Syntheses of 2-Alkylthio-1-[4-(*N*-α-ethoxycarbonylbenzyl)-aminobenzyl]-5-hydroxymethylimidazoles

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Dedicated to the memory of Professor Raymond N. Castle

Starting from the readily available *p*-nitrobenzylamine a series of 2-Alkylthio-1-[4-(*N*-α-ethoxycarbonylbenzyl)aminobenzyl]-5-hydroxymethylimidazoles were prepared.

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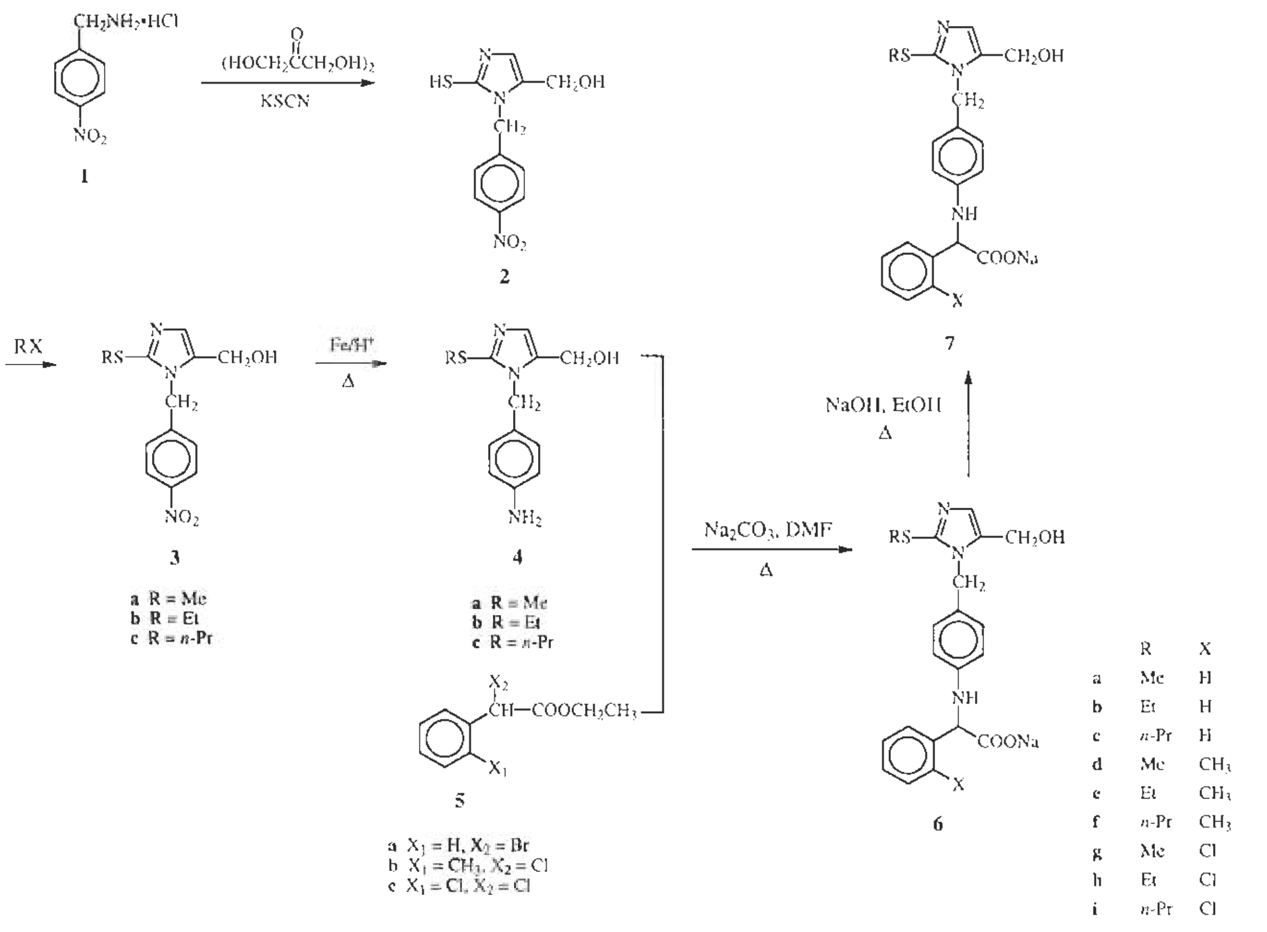
Renin angiotensin system (RAS) has a key role in the regulation of cardiovascular homeostasis and blood pressure in mamelians [1,2]. Since the angiotensin converting enzyme inhibitors (ACEIs) have side effects such as dry cough and angioedema, caused by potentiation of bradykinin, substance P and other active peptides, nonpeptide angiotensin II receptor antagonists are of interest [3,4,5].

In view of the potential activity of compounds containing the phenoxyphenylacetic acid moiety [6] or its analogue [7] in antagonizing angiotensin II, it was of interest to prepare the title compounds as possible effective drugs against hypertension. Our investigation of substituted phenylaminophenylacetic acids (**7**), AT_2 selective antagonist, began with the variation of the lower X group and substitution of the alkyl chain (R) at the 2-position of the imidazole ring. Although lasartan is more potent than its carboxylic acid analogue EXP 7711, it is shown that in the phenoxyphenyl-acetic series a carboxylic acid is preferred [6].

The structure-affinity relationship in the 2-position of the imidazole ring is very well defined and suggests a hydrophobic pocket into which an aliphatic chain of the proper length fits tightly. Focusing next on the lower

Scheme 1



phenyl ring of compound **7**, it appears that appropriate ortho substitution enhances binding affinity and that the substituent position ranking is ortho>meta>>para [6].

The ortho substituent imparts a favorable and more rigid conformation to the terminal aromatic ring to result in the enhancement of binding affinity [4]. The results suggest that the terminal aromatic ring may fit snuggly into a liophilic pocket in which there is insufficient room for substituents on this phenyl ring [7]. Since ortho substitution was more active than meta and para, we decided to synthesize the ortho-substituted derivatives, namely **7a** to **7i**. The syntheses of the desired compounds were accomplished according to Scheme I.

4-Nitrobenzylamine hydrochloride (**1**) [8] was stirred with 1,3-dihydroxyacetone dimmer and potassium thiocyanate to give 5-hydroxymethyl-2-mercapto-1-[(4-nitrophenyl)methyl]imidazole (**2**) [4]. Subsequent alkylation of compound **2** with alkylhalides afforded 2-alkylthio-5-hydroxymethyl-1-[(4-nitrophenyl)methyl]imidazole (**3**) [9,10,11], which was then catalytically reduced with iron powder and hydrochloric acid to give 2-alkylthio-1-[(4-aminophenyl)methyl]-5-hydroxymethylimidazole (**4**) [4,10,11].

A common alkylating agent **5** was prepared *via* either a Hell-Vollhard-Zelinsky or a Strecker synthesis [12-15]. Compound **5** was then utilized to alkylate compound **4** to provide 2-alkylthio-1-[4-(*N*-α-ethoxycarbonylbenzyl)-aminobenzyl]-5-hydroxymethylimidazoles (**6**) [16]. In the ^{1}H nmr spectra of compounds **6g** to **6i**, the δ value of the benzyl proton is greater than that in the other derivatives likely because of the greater deshielding effect of the chlorine atom compared with methyl or hydrogen. The esters **6** were hydrolyzed with one equivalent of sodium hydroxide to give **7a-i** (Table 1) and tested for pharmacological activity.

The structures of all compounds were confirmed by elemental analysis, ir, nmr and mass spectroscopy. The affinity of compounds **7a** to **7i** for the human AT_2 receptor were assessed in a radioligand binding assay, the most active compounds was **7e**. The results of pharmacological activity will be published elsewhere.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained using a Perkin-Elmer Model 781 or Nicolet FT-IR Magna 550 spectrographs; The ^{1}H nmr spectra were obtained on a Bruker FT-80 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were obtained on a Finnigan MAT TSQ 70 spectrometer at 70 eV. Column chromatography was carried out using silica gel (230-400 mesh).

2-Alkylthio-5-hydroxymethyl-1-[(4-nitrophenyl)methyl]-imidazole (3).

Compound **2** (10 mmoles) was dissolved in a minimum quantity of water and the solution was basified with a solution of 20% aqueous sodium hydroxide. Alkylhalide (11 mmoles) was added to the stirring solution. The progress of the reaction was monitored by tlc. When compound **2** was no longer present, the precipitate was filtered and washed with water to afford compounds **3a-c**.

5-Hydroxymethyl-2-methylthio-1-[(4-nitrophenyl)methyl]-imidazole (**3a**).

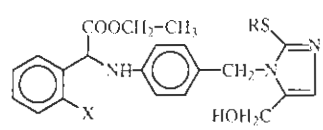
This compound was obtained in 95% yield [10,11], mp 154-156°; ir (potassium bromide): ν 3180 (OH), 1340, 1520 cm^{-1} (NO_2); ^{1}H nmr (deuteriochloroform): δ 8.20 (d, 2H, aromatic, J = 8 Hz) 7.23 (d, 2H, aromatic, J = 8 Hz), 7.02 (s, 1H, H-C_4 imidazole), 5.35 (s, 2H, N-CH_2), 4.49 (s, 2H, CH_2-O), 2.57 (s, 3H, CH_3), 2.20 ppm (s, 1H, OH).

Anal. Calcd. For $C_{12}H_{13}N_3O_3S$: C, 51.61; H, 4.66; N, 15.05. Found: C, 51.40; H, 4.78; N, 14.81.

2-Ethylthio-5-hydroxymethyl-1-[(4-nitrophenyl)methyl]-imidazole (**3b**).

This compound was obtained in 86% yield, mp 88-90°; ir (potassium bromide): ν 3400 (OH), 1510, 1350 cm^{-1} (NO_2); ^{1}H nmr (deuteriochloroform): δ 8.15 (d, 2H, aromatic, J = 8Hz),

Table 1



Compound	R	X	Yield [a]	Formula	Calcd./Found C%		Calcd./Found H%		Calcd./Found N%	
6a	Me	H	16	$C_{22}H_{25}N_3O_3S$	64.23	64.46	6.08	5.80	10.22	10.35
6b	Et	H	15	$C_{23}H_{27}N_3O_3S$	64.94	65.15	6.35	6.29	9.88	9.73
6c	*n*-Pr	H	17	$C_{24}H_{29}N_3O_3S$	65.60	65.41	6.61	6.48	9.57	9.78
6d	Me	Me	18	$C_{23}H_{27}N_3O_3S$	64.94	64.73	6.35	6.25	9.88	9.72
6e	Et	Me	19	$C_{24}H_{29}N_3O_3S$	65.60	65.81	6.61	6.80	9.57	9.78
6f	*n*-Pr	Me	17	$C_{25}H_{31}N_3O_3S$	66.23	66.01	6.84	6.62	9.27	9.49
6g	Me	Cl	18	$C_{22}H_{24}ClN_3O_3S$	59.26	59.02	5.39	5.58	9.43	9.68
6h	Et	Cl	16	C_{23}H26ClN_3O_3S	60.07	60.31	5.66	5.88	9.14	9.01
6i	*n*-Pr	Cl	20	$C_{24}H_{28}ClN_3O_3S$	60.82	60.60	5.91	5.71	8.87	8.99

7.24 (d,2H, aromatic, J = 8 Hz), 7.05 (s, 1H, H-C_4 imidazole), 5.41 (s, 2H, N-CH_2), 4.43 (s, 2H, CH_2-O), 3.02 (q, 2H, S-CH_2), 1.28 ppm (t, 3H, S-CH_3).

Anal. Calcd. For $C_{13}H_{15}N_3O_3S$: C, 53.24; H, 5.12; N, 14.33. Found: C, 53.17; H, 5.15; N, 14.37.

5-Hydroxymethyl-1-[(4-nitrophenyl)methyl]-2-propylthioimidazole (**3c**).

This compound was obtained as an oil in 77% yield; ir (chloroform): ν 3400 (OH), 1350, 1510 cm^{-1} (NO_2), ^1H nmr (deuteriochloroform): δ 8.14 (d, 2H, aromatic, J = 8 Hz), 7.21 (d, 2H, aromatic, J = 8 Hz), 6.86 (s, 1H, H-C_4 imidazole), 5.40 (s, 2H, N-CH_2), 4.44 (s, 2H, CH_2-O),2.95 (t, 2H, S-CH_2), 1.60 (m, 2H, CH_2), 0.92 ppm (t, 3H, CH_3).

Anal. Calcd. For $C_{14}H_{17}N_3O_3S$: C, 54.72, H, 5.54, N, 13.68. Found: C, 54.66; H, 5.41; N, 13.54.

2-Alkylthio-1-[(4-aminophenyl)methyl]-5-hydroxymethylimidazole (**4**).

2-Alkylthio-5-hydroxymethyl-1-[(4-nitrophenyl)methyl]-imidazole (**3**) (10 mmoles), iron (35 mmoles), glacial acetic acid (70 mmoles) and methanol (150 ml) were combined and refluxed for 2.5 hours. The solvent was removed under reduced pressure. The residue was diluted with water (150 ml) and extracted with chloroform (5×150 ml). The organic layer was dried (sodium sulfate) and concentrated. The oily residue was purified by column chromatography on silica gel eluting with chloroform to afford compounds **4a-c**.

1-[(4-Aminophenyl)methyl]-5-hydroxymethyl-2-methylthioimidazole (**4a**).

This compound was obtained as an oil in 96% yield; ir (chloroform): ν 3335, 3220 cm^{-1} (NH2); ^1H nmr (deuteriochloroform): δ 6.91 (d, 3H, aromatic and H-C_4 imidazole , J = 7 Hz), 6.56 (d, 2H, aromatic, J = 7 Hz), 5.13 (s, 2H, N-CH_2), 4.45 (s, 2H, CH_2-O), 2.45 ppm (s, 3H, CH_3).

Anal. Calcd. For $C_{12}H_{15}N_3OS$: C, 57.83; H, 6.02; N, 16.87. Found: C, 57.62; H, 6.24; N, 16.59.

1-[(4-Aminophenyl)methyl]-2-ethylthio-5-hydroxymethylimidazole (**4b**).

This compound was obtained as an oil in 89% yield; ir (chloroform):ν 3310, 3200 cm^{-1} (NH_2); ^1H nmr (deuteriochloroform): δ 6.81 (d, 3H, aromatic and H-C_4 imidazole, J = 8 Hz), 6.50 (d, 2H, aromatic, J = 8 Hz), 5.13 (s, 2H, N-CH_2), 4.37 (s, 2H, CH_2-O), 2.92 (q, 2H, S-CH_2), 1.21 ppm (t, 3H, CH_3).

Anal. Calcd. For $C_{13}H_{17}N_3OS$: C,59.32; H, 6.46; N, 15.97.Found: C, 59.43; H, 6.59; N, 15.73.

1-[(4-Aminophenyl)methyl]-5-hydroxymethyl-2-propylthioimidazole (**4c**).

This compound was obtained as an oil in 90% yield; ir (chloroform): ν 3350, 3250 cm^{-1} (NH_2); ^1H nmr (deuteriochloroform): δ 6.87 (d, 3H, aromatic and H-C_4 imidazole, J = 8 Hz), 6.53 (d, 2H, aromatic, J = 8Hz) , 5.15 (s, 2H,N-CH_2), 4.41 (s, 2H, CH_2-O), 3.46 (bs, 3H, NH_2 and OH), 3.00 (t, 2H, S-CH_2), 1.66 (m, 2H, CH_2), 0.97 ppm (t, 3H, CH_3).

Anal. Calcd. For $C_{14}H_{19}N_3OS$: C, 60.65; H, 6.86; N, 15.16. Found: C, 60.71; H, 6.69; N, 15.01.

2-Alkylthio-1-[4-(N-α-ethoxycarbonylbenzyl)aminobenzyl]-5-hydroxymethylimidazole (**6**).

A stirring suspension of 2-alkylthio-1-[(4-aminophenyl)-methyl]-5-hydroxymethylimidazole (**4**) (10 mmoles), anhydrous sodium carbonate (10 mmoles) and **5** (13 mmoles) in dimethylformamide (30 ml) was heated at 70° for 24 hours. After cooling, the mixture was evaporated under reduced pressure. The oily residue was acidified with a 15% solution of hydrochloric acid and extracted with chloroform. The aqueous layer was neutralized with a solution of sodium carbonate and extracted with chloroform. The organic layer was dried (sodium sulfate) and evaporated at reduced pressure to give an oily residue which was purified by column chromatography on silica gel (ethanol-chloroform; 13:87) to afford compounds **6a-i**.

5-Hydroxymethyl-1-[4-(N-α-ethoxycarbonylbenzyl)aminobenzyl]-2-methylthioimidazole (**6a**).

This compound was obtained as an oil in 16% yield; ir (chloroform): ν 3373 (OH), 1750 cm^{-1} (C=O); ^1H nmr (deuteriochloroform):δ 7.40-7.25 (m, 5H, aromatic), 6.88 (d, 3H, aromatic and imidazole H-C_4, J = 9 Hz), 6.48 (d, 2H, aromatic, J = 9 Hz), 5.08 (s, 1H, CH), 5.00 (s, 2H, N-CH_2), 4.42 (s, 2H, CH_2-O), 4.17 (m, 2H, O-CH_2), 2.52 (s, 3H, S-CH_3), 1.19 ppm (t, 3H, CH_3).

Anal. Calcd. For $C_{22}H_{25}N_3O_3S$: C, 64.23; H, 6.08; N, 10.22. Found: C, 64.46; H, 5.80; N, 10.35

Compounds **6b** to **6i** were prepared using a similar procedure (see Table 1).

2-Alkylthio-1-[4-(N-α-carboxybenzyl)aminobenzyl]-5-hydroxymethylimidazole Sodium Salt (**7**).

A solution of compound **6** (10 mmoles), 0.5 *N* sodium hydroxide in ethanol (20 ml, 10 mmoles), 2 ml of water, and 40 ml of ethanol was refluxed for 3 hours. The solvents were removed under reduced pressure to afford compounds **7a-7i** [7].

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