

ASYMMETRIC SYNTHESIS OF SALSOLIDINE

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Optically active salsolidine (8) was isolated by reduction of 2-alkyl-3,4-dihydro-6,7-dimethoxy-1-methylisoquinolinium iodides (6) with sodium borohydride followed by hydrogenolysis of N-alkylsalsolidines (7) with 10 % palladium hydroxide on charcoal. The optical purities ranged from 15 to 44 %.

Proskurina and Orekhov had isolated (-)-salsolidine from Salsola arbuscula,<sup>1</sup> which was then synthesized by Bischler-Napieralski reaction<sup>2,3</sup> and by Pictet-Spengler condensation,<sup>4,5</sup> followed by resolution.<sup>5</sup> Battersby and Edwards<sup>6</sup> determined that natural (-)-salsolidine had (S)-configuration by degradation to 2-carboxyethyl-(S)-alanine, which was prepared by cyanoethylation of (S)-alanine. We now wish to report the asymmetric synthesis of salsolidine by using optically active amines (2a - c).

The Schiff bases (3) were prepared by the reaction of 3,4-dimethoxyphenylacetaldehyde (1) with optically active amines (2) in dry benzene at room temperature and then reduced with sodium borohydride to give N-alkyl-3,4-dimethoxyphenethyl-

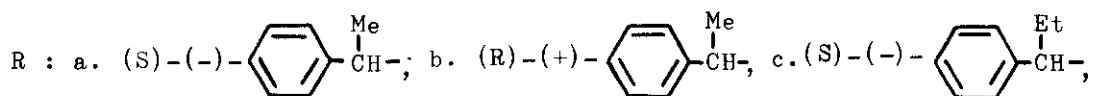
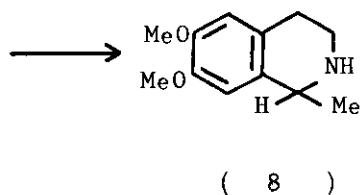
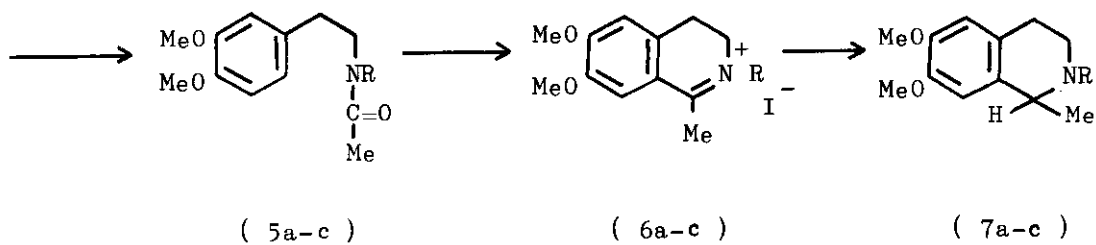
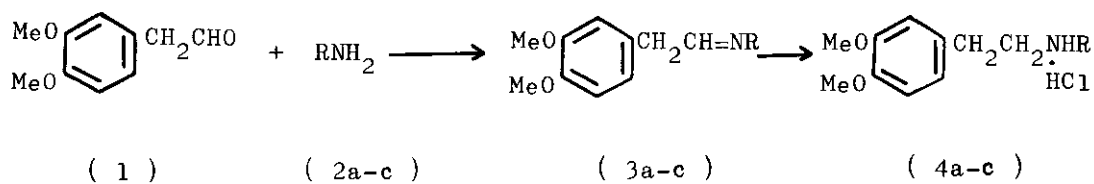


Table I      Synthesis of Optically Active Salsolidine

Compounds	Starting Material		Isolated Salsolidine	
	Configuration of R <sup>a</sup>	Configuration	$[\alpha]_D^{25}$ (EtOH) <sup>b</sup> (c = 0.5 - 2.1)	Optical Purity <sup>c</sup> %
6a	(S)-(-)-C <sub>6</sub> H <sub>5</sub> CH-   CH <sub>3</sub>	(S)-(-)	-21.6 ~ -26.1°	36 - 44
6b	(R)-(+)-C <sub>6</sub> H <sub>5</sub> CH-   CH <sub>3</sub>	(R)-(+)	+23.0 ~ +24.1°	39 - 41
6c	(S)-(-)-C <sub>6</sub> H <sub>5</sub> CH-   C <sub>2</sub> H <sub>5</sub>	(S)-(-)	- 8.8 ~ -12.6°	15 - 21

a (S)-(-)- $\alpha$ -Methylbenzylamine,  $[\alpha]_D^{24}$  -41.2° (benzene), (R)-(+)- $\alpha$ -methylbenzylamine,  $[\alpha]_D^{24}$  + 40.5° (benzene), (S)-(-)- $\alpha$ -ethylbenzylamine,  $[\alpha]_D^{24}$  - 20.8° (benzene).

b The specific rotation was measured by the use of a JASCO-ORD/UV-5 optical rotatory dispersion photometer.

c The optical purity is defined as  $[\alpha]_D^{\text{obsd.}}/[\alpha]_D^{\text{d}} \times 100$ . (S)-(-)-Salsolidine,  $[\alpha]_D^{22}$  - 59.5°  $\pm$  0.5° (EtOH).<sup>6</sup>

d The value of natural product.

amines which were isolated as the hydrochloride (4). Acetylation of these amines with acetic anhydride and pyridine gave N-alkyl-N-(3,4-dimethoxyphenethyl)acetamides (5) as an oil. Cyclization of 5 with phosphoryl chloride in dry toluene gave 2-alkyl-3,4-dihydro-6,7-dimethoxyisoquinolinium chlorides, which were converted with sodium iodide to the isoquinolinium iodides (6). The iodides (6) were reduced with sodium borohydride in methanol to give N-alkylsalsolidines (7), which were subsequently cleaved by hydrogenolysis with 10 % palladium hydroxide on charcoal to give salsolidine (8) after purification on silica gel thin layer chromatography. In this case the optically active compounds (7a-c) were not isolated to prevent from fractionation during purification. The results are summarized in Table I.

The optical purities of the synthetic salsolidine ranged from 15 to 44 %. When (S)-(-)-amines and (R)-(+)-amine were used, the resulting salsolidines were (S)- and (R)- configuration, respectively. The use of  $\alpha$ -methylbenzylamine gave a higher optical purity than the case of  $\alpha$ -ethylbenzylamine. This reaction using other resolving agents is now under examination.

#### REFERENCES

- 1 N. Proskurina and A. Orekhov, Bull. Soc. chim. France, 1939, 144.
- 2 E. Späth and F. Dengel, Ber., 1938, 71, 113.
- 3 I. Jezo, M. Karvas, and K. Tihlark, Chem. Zvesti, 1960, 14, 38.
- 4 O. Kovacs and G. Fodor, Ber., 1951, 84, 795.
- 5 C. Schöpf and H. Bayerle, Annalen, 1934, 513, 190.
- 6 A. R. Battersby and T. P. Edwards, J. Chem. Soc., 1960, 1214.

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