THE STRUCTURE AND THE SYNTHESIS OF SEVANINE

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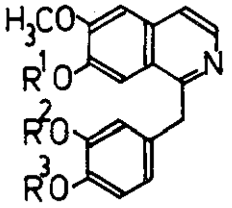
7-Hydroxy-6-methoxy-1-(3,4-methylenedioxybenzyl)-isoquinoline (II), which is identical with the alkaloid sevanine, was synthesized via two pathways.

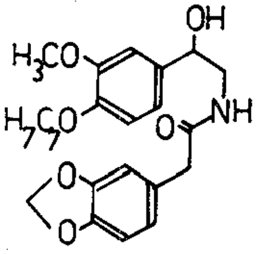
A short time back, a new alkaloid sevanine was isolated by us from Papaver macrostomum Boiss. et Huet (Papaveraceae). It was assigned[1] the structure 6,7-hydroxymethoxy-1-(3,4-methylenedioxybenzyl)isoquinoline on the basis of the UV, NMR and MS spectra. Methylation of sevanine with diazomethane gave the earlier described[2] 6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (I), mp 106-108°, NMR (δ, $CDCl_3$) 3.87s ($-OCH_3$), 3.97s ($-OCH_3$), 4.47s ($Ar-CH_2$), 5.82s ($O-CH_2-O$), 6.68bs (3H, Ar-H), 7.00s (1H, Ar-H), 7.27s (1H, Ar-H), 7.37d and 8.33d, J = 5.5Hz (3,4-H). For the determination of the location of the hydroxyl and methoxyl groups on the isoquinoline nucleus of sevanine, 7-hydroxy-6-methoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (II) was prepared.

Condensation of O-benzylvanillin with nitromethane in a solution of sodium methoxide gave 1-(4-benzyloxy-3-methoxyphenyl)-2-nitroethanol (yield 43%), mp 105-107°,[3] NMR (δ, $CDCl_3$) 2.87bs (CH-O$\underline{H}$), 3.87s (-OCH_3), 4.57m (-CH_2-NO_2), 5.13s (Ar-CH_2-O), 5.38m (-C$\underline{H}$(OH)-CH_2), 6.8-7.1m (3H, Ar-H), 7.3-7.5m (5H, Ar-H), which on reduction with $LiAlH_4$ afforded 28% of 2-amino-1-(4-benzyloxy-3-methoxyphenyl)ethanol (mp of acetate 128-136°), NMR of acetate (δ, DMSO-d_6) 1.90s (CH_3COO), 2.82m (2H), 3.87s (-OCH_3), 4.70m (5H), 5.15s (Ar-CH_2-O), 6.8-7.2m (3H, Ar-H), 7.48bs (5H, Ar-H). Reaction of this amine with 3,4-methylenedioxyphenylacetyl chloride yielded 1-(4-benzyloxy-3-methoxyphenyl)-2-(3,4-methylenedioxyphenylacetamido)ethanol (III) (yield 96%), mp 135-139°, NMR (δ, $CDCl_3$) 3.42s (-CO-NH), 3.2-3.6m (3H, one exchangeable D_2O), 3.82s (-OCH_3), 4.67m (-C$\underline{H}$(OH)-CH_2), 5.10s (Ar-CH_2-O), 5.90s (O-CH_2-O), 6.5-6.9m (6H, Ar-H), 7.1-7.5m (5H, Ar-H). UV (EtOH) λ_{max} 231 and 282 nm (logε 4.16 and 3.82). The cyclization of this amide with phosphorus oxychloride in toluene gave the 7-benzyloxy-6-methoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (IV) (yield 32%), mp 116-118°, NMR (δ, $CDCl_3$) 4.00s (-OCH_3), 4.38s (Ar-CH_2), 5.18s (Ar-CH_2-O), 5.85s (O-CH_2-O), 6.62bs (3H, Ar-H), 7.03s (1H, Ar-H), 7.2-7.6m (7H, Ar-H), 8.32d, J = 5.5Hz (3-H). Debenzylation of this compound with 20% hydrochloric acid produced 7-hydroxy-6-methoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (II) (yield 42%), mp 213-215°, which was found to be identical with natural sevanine.

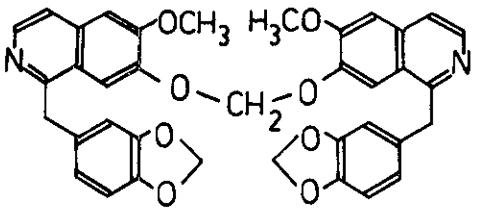
Sevanine (II) was also obtained by another route. Demethylation of papaverine with 47% hydrobromic acid afforded[4] the triphenol V. Reaction of this compound with methylene chloride and sodium hydroxide in dimethyl sulfoxide yielded 7-hydroxy-6-methoxy--1-(3,4-methylenedioxybenzyl)isoquinoline (II) (yield 10%). The major product of the reaction was the substance VI (yield 50%), mp 189-191°, NMR (δ, $CDCl_3$) 3.98s ($-OCH_3$), 4.40s ($Ar-CH_2$), 5.73s ($O-CH_2-O$), 5.85s ($Ar-O-CH_2-O-Ar$), 6.45d and 6.65d, J = 8.0Hz (Ar-H), 6.72s (Ar-H), 7.10s (Ar-H), 7.90s (Ar-H), 7.43d and 8.40d, J = 5.5Hz (3,4-H). UV (EtOH) λ_{max} 238, 287, 312 and 325 nm (log ε 5.10, 4.17, 3.84 and 3.81).



I $R^1 = CH_3$, $R^2 + R^3 = CH_2$
II $R^1 = H$, $R^2 + R^3 = CH_2$
IV $R^1 = C_7H_7$, $R^2 + R^3 = CH_2$
V $R^1 = R^2 = R^3 = H$



III



VI

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2 C. Mannich and O. Walther, Arch. Pharm., 1927, 265, 1; for the compound I reported mp 123°.

3 All the compounds gave correct elemental analyses; they had the correct molecular weight by mass spectrometry.

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