

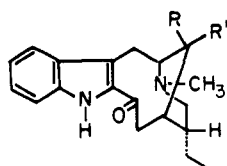
# Total Synthesis of Dregamine and Epidregamine. A General Route to 2-Acylindole Alkaloids

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**Abstract:** Dregamine (**1**) and epidregamine (**2**) have been prepared by stereoselective total synthesis. L(-)-Tryptophan was converted into the four isomeric 6(S)-cyanomethyl-3-ethyl-2-oxo-1,2,3,4,6,7,12a,12b-octahydroindolo[2,3-a]quinolizines **12–15**. Base-catalyzed transannular cyclization gave 16(R)- and 16(S)-cyano-16-decarbomethoxy-19,20(S)-dihydro-15(R)-hydropericyclivine (**17** and **16**), exemplifying the sarpagine skeleton. Subsequent ring opening and functional group elaboration provided a general route to 2-acylindole alkaloids.

Dregamine (**1**) and epidregamine (**2**) are representative of the 2-acylindole alkaloids<sup>1–3</sup> which have been interrelated with the sarpagine family<sup>4,5</sup> and, via the latter, with the



- 1 R = CO<sub>2</sub>Me, R' = H  
2 R = H, R' = CO<sub>2</sub>Me

ajmaline group.<sup>6–10</sup> The voacamine-type bisindole alkaloids<sup>11</sup> have been shown to incorporate a 2-acylindole system as a structural unit.<sup>12,13</sup> Recent efforts<sup>14–16</sup> have resulted in a revised structure for dregamine which is here confirmed by total synthesis.

Synthetic design was based on the strategy summarized in Figure 1. L(-)-Tryptophan provided both the ethanamine side chain and correct absolute stereochemistry for C<sub>5</sub> in the alkaloids. A tetracyclic intermediate such as **3** was envisaged as an ideal progenitor of the sarpagine skeleton, **4**, which could then be elaborated via ring cleavage and specific functionalization to the 2-acylindole system **5**.

Hydride reduction of L(-)-tryptophan and subsequent tosylation gave the ditosylate **7** which, on treatment with potassium cyanide and deprotection, afforded the nitrile **9** (Figure 2). Formylation to **10** was accomplished in 60% overall yield from tryptophan. Polyphosphate ester (PPE)<sup>17</sup> proved the reagent of choice for efficient cyclization to the 3(S)- $\beta$ -carboline **11** ([ $\alpha$ ]<sub>D</sub> +35°). This product was found to be unstable

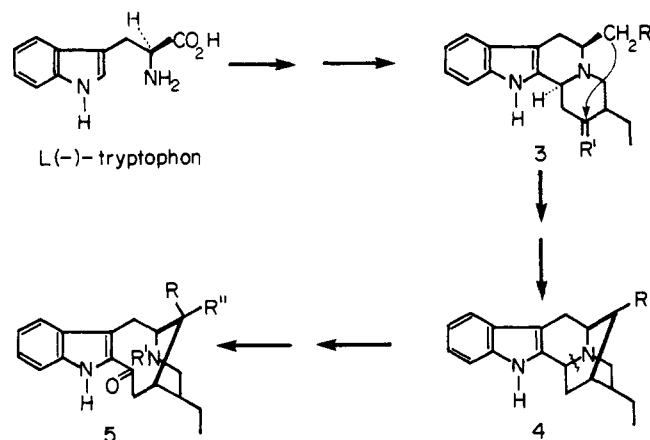


Figure 1.

on storage and was used directly in crude form for the annelation (viz., **11**  $\rightarrow$  **12**  $\rightarrow$  **15**).

Addition of **11** to 3-methylenepentane-2-one<sup>18,19</sup> under acid catalysis gave a mixture (75% yield from **10**) of the isomeric ketones **12–15**. Beckett et al.<sup>20</sup> had established physical criteria for the identification of normal, pseudo, allo, and epiallo configurations of corynantheidine-type alkaloids and exploitation of their method enabled assignment of absolute stereochemistry to the four ketones. Examination of Dreiding models readily established the most favored conformations as depicted in Figure 3. The presence of significant Bohlmann bands in the infrared spectra of **12**, **14**, and **15** immediately established a trans-diaxial relationship between the nitrogen lone pair and C<sub>12b</sub>-H in the most favored conformers of these isomers.<sup>20</sup> The absence of any such absorbances in the spectrum of **13** suggested the structure designated. The <sup>1</sup>H NMR spectra<sup>20</sup> of **12** and **13** exhibited C<sub>12b</sub>-H absorbances at  $\delta$  3.95 and 4.46, the latter with a bandwidth of 10 Hz, characteristic of normal and pseudo configurations, respectively. The corresponding signals for **14** and **15** appeared at  $\delta$  3.7 and 4.00 (12 Hz), compatible with allo and epiallo assignments, respectively. The stability gained by equatorial constraint of the ethyl group in **15** forces ring D into the conformation shown, thus explaining the presence of Bohlmann bands in the infrared spectrum of this epiallo isomer. The relatively high field chemical shift of the C<sub>12b</sub>-H is presumed due to shielding by the proximate nitrile function.

Thermal or acid/base-catalyzed epimerization<sup>21</sup> of **13** gave only **12**. Similarly **14** and **15** were interrelated, thus confirming

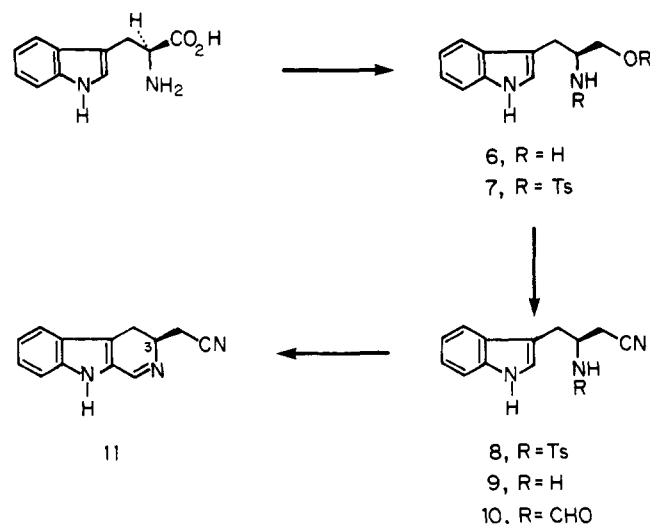


Figure 2.

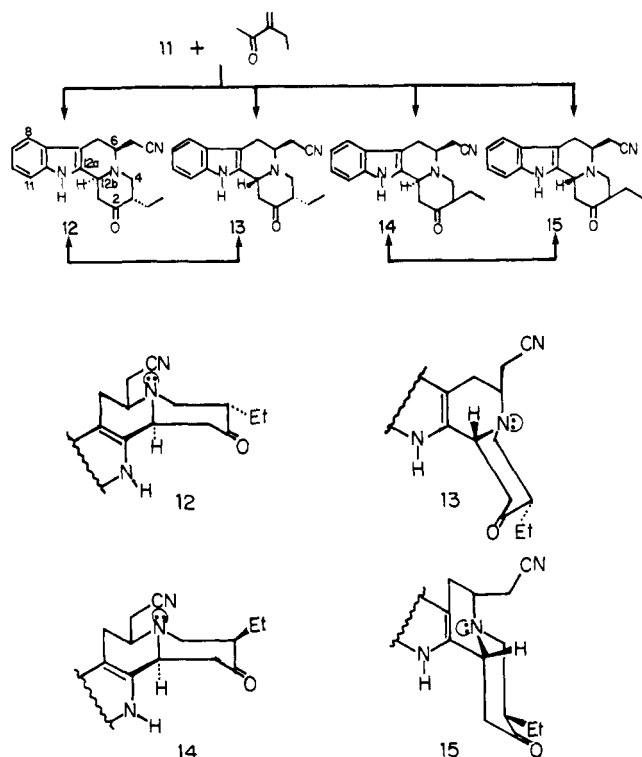
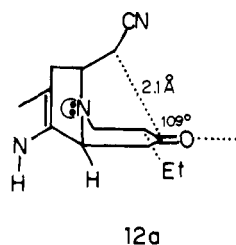


Figure 3.

that **12** and **13** had the same configuration at C<sub>3</sub> (NB indoloquinolizine numbering) while **14** and **15** belong to the antipodal series.

Further examination of the models clearly showed that the 12b (*R*) isomers, **13** and **15**, cannot cyclize (viz., 3 → 4) from any conformation. Whereas for the allo isomer **14**, nitrogen inversion to a conformer, suitable for cyclization, is rendered impossible by severe steric crowding between the nitrile and axial-ethyl functions, this inversion is quite facile for the normal isomer **12**. In fact the nucleophile trajectory, at ca. 109° to the plane of the carbonyl group, required<sup>22</sup> for ring closure is readily achieved in the conformation **12a**. Only minimal



torsional strain is required to bring C<sub>12b</sub>, C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, and C<sub>4</sub> into planarity, resulting in a nuclei separation of ca. 2.1 Å.

In the event, treatment of **12** with lithium diethylamide in tetrahydrofuran at 0 °C gave the more stable 16(*R*) nitrile **17** together with its 16(*S*) epimer, **16**, in the ratio ca. 2:1 (Figure 4). Both showed the characteristic mass spectral fragmentations of the sarpagine skeleton.<sup>23,24</sup> Isomerization of **16** to **17** was efficiently accomplished under the action of aqueous base, while **17** was unaffected by these conditions. The overall efficiency of the conversion, 11 → 17, was augmented by the observation that epimerization at C<sub>3</sub> in **14** was also possible. Treatment with sodium methoxide in methanol gave a mixture of **13**, **14**, and **15**, together with **17** arising via concomitant cyclization of **12**. Thus all four ketones could be utilized in the preparation of the sarpagine skeleton. The <sup>1</sup>H NMR spectra of **16** and **17** both showed the methyl triplet resonance at δ 0.93 (*J* = 6 Hz) while that of the acetate **18** appeared at δ 1.08

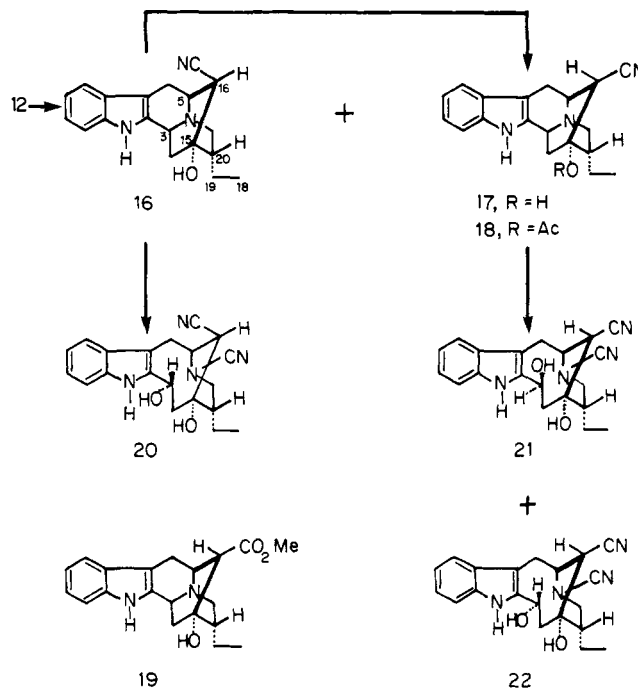


Figure 4.

owing to deshielding by the carbonyl group. These observations are consistent with 20(*S*) stereochemistry. The ester **19**, obtained by solvolysis of **17**, showed a carboxymethyl singlet resonance at δ 3.76 ppm, characteristic<sup>5</sup> for the exo configuration. Similar treatment (HCl/methanol) of **16** failed to yield the corresponding 16(*R*) ester.

At this point the conversion of the β-carboline **11** via four tetracyclic ketones to the required sarpagine skeleton, with the predicted stereochemical consequence at C<sub>20</sub>, had been achieved. Von Braun<sup>25</sup> cleavage of **16** gave a single product **20** for which the 3(*S*) configuration was assigned on the basis of the <sup>1</sup>H NMR spectrum. A double doublet (*J* = 12, 3 Hz) at δ 5.34 indicated that one of the C<sub>4</sub> hydrogens was trans diaxial to C<sub>3</sub>-H, possible only in the most favored conformation of **20**. This stereochemistry is also a consequence of attack from the least hindered side of the molecule. Analogous cleavage of **17** again gave a 3(*S*) isomer **22** together with its epimer **21**.

Manganese dioxide<sup>26</sup> oxidation of either **21** or **22** gave the acylindole **24**, thus confirming their epimeric nature at C<sub>3</sub>. Similar oxidation of **30** afforded the 16(*S*)acylindole **23**. Reaction of either series with thionyl chloride followed by base-catalyzed elimination gave **25**, 16(*S*) stereochemistry being a consequence of the stability of equatorial constraint of the ethyl and C<sub>16</sub> nitrile groups (Figure 5).

Conjugate reduction and concomitant cyanamide cleavage of **15**, with sodium borohydride in pyridine, gave **26** which, on oxidation, afforded the 2-acylindole **27**. The enhanced stability of the equatorial nitrile configuration with respect to the corresponding esters is presumed due to the greater steric requirements of the latter. In fact alkaline hydrolysis and acid-catalyzed esterification of **27** gave 16-epi-19,20(*S*)-dihydroperivine (**29**), identical with a sample prepared from perivine (**31**) by hydrogenation<sup>5,14</sup> and epimerization. The carbomethoxy singlet resonance at δ 3.68 ppm confirmed the orientation away from the shielding zone of the aromatic nucleus. Attempted acid-catalyzed solvolysis of the nitrile **27** succeeded in epimerizing the C<sub>16</sub> center to **28** with only a trace of **29** isolated. Hydrolysis and esterification of **28**, however, again afforded **29**. An examination of the infrared, ultraviolet, and mass spectral data<sup>5,27,28</sup> showed that **27** and **30** existed as 2-acylindoles, whereas for **28** and **29** the carbinolamine tautomer predominated.

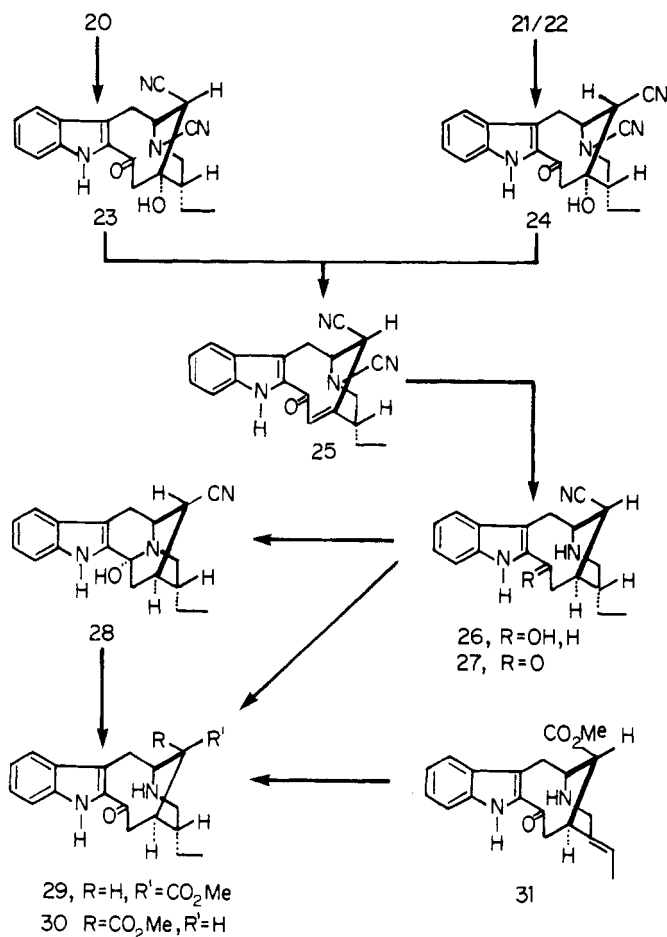


Figure 5.

Eschweiler-Clark reductive methylation<sup>5</sup> of **29** gave epidregamine (**2**), identical with an authentic sample. Base-catalyzed epimerization<sup>14</sup> of **2** afforded the alkaloid dregamine (**1**) as the minor component of the equilibrium mixture (ca. 4:1). The product thus obtained was identical, in all respects, with a sample of the natural product.

This synthesis confirms the recent structural assignments<sup>14-16</sup> for dregamine and provides synthetic entry into the sarpagine, 2-acylindole, and ajmaline alkaloid families.

### Experimental Section

Uncorrected melting points were determined on a Reichert micro hot stage. Infrared spectra were recorded on either a Perkin-Elmer 21 or 137 spectrophotometer. Ultraviolet spectra were recorded on a Cary 15 spectrophotometer. Mass spectra were recorded on an Atlas CH-4B or AEI MS-902 spectrometer. <sup>1</sup>H NMR spectra were recorded on a Varian HA-100 or XL-100 instrument with Me<sub>4</sub>Si as internal standard ( $\delta$  0 ppm). Optical rotations were measured on pyridine solutions using a Perkin-Elmer 141 polarimeter. Unless otherwise indicated all reactions were carried out in an atmosphere of dry nitrogen.

**2(S)-Amino-3-( $\beta$ -indolyl)propan-1-ol (6).** L-(+)-Tryptophan (20 g) and lithium aluminum hydride (15 g) were suspended in dry tetrahydrofuran (1 L) under reflux for 20 h. The cooled mixture was treated with saturated sodium sulfate solution, filtered, and evaporated to yield the alcohol **6** in 97% yield (18.2 g). An analytical sample was prepared by crystallization from benzene: mp 76.5–77.5 °C;  $[\alpha]_D^{20}$   $-20^\circ$  ( $c$  0.5, CHCl<sub>3</sub>),  $-13^\circ$  ( $c$  0.2, C<sub>5</sub>H<sub>5</sub>N); IR (KBr) 3480, 3340 cm<sup>-1</sup>; UV (MeOH) 229 nm ( $\epsilon$  7770), 276 (4270), 283 (4580), 292 (3990); <sup>1</sup>H NMR (CDCl<sub>3</sub>/CD<sub>3</sub>OD)  $\delta$  6.9–7.7 (6 H, m, aromatic H), 2.6–3.7 (5 H, m,  $-\text{CH}(\text{NH}_2)\text{CH}_2\text{Ar}$ ), 3.35 (2 H, m,  $-\text{CH}_2\text{OH}$ );  $m/e$  (calcd for C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O, 190.111) 190.110. Anal. (C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O) C, H, N.

**N,O-Ditosyl-2(S)-amino-3-( $\beta$ -indolyl)propan-1-ol (7).** The amino alcohol **6** (78.3 g) was dissolved in anhydrous pyridine (250 mL),

cooled to 0 °C, and treated with *p*-toluenesulfonyl chloride (240 g). The mixture was kept at 0 °C for 20 h, poured into saturated sodium chloride solution, and extracted with dichloromethane. The extract was washed with 1 N hydrochloric acid and saturated sodium chloride solution, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated under vacuum. Chromatography of the residue on silica gel afforded the ditosylate **7** (187 g, 90%) as a foam:  $[\alpha]_D^{20}$   $-29^\circ$  ( $c$  0.4, C<sub>5</sub>H<sub>5</sub>N); IR (CHCl<sub>3</sub>) 3478, 1325, 1150 cm<sup>-1</sup>; UV (MeOH) 272 nm ( $\epsilon$  7950), 280 (7760), 289 (6590); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.00 (1 H, bs,  $-\text{NH}$  indole), 6.76–7.78 (13 H, m, aromatic H), 3.45–4.15 (3 H, m,  $-(\text{TsNH})\text{CHCH}_2\text{OTs}$ ), 2.85 (2 H, m, ArCH<sub>2</sub>–), 2.38 (3 H, s,  $-\text{CH}_3$ ), 2.26 (3 H, 2  $-\text{CH}_3$ ); MS  $m/e$  (rel intensity) 171 (100), 155 (85), 130 (20).

**3(S)-Tosylamino-4-( $\beta$ -indolyl)butanonitrile (8).** Potassium cyanide (4.5 g) and **7** (22.1 g) were heated in refluxing, dry methanol (300 mL) for 2 h. The solvent was removed under vacuum and the residue treated with dichloromethane. Filtration and evaporation gave a crude product (21 g) which was chromatographed on silica gel. Recrystallization of the product provided **8** (15.5 g, 95%): mp 191–192 °C;  $[\alpha]_D^{20}$   $-49^\circ$  ( $c$  0.5, C<sub>5</sub>H<sub>5</sub>N); IR (Nujol) 3310, 3240, 2280, 1325, 1150 cm<sup>-1</sup>; UV (MeOH) 227 nm ( $\epsilon$  5630), 273 (6170), 281 (6280), 289 (5490); <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>)  $\delta$  6.6–7.6 (9 H, m, aromatic H), 3.65 (1 H, m,  $-\text{CH}(\text{NHTs})-$ ), 2.95 (2 H, d,  $J$  = 8 Hz, ArCH<sub>2</sub>–), 2.73 (2 H, m,  $-\text{CH}_2\text{CN}$ ), 2.28 (3 H, s,  $-\text{CH}_3$ ); MS  $m/e$  353 (M<sup>+</sup>), 130. Anal. (C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>SO<sub>2</sub>) C, H, N, S.

**3(S)-Amino-4-( $\beta$ -indolyl)butanonitrile (9).** Sodium (19 g) was added in small portions to a solution of **8** (82.5 g) in dry liquid ammonia (550 mL) at  $-78^\circ\text{C}$ . The solution was stirred for 30 min, ammonium chloride was added, and solvent was allowed to evaporate. The residue was partitioned between ethyl acetate and 2 N hydrochloric acid. The organic phase was washed with 2 N hydrochloric acid, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated under reduced pressure to give **9** (4.0 g). The aqueous layer was basified with 10 N ammonium hydroxide and extracted with ethyl acetate. The extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under vacuum to give **9** (41.5 g, 95%) as an amorphous solid: IR (CHCl<sub>3</sub>) 3480, 3340, 2240 cm<sup>-1</sup>; UV (MeOH) 273 nm ( $\epsilon$  4150), 281 (4390), 289 (3870); <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>)  $\delta$  6.97–7.68 (5 H, m, aromatic H), 4.02 (1 H, quintet,  $J$  = 6 Hz,  $-\text{CH}(\text{NH}_2)-$ ), 2.94 (2 H, dq,  $J$  = 15, 6 Hz,  $-\text{CH}_2\text{CN}$ ), 2.55 (2 H, d,  $J$  = 6 Hz, ArCH<sub>2</sub>–); MS  $m/e$  199 (M<sup>+</sup>), 183, 182, 159, 130. Calcd for C<sub>12</sub>H<sub>13</sub>N<sub>3</sub>: 199.110. Found: 199.111.

**3(S)-(N-Formylamino)-4-( $\beta$ -indolyl)butanonitrile (10).** Methyl formate (275 mL) and **9** (42.5 g) were stirred in a saturated solution of sodium methoxide in methanol (100 mL) for 4 h. Saturated sodium chloride solution was added and the mixture extracted with ethyl acetate. The extract was washed with 2 N hydrochloric acid and saturated sodium bicarbonate solution, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated under vacuum. Chromatography on silica gel gave **10** (30.8 g, 75%): mp (dichloromethane) 150–151.5 °C;  $[\alpha]_D^{20}$   $-20^\circ$  ( $c$  0.5, C<sub>5</sub>H<sub>5</sub>N); IR (Nujol) 3490, 3380, 2260, 1680 cm<sup>-1</sup>; UV (MeOH) 273 ( $\epsilon$  7340), 281 (7832), 289 (6886); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.53 (1 H, s,  $-\text{CHO}$ ), 8.06 (1 H, bs, indolic  $-\text{NH}$ ), 7.03–7.65 (5 H, m, aromatic H), 6.22 (1 H, d,  $J$  = 8 Hz,  $-\text{NHCHO}$ ), 4.51 (1 H, m, C<sub>3</sub> H), 3.01 (2 H, dd,  $J$  = 9, 6 Hz, C<sub>2</sub> H<sub>2</sub>), 2.60 (1 H, d,  $J$  = 5 Hz, C<sub>4</sub> H), 2.50 (1 H, d,  $J$  = 4 Hz, C<sub>4</sub> H); MS  $m/e$  227 (M<sup>+</sup>), 183, 131, 130. Calcd for C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O: 227.106. Found: 227.108. Anal. C, H, N.

**3(S)-Cyanomethyl-3,4-dihydro- $\beta$ -carboline (11).** A solution of PPE<sup>17</sup> (80 g) in anhydrous chloroform (100 mL) was added to a suspension of the nitrile **10** (5.0 g) in chloroform (120 mL) and stirring continued for 14 h. Water (100 mL) was added and the solution stirred for a further 5 h, basified with 10 N ammonium hydroxide solution, and extracted with ethyl acetate. The extract was washed with saturated sodium chloride solution, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated under vacuum. Chromatography of the residue (6.1 g) on silica gel gave **11** as a foam:  $[\alpha]_D^{20}$   $+35^\circ$  ( $c$  0.3, CHCl<sub>3</sub>); IR (CHCl<sub>3</sub>) 3462, 2250 cm<sup>-1</sup>; UV (MeOH) 235 nm ( $\epsilon$  10 105), 240 (9600), 318 (9646); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.04 (1 H, s,  $-\text{CH}=\text{N}-$ ), 8.33 (1 H, s,  $-\text{NH}$ ), 7.05–7.60 (4 H, m, aromatic H), 3.92 (1 H, m, C<sub>3</sub> H), 3.2–2.7 (4 H, m,  $-\text{CH}_2\text{CN}$  and ArCH<sub>2</sub>–);  $m/e$  209.095 (M<sup>+</sup>, calcd for C<sub>13</sub>H<sub>11</sub>N<sub>3</sub>, 209.095, 18%), 169 (100).

**The Isomeric 6(S)-Cyanomethyl-3-ethyl-2-oxo-1,2,3,4,6,7,12a,12b-octahydroindolo[2,3-a]quinolizines 12–15.** The crude dihydrocarboline **11** (6.1 g) and 3-methylenepentan-2-one (30 g) were stirred in dry methanol (100 mL), saturated with hydrogen chloride, at 70 °C for 18 h. The solvent was removed under vacuum and the residue together with *p*-toluenesulfonic acid (0.3 g) heated in acetone/water (10:1, 100 mL) under reflux for 15 h. The solvent was

evaporated under reduced pressure and the residue partitioned between ethyl acetate and 5% sodium bicarbonate solution. The organic layer was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. Chromatography on silica gel and fractional crystallization from chloroform/ether (1:1) afforded:

**6(S)-Cyanomethyl-3(R)-ethyl-2-oxo-12b(S)-1,2,3,4,6,7,12a,12b-octahydroindolo[2,3-a]quinolizine (14)**, 1.65 g, 25% from **10** as colorless prisms: mp 171 °C;  $[\alpha]_D +39^\circ$  ( $c$  0.5,  $\text{C}_5\text{H}_5\text{N}$ ); IR (CHCl<sub>3</sub>) 3465, 2805, 2245, 1705  $\text{cm}^{-1}$ ; UV (MeOH) 273 nm ( $\epsilon$  7186), 278 (7395), 288 (6000);  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  8.48 (1 H, s, -NH), 7.65–7.09 (4 H, m, aromatic H), 3.6–3.95 (2 H, m,  $\text{C}_{12}\text{H}$  and  $\text{C}_6\text{H}$ ), 0.98 (3 H, t,  $J = 7$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 307 ( $\text{M}^+$ , 61), 267 (100), 169 (37), 156 (60). Anal. ( $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}$ ) C, H, N.

**6(S)-Cyanomethyl-3(S)-ethyl-2-oxo-12b(S)-1,2,3,4,6,7,12a,12b-octahydroindolo[2,3-a]quinolizine (12)**, 1.44 g, 21% from **10a** as colorless needles: mp 188–189 °C;  $[\alpha]_D -73^\circ$  ( $c$  1.0,  $\text{C}_5\text{H}_5\text{N}$ ); IR (CHCl<sub>3</sub>) 3478, 2835, 2795, 2250, 1718  $\text{cm}^{-1}$ ; UV (MeOH) 228 nm ( $\epsilon$  5928), 273 (6722), 279 (6986);  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  7.98 (1 H, s, -NH), 7.6–7.1 (4 H, m, aromatic H), 3.95 (1 H, m,  $\text{C}_{12}\text{H}$ ), 3.42 (1 H, dd,  $J = 10$ , 4 Hz,  $\text{C}_6\text{H}$ ), 0.97 (3 H, t,  $J = 7.5$  Hz,  $-\text{CH}_2\text{CH}_3$ );  $m/e$  (rel intensity) 307 ( $\text{M}^+$ , 100), 267 (95), 169 (35), 156 (70). Anal. ( $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}$ ) C, H, N.

**6(S)-Cyanomethyl-3(R)-ethyl-1-oxo-12b(R)-1,2,3,4,6,7,12a,12b-octahydroindolo[2,3-a]quinolizine (15)**, 0.94 g, 14% from **10** as colorless needles: mp 179–180 °C;  $[\alpha]_D +92^\circ$  ( $c$  0.8,  $\text{C}_5\text{H}_5\text{N}$ ); IR (CHCl<sub>3</sub>) 3470, 2820, 2770, 2250, 1708  $\text{cm}^{-1}$ ; UV (MeOH) 273 nm ( $\epsilon$  6958), 279 (7265), 288 (6140);  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  8.05 (1 H, s, -NH), 7.1–7.7 (4 H, m, aromatic H), 4.00 (1 H, m,  $\text{C}_{12}\text{H}$ ), 3.74 (1 H, m,  $\text{C}_6\text{H}$ ), 0.92 (3 H, t,  $J = 7$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 307 ( $\text{M}^+$ , 100), 267 (90), 169 (37), 156 (70). Anal. ( $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}$ ) C, H, N.

**6(S)-Cyanomethyl-3(S)-ethyl-2-oxo-12b(R)-1,2,3,4,6,7,12a,12b-octahydroindolo[2,3-a]quinolizine (13)**, 1.08 g, 16% from **10** as an oil:  $[\alpha]_D -34^\circ$  ( $c$  0.3,  $\text{C}_5\text{H}_5\text{N}$ ); IR (CHCl<sub>3</sub>) 3475, 2252, 1710  $\text{cm}^{-1}$ ; UV (MeOH) 273 nm ( $\epsilon$  6966), 278 (7194), 288 (6100);  $^1\text{H}$  NMR (CDCl<sub>3</sub>) 8.39 (1 H, s, -NH), 7.1–7.5 (4 H, m, aromatic H), 4.46 (1 H, t,  $J = 5$  Hz,  $\text{C}_{12}\text{H}$ ), 3.3 (1 H, m,  $\text{C}_6\text{H}$ ), 0.89 (3 H, t,  $J = 7.5$  Hz,  $-\text{CH}_2\text{CH}_3$ );  $m/e$  307.1690 (calcd for  $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}$ , 307.1684), 267.1486 (calcd for  $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}$ , 267.1497), 169.0774 (calcd for  $\text{C}_{11}\text{H}_9\text{N}_2$ , 169.0766), 156.0815 (calcd for  $\text{C}_{11}\text{H}_{10}\text{N}$ , 156.0814).

**Epimerization of 15.** (1) A solution of **15** (30 mg) in diethylamine (2 mL) was stirred at ambient temperature for 2 h. Removal of the solvent under vacuum and chromatography on silica gel gave **15** (7 mg) and **14** (15 mg, 65%) identical with an authentic sample. (2) The ketone **15** (28 mg) and *p*-toluenesulfonic acid (10 mg) were stirred in dry acetone (5 mL) at reflux for 2 h. Removal of the solvent under vacuum and chromatography on silica gel gave **15** (8 mg) and **14** (7 mg, 35%) identical with an authentic sample. (3) The ketone **15** (21 mg) was heated in a glass capillary at 210 °C for 2 min. Chromatography on silica gel gave **15** (8 mg) and **14** (4 mg, 30%) identical with an authentic sample.

**Epimerization of 13.** (1) A solution of **13** (2.6 g) in dry diethylamine (15 mL) was stirred at ambient temperature for 14 h. Removal of the solvent under vacuum and chromatography on silica gel gave **13** (0.65 g) and **12** (1.15 g, 58%) identical with an authentic sample. (2) The ketone **13** (50 mg) and *p*-toluenesulfonic acid (10 mg) were stirred in dry acetone (5 mL) at reflux for 10 h. Removal of the solvent under vacuum and chromatography on silica gel gave **13** (11 mg) and **12** (17 mg, 43%) identical with an authentic sample. (3) The ketone **13** (27 mg) was heated to 220 °C for 1 min. as in (3) above to give **13** (9 mg) and **12** (7 mg, 39%) identical with an authentic sample.

**16(R)- and 16(S)-Cyano-16-decarbomethoxy-19,20(S)-dihydro-15(R)-hydroxypericyclivine (17 and 16).** The ketonitrile **12** (320 mg) was added to a solution of lithium diethylamide [prepared from *n*-butyllithium (8 mL of 2 M solution) and diethylamine (0.96 g) in dry tetrahydrofuran (120 mL)] at 0 °C. The solution was stirred for 30 min, diluted with saturated sodium chloride solution, and extracted with ethyl acetate. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under vacuum. Chromatography of the residue (400 mg) on silica gel gave **12** (63 mg), together with (1) the 16(R) derivative **17** (147 mg, 57%) as colorless needles (acetone–chloroform, 1:1) [mp 250 °C;  $[\alpha]_D +137^\circ$  ( $c$  0.1,  $\text{C}_5\text{H}_5\text{N}$ ); IR (Nujol) 2245  $\text{cm}^{-1}$ ; UV (MeOH) 272 nm ( $\epsilon$  8065), 277 (8186), 288 (6500);  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  7.79 (1 H, s, -NH), 7.1–7.5 (4 H, m, aromatic H), 4.16 (1 H, dd,  $J = 10$ , 2 Hz,  $\text{C}_3\text{H}$ ), 0.93 (3 H, t,  $J = 6$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 307 (85, calcd for  $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}$ , 307.1684; found 307.1684), 290 (35), 267

(30), 223 (47), 169 (100), 168 (45), 156 (34). Anal. ( $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}$ ) C, H, N] and (2) the 16(S) derivative **16** (64 mg, 25%) as colorless needles (acetone–chloroform, 1:1) [mp 278 °C;  $[\alpha]_D +158^\circ$  ( $c$  0.05,  $\text{C}_5\text{H}_5\text{N}$ ); IR (Nujol) 2245  $\text{cm}^{-1}$ ; UV (MeOH) 272 nm ( $\epsilon$  6395), 277 (6528), 288 (5117);  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  7.94 (1 H, s, -NH), 7.1–7.6 (4 H, m, aromatic H), 4.08 (1 H, dd,  $J = 9$ , 2 Hz,  $\text{C}_3\text{H}$ ), 0.93 (3 H, t,  $J = 6$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 307 ( $\text{M}^+$ , 100), 290 (39), 267 (46), 223 (30), 169 (75), 156 (25). Anal. ( $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}$ ), C, H, N.]

**Epimerization of 14.** The ketone **14** (50 mg) was stirred in refluxing methanol (5 mL) containing sodium methoxide (from 50 mg of sodium metal) for 48 h. The mixture was diluted with saturated sodium chloride solution and extracted with ethyl acetate. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed under vacuum. Chromatography on silica gel gave **14** (11 mg), **15** (5 mg, 13%), **13** (2 mg, 5%), and **17** (5 mg, 13%) identical with respective authentic samples.

**15(R)-Acetoxy-16(R)-cyano-16-decarbomethoxy-19,20(S)-dihydropericyclivine (18).** The alcohol **17** (20 mg) was stirred in refluxing acetic anhydride for 14 h. Removal of the solvent under vacuum and chromatography on silica gel afforded **18** (8 mg, 35%) as an oil: IR (CHCl<sub>3</sub>) 3450, 2218, 1700  $\text{cm}^{-1}$ ; UV (MeOH) 270 nm ( $\epsilon$  8240), 279 (8230), 286 (6530);  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  7.97 (1 H, s, -NH), 7.1–7.7 (4 H, m, aromatic H), 4.24 (1 H, d,  $J = 9$  Hz,  $\text{C}_3\text{H}$ ), 2.09 (3 H, s,  $-\text{OCOCH}_3$ ), 1.08 (3 H, t,  $J = 6.5$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 349.1765 ( $\text{M}^+$ , 41, calcd for  $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2$ , 349.1790), 290 (100), 223 (11), 169 (25), 168 (17).

**Epimerization of the Nitrile 16.** The nitrile **16** (15 mg) was stirred in a mixture of methanol (1 mL) and 6 N sodium hydroxide solution (0.1 mL) at reflux for 1 h. The mixture was diluted with saturated sodium chloride solution and extracted with ethyl acetate. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed under vacuum. Chromatography on silica gel gave the 16(R) derivative **17** (14 mg, 93%) identical with an authentic sample.

**19,20(S)-Dihydro-16(S)-epi-15(R)-hydroxypericyclivine (19).** The nitrile **17** (90 mg) was stirred in a mixture of methanol (4 mL) and concentrated hydrochloric acid (2 mL) under reflux for 16 h. The solvent was removed under vacuum and the residue partitioned between 2 N ammonium hydroxide solution and ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated under reduced pressure. Chromatography of the residue (100 mg) on silica gel gave the nitrile **17** (24 mg) and the ester **19** (32 mg, 45%) as colorless needles (chloroform): mp 225–227 °C;  $[\alpha]_D +98^\circ$  ( $c$  0.03,  $\text{C}_5\text{H}_5\text{N}$ ); IR (CHCl<sub>3</sub>) 3470, 1720  $\text{cm}^{-1}$ ; UV (MeOH) 272 nm ( $\epsilon$  8250), 282 (8300), 287 (6600);  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  8.10 (1 H, s, -NH), 7.1–7.5 (4 H, m, aromatic H), 3.76 (3 H, s,  $-\text{CO}_2\text{CH}_3$ ), 0.99 (3 H, m,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 340.1773 ( $\text{M}^+$ , 100, calcd for  $\text{C}_{20}\text{H}_{24}\text{H}_2\text{O}_3$ , 340.1787), 323 (14), 223 (38), 169 (81), 168 (55). Anal. ( $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$ ) C, H, N.

**3(S)-N-Cyano-16(S)-cyano-16-decarbomethoxy-19,20(S)-dihydro-15(R)-hydroxyperivinol (20).** The nitrile **16** (75 mg), cyanogen bromide (40 mg), and magnesium oxide (21 mg) in tetrahydrofuran–water (2:1, 15 mL) were heated in a sealed tube at 110 °C for 6 days. The mixture was diluted with saturated sodium chloride solution and extracted with ethyl acetate. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under vacuum. Chromatography of the residue on silica gel afforded **16** (9 mg) and **20** (36 mg, 52%) as colorless needles (dioxane–ether): mp 230 °C;  $[\alpha]_D +84^\circ$  ( $c$  0.04,  $\text{C}_5\text{H}_5\text{N}$ ); IR (Nujol) 3380, 2210  $\text{cm}^{-1}$ ; UV (MeOH) 275 nm ( $\epsilon$  5980), 283 (6300), 292 (5040);  $^1\text{H}$  NMR (acetone-*d*<sub>6</sub>)  $\delta$  6.9–7.6 (4 H, m, aromatic H), 5.34 (1 H, dd,  $J = 12$ , 3 Hz,  $\text{C}_3\text{H}$ ), 1.80 (2 H, m,  $-\text{CH}_2\text{CH}_3$ ), 0.92 (3 H, t,  $J = 7$  Hz,  $-\text{CH}_2\text{CH}_3$ );  $m/e$  350 ( $\text{M}^+$ , 100%), 332 (45). Anal. ( $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_2$ ) C, H, N.

**3(R)- and 3(S)-N-Cyano-16(R)-cyano-16-decarbomethoxy-19,20(S)-dihydro-15(R)-hydroxyperivinol (21 and 22).** The nitrile **17** (120 mg) was reacted with cyanogen bromide (100 mg) and magnesium oxide (50 mg), as described for the preparation of **20**, to give **17** (8 mg), together with (1) the 3(S) derivative **22** (80 mg, 61%) as colorless needles (dioxane–ether) [mp 233 °C;  $[\alpha]_D +38^\circ$  ( $c$  0.2,  $\text{C}_5\text{H}_5\text{N}$ ); IR (Nujol) 3380, 2219  $\text{cm}^{-1}$ ; UV (MeOH) 273 nm ( $\epsilon$  5500), 283 (5800), 292 (4640);  $^1\text{H}$  NMR (acetone-*d*<sub>6</sub>)  $\delta$  6.95–7.69 (4 H, m, aromatic H), 5.09 (1 H, dd,  $J = 11$ , 3 Hz,  $\text{C}_3\text{H}$ ), 1.80 (2 H, m,  $-\text{CH}_2\text{CH}_3$ ), 0.95 (3 H, t,  $J = 6$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  350 ( $\text{M}^+$ , 100). Anal. ( $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_2$ ), C, H, N] and (2) the 3(R) derivative **21** (33 mg, 26%) as colorless needles (dioxane–ether) [mp 295 °C;  $[\alpha]_D +29^\circ$  ( $c$  0.03,  $\text{C}_5\text{H}_5\text{N}$ ); IR (Nujol) 3400, 2220  $\text{cm}^{-1}$ ; UV (MeOH) 274 nm ( $\epsilon$  5300), 283 (5600), 292 (4560);  $^1\text{H}$  NMR ( $\text{C}_5\text{D}_5\text{N}$ )  $\delta$  8.70

(1 H, s, -NH), 7.25–7.70 (4 H, m, aromatic H), 0.75 (3 H, t,  $J = 7$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 350 ( $\text{M}^+$ , 100), 332 (7). Anal. ( $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_2$ ) C, H, N].

**N-Cyano-16(S)-cyano-16-decarbomethoxy-19,20(S)-dihydro-15(R)-hydroxyperivine (23).** Manganese dioxide (1.5 g) and the nitrile 20 (110 mg) were stirred in tetrahydrofuran (15 mL) for 14 h. The mixture was filtered and the filtrate evaporated under vacuum to give 23 (93 mg, 85%); mp 273 °C (dioxane-ether);  $[\alpha]_D^{+244}$  ( $c$  0.2,  $\text{C}_5\text{H}_5\text{N}$ ); IR (Nujol) 3640, 3468, 2225, 1628  $\text{cm}^{-1}$ ; UV (MeOH) 240 nm ( $\epsilon$  8850), 316 (16 000);  $^1\text{H}$  NMR ( $\text{C}_5\text{D}_5\text{N}$ )  $\delta$  8.67 (1 H, s, NH), 7.2–7.85 (4 H, m, aromatic H), 2.03 (2 H, m,  $-\text{CH}_2\text{CH}_3$ ), 0.85 (3 H, m,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 348 ( $\text{M}^+$ , 100), 330 (4), 157 (55). Anal. ( $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_2$ ) C, H, N.

**N-Cyano-16(R)-cyano-16-decarbomethoxy-19,20(S)-dihydro-15(R)-hydroxyperivine (24).** (1) Manganese dioxide (700 mg) and the alcohol 22 (40 mg) were stirred in tetrahydrofuran (10 mL) for 16 h. Filtration and evaporation gave 24 (35 mg, 88%) as needles from dioxane-ether: mp 295–297 °C;  $[\alpha]_D^{+54}$  ( $c$  0.04,  $\text{C}_5\text{H}_5\text{N}$ ); IR (Nujol) 3400, 3330, 2215, 1613  $\text{cm}^{-1}$ ; UV (MeOH) 230 nm ( $\epsilon$  8400), 315 (14 000);  $^1\text{H}$  NMR ( $\text{C}_5\text{D}_5\text{N}$ )  $\delta$  8.75 (1 H, s, -NH), 7.3–7.9 (4 H, m, aromatic H), 0.85 (3 H, t,  $J = 7$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 348 ( $\text{M}^+$ , 42), 330 (8), 157 (100). Anal. ( $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_2$ ) C, H, N. (2) Similar oxidation of 21 (35 mg) gave the ketone 24 (27 mg, 78%) identical with that obtained above.

**N-Cyano-16(S)-cyano-14,15-dehydro-16-decarbomethoxy-19,20(S)-dihydroperivine (25).** (1) The alcohol 24 (75 mg) and thionyl chloride (0.35 mL) were stirred in pyridine (2 mL) at  $-10$  °C for 20 min. The solution was diluted with ice-cold sodium hydroxide solution and extracted with ethyl acetate. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure. Chromatography of the residue on silica gel gave 25 (63 mg, 86%); mp (dioxane-ether) 264 °C;  $[\alpha]_D^{+42}$  ( $c$  0.06,  $\text{C}_5\text{H}_5\text{N}$ ); (Nujol) 3320, 2230, 1610  $\text{cm}^{-1}$ ; UV (MeOH) 245 nm ( $\epsilon$  9600), 336 (17 000);  $^1\text{H}$  NMR ( $\text{C}_5\text{D}_5\text{N}$ )  $\delta$  7.19–7.86 (4 H, m, aromatic H), 6.42 (1 H, s,  $\text{C}_{14}\text{H}$ ), 1.40 (2 H, m,  $-\text{CH}_2\text{CH}_3$ ), 0.84 (3 H, t,  $J = 7$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 330 ( $\text{M}^+$ , 88), 130 (100). Anal. ( $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}$ ) C, H, N. (2) Similar treatment of 23 gave 25 (91%) identical with that obtained above.

**16(S)-Cyano-16-decarbomethoxy-19,20(S)-dihydroperivinol (26).** Sodium borohydride (32 mg) and 25 (39 mg) were stirred in pyridine (4 mL) for 48 h. Triethylamine (3 mL) was added and the solution stirred for 30 min and filtered. The filtrate was evaporated and the residue chromatographed on silica gel to give the alcohol 26 (23 mg, 77%); mp (chloroform-ethyl acetate) 170 °C; UV (MeOH) 274 nm ( $\epsilon$  7100), 282 (7400), 292 (6480);  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  6.85–7.85 (4 H, m, aromatic H), 5.47 (1 H, m,  $\text{C}_3\text{H}$ ), 1.02 (3 H, t,  $J = 7$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 309 ( $\text{M}^+$ , 10), 291 (100), 223 (25), 169 (68), 168 (78), 156 (48). Anal. ( $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}$ ) C, H, N.

**16(S)-Cyano-16-decarbomethoxy-19,20(S)-dihydroperivine (27).** The alcohol 26 (50 mg) and manganese dioxide (800 mg) were stirred in tetrahydrofuran (5 mL) for 12 h. The mixture was filtered and the filtrate evaporated. Chromatography of the residue on silica gel afforded 27 (44 mg, 89%); mp (chloroform-ethyl acetate) 184 °C;  $[\alpha]_D^{-67}$  ( $c$  0.02,  $\text{C}_5\text{H}_5\text{N}$ ); IR (Nujol) 3460, 2240, 1640  $\text{cm}^{-1}$ ; UV (MeOH) 238 nm ( $\epsilon$  11 700), 315 (16 400);  $^1\text{H}$  NMR ( $\text{C}_5\text{D}_5\text{N}$ )  $\delta$  7.0–8.0 (4 H, m, aromatic H), 1.45 (2 H, m,  $-\text{CH}_2\text{CH}_3$ ), 1.12 (3 H, t,  $J = 7$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 307 ( $\text{M}^+$ , 52), 290 (20), 185 (65), 184 (50), 172 (100), 135 (9). Anal. ( $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}$ ) C, H, N.

**16(R)-Cyano-16-decarbomethoxy-19,20(S)-dihydro-3(R)-hydroxypericyclivine (28).** The nitrile 27 (45 mg) was stirred in a mixture of methanol (2 mL) and concentrated hydrochloric acid under reflux for 20 h. The solution was diluted with saturated sodium chloride solution, basified with concentrated ammonium hydroxide solution, and extracted with ethyl acetate. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under vacuum. Chromatography of the residue on silica gel gave 27 (4 mg), 29 (4 mg) and 28 (27 mg, 60%) as an oil: IR ( $\text{CHCl}_3$ ) 3450, 2230, 1635  $\text{cm}^{-1}$  (weak); UV (MeOH) 272 nm ( $\epsilon$  6405), 282 (6589), 288 (5830), 312 (2520);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.1 (1 H, bs, -OH), 8.18 (1 H, bs, -NH), 6.9–7.7 (4 H, m, aromatic H), 0.93 (3 H, t,  $J = 7$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 307.1694 ( $\text{M}^+$ , 90, calcd for  $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}$ , 307.1685), 290 (30), 185 (65), 184 (57), 172 (100), 135 (9).

**16-Epi-19,20(S)-dihydroperivine (29).** (1) The nitrile 27 (30 mg) was heated in a solution of sodium hydroxide (40 mg) in water-methanol (1:2, 5 mL) under reflux for 24 h. The solution was cooled, treated with concentrated hydrochloric acid (2 mL), and stirred for

6 h. The solution was diluted with saturated sodium chloride, basified with 2 N ammonium hydroxide, and extracted with ethyl acetate. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under vacuum. Chromatography of the residue on silica gel gave 29 (23 mg, 70%); mp (ether-chloroform) 157–159 °C  $[\alpha]_D^{+51}$  ( $c$  0.06, MeOH); IR ( $\text{CHCl}_3$ ) 3465, 1725, 1637  $\text{cm}^{-1}$  (weak); UV (MeOH) 274 nm ( $\epsilon$  4420), 280 (4580), 288 (4350), 312 (3475);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.69 (1 H, s, -NH), 6.85–7.45 (4 H, m, aromatic H), 3.68 (3 H, s,  $-\text{OCH}_3$ ), 0.86 (3 H, t,  $J = 6.5$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 340.1797 ( $\text{M}^+$ , 93, calcd for  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$ , 340.1787), 323 (42), 185 (71), 184 (100), 168 (35). Anal. ( $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$ ) C, H, N. (2) Similar treatment of 28 gave 29 (68%) identical with that obtained above. (3) The ester 30 (24 mg) was heated in sodium methoxide in methanol solution (30 mg of sodium metal in 5 mL of methanol) under reflux for 20 min. The solution was diluted with saturated sodium chloride solution and extracted with ethyl acetate. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. Chromatography on silica gel gave 29 (14 mg, 58%) identical with that obtained above:  $[\alpha]_D^{+61}$  ( $c$  0.2,  $\text{C}_5\text{H}_5\text{N}$ ),  $+53^\circ$  ( $c$  0.2, MeOH) (lit.<sup>29</sup>  $[\alpha]_D^{+56}$  (MeOH)).

**19,20(S)-Dihydroperivine (30).** Perivine 31 (50 mg) in ethanol (5 mL) was hydrogenated at ambient temperature and 1 atm of hydrogen in the presence of Adams catalyst. The catalyst was removed by filtration and the filtrate evaporated. Chromatography on silica gel gave 30 (40 mg, 81%) as an oil:  $[\alpha]_D^{+35}$  ( $c$  0.1,  $\text{C}_5\text{H}_5\text{N}$ ); IR ( $\text{CHCl}_3$ ) 3460, 1720, 1638  $\text{cm}^{-1}$ ; UV (MeOH) 235 nm ( $\epsilon$  12 500), 311 (13 400);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.67 (3 H, s,  $-\text{OCH}_3$ ), 1.05 (3 H, t,  $J = 6$  Hz,  $-\text{CH}_2\text{CH}_3$ ); MS  $m/e$  (rel intensity) 340 ( $\text{M}^+$ , 66), 323 (15), 185 (21), 184 (32), 168 (100).

**16-Epidregamine (2).** (1) Dregamine (1, 30 mg) was treated with sodium methoxide according to the literature procedure to give dregamine (1, 7 mg), and 16-epidregamine (2, 14 mg, 47%), mp 212–214 °C (lit.<sup>14</sup> 213–215 °C). (2) The ester 29 (28 mg) was hydrogenated in formalin-dioxane (1:20, 5 mL) containing a catalytic amount of formic acid and palladized charcoal for 24 h at 1 atm of hydrogen and ambient temperature. The mixture was filtered, diluted with saturated sodium chloride solution, and extracted with ethyl acetate. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. Chromatography of the residue on silica gel gave 16-epidregamine (2, 19 mg, 65%) identical with that prepared above.

**Dregamine (1).** 16-Epidregamine (2, 19 mg) was heated in sodium methoxide in methanol solution (24 mg of sodium metal in 5 mL of methanol) under reflux for 16 h. The solution was diluted with saturated sodium chloride solution and extracted with ethyl acetate. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. Chromatography of the residue on silica gel gave 16-epidregamine (12 mg) and dregamine (1, 3 mg, 37%), mp 137–140 °C (lit.<sup>30</sup> 137–141 °C).

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## References and Notes

- (1) J. A. Weisbach and B. Douglas, *Chem. Ind. (London)*, 623 (1965); 233 (1966).
- (2) W. I. Taylor in "The Alkaloids", Vol. 11, R. H. F. Manske, Ed., Academic Press, New York, N.Y., 1968, p 41.
- (3) S. Sakai, *Heterocycles*, 4, 131 (1976).
- (4) N. R. Farnsworth, W. D. Loub, R. N. Blomster, and M. Gorman, *J. Pharm. Sci.*, 53, 1558 (1964).
- (5) M. Gorman and J. Sweeney, *Tetrahedron Lett.*, 3105 (1964).
- (6) M. F. Bartlett, B. F. Lambert, H. M. Werblow, and W. I. Taylor, *J. Am. Chem. Soc.*, 85, 475 (1963).
- (7) J. D. Hobson and J. G. McCluskey, *J. Chem. Soc.*, 2015 (1967).
- (8) S. Masamune, S. K. Ang, C. Egli, N. Nakatsuka, S. K. Sarkar, and Y. Yasunari, *J. Am. Chem. Soc.*, 89, 2506 (1967).
- (9) E. van Tamelen and L. K. Oliver, *J. Am. Chem. Soc.*, 92, 2136 (1970).
- (10) E. van Tamelen and L. K. Oliver, *Bioorg. Chem.*, 5, 309 (1976).
- (11) A. A. Gorman, M. Hesse, and H. Schmid, *Spec. Period. Rep., Alkaloids*, 1, 242 (1971).
- (12) G. Buchi, R. E. Manning, and S. A. Monti, *J. Am. Chem. Soc.*, 86, 4631 (1964).
- (13) D. G. I. Kingston, B. B. Gerhart, and F. Ionescu, *Tetrahedron Lett.*, 649 (1976).
- (14) J. R. Knox and J. Slobbe, *Aust. J. Chem.*, 28, 1843 (1975), and references cited therein.
- (15) A. Husson, Y. Langlois, C. Riche, H. P. Husson, and P. Potier, *Tetrahedron*, 29, 3095 (1973).
- (16) A. Alond, A.-M. Bui, P. Potier, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, 41, 1878 (1976).

- (17) Y. Kanaoka, M. Machida, O. Yonemitsu, and Y. Ban, *Chem. Pharm. Bull.*, **13**, 1065 (1965).  
 (18) A. Brossi, L. H. Chopard-det-Jean, J. Wursch, and O. Schneider, *Helv. Chim. Acta*, **77**, 583 (1960).  
 (19) C. Szantay and J. Rohaly, *Chem. Ber.*, **96**, 1788 (1963).  
 (20) W. F. Trager, C. M. Lee, and A. H. Beckett, *Tetrahedron*, **23**, 365, 375 (1967), and references cited therein.  
 (21) T. Kametani and M. Ihara, *Heterocycles*, **5**, 649 (1976).  
 (22) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 738 (1976).  
 (23) K. Biemann, *J. Am. Chem. Soc.*, **83**, 4801 (1961).  
 (24) L. D. Antonaccio, N. A. Pereira, B. Gilbert, H. Vorbrueggen, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 2161 (1962).  
 (25) J. von Braun, *Chem. Ber.*, **44**, 1252 (1911).  
 (26) I. M. Goldman, *J. Org. Chem.*, **34**, 1979 (1969).  
 (27) T. Shiori and S. Yamada, *Tetrahedron*, **24**, 4159 (1968).  
 (28) T. Shiori, T. Nakashima, and S. Yamada, *Tetrahedron*, **24**, 4177 (1968).  
 (29) P. Mangeney, Y. Langlois, and P. Potier, *Tetrahedron*, **31**, 429 (1975).  
 (30) J. R. Knox and J. Slobbe, *Aust. J. Chem.*, **28**, 1813 (1975).

## Conformational Preferences of the Bridging Groups of Cyclo-L-cystine and the Active Fragments of Epipolythiodiketopiperazine Antibiotics<sup>1a</sup>

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**Abstract:** Simple quantum chemical calculations of the extended Hückel (EH) type have been performed for model systems to elucidate the conformational preferences of the bridging groups of cyclo-L-cystine (3,6-epi-CH<sub>2</sub>S<sub>2</sub>CH<sub>2</sub>-2,5-diketopiperazine) and the active fragments of 3,6-epi(dithio- and tetrathio-)2,5-diketopiperazine antibiotics. The conformational preferences inferred from the EH calculations are the same as those deduced from a classical analysis of the van der Waals interactions between the bridging atoms and the amide carbon and nitrogen atoms. They agree with the results of x-ray analyses of these compounds. Experimental and theoretical results indicate that hydrogen bonding to the carbonyl oxygens does not alter the conformational preference of any of these systems. A comparison of EH and ab initio results reveals that the EH model is inadequate for describing the effect of C=O...H—O hydrogen bonding on the peptide moiety.

### Introduction

The 2,5-diketopiperazine (DKP) ring bridged by a disulfide group across the 3,6 positions is now well established as the active fragment of a group of biologically interesting fungal metabolites that have toxic, antibacterial, antiviral, and cytostatic properties.<sup>2</sup>

Five of these metabolites have now been subjected to detailed structural analysis by x-ray crystallographic methods. They are sporidesmin,<sup>3</sup> gliotoxin,<sup>4</sup> antibiotic LL-S88α, which was shown to be acetylaranotin,<sup>5,6</sup> chaetocin,<sup>7</sup> and antibiotic A26771A.<sup>8</sup> In all of these compounds the helicity of the disulfide bond is such that each sulfur atom is closer to the adjacent carbonyl carbon atom (structure I, Figure 1) rather than to the adjacent nitrogen atom (IV, Figure 1). The CSSC dihedral angles (DAs) vary from 8° (chaetocin) to 18° (acetylaranotin), their signs being determined by the chirality of the asymmetric centers.

Molecular orbital calculations on compounds with amide groups<sup>9-13</sup> consistently show that amide carbon and nitrogen atoms are electron-deficient and electron-rich centers, respectively, provided that the calculation takes the "π" and "σ" electrons into account on an equal footing.<sup>9</sup> Experimental<sup>14,15</sup> and theoretical<sup>16-21</sup> work has established that the ground states of hydrogen disulfide, HSSH, and dimethyl disulfide, H<sub>3</sub>CSSCH<sub>3</sub>, have a clear preference for a twisted geometry in which the DA is ~90°. Hence it has been suggested that the observed conformational preference of the disulfide linkage in 3,6-epidithio-2,5-DKP systems is due to intramolecular electrostatic attraction between the sulfur lone-pair electrons and the positively charged amide carbon atoms<sup>8,18,20</sup> and to repulsion between the sulfur and nitrogen lone pairs.<sup>20</sup>

All naturally occurring, biologically active metabolites of this type were thought to contain epidithio bridges until Taylor and his coworkers isolated first an epitritio derivative and then an epitetrathio derivative, sporidesmin G, from natural sources.<sup>22,23</sup> On the basis of the above considerations one would expect the tetrasulfide bridge in an epitetrathio system to be skewed in such a way as to bring the inner sulfur atoms closer to the carbonyl carbons of the DKP ring (VI) than to the nitrogen atoms (V). The structures of three such systems have now been determined by x-ray crystallography. They include a synthetic system, 3,6-epitetrathio-*N*<sup>1</sup>,*N*<sup>4</sup>-dimethyl-2,5-DKP,<sup>24</sup> sporidesmin G etherate,<sup>25</sup> and a derivative of hyalodendrin.<sup>26</sup> In each case the tetrasulfide bridge is found to be twisted so that its inner sulfurs are closer to the nitrogens and its outer sulfurs are closer to the carbonyl carbons. It has been suggested that the nitrogen atoms in the tetrathio compounds are positively charged and that the observed stereochemistry is therefore a consequence of electrostatic attraction between the sulfur and nitrogen atoms.<sup>25</sup> This explanation rests, however, on the invalid assumption that the π-electron approximation holds for the amide group.<sup>9</sup>

Another bridged 2,5-DKP, cyclo-L-cystine, has been studied by a variety of spectroscopic techniques because of its importance as an experimental model for testing the theory of the chiroptical properties of disulfides.<sup>27-29</sup> In cyclocystine, the 2,5-DKP ring is bridged by a CH<sub>2</sub>S<sub>2</sub>CH<sub>2</sub> group across the 3,6 positions. As in the case of the dithio and tetrathio derivatives, one can try to predict the more likely helicity of the bridge from a consideration of the probable transannular electrostatic and nonbonded overlap interactions. Again a conformation (VIII) in which the sulfur atoms are proximate to the carbonyl carbon atoms is expected to be preferred over one (VII) in which the