# Synthesis of Cryptolepine and Cryptoteckieine from a Common Intermediate

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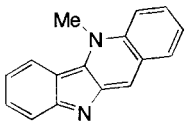
Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

Both cryptolepine **1** and cryptotackieine **3** have been synthesized from 1,3-bis(2-nitrophenyl)propan-2-one. The approach to **1** involved reduction of the $NO_2$ groups, oxidative cyclization with $PhI(OAc)_2$, and *N*-methylation, whereas **3** was obtained *via* bromination, *Favorskii* rearrangement, reduction (*in situ* cyclization), and *N*-methylation.

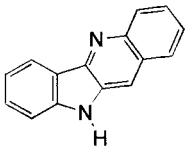
**Introduction.** – Over the past several years, we have been interested in exploiting apparent or hidden symmetry aspects of molecules for their synthesis [1]. This activity extends to a synthetic study in the series of the cryptolepine **1** [2] and related alkaloids. Here, we describe an approach to two representative structural types from 1,3-bis(2-nitrophenyl)propan-2-one.

Shrubs of the *Cryptolepis* genus, indigenous to tropical Africa, yield an extremely bitter sap, which turns red on exposure to air. They are used in the dyeing of leather and textiles, as well as in traditional medicine of West and Central Africa, including the treatment of malaria, infections of the respiratory, urogenital and urinary tracts, colic, and rheumatism. The roots of *C. sanguinolenta* (LINDL.) Schlechter (Periplocaceae) contain several alkaloids with indoloquinoline skeletons: quindoline **2** [3], cryptoteckieine **3** [4] (in [5] named neocryptolepine), cryptosanguinolentine **5** [4], and the dimeric cryptospirolepine **6** [6], cryptolepicarboline **7** [7], and cryptomisrine **8** [8]. Concerning synthesis of these substances, it is of interest to note that *Fichter* and *Boehringer* reported [9] the preparation of quindoline 72 years before its isolation from natural sources.

In view of both the intrinsic heterocyclic arrays and the diverse therapeutic value of these alkaloids, many chemists have engaged in their synthesis. Thus, quindoline was obtained from 3-aminoquinoline by way of *N*-phenylation and a Pd-catalyzed cyclization [10], from 2-iodo-3-fluoroquinoline by *Suzuki* coupling, followed by an intramolecular *N*-arylation [11]. For access to cryptoteckieine, the decomposition of 2-(1-benzotriazolyl)quinoline in polyphosphoric acid [12], intramolecular *N*-arylation of either 2-chloro-3-(2-aminophenyl)quinoline [13] or 3-(2-bromophenyl)-2-(tosylamino)quinoline [14] are quite useful. A more novel approach involving thermolysis of *N*-phenyl-*N*′-(2-ethynylphenyl)carbodiimide [15] unfortunately gave norcryptoteckieine only as a minor product in 16% yield. There is also a synthesis of cryptolepine starting from condensation of 3-acetoxy-1*H*-indole and isatin [16].



**1**



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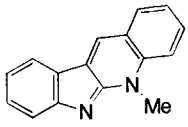

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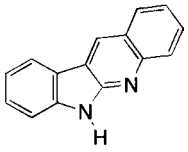

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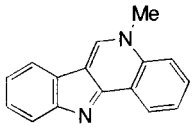

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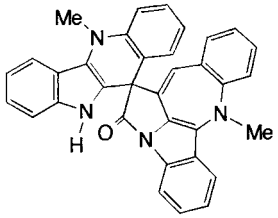

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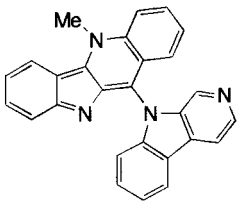

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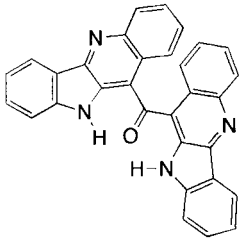

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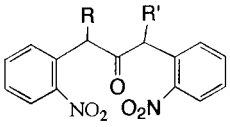
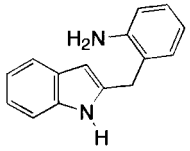
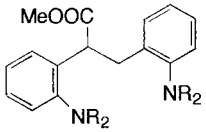


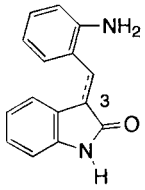
**9a** R = R' = H
**9b** R = H, R' = Br
**9c** R = R' = Br



**10**



**11a** R = O
**11b** R = H



**12a** saturated at C(3)
**12b** $\Delta^3$

**Results and Discussion.** – The route we chose for the elaboration of both the indolo[3,2-*b*]quinoline (quindoline) system and the isomeric indolo[2,3-*b*]quinoline framework was based on consideration of their accessibility from a common symmetrical intermediate, 1,3-bis(2-nitrophenyl)propan-2-one (**9a**).

The preparation of **9a** from (2-nitrophenyl)acetic acid is readily achieved by reaction with dicyclohexylcarbodiimide (DCC) [17]. Reduction of **9a** with sodium dithionite in aqueous MeOH led to the diamino ketone, which underwent spontaneous cyclization. Accordingly, the isolated product was 2-(2-aminobenzyl)-1*H*-indole (**10**). While the transformation of **10** into quidoline **2** by reaction with *N*-chlorosuccinimide and $Et_3N$ was very unsatisfactory, it was subsequently achieved with iodosobenzene diacetate as the reagent. This oxidizing agent is known to promote condensation of 2-substituted indoles with arylamines to form the 3-arylimino-3*H*-indoles [18], but, in our case, the initial product suffered isomerization to afford quindoline directly. Subsequently, a regioselective *N*-methylation of quindoline to furnish cryptolepine (**1**) was accomplished according to established procedure [10].

Our initial plan for the synthesis of cryptoteckieine called for the oxidation of **9a** to a trione with $SeO_2$. However, the desired transformation was unsuccessful, and only *o,o′*-dinitrobenzil was produced in low yield. The loss of a C unit may be due to the instability of the trione or an abnormal oxidative degradation of the highly reactive 1,2-dione intermediate.

In a revised approach, ketone **9a** was brominated, and the ensuing bromo ketone **9b** was exposed to MeONa to induce a *Favorskii* rearrangement. The resulting methyl ester **11a** was then reduced with sodium dithionite to the bis(2-aminophenyl) ester **11b**, which may be converted to a 3-substituted oxindole **12a**. On the other hand, by reduction with Fe powder in hot AcOH, norcryptoteckieine (**4**) could be obtained directly. Finally, *N*-methylation of **4** completed the synthesis of cryptoteckieine (**3**).

The alternative pathway to norcryptoteckieine (**4**) is *via Favorskii* rearrangement of the dibromo ketone **9c**. Owing to the generation of an (*E*)-ester, which, on reduction, led to (*E*)-3-(2-aminobenzylidene)oxindole (**12b**), this route became an impasse.

In summary, we demonstrated once again the economy and effectiveness of using a common intermediate for the synthesis of two different molecular skeletons by proper manipulation. It is a continuation along the line of our previous work concerning the access to occidol and tavacpallescensin, and cuparene and herbertene [1].

We thank the *National Science Council* of ROC for financial support.

**Experimental Part**

*General*. Column chromatography (CC) was performed on *Merck* silica gel. M.p.: uncorrected. IR Spectra: *BIO-RAD FTS* 165, $\tilde{\nu}$ in $cm^{-1}$. $^1H$- and $^{13}C$-NMR spectra: *Varian Unity-300* and *Bruker DRX-300*, $CDCl_3$ as solvent unless otherwise indicated, $\delta$ in ppm, $J$ in Hz. EI-MS: *TRIO-2000* and *JEOL SX-102A*, ionization potential 70 eV.

*1,3-Bis(2-nitrophenyl)propan-2-one* (**9a**). A soln. of (2-nitrophenyl)acetic acid (5.0 g, 27.6 mmol) in anh. THF (50 ml) was added slowly to dicyclohexylcarbodiimide (DCC; 6.0 g, 29 mmol) and 4-(dimethylamino)-pyridine (DMAP; 1.0 g, 8.18 mmol) in anh. THF (50 ml) at r.t. The mixture was then heated to reflux for 3 h, cooled, filtered, and evaporated under reduced pressure. The solid residue was recrystallized from AcOEt to afford **9a** (14.2 g, 86%). M.p. 138–139°. IR: 1723, 1547, 1519, 1408, 1347. H-NMR: 4.28 (*s*, 4 H); 7.35 (*d*, $J = 7.8$, 2 H); 7.46 (*t*, $J = 7.8$, 2 H); 7.58 (*t*, $J = 7.8$, 2 H); 8.10 (*d*, $J = 7.8$, 2 H). $^{13}C$-NMR: 47.8 (*t*); 125.2 (*d*); 128.5 (*d*); 130.1 (*s*); 133.8 (*d*); 134.0 (*d*); 148.3 (*s*); 201.1 (*s*). EI-MS: 300 (0.08, $M^+$), 251 (0.18), 224 (52), 164 (18), 142

(34), 136 (30), 98 (75), 56 (100). HR-MS: 300.0746 ($C_{15}H_{12}N_2O_5^+$; calc. 300.0747). Anal. calc.: C 60.00, H 4.03, N 9.33; found: C 60.05, H 4.39, N 9.37.

*2-(2-Aminobenzyl)-1*H*-indole* (**10**). A mixture of **9a** (3.0 g, 10 mmol), Fe powder (4.6 g, 82.38 mmol), glacial AcOH (54 ml), and EtOH (54 ml) was stirred and refluxed under $N_2$ for 3.5 h. On cooling, the liquid was poured into $H_2O$ (200 ml), neutralized with $Na_2CO_3$, and EtOH was removed *in vacuo*. Extraction of the aq. suspension with AcOEt (3 × 50 ml), followed by evaporation and CC (hexane/AcOEt 3:1), gave the crystalline **10** (2.1 g, 94.6%). M.p. 110–112°. IR: 3398, 3053, 3028, 1619, 1495, 1456, 1414, 1285. $^1$H-NMR: 3.46 (*s*, 2 H); 3.85 (*s*, 2 H); 6.25 (*s*, 1 H); 6.56 (*d*, *J* = 7.8, 1 H); 6.74 (*t*, *J* = 7.5, 1 H); 7.07 (*m*, 5 H); 7.48 (*m*, 1 H); 7.93 (*s*, 1 H). $^{13}$C-NMR: 31.1 (*t*); 100.4 (*d*); 110.5 (*d*); 116.2 (*d*); 118.9 (*d*); 119.6 (*d*); 119.7 (*d*); 121.2 (*d*); 123.0 (*s*); 128.1 (*d*); 128.3 (*s*); 130.4 *d*); 136.1 (*s*); 136.5 (*s*); 144.8 (*s*). EI-MS : 222 (70, $M^+$), 221 (100), 219 (19), 204 (34), 130 (44), 117 (28), 111 (28), 102 (30). HR-MS: 222.1163 ($C_{15}H_{14}N_2^+$; calc. 222.1158).

*Quindoline* (= *7*H*-Indolo[3,2-*b*]quinoline*; **2**). To a stirred soln. of **10** (3.0 g, 13.5 mmol) in anh. THF (50 ml) at r.t. was added phenyliodine diacetate (9.0 g, 28 mmol) in portions. After 3 h, the mixture was treated with 10% $NaHCO_3$ (50 ml) and evaporated. The residue was extracted with AcOEt (3 × 50 ml), dried ($Na_2SO_4$), evaporated, and chromatographed. Elution with hexane/AcOEt 3:1 provided **2** (1.2 g, 40.7%). M.p. 252–253° ([11]: 254–256°). IR: 3416, 1639, 1563, 1481, 1460, 1397, 1337. $^1$H-NMR ((D$_6$)DMSO): 7.28 (*t*, *J* = 7.5, 1 H); 7.64 (*m*, 4 H); 8.07 (*d*, *J* = 8.4, 1 H); 8.18 (*d*, *J* = 8.4, 1 H); 8.28 (*s*, 1 H); 8.38 (*d*, *J* = 7.5, 1 H); 11.45 (*s*, 1 H). $^{13}$C-NMR ((D$_6$)DMSO): 111.5 (*d*); 113.0 (*d*); 119.3 (*d*); 121.0 (*s*); 121.4 (*d*); 124.9 (*d*); 126.0 (*d*); 126.7 (*s*); 127.5 (*d*); 128.7 (*d*); 129.7 (*d*); 132.4 (*s*); 143.4 (*s*); 144.0 (*s*); 145.7 (*s*). EI-MS: 218 (100, $M^+$), 190 (11), 109 (14). HR-MS: 218.0844 ($C_{15}H_{10}N_2^+$; calc. 218.0845).

*Cryptolepine* (= *1-Methyl-1*H*-indolo[3,2-*b*]quinoline* **1**). MeI (5 ml) was added to a soln. of **2** (0.25 g, 1.15 mmol) in anh. THF (20 ml), and the mixture was heated under reflux for 18 h. After cooling to r.t., the precipitate (0.34 g) was collected and recrystallized from $H_2O$ to afford the bright yellow **1** · HI (0.30 g, 72.3%). M.p. 273-274° ([10]: 271–273°). IR: 3416, 1639, 1563, 1481, 1460, 1397, 1337. $^1$H-NMR ((D$_6$)DMSO): 4.83 (*s*, 3 H); 7.37 (*t*, *J* = 7.8, 1 H); 7.59 (*d*, *J* = 8.1, 1 H); 7.77 (*m*, 2 H); 8.04 (*t*, *J* = 7.8, 1 H); 8.34 (*d*, *J* = 7.8, 1 H); 8.53 (*t*, *J* = 9.0, 2 H); 9.00 (*s*, 1 H); 12.66 (*s*, 1 H). $^{13}$C-NMR ((D$_6$)DMSO): 40.4 (*q*); 113.3 (*d*); 113.8 (*s*); 117.8 (*d*); 121.9 (*d*); 125.0 (*d*); 126.2 (*d*); 126.3 (*s*); 127.5 (*d*); 130.1 (*d*); 133.0 (*d*); 133.3 (*s*); 134.3 (*d*); 135.5 (*s*); 137.9 (*s*); 145.8 (*s*). EI-MS: 233 (31), 232 (100, [$M$ – HI]$^+$), 218 (29), 217 (30), 190 (21). HR-MS: 233.1074 ($C_{15}H_{10}N_2^+$; calc. 233.1080).

Cryptolepine (**1**) was liberated from its hydroiodide by treatment with 5% $Na_2CO_3$ and extraction with $CHCl_3$. Chromatography over neutral alumina ($CH_2Cl_2$/MeOH 99:1) afforded **1** in 54.6% yield. M.p. 173–175° ([16]: 178–180°). IR: 1692, 1631, 1584, 1551, 1513, 1484, 1356. $^1$H-NMR: 4.49 (*s*, 3 H); 6.86 (*t*, *J* = 7.5, 1 H); 7.40 (*t*, *J* = 7.5, 1 H); 7.50 (*t*, *J* = 7.8, 1 H); 7.72 (*m*, 2 H); 7.91 (*t*, *J* = 7.8, 1 H); 8.00 (*d*, *J* = 7.8, 1 H); 8.57 (*s*, 1 H). $^{13}$C-NMR: 37.9 (*q*); 113.3 (*s*); 114.8 (*d*); 117.1 (*d*); 119.7 (*d*); 123.6 (*d*); 124.4 (*s*); 126.4 (*d*); 128.7 (*d*); 129.7 (*d*); 130.7 (*d*); 132.6 (*s*); 138.9 (*s*); 144.7 (*s*); 160.6 (*s*). EI-MS : 232 (100, $M^+$), 218 (14), 216 (25), 190 (15). HR-MS: 232.0998 ($C_{16}H_{12}N_2^+$; calc. 232.1002).

*1-Bromo-1,3-bis(2-nitrophenyl)propan-2-one* (**9b**). $Br_2$ (1 ml) was diluted with $CHCl_3$ (10 ml) and slowly added to a stirred soln. of **9a** (6.0 g, 20 mmol) at r.t. The resulting mixture was refluxed for 1.5 h, cooled, and concentrated *in vacuo* to give a rather unstable oil (7.43 g, 98%), which was used directly without further purification. $^1$H-NMR: 4.65 (*dd*, *J* = 17.8, 8.2, 2 H); 6.28 (*s*, 1 H); 7.37 (*d*, 1 H); 7.55 (*m*, 3 H); 7.68 (*t*, *J* = 8.2, 1 H); 7.86 (*d*, *J* = 8.2, 1 H); 8.03 (*t*, *J* = 8.2, 1 H); 8.09 (*d*, *J* = 8.2, 1 H). $^{13}$C-NMR: 45.2 (*t*); 49.2 (*q*); 124.9 (*d*); 125.1 (*d*); 128.7 (*d*); 128.9 (*s*); 129.9 (*d*); 130.1 (*s*); 133.5 (*d*); 133.6 (*d*); 133.8 (*d*); 133.9 (*d*); 147.2 (*s*); 148.6 (*s*); 196.1 (*s*).

*Methyl 2,3-Bis(2-nitrophenyl)propanoate* (**11a**). To an ice-cooled and stirred soln. of **9b** (7.43 g, 20 mmol) in dry $CHCl_3$ (30 ml) under $N_2$ was slowly added MeONa (3.3 g, 60 mmol) in MeOH (30 ml). After 20 min, the ice bath was removed, the mixture was kept overnight, and then poured into 5% HCl (50 ml). The product was isolated by extraction with $CH_2Cl_2$ (3 × 30 ml), concentration, and chromatography (hexane/AcOEt 3:1) to afford **11a** (3.76 g, 57%). M.p. 92–93°. IR: 1732, 1610, 1547, 1524, 1434, 1347, 1206, 1168. $^1$H-NMR: 3.37 (*dd*, *J* = 13.8, 7.7, 1 H); 3.62 (*s*, 3 H); 3.90 (*dd*, *J* = 13.8, 7.7, 1 H); 4.67 (*t*, *J* = 7.5, 1 H); 7.12 (*d*, *J* = 7.5, 1 H); 7.38 (*m*, 4 H); 7.52 (*t*, *J* = 7.5, 1 H); 7.88 (*t*, *J* = 8.0, 2 H). $^{13}$C-NMR: 35.5 (*t*); 47.6 (*d*); 52.4 (*q*); 124.8 (*d*); 124.9 (*d*); 127.9 (*d*); 128.5 (*d*); 129.4 (*s*); 130.8 (*d*); 131.7 (*s*); 132.5 (*d*); 133.2 (*d*); 133.5 (*d*); 148.9 (*s*); 149.4 (*s*); 171.8 (*s*). Anal. calc. for $C_{16}H_{14}N_2O_6$: C 58.18, H 4.27, N 8.48; found: C 58.22, H 4.26, N 8.75.

*3-(2-Aminobenzyl)-2,3-dihydro-1*H*-indol-2-one* (**12a**). A mixture of **11a** (1.0 g, 3.03 mmol) and $Na_2S_2O_6 \cdot 2H_2O$ (11.5 g, 66 mmol) in MeOH (40 ml) and $H_2O$ (20 ml) was refluxed for 18 h. Evaporation of MeOH was followed by extraction with AcOEt (3 × 50 ml). The dried extracts were concentrated, and the residue was chromatographed (hexane/AcOEt 9:1) to give **12a** (0.23 g, 32%). M.p. 148–150° (dec). IR: 3238, 2921, 2853, 1666, 1593, 1493, 1330. $^1$H-NMR: 3.37 (*d*, *J* = 5.7, 2 H); 4.00 (*t*, *J* = 6.3, 1 H); 4.41 (*s*, 2 H); 6.62 (*t*, *J* = 7.8, 1 H);

6.70 (*m*, 2 H); 7.01(*m*, 3 H); 7.17 (*t*, *J* = 7.2, 1 H); 7.25 (*d*, *J* = 7.5, 1 H); 7.89 (*s*, 1 H). $^{13}$C-NMR: 30.7 (*t*); 40.9 (*d*); 115.1 (*d*); 117.0 (*d*); 118.9 (*d*); 123.4 (*s*); 123.7 (*d*); 124.1 (*s*); 127.1 (*d*); 127.5 (*d*); 128.0 (*d*); 128.3 (*d*); 136.3 (*s*); 145.8 (*s*); 171.2 (*s*). EI-MS : 238 (9, $M^+$), 237 (4), 218 (8), 106 (100), 93 (46). HR-MS: 238.1116 ($C_{15}H_{14}N_2O^+$; calc. 238.1107).

*Norcryptotackieine* (= *7*H-*Indolo[2,3*-b*]quinoline*; **4**). A stirred mixture of **11a** (5.0 g, 15.2 mmol) and Fe powder (7.7 g, 137.9 mmol) in AcOH/EtOH 1:1 (180 ml) was refluxed under $N_2$ for 3 h. After cooling, it was diluted with $H_2O$ (250 ml), made basic with $Na_2CO_3$, and concentrated. The product was extracted with AcOEt and chromatographed to afford **4** (2.38 g, 72%). M.p. 336–338° ([14]: 338–340°). IR: 3141, 3118, 3029, 1580, 1548, 1477, 1494. $^1$H-NMR ((D$_6$)DMSO): 7.26 (*t*, *J* = 7.2, 1 H); 7.49 (*m*, 3 H); 7.71 (*t*, *J* = 7.2, 1 H); 7.96 (*d*, *J* = 8.4, 1 H); 8.10 (*d*, *J* = 8.4, 1 H); 8.25 (*d*, *J* = 8.4, 1 H); 9.00 (*s*, 1 H); 11.70 (*s*, 1 H). $^{13}$C-NMR ((D$_6$)DMSO): 110.9 (*d*); 117.9 (*s*); 119.6 (*d*); 120.3 (*s*); 121.8 (*d*); 122.7 (*d*); 123.7 (*s*); 127.0 (*d*); 127.5 (*d*); 128.2 (*d*); 128.7 (*d*); 141.4 (*s*); 146.3 (*s*); 152.9 (*s*). EI-MS : 218 (100, $M^+$), 190 (12), 163 (4), 108 (16). HR-MS: 218.0840 ($C_{15}H_{10}N_2^+$; calc. 218.0845).

*Cryptotackieine* (= *6-Methyl-6*H-*indolo[2,3*-b*]quinoline*; **3**). MeI (2 ml) was added to a soln. of **4** (1.0 g, 4.59 mmol) in THF (20 ml). After heating at reflux overnight, the solvent was removed from the mixture and the residue was chromatographed to provide **3** (1.02 g, 96%). M.p. 104–105° ([14]: 107–109°). IR: 1566, 1519, 1459, 1422, 1312, 1296, 1234, 1203. H-NMR ((D$_6$)DMSO): 4.30 (*s*, 3 H); 7.19 (*dd*, *J* = 7.5, 7.2, 1 H); 7.49 (*m*, 2 H); 7.57 (*dd*, *J* = 8.1, 1, 1 H); 7.83 (*t*, *J* = 7.2, 1 H); 7.97 (*d*, *J* = 8.1, 1 H); 8.13 (*d*, *J* = 7.5, 2 H); 8.94 (*s*, 1 H). $^{13}$C-NMR ((D$_6$)DMSO): 32.7 (*q*); 114.9 (*d*); 117.0 (*d*); 119.2 (*d*); 120.2 (*s*); 121.3 (*d*); 121.8 (*d*); 123.7 (*s*); 126.8 (*s*); 128.7 (*d*); 129.9 *d*); 130.6 (*d*); 130.7 (*d*); 136.5 (*s*); 155.5 (*s*); 156.1 (*s*). EI-MS : 232 (0.56, $M^+$), 218 (100), 190 (15), 109 (18). HR-MS: 232.0997 ($C_{16}H_{12}N_2^+$; calc. 232.1002).

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