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New Total Synthesis of Bikaverin

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Abstract: On the basis of non-catalysed thermal condensation of a Mannich base with a phenol, followed by dehydration to an o.quinonic chromene further isomerized to a p.quinonic one, the synthesis of bikaverin **7** has been achieved via a six-step route involving selective dealkylation of bikaverin-dimethylether **6**.

Bikaverin **7** is a naturally occuring pigment isolated from *Gibberella fujikuroi* and other fungi [1], and has a high cytotoxic activity.

Many methods have been developed for its synthesis [2]. The present paper describes a new approach, based on the seldom used[3] non-catalysed thermal condensation of the Mannich base **2** of 2-Hydroxy-5,7,8-trimethoxy-1,4-naphtoquinone **1** with orcinol monomethylether via the intermediate methylene-quinone.

2-Hydroxy-5,7,8-trimethoxy-1,4-naphtoquinone **1**[brown crystals, m.p.176° C, u.v./vis (EtOH) λ_{max}nm (log ε) 292(3.80), 495(3.60); M^+ 264; ^{1}H n.m.r.($CDCl_3$): 7,5,8 - OCH_3: 3.80 (s, 3H), 3.95 (s, 3H), 3.98 (s, 3H); 3-H: 6.20 (s, 1H); 7-H: 6.80 (s, 1H); 2-OH: 7.30 (s, 1H)] is prepared by condensation of 5,7,8-trimethoxy-α-tetralone with N, N-dimethyl-p.nitrosoaniline, following a standard set of reactions used for the synthesis of spinochrome D[4].

The Mannich base 2-Hydroxy-3- (N-piperidinomethylene)-5,7,8-trimethoxy-1,4-naphtoquinone **2** was obtained by reaction of **1** with formaldehyde and piperidine [brown crystals, m.p.160° C, M^+ 358, u.v./vis (EtOH) λ_{max}nm (log ε) 268 (3.80); ^{1}H n.m.r.($CDCl_3$): piperidine: 1.60 (m, 6H), 2.95 (m, 4H); 3-CH_2: 3.50 (s, 2H), 7,5,8- OCH_3: 3.83 (s, 3H), 3.95 (s, 3H), 3.98 (s, 3H); 2-OH: 6.40 (s, 1H); 7-H: 6.80 (s, 1H)].

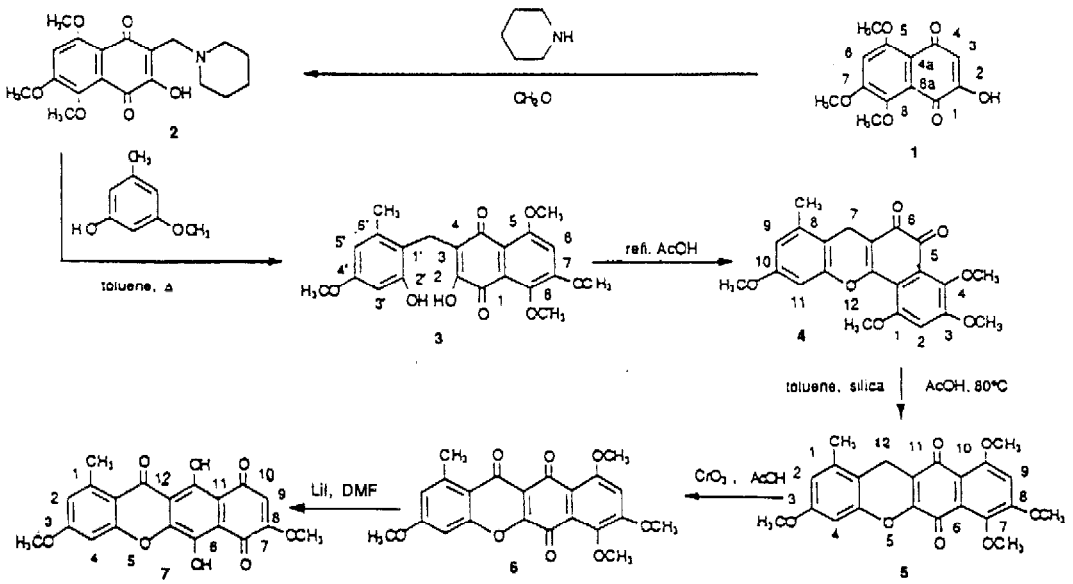
3 was obtained in a 40% yield by heating **2** one hour with 3-methoxy-5-methylphenol in refluxing toluene [orange needles, m.p.250° C(dec); u.v./vis (EtOH) λ_{max}nm (log ε) 234 (3.85), 267 (3.80); M^+ 412; ^{1}H n.m.r.($CDCl_3$): 3'-CH_3: 2.30 (s, 1H), 4',7,5,8- OCH3: 3.70 (s,3H), 3.80 (s,3H), 3.95 (s,3H), 3.98 (s, 3H), 2-OH: 6.30 (s,2H),7-H: 6.80 (s, 1H), 3-CH_2: 3.77 (s,2H), 5'-H: 6.55 (d,1H, J=2.5 Hz), 3'-H: 6.60 (d, 1H, J=2.5 Hz)].By heating 10 min at 110° C in anhydrous AcOH, **3** leads quantitatively to **4** which was characterized as an o.quinone by its u.v. spectrum and by condensation with ethylenediamine. [purple crystals, m.p. 230° C; u.v./vis (EtOH) λ_{max}nm (log ε): 245 (3.90), 268 (3.70), 340 (3.20), 400 (3.20, sh),500-540 (2.80); M^+ 396; ^{1}H n.m.r.($CDCl_3$): 8-CH_3: 2.20 (s,3H), 7-CH_2: 3.40 (s, 2H), 10,1,4,3- OCH3: 3.78 (s,3H), 3.80 (s,3H), 3.85 (s,6H), 11-H: 6.35 (d, 1H, J=2.5 Hz); 9-H: 6.45 (d, 1H, J=2.5 Hz), 2-H: 6.70 (s,1H)].

Isomerization of **4** to **5** was quantitatively carried out by treatment with a refluxing mixture toluene/AcOH

9:1 containing 20% silica, according to Kato's method[5] [yellow crystals, m.p. 220° C; u.v./vis (EtOH) λ_{max}nm (log ε): 230 (3.50), 270 (3.70), 400 (3.10, sh),500-520 (3.20); M^+ 396; ^{1}H n.m.r.($CDCl_3$): 1-CH_3: 2.38 (s, 3H), 12-CH_2: 3.62 (s,2H), 3,8,7,10- OCH3: 3.80 (s, 3H), 3.90 (s, 3H), 4.05 (s,3H), 4.07 (s,3H), 4-H: 6.55 (d, 1H, J=2.5 Hz),2-H: 6.60 (d, 1H, J=2.5 Hz), 9-H: 6.70 (s, 1H)].

Oxidization of chromene **5** to chromone **6** by usual reagents like cerium ammonium nitrate[6] or DDQ[7] was unsuccessful; it was achieved only in a 10% yield by chromium trioxide / AcOH[8] 2 min at 10° C . **6** was identified by comparison with Hauser's [2] authentic sample [orange crystals, m.p. 255° C (dec); u.v./vis (EtOH) λ_{max}nm (log ε):243 (4.85), 268 (4.50), 296 (3.40), 350 (3.20); M^+ 410; ^{1}H n.m.r.($CDCl_3$): 1-CH_3:280 (s, 3H), 3,8,7,10- OCH3: 3.89 (s,3H), 3.94 (s,3H), 3.98 (s, 3H), 4.00 (s, 3H), 4-H: 6.80 (d, 1H, J=2.5 Hz), 9-H: 6.85 (s,1H), 2-H: 6.90 (d, 1H, J=2.5 Hz)].

Selective dealkylation of **6** was carried out according to [2] by Li I / DMF and gave **7** which was identified with pure bikaverin by comparison of its data with those reported by Kjaer [1].



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