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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 arbusaula,[1] which was then synthesized by Bischler-Napieralski reaction[2,3] and by Pictet-Spengler condensation,[4,5] followed by resolution.[5] Battersby and Edwards[6] 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-

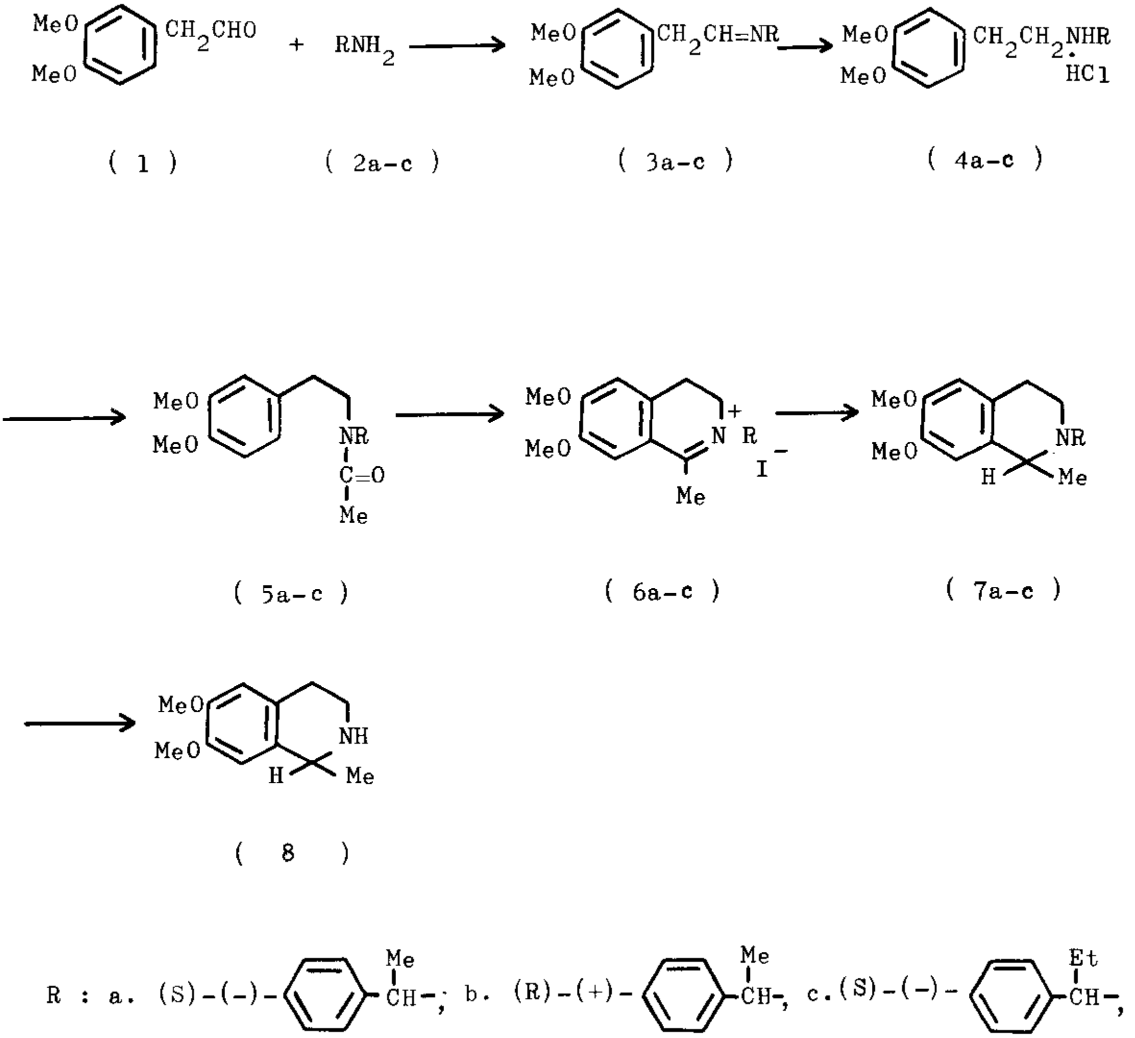
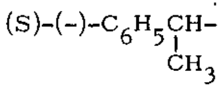
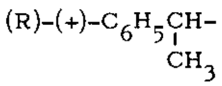
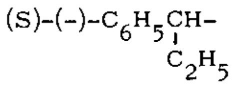

(1)
(2a–c)
(3a–c)
(4a–c)
(5a–c)
(6a–c)
(7a–c)
(8)
MeO
CH2CHO
RNH2
CH2CH=NR
CH2CH2NHR·HCl
NR
C=O
Me
N R
I–
NH
H
R : a. (S)-(–)-
CH–;
b. (R)-(+)-
CH–,
c.(S)-(–)-
Et
CH–,

Table I Synthesis of Opticaly Active Salsolidine

Starting Material		Isolated Salsolidine		
Compounds	Configuration of R[a]	Configuration	$[\alpha]_D^{25}$(EtOH)[b] (c = 0.5 - 2.1)	Optical Purity[c] %
6a	 $(S)\text{-}(-)\text{-}C_6H_5\underset{\displaystyle CH_3}{\underset{\vert}{C}}H\text{-}$	(S)-(-)	$-21.6 \sim -26.1^\circ$	36 - 44
6b	 $(R)\text{-}(+)\text{-}C_6H_5\underset{\displaystyle CH_3}{\underset{\vert}{C}}H\text{-}$	(R)-(+)	$+23.0 \sim +24.1^\circ$	39 - 41
6c	 $(S)\text{-}(-)\text{-}C_6H_5\underset{\displaystyle C_2H_5}{\underset{\vert}{C}}H\text{-}$	(S)-(-)	$-8.8 \sim -12.6^\circ$	15 - 21

a (S)-(-)-α-Methylbenzylamine, $[\alpha]_D^{24}$ -41.2° (benzene), (R)-(+)-α-methylbenzylamine, $[\alpha]_D^{24}$ $+40.5^\circ$ (benzene), (S)-(-)-α-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 $[\alpha]_D^{obsd.}/[\alpha]_D^{d}$ x 100. (S)-(-)-Salsolidine, $[\alpha]_D^{22}$ $-59.5^\circ \pm 0.5^\circ$ (EtOH).[6]

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 α-methylbenzylamine gave a higher optical purity than the case of α-ethylbenzylamine. This reaction using other resolving agents is now under examination.

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