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SYNTHESIS OF AN ANNULENOANNULENONE,
3*H*-BENZO[*e*]CYCL[3.3.2]AZIN-3-ONE

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Abstract - A new nitrogen-bridged annulenoannulene, 3*H*-benzo[*e*]cycl[3.3.2]-azin-3-one (**10a**) was synthesized from the starting phenylpyridine (**6**) via the reaction of the indolizine derivative (**9a**) with polyphosphoric acid (PPA) as the key step.

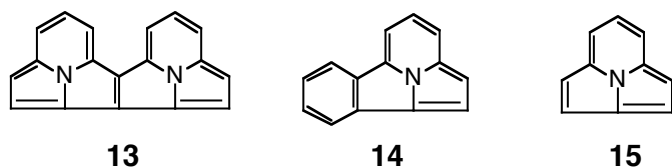
In view of the interest in heterocyclic annulene¹⁻⁶ we have previously reported a new nitrogen-bridged heterocyclic system, cyclazine (cycl[3.2.2]azines,⁷ benzocycl[3.2.2]azine,⁸ cycl[3.2.2]azinophanes,⁹ cycl[3.3.2]azinones,¹⁰ cycl[3.3.3]azines,^{5,6} 3*H*-cycl[3.2.2]azinocycl[3.3.2]azinone,^{11, 12} cycl[3.2.2]azino-cycl[3.2.2]azine¹³). However, there has been no report on the synthesis of the annulenoannulene, 3*H*-benzocycl[3.3.2]azin-3-one (**10a**). In this paper we wish to report a synthesis of the benzocyclazinones (**10a,b**) by the reaction of ethyl 2-phenylindolizine-3-carboxylate derivatives (**9a,b**) with PPA.

Our first attempt to synthesize **10a** from *o*-bromoacetophenone (**1**) as the starting compound was fruitless. *o*-Bromoacetophenone (**1**) was allowed to react with *N*-bromosuccinimide (NBS) in refluxing CHCl₃ for 6 h and then the crude dibromide was treated with pyridine, followed by the cyclization of the crude salt (**2**) with methyl acetylenecarboxylate (MAC) in DMSO with K₂CO₃ to give methyl 2'-bromobenzoylindolizine-1-carboxylate (**3**) in the yield of 30 % based on **1**. Heck reaction¹⁴ of **3** using Pd(OCOCH₃)₂, Ag₂CO₃, P(C₆H₅)₃, and tetrabutylammonium bromide in DMF for 20 h at 100°C under nitrogen atmosphere gave the undesired indenoindolizine derivative (**4**). Hydrolysis of **4** using 30 % NaOH in refluxing MeOH for 20 h followed by acidification with 10 % HCl gave the corresponding acid and then decarboxylation of the acid was conducted by Cu₂O in boiling nitrobenzene for 30 h to afford indenoindolizin-10-one (**5**) in the yield of 18 % based on **4**.

Our further attempt to synthesize **10** from 2-phenylpyridine (**6**) as the starting compound was fruitful.

2-Phenylpyridine (**6**) was reacted with ethyl bromoacetate for 5 h at 100°C, followed by the cyclization¹⁵ of the crude product (**7**) with MAC and K₂CO₃ in DMF at room temperature or **7** and 3,3-bis(methylthio)-2-benzenesulfonylacrylonitrile (**8**) with N(C₂H₅)₃ in refluxing EtOH to give the corresponding indolizine derivatives (**9a,b**). The desired 3*H*-benzocyclazinones (**10a,b**) were obtained by the reaction of **9a,b** with PPA for 10 h at 140°C.

The structure of **10a** was supported by a satisfactory elemental analysis and the signals of six doublets (7.12: C₁-H, d, *J* = 4.7 Hz; 7.96: C₁₀-H, d, *J* = 8.5 Hz; 8.20: C₈-H, d, *J* = 7.3 Hz; 8.13: C₂-H, d, *J* = 4.7 Hz; 8.50: C₇-H, d, *J* = 7.1 Hz; 8.78: C₄-H, d, *J* = 7.8 Hz) in the ¹H-NMR spectrum. Benzocyclazinone (**10a**) is pale orange crystals and soluble in most of organic solvents giving pale orange solutions. It is stable to heat, light, and acids. The selected chemical shifts of cyclazinone (**11**),¹⁶ benzocyclazinone (**10a**), and cyclazinocyclazinone (**12**)¹² are shown in Figure 1. The chemical shifts clearly show that there is the decreasing order of diatropicity of the cyclazinones (**12** > **11** > **10a**). Thus, the diatropicity of a cyclazinone ring is considerably decreased by fusion of a benzene ring and fusion of a second cyclazine increases the diamagnetic ring current of the cyclazinone ring. On the other hand we reported the synthesis of cycl[3.2.2]azinocycl[3.2.2]azine (**13**).¹³



Scheme 2

Then we pointed out that the diatropicity of a cycl[3.2.2]azine ring is considerably increased by fusion of a benzene ring; benzocycl[3.2.2]azine (**14**)⁸ to a more extent than cycl[3.2.2]azine (**15**),¹⁷ and fusion of a second cycl[3.2.2]azine; cycl[3.2.2]azinocycl[3.2.2]azine (**13**) also induces

the diamagnetic ring current of the cycl[3.2.2]azine ring, although to a more extent than benzene. Thus there is the decreasing order of diatropicity of the cycl[3.2.2]azines (**13** > **14** > **15**). The reasons for difference of the decreasing order of diatropicity between the cyclazines and the cyclazinones are unclear at present time. As pointed out in previous papers,^{10, 12, 18} the diamagnetic ring current is increased when cyclazinones are protonated. Thus, when **10a** is dissolved in CDCl₃ with CF₃COOD, the chemical shifts of **10a'** appear at a lower field as compared with **10a**. Furthermore, we are in the process of preparing other cyclazines 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 a FT/IR-430 (JASCO) spectrophotometer. UV spectra were recorded on a UV-310 (Shimadzu) spectrophotometer. ¹H-NMR and ¹³C-NMR spectra were obtained on a Gemini 300 (VARIAN) and a VARIAN UNITY plus 500 (VARIAN) spectrometers 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.

Methyl 3-(2-bromobenzoyl)indolizine-1-carboxylate (3)

A mixture of 2-bromoacetophenone (1.00 g, 5 mmol) and NBS (0.89 g, 5 mmol) in CHCl_3 (20 mL) was refluxed for 6 h. The reaction mixture was washed with 5% aq. Na_2CO_3 (10 mL), dried (Na_2SO_4 , 1 g), and evaporated under reduced pressure to give 2,2'-dibromoacetophenone. To a solution of crude 2,2'-dibromoacetophenone in acetone (5 mL) was added dropwise pyridine (0.4 g, 5 mmol) at 0 °C and the mixture was stirred for a day at rt. The resulting salt (**2**) was collected by filtration and washed with acetone. A mixture of the crude salt (**2**), MAC (0.40 g, 5 mmol), and K_2CO_3 (0.69 g, 5 mmol) in DMSO (30 mL) was stirred for 3 days at rt. The mixture was poured into ice-water and the resulting precipitate was collected by filtration, washed with water, and dried to give **3**.

3: mp 147-149 °C (MeOH), yield 0.54 g, 30 % (based on **1**). IR (KBr) 1615 (CO), 1698 (CO) cm^{-1} ; UV (EtOH) λ_{max} (log ϵ) 235 (4.26), 255 (4.07), 278 (4.23), 328 (3.90), 361 (4.17) nm; $^1\text{H-NMR}$ (CDCl_3) 3.88 (3H, s, CH_3), 7.17 (1H, t, $J = 6$ Hz, $\text{C}_6\text{-H}$), 7.35-7.55 (3H, m, Ar-H), 7.49 (1H, s, $\text{C}_2\text{-H}$), 7.68 (1H, d, $J = 8$ Hz, $\text{C}_6\text{-H}$), 8.41 (1H, t, $J = 9$ Hz, $\text{C}_8\text{-H}$), 10.05 (1H, d, $J = 7$ Hz, $\text{C}_5\text{-H}$). *Anal.* Calcd for $\text{C}_{17}\text{H}_{12}\text{NO}_3\text{Br}$: C, 57.00; H, 3.38; N, 3.91. Found: C, 57.26; H, 3.64; N, 3.79.

Methyl indeno[1,2-*b*]indolizin-10-one-5-carboxylate (4)

A mixture of **3** (1.07 g, 3 mmol), $\text{Pd}(\text{OCOCH}_3)_2$ (0.07 g, 0.6 mmol), $\text{P}(\text{C}_6\text{H}_5)_3$ (0.31 g, 1.2 mmol), Ag_2CO_3 (1.65 g, 6 mmol), and $(\text{C}_4\text{H}_9)_4\text{NBr}$ (0.58 g, 1.8 mmol) in DMF (60 mL) under the nitrogen atmosphere was stirred for 20 h at 100 °C. After filtration, the mixture was evaporated under reduced pressure. The residue was submitted to column chromatography on silica gel. From a fraction of benzene: CHCl_3 (1:1), **4** was obtained.

4: mp 201-202 °C (MeOH), yield 0.35 g, 43 %. IR (KBr) 1680 (CO), 1709 (CO) cm^{-1} ; UV (EtOH) λ_{max} (log ϵ) 223 (4.00), 240 (3.97), 272 (4.08), 300 (3.99), 320 (3.85), 335 (3.89), 445 (3.07) nm; $^1\text{H-NMR}$ (CDCl_3) 4.01 (3H, s, CH_3), 6.98 (1H, t, $J = 6.6$ Hz, $\text{C}_2\text{-H}$), 7.20 (1H, t, $J = 7.1$ Hz, $\text{C}_7\text{-H}$), 7.27 (1H, dd, $J = 6.6, 9.0$ Hz, $\text{C}_3\text{-H}$), 7.33 (1H, t, $J = 7.1$ Hz, $\text{C}_8\text{-H}$), 7.43 (1H, d, $J = 7.1$ Hz, $\text{C}_6\text{-H}$), 7.85 (1H, d, $J = 7.1$ Hz, $\text{C}_9\text{-H}$), 8.23 (1H, d, $J = 9.0$ Hz, $\text{C}_4\text{-H}$), 8.59 (1H, d, $J = 6.6$ Hz, $\text{C}_1\text{-H}$). *Anal.* Calcd for $\text{C}_{17}\text{H}_{11}\text{NO}_3$: C, 73.64; H, 4.00; N, 5.05. Found: C, 73.48; H, 4.17; N, 5.02.

Indeno[1,2-*b*]indolizin-10-one (5)

A mixture of **4** (0.83 g, 3 mmol) and 30 % aq. NaOH (17 mL) in MeOH (15 mL) was refluxed for 20 h. The mixture was poured into ice-water and acidified to litmus with 10 % HCl (20 mL). The resulting precipitate was collected by filtration, washed with water, and dried to give the acid. A mixture of the crude acid 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 a

fraction of benzene: CHCl₃ (5 : 1), **5** was obtained in the yield of 18 % (0.12 g) based on **4**.

5: mp 185-187 °C (MeOH); IR (KBr) 1666 (CO) cm⁻¹; UV (EtOH) λ_{max} (log ϵ) 262 (4.61), 278 (4.38), 288 (4.42), 326 (4.09), 337 (4.06), 441 (3.93) nm; ¹H-NMR (CDCl₃) 6.34 (1H, s, C₅-H), 6.77 (1H, t, *J* = 6.9 Hz, C₂-H), 6.96 (1H, dd, *J* = 6.9, 8.9 C₃-H), 7.12 (1H, t, *J* = 7.3 Hz, C₈-H), 7.17 (1H, d, *J* = 7.3 Hz, C₆-H), 7.23 (1H, t, *J* = 7.3 Hz, C₇-H), 7.36 (1H, d, *J* = 8.9 Hz, C₄-H), 7.39 (1H, d, *J* = 7.3 Hz, C₉-H), 8.46 (1H, d, *J* = 6.9 Hz, C₁-H); ¹³C-NMR (CDCl₃) 96.1, 114.7, 119.9, 120.7, 123.0, 123.4, 127.0, 128.4, 132.2, 137.8, 141.0, 144.9, 171.6, 178.1. *Anal.* Calcd for C₁₅H₉NO: C, 82.18; H, 4.14; N, 6.39. Found: C, 81.93; H, 4.13; N, 6.37. MS *m/z* 219.

Ethyl 1-cyano-2-methylthio-4-phenylindolizine-3-carboxylate (**9b**)

A mixture of 2-phenylpyridine (**6**) (15.5g, 0.1 mol) and ethyl bromoacetate (16.7 g, 0.1 mol) was heated for 5 h at 100 °C to give the salt (**7**). The mixture of the crude salt (**7**), **8** (28.5 g, 0.1 mol) and N(C₂H₅)₃ (20.2 g, 0.2 mol) in EtOH (200 mL) was refluxed for 10 h, after which the mixture was evaporated under reduced pressure and the residue was poured into ice-water. The mixture was extracted with CHCl₃ (3x100 mL) and the combined extracts were washed with water, dried (Na₂SO₄, 10 g), and evaporated under reduced pressure. The residue was then submitted to column chromatography on silica gel. From a fraction of benzene-CHCl₃ (5 : 1), the product (**9b**) was obtained.

9b: mp 134-137 °C (EtOH), yield 5.7 g, 17 % based on **6**. IR (KBr) 1700 (CO), 2211 (CN) cm⁻¹; UV (EtOH) λ_{max} (log ϵ) 240 (4.35), 270 (4.39), 347 (3.94) nm; ¹H-NMR (CDCl₃) 1.04 (3H, t, *J* = 7.4 Hz, CH₂CH₃), 2.73 (3H, s, SCH₃), 3.61 (2H, q, *J* = 7.4 Hz, CH₂CH₃), 6.83 (1H, d, *J* = 7.4 Hz, C₈-H), 7.35 (1H, dd, *J* = 7.4, 8.8 Hz, C₇-H), 7.42-7.51 (5H, m, Ar-H), 7.63 (1H, d, *J* = 8.8 Hz, C₆-H). *Anal.* Calcd for C₁₉H₁₆N₂O₂S: C, 67.84; H, 4.79; N, 8.33. Found: C, 67.66; H, 4.87; N, 8.08.

3H-Benzo[e]cycl[3.3.2]azin-3-one (**10a**)

A mixture of 2-phenylpyridine (**6**) (1.55 g, 10 mmol) and ethyl bromoacetate (1.67 g, 0.1 mol) was heated for 5 h at 100 °C to give the salt (**7**). A mixture of the crude salt (**7**), MAC (8.4 g, 10 mmol), and K₂CO₃ (1.38 g, 10 mmol) in DMSO (50 mL) was stirred for 3 days at rt. The mixture was poured into ice-water and extracted with CHCl₃ (3x100 mL). The extract was dried (Na₂SO₄, 10 g) and evaporated to give oily compound (**9a**). A mixture of the oily compound (**9a**) and PPA (100 mL) was heated for 10 h at 140°C. The mixture was poured into ice and made basic to litmus with K₂CO₃. The mixture was extracted with CHCl₃ (3x100 mL). The extract was dried (Na₂SO₄, 10 g) and evaporated. The residue was submitted to column chromatography on silica gel. From a fraction of benzene: CHCl₃ (6:1), **10a** was obtained in the yield of 12 % (0.26 g) based on **6**.

10a: mp 179-180 °C (MeOH); IR (KBr) 1618 (CO) cm⁻¹; UV (EtOH) λ_{max} (log ϵ) 235 (4.48), 259 (4.62), 273 (4.58), 313 (3.47), 365 (3.89), 405 (4.19), 426 (4.31) nm; ¹H-NMR (CDCl₃) 7.12 (1H, d, *J* = 4.7 Hz, C₁-H), 7.63 (1H, dd, *J* = 7.3, 8.5 Hz, C₉-H), 7.77-7.83 (2H, m, C_{5,6}-H), 7.96 (1H, d, *J* = 8.5 Hz, C₁₀-H),

8.13 (1H, d, $J = 4.7$ Hz, C₂-H), 8.20 (1H, d, $J = 7.3$ Hz, C₈-H), 8.50 (1H, d, $J = 7.1$ Hz, C₇-H), 8.78 (1H, d, $J = 7.8$ Hz, C₄-H); ¹H-NMR (F₃CCOOD in CDCl₃) 7.86 (1H, d, $J = 5.8$ Hz, C₁-H), 8.22-8.32 (2H, m, C_{5,6}-H), 8.60 (1H, t, $J = 8.3$ Hz, C₉-H), 8.64 (1H, d, $J = 8.3$ Hz, C₁₀-H), 8.76 (1H, d, $J = 5.8$ Hz, C₂-H), 8.99 (1H, d, $J = 7.7$ Hz, C₇-H), 9.06 (1H, d, $J = 8.3$ Hz, C₈-H), 9.17 (1H, d, $J = 7.1$ Hz, C₄-H); ¹³C-NMR (CDCl₃) 107.9, 112.2, 118.9, 120.5, 122.8, 123.3, 124.9, 126.8, 128.7, 128.9, 129.9, 131.1, 132.9, 136.6, 170.0. *Anal.* Calcd for C₁₅H₉NO: C, 82.18; H, 4.14; N, 6.39. Found: C, 82.26; H, 4.43; N, 6.43. MS m/z 219.

2-Methylthio-3H-benzo[e]cycl[3.3.2]azin-3-one (10b)

A mixture of **9b** (0.34 g, 1 mmol) and PPA (10 mL) was heated for 10 h at 140°C. The mixture was poured into ice-water and alkalized to litmus with K₂CO₃. The mixture was extracted with CHCl₃ (3x20 mL). The extract was dried (Na₂SO₄, 1 g) and evaporated. The residue was submitted to column chromatography on silica gel. From a fraction of benzene: CHCl₃ (6:1), **10b** was obtained in the yield of 34 % (0.09 g).

10b: mp 215-217 °C (MeOH); IR (KBr) 1614 (CO) cm⁻¹; UV (EtOH) λ_{max} (log ϵ) 217 (4.31), 247 (4.63), 272 (4.09), 315 (4.32), 394 (4.00), 415 (4.20) nm; ¹H-NMR (CDCl₃) 2.68 (3H, s, SCH₃), 6.88 (1H, s, C₁-H), 7.67 (1H, t, $J = 8$ Hz, C₉-H), 7.82-7.90 (3H, m, C_{5,6,10}-H), 8.17 (1H, d, $J = 8$ Hz, C₈-H), 8.57 (1H, d, $J = 6.6$ Hz, C₇-H), 8.83 (1H, d, $J = 6.8$ Hz, C₄-H). *Anal.* Calcd for C₁₆H₁₁NOS: C, 72.43; H, 4.18; N, 5.28. Found: C, 72.61; H, 4.05; N, 5.16

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