Studies on the Syntheses of Heterocyclic Compounds. Part 687.† Asymmetric Synthesis of Salsolidine

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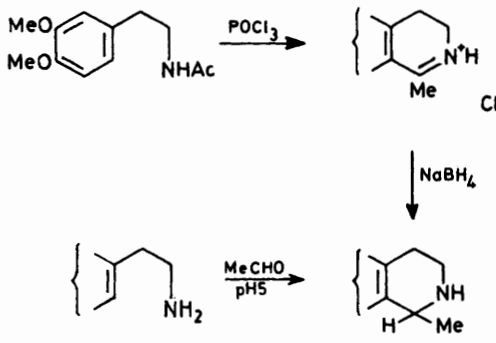
Syntheses of optically active salsolidine (8) were achieved by reduction of optically active *N*-alkyl-3,4-dihydro-6,7-dimethoxyisoquinolinium iodides (6b—e) with sodium borohydride, followed by hydrogenolysis of the resulting optically active *N*-alkylsalsolidines (7b—e) over 10% palladium hydroxide–charcoal. The optical purities of the salsolidine samples obtained were in the range of 15—44%.

PROSKURNINA AND OREKHOV isolated (—)-salsolidine from *Sasola arbusaula*;[1] the alkaloid has since been synthesized by a Bischler–Napieralski reaction[2,3] and by

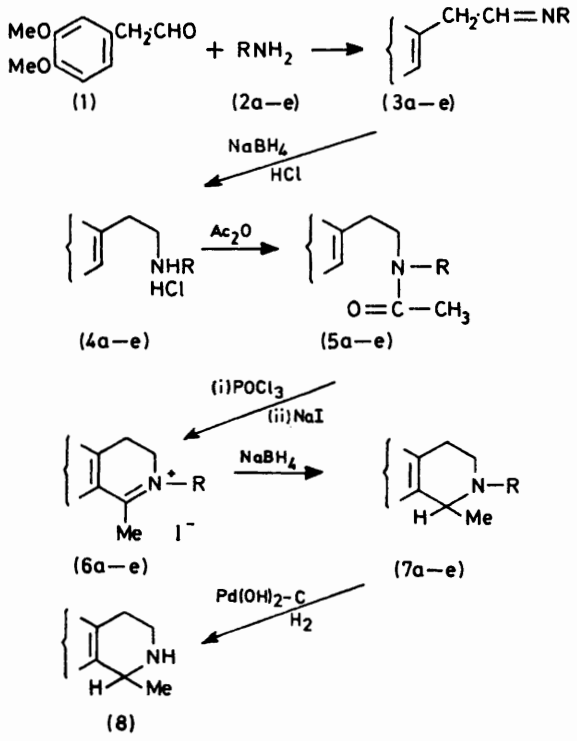


SCHEME 1

Pictet–Spengler condensation[4,5] followed by resolution (Scheme 1).[5] Battersby and Edwards[6] determined that natural (—)-salsolidine had the *S*-configuration by degradation to 2-carboxyethylamine, which was also prepared by cyanoethylation of (*S*)-alanine.

In the present study, we tried to apply the Bischler–Napieralski reaction to the asymmetric synthesis of salsolidine. The synthesis involved ring closure of *N*-acetyl-*N*-alkyl-3,4-dimethoxyphenethylamine with phosphoryl chloride, followed by reduction with sodium borohydride, and hydrogenolysis over 10% palladium hydroxide–charcoal. When the *N*-alkyl groups were chiral, optically active salsolidine was obtained (Scheme 2).

The alkyl groups used were derived from (a) benzylamine, (b) (+)-(*R*)-α-methylbenzylamine, (c) (—)-(*S*)-α-methylbenzylamine, (d) (—)-(*S*)-α-ethylbenzylamine, and (e) (—)-(*S*)-1-(1-naphthyl)ethylamine. 3,4-Dimethoxyphenylacetaldehyde (1) was prepared by the reaction of sodium 3-(3,4-dimethoxyphenyl)glycidate with acetic acid in dry benzene.[7] The Schiff's bases (3a—e) were obtained by the reaction of the aldehyde (1) with the amines (2a—e) in benzene; reduction with sodium borohydride then gave *N*-alkyl-(3,4-dimethoxyphenyl)-ethylamines, isolated as the hydrochlorides (4a—e) (Table 1). Acetylation with acetic anhydride–pyridine gave the *N*-acetyl-*N*-(3,4-dimethoxyphenethyl)acetamides (5a—e), which were refluxed with phosphoryl chloride in dry toluene for 3 h; treatment with sodium iodide then gave the *N*-alkyl-3,4-dihydro-6,7-dimethoxyisoquinolinium iodides (6a—e) (Table 2). Reduction with sodium borohydride gave the *N*-alkylsalsolidines



a; R = Ph b; R = (+)-(*R*)-PhCHMe c; R = (—)-(*S*)-PhCHMe
d; R = (—)-(*S*)-PhCHEt e; R = (—)-(*S*)-$C_{10}H_7$CHMe

SCHEME 2

(7a—e). *N*-Benzylsalsolidine (7a) was isolated, but the other, optically active *N*-alkylsalsolidines (7b—e) were not, in order to prevent loss of activity during purification. The *N*-alkylsalsolidines (7b—e) were

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[4] O. Kovacs and G. Fodor, *Chem. Ber.*, 1951, **84**, 795.
[5] C. Schöpf and H. Bayerle, *Annalen*, 1934, **513**, 190.
[6] A. R. Battersby and T. Edwards, *J. Chem. Soc.*, 1960, 1214.
[7] Y. Ban and T. Oishi, *Chem. and Pharm. Bull. (Japan)*, 1958, **6**, 574.

hydrogenolysed over 10% palladium hydroxide–charcoal to yield optically active samples [(b)—(e)] of salsolidine (Table 3). Optical purities were in the range 15—44%. When (−)-(*S*)-amine was used, (−)-(*S*)-salsolidine was formed, and (+)-(*R*)-amine gave (+)-(*R*)-salsolidine. α-Methylamine gave higher optical purity (36—44%) than α-ethylbenzylamine (15—21%). These results are similar to those obtained in asymmetric syntheses of amino-acids by reduction of an azomethine bond with sodium borohydride [8] (optical purities 9—36%). The increased optical purity in the present case may be ascribable to the facts that the substrates are cyclic compounds and the reduction involves a quaternary salt.

TABLE 1

N-Alkyl-3,4-dimethoxyphenethylamine hydrochlorides (4a—e)

	M.p. (°C)	$[\alpha]_D^{20}$ (EtOH) (°)	Yield (%) [a]	Formula	Microanalyses (%)			
(4a)	205—206		45	$C_{17}H_{21}NO_2$,HCl	Reqd.	C, 66.35	H, 7.2	N, 4.55
					Found	66.15	7.45	4.5
(4b) [b]	218—219	+69.9 (*c* 1.3)	49	$C_{18}H_{23}NO_2$,HCl	Reqd.	C, 67.15	H, 7.2	N, 4.35
					Found	66.8	7.55	4.7
(4c) [c]	217—218	−70.0 (*c* 2.1)	42	$C_{18}H_{23}NO_2$,HCl	Reqd.	C, 67.15	H, 7.2	N, 4.35
					Found	67.2	7.55	4.5
(4d) [d]	183—184	−57.5 (*c* 2.2)	42	$C_{19}H_{25}NO_2$,HCl	Reqd.	C, 67.95	H, 7.8	N, 4.15
					Found	67.95	8.0	3.95
(4e) [e]	217—218	+16.8 (*c* 2.4)	48	$C_{22}H_{25}NO_2$,HCl	Reqd.	C, 71.05	H, 7.05	N, 3.75
					Found	71.15	7.1	3.9

[a] From the aldehyde (1). [b] From (2b), $[\alpha]_D^{24}$ +40.5° (benzene). [c] From (2c), $[\alpha]_D^{24}$ −41.2° (benzene). [d] From (2d), $[\alpha]_D^{24}$ −20.8° (benzene). [e] From (2e), $[\alpha]_D^{24}$ −87.0° (benzene).

TABLE 2

N-Alkyl-3,4-dihydro-6,7-dimethoxyisoquinolinium iodides (6a—e)

	M.p. (°C)	$[\alpha]_D^{20}$ (EtOH) (°)	Yield (%) [a]	Formula	Microanalyses (%)			
(6a)	211—213		28	$C_{19}H_{22}INO_2$	Reqd.	C, 53.9	H, 5.25	N, 3.3
					Found	53.7	5.45	3.2
(6b)	205—206	−37.4 (*c* 2.3)	18	$C_{20}H_{24}INO_2$	Reqd.	C, 54.95	H, 5.55	N, 3.2
					Found	54.6	5.3	3.3
(6c)	207—208	+38.1 (*c* 1.2)	21	$C_{20}H_{24}INO_2$	Reqd.	C, 54.95	H, 5.55	N, 3.2
					Found	54.2	5.35	3.05
(6d)	185—186	+16.1 (*c* 1.2)	15	$C_{21}H_{26}INO_2$	Reqd.	C, 55.9	H, 5.8	N, 3.1
					Found	55.55	5.6	3.4
(6e)	Syrup	−13.3 (*c* 0.8)	23	$C_{24}H_{26}INO_2$				

[a] From the amines (4).

TABLE 3

Optically active salsolidine (8)

Sample	Configuration	$[\alpha]_D^{20}$ (EtOH) (°)	Optical purity (%) [a]
(b)	(+)-(*R*)	+23.0—24.1	39—41
(c)	(−)-(*S*)	−21.6—26.1	36—44
(d)	(−)-(*S*)	−8.8—12.6	15—21
(e)	(−)-(*S*)	−16.4—18.2	28—31

[a] Defined as ($[\alpha]_D$ obs./$[\alpha]_D$ natural) × 100 {(−)-(*S*)-salsolidine has $[\alpha]_D^{25}$ −59.3° (EtOH)}.[6]

EXPERIMENTAL

Hydrogenation was carried out in a Skita and Parr apparatus. Specific rotations were measured with a JASCO DIP 4 polarimeter (10 mm cell).

(−)-(S)-N-(3,4-*Dimethoxyphenethylidene*)-α-*methylbenzylamine* (3c).—A solution of (−)-(*S*)-α-methylbenzylamine (2c) (2.4 g, 0.02 mol) in benzene (10 ml) was gradually added to a solution of distilled 3,4-dimethoxyphenylacetaldehyde (1) [7] (3.6 g, 0.02 mol) in dry benzene (20 ml) cooled with ice–water. The mixture was set aside overnight at room temperature, filtered, and evaporated to dryness under reduced pressure to give the Schiff's base (3c), $\nu_{max.}$ (film) 1 640 cm^{-1} (C=N), which was hydrogenated without purification. The other Schiff's bases were prepared in a similar way.

(−)-(S)-N-(α-*Methylbenzyl*)-3,4-*dimethoxyphenethylamine Hydrochloride* (4c).—The crude Schiff's base (3c) was dissolved in 99% ethanol (30 ml). Sodium borohydride (0.8 g, 0.02 mol) was gradually added with cooling (ice–water). The mixture was then stirred for 3 h at room temperature, and added to aqueous 1% sodium hydrogen carbonate (20 ml). The ethanol was evaporated off under reduced pressure, and the aqueous solution was extracted with ether (2 × 20 ml). The extracts were dried (Na_2SO_4) and dry hydrogen chloride was introduced with cooling (ice–water). The precipitated *amine hydrochloride* (4c) was recrystallised from ethanol; yield 2.7 g (42%), m.p. 217—218°, $[\alpha]_D^{20}$ −70.0° (*c* 2.1 in EtOH). The other *N*-alkyl-3,4-dimethoxyphenethylamine hydrochlorides were prepared in a similar way (Table 1).

(−)-(S)-N-(3,4-*Dimethoxyphenyl*)-N-(α-*methylbenzyl*)-*acetamide* (5c).—A mixture of the amine hydrochloride (4c) (0.64 g, 2 mmol), acetic anhydride (0.26 g, 2.5 mmol), and pyridine (0.32 g, 4 mmol) in dry benzene (15 ml) was refluxed for 3 h with stirring. The solution was washed with N-hydrochloric acid (10 ml), aqueous 1% sodium hydrogen carbonate (10 ml), and water (10 ml), dried (Na_2SO_4), and distilled under reduced pressure to leave an oil, $\nu_{max.}$ (film) 1 630 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 275 and 230 nm, which was used without purification. The other acetylated compounds were prepared in a similar way.

[8] K. Harada and J. Oh-hashi, *Bull. Chem. Soc. Japan*, 1970, **43**, 960.

(−)-(S)-3,4-*Dihydro*-6,7-*dimethoxy*-1-(α-*methylbenzyl*)-*isoquinolinium Iodide* (6c).—The crude acetylated compound (5c) and phosphoryl chloride (1.2 g, 7.6 mmol) were dissolved in dry toluene (10 ml). The mixture was refluxed for 4 h, cooled, and added to dry n-hexane (15 ml); the solution was decanted to remove n-hexane (10 ml) three times, and then added to ethanolic 10% sodium iodide (1 ml). The ethanolic solution was evaporated to a one-third volume. After removal of the precipitated sodium chloride, the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol to give *pale yellow needles* (6c) (0.13 g, 15%), m.p. 207—208°, $\lambda_{max.}$ (EtOH) 312 nm, $[\alpha]_D^{20}$ +38.1° (*c* 1.2 in EtOH). The other quaternary salts (6) were made similarly (Table 2).

N-*Benzylsalsolidine* (7a).—To a solution of *N*-benzyl-3,4-dihydro-6,7-dimethoxyisoquinolinium iodide (6a) (0.5 g, 12 mmol) in 99% ethanol (20 ml) cooled in ice–water was gradually added sodium borohydride (0.1 g, 2.7 mmol). The mixture was then stirred for 30 min at room temperature, and evaporated to dryness under reduced pressure. The residue was dissolved in aqueous 1% sodium hydrogen carbonate (20 ml) and this solution was extracted with ether (2 × 15 ml). The extracts were dried (Na_2SO_4) and evaporated and the residue was recrystallised from ethanol to give the *product* (7a) (0.24 g, 67%), m.p. 135—136° (Found: C, 76.85; H, 7.85; N, 4.85. $C_{19}H_{23}NO_2$ requires C, 76.75; H, 7.85; N, 4.7%), $\lambda_{max.}$ (EtOH) 282 nm. The optically active compounds (7b—e), prepared in a similar way, were used without purification.

Salsolidine (8).—A solution of *N*-benzylsalsolidine (7a) (0.2 g, 0.7 mmol) in 99% ethanol (50 ml) was hydrogenolysed over 5% palladium hydroxide–charcoal (0.2 g) for 12 h. The product was isolated as the *hydrochloride* (0.11 g, 65%), m.p. 239—241° (Found: C, 58.85; H, 7.35; N, 5.75. $C_{12}H_{17}NO_2$,HCl requires C, 59.15; H, 7.45; N, 5.75%). $\lambda_{max.}$ (EtOH) 276 and 231 nm; δ($CDCl_3$) 3.47 (2 H, d, ArH), 6.17 (6 H, s, 2 × OMe), 6.11 (2 H, m, CH_2), 6.95 (1 H, q, CH_2), 7.23 (2 H, m, CH_2), 8.22 (1 H, s, NH), and 8.57 (3 H, d, CH_3). The optically active salsolidines were not isolated; their specific rotations were measured immediately after evaporation to dryness, followed by drying (NaOH).

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