STUDIES ON INDOLIZINE DERIVATIVES. VI.1
SYNTHESIS OF CYC{[3.2.2]}AZINOPHANE DERIVATIVE

Hiroshi Goto, Keiji Kurata, Hiroyoshi Awaya, Yoshinori Tominaga,
Yoshiro Matsuda, and Goro Kobayashi*
Faculty of Pharmaceutical Sciences, Nagasaki University,
Bunkyo-machi, Nagasaki, 852, Japan

Abstract — Bisindolizine derivative (10b) was obtained by the reaction of 1,4-di(2-pyridyl)butane (9) with bromomethyl tert-butyl ketone. Cycloaddition reaction of 10b with methyl propiolate afforded biscycl{[3.2.2]}azine derivative (11b), which was reduced by lithium aluminum hydride, followed by dehydration to give unstable [2.2.2.2](1,4)cyc{[3.2.2]}azinophane derivative (14).

The synthesis of layered periphenal conjugate system compound, cyclazinophane derivative, e.g., [2.2](1,4)cyc{[3.2.2]}azinophane (1) has not been reported, its n-n or n-n electron interaction is expected because 1 has the lone pair of center nitrogen atom.

As an extension of our cyclazine studies2, we have tried to synthesize 1, by the result of which [2.2.2.2](1,4)cyc{[3.2.2]}azinophane derivative (14) was obtained. In our initial approach, 1,4-bis(methoxycarbonyl)-2-methylcycl{[3.2.2]}azine (3) was obtained by the cycloaddition reaction of 1-methoxycarbonyl-2-methylindolizine (2)3 with methyl propiolate in the presence of 5% palladium carbon in boiling benzene under nitrogen atmosphere. Compound 3 showed mp 169-170°C; IR(KBr) cm⁻¹: 1708; UV \( \lambda_{\text{max}} \) nm (log ε): 224(4.39)sh, 260(4.71), 270(4.68)sh, 295(3.98), 306(3.91), 316(3.97), 392(4.28)sh, 402(4.42), 410(4.54); \( ^1\text{HNMR(CC14) } \delta: 2.92(3H, s, Me), 3.94 \) (6H, s, OMe), 7.85(1H, t, J=8Hz), 8.04(1H, d, J=8Hz), 8.20(1H, d, J=8Hz).

Compound 3 was reduced by lithium aluminum hydride in tetrahydrofuran (THF) at r.t. for 1 h to give 4-bis(hydroxymethyl)-2-methylcycl{[3.2.2]}azine (4) as pale yellow needles in 73% yield. Compound 4 showed mp 138-139°C; IR(KBr) cm⁻¹: 3320; UV \( \lambda_{\text{max}} \) nm (log ε): 228(4.38)sh, 246(4.48)sh, 256(4.52), 292(3.82)sh, 296(3.85),
Attempt to synthesize the desired intermediate, bisbromomethyl compound (5) from 4 was unsuccessful, because 4 was very unstable.

On the other hand, 2-(2-bromomethyl)pyridine (6) was treated with sodium sulfide in boiling EtOH for 5 h to give 1,5-di(2-pyridyl)diethylsulfide (7) in 85% yield. Compound 7 showed bp 210°C (5 mm); $^1$HNMR(CC$_6$D$_5$N): $^1$HNMR(CC$_6$D$_5$) $\delta$: 2.60 (3H, s, Me), 3.80 (3H, s, OMe), 4.94 (4H, d, J=6Hz, -CH$_2$-), 4.94 and 5.14 (each 1H, t, J=6Hz, OH), 7.60 (1H, s), 7.67 (1H, d, J=8Hz), 8.03 and 8.06 (each 1H, d, J=8Hz).

Compound 7 was treated with potassium permanganate to give sulfone derivative (8) in 47% yield. Compound 8 showed mp 75-77°C; IR(KBr) cm$^{-1}$: 1298, 1115; UV max nm(log ε): 250 (3.64)sh, 257 (3.80)sh, 263 (3.87), 269 (3.72)sh; $^1$HNMR(CDC$_3$) $\delta$: 3.20-3.60 (8H, m, -CH$_2$-), 7.20 (2H, d d, J=6Hz and 8Hz), 7.24 (2H, d, J=8Hz), 7.65 (2H, t, J=8Hz), 8.59 (2H, d, J=6Hz).

It was unsuccessful to obtain bisindolizine derivatives by the reaction of 7 or 8 and α-bromoketone derivatives.
\[
\text{HETEROCYCLES, Vol. 17, 1982}
\]

\[
\text{\begin{align*}
\text{CH}_2\text{CH}_2\text{Br} & \xrightarrow{\text{Na}_2\text{S}} \text{CH}_2\text{CH}_2\text{Br} \rightarrow \text{S} \rightarrow \text{SO}_2 \\
\text{Na} & \rightarrow \text{R} = \text{Me} \\
\text{R} = \text{t-Bu} & \rightarrow \text{HCECO}_2\text{Me} \\
\text{Pd-C} & \\
\text{R} = \text{Me} & \rightarrow 10a \\
\text{R} = \text{t-Bu} & \rightarrow 10b \\
\text{CO}_2\text{Me} & \\
\text{R} = \text{Me} & \rightarrow 11a \\
\text{R} = \text{t-Bu} & \rightarrow 11b \\
\text{CO}_2\text{Me} & \\
\text{R} & \\
\text{HCECO}_2\text{Me} & \\
\text{H} & \\
\text{Me} & \\
\text{CO}_2\text{Me} & \\
\text{H} & \\
\text{H} & \\
\text{Me} & \\
\text{Me} & \\
\text{LiAlH}_4 & \\
\rightarrow & \\
\text{CH}_2\text{OH} & \\
\text{CH}_2\text{OH} & \\
\text{13} & \rightarrow 11b \\
\text{14} & \}
\]
Next, 1,4-di(2-pyridyl)butane (9), which was obtained by the reaction of 6 with sodium in boiling toluene for 20 h in 50% yield, reacted with α-bromoacetone in dioxane at 100°C, and then treated with triethylamine to afford 1,2-bis(2-methyl-1-indoliziny1)ethane (10a) as colorless prisms in 50% yield.

Compound 9 showed bp 161°C (1 mm); \( ^1\)H NMR (CDCl\textsubscript{3}) \( \delta \): 1.76 and 2.72 (each 4H, m, -CH\textsubscript{2}-), 6.90 (2H, dd, J=5Hz and 8Hz), 6.98 (2H, d, J=8Hz), 7.40 (2H, t, J=8Hz), 8.39 (2H, d, J=5Hz).

Compound 10a showed mp 134-135°C; UV \( \text{EtOH} \) \( \lambda_{\text{max}} \) nm (log \( \varepsilon \)): 215 (4.48), 246 (4.76), 288 (3.46) sh, 297 (3.73), 308 (3.78), 366 (3.66); \( ^1\)H NMR (CDCl\textsubscript{3}) \( \delta \): 2.16 (6H, s, Me), 3.18 (4H, s, -CH\textsubscript{2}-), 6.21 (2H, t, J=7Hz), 6.42 (2H, dd, J=7Hz and 8Hz), 7.00 (2H, s), 7.06 (2H, d, J=8Hz), 7.70 (2H, d, J=7Hz).

In the same manner, 9 reacted with bromomethyl t-butyl ketone to afford bis-indolizine derivative (lob) in 30% yield. Compound lob showed mp 174-175°C; UV \( \text{EtOH} \) \( \lambda_{\text{max}} \) nm (log \( \varepsilon \)): 216 (4.64), 249 (4.91), 274 (4.40), 283 (4.36) sh, 311 (4.33), 402 (4.27) sh, 412 (4.31), 422 (4.31); \( ^1\)H NMR (CDCl\textsubscript{3}) \( \delta \): 1.44 (18H, s, t-Bu), 3.18 (4H, s, -CH\textsubscript{2}-), 6.24 and 6.41 (each 2H, t, J=8Hz), 7.06 (2H, s), 7.10 and 7.74 (each 2H, d, J=8Hz).

Compound 10a reacted with methyl propiolate in the presence of 5% palladium carbon in boiling benzene under nitrogen atmosphere to give 1,2-bis(4-methoxycarbonyl-2-methyl-1-cycl[3.2.2]azinyl)ethane (11a) as yellow needles in 11% yield, and bis-7,7a-dihydrocycl[3.2.2]azine derivative (12) as yellow crystals in 26% yield.

Compound 11a showed mp 200-201°C; IR (KBr) cm\textsuperscript{-1}: 1700; UV \( \text{EtOH} \) \( \lambda_{\text{max}} \) nm (log \( \varepsilon \)): 216 (4.64), 249 (4.91), 274 (4.40), 283 (4.36) sh, 311 (4.33), 402 (4.27) sh, 412 (4.31), 422 (4.31); \( ^1\)H NMR (CDCl\textsubscript{3}) \( \delta \): 2.32 (6H, s, Me), 3.38 (4H, s, -CH\textsubscript{2}-), 3.95 (6H, s, OMe), 7.38 and 8.20 (each 2H, d, J=8Hz), 7.58 (2H, s), 7.60 (2H, d, J=8Hz).

Compound 12 showed mp 236-237°C; IR (KBr) cm\textsuperscript{-1}: 1680; UV \( \text{EtOH} \) \( \lambda_{\text{max}} \) nm (log \( \varepsilon \)): 259 (4.55), 265 (4.43) sh, 309 (4.39), 354 (3.95), 398 (3.63) sh, 410 (3.58) sh, 422 (3.52) sh; \( ^1\)H NMR (CDCl\textsubscript{3}) \( \delta \): 2.00 (6H, s, Me), 2.48 (4H, s, -CH\textsubscript{2}-), 3.80 (6H, s, OMe), 2.14-2.56 (4H, m), 4.10-4.42 and 5.68-5.90 (each 2H, m), 6.27 (2H, s), 6.96 (2H, dd, J=8Hz and 3Hz).

As above, lob reacted with methyl propiolate only to give bis-cycl[3.2.2]azine derivative (11b) as yellow needles in 18% yield.

Compound 11b showed mp 246-247°C; IR (KBr) cm\textsuperscript{-1}: 1695; UV \( \text{EtOH} \) \( \lambda_{\text{max}} \) nm (log \( \varepsilon \)): 217 (4.64), 258 (4.93), 276 (4.44), 283 (4.40) sh, 312 (4.34), 406 (4.28) sh, 416 (4.32) sh, 426 (4.35); \( ^1\)H NMR (CDCl\textsubscript{3}) \( \delta \): 1.68 (18H, s, t-Bu), 3.75 (4H, s, -CH\textsubscript{2}-), 4.04 (6H, s, OMe), 7.48 and 8.30 (each 2H, d, J=8Hz), 7.64 (2H, t, J=8Hz), 8.16 (2H, s); MS m/z:
Compound 1\textsubscript{lb} was treated with lithium aluminum hydride in THF at 50°C for 3 h, and then chromatographic separation was carried out on a column of silica gel to afford yellow crystals (1\textsubscript{14}) which was very unstable in the presence of catalytic amount of acid in solvent. Expected reduced product (1\textsubscript{13}) was not obtained. Compound 1\textsubscript{14} showed mp 250°C (dec); UV \(\lambda_{\text{max}}^\text{Hexane} \) nm \(5\): 223, 252, 260sh, 301, 430sh, 440; \(1\)H NMR (CDCl\(_3\)) \(\delta\): 1.68 (36H, s, t-Bu), 3.75 (8H, s, -CH\(_2\)-), 4.90 (4H, s, -CH=CH-), 7.45 (4H, t, \(J=8\text{Hz}\)), 7.52 (4H, s), 7.72 (8H, d, \(J=8\text{Hz}\)); FD-MS m/z: 863(M\(^+\)-23).

Therefore it can be presumed that 1\textsubscript{lb} was reduced and then underwent bimolecular condensation to afford 5,13,23,31-tetra-t-butyl[2.2.2.2](1,4)cycl[3.2.2]azinophane-1,19-diene (1\textsubscript{14}), but its reaction mechanism was unknown. Further works on the synthesis of cycl[3.2.2]azinophane derivatives are in progress.

REFERENCES AND NOTES


4. K. Loffler, Ber., 1904, 37, 161.

5. Concentration is unknown because of insufficient solubility.

Received, 2nd September, 1981