A Simple and Mild Method for reducing Cyanohydrins to Amino-alcohols

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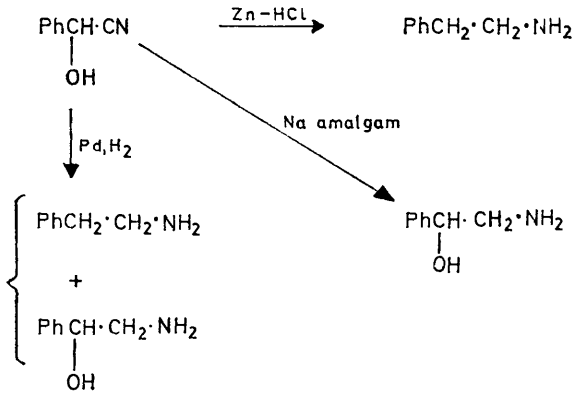
Various halogeno-hydroxy-methoxybenzaldehyde cyanohydrins have been reduced by diborane in 70—80% yield to amino-alcohols without loss of the halogeno-substituent or the alcoholic hydroxy-group.

REAGENTS for the reduction of cyanohydrins to the corresponding 2-amino-alcohols include zinc–hydrochloric acid,[1] sodium amalgam in neutral or acidic solution,[2] aluminium or magnesium amalgam in acetic acid,[3] lithium aluminium hydride,[4-6] and hydrogen with palladium,[7-9] platinum dioxide,[10,11] or Raney nickel analyst.[12] However all these methods induce hydrogenolysis of a bromine- or iodine–arene bond, and in some cases the CH·OH group is also hydrogenolysed (Scheme 1).[1,2,7-9] The latter reaction does not occur if an *ortho*-substituent is present,[13] as in the reduction of 2-chloro- and 2,3-dimethoxy-mandelonitrile with hydrogen over palladium.

The mild method described here makes possible the reduction of halogeno-benzaldehyde cyanohydrins which do not have a substituent *ortho* to the cyanohydrin system, without hydrogenolysis of the CH·OH or CX groups. The reducing agent is a *ca.* 0·7M-solution of diborane in tetrahydrofuran,[14] and yields are generally in the 70—80% range. The various alcohols obtained are shown in Scheme 2.

The starting halogeno-benzaldehydes were synthesized as shown in Scheme 3. Halogenated vanillins are directly obtained from vanillin. The 5-halogeno-isovanillin derivatives were obtained *via* selective methylation of the corresponding halogenated protocatechualdehydes,[15] since direct halogenation gives the 6-halogeno-derivatives.



SCHEME 1

The pattern of aromatic proton signals in the n.m.r. spectra of the amino-alcohols can be used to identify

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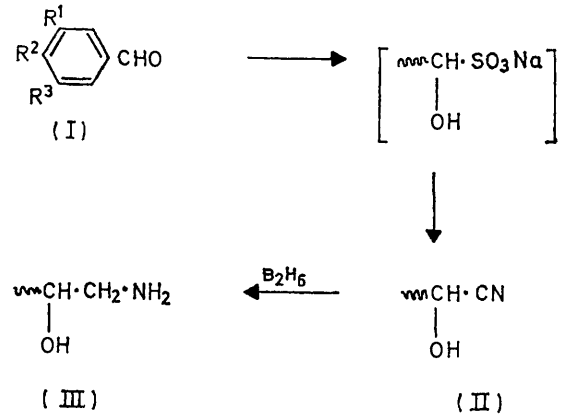
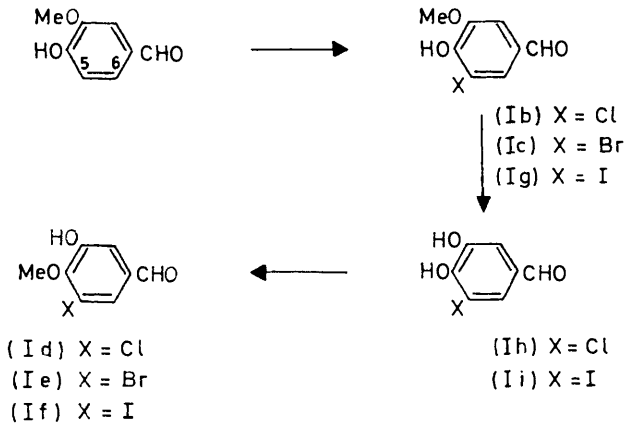
the halogen present in the aromatic nucleus. The difference between the chemical shifts of the two



a; R^1 = MeO R^2 = OH R^3 = H
b; R^1 = MeO R^2 = OH R^3 = Cl
c; R^1 = MeO R^2 = OH R^3 = Br
d; R^1 = OH R^2 = OMe R^3 = Cl
e; R^1 = OH R^2 = OMe R^3 = Br
f; R^1 = OH R^2 = OMe R^3 = I

SCHEME 2



SCHEME 3

doublets (J_{meta} 1·5—2·0 Hz) increases as the electronegativity of the halogen decreases (see Table).

X	Δδ (p.p.m.) for the 2 aromatic protons	Structure
Cl	0·08 ± 0·02	(IIIb), (IIId)
Br	0·20 ± 0·02	(IIIc), (IIIe)
I	0·40	(IIIf)

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded on a Perkin-Elmer R12 spectrometer (60 MHz) with deuterium oxide as solvent and sodium 3-trimethylsilylpropane-1-sulphonate as internal reference. R_F Values refer to t.l.c. on silica gel with (A) hexane–dioxan (6 : 4), (B) benzene–methanol–acetic acid (45 : 8 : 4), or (C) n-butanol–acetic acid–water (4 : 1 : 1) as solvent. The purity of the amines was determined by potentiometric titration in non-aqueous medium. Elemental analyses were performed on a Hewlett–Packard CHN Analyzer 185B.

Substituted Benzaldehydes.—5-Bromo-(Ic),[16] 5-chloro-(Ib),[17–20] and 5-iodo-vanillin (Ig) [18,19,21] and 5-bromoisovanillin (Ie) [15] were synthesized according to literature methods.

3-*Chloro*-4,5-*dihydroxybenzaldehyde* (Ih) (*5-chloroprotocatechualdehyde*). Anhydrous pyridine (55 ml, 0·7 mol) was added dropwise to a mixture of 5-chlorovanillin (Ib) (30 g, 0·16 mol) and aluminium chloride (24 g, 0·18 mol) in dichloromethane (200 ml). The mixture was then heated for 17 h at reflux temperature and poured into ice–water (500 ml). The white precipitate was filtered off, washed, and dried to yield the *product* (Ih) (80·3 g, 93%), m.p. 228—229°, purity by potentiometric titration, 99% (OH) (Found: C, 48·5; H, 3·0. $C_7H_5ClO_3$ requires C, 48·7; H, 2·9%), δ ($CDCl_3$) 9·73 (1H, s, CHO), 7·37 (1H, d, aromatic, J 1·8 Hz), and 7·28 (1H, d, aromatic J 2·0 Hz), R_F (A) 0·18 [2,4-dinitrophenylhydrazine (DNP) as reagent].

3-*Chloro*-5-*hydroxy*-4-*methoxybenzaldehyde* (Id) (*5-chloroisovanillin*). Sodium hydrogen carbonate (346·1 g, 4·12 mol) was added in portions to a hot solution (60°) of 5-chloroprotocatechualdehyde (Ih) (690·4 g, 4 mol) and methyl iodide (327 ml, 5·2 mol) in dimethylformamide (2·4 l). After 15 h stirring at 60°, the mixture was poured into water; the precipitate was filtered off, washed with water, and dried under vacuum at 50°. This crude product was dissolved in chloroform and the unchanged starting material was filtered off. The dried solution was passed through a column of silica gel G and concentrated to a small volume. The resulting crystals were filtered off, washed with cold chloroform (−30°), and dried to yield the *product* (Id) (285 g, 38%), m.p. 117—118° (Found: C, 51·5; H, 3·8. $C_8H_7ClO_3$ requires C, 51·5; H, 3·8%), δ ($CDCl_3$) 9·85 (1H, s, CHO), 7·48 (1H, d, aromatic, J 1·8 Hz), 7·39 (1H, d, aromatic, J 1·8 Hz), and 4·01 (3H, s, OMe), purity by potentiometric titration, 99% (OH), R_F (A) 0·72 (DNP and $FeCl_3$).

3,4-*Dihydroxy*-5-*iodobenzaldehyde* (Ii) (*5-iodoprotocatechualdehyde*). Aluminium chloride (73·4 g, 0·55 mol) was added to a suspension of 5-iodovanillin (Ig) (139·3 g, 0·5 mol) in anhydrous dichloromethane (600 ml). Anhydrous pyridine (174 ml, 2·2 mol) was then added dropwise. After 64 h at room temperature, the complex was hydrolysed in 4N-HCl and the resulting white precipitate was washed with cold water and dried to yield the product (Ii) (121 g, 92%), m.p. 198—199°, purity by potentiometric titration, 98% (OH) (Found: C, 31·9; H, 1·9. $C_7H_5IO_3$ requires C, 31·8; H, 1·9%), δ [$CDCl_3$–$(CD_3)_2SO$, 1 : 1] 9·70 (1H, s, CHO), 7·72 (1H, s, aromatic, J 1·8 Hz), and 7·33 (1H, s, aromatic, J 1·8 Hz), R_F (A) 0·20 (DNP and $FeCl_3$).

3-*Hydroxy*-5-*iodo*-4-*methoxybenzaldehyde* (If) (*5-iodoisovanillin*). Sodium hydrogen carbonate (50·4 g, 0·60 mol) was added in portions to a solution of 3,4-dihydroxy-5-iodobenzaldehyde (Ii) (152 g, 0·575 mol) and methyl iodide (47 ml, 0·725 mol) in dimethylformamide–acetone (1 : 1) (840 ml). After 7 h stirring at 65° and 15 h at room temperature, the mixture was concentrated and poured into cold water. The precipitate was filtered off, washed

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with cold water, and dissolved in chloroform. The solution was filtered, dried, passed through a column of silica gel G, and concentrated. The crystals were filtered off, washed with cold chloroform, and dried to yield the product (If) (82 g, 50%), m.p. 134—135·8°, purity by potentiometric titration, 100% (OH) (Found: C, 34·5; H, 2·5. $C_8H_7IO_3$ requires C, 34·6; H, 2·5%), δ ($CDCl_3$) 9·84 (1H, s, CHO), 7·84 (1H, d, aromatic, *J* 1·8 Hz), 7·45 (1H, d, aromatic, *J* 1·8 Hz), and 3·93 (3H, s, OMe), R_F (A) 0·9 ($FeCl_3$).

2-*Amino*-1-*phenylethanols*.— 2-*Amino*-1-(4-*hydroxy*-3-*methoxyphenyl*)*ethanol* (*normetanephrine*) (IIIa) *hydrochloride*. Vanillin (Ia) (152·14 g, 1 mol) was dissolved in 2M-sodium disulphite solution (2 l) at 40°. Potassium cyanide (260 g, 4 mol) in water (520 ml) was added to the cooled (0°) solution. After 5 min stirring, the solution was extracted with ether (4 × 500 ml). The extracts were washed twice with aqueous 2M-sodium disulphite and once with water, dried (Na_2SO_4), and concentrated to a small volume. The crude cyanohydrin (IIa) was precipitated in hexane (yield 150 g, 84%), m.p. 80—82° (lit.,[22] 83°), R_F (B) 0·32 ($FeCl_3$).

A solution of the crude cyanohydrin (IIa) (63 g, 0·35 mol) in anhydrous tetrahydrofuran (300 ml) was slowly added to 0·7M-diborane in tetrahydrofuran (500 ml) (exothermic!). Anhydrous tetrahydrofuran (650 ml) was added to the solidified complex and the mixture, after 1 h under reflux, was kept at room temperature for 12 h. The excess of diborane was destroyed by slow addition of ethyl alcohol (160 ml). A stream of hydrogen chloride was then passed through the mixture and the precipitated hydrochloride was filtered off, washed, and dried. Crystallization from ethanol–methanol (7 : 1) followed by methanol–ether (1 : 1) gave the pure amino-alcohol (IIIa) hydrochloride (32 g, 42%), m.p. 192—194° (decomp.) (lit.,[23] 192—193°), purity by potentiometric titration, 101% (NH_2), R_F (C) 0·44 (red colour with ninhydrin) (Found: C, 49·3; H, 6·35; N, 6·3. Calc. for $C_9H_{13}NO_3$,HCl: C, 49·2; H, 6·4; N, 6·4%), δ (D_2O) 7·14 (3H, m, aromatic), 5·06 (1H, dd, CH, *J* 7·2 and 5·4 Hz), 3·95 (3H, s, OMe), 3·35 (1H, d, *H*CH, *J* 5·4 Hz), and 3·34 (1H, d, HC*H*, *J* 7·2 Hz). Crude amino-alcohol (22 g, 29%) was recovered from the mother liquor.

2-*Amino*-1-(3-*chloro*-4-*hydroxy*-5-*methoxyphenyl*)*ethanol* (IIIb) *hydrochloride*. By the procedure just described, 5-chlorovanillin (Ib) (102·5 g, 0·55 mol), sodium disulphite (209 g, 1·1 mol), and potassium cyanide (150 g, 2·2 mol), yielded the crude cyanohydrin (IIb) (102·8 g, 88%), m.p. 110·5—113°, R_F (B) 0·49 ($FeCl_3$). This cyanohydrin (53·5 g, 0·25 mol) was reduced by 0·67M-diborane (373 ml). After acidification and crystallization from methanol–ether (1 : 1) gave the *amino-alcohol* (IIIb) *hydrochloride* (29·3 g, 42%), m.p. 226°, purity by potentiometric titration, 98% (NH_2), R_F (C) 0·53 (red colour with ninhydrin) (Found: C, 42·4; H, 5·15; N, 5·6. $C_9H_{12}ClNO_3$,HCl requires C, 42·5; H, 5·15; N, 5·5%), δ (D_2O) 7·16 and 7·10 (each 1H, d, aromatic, *J* 1·5 Hz), 5·06 (1H, dd, CH, *J* 7·8 and 4·8 Hz), 3·98 (3H, s, OMe), 3·37 (1H, d, *H*CH, *J* 4·8 Hz), and 3·34 (1H, d, HC*H*, *J* 7·8 Hz).

2-*Amino*-1-(3-*bromo*-4-*hydroxy*-5-*methoxyphenyl*)*ethanol* (IIIc) *hydrochloride*. 5-Bromovanillin (Ic) (231·5 g, 1 mol) was added to a stirred solution (60°) of sodium disulphite (380·22 g, 2 mol) in water (1·2 l). After 3 h the solution was cooled (5°) and unchanged 5-bromovanillin (17·8 g) was filtered off. By the procedure already described, the crude cyanohydrin (IIc) was obtained. This cyanohydrin (120 g, 0·46 mol) in tetrahydrofuran (500 ml) was added to 0·73M-diborane in tetrahydrofuran (800 ml) and the pure *amino-alcohol* (IIIc) *hydrochloride* was isolated (110 g, 79%), m.p. 216—218° (decomp.), purity by potentiometric titration, 100·5% (NH_2), R_F (C) 0·48 (red colour with ninhydrin) (Found: C, 36·4; H, 4·5; N, 4·45; O, 16·3. $C_9H_{12}BrNO_3$,HCl requires C, 36·2; H, 4·4; N, 4·7; O, 16·05%), δ (D_2O) 7·29 and 7·11 (each 1H, d, aromatic, *J* 1·5 Hz), 5·04 (1H, dd, CH, *J* 7·8 and 4·8 Hz), 3·96 (3H, s, OMe), 3·36 (1H, d, *H*CH, *J* 4·8 Hz), and 3·34 (1H, d, HC*H*, *J* 7·8 Hz).

2-*Amino*-1-(3-*chloro*-5-*hydroxy*-4-*methoxyphenyl*)*ethanol* (IIId) *hydrochloride*. 5-Chloroisovanillin (Id) (56 g, 0·3 mol), sodium disulphite (114 g, 0·6 mol), and potassium cyanide (78·13 g, 1·2 mol), yielded the crude cyanohydrin (IId) (58 g, 90%), m.p. 99—102°, R_F (A) 0·50 ($FeCl_3$). This cyanohydrin (53 g, 0·25 mol) was reduced by 0·67M-diborane (375 ml) as above. Acidification and crystallization in ether gave (IIId) *hydrochloride* (44 g, 69%), m.p. 195°, R_F (C) 0·35 (red colour with ninhydrin), purity by potentiometric titration, 96·6% (NH_2) (Found: C, 42·6; H, 5·1; N, 5·6. $C_9H_{12}ClNO_3$,HCl requires C, 42·55; H, 5·15; N, 5·5%), δ (D_2O) 7·15 and 7·05 (each 1H, d, aromatic, *J* 1·6 Hz), 5·04 (1H, dd, CH, *J* 7·2 and 4·2 Hz), 3·91 (3H, s, OMe), 3·37 (1H, d, *H*CH, *J* 4·2 Hz), and 3·30 (1H, d, HC*H*, *J* 7·2 Hz).

2-*Amino*-1-(3-*bromo*-5-*hydroxy*-4-*methoxyphenyl*)*ethanol* (IIIe) *hydrochloride*. 5-Bromovanillin (Ie) (115·5 g, 0·5 mol), sodium disulphite (190 g, 1 mol) and potassium cyanide (130·2 g, 2 mol) yielded the crude cyanohydrin (IIe) (117 g, 91%), m.p. 89—100°, R_F (B) 0·61 ($FeCl_3$). This cyanohydrin (103 g, 0·4 mol) was reduced by 0·64M-diborane (625 ml) as above. Acidification and crystallization in ether gave the *amino-alcohol* (IIIe) *hydrochloride* (90 g, 75%), m.p. 206—207°, purity by potentiometric titration, 97·5% (NH_2), R_F (C) 0·51 (red colour with ninhydrin) (Found: C, 49·35; H, 6·4; N, 6·35. $C_9H_{13}BrNO_3$,HCl requires C, 49·2; H, 6·4; N, 6·4%), δ (D_2O) 7·33 and 7·11 (each 1H, d, aromatic, *J* 2 Hz), 5·05 (1H, dd, CH, *J* 8·4 and 3·6 Hz), 3·91 (3H, s, OMe), 3·40 (1H, d, *H*CH, *J* 3·6 Hz), and 3·30 (1H, d, HC*H*, *J* 8·4 Hz).

2-*Amino*-1-(5-*hydroxy*-3-*iodo*-4-*methoxyphenyl*)*ethanol* (IIIf) *hydrochloride*. 5-Iodoisovanollin (If) (68 g, 0·25 mol), sodium disulphite (95 g, 0·5 mol) and potassium cyanide (49 g, 1 mol) yielded the crude cyanohydrin (IIf) (63 g, 83%), m.p. 75—79°, R_F (A) 0·52 ($FeCl_3$). This cyanohydrin (25·5 g, 0·08 mol) was reduced by 0·65M-diborane (125 ml), as above. Acidification and crystallization in ethyl acetate gave (IIIf) *hydrochloride* (14·4 g, 47%), m.p. 195—196·5°, R_F (C) 0·39 (red colour with ninhydrin), purity by potentiometric titration, 96% (NH_2) (Found: C, 31·3; H, 3·7; N, 4·15. $C_9H_{12}INO_3$,HCl requires C, 31·3; H, 3·8; N, 4·05%), δ (D_2O) 7·51 and 7·13 (each 1H, d, aromatic, *J* 1·8 Hz), 5·02 (1H, dd, CH, *J* 9·0 and 4·8 Hz), 3·84 (3H, s, OMe), 3·36 (1H, d, *H*CH, *J* 4·8 Hz), and 3·30 (1H, d, HC*H*, *J* 9·0 Hz).

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