DIMERIZATION OF INDOLO[1,2-*b*][2,7]NAPHTHYRIDINE-5,12-QUINONE

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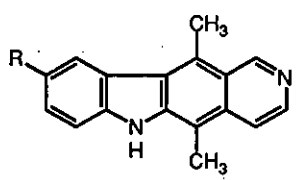
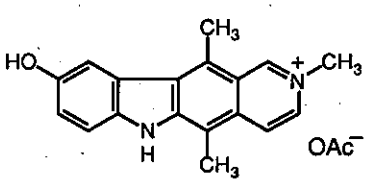
Abstract - Attempts to isomerize indolo[1,2-*b*][2,7]naphthyridine-5,12-quinone (**5**) to ellipticine quinone (**7**) with various nucleophiles (cyanide, methoxide, halide, thiophenoxide) lead instead to 6,6'-*bis*(indolo[1,2-*b*][2,7]naphthyridine-5,12-quinone) (**8**), the dimer of **5**.

The *Ochrosia* and *Aspidosperma* 6*H*-pyrido[4,3-*b*]carbazole alkaloids ellipticine (**1a**), 9-methoxyellipticine (**1b**), and 9-hydroxyellipticine (**1c**) are potent antitumor agents, and "elliptinium" (**2**) is used clinically as a drug to treat advanced breast cancer, myeloblastic leukemia, and some solid tumors.[1] Recent years have witnessed the development of second-generation ellipticine-derived antitumor agents, including the new clinical candidates datelliptium (**3**), and pazellipticine (**4**).[1a]



1a R = H
1b R = OCH_3
1c R = OH



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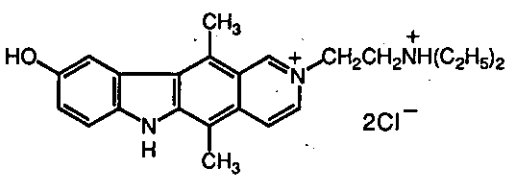

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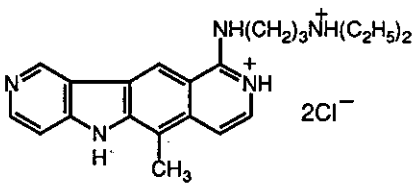

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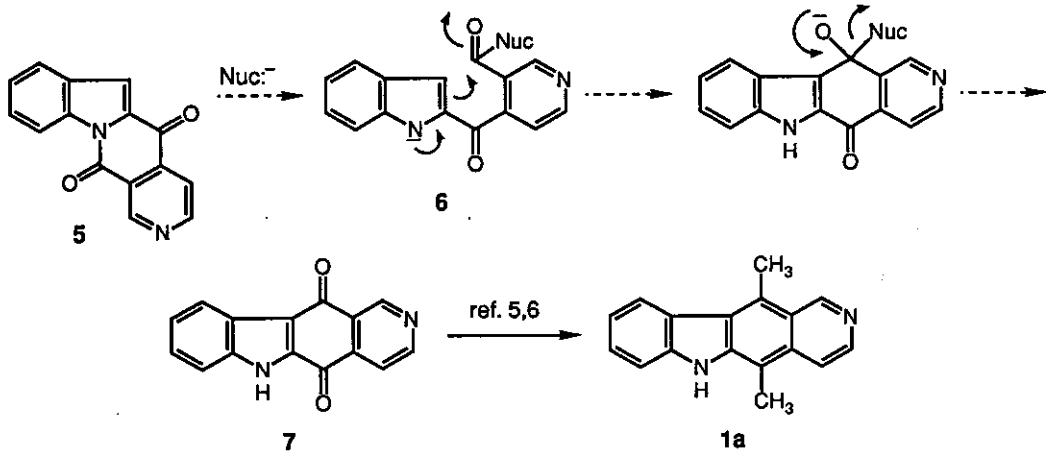
During our synthetic studies toward ellipticine[2,3] and related pyrido[4,3-*b*]carbazole alkaloids[3,4] from indolo[1,2-*b*][2,7]naphthyridine-5,12-quinone (**5**), it was of interest to attempt the isomerization of this keto lactam to ellipticine quinone (**7**), which had previously been converted into ellipticine by Joule[5] and Snieckus.[6] This

isomerization seemed particularly attractive since *N*-acylindoles are readily cleaved by nucleophiles[7] and our synthesis of ellipticine made use of this cleavage. Moreover, indolyl anions (e.g., **6**) are known to undergo C-3 cyclization.[8] Thus, we felt that a nucleophile catalyst would behave with keto lactam (**5**) as shown in Scheme I.

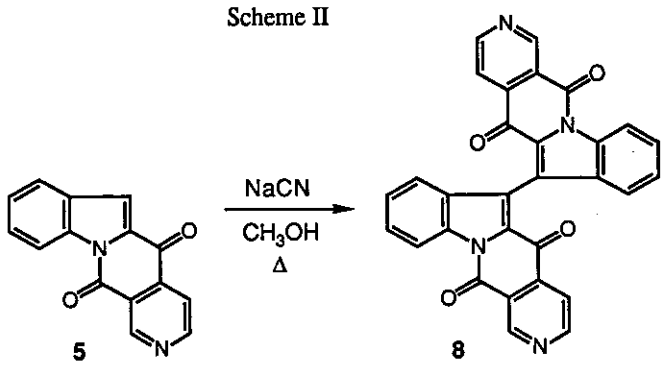
Scheme I



5 6 7 1a

In the event, treatment of keto lactam (**5**) with sodium cyanide (MeOH, reflux) resulted in the precipitation in high yield of an orange solid, from an initially dark green solution. This same solid also resulted when **5** was treated with KF, NaCl, $Mg(OMe)_2$, and NaSPh, in various solvents (benzene, THF, DMF, DMSO, HMPA). This material, mp >400 °C, clearly was not the expected ellipticine quinone (**7**). It was soluble only in solvents such as glacial HOAc, CF_3CO_2H, and hot pyridine. Spectral data suggested that the structure of this compound is that of keto lactam dimer (**8**) (Scheme II).

Scheme II

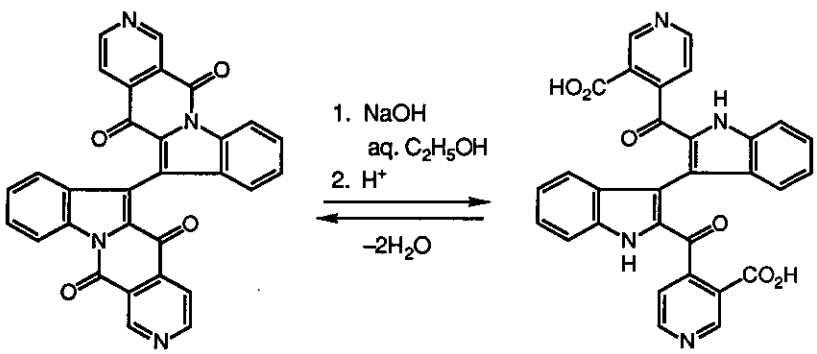


5 8

Uv: 244, 312, 386 nm
Ir: 1707, 1675 cm^{-1}

Uv: 246, 316, 394 nm
Ir: 1690, 1665 cm^{-1}

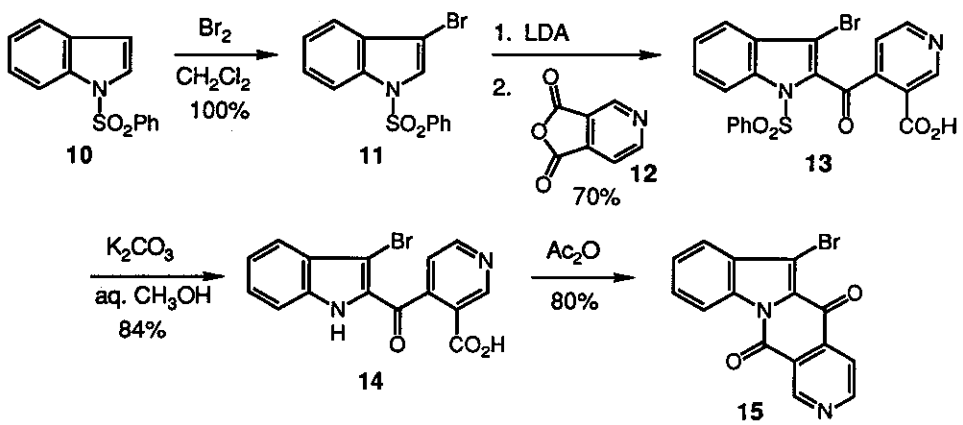
The mass spectrum of this compound shows a parent ion at *m/z* 494 with the base peak appearing at *m/z* 247, corresponding to the keto lactam (**5**) fragment. The uv and ir spectra are very similar to those of keto lactam (**5**), and the bathochromic shifts in both types of spectra are consistent with increased conjugation in **8** compared to keto lactam (**5**). In the ^{1}H nmr spectrum of **8**, the characteristic keto lactam H-6 singlet at 8.05 ppm is missing. Otherwise, the symmetrical nature of **8** is revealed by its ^{1}H and ^{13}C nmr spectra. As is the case with keto lactam (**5**),[2] treatment of **8** with aqueous base results in the hydrolysis to *bis*-keto acid (**9**), the structure of which is supported by spectral data and its similarity to the spectral data of the keto acid derived from keto lactam (**5**). Heating keto acid (**9**) in a melting point capillary at 230 °C converted it back to keto lactam dimer (**8**).



8 **9**

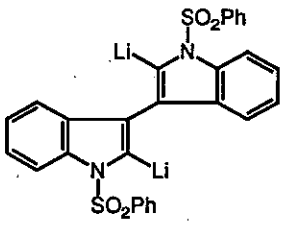
Attempts to synthesize keto lactam dimer (**8**) from bromo keto lactam (**15**), prepared as shown in Scheme III, by various coupling protocols (Cu; *t*-BuLi, Cu; *n*-Bu_3SnH, AIBN; Mg, *n*-BuLi; $Pd(PPh_3)_4$) have not been successful.

Scheme III



10 **11** **12** **13** **14** **15**

Likewise, attempts to apply our keto lactam synthesis to a synthesis of **8** via the known dilithio diindole (**16**)[9] have failed.



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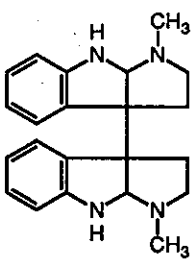
Although several very similar indole dimers are known (e.g., **17** - **22**),[10-14] their formation involves clearly defined oxidative free radical conditions. However, in the present case, the exact role of the nucleophile remains to be determined.



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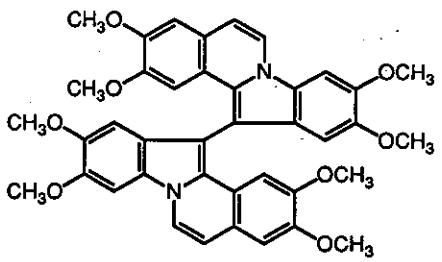

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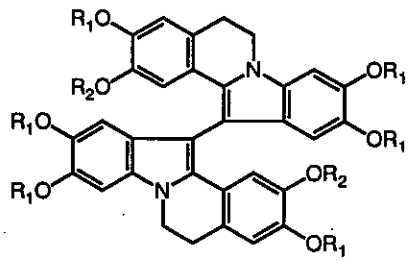
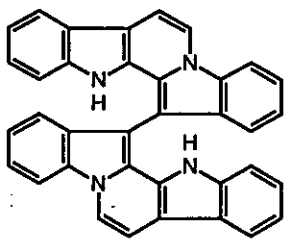


19 $R_1 = R_2 = H$
20 $R_1 = CH_3$, $R_2 = H$
21 $R_1 = CH_3$, $R_2 = Bn$



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EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer 599 spectrophotometer and are referenced to the 1601 cm^{-1} band of polystyrene. ^1H Nmr spectra (60 MHz) were recorded on a Varian EM-360A spectrometer. ^1H Nmr (300 MHz) and ^{13}C nmr (75 MHz)

were recorded on a Varian XL-300 multinuclear Fourier transform spectrometer. Unitary resolution mass spectra (ms) were obtained on a Finnigan 4023 GC/ms system. High resolution mass spectra (HRms) were recorded by Dr. Catherine Costello at National Institutes of Health regional facility at the Massachusetts Institute of Technology. Ultraviolet (uv) spectra were recorded on a Hewlett Packard 8451A diode array spectrophotometer. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Analytical thin-layer chromatography (tlc) was performed on pre-coated Silica Gel 60 F_{254} plates from EM Reagents. Visualization was accomplished with 254 and 365 nm uv light, iodine vapor, ceric ammonium sulfate spray (3% in 10% sulfuric acid) or "van Urk's reagent" spray (*p*-dimethylaminobenzaldehyde in ethanolic sulfuric acid). Flash chromatography was performed with EM Reagents Silica Gel 60 (230-400 mesh). All reactions were performed under a static head of predried ($CaSO_4$ tower) nitrogen or argon in glassware that had been dried for at least 12 h at 135 °C. Benzenesulfonyl chloride and 3,4-pyridinedicarboxylic anhydride were distilled prior to use.

Dimerization of Indolo[1,2-*b*][2,7]naphthyridine-5,12-quinone (5). To a stirred solution of **5** (0.10 g, 0.40 mmol) in dry MeOH (25 ml) was added NaCN (0.020 g, 0.40 mmol). The solution immediately turned from yellow to green. As the reaction was slowly warmed to reflux, the color became dark green and an orange precipitate began to form. After 24 h of reflux, the solution had faded to a pale green color. The mixture was cooled, and the precipitate was collected, washed with CH_2Cl_2, and dried in vacuo to yield 0.087 g (87%) of 6,6'-*bis*(indolo[1,2-*b*][2,7]naphthyridine-5,12-quinone) (**8**) as an orange powder: mp > 400 °C; ir (KBr) 1690, 1665, 1585, 1525, 1355, 1325, 1245, 745, 720 cm^{-1} (for comparison, ir of **5** (KBr) 1705, 1675, 1550, 1370, 1340, 1245, 750, 720 cm^{-1}); ^1H nmr (TFA-*d*) δ 10.07 (s, 2H), 9.36 (d, J = 6.0 Hz, 2H), 8.85 (d, J = 8.6 Hz, 2H), 8.75 (d, J = 6.0 Hz, 2H), 7.96 (m, 4H), 7.57 (m, J = 4.0 Hz, 2H) (for **5** (TFA-*d*) δ 9.88 (s, 1H), 9.27 (d, J = 6.0 Hz, 1H), 8.85 (d, J = 6.0 Hz, 1H), 8.48 (d, J = 8.5 Hz, 1H), 8.05 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.71 (m, 1H), 7.46 (m, 1H); ^{13}C nmr (TFA-*d*) δ 173.3, 157.1, 148.4, 146.9, 139.6, 136.4, 132.2, 131.7, 130.8, 130.1, 129.8, 126.7, 125.1, 120.0 (for **5** (TFA-*d*) δ 173.7, 156.9, 148.9, 148.5, 147.0, 140.8, 136.3, 135.0, 132.9, 131.5, 130.1, 127.8, 127.5, 127.1, 119.6); uv ($ClCH_2CH_2Cl$) 246, 316, 394 nm (for **5** 244, 312, 386); ms *m/z* 494 (M^+, 100%), 466, 465, 449, 411, 361, 332, 305, 247, 219, 206; HRms *m/z* Calcd (M^+) 494.1015, obsd 494.1021; Anal. Calcd for $C_{30}H_{14}N_4O_4$: C, 72.87; H, 2.85; N, 11.33. Found: C, 72.81; H, 2.89; N, 11.32.

Hydrolysis of 8. To a solution of NaOH (0.100 g, 2.50 mmol) in 95% EtOH (25 ml) was added **8** (0.134 g, 0.271 mmol). As the solution was warmed to reflux, the solid slowly went into solution to finally yield a red

solution. After being refluxed for 3 h, the reaction mixture was cooled and concentrated in vacuo. Water (25 ml) was added to the residue and the solution was slowly acidified at 0 °C with dilute HCl. The yellow precipitate was collected by filtration, washed well with water, and dried in vacuo to yield 0.134 g (93%) of diacid (**9**): mp > 400 °C (turns from yellow to orange at 230 °C); ir (KBr) 3550, 3300, 3050, 3000, 2500, 1705, 1635, 1490, 1460, 1410, 1320, 1245, 1090, 795, 740, 675 cm^{-1}; ^1H nmr (DMSO-d_6) δ 11.25 (s, 2H), 8.68 (s, 2H), 8.17 (d, J = 4.9 Hz, 2H), 7.25 (d of d, J = 9.0 Hz, 9.0 Hz, 4H), 7.11 (m, 2H), 7.06 (d, J = 4.9 Hz, 2H), 6.80 (m, 2H); ^{13}C nmr (DMSO-d_6) δ 188.8, 168.2, 150.8, 148.6, 147.6, 136.2, 133.3, 128.4, 124.4, 122.5, 120.2, 119.2, 113.9, 111.9; uv (95% EtOH) 208, 326 nm, ($ClCH_2CH_2Cl$) 238, 326 nm. uv ($ClCH_2CH_2Cl$) of **9** after heating at 230 °C was identical to that of **8**.

3-Bromo-1-phenylsulfonylindole (11). To a stirred solution of 1-phenylsulfonylindole[15] (**10**, 20.0 g, 77.8 mmol) in CH_2Cl_2 (125 ml) was added Br_2 (4.5 ml, 86 mmol) in CH_2Cl_2 (100 ml) dropwise with stirring over 1 h at room temperature, during which time HBr gas was evolved. After stirring for an additional 2 h, saturated aqueous sodium thiosulfate solution (250 ml) was added and the biphasic mixture was stirred for 15 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 ml). The combined organic phase was washed with saturated aqueous $NaHCO_3$ solution (2 x 200 ml), water (2 x 200 ml), brine (200 ml), dried (Na_2SO_4), concentrated in vacuo, and dried to yield 26.1 g (100%) of **11** as a white solid: mp 116-118 °C (lit.,[16] mp 122-123 °C); ir ($CHCl_3$) 1605, 1585, 1445, 1370, 1265 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.15-8.15 (m, 9H), 7.63 (s, 1H); ^{13}C nmr ($CDCl_3$) δ 137.7, 134.2, 134.1, 129.4, 129.3, 126.8, 125.8, 124.7, 123.9, 120.0, 113.5, 99.8.

3-Bromo-1-phenylsulfonylindol-2-yl 3-Carboxy-4-pyridyl Ketone (13). To a solution of lithium diisopropylamide (7.14 mmol) prepared from diisopropylamine (1.00 ml, 7.14 mmol) and *n*-BuLi (1.22 M in hexane; 6.00 ml, 7.32 mmol) in dry THF (40 ml) under N_2 at -78 °C was added dropwise with stirring over 20 min a solution of **11** (2.00 g, 5.95 mmol) in dry THF (40 ml). The mixture was stirred at -78 °C for 1 h, then cooled to -100 °C and treated as rapidly as possible with a solution of 3,4-pyridinedicarboxylic acid anhydride (**12**, 1.21 g, 8.11 mmol) in dry THF (40 ml) while maintaining efficient cooling and stirring. The mixture was allowed to slowly warm to room temperature with stirring over 18 h and then concentrated in vacuo. The resulting brown viscous oil was dissolved in H_2O (250 ml), cooled to 0 °C, and slowly acidified with dilute HCl. The resulting white precipitate was collected and dried in vacuo to give 2.53 g (88%) of crude product. Recrystallization from acetone yielded 2.01 g (70%) of **13** as a white powder: mp 234-236 °C (decomp.); ir

(KBr) 1715, 1675, 1450, 1365, 1260, 1175, 1070, 950, 860, 755, 735, 675 cm^{-1}; ^1H nmr (DMSO-d_6) δ 9.07 (s, 1H), 8.97 (d, 1H, J = 4.8 Hz), 8.14 (d, 1H, J = 8.0 Hz), 7.98 (d, 1H, J = 8.0 Hz), 7.79-7.56 (m, 7H), 7.50 (m, 1H); ^{13}C nmr (DMSO-d_6) δ 184.7, 166.5, 153.0, 150.1, 144.9, 136.6, 136.4, 135.1, 133.5, 129.72, 129.67, 128.6, 127.1, 126.7, 125.7, 123.0, 121.8, 115.7, 110.9; ms *m/z* 486 (M^++2), 484 (M^+), 328, 326, 264, 220, 164, 141, 77 (100%); Anal. Calcd for $C_{21}H_{13}N_2O_5BrS + C_3H_6O$: C, 53.05; H, 3.52; Br, 14.71; N, 5.15; S, 5.90. Found: C, 52.86; H, 3.30; Br, 14.95; N, 5.25; S, 6.05.

3-Bromoindol-2-yl 3-Carboxy-4-pyridyl Ketone (14). A magnetically stirred solution of keto acid (**13**) (1.00 g, 2.06 mmol), K_2CO_3 (1.2 g, 8.7 mmol), and H_2O (8 ml) in MeOH (25 ml), was heated under reflux for 45 min. The mixture was cooled and the MeOH was removed in vacuo. The dark, oily residue was dissolved in H_2O (100 ml), cooled to 0 °C, and slowly acidified with dilute HCl with stirring. The yellow precipitate was collected by filtration and dried in vacuo to yield 0.49 g of **14**. An additional 0.11 g of product was obtained by continuous extraction of the filtrate with CH_2Cl_2 to give a total of 0.60 g (84%) of **14**: mp 194-195 °C; ir (KBr) 1710, 1625, 1505, 1335, 1260, 1230, 740 cm^{-1}; ^1H nmr (DMSO-d_6) δ 12.38 (s, 1H), 9.22 (s, 1H), 8.94 (d, J = 4.3 Hz, 1H), 7.61 (d, J = 4.3 Hz, 1H), 7.50 (m, 2H), 7.41 (m, 1H), 7.20 (m, 1H); ^{13}C nmr (DMSO-d_6) δ 183.0, 165.6, 153.6, 151.8, 150.9, 148.6, 136.5, 131.0, 127.1, 124.6, 123.0, 121.6, 121.5, 120.6, 113.2. A satisfactory analysis could not be obtained for this product so it was used directly in the next step.

6-Bromoindolo[1,2-*b*][2,7]naphthyridine-5,12-quinone (15). A solution of **14** (0.60 g, 1.7 mmol) in Ac_2O (25 ml) was heated at 80 °C for 4 h. After cooling, most of the solvent was removed in vacuo, then H_2O (50 ml) and CH_2Cl_2 (50 ml) were added. The layers were separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extract was washed with H_2O (2 x 100 ml) and brine (100 ml), dried (Na_2SO_4), and adsorbed onto silica gel. Flash chromatography on silica gel with EtOAc gave 0.45 g (79%) of **15** as a yellow-green powder. Recrystallization from CH_2Cl_2/hexane gave the analytical sample as fine yellow needles: mp 230-232 °C (decomp.); ir ($CHCl_3$) 2980, 2920, 1705, 1680, 1600, 1535, 1450, 1365, 1335, 1255, 1220 cm^{-1}; ^1H nmr (DMSO-d_6) δ 9.35 (s, 1H), 9.16 (d, J = 4.7 Hz, 1H), 8.54 (d, J = 7.9 Hz, 1H), 8.18 (d, J = 4.7 Hz, 1H), 7.75 (m, 2H), 7.56 (m, 1H); ^{13}C nmr (DMSO-d_6) δ 174.1, 155.4, 150.0, 147.9, 134.7, 131.4, 131.2, 126.2, 126.0, 122.0, 120.8, 119.0, 118.3, 116.6, 108.7; ms *m/z* 328 (M^++ 2, 100%), 326 (M^+, 100%), 300, 298, 272, 270, 247, 219, 191, 164, 114; Anal. Calcd for $C_{15}H_7N_2O_2Br$: C, 55.07; H, 2.16; Br, 24.43; N, 8.56. Found: C, 54.82; H, 2.18; Br, 24.53; N, 8.49.

ACKNOWLEDGEMENT

This investigation was supported by PHS Grant GM-30761 awarded by the National Institutes of Health, and Merck Sharp and Dohme Research Laboratories. We thank the National Science Foundation for funds to purchase a Varian XL-300 nmr spectrometer. G.W.G. is very grateful to American Cyanamid for an Academic Achievement Award, and is especially indebted to Professor Marc Tius and his colleagues and students at the University of Hawaii at Manoa for their excellent facilities, wonderful hospitality, and Aloha spirit during a sabbatical year 1991-1992 when this manuscript was written.

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Received, 27th April, 1992