

Studies in the Dithiocarbamate Series. Part V.¹ The Reactions of Some *N*-(4-Hydroxybenzyl)-piperidines and -pyrrolidines with Carbonyl Sulphide

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The reactions of several *N*-(4-hydroxybenzyl)-piperidines and -pyrrolidines with carbonyl sulphide in ethanol have been studied. At 35–45°, high yields of *S*-4-hydroxybenzyl amine-1-carbothioates were obtained by 'insertion' reactions, whereas in refluxing ethanol the reactions yielded benzyl alcohols in high yields. Mechanisms are proposed for the reactions.

THE interaction of carbon disulphide with certain aromatic Mannich bases such as *N*-(4-hydroxybenzyl)-piperidines [*e.g.* (Ic)] has been shown^{2,3} to yield *p*-hydroxybenzyl dithiocarbamates by a three-stage process involving a *p*-quinone methide intermediate. An alternative 'one-step' synthesis⁴ involving a phenol, an aldehyde, an amine, and carbon disulphide is useful if the aldehyde is sufficiently reactive to participate in the Mannich reaction, and the success of the one-step synthesis probably depends on the initial formation of the Mannich base which then reacts with carbon disulphide. Both these syntheses therefore depend on the 'insertion' of carbon disulphide into Mannich bases; this reaction has now been further investigated with carbonyl sulphide in place of carbon disulphide.

¹ A. O. Fitton, J. Hill, M. Qutob, and A. Thompson, preceding paper.

² A. O. Fitton, A. Rigby, and R. J. Hurlock, *J. Chem. Soc. (C)*, 1969, 230.

The reactions were carried out on ethanolic solutions of various *N*-(4-hydroxybenzyl)-pyrrolidines (Ia and b) or -piperidines (Ic–e) through which a stream of carbonyl sulphide was bubbled, and monitored by t.l.c. Each reaction gave an *S*-4-hydroxybenzyl amine-1-carbothioate [*e.g.* (VI)] and a benzyl alcohol (VII), although the proportions of the products varied considerably according to the temperature of the reaction. Thus at 35–45°, *N*-(4-hydroxy-3,5-di-*t*-butylbenzyl)-piperidine (Ic) and carbonyl sulphide gave *S*-4-hydroxy-3,5-di-*t*-butylbenzyl piperidine-1-carbothioate (VIc) in 85% yield, whereas when the reaction was carried out in refluxing ethanol, 4-hydroxy-3,5-di-*t*-butylbenzyl alcohol (VIIa) was produced in 82% yield. At intermediate temperatures, a mixture of the two products was obtained. The results from other reactions carried out

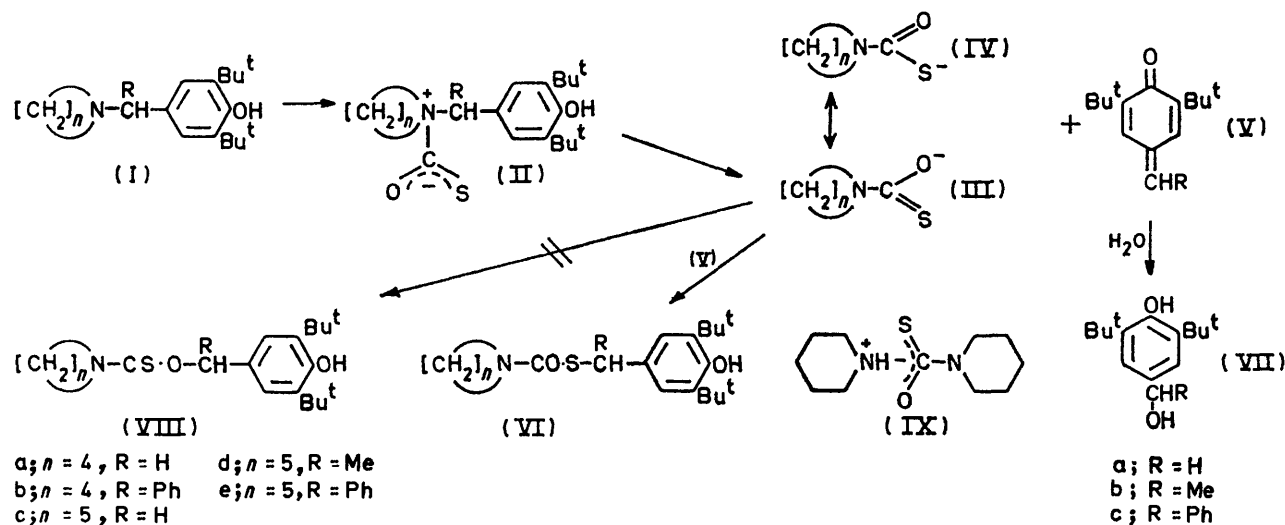
³ A. O. Fitton, M. Qutob, and W. Barber, *J. Chem. Soc. (C)*, 1971, 1245.

⁴ B.P. 722,870/1955; 996,224/1965; 1,024,651/1966.

at 35–45° are shown in Table 1. The reactions between *N*-(4-hydroxy- α -phenyl-3,5-di-*t*-butylbenzyl)pyrrolidine (Ib) and its piperidine analogue (Ie) with carbonyl sulphide both gave rise to the relatively unreactive quinone methide, 4-benzylidene-2,6-di-*t*-butylcyclohexa-2,5-dienone (Vc) in addition to the usual products.

In order to explain the results, it is postulated (see Scheme) that the Mannich base (I) first reacts with carbonyl sulphide to give a salt (II) which eliminates amine-1-carbothioate anion [(III) \leftrightarrow (IV)] and yields the *p*-quinone methide (V). This can either recombine

their formation is due to interaction of solvent moisture with the quinone methide. The intermediacy of alcohols formed by this route was recently postulated¹ to explain the eventual formation of carbonyl compounds during irradiation of *p*-hydroxybenzyl dithiocarbamates. Commercial ethanol normally contains at least 0.6% water, and this represents a large excess for interaction with the quinone methide. The extent of benzyl alcohol formation was considerably less when the reaction was carried out in absolute ethanol, and was zero when dry chloroform was employed as solvent. In



with the eliminated anion to yield the 4-hydroxybenzyl amine-1-carbothioate (VI) or react with solvent moisture to give the benzyl alcohol (VII).

These results differ from those obtained in the corresponding reactions² involving carbon disulphide in that first, benzyl alcohols are produced, and second, the Mannich bases (Ib and e) and carbonyl sulphide give rise to the isolable *p*-quinone methide (Vc). It is significant that although *p*-quinone methide participation in the carbon disulphide work was established indirectly,³ none was ever isolated. Although the presence of *p*-quinone methides in the present work was not generally established, it is reasonable to assume that they are involved, and it was shown, for example, that interaction of 4-ethylidene-2,6-di-*t*-butylcyclohexa-2,5-dienone (Vb) with piperidinium piperidine-1-carbothioate⁵ (IX) readily gave the product (VIc) as is postulated in the Scheme. The i.r. carbonyl absorption (at 1635 cm⁻¹) of this product, and indeed of all the insertion products, indicates that they possess the sulphur-bridged structure (VI) and not the alternative (VIII). This is presumably due to the higher nucleophilicity of sulphur compared with oxygen in the carbothioate anion [(III) \leftrightarrow (IV)].

Although it was originally thought that the benzyl alcohols could have arisen by dissociation of the unstable insertion product (VIII), it is now established that

these less polar solvents the rate of carbothioate formation (shown by t.l.c.) was reduced, but addition of water (0.5%) to the mixture rapidly led in both cases to extensive formation of benzyl alcohol.

The variation with temperature of the proportions of insertion product and benzyl alcohol can be explained in two ways. First, it was shown that at temperatures approaching the b.p. of ethanol, the insertion products are unstable, for although the carbothioate (VIc) for example was stable in ethanol at room temperature for at least 3 h, in boiling ethanol it rapidly lost carbonyl sulphide and re-formed the Mannich base (without formation of benzyl alcohol). Thus, when the insertion reactions were carried out in refluxing ethanol in the presence of an excess of carbonyl sulphide and solvent moisture, the initially formed carbothioate would decompose to the Mannich base. This on further reaction with carbonyl sulphide should lead to further quinone methide and a subsequent increase in the concentration of benzyl alcohol. On the other hand, it was shown that an ethanolic solution of the piperidinium salt (IX) also lost carbonyl sulphide on heating. Thus, when the insertion reactions were carried out in boiling ethanol, it is possible that the eliminated anion [(III) \leftrightarrow (IV)] could lose carbonyl sulphide, and the quinone methide would then be free to suffer attack by water to give the

benzyl alcohol or by amine to re-form the Mannich base.

Because of the thermal instability of the insertion products, the 'one-step' synthesis is not applicable, since the heat required to form the Mannich base prior to insertion of carbonyl sulphide also causes decomposition of the insertion product. Thus the products from attempted one-step syntheses were benzyl alcohols.

With the exception of (Id), the starting bases were obtained by the Mannich procedure. Compound (Id) was prepared by interaction of 4-ethylidene-2,6-di-*t*-butylcyclohexa-2,5-dienone with piperidine.²

EXPERIMENTAL

Silica gel for column chromatography was Hopkin and Williams M.F.C. grade; that for t.l.c. was Merck Kieselgel G. N.m.r. spectra were determined at 60 MHz for solutions in carbon tetrachloride with tetramethylsilane as internal reference. I.r. spectra were determined for Nujol mulls.

Mannich base (2 g) in ethanol (50 ml) for 4 h. After evaporation, the residue was column chromatographed. Elution with light petroleum (b.p. 60–80°) gave 4-benzylidene-2,6-di-*t*-butylcyclohexa-2,5-dienone (0.22 g), m.p. 74° (lit.,⁶ 72–74°). Elution with light petroleum (b.p. 60–80°)–benzene (1:1) gave 4-hydroxy- α -phenyl-3,5-di-*t*-butylbenzyl alcohol (0.36 g), m.p. 218° (Found: C, 80.5; H, 8.7. C₂₁H₂₈O₂ requires C, 80.65; H, 9.0%), followed by S-4-hydroxy- α -phenyl-3,5-di-*t*-butylbenzyl pyrrolidine-1-carbothioate (0.15 g), m.p. 135°. Elution with acetone gave starting material (0.8 g).

The corresponding reaction with the Mannich base (Ie) was shown by t.l.c. to give corresponding products.

(c) *Interaction of 4-ethylidene-2,6-di-*t*-butylcyclohexa-2,5-dienone with piperidinium piperidine-1-carbothioate.* A solution of the quinone methide (1.16 g) and the salt (1.04 g) in ethanol (5 ml) was stirred at 30–35° for 0.5 h. The precipitate gave S-4-hydroxy- α -methyl-3,5-di-*t*-butylbenzyl piperidine-1-carbothioate (1 g), m.p. 144°.

TABLE 1
S-4-Hydroxy-3,5-di-*t*-butylbenzyl amine-1-carbothioates (VI)

Starting Mannich base	Reaction time (h)	Product	Yield (%)	M.p. (°C)	Found (%)			Formula	Required (%)			$\nu_{\max.}/\text{cm}^{-1}$
					C	H	N		C	H	N	
(Ia)	2	(VIa)	95	121	68.6	8.9	3.75	C ₂₀ H ₃₁ NO ₂ S	68.7	8.9	4.0	1650
(Ib)	0.5	(VIb)	91	135	73.3	8.3	3.2	C ₂₆ H ₃₅ NO ₂ S	73.4	8.2	3.3	1650
(Ic)	2	(VIc)	85	108	69.3	9.2	3.8	C ₂₁ H ₃₃ NO ₂ S	69.4	9.1	3.85	1645
(Id)	1.5	(VIId)	80	144	70.3	9.2	3.5	C ₂₂ H ₃₅ NO ₂ S	70.0	9.3	3.7	1635
(Ie)	0.5	(VIe)	90	133	73.5	8.4	3.1	C ₂₇ H ₃₇ NO ₂ S	73.7	8.5	3.2	1640

S-4-Hydroxy-3,5-di-*t*-butylbenzyl Amine-1-carbothioates.—

(a) *General procedure.* Carbonyl sulphide was bubbled through a solution of the Mannich base (1 g) in ethanol (40 ml) at 35–45° for 0.5–2 h (see Table 1). The crude product was obtained by filtration after cooling, or by evaporation. The products (VIa, c, and d) were purified by crystallisation from ethanol, and (VIb and e) by crystallisation from light petroleum (b.p. 60–80°). The results are shown in Table 1; n.m.r. spectra are given in Table 2.

TABLE 2

N.m.r. spectra of amine-1-carbothioates (VI) (τ at 60 MHz)

Compound	Bu ^t	Amine ring			Aromatic H	
		α -CH ₂	other CH ₂	Benzyl CH		
(VIa)	8.6	8.15br	6.6br	5.95	4.9	2.9
(VIb)	8.6	8.5br	6.6br	4.95	4.15	2.7(m)
(VIc)	8.5	8.4br	6.5br	5.8	4.75br	2.75
(VIId)	8.5†	8.4br	6.5br	5.4(q) ‡	4.85	2.75
(VIe)	8.65	8.5br	6.6br	4.95	4.15	2.7(m)

* Exchangeable. † Benzylic Me also at this value. ‡ Ill-defined.

(b) *Reaction of N-(4-hydroxy- α -phenyl-3,5-di-*t*-butylbenzyl)-pyrrolidine with carbonyl sulphide in refluxing ethanol.* Carbonyl sulphide was bubbled through a solution of the

Formation of benzyl alcohols. (a) When the reactions described in (a) above were carried out in refluxing ethanol, benzyl alcohols were produced. The Mannich bases (Ia and c) gave 4-hydroxy-3,5-di-*t*-butylbenzyl alcohol (VIIa), m.p. 138° (lit.,⁷ 138°) in yields of 65 and 82%, respectively.

(b) *One-step synthesis.* Carbonyl sulphide was bubbled through a solution of 2,6-di-*t*-butylphenol (10.3 g), para-formaldehyde (1.5 g), and piperidine (4.2 g) in refluxing ethanol (75 ml) for 5 h. After cooling, the product was filtered off and gave 4-hydroxy-3,5-di-*t*-butylbenzyl alcohol (7.2 g), m.p. 138°.

Replacement of piperidine by pyrrolidine (3.5 g) in the foregoing reaction gave the benzyl alcohol (6.6 g).

Similarly, 2,6-di-*t*-butylphenol (5 g), benzaldehyde (2.5 g), and pyrrolidine (1.5 g) in ethanol (50 ml) gave 4-hydroxy- α -phenyl-3,5-di-*t*-butylbenzyl alcohol (3.3 g), m.p. 218°.

*Thermolysis of S-4-Hydroxy-3,5-di-*t*-butylbenzyl Amine-1-carbothioates.*—A solution of S-4-hydroxy-3,5-di-*t*-butylbenzyl piperidine-1-carbothioate (1 g) in ethanol (10 ml) was heated under reflux for 1 h, then evaporated. The residue gave N-(4-hydroxy-3,5-di-*t*-butylbenzyl)piperidine (0.62 g), m.p. 78°.

Similarly, S-4-hydroxy- α -phenyl-3,5-di-*t*-butylbenzyl pyrrolidine-1-carbothioate (1 g) gave the corresponding Mannich base (0.82 g), m.p. 105°.

[2/188 Received, 31st January, 1972]

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⁷ G. M. Coppinger and T. W. Campbell, *J. Amer. Chem. Soc.*, 1953, **75**, 734.