Crotsparinine, a Dihydroproaporphine Alkaloid from *Croton sparsiflorus*[1]

We recently reported the isolation of 2 proaporphine alkaloids, crotsparine and N, O-dimethyl crotsparine, from *Croton sparsiflorus* Morong[2]. Further search for new bases from this source has now yielded a new dihydroproaporphine alkaloid ($C_{17}H_{19}NO_3$), m.p. 184–185 °C, $(\alpha)_D + 215°$ (*c*, 2.37, $CHCl_3$); provisionally designated as crotsparinine.

Crotsparinine has been assigned the structure (I, R = Me; R′ = R″ = H). The presence of a secondary NH group, an –OH group and an enone system in the molecule was suggested by bands at 3485, 2890, 1665, 1604 and 1600 cm^{-1} in its IR-spectrum and by maxima at 228 nm (log ε, 4.28), and 285 nm (log ε, 3.10) in its UV-spectrum. The NMR-spectrum of crotsparinine revealed the presence of a methoxy group (τ 6.21) and confirmed the presence of the α,β-unsaturated ketone system which gives rise to an AB quartet at τ 3.88 and 3.06 (J_{AB},10 cps). The lone aromatic proton is responsible for a singlet at τ 3.5.

In the mass spectrum of the base, the molecular ion peak (M^+) is seen at m/e 285 and a M^{++} at m/e 142.5. Other significant peaks are at m/e 284, 256 and 223.

N-Methylation of crotsparinine with formaldehyde-formic acid yields N-methyl crotsparinine (I, R = R″ = Me, R′ = H) ($C_{18}H_{21}NO_3$), m.p. 160–161°, $(\alpha)_D + 244$ (*c*, 0.92, $CHCl_3$). This compound is isomeric with linearisine[3] (I, R′ = R″ = Me; R = H) and its mass spectrum (M^+, m/e 299; M^{++}, m/e 149.5 and similar fragmentation as observed with crotsparinine) and NMR-spectrum are in agreement with the structure (I, R = R″ = Me, R′ = H).

Crotsparinine, when treated with excess of methyl iodide in the presence of K_2CO_3 in acetone, gave N, O-dimethyl-crotsparinine methiodide, m.p. 239–241° identical with O-methyl linearine methiodide[4] and hydrogenation of N-methyl crotsparinine in the presence of Pd/C afforded N-methyldihydro crotsparinine ($C_{18}H_{23}NO_3$), m.p. 112–114°, identical with N-methyltetrahydro crotsparine (II). This compound has been obtained by reduction under similar conditions of N-methylcrotsparine[5]. Crotsparinine, therefore, has the structure I (R = Me, R′ = R″ = H)[6].

Zusammenfassung. Crotsparinin, ein neuer Vertreter der Proaporphine, wurde aus *Croton sparsiflorus* isoliert und seine Struktur aufgeklärt.

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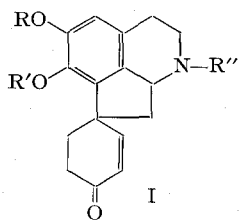
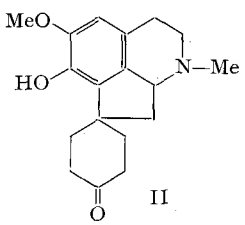
M. M. Dhar

Central Drug Research Institute,
Lucknow (India), 22 November 1968.



I



II

[1] Communication No. 1323 from the Central Drug Research Institute.
[2] D. S. Bhakuni and M. M. Dhar, Experientia *24*, 10 (1968).
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[5] D. S. Bhakuni and M. M. Dhar, unpublished data.
[6] We thank Dr. K. L. Stuart for a sample of linearisine and Dr. R. S. Kapil for mass spectra.

The Synthesis of Isohalfordin

In 1956, isohalfordin ($C_{14}H_{12}O_6$) was isolated, together with halfordin, from the bark of *Halfordia scleroxyla* F. Muell by Hegarty and Lahey[1]. The structure of isohalfordin was proposed as 3,5,6-trimethoxyfuro[2′,3′:7,8]coumarin (I) or 3,7,8-trimethoxyfuro[2′,3′:5,6]coumarin (II). Recently, on the basis of the NMR spectral analysis and degradative experiments, however, the revised structure was assigned as 3,4,8-trimethoxyfuro-[3′,2′:6,7]coumarin (III)[2]. In continuation of the syntheses of furocoumarin derivatives[3], the present paper will describe the total synthesis of III from 6,7-dihydroxy-2,3-dihydrobenzo[*b*]furan (IV)[4], confirming the revised structure of the natural compound.

Hoesch condensation of the benzofuran IV with methoxyacetonitril yielded 5-(ω-methoxyacetyl)-6,7-dihydroxy-2,3-dihydrobenzo[*b*]furan (V, m.p. 135–135.5°). The partial methylation of V with diazomethane gave 7-methoxy-derivative (V, m.p. 88–90°, IR 1625 cm^{-1} (Nujol). Found: C, 60.56; H, 5.98. $C_{12}H_{14}O_5$ requires: C, 60.50; H, 5.92%). By the procedure of Robertson's 4-hydroxycoumarin synthesis[5], the condensation of VI with ethyl carbonate in the presence of sodium gave 4′,5′-dihydrofuro[3′,2′:6,7]-3,8-dimethoxy-4-hydroxy-coumarin (VII, m.p. 175–176.5°, UV λ_{max}^{EtOH} nm (log ε): 244_{sh} (3.95), 295_{sh} (3.98), 319 (4.23), IR 3100_{sh}, 1700_{sh}, 1685, 1623, 1583 cm^{-1} (Nujol). Found: C, 58.82; H, 4.62. $C_{13}H_{12}O_6$ requires: C, 59.09; H, 4.58%) (Acetate of VII, m.p. 162.5–164°, IR 1775, 1712 cm^{-1} (Nujol)). Dihydroisohalfordin (VIII, m.p. 161.5–163°, UV λ_{max}^{EtOH} nm (log ε): 320 (4.21), IR 1690, 1623, 1587 cm^{-1} (Nujol). Found: C, 60.48; H, 5.14. $C_{14}H_{14}O_6$ requires: C, 60.43; H, 5.09%) was obtained by the methylation of VII. The dehydrogenation of VIII was carried out with 10% Pd-C in diphenyl ether giving a desired coumarin (III, m.p.

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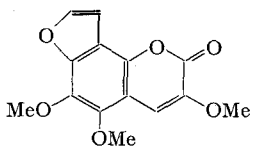

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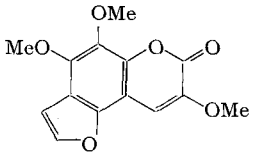

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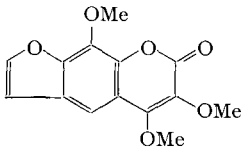
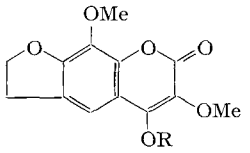
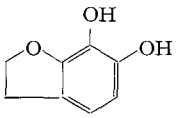


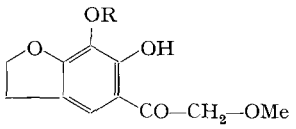
III



VII R = H
VIII R = Me



IV



V R = H
VI R = Me

153.5–155°, UVλ_{max}^{EtOH} nm (log ε): 240 (4.33), 245$_i$ (4.33), 259$_i$ (4.19), 299 (4.11), IR 1700, 1623, 1595 cm^{-1} (Nujol), NMR δ ppm: 7.79$_d$ (J = 2.5 Hz), 7.76$_s$, 6.90$_d$ (J = 2.5 Hz), 4.40$_s$, 4.31$_s$, 3.97$_s$ ($CDCl_3$). Found: C, 61.01; H, 4.41. $C_{14}H_{12}O_6$ requires: C, 60.87; H, 4.38%) (lit. m.p.[1] 151–152°, NMR[2] δ ppm: 7.76$_d$ (J = 2.5 Hz), 7.68$_s$, 6.88$_d$ (J = 2.5 Hz), 4.37$_s$, 4.30$_s$, 3.97$_s$). The properties of the synthetic III were in accordance with the reported ones[1,2] of the natural isohalfordin.

Zusammenfassung. Die Synthese von Isohalfordin (3,4,8-Trimethoxyfuro[3′,2′:6,7]cumarin) aus 6,7-Dihydroxy-2,3-dihydrobenzo[*b*]furan wird beschrieben.

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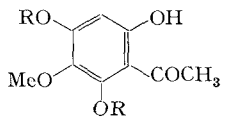
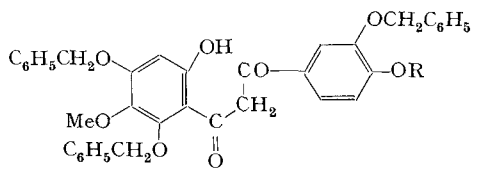
The Syntheses of 6-Methoxyluteolin and Desmethoxycentaureidin

Recently, 6-methoxyluteolin (5,7,3′,4′-tetrahydroxy-6-methoxyflavone) (I) and desmethoxycentaureidin (5,7,3′-trihydroxy-6,4′-dimethoxyflavone) (II) were isolated from *Rosmarinus officinalis* L.[1] and *Centaurea nigrescens* Willd.[2], respectively. These compounds have the closely related structures to axillarin and centaureidin. In previous papers[3], the authors reported the synthetic studies of the 5,7-dihydroxy-6-methoxyflavone derivatives. The present paper reports the syntheses of I and II from 3-methoxy-2,4,6-trihydroxyacetophenone (III)[4] via 2,4-dibenzyloxyl derivative (IV)[5].

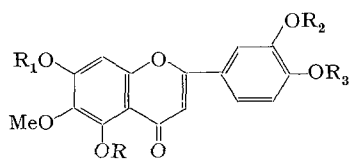
The ketone IV was esterified with 3,4-dibenzyloxybenzoyl chloride in the presence of anhydrous pyridine and then the resulting ester was converted to 4,6-dibenzyloxy-2-hydroxy-5-methoxy-ω-(3,4-dibenzyloxybenzoyl)-acetophenone (V, m.p. 136.5–137.5°. Found: C, 76.26; H, 5.47. $C_{44}H_{38}O_8$ requires: C, 76.06; H, 5.51%) by the BAKER-VENKATARAMAN transformation[6]. Cyclization of the diketone V with anhydrous sodium acetate in acetic acid afforded 5-hydroxy-6-methoxy-7,3′,4′-tribenzyloxyflavone (VI, m.p. 158–159° (143–145° sinter), UVλ_{max} nm (log ε): (EtOH) 242.5 (4.31), 277.5 (4.25), 337 (4.43); (EtOH-$AlCl_3$) 258.5 (4.21), 295 (4.28), 360 (4.38). Found: C, 75.98; H, 5.47. $C_{37}H_{30}O_7$ requires: C, 75.75; H, 5.16%). The debenzylation of VI with hydrogen gave the desired flavone (I, m.p. 264–266°, IR 3380, 1658, 1615, 1577, 1500 cm^{-1} (KBr), UVλ_{max} nm (log ε): (EtOH) 255 (4.21), 273 (4.21), 350 (4.42); (EtOH-AcONa) 276 (4.34), 366 (4.28). Found: C, 60.75; H, 3.63. $C_{16}H_{12}O_7$ requires: C, 60.76; H, 3.82%) (lit.[1], m.p. 258–262°, IR 3390, 1655, 1600, 1570, 1490 cm^{-1}, UV λ_{EtOH}^{max} nm: 256, 273, 348) (tetra-acetate: m.p. 202.5–203°, UV λ_{EtOH}^{max} nm (log ε): 265 (4.37), 302 (4.39). Found: C, 59.25; H, 4.44. $C_{24}H_{20}O_{11}$ requires: C, 59.50; H, 4.16%). Its triethyl derivative (VII, m.p. 152.5–153.5°, UVλ_{max} nm (log ε): (EtOH) 243.5 (4.26), 277 (4.15), 342 (4.42); (EtOH-$AlCl_3$) 261.5 (4.15), 293 (4.26), 368 (4.42). Found: C, 65.76; H, 6.18. $C_{22}H_{24}O_7$ requires: C, 65.99; H, 6.04%), obtained with diethyl sulfate, was also prepared from 2,4-diethoxy-3-methoxy-6-hydroxyacetophenone (VIII)[7] with 3,4-diethoxybenzoyl chloride via 6-methoxy-5,7,3′,4′-tetraethoxyflavone (IX, m.p. 142.5–143.5°. Found: C, 67.27;



III R = H
IV R = $C_6H_5CH_2$
VIII R = C_2H_5



V R = $C_6H_5CH_2$
X R = Me



I R = R_1 = R_2 = R_3 = H
II R = R_1 = R_2 = H, R_3 = Me
VI R = H, R_1 = R_2 = R_3 = $C_6H_5CH_2$
VII R = H, R_1 = R_2 = R_3 = C_2H_5
IX R = R_1 = R_2 = R_3 = C_2H_5
XI R = H, R_1 = R_2 = $C_6H_5CH_2$, R_3 = Me