[CONTRIBUTION FROM THE NEW YORK STATE AGRICULTURAL EXPERIMENT STATION, CORNELL UNIVERSITY]

Imides from Asparagine and Glutamine. II. α-Aminoglutarimide[1]

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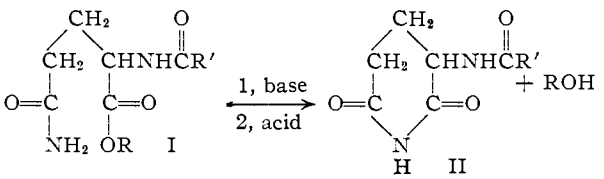
Hydrogenolysis of carbobenzoxy-DL-α-aminoglutarimide in the presence of hydrochloric acid yields DL-α-aminoglutarimide hydrochloride. Some of the properties of this compound are described. With weaker bases than those previously employed, the cyclization of carbobenzoxy-L-glutamine methyl ester gives carbobenzoxy-α-aminoglutarimide with partial retention of configuration. Treatment of the methyl esters of carbobenzoxy-L-glutamine and carbobenzoxy-L-isoglutamine with aqueous sodium hydroxide followed by hydrogenolysis gives mixtures of partially racemized glutamine and isoglutamine. This reaction was studied quantitatively.

Normally, treatment of N-acylamino acid esters with alkali yields the alcohol and a salt of the acylamino acid. However, the alkaline hydrolysis of N-acylasparagine and N-acylglutamine esters (I) is complicated by the ease of cyclization of these compounds to succinimide and glutarimide derivatives (II).[2-4] Alkaline hydrolysis of these imides



leads to opening of the imide rings in both possible ways. Thus, the over-all process of alkaline hydrolysis gives mixtures of products and is, in the case of the glutamine derivative, further complicated by racemization.[2,3] Because of the possible significance of these reactions during peptide synthesis and the cleavage of peptide chains,[3] studies of the reactions and of the properties of the imides are of importance.

As reported earlier,[2] hydrogenolysis of carbobenzoxy-DL-α-aminoglutarimide does not give pure α-aminoglutarimide. The hydrogenolysis product turns violet when exposed to air and becomes more intensely colored during storage at room temperature after evaporation of the solvent. That an aqueous solution of this mixture still contained large amounts of unchanged aminoglutarimide could be shown by paper chromatography. The solution had one broad absorption band in the visible region with a peak at 560 mμ, $E^{1\%}_{1cm}$ 60. The solution could be decolorized by catalytic hydrogenation or by treatment with sodium hydrosulfite. It seems likely that the pigment is a conversion product of aminoglutarimide, possibly formed by aerobic oxidation.

When the hydrogenolysis of the carbobenzoxy-DL-α-aminoglutarimide was carried out in the presence of a slight excess of hydrochloric acid, colorless, crystalline, water-soluble DL-α-aminoglutarimide hydrochloride was obtained. The hydrochloride has much less of a tendency to give the violet material and is not as readily hydrolyzed in water to glutamine and isoglutamine as the free aminoglutarimide. Hydrolysis of the imide with hot hydrochloric acid yielded DL-glutamic acid. When heated on a micro-hot-stage aminoglutarimide hydrochloride did not melt, but changed above 220° to a violet material which sublimed. The imide can be chromatographed on paper with water-saturated phenol, R_f 0.9, and with *n*-butyl alcohol, acetic acid and water (4:1:5), R_f 0.2. With ninhydrin it gives a salmon-red color, which exhibits an absorption maximum at 523 mμ in 95% ethanol.

The conditions previously used[2] to prepare carbobenzoxy-α-aminoglutarimide from carbobenzoxy-L-glutamine methyl ester gave completely racemized material. Since the formation of the imide from carbobenzoxyglutamine methyl ester does not involve direct reaction on the asymmetric carbon atom, it seemed possible that ring closure might be effected without racemization, if cyclization were catalyzed by the weakest base possible. No imide formation could be detected with triethylamine as the base. But by using equivalent amounts of ester and sodium methoxide in methanol at 0°, optically active carbobenzoxy-α-aminoglutarimide, $[\alpha]^{24}D$ −24.6° (*c* 1, methanol), was obtained. Imide with somewhat higher rotation, $[\alpha]^{24}D$ −35.3° (*c* 1, methanol), could be prepared by the addition of an equivalent amount of N-methylacetamide to the sodium methoxide. This effect of N-methylacetamide is attributed to its ability to lower the base strength. On the other hand, with excess sodium methoxide in methanol the optical rotation of the imide was lower, $[\alpha]^{24}D$ −10.7° (*c* 1, methanol). By hydrogenolysis of carbobenzoxy-α-aminoglutarimide which had a rotation of $[\alpha]^{24}D$ −35.3° (*c* 1, methanol) optically active α-aminoglutarimide hydrochloride was obtained, $[\alpha]^{24}D$ −53.5° (*c* 1, methanol). Acid hydrolysis to glutamic acid showed that approximately 40% of the material has been converted to the racemic form. The purity of these optically active preparations was checked chromatographically and by analysis.

We have shown earlier that treatment of carbobenzoxy-L-glutamine methyl ester and carbobenzoxy-L-isoglutamine methyl ester with aqueous sodium hydroxide does not lead to the isolation of an imide.[2] However, evidence for intermediate imide formation was obtained since alkaline hydrolysis followed by hydrogenolysis gave a mixture of glutamine and isoglutamine from either ester. In order to determine what fraction of the ester was hydrolyzed by way of the imide, the ratio of glutamine

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TABLE I

PRODUCTS FROM ALKALINE HYDROLYSIS FOLLOWED BY HYDROGENOLYSIS

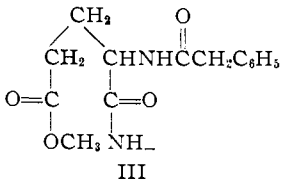
	Yield glutamine Mg.	σ	Yield isoglutamine Mg.	σ	Ratio glutamine/ isoglutamine	Hydrolysis through the imide, %	Racemization, %
Carbobenzoxy-DL-α-aminoglutarimide[a]	10.52[c]	1.54	2.24	0.84	4.7:1	..	..
Carbobenzoxy-L-glutamine methyl ester[b]	10.60[d]	0.97	2.25	.71	4.7:1	100	53
Carbobenzoxy-L-isoglutamine methyl ester[b]	8.34[e]	1.40	4.17	.58	2.0:1	80	43

[a] From 26.2 mg. of imide. [b] From 29.4 mg. of ester. [c] Mean of 14 determinations. [d] Mean of 23 determinations. [e] Mean of 11 determinations. σ Standard deviation. By the use of Student's t test it could be shown that the yields of glutamine and isoglutamine from carbobenzoxy-L-glutamine methyl ester and carbobenzoxy-DL-α-aminoglutarimide were not significantly different and that yields of the products from carbobenzoxy-L-isoglutamine methyl ester were different at the 99% level from those obtained with the other two compounds.

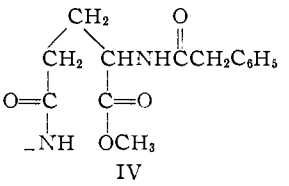
to isoglutamine, obtained after alkaline hydrolysis and hydrogenolysis, was determined by quantitative paper chromatography. By comparing these values to the ratio of glutamine to isoglutamine obtained on alkaline hydrolysis and hydrogenolysis of carbobenzoxy-DL-aminoglutarimide, the contribution that imide formation makes to the total hydrolysis of the esters could be calculated. Information on the extent of racemization during aqueous alkaline hydrolysis was also obtained. The results are summarized in Table I.

The hydrolysis and hydrogenolysis of carbobenzoxyaminoglutarimide yielded predominantly glutamine. This was the expected result since the lower electron density of the carbonyl group closest to the carbobenzoxyamido group favors attack by the hydroxyl ions at that site.[5]

The greater participation of the imide in the total de-esterification of carbobenzoxy-L-glutamine methyl ester as compared with carbobenzoxy-L-isoglutamine methyl ester is most likely due to differences in the nucleophilic character of the amide anions III and IV. The more nucleophilic the



III



IV

amide anion, the greater the extent of imide formation,[6] since competition between the anion and hydroxyl ion determines the proportion of hydrolysis through the imide for each ester. The location of the carbobenzoxyamido group would be expected to make III less nucleophilic than IV and therefore imide formation would be favored with IV.

De-esterification of the two esters with aqueous sodium hydroxide is accompanied by partial racemization. Of the various species present it would appear most likely that only the intermediate carbobenzoxy-α-aminoglutarimide is subject to racemization. This assumption is in accord with the experimental data. From Table I it is seen that the percentage hydrolysis through the imide is 20% greater for carbobenzoxy glutamine methyl ester than for the iso compound and that the extent of racemization is increased by an almost identical amount, 19%.

A comparison of the properties of the imides from glutamine and asparagine shows a number of similarities but also pronounced differences in behavior. Alkaline hydrolysis of aminosuccinimide, aminoglutarimide and their carbobenzoxy derivatives yields predominantly asparagine and glutamine and only smaller amounts of isoasparagine and isoglutamine. In respect to imide formation the carbobenzoxy amido esters of aspartic acid and glutamic acid also exhibit some similarity since with the normal amides as well as the iso compounds, imide formation was favored over normal saponification.

In common with the unsubstituted 5- and 6-membered cyclic imides[7] α-aminoglutarimide is much more rapidly hydrolyzed in alkali than aminosuccinimide. This difference in the rate of hydrolysis is explained by the generalization of Brown, Brewster and Schechter[8] that 6-membered rings with exo double bonds appear to be generally less stable and more susceptible to ring opening than 5-membered rings of this kind. Another striking difference in the behavior of the imides from asparagine and glutamine derivatives is that carbobenzoxy-α-aminoglutarimide is much more easily racemized than carbobenzoxyaminosuccinimide. This observation also seems to be in accord with the above generalization[8] since enolization should be favored in the 6-membered ring.

Another difference in the behavior of the two imides is that pigment formation has been observed only with aminoglutarimide and not with the 5-membered analog. Possibly this is also related to differences in the ring size since dehydrogenation of aminoglutarimide could lead to 2,6-dihydroxypyridine derivatives, compounds known to be oxidized to colored products.[9]

It seemed of interest to obtain some information on the growth response of a biological system to aminoglutarimide. The utilization of DL-α-aminoglutarimide by *Lactobacillus plantarum* var. *arabinosus* in glutamic acid-free, synthetic medium was therefore investigated. The growth response obtained was somewhat similar to that of glutamine. However, the amount of cell growth obtained per microgram imide was much less than that given by an equivalent quantity of glutamine. It was

(5) Similar results were obtained by Clayton, Kenner and Sheppard[4] who reported that the alkaline hydrolysis of the imide from benzoyl-DL-glutamylglycine cyclohexylamide yielded 85% of the γ-isomer and 13% of the α-compound.

(6) Differences in the electrophilic character of the carbomethoxy groups of the two esters might be expected to have little effect on the extent of de-esterification through saponification or imide formation, since both these processes are competing for the same carbomethoxy group.

(7) S. S. G. Sircar, *J. Chem. Soc.*, 600, 1252 (1927).

(8) H. C. Brown, J. H. Brewster and H. Schechter, THIS JOURNAL, **76**, 467 (1954).

(9) G. Errera, *Ber.*, **31**, 1241 (1898).

found, though, that cell growth could be increased somewhat by increasing the initial *p*H of the medium, by increasing its buffer capacity or by adding the imide to the medium several hours before inoculation. Since *L. plantarum* produces acids during growth these observations indicate that hydrolysis precedes utilization of the imide. It was therefore concluded that DL-α-aminoglutarimide is not utilized as such, that it is not a potent growth inhibitor and that the observed growth is due to non-enzymatic hydrolysis of the imide to glutamine and isoglutamine.

Experimental[10]

Reaction of Carbobenzoxy-DL-α-aminoglutarimide with Ammonia.—To 100 mg. of carbobenzoxy-DL-α-aminoglutarimide was added with shaking 2 ml. of 28% aqueous ammonia. The product started to precipitate before all the starting material had dissolved. The mixture was filtered after overnight storage at room temperature. The yield of carbobenzoxy-DL-glutamic acid diamide was 77 mg. (71%), m.p. 181–183°, m.p. was unchanged by recrystallization from aqueous dimethylformamide or from 95% ethanol.

Anal. Calcd. for $C_{13}H_{17}N_3O_4$: N, 15.05. Found: N, 14.8.

Hydrogenolysis of Carbobenzoxy-DL-α-aminoglutarimide. (a) In the Absence of Acid.—A mixture of 200 mg. of carbobenzoxy-DL-α-aminoglutarimide in 5 ml. of methanol and 50 mg. of palladium black was shaken with hydrogen at room temperature for 2 hours. During the filtration the solution turned violet. Evaporation of the solvent in vacuum yielded crystals which were tinted violet at the surface, m.p. approximately 120° with decomposition to a violet solid. Storage of the hydrogenolysis product at room temperature caused a measurable increase in the color intensity. The amount of pigment could be increased further by periodically dissolving the material in water and evaporating the solvent in vacuum. In 13 days $E^{1\%}_{1\,cm.}$ at 560 mμ in water increased from 0.75 to 60. However, the preparation still consisted predominantly of unchanged aminoglutarimide. An aqueous solution of this mixture could be decolorized by hydrogenation with palladium black at room temperature and atmospheric pressure, with nitrous acid, and with sodium hydrosulfite. Cupric nitrate precipitates the colored material. DL-α-Aminoglutarimide hydrolyzes slowly at room temperature in aqueous solution to a mixture of glutamine and isoglutamine.

(b) In the Presence of Hydrochloric Acid.—Hydrogen was bubbled at room temperature and atmospheric pressure through a mixture of 1.05 g. of carbobenzoxy-DL-α-aminoglutarimide in 4.1 ml. of 0.99 *N* hydrochloric acid and 15 ml. of methanol in the presence of 200 mg. of palladium black. Sufficient water was added during the hydrogenolysis to keep the product in solution. After 1.5 hours the mixture was filtered and the filtrate concentrated in vacuum below 50° to 5 ml. On the addition of 20 ml. of *n*-propyl alcohol and storage overnight at 0° the product crystallized, yielding 0.565 g. (86%) of DL-α-aminoglutarimide hydrochloride. The latter was recrystallized in 70% yield on the addition of 15 ml. of propanol to the filtrate from 0.550 g. of crude product in 3.5 ml. of water. The compound, which does not melt, is changed to a violet, water-insoluble material above 220°. The hydrochloride is optically inactive and forms no more than traces of violet material on storage at room temperature for 12 months; the amino group has a pK_a 6.8 in water.

Anal. Calcd. for $C_5H_8N_2O_2 \cdot HCl$: C, 36.49; H, 5.51; N, 17.02; neut. equiv., 164.6. Found: C, 36.75; H, 5.87; N, 16.75; neut. equiv., 166.

Preparation of Optically Active Carbobenzoxy-α-aminoglutarimide.—Under the previously described conditions for cyclization[2], sodium methoxide in benzyl alcohol, only racemized imide was obtained. Therefore the cyclization was attempted under milder conditions.

Refluxing 294 mg. of carbobenzoxy-L-glutamine methyl ester with 5 ml. of triethylamine for 2 hours yielded only unchanged starting material. Since the ester was only partially soluble in the hot triethylamine, the cyclization attempt was repeated with a mixture of 1,4-dioxane and triethylamine. Again only unchanged ester was obtained after reflux.

Optically active imide was obtained by adding at 0°, 294 mg. of carbobenzoxy-L-glutamine methyl ester to a solution of 1.5 ml. of methanol containing sodium methoxide from 23.0 mg. of sodium. After 15 minutes at 0°, 0.1 ml. of acetic acid was added followed by 10 ml. of water. The mixture was stored at 0° overnight, yielding 230 mg. (84%) of carbobenzoxy-α-aminoglutarimide, m.p. 134–136° (transition 121°), $[\alpha]^{24}D$ −24.6° (*c* 1, methanol).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.33; N, 10.7. Found: C, 59.15; H, 5.19; N, 10.3.

Under similar conditions the addition of one equivalent of N-methylacetamide to this system gave imide with a somewhat higher rotation, $[\alpha]^{24}D$ −35.3° (*c* 1, methanol).

Preparation of Optically Active α-Aminoglutarimide Hydrochloride.—Hydrogen was bubbled at room temperature and atmospheric pressure for two hours through a mixture of 80 mg. of carbobenzoxy-α-aminoglutarimide, $[\alpha]^{24}D$ −35.3° (*c* 1, methanol), in 5 ml. of methanol and 0.5 ml. of 1 *N* hydrochloric acid plus 30 mg. of palladium black. The mixture was filtered, the catalyst washed with methanol and the combined washings and filtrate concentrated in vacuum. The yield of crystalline α-aminoglutarimide hydrochloride was 44.7 mg., 87% of the theoretical yield, $[\alpha]^{24}D$ −53.5° (*c* 1, methanol). By chromatographic analysis the material was shown to be indistinguishable from the racemized product and was practically free of glutamine and isoglutamine. It was recrystallized from aqueous solution by the addition of *n*-propyl alcohol for analysis.

Anal. Calcd. for $C_5H_8N_2O_2 \cdot HCl$: C, 36.49; H, 5.51; N, 17.02. Found: C, 36.76; H, 5.66; N, 17.2.

A solution of 68.3 mg. of the above α-aminoglutarimide hydrochloride in 2 ml. of 6 *N* hydrochloric acid was refluxed 3 hours, cooled and the volume adjusted to 5 ml. with 6 *N* hydrochloric acid. The resulting glutamic acid solution had a specific rotation of $[\alpha]^{24}D$ +18.4° (*c* 1.2 in 6 *N* hydrochloric acid), indicating approximately 40% conversion to the racemic form.

Alkaline Hydrolysis of Carbobenzoxy-L-glutamine Methyl Ester, Carbobenzoxy-L-isoglutamine Methyl Ester and Carbobenzoxy-DL-α-aminoglutarimide.—The addition of 1.1 ml. of 0.97 *N* sodium hydroxide to 29.4 mg. of ester or 26.2 mg. of imide (0.1 millimole) caused the compounds to go rapidly into solution. After storage at room temperature for 2 hours the solution was acidified with 1.15 ml. of 0.97 *N* hydrochloric acid, 15 mg. of palladium black was added and hydrogen was bubbled through the mixture at room temperature for one hour. The mixture was filtered, the catalyst washed with water and the combined washings and filtrate made up to 10 ml. Aliquots of 5, 10 and 20 microliters were chromatogramed on Whatman No. 1 paper for 16 hours with *n*-butyl alcohol, acetic acid and water (4:1:5). The papers were dried at room temperature. The amino acid spots were detected by spraying with a 1% ninhydrin solution in 95% ethanol containing 2% collidine–lutidine mixture (1:3) and developed for one hour in a 40° cabinet through which water-saturated air was passed. Immediately after development the spots were cut out and the pigment was extracted with 50% ethanol. After storage in the dark for one hour the optical density at 570 mμ was determined. Chromatograms with known concentrations of glutamine and isoglutamine were run with each unknown and these served for the construction of calibration curves. The only products detected were glutamine and isoglutamine. The absence of glutamic acid could be shown by chromatograming with water-saturated phenol. Hydrogenolysis of carbobenzoxyglutamine and carbobenzoxyisoglutamine gave only glutamine and isoglutamine, respectively.

Estimation of the Extent of Racemization of Carbobenzoxy-L-glutamine Methyl Ester and Carbobenzoxy-L-isoglutamine Methyl Ester during Alkaline Hydrolysis.—To 294 mg. (1 millimole) of the carbobenzoxy esters 1.2 ml. of 1 *N* sodium hydroxide was added and the solution stored at room temperature overnight. After acidification with 2 ml. of concentrated hydrochloric acid, the mixture was refluxed eight hours, cooled and extracted with benzene to remove benzyl alcohol. The aqueous phase was diluted

(10) All melting points were determined on a microscope hot-stage and are corrected. Analyses are by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England.

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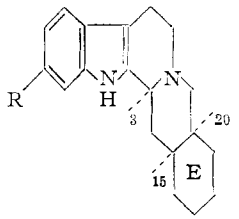
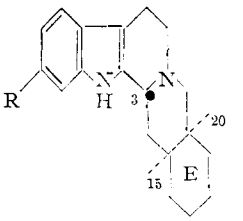
Racemic alloyhimbane and epialloyohimbane and the 11-methoxy analogs have been prepared by a series of facile reactions. The key bicyclic (ring DE) intermediate, a *cis*-fused decahydroisoquinoline-3-carboxylic acid, was obtained by hydrogenation of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid using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