

THE NOVEL SELF-CONDENSATION OF A CHROMANONE IMINE TO  
FORM A DERIVATIVE OF 5H-2,3-BENZOPYRANO [4,5-b] PYRIDINE.

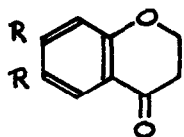
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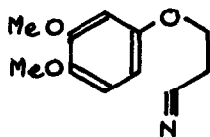
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In order to extend the enamine synthesis of pyrones<sup>1</sup> to certain pyranopyran derivatives we attempted to convert chroman-4-one (1) into the pyrrolidine enamine. There was no reaction during 24 h even with catalytic aids.<sup>2</sup> Chromanone also resisted imine formation with cyclohexylamine or aniline whether or not zinc chloride was present or refluxing *m*-cymene was used as solvent.<sup>3</sup> 6,7-Dimethoxychroman-4-one (2) resisted pyrrolidine with calcium chloride<sup>4</sup> or titanium IV chloride<sup>5</sup> catalysts, and also exposure to pyrrolidinium perchlorate.<sup>6</sup> Strongly basic conditions cannot be used because of ring opening and consequent side-reactions.

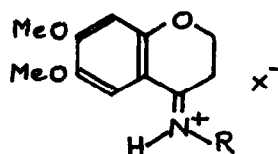
A chromanone imine was then obtained by another route. 3,4-Dimethoxyphenol (0.1 mole) and vinyl cyanide (0.6 mole) heated with sodium ( $4.5 \times 10^{-3}$  mole) for 5 h at 140° gave 2(3,4-dimethoxyphenoxy)ethyl cyanide (3), m.p. 59° (42%) (Found: C, 63.9; H, 6.4; N, 6.8%;  $\underline{M}$  (mass spectrum) 207.  $C_{11}H_{13}NO$ , requires C, 63.8; H, 6.3; N, 6.8%;  $\underline{M}$  207). The compound had  $\nu_{max}$  (mull) 2290 (CN)  $cm^{-1}$  and  $\tau$  (CDCl<sub>3</sub>) 6.15 (s, OCH<sub>3</sub>), 6.11 (s, OCH<sub>3</sub>), 7.23 (t, J 6.5 Hz; CH<sub>2</sub>CN), 5.85 (t, J 6.5 Hz; OCH<sub>2</sub>), and multiplets at 3.7-3.1 (3H; ArH). Electron release from the three ether oxygen atoms in this compound permits very easy electrophilic substitution. Accordingly, when the cyanide (1.32 g) in ether (200 ml; sodium dried) was saturated with hydrogen chloride at 0° it converted nearly quantitatively during 3 h into a yellow-green crystalline mass of 6,7-dimethoxychroman-4-one immonium chloride (4), m.p.



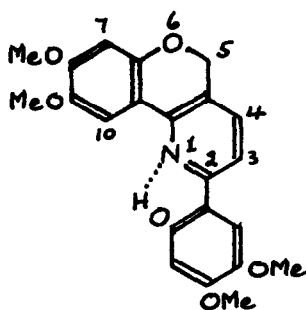
- (1) R = H  
(2) R = MeO



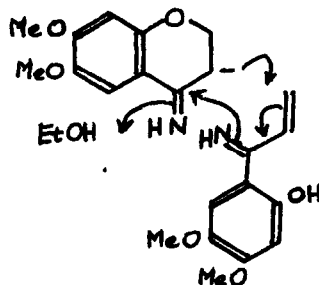
(3)



- (4) R = H; X = Cl  
(5) R = Me; X = I



(6)



(7)



(8)

234° (after charring at about 200°),  $\nu_{\max}$  (mull) 1643  $\text{cm}^{-1}$  ( $\text{O}=\text{N}^+$ ),  $\tau$  ( $\text{F}_3\text{CCO}_2\text{H}$ ) 5.98 ( $\text{OCH}_3$ ), 5.94 ( $\text{OCH}_3$ ), 6.72 (t,  $\underline{J}$  7 Hz;  $\text{OCH}_2\text{CH}_2$ ), 5.43 (t,  $\underline{J}$  7 Hz;  $\text{OCH}_2\text{CH}_2$ ), 3.33 (s,  $\text{ArH}$  at C(8)), 2.56 (s,  $\text{ArH}$  at C(5)), 1.06 (br,  $\text{NH}$  anti to Ar), and 0.67 (br.  $\text{NH}$  syn to Ar) (Found: C, 53.8; H, 6.1; N, 5.8.  $\text{C}_{11}\text{H}_4\text{ClNO}_3$  requires C, 54.2; H, 5.8; N, 5.8%). In the mass spectrometer the parent ion appeared to be that at  $m/e$  207 which corresponds to the imine base,  $\text{C}_{11}\text{H}_4\text{NO}_3$ . Treatment of the salt with water induced quantitative hydrolysis to the dimethoxychromanone (2) thus providing a better synthesis than that available previously?

Next, the imine salt (4) (0.24 g) was treated with iodomethane (2 ml) and sodium carbonate (0.11 g) in refluxing 1,2-dimethoxyethane (10ml; dried with  $\text{LiAlH}_4$ ) for 4 h. The product (81%) was 6,7-dimethoxychroman-4-one methyliminium iodide (6) m.p. 189° (charring),  $\nu_{\max}$  (mull) 1615  $\text{cm}^{-1}$  ( $\text{C}=\text{N}^+$  and aromatic) (Found: C, 41.0; H, 4.8; N, 3.7.  $\text{C}_{12}\text{H}_{16}\text{INO}_3$  requires C, 41.2; H, 4.6; N, 4.0%). The n.m.r. spectrum resembled that of (4) very closely but included a doublet ( $\underline{J}$  5Hz) at  $\tau$  6.48 ( $\text{NCH}_3$ ) and a broad multiplet at 0.10 ( $\text{NH}$ ). The mass spectrum indicated a parent ion at  $m/e$  222 corres-

ponding to the free base,  $C_{12}H_{15}NO_3$ . No isomer was noted, nor any dialkylation product. We attribute this to the steric hindrance offered by the aryl ring to a syn methyl group, and note that this effect would contribute to the resistance of chromanones to enamine formation with secondary amines.

For the alkylation a non-hydroxylic solvent is essential. In refluxing ethanol (8 ml) for 2 h, the salt (4) (0.20 g) reacts with sodium carbonate (0.50 g) evolving ammonia. The addition of iodomethane is immaterial and the product (61%) is 8,9-dimethoxy-2(2'-hydroxy-4',5'-dimethoxyphenyl)-5H-2,3-benzopyrano [4,5-b] pyridine (6) crystallising from ethanol in fine yellow needles, m.p.  $201^\circ$  (Found: C, 66.95; H, 5.34; N, 3.9.  $C_{22}H_{21}NO_6$  requires C, 66.8; H, 5.35; N, 3.5%). The phenolic group is very strongly hydrogen bonded so it could not be acetylated by standard methods, its band in the i.r. spectrum was very broad and shifted to  $2720\text{ cm.}^{-1}$ , and in the n.m.r. spectrum it resonated at  $\tau$  -4.5 (removed by deuteration). The n.m.r. spectrum also evidences four methoxyl groups (one at  $\tau$  6.05; three at 6.13), and four benzenoid protons (one at 3.50, one at 3.44, and two at 2.54; assigned to positions 3', 7, 10, and 6', respectively). The pyridine protons resonate at 2.81 and 2.57, and by analogy can be assigned to positions 3 and 4, respectively, though the coupling constant (4.7 Hz) is rather smaller than in simpler analogues. The cyclic methylene group produces a singlet at  $\tau$  4.86. The mass spectrum is that of an unusually stable compound, the molecular ion  $m/e$  395 and an ion  $m/e$  380 formed by loss of methyl providing the only marked features.

This information does not exclude certain related isomers but mechanistic considerations do. The base would convert the imine into a carbanion and then into an unsaturated imine, both shown in diagram (7), so that a Michael addition of one to the other could occur followed by cyclisation to (8). Ammonia would readily be eliminated and finally, by aerial oxidation, two hydrogen atoms as is usual with dihydropyridine derivatives.

References.

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