STUDIES ON INDOLIZINE DERIVATIVES. VI.[1]
SYNTHESIS OF CYCL[3.2.2]AZINOPHANE DERIVATIVE

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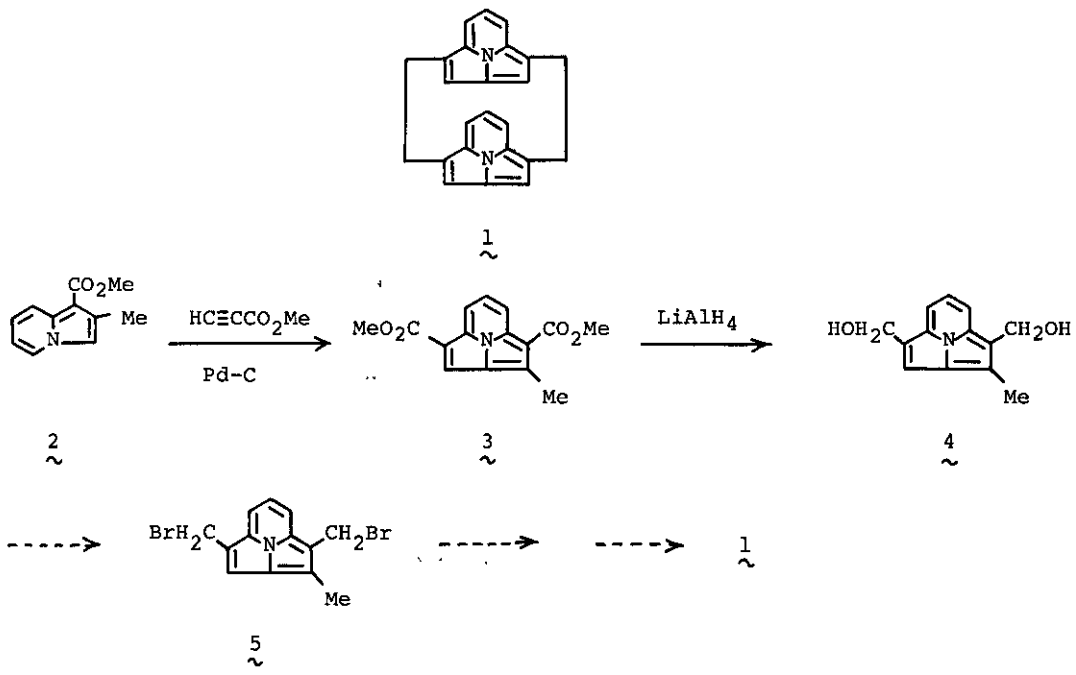
Abstract — Bisindolizine derivative (10b) was obtained by the reaction of 1,4-di(2-pyridyl)butane (9) with bromomethyl t-butyl ketone. Cycloaddition reaction of 10b with methyl propiolate afforded biscycl[3.2.2]azine derivative (11b), which was reduced by lithium aluminum hydride, followed by dehydration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

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

As an extention of our cyclazine studies[2], we have tried to synthesize 1, by the result of which [2.2.2.2](1,4)cycl[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 cycloaddtion 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 λ_{max}^{EtOH} 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}HNMR(CCl_4) δ: 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 λ_{max}^{EtOH} nm(log ε): 228(4.38)sh, 246(4.48)sh, 256(4.52), 292(3.82)sh, 296(3.85),



1 2 3 4 5

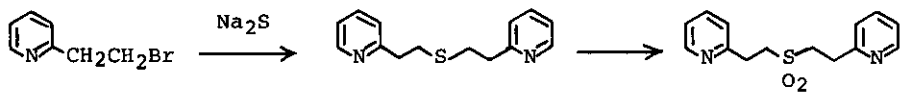
301(3.80)sh, 416(3.78); ^{1}HNMR(DMSO-d_6) δ: 2.60(3H, s, Me), 3.80(3H, s, OMe), 4.94(4H, d, J=6Hz, -CH_2-), 4.94 and 5.14(each 1H, t, J=6Hz, OH), 7.60(1H, s), 7.67(1H, d, J=8Hz), 8.03 and 8.06(each 1H, d, J=8Hz).

Attempt to synthesize the desired intermediate, bisbromomethyl compound (5) from 4 was unsuccessful, because 4 was very unstable.

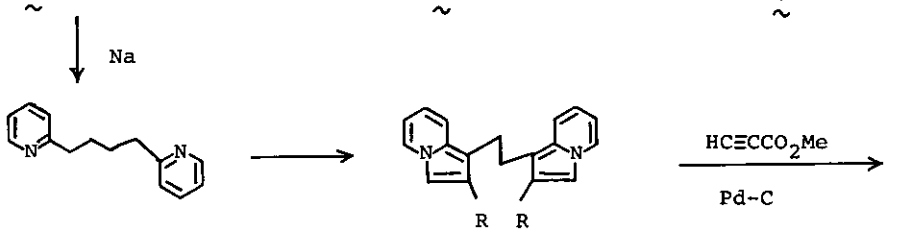
On the other hand, 2-(2-bromomethyl)pyridine (6)[4] was treated with sodium sulfide in boiling EtOH for 5 h to give 1,5-di(2-pyridyl)diethylsulfide (7) in 85% yield. Compound 7 showed bp 210°C (5 mm); ^{1}HNMR(CCl_4) δ: 2.80-3.00(8H, m, -CH_2-), 7.00 (2H, d d, J=6Hz and 8Hz), 7.07(2H, d, J=8Hz), 7.50(2H, t, J=8Hz), 8.46(2H, d, J=6Hz).

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 λ_{max}^{EtOH} nm(log ε): 250(3.64)sh, 257(3.80)sh, 263(3.87), 269(3.72)sh; ^{1}HNMR($CDCl_3$) δ: 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.

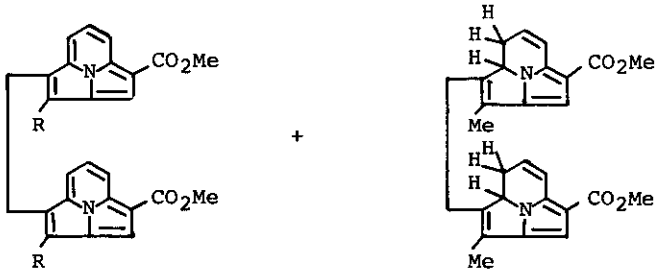


6 7 8



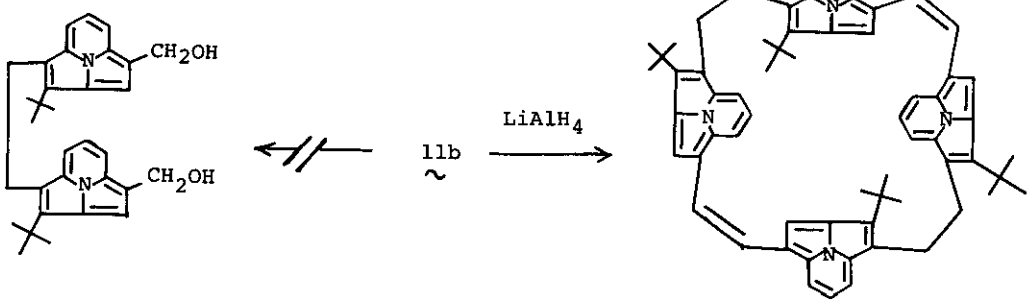
9

10a R= Me
10b R= t-Bu



11a R= Me
11b R= t-Bu

12



13 11b 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-indolizinyl)ethane (10a) as colorless prisms in 50% yield.

Compound 9 showed bp 161°C (1 mm); ^{1}HNMR(CCl_4) δ: 1.76 and 2.72(each 4H, m, $-CH_2-$), 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 λ_{max}^{EtOH} nm(log ε): 215(4.48), 246(4.76), 288(3.46)sh, 297(3.73), 308(3.78), 366(3.66); ^{1}HNMR($CDCl_3$) δ: 2.16(6H, s, Me), 2.86(4H, s, $-CH_2-$), 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 (10b) in 30% yield. Compound 10b showed mp 174-175°C; UV λ_{max}^{EtOH} nm(log ε): 244(4.76), 286(3.63)sh, 296(3.69), 306(3.73), 364(3.63); ^{1}HNMR ($CDCl_3$) δ: 1.44(18H, s, t-Bu), 3.18(4H, s, $-CH_2-$), 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^{-1}: 1700; UV λ_{max}^{EtOH} nm(log ε): 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}HNMR($CDCl_3$) δ: 2.32(6H, s, Me), 3.38(4H, s, $-CH_2-$), 3.95(6H, s, OMe), 7.38 and 8.20(each 2H, d, J=8Hz), 7.58(2H, t, J=8Hz), 7.88(2H, s).

Compound 12 showed mp 236-237°C; IR(KBr) cm^{-1}: 1680; UV λ_{max}^{EtOH} nm(log ε): 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}HNMR($CDCl_3$) δ: 2.00(6H, s, Me), 2.48(4H, s, $-CH_2-$), 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, 10b reacted with methyl propiolate only to give biscycl[3.2.2]azine derivative (11b) as yellow needles in 18% yield.

Compound 11b showed mp 246-247°C; IR(KBr) cm^{-1}: 1695; UV λ_{max}^{EtOH} nm(log ε): 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}HNMR($CDCl_3$) δ: 1.68(18H, s, t-Bu), 3.75(4H, s, $-CH_2-$), 4.04(6H, s, OMe), 7.48 and8.30(each 2H, d, J=8Hz), 7.64(2H, t, J=8Hz), 8.16(2H, s); MS m/z:

536(M^+).

Compound 11b 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 (14) which was very unstable in the presence of catalytic amount of acid in solvent. Expected reduced product (13) was not obtained.

Compound 14 showed mp 250°C (dec); UV $\lambda_{max}^{n\text{-Hexane}}$ nm [5] : 223, 252, 260sh, 301, 430sh, 440; ^{1}HNMR($CDCl_3$) δ: 1.68(36H, s, t-Bu), 3.75(8H, s, $-CH_2-$), 4.90(4H, s, -CH=CH-), 7.45(4H, t, J=8Hz), 7.52(4H, s), 7.72(8H, d, J=8Hz); FD-MS m/z: 863(M^+-23).

Therefore it can be presumed that 11b was reduced and then underwent bimoleculer condensation to afforded 5,13,23,31-tetra-t-butyl[2.2.2.2](1,4)cycl[3.2.2]azinophane-1,19-diene (14), but its reaction mechanism was unknown.

Further works on the synthesis of cycl[3.2.2]azinophane derivatives are in progress.

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4. K. Loffler, Ber., 1904, 37, 161.
5. Concentration is unknown because of insufficient solubility.

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