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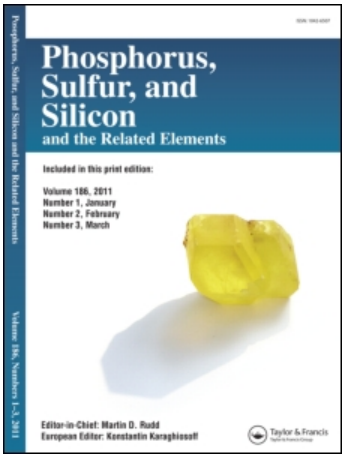

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REACTIONS OF *CIS*-3,5-DIBROMO-4-OXO-2,2,6,6-TETRAMETHYLPIPERIDIN-1-YLOXY WITH NITROGEN AND PHOSPHORUS NUCLEOPHILES

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The title free radical can be used to spin label biochemically important amines, but not those which it oxidizes, e.g., epinephrine (adrenaline), and diamines. Product analysis of the reaction between the radical and triethyl phosphite gives evidence that the first step in the Perkow reaction may occur *via* halogen attack giving enolate bromophosphonium ion pair as the common intermediate.

Key words: Spin labelling; L-amino alcohols; ephedrine; diamines; Perkow reaction; mechanism.

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INTRODUCTION

The free radical *cis*-3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidin-1-yloxy, 1, was introduced as a selective spin labelling agent for primary and secondary amino functions.[1] It reacts directly, *via* Favorskii rearrangement, with amines of sufficiently high basicity giving spin labelled amides, 2, in the presence of —OH, —SH and $—COO^-$ groups. Thus, spin labelled penicillin[2] and antiarrhythmic drugs[3,4] have been prepared.

Although the use of nitroxyl radicals has shifted towards *functional* biological systems, e.g. as contrast agents for NMR imaging (for pertinent references see Reference 5) they, as probes, can still afford valuable information on the structure and dynamics of membranes, proteins and enzymes.[6] Radical-metal spin-spin interaction is also of value for understanding intra-molecular electron-electron exchange.[7]

Herein we report on the usefulness of 1 to spin label various biochemically important amines as well as on its reaction with triethyl phosphite which bears on the mechanism of the Perkow reaction.

RESULTS AND DISCUSSION

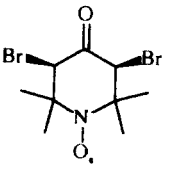
The reaction of 1 with L-valinol, L-leucinol and L-prolinol gave 2a–2c as oils which crystallized with difficulty. Since these amino alcohols are inhibitors of protein synthesis,[8] 2a–2c can be useful for further studies on the subject.

From the adrenergic compounds only (-)-ψ-ephedrine could be labelled to 2d. Dopamine, (±)epinephrine (adrenaline) and norepinephrine (noradrenaline) suf-

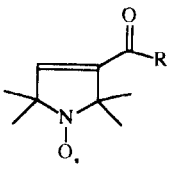
fered rapid oxidation by 1. Spin labelled adrenergic compounds could be used to monitor the free *vs* bound mother compounds.

Spin labelling one $—NH_2$ of an unprotected ethylenediamine gave an oil which was difficult to purify while spin labelling both $—NH_2$ groups of diamines to give dinitroxyl compounds was easy. Dinitroxyls 3 and 4 (n = 2, 3, 4, 6) had been prepared by us some years ago. The preparation of 3 and a more complete series of 4 (n = 2–10) has already been published by Brik[9] and supplementary analytical data on 3 and 4a–4d are shown in Table I. The biradicals can be used as radiosensitizers[10] and as ligands for complex formation.

While nitrogen nucleophiles react with 1 presumably by abstracting the α-hy-



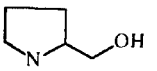
1



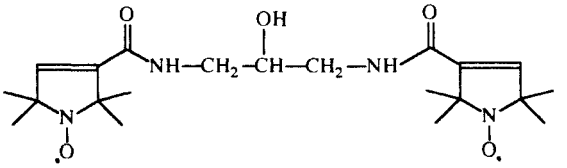
2

a. R = NH—CH(CH$_2$OH)—CHMe$_2$

b. R = NH—CH(CH$_2$OH)—CH$_2$—CHMe$_2$

c. R = 

d. R = N(CH$_3$)—CH(CH$_3$)—CH(OH)— 



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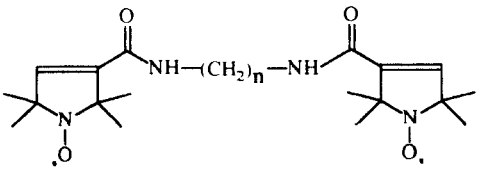

4

a. n = 2 b. n = 3
c. n = 4 d. n = 6

Formulae 1 - 4

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drogen,[1] trialkyl phosphite can attack[11] at the α-carbon, the carbonyl carbon, the carbonyl oxygen or the α-bromine of 1 giving eventually the Perkow product 8.

The reaction of 1 with triethyl phosphite can be effected in acetonitrile or ether/acetonitrile, but not in ether, at room temperature. The reaction gave at least 6 products, 4 of which were isolated in pure form accounting for 82% of the radical 1 used.

The IR spectrum of 5 in KBr showed absence of phosphoryl group and presence of weak absorptions at 3089 and 1664 cm^{-1} due to H—C=C—O grouping and a very strong peak at 1743 cm^{-1} due to C=O stretching.[12a,b] An analogous enol ester had C=O stretching at 1740 cm^{-1}.[1] A weak peak in the spectrum of 5 at 1628 cm^{-1} could not be assigned.

Compound 6 showed no phosphoryl and C=C absorptions in the IR spectrum (KBr). A strong peak at 1738 cm^{-1} was indicative of a cyclic ketone bearing equatorial α-halogen.[12c] The radical 1 has equatorial bromine atoms (from x-rays analysis).[1] From other experiments we isolated and recrystallized two compounds which had the same R_f value and exactly the same IR (in KBr) spectra with 6 but different melting points and UV (in methanol) spectra: [77°C; λ_{max} 221 nm, ε_M 5.7 × 10^3, λ 209 nm, ε_M 5.6 × 10^3 and 154°C dec.; λ_{max} 201 nm, ε_M 7.5 × 10^3, λ_{sh} 219; found C 43.85, H 5.95%]. It seems that these 3 compounds are cis/trans isomers. 6 reacted very slowly (31 days at room temperature) with excess triethyl

TABLE I

Yields and analytical data of the spin labelled amides from L-amino alcohols, ephedrine and diamines

Compound	Yield, %	M.p., °C	% Analyses calcd (found) C	H	UV (in MeOH) λ_{max}, nm	λ_{sh}, nm	ε_{max}, x10^3	IR (in CH_2Cl_2) amide I cm^{-1}	C=C cm^{-1}	N-O· cm^{-1}
2a	74	140-2	62.42 (62.71)	9.36 (9.20)	219	235	7.9	1665s	1620m	1360m
2b	55	104-6	63.57 (63.41)	9.60 (9.52)	212	235	10.0	1665s	1620s	1360m
2c	44	94-6	62.89 (62.35)	8.68 (8.68)	218	236	8.7	1650m	1610s	1365m
2d	80	131-3	68.85 (68.87)	8.21 (8.31)	206	-	9.2	1649m	1610s	1361m
3	43	~77*	59.70 (59.27)	8.11 (7.94)	213	235	15.0	1660s	1620s	1360m
4a	60	238 d	61.20 (60.94)	8.22 (8.36)	216	235	14.7	1660s	1610s	1355m
4b	67	186-8	62.04 (62.32)	8.43 (8.52)	213	235	12.7	1665s	1620s	1360m
4c	64	210 d	62.83 (62.82)	8.63 (8.74)	213	235	14.0	1660s	1615s	1355m
4d	80	158-9	64.26 (64.26)	8.99 (9.10)	218	235	19.0	1660s	1620s	1360m

* no clear m.p

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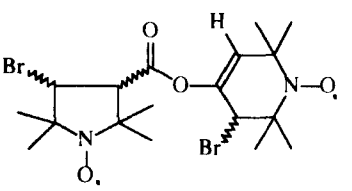

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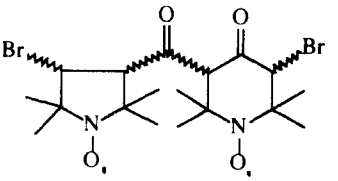

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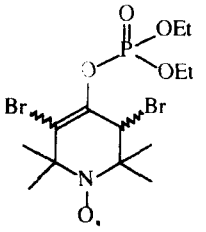

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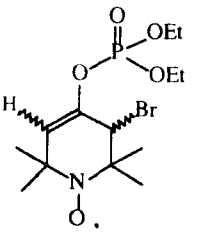

8

Formulae 5 - 8

phosphite in acetonitrile to give a major spot at R_f 0.27 (ether/hexane 1:1 v/v) presumed to be the Perkow product of 6.

The Perkow product 8 was a dark red viscous oil and its IR spectrum (neat) showed a medium-to-weak peak at 1685 cm^{-1} which was 25 cm^{-1} higher than the normal range of enol phosphate C=C stretching.[13] The H—C=C stretching was too weak to be clearly seen at 3000–3100 cm^{-1}. The P=O absorption was in the normal range while the P—O—C absorption was at lower frequency than normally found (1165–1155 cm^{-1}).[13]

Compound 7 was a dark red (indicative of a 6-membered nitroxyl) oil, slightly less polar than 8 and its IR spectrum (neat) showed that it was a phosphate ester with P=O and P—O—C absorptions as in 8. A medium-to-strong peak at 1664 cm^{-1} was by ~20 cm^{-1} lower than the corresponding peak of 8 indicative of the presence of C=C—X (X=Cl, Br or I) grouping.[14] There also was a very weak peak at 1727 cm^{-1}, the intensity of which varied in different samples, and was attributed to a contaminant, probably the Perkow product of 6, thus explaining the slightly higher %C found.

The phosphate enol esters, 7 and 8, in acetonitrile were very slowly hydrolysed by 0.2 M HCl at room temperature giving less and more polar products (TLC analysis) while by 0.2 M NaOH they reacted faster giving only more polar compounds, indicative of nucleophilic attack by HO^- on —Br and not on the phosphate group.[13]

While 2,6-dibromocyclohexanone gave a Perkow + Arbusov product[13] (Reference 41 on page 611 is wrongly cited in the review of Lichtenthaler[13]) the Arbusov

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product of 8 was not formed in our system at room temperature even when excess triethyl phosphite was used.

A reasonable mechanism by which 6–8 arise is shown in Scheme 1. Triethyl phosphite abstracts α-Br giving an ion pair (intimate or solvent separated) [(9, 10) + 11]. Enolate bromophosphonium ion pairs have previously been postulated in reaction of α-bromoketones with tricovalent organophosphorus compounds.[15] Attack of 9 or 10 on the positive carbonyl carbon of 1 gives, *via* Favorskii rearrangement, the by-products 6 (major) and 5 (minor) with expulsion of Br^-. This Br^- then dealkylates 11 giving the phosphorobromidate 12 which, in turn, phosphorylates the enol form of 1, 1′, to give 7. Such a mechanism requires that the moles of 7 be equal to the moles of 5 + 6 and this was indeed found (0.463 mmol 7 *vs* 0.445 mmol 5 + 6). An analogous by product to 7 has been isolated by Koziara et al.[16] Attack of 10 on 11 can form irreversibly[15] a quasi-phosphonium intermediate[11] which is dealkylated by Br^- to give the Perkow product 8. From the relative amounts of 5, 6 and 8 it seems that 9 attacks the carbonyl carbon of 1 giving 6 while 10 prefers to attack 11 giving 8.

Relatively few examples are found in the literature pertaining to the initial attack of phosphines[15] and phosphites[16–19] on the α-halogenoketones. The substrates are α-bromoketone[15] α,α-dibromoketones[16,17] or trichloroacetic acid derivatives,[19] i.e., compounds with sufficiently positive α-halogen.

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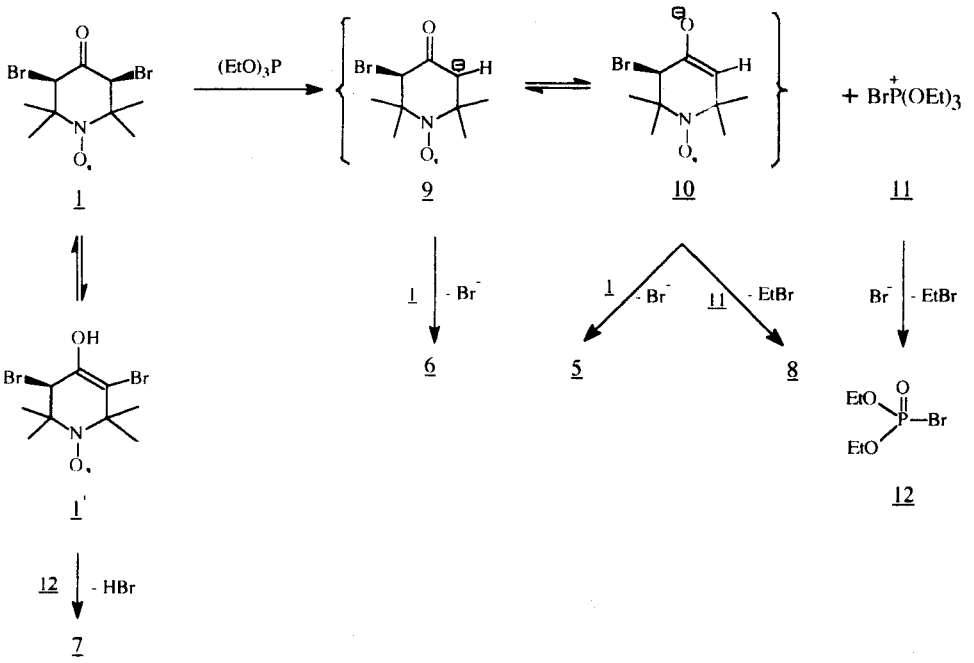
EXPERIMENTAL

The radical 1 was prepared as described,[1] and it is also commercially available (Lancaster Synthesis Ltd., Eastgate, White Lund, Morecambe, Lancs., LA3 3DY, England). L-Valinol, L-leucinol,



Scheme 1

TABLE II

Yields and analytical data of the products from the reaction of 1 with triethyl phosphite

Compound	% radical 1 used	M.p., °C	% Analyses calcd (found) C	H	UV (in MeOH) λ_{max}, nm	$\lambda_{sh.}$, nm	ε_{max}, x10^3	IR [neat or disk (KBr)] N-O• cm^{-1}	P=O cm^{-1}	P-O-C cm^{-1}
5	2.4	159-160	43.56	5.69	215	-	2.7	1360m	-	-
			(43.64)	(5.56)						
6	42.1	80-2	43.56	5.69	213	-	9.1	1365s	-	-
			(43.45)	(5.95)						
7	23.2	-	33.64	4.99	201	222	13.4	1366m	1287s	1036vs
			(34.45)	(5.21)						
8	14.8	-	40.53	6.26	210	-	7.1	1360m	1278s	1036vs
			(40.36)	(6.35)						

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L-prolinol and 1,3-diamino-2-hydroxypropane were from Aldrich while (-)-ψ-ephedrine was from Sigma. Acetonitrile was dried over A_4 molecular sieves. TLCs were run on microslides coated with silica gel type 60H (Merck); visualization was effected by spraying with 35% H_2SO_4 and charring. Silica gel Si60 (Serva) was used for column chromatogrphy. IR and UV spectra were taken on Perkin Elmer models 16 PC FT-IR and 551 S instruments respectively.
Elemental analyses were done by the Centre National de la Recherche Scientifique, Vernaison, France and by Dr. J. Mantzos of National Hellenic Research Foundation, Athens, Greece.

Reaction of 1 *with amines.* To a solution of 1 mmol of —NH_2 or =NH grouping in dichloromethane (4–10 ml) containing 2 mmol triethylamine, 1 mmol radical 1 was added and stirred for 2 h at room temperature. Concentration and silica gel chromatography (~20 g/mmol, elution with CH_2Cl_2/Me_2CO 6:1 or 3:1 v/v) gave the products: 2a, yellow powder; 2b, yellow crystals after trituration with hexane; 2c, sticky orange oil which forms yellow crystals after 3 months at −20°C; 2d, oil which forms yellow crystals after 3-4 days; 3, sticky yellow foam; 4a–d, yellow crystals. Data are shown in Table I.

Reaction of 1 *with triethyl phosphite.* A suspension of 2 mmol of radical 1 and 2 mmol triethyl phosphite in dry acetonitrile (10 ml) was stirred at room temperature for 5 h. Clear solution resulted after 4 h. TLC revealed the presence of at least 6 compounds. The solution was concentrated and applied onto silica gel (100 g in ether/hexane 1:1 v/v). Elution was effected with ether/hexane 1:1 v/v till the first orange band appeared and then with ether. The compounds isolated in pure by TLC state were (R_f in ether/hexane 1:1 v/v, weight in mg, color): 5 (0.67, 12, orange crystals), 6 (0.57, 209 orange crystals), 7 (0.30, 215, dark red oil) and 8 (0.17, 114, dark red oil). 5 and 6 were recrystallized from hexane. Data are shown in Table II.

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REFERENCES

1. N. W. Alcock, B. T. Golding, P. V. Ioannou and J. F. Sawyer, *Tetrahedron*, **33,** 2969 (1977).
2. D. Cookson, R. J. P. Williams, B. T. Golding and P. V. Ioannou, *J. Inorg. Nucl. Chem.*, **41,** 1089 (1979).
3. Y. Yost and J. L. Holtzman, *Org. Prep. Proc. Int.*, **17,** 239 (1985).

4. O. Hankovszky, K. Hideg, I. Bódi and L. Frank, *J. Med. Chem.*, **29,** 1138 (1986).
5. G. Sosnovsky, N. V. M. Rao, S. W. Li and H. M. Swartz, *J. Org. Chem.*, **54,** 3667 (1989).
6. L. J. Berliner (Editor), "Spin Labeling. Theory and Applications," (Academic Press, New York, 1976).
7. G. R. Eaton and S. S. Eaton, *Acc. Chem. Res.*, **21,** 107 (1988).
8. a) F. Rouget and F. Chapeville, *Eur. J. Biochem.*, **4,** 305 (1968); b) B. S. Hansen, M. H. Vaughan and L.-J. Wang, *J. Biol. Chem.*, **247,** 3854 (1972).
9. M. E. Brik, *Synth. Commun.*, **20,** 1487 (1990).
10. B. C. Millar, T. C. Jenkins and E. M. Fielden, *Radiat. Res.*, **90,** 271 (1982).
11. a) P. A. Chopard, V. M. Clark, R. F. Hudson and A. J. Kirby, *Tetrahedron*, **21,** 1961 (1965); b) R. F. Hudson, "Structure and Mechanism in Organo-phosphorus Chemistry," (Academic Press, London, 1969) pp. 153–160.
12. A. D. Cross and R. A. Jones, "An Introduction to Practical Infra-red Spectroscopy," (Butterworths, London, 1969), 3rd ed., a) p. 74, b) p. 87, c) p. 85.
13. F. W. Lichtenthaler, *Chem. Rev.*, **61,** 607 (1961).
14. S. F. Dyke, A. J. Floyd, M. Sainsbury and R. S. Theobald, "Organic Spectroscopy: an Introduction," (Penguin, London, 1971), p. 69.
15. I. J. Borowitz and R. Virkhaus, *J. Am. Chem. Soc.*, **85,** 2183 (1963).
16. A. Koziara, B. Mlotkowska, P. Majewski, B. Sledzinski and A. Zwierzak, *Pol. J. Chem.*, **55,** 399 (1981).
17. I. J. Borowitz, K. C. Yee and R. K. Crouch, *J. Org. Chem.*, **38,** 1713 (1973).
18. L. Toke, I. Petnehazy, G. Szakal, H. R. Hudson, L. Powroznyk and C. J. Christopher, *ACS Symp. Ser.*, **171,** 513 (1981).
19. S. A. Levmontov, S. I. Zavorin, I. I. Sukhozhenko, A. N. Pushin and I. V. Martynov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 468 (1991).

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