Studies in the Dithiocarbamate Series. Part II.[1] The Reaction of Substituted *N*-Benzylpiperidines with Carbon Disulphide

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A series of substituted *N*-benzylpiperidines has been prepared, and their reaction with carbon disulphide studied. When the benzyl group possesses a 4-hydroxy-substituent together with 3,5-substituents such as alkyl and methoxy- the reaction leads to dithiocarbamate formation by ' insertion ' of carbon disulphide between the benzylic carbon atom and nitrogen. A three-stage mechanism is proposed, one stage involving the formation of a *p*-quinone methide as a transient intermediate. An alternative two-stage mechanism is considered but shown to be less likely.

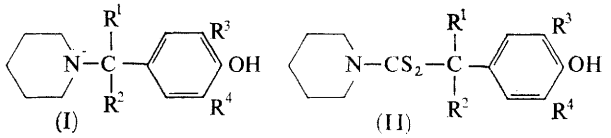
WHEREAS the reaction between carbon disulphide and primary or secondary amines is well-known, that between carbon disulphide and tertiary amines has been less studied. With certain tertiary amines, dithiocarbamate formation occurs by ' insertion ' of carbon disulphide into a carbon–nitrogen bond of the amine. Thus, the Mannich base *N*-(4-hydroxy-3,5-di-t-butylbenzyl)piperidine (Ia) was recently shown [1] to yield-4-hydroxy-3,5-di-t-butylbenzyl piperidine-1-carbodithioate (IIa) on treatment with carbon disulphide, and several similar reactions have been reported,[2] although few mechanistic details are available. Insertion occurs only between a benzylic carbon atom and nitrogen; we have investigated the structural requirements for this insertion to occur.

Dithiocarbamates were readily formed [1] from the *N*-benzylpiperidines (Ib) and (Ic) which differ from (Ia) in possessing one or more methyl groups on the benzylic carbon; similarly the presence of 3- and 5-t-butyl groups is not essential since *N*-(4-hydroxy-3,5-dimethyl-

[1] Part I, A. O. Fitton, A. Rigby, and R. J. Hurlock, *J. Chem. Soc.* (*C*), 1968, 996.

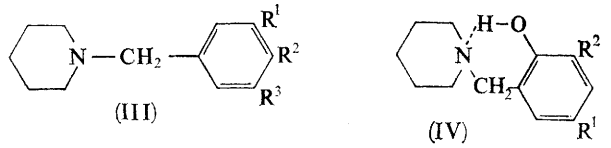
[2] B.P. 966,244; H. Ulrich and A. A. R. Sayigh, *Angew. Chem. Internat. Edn.*, 1966, **5**, 844.

benzyl)piperidine (Id) also yielded a dithiocarbamate (IId) in yield comparable to that obtained from (Ia). *N*-(2-Hydroxy-3,5-dimethylbenzyl)piperidine, where the nitrogen is intramolecularly hydrogen-bonded through



(I) (II)

a; $R^1 = R^2 = H$, $R^3 = R^4 = Bu^t$.
b; $R^1 = H$, $R^2 = Me$, $R^3 = R^4 = Bu^t$.
c; $R^1 = R^2 = Me$, $R^3 = R^4 = Bu^t$.
d; $R^1 = R^2 = H$, $R^3 = R^4 = Me$.
e; $R^1 = R^2 = H$, $R^3 = R^4 = OMe$.

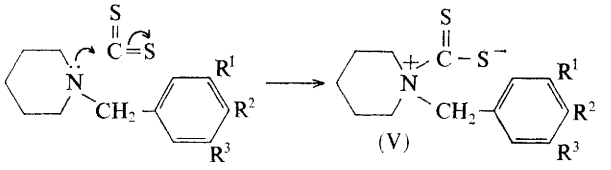


(III) (IV)

a; $R^1 = R^2 = R^3 = H$.
b; $R^1 = R^3 = H$, $R^2 = OH$.
c; $R^1 = R^3 = H$, $R^2 = OMe$.
d; $R^1 = R^3 = Me$, $R^2 = H$.
e; $R^1 = R^3 = Me$, $R^2 = OMe$.
f; $R^1 = R^2 = R^3 = OMe$.
g; $R^1 = H$, $R^2 = OH$, $R^3 = NO_2$.

a; $R^1 = R^2 = H$.
b; $R^1 = R^2 = Me$.
c; $R^1 = Me$, $R^2 = Bu^t$.

the adjacent hydroxy-group (IVb) (i.r. and n.m.r. evidence), under similar conditions also did not react with carbon disulphide, nor did the methiodide of *N*-(4-hydroxy-3,5-dimethylbenzyl)piperidine. This suggested that the initial stage of the insertion reaction requires the lone pair of electrons on the nitrogen to be available for attack on the carbon disulphide. In both these reactions, the presence of unchanged carbon disulphide was shown by its characteristic i.r. absorption at 2150 cm.$^{-1}$.



(V)

N-(2-Methoxy-3,5-dimethylbenzyl)piperidine however, in which hydrogen bonding is precluded, also did not react with carbon disulphide, nor did *N*-(4-methoxy-3,5-dimethylbenzyl)piperidine (IIIe). The phenolic grouping is thus an important factor in dithiocarbamate formation, although not the sole one, since *N*-(4-hydroxybenzyl)piperidine (IIIb) did not react with carbon disulphide.

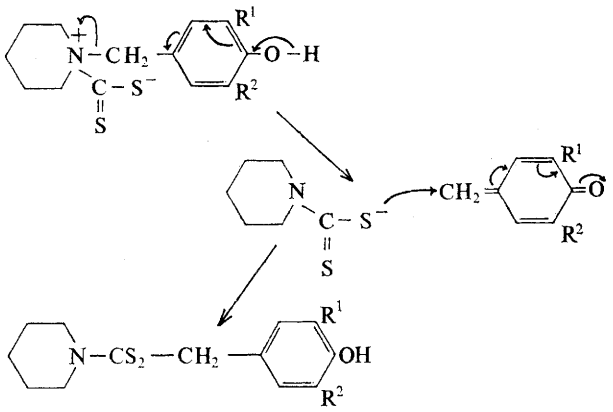
In order to examine the effect of substituents, a series of *N*-benzylpiperidines was prepared, and each was submitted to reaction with carbon disulphide. The results are shown in the Table. With the exception of the methiodide mentioned earlier, and compounds (IVa—IVc), the initial reaction with carbon disulphide appeared to take place in each case, since the i.r. absorption of the latter (2150 cm.$^{-1}$) disappeared on addition of the *N*-benzylpiperidine.

Reaction of Mannich bases with carbon disulphide

Mannich base	Reaction time (hr.)	Product	Yield (%)
(Ia)	3	(IIa)	90
(Ib)	2	(IIb)	86
(Ic)	2	(IIc)	60
(Id)	3	(IId)	90
(Ie)	5	(IIe)	70
(IIIa—IIIg)	10	None *	
(IV—IVc)	10	None *	

* >90% recovery of starting material.

The results show that dithiocarbamates are formed when the benzene ring of the *N*-benzylpiperidine possesses a 4-hydroxy-substituent and substituents in the 3- and 5-positions which exert either $+I$ or $-I$ effects. These factors suggest that the intermediate (V) breaks down to give a *p*-quinone methide by elimination of piperidine-1-carbodithioate anion and that the latter then reacts with the quinone methide to yield the observed product. (Scheme).



Scheme

It is significant that the benzene ring substituents which promote dithiocarbamate formation are those which favour the formation and stabilisation of *p*-quinone methides.[3] The driving force for the elimination is presumably the electron-attracting effect of the quaternary nitrogen, and the fission of the benzylic carbon–nitrogen bond is assisted by the presence of the 4-hydroxy-group, which enables the electron transfer to extend through the molecule with loss of the phenolic proton and formation of the quinone methide. There is no such assistance in the case of the nitro-compound (IIIg), where the electrons from the hydroxy-group are supplied to the *o*-nitro-group.

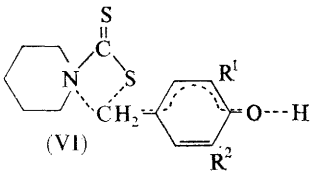
The elimination stage of the reaction resembles the decomposition of 4-hydroxy-3,5-di-t-butylbenzyl piperidine-1-carbodithioate (IIa) in the presence of transition metal salts.[1] Here the driving force is the complexing of the transition metal ion with the dithiocarbamate system, and the products provided indirect evidence that the quinone methide, 4-methylene-2,6-di-t-butylcyclohexa-2,5-dienone was an intermediate. This quinone methide has now been trapped as 2,4-di-t-butyl-9-methylspiro[5,5]undeca-1,4,8-trien-3-one by the

[3] L. J. Filar and S. Winstein, *Tetrahedron Letters*, 1960, 9.

method of McClure.[4] Removal of the dithiocarbamate anion from the potential equilibrium mixture as nickel piperidine-1-carbodithioate probably facilitated the trapping of the quinone methide, since all attempts to trap a similar intermediate in the reactions of *N*-(4-hydroxybenzyl)piperidines with carbon disulphide which gave dithiocarbamates proved abortive. Similarly, no trace of the usual dimeric products [5] associated with quinone methides was detected, suggesting that once formed, the quinone methide is held close to the piperidine-1-carbodithioate anion, possibly in a solvent cage, and that any reaction other than recombination with the eliminated anion is precluded.

On the other hand, failure to trap the quinone methides or to observe their derivatives could indicate that dithiocarbamate formation from the intermediate (V) occurs by way of a synchronous mechanism without the separation of a discrete quinone methide. This would involve nucleophilic attack of the thioanion at the benzylic carbon with simultaneous displacement of the amine, through the transition state (VI). The stability of this transition state will depend on the nature of the group attached to the benzylic carbon, and any group able to delocalise a positive or negative charge at this position should facilitate this S_Ni-type reaction.[6]

On this basis it is difficult to reconcile the experimental results with the electronic nature of the various groups attached to the benzylic carbon in the transition state. Thus (see VI) the phenyl group would delocalise a



(VI)

positive (or negative) charge on the benzyl carbon, but the necessity of a 4-hydroxyphenyl group to promote dithiocarbamate formation indicates that additional electron release would be required from the 4-hydroxy-group. However, the 4-hydroxyphenyl group itself does not facilitate insertion in contrast to the 4-hydroxy-3,5-dimethoxyphenyl group, for example, which as a whole is *less* electron-releasing owing to the $-I$ effect of the methoxy-groups. This anomaly does not arise on the discrete quinone methide theory.

The *N*-benzylpiperidines [with the exception of (IIIb) and (IIIg)] were prepared either by the classical Mannich procedure [7] from the phenol, formaldehyde and piperidine, by interaction of a quinone methide with piperidine,[1] or (see Experimental section) by lithium aluminium hydride reduction of the corresponding amides. The latter were obtained from suitably substituted bromobenzenes by treatment with n-butyl-lithium and carbon dioxide to give the carboxylic acids, conversion of the acids into their acid chlorides, and finally condensation of the acid chlorides with piperidine.

N-(4-Hydroxybenzyl)piperidine (IIIb) was prepared by the method of Sam and Nobles [8] and nitrated to give *N*-(4-hydroxy-3-nitrobenzyl)piperidine (IIIg).

EXPERIMENTAL

N-Benzylpiperidines.—*4-Methoxy-3,5-dimethylbenzoic acid.* n-Butyl-lithium in n-hexane (2·25 mmoles/ml., 28 ml.) was cautiously added to a stirred solution of 4-bromo-2,6-dimethylanisole (13·1 g.) in sodium-dried ether (100 ml.) at 0—5°, under dry nitrogen. The mixture was stirred at room temperature for 20 hr. then added to solid carbon dioxide (*ca.* 100 g.) under ether. The ethereal solution was washed with an excess of 4N-hydrochloric acid and then with water, then extracted with 4N-sodium hydroxide. The combined extracts were acidified with concentrated hydrochloric acid and the precipitate was extracted with ether. Removal of the solvent left a white solid which was washed with light petroleum (b.p. 40—60°) to yield 4-methoxy-3,5-dimethylbenzoic acid (4 g.) as needles, m.p. 196—198° (lit.,[9] 188—189°).

By a similar procedure 2-bromo-4,6-dimethylanisole (15 g.) yielded 2-methoxy-3,5-dimethylbenzoic acid (3·3 g.) as plates, m.p. 99° (from aqueous ethanol) (lit.,[10] 97—98°).

4-Methoxy-3,5-dimethylbenzoyl chloride. 4-Methoxy-3,5-dimethylbenzoic acid (3·2 g.) in thionyl chloride (20 ml.) was heated under reflux for 0·5 hr.; excess of thionyl chloride was then distilled off. The residue afforded *4-methoxy-3,5-dimethylbenzoyl chloride* (2·5 g.) as needles, m.p. 40° [from light petroleum (b.p. 40—60°)] (Found: C, 60·3; H, 5·6. $C_{10}H_{11}ClO_2$ requires C, 60·4; H, 5·6%).

By a similar procedure, 2-methoxy-3,5-dimethylbenzoic acid (1·8 g.) afforded *2-methoxy-3,5-dimethylbenzoyl chloride* (1·4 g.) as plates, m.p. 38—39° [from light petroleum (b.p. 40—60°)] (Found: C, 60·8; H, 5·3. $C_{10}H_{11}ClO_2$ requires C, 60·4; H, 5·6%) and 3,4,5-trimethoxybenzoic acid (18 g.) yielded 3,4,5-trimethoxybenzoyl chloride (20·3 g.) as needles, m.p. 83—84° (lit.,[11] 77—78°).

N-(4-Methoxy-3,5-dimethylbenzoyl)piperidine. 4-Methoxy-3,5-dimethylbenzoyl chloride (2 g.) in light petroleum (b.p. 40—60°) (15 ml.) was added dropwise during 10 min. to a stirred solution of piperidine (2·1 g.) in light petroleum (b.p. 60—80°) (25 ml.). The slurry was stirred overnight then filtered. The filtrate was washed successively with N-hydrochloric acid and water, then dried ($MgSO_4$). The solvent was evaporated off and the residue gave *N-(4-methoxy-3,5-dimethylbenzoyl)piperidine* (2·2 g.) as plates, m.p. 107° (from aqueous ethanol) (Found: C, 72·9; H, 8·8. $C_{15}H_{21}NO_2$ requires C, 72·9; H, 8·6%).

By a similar procedure 2-methoxy-3,5-dimethylbenzoyl chloride (1·0 g.) yielded 2-methoxy-3,5-dimethylbenzoylpiperidine (0·9 g.) and 3,4,5-trimethoxybenzoyl chloride (20·3 g.) yielded *N*-(3,4,5-trimethoxybenzoyl)piperidine (11·2 g.), both of which were used directly in subsequent experiments.

[4] J. D. McClure, *J. Org. Chem.*, 1962, **27**, 2365.
[5] A. O. Fitton, A. Rigby, and R. J. Hurlock, *Chem. Comm.*, 1967, 163, and references therein.
[6] E. S. Gould, 'Mechanism and Structure in Organic Chemistry,' Holt, Rinehart, and Winston, New York, 1959, p. 282.
[7] F. F. Blicke, *Org. Reactions*, 1942, **1**, 303.
[8] J. Sam and D. M. Nobles, *J. Pharm. Sci.*, 1967, **56**, 729.
[9] G. Baddeley, N. H. P. Smith, and M. A. Vickars, *J. Chem. Soc.*, 1956, 2455.
[10] W. M. Lauer and D. W. Wujciak, *J. Amer. Chem. Soc.*, 1956, **78**, 5601.
[11] St. v. Kostanecki and J. Tambor, *Ber.*, 1906, **39**, 4022.

N-(4-*Methoxy*-3,5-*dimethylbenzyl*)*piperidine*. *N*-(4-Methoxy-3,5-dimethylbenzoylpiperidine (0·5 g.) in dry ether (20 ml.) was added dropwise during 0·5 hr. to a stirred slurry of lithium aluminium hydride (0·5 g.) in dry ether (40 ml.) and the mixture was stirred and heated under reflux for 24 hr., then cooled to 0°. Excess of lithium aluminium hydride was decomposed by dropwise addition of ethyl acetate (5 ml.). Water (*ca.* 10 ml.) and more ether were added to the mixture, which was filtered, and the ethereal filtrate was washed with water and dried. The solvent was evaporated off and the residue was distilled to yield N-(4-*methoxy*-3,5-*dimethylbenzyl*)*piperidine* (0·4 g.) as an oil, b.p. 166°/9 mm. (Found: C, 77·6; H, 9·8. $C_{15}H_{23}NO$ requires C, 77·2; H, 9·9%).

Similarly, *N*-(2-methoxy-3,5-dimethylbenzoyl)piperidine (0·8 g.) yielded N-(2-*methoxy*-3,5-*dimethylbenzyl*)*piperidine* (0·7 g.) as a pale yellow oil, b.p. 100°/0·5 mm. (Found: C, 77·4; H, 10·2. $C_{15}H_{23}NO$ requires C, 77·3; H, 9·9%) and *N*-(3,4,5-trimethoxybenzoyl)piperidine (3 g.) yielded *N*-(3,4,5-trimethoxybenzyl)piperidine (0·5 g.) as prisms, m.p. 42° [from light petroleum (b.p. 40—60°)] (lit.,[12] 43—44°).

N-(4-*Hydroxy*-3-*nitrobenzyl*)*piperidine*. *N*-(4-Hydroxybenzyl)piperidine (0·5 g.) in 4N-acetic acid (5 ml.) was added dropwise during 5 min. to stirred nitric acid (*d* 1·42; 10 ml.) at room temperature. The mixture was stirred for a further 3 hr. then neutralised with sodium carbonate and repeatedly extracted with ether. Evaporation of the dried extracts left a semi-solid residue which was chromatographed on a silica gel column with chloroform as eluant to yield *N*-(4-hydroxy-3-nitrobenzyl)piperidine (0·3 g.) as yellow needles, m.p. 142° (lit.,[13] 140°).

Reaction of N-*benzylpiperidines with Carbon Disulphide*.—A solution of the *N*-benzylpiperidine (1 mol.) and carbon disulphide (1 mol.) in ethanol was heated under reflux for up to 10 hr. then evaporated. The residue gave either starting material or a dithiocarbamate which was crystallised (see Table). The following compounds were prepared by this method: 4-*Hydroxy*-3,5-*dimethylbenzyl piperidine*-1-*carbodithioate*, m.p. 121° (Found: C, 61·0; H, 7·2; N, 4·5; S, 21·9. $C_{15}H_{24}NOS_2$ requires C, 61·2; H, 7·1; N, 4·8; S, 21·7%), and 4-*hydroxy*-3,5-*dimethoxybenzyl piperidine*-1-*carbodithioate*, m.p. 86° (Found: C, 55·1; H, 7·4; N, 4·1; S, 19·2. $C_{15}H_{24}NO_3S_2$ requires C, 55·1; H, 7·3; N, 4·3; S, 19·6%). Details of other dithiocarbamates mentioned in this paper are given elsewhere.[1]

Decomposition of 4-*Hydroxy*-3,5-*di-t-butylbenzyl Piperidine*-1-*carbodithioate in the Presence of Isoprene*.—A mixture of 3,5-di-t-butyl-4-hydroxybenzyl piperidine-1-carbodithioate (7·5 g.), nickel acetate (2·48 g.), and isoprene (25 ml.) in ethanol (25 ml.) was heated under reflux for 4 hr. then cooled and filtered. The residue was reslurried with hot ethanol (15 ml.) and filtered, and the filtrates were combined and cooled to precipitate starting material (3·7 g.). After filtration, the filtrate was evaporated and the residue was dissolved in ether. The solution was filtered, then chromatographed on silica gel (0·05—0·2 mm.) in benzene–light petroleum (b.p. 60—80°). Successive fractions yielded 2,4-di-t-butyl-9-methylspiro[5,5]undeca-1,4,8-trien-3-one (0·1 g.) as needles, m.p. 72° (lit.,[4] 73—74°), 3,5,3′,5′-tetra-t-butylstilbene-4,4′-quinone (5 mg.), m.p. 300° (decomp.) [lit.,[14] 315° (decomp.)], and starting material (1·1 g.).

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[12] K. Hejno and Z. Arnold, *Chem. listy*, 1953, **47**, 601.
[13] K. Auwers and A. Dombrowski, *Annalen*, 1906, **344**, 280.
[14] C. D. Cook, *J. Org. Chem.*, 1953, **18**, 261.