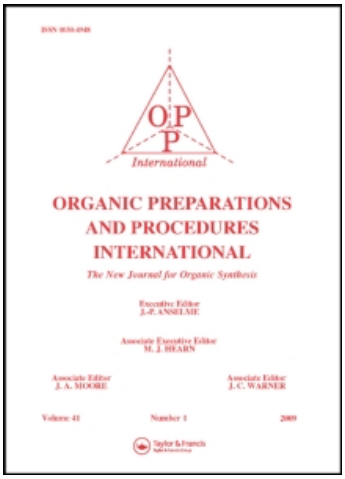

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A SIMPLE, ONE-POT PROCEDURE FOR THE PREPARATION OF DOPAMINERGIC ALKYLTHIOAPOMORPHINES

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A SIMPLE, ONE-POT PROCEDURE FOR THE PREPARATION OF DOPAMINERGIC ALKYLTHIOAPOMORPHINES

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(06/14/97)

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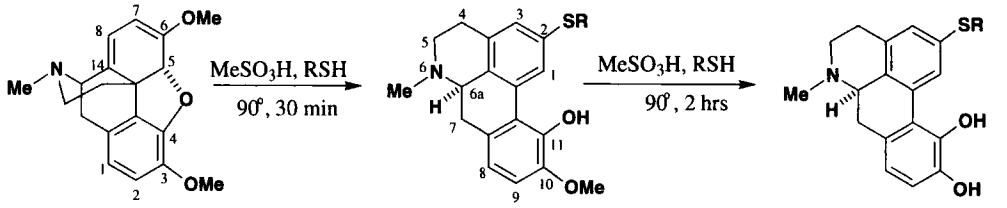
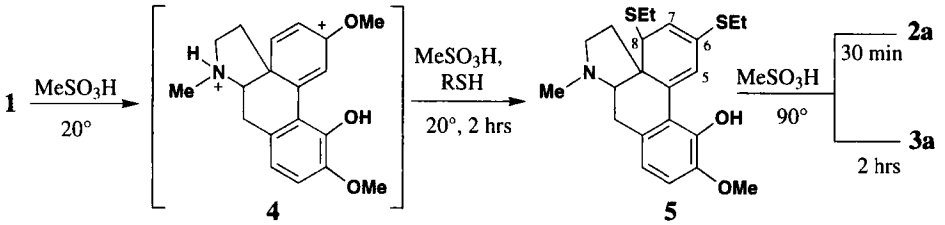
Our studies have shown that the methanesulfonic acid/thiol multi-functional reagent–combination is suitable for the conversion of natural thebaine (**1**) into 2-alkylthioapocodeines (**2a,b**) and 2-alkylthioapomorphines (**3a,b**). During the transformation, rearrangement of the skeleton, introduction of the alkylthio function, and cleavage of the phenol ether function proceed in three consecutive steps, which can be performed in a convenient, one-pot operation.



1 **2** **3**

In a preceding paper,[1] we have reported that the rearrangement of thebaine (**1**) with methanesulfonic acid in the presence of alcohols (ethanol, propanol, butanol) gives rise to the corresponding 2-alkoxyapocodeines, as the major products, accompanied by a by-product, 2-methoxyapocodeine. The formation of the main products is explained by partial transetherification of the methoxonium ion intermediate (**4**) of the rearrangement.[2]



4 **5**

In the presence of methanesulfonic acid/ethanethiol, the conversion of thebaine (**1**) was complete in 2 hours at 20°, and 6,8-diethylthiodeoxymetacodeine (**5**) was isolated, whose structure was determined by NMR and mass spectrometric measurements. Compound **5** is rather unstable even at ambient temperature, and on heating in methanesulfonic acid for 30 min, it is transformed into **2a**, whereas further heating leads to the conversion into **3a**. These findings suggest that development of the aporphine skeleton proceeds *via* the intermediacy of **5**, and also, that the cleavage of the phenol ether moiety is facilitated by the thiol, as acceptor of the methyl group, being cleaved during the rearrangement.

According to preliminary neuropharmacological studies, the new alkylthioapomorphines **3a** and **3b** appear to be effective dopamine D_2 agonist compounds.[3]

EXPERIMENTAL SECTION

Commercially available reagents and compounds were purchased from the Aldrich chemical company. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Thin layer cromatography was performed on precoated Merck 5554 Kieselgel 40 F_{254} foils. The spots were visualized with Dragendorff's reagent. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP 200 SY spectrometer, chemical shifts are reported in ppm (δ) from internal TMS, coupling constants (J) are given in Hz. Mass spectra were measured with a VG-7035 (GC-MS-DS) instrument at 70 eV using direct inlet system. Optical rotations were carried out by using a Perkin Elmer 311 polarimeter.

2-Alkylthioapocodeines (2a and 2b). General Procedure A.- A solution of thebaine (**1**) (1.0 g, 3.1 mmol) in a mixture of methanesulfonic acid (5 mL) and the appropriate thiol (12.4 mmol) at 20° was heated at 90° for 30 min; after cooling to room temperature, it was poured dropwise added to a stirred solution of potassium hydrogen carbonate (20 g) in water (100 mL) and extracted with chloroform (3 x 30 mL). The combined extracts were washed with saturated brine, dried ($MgSO_4$) and concentrated to give a crude syrupy mixture of the corresponding 2-alkylthioapocodeines (**2a, 2b**) and 2-alkylthioapomorphines (**3a, 3b**), which were separated by means of column chromatography (Kieselgel 40, 9:1 benzene-methanol) to isolate the following compounds:

2-Ethylthioapocodeine (2a) from ethanethiol and methanesulfonic acid, as the first-eluted compound. Yield: 0.46 g (42%), mp. 116-118° (diethyl ether). ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (t, 3H, C-CH_3), 2.55 (s, 3H, N-CH_3), 2.6-3.3 (m, 8H, CH), 3.95 (s, 3H, O-CH_3), 6.3 (s, 1H, OH), 6.8 (s, 2H, Ar-H), 7.05 (s, 1H, 3-H), 8.25 (s, 1H, 1-H). MS: m/e = 341 (M^+). $[\alpha]^2{}_D{}^0$ = -92° (c = 0.1, $CHCl_3$).

Anal. Calcd for $C_{20}H_{23}NO_2S$: C, 70.33; H, 6.78; N, 4.10; S, 9.38
Found: C, 70.55; H, 6.98; N, 3.95; S, 9.53

2-Ethylthioapomorphine (3a), as the second-eluted compound, which was converted into the HCl salt, 0.14 g (12%). The physical data of this compound are given in the following section.

2-Propylthioapocodeine (2b) from propanethiolic methanesulfonic acid, as the first-eluted compound. Yield: 0.58 g (51%), mp. 130-131° (EtOH). ^1H NMR (200 MHz, $CDCl_3$): δ 1.05 (t, 3H, C-CH_3), 1.7 (m, 2H, CH), 2.6 (s, 3H, N-CH_3), 2.6-3.4 (m, 8H, CH), 3.9 (s, 3H, O-CH_3), 6.75 (s, 1H, OH), 6.8 (s, 2H, Ar-H), 7.05 (s, 1H, 3-H), 8.25 (s, 1H, 1-H). MS: m/e = 355 (M^+). $[\alpha]^{20}_D$ = -140° (c = 0.1, $CHCl_3$).

Anal. Calcd $C_{21}H_{25}NO_2S$: C, 70.94 H, 7.08; N, 3.94; S, 9.01. Found: C, 70.69; H, 7.28; N, 3.71; S, 9.28

2-Propylthioapomorphine (3b), as the second-eluted compound, which was converted into its HCl salt, 0.1 g (8%). The physical data of this compound are given in the following section.

2-Alkylthioapomorphines (3a, 3b). General Procedure B.- Thebaine (**1**) (1.0 g, 3.1 mmol) was dissolved in a mixture of methanesulfonic acid (5 mL) and the appropriate thiol (12.4 mmol) at 20°. The mixture was heated at 90° for 4 h (in the case of ethanethiol the loss of the reagent due to evapora-

tion was compensated by the addition of 1 mL of the thiol every hour). After cooling to room temperature, the mixture was added dropwise to a stirred solution of potassium hydrogen carbonate (20 g) in water (100 mL) with external cooling with ice-water and then extracted with ethyl acetate (3 x 30 mL). The combined extracts were washed with a saturated brine, dried ($MgSO_4$), and concentrated to a thick syrup. It was dissolved in ether, filtered and the filtrate was evaporated to dryness. The residue was dissolved in ethanol (1 mL) and acidified to pH 3 with an ethanolic HCl solution. Upon addition of ether to the acidic solution the corresponding 2-alkylthioapomorphine-HCl salt was isolated.

The following compounds were obtained according to this procedure:

2-Ethylthioapomorphine Hydrochloride (3a•HCl) from ethanethiol and methanesulfonic acid. Yield: 0.38 g (35%), mp. 177-180°. ^{1}H NMR (200 MHz, CD_3OD): δ 1.3 (t, 3H, C-CH_3), 2.5-2.8 (m, 2H, CH), 2.9 (s, 3H, N-CH_3), 2.95-3.3 (m, 6H, CH), 6.6 (s, 2H, 8-H and 9-H), 7.1 (s, 1H, 3-H), 8.35 (s, 1H, 1-H). MS (from base): m/e = 327 (M^+). $[\alpha]_D^{20}$ = -135° (c = 0.2, CH_3OH).

Anal. Calcd $C_{19}H_{21}NO_2S$•HCl (363.9): C, 62.70; H, 6.09; N, 3.84; S, 8.81

Found: C, 62.51; H, 6.12; N, 3.58; S, 8.93

2-Propylthioapomorphine Hydrochloride (3b•HCl) from propanethiol and methanesulfonic acid. Yield: 0.46 g, (38%), mp. 161-165°, ^{1}H NMR (200 MHz, CD_3OD): δ 1.05 (t, 3H, C-CH_3), 1.7 (m, 2H, CH), 2.6 (m, 2H, CH), 2.8 (s, 3H, N-CH_3), 2.9-3.6 (m, 6H, CH), 6.7 (s, 2H, Ar-H), 7.05 (s, 1H, 3-H), 8.3 (s, 1H, 1-H). MS (from base): m/e = 341 (M^+). $[\alpha]_D^{20}$ = -130° (c = 0.2, CH_3OH).

Anal. Calcd $C_{20}H_{23}NO_2S$•HCl: C, 63.55; H, 6.40; N, 3.70; S, 8.48

Found: C, 63.28; H, 6.28; N, 3.62; S, 8.64

6,8-Diethylthiodesoxymetacodeine (5).- Thebaine (**1**) (1.0 g, 3.1 mmol) was dissolved in a mixture of methanesulfonic acid (5 mL) and ethanethiol (12.4 mmol) at 20°. Stirring was continued at this temperature for 2 h and the mixture was then worked up as described in *general procedure A* to yield 0.65 g (50%) of an oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.2 (t, 3H, C-CH_3), 1.3 (t, 3H, C-CH_3), 2.3 (s, 3H, N-CH_3), 2.4-3.1 (m, 10H, CH), 3.5 (d, *J* = 6Hz, 1H, 8-H), 3.9 (s, 3H, O-CH_3), 5.7 (d, *J* = 6Hz, 1H, 7-H), 6.1 (s, 1H, OH); 6.6-6.8 (m, 2H, Ar-H), 6.7 (s, 1H, 5-H), ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 145.23 (4-C), 144.02 (3-C), 137.49 (13-C), 132.95 (12-C), 130.49 (11-C), 122.86 (5-C), 119.32 (7-C), 119.10 (1-C), 110.05 (2-C), 68.98 (8-C), 56.04 (O-Me), 40.24 (N-Me), 14.72 (C-Me), 14.2 (C-Me). MS: m/e = 403 (M^+).

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REFERENCES

1. S. Berényi, M. Czirják and S. Makleit, *J. Chem Soc. Perkin Trans. 1*, 2137 (**1993**).

2. E. Granchelli, C. N. Filer, A. H. Soloway and J. L. Neumeyer, *J. Org. Chem.*, **45** 2275 (1980).

3. F. Auth, I. Laszlovszky, B. Kiss, E. Kárpáti, S. Berényi, Cs. Csutorás, S. Makleit and M. Lõw, *J. Neurochem. Suppl. 2*, **66** S13 (1996).

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REGIOSELECTIVE EPOXIDE RING-OPENING TO THE ENANTIOMERICALLY PURE α-HYDROXY ANALOGUE OF S-*tert*-BUTYL CYSTEINE

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(07/14/97)

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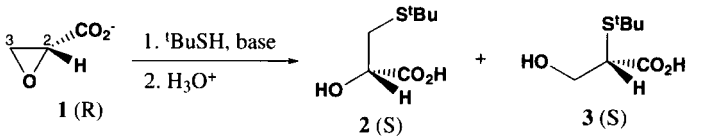
Our interest in α-hydroxy acids arose in connection with other work in which we required 2-hydroxy-3-mercapto propanoic acid in an optically active form. One usual method to prepare α-hydroxy acids is to convert α-amino acids by nitrous acid deamination.[1] However when initiated from cysteine, this reaction occurred with thiiran formation[2] and β-elimination, while with cystine, it yielded to many unwanted sulphur containing compounds,[3] resulting from oxidation side-reactions. Since it is known that thiolates open epoxides, we decided to investigate the reaction of potassium glycidate with *tert*-butyl thiol to lead to a S-protected hydroxy analogue of cysteine.



In a previous paper,[4] we showed that the ring-opening reaction of the epoxide (**1**) does in fact lead to two stereochemically pure alcohols: reaction at the β-carbon C-3 gives the desired α-hydroxy acid (**2**) whereas reaction at the α-carbon C-2 yields the β-hydroxy acid (**3**) with total inversion of configuration. Using *tert*-butyl mercaptan anion with potassium as counterion (*t*-BuSH/KOH, pH 10) gave two products (**2**) and (**3**) in a ratio of 85:15 respectively (Table, Entry 1). These two compounds have been isolated by preparative HPLC, allowing the targeted compound (**2**) to be fully characterized for the first time.[4] Unfortunately, this purification technique is rather expensive and not very convenient for the preparation of large quantities of compounds. The solution we proposed was to introduce the hydroxy analogue of cysteine into the targeted depsidipeptide as a mixture of (**2**) and (**3**) and to carry out the purification step afterwards, since a classical chromatography column of the crude coupling mixture proved to be efficient. Obviously, it would be preferable to suppress the formation of the unwanted compound (**3**) by increasing the regioselectivity of the ring-opening reaction.