Anal. Calcd. for $C_{28}H_{33}O_8N$: C, 65.55; H, 6.5. Found: C, 65.88; H, 6.27.

α-Bromocamphor-π-sulfonate.—The above bidibenzoyl-L-tartrate (230 mg.) was converted into the free base in the usual way. When a concentrated solution of free α-bromocamphor-π-sulfonic acid was added to the solution of the base in 10 cc. of absolute ether, the salt deposited. Recrystallized from ethyl acetate, it formed glistening prisms, m. p. 170–172°, $[\alpha]_D$ +71.4° (in methanol).

Anal. Calcd. for $C_{20}H_{35}O_4NBrS$: C, 51.6; H, 7.58. Found: C, 51.91; H, 7.35.

***d,l*-N-Methyl-*trans*-decahydroisoquinoline Bidibenzoyl-L-tartrate.**—When 150 mg. of pure racemic N-methyl-*trans*-decahydroisoquinoline in the minimum amount of methanol was added to 300 mg. of dibenzoyl-L-tartaric acid in 3 cc. of hot methanol, the solution solidified to a crystalline mush. The crystals were collected and washed with methanol–ether (1:3); m. p. 154–155° (dec.). The mixed melting point with the salt of the resolved *d*-base was 155°, $[\alpha]_D$ 84.9° (in methanol, *c*, 1.56). This salt is distinctly more soluble in methanol than that of the resolved base. After three recrystallizations from methanol the m. p. rose to 158°, $[\alpha]_D$ +86.2° (in methanol, *c*, 1.67). The hydrochloride from this recrystallized material melted at 224–226° and showed no, or possibly a minute positive, rotation. This result shows that dibenzoyl-L-tartaric acid in this special case is only suitable for characterization but not for the preparation of the optically active base.[38]

(36) The formation of partial racemates is a well-known phenomenon which in some cases has made it impossible to achieve satisfactory resolution, *cf.* Prelog, *Ann.*, **545**, 253 (1940). Our experiments do not exclude partial racemization of the natural base and an exactly compensating partial resolution of the synthetic base. However, such circumstance would not invalidate the stereochemical evidence bearing on the configuration of yohimbine.

***d,l*-N-Methyl-*trans*-decahydroisoquinoline Picrolonate.**—The water insoluble salt was recrystallized from methanol from which it appeared in the form of stout hard prisms, m. p. 216–219° (red melt, sintering at 198°).

***d,l*-N-Methyl-*cis*-decahydroisoquinoline Hydrochloride.**—The pure picrate (m. p. 210°, ref. 3) was decomposed with hydrochloric acid and ether. The colorless aqueous solution, on evaporation, left the crystalline hydrochloride which, after microsublimation from slide to slide (at 140°), melted at 164–165°.

Summary

The distillation of yohimbic acid with thallous oxide yielded a base, $C_{19}H_{24}N_2$, to which the structure of a tetracyclic base, *chano*desoxyyohimbol, was assigned. Hydrogenation of this base gave *chano*dihydrodesoxyyohimbol, isomeric but not identical with the alkaloid quebrachamine. The Hofmann degradation of *chano*dihydrodesoxyyohimbol lead to an optically active N-methyl-*trans*-decahydroisoquinoline which was found to be identical with the synthetic resolved base and its derivatives.

These results lead to the conclusion that in yohimbine itself rings D and E are *trans*-locked.

CONVERSE MEMORIAL LABORATORY
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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

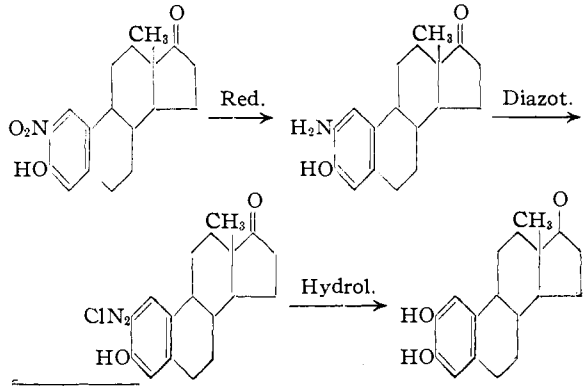
Estracatechol[1,2]

BY JOSEPH B. NIEDERL AND H. J. VOGEL

Three estrone derivatives substituted in the aromatic ring "A" have been reported to date: a monobromo compound,[3] a sulfonic acid[4] and a carboxylated estrone.[5]

In this paper the preparation of a new estrone derivative formed by the introduction of a phenolic hydroxyl group has been described. The transformation *in vivo* of estrone into a compound which is hydroxylated in the aromatic ring has been suggested in connection with investigations on the fate of estrone in the organism.[6,7] Since phenolic oxidases may change phenols to catechols and since the action of such enzymes on estrone leads to loss of estrogenic activity, it is believed that the inactivated product may be an ortho-dihydric phenol. This view has now been strengthened, because the present investigation has revealed that a catechol analog of estrone actually lacks estrogenic potency. Other points of interest relating to possible estrogen catabolites have been discussed by O. W. Smith[8] who postulated that these substances may have a physiological action of their own.

The semi-micro synthesis of the new hydroxyestrone, 2,3-estracatechol, has been accomplished through a series of reactions



(1) Presented before the Division of Organic Chemistry at the New York Meeting of the American Chemical Society, September, 1947, and before the Division of Biochemistry at the Meeting-in-Miniature of the Philadelphia Section of the American Chemical Society, January, 1949.

(2) From the Ph.D. thesis submitted by H. J. Vogel to the faculty of the Graduate School of Arts and Sciences of New York University.

(3) G. F. Marrian and G. A. D. Haslewood, *J. Soc. Chem. Ind.*, **51**, 277 (1932).

(4) A. Butenandt and H. Hofstetter, *Z. physiol. Chem.*, **259**, 222 (1939).

(5) J. B. Niederl, U. S. Patent 2,322,311 (1944).

(6) W. W. Westerfeld, *Biochem. J.*, **34**, 51 (1940).

(7) M. Graubard and G. Pincus, *Endocrinology*, **30**, 265 (1942).

(8) O. W. Smith, *Endocrinology*, **35**, 146 (1944).

Nitroestrone was selected as the starting material, since a previous attempt to obtain an aminoestrone by reduction of an azodye[9] had not been fruitful. It was found that the desired mononitroestrone can be readily prepared as a yellow, crystalline substance by treatment of estrone in glacial acetic acid with one equivalent of concentrated nitric acid. This nitro compound is formulated as 2-nitroestrone in analogy with the closely related case of ar-tetrahydro-2-naphthol which yields a uniform mononitration product[10] whose orientation has been established on the basis of the work of Schroeter.[11]

2-Nitroestrone and its methyl ether are reducible to the corresponding amines. Both amines form relatively stable, water-soluble diazonium salts. Estrone-2-diazonium chloride, being an orthohydroxydiazonium compound, requires an excess of free alkali for coupling, while its methyl ether readily couples with R-salt in the presence of sodium carbonate. Both diazonium chlorides evolve nitrogen slowly and incompletely on heating their aqueous solutions. As in similar cases,[12] the addition of cupric sulfate facilitates the formation of the respective hydroxy compounds. 2,3-Estracatechol and its 3-methyl ether yield semicarbazones, indicating that the keto group at C_{17} is intact.

Experimental

2-Nitroestrone.—One gram of estrone is dissolved in 25 cc. of hot glacial acetic acid. After cooling to about 35° and before crystallization sets in, 0.25 cc. of nitric acid (sp. gr. 1.42) is added dropwise from a calibrated semi-micro pipet with stirring. The resulting orange red solution is allowed to stand at room temperature (22°) for twenty-four hours. At this stage a portion of the product may crystallize. The reaction mixture is poured with stirring into 250 cc. of water and the yellow precipitate obtained is filtered, washed with water and dried *in vacuo;* yield 1.05 g. (90%). After recrystallization from glacial acetic acid, the product melts at 258°.

Anal. Calcd. for $C_{18}H_{21}O_4N$: C, 68.6; H, 6.7; N, 4.4; mol. wt., 315. Found: C, 68.6; H, 6.7; N, 4.4; mol. wt., 303.

2-Nitroestrone Methyl Ether.—Treatment of 1 g. of 2-nitroestrone with 0.15 g. of sodium in 20 cc. of ethanol and 6 cc. of methyl iodide yields 1 g. of the methyl ether; m. p. 150°.

Anal. Calcd. for $C_{19}H_{23}O_4N$: N, 4.3. Found: N, 4.3.

2-Nitroestrone *p*-Nitrobenzyl Ether.—One hundred mg. of 2-nitroestrone and 69 mg. of *p*-nitrobenzyl bromide are refluxed in alcoholic sodium hydroxide to yield 80 mg. of the *p*-nitrobenzyl ether; m. p. 180° (dec.).

Anal. Calcd. for $C_{25}H_{26}O_6N_2$: N, 6.2. Found: N, 5.9.

2-Nitroestrone Semicarbazone.—Fifty mg. of 2-nitroestrone, 200 mg. of semicarbazide hydrochloride, 200 mg. of anhydrous sodium acetate and 2 cc. of 95% ethanol are refluxed yielding 30 mg. of the semicarbazone; m. p. above 250° (dec.).

Anal. Calcd. for $C_{19}H_{24}O_4N_4$: N, 15.0. Found: N, 14.5.

Solution of Estrone-2-diazonium Chloride (or its Methyl Ether).—A mixture of 200 mg. of 2-nitroestrone (or its methyl ether), 3.6 cc. of glacial acetic acid and 0.4 cc. of concentrated hydrochloric acid is heated to the boiling point. Four hundred mg. of zinc dust is added in portions to the boiling solution and refluxing is continued for a total of twenty minutes. After cooling to 25°, the supernatant solution is decanted from excess zinc into 16 cc. of water and 0.2 cc. of concentrated hydrochloric acid. The mixture containing 2-aminoestrone hydrochloride (or its methyl ether) is chilled in ice and 50 mg. of sodium nitrite in 1 cc. of water are added. The reaction mixture is kept in ice for ten minutes and 0.2 cc. of 40% aqueous urea solution is introduced. After filtration, a clear solution of estrone-2-diazonium chloride (or its methyl ether) is obtained.

Estrone-(2-azo-1′)-2′-naphthol.—A cold solution of estrone-2-diazonium chloride prepared as described from 100 mg. of 2-nitroestrone is poured into an ice-cold solution of 50 mg. of 2-naphthol in 3 cc. of water and 7 cc. of 25% aqueous sodium hydroxide. A deep purple precipitate in an amber alkaline mother liquor is obtained. The product is filtered, washed with water and dried *in vacuo;* yield 50 mg.

Anal. Calcd. for $C_{28}H_{28}O_3N_2$: N, 6.4. Found: N, 6.4.

Estrone Methyl Ether-(2-azo-1′)-2′-naphthol.—Estrone methyl ether-2-diazonium chloride from 100 mg. of 2-nitroestrone methyl ether is coupled with 2-naphthol as above. The resulting wine-red precipitate is very finely divided. On addition of 4 *N* hydrochloric acid to *p*H 6 the dye flocculates. The product is filtered, washed with water, dilute hydrochloric acid and again with much water. It is dried *in vacuo;* yield 65 mg.

Anal. Calcd. for $C_{29}H_{30}O_3N_2$: N, 6.2. Found: N, 6.2.

Estrone Methyl Ether-(2-azo-4′)-estrone.—A cold solution of estrone methyl ether-2-diazonium chloride, prepared as described from 100 mg. of 2-nitroestrone methyl ether, is poured with stirring into an ice-cold solution of 100 mg. of estrone in aqueous alcoholic alkali, the latter solution being prepared by adding to the estrone, in the order given, 2 cc. of ethanol, 2 cc. of 25% aqueous sodium hydroxide, 5 cc. of 25% aqueous sodium hydroxide and 1 cc. of water. A deep brownish purple precipitate appears in an orange alkaline mother liquor. The product is filtered on sintered glass, washed with 1 *N* sodium hydroxide in 10% aqueous ethanol, 20% aqueous ethanol containing a trace of alkali and finally with 25% aqueous ethanol. After drying *in vacuo*, the product is extracted with 3 cc. of 1.5 *N* sodium hydroxide in 20% aqueous ethanol. The material is filtered on glass, washed with 20% ethanol and dried *in vacuo;* yield, 30 mg.

Anal. Calcd. for $C_{37}H_{44}O_4N_2$: N, 4.8. Found: N, 5.1.

2,3-Estracatechol.—A solution of estrone-2-diazonium chloride is prepared as described from 800 mg. of 2-nitroestrone. A hot solution of 8 g. of cupric sulfate pentahydrate in 16 cc. of water is added and the mixture is heated in a boiling water-bath for fifteen minutes. After cooling, the reaction mixture is kept at 5° for twenty-four hours. The resulting dark reddish brown product is filtered, washed with water and dried *in vacuo*. The crude material weighing 400 mg., 7.2 cc. of glacial acetic acid and 0.8 cc. of concentrated hydrochloric acid are heated to the boiling point. Eight hundred mg. of zinc dust is added in portions to the boiling solution and refluxing is continued for a total of thirty minutes. After cooling, the supernatant solution is decanted into 40 cc. of water. The precipitate obtained is filtered, washed with 20% aqueous acetic acid and water and dried *in vacuo;* yield 245 mg. (34% on the basis of 2-nitroestrone used); m. p. 200° (dec.). The product may be recrystallized from ethanol as microscopic rods.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.5; H, 7.7. Found: C, 75.2; H, 7.7.

2,3-Estracatechol Diacetate.—Forty mg. of 2,3-estracatechol and 1 cc. of acetic anhydride are refluxed for one hour. After cooling, 5 cc. of water is added and the excess acetic anhydride is allowed to hydrolyze. The resulting precipitate is filtered, washed with water and dried *in*

(9) L. F. King and W. R. Franks, THIS JOURNAL, **63**, 2045 (1941).

(10) H. Thoms and W. Kross, *Arch. Pharm.*, **265**, 336 (1927).

(11) G. Schroeter, *Ann.*, **426**, 83 (1922). Coupling, however, leads to substitution in the 1-position of ar-tetrahydro-2-naphthol.

(12) W. H. Mills and I. G. Nixon, *J. Chem. Soc.*, 2510 (1930).

vacuo; yield 30 mg.; m. p. 155° (dec.). The product may be recrystallized from ethanol.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.4; H, 7.0. Found: C, 71.6; H, 6.7.

2,3-Estracatechol Semicarbazone.—Forty mg. of 2,3-estracatechol, 200 mg. of semicarbazide hydrochloride, 200 mg. of anhydrous sodium acetate and 2 cc. of 95% ethanol are refluxed with stirring for five minutes. After cooling, 3 cc. of water is added dropwise. The resulting precipitate is filtered, washed with water and dried *in vacuo;* yield 25 mg.; m. p. above 250° (dec.). The product may be recrystallized from ethanol.

Anal. Calcd. for $C_{19}H_{25}O_3N_3$: N, 12.2. Found: N, 11.9.

2,3-Estracatechol 3-Methyl Ether.—A solution of estrone methyl ether-2-diazonium chloride is prepared as described from 200 mg. of 2-nitroestrone methyl ether. Twenty-five cc. of water is added and the mixture is extracted with five 40-cc. portions of ethyl acetate. The aqueous phase is separated and mixed with a solution of 1 g. of cupric sulfate pentahydrate in 4 cc. of hot water. The reaction mixture is heated in a boiling water-bath for fifteen minutes, cooled and kept at 5° for twenty-four hours. The crude product, after filtering, washing with water and drying, weighs 50 mg. and is treated with zinc and acid as described under 2,3-estracatechol; yield 25 mg.; m. p. 105° (dec.).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 76.0; H, 8.0. Found: C, 75.9; H, 7.9.

2,3-Estracatechol 3-Methyl Ether Semicarbazone.—Thirty mg. of 2,3-estracatechol 3-methyl ether is treated as described under 2,3-estracatechol semicarbazone; yield 26 mg.; m. p. 249°.

Anal. Calcd. for $C_{20}H_{27}O_3N_3$: N, 11.8. Found: N, 11.6.

Physiological Tests.—The results of estrogenic assays are summarized in Table I.

TABLE I

ESTROGENIC ACTIVITY IN RATS

Compound	No. of rats	Dose,[a] gammas	Response, %
Estrone, U. S. P. (control)	10	0.65	50
2-Nitroestrone	6	2	33
2,3-Estracatechol	10	20	0
2,3-Estracatechol 3-methyl ether	10	13	0

[a] Injected subcutaneously in sesame oil.

Summary

1. The semi-micro synthesis of crystalline 2,3-estracatechol (2-hydroxyestrone) *via* the corresponding nitro, amino and diazonium compounds has been reported. The final product and its intermediates have been characterized by the preparation of derivatives.

2. The results of estrogenic assays have been presented. The lack of estrogenic activity of 2,3-estracatechol and its 3-methyl ether is in harmony with the view that hydroxylation may be involved in the *in vivo* degradation of estrone.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, EMORY UNIVERSITY]

Synthesis of Terpinyl Ethers from *d*-Limonene

BY E. EARL ROYALS

The reaction of methanol with trimethylethylene in the presence of sulfuric acid to form methyl *t*-amyl ether was observed by Reychler[1] in 1907. Evans and Edlund more recently[2] made an extensive study of the reaction of olefins with alcohols in the presence of acid catalysts. These workers found that trisubstituted and unsymmetrically disubstituted olefins react readily with primary alcohols to yield tertiary alkyl ethers. Other types of olefins and secondary alcohols are less suitable reactants. The equilibrium nature of the reaction was demonstrated. Several applications of this etherification reaction have been made in the terpene field. Semmler produced[3] ethyl ethers from camphene, nopinene and sabinene, but was unable to obtain an ether from limonene. Other early workers reported only resinification on treatment of limonene with alcoholic sulfuric acid.[4] More recently, Treibs[5] studied the sulfuric acid catalyzed reaction of methyl alcohol with several cyclohexene derivatives. His conclusions regarding the influence of olefin structure on the etherification reaction were similar to those of Evans and Edlund.[2] He was not, however, able to obtain an ether from limonene (carven); this diolefin, according to Treibs, gave a diether in small yield, the principal reaction being dimerization. Despite these negative reports as to the ability of limonene to react additively with alcohols, several recent patents[6] describe the formation of terpene ethers by reaction of various terpenes, including dipentene, with alcohols in the presence of acid catalysts. Most of the examples in these patents, however, describe the use of α-pinene as terpene reactant.

We have found that *d*-limonene reacts readily with anhydrous primary alcohols to yield terpene ethers. It is believed on the basis of evidence presented below that these ethers are principally α-terpinyl alkyl ethers, although isomeric terpene ethers may be present. In Table I are presented data on the synthesis and properties of various terpinyl alkyl ethers derived from *d*-limonene by a standard procedure, namely,

(1) Reychler, *Bull. soc. chim. Belg.*, **21**, 71 (1907).

(2) Evans and Edlund, *Ind. Eng. Chem.*, **28**, 1186 (1936).

(3) Semmler, *Ber.*, **33**, 3420 (1900).

(4) Clover, *Chem. Zentr.*, **78**, I, 1793 (1907); Wall, *Ann.*, **239**, 15 (1887).

(5) Treibs, *Ber.*, **70**, 593 (1937).

(6) See, for example: U. S. Patents 900,136, 2,220,462, 2,309,017, 2,321,978, 2,347,337, 2,388,765; British Patents 494,504, 556,579; French Patent 818,787; German Patents 711,915, 711,916.