Adrenergic Agents, II[1]:

1-Aryl-N^2-alkyl-ethanediamines as Isosters of Adrenergic Arylethanolamines

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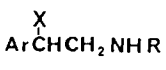
A family of 1-aryl-N^2-alkyl-ethanediamines **1** isosteric with the N-alkyl-arylethanolamines are described. Although the prepared compounds were generally less potent than the N-alkyl-arylethanolamines, the 1-aryl-N'-(phenylmethyl)-N-alkyl-1,2-ethanediamines derivatives **6**, are more active than the debenzylated free amino analogs **1**, which may be indicative of the importance of the lipophilicity of the substituent at the alpha position to the aromatic ring.

Adrenerge Wirkstoffe, 2. Mitt.[1]: 1-Aryl-N^2-alkyl-ethandiamine als Isostere adrenerger Arylethanolamine

Eine Serie von 1-Aryl-N^2-alkyl-ethandiaminen **1** wird beschrieben, die isoster mit N-Alkyl-arylethanolaminen sind. Obwohl die dargestellten Verbindungen allgemein weniger wirksam als die N-Alkyl-arylethanolamine sind, sind die 1-Aryl-N'-(phenylmethyl)-N-alkyl-1,2-ethandiamine **6** wirksamer als die debenzylierten freien Amine **1**. Das weist auf die Bedeutung der Lipophilie des Substituenten in α-Stellung zum aromatischen Ring hin.

Structure-activity relationship studies on catecholamines have dealt primarily with derivatives of type A (X=OH) [2]. Most reported studies on these compounds have been concerned with modifications of the Ar and R groups, with only a relatively small number of investigations dealing with compounds where X was other than OH. Some of the variants of X described include: CH_2OH [3], SH, SMe and SSO_3H [4], SO_3H [5], Cl and Br [6], and OMe [7]. Invariably these derivatives showed decreased biological activity as compared to the X=OH analogs.

In connection with our work on adrenergic amine derivatives [1], we describe the synthesis and biological evaluation of a number of novel compounds, in which the X=OH group has been replaced by bioisosteric X=amino groups. This type of structural modification has attracted some interest. The earliest work [8], where in the compounds studied R=Me, indicated a reduced pressor activity with a concomitant decrease in toxicity as compared to epinephrine. More recently, a reduction in beta-blocking activity was observed for the X=NH_2 analog of pronethalol [9], (X=OH, Ar=2-naphthyl, R=isopropyl), and a Japanese patent [10] has claimed that the isoster of isoproterenol (X=OH, Ar=3,4-dihydroxyphenyl, R=isopropyl) where X=NH_2, showed stronger activity on the heart muscle than on the respiratory organ smooth muscle.



A

Chemistry

Three alternative synthetic routes to derivatives **1** are shown in the Scheme.

Path A: A modified *Strecker* reaction provided the N-benzylamino nitriles **3** which were readily reduced to **4** [11]. Subsequent reductive condensation provided the diamines **6** [12]. The course of hydrogenolytic debenzylation of **6** favored the least-substituted phenyl ring [13], to give the desired diamines **1**. This reaction, however, was unsuitable for halo-substituted aryl derivatives, which underwent concomitant hydrogenolytic dehalogenation [14], independent of the concentration of catalyst. By this method primary and secondary alkylamino derivatives can be prepared, but it is unsuitable for R = N-tert-butyl products.

Path B: The attempted direct reductive condensation of **3** to **6** failed, due to hydrogenolytic removal of the cyano group [15] to give **5**. This problem was overcome by carrying out the conversion sequence **2** → **7** → **8** → **9** while replacing the N-benzyl by an N-acetyl protective group, however the low overall yields (20-52%) made this approach less desirable.

Path C: Classical methodology was used in the synthesis of the amino amides **13** which were reduced to the desired diamines **1**, preferentially ith B_2H_6 [16], since $LiAlH_4$ gave much lower yields. This sequence, although longer, has the advantage of being suitable for R = second. (series I) as well as *tert*-alkylamino derivatives (series II).

Biological Evaluation

The activity of the compounds was evaluated in vitro by *Gilman's* procedure, [17] where the quantity of cyclic AMP formed upon activation of adenyl cyclase by adrenergic agents was measured. The activity of the agents toward β-receptors, is proportional to the increase in concentration of the measured cyclic AMP [18].

In general, it was noted that the potency of the tested compounds was relatively small, where the most active compound of type **1**, 1-(4-hydroxyphenyl)-N^2-(1-methyl-ethyl)-ethanediamine dihydrochloride **1h-I**, was 5000 time less potent than isoproterenol. In the series of compounds of type

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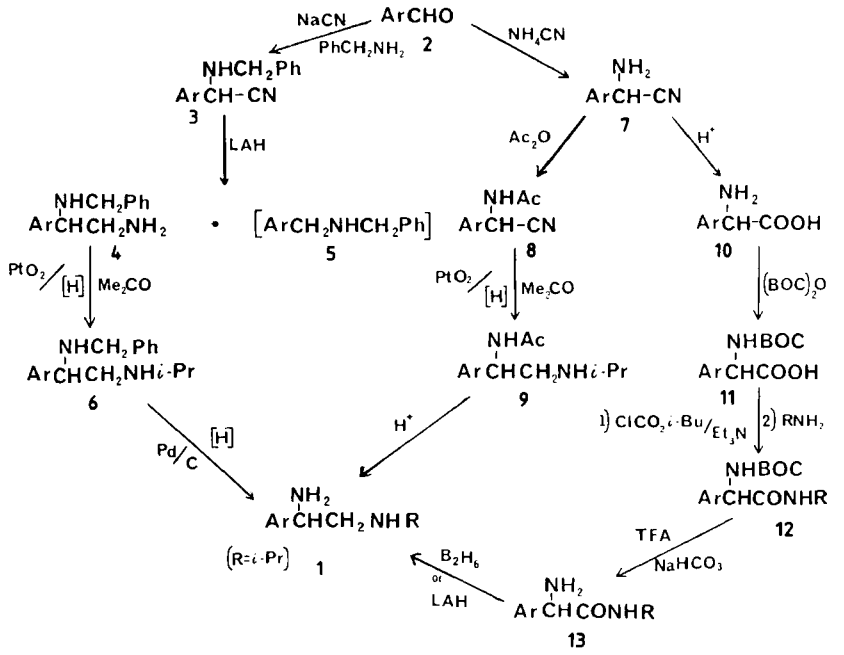

R = i-propyl (**I**); tert-butyl (**II**)

Ar: a = o-Cl-C_6H_4-; b = p-Me-C_6H_4-; c = 2-naphthyl; d = 2,3-di-MeO-C_6H_3-; e = p-Me_2N-C_6H_4-; f = 2-furanyl; g = p-HO-C_6H_4-; h = p-MeO-C_6H_4-; i = 3,4-di-Cl-C_6H_3-

6. the most potent one was 1-(4-dimethylaminophenyl)-N^2-(1-methyl)ethyl-N^1-(phenylmethyl)-1,2-ethanediamine trihydrochloride **6e** with a potency 114 times smaller than that of the standard isoproterenol. In spite of this general low potency, it should be noted thath the activity of the N-benzyl derivatives **6**, was higher than that of the debenzylated free amines **1**. For instance, **6d** and **6b** were respectively 1800 and 179 times more active than **1d** and **1b**, and the activity of **6f** was lost completely upon debenzylation to **1f**. In this more active family of N-benzyl derivatives, substitution of the phenyl ring with electron donating substituents, brought about an increase in activity, whereas electron withdrawing groups caused a decrease in activity, i.e. **6e** and **6d** were respectively 2000 and 500 times more potent than **6a**. The higher activity of the N-benzyl derivatives **6** compared to that of the primary amines **1** may be indicative of a direct correlation between lipophilic character and activity in these molecules.

Experimental Part

General remarks: ^{1}H-NMR spectra: Varian Ft-80A and Brucker WH-270, Me_2SO-d_6/TMS (unless an other solvent is indicated). - Mass spectra: Varian Mat 731. - Progress of reactions was monitored by tlc on silica gel (Merck, Art. 5554) or alumina (Riedel-de Haen, Art. 37349). - Flash chromatography: silica gel (Merck, Art. 9385).

α-(Arylmethyl)amino-benzeneacetonitriles (**3**)

The procedure used was analogous to that of *Matier* [11]. An initial increase in reaction temp. up to ca 40°C was observed, upon addition of the aldehyde to the solution of benzyl amine hydrochloride and NaCN.

2-Chloro-α-[(phenylmethyl)amino]-benzeneacetonitrile (**3a**)

M.p. 195-196°C (lit. [11] m.p. 153-155°C). - ^{1}H-NMR: 7.59-7.37 (10H, m, ArH and exchangeable NH), 5.67 (1H, s, CH), 4.21 (2H, AB "quartet", CH_2). - MS (EI) m/z: 258/256 (M^+), 232/230 (M^+ - CN), 167/165 (M^+ - $PhCH_2$), 157/155 (M^+-$PhCH_2NH$), 106 ($PhCH_2NH^+$), 91 ($C_7H_7^+$).

4-Methyl-α-[(phenylmethyl)amino]-benzeneacetonitrile (**3b**)

M.p. 248-249°C (lit.[11] m.p. 150-152°C). - ^{1}H-NMR (+ D_2O): 7.70-7.30 (9H, m, ArH), 5.92 (1H, s, CH), 4.15 (2H, AB "quartet", CH_2), 2.36 (3H, s, Me). - MS(EI) m/z: 236 (M^+), 221 (M^+ - Me), 210 (M^+ - CN), 209 (M^+ - HCN), 145 (M^+ - $PhCH_2$), 130 (M^+ - $PhCH_2NH$), 106 ($PhCH_2NH^+$), 91 ($C_7H_7^+$).

α-[(Phenylmethyl)amino]-2-naphthalenacetonitrile (**3c**)[22]

M.p. 57-58°C. - ^{1}H-NMR (+ D_2O): 8.06-7.25 (12H, m, ArH), 5.16 (1H, s, CH), 3.86 (2H, s, CH_2). - MS(EI) m/z: 272 (M^+), 246 (M^+ - CN), 245 (M^+ - HCN), 181 (M^+ - $PhCH_2$), 166 (M^+ - $PhCH_2NH$), 106 ($PhCH_2NH^+$) 91 ($C_7H_7^+$).

2,3-Dimethoxy-α-[(phenylmethyl)amino]-benzeneacetonitrile (**3d**)

M.p. 213-214°C. - ^{1}H-NMR: 7.63-7.18 (9H, m, ArH and exchangeable NH), 5.74 (1H, s, CH), 4.20 (2H, AB quartet, J = 13 Hz, CH_2), 3.85 (3H, s, OMe), 3.81 (3H, s, OMe). - MS(EI) m/z: 282 (M^+), 256 (M^+ - CN), 191 (M^+ - $PhCH_2$), 176 (M^+ - $PhCH_2NH$), 106 ($PhCH_2NH^+$), 91 ($C_7H_7^+$).

4-Dimethylamino-α-[(phenylmethyl)amino]-benzeneacetonitrile (**3e**)

M.p. 136-138°C. - ^{1}H-NMR (+ D_2O): 7.33 (4H, AB "quartet", J = 9 Hz, ArH), 7.46 (5H, s, PH), 5.90 (1H, s, CH), 4.08 (2H, AB "quartet", CH_2), 3.02 (6H, s, Me_2N). - MS(EI) m/z: 239 (M^+ - CN), 174 (M^+ - $PhCH_2$), 159 (M^+ - $PhCH_2NH$), 106 ($PhCH_2NH^+$), 91 ($C_7H_7^+$). - $C_{17}H_{19}N_3$ (265) Calc. C 60.36 H 6.27 Found C 60.14 H 6.40.

α-[(Phenylmethyl)amino]-2-furanacetonitrile (**3f**)

M.p. 168-169°C. - ^{1}H-NMR: 7.89 (1H, d, J = 1.8 Hz, Ar), 6.88 (1H, d, J = 3.2 Hz, ArH), 6.62 (1H, dd, J = 3.2, 1.8 Hz, Ar), 7.47-7.33 (6H, m, Ph + exchangeable NH), 6.18 (1H, s, CH), 4.07 (2H, s, CH_2). - MS(EI) m/z: 212 (M^+), 186 (M^+ - CN), 185 (M^+ - HCN), 121 (M^+ - $PhCH_2$), 106 (M^+ - $PhCH_2NH$). - $C_{13}H_{12}N_2O$ (212) Calc. C 62.78 H 5.27 N 11.27 Found C 62.97 H 5.50 N 10.96.

1-Aryl-N^1-(arylmethyl)-1,2-ethanediamines **4** *and (Arylmethyl)-benzenemethaneamines* **5**

Compounds **4** were prepared by *Matier's* procedure [18]. In the course of the reduction of **3c** and **3d**, part of the starting materials underwent denitrilation to the corresponding (arylmethane)-phenylmethaneamines **5**, which were separated from the desired **4** by chromatography on silica gel. The less polar **13** were eluted with EtOAc and subsequently **4** were eluted with MeOH/AcOH. The elutent was evaporated and the diamines **4** were obtained as hydrochlorides upon addition of methanolic HCl.

1-(2-Chlorophenyl)-N^1-(phenylmethyl)-1,2-ethanediamine dihydrochloride (**4a**)

M.p. 218-223°C (lit.[11]) m.p. 218-223°C). - ^{1}H-NMR ($CDCl_3$): 7.53-7.11 (9H, m, ArH), 4.11 (1H, dd, J = 7.7, 4.6 Hz, CH), 3.66 (2H, m, Ph-CH_2), 3.37 (1H, m, NH), 2.90 (1H, dd, J = 12, 7.7 Hz, CH_2), 2.63 (1H, dd, J = 12, 4.6 Hz, CH_2), 1.64 (2H, br s, NH_2). - MS(EI) m/z: 263/261 (MH^+), 246/244 (M^+ - NH_2), 232/230 (M^+ - CH_2NH_2), 156/154 (M^+ - $PhCH_2NH$), 91 ($C_7H_7^+$).

1-(4-Methylphenyl)-N^1-(phenylmethyl)-1,2-ethanediamine dihydrochloride (**4b**)

M.p. 244-247°C (lit.[11]) m.p. 244-247°C). - ^{1}H-NMR (+ D_2O): 7.46-7.17 (9H, m, ArH); 4.14 (1H, m, CH), 3.66 (2H, s, Ph-CH_2), 3.19 (2H, m, CH_2), 2.34 (3H, s, Me). - MS(EI) m/z: 241 (MH^+), 220 (M^+ - CH_2NH_2), 134 (M^+ - $PhCH_2NH$), 106 ($PhCH_2NH_2^+$), 91 ($C_7H_7^+$).

1-(2-Naphthalenyl)-N^1-(phenylmethyl)-1,2-ethanediamine dihydrochloride (**4c**)

^{1}H-NMR (+ D_2O): 8.20-7.33 (12H, m, ArH), 4.35 (1H, m, CH), 3.82 (4H, m, 2 $PhCH_2$). - MS(EI) m/z: 277 (MH^+), 246 (M^+ - CH_2NH_2), 106 ($PhCH_2NH_2^+$), 91 ($C_7H_7^+$).

1-(2,3-Dimethoxyphenyl)-N^1-(phenylmethyl)-1,2-ethanediamine dihydrochloride (**4d**)

M.p. 218-220°C. - ^{1}H-NMR (+ D_2O): 7.44-7.23 (8H, m, ArH), 4.89 (1H, br t, CH), 4.36-3.36 (4H, M, 2 $PhCH_2$), 3.87 (3H, s, OMe), 3.83 (3H, s, OMe). MS(EI) m/z: 287 (MH^+), 270 (M^+ - NH_2), 256 (M^+ - CH_2NH_2), 180 (M^+ - $PhCH_2NH$). - $C_{17}H_{22}N_2O_2 \cdot HCl$ (322.5) Calc. C 56.8 H 6.73 N 17.3 Found C 57.0 H 6.76 N 17.1.

1-(4-Dimethylaminophenyl)-N^1-(phenylmethyl)-1,2-ethanediamine dihydrochloride (**4e**)

M.p. 157-158°C. - ^{1}H-NMR (+ D_2O): 7.20, 6.77 (4H, "q", J = 8.6 Hz, ArH), 7.31 (5H, s, Ph), 3.72 (1H, br t, CH), 3.51 (2H, m, $PhCH_2$), 2.98 (2H, m, CH_2), 2.89 (6H, s, NMe_2). - MS(EI) m/z: 270 (MH^+), 253 (M^+ - NH_2), 239 (M^+ - CH_2NH_2), 163 (M^+ - $PhCH_2NH$), 106 ($PhCH_2NH_2^+$), 91 ($C_7H_7^+$).

1-(2-Furanyl)-N^1-(phenylmethyl)-1,2-ethanediamine dihydrochloride (**4f**)

M.p 192-194°C. - ^{1}H-NMR: 7.87 (1H, br s, ArH), 7.40 (5H, br s, Ph), 6.92 (1H, d, J = 3.2 Hz, ArH), 6.63 (1H, dd, ArH), 4.87 (1H, m, CH), 3.91 (2H, m, Ph-CH_2), 2.95 (3H, br, NH, NH_2). - MS(EI) m/z: 217 (MH^+), 200 (M^+ - NH_2), 186 (M^+ - CH_2NH_2), 149 (M^+ - furanyl). - $C_{13}H_{16}N_2O \cdot 2$ HCl (289) Calcd. C 54.0 H 6.27 N 9.7 Cl 24.5 Found C 53.9 H 6.36 N 9.3 Cl 24.9.

1-(4-Methoxylphenyl)-N^1-(phenylmethyl)-1,2-ethanediamine dihydrochloride (**4h**)

^{1}H-NMR ($CDCl_3$): 7.86-6.65 (9H, m, ArH), 3.77 (3H, s, OMe), 3.59 (1H, dd, J = 7.2, 5.6 Hz, CH), 2.84 (2H, s, $PhCH_2$), 2.76 (2H, br d, CH_2), 1.42 (3H, br s, NH, NH_2).

N-(2-Naphthalenyl)methyl-benzenemethanamine (**5c**)

^{1}H-NMR (+ D_2O: 8.05-7.50 (12H, m, ArH), 4.36 (2H, s, $ArCH_2$), 4.24 (2H, s, $PhCH_2$). - MS(EI) m/z: 247 (M^+), 156 (M^+ - $PhCH_2$), 141 (M^+ - $PhCH_2NH$), 106 ($PhCH_2NH_2^+$), 91 ($C_7H_7^+$).

N-(2,3-Dimethoxyphenyl)methyl-benzenemethanamine (**5d**)

^{1}H-NMR: 7.64-7.06 (8H, m, ArH), 4.12 (2H, s, $PhCH_2$), 4.03 (2H, s, CH_2), 3.81 (s, 3H, OMe), 3.68 (3H, s, OMe). - MS(EI) m/z: 258 (MH^+), 166 (M^+ - $PhCH_2$), 151 (M^+ - $PhCH_2NH$), 106 ($PhCH_2NH_2^+$), 91 ($C_7H_7^+$). - $C_{16}H_{19}NO_2 \cdot HCl \cdot H_2O$ (311.5) Calc. C 61.63 H 7.11 Found C 61.83 H 7.10.

1-Aryl-N'-(arylmethyl)-N-(2-methylethyl)-1,2-ethanediamines **6**

PtO_2 (*Adam's* catalyst) (0.5 g) was activated by pressurizing to 40 lb/in^2, with H_2 in EtOH (10 ml), for 20 min. The desired compound **4** (up to 15 mmol) as free amine, dissolved in absol. EtOH (20 ml), was then added followed by AcOH (2 ml) and acetone (1 ml). The mixture, in a *Parr* apparatus at 40 lb/in^2, was stirred at room temp. until not further decrease in hydrogen pressure was detected (1-3 h). The catalyst was removed and the filtrate was evaporated to dryness. The residue was redissolved in ether and precipitated as the hydrochloride with methanolic HCl.

1-(2-Chlorophenyl)-N^2-(1-methyl)ethyl-N^1-(phenylmethyl)-1,2-ethanediamine dihydrochloride (**6a**)

M.p. 215-216°C. - ^{1}H-NMR (+ D_2O): 7.88-7.49 (3H, m, ArH), 7.44 (5H, s, Ph), 5.20 (1H, m, PhCH), 3.90-3.33 (5H, m, CH_2's and $\underline{CH}Me_2$), 1.28 (6H, d, J = 6.5 Hz, $CH\underline{Me}_2$). - MS(EI) m/z: 305/303 (MH^+), 198/196 (M^+ - $PhCH_2NH$), 246/244 (M^+ - Me_2CHNH), 232/230 (M^+ - $Me_2CHNHCH_2$), 106 ($PhCH_2NH_2^+$), 91 ($C_7H_7^+$). - $C_{18}H_{23}ClN_2$ (302.5) Calc. C 57.5 H 6.65 Found C 57.4 H 6.79.

1-(4-Methylphenyl)-N^2-(1-methyl)ethyl-N^1-(phenylmethyl)-1,2-ethanediamine dihydrochloride (**6b**)

M.p. 214-216°C. - ^{1}H-NMR (+ D_2O): 7.47 (4H, AB "quartet", J = 8 Hz, ArH), 7.43 (5H, s, Ph), 4.73 (1H, m, PhCH), 4.02-3.21 (5H, m, CH_2's and $\underline{CH}Me_2$), 2.34 (s, 3H, $\underline{Me}Ar$), 1.26 (6H, d, J = 6.5 Hz, $CH\underline{Me}_2$). - MS(EI) m/z: 273 (MH^+), 224 (M^+ - Me_2CHNH), 210 (M^+ - $Me_2CHNHCH_2$), 176 (M^+ - $PhCH_2NH$). - $C_{19}H_{16}N_2 \cdot 2HCl$ (345) Calc. C 64.2 H 7.94 N 7.9 Cl 19.9 Found C 64.1 H 7.87 N 7.6 Cl 19.7.

1-(2-Naphthalenyl)-N^2-(1-methyl)ethyl-N^1-(phenylmethyl)-1,2-ethanediamine dihydrochloride (**6c**)

^{1}H-NMR: 8.25-7.32 (12H, m, ArH + exchangeable NH), 5.04 (1H, br band, ArCH), 4.21-3.37 (5H, m, CH_2's + $C\underline{H}Me_2$), 1.30 (6H, d, J = 6.3 Hz, $CH\underline{Me}_2$. - MS(EI) m/z: 319 (MH^+), 246 (M^+ - Me_2CHNH), 212 (M^+ - $PhCH_2NH$). - $C_{22}H_{26}N_2 \cdot HCl$ (354.5) Calc. C 66.0 H 7.30 Found C 65.7 H 7.42.

1-(2,3-Dimethoxyphenyl)-N^2-(1-methyl)ethyl-N^1-(phenylmethyl)-1,2-ethanediamine dihydrochloride (**6d**)

^{1}H-NMR (+ D_2O): 7.44-7.26 (8H, m, ArH), 4.81 (1H, m, PhC<u>H</u>), 3.78 (3H, s, OMe), 3.86 (3H, s, OMe), 4.00 (5H, m, CH_2's and C<u>H</u>Me_2), 1.27 (6H, d, J = 6.5 Hz, CH<u>Me</u>$_2$). - MS(EI) m/z: 329 (MH^+), 270 (M^+ - Me_2CHNH), 256 (M^+ - $Me_2CHNHCH_2$), 222 (M^+ - $PhCH_2NH$), 106 ($PhCH_2NH_2^+$). - $C_{20}H_{28}N_2O_2 \cdot 2$ HCl (401) Calc. C 59.8 H 7.53 N 7.0 Cl 17.7 MeO 15.5 Found C 59.8 H 7.67 N 6.9 Cl 17.2 MeO 15.2.

1-(4-Dimethylaminophenyl)-N^2-(1-methyl)ethyl-N^1-(phenylmethyl)-1,2-ethanediamine trihydrochloride (**6e**)

M.p. 177-178°C. - ^{1}H-NMR (+ D_2O): 7.86-7.34 (9H, m, ArH), 4.87 (1H, m, PhCH), 3.58 (5H, m, CH_2's + C<u>H</u>Me_2), 3.15 (6H, s, NMe_2), 1.27 (6H, d, J = 6.0 Hz, CH<u>Me</u>$_2$). - MS(EI) m/z: 312 (MH^+), 253 (M^+ - Me_2CHNH), 239 (M^+ - $Me_2CHNHCH_2$), 205 (M^+ - Me_2CHNH). - $C_{20}H_{29}N_3 \cdot 3$ HCl (420.5) Calc. C 57.1 H 7.66 N 10.0 Found C 57.1 H 7.69 N 10.2.

1-(2-Furanyl)-N^2-(1-methyl)ethyl-N^1-(phenylmethyl)-1,2-ethanediamine dihydrochloride (**6f**)

M.p. 161-162°C. - ^{1}H-NMR: 7.46 (1H, br s, ArH), 7.42 (5H, br s, Ph + exchangeable NH), 6.90 (1H, d, Ar), 5.04 (1H, m, PhCH), 3.81 (5H, m, CH_2's and C<u>H</u>Me_2), 1.28 (6H, d, J = 6.4 Hz, CH<u>Me</u>$_2$). - MS(EI) m/z: 259 (MH^+), 191 (M^+ - furanyl), 189 (M^+ - $Me_2CHNHCH_2$), 152 (M^+ - $PhCH_2CH$). - $C_{16}H_{22}N_2O \cdot 2$ HCl (331) Calc. C 58.0 H 7.30 N 8.5 Cl 21.4 Found C 58.2 H 7.31 N 8.2 Cl 21.0.

1-(4-Methoxyphenyl)-1-N^2-(1-methyl)ethyl-N^1-(phenylmethyl)-1,2-ethanediamine dihydrochloride (**6h**)

M.p. 128-132°C. - ^{1}H-NMR: 7.40 (4H , AB "quartet", J = 8.6 Hz, ArH), 7.42 (5H, s, Ph), 4.86 (1H, m, PhCH); 3.81 (3H, s, OMe), 4.36-3.18 (5H, m, CH_2's + C<u>H</u>Me_2).

1-Aryl-N^2-(1-methyl)ethyl-ethanediamines **1**

Method I: (**6** → **1**): The hydrogenolytic removal of the N-benzylic group from the hydrochlorides of compounds **6** (5 mmol) was carried out during ca. 6 h, in MeOH in a *Parr* hydrogenator at 40 lb/in^2, at room temp. over 10% Pd/C (0.5 g). The products were obtained upon filtration of the catalyst and evaporation of the solvent, and were recrystallized from MeOH/ether mixtures. **6a** also underwent hydrogenolysis of the *o*-chloro atom to give a 1:1 mixture of **1a-I** and the corresponding dechlorinated product, which were separated by prep. TLC on silica gel with EtOAc-MeOH (2:3).

Method II: (**2** → **7** → **10** → **11** → **12** → **13** → **1**): To a cooled (10-15°C) solution of conc. NH_4OH (80 ml), was added glacial AcOH (13 ml). The mixture was allowed to reach room temp. followed by sequential portion wise addition of NaCN (4.37 g, 90 mmol) and a suitable aldehyde **2** (75 mmol), and was stirred at 35°C until no more aldehyde could be detected by tlc (ca. 4 h). The mixture was then diluted with 150 ml of H_2O and was extracted with CH_2Cl_2. The org. phase was extracted with 20% HCl and the aqueous solution was refluxed for 18 h. Evaporation of the solvent gave the amino acids **10** (ca. 65% yield). The BOC-derivatives **11** were prepared according to known procedures[19] and the amides **12** were obtained by *Spencer's* method[20]. Removal of the BOC groups was carried out with trifluoroacetic acid (TFA) at 20-60°C. The free amino amides **13** were obtained upon evaporation of the excess TFA, dissolving the residues in EtOAc, and neutralizing the TFA salt solutions thus obtained with saturated aqueous Na_2CO_3. Drying and evaporation of the EtOAc solutions gave **13**. The reduction of the amido group of **13** was carried out with diborane-THF[21] or with $LiAlH_4$[16] to give **1**. This sequence is exemplified by the series of 3,4-dichlorophenyl derivatives (10i → 11i → 12i → 13i → 1i).

Method III: (2 → 7 → 8 → 9 → 1): An acetic anhydride:acetic acid solution of an amino-arylacetonitrile **7**, prepared as described in *Method II*, was stirred at room temp. for ca. 12 h. The solvent was evaporated and the residue was recrystallized from acetonitrile to give the respective α-acetoamide-arylacetonitrile **8**. Reductive condensation of **8** (10 mmol) with acetone (2 ml) was carried out in the course of ca. 12 h, in MeOH:AcOH (2:1) (30 ml) in a *Parr* hydrogenator at 40 lb/in^2, at room temp. over PtO_2 (0.35 g), untill three equivalents of hydrogen were consumed. The products were obtained upon filtration, evaporation, addition of gaseous HCl and recrystallization from MeOH/ether mixtures.

1-(2-Chlorophenyl)-N^2-(1-methyl)ethyl-ethanediamine dihydrochloride (**1a-I**)

^{1}H-NMR (+ D_2O): 7.85-7.45 (4H, m, Ar), 5.13 (1H, dd, J = 8.8, 5.5 Hz, ArCH), 3.46 (3H, m, CH_2 + Me_2C<u>H</u>), 1.31 (6H, d, J = 6.5 Hz, <u>Me</u>$_2$CH).

1-(4-Methylphenyl)-N^2-(1-methyl)ethyl-ethanediamine dihydrochloride (**1b-I**)

M.p. 216-220°C. - ^{1}H-NMR (+ D_2O): 7.40 (4H, AB "quartet", J = 8 Hz ArH), 4.75 (1H, m, ArCH), 3.47 (3H, m, CH_2 + Me_2C<u>H</u>), 2.34 (3H, s, <u>Me</u>Ar), 1.28 (6H, d, J = 6.4 Hz, <u>Me</u>$_2$CH). - MS(CI) m/z: 193 (M^+), 177 (M^+ - Me), 176 (M^+ - NH_2), 134 (M^+ - Me_2CHNH), 120 (M^+ - $Me_2CHNHCH_2$). - $C_{12}H_{20}N_2 \cdot 2$ HCl (265) Calc. C 54.3 H 8.36 N 10.6 Found C 54.3 H 58.3 N 10.4.

1-(2,3-Dimethoxyphenyl)-N^2-(1-methyl)ethyl-ethanediamine dihydrochloride (**1d-I**)

M.p. 166-167°C. - ^{1}H-NMR (+ D_2O, + TFA): 7.20 (3H, br s, ArH), 4.96 (H, m, ArC<u>H</u>), 3.94 (3H, s, MeO), 3.88 (3H, s, MeO), 3.41 (3H, m, CH_2 + Me_2C<u>H</u>), 1.32 (6H, d, J = 6.5 Hz, <u>Me</u>$_2$CH). - MS(CI) m/z: 239 (MH^+), 222 (M^+ - NH_2), 207 (M^+ - MeO), 180 (M^+ - Me_2CHNH), 166 (M^+ - $Me_2CHNHCH_2$). - $C_{13}H_{22}N_2O_2$ (238) Calc. C 50.2 H 7.77 Cl 22.8 Found C 50.1 H 7.79 Cl 23.2.

1-(4-Dimethylaminophenyl)-N^2-(1-methyl)ethyl-ethanediamine trihydrochloride (**1e-I**)

M.p. 184-187°C. - ^{1}H-NMR (+ D_2O): 7.60 (4H, AB "quartet", J = 8.8 Hz, ArH), 4.81 (1H, m, ArC<u>H</u>), 3.45 (1H, m, Me_2C<u>H</u>), 3.18 (2H, m, CH_2), 3.16 (6H, s, Me_2N), 1.28 (6H, d, J = 6.5 Hz, <u>Me</u>$_2$CH). - MS(CI) m/z: 222 (MH^+), 205 (M^+ - NH_2), 149 (M^+ - $Me_2CHNHCH_2$). - $C_{13}H_{23}N_3 \cdot 3$ HCl (330.5) Calc. C 46.0 H 8.01 N 12.4 Found C 46.0 H 8.02 N 12.1.

1-(2-Furyl)-N^2-(1-methyl)ethyl-ethanediamine dihydrochloride (**1f-I**)

M.p. 100-101°C. - ^{1}H-NMR (+ D_2O): 7.8 (1H, d, J = 1.7 Hz, ArH), 6.74 (1H, dd, J = 3.3, 1.7 Hz, ArH), 6.57 (1H, d, J = 3.3 Hz, ArH) 4.78 (1H, m, ArC<u>H</u>), 3.48 (2H, m, CH_2), 3.36 (1H, m, Me_2C<u>H</u>), 1.26 (6H, d, J = 6.6 Hz, <u>Me</u>$_2$CH). - MS(EI) m/z: 169 (MH^+), 152 (M^+ - NH_2), 110 (M^+ - Me_2CHNH), 96 (M^+ - $Me_2CHNHCH_2$). - $C_9H_{16}N_2O \cdot 2HCl \cdot H_2O$ (259) Calc. C 41.7 H 7.78 Found C 41.8 H 7.79.

1-(4-Hydroxyphenyl)-N^2-(1,1-dimethyl)ethyl-ethanediamine dihydrochloride (**1g-II**)

^{1}H-NMR: 8.50 (1H, br s, exchangeable NH), 7.64 (4H, AB "quartet", J = 8.6 Hz, ArH), 4.78 (1H, m, ArC<u>H</u>), 3.92 (2H, m, CH_2) 1.23 (9H, s, T-Bu).

1-(4-Hydroxyphenyl)-N^2-(1-methyl)ethyl-ethanediamine dihydrochloride (**1h-I**)

^{1}H-NMR: 9.25 (3H, br band, NH + NH_2), 7.32 (4H, AB "quartet", J = 8.5 Hz, ArH), 4.77 (1H, m, ArC<u>H</u>), 3.78 (3H, s, MeO), 3.36 (3H, m, CH_2 + Me_2C<u>H</u>), 1.27 (6H, d, J = 6.5 Hz, <u>Me</u>$_2$CH).

1-(4-Methoxyphenyl)-N²-(1,1-dimethyl)ehyl-ethanediamine dihydrochloride (**1h-II**)

^{1}H-NMR (+ D_2O: 7.27 (4H, AB "quartet", J = 8.4 Hz, ArH), 4.55 (1H, m, J = 8.8, 5.5 Hz, ArCH), 3.78 (3H, s, MeO), 3.55 (2H, m, CH_2), 1.34 (9, s, t-Bu).

α-Amino-3,4-dichloro-phenylacetic acid (**10i**)

^{1}H-NMR: 7.45-7.82 (4H, m, ArH), 7.02 (2H, br band, exchangeable NH_2), 4.95 (1H, s, CH). - MS(Cl) m/z: 224/222/220 (MH^+), 207/205/203 (M^+ - NH_2), 178/176/174 (M^+ - COOH).

3,4-Dichloro-α-[[(1,1-dimethylethoxy)carbonyl]amino]-benzeneacetic acid (**11i**)

^{1}H-NMR ($CDCl_3$): 7.76-7.06 (3H, m, Ar), 5.20 (1H, m, CH), 1.48 (9H, s, t-Bu). - MS(Cl) m/z: 324/322/320 (MH^+), 278/276/274 (M^+ - COOH), 207/205/203 (M^+ - NH-t-Boc).

3,4-Dichloro-α-[[(1,1-dimethylethoxy)carbonyl]amino]-N-(1-methyl)-ethyl-benzeneacetamide (**12i**)

M.p. 146-147°C. - ^{1}H-NMR ($CDCl_3$) 7.50-7.20 (3H, m, ArH), 5.09 (1H, d, J = 7.0 Hz, Ar-CH), 4.01 (1H, septet, $CHMe_2$), 1.42 (9H, s, t-Bu), 1.08 (6H, d, J = 6.5 Hz, $CHMe_2$). - MS(Cl) m/z: 365/363/361 (MH^+), 279/277/275 (M^+ - $CONHCHMe_2$), 248/246/244 (M^+ - NH-t-Boc). - $C_{16}H_{22}Cl_2N_2O_3$ (361) Calc. C 53.2 H 6.14 N 7.8 Cl 19.6 Found C 53.3 H 6.30 N 7.4 Cl 20.0.

α-Amino-3,4-dichloro-N-(1-methyl)ethyl-benzeneacetamide (**13i**)

^{1}H-NMR ($CDCl_3$) 7.50 (1H, d, J = 2.05 Hz, H-2), 7.42 (1H, d, J = 8.3 Hz, H-5), 7.24 (1H, dd, J = 8.3, 2.05 Hz, H-6), 4.43 (1H, s, ArCH), 4.01 (1H, septet, $CHMe_2$), 1.14 (6H, d, J = 6.7 Hz, $CHMe_2$).

1-(3,4-Dichlorophenyl)-N¹-(1-methyl)ethyl-1,2-ethylenediamine dihydrochloride (**1i**)

^{1}H-NMR (+ D_2O): 7.79 (1H, s, H-2), 7.53 (2H, m, H-5, H-6), 4.83 (H, dd, ArCH), 3.52 (septet, partially overlapping the HOD peak, $CHMe_2$), 1.26 (6H, d, J = 6.6 Hz, Me_2CH). - MS(Cl) m/z: 251/249/247 (MH^+), 234/232/230 (M^+ - NH_2), 192/190/188 (M^+ - $NHCHMe_2$), 178/176/174 (M^+ - CH_2N-iPr). - $C_{11}H_{16}Cl_2N_2$ · 2HCl · 0.5 H_2O (301) Calc. C 40.1 H 5.82 Found C 40.2 H 6.04.

α-Acetamido-2-chloro-benzeneacetonitrile (**8a**)

M.p. 144-145.5°C. - ^{1}H-NMR: 9.19 (1H, d, J = 7.4 Hz, exchangeable NH), 7.70-7.41 (4H, m, ArH), 6.20 (1H, d, J = 7.4 Hz, CH), 1.93 (3H, s, Me). - MS(EI) m/z: 211/209 (M^+), 184/182 (M^+ - CN), 173 (M^+ - Cl), 152/150 (M^+ - NHAc). - $C_{10}H_8ClNO_2$ (209.5) Calc. C 57.3 H 3.85 Found C 57.4 H 4.08.

N-[1-(2-Chlorophenyl)-2-(1-methyl)ethylamino]ethyl-acetamide hydrochloride **9a**

M.p. 219-220°C. - ^{1}H-NMR: 7.56-7.35 (4H, m, ArH), 5.43 (1H, m, CH), 3.49-3.14 (3H, m, CH_2NHCH), 1.19 (3H, s, Ac), 1.29 (6H, d, J = 6.4 Hz, Me). - MS(EI) m/z: 257/255 ($M^{+\cdot}$), 198/196 (M^+ - $NHCHMe_2$, - NHAc), 191 (M^+ - Cl). $C_{13}H_{19}ClN_2O$ · HCl (287) Calc. C 53.6 H 6.92 Found C 53.4 H 6.97.

References

1 A. Nudelman and R.J. McCaully, Eur. J. Med. Chem. *16*, 333 (1981).
2 a) G. Kunos, Ed., "Adrenoceptors and Catecholamine Action", pp. 3-10, Wiley-Interscience, Montreal 1981.
b) M.E. Wolf, Ed., "Burger's Medicinal Chemistry", 4th edition, pp. 245-266, Wiley-Interscience, N.Y. 1981.
3 T. Jen, S.S. Frazee, M.S. Schwartz, K.F. Erhard, and C. Kaiser, J. Med. Chem. *10*, 1263 (1977).
4 S. Rachlin and J. Enemark, J. Med. Chem. *12*, 1089 (1969).
5 J.G. Henkel, N. Sikand, A. Makriyannis, and G. Gianutsos, J. Med. Chem. *24*, 1258 (1981).
6 R.A. Heacock, G. Hutzinger, and B.D. Scott, Can. J. Chem. *43*, 2437 (1965).
7 B.F. Tullar, J. Am. Chem. Soc. *70*, 2067 (1948).
8 a) R. Duschinsky, L.A. Dolan, L.O. Randall, and G. Lehmann, J. Am. Chem. Soc. *69*, 3150 (1947).
b) G. Lehmann and L.O. Randall, J. Pharmacol. Exp. Ther. *93*, 114 (1948).
9 R. Howe, J. Med. Chem. *13*, 398 (1970).
10 K. Takahashi, M. Murakami, K. Murase, T. Mase, and A. Ida, Japan Kokai 78 02, 432 11 Jan. 1978, Appl. 24 June 1976; C.A. *89*, 129246b (1978).
11 W.L. Matier, D.A. Owens, W.T. Comer, D. Deitchman, H.C. Ferguson, R.J. Seidehamel, and J.R. Young, J. Med. Chem. *16*, 901 (1973).
12 M.E. Hancock and A.C. Cope, in "Organic Syntheses", Coll. Vol. III, p. 501, 1955.
13 R. Baltzly and J.S. Buck, J. Am. Chem. Soc. *65*, 1984 (1943).
14 H.O. House, "Modern Synthetic Reactions", 2nd. ed., p. 14, W.A. Benjamin, Inc., London 1972.
15 M. Rabinovitz, in "The Chemistry of Functional Groups. The Chemistry of the Cyano Group", p. 323, S. Patai, Ed., John Wiley & Sons, London 1970.
16 a) C.F. Lane, in "Synthetic Reagents", Vol. 3, pp. 68-72, J.S. Pizey, Ed., Ellis Horwood Ltd., Chichester 1977.
b) H.C. Brown und P. Heim, J. Org. Chem. *38*, 912 (1973).
17 a) A.G. Gilman, Proc. Natl. Acad. Sci. USA, *67*, 305 (1970).
b) K.A. Jacobson, D. Marr-Leisy, R.P. Rosenkranz, M.S. Verlander, K.L. Melmon, and M. Goodman, J. Med. Chem. *26*, 492 (1983).
18 R.J. Lefkowitz, L.E. Limbird, C. Nukherj, and M.G. Caron, Biochem. Biophys. Acta *11*, 457 (1976).
19 A. Nudelman, A. Patchornick, R.C. Erickson, E. Karoly-Hafely, and F. Brown, J. Antibiotics *33*, 76 (1980).
20 J.L. Spencer, E.H. Flynn, R.W. Roeske, F.Y. Siu, and R.R. Chauvette, J. Med. Chem. *9*, 746 (1966).
21 K. Wiesner, Z. Valenta, D.E. Orr, V. Liede, and G. Kohan, Can. J. Chem. *46*, 3617 (1968).
22 C.C. Beard, M.B. Wallach, and K. Weinhardt, U.S. Patent 4, 110, 463 (1978); C.A. *90*, 87463h (1979).

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