Tetrahedron Letters,Vol.29,No.29,pp 3545-3546,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF DIAZAQUINOMYCIN A AND B: THE FIRST DOUBLE KNORR CYCLIZATION

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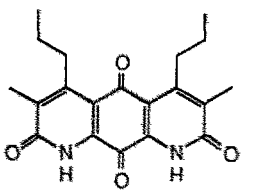
Abstract. *The first syntheses of diazaquinomycin A (1) and diazaquinomycin B (11) are described. The key reaction is the tandem double Knorr cyclization/oxidation of 10 to 1 (Eq. 1).*

The antibiotic diazaquinomycin A is the sole recorded example of the tricyclic 1,8-diazaanthraquinone ring system. The 1983 assignment[1] of structure **1** to diazaquinomycin A rests on an analysis of spectroscopic data and to date has not been confirmed by independent means. We now report a short synthesis of diazaquinomycin A which not only affirms the structure attributed to **1** but also provides ready access to it.

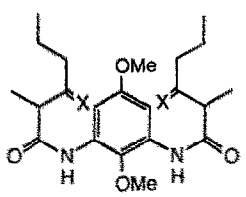


1

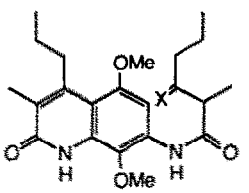
From a retrosynthetic standpoint diazaquinomycin A may be regarded as a bis 2-quinolone. Simple 2-quinolones are frequently accessible by the Knorr cyclization[2] of ß-keto anilides. By extension, **1** might be available by a "double" Knorr cyclization, but successful double Knorr cyclizations are unknown[2] and the only reported attempt[3] to achieve one failed under a wide variety of reaction conditions.

Negative precedent notwithstanding, the brevity of a double Knorr cyclization route to **1** remained attractive.

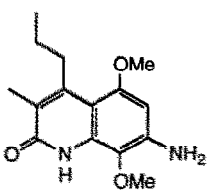
Initial attempts to access the ring system of **1** from **2** or **3** served to corroborate the pessimistic prognosis of precedent: myriad permutations of acid catalyst,[4] solvent, and temperature failed to give any detectable (MS, NMR) tricyclic material. In general the first Knorr cyclization proceeded smoothly to give **4** or **5** but continued reaction or isolation of **4** or **5** and (re)submission to putative cyclization conditions were unrewarding: amino quinolone **6** is usually the product obtained under reaction conditions that cause **4** or **5** to react, even when moisture is rigorously excluded.



2, X = O
3, X = -OCH_2CH_2O-



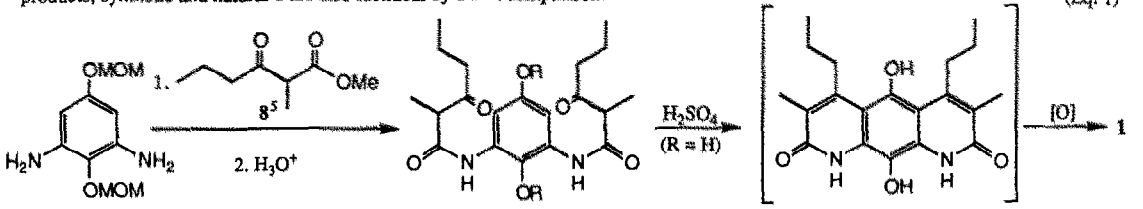
4, X = O
5, X = -OCH_2CH_2O-



6

Since phenols are more reactive toward electrophilic aromatic substitution than anisoles, hydroquinone **10**, prepared in two steps from **7** as indicated (Eq. 1), was substituted for **2**. In contrast to **2**, **10** is not only an excellent substrate for the double Knorr cyclization, but oxidation of the initial tricyclic product (**11** = diazaquinomycin B) occurs spontaneously under the reaction conditions yielding diazaquinomycin A (**1**) directly. The yield for the one-pot conversion of **10** to **1** is 95%. If desired, **11** can be isolated and oxidized to **1** in a separate step. Spectra of synthetic diazaquinomycin A and B are in agreement with those reported[1] for the natural products; synthetic and natural **1** are also identical by direct comparison.[6,7]

(Eq. 1)



7 **9**, R = MOM **10**, R = H **11**

Acknowledgments. We thank Dr S. Ōmura for a sample of **1** and NIH for partial support.

References and Notes

1. S. Ōmura, A. Nakagawa, H. Aoyama, K. Hinotozawa and H. Sano, *Tetrahedron Lett.* **1983**, *24*, 3643.

2. For a review see G. Jones in *Quinolines, Part 1* (G. Jones, Ed.); Wiley: New York, 1977; Chapter 2.

3. R. M. Forbis and K. L. Rinehart, Jr., *J. Am. Chem. Soc.* **1973**, *95*, 5003.

4. Acids examined include conc. H_2SO_4, 30% oleum, conc. H_2SO_4/P_2O_5, 85% H_3PO_4, PPA, CF_3COOH, liquid HF, HBr/HOAc, CF_3SO_3H, $CF_3SO_3H/SbF_5/CF_3COOH$, $TiCl_4$, BF_3·Et_2O and BBr_3. Thermolyses neat and in refluxing diphenyl ether were also unsuccessful.

5. S. N. Huckin and L. Weiler *J. Am. Chem. Soc.* **1974**, *96*, 1082.

6. **Salient experimental details. 1**: *i*: 91 mg **10** in 5 mL conc. H_2SO_4 at 110 °C for 1.5 h, poured onto ice; orange solid washed with H_2O, EtOH → 78 mg **1** (95%); *ii*: 90 mg **11** in 10 mL 1:5 MeOH/CH_2Cl_2 stirred at 20 °C in open flask 2 h → 29 mg **1** (100%), mp 295 °C (dec) (HOAc/EtOH). **2** (same proced. as for **9**): 2.5 g 1,3-diamino-2,5-dimethoxybenzene (**12**),[8] 30 mL **8**[5] → 4.8 g **2** (76%), mp 93-94°C (EtOAc/pet ether). **3**: from **8** in two steps: *i*: 11.0 g **8**, 8.0 g ethylene glycol, 100 mg *p*-TsOH, 35 mL toluene, reflux 24 h (Dean Stark apparatus) → 8.4 g ethylene ketal of ethyl 2-methyl-3-ketohexanoate (**13**), bp 120-121 °C/12 torr; *ii*: 8.0 g **13**, 2.5 g **12**, 15.5 mL of 2M $AlMe_3$ in hexane,[9] reflux in benzene 2 days → 5.3 g **3** (71%), mp 125-127 °C (EtOAc/pet ether). **4**: 1.0 g **2** in 50 mL CF_3CO_2H at 20 °C 3 h → 0.95 g **4** (100%), mp 175-177 °C (benzene/pet ether). **6**: 10.0 g **2** in 200 mL conc. H_2SO_4 at 20 °C for 60 min → 6.5 g **6** (100%), mp 220-221 °C (EtOAc). **7**: *i*: 5 g 2,6-dinitrohydroquinone (**14**),[8] 9.15 mL *N,N*-diisopropylethylamine, 4.8 mL MOM-Cl, 100 mL THF, 0 °C 30 min, reflux 12.5 h → 5.9 g (82%) 2,5-bis(methoxymethoxy)-1,3-dinitrobenzene (**15**), bp 60-63 °C/0.25 torr; *ii*: 2.0 g **15**, 500 mg Raney Ni (Fluka) in 200 mL EtOAc, 1.2 atm H_2, 20 °C, 3.5 h → 1.6 g **7** (100%, oil). **9**: 870 mg **7** in 10 mL **8** boiled 40 min; recover excess **8** on kugelrohr (50 °C/0.5 torr); flash column chromatography (FCC) (silica, 2:1 EtOAc/pet ether) → 1.68 g **9** (92%), mp 64.0-65.5 °C (ether/pet ether). **10**: 1.36 g **9** stirred in 1 N HCl/THF/acetone (1:1:1, 300 mL) at 65 °C 23 h; FCC (silica, 2:1 EtOAc/pet ether) → 0.90 g **10** (81%), mp 74.0-75.0 °C (HOAc/pet ether). **11**: 195 mg **10** refluxed 22 h in 10 mL CF_3CO_2H under Ar, evap. CF_3CO_2H, wash residue with EtOAc → 105 mg (60%) **11** (pale yellow solid), mp 304°C (dec).

7. **IR and ^{1}H NMR data for selected new compounds. 2**: IR (KBr) υ 1695, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (6H, t, J = 7.7 Hz), 1.53 (6H, d, J = 7.3 Hz), 1.63 (4H, m), 2.61 (4H, t, J = 7.2 Hz), 3.60 (2H, q, J = 7.3 Hz), 3.78 (3H, s), 3.79 (3H, s), 7.69 (2H, s), 8.90 (2H, br s). **3**: IR (KBr) υ 1665, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (6H, t, J = 7.5 Hz), 1.30 (6H, d, J = 7.5 Hz), 1.41 (4H, m), 1.68 (4H, m), 2.86 (2H, q, J = 7.5 Hz), 3.75 (3H, s), 3.79 (3H, s), 4.08 (8H, m), 7.75 (2H, s), 8.89 (2H, br s). **4**: IR (KBr) υ 1640, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, t, J = 7.6 Hz), 1.05 (3H, t, J = 7.6 Hz), 1.56 (3H, d, J = 7.3 Hz), 1.65 (4H, overlapping m), 2.24 (3H, s), 2.63 (2H, t, J = 7.4 Hz), 3.05 (2H, t, J = 8.3 Hz), 3.65 (1H, q, J = 7.3 Hz), 3.82 (3H, s), 3.90 (3H, s), 7.77 (1H, s), 9.09 (1H, br s), 9.12 (1H, br s). **6**: IR (KBr) υ 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, t, J = 7.3 Hz), 1.53 (2H, m), 2.20 (3H, s), 3.00 (2H, t, J = 8.0 Hz), 3.75 (3H, s), 3.83 (3H, s), 4.03 (2H, br s), 6.05 (1H, s), 8.89 (1H, br s). **7**: IR (neat) υ 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.43 (3H, s), 3.56 (3H, s), 3.88 (4H, br s), 4.93 (2H, s), 5.03 (2H, s), 5.86 (2H, s). **9**: IR (KBr) υ 1720, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ 0.92 (6H, t, J = 7.4 Hz), 1.49 (6H, d, J = 7.3 Hz), 1.63 (4H, apparent sextet, J ~ 7.4 Hz), 2.58 (2H, t, J = 7.3 Hz), 2.59 (2H, t, J = 7.3 Hz), 3.47 (3H, s), 3.56 (1H, q, J = 7.3 Hz), 3.57 (1H, q, J = 7.3 Hz), 3.68 (3H, s), 4.94 (1H, d, J = 5.8 Hz), 5.09 (1H, d, J = 5.8 Hz), 5.15 (2H, s), 7.81 (2H, s), 8.92 (2H, br s). **10**: IR (KBr) υ 1710, 1655 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.83 (6H, t, J = 7.3 Hz), 1.23 (6H, d, J = 7.0 Hz), 1.49 (4H, apparent sextet, J = 7.3 Hz), 2.53 (2H, t, J = 7.3 Hz), 2.54 (2H, t, J = 7.3 Hz), 3.88 (2H, q, J = 7.0 Hz), 6.96 (2H, s), 8.61 (1H, br s), 9.05 (1H, br s), 9.84 (2H, br s). **11**: IR (KBr) υ 3300, 1615 cm^{-1}. **13** IR (neat) υ 1730 cm^{-1};^{1}H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7.4 Hz), 1.21 (3H, d, J = 7.3 Hz), 1.27 (3H, t, J = 7.3 Hz), 1.36 (2H, m), 1.69 (2H, m), 2.80 (1H, q, J = 7.3 Hz), 3.96 (4H, m), 4.19 (2H, q, J = 7.3 Hz). **15**: ^{1}H NMR ($CDCl_3$) δ 3.49 (3H, s), 3.50 (3H, s), 5.13 (2H, s), 5.23 (2H, s), 7.67 (2H, s). Satisfactory combustion analyses were obtained for **1**, **2**, **3**, **4**, **6**, **9**, **10**, **13**, and **15**.

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(Received in USA 4 May 1988)