An Efficient *O*-Dealkylation Procedure for the Synthesis of (3a*S*,*cis*)-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethylpyrrolo[2,3-*b*]indol-5-yl-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate

Zhongli Gao,* Thomas B. K. Lee,† and Barbara S. Rauckman

Hoechst Marion Roussel, Inc., Route 202-206, P. O. Box 6800, Bridgewater, NJ 08807

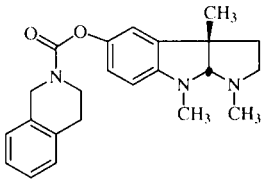
Received August 10, 1999

The title compound is synthesized in high yields and purity from (-)-eserethole (**2a**) *via* a lithium bromide catalyzed hydrobromic acid *O*-dealkylation procedure as the key step.

J. Heterocyclic Chem., **37**, 331 (2000).

The title compound (**1**) is a cholinesterase inhibitor [1] currently undergoing clinical trials for the treatment of Alzheimer's disease. With an increasing demand for **1** for clinical trials, a chemical process for the large-scale synthesis of this compound is highly desired. Although a process using (-)-eserethole (**2a**) as the starting material has been developed in this laboratory [2], it has become more restrictive for production scale synthesis because the process involved the use of dichloroethane as the reaction solvent and required column chromatography for final product purification. Dichloroethane is a carcinogenic suspect agent. The use of column chromatography in purification has a major impact on cost and capacity for production. For these reasons, we embarked on the search for a more practical process.

The first task in this endeavor centered on the *O*-dealkylation of **2**. As observed previously [1-2], the *O*-dealkylation product eseroline (**3**) is extremely sensitive to air oxidation and is thermally unstable. This presents a substantial challenge in the development of an *O*-dealkylation methodology which meets the production requirements. Although the *O*-dealkylation methodologies



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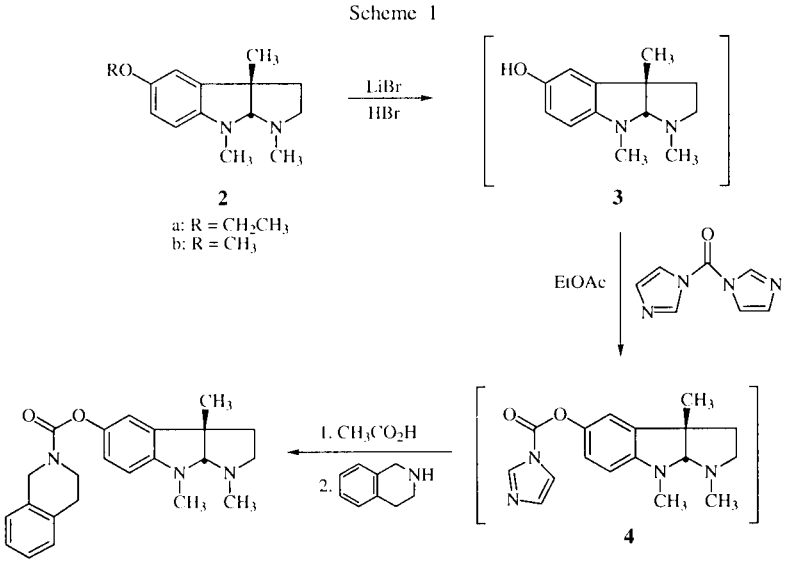
for phenol ethers have been well-documented in the literature [3], none of the methods meets the current production requirements such as: (1) exclusion of halogenated solvents; (2) environmental compatibility; (3) high product yields and purity; and (4) no column chromatography.

Since **3** is unstable, it would be desirable to minimize the reaction time and eliminate the isolation of this intermediate. Early attempts to use aqueous hydrobromic acid (48%), a well-known dealkylating agent [4], gave unsatisfactory results. The reaction required more than 14 hours and gave rise to a large amount of decomposition impurities (Table 1, Entry 1-3). We describe herein a practical *O*-dealkylation procedure which leads to a process suitable for the multi-kilogram scale synthesis of **1**.

Scheme 1



As shown in Scheme 1, the mixture of **2a** and lithium bromide in aqueous hydrobromic acid is heated at 90-100° for 5 hours under nitrogen. The mixture is then cooled and poured into cold water. The acidic solution is basified with potassium hydroxide (10-20%) and extracted with ethyl acetate. This ethyl acetate solution is dried and used directly in the next step of the reaction without isolation of the product. This method provides crude **3** in 90-94% yield and 97-98% purity (HPLC).

Detailed studies revealed that the *O*-dealkylation of **2** using aqueous hydrobromic acid was accelerated by lithium bromide (Table 1, Entry 4-6). The reaction rate increases as the amount of lithium bromide increases, with the limitation of the solubility of lithium bromide. The *O*-dealkylation reaction without lithium bromide under the same conditions is extremely slow (Table 1, Entry 4). The catalytic effect of halides increases in the order of: lithium bromide >> sodium bromide > potassium bromide (Table 1, Entry 6-8); lithium iodide ~ lithium bromide >> lithium chloride (Table 1, Entry 6, 9-10). No catalytic effect was observed with ammonium bromide, triethylammonium bromide or lithium chloride. The use of 1-3 equivalents of hydriodic acid in aqueous hydrobromic acid was found to be effective in the *O*-dealkylation of **2** (Table 1, Entry 11). This is foreseeable because the *O*-dealkylation reaction is enhanced by the good nucleophile iodide and higher acidity of the reaction medium contributed from hydroiodic acid. The concentration of hydrobromic acid also affects the reaction rate (Table 1, Entry 12-14). The rate increases as the hydrobromic acid concentration increases. This is due to the fact that higher acidity of the reaction medium increases the concentration of protonated **2** which is believed to be the intermediate towards the *O*-dealkylation.

Conversion of **3** to the final product **1** was accomplished by the sequential treatment of crude **3** in ethyl acetate with 1,1-carbonyl-diimidazole (CDI), acetic acid and 1,2,3,4-tetrahydroisoquinoline at room temperature. The overall yield of **1** from **2**a is 70-73% and the final product purity is > 99.0% (HPLC).

In conclusion, a practical process for the multi-kilogram production of **1** was developed. This process gives **1** in high yields, high purity, and does not involve isolated intermediates, halogenated solvents or column chromatography. During this synthetic study, a new and efficient *O*-dealkylation procedure was developed.

EXPERIMENTAL

High performance liquid chromatographic analyses were performed on a Perkin-Elmer TurboLC plus HPLC. Melting point was determined on a Perkin-Elmer DSC 7. Nuclear magnetic resonance spectrum was taken on a Varian XL-200; chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Infrared spectrum was taken on a Perkin-Elmer 1420 Ratio Recording Infrared Spectrophotometer. Mass spectrum was determined in the electron impact mode by direct insertion at 70 eV with a Finnigan 4000 GC-MS equipped with a INCOS data system. Elemental analysis was performed by Robertson Microlit Laboratories, Madison, NJ.

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72 g of lithium bromide was dissolved in 36 ml of water and 40 ml of 48% aqueous HBr. The clear solution was cooled in an ice bath. To this cold solution was added 20 g (81.2 mmol) of eserethole (**2**). The mixture was then heated in an oil bath to 90-100° for 5 hours. The mixture was cooled to room temperature and

Table 1

O-dealkylation of **2**

Entry	R	Concentration of of hydrobromic acid (%)	Volume (ml/g of **2**)	Additives	Amount (equivalent to **2**)	Reaction Time (h)	Conversion [a] (%)	Yield of **3** [b] (%)
1	Me	48	10	-	0	14.0	97	91.9
2	Et	48	10	-	0	14.0	91	88.8
3	Et	48	4	-	0	14.0	82	35.3
4	Et	24	8	-	0	9.0	11	9.0
5	Et	24	4	LiBr	5	9.0	91	77.0
6	Et	24	4	LiBr	10	5.0	98	95.0
7	Et	24	8	NaBr	10	9.0	59	49.3
8	Et	24	8	KBr	10	9.0	22	18.7
9	Et	24	8	LiCl	10	9.0	20	17.0
10	Et	24	8	LiI	10	5.0	98	94.8
11	Et	24	4	HI (57%)	3	16.0	91	77.4
12	Et	36	8	LiBr	10	5.0	100	95.9
13	Et	12	8	LiBr	10	9.0	33	27.8
14	Et	6	8	LiBr	10	9.0	14	10.9

[a] Relative area by HPLC. [b] External standard HPLC.

poured into 600 ml of ice water. The acidic solution was basified with potassium hydroxide (10%) to pH 9.5-10 and extracted with ethyl acetate (2 x 200 ml). The combined extracts were dried over 40 g of potassium carbonate and filtered under nitrogen. The filtrate, containing 16.0 g (90% by hplc) of eseroline, was concentrated to 100 ml of total volume and treated with 15.1 g (94 mmol) of 1,1-carbonyldiimidazole (CDI), followed by 14.8 ml of acetic acid and 12.0 g (90 mmol) of 1,2,3,4-tetrahydroisoquinoline. The mixture was allowed to stir overnight at ambient temperature under nitrogen. The reddish reaction mixture was washed with 40 ml of water. The aqueous solution was back extracted with ethyl acetate (40 ml). The combined ethyl acetate extract was then extracted twice with dilute hydrochloric acid. The combined acidic extract was neutralized with sodium hydroxide to pH 7.0 and extracted with cyclohexane (2 x 120 ml). After drying with potassium carbonate, the solution was treated with 25 g of alumina (activated, neutral, Brockmann I, 150 mesh, Aldrich) and concentrated to a residue which was crystallized to obtain 22.8 g (74.3%) of **1** as a white granular crystalline solid (99.5% purity by hplc); mp 77-78°; ir (chloroform): 3010, 2960, 2870, 1717, 1618, 1500, 1455, 1422; ^{1}H nmr (deuteriochloroform): δ 7.18 (m, 4H), 6.80 (m, 2H), 6.35 (d, 1H), 4.75 (br, d, 2H), 4.11 (s, 1H), 3.81 (m, 2H), 2.94 (m, 2H), 2.91 (s, 3H), 2.69 (m, 2H), 2.53 (s, 3H), 1.93 (m, 2H), 1.41 (s, 3H); ms: 377 (M^+), 333, 217, 174, 160, 142, 132, 117.

Anal. Calcd. for $C_{23}H_{27}O_2N_3$: C, 73.18; H, 7.21; N, 11.13. Found: C, 72.97; H, 7.12; N, 11.05.

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† Current address: Pharmaceutical Process Development, Roche Carolina, Inc., 6173 E. Old Marion Highway, Florence, SC 29506-9300.

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