An Efficient Synthesis of (±)-Latifine Dimethyl Ether

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4,5-Dimethoxy-3-(4′-methoxyphenyl)phthalide (**2**) was hydrogenolysed to give 3,4-dimethoxy-2-(4′-methoxybenzyl)benzoic acid (**3**). The *N*-methylamide of (**3**) was lithiated and treated with dimethylformamide to furnish 3,4-dihydro-3-hydroxy-5,6-dimethoxy-4-(4′-methoxyphenyl)-2-methylisoquinolin-1(2*H*)-one (**5**). Reduction of compound (**5**) with lithium aluminium hydride gave (±)-latifine dimethyl ether (**7**).

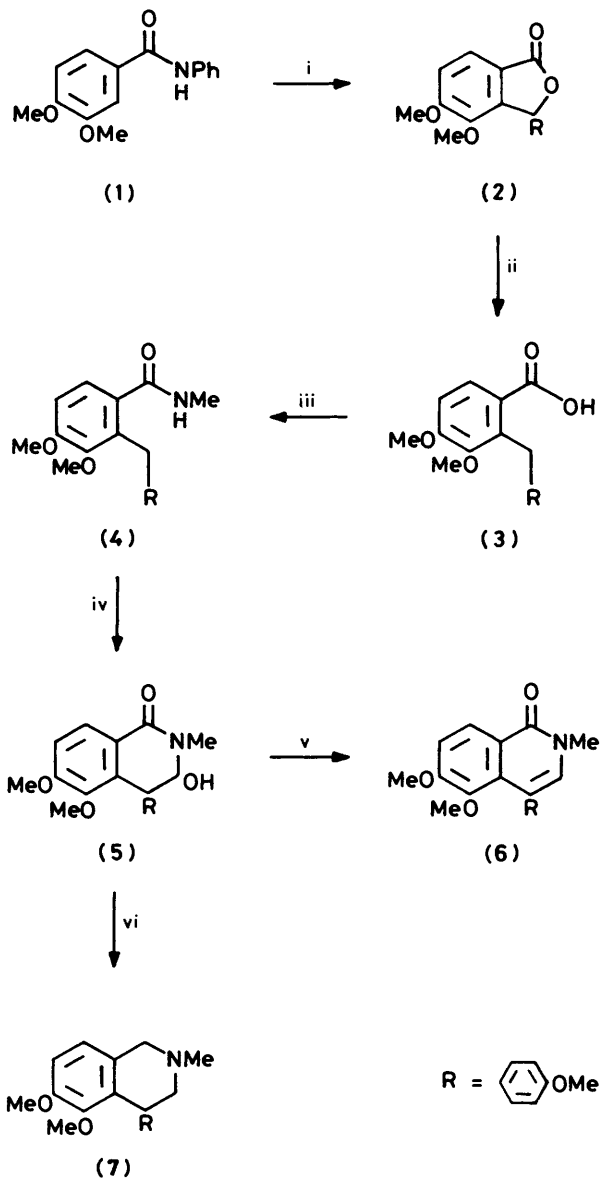
Latifine (**11**), an isoquinoline alkaloid, has been isolated from *Crinum latifolium L.*[1] and is reported to be a possible anabolic or catabolic metabolite of *O*,*N*-dimethylnorbelladine. Total syntheses of (±)- and (+)-latifine have been reported.[2–4]

Latifine has two novel features: i, it has a 4-aryl group in an isoquinoline system and ii, it is oxygenated at the less usual 5,6-positions. Because of these features, synthesis by the usual methods[5a,b] is difficult.

Recently we reported[6] a synthesis of cherylline, another of the rare 4-aryltetrahydroisoquinoline alkaloids, but oxygenated at the more usual 6,7-positions. This method was adaptable to the synthesis of latifine. The synthesis of (±)-latifine dimethyl ether is reported in this paper.

The key intermediate in the synthesis of latifine was 3,4-dimethoxy-2-(4′-methoxybenzyl)benzoic acid (**3**) which was conveniently obtained by the route shown in Scheme 1. Thus *N*-phenyl-3,4-dimethoxybenzamide was lithiated with butyllithium in ether, specifically at the 2-position.[7a,b] Addition of 4-methoxybenzaldehyde to the solution of the metallated amide furnished the 3-arylphthalide (**2**) in 70% yield. Hydrogenolysis of the phthalide (**2**) to 3,4-dimethoxy-2-(4′-methoxybenzyl)-benzoic acid (**3**) by H_2–Pd/C was not achieved under a variety of experimental conditions; however, with the Et_3SiH–CF_3CO_2H,[8] conversion in 88% yield was obtained. The acid (**3**) was converted into the *N*-methylamide (**4**) (76%) and lithiated with BuLi in ether. Further treatment with dimethylformamide gave a compound (72%), which (although not completely characterised) had i.r. and n.m.r. spectra (see Experimental section) consistent with the amidol structure (**5**). In conformity with this structure the compound was dehydrated to the isoquinolone (**6**), which had elemental analysis and spectral data as expected. The amidol was reduced with lithium aluminium hydride (LAH) in tetrahydrofuran (THF) to give (±)-latifine dimethyl ether (**7**) (66%).

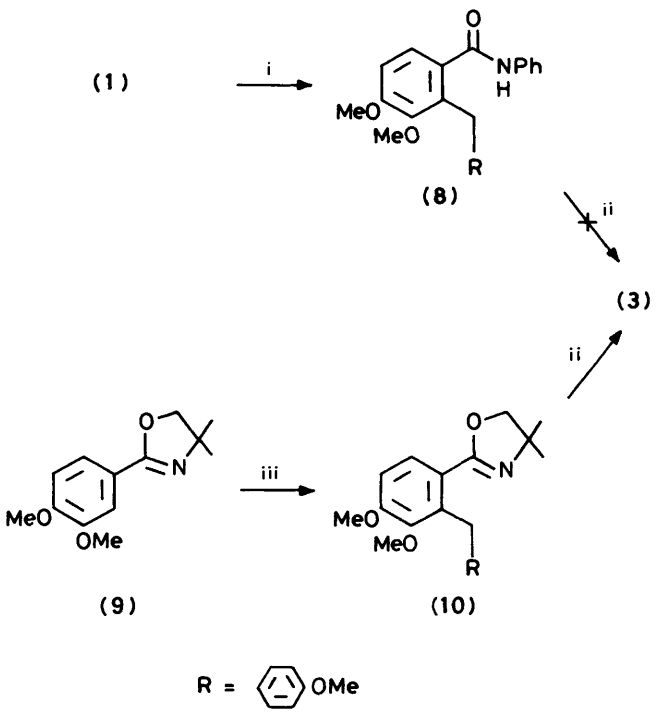
Direct preparation of the acid (**3**), by lithiation of the *N*-phenyl-3,4-dimethoxybenzamide (**1**) or the dihydro-oxazole derivative[9] (**9**) of 3,4-dimethoxybenzoic acid, followed by treatment with 4-methoxybenzyl bromide, and hydrolysis (Scheme 2) gave the 2-(4′-methoxybenzyl) derivatives (**8**) and (**10**) in 72 and 68% yield respectively. However, hydrolysis[10] of (**8**) to the acid (**3**) could not be achieved and hydrolysis of (**10**) proceeded in poor yields (22%). Introduction of the 4-methoxybenzyl group in the aromatic ring through lithiation of *N*-methyl-3,4-dimethoxybenzamide was also unsuccessful.



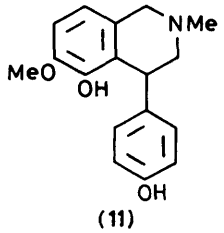
Scheme 1. *Reagents:* i, BuLi, TMEDA, 4-$MeOC_6H_4CHO$; ii, Et_3SiH, CF_3CO_2H; iii, $SOCl_2$ then $MeNH_2$; iv, BuLi, DMF; v, H_2SO_4; vi, $LiAlH_4$

Experimental

Capillary m.p.s were determined on Gallenkamp m.p. apparatus and are uncorrected. I.r. spectra were recorded for Nujol mulls on a Perkin-Elmer 337 instrument and ^1H n.m.r. spectra for solutions in deuteriochloroform on a Perkin-Elmer R-32 spectrometer with tetramethylsilane as an internal standard. Elemental analysis was performed on Hosli C, H analyser.



Scheme 2. *Reagents:* i, BuLi, TMEDA, 4-$MeOC_6H_4CH_2Br$; ii, HCl; iii, BuLi, 4-$MeOC_6H_4CH_2Br$



N-*Phenyl*-3,4-*dimethoxybenzamide* (**1**).—3,4-Dimethoxybenzoic acid (5.46 g, 30 mmol) was refluxed in thionyl chloride (7.5 ml, 100 mmol) at 80 °C for 2.5 h. The excess of thionyl chloride was distilled off to give the acid chloride (6 g, 100%) as a colourless solid which was thoroughly dried under reduced pressure. The acid chloride was dissolved in dry ether (25 ml) and added dropwise to a stirred solution of aniline (3.25 ml, 35 mmol) in 10% sodium hydroxide at 0 °C. The reaction mixture was stirred for 30 min and the precipitated amide filtered off, dried, and crystallised from ethanol to give the title compound (6.15 g, 82%) as colourless needles, m.p. 162—163 °C (lit.,[11a,b] 162—163 °C); $\nu_{max.}$(Nujol) 3 260 and 1 650 cm^{-1}; δ 3.9 (6 H, 2 × s, 2 × Me), 6.8 (1 H, d, *J* 9 Hz, 5-ArH), 7.1—7.5 (6 H, m, ArH), 7.7 (1 H, d, *J* 9 Hz, 6-ArH), and 8.8 (1 H, br s, exchangeable, NH) (Found: C, 69.85; H, 5.9. Calc. for $C_{15}H_{15}NO_3$: C, 70.03; H, 5.83%).

4,5-*Dimethoxy*-3-(4′-*methoxyphenyl*)*phthalide* (**2**).—Butyllithium in ether (0.6M, 66 ml, 40 mmol) was added dropwise to an ice-cold solution of *N*-phenyl-3,4-dimethoxybenzamide (**1**) (2.57 g, 10 mmol) in freshly distilled and dry THF (75 ml), in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (4.60 ml, 40 mmol) at 0 °C, and the red solution of the metallated amide stirred for 30 min. 4-Methoxybenzaldehyde (5.44 ml, 40 mmol) in THF (10 ml) was added dropwise. A colourless solution was obtained which was stirred for 2 h at 25 °C. The THF was evaporated under reduced pressure and the thick residue decomposed with conc. HCl until it became strongly acidic. This was extracted with methylene dichloride (3 × 50 ml), and the organic extract washed successively with water (2 × 50 ml), saturated aqueous hydrogen carbonate (2 × 50 ml), and brine (50 ml), dried (Na_2SO_4), and evaporated. The solid obtained was crystallised from methylene dichloride–methanol to give the *phthalide* (**2**) (2.1 g, 70%) as colourless flakes, m.p. 105 °C; $\nu_{max.}$(Nujol) 1 780 and 1 620 cm^{-1}; δ 3.42 (3 H, s, 4-OMe), 3.8 (3 H, s, 5-OMe), 4.0 (3 H, s, 4′-OMe), 6.5 (1 H, s, 3-H), 6.9 (1 H, d, *J* 9 Hz, 6-H), 7.2 (4 H, m, Ar′H), and 7.7 (1 H, d, *J* 9 Hz, 7-H) (Found: C, 67.8; H, 5.45. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%).

3,4-*Dimethoxy*-2-(4′-*methoxybenzyl*)*benzoic Acid* (**3**).—The phthalide (**2**) (3.0 g, 10 mmol) was stirred with triethylsilane (4.0 ml, 25 mmol) and trifluoroacetic acid (5.0 ml, 130 mmol) at 25 °C for 24 h. The reaction mixture was decomposed with water (15 ml) and extracted with methylene dichloride (3 × 25 ml). The combined extracts were washed thoroughly with water (2 × 50 ml), dried (Na_2SO_4), and evaporated. The solid obtained was crystallised from methylene dichloride–hexane to give the *title compound* (2.65 g, 88%) as granules, m.p. 126 °C; $\nu_{max.}$(Nujol) 1 690 and 2 800—3 300br cm^{-1}; δ 3.55 (3 H, s, 3-OMe), 3.65 (3 H, s, 4′-OMe), 3.85 (3 H, s, 4-OMe), 4.4 (2 H, s, $-CH_2-$), 6.65 (4 H, m, Ar′H), 6.95 (1 H, d, *J* 9 Hz, 5-H), 7.75 (1 H, d, *J* 9 Hz, 6-H), and 9.5 (1 H, br, exchangeable, $-CO_2H$) (Found: C, 67.75; H, 6.0. $C_{17}H_{18}O_5$ requires C, 67.54; H, 6.0%).

N-*Methyl*-3,4-*dimethoxy*-2-(4′-*methoxybenzyl*)*benzamide* (**4**).—The acid (**3**) (3.0 g, 10 mmol) was dissolved in freshly distilled dry THF (15 ml), thionyl chloride (2.2 ml, 30 mmol) was added at 0 °C and the mixture stirred for 30 min then brought to room temperature. Stirring was continued for a further 30 min after which the excess of thionyl chloride and THF was removed under reduced pressure to give thick red liquid. This was dissolved in dry ether (10 ml) and added slowly to an ice-cold aqueous solution of *N*-methylamine (30 ml, 35% w/v). The precipitated amide was extracted with methylene dichloride (3 × 30 ml). The combined extracts were washed with 2M HCl (3 × 20 ml), water (3 × 20 ml), and brine (20 ml), dried (Na_2SO_4), and concentrated to give a solid which was crystallised from methylene dichloride–hexane to give the *title compound* (2.6 g, 76%) as a colourless powder, m.p. 145—147 °C; $\nu_{max.}$(Nujol) 1 645 and 3 270 cm^{-1}; δ 2.7 (3 H, d, *J* 5 Hz, NHMe), 3.6 (3 H, s, 3-OMe), 3.75 (3 H, s, 4-OMe), 3.8 (3 H, s, 4′-OMe), 4.2 (2 H, s, $-CH_2-$), 5.6 (1 H, br s, exchangeable, NH), 6.6—6.95 (5 H, m, ArH and Ar′H), and 6.98 (1 H, d, *J* 9 Hz, 6-H) (Found: C, 68.65; H, 6.7. $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.71%).

3,4-*Dihydro*-3-*hydroxy*-5,6-*dimethoxy*-4-(4′-*methoxyphenyl*)-2-*methylisoquinolin*-1(2H)-*one* (**5**).—The *N*-methylbenzamide (**4**) (630 mg, 2 mmol) was dissolved in freshly distilled and dry THF (30 ml) and cooled to 0 °C. Butyl-lithium in ether (0.6M, 10 ml, 6 mmol) was added to give a blood-red solution of the metallated amide. This was stirred for 30 min then dry dimethylformamide (DMF) (0.5 ml, 6 mmol) was added in one portion. The reaction mixture became colourless. The solution was stirred for a further 30 min, THF was evaporated under reduced pressure, and the thick yellowish residue was decomposed with water and extracted with ether (3 × 25 ml). The combined ether extracts were washed with water (2 × 25 ml) and brine (25 ml), and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a thick yellow liquid which was washed with hot hexane to give the title compound (490 mg, 72%); $\nu_{max.}$(Nujol) 1 650 and 3 000—3 400br cm^{-1}; δ 2.9 (3 H, s, NMe), 3.3 (3 H, s, 5-OMe), 3.6 (3 H, s, 6-OMe), 3.7 (3 H, s, 4′-OMe), 4.45 (1 H, br s, 4-H), 4.8 (1 H, br s, 3-H), 6.5—6.85 (5 H, m, ArH), and 7.6 (1 H, d, *J* 9 Hz, 8-H).

5,6-*Dimethoxy*-4-(4′-*methoxyphenyl*)-2-*methylisoquinolin*-1(2H)-*one* (**6**).—The compound (**5**) (160 mg, 0.46 mmol) was dissolved in THF (2 ml) and stirred with 1M H_2SO_4 (2 ml) at room temperature for 30 min. Water (10 ml) was added and the mixture extracted with ether (3 × 10 ml). The combined ether extracts were washed with water (15 ml) and brine (15 ml), dried (Na_2SO_4), and concentrated to give a solid which was crystallised from ether–hexane to give the *title compound* (130 mg, 80%), m.p. 129—132 °C; $\nu_{max.}$(Nujol) 1 610 and 1 650 cm^{-1}; δ 3.1 (3 H, s, NMe), 3.5 (3 H, s, 5-OMe), 3.8 (3 H, s, 6-OMe) 3.9 (3 H, s, 4′-OMe), and 6.7—7.2 (7 H, m, ArH) (Found: C, 70.05; H, 6.05. $C_{19}H_{19}NO_4$ requires C, 70.14; H, 5.89%).

(±)-*Latifine Dimethyl Ether* (**7**).—Compound (**5**) (345 mg, 1 mmol) was added to a suspension of lithium aluminium hydride (LAH) (160 mg, 4.3 mmol) in freshly distilled and dry THF (10 ml) and the suspension stirred under reflux for 30 min. The solution was cooled to 0 °C, ether (25 ml) saturated with water was slowly added, and stirring was continued for a further 10 min. The ether layer was decanted off and the sticky mass washed with ether and methylene dichloride several times (total volume 100 ml). The organic layer was washed with water (25 ml) and dried (Na_2SO_4). The thick brown coloured residue obtained after evaporation of solvent was purified by flash chromatography over silica gel (finer than 200 mesh), with chloroform–ethanol (97:3) as eluant and crystallised from methylene dichloride–hexane to give the *title compound* (230 mg, 66%) as red crystals, m.p. 87—88 °C; $\nu_{max.}$(Nujol) 1 620 cm^{-1}; δ 2.3 (3 H, s, NMe), 2.67 (2 H, d, *J* 5 Hz, 3-H_2), 3.15 (3 H, s, 5-OMe), 3.75 (3 H, s, 6-OMe), 3.8 (3 H, s, 4′-OMe), 3.3 and 3.8 (each 1 H, d, *J* 13 Hz, 1-H_2), 4.2 (1 H, t, *J* 5 Hz, 4-H), 6.7 (4 H, m, Ar′H), 7.05 (2 H, d, *J* 9 Hz, 7-, 8-H) (Found: C, 72.6; H, 7.4. $C_{19}H_{23}NO_3$ requires C, 72.82; H, 7.40%).

N-*Phenyl*-3,4-*dimethoxy*-2-(4′-*methoxybenzyl*)*benzamide* (**8**).—*N*-Phenyl-3,4-dimethoxybenzamide (**1**) (2.57 g, 10 mmol) was dissolved in freshly distilled and dry THF (75 ml) and BuLi in ether (0.6M, 66 ml, 40 mmol) was added dropwise at −5 °C in the presence of TMEDA (4.6 ml, 40 mmol). The metallated mixture was stirred for 30 min and treated with 4-methoxybenzyl bromide (8.04 g, 40 mmol). The reaction mixture was allowed to reach room temperature slowly within 1.5 h. Work-up and purification gave the *title compound* (2.9 g, 72%), m.p. 148—149 °C (needles from ethanol); $\nu_{max.}$(Nujol) 1 650 and 3 280 cm^{-1}; δ 3.7 (6 H, s, 3-, 4-Me), 3.8 (3 H, s, 4′-OMe), 4.15 (2 H, s, $-CH_2-$), and 6.65—7.3 (12 H, m, ArH and NH) (Found: C, 73.4; H, 6.25; $C_{23}H_{23}NO_4$ requires C, 73.19; H, 6.14%).

4,5-*Dihydro*-2-(3′,4′-*dimethoxyphenyl*)-4,4-*dimethyloxazole* (**9**).—3,4-Dimethoxybenzoic acid (2.7 g, 15 mmol) was converted into the dihydro-oxazole derivative (2.25 g, 96%) by a reported procedure;[9] $\nu_{max.}$(Nujol) 1 640 cm^{-1}; δ 1.25 (6 H, s, 4-Me × 2), 3.8 (6 H, s, 3′-, 4′-OMe), 3.95 (2 H, s, $-OCH_2-$), 6.7 (1 H, dd, *J* 9, 2 Hz, 5′-H), 7.3 (2 H, m, 2′-, 6′-H) (Found: C, 66.76; H, 7.44; $C_{13}H_{17}NO_3$ requires C, 66.38; H, 7.23%).

4,5-*Dihydro*-2-[3,4-*dimethoxy*-2-(4′-*methoxybenzyl*)*phenyl*]-4,4-*dimethyloxazole* (**10**).—The dihydro-oxazole (**9**) (1.18 g, 5 mmol) was dissolved in dry ether (5 ml) and BuLi in ether (0.6M, 16 ml, 10 mmol) was added at room temperature upon which the reaction mixture became red in colour. The solution of the metallated dihydro-oxazole was cooled to −5 °C for 15 min then treated with 4-methoxybenzyl bromide (2.01 g, 10 mmol). The reaction mixture became colourless. The mixture was stirred for 30 min, and, after work-up and purification by flash chromatography [silica gel finer than 200 mesh, EtOAc–benzene (12:88) as eluant] the *title compound* (1.1 g, 68%) was obtained as a thick red oil; $\nu_{max.}$(Nujol) 1 650 cm^{-1}; δ 1.1 (6 H, s, 4-Me × 2), 3.4 (3 H, s, 3′-OMe), 3.5 (3 H, s, 4′-OMe), 3.7 (5 H, s, 2′-OMe and $-OCH_2-$), 4.3 (2 H, s, dibenzyl $-CH_2-$), 6.45—6.9 (5 H, m, ArH), and 7.35 (1 H, d, *J* 9 Hz, 6′-H) (Found: C, 70.75; H, 7.10. $C_{21}H_{25}NO_4$ requires C, 70.96; H, 7.09%).

3,4-*Dimethoxy*-2-(4′-*methoxybenzyl*)*benzoic Acid* (**3**) *from Dihydro-oxazole* (**10**).—Compound (**10**) (1 g, 3.3 mmol) was stirred in 5M HCl (25 ml) at 130 °C for 12 h after which the reaction mixture was made basic by $NaHCO_3$ and extracted with ether. The ether extract gave the unchanged compound (**10**). The basic aqueous layer was made acidic with conc. HCl and extracted with ethyl acetate (2 × 15 ml). The combined ethyl acetate extracts were washed with water (15 ml) and brine, and evaporation of the solvent gave the acid (**3**) which was crystallised from methylene dichloride–hexane to give pure (3) (22%), identical with the compound described earlier.

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References

1 S. Kobayashi, T. Tokumoto, and Z. Taira, *J. Chem. Soc., Chem. Commun.*, 1984, 1043.
2 S. Takano, M. Akiyama, and K. Ogasawara, *Chem. Lett.*, 1985, 505.
3 S. Takano, M. Akiyama, and K. Ogasawara, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2447.
4 (*a*) S. Kobayashi, T. Tokumoto, S. Iguchi, M. Kihara, Y. Imakura, and Z. Taira, *J. Chem. Res.*, 1986, (*S*), 280; (*M*), 2447.
5 (*a*) W. M. Whaley and T. R. Govindachari, *Org. React.*, 1951, **6**, 74, 151; (*b*) W. J. Gensler, *ibid.*, 1961, **6**, 191.
6 N. S. Narasimhan and P. A. Patil, *J. Chem. Soc., Chem. Commun.*, 1987, 191.
7 (*a*) J. P. Rizzi and A. S. Kende, *Tetrahedron*, 1984, **40**, 4693; (*b*) J. E. Baldwin and K. W. Bair, *Tetrahedron Lett.*, 1978, **29**, 2559.
8 D. N. Fursanov, Z. N. Parnes, and N. M. Loim, *Synthesis*, 1974, **9**, 633.
9 G. E. Maciel, M. P. Shatlock, R. A. Houtchens, and W. S. Coughey, *J. Am. Chem. Soc.*, 1980, **102**, 6885.
10 C. R. Ellefson, *J. Org. Chem.*, 1979, **44**, 1533.
11 (*a*) H. Suzuki, J. Tsuji, Y. Hiroi, N. Sato, and A. Osuka, *Chem. Lett.*, 1983, 449; (*b*) V. Joshi, S. S. Jalisatgi, and M. I. Hari, *Indian J. Chem., Sect. B*, 1986, **25**, 83.

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