A ONE-STEP SYNTHESIS OF FICINE AND ISOFICINE

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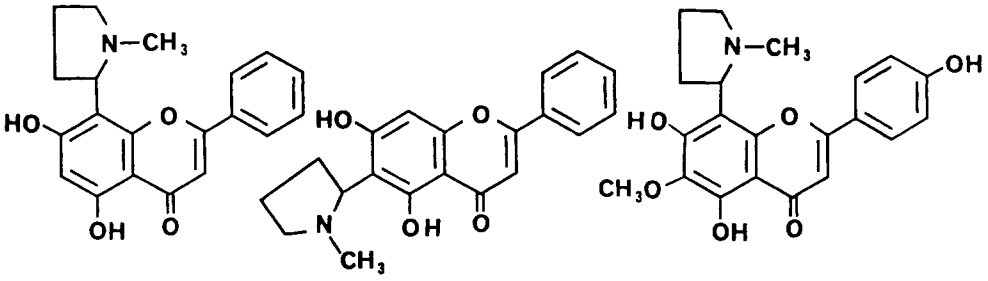
ABSTRACT.—Ficine and isoficine, flavonoidal alkaloids, have been synthesized by a one-step reaction between chrysin and *N*-methyl-Δ^1-pyrrolinium acetate. This synthesis is considered to be analogous to the proposed biosynthesis of these compounds in the plant.

Alkaloids which contain the flavonoid nucleus are rare; only three examples are known. In 1965 Johns *et al.* (1) found that the major base in *Ficus pantoniana* King is ficine (**1**) accompanied by small amounts of an isomer, isoficine (**2**). More recently, Takagi *et al.* (2) isolated phyllospadine (**3**) from the sea-grass *Phyllosphadix iwatensis*. No biosynthetic studies have been carried out on these alka-



(1) (2) (3)

loids; however, it seems probable that the immediate precursor of the *N*-methylpyrrolidine moiety of these alkaloids is the *N*-methyl-Δ^1-pyrrolinium salt (**4**). It is well established that this iminium salt is a precursor of the *N*-methylpyrrolidine rings found in nicotine (3,4) and the tropane alkaloids (5), and it is derived from ornithine (**5**). Thus, ring A of the flavone chrysin (**6**) is activated by the hydroxyl groups for electrophilic attack by the iminium salt at the C–6 or C–8 positions. Reaction at C–8 affords ficine, as illustrated in figure 1. Biomimetic syntheses (i.e., syntheses under "physiological conditions") of nicotine (6), brevicolline (7) and analogs of macrostomine (8) with the pyrrolinium salt **4** have been achieved.

(RS)-Ficine has been previously obtained by a nine-step synthetic sequence starting with 1,3,5-trimethoxybenzene (9). It has now been shown that the reaction of chrysin with the pyrrolinium salt **4** yields a (45:55) mixture of ficine and isoficine. Initial reactions were carried out in 5% aqueous acetic acid (pH = 2.6) at 25°. However, chrysin is only sparingly soluble in this solvent, and subsequent reactions were conducted in 90% acetic acid, which is admittedly not very physiological. Ficine and isoficine were readily separated from each other by tlc on silica gel. In the original publication on ficine and isoficine (1), the chirality of the alkaloids was not reported; however, S. R. Johns has informed me that the ficine as isolated was optically active with an $[\alpha]_D - 60°$. A sample of this ficine provided by Dr. Johns (Division of Applied Organic Chemistry CSIRO, Victoria, Australia) had uv, ms and chromatographic properties identical with the synthetic material. In contrast to earlier observations (1), we experienced no problems in obtaining a molecular ion in the mass spectrometer, possibly

[1]Contribution No. 181 from this laboratory. This paper is dedicated to Sir Jerry Price, a pioneer in the study of the natural products found in Australian plants, who celebrated his seventieth birthday on March 25, 1982.

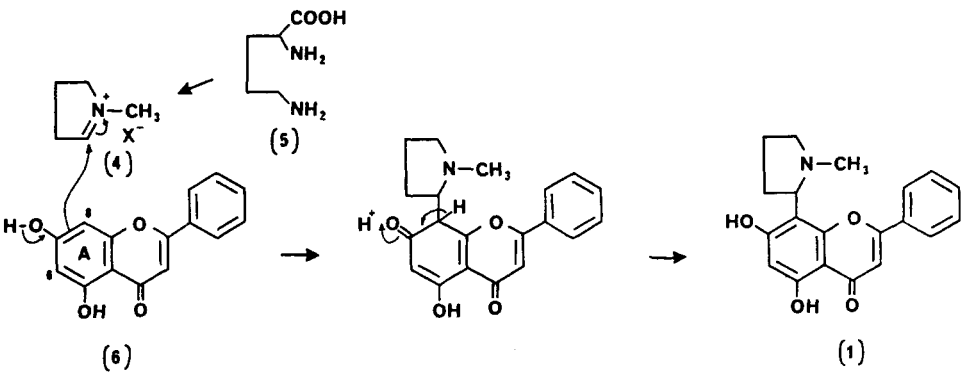


FIGURE 1. Proposed Biosynthesis of Ficine.

because a lower inlet temperature (200° rather than 290°) was used. No sample of isoficine was available for direct comparison. However, our synthetic sample of ficine equilibrated to a mixture of ficine and isoficine on heating with hydrochloric acid as previously described (1).

The pyrrolinium salt 4 was formerly obtained by the partial reduction of *N*-methyl-2-pyrrolidone with lithium aluminum hydride (4,10). We have found that better and more consistent yields of the iminium salt are obtained by treatment of the lactam with sodium aluminum hydride in refluxing ether (11) followed by quenching with acetic acid.

EXPERIMENTAL[2]

(*RS*)-FICINE AND ISOFICINE.—*N*-Methyl-2-pyrrolidone, dried over P_2O_5 and distilled, (198 mg, 2 mmol) was added to a suspension of sodium aluminum hydride (54 mg, 1 mmol) in ether (10 ml), and the mixture was refluxed for 2 h. The cooled reaction mixture was then added to ice (~30 g) and acetic acid (2 ml). The clear solution obtained after filtering through celite was assayed by uv spectroscopy. The absorption at 265 nm is characteristic for the *N*-methyl-Δ^1-pyrrolinium salt (4); the yield, based on an extinction coefficient (ϵ) of 2240, was >95%. This aqueous solution of the pyrrolinium acetate (50 ml) was added to a solution of chrysin (254 mg, 1 mmol) in acetic acid (500 ml), and the pale yellow solution was stirred for 7 days at room temperature. The solution was then evaporated to dryness at 25°, and the residue was made basic with aqueous ammonia and extracted with chloroform. The dried ($MgSO_4$) extract was evaporated, and the residue was subjected to tlc on several plates of silica gel PF-254 (Merck) developed with a mixture of chloroform, ethanol, and concentrated ammonia (90:10:1). Observation of the plate under uv light revealed unreacted chrysin (R_f 0.1–0.2) and two very narrow discrete zones at R_f 0.45. Natural ficine had the same R_f as the upper discrete zone. Good separation of these zones was achieved by developing the plates several times with the above solvent mixture. The zones were extracted by placing the scraped-off silica gel in a column and eluting with ethyl acetate (~500 ml). Extraction with boiling ethyl acetate in a Soxhlet caused some decomposition of the alkaloids. Evaporation of the ethyl acetate yielded ficine and isoficine. Assay of the products by uv spectroscopy indicated that the yields of ficine and isoficine were 12.0 mg (3.6%) and 14.6 mg (4.3%), respectively.

The synthetic (*RS*)-ficine was sublimed (150°, 10^{-4} mm), and it was obtained as pale yellow primsmatic needles, mp 243–244°, with some browning on melting (lit. (9) mp 233°). Its uv spectrum was identical with that of natural ficine, λmax (95% ethanol) 275 (Log ϵ 4.5), 327 nm (Log ϵ 4.0). These absorptions were shifted to 282 and 349 nm with a slight reduction in extinction coefficient when the solution was made basic with NaOH. The electron impact mass spectrum of this synthetic ficine and the natural alkaloid were almost identical. The fragmentation pattern obtained at 20 EV with an inlet temperature of 200° was as follows. In parentheses the relative intensities for the synthetic ficine and the natural alkaloid are recorded for all peaks greater than 10% of the parent peak at 337, which is the molecular ion ($C_{20}H_{19}NO_4$) *m/e*: 338 (synthetic: 25, natural: 29), 337 (100, 100), 336 (29, 29), 322 (9, 10), 309 (29, 30), 295 (19, 18), 294 (54, 48), 281 (13, 14), 280 (38, 39), 279 (27, 25), 268 (18, 17), 267 (18, 16), 105 (12, 10), 84 (97, 92-*N*-methylpyrrolinium ion), 83 (18, 10).

The (*RS*)-isoficine on sublimation (120°, 10^{-4} mm) was obtained as pale yellow rhombic crystals, mp 213–215° (lit (1) mp 168°); uv spectrum λmax (95% ethanol) 275 (Log ϵ 4.5), 231

[2]Mass spectra were determined by Dr. Roger Upham and his associate, Thomas L. Guggenheim, on an AEI-30 spectrometer. Uv spectra were determined on a Cary 17D spectrometer (purchased with NSF equipment grant CHE 78-23857). Melting points were determined on a microscope hot stage and are corrected.

nm (Log ϵ 4.0) with bathochromic shifts to 280 and 262 nm on the addition of NaOH. Mass spectrum (20 EV, inlet temp 125°) *m/e* (relative intensities): 338 (14), 337 (51), 323 (21), 322 (100), 305 (22), 294 (12), 281 (16), 280 (31), 279 (14), 254 (17-chrysin), 113 (14), 84 (11).

The synthetic ficine was heated with concentrated HCl in a sealed tube as previously described (1). Two compounds were observed when the reaction mixture was subjected to tlc. These compounds had the same R_f as ficine and isoficine previously obtained in the biomimetic synthesis.

Small amounts of ficine and isoficine were also produced when the reaction between chrysin and *N*-methyl-Δ^1-pyrrolinium acetate was carried out in 5% acetic acid. However, under these conditions most of the chrysin remained undissolved in the aqueous acetic acid.

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