The Total Synthesis of (±)-Dasycarpidone, (±)-Epidasycarpidone, and (±)-Epiuleine[1,2]

LLOYD J. DOLBY[3]* AND HELMUT BIERE

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

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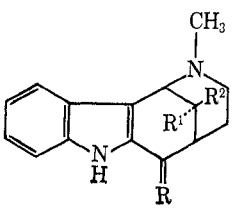
The syntheses of the indole alkaloids dasycarpidone, epidasycarpidone, and epiuleine in racemic form are described. The important intermediate in the synthetic scheme is *N*-methyl-3-ethyl-4-carbomethoxy-2-piperidone which is prepared by decarbomethoxylating *N*-methyl-3-ethyl-4,4-dicarbomethoxy-2-piperidone obtained from the condensation of dimethyl malonate with *N*-methyl-*N*-(2-chloroethyl)-α-bromobutyramide. Vilsmier condensation of *N*-methyl-3-ethyl-4-carbomethoxy-2-piperidone with indole followed by sodium borohydrate reduction afforded 3-[2-(*N*-methyl-3-ethyl-4-carbomethoxypiperidyl)]indole which was saponfied and cyclized with polyphosphoric acid to give (±)-dasycarpidone and (±)-epidasycarpidone. Racemic epiuleine was obtained from (±)-epidasycarpidone by treatment with methyl lithium followed by dehydration on alumina.

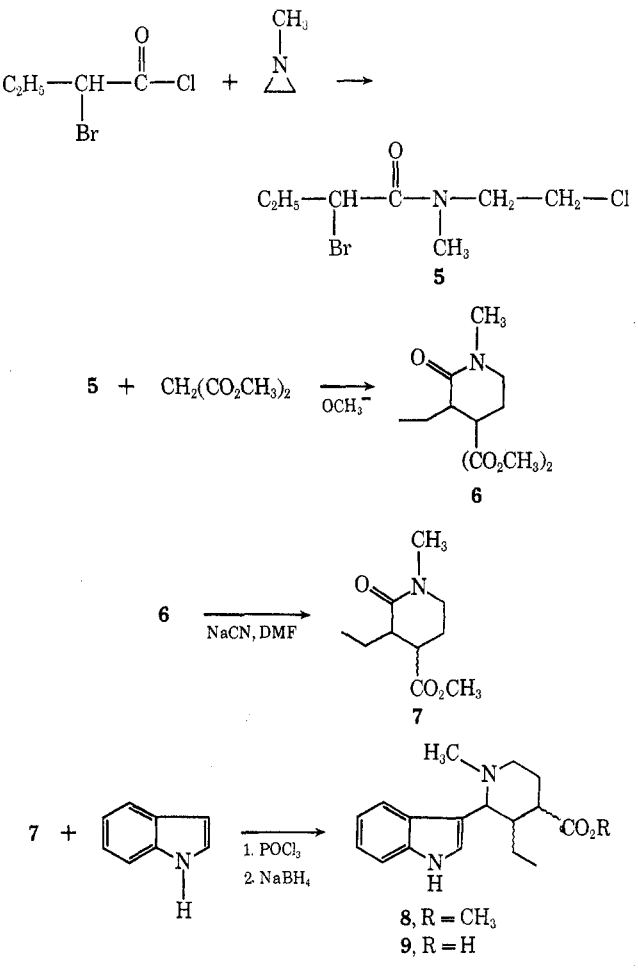
Of the large number of indole alkaloids which have been found in nature only a few lack a tryptamine moiety as part of their structures. Four closely related members of this group are uleine,[4] epiuleine,[5] dasycarpidone,[6] and epidasycarpidone.[5] We wish to report the total synthesis of the latter three of these compounds in racemic form and, since dasycarpidone has been converted to uleine, this work constitutes a formal total synthesis of the fourth member as well. The total synthesis of this group has also been achieved by a quite different route.[7]



	R	R¹	R²
Uleine (1)	CH_2	C_2H_5	H
Epiuleine (2)	CH_2	H	C_2H_5
Dasycarpidone (3)	O	C_2H_5	H
Epidasycarpidone (4)	O	H	C_2H_5

Our approach takes advantage of the ease of electrophilic substitution at both the α and β positions of the indole ring. Thus the synthetic scheme consists of simply attaching an appropriately substituted piperdine derivative at the α and β positions of indole itself. The key steps leading to (±)-dasycarpidone and (±)-epidasycarpidone are outlined in Scheme I. *N*-methylaziridine reacts smoothly in cold benzene solution with α-bromobutyrl chloride to afford *N*-(2-chloroethyl)-*N*-methyl-α-bromobutyramide (**5**) which was used directly in the next step. The amide **5** was condensed with dimethyl malonate under conditions similar to those used for the preparation of ethyl 1,1-cyclobutanedicarboxylate.[8] The expected product, *N*-methyl-3-ethyl-4,4-dicarbomethoxy-2-piperidone (**6**), was obtained in 65% yield based on *N*-methylaziridine. All of the spectral properties of **6** (Experimental Section) are in accord with the piperidone structure. This efficient synthesis of the required piperidine derivatives provides a new and perhaps generally useful approach to 1,3,4-trisubstituted 2-piperidones.[9]

SCHEME I



Our hope was that the piperidone diester **6** could be combined with indole in a Vilsmier condensation. A

* To whom correspondence should be addressed.

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(2) A portion of this work was published in preliminary form: L. J. Dolby and H. Biere, *J. Amer. Chem. Soc.*, **90**, 2699 (1968).

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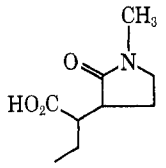
(9) Some preliminary experiments indicated that condensation of α-bromobutanoyl chloride with aziridine did yield the dihaloamide. However, the desired alkylation of malonic ester was prevented by oxazoline formation.

previous study by Szmuszkovicz and coworkers illustrated the synthetic utility of the condensation of lactams and indole by means of phosphorus oxychloride.[10] However, the diester **6** proved to be very unreactive and we were not able to obtain useful material from attempted condensations with indole. In order to increase the reactivity of the amide grouping, the piperidone diester was decarbomethoxylated in 70% yields by treatment with sodium cyanide in hot *N,N*-dimethylformamide (DMF), a modification of the procedure reported by Krapcho, Glynn, and Grenon.[11]

More usual hydrolysis and decarboxylation procedures gave material which showed complex carbonyl absorption in its infrared spectrum. In particular absorption at 1680 cm^{-1} was ascribed to the presence of pyrrolidones which is not unexpected since hydrolysis of the piperidone ring followed by cyclization involving the C-4 carboxyl group would give a mixture of stereoisomers of the pyrrolidonecarboxylic acid **10**.



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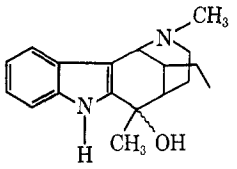
The *N*-methyl-3-ethyl-4-carbomethoxy-2-piperidone obtained from the sodium cyanide treatment of **6** was clearly a mixture of diastereomers as indicated by its nmr spectrum. The ester mixture was used directly in the Vilsmier condensation with indole since the remaining stages of the synthesis allow ample opportunity for epimerization. The product from the Vilsmier condensation was not isolated. The reaction mixture was diluted with ammonia and treated with sodium borohydride to give in about 65% yield a mixture of stereoisomers of ester **8**. This mixture was suitable for the next steps in the conversion to dasycarpidone and epidasycarpidone. One diastereomer was obtained in pure form by chromatography over alumina, but the stereochemistry of this material was not established.

Preliminary attempts to effect the final ring closure using ester **8** were quite discouraging. Reasonable mechanisms can be written for base induced cyclization as well as acid-catalyzed cyclization. However, treatment of the ester **8** with sodium hydride, methylmagnesium iodide, or polyphosphoric acid gave no materials showing 2-acylindole absorption in the ultraviolet region. Accordingly, the ester was saponified and it was quickly found that polyphosphoric acid cyclization gave a mixture of 2-acylindoles. The best cyclization conditions we found gave a 2-acylindole mixture in 65% yield and pure (±)-epidasycarpidone could be as obtained in 54% yield. The (±)-epidasycarpidone was identified from its spectral properties and tlc comparison with a sample of (±)-epidasycarpidone kindly provided by Professor J. A. Joule. (±)-Dasycarpidone was also present in the products from some of the cyclization reactions. The dasycarpidone was extremely difficult to separate from some of the by-products from the cyclization. In one cyclization experiment using carefully recrystallized amino acid 9, (±)-epidasycarpidone was isolated in 47% yield by direct crystallization and dasycarpidone could not be detected by tlc. In a similar experiment using crude amino acid, pure (±)-dasycarpidone was isolated in 0.7% yield by repeated preparative tlc. These results suggest that the purified amino acid has the trans–cis stereochemistry which leads directly to epidasycarpidone and dasycarpidone is formed from all cis isomer which is present in relatively small amounts in the crude acids prepared from the ester mixture **8**. However, it is not impossible that the amino acid **8** is epimerized in polyphosphoric acid solution and prior to cyclization Moreover, a plausible mechanism can be written for the interconversion of dasycarpidone and epidasycarpidone in acid solution although Joule and his coworkers found no evidence of this interconversion in hot acetic acid. In any event, all samples of the amino acid **8** gave predominantly (±)-epidasycarpidone which could easily be isolated in 40% yields and improved by chromatographic separation of the mother liquors.

The remaining synthetic problem was the conversion of the carbonyl group to an *exo*-methylene. Preliminary studies with 1-ketotetrahydrocarbazole indicated that the Wittig reaction would not be useful for this transformation although Joule and coworkers successfully converted dasycarpidone into uleine in 13% yield by this method. Moreover, we were unable to effect the addition of methylmagnesium iodide to the carbonyl group of 1-ketotetrahydrocarbazole but methyllithium reacted quite normally. Accordingly, (±)-epidasycarpidone was treated with methyllithium to give the carbinol **11** in excellent yields.



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The nicely crystalline carbinol appeared to be a single diastereomer, but the stereochemistry was not determined. The carbinol could be dehydrated in poor yield to (±)-epiuleine by exposure to 85% phosphoric acid, but the conversion was quite efficient using alumina as the dehydrating agent. A very simple procedure converted the carbinol to (±)-epiuleine in 77% yield. The (±)-epiuleine thus obtained was identical with the (±)-epiuleine prepared by Joule and his coworkers.

Experimental Section[12]

***N*-Methyl-*N*-(2-chloroethyl)-α-bromobutyramide (5).**—α-Bromobutyryl chloride (185 g, 1 mol), prepared as previously

(10) G. A. Youngdale, D. G. Anger, W. C. Anthony, J. P. DaVanzano, M. E. Greig, R. V. Heinzelman, H. H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, **7**, 415 (1964).

(11) A. P. Krapcho, G. A. Glynn, and B. J. Grenon, *Tetrahedron Lett.*, 215 (1967).

(12) Melting points and boiling points are uncorrected. Ultraviolet spectra were measured on ethanol solutions using a Cary Model 15 spectrophotometer and infrared spectra were determined with a Beckman IR-5A infrared spectrophotometer. A Varian Associates A-60 instrument was used for nmr spectra. Chemical shifts are reported as δ values with tetramethylsilane as internal standard. Mass spectra were measured with a CEC 101 mass spectrometer. Combustion analyses were performed by Berkeley Analytical Laboratories, Berkeley, Calif.

described,[13] and freshly distilled *N*-methylaziridine (57 g, 1 mol) dissolved in 50 ml of dry benzene were added concurrently from two dropping funnels to 300 ml of dry benzene cooled to the freezing point with vigorous stirring. The rate of addition was adjusted so the temperature did not rise above 10°. The benzene solution was filtered to remove a small amount of polymer and used directly in the next step: nmr (benzene) 2.74 (singlet, three protons, *N*-CH_3), 3.44 ppm (broad singlet, four protons, *N*-CH_2CH_2Cl).

***N*-Methyl-3-ethyl-4,4-dicarbomethoxy-2-piperidone (6).**—The benzene solution of *N*-methyl-*N*-(2-chloroethyl)-α-bromobutyramide obtained above and 500 ml of 2 *N* sodium methoxide were added concurrently to a stirred and refluxing solution of sodium dimethyl malonate prepared from 500 ml of 2 *N* sodium methoxide and 132 g (1 mol) of dimethyl malonate. After completion of the addition (*ca.* 2 hr) the mixture was heated under reflux for 75 min. The cooled mixture was neutralized with acetic acid, filtered, and concentrated under reduced pressure. The residue was taken up in chloroform, filtered, and washed with water. Distillation under reduced pressure afforded 170 g (*ca.* 65%) of material, bp 120–160° (1.0 mm), collected in several fractions. The material appeared to be nearly pure **6** and the higher boiling fractions crystallized on standing. Tlc on silica gel G (according to Stahl) with ethyl acetate indicated diester (R_f 0.3) and monoesters (R_f 0.6). In a similar experiment on 0.75 mol scale the crystalline diester (mp 78–79° from ether–*n*-hexane) was isolated in 51% yield. The infrared spectrum showed $\nu_{max}^{CHCl_3}$ 1730 and 1640 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 55.60; H, 7.52; N, 5.59.

***N*-Methyl-3-ethyl-4-carbomethoxy-2-piperidone (7).**—To a solution of sodium cyanide (6.5 g, 0.13 mol) in DMF (100 ml) was added 23 g (0.09 mol) of **6**. The solution was heated under reflux and gas evolution was monitored with a gas burette. In 10 min 250 ml of gas was evolved (calculated for 1 equiv of carbon dioxide 2 l.) and gas evolution stopped. A white precipitate formed during this time. The mixture was heated at 150° for an additional 2 hr. The solution was filtered and concentrated under reduced pressure. The residue was taken up in chloroform and washed with water. The crude product was distilled under reduced pressure to yield 12.4 g (70%) of **7** as a mixture of diastereomers, bp 110–120° (0.4 mm). The infrared spectrum showed $\nu_{max}^{CHCl_3}$ 1730 and 1630 cm^{-1}; nmr ($CDCl_3$) 3.72 ppm (singlet, three protons, CO_2CH_3), 2.95 (singlet, three protons, *N*-CH_3), and *ca.* 0.9 (two overlapping triplets, three protons, CH_2CH_3).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03 Found: C, 59.71; H, 8.67; N, 6.98.

3-[2-(*N*-Methyl-3-ethyl-4-carbomethoxypiperidyl)]indole (8).—Piperidone **7** (12 g, 0.06 mol) was added to freshly distilled phosphorus oxychloride (12 g). The mixture was stirred at room temperature for 2 hr after which 7 g (0.06 mol) of indole was added. The mixture was then heated at 80° for 1 hr during which it became very viscous. After dilution with 1,2-dichloroethane heating was continued for 10 hr. Aliquots of the reaction mixture showed increasing absorption at 335 mμ which disappeared on addition of sodium borohydride. The cooled reaction mixture was diluted with methanol (50 ml) and made slightly alkaline by addition of 25% aqueous ammonia after which it was slowly added to a solution of sodium borohydride (4.0 g) in aqueous methanol. The methanol was boiled off and the resulting mixture was extracted with chloroform. The chloroform solution was extracted several times with 12% hydrochloric acid. The hydrochloric acid extracts were made strongly alkaline and extracted with chloroform to afford 11.8 g (66%) of crude **8** which was suitable for preparation of the amino acid **9**. A portion of crude **8** was filtered through neutral activity II alumina and crystallized to give a pure diastereomer of **8**: mp 140–141° (from benzene–hexane); nmr ($CDCl_3$) 0.64 (triplet, three protons, J = 6 Hz, CH_2CH_3), 2.01 (singlet, three protons, *N*-CH_3), and 3.72 ppm (singlet, three protons, CO_2CH_3).

Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.78; H, 8.16; N, 9.01.

Amino Acid 9.—A solution of crude **8** (11.8 g, 0.039 mol) in dioxane (50 ml) was added to 400 ml of 1.1 *N* barium hydroxide (aqueous) and the resulting mixture was refluxed under nitrogen for 6 hr after which it was filtered and neutralized while hot with 20% sulfuric acid. The barium sulfate was collected and washed with hot water. The combined aqueous solutions were lyophilized to yield 6.8 g (59%) of the amino acid mixture as a white solid. A single isomer, mp 235–238° dec, could be obtained by crystallization from ethyl acetate–methanol: nmr (pyridine-d_5–D_2O) 0.83 (triplet, three protons, J = 7 Hz, CH_2CH_3) and 2.76 ppm (singlet, three protons, *N*-CH_3).

Anal. Calcd for $C_{17}H_{22}N_2O_2.2H_2O$: C, 63.33; H, 8.13; N, 8.69. Found: C, 62.86; 63.00; H, 7.14. 7.60; N, 8.62, 8.74.

(±)-Epidasycarpidone (4).—A sample of pure recrystallized amino acid **9** (0.318 g, 0.97 mmol) was mixed with 4 g of polyphosphoric acid and slowly heated to 75° with stirring and maintained at that temperature for 1 hr. The mixture was poured into 150 g of ice–water with vigorous stirring and then basified with 25% aqueous ammonia. The basic solution was extracted with ether and the ether extracts were washed with water, dried, and concentrated to a small volume. (±)-Epidasycarpidone, mp 168–169° (0.122 g, 47%), crystallized in large cubes. The (±)-epidasycarpidone was identified by comparison of its mass spectrum with the published spectrum of dasycarpidone.[6] Epidasycarpidone and dasycarpidone are reported to show the same mass spectrum in accord with our observations.[5] Comparison of the behavior on tlc of our (±)-epidasycarpidone with a sample provided by Professor Joule confirmed the identification. The mother liquors from the isolation of (±)-epidasycarpidone contained additional epidasycarpidone and several other side products but (±)-dasycarpidone could not be detected by tlc. Using silica gel G and benzene–ethyl acetate–ethanol (2:2:1 v/v) epidasycarpidone (R_f 0.50) and dasycarpidone (R_f 0.3) are readily separated.

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.99; H, 7.46; N, 10.01.

The picrate, mp 230 dec from ethyl acetate, was obtained by treatment with saturated picric acid in 95% ethanol.

Anal. Calcd for $C_{23}H_{23}N_5O_8$: C, 55.53; H, 4.66; N, 14.08. Found: C, 55.37; H, 4.52; N, 13.97.

(±)-Dasycarpidone.—A sample of crude amino acid (0.790 g, 3.3 mmol) was cyclized as described above. Preparative tlc of the entire crude product afforded 350 mg (54%) of (±)-epidasycarpidone and 100 mg of crude (±)-dasycarpidone. The crude dasycarpidone was subjected to repeated preparative tlc to give 5 mg (0.7%) of amorphous (±)-dasycarpidone (dasycarpidone has never been obtained in crystalline form) which showed the same infrared spectrum as natural dasycarpidone[14] and the same mass spectrum as observed for epidasycarpidone.

1-Methyl-3-epi-dasycarpidol.—A solution of (±)-epidasycarpidone (300 mg) in 3 ml of dry tetrahydrofuran under nitrogen was treated with 2 ml of 2 *N* methyllithium in ether. After 10 min the ultraviolet spectrum of the reaction mixture showed no 2-acylindole absorption at 314 mμ. The reaction mixture was hydrolyzed with water and extracted with ether to yield 0.310 g (97%) of carbinol **11**, mp 165–167° dec from methylene chloride.

Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 75.80; H, 8.36; N, 9.68.

(±)-Epiuleine.—An ether solution of the carbinol obtained above (0.100 g, 0.35 mmol) in ether was added to 3.5 g of activity I neutral alumina in an erlenmeyer flask. The ether was removed with a nitrogen stream and the material was heated for 30 min at 90–95° in an oven. The material was extracted from the alumina with ether and chromatographed over activity II neutral alumina with ether–benzene to give (±)-epiuleine, 50 mg (77% based on unrecovered carbinol), and recovered carbinol (30 mg). (±)-Epiuleine shows mp 135–136° after crystallization from petroleum ether (bp 30–60°). The (±)-epiuleine thus obtained was identical by uv, ir, mass spectrum, mixture melting point, and tlc with a sample prepared by Joule and coworkers and compared with natural epiuleine.[15]

Registry No.—**2**, 19775-51-0; **3**, 18700-27-1; **4**, 18688-38-5; **4** picrate, 26146-13-4; **6**, 26154-16-5; **7**, 18813-70-2; **8**, 18688-39-6; **9**, 26154-19-8; **11**, 26211-02-9.

(13) S. R. Safir, H. Dalalian, W. Fanshawe, K. Cyr, R. Lopresti, R. Williams, S. Upham, L. Goldman, and S. Kushner, *J. Amer. Chem. Soc.*, **77**, 4840 (1955).

(14) We are indebted to Professor Carl Djerassi for providing us with spectra of dasycarpidone.

(15) We are grateful to Professor J. A. Joule, University of Manchester, for carrying out this comparison and for communicating his results to us before publication.