[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Construction of the C-D-E Ring Skeleton of Yohimbine

BY EUGENE E. VAN TAMELEN, DAVIE L. HUGHES AND CHARLES W. TAYLOR

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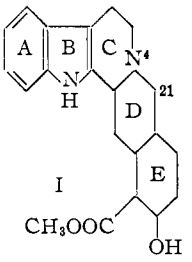
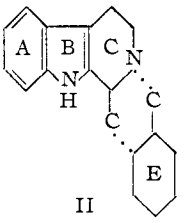
The Michael product arising from the addition of ethyl 2-pyridylacetate to 1-cyanocyclohexene has been transformed through a reduction and cyclization sequence to 11-azatetradecahydroanthracene, which constitutes the C-D-E ring system of the yohimbine skeleton.

In connection with a general program dealing with the synthesis of the ring system present in the alkaloid yohimbine (I) and related substances,

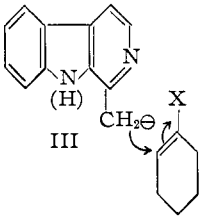


I

we had occasion to study an approach involving ring D formation by way of attachment of a ring E component to an intact A-B-C system, as represented in the expression II. Such a plan is exemplified by the Michael addition of the harman



II

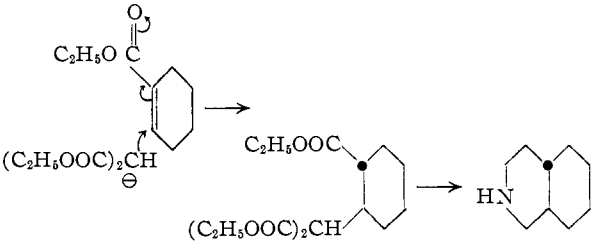


III

IV, X = $-COOCH_3$
V, X = $-CN$

anion III to methyl cyclohexene-1-carboxylate (IV) or 1-cyanocyclohexene (V), followed by ring closure through N-4 and C-21 and reduction of the C-ring. The metallic salts of harman and harmine have previously been employed in similar operations: (i) the addition to the carbonyl group of 2,6-dimethylcyclohexanone, yielding the expected *t*-alcohol[1] and (ii) as the harman N-methyl derivative, addition to 2-isopropoxycylohexanone, affording, after hydrolysis, the alkaloid sempervirine as the N-methyl quaternary salt.[2]

As a simple model for the route outlined above, we carried out the addition of ethyl 2-pyridylacetate to 1-cyanocyclohexene (Chart I), accomplished by refluxing the reactants in anhydrous ethanolic sodium ethoxide for 24 hr. The product VI was obtained initially as a yellow-orange, viscous oil, b.p. 166–170° (0.5 mm.), which, on standing, crystallized. Since the solid obtained from the analytically pure distillate, even after crystallization from ethanol, melted over a wide range (70–100°), it probably consists of a mixture of diastereomers. The Michael reaction is generally acknowledged to give rise to the more stable (in this case, *trans*) addition product,[3] and this view is borne out in a case similar to the present one: the addition of malonic ester to ethyl cyclohexene-1-carboxylate,[4] the product of this reaction having been converted[4] through a series of steps to *trans*-



decahydroisoquinoline. In an additional case, we added malonic ester to 1-cyanocyclohexene and obtained the liquid diethyl 2-cyanocyclohexylmalonate, which was shown to be the *trans* isomer by partial hydrolysis in good yield to *trans*-hexahydrohomophthalimide,[5] convertible to the *trans*-perhydroisoquinoline. Thus the product VI is most likely a mixture of ethyl *trans*-(α-2′-cyanocyclohexyl)-pyridylacetates, epimeric around the α-carbon atom. The *trans* configuration specified is, incidentally, the desired one, because yohimbine possesses the D-E *trans* ring system.[5,6]

Support for this conclusion concerning the stereochemical nature of VI was secured in connection with the next two steps in the sequence: selective hydrolysis of the carbomethoxyl function and consequent decarboxylation to 2-(2′-cyanocyclohexylmethyl)-pyridine (VII), which was obtained in high yield (86%) as a colorless oil, distilling over a temperature range 149–152°. Hydrolysis of the nitrile was accomplished by refluxing in aqueous hydrochloric acid and resulted in a 95% yield of crystalline 2-(α-picolyl)-cyclohexanecarboxylic acid (VIII), the melting point of which (137.5–139°) was not raised by recrystallization of the crude product.[7] It is evident that the nitrile VII must therefore be stereochemically pure and, further, that the inhomogeneity of VI is associated

(1) C. F. Huebner, H. B. MacPhillamy, A. F. St. André and E. Schlittler, THIS JOURNAL, **77**, 472 (1955).

(2) R. B. Woodward and W. M. McLamore, *ibid.*, **71**, 379 (1949).

(3) F. Bergmann, D. Ginsberg and R. Pappo, forthcoming chapter in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y.

(4) L. Helfer, *Helv. Chim. Acta*, **9**, 814 (1926).

(5) E. van Tamelen and M. Shamma, THIS JOURNAL, **76**, 950 (1954).

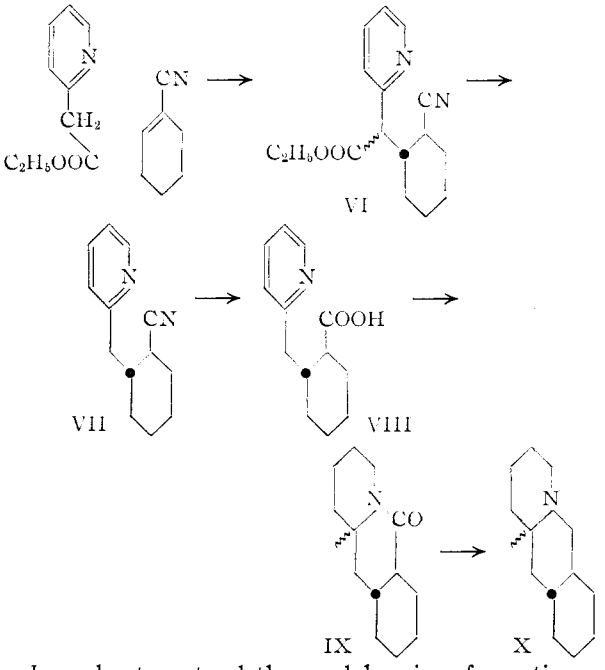
(6) E. Van Tamelen, M. Shamma and P. Aldrich, *ibid.*, **78**, 4628 (1956)

(7) The acid could be secured through direct acid hydrolysis of the cyano ester VI, although the yield was not nearly so high.

with diastereoisomerism around the asymmetric center which is lost in the conversion of VI to VII.

Picolylsodium was added to cyanocyclohexene in ether so as possibly to obtain the nitrile VII through a more direct route; however, the only product isolated in our hands was a high boiling liquid, the analysis of which indicated it to be the 1:2[8] (pyridylacetic ester:cyanocyclohexene) addition product. The addition of ethyl pyridylacetate to IV did not appear to be satisfactory.

CHART I

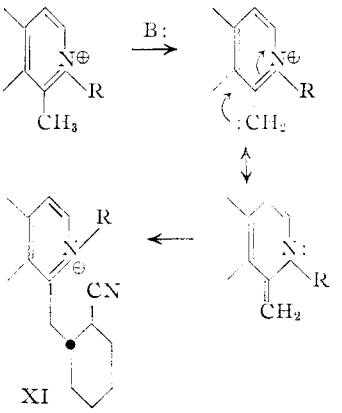


In order to extend the model series of reactions, the pyridyl acid VIII was converted, through stepwise reduction and cyclization, to 11-azatetradecahydroanthracene (X), which embodies the C-D-E ring skeleton of yohimbine. Initial reduction of VIII was accomplished in ethanolic hydrochloric acid with Adams catalyst; cyclization accompanied the isolation and purification, the lactam IX being obtained as a high boiling, immobile oil. Lithium aluminum hydride served to reduce this intermediate to the desired tertiary amine X, which was obtained as a low-melting, crystalline solid and was characterized by means of a picrate, m.p. 162.5–164.5°.

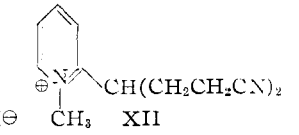
Attempts to obtain this same end-product through a direct reductive cyclization[9] of the pyridylnitrile VII were unsatisfying in that, although the proper amount of hydrogen was consumed and the semi-crystalline product appeared to possess tertiary nitrogen only, no single isomer, either as the free base or as a salt, was procured.

The substitution of a β-carboline for a pyridine residue in the above series would lead to a D-E *trans*-yohimbane, and therefore the route starting with harman was initiated. However, numerous trials involving addition of the base, either as a sodium or lithium salt or as an unisolated C-1 carbethoxylated derivative, to cyanocyclohexene, were unsuccessful; only intractable products and recovered harman could be isolated.

In the hope of developing a more versatile route to the desired ring systems, several attempts were made to condense cyanocyclohexene with N-methyl-α-picolinium iodide and the N-benzyl quaternary chloride of harman, both of which, by virtue of the positive charge in the pyridinium



ring, might be expected to yield easily the anion required for addition to the unsaturated nitrile. Although a variety of basic catalysts and temperature conditions were employed, addition products of the type XI could not be obtained, starting materials being almost invariably recovered. Since the proposed reactions failed and since there is apparently no record of a Michael addition involving a picoline quaternary salt as an addend, it became of interest to supply an example; and therefore the simple cyanoethylation reaction utilizing α-picoline methiodide was attempted. In a single experiment, refluxing the components with a catalytic amount of sodium methoxide in methanol for 12-hr. afforded a solid product, the analysis and infrared spectrum of which indicated it to be a bis-condensation product, probably XII. The reluctance of α-picolinium methiodide to undergo the Michael



reaction—at least with 1-cyanocyclohexene—contrasts sharply with its participation as the base in the aldol condensation, in which role it is oftentimes strikingly efficient.

Acknowledgment.—This work was supported in part by a grant (G3892) from the Department of Health, Education and Welfare.

Experimental

Ethyl *trans*-α-(2′-Cyanocyclohexyl)-2-pyridylacetate (VI).—Ethyl 2-pyridylacetate[10] (33.0 g., 0.2 mole) and 1-cyanocyclohexene[11] (20.4 g., 0.19 mole) were dissolved in a solution of 0.2 mole of sodium methoxide in 120 ml. of absolute ethanol. While the reaction mixture was protected from the atmosphere by means of calcium chloride drying tubes, it was refluxed for 24 hr. After the reaction mixture had

(8) *Cf.* M. J. Weiss and C. R. Hauser, THIS JOURNAL, **71**, 2026 (1949).

(9) V. Boekelheide, W. J. Linn, P. O'Grady and M. Lamborg, *ibid.*, **75**, 3213 (1953).

(10) R. B. Woodward and E. C. Kornfeld, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., p. 413.

(11) R. van Coillie, *Bull. soc. chim. Belg.*, **42**, 419 (1933).

cooled to room temperature, it was poured onto a mixture of 19 ml. of concentrated hydrochloric acid and about 200 g. of ice. After adjusting the *p*H to 10 through the use of 5% aqueous sodium hydroxide, the resulting mixture was extracted four times with ether. The ether extracts were washed with water, dried over magnesium sulfate and reduced in volume by evaporation with a stream of air. Vacuum distillation afforded 23.0 g. (44%) of a viscous liquid boiling over the range 166–170° (0.5 mm.). The separation of this material into three fractions on distillation gave cuts with an essentially constant refractive index ($n^{25}D$ 1.5163). A middle cut was taken for analysis.

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.30. Found: C, 70.37; H, 7.10; N, 9.99.

On standing the colored oil partially solidified, and the resulting semi-crystalline material was crystallized from 95% ethanol to give about a 70% recovery of nicely crystalline product which melted, however, over the range 70–100°. No attempt was made to separate the mixture of epimers into the pure components.

Diethyl *trans*-2-Cyanocyclohexylmalonate.[12]—To a solution of sodium ethoxide prepared by dissolution of 11.5 g. (0.5 mole) of sodium metal in 250 ml. of absolute ethanol was added 81.5 g. (0.51 mole) of redistilled diethyl malonate. The resulting solution of sodio diethyl malonate was heated to reflux, and 61.0 g. (0.57 mole) of cyanocyclohexene was added dropwise over a period of 10 minutes. During this entire operation and the following 72-hr. period of refluxing, the reaction mixture was protected from moisture with drying tubes. The cooled reaction mixture was poured into a solution of 45 ml. of concentrated hydrochloric acid in 500 ml. of water, and the resulting mixture was extracted with ether. After the ether extracts were washed with saturated sodium bicarbonate and evaporated down, the residue was distilled, yielding 47 g. (35%) of diethyl *trans*-2-cyanocyclohexylmalonate, b.p. 185–212° (8.0 mm.).

Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.26; H, 7.67; N, 5.57.

Dilute hydrochloric acid hydrolysis of 1.0 g. of the cyano diester yielded 0.69 g. (100%) of *trans*-2-carboxycyclohexaneacetic acid, m.p. 149–152° (m.p. 154–155° after recrystallization from water; reported m.p. 157°[13]), which was further characterized by conversion to the anhydride, m.p. 77° (reported m.p. 81°[13]).

The imide derived from *trans*-2-carboxycyclohexaneacetic acid was obtained through selective hydrolysis of the cyanocyclohexylmalonic ester. One gram of the latter was refluxed for 3 hr. in a solution of 2.2 equivalents of potassium hydroxide in 25 ml. of ethanol. Three milliters of concentrated hydrochloric acid was added to the reaction mixture, after which the volume was reduced as much as possible with an air stream. The residue was then heated for 1 hr. at 150° in order to cyclize the amide presumed to be the intermediate. Crystallization of the cooled residue from hot methanol afforded 0.33 g. (53%) of *trans*-hexahydrohomophthalimide, m.p. 186–187° (reported m.p. 187°).

***trans*-2-(2′-Cyanocyclohexylmethyl)-pyridine (VII).**—The controlled hydrolysis of VI was accomplished by using 7.0 g. (0.0256 mole) of crystalline starting material and an equivalent amount of potassium hydroxide (35.2 ml. of an aqueous 0.732 *N* solution) in approximately 30 ml. of methanol. After 6 hr. of refluxing, titration of an aliquot from the reaction mixture showed that 94% of the base had been consumed. The refluxing was continued for 3 more hr., and then the solvent was evaporated. The product remaining was dissolved in 15 ml. of water and the solution was extracted with ether. Using 5% hydrochloric acid, the *p*H was adjusted to 6, at which point carbon dioxide was evolved spontaneously from the intermediate cyanoacid; simultaneously the oily nitrile VII separated. After being heated on the steam-bath for 20 minutes to ensure complete decarboxylation, the mixture was made basic (*p*H 9) and then extracted several times with ether. Distillation of the residue remaining after removal of the solvent afforded 4.55 g. (86%) of product, b.p. 149–152° (0.1 mm.), $n^{25}D$ 1.5262.

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05. Found: C, 77.70; H, 8.04.

(12) Procedure due to Mr. G. G. Knapp.

(13) A. Windaus, W. Hückel and G. Reverey, *Ber.*, **56**, 91 (1923).

***trans*-2-(α-Picolyl)-cyclohexanecarboxylic Acid (VIII).**—The nitrile VII (1.0 g., 0.005 mole) was refluxed for 10 hr. with 5 ml. of concentrated hydrochloric acid diluted with 2 ml. of water. After neutralization (*p*H 6.5–7.5) of the acid solution with 20% sodium hydroxide, a white solid precipitated, which was filtered off and dried. The yield of product was 1.07 g. (95%), melting at 137.5–139.0°. Recrystallization from aqueous ethanol did not raise the melting point.

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82. Found: C, 71.16; H, 7.73.

The same acid could be obtained through direct hydrolysis of the cyano ester VI. Six and forty-five hundredths grams (0.0237 mole) of the latter compound was dissolved in 15 ml. of concentrated hydrochloric acid diluted with 25 ml. of water, and the solution was refluxed for 20 hr. After neutralization of the hot reaction mixture with 20% sodium hydroxide (*p*H approximately 6), evolution of carbon dioxide was observed; refluxing was continued at *p*H 7 in order to effect complete decarboxylation. The *p*H was again brought to 6, and the water was removed by evaporation on a steam-bath. The solid remaining was then extracted with acetone, and the extracts were taken to dryness. Recrystallization of the solid from aqueous methanol gave 1.0 g. (20%) of crystalline product, m.p. 130–132° (with previous softening at 129°). No depression of melting point was observed on admixture with the acid obtained from the nitrile VII.

13,14-*trans*-9-Keto-11-azatetradecahydroanthracene (IX).—Two grams (0.00913 mole) of *trans*-2-(α-picolyl)-cyclohexanecarboxylic acid (VIII), dissolved in a mixture of pure ethanol (25 ml.), concentrated hydrochloric acid (5 ml.) and water (20 ml.), was reduced catalytically over 100 mg. of Adams catalyst in a low pressure shaker at room temperature. Within 16 hr. three moles of hydrogen had been taken up and the consumption had ceased. After removal of the catalyst by filtration and concentration of the solution to one-third of original volume, 20% sodium hydroxide was added to neutrality. The oil which slowly separated was taken up in ether. After standing for three days the aqueous solution deposited an additional quantity of liquid, which presumably was the lactam IX formed by the further, slow cyclization of the unisolated piperidylmethylcyclohexanecarboxylic acid. The ether extract of this material was combined with that previously obtained, and, after evaporation of the solvent, the product was distilled. Nine-tenths of a gram of lactam, b.p. 126–130° (0.15 mm.), was obtained, which constituted a 47% yield.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21. Found: C, 75.07; H, 9.58.

11-Azatetradecahydroanthracene (X).—A solution of 0.690 g. (0.00334 mole) of lactam IX in 50 ml. of absolute ether was added dropwise to a rapidly stirred suspension of 0.3 g. (0.079 mole) of lithium aluminum hydride in 25 ml. of absolute ether. The suspension was then stirred for 1 hr. About 10 ml. of water was added to decompose the excess hydride, which was followed by 10 ml. of 5% aqueous sodium hydroxide. The ether layer and three ethereal extracts of the aqueous basic phase were combined and concentrated to a volume of about 10 ml. The organic base was then extracted with 5% hydrochloric acid; the acid extract was neutralized; and the free amine was again extracted with ether. Sublimation of the crude solid remaining after evaporation of the solvent gave 0.30 g. (46%) of product (m.p. 44–48°), which came over at *ca.* 80° (0.3 mm.) (bath temperature). The infrared spectrum of the solid indicated no–NH absorption and no indication of carbonyl groupings. It is evident, on the basis of the melting point range, that the material is a mixture, probably of diastereomers isomeric around the 12-position.

Anal. Calcd. for $C_{13}H_{23}N$: C, 80.76; H, 11.99. Found: C, 80.69; H, 11.51.

A picrate was prepared by adding 1 ml. of saturated ethanolic picric acid to a solution of 30 mg. of the amine X in 1 ml. of ethanol. The crystalline salt was recrystallized four times from absolute ethanol, after which it melted at 162.5–164.5°.

Anal. Calcd. for $C_{13}H_{23}N \cdot C_6H_3N_3O_7$: C, 54.02; H, 6.02. Found: C, 54.24; H, 6.31.

Addition of α-Picoline Methiodide to Acrylonitrile.—α-Picoline methiodide (2.0 g., 0.0085 mole) and acrylonitrile (5 ml., 0.075 mole) were dissolved in 25 ml. of absolute meth-

anol containing approximately 2 mg. of sodium methoxide. After refluxing 12 hr., the solution was neutralized and concentrated to a small volume. A solid product remained, which, after being recrystallized from ethanol, melted at 139.5–140.5° (34% yield). The analysis and infrared absorption spectrum (pyridinium ring[14] and nitrile absorption) indicated the substance to be the 1:2 (picoline methiodide: acrylonitrile) condensation product.

Anal. Calcd. for $C_{13}H_{16}N_2I$: C, 45.73; H, 4.73. Found: C, 46.15; H, 4.78.

Addition of α-Picolyl Sodium to 1-Cyanocyclohexene.—To an ether suspension of sodium amide freshly prepared from 2.3 g. of sodium and liquid ammonia there was added dropwise 10.2 g. of 1-cyanocyclohexene dissolved in 20 ml. of dry ether. The addition was carried out over a period of 1 hr. in a system protected from atmospheric moisture. After being refluxed for 18 hr., the mixture was cooled to room temperature, poured into an ice–water mixture and neutralized with dilute hydrochloric acid. Ether extraction, followed by a sodium bicarbonate wash, drying and removal of ether yielded a residue, the fractionation of which gave a forerun of recovered α-picoline and 1.0 g. of product, b.p. 150–162° (0.4 mm.), $n^{25}D$ 1.5100. The boiling point range and analysis indicated a mixture of isomers, which was not separated but which appeared to consist of 1:2 (picoline:1-cyanocyclohexene) condensation products.

Anal. Calcd. for $C_{20}H_{25}N_3$: C, 78.13; H, 8.20. Found: C, 78.26; H, 8.20.

MADISON, WISCONSIN

(14) Mr. John Baran of this Laboratory has shown that the N-alkyl pyridinium ring exhibits bands at 6.18, 6.36 and 6.61 μ in the infrared, whereas the pyridine system absorbs at 6.29, 6.38 and 6.78 μ.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

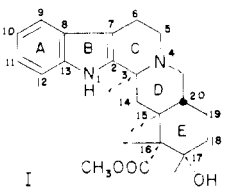
The Stereospecific Synthesis of *dl*-Yohimbane. Stereochemistry of Yohimbine[1]

BY EUGENE E. VAN TAMELEN, MAURICE SHAMMA AND PAUL ALDRICH

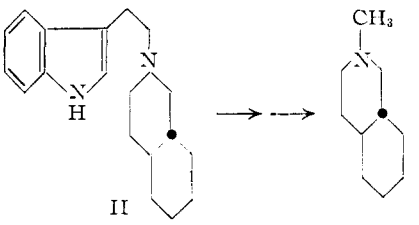
RECEIVED APRIL 26, 1956

Proceeding from *dl-trans*-2-hydrindanone, the stereospecific synthesis of *dl*-yohimbane establishes the D/E ring juncture of the parent natural product yohimbine (I),[2] as *trans*.

The stereochemical relationships expressed in the formula I for yohimbine are based[3] upon (1) certain eliminations and epimerizations bearing configurational significance which the alkaloid or closely related substances undergo,[3a-c] and (2) the Hofmann degradation of dihydro*chano*desoxyyohimbol (II) to *d*-N-methyl-*trans*-decahydroisoquinoline, a result which was taken[3d] to indicate a *trans* D/E ring juncture for yohimbine itself. The base II results from the catalytic hydrogenation of *chano*desoxyyohimbol, an unusual product obtained by heating yohimbic acid at 280° *in vacuo* with either thallous oxide or carbonate.[3d] Now the position of the double bond in *chano*desoxyyohimbol remains uncertain; and it is clear that its termination at C_{15} (or C_{20})—a distinct possibility in view of the drastic treatment required for its production—invalidates any configurational deductions which can be made regarding the *chano* base and therefore the D/E juncture of yohimbine, since the stereochemical outcome of the reduction to II would not be clear. Because of the ambiguities[4] involved in assigning, on the basis of rela-



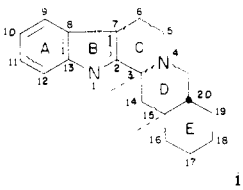
I



II

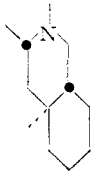
(1) First reported in a Communication to the Editor, THIS JOURNAL, **76**, 950 (1954).

(2) In the interests of rational nomenclature we wish to propose the generic term *yohimbane* for the ring system (i) and that substances

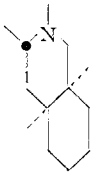


i

possessing this 3,15,20-*cis*,*trans*-pentacyclic system be named as derivatives of yohimbane. We suggest further that the system featuring the 3,15,20-all-*cis* arrangement (ii) be designated as *alloyohimbane* and that the epimers at C_3 of (i) and (ii) be termed, respectively, *epiyohimbane* (iii) and *epialloyohimbane* (iv). Finally, it seems worthwhile to continue application (*cf.* C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St. André, *Experientia*, **11**, 303 (1955)) of the configurational conventions used commonly in the steroids series, *viz.*, α-, signifying a substituent placed below the plane of the fused system (dotted line); and β-, denoting a substituent attached above the plane (solid line). Formula (i) features an α-oriented C_3-hydrogen, a choice in keeping with the absolute stereochemical assignment made by Klyne, *Chem. and Ind.*, **14**, 1032 (1954).



iii



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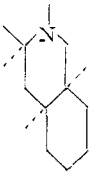

ii

Thus yohimbine becomes, systematically, 16α-carbomethoxy-17α-hydroxyyohimbane; and reserpine, 11,17α-dimethoxy-16β-carbomethoxy-18β-(3′,4′,5′-trimethoxybenzoyloxy)-*epi*alloyohimbane.

(3) (a) G. Stork, as quoted by B. Witkop and S. Goodwin, THIS JOURNAL, **75**, 3371 (1953); (b) M.-M. Janot, R. Goutarel, A. LeHir, M. Armin and V. Prelog, *Bull. soc. chim.*, 1085 (1952); (c) R. Cookson, *Chem. and Ind.*, **15**, 337 (1953); (d) B. Witkop, THIS JOURNAL, **71**, 2559 (1949).

(4) See, for example, W. G. Dauben, R. C. Tweit and C. Mannerskantz, *ibid.*, **76**, 4420 (1954).