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

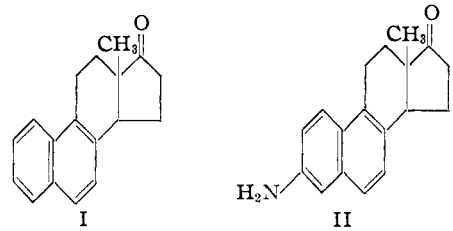
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

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.

was heated briefly at 250° with an equal weight of 5% palladium on charcoal according to the described method[5] epimerization at C_{14} occurred to yield the diastereoisomer *d*-desoxyisoequilenin (I). In view of the total synthesis of *d*-equilenin[6] the present work represents a total synthesis of *d*-desoxyequilenin and a new total synthesis of *d*-desoxyisoequilenin.[7]

Both Marker and Rohrmann and Prelog and Fuehrer correlated the configuration at the C/D ring juncture of their compounds with that of *d*-equilenin. Marker and Rohrmann did this by the catalytic hydrogenation in an acid medium of 11-ketodesoxyequilenin, the precursor of *d*-desoxyequilenin,[3] and Prelog and Fuehrer by the reduction of *d*-desoxyequilenin itself under the same conditions.[2] The product in both cases was *d*-1,2,-3,4-tetrahydro-α-dihydrodesoxyequilenin, which was identical with that obtained by the catalytic hydrogenation of *d*-equilenin in an acid solution.[8] Recent experiments (to be published soon) have shown that no epimerization at C_{14} occurs under the conditions of these hydrogenations.[9] Thus the view of Marker and Rohrmann and of Prelog and Fuehrer in regard to the configurations is correct. The present conversion of *d*-equilenin into *d*-desoxyequilenin is independent proof that the two compounds have the same configuration at C_{13} as at C_{14}. On the basis of the isomerization experiments with equilenin,[5] the configuration at the C/D ring juncture of *d*-desoxyequilenin is *trans*, which is confirmed by the present isomerization of *d*-desoxyequilenin to its C_{14} epimer *d*-desoxyisoequilenin.

We are grateful to Parke, Davis and Company for a generous gift of *d*-equilenin.

Experimental[10]

The Bucherer Reaction on *d*-Equilenin.—To an aqueous solution of ammonium bisulfite, prepared by passing 2.5 g. of sulfur dioxide into 10 cc. of cold concentrated aqueous ammonia (specific gravity 0.9), was added 0.9 g. of *d*-equilenin and the resulting suspension was enclosed in a sealed combustion tube of approximately 25 cc. volume. The tube was shaken and heated at 170 ± 20° for twelve hours in an Aminco shaker. The amine (II) had agglomerated in a black tarry lump which, when filtered off and heated with concentrated hydrochloric acid, disintegrated into a grey insoluble powder of the hydrochloride. The latter was collected on a filter, washed with concentrated hydrochloric acid (it is slightly soluble in dilute hydrochloric acid), and converted back to the amine (II) by heating it with 15 cc. of 5% aqueous sodium hydroxide on a steam-bath for fifteen minutes. The insoluble amorphous powder of amine (II), which now should be free of unreacted *d*-equilenin, was filtered off, washed with water, and dried *in vacuo* over potassium hydroxide; yield, 0.8 g.; m. p. 195–200° dec. After sublimation at 160–180° and 0.02 mm., the colorless elongated prisms of ***d*-3-aminodesoxyequilenin (II)** melted at 219–220° dec., when placed into the melting point bath at room temperature; yield, 0.64 g. (71%). The melting point remained unchanged after recrystallization from benzene or methanol. It rose, however, to 226–227° when the melting point tube was evacuated and placed into the bath at 210°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.88; H, 7.31; N, 5.04.

The **N-acetyl derivative** of II, prepared by treating a stirred suspension of 15 mg. of II in 1 cc. of water with 10 drops of acetic anhydride at room temperature for ten minutes, crystallized from methanol with a mole of the solvent in flat colorless prisms; yield, 13 mg.; m. p. 250–252° (vac.) when placed in the bath at room temperature and 264.5–265.5° (vac.) when placed in the bath at 200°. The same acetyl compound was obtained by heating a sample of II in acetic anhydride and benzene.

Anal. Calcd. for $C_{20}H_{21}NO_2 \cdot CH_4O$: C, 74.31; H, 7.43; N, 4.13. Found: C, 74.12; H, 7.26; N, 4.09.

Conversion of *d*-3-Aminodesoxyequilenin (II) into *d*-Equilenin.—Excess sodium nitrite was added to a hot solution of 20 mg. of II in 3 cc. of 50% sulfuric acid. The solution immediately became yellow-red, nitrogen was evolved, and *d*-equilenin precipitated as a dark solid. After sublimation at 180–200° and 0.01 mm. the product (14 mg.) melted at 254–256° (vac.) alone and when mixed with an authentic sample [m. p. 258–259° (vac.)]. Its methyl ether, prepared with dimethyl sulfate, after sublimation at 120–140° and 0.02 mm., melted at 186–192° alone and when mixed with an authentic sample (m. p. 196–197°).

***d*-Desoxyequilenin (I).**—To a suspension of 169 mg. of *d*-3-aminodesoxyequilenin (II) as the hydrochloride in 7 cc. of 15% hydrochloric acid, cooled to −12° in a salt–ice bath, was added a cold solution of 100 mg. of sodium nitrite in 3 cc. of water in small portions with stirring over a period of forty-five minutes. To the clear light yellow solution of the diazonium chloride at −12° was added 5 cc. of 50% hypophosphorous acid. After standing at 2° for twenty hours, the mixture, which contained a dark precipitate, was heated on a steam-bath for five minutes and extracted with benzene. The organic layer was washed with 1% aqueous sodium hydroxide and water to remove any *d*-equilenin. After drying, the benzene solution was concentrated, leaving 130 mg. of dark brown residue, which was dissolved in 5 cc. of benzene, adsorbed on a column of 5 g. of activated alumina (Merck, according to Brockmann), and eluted with 25 cc. of benzene. On evaporation, 120 mg. (76%) of *d*-desoxyequilenin (I) was obtained as a colorless crystalline residue, m. p. 151–155°. It crystallized from methanol containing a few drops of acetone in colorless plates, m. p. 156–157°, which sublimed at 115–120° and 0.01 mm. as colorless glistening needles, m. p. 156–158°; after recrystallization from petroleum ether (b. p. 60–75°) it melted at 160–161° (reported, 156–158°,[3] 155–157°).[2] Optical rotation: $[\alpha]^{27}D$ + 115° (*c* = 0.325, in chloroform) (reported, $[\alpha]^{22}D$ + 117 ± 3°).[2]

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 85.81; H, 7.50.

The **2,4-dinitrophenylhydrazone** crystallized from **ethyl acetate–ethanol in orange prisms; m. p. 250–252° dec.**

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

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

(7) Another synthesis of *d*-desoxyisoequilenin from *d*-equilenin has been described recently.[5] *dl*-Desoxyequilenin (previously called β-17-equilenone) and *dl*-desoxyisoequilenin (α-17-equilenone) were synthesized by Bachmann and Wilds, THIS JOURNAL, **62**, 2084 (1940). The total synthesis of *d*- and *l*-desoxyisoequilenin will be described in a forthcoming paper.

(8) Marker, Kamm, Oakwood and Tendick, THIS JOURNAL, **59**, 768 (1937); Ruzicka, Mueller and Moergeli, *Helv. Chim. Acta*, **21**, 1394 (1938). The product of the reduction was called 5,7,9-estratriene-17-ol by these authors.

(9) If such an epimerization could have occurred it would have been impossible to decide on the basis of the results of the hydrogenation whether or not the desoxy compound and *d*-equilenin have the same configuration at the C/D ring juncture. The possibility of such an epimerization could not be excluded with certainty in view of the epimerizations at C_{14} which some steroids of the *trans* series suffered when heated briefly at 250° with palladium.

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

Anal. Calcd. for $C_{24}H_{22}N_4O_4$: C, 66.96; H, 5.15; N, 13.02. Found: C, 66.65; H, 5.02; N, 13.30.

The **oxime** crystallized from petroleum ether (b. p. 60–75°) in fine colorless needles; m. p. 179.5–180.5°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.27; H, 7.50; N, 5.80.

The *sym.* **trinitrobenzene complex** crystallized from ethanol in orange yellow needles; m. p. 155–156°.

Anal. Calcd. for $C_{24}H_{21}N_3O_7$: C, 62.20; H, 4.57. Found: C, 61.86; H, 4.37.

Epimerization of *d*-Desoxyequilenin (I).—A mixture of 8 mg. of *d*-desoxyequilenin (I) and 8 mg. of 5% palladium on charcoal was heated at 250° under an atmosphere of nitrogen for eight minutes. The product was separated from the catalyst by filtration of a benzene solution. After evaporation and crystallization from petroleum ether (b. p. 60–75°), *d*-desoxyisoequilenin (I) was obtained in colorless prisms; m. p. 106–107° alone and when mixed with a sample obtained by another synthesis (m. p. 107.5–108.5°).[5]

Summary

The application of the Bucherer reaction to *d*-equilenin yielded *d*-3-aminodesoxyequilenin, which represents a new type of steroid amine. Diazotization of the amino group and hydrolysis regenerated *d*-equilenin, while reduction of the diazonium chloride with hypophosphorous acid afforded *d*-desoxyequilenin, which has recently been isolated from the urine of pregnant mares. *d*-Desoxyequilenin was converted into *d*-desoxyisoequilenin by epimerization with palladium.

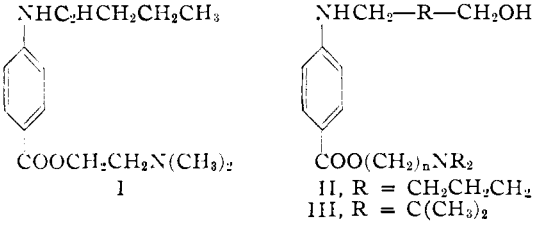
ANN ARBOR, MICHIGAN RECEIVED JULY 14, 1949

[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

Dialkylaminoalkyl 4-Alkylaminobenzoates

BY R. O. CLINTON, U. J. SALVADOR, S. C. LASKOWSKI AND J. S. BUCK

In spite of the high local anesthetic activity observed with tetracaine[1] (I), very few basic esters of this type have been investigated. Rab-



I

II, R = $CH_2CH_2CH_2$

III, R = $C(CH_3)_2$

inovich, Konavalova and Uretskaya[2] prepared the tropine, pseudotropine and N-β-hydroxyethylnortropidine esters of 4-butylaminobenzoic acid, and Mndzhoyan[3] has similarly recorded the synthesis of several 1,3-bisdialkylamino-2-propyl 4-butylaminobenzoates. Homologous series (*e. g.*, 2 - diethylaminoethyl 4 - propylaminobenzoate) have also been investigated by Eisleb[4] and by Reasenberg and Goldberg.[5] However, in the latter types the local anesthetic activity is less than that of the corresponding 4-butylaminobenzoates.[1a] In the 4-butylaminobenzoate series, the only simple basic esters reported are tetracaine[1] and the corresponding 2-diethylaminoethyl analog.[6]

In the present work we have prepared a number of dialkylaminoalkyl 4-butylaminobenzoates for the purpose of determining the effect of ester side-chain variance upon activity and toxicity. The investigation was extended to include several dialkylaminoalkyl 4-(5-hydroxyamylamino)-benzoates, (II), and a dialkylaminoalkyl 4-(2,2-dimethyl-3-hydroxypropylamino)-benzoate, (III), in order to evaluate the effect of a hydroxyl group in the 4-alkylamino chain upon the therapeutic index. These types of tetracaine analog have not been previously prepared.

The dialkylaminoalkyl 4-nitrobenzoates were prepared in the conventional manner from 4-nitrobenzoyl chloride and an ω-dialkylaminoalkanol. The 4-nitrobenzoates were readily reduced by any of the standard methods to the 4-aminobenzoates. The 4-alkylaminobenzoates were prepared from the parent 4-aminobenzoates by reductive alkylation with an aldehyde (or ω-hydroxyaldehyde) in the presence of zinc dust and acetic acid.[7] Contrary to the observations of Shapiro,[1b] in our hands this method gave better yields than the alternative routes from 4-butylaminobenzoyl chloride hydrochloride[2,3,8] or alkylation with an alkyl halide and an alkali carbonate.[1b,4] The new compounds in the above series are listed in Table I.

Preliminary testing[9] of the dialkylaminoalkyl 4-butylaminobenzoates indicated for certain members of the series a higher local anesthetic activity than that of tetracaine, both topically and by infiltration. However, in general, this greater activity was accompanied by a proportionate increase in toxicity. Apparently no member of the series possessed a therapeutic index greatly exceeding that of tetracaine.

The inclusion of a hydroxyl group in the 4-

(1) (a) Eisleb, German Patent 582,715, U. S. Patent 1,889,645; (b) Shapiro, *J. Soc. Chem. Ind.*, **64**, 177 (1945).

(2) Rabinovich, Konavalova and Uretskaya, *J. Gen. Chem. (U. S. S. R.)*, **9**, 41 (1939) [*Chem. Abstr.*, **33**, 6323 (1939)].

(3) Mndzhoyan, *ibid.*, **16**, 1033 (1946) (*Chem. Abstr.*, **41**, 2737 [1947]).

(4) Eisleb, German Patents 431,166 and 437,976 (*Frdl.*, **15**, 1440, 1442 (1925–1927)), U. S. Patent 1,550,350.

(5) Reasenberg and Goldberg, THIS JOURNAL, **67**, 933 (1945).

(6) Skita and Stühmer, German Patent 716,668 (*Chem. Abstr.*, **38**, 2345 (1944)).

(7) (a) German Patent 491,856 (*Frdl.*, **16**, 356 (1927)); (b) Clinton, Salvador, Laskowski and Suter, THIS JOURNAL, **70**, 950 (1948).

(8) Graf and Langer, *J. prakt. Chem.*, **148**, 161 (1937).

(9) Complete results will be published at a later date by Dr. F. P. Luduena of these laboratories.