# Synthesis of the Hypotensive Agent 8-Amino-7-[2-hydroxy-3-morpholinopropyl]theophylline (P23) and Analogs



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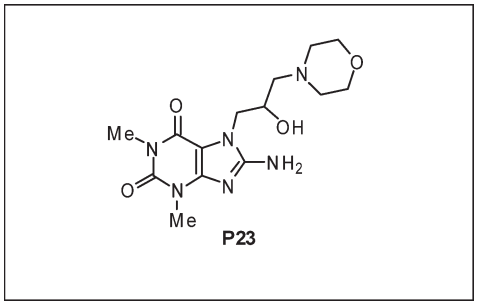
Received July 25, 2008
DOI 10.1002/jhet.51
Published online 23 March 2009 in Wiley InterScience (www.interscience.wiley.com).




**P23**

Synthesis of a number of 7,8-disubstituted theophyllines including enantiomers of the hypotensive agent **P23** is described.

*J. Heterocyclic Chem.,* **46**, 191 (2009).

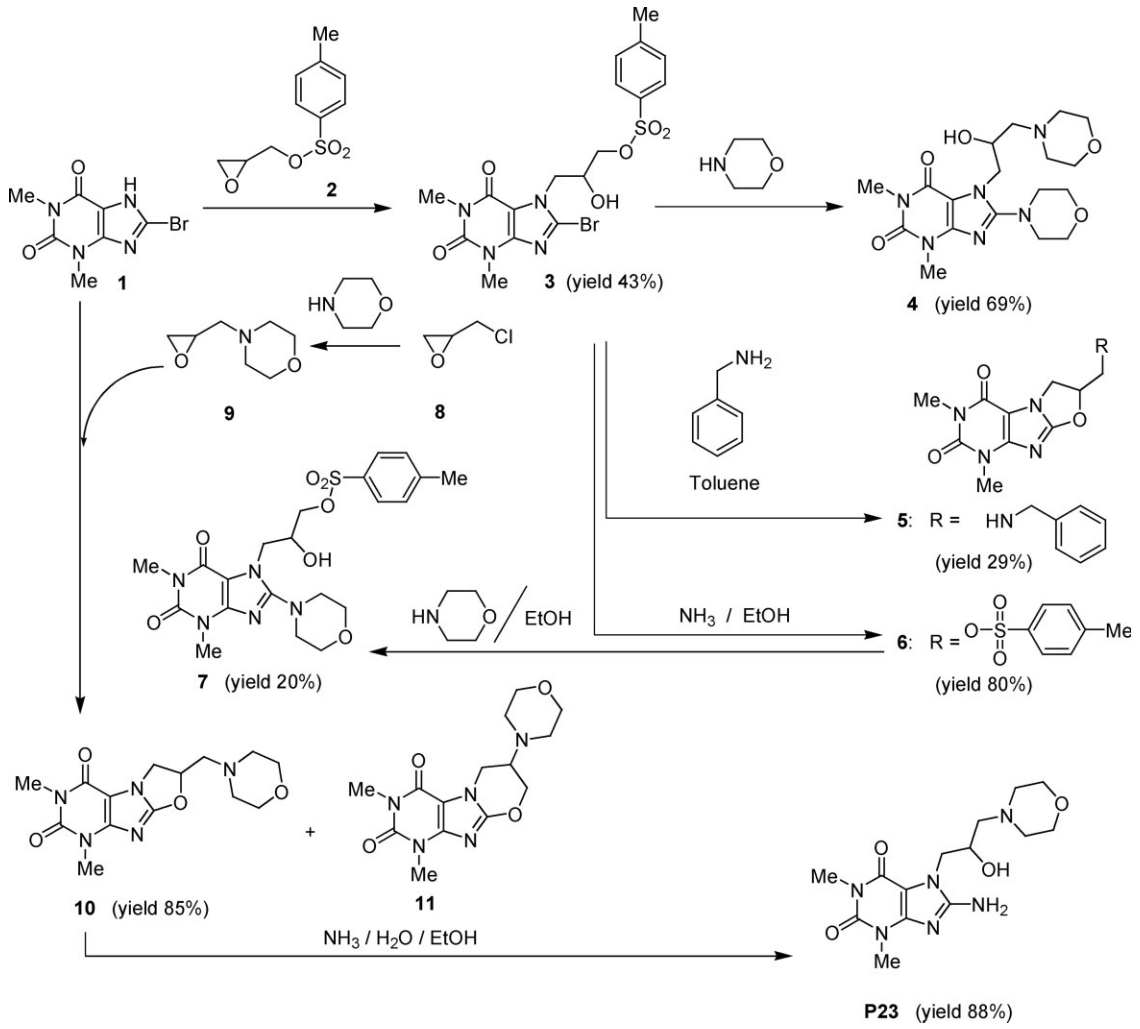
## INTRODUCTION

*N*-Methyl derivatives of xanthine including caffeine, theobromine, and theophylline show diverse biological activities. An additional substitution of these compounds results in modulation of their biological responses. In particular, a 7,8-disubstituted theophylline **P23** (structure in Scheme 1) was synthesized two decades ago and protected by patents as a potent hypotensive agent that acts on the cardiovascular system [1]. The original synthesis of **P23** was based on a reaction of theophylline with racemic epichlorohydrin to give the racemic intermediate and final products. No attempts were made to synthesize enantiomers of **P23**, which is a requirement of the current drug development process. More specifically, two enantiomers of a chiral drug candidate must be biologically assayed. Since the patent protection of the chemistry leading to the racemate of **P23** has recently expired, the patented information is in the public domain. Therefore, it was of interest to review the previously published chemistry in an attempt to synthesize enantiomers of **P23**. Unfortunately, we have found that the use of enantiomerically pure epichlorohydrin instead of a racemic substrate in the reaction with 8-bromotheophylline (**1**) results in an extensive racemization of the intermediate adduct. Additional methodologies are illustrated in Scheme 1.

To test the feasibility of the designed synthetic routes, the first experiments involved the reaction of **1** with racemic reagents, namely 2,3-epoxypropyl 4-toluenesulfonate (**2**) and 2,3-epoxypropylmorpholine (**9**).

Compound **2** [2] and the reagent **9** [3] were synthesized by using the published procedures. Treatment of **1** with **2** gave the expected adduct **3** in 43% yield. It was believed that a selective nucleophilic displacement of the tosylate function in **3** by the reaction with morpholine followed by the addition of ammonia to the C=N—Br moiety of the resultant intermediate product and then elimination of bromide anion would produce the desired product **P23**. Unfortunately, the treatment of **3** with morpholine resulted in the displacement and addition reactions simultaneously to give a dimorpholino derivative **4**. On the other hand, it was thought that the addition reaction of less sterically hindered benzylamine with the C=N—Br moiety of **3** would be a selective process. The benzyl group could be removed later by hydrogenation. To our surprise a tricyclic product **5** was formed instead, showing that the third ring system is formed by the benzylamine-aided ionization of the hydroxyl function in the side chain followed by addition of the alkoxide anion to the C=N—Br moiety and a subsequent elimination of bromide. The treatment of **3** with ammonia also resulted in cyclization, however, without nucleophilic displacement of the tosylsulfonyl group, to give **6** as the final product. Another surprising result was obtained upon an attempted nucleophilic displacement of the tosylsulfonyl group in **6** by treatment with morpholine. Thus, the tosylsulfonyl group was retained in the bicyclic product **7**. The loss of the third ring can be explained in terms of the addition reaction

**Scheme 1**




of morpholine to the C=N function of **6** followed by elimination of alkoxide anion from the resultant adduct.

The successful preparation of **P23** that is also amendable to the synthesis of individual enantiomers is based on the reaction of 8-bromotheophylline (**1**) with *N*-(2,3-epoxypropyl)morpholine (**9**). Reagent **9** is not a commercial product and was obtained by the reaction of morpholine with epichlorohydrin (**8**) which is available in the form of a racemate or individual enantiomers. It has been suggested previously that the reaction of morpholine with an optically active substrate (*S*)-(+)-**8** is accompanied by extensive racemization of the epoxyamino product (*S*)-(−)-**9** [3-5]. We have shown that the racemization can be minimized by using mild conditions. As can be seen from the experimental part, the absolute values of the optical rotations for the enantiomers of **9** obtained by us are virtually identical. The greater optical purity of our sample of (−)-**9** is indicated by the absolute rotation, $[\alpha]_D = -25.4^\circ$ (c = 10% in toluene), as opposed to the value published previously, $[\alpha]_D = -20.2^\circ$, and measured under similar conditions [3]. The optical rotation of the (+)-**9** enantiomer has not been reported previously.

We have published recently that the treatment of 8-bromotheophylline (**1**) with the reagent **9** yields the oxazoline derivative **10** and, depending on conditions, varying amounts of the rearrangement product **11**. Relatively short reaction time and temperature favour the formation of **10** which can be obtained in an 85% yield. Conversely, heating the mixture at an elevated temperature for a prolonged period of time results in an efficient rearrangement of the initially formed compound **10** to the oxazine derivative **11** [6].

The racemic compound **10** was treated with ammonia in aqueous ethanol to give racemic product **P23**.

After optimization of the conditions a similar treatment of the enantiomers of **10** furnished optically active samples of **P23**. Their enantiomeric excess (defined as

the percent excess of the enantiomer over the racemate) was calculated by analysis of the $^1$H NMR spectra of diastereomeric esters of the samples of **P23** with (*S*)-(+)-α-methoxyphenylacetic acid. The procedure has been published previously [7], and the relative intensity of the singlets for the methine protons MeOC**H**(Ph)COO (δ 4.70-4.80) is the most informative. The obtained values of the enantiomeric excess for the samples containing (+)-**P23** and (−)-**P23** as the major enantiomers were 54% and 58%, respectively. These values correspond to the enantiomerically enriched samples containing 77% and 79% of the major enantiomer, respectively. The partial racemization observed for the synthesis of **P23** may be related to the partial racemization of **9**, as already mentioned [3]. Nevertheless, on the basis of the stereospecific chemistry involved, it can be safely assumed that the absolute configuration of the major enantiomer in the samples, (*R*)-(−)-**P23** and (*S*)-(+)-**P23**, are as shown. More specifically, the chemical transformations **8** → **9** → **10** → **P23** do not involve stereocenters in these compounds and, as a result, the absolute configurations, *R* or *S*, are retained in the intermediate and final products.

## EXPERIMENTAL

Melting points (Pyrex capillary) are uncorrected. Electron-impact mass spectra (ei-ms) were recorded at 70 eV. High resolution time-of-flight mass spectra were recorded using electron-spray ionization (*high resolution ms*) with 0.5% ammonia in methanol for the negative ion mode and 0.1% formic acid in methanol for the positive ion mode. $^1$H NMR spectra were obtained at 300 MHz in deuteriochloroform solution with the solvent used as an internal standard. All commercial reagents were purchased from Aldrich or Fluka and used without purification.

**8-Bromo-7-[2-hydroxy-3-(4-tolylsulfonyloxy)propyl]theophylline [(±)-3].** A solution of (±)-2,3-epoxypropyl 4-toluenesulfonate (**2**, 0.27 g, 1.2 mmol), 8-bromotheophylline (**1**, 0.21 g, 0.8 mmol), and a catalytic amount of pyridine (0.02 g, 0.2 mmol) in *n*-propanol (2.5 mL) was heated under reflux for 1 hour. After cooling the mixture was concentrated on a rotary evaporator, and the residue was subjected to silica gel chromatography eluting with dichloromethane/methanol (49:1). Product (±)-**3** was obtained in a 43% yield, mp 78–79°C; $^1$H NMR: δ 2.46 (s, 3H), 3.38 (s, 3H), 3.56 (s, 3H), 3.80 (br s, 1H), 4.12–4.18 (m, 3H), 4.48 (d, $J$ = 1.4 Hz, 2H), 7.38 (d, $J$ = 8.5 Hz, 2H), 7.85 (d, $J$ = 8.5 Hz, 2H). *High resolution ms.* Calcd for $C_{17}H_{20}{}^{79}BrN_4O_6{}^{32}S$ ($M^+$ + 1): m/z 487.0287. Found: m/z 487.0290.

**7-(2-Hydroxy-3-morpholinopropyl)-8-morpholinotheophylline [(±)-4].** A solution of (±)-**3** (0.05 g, 0.10 mmol) and morpholine (0.02 g, 0.21 mmol) in toluene (5 mL) was heated under reflux for 1.5 hours. The mixture was concentrated on a rotary evaporator, and the residue was subjected to silica gel chromatography eluting with dichloromethane/methanol (49:1). Compound **4** was obtained in a 69% yield, mp 175–176°C; $^1$H NMR: δ 2.46 (m, 4H), 2.63 (m, 2H), 3.22 (m, 2H), 3.46 (m, 2H), 3.37 (s, 3H), 3.54 (s, 3H), 3.70 (m, 4H), 3.83 (m, 4H), 4.04 (m, 2H), 4.18 (m, 1H), 4.30 (m, 1H); ei-ms: m/z 408 ($M^+$, 10), 308 (50), 265 (10), 126 (50), 100 (100). *High resolution ms.* Calcd. for $C_{18}H_{27}N_6O_5$ ($M^-$ − 1): m/z 407.2043. Found: m/z 407.2055.

**7-[(Benzylamino)methyl]-1,3-dimethyl-6,7-dihydro-oxazolo[2,3-*f*]purine-1*H*,3*H*-2,4-dione [(±)-5].** A solution of **2** (0.05 g, 0.10 mmol) and benzylamine (0.02 g, 0.20 mmol) in toluene (5 mL) was heated under reflux. The reaction was completed after 1.5 hours, as judged by TLC analysis on silica gel eluting with chloroform/methanol (9:1). The resultant precipitate of benzylammonium 4-toluenosulfonate was filtered off and the solution was concentrated on a rotary evaporator. Product **5** was isolated by chromatography on silica gel eluting with chloroform/methanol (9:1), yield 29%, mp 252–253°C; $^1$H NMR: δ 3.30 (s, 3H), 3.35 (s, 2H), 3.49 (s, 3H), 3.80 (s, 1H), 4.40 (m, 2H), 4.47 (m, 1H), 4.80 (m, 2H), 7.30 (m, 5H); ei-ms: m/z 341 ($M^+$, 100), 250 (25), 91 (40). *High resolution ms.* Calcd. for $C_{17}H_{20}N_5O_3$ ($M^+$ + 1): m/z 342.1566. Found: m/z 342.1570.

**7-[(4-Tolylsulfonyloxy)methyl]-1,3-dimethyl-6,7-dihydro-oxazolo[2,3-*f*]purine-1*H*,3*H*-2,4-dione [(±)-6].** Gaseous ammonia was slowly bubbled at 0° through a solution of **3** (0.27 g, 0.6 mmol) in anhydrous ethanol. After 3 hours the resultant precipitate of **6** was collected by filtration and dried at 25°; yield 80%, mp 215–220°C; $^1$H NMR: δ 2.50 (s, 3H), 3.42 (s, 3H), 3.55 (s, 3H), 4.40 (m, 4H), 5.68 (m, 1H), 7.42 (d, $J$ = 8.5 Hz, 2H), 7.80 (d, $J$ = 8.5 Hz, 2H); ei-ms: m/z 406 ($M^+$, 100), 234 (25), 91 (30). *High resolution ms.* Calcd. for $C_{17}H_{17}N_4O_6{}^{32}S$ ($M^-$ −1): m/z 405.0869. Found: m/z 405.0883.

**7-[2-Hydroxy-3-(4-tolylsulfonyloxy)propyl]-8-morpholinotheophylline (±)-7].** A mixture of (±)-**6** (0.03 g, 0.08 mmol), morpholine (0.015 g, 0.16 mmol), and ethanol (2 mL) was stirred at 25°C for 24 h. Concentration of the mixture on a rotary evaporator followed by chromatography of the residue on silica gel eluting with dichloromethane/methanol (49:1) gave product 7 in a 20% yield, mp 163–164°C; $^1$H NMR: δ 2.50 (s, 3H), 3.31 (m, 4H), 3.40 (s, 3H), 3.57 (s, 3H), 3.88 (m, 4H), 3.94 (m, 1H), 4.25 (m, 4H), 5.52 (br s, 1H), 7.42 (d, $J$ = 8.2 Hz, 2H), 7.82 (d, $J$ = 8.2 Hz, 2H). *High resolution ms.* Calcd. for $C_{21}H_{28}N_5O_7{}^{32}S$ ($M^+$ + 1): m/z 494.1709. Found: m/z 494.1685.

**(±)-*N*-(2,3-Epoxypropyl)morpholine [(±)-9].** A mixture of morpholine (8.5 g, 0.1 mol) and water (0.5 mL) was treated dropwise with (±)epichlorohydrin (**8**, 9.25 g, 0.1 mol) in such a way that the temperature did not exceed 35 °C (exothermic reaction). After the addition was completed (1.5 h), the mixture was treated with an aqueous solution of sodium hydroxide (38%, 12.5 g) and then stirred for an additional 1 hour. The precipitate of sodium chloride was filtered off, and the filter and the flask was washed with ether (3 × 30 mL). The ether solution was dried (anhydrous $K_2CO_3$), then concentrated on a rotary evaporator, and the oily residue was distilled under reduced pressure (45–48°C/20 mmHg). Racemic product **9** was obtained in a 40% yield and its $^1$H NMR spectrum was virtually identical with that reported [3] for the compound obtained by using a different synthetic route.

**(2*R*)-(+)-*N*-(2,3-Epoxypropyl)morpholine [(2*R*)-(+)-9].** The reaction with (2*R*)-(−)-epichlorohydrin with morpholine and

workup were conducted as described above; $[\alpha]_D = +24.1°$ (c = 10% in toluene).

**(2*S*)-(-)-*N*-(2,3-Epoxypropyl)morpholine [(2*S*)-(−)-9].** The reaction with (2*S*)-(+)-epichlorohydrin with morpholine and workup were conducted as described above; $[\alpha]_D = -25.4°$ (c = 10% in toluene); reported $[\alpha]_D = -20.2°$ in toluene [3].

**1,3-Dimethyl-7-morpholinomethyl-6,7-dihydrooxazolo-[2,3-*f*]-purine-1*H*,3*H*-2,4-dione [(±)-10, (7*S*)-(−)-10 and (7*R*)-(+)-10].** A mixture of 8-bromotheophylline (**1**, 0.39 g, 1.5 mmol), racemic compound **9** (0.31 g, 2 mmol), and pyridine (0.08 g, 1 mmol) in ethanol (5 mL) was stirred at room temperature for up to 10 days until TLC analysis (silica gel, chloroform/triethylamine, 9:1) showed the absence of **1** and/or the presence of a small amount of a byproduct **11**. Then the mixture containing precipitate of **10** was cooled to 0°C for an additional 24 h and filtered. Product (±)-**10** was obtained in an analytically pure form by chromatography on silica gel eluting with chloroform/methanol (9:1): yield 85%, mp 230–231°C. A similar treatment of **1** with (R)-(+)-**9** gave (R)-(+)-**10**, mp 176–178°C, $[\alpha]_D = +55.3°$ (c = 3% in dichloromethane/metanol, 49:1). A similar treatment of **1** with (*S*)-(−)-**9** gave (*S*)-(−)-**10**, mp 180–182°C, $[\alpha]_D = -49.7°$ (c = 3% in dichloromethane/methanol, 49:1). The $^1$H NMR spectra of these three products were virtually identical with that reported previously for (±)-**10** [6]; ei-ms (identical in all cases): m/z 321 ($M^+$, 30), 234 (40), 126 (55), 113 (20), 100 (100). Anal. Calcd. for $C_{14}H_{19}N_5O_4$ [(±)-**10**]: C, 52.33; H, 5.95; N, 21.79. Found: C, 52.06; H, 5.93; N, 21.53.

**8-Amino-7-(2-hydroxy-3-morpholinopropyl)theophylline [(±)-P23, (*S*)-(+)-P23, and (*R*)-(−)-P23].** A mixture of (±)-**10** (0.32 g, 1.0 mmol), aqueous ammonia (25%, 10 mL), and ethanol (15 mL) was heated in a pressure vessel to 110°C for 6 hours. After cooling the mixture was concentrated on a rotary evaporator and subjected to silica gel chromatography eluting with chloroform/methanol (49:1), yield 88%, mp 221–222°C (reported [1] mp 226–228°C for the racemic product); $^1$H NMR: δ 2.44 (m, 2H), 2.66 (m, 4H), 3.37 (s, 3H), 3.50 (s, 3H), 3.66 (m, 4H), 4.18 (m, 1H), 4.40 (m, 2H), 4.50 (br s, 1H), 5.74 (br s, 2H); ei-ms: m/z 338 (20), 238 (45), 126 (50), 100 (100). The treatment of (7S)-(−)-**10** with ammonia gave (*S*)-(+)-**P23**, $[\alpha]_D = +5.3°$ (c = 2.2% in dichloromethane/methanol, 49:1). The treatment of (7*R*)-(+)-**10** with ammonia gave (*R*)-(−)-**P23**, $[\alpha]_D = -8.0°$ (c = 2.2% in dichloromethane/methanol, 49:1). The mp, NMR and ms data reported above are identical for all three products. Anal. Calcd. for $C_{14}H_{22}N_6O_4$ [(+)-**P23**]: C, 49.72; H, 6.55; N, 24.84. Found: C, 49.49; H, 6.90; N, 24.51.

**Derivatization of P23 for analysis of the enantiomeric excess by $^1$H NMR.** Esterification of the secondary alcohol function of **P23** with (*S*)-(+)-α-methoxyphenylacetic acid was conducted by using a published procedure [7]. The ester was purified by chromatography on silica gel eluting with chloroform/methanol (49:1). The $^1$H NMR spectra of the diastereomeric derivatives were taken in deuteriochloroform, and the ratio of the signals of the methine protons MeOCH(Ph)COO (δ 4.70–4.80) were analyzed [7].

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