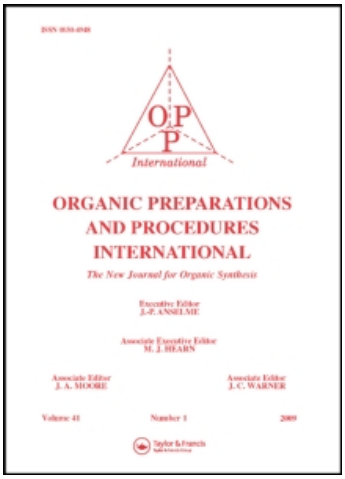


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# *o*-AMINOMETHYL DERIVATIVES OF PHENOLS. PART 1. BENZYLAMINES: PROPERTIES, STRUCTURE, SYNTHESIS AND PURIFICATION

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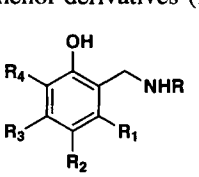
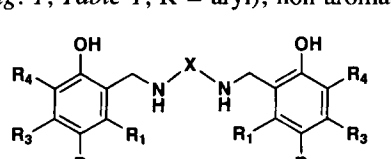
## INTRODUCTION

The subject of our literature review regards *o*-aminomethyl derivatives of phenols - their properties and applications, structure and stability, synthesis and purification. *Part 1* of this review will deal with substances possessing the benzylamine structure as the core; those bearing benzoxazines and dibenzylamines will be surveyed in a second review.[1] These benzylamines are compounds with many interesting properties and of wide and increasing potential applications. They have been used as: a) complexing agents[2-16] and metal ion extractants[3,4] b) catalysts or components of catalysts[5-7,14-17] c) intermediates in organic synthesis[18-20] d) biologically active compounds.[21-26] Thus, the possibility of obtaining them from inexpensive and easily accessible raw materials adds to the interest in further research.

For the purpose of this review, benzylamines have been divided into six categories: aromatic amine phenol derivatives (**1**) (*Fig. 1*, *Table 1*, R = aryl), non-aromatic amine phenol




**1** and **2**



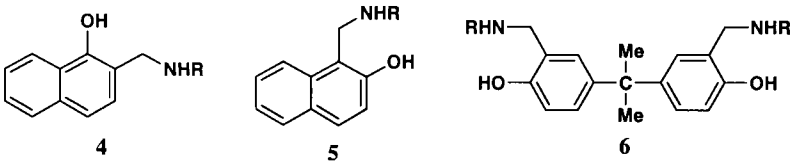

**3**

**1:** R = Aryl; $R_1$ = H, Me; $R_2$ = H, Me, *t*-Bu, $CO_2H$, $CO_2R_5$, $NO_2$, OH, OMe, OBn, Cl, Br; $R_3$ = H, Me, $NO_2$, OMe, Br; $R_4$ = H, Me, *i*-Pr, *t*-Bu, $NO_2$, I.

**2:** R = $C_1$-$C_{18}$ alkyl, Bn, allyl, substituted or unsubstituted cyclohexyl; $R_1$ = H, Me, Cl, Br; $R_2$ = H, Me, *t*-Bu, $C(Me)_2Et$, $CH(CH_2i\text{-}Pr)_2$, allyl, COPh, NHCOMe, $NO_2$, OH, OMe, OBn, Cl, Br; $R_3$ = H, Me, $NO_2$, Br; $R_4$ = H, Me, *i*-Pr, *t*-Bu, $C_8H_{17}$, Ph, vinyl, $NO_2$, OMe, Cl, Br, I.

**3:** X = $C_2$-$C_6$ branched or not aliphatic chain, $C_2$ part of the aromatic or cyclohexyl ring; $R_1$ = H; $R_2$ = H, Me, *t*-Bu, $C_8F_{17}$, Cl; $R_3$ = H, Me; $R_4$ = H, Me, *t*-Bu, $C_8F_{17}$.

**Fig. 1**




4 5 6

**4:** R = Alkyl, Bn. **5:** R = Aryl, alkyl or substituted alkyl. **6:** R = Alkyl or substituted alkyl.

**Fig. 1** (cont'd)

derivatives (**2**) (*Fig. 1*, *Table 2*, R = non-aryl), diamine phenol derivatives (tetrahydrosalens) (**3**) (*Fig. 1*, *Table 3*), 1-naphthol derivatives (**4**) (*Fig. 1*, *Table 4*), 2-naphthol derivatives (**5**) (*Fig. 1*, *Table 5*), bisphenol A derivatives (**6**) (*Fig. 1*, *Table 6*). In spite of the considerable practical importance of these benzylamines, reports on methods of their preparation are rather scarce. Many references are old or not readily accessible. Some reports are contained in patents, brief information in Chemical Abstracts or only notes in experimental sections. The present review evaluates available information on the properties, applications, structure, stability and preparation of these benzylamines up to the year 2005.



## I. PROPERTIES AND APPLICATIONS

One of the most important features of benzylamines **1-3** is their ability to form complexes with metal ions. A relatively small number of such complexes has been isolated, due to the fact that the nitrogen atom has greater coordination ability than the oxygen atom and mostly mixtures of polynuclear complexes with metal-nitrogen bonds are formed.[2] Beretka *et al.* were the first to investigate the complexing ability of benzylamines **1** in 1964.[3] They observed that the compounds selectively bound copper ions and they did not form complexes with nickel, cobalt, zink or manganese even at high pH. Crystalline complexes of $Cu(L)CH_3COO$ structure (L = benzylamine ligand) were isolated.[3] Butvin *et al.* investigated the extraction of some metal ions from their aqueous solutions with benzylamines **2**. They observed low extraction efficiency for Co(II), Zn(II) and Pb(II) and neither Cd(II), Ni(II) nor Mn(II) ions were transferred into the organic phase over the pH range (3-8.5) studied. Cu(II) ions were quantitatively extracted at pH > 5.4. Benzylamines **2** were stable under experimental conditions and the efficiency of extraction strongly depended on their hydrophobicity.[4] Complexes of benzylamines **1** and **2** with ferrous ions have been used as catalysts for the regioselective oxidation of aliphatic[5] and aromatic[6] compounds resulting in the formation of primary alcohols. The complexes were generated *in situ* using a water/acetonitrile at a pH ~ 6 buffer. Some complexing benzylamines **2** have been described as active corrosion inhibitors for steel protection[27] and as light-sensitive materials in photography.[28]

Benzylamines **3**, known also as salans or tetrahydrosalens, are used as ligands in olefin polymerization catalysts.[7] They exhibit higher basicity and greater structural flexibility then salens (their dehydrogenated analogs).[10,29-32] Benzylamines **3** contain four active centers, two hydroxy and two amino, that can form covalent or coordinate bonds with more than one metal

ion to create polymeric structures.[13] Complexes of benzylamines **3** with transition metal ions such as Ti, V and Mn,[8] Cr,[9] Zn, Ni,[31,32] Cu,[10,31] Mo[11] and main groups metals such as Sn,[8,32] Pb[12] and Al[13] have been described. Complexes of optically active benzylamines **3** were used as catalysts in the asymmetric hydrophosphonylation of carbonyl compounds,[14] alkylation of aromatic aldehydes[15] or in the enantioselective epoxidation of alkenes.[16] It was observed that even optically inactive benzylamines **3** can form complexes that contain stereogenic centers and can be applied as catalysts in diastereoselective synthesis.[16] Complexing properties of benzylamines **4-6** were not described.

Compounds of type **1** and of type **2** have been used as intermediates in the synthesis of biologically active compounds,[18] *e. g.* of respective tertiary amines.[19] In the reaction of benzylamines **3** with ketones, a new class of complexing agents containing a 1,3-diamino five-membered ring was synthetized.[20] Optically active benzylamines **2** have been applied as catalysts in asymmetric synthesis.[33] Both benzylamines **1** and **2** are components of specific phenol resins.[34,35]

Some benzylamines **1** exhibit high biological activity against strains of *Staphylococcus Aureus* and *Escherichia Coli* and in most cases, it is higher than that of analogous tertiary benzylamines.[21] Other compounds have shown to be EGF receptor inhibitors.[25] Antimalarial,[36] antitussive[37] and antiinflammantory[38] activity of benzylamines **2** were also described. Penicillin salts of benzylamines **3** showed local anesthetic activity.[22] Benzylamines **2** and **5** revealed strong cytostatic activity[23] and benzylamines **6** possess laxative[24] action. Benzylamines **1-6** can form stable and crystalline hydrochlorides, a property which is often useful in their isolation and purification.



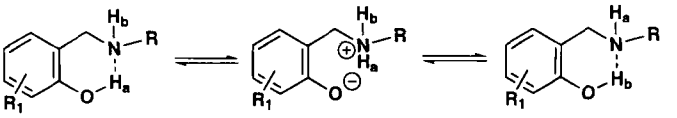
## II. STRUCTURE AND STABILITY

The benzylamines of this review contain a phenolic hydroxy and a secondary amino groups. Although the oxygen and nitrogen atoms are separated by four bonds, IR analysis has shown that the amine nitrogen and phenol hydrogen of benzylamines **1** form intramolecular hydrogen bonds (*Scheme 1*) that changes the nitrogen atom hybridization.[39] In case of some


**Scheme 1**

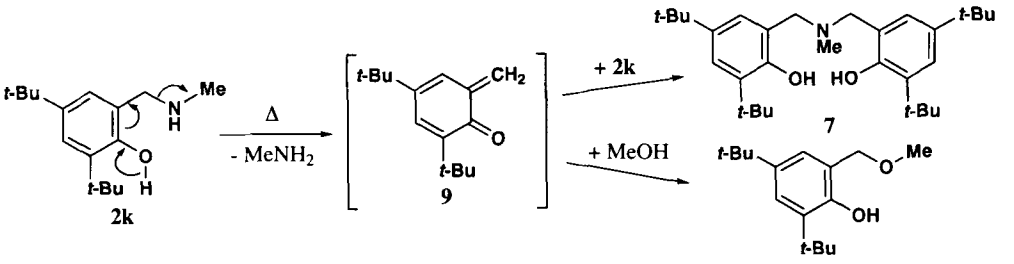
benzylamines **1**, the presence of the resulting six-membered ring makes the benzylic hydrogens magnetically different in $^1$H NMR spectra. Intramolecular hydrogen exchange between phenolic hydrogen and the amine nitrogen via an internal salt intermediate in benzylamines **1** has also been observed (*Scheme 2*).[40]

Benzylamines **2** exhibit limited thermal stability.[41-43] This feature can seriously affect the effectiveness of their preparation, purification and use in various applications. Heating **2k** (*Scheme 3*, *Fig. 1*, *Table 2*) at approximately 100°C (for 48 h) resulted in its transformation to



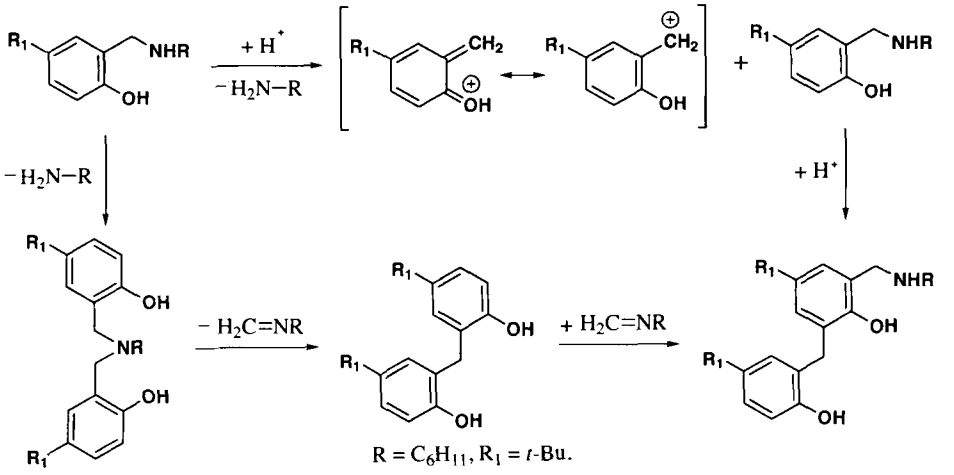
Scheme 2

compound **7** (12% yield). In methanol at reflux, the etherification of the **2k** methylene group took place and compound **8** was formed. Sparfel *et al.* proposed the mechanism for the observed



Scheme 3

transformations, *via* the quinone methide intermediate **9**.[41] According to Burke *et al.*[42], at temperatures above 165°C benzylamines **2** undergo polymerization with the liberation of primary aliphatic amine. A proposed mechanism for this is given in *Scheme 4*.



$R = C_6H_{11}$, $R_1$ = *t*-Bu.

Scheme 4

The thermolysis of benzylamines **1** and **2** was carried out by Vinogradova *et al.*[43] at 200-245°C for 5 min. The authors suggest formation of quinone methide intermediate in this process and observed liberation of the amine. No other thermolysis products were identified. In addition, complexes of benzylamines **3** with metal ions in the presence of oxygen undergo dehydrogenation. The process is stepwise and in case of Ni[44] and Cu,[10,13] the products of dehydrogenation of only one C–N bond were isolated.

**Table 1**. Structure, Preparation and Properties of Benzylamines **1**

| Cmpd | R | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| **1a** | Ph | H | H | H | H | 66 | **D** | 95 | 50 |
| | | | | | | ---- | **E** | 106[54] | 3,5,6 |
| | | | | | | | | 116[56] | 54,56,63 |
| | | | | | | | | 114-115[63] | |
| | | | | | | 83[43] | **F** | 112[43] | 43,64 |
| | | | | | | 54[65] | | 110-111[65] | 65 |
| | | | | | | 30 | **G** | 108 | 88 |
| | | | | | | ---- | ---- | ---- | 26[j] |
| **1b** | Ph | H | H | Me | H | 66 | **E** | 116 | 62 |
| **1c** | Ph | H | H | $NO_2$ | H | ---- | **F** | ---- | 66 |
| | | | | | | ---- | ---- | ---- | 26[j] |
| **1d** | Ph | H | H | OMe | H | ---- | **F** | ---- | 66 |
| | | | | | | ---- | ---- | ---- | 26[j] |
| **1e** | Ph | H | Me | H | H | ---- | **E** | 101 | 61 |
| | | | | | | 65 | **G**[n] | 95-96 | 88 |
| **1f** | Ph | H | *t*-Bu | H | H | 70 | **G** | 82-83 | 88 |
| **1g** | Ph | H | $CO_2H$ | H | H | ---- | **A**[b] | ---- | 48 |
| **1h** | Ph | H | $CO_2Me$ | H | H | 93 | **A**[b] | 99 | 48 |
| **1i** | Ph | H | $CO_2Et$ | H | H | ---- | **A**[b] | ---- | 48 |
| **1j** | Ph | H | $CO_2Pr$ | H | H | ---- | **A**[b] | ---- | 48 |
| **1k** | Ph | H | $CO_2Bu$ | H | H | ---- | **A**[b] | ---- | 48 |
| **1l** | Ph | H | $CO_2Bn$ | H | H | ---- | **A**[b] | ---- | 48 |
| **1m** | Ph | H | OMe | H | H | 77 | **F** | 82-84 | 65 |
| **1n** | Ph | H | OBn | H | H | 71 | **G**[n] | 90-91 | 88 |
| **1o** | Ph | H | Cl | H | H | 81 | **F** | 114-118 | 64 |
| **1p** | Ph | H | Br | H | H | 36 | **G**[a] | 109-110 | 88 |
| **1q** | Ph | H | Me | H | Me | 67 | **C**[d] | 87 | 34 |
| **1r** | Ph | H | $NO_2$ | H | $NO_2$ | 98 | **A**[b] | 92 | 49[k,m] |
| **1s** | $R_5$ | H | H | H | H | 93 | **F** | 118-120 | 43 |
| | | | | | | ---- | **E** | 116[54] | 3,54 |
| | | | | | | | | 122[63] | 63 |
| | | | | | | ---- | ---- | ---- | 26[j] |
| **1t** | $R_5$ | H | H | H | Me | 60 | **C**[e] | 96 | 34 |
| **1u** | $R_5$ | H | Me | H | H | ---- | **C**[e] | 106 | 35 |
| **1v** | $R_5$ | H | *t*-Bu | H | H | 50 | **C**[g] | 85 | 34 |
| **1w** | $R_5$ | H | Me | H | Me | ---- | **C**[f] | 92 | 35 |
| | | | | | | 63 | **C**[e] | 98 | 34 |
| **1x** | $R_5$ | Me | H | H | Me | 61 | **C**[e] | 143 | 34 |
| **1y** | $R_5$ | Me | H | H | *i*-Pr | ---- | **C**[e] | 106 | 35 |

**Table 1**. Continued...

| Cmpd | R | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| **1z** | $R_5$ | Me | H | Me | H | 61 | **C**[e] | 125 | 34 |
| **1aa** | $R_5$ | Me | Br | H | Me | ---- | **C**[e] | 137 | 35 |
| **1ab** | $R_5$ | Me | Br | H | *i*-Pr | ---- | **C**[e] | 110 | 35 |
| **1ac** | $R_5$ | H | H | H | H | ---- | **E** | 115[63] | 3,63 |
| | | | | | | ---- | **F** | 112-113[39] | 39[l],66 |
| | | | | | | ---- | ---- | ---- | 26[j] |
| **1ad** | $R_6$ | H | H | H | H | ---- | **E** | 175.5[h,63] | 3,63 |
| **1ae** | $R_6$ | H | *t*-Bu | H | H | 50 | **F** | 91-94 | 77 |
| | | | | | | 42 | **G** | 62-80 | 77 |
| | | | | | | 82 | **H** | 93-94 | 77 |
| **1af** | $R_6$ | H | *t*-Bu | H | *t*-Bu | 94 | **G** | 149-151 | 40 |
| **1ag** | $R_7$ | H | H | H | H | 53[71] | **F** | 116[71] | 66,70, 71[j-m] |
| **1ah** | $R_8$ | H | H | H | H | 91 | **F** | 170 | 71[j-m] |
| **1ai** | $R_9$ | H | H | H | H | 90 | **F** | 125-127 | 43 |
| **1aj** | $R_{10}$ | H | H | H | H | ---- | ---- | ---- | 26[j] |
| **1ak** | $R_{10}$ | H | OH | H | H | ---- | **E** | 174-176 | 25 |
| **1al** | $R_{11}$ | H | OH | H | H | ---- | **E** | 132-133 | 25 |
| **1am** | $R_{12}$ | H | OMe | H | H | 63 | **F** | 126-129 | 65 |
| **1an** | $R_{13}$ | H | *t*-Bu | H | I | ---- | **F** | 134-136 | 65 |
| **1ao** | $R_{14}$ | H | H | H | H | ---- | **F** | ---- | 66 |
| | | | | | | ---- | ---- | ---- | 26[j] |
| **1ap** | $R_{15}$ | H | H | H | H | ---- | **A**[c] | 125 | 45 |
| | | | | | | 88[78] | **F** | 136-137[78] | 66,78 |
| **1aq** | $R_{15}$ | H | Me | H | $NO_2$ | 95 | **A**[b] | 160 | 49[k,m] |
| **1ar** | $R_{15}$ | H | $NO_2$ | H | $NO_2$ | 97 | **A**[b] | 203 | 49[k,m] |
| **1as** | $R_{15}$ | H | Br | H | $NO_2$ | 98 | **A**[b] | 162 | 49[k,m] |
| **1at** | $R_{16}$ | H | H | H | H | 99[71] | **F** | 133-134[71] | 66,70, 71[j,k,l,m] |
| | | | | | | ---- | ---- | ---- | 26[j] |
| **1au** | 4-ClPh | H | H | H | H | ---- | **E** | 121[63] | 3,63 |
| | | | | | | ---- | **F** | ---- | 64 |
| **1av** | 3-ClPh | H | H | H | H | ---- | **E** | ---- | 3 |
| | | | | | | ---- | **F** | 109 | 39[l] |
| **1aw** | 2-ClPh | H | H | H | H | ---- | **E** | ---- | 3 |
| | | | | | | ---- | **F** | 55-57 | 64 |
| **1ax** | $R_{17}$ | H | H | H | H | 92 | **F** | 121 | 71[j-m] |
| **1ay** | $R_{17}$ | H | H | Br | H | ---- | **F** | ---- | 66 |
| | | | | | | ---- | ---- | ---- | 26[j] |
| **1az** | 4-IPh | H | H | H | H | 98[71] | **F** | 130[71] | 70,71[j-m] |

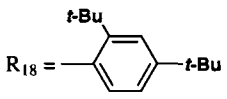
**Table 1**. Continued...

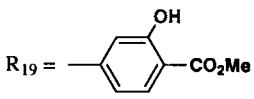
| Cmpd | R | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| **1ba** | $R_{18}$ | H | *t*-Bu | H | *t*-Bu | 26 | **H** | 146-150 | 77 |
| **1bb** | $R_{19}$ | H | OH | H | H | ---- | **E** | 189-190 | 25 |
| **1bc** | $R_{20}$ | H | H | H | H | ---- | **E** | 155-156 | 25 |
| **1bd** | $R_{20}$ | H | OH | H | H | ---- | **E** | 245[i] | 25 |
| **1be** | $R_{21}$ | H | H | H | H | 65 | **E** | 145-147 | 25[m] |
| **1bf** | $R_{21}$ | H | OH | H | H | ---- | **E** | 194-195 | 25 |
| **1bg** | $R_{22}$ | H | OH | H | H | ---- | **E** | 141-142 | 25 |
| **1bh** | $R_{23}$ | H | *t*-Bu | H | *t*-Bu | 100 | **E** | ---- | 55 |
| **1bi** | $R_{24}$ | H | H | H | H | ---- | **E** | 147 | 54 |
| | | | | | | 92 | **F** | 145-147 | 43 |

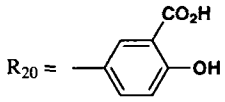
$R_5$ = **4-MePh** $R_6$ = **2-MePh** $R_7$ = **4-CNPh** $R_8$ = **4-C(NH$_2$)=N(Boc)Ph**

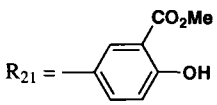
$R_9$ = **4-C(O)MePh** $R_{10}$ = **3-CO$_2$HPh** $R_{11}$ = **3-CO$_2$MePh** $R_{12}$ = **4-NHC$_2$H$_4$CMe$_3$Ph**

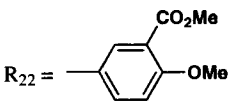
$R_{13}$ = **4-NHC(O)MePh** $R_{14}$ = **4-NEt$_2$Ph** $R_{15}$ = **4-NO$_2$Ph** $R_{16}$ = **4-OMePh** $R_{17}$ = **4-BrPh**

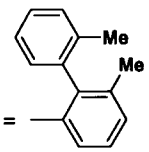


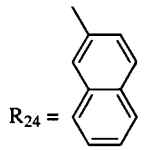



a) In text; b) From benzyl chloride; c) From benzyl alcohol; d) From benzylamine salt; e) From dibenzylamine; f) From imine; g) From tribenzylamine; h) Hydrochloride; i) Decomposition; j) $^{13}$C NMR data; k) MS data; l) IR data; m) $^1$H NMR data, n) In petroleum

**Table 2**. Structure, Preparation and Properties of Benzylamines **2**

| Cmpd | R | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| **2a** | Me | H | H | H | H | 95 | **B** | ---- | 18 |
| | | | | | | ---- | **E** | 58 | 56 |
| | | | | | | ---- | **E**[b] | | 67[e] |
| | | | | | | 100 | **E**[c] | | 73 |
| | | | | | | 67[f] | **H** | 144-145[d] | 83 |
| | | | | | | 76 | | 45-47 | |
| | | | | | | 37 | **I** | 146-147[d] | 87 |
| **2b** | Me | H | H | H | OMe | 97 | **F** | 92-94 | 68[e] |
| **2c** | Me | H | H | $NO_2$ | H | 25 | **F** | 243[d,g] | 67[e] |
| **2d** | Me | H | H | Cl | H | ---- | **F** | ---- | 67 |
| **2e** | Me | H | $NO_2$ | H | H | ---- | **F** | ---- | 67 |
| **2f** | Me | H | OH | H | H | 100 | **F**[c] | ---- | 73 |

**Table 2**. Continued...

| Cmpd | R | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| **2g** | Me | H | Cl | H | H | 36 | **F**[b] | 191[d,g] | 67[e] |
| **2h** | Me | H | Br | H | H | ---- | **F**[b] | ---- | 67 |
| **2i** | Me | H | Me | H | Me | 98 | **F**[v] | 27-28 | 76 |
| **2j** | Me | H | Me | H | *t*-Bu | 96 | **F**[v] | 97 | 76 |
| **2k** | Me | H | *t*-Bu | H | *t*-Bu | 65 | **G** | 68-69 | 41[e,l,y] |
| **2l** | Me | H | Cl | H | Cl | 61 | **G** | 191-192 | 80 |
| | | | | | | 52[f] | | 199-200[d] | 87 |
| **2m** | Me | H | Br | H | Br | 73 | **G** | 194-195 | 80 |
| **2n** | Me | H | OH | Me | H | 74 | **H** | 198-200[d] | 28[e] |
| **2o** | Me | Me | Cl | H | *i*-Pr | 40 | **H** | 172-174[d] | 101 |
| **2p** | Et | H | H | H | H | 95 | **B** | ---- | 18 |
| | | | | | | ~90 | **E** | ---- | 57 |
| **2q** | Et | H | $NO_2$ | H | H | ~90 | **E** | ---- | 57 |
| **2r** | Et | H | Cl | H | H | ~90 | **E** | ---- | 57 |
| **2s** | Et | H | Br | H | H | ~90 | **E** | ---- | 57 |
| **2t** | Et | H | OH | Me | H | 51 | **H** | 171-172[d] | 28[e] |
| **2u** | Et | Me | Me | H | H | ---- | ---- | oil | 104 |
| **2v** | *n*-Pr | H | H | H | H | 95 | **B** | ---- | 18 |
| | | | | | | ~90 | **E** | ---- | 57 |
| **2w** | *n*-Pr | H | Cl | H | H | ~90 | **E** | ---- | 57 |
| **2x** | *n*-Pr | H | OH | Me | H | 52 | **H** | 168-170[d] | 28[e] |
| **2y** | *n*-Bu | H | H | H | H | >85 | **E** | ---- | 4,5,6 |
| | | | | | | 95 | **F**[h,i] | ---- | 75 |
| | | | | | | ---- | **G** | oil | 21 |
| **2z** | *n*-Bu | H | Me | H | Me | ---- | **G** | ---- | 84[j] |
| **2aa** | *n*-Bu | H | OH | Me | H | 49 | **H** | 167-168[d] | 28[e] |
| **2ab** | $C_5H_{11}$ | H | H | H | H | ---- | **G** | oil | 21 |
| **2ac** | $C_6H_{13}$ | H | H | H | H | ---- | **D** | ---- | 53 |
| | | | | | | ---- | **G** | oil | 21 |
| **2ad** | $C_7H_{15}$ | H | H | H | H | ---- | **G** | oil | 21 |
| **2ae** | $C_8H_{17}$ | H | H | H | H | ---- | **E** | ---- | 4,5,6 |
| | | | | | | ---- | **G** | oil[21] | 17,21 |
| **2af** | $C_{10}H_{21}$ | H | H | H | H | ---- | **G** | oil | 21 |
| **2ag** | $C_{11}H_{23}$ | H | H | H | H | ---- | **G** | 35-36 | 21 |
| **2ah** | $C_{12}H_{25}$ | H | H | H | H | ---- | **E** | ---- | 4,5,6 |
| | | | | | | ---- | **G** | 47 | 21 |
| **2ai** | $C_{15}H_{31}$ | H | H | H | H | ---- | **G** | 58 | 21 |
| **2aj** | $C_{16}H_{33}$ | H | H | H | H | ---- | **G** | 60-61 | 21 |

**Table 2.** Continued...

| Cmpd | R | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| **2ak** | $C_{18}H_{37}$ | H | H | H | H | ---- | **E** | ---- | 6 |
| | | | | | | ---- | **G** | 67-68 | 21 |
| **2al** | –*n*-PrOH | H | $R_5$ | H | OMe | 54 | **G** | 90 | 90[e] |
| **2am** | –*n*-PrOMe | H | $R_5$ | H | OMe | 25 | **G** | 60 | 90[e] |
| **2an** | –*n*-PrOEt | H | $R_5$ | H | OMe | 21 | **G** | 40 | 90[e] |
| **2ao** | $-C_2H_4Ph$ | H | H | H | OMe | ---- | **E** | 138[k] | 60 |
| **2ap** | $-C_2H_4Ph$ | H | NHAc | H | H | ---- | **H** | 148-149 | 23 |
| **2aq** | $-C_2H_4Ph$ | H | OMe | H | H | ---- | **H** | 79-81, 122-123[d] | 23 |
| **2ar** | $R_6$ | H | H | H | OMe | ---- | **E** | 148-149[k] | 60 |
| **2as** | $R_7$ | H | H | H | OMe | ---- | **E** | 136-137[k] | 60 |
| **2at** | $-C_2H_4OH$ | H | H | H | H | 94 | **F** | 152-154[d] | 72[e,j,l,m] |
| | | | | | | 96[f] | **H** | 151-152[d,g] | 83 |
| | | | | | | 74 | | 64-65 | |
| **2au** | $-C_2H_4OH$ | H | H | H | Ph | 26 | **G** | 116 | 85 |
| | | | | | | 38 | | | |
| **2av** | $-C_2H_4OH$ | H | *t*-Bu | H | H | 43 | **G** | 127-128 | 85 |
| **2aw** | $-C_2H_4OH$ | H | $R_8$ | H | H | ---- | **G** | 114 | 85 |
| **2ax** | $-C_2H_4OH$ | H | COPh | H | H | ---- | **G** | 188-189 | 85 |
| **2ay** | $-C_2H_4OH$ | H | $NO_2$ | H | H | ---- | **G** | 195-196 | 85 |
| **2az** | $-C_2H_4OH$ | H | Me | H | $NO_2$ | ---- | **G** | 205-206 | 85 |
| **2ba** | $-C_2H_4OH$ | H | $R_5$ | H | OMe | 49 | **G** | 97 | 90[e] |
| **2bb** | $-C_2H_4OH$ | H | Cl | H | Ph | ---- | **G** | 182-183[d] | 85 |
| **2bc** | $-C_2H_4OH$ | H | Cl | H | Cl | 30 | **G** | 199-200 | 85 |
| **2bd** | $-C_2H_4OMe$ | H | $R_5$ | H | OMe | 28 | **G** | 62 | 90[e] |
| **2be** | $-C_2H_4OEt$ | H | $R_5$ | H | OMe | 21 | **G** | 54 | 90[e] |
| **2bf** | $R_5$ | H | H | H | H | ~90 | **E** | ---- | 57 |
| **2bg** | $R_5$ | H | Cl | H | H | ~90 | **E** | ---- | 57 |
| **2bh** | $R_5$ | H | Br | H | H | ~90 | **E** | ---- | 57 |
| **2bi** | $R_9$ | H | $NO_2$ | H | H | 29 | **A**[s] | 247[d,g] | 47 |
| **2bj** | $R_9$ | H | Cl | H | H | ~90 | **E** | ---- | 57 |
| **2bk** | $R_9$ | H | Br | H | H | ~90 | **E** | ---- | 57 |
| **2bl** | $R_{10}$ | H | $R_5$ | H | OMe | 51 | **G** | 113 | 90[e] |
| **2bm** | $R_{11}$ | H | $R_5$ | H | OMe | 21 | **G** | 86 | 90[e] |
| **2bn** | Bn | H | H | H | H | 95 | **B** | ---- | 18 |
| | | | | | | ---- | **E** | ---- | 5,6 |
| | | | | | | 91 | **F** | 190-193 | 43 |
| | | | | | | ---- | **F** | ---- | 66 |
| | | | | | | 90 | **F**[h,i] | ---- | 75 |

**Table 2.** Continued...

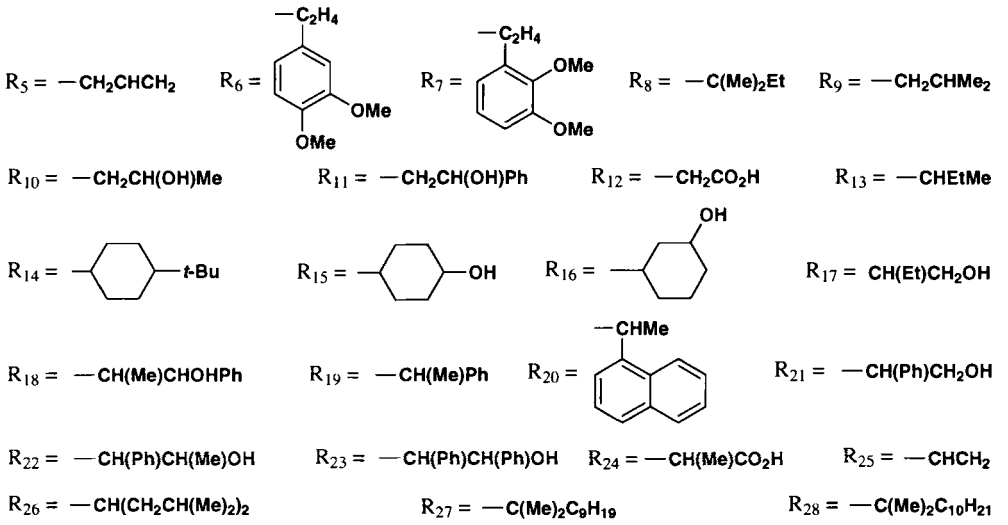
| Cmpd | R | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| **2bo** | Bn | H | OH | H | H | 40 | **H**[n] | 165-166[d] | 28 |
| | | | | | | 75 | **H** | 176-177[d] | 86[e] |
| | | | | | | | | 120-121 | |
| **2bp** | Bn | H | OBn | H | H | 90 | **H** | 90-91 | 86 |
| | | | | | | | | 170-171[d] | |
| **2bq** | Bn | H | OH | Me | H | 71 | **H**[n] | 207-209[d] | 28[e] |
| **2br** | Bn | H | Cl | H | Cl | 72 | **G** | 112-113 | 80 |
| **2bs** | Bn | H | Br | H | Br | ---- | **A**[t] | 129-130 | 46 |
| **2bt** | Bn | Br | Br | Br | Br | ---- | **A**[t] | 170-171 | 46 |
| **2bu** | $R_{12}$ | H | OMe | H | H | ---- | **H** | 223-224 | 23 |
| **2bv** | $R_{12}$ | H | Me | H | Me | ---- | **G** | ---- | 84[j] |
| **2bw** | *i*-Pr | H | H | H | H | 90[57] | **E** | 52[56] | 56,57 |
| | | | | | | ---- | ---- | ---- | 26[j] |
| **2bx** | *i*-Pr | H | $NO_2$ | H | H | 38 | **A**[s] | 238[d,g] | 47 |
| | | | | | | ~90 | **E** | ---- | 57 |
| **2by** | *i*-Pr | H | OH | H | H | 77 | **G** | 160-162 | 86 |
| **2bz** | *i*-Pr | H | Cl | H | H | ~90 | **E** | ---- | 57 |
| **2ca** | *i*-Pr | H | Br | H | H | ~90 | **E** | ---- | 57 |
| **2cb** | *i*-Pr | H | Cl | H | Cl | ~90 | **E** | ---- | 57 |
| **2cc** | *i*-Pr | H | Br | H | Br | ~90 | **E** | ---- | 57 |
| **2cd** | *i*-Pr | H | OH | Me | H | 59 | **H**[n] | 178-180[d] | 28[e] |
| **2ce** | *i*-Pr | Me | H | Me | H | ---- | ---- | ---- | 26[j] |
| **2cf** | *i*-Pr | Me | H | H | Me | ---- | **F** | ---- | 66 |
| **2cg** | $R_{13}$ | H | OH | H | H | 2 | **G** | 115-116 | 86 |
| **2ch** | $C_6H_{11}$ | H | H | H | H | 28 | **G** | 58-60 | 83 |
| | | | | | | | | 209-210[d] | |
| | | | | | | 83, 99[f] | **H** | 58-59 | 83 |
| | | | | | | | | 209-210[d,g] | |
| | | | | | | 96 | **H**[p] | 57-59 | 83 |
| | | | | | | 100 | **I** | 58-60 | 83 |
| **2ci** | $C_6H_{11}$ | H | NHAc | H | H | ---- | **H** | 163-164 | 23 |
| | | | | | | | | 156-157[d] | |
| **2cj** | $C_6H_{11}$ | H | OH | H | H | 88 | **G** | 172-173 | 86 |
| **2ck** | $C_6H_{11}$ | H | OBn | H | H | 81 | **H** | 203-205[d] | 86 |
| **2cl** | $C_6H_{11}$ | H | Br | H | H | 53 | **G** | 87-88 | 83 |
| **2cm** | $C_6H_{11}$ | H | Me | H | Me | 36[81] | **G** | ---- | 81,84[j] |
| | | | | | | 68 | **H**[n] | 51 | 81 |
| | | | | | | 96[f] | | 214-215[d] | |

**Table 2.** Continued...

| Cmpd | R | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| **2cn** | $C_6H_{11}$ | H | *t*-Bu | H | Me | 97 | **E**[u] | 230[d] | 42 |
| | | | | | | 86[f] | **G**[q] | 69-70 | 42 |
| | | | | | | | | 230[d] | |
| **2co** | $C_6H_{11}$ | H | Cl | H | Cl | 67 | **H** | 157-158 | 80 |
| | | | | | | 74[f] | | 237-238[d] | |
| **2cp** | $C_6H_{11}$ | H | Br | H | Br | 90 | **G** | 168-169 | 80 |
| **2cq** | $R_{14}$ | H | Br | H | Br | ---- | **A**[t] | 188-191 | 38 |
| **2cr** | $R_{15}$ | H | H | H | Br | ---- | **C**[w] | 194-194 | 37 |
| **2cs** | $R_{15}$ | H | Br | H | Br | ---- | **A**[t] | 212-218[d] | 38 |
| | | | | | | ---- | **C**[w] | 212-218[d] | 37 |
| **2ct** | $R_{16}$ | H | Br | H | Br | ---- | **A**[t] | 128-136[d] | 38 |
| **2cu** | $R_{17}$ | H | $R_5$ | H | OMe | 59 | **G** | 73 | 90[e] |
| **2cv** | $R_{18}$ | H | H | H | H | 71 | **F** | 50-52[d] | 72[e,j,l,m] |
| **2cw** | $R_{19}$ | H | H | H | H | 100 | **E** | 141-142[o] | 33[e,j,l,m] |
| **2cx** | $R_{19}$ | H | NHAc | H | H | ---- | **H** | 145-146 | 23 |
| | | | | | | | | 133-135[d] | |
| **2cy** | $R_{19}$ | H | OH | H | H | 33 | **G** | 153-153.5 | 86 |
| **2cz** | $R_{20}$ | H | H | H | H | 100 | **E** | 172-173[o] | 33[e,j,l,m] |
| **2da** | $R_{21}$ | H | H | H | H | 77 | **F** | 83-85[d] | 72[e,j,l,m] |
| **2db** | $R_{22}$ | H | H | H | H | 64 | **F** | 164-166[d] | 72[e,j,l,m] |
| **2dc** | $R_{23}$ | H | H | H | H | 93 | **F** | 188-190[d] | 72[e,j,l,m] |
| **2dd** | $R_{24}$ | H | H | H | H | ---- | **F** | ---- | 66 |
| | | | | | | ---- | ---- | ---- | 26[j] |
| **2de** | $R_{24}$ | H | Me | H | Me | ---- | **G** | ---- | 84[j] |
| **2df** | $R_{24}$ | Me | H | H | Me | ---- | **F** | ---- | 66 |
| **2dg** | $R_{24}$ | Me | H | Me | H | ---- | ---- | ---- | 26[j] |
| **2dh** | *t*-Bu | H | H | H | H | ---- | **E** | 35 | 56 |
| | | | | | | 95 | **F** | ---- | 43 |
| | | | | | | 15 | ----[x] | ---- | 103 |
| **2di** | *t*-Bu | H | *t*-Bu | H | H | 98 | **G**[r] | 58-61 | 98 |
| **2dj** | *t*-Bu | H | NHAc | H | H | ---- | **G** | ---- | 36[e,l,m] |
| **2dk** | *t*-Bu | H | $NO_2$ | H | H | 20 | **A**[s] | 275[d,g] | 47 |
| **2dl** | *t*-Bu | H | OH | H | H | 61 | **I** | 213-214[d] | 86 |
| **2dm** | *t*-Bu | H | OBn | H | H | 77,65 | **H** | 70-71 | 86 |
| | | | | | | | | 233-234[d] | |
| **2dn** | *t*-Bu | H | Br | H | H | 70 | **D** | ---- | 51 |
| **2do** | *t*-Bu | Cl | Cl | H | Cl | 50 | **G**[r] | 179[g] | 98 |
| | | | | | | 84 | | 180-181[g] | |
| **2dp** | *t*-Oc | H | H | H | H | 97 | **G**[r] | oil | 98 |
| **2dq** | *t*-Oc | H | H | H | $R_{25}$ | 92 | **G**[r] | oil | 98 |

**Table 2**. Continued...

| Cmpd | R | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| **2dr** | *t*-Oc | H | H | H | Ph | ---- | **G**[r] | ---- | 98 |
| **2ds** | *t*-Oc | H | $R_{26}$ | H | H | ---- | **G**[r] | 50-54 | 98 |
| **2dt** | *t*-Oc | H | *t*-Bu | H | H | ---- | **G**[r] | ---- | 98 |
| **2du** | *t*-Oc | H | OH | H | H | 67, 35[f] | **G** | 125-126 | 86 |
| | | | | | | | | 242-244[d] | |
| **2dv** | *t*-Oc | H | *t*-Bu | H | Br | ---- | **G**[r] | 74-79 | 98 |
| **2dw** | *t*-Oc | H | Br | H | Br | 86 | **G**[r] | 148-149 | 98 |
| **2dx** | $R_{27}$ | H | H | H | $R_{28}$ | 97 | **G**[r] | oil | 98 |
| **2dy** | $R_{29}$ | H | $NO_2$ | H | Cl | ---- | **G**[r] | ---- | 98 |



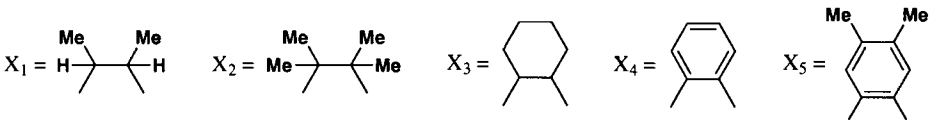

a) In text; b) $NaBH_4$ as reducing agent; c) $H_2$/Pd/C as reducing system; d) Hydrochloride; e) $^1H$ NMR data; f) As hydrochloride; g) Decomposition; h) *In situ* reduction of the imine; i) $B_{10}H_{14}$ as reducing agent; j) $^{13}C$ NMR data; k) As picrate; l) IR data; m) MS data; n) From benzoxazine hydrochloride; o) *N,O*-dibenzoyl derivative; p) From 4-Br derivative; q) Isobutanol as solvent; r) Imine as reagent; s) Benzyl chloride as reagent; t) Benzyl bromide as reagent; u) $LiAlH_4$ as reducing agent; v) $H_2$/Pd/$BaSO_4$ as reducing system; w) From 2-hydroxyamine salt; x) Isolated as by-product; y) MS spectra.

**Table 3**. Structure, Preparation and Properties of Benzylamines **3**

| Cmpd | X | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| **3a** | $-C_2H_4-$ | H | H | H | H | ---- | **E**[h] | ---- | 8[b] |
| | | | | | | ---- | **E** | ---- | 12 |
| | | | | | | 62[l] | **E**[f] | 121-123 | 22 |
| | | | | | | | | 206-207[g] | |
| | | | | | | ---- | **E** | 126 | 63 |

**Table 3**. Continued...

| Cmpd | X | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 98 | **F** | 117 | 16[b-e] |
| | | | | | | 87 | **G**[l] | 118 | 20,[b] 96 |
| | | | | | | ---- | ---- | ---- | 32 |
| **3b** | $-C_2H_4-$ | H | H | H | Me | 71 | **G**[l] | 129 | 20,[b] 96 |
| **3c** | $-C_2H_4-$ | H | H | H | *t*-Bu | ---- | **E** | ---- | 44 |
| **3d** | $-C_2H_4-$ | H | H | Me | H | 83 | **G**[l] | 151 | 20,[b] 96 |
| **3e** | $-C_2H_4-$ | H | Me | H | H | 89 | **G**[l] | 140 | 20,[b] 96 |
| **3f** | $-C_2H_4-$ | H | Cl | H | H | 90 | **G**[l] | 146 | 20,[b] 89[b,c] |
| | | | | | | ---- | ----[m] | 138 | |
| **3g** | $-C_2H_4-$ | H | Me | H | Me | ---- | **G** | ---- | 91 |
| **3h** | $-C_2H_4-$ | H | Me | H | *t*-Bu | 55 | **E**[i] | 137 | 44[b,d,e] |
| | | | | | | ---- | **E** | ---- | 44 |
| | | | | | | ---- | ---- | ---- | 10 |
| **3i** | $-C_2H_4-$ | H | *t*-Bu | H | *t*-Bu | 70 | **E**[i] | 187 | 9[b,d] |
| | | | | | | ---- | **E** | ---- | 13 |
| | | | | | | 91 | **F** | 174 | 16[b-e] |
| | | | | | | 90[7] | **G** | ---- | 7,[b] 91,92 |
| **3j** | $-C_2H_4-$ | H | Cl | H | *t*-Bu | ---- | **E** | ---- | 44 |
| **3k** | $-C_3H_6-$ | H | H | H | H | 80 | **F** | 108 | 69 |
| | | | | | | ---- | ---- | ---- | 32 |
| **3m** | $-C_3H_6-$ | H | *t*-Bu | H | *t*-Bu | 87 | **G** | ---- | 7[b] |
| **3n** | $-C_4H_8-$ | H | H | H | H | ---- | **E** | ---- | 58 |
| | | | | | | ---- | ---- | ---- | 32 |
| **3o** | $-C_6H_{12}-$ | H | H | H | H | ---- | ---- | ---- | 32 |
| **3p** | $X_1$ | H | Me | H | *t*-Bu | ---- | **E** | 123 | 10[b,d] |
| **3q** | $X_2$ | H | Me | H | *t*-Bu | ---- | **E** | ---- | 10 |
| | | | | | | 55 | **E**[i] | 234 | 31[b,d] |
| **3r** | $X_2$ | H | Cl | H | *t*-Bu | ~55 | **E**[i] | 223 | 31[b,d] |
| **3s** | $X_3$ | H | H | H | H | ---- | ---- | ---- | 14 |
| **3t** | $X_3$ | H | *t*-Bu | H | *t*-Bu | 100 | **F** | 140 | 16[b-e] |
| | | | | | | 90 | **G** | ---- | 7[b] |
| | | | | | | ---- | ---- | ---- | 14,15 |
| **3u** | $X_3$ | H | $C_8F_{17}$ | H | $C_8F_{17}$ | 15 | **E** | ---- | 59[b,j] |
| **3v** | $X_4$ | H | H | H | H | 75 | **E** | ---- | 11[c,d] |
| | | | | | | ---- | ---- | ---- | 32 |
| **3w** | $X_4$ | H | Me | H | *t*-Bu | ---- | **E** | 133 | 10[b,d] |
| **3x** | $X_5$ | H | H | H | H | ---- | **E** | ---- | 29 |
| | | | | | | ---- | ---- | ---- | 32 |




a) In text; b) $^1H$ NMR data; c) $^{13}C$ NMR data; d) IR data; e) MS data; f) $H_2/Pd/BaSO_4$ as reducing system; g) Hydrochloride; h) $NaBH_4$ as reducing agent; i) $NaBH_3(CN)$ as reducing agent; j) $^{19}F$ NMR data; k) Transformation of the hydrochloride to amine with 60% yield; l) Two stage process; m) Isolated as by-product.

**Table 4.** Structure, Preparation and Properties of Benzylamines **4**

| Cmpd | R | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|
| **4a** | Bn | 72 | **G** | 155-211[e,i] | 93[f-h] |
| | | 69 | **G**[b,d] | 155-211[e,i] | 93[f-h] |
| **4b** | *i*-Pr | 72 | **G**[b,d] | 149[e] | 93[f-h] |
| **4c** | *t*-Bu | 21 | **G**[b,c] | 155[e] | 93 |
| | | 72 | **G**[b,d] | 165[e] | 93[f-h] |
| **4d** |  | 79 | **G**[j] | 180[e,i] | 93[f-h] |

a) In text; b) Triazine as reagent; c) EtOH as solvent; d) $CH_2Cl_2$ as solvent; e) Hydrochloride; f) $^1H$ NMR data; g) IR data; h) MS data; i) Decomposition; j) Imine as reagent.

**Table 5.** Structure, Preparation and Properties of Benzylamines **5**

| Cmpd | R | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|
| **5a** | Me | 94 | **H** | 202-204[b,c] | 102 |
| **5b** | *n*-Bu | 60 | **H** | 143-145 | 102 |
| **5c** | Bn | 86 | **H** | 170-172[b] | 102 |
| **5d** | $CH_2CO_2H$ | ---- | **H** | 232-234 | 23 |
| **5e** | $C_6H_{11}$ | 93 | **H** | 192-193[b,c] | 102 |
| **5f** | CH(Me)Ph | ---- | **H** | 158-160[b] | 23 |
| **5g** | *t*-Oc | ---- | **G**[d] | 81-84 | 98 |
| **5h** | 4-MePh | 34 | **H** | 134-135 | 82 |
| **5i** | 4-BrPh | 56 | **G** | 132-133 | 82 |

a) In test; b) Hydrochloride; c) Decomposition; d) Imine as substrate.

**Table 6.** Structure, Preparation and Properties of Benzylamines **6**

| Cmpd | R | Yield (%) | Method[a] | mp. (°C) | Ref. |
|---|---|---|---|---|---|
| **6a** | *n*-Bu | 80 | **G** | 70-72[b,c] | 24 |
| **6b** |  | 85 | **G** | oil | 24 |
| **6c** | $C_6H_{11}$ | 88 | **G** | 67-70[b,c] | 24 |
| **6d** | *t*-Oc | ---- | **G**[d] | 92-100 | 98 |

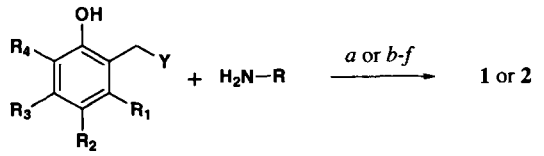
a) In text; b) Hydrochloride; c) Decomposition; d) Imine as substrate

## III. METHODS OF SYNTHESIS

Nine methods for the synthesis of benzylamines **1-6** are reviewed (*Tables 1-6*).

### *1. N-Benzylation of Primary Amines with 2-Hydroxybenzyl Alcohols or Halides (Method A)*

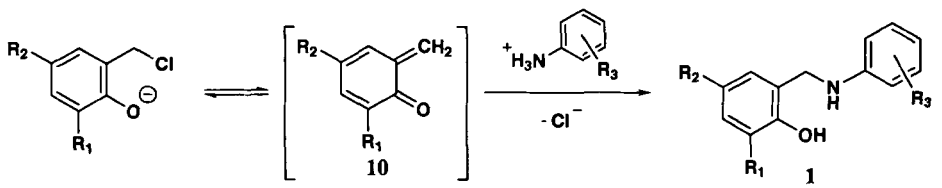
The method has been known since 1899, when Paal and Härtel obtained aromatic benzylamine **1ap** (*Table 1*) by fusion of 2-hydroxybenzyl alcohol with 1.5 eq. of 2-nitroaniline. The reaction was carried out without solvent at 140-150°C for one hour. The crystalline product was obtained after dilution of the mixture with aqueous NaOH and subsequent neutralization with carbonic acid.[45] Auwers and Schröter[46] modified the method by applying 2-hydroxybenzyl bromide instead of the corresponding alcohol and introduction of benzene to the reaction system. Since 1948, benzyl bromides have been replaced by benzyl chlorides.[47,48] The syntheses were carried out in ethanol[38,47] or DMSO,[49] with the best yields achieved in DMSO or without any solvent (*Scheme 5, Fig. 1, Table 1-2*).




*a*) Y = OH, no solvent, 140-150°C, 1 h (**1ap**).[45] *b*) Y = Br, Ph, rt (**2bs, 2bt**).[46] *c*) Y = Br, EtOH, reflux, 3 h (**2cq, 2cs, 2ct**).[38] *d*) Y = Cl, EtOH, reflux, 3 h (20-38%) (**2bi, 2bx, 2dk**).[47] *e*) Y = Cl, no solvent, 95°C, 20 min. (99%) (**1g-1l**).[48] *f*) Y = Cl, $(Me)_2SO$, rt, 1 h-1 week (95-98%) (**1r, 1aq-1as**).[49] R, $R_1$-$R_4$ - according to *Fig. 1, Table 1* and *2*

**Scheme 5**

Stein *et al.* investigated the kinetics of *N*-benzylation of aniline with 2-hydroxybenzyl chloride utilizing conductivity measurements.[49] The study was useful in explaning the reaction *via* a two-step mechanism. Slow and reversible dehydrohalogenation of 2-hydroxybenzyl chloride to the quinone methide **10**, which reacts further with the primary amine, gives benzylamines **1** (*Scheme 6, Fig. 1, Table 1*).




$R_1$-$R_3$ = Br, $NO_2$ or Me

**Scheme 6**

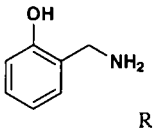
The *N*-alkylation of primary amines was often successfully applied in the synthesis of aromatic benzylamines **1** (*Fig. 1, Table 1*). Non-aromatic benzylamines **2** were rarely obtained by this method in low yields (20 to 38%) (*Fig. 1, Table 2*). Examples of the preparation of benzylamines **3-6** by this method were not identyfied.

***2-Nitro-6-(phenylaminomethyl)-p-cresol (1r). Typical Procedure.***[49] *A solution of the appro-*

*priate chloromethylated phenol (1.5 g, 7.44 mmol) in $Me_2SO$ (20 mL) was dropped at room temperature into aniline (70 g, 0.75 mol) in $Me_2SO$ (480 mL). Excess of aniline and $Me_2SO$ was removed in vacuo, and the remaining red oil was purified by column chromatography (silica gel; $CHCl_3$ as eluent) to yield the product (1.88g, 98%) as a red oil which finally solidified to form orange crystals, mp. 92.1°C*

### *2. N-Alkylation of Primary 2-Hydroxybenzylamines with Alkyl Halides (Method B)*

This method was used for the synthesis of benzylamines **2** by Bar-Haim and Kol (*Scheme 7, Fig. 1, Table 2*).[18] High yields (95%) of the desired products were achieved due to the use of 9-BBN which creates intermediate chelates with the parent benzylamine preventing formation of *N,N*-dialkyl products.




1. 9-BBN, 2. *t*-BuOK
3. X-R, 4. HCl

**2a, 2p, 2v, 2bn**

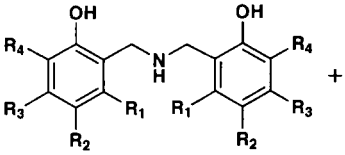
R = Me, Et, *n*-Pr, Bn; X = Cl, Br, I

**Scheme 7**

***Benzylamine 2a. Typical Procedure.***[18] *To a solution of 2-hydroxybenzylamine (1) (1.50 g, 12.2 mmol) in 50 mL THF, was added dropwise, while stirring, one equiv of 9-BBN in hexane (24.4 mL, 12.2 mmol) under nitrogen atmosphere. The reaction mixture was left to stir at RT until hydrogen evolution ceased. The solvents were removed under vacuum, and the air-sensitive white solid that had formed was washed several times with pentane, and dried under vacuum to give 1-BBN in quantitative yield. Potassium tert-butoxide (1.80 g, 16.2 mmol) in THF (25 mL) was added under nitrogen atmosphere at RT, and the reaction mixture was strirred for 10 min. Methyl iodide (2.30 g, 17 mmol) was added and an immediate precipitation of a white solid KI was observed. Filtration, removal of the solvent under reduced pressure, and pentane washings led to 1-BBN-Me as a white solid in quantitative yield. To solid 1-BBN-Me (0.50 g, 1.9 mmol) was added a 1N HCl (15 mL) and the reaction mixture was left to stir at RT until it became clear (two days). Washings with ether, addition of sodium carbonate, extractions with methylene chloride, drying over sodium sulfate, and solvent removal under vacuum gave* **2a** *as colorless oil in 95% yield.*

### *3. Fusion of Secondary Dibenzylamines or their Imine Analogs, Tribenzylamines or Salts of Benzylamines with Primary Amines (Method C)*

Few benzylamines **1** are obtained by heating of secondary dibenzylamines with *p*-toluidine or aniline. The reactions were carried out without solvent using an excess of the aromatic amine. (*Scheme 8, Fig 1, Table 1*).[34,35] The products were separated from the reaction mixtures by the

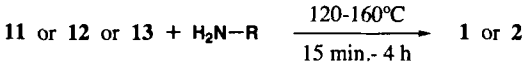



R = Ph or 4-MePh; $R_1$-$R_4$ = H, Me, *i*-Pr, *t*-Bu or Br

**Scheme 8**

steam distillation. The resulting organic portion of the distillate was triturated with methanol and the solids recrystallized from light petrol, hexane or cyclohexane (61-67%).

Benzylamines **1** or **2** (*Fig. 1, Table 1-2*) were synthesized under similar reaction conditions from imine **11**,[35] tribenzylamine **12** (yield 50%),[34] or salts of benzylamines **13** (*Scheme 9, Fig. 2*).[37] This method is of synthetic value only in the case of benzylamine salts **13** (*Fig. 2*) as




**Scheme 9**

substrate. The syntheses from **11** and **12** were conducted to investigate the structure and chemical properties of phenol-hexamethylenetetramine resins and are of rather low practical importance due to the expected difficulties in efficient preparation of the parent molecules.

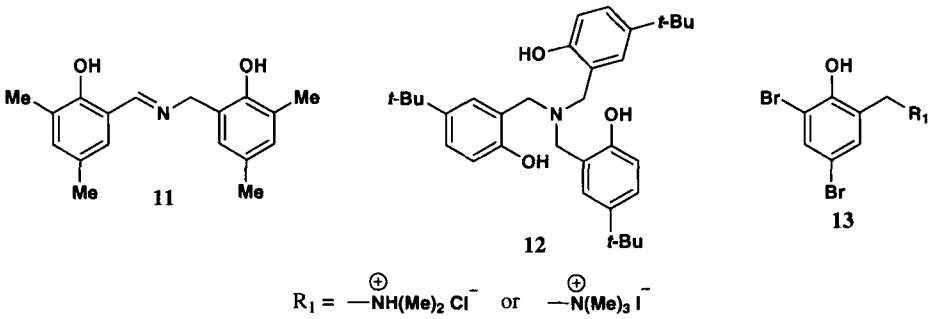
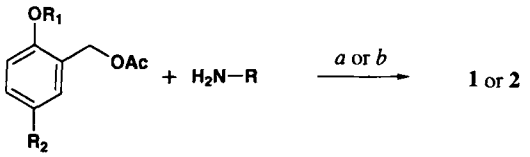



**Fig. 2**

***Benzylamine 1q. Typical Procedure.***[34] *0.5 g of the appropriate dibenzylamine and 1.0 g of aniline were heated at 160°C for 2 h. The resulting mixture was separated by steam distillation. The product was purified by trituration with methanol and subsequent crystallization from light petrol. Yield 67%, mp. 87°C.*

### *4. Reaction of Benzyl Acetates with Primary Amines (Method D)*

Loubinoux *et al.* obtained aromatic benzylamine **1a** (*Fig. 1, Table 1*) using the reaction of 2-hydroxybenzyl acetate with aniline carried out in benzene at 45°C for 6 h (*Scheme 10*). The product was purified by column chromatography (66%).[50]




*a*) R = Ph; $R_1$-$R_2$ = H, Ph, 45°C, 6 h (66%) (**1a**).[50] *b*) R = *t*-Bu; $R_1$= C(O)Me; $R_2$ = Br; *i*-PrOH, reflux, 4 h (70%) (**2dn**).[51]

**Scheme 10**

Benzylamine **2do** was obtained by Haddad *et al.* in 70% yield by treatment of *O*-acyl-benzyl acetate with *tert*-butylamine under reflux in isopropanol for 4 h (*Scheme 10*, *Fig. 1*, *Table 2*).[51] The purification procedure was not described. Both Loubinoux *et al.*[50] and Haddad *et al.*[51] suggest the formation of a quinone methide intermediate (*Fig. 3*). Similar conclusions were drawn by Lin and Sartorelli[52] and Takahashi *et al.*[53] exploring the reactivity of 2-hydroxybenzyl esters as novel precursors of quinone methide intermediates.

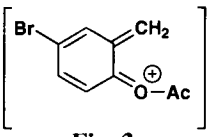
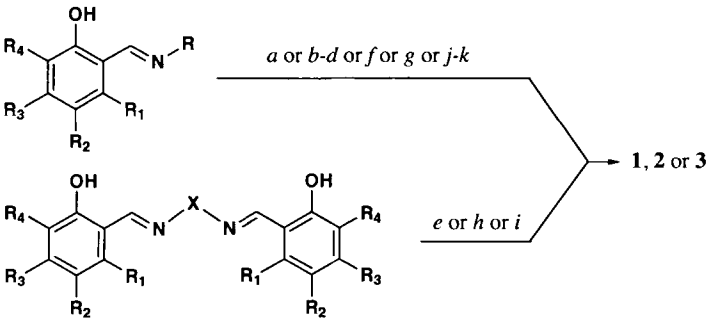



**Fig. 3**

***Benzylamine 2do. Typical Procedure.***[51] *Treatment of the appropriate benzyl acetate (Scheme 10) with* t-$BuNH_2$ *in isopropanol under reflux for 4 h provided* **2do** *in 70% yield.*

### *5. Reduction of 2-Hydroxybenzylimines (Method E)*

Reduction of 2-hydroxybenzylimines is one of the oldest and most popular methods of synthesis benzylamines **1**, **2** and **3**. In 1887, Emmerich described the reduction of 2-hydroxybenzylimines with sodium or sodium amalgam in ethanol.[54] The mixture was acidified and then basified with sodium bicarbonate. The product was separated by extraction with ether and subsequent crystallization from ethanol. Although it was claimed that better results were achieved using sodium amalgam, no yields were given (*Scheme 11*, *Fig 1*, *Table 1-3*). Since then, a variety




*a*) Na/NaHg, EtOH, reflux (**1a**, **1s**, **1bi**).[54] *b*) $LiAlH_4$, $Et_2O$, rt, 1-15 h (97-100%) (**2cn**,[42] **1a**,[56] **1bh**[55]). *c*) $NaBH_4$, MeOH, rt-reflux, 5 min.-0.5 h (75-85%) (**2y**, **2ae**, **2ah**,[4] **3v**[11]). *d*) $NaBH_4$, EtOH, rt-60°C, 1-16 h (19-100%) (**2p-s**, **2v**, **2w**, **2bc**, **2bf-k**, **2bz**, **2ca-c**,[57] **2cw**,[33] **3n**[38]). *e*) $Na[BH_3(CN)]$, $MeCO_2H$, $Cl_2FCCF_2Cl$, $N_2$, rt, 2-7 h (55-95%) (**3u**,[59] **3c**, **3h**, **3j**,[44] **3i**,[9] **3q**, **3r**[31]). *f*) $H_2$/10%Pd/C, EtOH, rt (**2ao**, **2ar**, **2as**).[60] *g*) $H_2$/10%Pd/C, MeOH, rt, 4 h (65%) (**1ak**, **1al**, **1bb-g**).[25] *h*) $H_2$/Pd/$BaSO_4$, BuOH, 80-90°C, 4-6 h (62%) (**3a**).[22] *i*) $H_2$/Pt Adam's catalyst, EtOH, rt (**1a**, **1s**, **1ac**, **1ad**, **1au-w**,[3] **1a**, **1s**, **1ac**, **1ad**, **1au**, **3a**[31]). *j*) Zn/$MeCO_2H$, reflux (**1e**).[61] *k*) hydrazine deriv., EtOH, reflux, 1.5 h (**1b**).[62]

**Scheme 11**

of different reducing agents, such as sodium or lithium aluminum hydride,[55,56] sodium borohydride,[5,11,33,57,58] sodium cyanoborohydride,[9,31,44,59] hydrogen and metal catalysts,[22,60,61] and hydrazine derivatives[62] have been used in this process. Reactions were most frequently carried

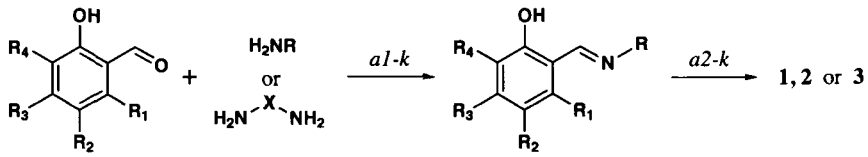
out in ethanol,[3,33,54,57,58,60,62,63] methanol[4,11,25] or diethyl ether.[42,55,56] Room temperature and reaction times of 0.5-16 h were generally used however, sometimes the mixture was refluxed for 5-90 min. The practical importance of this method strongly depends on the availability of the parent imine which can easily be synthetised by condensation of the appropriate 2-hydroxybenzaldehyde with a primary amine. It is the method of choice if the aldehyde is easy to prepare or it is a commercial product.

***N-alkyl-2-hydroxybenzylamines. General Procedure.***[57] *To a suspension of sodium boronhydride (1.9 g, 0.05 mol) in ethanol (50 mL) was added dropwise a solution of a Schiff base (0.1 mol) in 30 mL of ethanol. The temperature of the reaction mixture being maintained below 10°C. After the addition, stirring was done for 16 h at room temperature, before the reaction mixture was evaporated* in vacuo *to give a white solid. The product was dissolved in 100 mL of water, and the pH value of the aqueous solution was adjusted to 1 by the addition of 5% HCl. The solution was extracted twice with $CH_2Cl_2$ (50 mL), and the pH value of the solution was then adjusted to 9 by the addition of 5% sodium hydroxide solution. The resulting suspension was extracted twice with $CH_2Cl_2$ (100 mL). The organic layer was dried over anhydrous sodium sulfate and than evaporated* in vacuo *to give the corresponding* N*-alkyl-2-hydroxybenzylamine as a slightly yellow liquid in about a 90% yield.*



### *6. From 2-Hydroxybenzaldehydes (Method F)*

A two-stage method of synthesis of benzylamines **1-3** from 2-hydroxybenzaldehydes and the appropriate primary amine or diamine was described for the first time in 1966 by Derieg and Sternbach[64] and since then it has been widely used (*Scheme 12*, *Fig. 1*, *Table 1-3*). In the




*a1*) MeOH, rt-reflux, 5 min.-several h. *a2*) $NaBH_4$, MeOH, 5-50°C, 0.5-12 h (25-100%) (**1a**, **1m**, **1am**, **1an**,[65] **1c**, **1d**, **1ac**, **1ag**, **1ao**, **1ap**, **1at**, **1ay**, **2dd**, **2df**,[66] **2c-e**, **2g**, **2h**,[67] **2b**,[68] **3a**, **3i**, **3t**,[16] **3k**[69]). *b1*) MeOH, rt, 3 h. *b2*) $H_2$/Pd/C, MeOH, rt (77%) (**1m**).[65] *c1*) $C_6H_6$, reflux. *c2*) $NaBH_4$, EtOH, rt, several h (59-94%) (**1a**, **1o**, **1au**, **1aw**).[64] *d1*) $C_6H_6$, reflux. *d2*) $NaBH_4$, MeOH, 0-10°C (**1a**, **1s**, **1ai**, **1bi**, **2bn**, **2dh**).[43] *e1*) EtOH, reflux. *e2*) $NaBH_4$, EtOH, rt (53-100%) (**1ag**, **1at**, **1az**,[70] **1ag**, **1ah**, **1at**, **1ax**, **1az**,[71] **2f**[73]). *f1*) EtOH. *f2*) $H_2$/10%Pd/C, EtOH (**1ac**, **1av**).[39] *g1*) Montmorillonite K10 clay, microwave, 2 min.. *g2*) $NaBH_4$, Montmorillonite K10 clay, $H_2O$, 65°C, 30 s (90%) (**1ap**).[78] *h1*) no data. *h2*) $H_2$/Pd/$BaSO_4$ (96-98%) (**2i**, **2j**).[76] *i1*) THF/MeOH, reflux, 4 h. *i2*) $NaBH_4$, THF/MeOH (71-94%) (**2at**, **2cv**, **2da-c**).[72] *j1*) rt, 0,5 h. *j2*) $H_2$/5%Pt/C, EtOH, rt (50%) (**1ae**).[77] *k1= k2*) $B_{10}H_{14}$, MeOH (**2y**, **2bn**).[75] R, X, $R_1$-$R_4$ - according to *Fig.1*, *Tables 1-3*

**Scheme 12**

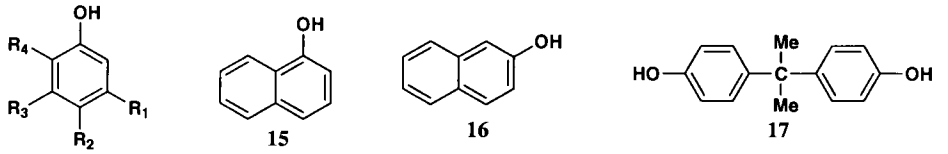
first step, the corresponding imine is prepared and then it is reduced to the desired amine. The synthesis is carried out as a "one pot" process; purification of the intermediate imine is not required. Both stages of the process are usually run in the same solvent, such as methanol,[16,65-69] ethanol[39,58,70,71] or a methanol/THF mixture.[72] In some cases, the condensation was carried out in benzene and reduction in methanol[43] or ethanol after removal of the aromatic solvent.[64] Several reducing agents such as sodium borohydride,[16,43,58,64-74] decaborane[75] or hydrogen over a metal

catalyst[39,65,76,77] were used. The condensations were usually performed under reflux or at room temperature. The subsequent reductions were commonly performed at room temperature for up to several hours. The time of the synthesis of benzylamine **1ap** was reduced to few minutes at microwave conditions on montmorillonite K10 clay.[78] Bea *et al.* performed the both steps of synthesis at the same time by mixing the appropriate 2-hydroxybenzaldehyde with amine and decaborane as the reducing agent in methanol. The synthesized benzylamines were often isolated and characterized as their hydrochloride salts.[43,67,72] Althgough this is one of the most popular methods of synthesis of benzylamines, its major drawback is the limitation of the structural diversity of the benzylamines which can be obtained. The necessity of preparation of the appropriate aldehyde makes the process much less cost-effective.

***Benzylamine 3k. Typical Procedure.***[69] *A mixture of salicylaldehyde (4.2 g, 40 mmol) and 1,3-diaminopropane (1.6 g, 20 mmol) in MeOH (100 mL) was refluxed for 1 h. The solution was cooled to room temperature and treated with small portions of an aqueous solution of* $NaBH_4$. *Stirring was continued for 1 h. The reduction was considered complete when the yellow solution became colourless. A major part of the solvent was removed on a rotary evaporator, the residue was diluted with water (250 mL), acidified with HCl (6 M) to* ca *pH 2 and kept at room temperature for 30 min. It was then treated slowly with ammonia to pH~10 and extracted with* $CHCl_3$ *(2 x 50 mL). The* $CHCl_3$ *solution was dried over* $Na_2SO_4$ *and evaporated to dryness. The white solid product was recrystallized from* $CHCl_3$*-MeOH (1:1), mp. 108°C; yield 4.69 g (80%).*

### *7. Mannich Reaction (Method G)*

In the classical Mannich-type reaction[6,79] leading to benzylamines **1-6**, phenols with at least one "active" hydrogen atom at the *ortho*-position (**14-17**) (*Fig. 4*), are reacted with formaldehyde and primary amine or diamine (*Scheme 13, Fig. 1, Table 1-6*).



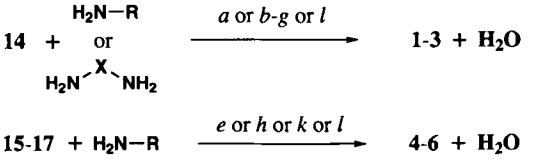

$R_1$-$R_4$ - according to *Fig. 1, Table 1-3*

**Fig. 4**

The reactions were usually carried out in water-miscible solvents such as dioxane,[80-84] methanol,[7,85,86] ethanol[84,87] or isobutanol,[42] using a saturated aqueous solution of formaldehyde (formalin).[7,42,80-83,85,86] Examples of reactions performed in water[40,77] or in a heterogeneous water-hydrocarbon system have also been described.[88] When paraformaldehyde as the source of formaldehyde was used, the solvents were methanol[82,85] or ethanol.[88,89] The reactions were run at reflux for 1-12 h[7,40,77,81,82,85-88,90] or at room temperature for 2-5 days.[24,80,82,84,87] The latter conditions led to better yields.

The synthesis of benzylamines **1-6** in the Mannich reaction is a "one pot" process. The desired products often crystallized from the reaction mixtures and were purified by recrystalliza-

tion.[7,77,81,85,88,91,92] They were also isolated in the form of their hydrochloride salts after acidification of the reaction mixture with concentrated hydrochloric acid or gaseous HCl.[77,80,83,93] The hydrochlorides were converted to the free benzylamines by treatment with $K_2CO_3$,[83] ethanolamine[80] or aqueous ammonia.[77] Alternatively, phenols can react in a non-aqueous system




*a*) $CH_2O$, $H_2O$, dioxane, 5°C-rt, 3-5 days (67%) (**2l, 2m, 2br, 2cp**).[80] *b*) $CH_2O$, $H_2O$, dioxane, reflux, 2-5 h (17-36%) ( **2cm**,[81] **5i**[82]). *c*) $CH_2O$, $H_2O$, dioxane/MeOH, reflux, 2 h (28%) (**2ch, 2cl**).[83] *d*) $CH_2O$, $H_2O$, izobutanol, reflux, 7 h (86%) (**2cn**).[42] *e*) $CH_2O$, $H_2O$, MeOH, rt, 24-65 h or reflux 1.5-2 h (26-100%) (**2au-z, 2bb, 2bc**,[85] **2by, 2cg, 2cj, 2ck, 2cy, 2du**,[86] **3h, 3t**[7]). *f*) $CH_2O$, $H_2O$, EtOH, 37°C, 3-4 days (**2z, 2bv, 2cm, 2de**).[84] *g*) $CH_2O$, $H_2O$, EtOH, rt, 1-5 h then reflux, 3 h (52%) (**2l**).[87] *h*) $CH_2O$, $H_2O$, EtOH, rt, 1 h, then 40-45°C, 5 h (80-88%) (**6a-c**).[24] *i*) $CH_2O$, $H_2O$, $Ba(OH)_2$, $H_2O$, 96°C, 2.5 h (26-42%) (**1ae, 1ba**,[77] **1af**[40]). *j*) $CH_2O$, $H_2O$, $C_nH_m$, 90-95°C, 1-5 h (36-71%) (**1a, 1f, 1e**).[88] *k*) $CH_2O$, MeOH, rt, 2-5 days (56%) (**5i**).[82] *l*) $CH_2O$, EtOH, reflux, 1-12 h (21-86%) (**2al-n, 2ba, 2bd, 2be, 2bl, 2bm, 2cu**,[90] **4a-d**[93]). R - according to *Table 1-6*.

**Scheme 13**

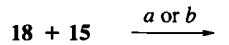
with the products derived from the condensation of amines with formaldehyde. Such amines usually have the structure of 1,3,5-trialkylhexahydro-1,3,5-triazines (**18**) (*Fig. 5*)[94] and 1,3,6,8-tetraazatricyklo[4.4.1.1]dodecane for ethylenediamine (**19**) (*Fig. 5*).[95,96] Compounds **18** were utilized by Möhrle and Tröster in the synhesis of benzylamines **4** (*Scheme 14*).[93]


**18** **19**

R - according to *Table 4*.

**Fig. 5**

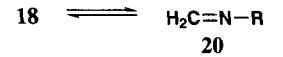
The reactions were performed in ethanol (21%) or methylene chloride (33-79%) at room temperature for 2-3 hours. After evaporation of the solvent, the oily residue was dissolved in ether and treated with gaseous HCl, to give crystalline hydrochlorides. Our own, hitherto




*a*) $CH_2Cl_2$, rt, 2-3 h (33-79%) (**4a-d**).[93] *b*) EtOH, rt, 2 h (21%) (**4b**)[93]

**Scheme 14**

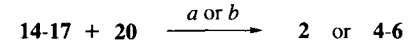
unpublished results concerning the synthesis of benzylamines **2** in a non-aqueous system using **18**, resulted in relatively high yields of the desired products. The triazines **18** are able to depolymerize resulting in methylene imines **20** (*Scheme 15*),[97] with the equilibrium dependent on pH.[93]




R = Alkyl or aryl

**Scheme 15**

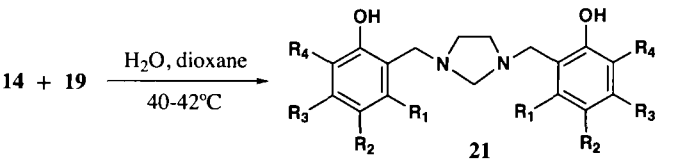
The methylene imines **20**, in which the nitrogen atom was connected to a quaternary carbon atom, were employed in the synthesis of benzylamines **2** and **4-6** (*Scheme 16, Fig. 1, Tables 2* and *4-6*).[98]




*a*) 100°C, 1-2.5 h (50-98%). *b*) $C_6H_6$, rt, several hours (84%)

**Scheme 16**

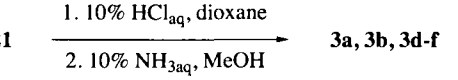
The product **19** was used in the two-step synthesis of benzylamines **3**. In the first step, the corresponding imidazoline **21** (*Scheme 17*) was obtained and then was hydrolyzed to the




$R_1$-$R_4$ - according to *Table 3*.

**Scheme 17**

desired benzylamine **3** (*Scheme 18, Fig. 1, Table 3*).[32,89,95] The reactions were performed in aqueous dioxane solutions at 40-42°C and monitored by TLC. The products were purified by column chromatography, albeit only low yields of **21** were achieved (20-30%).




**Scheme 18**

The hydrolysis was carried out in an aqueous dioxane solution of HCl. The resulting hydrochlorides were transformed into corresponding benzylamines with aqueous ammonia in methanol and the products precipitated in good yields (71-90%).

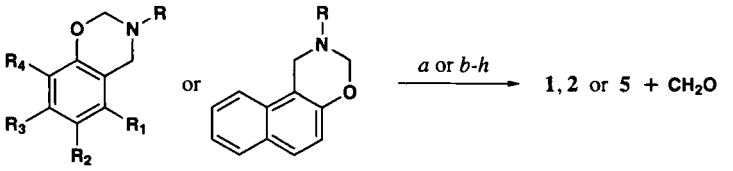
The yields of benzylamines in the Mannich reaction strongly depend on the molar ratio of the reagents and on the reaction time. The products are reactive towards some materials of the reaction mixture and many side-products can be formed.[21,79,99,100] In spite of these drawbacks, the Mannich reaction is one of the most popular methods of synthesis of benzylamines **1-6** with a wide range of commercially available parent substances.

***2-Cyclohexylaminomethyl-4,6-dichlorophenol (2co). Typical Procedure.***[80] *Cyclohexylamine (4.95 g, 0.05 mole) in 15 mL of dioxane was added dropwise to a solution of 7.5 mL of 37% aqueous formaldehyde (0.1 mole) in 10 mL of dioxane. 2,4-dichlorophenol (16.4 g, 0.1 mole) in*

*25 mL of dioxane was added, and the resulting solution was shaken thoroughly, stoppered, and kept at room temperature for 5 days. The solvents were removed under reduced pressure and the yellow liquid residue dissolved in 20 mL of warm methanol. Upon cooling, a solid (9 g, 67% yield) precipitated and was isolated by filtration, mp. 157-158°C after recrystallization from methanol. In another run under comparable conditions the product was isolated as the hydrochloride, 11.5 g, 74% yield, mp. 237-238°C after recrystallization from ethanol-water (1:1).*

### *8. Hydrolysis of 3,4-Dihydro-3-alkyl-2H-1,3-benzoxazines (Method H)*

Hydrolysis of the title benzoxazines was first described by Burke in 1942,[81] and mainly employed in synthesis of benzylamines **2** or **5** but rarely in the synthesis of benzylamines **1** (*Scheme 19*, *Fig 1*, *Tables 1*, *2* and *5*). In the reaction, the formaldehyde generated can cause formation of side-products, and thus its elimination from the reaction mixture is essential.




*a*) 1. HCl, $CH_2Cl_2$; 2. $H_2O$, rt, $N_2$, 4 days; 3. $H_2O$, $NaHCO_3$ (**2ap**, **2aq**, **2bu**, **2ci**, **2cx**, **5d**, **5f**).[23] *b*) 1. HCl, $Et_2O$, -15°C; 2. EtOH; 3. $NH_4OH$, $H_2O$ (26-82%) (**1ae**, **1ba**).[77] *c*) 1. HCl, EtOH, reflux (99%) 2. $K_2CO_3$, $H_2O$, rt (83%) (**2a**, **2at**, **2ch**,).[83] *d*) HCl, $H_2O$ (40-74%) (**2n**, **2t**, **2x**, **2aa**, **2bo**, **2bq**, **2cd**).[28] *e*) HCl, $H_2O$, EtOH, reflux, distillation (40-95%) (**2o**,[101] **2bo**, **2dm**, **2ck**,[86] **2cm**[81]). *f*) HCl, $H_2O$, PrOH, distillation (93%) (**5a-c**, **5e**).[102] *g*) $H_2SO_4$, $H_2O$, $(NO_2)_2PhN{=}NH$, EtOH, rt, 45 min. (34%) (**5h**).[82] *h*) EtOH, reflux (89%) (**2co**).[80] R, $R_1$-$R_4$ - according to *Tables 1*, *2* and *5*

**Scheme 19**

The reactions were carried out in boiling aqueous ethanol[81,83,86,101] or propanol[102] solutions of HCl. The evolving formaldehyde was removed by distillation. Heating was continued until no formaldehyde was observed in the distillate. The hydrolysis was also performed in aqueous HCl[28] or in pure ethanol.[80] The resulting benzylamine hydrochlorides crystallized from the reaction mixtures during evaporation of the solvent.[81,86,101] Some of them were converted into free amines with aqueous $K_2CO_3$ solution.[83]

Kuehne and Konopka[23] obtained benzylamines from benzoxazines in a three-stage process. The benzoxazine was transformed into its hydrochloride with gaseous HCl in methylene chloride. After evaporation of the solvent, the salt formed was dissolved in a small amount of water, and a slow stream of nitrogen was passed through the solution for 4 days to remove the formaldehyde. The resulting benzylamine hydrochloride was transformed into free benzylamine by treatment with $NaHCO_3$ solution.[23]

The hydrolysis was also carried out by treatment the benzoxazine with sulfuric acid in ethanol at room temperature in the presence of 2,4-dinitrophenylhydrazine. The latter was applied to trap the evolving formaldehyde in the form of the corresponding hydrazone.[82] Benzylamines were also isolated as by-products in the synthesis of benzoxazines.[103] The hydrolysis is quantitative and seems to be a convenient method for benzylamine preparation if the parent benzoxazines are readily available.

***2-Cyclohexylaminomethylphenol (2ch). Typical Procedure.***[83] *To the solution of 10.85 g (0.05 mole) of the corresponding benzoxazine in boiling ethanol was added portionwise 5 mL of concentrated hydrochloric acid (0.06 mole) in 15 mL of ethanol. The reaction mixture was boiled until formaldehyde was no longer evolved. Upon cooling, 10.2 g of a crystalline hydrochloride separated; mp. 209-210°C (dec.) after recrystallization from ethanol. An additional 1.8 g of product was obtained from the mother liquor; yield 99%. The free base was obtained by addition of excess solid potassium carbonate to 6.5 g of hydrochloride (0.027 mole) in 200 mL of distilled water. The product (4.6 g, 83% yield) was separated by filtration and washed with water, mp. 58-59°C, after recrystallization from petroleum ether.*

### *9. Dehalogenation and Debenzylation of Benzylamines (Method I)*

Dehalogenation or debenzylation were performed in order to transform the existing benzylamine **2** structure into another one. Removal of the halogen substituent from aromatic ring of benzylamine **2** was performed under reducing conditions (*Scheme 20, Fig. 1, Table 2*).

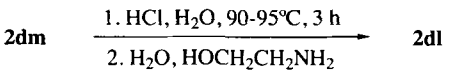

*a*) $H_2$, $H_2O$, $PtO_2$ (37%) (**2a**).[87] *b*) 1. Na, $NH_{3liq}$, $Et_2O$, -75°C, 4 min.; 2. $H_2O$, HCl; 3. $HOC_2H_4NH_2$ (100%) (**2ch**)[83]

**Scheme 20**

Blicke and McCarty obtained benzylamine **2a** as its hydrochloride in the reaction of the corresponding halogenated benzylamine **2l** hydrochloride with hydrogen on platinum oxide catalyst in water.[87] After removal of the catalyst and solvent evaporation the product was purified by crystallization (37%).

A similar transformation was performed by Burke and Stephens[83] by treatment of **2cl** with sodium in a liquid ammonia/ether system at –75°C. After evaporation of the ammonia, the resulting mixture was dissolved in water, acidified with concentrated hydrochloric acid and then basified with 2-aminoethanol. The mixture was concentrated and the solid benzylamine **2ch** was separated and recrystallized from petroleum ether (100%).

Benzylamine **2dm** hydrochloride was debenzylated in water with an excess of HCl at 90-95°C for 3 h to give **2dl** (*Scheme 21, Fig. 1-2, Table 2*).[86] The resulting hydrochloride was transformed into the free benzylamine by means of 2-aminoethanol (61%).




**Scheme 21**

***2-Cyclohexylaminomethylhydroquinone (2dl). Typical Procedure.***[86] *A 20.4 g sample of 2dm (Table 2), (0.059 mole) in 55 mL of concentrated hydrochloric acid was refluxed for 1 h. After cooling, an additional 30 mL of concentrated hydrochloric acid was added and the mixture warmed under reflux for 2 h at 90-95°C. The resulting light brown solid was separated by filtration, washed with six 20 mL portions of ether, and dissolved in hot water. After cooling, 2-aminoethanol was added to the aqueous solution until no further solid (7.6 g) separated; mp. 169-171°C after recrystallization from ethanol-petroleum ether (1:1). An additional 1.3 g was obtained by adding 2-aminoethanol to the original filtrate after separation of the ether, 68% total yield.*

## IV. SUMMARY

A review of properties and application, structure and stability as well as methods of preparation of benzylamines **1-6** has been presented. The compounds described have been tabulated according to their structures following the Cahn, Ingold and Prelog system.[105]

Nine different methods of benzylamines **1-6** synthesis described in the literature were reviewed. It can be concluded that the simple, efficient and economical synthesis of those valuable compounds, starting from basic materials such as phenols and primary amines, is not an easy task. They can be selectively obtained from phenols in a three stage process: phenol → *o*-hydroxybenzaldehyde → benzylimine → benzylamine, but this process is neither a cheap nor a simple one and requires separation of intermediate products. If the *o*-hydroxybenzaldehyde is a commercial product, the procedure can be shortened to two steps (Method F). Unfortunately, the diversity of commercially available aldehydes is much lower than that of phenols. The economical efficiency of the other methods of synthesis (Methods A-E and H) is also limited by the availability of the parent compounds. The Mannich reaction (Method G) seems to be the simplest and potentially the most efficient method of benzylamines **1-6** synthesis. This "one pot" process utilizes cheap and easily accessible raw materials such as phenols, amines and formaldehyde and is the most universal method for benzylamines synthesis. Unfortunately, many possible side-reactions involving not only substrates but also products can take place in the system resulting in lower yields. The efficiency of the process strongly depends on reaction time, molar ratio of reagents and other reaction conditions, so careful optimization should result in high yield of benzylamines. Crystallization, transformation to crystalline hydrochlorides, or column chromatography were most often used for the purification of benzylamines.

Among different possible fields of application of benzylamines, their use as complexing agents and catalysts is especially interesting. The branch of application results from specific structure, containing complexing center and the other parts of the molecule that influence the solubility, hydrophobicity, stability and other physiochemical properties of benzylamines.



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