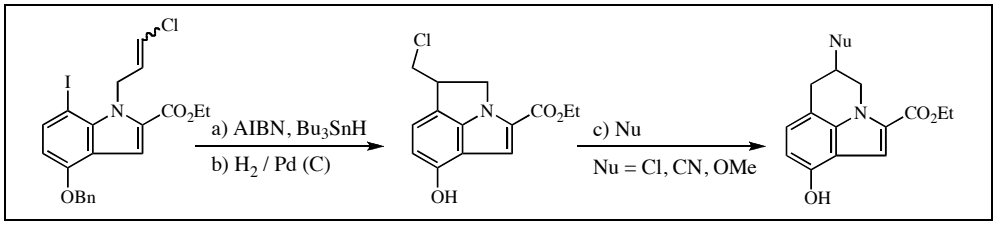
A Facile Rearrangement of Pyrroloindoline derivative to Pyrroloquinoline: A New Analogues of Duocarmycins

Naim H. Al-Said*, Khaled Q. Shawakfeh and Baha A. Hammad

Department of Applied Chemical Sciences, Jordan University of Science and Technology, P. O. Box 3030, Irbid 22110, Jordan. E-mail: naim@just.edu.jo

Received October 8, 2007

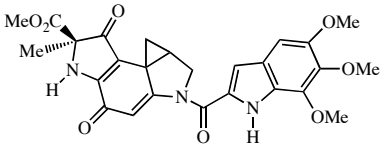


Free-radical generated at C-7 position of indole derivative bearing N-(3'-chloroallyl) group prompted a regioselective intramolecular cyclization to furnish pyrroloindoline derivative, through the more favorable *5-exo-trig* cyclization mode. The pyrroloindoline compound smoothly rearranged to pyrroloquinoline under mild conditions.

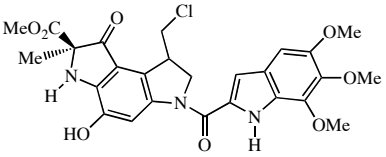
J. Heterocyclic Chem., **45**, 1333 (2008).

INTRODUCTION

Duocarmycins (**1**-**3**, Figure 1) [1-3] are natural potent antitumor antibiotics that afford their biological activity through selective covalent binding with adenine-N3 within the minor groove of the DNA by its cyclopropylindole (CPI) unit. It has been shown that duocarmycins **2** and **3** readily lose HCl to generate the active cyclopropane-containing drug (**1**) [4-8].



Duocarmycin A (**1**)



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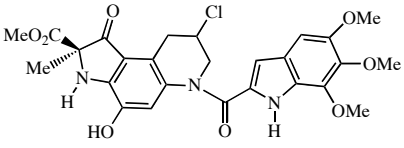


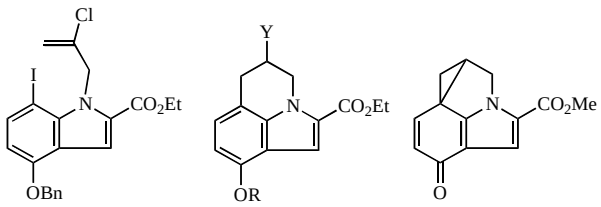
Duocarmycin C1 (**3**)

Figure 1. Structures of some duocarmycins.

It is believed that the stability of these drugs is mainly due to the conjugation of the electron pair on the nitrogen atom with cyclopropylindoline moiety. The non-covalent binding to DNA induces a change in the conformation of the amide group, disrupts the stabilization and activates the cyclopropane for nucleophilic attack by adenine-N3 [7,9,10].

The synthesis of different analogues of duocarmycins allows establishing some important molecular requirements for biological activity [11-16]. Nevertheless, no attempt was made to prepare conjugated analogs in which the lone pair on the nitrogen atom has permanent predetermined orientation.

We have previously reported the free radical-promoted ring closure of indole compound **4** bearing a radical acceptor (2'-chloroallyl) attached onto the indole nitrogen to furnish regioselectively the choropyrroloquinoline derivative **5** through 6-*endo-trig* cyclization mode [17]. Hydrogenolysis (H_2/Pd on C) of the benzyl group in **5** not only furnished the corresponding phenol derivative **6**, but also small amount of the unexpected dehalogenated phenol **7**.



4 **5**: R = Bn; Y = Cl **8**
6: R = H; Y = Cl
7: R = H; Y = H

It was hypothesized that compound **7** is generated from the reduction of cyclopropane system **8**, formed *in situ* from **7** after losing HCl [17]. Despite the conversion of **5** to cyclopropylindole **8** proved unsuccessful under various conditions, the formation of the minor product **7** was encouraging for the construction of a new DNA alkylating unit similar to CPI subunit found in duocarmycins.

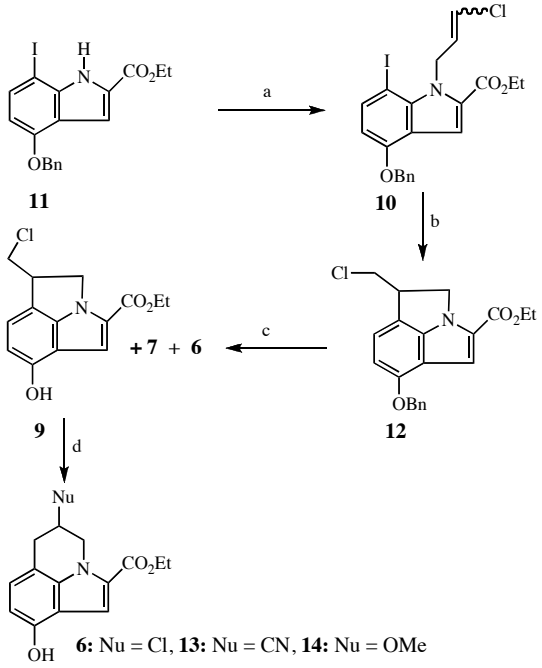
Now, we wish to report the conclusive chemical evidence for the ring expansion through an *in situ* formation of the biological important cyclopropylindoline system from suitably functionalized pyrroloindoline derivatives.

RESULTS AND DISCUSSION

In order to validate the proposal of *in-situ* formation of cyclopropane system **8**, we have directed our interest to the construction of the related pyrroloindoline system **9** [18]. Since the expansion of the five-membered ring in pyrroloindoline into six-membered ring in pyrrolo-quinoline proceeds through **8** as an intermediate. From retrosynthetic perspective, we considered the construction of **9** *via* free radical cyclization of *N*-(3'-chloroallyl)-7-iodoindole derivative **10** (Scheme 1) followed by hydrogenolysis of the benzyl group. Our synthetic sequence started with the known 7-iodoindole derivative **11** [17], which was smoothly converted into the required indole compound **10** as a *cis*/*trans* mixture in excellent yield. The *cis*/*trans* mixture was not separated. It was subjected to a free-radical cyclization using toluene at reflux in the presence of Bu_3SnH and a catalytic amount of AIBN. To our pleasant surprise, this reaction afforded chloropyrroloindoline **12** in good (75-85%) yield through the 5-*exo*-trig cyclization mode. It is noteworthy that this reaction furnished exclusively the chloropyrroloindoline **12** and we did not observed formation of pyrroloquinoline derivative, suggesting that the 5-*exo*-trig cyclization mode is preferred over the 6-*endo*-trig mode. The opposite appears to be the case with N-allyl and N-(2'-choroally) indole derivatives. This result clearly suggests that the strain in the saturated five-membered ring is not the deterrent factor in the formation of pyrroloindoline compound. Removal of the benzyl-protecting group from **12** was effected under mild conditions (H_2 balloon, Pd/C, 15 min) to afford chloropyrroloindoline **9** in good yield. The experimental conditions *i.e.*, solvent and time, were crucial for the formation of **9** as the only product. In fact, conducting the reaction for 2 h, the known compounds **6** and **7** [17] were isolated, probably due to the formation of cyclopropyl-pyrroloindole derivative **8**.

With a convenient access to **9**, we explored the formation and isolation of the biologically important cyclopropylpyrroloindole derivative **8**. Thus, compound **9** was stirred in mild basic conditions (K_2CO_3, acetone or NaH, THF) at room temperature. The starting material was consumed in short time (45 minutes). We were surprised to find that the structure of the exclusive product **6**, separated in excellent yield (91%) by column chromatography on silica gel, did not correspond to the required compound **8**. The spectroscopic (^1H NMR, ^{13}C NMR) and physical properties (melting point, R_f) of the isolated product **6** were identical in all respects with those of the compound prepared in our laboratory [17]. We further observed that K_2CO_3 is not necessary for this rearrangement. Thus, the phenol derivative **9** was converted to **6** just by stirring in dry solvent (acetone, THF) for 24 hrs. It is quite interesting that this rearrangement actually did occur in a pure solid sample of **9**. TLC indicated that pure **9** became contaminated with the rearranged product **6** after storage for several weeks. Furthermore, we observed that the benzyloxy derivative **12** was stable under neutral and basic conditions in different solvents (THF, acetone, DMF).

Scheme 1



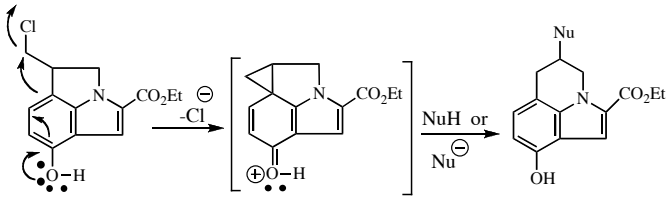
Reagents and conditions: (a) NaI, K_2CO_3, DMF, $ClCH_2CH$=CHCl, 98%; (b) Toluene, Bu_3SnH, AIBN, 85%; (c) H_2, Pd/C, hexane-EtOAc (9:1), 15 min, 90%; d) for **6**: K_2CO_3, Acetone, rt, 95%; for **13** KCN, Acetone, rt; 90%; for **14**: MeOH, rt.

To collect more information, some supporting experiments were conducted. In one experiment, the reaction was carried out in the presence of KCN in acetone at room temperature for 0.5 hr. The cyano derivative **13** was formed and isolated from the reaction mixture in 90% yield. In another experiment, the reaction was carried out in methanol to afford the methyl ether derivative **14** contaminated with inseparable impurities.

A mechanistic rationalization for the formation of **6** can be made along the following lines (Scheme 2). Once

formed, the phenole derivative **9** can undergo cyclization to furnish the intermediate **8** or its protonated form **15**. The next step presumably involves nucleophilic attack at C to regenerate the aromatic system. Cleavage of C-C bond would eradicate the strain in the cyclopropylindoline unit and gives a stable six-membered ring. The use of K_2CO_3 accelerates the reactions by forming the corresponding phenoxide anion.

Scheme 2



9 **15**

A mechanistic rationalization

In conclusion, a free-radical generated at C-7 position of indole derivative bearing N-(3'-chloroallyl) group has been demonstrated to furnish pyrroloindoline derivative, through *5-exo-trig* cyclization mode. Furthermore, we have shown that properly substituted pyrroloindoline derivative smoothly rearranged to pyrroloquinoline, even in a solid state, confirming that the conjugation of the lone pair of electron on the nitrogen atom of the carboxamido group of duocarmycins is crucial for the stability of the cyclopropylindoline moiety.

EXPERIMENTAL

Melting points were measured using an electrothermal digital melting point apparatus and were uncocorrected. IR spectra were recorded using a Nicolet-Impact 410 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400S spectrometer. The chemical shifts are given in δ ppm relative to TMS as the internal standard. Microanalytical determinations were performed on a Perkin Elmer 2400 Series PCII apparatus. Analytical thin-layer chromatography (TLC) was done on silica gel 60 F254 coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). Column chromatography was done using silica gel 60 (230–400 mesh) from Aldrich.

Ethyl 4-(benzyloxy)-1-(3-chlorallyl)-7-iodo-1*H*-indole-2-caboxylate (10). A mixture of indole **11** (0.53 g, 1.26 mmol), potassium carbonate (0.35 g, 2.53 mmol), sodium iodide (0.15 g, 1.00 mmol) and *cis*/*trans* mixture of 1,3-dichloropropene (0.62 g, 5.04 mmol) in DMF (50 ml) was stirred at 50 ºC for 19 h. The solvent was evaporated under reduced pressure, diluted with H_2O (150 mL), and extracted with ethyl acetate (3 x 60 mL). The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resultant crude product was purified by column chromatography eluting with 2.5% ethyl acetate in hexane to afforded **10** as a mixture of E and Z isomers, 0.62 g (100%); ir (KBr): 1715, 1648 and 1605 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (m, 7H, Ar-H), 6.28 (d, J = 8.2 Hz, 1H, Ar-H), 6.08 (m, 1H, CHCl), 5.84 (m, 1H, CH), 5.08 (bs, 2H, CH_2N), 5.11 (s, 2H, -OCH_2Ph), 4.28 (q, J = 7.3 Hz, 2H, OCH_2), 1.32 (t, J = 7.3 Hz, 3H, -CH_3); EIMS *m/z*: 495.3 (M^+).

Ethyl 8-benzyloxy-5-(chloromethyl)-4,5-dihydro-1*H*-pyrrolo[3,2,1-*hi*]indoline-2-carboxylate (12). A solution of **10** (0.268 g, 0.602 mmol), Bu_3SnH (97%, 0.18 g, 0.600 mmol), and a catalytic amount of AIBN (93 mg) in 50 mL of toluene was degassed with nitrogen for 5 min, and heated at reflux. After 30 min, an additional 0.2 g of Bu_3SnH was added and refluxed for 10 min. The reaction mixture was cooled to room temperature, and concentrated. The crude product was purified by column chromatography eluting with 3% ethyl acetate in hexane to afford a white solid of **12**, 0.176 g (79%), mp 110-112º; ir (KBr disk): 1710 and 1608 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 6H, Ar-H), 6.90 (d, J = 7.4 Hz, 1H, Ar-H), 6.39 (d, J = 7.6 Hz, 1H, Ar-H), 5.18 (s, 2H, -OCH_2), 4.80 (dd, J = 12.1, 8.4 Hz, 1H, -NCHH), 4.55 (dd, J = 12.1, 4.4 Hz, 1H), 4.30 (m, 3H), 3.82 (dd, J = 10.8, 5.6 Hz, 1H), 3.65 (dd, J = 10.8, 8.6 Hz, 1H) 1.33 (t, J = 7.10 Hz, 3H, -CH_3); ^{13}C-NMR(100 MHz, $CDCl_3$) δ: 161.8, 153.2, 150.8, 137.1, 128.5, 127.9, 127.4, 126.5, 118.5, 110.6, 109.7, 104.2, 70.8, 60.7, 56.4, 49.4, 46.8, 14.4; EIMS *m/z*: 369.6 (M^+). *Anal*. Calcd. for $C_{21}H_{20}NClO_3$: C, 68.20; H, 5.45; N, 3.79. Found: C, 68.54; H, 5.38; N, 3.86.

Ethyl 5-(chloromethyl)-8-hydroxy-4,5-dihydro-4*H*-pyrrolo-[3,2,1-*hi*]indoline-2-carboxylate (9). A solution of **12** (0.22 g, 0.959 mmol), and 5.0% Pd/C (100 mg) in ethyl acetate (50 mL) was degassed by nitrogen gas. The reaction mixture was placed under an atmosphere of H_2 and stirred at 35ºC for 15 min. The reaction mixture was filtered through celite and washed several times with ethyl acetate. The combined organic solvent was removed *in vacuo*, and the resulting crude product was purified by chromatography eluting with 5-15% ethyl acetate in hexane to give the expected phenol **9** as a white solid, 0.150 g (90%), mp 160º; ir (KBr disk): 3300, 1689, 1606 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (s, 1H), 6.87 (d, J = 7.1 Hz, 1H), 6.31 (d, J = 7.1 Hz, 1H), 5.28 (bs, 1H), 4.82 (dd, J = 11.9, 8.2 Hz, 1H), 4.56 (dd, *J* = 11.9, 4.3 Hz, 1H), 4.32 (m, 3H), 3.83 (dd, J =10.9, 5.7 Hz, 1H), 3.56 (dd, J =10.9, 8.6 Hz, 1H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 150.9, 149.6, 126.8, 119.4, 118.2, 109.7, 108.2, 106.0, 60.8, 56.6, 49.5, 46.8, 14.5; EIMS *m/z*: 279.4 (M^+). *Anal*. Calcd. for $C_{14}H_{14}NClO_3$: C, 60.11; H, 5.04; N, 5.01. Found: C, 60.21; H, 5.13; N, 4.93.

Ethyl 5-chloro-9-hydroxy-5,6-dihydro-4*H*-pyrrolo[3,2,1-*hj*]-quinoline-2-carboxylate (6).

Method A. A solution of compound **12** (10 mg, 35.8 μmol), potassium carbonate (20 mg, 144.7 μmol), in acetone (10 mL), was stirred for 45 minutes. The solvent was then evaporated under reduced pressure. The residue was purified by chromatography (5-15% ethyl acetate in hexane) to afford phenol **6** as a white solid 9.1 mg (91%), mp 244º; ir (KBr disk), 3275, 1671, 1606 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H, Pyr-H), 6.84 (d, J = 7.5 Hz, 1H, Ar-H), 6.38 (d, J = 7.4 Hz, Ar-H), 6.38 (d, J = 7.4 Hz, 1H, Ar-H), 5.02 (bs, 1H, -OH), 4.81 (dd, J = 14.0, 3.3 Hz, 1H, -NCHH-), 4.60 (m, 3H, CHCl and NCHH), 4.32 (q, J = 7.2, 2H, -OCH_2), 3.36 (dd, J = 16.2, 8.2 Hz, 1H, CHH-), 3.14 (dd, J = 16.2, 5.4 Hz, 1H, CH), 1.35 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR(100 MHz, $CDCl_3$) δ: 161.9, 152.9, 139.3, 127.4, 123.4, 114.1, 111.5, 106.5, 104.7, 60.5, 52.2, 50.9,

34.4, 14.2. *m/z* 279.1 (M^+). *Anal*. Calcd. for $C_{14}H_{14}NClO_3$: C, 60.11; H, 5.04; N, 5.01. Found: C, 60.50; H, 5.11; N, 5.12.

Method B. A solution of compound **12** (10 mg, 35.8, μmol), and sodium hydride washed with THF (2.0 mg, 160 μmol), was dissolved in THF (10 mL), and stirred for 30 minutes. The solvent was then evaporated under reduced pressure. The residue was purified by chromatograph (5-15% ethyl acetate in hexane) to afford the phenol **6** as a white solid 9.5 mg (95%).

Ethyl 5-cyano-9-hydroxy-5,6-dihydro-4*H*-pyrrolo[3,2,1-*hj*]quinoline-2-carboxylate (13). A solution of compound **12** (10 mg, 35.8 μmol), potassium cyanide (10 mg, 210 μmol), in acetone (10 mL), was stirred for 30 minuets. The solvent was evaporated under reduced pressure, and residue was purified by chromatograph (5-15% ethyl acetate in hexane) to afford phenol **13** as a white solid 9.0 mg (90%), mp 264°; ir (KBr) 3284, 2245, 1673, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (s, 1H, pyr-H), 6.88 (d, J = 7.2 Hz, 1H, Ar-H), 6.39 (d, J = 7.4 Hz, 1H, Ar-H), 4.85 (dd, J = 13.1, 3.9 Hz, 1H, NCHH)), 5.25 (bs, 1H, OH), 4.60 (dd, J = 13.3, 7.3 Hz, 1H, NCHH), 4.35 (q, J = 7.2 Hz, 1H, OCH_2), 3.35 (m, 1H, CHCN), 3.24 (dd, J =15.9, 4.4 Hz, 1H, CHH), 3.17 (dd, J =15.9, 8.5 Hz, 1H, CHH), 1.35 (t, J = 7.2 Hz, 3H, CH_3), ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 152.1, 139.9, 127.3, 123.7, 118.2, 113.9, 111.0, 104.5, 106.1, 61.1, 50.8, 34.3, 30.2, 14.4; EIMS: *m/z* 270.2 (M^+). *Anal*. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.59; H, 5.36; N, 10.46.

Acknowledgement. We thank the Deanship of Research at Jordan University of Science and Technology for financial support, Grant No 135/2005.

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