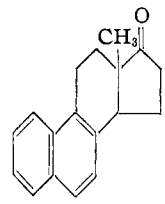
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Conversion of *d*-Equilenin into its 3-Amino Analog. Synthesis of *d*-Desoxyequilenin

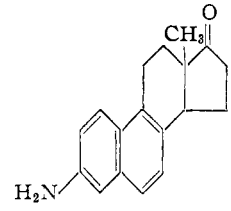
BY W. E. BACHMANN AND ANDRE S. DREIDING[1]

Recently Prelog and Fuehrer[2] isolated *d*-desoxyequilenin (I) from the neutral fraction of the urine of pregnant mares and found that it possessed slight estrogenic activity. Previously, Marker and Rohrmann[3] had postulated the presence of *d*-desoxydihydroequilenin in the non-phenolic carbinol fraction, for on oxidation they obtained 11-ketodesoxyequilenin. Reduction of one of the keto groups of this compound yielded a product which they apparently considered to be *d*-desoxyequilenin (I).[4] The melting point of their compound agrees with that reported later for *d*-desoxyequilenin isolated directly from the urine.

We have now synthesized *d*-desoxyequilenin from *d*-equilenin by replacement of the 3-hydroxyl group in the latter with an amino group, diazotization, and reduction of the diazonium salt. *d*-Equilenin reacted smoothly with aqueous ammonium bisulfite at 170° (Bucherer reaction) to give *d*-3-aminodesoxyequilenin (II) in 71% yield. Since treatment of a hot solution of II in sulfuric



I



II

acid with sodium nitrite regenerated *d*-equilenin, no rearrangement or epimerization had taken place during the Bucherer reaction. A stable aqueous solution of the diazonium chloride was obtained by treating the insoluble hydrochloride of II with aqueous sodium nitrite at −12°. Reduction of the diazonium group by hypophosphorous acid gave *d*-desoxyequilenin in 76% yield. Its properties agreed with those of the compound (I) obtained from natural sources.[2,3] When it

(1) Horace H. Rackham Postdoctoral Fellow in the Horace H. Rackham School of Graduate Studies, 1948/1949.

(2) Prelog and Fuehrer, *Helv. Chim. Acta*, **28**, 583 (1945).

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

(4) Unfortunately Marker and Rohrmann did not name the compound in the experimental part and the result is somewhat obscure in the discussion. The word desoxyequilenin appears at the end of the appropriate paragraph in the discussion section but is used erroneously for the hydrocarbon which resulted from the Clemmensen reduction of both carbonyl groups of 11-ketodesoxyequilenin. This may account for Prelog and Fuehrer apparently overlooking the compound and its probable identity with their *d*-desoxyequilenin.