small volume and diluted with cyclohexane. The azulene was liberated by chromatographic adsorption on alumina and eluted with cyclohexane. The trotylate, prepared from the eluate, was recrystallized twice from ethanol. The violet-black needles melted at 58–59°. The azulene was again liberated by chromatographic adsorption; the picrate, black needles, melted at 96–98°. The amount of this derivative was not sufficient to permit recrystallization.

The ultraviolet spectrum of 5.6 mg. of the azulene in 5 ml. of *n*-pentane, after regeneration from the picrate and its mother liquors, is reproduced in Fig. 1. The extinction coefficients were larger and the bands somewhat sharper than in the spectrum taken before conversion to the trinitrobenzolate, thus indicating slightly greater purity. The only significant difference was the appearance of a new band at 740 mμ which had not been observed previously. Other faint bands in the visible spectrum (not shown) occurred at 700–710, 665–670, 605–615 and 560 mμ. Maxima and extinction coefficients in the ultraviolet range are tabulated.

mμ	log ε	mμ	log ε
245	4.44	338	3.57
285	4.67	342	3.61
289	4.64	351	3.68
306	4.04	369	3.43

The non-azulenic portion of fraction A weighed 0.64 g. and gave a deep-blue color on treatment with a dilute solution of bromine in chloroform.[6] Distillation at 70–80° (0.5 mm.) gave a colorless liquid which had the analysis of a sesquiterpene. It did not yield a picrate or trinitrobenzolate.

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 87.99; H, 12.00.

The non-azulenic portion of fraction B weighed 1.27 g. and gave a deep purple color on treatment with a dilute solution of bromine in chloroform. Vacuum distillation did not yield fractions boiling within a small temperature range.

Summary

The catalytic reduction of helenalin has been studied. Two new products, dihydrohelenalin and hexahydrohelenalin, have been obtained in addition to the previously known tetrahydrohelenalin. Dihydrohelenalin retains the α,β-unsaturated ketone system of helenalin. Hexahydrohelenalin is completely saturated and contains a hydroxyl in place of the ketone group. The reactions of these compounds have been studied.

The hydroxyl group of helenalin has been shown to be secondary.

Dehydrogenation of hexahydrohelenalin with palladized charcoal yields a blue azulene of formula $C_{15}H_{18}$. Spectroscopic evidence suggests the presence of alkyl substituents in at least positions 1 and 4 of the azulene nucleus. The bearing of these results on the structure of helenalin is discussed.

URBANA, ILLINOIS RECEIVED FEBRUARY 11, 1949

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

On the Stereochemistry of Yohimbine[1]

BY BERNHARD WITKOP

In the present paper, a method is shown by which yohimbine (I) can be degraded to an optically active N-methyl-*trans*-decahydroisoquinoline. The identification of this base with synthetic resolved material subsequently establishes the stereochemical relationship of carbon atoms 15 and 20 in yohimbine.

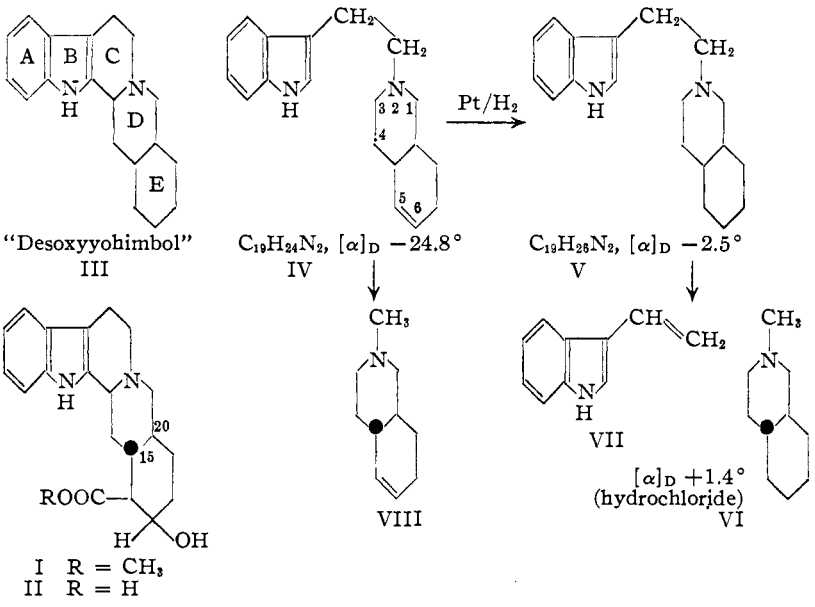
By treatment of yohimbic acid (II) with thallous oxide, a base, $C_{19}H_{24}N_2$, has been obtained,[2] for which the name desoxyyohimbol and the tentative structure (III) was proposed. It has now been found that this compound gives strong positive Hopkins–Cole and Ehrlich reactions, as well as chromoisomeric picrates (yellow → red). Thus ring C has been opened between carbon atoms 2 and 3. Since "desoxyyohimbol" is accordingly tetracyclic, one double bond must be present. And, in fact, "desoxyyohimbol" is readily hydrogenated to a dihydro derivative, $C_{19}H_{26}N_2$ (V). It is likely that this double bond arises directly from the dehydration of the secondary alcohol function of yohimbine (*cf.* apoyohimbine), and the double bond may be placed provisionally in the 5,6-positions of the hydrogenated isoquinoline nucleus (IV). The inappropriate name "desoxyyohimbol" should be corrected to *chano*desoxyyohimbol.

Confirmation of the formulas (IV) and (V) is obtained through the Hofmann degradation which, in case of the latter, leads to an N-methyldecahydroisoquinoline (yield 79%) isolated as the picrate, m. p. 234–237°. On admixture with synthetic N-methyl-*trans*-decahydroisoquinoline picrate (m. p. 234–237°), obtained from the mixture of *cis*- and *trans*-decahydroisoquinolines by selective dehydrogenation with palladium,[3] no depression was observed. Although these observations offer strong evidence for the *trans* configuration of I, the proof is only conclusive if VI is optically active showing that the configuration of 15,20-atoms was not altered during the degradative process. This was indeed found to be the case. The hydrochloride of VI in alcoholic solution exhibited a small but distinct dextrorotation (1.4°), proving that none of the three degradative operations, *viz.*, distillation with thallous oxide

(1) Presented in part before the Division of Organic Chemistry of the American Chemical Society at the Chicago meeting, April, 1948.

(2) Witkop, *Ann.*, **554**, 83 (1943).

(3) Witkop, THIS JOURNAL, **70**, 2617 (1948).



(or thallous carbonate),[4] hydrogenation with platinum in glacial acetic acid,[5] and finally preparation of the quaternary base[6] and Hofmann elimination, caused inversion.

Using Raney nickel instead of the platinum catalyst employed previously[3] N-acetyltetrahydroisoquinoline[7] was readily reduced to decahydroisoquinoline and N-ethyldecahydroisoquinoline in ratios dependent on the nature of the solvent (Table I). A better result was obtained with isoquinoline itself which, in analogy to quinoline,[8] was reduced in almost quantitative yield to a mixture of the decahydro bases containing at least 80% of the *trans* isomer.

The kindred *trans*-decahydroquinoline[9] (m. p. 48°) has been resolved previously, partially by Veneziani,[10] and completely by Mascarelli,[11] with bromocamphorsulfonic acid. In the present investigation, D-tartaric acid was used to resolve *rac*-N-methyl-*trans*-decahydroisoquinoline. The hydrochloride of the resolved base had the same physical properties and small dextrorotation[12] as the hydrochloride of VI (Tables II and III).

TABLE I

HYDROGENATION OF N-ACETYLTETRAHYDROISOQUINOLINE AND ISOQUINOLINE (3000 LB./SQ. IN.)

	Mole	°C.	*t*, hr.	Ni, g.	Solvent	Percentage of products
N-Acetyltetrahydroisoquinoline	0.007	164	17	1	Ethyl alcohol	60 N-ethyldecahydro- 40 N-acetyldecahydro bases
N-Acetyltetrahydroisoquinoline	.02	160	18	2	Methylcyclohexane	35 basic 65 non-basic
N-Acetyltetrahydroisoquinoline	.16	140	16	8	Methylcyclohexane	30 basic 70 non-basic
Isoquinoline	.07	170	20	5	Methylcyclohexane	95 decahydro bases
	.43	180	15	15	Methylcyclohexane	about 80% *trans*

The similar properties of the salts of the synthetic and natural bases is convincing evidence for their identity. Table II demonstrates the differences of the melting points of some salts of the *cis* series. The infrared absorption spectra of the *cis* and *trans* compounds (Figs. 1 and 2) emphasize this difference, whereas the spectrum of the natural base (Fig. 3) is identical in every respect with the synthetic *trans* compound.

(4) At the outset of this investigation the procedure described previously (ref. 2) was used with slight modifications (*cf.* section A in the experimental part). Still milder conditions were employed in the preparation of the *chano*desoxyyohimbol from which the optically active N-methyl-*trans*-decahydroisoquinoline was obtained (section B, experimental part). It may be mentioned that even more rigorous conditions fail to change the configuration of rings D and E; thus, the same yohimbone is obtained in the Oppenauer dehydrogenation as that prepared by soda-lime distillation (350°) of yohimbine. In general, interconversions in the perhydro(iso)quinoline series have not been observed. The finding that the action of boiling hydrochloric acid is sufficient to effect the rearrangement from *cis*- to *trans*-decahydroquinoline [Clemo, Cook and Raper, *J. Chem. Soc.*, 1183 (1938)] could not be reproduced by Prelog and Szpilfogel, *Helv. Chim. Acta*, **28**, 1687 (1945); *cf.* Helfer, *ibid.*, **9**, 1814 (1926).

(5) The double bond in IV would be in the same position as in apoyohimbine. For the significance of a possible migration of this double bond with regard to the stereochemistry of the molecule see footnote 15.

(6) Easy racemization of optically active ammonium bases has been observed only in those cases where the quaternary nitrogen atom is immediately adjacent to the asymmetric carbon atom; *cf.* 1-nicotine bismethiodide, Späth and Bobenberger, *Ber.*, **77**, 362 (1944). An explanation for this phenomenon was recently furnished by the assumption of an "ylide" intermediate [Wittig, Mangold and Felletschin, *Ann.*, **560**, 116 (1948)].

(7) *Cf.* Woodward and Doering, THIS JOURNAL, **67**, 870 (1945).

(8) Adkins, "Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts," The University of Wisconsin Press, Madison, Wis., 1937, p. 61, Table 21.

(9) At the time when Mascarelli carried out the resolution (1914), he considered only one form capable of existing. Much later (1927) Hückel showed this form (m. p. 48°) to be *trans*.

(10) Veneziani, *Atti R. Acc. Linc.*, [5] **22**, II, 155 (1913); *Chem. Zentr.*, **84**, II, 1492 (1913).

(11) Mascarelli and Nigrisoli, *Atti R. Acc. Linc.*, [5] **23**, II, 276 (1914); *Gazz. chim. ital.*, **45**, I, 106, 127 (1915); *Chem. Zentr.*, **86**, I, 745, 1212 (1915).

(12) Likewise, the rotation of the hydrochloride is considerably smaller than that of the free *trans*-decahydroquinoline (±4.5°), Mascarelli, *ibid.*, [5] **23**, II, 281 (1914); *cf.* Marckwald, *Ber.*, **29**, 43 (1896).

TABLE II

	Hydrochloride	Picrate	Picrolonate	Chloroaurate
N-Methyl-*trans*-decahydroisoquinoline from yohimbine	225–227	234–237	199–201	90–92
Synthetic, resolved	225–227	234–237	202	90–93
Synthetic, racemic	224–226	234–236	216–219	85–87
d,l-N-Methyl-*cis*-decahydroisoquinoline	164–165	210		

etc.), and simplify attempts to synthesize the yohimbine skeleton.[14]

The second fragment in the Hofmann degradation of *chano*dihydrodesoxyyohimbol (V), presumably β-vinylindole (VII), could not be isolated. It is probable that this material polymerized under the conditions of the reaction. In the same way, from *chano*desoxyyohimbol (IV), an N-methyl-*trans*-octahydroisoquinoline, presumably VIII, was isolated in the form of the picrate.

The mother liquors from the isolation of IV contain lesser amounts of another base which was not isolated. Catalytic hydrogenation of mother liquors from the purification of IV leads to the isolation of *chano*isodesoxyyohimbol, presumably XI. It was not possible to decide whether the isomer originated from IV by migration of the double bond, or from a tetradehydro compound

TABLE III

N-Methyl-*trans*-decahydroisoquinoline	Hydrochloride $[\alpha]_D$	Bi-*d*-tartrate M. p., °C.	Bi-*d*-tartrate $[\alpha]_D$	Bidibenzoyl-L-tartrate M. p., °C.	Bidibenzoyl-L-tartrate $[\alpha]_D$	*d*-Bromocamphorsulfonate M. p., °C.	*d*-Bromocamphorsulfonate $[\alpha]_D$
Natural (from yohimbine)	+1.4			167–168	+82.2°		
Synthetic *d*-antipode	+1.6	167–169	+14.6	167–168	+82.5°	170–172	+71.4°
Synthetic, racemic				154–155	+84.9°	157–159	+64.9°

From these results, therefore, it may be inferred that in yohimbine itself rings D and E are *trans*-locked (I). The sequence of reactions should prove a useful approach to the stereochemistry of the numerous yohimbine isomers found in nature (*e. g.*, alloyohimbine, yohimbene, rauwolscine,[13]

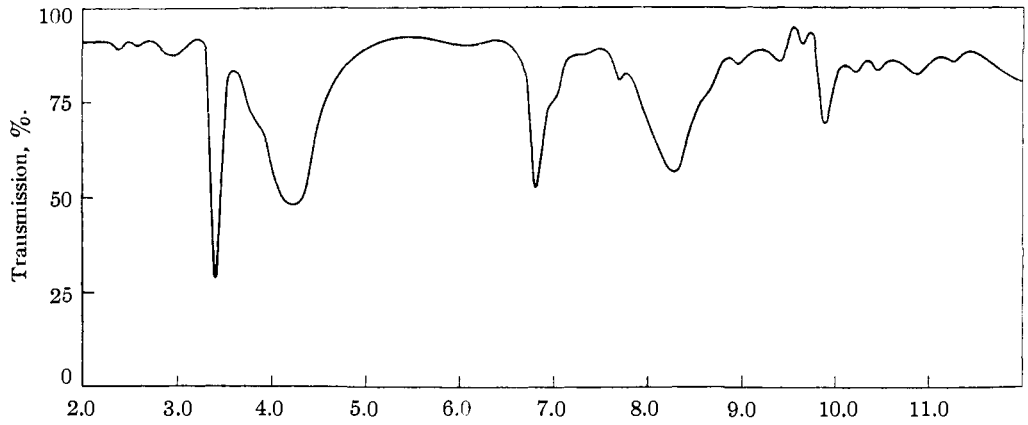


Fig. 1.—Wave length in microns: *d,l*-N-methyl-*cis*-decahydroisoquinoline hydrochloride in chloroform.

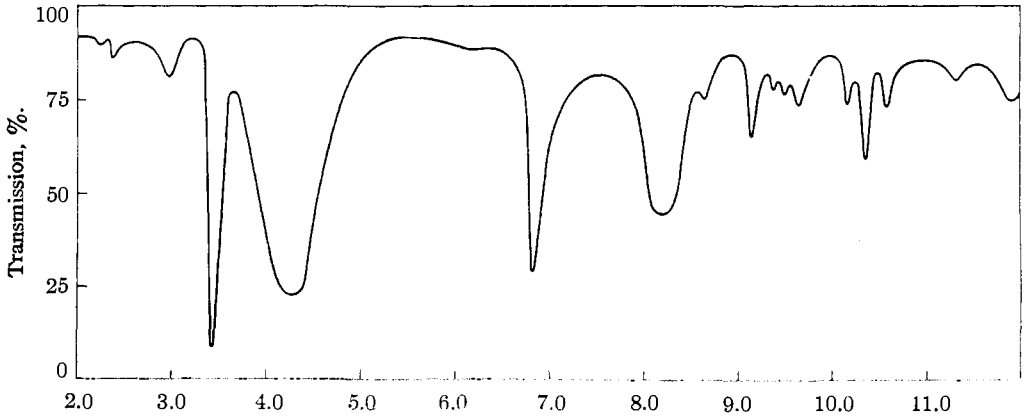


Fig. 2.—Wave length in microns: *d,l*-N-methyl-*trans*-decahydroisoquinoline hydrochloride (synthetic) in chloroform.

(13) Mokerjee, *J. Indian Chem. Soc.*, **23**, 6 (1946).

(14) Schlittler and Allemann, *Helv. Chim. Acta*, **31**, 131 (1948).

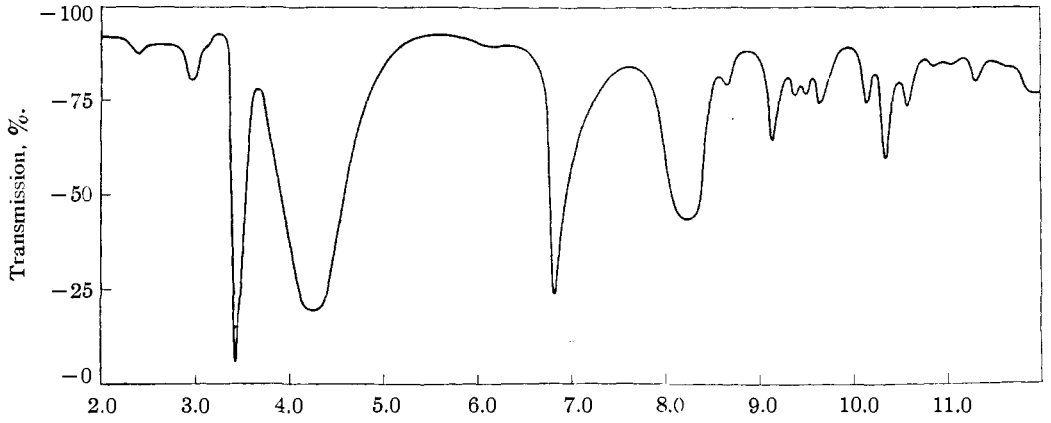
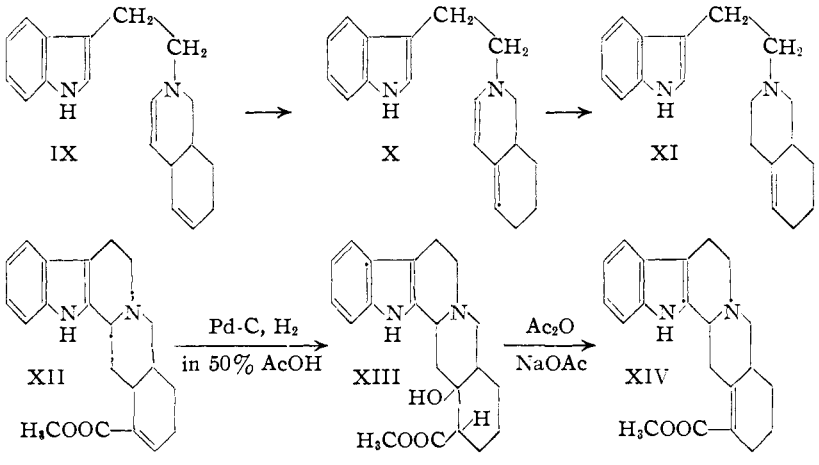
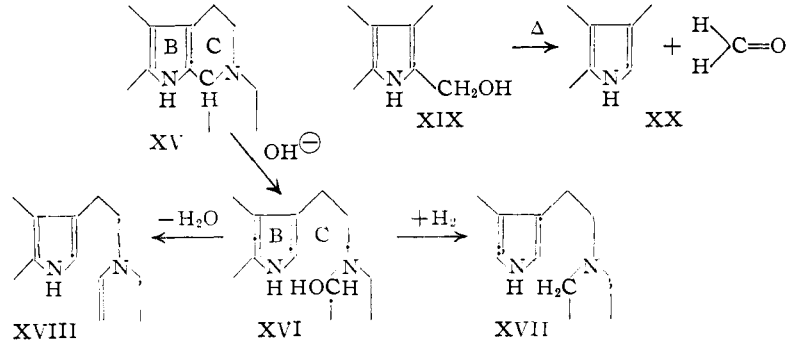


Fig. 3.—Wave length in microns: *d*-N-methyl-*trans*-decahydroisoquinoline hydrochloride (from yohimbine) in chloroform.

(IX → X) by partial hydrogenation. There is some indication that, at least in the case of apoyohimbine (XII), m. p. 252°, migration of the double bond can occur to give isomeric apoyohimbines (m. p. 230° and 201°). XIV is obtained from XII by a sequence of reactions that is better expressed by the changes XIII, XIV than by the improbable reverse addition of the elements of water to form α-isoyohimbine.[2] Though the conjugated carbethoxy group in apoyohimbine (XII) devaluates the comparison somewhat, it may be possible that the double bond in XI, like that in XIV, is not too easily hydrogenated.[15] The negative rotation of XI would exclude the alternative possibility of the double bond between the two angular carbon atoms. It may be mentioned that XI gave two, probably diastereoisomeric, methiodides.[16]



There now remains a consideration of the mode of formation of *chano*desoxyyohimbol (IV). It can be recognized from the partial formula (XV) that in yohimbine a change leading to XVI or XVII is possible, analogous to the splitting of quinamine[17] partial structure (XIX) to formaldehyde and an α-unsubstituted indole derivative (XX). The possible formation of IX can be similarly interpreted (XVIII). The formation of *chano*desoxyyohimbol (IV) may well involve a hydrogen transfer reaction in which the group >C(OH)–N< in XVI is reduced by the secondary alcohol group at carbon atom 17. The concomitant formation of yohimbone[18] supports this view.[19]



It is of interest that *chano*dihydrodesoxyyohimbol (V) is an isomer of quebrachamine, an alka-

(15) The hydrogenation of the isomeric IV proceeds so rapidly that any intermediate migration of the double bond which might jeopardize the stereochemical inferences can be safely discarded.

(16) *Cf.* L. E. Craig, *Chem. Rev.*, **42**, 390 (1948).

(17) Kirby, *J. Chem. Soc.*, 528 (1945).

(18) This formation of yohimbone is dependent on the slightest changes of experimental conditions. Whilst method A yielded only negligible amounts of yohimbone, so much of it (together with other bases) was formed using method B, that a special procedure had to be developed to effect separation (*cf.* experimental part).

(19) *Cf.* Hess, *Ber.*, **46**, 3113, 4104 (1913).

loid isolated from quebracho bark, together with quebrachine or yohimbine, by Hesse[20] and by Ewins.[21] It was last studied by Field.[22] An α-unsubstituted indole ring was suggested by a positive Hopkins–Cole reaction.[23] The indole ring also shows up clearly in the absorption spectrum (Fig. 4), which is very similar to that of yohimbine. Field[22] considered a possible relationship between the two alkaloids. The structure V, merely conjecturally, was considered for quebrachamine by Scholz.[24] The red picrate of *chano*dihydrodesoxyyohimbol (V) has the same melting point as quebrachamine picrate, but shows a deep mixed melting point depression. The free base has a lower melting point (130°) than quebrachamine (147°), and as the optical activities differ widely (V: $[\alpha]_D$ −2.5°; quebrachamine: $[\alpha]_D$ −109.5°), identity is excluded. On the other hand, the presence of two asymmetric carbon atoms permits the possibility that quebrachamine might be a diastereomer of V. In this case, it should have been possible to arrive at another isomer, possibly identical with quebrachamine, by starting with alloyohimbic or yohimbenic acid, in which ring D and E might have the *cis* configuration. Attempts in this direction were discontinued when other evidence rendered unlikely the possibility of diastereoisomerism.

Though neither quebrachamine nor *chano*dihydrodesoxyyohimbol possess N-methyl groups, they yield different quantities of volatile iodides in the Herzig–Meyer reaction. The determinations, which are well reproducible, give two times more "NCH_3" in the case of quebrachamine. According to formula V the dehydrogenation of quebrachamine should give isoquinoline or possibly Bz-tetrahydroisoquinoline.[3] However, a different degradation product is obtained.[25]

Pharmacological Action.—Dr. Raymond-Hamet, Paris, kindly investigated some pharmacological properties of *chano*desoxyyohimbol,[26] and of its dihydro derivative,[27] and found them to be related to yohimbine and not to quebrachamine. Following our scheme[3] (used lately also by other authors[28,29]) of testing quaternary bases possibly related to the structure of the alkaloids from calabash curare,[30] we found no curariform activity for the methochlorides of *chano*desoxyyohimbol, *chano*dihydrodesoxyyohimbol, and quebrachamine, in doses of 12.5 mg./kg. frog.

(20) Hesse, *Ann.*, **211**, 249 (1882).
(21) Ewins, *J. Chem. Soc.*, **105**, 2738 (1914).
(22) Field, *ibid.*, **125**, 1444 (1924).
(23) Yohimbine also gives a positive Hopkins-Cole test if a trace of copper ion is present and the reaction is carried out according to Winkler, *Z. physiol. Chem.*, **228**, 50 (1934).
(24) Scholz, Dissertation, Eidgenössische Technische Hochschule, Zürich, 1934, p. 32.
(25) These results will be discussed in a forthcoming publication.
(26) Raymond-Hamet, *Compt. rend.*, **217**, 303 (1943).
(27) Raymond-Hamet, private communication.
(28) Karrer and Waser, *Helv. Chim. Acta*, **32**, 409 (1949).
(29) Craig and Tarbell, THIS JOURNAL, **71**, 462 (1949).
(30) Wieland, Witkop and Bähr, *Ann.*, **558**, 144 (1947).

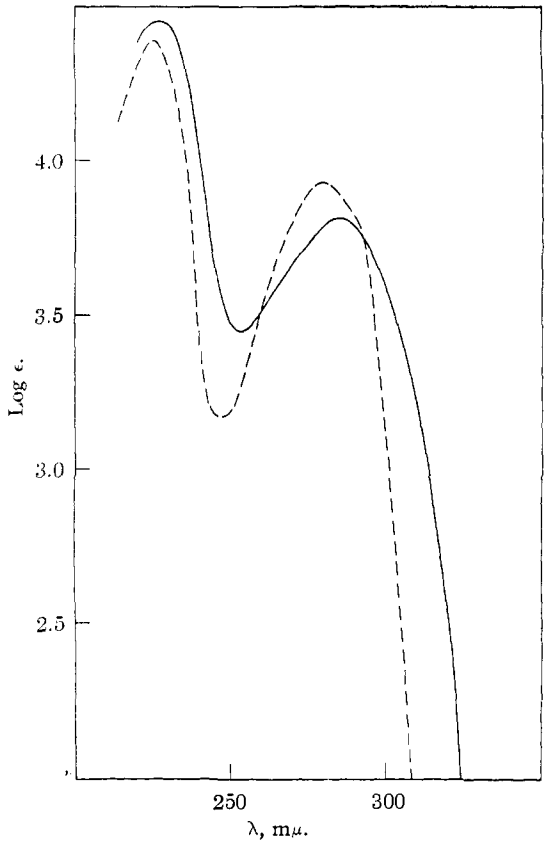


Fig. 4.—Quebrachamine, ———; yohimbine, - - - - - (in ethanol).

Experimental[31]

*Chano*desoxyyohimbol

Method A.—The previously reported procedure for the preparation of "desoxyyohimbol"[3] gives appreciably better yields, when modified as in the following. More than 3–5 g. of yohimbic acid should not be taken for each distillation, as the strong evolution of gas then impairs the vacuum so as to necessitate temperatures above 300° which definitely must be avoided, since tetrahydroisoyobyrine is then formed. The ratio of yohimbic acid to thallous oxide should be 5:1. Maintenance of these conditions leads to a honey-yellow glassy distillate which, on rubbing with methanol, *immediately* gives the pure base IV which, after recrystallization from the same solvent, forms colorless needles, m. p. 151°. The yield is 8–12%. The fluffy sublimate that is sometimes observed during the distillations, is yohimbone; silky needles from methanol, m. p. 295°.

Method B.—Changes in the pumping system improved the pumping speed sufficiently to permit a decrease in bath temperature to 280°. The average pressure during distillation was maintained at 0.01 mm., using a three-stage mercury pump in conjunction with a high-speed oil pump (instead of the water aspirator used under A). Thallous oxide was replaced by thallous carbonate. Two traps in series (cooled with dry ice–acetone) were used to prevent the fluffy sublimate (yohimbone), formed during distillation, from entering the mercury pump. Thirty-five distillations, using 2 g. of yohimbic acid and 0.4 g. of thallous carbonate in each one, yielded 25 g. of yellow glassy distillate. On standing, the solution of the pulverized material in methanol deposited 3.5 g. of yohimbone

(31) All melting points are corrected.

(m. p. 302° after two recrystallizations). After concentration the darkening mother liquors deposited 1.5 g. of crystalline material, m. p. 135–144°. Since purification of this mixture proved to be very difficult, the following procedure was applied. The mother liquors were evaporated to dryness and separated into a benzene-soluble (12.5 g.) and a benzene-insoluble fraction (9 g.). The first fraction was filtered through a column containing about 100 g. of aluminum oxide, yielding 8.5 g. of light yellow partly crystalline material. This fraction, together with the crystalline mixture mentioned above (m. p. 135–144°), was taken up in 500 cc. of dilute hydrochloric acid and converted into the picrate. The carefully dried picrate was extracted five times with small portions of cold methanol and five times with cold acetone. By recrystallizing 8 g. of the residual picrate from acetone, using a Soxhlet extractor with thimble, a mixture of light fluffy yellow needles and beautiful heavy red rods was obtained. The latter, *chano*desoxyyohimbol picrate (m. p. 224°), was separated mechanically using a sieve (80 mesh) that allowed only the yellow picrate and some smaller crystals of the red picrate to pass through. In this fashion 3.6 g. of the red picrate was obtained and after one more recrystallization from acetone, converted into the free base by grinding up the picrate with dilute alkali and extraction with ether. The free base (1.9 g.) crystallized from ether in nice cubes, m. p. 151°.

The yellow picrates that went through the sieve consisted of a mixture resisting purification. Repeated crystallizations from acetone yielded needles, m. p. 245° (dec.), and another picrate from the mother liquors, yellow needles, m. p. 224°. The mixed melting point determinations with yobyrine picrate (m. p. 250°), and with tetrahydroisoyobyrine picrate (m. p. 228°), respectively, were not sharp, suggesting further contaminants.

*Chano*dihydrodesoxyyohimbol (V).—When 720 mg. of *chano*desoxyyohimbol in 5 cc. of glacial acetic acid was added to 50 mg. of freshly reduced platinum oxide in 3 cc. of glacial acetic acid, 62.5 cc. of hydrogen (calcd., 62 cc. under atmospheric conditions) was taken up in the course of fifteen minutes. After addition of water the platinum was removed by filtration and the hydrogenation product precipitated with dilute alkali. The dried ether extract left 730 mg. of the colorless base, which formed beautiful prisms on recrystallization from methanol, m. p. 130°, $[\alpha]_D$ −2.5°. The crystals as well as the mother liquors turn slightly pink on prolonged exposure to air and light.

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.84; H, 9.25. Found: C, 80.72; H, 9.11.

The Hopkins–Cole reaction with glyoxylic and concd. sulfuric acids is dark blue in the interphase; quebrachamine and *chano*desoxyyohimbol give this reaction in the same way. The Ehrlich reaction is purple-red on warming and persists on cooling.

Volatile iodides in the Herzig–Meyer determination:

*Chano*dihydrodesoxyyohimbol....	2.18%	"NCH_3"
Quebrachamine.....	4.45%	
Yohimbol.....	3.04%	

Picrate.—From the solution of *chano*dihydrodesoxyyohimbol in dilute mineral acid, aqueous picric acid precipitated the flocculent *yellow* picrate which, after recrystallization from acetone, formed *red* rods, melting at 190°. The mixed melting point with quebrachamine picrate (m. p. 190°) was 165°.

Anal. Calcd. for $C_{25}H_{29}O_7N_5$: C, 58.70; H, 5.72. Found: C, 58.85; H, 5.54.

*Chano*isodesoxyyohimbol (presumably XI).—The methanolic mother liquor from the preparation of chanodesoxyyohimbol using method A, darkened and became strongly fluorescent on standing. It was evaporated, the residue taken up in benzene and filtered through aluminum oxide. When this solution was evaporated to dryness and taken up in methanol, a second crop of *chano*desoxyyohimbol was obtained. Concentration of the mother liquor gave further crystalline material which showed an unsharp melting point (130–150°). Dissolved in 8 cc. of glacial acetic acid, 280 mg. of this mixture took up 1.5 mole of hydrogen in the presence of 100 mg. of platinum oxide within five hours. After separation of the platinum, the base was precipitated with ammonia, filtered and dried. The base was obtained in the form of fine needles from methanol in which it is much less soluble than its isomer IV; m. p. 206°. The compound is levorotatory. The Hopkins–Cole reaction is violet, the Ehrlich reaction crimson.[32]

Anal. Calcd. for $C_{19}H_{24}N_2 \cdot H_2O$ (dried at room temperature): C, 76.51; H, 8.72. Found: C, 76.86; H, 8.46. Calcd. for $C_{19}H_{24}N_2$ (dried *in vacuo* at 100°): C, 81.43; H, 8.64. Found: C, 81.52, 81.42; H, 8.80, 8.81.

Methiodide (A).—On addition of excess methyl iodide to the ether solution of *chano*isodesoxyyohimbol, the colorless methiodide soon separated. On recrystallization from methanol two fractions were obtained. Methiodide (A) was a crystalline powder, not readily soluble in methanol, and, on recrystallization, sometimes appearing in the form of a gel which became crystalline on standing. This methiodide (A) did not melt, but showed progressive charring toward 280°.

Anal. Calcd. for $C_{19}H_{24}N_2 \cdot CH_3I$: C, 56.87; H, 6.45. Found: C, 56.93; H, 6.74.

Methiodide (B).—The mother liquors contain a methiodide that is much more soluble in methanol than methiodide (A). Recrystallized from methanol–ether, methiodide (B) forms fine soft colorless needles, m. p. 254°.

Anal. Calcd. for $C_{19}H_{24}N_2 \cdot CH_3I$: C, 56.87; H, 6.45. Found: C, 56.26; H, 6.66.

N-Methyl-*trans*-octahydroisoquinoline (VIII) Picrate.—*Chano*desoxyyohimbol methiodide (softening at 198°) was converted into the free ammonium base by thallous oxide; 0.2 g. of the amorphous quaternary base was heated in the vacuum of the water aspirator. At 170° (bath) a distillate was obtained that had the odor and the alkaline reaction of a volatile amine. Upon addition of water, colorless needles (crystalline hydrate?) formed which dissolved in more water. From this solution aqueous picric acid produced an immediately crystalline picrate which, on recrystallization from methanol, formed short yellow needles, m. p. 229–231° (210°, transformation into short prisms).

Anal. Calcd. for $C_{10}H_{17}N \cdot C_6H_3O_7N_3$: C, 50.53; H, 5.26. Found: C, 50.83, 50.70; H, 5.21, 5.35.

It was noticed during the Hofmann degradation that the reaction mixture showed appreciable foaming though there was no longer any distillation of volatile amine (splitting of methanol). The hardly volatile residue possessed a faint indole odor.

***d*-N-Methyl-*trans*-decahydroisoquinoline (VI) Hydrochloride.**—The solution of *chano*dihydrodesoxyyohimbol in methanol was left at room temperature with excess methyl iodide for twenty-four hours. The methiodide, precipitated by adding an excess of ether, proved difficult to crystallize. A small sample was converted into the quaternary picrate, fine needles from methanol, m. p. 223–225°. The amorphous methiodide (0.6 g.) was converted into the carbonate with thallous carbonate. By heating this carbonate to 180° at 30 mm. pressure a colorless oil was obtained which solidified in the Dry Ice-cooled receiver. This amine, liquid at room temperature, was neutralized with dilute hydrochloric acid and evaporated to dryness in the desiccator. The crystalline residue was triturated several times with small portions of absolute

(32) These color reactions and the analytical results exclude identity with Wibaut's decahydroyobyrine (m. p. 228°), octahydroisoyobyrine (m. p. 178°) [Wibaut and van Gastel, *Rec. trav. chim.*, **54**, 90 (1935)], and hexahydroyobyrine or tetrahydroyobyrine [*Ann.*, **554**, 114 (1943); *cf.* Karrer and Waser, *Helv. Chim. Acta*, **32**, 409 (1949)], formed by hydrogenation of (tetrahydroiso)-yobyrine possibly present in the mother liquors of *chano*desoxyyohimbol as suggested by the results of method B.

ether in order to remove the last traces of water. The dry hydrochloride (from *chano*desoxyyohimbol using method B) weighed 192 mg. (79% yield of the theoretical amount from the methiodide). Recrystallization from alcohol–ether (1:4) yielded beautiful prisms, m. p. 225–227°. Observing the usual precautions in measuring small rotations,[33] five separate determinations showed a distinct dextrorotation: $[\alpha]_D$ 1.4° (in water, *c*, 4.9).

Anal. Calcd. for $C_{10}H_{19}N\cdot HCl$: C, 63.29; H, 10.63. Found: C, 62.84; H, 10.68.

Picrate.—On addition of aqueous picric acid to a solution of the above hydrochloride the picrate deposited in fine yellow needles, m. p., after recrystallization from acetone, 234–237°, crystalline transformation at 210°; no depression was observed on admixture with synthetic *d*-N-methyl-*trans*-decahydroisoquinoline picrate (*vide infra*).

Anal. Calcd. for $C_{10}H_{19}N\cdot C_6H_3O_7N_3$: C, 50.26; H, 5.7. Found: C, 50.30; H, 5.75.

Picrolonate.—The picrolonate crystallized directly from water. Recrystallized from methanol, it formed tufts of golden needles, m. p. 199–201°.

Anal. Calcd. for $C_{10}H_{19}N\cdot C_{10}H_8O_5N_4$: C, 57.55; H, 6.52. Found: C, 57.94; H, 6.28.

Chloroaurate.—Upon addition of aqueous gold chloride to the solution of the hydrochloride in dilute hydrochloric acid, a cloudiness occurred that turned into an oily precipitate which became crystalline on standing and scratching; m. p. 90–92°.

Anal. Calcd. for $C_{10}H_{19}N\cdot HAuCl_4$: C, 24.35; H, 4.4; Au, 40.0. Found: C, 24.37; H, 4.02; Au, 40.37.

The chloroplatinate was found to be too soluble in water as to be useful for characterization.

Bidibenzoyl-L-tartrate.—When a hot solution of 140 mg. of dibenzoyl-L-tartaric acid in 5 cc. of methanol was added to a solution of 70 mg. of *d*-N-methyl-*trans*-decahydroisoquinoline (free base prepared from hydrochloride) in 3 cc. of methanol, immediate but slow crystallization occurred. After standing overnight at 0°, the beautiful prisms were collected and washed with methanol, m. p. 167–168° (dec.); $[\alpha]_D$ 82.2° (in methanol, *c*, 2.02). On admixture with synthetic *d*-N-methyl-*trans*-decahydroisoquinoline bidibenzoyl-L-tartrate no depression was observed.

Anal. Calcd. for $C_{28}H_{33}O_8N$: C, 65.55; H, 6.5. Found: C, 65.55; H, 6.23.

Preparation of *trans*-Decahydroisoquinoline[34]

Isoquinoline Bioxalate.—When the hot methanolic solutions of equimolar amounts of commercial isoquinoline and oxalic acid (containing two molecules of water) were combined, the acidic oxalate separated in colorless crystals. On recrystallization from methanol fine needles were obtained, m. p. 148°.

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.26; H, 4.1. Found: C, 60.6; H, 3.82.

N-Ethyldecahydroisoquinoline Picrate.—Pure isoquinoline (prepared from the bioxalate) was hydrogenated to the py-tetrahydro compound (with platinum oxide in glacial acetic acid) and converted into N-acetyltetrahydroisoquinoline, needles from petroleum ether, m. p. 45°. When 1.2 g. of the acetyl compound was heated in 50 cc. of absolute ethyl alcohol in the presence of 1 g. of Raney nickel at 164° for seventeen hours (3000 lb./sq. in.), 3.3 moles of hydrogen (calculated from the pressure drop) was taken up. After removal of the nickel, the hydrogenation product was dissolved in ether. The ethereal solution was extracted several times with dilute acid. After liberation of the bases with alkali, they were taken up again in ether. After evaporation of the ether 0.7 g. of an oily base was obtained which could not be acetylated with acetic anhydride. The picrate of this base crystallized from aqueous solution and was recrystallized from methanol, yellow platelets, m. p. 154°.

Anal. Calcd. for $C_{11}H_{21}N\cdot C_6H_3O_7N_3$: C, 51.51; H, 6.08. Found: C, 51.56; H, 5.80.

Since mixtures of *cis* and *trans* derivatives usually melt over a wide range, the sharp melting point of the picrate would suggest the presence of only one isomer, presumably the *trans* compound.

Benzoyl-*trans*-decahydroisoquinoline.—When 55 g. of pure isoquinoline in 400 cc. of methylcyclohexane was hydrogenated in the presence of 15 g. of Raney nickel (180°, 4000 lb./sq. in. initial pressure), the pressure drop after fifteen hours indicated an uptake of 5 moles of hydrogen. The mixture of the hydrogenated bases (58 g.), after removal of the catalyst and the solvent, was refluxed in the presence of 1 g. of highly active palladium black. In the course of twenty-four hours about 5.4 liters of hydrogen was liberated. At the end of the selective dehydrogenation the rate of hydrogen evolution slowed down to about 150 cc./hour compared with about 750 cc./hour at the beginning. The final rate was not changed after the addition of 100 mg. of fresh palladium black.[35] The mixture resulting from the selective dehydrogenation was then distilled (70–105° at 2 mm.) and treated with acetic anhydride in ether. After the acetylation was completed the basic constituents (isoquinoline and bz-tetrahydroisoquinoline) were removed by extraction with dilute acid. The oily acetyl product was saponified by refluxing it with 4 *N* hydrochloric acid for four hours. After evaporation *in vacuo* the dry hydrochloride was recrystallized twice from ethyl alcohol, m. p. 222–224°. The benzoyl derivative, prepared from the solution of the hydrochloride in pyridine and benzoyl chloride, crystallized from ether or petroleum ether in cubes, m. p. 97–99°.

Anal. Calcd. for $C_{16}H_{21}ON$: C, 79.01; H, 8.72. Found: C, 78.92; H, 8.80.

Resolution of *d,l*-N-Methyl-*trans*-decahydroisoquinoline

***d*-N-Methyl-*trans*-decahydroisoquinoline D-Bitartrate.**—A solution of 1.5 g. of D-tartaric acid in the minimum amount of hot alcohol was added to 1.53 g. of purest N-methyldecahydroisoquinoline (prepared by the methylation[3] of the base from purest *trans*-decahydroisoquinoline hydrochloride) in 4 cc. of methanol. After three days in the ice box, 1.41 g. of big prisms was obtained, m. p. 158–160°, sintering at 152°. Five recrystallizations from ethyl alcohol yielded prisms melting at 167–169°, $[\alpha]_D$ +14.6° (in water, *c*, 2.05).

Anal. Calcd. for $C_{14}H_{25}O_6N$: C, 55.44; H, 8.31. Found: C, 55.60; H, 8.24.

The combined ethanolic mother liquors became sirupy on concentration and did not deposit any crystalline material on standing for two weeks.

***d*-N-Methyl-*trans*-decahydroisoquinoline Hydrochloride.**—The above bitartrate was decomposed with strong alkali and the base was extracted with ether. When hydrogen chloride was passed through the dry ethereal solution, the hydrochloride separated in fine needles, m. p., after recrystallization from alcohol–ether (1:4), 225–227°, $[\alpha]_D$ +1.6° (in water, *c*, 6.6).

Picrate.—Needles from acetone, m. p. 234–237°, crystalline transformation, 200–210°.

Chloroaurate.—Upon addition of aqueous gold chloride to the solution of the hydrochloride, the oily chloroaurate deposited and became crystalline on standing and scratching, m. p. 90–93°.

Bidibenzoyl-L-tartrate.—The salt was prepared in the same way as described with the natural base, starting with 230 mg. of free base, prepared from the above hydrochloride, and 550 mg. of dibenzoyl-L-tartaric acid. Recrystallization from methanol gave prisms, m. p. 167–168° (dec.), $[\alpha]_D$ +82.5° (in methanol, *c*, 1.68).

(33) Davis and Ackermann, THIS JOURNAL, 67, 488 (1945).

(34) These experiments were carried out with the assistance of Mr. Jerrold Meinwald.

(35) The total volume of liberated hydrogen would point to the presence of 9–16% of *cis*-decahydroisoquinoline in the mixture of the perhydro bases, depending on whether one bases the calculation on partial or complete dehydrogenation of the *cis* compound.

Anal. Calcd. for $C_{28}H_{33}O_5N$: 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.[36]

(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.

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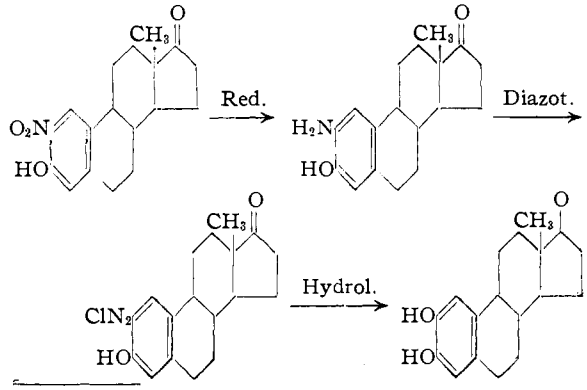
Estracatechol[1,2]

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).