SYNTHESIS OF A NEW ANNULENOANNULENE, CYCL[3.2.2]AZINO[1,2-*a*]CYCL[3.2.2]AZINE

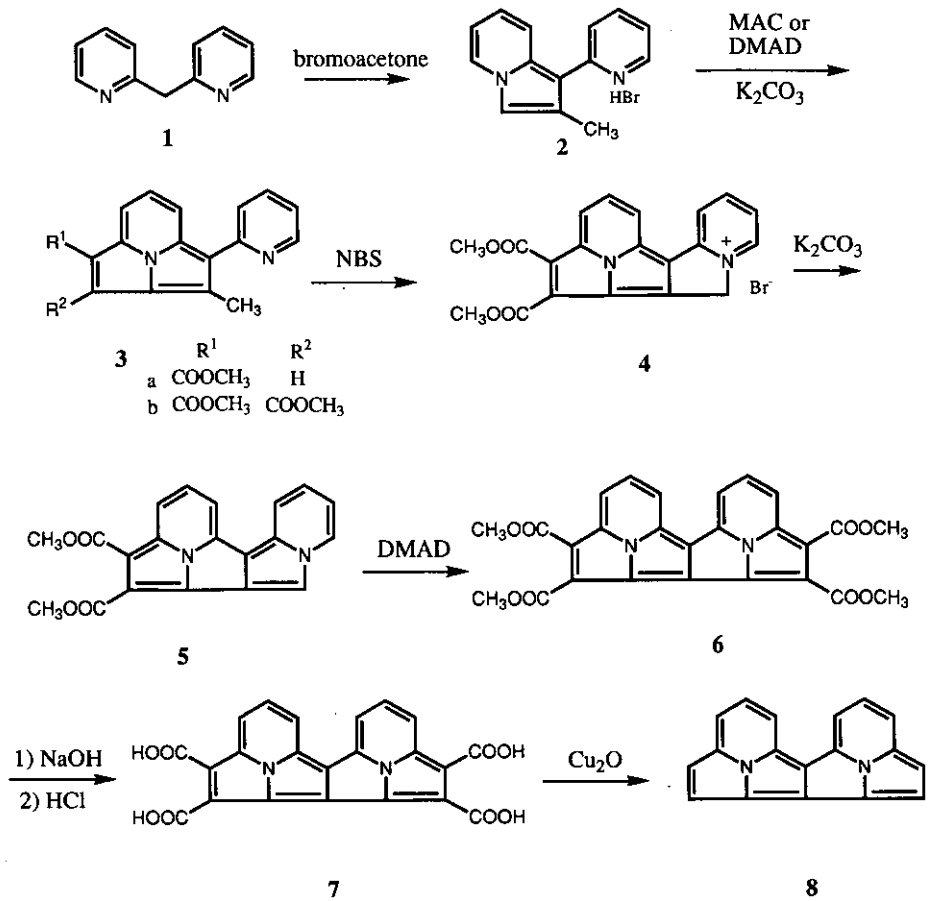
Yoshiro Matsuda,* Shinya Kohra, Keisuke Katou, Takahiro Itou, and Takashi Uemura

Faculty of Environmental Studies, Nagasaki University, 1-14 Bunkyo-machi Nagasaki 852, Japan

Abstract - A new nitrogen-bridged annulenoannulene, cycl[3.2.2]azino[1,2-*a*]-cycl[3.2.2]azine (**8**) was synthesized from the starting bispyridylmethane (**1**) *via* cycloaddition reaction of the indolizinocyclazine derivative (**5**) with dimethyl acetylenedicarboxylate (DMAD) as the key step.

In view of the interest in heterocyclic annulene[1-5] we have previously reported a new nitrogen-bridged heterocyclic system, cyclazine (cycl[3.2.2]azines,[6] cycl[3.2.2]azinophanes,[7] cycl[3.3.2]azinones,[8] cycl-[3.3.3]azines,[5] 3*H*-cycl[3.2.2]azinocycl[3.3.2]azinone[9]). However, there has been no report on the synthesis of the annulenoannulene, cycl[3.2.2]azinocycl[3.2.2]azine (**8**). In this paper we wish to report a novel synthesis of **8** *via* tetramethyl cycl[3.2.2]azino[1,2-*a*]cycl[3.2.2]azine-1,2,3,4-tetracarboxylate (**6**) by the cyclization of the key intermediate, indolizinocycl[3.2.2]azine derivative (**5**) with dimethyl acetylenedicarboxylate (DMAD).

The starting bispyridylmethane (**1**) used in the present work was prepared according to Newkome's method.[10] The reaction of **1** with bromoacetone in acetonitrile at room temperature for a week gave pyridylindolizine hydrobromide (**2**). After many attempts to obtain pyridylcyclazine (**3**), the synthesis of the desired compounds (**3a, b**) was achieved on employing the procedure of Farquhar.[11] Treatment of **2** with methyl acetylenecarboxylate (MAC) or DMAD in the presence of K_2CO_3 in nitrobenzene for 20 h at 120 ℃ afforded the pyridylcyclazine derivatives (**3a, b**). Compound (**3b**) was allowed to react with *N*-bromosuccinimide (NBS) in refluxing CH_2Cl_2 for 6 h and then the reaction mixture was treated with aq. K_2CO_3 to give the key intermediate, indolizinocyclazine derivative (**5**), followed by the cyclization of the crude product (**5**) with DMAD in refluxing xylene to give tetramethyl cyclazinocyclazine-1,2,3,4-tetracarboxylate (**6**) in 30% yield based on **3**. Hydrolysis of **6** using 30 % aq. NaOH in refluxing MeOH for 20 h followed by acidification with 10 % HCl gave the corresponding tetra acid (**7**). Decarboxylation of the tetra acid (**7**) was conducted by Cu_2O in boiling nitrobenzene for 30 h to afford the desired [10]annuleno[10]annulene, cycl[3.2.2]azino[1,2-*a*]cycl[3.2.2]azine (**8**) in 17 % based on **6**.



Scheme 1

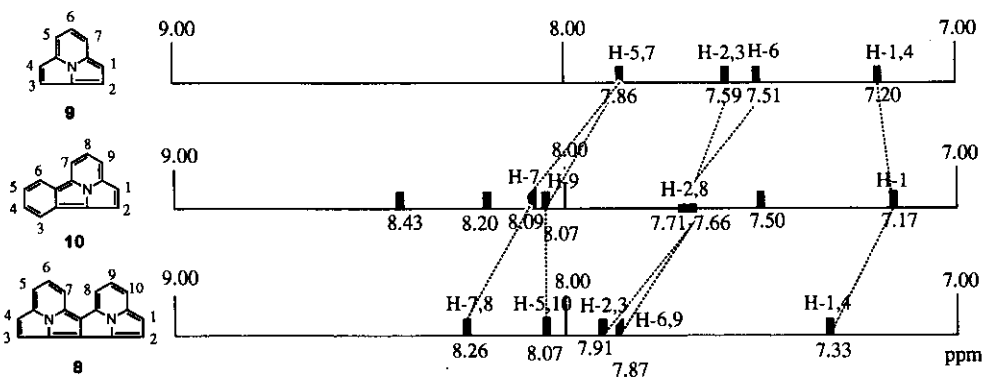


Figure 1. ^{1}H-NMR spectra of **8**, **9**, and **10**

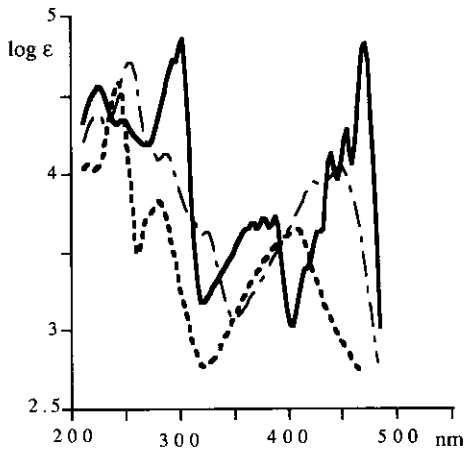


Figure 2. UV spectra of **8** (——), **9** (-----), and **10** (-·-·)

The structure of **8** was supported by a satisfactory elemental analysis and the signals of four doublets (7.33: $C_{1,4}$-H, d, J = 5 Hz; 7.91: $C_{2,3}$-H, d, J = 5 Hz; 8.07: $C_{5,10}$-H, d, J = 8 Hz; 8.26: $C_{7,8}$-H, d, J = 8 Hz) and a triplet (7.87: $C_{6,9}$-H, t, J = 8 Hz) in the ^{1}H-NMR spectrum. Cyclazinocyclazine (**8**) is yellow crystals and soluble in most of organic solvents giving pale yellow solutions. It is stable to heat, light, and acids.

The UV spectra (in EtOH) of cycl[3.2.2]azine (**9**),[12] benzo[a]cycl[3.2.2]azine (**10**),[13] and cycl[3.2.2]azino-[1,2-a]cycl[3.2.2]azine (**8**) are illustrated in Figure 2 and it is evident that the main maxima of the cyclazines (**8**-**10**) exhibit a bathochromic shift as larger conjugated system.

The ^{1}H-NMR spectra of cyclazine (**9**),[12] benzocyclazine (**10**),[13] and cyclazinocyclazine (**8**) are shown in Figure 1. The ^{1}H-NMR spectra clearly show that there is the decreasing order of diatropicity of the cyclazines (**8** > **10** > **9**). Thus, the diatropicity of a cyclazine is considerably increased by fusion of a benzene ring and fusion of a second cyclazine also induces the diamagnetic ring current of the cyclazine to a more extent than benzene. On the other hand Cresp and Sondheimer reported the synthesis of bisdehydro-[14]annulene (**11**), benzobisdehydro[14]annulene (**12**), and bisdehydro[14]annulenobisdehydro[14]-annulene (**13**).[14,15] Then they pointed out that the diatropicity of a bisdehydro[14]annulene is considerably reduced by fusion of a benzene ring and fusion of a second bisdehydro[14]annulene also reduces the diamagnetic ring current of the bisdehydro[14]annulene, although to a lesser extent than benzene. Thus there is the decreasing order of diatropicity of the bisdehydroannulenes (**11** > **13** > **12**). The reasons for difference of the decreasing order of diatropicity between the cyclazines and the dehydro[14]annulenes are unclear at present time. Furthermore, we are in the process of preparing other cyclazines and making their quantum chemical calculation with the hope of expanding understanding of these interesting compounds.

EXPERIMENTAL

Melting points were determined with a Mitamura Mel-Temp and are uncorrected. IR spectra were recorded in KBr pellets on an IR 810 (JASCO) spectrophotometer. UV spectra were recorded on a UV-310 (Shimazu) spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Gemini 300 (VARIAN) and a VARIAN UNITY plus 500 (VARIAN) spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ). Elemental analyses (C,H,N) of all compounds described here were performed on a Yanagimoto MT-2 CHN recorder.

1-(2-Pyridyl)-2-methylindolizine Hydrobromide (2)

To a solution of bromoacetone (0.41 g, 3 mmol) in CH_3CN (10 mL) was added dropwise a solution of **1** (0.51 g, 3 mmol) in CH_3CN (3 mL) at 0 ℃ and the mixture was stirred for a week at rt. The resulting precipitates were collected by filtration, washed with CH_3CN, and recrystallized from MeOH to give **2**.

2: mp 267-270 ℃, yield 0.23 g, 27 %. IR (KBr) 1590, 1610 cm^{-1}; UV (EtOH) λmax (log ε) 238 (4.46), 283 (3.67), 333 (3.96), 409 (3.85) nm; ^{1}H-NMR (DMSO-d_6) 2.42 (3H, s, CH_3), 6.83 (1H, t, J = 7 Hz, C_7-H), 7.65 (1H, s, C_3-H), 7.69 (1H, dd, J = 7, 9 Hz, C_6-H), 7.73 (1H, t, J = 7 Hz, $C_{5'}$-H), 7.77 (1H, d, J = 9 Hz, C_5-H), 8.03 (1H, d, J = 7 Hz, $C_{3'}$-H), 8.42 (1H, d, J = 7 Hz, C_8-H), 8.43 (1H, t, J = 7 Hz, $C_{4'}$-H), 8.72 (1H, d, J = 7 Hz, $C_{6'}$-H). *Anal.* Calcd for $C_{14}H_{13}N_2Br$: C, 58.15; H, 4.53; N, 9.69. Found: C, 57.92; H, 4.58: N, 9.58.

Methyl 1-(2-pyridyl)-2-methylcycl[3.2.2]azine-4-carboxylate (3a)

A suspension of **2** (0.20 g, 0.69 mmol), MAC (0.07 g, 0.83 mmol), and K_2CO_3 (0.19 g, 1.38 mmol) in nitrobenzene (10 mL) was stirred for 20 h at 120 ℃. After evaporation of the solvent, the residue was poured into ice, extracted with $CHCl_3$, dried (Na_2SO_4, 1 g), and evaporated. The residue was submitted to column chromatography on silica gel. From a fraction of benzene: $CHCl_3$ (6:1), **3a** was obtained.

3a: mp 136-137 ℃, yield 0.09 g, 43 %. IR (KBr) 1700 cm^{-1}; UV (EtOH) λmax (log ε) 208 (4.52), 249 (4.41), 277 (4.46), 285 (4.45), 418 (4.26) nm; ^{1}H-NMR ($CDCl_3$) 2.92 (3H, s, CH_3), 4.02 (3H, s, OCH_3), 7.24 (1H, m, $C_{5'}$-H), 7.72 (1H, d, J = 8 Hz, $C_{3'}$-H), 7.82 (1H, t, J = 8 Hz, $C_{4'}$-H), 7.89 (1H, t, J = 8 Hz, C_6-H), 8.11 (1H, s, C_3-H), 8.29 (1H, d, J =8 Hz, C_5-H), 8.33 (1H, d, J = 8 Hz, C_7-H), 8.80 (1H, m, $C_{6'}$-H). *Anal.* Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.26; H, 4.88: N, 9.41.

Dimethyl 1-(2-pyridyl)-2-methylcycl[3.2.2]azine-3,4-dicarboxylate (3b)

A suspension of **2** (0.20 g, 0.69 mmol), DMAD (0.12 g, 0.83 mmol), and K_2CO_3 (0.19 g, 1.38 mmol) in nitrobenzene (10 mL) was stirred for 20 h at 120 ℃. After evaporation of the solvent, the residue was poured into ice, extracted with $CHCl_3$, dried (Na_2SO_4, 1 g), and evaporated. The residue was submitted to column chromatography on silica gel. From a fraction of benzene: $CHCl_3$ (6:1), **3b** was obtained.

3b: mp 150-152 ℃, yield 0.11 g, 47 %. IR (KBr) 1700, 1730 cm^{-1}; UV (EtOH) λmax (log ε) 262 (4.52), 424 (4.23) nm; ^{1}H-NMR ($CDCl_3$) 2.92 (3H, s, CH_3), 4.02 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 7.28 (1H, t, J = 8 Hz, $C_{5'}$-H), 7.72 (1H, d, J = 8 Hz, $C_{3'}$-H), 7.85 (1H, t, J = 8 Hz, $C_{4'}$-H), 7.93 (1H, t, J = 8 Hz, C_6-H), 8.33 (1H, d, J = 8 Hz, C_5-H), 8.38 (1H, d, J = 8 Hz, C_7-H), 8.83 (1H, d, J = 8 Hz, $C_{6'}$-H). *Anal.* Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.72; H, 4.73: N, 7.77.

Tetramethyl cycl[3.2.2]azino[1,2-*a*]cycl[3.2.2]azine-1,2,3,4-tetracarboxylate (6)

A solution of compound (**3b**) (0.14 g, 0.4 mmol) and *N*-bromosuccinimide (NBS) (0.14 g, 0.8 mmol) in CH_2Cl_2 (10 mL) in the presence of benzoyl peroxide was refluxed for 6 h. The reaction mixture was washed with 5% aq. K_2CO_3 solution, dried (Na_2SO_4, 1 g), and evaporated under reduced pressure to give **5**. A solution of the crude product (**5**) and DMAD (0.11 g, 0.8 mmol) in xylene (10 mL) was refluxed for 20 h. The reaction mixture was evaporated under reduced pressure and the residue was submitted to column chromatography on silica gel. From a benzene-$CHCl_3$ (1:1) fraction, compound (**6**) was obtained.

6: mp >360℃, 0.06 g, 30 % based on **3**. IR (KBr) 1700 (CO), 1720 (CO) cm^{-1}; UV ($CHCl_3$) λmax (log ε) 319 (4.67), 362 (1.90), 407 (2.56), 483 (4.55), 495 (5.51) nm; ^{1}H-NMR ($CDCl_3$) 4.05 (6H, s, 2xOCH_3), 4.27 (6H, s, 2xOCH_3), 7.87 (2H, t, J = 8 Hz, $C_{6,9}$-H), 8.07 (2H, d, J = 8 Hz, $C_{7,8}$-H), 8.21

(2H, d, J = 8 Hz, $C_{5,10}$-H); ^{13}C-NMR ($CDCl_3$) 51.8, 53.2, 110.7, 111.8, 116.2, 117.2, 121.4, 123.5, 124.7, 125.5, 126.0, 129.8, 163.9, 165.6. MS m/z 486 (M^+). *Anal.* Calcd for $C_{26}H_{18}N_2O_8$: C, 64.20; H, 3.73; N, 5.76. Found: C, 64.32; H, 3.76; N, 5.45.

Cycl[3.2.2]azino[1,2,-*a*]cycl[3.2.2]azine (8)

A mixture of **6** (0.15 g, 0.31 mmol) and 30 % aq. NaOH (17 mL) in MeOH (15 mL) was refluxed for 20 h The mixture was poured into ice and acidified to litmus with 10 % HCl. The resulting precipitate was collected by filtration, washed with water, and dried to give the tetra acid (**7**). A mixture of the crude tetra acid (**7**) and Cu_2O (0.3 g) in nitrobenzene (60 mL) was refluxed for 30 h. The mixture was evaporated under reduced pressure. The residue was submitted to column chromatography on silica gel. From hexane fraction, **8** was obtained.

8: mp 192-195 ℃, yield 0.08 g, 17 % based on **6**. IR (KBr) 1620, 1590 cm^{-1}; UV (EtOH) λmax (log ε) 228 (4.55), 250 (4.35), 296 (4.74) 302 (4.87), 440 (4.14), 455 (4.29), 470 (4.83) nm; ^{1}H-NMR ($CDCl_3$) 7.33 (2H, d, J = 5 Hz, $C_{1,4}$-H), 7.87 (2H, t, J = 8 Hz, $C_{6,9}$-H), 7.91 (2H, d, J = 5 Hz, $C_{2,3}$-H), 8.07 (2H, d, J = 8 Hz, $C_{5,10}$-H), 8.26 (2H, d, J = 8 Hz, $C_{7,8}$-H); ^{13}C-NMR ($CDCl_3$) 108.2, 108.4, 112.7, 115.5, 118.0, 118.9, 120.8, 125.4, 125.9, 130.4. *Anal.* Calcd for $C_{18}H_{10}N_2$: C, 85.02; H, 3.96; N, 11.02. Found: C, 84.89; H, 3.88; N, 11.11.

REFERENCES AND NOTES

1. A. Taurin, *J. Chem. Hetrocycl. Compd.*, 1977, **30**, 245.
2. W. Flitsh and U. Kramer, *Adv. Heterocycl. Chem.*, 1979, **22**, 321.
3. K. Matsumoto, T. Uchida, and S. Yamauchi, *J. Syn. Org. Chem. Japan*, 1977, **35**, 739.
4. S. S. J. Lee and J. M. Cook, *Heterocycles*, 1983, **20**, 87.
5. Y. Matsuda and H. Gotou, *Heterocycles*, 1989, **26**, 2757.
6. C. Maseda, M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, 1974, **94**, 839.
7. Y. Matsuda, H. Gotou, K. Katou, H. Matsumoto, M. Yamashita, K. Takahashi, and S. Ide, *Heterocycles*, 1990, **31**, 983.
8. Y. Matsuda, Y. Tominaga, Y. Tajima, H. Awaya, K. Kurata, and H. Gotou, *Yakugaku Zasshi*, 1986, **106**, 1098.
9. Y. Matsuda, H. Gotou, M. Yamashita, K. Takahashi, S. Ide, K. Furuno, K. Torisu, T. Itou, and C. Motokawa, *Heterocycles*, 1992, **34**, 2277.
10. G. R. Newkome, Y. J. Joo, D. W. Evans, S. Pappalardo, and F. R. Fronczek, *J. Org. Chem.*, 1988, **53**, 786.
11. D. Farquhar, T. T. Gough, D. Leaver, J. F. Miller, J. W. Dick, and M. A. Jessep, *J. Chem. Soc., Perkin Trans. I*, **1984**, 2553.
12. R. J. Windgassen,Tr., W. H. Saundefs, Jr., and V. Boekelheide, *J. Am. Chem. Soc.*, 1959, **81**, 1459.

13. Y. Tominaga, Y. Shiroshita, H. Gotou, and Y. Matsuda, *Heterocycles*, 1986, **24**, 3071.
14. T. M. Cresp and F. Sondheimer, *J. Am. Chem. Soc.*, 1975, **97**, 4412.
15. M. Nakagawa, "The Chemistry of Annulenes", Osaka University Publ. Soc., Osaka, 1996.

Received, 5th August, 1997