Preparation of *N,O*-Aminals as Synthetic Equivalents of $H_2C=NAr$ and $(H_2C=NHAr)^+$ Ions: Neutral- and Acid-promoted Transformations

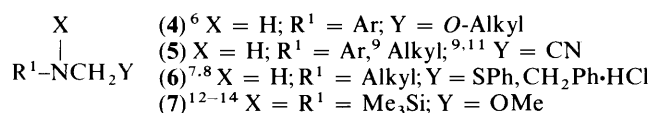**José Barluenga, Ana M. Bayón, and Pedro Campos**
Departamento de Química Orgánica, Facultad de Química, Universidad de Oviedo, 33007-Oviedo, Spain
**Gregorio Asensio, Elena Gonzalez-Nuñez, and Yolanda Molina**
Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, 46010-Valencia, Spain

A general method for the synthesis of *N,O*-aminals derived from primary aromatic amines is described. The reactivity of these compounds under neutral and acidic conditions has been studied and the title compounds can be envisaged as general purpose $H_2C=NAr$ or $(H_2C=NHAr)^+$ equivalents. *N,O*-Aminals have been converted into perhydrotriazines by moderate heating and into bis(4-aminoaryl)methane derivatives or *N*-benzylarylamines, respectively when heated in acidic media with pH control. Reduction of *N,O*-acetals with sodium cyanoborohydride has revealed that the C–O bond is broken exclusively in acidic media.

The Mannich reaction is an important tool in synthetic organic chemistry but for many years its use has been limited to secondary amines.[1] This limitation is because the products initially formed in the condensation of formaldehyde and ammonia or primary amines undergo a series of transformations with participation of the remaining N–H bonds, leading to mixtures of different compounds, the nature of which mainly depends upon such reaction conditions as the amine:formaldehyde ratio used, pH, and temperature. When aromatic amines are involved, the situation becomes even more complex[2–5] since products of aminomethylation of the aromatic ring are formed, particularly under acid catalysis, resulting in conflicting reports. In order to overcome these difficulties a number of papers have appeared in the last few years dealing with the production of efficient synthetic equivalents for methyleneamines $H_2C=NAr$ (1),[6] $H_2C=NR$ (2),[7–11] and $H_2C=NH$ (3)[12–14] based on the formation of their masked forms, (4)—(7), which can undergo the elimination of the group Y to afford *in situ* the reactive methyleneamines or their protonated forms.

$$
\begin{array}{ll}
X & \quad (4)^6\ X = H; R^1 = Ar; Y = O\text{-Alkyl} \\
| & \quad (5)\ X = H; R^1 = Ar,^9\ Alkyl;^{9,11}\ Y = CN \\
R^1\text{--NCH}_2Y & \quad (6)^{7,8}\ X = H; R^1 = Alkyl; Y = SPh, CH_2Ph\cdot HCl \\
& \quad (7)^{12-14}\ X = R^1 = Me_3Si; Y = OMe
\end{array}
$$

These compounds are capable of being used in the formal context of Mannich reactions[8–10] and also in other processes such as the general monomethylation of primary amines[15] by reduction with complex hydrides. Interest in the study of synthetic equivalents of iminium ions has grown recently because its potential in interstellar chemistry[14] and prebiotic synthesis,[16] and also because it has been suggested that iminium ions are generated by enzymatic oxidation of *N*-alkyl compounds to α-carbinolamines in the metabolism of *N*-alkyl xenobiotic molecules.[17] A different approach to *N*-alkylmethyleneamine derivatives (Scheme 1), is the acid-promoted rupture
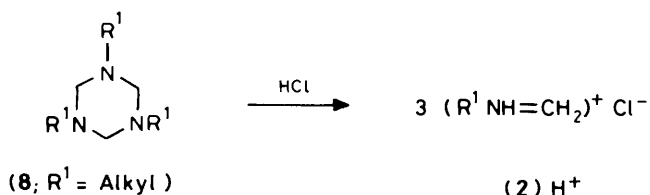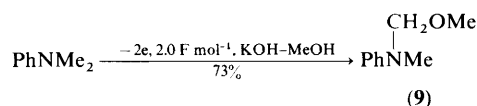
of aliphatic perhydrotriazines (8; R^1 = alkyl) which afford *N*-alkylmethyleneiminium salts[18] (2)·H^+. This reaction has been employed in the synthesis of β-aminocarboxylates[19] and in aza-Diels–Alder reactions.[20] This approach cannot be applied at all with success for *N*-arylmethyleneamines (1) since these readily undergo acid-promoted ring aminomethylation.
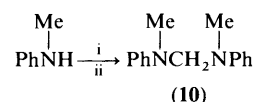
Results and Discussion

We report here on the chemical synthesis of *N*-alkoxymethylarylamines (4; R^1 = Ar) derived from primary aromatic amines and some of their properties which show how these compounds can be envisaged as general purpose $CH_2=NHAr^+$ (1)·H^+ synthetic equivalents.
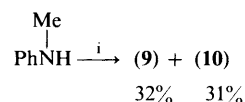
The preparation of tertiary *N,O*-acetals (9) and their use in synthesis[21] has been described elsewhere and result from the anodic oxidation[22] of the corresponding tertiary amine (Scheme 2). Other attempts for alternative syntheses of α-methoxylated *N,N*-dialkylanilines by chemical methods have been described by Shono *et al.*,[21] using the alkylation of *N*-methylaniline with chloromethyl methyl ether (Scheme 3) and by Mannich reaction of *N*-methylaniline with formaldehyde and methanol (Scheme 4). The results of the two latter processes, however, were not found to be satisfactory.

$$
PhNMe_2 \xrightarrow[73\%]{-2e,\ 2.0\ F\ mol^{-1},\ KOH-MeOH} PhN\overset{\displaystyle CH_2OMe}{\underset{\displaystyle |}{Me}}
$$

(9)

Scheme 2.[21]

$$
Ph\overset{Me}{\overset{|}{N}}H \xrightarrow{\ i\ } \xrightarrow{\ ii\ } Ph\overset{Me}{\overset{|}{N}}CH_2\overset{Me}{\overset{|}{N}}Ph
$$

(10)

Scheme 3. *Reagents:* i, NaH; ii, $ClCH_2OMe$[21]

$$
Ph\overset{Me}{\overset{|}{N}}H \xrightarrow{\ i\ } (9) + (10)
$$

$$
32\% \quad 31\%
$$

Scheme 4. *Reagents:* i, $(CH_2O)_n$–MeOH[21]

$$
\mathbf{(8; R^1 = Alkyl)} \xrightarrow{\ HCl\ } 3\ (R^1NH=CH_2)^+\ Cl^-
$$

$$
\mathbf{(2)\ H^+}
$$

Scheme 1.

By contrast, we have found that primary aromatic amines react with paraformaldehyde (see the Experimental section) and sodium alkoxide in the corresponding alcohol to afford N-alkoxymethylarylamines (4; R^1 = Ar) in nearly quantitative yields (Scheme 5, Table).

$$R^1NH_2 + (CH_2O)_n + NaOR^2 \xrightarrow{i} R^1NH-CH_2-OR^2$$

$$(4)$$
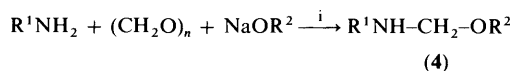
$R^1 = Ar$

Scheme 5. *Reagents:* i, R^2OH

As is usual in the course of condensation reactions of amines and formaldehyde, careful control of the reaction conditions must be observed in order to avoid side-reactions and obtain reproducible experiments. Full details are given in the Experimental section. N,O-Acetals (4; R^1 = Ar) are obtained as practically pure oils (by n.m.r. spectroscopy) as the residue of removal of the solvents under reduced pressure (10^{-3} Torr), are stable at room temperature for several hours, and can be stored at -18 °C for months without noticeable decomposition. However, column chromatography with neutral, basic, or acidic adsorbents causes decomposition of these acetals giving complex mixtures after elution as determined by n.m.r. spectroscopy. While compounds (4; R^1 = Ar) display a single signal in the methylene region in the ^1H and ^{13}C n.m.r. spectra, several types of methylene groups are observed after column chromatography. Attempts to generalize this preparation to include the case of N-methoxymethylalkylamines (4; R^1 = alkyl) were unsuccessful leading in all instances to the exclusive formation of the corresponding alkylperhydrotriazine (8; R^1 = alkyl) [Scheme 6, path (b)].
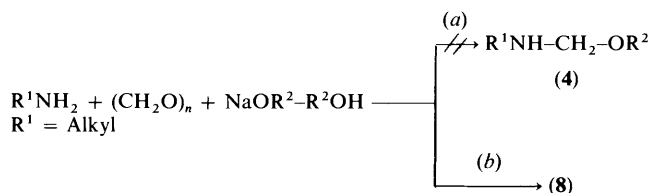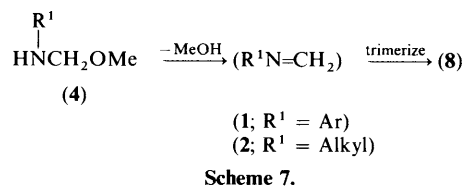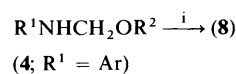
Scheme 6.

Thus, the result of the reaction of primary aromatic amines with formaldehyde and an alkoxide in alcohol is an exception to the usual, well known reaction of primary amines and formaldehyde in aqueous basic media (usually potassium carbonate) leading to perhydrotriazines (8), while aliphatic amines follow the usual reaction path under our particular basic conditions. A further difference in the course of the reaction with either aromatic or aliphatic amines is the reaction rate. Aliphatic amines afford compounds (8; R^1 = alkyl) in a few minutes in a strongly exothermic reaction, while the conversion of aromatic amines into compounds (4; R^1 = Ar) takes about 5 h at room temperature to reach completion. When the reaction mixture is quenched after 1 h with ice-cooled water most of the starting aromatic amine is recovered unchanged. In fact, the formation of (8; R^1 = alkyl) does not rule out aliphatic N,O-acetals (4; R^1 = alkyl) as reaction intermediates which could undergo a fast β-elimination of alkoxide. The β-elimination is expected to be easier in aliphatic N,O-acetals (4; R^1 = alkyl) than in their aromatic counterparts (4; R^1 = Ar) due to the enhanced nitrogen basicity of the former ones (Scheme 7). The nature of the alcohol exerts no significant effect on the course of the trimerization reaction and this is exemplified for methanol in Scheme 7.

Table. Synthesis of compounds (4), (8), (11), and (12)

Scheme	Compd.	R^1	R^2	R^3	Yield (%)
5	(4a)	Ph	Me		85
5	(4b)	o-MeC$_6$H$_4$	Me		80
5	(4c)	m-MeC$_6$H$_4$	Me		90
5	(4d)	p-MeC$_6$H$_4$	Me		82
5	(4e)	o-MeOC$_6$H$_4$	Me		85
5	(4f)	p-MeOC$_6$H$_4$	Me		72
5	(4g)	o-EtOC$_6$H$_4$	Me		74
5	(4h)	p-NO$_2$C$_6$H$_4$	Me		69
5	(4i)	Ph	Et		75
5	(4j)	Ph	Pr		75
5	(4k)	Ph	Bu		82
8	(8a)	Ph			92
8	(8b)	o-MeC$_6$H$_4$			84
8	(8c)	m-MeC$_6$H$_4$			93
8	(8d)	p-MeC$_6$H$_4$			82
8	(8e)	p-MeOC$_6$H$_4$			81
6	(8l)	Ph			89
6	(8m)	Bu			93
6	(8n)	Bu^t			79
6	(8o)	cyclo-C$_6$H$_{11}$			85
6	(8p)	CH$_2$=CHCH$_2$			87
6	(8q)	Dodecyl			77
9	(11a)	Ph		H	76
9	(11b)	o-MeC$_6$H$_4$		3-Me	82
9	(11c)	m-MeC$_6$H$_4$		2-Me	84
9	(11h)	o-MeOC$_6$H$_4$		3-MeO	79
10	(12a)	Ph		H	70
10	(12b)	o-MeC$_6$H$_4$		3-Me	79
10	(12c)	m-MeC$_6$H$_4$		2-Me	83

$$R^1$$
$$|$$
$$HNCH_2OMe \xrightarrow{-MeOH} (R^1N=CH_2) \xrightarrow{trimerize} (8)$$

$$(4)$$

$$(1; R^1 = Ar)$$
$$(2; R^1 = Alkyl)$$

Scheme 7.

Aromatic N,O-*Acetals as Synthetic* ArNHCH$_2$$^+$ *Equivalents.*—Aromatic N,O-acetals (4; R^1 = Ar) undergo a series of controlled transformations under neutral or acidic conditions which are useful from a synthetic point of view. The heating of compounds (4; R^1 = Ar) for several hours at *ca.* 30 °C results in a quantitative transformation into the corresponding arylperhydrotriazine (8; R^1 = Ar). This reaction is greatly accelerated if the heating is carried out under reduced pressure in such a way that the alcohol eliminated in the trimerization process is removed. The same result is obtained when compounds (4; R^1 = Ar) are allowed to stand at room temperature for a long period of time. Heating of N,O-acetals (4; R^1 = Ar) in different types of solvent (protic or aprotic) also results in transformation into compounds (8; R^1 = Ar) which precipitate from the solution as white crystalline solids.

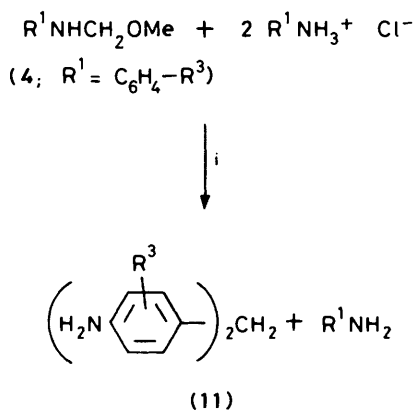$$R^1NHCH_2OR^2 \xrightarrow{i} (8)$$

$$(4; R^1 = Ar)$$

Scheme 8. *Reagents:* i, heat

Compounds (8; R^1 = Ar) obtained as described above are not contaminated by any polymeric or dimeric material as can be ascertained from their ^1H and ^{13}C n.m.r. spectra which were recorded from clear solutions obtained after complete dissolu-

tion of the corresponding solid sample. It is noteworthy that the temperature at which N,O-acetals ($\mathbf{4}$; R^1 = Ar) are converted into compounds ($\mathbf{8}$; R^1 = Ar) is much lower than that necessary for the formation of the perhydrotriazine ($\mathbf{8a}$) by direct reaction of aniline and paraformaldehyde (over 100 °C).[5] This indicates that, in the latter case, the heating is probably necessary to depolymerize the paraformaldehyde, since removal of water is reported to have no effect on the course of the reaction.
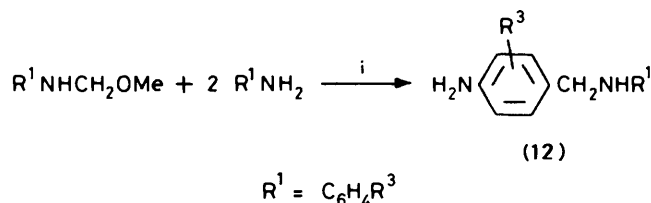
Acid-promoted Transformations of N,O-*Acetals* ($\mathbf{4}$; R^1 = Ar).—In acidic solution, aromatic amines, including tertiary amines, react with formaldehyde to afford resins involving the formation of nuclear methylene linkages.[23] However, the nature of the products depends on the stoicheiometry used, and very significantly, on the acid concentration in the reaction medium. Careful control of the reaction conditions controls in part the formation of different classes of products with definite composition.[4,24,25] In fact, these processes have received much attention because of the industrial applications of the compounds so synthesized.

We found that the treatment of N,O-acetals ($\mathbf{4}$; R^1 = Ar), in which the *para* position is free of substituents, with a two-fold excess of the corresponding amine hydrochloride in boiling 50% aqueous methanol gives rise to the bis(4-aminoaryl)methane derivatives ($\mathbf{11}$) which are isolated following the removal of the solvents and the excess of the amine, with >95% purity as determined by n.m.r. analysis of the crude distillation residue. The symmetry of the products was determined by the presence of a single set of signals for both aromatic rings in the ^{1}H and ^{13}C n.m.r. spectra. The acid is added in the masked form of an amine hydrochloride as a simple and practical way of controlling with precision the amine:acid ratio. An increase in the acid concentration results in the formation of side-products of indeterminate composition (Scheme 9).

$$R^1NHCH_2OMe + 2 R^1NH_3^+ Cl^-$$

$$(\mathbf{4}; \ R^1 = C_6H_4-R^3)$$

$$\left(H_2N \underset{R^3}{\diagup\!\!\!\diagup\!\!\!\diagdown\!\!\!\diagdown} \!-\! \right)_2 CH_2 + R^1NH_2$$

$$(\mathbf{11})$$

Scheme 9. *Reagents:* i, 50% aqueous MeOH; 2 h, reflux

When N,O-acetals ($\mathbf{4}$; R^1 = Ar) are treated for 4 h at 60 °C with two equivalents of the corresponding aromatic amine in a 2:3 mixture of methanol and a pH 4.62 sodium acetate–acetic acid buffer solution (pH of the reaction mixture *ca.* 5.7, see the Experimental section) aminobenzylarylamines ($\mathbf{12}$) are obtained with good yields (Scheme 10). Longer heating times resulted in the progressive formation of the diamines ($\mathbf{11}$). Compounds ($\mathbf{12}$) are stable enough to allow the elimination of the excess of amine by distillation under reduced pressure up to 80 °C without noticeable decomposition or rearrangement in the absence of acid catalysts. Purification of the distillation residue by column chromatography (silica) also can be carried out. By contrast, compounds ($\mathbf{12}$) are unstable in the presence of
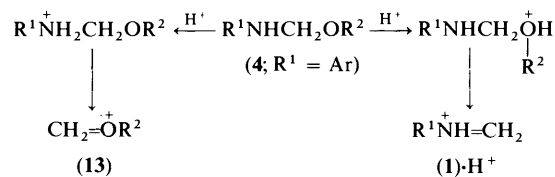
$$R^1NHCH_2OMe + 2 R^1NH_2 \xrightarrow{i} H_2N \underset{R^3}{\diagup\!\!\!\diagup\!\!\!\diagdown\!\!\!\diagdown} CH_2NHR^1$$

$$(\mathbf{12})$$

$$R^1 = C_6H_4R^3$$

Scheme 10. *Reagents:* i, NaOAc–HOAc; MeOH; 3 h, reflux

$$(\mathbf{12}; R^1 = Ar) + R^1NH_3^+Cl^- \xrightarrow{i} (\mathbf{11})$$

Scheme 11. *Reagents:* i, MeOH; reflux

acids and give rise to diamines ($\mathbf{11}$) when heated in the presence of an equimolar amount of the corresponding amine hydrochloride (Scheme 11).

To account for the above results N,O-acetals ($\mathbf{4}$; R^1 = Ar) must be considered as a masked form of the unstable methyleneamines ($\mathbf{1}$) which are produced by elimination of alcohol promoted either by heating under neutral conditions or upon protonation under acid catalysis. The different classes of diamines synthesized [($\mathbf{11}$) and ($\mathbf{12}$)] can result from the intermediate protonated methyleneamines ($\mathbf{1}$)·H^+ following the scheme proposed by Wagner[24] for the acid-induced reactions of formaldehyde and amines. However, alternatives to Wagner's scheme can be envisaged if we take into account the fact that N,O-acetals ($\mathbf{4}$; R^1 = Ar) have two sites of different basicity, and upon protonation can consequently yield two types of alkylating species; the protonated methyleneamines ($\mathbf{1}$)·H^+ and/or the oxonium ions ($\mathbf{13}$) (Scheme 12).

$$R^1\overset{+}{N}H_2CH_2OR^2 \xleftarrow{H^+} R^1NHCH_2OR^2 \xrightarrow{H^+} R^1NHCH_2\overset{+}{O}H$$

$$(\mathbf{4}; R^1 = Ar)$$

$$CH_2=\overset{+}{O}R^2 \qquad\qquad R^1\overset{+}{N}H=CH_2$$

$$(\mathbf{13}) \qquad\qquad (\mathbf{1})\cdot H^+$$

Scheme 12.

To clarify the true mechanism or see if both operate simultaneously we treated the N,O-acetals ($\mathbf{4}$; R^1 = Ar) with aromatic amines and hydrochloric acid in the presence of sodium cyanoborohydride as a way to trap the intermediates ($\mathbf{1}$)·H^+ and/or ($\mathbf{13}$) (Scheme 13). Sodium cyanoborohydride has been used

$$(\mathbf{4a}) + NaB(CN)_3H \xrightarrow{i} PhNHMe$$
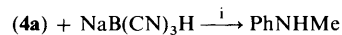
Scheme 13. *Reagents:* i, HCl–MeOH (pH 3)

successfully in the reductive amination of aldehydes and ketones and also in the reduction of acetals involving, in the latter case, the trapping of the intermediate oxonium ion.[26] When the N,O-acetal ($\mathbf{4a}$) was treated with a methanolic solution of sodium cyanoborohydride and hydrochloric acid at pH 3 (methyl orange), N-methylaniline was isolated practically pure. From this observation can be deduced, at least, that at pH 3, no breakage of the C–N bond takes place in the protonated form of compounds ($\mathbf{4}$; R^1 = Ar). When similar experiments were performed at pH 4 or higher, the reaction was not clean and mixtures of products were obtained. These results show once more the extreme importance of careful selection of proper reaction conditions for reactions involving methyleneamines

(1) to be synthetically useful processes. The reduction of compounds (4; R^1 = Ar) in alkaline sodium borohydride also gave N-methylarylamines in good yield.[15]

Experimental

I.r. spectra were recorded on a Pye–Unicam SP-1000 instrument. N.m.r. spectra (^{1}H and ^{13}C) were recorded on Varian EM-390 and Bruker WP 80 SY spectrometers in deuteriochloroform or carbon tetrachloride, with tetramethylsilane as an internal standard. Solvents were washed with aqueous potassium hydroxide (1M) when used for recording the spectra of compounds (4) to avoid acid-catalysed rearrangements. Gas–liquid chromatographic analyses (g.l.c.) were performed on a Varian Aerograph-2800 (column Chrom. G, 1.5% OV-101). Melting points are uncorrected.

Typical Experimental Procedure for Compounds (4; R^1 = Ar).—N-(*Methoxymethyl*)*aniline* (4a). Sodium (2.3 g, 100 mmol) was slowly added to MeOH (30 ml). Once the evolution of hydrogen had ceased, aniline (1.8 g, 20 mmol) was added and the resulting hot solution was poured onto a suspension of paraformaldehyde (0.84 g, 28 mmol) in MeOH (20 ml). The resulting mixture was stirred for 5 h at room temperature and then hydrolysed with ice-cooled water and extracted with ether. The organic layer was dried (Na_2SO_4) and the solvents and the excess of alcohol were evaporated under reduced pressure, taking care that the temperature remained below 25 °C, to yield the product (85%) as an oily residue that can be stored at -18 °C for several months without noticeable decomposition; $\nu_{max.}$(film) 690, 750, 1 060, 1 600, and 3 400 cm^{-1}; δ_H(CDCl$_3$) 3.2 (3 H, s), 4.6 (2 H, s), 4.7 (1 H, br s), and 6.4—7.2 (5 H, m); δ_C(CDCl$_3$) 53.9 (q), 76.9 (t), 114.0 (d), 118.8 (d), 129.7 (d), and 147.0 (s).

2-[N-(*Methoxymethyl*)]*toluidine* (4b). This was prepared following the general method described for (4a) (oil, 80%), $\nu_{max.}$(film) 770, 1 030, 1 260, 1 510, 1 605, 2 900, and 3 450 cm^{-1}; δ_H(CDCl$_3$) 2.0 (3 H, s), 3.2 (3 H, s), 4.4 (1 H, br s), 4.6 (2 H, s), and 6.2—6.9 (4 H, m); δ_C(CDCl$_3$) 18.2 (q), 54.5 (q), 75.9 (t), 112.8 112.8 (d), 116.1 (d), 119.3 (d), 128.1 (d), 131.5 (s), and 146.4 (s).

3-[N-(*Methoxymethyl*)]*toluidine* (4c). This was prepared following the general method described for (4a) (oil, 90%), $\nu_{max.}$(film) 710, 790, 910, 1 090, 1 200, 1 630, 2 900, and 3 420 cm^{-1}; δ_H(CDCl$_3$) 2.3 (3 H, s), 3.3 (3 H, s), 4.6 (2 H, s), 5.2 (1 H, br s), and 6.4—7.1 (4 H, m); δ_C(CDCl$_3$) 16.5 (q), 48.6 (q), 71.8 (t), 106.0 (d), 109.5 (d), 114.5 (d), 124.2 (d), 133.9 (s), and 141.8 (s).

4-[N-(*Methoxymethyl*)]*toluidine* (4d). This was prepared following the general method described for (4a) (oil, 82%), $\nu_{max.}$(film) 815, 900, 1 080, 1 260, 1 600, and 3 400 cm^{-1}; δ_H(CDCl$_3$) 2.2 (3 H, s), 3.2 (3 H, s), 4.5 (1 H, br s), 4.7 (2 H, s), and 6.4—7.0 (4 H, m); δ_C(CDCl$_3$) 21.3 (q), 54.3 (q), 77.9 (t), 114.7 114.7 (d), 128.0 (s), 130.7 (d), and 145.4 (s).

2-[N-(*Methoxymethyl*)]*anisidine* (4e). This was prepared following the general method described for (4a) (oil, 85%), $\nu_{max.}$(film) 790, 970, 1 250, 1 480, 1 530, 1 615, 1 900, and 3 450 cm^{-1}; δ_H(CDCl$_3$) 3.5 (6 H, s), 4.4 (1 H, br s), 4.6 (2 H, s), and 6.4 (4 H, s); δ_C(CDCl$_3$) 56.1 (q), 77.3 (t), 11.9 (d), 116.1 (d), 119.1 (d), 122.3 (d), 138.1 (s), and 148.5 (s).

4-[N-(*Methoxymethyl*)]*anisidine* (4f). This was prepared following the general method described for (4a) (oil, 72%), $\nu_{max.}$(Nujol) 770, 830, 1 050, 1 250, 1 530, and 3 400 cm^{-1}; δ_H(CDCl$_3$) 3.3 (3 H, s), 3.4 (1 H, br s), 3.7 (3 H, s), 4.5 (2 H, s), and 6.6—6.9 (4 H, m); δ_C(CDCl$_3$) 52.7 (q), 54.5 (q), 76.5 (t), 113.7 (d), 113.8 (d), 139.3 (s), and 151.8 (s).

2-[N-(*Methoxymethyl*)]*ethoxyaniline* (4g). This was prepared following the general method described for (4a) (oil, 74%), $\nu_{max.}$(film) 750, 920, 1 100, 1 260, 1 610, and 3 400 cm^{-1}; δ_H(CDCl$_3$) 1.2 (3 H, t), 3.2 (3 H, s), 3.9 (2 H, q), 4.5 (1 H, br s),

4.6 (2 H, s), and 6.7 (4 H, s); δ_C(CDCl$_3$) 14.0 (q), 62.8 (q), 62.9 (t), 75.5 (t), 110.2 (d), 116.5 (d), 117.1 (d), 120.1 (d), 135.4 (s), and 145.3 (s).

4-[N-(*Methoxymethyl*)]*nitroaniline* (4h). This was prepared following the general method described for (4a) (solid, 69%), $\nu_{max.}$(Nujol) 700, 750, 840, 930, 1 250, 1 600, and 3 360 cm^{-1}; δ_H[(CD$_3$)$_2$SO] 3.7 (3 H, s), 4.5 (2 H, d), and 6.4—8.0 (4 H, m); δ_C[(CD$_3$)$_2$SO] 54.1 (q), 75.8 (t), 112.4 (d), 126.0 (d), 139.2 (s), and 152.6 (s).

N-(*Ethoxymethyl*)*aniline* (4i). This was prepared following the general method described for (4a) using ethanol instead of methanol (oil, 75%), $\nu_{max.}$(film) 690, 750, 1 000, 1 100, 1 290, 1 520, 1 610, 2 900, and 3 400 cm^{-1}; δ_H(CDCl$_3$) 1.2 (3 H, t), 3.5 (2 H, q), 4.6 (2 H, s), 4.6 (1 H, br s), and 6.5—7.2 (5 H, m); δ_C(CDCl$_3$) 14.9 (q), 61.6 (t), 74.9 (t), 113.5 (d), 118.1 (d), 129.1 (d), and 146.8 (s).

N-(*Propoxymethyl*)*aniline* (4j). This was prepared following the general method described for (4a) using propanol instead of methanol (oil, 75%), $\nu_{max.}$(film) 700, 760, 1 100, 1 300, 1 600, and 3 400 cm^{-1}; δ_H(CDCl$_3$) 0.9 (3 H, t), 1.5 (2 H, m), 3.3 (2 H, t), 4.6 (2 H, s), 4.6 (1 H, br s), and 6.3—7.2 (5 H, m); δ_C(CDCl$_3$) 10.2 (q), 22.8 (t), 67.9 (t), 75.3 (t), 113.5 (d), 118.0 (d), 128.9 (d), and 146.8 (s).

N-(*Butoxymethyl*)*aniline* (4k). This was prepared following the general method described for (4a) using butanol instead of methanol (oil, 82%), $\nu_{max.}$(film) 660, 765, 1 090, 1 270, 1 530, 1 620, 2 950, and 3 420 cm^{-1}; δ_H(CDCl$_3$) 0.9 (3 H, t), 1.5 (4 H, m), 3.5 (2 H, t), 4.5 (1 H, br s), 4.7 (2 H, s), and 6.5—7.2 (5 H, m); δ_C(CDCl$_3$) 15.1 (q), 20.7 (t), 33.1 (t), 67.3 (t), 76.6 (t), 114.8 (d), 119.4 (d), 130.2 (d), and 147.8 (s).

Typical Experimental Procedure for the Preparation of Compounds (8; R^1 = Ar).—1,3,5-*Triphenylperhydro*-1,3,5-*triazine* (8a). N-(Methoxymethyl)aniline (4a) (2.74 g, 20 mmol) was heated at 50 °C under reduced pressure (10^{-3} Torr) for 30 min, during which time the starting oil was converted into a white solid. Recrystallization of this from cyclohexane–benzene gave (8a) (92%), m.p. 138 °C (lit.,[5] m.p. 138 °C); $\nu_{max.}$(Nujol) 690, 750, 930, 970, 1 160, 1 230, 1 340, 1 380, 1 500, 1 600, and 2 900 cm^{-1}; δ_H(CDCl$_3$) 4.8 (6 H, s), and 6.7—7.2 (15 H, m); δ_C(CDCl$_3$) 68.4 (t), 117.6 (d), 120.8 (d), 129.1 (d), and 148.5 (s).

1,3,5-*Tris*(o-*tolyl*)*perhydro*-1,3,5-*triazine* (8b). This was prepared following the general method described for (8a). The product was recrystallized from hexane–chloroform (84%), m.p. 109 °C (lit.,[27] m.p. 110—111 °C); $\nu_{max.}$(Nujol) 730, 760, 970, 1 200, 1 250, 1 620, 2 900, and 3 000 cm^{-1}; δ_H(CDCl$_3$) 2.1 (9 H, s), 4.2 (6 H, s), and 6.5—7.3 (12 H, m); δ_C(CDCl$_3$) 17.8 (q), 71.9 (t), 121.5 (d), 123.8 (d), 126.2 (d), 130.9 (d), 133.1 (d), and 147.8 (s).

1,3,5-*Tris*(m-*tolyl*)*perhydro*-1,3,5-*triazine* (8c). This was prepared following the general method described for (8a). The product was recrystallized from hexane–chloroform (93%), m.p. 105 °C; $\nu_{max.}$(Nujol) 770, 990, 1 165, 1 275, 1 325, 1 400, 1 460, 1 505, 1 590, 1 610, and 2 900 cm^{-1}; δ_H(CDCl$_3$) 2.1 (9 H, s), 4.6 (6 H, s), and 6.1—7.0 (12 H, m); δ_C(CDCl$_3$) 21.5 (q), 68.3 (t), 114.6 (d), 118.2 (d), 121.5 (d), 128.8 (d), 138.6 (s), and 148.6 (s).

1,3,5-*Tris*(p-*tolyl*)*perhydro*-1,3,5-*triazine* (8d). This was prepared following the general method described for (8a). The product was recrystallized from hexane–chloroform (82%), m.p. 126 °C (lit.,[27] m.p. 128.1 °C); $\nu_{max.}$(Nujol) 790, 870, 940, 1 190, 1 220, 1 600, and 2 900 cm^{-1}; δ_H(CDCl$_3$) 2.2 (9 H, s), 4.7 (6 H, s), and 6.5—7.0 (12 H, m); δ_C(CDCl$_3$) 20.6 (q), 69.9 (t), 118.1 (d), 130.5 (s), 129.8 (d), and 146.6 (s).

1,3,5-*Tris*(p-*anisidino*)*perhydro*-1,3,5-*triazine* (8e). This was prepared following the general method described for (8a). The product was recrystallized from hexane–chloroform (81%), m.p. 125 °C; $\nu_{max.}$(Nujol) 820, 1 030, 1 260, 1 520, and 3 000 cm^{-1}; δ_H(CDCl$_3$) 3.7 (9 H, s), 4.7 (6H, s), and 6.6—7.0 (12 H, m);

$\delta_C(CDCl_3)$ 55.3 (q), 70.9 (t), 114.9 (d), 119.91 (d), 142.5 (s), and 154.4 (s).

Attempted Synthesis of Compounds (**4**; R^1 = Alkyl).—*Synthesis of Compounds* (**8l—q**). When the procedure described for the synthesis of compounds (**4**; R^1 = Ar) was used with aliphatic amines the products were the corresponding perhydrotriazines (**8l—q**) (see Table).

1,3,5-*Tribenzylperhydro*-1,3,5-*triazine* (**8l**). This was prepared following the general method described for (**4a**). The product was recrystallized from hexane (89%), m.p. 46 °C (lit.,[28] m.p. 43—46 °C): $v_{max.}$(Nujol) 700, 750, 1 500, 1 600, 2 900, and 3 000 cm^{-1}; $\delta_H(CDCl_3)$ 3.2 (6 H, s), 3.6 (6 H, s), and 7.1 (15 H, s); $\delta_C(CDCl_3)$ 58.2 (t), 75.1 (t), 128.3 (d), 129.5 (d), 130.1 (d), and 140.0 (s).

1,3,5-*Tributylperhydro*-1,3,5-*triazine* (**8m**). This was prepared following the general method described for (**4a**). The liquid product (93%) had b.p. > 112 °C/0.4 mmHg, $v_{max.}$(film) 900, 1 100, 1 190, 1 380, 1 450, and 2 800 cm^{-1}; $\delta_H(CDCl_3)$ 1.0 (9 H, t), 1.3 (12 H. m), 2.2 (6 H, t), and 3.1 (6 H, s); $\delta_C(CDCl_3)$ 14.1 (q), 20.7 (t), 29.9 (t), 52.6 (t), and 74.9 (t).

1,3,5-*Tri-t-butylperhydro*-1,3,5-*triazine* (**8n**). This was prepared following the general method described for (**4a**). The liquid product (79%) showed $v_{max.}$(film) 700, 910, 1 200, 1 380, 1 630, and 2 900 cm^{-1}; $\delta_H(CDCl_3)$ 1.0 (27 H, s), and 3.2 (6 H, s); $\delta_C(CDCl_3)$ 26.8 (q), 63.3 (s), and 80.8 (t).

1,3,5-*Tricyclohexylperhydro*-1,3,5-*triazine* (**8o**). This was prepared following the general method described for (**4a**). The product was recrystallized from hexane (85%), m.p. 72 °C (lit.,[29] m.p. 73 °C); $v_{max.}$(Nujol) 880, 1 000, 1 100, 1 200, and 2 900 cm^{-1}; $\delta_H(CDCl_3)$ 1.0—1.7 (30 H, m), 2.2 (3 H, m), and 3.2 (6 H, s); $\delta_C(CDCl_3)$ 25.9 (t), 26.1 (t), 30.1 (t), 58.6 (d), and 68.4 (t).

1,3,5-*Triallylperhydro*-1,3,5-*triazine* (**8p**). This was prepared following the general method described for (**4a**). The liquid product (87%) had b.p. > 92 °C/0.4 mmHg; $v_{max.}$(film) 900, 1 000, 1 190, 1 270, 1 620, 2 900, and 3 010 cm^{-1}; $\delta_H(CDCl_3)$ 3.0 (6 H, m), 3.2 (6 H, s), and 4.9—5.9 (9 H, m); $\delta_C(CDCl_3)$ 57.1 (t), 74.8 (t), 117.7 (t), and 137.2 (d).

1,3,5-*Tridodecylperhydro*-1,3,5-*triazine* (**8q**).[27] This was prepared following the general method described for (**4a**). The waxy liquid product (77%) showed $v_{max.}$(Nujol) 720, 900, 1 100, and 2 900 cm^{-1}; $\delta_H(CDCl_3)$ 0.9 (9 H, t), 1.2 (60 H, m), 2.3 (6 H, t), and 3.2 (6 H, s).

Bis(4-*aminophenyl*)*methane* (**11a**). *Typical Experimental Procedure for the Preparation of Compounds* (**11**).—To a stirred solution of (**4a**) (2.74 g, 20 mmol) in methanol (20 ml) was added aniline hydrochloride (5.18 g, 40 mmol) dissolved in water (20 ml). The resulting mixture was heated under reflux for 3 h and then hydrolysed with aqueous potassium hydroxide (1M; 50 ml) and extracted with ether. The organic layer was dried (Na$_2$SO$_4$), the solvent was evaporated, and the excess of aniline was distilled off under reduced pressure (10^{-1} Torr) to give (**11a**) as the distillation residue. This was recrystallized from hexane (76%), m.p. 92 °C (lit.,[30] 94 °C); $v_{max.}$(Nujol) 810, 1 250, 1 510, 1 630, and 3 400 cm^{-1}; $\delta_H(CDCl_3)$ 3.4 (4 H, s), 3.7 (2 H, s), and 6.4—6.9 (8 H. m); $\delta_C(CDCl_3)$ 40.0 (t), 114.4 (d), 128.7 (d), 130.9 (s), and 143.8 (s).

Bis(4-*amino*-3-*methylphenyl*)*methane* (**11b**). This was prepared following the general method described for (**11a**). The product was recrystallized from hexane (82%), m.p. 147 °C (lit.,[31] m.p. 149 —155 °C); $v_{max.}$(Nujol) 820, 1 270, 1 500, and 1 620 cm^{-1}; $\delta_H(CDCl_3)$ 2.1 (6 H, s), 3.3 (4 H, s), 3.7 (2 H, s), and 6.4—6.8 (6 H, m); $\delta_C(CDCl_3)$ 17.1 (q), 40.3 (t), 115.1 (d), 122.3 (d), 127.2 (d), 130.8 (s), 132.2 (s), and 142.4 (s).

Bis(4-*amino*-2-*methylphenyl*)*methane* (**11c**). This was prepared following the general method described for (**11a**). The product was recrystallized from hexane (84%), m.p. 119—

120 °C (lit.,[31] m.p. 123 °C); $v_{max.}$(Nujol) 765, 1 220, 1 310, 1 510, 1 590, 1 630, 3 010, and 3 400 cm^{-1}; $\delta_H(CDCl_3)$ 2.1 (6 H, s), 3.4 (4 H, s), 3.7 (2 H, s), and 6.3—6.8 (6 H, m); $\delta_C(CDCl_3)$ 18.7 (q), 34.3 (t), 112.1 (d), 117.5 (d), 128.2 (d), 129.2 (s), 136.4 (s), and 143.9 (s).

Bis(4-*diamino*-2-*methoxyphenyl*)*methane* (**11h**). This was prepared following the general method described for (**11a**). The product was recrystallized from hexane (79%), m.p. 95 °C; $v_{max.}$(Nujol) 730, 1 030, 1 150, 1 250, 1 620, and 3 460 cm^{-1}; $\delta_H(CDCl_3)$ 3.7 (6 H, s), 3.8 (2 H, s), and 6.5 (6 H, s); $\delta_C(CDCl_3)$ 40.2 (t), 54.4 (q), 110.3 (d), 114.0 (d), 120.3 (d), 131.0 (s), 133.3 (s), and 146.4 (s).

Typical Experimental Procedure for Compounds (**12**).—N-(4-*Aminobenzyl*)*aniline* (**12a**). To a stirred solution of (**4a**) (2.74 g, 20 mmol) in methanol (20 ml) were added aniline (1.86 g, 20 mmol) and a solution of acetic acid–sodium acetate buffer (pH 4.7) (30 ml). The mixture was heated under reflux for 4 h and then extracted with ether. The organic layer was dried (Na$_2$SO$_4$), and the solvent and the excess of amine were evaporated under reduced pressure (10^{-1} Torr) below 80 °C to give compound (**12a**) as the oily distillation residue (70%) (lit.,[32] m.p. 49—50 °C); $v_{max.}$(film) 690, 750, 820, 1 180, 1 250, 1 320, 1 500, 1 520, 1 600, 1 625, 3 010, and 3 410 cm^{-1}; $\delta_H(CDCl_3)$ 3.5 (3 H, s), 4.0 (2 H, s), and 6.4—7.1 (9 H, m); $\delta_C(CDCl_3)$ 47.6 (t), 112.2 (d), 114.4 (d), 116.6 (d), 126.6 (s), 127.6 (d), 128.5 (d), 145.4 (s), and 147.6 (s).

2-[N-(4-*Amino*-3-*methylbenzyl*)]*toluidine* (**12b**). This was prepared following the general method described for (**12a**) (oil, 79%), $v_{max.}$(film) 690, 1 190, 1 450, 1 500, 2 900, 3 000, and 3 350 cm^{-1}; $\delta_H(CDCl_3)$ 2.1 (6 H, s), 3.6 (3 H, s), 4.0 (2 H, s), and 6.3—7.1 (7 H, m).

3-[N-(4-*Amino*-2-*methylbenzyl*)]*toluidine* (**12c**). This was prepared following the general method described for (**12a**) (oil, 83%), $v_{max.}$(film) 755, 820, 1 135, 1 215, 1 275, 1 320, 1 445, 1 500, 1 520, 1 590, 1 610, 1 625, 2 900, 3 010, and 3 450 cm^{-1}; $\delta_H(CDCl_3)$ 1.9 (6 H, s), 3.3 (3 H, s), 4.0 (2 H, s). and 6.3—6.9 (7 H, m).

Transformation of Compounds (**12**) *into Compounds* (**11**).—The treatment of compounds (**12**) with a two-fold excess of the amine hydrochloride following the general method described for the transformation of compounds (**4**) into (**11**), also gives rise to compounds (**11**) with comparable yields.

N-*Methylaniline*. To a stirred solution of (**4a**) (2.74 g, 20 mmol) in methanol (40 ml) were added sodium cyanoborohydride (1.41 g, 22.5 mmol) and Methyl Orange. To the orange solution a 2M methanolic hydrochloric acid was slowly added dropwise until a red colouration was achieved which remained unchanged for 15 min. The solution was then stirred at room temperature for an additional 45 min whereupon the methanol was evaporated. The residue was made alkaline with 1M sodium hydroxide, extracted with methylene dichloride, and the organic layer was dried (Na$_2$SO$_4$). After the solvents had been removed under reduced pressure, methylaniline was obtained as the distillation residue (1.9 g, 90%).

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