with 20 ml. of water and passed over a column of 5 g. of Dowex 2 in the hydroxide form (20–50 mesh). The column was washed with water until the effluent was neutral. The glutamic acid was eluted with 0.25 *N* hydrochloric acid. Five-ml. fractions were collected and the fractions giving a positive ninhydrin test (usually fractions 5 through 9) were combined, the solvent was evaporated in vacuum and the crystalline residue was freed from excess hydrochloric acid by repeated additions and evaporations of 5-ml. portions of water. After drying in a vacuum desiccator over phosphorus pentoxide and potassium hydroxide the material was weighed and the optical rotation in 6 *N* hydrochloric acid determined. In order to show that the decrease in the specific rotation of the glutamic acid was caused by the alkaline treatment of the esters, hydrolysis to glutamic acid was also brought about by refluxing carbobenzoxy-L-glutamine methyl ester without prior treatment with alkali. The yields of glutamic acid averaged 93%. The glutamic acid obtained from alkaline de-esterification of carbobenzoxy-L-glutamine methyl ester had a specific rotation of $[\alpha]^{24}D$ +14.2° (*c* 1 in 6 *N* hydrochloric acid) and, from carbobenzoxy-L-isoglutamine methyl ester, $[\alpha]^{24}D$ +17.1° (*c* 1 in 6 *N* hydrochloric acid). Acid hydrolysis of carbobenzoxy-L-glutamine methyl ester yielded glutamic acid with a specific rotation of $[\alpha]^{24}D$ +30.0° (*c* 1 in 6 *N* hydrochloric acid) and carbobenzoxy-DL-α-aminoglutarimide, $[\alpha]^{24}D$ 0° (*c* 1 in 6 *N* hydrochloric acid).

Growth Response of *Lactobacillus plantarum* to DL-Aminoglutarimide.—The general procedure used has been described previously.[11] In the synthetic medium DL-aminoglutarimide was substituted for L-glutamic acid. A lag phase of from 4 to 6 hours was observed. This is similar to that obtained with L-glutamine.[11] The maximum amount of growth obtained with DL-α-aminoglutarimide at *p*H 6.1 was only 20–30% of that given by an equivalent amount of L-glutamine. A small increase in the maximum amount of growth could be obtained with the imide, by raising the *p*H of the growth medium, by increasing its buffering capacity, or by storing the growth medium at 35° prior to inoculation.

Acknowledgment.—We wish to thank Mrs. Carole B. Karash for technical assistance and Dr. R. S. Shallenberger for the statistical analysis.

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GENEVA, NEW YORK

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

New Total Synthesis of *dl*-Alloyohimbane and *dl*-Epialloyohimbane and their 11-Methoxy Derivatives

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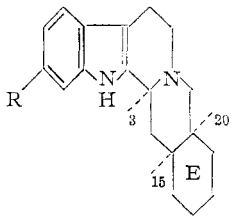
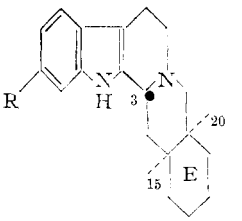
Racemic alloyhimbane and epialloyohimbane and the 11-methoxy analogs have been prepared by a series of facile reactions. The key bicyclic (ring DE) intermediate, a *cis*-fused decahydroisoquinoline-3-carboxylic acid, was obtained by hydrogenation of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid using rhodium-on-alumina catalyst.

This paper describes a convenient synthesis of *dl*-allo- and epialloyohimbane (I and II) and the corresponding 11-methoxy derivatives (Ia and IIa). The starting point for this synthesis was 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid which constitutes the potential D and E rings of the pentacyclic bases. Since these pentacyclic ring systems occur as the nuclei of reserpine,[1a] deserpidine[1b] and related alkaloids, it is important to be able to prepare such systems by a general unequivocal method capable of producing ring E substituted derivatives for pharmacological evaluation.



I, R = H
Ia, R = —OCH_3



II, R = H
IIa, R = —OCH_3

Previously the pentacyclic bases *dl*-alloyohimbane (I) (C_3, C_{15}, C_{20} *cis*) and its isomer epialloyohimbane (II) (C_3 *trans;* C_{15}, C_{20} *cis*) have been obtained through total synthesis by Stork and Hill[2] and through partial synthesis by Wenkert and Liu[3] as well as by LeHir, Janot and Goutarel.[4] Racemic 11-methoxyalloyohimbane (Ia) has been prepared by E. E. van Tamelen, *et al.*,[5a] and Huebner, *et al.*[1b] Huebner[5b] has shown that prolonged acid treatment of this allo isomer provides *dl*-11-methoxyepialloyohimbane as the major product.

Our approach to a general synthesis depended upon the unambiguous preparation of suitably substituted *cis*-decahydroisoquinolines which would serve as the D and E rings of the pentacyclic ring skeleton. Previous attempts[6] toward the preparation of these *cis* ring systems indicated that the reduction of hydroxyisoquinolines with noble metals in acetic acid proceeded to the *cis*-decahydroisoquinolines but with concomitant loss of the hydroxyl group. Hydrogenations of similar compounds over Raney nickel catalyst yielded mixtures of the stereoisomeric decahydroisoquinolines.[7]

In the present work the desired *cis* isomer was obtained by catalytic hydrogenation of a selected tetrahydroisoquinoline using rhodium-on-alumina catalyst. That this substance possessed the *cis* configuration in the bicyclic form was evidenced by its conversion through a series of reactions to the

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(2) G. Stork and R. Hill, THIS JOURNAL, **76**, 949 (1954); **79**, 495 (1957).

(3) E. Wenkert and L. Liu, *Experientia*, **11**, 302 (1955).

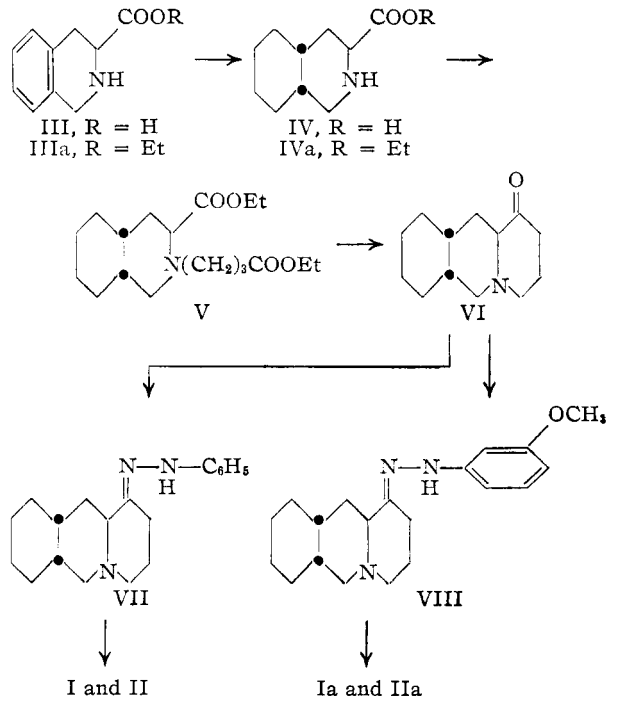
(4) A. LeHir, M. Janot and R. Goutarel, *Bull. soc. chim.*, 1091 (1952).

(5) (a) E. E. van Tamelen, P. Hance, K. Siebrasse and P. Aldrich, THIS JOURNAL, **77**, 3930 (1955); (b) C. Huebner, *Chemistry & Industry*, 1186 (1955).

(6) R. B. Woodward and W. E. Doering, THIS JOURNAL, **67**, 865 (1945).

(7) A. Pinder and A. R. Marchant, *J. Chem. Soc.*, 327 (1956).

known *dl*-allo- and epialloyohimbanes. This same procedure, with slight modifications, was employed for the facile synthesis of *dl*-11-methoxyallo- and epialloyohimbane.



When 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid[8] was hydrogenated over 5% rhodium-on-alumina catalyst at 50°, three moles of hydrogen was consumed, and the crystalline *cis*-decahydroisoquinolinecarboxylic acid IV was isolated in 41% yield.

The substituents on the tetrahydroisoquinoline molecule have a great influence on the outcome of the rhodium-on-alumina reduction, for when the corresponding ester IIIa is employed, the alcohol results and no ring reduction occurs. However, preliminary evidence shows that tetrahydroisoquinolines substituted in the aromatic portions of the molecule are reduced in the desired manner and the substituents are retained.

By a series of reactions, analogous to those employed by Swan[9] for the synthesis of yohimbone, the ethyl ester IVa was alkylated with ethyl γ-bromobutyrate yielding the diester V. Dieckmann cyclization with sodium hydride in toluene, followed by acid hydrolysis and decarboxylation, converted the diester to the tricyclic ketone, *cis*-1-keto-perhydroquinolizine (VI). The reaction of VI with phenylhydrazine and subsequent treatment of the hydrazone VII with hot ethanolic hydrochloric acid furnished the desired *dl*-allo- and epialloyohimbane (I and II) as a mixture of hydrochlorides. Basification and chromatographic separation of the mixed bases yielded the pure isomers, the allo predominating. Under Huang-Minlon reduction conditions,[10] this allo isomer was epimerized to a large extent to epialloyohimbane. The interconversion of these isomers can be explained by the acidic and basic equilibration studies of Wenkert and Liu[3] which indicate that mixtures of bases can be expected.

The *m*-methoxyphenylhydrazone, which formed readily upon treatment of the ketone VI with *m*-methoxyphenylhydrazine, underwent the Fischer indole reaction giving *dl*-11-methoxyallo- and epialloyohimbane (Ia and IIa) as a mixture of hydrochlorides. The free bases were obtained by neutralization and chromatographic separation, the major portion, as before, being the allo isomer. Again, this allo isomer under alkaline conditions was epimerized to the epiallo isomer.

The successful applications of this method to the synthesis of the pentacyclic bases are encouraging and experiments are in progress to determine the generality of this procedure for obtaining derivatives substituted at various positions in these ring systems.

During these investigations *l*-yohimbane was required for comparison studies. The ethanedithiol derivative of *l*-yohimbone was formed readily, and upon treatment with freshly prepared W-7 Raney nickel catalyst in dioxane was converted to *l*-yohimbane. Previous attempts to desulfurize *l*-yohimbone ethanethiol were reported to be unsuccessful.[11]

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Experimental

3-Carboxy-1,2,3,4-tetrahydroisoquinoline (III).—The modified procedure of Julian[8] was followed for the condensation of phenylalanine with formaldehyde to furnish the isoquinolinecarboxylic acid in 70% yield. The corresponding ethyl ester IIIa was prepared by the method of Archer.[12]

***cis*-3-Carboxydecahydroisoquinoline (IV).**—A mixture of 20 g. 3-carboxy-1,2,3,4-tetrahydroisoquinoline in 300 ml. of 50% ethanol and 5 g. of 5% rhodium-on-alumina catalyst (J. T. Baker Chemical Co.) absorbed three moles of hydrogen at 50–100° and 15 atmospheres. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo*. The product was recrystallized three times from ethanol, m.p. 256–257°, yield 8.2 g. (41%).

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.55; N, 7.64. Found: C, 65.45; H, 9.35; N, 7.46.

The hydrochloride salt was crystallized from ethanol–ether, m.p. 235–236°.

Anal. Calcd. for $C_{10}H_{17}NO_2 \cdot HCl$: C, 54.67; H, 8.26; N, 6.38. Found: C, 54.66; H, 8.49; N, 6.10.

3-Hydroxymethyl-1,2,3,4-tetrahydroisoquinoline.—A solution of 20.3 g. (0.1 mole) of ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate in 50 ml. of absolute ethanol was hydrogenated over 5 g. of rhodium-on-alumina catalyst at 50° and 50 atmospheres for 17 hours. The product was isolated by distillation followed by crystallization from benzene as colorless plates, m.p. 82–83.5°, yield 6.0 g. (36%).

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.72; H, 8.22; N, 8.49.

The hydrochloride salt was crystallized from ethanol–ether, m.p. 185–188°.

Anal. Calcd. for $C_{10}H_{13}NO \cdot HCl$: C, 60.15; H, 7.07; N, 7.02. Found: C, 59.84; H, 7.29; N, 6.78.

(8) P. Julian, W. Karpel, A. Magnani and E. Meyer, THIS JOURNAL, **70**, 182 (1948).

(9) G. A. Swan, *J. Chem. Soc.*, 1534 (1950).

(10) Huang-Minlon, THIS JOURNAL, **71**, 3301 (1949).

(11) G. A. Swan, *J. Chem. Soc.*, 659 (1952).

(12) S. Archer, *J. Org. Chem.*, **16**, 431 (1951).

Ethyl *cis*-Decahydroisoquinoline-3-carboxylate Hydrochloride (IVa).—By the procedure of Brenner and Huber,[13] 1.3 ml. of thionyl chloride in 10 ml. of absolute ethanol was allowed to react with 2.0 g. of *cis*-decahydroisoquinoline-3-carboxylic acid. Recrystallization from benzene–ether gave 1.5 g. (56%) of ester as colorless solid, m.p. 166–168°.

Anal. Calcd. for $C_{12}H_{21}NO_2 \cdot HCl$: C, 58.65; H, 9.02; N, 5.70. Found: C, 58.42; H, 8.99; N, 5.48.

Ethyl 2-(γ-Carbethoxypropyl)-*cis*-decahydroisoquinoline-3-carboxylate (V).—A mixture of 100 g. (0.475 mole) of the above ester, 92.5 g. (0.475 mole) of ethyl γ-bromobutyrate and 65.5 g. (0.475 mole) of anhydrous potassium carbonate was heated with stirring for 27 hours. The mixture was cooled, poured onto crushed ice and the mixture extracted with ether. The residue obtained on evaporation of the ether was distilled, b.p. 168–172° (0.75 mm.), $n^{25}D$ 1.4768, yield 110.6 g. (75.5%).

Anal. Calcd. for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.26; H, 9.57; N, 4.57.

***cis*-1-Ketoperhydroquinolizine (VI).**—To a suspension of 4.8 g. (0.2 mole) of sodium hydride in 25 ml. of dry toluene was added dropwise a solution of 32.5 g. (0.1 mole) of diester V in toluene over a period of 45 minutes. Following the addition, the reaction mixture was heated at reflux for 5 hours. To the stirred, cooled mixture was added cautiously 10 ml. of ethanol followed by 10 ml. of water. Concentrated hydrochloric acid (200 ml.) was then introduced, and the reaction mixture was heated under reflux for 17 hours. The mixture was evaporated to dryness *in vacuo*, the residue dissolved in 50 ml. of water and then basified with solid potassium carbonate. Ether extraction followed by drying and evaporation of the solvent left a residue which crystallized as colorless needles from absolute ethanol, m.p. 103–104°, yield 10.6 g. (51%).

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.31; N, 6.76. Found: C, 74.86; H, 10.33; N, 6.57.

The hydrochloride salt was crystallized from ethanol–ether, m.p. 208–210°.

Anal. Calcd. for $C_{13}H_{21}NO \cdot HCl$: C, 64.05; H, 9.10; N, 5.75. Found: C, 63.71; H, 9.23; N, 5.52.

***cis*-1-Ketoperhydroquinolizinephenylhydrazone (VII).**—A solution of 1.1 g. (0.01 mole) of purified phenylhydrazine and 2.0 g. (0.0096 mole) of tricyclic ketone VI in 10 ml. of absolute ethanol was heated under reflux for 2.5 hours. The mixture was evaporated *in vacuo*, and the residue was recrystallized twice from absolute ethanol–ether and obtained as yellow prisms, m.p. 127–129°, yield 1.4 g.

***dl*-Alloyohimbane and *dl*-Epialloyohimbane (I and II).**—A solution of 1.4 g. of the recrystallized phenylhydrazone of the tricyclic ketone VII in 75 ml. of absolute ethanol was saturated with dry hydrogen chloride and then heated at reflux for 3 hours. The mixture of hydrochloride salts was obtained by evaporation *in vacuo*. Careful neutralization with sodium hydroxide solution followed by ether extraction and chromatography of the residue on alumina furnished the pure *dl*-alloyohimbane and *dl*-epialloyohimbane in about a 5:1 ratio. Each of these were identical in all respects (X-ray, infrared and ultraviolet spectra, and melting points) to previously prepared bases.[14]

The allo isomer hydrochloride was obtained directly from the mixed hydrochlorides by several recrystallizations from aqueous ethanol, m.p. 294–297°.

Anal. Calcd. for $C_{19}H_{24}N_2 \cdot HCl$: C, 72.01; H, 7.95; N, 8.84. Found: C, 71.79; H, 8.11; N, 8.68.

***cis*-1-Ketoperhydroquinolizine-*m*-methoxyphenylhydrazone (VIII).**—A solution of 1.7 g. (0.0123 mole) of purified *m*-methoxyphenylhydrazine and 2.6 g. (0.013 mole) of tricyclic ketone VI in 10 ml. of absolute ethanol was heated under reflux for 2.5 hours. The mixture was evaporated *in vacuo*, and the hydrazone was recrystallized twice from 95% ethanol and obtained as yellow prisms, m.p. 119–121°, yield 1.4 g.

***dl*-11-Methoxyalloyohimbane and *dl*-11-Methoxyepialloyohimbane (Ia and IIa).**—A solution of 2.5 g. of the purified *m*-methoxyphenylhydrazone of the tricyclic ketone VIII in 75 ml. of absolute ethanol was saturated with dry hydrogen chloride and then heated at reflux for 2.5 hours. Evaporation *in vacuo* yielded the mixture of hydrochloride salts.

Employing the same isolation methods as used for *dl*-alloyohimbane furnished pure *dl*-11-methoxyalloyohimbane and *dl*-11-methoxyepialloyohimbane in a 5:1 ratio, each of which was identical in all respects to authentic samples.

Equilibration Studies. A.—A solution of 180 mg. of *dl*-alloyohimbane, 4 ml. of diethylene glycol and 500 mg. of potassium hydroxide was heated at 190–200° under a nitrogen atmosphere for one hour. The solution, which had turned slightly yellow in color, was poured into ice-water. Filtration of the precipitate and recrystallization from ethanol gave 91 mg. of *dl*-epialloyohimbane, m.p. 186–188°, *pK* 7.75, identical in every respect with a known sample. A small amount, 22 mg., of *dl*-alloyohimbane was recovered.

B.—The same conditions were followed for the equilibration of 300 mg. of *dl*-11-methoxyalloyohimbane (*pK* 7.35). The solution, much darker in color in this experiment, was poured into ice-water, and the precipitate collected on a filter. After recrystallization from methanol, 110 mg. of *dl*-11-methoxyepialloyohimbane was obtained, m.p. 203–205°, *pK* 7.90. In this case also, a small amount of starting material was obtained.

***l*-Yohimbone Ethanedithiol.**—Dry hydrogen chloride was bubbled into a cold solution of 1.0 g. of *l*-yohimbone and 5 ml. of ethanedithiol in 40 ml. of glacial acetic acid for 15 minutes, and the reaction mixture was allowed to remain at room temperature overnight. The product was removed by filtration, added to water and basified with ammonium hydroxide solution to liberate the free base as a colorless solid, m.p. 158–161°, yield 1.03 g.

Anal. Calcd. for $C_{21}H_{26}N_2S_2$: N, 7.56. Found: N, 7.27.

***l*-Yohimbane.**—A mixture of 200 mg. of the ethanedithiol derivative, 50 ml. of purified dioxane and 2 ml. of a dense Raney nickel suspension (freshly prepared W-7) was stirred and heated at reflux for 16 hours. The catalyst was removed by filtration, and the filtrate evaporated *in vacuo*. Chromatography of the residue on alumina furnished 60 mg. of *l*-yohimbane, m.p. 207–208°, identical with material obtained by Huang-Minlon reduction conditions on *l*-yohimbone.

INDIANAPOLIS, INDIANA

(13) M. Brenner and W. Huber, *Helv. Chim. Acta*, **36**, 1109 (1953).

(14) Authentic samples were kindly supplied by Drs. E. Wenkert and E. van Tamelen.