SYNTHESIS OF A NEW ANNULENOANNULENONE, 3*H*-CYCL[3.2.2]AZINO[2,1-*e*]CYCL[3.3.2]AZIN-3-ONE

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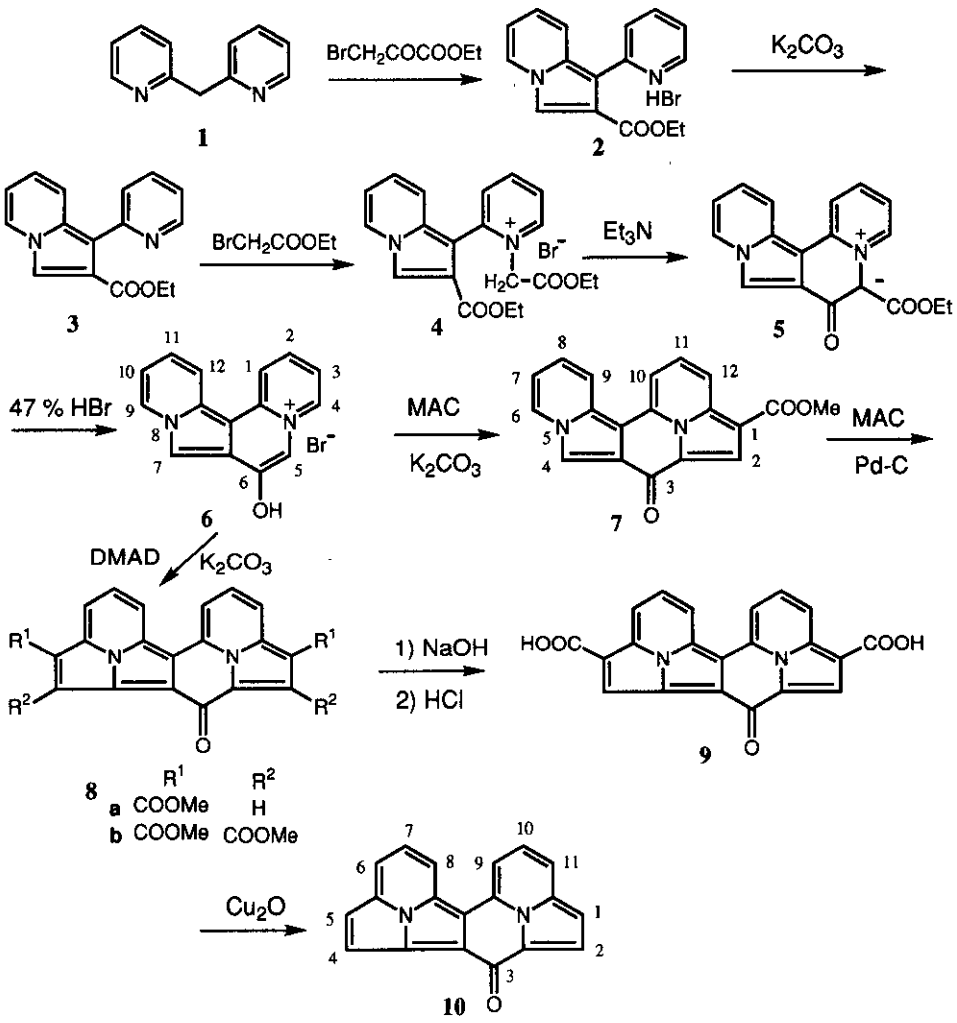
Abstract - A new nitrogen-bridged annulenoannulenone, 3*H*-cycl[3.2.2]azino-[2,1-*e*]cycl[3.3.2]azin-3-one (**10**) was synthesized from bispyridylmethane (**1**) *via* cycloaddition reaction of indolizinoquinolizinium salt (**6**) with methyl acetylene-carboxylate (MAC) as the key step.

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] benzocycl[3.2.2]azine,[9] cycl[3.2.2]azino[1,2-*a*]cycl[3.2.2]azine[10]). However the literature was devoid of annulenoannulenone containing cycl[3.3.2]azinone nucleus which was characterized as a nitrogen-bridged annulenone. As a part of our continuing work on the synthesis of cyclazines, we have reported the synthesis of tetramethyl 3*H*-cycl[3.2.2]azino[2,1-*e*]cycl[3.3.2]azin-3-one-1,2,4,5-tetra-carboxylate in the preliminary communication.[11] In this paper we wish to report a more detailed description of the earlier experiments, the synthesis of 3*H*-cycl[3.2.2]azino[2,1-*e*]cycl[3.3.2]azin-3-one (**10**) as the parent compound, and the examination of it's ^{1}H-NMR spectroscopy.

The starting bispyridylmethane (**1**) used in the present work was prepared according to Newkome's method.[12] The reaction of **1** with ethyl bromopyruvate in acetonitrile at room temperature for a week gave pyridylindolizine hydrobromide (**2**) in good yield. Treatment of the hydrobromide (**2**) with aq. K_2CO_3 afforded the free base, pyridylindolizine (**3**) which was allowed to react with ethyl bromoacetate in acetonitrile at room temperature for a week. The crude salt (**4**) resulted above was refluxed with triethylamine in EtOH to produce the cyclic ylide (**5**) in 93 % yield from **3**. Heating of **5** in refluxing 47 % hydrobromic acid for 30 min gave the salt (**6**) through decarboxylation. After many attempts to obtain cyclazinocyclazinones (**8a, b**), the synthesis of the desired compounds (**8a, b**) was achieved on employing the procedure of Farquhar.[13] Reaction of **6** with methyl acetylenecarboxylate (MAC) in the presence of K_2CO_3 in nitrobenzene for 20 h at 120 ℃ gave methyl 3*H*-indolizinocycl[3.3.2]azin-3-one-5-carboxylate (**7**) and then heating of **7** with MAC in the presence of 5 % Pd-C in nitrobenzene under N_2 atmosphere for 20 h at 100 ℃ afforded the desired annulenoannulenone, dimethyl 3*H*-cycl[3.2.2]azino[2,1-



Scheme 1

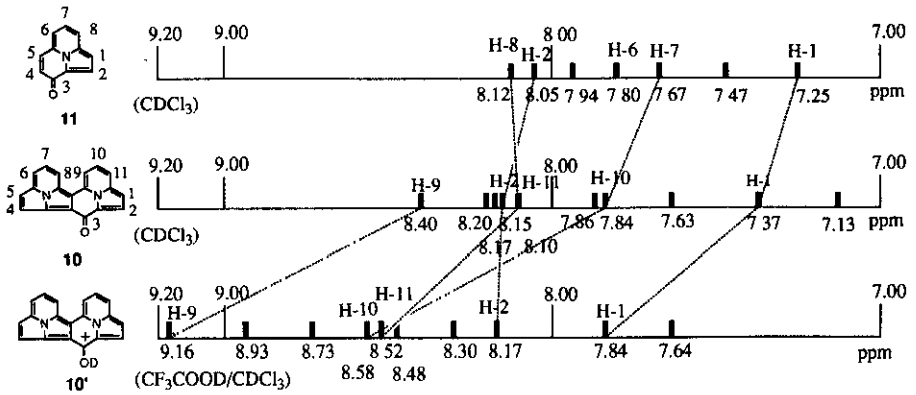


Figure 1. ^{1}H-NMR spectra of **10**, **10'**, and **11**

e]cycl[3.3.2]azin-3-one-1,5-dicarboxylate (**8a**). On the other hand reaction of **6** with dimethyl acetylenedicarboxylate (DMAD) in the presence of K_2CO_3 in refluxing nitrobenzene for 20 h gave tetramethyl 3*H*-cycl[3.2.2]azino[2,1-*e*]cycl[3.3.2]azin-3-one-1,2,4,5-tetracarboxylate (**8b**). Hydrolysis of **8a** using 30 % aq. NaOH in refluxing MeOH for 20 h followed by acidification with 10 % HCl gave the corresponding diacid (**9**). Decarboxylation of the diacid (**9**) was conducted by Cu_2O in boiling nitrobenzene for 30 h to afford the desired [10]annuleno[11]annulenone, cycl[3.2.2]azino[2,1-*e*]cycl[3.3.2]azin-3-one (**10**) in 33 % based on **8a**.

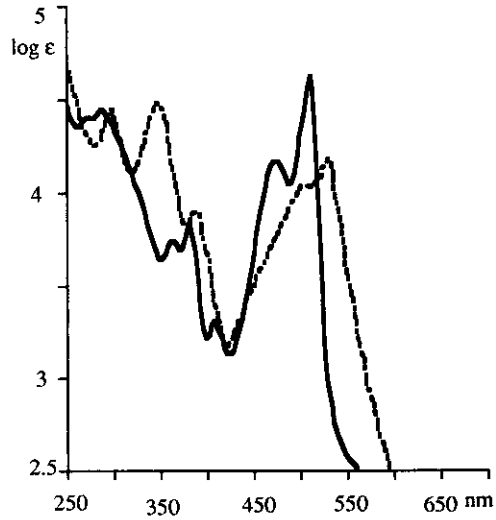


Figure 2. UV spectra of **10** (EtOH) (——) and **10"** (5 % CF_3COOH-EtOH) (-----)

The structure of **10** was supported by a satisfactory elemental analysis and the signals of eight doublets (7.13: C_5-H, J = 5 Hz; 7.37: C_1-H, J = 5 Hz; 7.86: C_6-H, J = 8 Hz; 8.10: C_{11}-H, J = 8 Hz; 8.15: C_2-H, J = 5 Hz; 8.17: C_4-H, J = 5 Hz; 8.20: C_8-H, J = 8 Hz; 8.40: C_9-H, J = 8 Hz) and two triplets (7.63: C_7-H, J = 8 Hz; 7.84: C_{10}-H, J = 8 Hz) in the ^{1}H-NMR spectrum. Cyclazinocyclazin-3-one (**10**) is yellow crystals and soluble in most of organic solvents giving orange solutions. It is stable to heat and light.

The UV spectra of cyclazinocyclazin-3-one (**10**) and protonated cyclazinocyclazin-3-one (**10"**) are illustrated in Figure 2 and it is evident that protonation with the acid causes the main maxima to shift to higher wavelengths.

The ^{1}H-NMR spectra of cyclazin-3-one (**11**),[13] cyclazinocyclazin-3-one (**10**) and deuteronated cyclazinocyclazin-3-one (**10'**) are shown in Figure 1. The ^{1}H-NMR spectra of **10** and **11** indicate the existence of a diamagnetic ring current, since the protons of **10** and **11** resonate at lower field than those of cycl[3.2.2]azine (**12**)[10, 14] (7.20-7.86 ppm). It has already been found that the diatropicity of a cycl[3.2.2]azine is considerably increased by fusion of a second cycl[3.2.2]azine ring as compared **12** with cycl[3.2.2]azinocycl[3.2.2]azine (**13**).[10] It is evident from the ^{1}H-NMR spectra of **10** and **11** that fusion of a cycl[3.2.2]azine also induces the diamagnetic ring current of the cyclazin-3-one. As pointed out in previous papers,[8, 15, 16] the diamagnetic ring current is increased when cyclazinocyclazinone (**10**) is protonated. Thus, when **10** is dissolved in $CDCl_3$ with CF_3COOD, the ^{1}H-NMR spectrum of **10'** shows downfield shifts as compared with **10**.

EXPERIMENTAL

Melting points were determined with a Mitamura Mel-Temp and are uncorrected. IR spectra were recorded in KBr pellets on a 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.

Ethyl 1-(2-Pyridyl)indolizine-2-carboxylate Hydrobromide (2)

To a solution of ethyl bromopyruvate (0.39 g, 2 mmol) in CH_3CN (10 mL) was added dropwise a solution of **1** (0.34 g, 2 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 213-215 ℃, yield 0.56 g, 81 %. IR (KBr) 1710 (CO) cm^{-1}; UV (EtOH) λmax (log ε) 202 (3.92), 225 (4.11), 247 (4.00), 306 (3.47), 365 (3.52), 380 (3.49) nm; ^{1}H-NMR (DMSO-d_6) 1.22 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 4.24 (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$), 6.87-7.25 (2H, m, Ar-H), 7.69 (1H, d, J = 8 Hz, Ar-H), 7.88 (1H, t, J = 8 Hz, Ar-H), 8.16 (1H, d, J = 8 Hz, Ar-H), 8.42 (1H, s, C_3-H), 8.46-8.65 (2H, m, Ar-H), 8.87 (1H, d, J = 6 Hz, Ar-H). *Anal.* Calcd for $C_{16}H_{15}N_2O_2Br$: C, 55.35; H, 4.35; N, 8.07. Found: C, 55.15; H, 4.44; N, 8.01.

Ethyl 1-(2-Pyridyl)indolizine-2-carboxylate (3)

A solution of **2** (0.35 g, 1 mmol) in water (10 mL) was made basic to litmus with K_2CO_3 and extracted with $CHCl_3$ (3x10 mL). The extract was dried (Na_2SO_4, 1 g) and evaporated under reduced pressure. The residue was recrystallized from hexane-CH_2Cl_2 to give compound (**3**)

3: mp 56-57 ℃, yield 0.26 g, 97 %. IR (KBr) 1700 (CO) cm^{-1}; UV (EtOH) λmax (log ε) 202 (4.32), 232 (4.53), 249 (4.47), 309 (3.93), 364 (3.88) nm; ^{1}H-NMR ($CDCl_3$) 1.28 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 4.28 (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$), 6.48-85 (2H, m, Ar-H), 7.07-29 (1H, m, Ar-H), 7.86 (1H, s, C_3-H), 7.59-7.89 (4H, m, Ar-H), 8.68 (1H, d, J = 7 Hz, C_5-H). *Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.15; H, 5.37; N, 10.55.

Ethyl 6*H*-6-Oxoindolizino[1,2-*a*]quinolizin-4a-ium-5-ide-5-carboxylate (5)

To a solution of ethyl bromoacetate (0.17 g, 1 mmol) in CH_3CN (10 mL) was added dropwise a solution of **3** (0.27 g, 1 mmol) in CH_3CN (3 mL) at 0 ℃. After the mixture was stirred for a week at rt, the mixture was evaporated under reduced pressure. A solution of the residue and triethylamine (0.23 g, 2.3 mmol) in EtOH (20 mL) was refluxed for 5 h and the mixture was evaporated under reduced pressure. The residue was submitted to column chromatography on silica gel. From a $CHCl_3$ fraction, compound (**5**) was obtained.

5: mp 243-245 ℃ ($CHCl_3$-MeOH), yield 0.29 g, 93 % based on **3**. IR (KBr) 1680 (CO), 1520 (CO) cm^{-1}; UV (EtOH) λmax (log ε) 200 (4.28), 238 (4.26), 290 (4.26), 340 (4.29), 415 (4.08) nm; ^{1}H-NMR ($CDCl_3$) 1.51 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 4.53 (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$), 7.08 (1H, t, J = 7 Hz, Ar-H), 7.24 (1H, dt, J = 7 Hz, 2 Hz, Ar-H), 7.30 (1H, t, J = 8 Hz, Ar-H), 7.70 (1H, t, J = 7 Hz, Ar-H), 8.21(1H, d, J = 7 Hz, Ar-H), 8.34 (1H, d, J = 8 Hz, Ar-H), 8.42 (1H, d, J = 7 Hz, Ar-H), 8.45 (1H, s, C_8-H), 9.18 (1H, d, J = 7 Hz, Ar-H). *Anal.* Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.45; H, 4.57; N, 9.25.

6*H*-6-Oxoindolizino[1,2-*a*]quinolizin-4a-ium-5-ide Hydrobromide (6)

A solution of **5** (0.31 g, 1 mmol) in 47 % HBr (20 mL) was refluxed for 30 min. The mixture was evaporated under reduced pressure and the residue was recrystallized from MeOH to give compound (**6**).

6: mp 354-356 ℃, yield 0.27 g, 85 %. IR (KBr) 1630 (CO) cm^{-1}; UV (EtOH) λmax (log ε) 200 (4.00), 225 (3.98), 240 (3.95), 262 (3.88), 278 (3.87), 322 (4.15), 380 (3.68) nm; ^{1}H-NMR (DMSO-d_6) 7.37-7.78 (3H, m, Ar-H), 8.09-8.28 (1H, m, Ar-H), 8.13 (1H, s, Ar-H), 8.51 (1H, s, Ar-H), 8.78-9.21 (4H, m, Ar-H). *Anal.* Calcd for $C_{15}H_{11}N_2OBr$: C, 57.16; H, 3.52; N, 8.89. Found: C, 57.23; H, 3.63; N, 8.74.

Methyl 3*H*-Indolizino[2,1-*e*]cycl[3.3.2]azin-3-one-1-carboxylate (7)

A suspension of **6** (1 g, 3.17 mmol), MAC (0.32 g, 3.80 mmol), and K_2CO_3 (0.87 g, 6.34 mmol) in nitrobenzene (10 mL) was stirred for 20 h at 120 ℃. After evaporation of the solvent, the residue was poured to ice, extracted with $CHCl_3$, and the extract was dried (Na_2SO_4, 1 g), and evaporated. The residue was submitted by silica gel column chromatography. From a fraction of benzene: $CHCl_3$ (6:1), compound (**7**) was obtained.

7: mp 340-343 ℃ ($CHCl_3$-MeOH), yield 0.26 g, 26 %. IR (KBr) 1705 (CO), 1620 (CO) cm^{-1}; UV ($CHCl_3$) λmax 341, 358, 398, 430, 456, 511 nm; ^{1}H-NMR (CF_3COOD) 4.32 (3H, s, OCH_3), 8.42 (1H, t, J = 7 Hz, Ar-H), 8.95 (2H, dd, J = 7, 1 Hz, Ar-H), 9.29 (1H, s, Ar-H), 9.48-67 (5H, m, Ar-H). *Anal.* Calcd for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.82; N, 8.86. Found: 72.24; H, 3.77; N, 8.80.

Dimethyl 3*H*-Cycl[3.2.2]azino[2,1-*e*]cycl[3.3.2]azin-3-one-1,5-dicarboxylate (8a)

A suspension of **7** (1 g, 3.16 mmol) and MAC (0.64 g, 7.59 mmol) containing 5 % Pd-C (0.50 g) in nitrobenzene (100 mL) under N_2 atmosphere was heated at 100 ℃ for 20 h. The reaction mixture was filtrated and the organic layer was evaporated. The residue was recrystallized from CF_3COOH-MeOH to give **8a**.

8a: mp > 400 ℃, 0.31 g, 25 %. IR (KBr) 1715 (CO), 1610 (CO) cm^{-1}; UV ($CHCl_3$) λmax (log ε) 363 (3.97), 402 (4.02), 459 (4.14), 485 (4.15), 511 (4.02) nm; UV (5% CF_3COOH in $CHCl_3$) λmax (log ε) 359 (4.23), 515 (3.78) nm; ^{1}H-NMR (CF_3COOD) 4.30 (3H, s, OCH_3), 4.32 (3H, s, OCH_3), 8.61 (1H, t, J = 8 Hz, Ar-H), 8.82-9.61 (6H, m, Ar-H), 8.96 (1H, s, Ar-H), 9.50 (1H, s, Ar-H). *Anal.* Calcd for $C_{23}H_{14}N_2O_5$: C, 69.35; H, 3.54; N, 7.03. Found: C, 69.66; H, 3.72; N, 6.83

Tetramethyl 3*H*-Cycl[3.2.2]azino[2,1-*e*]cycl[3.3.2]azin-3-one-1,2,4,5-tetracarboxylate (8b)

A suspension of **6** (0.22 g, 0.69 mmol), DMAD (0.12 g, 0.83 mmol), and K_2CO_3 (0.19 g, 1.38 mmol) in refluxing nitrobenzene (10 mL) was stirred for 20 h. After evaporation of the solvent, the residue was poured to ice, extracted with $CHCl_3$, and the extract was dried (Na_2SO_4, 1 g), and evaporated. The residue was submitted by silica gel column chromatography. From a fraction of $CHCl_3$: acetone (6:1), compound (**8b**) was obtained.

8b: mp > 400 ℃ (CF_3COOH-MeOH), yield 0.26 g, 73 % (lit.,[11] mp > 400 ℃).

3*H*-Cycl[3.2.2]azino[2,1-*e*]cycl[3.3.2]azin-3-one (10)

A mixture of **8a** (0.18 g, 0.45 mmol) and 30 % aq. NaOH (12 mL) in MeOH (10 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 diacid (**9**). A mixture of the crude diacid (**9**) and Cu_2O (0.16 g) in nitrobenzene (50 mL) was refluxed for 30 h. The mixture was evaporated under reduced pressure. The residue was submitted by silica gel column chromatography. From $CHCl_3$ fraction, compound (**10**) was obtained.

10: mp 267-270 ℃ (CH_2Cl_2-EtOEt), 0.04 g, 33 % based on **8a**. IR (KBr) 1580 cm^{-1} ; UV (EtOH) λmax (log ε) 243 (4.50), 271 (4.41), 288 (4.45), 362 (3.74), 381 (3.84), 409 (3.31), 478 (4.16), 514 (4.56) nm; UV (5% CF_3COOH in EtOH) λmax (log ε) 298 (4.45), 351 (4.47), 390 (3.90), 503 (4.04), 532 (4.18) nm; ^{1}H-NMR ($CDCl_3$) 7.13 (1H, d, J = 5 Hz, C_5-H), 7.37 (1H, d, J = 5 Hz, C_1-H), 7.63 (1H, t, J = 8 Hz, C_7-H), 7.84 (1H, t, J = 8 Hz, C_{10}-H), 7.86 (1H, d, J = 8 Hz, C_6-H), 8.10 (1H, d, J = 8 Hz, C_{11}-H), 8.15 (1H, d, J = 5 Hz, C_2-H), 8.17 (1H, d, J = 5 Hz, C_4-H), 8.20 (1H, d, J = 8 Hz, C_8-H), 8.40 (1H, d, J = 8 Hz, C_9-H). ^{1}H-NMR (CF_3COOD in $CDCl_3$) 7.64 (1H, d, J = 5 Hz, C_5-H), 7.84 (1H, d, J = 5 Hz, C_1-H), 8.17 (1H, d, J = 5 Hz, C_2-H), 8.30 (1H, t, J = 8 Hz, C_7-H), 8.48 (1H, d, J = 8 Hz, C_6-H), 8.52 (1H, d, J = 8 Hz, C_{11}-H), 8.58 (1H, t, J = 8 Hz, C_{10}-H), 8.73 (1H, d, J = 5 Hz, C_4-H), 8.93 (1H, d, J = 8 Hz, C_8-H), 9.16 (1H, d, J = 8 Hz, C_9-H); ^{13}C-NMR ($CDCl_3$) 108.89, 111.82, 112.26, 114.07, 116.22, 116.57, 117.94, 120.10, 120.49, 122.25, 123.01, 123.61, 125.80, 127.31, 127.88, 127.95, 131.07, 136.49, 167.77. *Anal.* Calcd for $C_{19}H_{10}N_2O$: C, 80.84; H, 3.57; N, 9.92. Found: C, 80.97; H, 3.76; N, 9.68. HRMS Calcd: 282.0793. Found: 282.0797.

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