

Reactivity of Mannich Bases. Part XIII.¹ Mechanism of the Reaction between Aminomethylnaphthols and Benzenethiols

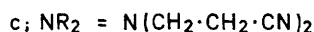
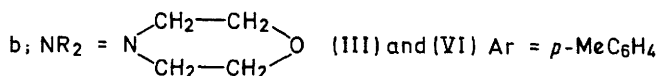
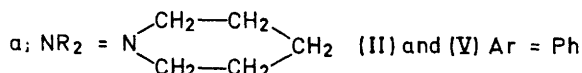
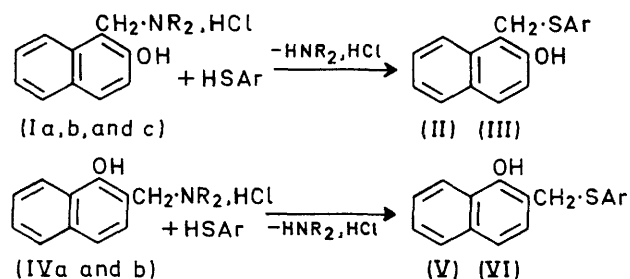
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Replacement of the alkylamino-group by an arylthio-group in some α - and β -naphthol Mannich bases has been studied. Variations in the hydrogen ion concentration, in the alkylamine group, and in the benzenethiol reagent were investigated, and the isotope effect was examined. The results indicate the occurrence of an elimination-addition reaction and an *E1cB*-type mechanism.

THE kinetics of the reactions between ketonic^{2,3} or indolic Mannich bases⁴ and benzenethiols have been investigated, and an elimination-addition has been proposed. Other kinetic studies on phenolic Mannich bases with triethyl phosphite indicated an S_N1 mechanism.⁵

In the present work the reactivity of some naphtholic Mannich bases towards benzenethiols was examined in order to elucidate the reaction mechanism. The effects of acidity, the alkylamino-residue of the base, and the benzenethiol on the kinetics of the reactions have been studied; the isotope effect of deuterium at the naphthol hydroxy-group was also investigated.

All the hydrochlorides of the Mannich bases (Ia, b, and c) and (IVa and b) examined reacted in aqueous-alcoholic solutions with benzenethiol or toluene-*p*-thiol to give the sulphides (II), (III), (V), and (VI).



Chromatography of the reaction mixtures occasionally showed traces of α - or β -naphthol.

Compounds (Ic), (III), (V), and (VI) were characterized by elemental analysis and spectroscopic data.

¹ Part XII, F. Andreani, R. Andrisano, C. Della Casa, and M. Tramontini, *J. Chem. Soc. (C)*, 1970, 1157.

² R. Andrisano, A. S. Angeloni, P. De Maria, and M. Tramontini, *J. Chem. Soc. (C)*, 1968, 2307.

³ A. S. Angeloni, L. Angiolini, P. De Maria, and A. Fini, *J. Chem. Soc. (C)*, 1968, 2295.

⁴ E. Baciocchi and A. Schioli, *J. Chem. Soc. (B)*, 1968, 1124.

EXPERIMENTAL

I.r. and u.v. spectra were recorded with Beckmann IR 5 and Unicam SP 800 spectrophotometers. The pK_a values were determined with a Beckmann Zeromatic II pH Meter.

TABLE I
Reaction of naphtholic base hydrochlorides with benzenethiols

Bases		Sulphides	
	$\lambda_{\text{max.}}/\text{nm}$ (log ϵ) (in water) of the hydrochlorides	pK_a * (at 25°)	Yield (%)
(Ia) ^a	278 (3.70)	6.4	(II) ^b 60 † (III) 43
(Ib) ^a	278 (3.76)	5.6	(II) ^b 45 (III) 38
(Ic)	278 (3.74)	2.8	(II) ^b 98
(IVa) ^a	290 (3.62)	6.0	(V) 14 (VI) 7
(IVb) ^a	290 (3.61)	5.4	(V) 31 (VI) 30

* The pK_a values are expected to be less if measured in alcohol-water mixture (see J. A. Gowland and G. H. Schmid, *Canad. J. Chem.*, 1969, **47**, 2953). † Yield after 14 h; only traces of sulphide were obtained after 1 h.

^a R. L. Shriner, G. F. Grillo, and W. D. Teeters, *J. Amer. Chem. Soc.*, 1946, **68**, 946. ^b F. Poppelsdorf and S. J. Holt, *J. Chem. Soc. (C)*, 1954, 1124.

Naphtholic Mannich Bases (I) and (IV) and Hydrochlorides.—Bases (Ia and b) and (IVa and b) were prepared according to literature methods (see Table I).

1-*NN*-Bis-(2-cyanoethyl)aminomethyl-2-naphthol (Ic) was prepared by adding a solution of β -naphthol (0.08 mol) in 95% ethanol (45 ml) to a stirred mixture of bis-(2-cyanoethyl)amine (0.1 mol) and 30% formaldehyde (0.08 mol), at 5°. The stirred mixture was gently heated for 1 h at 30°, the solvent was removed *in vacuo*, and the oily residue was worked-up with ether. The resulting solid (98%) had m.p. 99–100° (from ethanol) (Found: C, 73.0; H, 6.2; N, 14.8. C₁₇H₁₇N₃O requires C, 73.1; H, 6.15; N, 14.85%), $\nu_{\text{max.}}$ (KBr) 2240 (CN) cm⁻¹, $\lambda_{\text{max.}}$ (0.01N-HCl) 225, 278, 290, and 332 nm (log ϵ 4.78, 3.74, 3.68, and 3.49).

The hydrochloride of (IVb) was prepared according to the literature method [see footnote (a) in Table I].

The hydrochlorides of (Ia and b) and (IVa) were prepared by the slow addition of ether saturated with dry hydrogen chloride to an anhydrous ethereal solution of the purified base. The compound was quickly filtered off, washed with anhydrous ether, and dried for some days *in vacuo* (CaCl₂).

1-Piperidinomethyl-2-naphthol (Ia) hydrochloride had

⁵ B. E. Ivanov, L. A. Valitova, and T. G. Vavilova, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, (4), 1968, 768.

m.p. 160–162° (lit.,⁶ 145°; lit.,⁷ 148–150°) (Found: C, 69.2; H, 7.55; Cl, 12.55; N, 4.9. $C_{16}H_{20}ClNO$ requires C, 69.2; H, 7.25; Cl, 12.75; N, 5.05%).

1-Morpholinomethyl-2-naphthol (Ib) hydrochloride had m.p. 190–192° (lit.,⁶ 177°) (Found: C, 64.15; H, 6.45; Cl, 12.4; N, 5.1. $C_{15}H_{18}ClNO_2$ requires C, 64.4; H, 6.5; Cl, 12.65; N, 5.0%).

2-Piperidinomethyl-1-naphthol (IVa) hydrochloride had m.p. 193–195° (from ethanol) (Found: C, 69.3; H, 7.55; Cl, 12.65; N, 5.1. $C_{16}H_{20}ClNO$ requires C, 69.2; H, 7.25; Cl, 12.75; N, 5.05%).

Attempts to prepare the hydrochloride of 1-*NN*-bis-(2-cyanoethyl)aminomethyl-2-naphthol (Ic) were unsuccessful; bis-(2-cyanoethyl)amine hydrochloride was always recovered.

Reactions of the Hydrochlorides of the Mannich Bases (I) and (IV) with Benzenethiols.—A mixture of the Mannich base hydrochloride * (0.01 mol) and benzenethiol (0.01 mol) in ethanol–water (1 : 1; 50 ml) was boiled for 1 h. The resulting mixture was diluted with water, acidified with conc. hydrochloric acid, and extracted with ether. The organic layer was dried and the solvent was removed. The residue was worked up with light petroleum to give the aryl hydroxynaphthylmethyl sulphide (for yields see Table 1). Mannich base was recovered from the aqueous layer.

1-Phenylthiomethyl-2-naphthol (II) was identical with an authentic sample (see Table 1).

1-*p*-Tolylthiomethyl-2-naphthol (III) had m.p. 106–107° (from light petroleum) (Found: C, 76.9; H, 5.75; S, 11.15. $C_{18}H_{16}OS$ requires C, 77.1; H, 5.75; S, 11.45%), $\nu_{\max}$ (KBr) 3450 (OH) cm^{-1} , $\lambda_{\max}$ (ethanol) 230, 254infr, 282, 293, and 339 nm (log ϵ 4.77, 4.09, 3.96, 3.89, and 3.68).

2-Phenylthiomethyl-1-naphthol (V) had m.p. 101–102° (from light petroleum) (Found: C, 76.45; H, 5.35; S, 12.0. $C_{17}H_{14}OS$ requires C, 76.65; H, 5.3; S, 12.05%), $\nu_{\max}$ (KBr) 3500 (OH) cm^{-1} , $\lambda_{\max}$ (ethanol) 239, 280infr, 311infr, and 327 nm (log ϵ 4.61, 3.98, 3.56, and 3.45).

2-*p*-Tolylthiomethyl-1-naphthol (VI) had m.p. 100–101° (from light petroleum) (Found: C, 76.85; H, 5.65; S, 11.3. $C_{18}H_{16}OS$ requires C, 77.1; H, 5.75; S, 11.45%), $\nu_{\max}$ (KBr) 3350 (OH) cm^{-1} , $\lambda_{\max}$ (ethanol) 239, 280infr, 311infr, and 328 nm (log ϵ 4.69, 3.87, 3.60, and 3.46).

Kinetics of the Reaction of Mannich Bases (I) and (IV) with Benzenethiols.—An ethanolic 0.1M-solution of the benzenethiol, made up to volume at 50°, was used as the stock solution; it was stable over long periods at low temperatures. The base or the corresponding hydrochloride was weighed out for each kinetic experiment because the solutions were unstable.

The initial concentrations of the base and the benzenethiol were in the range 0.0012–0.010M in ethanol–water (1 : 1); the reaction mixture was kept at $50 \pm 0.1^\circ$.

The following buffer solutions † were used: pa_H^* 1.05–5.90, hydrochloric acid–sodium citrate; pa_H^* 5.90–7.45, sodium hydroxide–sodium citrate; pa_H^* 6.95–8.90, potassium dihydrogen phosphate–disodium hydrogen phosphate.

Withdrawals were made at fixed times; the reaction was

* Free base (Ic) in the presence of an equimolar amount of conc. hydrochloric acid.

† The quantity $pa_H^* = pH - \delta$, as defined by R. G. Bates, 'Determination of pH; Theory and Practice', Wiley, New York, 1965, p. 223, was used to express acidity in the alcohol–water mixtures used. The pH values were obtained with a pH meter standardized with an aqueous buffer solution; the δ corrections were neglected because they were small for the ethanol–water (1 : 1) mixture.

stopped by lowering the temperature and adding conc. hydrochloric acid. The unchanged base was separated by dilution with water and extraction with ether. After further extraction with cyclohexane, the aqueous layer was made up to volume for the u.v. spectrophotometric determination of the base, at the wavelength maximum listed in Table 1. The optical density approaches zero towards the end of the reaction.

The rate constant, k , was calculated from the slope of the straight line plot of $\log [a/(a-x)]$ vs. t (Figure 1). A linear dependence was observed for at least three half lives.

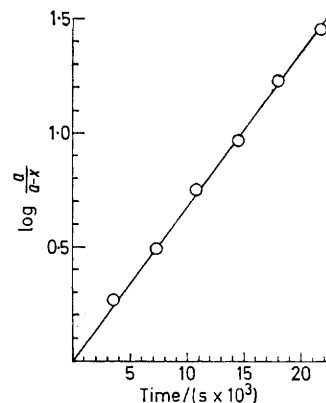


FIGURE 1 Kinetics of the reaction between 2-piperidinomethyl-1-naphthol (IVa) and toluene-*p*-thiol at 50°; $pa_H^* = 6.50$

The constant does not depend on the concentrations of the reactants, on the nature of the benzenethiol, or on the type of buffer used.

The results are collected in Tables 2–4.

TABLE 2

First-order rate constants for the reactions of naphtholic bases with toluene-*p*-thiol at 50°

pa_H^*	$10^4 k/s^{-1}$				
	(Ia)	(Ib)	(Ic)	(IVa)	(IVb)
1.15			7.9		
2.40			21		
3.60		0.14			
3.70			20		0.36
4.50			21	0.019	1.2
4.70		1.3			
4.80	0.034				
5.25	0.11				
5.80	0.26				
5.85			24	0.33	4.2
5.90		3.3 †			
6.00		5.3			
6.35	0.96				
6.50				1.6 †	
6.90	1.3 †			1.8	4.6
6.95	1.4 †	6.1			
7.40			24	2.5	5.2
7.45	3.6				
8.00	3.8	8.2		2.9	5.5 ‡
8.45				3.0	5.5 ‡
8.50	5.0	8.5			
9.00	5.1				

† See Table 4. ‡ See Table 3.

⁶ M. Julia and G. Tchernoff, *Bull. Soc. chim. France*, 1955, 830.

⁷ R. Andrisano, C. Della Casa, and M. Tramontini, *Ann. Chim. (Italy)*, 1967, **57**, 1073.

Kinetic Experiments on 1-Morpholinomethyl-2-naphthol.—The deuteriated compound was obtained by several recrystallizations of (Ib) from ethan[²H]ol. Complete isotopic exchange of the hydroxy-hydrogen was demonstrated by n.m.r. spectroscopy.

The kinetic determination with toluene-*p*-thiol was performed at $pa_H^* = 8.00$ in deuterium oxide-ethan[²H]ol, as described.

The rate constant, k , was $8.8 \times 10^{-4} \text{ s}^{-1}$ with an isotope effect $k_H/k_D = 0.93$ (k_H and k_D are the rate constants for the normal and the deuteriated compound respectively).

TABLE 3

Examples of variation in the initial concentrations for the kinetics of the reaction of 1-piperidinomethyl-2-naphthol (Ia) and 2-morpholinomethyl-1-naphthol (IVb) with toluene-*p*-thiol at 50°

$pa_H^* = 6.95$			$pa_H^* = 8.00$		
[(Ia)]/ M	$\frac{[p\text{-MeC}_6\text{H}_4\cdot\text{SH}]}{[\text{M}]}$	$10^4 k \dagger$ s^{-1}	[(IVb)]/ M	$\frac{[p\text{-MeC}_6\text{H}_4\cdot\text{SH}]}{[\text{M}]}$	$10^4 k \dagger$ s^{-1}
0.0050	0.0050	1.4	0.0050	0.0050	5.5
0.0025	0.0050	1.5	0.0025	0.0050	5.5
0.0012	0.0050	1.4	0.0012	0.0050	5.5
0.0025	0.0100	1.4	0.0012	0.0100	5.5
0.0025	0.0075	1.6	0.0025	0.0100	5.4
0.0025	0.0025	1.4	0.0025	0.0075	5.3
			0.0025	0.0025	5.5

† First-order rate constants.

TABLE 4

First-order rate constants for the reactions with benzenethiols at 50°

Benzenethiols	pa_H^*	$10^4 k/\text{s}^{-1}$			
		(Ia)	(Ib)	(IVa)	(IVb)
<i>p</i> -MeC ₆ H ₄ ·SH	5.90		3.3		
PhSH	5.90		3.8		
<i>p</i> -MeC ₆ H ₄ ·SH	6.50			1.6	
PhSH	6.50			1.5	
<i>p</i> -MeC ₆ H ₄ ·SH	6.90	1.3			
PhSH	6.90	1.3			
<i>p</i> -MeC ₆ H ₄ ·SH	8.45				5.5
PhSH	8.45				5.5

Dissociation Constants of the Naphtholic Mannich Bases.—The pK_a values for the hydrochlorides of (Ia, b, and c and (IV)a and b) were determined by potentiometric titration with sodium hydroxide solution. [To prepare a solution of the hydrochloride of (Ic) the required amount of hydrochloric acid was added to a stirred suspension of the free base in water.]

The pK_a values are listed in Table 1.

DISCUSSION

At all pa_H^* values used the reaction between the naphtholic Mannich bases and benzenethiols followed first-order kinetics with respect to the benzenethiol, since

⁸ H. R. Snyder and J. H. Brewster, *J. Amer. Chem. Soc.*, 1949, **71**, 1058.

⁹ R. Pummerer and I. Veit, *Ber.*, 1953, **86**, 412.

¹⁰ V. H. V. Euler and H. Hasselquist, *Arkiv Kemi*, 1953, **6**, 139.

¹¹ F. Poppelsdorf and S. J. Holt, *J. Chem. Soc. (C)*, 1954, 4094.

the observed rate constants which were first-order in base were independent of the initial base and benzenethiol concentrations (see Tables 3 and 4).

The results in Table 2 and in Figure 2 indicate that in all cases the rate constant increases with increasing pa_H^* ; this increase tends to zero for the free base.

Examination of the β -naphthol bases (Ia, b, or c) or the α -naphthol bases (IVa or b) at any specified pa_H^* shows that the rate constants are higher for the bases with smaller pK_a . Examination of the piperidino- (Ia) or (IVa) or morpholino-bases (Ib) or (IVb) at pa_H^* values of the 'plateau' shows higher rate constants for the β -naphthol derivatives.

The shape of the $\log k$ vs. pa_H^* plot and the work of Snyder and Brewster on the reactivity of α -dimethylaminomethyl- β -methoxynaphthalene⁸ rule out a substitution mechanism and the results seem better explained by an elimination-addition mechanism [steps (A)–(C)].

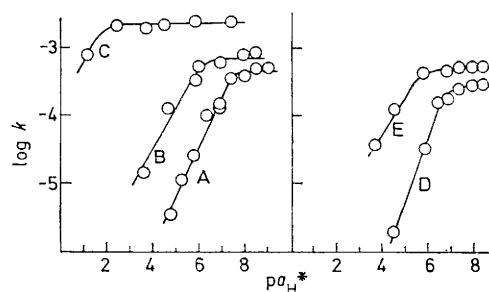


FIGURE 2 Change of $\log k$ with pa_H^* in reaction between toluene-*p*-thiol and A, 1-piperidinomethyl-2-naphthol (Ia); B, 1-morpholinomethyl-2-naphthol (Ib); C, 1-NN-bis-(2-cyanoethyl)aminomethyl-2-naphthol (Ic); D, 2-piperidinomethyl-1-naphthol (IVa); and E, 2-morpholinomethyl-1-naphthol (IVb), at 50°

Stage (A) is an acid-base equilibrium which, for a given hydrogen ion concentration, depends only on the pK_a of the base. The slow stage corresponds to reaction (B), which proceeds by first-order kinetics with respect to the concentration of the base. Stage (C) involves a quinone methide, the addition of benzenethiol to which is fast and irreversible. We were unable to isolate this intermediate; however, quinone methides are known to be too reactive to be isolable.^{7,9-14}

The increase in reactivity observed with decreasing proton concentration of the medium agrees with this hypothesis, since equilibrium (A) is shifted towards the formation of the free base (see also ref.² and refs. cited therein).

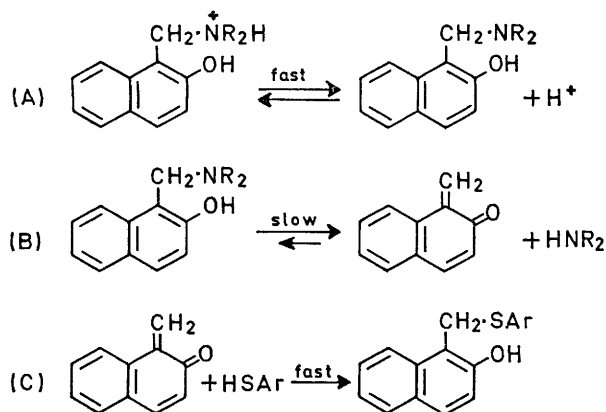
The $\log k$ vs. pa_H^* plot, for $pa_H^* > pK_a$ (base) (Figure 2), rules out a base-catalysed mechanism for the elimination stage.

¹² P. D. Gardner, H. S. Rafsanjani, and L. Rand, *J. Amer. Chem. Soc.*, 1959, **81**, 3364.

¹³ W. J. Burke, W. A. Nasutavicus, and C. Weatherbee, *J. Org. Chem.*, 1964, **29**, 407.

¹⁴ Y. Ogata, A. Kawasaki, and T. Goto, *Tetrahedron*, 1969, **25**, 2589.

An *E1* mechanism is in agreement with decreasing reactivity in the series bis-(2-cyanoethyl)amino- > morpholino- > piperidino-derivative, but it does not explain the plots of $\log k$ vs. pK_a^* .



An analogous scheme can be written for the α -naphtholic Mannich bases.

Therefore, from experimental data and the foregoing considerations, and from the absence of an isotope effect (see Experimental section), we suggest that the rate-determining step (B) of the reaction could involve an

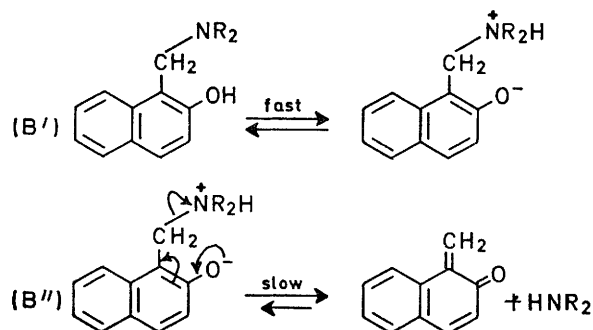
E1cB-type mechanism. The isotope effect does not agree with an alternative concerted mechanism.

The fast equilibrium (B') results in protonation of the amino-group and formation of the naphthoxide ion.

In the slow stage (B'') the leaving group is $-\text{HNR}_2^+$.

The higher reactivity of the less basic amine is in agreement with the suggested mechanism.

The higher reactivity of the β -naphtholic bases with respect to the corresponding α -naphthol derivatives may be due to a greater resonance stabilization of the ionic species in (B'') in the case of the α -naphthol derivatives.



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