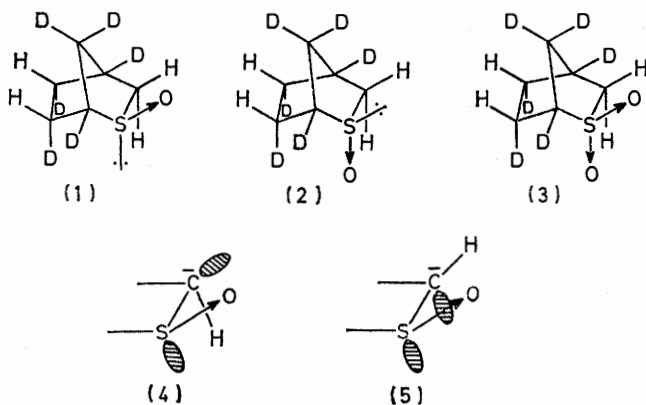


Stereochemistry of Hydrogen–Deuterium Exchange α to the Sulphinyl Group in 2*H*-Naphtho[1,8-*bc*]thiophen Derivatives

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The rate of deuterium exchange in MeONa–MeOD of α -protons having an equal stereochemical relation to a sulphinyl group was found to follow an opposite trend in 2*H*-naphtho[1,8-*bc*]thiophen derivatives (6)–(8) to that previously observed in 2-thiabicyclo[2.2.1]heptane derivatives (1) and (2), for which tetrahedral α -sulphinyl carbanions of different stability had been proposed as intermediates in the exchange process. The experimental results were rationalized by assigning to tetrahedral and planar α -sulphinyl carbanions a separate role in determining, according to their relative stability, the rate of proton abstraction or the stereochemistry of the exchange, or both.

In previous studies^{1,2} on base-catalysed hydrogen–deuterium exchange in MeOD of methylene protons of hexadeuteriated *endo*- and *exo*-2-thiabicyclo[2.2.1]heptane 2-oxide (1) and (2), deuterium consistently



replaced the proton eclipsed by the sulphinyl oxygen faster than the diastereotopic proton eclipsed by the sulphur lone-pair, although base attack at the *exo*-face

¹ R. R. Fraser, F. J. Schuber, and Y. Y. Wigfield, *J. Amer. Chem. Soc.*, 1972, **94**, 8795.

of these bicyclic systems is sterically preferred, as found² for the corresponding sulfone (3). This was considered a clear indication that isotopic exchange in these sulfoxides occurred through the diastereomeric tetrahedral carbanions (4) and (5), that with two eclipsed electron pairs having the lower stability.

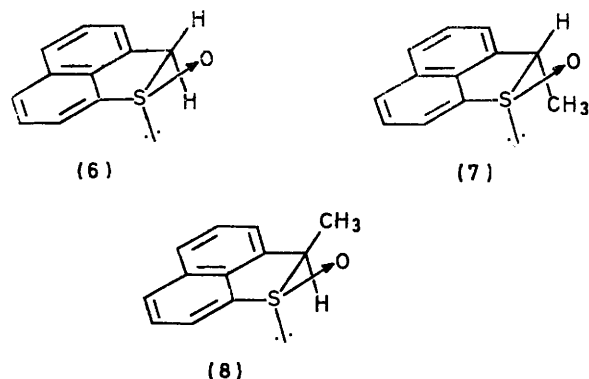
Our study² has now been extended to 2*H*-naphtho[1,8-*bc*]thiophen 1-oxide (6) which, in common with substrates (1) and (2), has approximately the same orientation for the methylene protons as for the sulphinyl group, but steric preferences due to the molecular skeleton are no longer present.

Diastereomeric *trans*- and *cis*-2-methyl-2*H*-naphtho[1,8-*bc*]thiophen 1-oxide (7) and (8) were also included in order to establish to what extent deuterium exchange of a single α -proton, eclipsed by a sulphinyl oxygen or sulphur lone-pair, respectively, occurs with inversion or retention of configuration at the α -carbon atom.

While tetrahedral α -sulphinyl carbanions could be safely considered^{1,2} to be the intermediates of the isotopic exchange in sulfoxides (1) and (2), in the case of compounds (6)–(8) proper consideration must be

² U. Folli, D. Iarossi, I. Moretti, F. Taddei, and G. Torre, preceding paper.

given to the possibility of planar carbanions (electron pair in a $2p$ orbital) playing a role as intermediates, since the carbanion is now generated α to an extensive



aromatic π -system and the right orientation and geometry for a p - π conjugative stabilization can be achieved without torsion of bonds being implicated.

If sulfoxide (6) is regarded as benzyl phenyl sulfoxide frozen in a fixed conformation through benzocyclization, an interesting structural relation can be recognized between the present substrates and benzyl sulfoxides, which have been extensively used³ to study the stability and stereochemical behaviour of open chain α -sulphinyl carbanions.

RESULTS AND DISCUSSION

The synthesis, ¹H n.m.r. spectra, and configurational assignments of sulfoxides (6)–(8) are reported separately.⁴

The kinetic measurements of hydrogen–deuterium exchange and concurrent isomer interconversion were taken for 0.0035M-MeONa and 0.05M-substrate in MeOD at 25°. Good first-order plots were obtained from at least five experimental measurements below 50% reaction, from which the pseudo-first-order rate constants of the Table were derived. In the case of the diastereomeric sulfoxides (7) and (8), changes in the *cis*–*trans*-mixture were followed even after complete exchange at the methine proton had occurred in order to

* Concurrently, however, solvent reorganization may lead to a symmetrically solvated carbanion, from which both inverted and retained exchange products are generated (for the sake of simplicity, this step has not been included in Scheme 1).

³ (a) A. Rauk, E. Buncel, R. Y. Moir, and S. Wolfe, *J. Amer. Chem. Soc.*, 1965, **87**, 5498; (b) S. Wolfe and A. Rauk, *Chem. Comm.*, 1966, 778; (c) M. Nishio, *ibid.*, 1968, 562; (d) A. Rauk, S. Wolfe, and I. C. Csizmadia, *Canad. J. Chem.*, 1969, **47**, 113; (e) J. E. Baldwin, R. E. Hackler, and R. M. Scott, *Chem. Comm.*, 1969, 1415; (f) M. Cinquini, S. Colonna, U. Folli, and F. Montanari, *Boll. sci. Fac. Chim. ind. Bologna*, 1969, **27**, 203; (g) T. Durst, R. R. Fraser, M. R. McClory, R. B. Swingle, and Y. Y. Wigfield, *Canad. J. Chem.*, 1970, **48**, 2148; (h) T. Durst, R. Viau, and M. R. McClory, *J. Amer. Chem. Soc.*, 1971, **93**, 3077; (i) K. Nishiata and M. Nishio, *Chem. Comm.*, 1971, 958; (j) T. Durst, R. Viau, R. VanDenElzen, and C. H. Nguyen, *ibid.*, p. 1334; (m) K. Nishiata and M. Nishio, *Tetrahedron Letters*, 1972, 4839; (n) K. Nishiata and M. Nishio, *J.C.S. Perkin II*, 1972, 1370; (o) R. Viau, T. Durst, *J. Amer. Chem. Soc.*, 1973, **95**, 1346; (p) M. B. D'Amore and J. I. Brauman, *J.C.S. Chem. Comm.*, 1973, 398.

establish the equilibrium composition in the reaction medium.

Rates of deuterium exchange^a of α -protons^b in sulfoxide (6) and diastereomeric sulfoxides *trans*-(7) and *cis*-(8)

	(6)	<i>trans</i> -(7)	<i>cis</i> -(8)
H _c	280	9.3	
H _t	640		32
k _c /k _t	1 : 2.3		1 : 3.4

Rates of formation^a of α -deuteriated *cis*- and *trans*-isomers (k_{cis} and k_{trans} respectively) from diastereomeric sulfoxides *trans*-(7) and *cis*-(8)

	<i>trans</i> -(7)	<i>cis</i> -(8)
k _{cis}	8.1	30
	(Inversion)	(Retention)
k _{trans}	1.2	1.9
	(Retention)	(Inversion)
k _{cis} /k _{trans}	6.7 : 1	16 : 1
(k _{cis} /k _{trans}) _{eq.} ^c	(Inversion/retention) 2.3 : 1	(Retention/inversion) 2.3 : 1

^a Pseudo-first-order rate constants ($\times 10^5$ s⁻¹) for 0.0035M-MeONa and 0.05M-substrate in MeOD at 25°. ^b Protons are characterized by subscripts *c* and *t*, for *cis* and *trans* (relative to the sulphinyl oxygen). ^c Ratio at equilibrium of α -deuteriated *cis*–*trans*-isomers.

It can be seen from the Table that an α -proton eclipsed by the sulphur lone-pair has greater kinetic acidity than that of a diastereotopic proton eclipsed by the sulphinyl oxygen. The trend is common to all substrates (6)–(8) and is opposite to that found^{1,2} in the bicyclic sulfoxides (1) and (2).

Confining the discussion to the methylenic sulfoxide (6), which, structurally, is more directly comparable with (1) and (2), the hypothesis of a planar carbanion occurring as the intermediate in exchange should rightly be taken into consideration. The planar intermediate, however, must derive from rehybridization of diastereomeric sp^3 -carbanions [type (4) or (5)] initially developed along with α -proton abstraction so that abstraction of H_c must be associated with a lower activation energy,⁵ rehybridization taking place as soon as the transition state for proton abstraction has been overcome.

According to earlier observations⁶ concerning the stereochemistry of isotopic exchange through planar carbanions as intermediates, exchange with inversion of configuration is favoured in protic solvents of high dielectric constant like methanol, since an asymmetrically solvated planar carbanion is formed by α -proton abstraction (Scheme 1) and deuterium capture at the rear side of the departing proton can directly occur with formation of inverted exchange product.*

The experimental results for sulfoxide (6) can then be rationalized as follows: deuterium is found to appear faster at the *trans*-position because H_c is abstracted faster, and the stereochemistry of deuteration is mainly inversion for both α -protons (Scheme 1).

Deuterium exchange at the methine proton of diastereomeric α -methyl derivatives (7) and (8) produced in both cases an equilibrated mixture in which

⁴ U. Folli, D. Iarossi, and F. Taddei, *J.C.S. Perkin II*, 1974, 933.

⁵ Ref. 1, Appendix.

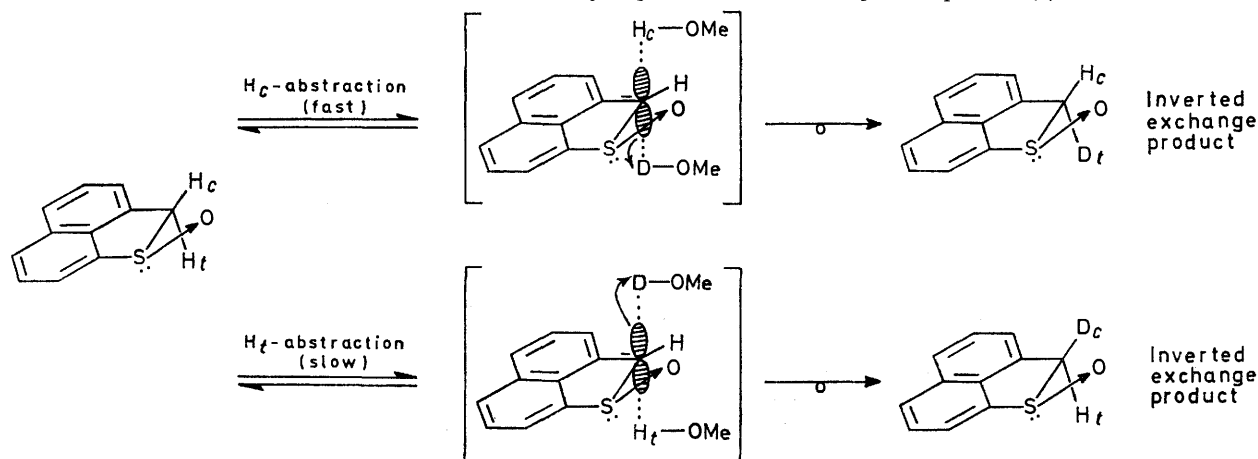
⁶ D. J. Cram, 'Fundamentals of Carbanion Chemistry,' Academic Press, New York, 1965, p. 95.

the *cis-trans* ratio of α -deuteriated isomers was 2:3:1, the *cis*-isomer being thermodynamically more stable (free energy difference 0.5 kcal mol⁻¹).^{*} Under kinetic control, however, the more stable *cis*-isomer (8) was found to exchange faster than (7) (3.4:1), and to produce the α -deuteriated *cis*-isomer (retained product)

slowly equilibrates with (10). This is shown by means of Scheme 2, where, for the sake of simplicity, not all the possible steps have been included.

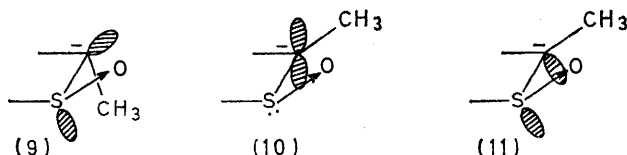
A rather unexpected conclusion which emerges in any attempt to rationalize the present experimental results based on the hypothesis⁵ that the transition state free

SCHEME 1 Predominant stereochemical course of the hydrogen-deuterium exchange in sulphoxide (6) in MeO⁻-MeOD.



in a ratio (16:1) far exceeding that measured at equilibrium; conversely, the *trans*-isomer (7) produced the α -deuteriated *cis*-isomer (inverted product) in a ratio substantially exceeding (6.7:1) that measured at equilibrium.

The stereochemistry of deuterium exchange at the methine proton of *trans*-isomer (7) (inverted product formation exceeding the epimeric composition at the equilibrium) is identical with that expected for deuteriation in MeOD of a planar carbanionic intermediate (10), as already discussed. Here again, the rate of proton abstraction will be governed by the relative stability of the tetrahedral carbanion (9) developing along with proton abstraction. The exchange with a high degree of retention of configuration observed for *cis*-isomer (8) in MeOD medium is, on the other hand, compatible only with a tetrahedral carbanion (11) governing not only the rate of proton abstraction but also the stereochemistry of the deuteriation step (retention). The reason for this different behaviour may be easily deduced:



while carbanion (9) must be less stable than the planar species (10), carbanion (11) must be more stable and an energy barrier is associated with its interconversion to the planar species (10). In these conditions carbanion (11), unlike (9), can act as a true intermediate and only

^{*} The same ratio was obtained⁴ by epimerization of (7) and (8) in MeONa-MeOH. The estimated stability difference thus applies to isomeric *trans*-(7) and *cis*-(8), as well as to the corresponding α -deuterio-derivatives.

energy for proton abstraction resembles that of the carbanion being initially formed, is that a tetrahedral carbanion (11), which has an α -methyl substituent *cis* to the sulphinyl oxygen and two eclipsed electron pairs, is more stable than a diastereomeric carbanion (9). A *cis*- α -methyl substituent in the five-membered ring is then able to reverse the carbanion stability order previously established;^{1,2} it must be also responsible for the greater thermodynamic stability of *cis*-isomer (8) over *trans*-isomer (7) (0.5 kcal mol⁻¹) while an opposite stability order would be expected on the grounds of steric repulsions. However, in order to account for the faster exchange of the more stable isomer (3.4:1), the difference in stability between the initial states should be transferred, substantially enhanced, to the corresponding carbanions (11) and (9). Exchange in these α -methyl derivatives seems therefore to be dominated by an apparently minor structural detail, which predominates over the electronic effects exerted by the sulphinyl group on an adjacent carbanion electron pair as a function of their mutual orientation, which, in turn, cannot be very relevant.²

It is noteworthy that a common driving force can be recognized for the stereochemistry of base-catalysed deuterium exchange or exchange-elimination which has been reported⁷ for several thiolan S-oxide derivatives, since the observed trend is to establish (inversion) or preserve (retention) a *cis*-relationship between an α -methyl substituent and the sulphinyl oxygen. Also pertinent to the present results is the greater thermodynamic stability observed⁸ for the *cis*-2-methyl-

⁷ R. Lett, S. Bory, B. Moreau, and A. Marquet, *Tetrahedron Letters*, 1971, 3255.

⁸ J. J. Rigau, C. C. Bacon, and C. R. Johnson, *J. Org. Chem.*, 1970, **35**, 3655.

thiolan 1-oxide (12) over the *trans*-isomer (13). This has been correlated⁸ with the axial over equatorial preference at equilibrium shown by the sulphanyl oxygen in sulphoxides of the thian series,⁹ which has been theoretically justified.¹⁰

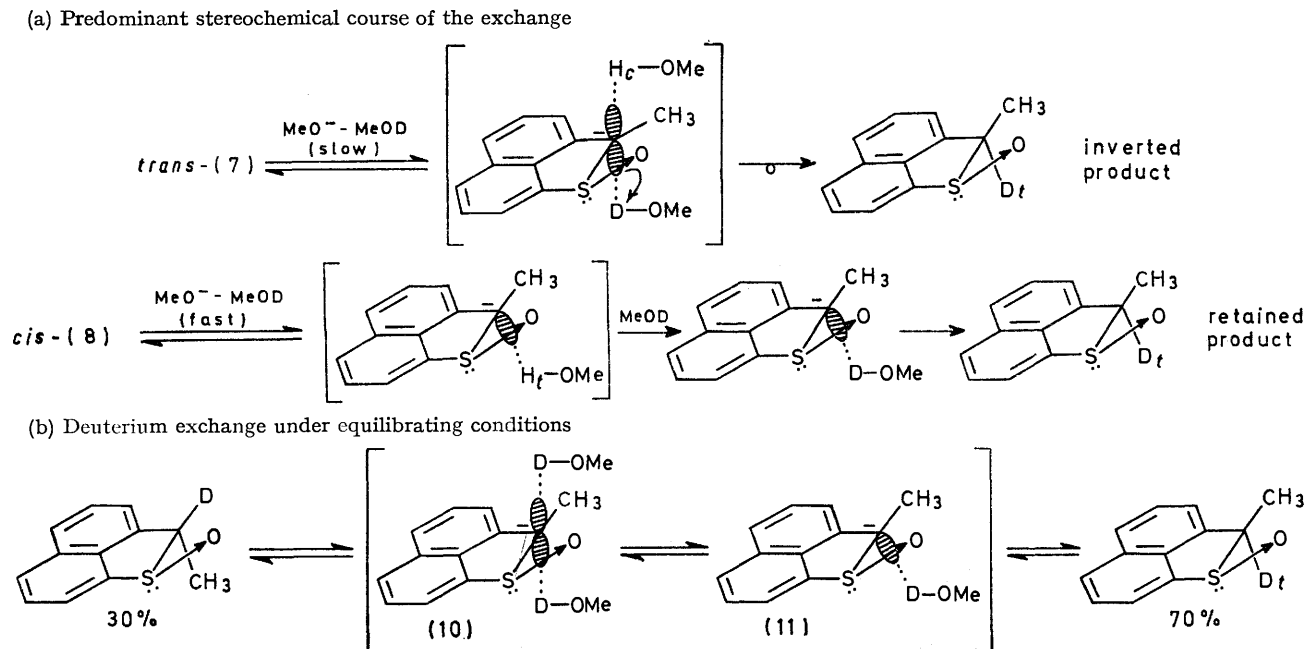
Although in other instances^{3b,11} it has been ascertained

of solvent influences on the stereochemistry of the isotopic exchange in cyclic sulphoxides.

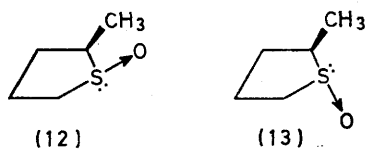
EXPERIMENTAL

¹H N.m.r. spectra were recorded on a JEOL JNM-C-60HL spectrometer. Optical rotations were measured on a

SCHEME 2 Deuterium exchange in isomeric sulphoxides *trans*-(7) and *cis*-(8) in MeOD.



that α -carbanion formation does not affect the sulphur configuration, in the case of planar α -sulphanyl carbanions of the 2*H*-naphtho[1,8-*bc*]thiophen series the



inversion barrier at sulphur, as found for thiophen sulphoxides,¹² might be expected to be lower than usual, since in the transition state for the inversion a system of 14 π -electrons (including sulphur lone-pair and carbanion electron pair) would be present. In such an event stereomutation at sulphur could interfere with the stereochemistry of isotopic exchange at the α -carbon. To exclude the latter possibility, compound (6) was obtained in a partially active form through asymmetric oxidation¹³ of 2*H*-naphtho[1,8-*bc*]thiophen with (1*S*)-(+)-percamphoric acid and found to be perfectly optically stable in conditions in which α -protons exchange rapidly.

Work is in progress to include a more detailed study

⁹ (a) J. C. Martin and J. J. Uebel, *J. Amer. Chem. Soc.*, 1964, **86**, 2936; (b) C. R. Johnson and D. McCants, *ibid.*, 1965, **87**, 1109, (c) J. B. Lambert, R. C. Keske, and D. K. Weary, *ibid.*, 1967, **89**, 5921; (d) J. B. Lambert, and R. C. Keske, *J. Org. Chem.*, 1966, **31**, 3429; (e) J. B. Lambert, D. S. Bailey, and C. E. Mixan, *ibid.*, 1972, **37**, 377; (f) J. B. Lambert, C. E. Mixan, and D. H. Johnson, *Tetrahedron Letters*, 1972, 4335.

Perkin-Elmer model 141 polarimeter. The synthesis, ¹H n.m.r. spectra, and configurational assignments for sulphoxides (6)–(8) are reported separately.⁴

Kinetics.—For compounds (6)–(8) two separate kinetic runs were carried out as follows: 0.014*M*-MeONa in MeOD (10 ml) was placed in a long-necked reaction flask (50 ml), MeOD (20 ml) was added, and the solution was stored in a thermostat at $25 \pm 0.1^\circ$. At zero time, 0.2*M*-substrate in MeOD (10 ml) was added, and the flask was sealed with a silicon rubber cap. Five samples were withdrawn with a syringe and injected into a mixture of 0.03*M*-HCl (5 ml) and CH_2Cl_2 (5 ml), the aqueous phase was extracted with CH_2Cl_2 ($\times 3$), the CH_2Cl_2 solution was washed with water, dried (MgSO_4), and evaporated *in vacuo*. The residue was submitted to ¹H n.m.r. analysis as described below. In the graphical derivation of exchange rate constants, an integrated pseudo-first-order rate equation was applied as described in ref. 2. The intensities of the signals were obtained as a mean value of at least four integrations of the signal areas.

(a) Samples from (6) were dissolved in MeCN (0.5 ml) and submitted to ¹H n.m.r. analysis, using the multiplet at δ 7.30–8.20 (6H, ArH) as reference area. Rate constants of exchange at the *cis* to SO and *trans* to SO protons were derived from the intensities of the corresponding signals.

¹⁰ M. L. Allinger, J. A. Hirsh, M. A. Miller, and I. J. Tyminsky, *J. Amer. Chem. Soc.*, 1969, **91**, 337.

¹¹ D. J. Cram and S. H. Pine, *J. Amer. Chem. Soc.*, 1963, **85**, 1086.

¹² W. L. Mock, *J. Amer. Chem. Soc.*, 1970, **92**, 7610.

¹³ U. Folli, D. Iarossi, and F. Montanari, *J. Chem. Soc. (C)*, 1968, 1317.

This proton assignment in MeCN solution was derived from that previously established⁴ in CDCl₃ solution. MeCN was preferred to CDCl₃ in these measurements to obtain a more accurate evaluation of reference proton areas.

(b) Samples from (7) and (8) were dissolved in CDCl₃ (0.4 ml) and submitted to ¹H n.m.r. analysis, using the intensity of methyl resonances⁵ (which practically overlap) as the reference area. Rate constants of exchange were derived from the intensities of the corresponding methine signals.⁴ Inversion without exchange would have been detected, if it had occurred, since the methine protons have different chemical shift in CDCl₃ solution.⁴

(c) Samples from (7) and (8) after analysis in CDCl₃ solution [see (b)], were recovered, and a portion (0.05 g) was dissolved in a 0.047M-Eu(dpm)₃ solution in CDCl₃ (0.4 ml; molar ratio Eu/SO 0.077) and submitted again to n.m.r. analysis. Under these conditions *cis*- and *trans*-isomers can be quantitatively determined from the intensity of methyl resonances,⁴ so that pseudo-first-order rates of formation of inverted and retained α -deuteriated product could be derived for either isomer. The results are reported in the Table (see Discussion).

Asymmetric Synthesis of Compound (6).—A cold CHCl₃ solution of (1S)-(+)-percamphoric acid¹⁴ (1 mol. equiv.) was slowly added with stirring to 2*H*-naphtho[1,8-*bc*]-thiophen⁴ (3.03 g) in CHCl₃ (150 ml) cooled at *ca.* -5°. When oxidation was complete (negative iodometric test), the precipitated camphoric acid was filtered off and the CHCl₃ solution washed with aqueous NaHCO₃ ($\times 5$) and with water. After drying (MgSO₄) and evaporation of the solvent a solid residue remained (3.1 g), m.p. 110–115°, which, after treatment in hot CH₃CN with decolourizing carbon, had $[\alpha]_D -8.23^\circ$ (*c* 3.76, MeOH) and the same spectroscopic properties as racemic (6).⁴

Optical Stability of (6) in MeOH–MeONa.—A solution of partially optically active (6) (0.1027 g) was dissolved in a 0.14M-MeONa (1.5 mol. equiv.) in MeOH (5.85 ml). The optical rotation was measured and after 20 h found to be unchanged.

We thank the Italian CNR for financial support.

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¹⁴ N. A. Miles and A. McAlevy, *J. Amer. Chem. Soc.*, 1933, **55**, 349.