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# PREPARATION, CRYSTAL STRUCTURE AND REACTIONS OF A NEW SPIN-LABELLING REAGENT, *CIS*-3,5-DIBROMO-4-OXO-2,2,6,6-TETRAMETHYLPIPERIDIN-1-YLOXY

## CRYSTAL STRUCTURE OF A DERIVED *BIS*-NITROXIDE

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**Abstract**—Methods for the preparation of *cis* - 3,5 - dibromo - 4 - oxo - 2,2,6,6 - tetramethylpiperidin - 1 - yloxy (**2b**) and its use as a convenient, selective spin-labelling reagent for amino functions, are described. The crystal and molecular structures of **2b** and the *bis*-nitroxide **4** - [(2',2',5',5' - tetramethylpyrrolin - 1 - yloxy) - 3' - carbonyloxy] - 2,2,6,6 - tetramethyl - 3,5 - dibromo - 3,4 - dehydropiperidin - 1 - yloxy (**3**) [obtained on treatment of **2b** with triethylamine] have been determined by conventional heavy-atom techniques. In **2b** the individual molecules have mirror symmetry with the bromine atoms equatorial. The N–O bond length is 1.278(5) Å, CN̂C is 125.1(3)° and the N–O bond makes an angle of 24.2° with the CN̂C plane. In **3** there are two different nitroxide groups. The pyrrolinyloxy ring is virtually planar with a N–O bond length of 1.252(13) Å and CN̂C of 113.1(10)°. The 6-membered ring exists in a sofa conformation with a pseudoaxial Br atom. Its nitroxide group is tetrahedrally distorted. The N–O bond length is 1.268(15) Å, CN̂C is 121.7(10)° and the N–O bond makes an angle of 16.0° with the CN̂C plane. The packing of **3** is dictated by a short Br....O secondary bond of 3.09(1) Å, 0.28 Å less than the sum of the van der Waal's radii resulting in dimeric units related by a centre of symmetry.

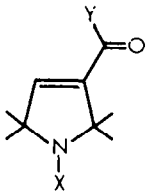
We wished to use spin-labelled probes for studies of the biochemistry of β-lactam antibiotics and for investigations of adenosylcobalamin-dependent enzymatic reactions. The most widely used spin-labels are the stable nitroxide radicals derived either from oxazolidines, 2,2,5,5-tetramethylpyrrolines, 2,2,5,5-tetramethylpyrrolidines or 2,2,6,6-tetramethylpiperidines.[1] We envisaged preparing a spin-labelled penicillin by coupling 6-aminopenicillanic acid with 3 - carboxy - 2,2,5,5 - tetramethyl - 3 - pyrrolin - 1 - yloxy (**1a**). The use of an achiral nitroxide such as **1a** was preferred to avoid the formation and perhaps difficult separation of diastereoisomers if a chiral nitroxide were used (e.g. rac. - 3 - carboxy - 2,2,5,5 - tetramethyl-pyrrolidin - 1 - yloxy).

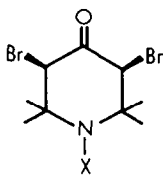
While attempting to effect such a coupling, it occurred to us that the desired objective might be more easily achieved by exploiting the acylating ability of 3,5 - dibromo - 4 - oxo - 2,2,6,6 - tetramethylpiperidine (**2a**). The hydrobromide of this substance is the cornerstone of the synthesis of numerous nitroxides from 4 - oxo - 2,2,6,6 - tetramethylpiperidine, since treating **2a**-hydrobromide with ammonia gives **1b** which, after oxidation to the corresponding nitroxide (**1c**) can be transformed to other pyrroline nitroxides and to pyrrolidine nitroxides.[2] Pauly[3] had shown that **2a** also reacts with primary and secondary amines of sufficiently high basicity (e.g. benzylamine and piperidine, but not aniline) to give 3 - (N - substituted) - aminocarbonyl - 2,2,5,5 - tetramethyl - 3 - pyrrolines (**1d**). The nitroxide of **2a**, 3,5 - dibromo - 4 - oxo - 2,2,6,6 - tetramethylpiperidin - 1 - yloxy (**2b**) ought to behave similarly, thereby providing a direct entry to 3 - (N - substituted) - aminocarbonyl - 2,2,5,5 - tetramethyl - 3 - pyrrolin - 1 - yloxy radicals (**1e**). Similar considerations led us to investigate 3 - bromo - 4 - oxo - 2,2,6,6 - tetramethylpiperidin - 1 - yloxy as a potential precursor of 3 - (N - substituted) - aminocarbonyl - 2,2,5,5 - tetramethyl - 3 - pyrrolidin - 1 - yloxy radicals. However, whilst **2b** was highly suitable for its intended purpose, the monobromo analogue could not be readily prepared in pure form and in any case was found to be too unreactive for the direct acylation of amines.[4]

A preliminary communication describing a preparation of **2b** and its conversion to amides (**1e**) has been published.[5]

### RESULTS AND DISCUSSION

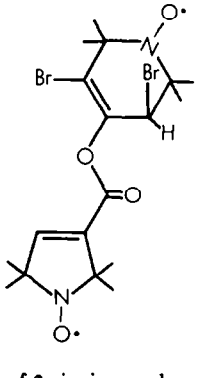
(a) *Synthesis of* **2a** *and* **2b**. The hydrobromide of **2a** has been prepared by brominating 4 - oxo - 2,2,6,6 - tetramethylpiperidine with either bromine in 60% hydrobromic acid at 90°[6] or bromine in glacial acetic acid at room temperature.[7] Examination of the crude products from these reactions by $^1$H NMR spectroscopy suggests that they are mixtures of two isomers [*cis* - **2a** + rac. - *trans* - **2a** assuming, by analogy with the behaviour of cyclohexanones,[8] that the major products are 3,5-dibromo isomers]. However, the ratio of these isomers differs: 2:1 (method of Ref. 6), 4:6 (method of Ref. 7*a*). Treatment of either of these mixtures with mild base gives, as expected, a product which is a mixture of two isomers ($^1$H NMR analysis). This product can be recrystallised from ethyl acetate to give a pure isomer of **2a** [29–43% yield] only when **2a** is prepared by the method of Pauly.[6] Presumably the isomer of **2a** which crystallises is that which predominates in the mixture. When **2a** is prepared by the method of Ref. 7*a*, this isomer is the minor component of the mixture and cannot be crystallised from ethyl acetate. That this isomer is *cis* - 3,5 - dibromo - 4 - oxo - 2,2,6,6 - tetramethylpiperidine is indicated by the resonance of its protons (2 × C<u>H</u>Br) at δ 4.54 [*cf. cis* - 2,6 - dibromo - 3,3,5,5 - tetramethylcyclohexanone (C<u>H</u>Br: δ 4.78) and data for other model compounds in Ref. 9]. The stereochemistry of the





(1a) X = O·, Y = OH
(1b) X = H, Y = $NH_2$
(1c) X = O·, Y = $NH_2$
(1d) X = H, Y = NHR (various R)
(1e) X = O·, Y = NHR (various R)
(1f) X = O·, Y = N - cyclohexylamino
(1g) X = O·, Y = NH-$CH_2$Ph (Ph = phenyl)
(1h) X = O·, Y = NH -$CH_2CH_2OH$
(1i) X = O·, Y = NH - $CH_2CO_2Et$
(1j) X = O·, Y = N -piperidinyl
(1k) X = O·, Y = $NHCH_2CHOHCH_2OH$
(1l) X = O·, Y = $OCHMe_2$
(1m) X = O·, Y = OEt

(2a) X = H
(2b) X = O·



(3)

crystallised isomer of **2a** is rigorously proved to be *cis* by its conversion to **2b**, the structure of which has been established by X-ray analysis (see below).

Optimal conditions for the preparation of **2b** by oxidising pure or crude **2a** with *m*-chloroperbenzoic acid[10,11] are detailed in the Experimental. This reaction goes efficiently in diethyl ether [>70% of **2b** routinely obtained], but not in dichloromethane (0% yield of **2b**). The nitroxide (**2b**) is insoluble in ether and precipitates as it is formed and is thereby protected from further oxidation. However, in dichloromethane (**2b**) is more soluble and is further oxidised, presumably at a rate comparable to its rate of formation. A preliminary investigation of the products from over-oxidation of **2b** shows one of them to contain an isopropenyl group, which must arise by cleavage of the ring of **2b** and loss of a proton from one of its Me groups.

Initially, we used the pure *cis*-**2a** to prepare **2b**. This requires that **2a**-hydrobromide be prepared by Pauly's method.[6] It was subsequently found that due to the favourable solubility properties of **2b** it could be obtained by directly oxidising the crude **2a** (mixture of isomers prepared by either method[6,7a]) with *m*-chloroperbenzoic acid.

(b) *Reactions of* **2b** *with amines.* Addition of a primary or secondary amine to a stirred suspension of **2b** in dichloromethane brings about a rapid reaction leading to 3 - (N - substituted) - aminocarbonyl - 2,2,5,5 - tetramethyl - 3 - pyrrolin - 1 - yloxy radicals. Either at least 3 equivalents of the amine are used, or if desired, one equivalent of the reacting amine is added, with two equivalents of triethylamine. The product amides (**1f–1k**) from these reactions can be easily isolated chromatographically and are analytically pure. Their structures are confirmed by analytical data, IR spectra [*inter alia* absorptions at *ca.* 1665 (amide I), 1620 (C=C stretch) and 1360 $cm^{-1}$ (N–O·) (in $CHCl_3$)] ESR spectra (characteristic triplet) and mass spectra (characteristic M–NO fragment). The ease of preparation of **2b**, its high reactivity and selectivity towards amino functions [in the presence of other functional groups: hydroxy (*vide infra*), carboxyl anion and sulphide] and the simplicity of experimental operations using it, make **2b** an advantageous reagent for preparing 3 - (N - substituted) - aminocarbonyl - 2,2,5,5 - tetramethyl - 3 - pyrrolin - 1 - yloxy radicals (**1f–1k**), which include the potential substrate (**1k**) for glycerol dehydrase. The application of **2b** to the preparation of a spin-labelled pencillin and spin-labelled phospholipid will be described elsewhere. Previously, amides of the type **1f–1k** have been prepared by coupling an amine with a suitably activated derivative of the acid (**1a**). Our procedure is much easier.

(c) *Conversion of* **2b** *to* **3**. The reaction between **2b** and aminoalcohols (e.g. with ethanolamine → **1h**) results in selective acylation of their amino function. When **2b** was stirred with triethylamine (2 mol equiv) and isopropanol (1 mol equiv) in dichloromethane, a compound of molecular formula $C_{18}H_{26}Br_2N_2O_4$ was obtained. This substance also arises from treating **2b** with triethylamine alone and is a by-product from reactions between **2b** and amino compounds of relatively low basicity (e.g. ethyl glycinate).

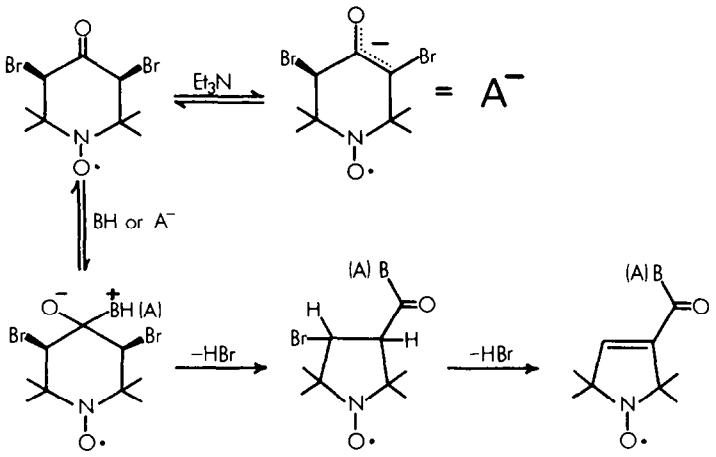
When **2b** is treated with triethylamine (3.3 mol equiv) in isopropanol as solvent, an approximately 1:1 mixture of a compound presumed to be the ester (**1l**) and the substance $C_{18}H_{26}Br_2N_2O_4$ is formed. However, sodium ethoxide (2 mol equiv) in ethanol converts **2b** exclusively to the ester **1m**.

The structure of the substance $C_{18}H_{26}Br_2N_2O_4$ was rigorously established as **3** by X-ray crystallography (see below).

(d) *Mechanism of the formation of amides by reacting amines with* **2b** *and the origin of* **3**. Apart from its obvious relationship to the Favorskii rearrangement, the detailed mechanisms of the conversions of **2b** to amides (**1f–1k**) and to **3** cannot be specified without further studies. The reactions between **2b** and primary and secondary amino functions could go via a "semi-benzilic" pathway (Scheme 1). The reactive intermediates of Scheme 1 could also arise on treating **2b** with triethylamine, which might induce a reaction between **2b** and its anion. **3** is rather unreactive towards nucleophiles, being only slowly converted to **1g** on incubation with benzylamine.

## DISCUSSION OF CRYSTALLOGRAPHIC RESULTS

The crystals of **2b** contain discrete molecules possessing mirror symmetry, the carbonyl and nitroxide bonds lying in the mirror plane. The conformation adopted by the piperidine ring is a slightly flattened chair with the bromine atoms equatorial (Fig. 1). The CO group is planar although the N–O bond makes an angle of 24.2° with the CNC plane. This angular distortion at nitrogen




Scheme 1. Possible mechanisms for the formation of amides (**1e**) and *bis*-Nitroxide (**3**). [BH = primary or secondary amine; $A^-$ = anion of (**2b**)].

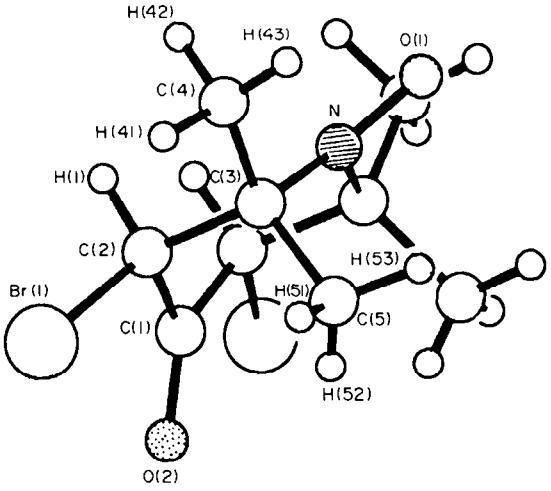



Fig. 1. The molecule of **2b**: large circles represent Br atoms, stippled circles O atoms and shaded circles N atom(s).

towards tetrahedral is typical of 6-membered rings containing the nitroxide bond and is discussed below.

The Br atoms of **2b** prefer to be equatorial as a consequence of the "reflex effect"[12] which originates in the mutual repulsion of two bulky axial substituents. In this case, with bromine equatorial, the puckering in the ring, as seen in the torsion angles (Table 1) increases the 1,3-diaxial separations of the bulkier Me groups and hence reduces non-bonding repulsions. Similar effects occur in 2 - bromo - and 2,6 - dibromo - 3,3,5,5 - tetramethylcyclohexanone which are both known from crystallographic results to contain equatorial Br atoms.[13] Other workers using dipole moment measurements or the chemical shifts of the bromomethine proton in brominated tetrahydropyranone or cyclohexanone rings have also shown that conformations with bromine equatorial may be favoured despite the intramolecular electrostatic repulsion between the C–Br and C=O dipoles.[9,14]

In the present structure the intramolecular Br....O (CO) separation is 3.045 Å, less than the sum of the appropriate van der Waal's radii. Comparatively short Br....O contacts of 2.97–2.99 were found in the two bromocyclohexanone structures noted above and also in 2,4 - dibromo - 1,5 - diphenyl penta - 1,4 - dien - 3 - one which has the ZZ configuration about the two double bonds (due again to the steric requirements of other bulkier groups)[15] resulting in adjacent Br and O and Br....O of 2.93–2.95 Å. Other evidence of strain in the piperidine ring is the small C(2)–C(1)–C(2') angle (108.2(6)°) which reduces the repulsion between the C–Br and C=O dipoles.

The packing of the individual molecules of **2b** is dictated by normal van der Waal's forces (Fig. 2). There appears to be no close intermolecular interactions involving the nitroxide bond (in contrast to 9 - aza -

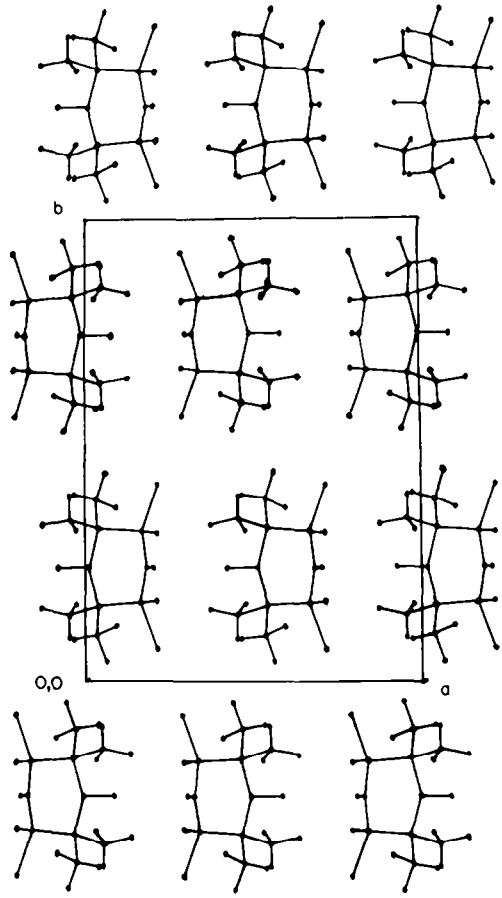



Fig. 2. Packing diagram for **2b** (viewed down *c*).

Table 1. Atomic co-ordinates ($\times 10^4$) and anisotropic temperature factors† ($\times 10^3$) with standard deviations in parentheses

(a) 3,5-dibromo-4-oxo-2,2,6,6-teramethylpiperidin-1-yloxy (2b)

| Atom | X | Y | Z | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{12}$ | $U_{13}$ | $U_{23}$ |
|---|---|---|---|---|---|---|---|---|---|
| Br(1) | 2127.1(3) | 736.0(2) | -961.5(6) | 40.6(2) | 29.1(2) | 59.3(3) | 6.8(2) | 8.8(2) | -4.5(2) |
| O(1) | -776(3) | 2500(0) | 3776(7) | 43(2) | 45(2) | 45(2) | 0(0) | 24(2) | 0(0) |
| O(2) | 1998(3) | 2500(0) | -2817(6) | 52(2) | 38(2) | 34(2) | 0(0) | 14(2) | 0(0) |
| N | 106(3) | 2500(0) | 2499(7) | 23(2) | 28(2) | 28(2) | 0(0) | 1(2) | 0(0) |
| C(1) | 1821(3) | 2500(0) | -835(10) | 21(2) | 28(2) | 42(3) | 0(0) | 0(2) | 0(0) |
| C(2) | 1654(3) | 1735(2) | 627(6) | 25(1) | 25(1) | 33(2) | 2(1) | -2(1) | -3(1) |
| C(3) | 405(3) | 1666(2) | 1486(5) | 28(2) | 26(1) | 28(2) | -1(1) | 2(1) | -2(1) |
| C(4) | 337(4) | 1027(2) | 3390(7) | 60(3) | 32(2) | 36(2) | -1(2) | 8(2) | 6(2) |
| C(5) | -450(3) | 1463(3) | -371(7) | 29(2) | 44(2) | 40(3) | -5(2) | -1(2) | -8(2) |

| Atom | X | Y | Z | U | Atom | X | Y | Z | U |
|---|---|---|---|---|---|---|---|---|---|
| H(1) | 2169(29) | 1777(20) | 2009(56) | 26(8) | H(51) | -393(36) | 943(31) | -743(67) | 52(12) |
| H(41) | 583(36) | 502(30) | 2745(76) | 63(13) | H(52) | -315(37) | 1774(29) | -1642(73) | 53(13) |
| H(42) | 841(38) | 1181(28) | 4709(79) | 61(13) | H(53) | -1213(37) | 1575(23) | 253(60) | 44(11) |
| H(43) | -479(41) | 924(27) | 3985(69) | 62(12) | | | | | |

(b) The ester (3) derived from (2b)

| Atom | X | Y | Z | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{12}$ | $U_{13}$ | $U_{23}$ |
|---|---|---|---|---|---|---|---|---|---|
| Br(1) | 2182.9(13) | 761.1(5) | 1120.8(11) | 83.4(11) | 43.1(9) | 78.1(11) | 12.1(11) | 3.5(12) | 19.8(10) |
| Br(2) | 1733.2(17) | 1967.8(6) | -1660.5(12) | 131.1(16) | 85.1(13) | 50.9(9) | 25.9(13) | -5.0(13) | 15.5(11) |
| O(1) | 511(9) | 2366(3) | 1186(8) | 76(8) | 61(9) | 100(10) | 30(7) | 21(8) | -8(7) |
| O(2) | 7801(7) | 209(2) | -1806(6) | 21(6) | 48(6) | 69(6) | 14(5) | 9(6) | 3(5) |
| O(3) | 5067(8) | 1325(3) | 418(6) | 69(8) | 99(8) | 49(6) | 31(6) | -32(6) | -50(6) |
| O(4) | 3507(7) | 1186(3) | -640(6) | 30(6) | 57(6) | 45(6) | 22(5) | 4(5) | -18(5) |
| N(1) | 1317(10) | 2097(4) | 859(8) | 36(10) | 32(9) | 52(8) | 9(7) | 12(7) | -17(7) |
| N(2) | 6817(9) | 401(3) | -1665(7) | 31(7) | 37(7) | 43(6) | 11(6) | 9(7) | -8(6) |
| C(1) | 2132(13) | 1360(4) | 678(11) | 42(11) | 13(8) | 51(9) | 16(9) | -8(9) | -6(8) |
| C(2) | 2801(13) | 1489(5) | -94(9) | 26(10) | 54(12) | 18(8) | -1(10) | 4(9) | -16(8) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| C(3) | 2851(11) | 1956(4) | -462(9) | 50(10) | 29(9) | 54(9) | 10(10) | -12(9) | 0(8) |
| C(4) | 2441(13) | 2260(4) | 411(11) | 53(13) | 20(9) | 76(12) | 7(8) | 17(10) | 1(8) |
| C(5) | 1200(11) | 1639(4) | 1243(9) | 62(11) | 36(10) | 32(9) | 5(9) | 15(8) | 5(8) |
| C(6) | 1444(12) | 1637(5) | 2413(11) | 93(12) | 83(12) | 58(10) | -23(10) | 11(11) | -2(10) |
| C(7) | -74(11) | 1473(4) | 1014(11) | 42(10) | 78(10) | 97(12) | 17(8) | 23(10) | -15(9) |
| C(8) | 3449(12) | 2287(5) | 1134(12) | 77(11) | 85(14) | 110(15) | -25(10) | -14(12) | -33(11) |
| C(9) | 2209(13) | 2727(4) | -45(12) | 117(13) | 31(9) | 150(14) | -11(10) | 21(13) | -6(9) |
| C(10) | 4659(11) | 1139(4) | -306(8) | 35(10) | 40(8) | 35(8) | 15(8) | -7(8) | -10(7) |
| C(11) | 5306(13) | 827(4) | -978(10) | 46(12) | 32(10) | 26(10) | 13(9) | 9(9) | -7(8) |
| C(12) | 4845(11) | 633(4) | -1802(12) | 45(11) | 24(9) | 47(12) | 5(8) | 17(10) | -10(8) |
| C(13) | 5762(11) | 355(4) | -2342(11) | 32(10) | 32(9) | 35(11) | 0(9) | -16(9) | -10(9) |
| C(14) | 6612(13) | 700(4) | -804(10) | 38(10) | 49(10) | 46(10) | 8(9) | 2(9) | -5(8) |
| C(15) | 6036(13) | 531(5) | -3424(12) | 82(13) | 77(13) | 55(12) | -4(10) | -10(11) | -1(10) |
| C(16) | 5435(10) | -128(4) | 2425(12) | 11(9) | 64(11) | 111(11) | 7(9) | -4(9) | -23(12) |
| C(17) | 6817(13) | 463(4) | 199(10) | 89(13) | 67(11) | 42(9) | 26(10) | -15(10) | -4(8) |
| C(18) | 7472(12) | 1103(5) | -886(10) | 60(12) | 53(10) | 91(12) | 5(9) | -4(10) | -28(10) |

| Atom | X | Y | Z | U | Atom | X | Y | Z | U |
|---|---|---|---|---|---|---|---|---|---|
| H(31) | 3863(58) | 2020(23) | -1073(52) | 68(27) | H(121) | 3909(87) | 587(35) | -2029(76) | 114(46) |
| H(61) | 1002(54) | 1422(21) | 2518(54) | -6(19) | H(151) | 6831(133) | 456(52) | -3722(105) | 84(64) |
| H(62) | 684(76) | 1812(27) | 2666(66) | 64(30) | H(152) | 6369(80) | 784(33) | -3307(69) | 46(31) |
| H(63) | 2044(64) | 1797(19) | 2664(48) | 6(21) | H(153) | 5353(68) | 444(23) | -3776(55) | 5(25) |
| H(71) | -87(65) | 1468(23) | 312(56) | 3(25) | H(161) | 6123(54) | -255(19) | -2631(49) | -5(20) |
| H(72) | -607(58) | 1649(22) | 1396(50) | 15(23) | H(162) | 4670(64) | -161(21) | -2724(56) | 11(24) |
| H(73) | 68(75) | 1126(30) | 1225(65) | 28(32) | H(163) | 5097(57) | -189(20) | -1714(54) | -11(21) |
| H(81) | 4373(84) | 2403(31) | 933(79) | 74(36) | H(171) | 6280(111) | 221(41) | 356(96) | 163(47) |
| H(82) | 3381(79) | 2474(35) | 1611(70) | 66(31) | H(172) | 6791(81) | 680(34) | 716(67) | 101(33) |
| H(83) | 3599(73) | 2124(29) | 1498(61) | 78(28) | H(173) | 7804(95) | 378(33) | 239(73) | 103(38) |
| H(91) | 1543(101) | 2706(34) | -320(93) | 108(42) | H(181) | 8058(76) | 964(27) | -839(62) | 20(31) |
| H(92) | 3201(156) | 2792(50) | -265(123) | 215(73) | H(182) | 7335(63) | 1195(21) | -1611(53) | 45(23) |
| H(93) | 1846(83) | 2888(27) | 587(67) | 27(31) | H(183) | 7296(83) | 1321(30) | -400(70) | 48(34) |

†In the form $\exp\{-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)\}$.

Table 2. Bond distances (Å), bond and torsion angles (°) with standard deviations in parentheses

(a) 3,5-dibromo-4-oxo-2,2,6,6-tetramethylpiperidin-1-yloxy (2b) †

(i) Distances

| | | | |
|---|---|---|---|
| Br(1)-C(2) | 1.941(3) | C(2)-H(2) | 1.02(3) |
| N-O(1) | 1.278(5) | C(4)-H(41) | 0.97(5) |
| N-C(3) | 1.510(4) | C(4)-H(42) | 1.01(5) |
| O(2)-C(1) | 1.195(7) | C(4)-H(43) | 1.03(5) |
| C(1)-C(2) | 1.518(5) | C(5)-H(51) | 0.87(5) |
| C(2)-C(3) | 1.548(5) | C(5)-H(52) | 0.92(4) |
| C(3)-C(4) | 1.529(5) | C(5)-H(53) | 0.98(4) |
| C(3)-C(5) | 1.522(5) | | |

(ii) Angles

| | | | |
|---|---|---|---|
| Br(1)-C(2)-C(1) | 110.8(3) | Br(1)-C(2)-H(2) | 106.2(18) |
| Br(1)-C(2)-C(3) | 111.6(2) | C(1)-C(2)-H(2) | 109.3(18) |
| O(1)-N-C(3) | 115.0(2) | C(3)-C(2)-H(2) | 107.1(19) |
| C(3)-N-C(3') | 125.1(3) | C(3)-C(4)-H(41) | 106.1(27) |
| O(2)-C(1)-C(2) | 125.8(2) | C(3)-C(4)-H(42) | 112.2(26) |
| C(2)-C(1)-C(2') | 108.2(4) | C(3)-C(4)-H(43) | 114.2(24) |
| C(1)-C(2)-C(3) | 111.5(3) | H(41)-C(4)-H(42) | 110.3(36) |
| C(2)-C(3)-N | 106.6(3) | H(41)-C(4)-H(43) | 105.6(35) |
| C(4)-C(3)-C(5) | 111.0(3) | H(42)-C(4)-H(43) | 108.2(35) |
| C(4)-C(3)-N | 106.8(3) | C(3)-C(5)-H(51) | 109.9(28) |
| C(4)-C(3)-C(2) | 109.9(3) | C(3)-C(5)-H(52) | 111.5(27) |
| C(5)-C(3)-N | 109.1(3) | C(3)-C(5)-H(53) | 106.3(22) |
| C(5)-C(3)-C(2) | 113.1(3) | H(51)-C(5)-H(52) | 107.6(39) |
| | | H(51)-C(5)-H(53) | 110.0(36) |
| | | H(52)-C(5)-H(53) | 111.5(35) |

(iii) Torsion angles ‡

| | |
|---|---|
| C(2)-C(3)-N-C(3') | 42.58 |
| C(1)-C(2)-C(3)-N | -50.53 |
| C(3)-C(2)-C(1)-C(2') | 65.51 |

(b) The ester (3) derived from (2b)

(i) Distances

| Ring 1 | | Ring 2 | |
|---|---|---|---|
| Br(1)-C(1) | 1.916(11) | N(2)-O(2) | 1.252(13) |
| Br(2)-C(2) | 1.988(12) | N(2)-C(13) | 1.468(16) |
| N(1)-O(1) | 1.286(15) | N(2)-C(14) | 1.461(16) |
| N(1)-C(4) | 1.462(18) | C(11)-C(12) | 1.325(20) |
| N(1)-C(5) | 1.489(17) | C(11)-C(14) | 1.517(20) |
| C(1)-C(2) | 1.306(19) | C(12)-C(13) | 1.496(19) |
| C(1)-C(5) | 1.525(18) | C(13)-C(15) | 1.533(21) |
| C(2)-C(3) | 1.502(20) | C(13)-C(16) | 1.519(18) |
| C(3)-C(4) | 1.532(18) | C(14)-C(17) | 1.505(18) |
| C(4)-C(8) | 1.461(20) | C(14)-C(18) | 1.560(19) |
| C(4)-C(9) | 1.562(17) | Ester linkage | |
| C(5)-C(6) | 1.541(18) | C(2)-O(4) | 1.403(16) |
| C(5)-C(7) | 1.529(18) | C(10)-O(3) | 1.188(14) |
| | | C(10)-O(4) | 1.356(14) |
| | | C(10)-C(11) | 1.476(18) |

Hydrogen atoms

| | | | |
|---|---|---|---|
| C(3)-H(31) | 1.39(6) | C(6)-H(63) | 0.89(7) |
| C(6)-H(61) | 0.83(6) | C(15)-H(151) | 0.99(15) |
| C(6)-H(62) | 1.05(8) | C(15)-H(152) | 0.87(10) |

*Table 2. (Contd)*

| | | | |
|---|---|---|---|
| Hydrogen atoms | | | |
| C(15)-H(153) | 0.92(8) | C(12)-H(121) | 1.08(9) |
| C(7)-H(71) | 0.91(7) | C(16)-H(161) | 0.90(6) |
| C(7)-H(72) | 0.94(7) | C(16)-H(162) | 0.94(7) |
| C(7)-H(73) | 1.10(9) | C(16)-H(163) | 1.01(7) |
| C(8)-H(81) | 1.11(10) | C(17)-H(171) | 0.97(12) |
| C(8)-H(82) | 0.84(10) | C(17)-H(172) | 0.94(10) |
| C(8)-H(83) | 0.71(8) | C(17)-H(173) | 1.13(11) |
| C(9)-H(91) | 0.82(11) | C(18)-H(181) | 0.78(9) |
| C(9)-H(92) | 1.15(17) | C(18)-H(182) | 0.99(7) |
| C(9)-H(93) | 1.04(9) | C(18)-H(183) | 0.94(9) |

(ii) Angles

| Ring 1 | | Ring 2 | |
|---|---|---|---|
| Br(1)-C(1)-C(2) | 120.0(10) | O(2)-N(2)-C(13) | 124.3(10) |
| Br(1)-C(1)-C(5) | 114.0(9) | O(2)-N(2)-C(14) | 122.6(10) |
| Br(2)-C(3)-C(2) | 104.0(9) | C(13)-N(2)-C(14) | 113.1(10) |
| Br(2)-C(3)-C(4) | 112.5(9) | C(12)-C(11)-C(14) | 112.0(12) |
| O(1)-N(1)-C(4) | 120.5(11) | C(11)-C(12)-C(13) | 111.6(12) |
| O(1)-N(1)-C(5) | 115.3(10) | C(12)-C(13)-N(2) | 102.0(11) |
| C(4)-N(1)-C(5) | 121.7(10) | C(11)-C(14)-N(2) | 101.2(10) |
| C(5)-C(1)-C(2) | 125.9(11) | C(15)-C(13)-C(16) | 108.7(12) |
| C(1)-C(2)-C(3) | 123.3(12) | C(17)-C(14)-C(18) | 110.2(11) |
| C(2)-C(3)-C(4) | 109.1(10) | C(15)-C(13)-N(2) | 110.8(10) |
| C(3)-C(4)-N(1) | 109.9(10) | C(15)- C(13)-C(12) | 111.5(11) |
| C(1)-C(5)-N(1) | 107.6(10) | C(16)-C(13)-N(2) | 108.9(10) |
| C(8)-C(4)-C(9) | 108.6(11) | C(16)-C(13)-C(12) | 114.8(11) |
| C(6)-C(5)-C(7) | 110.6(10) | C(17)-C(14)-N(2) | 109.8(11) |
| C(6)-C(5)-N(1) | 108.5(10) | C(17)-C(14)-C(11) | 113.3(11) |
| C(6)-C(5)-C(1) | 110.6(11) | C(18)-C(14)-N(2) | 110.2(10) |
| C(7)-C(5)-N(1) | 109.0(10) | C(18)-C(14)-C(11) | 111.8(11) |
| C(7)-C(5)-C(1) | 110.4(10) | Ester linkage | |
| C(8)-C(4)-N(1) | 114.6(12) | O(3)-C(10)-O(4) | 124.1(11) |
| C(8)-C(4)-C(3) | 106.3(11) | O(3)-C(10)-C(11) | 126.1(12) |
| C(9)-C(4)-N(1) | 108.6(11) | O(4)-C(10)-C(11) | 109.7(10) |
| C(9)-C(4)-C(3) | 108.6(11) | C(2)-O(4)-C(10) | 115.7(9) |
| | | C(1)-C(2)-O(4) | 120.3(12) |
| | | C(3)-C(2)-O(4) | 116.3(10) |
| | | C(10)-C(11)-C(12) | 125.2(13) |
| | | C(10)-C(11)-C(14) | 122.8(11) |

Methyl groups

| | | | |
|---|---|---|---|
| H(61)-C(6)-H(62) | 83(6) | H(151)-C(15)-H(152) | 84(11) |
| H(61)-C(6)-H(63) | 145(6) | H(151)-C(15)-H(153) | 118(10) |
| H(62)-C(6)-H(63) | 102(6) | H(152)-C(15)-H(153) | 134(8) |
| H(71)-C(7)-H(72) | 122(6) | H(161)-C(16)-H(162) | 127(6) |
| H(71)-C(7)-H(73) | 104(6) | H(161)-C(16)-H(163) | 120(6) |
| H(72)-C(7)-H(73) | 120(6) | H(162)-C(16)-H(163) | 91(6) |
| H(81)-C(8)-H(82) | 92(8) | H(171)-C(17)-H(172) | 112(9) |
| H(81)-C(8)-H(83) | 99(8) | H(171)-C(17)-H(173) | 114(9) |
| H(82)-C(8)-H(83) | 90(10) | H(172)-C(17)-H(173) | 99(7) |
| H(91)-C(9)-H(92) | 140(12) | H(181)-C(18)-H(182) | 111(7) |
| H(91)-C(9)-H(93) | 92(10) | H(181)-C(18)-H(183) | 121(8) |

Table 2. (*Contd*)

| | | | |
|---|---|---|---|
| Methyl groups | | | |
| H(92)-C(9)-H(93) | 104(7) | H(182)-C(18)-H(183) | 114(7) |
| H(121)-C(12)-C(11) | 130(5) | Br(2)-C(3)-H(31) | 93(3) |
| H(121)-C(12)-C(13) | 117(6) | C(2)-C(3)-H(31) | 110(3) |
| | | C(4)-C(3)-H(31) | 125(3) |
| (iii) Torsion angles | | | |
| Ring 1 | | Ring 2 | |
| C(5)-C(1)-C(2)-C(3) | +7.60 | C(14)-C(11)-C(12)-C(13) | +1.88 |
| C(1)-C(2)-C(3)-C(4) | +21.92 | C(11)-C(12)-C(13)-N(2) | -2.89 |
| C(2)-C(3)-C(4)-N(1) | -48.33 | C(12)-C(13)-N(2)-C(14) | +2.93 |
| C(3)-C(4)-N(1)-C(5) | +53.73 | C(13)-N(2)-C(14)-C(11) | -1.93 |
| C(4)-N(1)-C(5)-C(1) | -24.38 | N(2)-C(14)-C(11)-C(12) | 0.0 |
| N(1)-C(5)-C(1)-C(2) | - 7.99 | | |

†Primed numbers refer to the atom related by the mirror plane.
‡As defined by R. Bucourt, "Topics in Stereochemistry", Vol.8, p.159, Interscience-Wiley.

bicyclo[3,3,1]nonan - 3 - one - 8 - oxyl, for example, in which two nitroxide bonds lie around a centre of symmetry forming a rectangle with sides 1.289 and 2.278 Å).[16]

In **3** individual molecules contain nitroxide bonds in two different ring environments (Fig. 3). In contrast to **2b** the crystal packing (Fig. 4) does seem to involve Br....O secondary bonds[17] of 3.086(8) Å between Br(1) and the oxygen O(2) of the pyrrolin-yloxy ring, resulting in dimeric units about inversion centres (Fig. 4). This secondary bond is 0.28 Å less than the sum of the van der Waal's radii:† the C-Br....O angle is 178.4(4)° and the N-O....Br angle is 114.2(6)°. Similar Br....O secondary bonds are important in determining the packing in several brominated steroids,[18] certain acid-base structures involving Watson-Crick pairs of molecules[19] and several other organic and inorganic structures.[20] Typical distances for the Br....O contact in these structures are from 2.91 to 3.35 Å and all involve a nearly linear C-Br....O group. Other authors have described these as donor-acceptor or charge transfer interactions.[21]

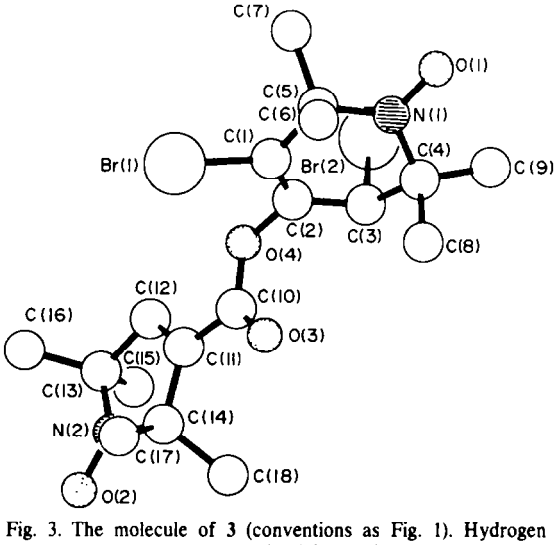


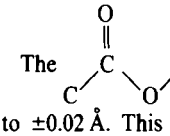

Fig. 3. The molecule of **3** (conventions as Fig. 1). Hydrogen atoms are omitted for clarity.

†After H. Bondi, *J. Phys. Chem.* **68**, 441 (1964).

The C-Br distance in **2b** is 1.941(3) Å whilst in ring **1** of **3** there are two different C-Br distances of 1.988(12) (C($sp^3$)-Br) and 1.916(11) Å (C($sp^2$)-Br) as expected, since the hybridisation of the C atom changes. Accepted values for C($sp^2$)-Br and C($sp^3$)-Br are 1.89(1) Å and 1.937(3) Å respectively,[22] but the value of 1.988 Å for C(3)-Br(2) is significantly longer. (The C-Br distance in **2b** is typical of C($sp^3$)-Br, however). The lengthening of the C(3)-Br(2) bond is probably a consequence of repulsive non-bonded contacts. The conformation that ring 1 adopts also forces close intramolecular contacts of 3.361(8) (Br(2)....O(2)) and 3.008(8) Å (Br(1)....O(2)) involving the Br atoms. The remaining distances and angles in **2b** and **3** are within normal ranges.

The pyrrolinyloxy ring is virtually planar with atom C(13) deviating from the plane of the ring by only 0.025 Å. The nitroxide bond makes an angle of 0.5° with the CNC plane. The second 6-membered ring, however, adopts a "sofa" conformation (Fig. 5) with C(4) 0.60 Å above the plane of N(1), C(2), C(3) and C(5). [C(1) is 0.08 Å above the plane]. The Br atom, Br(2), is in a pseudo-axial position. In this ring the N-O bond makes an angle of 16.04° with the CNC plane.

Strain in both rings also produces twisting about the double bonds C(1)=C(2) and C(11)=C(12). The more pronounced twisting in ring 1 reduces the repulsive interactions between its bromine atoms and also between the vinylic bromine and ester O atoms.

The  C group linking the two rings is planar to ±0.02 Å. This group makes angles of 87.3° and 1.9° with the ring planes of ring 1 and ring 2 respectively (Table 3).

*The nitroxide group*

A tabulation of relevant distances and angles in mole-

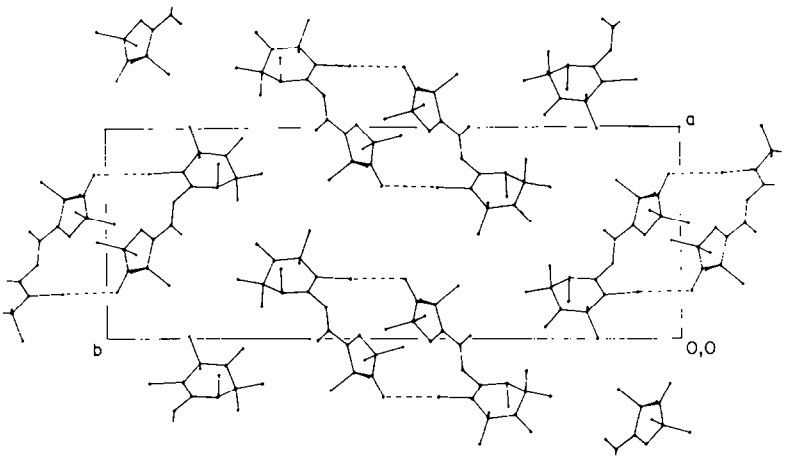



Fig. 4. Packing diagram for 3 (viewed down (*c*)).

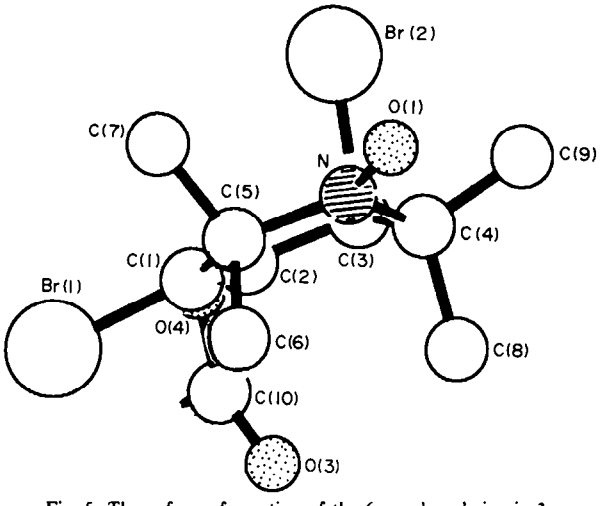



Fig. 5. The sofa conformation of the 6-membered ring in 3.

cules containing the nitroxide group has been given by Lajzerowicz-Bonnet.[23] More recent results[24–26] and data for acyclic nitroxides[27–30] are collected in Table 4.

It appears that variations in the dimensions and angles of the $\begin{matrix} C \\ \diagdown \\ \quad N\text{–}\dot{O} \\ \diagup \\ C \end{matrix}$ groups are the outcome of geometrical constraints arising because the molecules adopt conformations which minimise non-bonded interactions. The nitroxide group in ring systems is normally planar if the *ring* is planar (e.g. in derivatives of 2,2,5,5 - tetramethylpyrrolin - 1 - yloxy where planarity of the nitroxide group presumably minimises repulsive interactions between O and methyls); otherwise it may be pyramidal (e.g. in derivatives of 2,2,6,6 - tetramethylpiperidin - 1 - yloxy where a pyramidal nitroxide group will minimise repulsive interactions between O and methyls). With acyclic nitroxides the non-bonded contact distances involving the oxygen atom may force the nitroxide group to be planar. Packing arrangements, expecially when hydrogen bonds are formed, can also slightly alter the shapes of nitroxide groups.

†The value of 30.5° is for 9 - azabicyclo[3,3,1]nonan - 3 - one - 9 - oxyl, where there is a repulsive interaction between the nitroxide and carbonyl bonds and a more reasonable range is perhaps 15.8–24.9°.

The theoretical geometry of the nitroxide group has been investigated by a CNDO calculation on *bis*(trifluoromethyl)nitroxide which found that r(N–O) = 1.26(1) Å, and a minimum energy for the molecule occurs with an angle of 10° between the N–O bond and the CN̂C plane. However, very little energy is required to change this angle in the range 0° to 30°.[31] An *ab initio* calculation on $H_2N\dot{O}$ reached similar conclusions: the out-of-plane angle is 26°, HN̂H is 116° and the N–O bond length is 1.34 Å.[32]

The observed N–O bond lengths in our work are 1.285(9) Å for **2b**; 1.286(15) Å (ring 1) and 1.252(13) Å (ring 2) for **3**. The corresponding CN̂C angles are 125.1(3)° for **2b**; 121.7(10)° (ring 1) and 113.1(10)° (ring 2) for **3**. The N–O distances are within the ranges quoted in Ref. 22 and Table 4. The angles between the N–O bonds and the CNC planes in the 6-membered rings are also within the observed range (15.8–30.5°†).[22]

The two N–O distances in the 6-membered rings are very similar, but the shorter N–O distance in the 5-membered ring 2 of **3** is not significantly different. The deviation from planarity of a nitroxide group would be expected to decrease $\pi$-overlap between the N and O and hence slightly lengthen the N–O bond. Similarly the CN̂C would be expected to decrease and the C–N distance to increase. The evidence here and in other nitroxide structures, however, is not sufficiently accurate to prove these points conclusively.

Table 3. Least squares planes for (3). Equations of the least-squares mean planes are given as PI + QJ + RK = S† in orthogonal space. Deviations of certain atoms from these planes are shown and atoms defining the plane are marked with an asterisk

| Plane 1 | P | Q | R | S |
|---|---|---|---|---|
| | 0.7153 | 0.1862 | 0.6736 | 2.9757 |
| Atom, deviation (Å) | | | | |
| Br(1) | 0.167 | | C(3)* | -0.009 |
| Br(2) | -1.935 | | C(4) | 0.602 |
| O(1) | -0.192 | | C(5)* | -0.009 |
| O(4) | -0.080 | | C(6) | 1.206 |
| N(1)* | 0.009 | | C(7) | -1.313 |
| C(1) | 0.079 | | C(8) | 2.049 |
| C(2)* | 0.008 | | C(9) | 0.284 |

| Plane 2 | P | Q | R | S |
|---|---|---|---|---|
| | 0.2974 | 0.7482 | -0.5931 | 4.3751 |
| Atom, deviation (Å) | | | | |
| O(3)* | -0.003 | | C(10)* | -0.005 |
| O(4)* | -0.022 | | C(11)* | 0.013 |
| C(2)* | 0.017 | | C(12) | 0.052 |
| N(2) | 0.068 | | C(13) | 0.136 |
| O(2) | 0.063 | | C(14) | 0.020 |

| Plane 3 | P | Q | R | S |
|---|---|---|---|---|
| | 0.2947 | 0.7690 | -0.5673 | 4.3917 |
| Atom, deviation (Å) | | | | |
| O(2) | -0.025 | | C(14)* | 0.000 |
| N(2)* | 0.000 | | C(15) | 1.344 |
| C(11)* | 0.000 | | C(16) | -1.131 |
| C(12)* | 0.000 | | C(17) | -1.226 |
| C(13) | 0.046 | | C(18) | 1.287 |

Angles between planes:- (1)-(2) 87.28° (1)-(3) 88.38° (2)-(3) 1.90°

† With the orthogonal unit vector I parallel to a, K perpendicular to a in the ac plane and J perpendicular to the ac plane.

Table 4. Structural data on nitroxides from Refs. 24–30

| Nitroxide | N-O (Å) | $\hat{CNC}$ (°) |  | Conformation of 5-membered ring | Ref. |
|---|---|---|---|---|---|
| 2, 2, 5, 5-Tetramethyl-3-hydroxypyrrolidin-1-yloxy | 1.265(5) | 115.3 | Planar | Twist | 24 |
| 2, 2, 5, 5-Tetramethylpyrrolidin-3-on-1-yloxy oxime* | 1.272(5) | 117.1(4) | Virtually planar | Slightly distorted Envelope | 25 |
| 3-Aminocarbonyl-2, 2, 5, 5-tetramethylpyrrolidin-1-yloxy | 1.268(3) | 115.0(2) | Virtually planar | Twist | 26 |
| bis (p-Anisyl)nitroxide | 1.23(5) | 124(5) | Planar | – | 27 |
| bis (t-Butyl)nitroxide | 1.28(2) | 124(5) | Probably planar | – | 28 |
| bis (Trifluoromethyl)nitroxide | 1.26(3) | 121(2) | Non-planar† | – | 28 |
| Fremy's salt (K nitrosodisulphonate, triclinic form) | 1.28(4) | ** | Small deviation from planarity | – | 29 |
| t-Butylferrocenyl nitroxide | 1.20 | (not given) | | – | 30 |

* Data for optically active form. This molecule also crystallises as a racemate with two independent molecules in the asymmetric unit. The N-O bond lengths are 1.261(5) and 1.276(5) Å and the corresponding $\hat{CNC}$ are 115.3(4)° and 116.5(3)°. [25]

** Corresponding angle $\hat{SNS}$ is 118(2)°.

† The N-O bond makes an angle of 22(3)° with the $\hat{CNC}$ plane.

## EXPERIMENTAL

All solvents were either AnalaR or purified by standard methods. Reagents were commercially available materials used as supplied. Fison silica gel (80–200 mesh) was used for column chromatography. Thin-layer plates were prepared from Machery and Nagel silica gel N. Spots were detected by spraying with 35% sulphuric acid and charring. M.ps were determined for samples in open capillaries and are corrected. Concentrations of solutions for $^1$H NMR spectroscopy (tetramethylsilane reference) were *ca* 10% and for IR spectroscopy *ca.* 2%. Elemental analyses were carried out by CHN Analyses Ltd.

3,5 - *Dibromo* - 4 - *oxo* - 2,2,6,6 - *tetramethylpiperidine hydrobromide* was prepared directly from 4 - oxo - 2,2,6,6 - tetramethylpiperidine hydrochloride either by the method of Ref. 6 [97.5%, mixture of isomers; $\delta$ ($^2H_6$-DMSO),† 1.40 (s, 0.67 × 6H, 2 × Me), 1.77 (s, 0.67 × 6H, 2 × Me), 5.63 (s, 0.67 × 2H, 2 × CHBr), 1.56 (s, 0.33 × 6H, 2 × Me), 1.68 (s, 0.33 × 6H, 2 × Me), 5.48 (s, 0.33 × 2H, 2 × CHBr)] or according to Ref. 7*a* [72–78% mixture of isomers; $\delta$ ($^2H_6$-DMSO)† same signals as material prepared by the method of Ref. 6 but ratio of isomers (based on integrals) 4:6 instead of 2:1].

3,5 - *Dibromo* - 4 - *oxo* - 2,2,6,6 - *tetramethylpiperidine* (**2a**) was prepared (cf. Ref. 6) by stirring a suspension of the above hydrobromide mixture either in aqueous 10% $Na_2CO_3$ (0.9 mol $Na_2CO_3$/mol hydrobromide) or with a stoichiometric amount of $KHCO_3$ aq, in each case at 0°/15 min. Filtration of the resulting chalky solid, washing with water and recrystallisation from hot EtOAc (*ca.* 10 ml/g) gave, after cooling at −20°, 3,5 - dibromo - 4 - oxo - 2,2,6,6 - tetramethylpiperidine: 20–43%, no clear m.p. (turns black at 145°), $\delta$ (sat soln in $CDCl_3$) 1.26 (s, 6H, 2 × Me), 1.44 (s, 6H, 2 × Me) 2.00 (b, 1H, NH) and 4.54 (s, 2H, 2 × CHBr; $\nu_{max}$ (Nujol) 3120 m and 1715 s cm$^{-1}$; $\nu_{max}$ ($CH_2Cl_2$) 3340w and 1748s cm$^{-1}$; $R_f$ ($CHCl_3$) 0.40.

3,5 - *Dibromo* - 4 - *oxo* - 2,2,6,6 - *tetramethylpiperidin* - 1 - *yloxy* (**2b**)

(A) To a stirred suspension of 3,5 - dibromo - 4 - oxo - 2,2,6,6 - tetramethylpiperidine (1.718 g, 5.5 mmol) in ether (50 ml) was added a soln of *m*-chloroperbenzoic acid (1.42 g, 7.75 mmol) in ether (10 ml). The resulting pink suspension was stirred at r.t./20 hr. More *m*-CPBA acid (0.53 g, 2.92 mmol) was added and stirring was continued for 7 h. The suspension was filtered and the resulting pink solid was recrystallised from EtOAc (64 ml, warm until all solid goes into soln and then filter, cool filtrate at −20° overnight) to give the title compound (1.38 g, 78%) m.p. 165° dec., $R_f$ 0.82 ($CHCl_3$–acetone, 24:1) $\nu_{max}$ ($CHCl_3$) 1757s and 1367s cm$^{-1}$, *m/e* 330, 328 and 326 (all $M^+$). [Found: C, 33.22; H, 4.29. $C_9H_{14}Br_2NO_2$ requires: C, 32.95; H, 4.30%].

(B) **2a**-Hydrobromide (11.82 g, 0.03 mol) [prepared by the method of Ref. 7*a*] in water (17 ml) was stirred in an ice-cold $KHCO_3$ aq (3.0 g, 0.03 mol) in water (46 ml) for 10 min. Filtration, washing with water and drying gave crude **2a** (6.55 g). 3.554 g (0.0113 mol) of this product was taken up in boiling EtOAc (35 ml) and filtered from insoluble material. The filtrate was evaporated to a residue (2.94 g). This was suspended in ether (72 ml) and treated with a soln of *m*-CPBA (2.4 g, 0.0141 mol) in ether (30 ml). The suspension was stirred for 24 h/r.t. and then more *m*-CPBA (0.91 g, 0.054 mol) was added followed by stirring for 7 h/r.t. Filtration gave a pink solid (2.06 g) which was recrystallised from EtOAc (87 ml) to give **2b** (1.81 g, 34% overall from **2a**-hydrobromide), m.p. 168–170° dec.

(C) **2a**-Hydrobromide (11.82 g, 0.03 mol) [prepared by the method of Ref. 7*b*] suspended in water (17 ml) was stirred in an ice-water bath and was treated (frothing!) with an ice-cold $KHCO_3$ aq (3.0 g, 0.03 mol) in water (46 ml). After stirring for 10 min the mixture was filtered and the solid was washed with water and dried to give crude **2a** (8.04 g). 5.04 g (0.0161 mol based on pure **2a**) of this product was taken up in boiling EtOAc (50 ml) and filtered from insoluble material. The filtrate was cooled and evaporated to a residue (4.25 g). This was suspended in ether (110 ml) and treated with a soln of *m*-CPBA (3.5 g, 0.0203 mol) in ether (40 mol). A clear reddish soln was obtained which soon began to precipitate a pink solid. After stirring for 24 h/r.t. more *m*-CPBA (0.99 g, 0.0077 mol) was added and stirring was continued for 7 hr. Filtration gave 1.58 g of solid which was recrystallised from EtOAc (66 ml) to afford **2b** (1.326 g, 21% overall from **2a**-hydrobromide), m.p. 168–170° dec.

*Reaction of* **2b** *with sodium ethoxide*

To a stirred suspension of **2b** (118 mg, 0.365 mmol) in dichlormethane (2 ml) was added 1.8 M NaOEt in EtOH (0.7 ml, 12 mmol). During the addition the mixture turned yellow and a white ppt appeared. After stirring the mixture for 10 min/r.t., water and ether were added. The ether layer was separated and was washed with dil. $H_2SO_4$, 5% $KHCO_3$ aq and water. The resulting yellow ethereal soln was dried and the ether was removed leaving yellow crystals which were recrystallised from *n*-hexane to give 3 - ethoxycarbonyl - 2,2,5,5 - tetramethylpyrrolin - 1 - yloxy (38 mg; 50%), m.p. 107–9° (lit.[2]). [Found: C, 62.04; H, 8.56. $C_{11}H_{18}NO_3$ requires: C, 62.24; H, 8.55%].

*Reaction of* **2b** *with triethylamine*

*Preparation of* 4 - [(2',2',5',5' - *tetramethylpyrrolin* - 1' - *yloxy*) - 3' - *carbonyloxy*] - 2,2,6,6 - *tetramethyl* - 3,5 - *dibromo* - 3,4 - *dehydropiperidin* - 1 - *yloxy* (**3**). To a stirred suspension of **2b** (118 mg, 0.36 mmol) in dichloromethane (2 ml) was added triethylamine (110 mg) in dichloromethane (1 ml). A clear green-orange soln was formed which was stirred for 1.5 hr/r.t. Excess ether was added and the white ppt was filtered off. The filtrate was washed with dil $H_2SO_4$, 5% $KHCO_3$ aq and water. The ethereal soln was dried and evaporated to yellow-orange crystals which were recrystallised from *n*-hexane to give 3 (46 mg, 52%), m.p. 160° dec. An analytical sample had m.p. 166–7° dec, $\nu_{max}$ 1740s (ester C=O). [Found: C, 44.02, H, 5.36. $C_{18}H_{26}Br_2N_2O_4$ requires: C, 43.82; H, 5.31%].

*Reactions of* **2b** *with amines*

*Preparation of radicals* **1f–1l**). The synthesis and characterisation of compounds **1f–1g** is given in the preliminary communication.[5] In the preparation of compounds **1f–1h** and **1j**, 3 mol equivs of amine/mol equiv **2b** were used. For the preparation of compounds **1i** and **1k** 1 mol equiv amine + 2 mol equiv triethylamine were used, as in the following typical procedure: rac. - 3 - aminopropan - 1,2 - diol (461 mg, 5.1 mmol) was dispersed in dichloromethane (20 ml) containing triethylamine (1.4 ml, 10.2 mmol) by stirring. 3,5 - Dibromo - 4 - oxo - 2,2,6,6 - tetramethylpiperidine - 1 - yloxy (1.65 g, 5.1 mmol) was added and the mixture was stirred for 5 hr/r.t. Evaporation gave a semi-solid mass which was chromatographed on silica gel (100 g made up in $CH_2Cl_2$–acetone 1:1, elution with the same solvent mixture at 2 ml/min). Product was eluted after 560 ml of this solvent mixture had passed through the column. Evaporation of product-containing fractions, followed by addition of dichloromethane, gave yellow crystals of analytically and chromatographically pure **1k** (500 mg, 38%), $\nu_{max}$ (in Nujol) 3400–3300s (OH), 1654s (amide I), 1615s (C=C) and 1368m (N–O$^·$) cm$^{-1}$, *m/e* 257 ($M^+$, 5), 227(25), 136(64) and 110(100). [Found: C, 55.75; H, 8.10, N, 10.88. Calc. for $C_{12}H_{21}N_2O_4$: C, 56.01; H, 8.23; N, 10.89%].

*X-ray crystallography*

(a) 3,5 - *Dibromo* - 4 - *oxo* - 2,2,6,6 - *tetramethylpiperidin* - 1 - *yloxy*. Air-stable orange-red crystals of **2b** occur as chunky prisms or as elongated hexagonal plates. One prism was mounted and used for data collection. *Crystal data*: $Br_2O_2NC_9H_{14}$, orthorhombic, $a = 11.665(2)$, $b = 5.938(1)$, $c = 16.067(3)$ Å, $U = 1113.0(4)$ Å, $D_c = 1.957$, $Z = 4$. Mo $K_\alpha$-radiation, $\lambda = 0.71069$ Å; $\mu$(Mo-$K_\alpha$) = 76.85 cm$^{-1}$, F(000) = 644. Systematic absences *hk*O, $h \neq 2n$, O*kl*, $k + l \neq 2n$ indicate space groups Pnma or Pn2$_1$a (non-standard setting of Pna2$_1$ (No. 33)).

Unit cell dimensions and data were measured using a Syntex P2$_1$ diffractometer. Reflections were measured using $\theta - 2\theta$ scans over a scan range ($K_{\alpha_1} - 0.65$) to ($K_{\alpha_2} + 0.65$) to a maximum $2\theta$ of

†As the hydrobromide slowly decomposes in DMSO at r.t., its spectrum was run immediately.

55° in two shells. A variable scan rate of 1.0°/min to 29.5°/min depending on the intensity of a preliminary 2 sec count was used. Background counts were recorded at each end of the scan, each for one quarter of the scan time. The intensities of four standard reflections were monitored every 70 reflections. These reflections showed no significant loss in intensity. 1527 data were collected, of which 823 were considered observed and used in refinement ($I/\sigma(I) \geq 3.0$).

Lorentz, polarisation and absorption corrections were applied, the last with the program ABSCOR.[33] With four molecules in the unit cell, space group *Pnma* requires mirror symmetry in the molecule. A Patterson synthesis was successfully interpreted for the vectors generated by a single bromine atom in space group *Pnma* and the subsequent satisfactory refinement confirms this choice. The remaining atoms were located in subsequent Fourier maps. Least squares refinement with anisotropic temperature factors for all non-hydrogen atoms produced a final R factor of 0.026 (weighted R of 0.025).

The weighting scheme used gives reflections within the ranges $15.0 \leq F \leq 45.0$ and $0.265 \leq \sin\theta \leq 0.50$ weights of $(1/\sigma(F))^2$. Other reflections are weighted by the equation $W = X^*Y^*(1/\sigma(F))^2$ where $X = \sin\theta/0.265$ if $\sin\theta < 0.265$ or $X = 0.50/\sin\theta$ if $\sin\theta > 0.50$ and $Y = F/15.0$ if $F < 15.0$ or $Y = 45.0/F$ if $F > 45.0$. Using this weighting scheme, one reflection with a very bad $\omega^*(\Delta F)^2$ was rejected from the refinement.

(b) 4 - [(2',2',5',5' - *Tetramethylpyrrolin* - 1' - *yloxy*) - 3' - *carbonyloxy*] - 2,2,6,6 - *tetramethyl* - 3,5 - *dibromo* - 3,4 - *dehydropiperidin* - 1 - *yloxy* (**3**). Air-stable orange-red crystals of **3** slowly recrystallised from boiling *n*-hexane as thin plates. One such plate was found to extinguish under crossed polars along the diagonal of the plate.

*Crystal data.* $Br_2O_4N_2C_{18}H_{26}$, orthorhombic, $a = 11.089(2)$, $b = 30.477(6)$, $c = 12.970(2)$ Å, $U = 4383.3(14)$ Å,[3] $D_c = 1.498$, $Z = 8$, $MoK_\alpha$-radiation, $\lambda = 0.71069$ Å; $\mu(Mo\text{-}K_\alpha) = 39.41\ cm^{-1}$, $F(000) = 2000$. Systematic absences $Okl$, $k \neq 2n$; $hOl$, $l \neq 2n$; $hkO$, $h \neq 2n$ indicate space group *Pbca* (No. 61).

Unit cell dimensions and data were measured using a Syntex $P2_1$ diffractometer (graphite monochromator). Reflections were measured using $\theta - 2\theta$ scans over a scan range $(K_{\alpha 1} - 0.7)$ to $(K_{\alpha 2} + 0.7)$ to a maximum $2\theta$ of 50°. The intensities of three standard reflections were monitored every 100 reflections. These reflections showed no significant loss in intensity. Other conditions were the same as in (a).

4399 data were collected, of which 1104 were considered observed and used in refinement ($I/\sigma(I) \geq 3.0$).

Lorentz, polarisation and absorption corrections were applied, the last with the program ABSCOR.[33] The two bromine atoms were readily located on a Patterson synthesis and the remaining light atoms found by Fourier methods. Least squares refinement, using three blocks with anisotropic temperature factors for all non-H atoms and including a correction for the effects of anomalous dispersion, produced a final R factor of 0.048 (weighted R of 0.035). The weights used were based on counting statistics.

For both **2b** and **3**, scattering factors for neutral Br, C, N, O and H were from Ref. 34 in the analytical form. Computing was carried out with the XRAY system (1972)[35] on a CDC 7600 computer, and XRAY 76 (1976) on a Burroughs B6700 computer.[36]

Final co-ordinates and temperature factors are in Table 1. Significant bond lengths, bond angles and torsion angles are given in Table 2, and molecular planes for **3** in Table 3. Structure factor listings for both compounds are available on request.

## REFERENCES


[1] *Spin labelling: Theory and Applications* (Edited by L. J. Berliner) especially Chap. 5. Academic Press, London (1976).

[2] E. G. Rozantsev, *Free Nitroxyl Radicals.* especially Chap. 9. Plenum Press, London (1970).

[3] H. Pauly and C. Boehm, *Ber. Dtsch. Chem. bes.* **33**, 919 (1900).

[4] Bromination of 4 - oxo - 2,2,6,6 - tetramethylpiperidin - 1 - yloxy with phenyltrimethyl-ammonium perbromide in tetrahydrofuran (*Organic Syntheses* **53**, 111 (1973)) gave a solid product presumed to be 3 - bromo - 4 - oxo - 2,2,6,6 - tetramethylpiperidin - 1 - yloxy. However, the yield of ~90% pure (tlc) material was low. After incubating this substance for 17 hr/r.t. with benzylamine (2 mol equiv) in $CH_2Cl_2$, work up did not afford 3 - (N - benzyl)aminocarbonyl - 2,2,5,5 - tetramethylpyrrolidin - 1 - yloxy. However, treatment of the monobromonitroxide with NaOH aq in dioxan gave 3 - carboxy - 2,2,6,6 - tetramethylpyrrolidin - 1 - yloxy [m.p. 193–4° dec, 15% overall yield (3 steps) from 4 - oxo - 2,2,6,6 - tetramethylpiperidine; cf. 47% overall yield (5 steps) claimed in Ref. 2].

[5] B. T. Golding, P. V. Ioannou and M. M. O'Brien, *Synthesis* 462 (1975).

[6] H. Pauly, *Ber. Dtsch. Chem. bes.* **31**, 670 (1898).

[7] [a]Ref. 2, p. 203; [b]C. Sandris and G. Ourisson, *Bull. Soc. Chim. Fr.* 345 (1958).

[8] E. W. Garbisch, *J. Org. Chem.* **30**, 2109 (1965).

[9] A. Baretta, J. P. Zahra, B. Waegell and C. W. Jefford, *Tetrahedron* **26**, 15 (1970).

[10] J. F. W. Keana, S. B. Keana and D. Beetham, *J. Am. Chem. Soc.* **89**, 3055 (1967).

[11] Professor J. D. Morrisett has informed us that he has also prepared **2b** in a similar manner from **2a**.

[12] C. Sandris and G. Ourisson, *Bull. Soc. Chim. Fr.* 1524 (1958); J.-F. Biellmann, R. Hanna, G. Ourisson, C. Sandris and B. Waegell, *Ibid.* 1429 (1960).

[13] L. C. G. Goaman and D. F. Grant, *Acta Cryst.* **17**, 1604 (1964).

[14] B. Waegell and G. Ourisson, *Bull. Soc. Chim. Fr.* 503 (1963).

[15] N. W. Alcock and J. F. Sawyer, *Acta Cryst.* **B32**, 285 (1976).

[16] A. Capiomont, B. Chion and J. Lajzerowicz, *Acta Cryst.* **B27**, 322 (1971).

[17] The name "secondary bond" has been proposed for certain inter- and intramolecular contact distances in the crystal which are less than the sum of the van der Waal's radii for the atoms concerned and which appear to be stereochemically important. These bonds are best described in terms of 3c–4e molecular orbitals. See N. W. Alcock, *Advan. Inorg. Chem. Radiochem.* **15**, 1 (1973).

[18] D. N. Peck, W. L. Duax, C. Eger and D. A. Norton, *Amer. Cryst. Assoc.* Abstracts, **L6**, 71 (Summer 1970); D. N. Peck, D. A. Langs, C. Eger and W. L. Duax, *Cryst. Struct. Comm.* **3**, 451 (1974); D. N. Peck, D. A. Langs, C. Eger and W. L. Duax, *Ibid.* **3**, 573 (1974).

[19] H.-S. Shieh and D. Voet, *Acta Cryst.* **B32**, 2354 (1976).

[20] K. Olie and F. C. Mijlhoff, *Ibid.* **B25**, 974 (1969); (see also L. K. Templeton, *Acta Cryst.* **B27**, 1678 (1971); P. Groth and O. Hassel, *Acta Chem. Scand.* **16**, 2311 (1962).

[21] O. Hassel, *Science* **170**, 497 (1970).

[22] Chem. Soc. Special Publ., No. 11, London (1958).

[23] J. Lajzerowicz-Bonnet, Chap. 6 in Ref. 1.

[24] B. Chion, J. Lajzerowicz, A. Collet and J. Jacques, *Acta Cryst.* **B32**, 339 (1976).

[25] B. Chion and J. Lajzerowicz, *Ibid.* **B31**, 1430 (1975).

[26] B. Chion and M. Thomas, *Ibid.* **B31**, 472 (1975).

[27] A. W. Hansen, *Ibid.* **6**, 32 (1953).

[28] B. Anderson and P. Anderson, *Acta Chem. Scand.* **20**, 2728 (1966); C. Glidewell, D. W. H. Rankin, A. G. Robiette, G. M. Sheldrick and S. M. Williamson, *J. Chem. Soc.* (A), 478 (1971).

[29] R. A. Howie, L. S. D. Glasser and W. Moser, *Ibid.* (A), 3043 (1968), and refs therein.

[30] A. R. Forrester, S. P. Hepburn, R. S. Dunlop and H. H. Mills, *Ibid.* Chem. Comm. 698 (1969).

[31] G. R. Underwood and V. L. Vogel, *Mol. Phys.* **19**, 621 (1970).

[32] A. W. Salotto and L. Burnelle, *J. Chem. Phys.* **53**, 333 (1970).

[33] N. W. Alcock, *The Analytical Method for Absorption Correction*, in *Crystallographic Computing* (Edited by F. Ahmed). Munksgaard, Copenhagen (1970).

[34] D. T. Cromer and J. B. Mann, *Acta Cryst.* **A24**, 321 (1968).

[35] X-RAY system (1972). Technical Report TR-192 of the Computer Science Centre, Univ. of Maryland, June (1972).

[36] X-RAY system (1976). Technical Report TR-446 of the Computer Science Center, Univ. of Maryland, March (1976).