Studies on the Syntheses of Heterocyclic Compounds. CCCXCIV.[1] Total Syntheses of (±)-Dasycarpidone and (±)-3-Epidasycarpidone. Formal Total Syntheses of (±)-Uleine and (±)-3-Epiuleine

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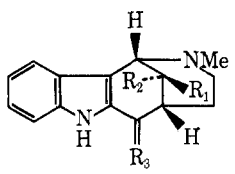
Syntheses of the racemic forms of the indole alkaloids, dasycarpidone (**1**), 3-epidasycarpidone (**3**), uleine (**2**), and 3-epiuleine (**4**), together with that of so-called isodasycarpidone (**15**) and isoepidasycarpidone (**16**), are described. The key step in the approach to the compounds **7** and **8** involved a condensation of indolylmagnesium bromide with methyl 3-ethylisonicotinate 1-oxide (**6**).

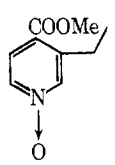
In our previous paper,[2] we reported a synthesis of deethyldasycarpidone (**5**) by the Grignard reaction. We now wish to report syntheses of (±)-dasycarpidone (**1**) and (±)-3-epidasycarpidone (**3**) by the above reaction. An alternative and different approach to the total synthesis of **1** and **3** has been reported.[3,4] Our synthesis is based on the production of intermediate **7** by a Grignard reaction.



1, $R_1 = H$; $R_2 = Et$; $R_3 = O$
2, $R_1 = H$; $R_2 = Et$; $R_3 = CH_2$
3, $R_1 = Et$; $R_2 = H$; $R_3 = O$
4, $R_1 = Et$; $R_2 = H$; $R_3 = CH_2$
5, $R_1 = R_2 = H$; $R_3 = O$

Grignard condensation of indolylmagnesium bromide with methyl 3-ethylisonicotinate 1-oxide (**6**) in tetrahydrofuran and methylene dichloride in the presence of benzoyl chloride was carried out to give a mixture of the desired condensation product **7** and its structural isomer **8**, both of which were separated as described in the Experimental Section. The ir spectrum ($CHCl_3$) of both **7** and **8** showed an absorption band due to indole NH at 3430 cm^{-1} and an ester carbonyl band at 1725 cm^{-1}. An absorption band due to the C=C double bond was very weak in **7** but was observed at 1600 cm^{-1} in **8** as a very strong absorption. The nmr spectra (δ) of both compounds lacked a signal due to an indole β proton, but the N hydrogen of the indole ring was observed. The signal of the methyl group was observed at 3.92 in **7** and at 3.96 ppm in **8**. The other methyl signal due to the ethyl group of **7** resonated at 1.0 ppm, whereas that of **8** resonated at 1.27 ppm. An ortho coupling in the pyridine ring was observed in **7** but was absent in **8**. The mass spectra of both compounds showed the same molecular ions at *m/e* 280. Treatment of **7** with methyl iodide in methanol gave a pyridinium methiodide (**9**), which on catalytic reduction yielded a stereoisomeric mixture of the amino esters **11**. After normal saponification, the resulting amino acids **13** were heated with polyphosphoric acid at 90–95° by Dolby's method[4] to yield a mixture of 2-acylindoles, which on preparative thick layer chromatography afforded (±)-dasycarpidone (**1**) and (±)-3-epidasycarpidone (**3**), the ratio of the two compounds being about 2:1. Our synthetic syrupy dasycarpidone (**1**) had uv, ir, nmr, and mass spectra identical with published physical data.[5] The identity of synthetic **1** was also confirmed by the formation of crystalline picrate, mp 239–240° dec (lit.[4] 240°). The mass spectrum of (±)-3-epidasycarpidone (**3**), mp 166–168° (lit. 168–169°,[4] 164–166°[6]) was identical with that of dasycarpidone, and the nmr and uv absorptions coincided with those reported for (±)-3-epidasycarpidone[5] (**3**). Furthermore, ir spectra and tlc behavior of **1** and **3** were identical with those of authentic samples donated by Professor Joule. Since **1** and **3** had been converted into uleine (**2**) and 3-epiuleine (**4**) by Joule and his coworkers,[3] an alternative formal total synthesis of **2** and **4** has been accomplished.

The so-called (±)-isodasycarpidone (**15**) and (±)-iso-5-epidasycarpidone (**16**) were synthesized as follows. Treatment of **8** with methyl iodide afforded a pyridinium methiodide **10**, whose catalytic reduction yielded a mixture of the amino esters **12**. Normal sa-



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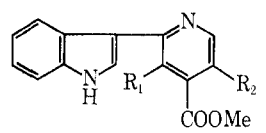
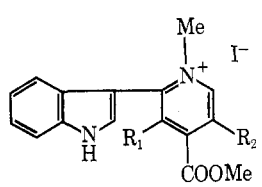
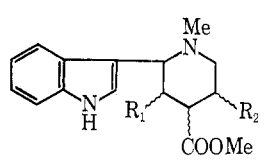


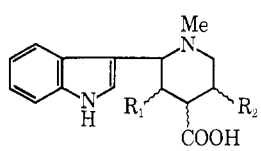
7, $R_1 = Et$; $R_2 = H$
8, $R_1 = H$; $R_2 = Et$



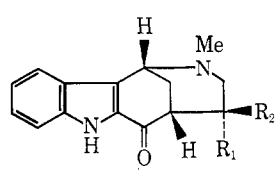
9, $R_1 = Et$; $R_2 = H$
10, $R_1 = H$; $R_2 = Et$



11, $R_1 = Et$; $R_2 = H$
12, $R_1 = H$; $R_2 = Et$



13, $R_1 = Et$; $R_2 = H$
14, $R_1 = H$; $R_2 = Et$



15, $R_1 = Et$; $R_2 = H$
16, $R_1 = H$; $R_2 = Et$

(1) Part CCCXCIII: T. Kametani, K. Takahashi, S. Shibuya, and K. Fukumoto, *J. Chem. Soc. C*, in press.
(2) T. Kametani and T. Suzuki, *ibid.*, in press.
(3) A. Jackson, N. D. V. Willson, A. J. Gaskell, and J. A. Joule, *ibid.*, 2738 (1969).
(4) L. J. Dolby and H. Biere, *J. Amer. Chem. Soc.*, **90**, 2699 (1968).
(5) J. A. Joule, M. Ohashi, B. Gilbert, and C. Djerassi, *Tetrahedron*, **21**, 1717 (1965).
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ponification afforded the amino acids **14**, which were heated with polyphosphoric acid to yield a mixture of 2-acylindoles. Careful thick layer chromatography afforded (±)-isodasycarpidone (**15**) and (±)-isoepidasycarpidone (**16**); the ratio of both compounds was also about 2:1. The ir spectra ($CHCl_3$) of both compounds showed absorption bands at 3430 (indole NH), 2780 (NMe), and 1645 cm^{-1} (conjugated C=O), but differences in the finger print region were observed. In the nmr spectra of the two epimers of isodasycarpidone, the methyl protons due to the ethyl group of (±)-isodasycarpidone (**15**) resonated at 1.0 ppm, whereas the corresponding signal of (±)-iso-5-epidasycarpidone (**16**) was observed at 1.1 ppm. Since the ethyl group of **15** lies over the aromatic π-electron system, this epimer would be expected to show a methyl signal at a higher field as in the case of (±)-dasycarpidone and (±)-3-epidasycarpidone.[6] It is interesting that catalytic reduction of the pyridinium methiodides **9** and **10** afforded a higher ratio of dasycarpidone to epidasycarpidone type compounds than Dolby's method.[4]

Experimental Section[7]

Methyl 3-Ethylisonicotinate 1-Oxide (6).—To a mixture of 120 ml of acetic acid and 21 ml of 30% hydrogen peroxide was added 10 g of methyl 3-ethylisonicotinate; the mixture was heated at 70–80° for 24 hr. After the reaction mixture had been condensed to one-third volume under reduced pressure, the resulting residue was basified with potassium carbonate and extracted with chloroform. The extract was dried over K_2CO_3 and evaporated to give a syrup, whose recrystallization from benzene–hexane gave 8 g of the *N*-oxide **6** as colorless needles: mp 69–70°; ir ($CHCl_3$) 1720, 1665, 1140, and 1100 cm^{-1}.

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.96; H, 5.98; N, 8.01.

3-Ethyl-2-(3-indolyl)-4-methoxycarbonylpyridine (7) and 5-Ethyl-2-(3-indolyl)-4-methoxycarbonylpyridine (8).—A solution of 16 g of indole in 150 ml of tetrahydrofuran was added to a solution of ethylmagnesium bromide (prepared by the reaction of 18 g of ethylbromide with 4 g of magnesium turnings at −10° for 10 min). The reaction mixture was stirred at room temperature for 30 min, and then 500 ml of methylene dichloride was added in order to bring the complex into solution. To a cooled solution at −30° was added a mixture of 20 g of methyl 3-ethylisonicotinate 1-oxide (**6**) and 18.2 g of benzoyl chloride at this temperature within 30 min. The mixture was stirred at 50° for 24 hr and then decomposed with a solution of 7 g of ammonium chloride in 100 ml of water. After the solvent had been distilled off *in vacuo*, the resultant residue was extracted with ether. The extract was then washed with water and again extracted with 10% hydrochloric acid solution. The acidic solution was basified with ammonia and then extracted with chloroform. The extract was washed with sodium chloride solution, dried over K_2CO_3, and evaporated to give 8.6 g of a brown syrup, which was chromatographed on 200 g of silica gel using chloroform as an eluent. Evaporation of the above eluate afforded a mixture of 3 g of compounds **7** and **8**, which were triturated with methanol to separate **7** as crystals. Recrystallization from methanol–ether afforded 900 mg of colorless prisms: mp 185–186°; ir ($CHCl_3$) 3430, 1725 cm^{-1}; nmr δ ($CDCl_3$) 1.0 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.7 (2 H, q, J = 7.0 Hz, CH_2CH_3), 3.92 (3 H, s, CO_2CH_3), 6.95–7.2 (4 H, m, Ar H), 7.4–7.65 (1 H, m, Ar H), 7.43 (1 H, d, J = 6 Hz, 5-H), 8.56 (1 H, d, J = 6 Hz, 6-H), 9.0–9.2 (1 H, NH of indole ring, exchanged with D_2O); m/e 280 (M^+), 255, 249, and 221.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.75; H, 5.35; N, 9.95.

An excess of ether saturated with hydrogen chloride gas was added to the above filtrate, and the hydrochloride of **8** was obtained. Recrystallization from methanol–ether afforded 450 mg of yellow needles: mp 178–180°; ir (KBr) 3400, 1730, 1640, and 1600 cm^{-1}; m/e 280 (M^+), 255, 249, and 221.

Anal. Calcd for $C_{17}H_{17}ClN_2O_2$: C, 64.45; H, 5.40; N, 8.84. Found: C, 64.90; H, 5.58; N, 9.04.

The above hydrochloride was freed to give compound **8** (360 mg) as a pale yellow syrup, whose recrystallization from chloroform–hexane afforded colorless needles: mp 99–100°; ir ($CHCl_3$) 3430, 1725, and 1600 cm^{-1}; nmr δ ($CDCl_3$) 1.27 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.94 (2 H, q, J = 7.0 Hz, CH_2CH_3), 3.96 (3 H, s, CO_2CH_3), 7.2–7.4 (3 H, m, Ar H), 7.72 (1 H, d, J = 3.0 Hz, Ar H), 8.06 (1 H, s, 3-H), 8.35 (1 H, m, Ar H), 8.63 (1 H, s, 6-H), 8.75–8.9 (1 H, NH of indole ring, exchanged with D_2O); m/e 280 (M^+).

3-Ethyl-2-(3-indolyl)-4-methoxycarbonyl-1-methylpyridinium Iodide (9).—To a solution of 300 mg of **7** in 50 ml of methanol was added 10 ml of methyl iodide, and the mixture was refluxed for 4 hr. The solvent and reagent were evaporated to give 480 mg of a yellow syrup (**9**) [ir ($CHCl_3$) 3430, 2920, and 1740 cm^{-1}; nmr δ ($CDCl_3$) 0.9 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.92 (2 H, q, J = 7.0 Hz, CH_2CH_3), 4.0 (3 H, s, NMe), 4.55 (3 H, s, CO_2CH_3)], whose crystallization was so difficult that it was used in the following reaction.

3-Ethyl-2-(3-indolyl)-4-methoxycarbonyl-1-methylpiperidine (11).—The methiodide **9** (480 mg) was reduced with hydrogen in methanol over Adams catalyst at atmospheric pressure and room temperature. The solution was filtered and then evaporated to give a residue which was basified with 10% ammonia and extracted with ether. The extract was washed with sodium chloride solution, dried over K_2CO_3, and distilled off to give 320 mg of a stereoisomeric mixture of amino ester **11**: ir ($CHCl_3$) 3430, 2900, 2750, and 1720 cm^{-1}; m/e 300 (M^+).

3-Ethyl-4-hydroxycarbonyl-2-(3-indolyl)-1-methylpiperidine (13), (±)-Dasycarpidone (1), and (±)-3-Epidasycarpidone (3).—A mixture of 269 mg of the amino ester **11**, 1 g of potassium hydroxide, 10 ml of water, and 20 ml of ethanol was refluxed for 3 hr. The above mixture was then neutralized with concentrated hydrochloric acid, and the solvent was evaporated completely to give a residue, which was extracted with dry ethanol to give 200 mg of the carboxylic acid **13** as a powder. Without purification, the acid **13** was treated with polyphosphoric acid (prepared from 2 ml of phosphoric acid and 4 g of phosphorus pentoxide) at 90–95° for 1.5 hr. After the addition of 5 ml of water, the reaction mixture was basified with ammonia and then extracted with ether. The extract was washed with sodium chloride solution, dried over K_2CO_3, and distilled off to give 70 mg of a pale yellow syrup. Preparative thick layer chromatography (ethyl acetate–benzene–methanol, 2:2:1) on silica gel afforded 34 mg of (±)-dasycarpidone (**1**) [ir ($CHCl_3$) 3400, 2900, 2875, and 1640 cm^{-1}; uv (EtOH) 316 and 237 nm (log ϵ 4.30 and 4.15); nmr δ ($CDCl_3$) 0.88 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.34 (3 H, s, NMe), 4.25 (1 H, d, J = 2.5 Hz, β-indolic CHN), 7.0–7.8 (4 H, m, Ar H), 10.20–10.50 (1 H, NH of indole ring, exchanged with D_2O); m/e 268 (M^+), 253, 239, 225, 211, 198, and 183], whose picrate was recrystallized from ethanol to afford a yellow powder [mp 239–240° dec (lit.[4] 240°)] and 15 mg of (±)-3-epidasycarpidone (**3**) [ir 3400, 2800, 2775, and 1650 cm^{-1}; uv (EtOH) 314 and 238 nm (log ϵ 4.01 and 3.88); nmr δ ($CDCl_3$) 1.08 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.3 (3 H, s, NMe), 4.2 (1 H, d, J = 2.5 Hz, β-indolic CHN), 7.0–7.8 (4 H, m, Ar H), 9.6–9.9 (1 H, NH of indole ring, exchanged with D_2O); m/e 268 (M^+), 253, 239, 225, 211, 198, and 183], which was triturated with methanol to give crystals. Recrystallization of **3** from ethanol–ether gave colorless cubes, mp 166–168° (lit. 168–169°,[4] 164–166°[6])].

5-Ethyl-2-(3-indolyl)-4-methoxycarbonyl-1-methylpyridinium Iodide (10).—To a solution of 360 mg of **8** in 40 ml of methanol was added 10 ml of methyl iodide, and the mixture was refluxed for 6 hr. The solvent and reagent were evaporated to give 559 mg of a yellow syrup, whose recrystallization from methanol–ether gave the methiodide **10** as yellow needles: mp 140–142°; ir ($CHCl_3$) 3430, 2920, and 1730 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}IN_2O_2$: N, 6.63. Found: N, 6.77.

5-Ethyl-2-(3-indolyl)-4-methoxycarbonyl-1-methylpiperidine (12).—The methiodide **10** (519 mg) was reduced with hydrogen in methanol over Adams catalyst at atmospheric pressure and room temperature. After the solution had been filtered and evaporated, the residue was basified with 10% ammonia and

(7) The ir spectra were taken in chloroform unless otherwise noted with a Hitachi EPI-S2 spectrometer. Uv spectra were taken in ethanol solution on a Hitachi EPS-3 recording spectrometer. Mass spectra were measured on a Hitachi RMU-7 mass spectrometer. Nmr spectra were measured in deuteriochloroform solution, using tetramethylsilane as an internal standard, on a Hitachi R-20 instrument. The melting points are uncorrected.

extracted with ether. The extract was washed with sodium chloride solution, dried over K_2CO_3, and distilled off to give 330 mg of a stereoisomeric mixture of amino ester **12** [ir ($CHCl_3$) 3450, 2900, 2750, 1720, and 1600 cm^{-1}; *m/e* 300 (M^+)], which was used in the following reaction without purification because of difficult crystallization.

(±)-Isodasycarpidone (15) and (±)-Iso-5-epidasycarpidone (16).—A mixture of 300 mg of the amino esters **12**, 1 g of potassium hydroxide, 10 ml of water, and 20 ml of ethanol was refluxed for 5 hr. The resulting mixture was neutralized with concentrated hydrochloric acid and the solvent was evaporated completely to give a residue, which was extracted with dry ethanol. Removal of the extract gave 270 mg of 5-ethyl-4-hydroxycarbonyl-2-(3-indolyl)-1-methylpiperidine (**14**) as a powder, which was treated with polyphosphoric acid (prepared from 2 ml of phosphoric acid and 4 g of phosphorus pentoxide) at 90–95° for 1 hr. To the reaction mixture was added 5 ml of water, and the resulting mixture was basified with ammonia and extracted with ether. The extract was washed with sodium chloride solution, dried over K_2CO_3, and distilled off to give 98 mg of a pale yellow syrup, whose preparative thick layer chromatography (ethyl acetate–benzene–methanol, 2:2:1) on silica gel afforded 16 mg of (±)-isodasycarpdione (**15**) and 9 mg of (±)-iso-3-epidasycarpidone (**16**). Recrystallization of **15** from methanol–ether gave colorless needles: mp 220–221°; ir ($CHCl_3$) 3430, 2900, 2780, and 1645 cm^{-1}; nmr δ ($CDCl_3$) 1.0 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.25 (3 H, s, NMe), 4.3 (1 H, t, J = 2.5 Hz, β-indolic CHN), 7.0–7.8 (4 H, m, Ar H), 9.7–10.0 (1 H, NH of indole ring, exchanged with D_2O); *m/e* 268 (M^+), 253, 240, 225, 211, 196, and 183.

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 75.56; H, 7.87; N, 10.70.

Recrystallization of **16** from methanol–ether gave colorless needles: mp 201–202°; ir 3430, 2900, 2780, and 1645 cm^{-1}; nmr δ ($CDCl_3$), 1.1 (3 H, t, J = 7.0 Hz, CH_2CH_3), 2.3 (3 H, s, NMe), 4.35 (1 H, t, J = 2.5 Hz, β-indolic CHN), 7.0–7.8 (4 H, m, Ar H), 10.4–10.8 (1 H, NH of indole ring, exchanged with D_2O); *m/e* 268 (M^+), 253, 240, 225, 211, 196, and 183.

Registry No.—**1**, 18700-27-1; **2**, 19775-50-9; **3**, 18688-38-5; **4**, 19775-51-0; **6**, 28199-31-7; **7**, 28199-32-8; **8**, 28199-33-9; **8** HCl, 28199-34-0; **9**, 28199-35-1; **10**, 28199-36-2; **15**, 28192-70-3; **16**, 28192-71-4.

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Notes

Studies on the Syntheses of Heterocyclic Compounds. CCCXCV. The Synthesis of Homopetaline-Type Compounds

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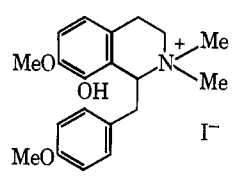
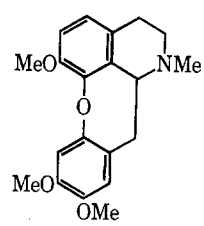
Petaline (**1**)[1,2] and cularine (**2**)[3] are benzylisoquinoline alkaloids having the oxygenated function at the C-7 and C-8 positions on the isoquinoline ring. The former was synthesized by Brossi[4] and the latter by Kametani.[5–7]



1



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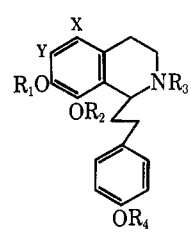

3, $R_1 = R_3 = R_4 = Me$; $R_2 = X = Y = H$
9, $R_1 = R_3 = R_4 = Me$; $R_2 = Y = H$; $X = Br$
13, $R_1 = R_2 = R_3 = R_4 = Me$; $X = H$; $Y = NHCOOEt$
14, $R_1 = R_2 = R_3 = R_4 = Me$; $X = H$; $Y = NH_2$
15, $R_1 = R_2 = R_3 = R_4 = Me$; $X = Y = H$
16, $R_1 = R_3 = Me$; $R_2 = R_4 = X = Y$ H

Several unsuccessful attempts have been made[8,9] to prepare 7,8-dioxygenated isoquinolines by the Bischler–Napieralski or Pictet–Spengler reaction. Therefore, we reinvestigated the synthesis of 7,8-dioxygenated isoquinolines by the above two methods.

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