remain at room temperature for 2 hr, after which time the excess reagent was removed at 50°. The crude syrup so obtained was dissolved in methylene chloride and partitioned successively between saturated sodium bicarbonate and water. The methylene chloride layer was dried over sodium sulfate and concentrated at 40°. The resulting syrup was dissolved in 200 ml of ethyl acetate (previously dried over drierite) and transferred to a Parr reaction bottle containing 1.0 g of platinum catalyst (Adam's catalyst) which had been prepared from platinum oxide and washed several times by decantation using dry ethyl acetate. Diethylamine (25 ml) was added and hydrogenation was conducted starting with a hydrogen pressure of 50 psi. When the consumption of hydrogen was complete, the catalyst was removed by filtration and the filtrate concentrated at 50°. The product so obtained was dissolved in methylene chloride and extracted three times with water. The methylene chloride layer was dried and concentrated to yield the acetylated 1,5-anhydroalditol as a syrup which was dissolved in methanol (200 ml) and treated with approximately 0.5 g of sodium. After 4 hr at room temperature, Dowex 50W-X8 (H^+) (50 ml) was added and the mixture stirred for 30 min. Removal of the resin by filtration and evaporation of the solvent afforded the free 1,5-anhydroalditol.

If appreciable reducing sugar was present (Benedict's test), the product was dissolved in 100 ml of 0.5 *N* aqueous sodium hydroxide and aerated overnight, after which time the solution was treated batchwise with 150 ml of Dowex 50W-X8 (H^+) to remove sodium ions and then with Rexyn 203 to remove organic acids. Removal of the solvent at 60° afforded the 1,5-anhydroalditol which in most cases was essentially pure and crystallized spontaneously. The yields given in Table I were estimated on the basis of the weight of the material obtained at this stage and the amount of impurity present in it as evaluated by gas chromatography carried out on the silyl and acetyl derivatives. In all cases ethanol proved to be a satisfactory solvent for recrystallization.

1,5-Anhydroribitol.—D-Ribose (5.00 g) was converted to 2,3,4-tri-*O*-benzoyl-β-D-ribopyranosyl bromide[4] which was hydrogenated as described for the acetylglycosyl halides. The product was isolated and debenzoylated using similar procedures and gave a crystalline mass which was shown by gas chromatographic analysis of the silyl derivatives to be at least 95% 1,5-anhydroribitol. Pure material was obtained by recrystallization from ethanol.

Platinum- and Palladium-Catalyzed Reductions of III and IX.—Experiments involving the reduction of III and IX by platinum were performed by prereducing platinum oxide in the solvent for the hydrogenation, then adding the compound in crystalline form. Unless otherwise stated, the ratio of compound to catalyst is 1.5–2.0:1.0 mole/mole. When the reduction was performed in the presence of a modifier, the modifier was added with the substrate after the reduction of the catalyst.

Palladium catalyst was prepared from 10% palladium chloride on charcoal by reduction in the appropriate solvent followed by filtration and washing with the solvent to remove hydrogen chloride. When the consumption of hydrogen was complete, the catalyst (platinum or palladium on charcoal) was removed by filtration and gas chromatographic analysis was conducted on the filtrate (acetyl derivatives) or on the silyl derivatives after isolation and deacetylation of the products.

1,5-Anhydro-2,3-dideoxy-4,6-*O*-benzylidene-D-*erythro*-hexitol was prepared by the procedure given by Bergmann and Breuers[5] from 1,5-anhydro-2,3-dideoxy-D-*erythro*-hexitol obtained by deacetylation of the product of the platinum–diethylamine reduction of tetra-*O*-acetyl-2-hydroxy-D-glucal (III) and tri-*O*-acetyl-D-glucal (IX). The product was recrystallized from acetone–water (1:1) and had mp 137.5–138.5° and $[\alpha]_D$ −4.1 ±0.2° (*c* 8.87, tetrachloroethylene) (lit. mp 137–137.5°, $[\alpha]^{26}_D$ 0° using a 2% solution in a 0.5-dm tube).[5]

1,5-Anhydro-2-deoxy-D-*arabino*-hexitol was prepared by catalytic deacetylation of tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hexitol (VI). The product, after several recrystallizations from ethanol–hexane, had mp 76–77° and $[\alpha]^{29}_D$ +16.4° (*c* 7.39, water). Fischer[15] reported mp 86–87° and $[\alpha]^{19}_D$ +16.37°. A sample prepared according to Fischer also had mp 76–77° alone and mixed with the isolated material.

Registry No.—II, 13137-69-4; III, 3366-47-0; IV, 13121-61-4; V, 13391-23-6; VI, 13035-12-6; IX, 2873-29-2.

(15) E. Fischer, *Ber.*, **47**, 196 (1914).

Inside Yohimbanes. The Dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine System

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The condensation of tryptamine with 2-formylcyclohexaneacetic acid produced the two *trans* epimers of 1,2,3,4,4a,5,6,8,9,14,14b,14c-dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizin-6-one. Reduction of the lactams afforded *trans,anti-* and *trans,syn*-1,2,3,4,4a,5,6,8,9,14,14b,14c-dodecahydrobenz[*a*]indolo[3,2-*h*]quinolines (**4** and **6**). By an oxidation and subsequent reduction, the *cis,syn* and *cis,anti* isomers (**9** and **11**) were obtained. The stereochemistry of the four isomers was assigned on the basis of chemical, nuclear magnetic resonance, and infrared data.

During our work on the total synthesis of yohimbane[1] we became interested in the possibility of obtaining the inside yohimbanes[2] (**4**, **6**, **9**, and **11**). This system should be available from the condensation of tryptamine (**1**) with 2-formylcyclohexaneacetic acid (**2**) and subsequent reduction of the lactam function. The acid aldehyde **2**, whose preparation has been described in our earlier work,[1] is a mixture of isomers in which the *trans* is predominant.

When the condensation of **1** and **2** was carried out in glacial acetic acid a good yield of crude lactam was obtained. Fractional crystallization afforded a 60% yield of one isomer (**3**). Reduction of lactam **3** with lithium aluminum hydride gave the first isomer (**4**) of the inside yohimbane system. The second and third crops from the crystallization of the crude lactam contained at least one more lactam, as evidenced by thin layer chromatography. Reduction of these crops, followed by column chromatography, afforded a second base (**6**) which was isomeric with compound **4** (see Scheme I).

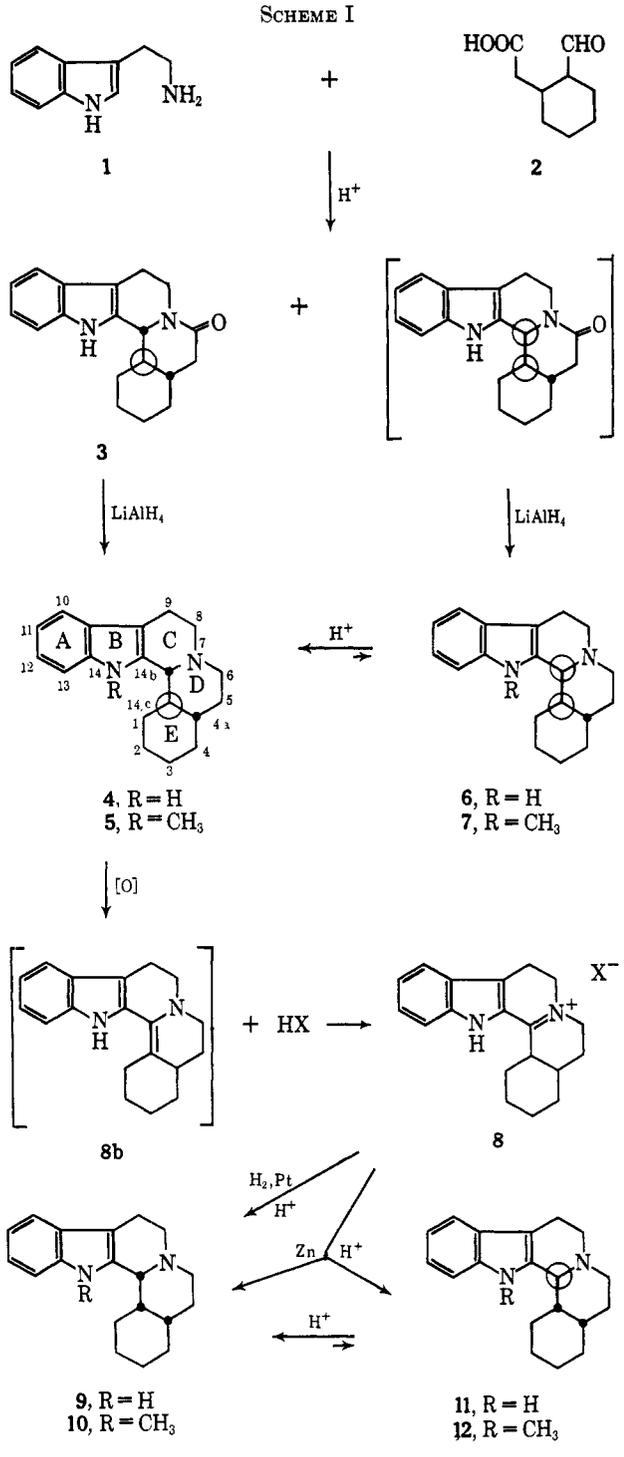
Since it did not seem feasible to obtain the other stereoisomers from the condensation, we turned to an indirect oxidation–reduction scheme. The *t*-butyl hypochlorite oxidation[3] of **4** gave the dehydro compound **8**. Since this reaction proceeds through the base of the dehydro compound (**8b**), in which there is no stereo-

(1) G. C. Morrison, W. A. Cetenko, and J. Shavel, Jr., *J. Org. Chem.*, **31**, 2695 (1966).

(2) An aromatic ring E version of this system has been described by S. Sygasawa and Y. Deguchi, *Chem. Pharm. Bull.*, **8**, 879 (1960).

(3) W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **10**, 1414 (1956).

SCHEME I



chemistry,[4] the D/E ring fusion of the salt is independent of the starting material. We have no direct evidence to decide the stereochemistry of the **8**, nor does an examination of the Dreiding models suggest an obvious solution. Catalytic reduction of **8** produced the third isomer (**9**). Zinc–acid reduction, in addition to **9**, gave the final isomer (**11**).

A priori it might be reasoned that **4** and **6** belong to the *trans* series since they are derived from a starting material consisting mostly of *trans* acid aldehyde. Therefore, the two isomers (**9** and **11**) arising from the reduction of the dehydro compound would be the *cis* epimers. To establish that these pairs are indeed epimeric we turned to the acid-catalyzed epimerization[5] of C_{14b}.

(4) In the base the double bond is in the $C_{14b,14c}$ position. See H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Org. Chem.*, **30**, 105 (1965).

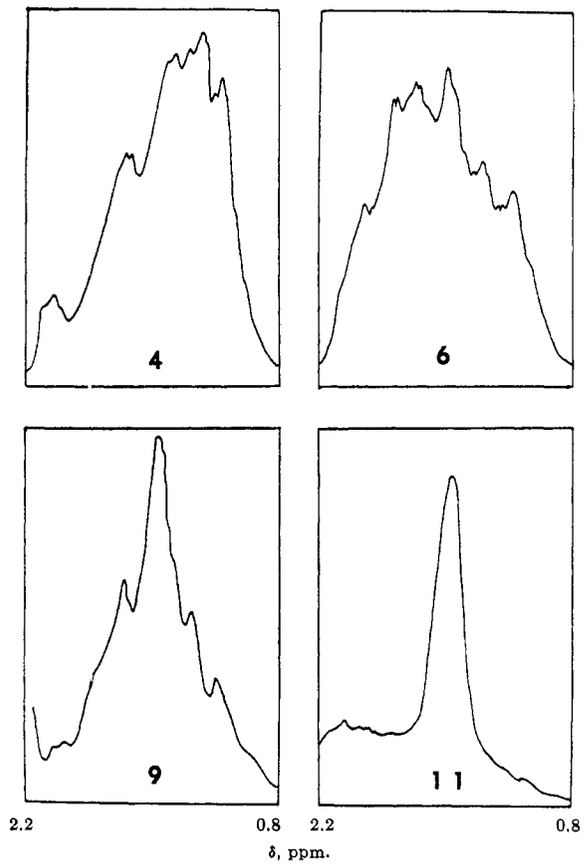


Figure 1.—Nmr spectra of the inside yohimbanes.

Experimentally we observed that either **4** or **6** was converted into a mixture[6] containing a large predominance of **4** and that **9** or **11** gave mostly isomer **9**. These data establish conclusively that **4** and **6** have a common D/E ring fusion as do **9** and **11**.

To resolve the stereochemistry of the isoquinoline ring fusion in the epimeric pairs we have utilized an extension of the observation[7] that *trans*-decalin shows a broad methylene envelope (W_H = 50 cps), whereas *cis*-decalin, owing to conformational flipping,[8] has a narrow band (W_H = 10 cps). The nuclear magnetic resonance (nmr) spectra of all four stereoisomers show an envelope of twelve hydrogens in the 0.8- to 2.2-ppm region to which we have assigned the protons of the decahydroisoquinoline system which are not α to the nitrogen.[9] Epimers **4** and **6** have envelopes of W_H = 45 and 55 cps, respectively (Figure 1), indicative of *trans* fused systems. Isomer **11** shows the characteristic *cis* envelope (W_H = 9 cps) and **9** has an intermediate width pattern (W_H = 25 cps). The variation in peak half-width is readily explainable on examination of the possible conformations for the *cis* epimers (Figure 2). All three conformations of the *cis,anti*[10] isomer have approximately the same thermodynamic stability[11] which is a

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

(6) The relative amounts of isomers were estimated from size of spots on thin layer chromatograms. The equilibration mixture of each pair showed no sign of the other two isomers.

(7) J. Musher and R. E. Richards, *Proc. Chem. Soc.*, 230 (1958).

(8) For another interpretation, see F. G. Riddell and M. J. T. Robinson, *Chem. Commun.*, 227 (1965), and references therein.

(9) Of these twelve, three are β to the nitrogen and may be slightly affected; however, this factor has been neglected in our analysis.

(10) *cis* and *trans* refer to the relationship of the hydrogens at C_{14a} and C_{14c}. *syn* and *anti* refer to the hydrogens at C_{14b} and C_{14c}.

(11) Estimated on the basis of butane gauche interactions and interference of the indole N–H with the hydrogens at C_1 in the Dreiding models.

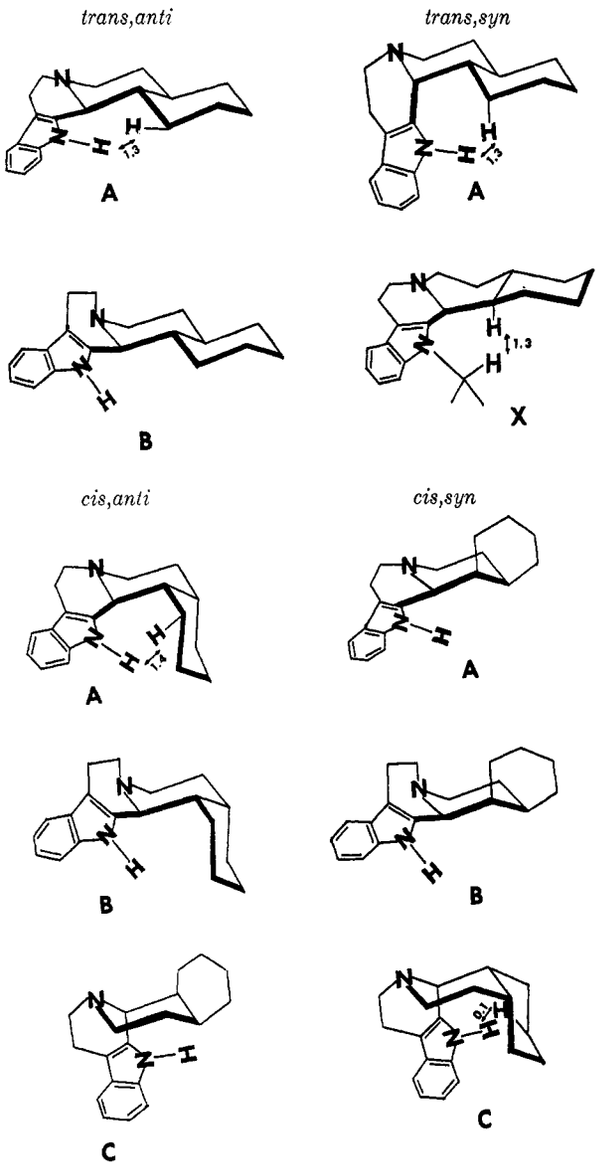


Figure 2.—Conformations of the inside yohimbanes. Distances of less than 2 A between hydrogens are noted.

prerequisite for conformational flipping. However, in the *cis,syn* system conformation A is considerably favored over B and C. Since the hydrogens of the *cis,syn* isomer will not reside equally in an axial and equatorial environment, a broadening of the pattern is to be expected. Thus, the band half-widths of **9** and **11**, in addition to determining the stereochemistry of the D/E ring fusion, also suggest the assignment of **9** as *cis,syn* and **11** as *cis,anti*.

The stereochemistry of **9** and **11** can be deduced by another independent approach. The lack of a signal in the 3.2–4.5-ppm region of the nmr spectrum of **9** is evidence for a *trans*-quinolizidine conformation.[12] This is confirmed by the presence of Bohlmann bands in the infrared spectrum[13] (Figure 3). Since the *trans,syn* configuration does not have a *trans*-quinolizidine conformation it is eliminated as a possibility for **9**. However, the other three configurations satisfy this criteria. When dimethyl sulfoxide is used as the solvent for determining the nmr spectrum, a broad singlet

(12) M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3364 (1964).

(13) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

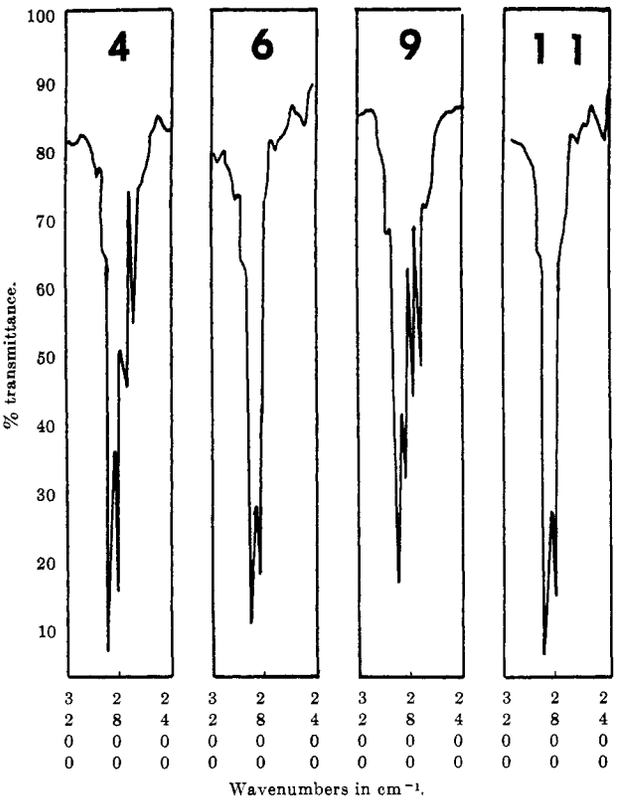


Figure 3.—Infrared spectra of the inside yohimbanes.

(W_H = 6 cps) can be observed just downfield from the methylene envelope at 3.2 ppm. This signal represents the hydrogen at C_{14b} as is shown by its absence in the corresponding deuterated derivative. The splitting pattern[14] of this hydrogen indicates that it forms a 60 or 120° dihedral angle with the hydrogen at C_{14c}, thus eliminating the *trans,anti* conformation A which requires a 180° dihedral angle.

The spectral data for **9** is compatible with the favored conformation A of the *cis,syn* system, but could also be explained by the *cis,anti* system, conformation A being responsible for the Bohlmann bands and the nmr data resulting from an average of the three conformations. This ambiguity was resolved by an examination of the spectra of the other *cis* epimer (**11**) which show a hydrogen at 4.02 ppm (W_H = 5.0 cps) and no Bohlmann bands, both of which are characteristic of a *cis*-quinolizidine system. These data are incompatible with the thermodynamically favored conformation A of the *cis,syn* system, but nicely fit for a mixture of the three *cis,anti* conformations, the lack[15] of Bohlmann bands indicating that A is present to only a small extent. This evidence is consistent with the previous assignments of **9** as *cis,syn* and **11** as *cis,anti*, which were based on the methylene envelope.

The assignment of the *trans* epimeric pair (**4** and **6**) is a relatively simple case since only the *anti* isomer has a *trans*-quinolizidine conformation. Thus, isomer **4** whose nmr spectrum has no signal in the 3.3- to 4.5-ppm region and whose infrared spectrum shows Bohl-

(14) In a system of this type 180° coupling is indicated by a peak separation of approximately 10 cps, whereas 60° coupling results in a broad singlet as shown by A. I. Meyers, B. J. Betrus, N. K. Ralhan, and K. B. Rao [*J. Heterocyclic Chem.*, **1**, 13 (1964)].

(15) A careful comparison of the Bohlmann region in the infrared spectrum of **11** with that of **6**, which cannot have Bohlmann bands, suggests weak absorption.

mann bands must have the *trans,anti* configuration. As expected the *trans,syn* isomer, **6** has a signal at 4.3 ppm (W_H = 6.5 cps) and no Bohlmann bands.

As further support for these assignments we have converted the four isomers into the corresponding N-methyl derivatives. The *cis*-N-methyl compounds would be expected to have conformations similar to their parents since their favorable conformations have no serious steric interactions between the hydrogen on the indole nitrogen and the hydrogens at C_1. Indeed, there are no significant changes in the Bohlmann bands, methylene envelope half-width, or signal for H_{14b} in the *cis*-N-methyl derivatives. In the *trans* series the steric interactions are quite serious, 1.3 A in the *anti* isomer and 1.3 A in the *syn* case. The *trans,anti* isomer, which has been shown to be primarily in conformation A, cannot accept a methyl substituent without the hydrogens of the methyl group almost overlapping the equatorial hydrogen at C_1. The expected shift to conformation B for the N-methyl derivative **5** is borne out by the infrared spectrum which has no Bohlmann bands and the nmr spectrum which shows a doublet at 3.65 ppm (J = 9 cps). In the *trans,syn* case the insertion of a N-methyl group causes an even worse interaction. The presence of Bohlmann bands in the infrared spectrum and a signal at 3.7 ppm (J = 6 cps) in the nmr spectrum of **7** demonstrate a shift to conformation X in which ring D is a twist boat.

Experimental Section

The melting points were determined using a Thomas–Hoover apparatus which had been calibrated against known standards. The infrared spectra were recorded with a Baird Model 455 instrument on chloroform solutions. The nmr spectra were determined with a Varian Associates A-60 spectrometer on deuteriochloroform solutions unless noted. Thin layer chromatography was carried out on silica gel G (Stahl) using 0.2:1:0.5 mixture of acetone–benzene–*n*-heptane as the eluent in an ammonia atmosphere, the chromatograms being developed by spraying with a solution of potassium iodoplatinate.

***trans,anti*-1,2,3,4,4a,5,6,8,9,14,14b,14c-Dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizin-6-one (3).**—A solution of 94 g of tryptamine and 100 g of 2-formylcyclohexaneacetic acid in 860 ml of acetic acid was refluxed for 2 hr. On standing there was deposited a solid which after trituration with 3 l. of hot ethanol gave 106 g (61%) of a crystalline solid, mp 266–268°. Recrystallization from ethanol gave an analytical sample, mp 267.5–268.5°.

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.23; H, 7.61; N, 9.66.

Further concentration of the above mother liquor gave mixed 1,2,3,4,4a,5,6,8,9,14,14b,14c-dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizin-6-ones with wide melting ranges between 215 and 262°.

***trans,anti*-1,2,3,4,4a,5,6,8,9,14,14b,14c-Dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine (4).**—To a suspension of 4.0 g of lithium aluminum hydride in 220 ml of tetrahydrofuran was added a solution of 2.25 g of *trans,anti*-1,2,3,4,4a,5,6,8,9,14,14b,14c-dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizin-6-one in 400 ml of warm tetrahydrofuran at a rate such that the mixture did not reflux. After the addition had been completed, the mixture was refluxed for 5 hr. The excess lithium aluminum hydride was destroyed by the cautious dropwise addition of water. The reaction mixture was filtered and the solvent was removed. Recrystallization of the residue from ethanol gave 1.6 g (74%) of a solid, mp 171–172° (evacuated capillary).

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.44; H, 8.71; N, 10.21.

***trans,syn*-1,2,3,4,4a,5,6,8,9,14,14b,14c-Dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine (6).**—The reduction of 47 g of mixed 1,2,3,4,4a,5,6,8,9,14,14b,14c-dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizin-6-ones by the procedure used for the *trans,anti* isomer gave an amorphous solid. Chromatography on alumina gave on elution with benzene a solid, which, after recrystallization from methanol, afforded 3.0 g (7%) of a solid, mp 136–137°. Recrystallization from Skellysolve B gave an analytical sample, mp 136.5–137.5°.

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.68; H, 8.60; N, 9.77.

2,3,4,4a,5,6,8,9,14,14c-Decahydro-1H-benz[*a*]indolo[3,2-*h*]quinolizinium Chloride (8).—A solution of 10.9 g of *trans,anti*-1,2,3,4,4a,5,6,8,9,14,14b,14c-dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine and 5.5 ml of triethylamine in 500 ml of methylene chloride was cooled to −10° and over a 40-min interval a solution of 4.9 g of *t*-butyl hypochlorite in 30 ml of carbon tetrachloride was added with cooling such that the temperature remained at −10°. After the addition had been completed, stirring was continued at −10° for 10 min and then the cooling bath was removed and stirring was continued for 15 min. The reaction mixture was washed with water, dried over sodium sulfate, and made acidic with ethereal hydrogen chloride, and the solvent was removed. The residue, after three recrystallizations from ethanol–dioxane, gave 7.5 g (61%) of a solid, mp 251–252°.

Anal. Calcd for $C_{19}H_{23}N_2Cl$: C, 72.48; H, 7.36; N, 8.90; Cl, 11.26. Found: C, 72.78; H, 7.32; N, 8.72; Cl, 11.25.

***cis,syn*-1,2,3,4,4a,5,6,8,9,14,14b,14c-Dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine (9).**—To a solution of 14.5 g of 2,3,4a,-5,6,8,9,14,14c-decahydro-1H-benz[*a*]indolo[3,2-*h*]quinolizinium chloride in 230 ml of ethanol was added 1.0 g of platinum oxide and the mixture was hydrogenated. After 5 min, the theoretical hydrogen had been absorbed. The reaction mixture was shaken with 70 ml of 10% sodium hydroxide solution and 500 ml of chloroform. The solution was filtered, the solvent was removed, and the residue was dissolved in 1 l. of chloroform. The chloroform solution was washed with water and dried over sodium sulfate, and the solvent was removed. Recrystallization of the residue from ethanol gave 10.9 g (80%) of a solid, mp 121–122° or 146–147°.

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.59; H, 8.55; N, 9.83.

***cis,syn*-1,2,3,4,4a,5,6,8,9,14,14b,14c-Dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine-14b-*d*.**—To a solution of 1.0 g of 2,3,4,-4a,5,6,8,9,14,14c-decahydro-1H-benz[*a*]indolo[3,2-*h*]quinolizinium chloride in 16 ml of deuterium oxide was added a solution of 0.42 g of sodium borodeuteride in 8 ml of deuterium oxide. After stirring for 15 min the reaction mixture was extracted with methylene chloride. The methylene chloride layer was washed with water and dried over sodium sulfate, and the solvent was removed. Recrystallization of the residue from methanol gave 0.44 g of a solid which was chromatographed on alumina. Elution with benzene gave, after recrystallization from ethanol, 0.15 g (15%) of a solid, mp 121–122°, λ_{max}^{Nujol} 2000 cm^{-1} (CD).

Anal. Calcd for $C_{19}DH_{23}N_2$: C, 81.07; H, 8.95; N, 9.95. Found: C, 81.05; H, 8.97; N, 9.81.

***cis,anti*-1,2,3,4,4a,5,6,8,9,14,14b,14c-Dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine (11).**—To a refluxing solution of 50 g of 2,3,4,4a,5,6,8,9,14,14c-decahydro-1H-benz[*a*]indolo[3,2-*h*]quinolizinium chloride, 145 ml of perchloric acid (70%), and 725 ml of water in 2.9 l. of methanol was added 145 g of zinc dust, portionwise, during a 1-hr period. After the addition had been completed, heating was continued for 2.5 hr. The unreacted zinc was removed by filtration. The solution was concentrated to dryness, made basic with 20% sodium hydroxide solution, and extracted with chloroform. The chloroform layer was washed with water and dried over sodium sulfate, and the solvent was removed. The residue (40 g) was chromatographed on 1.6 kg of alumina. Elution with benzene–ether gave 13.9 g (29%) of a crystalline solid, mp 182–185°. Recrystallization from ethanol gave an analytical sample, mp 192–193°.

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.28; H, 8.85; N, 9.90.

The early fractions from the column gave 8.7 g (18%) of the *cis,syn* siomer.

General Procedure for 1,2,3,4,4a,5,6,8,9,14,14b,14c-Dodecahydrobenz-14-methyl[*a*]indolo[3,2-*h*]quinolizines.—A mixture of 10 g of the 1,2,3,4,4a,5,6,8,9,14,14b,14c-dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine, 20 g of sodium hydride dispersion (55% in mineral oil), 75 ml of dimethyl carbonate, and 500 ml of tetrahydrofuran was refluxed for 20 hr. The excess sodium hydride was destroyed by the dropwise addition of water and the solvent was removed *in vacuo* on the steam bath. The residue was treated with 1 l. of chloroform and 100 ml of water. The chloroform layer was washed with water and dried over sodium sulfate, and the solvent was removed.

The *trans,anti* isomer **5** was obtained by trituration of the crude product with Skellysolve B as a crystalline solid, mp 142–143°, in 61% yield. Recrystallization from Skellysolve B gave an analytical sample, mp 145–146°.

Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.67; H, 9.10; N, 9.23.

The *trans,syn* isomer **7** was obtained by dissolving the crude product in ether and adding excess hydrogen bromide. The resulting salt was shaken with 10% sodium hydroxide solution and methylene chloride. The methylene chloride layer was washed with water and dried over sodium sulfate, and the solvent was removed. Recrystallization of the residue from methanol gave a solid, mp 125–126°, in 38% yield.

Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.30; H, 8.80; N, 9.27.

The *cis,syn* isomer **10** was obtained by crystallization of the crude product from Skellysolve B as a solid, mp 144–149°, in 55% yield. Recrystallization from methanol gave an analytical sample, mp 150–151°.

Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.52; H, 8.87; N, 9.38.

The *cis,anti* isomer **12** was obtained by crystallization of the crude product from Skellysove B as a solid, mp 110–111°, in 36% yield. Recrystallization from methanol gave an analytical sample, mp 112–113°.

Anal. Calcd for $C_{20}H_{26}N_2$: C, 81.58; H, 8.90; N, 9.52 Found: C, 81.77; H, 9.11; N, 9.30.

Registry No.—**3,** 13388-62-0; **4,** 13388-63-1; **5,** 13388-64-2; **6,** 13388-65-3; **7,** 13428-18-7; **8,** 13388-66-4; **9,** 13388-67-5; **9**-14b-*d*, 13388-68-6; **10,** 13388-69-7; **11,** 13388-70-0; **12,** 13388-71-1.

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Sulfur-Containing Polypeptides. VII. Synthesis of S-Trityl-L-cysteine Peptides Using Acid-Labile Amino and Carboxy Protective Groups[1-3]

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The development of a versatile synthetic route to L-cysteine containing polypeptides employing acid-labile protective groups which can be removed cleanly in the presence of the S-trityl thioether moiety has facilitated the synthesis of *t*-butyl N-carbobenzoxy-S-trityl-L-cysteinyl-S-benzhydryl-L-cysteinylglycyl-L-phenylalanylglycyl-S-trityl-L-cysteinyl-L-phenylalanylglycinate (I) in good over-all yield.

Previous reports have considered synthetic routes to suitably protected cysteine derivatives[6] and selective oxidation[7] of S-trityl thioethers of cysteine. These studies have provided a basis for preparation of peptides containing several cysteine residues. The present report describes the synthesis of such a molecule and summarizes our efforts to develop amino and carboxyl protective groups that are compatible with S-trityl thioethers.

The synthetic goal of these experiments was the protected octapeptide derivative, *t*-butyl N-carbobenzoxy-S-trityl-L-cysteinyl-S-benzhydryl-L-cysteinylglycyl-L-phenylalanylglycyl-S-trityl-L-cysteinyl-L-phenylalanylglycinate (I). This substance was desired as the precursor to a molecule containing three disulfide bridges, shown schematically as IV. The projected synthesis of IV (Scheme I) is designed to permit stepwise introduction of the three disulfide bonds and provide a model from which synthesis of more complex related peptides can be achieved. Octapeptide II is the key intermediate in the synthesis of IV; thus the protective groups incorporated into I must permit the selective oxidation of cysteine residues I and VI and removal of the carboxyl protective group in a subsequent step. Chain extension of II, using an ester containing an S-trityl-L-cysteine residue, would lead to the A chain, III. This segment of the molecule contains the intact intrachain disulfide bridge and two cysteine residues with S-protective groups that can be selectively removed. Oxidation of III, using the appropriate B chain, should provide IV.

Our approach to the preparation of I was governed by the need to obtain this substance in quantity and the desire to develop a method of synthesis that could be utilized for other molecules containing intact disulfide bridges. However, an obstacle to the successful preparation of molecules similar to I and II concerns the availability of amino and carboxyl protective groups that can be cleanly removed in the presence of the S-trityl group. The elegant work of Zervas, *et al.*,[8] which resulted in the synthesis of Va–c, provided significant data on the compatibility of various N-protective groups with the S-trityl residue. The approach adopted in this synthesis involved the use of a methyl ester as the carboxyl protective group and allowed elongation of V from the C-terminal serine methyl ester residue. Although utilization of acid-stable esters simplifies the coupling and chain-extension steps of their synthesis, removal of esters with alkali could lead to

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(3) The following abbreviations have been employed in the text: Z = carbobenzoxy; Tr = trityl; Bzh = benzhydryl; t_{Bu} = *t*-butyl; BOC = *t*-butyloxycarbonyl; Bz = benzoyl; *o*-NPS = *o*-nitrophenylsulfenyl; DCC = N,N-dicyclohexylcarbodiimide; WSC = 1-ethyl-3-(3-N,N-dimethylaminopropyl)carbodiimide hydrochloride; Phth = phthaloyl; EOCP = ethoxycarbonylphthalimide; BHOC = benzhydryloxycarbonyl; DMF = N,N-dimethylformamide; Ox^- = oxalate.

(4) Le Doux Fellow, 1965–1966.

(5) Abstracted in part from a dissertation by J. T. Staples submitted to the University of North Carolina in partial fulfillment of the requirements for the Ph.D. degree, June 1966.

(6) R. G. Hiskey and J. B. Adams, Jr., *J. Org. Chem.*, **31**, 2178 (1966).

(7) R. G. Hiskey and D. N. Harpp, *J. Am. Chem. Soc.*, **87**, 3965 (1965); R. G. Hiskey, T. Mizoguchi, and E. L. Smithwick, Jr., *J. Org. Chem.*, **32**, 97 (1967).

(8) L. Zervas, I. Photaki, A. Cosmatos, and D. Borovas, *J. Am. Chem. Soc.*, **87**, 4922 (1965), and earlier references cited.