Synthetic Approaches to Steroidal Alkaloids III (1). An Attempted Synthesis of Ring-E of Veratramine

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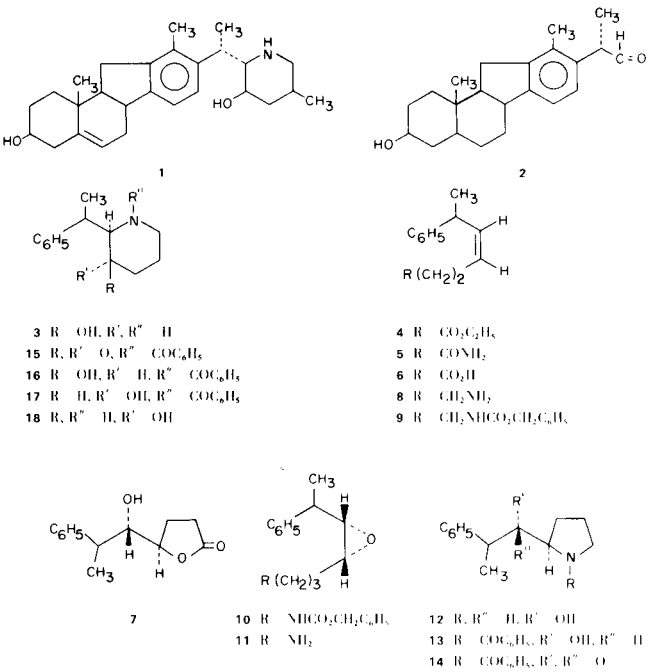
In an effort to devise an alternative synthesis of the hydroxypiperidine ring present in the alkaloid veratramine, a model synthesis starting from *cis*-6-phenyl-4-heptenoic acid was explored. This acid was converted to the epoxide of *cis*-6-phenyl-1-amino-4-heptene which on heating gave 2-(1-hydroxy-2-phenylpropyl)pyrrolidine as the only product. As a reference compound, 2-(1-phenylethyl)-3-hydroxypiperidine was synthesized using a variation of an established procedure.

In the two total syntheses of veratramine (**1**) reported to date (3), one of the principal synthetic obstacles was the construction of the heterocyclic portion of the molecule which contains three chiral centers and has a fourth such center located adjacent to it at C-20. In an effort to devise a possible stereoselective synthesis of this portion of the veratramine molecule, it was envisioned that reaction of an appropriate Wittig reagent with aldehyde **2** (4), having the correct stereochemistry at C-20, would lead to such a synthesis. Since aldehyde **2** is available only by total synthesis (3a,5), or degradation of either veratramine (4) or hecogenin (6), our initial goal was the synthesis of the model compound, 2-(1-phenylethyl)-3-hydroxypiperidine (**3**), using 2-phenylpropionaldehyde as starting material.

Reaction of this aldehyde with the Wittig reagent derived from ethyl γ-bromobutyrate, under carefully controlled conditions (see Experimental), led to a single unsaturated ester in 75% yield. On the basis of the known steric course of the Wittig reaction, it was anticipated that this reaction would lead to a predominance of the *cis* ester (**4**) (7), however, unexpectedly no trace of an isomer could be detected by any of the conventional techniques. This material showed the infrared absorption at 13.5 μ, characteristic of a *cis* olefin (8), and this tentative structural assignment was confirmed by decoupling experiments in the nmr. Irradiation of the benzyl proton at δ 3.70 reduced the multiplet of the adjacent vinyl proton to a doublet with a coupling constant of 10 Hz, characteristic of a *cis*-olefin (9). Some efforts were made to obtain the *trans* isomer of this ester, either by modifying the conditions of the Wittig reaction (see Experimental) or by isomerization using chemical



of photochemical methods. The former experiments afforded only the *cis* ester in mediocre yield, while the latter led to either the recovery of unchanged starting material or products of gross decomposition.

Ester **4** was converted to the amide **5** *via* the corresponding acid (6) in the customary manner. However, attempted conversion of **5** to the epoxide using *m*-chloroperbenzoic acid afforded a compound, $C_{13}H_{16}O_3$, which on the basis of a carbonyl band in the infrared at 5.66 μ, and a hydroxyl peak at 2.90 μ was assigned the γ-lactone structure (**7**). This structural assignment was

confirmed by the nmr which showed one proton multiplets at δ 3.54 and 4.26 for the protons adjacent to oxygen as well as a high field methyl doublet and an aromatic singlet. This lactone apparently arises during the course of the epoxidation by interaction of the oxygen of the amide function of **5** with an intermediate which would normally lead to an epoxide (10).

This problem was circumvented by reduction of **5** to the amine (**8**), which was then protected as the carbobenzoxy derivative (**9**). Reaction of **9** with *m*-chloroperbenzoic acid proceeded smoothly to give the unstable epoxide (**10**). Hydrogenolysis of **10** gave amino epoxide **11** which was, without isolation, heated to effect cyclization.

Although this reaction could conceivably afford a piperidine derivative (**3**), a pyrrolidine derivative (**12**), or a mixture of both compounds, only one product, an air-sensitive, crystalline amino alcohol, could be detected in the reaction products. It has been noted, that in the mass spectrum veratramine shows a strong peak at m/e 114 corresponding to a fragment $C_6H_{12}NO$ derived from the piperidine ring present in the molecule (11). By a similar line of reasoning, compound **3** should show a strong peak at m/e 100, while a compound of structure **12** would not. The mass spectrum of the reaction product showed only a minimal peak at m/e 100, but a strong peak at m/e 70, corresponding to a fragment C_4H_8N derived from the pyrroliding ring of **12**. This assignment of structure was confirmed by conversion of **12** to the benzamide (**13**) *via* the *N,O*-dibenzoyl derivative. This crystalline amide showed a strong mass spectral peak, m/e 174, which cannot readily be explained in terms of a piperidine structure. Two phase oxidation of **13**, under conditions which have been shown not to epimerize centers adjacent to a carbonyl group (12) gave a single keto amide (**14**). The nmr spectrum of this compound showed the benzyl proton as a multiplet at δ 4.03 and a second low field proton as a triplet at δ 4.40, in agreement with the assigned structure.

Although it is known that cyclization reactions of amino compounds to afford pyrrolidine derivatives are somewhat more favorable than those to give piperidines (13), it was not anticipated that a pyrrolidine would be the exclusive product from the cyclization of **11** (14). Since steric considerations indicated that cyclization to a hydroxy piperidine would proceed more favorably with the *trans*-isomer of **11** several attempts (see above) were made to prepare this compound, however, these efforts proved fruitless.

During the course of this work, it became apparent that a reference sample of the desired hydroxy piperidine was essential for comparison purposes. The most attractive approach to this compound appeared to be *via* the route used by Johnson for the synthesis of the heterocyclic ring of veratramine (3a). The conversion of α-phenylpropionaldehyde to the *N*-benzoyl oxopiperidine (**15**) proceeded smoothly, following the established procedures. (See Experimental) (15).

Although it would be anticipated that **15** would have been obtained as a mixture of diastereomers (16), the keto amide was obtained as a sharp melting solid, which was homogeneous to tlc. Apparently, one diastereomer is sufficiently more stable than the other that it is obtained as essentially the only isolable product (17).

Borohydride reduction of **15** led to two alcohols in a ratio of approximately five to one. The nmr spectrum of the major reaction product showed the C-3 carbinol proton as a broad multiplet ($W_{1/2}$ 20 Hz) at δ 4.06, indicating that the hydroxyl group is equatorial. The C-2 proton appeared as a quartet with apparent coupling constants of 9 Hz and 6 Hz at δ 5.39. Since it has been shown that for the *N*-acetyl derivative of **15**, the coupling constant between the benzyl and C-2 protons is 9 Hz (16), and for the epimer of this compound is 11 Hz (see below) the coupling constant between C-2 and C-3 must be 6 Hz. These data, plus the low field at which this proton appears, indicate that this proton is equatorial, with the phenethyl group axial. This is not unexpected for a compound of structure **16**, in view of the conformation of various *N*-benzoylveratramine derivatives described by Johnson (18).

The nmr spectrum of the minor product of the reduction showed the C-3 carbinol proton as a multiplet ($W_{1/2}$ 14 Hz) at δ 3.79, with the C-2 proton as a quartet at δ 5.25. In decoupling experiments it was found that irradiation of the benzyl proton at δ 3.40 reduced the C-2 proton to a doublet, J = 3 Hz, indicating that the C-2 and C-3 protons do not have a *trans* diaxial relationship. Irradiation of the C-3 proton also reduced this quartet to a doublet, J = 11 Hz, caused by coupling between the C-2 and benzyl protons. Irradiation of the C-2 proton reduced the C-3 proton to a symmetrical triplet, J = 7 Hz, characteristic of an equatorial proton. On the basis of these data, it is apparent that this amino alcohol is **17** with, as expected, (18) both substituents axial (19).

The mass spectra of **16** and **17** were very similar and were in agreement with the assigned structures, showing a base peak, m/e 204, corresponding to a fragment $C_{12}H_{14}NO_2$, arising from the piperidine ring. Compounds **16** and **17** were markedly different in their physical properties from the amino alcohol assigned structure **13**.

The major product from the borohydride reduction was converted to the corresponding amino alcohol (**3**) either by direct hydrolysis or by reduction to the *N*-benzylamino alcohol followed by hydrogenolysis. The properties of **3** were in agreement with the assigned

structure, in particular the mass spectrum which showed a base peak m/e 100, as expected for a veratramine analog. Again, the properties of **3** were markedly different from those of amino alcohol **12**. A lack of material prevented the conversion of the epimeric amino alcohol (**17**) to amino alcohol **18**.

EXPERIMENTAL (20)

Ethyl *cis*-6-Phenyl-4-heptenoate. A.

To 4.5 g. of sodium hydride (173 mmoles) was added in a nitrogen atmosphere 200 ml. of dimethyl sulfoxide (distilled from calcium hydride) and the mixture heated at 70° for one hour to give a pale green solution. The solution was cooled to room temperature and 62 g. (135 mmoles) of 3-carbethoxypropyltriphenylphosphonium bromide (21) slurried in 300 ml. of dimethyl sulfoxide was added. After 10 minutes, 13.4 g. (100 mmoles) of 2-phenylpropionaldehyde in 100 ml. of dimethyl sulfoxide was added in one portion and the mixture was heated at 63° for 20 hours. After cooling to room temperature, the reaction mixture was poured into an ice-water slurry and extracted with pentane. The pentane solution was washed once with a mixture of 100 ml. of dimethyl sulfoxide and 300 ml. water followed by three portions of water and two portions of brine, dried, filtered, and the filtrate concentrated to 50 ml. and cooled in an ice-bath. The precipitated triphenylphosphine oxide was filtered off and the pentane solution filtered through a column of alumina to give 17.0 g. of crude product. Distillation gave 1.4 g. of 3-phenylpropionaldehyde (b.p. 40-45°/0.15 mm), and 15.2 g. of unsaturated ester (b.p. 91-96°/0.15 mm, 75% based on aldehyde consumed). Redistillation of a portion of the product provided the analytical sample; ir μ: 5.76 and 13.5; nmr δ: 1.11 (t, 3H, J = 6.5 Hz, CH_3-CH_2-), 1.26 (d, 3H, J = 6 Hz, CH_3CH), 3.68 (m, 1 H, CH_3CH), 4.02 (q, 2H, CH_3CH_2), 5.19 (m, 2H, CH=CH), 6.97 (br s, 5H, Ar H).

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: 77.41; H, 8.79.

B.

To a suspension of 4.56 g. (10 mmoles) of phosphonium salt in 40 ml. of anhydrous ether at room temperature was added slowly in a nitrogen atmosphere, 7 ml. of 1.6 *N n*-butyllithium in hexane (11 meq.). After two hours, 0.8 g. (6 mmoles) of 2-phenylpropionaldehyde in 40 ml. of anhydrous ether was added and the mixture stirred for 18 hours. Since the salt was not completely consumed, an additional 4 ml. of butyllithium were added and the mixture again stirred for 18 hours. The ether was replaced by 60 ml. of tetrahydrofuran (freshly distilled from calcium hydride) and was heated at reflux for 18 hours. The bulk of the tetrahydrofuran was removed and the contents were diluted with water and extracted with pentane; the pentane solution was washed with 1:1 tetrahydrofuran/water, water and brine, dried and the solvent evaporated to give 1.32 g. of oil. The crude product was dissolved in pentane and filtered through 40 g. of Merck acid washed alumina to give 0.624 g. (27%) of ester containing a trace of aldehyde. This material was identical to that prepared in part (A) above.

C.

To a solution of sodium ethoxide, prepared from 0.75 g. of sodium, in dimethylformamide, was added 13.68 g. (30 mmoles) of phosphonium salt and 4.5 g. (30 mmoles) of dry sodium iodide. The slurry was diluted with 25 ml. of dimethylformamide, stirred for one hour at room temperature, and 2.52 g. of 2-phenylpropionaldehyde in 2 ml. of dimethylformamide was added in one portion and the mixture stirred overnight at room temperature. The contents were diluted with water and extracted with hexane. After removal of most of the triphenylphosphine oxide by crystallization, the residue was dissolved in hexane and filtered through a column of Merck acid washed alumina. Elution with 1:1 hexane:benzene gave first 0.5 g. of recovered aldehyde and then 0.5 g. of ester contaminated with a trace of aldehyde. The yield of crude ester identical to that prepared in part A above was 29%.

cis-6-Phenyl-4-heptenoic Acid.

A solution of 28.83 g. (89.7 mmoles) of ethyl *cis*-6-phenyl-4-heptenoate in 250 ml. of 10% ethanolic potassium hydroxide was heated at reflux for 18 hours. Most of the alcohol was removed and the residue diluted with 500 ml. of water and extracted with pentane. The aqueous solution was acidified with 10% hydrochloric acid and extracted with four portions of methylene chloride. The methylene chloride solution was washed well with water and brine, dried and the solvent removed to give 18.33 g. (99%) of acid. Distillation at 119-128° (air-bath) at 0.05 mm provided the analytical sample; ir μ: 3.50 and 5.82; nmr δ: 1.30 (d, J = 7, 2H CH_3CH), 3.78 (m, 1 H, CH_3CH), 5.38 (m, 2H, CH=CH), 7.20 (br s 5H, Ar H).

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.48; H, 8.07.

cis-6-Phenyl-4-heptenamide.

A solution of 7.68 g. (37.8 mmoles) of *cis*-6-phenyl-4-heptenoic acid in 50 ml. of benzene containing 0.5 ml. of pyridine was cooled below room temperature and 25 g. (800 mmoles) of oxalyl chloride were added in one portion and the mixture stirred for 15 hours at room temperature. The solvent and the excess oxalyl chloride were removed under reduced pressure, and the residue dissolved in 100 ml. of dry chloroform, cooled in an ice-bath and saturated with dry ammonia. The excess ammonia and chloroform were removed and the residue redissolved in ether and washed with dilute hydrochloric acid, 5% aqueous sodium bicarbonate and brine. The ether solution was dried and the ether removed to yield 7.1 g. (93%) of crude amide. Chromatography on Merck acid washed alumina and elution with methylene chloride gave a total of 6.82 g. (90%) of amide which was homogeneous to tlc; ir μ: 3.02, 3.15, 6.00; nmr δ: 1.22 (d, J = 6, 3H, CH_3CH), 3.78 (m, 1 H, CH_3CH), 5.49 (m, 2H CH=CH), 7.21 (br s, 5H, Ar H); mass spectrum m/e (relative intensity) 204(20), 203(100), 189(0), 144(54), 129(44), 105(41), 91(10), 77(15), 59(15), 45(10).

5-(1-Hydroxy-2-phenylpropyl)butyrolactone (**7**).

To a cold solution of 1.0 g. of amide **5** in 50 ml. of methylene chloride was added slowly 2.10 g. (10 mmoles) of 85% *m*-chloroperbenzoic acid, and the mixture was stirred for 1.5 hours in an ice bath and a further 20 hours at room temperature. The suspension was filtered and the solution washed with cold 5% sodium bisulfite, saturated sodium bicarbonate, water and brine. After drying, the solvent was removed to give 1.09 g. of crude product. Tlc showed the presence of starting material and the reaction product was reoxidized with 1.10 g. of peracid using the above conditions and the product isolated to give 1.10 g. of crude compound. Chromatography on silica gel and elution with 2% methanol in benzene gave 0.592 g. (67%) of lactone **7**. Recrystallization from acetone/pentane gave white needles m.p. 147.5-148°; ir μ: 2.90, 5.66, 8.35, 10.9; nmr δ 1.41 (d, J = 7

Hz, 3H, CH_3CH), 3.58 (m, 1 H, CH OH), 4.25 (m, 1 H, CHO), 7.28 (br s, 5H, Ar H).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.43; H, 7.36, (22).

cis-6-Phenyl-1-amino-4-heptene.

A solution of 6.15 g. (30 mmoles) of amide **5** in 300 ml. of ether was added dropwise with stirring and cooling to a suspension of 6.3 g. of lithium aluminum hydride in 1.2 l. of dry ether. The reaction mixture was refluxed for 18 hours and stirred for another 2 hours at room temperature. The excess lithium aluminum hydride was destroyed with small chunks of ice with cooling and stirring. The ether solution was decanted and extracted with three portions of cold 10% hydrochloric acid. The acid solution was washed once with ether and then made basic with dilute aqueous sodium hydroxide. The alkaline solution was extracted with three portions of ether and the ether solution was washed with water, brine, dried, and the solvent removed to give 4.60 g. (80%) of amine. The crude product was dissolved in benzene and filtered through Merck alumina to give 4.80 g. of pure amine. A pure (tlc) portion of the amine was distilled at 88-91° (air-bath) and 0.35 mm to provide the analytical sample; ir μ 2.94, 3.05; nmr δ: 1.28 (d, J = 6 Hz, CH_3CH), 2.53 (m, 2H, CH_2NH_2), 3.77 (m, 1 H, CH_3CH), 5.41 (m, 2H, CH=CH), 7.17 (br s, 5H, Ar H).

Anal. Calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.33; H, 10.17; N, 7.34.

N-Carbobenzyloxy-6-phenyl-1-amino-4-heptene.

To 10.1 g. (53.3 mmoles) of *cis*-6-phenyl-1-amino-4-heptene was added, with vigorous stirring at 0-5°, 11 ml. (75 mmoles) of benzyloxycarbonyl chloride with the simultaneous addition of 40 ml. of 2*N* sodium hydroxide at a rate suitable to maintain a *p*H of 10-11. The reaction mixture was stirred at room temperature for 21 hours and then extracted with three portions of methylene chloride. The methylene chloride solution was washed with water, 10% hydrochloric acid, water and brine, dried, and the solvent removed to give 17.34 g. of crude product containing some benzyl alcohol. Benzyl alcohol was removed as the azeotrope with water under reduced pressure with heating on the steam bath. The residue was dissolved in benzene and filtered through a small alumina column to give 16.35 g. (95%), of pure (tlc) amide as a colorless gum; ir μ: 3.0, 5.75, 5.80; nmr δ 1.22 (d, J = 6 Hz, CH_3CH), 2.98 (m, 2H, CH_2NH), 3.59 (m, 1 H, CH_3CH), 4.90 (s, 2H, Ar CH_2), 5.22 (m, 2H, CH=CH), 7.02 (m, 10H, Ar H).

N-Carbobenzyloxy-1-amino-6-phenyl-4,5-oxidoheptane.

A solution of 16.0 g. (50 mmoles) of *N*-carbobenzyloxy-1-amino-6-phenyl-4-heptene in 400 ml. of dry chloroform was cooled in an ice-bath and 21.6 g. (125 mmoles) of *m*-chloroperbenzoic acid were added slowly during 5 minutes. The mixture was stirred in an ice-bath for 2 hours and then at room temperature for 11 hours, filtered, washed with cold sodium bisulfite solution, aqueous sodium bicarbonate and saturated brine solution, dried and the solvent evaporated to give 16.60 g. (99%) of pure (tlc) product; ir μ 5.82, 8.0 and 12.12; nmr δ: 1.39 (d, J = 6 Hz, 3H, CH_3CH), 2.89 (br m, 5H, CH_3CH, CH_2NH, CH-CH), 4.93 (s, 2H, Ar CH_2), 7.03 (m, 10H, Ar H). (23).

2-(1-Hydroxy-2-phenylpropyl)pyrrolidine (**12**).

A solution of 16.30 g. (48 mmoles) of *N*-carbobenzyloxy-1-amino-6-phenyl-4,5-oxidoheptane in 350 ml. of absolute ethanol was hydrogenolyzed with 6.0 g. of 5% palladium on carbon at atmospheric pressure and room temperature. During one hour, one equivalent of hydrogen was absorbed. The catalyst was filtered out through Celite and the filtrate was heated at reflux 16 hours under a nitrogen atmosphere. Distillation of the ethanol gave 9.80 g. of oil which crystallized on standing. Recrystallization from methylene chloride-ether gave white crystals, m.p. 148-149°; nmr δ: 1.29 (d, J = 7 Hz, 3H, CH_3CH), 2.88 (br m, 3H, CH-NH-CH_2), 3.12 (m, 1 H, CH_3CH), 3.52 (m, 1 H, CH OH), 6.80 (s, 5H, Ar H); mass spectrum m/e (rel. intensity) 206(8), 205(6), 105(100), 91(52), 92(20), 77(33), 70(25). This material very readily absorbed atmospheric carbon dioxide and on repeated attempts would not provide acceptable analytical data.

1-Benzoyl-2-(1-hydroxy-2-phenyl)propylpyrrolidine (**13**).

To a solution of 3.66 g. (17.85 mmoles) of 2-(1-hydroxy-2-phenyl)propylpyrrolidine in 100 ml. of dry pyridine, cooled in an ice-bath, was added slowly 9.75 ml. of benzoyl chloride. The reaction mixture was stirred at room temperature for 30 hours, ice was added, the mixture stirred for 30 minutes and then poured into a mixture of ice and 6*N* hydrochloric acid. The aqueous solution was extracted with methylene chloride, the methylene chloride solution was washed with water, saturated sodium bicarbonate and brine, dried and the solvent removed to give 82% of crude product. Tlc (silica gel G/7% acetone in benzene) showed two components with R_f 0.49 and 0.33. A 6.0 g. portion of this material was dissolved in benzene and chromatographed on Merck acid washed alumina. Elution with 25% hexane-benzene and 1% acetone in benzene gave 3.35 g. of amide ester as a colorless glass; ir μ: 5.50, 6.10; nmr δ: 1.32 (d, J = 6 Hz, 3H, CH_3CH), 3.15 (m, 3H, CHN, CH_3CH), 4.54 (m, 1 H, CHO), 5.07 (m, 1 H, NCH), 7.15 (m, 15H, Ar H). This material was hydrolyzed to the amide without further purification.

A solution of 2.80 g. (6.75 mmoles) of the amide ester in 150 ml. of 1% methanolic potassium hydroxide was stirred at room temperature for 24 hours, the base strength was then increased to 2% and the mixture again left at room temperature for 32 hours. Methanol was distilled off at reduced pressure with gentle warming and the contents were diluted with 50 ml. of water, extracted with methylene chloride and the methylene chloride extracts washed with water, dilute hydrochloric acid, water and brine and the solvent removed to give 1.73 g. (5.6 mmoles, 83%) of solid. Crystallization from benzene-hexane provided the analytical sample m.p. 128-128.5°; ir μ: 3.04, 6.26, 6.38; nmr δ: 1.20 (d, J = 6 Hz, 3H, CH_3CH), 2.72 (m, 1 H, $CHOH$), 3.20 (m, 1 H, N-CH), 3.55 (m, 1 H, CH_3CH), 4.24 (m, 1 H, NCH), 4.52 (m, 1 H, NCH), 6.82 (m, 1 OH, Ar H); mass spectrum m/e (rel. intensity): 310(0.7), 309(1.3), 291(5), 277(3), 206(7), 188(33), 175(12), 105(100), 83(23), 77(20).

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.41; H, 7.35; N, 4.40.

1-Benzoyl-2-(1-keto-2-phenyl)propylpyrrolidine (**14**).

An oxidizing solution was made by mixing 3.0 g. of chromium trioxide, 3.0 g. of sodium dichromate, 4.8 ml. of acetic acid and 24 ml. of water to give in total 33 ml. of reagent. To 2.8 ml. of this solution, cooled in an ice-bath, was added a cold solution of 0.20 g. (0.69 mmoles) of hydroxy amide **13** in 10 ml. of benzene. The mixture was stirred at 0-10° for two hours in an ice-bath and then at room temperature for 30 hours. An additional 20 ml. of benzene was added, the benzene layer was separated and washed with water, sodium bicarbonate and brine, dried, and the solvent removed to give 0.151 g. (75%) of material which would

not crystallize. Tlc (silica gel G, 10% acetone in benzene) showed that this material was homogeneous; ir μ 6.15; nmr δ 1.38 (d, J = 6 Hz, 3H, CH_3CH), 3.28 (m, 2H, NCH_2), 4.08 (m, 1 H, CH_3CH), 4.41 (m, 1 H, NCH), 6.92 (m, 10 H, Ar H); mass spectrum, m/e (rel. intensity): 308(2), 307(1), 189(11), 188(69), 173(26), 106(25), 105(100), 76 (50).

2-(3-Carbo-*t*-butoxypropylamino)-3-phenylbutyronitrile.

To a solution of 20.82 g. (130 mmoles) of *t*-butyl-4-aminobutyrate and 16.25 g. (123 mmoles) of 2-phenylpropionaldehyde in 900 ml. of absolute ethanol, was added 900 ml. of water. To the cloudy suspension was then added, with stirring, 17.75 g. (92.25 mmoles) of sodium *meta*-bisulfite. After stirring for 2.5 hours at room temperature, a solution of 8.82 g. (135 mmoles) of potassium cyanide in 300 ml. of ethanol/water (1:1) was added and the solution stirred for 64 hours at room temperature under nitrogen. The reaction mixture was diluted with water and extracted with four portions of methylene chloride. The extracts were washed with saturated sodium bicarbonate, 1 *N* hydrochloric acid, water and saturated brine, dried and the solvent removed at 40°. The excess aldehyde was removed under reduced pressure (0.35 mm) at 40-50° to give 29.56 g. (82%) of amino nitrile as a thick syrup. Tlc (alumina, 2% acetone in benzene) showed one major component with a trace of impurity; ir μ: 4.42, 5.80, 2.08 and 3.41, 5.05. This material was used in the next step without further purification.

N-Benzoyl-2-(3-carbo-*t*-butoxypropylamino)-3-phenylbutyronitrile.

To a solution of 29.0 g. (96 mmoles) of the crude amino nitrile in 500 ml. of pyridine was added 50 ml. of benzoyl chloride. After keeping the solution for 27 hours at room temperature, ice was added, the mixture was stirred for 40 minutes, then poured into a slurry of 2.5 l. of 6*N* hydrochloric acid and about 1 kg. of ice. The mixture was extracted with four portions of methylene chloride, the methylene chloride solution was washed with water, saturated sodium bicarbonate, brine, dried and the solvent distilled out, yielding 37.35 g. (95%) of crude amide. On crystallization of the residue from methanol, and then from ether-pentane, 15.89 g. of white solid, m.p. 92-100°, was obtained. Recrystallization from ethanol gave the analytical sample, m.p. 108-110°; ir μ: 5.76, 6.10.

Anal. Calcd. for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 74.12; H, 7.35; N, 6.74.

1-Benzoyl-2-(1-phenylethyl)-3-amino-4-*t*-butoxycarbonyl-3-piperidine.

A suspension of 1.05 g. (40 mmoles) of sodium hydride in 75 ml. of dry dimethylsulfoxide (freshly distilled from calcium hydride), was heated at 73° for 1.5 hours in a nitrogen atmosphere. The mixture was cooled to room temperature and added to a solution of 4.32 g. of amido nitrile in 100 ml. of dry dimethyl sulfoxide. The reaction mixture was stirred for 2 hours at room temperature, then poured over 300 g. of crushed ice containing 16 ml. of glacial acetic acid. The resulting mixture was extracted with three portions of methylene chloride, the extracts were washed with water, 1*N* hydrochloric acid, saturated sodium bicarbonate and brine, dried and the solvent removed to give 3.44 g. of brown solid. A 3.24 g. portion of the crude product was chromatographed on Florisil to give 2.91 g. (74%) of enaminoester as a white solid on elution with 25% acetone in benzene. The analytical sample was crystallized from methylene chloride-ether as white oblong plates m.p. 177-178°; ir μ: 2.92, 3.01, 6.0 and 6.45, 6.15; nmr δ: 1.31 (s, 9H, $(CH_3)_3C$), 1.54 (d, J = 6 Hz, CH_3CH), 2.20 (m, 2H, CH_2-C=), 3.22 (m, 3H, CH_3CH, NCH_2), 5.78 (m, 1 H, C=CH-N), 7.09 (m, 10H, Ar H).

Anal. Calcd. for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 73.67; H, 7.45; N, 7.00.

1-Benzoyl-2-(1-phenylethyl)-3-piperidone (**15**).

Dry gaseous hydrogen chloride was bubbled in a slow stream through a solution of 0.386 g. (0.95 mmoles) of the enaminoester in 18.5 ml. of acetic acid for one hour while cooling the contents in an ice-bath. The yellow solution was kept at room temperature for one hour and the acetic acid was then azeotropically removed with water at steam-bath temperature and reduced pressure. The contents were diluted with water and extracted with methylene chloride. The methylene chloride solution was washed with water and brine solution, dried, and the solvent was removed. The residue was redissolved in 20 ml. of ethyl acetate and heated at reflux for 2 hours under a nitrogen atmosphere. The solvent was removed to yield 0.260 g. of semi-solid, which on crystallization from benzene-hexane gave 0.236 g. (81%) of piperidone, m.p. 129-131°. Recrystallization from the same solvents gave the analytical sample, m.p. 131-133°; ir μ: 5.86, 6.12; nmr δ: 1.28 (d, J = 6, 3H, CH_3CH), 2.53 (m, 2H, $CH_2C(=O)$), 3.38 (m, 3H, CH_3CH, NCH_2), 5.38 (m, 1 H, CH-N), 7.25 (m, 10H, Ar H); mass spectrum m/e (rel. intensity): 308(2), 307(55), 203(14), 202(100), 201(23), 106(7), 105(92), 77(42).

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.97; H, 6.88; N, 4.61.

1-Benzoyl-2-(1-phenylethyl)-3-hydroxypiperidine and 1-Benzoyl-2-(1-phenylethyl)-3-epihydroxypiperidine (**16** and **17**).

A mixture of 0.4 g. (1.3 mmoles) of piperidone **15** and 0.6 g. of sodium borohydride in 50 ml. of 2-propanol was heated at reflux for 14 hours under a nitrogen atmosphere. The 2-propanol was removed at reduced pressure, the residue was diluted with water and extracted with chloroform. The chloroform solution was washed with 2*N* sodium hydroxide, 10% hydrochloric acid and brine, dried and the solvent removed to give 0.389 g. of crystals, m.p. 150-153°. The mother-liquors were chromatographed on Merck acid-washed alumina to give 0.20 g. of a mixture, which was rechromatographed on Merck acid-washed alumina. Elution with chloroform gave 0.083 g. of **17**, m.p. 125-128°. Recrystallization from methylene chloride-pentane gave the analytical sample, m.p. 129-130°; ir μ: 2.90, 6.15; nmr δ: 1.26 (d, J = 6 Hz, 3H, CH_3CH), 3.30 (m, 2H, CH_3CH, NCH), 3.79 (m, $W_{1/2}$ = 14 Hz, CHOH), 4.22 (m, 1H, NCH), 5.23 (q, J = 11 Hz, J = 3 Hz, 1H, NCH), 7.12 (m, 10H, Ar H); mass spectrum m/e (rel. intensity): 310(14), 309(19), 294(2), 293(6), 291(1), 276(2), 205(98), 204(100), 187(43), 186(21), 105(24), 99(40), 92(38), 90(4), 81(87), 77(45).

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.59; H, 7.46; N, 4.49.

Elution with 2.5% ethyl acetate in chloroform gave 0.051 g. of solid (**16**), m.p. 150-153°, identical to that obtained by direct crystallization. Recrystallization from methylene chloride-pentane provided the analytical sample, m.p. 153-154°; ir μ: 2.95, 6.20; nmr δ: 161 (d, J = 6 Hz, 3H, CH_3CH), 2.90 (m, 1H, NCH), 3.39 (m, 1H, CH_3CH), 4.06 (m, $W_{1/2}$ 20 Hz, CHOH), 4.80 (m, 1H, NCH), 5.39 (q, J = 6 Hz, 1H, NCH), 7.28 (m, 10H, Ar H); mass spectrum m/e (rel. intensity): 310(14), 309(19), 294(2), 293(6), 291(1), 276(2), 205(98), 204(100), 187(43), 186(21), 105(24), 99(40), 92(38), 90(4), 81(87), 77(45).

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.79; H, 7.47; N, 4.64.

1-Benzyl-2-(1-phenylethyl)-3-hydroxypiperidine.

A solution of 0.095 g. of amido alcohol **16** in 20 ml. of tetrahydrofuran was added dropwise to 0.20 g. of lithium aluminum hydride in 25 ml. of tetrahydrofuran. The reaction mixture was heated at reflux for 20 hours with vigorous stirring, in a nitrogen atmosphere. The reaction flask was cooled and the excess lithium aluminum hydride was destroyed with a small piece of ice. The inorganic solid was filtered from the solution, the tetrahydrofuran evaporated and the product was filtered through silica gel. Elution with 5% methanol in ethyl acetate gave 0.081 g. (90%) of a homogeneous (tlc) oil; mass spectrum m/e (rel. intensity) 296(1), 295(1), 206(2), 191(52), 190(100), 172(3), 105(37), 100(58), 91(84).

2-(1-Phenylethyl)-3-hydroxypiperidine (**3**). A.

A solution of 0.066 g. of amido alcohol **16** in 8 ml. of ethylene glycol containing 0.5 g. potassium hydroxide and 0.3 ml. of hydrazine hydrate was heated at reflux for 2.5 hours under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, diluted with water and saturated sodium bicarbonate solution and extracted with chloroform. The chloroform solution was washed with water and brine, dried, and the solvent removed to give 0.048 g. of oil. Tlc (alumina 10% methanol in benzene) indicated the material was homogeneous. The oil was dissolved in hexane and filtered through an alumina column. Elution with benzene-methylene chloride gave 0.035 g. (84%) of pure amino alcohol **18**; ir μ: 2.85, 2.95; nmr δ: 1.25 (d, J = 6 Hz, 3H, CH_3CH), 2.71 (m, 4H, CH_3CH, $CHNCH_2$), 3.90 (m, $W_{1/2}$ = 7 Hz, 1H, CHOH), 7.02 (br s, 5H, Ar H); mass spectrum m/e (rel. intensity) 206(1), 205(2), 204(1), 160(52), 106(10), 105(11), 101(16), 100(100), 91(13), 82(7), 77(5), 71(4), 70(3).

B.

A 0.060 g. portion of *N*-benzylamino alcohol was dissolved in 20 ml. of absolute alcohol and was hydrogenolyzed using 0.15 g. of 5% palladium on charcoal. After filtering out the catalyst and removing the solvent 0.036 g. of oil was obtained. This material was identical to that obtained in part A above

REFERENCES

(1) Part II: J. W. Huffman and R. R. Sobti, *Steroids*, **16**, 755 (1970). This work was supported in part by Grant HE-11170 from the National Heart Institute and Career Program Award GM-5433 from the National Institute of General Medical Sciences.

(2) Abstracted from the dissertation submitted by S. N. Singh in partial fulfillment of the requirements for the Ph.D. degree, Clemson University, Dec. 1972.

(3a) W. S. Johnson, H. A. P. de Jongh, C. E. Coverdale, J. W. Scott and U. Burckhardt, *J. Am. Chem. Soc.*, **89**, 4523 (1967); (b) T. Masumane, M. Takasugi, A. Murai and K. Kobayashi, *ibid.*, **89**, 4521 (1967), *Tetrahedron*, **27**, 3369 (1971).

(4) R. W. Franck, G. P. Rizzi and W. S. Johnson, *Steroids*, 463 (1964).

(5a) W. S. Johnson, J. M. Cox, D. W. Graham and H. W. Whitlock, *J. Am. Chem. Soc.*, **89**, 4524 (1967); (b) W. S. Johnson, N. Cohen, E. R. Habicht, D. P. G. Hamon, G. P. Rizzi and D. J. Faulkner, *Tetrahedron Letters*, 2829 (1968).

(6a) H. Mitsuhashi and K. Shibata, *ibid.*, 2281 (1964); (b) W. F. Johns and I. Laos, *J. Org. Chem.*, **30**, 4220 (1965).

(7) M. Schlosser, "Topics in Stereochemistry," Vol. 5, E. L. Eliel and N. L. Allinger, Ed., Wiley-Interscience, New York, 1970, pp. 1-30.

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1954, p. 31.

(9a) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon, New York, 1969, p. 302. (b) The authors would like to thank Dr. John Jacobus of this department for carrying out the decoupling experiments at 90 mHz.

(10) Although this and most other reactions in this series would be expected to lead to a mixture of diastereomers due to the presence of a chiral center at the benzyl carbon atom, in no case was any evidence found for the presence of more than one isomer. No attempt has been made to assign stereochemistry at this center in these compounds. This rather high degree of stereoselectivity is presumably due to conformational factors which operate in this series. The realtive stereochemistry of the oxygen atoms in lactone **7** is based on the usually accepted mode of epoxidation of olefins.

(11) H. Budzikiewicz, *Tetrahedron*, **20**, 2267 (1964).

(12a) J. W. Huffman, J. A. Alford and R. R. Sobti, *J. Org. Chem.*, **35**, 473 (1970); (b) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).

(13) B. Capon, *Quart. Rev.*, **18**, 45 (1964).

(14) While this work was in progress, E. J. Corey, H. S. Sachdev, J. Z. Gougoutas and W. Saenger, *J. Am. Chem. Soc.*, **92**, 2488 (1970) reported that cyclization of a similar amine epoxide gave a pyrrolidine derivative as the only isolable reaction product.

(15) The authors would like to thank Professor W. S. Johnson for supplying them with the unpublished details of experiments described in reference (3a).

(16) T. Masamune, H. Hayashi, M. Takarugi and S. Fukuoka, *J. Org. Chem.*, **37**, 2243 (1972) have prepared the *N*-acetyl derivative of both diastereomers of **15** and find that they have rather different physical properties. These compounds are described in the microfilm edition of the journal.

(17) Attempted base equilibration of **15** led to a slight decrease in melting point, but no significant changes in the spectral properties, indicating the probable formation of at least some of the isomer. The nmr spectrum of **15** showed the C-2 proton as a rather broad peak, rather than the expected doublet, due apparently to rotational diastereoisomerism about the amide bond and/or long range coupling.

(18) J. W. Scott, L. J. Durham, H. A. P. deJongh, U. Burckhardt and W. S. Johnson, *Tetrahedron Letters*, 2381 (1967).

(19) The authors would like to thank Mr. C. V. Hinton of this department for carrying out these decoupling experiments at 90 mHz.

(20) All melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were taken as potassium bromide disks or liquid films on sodium chloride plates using a Perkin-Elmer Model 137 spectrophotometer and are reported in microns. Nuclear magnetic resonance spectra were obtained with a Varian Associates A-60 nuclear magnetic resonance spectrophotometer in deuteriochloroform unless states otherwise. Decoupling experiments were obtained on a Bruker HX-90. All spectra are reported in parts per million relative to tetramethylsilane as internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Mass spectra at 70 eV were obtained from the Research Triangle Center, Raleigh, N. C., using an MS 903 mass spectrometer or in this department using a DuPont 21-490 mass spectrometer.

(21) P. E. Sonnett, *J. Org. Chem.*, **34**, 1147 (1969).

(22) Although this material was homogeneous to tlc, acceptable analytical data could not be obtained.

(23) Both this compound and the carbobenzoxy derivative of the unsaturated amine are viscous oils and are relatively unstable. Consequently, they were used for the succeeding steps without additional purification.