

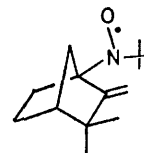
Syntheses and Chiroptical Properties of Some Optically Active Decahydroquinoline Nitroxide Radicals

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The syntheses of five optically active nitroxide radicals of the 2,2,8a-trimethyldecahydroquinoline type are described, together with their o.r.d. and c.d. spectra. In the case of (–)-*trans*-2,2,8a-trimethyloctahydro-4-oxoquinolin-1-oxyl (24), evidence is presented which indicates that the signs of the back octants associated with the nitroxide chromophore are the same as those dictated by the carbonyl Octant Rule. On this basis conformational assignments are suggested for other six-membered ring nitroxides in this series.

THE past decade has witnessed intensive research in the area of nitroxide radical chemistry. The unique properties of these species have generated considerable interest from theoretical, spectroscopic (principally e.s.r. and n.m.r.), and chemical standpoints.¹ In addition they have found increasing application in other allied sciences, particularly those of biochemistry and polymer chemistry. To date, however, very few optically active nitroxide radicals have been prepared and of those only the camphenyl nitroxide (1) has been examined by c.d. spectroscopy.² In view of the close similarity in symmetry and

electronic configuration of the carbonyl group and the nitroxide function (see Discussion section) we have



(1)

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¹ See A. R. Forrester, J. M. Hay, and R. H. Thomson, 'Organic Chemistry of Stable Free Radicals,' Academic Press, New York, 1968; E. G. Rozantsev, 'Free Nitroxyl Radicals,' Plenum Press, New York, 1970; E. G. Rozantsev and V. D. Sholle, *Synthesis*, 1971, 190; 401.

initiated an investigation of the chiroptical properties (c.d. and o.r.d.) of some stable cyclic nitroxide radicals. In particular, we wished to ascertain if the Cotton effect associated with the nitroxide chromophore could be

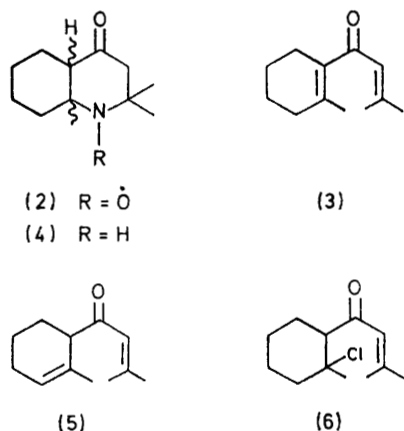
² Y. Brunel, H. Lemaire, and A. Rassat, *Bull. Soc. chim. France*, 1964, 1895.

interpreted qualitatively in terms of the Octant Rule³ which has served so admirably in the case of the carbonyl chromophore. Furthermore, we anticipated that the information from the o.r.d. and c.d. spectra could be a useful means of determining the conformation(s) of six-membered nitroxide radicals.

The u.v. spectra of di-*t*-alkyl nitroxides show two distinct bands at *ca.* 230 (ϵ *ca.* 2500) and 410–450 nm (5–15). By measuring the effect of solvent polarity on the positions of these absorptions, Rassat *et al.*⁴ have assigned the band at *ca.* 430 nm to an $n \rightarrow \pi^*$ transition and the 230 nm band to a $\pi \rightarrow \pi^*$ transition. The lower energy transition is ideally suited for both o.r.d. and c.d. studies.

Synthesis.—From a consideration of suitable types of nitroxide radical for such studies we concluded that the two keto-nitroxides (2) and their derivatives could yield valuable information, especially in the case of the more rigid *trans*-fused isomer. These were chosen because the data associated with the internal keto 'chiroptical handle' would hopefully allow us to assign a particular conformation to the molecule which would then become our basis for interpretation of the data associated with the nitroxide chromophore. Implicit in this approach is the fact that the $n \rightarrow \pi^*$ transitions of the carbonyl and nitroxide groups are of sufficiently different energies to permit their independent observation by o.r.d. and c.d.

Thus, our synthetic strategy was largely dictated by the well-documented reaction of phorone with ammonia to give triacetoneamine. The formation of the requisite cross-conjugated dienone (3) could not be achieved,



however, by the straightforward Friedel–Crafts acylation of 1-methylcyclohexene with β,β -dimethylacryloyl chloride. In the presence of tin(IV) chloride the two major products are the dienone (5) and the chloro-ketone (6). As a result of a detailed study of effective reagents for dehydrochlorination and isomerisation, conditions were determined which converted the crude mixture of

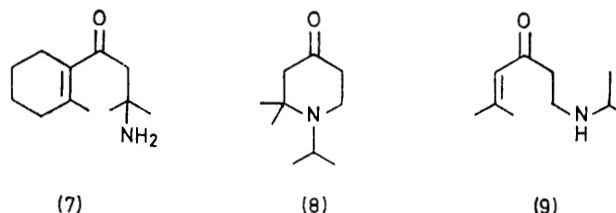
³ W. Moffitt, R. B. Woodward, A. Moscovitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013.

⁴ R. Briere, H. Lemaire, and A. Rassat, *Bull. Soc. chim. France*, 1965, 3273.

⁵ C. D. Nenitzescu and A. T. Balaban, 'Friedel–Crafts and Related Reactions,' ed. G. A. Olah, Interscience, New York, 1964, vol. III, part 2, ch. XXXVII.

(5) and (6) into a mixture of (3) and (5) in the ratio of 2.5–3 : 1. The predominant formation of the β,γ -unsaturated ketone (5) in the Friedel–Crafts reaction and the incomplete isomerisation have been noted before.⁵

In view of the rather difficult task of separating the two dienones (3) and (5), the mixture was treated with concentrated aqueous ammonia yielding a complex mixture of basic and neutral material. Extraction and chromatographic separation of the basic components indicated that both the desired amino-ketones (4) (*cis* and *trans*) together with some or all of the four possible monocyclic Michael adducts were formed. Refluxing the crude basic components in ethanol effected deamination of the monocyclic compounds thus facilitating the purification of the amino-ketones (4). It is noteworthy that although the *cis*- and *trans*-amino-ketones developed as separate components on both analytical and preparative t.l.c. plates, all attempts to separate them by the latter technique were fruitless. Thus, after eluting the separated bands, examination by analytical t.l.c. and n.m.r. showed that each fraction contained the original



mixture of amino-ketones. This result can be accommodated by either (a) base-catalysed epimerisation or (b) the equilibration of the *cis*- and *trans*-isomers *via* the open chain form (7). The second explanation is supported by the results of Mistryukov *et al.*⁶ who has shown by t.l.c. and u.v. analysis that the piperidone (8) is in equilibrium with the amino-enone (9).

To circumvent this unexpected problem the mixture of amino-ketones (4) was oxidised with either hydrogen peroxide–sodium tungstate or *m*-chloroperbenzoic acid to give a mixture of the keto-nitroxides (2). Due to the very similar polarities of these two isomers, separation by preparative t.l.c. could only be achieved with great difficulty (they proved to be unstable to preparative g.l.c. conditions). Reduction of the amino-ketones (4) with lithium tri-*t*-butoxyaluminium hydride⁷ yielded three amino-alcohols (10) which were oxidised to the corresponding nitroxide-alcohols (11).

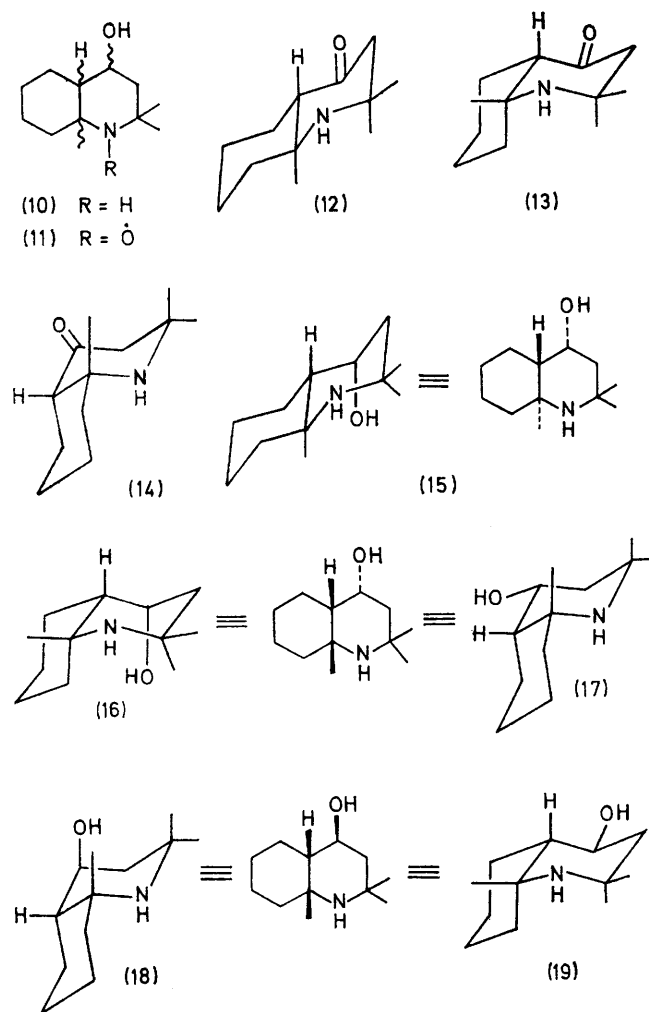
This same mixture of nitroxide-alcohols could be obtained more conveniently from the keto-nitroxides (2) by lithium tri-*t*-butoxyaluminium hydride reduction. Since the separation of these compounds proved difficult, the crude mixture was treated with diethyltrimethylsilylamine, a reagent known to effect selective trimethylsilylation of equatorial hydroxy-groups.⁸ Careful

⁶ E. A. Mistryukov, N. I. Aronova, and V. F. Kucherov, *Izvest. Akad. Nauk. SSR, Otdel. khim. Nauk.*, 1962, 870.

⁷ H. C. Brown and C. J. Shoaf, *J. Amer. Chem. Soc.*, 1964, **86**, 1079.

⁸ I. Weisz, K. Felfoldi, and K. Kovacs, *Synthesis*, 1970, 26.

monitoring of the progress of this reaction indicated that two of the alcohols reacted considerably faster than the third. The resultant mixture of one alcohol and two trimethylsilyl ethers could be readily separated by



chromatographic means and basic hydrolysis of each trimethylsilyl ether yielded the parent nitroxide-alcohol. In this way three pure nitroxide-alcohols were obtained. Each of these was reduced to the corresponding amino-alcohol by hydrogenation over Raney nickel.⁹

Our basis for stereochemical assignment of these latter compounds rests on the following considerations. (a) Eliel and Senda¹⁰ have shown that in the lithium tri-*t*-butoxyaluminum hydride reduction of 3,3,5,5-tetramethylcyclohexanone the rate of equatorial attack is greater than that of axial attack by a factor of 4,900; (b) the known selectivity of equatorial hydroxy-groups to trimethylsilylation with diethyltrimethylsilylamine;⁸ (c) an n.m.r. analysis¹¹ of the three amino-alcohols (*vide*

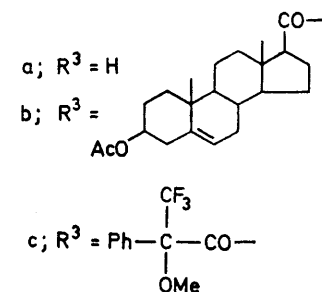
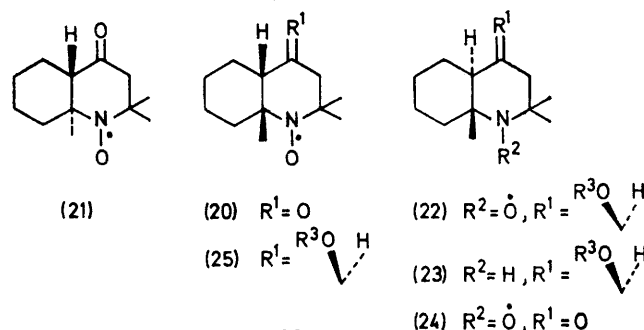
⁹ E. G. Rozantsev, A. B. Shapiro, and N. N. Komzolova, *Bull. Acad. Sci. USSR*, 1965, 1067.

¹⁰ E. L. Eliel and Y. Senda, *Tetrahedron*, 1970, **26**, 2411.

¹¹ Cf., C. A. Grob and S. W. Tam, *Helv. Chim. Acta*, 1965, **48**, 1317. We are grateful to Professor Grob for sending us the n.m.r. spectra of all four decalin-1-ol isomers.

infra). If we assume that both the six-membered rings in the *trans*-(12) and *cis*-(13) and (14) amino-ketones are in chair conformations and there is a strong preference for equatorial attack by the bulky reducing agent, then the expected amino-alcohols are (15), (16), and (18) respectively. To relieve 1,3-diaxial interactions we would expect (16) and (18) to exist predominantly as (17) and (19).

The n.m.r. spectrum of the amino-alcohol derived from the nitroxide-alcohol which was unreactive towards diethyltrimethylsilylamine exhibited a one proton multiplet at τ 5.97 (w , 8 Hz) which is consistent with structure (15)—an equatorial proton coupling with one equatorial and two axial protons. Furthermore, two of the methyl groups in this compound appeared *ca.* 0.3 p.p.m. downfield from the third. This deshielding of methyl groups in a 1,3 diaxial relationship to a hydroxy-group is well established¹² and hence reinforces the structural assignment. The n.m.r. spectrum of the second amino-alcohol displayed a one proton septet at τ 5.67 (J 11, 6, and 4 Hz) which is entirely consistent with the structure (17)—an axial proton coupling with one axial and two equatorial protons. Finally the n.m.r. spectrum of the third amino-alcohol showed a one proton sextet at τ 5.95 (J 11, 11, and 4 Hz) in agreement with that expected of structure (19)—an axial proton coupling with one equatorial and two axial protons. These assignments were placed on a firmer footing by the demonstration that Pfitzner-Moffatt¹³ oxidation of the two nitroxide-alcohols corresponding to (17) and (19) gave the *same cis*-keto-nitroxide

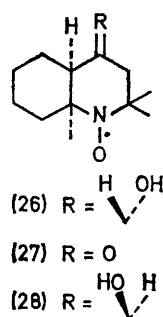


(20) as evidenced by t.l.c., g.l.c., and i.r. comparison. Using the same oxidative method the nitroxide-alcohol corresponding to (15) was converted into the *trans*-keto-nitroxide (21).

¹² W. S. Johnson, A. van der Gen, and J. J. Swoboda, *J. Amer. Chem. Soc.*, 1967, **89**, 170.

¹³ K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1965, **87**, 5661.

Having thus developed a viable synthetic route to two nitroxide radicals of the *trans*-fused series and three of the *cis*-fused series, we turned our attention to the problems of resolution.* The first experiments were conducted with the racemic *trans,cis*-nitroxide-alcohol (22a) since this molecule should have a fairly rigid skeleton. Using 3 β -acetoxy- Δ^5 -etienoyl chloride, a reagent which has enjoyed considerable success in the resolution of alcohols,^{14,15} the racemic alcohol was converted into the diastereoisomeric etienates (22b). In our hands, however, this mixture could not be separated even by multiple development on an analytical t.l.c. plate. Partial resolution was eventually achieved by triangular crystallisation of the diastereoisomeric salts obtained from the reaction of (–)- α -bromocamphor- π -sulphonic acid with the corresponding racemic amino-alcohol (23a). The partially resolved amino-alcohol (23a) was oxidised to the nitroxide-alcohol (22a), which, in turn was oxidised to the keto-nitroxide (24).



In the case of the *cis,trans*-nitroxide-alcohol (25a) separation of the diastereoisomeric etienates was achieved successfully. Not only did preparative t.l.c. effect a reasonable separation but two recrystallisations proved to be equally efficient. By basic hydrolysis of the two etienates, the nitroxide-alcohols (25a) and (26) were obtained the latter of which was used for further preparative work. Pfizner–Moffatt oxidation¹³ of (26) yielded the keto-nitroxide (27). To obtain the epimeric alcohol (28), the optically active ketone (27) was reduced with lithium tri-*t*-butoxyaluminium hydride to a mixture of (26) and (28), which were separated *via* the trimethylsilyl ethers as before.

To quantify the o.r.d. and c.d. data we required to ascertain the optical purity of the partially (or otherwise) resolved compounds. For this purpose we chose the method of Mislow and Raban¹⁶ as modified by Mosher.¹⁷ Thus, reaction of the racemic nitroxide-alcohol (22a) with (+)-methoxytrifluoromethylphenylacetyl chloride gave a diastereoisomeric mixture of esters (22c) which were reduced to the corresponding amines by catalytic hydrogenation over Raney nickel. Expansion of the 100 MHz n.m.r. spectrum of this mixture showed two

methoxy-signals at τ 6.42 and 6.48. These were quartets (J 1.2 Hz) caused by long-range coupling to the three fluorine atoms. These two signals were in the expected 1 : 1 ratio. In addition, two methyl singlets at τ 8.90 and 9.08 were sufficiently clear of the rest of the signals to allow integration. Again, these were in a 1 : 1 ratio. This procedure was repeated with the (–)-*trans,cis*-nitroxide-alcohol (22a). The n.m.r. spectrum of the resultant amino-ester mixture showed two methoxy-quartets at τ 6.41 and 6.47 in a 1 : 2.4 ratio. There were also four methyl signals sufficiently upfield to allow integration. One pair at τ 8.93 and 8.99 were in a 1 : 2.4 ratio, while the second pair at τ 9.05 and 9.17 were in a 1 : 2.3 ratio. Averaging these ratios gives a value of 41% for the enantiomeric purity of (22a). It is obvious from the above chemical shifts that there are significant shifts of the resonances between esters of the racemic material and esters of the optically active compounds. It is thought that the changes in the asymmetric environment of a given proton as caused by solute–solute interactions are responsible for this effect.

An attempt to cross-check the enantiomeric purity from the ¹⁹F n.m.r. spectrum was surprisingly unsuccessful. The esters from the racemic alcohol did indeed show two signals separated by 12 Hz in a 1 : 1 ratio. However, the material derived from the optically active alcohol showed only one peak. It is considered that the induced chemical shifts noted above have this time caused accidental coincidence of the signals. To our knowledge this has not been recorded before and thus would appear to limit the reliability of the method if only one type of spectrum is obtained. Thus, fortuitously the ¹H n.m.r. spectrum gave three independent integrations signalling an optical purity of 41% for (22a).

The racemic *cis,trans*-nitroxide-alcohol (25a) was likewise converted into the ester mixture (25c) and then, by reduction, to the corresponding amino-ester mixture. Similarly, the optically active alcohol (25a) was converted into the corresponding amino-ester. The amino-ester mixture from the racemic alcohol showed two methoxy-quartets at τ 6.41 and 6.45 in a 1 : 1 ratio, while the ester from the optically active alcohol showed only one methoxy-quartet at τ 6.45. This shows that the alcohol (25a) is at least 95% optically pure (allowing for experimental error in integration). In this instance the ¹⁹F n.m.r. spectra were in accord with this conclusion. Since most of the transformations described in the *cis*-series were carried out on the antipodal alcohol (26), an enantiomeric purity of 66% was used for this compound. These values were used to correct all o.r.d. and c.d. data and are only held to be correct to $\pm 5\%$.

The one remaining problem was to determine the absolute configuration of these compounds. The ob-

* At this point in the paper the absolute stereochemistries of the resolved compounds are as depicted for simplicity. The nomenclature used for the nitroxide-alcohols (e.g. *trans,cis*) denotes the ring fusion stereochemistry followed by the relationship of the 4a-hydrogen with respect to the 4-hydrogen atom.

¹⁴ S. H. Wilen in 'Topics in Stereochemistry,' eds. N. L. Allinger and E. L. Eliel, Wiley-Interscience, New York, 1971, vol. 6, 107.

¹⁵ J. Staunton and E. J. Eisenbraun, *Org. Synth.*, 1962, **42**, 4.

¹⁶ M. Raban and K. Mislow, *Tetrahedron Letters*, 1965, 4249.

¹⁷ J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

vious choice was the application of Horeau's method¹⁸ of asymmetric esterification to the alcohols (22a) and (26). Accordingly, (+)-*cis,trans*-nitroxide alcohol (26) was reacted with an excess of α -phenylbutyric anhydride in pyridine.¹⁹ The crude product showed no trace of starting alcohol by t.l.c. and i.r. analysis. The excess of α -phenylbutyric acid recovered after reaction had $[\alpha]_{589}^{20} +1.2^\circ$. This corresponds to an optical yield of 11% and allows a safe assignment of the *R* configuration to the C-4 position of this compound. The complete absolute stereochemistry of (26) is thus defined as 4*R*, 4*aR*, 8*aS*.

Application of this method to (–)-*trans,cis*-nitroxide-alcohol (22a) was complicated by the fact that esterification was incomplete. However, by making a correction for unreacted alcohol it was possible to show that an optical yield of >20% was involved. The α -phenylbutyric acid recovered was laevorotatory and hence the configuration *S* could be assigned to position 4 of this compound and its absolute configuration thus designated 4*S*, 4*aR*, 8*aR*.

RESULTS AND DISCUSSION

The Octant Rule³ has enjoyed considerable success in the interpretation of the chiroptical properties of asymmetrically-substituted ketones.²⁰ It is now well established that the sign and amplitude of the Cotton effect associated with the $n \rightarrow \pi^*$ transition of the carbonyl chromophore can yield valuable information concerning configurational and conformational assignments.^{21,22}

A consideration of the partial molecular orbital energy diagram (Figure 1) of the nitroxide group⁴ illustrates the similarity with that corresponding to the carbonyl group. This similarity becomes even more pronounced with reference to the $n \rightarrow \pi^*$ excited state of the carbonyl group. More precisely the nitroxide group is isoelectronic with a ketyl grouping. Rassat²³ has discussed the analogy between the ground state electronic configuration of a nitroxide and the $n \rightarrow \pi^*$ excited state of a carbonyl group in terms of the geometry of both states. Thus, in the $^1n \rightarrow \pi^*$ and $^3n \rightarrow \pi^*$ states of formaldehyde, the C–O axis subtends an angle with the HCH plane of *ca.* 27 and 35° respectively.²⁴ This pyra-

midal configuration of *C_s* symmetry has also been determined theoretically in the case of H₂NO²⁵ and is reflected in a number of nitroxide radicals whose structures have been determined by spectroscopic techniques.^{26–28} These results indicate that the angle between the N–O bond and the CNC plane varies from 16 to 24°.

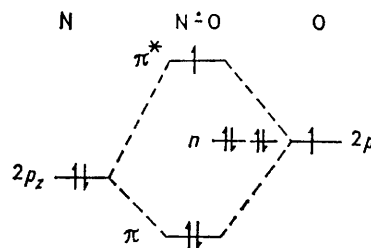


FIGURE 1

Thus the overall picture which emerges is that the nitroxide group bears a close resemblance to the carbonyl group and on this basis we have attempted to analyse the c.d. and o.r.d. spectra of a number of optically active nitroxide radicals using the carbonyl Octant Rule as our guideline.

Before proceeding to an interpretation of the c.d. and o.r.d. results, however, it is necessary to summarise briefly what is known about the conformations of suitably methylated cyclohexane derivatives and monocyclic nitroxides. It might be expected that a combination of sizeable non-bonded interactions and one *sp*² centre would be sufficient to encourage a favourable twist conformation in 3,3,5,5-tetramethylcyclohexanone. However, the available chemical²⁹ and n.m.r. evidence,^{30,31} together with the conformational calculations of Allinger *et al.*³² suggest that this molecule and related compounds exist in flattened chair conformations. This is certainly true in the case of 2,2,6,6-tetramethyl-4-piperidone hydrochloride whose X-ray structural analysis clearly indicates the anticipated distortions of dihedral and valence angles.³³

The principal source of information concerning the conformational preferences of monocyclic nitroxides is

¹⁸ A. Horeau, *Tetrahedron Letters*, 1961, 506.

¹⁹ W. Herz and H. Kagan, *J. Org. Chem.*, 1967, **32**, 216.

²⁰ C. Djerassi, 'Optical Rotatory Dispersion,' McGraw-Hill, New York, 1960; P. Crabbe, 'Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,' Holden-Day, San Francisco, 1965; 'Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,' ed. G. Snatzke, Heyden, London, 1967.

²¹ For theoretical treatments see, J. C. Tai and N. L. Allinger, *J. Amer. Chem. Soc.*, 1966, **88**, 2179; G. Wagnière, *ibid.*, p. 3937; Y.-H. Pao and D. P. Santry, *ibid.*, p. 4157; C. W. Deutsche, D. A. Lightner, R. W. Woody, and A. Moscovitz, *Ann. Rev. Phys. Chem.*, 1969, **20**, 407.

²² C. Coulombeau and A. Rassat, *Bull. Soc. chim. France*, 1971, 516, and references therein.

²³ A. Rassat, 'Colloques Internationaux du Centre National de la Recherche Scientifique,' No. 164, 1966, 427 (*Chem. Abs.*, **67**, 59,355f).

²⁴ G. Berthier and J. Serre, in 'The Chemistry of the Carbonyl Group,' ed. S. Patai, Interscience, London, 1966, ch. 1, and references therein.

²⁵ A. W. Salotto and L. Burnelle, *J. Chem. Phys.*, 1970, **53**, 333; see also O. Kikuchi, *Bull. Chem. Soc. Japan*, 1969, **42**, 47.

²⁶ L. J. Berliner, *Acta Cryst.*, 1970, **B26**, 1198; P. J. Lajzéro-wicz-Bonneteau, *Acta Cryst.*, 1968, **B24**, 196.

²⁷ C. Glidewell, D. W. H. Rankin, A. G. Robiette, G. M. Sheldrick, and S. M. Williamson, *J. Chem. Soc. (A)*, 1971, 478; see also G. R. Underwood and V. L. Vogel, *Mol. Phys.*, 1970, **19**, 621.

²⁸ D. M. Hawley, G. Ferguson, and J. M. Robertson, *J. Chem. Soc. (B)*, 1968, 1255. For two other nitroxides see A. Capiomont, B. Chion, and J. Lajzéro-wicz, *Acta Cryst.*, 1971, **B27**, 322; A. Rassat and J. Ronzaud, *J. Amer. Chem. Soc.*, 1971, **93**, 5041.

²⁹ H. Piotrowska, W. Wojnarowski, B. Waegell, and G. Ourisson, *Bull. Soc. chim. France*, 1965, 3511, and references therein on the 'Reflex Effect.'

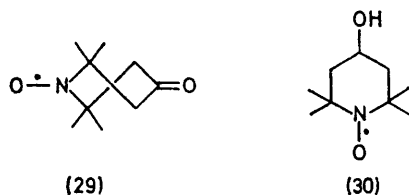
³⁰ M. Fétizon, J. Goré, P. Laszlo, and B. Waegell, *J. Org. Chem.*, 1966, **31**, 4047.

³¹ M. St-Jacques, M. Bernard, and C. Vaziri, *Canad. J. Chem.*, 1970, **48**, 2386.

³² N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, 1969, **91**, 337.

³³ B. Rees and R. Weiss, *Acta Cryst.*, 1971, **B27**, 932.

derived from the elegant spectroscopic studies by Rassat and his co-workers.^{4,34,35} In the case of the keto-nitroxide (29), their results, taken in conjunction with a dipole



moment study³⁶ indicate a twist-boat conformation, similar to that suggested³⁷ for cyclohexa-1,4-dione. On the other hand for those monocyclic nitroxides with no sp^2 hybridised carbon atoms *e.g.* (30), the weight of evidence is in favour of a flattened chair conformation. This fact can be adjudged not only on the basis of e.s.r. spectra but with even greater certainty from a study of n.m.r. spectra obtained at high magnetic field.^{35,38} This is also consistent with the X-ray analysis of (30).²⁶

The c.d. curves of the decahydroquinoline nitroxides

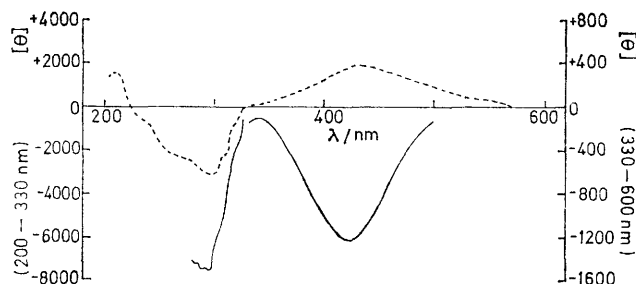


FIGURE 2 C.d. curves of (24), —; and (27) ----

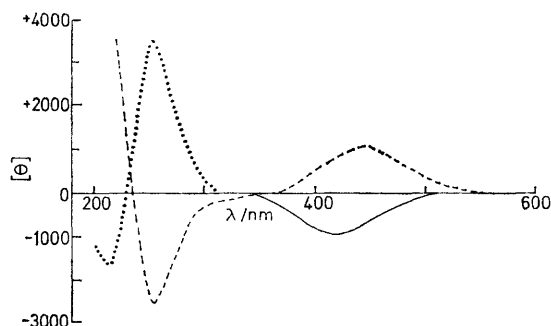


FIGURE 3 C.d. curves of (22a), —; (26) ----; and (28) ····

(24), (27), (22a), (26), and (28) are shown in Figures 2 and 3 and the u.v., c.d., and o.r.d. data of these compounds are collated in Tables 1–3. Compounds (24), (27), (22a), and (26) all show c.d. maxima in the region 420–450 nm due to the $n \rightarrow \pi^*$ transition of the nitroxide function. At the concentration used the (+)-*cis,cis*-alcohol (28) did not show a maximum in this region.

³⁴ A. Rassat, *Pure Appl. Chem.*, 1971, **25**, 623.

³⁵ R. Brière, H. Lemaire, A. Rassat, P. Rey, and A. Rousseau, *Bull. Soc. chim. France*, 1967, **4479**; see also R. W. Kreilick, *J. Chem. Phys.*, 1967, **46**, 4260.

This implies that this compound (in terms of the groups surrounding the nitroxide) must be 'symmetrical' (*vide infra*). In addition, the two keto-nitroxides show maxima at *ca* 300 nm caused by the $n \rightarrow \pi^*$ transition of the carbonyl group. The spectra of the two *cis*-alcohols were obtained down to almost 200 nm showing

TABLE 1

$n \rightarrow \pi^*$ Transition of N=O						
Compound	U.v. λ_{\max}/nm	ϵ	C.d. λ_{\max}/nm	$[\theta]$	O.r.d. λ_{\max}/nm	a
(24)	422	6.8	425	–1240	428	–6.4
(27)	430	6.8	432	+370		
(22a)	440	9.9	423	–977	425	–10.9
(26)	432	14.5	445	+1070	440	+15.7
(28)	442	13.6				

TABLE 2

$n \rightarrow \pi^*$ Transition of C=O			
Compound	C.d. λ_{\max}/nm	$[\theta]$	O.r.d.
(24)	296	–7640	Only first extremum observed
(27)	299	–3100	

TABLE 3

Other transitions						
Compound	U.v. λ_{\max}/nm	ϵ	C.d. λ_{\max}/nm	$[\theta]$	O.r.d. λ_{\max}/nm	a
(24)	234	2200				
(27)	239	2050				
(22a)	243	2600				
(26)	245	1800	254	–2590	Only first extremum observed	
(28)	243	1840	252 216	+3550 –1570	252	+55.9

maxima at 252 and 254 nm due to the $\pi \rightarrow \pi^*$ transition of the nitroxide. It is interesting that the alcohol (28) shows another maximum in this region at 216 nm while (26) seems to indicate the start of a maximum at about this wavelength. Thus it seems that these compounds have another electronic transition in this region which is not resolved in the u.v. spectra. This ability of c.d. spectra to unmask hidden transitions in the u.v. spectra is well known. This absorption could be possibly a $n \rightarrow \sigma^*$ or $\pi \rightarrow \sigma^*$ transition of the nitroxide group.

The o.r.d. curves, being less selective in terms of electronic transitions, were less informative in view of the background curves of these molecules. Indeed, the carbonyl Cotton effect and background curve of the *cis*-keto-nitroxide (27) so dominated the spectrum that the Cotton effect of the nitroxide was not observable. However, the Cotton effects of the nitroxide function of compounds (24), (22a), and (26) were clearly seen as were the first extrema of the carbonyl Cotton effects of (24) and (27).

The compounds most likely to be amenable to con-

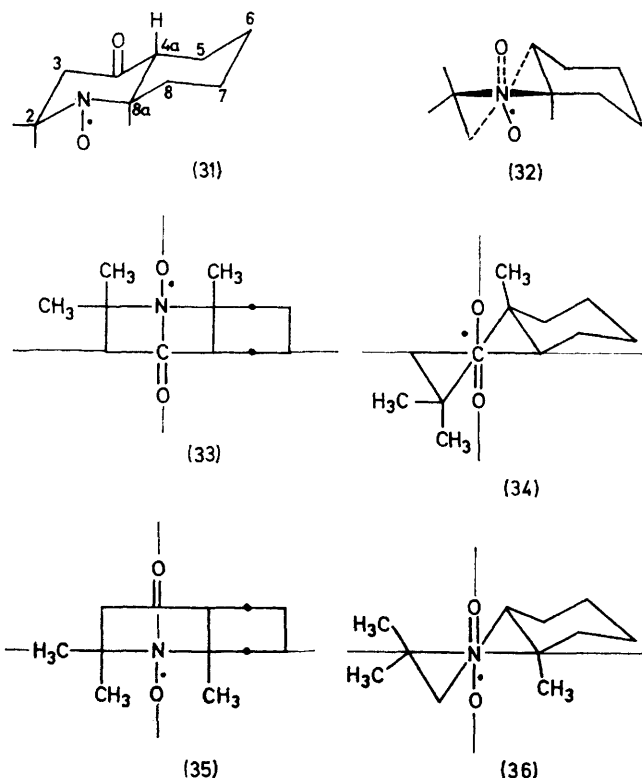
³⁶ E. G. Rozantsev and E. N. Gur'yanova, *Bull. Acad. Sci. USSR*, 1966, 936.

³⁷ P. Dowd, T. Dyke, and W. Klemperer, *J. Amer. Chem. Soc.*, 1970, **92**, 6327, and references therein.

³⁸ R. Brière, H. Lemaire, A. Rassat, and J.-J. Dunand, *Bull. Soc. chim. France*, 1970, 4220.

formational analysis are the *trans*-fused compounds (24) and (22a). The most probable conformations of the keto-nitroxide (24) are the all-chair conformer (31) and the chair-twist conformer (32). The former has a severe 1,3 diaxial interaction between the methyl groups at C-2 and C-8a. This amounts to about 3 kcal mol⁻¹³⁹ and would probably mean that in such a conformation, the piperidino-oxy-ring would be considerably flattened.

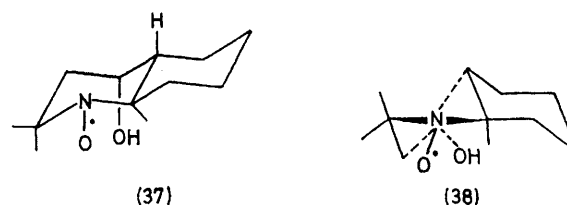
To exploit the internal 'chiroptical handle' we first of all considered the carbonyl octant projections of (31) and (32), viz., (33) and (34). Analysis of projection (33) shows that only the equatorial 2-methyl and the 7- and 8-methylene groups contribute to the rotatory power of the carbonyl group. Since these are of opposite sign with the former probably predominating²² a weak positive maximum is expected for the carbonyl c.d. curve. On the other hand, the carbonyl projection (34) suggests a strong negative c.d. maximum. This is entirely consistent with the observed o.r.d. and c.d. curves and thus we strongly favour the chair-twist conformer (32) for the *trans*-fused keto-nitroxide (24). Using this as our conformational basis, analysis of the nitroxide projection (36) in terms of the carbonyl octant signs would predict a



sizeable negative Cotton effect which is in accord with the observed data. Application of the same principles to projection (35) would suggest a small negative Cotton effect. Thus we have the first indication that the signs

of the back octants associated with the nitroxide chromophore follow those of the carbonyl group.

Using this information as our guideline we have attempted to interpret the c.d. and o.r.d. spectra of the other four optically active nitroxides. The all-chair conformation (37) of the *trans*,*cis*-alcohol (22a) has a nitroxide octant projection suggesting a negative c.d. maximum as has the chair-twist conformer (38). The similarity of the spectra of (22a) to those of the ketone (24) suggests that conformation (38) may be preferred. This is reasonable since in the all-chair conformation (37) there exists a *syn*-triaxial interaction between the methyl groups and the hydroxy-group which would total *ca.* 8.5 kcal mol⁻¹⁴⁰ in a perfect chair. This is also consistent with the chemical evidence (lack of reaction with diethyltrimethylsilylamine) which suggests that the hydroxy-group must be reasonably hindered.



If the energy differences between the different possible conformations are reasonably small then it is expected that more than one conformer will be appreciably populated. The observed c.d. and o.r.d. curves in this case will be the weighted sum of those of the individual conformers. Thus, the observed spectrum is usually dominated by the conformer with the strongest rotatory power and not necessarily by the most abundant.²⁰ This limitation must be borne in mind in the above and subsequent arguments.

A reasonable analogy for the *trans*-fused compounds is provided by the D-homosteroids (39) and (40) which were studied by Allinger *et al.*⁴¹ Using the generally accepted values for non-bonded and torsional energies, they deduced that a twist conformation for ring D in these compounds would be preferred. This was supported by o.r.d.⁴² and dipole moment measurements.

TABLE 4

Conformation	Predicted sign of N ⁺ O Cotton effect	Predicted sign of C=O Cotton effect
(41)	-ve	-ve
(42)	+ve	-ve
(43)	?	very -ve
(44)	+ve	+ve
Observed	+ve	very -ve

In view of their greater conformational mobility the *cis*-fused compounds (26)–(28) are less amenable to definitive interpretation. For the *cis*-ketone (27) we have assumed four possible conformations (neglecting

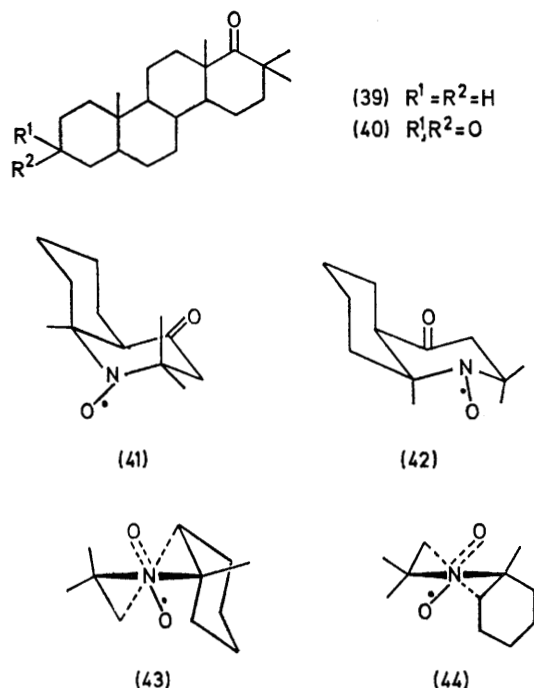
³⁹ E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Wiley, New York, 1965.

⁴⁰ E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, 1965, **87**, 5031.

⁴¹ N. L. Allinger, J. Allinger, and M. A. DaRooge, *J. Amer. Chem. Soc.*, 1964, **86**, 4061.

⁴² M. Uskovic, M. Gut, E. N. Trachtenberg, W. Klyne, and R. I. Dorfman, *J. Amer. Chem. Soc.*, 1960, **82**, 4965.

regular boats), *viz.*, (41)–(44). Consideration of the carbonyl and nitroxide octant projections for these allows the construction of Table 4 of predicted signs for the Cotton effects. Reference to the data in Tables 1 and 2 suggests that conformations (41) and (44) are not favoured or at most, make very little contribution to the



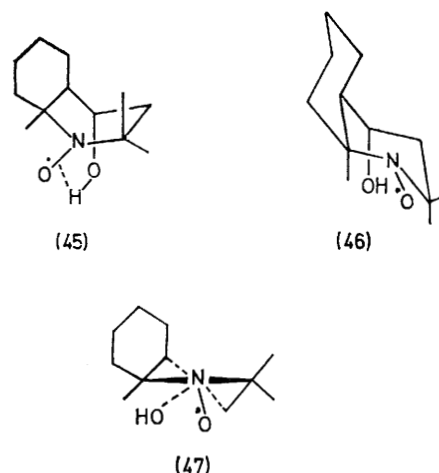
c.d. curve. However, it is difficult to estimate what sign the nitroxide function in the chair-twist conformation (43) will have, since in its octant projection there are substituents in all four octants which do not readily cancel one another. However, in the carbonyl projection of (43) all contributing substituents are in negative octants, as in the case with the *trans*-keto-nitroxide (24), and a strong negative c.d. maximum is expected and observed. This may be tempered to some extent by the presence of other conformers of lesser rotatory power and thus not be as strong as the *trans*-compound. A reasonable explanation is that this compound is an equilibrium mixture of conformers (42) and (43) although the presence of small proportions of the conformers (41) and (44) cannot be excluded.

The *cis,cis*-isomer (28), as noted before, does not show a c.d. maximum in the 400–450 nm region, or at least the Cotton effect is too weak to be observable at the concentration used (which was approximately the same as for the other *cis*-compounds). This means that, in the octant projections of the preferred conformer, the contributions from substituents in the negative octants must exactly balance out the contributions from the substituents occupying positive octants. Alternatively, the conformational equilibrium must be such that the rotatory power of one or more conformers balances the rotatory power of the other(s). This may be more

likely since it is difficult to draw an octant diagram in which contributions cancel out.

It is significant that the i.r. spectrum of the *cis,trans*-alcohol (26) shows two hydroxy-bands at 3630 and 3600 cm^{-1} . These bands are independent of concentration and hence are indicative of a weak hydrogen bond between the hydroxy-group and the nitroxide function. This can only be realised in the boat conformation (45) which would indeed be predicted to show a positive c.d. maximum. However, the chemical behaviour of this compound (fast reaction with diethyltrimethylsilylamine) indicates that other conformations in which the hydroxy-group is more exposed than in (45) must be present. A consideration of some of the other possible conformations indicates that (46) and (47), for example, would be expected to show positive c.d. maxima and hence cannot be discounted.

Conclusions.—From this preliminary investigation we believe that valuable information can be gained from the o.r.d. and c.d. spectra of stable six-membered ring nitroxide radicals concerning the electronic transitions and conformational assignments. In particular, the data associated with the *trans*-fused keto-nitroxide (24) lends compelling support to the hypothesis that the nitroxide group can be treated qualitatively in terms of the carbonyl Octant Rule with reference to the back octants. The inherent problems of this investigation which render interpretations based on the carbonyl Octant Rule less secure are the undoubted distortion of the substituted piperidino-oxy-ring and the possibility of electronic interaction between the nitroxide chromophore and those of the carbonyl and hydroxy-groups.⁴³ To overcome these problems, however, we are currently investigating the syntheses of nitroxide radicals which will



permit both qualitative and quantitative comparisons with similarly substituted cyclohexanones.

EXPERIMENTAL

All m.p.s were recorded on a Kofler hot-stage and are uncorrected. I.r. spectra were recorded on Perkin-Elmer 257

⁴³ J. Hudec, *Chem. Comm.*, 1970, 829.

or Unicam SP 200 instruments and u.v. spectra were recorded on a Unicam SP 800 instrument using either ethanol or methanol as solvent. N.m.r. spectra were recorded on Varian T-60 or Varian HA-100 spectrometers using tetramethylsilane as internal standard and deuteriochloroform as solvent unless otherwise stated. E.s.r. spectra were recorded on a Decca X3 instrument, operating in the X-band region at a frequency of 9270 MHz. Mass spectra were recorded on a AEI MS 12 instrument. All rotations were measured on a Perkin-Elmer 141 polarimeter and o.r.d. and c.d. curves were recorded in methanol solution using a Carey 60 spectropolarimeter.

G.l.c. was performed on Pye Argon instruments using 4 feet packed columns and argon as carrier gas. T.l.c. was carried out using Kieselgel silica while column chromatography was carried out with Woelm alumina. Light petroleum refers to the fraction boiling in the range 60–80 °C.

2-Methylcyclohex-1-enyl 2-Methylprop-1-enyl Ketone (3).—To a stirred solution of 1-methylcyclohexene (2.39 g) and β,β -dimethylacryloyl chloride (2.15 g) at 0 °C was added dropwise tin(IV) chloride (0.1 ml, 0.23 g). The mixture was stirred at ambient temperature for 3 h and then hydrolysed by pouring into 3N-hydrochloric acid (10 ml). The resultant mixture was extracted thoroughly with ether and the organic extracts were washed successively with dilute hydrochloric acid, saturated sodium bicarbonate solution, and brine. After drying (MgSO_4) the solvent was removed to yield a brown oil (3.3 g) which was distilled yielding two main fractions. Fraction 1 (0.76 g) had b.p. 35–40 °C at 14 mmHg and fraction 2 (1.40 g) had b.p. 118–128 °C at 14 mmHg.

Fraction 1 showed no i.r. absorption in the hydroxy or carbonyl regions and its simple n.m.r. spectrum, τ 7.8–8.6 τ and 8.43 (s) suggested that it was 1-chloro-1-methylcyclohexane.

Fraction 2 showed two peaks on g.l.c. (retention times 11.3 and 21.3 min on 5% QF-1 at 100 °C and gas flow rate 70 ml min⁻¹), which corresponded to the ketones (5) and (6). This mixture was separated into its components by preparative t.l.c., developing three times with ethyl acetate–light petroleum (1:49) to give *2-chloro-2-methylcyclohexyl 2-methylprop-1-enyl ketone* (6), ν_{max} (film) 1680 and 1620 cm⁻¹, τ 3.84 (1H, m), 6.96 (1H, m), 7.86 (3H, d, J 1 Hz), 8.10 (3H, d, J 1 Hz), 8.36 (3H, s), and 7.8–8.7 (8H, m) (Found: C, 67.2; H, 8.9. $\text{C}_{12}\text{H}_{19}\text{ClO}$ requires C, 67.15; H, 8.85%), and *2-methylcyclohex-2-enyl 2-methylprop-1-enyl ketone* (5), ν_{max} (CHCl_3) 1682 and 1617 cm⁻¹, τ 3.87 (1H, m), 4.37 (1H, m), 6.95 (1H, m), 7.82 (3H, d, J 1 Hz), 8.08 (3H, d, J 1 Hz), 8.37 (3H, m), and 7.7–8.6 (6H, m), λ_{max} (EtOH) 242 nm (ϵ 8600) (Found: C, 80.55; H, 10.15. $\text{C}_{12}\text{H}_{18}\text{O}$ requires C, 80.85; H, 10.2%).

In order to maximise the yield of the desired cross-conjugated dienone (3), small samples of the crude Friedel-Crafts product were treated under various acid and base conditions both in the cold and at reflux temperatures, e.g. pyridine, diethylaniline, HCl–HOAc, H_2SO_4 (50%), oxalic acid (10%), and toluene-*p*-sulphonic acid–benzene. The best ratio of (3) : (5) (ca. 2.5 : 1) was obtained after successive treatments with diethylaniline followed by toluene-*p*-sulphonic acid–benzene at reflux temperatures. In a typical run the crude Friedel-Crafts product (95 g) was refluxed in diethylaniline (100 ml) for 1½ h, cooled, and dissolved in ethyl acetate. The resultant solution was extracted with dilute hydrochloric acid, sodium bicarbonate

solution, and brine. After drying (MgSO_4) and removal of the solvent a red oil was obtained which was dissolved in benzene (1.25 l). Toluene-*p*-sulphonic acid (10 g) was added and the mixture refluxed for 3½ h. After cooling and extracting with hydrochloric acid, sodium bicarbonate solution, and brine, the mixture was dried (MgSO_4). Removal of the solvent yielded a red oil (53 g) which, on distillation, yielded a mixture of the cross-conjugated (3) and β,γ -unsaturated dienones (5) in a 2.5 : 1 ratio (37.0 g) b.p. 120–127 °C at 12 mmHg. Separation by preparative t.l.c. [ethyl acetate–light petroleum (1 : 49)] yielded a pure sample of the ketone (3), ν_{max} (CHCl_3) 1664 and 1610 cm⁻¹, τ 3.90 (1H, m), 7.90 (3H, d, J 1 Hz), 8.14 (3H, d, J 1 Hz), and 7.7–8.5 (11H, m), λ_{max} (EtOH) 248 nm (ϵ 8400) (Found: C, 80.7; H, 10.1. $\text{C}_{12}\text{H}_{18}\text{O}$ requires C, 80.85; H, 10.2%).

cis- and trans-2,2,8a-Trimethyloctahydro-4-quinolone (4).—A mixture of the above dienones (35.0 g), dioxan (50 ml), and concentrated ammonia solution (150 ml; d 0.88) was stirred vigorously in a securely stoppered flask for 3 days. The resultant mixture was acidified by addition of dilute hydrochloric acid and extracted with ether to remove any neutral material. The mixture was then basified and saturated with solid potassium carbonate. Extraction with ether, drying (MgSO_4) and removal of the solvent yielded an orange oil (23.8 g). This was refluxed in ethanol (250 ml) for 4 h and the basic material separated from the neutral as above to yield a brown oil (9.4 g). This material showed two closely running spots on analytical t.l.c. using light petroleum–ethyl acetate–diethylamine (8 : 2 : 1) and two peaks on analytical g.l.c. (retention times 5.8 and 8.6 min on 1% NGS at 100 °C and carrier gas flow rate 60 ml min⁻¹), ν_{max} (film) 1702 cm⁻¹, τ 7.6–8.8 τ , 8.67 (s), 8.73 (s), and 8.91 (s). All attempts to separate the two isomeric ketones by various chromatographic techniques were unsuccessful.

The crude product from the addition of ammonia to the dienone mixture was observed to contain a much more polar component(s) which was isolated by preparative t.l.c., ν_{max} (film) 3450, 1705, 1680, and 1600 cm⁻¹, τ 4.35 (v. small peak), 7.0–8.6 (complex), and 8.77 (sharp intense s). This would appear to be a mixture of the non-cyclised, mono- and di-adducts which was confirmed by the fact that refluxing this material in ethanol solution for 4 h regenerated the dienone mixture.

*Lithium Tri-*t*-butoxyaluminium Hydride Reduction of cis- and trans-2,2,8a-Trimethyloctahydro-4-quinolone* (4).—To a stirred solution of lithium tri-*t*-butoxyaluminium hydride (290 mg) in tetrahydrofuran (2 ml) was added a mixture of the amino-ketones (86 mg) in tetrahydrofuran (2 ml). After stirring for 4 h, the mixture was decomposed with saturated sodium sulphate solution and filtered. The solid residue was washed thoroughly with chloroform and the combined organic extracts dried (MgSO_4). Removal of the solvent yielded a clear viscous oil (71 mg) containing a mixture of the three isomeric amino-alcohols (10).

Oxidation of the 2,2,8a-Trimethyldecahydro-4-quinolol Mixture (10) to the *4-Hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl Mixture* (11).—The mixture of amino-alcohols (10) (881 mg) was dissolved in methanol (10 ml). To this was added sodium tungstate (32 mg), ethylenediaminetetraacetic acid (42 mg), water (1 ml), and hydrogen peroxide solution (2 ml; 30%). The mixture was stirred at room temperature for 3½ days, filtered, most of the methanol removed under reduced pressure, saturated with potassium carbonate, and thoroughly extracted with benzene. After

drying (K_2CO_3), removal of the solvent yielded a red viscous oil (747 mg).

Oxidation of cis- and trans-2,2,8a-Trimethyloctahydro-4-quinolone (4) to the Corresponding Keto-nitroxide Radicals (2).

—(a). A mixture of *cis* and *trans*-2,2,8a-trimethyloctahydro-4-quinolone (4) (1.1 g) was dissolved in a mixture of water and methanol (1 : 1; 25 ml). Sodium tungstate (27 mg), the disodium salt of ethylenediaminetetra-acetic acid (38 mg), and hydrogen peroxide solution (1.5 ml; 30%) were added. The mixture was stirred for 5 days, saturated with potassium carbonate and extracted with ether. The ethereal extracts were washed thoroughly with 1N-sulphuric acid, saturated sodium bicarbonate solution, and brine. Drying ($MgSO_4$) and removal of the solvent yielded a red oil (415 mg), ν_{max} (film) 1712 cm^{-1} . This showed two closely running spots on t.l.c. and two peaks on g.l.c. (retention times 24.8 and 34.7 min, 1% NGS, 100 °C, flow rate 65 ml min^{-1}).

(b). To a stirred solution of the mixture of amino-ketones (4) (8.1 g) in tetrahydrofuran (100 ml) at 0 °C was added dropwise a solution of *m*-chloroperbenzoic acid (10.0 g) in tetrahydrofuran (50 ml). After the addition was complete (10 min) the mixture was stirred for a further 20 min and then transferred to a separatory funnel. Ether was added and the solution extracted four times with saturated sodium bicarbonate solution (500 ml), dried ($MgSO_4$), and the solvent was removed to yield a red oil (8.2 g) which was dissolved in benzene and percolated through a short column of neutral alumina. T.l.c. showed the presence of the two keto-nitroxides (2) which could be separated by careful preparative t.l.c.

Reduction of the Keto-nitroxide Mixture (2) to the Hydroxy-nitroxide Mixture (11).—A solution of lithium tri-*t*-butoxy-aluminium hydride was prepared by adding dry *t*-butanol (20.9 g) dropwise to a stirred solution of lithium aluminium hydride (3.98 g) in dry tetrahydrofuran (150 ml) over a period of 1 h. To this was added, at 0 °C, a solution of the keto-nitroxides (2) (7.1 g) in tetrahydrofuran (50 ml) over a period of 30 min and the mixture was stirred at ambient temperature for a further 3 h. The complex was decomposed by dropwise addition of saturated sodium sulphate solution at 0 °C. The resultant mixture was filtered, dried ($MgSO_4$), and the solvent was removed to yield a dark red oil (7.06 g), ν_{max} (film) 3500 cm^{-1} . This showed two spots on t.l.c. and two peaks on g.l.c. on a variety of columns. A small sample of this was converted to the trimethylsilyl ether derivatives by shaking with trimethylsilyl chloride and hexamethyldisilazane in dry pyridine for 5 min. Removal of the solvent and dissolution of the residue in ether followed by filtration gave a solution suitable for g.l.c. analysis. This showed three peaks by g.l.c. (retention times 13.3, 17.5, and 27.8 min on a 5% QF.1 column at 125 °C and a gas flow rate of 65 ml min^{-1}).

Separation of the Hydroxy-nitroxide Mixture (11).—The alcohol mixture (11) (7.6 g) was dissolved in acetone (12 ml) and diethyltrimethylsilylamine (12 ml) was added. The mixture was allowed to stand at room temperature for 5 h and then all volatile materials were removed on a rotatory evaporator. The resultant red oil was chromatographed on neutral alumina (grade III; 200 g), to give the following fractions. Fractions 2–16 (1% ether–light petroleum) gave a red oil (3.30 g), a mixture of two trimethylsilyl ethers. Fractions 17–36 (5% ether–light petroleum) gave a red oil (1.17 g), the more polar trimethylsilyl ether. Fractions 50–60 (60% ether–light petroleum) gave an orange solid (1.94 g), nitroxide-alcohol [(±)-(22a)].

The trimethylsilyl ethers in fractions 2–16 were separated by preparative t.l.c. on 100 cm × 20 cm × 0.1 mm silica gel plates eluting with 12% ether–light petroleum. Combination of pure components gave less polar trimethylsilyl ether (1.31 g), ν_{max} (film) 1250, 860, and 768 cm^{-1} and more polar trimethylsilyl ether (2.82 g), ν_{max} (film) 1250, 858, and 760 cm^{-1} .

(±)-*trans,cis*-4-Hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (22a).—Recrystallisation of fractions 50–60 from benzene–light petroleum gave pure *nitroxide* (22a) (1.69 g), m.p. 116–118 °C, ν_{max} (Nujol) 3440 and 1346 cm^{-1} , ν_{max} (CCl_4 , at high dilution) 3630 cm^{-1} , a_N ($CHCl_3$) 15.9 G, g 2.0063, λ_{max} (EtOH) 440 (ϵ 9.9) and 243 nm (2600) (M^+ , 212) (Found: C, 67.65; H, 10.65; N, 6.4. $C_{12}H_{22}NO_2$ requires C, 67.9; H, 10.45; N, 6.6%).

(±)-*cis,cis*-4-Hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (28).—The less polar trimethylsilyl ether (1.31 g), methanol (100 ml), potassium hydroxide solution (10 ml; 4%), and benzene (25 ml) was heated under reflux for 8 h. The methanol was removed on a rotatory evaporator and the aqueous residue was thoroughly extracted with ether. The ethereal extracts were washed with brine, dried ($MgSO_4$), and the solvent was removed to yield a red oil (990 mg) which slowly solidified on standing. This was pure *nitroxide* (28), m.p. 81–84.5 °C, ν_{max} (Nujol) 3480 cm^{-1} , ν_{max} (CCl_4 , at high dilution) 3620 cm^{-1} , a_N ($CHCl_3$) 16.2 G, g 2.0067, λ_{max} (EtOH) 442 (ϵ 13.6) and 243 nm (1840) (M^+ , 212. $C_{12}H_{22}NO_2$ requires M , 212.3) (Found: C, 67.75; H, 10.4; N, 6.55).

(±)-*cis,trans*-4-Hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (25a), (26).—The more polar trimethylsilyl ether (2.82 g) was hydrolysed as described above to yield a red solid (2.00 g) which on recrystallisation from benzene–light petroleum gave pure *nitroxide* (25a), (26), m.p. 104–106 °C, ν_{max} (Nujol) 3450 cm^{-1} , ν_{max} (CCl_4 , at high dilution) 3630 and 3600 cm^{-1} (no change on further dilution), a_N ($CHCl_3$) 15.9 G, g 2.0064, λ_{max} (EtOH) 432 (ϵ 14.5) and 245 nm (1800) (M^+ , 212) (Found: C, 68.0; H, 10.35; N, 6.45).

(±)-*trans,cis*-4-Hydroxy-2,2,8a-trimethyldecahydroquinoline (15).—(±)-*trans,cis*-4-Hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (22a) (1.69 g) was dissolved in methanol (100 ml) and about one half-teaspoon of Raney nickel (W-2; ca. 1.5 g) was added. The flask was attached to a hydrogenator and hydrogenation allowed to take place in the usual fashion. After 2½ h, hydrogen uptake had ceased (250 ml; 93% of theory). The catalyst was filtered and washed thoroughly with methanol. Removal of the solvent yielded a slightly yellow oil (1.65 g) which crystallised on standing. A sample of this was sublimed at 0.1 mmHg (block temperature 120°C) to yield pure *amino-alcohol* (15) as a white solid, m.p. 126–127 °C, ν_{max} (Nujol) 3200 $br\ cm^{-1}$, ν_{max} (CCl_4 , at high dilution) 3630 cm^{-1} , τ 5.97 (1H, w_t 8 Hz), 7.70–8.80 (13H, m, two disappear on D_2O exchange), 8.54 (3H, s), 8.58 (3H, s), and 8.87 (3H, s) (Found: C, 72.95; H, 11.65; N, 6.95. $C_{12}H_{23}NO$ requires C, 73.05; H, 11.75; N, 7.1%).

(±)-*cis,cis*-4-Hydroxy-2,2,8a-trimethyldecahydroquinoline (16), (17).—Hydrogenation of (±)-*cis,cis*-4-hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (28) (105 mg) over Raney nickel (W-2) as described above, gave pure *amino-alcohol* (90 mg), m.p. 81–83 °C (after sublimation), ν_{max} (Nujol) 3430, 3320, and 3260 cm^{-1} , ν_{max} (CCl_4 , at high dilution) 3625 cm^{-1} , τ 5.67 (1H, septet, J 11, 6, and 4 Hz), 8.0–9.0 (13H, m, two disappear on D_2O exchange), 8.77 (6H, s), and 8.83 (3H, s) (Found: C, 73.1; H, 11.95; N, 6.95%).

(\pm)-*cis,trans*-4-Hydroxy-2,2,8a-trimethyldecahydroquinoline (18), (19).—Hydrogenation of (\pm)-*cis,trans*-4-hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (25a), (26) (90 mg) over Raney nickel (W-2) as described above yielded pure *amino-alcohol* as a white solid (86 mg), m.p. 89–91.5 °C (after sublimation), ν_{\max} (Nujol) 3100vbr cm^{-1} , ν_{\max} (CCl_4 , at high dilution) 3630 and 3605 cm^{-1} , unchanged on further dilution, τ 5.95 (1H, sextet, J 11, 11, and 4 Hz), 7.7–8.9 (13H, m, two disappear on D_2O exchange), 8.75 (3H, s), 8.82 (3H, s), and 8.85 (3H, s) (Found: C, 73.15; H, 11.85; N, 6.95%).

(\pm)-*trans*-2,2,8a-Trimethyloctahydro-4-oxoquinolin-1-oxyl (21), (24).—To a stirred mixture of (\pm)-*trans,trans*-4-hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (22a) (54 mg, 0.25 mmol), dicyclohexylcarbodi-imide (150 mg, 0.25 mmol), dimethyl sulphoxide (1 ml), and benzene (1 ml) was added pyridinium trifluoroacetate (24 mg, 0.125 mmol).¹³ A white precipitate formed within a few min and stirring was continued for 18 h. The mixture was filtered to remove dicyclohexylurea, diluted with ethyl acetate, and washed thoroughly with water. After drying (MgSO_4) and removal of the solvent, a red oil (92 mg) was obtained. Residual dicyclohexylurea was removed by preparative t.l.c. (50% ether–light petroleum) to yield a yellow crystalline solid which was sublimed at reduced pressure to yield the *nitroxide* as a yellow solid, m.p. 64–67 °C, ν_{\max} (CCl_4) 1722 and 1362 cm^{-1} , a_N (CHCl_3) 15.1 G, g 2.0071, λ_{\max} (MeOH) 422 (ϵ 6.8) and 234 nm (220) M^+ , 210. $\text{C}_{12}\text{H}_{20}\text{NO}_2$ requires M , 210.3 (Found: C, 68.55; H, 9.3; N, 6.4. $\text{C}_{12}\text{H}_{20}\text{NO}_2$ requires C, 68.55; H, 9.6; N, 6.65%).

(\pm)-*cis*-2,2,8a-Trimethyloctahydro-4-oxoquinolin-1-oxyl (20), (27).—(a). Oxidation of (\pm)-*cis,trans*-4-hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (25a), (26) (58 mg) by the above method yielded the *nitroxide* (51 mg) as a red oil after purification by t.l.c. and short-path distillation, b.p. 90–95 °C at 0.2 mmHg, ν_{\max} (CCl_4) 1719 and 1355 cm^{-1} , a_N (CHCl_3) 15.2 G, g 2.0064, λ_{\max} (MeOH) 430 (ϵ 6.8) and 239 nm (2050) (M^+ , 210) (Found: C, 68.5; H, 9.55; N, 6.55%).

(b). Oxidation of (\pm)-*cis,cis*-4-hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (28) (54 mg) by the usual procedure gave the *nitroxide* (20), (27) (45 mg), identical to that in (a) above by t.l.c., g.l.c. and i.r. comparison.

G.l.c. also showed that no epimerisation at C-4a had occurred during these oxidations.

Resolution of (\pm)-trans,cis-4-Hydroxy-2,2,8a-trimethyldecahydroquinoline (23a).—A solution of the *amino-alcohol* (3.19 g, 16.2 mmol) and ammonium (–)- α -bromocamphor- π -sulphonate (5.31 g, 16.2 mmol) in methanol (250 ml) was heated on a steam-bath until no more ammonia was evolved. The solvent was removed on a rotatory evaporator to yield a white crystalline solid which was systematically recrystallised from ethanol.

A portion of the fifth crop (100 mg) was decomposed on a basic ion-exchange column and sublimed to yield the *amino-alcohol* (33 mg), $[\alpha]_{589}^{18}$ –5.6, $[\alpha]_{365}^{18}$ –18.3° (c 1.4 in MeOH).

The 'tail' mother liquor fractions after five rounds of recrystallisation were also decomposed to yield the crystalline *amino-alcohol* (396 mg), $[\alpha]_{589}^{18}$ +12.8, $[\alpha]_{365}^{18}$ +38.6° (c 0.9 in MeOH). This material was used for the preparation of optically active *nitroxide* radicals of the *trans*-series.

Resolution of (\pm)-cis,trans-Nitroxide-alcohol (25a), (26).—From 3 β -acetoxy- Δ^5 -etienic acid (4.3 g) and the *cis,trans*-nitroxide-alcohol (2.1 g) was prepared the etienate which was chromatographed on neutral alumina (grade III; 200 g).

Elution with solvent systems ether–light petroleum (1 : 9)–(1 : 6) gave the etienate (4.5 g) as a red solid.

Two recrystallisations of this material from methanol gave red needles (1.1 g), m.p. 202–216 °C, $[\alpha]_{589}^{18}$ –52.1° (c 0.1 in tetrahydrofuran). The combined mother liquors were concentrated and crystallised to yield needles (1.1 g), m.p. 160–195 °C. The mother liquors from this fraction were evaporated to dryness to yield a red solid (1.9 g), m.p. 120–150 °C.

The etienate (1.9 g; m.p. 120–150 °C) was dissolved in ethanol (100 ml) and to this was added a solution of sodium hydroxide in water (3 g in 20 ml). The mixture was refluxed for 16 h, cooled, and most of the ethanol was removed on a rotatory evaporator. The resultant mixture was extracted thoroughly with ether, the ethereal layer washed with dilute sodium hydroxide solution and brine, and dried (MgSO_4). Removal of the solvent yielded a red oil (537 mg) which slowly solidified. This was chromatographed on neutral alumina (grade III; 20 g) eluting with ether–light petroleum (3 : 7) to yield (+)-*cis,trans*-4-hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (26) as a red solid, $[\alpha]_{589}^{18}$ +64.9° (c 0.98 in MeOH).

Hydrolysis of the etienate (m.p. 202–216 °C) gave the enantiomeric *nitroxide-alcohol* (25a), $[\alpha]_{589}^{18}$ –98.5° (c 0.39 in MeOH).

(–)-*cis*-2,2,8a-Trimethyloctahydro-4-oxoquinolin-1-oxyl (27).—Oxidation of the (+)-*cis,trans*-nitroxide-alcohol ($[\alpha]_{589}^{18}$ +64.9°) using dimethyl sulphoxide, dicyclohexylcarbodi-imide, and pyridinium trifluoroacetate as before gave the (–)-*nitroxide* as a red oil, $[\alpha]_{589}^{18}$ –50.4° (c 0.27 in MeOH).

(+)-*cis,cis*-4-Hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (28).—To a stirred mixture of tetrahydrofuran (2 ml) and lithium aluminium hydride (45 mg) was added *t*-butanol (236 mg) in tetrahydrofuran (2 ml) followed by the (–)-*cis*-ketone (27) (80 mg) in tetrahydrofuran (0.6 ml). The mixture was stirred at room temperature for 16 h and decomposed by the sodium sulphate technique. The red oil thus obtained (78 mg) was dissolved in acetone (0.5 ml) and diethyltrimethylsilylamine (0.3 ml) was added. The mixture was allowed to stand at room temperature for 5 h, the solvent removed, and the red oil obtained was separated by preparative t.l.c. into components. The material from the top band (38 mg) was hydrolysed by refluxing with sodium hydroxide solution (0.5 ml; 4%) in a mixture of methanol (5 ml) and benzene (0.5 ml) for 12 h. The usual work-up followed by preparative t.l.c. yielded the (–)-*nitroxide* (28) as a red oil, $[\alpha]_{589}^{18}$ +11.8° (c 0.48 in MeOH).

(–)-*trans,cis*-4-Hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (22a).—A mixture of (+)-*trans,cis*-4-hydroxy-2,2,8a-trimethyldecahydroquinoline (23a) (298 mg), sodium tungstate (19 mg), the disodium salt of ethylenediamine-tetra-acetic acid (29 mg), hydrogen peroxide solution (1.5 ml; 30%), water (7.5 ml), and methanol (7.5 ml) was stirred at room temperature for 6 days. The mixture was then extracted with ether, washed with sodium bicarbonate solution and brine, dried (MgSO_4), and the solvent was removed to yield a red solid (243 mg) which was purified by preparative t.l.c. Sublimation yielded the (–)-*trans,cis*-nitroxide-alcohol (22a) as a red solid (204 mg), $[\alpha]_{589}^{18}$ –39.6° (c 0.73 in MeOH).

(–)-*Trans*-2,2,8a-Trimethyloctahydro-4-oxoquinolin-1-oxyl (24).—Oxidation of the (–)-*trans,cis*-nitroxide-alcohol (27 mg) by the usual method gave (–)-*nitroxide* (24) as a yellow solid (21 mg), $[\alpha]_{589}^{18}$ –105° (c 0.72 in MeOH).

*Determination of the Absolute Configuration of (–)-trans, cis-4-Hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (22a) by Horeau's Method.*¹⁸— α -Phenylbutyric anhydride was prepared by refluxing α -phenylbutyric acid (1.2 g) in acetic anhydride (12 ml) for 16 h. Removal of the solvent, azeotroping several times with toluene, yielded a clear, slightly yellow oil, ν_{\max} (film) 1810 and 1740 cm^{-1} , which was used without further purification.

A solution of the above anhydride (121 mg, 0.27 mmol), (–)-*trans, cis*-nitroxide-alcohol (25 mg, 0.12 mmol), and dry pyridine (2.5 ml) was allowed to stand at room temperature overnight. Water (1 ml) was added, the mixture allowed to stand for 5 h and then diluted with ether. The organic layer was extracted three times with saturated sodium bicarbonate solution. This bicarbonate extract was acidified with sulphuric acid and thoroughly extracted with chloroform. The chloroform extracts were washed with water, dried (MgSO_4), and the solvent removed to yield α -phenylbutyric acid as a slightly yellow oil which slowly solidified. This was shown to be pure by n.m.r. analysis.

The neutral ethereal extracts were washed thoroughly with 1*N*-hydrochloric acid, water, and dried (MgSO_4). Removal of the solvent yielded a red oil (36 mg) which was separated by preparative t.l.c. into two components. The more polar component was the starting alcohol (8 mg) and the less polar was the α -phenylbutyrate (18 mg), ν_{\max} (CCl_4) 1740 cm^{-1} . α -Phenylbutyric acid had $[\alpha]_{589}^{18} -1.46^\circ$ (*c* 3.5 in C_6H_6).

Based on the amount of ester isolated (18 mg, 0.051 mmol) and an optical purity of 43% for the nitroxide-alcohol, we can calculate that for 100% induction of asymmetry the rotation of the α -phenylbutyric acid would have been -9.96° . Hence optical yield = 35. Based on the maximum amount of alcohol that might have reacted (17 mg), the optical yield is calculated to be 20%.

Determination of Absolute Configuration of (+)-cis, trans-4-Hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (26).— α -Phenylbutyric anhydride (113 mg, 0.25 mmol), (+)-*cis, trans*-nitroxide-alcohol (21 mg, 0.098 mmol), and dry pyridine (2.5 ml) was allowed to stand at room temperature for 18 h. Water (1 ml) was added and the mixture was allowed to stand for 3 h. Work-up as above gave α -phenylbutyric acid (90 mg) and a red oily ester (30 mg) which showed no trace of unchanged alcohol by t.l.c. and i.r. analysis, ν_{\max} (film) 1740 cm^{-1} . α -Phenylbutyric acid had $[\alpha]_{589}^{18} +1.2^\circ$ (*c* 4.5 in C_6H_6). Therefore, optical yield = 11%.

Determination of Optical Purity of (–)-trans, cis-4-Hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (22a).—A solution of (+)-methoxytrifluoromethylphenylacetic acid (100 mg) in thionyl chloride (4 ml) was refluxed for $4\frac{1}{2}$ h. Excess of thionyl chloride was removed under vacuum, the last traces being removed by azeotroping with benzene. The resultant acid chloride was dissolved in dry pyridine (1.5 ml) and to this was added a solution of (\pm)-*trans, cis*-nitroxide-alcohol (22a) (49 mg) in dry pyridine (1.5 ml) with stirring at 0 $^\circ\text{C}$. The mixture was stirred at ambient temperature for 22 h, then diluted with ether, washed thoroughly with 1*N*-hydrochloric acid, saturated sodium bicarbonate solution, and brine, and dried (MgSO_4). Removal of the solvent yielded a red oil which was purified by preparative t.l.c.,

using ether–light petroleum (1 : 1) as solvent, to yield a red oil (73 mg), ν_{\max} (CCl_4) 1750 cm^{-1} . A sample of this ester (65 mg) was dissolved in methanol (10 ml) and Raney nickel was added. Hydrogenation in the usual manner, filtration and removal of the solvent yielded a clear oil (64 mg), ν_{\max} (film) 1740 cm^{-1} , τ 2.4–2.6 (5H, m), 4.70 (1H, m), 5.40br (1H, disappears on D_2O exchange), 6.45 (3H, m), 8.0–9.2 (20H, complex multiplet).

The spectrum was run at 100 MHz with scale expansions in the τ 6.4–6.5 and 8.9–9.2 regions. The methoxy-region showed two quartets centred at τ 6.42 and 6.48 (*J* 1.2 Hz) which were almost completely separated and in a 1 : 1 ratio. In the methyl region two singlets were observed at τ 8.90 and 9.08 sufficiently separated to permit integration. These were also in 1 : 1 ratio.

The same procedure was repeated on a sample of (–)-*trans, cis*-nitroxide-alcohol (22a). The amino-ester thus obtained had in general terms a very similar n.m.r. spectrum to that above but there were significant differences in the chemical shifts of individual peaks. The methoxy-region showed two quartets at τ 6.41 and 6.47 in a ratio of 1 : 2.4. The methyl region showed four peaks far enough upfield from the rest of the spectrum to allow the areas under them to be measured at τ 8.93, 8.99, 9.05, and 9.17 in ratios of 2.4 : 1 and 2.3 : 1. The average of these gives an optical purity of 43% for this compound.

The ^{19}F n.m.r. spectrum of the diastereoisomeric mixture showed two peaks in a 1 : 1 ratio (separation 12 Hz) at 70.6 p.p.m. upfield from CFCl_3 . The partially resolved material only showed one peak in this region.

Determination of Optical Purity of (–)-cis, trans-4-Hydroxy-2,2,8a-trimethyldecahydroquinolin-1-oxyl (25a).—The above procedure was carried out with samples of racemic and optically active *cis, trans*-nitroxide-alcohols (25a). The n.m.r. spectra of the (+)methoxytrifluoromethylphenylacetates obtained after reduction of the nitroxide group were recorded. Racemic amino-esters: τ 2.4–2.7 (5H, m), 4.48 (1H, m), 6.43 (3H, m), and 7.8–8.9 (21H, complex multiplet). Expansion of the methoxy-region showed two quartets at τ 6.41 and 6.45 (*J* 1.1 Hz) in a ratio of 1 : 1. Optically active amino-ester: τ 2.4–2.7 (5H, m), 4.51 (1H, m), 6.45 (3H, m), and 7.8–8.8 (21H, complex multiplet). Expansion of the methoxy-region showed only one quartet at τ 6.45 and hence we may conclude that this compound is at least 95% optically pure.

The ^{19}F n.m.r. spectrum of the diastereoisomeric mixture showed two peaks in a 1 : 1 ratio (separation 8 Hz) at 71.8 p.p.m. upfield from CFCl_3 . The resolved compound only showed one peak in this region.

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