Conformational Behaviour of Medium-sized Rings. Part 10.[1] Dithiosalicylides and Trithiosalicylides

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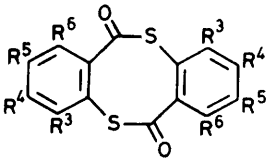
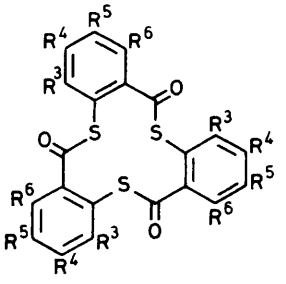
The trithiosalicylide derivatives (8)—(11) have been synthesised and shown by temperature-dependent ^{1}H n.m.r. spectroscopy to exist in solution as ring inverting (35a) ⇌ (35b) enantiomeric helical conformations with *trans*-thioester linkages. The free energies of activation for these conformational changes are *ca.* 10 kcal mol^{-1} higher than those for the similar process in the corresponding trisalicylides. In contrast with the trisalicylides, the trithiosalicylides can only ring invert between enantiomeric helical conformations *via* intermediates containing a *cis*-thioester linkage. The dithiosalicylide derivatives (3)—(7) have been synthesised; the temperature dependence of the ^{1}H n.m.r. spectrum of di-*o*-thiothymotide (7) has been interpreted in terms of ring inversion (40a) ⇌ (40b) between enantiomeric boat conformations. Comparison of the $\Delta G^{\ddagger}$ value of 24.6 kcal mol^{-1} for this conformational change with that of 17.7 kcal mol^{-1} previously obtained for di-*o*-thymotide (41) suggests that *cis*-thioester linkages are subject to more resonance stabilisation than are *cis*-ester linkages.

ALTHOUGH the conformational behaviour of di- and trisalicylides in solution has been investigated [1] in considerable detail by dynamic ^{1}H n.m.r. spectroscopy, the corresponding di- and tri-thiosalicylides have received scant attention in this regard since the parent compounds (1) [2,3] and (2) [3] were first reported in the literature. Dipole moment measurements (reported in ref. 3) on dithiosalicylide (1) (6.39D) and trithiosalicylide (2) (1.54 ± 0.02D) led to the conclusion that their conformational properties resembled respectively those of the closely related di- and tri-salicylide derivatives.[1,4] In this paper we report [5] the synthesis of some suitably substituted di- (3)—(7) and tri- (8)—(11) thiosalicylides and discuss [5] the conformational behaviour in solution of those derivatives where dynamic ^{1}H n.m.r. spectroscopy is feasible.

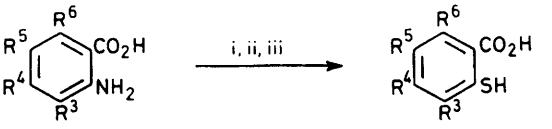


(1) $R^3 = R^4 = R^5 = R^6 = H$
(3) $R^3 = Me$; $R^4 = R^5 = R^6 = H$
(4) $R^3 = R^4 = R^6 = H$; $R^5 = Me$
(5) $R^3 = R^4 = R^5 = H$; $R^6 = Me$
(6) $R^3 = R^6 = Me$; $R^4 = R^5 = H$
(7) $R^3 = CHMe_2$; $R^4 = R^5 = H$; $R^6 = Me$



(2) $R^3 = R^4 = R^5 = R^6 = H$
(8) $R^3 = Me$; $R^4 = R^5 = R^6 = H$
(9) $R^3 = R^4 = R^6 = H$; $R^5 = Me$
(10) $R^3 = R^4 = R^5 = H$; $R^6 = Me$
(11) $R^3 = R^6 = Me$; $R^4 = R^5 = H$

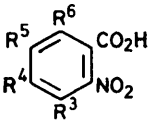
A number of methyl substituted 2-mercaptobenzoic acids [*viz.* (18), (19),[6] (20),[7] and (21)] were prepared—by adaption of a published procedure [8] for obtaining thiosalicylic acid (17) from anthranilic acid (12)—from the corresponding 2-aminobenzoic acid derivatives [*viz.* (13),[9] (14),[9] (15),[10] and (16) [11]] by a sequence of reactions (see Scheme 1) involving (i) diazotisation of the amino-



(12) $R^3 = R^4 = R^5 = R^6 = H$ (17)
(13) $R^3 = Me$; $R^4 = R^5 = R^6 = H$ (18)
(14) $R^3 = R^4 = R^6 = H$; $R^5 = Me$ (19)
(15) $R^3 = R^4 = R^5 = H$; $R^6 = Me$ (20)
(16) $R^3 = R^6 = Me$; $R^4 = R^5 = H$ (21)

SCHEME 1 *Reagents:* i, $NaNO_2$, HCl; ii, $Na_2S{\cdot}2H_2O$, S, NaOH; iii, Zn, HOAc

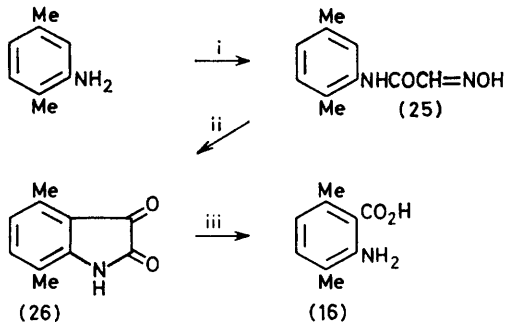
group, (ii) conversion of the diazonium salt into a disulphide, and (iii) reduction of the disulphide link to afford the desired thiol function. 2-Amino-3-methyl- (13), -5-methyl- (14), and -6-methyl- (15) benzoic acids were obtained by catalytic reduction with hydrazine hydrate [12] of the corresponding 2-nitromethylbenzoic acid derivatives (22), (23), and (24). 2-Amino-3,6-dimethylbenzoic acid (16) was prepared [11] from 2-amino-1,4-dimethylbenzene by the reaction sequence shown in Scheme 2 involving (i) conversion of the aromatic amine



(22) $R^3 = Me$; $R^4 = R^5 = R^6 = H$
(23) $R^3 = R^4 = R^6 = H$; $R^5 = Me$
(24) $R^3 = R^4 = R^5 = H$; $R^6 = Me$

into 2′,5′-dimethylhydroxyiminoacetanilide (25) followed by (ii) formation of 4,7-dimethylisatin (26), and (iii) oxidation yielding compound (16). 3-Isopropyl-6-methyl-2-mercaptobenzoic acid (thiothymotic acid) (31)

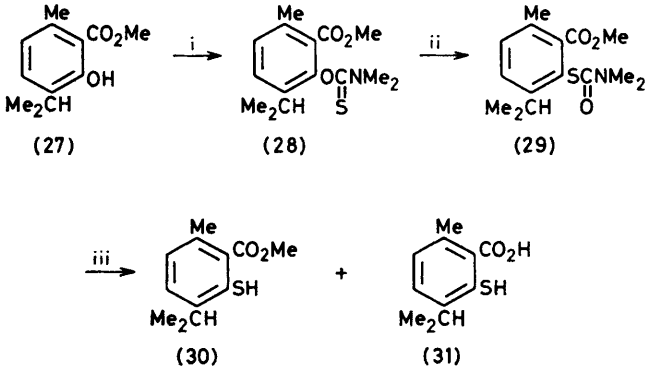
was synthesised (see Scheme 3) from the methyl ester (27) of thymotic acid [13] in three steps: (i) formation of the *O*-aryl dimethylthiocarbamate (28) by treatment of (27) with dimethylthiocarbamoyl chloride [14] in dimethylformamide in the presence of sodium hydride, (ii) thermal rearrangement [15] of (28) to afford the *S*-aryl dimethylthiocarbamate (29), and (iii) conversion into a



SCHEME 2 *Reagents:* i, $Cl_3CCHO{\cdot}H_2O$, $NH_2OH{\cdot}HCl$; ii, concentrated H_2SO_4; iii, NaOH, H_2O_2 then HCl

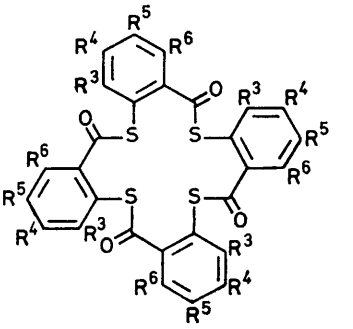
mixture of thiothymotic acid (31) and its methyl ester (30).

Cyclisation of the 2-mercaptobenzoic acid derivatives (17)—(21) in dry toluene in the presence of phosphoric anhydride [3] led to the isolation of the appropriate di- [*i.e.* (1), (3), (4), (5), and (6), respectively] and tri- *i.e.* (2), (8), (9), (10), and (11), respectively] thiosalicylide derivatives. Only the parent compounds—the di- (1) and tri- (2) thiosalicylides—were known [3] when this in-

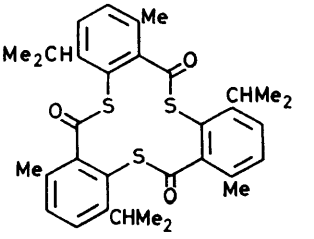


SCHEME 3 *Reagents and conditions:* i, Me_2NCSCl, NaH, Me_2NCHO; ii, heat, 320—340 °C for 2 min; iii, MeOH, HCl then H_2O

vestigation was initiated. Subsequently, dithiosalicylide (1) has been prepared from a range of diverse precursors in a variety of different manners.[16] Tetrathiosalicylide (32) was also characterised during the earlier dehydrations reported [3] on thiosalicylic acid (17). Thus, it is not surprising that, during the present investigation, tetra-3-methylthiosalicylide (33) was obtained albeit in low yield from the cyclisation of 3-methylthiosalicylic acid (18). The only cyclic product which was identified from the cyclisation of thiothymotic acid (31) was di-*o*-thiothymotide (7); no tri-*o*-thiothymotide (34) was isolated.



(32) $R^3 = R^4 = R^5 = R^6 = H$
(33) $R^3 = Me$; $R^4 = R^5 = R^6 = H$



(34)

EXPERIMENTAL

The general methods have been discussed in Part 3 [17] and 6.[18]

Thiosalicylic Acid (*2-Mercaptobenzoic Acid*) (17).[8]—Anthranilic acid (12) (13.7 g) was converted by a literature procedure into thiosalicylic acid (17) (6.6 g, 43%), m.p. 163—164 °C (lit.,[8] m.p. 163—164 °C), $\nu_{max.}$ 2 600 (SH) and 1 660 cm^{-1} (CO); τ [$CDCl_3$–$(CD_3)_2CO$] 0.74 (1 H, bs, CO_2H), 1.93 (1 H, d, J 7.0 Hz, 6-H), 2.54—2.98 (3 H, m, other ArH), and 4.88 (1 H, bs, 3-SH).

Dithiosalicylide (1) [3] *and Trithiosalicylide* (2).[3]—Thiosalicylic acid (17) (2.4 g) and phosphoric anhydride (8 g) were heated under reflux in dry toluene (35 ml) for 5.5 h. After cooling, the solid material was collected and extracted with hot chloroform. When the toluene solution was left to stand in an ice-bath the cyclic trimer crystallised. The crude product was collected and recrystallised from chloroform giving trithiosalicylide (2) (140 mg, 7%), m.p. 257—258° (lit.,[3] m.p. 257—258°) [Found: M (mass spec.), 408. Calc. for $C_{21}H_{12}O_3S_3$: M, 408], τ ($CDCl_3$), 2.32—2.54 (m, ArH). The toluene mother liquors and the chloroform solution were then combined, washed with aqueous sodium hydrogencarbonate solution (5%), dried, and evaporated under reduced pressure to give a residue. This was examined by t.l.c. on silica gel using benzene–light petroleum (b.p. 60—80 °C) (10 : 1) as eluant. Two components were observed. The faster-moving component was separated by preparative t.l.c. on silica gel and recrystallised from chloroform to give dithiosalicylide (1) (126 mg, 6%), m.p. 175 °C (lit.,[3] m.p. 176—177 °C) [Found: M (mass spec.), 272. Calc. for $C_{14}H_8O_2S_2$: M, 272], τ ($CDCl_3$), 2.57—2.92 (ABCD system, ArH). The slower-moving component was found to correspond to the cyclic trimer (2).

3-Methyl-2-nitrobenzoic Acid (22).[19]—*m*-Toluic acid (100 g) was added slowly with stirring to fuming nitric acid (400

ml). Solid CO_2 was added directly to the reaction mixture to maintain the temperature between 0—5 °C during the addition and for 0.5 h afterwards. The mixture was then allowed to warm up to 5 °C, collected, and washed to give 3-methyl-2-nitrobenzoic acid (22) (50 g, 38%), m.p. 215—220 °C (lit.,[19] m.p. 213—220 °C) [Found: *M* (mass spec.), 181. Calc. for $C_8H_7NO_4$: *M*, 181], τ [$CDCl_3$–$(CD_3)_2CO$], 1.55 (1 H, bs, CO_2H), 2.11 (1 H, dd, $J_{5,6}$ 8 Hz, $J_{4,6}$ 2 Hz, 6-H), 2.32—2.61 (2 H, m, 4-H and 5-H), and 7.67 (3 H, s, Me).

2-*Amino*-3-*methylbenzoic Acid* (13).—Hydrazine hydrate (10 ml) was added to 3-methyl-2-nitrobenzoic acid (22) (10 g) dissolved in ethanol (100 ml) and the reaction mixture was heated to +40 °C. A small amount of Raney nickel was added to the reaction mixture which was maintained at +40 °C on a steam-bath. Further batches of Raney nickel were added after 1 h and then after 2 h. The solution was then heated under reflux to drive off the dissolved gases. The hot solution was filtered to remove the catalyst, treated with charcoal, and filtered again. The solution was cooled and a large excess of water was added to precipitate 2-amino-3-methylbenzoic acid (13) (5.47 g, 66%), m.p. 172 °C (lit.,[9] m.p. 175 °C) [Found: *M* (mass spec.), 151. Calc. for $C_8H_9NO_2$: *M*, 151], $\nu_{max.}$ 3 500, 3 350 (NH_2), and 1 660 cm^{-1}; (CO) τ [$CDCl_3$–$(CD_3)_2CO$] 2.19 (1 H, d, $J_{5,6}$ 8 Hz, 6-H), 2.82 (1 H, d, $J_{4,5}$ 8 Hz, 4-H), 2.99 (3 H, bs, NH_2 and CO_2H), 3.45 (1 H, t, $J_{4,5} = J_{5,6}$ 8 Hz, 5-H), and 7.83 (3 H, s, Me).

2-*Mercapto*-3-*methylbenzoic Acid* (18).—2-Amino-3-methylbenzoic acid (13) (15.1 g) was converted by adaption of a literature procedure [8] into 2-*mercapto*-3-*methylbenzoic acid* (18) (5.5 g, 33%), m.p. 160—165 °C [Found: C, 56.9; H, 4.5; S, 18.9%; *M* (mass spec.), 168. $C_8H_8SO_2$ requires C, 57.1; H, 4.8; S, 19.0%; *M*, 168], $\nu_{max.}$ 2 550 (SH) and 1 670 cm^{-1} (CO); τ [$CDCl_3$–$(CD_3)_2CO$] 0.89 (1 H, bs, CO_2H), 1.99 (1 H, d, $J_{5,6}$ 8 Hz, 6-H), 2.70 (1 H, d, $J_{4,5}$ = 9 Hz, 4-H), 2.96 (1 H, t, $J_{4,5} = J_{5,6}$ = 8 Hz, 5-H), 2.96 (1 H, s, SH), and 7.64 (3 H, s, Me).

Di-3-*methylthiosalicylide* (3), *Tri*-3-*methylthiosalicylide* (8), *and Tetra*-3-*methylthiosalicylide* (33).—2-Mercapto-3-methylbenzoic acid (18) (2.4 g) and phosphoric anhydride (8 g) were heated under reflux in dry toluene (35 ml) for 5.5 h. After cooling, the solid material was collected and extracted with hot chloroform. When the toluene solution was allowed to stand in an ice-bath, a mixture of three compounds crystallised out together as indicated by a t.l.c. examination on silica gel using chloroform–cyclohexane (10 : 1) as eluant. The toluene mother liquors and the chloroform solution were combined and washed with aqueous sodium hydrogencarbonate solution (5%), dried, and evaporated under reduced pressure to give a residue. This was examined by t.l.c. as described above. Three components were identified. The fastest-moving component separated by preparative t.l.c. on silica gel was recrystallised from methanol to afford *di*-3-*methylthiosalicylide* (3) (100 mg, 4%), m.p. 245—250 °C [Found: C, 63.5; H, 4.2; S, 21.2%; *M* (mass spec.), 300.0275. $C_{16}H_{12}O_2S_2$ requires C, 64.0; H, 4.0; S, 21.3%; *M*, 300.0279], τ ($CDCl_3$) 2.70—3.08 (6 H, m, ArH), and 7.70 (6 H, s, 2 × Me). The intermediate component separated by preparative t.l.c. on silica gel was recrystallised from methanol to afford *tri*-3-*methylthiosalicylide* (8) (150 mg, 7%), m.p. 300—302 °C [Found: C, 63.0; H, 3.9; S, 21.1%; *M* (mass spec.), 450.0431. $C_{24}H_{18}O_3S_3$ requires C, 64.0; H, 4.0; S, 21.3%; *M*, 450.0418], τ ($CDCl_3$) 2.46—2.68 (9 H, m, ArH) and 7.46 and 7.56 (9 H, 2 × s in ratio of 2 : 1, 3 × Me). The slowest-moving component separated by preparative t.l.c. was recrystallised from dioxan to afford *tetra*-3-*methylthiosalicylide* (33) (10 mg, 0.4%), m.p. 320 °C [Found: C, 63.3; H, 4.3; S, 21.5%; *M* (mass spec.), 600.0549. $C_{32}H_{24}O_4S_4$ requires C, 64.0; H, 4.0; S, 21.3%; *M*, 600.0557].

2-*Amino*-5-*methylbenzoic Acid* (14).—Catalytic reduction of 5-methyl-2-nitrobenzoic acid (23) (10 g) as described previously for the 3-methyl derivative (22) afforded 2-amino-5-methylbenzoic acid (14) (5.4 g, 65%), m.p. 175 °C (lit.,[9] m.p. 175 °C) [Found: *M* (mass spec.) 151. Calc. for $C_8H_9NO_2$: *M*, 151], $\nu_{max.}$ 3 400, 3 300 (NH_2), and 1 670 cm^{-1} (CO); τ [$CDCl_3$–$(CD_3)_2CO$] 2.33 (1 H, d, $J_{4,6}$ 2 Hz, 6-H), 2.94 (1 H, dd, $J_{3,4}$ 8 Hz, $J_{4,6}$ 2 Hz, 4-H), 3.32 (3 H, bs, CO_2H and NH_2), 3.37 (1 H, d, $J_{3,4}$ 8 Hz, 3-H), and 7.80 (3 H, s, Me).

2-*Mercapto*-5-*methylbenzoic Acid* (19).—2-Amino-5-methylbenzoic acid (14) (15.1 g) was converted by adaption of a literature procedure [8] into 2-mercapto-5-methylbenzoic acid (19) (8.0 g, 48%), m.p. 155—157 °C (lit.,[6] m.p. 155—157 °C) [Found: *M* (mass spec.), 168. Calc. for $C_8H_8SO_2$: *M*, 168], $\nu_{max.}$ 2 600 (SH) and 1 670 cm^{-1} (CO); τ [$CDCl_3$–$(CD_3)_2CO$] 1.21 (1 H, bs, CO_2H), 2.07 (1 H, bs, 6-H), 2.81 (2 H, bs, 3-H and 4-H), 5.22 (1 H, bs, SH), and 7.66 (3 H, s, Me).

Di-5-*methylthiosalicylide* (4) *and Tri*-5-*methylthiosalicylide* (9).—2-Mercapto-5-methylbenzoic acid (19) (2.4 g) and phosphoric anhydride (8 g) were heated under reflux in dry toluene (35 ml) for 5.5 h. After cooling, the solid material was collected and extracted with hot chloroform. A compound which crystallised from the toluene solution when it was allowed to stand in an ice-bath was characterised as *tri*-5-*methylthiosalicylide* (9) (204 mg, 10%), m.p. 250—255 °C [Found: C, 63.4; H, 4.4; S, 21.2%; *M* (mass spec.), 450. $C_{24}H_{18}O_3S_3$ requires C, 64.0; H, 4.0; S, 21.3%; *M*, 450], τ ($CDCl_3$–CS_2), 2.46—2.68 (9 H, m, ArH) and 7.56 (9 H, s, 3 × Me). The toluene mother liquors and the chloroform solution were then combined, washed with aqueous sodium hydrogencarbonate (5%), dried, and evaporated under reduced pressure to give a residue. This was examined by t.l.c. on silica gel using light petroleum (b.p. 60—80 °C)–ethyl acetate (10 : 1) as eluant. Two components were identified. The faster-moving component was separated by preparative t.l.c. on silica gel and recrystallised from chloroform to afford *di*-5-*methylthiosalicylide* (4) (18 mg, 1%), m.p. 155—157 °C, [Found: *M* (mass spec.), 300. $C_{16}H_{12}O_2S_2$ requires *M*, 300], τ ($CDCl_3$)] 2.74—3.08 (6 H, m, ArH) and 7.64 (6 H, s, 2 × Me). The slower-moving component was found to correspond to the cyclic trimer (9).

2-*Amino*-6-*methylbenzoic Acid* (15).—Reduction of 6-methyl-2-nitrobenzoic acid (24) (10 g) as described previously for the 3-methyl derivative (22) afforded 2-amino-6-methylbenzoic acid (15) (5.57 g, 67%), m.p. 123 °C (lit.,[10] m.p. 125—126 °C] [Found: *M* (mass spec.), 151. Calc. for $C_8H_9NO_2$: *M*, 151], $\nu_{max.}$ 3 500 (NH_2) and 1 620 cm^{-1} (CO); τ [$CDCl_3$–$(CD_3)_2CO$], 2.83 (1 H, t, $J_{3,4} = J_{4,5}$ = 8 Hz, 4-H), 3.40 and 3.43 (2 H, 2 × d, $J_{3,4} = J_{4,5}$ = 8 Hz, 3-H and 5-H), 4.30 (1 H, bs, CO_2H), 6.97 (2 H, bs, NH_2), and 7.39 (3 H, s, Me).

2-*Mercapto*-6-*methylbenzoic Acid* (20).—2-Amino-6-methylbenzoic acid (15) (15.1 g) was converted by adaption of a literature procedure [8] into 2-mercapto-6-methylbenzoic acid (20) (5.0 g, 29%), m.p. 110 °C (lit.,[7] m.p. 110—111 °C) [Found: *M* (mass spec.), 168. Calc. for $C_8H_8O_2S$: *M*, 168], $\nu_{max.}$ 2 650 (SH) and 1 700 cm^{-1} (CO); τ ($CDCl_3$)–0.68 (1 H, bs, CO_2H), 2.72—3.08 (3 H, m, ArH), 6.18 (1 H, bs, SH), and 7.53 (3 H, s, Me).

Di-6-methylthiosalicylide (5) *and Tri-6-methylthiosalicylide* (10).—2-Mercapto-6-methylbenzoic acid (20) (2.4 g) and phosphoric anhydride (8 g) were heated under reflux in dry toluene (35 ml) for 5.5 h. After cooling, the solid material was collected and extracted with hot chloroform. When the toluene solution was left to stand in an ice-bath the cyclic trimer crystallised. The crude product was collected and recrystallised from methanol to give *tri-6-methylthiosalicylide* (10) (160 mg, 8%), m.p. > 300 °C [Found: C, 63.0; H, 4.3; S, 21.0%; *M* (mass spec.), 450 $C_{24}H_{18}O_3S_3$ requires C, 64.0; H, 4.0; S, 21.3%; *M*, 450], τ ($CDCl_3$) 2.59 (9 H, bs, ArH) and 7.50 (9 H, bs, 3 × Me). The toluene mother liquors and the chloroform solution were then combined, washed with aqueous sodium hydrogencarbonate (5%), dried, and evaporated under reduced pressure to give a residue. This was examined by t.l.c. on silica gel using light petroleum (b.p. 60—80 °C)–ethyl acetate (10 : 1) as eluant. Two components were observed. The faster-moving component was separated by preparative t.l.c. on silica gel and recrystallised from methanol to afford *di-6-methylthiosalicylide* (5) (700 mg, 31%), m.p. 155 °C [Found: C, 64.0; H, 4.4; S, 21.2%; *M* (mass spec.), 300. $C_{16}H_{12}O_2S_2$ requires C, 64.0; H, 4.0; S, 21.3%; *M*, 300], τ ($CDCl_3$) 2.75—3.01 (6 H, m, ArH) and 7.75 (6 H, s, 2 × Me). The slower-moving component corresponded to the cyclic trimer (10).

2′,5′-Dimethylhydroxyiminoacetanilide (25).[11]—A solution of 2-amino-1,4-dimethylbenzene (24.2 g) in a mixture of concentrated hydrochloric acid (20.5 g) and water (300 ml) was added to a solution of chloral hydrate (36 g) and sodium sulphate (520 g) in water (2 500 ml). A solution of hydroxylamine hydrochloride (44 g) in water (500 ml) was added to the reaction mixture. The stirred suspension was heated to reflux temperature during 1 h and then refluxed for 5 min. After rapid filtration through cotton and cooling of the solution, a crystalline product was obtained and characterised as 2′,5′-dimethylhydroxyiminoacetanilide (25) (30.0 g, 78%), m.p. 155—160 °C (lit.,[11] m.p. 153—156 °C) [Found: *M* (mass spec.), 192. Calc. for $C_{10}H_{12}N_2O_2$: *M*, 192], $\nu_{max.}$ 3 400 (CONH) and 1 660 cm^{-1} (CO); τ [$CDCl_3$–$(CD_3)_2CO$] −0.92 (1 H, bs, NH), 1.71 (1 H, bs, NOH), 2.22 (1 H, bs, 6-H), 2.40 (1 H, s, C*H*=NOH), 2.92 and 3.02 (2 H, AB system with broadening of the B portion, J_{AB} 8 Hz, 3-H and 4-H), and 7.66 and 7.74 (6 H, 2 × s, 2 × Me).

4,7-Dimethylisatin (26).—2′,5′-Dimethylhydroxyiminoacetanilide (25) (78.7 g) was added portionwise to a stirred mixture of sulphuric acid (400 g, 96%) and water (44 g) during 45 min. During the addition the temperature was kept between 60 and 65 °C. The mixture was heated to 75 °C for 10 min and then poured onto ice (2 kg). The red product was filtered off, washed with ice-cold water, and dried to give 4,7-dimethylisatin (26) (51.5 g, 72%), m.p. 265—270 °C (lit.,[11] m.p. 260—264 °C) [Found: *M* (mass spec.), 175. Calc. for $C_{10}H_9NO_2$: *M*, 175], $\nu_{max.}$ 3 500 (NH) and 1 630 cm^{-1} (CO); τ [$(CD_3)_2CO$–$(CD_3)_2SO$] −0.92 (1 H, bs, NH), 2.76 and 3.24 (2 H, AB system, J_{AB} 8 Hz, 5-H and 6-H), and 7.56 and 7.80 (6 H, 2 × s, 2 × Me).

2-Amino-3,6-dimethylbenzoic Acid (16).[11]—Hydrogen peroxide (10%) was added dropwise to a stirred suspension of 4,7-dimethylisatin (26) (48 g) in aqueous sodium hydroxide (200 g, 10%) until an acidified test sample no longer gave red spots of the isatin. The temperature was maintained between 85 and 90 °C during the addition. The solution was treated with charcoal, filtered, and acidified with 3N-hydrochloric acid until the pH was 3.6—3.7. A crystalline product was obtained which was collected and identified as 2-amino-3,6-dimethylbenzoic acid (16) (23.0 g, 51%), m.p. 118—122 °C (lit.,[11] m.p. 108—118 °C) [Found: *M* (mass spec.), 165. Calc. for $C_9H_{11}NO_2$: *M*, 165], $\nu_{max.}$ 3 400 (NH_2) and 1 670 cm^{-1} (CO).

2-Mercapto-3,6-dimethylbenzoic Acid (21).—2-Amino-3,6-dimethylbenzoic acid (16) (16.5 g) was converted by adaptation of a literature procedure [8] into 2-mercapto-3,6-dimethylbenzoic acid (21) (1.25 g, 7%) [Found: *M* (mass spec.), 182. Calc. for $C_9H_{10}O_2S$: *M*, 182], $\nu_{max.}$ 2 550 (SH) and 1 700 cm^{-1} (CO).

Di-3,6-dimethylthiosalicylide (6) *and Tri-3,6-dimethylthiosalicylide* (11).—2-Mercapto-3,6-dimethylbenzoic acid (21) (2.4 g) and phosphoric anhydride (8 g) were heated under reflux in dry toluene (35 ml) for 5.5 h. After cooling, the solid material was collected and extracted with hot chloroform. The toluene mother liquors and the chloroform solution were then combined, washed with aqueous sodium hydrogencarbonate solution (5%), dried, and evaporated under reduced pressure to afford a residue. This was examined by t.l.c. on silica gel using chloroform–cyclohexane (10 : 1) as the eluant. Two components were identified. The faster-moving component was separated by preparative t.l.c. on silica gel and recrystallised from methanol to give *di-3,6-dimethylthiosalicylide* (6) (350 mg, 31%), m.p. 235 °C [Found: C, 65.7; H, 5.3; S, 19.5%; *M* (mass spec.), 328. $C_{18}H_{14}O_2S_2$ requires C, 65.4; H, 5.4; S, 19.4%; *M*, 328], τ ($CDCl_3$) 3.04 (4 H, s, ArH) and 7.68 and 7.76 (12 H, 2 × s, 2 × Me, and 2 × Me). The slower-moving component was separated by preparative t.l.c. on silica gel and recrystallised from methanol to give *tri-3,6-dimethylthiosalicylide* (11) (75 mg, 7%), m.p. >300 °C [Found: *M* (mass spec.), 492. $C_{27}H_{24}O_3S_3$ requires *M*, 492], τ ($CDCl_3$) 2.54—2.84 (6 H, m, ArH) and 7.38—7.64 (18 H, 6 × s, 6 × Me).

Thymotic Acid Methyl Ester (27).—Thymotic acid [13] was dissolved in ether and an equivalent amount of diazomethane in ethereal solution was added. After a short time at room temperature, the ethereal solution was washed with 10% sodium carbonate solution and then with 10% sodium hydroxide solution. The ethereal solution was concentrated to a residual oil which was distilled to give the *methyl ester* (27), b.p. 162—166 °C at 1.0 mmHg, τ ($CDCl_3$) −1.6 (1 H, bs, OH), 2.82 and 3.39 (2 H, AB system, J_{AB} 8 Hz, ArH), 6.12 (3 H, s, CO_2Me), 6.66 (1 H, m, *J* 7 Hz, C*H*Me_2), 7.54 (3 H, s, Ar*Me*), and 8.80 (3 H, d, *J* 7 Hz, CH*Me*$_2$).

O-Aryl Dimethylthiocarbamate (28) *of Thymotic Acid Methyl Ester* (27).—Sodium hydride (1.2 mol) was added slowly at 0 °C to a 5% solution of the methyl ester (27) in *N,N*-dimethylformamide. A 20% solution of dimethylthiocarbamoyl chloride (1.2 mol) in *N,N*-dimethylformamide was then added and the reaction mixture was warmed to 50 °C before being allowed to stand overnight at room temperature. After careful addition of water, the reaction mixture was extracted with ether. The ethereal solution was washed in turn with water, 40% sodium hydroxide solution, 5% hydrochloric acid, and finally with water again. The ethereal solution was concentrated to a residue which was extracted several times with boiling light petroleum (b.p. 60—80 °C). Whilst still warm the extracts were chromatographed on a column of alumina. The product which eluted crystallised as prisms from the solvent and was characterised as the *O-aryl dimethylthiocarbamate* (28), m.p. 49 °C [Found: *M* (mass spec.), 295.1244. $C_{15}H_{21}NO_3S$ requires 295.1241], τ (C_5H_5N) 6.19 (3 H, s, CO_2Me), 6.63 and 6.73 (6 H, 2 × s, NMe_2), 6.80 (1 H, m, *J* 7 Hz, C*H*Me_2), 7.65 (3 H, s, Ar*Me*), and 8.70 and 8.85 (6 H, 2 × d, *J* 7 Hz, CH*Me*$_2$). At room temper-

ature, torsion around the C–N and Ar–O bonds is slow on the ^{1}H n.m.r. time scale. On raising the temperature of the pyridine solution to +110 °C, the two singlets for the NMe_2 function coalesce to one singlet at τ 6.69 and the two doublets for the isopropyl methyl groups coalesce to one doublet (J 7 Hz) centred upon τ 8.80.

S-Aryl Dimethylthiocarbamate (29) *of Thiothymotic Acid Methyl Ester* (30).—The *O*-aryl dimethylthiocarbamate (28) (10 g) in a 50-ml round bottomed flask purged with nitrogen was immersed in a metal bath at 320—340 °C for 2 min, during which time vigorous refluxing of the contents occurred. After cooling the contents of the flask were dissolved in a small amount of benzene–light petroleum (b.p. 60—80 °C) and subjected to column chromatography on alumina (200 g) with ether–light petroleum as eluant. The S-*aryl dimethylthiocarbamate* (29) was eluted as an oil just after unconverted starting material. The oil eventually solidified when allowed to stand in light petroleum to give a solid, m.p. 40—45 °C [Found: M (mass spec.), 295.1245. $C_{15}H_{21}NO_3S$ requires 295.1241], τ ($CDCl_3$) 2.55—2.91 (2 H, m, ArH), 6.16 (3 H, s, CO_2Me), 6.53 (1 H, m, J 7 Hz, C*H*Me_2), 7.01 (6 H, s, NMe_2), 7.75 (3 H, s, Ar*Me*), and 8.80 (6 H, d, J 7 Hz, CH*Me*$_2$). When the solution was cooled down to *ca.* −50 °C, the singlet for the NMe_2 function separated into two singlets while the doublet for the isopropyl methyl groups became progressively broader.

Thiothymotic Acid (31) *and its Methyl Ester* (30).—The *S*-aryl dimethylthiocarbamate (29) (10 g) was heated under reflux for 10 h in a mixture of methanol (150 ml) and concentrated hydrochloric acid (50 ml). After cooling and dilution of the reaction mixture with water, it was extracted with chloroform. The chloroform solution was concentrated to give an oil which was subjected to column chromatography on silica gel with benzene as eluant. One fraction crystallised from light petroleum (b.p. 60—80 °C) and was characterised as the *methyl ester* (30), m.p. 90 °C [Found: M (mass spec.), 224.0862. $C_{12}H_{16}O_2S$ requires 224.0867], τ ($CDCl_3$) 2.72 and 2.92 (2 H, AB system, J_{AB} 8 Hz, ArH), 6.22 (3 H, s, CO_2Me), 6.55 (1 H, m, J 7 Hz, C*H*Me_2), 7.64 (3 H, s, Ar*Me*), and 8.77 (3 H, d, J 7 Hz, CH*Me*$_2$). The other fraction crystallised from ethyl acetate–cyclohexane. The crystals sublimed above 200 °C. This compound was characterised as *thiothymotic acid* (31), τ ($CDCl_3$–D_2O) 2.60—2.96 (2 H, m, ArH), 6.20 (1 H, m, J 7 Hz, C*H*Me_2), 7.66 (3 H, s, Ar*Me*), and 8.77 (6 H, d, J 7 Hz, CH*Me*$_2$).

Di-o-thiothymotide (7).—Thiothymotic acid (31) (2.5 g) and phosphoric anhydride (10.3 g) were heated under reflux in dry toluene (45 ml) for 4 h. After cooling, the toluene solution was separated from the solid cake which formed on the surface of the reaction mixture. The solid product was triturated with hot chloroform. The toluene and chloroform solutions were not combined because t.l.c. examination indicated the presence of more products in the latter than in the former. After independent evaporation of the solvents, separate recrystallisation of the solid residues from methanol gave *di-o-thiothymotide* (7) (0.28 g, 12%) as colourless needles, m.p. 203 °C [Found: C, 68.8; H, 6.47; S, 16.8%; M (mass spec.), 384.1222. $C_{22}H_{24}O_2S_2$ requires C, 68.8; H, 6.25; S, 16.7%; M, 384.1218], τ ($CDCl_3$) 2.97 (4 H, s, ArH), 6.48 (2 H, m, J 7 Hz, C*H*Me_2), 7.76 (6 H, s, 2 × Ar*Me*), and 8.89 and 8.96 (12 H, 2 × d, J 7 Hz, 2 × CH*Me*$_2$).

Determination of Rates of Conformational Changes by Dynamic ^{1}H *N.m.r. Spectroscopy*.—The methods used are fully described in Parts 6 [18] and 9.[1] The computer programs (coded in FORTRAN IV) used to generate the theoretical line shapes are now described for the general methods I—III.

Method I. A program (IV) † for exchange of nuclei between three equally populated sites, A, B, and C, with no mutual coupling. The constitutionally homotopic aryl methyl groups of the tri-3-methyl- (8) and tri-6-methyl- (10) thiosalicylides both gave three singlet signals of equal

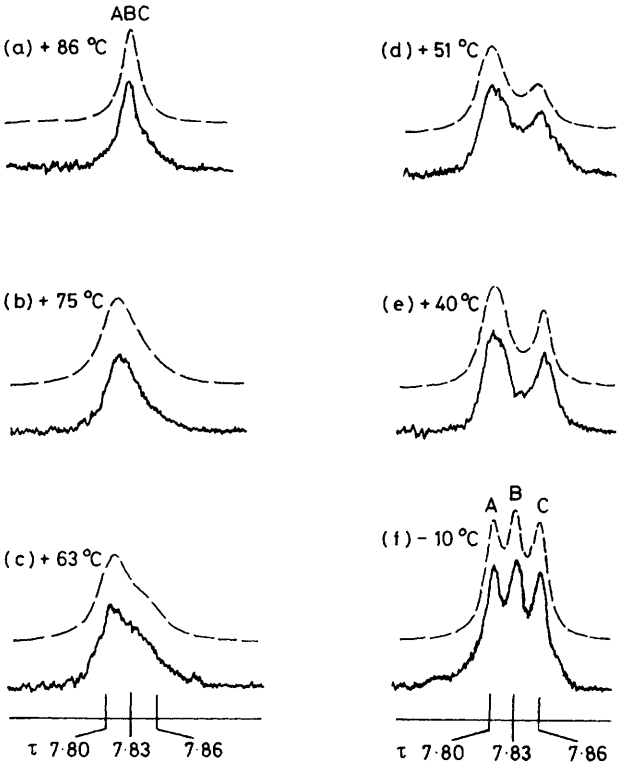


FIGURE 1 Observed (full line) and computed (broken line) spectra of the aryl methyl protons of tri-3-methylthiosalicylide (8) using program IV for exchange of protons between three equally populated sites A, B, and C (the input values for all the rate constants, k_{AB} *etc.* were the same and so they will be referred to collectively as k): (a) at +86 °C, k 118 s^{-1}; (b) at +75 °C, k 20.6 s^{-1}; (c) at +63 °C, k 14.3 s^{-1}; (d) at +51 °C, k 4.8 s^{-1}; (e) at +40 °C, k 3.1 s^{-1}; (f) at −10 °C, k 1.2 s^{-1}

intensities at low temperatures which coalesced to one singlet at higher temperatures. The spectral line shapes were simulated using program IV. Clearly, the aryl methyl groups in these two derivatives are behaving as diastereotopic probes at low temperatures on the ^{1}H n.m.r. time scale. Calculated and observed spectra are shown in Figures 1 and 2 for compounds (8) and (10), respectively. In the case of tri-5-methylthiosalicylide (9), the constitutionally homotopic aryl methyl groups gave two singlet signals with a ratio of intensities of 2 : 1 at low temperatures which coalesced to one singlet at higher temperatures. Obviously, the three aryl methyl groups in this derivative are also diastereotopic at low temperatures on the ^{1}H n.m.r. time scale despite the fact that two of the three signals exhibit isochronous be-

† The program numbers (*viz.* IV and VII) established in Parts 6 [18] and 9 [1] will be adhered to in this paper; these programs will form the basis of a collection for reference in future Parts of this series.

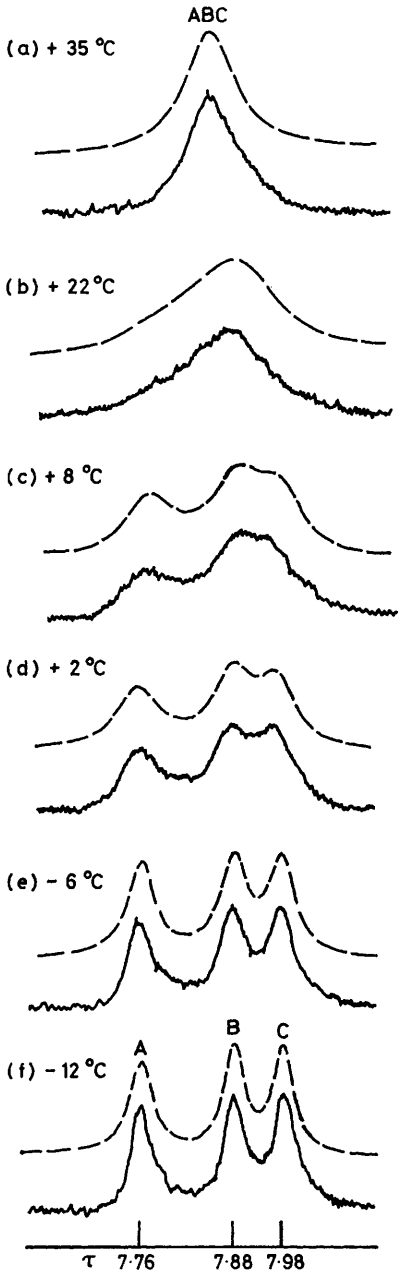


FIGURE 2 Observed (full line) and computed (broken line) spectra of the aryl methyl protons of tri-6-methylthiosalicylide (10) using program IV for exchange of protons between three equally populated sites A, B, and C (the input values for all the rate constants, k_{AB} *etc.* were the same and so they will be referred to collectively as k): (a) at +35 °C, k 127 s^{-1}; (b) at +22 °C, k 42.4 s^{-1}; (c) at +8 °C, k 12.8 s^{-1}; (d) at +2 °C, k 5.3 s^{-1}; (e) at −6 °C, k 1.4 s^{-1}; (f) at −12 °C, k 1.2 s^{-1}

haviour. By allowing superimposition of sites A and B at low temperatures, the spectral line shapes of compound (9) were simulated using this three site program as shown in Figure 3 by the calculated and observed spectra.

Method II. The tri-3,6-dimethylthiosalicylide (11) exhibited two sets (1 and 2) of three singlet signals (A, B, and C) of equal intensities for the two diastereotopic sets of three constitutionally heterotopic aryl methyl groups at room temperature which coalesced to give two broad signals of equal intensities at high temperatures. The spectral line shapes arising from the two exchange processes involving sites A1, B1, and C1, and A2, B2, and C2 were simulated by

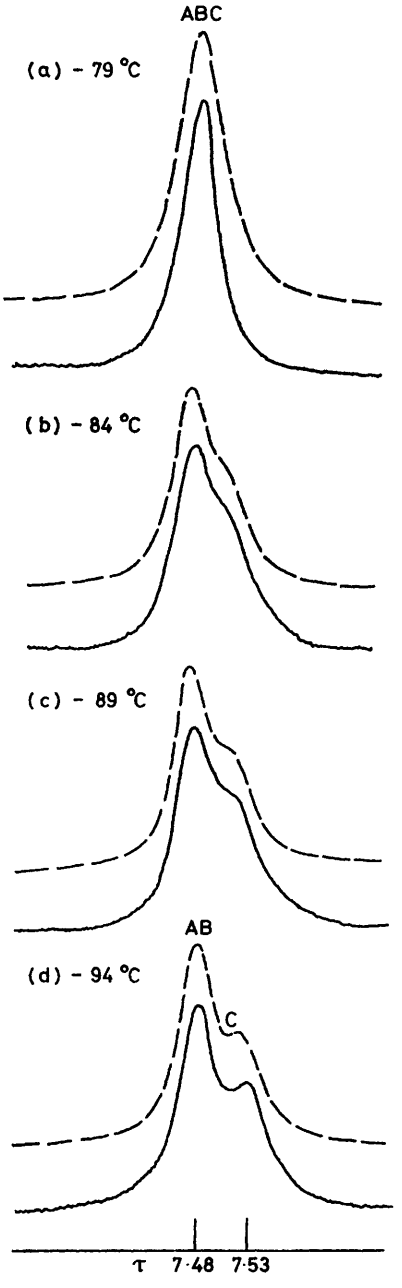


FIGURE 3 Observed (full line) and computed (broken line) spectra of the aryl methyl protons of tri-5-methylthiosalicylide (9) using program IV for exchange of protons between three equally populated sites A, B, and C (the input values for all the rate constants, k_{AB} *etc.* were the same and so they will be referred to collectively as k): (a) at −79 °C, k 8.6 s^{-1}; (b) at −84 °C, k 3.5 s^{-1}; (c) at −89 °C, k 2.0 s^{-1}; (d) at −94 °C, k 0.5 s^{-1}

carrying out two independent computations with program IV on the two sets of signals and obtaining the total line shapes by summation. The calculated and observed spectra for compound (11) are shown in Figure 4.

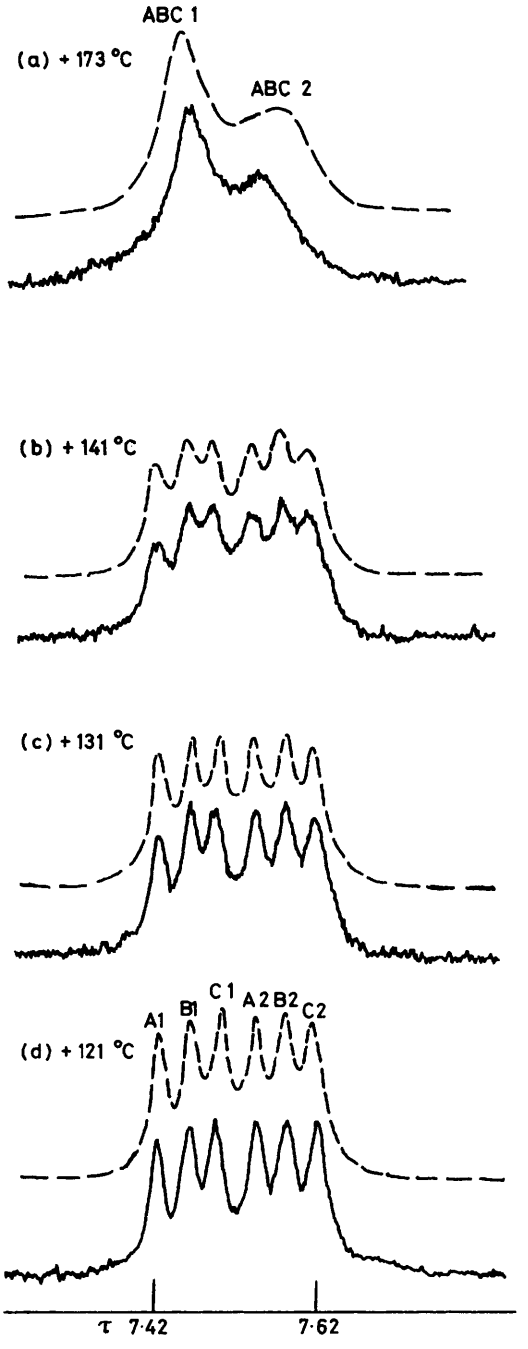


FIGURE 4 Observed (full line) and computed (broken line) spectra of the aryl methyl protons of tri-3,6-dimethylthiosalicylide (11) using program IV for exchange of protons between two pairs of three equally populated sites A1, B1, and C1, and A2, B2, and C2 (the input values for all the rate constants k_{A1B1}, k_{B2B2} *etc.* were the same and so they will be referred to collectively as k): (a) at +173 °C, k 14.3 s^{-1}; (b) at +141 °C, k 1.55 s^{-1}; (c) at +131 °C, k 0.75 s^{-1}; (d) at +121 °C, k 0.43 s^{-1}

Method III. A program (VII) † for exchange of nuclei (which are coupled to an independent but common nucleus) between two equally populated sites A/A′ and B/B′ with no mutual coupling. The constitutionally homotopic isopropyl groups of di-*o*-thiothymotide (7) gave two overlapping doublets of equal intensities at low temperatures which coalesced to one doublet at high temperatures. Clearly, the prochiral methyl groups within the two isopropyl groups are behaving as diastereotopic probes at room temperature on the ^{1}H n.m.r. time scale. Thus, spectral line shapes could be simulated using this program. Calculated and observed spectra are shown in Figure 5.

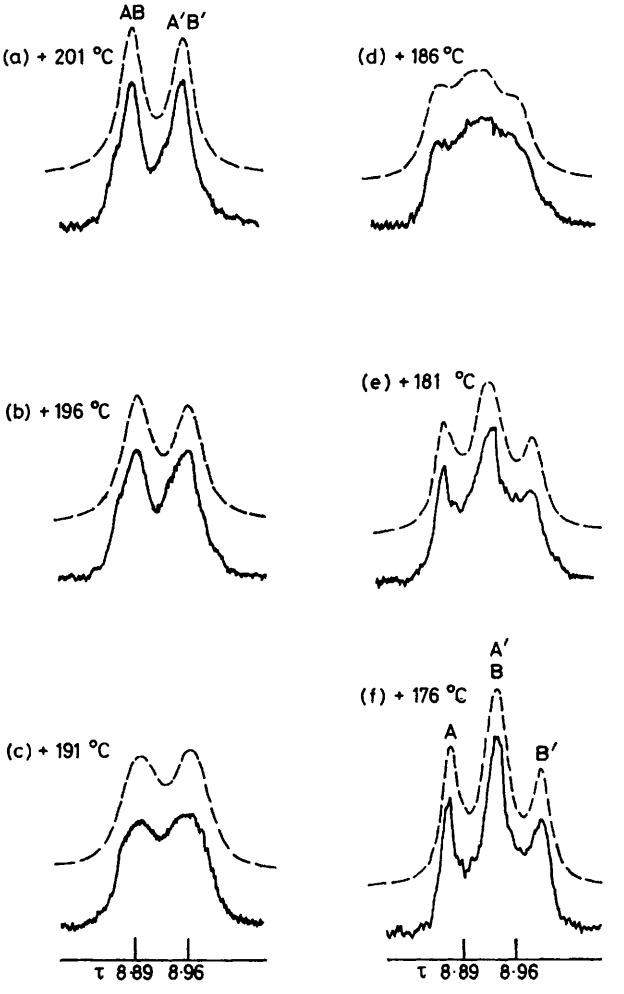


FIGURE 5 Observed (full line) and computed (broken line) spectra of the isopropyl methyl groups of di-*o*-thiothymotide (7) using program VII for exchange of protons (which are coupled to another common proton) between two equally populated sites A/A′ and B/B′ (a) at +201 °C, k_{AB} 59.7 s^{-1}; (b) at +196 °C, k_{AB} 41.5 s^{-1}; (c) at +191 °C, k_{AB} 28.8 s^{-1}; (d) at +186 °C, k_{AB} 17.9 s^{-1}; (e) at +181 °C, k_{AB} 10.4 s^{-1}; (f) at 176 °C, k_{AB} 7.24 s^{-1}

RESULTS AND DISCUSSION

The temperature-dependent ^{1}H n.m.r. spectra and the conformational properties of trithiosalicylide (2) and its derivatives (8)—(11) are presented first, and then the discussion of the corresponding results for di-*o*-thiothymotide (7) follows.

The Temperature-dependent ^{1}H *N.m.r. Spectra and the Conformational Properties of Trithiosalicylide* (2) *and its* 3- (8), 5- (9), *and* 6- (10) *Methyl, and* 3,6-*Dimethyl* (11)

† See footnote on page 1641.

Derivatives.—An attempt to investigate the conformational behaviour of trithiosalicylide (2) by dynamic ^{1}H n.m.r. spectroscopy in a range of solvents including dideuteriodichloromethane and trifluoroacetic acid was thwarted by the poor solubility of (2) particularly at temperatures below 0 °C. In the knowledge that the incorporation of aryl methyl substituents (i) usually leads to better solubilities amongst the trisalicylide derivatives [1,4] and (ii) has no significant influence upon the conformational behaviour of the twelve-membered rings provided [4] the substituents do not occupy *ortho*-positions on the aromatic rings, we turned our attention to a variable-temperature ^{1}H n.m.r. spectroscopic study (see Figure 3) in carbon disulphide–deuteriochloroform (1 : 1) on tri-5-methylthiosalicylide (9) as a suitable model compound for (2) since it lacks methyl substituents in the *ortho*-positions (*i.e.* on C-3 and C-6) of the aromatic rings. One singlet signal was observed at τ 7.56 for the aryl methyl protons at room temperature. However, in the temperature range of −79 °C down to −94 °C, initial broadening of the signal occurred and eventually it separated out into two singlets at τ 7.48 and 7.53 with relative intensities of 2 : 1.

The incorporation of alkyl substituents into the *ortho*-positions of the aromatic rings in derivatives of trisalicylides and 5,6,11,12,17,18-hexahydro[*a*,*e*,*i*]cyclododecene leads [1,4,18] to appreciable increases in the energy barriers to conformational inversions † and interconversions.† Consequently, we decided to appeal to this effect in the trithiosalicylide series in the hope that it would help to resolve the matter of their conformational behaviour in solution with more certainty. There was also the prospect of being able to raise the energy barriers to conformational changes sufficiently to permit *isolation* of conformational isomers amongst the more highly substituted derivatives, *e.g.* tri-*o*-thiothymotide (34), and perhaps observe spontaneous resolution on crystallisation. With these objectives in mind, three derivatives [*viz.* (8), (10), and (11)] of (2) were subjected to detailed investigations by dynamic ^{1}H n.m.r. spectroscopy. The results, which are manifest in the temperature dependences of the signals for the aryl methyl groups are summarized in Figures 1, 2, and 4 for compounds (8), (10), and (11), respectively. In the case of the 3-methyl derivative (8), three equal intensity singlet signals were observed (see Figure 1) at τ 7.80, 7.83, and 7.86 in pentadeuteriopyridine at −10 °C. On raising the temperature to +86 °C, these signals gradually coalesced to give one broad signal. A rather similar situation in qualitative terms at least was observed (see Figure 2) for the 6-methyl derivative (10) in nitrobenzene. Three equally intense singlets resonating at τ 7.76, 7.88, and 7.98 at −12 °C coalesced to one broad singlet as the temperature was raised to +35 °C. Not surprisingly, in view of these spectroscopic results for compounds (8) and (10), the partial ^{1}H n.m.r. spectrum of tri-3,6-dimethylthiosalicylide (11) at room temperature in deuteriochloroform consisted of six singlets of equal intensities between τ 7.38 and 7.64 for the aryl methyl groups. This spectrum remained essentially unchanged when the solution was heated up to +55 °C. Eventually, temperature dependence was observed (see Figure 4) for the aryl methyl groups in the range +121 to +173 °C. The six singlets which were still clearly resolved at +121 °C coalesced to give two broad singlets at +173 °C. Line-shape analyses of the spectra recorded in Figures 1—4 gave the free energies of activation listed in the Table for the conformational changes occurring in compounds (8)—(11).

There is no experimental evidence for the population of more than *one* type of ground-state conformation in solution. The fact that the constitutionally homotopic aryl methyl groups in compounds (8)—(11) become anisochronous at low temperatures indicates that this conformation is asymmetric and is, therefore, associated with diastereotopic aryl methyl groups. Acceptance of the requirement for ground-state conformations with C_1 symmetry and inspection of both framework and space-filling molecular models suggest that the molecules (8)—

TABLE

Thermodynamic parameters associated with conformational changes in the trithiosalicylide (8)—(11) and trisalicylide (37)—(39) derivatives

Compound	Solvent	Propeller (%)	Helix (%)	$\Delta G^{\ddagger}$/kcal mol^{-1}	Process
Tri-5-methylthiosalicylide (9)	CD_2Cl_2–CS_2 (1 : 1)	0	100	10.4 ± 0.1 [e]	H ⇌ H*
Tri-6-methylthiosalicylide (10)	C_5D_5N	0	100	15.1 ± 0.2 [e]	H ⇌ H*
Tri-3-methylthiosalicylide (8)	C_5D_5N	0	100	17.9 ± 0.4 [e]	H ⇌ H*
Tri-3,6-dimethylthiosalicylide (11)	$C_6H_5NO_2$	0	100	24.0 ± 0.1 [e]	H ⇌ H*
Tri-*m*-cresotide [a] (38)	$CDCl_3$–CS_2 (1 : 1)			< 10	P → H
				< 10	H → P
				< 10	H ⇌ H*
Tri-*o*-cresotide [a] (37)	CD_2Cl_2–CS_2	90 [c]	10 [c]	13.8 ± 0.1 [e]	P → H
				13.3 ± 0.1 [e]	H → P
				< 10	H ⇌ H*
Tri-3,6-dimethylsalicylide [b] (39)	$CDCl_3$	67 [f]	33 [d]	18.0 ± 0.5 (60 °C)	P → H
				14.3 ± 0.5 (−10 °C)	H ⇌ H*

[a] From ref. 1. [b] From ref. 4. [c] At −38 °C. [d] At −10 °C. [e] Determined by ^{1}H n.m.r. line-shape methods. [f] These values are approximate and are based upon the coalescence temperatures only.

† We find it convenient to refer to pseudorotational processes (i) connecting enantiomers as *inversions* and (ii) connecting diastereoisomers as *interconversions*.

(11) all adopt enantiomeric helical † conformations (35a and b) in which the three thioester groups all assume *trans*-geometries and are oriented relative to each other such that one sulphur atom is pointing towards the opposite face of the twelve-membered ring from the other two sulphur atoms. Additional support for these conformational assignments comes from the *X*-ray crystal

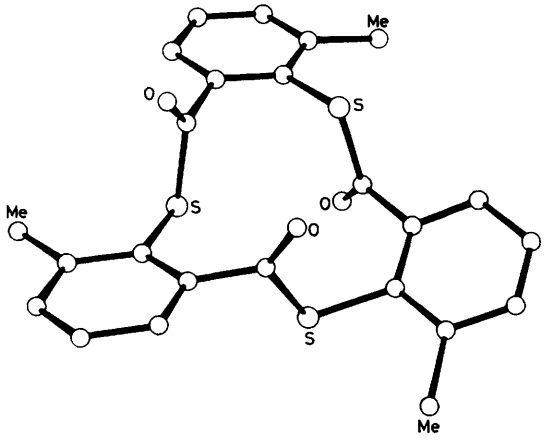


FIGURE 6 The structure of tri-3-methylthiosalicylide (8) in the solid state [20]

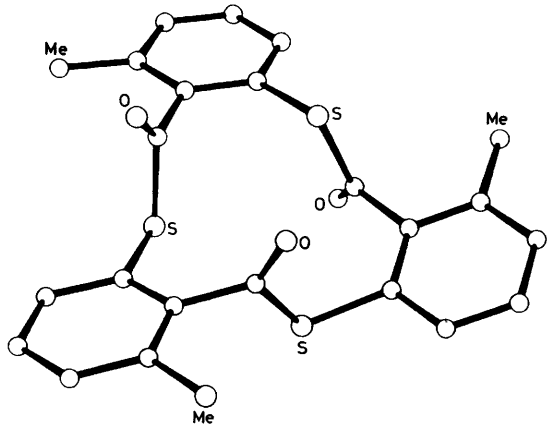
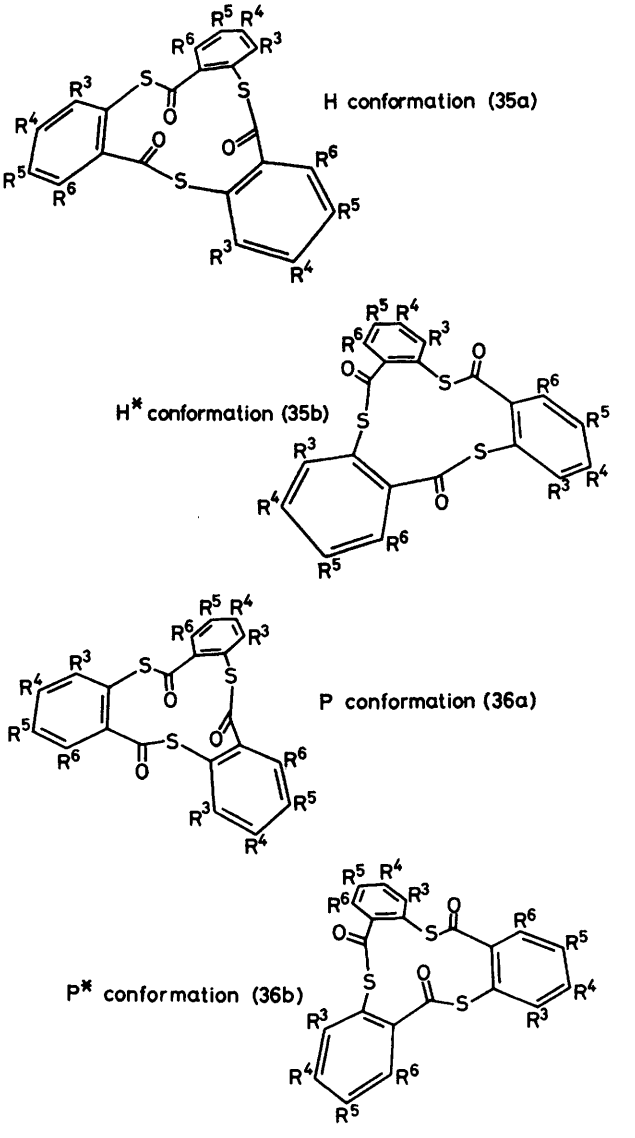


FIGURE 7 The structure of tri-6-methylthiosalicylide (10) in the solid state [20]

structures (see Figures 6 and 7, respectively) of the tri-3- (8) and tri-6- (10) methylthiosalicylides ‡ which reveal [20] that conformations of the helical type are also adopted in the solid state. It would appear that the main reason why the propeller † conformations (36a and b) are not populated as ground state conformations in the trithiosalicylide series, whereas they are populated significantly in the trisalicylide series,[1,4] is the relatively greater destabilising nonbonded interactions that result when three sulphur atoms are oriented towards the same face of the



twelve-membered ring. The van der Waals radii of oxygen and sulphur are 1.65 and 2.00 Å, respectively. In this regard it is significant that 6*H*,12*H*,18*H*-tribenzo[*b*,*f*,*j*][1,5,9]-trithiacyclododecin, which crystallises [22] in a helical conformation, also adopts [23] this conformation exclusively in solution. It follows that the free energies of activation recorded in the Table for conformational changes can be equated with a ring inversion process (35a ⇌ 35b) between enantiomeric helical conformations, denoted by H and H*. The site exchanges between sites A, B, and C involving three diastereotopic methyl groups of the H and H* conformations (35a and b) can only be fully understood by reference to Figures 8 and 9. The designations R_A, R_B, and R_C in Figure 8 of

† The definition of the conformational descriptors 'helical' and 'propeller' is discussed at some length in Part 9 [1] of this series.

‡ Crystals of tri-3-methylthiosalicylide (8) belong to a space group [$P2_1/c$ (No. 14)] containing equal numbers of enantiomeric molecules. Thus, this compound (8) exists as a racemic modification in the solid state. Tri-6-methylthiosalicylide (10) crystallises in the orthorhombic space group $P2_12_12_1$ which can only contain molecules of one chirality. Thus, this compound (10) exhibits spontaneous resolution, *cf.* tri-*o*-thymotide,[21] on crystallisation.

the three diastereotopic methyl groups of the helical conformations (35a and b) in compounds (8)—(10) do not reflect the relative chemical shifts of their protons. Assignments are also arbitrary in the association (see Figure 4) of sites A1, B1, and C1 and A2, B2, and C2 with the two diastereotopic sets of constitutionally groups are indicated as being oriented above (●) or below (○) the mean plane. Inspection of space-filling molecular models reveals that the trithiosalicylides cannot under go pedalling [1,18,23] of the *trans*-thioester linkages after the manner proposed [4,23] for the *trans*-ester linkages in the corresponding trisalicylides by reason of the greater

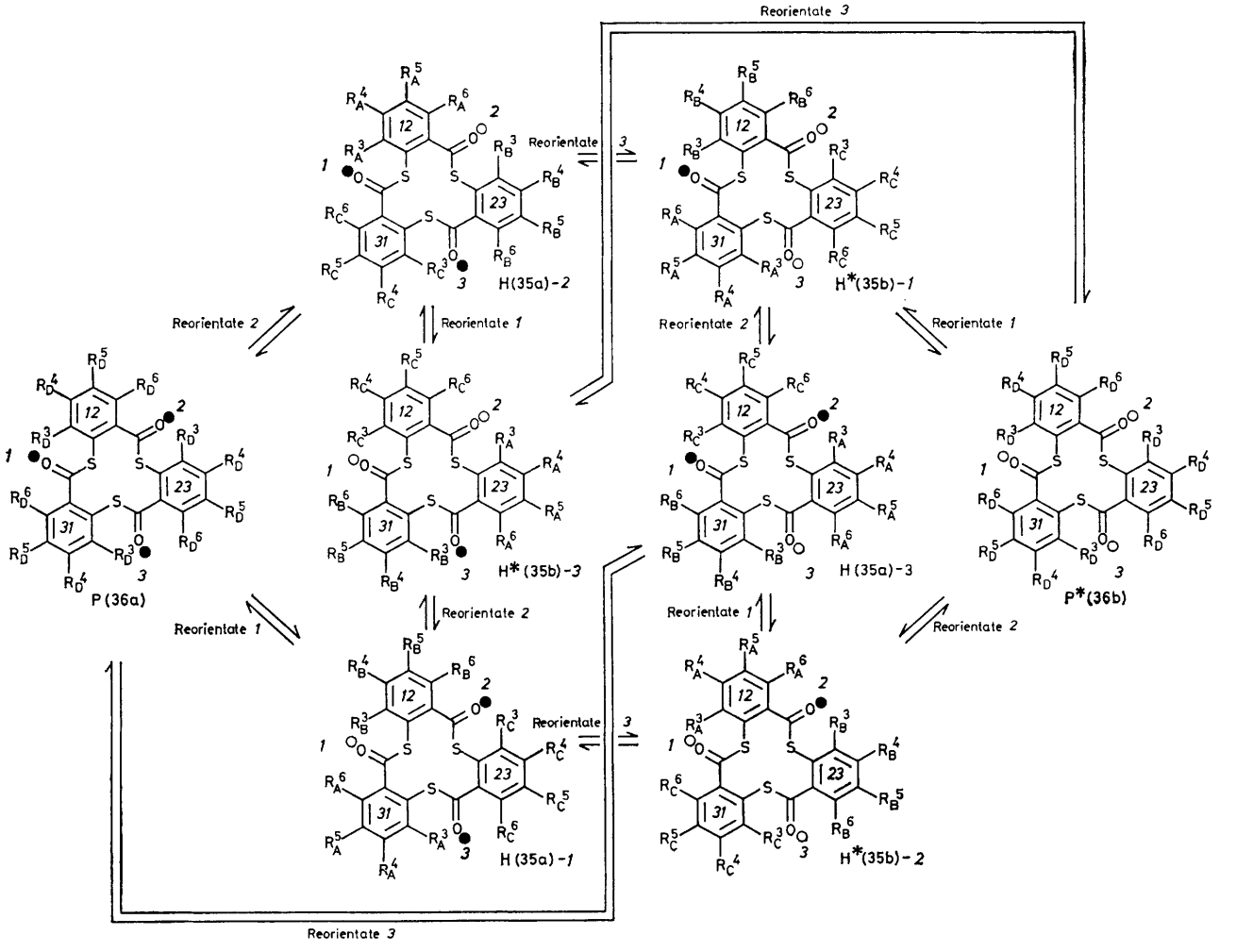


FIGURE 8 Conformational itinerary and site-exchange scheme for different nuclei and groups of nuclei involving the H (35a), H* (35b), P (36a), and P* (36b) conformations of compounds (8; R^3 = Me, R^4 = R^5 = R^6 = H), (9; R^3 = R^4 = R^6 = H, R^5 = Me), (10; R^3 = R^4 = R^5 = H, R^6 = Me), and (11; R^3 = R^6 = Me, R^4 = R^5 = H): ● = a carbonyl group above the mean plane of the ring and ○ = a carbonyl group below the mean plane of the ring

heterotopic methyl groups in compound (11). Despite the fact that the propeller conformations (36a and b) denoted by P and P* are not detectable for compounds (8)—(11) by ^{1}H n.m.r. spectroscopy at low temperatures, they can be implicated as intermediates in the site exchange processes involving the helical conformations (35a and b). The site which would be occupied by the homotopic aryl methyl groups of the propeller conformations (36a and b) is designated as D in Figures 8 and 9. In Figure 8, the conformations are drawn such that the me an plane of the twelve-membered ring lies in the plane of the paper and the carbonyl steric demands of sulphur atoms compared with oxygen atoms. Consequently, reorientations must proceed *via* intermediates where one of the three thioester units assumes a *cis*-geometry. This kind of reorientation mechanism entails the sequential passage of the carbonyl group and the sulphur atom (or *vice versa*) of the thioester unit through the mean plane of the twelve-membered ring such that the carbonyl oxygen atom and the sulphur atom remain oriented away from the centre of the macrocyclic ring. The complete site exchange scheme for R_A, R_B, R_C, and R_D is shown in Figure 8 and is summarized by the cubic array diagram in Figure 9. Figures 8 and

9 show that the H ⇌ H* inversion process is associated with a first-order rate constant k which, in turn, is related to the rate constants for the aryl methyl group exchanges [$R_A \longrightarrow R_B$, $R_A \longrightarrow R_C$, $R_B \longrightarrow R_A$, $R_B \longrightarrow R_C$, $R_C \longrightarrow R_A$, $R_C \longrightarrow R_B$]. Thus, the rate constants

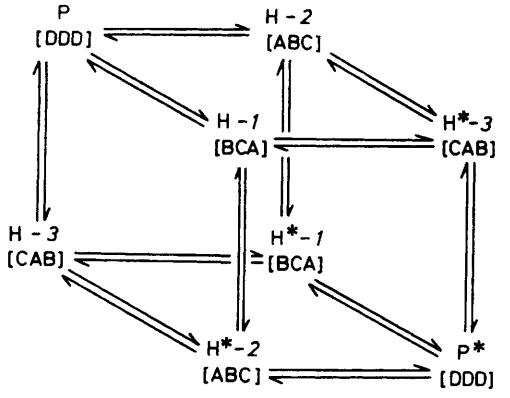
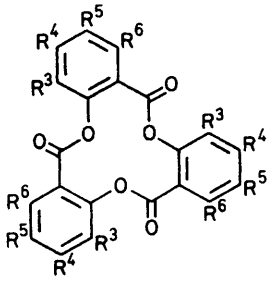


FIGURE 9 Cubic array diagram showing the site exchanges for different nuclei and groups of nuclei involving H (35a), H* (35b), P (36a), and P* (36b) conformations of compounds (8)—(11). The sites indicated in square brackets read from left to right corresponding to the nuclei associated with the aromatic rings *12*, *23*, and *31* in the formulae in Figure 8. [The aromatic rings are given the descriptors *12*, *23*, and *31* according as to whether they lie between thioester linkages *1* and *2*, *2* and *3*, or *3* and *1*]

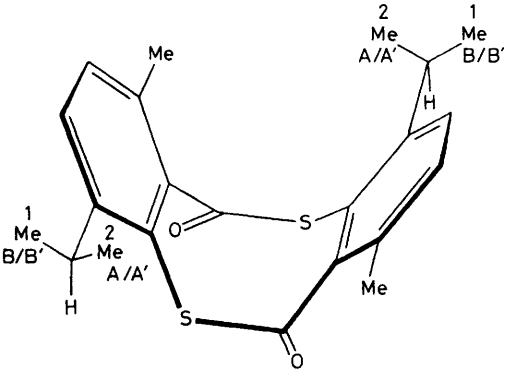
for H ⇌ H* ring inversion at different temperatures were determined (see Figures 1—4) by comparing experimental ^{1}H n.m.r. spectra for the aryl methyl groups in compounds (8)—(11) with theoretical spectra generated by the line-shape procedure described in methods I and II (see Experimental section). Values for the free energies of activation for the H ⇌ H* ring inversion process were determined at various temperatures. The



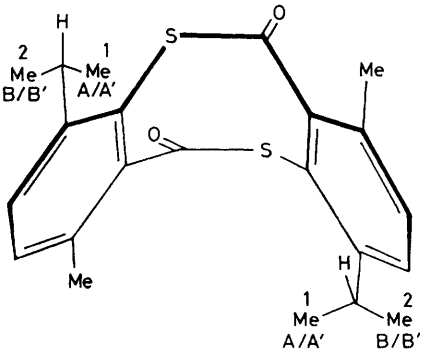
(37) R^3 = Me; R^4 = R^5 = R^6 = H
(38) R^3 = R^5 = R^6 = H; R^4 = Me
(39) R^3 = R^6 = Me; R^4 = R^5 = H

Table records the average values for $\Delta G^{\ddagger}$ (H ⇌ H*) in compounds (8)—(11) and compares them with the values in the literature for tri-*m*- (38) and tri-*o*- (37) cresotides [1] and tri-3,6-dimethylsalicylide (39).[4] The $\Delta G^{\ddagger}$ values are higher by *ca.* 10 kcal mol^{-1} for the trithiosalicylides than for the corresponding trisalicylides. In addition to steric strain—mainly angle strain in the twelve-membered ring and nonbonded interactions involving the aryl methyl groups—a ring-inversion mechanism for the trithiosalicylides implicating intermediates with *cis*-thioester linkages means that resonance stabilisation is lost within this thioester linkage at the associated transition states between *trans*- and *cis*-geometries. The rate-determining transition state is probably the one in which the carbonyl group passes through the mean plane of the ring during interconversion between a *trans*- and a *cis*-thioester linkage. This conclusion is based upon an examination of space-filling molecular models which also suggests that the nonbonded interaction of the carbonyl oxygen atom in this transition state with a 3-methyl group should be greater than that with a 6-methyl group. This prediction is in accordance with the higher (by 2.8 kcal mol^{-1}) $\Delta G^{\ddagger}$ value for tri-3-methylthiosalicylide (8) compared with that for the tri-6-methylthiosalicylide (10). Finally, it is interesting to note that the predicted free energy of activation for H ⇌ H* ring inversion in tri-3,6-dimethylthiosalicylide (11) of 22.6 kcal mol^{-1} based upon application of the additivity principle (*i.e.* 10.4 + 4.7 + 7.5 = 22.6) to compounds (8)—(10) is 1.6 kcal mol^{-1} less than the experimentally determined value of 24.0 kcal mol^{-1}. Clearly, the rate-determining transition state to H ⇌ H* ring inversion in compound (11) comprises destabilising interactions involving the 3- and 6-methyl groups of mutual—albeit small—significance!

The Temperature-dependent ^{1}H *N.m.r. Spectra and Conformational Properties of Di-o-thiothymotide* (7).—Of

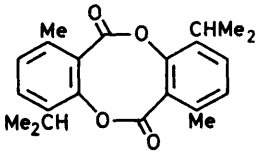


B conformation (40a)



B* conformation (40b)

the dithiosalicylides (1) and (3)—(7) available for stereo chemical investigation, only di-*o*-thiothymotide (7) carries suitable ^{1}H n.m.r. probes in the form of the two prochiral methyl groups in the two isopropyl functions for examination of the expected [1,24] ring-inversion process between enantiomeric boat conformations (40a and b) denoted by B and B*. The ^{1}H n.m.r. of (7) in deuteriochloroform exhibits two sharp doublets for the isopropyl methyl groups



(41)

which remain unchanged when the solution is heated up to +60 °C. In the event, a very high boiling solvent (nitrobenzene) was necessary in order to study the conformational changes of this molecule by dynamic ^{1}H n.m.r. spectroscopy. Figure 5 shows that the two overlapping doublets A/A′ and B/B′ for the diastereotopic methyl groups Me [1] and Me [2] which were observed at τ 8.89 and 8.96 in nitrobenzene at +176 °C coalesced to one doublet as the temperature was raised to +201 °C. [The designations $Me_{A/A'}$ and $Me_{B/B'}$ of the two pairs of diastereotopic methyl groups in the enantiomeric boat conformations (40a and b) do not reflect the relative chemical shifts of the methyl protons. Individual assignments are quite arbitrary.] Line-shape analysis (see Figure 5) employing method III (see Experimental section) afforded a $\Delta G^{\ddagger}$ value of 24.6 kcal mol^{-1} for the B $\rightleftharpoons$ B* ring inversion. This value may be compared with that of 17.7 kcal mol^{-1} found [1,24] for di-*o*-thymotide (41). There is little doubt that the *cis*-thioester and *cis*-ester linkages in the enantiomeric boat conformations of (7) and (41) respectively must lose most of their resonance stabilisation by becoming non-planar (*cf.* refs. 1 and 24) in the transition states associated with their ring inversions. Comparison of the $\Delta G^{\ddagger}$ values for (7) and (41) suggests that the resonance stabilisation in a *cis*-thioester linkage surpasses that in a *cis*-ester linkage.

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REFERENCES

[1] Part 9, W. D. Ollis, J. S. Stephanatou, and J. F. Stoddart, preceding paper.
[2] R. Anschütz and E. Rhodius, *Chem. Ber.*, 1914, **47**, 2733.
[3] W. Baker, A. S. El Nawawy, and W. D. Ollis, *J. Chem. Soc.*, 1952, 3163.
[4] A. P. Downing, W. D. Ollis, and I. O. Sutherland, *J. Chem. Soc. B*, 1970, 24.
[5] Preliminary report, G. B. Guise, W. D. Ollis, J. A. Peacock, J. S. Stephanatou, and J. F. Stoddart, *Tetrahedron Lett.*, 1980, **21**, 4203.
[6] F. Krollpfeiffer, H. Schultze, E. Schlumbohn, and E. Sommermeyer, *Chem. Ber.*, 1925, **58**, 1668.
[7] L. Amoretti and G. Pagani, *Farmaco Ed. Sci.*, 1967, **22**, 917.
[8] C. F. H. Allen and D. D. MacKay, *Org. Synth.*, Coll. Vol. 2, Wiley, New York, 1943, p. 580.
[9] W. Findeklee, *Chem. Ber.*, 1905, **38**, 3553.
[10] S. Gabriel and A. Thieme, *Chem. Ber.*, 1919, **52**, 1079.
[11] S. Gronowitz and G. Hansen, *Ark. Kemi*, 1967, **27**, 145.
[12] D. Balcom and A. Furst, *J. Am. Chem. Soc.*, 1953, **75**, 4334.
[13] W. Baker, B. Gilbert, and W. D. Ollis, *J. Chem. Soc.*, 1952, 1443.
[14] R. H. Gashorn, W. W. Levis, jun., E. Jaul, and E. J. Ritter, *Org. Synth.*, Coll. Vol. 4, Wiley, New York, 1963, p. 307.
[15] *Cf.* A. Schönberg and L. Vargha, *Chem. Ber.*, 1930, **63**, 178; D. H. Powers and D. S. Tarbell, *J. Am. Chem. Soc.*, 1956, **78**, 70; H. Kwart and E. R. Evans, *J. Org. Chem.*, 1966, **31**, 410; M. S. Newman and H. A. Karnes, *J. Org. Chem.*, 1966, **31**, 3980; H. Kwart and M. Cohen, *Bol. Inst. Quim.*, 1967, **19**, 93.
[16] O. L. Chapman and C. L. McIntosh, *J. Am. Chem. Soc.*, 1970, **92**, 7001; A. T. Fanning, jun., and T. D. Roberts, *Tetrahedron Lett.*, 1971, 805; A. T. Fanning, jun., G. R. Bickford, and T. D. Roberts, *J. Am. Chem. Soc.*, 1972, **94**, 8505; T. Otohiko, T. Masashi, K. Shuji, and T. Kaniaki, *Chem. Lett.*, 1972, 827.
[17] Part 3, W. D. Ollis and J. F. Stoddart, *J. Chem. Soc., Perkin Trans. 1*, 1976, 926.
[18] Part 6, D. J. Brickwood, W. D. Ollis, J. S. Stephanatou, and J. F. Stoddart, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1398.
[19] A. Tomisek, B. Graham, A. Griffith, C. S. Pease, and B. E. Christensen, *J. Am. Chem. Soc.*, 1946, **68**, 1587.
[20] D. J. Williams, Ph.D. Thesis, Imperial College London, May 1978; E. Gil, A. Quick, and D. J. Williams, *Tetrahedron Lett.*, 1980, **21**, 4207.
[21] A. C. D. Newman and H. M. Powell, *J. Chem. Soc.*, 1952, 3747.
[22] L. Parkanyi, A. Kalman, and M. Nógrádi, *Acta Cryst.*, 1975, **B31**, 2716.
[23] Part 8, W. D. Ollis, J. S. Stephanatou, J. F. Stoddart, and M. Nógradí, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1421.
[24] W. D. Ollis and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, 1973, 571.