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Chemo- and stereoselective synthesis of benzocycloheptene and 1-benzoxepin derivatives as α-sympathomimetic and anorexigenic agents

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Abstract—The synthesis and pharmacological evaluation of *cis*- and *trans*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols **4a**–**c** and **5a**–**c** and *cis*- and *trans*-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols **4d**–**f** and **5d**–**f** were carried out. Chemo- and stereoselective synthesis of **5a**–**f** was achieved by reduction of corresponding α-amino ketones **3a**–**f** with $LiAl(t\text{-}BuO)_3H$. *cis*-4-Amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol **4d** and *trans*-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol **5d** exhibited marked anorexigenic activity in mice at a dose of LD_{50} 800 and 500 mg/kg and ED_{50} 75 and 55 mg/kg, respectively, while the analog *cis*-2,3-dihydroxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol **8** showed typical α-sympathomimetic activity.

Obesity and its associated diseases are an increasing challenge in medicine.[1] Obesity is a worldwide health problem. It has been estimated that nearly 300,000 deaths/annually in U.S.A. are attributed to obesity.[2] Anorexigenic drug, sibutramine is being recently used in addition to fluoxetine, phentermine, and dexfenfluramine.[3] α-Sympathomimetic drugs constitute phenethylamines, catecholamines, and related adrenergic amines,[4] which can assume a number of permissible conformations at the receptor site. Rigid analogs with severely limited permissible conformations can prove helpful in this analysis. In connection with the study of agents acting on adrenergic receptor, a new route describing chemo- and stereoselective synthesis of *cis*- and *trans*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols **4a**–**c** and **5a**–**c** and *cis*- and *trans*-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols **4d**–**f** and **5d**–**f** is being reported. Compounds **4a**–**c** and **5a**–**c** have been shown to possess typical α-sympathomimetic activity. We have carried out detailed pharmacological evaluation of *cis*- and *trans*-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols **4d**–**f** and **5d**–**f**. These amino alcohols have been found to possess marked anorexigenic activity. The results of anorexigenic activity of **4d**–**f** and **5d**–**f** are shown in Table 1. Effect on blood pressure and interaction with adrenaline, histamine, and acetylcholine was studied in anesthetized (pentobarbitone 35.0 mg/kg iv) cats using 2.5 mg/kg of each compound. The anorexigenic activity was tested by measuring the reduction of milk intake in overnight fasted mice. Gross behavioral effects and acute toxicity (ALD_{50}) of the compounds **4d**–**f** and **5d**–**f** was studied in albino mice by intraperitoneal administration of these compounds suspended in gum acacia using five animals per dose.

The compounds **4d**–**f** and **5d**–**f** in general exhibited a weak stimulant action and marked anorexigenic activity. The most marked anorexigenic activity was shown by *cis*- and *trans*-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols **4d** and **5d**. Their LD_{50} in mice is 800 and 500 mg/kg and ED_{50} is 75 and 55 mg/kg, respectively. Replacement of R^1 by methyl group did not show any anorexigenic activity. Replacement of R^1 by methoxy group also did not cause any anorexigenic activity in both *cis*- and *trans*-isomers. The marked anorexigenic activity

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Table 1. Anorexigenic activity of compounds **4d–f** and **5d–f**

Compounds	R	R^1	ALD_{50} mg/kg ip (in mice)	Gross effect (mice) ip	Effect on blood pressure, change in mm (duration in minutes)	Anorexigenic activity in mice, ED_{50} mg/kg, ip
4d	H	H	800	Stimulation[a]	44 ↓ (transient)	75
5d	H	H	500	Stimulation	32 ↓ 40	55
4e	H	Me	300	Stimulation	10 ↓ (transient)	NE
5e	H	Me	150	Stimulation	38 ↓ 160	NE
4f	H	OMe	150	Stimulation	20 ↓ (transient)	NE
5f	H	OMe	150	Stimulation	40 ↓ (transient)	NE

NE = No effect.

[a] Increase in spontaneous motor activity, respiration, reactivity, tremors, and convulsions.

Table 2. Pharmacological activity of compounds **4a–c**, **4g**, and **5a**

Compounds	R	R^1	ALD_{50} mg/kg ip (in mice)	Gross effect (mice) ip	Protection against amphetamine toxicity ED_{50} mg/kg, pc	Effect on blood pressure, change in mm Hg (duration in minutes)
4a	H	H	150	Tranquilizer	73	NE
4b	Me	Me	150	NE	NE	NE
4c	OMe	OMe	150	NE	NE	NE
4g	OH	OH	150	Depression	NE	51 (13′)
5a	H	H	150	NE	NE	NE

NE = No effect.

exhibited by *cis*- and *trans*-amino alcohols **4d** and **5d** refers these as lead compounds of the series.

The compounds **4a–c** and **5a–c** were evaluated for their pharmacological activity by standard methods and these are reported in Table 2. *cis*-6-Amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol[5] **4a** has LD_{50} 150 mg/kg, ip in mice. It gave protection against amphetamine toxicity (ED_{50} 73 mg/kg, po). It showed typical effects of a tranquilizer in the EEG in rabbits. The corresponding *trans*-isomer **5a** did not show any tranquilizing activity. The reason for the activity of *cis*-isomer **4a** compared to the *trans*-isomer **5a** indicates that ephedrine configuration is necessary for activity of these compounds (Fig. 1). *cis*-2,3-Dihydroxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol **4g** in gross observation studies in mice LD_{50} 150 mg/kg ip showed only slight depression and no other prominent effect. In normal anesthetized cats at a dose of 1 mg/kg iv, it caused 51 mm Hg fall of BP for 13 min. The responses to epinephrine, norepinephrine, and tyramine were potentiated by pretreatment with the compound. It showed stimulant effect on rabbit heart in vitro, which could be blocked by a β-blocker (DCI). Thus **4d** has a direct sympathomimetic effect, stimulating the α-adrenergic receptors. The corresponding *trans*-isomer **5g** did not show any

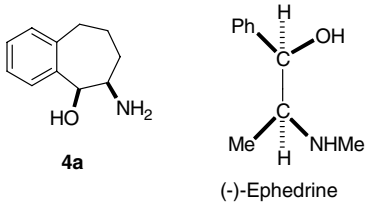
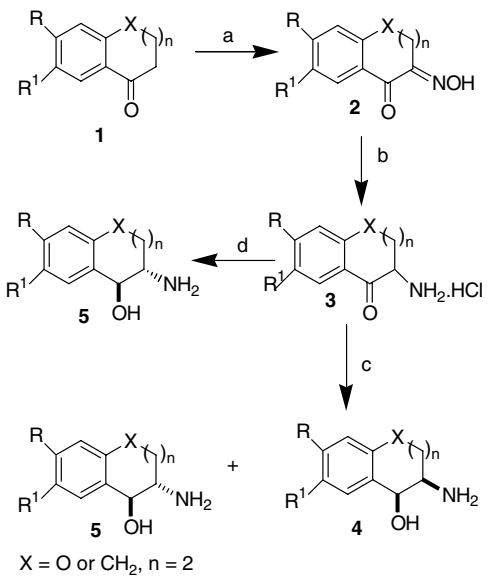


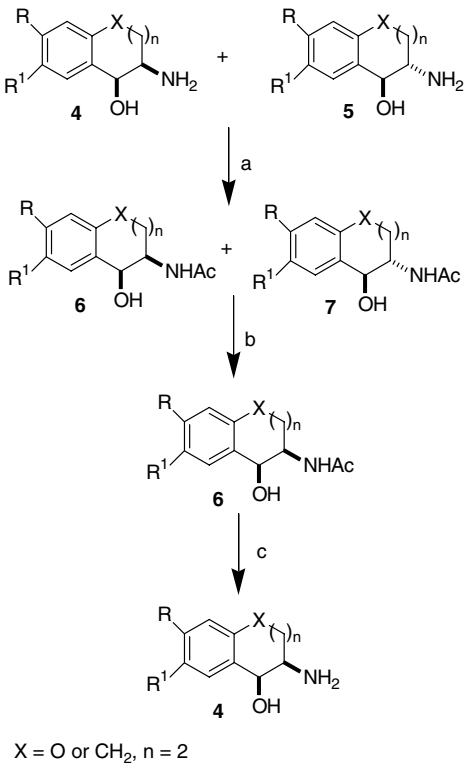
Figure 1.



Scheme 1. Reagents and conditions: (a) KOEt, *n*-BuONO; (b) 10% Pd/C, H_2; (c) $LiAlH_4$, $NaBH_4$ or 10% Pd/C, H_2; (d) $LiAl(t\text{-}BuO)_3H$.

sympathomimetic activity. The synthesis of *trans*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclo-hepten-5-ols **5a–c** and *trans*-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols **5d–f** and corresponding *cis*-isomer is shown in Schemes 1 and 2.

Oximino ketones **2a–f** obtained by nitrosation of the ketones **1**, on catalytic reduction in presence of 10% Pd/C gave α-amino ketones, which were converted into hydrochlorides **3a–f** by treatment with ethereal HCl. The synthetic data for compounds **2** and **3** are given in Tables 3 and 4, respectively. We have devised a new route for the synthesis of *cis*- or *trans*-amino alcohols by



Scheme 2. Reagents and conditions: (a) Ac_2O, MeOH; (b) benzene, fractional crystallization; (c) 10% aq NaOH.

Table 3. Synthetic data for compounds **2**

Compounds	X	*n*	R	R^1	Mp °C	Yield %
2a	CH_2	2	H	H	127–128	60
2b	CH_2	2	Me	Me	192	70
2c	CH_2	2	OMe	OMe	173	73
2d	O	2	H	H	125–127	69
2e	O	2	H	Me	123–124	88
2f	O	2	H	OMe	118–119	82

Table 4. Synthetic data for compounds **3**

Compounds	X	*n*	R	R^1	Mp °C	Yield %
3a	CH_2	2	H	H	183	90
3b	CH_2	2	Me	Me	205–207	85
3c	CH_2	2	OMe	OMe	168–170	88
3d	O	2	H	H	208–210	62
3e	O	2	H	Me	198–200	53
3f	O	2	H	OMe	189–190	72

Table 5. Synthetic data for compounds **4**

Compounds	X	*n*	R	R^1	Mp °C HCl	Yield %
4a	CH_2	2	H	H	278	90
4b	CH_2	2	Me	Me	292	88
4c	CH_2	2	OMe	OMe	230	45
4d	O	2	H	H	260	78
4e	O	2	H	Me	252	73
4f	O	2	H	OMe	240	88

Table 6. Synthetic data for compounds **5**

Compounds	X	*n*	R	R^1	Mp °C	Yield %
5a	CH_2	2	H	H	147–48	87
5b	CH_2	2	Me	Me	178–180	90
5c	CH_2	2	OMe	OMe	135	89
5d	O	2	H	H	153–154	3
5e	O	2	H	Me	148–149	92
5f	O	2	H	OMe	143–144	85

use of $LiAl(t\text{-}BuO)_3H$ or conversion into acetamido alcohols **6** as shown in Schemes 1 and 2. It seemed essential to devise method for exclusive synthesis of *cis*- and *trans*-isomers as reduction of α-amino ketones **3a**–**f** with $LiAlH_4$, $NaBH_4$, or 10% Pd/C,H led to mixture of *cis*- and *trans*-amino alcohols **4a**–**f** and **5a**–**f** in varied proportions, which were difficult to separate. α-Amino ketones **3** on reduction with $LiAl(t\text{-}BuO)_3H$ in THF gave exclusively *trans*-amino alcohols **5** (Table 5). *cis*-Amino alcohols **4** were synthesized by conversion of mixture of **4** and **5** obtained by reduction of α-amino ketones **3** into acetamido alcohols **6a**–**f** and **7a**–**f**. *cis*-Acetamido alcohols **6** could be isolated as insoluble part by fractional crystallization with benzene from mixture of **6a**–**f** and **7a**–**f**. Compound **6** on hydrolysis with aqueous NaOH resulted in isolation of *cis*-amino alcohols **4a**–**f** (Table 6).[5] Thus both *cis*- and *trans*- isomers can be synthesized in pure form according to Schemes 1 and 2. The structures of these compounds were elucidated on the basis of ^1H NMR spectra.

In conclusion we have devised new route for synthesis of *cis*- and *trans*-amino alcohols **4a**–**f** and **5a**–**f**[6,7] having marked pharmacological activity. Both compounds **4d** and **5d** are lead compounds for anorexigenic activity in mice whereas **4a** is a lead compound as tranquilizer and **4g** has α-sympathomimetic activity.

Acknowledgements

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6. *General procedure for stereoselective synthesis of* **5**: LiAl $(t\text{-}BuO)_3H$ (0.47 g, 15 mmol) was added to a solution of

3a–**f** (10 mmol) in anhydrous THF (5 mL) with stirring at room temperature. The reaction mixture was stirred at 30 °C for 12 h diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and filtrate concentrated in vacuo. The residue was crystallized from $CHCl_3$–*n*-C_6H_{12} to give crystalline **5a**–**f**. For example, *trans*-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (**5d**) yield 83%; mp 153–154 °C; IR 3350 (OH) and 3300 (NH)/cm; ^{1}H NMR δ 2.02 (br h, 3H, OH, NH_2 exchangeable by D_2O), 2.75 (m, 2H, C_3–H), 3.20 (br h, 1H, C_4–H), 4.02 (t, $J = 7.05$ Hz, C_2–H), 4.47 (d, 1H, $J_{4a,5a} = 8.0$ Hz, C_5–H), 6.8–7.4 (m, 3H, Ar–H), 7.65 (m, 1H, Ar–H). Anal. Calcd for $C_{10}H_{13}NO_2$·HCl (215.5): C, 67.03; H, 7.27; N, 7.82. Found: C, 66.70; H, 7.34; N, 7.63.

7. *General procedure for synthesis of* **4**: A mixture of *cis*-acetamido alcohol **6a**–**f**: (2.5 mmol) MeOH (30 mL) and 10% aqueous NaOH (20 mL) was refluxed on a steam bath for 12 h. The solution was cooled and solvent MeOH removed under reduced pressure. The solid product on cooling was filtered, washed with H_2O, dried, and crystallized with $CHCl_3$–*n*-C_6H_{12}. For example, *cis*-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol hydrochloride (**4d**) yield 90%; mp 278 °C; IR (free base) 3335, 3275, 1000, 960, 950, and 660/cm; ^{1}H NMR: δ 2.08 (br h, 3H, OH, NH_2 exchangeable by D_2O), 2.78 (m, 2H, C_3–H), 3.25 (br h, 1H, C_4–H), 4.02 (t, $J = 7.05$ Hz, C_2–H), 4.82 (d, 1H, $J_{4a,5e} = 1.5$ Hz, C_5–H), 6.8–7.5 (m, 4H, Ar–H). Anal. Calcd for $C_{10}H_{13}NO_2$·HCl (215.5): C, 67.03; H, 7.27; N, 7.82. Found: C, 66.70; H, 7.60; N, 7.54.