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STRUCTURE DETERMINATION OF CANDIDINE, A VIOLET INDOLIC CONSTITUENT FROM CULTURE SOLUTIONS OF *CANDIDA LIPOLYTICA*

Jan Bergman and Ulf Tilstam
Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden

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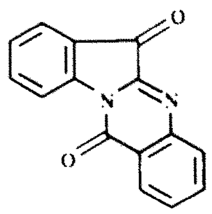
Abstract A violet indolic constituent, candidine, isolated from culture solutions of *Candida lipolytica* has been identified as 6,12-dihydro-6-(3-oxoindolid-2-ene)-12-oxoindolo[2,1-*b*]quinazoline by an independent synthesis (condensation of 6,12-dihydro-6,12-dioxoindolo[2,1-*b*]quinazoline with 1-acetylindoxyl).

Zähner and Fiedler have isolated the antibiotic tryptanthrin (**1**) from the culture solutions of the yeast *Candida lipolytica* after addition of tryptophan (**2**) and anthranilic acid (**3**). When feeding tryptophan and substituted anthranilic acids, or substituted tryptophans and anthranilic acid, the expected substituted derivates of tryptanthrin could be isolated.[1,2] In addition to tryptanthrin (**1**) Fiedler could isolate[2] indole-3-acetic acid, N-formylanthranilic acid, tryptophol (**4**) plus an unidentified violet compound, with the composition $C_{23}H_{13}N_3O_2$, whose structure now has been determined. The compound has also been given the name candidine.

We have recently shown[3] that tryptanthrin (**1**) is a congener with indirubin (**5**) in the fruits of the cannon ball tree. Consequently we did suspect that candidine might be related with indirubin and/or tryptanthrin. The composition $C_{23}H_{23}N_3O_2$ and the mass spectral data: (parent ion peak (base peak), at *m/z* 363, strong peaks at *m/z* 335 (M – 28) and *m/z* 259) were indicative of structures **6** or **7**.

Compound **6** was synthesized by condensation of



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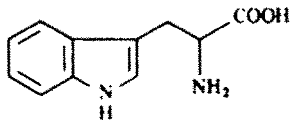

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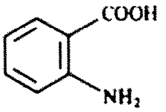

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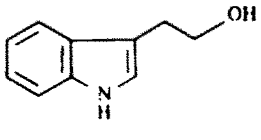

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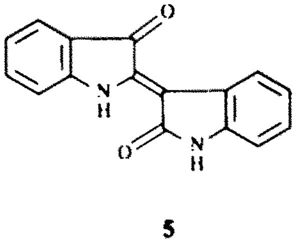

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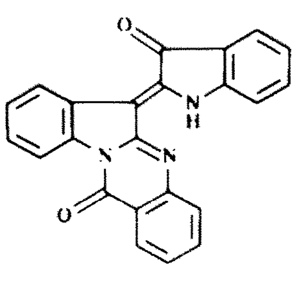

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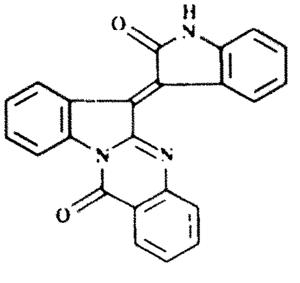

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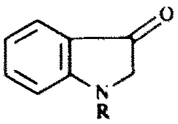
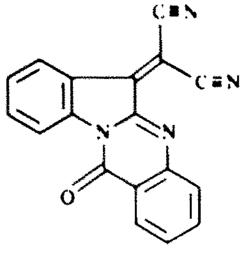


8a R = COCH$_3$
8b R = H



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tryptanthrin with N-acetylindoxyl (**8a**) followed by mild hydrolysis. Hydrolysis under more severe conditions resulted in a retroaldol condensation and reformation of tryptanthrin. Direct comparison of the synthetic compound **6** with the natural product proved their identity. Actually compound **6** had been briefly described in 1922 by Martinet and Grosjean as a condensation product of indoxyl (**8b**) and **1**.

In connection with the present study it was also found that tryptanthrin did condense readily with active methylene compounds. Thus **1** and oxindole gave 7. Similarly **1** and $CH_2(C{\equiv}N)_2$ under mild conditions gave 9.

EXPERIMENTAL

Candidine (**6**). Tryptanthrin[3] (**1**, 2.48 g, 0.01 mol) and **8a** (1.75 g, 0.01 mol) were dissolved in AcOH (50 ml) and piperidine (2 ml) was added. The mixture was boiled for 24 hr, cooled and the violet solid formed collected, washed with EtOH and dried: yield 1.8 g (50%): m.p. 269–270° (lit.[4] m.p. 267°); UV/VIS λ_{max} ($CHCl_3$) 244 (log ε 4.34), 250 (4.36), 282 (4.21), 538 (3.95), 573 (4.11) nm; IR (KBr) 3210, 2730, 1690, 1650, 1625, 1600, 1460, 1355, 1315, 740 cm^{-1}; MS, *m/z* 364 (M + 1, 23), 363 (M, 100), 335 (37), 259 (10), 258 (11), 242 (9).

6,12-*Dihydro*-6-(2-*oxoindolid*-3-*ene*)-12-*oxoindole*[2,1-b]-*quinazoline* (7). Tryptranthrin (1.24 g) and oxindole (0.67 g) were dissolved in AcOH (30 ml) and BF_3-etherate (2 ml) was added, whereupon the mixture was boiled (1 hr), cooled and the solid formed collected, washed with EtOH and dried.

The crude product was chromatographed on a silica gel column using CH_2Cl_2 containing MeOH (5%) as eluent. The isolated yield of 7 was 180 mg (10%): m.p. 229–232°; UV/VIS λ_{max} ($CHCl_3$) 248 (log ε 4.50), 254 (4.58), 280 (3.95), 538 (3.33), 572 (3.45) nm; IR (KBr) 3050, 1725, 1690, 1675, 1590, 1455, 1350, 1310, 750 cm^{-1}; MS, *m/z* 364 (M + 1, 27), 363 (M, 100), 335 (58), 259 (24), 258 (20), 234 (10), 232 (12), 230 (12), 149 (17).

6,12-*Dihydro*-6-(*dicyanomethylene*)-12-*oxoindole*[2,1-b]-*quinazoline* (**9**). Tryptanthrin (2.48 g) was dissolved in dimethyl sulfoxide and malonodinitrile (0.66 g) was added. The mixture was warmed to 50° for 30 min and then poured into ice/water and collected: yield 1.95 g (66%): m.p. > 260°; IR (KBr) 2220 (C≡N), 1700, 1600, 1565, 1455, 1355, 1320, 780, 775, 685 cm^{-1}; MS, *m/e* 296 (M, 8), 271 (6), 178 (8), 162 (24), 146 (44), 130 (27), 119 (100), 104 (24).

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