# "Vinylogs" and "Acetylenylogs" of β-Adrenergic Agents

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***Key Words:*** *β-adrenergic agents; vinylogs; adrenergic antagonists; $\beta_1$-adrenoceptors*

## Summary

Vinylogous (Groups **III** and **V**) and acetylenologous (Group **IV**) analogs of the classical β-adrenergic agents – stimulants and blockers – were prepared in order to evaluate the effect of degree of saturation, position of unsaturation and rigidity of the chain linking the aromatic ring and the amino containing functional group on biological activity. Derivatives from Group **III**, which represent 4-aryl-3-butenyl-2-ol-amine analogs of Group **II**, retained $\beta_1$-adrenoceptor antagonist activity albeit substantially less potent (50–200-fold) than that possessed by their aryloxy counterparts. Consistent with the SAR for Group **II** compounds, substitution at position 2 of the aromatic ring yielded the most potent antagonists (**5a, 5d, 5g**), with $K_B$'s ranging from 73–93 nM while 3,4-dichloro substitution (**5e**) markedly reduced antagonist potency ($K_B$ = 2,400 nM). Agonist activity was also noted for **5b** and **5d**, suggesting that these compounds may be best classified as partial agonists. Representatives from Groups **IV** and **V** were inactive as antagonists at the $\beta_1$-adrenoceptor confirming the importance of the spatial relationship between the hydroxyl and the amino nitrogen.

## Introduction

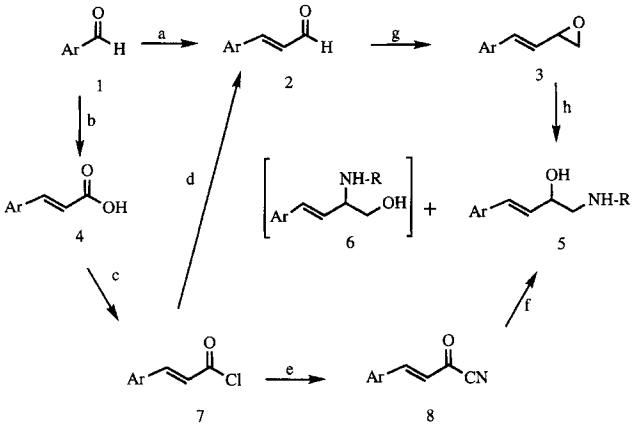
Large numbers of compounds possessing agonistic and antagonistic activities towards β-adrenoceptors have been prepared and their structure activity relationships have been recently reviewed[1a]. Many of the agonists, typically, belong to the family of arylethanolamines **I**, although some agents, e.g., sotalol are antagonists[1b], and the antagonists to the 3-aryloxy-2-propanolamines **II**, although catechol analogs of phenoxypropanolamines can be full agonists[1c]. The aim of these investigations was to evaluate derivatives of formula **III** which could be considered on one hand to be vinylogs of **I** and on the other isosters of **II**, where the CH=CH spacer group would replace the $OCH_2$ functionality. One patent on derivatives of formula **III**, claimed compounds substituted at the aromatic ring with alkyl, alkoxy and halo groups, which possessed analgesic and strong, long lasting β-sympatholytic activity[2]. Our investigations dealt primarily with derivatives **III** substituted at the aromatic ring with electron withdrawing substituents. In addition to these, two other types of isosters of formulas **IV** and **V** were prepared. The former, which possess an acetylenic group, was prepared in order to evaluate the effect of the degree of saturation and rigidity on the biological activity, and the latter in order to determine the influence of the position of the double bond along the chain.

**Chart I.** General formulas of adrenergic agents

| Family | Structure | Description |
|---|---|---|
| I | Ar———CH(OH)———$CH_2$-NH-R | Agonists/Antagonists |
| II | Ar—$OCH_2$—CH(OH)———$CH_2$-NH-R | Antagonists/Agonists |
| III | Ar-CH=CH-CH(OH)———$CH_2$-NH-R | "Vinylogs" of agonists / isosters of antagonists |
| IV | Ar———CH(OH)—C≡C—$CH_2$-NH-R | "Acetylenylogs" of agonists |
| V | Ar———CH(OH)-CH=CH—$CH_2$-NH-R | "Vinylogs" of agonists |

## Chemistry

Vinylogs **5** (compounds of type **III**) were prepared by two procedures as shown in Scheme I.




a) MeCHO/NaOH/$Ac_2O$/$H^+$; b) $(EtO)_2POCH_2CO_2Et$/base/$H^+$; c) $SOCl_2$; d) LiAlH(O-t-Bu)$_3$; e) $Bu_3SnCN$; f) acetone/$LiAlH_4$; g) $Me_2S^+I^-$/base; h) $RNH_2$/MeOH
R = t-Bu; R' = i-Pr

Ar: a) 2-$NO_2$-$C_6H_4$; b) 3-$NO_2$-$C_6H_4$; c) 2-Cl-$C_6H_4$ ; d) 4-Cl-$C_6H_4$; e) 3,4-di-Cl-$C_6H_3$; f) 4-F-$C_6H_4$; g) 2-$CF_3$-$C_6H_4$; h) 3-$CF_3$-$C_6H_4$; i) MeO-$C_6H_4$; j) $Me_2N$-$C_6H_4$; k) 1 n-naphthalenyl

**Scheme I**

Cinnamaldehydes **2**, prepared by condensation of aromatic aldehydes **1** with acetaldehyde or by reduction of the corresponding cinnamoyl chlorides **7**, were converted to unsaturated epoxides **3**. Treatment of **3** with isopropyl or *tert*-butylamine gave mixtures of the desired amino alcohols **5** and their isomers **6** that were readily separated by flash chromatography. Alternatively, **7** were converted into acyl cyanides **8** which underwent reductive condensation in the presence of acetone to give **5** (R= isopropyl). The yields of cinnamaldehydes **2** obtained when prepared by condensation of **1** and acetaldehyde in the presence of a considerable excess of the acetaldehyde, were between 6–48% higher than those

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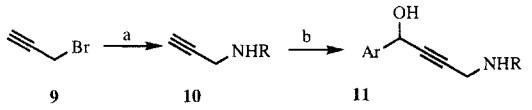
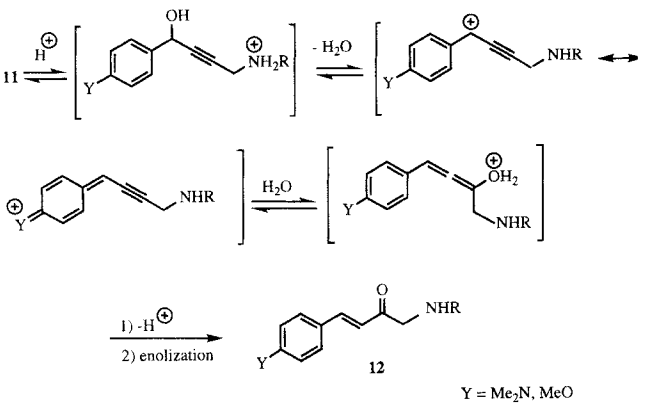


a) $RNH_2$; b) n-BuLi/ArCHO

Scheme II

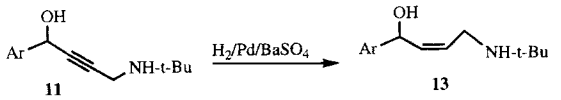
obtained by standard procedures[3]. Epoxidation of **2** was best accomplished by a modified Corey epoxidation[4].

Acetylenic derivatives **11** (general formula **IV**) were prepared as shown in Scheme II. In order to prevent the formation of bis-acetylenic amines $(HC{\equiv}C\text{-}CH_2)_2NR$, propargyl bromide was added dropwise to an excess of amine. The optimal temperature for reaction of the lithiated acetylides and the aryl aldehydes depended upon the aromatic substituent. With strong electron withdrawing groups (Y = $NO_2$), cooling to –70 °C was required. With weak electron withdrawing groups (Y = Cl) and electron donating groups (Y = MeO, $Me_2N$), the reaction was initially run at –25 °C, then allowed to reach room temperature and eventually heated to 50 °C to reach completion. To make all the compounds water soluble for biological administration, the hydrochloride salts were prepared. On conversion of the free amines to their salts using ethereal HCl, compounds **11m'** (Y = 4-MeO) and **11n** (Y = 4-$Me_2N$) bearing electron donating substituents rearranged to give α,β-unsaturated ketones **12** (Scheme III). The proposed rearrangement mechanism is favored by substituents possessing a non bonding pair of electrons where the carbocation is stabilized by resonance through the aromatic ring. A competing side reaction in all cases was the Cannizzaro disproportionation, minimized by ensuring dry reaction conditions.



Scheme III

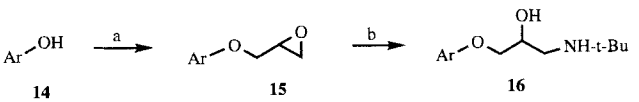
Vinylogs of type **V** were obtained by reduction of acetylenic derivatives **IV**. For acetylenes **11** bearing non-reducible aromatic substituents, catalytic hydrogenation was the choice of reduction to yield the *cis*-vinylogs **13** where $Pd/BaSO_4$ was reported[5] to be the most effective catalyst (Scheme IV). Commonly, quinoline would be required to poison the catalyst in order to prevent further reduction to a saturated bond. In our case, the amine function itself served the purpose of catalyst poison. These reduction conditions were also suitable for reducing the triple bonds to double bonds in compounds containing readily reducible aromatic nitro groups. Attempts



Scheme IV

to carry out this selective reduction with $AlH_3$[6], $BH_3{\cdot}SMe_2$[7], or mesityl$_2$BH[8], were not successful.

For comparison purposes various derivatives possessing classical aryloxypropanolamine structures were prepared from the corresponding phenols, epichlorohydrin and a primary amine (Scheme V).



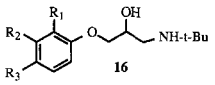
a) epichlorohydrin/NaOH; b) t-$BuNH_2$

Scheme V

## Biological Results and Discussion

The $\beta_1$-adrenoceptor activity of selected representatives from each group was quantified using the isolated, spontaneously beating rat atrial pairs preparation. Compounds from Group II, having the classic 3-aryloxy-2-propanolamine structure possessed reasonably potent β-adrenoceptor antagonist activity (Table 1). The most potent representatives, compounds **16c** ($K_B$ = 0.4 nM) and **16a** ($K_B$ = 1.5 nM), were monosubstituted at the 2-position on the aromatic ring while the least potent compounds ($K_B$ = 58 – 80 nM) were monosubstituted at the 3-position (**16b, 16h**) or disubstituted at positions 3 and 4 (**16e**) of the aromatic ring. Compounds **16a**, **16b** and **16c** also tended to increase the spontaneous rate of contraction of the atrial preparation immediately following their addition to the organ bath suggesting that these compounds may be more correctly classified as partial agonists rather than pure antagonists. Compounds from Group III, which represent 4-aryl-3-butenyl-2-ol-amine analogs of Group II, retained $\beta_1$-adrenoceptor antagonist activity albeit substantially less potent (50–200-fold) than that possessed by their aryloxy counterparts (Table 2). Consistent with the SAR for Group II compounds, substitution at position 2 of the aromatic ring yielded the most potent antagonists (**5a, 5d, 5g**), with $K_B$'s ranging from 73–93 nM while 3,4-dichloro substitution (**5e**) markedly reduced antagonist potency ($K_B$ = 2,400 nM). Agonist activity was also noted for **5a** and **5d**, suggesting that these compounds may be best classified as partial agonists. Compounds in Group V are isosters of Group III formed during synthesis, where the position of the hydroxyl group and the double bond are transposed. Representatives from Group V were, as expected, inactive as antagonists at the $\beta_1$-adrenoceptor confirming the importance of the spatial relationship between the hydroxyl and the amino nitrogen. Similarly, 4-aryl-3-butynly-2-ol-amine analogs, Group IV, were inactive at the $\beta_1$-adrenoceptor.

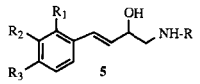
**Table 1.** Inhibition by selected aryloxypropanolamines of the chronotropic response to isoproterenol in the isolated rat atrial pairs preparation.



16

| no. | $R_1$ | $R_2$ | $R_3$ | Rat atrial pairs $K_B$ (nM) | Remarks |
|---|---|---|---|---|---|
| **16a** | $NO_2$ | H | H | 1.5 | Increased atrial rate by 26 bpm at 30 nM; 82 bpm at 300 nM |
| **16b** | H | $NO_2$ | H | 80 | Increased atrial rate by 25 bpm at 300 nM |
| **16c** | Cl | H | H | 0.4 | Increased atrial rate by 56 bpm at 300 nM |
| **16e** | H | Cl | Cl | 63 | |
| **16h** | H | $CF_3$ | H | 58 | |

**Table 2.** Inhibition by selected aryl-1-butenyl-3-olamines of the chronotropic response to isoproterenol in the isolated rat atrial pairs preparation



5

| no. | $R_1$ | $R_2$ | $R_3$ | Rat atrial pairs $K_B$ (nM) | Remarks |
|---|---|---|---|---|---|
| **5a** | $NO_2$ | H | H | 84 | Increased atrial rate by 41 bpm at 0.3 µM |
| **5d** | Cl | H | H | 93 | Increased atrial rate by 22 bpm at 1 µM |
| **5e** | H | Cl | Cl | 2,400 | Reduced atrial rate by 63 bpm at 3 µM |
| **5g** | $CF_3$ | H | H | 73 | |

The results observed with the phenoxypropanolamines bearing electron withdrawing ring substituents are similar to previously reported data on the effect of alkyl substitution on $\beta_1$-adrenoceptor antagonist potency in this structural series. The potency of the 2-$NO_2$ (**16a**) or 2-Cl (**16c**) substituted analogs is of the same magnitude as that reported for the corresponding 2-methyl or 2-isopropyl derivatives of 2-phenoxy-3-tert-butylamino-2-propanol (0.3 nM) or the ring-unsubstituted molecule (0.8 nM)[11]. The potency ratio between the 2-$NO_2$ (**16a**) and 3-$NO_2$ (**16b**) analogs is almost identical to that observed between the 2- and 3-methyl substituted derivatives of this molecule[11]. Hence it appears that the effects of ring substitution on $\beta_1$-adrenoceptor antagonist potency are due to steric, rather than electronic properties.

To our knowledge, the affinity of 4-aryl-3-butenyl-1-olamines for the β-adrenoceptor has not been previously reported. While these compounds are about 100 fold less potent than the corresponding phenoxypropanolamines, they have $\beta_1$-adrenoceptor affinities of the same magnitude as the arylethanolamine b-adrenoceptor antagonists, including DCI (dichloroisoproterenol), INPEA, pronethalol, and sotalol[11]. It is interesting that introduction of the vinyl linkage does not appear to reduce the $\beta_1$-adrenoceptor antagonist potency of arylethanolamines, in contrast to insertion of a single methylene carbon which, in general, substantially reduces β-adrenoceptor antagonist affinity[9,10].

The stereoselective interaction of both arylethanolamines and phenoxypropanolamines with the $\beta_1$-adrenoceptor would suggest that the relative orientation of the β-hydroxyl group and amine nitrogen is a critical determinant of receptor affinity. Hence, it is not surprising that analogs (compounds **11** and **13**) in which the distance between these structural elements is altered show virtually no affinity to the receptor.

## Acknowledgment

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## Experimental Part

*General Remarks*

$^1$H-NMR spectra were obtained on Brucker AM-300 and AC-200 spectrometers. Chemical shifts are expressed in ppm downfield from $Me_4Si$ used as internal standard. $CDCl_3$ was used as solvent, unless otherwise stated. Mass spectra were obtained on a Finnigan 4021 spectrometer (CI = chemical ionization; EI = electron ionization). Progress of the reactions was monitored by TLC on silica gel (Merck, Art. 5554). Flash chromatography was carried out on silica gel (Riedel-de Haen, 32–63 µm). Melting points were determined on a Fisher-Johns' apparatus.

*Cinnamaldehydes (**2**) – Procedure 1*

To an aldehyde (33 mmol) in a three necked flask cooled in a salt-ice bath was added dropwise with stirring acetaldehyde (40 mL) until a clear solution was obtained. Methanolic KOH (2.1 mL of a 20% solution) was added dropwise keeping the internal temperature between 0–5 °C. Stirring was continued for 2 h. $Ac_2O$ (16 mL) was added and the mixture heated to 100 °C for 30 min. The mixture was poured into an Erlenmeyer flask containing water (120 mL) to which concentrated HCl (16 mL) was added and the vessel heated to 100 °C for 20 min, then allowed to cool overnight. The solid obtained was filtered and purified by distillation or crystallization to give cinnamaldehydes **2.**

*3-Nitrocinnamaldehyde (**2b**)*[3c]

From 3-nitrobenzaldehyde, recrystallized from AcOH (82%): mp 113–114 °C (lit.[111] mp 117–119 °C); $^1$H-NMR δ 6.83 (dd, *J* = 16, 7 Hz, 1 H, CH=C*H*), 7.55 (d, *J* = 16 Hz, 1 H, C*H*=CH), 7.65 (t, *J* = 8 Hz, 1 H, H-5), 7.90 (dt, *J* = 8, 1 Hz, 1 H, H-6), 8.31 (ddd, *J* = 8, 2, 1 Hz, 1 H, H-4), 8.43 (t, *J* = 2 Hz, 1 H, H-2), 9.79 (d, *J* = 7 Hz, 1 H, CHO); MS (EI) *m/e*: 177 ($M^+$, 27), 176 ($M^+$ – H, 13), 160 ($M^+$ – OH, 100), 130 ($M^+$ – $HNO_2$, 48), 103 ($C_8H_7^+$, 36), 102 (PhCCH, 55), 77 ($C_6H_5^+$, 61). Anal. Calcd for ($C_9H_7NO_3$) C 61.02 H 3.98 Found C 60.61 H 3.91

*2-Chlorocinnamaldehyde (**2c**)*[3c]

From 2-chlorobenzaldehyde, distilled at the Kugelrohr (125 °C/0.2 Torr) (75%); mp 51–53 °C (lit.[111] mp 60–62 °C); $^1$H-NMR δ 6.70 (dd, *J* = 16, 8 Hz, 1 H, CH=C*H*), 7.31 (td, *J* = 7, 2 Hz, 1-H, H-5), 7.36 (td, *J* = 7, 2 Hz, 1-H, H-4), 7.45 (dd, *J* = 7, 2 Hz, 1 H, H-3), 7.65 (dd, *J* = 7, 2 Hz, 1 H, H-6), 7.93 (d, *J* = 16 Hz, 1 H, C*H*=CH), 9.74 (d, *J* = 8 Hz, 1 H, CHO); MS (EI) *m/e*: 166, 168 ($M^+$, 11, 4), 165, 167 ($M^+$ – H, 6, 5), 131 (Ph-CH=CH-$CO^+$, 100), 103 ($C_8H_7^+$, 20), 77 ($C_6H_5^+$, 12). Anal. ($C_9H_7ClO$•0.25$H_2O$) C 63.17 H 4.42 Found C 63.30 H 4.48.

*3,4-Dichlorocinnamaldehyde (**2e**)*[3c]

From 3,4-dichlorobenzaldehyde. The overnight cooling was allowed to proceed with stirring resulting in precipitation of the product. This precipitate was filtered and recrystallized twice from EtOH (1.9 g) mp 95.5–96 °C (lit.[112] 93–95 °C); The remaining crude was distilled at the Kugelrohr (bp 50 °C/0.1 Torr) and then recrystallized from ethanol to give a further 1.31 g (55%); $^1$H-NMR δ 6.69 (dd, *J* = 16, 8 Hz, 1 H, CH=C*H*), 7.39 (d, *J* = 16 Hz, 1 H, C*H*=CH), 7.40 (dd, *J* = 8, 2 Hz, 1 H, H-6), 7.53 (d, *J* = 8 Hz, 1 H, H-5), 7.66 (d, *J* = 2 Hz, 1 H, H-2), 9.72 (d, *J* = 8 Hz, 1 H, CHO); MS (EI) *m/e*: 200, 202, 204 ($M^+$, 43, 28, 4), 199, 201, 203 ($M^+$ – H, 19, 17, 5), 165, 167 ($M^+$ – Cl, 100, 32), 137, 139 ($M^+$ – Cl – CO, 32, 9), 102 (PhCCH, 15), 75 ($C_6H_3^+$). Anal. ($C_9H_6Cl_2O$) C 53.77 H 3.01 Found C 59.85 H 3.50 .

*2-Trifluoromethylcinnamaldehyde (**2g**)*[3d]

From 2-trifluoromethylbenzaldehyde, distilled at the Kugelrohr (bp 100 °C/0.07 Torr) (79%): mp 37–39 °C (lit.[113] bp 63–70 °C/0.5 Torr); $^1$H-NMR δ 6.70 (dd, *J* = 16, 8 Hz, 1 H, CH=C*H*), 7.54 (bt, *J* = 7 Hz, 1-H, H-5), 7.64 (bt, *J* = 7 Hz, 1-H, H-4), 7.77 (br d, 2 H, H-3 + H-6), 7.89 (dq, $J_{HH}$ = 16, $^5J_{FH}$ = 2 Hz, 1 H, C*H*=CH), 9.77 (d, *J* = 8 Hz, 1 H, CHO); MS (EI) *m/e*: 200 ($M^+$, 12), 199 ($M^+$ – H, 14), 171 ($M^+$ – CHO, 7), 151 ($M^+$ – CHO – HF, 55), 131 (Ph-CH=CH-$CO^+$, 100), 103 ($C_8H_7^+$, 12). Anal. ($C_{15}H_{20}F_3NO$•HCl) C 55.64 H 6.54 N 4.32 Found C 55.23 H 6.49 N 4.15.

*3-(1-Naphthalenyl)-2-propenal (**2k**)*

To a stirred solution of 3-(1-naphthalenyl)-2-propenoyl chloride (3 g, 13.7 mmol) in diglyme (15 mL), under $N_2$ at –78 °C, in the course of 1 h was dropwise added $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.02 g, 4 mmol) in diglyme (20 mL). At the end of the addition the reaction mixture was allowed to reach room temperature and was poured into crushed ice. The precipitate obtained was filtered, dried and recrystallized from 95% EtOH to give **2n** (0.8 g, 30%), mp 48–50 °C (lit.[3b] bp 220 °C/10 Torr).

*Arylethen-1-yl-oxiranes (**3**) – Procedure 2*

To a stirred solution of a cinnamaldehyde **2** (4 g, 20 mmol) in $CH_2Cl_2$ (100 mL) was added $Me_3S^+I^-$ (4.9 g, 24 mmol), $Bu_4N^+Br^-$ (32 mg) and NaOH (20 mL of a 50% solution.). The mixture was refluxed for 24 h, then poured into water (100 mL). The organic phase was retained and the aqueous phase extracted with $CH_2Cl_2$ (20 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, evaporated and the residue was purified by Kugelrohr distillation.

*2-(2-Nitrophenyl)ethen-1-yl-oxirane (**3a**)*

From 2-nitrocinnamaldehyde (83%); mp 34–36 °C; bp 150 °C/0.1 Torr; $^1$H-NMR δ 2.80 (dd, *J* = 5, 3 Hz, 1 H, C*H*H$^1$), 3.10 (dd, *J* = 5, 4 Hz, 1 H, CH*H*$^1$), 3.58 (ddd, *J* = 8, 4, 3 Hz, 1 H, CH-C*H*), 5.86 (dd, *J* = 16, 8 Hz, 1 H, CH=C*H*), 7.32 (d, *J* = 16 Hz, 1 H, C*H*=CH), 7.38–7.48 (m, 1 H, H-4), 7.54–7.64 (m, 2 H, H-5 + H-6), 7.95 (d, *J* = 8 Hz, 1 H, H-3); MS (CI) (*iso*-Bu) *m/e*: 192 ($MH^+$, 100), 174 ($MH^+$ – $H_2O$, 19), 162 ($MH^+$ – $CH_2O$, 6), 146 ($MH^+$ – $NO_2$, 37). Anal. ($C_{10}H_9NO_3$) C 62.82 H 4.74 N 7.33 Found C 63.01 H 4.62 N 7.09. HRMS calcd for $C_{10}H_9NO_3$ ($M+1^+$) 192.066068, Found 192.064983.

*2-(3-Nitrophenyl)ethen-1-yl-oxirane (**3b**)*

From **2b** (78%); bp 160 °C/0.08 Torr; mp 56–57 °C; $^1$H-NMR δ 2.81 (dd, *J* = 5, 3 Hz, 1 H, C*H*H$^1$), 3.10 (dd, *J* = 5, 4 Hz, 1 H, CH*H*$^1$), 3.56 (dddd, *J* = 8, 4, 3, 0.5 Hz, 1 H, CH-C*H*), 6.06 (dd, *J* = 16, 8 Hz, 1 H, CH=C*H*), 6.86 (d, *J* = 16 Hz, 1 H C*H*=CH), 7.51 (t, *J* = 8 Hz, 1 H, H-5), 7.69 (dt, *J* = 8, 1 Hz, 1 H, H-6), 8.11 (ddd, *J* = 8, 2, 1 Hz, 1 H, H-4), 8.22 (dd, *J* = 2, 1.5 Hz, 1 H, H-2); MS (EI) *m/e*: 191 ($M^+$, 14), 174 ($M^+$ – OH, 9), 163 ($M^+$ – CO, 44), 145 ($M^+$ – $NO_2$, 7), 144 ($M^+$ – $HNO_2$, 13), 115 ($C_9H_7^+$, 100), 103 ($C_8H_7^+$, 6), 102 (PhCCH, 6), 77 ($C_6H_5^+$, 8) Anal. ($C_{10}H_9NO_3$) C 62.82 H 4.74 N 7.33 Found C 62.59 H 4.62 N 6.99.

*2-(2-Chlorophenyl)ethen-1-yl-oxirane (**3c**)*

From **2c** (86%); bp 80 °C/0.2 Torr; $^1$H-NMR δ 2.79 (dd, *J* = 5, 3 Hz, 1 H, C*H*H$^1$), 3.08 (dd, *J* = 5, 4 Hz, 1 H, CH*H*$^1$), 3.58 (dddd, *J* = 8, 4, 3, 0.5 Hz, 1 H, CH-C*H*), 5.86 (dd, *J* = 16, 8 Hz, 1 H, CH=C*H*), 7.16–7.26 (m, 3 H, C*H*=CH + H-4 + H-5), 7.32–7.40 (m, 1 H, H-3), 7.48–7.56 (m, 1 H, H-6); MS (EI) *m/e*: 180, 182 ($M^+$, 14, 5), 152, 154 ($M^+$ – CO, 26, 9), 145 ($M^+$ – Cl, 30), 115 ($C_9H_7^+$, 100), 103 ($C_8H_7^+$, 4), 102 (PhCCH, 3), 77 ($C_6H_5^+$, 4). Anal. ($C_{10}H_9ClO$) C 66.49 H 5.02 Found C 65.82 H 5.25.

*2-(3,4-Dichlorophenyl)ethen-1-yl-oxirane (**3e**)*

From **2e** (85%); bp 160 °C/0.1 Torr; $^1$H-NMR δ 2.77 (dd, *J* = 5, 3 Hz, 1 H, C*H*H$^1$), 3.08 (dd, *J* = 5, 4 Hz, 1 H, CH*H*$^1$), 3.51 (dddd, *J* = 8, 4, 3, 0.5 Hz, 1 H, CH-C*H*), 5.89 (dd, *J* = 16, 8 Hz, 1 H, CH=C*H*), 6.71 (d, *J* = 16 Hz, 1 H, C*H*=CH), 7.20 (dd, *J* = 8, 2 Hz, 1 H, H-6), 7.39 (d, *J* = 8 Hz, 1 H, H-5), 7.45 (d, *J* = 2 Hz, 1 H, H-2); MS (EI) *m/e*: 214, 216, 218 ($M^+$, 22, 14, 2), 186, 188, 190 ($M^+$ – CO, 41, 26, 4), 179, 181 ($M^+$ – Cl, 34, 11), 150, 152 ($M^+$ – Cl – CO, 30, 11), 149, 151 ($M^+$ – Cl – CHO, 100, 51), 115 ($C_9H_7^+$, 29).

*2-(2-Trifluoromethylphenyl)ethen-1-yl-oxirane (**3g**)*

From **2g** (91%); bp 80 °C/0.07 Torr; $^1$H-NMR δ 2.79 (dd, *J* = 5, 3 Hz, 1 H, C*H*H$^1$), 3.08 (dd, *J* = 5, 4 Hz, 1 H, CH*H*$^1$), 3.57 (dddd, *J* = 8, 4, 3, 0.5 Hz, 1 H, CH-C*H*), 5.86 (dd, *J* = 16, 8 Hz, 1 H, CH=C*H*), 7.20 (dq, $J_{HH}$ = 16, $^5J_{FH}$ = 2 Hz, 1 H, C*H*=CH), 7.36 (br t, *J* = 8 Hz, 1 H, H-5), 7.50 (br t, *J* = 7 Hz, 1 H, H-4), 7.61 and 7.65 (both d, *J* = 7 Hz, 2 H, H-3 + H-6); MS (EI) *m/e*: 214 ($M^+$, 19), 197 ($M^+$ – OH, 72), 186 ($M^+$ – CO, 26), 177 ($M^+$ – OH – HF, 100), 115 ($C_9H_7^+$, 25). Anal. ($C_{11}H_9F_3O$•0.25$H_2O$) C 60.41 H 4.37 Found C 60.41 H 4.16.

*2-(1-Naphthalenyl)ethen-1-yl-oxirane (**3k**)*

From **2k** (82%); bp 112 °C/0.5 Torr; $^1$H-NMR δ 2.72 (dd, *J* = 1, 2.5 Hz, 1 H, OCH*H*), 3.20 (dd, *J* = 2.5, 4 Hz, 1 H, OC*H*H), 3.55 (dddd, *J* = 1, 2.5, 4, 8 Hz, 1 H, CHO), 6.85 (dd, *J* = 8, 16 Hz, 1 H, ArCH=C*H*), 7.4–7.6 (m, 3 H, H-3, H-6, H-7), 7.80 (d, *J* = 8 Hz, 1 H, H-5), 7.90 (two superimposed d, *J* = 8 Hz, 2 H, H-2, H-4), 8.13 (d, *J* = 8 Hz, 1 H, H-7), 8.21 (d, *J* = 16 Hz, 1 H, Ar*CH*). MS (CI) (*iso*-Bu) *m/e*: 197 ($MH^+$), 179 ($MH^+$ – $H_2O$).

*3-(1-Naphthalenyl)-2-propenoyl Cyanide (**8k**)*

A mixture of 3-(1-naphthalenyl)-2-propenoyl chloride **7n** (1.2 g, 5.5 mmol)[14] and $Bu_3SnCN$ (1.43 g, 4.6 mmol)[15] was heated for ca. 20 min at 75 °C until a homogeneous solution was obtained. The solution was heated in a Kugelrohr apparatus at 80 °C/1 Torr to remove $Bu_3SnCl$. The residue solidified upon cooling and was recrystallized from $CHCl_3$/pentane (3:1) to give **8n** (1 g, 88%), mp 180–182.

*1-tert-Butylamino-4-(aryl)but-3-en-2-ols (**5**) and 2-tert-butylamino-4-(aryl)but-3-en-1-ols (**6**) – Procedure 3*

To a solution of an epoxide **3** (5–15 mmol) in MeOH (10 mL) was added *tert*-$BuNH_2$ (10 mL) and the mixture was stirred for 4–6 days or was refluxed for 15 h. Excess MeOH and amine were evaporated and the residual mixture of isomers **5** and **6** was separated using flash chromatography (eluent: $CHCl_3$:MeOH:$NH_4OH$, 70:10:1). The products were further converted to the corresponding hydrochlorides.

*1-tert-Butylamino-4-(2-nitrophenyl)but-3-en-2-ol (**5a**)*

From **3a** (71%); mp 60–61.5 °C; mp of hydrochloride 187–188 °C; $^1$H-NMR δ 1.21 (s, 9 H, *t*-Bu), 2.66 (dd, *J* = 12, 8 Hz, 1 H, CH*H*$^1$), 2.95 (dd, *J* = 12, 4 Hz, 1 H, C*H*H$^1$), 4.42 (m, 1 H, C*H*-OH), 6.18 (dd, *J* = 16, 6 Hz, CH=C*H*), 7.14 (dd, *J* = 16, 1 Hz, 1 H, C*H*=CH), 7.38 (ddd, *J* = 8, 7, 2 Hz, 1 H, H-4), 7.48–7.66 (m, 2 H, H-5 + H-6), 7.92 (dd, *J* = 8, 1 Hz, 1 H, H-3); MS (EI) *m/e*: 265 ($MH^+$, 78), 249 ($MH^+$ - 16, 7), 231 ($M^+$ – Me – $H_2O$, 3), 86 ($CH_2$=$NH^+$-*t*-Bu, 100). HRMS calcd for $C_{14}H_{20}N_2O_3$ (M+1$^+$) 265.158856 Found 265.155197. Anal. $C_{14}H_{20}N_2O_3$•HCl•2.5$H_2O$) C 48.62 H 7.58 N 8.10 Found C 48.66 H 6.97 N 7.81.

*2-tert-Butylamino-4-(2-nitrophenyl)but-3-en-1-ol (**6a**)*

**6a** (11%); mp 105–106 °C; mp of hydrochloride 218–219 °C (at 205 °C dec. begins); $^1$H-NMR δ 1.18 (s, 9 H, *t*-Bu), 3.31 (dd second order, 1 H, C*H*H$^1$), 3.61 (m, 2 H, CH*H*$^1$ + CH-N), 6.09 (dd, *J* = 16, 7 Hz, 1 H, CH=C*H*), 7.01 (d, *J* = 16 Hz, 1 H, C*H*=CH), 7.32–7.48 (m, 1 H, H-4), 7.50–7.66 (m, 2 H, H-5 + H-6), 7.95 (d, *J* = 8 Hz, 1 H, H-3); MS (EI) *m/e*: 265 ($MH^+$, 19), 249 ($MH^+$ – 16, 4), 233 ($MH^+$ – H – $CH_2OH$, 100), 177 (BP – $C_4H_8$, 98). Anal. ($C_{14}H_{20}N_2O_3$•HCl) C 55.91 H 7.04 N 9.31 Found C 55.51 H 6.97 N 9.17.

*1-tert-Butylamino-4-(3-nitrophenyl)but-3-en-2-ol (**5b**)*

From **3b** (61%); mp 83–84 °C; mp of hydrochloride 196–196.5 °C; $^1$H-NMR δ 1.13 (s, 9 H, *t*-Bu), 2.57 (dd, *J* = 12, 8 Hz, 1 H, CH*H*$^1$), 2.88 (dd, *J* = 12, 4 Hz, 1 H, C*H*H$^1$), 4.28 (dddd, *J* = 8, 5, 4, 1 Hz, 1 H, C*H*-OH), 6.35 (dd, *J* = 16, 5 Hz, CH=C*H*), 6.76 (dd, *J* = 16, 1 Hz, 1 H, C*H*=CH), 7.48 (t, *J* = 8 Hz, 1 H, H-5), 7.68 (dt, *J* = 8, 1 Hz, 1 H, H-4), 8.08 (ddd, *J* = 8, 2, 1 Hz, H-6), 8.24 (t, *J* = 2 Hz, 1 H, H-2); MS (EI) *m/e*: 265 ($MH^+$, 22), 249 ($MH^+$ – 16, 2), 231 ($M^+$-Me – $H_2O$, 19), 86 ($CH_2$=$NH^+$-*t*-Bu, 100). Anal. ($C_{14}H_{20}N_2O_3$·HCl) C 55.91 H 7.04 N 9.31 Found C 55.87 H 7.06 N 9.00.

*2-tert-Butylamino-4-(3-nitrophenyl)but-3-en-1-ol (**6b**)*

**6b** 0.45 g (29%); mp 50–51°C; mp of hydrochloride 235 °C (dec.); $^1$H-NMR δ 1.17 (s, 9 H, *t*-Bu), 3.31 (dd second order, 1 H, C*H*H$^1$), 3.52–3.66 (m, 2 H, CH*H*$^1$ + CH-N), 6.27 (dd, *J* = 16, 7 Hz, 1 H, CH=C*H*), 6.58 (d, *J* = 16 Hz, 1 H, C*H*=CH), 7.49 (t, *J* = 8 Hz, 1 H, H-5), 7.66 (dt, *J* = 8, 1 Hz, 1 H, H-4), 8.08 (ddd, *J* = 8, 2, 1 Hz, 1 H, H-6), 8.21 (t, *J* = 2 Hz, 1 H, H-2); MS (EI) *m/e*: 265 ($MH^+$, 1), 249 ($MH^+$ - 16, 1), 233 ($MH^+$ – H – $CH_2OH$, 57), 177 ($MH^+$ – H – $CH_2OH$ – $C_4H_8$, 100). Anal. ($C_{14}H_{20}N_2O_3$•HCl) C 55.91 H 7.04 N 9.31 Found C 55.65 H 7.01 N 8.91.

*1-tert-Butylamino-4-(2-chlorophenyl)but-3-en-2-ol (**5c**)*

From **3c** (52%); mp 195–196 °C; mp of hydrochloride 195.5–196 °C; $^1$H-NMR δ 1.17 (s, 9 H, *t*-Bu), 2.62 (dd, *J* = 12, 8 Hz, 1 H, CH*H*$^1$), 2.89 (dd, *J* = 12, 4 Hz, 1 H, C*H*H$^1$), 4.36 (dddd, *J* = 8, 6, 4, 1 Hz, 1 H, C*H*-OH), 6.19 (dd, *J* = 16, 6 Hz, CH=C*H*), 7.06 (dd, *J* = 16, 1 Hz, 1 H, C*H*=CH), 7.12–7.28 (m, 2 H, H-4 + H-5), 7.35 (dd, *J* = 7, 2 Hz, 1 H, H-3), 7.54 (dd, *J* = 7, 3 Hz, 1 H, H-6); MS (EI) *m/e*: 254 ($MH^+$, 4), 238 ($MH^+$ – 16, 0.5), 220, 222 ($M^+$ – Me – $H_2O$, 11, 3), 86 ($CH_2$=$NH^+$-*t*-Bu, 100). Anal. ($C_{14}H_{20}ClNO$•HCl) C 57.94 H 7.29 N 4.83 Found C 57.65 H 7.23 N 4.63.

*2-tert-Butylamino-4-(2-chlorophenyl)but-3-en-1-ol (**6c**)*

**6c** (31%); mp 101–102 °C; mp of hydrochloride 203–203.5 °C (at 195 °C dec. begins); $^1$H-NMR δ 1.21 (s, 9 H, *t*-Bu), 3.37 (td second order, 1 H, C*H*H$^1$), 3.56–3.72 (m, 2 H, CH*H*$^1$ + CH-N), 6.16 (dd, *J* = 16, 8 Hz, 1 H, CH=C*H*), 6.92 (d, *J* = 16 Hz, 1 H, C*H*=CH), 7.12–7.24 (m, 2 H, H-4 + H-5), 7.35 (dd, *J* = 7, 2 Hz, 1 H, H-3), 7.50 (dd, *J* = 7, 2 Hz, 1 H, H-6); MS (EI) *m/e*: 222, 224 ($M^+$ -$CH_2OH$, 68, 15), 166, 168 ($M^+$ – $CH_2OH$ – $C_4H_8$, 100, 14). Anal. ($C_{14}H_{20}ClNO$•HCl) C 57.93 H 7.29 N 4.83 Found C 57.85 H 7.28 N 4.61.

*1-tert-Butylamino-4-(3,4-dichlorophenyl)but-3-en-2-ol (**5e**)*

From **3e** (64%); mp 70.5–71 °C; mp of hydrochloride 223–223.5 °C; $^1$H-NMR δ 1.12 (s, 9 H, *t*-Bu), 2.54 (dd, *J* = 12, 8 Hz, 1 H, CH*H*$^1$), 2.84 (dd, *J* = 12, 4 Hz, 1 H, C*H*H$^1$), 4.23 (dddd, *J* = 8, 5, 4, 1 Hz, 1 H, C*H*-OH), 6.19 (dd, *J* = 16, 5 Hz, 1 H, CH=C*H*), 6.59 (dd, *J* = 16, 1 Hz, 1 H, C*H*=CH), 7.19 (dd, *J* = 8, 2 Hz, 1 H, H-6), 7.37 (d, *J* = 8 Hz, 1 H, H-5), 7.45 (d, *J* = 2 Hz, 1 H, H-2); MS (CI) (*iso*-Bu) *m/e*: 344, 346, 348 ($MC_4H_9^+$, 15, 11, 1), 326 ($MC_3H_3^+$, 5), 288, 290, 292 ($MH^+$, 100, 91, 12), 254, 256 ($MH^+$ – Cl – H, 2, 1), 214, 216, 218 ($MH^+$ – $C_4H_9NH_3$, 2, 1, 0.1), 86 ($CH_2$=$NH^+$ – *t*-Bu, 100). Anal. ($C_{14}H_{19}Cl_2NO$•HCl) C 51.79 H 6.21 N 4.31 Found C 51.67 H 6.17 N 4.13.

*2-tert-Butylamino-4-(3,4-dichlorophenyl)but-3-en-1-ol (**6e**)*

**6e** (13%); mp 77–78 °C; mp of hydrochloride 200 °C (dec.); $^1$H-NMR δ 1.15 (s, 9 H, *t*-Bu), 3.27 (m, 1 H, C*H*H$^1$), 3.48–3.58 (m, 2 H, CH*H*$^1$ + CH-N), 6.10 (ddm, *J* = 16, 7 Hz, 1 H, CH=C*H*), 6.41 (d, *J* = 16 Hz, 1 H, C*H*=CH), 7.16 (dd, *J* = 8, 2 Hz, 1 H, H-6), 7.37 (d, *J* = 8 Hz, 1 H, H-5), 7.42 (d, *J* = 2 Hz, 1 H, H-2); MS (CI) (*iso*-Bu) *m/e*: 344, 346, 348 ($MC_4H_9^+$, 16, 13, 1), 326, 328, 330 ($MC_3H_3^+$, superimposed), 330, 332, 334 ($MC_3H_7^+$, superimposed), 288, 290, 292 ($MH^+$, 100, 76, 18), 270, 272, 274 ($MH^+$ – $H_2O$, 11, 10, 3), 256, 258, 260 ($MH^+$ – $CH_2OH_2$, 15, 12, 3), 215, 217, 219 ($MH^+$ – $C_4H_9NH_2$, 13, 9, 2). Anal. ($C_{14}H_{19}Cl_2NO$•HCl•0.25$H_2O$) C 51.08 H 6.27 N 4.25 Found C 51.08 H 6.15 N 4.09.

*1-tert-Butylamino-4-(2-trifluoromethylphenyl)but-3-en-2-ol (**5g**)*

From **3i** (49%); mp 50–51 °C; mp of hydrochloride 166.5–167 °C; $^1$H-NMR δ 1.12 (s, 9 H, *t*-Bu), 2.60 (dd, *J* = 12, 8 Hz, 1 H, CH*H*$^1$), 2.83 (dd, *J* = 12, 4 Hz, 1 H, C*H*H$^1$), 4.30 (dddd, *J* = 8, 6, 4, 1.5 Hz, 1 H, C*H*-OH), 6.17 (dd, *J* = 16, 6 Hz, CH=C*H*), 7.04 (ddq, *J* = 16, $^5J_{FH}$ = 2, *J* = 1.5 Hz, 1 H, C*H*=CH), 7.33 (br t, *J* = 7 Hz, 1 H, H-5), 7.49 (tm, *J* = 8 Hz, 1 H, H-4), 7.62 (dm, *J* = 9 Hz, 2 H, H-3 + H-6); MS (EI) *m/e*: 288 ($MH^+$, 80), 272 ($MH^+$ – 16, 4), 254 ($M^+$ – Me – $H_2O$, 21), 86 ($CH_2$=$NH^+$ – *t*-Bu, 100). Anal. ($C_{15}H_{20}F_3NO$•HCl) C 55.64 H 6.54 N 4.32 Found C 55.23 H 6.49 N 4.15.

*2-tert-Butylamino-4-(2-trifluoromethylphenyl)but-3-en-1-ol (**6g**)*

**6g** (23%); mp 77–77.5 °C; mp of hydrochloride 178–178.5 °C (at 172 °C dec. begins); $^1$H-NMR δ 1.16 (s, 9 H, *t*-Bu), 3.28 (dd second order, 1 H, C*H*H$^1$), 3.57 (m, 2 H, CH*H*$^1$ + CH-N), 6.06 (dd, *J* = 16, 7 Hz, 1 H, CH=C*H*), 6.89 (dq, $J_{HH}$ = 16, $^5J_{FH}$ = 2 Hz, 1 H, C*H*=CH), 7.34 (br t, *J* = 8 Hz, 1 H, H-5), 7.49 (bt, *J* = 8 Hz, 1 H, H-4), 7.57 [ (bd, *J* = 10 Hz) and 7.62 (bd, *J* = 8 Hz) 2 H, H-3 + H-6]; MS (EI) *m/e*: 288 ($MH^+$, 2), 272 ($MH^+$ – 16, 1) 256 ($MH^+$ – H – $CH_2OH$, 56), 200 ($MH^+$ – H – $CH_2OH$ – $C_4H_8$, 100), 180 (BP – HF, 13), 160 (BP – 2HF, 15). Anal. ($C_{15}H_{20}F_3NO$•HCl) C, H, N.

*1-Isopropylamino-4-(1-naphthalenyl)but-3-en-2-ol (**5k**)*

To a solution of $LiAlH_4$ (1.52 g, 0.04 mol) in dry ether (50 mL), under $N_2$, at –5 °C, was dropwise added a solution of **8n** (2.07 g, 0.01 mol) in acetone (5.8 g, 0.1 mol). The mixture was stirred at 0 °C for 3 h and at room temperature overnight. The reaction was worked up by a standard procedure [16] to give 5n (0.9 g, 35%), mp 95–97 °C; $^1$H-NMR δ 1.13 (d, *J* = 6 Hz, 3 H, Me), 1.17 (d, *J* = 6 Hz, 3 H, Me'), 2.85 (dd, *J* = 8, 12 Hz, 1 H, C*H*HN), 2.96 (septet, *J* = 6 Hz, 1 H, C*H*Me$_2$), 3.22 (dd, *J* = 4, 12 Hz, 1 H, CH*H*N), 4.55 (m, 1 H, C*H*OH), 6.50 (dd, *J* = 8, 16 Hz, 1 H, ArCH=C*H*), 7.4–7.6 (m,

3 H, H-3, H-6, H-7), 7.80 (d, $J$ = 8 Hz, 1 H, H-5), 7.90 (two superimposed d, $J$ = 8 Hz, 2 H, H-2, H-4), 8.13 (d, $J$ = 8 Hz, 1 H, H-8), 8.21 (d, $J$ = 8 Hz, 1 H, ArC*H*). MS (CI) (*iso*-Bu) *m/e*: 256 ($MH^+$, 0.2), 238 ($MH^+ - H_2O$), 197 ($MH^+$ – *i*-$PrNH_2$), 72 (*i*-Pr-$NHCH_2^+$).

*tert-Butylpropargylamine* (**10**)

To a stirred solution of *tert*-$BuNH_2$ (25.7 g, 350 mmol) in ether (20 mL), was dropwise added propargyl bromide (13.9 g, 120 mmol) in ether (15 mL). After 30 h, NaOH (10 g, 250 mmol) in water (15 mL) was added. A white precipitate of NaBr formed. The organic phase was decanted, the precipitate dissolved in water (10 mL) and the solution extracted with ether (15 mL). The combined organic phase was washed with brine, dried overnight ($K_2CO_3$), filtered and distilled to give **10** (8 g, 60%): bp 48 °C/18 Torr (lit.[17] 37–39 °C/26 Torr); $^1$H-NMR δ 1.13 (br s, 9 H, *t*-Bu), 1.33 (br s, 1 H, NH), 2.19 (t, $J$ = 2 Hz, 1 H, HCC), 3.38 (d, $J$ = 2 Hz, 2 H, $CH_2$).

*Isopropylpropargylamine* (**10′**)

Compound **10′** was prepared from *iso*-$PrNH_2$ (17.7 g, 300 mmol) and propargyl bromide (11.9 g, 100 mmol) as described for **10** (4.6 g, 47%); bp 36 °C/18 Torr (lit.[18] bp 108–110 °C); $^1$H-NMR δ 1.06 (d, $J$ = 6 Hz, 6H, Me), 1.38 (br s, 1 H, NH), 2.20 (t, $J$ = 2 Hz, 1 H, HCC), 3.04 (sptet, $J$ = 6 Hz, 1 H, NH-C*H*), 3.44 (d, $J$ = 2 Hz, 2 H, $CH_2$).

*1-(Substituted)aryl-4-alkylamino-2-butyn-1-ols* (**11**) – *Procedure 4*

To an alkyl-propargylamine (16.2 mmol) in THF (3 mL) under $N_2$ at –30 °C was rapidly added *n*-BuLi (10.2 mL of a 1.6 M solution, 16.4 mmol) and the mixture was stirred for 30 min. To the white suspension obtained was added dropwise an araldehyde (2.0 g, 16.2 mmol) in THF (7 mL) and the mixture was stirred for 1 h at –70 °C, then allowed to reach room temperature. In some cases the reaction mixture was finally warmed to 45 °C for 10 min. The reaction was quenched with water (5 mL) and acidified with dilute HCl to pH 1.5. The aqueous phase was separated, basified with concentrated NaOH to pH 12 and extracted with ether (2 × 15 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), mixed with charcoal, filtered and the solvents were evaporated. The products **11** were isolated as the corresponding hydrochlorides.

*1-(2-Nitrophenyl)-4-tert-butylamino-2-butyn-1-ol* (**11a**)

From 2-nitrobenzaldehyde, isolated as an oil (64%); mp of hydrochloride 143–143.5 °C; $^1$H-NMR δ 1.12 (s, 9 H, *t*-Bu), 3.45 (d, $J$ = 2 Hz, 2 H, $CH_2$), 6.09 (br s, 1 H, CH), 7.47 (td, $J$ = 8, 1 Hz, 1 H, H-4), 7.66 (td, $J$ = 8, 1 Hz, 1 H, H-5), 7.94 (dd, $J$ = 8, 1 Hz, 1 H, H-6), 7.99 (dd, $J$ = 8, 1 Hz, 1 H, H-3); MS (CI) (*iso*-Bu) *m/e*: 319 ($MC_4H_9^+$, 0.2), 301 ($MC_3H_3^+$, 4), 263 ($MH^+$, 100), 247 ($MH^+$ – O, 9) 245 ($MH^+ - H_2O$, 7), 207 ($MH^+$-$C_4H_8$, 5), 86 ($CH_2$=$NH^+$-t-Bu, 9) ; MS (EI) *m/e*: 247 ($M^+$ – Me, 100), 86 ($CH_2$=$NH^+$-*t*-Bu, 2). Anal. ($C_{14}H_{19}N_2O_3$•HCl) C 56.28 H 6.40 N 9.37 Found C 55.63 H 6.39 N 9.0.

*1-(3-Nitrophenyl)-4-tert-butylamino-2-butyn-1-ol* (**11b**)

From 3-nitrobenzaldehyde, free amine was recrystallized from ether (42%); mp 102–103 °C; mp of hydrochloride 147–148 °C; $^1$H-NMR δ 1.16 (s, 9 H, *t*-Bu), 3.51 (d, $J$ = 2 Hz, 2 H, $CH_2$), 5.59 (br s, 1 H, CH), 7.55 (t, $J$ = 8 Hz, 1 H, H-5), 7.87 (dm, $J$ = 8 Hz, 1 H, H-6), 8.18 (ddd, $J$ = 8, 2, 1 Hz, 1 H, H-4), 8.42 (t, $J$ = 2 Hz, 1 H, H-2); MS (CI) (*iso*-Bu) *m/e*: 301 ($MC_3H_3^+$, 4), 263 ($MH^+$, 100), 247 ($MH^+$ – O, 11), 245 ($MH^+ - H_2O$, 6), 207 ($MH^+$ – $C_4H_8$, 12), 189 ($MH^+$-$C_4H_9NH_3$, 3), 86 ($CH_2$=$NH^+$-t-Bu, 2). Anal. ($C_{14}H_{19}N_2O_3$•HCl) C H N Found C 56.28 H 6.40 N 9.37 Found C 56.28 H 6.35 N 9.1.

*1-(2-Chlorophenyl)-4-tert-butylamino-2-butyn-1-ol* (**11c**)

From 2-chlorobenzaldehyde (40%); mp of hydrochloride 176.5–177 °C; $^1$H-NMR δ 1.10 (s, 9 H, *t*-Bu), 3.44 (d, $J$ = 2 Hz, 2 H, $CH_2$), 5.86 (t, $J$ = 2 Hz, 1 H, CH), 7.23 (td, $J$ = 7, 2 Hz, 1 H, H-5), 7.26 (td, $J$ = 7, 2 Hz, 1 H, H-4), 7.36 (dd, $J$ = 7, 2 Hz, 1 H, H-6), 7.80 (dd, $J$ = 7, 2 Hz, 1 H, H-3); MS (CI) (*iso*-Bu) *m/e*: 290, 292 ($MC_3H_3^+$, 4, 2), 252, 254 ($MH^+$, 100, 41), 236, 238 ($MH^+$ – O, superimposed), 234, 236 ($MH^+ - H_2O$, superimposed), 218, 220 ($MH^+$ – Cl + H, 2, 1), 196, 198 ($MH^+ - C_4H_8$, 2, 0.6), 178, 180 ($MH^+ - C_4H_9NH_3$, 5, 2). Anal. ($C_{14}H_{19}ClNO$•HCl) C 58.34 H 6.64 N 4.85 Found C 58.10 H 6.51 N 4.66.

*1-(2-Chlorophenyl)-4-isopropylamino-2-butyn-1-ol* (**11c′**)

From 2-chlorobenzaldehyde (3%); mp 135–138 °C; mp of hydrochloride 148–148.5 °C; $^1$H-NMR δ 1.10 (d, $J$ = 6 Hz, 6 H, Me), 3.08 (septet, $J$ = 6 Hz, 1 H, NH-C*H*), 3.55 (d, $J$ = 2 Hz, 2 H, $CH_2$), 5.43 (br t, $J$ = 2 Hz, 1 H, C*H*-OH), 7.25–7.43 (m, 3 H, H-4 + H-5 + H-6), 7.76 (dm, $J$ = 7 Hz, 1 H, H-3); MS (CI) (*iso*-Bu) *m/e*: 294, 296 ($MC_4H_9^+$, 2, 1), 280, 282 ($MC_3H_7^+$, superimposed), 276, 278 ($MC_3H_3^+$, superimposed), 238, 240 ($MH^+$, 100, 32), 222, 224 ($MH^+$ – O, superimposed), 220, 222 ($MH^+ - H_2O$, superimposed), 204, 206 ($MH^+$ – Cl + H, 0.8, 0.2), 178, 180 ($MH^+ - C_3H_7NH_3$, 0.7, 0.2).

*1-(4-Chlorophenyl)-4-isopropylamino-2-butyn-1-ol* (**11d′**)

From 4-chlorobenzaldehyde (7%); mp of hydrochloride 147–147.5 °C; $^1$H-NMR δ 1.06 (d, $J$ = 6 Hz, 6 H, Me), 2.98 (septet, $J$ = 6 Hz, 1 H, NH-C*H*), 3.49 (d, $J$ = 2 Hz, 2 H, $CH_2$), 5.44 (br s, 1 H, C*H*-OH), 7.34 (dm, $J$ = 8 Hz, 2 H, H-2 + H-6), 7.47 (dm, $J$ = 8 Hz, 2 H, H-3 + H-5); MS (CI) (*iso*-Bu) *m/e*: 294 ($MC_4H_9^+$, 0.2), 280 282 ($MC_3H_7^+$, 1, 0.1), 276, 278 ($MC_3H_3^+$, 2, 1), 238, 240 ($MH^+$, 100, 31), 222, 224 ($MH^+$ – O, superimposed), 220, 222 ($MH^+ - H_2O$, superimposed). Anal. ($C_{13}H_{16}ClNO$•HCl) C 56.95 H 6.25 N 5.11 Found C 56.90 H 6.28 N 4.96.

*1-(3,4-Dichlorophenyl)-4-tert-butylamino-2-butyn-1-ol* (**11e**)

From 3,4-dichlorobenzaldehyde (56%); mp 85–89 °C; mp of hydrochloride 173–174 °C; $^1$H-NMR δ 1.15 (s, 9 H, *t*-Bu), 3.48 (d, $J$ = 2 Hz, 2 H, $CH_2$), 5.42 (br s, 1 H, CH), 7.34 (dd, $J$ = 8, 2 Hz, 1 H, H-6), 7.42 (d, $J$ = 8 Hz, 1 H, H-5), 7.62 (d, $J$ = 2 Hz, 1 H, H-2); MS (CI) (*iso*-Bu) *m/e*: 324, 326, 328 ($MC_3H_3^+$, 4, 3, 1), 286, 288, 290 ($MH^+$, 100, 89, 18), 270, 272, 274 ($MH^+$ – O, superimposed), 268, 270, 272 ($MH^+ - H_2O$, superimposed), 252, 254 ($MH^+$-Cl + H, 8, 2), 234, 236 ($MH^+$-Cl + H – $H_2O$, 12, 5), 230, 232, 234 ($MH^+ - C_4H_8$, 7, 5, superimposed), 212, 214, 216 ($MH^+$-$C_4H_9NH_3$, 15, 11, 2). Anal. ($C_{14}H_{17}Cl_2NO$•HCl•0.25$H_2O$) C 51.40 H 5.70 N 4.28 Found C 51.60 H 5.62 N 4.17.

*1-(2-Trifluoromethylphenyl)-4-tert-butylamino-2-butyn-1-ol* (**11g**)

From 2-trifluoromethylbenzaldehyde (60%); mp 92–93 °C; mp of hydrochloride 164–164.5 °C; $^1$H-NMR δ 1.11 (s, 9 H, *t*-Bu), 3.45 (d, $J$ = 2 Hz, 2 H, $CH_2$), 5.87 (br s, 1 H, CH), 7.42 (t, $J$ = 8 Hz, 1 H, H-5), 7.61 (t, $J$ = 8 Hz, 1 H, H-4), 7.63 (d, $J$ = 8 Hz, 1 H, H-6), 8.01 (d, $J$ = 8 Hz, 1 H, H-3); MS (CI) (*iso*-Bu) *m/e*: 342 ($MC_4H_9^+$, 0.5), 324 ($MC_3H_3^+$, 4), 286 ($MH^+$, 100), 270 ($MH^+$ – O, 10),268 ($MH^+ - H_2O$, 45), 230 ($MH^+ - C_4H_8$, 2), 212 ($MH^+ - C_4H_9NH_3$, 5), 86 ($CH_2$=$NH^+$-t-Bu, 4); MS (EI) *m/e*: 270 ($M^+$ – Me, 100), 252 (BP – $H_2O$, 45). Anal. ($C_{15}H_{18}F_3NO$•HCl) C 55.99 H 5.95 N 4.35 Found C 55.71 H 5.90 N 4.19.

*1-(4-Methoxyphenyl)-4-isopropylamino-2-butyn-1-ol* (**11i′**)

From *p*-anisaldehyde (14%); $^1$H-NMR δ 1.08 (d, $J$ = 6 Hz, 6 H, Me), 3.03 (septet, $J$ = 6 Hz, 1 H, NH-C*H*), 3.53 (d, $J$ = 2 Hz, 2 H, $CH_2$), 3.82 (s, 3 H, MeO), 5.43 (br t, $J$ = 2 Hz, 1 H, C*H*-OH), 6.91 (dm, $J$ = 8 Hz, 2 H, H-3 + H-5), 7.47 (dm, $J$ = 8 Hz, 2 H, H-2 + H-6).

*1-(4-Dimethylaminophenyl)-4-tert-butylamino-2-butyn-1-ol* (**11j**)

From 4-dimethylaminobenzaldehyde. The free base was recrystallized from ether (33%); $^1$H-NMR δ 1.14 (s, 9 H, *t*-Bu), 2.95 (s, 6 H, Me), 3.49 (d, $J$ = 2 Hz, 2 H, $CH_2$), 5.39 (br t, $J$ = 2 Hz, 1 H, CH), 6.71 (dm, $J$ = 9 Hz, 2 H, H-3 + H-5), 7.40 (dm, $J$ = 9 Hz, 2 H, H-2 + H-6); MS (CI) (*iso*-Bu) *m/e*: 261 ($MH^+$, 93), 243 ($MH^+ - H_2O$, 100), 187 ($MH^+ - C_4H_9NH_3$, 3), 150 ($Me_2N[C_7H_5]^+OH$, 2), 122 ($Me_2NH^+$-Ph, 2), 86 ($CH_2$=$NH^+$-*t*-Bu, 0.4).

*1-(4-Methoxyphenyl)-4-isopropylamino-2-buten-3-one* (**12i**)

In the course of the preparation of the hydrochloride salt of **11i′** compound **12i** was isolated (9%); it decomposed above 170 °C; $^1$H-NMR (DMSO - D-6) δ 1.28 (d, $J$ = 7 Hz, 6 H, Me), 3.35 (septet, $J$ = 7 Hz, 1 H, NCH), 3.83 (s, 3 H,

MeO), 4.32 (s, 2 H, $CH_2$), 6.84 (d, $J$ = 16 Hz, 1 H, CH=C*H*), 7.05 (d, $J$ = 8 Hz, 2 H, H-3 + H-5), 7.74 (d, $J$ = 8 Hz, 2 H, H-2 + H-6), 7.78 (d, $J$ = 16 Hz, 1 H, C*H*=CH); MS (CI) (*iso*-Bu) *m/e*: 234 ($MH^+$, 73), 177 ($MH^+$ – $Me_2C$=NH, 0.5).

*1-(Aryl)-4-tert-butylamino-2-buten-1-ols Hydrochlorides (**13**) – Procedure 5*

A stirred mixture of alkyne **11** (2.8–3.6 mmol) in MeOH (50 mL) was hydrogenated at room temperature and atmospheric pressure over 10% $Pd/BaSO_4$ (0.2 g). Within 5 min the calculated amount of $H_2$ was absorbed. The product **13** was obtained upon filtration of the mixture, concentration of the residue and purification by flash chromatography (eluent: $CHCl_3$:MeOH:$NH_4OH$, 70:10:1).

*1-(2-Nitrophenyl)-4-tert-butylamino-2-buten-1-ol (**13a**)*

From **11a** (38%); free base mp 74.5–75.5 °C; hydrochloride mp 117–117.5 °C; $^1$H-NMR δ 1.19 (s, 9 H, *t*-Bu), 3.20–3.44 (A B q of d, $J$ = 12, 6, 5 Hz, 2 H, $CH_2$), 5.74–5.89 (m, 2 H, CH=CH), 6.02 (d, $J$ = 4 Hz, 1 H, C*H*-OH), 7.40 (t, $J$ = 8 Hz, 1 H, H-4), 7.63 (t, $J$ = 8 Hz, 1 H, H-5), 7.91 (d, $J$ = 8 Hz, 1 H, H-6), 7.96 (d, $J$ = 8 Hz, 1 H, H-3); MS (EI) *m/e*: 265 ($MH^+$, 100), 263 ($M^+$ – H, 4), 249 ($MH^+$ – O, 72), 247 ($MH^+$ – $H_2O$, 31), 231 ($MH^+$ – H – Me – $H_2O$, 12), 191 ($MH^+$ – $C_4H_9NH_3$, 8), 173 ($MH^+$ – $C_4H_9NH_3$ – $H_2O$, 18), 74 ($C_4H_9NH_3^+$, 4). HRMS calcd for $C_{14}H_{20}N_2O_3$ (M+1$^+$) 265.158856 Found 265.155218.

*1-(3-Nitrophenyl)-4-tert-butylamino-2-buten-1-ol (**13b**)*

From **11b** (43%); free base mp 92.5–93.5 °C; hydrochloride mp 180.5–181.5 °C; $^1$H-NMR δ 1.19 (s, 9 H, *t*-Bu), 3.23–3.44 (A B q of dm, $J$ = 12, 6, 5 Hz, 2 H, $CH_2$), 5.51 (d, $J$ = 4 Hz, 1 H, C*H*-OH), 5.80–5.93 (m, 2 H, CH=CH), 7.51 (t, $J$ = 8 Hz, 1 H, H-5), 7.76 (dq, $J$ = 8, 1 Hz, 1 H, H-6), 8.10 (ddd, $J$ = 8, 2, 1 Hz, 1 H, H-4), 8.29 (t, $J$ = 2 Hz, 1 H, H-2); MS (EI) *m/e*: 265 ($MH^+$, 19), 249 ($MH^+$ – O, 43), 231 ($MH^+$ – H – Me – $H_2O$, 100), 191 ($MH^+$ – $C_4H_9NH_3$, 28), 185 (BP – $NO_2$, 7), 174 ($MH^+$ – $C_4H_9NH_3$ – OH, 22), 74 ($C_4H_9NH_3^+$, 28).

*1-(2-Chlorophenyl)-4-tert-butylamino-2-buten-1-ol (**13c**)*

From **11c** (47%); free base mp 76.5–77 °C; hydrochloride mp 131–131.5 °C; $^1$H-NMR δ 1.20 (s, 9 H, *t*-Bu), 3.22–3.51 (A B q of d, $J$ = 12, 6, 6 Hz, 2 H, $CH_2$), 5.68–5.90 (m, 3H, CH-CH=CH), 7.19 (td, $J$ = 8, 2 Hz, 1 H, H-5), 7.26 (td, $J$ = 8, 2 Hz, 1 H, H-4), 7.32 (dm, $J$ = 8 Hz, 1 H, H-6), 7.68 (dd, $J$ = 8, 2 Hz, 1 H, H-3); MS (CI) (*iso*-Bu) *m/e*: 296, 298 ($MC_3H_7^+$, 2, 1), 292, 294 ($MC_3H_3^+$, 2, 1), 254, 256 ($MH^+$, 100, 47), 236, 238 ($MH^+$ – $H_2O$, 30, 9), 220 ($MH^+$ – Cl + H, 3), 180, 182 ($MH^+$ – $C_4H_9NH_3$, 6, 2), 74 ($C_4H_9NH_3^+$, 3).

*1-(3,4-Dichlorophenyl)-4-tert-butylamino-2-buten-1-ol (**13e**)*

From **11g** (50%); free base mp 91.5–92.5 °C; hydrochloride mp 199–199.5 °C; $^1$H-NMR δ 1.17 (s, 9 H, *t*-Bu), 3.20–3.39 (A B q of d, $J$ = 12, 6, 5 Hz, 2 H, $CH_2$), 5.37 (d, $J$ = 4 Hz, 1 H, C*H*-OH), 5.75–5.89 (m, 2H, CH=CH), 7.22 (ddd, $J$ = 8, 2, 0.5 Hz, 1 H, H-5), 7.40 (d, $J$ = 8 Hz, 1 H, H-6), 7.52 (dd, $J$ = 2, 0.5 Hz, 1H, H-2); MS (CI) (*iso*-Bu) *m/e*: 344, 346, 348 ($MC_4H_9^+$, 5, 4, 0.2), 330, 332, 334 ($MC_3H_7^+$, superimposed), 326, 328, 330 ($MC_3H_3^+$, superimposed), 288, 290, 292 ($MH^+$, 100, 66, 13), 270, 272, 274 ($MH^+$ – $H_2O$, 19, 12, 2), 254, 256 ($MH^+$ – Cl + H, 3, 1), 236, 238 ($MH^+$ – Cl – $H_2O$ + H , 0.3, 0.1), 214, 216 ($MH^+$ – $C_4H_9NH_3$, 2, 1), 74 ($C_4H_9NH_3^+$, 3). Anal. ($C_{14}H_{19}Cl_2NO$•HCl•0.5$H_2O$) C 50.39 H 6.34 N 4.20 Found C 50.65 H 6.17 N 4.10.

*1-(2-Trifluoromethylphenyl)-4-tert-butylamino-2-buten-1-ol (**13g**)*

From **11g** (60%); free base mp 68–68.5 °C; hydrochloride mp 171.5–172 °C; $^1$H-NMR δ 1.19 (s, 9 H, *t*-Bu), 3.24–3.45 (A B q of d, $J$ = 13, 6, 5 Hz, 2 H, $CH_2$), 5.69–5.86 (m, 3 H, CH-CH=CH), 7.34 (t, $J$ = 8 Hz, 1 H, H-5), 7.57 (t, $J$ = 8 Hz, 1 H, H-4), 7.61 (d, $J$ = 8 Hz, 1 H, H-6), 7.85 (d, $J$ = 8 Hz, 1 H, H-3); MS (CI) ($NH_3$) *m/e*: 288 ($MH^+$, 100).

*1-(Aryloxy)-3-tert-butylamino-2-propanols (**16**) – Procedure 6*

To a phenol **14** (4.02 g, 24.8 mmol) and NaOH (1.1 g, 27.5 mmol) in water (10 mL) was added epichlorohydrin (3.1 mL, 40 mmol) and the stirred solution was refluxed for 4 h. A precipitate formed. The mixture was extracted with EtOAc (15 mL) and ether (15 mL), the combined organic phase was evaporated and excess epichlorohydrin was removed under high vacuum. The residue was dissolved in MeOH (10 mL), *tert*-$BuNH_2$ (10 mL) was added and the mixture was refluxed for 24 h. A precipitate formed. Excess amine was evaporated and the residue was dissolved in EtOAc (10 mL), then acidified to pH 1.5 with dilute HCl. The combined aqueous phase was basified to pH 10 with concentrated NaOH and extracted with EtOAc (15 mL) and ether (15 mL). The organic phase was separated and the aqueous phase basified to pH 12 and extracted as before. The combined organic phase was washed with brine, dried ($Na_2CO_3$), mixed with charcoal, filtered and the solvents were evaporated. Traces of solvents and *tert*-$BuNH_2$ were removed under high vacuum to give **16**, isolated as the corresponding hydrochloride salts.

*1-(2-Nitrophenoxy)-3-tert-butylamino-2-propanol (**16a**)*

From 2-nitrophenol (15%); hydrochloride mp 121–121.5 °C (lit.[19] mp 113–114 °C); $^1$H-NMR δ 1.16 (s, 9 H, *t*-Bu), 2.72–2.95 (A B q of d, $J$ = 12, 6, 5 Hz, 2 H, C$H_2$-NH), 3.90–4.05 (m, 1 H, CH), 4.11–4.23 (m, 2 H, $OCH_2$), 7.04 (ddd, $J$ = 8, 7, 2 Hz, 1 H, H-4), 7.11 (dd, $J$ = 7, 2 Hz, 1 H, H-6), 7.53 (ddd, $J$ = 8, 7, 2 Hz, 1 H, H-5), 7.87 (dd, $J$ = 8, 2 Hz, 1 H, H-3); MS (CI) (*iso*-Bu) *m/e*: 325 ($MC_4H_9^+$, 17), 311 ($MC_3H_7^+$, 2), 269 ($MH^+$, 100), 253 ($MH^+$ – O, 0.4), 213 ($MH^+$ – $C_4H_8$, 0.2), 86 ($CH_2$=$NH^+$-*t*-Bu, 0.4).

*1-(3-Nitrophenoxy)-3-tert-butylamino-2-propanol (**16b**)*

From 3-nitrophenol (54%); free base mp 147–148.5 °C (lit.[20] mp 147–149 °C); hydrochloride mp 120–120.5 °C (lit.[17] mp 129–131 °C); $^1$H-NMR δ 1.16 (s, 9 H, *t*-Bu), 2.65–2.95 (A B q of d, $J$ = 12, 8, 4 Hz, 2 H, C$H_2$-NH), 3.96–4.20 (m, 3 H, $CH_2$-CH), 7.27 (ddd, $J$ = 8, 3, 1 Hz, 1 H, H-6), 7.43 (t, $J$ = 8 Hz, 1 H, H-5), 7.76 (t, $J$ = 3 Hz, 1 H, H-2), 7.84 (ddd, $J$ = 8, 3, 1 Hz, 1 H, H-4); MS (CI) (*iso*-Bu) *m/e*: 325 ($MC_4H_9^+$, 19), 307 ($MC_3H_3^+$, 3), 269 ($MH^+$, 100), 253 ($MH^+$ – O, 3), 239 ($MH^+$ – NO, 2), 224 ($MH^+$ – $NO_2$ + H, 0.2), 213 ($MH^+$ – $C_4H_8$, 2).

*1-(2-Chlorophenoxy)-3-tert-butylamino-2-propanol (**16c**)*

From 2-chlorophenol (78%): free base mp 78–79.5 °C; hydrochloride mp 144.5–145 °C (lit.[21] mp 143–145 °C); $^1$H-NMR δ 1.19 (s, 9 H, *t*-Bu), 2.77–3.03 (A B q of dm, $J$ = 12, 6, 5 Hz, 2 H, C$H_2$-NH), 4.03–4.14 (m, 3 H, $CH_2$-CH), 6.93 (td, $J$ = 8, 2 Hz, 1 H, H-4) 6.97 (dd, $J$ = 8, 2 Hz, 1 H, H-6), 7.23 (ddd, $J$ = 8, 7, 2 Hz, 1 H, H-5), 7.38 (dd, $J$ = 8, 2 Hz, 1 H, H-3); MS (EI) *m/e*: 257 ($M^+$, 0.4), 242, 244 ($M^+$ – Me, 90, 24), 128, 130 ($C_6H_5ClO^+$, 24, 5), 86 ($CH_2$=$NH^+$-*t*-Bu, 100).

*1-(3,4-Dichlorophenoxy)-3-tert-butylamino-2-propanol (**16e**)*

From 3,4-dichlorophenol (76%): free base mp 69–71 °C; hydrochloride mp 196–196.5 °C (lit.[22] mp 197–198 °C); $^1$H-NMR δ 1.14 (s, 9 H, *t*-Bu), 2.59–2.92 (A B q of dm, $J$ = 12, 8, 4 Hz, 2 H, C$H_2$-NH), 3.87–4.03 (m, 3 H, $CH_2$-CH), 6.79 (dd, $J$ = 9, 3 Hz, 1 H, H-6), 7.03 (d, $J$ = 3 Hz, 1 H, H-2), 7.32 (d, $J$ = 9 Hz, 1 H, H-5); MS (EI) *m/e*: 292, 294, 296 ($MH^+$, 3, 1, 0.1), 276, 278, 280 ($MH^+$ – 16, 78, 46, 5), 175, 177, 179 ($Cl_2Ph$-O=$CH_2^+$, 5, 3, 0.2), 86 ($CH_2$=$NH^+$-*t*-Bu, 100).

*1-(3-Trifluoromethyl)phenoxy-3-tert-butylamino-2-propanol (**16h**)*

From 3-trifluoromethylphenol (58%): free base mp 80–83 °C; hydrochloride mp 152.5–153 °C (lit.[21] mp 154–156 °C); $^1$H-NMR δ 1.15 (s, 9 H, *t*-Bu), 2.63–2.96 (AB q of d, $J$ = 12, 7, 4 Hz, 2 H, C$H_2$-NH), 3.90–4.10 (m, 3 H, $CH_2$-CH), 7.04–7.32 (m, 3 H, H-2 + H-4 + H-6), 7.40 (t, $J$ = 8 Hz, 1 H, H-5); MS (CI) (*iso*-Bu) *m/e*: 348 ($MC_4H_9^+$, 16), 334 ($MC_3H_7^+$, 4), 330 ($MC_3H_3^+$, 3), 292 ($MH^+$, 100), 276 ($MH^+$ – O, 2), 86 ($CH_2$=$NH$-*t*-$Bu^+$, 4).

## Biological Methods

Adult male Sprague-Dawley strain rats weighing between 250–400 g were deeply anesthetized via an intraperitoneal injection of 0.5 mL of a 32% pentobarbital solution. The thoracic cavity was opened and the right and left atria quickly dissected as a pair from the rest of the heart and placed in room temperature Krebs-Henseleit solution of the following composition (mmol/l): NaCl, 119; $CaCl_2$, 2.5; $KH_2PO_4$, 1.2; $MgSO_4$, 1.5; KCl, 4.7; $NaHCO_3$, 25; glucose, 11; and disodium EDTA 0.03. The atrial pair was suspended (by means of surgical thread secured to the apex of each atrium) between a Grass FT03D isometric force-displacement transducer and a stationary glass rod in standard organ baths containing Krebs-Henseleit solution that was maintained at 37 °C and aerated continuously with a 95% $O_2$/5% $CO_2$ mixture. A resting tension (approximately 1–2 g) sufficient to allow the recording of atrial contractions was applied to each atrial pair. The rate of atrial contractions was recorded from cardiotachometers triggered by the atrial pulses on a Narco Biosystems MK-IV physiograph. Following a 20–30 min equilibration period a cumulative concentration-response curve to isoproterenol was obtained for each atrial pair. At the completion of the concentration-response curve, the isoproterenol was rinsed from the bath. When atrial rate returned and stabilized at near baseline levels, the tissues were exposed to a concentration of the test agent. After a 20 min equilibration period the isoproterenol concentration-response curve was repeated in the presence of the test agent. An effective concentration ($EC_{50}$) for isoproterenol was calculated in the presence and absence of the test agent. The $EC_{50}$ is the concentration of isoproterenol that produced a half-maximal increase in the rate of atrial contraction. The magnitude of the shift in the $EC_{50}$ produced by the test agent was used to calculate a dissociation constant ($K_B$), an estimate of potency, using the formula:

$$K_B = \frac{\text{Concentration of Test Agent}}{(\text{Shift in } EC_{50}) - 1}$$

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