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The Activation of Aminals and Aminol Ethers by Sulfur Dioxide and their Reactions with Electron Rich Aromatic Compounds

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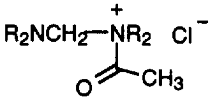
Abstract: Reactions of bis(dialkylamino)methanes and ethoxydialkylaminomethanes with nucleophilic aromatic heterocycles in the presence of sulfur dioxide result in the formation of the expected Mannich bases in good yields. Reactions of phenols are similarly activated by sulfur dioxide which lead to improved regioselectivity: in particular the reactions of 2,5-dimethylphenol result in the formation of 2-dialkylaminomethyl-3,6-dimethylphenol whereas reaction occurs at the 4-position using the classical procedures. © 1997 Elsevier Science Ltd.

Introduction

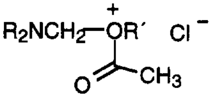
The Mannich reaction provides an excellent method for carbon-carbon bond formation and its importance is reflected in the ever increasing number of suitable substrates and reaction conditions that have been developed.[1] Some important experimental modifications involve the use of preformed iminium salts[2] which can be prepared by a number of methods including the reactions of acetyl chloride with aminals,[3] of trifluoroacetic anhydride with *N*-oxides,[4] and of trichloromethylsilane with aminol ethers.[5] Our investigation of new methods for the α-aminoalkylation of aromatic substrates using non-aqueous aprotic conditions has been focused on "one-pot" reaction systems that do not involve the isolation of reactive intermediates. Our aim was to devise conditions in which the accumulation of hydrogen chloride in the reaction mixtures would be avoided. We reported recently the activation of aminals and aminol ethers by chlorosilane derivatives and provided evidence that implicated the involvement electrophilic intermediates other than iminium salts in the Mannich reactions of electron rich aromatic compounds, including the catalytic effect of chlorotrimethylsilane in reactions using aminals.[6]

The preparation of iminium salts by the reaction of aminals with acetyl chloride[3] led us to a brief investigation of the *in situ* reactions of *N*-methylpyrrole with aminals and aminol ethers. The participation of the acyl ammonium salts (**1**) and oxonium analogues (**2**), as the most likely reactive intermediates, was suggested because no precipitation of iminium salts was observed during the course of the reactions.[7] A limited success in this system was achieved due to the reaction of amino group with acetyl chloride which resulted in the disintegration of some product and the co-formation of the dipyrrylmethane (**3**). This observation prompted our attention in the use of sulfur dioxide as a non-protic acid anhydride reagent. It was envisaged that this relatively mild reagent would form weakly acidic by-products avoiding the generation of hydrogen chloride in the reaction mixture. We reported previously some of our preliminary results of the use of sulfur dioxide in the Mannich reactions of aromatic heterocycles[7] and phenols.[8] The present paper gives a detailed account of our extensive investigations including full experimental procedures.



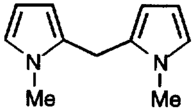
$R_2NCH_2-\overset{+}{N}R_2(COCH_3)\ Cl^-$

(1)



$R_2NCH_2-\overset{+}{O}R'(COCH_3)\ Cl^-$

(2)

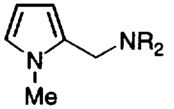


(3)

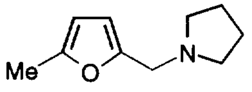
Results and Discussion

In our initial investigations, no change was observed on the ^{13}C nmr spectrum of bis(*N,N*-dimethylamino)-methane, determined in a mixture of CD_3CN and sulfur dioxide over a period of 24 hours. However, after the addition of 1 mole equivalent of *N*-methylpyrrole the spectrum showed signals within 1 hour that could be assigned to 2-(*N,N*-dimethylaminomethyl)-1-methylpyrrole and *N,N*-dimethylaminosulphinate. When reactions were carried out on a preparative scale by the addition of a 22 molar excess of sulfur dioxide to a mixture of the substrate and a Mannich reagent precursor we were able to isolate good yields of monoaminoalkylated derivatives of *N*-methylpyrrole (**4a-c**), 2-methylfuran (**5**), indole (**6**), and *N*-methylindole (**7**). Although we also isolated small amounts of the disubstituted derivatives of *N*-methylpyrrole (**8a-c**) in some reactions carried out with equimolar amounts of reagents, we failed to obtain a Mannich base from an attempted reaction of furan with ethoxy-*N*-pyrrolidinylmethane and sulfur dioxide. This suggests that an intermediate formed between the aminol ether and sulfur dioxide is not electrophilic enough to react with the relatively weakly nucleophilic furan. We had shown previously that furan does react efficiently with *N,N*-dimethylmethyleneiminium chloride[2e] but less efficiently in a reaction of furan with bis(*N,N*-dimethylamino)methane in the presence trichloromethylsilane.[6b]

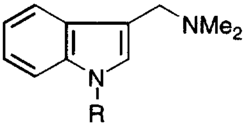
In our early experiments the reactions were carried out at low temperature but it was later realised that, despite the low boiling point of sulfur dioxide, sulfur dioxide is quite soluble in acetonitrile at higher temperatures and that the reactions could therefore be performed at room temperature. It is noteworthy that no precipitation of an iminium salt was observed but clear yellow solutions persisted during the course of the reactions. It is therefore possible that the reactive intermediates in these reactions may be the dipolar species (**9**) and (**10**) rather than the related iminium ions.



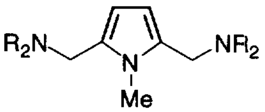
(**4a**) $R_2 = Me_2$
(**4b**) $R_2 = (CH_2)_5$
(**4c**) $R_2 = O(CH_2CH_2)_2$
(**4d**) $R_2 = (CH_2)_4$



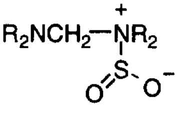
(5)



(**6**) R = H
(**7**) R = Me

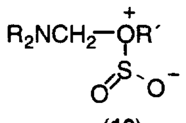


(**8a**) $R_2 = Me_2$
(**8b**) $R_2 = (CH_2)_5$
(**8c**) $R_2 = O(CH_2CH_2)_2$



$R_2NCH_2-\overset{+}{N}R_2-S(=O)O^-$

(9)



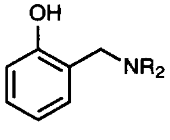
$R_2NCH_2-\overset{+}{O}R'-S(=O)O^-$

(10)

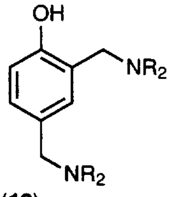
Following the successful use of sulfur dioxide in the aminoalkylation of aromatic heterocycles, it was anticipated that this methodology could be extended to phenols. The Mannich reaction of phenols has been extensively studied over the years and the precise reaction conditions needed have been shown to depend on the nucleophilicity of the phenol under investigation and also on the amine used. The introduction of the aminomethyl group usually occurs at an *ortho* position with resulting increase of electron density on the ring leading to polysubstitution which is reminiscent of Friedel-Crafts alkylation. For example, when phenol was heated at *ca* 60°C for 2 hours with aqueous dimethylamine and formalin, the 2,4,6-triaminoalkylated product was isolated in 86% yield.[9]

An investigation of the reactions of 3-pentadecylphenol with formaldehyde and a number of secondary amines revealed the stepwise introduction of dialkylaminomethyl groups.[10] An enhancement in the rates of reactions of various phenols was observed by increasing the amount of water in the medium. The involvement of an aminal as the reactive intermediate and the effect of water for the possible formation of an expanded cyclic transition state was suggested. The mechanism of the Mannich reaction involving phenols has been the subject of many investigations.[11] The condensation of 2,4-dimethylphenol with morpholine and formaldehyde at pH 9-10.45 supports the view that dimorpholinylmethane is the intermediate in the reaction.[12] The reaction of 2-naphthol with ethoxy-*N*-piperidylmethane in dioxan is, as far as we are aware, the only previously case of an aminol ether being used in a non-protic solvent.[13] Preformed iminium salts have been used in the presence of potassium carbonate in aprotic solvents for the regioselective *ortho*-aminoalkylation of monosubstituted electron rich phenols such as *ortho*-cresol and 2-t-butylphenol. It was suggested that solid-liquid phase transfer conditions exist in such systems and that the reactions proceed via a reactive "ion-pair" which collapses to give *ortho*-aminoalkylation products.[14]

As in the cases of π–excessive heterocycles we carried out our initial reactions by adding a large excess (22 mol. excess) of sulfur dioxide to a mixture of a phenol and an aminal or aminol ether in acetonitrile at room temperature. Parallel reactions were also carried out in the absence of sulfur dioxide in order to examine the relative acidity of the phenols and to monitor the effect of sulfur dioxide in the reaction. Although phenol and 2,4-dimethylphenol reacted with aminals in the absence of sulfur dioxide producing relatively low yields of the corresponding Mannich bases, the yields of the products were significantly improved in the presence of sulfur dioxide. On the other hand the presence of sulfur dioxide did not have the same effect in the reactions using aminol ethers, as shown in **Table 1**. It can be concluded that phenol and 2,4-dimethylphenol are not acidic enough to activate an aminal but the presence of sulfur dioxide implicates the participation of the dipolar species (**9**) which would account for the increased electrophilicity of the reagent affording reasonable yields of Mannich bases (**11-13**) under very mild conditions.



(11)



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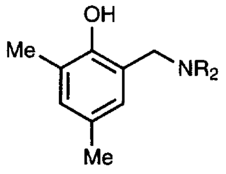


(13)

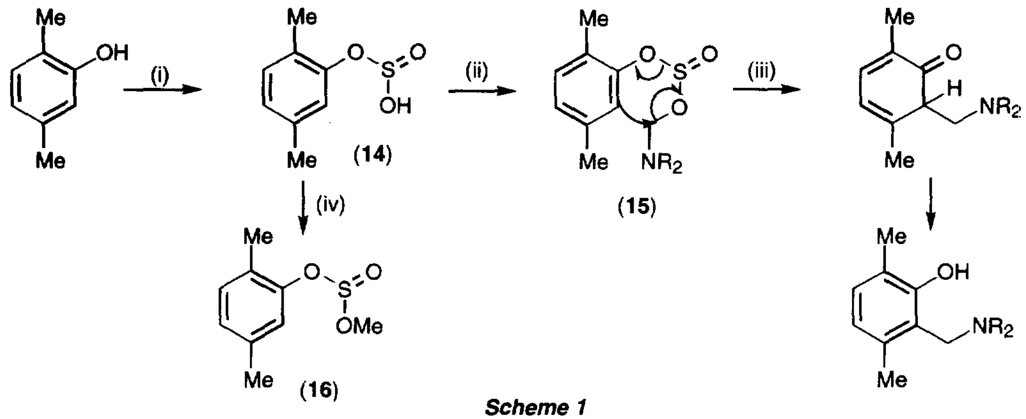
(**a**) $R_2 = Me_2$
(**b**) $R_2 = (CH_2)_5$
(**c**) $R_2 = Et_2$

These results stimulated our interest in an investigation of regioselectivity in the Mannich reactions of phenols and we turned our attention to 2,5-dimethylphenol because it provides two equally activated positions for aromatic electrophilic substitution, having an *ortho* and the *para* position vacant. It is reported in the literature,[15] that under classical aqueous conditions aminoalkylation takes place exclusively at the *para* position, although this result is questioned in Hellman and Opitz's book.[16] We confirmed the literature result. The effect of sulfur dioxide in the Mannich reaction of 2,5- dimethylphenol in non-aqueous aprotic conditions has been investigated in detail. As in the cases of other phenols we initially carried out reactions by adding a 22 molar excess of sulfur dioxide to the mixture of the reagent and 2,5-dimethylphenol in acetonitrile at room temperature. Again duplicate reactions were also carried out in the absence of sulfur dioxide. In each reaction three products were isolated indicating that amino-alkylation took place at all the available positions. It was noticed, however, that the presence of sulfur dioxide in the reaction mixture promoted aminoalkylation at the *ortho* position at the expense of reaction at the *para* position. This observation suggested that sulfur dioxide exerted some degree of regioselectivity towards the 2-position. The regioisomers, which may easily be identified by ^{1}H nmr spectroscopy, were not formed reversibly. Each product was allowed to stand at room temperature in acetonitrile in the presence or absence of sulfur dioxide for several days. After removing the solvent *in vacuo* the product was isolated unchanged: no isomerisation was detected by ^{1}H nmr spectroscopy.

Table 1 Reactions of Phenol and 2,4-Dimethylphenol

Phenol	**Reagent**	**SO_2** (Molar Ratio)	**Time (h)**	**Product(s) Yield (%)**	**% S.M. Recovered**
C_6H_5OH	$(Me_2N)_2CH_2$	22	42	**11a** (47); **12a** (6)	40
		0	41	**11a** (14); **12a** (0)	80
	$[(CH_2)_5N)_2CH_2$	22	42	**11b** (48); **12b** (9)	42
		0	41	**11b** (18); **12b** (0)	75
	$(CH_2)_5NCH_2OEt$	22	43	**11b** (51); **12b** (10)	43
		0	43	**11b** (62); **12b** (16)	23
2,4-$Me_2C_6H_3OH$	$(Me_2N)_2CH_2$	22	41	**13a** (59)	24
		0	42	**13a** (19)	78
	$[(CH_2)_5N)_2CH_2$	22	42	**13b** (68)	25
		0	42	**13b** (27)	67
	$(Et_2N)_2CH_2$	22	42	**13c** (72)	20
		0	42	**13c** (40)	54
	Et_2NCH_2OEt	22	42	**13c** (52)	46
		0	42	**13c** (51)	46

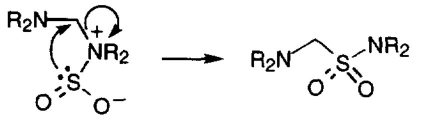
Although our initial nmr experiments indicated that both aminals and aminol ethers are relatively stable in the presence of sulfur dioxide at low temperatures later nmr experiments indicated that aminals and aminol ethers may react with sulfur dioxide above room temperature. It was possible that some of the Mannich reagent had been destroyed by the large excess of sulfur dioxide. It was decided, therefore, to alter the reaction conditions. The amount of sulfur dioxide was reduced and was added to 2,5-dimethylphenol 24 hours prior to the addition of the Mannich reagent. It was envisaged that the phenol could interact with sulfur dioxide forming a half-sulphite ester (**14**), and that after reaction with a Mannich reagent to form an aminol ester (**15**), collapse with the loss of sulfur dioxide as shown in **Scheme 1**, would afford exclusively the *ortho*-aminoalkylation product. Although our attempts to isolate the half-sulphite ester (**14**) failed, evidence for the formation of the intermediate was obtained by a reaction with diazomethane. A methoxy group was detected as a singlet at δ_H 3.63 ppm in the ^{1}H nmr spectrum of the crude reaction mixture which suggested the presence of the half-sulphinate ester (**16**).



Scheme 1

(i) SO_2, MeCN; (ii) R_2NCH_2OEt, - EtOH or $(R_2N)_2CH_2$, $-R_2NH$; (iii) $-SO_2$; (iv) CH_2N_2

A number of reactions were carried out with reduced amounts of sulfur dioxide and the results are summarised in **Table 2**. Although some attempt was made to optimise certain of the reactions further improvements may still be possible. The best reaction conditions attained involved the initial reaction of the phenol in acetonitrile with 2.2 mol. equivalents of sulphur dioxide at room temperature, followed by the addition of 2 molar excess of an aminol ether, followed by a brief period where the mixture was heated under reflux. It can be argued that as the temperature is raised both aminals and aminol ethers are converted by sulphur dioxide into products that cannot function as Mannich reagents. It is possible that the dipolar species (**9**) and (**10**) may undergo a rearrangement in which a carbon-sulphur bond is formed. Such a rearrangement process would resemble that involved in the formation of bisulphite adducts from aldehydes, ketones, and aminomethanesulphonic acids.[17]



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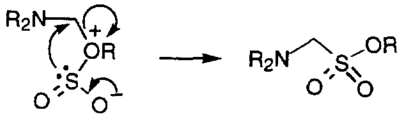

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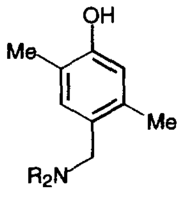

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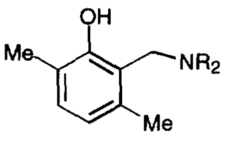

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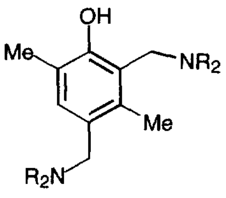

(19)

(a) $R_2 = Et_2$
(b) $R_2 = (CH_2)_5$
(c) $R_2 = O(CH_2CH_2)_2$
(d) $R_2 = (CH_2)_4$

TABLE 2. Reactions of 2,5-Dimethylphenol

Reagent (s)	Temp	Time	Products - Yield (%)			% S.M.
		(h)	17	18	19	recov.
$(Et_2N)_2CH_2$	r.t.	42	a (38)	a (22)	a (20)	19
$(Et_2N)_2CH_2 + SO_2$ (22mol)	r.t.	42	a (2)	a (42)	a (4)	19
Et_2NCH_2OEt	r.t.	42	a (31)	a (12)	a (10)	42
Et_2NCH_2OEt	reflux	2	a (28)	a (19)	a (6)	33
$Et_2NCH_2OEt + SO_2$ (22mol)	r.t.	42	a (9)	a (25)	a (17)	46
$Et_2NCH_2OEt + SO_2$ (2.2mol)	r.t.	42	a (0)	a (35)	a (21)	53
Et_2NCH_2OEt (2mol) + SO_2 (2.2mol)	reflux	2	a (0)	a (66)	a (0)	30
$[(CH_2)_5N]_2CH_2$	r.t.	42	b (24)	b (24)	b (10)	40
$[(CH_2)_5N]_2CH_2 + SO_2$ (22mol)	r.t.	42	b (7)	b (40)	b (21)	26
$(CH_2)_5NCH_2OEt$	r.t.	42	b (51)	b (17)	b (16)	11
$(CH_2)_5NCH_2OEt$	reflux	2	b (33)	b (31)	b (15)	16
$(CH_2)NCH_2OEt + SO_2$ (22mol)	r.t.	42	b (25)	b (18)	b (26)	28
$(CH_2)_5NCH_2OEt$ (1.5mol)+ SO_2 (2.2mol)	reflux	0.5	b (0)	b (67)	b (19)	15
$O(CH_2CH_2)NCH_2OEt$ (2mol) + SO_2 (2.2mol)	reflux	2	c (0)	c (59)	c (17)	21
$(CH_2)_4NCH_2OEt$ (2mol)+ SO_2 (2.2mol)	reflux	2	d (0)	d (48)	d (20)	31

In conclusion, the results presented herein demonstrate that the presence of sulfur dioxide can provide a mild method for the activation of Mannich reagents in reactions with nucleophilic aromatic compounds and also provide the means of controlling regioselective Mannich reactions of phenols under very mild conditions.

Acknowledgements

We thank the University for research training awards (to G.P. and R.F.W.) and Dr D.W. Payling (the former Fisons plc) for help in obtaining some mass spectra.

Experimental

Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer; only selected absorbances are reported. Spectra were recorded as thin films (film) or nujol mulls (nujol) ^1H nmr Spectra were recorded on Varian EM 360 A (60 MHz) or Bruker ACF-250 (250 MHz) spectrometers and ^{13}C nmr spectra were recorded on Bruker WP 80 (20.1 MHz) together with off resonance decoupling or Bruker ACF-250 (62.9 MHz) spectrometers in $CDCl_3$ using TMS as a reference unless otherwise stated. The values of coupling constants are given in Hz and multiplicities are reported as singlet (s), doublet (d), triplet (t), double triplet (dt), quartet (q), multiplet (m). Mass spectra were recorded by electron impact using a Kratos (M.S.80) spectrometer or by fast atom bombardment (FAB) using a V.G.70-250 S spectrometer. Melting Points were recorded using a Kofler hot stage apparatus and are uncorrected.

Reactions of Heterocycles in the Presence of Sulphur Dioxide—General Method

Sulphur dioxide (22 molar excess), was added to a mixture of heterocycle (1.1 equiv.) and an aminal or an aminol ether (1 equiv.) in acetonitrile under dry nitrogen at 0°C. The mixture was allowed to stand at room temperature for a specified length of time, quenched with water and concentrated *in vacuo*. The residue was acidified to pH 2 with 2M HCl when necessary, washed with dichloromethane (3x30 ml) and then basified with 4M NaOH and extracted with dichloromethane (4x40 ml). The combined organic extracts from the basic solution were dried, concentrated *in vacuo*, and the residue was distilled (Kugelrohr) or recrystallised from a suitable solvent. All of the compounds produced in reactions with N-methylpyrrole, indole and 2-methylfuran were characterised by the identity of spectroscopic data with those reported for the same compounds previously.[6b]

Reaction of *N*-Methylpyrrole with Bis(*N*,*N*-dimethylamino)methane

A mixture of sulphur dioxide (25 ml), *N*-methylpyrrole (2.23g, 27.5 mmol) and bis(*N*,*N*-dimethylamino)-methane (2.56g, 25 mmol) in acetonitrile (75 ml) for 4 days afforded *2-(N,N-dimethylaminomethyl)-1-methylpyrrole* (**4a**) (1.99g, 58%), b.p. 58°C/5mmHg, (lit.[18] 53-54°C/6mmHg) and *2,5-bis(N,N-dimethylaminomethyl)-1-methylpyrrole* (**8a**) (0.09g, 4%), b.p. 87°C/3mmHg, (lit.[18] 87-88°C/3.5mmHg).

Reaction of *N*-methylpyrrole with Di(*N*-piperidinyl)methane

A mixture of sulphur dioxide (25 ml), *N*-methylpyrrole (2.23g, 27.5 mmol) and di(*N*-piperidinyl)methane (4.56g, 25 mmol) in acetonitrile (75 ml) for 4 days gave *2-(N-piperidinylmethyl)-1-methylpyrrole* (**4b**) (3.30g, 74%), b.p. 120°C/5mmHg, (lit.[18] 97°C/5mmHg) and *2,5-bis(N-piperidinyl-methyl)-1-methylpyrrole* (**8b**) (0.23g, 7%), b.p. 150°C/0.4mmHg, (lit.[18] 165-167°C/3mmHg).

Reaction of *N*-Methylpyrrole with Di(*N*-morpholinyl)methane

A mixture of sulphur dioxide (15 ml), *N*-methylpyrrole (1.22g, 15 mmol) and di(*N*-morpholinyl)methane (2.25g, 12.5 mmol) in acetonitrile (75 ml) for 3 days afforded *2-(N-morpholinylmethyl)-1-methylpyrrole* (**4c**) (1.11g, 49%), b.p. 100°C/0.5mmHg, (lit.[18] 110°C/3.5mmHg) and *2,5-bis(N-morpholinylmethyl)-1-methylpyrrole* (**8c**) (0.17g, 10%), m.p. 70-72°C (from ethyl acetate) (lit.[6b] 70-72°C).

2-(*N*-Pyrrolidinylmethyl)-1-methylpyrrole (4c)

A mixture of sulphur dioxide (25 ml), *N*-methypyrrole (2.23g, 27.5 mmol) and di(*N*-pyrrolidinyl)methane (3.86g, 25 mmol) in acetonitrile (75 ml) for 4 days gave the *title compound* as a colourless oil (3.40g, 83%), b.p. 100°C/4mmHg (lit.[6b] 100°C/4mmHg).

5-Methyl-2-(*N*-pyrrolidinylmethyl)furan (5)

A mixture of sulphur dioxide (20 ml), 2-methylfuran (1.81g, 22 mmol) and ethoxy-*N*-pyrrolidinylmethane (2.58g, 20 mmol) in acetonitrile (70 ml) for 2 days afforded the *title compound* as a colourless oil (2.25g, 68%), b.p. 72-74°C/2.8mmHg (lit.[6b] 72-74°C/2.8mmHg).

3-(*N*,*N*-Dimethylaminomethyl)indole (6)

A mixture of sulphur dioxide (50 ml), indole (5.86g, 50 mmol) and bis(*N*,*N*-dimethylamino)methane (5.11g, 50 mmol) in acetonitrile (150 ml) for 4 days gave the *title compound* as a white solid (8.36g, 96%), m.p. 134-135°C, (from acetone), (lit.[19] m.p. 134°C).

3-(*N,N*-Dimethylaminomethyl)-1-methylindole (7)

A mixture of sulphur dioxide (20 ml), *N*-methylindole (2.62g, 20 mmol) and bis(*N,N*-dimethylamino)methane (2.04g, 20 mmol) in acetonitrile (120 ml) for 2 days afforded the *title compound* as a pale yellow oil (3.03g, 81%), b.p. 98°C/0.2mmHg, (lit.^{20} b.p. 94-96°C/0.2mmHg).

Reactions of Phenol and 2,4-Dimethylphenol in the Presence of Sulphur Dioxide

General Method (A)

Sulphur dioxide (22 molar excess) was added to a mixture of the phenol (1.1 equiv.) and the Mannich reagent (1.0 equiv.) in acetonitrile at 0°C under dry nitrogen. The mixture was then allowed to stand at room temperature for a specified length of time. Water (20 ml) was added and the solvent was removed *in vacuo*. The residue was acidified to pH 1 with 2M hydrochloric acid and was extracted with ether (3 x 30 ml). The combined organic extracts were dried and concentrated *in vacuo* to give the unreacted phenol. The aqueous layer was then carefully basified to pH9 with 2M NaOH and extracted with ether (3 x 40 ml). The combined organic extracts were dried, concentrated *in vacuo*, and the residue was distilled (Kugelrohr) or recrystallised from a suitable solvent.

Reaction of Phenol with Bis(*N,N*-dimethylamino)methane

Phenol (2.59g, 27.5 mmol), bis(*N,N*-dimethylamino)methane (2.56g, 25 mmol) and sulphur dioxide (25 ml) in acetonitrile (75 ml) for 42 hours gave two products after Kugelrohr distillation. First fraction *2-(N,N-dimethylaminomethyl)phenol* (**11a**) (1.77g, 47%), b.p. 60°C/5mmHg, (lit.^{14} b.p. 100-101°C/12mmHg); δ_H (60 MHz) 2.27 (6H, s, NCH_3), 3.55 (2H, s, CH_2N), 6.67-7.30 (4H, m, PhH) and 10.47 (1H, s, D_20 ex. OH) ppm; δ_C (20.1 MHz) 42.2 (q, NCH_3), 62.7 (t, CH_2N), 116.1 (d, C-6), 119.1 (d, C-4), 128.4 (s, C-2), 128.8 (d, C-5), 129.6 (d, C-3), and 158.2 (s, C-1) ppm; (m/z); 151 (M^+, 100%), M^+ measured 151.0989; Calc. for $C_9H_{13}NO$ 151.0997.

Second fraction *2,4-bis(N,N-dimethylaminomethyl)phenol* (**12a**) (0.15g, 6%), b.p. 110°C/0.3mmHg, δ_H (60 MHz) 2.27 (12H, s, NCH_3), 3.43 (2H, s, CH_2N), 3.57 (2H, s, CH_2N), 6.60-7.27 (3H, m, PhH), and 9.17 (1H, br.s. D_2O ex. OH) ppm; (m/z); 208 (M^+, 34.1%) 164 (100) M^+ measured 208.1581; $C_{12}H_{20}N_2O$ requires 208.1575.

Reaction of Phenol with Ethoxy-*N*-piperidinylmethane

Phenol (2.35g, 25 mmol), ethoxy-*N*-piperidinylmethane (3.58g, 25 mmol) and sulphur dioxide (25 ml) in acetonitrile (75 ml) at room temperature for 43 hours gave two products after Kugelrohr distillation. First fraction *2-(N-piperidinylmethyl)phenol* (**11b**) (2.44g, 51%), b.p. 100°C/2mmHg; ν_{max} (film) 3340 (OH), 1590 (aromatic ring) cm^{-1}; δ_H (60 MHz) 1.07-1.83 (6H, m, 3′-H, 4′-H, and 5′-H), 2.10-2.63 (4H, m, 2′-H and 6′-H), 3.55 (2H, s, CH_2N), 6.47-7.30 (4H, m, PhH), and 11.0 (1H, s, D_2O ex. OH) ppm; δ_C (20.1M) 24.0 (t, C-4′), 25.8 (t, C-3′and C-5′), 53.7 (t, C-2′and C-6′), 62.1 (t, CH_2N), 116.0 (d, C-6), 118.8 (d, C-4), 121.6 s, C-2), 128.5 (d, C-5), 129.4 (d, C-3, and 158.3 (s, C-1) ppm; (m/z); 191 (M^+, 100%), M^+ measured 191.1313; $C_{12}H_{17}NO$ requires 191.1310.

Second fraction *2,4-di(N-piperidinylmethyl)phenol* (**12b**) (0.35g, 10%), b.p. 150°C/0.2mmHg; δ_H (60 MHz) 1.27-1.80 (12H, m, 3′-H, 4′-H, and 5′-H), 2.20-2.63 (8H, m, 2′-H and 6′-H), 3.38 (2H, s, 4-CH_2N), 3.60 (2H, s, 2-CH_2N), 6.50-7.20 (3H, m, PhH), and 10.27 (1H, br.s. D_2O ex. OH) ppm; (m/z); 288 (M^+, 1.0%), 84 (100), M^+ measured 288.2189; $C_{18}H_{28}N_2O$ requires 288.2201.

2-(*N*,*N*-Dimethylaminomethyl)-4,6-dimethylphenol (13a)

2,4-Dimethylphenol (2.69g, 22 mmol), bis(*N*,*N*-dimethylamino)methane (2.04g, 20 mmol) and sulphur dioxide (22 ml) in acetonitrile (75 ml) for 41 hours gave the *title compound* as colourless oil (2.13g, 59%), b.p. 70°C/0.5mmHg, (lit.[21] b.p. 90°C/0.9mmHg); ν_{max} (film) 3304 (OH), 1610 (aromatic ring) cm^{-1}; δ_H (60 MHz) 2.23 (6H, s, CH_3), 2.30 (6H, s, NCH_3), 3.53 (2H, s, $ArCH_2$), 6.50-6.67 (1H, br.s, 3-H), 6.77-6.94 (1H, br.s, 5-H), and 10.63 (1H, br.s, D_2O ex. OH) ppm; δ_C (20.1 MHz) 15.6 (q, 4-CH_3), 20.4 (q, 6-CH_3), 44.2 (q, NCH_3), 63.0 (t, $ArCH_2$), 121.0 (s, C-6), 124.3 (s, C-2), 126.5 (d, C-3), 127.1 (s, C-4), 130.7 (d, C-5), and 154.0 (s, C-1) ppm; (m/z); 179 (M^+, 100%) M^+ measured 179.1304; Calc. for $C_{11}H_{17}NO$ 179.1310.

2-(*N*-Piperidinylmethyl)-4,6-dimethylphenol (13b)

2,4-Dimethylphenol (2.44g, 20 mmol), di(*N*-piperidinyl)methane (4.01g, 22 mmol) and sulphur dioxide (20 ml) in acetonitrile (75 ml) for 42 hours afforded the *title compound* as colourless oil (3.01g, 68%), b.p. 110°C/0.2mmHg (lit.[22], m.p. 90°C, maleate salt); ν_{max} (film) 3310 (OH), 1608 (aromatic ring) cm^{-1}; δ_H (60 MHz) 1.26-1.87 (6H, m, 3'-H, 4'-H, and 5'-H), 2.22 (6H, s, 4 and 6-CH_3), 2.28-2.33 (4H, m, 2'-H and 6'-H), 3.58 (2H, s, $ArCH_2$), 6.50-6.63 (1H, br.s, 3-H), 6.77-6.93 (1H, br.s, 5-H), and 10.87 (1H, br.s, D_2O ex. OH) ppm; δ_C (20.1 MHz) 15.7 (q, 4-CH_3), 20.4 (q, 6-CH_3), 24.1 (t, C-4'), 26.0 (t, C-3'and C-5'), 53.8 (t, C-2'and C-6'), 62.3 (t, $ArCH_2$), 120.6 (s, C-6), 124.3 (s, C-2), 126.6 (d, C-3), 127.1 (s, C-4), 130.5 (d, C-5), and 154.0 (s, C-1) ppm; (m/z): 219 (M^+, 48%), 84 (100), M^+ measured 219.1613; $C_{14}H_{21}NO$ requires 219.1623.

2-(*N*,*N*-Diethylaminomethyl)-4,6-dimethylphenol (13c)

2,4-Dimethylphenol (2.44g, 20 mmol), 2,5-bis(*N*,*N*-diethylamino)methane (3.48g, 22 mmol) and sulphur dioxide (20 ml) in acetonitrile (60 ml) at room temperature for 42 hours afforded *title compound* as colourless oil (2.99g, 72%), b.p. 90°C/0.1mmHg; ν_{max} (film) 3308 (OH), 1610 (aromatic ring) cm^{-1}; δ_H (60 MHz) 1.10 (6H, t, *J* 7.5 NCH_2CH_3), 2.23 (6H, s, 4 and 6-CH_3), 2.63 (4H, q, *J* 7.5, NCH_2CH_3), 3.70 (2H, s, $ArCH_2$), 6.57-6.73 (1H, br.s, 3-H), 5.80-5.97 (1H, br.s, 5-H), and 10.93 (1H, br.s, D_2O ex., OH) ppm; δ_C (20.1 MHz) 11.3 (q, NCH_2CH_3), 15.6 (q, 4-CH_3), 20.4 (q, 6-CH_3), 46.4 (t, NCH_2CH_3), 57.0 (t, $ArCH_2$), 121.2 (s, C-6), 124.3 (s, C-2), 126.6 (d, C-3), 127.1 (s, C-4), 130.4 (d, C-5), and 154.2 (s, C-1) ppm; (m/z); 207 (M^+, 49.9%), 58 (100), M^+ measured 207.1615; $C_{13}H_{21}NO$ requires 207.1623.

Reactions of 2,5-Dimethylphenol in the Presence of Sulphur Dioxide

General Method (B)

2,5-Dimethylphenol (1 equiv.), an aminal or aminol ether (1.1 equiv.) and sulphur dioxide (specified molar ratio) in acetonitrile were allowed to react at room temperature or under reflux for a specified length of time. Following the work-up procedure described above (General Method A) the crude product was isolated as an oily solid. Recrystallisation from petroleum ether (40-60°C) afforded the *para-* substituted Mannich bases (**17a-b**). The mother liquor was then concentrated *in vacuo* and the residue was distilled (Kugelrohr) to give the *ortho*-isomers (**18a-d**), and the 2,4-disubstituted products (**19a-d**) were isolated by Kugelrohr distillation or recrystallisation from a suitable solvent.

Reaction of 2,5-Dimethylphenol with Ethoxy-*N,N*-diethylaminomethane

2,5-Dimethylphenol (3.05g, 25 mmol), ethoxy-*N,N*-diethylaminomethane (3.61g, 27.5 mmol) and sulphur dioxide (25 ml) in acetonitrile (75 ml) at room temperature for 42 hours afforded three products.

First product *4-(N,N-diethylaminomethyl)-2,5-dimethylphenol* (**17a**) (0.49g, 9%), m.p. 104-105°C (from petroleum ether 40-60°C), ν_{max} (nujol) 3040 (OH), 1610 (aromatic ring) cm^{-1}; δ_H (60 MHz) 1.10 (6H, t, *J* 7.5, $NCH_2C\mathit{H}_3$), 2.13 (6H, s, 2 and 5-CH_3), 2.62 (4H, q, *J* 7.5, $NC\mathit{H}_2CH_3$), 3.38 (2H, s, CH_2N), 6.07 (1H, s, 6-H), 6.82 (1H, s, 3-H), and 6.93 (1H, s, D_2O ex. OH) ppm; δ_C (20.1 MHz) 11.0 (q, $NCH_2\mathit{C}H_3$), 16.0 (q, 5-CH_3), 19.4 (q, 2-CH_3), 46.6 (t, $N\mathit{C}H_2CH_3$), 54.9 (t, 4-CH_2N), 118.4 (d, C-6), 122.4 (s, C-2), 127.7 (s, C-4), 133.5 (d, C-3), 136.1 (s, C-5), and 154.2 (s, C-1) ppm; (m/z); 207 (M$^+$, 20.6%), 135 (100), M$^+$ measured 207.1629; $C_{13}H_{21}NO$ requires 207.1623.

Second product *6-(N,N-diethylaminomethyl)-2,5-dimethylphenol* (**18a**) (2.12g, 25%), b.p. 110°C/ 0.2mmHg; ν_{max} (film) 3040 (OH), 1610 (aromatic ring) cm^{-1}; δ_H (60 MHz) 1.12 (6H, t, *J* 7.5, $NCH_2C\mathit{H}_3$), 2.23 (6H, s, 2 and 5-CH_3), 2.63 (4H, q, *J* 7.5, $NC\mathit{H}_2CH_3$), 3.77 (2H, s, 6-CH_2N), 6.53 (1H, d, J_{AB} 8, 4-H), 6.93 (1H, d, J_{AB} 8, 3-H), and 11.90 (1H, s, D_2O ex. OH) ppm; δ_C (20.1 MHz) 11.3 (q, $NCH_2\mathit{C}H_3$), 15.6 (q, C-5-CH_3), 19.5 (q, 2-CH_3), 46.5 (q, $N\mathit{C}H_2CH_3$), 52.8 (t, 6-CH_2N), 119.4 (s, C-6), 120.3 (d, C-4), 122.8 (s, C-2), 129.1 (d, C-3), 133.7 (s, C-5), and 157.1 (s, C-1) ppm; (m/z); 207 (M$^+$, 23.5%), 58 (100), M$^+$ measured 207.1629; $C_{13}H_{21}NO$ requires 207.1623.

Third product *4,6-bis(N,N-diethylaminomethyl)-2,5-dimethylphenol* (**19a**) (0.63g, 17%), b.p. 150°C/ 0.1mmHg; ν_{max} (film) 3420 (OH), 1614 (aromatic ring) cm^{-1}; δ_H (60 MHz) 1.12 (12H, t, *J* 7.5, $NCH_2C\mathit{H}_3$), 2.10 and 2.20 (6H, s, 2 and 5-CH_3), 2.53 (8H, q, *J* 7.5, $NC\mathit{H}_2CH_3$), 3.43 (2H, s, 4-CH_2N), 3.80 (2H, s, 6-CH_2N), 6.93 (1H, s, 3-H), and 7.73 (1H, br.s, D_2O ex., OH) ppm; δ_C (20.1 MHz) 11.4 (q, $NCH_2\mathit{C}H_3$), 14.7 (q, 5-CH_3), 15.6 (q, 2-CH_3), 46.5 (t, $N\mathit{C}H_2CH_3$), 53.1 (t, 6-CH_2N), 56.5 (t, 4-CH_2N), 119.7 (s, C-6), 121.2 (s, C-2), 127.3 (s, C-4), 132.0 (d, s, C-3), 133.3 (s, C-5), and 155.9 (s, C-1) ppm; (m/z); 292 (M$^+$, 6.2%), 84 (100), M$^+$ measured 292.2514; $C_{18}H_{32}N_2O$ requires 292.2515.

Reaction of 2,5-Dimethylphenol with Ethoxy-*N*-piperidinylmethane

2,5-Dimethylphenol (3.05g, 25 mmol), ethoxy-*N*-piperidinylmethane (3.94g, 27.5 mmol) and sulphur dioxide (25 ml) in acetonitrile (75 ml) at room temperature for 42 hours afforded three products.

First product *4-(N-piperidinylmethyl)-2,5-dimethylphenol* (**17b**) (1.39g, 25%), m.p. 132-134°C from petroleum ether (40-60°C), (lit.[15], m.p. 131.5-132°C); ν_{max} (nujol) 3064 (OH), 1616 (aromatic ring) cm^{-1}; δ_H (60 MHz) 1.30-1.53 (6H, m, 3′-H, 4′-H, and 5′-H), 2.13 (6H, s, CH_3), 2.27-2.63 (4H, m, 2′-H and 6′-H), 3.30 (2H, s, $ArCH_2$), 5.57 (1H, br.s, D_2O ex., OH), 6.12 (1H, s, 6-H), and 6.88 (1H, s, 3-H) ppm; δ_C (20.1 MHz) 15.4 (q, 5-CH_3), 18.8 (q, 2-CH_3), 24.1 (t, C-4′), 25.0 (t, C-3′and C-5′), 54.6 (t, C-2′and C-6′), 60.5 (t, 4-CH_2N), 117.6 (d, C-6), 121.5 (s, C-2), 126.4 (s, C-4), 133.0 (d, C-3), 135.7 (s, C-5), and 153.4 (s, C-1) ppm; (m/z); 219 (M$^+$, 40.2%), 134 (100), M$^+$ measured 219.1612; $C_{14}H_{21}NO$ requires 219.1623.

Second product *6-(N-piperidinylmethyl)-2,5-dimethylphenol* (**18b**) (0.99g, 18%), b.p. 110°C/0.2mmHg, ν_{max} (film) 3040 (OH), 1616 (aromatic ring) cm^{-1}; δ_H (60 MHz) 1.37-1.63 (6H, m, 3′-H, 4′-H, and 5′-H), 2.20 (6H, s, CH_3), 2.18-2.57 (4H, m, 2′-H and 6′-H), 3.67 (2H, s, $ArCH_2$), 6.52 (1H, d, J_{AB} 8, 4-H), 6.93 (1H, d, J_{AB} 8, 3-H) and 10.93 (1H, br.s, D_2O ex. OH) ppm; δ_C (20.1 MHz) 15.7 (q, C-5-CH_3), 19.5 (q, 2-CH_3), 24.0 (t, C-4′), 25.8 (t, C-3′and C-5′), 53.8 (t, C-2′and C-6′), 57.9 (t, $ArCH_2$), 118.8 (s, C-6), 120.3

(d, C-4), 122.5 (s, C-2), 129.1 (d, C-3), 133.6 (s, C-5), and 156.8 (s, C-1) ppm; (m/z); 219 (M^+, 0.4%), 98 (100), M^+ measured 219.1612; $C_{14}H_{21}NO$ requires 219.1623.

Third product *4,6-bis(N-piperidinylmethyl)-2,5-dimethylphenol* (**19b**) (1.25g, 31%), b.p. 160°C /0.1mmHg; δ_H (60 MHz) 1.00-1.87 (12H, m, 3′, 3″, 4′, 4″, 5′, 5″-H), 2.20 (s, 6H, CH_3), 2.27-2.73 (8H, m, 2′, 2″, 6′, and 6″-H), 3.30 (2H, s, 4-CH_2N), 3.72 (2H, s, 2-CH_2N), 6.88 (1H, s, 3-H), and 11.17 (1H, br.s, D_2O ex. OH) ppm; δ_C (20.1 MHz) 14.7 (q, C-5-CH_3), 15.6 (q, 2-CH_3), 24.0 (t, C-4″), 24.6 (t, C-4′), 25.8 (t, C-3″ and C-5″), 26.1 (t, C-3′and C-5′), 53.8 (t, C-2″ and C-6″), 54.4 (t, C-2′and C-6′), 58.3 (t, 6-CH_2N), 62.4 (t, 4-CH_2N), 119.3 (s, C-6), 121.1 (s, C-2), 126.7 (s, C-4), 131.9 (d, C-3), 133.5 (s, C-5), and 155.8 (s, C-1) ppm; (m/z); 316 (M^+, 20.6%), 232 (100), M^+ measured 316.2517; $C_{20}H_{32}N_2O$ requires 316.2515.

Reaction of 2,5-Dimethylphenol with Ethoxy-*N*-morpholinylmethane

2,5-Dimethylphenol (2.44g, 20 mmol), sulphur dioxide (2 ml) and ethoxy-*N*-morpholinylmethane (5.81g, 40 mmol) were heated under reflux in acetonitrile (80 ml) for 2 hours to afford the crude product as a white solid. Recrystallisation from ethyl acetate gave *6-(N-morpholinylmethyl)-2,5-dimethylphenol* (**18c**) (2.62g, 59%), m.p. 98-99°C (lit.[23], hydrochloride salt m.p. 188-90°C, from isopropanol), ν_{max} (nujol) 3040 (OH), 1610 (aromatic ring) cm^{-1}; δ_H (60 MHz) 2.20 (6H, s, 2 and 5-CH_3), 2.33-2.73 (4H, m, 3′-H and 5′-H), 3.50-3.90 (2H, s, CH_2N and 4H, m, 2′-H and 6′-H), 6.53 (1H, d, J_{AB} 8, 4-H), 6.93 (1H, d, J_{AB} 8, 3-H), and 10.07 (1H, br.s, D_2O ex. OH) ppm; δ_C (20.1 MHz) 15.6 (q, 5-CH_3), 19.5 (q, 2-CH_3), 52.8 (t, C-3′and C-5′), 57.5 (t, 6-CH_2N), 66.7 (t, C-2′and C-6′), 118.0 (s, C-6), 120.8 (d, C-4), 122.7 (s, C-2), 129.5 (d, C-3), 133.9 (s, C-5), and 156.3 (s, C-1) ppm; (m/z); 221 (M^+, 72.2%), 134 (100), M^+ measured 221.1416; $C_{13}H_{19}NO_2$ requires 221.1405.

The mother liquor was concentrated *in vacuo* to yield a white solid which was recrystallised from water to give *4,6-bis(N-morpholinylmethyl)-2,5-dimethylphenol* (**19c**) (1.07g, 17%)., m.p. 115-116°C, (lit.[23], dihydrochloride salt m.p. 236-7°C, from aqueous isopropanol); δ_H (250 MHz) 2.17 (3H, s, 2-CH_3), 2.23 (3H, s, 5-CH_3), 2.38-2.56 (8H, s, 2′-H and 6′-H), 3.34 (2H, s, 4-CH_2N), 3.64-3.77 (8H, m, 3′-H and 5′-H), 3.75 (2H, s, 6-CH_2N), and 6.88 (1H, s, 3-H) ppm; δ_C (62.9 MHz) 14.8 (5-CH_3), 15.5 (2-CH_3), 52.8 (C-3″ and C-5″), 53.5 (C-3′and C-5′), 57.8 (6-CH_2N), 62.0 (4-CH_2N), 66.8 (C-2″ and C-6″), 67.1 (C-2′and C-6′), 118.6 (C-6), 121.4 (C-2), 126.2 (C-4), 132.4 (C-3), 133.8 (C-5), and 155.4 (C-1) ppm; (m/z); 320 (M^+, 25%), 234 (100), M^+ measured 320.2097; $C_{18}H_{28}N_2O_3$ requires 320.2100.

Reaction of 2,5-Dimethylphenol with Ethoxy-*N*-pyrrolidinylmethane

2,5-Dimethylphenol (2.44g, 20 mmol), sulphur dioxide (2 ml) and ethoxy-*N*-pyrrolidinylmethane (5.17g, 40 mmol) in acetonitrile (80 ml) were heated under reflux for 2 hours giving two products after Kugelrohr distillation. First fraction *6-(N-pyrrolidinylmethyl)-2,5-dimethylphenol* (**18d**) (1.98g, 48%), b.p. 120°C/ 0.2mmHg; δ_H (60 MHz) 1.63-2.00 (4H, m, 3′-H and 4′-H), 2.20 (6H, s, 2 and 5-CH_3), 2.40-2.78 (4H, m, 2′ and 5′-H), 3.80 (2H, s, CH_2N), 6.38 (1H, d, J_{AB} 8, 4-H), 6.78 (1H, d, J_{AB} 8, 3-H), and 11.50 (1H, s, D_2O ex. OH) ppm; δ_C (20.1 MHz) 15.7 (q, 5-CH_3), 19.4 (q, 2-CH_3), 23.7 (t, C-3′ and C-4′), 53.5 (t, C-2′ and C-5′), 54.7 (t, CH_2N), 119.6 (s, C-6), 120.3 (d, C-4), 122.5 (s, C-2), 129.1 (d, C-3), 133.0 (s, C-5), and 156.8 (s, C-1) ppm; (m/z); 205 (M^+, 65.9%), 70 (100), 134 (78.8%), M^+ measured 205.1456; $C_{13}H_{19}NO$ requires 205.1466.

Second fraction *4,6-bis(N-pyrrolidylmethyl)-2,5-dimethylphenol* (**19d**) (1.16g, 20%), b.p. 140°C/ 0.02mmHg; δ_H (60 MHz) 1.67-2.00 (8H, m, 3′-H and 4′-H), 2.17 and 2.23 (3H, s, 2 and 5-CH_3), 2.47-2.83 (8H, m, 2′-H and 5′-H), 3.53 (2H, s, 4-CH_2N), 3.83 (2H, 6-CH_2N), 6.93 (1H, s, 3-H), and 10.00 (1H, br.s. D_2O ex. OH) ppm; (m/z); 288 (M^+, 0.1%), 70 (100), M^+ measured 288.2082; $C_{18}H_{28}N_2O$ requires 288.2201.

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