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Syntheses of 1,2,3,4-Tetrahydroisoquinolines from N-Sulfonylphenethylamines and Aldehydes

Kazuo Ito and Hitoshi Tanaka

Faculty of Pharmacy, Meijo University[1]

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N-Sulfonylphenethylamines (**6**—**9**) have been readily condensed with formaldehyde under mild acidic condition to the corresponding N-sulfonyl-1,2,3,4-tetrahydroisoquinolines (**14**—**17**) in excellent yields. Condensation of sulfonamide (**10**) with formaldehyde under similar condition gave a mixture of two cyclization products (**18** and **19**). In the case of similar condensation of 3,4-disubstituted-N-sulfonamides (**11** and **12**) with formaldehyde, 6,7-disubstituted products (**20** and **21**) were obtained alone. Similar reaction of sulfonamides (**6**, **11** and **12**) with aliphatic aldehydes or aromatic aldehydes also afforded the corresponding N-tosyl-1,2,3,4-tetrahydroisoquinolines (**22**—**27**).

Furthermore, 1-benzyl-N-tosyl-1,2,3,4-tetrahydroisoquinolines (**31** and **37**) were similarly synthesized from sulfonamide (**12** or **13**) and phenyl acetaldehyde (**30** or **36**). Birch reduction of (**37**) afforded the racemic form (**33**) of natural N-nororientaline, which was previously isolated by us from the leaves of *Erythrina* X *bidwillii* (Leguminosae).

Keywords——Pictet-Spengler reaction; syntheses of 1,2,3,4-tetrahydroisoquinolines; condensation of N-sulfonylphenethylamines and aliphatic aldehydes; condensation of N-sulfonylphenethylamines and aromatic aldehydes; synthesis of 1-benzyl-1,2,3,4-tetrahydroisoquinoline; synthesis of N-nororientaline

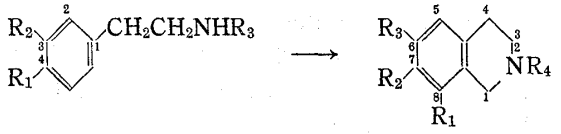
In our previous paper,[2] we reported that the benzyne reaction of various N-sulfonylphenethylamines with methylsulfinyl carbanion in dimethyl sulfoxide afforded readily the corresponding indoline derivatives along with thiophenol compounds.

This paper is concerned with Pictet-Spengler condensation of various N-sulfonyl phenethylamines with aldehydes to give 1,2,3,4-tetrahydroisoquinoline derivatives. Generally, such a type of condensation of phenethylamines with various aldehydes is a well-known[3] synthetic method of 1,2,3,4-tetrahydroisoquinolines. For example, a biogenetic type synthesis of *S* (+)-laudanosine from L-3,4-dihydroxy-phenylalanine derivative has been recently accomplished by Yamada, *et al.*[4] in the application of diastereoisomeric mixture of the Pictet-Spengler products. However, it is also known[3] that this condensation offers some disadvantage in yields of 1,2,3,4-tetrahydroisoquinolines because of 1 side reaction encountered frequently, and 2 the drastic conditions generally employed, if these phenethylamines lack alkoxyl or hydroxyl group at the *para* position to the position of ring closure.

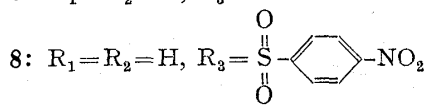
We anticipated that a variety of N-sulfonylphenethylamines could be easily condensed with aldehydes under mild conditions to afford the corresponding 1,2,3,4-tetrahydroisoquinoline derivatives.

The initial compounds of this condensation, sulfonamides (**6**—**13**) were synthesized from the corresponding phenethylamines (**1**, **2**,[5] **3**, **4**, and **5**[6]) and several sulfonyl chlorides

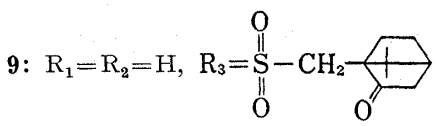
1) Location: *Yagoto, Tenpaku-ku, Nagoya.*
2) K. Ito, H. Tanaka, and M. Kayama, *Chem. Pharm. Bull.* (Tokyo), **25**, 1249 (1977).
3) H. Adkins, F.C. McGrew, A.H. Blatt, C. Niemann, A.C. Cope, and H.R. Snyder, "Organic Reactions," Vol. 6, ed. by W.M. Whaley and T.R. Govindachari, J. Wiley and Sons, Inc., New York, 1951, p. 151.
4) S. Yamada, M. Kondo, and T. Shioiri, *Tetrahedron Letters*, **1972**, 2215.
5) L. Helfer, *Helv. Chim. Acta.*, **7**, 945 (1924).
6) J.M. Bobbitt and T.T. Chair, *J. Org. Chem.*, **24**, 1106 (1959).



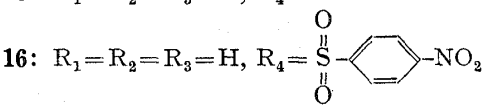
1: $R_1=R_2=R_3=H$
2: $R_1=H$, $R_2=OCH_3$, $R_3=H$
3: $R_1+R_2=OCH_2O$, $R_3=H$
4: $R_1=R_2=OCH_3$, $R_3=H$
5: $R_1=OCH_2C_6H_5$, $R_2=OCH_3$, $R_3=H$
6: $R_1=R_2=H$, $R_3=Ts$
7: $R_1=R_2=H$, $R_3=Ms$



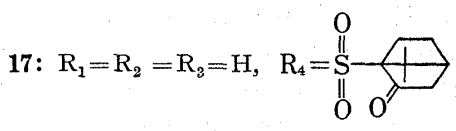
9: $R_1=R_2=H$, $R_3=$



10: $R_1=H$, $R_2=OCH_3$, $R_3=Ts$
11: $R_1+R_2=OCH_2O$, $R_3=Ts$
12: $R_1=R_2=OCH_3$, $R_3=Ts$
13: $R_1=OCH_2C_6H_5$, $R_2=OCH_3$, $R_3=Ts$
14: $R_1=R_2=R_3=H$, $R_4=Ts$
15: $R_1=R_2=R_3=H$, $R_4=Ms$



17: $R_1=R_2=R_3=H$, $R_4=$



18: $R_1=OCH_3$, $R_2=R_3=H$, $R_4=Ts$
19: $R_1=R_2=H$, $R_3=OCH_3$, $R_4=Ts$
20: $R_1=H$, $R_2+R_3=OCH_2O$, $R_4=Ts$
21: $R_1=H$, $R_2=R_3=OCH_3$, $R_4=Ts$

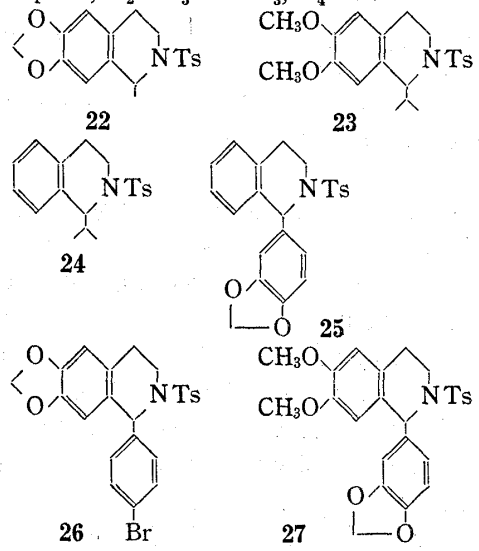


Chart 1

(*p*-toluenesulfonyl chloride, methanesulfonyl chloride, *p*-nitrobenzenesulfonyl chloride and *d*-camphor-10-sulfonyl chloride[7]) by Schotten-Baumann method.

N-Sulfonylphenethylamines (**6**—**9**) reacted readily with a slight excess of formaldehyde in chloroform including a solution of boron trifluoride at room temperature affording N-sulfonyl-1,2,3,4-tetrahydroisoquinolines (**14**—**17**) in excellent yields. Alteration of the acidic solution of boron trifluoride to phosphorus oxychloride, concentrated sulfuric acid or hydrochloric acid did not influence upon the result. The structures of the cyclized compounds were confirmed by their nuclear magnetic resonance (NMR) spectra,[8] which showed a sharp singlet due to one-methylene protons at 5.50—5.74. These signals of consideraly low-τ value can be assigned to the protons (C_1—H) of a methylene group attached to both an aromatic ring and nitrogen atom. Further structural proof was obtained from elemental analyses and infrared (IR) spectra of these substances.

Thus, this condensation method using N-sulfonylphenethylamines would be proceeded successfully for the syntheses of 1,2,3,4-tetrahydroisoquinolines lacking substituted groups in their benzene rings.

Treatment of **10** with formaldehyde under similar mild condition afforded a mixture of two products in the ratio of 12.5: 1, which was subjected to chromatographical separation on silica gel. The structures of these products (**18** and **19**) were confirmed on the basis of their NMR spectra.

7) H. Sutherland and R.L. Shriner, *J. Am. Chem. Soc.*, **58**, 62 (1936).
8) NMR spectra were determined on a Nippon Denshi PS-100 spectrometer in $CDCl_3$ with TMS as an internal standard and chemical shift were given in τ-value.

The minor substance (**18**), colorless needles, mp 136°, was obtained from the first fraction of chromatography. The NMR spectrum of **18** showed a singlet due to the methylene group at 5.84, which was assigned to C_1–H. In the aromatic region, **18** exhibited a one-proton triplet centered at 2.93 (J=9 Hz) and a two-proton doublet (two overlapping doublets) centered at 3.37 (J=9 Hz). This pattern of a triplet and doublets in aromatic region, as observed for **18**, is characteristic of C–8 oxygenated tetrahydroisoquinoline derivative. These facts sugges ted that the structure of this might be N-tosyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**18**) and hence the cyclization took place at the *ortho* position to methoxyl group in **10**.

The secondary major substance (**19**), colorless plates, mp 135°, showed quite similar NMR spectrum as that of **18** except for aromatic protons. In the aromatic proton region **19** exhibited a one-proton doublet centered at 3.08 (J=9 Hz), a one-proton doublet of doublets centered at 3.33 (J=9 and J=3 Hz) and a one-proton doublet centered at 3.45 (J=3 Hz). This pattern is indicative of C-6 oxygenated tetrahydroisoquinoline derivative. These data revealed that the structure of this compound might be N-tosyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**19**) and hence the cyclization occurred at the *para* position to methoxyl group in **10**.

Therefore, it has been confirmed that the cyclization of **10** with formaldehyde takes place at both *ortho* and *para* position to methoxyl group in **10**.

In the case of condensation of 3,4-disubstituted-N-sulfonylphenethylamine (**11** or **12**) with formaldehyde under similar conditions to those described above, the sole product (**20** or **21**) was isolated in each reaction. In their NMR spectra, these compounds displayed a characteristic singlet at 5.85 and 5.82, which is attributable to C_1–H. They also showed sharp singlet due to C_5–H and C_8–H at 3.53 and 3.48 in **20**, and 3.49 and 3.45 in **21**. Therefore, the reaction of **11** or **12** with formaldehyde affords 6,7-disubstituted tetrahydroisoquinoline alone.

In an attempt to evaluate the scope of this reaction, condensation of N-tosylphenethylamines with aliphatic aldehydes or aromatic aldehydes was examined under similar reaction condition.

The sulfonamide (**11** or **12**) was readily condensed with aliphatic aldehydes (acetaldehyde and isobutylaldehyde) to give the corresponding N-tosyl-1-alkyl-tetrahydroisoquinoline (**22** or **23**, respectively). On the other hand, condensation of **6** with isobutylaldehyde under similar mild condition did not give the desired cyclization product, but in refluxing chloroform **6** was readily condensed with isobutylaldehyde to afford the cyclized product (**24**).

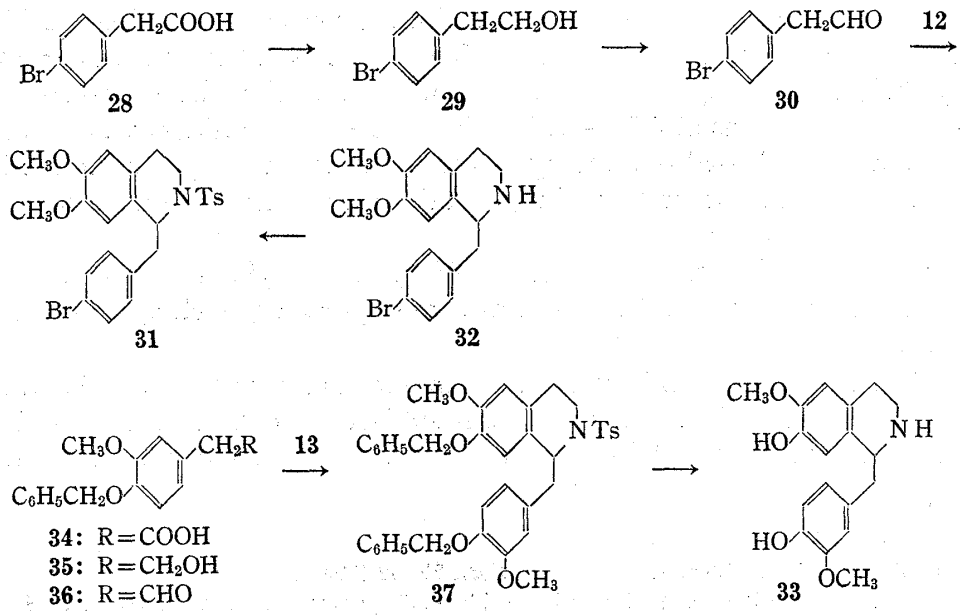


Chart 2

Furthermore, when **6**, **11**, or **12** was reacted with aromatic aldehydes such as piperonal and *p*-bromobenzaldehyde,[9] we have failed in obtaining the desired cyclized product and the starting substance was recovered almost completely. Consequently, it was necessary to apply more drastic condition such as reflux in order to achieve condensation with aromatic aldehydes. The structures of these products were ascertained to be N-tosyl-tetrahydroisoquinolines (**22**—**27**) from the data of their NMR spectra[10] and elemental analyses.

We subsequently examined the condensation of **12** with 4-bromo-phenyl acetaldehyde (**30**). **30** was easily obtained as follows: 4-Bromo-phenylacetic acid (**28**) was prepared according to the method described in the literature.[11] The acid (**28**) was readily submitted to hydroboration using sodium borohydride and boron trifluoride in tetrahydrofuran to give the corresponding alcohol (**29**), followed by oxidation with pyridinium chlorochromate (p.c.c.)[12] to afford **30** in good yield.

The condensation of **12** with the aldehyde (**30**) was carried out under the same reaction condition as that used for formation of **14** and the resulting product, mp 136°, was identical with N-tosyl-4-bromo-3,4-dimethoxyl-1,2,3,4-tetrahydroisoquinoline (**31**), mp 135°, which was derived by N-tosylation from a secondary base (**32**),[11] in comparison of their mixed melting point, IR and NMR spectra.

Thus, the synthesis of 1-benzyl-tetrahydroisoquinoline derivatives in the application of above-mentioned one-step condensation is more advantageous, compared with the method by Schotten-Baumann reaction and subsequent Bischler-Napieralski condensation.

Finally, this reaction has been applied to the synthesis of naturally occurring tetrahydrobenzylisoquinoline, N-nororientaline (**33**),[13] previously isolated by us from the leaves of *Erythrina* X *bidwillii* (Leguminosae). The sulfonamide (**13**) was allowed to react with an excess of 3-methoxy-4-benzyloxyphenyl acetaldehyde (**36**), which was prepared *via* hydroboration of 3-methoxy-4-benzyloxyphenylacetic acid (**34**) and subsequent p.c.c. oxidation. In NMR spectrum of the resulting N-tosyl-tetrahydroisoquinoline (**37**), a characteristic triplet due to C_1–H was similarly observed at 5.02. Birch reduction of **37** with lithium in liquid ammonia gave the product of secondary amine (**33**), which was proved to be the racemic form of natural N-nororientaline by complete identity of their IR ($CHCl_3$) and NMR spectra.

Experimental[14]

Preparation of N-Sulfonylphenethylamine (6—13)——To a solution of **1** (1.5 g, 9.55 mmol) in dry pyridine (15 ml) was added tosyl chloride (2.5 g, 14.16 mmol) with stirring over about 5 min. After stirring for 2 hr, water was added and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed thoroughly with 5% HCl and water, dried over Na_2SO_4 and evaporated. The residue was recrystallized from a mixture of benzene and ligroin to give **6** (2.6 g).

The sulfonamides (**6**—**13**) thus prepared are listed in Table I.

N-Sulfonyl-1,2,3,4-tetrahydroisoquinoline (14—17)——General Procedure: To a mixture of **6** (210 mg, 0.764 mmol) in $CHCl_3$ (10 ml) and 6 drops of BF_3-etherate was added dropwise 37% formaldehyde (0.05 ml) with stirring at room temperature. The mixture was stirred for 15 min at the same temperature. Completion of the reaction was checked by thin-layer chromatography (TLC).[15] The resulting acidic mixture was

9) This compound was selectively used from the reason of high resolvability of aromatic proton signals in its NMR spectrum.

10) The NMR spectra of N-tosyl-1-aryl-tetrahydroisoquinolines (**25**, **26** and **27**) exhibited a one-proton multiplet of C_3–H shifted to more lower field than usual proton signal of C_3–H by anisotropic effect of sulfonyl group.

11) M. Tomita and J. Niimi, *Yakugaku Zasshi*, **78**, 1229 (1958).

12) E.J. Corey and J.W. Suggs, *Tetrahedron Letters*, **1975**, 2647.

13) K. Ito, H. Furukawa and H. Tanaka, *Yakugaku Zasshi*, **93**, 1211 (1973).

14) All melting points were uncorrected. Column chromatography was performed on silica gel (kieselgel 60 Merck). TLC was carried out on silica gel HF_{254} Merck, Type 60 and detected by aqueous solution of $KMnO_4$.

15) N-Sulfonyltetrahydroisoquinolines have higher *Rf* values than those of initial substances (**6**—**9**).

Table I

Comd. No.	Yield (%)	mp (°C) ( ): cryst. solvt	Appearance (colorless)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR $\nu_{max}^{CHCl_3}$ cm^{-1} NH	SO_2
6[a]	57.8	63—64 (benzene-ligroin)	Needles	$C_{15}H_{17}NO_2S$	65.43 (65.47)	6.22 (6.19)	5.09 (5.23)	3360	1340 1160
7[b]	60.8	58 (benzene-ligroin)	Needles	$C_9H_{13}NO_2S$	54.25 (54.38)	6.58 (6.57)	7.03 (7.17)	3400	1330 1150
8	60.4	95 (benzene)	Needles	$C_{14}H_{14}N_2O_4S$	54.89 (54.70)	4.61 (4.51)	9.14 (9.03)	3400	1350 1160
9[c]	61.4		Oil[d]	$C_{18}H_{25}NO_3S$				3380	1340 1150
10	51.9		Oil[e]	$C_{16}H_{19}NO_3S$				3360	1340 1160
11	70.9	95 (benzene)	Needles	$C_{16}H_{17}NO_4S$	60.17 (60.06)	5.37 (5.29)	4.39 (4.28)	3380	1340 1160
12	53.9	135—136 (benzene)	Needles	$C_{17}H_{21}NO_4S$	60.87 (61.05)	6.31 (6.31)	4.18 (4.13)	3380	1350 1160
13	69.4		Oil[f]	$C_{23}H_{25}NO_4S$				3400	1350 1155

a) Ts: tosyl group.
b) Ms: methanesulfonyl group.
c) Prepared from *d*-camphor-10-sulfonyl chloride.
d) Mass spectrum[g] *m/e*: 335 (M^+).
e) Mass spectrum *m/e*: 305 (M^+).
f) Mass spectrum *m/e*: 411 (M^+).
g) Mass spectra were determined on the Hitachi RMU-6 mass spectrometer using a indirect inlet system.

Table II.

Compd. No.	Yield (%)	mp (°C) ( ): cryst. solvt	Appearance (colorless)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR $\nu_{max}^{CHCl_3}$ cm^{-1} SO_2	NMR τ ($CDCl_3$) C_1-H (2H. s[a])	C_5-H and C_8-H (each s., 1H)
14	95.8	147[b] (benzene)	Needles	$C_{16}H_{17}NO_2S$	66.87 (66.89)	5.96 (5.90)	4.87 (4.75)	1350 1170	5.74	
15	91.8	129—130 (benzene)	Prisms	$C_{10}H_{13}NO_2S$	56.85 (56.75)	6.20 (6.24)	6.63 (6.63)	1350 1160	5.56	
16	97.1	161 (benzene)	Needles	$C_{15}H_{14}N_2O_4S$	56.59 (56.81)	4.43 (4.35)	8.80 (8.61)	1350 1160	5.65	
17	92.9	160[c] (benzene-ligroin)	Needles	$C_{19}H_{25}NO_3S$	65.68 (65.58)	7.25 (7.31)	4.03 (4.06)	1350 1150	5.50	
20	91.6	149 (benzene)	Needles	$C_{17}H_{17}NO_4S$	61.62 (61.67)	5.17 (5.08)	4.23 (4.15)	1360 1170	5.85	3.48, 3.53
21	82.1	144—145 (MeOH)	Prisms	$C_{18}H_{21}NO_4S$	62.23 (61.93)	6.09 (6.16)	4.03 (3.89)	1360 1160	5.82	3.45, 3.49

a) Abbreviation; s=singlet.
b) lit. mp[d] 145—146°.
c) $[\alpha]_D^{25}$ +25.5 (*c*=0.26 in $CHCl_3$).
d) M. Natsume, S. Kumadaki, K. Kiuchi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1592 (1972).

poured into water and neutralized with NH_4OH. The $CHCl_3$ layer was separated and aqueous layer was extracted with $CHCl_3$. The combined $CHCl_3$ solution was washed with water, dried over Na_2SO_4 and evaporated. The residue was recrystallized from benzene to afford **14** (210 mg).

The N-sulfonyltetrahydroisoquinolines (**14**—**17**) thus prepared are summarized in Table II.

N-Tosyl-8-methoxyl-1,2,3,4-tetrahydroisoquinoline (18) and N-Tosyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (19)——A solution of **10** (500 mg) in $CHCl_3$ (20 ml), 8 drops of BF_3-etherate and 37% formaldehyde (0.1 ml) was reacted under the same condition as for **14**. The reaction mixture was similarly treated to afford brownish oil. This oil was chromatographed on a silica gel column using benzene. The benzene

fraction eluted primarily was evaporated and the residue was recrystallized from MeOH. Colorless needles, mp 136° (30 mg) (**18**). TLC ($CHCl_3$, Rf=0.48). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1170, 1350 (SO_2). NMR ($CDCl_3$) τ: 7.59 (3H, s, CH_3), 7.11 (2H, t, J=6 Hz, C_4–H), 6.68 (2H, t, J=6 Hz, C_3–H), 6.24 (3H, s, OCH_3), 5.84 (2H, s, C_1–H), 3.37 (2H, d, J=9 Hz, C_5–H and C_7–H), 2.93 (1H, t, J=9 Hz, C_6–H), 2.73 (2H, d, J=8 Hz, 2×arom. H), 2.29 (2H, d, J=8 Hz, 2×arom. H). *Anal.* Calcd. for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41. Found: C, 64.05; H, 5.96; N, 4.43.

The benzene fraction eluted secondarily was evaporated and the residue was recrystallized from MeOH. Colorless plates, mp 135° (379 mg) **19**. TLC ($CHCl_3$, Rf=0.39). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1350, 1170 (SO_2). NMR ($CDCl_3$) τ: 7.59 (3H, s, CH_3), 7.13 (2H, t, J=6 Hz, C_4–H), 6.68 (2H, t, J=6 Hz, C_3–H), 6.27 (3H, s, OCH_3), 5.84 (2H, s, C_1–H), 3.45 (1H, d, J=3 Hz, C_5–H), 3.33 (1H, dd, J=9, 3 Hz, C_7–H), 3.08 (1H, d, J=9 Hz, C_8–H), 2.73 (2H, d, J=8 Hz, 2×arom. H), 2.33 (2H, d, J=8 Hz, 2×arom. H). *Anal.* Calcd. for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41. Found: C, 64.22; H, 5.92; N, 4.63.

Condensation of 6, 11 or 12 with Aliphatic Aldehydes (Formation of 22, 23 or 24)——i) To a mixture of **11** (200 mg) in $CHCl_3$ (15 ml) and 5 drops of BF_3-etherate was added dropwise acetaldehyde (50 mg) with stirring under ice cooling. Stirring was continued for 2 hr at 5—10°. The resulting mixture was treated in the manner described for the synthesis of **14**. The oily residue was purified by silica gel column chromatography using benzene as an eluent to yield pure product, which was recrystallized from EtOH. Colorless prisms. mp 116—117° (202 mg) **22**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1340, 1160 (SO_2). NMR ($CDCl_3$) τ: 8.58 (3H, d, J=7 Hz, CH_3), 7.65 (3H, s, CH_3), 7.56—7.32 (2H, m, C_4–H), 6.84—6.48 (1H, m, C_3–H), 6.36—6.04 (1H, m, C_3–H), 5.02 (1H, q, J=7 Hz, C_1–H), 3.65 (1H, s, C_5–H or C_8–H), 3.54 (1H, s, C_5–H or C_8–H), 2.86 (2H, d, J=8 Hz, 2×arom. H), 2.36 (2H, d, J=8 Hz, 2×arom. H). *Anal.* Calcd. for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.46; H, 5.51; N, 3.88.

ii) To a solution of **12** (200 mg) in $CHCl_3$ (15 ml) and 6 drops of BF_3-eherate was added dropwise isobutylaldehyde (80 mg) with stirring at room temperature. After stirring for 1.5 hr at the same temperature, the resulting mixture was similarly treated to give an oily residue. The residue was purified by column chromatography on silica gel using $CHCl_3$, which was recrystallized from EtOH. Colorless needles. mp 99° (180 mg) **23**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1345, 1160 (SO_2). NMR ($CDCl_3$) τ: 8.98 (6H, d, J=8 Hz, 2×CH_3), 8.24—7.84 (1H, m, C<u>H</u>$(CH_3)_2$), 7.72 (3H, s, CH_3), 7.68—7.40 (2H, m, C_4–H), 6.26, 6.18 (6H, 2×s, 2×OCH_3), 6.68—6.08 (2H, m, C_3–H), 5.54 (1H, d, J=8 Hz, C_1–H), 3.73 (1H, s, C_5–H or C_8–H), 3.53 (1H, s, C_5–H or C_8–H), 3.00 (2H, d, J=8 Hz, 2×arom. H), 2.54 (2H, d, J=8 Hz, 2×arom. H). *Anal.* Calcd. for $C_{21}H_{27}NO_4S$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.68; H, 7.01; N, 3.46.

iii) A mixture of **6** (200 mg) and isobutylaldehyde (95 mg) dissolved in a solution of $CHCl_3$ (20 ml) and $POCl_3$ (3 ml) was heated under reflux for 4 hr. A brownish oil obtained by the work-up was purified by column chromatography on silica gel using benzene and *n*-hexane (1: 1) mixture, and subsequently recrystallized from EtOH. Colorless needles, mp 76° (210 mg) **24**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1350, 1165 (SO_2). NMR ($CDCl_3$) τ: 8.25 (6H, s, 2×CH_3), 7.92—7.72 (1H, m, C<u>H</u>$(CH_3)_2$), 7.61 (3H, s, CH_3), 7.36—7.14 (2H, m, C_4–H), 6.88—6.64 (2H, m, C_3–H), 5.02 (1H, br. s, C_1–H), 3.12—2.68 (4H, m, 4×arom. H), 2.79 (2H, d, J=8 Hz, 2×arom.H), 2.44 (2H, d, J=8 Hz, 2×arom. H). *Anal.* Calcd. for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04; N, 4.25. Found: C, 68.97; H, 6.94; N, 4.13.

Condensation of 6, 11 or 12 with Aromatic Aldehydes (Formation of 25, 26 or 27)——i) A mixture of **6** (200 mg) and piperonal (150 mg) dissolved in a solution of toluene (20 ml) and $POCl_3$ (4 ml) was heated under reflux for 3 hr. A brownish oil obtained by the work-up was submitted to column chromatography on silica gel using benzene, followed by recrystallization from benzene. Colorless prisms, mp 218—220° (220 mg) **25**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1340, 1160 (SO_2). NMR ($CDCl_3$) τ: 7.71 (3H, s, CH_3), 7.56—7.30 (2H, m, C_4–H), 6.92—6.52 (1H, m, C_3–H), 6.42—6.12 (1H, m, C_3–H), 4.19 (2H, s, OCH_2O), 3.96 (1H, s, C_1–H), 3.60—3.32 (3H, m, 3×arom. H), 3.24—2.88 (4H, m, 4×arom. H), 3.04 (2H, d, J=8 Hz, 2×arom. H), 2.56 (2H, *d*, J=8 Hz, 2×arom. H). *Anal.* Calcd. for $C_{23}H_{21}NO_4S$: C, 67.79; H, 5.19; N, 3.44. Found: C, 67.77; H, 5.00; N, 3.33.

ii) A mixture of **11** (200 mg) and *p*-bromobenzaldehyde (180 mg) dissolved in a solution of $CHCl_3$ (20 ml) and $POCl_3$ (1 ml) was heated under reflux for 6 hr. Work-up in the above manner gave crude crystals, which was recrystallized from MeOH. Colorless needles, mp 159—160° (250 mg) **26**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1360, 1170 (SO_2). NMR ($CDCl_3$) τ: 7.65 (3H, s, CH_3), 7.88—7.36 (2H, m, C_4–H), 7.00—6.58 (1H, m, C_3–H), 6.44—6.12 (1H, m, C_3–H), 4.14 (2H, s, OCH_2O), 4.00 (1H, s, C_1–H), 3.64 (1H, s, C_5–H or C_8–H), 3.60 (1H, s, C_5–H or C_8–H), 2.96 (2H, d, J=8 Hz, 2×arom. H), 2.91 (2H, d, J=7 Hz, 2×arom. H), 2.64 (2H, d, J=7 Hz, 2×arom. H), 2.48 (2H, d, J=8 Hz, 2×arom. H). *Anal.* Calcd. for $C_{23}H_{20}BrNO_4S$: C, 56.80; H, 4.14; N, 2.88. Found: C, 56.94; H, 4.05; N, 3.01.

iii) A mixture of **12** (200 mg) and piperonal (140 mg) dissolved in a solution of toluene (20 ml) and $POCl_3$ (1 ml) was heated under reflux for 2 hr. A brownish oil obtained by the work-up was submitted to column chromatography on silica gel using benzene, followed by recrystallization from benzene. Colorless needles, mp 154—155° (270 mg) **27**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1350, 1170 (SO_2). NMR ($CDCl_3$) τ: 7.67 (3H, s, CH_3), 7.80—7.32 (2H, m, C_4–H), 7.00—6.54 (1H, m, C_3–H), 6.40—6.00 (1H, m, C_3–H), 6.26, 6.20 (6H, 2×s, 2×OCH_3), 4.12 (2H, s, OCH_2O), 3.96 (1H, s, C_1–H), 3.60 (2H, s, 2×arom. H), 3.44—3.20 (3H, m, 3×arom. H),

2.93 (2H, d, J=8 Hz, 2×arom. H), 2.46 (2H, d, J=8 Hz, 2×arom. H). *Anal.* Calcd. for $C_{25}H_{25}NO_6S$: C, 64.22; H, 5.39; N, 3.00. Found: C, 64.52; H, 5.38; N, 2.85.

***p*-Bromophenethyl Alcohol (29)**——To a stirred solution of **28**[11] (5 g) dissolved in THF (40 ml) was gradually added $NaBH_4$ (0.8 g) and then BF_3-etherate (2 ml) was added dropwise to this stirred mixture in an ice-water bath. The mixture was stirred at room temperature for 5 hr and decomposed with EtOH and water, followed by evaporation. The residue dissolved in $CHCl_3$ was washed with water and dried over Na_2SO_4, followed by evaporation. Colorless oil,[16] (4.5 g) **29**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (OH). NMR ($CDCl_3$) τ: 7.32 (2H, t, J=6 Hz, $\underline{CH_2}CH_2OH$), 6.87 (1H, s, OH), 6.36 (2H, t, J=6 Hz, $CH_2\underline{CH_2}OH$), 3.04 (2H, d, J=9 Hz, 2×arom. H), 2.70 (2H, d, J=9 Hz, 2×arom. H).

***p*-Bromophenyl Acetaldehyde (30)**——To a stirred solution of p.c.c (500 mg) dissolved in dry CH_2Cl_2 (10 ml) was added dropwise a solution of **29** (100 mg) in dry CH_2Cl_2 (5 ml) over 30 min under ice cooling. After stirring at room temperature for 1 hr, anhydrous ether (50 ml) was added to the mixture and the supernatant solution was decanted from the black gum. The insoluble material was washed thoroughly 3 times with 10 ml of anhydrous ether. The combined solution was passed through a short pad of silica gel and solvents were evaporated. Colorless oil,[17] (95 mg) **30**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2820, 2720, 1730 (CHO). NMR ($CDCl_3$) τ: 6.40 (2H, d, J=2 Hz, CH_2), 3.00 (2H, d, J=9 Hz, 2×arom. H), 2.58 (2H, d, J=9 Hz, 2×arom. H), 0.40 (1H, t, J=2 Hz, CHO).

1-(4′-Bromobenzyl)-6,7-dimethoxy-N-tosyl-1,2,3,4-tetrahydroisoquinoline (31)——A mixture of **12** (100 mg) and **30** (120 mg) in $CHCl_3$ (10 ml) and 8 drops of BF_3-etherate was stirred at room temperature for 2 hr, and then poured into water. An oil obtained by the work-up was purified by column chromatography on silica gel using benzene, and recrystallized from EtOH. Colorless needles, mp 136° (95 mg) **31**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1350, 1160 (SO_2). NMR ($CDCl_3$) τ: 7.66 (3H, s, CH_3), 6.36, 6.24 (6H, 2×s, 2×OCH_3), 5.00 (1H, t, J=7 Hz, C_1–H), 3.88 (1H, s, arom. H), 3.62 (1H, s, arom. H), 3.18 (2H, d, J=8 Hz, 2×arom. H), 2.94 (2H, d, J=9 Hz, 2×arom. H), 2.76 (2H, d, J=9 Hz, 2×arom. H), 2.58 (2H, d, J=8 Hz, 2×arom. H). *Anal.* Calcd. for $C_{25}H_{26}BrNO_4S$: C, 58.14; H, 5.07; N, 2.71. Found: C, 58.36; H, 5.06; N, 2.55.

N-Tosylation of 1-(4′-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (32) (Formation of 31)——To a stirred solution of **32**[11] (100 mg) dissolved in pyridine (10 ml), tosyl chloride (70 mg) was added under ice cooling. The mixture was stirred at room temperature for 2 hr, and poured into water. The resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with 5% HCl and water, dried over Na_2SO_4 and evaporated. The obtained residue was recrystallized from EtOH. Colorless needles, mp 135° (97 mg) **31**.

This compound (**31**) was identical with the product, which was synthesized as described above from **12** and **30**, by mixed melting point and comparison of their IR and NMR spectra.

3-Methoxy-4-benzyloxyphenethyl Alcohol (35)——To an ice-cooled mixture of **34**[18] (4.8 g) and $NaBH_4$ (1 g) in THF (30 ml) was added dropwise BF_3-etherate (1.5 ml) with stirring and the mixture was stirred at room temperature for 5 hr. The mixture was similarly treated as described for the synthesis of **29** to give a crude product, which was recrystallized from benzene. Colorless needles, mp 71—72° (lit.[19] mp 70—70.5°) (3.8 g) **35**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH). NMR ($CDCl_3$) τ: 8.47 (1H, s, OH), 7.24 (2H, t, J=7 Hz, $\underline{CH_2}CH_2OH$), 6.22 (2H, t, J=$CH_2\underline{CH_2}OH$), 6.16 (3H, s, OCH_3), 4.49 (2H, s, $OC\underline{H_2}C_6H_5$), 3.52—3.16 (3H, m, 3×arom. H), 2.84—2.52 (5H, m, 5×arom. H).

4-Benzyloxy-3-methoxyphenyl Acetaldehyde (36)——To a stirred solution of p.c.c (2.5 g) dissolved in dry CH_2Cl_2 (50 ml) was added dropwise a solution of **35** (1 g) in dry CH_2Cl_2 (10 ml) for 30 min under ice cooling. The mixture was stirred at room temperature for 2 hr. The mixture was treated as described for the synthesis of **30** to afford almost pure product. Colorless oil,[20] (700 mg) (**36**). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2820, 2720, 1720 (CHO). NMR ($CDCl_3$) τ: 6.46 (2H, d, J=2 Hz, $C\underline{H_2}CHO$), 6.18 (3H, s, OCH_3), 4.94 (2H, s, $OC\underline{H_2}$-C_6H_5), 3.48—3.12 (3H, m, 3×arom. H), 2.70 (5H, br. s, 5×arom. H), 0.46 (1H, t, J=2 Hz, CHO).

1-(3′-Methoxy-4′-benzyloxy)-6-methoxy-7-benzyloxy-N-tosyl-1,2,3,4-tetrahydroisoquinoline (37)——To a solution of **13** (600 mg) and **36** (570 mg) in $CHCl_3$ (30 ml) was added dropwise $POCl_3$ (1 ml), and stirred at room temperature for 2 hr. Treatment described for **14** gave a brownish oil. The oily residue was submitted to column chromatography on silica gel using benzene and $CHCl_3$ (1: 1) mixture, and subsequently recrystallized from EtOH. Colorless needles, mp 119—120° (570 mg) **37**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1340, 1155 (SO_2). NMR ($CDCl_3$) τ: 7.64 (3H, s, CH_3), 6.28, 6.21 (6H, 2×s, 2×OCH_3), 5.14 (2H, s, $OC\underline{H_2}C_6H_5$), 5.02 (1H, t, J=7 Hz, C_1-H), 4.92 (2H, s, $OC\underline{H_2}C_6H_5$), 2.94 (2H, d, J=8 Hz, 2×arom. H), 2.64 (10H, br. s, 10×arom. H), 2.61 (2H, d, J=8 Hz, 2×arom. H). *Anal.* Calcd. for $C_{39}H_{39}NO_6S$: C, 72.09; H, 6.05; N, 2.16. Found: C, 72.00; H, 5.99; N, 2.10.

***dl*-1-(3′-Methoxy-4′-hydroxybenzyl)-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (*dl*-Nororientaline (33))**——A solution of **37** (370 mg) in dry THF (15 ml) and absolute EtOH (3 ml) was added dropwise

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to a solution of Li (800 mg) in liquid NH_3 (80 ml) with stirring. The reaction mixture was stirred for 30 min, and then treated with absolute EtOH (10 ml) to destroy excess Li. NH_3 was evaporated, and the residue was diluted with water. The resultant suspension was neutralized with dil. HCl and extracted with ether. The ethereal layer was washed with water and dried over Na_2SO_4, followed by evaporation. The brown-red oil obtained was purified by column chromatography on silica gel using MeOH and $CHCl_3$ (1: 10) mixture. Colorless oil, (52 mg) **33**. TLC, $Rf=0.36$ (MeOH: acetone=1: 1). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (OH). NMR ($CDCl_3$) τ: 6.20, 6.19 (6H, 2×s, 2×OCH_3), 5.96 (1H, d. d, $J=4$, 10 Hz, C_1-H), 5.52 (3H, br. s, NH and 2×OH), 3.48—3.08 (5H, m, 5×arom. H). Hydrochloride: Colorless needles, mp 248—250° (decomp.) (lit.[21] mp 250—252°).

This compound (**33**) was completely identical with natural N-nororientaline,[13] previously isolated by us, by their comparison of IR ($CHCl_3$) and NMR ($CDCl_3$) spectra.

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