A SIMPLE SYNTHESIS OF TRYPTANTHRIN

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Abstract: A simple synthetic procedure for tryptanthrin was established from oxindole *via* indolo[2,1-*b*]quinzolin-12(6*H*)-one as a key intermediate.

Tryptanthrin **4** is an indoloquinazoline alkaloidal antibiotic substance isolated first from the culture of the yeast *Candida lipolytica* (1) and later *Strobilanthes cusia* (2) as well as other higher plant sources (3). Higher plants include Chinese traditional medicine 'Qing Dai' (*Isatis indigotica*) which has been used as anti-inflammatory agent. Isolated tryptanthrin showed antifungal activity (MIC = 5 μg/mL) (4). Antibacterial spectrum of tryptanthrin was studied to show specificity against dermatophytic species with MIC's of 3.1-6.3 5 μg/mL (5). Additional various biological activities such as antituberculosis (MIC = 10 μg/mL) (6), COX-2 inhibitory (IC_{50} = 64 nM) (7), and cytotoxic (8) activities have been reported. In addition to such biological properties, tryptanthrin also has an electron transportability, thus having potentials for photoelectronic photoreceptor (9). Such a variety of intriguing activities led efforts not only to find other plant sources but also to trigger the development of new methods for the total synthesis (10) as well as cultivation methods (11).

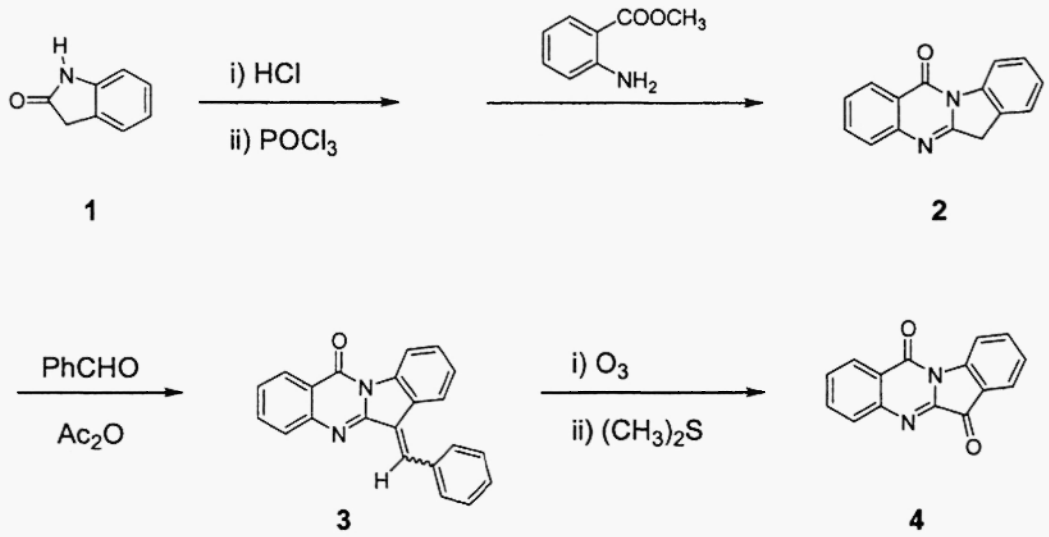
In fact, tryptanthrin had long been known as anhydroisatin-α-anthranilide, obtained as an oxidation product of indigo (12) as well as other methods (13). The structure of tryptanthrin, however, remained in controversy until X-ray crystallography confirmed the present structure (14).

For the synthesis of the derivatives of tryptanthrin and related compounds, only few methods have been reported for the introduction of very limited substituent at C6 (15). We herein described a simple synthetic procedure for tryptanthrin from readily available starting materials, which would be a useful method to introduce a substituent at C6.

Synthesis

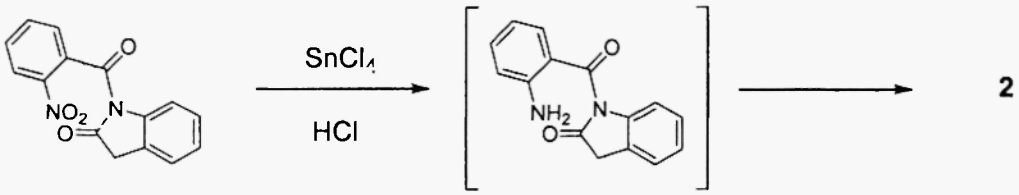
The prerequisite starting compound **2** was prepared by employing previously reported procedure for the synthesis of 4(3*H*)-quinazolinones (16). HCl salt of commercially available oxindole (**1**) was, thus treated with $POCl_3$ and followed by reaction with methyl anthranilate to lead indolo[2,1-*b*]quinazolin-12(6*H*)-one (**2**) in 82% yield. Thummel's (17) two-step introduction of keto group at the *peri*-position of 2,3-cycloalkenopyridines was employed for the introduction of carbonyl group at C6 of **2**. Condensation of **2** with benzaldehyde in the presence of Ac_2O afforded corresponding benzylidene compounds (**3**) in 89% yield.

The *E*- and *Z*-isomer through the benzylidene double bond were formed as expected in a ratio of 6:1, which were separated by column chromatography and assigned by comparing ^{1}H NMR spectrum as well as double quantum COSY experiments. The benzylidene proton of *E*-isomer was resonanced at δ 8.69 due to deshielding effect of lone pairs of N1, while that of *Z*-isomer resonanced at δ 7.26. Ozonolysis of **3**, followed by reductive work up afforded desired tryptanthrin in 76% yield.



1 **2** **3** **4**

It is worthwhile to note that a second synthetic approach towards starting **2** has been additionally exploited by reductive cyclization of *N*-(2-nitrobenzoyl)oxindole **5** (18). The reductive cyclizations of nitro compounds related to **5** were previously pursued for the preparation of 2,3-cycloalkeno-4(3*H*)-quinazolinones (9e). Although such a reaction required CO, transition metal catalyst, and medium pressure (30-50 psi), conventional reduction of **5** by either $SnCl_4$/HCl or H_2NNH_2-H_2O in the presence of Pd-C proceeded smoothly without either such a catalyst or pressure to afford **2** in 87-90% yields. Interestingly no trace of corresponding amino compound 6 was observed.



5 **6** **2**

In conclusion, tryptanthrin was prepared from readily available oxindole *via* indolo[2,1-*b*]quinzolin-12(6*H*)-one as a key intermediate. This procedure provided an easy access to functionalize C6 position as well as to introduce (a) substituent(s) at C6 position.

Experimental

Melting points were determined using a Fischer-Jones melting points apparatus and are not corrected. IR spectra were obtained using a Perkin-Elmer 1330 spectrophotometer. NMR spectra were obtained using a Bruker-250 spectrometer 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR and are reported as ppm from the internal standard TMS. Elemental analyses were taken on a Hewlett-Packard Model 185B elemental analyzer.

Indolo[2,1-*b*]quinzolin-12(6*H*)-one (2)

Method A: To a solution of oxindole (2.64 g, 0.02 mol) in $CHCl_3$ (20 mL) was passed dry HCl gas. The lactam-HCl salt precipitated was collected and suspended in $POCl_3$ (5 mL). The suspension was warmed to 40 °C and stirred for 2 h to give a clear solution. Removal of excess $POCl_3$ *in vacuo* afforded an oil, which was neither isolated nor characterized, but instead was dissolved in dry THF (100 mL). Into this solution was added methyl anthranilate (4.54 g, 0.03 mol). The mixture was stirred for 12 h at room temperature and diluted with water (20 mL). The reaction mixture was made basic with NH_4OH (10 mL) and extracted with CH_2Cl_2 (30 mL x 3). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent gave a yellow solid which was sublimed under reduced pressure (105 °C/0.05 mmHg) to yield 3.84 g (82%) of **2** as yellow needles: mp 214-215 °C [lit. (19) mp 213-215 °C]. IR (KBr) υ 1680, 1605, 1560, 1465, 1360, 1330, 1310, 775, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$), 400 MHz) δ 8.62 (d, *J* = 8.1 Hz, 1H), 8.44 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.79 (ddd, *J* = 8.0, 7.8, 1.6 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.53 (ddd, *J* = 8.0, 7.8, 1.2 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.34 (td, *J* = 8.0, 1.4 Hz, 1H), 4.25 (s, 2H).

Method B: To a solution of *N*-(2-nitrobenzoyl)oxindole (2.80 g, 0.01 mol) and $SnCl_4$ (10g) in EtOH (50 mL) was added conc. HCl (15 mL). The resulting mixture was refluxed for 1 hr. After cooling to room temperature the mixture was poured to ice water and made basic with aq. NaOH. The greenish yellow precipitate was collected and washed with water to give yellow needles (mp 213-215 °C), whose spectral data were identical to those obtained by Method A.

6-Phenylmethylideneindolo[2,1-*b*]quinoazolin-12(6*H*)-one (3): A mixture of 2.34 g (0.01 mol) of **2** and 6.36 g (0.06 mol) of benzaldehyde in 20 mL of Ac_2O was refluxed for 48 h. After distilling off excess Ac_2O, the resulting mixture was poured to 40 mL of 50% NaOH and extracted with CH_2Cl_2 (30 mL x 3). Organic layers were dried over $MgSO_4$. Evaporation of the solvent gave a greenish yellow solid, which was chromatographed on silica gel eluting with CH_2Cl_2. The early fractions (R_f = 0.65) afforded 2.56 g (79%) of yellow needles after recrystallization from the eluent as an *E*-isomer: mp 161-162 °C. IR (KBr) υ 3026, 1679, 1628, 1580, 1559, 1466, 775, 768, 747 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.69 (d, *J* = 8.4 Hz, 1H), 8.43 (dd, *J* = 8.0, 0.8 Hz, 1H), 8.35 (s, benzylidene H, 1H), 7.82-7.75 (m, 3H), 7.70 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.53-7.45 (m, 4H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.15 (td, *J* = 8.0, 0.8 Hz, 1H). *Anal.* Calcd for $C_{22}H_{14}N_2O$: C, 81.94; H, 4.38; N, 8.72. Found: C, 82.02; H, 4.36; N, 8.75. The latter fractions (R_f = 0.55) afforded 0.32 (10%) of *Z*-isomer as yellow needles: mp 146-47 °C. IR (KBr) υ 3027, 1679, 1629, 1580, 1558, 1467, 775, 768, 748 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.66 (d, *J* = 8.4 Hz, 1H), 8.59 (dd, *J* = 8.0, 0.8 Hz, 1H), 8.43 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.80-7.74 (m, 3H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.53-7.40 (m 5H), 7.35 (td, *J* = 8.0, 0.8 Hz, 1H), 7.26 (s, benzylidene H, 1H).

Trypthanthrin (4): A solution of 3.22 g (0.01 mol) of **3** as a mixture in 200 mL of CH_2Cl_2 was cooled in an acetone-dry ice bath and O_3 was bubbled through the solution. Excess O_3 was purged and 20 mL of $(CH_3)_2S$ was added to the mixture. Evaporation of the solvent afforded 2.48 g of semi-solid, which was chromatographed on silica gel, eluting with CH_2Cl_2:EtOAc (1:1). The latter fractions gave 2.06 g (83%) of yellow needles after recrystallization from the eluent: mp 269-270 °C [lit. (10a) mp 267-268 °C, lit.(12) mp 261 °C]. IR (KBr) υ 3032, 1725, 1675, 1565, 1435, 1327, 1245, 1138, 947 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68

(d, J = 8.0 Hz, H10), 8.48 (ddd, J = 8.2, 1.5, 0.8 Hz, H1), 8.10 (ddd, J = 8.0, 1.2, 0.6 Hz, H4), 7.96 (ddd, J = 7.8, 1.4, 0.6 Hz, H7), 7.91 (ddd, J = 8.2, 7.5, 1.5 Hz, H3), 7.85 (ddd, J = 8.0, 7.8, 1.3 Hz, H9), 7.72 (ddd, J = 8.2, 7.8, 1.5 Hz, H2), 7.45 (ddd, J = 8.0, 7.5, 1.2 Hz, H8). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 182.4, 157.7, 146.4, 146.0, 145.0, 137.7, 135.1, 129.9, 129.8, 126.9, 126.9, 124.7, 123.3, 122.2, 117.0.

Acknowledgement: Support by Korean Research Foundation Grant (KRF-2002-005-E00019) is gratefully acknowledged.

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(18) Compound **5** was prepared by reacting oxindole with 2-nitrobenzoyl chloride in the presence of NaH in 65% yield.

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Received on July 29, 2003.