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

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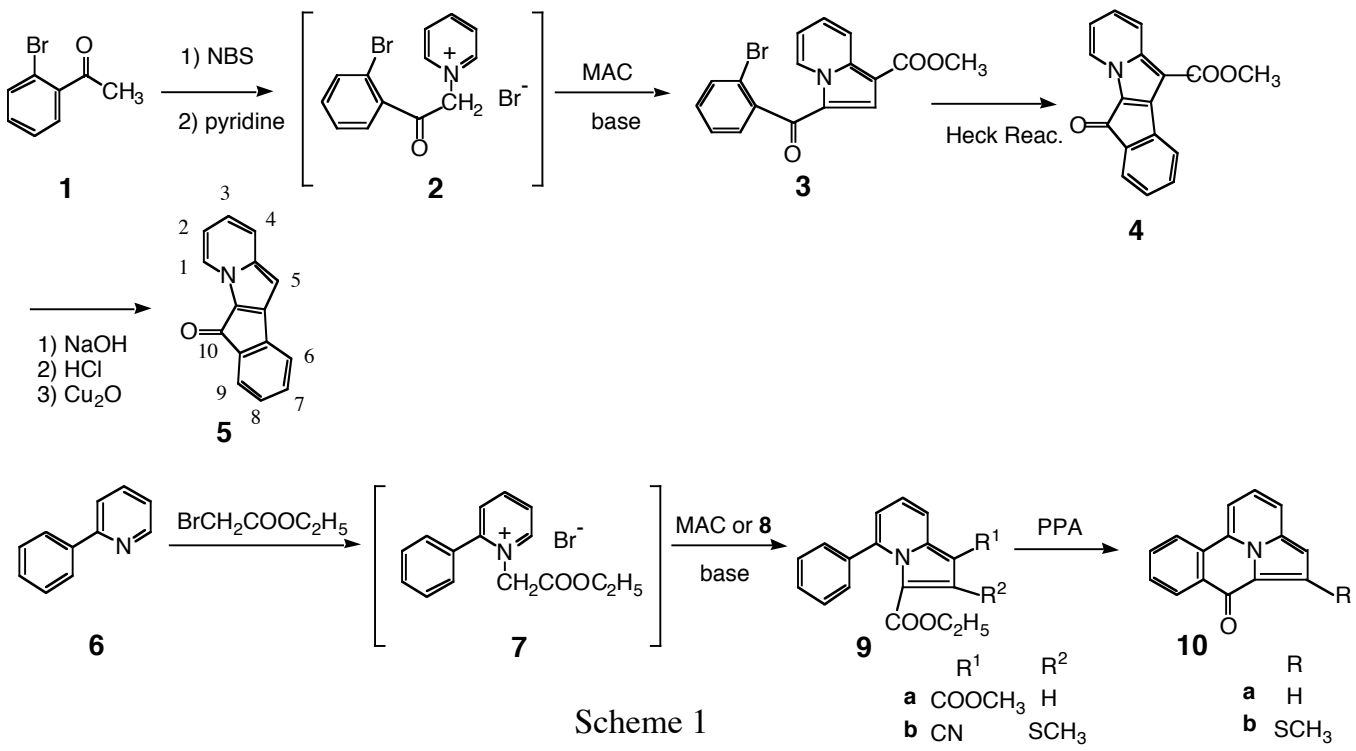
Abstract - A new nitrogen-bridged annulenoannulenone, 3*H*-benzo[*e*]cycl[3.3.2]-azin-3-one (**10a**) was synthesized from the starting phenylpyridine (**6**) *via* the reaction of the indolizine derivative (**9a**) with polyphosphoric acid (PPA) as the key step.

In view of the interest in heterocyclic annulene[1-6] 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]azine[13]). However, there has been no report on the synthesis of the annulenoannulenone, 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-arboxylate 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 $CHCl_3$ 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 K_2CO_3 to give methyl 2'-bromobenzoylindolizine-1-carboxylate (**3**) in the yield of 30 % based on **1**. Heck reaction[14] of **3** using $Pd(OCOCH_3)_2$, Ag_2CO_3, $P(C_6H_5)_3$, and tetrabutylanmonium bromide in DMF for 20 h at 100°C under nitrogen atmosphere gave the undesired indenoindolizine derivative (**4**). Hydroysis 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 Cu_2O 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.



Scheme 1

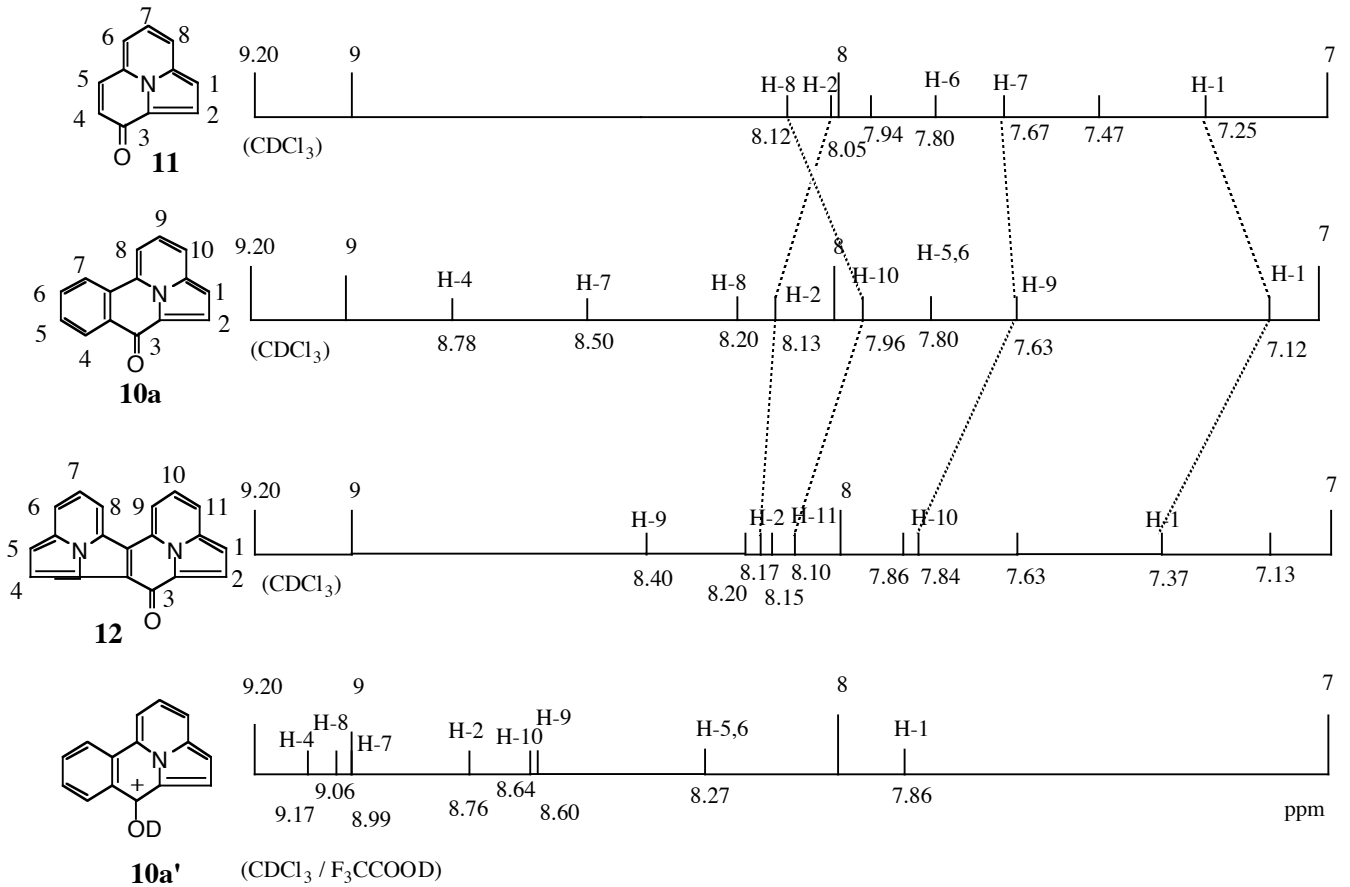
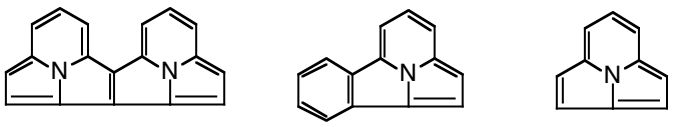


Figure 1 Chemical Shifts of **10a, 10a', 11,** and **12**

2-Phenylpyridine (**6**) was reacted with ethyl bromoacetate for 5 h at 100°C, followed by the cyclization[15] of the crude product (**7**) with MAC and K_2CO_3 in DMF at room temperature or **7** and 3,3-bis(methylthio)-2-benzenesulfonylacrylonitrile (**8**) with $N(C_2H_5)_3$ 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: C_1-H, d, J = 4.7 Hz; 7.96: C_{10}-H, d, J = 8.5 Hz; 8.20: C_8-H, d, J = 7.3 Hz; 8.13: C_2-H, d, J = 4.7 Hz; 8.50: C_7-H, d, J = 7.1 Hz; 8.78: C_4-H, d, J = 7.8 Hz) in the ^{1}H-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]



13 **14** **15**

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; cyccl[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 $CDCl_3$ with CF_3COOD, 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. ^{1}H-NMR and ^{13}C-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 (□). 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) □max (log □) 235 (4.26), 255 (4.07), 278 (4.23), 328 (3.90), 361 (4.17) nm; ^{1}H-NMR ($CDCl_3$) 3.88 (3H, s, CH_3), 7.17 (1H, t, *J* = 6 Hz, C_6-H), 7.35-7.55 (3H, m, Ar-H), 7.49 (1H, s, C_2-H), 7.68 (1H, d, *J* = 8 Hz, $C_{6'}$-H), 8.41 (1H, t, *J* = 9 Hz, C_8-H), 10.05 (1H, d, *J* = 7 Hz, C_5-H). *Anal.* Calcd for $C_{17}H_{12}NO_3Br$: 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** (1.07g, 3 mmol), $Pd(OCOCH_3)_2$ (0.07 g, 0.6 mmol), $P(C_6H_5)_3$ (0.31 g, 1.2 mmol), Ag_2CO_3 (1.65 g, 6 mmol), and $(C_4H_9)_4NBr$ (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) □max (log □) 223 (4.00), 240 (3.97), 272 (4.08), 300 (3.99), 320 (3.85), 335 (3.89), 445 (3.07) nm; ^{1}H-NMR ($CDCl_3$) 4.01 (3H, s, CH_3), 6.98 (1H, t, *J* = 6.6 Hz, C_2-H), 7.20 (1H, t, *J* = 7.1 Hz, C_7-H), 7.27 (1H, dd, *J* = 6.6, 9.0 Hz, C_3-H), 7.33 (1H, t, *J* = 7.1 Hz, C_8-H), 7.43 (1H, d, *J* = 7.1 Hz, C_6-H), 7.85 (1H, d, *J* = 7.1 Hz, C_9-H), 8.23 (1H, d, *J* = 9.0 Hz, C_4-H), 8.59 (1H, d, *J* = 6.6 Hz, C_1-H). *Anal.* Calcd for $C_{17}H_{11}NO_3$: 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: $CHCl_3$ (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) λmax (log ε) 262 (4.61), 278 (4.38), 288 (4.42), 326 (4.09), 337 (4.06), 441 (3.93) nm; ^{1}H-NMR ($CDCl_3$) 6.34 (1H, s, C_5-H), 6.77 (1H, t, *J* =6.9 Hz, C_2-H), 6.96 (1H, dd, J = 6.9, 8.9 C_3-H), 7.12 (1H, t, *J* = 7.3 Hz, C_8-H), 7.17 (1H, d, *J* = 7.3 Hz, C_6-H), 7.23 (1H, t, *J* = 7.3 Hz, C_7-H), 7.36 (1H, d, *J* = 8.9 Hz, C_4-H), 7.39 (1H, d, *J* = 7.3 Hz, C_9-H), 8.46 (1H, d, *J* = 6.9 Hz, C_1-H); ^{13}C-NMR ($CDCl_3$) 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 $C_{15}H_9NO$: 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 $N(C_2H_5)_3$ (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 $CHCl_3$ (3x100 mL) and the combined extracts were washed with water, dried (Na_2SO_4, 10 g), and evaporated under reduced pressure. The residue was then submitted to column chromatography on silica gel. From a fraction of benzene-$CHCl_3$ (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) λmax (log ε) 240 (4.35), 270 (4.39), 347 (3.94) nm; ^{1}H-NMR ($CDCl_3$) 1.04 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 2.73 (3H, s, SCH_3), 3.61 (2H, q, *J* = 7.4 Hz, $C\underline{H}_2CH_3$), 6.83 (1H, d, *J* = 7.4 Hz, C_8-H), 7.35 (1H, dd, *J* = 7.4, 8.8 Hz, C_7-H), 7.42-7.51 (5H, m, Ar-H), 7.63 (1H, d, *J* = 8.8 Hz, C_6-H). *Anal.* Calcd for $C_{19}H_{16}N_2O_2S$: C, 67.84; H, 4.79; N, 8.33. Found: C, 67.66; H, 4.87; N, 8.08.

3*H*-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 K_2CO_3 (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 $CHCl_3$ (3x100 mL). The extract was dried (Na_2SO_4, 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 K_2CO_3. The mixture was extracted with $CHCl_3$ (3x100 mL). The extract was dried (Na_2SO_4, 10 g) and evaporated. The residue was submitted to column chromatography on silica gel. From a fraction of benzene: $CHCl_3$ (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) λmax (log ε) 235 (4.48), 259 (4.62), 273 (4.58), 313 (3.47), 365 (3.89), 405 (4.19), 426 (4.31) nm; ^{1}H-NMR ($CDCl_3$) 7.12 (1H, d, *J* =4.7 Hz, C_1-H), 7.63 (1H, dd, *J* =7.3, 8.5 Hz, C_9-H), 7.77-7.83 (2H, m, $C_{5,6}$-H), 7.96 (1H, d, *J* = 8.5 Hz, C_{10}-H),

8.13 (1H, d, *J* = 4.7 Hz, C_2-H), 8.20 (1H, d, *J* = 7.3 Hz, C_8-H), 8.50 (1H, d, *J* = 7.1 Hz, C_7-H), 8.78 (1H, d, *J* = 7.8 Hz, C_4-H); ^{1}H-NMR (F_3CCOOD in $CDCl_3$) 7.86 (1H, d, *J* =5.8 Hz, C_1-H), 8.22-8.32 (2H, m, $C_{5,6}$-H), 8.60 (1H, t, *J* = 8.3 Hz, C_9-H), 8.64 (1H, d, *J* = 8.3 Hz, C_{10}-H), 8.76 (1H, d, *J* = 5.8 Hz, C_2-H), 8.99 (1H, d, *J* = 7.7 Hz, C_7-H), 9.06 (1H, d, *J* = 8.3 Hz, C_8-H), 9.17 (1H, d, *J* = 7.1 Hz, C_4-H); ^{13}C-NMR ($CDCl_3$) 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 $C_{15}H_9NO$: 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-3*H*-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 K_2CO_3. The mixture was extracted with $CHCl_3$ (3x20 mL). The extract was 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), **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) λmax (log ε) 217 (4.31), 247 (4.63), 272 (4.09), 315 (4.32), 394 (4.00), 415 (4.20) nm; ^{1}H-NMR ($CDCl_3$) 2.68 (3H, s, SCH_3), 6.88 (1H, s, C_1-H), 7.67 (1H, t, *J* = 8 Hz, C_9-H), 7.82-7.90 (3H, m, $C_{5,6,10}$-H), 8.17 (1H, d, *J* = 8 Hz, C_8-H), 8.57 (1H, d, *J* = 6.6 Hz, C_7-H), 8.83 (1H, d, *J* = 6.8 Hz, C_4-H). *Anal.* Calcd for $C_{16}H_{11}NOS$: C, 72.43; H, 4.18; N, 5.28. Found: C, 72.61; H, 4.05; N, 5.16

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. Jpn.*, 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. Y. Matsuda, *Yakugaku Zasshi*, 2001, **121**, 971.
7. C. Maseda, M. Sone, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, 1974, **94**, 839.
8. Y. Tominaga, Y. Shiroshita, H. Gotou, and Y. Matsuda, *Heterocycles*, 1986, **24**, 3071.
9. Y. Matsuda, H. Gotou, K. Katou, H. Matsumoto, M. Yamashita, K. Takahashi, and S. Ide, *Heterocycles*, 1990, **31**, 983.
10. Y. Matsuda, Y. Tominaga, Y. Tajima, H. Awaya, K. Kurata, and H. Gotou, *Yakugaku Zasshi*, 1986, **106**, 1098.
11. Y. Matsuda, H. Gotou, M. Yamashita, K. Takahashi, S. Ide, K. Furuno, K. Torisu, T. Itou, and C.

Motokawa, *Heterocycles*, 1992, **34**, 2277.

12. Y. Matsuda, S. Kohra, K. Katou, T. Itou, and T. Uemura, *Heterocycles*, 1998, **48**, 2573.
13. Y. Matsuda, S. Kohra, K. Katou, T. Itou, and T. Uemura, *Heterocycles*, 1997, **45**, 2223.
14. a) R. F. Heck, *Org. Reac.*, 1979, **27**, 345. b) T. Sakamoto, Y. Kondo, and H. Yamanaka, *Heterocycles*, 1993, **36**, 2437.
15. Y. Tominaga and Y. Matsuda, *J. Syn. Org. Chem. Jpn.*, 1985, **43**, 669.
16. 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.
17. R. J. Windgassen, Tr., W. H. Saundefs, Jr., and V. Boekelheide, *J. Am. Chem. Soc.*, 1959, **81**, 1459.
18. M. Nakagawa, "The Chemistry of Annulenes", Osaka University Publ. Soc., Osaka, 1996.