69. Aromatization of 1-Benzyltetrahydroisoquinolines: Racemization of (−)-(*S*)-(*N*-nor)-Reticuline

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Dedicated to Prof. *Yoshio Ban* on the occasion of his 60th birthday

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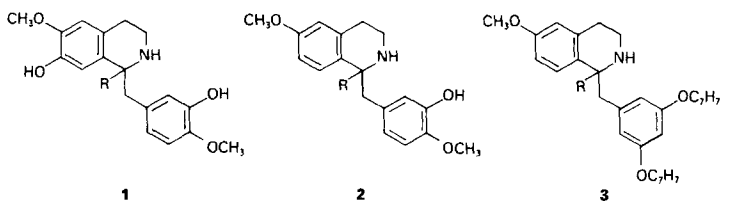
Summary

Aromatization in the series of optically active 1-benzyltetrahydroisoquinolines has been accomplished with (−)-(*S*)-(*N*-nor)-reticuline (**1b**) and analogs. Direct catalytic or chemical reduction of the isoquinoline **4** obtained could not be achieved in a practical way but **4** was converted into **1** in three steps (**4**→**8**→**9**→**1**), in 55% overall yield. Partial *O*-methylation of the isoquinoline **4** gave the isoquinoline alkaloid palaudine (**5**), before papaverine (**6**) was formed.

The optically active 1,2,3,4-tetrahydroisoquinolines (TIQ) **1a** [1] and **2a** [2] [3] are key intermediates in total syntheses of natural opium alkaloids [2–4]; and **3a**, its corresponding diphenol (H instead of C_7H_7) or ether analogs (CH_3 instead of C_7H_7), will ultimately be needed for a total synthesis of (−)-3-deoxydihydromorphine [5], already accomplished with racemic material [4] [6]. TIQ **1a** and **2a** were obtained by chemical resolution, affording besides the wanted (+)-(*R*)-enantiomers **1a** and **2a** almost equal amounts of the unwanted (−)-(*S*)-enantiomers **1b** and **2b**.

Scheme 1



a - Series : R= ⁻H (*R*-config.)
b - Series : R= ⁻⁻⁻H (*S*-config.)

We now demonstrate that the unwanted (−)-(*S*)-(*N*-nor)-reticuline (**1b**) can be converted into the racemic **1** by aromatization of the TIQ system, as in the octahydroisoquinoline series [7]. Heating **1b** or **1** in toluene in the presence of

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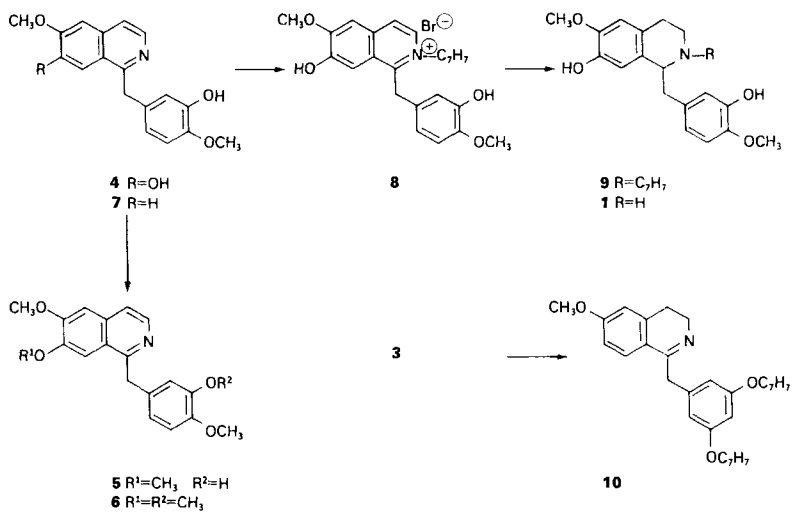
Scheme 2



Pd/C gave the aromatic isoquinoline **4** (85–95%). The isoquinoline structure of **4** was evident from its spectral properties (see exper. part), but could also be corroborated by *O*-methylation with ethereal diazomethane in methanol. In this methylation the trimethyl-ether alkaloid palaudine (**5**) was formed before papaverine (**6**). The successful partial *O*-methylation of **4** could be monitored by TLC., and the phenolic group methylated first shown to be at C(7) (pKa_2 9.0), as evidenced by a comparison of the p*K*a-values measured for the phenolic groups in **4**, **5** and **7**[1]).

Similar dehydrogenation of **2b** afforded the aromatic monophenol **7** (97%). Dehydrogenation of the dibenzyloxy-TIQ **3** gave a complex mixture, chromatography of which afforded in 16% yield the 3,4-dihydroisoquinoline **10**, easily reduced to **3** with sodium borohydride in methanol. Although conversion of optically active TIQ **3** into the racemate seems feasible *via* 3,4-dihydroisoquinoline intermediates [8], the present procedure does not seem suitable for this purpose.

Catalytic hydrogenation, successful with papaverine (**6**) [9], was unusually difficult with **4**. The results (see *Table*), together with the finding that **1** produced a variety of products when left in acetic acid over Pt under H_2, makes unlikely a high yield for the catalytic reduction of **4** to **1**. Similar difficulties were encountered in the reduction of **4** with sodium in liquid ammonia at $-78°$ [10] and with sodium in alcohols [7]. Partial conversion of **4** into **1** by treatment with sodium in boiling propanol or butanol (but not ethanol, see *Table*) was detected by TLC. analysis. Again, isolation of the diphenol **1** in good yield from these mixtures will be difficult and attempts to pursue this line were abandoned.

[1]) The p*K*a were determined by Dr. *V. Toome*, Hoffmann-La Roche, Inc., Nutley, New Jersey, by measurement of UV. absorptions in a range of buffered solutions according to *A. Albert & E.P. Sergeant*, 'The Determination of Ionization Constants, a Laboratory Manual', Chapman and Hall, Ltd. London, England, 1971, p. 44.

Table. *Catalytic and chemical reductions of the isoquinoline* **4**

Exper.	Reagent/Solvent	Pression of H_2 (atm.)	Temp. (°C)	Time (h)	Analysis of the reaction mixture[a])
1	*Raney* Ni/EtOH	155	150	4	many spots
2	PtO_2/AcOH	4	25	18	Several spots; main spot (Rf 0.25, A) corresponding to **1**
3	Na/EtOH	–	reflux	1	mostly starting material
4	Na/Propanol	–	reflux	1	main spot (Rf 0.25, A) corresponding to **1**; at least 3 other significant spots
5	Na/Butanol	–	reflux	1	Similar results as in experiment 4
6	Na/NH_3-EtOH	–	−78	2	many spots; some starting material; main spot (Rf 0.3, B)

[a]) The basic materials obtained in the usual way were for TLC. analysis: *Analtech* silica gel GF-TLC. plates. Solvent systems: A. $CHCl_3$/MeOH/conc. aqueous ammonia 90:9:1; B. CH_2Cl_2/MeOH 10:1. Detection: UV. light and I_2 vapors.

Reported data suggested [7] that a conversion of **4** into **1** could be accomplished *via* an *N*-benzylisoquinolinium bromide. The quaternary salt **8** was obtained in good yield from **4** and benzyl bromide in boiling acetone, but not in cyclohexanone or in toluene. Reduction of **8** with sodium borohydride in methanol afforded the oily base **9**, readily *N*-debenzylated to **1** in acetic acid solution over Pd/C at RT. In one experiment gram-quantities of **1b** were converted into **1** *via* **4**, **8** and **9**, without especially purifying the intermediates, to afford **1** in 55% overall yield. This material could easily be resolved by the reported procedure to give optically active material of good optical purity [1].

A conversion of 'unwanted' optically active TIQ **1a** (**1b**) or **2a** (**2b**) into racemic material will afford a significantly higher yield of the 'wanted' enantiomer by the reported reaction sequence. This sequence, as demonstrated with **3**, can however not indiscriminantly be applied to any 1-benzyl-TIQ.

We thank Drs. *F.L. Hsu* and *K.C. Rice* for providing us with the TIQ needed in these investigations.

Experimental Part

General remarks. Thin layer chromatography (TLC., analytical): *Analtech* plates silica gel GF or *Merck* plates silica gel 60 F_{254} in connection with CC. The reaction was followed either with $CHCl_3/CH_3OH/NH_3$ 90:9:1 (system A) or CH_2Cl_2/CH_3OH 10:1 (system B). The products were recognized by UV. light (254 and 350 nm) or iodine vapors. Preparative column chromatography (CC.): *Merck* silica gel 60 (particle size 0.063–0.2 mm). Melting points (m.p.) were determined on a Uni-Melt *Thomas Hoover* capillary apparatus and are uncorrected. Optical rotation measurements: *Perkin-Elmer* 241 MC polarimeter. Concentrations (*c*) and solvents are listed. UV. spectra (C_2H_5OH): *Hewlett Packard* 8450A spectrophotometer; λ_{max} in nm (ε-values). IR. spectra ($CHCl_3$ if not otherwise stated): *Beckman* IR 4230 spectrophotometer; γ_{max} in cm^{-1}; *s* strong, *m* medium, *w* weak,

br. broad. ^{1}H-NMR. spectra ($CDCl_3$ if not otherwise stated): 100 MHz (*JEOL* FX-100); δ ppm; abbreviations, *s* singlet, *d* doublet, *t* triplet, *qa* quadruplet, *m* multiplet, *J* spin-spin coupling constant in Hz, *w* 1/2 half-width in Hz. Mass spectra (MS.): *Finnigan* 1015D instrument, chemical ionization.

4′,6-O,O-Dimethylpapaveroline (**4**). – a) *From* (±)-*(N-nor)-reticuline* (**1**). A suspension of 1.89 g of 10% Pd/C in 120 ml of toluene was stirred under reflux in argon for 30 min. A solution of 4.00 g (12.86 mmol) of **1** in 75 ml hot toluene was then rapidly added, and the mixture was stirred under reflux for 4.75 h (bath temperature: 130°). The catalyst was removed by filtration through *Celite*. The filter cake was washed with boiling acetone (4× 40 ml). The solvents were evaporated and the resulting solid was dried *in vacuo* at 50° to afford 3.53 g (89%) amorphous, nearly pure isoquinoline 1.6 g of **4** was stirred in 10 ml boiling acetone for 10 min. After cooling to 5°, the solid was filtered off, washed with cold acetone (2× 10 ml) and dried at 50° *in vacuo* to afford 1.1 g of pure **4**, m.p. 172–173°. – UV.: 239 (60,720), 281 (7420), 321 (4610) and 331 (5233). – IR.: 3545*s*, 3220*w* br., 2845*m*, 1638*w*, 1619*w*, 1595*m*, 1578*w*, 1501*m*, 1476*s*, 1453*m*, 1432*m*, 1353*w*, 1158*m*, 1131*m*, 1038*w*, 999*m*, 958*w*, 888*w*, 868*s*, 833*m*. – ^{1}H-NMR.: 3.76 and 4.00 (2 *s*, $H_3CO-C(4')$ and $H_3CO-C(6)$); 4.40 (*s*, 2 H–C–C(1)); 4.0–5.5 (*m*, HO–C(3′) and HO–C(7)); 6.65–6.9 (*m*, 3 arH); 7.02 (*s*, arH); 7.36 (*d*, $J(3,4)=6$, H–C(4)); 7.48 (*s*, arH); 8.22 (*d*, $J(3,4)=6$, H–C(3)). – MS.: 311 (M^+). – pKa_1 6.4, pKa_2 9.0, pKa_3 10.5.

$C_{18}H_{17}NO_4$ (311.34) Calc. C 69.44 H 5.50 N 4.49% Found C 69.35 H 5.60 N 4.48%

b) *From* (–)-*(S)-(N-nor)-reticuline* (**1b**). A solution of 200 mg (0.63 mmol) of **1b**[2]) in 5.5 ml $CH_3OH/CHCl_3$ 1:10 was evaporated to dryness, the residue dried *in vacuo*, dissolved in 6 ml boiling toluene and treated as described for **1**. The yield of crude **4** was 183 mg (93%).

Sulfate of **4**. A mixture of 1.20 g (3.86 mmol) of crude **4** and 50 ml CH_3OH was heated to solution then cooled to 45°. Conc. sulfuric acid (103 µl, 1.93 mmol) was added dropwise to afford immediately a white precipitate. After cooling to 5°, the solid was filtered off, washed with CH_3OH (25°, 3× 6 ml) and ether (25°, 6 ml) and dried *in vacuo* at 70°. Yield: 1.03 g (74%) of $\mathbf{4} \cdot \frac{1}{2}\ H_2SO_4$, m.p. 269–271°. Recrystallization from H_2O gave pure material, m.p. 270–272°.

$C_{18}H_{17}NO_4 \cdot \frac{1}{2}\ H_2SO_4$ (360.38) Calc. C 59.99 H 5.03 N 3.88% Found C 60.06 H 5.09 N 3.89%

Benzylisoquinolinium bromide **8**. To a solution of 1.47 g (4.70 mmol) of **4** in 50 ml boiling acetone (freshly distilled over P_2O_5) was added at once 2.74 g (1.90 ml, 16 mmol) of benzyl bromide. The mixture was stirred for 24 h at 60° (bath temperature) under argon. The solid was filtered off after cooling of the suspension to 30°, washed with ether (25°, 3× 15 ml) with acetone (4°, 2× 15 ml) and again with 15 ml ether and dried at RT. *in vacuo* overnight to afford 1.83 g (81%) of the bromide **8**[3]), m.p. 202–204°. Recrystallization from ethanol/ether gave a pure sample, m.p. 206–208°. IR. (KBr): 3180*m* br., 1622*m*, 1601*m*, 1509*s*, 1492*s*, 1456*m*, 1433*s*, 1361*m*, 1296*s*, 1274*s*, 1227*s*, 1194*m*, 1172*m*, 1151*m*, 1124*m*, 1070*w*, 1022*m*, 966*w*, 897*w*, 871*m*, 837*m*, 802*w*, 792*w*, 780*w*, 762*w*, 736*m*, 699*m*, 647*w*. – MS.: 402 ($M^+ - Br$).

$C_{25}H_{24}BrNO_4$ (482.39) Calc. C 62.24 H 5.01 N 2.90% Found C 62.42 H 5.18 N 2.55%

N-Benzyl-(N-nor)-reticuline (**9**). To a stirred solution of 732 mg (1.52 mmol) of **8** in 15 ml CH_3OH was added 322 mg (8.51 mmol) of $NaBH_4$ in small portions during 5 min under ice-cooling. The solution was stirred for a further 15 min at RT., concentrated to 1/4 of its volume, diluted with 4 ml 2N HCl and 16 ml H_2O and the aqueous solution was washed with ether (2× 10 ml), adjusted to pH 9.34 with conc. NH_4OH-solution and extracted with ether (4× 40 ml). The organic phase was dried (Na_2SO_4), evaporated to a solid which was dried overnight at RT. *in vacuo*. Chromatography of the residue on 115 g silica gel in CH_2Cl_2/CH_3OH 25:1 yielded 503 mg (82%) of the amorphous base **9**. – UV.: 285 (2945). – IR. (CCl_4): 3545*s*, 3070*w*, 3050*w*, 3010*m*, 2990*m*, 2825*m*, 2790*w*, 1626*w*, 1594*m*, 1502*s*, 1465*m*, 1455*m*, 1444*m*, 1362*m*, 1312*w*, 1275*s*, 1235*s*, 1207*s*, 1178*m*, 1160*m*, 1151*m*, 1132*m*, 1113*m*, 1100*m*, 1076*w*, 1035*m*, 947*w*, 873*m*, 697*m*. – ^{1}H-NMR.: 2.2–4.2 (*m*, H–C(1), 2 H–C(3), 2 H–C(7), 2 H–C–C(1) and 2 H–C–N(2)); 3.86 and 3.88 (2 *s*, $H_3CO-C(4')$ and $H_3CO-C(6)$); 4.2–6.2

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[2]) Pure **1b**, less soluble in boiling toluene than the corresponding racemic material, was advantageously dissolved first in $CH_3OH/CHCl_3$.

[3]) TLC. (system B) showed 2 small impurities. The faster running spot (Rf 0.3) corresponded to starting material and the other one (Rf 0.15) based on MS. probably to *O,N*-dibenzylated species.

(*m*, HO–C(3′) and HO–C(7)); 6.42 (*s*, arH); 6.4–6.85 (*m*, 4 arH); 6.85–7.4 (*m*, 5 arH). – MS.: 405 (M^+).

No crystalline hydrochloride or hydrobromide could be obtained.

N-Debenzylation of **9** *to* (±)-*(N-nor)-reticuline* (**1**). A solution of 200 mg (0.49 mmol) of **8** in 2 ml glacial AcOH was stirred in the presence of 200 mg of 10% Pd/C and H_2 under atmospheric pressure. After 60 min, the catalyst was removed by filtration through *Celite* and washed with AcOH (3×1.5 ml). Filtrate and washings were concentrated to 1 ml by evaporation, diluted with 10 ml H_2O, adjusted to pH 9.2 with conc. NH_4OH-solution and extracted with $CHCl_3$ (4×25 ml). The combined organic phases were evaporated to a foam which was stirred in 5 ml boiling ether for 15 min, filtered and dried *in vacuo* overnight to afford 134 mg (86%) of **1**, essentially homogenous on TLC. in systems A and B, m.p. 150–153°.

Conversion of **1b** *into* **1** *without purification of the intermediates.* A solution of 1.56 g (5 mmol) of **1b** in 30 ml toluene was treated with a suspension of 730 mg of 10% Pd/C in 45 ml toluene to afford 1.47 g (4.70 mmol) of **4**. Conversion of this material in 50 ml acetone with 2.7 ml (22.70 mmol) of benzyl bromide furnished 1.83 g (3.80 mmol) of the bromide **8**, which was dissolved in 40 ml CH_3OH. To this solution (stirred under argon, ice-cooled) was added 805 mg (20.97 mmol) of solid $NaBH_4$ in small portions during 20 min. The reaction mixture was stirred for additional 15 min, concentrated to 10 ml by evaporation, diluted with 10 ml 2N HCl and 40 ml H_2O, and extracted with ether (2×40 ml). The aqueous layer was adjusted to pH 9.05 with conc. NH_4OH-solution and extracted with ether (4×80 ml). The organic fractions were dried (Na_2SO_4), evaporated to a foam which was dried overnight *in vacuo*. The resulting residue (1.51 g) was dissolved in 15 ml glacial AcOH and reduced with 1.50 g of 10% Pd/C under a H_2-balloon during 2.75 h. The catalyst was removed by filtration through *Celite* and washed with 5 ml AcOH. The filtrate was concentrated to a volume of 5 ml, diluted with 40 ml H_2O, adjusted to pH 9.2 with conc. NH_4OH-solution and extracted with $CHCl_3$ (4×100 ml). After drying (Na_2SO_4) and evaporation of the organic phase, the residue was dried *in vacuo*, suspended in 10 ml boiling ether for 15 min, filtered and dried *in vacuo* again. Yield: 862 mg (55% overall, 2.73 mmol) of **1**, with only small impurities on TLC. (system A and B).

The optical resolution of this material by the published procedure gave the 'wanted' optical antipode **1a** in good quality, m.p. 168–169° ([1]: 171.5–172.5°), $[\alpha]_D^{23} = +32.8°$ ($c = 0.60$, $CHCl_3$) ([1]: $[\alpha]_D^{23} = +31.7°$ ($c = 0.65$, $CHCl_3$)).

1-(3′-Hydroxy-4′-methoxybenzyl)-6,7-dimethoxyisoquinoline, palaudine (**5**). An ice-cooled solution of 30 mg (0.01 mmol) of **4** in 2 ml CH_3OH was treated with 0.25M ethereal diazomethane (6×0.5 ml) during 80 min until there was essentially one new spot on TLC. in system A (Rf 0.4). After addition of 0.2 ml of glacial AcOH and evaporation, the residue was dissolved in 5 ml H_2O, the solution adjusted to pH 7 and extracted with $CHCl_3$ (3×15 ml). Chromatography of the residue obtained from the organic phase on 8 g silica gel in CH_2Cl_2/CH_3OH 25:1 gave an oily residue which crystallized after addition of a few drops of ether. Yield: 22 mg (70%) of **5** m.p. 171–174° (dec.) ([11]: 175–176°). – ^{1}H-NMR.: 3.81, 3.88 and 3.99 (3 *s*, H_3CO–C(4′), H_3CO–C(6) and H_3CO–C(7)); 4.48 (*s*, 2 H–C–C(1)); 6.6–6.9 (*m*, 3 arom. H); 7.02 and 7.31 (2 *s*, each arom. H); 7.37 (*d*, $J(3,4) = 6$, H–C(4)); 8.27 (*d*, $J(3,4) = 6$, H–C(3)). – pKa_1 6.5, pKa_2 10.3.

Preparation of papaverine (**6**). Compound **4** (28 mg, 0.09 mmol) was treated with 6 ml of 0.25M ethereal diazomethane as described above. Usual work-up afforded 22 mg (72%) of **6**, m.p. 143–144° ([12]: 147°) after crystallization from ethanol.

1-(3′-Hydroxy-4′-methoxybenzyl)-6-methoxyisoquinoline (**7**). The general procedure was similar to the preparation of **4**. In this case 898 mg (3 mmol) of **2b** in 30 ml toluene (suspension) was treated with 450 mg 10% Pd/C suspended in 30 ml of toluene. After 45 min the mixture was worked up in the usual way. The resulting 864 mg (97%) of crude **7** were crystallized from 12 ml CH_3OH to afford 630 mg of pure material, m.p. 156–158.5° (long thin needles). – UV.: 233 (58,880), 283 (8112). – IR.: 3545*m*, 2840*w*, 1627*s*, 1596*m*, 1571*m*, 1500*m*, 1474*m*, 1444*m*, 1412*m*, 1380*m*, 1351*m*, 1147*m*, 1131*m*, 1079*w*, 1051*w*, 1031*m*, 1020*m*, 957*w*, 945*w*, 857*m*. – ^{1}H-NMR.: 3.79 and 3.90 (2 *s*, H_3CO–C(4′) and H_3CO–C(6)); 4.48 (*s*, 2 H–C–C(1)); 6.4–6.85 (*m*, 3 arom. H); 6.85–7.24 (*m*, 3 arom. H); 7.38 (*d*, $J(3,4) = 6$, H–C(4)); 8.01 (*d*, $J = 9$, arH); 8.28 (*d*, $J(3,4) = 6$, H–C(3)). – MS.: 295 (M^+). – pKa_1 6.3, pKa_2 10.2.

$C_{18}H_{17}NO_3$ (295.34) Calc. C 73.20 H 5.80 N 4.74% Found C 72.97 H 5.90 N 4.64%

Dehydrogenation of **3** *to 1-[3',5'-bis(benzyloxy)benzyl]-6-methoxy-3,4-dihydroisoquinoline* (**10**). A solution of 1,56 g (3,35 mmol) of **3** [6] in 25 ml toluene was added to 500 mg of 10% Pd/C in 30 ml toluene and stirred under reflux in argon. After 4.5 h 300 mg of 10% Pd/C was added and stirring continued for 4 days under the same conditions as above. The residue (1.04 g) obtained from the organic solution after filtration through *Celite* was chromatographed several times on silica gel in CH_2Cl_2/CH_3OH 30:1 to yield 258 mg (16%) of oily **10**. – UV. (C_2H_5OH/0.01N HCl): 329 (1428). – IR. (CCl_4): 3110*w*, 3090*w*, 3065*w*, 3030*w*, 1608*s*, 1501*m*, 1458*m*, 1438*m*, 1376*m*, 1349*m*, 1316*m*, 1296*m*, 1286*m*, 1255*m*, 1159*s*, 1122*w*, 1075*w*, 1052*m*, 1032*m*, 869*w*, 848*w*, 695*m*. – ^{1}H-NMR.: 2.4–2.8 and 3.45–3.90 (2 *m*, 2 H–C(3) and 2 H–C(4)); 3.80 (*s*, H_3CO–C(6)); 3.95 (*s*, 2 H–C–C(1)); 4.98 (*s*, 2 H–C–O–C(3') and 2 H–C–O–C(5')); 6.2–6.8 and 6.9–7.6 (2 *m*, 11 arom. H). – MS.: 463 (M^+).

Reduction of 11 mg (0.02 mmol) of **10** in CH_3OH with $NaBH_4$ was done in the usual way, and afforded after purification by chromatography on 5 g silica gel in CH_2Cl_2/CH_3OH 20:1 7 mg of **3**, identical with an authentic sample.

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