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THE STRUCTURE OF ERYTHROCULINE

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Isolations of several alkaloids from the bark and stem of Cocculus laurifolius DC have been reported by Tomita et al.[2] We explored the alkaloid constituents of the leaves of this plant and isolated a new alkaloid which was designated as erythroculine. Now, the structure establishment of erythroculine (I) is presented.

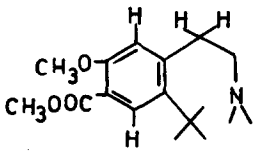
Erythroculine, oil, $[\alpha]_D$ +194° (c, 2.02, $CHCl_3$); λ_{max} 304 mμ (log ε 3.62)*, ν_{max} 1710 (C=O), 1610, 1495, 1580 cm^{-1} (aromatic ring); NMR τ, 2.51, 3.29 (each 1H, s, aromatic proton), 4.37 (1H, m, olefinic proton), 6.12 (6H, s, OCH_3), 6.71 (3H, s, OCH_3) crystallized as its styphnate, m.p. 193-6°, $C_{20}H_{25}O_4N.C_6H_3O_8N_3$.* Reduction of (I) with lithium aluminum hydride afforded erythroculinol (II), m.p. 150-2°, $C_{19}H_{25}O_3N$; $[\alpha]_D$ +210°(c, 1.02, $CHCl_3$); λ_{max} 280 (log ε 3.40), 284 mμ (log ε 3.41); ν_{max} 3600 cm^{-1}(OH); NMR τ, 3.05, 3.39 (each 1H, s, aromatic proton), 4.40 (1H, m, olefinic proton), 5.39 (2H, s, $-C\underline{H}_2-OH$), 6.14, 6.72 (each 3H, s, OCH_3). The presence of a carbomethoxyl group on a benzene ring in (I) was shown by comparison of the spectral data of (I) with those of (II).

Treatment of (I) with boron trichloride afforded a phenolic compound (III), oil, ν_{max} 3200 (OH), 1675 cm^{-1}(C=O), which was induced to the crystalline picrate, m.p. 205-7°, $C_{19}H_{23}O_4N.C_6H_3O_7N_3$. The remarkable bathochromic shift of the carbonyl band compared with that of (I) suggested that one of two methoxyl groups would be situated at an ortho position to the carbomethoxyl group. From the examinations of the NMR spectra of (I) and (II), the following deductions on the substitution pattern of the benzene ring were obtained. Thus, the appearance of two singlet signals at 3.29 and 2.51 τ, respectively, suggests that two benzene protons are situated in the para position, and the broad shape of the former indicates the

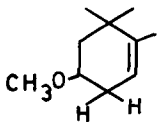
* Satisfactory elemental analysis data were obtained for all crystalline compounds and all UV spectra were measured in ethanol.

possibility of coupling between the proton of this signal and the benzylic proton.[3] Deuterium exchange experiment of (II) with D_2O-sodium hydroxide solution showed that the proton of the signal at 3.29 τ would be situated at the ortho position to a methoxyl group since the relative intensity of the signal concerned decreased by this treatment. Moreover, the sharp signal at 2.51 τ shows the absence of the benzylic proton to be coupled with the proton of this signal. The formation of erythroculinol methiodide, m.p. 226-7°, $[\alpha]_D$ +210° (c, 0.5, MeOH) and the lack of the signal due to NH in the i.r. and NMR spectra of (I) suggest that the nitrogen is tertiary. In the NMR spectrum, the methine base (V) showed the spectrum to be expected for the ABX spin system, 2.07 (1H, q, J 11, 18 cps), 4.77 (1H, q, J 11, 2 cps), 4.50 (1H, q, J 2, 18 cps). From the foregoing results, the partial structure around the benzene ring could be represented by the formula (A).

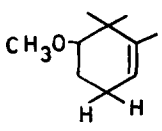
Catalytic hydrogenation of (I) over PtO_2 afforded dihydroerythroculine (VI) as the sole product, and no olefinic proton signal was observed in the NMR spectrum of (VI), and its UV spectrum revealed the maximum at 304 mμ where (I) showed the maximum suggesting that the trisubstituted double bond in (I) should be an isolated double bond.



(A)



(B)



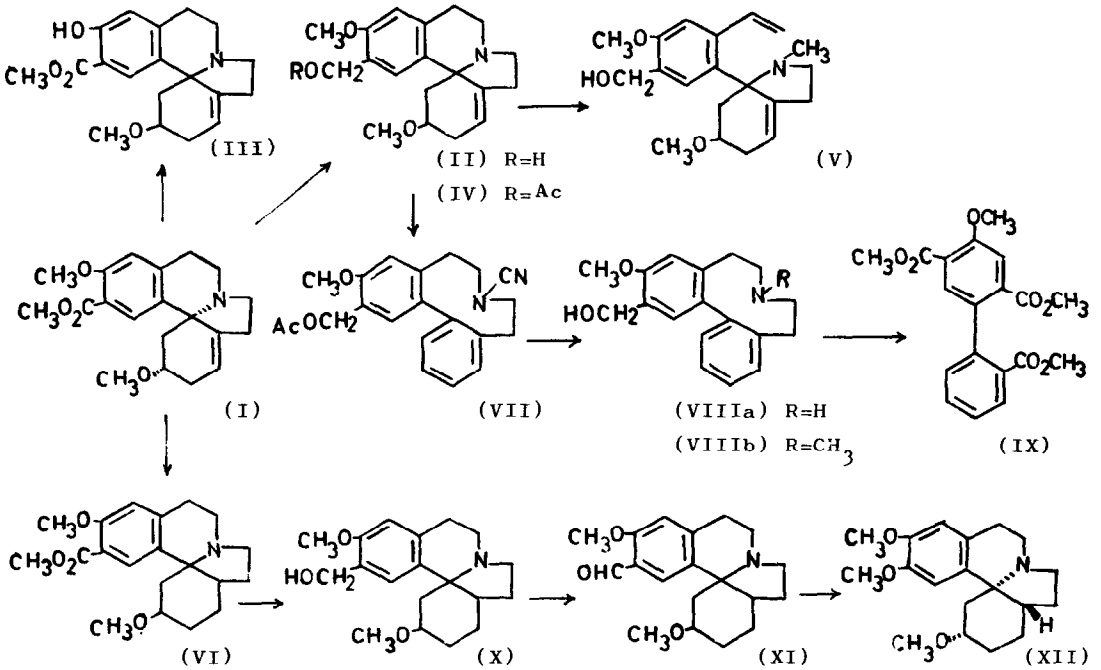
(B')

The information of the skeletal structure of (I) was obtained from the mass spectral observation. The spectrum of (II) showed the base peak ion at m/e 257 (M^+-58) which seems to arise from the cyclohexene ring with a methoxyl group by the retro Diels-Alder type fragmentation and is diagnostically important peak[4] for the erythrina alkaloids. Thus, the partial structure (B) or (B') is allocated to erythroculine.

Acetylation of (II) gave erythroculinol acetate (IV), oil, which was then submitted to von Braun degradation to give a cyano compound (VII), oil, λ_{max} 284 mμ (log ε 3.45); ν_{max} 2220 cm^{-1} (N-CN); NMR τ, 2.63-2.80 (4H) and 2.88, 3.23 (each 1H, s, aromatic proton), 6.58-6.85 (4H, m, benzylic methylene protons), 7.25-7.48 (4H, m, methylenes adjacent to N). The UV spectrum

revealed a characteristic absorption band for the hindered biphenyl chromophore, and in the NMR spectrum, four aromatic protons were newly observed and one of two methoxyl groups of (I) disappeared. These observations are well explained by assuming dehydrobromination and elimination of a methoxyl group from the von Braun degradation product to cause aromatization of the cyclohexene ring, and this type of reaction is one of the characteristic reactions for the erythrina alkaloids.[5] The signals at 6.58-6.85 and 7.25-7.48 τ (each 4H) are expected for the A_2B_2 spin system suggesting the intervention of two ethylene groups between the nitrogen and aromatic rings.

Reduction of (VII) with lithium aluminum hydride, followed by N-methylation afforded an N-methyl compound (VIIIb), oil, NMR τ, 7.68 (3H, s, $N\text{-}CH_3$) and its picrate, m.p. 209-212°, $C_{19}H_{23}O_2N.C_6H_3O_7N_3$, crystallized. The product from successive two times Hofmann degradations of (VIIIb) methohydroxide, without purification, was oxidized with potassium permanganate and esterification of the product gave 4-methoxy-2,5,2'-tricarbomethoxy biphenyl (IX) which was identified with a sample obtained through well established synthetic route**, by t.l.c., i.r., NMR spectral comparisons.



** The details of the synthesis of this compound will be reported in a full paper.

An attempt was then made by means of chemical correlation of (I) with tetrahydroerysotrine (XII)[6] to establish firmly the position of a methoxyl group on a cyclohexene ring and the stereochemistry of this alkaloid. Reduction of (VI) with lithium aluminum hydride gave dihydroerythroculinol (X), oil, which was oxidized with AgO to give an aldehyde (XI), oil, NMR τ, -0.4 (1H, s, -CHO), picrate, m.p. 219-220°, $C_{19}H_{25}O_3N.C_6H_3O_7N_3$, in good yield. Baeyer-Villiger oxidation with performic acid, followed by methylation with diazomethane resulted in the compound (XII), its picrate, m.p. 145-6° which was proved to be completely identical with an authentic sample of tetrahydroerysotrine picrate (Lit.[6] m.p. 153°) by m.m.p. and comparison of i.r. spectra.

Consequently, erythroculine is represented by the stereostructure (I). From the view point of biosynthesis of erythrina alkaloids, the carbomethoxyl group on the benzene ring in erythroculine is unusual and the isolation of this alkaloid makes the third report of erythrina alkaloids[7] in Cocculus species.

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