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REGIOSPECIFIC SYNTHESIS OF RUBRANINE

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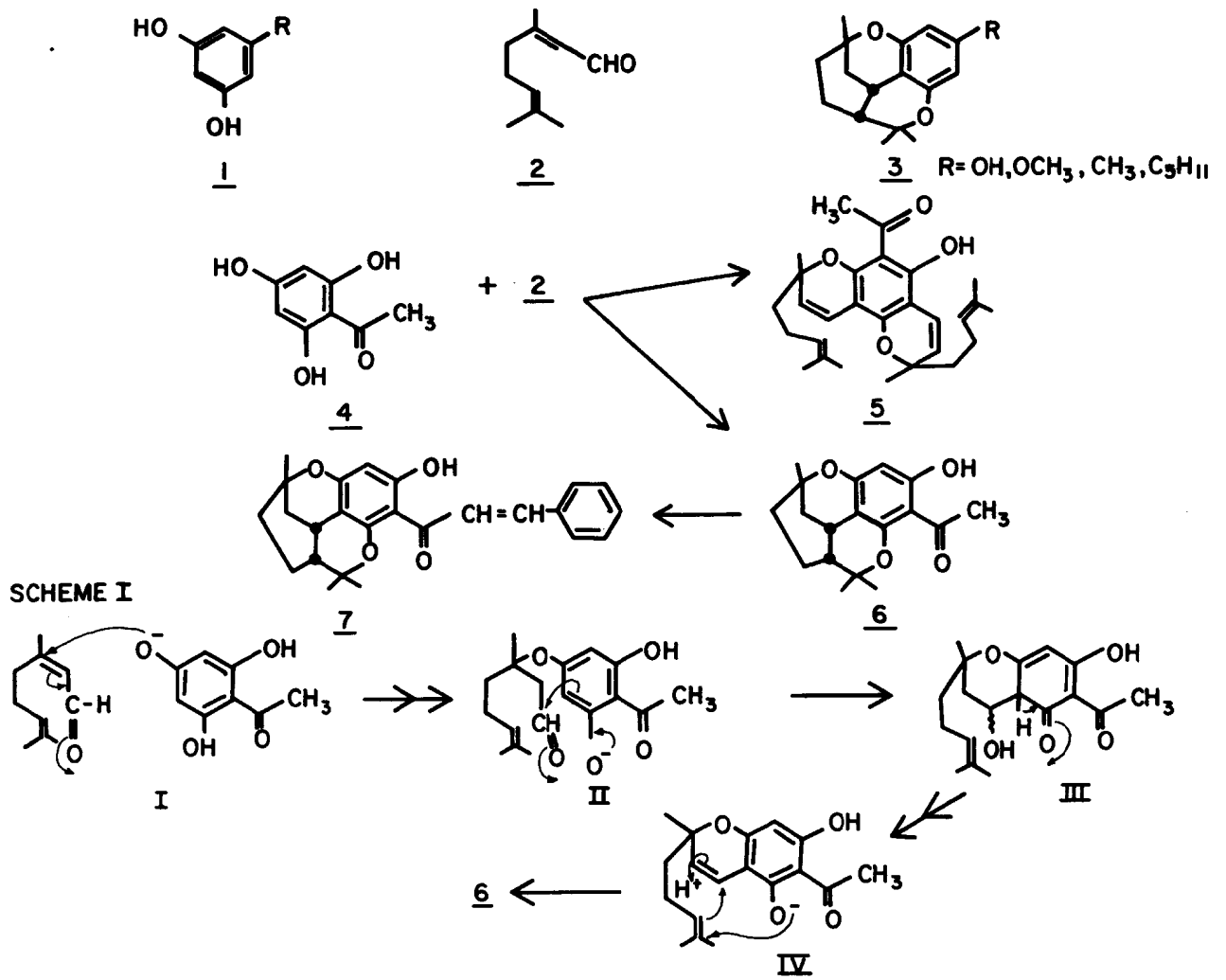
We have previously reported the pyridine catalyzed condensation between substituted resorcinols (1) and citral (2) to give various novel compounds depending upon the substitution on resorcinol. The reaction between phloroglucinol, phloroglucinol monomethyl ether[2], orcinol, olivetol (R = OH, OCH_3, CH_3, C_5H_{11}, respectively) and citral in pyridine results in the formation of tetracyclic ethers 3 as the constituent in largest yield. We have found that when one of the hydroxy group is intramoleculary hydrogen bonded to a carbonyl group no detectable quantity of tetracyclic ethers of type 3 is formed.[3] Similar results have also been reported by Crombie and his co-workers.[4]

We now wish to report in this communication that the reaction of phloroacetophenone (4) with citral (2) in pyridine provides a simple, regiospecific two-step synthesis of the naturally-occurring optically inactive chalcone rubranine (7) previously isolated from rose wood, Aniba rosaeodora (Ducke).[5,6] We have also observed that in the initial condensation a hydrogen bonded (chelated) hydroxyl group has participated in the formation of a tetracyclic ether (6) or in a fusion of a second citral unit to form an additional chromene ring as in (5).

We have found that heating equimolar quantities of 2, 4 and pyridine under reflux for 8 hr gave a mixture consisting mainly of two products, which was chromatographed on Florisil. Elution with 2:98 ether-petroleum ether (30-60°) gave in 18% yield, a yellowish oil homogenous on tlc, nmr ($CDCl_3$) δ 1.40 and 1.42 (6H, 2s, α to O-$\underline{CH_3}$), 1.56 and 1.64 (6H, each 2s, olefinic $\underline{CH_3}$), 2.60 (3H, s, CO-$\underline{CH_3}$), 4.95 and 5.06 (2H, broad m, olefinic H), 5.32 (2H, d, A part of AB quartet J_{AB}10Hz, 2 olefinic H), 6.61 (1H, d, B part of AB quartet J_{AB}10Hz, olefine H), 6.68 (1H, d, B part of AB quartet J10Hz, olefinic H), 13.91, s, OH, D_2O exchangeable); ir (CCl_4) ν_{max} 3200-3500 broad (OH), 1630 (aromatic), 1640 (C = O) cm^{-1}. The mass spectrum indicated a molecular weight of 436 corresponding to a 2:1 adduct of 2 and 4. The spectroscopic data for 5 makes the structural assignment secure.


HO
R
OH
1
CHO
2
O
R
O
3
R= OH, OCH3, CH3, C5H11
H3C
O
OH
HO
OH
CH3
O
OH
4
+ 2
O
O
5
O
OH
CH=CH
O
7
O
OH
CH3
O
6
SCHEME I
O⁻
OH
C-H
CH3
O
OH
O
I
O
OH
CH
CH3
O
O⁻
O
II
O
OH
CH3
H
OH
O
III
O
OH
CH3
H+
O⁻
O
IV
6

Elution with petroleum ether-ether (95:5 and 93:7) afforded a crystalline compound mp 140° in 66% yield which we considered to be tetracyclic ether 6, nmr ($CDCl_3$) δ 1.10, 1.37, 1.57 (9H, 3s, 3-CH_3), 2.61 (3H, s, $COCH_3$), 1.68 to 2.5 (7H, m, methylene and methine H), 2.75 (1H, m, benzylic H), 6.05 (1H, s, aromatic H), 13.33 (1H, s, OH, D_2O exchangeable), ir (KBr) ν_{max} 3200-3500 broad (OH), 1612 (C = O), 1582 (aromatic), 1160 and 1060 cm^{-1} (strong ether bands), uv λ_{max}^{EtOH} 233 (16229), 293 (19,275), 335, minimum at 255 nm. The mass spectrum confirms the molecular composition $C_{18}H_{22}O_4$ calcd. 302.1518, found 302.1516). In addition to the molecular ion peak, the mass spectrum showed principal ions 287 (M = 15), 259 and 219 (base peak). Further the uv, nmr and mass spectral data of the synthetic product 6 is in complete agreement with that of a degradation product of rubranine.[5] The phenolate anion is well known to participate as a donor in Michael type addition reactions.[7] Isolation of one single product 6 suggests that Michael addition of the phenolate anion to the α,β-unsaturated aldehyde precedes the C - C bond formation. If the C - C bond formation takes place first, then chromene formation could take place with the participation of either of the adjacent hydroxy groups, since some of the time two hydroxy groups are nearly chemically equivalent. Further, nucleophilic addition to the carbonyl group would be more facile when the aldehyde is saturated as in II than when it is unsaturated. We prefer this mechanism (scheme I) to those previously suggested by us[2b] and by Crombie and coworkers.[4d] We feel this mechanism may be operative in the formation of other chromenes. The mechanism is outlined in scheme I.

Aldol condensation of the tetracyclic ketone 6 with benzaldehyde in the presence of potassium hydroxide (30%) under controlled conditions, and after very careful workup, furnished a yellow solid mp 191° (100%), from which the pure compound could be isolated by crystallization from methanol as golden yellow crystals mp 193°, in 95% yield, homogenous by tlc, nmr ($CDCl_3$) δ 1.06, 1.38, 1.64 (9H, 3s, 3 - CH_3) 1.85 to 2.52 (7H, m, methine and methylene H), 2.74 (1H, m, benzylic H), 6.10 (1H, s, aromatic H), 7.40 (5H, m, s aromatic protons) 7.73 (1H, d, J16Hz CH = CH), 8.30 (1H, d J16Hz - CH = CH-), 13.92 (1H, s, OH, D_2O exchangeable), λ_{max}^{EtOH} 222 (26,500), 347 (26,500) inflexion at 320, and minimum at 260 nm, ν_{max} 3150-3600 (OH), 1634 (chelated unsaturated ketone) cm^{-1}. The mass spectrum confirms the molecular composition $C_{25}H_{26}O_4$ (m/e calcd. for $C_{25}H_{26}O_4$ 390.1831 found 390.1834) indicating 1:1 adduct of the tetracyclic ether and benzaldehyde. The uv, and nmr spectra were identical with those of natural rubranine;[5] and hence this work constitutes a regiospecific synthesis of this novel natural chalcone.

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