Acetylenic Chemistry: Part 13 [1]. Synthesis of Oxazoles and Oxazoloquinazolines from *o*-Amino-*N*-(1,1-disubstituted-propynyl)benzamide

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Conversion of isatoic anhydride to *o*-amino-*N*-(1,1-disubstituted-propynyl)benzamides **3a-c** followed by reflux in ethanolic potassium hydroxide gave 2-(*o*-aminophenyl)-4,4-disubstituted-5-methylene-4*H*-oxazoles **4a-c**. The treatment of same **3a-c** with triphosgene in pyridine with subsequent reflux gave **4a-c** and 2-methylene-3,3-disubstituted-oxazolo[2,3-*b*]quinazolin-5(3*H*)-ones **5a-c**.

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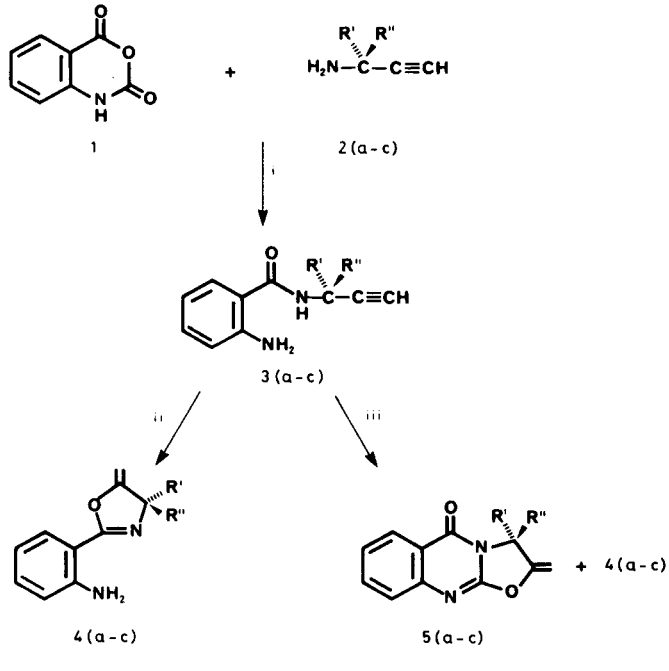
In continuation of our studies on the synthesis of heterocyclic compounds *via* acetylenes [3], some oxazoles and oxazoloquinazolines were prepared from *o*-amino-*N*-(1,1-disubstituted-propynyl)benzamide derived from isatoic anhydride (**1**). Isatoic anhydride (**1**) is useful in the synthesis of heterocyclic compounds [4,5,6]. Compounds containing the quinazoline unit in their structures are known to be biologically versatile compounds, possessing several pharmacological properties [7,8]. The reactions of the amines **2a-c** with isatoic anhydride (**1**) in dimethylformamide [9] gave good yields of the corresponding benzamides **3a-c**. The formation of oxazoles **4a-c** together with oxazoloquinazolines **5a-c**, apart from the synthesis from the benzamides **3a-c** with potassium hydroxide in refluxing ethanol, is as a result of angular cyclisation probably prompted by either the initial exothermic reactions on the addition of triphosgene [10] and/or in refluxing pyridine. This was confirmed by refluxing the benzamides **3a-c** in pyridine which also resulted in the oxazoles **4a-c**. The oxazoles from both pathways had identical spectroscopic as well as physical properties. The substitution on the benzamides, **3a-c** appears to influence the reaction with triphosgene to give the desired oxazoloquinazoline **5a-c** [9,11]. Pyridine was used as a solvent as well as a proton acceptor in this reaction.

Scheme



The presence of an exocyclic methylene group (=CH_2) in the ir absorption of the oxazoles **4a-b** was evident at 1695 cm^{-1}. Other diagnostic absorptions were at 3500-3300 cm^{-1} (NH_2), 1640 cm^{-1} (C=N) and 1600 cm^{-1} (C=C). A two doublet centered between δ 4.0 and 5.0, J = 2.7 Hz indicated the *trans* and *cis* protons of the exocyclic methylene group. The ms showed m/z 118 as base peak which is evident for the presence of $C_7H_6N^+$ [12].

The oxazoloquinazolines **5a-c** also exhibited ir absorptions at 1705 cm^{-1} evident for carbonyl group, 1695 cm^{-1} for exocyclic methylene group, 1640 cm^{-1} (C=N) and 1600 (C=C) cm^{-1}. The *trans* and *cis* protons of the exocyclic methylene group were centered as two doublets between δ 4.40 and 5.10, J = 3.9 Hz.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and were uncorrected. The ir spectra were recorded on a Pye Unicam SP3-200 ir spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded in deuteriochloroform at 200 MHz with tetramethylsilane as internal reference on a Bruker WM 300 spec-

trometer. Mass spectra were obtained on a Varian MAT 44S instrument at 70 eV.

Silica-gel 60 F_{254} (pre-coated aluminium sheets, 0.2 mm thickness, Merck 5549) were used for analytic tlc. All solvents employed were dried by standard methods. Isatoic anhydride (Merck) was recrystallised from dimethylformamide. Bis(trichloromethyl)carbonate (triphosgene) was obtained from Merck Co. 1,1-Dimethyl-2-propynylamine, 1,1-diethyl-2-propynylamine and 1-ethynylcyclohexylamine were obtained from Aldrich Chemical Co.

General Procedure for the Synthesis of *o*-Amino-*N*-(1,1-disubstituted-propynyl)benzamides **3a-c**.

To a stirred solution of isatoic anhydride (**1**) (0.02 mole) in 20 ml of dimethylformamide warmed to 50° was added the amine **2a-c** (0.03 mole) in 20 ml of dimethylformamide dropwise over a period of 30 minutes. The reaction mixture was maintained at 50° between 2-4 hours until tlc indicated disappearance of isatoic anhydride, then cooled to room temperature, poured into 200 ml of water and adjusted to *p*H 9 with 50% sodium hydroxide solution. The solid precipitate obtained was removed by filteration, washed free of the base with 3 x 20 ml portions of water, dried and purified through column chromatography (dichlormethane). The amides were recrystallised from appropriate solvents.

o-Amino-*N*-(1,1-dimethylpropynyl)benzamide (**3a**).

1,1-Dimethyl-2-propynylamine 2.49 g, (0.03 mole) was added to isatoic anhydride 3.26 g (0.02 mole) in dimethylformamide and treated as above which gave from dichloromethane-petroleum ether (30-40°) *o*-amino-*N*-(1,1-dimethylpropynyl)benzamide, 2.62 g (65%), mp 121-123°; ir (potassium bromide): 3490, 3380 (NH, NH_2), 1640, 1610 (C=O, amide) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.73 (s, 6H, 2 x CH_3), 2.39 (s, 1H, ≡CH), 5.34 (s, broad, 2H, NH_2), 6.14 (s, broad, 1H, NH), 6.61 (t, J = 7.9 Hz, 1H, H-5), 6.66 (d, J = 8.1 Hz, 1H, H-3), 7.18 (ddd, J = 1.0, 7.1, 7.7 Hz, 1H, H-4), 7.28 (dd, J = 1.6, 7.8 Hz, H-6); ^{13}C nmr (deuteriochloroform): δ 29.3 (2 x CH_3), 47.9 (> $C(CH_3)_2$), 69.5 (≡*C*H), 87.6 (C≡), 116.6 (C-1), 116.8 (C-3), 117.8 (C-5), 127.6 (C-6), 132.7 (C-4), 149.3 (C-2), 169.2 (C=O); ms: 202 (56, M^+), 174 (12), 136 (20), 119 (100), 92 (50), 65 (42).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.95; H, 7.32; N, 13.51.

o-Amino-*N*-(1,1-diethylpropynyl)benzamide (**3b**).

1,1-Diethyl-2-propynylamine 3.33 g, (0.03 mole) was added to isatoic anhydride 3.26 g (0.02 mole) in dimethylformamide and treated as above. The resulting oily product after pouring the reaction mixture into water was extracted with 3 x 30 ml of dichlormethane, dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo*. Purification by column chromatography (dichloromethane) gave a yellowish oily compound which slowly crystallised at room temperature. This compound **3b** was recrystallised from pentane as white flakes, 1.84 g (40%) mp 42-43°; ir (potassium bromide): 3460, 3320 (NH, NH_2), 1640, 1630 (C=O, amide) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.0 (t, J = 7.4 Hz, 6H, 2 x CH_2 CH_3), 1.82, 2.29 (m, 4H, 2 x CH_2 CH_3), 2.41 (s, 1H, ≡CH), 5.44 (s, broad, 2H, NH_2), 6.10 (s, broad, 1H, NH), 6.54 (t, J = 7.2 Hz, 1H, H-5), 6.59 (d, J = 8.3 Hz, 1H, H-3), 7.14 (ddd, J = 1.3, 7.2, 8.0 Hz, 1H, H-4), 7.29 (dd, J = 1.4, 7.8 Hz, 1H, H-6); ^{13}C nmr (deuteriochloroform): δ 8.8 (2 x CH_2 CH_3), 30.8 (2 x CH_2 CH_3), 57.6 (> $C(CH_2\ CH_3)_2$), 72.0 (≡CH), 85.7 (*C*≡), 116.9 (C-3), 117.1 (C-1), 117.7 (C-5), 127.6 (C-6), 132.6 (C-4), 149.1 (C-2), 169.1 (C=O); ms: 230 (6, M^+), 202 (24), 120 (84), 104 (100), 92 (30), 77 (56).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 73.00; H, 7.83; N, 12.11.

o-Amino-*N*-cyclohexylpropynylbenzamide (**3c**).

1-Ethynylcyclohexylamine 3.75 g, (0.03 mole) was added to isatoic anhydride 3.26 g (0.02 mole) in dimethylformamide and treated as above which gave from ethanol *o*-amino-*N*-cyclohexylpropynylbenzamide, 3.9 g (81%), mp 144-145°; ir (potassium bromide): 3500, 3400 (NH, NH_2), 1640, 1610 (C=O, amide) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.57-2.29 (m, broad, 10H, cyclohexyl CH_2), 2.45 (s, 1H, ≡CH), 5.53 (s, broad, 2H, NH_2), 6.03 (s, broad, 1H, NH), 6.61 (ddd, J = 1.2, 7.2, 7.8 Hz, 1 Hz, H-5), 6.67 (dd, J = 0.6, 8.2 Hz, 1H, H-3), 7.22 (ddd, J = 1.5, 7.2, 8.2 Hz, 1H, H-4), 7.31 (dd, J = 1.5, 7.8 Hz, 1H, H-6); ^{13}C nmr (deuteriochloroform): δ 22.6 (C-3′, 4′), 25.4 (C-5′), 37.3 (C-2′, 6′), 52.0 (*C*≡), 71.7 (≡CH), 86.0 (C-1′), 116.8 (C-1), 116.8 (C-3), 117.8 (C-5), 127.6 (C-6), 132.7 (C-4), 149.4 (C-2), 169.0 (C=O); ms: 242 (14, M^+), 214 (14), 188 (20), 136 (10), 120 (100), 92 (60), 77 (60).

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.29; H, 7.40; N, 11.57.

General Procedure for the Synthesis of 2-(*o*-Aminophenyl)-4,4-disubstituted-5-methylene-4*H*-oxazoles **4a-c**.

o-Amino-*N*-(1,1-disubstituted-propynyl)benzamides **3a-c** (0.005 mole) was dissolved in 15 ml of ethanol and ethanolic potassium hydroxide (0.006 mole) was added. The reaction mixture was stirred and gently heated to reflux until tlc indicated complete disappearance of the benzamide (3-5 hours). The reaction mixture was cooled to room temperature, adjusted to *p*H 7-8 with acetic acid and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed *in vacuo* to give a yellow oil which was purified by column chromatography (dichloromethane). The oils obtained were converted to their picrates by standard methods.

2-(*o*-Aminophenyl)-4,4-dimethyl, 5-methylene-4*H*-oxazole (**4a**).

Potassium hydroxide 0.336 g (0.006 mole) was added to *o*-amino-*N*-(1,1-dimethylpropynyl)benzamide 1.01 g (0.005 mole) in ethanol and treated as above to give a yellow oil 0.85 g (85%); ir (film): 3495, 3335 (NH_2), 1695 (C=CH_2), 1635 (C=N) cm^{-1}. ^1H nmr (deuteriochloroform): δ 1.43 (s, 6H, 2 x CH_3), 4.20 (d, J = 3.0 Hz, 1H, =CH_{trans}), 4.71 (d, J = 2.7 Hz, 1H, =CH_{cis}), 6.04 (s, broad, 2H, NH_2), 6.63 (ddd, J = 1.2, 7.0, 8.1 Hz, 1H, H-5′), 6.65 (dd, J = 1.0, 8.1 Hz, 1H, H-3′), 7.19 (ddd, J = 1.6, 7.0, 8.5 Hz, 1H, H-4′), 7.76 (dd, J = 1.6, 8.3 Hz, 1H, H-6′); ^{13}C (deuteriochloroform): δ 30.2 (2 x CH_3), 69.3 (C-4), 81.8 (=CH_2), 108.4 (C-1′), 116.1 (C-3′), 116.4 (C-5′), 129.9 (C-6′), 132.6 (C-4′), 149.1 (C-2′), 160.4 (C-5), 167.1 (C-2); ms: 202 (50, M^+), 187 (48), 159 (32), 145 (52), 118 (100), 104 (15), 91 (50), 77 (15), 65 (50); Found: M^+ 202.1102. $C_{12}H_{14}N_2O$ requires M, 202.1106. The picrate gave orange crystals mp 138-140°.

Anal. Calcd. for $C_{18}H_{17}N_5O_8 \cdot H_2O$: C, 48.11; H, 4.26; N, 15.59. Found: C, 48.45; H, 4.18; N, 15.58.

2-(*o*-Aminophenyl)-4,4-diethyl-5-methylene-4*H*-oxazole (**4b**).

Potassium hydroxide 0.336 g (0.006 mole) was added to *o*-amino-*N*-(1,1-diethylpropynyl)benzamide, 1.15 g (0.005 mole) in ethanol and treated as above to give a yellow oil 1.04 g (90%); ir

(film): 3490, 3340 (NH_2), 1695 (C=CH_2), 1630 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.85 (t, J = 7.1 Hz, 6H, 2 x CH_2 CH_3), 1.51, 1.98 (m, 4H, 2 x CH_2 CH_3), 4.16 (d, J = 2.6 Hz, 1H, $=CH_{trans}$), 4.89 (d, J = 2.6 Hz, 1H, $=CH_{cis}$), 6.14 (s, broad, 2H, NH_2), 6.71 (ddd, J = 1.2, 7.1, 7.3 Hz, 1H, H-5'), 6.75 (dd, J = 1.1, 8.2 Hz, 1H, H-3'), 7.27 (ddd, J = 1.5, 7.5, 7.9 Hz, 1H, H-4'), 7.81 (dd, J = 1.6, 8.4 Hz, 1H, H-6'); ^{13}C nmr (deuteriochloroform): δ 7.9 (2 x CH_2 CH_3), 33.8 (2 x CH_2 CH_3), 76.9 (C-4), 82.4 (=CH_2), 108.0 (C-1'), 115.7 (C-3'), 116.0 (C-5'), 129.6 (C-6'), 132.3 (C-4'), 149.0 (C-2'), 160.5 (C-5), 163.4 (C-2); ms: 230 (28, M^+), 201 (100), 173 (8), 159 (10), 135 (4), 118 (100), 92 (40), 77 (20), 65 (44). (Found: M^+ 230.1415. $C_{14}H_{18}N_2O$ requires M, 230.1419). The picrate gave yellow crystals mp 140-141°.

Anal. Calcd. for $C_{20}H_{21}N_5O_8 \cdot H_2O$: C, 50.32; H, 4.86; N, 14.67. Found: C, 50.33; H, 4.67; N, 14.65.

2-(*o*-Aminophenyl)-4-cyclohexyl-5-methylene-4*H*-oxazole (**4c**).

Potassium hydroxide 0.336 g (0.006 mole) was added to *o*-amino-*N*-cyclohexylpropynylbenzamide, 1.21 g (0.005 mole) in ethanol and treated as above to give a yellow oil 0.992 g (82%); ir (film): 3500, 3320 (NH_2), 1700 (C=CH_2), 1640 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.33-1.86 (m, broad, 10H, cyclohexyl CH_2), 4.20 (d, J = 2.7 Hz, 1H, $=CH_{trans}$), 4.72 (d, J = 2.7 Hz, 1H, $=CH_{cis}$), 6.15 (s, broad, 2H, NH_2), 6.68 (ddd, J = 1.2, 7.3, 7.6 Hz, 1H, H-5'), 6.72 (dd, J = 0.9, 8.3 Hz, 1H, H-3'), 7.24 (ddd, J = 1.6, 7.2, 8.3 Hz, 1H, H-4'), 7.76 (dd, J = 1.6, 8.4 Hz, 1H, H-6'); ^{13}C nmr (deuteriochloroform): δ 22.6 (C-3'', 4''), 25.8 (C-2''), 39.6 (C-1'', 5''), 72.3 (C-4), 82.1 (=CH_2), 108.6 (C-1'), 116.1 (C-3'), 116.5 (C-5'), 129.9 (C-6'), 132.6 (C-4'), 149.2 (C-2'), 160.2 (C-5), 167.4 (C-2); ms: 242 (42, M^+), 214 (8), 199 (16), 187 (6), 171 (8), 118 (100), 109 (10), 91 (32), 67 (36). (Found: M^+ 242.1415 $C_{15}H_{18}N_2O$ requires 242.1419). The picrate gave yellow needles mp 163-164°.

Anal. Calcd. for $C_{21}H_{21}N_5O_8 \cdot H_2O$: C, 51.54; H, 4.74; N, 14.31. Found: C, 51.66; H, 4.73; N, 14.27.

General Procedure for the Synthesis of 2-Methylene-3,3-disubstituted-oxazolo[2,3-*b*]quina-5(3*H*)-ones **5a-c**.

To a well-stirred and ice-cooled solution of (0.005 mole) *o*-amino-*N*-(1,1-disubstituted-propynyl)benzamides **3a-c** in 15 ml of pyridine was added triphosgene [11] (0.005 mole). The reaction mixture was allowed to attain room temperature and then slowly heated to reflux and maintained at reflux for 6-8 hours, then cooled to room temperature. Excess pyridine was neutralised with 5% hydrochloric acid and then extracted into dichloromethane. The organic layer was washed with 5% sodium hydroxide at *p*H 8, dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo* to give a viscous brown oil in all cases. Column chromatography (dichloromethane) gave oxazoles **4a-c** as the first eluates. The oxazoloquinazolines **5a-c** were obtained as the second eluates.

2-Methylene-3,3-dimethyloxazolo[2,3-*b*]quinazolin-5-(3*H*)-one (**5a**).

Triphosgene, 0.495 g (0.005 mole) was added to *o*-amino-*N*-(1,1-dimethylpropynyl)benzamide, 1.01 g, (0.005 mole) in pyridine and treated as above to give from pentane **5a** as colourless crystals, 0.456 g (50%) mp 82-83°; ir (potassium bromide): 1700 (C=O), 1690 (C=CH_2), 1630 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.89 (s, 6H, 2 x CH_3), 4.52 (d, J = 4.0 Hz, 1H, $=CH_{trans}$), 4.95 (d, J = 4.0 Hz, 1H, $=CH_{cis}$), 7.37 (ddd, J = 1.2, 6.9, 7.1 Hz, 1H, H-7), 7.56 (dd, J = 1.0, 7.5 Hz, 1H, H-9), 7.70 (ddd, J = 1.6, 7.0, 7.1 Hz, 1H, H-8), 8.19 (dd, J = 1.2, 7.8 Hz, 1H, H-6); ^{13}C nmr (deuteriochloroform): δ 26.2 (2 x CH_3), 63.8 (C-4), 86.0 (=CH_2), 120.0 (C-6a), 125.2 (C-9), 126.5 (C-7), 126.7 (C-6), 134.9 (C-8), 148.3 (C-9a), 152.7 (C-3), 160.6 (C-1a), 161.1 (C-5); ms: 228 (100, M^+), 213 (100, M-CH_3), 185 (10), 146 (36), 117 (26), 90 (74), 63 (27).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.57; H, 5.51; N, 12.35.

2-Methylene-3,3-diethyloxazolo[2,3-*b*]quinazolin-5(3*H*)-one (**5b**).

Triphosgene, (0.495 g, 0.005 mole) was added to *o*-amino-*N*-(1,1-diethylpropynyl)benzamide (1.15 g, 0.005 mole) in pyridine and treated as above to give **5b** as a yellow oil, 0.345 g (31%); ir (film): 1710 (C=O), 1700 (C=CH_2), 1640 (C=N) cm^{-1}, ^1H nmr (deuteriochloroform): δ 0.82 (t, J = 7.4 Hz, 6H, 2 x CH_2 CH_3), 1.72, 2.77 (m, 4H, 2 x CH_2 CH_3), 4.44 (d, J = 3.9 Hz, 1H, $=CH_{trans}$), 5.07 (d, J = 3.9 Hz, 1H, $=CH_{cis}$), 7.39 (ddd, J = 0.8, 7.1, 7.9 Hz, 1H, H-7), 7.57 (dd, J = 0.7, 8.2 Hz, 1H, H-9), 7.74 (ddd, J = 1.1, 7.1, 7.9 Hz, 1H, H-8), 8.20 (dd, J = 1.6, 8.0 Hz, 1H, H-6); ^{13}C nmr (deuteriochloroform): δ 7.8 (2 x CH_2 CH_3), 30.9 (2 x CH_2 CH_3), 73.0 (C-4), 86.8 (=CH_2), 119.8 (C-6a), 125.5 (C-9), 126.8 (C-6), 127.2 (C-7), 135.3 (C-8), 148.9 (C-9a), 153.9 (C-3), 157.6 (C-6), 168.8 (C-1a); ms: 256 (46, M^+), 241 (10, M-CH_3), 227 (100, M-CH_2 CH_3), 213 (4), 201 (3), 184 (2), 163 (8), 146 (30), 118 (28), 90 (18), (Found): M^+ 256.1216 $C_{15}H_{16}N_2O_2$ requires 256.1212).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.24; H, 6.43; N, 10.84.

2-Methylene-3-cyclohexyloxazolo[2,3-*b*]quinazolin-5(3*H*)-one (**5c**).

Triphosgene (0.495 g, 0.005 mole) was added to *o*-amino-*N*-cyclohexylpropynylbenzamide (1.21 g, 0.005 mole) in pyridine and treated as above to give **5c** as white crystals from methanol, 0.389 g (35%) mp 121-122°; ir (potassium bromide): 1720 (C=O), 1700 (C=CH_2), 1640 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.51-1.98 (m, broad, 8H, cyclohexyl), 2.8-3.1 (m, broad, 2H, cyclohexyl), 4.8 (d, J = 3.7 Hz, 1H, $=CH_{trans}$), 5.0 (d, J = 3.8 Hz, 1 Hz, $=CH_{cis}$), 7.36 (ddd, J = 1.2, 7.1, 8.2 Hz, 1H, H-7), 7.56 (dd, J = 1.1, 8.2 Hz, 1H, H-9), 7.71 (ddd, 1.5, 7.2, 8.4 Hz, 1H, H-8), 8.19 (dd, J = 1.5, 8.0 Hz, 1H, H-6); ^{13}C nmr (deuteriochloroform): δ 21.3 (C-3', 4'), 23.7 (C-5'), 31.4 (C-2', 6'), 67.3 (C-4), 89.9 (=CH_2), 120.6 (C-6a), 125.4 (C-9), 126.7 (C-7), 127.1 (C-6), 135.2 (C-8), 148.7 (C-9a), 153.2 (C-3), 159.1 (C-5), 161.2 (C-2b); ms: 268 (100, M^+), 240 (31, M-CO), 213 (33), 198 (6), 163 (56), 146 (52), 130 (14), 106 (28), 90 (57), 77 (28).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.98; H, 6.13; N, 10.45.

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