SHORT-STEP SYNTHESIS OF RUTECARPINE AND TRYPTANTHRIN VIA INTRAMOLECULAR AZA-WITTIG REACTION[1]

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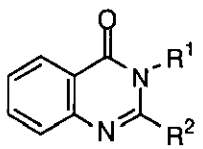
Abstract---A convenient short-step synthesis of rutecarpine and tryptanthrin as quinazoline alkaloids containing indole skeleton *via* intramolecular aza-Wittig reaction was described.

Recently we have developed a new efficient route to quinazolinones (**1**) as well as simple alkaloids (**2** and **3**) *via* intramolecular aza-Wittig reaction (Scheme 1).[2,3] This aza-Wittig methodology has been extended to develop a new lactam-ring-enlargement reaction *via* quinazolinone annelation, followed by reductive ring cleavage.[4] In this paper we would like to demonstrate the utility of this quinazolinone annelation for synthesis of pharmacologically important alkaloids such as rutecarpine (**8**) and tryptanthrin (**9**).



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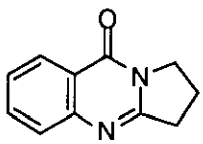

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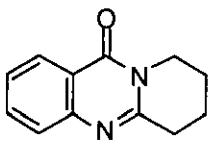

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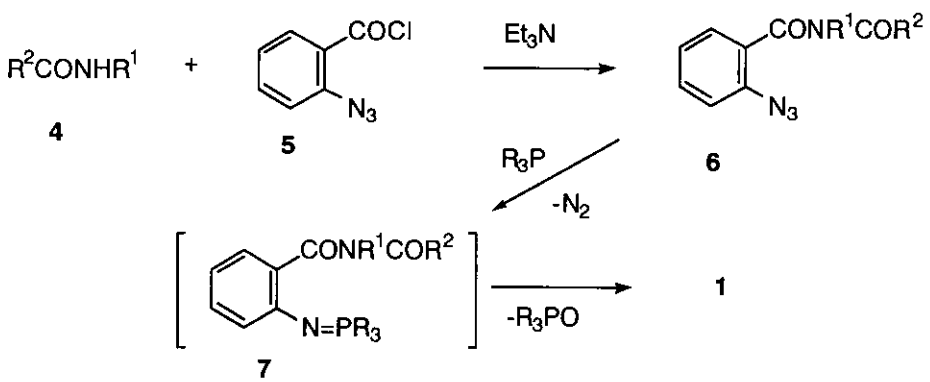
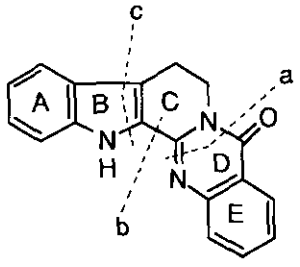
Scheme 1





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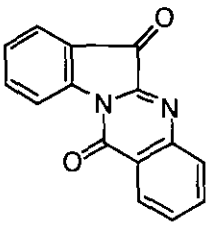

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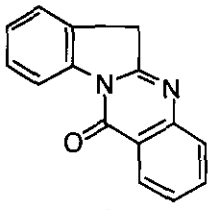

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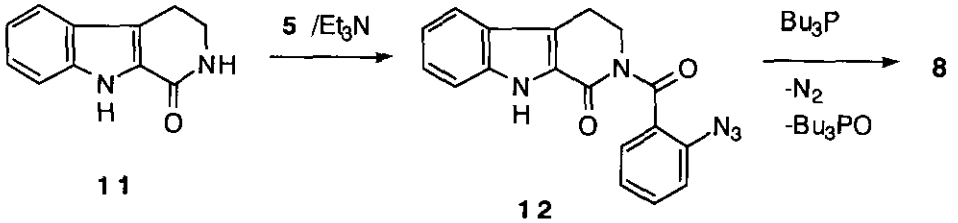
Rutecarpine (8,13-dihydroindolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5(7*H*)-one) (**8**) is an alkaloid of *Evodia rutaecarpa*,[5] and is known as one of the constituents involved in the Chinese drugs 'Wou-Chou-Yu'[6] and 'Shih-Hu'.[7] Several syntheses of **8** have been reported based on respective unique retrosynthetic analyses **a**,[8] **b**,[9] and **c**[10] (see dotted lines in the structure **8**). Among these routes, **a** provides obviously the most straightforward synthesis of **8** by our quinazolinone annelation of 1,2,3,4-tetrahydro-1-oxo-β-carboline (**11**).[11] This route was previously fulfilled elegantly *via* iminoketene cycloaddition and/or isatoic anhydride condensation methods by Kametani and his coworkers.[8] We examined the quinazolinone annelation method utilizing intramolecular aza-Wittig reaction as an alternative synthesis of **8**. The carboline (**11**) was *o*-azidobenzoylated with **5** (Et_3N-C_6H_6) to afford the imide (**12**) as a pale yellow solid (49%),[12,13] which was treated with tributylphosphine at 60 °C in benzene for 2 h to give rutecarpine (**8**) in 71% yield (Scheme 2).[14] The condensation of isatoic anhydride with **11** at 190-200 °C is reported to afford **8** in 42.3% yield.[8c] Thus, the present quinazolinone annelation of **11** by intramolecular aza-Wittig reaction provides an alternative route to rutecarpine (**8**) under very mild conditions.

Scheme 2

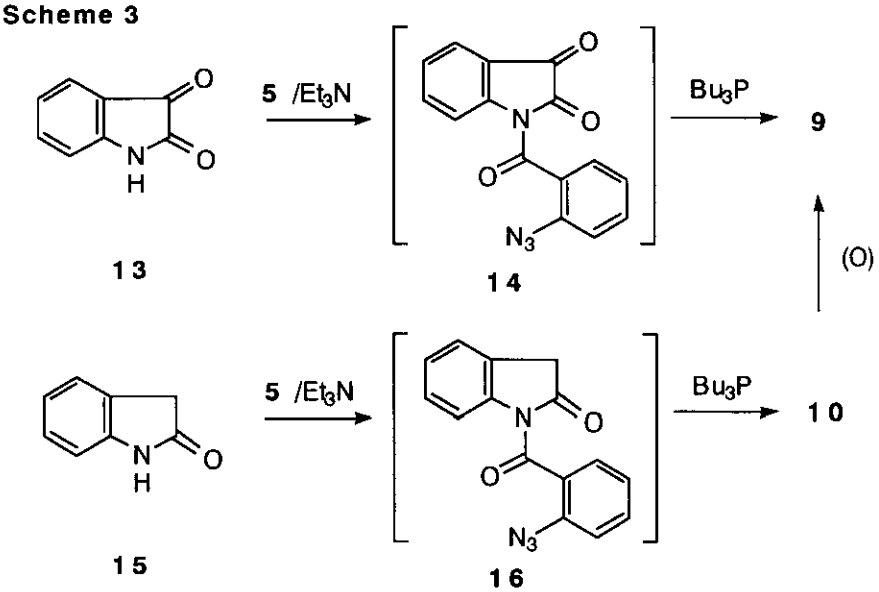


11 **12**

Tryptanthrin (6,12-dihydro-6,12-dioxoindolo[2,1-*b*]quinazoline) (**9**) is a simple alkaloid isolated from various sources, i.e., from fruits of the cannon ball tree, *Couroupita quianensis Aubl.*,[15] from leaves of *Strobilanthes cusia* O. Kuntze,[16] from *Polygonum tinctorium* and *Isatis tinctoria*,[17] and also from the culture solution of the yeast *Candida liplytica*.[18] Furthermore, tryptanthrin has an antimycotic activity and is known as the active principle of a traditional remedy in Okinawa against dermatophytic infections.[16] Although synthetic work related to **9** has a long history[19] but more flexible useful syntheses have been reported only recently.[19-23] Among these syntheses, the most efficient and widely used method involves the condensation of isatin and isatoic anhydride. A new synthesis by cyclization of 3-chlorophenyl-2-methyl-4(3*H*)-quinazolinones has been reported

very recently.[24] We examined quinazolinone annelation of isatin by intramolecular aza-Wittig reaction as an alternative method. Isatin (**13**) was treated with an equimolar amount of *o*-azidobenzoyl chloride (**5**) in dioxane in the presence of triethylamine to give **14** which was without isolation treated with tributylphosphine at room temperature for 2 h. Chromatography of the crude product afforded tryptanthrin (**9**) in 32% yield as a yellow solid.[25] The *o*-azidobenzoylation in the presence of 10 mol% of 4-dimethylaminopyridine raised the yield of **9** to 43% but *o*-azidobenzoylation using sodium hydride or carbonyldiimidazole did not give better results (Scheme 3). Similarly, oxindole (**15**) was *o*-azidobenzoylated, followed by treatment with tributylphosphine to afford indolo[2,1-*b*]quinazolin-12(6*H*)-one (**10**) in 26% yield. This compound is known to be very sensitive to oxidant (air) and decomposed gradually to a complex product-mixture on standing in the atmosphere.[27] After air was bubbled through a benzene solution of this mixture for 12 h, purification by silica gel chromatography gave tryptanthrin (**9**) in 14 % yield. Thus, intramolecular aza-Wittig method provides an alternative simple method for synthesis of **9** and its analogues under mild conditions.

Scheme 3



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12. All new compounds reported had spectral and microanalytical properties in agreement with the given structures. Melting points were taken with a Yanagimoto micro-melting point apparatus and are uncorrected.
13. Compound (**12**): mp 190 °C (decomp.); ^{1}H nmr (200 MHz, $CDCl_3$) δ 8.84 (br s, 1H), 7.70-7.66 (m, 1H), 7.52-7.14 (m, 7H), 4.46 (t, J= 6.4 Hz, 2H), 3.23 (t, J= 6.4 Hz, 2H).
14. Rutecarpine (**8**): mp 262-264 °C (CH_2Cl_2) (lit.,[8b] 259 °C); Spectral data and Rf values were same with those of an authentic sample prepared by the known method.
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25. Tryptanthrin (**9**): To a stirred solution of isatin (**13**) (271 mg, 1.84 mmol), triethylamine (186 mg, 1.84 mmol), and 4-dimethylaminopyridine (22 mg, 0.18 mmol) in dioxane (10 ml) was added dropwise a solution of *o*-azidobenzoyl chloride (**5**) prepared from the corresponding acid (300mg, 1.84 mmol) in dioxane (3 ml) under nitrogen. After 3 h at room temperature, the mixture was filtered under nitrogen, and to the filtrate was added tributylphosphine (409 mg, 2.02 mmol) with stirring under nitrogen. After the stirring was continued for 2 h at room temperature, the solvent was evaporated under reduced pressure to give crude product which was chromatographed on a silica gel column eluting with dichloromethane to afford **9** as a yellow solid (197 mg, 43.1%); mp 259-262 °C (lit.,[20] 263.5-265.5 °C). Spectral data and Rf values were in agreement with those of an authentic sample prepared by the known method.
26. Compound (**10**): mp 210-213 °C (decomp.) (lit.,[27] 215-217 °C). Spectral data were in accord with the reported values.
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