which was depressed by the same derivative of the hydroxyketone.

Anal. Calcd. for $C_{30}H_{24}N_4O_6$: C, 67.1; H, 4.5; N, 10.4. Found: C, 66.7; H, 4.8; N, 10.2.

Oxidation of the Hydroxyketone.—Lead tetraacetate (220 mg.) was added portionwise over a six-hour period to a solution of 194 mg. of crude hydroxyketone (m. p. 152–157°) in 10 ml. of acetic acid and 2 ml. of water kept at 90–95°; frequent tests with starch-potassium iodide paper showed that the oxidizing agent was being consumed. The lemon-yellow solution, after removal of the lead as lead sulfate, was warmed with methanolic 2,4-dinitrophenylhydrazine reagent for a few minutes. After three recrystallizations of the product (230 mg.) from ethyl acetate–methanol the **mono-2,4-dinitrophenylhydrazone** presumably of 1-phenylglyoxylyl-2-carbomethoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene (IV) was obtained as microscopic crimson plates; m. p. 214–215°.

Anal. Calcd. for $C_{31}H_{26}N_4O_7$: C, 65.7; H, 4.6; N, 9.9. Found: C, 65.7; H, 4.3; N, 10.2.

Fusion of a sample of the crude oxidation product with potassium hydroxide yielded an acid which after evaporative distillation crystallized from acetone–petroleum ether in platelets; m. p. 183–185° alone, and 188–191° when mixed with a sample of 2-methyl-1,2,3,4-tetrahydrophenanthrene-2-carboxylic acid (m. p. 190–191°). The latter acid was prepared by refluxing a solution of 1.3 g. of 1-keto-2-carbomethoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene with amalgamated zinc and hydrochloric acid for twenty-three hours, analogous to the preparation of the 7-methoxy derivative.[10] The isolated product was treated with diazomethane and evaporatively distilled at 100–120° at 0.05 mm. and the distillate was hydrolyzed with hot 14% aqueous-methanolic potassium hydroxide to the acid (330 mg.), which gave no test for carbonyl group. After evaporative distillation at 0.05 mm. and three recrystallizations from methanol the **2-methyl-1,2,3,-4-tetrahydrophenanthrene-2-carboxylic acid** formed colorless platelets; m. p. 192–193°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 80.0; H, 6.7.

A solution of 260 mg. of the crude oxidation product in 40 ml. of methanol, 2 ml. of Superoxol (30% hydrogen peroxide) and 4 ml. of *N* sodium hydroxide was stirred for twelve hours at room temperature. After the removal of the solvents at 60° in a current of air, the residue was boiled with water and the aqueous solution, after removal of a small amount of insoluble liquid with benzene, chloroform, and ethyl acetate, was filtered and acidified. The precipitated acidic material (120 mg.), isolated with ether, was evaporatively distilled at 130–160° and 0.05 mm. The crystalline product (33 mg. or 40%, m. p. 121–122°) which collected at the upper end of the tube, proved to be benzoic acid. The higher-boiling distillate (50 mg.) was a viscous liquid which is being investigated further.

trans-**2-Carbomethoxy-2-methyl-1-phenacyl-1,2,3,4-tetrahydrophenanthrene.**—The phenyl ketone obtained by reaction of diphenylcadmium with the acid chloride of 0.05 g. of *trans*-2-carbomethoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene-1-acetic acid (m. p. 155–157°)[5] crystallized from methanol in colorless needle-like prisms; yield, 0.33–0.36 g. (56–62%); m. p. 119–120°. After three recrystallizations a sample melted at 120–121°; it gave an orange color with concentrated sulfuric acid.

Anal. Calcd. for $C_{25}H_{24}O_3$: C, 80.6; H, 6.5. Found: C, 80.0; H, 6.6.

The **2,4-dinitrophenylhydrazone** after two recrystallizations from ethyl acetate–methanol formed red rectangular plates; m. p. 215–216°.

Anal. Calcd. for $C_{31}H_{28}O_6$: C, 67.4; H, 5.1; N, 10.1. Found: C, 67.6; H, 5.2; N, 9.9.

Bromination of 330 mg. of the phenyl ketone (m. p. 119–121°) in 8 ml. of acetic acid by the procedure described for the *cis* isomer gave 370 mg. of solid which was purified by passage of a 1:2 benzene–petroleum ether solution through alumina. After one recrystallization from petroleum ether the **monobromo derivative** melted at 126–130°; yield, 200 mg. (50%). After another recrystallization the bromo derivative formed colorless rosettes; m. p. 129–130°.

Anal. Calcd. for $C_{25}H_{23}BrO_3$: C, 66.5; H, 5.1; Br, 17.7. Found: C, 65.7; H, 5.1; Br, 17.7.

Summary

The *cis* and *trans* forms of 2-carbomethoxy-2-methyl-1-phenacyl-1,2,3,4-tetrahydrophenanthrene have been prepared by the reaction of diphenylcadmium with the corresponding acid chlorides. The formation of the *cis* 1,2-ketol and a study of its behavior toward oxidizing agents are described.

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(10) Heer and Miescher, *Helv. Chim. Acta*, **28**, 1506 (1945).

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

Studies on the Configuration of the C/D Ring Juncture of Steroids. The Lactams Corresponding to Desoxyequilenin and Desoxyisoequilenin[1]

BY W. E. BACHMANN AND FAUSTO RAMIREZ[2]

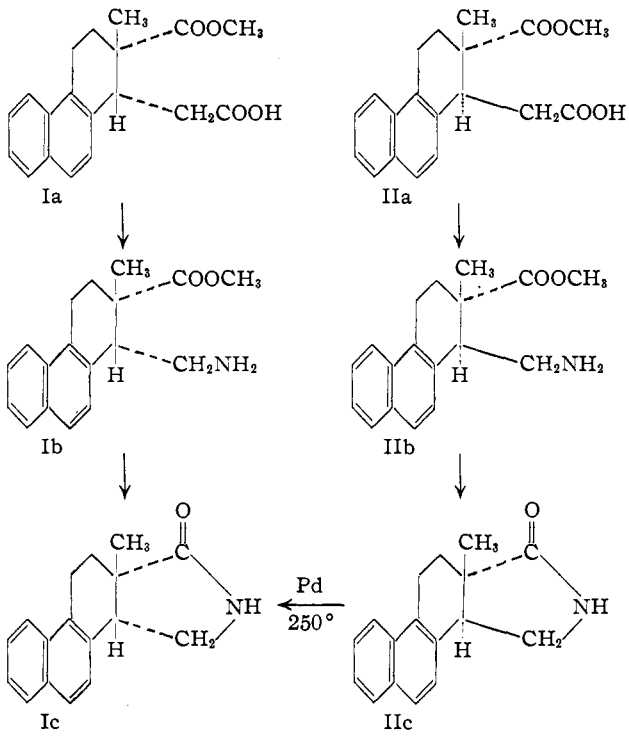
Although a *trans* configuration has been assigned to the C/D ring juncture of the female sex hormones, more experimental evidence is desirable in order to establish unequivocally this configuration.[3] We have investigated the nature of the C/D ring configuration in desoxyequilenin and desoxyisoequilenin by degrading the two diastereoisomeric 2-carbomethoxy-2-methyl-1,2,3-4-tetrahydrophenanthrene-1-acetic acids (Ia and IIa) in the form of racemic mixtures to the aminoesters (Ib and IIb) by the Curtius reaction and studying the tendency of the aminoesters to form lactams (Ic and IIc).

The acid chlorides of Ia and IIa were converted into azides by reaction with sodium azide in aqueous acetone. Rearrangement of the azides and hydrolysis of the resulting isocyanates with concentrated hydrochloric acid gave the hydrochlorides of the *cis* and *trans* forms of the aminoesters Ib and IIb in 71–80% over-all yields. A

(1) From the Ph.D. dissertation of Fausto Ramirez, 1949.

(2) Cobb Chemical Laboratory, University of Virginia.

(3) (a) Shoppee, *Nature*, **161**, 207 (1948); (b) Heer and Miescher, *Helv. Chim. Acta*, **29**, 1895 (1946); (c) Heer and Miescher, *ibid.*, **30**, 550 (1947); (d) Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, 3rd ed., p. 626.



comparison of the relative tendencies of the aminoesters to form lactams was obtained by treating an aqueous solution of each of the aminoester hydrochlorides with one equivalent of alkali, quickly extracting the product into ether, and then extracting any aminoester remaining in the ether with dilute acid. Under identical conditions *dl*-16-azadesoxyisoequilenin, the lactam corresponding to desoxyisoequilenin, was formed in 60% yield but none of the lactam corresponding to desoxyequilenin was produced.[4] In line with this result was the isolation of the aminoester and the amino acid of the desoxyequilenin series, while the corresponding compounds of the desoxyisoequilenin series were not isolated on account of their readiness to cyclize to the lactam. *dl*-16-Azadesoxyequilenin could be prepared by allowing the aminoester to stand in the presence of alkali for a longer time.

A further difference in the two series was found in the relative stability of the lactams to hydrolysis. 16-Azadesoxyisoequilenin was very resistant to hydrolysis, but 16-azadesoxyequilenin could be hydrolyzed quantitatively to the amino acid. Furthermore, 16-azadesoxyequilenin was isomerized completely to 16-azadesoxyisoequilenin by the action of palladium–charcoal at 250°, conditions under which a *trans*-8-methylhydrindane structure is isomerized to the more stable *cis* configuration.[5] All of these results are in agreement with the view that 16-azadesoxyisoequilenin is the *cis* lactam (Ic) and 16-azadesoxyequilenin is the *trans* lactam (IIc), and are in concordance with the results obtained from a study of the isomerization of the steroids themselves.[5]

(4) A brief communication appeared in THIS JOURNAL, **71**, 2273 (1949).

(5) Bachmann and Dreiding, *ibid.*, **72**, 1323 (1950).

Experimental

Curtius Degradation of the Acid Esters.—The required *cis* and *trans* 2-carbomethoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene-1-acetic acids were prepared by the procedures employed by Bachmann and Wilds.[6] The only modification was the use of efficient stirring under nitrogen during the decarbonylation of a relatively large quantity (83 g.) of the glyoxalate in the presence of powdered glass (90 g.). The pyrolysis was carried out in a 2-l. round-bottomed flask; the ejection of carbon monoxide was complete in twenty minutes; yield of 1-keto-2-carbomethoxytetrahydrophenanthrene, 58 g. (75%).

To an ice-chilled suspension of 1 g. of *cis* or *trans* 2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid in 10 ml. of dry benzene and 3 drops of pyridine was added dropwise with swirling 1.7 ml. of pure thionyl chloride. After being swirled frequently at room temperature for one hour the mixture was kept at 40–50° for fifteen minutes. The solvent was removed under reduced pressure and 20 ml. of benzene was added and also removed in the same manner. To a chilled solution of the acid chloride in 20 ml. of acetone was added dropwise with swirling and cooling a solution of 1 g. of sodium azide in 4 ml. of water; the acid azide precipitated as a colorless liquid. After one-half hour in a refrigerator, addition of water and stirring induced crystallization of the azide (1.01 g.) which was collected and dried in a vacuum desiccator over calcium chloride in a cool place. When heated the azides (*cis* and *trans*) decomposed at about 80° with vigorous evolution of gas but did not explode when heated on a spatula.

A solution of the dried azide in 20 ml. of dry benzene was refluxed; the vigorous gas evolution, which was followed by bubbling through a mercury trap, ceased after about twenty minutes, but the heating was continued for a total of four hours. Ten ml. of concentrated hydrochloric acid was added to the solution of the isocyanate, and the mixture was heated on a steam cone with efficient swirling for thirty minutes; a voluminous colorless precipitate of the amino ester hydrochloride appeared. After removal of the solvents under reduced pressure, the residual amino ester hydrochloride was dried in a vacuum desiccator over calcium chloride; yield, 0.84 g. (*trans* form) (m. p. 235–240°) and 0.95 g. (*cis* form) (m. p. 195–197°). The compounds were recrystallized by adding ethyl acetate to a methanolic solution and concentrating on a steam cone until crystals appeared. After three recrystallizations the *cis* **1-aminomethyl-2-carbomethoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene hydrochloride** formed colorless threads; m. p. 212–213° dec. with gas evolution. The hydrochloride is soluble in warm water, very soluble in methanol, slightly soluble in acetone and insoluble in ethyl acetate. After two recrystallizations the *trans* isomer formed colorless threads: m. p. 241–242° dec.

Anal. Calcd. for $C_{18}H_{22}ClNO_2$: C, 67.59; H, 6.93; Cl, 11.08; N, 4.38. Found: (*cis* form) C, 67.50; H, 6.93; Cl, 11.07; N, 4.27; (*trans* form) C, 67.55; H, 6.94; Cl, 11.44; N, 4.27.

The picrates were prepared by a procedure which avoided the liberation of the unstable amino esters. To a warm solution of 80 mg. of the amino ester hydrochloride in 12 ml. of absolute ethanol was added 100 mg. of picric acid, and to the clear warm solution was added a solution

(6) Bachmann and Wilds, *ibid.*, **62**, 2084 (1940). The acid designated there as the α acid has been shown to have the configuration of desoxyisoequilenin and according to the evidence now accumulated is the *cis* acid; the β acid corresponds to desoxyequilenin. The evidence for these correlations will be published soon

of 10 mg. of sodium hydroxide in 2 ml. of ethanol. After a few minutes of boiling on a steam cone, the picrate began to crystallize. After one recrystallization from absolute ethanol the picrate (50 mg.) of the *cis* amino ester was obtained as canary yellow needles; m. p. 194–195°. The picrate (100 mg.) of the *trans* amino ester crystallized in glistening deep-yellow rhombic plates; m. p. 239–240°.

Anal. Calcd. for $C_{24}H_{24}N_4O_9$: C, 56.24; H, 4.72; N, 10.93. Found: (*cis* form) C, 56.43; H, 4.73; N, 10.78; (*trans* form) C, 56.25; H, 4.54; N, 10.88.

The free *trans* aminoester was obtained as a colorless liquid by addition of one equivalent of alkali to a solution of the hydrochloride.

Formation of the Lactams. (a) **16-Azadesoxyisoequilenin.**—To a solution of the isocyanate prepared by rearrangement of 0.67 g. of the azide of the *cis* acid ester in 20 ml. of benzene as described was added 15 ml. of 50% aqueous potassium hydroxide, and the mixture was heated on a steam-bath for a short time. The solid isolated from the benzene was refluxed with 25 ml. of water, 10 ml. of methanol and 8 ml. of 50% aqueous potassium hydroxide for two and one-half hours, the methanol was removed in a current of air and the suspension was acidified. After sublimation of the solid (0.44 g.) at 0.05 mm., the *dl*-16-azadesoxyisoequilenin (Ic) crystallized from methanol in colorless elongated prisms; m. p. 205–206°.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.2; H, 6.8; N, 5.6. Found: C, 81.1; H, 6.9; N, 5.4.

A quantitative yield of the same lactam (m. p. 205°) was obtained when a mixture of 100 mg. of the hydrochloride of the aminoester (Ib), 2 ml. of 10% aqueous sodium hydroxide and 20 ml. of methanol was refluxed for twenty-four hours. By reducing the time of refluxing to a few minutes the method is a convenient one for preparing the lactam.

When a mixture of 300 mg. of the aminoester hydrochloride, 5 ml. of methanol and 3 ml. of 45% aqueous potassium hydroxide was refluxed for two and one-half hours, 150 mg. of the lactam (m. p. 205–206°) was formed. The small amounts of amino acid obtained by cautious acidification of the alkaline solutions appeared to cyclize rapidly to the lactam for the isolated product melted at 193–200°.

The lactam (54 mg.) was recovered unchanged after boiling with a mixture of methanol (0.5 ml.), potassium hydroxide (0.42 g.) and water (0.3 ml.) for three hours. Even after boiling for forty hours with 50% aqueous methanolic potassium hydroxide 38% of the lactam was recovered.

(b) **16-Azadesoxyequilenin.**—A mixture of 200 mg. of crude aminoester hydrochloride (m. p. 235–240°) of the *trans* series (IIb), 3.3 ml. of methanol and 2 ml. of 45% aqueous potassium hydroxide was refluxed for five hours. After the removal of the methanol, the suspension was boiled with water and filtered, leaving 80 mg. of solid; m. p. 232–234°. After two recrystallizations from methanol the *dl*-16-azadesoxyequilenin (IIc) formed colorless rhombic plates; m. p. 234–236°. A mixture of the racemic diastereoisomeric lactams melted at 180–200°.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.2; H, 6.8; N, 5.6. Found: C, 81.2; H, 6.8; N, 5.3.

Acidification of the alkaline filtrate gave a precipitate of the amino acid which dissolved in excess acid. By careful acidification 100 mg. of the amino acid was obtained. After one recrystallization from methanol the amino acid possessed a decomposition point of about 270°. The picrate, which was prepared in boiling methanolic solution, was found to be more satisfactory for identification. After two recrystallizations from 95% ethanol the picrate of 1-aminomethyl-2-methyl-1,2,3,4-tetrahydrophenanthrene-2-carboxylic acid formed short yellow needles; m. p. 252–254°.

Anal. Calcd. for $C_{25}H_{22}N_4O_9$: C, 55.4; H, 4.4; N, 11.2. Found: C, 55.1; H, 4.3; N, 10.6.

When a solution of 140 mg. of the aminoester hydrochloride, 20 ml. of methanol and 2 ml. of 10% sodium hydroxide was refluxed for twenty-four hours, 60 mg. of the lactam and 20 mg. of the amino acid were obtained. Complete hydrolysis of the lactam (24 mg.) to the amino acid (81% of pure picrate) was effected by refluxing with 2 ml. of water, 2 ml. of methanol and 0.5 g. of potassium hydroxide for five hours.

Comparison of the Relative Rates of Formation of the Lactams.—A solution of 84 mg. of the aminoester hydrochloride (*cis* or *trans*) in 25 ml. of warm water was cooled to 30°, the solution was covered with 50 ml. of ether, and 3.6 ml. of 0.1 *N* sodium hydroxide was added dropwise in the course of ten minutes. The mixture was swirled in order that the precipitate which formed with each drop of alkali was immediately taken up by the ether. The ether layer was quickly separated and shaken with 5% hydrochloric acid in order to extract aminoester. Any lactam that was formed remained in the ether layer.

From the *cis* aminoester hydrochloride (m. p. 212–213°) 40 mg. (60%) of the lactam (m. p. 203–205°) was obtained. From the *trans* aminoester hydrochloride (m. p. 241–242°) no lactam was produced.

Epimerization of 16-Azadesoxyequilenin to 16-Azadesoxyisoequilenin.—Following the procedure of Bachmann and Dreiding,[5] a mixture of 25 mg. of *dl*-16-azadesoxyequilenin (m. p. 234–236°) and 25 mg. of 5% palladium on charcoal catalyst (Wilkens–Anderson Co.) was heated under nitrogen at 245–250° (bath temperature) for eight minutes. Evaporation of a filtered benzene extract of the product yielded 23 mg. of *dl*-16-azadesoxyisoequilenin; m. p. 199–203°; mixed m. p. 200–205°. After one recrystallization from methanol the lactam melted at 205–206°.

Summary

The *cis* and *trans* forms of *dl*-1-aminomethyl-2-carbomethoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene hydrochlorides were prepared in good yields by the Curtius reaction. From the aminoesters the lactams, *dl*-16-azadesoxyisoequilenin and *dl*-16-azadesoxyequilenin, were prepared by cyclization. The less rapid formation of 16-azadesoxyequilenin, its greater susceptibility to cleavage by aqueous alkali, and its conversion into the diasteromeric lactam by palladium at 250° are considered evidence of a *trans* ring in this lactain.

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