Synthesis of Dihydrobenzofurans from Phenolic Mannich Bases and their Quaternized Derivatives

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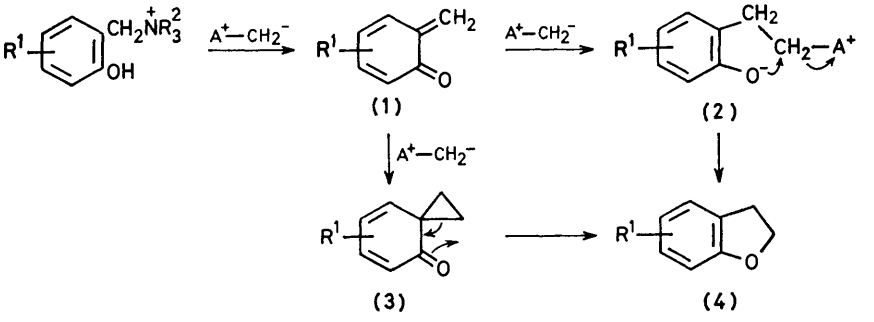
Reaction of dimethylsulphoxonium methylide with quaternized derivatives of phenolic Mannich bases, and in certain cases with the bases themselves, constitutes a useful synthesis of dihydrobenzofurans. On the other hand treatment of those same quaternized derivatives with diazomethane may be a useful alternative procedure for the preparation of coumarans with base-sensitive groups.

SOME time ago, while working with colchicine derivatives, we described the preparation of a dihydrofurothiocolchicine through the reaction of diazomethane with a Mannich base methiodide derived from 3-demethylthiocolchicine.[1]

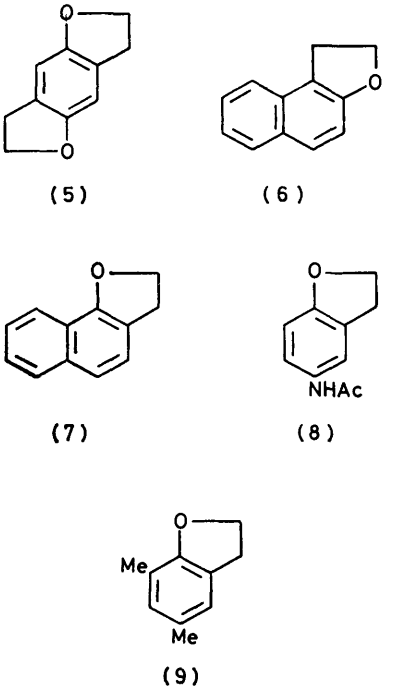


Owing to the mild conditions required, this new type of cyclization induced by diazomethane seemed to be an interesting method of access to coumarans which are otherwise difficult to obtain.[2] Almost at the same time as our initial report appeared the preparation of dihydrobenzofurans from phenolic Mannich base methiodides was described by two groups of workers.[3,4]

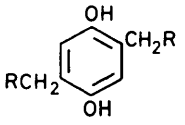
In those cyclizations involving carbenoid reagents $A^+-CH_2^-$ and the methiodides of phenolic Mannich bases the quinone methide (1) is generally supposed to be the intermediate.[1,4] Michael addition of the reagent to give the betaine (2), or the formation of an unstable spiroketone (3), can finally lead to the dihydrobenzofuran (4).

Intramolecular displacement in the betaines (2) to afford coumarans is a known reaction,[5] and the well documented isomerization of cyclopropyl ketones and cyclopropyl aldehydes to dihydrofurans[6] shows that rearrangement of (3) to (4) is also a feasible process.

As a continuation of our first observation and in order to compare the two methods we report now on the preparation of some simple coumarans, namely 2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b'*]difuran (5), 1,2-dihydronaphtho[2,1-*b*]furan (6), 2,3-dihydronaphtho[1,2-*b*]furan (7), 5-acetamido-2,3-dihydrobenzo[1,2-*b*]furan (8), and 2,3-dihydro-5,7-dimethylbenzo[1,2-*b*]furan (9), by the reaction of Mannich bases, Mannich base methiodides, and Mannich base *N*-oxides derived from hydroquinone, 2-naphthol, 1-naphthol, 4-acetamidophenol, and 2,4-dimethylphenol with diazomethane and with dimethylsulphoxonium methylide. In the case of hydroquinone derivatives the reactions leading to the coumaran (5) were carried out only with the dimethiodide (10f). For comparison purposes we also used, in some reactions, 1-hydroxymethyl-2-naphthol (11a) and 1-morpholinomethyl-2-naphthol hydrochloride (10e).HCl. In theory,



quaternized derivatives of phenolic Mannich bases other than their methiodides, such as their simple salts or their *N*-oxides, should react in the same manner as the methiodides, and even the bases themselves, when



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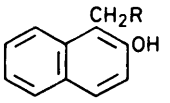

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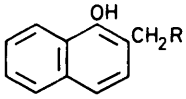

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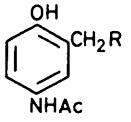

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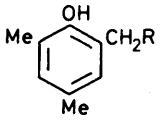

(14)

a; R = OH
b; R = NMe_2
c; R = NEt_2
d; R = $\overline{N{\cdot}[CH_2]_4{\cdot}CH_2}$
e; R = $\overline{N{\cdot}[CH_2]_2{\cdot}O{\cdot}[CH_2]_2}$
f; R = $NMe_2{\cdot}MeI$
g; R = $NEt_2{\cdot}MeI$
h; 
i; 
j; R = $N(O)Me_2$
k; R = $N(O)Et_2$
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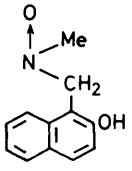
m; R = 

treated with a sufficiently strong base, might give rise to the quinone methides. Analogously, (11a) could also behave as a source of quinone methide by undergoing loss of water.

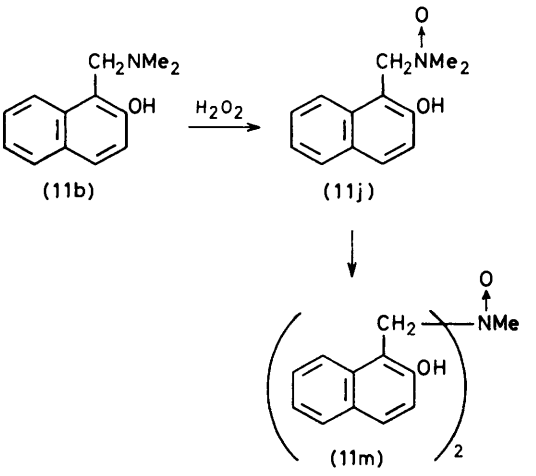
RESULTS AND DISCUSSION

The Mannich bases (10b), (11b—e), (12b—e), (13b—e), and (14b) were mostly known products, which were prepared according to literature methods. We were unable to isolate 2-dimethylaminomethyl-1-naphthol (12b) or 2-diethylaminomethyl-1-naphthol (12c) in an analytically pure form. After purification by column chromatography on silica gel the oily bases showed only small amounts of impurities and were used subsequently in this form. The two bases (12b,c) were characterized as their hydrochlorides.

Purification of the methiodides (10f), (11f), (13f—i), and (14f), which gave satisfactory N analyses, was not attempted (in order to avoid decomposition) and they were used directly in the crude form. It was not possible, under normal reaction conditions, to quaternize 1-piperidinomethyl-2-naphthol (11d) with methyl iodide, nor 4-acetamido-2-diethylaminomethylphenol (13c) with ethyl iodide. Attempts to N-methylate Mannich bases from 1-naphthol led mainly to decomposition products.

The *N*-oxides (11j), (11l,m), (13j,k), and (14j) were prepared by reaction of the corresponding Mannich bases with hydrogen peroxide or with perphthalic acid. Attempts to prepare the *N*-oxides of 2,5-bis(dimethylaminomethyl)hydroquinone (10b), 2-diethylaminomethyl-1-naphthol (12c), 2-dimethylaminomethyl-1-naphthol (12b), 1-piperidinomethyl-2-naphthol (11d), or 1-morpholinomethyl-2-naphthol (11e) using hydrogen peroxide were unsuccessful.

According to the literature,[7,8] treatment of 1-dimethylaminomethyl-2-naphthol (11b) with 30% hydrogen peroxide affords only the expected *N*-oxide (11j). We have found that with short reaction times this normal *N*-oxide is effectively the main product, but if the reaction is allowed to run for several days (11j) undergoes a condensation process to give finally *N*,*N*-bis-(2-hydroxy-1-naphthylmethyl)methylamine *N*-oxide (11m). Although trimethylamine *N*-oxide is very possibly the other product this was not investigated.

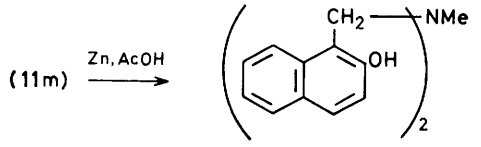


This reaction is analogous to the transalkylation observed when gramine (3-dimethylaminomethylindole) is treated with methyl iodide.[9]

The structure of the *N*-oxide (11m) was confirmed by reducing it with zinc and acetic acid to the known[10] *N*,*N*-bis-(2-hydroxy-1-naphthylmethyl)methylamine (15), which did not regenerate (11m) on treatment with hydrogen peroxide.

A compound used in our study, 1-hydroxymethyl-2-naphthol (11a), has been incorrectly described in some early publications.[11] This unstable substance was fully characterized some years ago as a low m.p. solid, prepared by $LiAlH_4$ reduction of 2-hydroxy-1-naphthalene-

carbaldehyde.[12] We were able to prepare it in a much simpler way by hydroxymethylation of 2-naphthol with aqueous formaldehyde in the presence of exactly 1 equiv. of sodium hydroxide. Subsequent careful neutralization leads to direct crystallization of pure compound (11a) from the reaction mixture. If too much



(15)

acid is added the product is rapidly transformed into bis-(2-hydroxy-1-naphthyl)methane (16), a solid which melts at *ca.* 200 °C. This extreme sensitivity to acids is the reason why (11a) has been frequently and inadvertently obtained as its mixture with (16).

TABLE 1

Preparation of dihydrobenzofurans (5)—(9)

Starting material	Product	Method: Reaction with CH_2N_2 at 3 °C (% yield; *t*/h)	Method: Reaction with $Me_2S^+(:O)-CH_2$ (% yield; *t*/h; *T*/°C)
(10f)	(5)	0 [a]; 24	27 [b]; 4; 50
(11b)	(6)	0 [c]; 48	38; 2; 80
(11e)	(6)	0 [d]; 48	7 [e]; 4; 100
(11e)·HCl	(6)	0 [f]; 48	23; 5; 80
(11f)	(6)	23 [g]; 16	53; 16; 20
(11j)	(6)	25; 48	92; 2.5; 60
(11l)	(6)	28; 72	97; 2; 60
(11m)	(6)	20; 96	79; 48; 20
(12b)	(7)	*h*	40; 2; 65
(12c)	(7)	4 [i]; 24	53 [i]; 16; 60
(12e)	(7)	*h*	5 [i]; 16; 70
(13b)	(8)	8 [j]; 96	*h*
(13c)	(8)	4 [k]; 72	13; 3; 60
(13f)	(8)	27 [l]; 24	81; 4; 20
(13g)	(8)	39; 120	64; 4; 20
(13h)	(8)	22 [m]; 72	60; 4; 20
(13i)	(8)	13; 72	83; 4; 20
(13j)	(8)	10 [n]; 72	0 [f]; 48; 20
(13k)	(8)	0 [f]; 120	0; 120; 20
(14b)	(9)	*h*	39; 20; 60
(14f)	(9)	39 [o]; 120	81; 24; 20
(14j)	(9)	0 [p]; 72	43 [q]; 16; 60

[a] Trimethylamine methiodide (37% yield) also obtained. [b] No reaction observed at 20 °C. [c] 98% Of the Mannich base was recovered. [d] 91% Of the Mannich base was recovered. [e] Obtained as a mixture (21% yield) with two other products, in *ca.* 1 : 1 : 1 proportions. [f] No reaction (t.l.c.). [g] Trimethylamine methiodide (61% yield) also obtained. [h] Reaction not attempted. [i] Contaminated product (t.l.c.). [j] 36% Of the Mannich base was recovered. [k] 68% Of the Mannich base was recovered. [l] Trimethylamine methiodide (90% yield) also obtained. [m] *N*-Methylpiperidine methiodide (34% yield) also obtained. [n] The main product was the methyl ether of (13j). [o] Trimethylamine methiodide (42% yield) also obtained. [p] 90% Of (14j) was recovered. [q] 16% Of (14j) was recovered.

The main results obtained in the reactions of the phenolic Mannich bases and their quaternized derivatives with diazomethane and with dimethylsulphoxonium methylide are summarized in Table 1.

Of the furans thus prepared, all but (6) are apparently new products which were characterized by elemental analysis and spectral data.

From the results shown in Table 1 it appears in the first place that, in agreement with our previous observations,[1] the phenolic Mannich bases react very sluggishly, or not at all, with diazomethane. On the other hand all the methiodides we studied, except (10f), reacted with diazomethane to afford the expected furans, although in modest yields. Of the six *N*-oxides used in our work the ones derived from 2-naphthol and 2,4-dimethylphenol Mannich bases underwent reaction with diazomethane giving the furans in moderate-to-good yields. In the case of the *N*-oxide (13j) *O*-methylation was the predominant reaction. In the reactions with diazomethane the better results obtained with the *N*-oxides in the 2-naphthol series probably reflect the ease of formation of a quinone methide adjacent to an aromatic ring as compared with the series from 4-acetamidophenol and 2,4-dimethylphenol in which formation of the quinone methide implies the disappearance of the only aromatic ring.

Dimethylsulphoxonium methylide reacted with the Mannich bases and their quaternized derivatives, except the *N*-oxides in the 4-acetamidophenol series. The resulting yields of furans were consistently higher than those obtained in the reactions with diazomethane. In the reaction of the ylide with the hydrochloride (11e).HCl the fact that the yield of the furan (6) is higher than that obtained in the reaction of the same ylide with the free Mannich base (11e) clearly shows that this base is not an important intermediate in the process.

With the exception of the dimethiodide (10f) which required higher temperatures to react with the ylide, all the other methiodides were sufficiently reactive at room temperature. With the *N*-oxides, heating to 60—70 °C was necessary to obtain the furans and, not surprisingly, with the Mannich bases themselves even higher temperatures were required. In the case of the *N*-oxides of the 4-acetamidophenol series negative results were obtained probably because no heating was applied in order to avoid *N*-deacetylation by the strongly basic ylide.

Treatment of the *N*-oxide (11m) with diazomethane gave, besides the desired furan (6), two unidentified products. Formation of by-products in such a reaction is not surprising if one postulates that attack of diazomethane on (11m) might fragment the *N*-oxide to give the quinone methide and a secondary amine derivative which could undergo further reaction with diazomethane or with the quinone methide itself. The main process is not essentially different from that taking place in the reaction of (11m) with dimethylsulphoxonium methylide, but in this case the high yield of furan would indicate that the secondary amine intermediate also reacts with the ylide, present in excess, to generate more quinone methide and, thence, more furan.

Since it was not possible to prepare any sufficiently pure quaternized derivative in the 1-naphthol series the naphthofuran (7) had to be obtained from the reaction

of the corresponding free Mannich bases with dimethylsulphoxonium methylide. The yields of pure product were satisfactory taking into account that careful column chromatography on silica gel was required to remove small amounts of impurities.

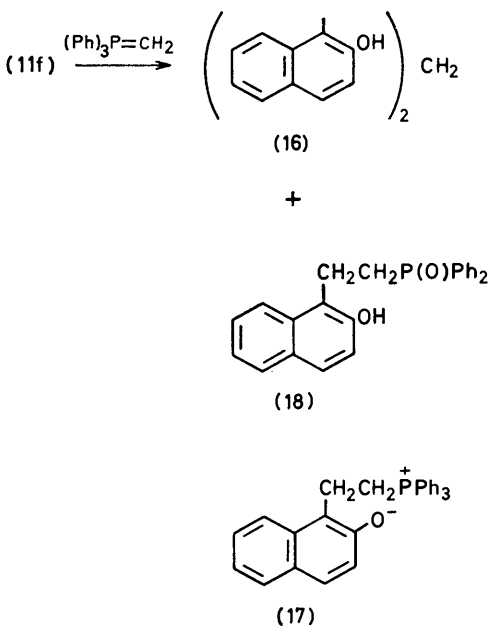
Dimethylsulphoxonium methylide reacted with (11a) to give almost exclusively (16). Similar formation of bis(hydroxyphenyl)methanes has been observed on treatment of phenolic Mannich base methiodides with potassium hydroxide in methanol,[13] and in the thermal decomposition of phenolic Mannich bases.[7,14,15]

Clearly the reactions carried out with dimethylsulphoxonium methylide are of a more general character and give higher yields of dihydrobenzofurans than those with diazomethane, but from the five series we have studied it is difficult to generalize about the best phenolic derivative to be used as starting material. Thus, although good yields were obtained, in general, with the Mannich base *N*-oxides, the fact that their reaction with the ylide required heating limits somewhat the utilization of such derivatives as general starting materials for the preparation of coumarans. On the other hand, in view of the milder conditions required for the reaction of the ylide with the methiodides of phenolic Mannich bases, these derivatives are definitely good starting materials for the synthesis of dihydrobenzofurans. When the preparation of quaternized derivatives of phenolic Mannich bases is not possible, owing to their unstable character (as in the case of the 1-naphthol bases) reaction of those same bases, in particular those prepared from low molecular-weight secondary amines, with dimethylsulphoxonium methylide may prove to be a useful alternative route to the desired coumarans.

Although other carbenoid reagents such as phosphoranes, dimsyl sodium, and dimethylsulphonium methylide could, in theory, react with phenolic Mannich bases or their quaternized derivatives to afford coumarans, in fact negative results were obtained in some exploratory experiments using the first two reagents. Thus, reaction of (11b), or its *N*-oxide (11j), with dimsyl sodium only gave, after 24 h at 65 °C, a 30—40% recovery of unchanged starting material, whereas treatment of the methiodide (11f) with the same reagent afforded mainly the bisnaphthol (16). On the other hand, reaction of (11f) with methylenetriphenylphosphorane afforded (16) and 2-(2-hydroxy-1-naphthyl)-ethyldiphenylphosphine oxide (18), thus showing that intramolecular cyclization of the intermediate betaine (17) to the naphthofuran (6) does not take place easily.

Our results confirm that reaction of dimethylsulphoxonium methylide with quaternized derivatives of phenolic Mannich bases and, in certain cases, with the bases themselves, is a convenient method for the preparation of dihydrobenzofurans or dihydronaphthofurans. On the other hand, treatment of these quaternized derivatives with diazomethane may constitute a useful alternative synthesis of coumarans with base-sensitive functional groups.

In connection with our results it is of interest that



reaction of phenolic Mannich base methiodides with carbonyl-stabilized sulphonium ylides has recently been successfully applied to the synthesis of 2-acyl-substituted 2,3-dihydrobenzofurans.[16]

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. T.l.c. was performed on Kieselgel PF_{254} (0.25 mm) and column chromatography was on Woelm neutral alumina (Activity II), or Carlo Erba silica gel. I.r. spectra were obtained on a Perkin-Elmer 257 spectrophotometer and ^1H n.m.r. spectra were determined with a Hitachi Perkin-Elmer R24A spectrometer at 60 MHz, using $SiMe_4$ as internal standard.

TABLE 2

Mannich bases

Product	Yield (%)	M.p. (°C)	Literature m.p. (°C)	Literature reference
(10b)	54	191	190	17
(11b)	93	74—75	76—76.5	18
(11d)	87	96	93—94	18
(11e)	94	116.5	116.5—117	18
(12c)	79	*a*		19
(12d)	87	132—134	133.5—134.5	20
(12e)	40	81—82	71.5—72.5	20
(13b)	49	117	110	21
(13c)	74	133	135	22
(13d)	77	163—164	159	23
(13e)	44	135	133	22
(14b)	96	77—78	*b*	7

[a] The hydrochloride had m.p. 148—150 °C (lit.,[19] m.p. 150 °C). [b] Described in the literature [7] as a liquid, b.p. 90 °C at 0.9 mmHg (Found: C, 73.8; H, 9.5; N, 7.9. Calc. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81%).

Preparation of Phenolic Mannich Bases.—All the Mannich bases except (12b) were known products which were prepared according to literature methods. Yields, physical constants, and literature references are listed in Table 2.

2-Dimethylaminomethyl-1-naphthol (12b).—A solution of paraformaldehyde (0.693 g, 23 mmol) in 40% aqueous

dimethylamine (3 ml, 23 mmol) was added dropwise over 45 min to a stirred solution of 1-naphthol (3.03 g, 21 mmol) in 96% ethanol (10 ml). The solvent was removed under reduced pressure and the residue was dehydrated by addition of ethanol and benzene followed by concentration under reduced pressure. The residue was then chromatographed on silica gel (100 ml), benzene, benzene–methylene dichloride (1 : 1), and methylene dichloride being used successively as eluants. The intermediate fractions containing the product were combined and concentrated under reduced pressure to afford the *Mannich base* (12b) (3.67 g, 87%) as a pale pink oil which was shown to be slightly impure (t.l.c.). The *hydrochloride* had m.p. 160—162 °C (from EtOH–Et_2O) (Found: C, 65.65; H, 6.8; Cl, 14.75; N, 5.95. $C_{13}H_{16}ClNO$ requires C, 65.70; H, 6.78; Cl, 14.92; N, 5.89%).

Preparation of Mannich Base Methiodides.—The methiodides were prepared by treating the phenolic Mannich bases with a three-fold excess of methyl iodide, according to the conditions summarized in Table 3, which also shows m.p.s and N analyses. Oily methiodides (13g—i) were transformed into solids with definite m.p.s on treatment with acetone.

Preparation of Mannich Base N-*Oxides.*—(*a*) The phenolic Mannich base (5 mmol) was dissolved in methanol (5 ml) and treated with 30% hydrogen peroxide (1.5 ml) according to the conditions indicated in Table 4. The excess of H_2O_2 was decomposed by addition of a small amount of 5% Pt on charcoal, and the solution was filtered and evaporated to dryness. The residue was essentially pure *N*-oxide which was crystallized from an appropriate solvent or was used in the amorphous form for subsequent reactions.

(*b*) The Mannich base (8 mmol) was dissolved in methylene dichloride (90 ml) and treated with a solution of perphthalic acid (12 mmol) in ether during the period of time indicated in Table 4. The organic solution was then washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated to dryness. The residue was crystallized from an appropriate solvent.

^1H *N.m.r. Data.*—As shown from the spectral data in Table 5 quaternization of the Mannich bases produces an

TABLE 3

Mannich base methiodides

Product	Reaction conditions (solvent; *t*/h) [a]	Yield (%)	M.p. (°C)	N Analysis (%) Calculated	Found
(10f)	CH_2Cl_2; 24	97	260 (decomp.)	5.51	5.42
(11f)	C_6H_6; 48	70 [b]	135—137	4.07	4.12
(13f)	CH_2Cl_2; 24	100	235—238 (decomp.)	8.0	7.80
(13g)	CH_2Cl_2; 72	93	157—160	7.40	7.53
(13h)	CH_2Cl_2; 140	90	186—190 (decomp.)	7.18	7.06
(13i)	CH_2Cl_2; 120	95	211—214 (decomp.)	7.14	7.06
(14f)	C_6H_6; 72	80	195—200 (decomp.) [c]	3.46	3.64

[a] The methylations were carried out at room temperature. [b] Yield of purified product. In this reaction tetramethylammonium iodide and bis-(2-hydroxy-1-naphthyl)methane (16) are formed as by-products. The crude methiodide (11f) was purified by dissolution in acetone, filtering off the insoluble tetramethylammonium iodide, and precipitating (11f) with ether. According to the literature,[7] this methiodide is too unstable to be purified for analysis. [c] Lit.,[7] m.p. 182 °C.

TABLE 4

Mannich base *N*-oxides

Product	Reaction conditions [a] (oxidant; solvent; *t*/h)	Yield (%)	M.p. (°C) (crystallization solvent)	Analysis (%) Calculated	Found
(11j)	H_2O_2; MeOH; 3	62 [b]	140 [c] (CH_2Cl_2–Et_2O)	C 66.36 [d] H 7.28 N 5.95	66.28 [d] 7.43 6.0
(11j)	*o*-$C_6H_4(CO_2H)CO_3H$ Et_2O; 1.25	27	140 (CH_2Cl_2–Et_2O)		
(11l)	*o*-$C_6H_4(CO_2H)CO_3H$ Et_2O; 1	67	166 (CH_2Cl_2–Et_2O)	C 69.48 H 6.61 N 5.40	69.63 6.73 5.71
(11m)	H_2O_2; MeOH; 96	65 [b]	205 [c] (CH_2Cl_2–MeOH)	C 76.86 H 5.89 N 3.90	76.97 5.95 3.78
(13j)	H_2O_2; MeOH; 72	88	207—208 (MeOH–THF) [e]	C 58.91 H 7.19 N 12.49	59.28 7.21 12.35
(13k)	H_2O_2; MeOH; 96	80 [f]	70—74 (AcOEt)	C 54.15 [g] H 8.39 N 9.72	54.43 [g] 8.45 9.65
(14j)	H_2O_2; MeOH; 3	89	135 [h] (MeOH–H_2O)	C 61.95 [i] H 8.98 N 6.57	61.89 [i] 9.04 6.53

[a] The reactions were conducted at room temperature. [b] The product crystallized on addition of water. [c] According to our observations the literature m.p.s for (11j) 173—175 °C (ref. 7), and 155—156 °C (ref. 8) correspond to those of mixtures of the N-oxides (11j) and (11m). [d] The analysis corresponds to that of a monohydrate. [e] THF = tetrahydrofuran. [f] The product was purified by chromatography on silica gel. [g] The analysis corresponds to that of a dihydrate. [h] Lit.,[7] m.p. 115 °C. [i] The analysis corresponds to that of a hemihydrate.

TABLE 5

^{1}H N.m.r data of Mannich bases and their quaternized derivatives

Product	Solvent	Ar–H	Resonances (δ, multiplicity, integral) ArCH_2N	NCH_3 or NCH_2R'	Others
(10b)	$CDCl_3$	6.42, s, 2 H	3.49, s, 4 H	2.20, s, 12 H	9.12, s, 2 H(OH)
(11b)	CCl_4	7.70—6.85, complex, 6 H	3.84, s, 2 H	2.20, s, 6 H	11.30, s, 1 H(OH)
(11j)	$CDCl_3$	8.00—7.00, complex, 6 H	5.25, s, 2 H	3.25, s, 6 H	(OH) [a]
(15)	$CDCl_3$–$(CD_3)_2SO$	7.90—6.90, complex, 12 H	4.08, s, 4 H	2.15, s, 3 H	9.60, s, 2 H(OH)
(11m)	$CDCl_3$–$(CD_3)_2SO$	8.40—7.15, complex, 12 H	5.30, d, *J* 12 Hz, 2 H [b] 5.10, d, *J* 12 Hz, 2 H [b]	3.10, s, 3 H	13.40, s, 1—2 H (OH)
(11e)	CCl_4	7.75—6.86, complex, 6 H	3.90, s, 2 H	3.55, t, *J* 6 Hz, 4 H	2.45, t, *J* 6 Hz, 4 H (OCH_2)
(11l)	$CDCl_3$	8.00—7.30, complex, 6 H	5.15, s, 2 H	4.70—4.10, complex, 4 H	3.90—3.40, complex, 4 H (OCH_2)
(12b)	CCl_4	7.60—6.60, complex, 6 H	3.40, s, 2 H	2.00, s, 6 H	11.00, s, 1 H(OH)
(13b)	$CDCl_3$	7.30, s, (3-H) 7.20, d, *J* 9 Hz (5-H) 6.75, d, *J* 9 Hz (6-H)	3.51, s, 2 H	2.30, s, 6 H	2.10, s, 3 H (CH_3CO) 8.60, s, (NH) 10.60, s, (OH)
(13f)	D_2O	7.45, s, (3-H) 7.35, d, *J* 9 Hz (5-H) 7.05, d, *J* Hz (6-H)	4.45, s, 2 H	3.15, s, 9 H	2.20, s, 3 H (CH_3CO)
(13j)	D_2O	7.15, m, 2 H (3-H, 5-H) 6.80, d, *J* 9 Hz (6-H)	4.35, s, 2 H	3.10, s, 6 H	2.00, s, 3 H (CH_3CO)
(13c)	$CDCl_3$	7.29, s, (3-H) 7.15, d, *J* 9 Hz (5-H) 6.70, d, *J* 9 Hz (6-H)	3.65, s, 2 H	2.55, q, *J* 8 Hz, 4 H	2.10, s, 3 H (CH_3CO) 1.45, t, *J* 8 Hz, 6 H (CH_3CH_2) 8.50, s, (NH) 11.00, s, (OH)
(13g)	$CDCl_3$–$(CD_3)_2SO$	7.80, s, (3-H) 7.60, d, *J* 9 Hz (5-H) 7.02, d, *J* 9 Hz (6-H)	4.57, s, 2 H	3.55, q, *J* 7 Hz, 4 H	3.08, s, 3 H (NCH_3) 2.20, s, 3 H (CH_3CO) 1.55br, s, 6 H (CH_3CH_2) 9.75br, s, 2 H (OH, NH)
(13h)	$CDCl_3$–$(CD_3)_2SO$	7.60, s, (3-H) 7.45, d, *J* 9 Hz (5-H) 6.87, d, *J* 9 Hz (6-H)	4.45, s, 2 H	3.45br, s, 4 H	3.00, s, 3 H (NCH_3) 2.05, s, 3 H (CH_3CO) 1.85br, s, 6 H ($NCH_2[CH_2]_3CH_2$) 9.55br, s, 2 H (OH, NH)
(13i)	$CDCl_3$–$(CD_3)_2SO$	7.80, s, (3-H) 7.52, d, *J* 9 Hz (5-H) 7.00, d, *J* 9 Hz (6-H)	4.75, s, 2 H	4.07br, s, 4 H	3.60br, s, 4 H (OCH_2) 3.43, s, 3 H (NCH_3) 2.10, s, 3 H (CH_3CO) 9.95, s, (OH) 9.75, s, (NH)
(13k)	$CDCl_3$	7.50, s, (3-H) 7.32, d, *J* 9 Hz (5-H) 6.83, d, *J* 9 Hz (6-H)	4.40, s, 2 H	3.35, q, *J* 8 Hz, 4 H	2.25, s, 3 H (CH_3CO) 1.45, t, *J* 8 Hz, 6 H (CH_3CH_2) 9.16, s, (NH) (OH) [a]
(14b)	CCl_4	6.42, s, (3-H) 6.35, s, (5-H)	3.36, s, 2 H	2.16, s, 6 H	2.05, s, 3 H ($ArCH_3$) 2.00, s, 3 H ($ArCH_3$) 9.50, s, (OH)
(14f)	D_2O	7.10, s, (3-H) 7.05, s, (5-H)	4.35, s, 2 H	3.00, s, 9 H	2.15, s, 6 H ($ArCH_3$)
(14j)	$CDCl_3$–$(CD_3)_2SO$	6.95, s, (3-H) 6.71, s, (5-H)	4.42, s, 2 H	3.20, s, 6 H	2.17, s, 6 H ($ArCH_3$) (OH) [a]

[a] Not observed. [b] Diastereotopic hydrogens.

important downfield shift for the protons of the *N*-alkyl groups. This shift ranges from 0.75 to 1.06 p.p.m. in the products with one benzene ring, and from 0.85 to 1.41 p.p.m. for the derivatives with two aromatic rings. There seem to be no significant differences in the downfield shifts of those *N*-alkyl protons between the methiodides and the *N*-oxides, as compared with the bases.

Reduction of N,N-*Bis*-(2-*hydroxy*-1-*naphthylmethyl*)-*methylamine* N-*oxide* (11m).—The *N*-oxide (0.5 g, 1.4 mmol) was dissolved in hot acetic acid (10 ml), and the solution was allowed to cool to room temperature; it was then stirred and treated with zinc powder (1.5 g) added as small portions. The mixture was stirred for 2—3 h, filtered, and the insoluble part washed with methanol. The filtrate was made basic with concentrated ammonia and extracted with methylene dichloride. The extract was washed with water, dried, and concentrated under reduced pressure to give a residue which crystallized on addition of methanol. The product (0.200 g, 42%), m.p. 160—164 °C, was identified as *N,N*-bis-(2-hydroxy-1-naphthylmethyl)methylamine (15) by comparison with an authentic sample prepared by Mannich reaction of 2-naphthol with formaldehyde and methylamine.[10]

1-*Hydroxymethyl*-2-*naphthol* (11a).—A solution of 2-naphthol (5 g, 34.7 mmol) in 1M NaOH (34.7 ml, 34.7 mmol) was cooled in an ice–water bath and treated, dropwise, with 37% formaldehyde (4 ml, 50 mmol). The mixture was stirred at the same temperature for *ca.* 45 min and then carefully neutralized with 1M HCl (35 ml). The solid which formed was filtered off, washed with water, and dried under reduced pressure to give the diol (11a) (5.45 g, 90%), m.p. 92—94 °C (lit.,[12] m.p. 85 °C). Crystallization from benzene afforded analytically pure product, m.p. 93—94 °C (Found: C, 75.55; H, 5.9. Calc. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79%). The product is highly sensitive to acids and heat, decomposing to the bisnaphthol (16).

2,3,6,7-*Tetrahydrobenzo*[1,2-b:4,5-b']*difuran* (5).—To a stirred suspension of sodium hydride (1.9 g, 79 mmol) in dimethyl sulphoxide (DMSO) (70 ml) was added trimethylsulphoxonium iodide (17.4 g, 79 mmol) and stirring was continued for 1.5 h at room temperature. The dimethiodide (10f) (6.7 g, 13 mmol) was added and the reaction mixture was heated at 60 °C for 4 h. The cooled solution was diluted with water (100 ml) and extracted with ethyl acetate (3 × 60 ml). The organic layers were washed with water, combined, dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel (40 ml) using benzene as eluant. The fractions containing the product were combined and concentrated to give a solid which was triturated under benzene, filtered off, and dried. The *product* (5) (0.570 g, 27%), m.p. 153 °C, did not change its m.p. after a further recrystallization from methylene dichloride–hexane; δ ($CDCl_3$) 6.62 (2 H, s, aromatic), 4.50 (4 H, t, *J* 9 Hz, OCH_2), and 3.10 (4 H, t, *J* 9 Hz, $ArCH_2$).

1,2-*Dihydronaphtho*[2,1-b]*furan* (6).—(*a*) The 2-naphthol derivative (11b,e,f,j,l,m) or (11e).HCl (10 mmol) was dissolved in a mixture of methanol (6 ml) and dimethylformamide (6 ml), the solution was cooled to 5 °C, and treated with a cold solution of diazomethane (100 mmol) in methylene dichloride. The mixture was left in a refrigerator at 3 °C for the time indicated in Table 1. Any solid formed was filtered off and the filtrate was concentrated under reduced pressure. Water was added to the residue and the mixture was extracted with ether (3 × 50 ml). The organic layers were washed successively with 1M NaOH, 1M HCl, and water, combined, dried, and evaporated to dryness. The oily residue was chromatographed on silica gel (30 ml) using hexane–benzene (4 : 1) as eluant. The fractions containing the product were combined and concentrated under reduced pressure to afford the naphthofuran (6) as an oil, b.p. 170 °C at 23 mmHg (lit.,[4] b.p. 162 °C at 14 mmHg); δ (CCl_4) 7.50—6.65 (6 H, m, aromatic), 4.15 (2 H, t, *J* 9 Hz, OCH_2), and 2.73 (2 H, t, *J* 9 Hz, $ArCH_2$).

(*b*) To a stirred suspension of sodium hydride (0.72 g, 30 mmol) in DMSO (30 ml) was added trimethylsulphoxonium iodide (6.6 g, 30 mmol) and stirring was continued for 1.5 h at room temperature with exclusion of atmospheric moisture. To the solution of dimethylsulphoxonium methylide thus formed was added the phenolic derivative (11b,e,f,j,l,m) or (11e).HCl (10 mmol) and the mixture was submitted to the conditions specified in Table 1. Cold water (100 ml) was added and the mixture was extracted with ether (3 × 60 ml). The organic extracts were washed with 1M NaOH, 1M HCl, and water, combined, dried, and concentrated. Chromatography of the residue on silica gel (30 ml) with methylene dichloride as eluant gave (6), identical in all respects (b.p., t.l.c., i.r., and ^1H n.m.r.) with the product obtained by method (a).

2,3-*Dihydronaphtho*[1,2-b]*furan* (7).—Following essentially the procedures described in the two foregoing experiments, reaction of the 1-naphthol derivative (12c) with diazomethane, or reaction of (12b,c,e) with dimethylsulphoxonium methylide, afforded crude (7). Reaction of (12b) (6.22 g, 31 mmol) and the ylide (81 mmol) gave the crude furan (2.60 g) which was chromatographed on silica gel (65 ml). Slow elution with hexane separated first some non-polar products and then pure *naphthofuran* (7) (2.0 g, 40%), b.p. 80—82 °C at 0.5 mmHg, n_D^{20} 1.6463, δ (CCl_4) 7.85—6.80 (6 H, complex, aromatic), 4.25 (2 H, t, *J* 8.5 Hz, OCH_2), and 2.80 (2 H, t, *J* 8.5 Hz, $ArCH_2$) (Found: C, 84.55; H, 5.95. $C_{12}H_{10}O$ requires C, 84.68; H, 5.92%).

5-*Acetamido*-2,3-*dihydrobenzo*[1,2-b]*furan* (8).—Following the above procedures, the 4-acetamidophenol derivatives (13b,c,f—k) were treated with diazomethane, or with the dimethylsulphoxonium ylide, according to the conditions shown in Table 1. In most cases it was not necessary to resort to column chromatography to obtain the product in pure form. The *coumaran* (8) has two forms which differ in their m.p.s and their i.r. spectra. Form A was obtained by crystallization from ether, m.p. 93 °C; $\nu_{max.}$ (Nujol) 3 320, 1 675, 1 662, 1 620, and 1 550 cm^{-1}. Form B was obtained by crystallization from methylene dichloride, m.p. 95 °C; $\nu_{max.}$ (Nujol) 3 270, 1 660, 1 650, 1 610, and 1 540 cm^{-1}; δ ($CDCl_3$) 8.15 (1 H, s, NH), 7.5 (1 H, s, 4-H), 7.15 (1 H, d, *J* 9 Hz, 6-H), 6.72 (1 H, d, *J* 9 Hz, 7-H), 4.60 (2 H, t, *J* 8.5 Hz, OCH_2), 3.10 (2 H, t, *J* 8.5 Hz, $ArCH_2$), and 2.10 (3 H, s, CH_3CO) (Found: C, 68.0; H, 6.1; N, 7.85. $C_{10}H_{11}NO_2$ requires C, 67.75; H, 6.25; N, 7.90%).

Reaction of (5-*Acetamido*-2-*hydroxybenzyl*)*dimethylamine* N-*Oxide* (13j) *with Diazomethane*.—Treatment of the *N*-oxide (13j) with diazomethane afforded a mixture of products which was separated by column chromatography on silica gel. Elution with methylene dichloride–MeOH (98 : 2) gave the expected coumaran (8) in 10% yield. Further elution with methylene dichloride–MeOH (95 : 5) afforded (5-*acetamido*-2-*methoxybenzyl*)*dimethylamine* N-*oxide* in 45% yield, m.p. 208 °C (from EtOH–AcOEt); $\nu_{max.}$ (Nujol) 3 200, 1 680, 1 630, 1 610, and 1 570 cm^{-1}; δ [$CDCl_3$–$(CD_3)_2SO$] 10.0 (1 H, s, NH), 7.70 (2 H, m, 4- and 6-H), 6.90 (1 H, d, *J* 10 Hz, 3-H), 4.45 (s, H_2O of hydration), 3.80 (2 H, s,

$ArCH_2$), 3.56 (3 H, s, OCH_3), 3.05 (6 H, s, NCH_3), and 2.04 (3 H, s, CH_3CO) (Found: C, 56.1; H, 7.85; N, 10.8. $C_{12}H_{17}N_2O_3.H_2O$ requires C, 56.23; H, 7.87; N, 10.93%).

2,3-Dihydro-5,7-dimethylbenzo[1,2-b]*furan* (9).—Reaction of the 2,4-dimethylphenol derivatives (14b,f,j) with diazomethane or with dimethylsulphoxonium methylide afforded the *coumaran* (9) as an oil, b.p. 117—119 °C at 46 mmHg; δ ($CDCl_3$) 6.82 (1 H, s, 4- or 6-H), 6.75 (1 H, s, 6- or 4-H), 4.50 (2 H, t, *J* 9 Hz, OCH_2), 3.10 (2 H, t, *J* 9 Hz, $ArCH_2$), 2.10 (3 H, s, $ArCH_3$), and 2.02 (3 H, s, $ArCH_3$) (Found: C, 81.15; H, 8.55. $C_{10}H_{12}O$ requires C, 81.04; H, 8.16%).

Reaction of 1-Hydroxymethyl-2-naphthol (11a) *with Dimethylsulphoxonium Methylide.*—To a solution of dimethylsulphoxonium methylide (34.5 mmol) in DMSO (30 ml) was added (11a) (2.0 g, 11.5 mmol) and the mixture was stirred for 1.5 h at room temperature and for 4 h at 80—90 °C under nitrogen. The cooled mixture was diluted with water (100 ml) and extracted with ethyl acetate (3 × 25 ml). The organic layers were washed twice with water, combined, dried, and evaporated to dryness under reduced pressure. The oily residue crystallized on addition of benzene to afford 1,1′-methylenebis-(2-naphthol) (16), m.p. 204 °C (lit.,[21] m.p. 194 °C).

Reaction of Methylenetriphenylphosphorane with 1-Dimethylaminomethyl-2-naphthol Methiodide (11f).—The methiodide (11f) (1.71 g, 5 mmol) was added to a solution of methylenetriphenylphosphorane (15 mmol) in DMSO (15 ml) and the mixture was stirred for 16 h at room temperature and then for 2 h at 65 °C. After quenching with water (50 ml) the solution was extracted with ethyl acetate (3 × 25 ml); the extracts were washed twice with water, combined, dried, and evaporated to dryness under reduced pressure. The oily residue was chromatographed on silica gel (100 ml). Elution with benzene–methylene dichloride (1 : 1) afforded 1,1′-methylenebis-(2-naphthol) (16) (105 mg). Elution with methylene dichloride gave a mixture of products which crystallized from a minimum amount of methylene dichloride to give white crystals (160 mg, 9%) of 2-(2-hydroxy-1-naphthyl)ethyldiphenylphosphine oxide (18), m.p. 264—266 °C; $\nu_{max.}$ (Nujol) 3 300—3 050 (br, OH) and 1 150 (R_3PO) cm^{-1}; δ [$CDCl_3$–$(CD_3)_2SO$] 9.60 (1 H, s, OH), 8.05—6.95 (complex, aromatic), 3.10 (2 H, complex, $ArCH_2$), and 2.04 (2 H, complex, PCH_2) (Found: C, 77.2; H, 5.7; P, 8.05. $C_{24}H_{21}O_2P$ requires C, 77.40; H, 5.67; P, 8.32%). Elution with methylene dichloride–methanol (99 : 1) gave methyldiphenylphosphine oxide (1.10 g, 34%), m.p. 110—110 °C (from hexane) (lit.,[25] m.p. 111—112 °C), originating from the hydrolysis of the excess of phosphorane used in the reaction.

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