Tetrahedron. Vol. 32, pp. 1873 to 1879. Pergamon Press 1976. Printed in Great Britain

CONFORMATIONAL EFFECTS IN COMPOUNDS WITH 6-MEMBERED RINGS–X

SYNTHESIS OF *CIS*- AND *TRANS*-3,5-DI-t-BUTYLTHIAN AND SULPHONIUM SALT FORMATION FROM THIANS

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(*Received in UK* 31 *December* 1975; *Accepted for publication* 24 *February* 1976)

Abstract—Convenient stereospecific syntheses of *cis*- and *trans*-3,5-di-t-butylthian (**1** and **2**) have been developed. The reaction between anancomeric thians with unhindered S atoms and methyl iodide has been investigated and a range of kinetic (from 6.5 up to 11:1) and thermodynamic (from 1.25 up to 2.8:1) stereoselectivities, with equatorial S-Me always favoured, have been observed. It is concluded that the observed stereoselectivities are best explained by steric hindrance at the axial site on sulphur and that twist conformers do not contribute significantly to the reactivity of most thians in such reactions. The contrast between relative kinetic and thermodynamic stereoselectivities shown in the reactions between methyl iodide and either N-methylpiperidines *or* thians is explained by different directions of approach to these 6-membered rings during axial attack.

Acid anhydrides have been isolated from the oxidation of β-diketones by ozone and by chromic acid.

It is necessary to determine the reactivity of twist[1] conformers (T) of 6-membered ring compounds before one can validly interpret the reactivity of a compound existing predominantly in chair conformers E and A by means of approximate relationships[2] such as

$$k_{obs} \simeq n_E k_E + n_A k_A \qquad (1)$$

because these assume that $n_T k_T$ can be neglected because n_T is small, i.e. the low concentration of twist conformers is not offset by high reactivity relative to chair conformers. It is already known that twist and chair conformers may differ substantially in reactivity ($k_T > k_A$ or k_E potentially leading to large errors), e.g. in reactions involving change in hybridisation of a ring atom, as in the solvolysis of tosylates[3] (twist *more* reactive than chair) or nucleophilic addition to a carbonyl group[4] (twist *less* reactive than chair) and there is no reason for supposing that twist conformers can always be neglected safely. A reasonable check on the validity of equations such as (1) for a given reaction is to have a pair (or larger set) of compounds in which steric effects of alkyl substituents substantially alter the relative concentrations of chair and twist conformers, as in the thians **1** and **2** (Fig. 1).

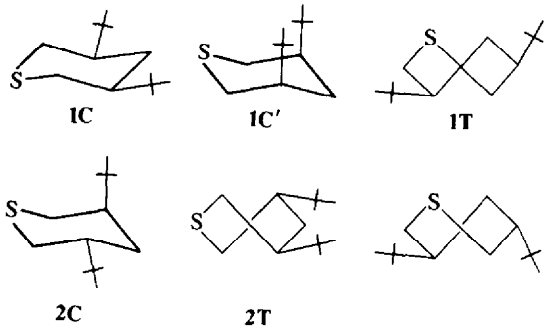


Fig. 1. Conformational equilibria in *cis*- and *trans*-3,5-di-t-butylthian. The twist conformers are drawn with the t-butyl groups in relatively unhindered positions but as yet there is no evidence for the preferred conformation of the ring in the twist conformers of thians. It is assumed that the chair conformer 1C is much more stable than the other conformers 1C' and 1T (one only of a pair of enantiomeric twist conformers is shown). In the *trans*-isomer **2** (only one entantiomeric form is shown) it appears (see text) that the twist conformer 2T is significantly more stable than the chair 2C, in which ring inversion produces no change.

The very large substituents required to substantially destabilise chair relative to twist conformers[5] strongly modify the properties of adjacent functional groups[6] so that such t-butyl groups should be at positions 3 and 5 in a monofunctional derivative of cyclohexane or in a heterocyclic compound with one heteroatom, if the latter is the reactive centre. Our first objective has been the preparation of the anancomeric thians **1** and **2**. Meso (**6**) and racemic (**7**) 2,4-di-t-butyl-glutaric acid are attractive intermediates for the synthesis of **1** and **2** and analogous heterocyclic compounds. Eberson's synthesis of **6** and **7**,[7] however, was neither stereospecific nor readily adapted to large scale working. We accordingly sought a more general route using the readily available 4,6-di-t-butylresorcinol (**3**) as the starting material.[8,9] This paper describes (a) the preparation and hydrolytic cleavage of *cis*- (**4**) and *trans*- (**5**) di-t-butyl-cyclohexane-1,3-dione, (b) the conversion of **4** and **5**, via **6** and **7**, into the thians **1** and **2**, and (c) a study of factors influencing sulphonium salt formation from thians.

Routes for the rational stereoselective syntheses of the thians **1** and **2** were based originally on the predicted relative stabilities of pairs of cyclic and of acyclic diastereomers with two t-butyl groups in a 1,3-relationship. In the cyclic compounds it was expected that, e.g. **4** would be more stable than **5**, as well as being formed selectively by catalytic hydrogenation of **3**. In contrast simple conformational arguments lead to the expectation that racemic or threo diastereomers of acyclic compounds such as **7** or **9**, from which *trans* cyclic compounds may be formed, would be more stable than meso or erythro forms such as **6** or **8** (Fig. 2). If the latter were prepared by ring opening reactions from **4** acid or

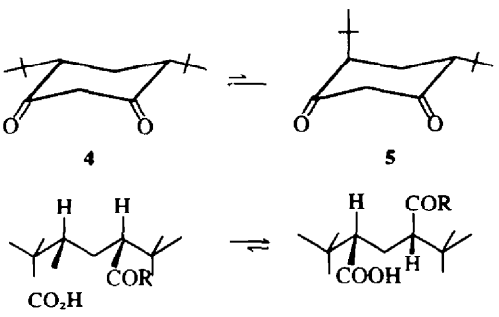


Fig. 2. *Expected* relative stabilities of derivatives of *cis*- and *trans*-1,3-di-t-butylcyclohexane, e.g. **4** and **5**, and of *erythro* (or *meso*) and *threo* (or (±)) 3,5-disubstituted derivatives of 2,2,6,6-tetramethylhexane, e.g. **8** and **9** (or **6** and **7**). The expectations are generally borne out in practice except for the anions of the diones **4** and **5**.

base catalysed epimerisation should lead to **7** and **9** (via **10**).

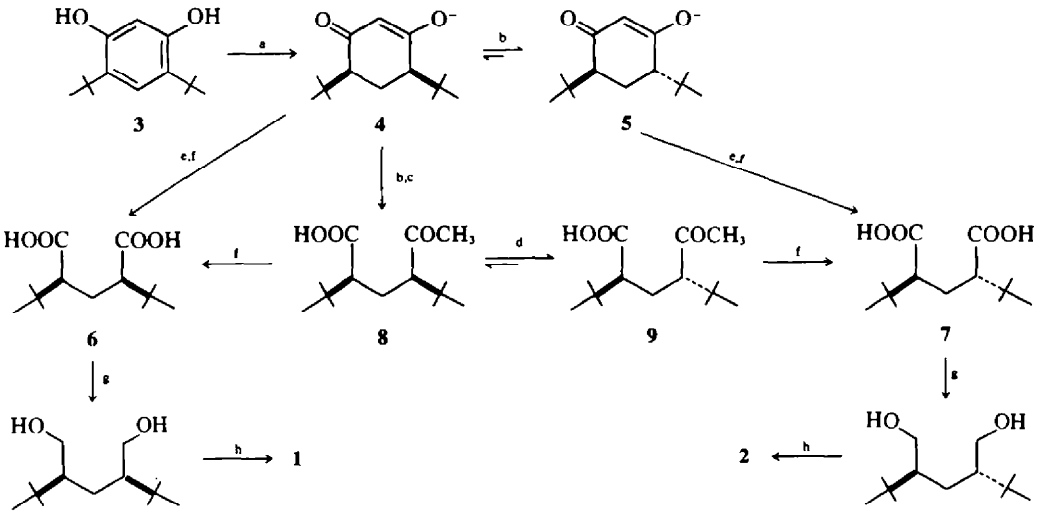
The surprising observation[8] that **4** can be converted into **5**, contrary to expectations based on simple conformational arguments, opened up new routes to *trans*-1,3-di-t-butyl derivatives of 6-membered ring compounds. This was very fortunate because the predicted isomerisation of, e.g. **8–9** is very inconvenient in practice (see below).

The synthesis of **1** and **2** outlined in Scheme 1 uncovered unexpected difficulties that require comment, as well as the equally unexpected but very useful isomerisation of **4–5**.[8] The diones **4** and **5** differ strikingly in physical properties (Experimental). The *cis*-dione **4** exists in the diketo form in the solid and compared with simple cyclohexane-1,3-diones[10] has a low tendency to enolise in solution. In contrast the *trans*-dione **5** is enolic in the solid and is always more enolised than the *cis* form under the same conditions in solution.

The isolation of **5** from a high temperature hydrogenation[8] prompted an investigation of the base catalysed equilibrium between **4** and **5**. When either **4** or **5** was heated with an excess of aqueous NaOH at 100° the resulting mixture contained **4** and **5** in a ratio ~ 1:15 but with a substantial loss due to hydrolysis to the *erythro*-keto acid **8** (see below). When water was replaced by ethanol or t-butyl alcohol the ring opening reaction was suppressed but the equilibrium then favoured **4**. This unusually large solvent effect on a apparently simple equilibrium can be rationalised by supposing that in the enolate anion of **5** solvation is much less hindered at one O atom than at the other, which is as hindered as both the O atoms in the anion of **4**. As would be expected from what is known about the action of alkali on simple β-diketones[11] ring opening was minimised by using exactly equivalent amounts of **4** and sodium hydroxide (Experimental).

Before the best conditions for the isomerisation of **4–5** had been found the keto-acid formed by the hydrolysis of **4** or **5** was investigated as a possible intermediate for the preparation of the racemic acid **7**. Because the keto-acid had been formed in hot alkaline solution it was expected to be the more stable *threo* stereoisomer **9** resulting from base catalysed epimerisation at C-4 (Fig. 2). Many attempts to oxidise the supposed *threo*-acid **9** were unsuccessful (Experimental) until it was treated with hot fuming nitric acid to give a good yield of the *meso* acid **6**, thereby establishing that the keto-acid was **8**, the unexpected *erythro*-isomer. When the *erythro*-acid **8** was heated with aqueous sodium hydroxide at 120° for 3 weeks the *threo*-acid **9** was formed in about 60% yield, although the reaction had probably still not reached equilibrium. Under more vigorous conditions the keto-acids were destroyed by alkali. The *threo*-acid **9** was oxidised to the racemic acid **7** by fuming nitric acid. Although the isomerisation of **8–9** confirms the correctness of the predicted relative stabilities of these keto-acids it is not practicable for preparative work. It is noteworthy that the *threo*-acid **9** cannot be detected by TLC in the initial products formed by hydrolysis of either of the diones **4** and **5** (Experimental).

2,4-Di-t-butylglutaric acid has been prepared from ethyl cyanoacetate by Eberson,[7] who separated the two diastereoisomers by fractional crystallisation but did not establish their configuration. We anticipated that the diones **4** and **5** would be readily oxidised without

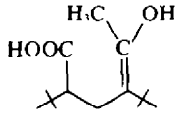


a: NaOH, H_2O, H_2 (Raney Ni). b: Na salt in H_2O, 100°. c: 4.5M NaOH, 100°, 3 days. d: 4M NaOH, 120°, 20 days. e: H^+. f: f. HNO_3. g: CH_2N_2 *or* dihydropyran; $LiAlH_4$. h: TosCl, pyridine; Na_2S, H_2O.

Scheme 1.

epimerisation to **6** and **7**, thereby establishing the configurations of the latter and avoiding a tedious separation. The diones **4** and **5**, however, reacted with sodium hypobromite[12] to give dibromo-derivatives which resisted further attack. Stronger and less selective oxidising agents were more successful. Oxone in various solvents and chromic acid in aqueous acetic acid oxidised the diones in fair yields to mixtures of acids and *anhydrides*. The formation of anhydrides in the oxidation of β-diketones would not be detected ordinarily but the anhydrides of the acids **6** and **7** are very resistant to hydrolysis. Finally it was found that fuming nitric acid oxidised the diones **4** and **5** to the acids **6** and **7** in high yield and stereochemical purity.

The *meso*-acid **6** is unexceptional in all respects but the racemic acid **7** is anomalous in two ways. Firstly the mass spectrum showed no ion corresponding to the molecular ion, $m/e = 244$, the highest mass peak observed, $m/e = 226$, corresponding to loss of water. This loss of water may be caused by thermal dehydration to the anhydride before ionisation but it is striking that it only occurs in the racemic acid **7**, in which the carbonyl groups are expected to be held apart (Fig. 2) and not in the *meso*-acid **6**. In the second place the infrared spectrum of solid **7** shows intense absorption at 1730 and 1632 cm^{-1}; no change was observed when deuterium replace protium in the carboxyl groups, but in C_6D_5CN a single CO band was observed at 1710 cm^{-1}.



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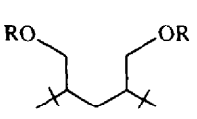

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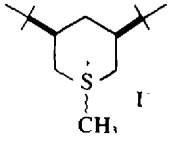
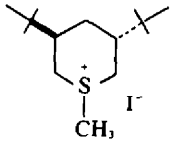


12: ax-Me
13: eq-Me



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The ^1H NMR spectrum of **1** (Table 1) is consistent with a predominance of the chair conformer **1C** (Fig. 1). The NMR spectra of the *trans* isomer **2** are consistent with a twist conformer such as **2T** rather than the chair conformer **2C**, although the presence of some of the latter is not ruled out by the available evidence. The ^1H chemical shifts of the t-butyl protons in **1** and in **2** are almost identical, whereas if **2** were in the chair **2C** these protons would be deshielded by proximity to the S atom of one methyl group at a time, so that the observed average shift should be larger in **2** than in **1**. The vicinal coupling constants $J_{2,3}$ are ~3 (*cis* protons) and ~11 Hz (*trans* protons) in both **1** and **2**, as expected for conformers **1C** and **2T**, whereas in the chair conformer **2C** one *trans* coupling would be relatively samll and the average should be ~7 Hz. The ^{13}C chemical shifts show an even more striking similarity for the t-butyl carbones in the two compounds and indicate that the t-Bu groups are unhindered in both. The ring C atoms in **2** are markedly shielded relative to related atoms in **1** (Table 1).

When this work began only one study of the stereochemistry of the reaction between thians and alkylating agents to give thianium (sulphonium) salts had been reported.[13] Because our results (Table 2 and below) differed markedly from those reported[13] we reinvestigated 4-phenylthian **15**. When this work was almost completed Eliel and Willer,[14] apparently unaware of the earlier work, gave results for 4-t-butylthian (**18**), including X-ray diffraction analysis of **19**-ClO_4^- and **20**-ClO_4 establishing the structures beyond doubt and ^{13}C chemical shifts to characterise equatorial and axial $\overset{+}{S}$-Me groups[14] (Experimental).

The thians **1** and **2** reacted with methyl iodide (no

Table 2. Kinetic and equilibrium ratios of products formed from thians and methyl iodide in CD_3CN

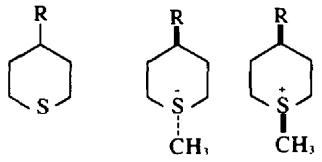
Thian	Kinetic control (15°) [eq]/[ax]	$\delta\Delta G^{\ddagger}$(a−e) (kJ mol^{-1})	Equilibrium control (100°) [eq]/[ax]	$\Delta G°$(e→a) [kJ mol^{-1}]
1	11 ± 1	5.75 ± 0.2	2.8 ± 0.1	3.2 ± 0.1
15a	6.5 ± 0.5[a] [3.4][b]	4.5 ± 0.2		
	3.35[c]	2.9		
15b	6.5 ± 0.5	4.5 ± 0.2	1.25 ± 0.05	0.7 ± 0.1
18[d]	3.7[6]	3.1[7]	1.2[7]	0.74
(21[e]	30 ± 6	8.1 ± 0.5	120 ± 20	11.3 ± 0.5)

[a] Corrected for background absorption. [b] See text. [c] Ref. 13. [d] Ref. 14. [e] See text; the data is corrected for the heavily biased conformational equilibrium in **21**.

Table 1. ^1H NMR chemical shifts (±0.02 ppm unless otherwise indicated) of thians (~0.25 M) in CD_3CN relative to Me_4Si as internal standard

Thian	2(6)-H eq	2(6)-H ax	3(5)-H eq	3(5)-H ax	4-H eq	4-H ax	$\overset{+}{S}$-Me	C-substituent
1	2.55	2.32	—	1.38	0.9 ± 0.1	0.75	—	0.88
2	2.45[a]	2.35[b]	—	1.5 ± 0.3			—	0.87
12	3.77	3.18	—	1.62			3.07	0.97
13	3.3 ± 0.1		—	1.97			2.93	0.95
14	3.71	2.83[c]	—	1.6 ± 0.3			3.02	0.93
	3.2 ± 0.1 (2H)							0.97
15	2.75 (±0.2)	1.9 ± 0.3			—	2.58	—	7.25 ± 0.1
16	3.3	3.1	2.3		—	3.0	3.07	7.3 ± 0.1
17[d]					—		3.01	

[a] *Trans* to adjacent t-butyl group. [b] *Cis* to adjacent t-butyl group. [c] Configurations not assignable. [d] Studied as minor product in mixture with **16**.



R = Ph, d_0:	**15a**	**16a**	**17a**
d_4:	**15b**	**16b**	**17b**
R = t-Bu	**18**	**19**	**20**

solvent) to give the corresponding sulphonium salts (**12**:**13** ≃ 11:1, separated by crystallisation, from **1**; **14** from **2**). The mixture of **12** and **13** was analysed by ^{1}H NMR using the S-Me signals with correction for the background absorption (2(6)-axial protons) being made by running a parallel experiment with CD_3I. The ratio 11 ± 1:1, determined by three workers, is notably higher than the ratio 3.35:1 for **16** and **17** from **15** reported by Cook *et al.*[13] and we therefore reinvestigated these reactions. 4-Phenylthian-d_0 (**15a**) and its 2,2,6,6-d_4 derivative (**15b**) were prepared from 3-phenylglutaric acid by a route similar to that used to convert **6** or **7** into **1** or **2**.

The reaction between a thian and methyl iodide in a polar solvent, e.g. acetonitrile,† to form diastereomeric salts is essentially complete and *kinetically* controlled at room temperature but at 100° an equilibrium mixture with an appreciable amount of free thian and methyl iodide is formed in a reasonable time.[13] By the use of CD_3·CN we eliminated the need to isolate the products (cf. Table 2; contrast Ref. 13) and a complete set of data for a given thian was obtainable from a single sample sealed under nitrogen in an NMR tube. The results (Table 2) confirmed that there is a real difference between **1** and **15a** but our value for the kinetically controlled ratio of products **16a**:**17a** = 6.5:1 was substantially higher than that reported by Cook *et al.*[13] although similar to Eliel and Willer's result for **18**[14] (Table 2). We accordingly (a) studies the reaction of **15b** with methyl iodide, thereby removing the background absorption in the S-Me region of spectra of **15a** and **17a**, and (b) repeated the published experiments on **15a** as closely as possible. We were able to reproduce the published ratio [**16a**]/[**16b**] = 3.35 by using the peak heights‡ of partly overlapping S-Me signals in *unexpanded* spectra in $(CD_3)_2SO$ with no correction for background absorption and conclude that there is no real difference between our results and those of Cook *et al.*[13]

The kinetically and thermodynamically controlled ratios of products for thianium salt formation are notable in three respects. In the first place there is a substantial difference between **1** and **15** or **18**. Secondly the kinetic stereoselectivity is considerably higher than the thermodynamic, as judged by the free energy differences $\sigma\Delta G^{\ddagger}_{288}$ and ΔG°_{373} (Table 2). Lastly the relative changes in strain energies from starting materials to transition states and to the products are different for the reactions of thians and of piperidines with methyl iodide.

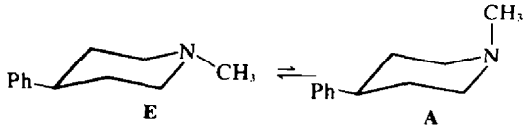
The differences in stereoselectivity observed in reactions of methyl iodide with **1**, **15** and **18** (Table 2) might be attributed to (a) different inductive effects of phenyl and t-butyl, (b) different amounts of reaction via twist conformers, (c) differences in steric strains in axial attack on sulphur, and (d) the possible sensitivity to small changes in ring geometry of the stereoelectronic effect discussed by Klein.[15] Differences in inductive effects are probably unimportant because **15** and **23** show similar stereoselectivities (Table 2, comparing data obtained by the same workers[13]). The possible importance of twist conformers has been tested by comparing the reactivities of **1**, **2**, **15**, and dimethyl sulphide competing for a limited amount of methyl iodide (Table 3). Since **2** is only marginally more reactive than **1** we conclude that twist conformers do not have high reactivity relative to chairs in this instance and do not account for the differences in stereoselectivity observed. The somewhat greater rate of attack at the unhindered equatorial site in **1** relative to one side of the sulphur in dimethyl sulphide shows the relatively small importance of the inductive effect of the extra atoms in the thian ring, although the inductive effect of the relatively distant 4-phenyl group in **15b** is significant. Since **2** is apparently largely in a twist conformer the small difference in reactivity between **1** (equatorial site) and **2** competing kinetically and thermodynamically for methyl iodide implies that torsion barriers for C–S single bonds are very similar in sulphides, sulphonium ions and the transition states leading from one to the other. Increased steric hindrance to axial attack on **1** relative to **15** and **18** resulting from distortion of the ring in **1** by the 3- and 5-t-Bu groups is at present the best explanation of the high stereoselectivity shown by **1**.

Table 3. Relative rates of reaction of sulphides with methyl iodide in CD_3CN at 15°

Sulphide	Total relative rate	Axial attack	Equatorial attack
Me_2S	2[a]	(1)	(1)
Thian	2	0.4[b]	1.6[b]
1	2.2_2	0.1_8	2.0_4
2	3.2_6	(1.6_3)[c]	(1.6_3)[c]
15b	0.48	0.06_4	0.41_6

[a] Rates are quoted relative to one side of Me_2S, which has two homotopic sites for reaction. [b] The total rate is divided between the two sites assuming that the selectivity is similar to that found for **18** (see Table 2). [c] The total rate is divided equally between the two sites assuming that the conformation is 2T (Fig. 1).

The greater kinetic than thermodynamic selectivity (Table 2) in the reactions of anancomeric thians with methyl iodide may plausibly be attributed to differences in



E **A**

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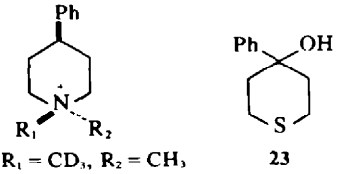

22E: $R_1 = CD_3$, $R_2 = CH_3$
22A: $R_1 = CH_3$; $R_2 = CD_3$

23

†Several solvents (CD_3OD, $(CD_3)_2CO$, $(CD_3)_2SO$, D_2O/pyridine, orthochlorophenol), including those used previously,[13] were tested fur running spectra but CD_3·CN was the only one suitable as both a reaction (20° and 100°) and spectroscopic solvent.

‡There is no detectable difference in the width of axial and equatorial S-Me signals in **12** and **13** or **16** and **17** so that peak heights may be used quantitatively when signals do not overlap.

steric hindrance in transition states and products if it is remembered that "normal" CSC bond angles (98° in Me_2S;[16] 106.8° in the ring 19[14]) are considerably smaller than tetrahedral (109.47°). This implies that axial attack by methyl iodide along the direction of the developing S–Me bond can bring the methyl group closer to the 3- and 5-methylene groups in the transition state than in the final product (Fig. 3), in which the CSC bond angle is enlarged by non-bonded repulsions (to 115.3 ± 0.6° in the ring in **20**[14]). Alternatively the kinetic and thermodynamic selectivities may both be stereoelectronic in origin, as has been proposed by Klein.[15] This implies a redistribution of charge on sulphur favouring equatorial attack as well as disfavouring axial attack. If one allows for a small inductive effect for the ring atoms C-3 to C-5 in thians, however, the data in Table 3 imply that stereoselectivity results largely, if not entirely, from low reactivity to axial attack. We conclude that steric hindrance to the latter is the more satisfactory explanation for the observed stereoselectivity, particularly the high value found for **1**.

The contrast between thians, e.g. **15**, and piperidines, e.g. **21**, in the stereoselectivities of their reactions with alkylating agents has been noted but not explained previously.[17] The thian **15** with methyl iodide gives rise to two different products, **16** and **17**, whereas the piperidine **21** has two conformers **21A** and **21E**, and reacts with methyl iodide-d_3 to give a single product, **22**, apart from the isotopic differentiation. In order to compare kinetic and thermodynamic selectivity in attack at the two sites on sulphur in **15** with attack on the two conformations at nitrogen in **21** the experimental ratio of products [**22E**/**22A**] = 0.25[18] from **21** must be corrected for the conformational equilibrium in the latter (**21E**:**21A** = 120 ± 20:1;[19] allowance must be made for conformers with axial phenyl[18]) giving the ratio of rate constants R = k(**21E**)/k(**21A**) = 30 ± 6, i.e. $\delta\Delta G^{\ddagger}_{288} = 8.1$ kJ mol^{-1}. The difference in the increase in strain between the starting materials (**21E**) and **21A**) and the products (**22E** and **22A**), which have the same free energy,† is numerically simply the conformational free energy difference for **21**, i.e. 11.3 kJ mol^{-1}.[19] This shows that the increase of strain energies in going from **22E** or **21A** to **22E** or **22A** is *less* in the transition states than in the products.‡ This is understandable if electrophilic attack on **21E** is along a truly "axial" direction perpendicular to the mean plane of the ring (Fig. 3), with the steric strain increasing monotonically with the extent of N–CD_3 bond formation, in contrast to **15** where axial approach (apart from distortions needed to minimise strain) is probably across the top of the ring and steric hindrance can reach a maximum before S–CH_3 bond formation is complete (Fig. 3).

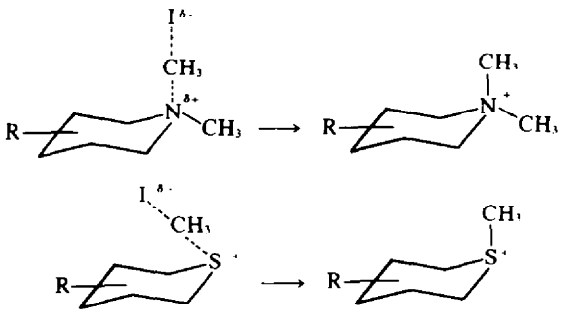

Fig. 3. Differences in direction of approach of methyl iodide to the axial unshared pair at nitrogen in *N*-methyl-piperidine with the *N*-methyl group equatorial and to the axial side of the unshared pair in a largely 3p orbital on sulphur in a thian. It is suggested that the initial approach in the latter is approximately orthogonal to the plane C(2)–S–C(6), forcing the incoming methyl group close to the axial hydrogen atoms on C(3) and C(5), although the fully formed *S*-methyl bond is directed axially.[14]

EXPERIMENTAL

The IR, PMR and mass spectra of all new compounds were consistent with the structures assigned, except for anomalies noted above and for the thianium iodides which were not subjected to mass spectrometry. TLC was performed on unbaked Kieselgel H plates using chloroform–ethanol (19:1); the plates were developed by iodine. ^{1}H NMR spectra were measured on a Perkin–Elmer R32 (90 MHz) spectrometer and ^{13}C spectra on a Bruker WH 90 (22.63 MHz) spectrometer. Assignments of ^{13}C chemical shifts (Table 1) were based on off-resonance decoupling for the thians **1** and **2** and by deuterium labelling in the sparingly soluble salts **12–14** for the S–Me groups.

4,6-Di-t-butylresorcinol. Resorcinol (750 g), phosphoric acid (87%, d 1.75) and t-BuOH (1320 g) were warmed to 50° and then shaken vigorously until the mixture changed into a thick slurry (10–15 min). After standing for 1 hr the mixture was diluted with water (4 l) and the solid was collected, washed with water and aqueous MeOH (2:1), and air-dried until the weight was *ca.* 2.4 kg. Recrystallisation from aqueous MeOH (1:1, 8 l) at 0° gave 4,6-di-t-butylresorcinol dihydrate (1.53 kg), m.p. 106–115°, raised to m.p. 121–123° (lit.[9] 123°) by dehydration over KOH at *ca.* 10 mm at room temp. Careful treatment of the mother liquors with water precipitated a second crop of slightly less pure material (205 g after washing with aqueous MeOH and hexane, and drying in air at room temp.) giving a total yield of 98%.

Cis- (4) *and* trans- (5) *4,6-di-t-butylcyclohexan-1,3-dione.* A soln of 4,6-di-t-butylresorcinol dihydrate (193.5 g) and NaOH (containing *c* 4% water, 36 g) in water (300 ml) and EtOH (60 ml) was hydrogenated (3–5 hr) over Raney nickel W4 (10 g) at 70–80°/100 atm. The mixture was filtered and acidified with conc. HCl (150 ml) and ice (150 g) to give cis-*4,6-di-t-butylcyclohexan-1,3-dione* (90–95%), m.p. 46–49°, raised to 51–52° by two crystallisations from pentane at −60° followed by sublimation at 80°/0.4 mm (Found: C, 75.02; H, 10.88. $C_{14}H_{24}O_2$ requires: C, 74.95; H, 10.78%). When the hydrogenation was conducted in water (260 ml) and NaOH (31.5 g, i.e. 1.01 equivalents allowing for *c* 4% water) and the excess hydrogen was released before heating the resulting soln at 100°/12 hr, the Na salt of the *cis*-dione was converted into the Na salts of the *trans*-dione **5** and the *erythro*-ketoacid **8** (TLC): *threo*-9 could not be detected (TLC). The mixture was filtered, acidified with conc. HCl (150 ml) and ice (150 g) to give (±)-trans *4,6-di-t-butylcyclohexan-1,3-dione* (156 g), m.p. 130–136°, raised to m.p. 137–139° by crystallisation from EtOAc (Found: C, 75.01; H, 10·62%).

The diones **4** and **5** were converted by the action of NaOBr in MeOH into their *2,2-dibromo derivatives*, *cis*-isomer, m.p. 128° (Found: C, 44.29; H, 5.86; Br, 41.92. $C_{14}H_{22}O_2Br_2$ requires: C, 44.16; H, 5.83; Br, 42.02%), and *trans*-isomer, m.p. 116° (Found: C, 43.77; H, 5.80; Br, 41.05%).

(±)-Erythro-(**8**) *and* threo(**9**)-*2,4-di-t-butyl-5-oxohexanoic acid.* A suspension of *cis*-4,6-di-t-butylcyclohexan-1,3-dione (50 g) in 4.5 M NaOH (250 ml) was boiled under reflux (3 days) and then acidified to give (±)-**8**, m.p. 107–109° after crystallisation from hexane (Found: C, 69.54; H, 10.52. $C_{14}H_{26}O_3$ requires: C, 69.38; H, 10.81%). When the *erythro* acid **8** (0.5 g) was heated in

†This neglects a small isotope effect, which is probably > 50 J mol^{-1}.[20]

‡Qualitatively this conclusion depends only on the ratio of products being less than unity. It is useful, however, to compare the two differences quantitatively and this requires an estimate of the conformational equilibrium in **21**.

3.75 M NaOH in a polypropylene tube in a sealed glass tube at 120°/20 days it was converted into a mixture of **8** (40%) and the threo *acid* **9** (60%). The former was removed by crystallisation from pentane at −60° and evaporation of the solvent from the filtrate left the nearly pure (TLC and NMR) **9**. The latter could not be crystallised but was characterised by its NMR spectrum and by oxidation with fuming HNO_3 to the acid **7**.

Meso- (**6**) *and* (±)- (**7**) *2,4-di-t-butylglutaric acid and anhydride*

(a) *cis*-Di-t-butycyclohexan-1,3-dione (50 g) was added during 1 hr to fuming HNO_3 (*d* 1.50, 300 ml) maintained at < 20°. The mixture was stirred at 50–55° for 3 hr and poured into H_2O (2 l) giving *meso*-2,4-di-t-butylglutaric acid (95–99%), m.p. 200–204°, raised to 207–209° by crystallisation from aqueous acetone or EtOAc (Found: C, 64.29; H, 9.74. $C_{13}H_{24}O_4$ requires: C, 63.93; H, 9.83%). A similar oxidation of the *trans*-dione **3** gave the (±)-acid (94%), m.p. 196–210° raised to 214–216° by crystallisation from EtOAc (Found: C, 64.22; H, 90%). When either acid was crystallised from EtOD–D_2O the corresponding O-deuterated acid was obtained. IR spectra: **6**, ν (C=O) 1710 cm^{-1} (Nujol mull); **7**, ν (C=O), 1740, 1635 cm^{-1} (Nujol mull), 1710 cm^{-1} (CD_3CN). The O–d acids showed the expected changes in the OH stretching bands but the C=O absorptions were essentially unchanged.

(b) Ozone was passed into a soln of the *cis* **4** or *trans*-dione **5** (5 g) in EtOAc (25 ml) and AcOH (25 ml) at 0°/6 hr. The solvent was evaporated and the residue was separated into acidic and neutral fractions. Sublimation of the latter at 80°/0.1 mm gave the *meso*- or (±)-anhydride (up to 4 g). The meso-*anhydride* had m.p. 88–90° (Found: C, 68.19; H, 9.80. $C_{13}H_{22}O_3$ requires: C, 68.99; H, 9.80%) and the (±)-*anhydride* has m.p. 104–107° (Found: C, 68.68; H, 9.78%). The anhydrides were very resistant to hydrolysis by dilute acid or alkali and were best hydrolysed by cold fuming HNO_3 to give the corresponding acids almost quantitatively.

(c) The *cis*-dione **4** (50 g) in AcOH–H_2O (9:1, 400 ml) was treated with Jones' chromic acid[21] (234 ml) during 0.75 hr at 20° and gave the *meso*-acid (64–72%) and *meso*-anhydride (18–28%), which were separated with alkali. The low solubility of the Na and K salts made the separation extremely tedious. An analogous small scale oxidation of the *trans*-dione (**5**) in AcOH–Me_2CO (60:40) gave a low yield of the (±)-acid.

The acids with diazomethane in ether gave the dimethyl *esters*, *meso* m.p. 37° (Found: C, 65.97; H, 9.99. $C_{15}H_{24}O_4$ requires: C, 66.14; H, 10.36%), (±) m.p. 55–57° (Found: C, 66.36; H, 10.20%). The esters regenerated the acids without epimerisation when heated with fuming HNO_3 at 60°/4 hr. The di-tetrahydropyranyl esters were prepared using a 100% excess of dihydropyran in benzene and were reduced without purification.

Meso- *and* (±)-*2,4-di-t-butylpentan*-1,5-*diyl di-tosylate*

(a) The acid **6** (45 g) in diglyme (150 ml) was added during 2 hr to LAH (15.75 g) in diglyme (130 ml) and the mixture was heated and stirred (4 days) under reflux in an oil bath at 200°. The mixture was worked up with 10% H_2SO_4 (500 ml) and ether, unchanged **6** was extracted with dil NaOHaq., and the organic solvents were removed, finally at 100°/1 mm. The residual oil (30 g) in pyridine (30 ml) was added slowly to tosyl chloride (79.5 g) in pyridine (100 ml) maintained below 10°. The mixture was kept at 0°/12 hr and worked up with ice, ether and HCl to give an oil (54 g) which very slowly crystallised from MeOH at 0° to give meso-**11** (R=Tos) (13.2 g, 22%), m.p. 67.5–69° (Found: C, 61.65; H, 7.63; S, 12.25. $C_{27}H_{40}S_2O_6$ requires: C, 61.83; H, 7.64; S, 12.22%). The mother liquors could not be induced to crystallise but could be used to prepare the thian (see below). When **7** was treated under the same conditions the reduction was less than 50% complete after 4 days.

(b) Dimethyl (±)-2,4-di-t-butylglutarate (9 g) was reduced with LAH (2.2 g) in ether to give (±)-**11** (R=H) (6.5 g, 92%) which under the conditions described in (a) above was converted into (±)-**11** (R=Tos) (12.5 g, 80% from the ester), m.p. 79–81° (Found: C, 61.62; H, 7.44; S, 12.45%). The *meso* dimethyl and the two tetrahydropyranyl esters were reduced in similar yields.

cis- (1) *and* trans- (2) *3,5-Di-t-butylthian*. A heterogeneous mixture of the *meso*-**11** (R=Tos) (9.9 g) and $Na_2S{\cdot}9H_2O$ (30 g) in H_2O (100 ml) was boiled under reflux for 4 days. The resulting oil (3.1 g) crystallised from pentane at −40° to give cis-3,5-*di-t-butylthian* (0.9 g), m.p. 39–41° (Found: C, 72.47; H, 11.88; S, 15.18. $C_{13}H_{26}S$ requires: C, 72.84; H, 12.23; S, 14.93%). The mother liquors were used to prepare the 1-methyl thianium iodide from which the pure thian could be recovered quantitatively by pyrolysis at 200°/20 mm. Analogously (±)-**11** (R=Tos) (3 g) gave trans-3,5-*di-t-butylthian* (1.12 g, 92%) which collected in the reflux condenser and after sublimation had m.p. 55–57° (Found: C, 72.84: H, 12.01; S, 15.10%).

1-*Methyl*-3,5-*di-t-butylthianium iodide*. Crude *cis*-3,5-di-t-butylthian (2.7 g) and MeI (1.1 ml) after 6 hr gave a semi-solid product which was washed with MeI leaving *cis,cis*- and *trans,cis*-1-methyl thianium iodide (1.76 g). The mixture was dissolved in nitromethane (15 ml) which was then allowed to evaporate during 3 days leaving one crystal of the cis,cis-*isomer* (1.12 g), m.p. 162–163° (dec) (Found: S, 9.06; I, 34.75. $C_{14}H_{29}Si$ requires: S, 9.00; I, 35.61%), ^{13}C δ $\overset{+}{S}$–Me = 26.25 ppm (in Cd.OD–$CDCl_3$, 1:1) (*cf* 19, 25.48 ppm[14]), fine needles of the trans, cis-*isomer* (110 mg) which after repeated crystallisation from MeOH gave a pure sample (31 mg), m.p. 204–206° (Found: C, 47.40; H, 7.96. $C_{14}H_{29}SI$ requires: C, 47.19; 8.20%), ^{13}C δ $\overset{+}{S}$–Me = 19.23 ppm (*cf* 20, 16.61 ppm[14]) composition. When the pure thian (20 mg) reacted with MeI -d_0 or -d_3 (0.04 ml) in MeCN (0.4 ml) the NMR spectrum of the products showed no absorption bands except those attributable to **12** and **13** (11:1). (±)-*trans*-3,4-Di-t-butylthian (0.14 g) reacted with MeI (1 ml) at room temp. giving **14** (0.23 g), m.p. 150–151° (Found: S, 8.75; I, 34.95%), ^{13}C δ $\overset{+}{S}$–Me = 25.23 ppm.

4-*Phenylthian* (**15a** and **15b**). Dimethyl 3-phenylglutarate (50 g)[22] in dry dioxane (100 ml) was added slowly to a suspension of LAH (11 g) in boiling dioxane (150 ml). The mixture was boiled under reflux (12 h) and worked up to give crude 3-phenylpentan-1,5-diol as a colourless viscous liquid. The latter (36 g) in dry pyridine (120 ml) was added slowly to an ice-cold stirred suspension of toluene-*p*-sulphonyl chloride (140 g) in pyridine (120 ml). The mixture was left at 0° (12 hr) and then worked up with ice (500 g) and ether (3 × 200 ml). The ethereal extracts were washed with ice-cold 5M HCl with brine, dried and the ether was evaporated leaving the di-tosylate (70 g), m.p. 73–74°. The di-tosylate (15 g) was boiled under reflux (5 days) with $Na_2S{\cdot}9H_2O$ (50 g) in water (100 ml), giving 4-phenylthian (3.8 g, sublimed), m.p. 53–54° (lit.[13] m.p. 55°). A similar sequence of reactions beginning with dimethyl 3-phenylglutarate (2.2 g) and LAD (0.5 g) gave **15b** (38% overall), m.p. 51–53°.

Competitive reactions between sulphides and methyl iodide. The less volatile sulphides **10**, **11** and **15b** were weighed out to give ~0.2 M solns for each reaction while dimethyl sulphide was made up as a stock 0.1 M soln in $CD_3{\cdot}Cn$. Binary mixtures of sulphides in $CD_3{\cdot}CN$ (0.5 ml in an NMR tube) where treated with ~½ molecular equiv. of MeI, weighed directly into the tube, and kept at 20° until the reaction was complete (1–3 days). The relative amounts of sulphonium salts and unchanged sulphides for competition experiments with **10** or **11** and dimethyl sulphide could be determiend by integrating the sharp $\overset{+}{S}$–Me, S–Me and t-Bu signals on highly expanded spectra. In reactions involving **13b**, however, the latter had to be estimated by difference from the initial weights of reactants and the relative amounts of products, and errors resulting from the volatility of dimethyl sulphide and MeI increase the uncertainty of the derived relative rates (Table 4).

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