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DITHIOSALICYLIDES AND TRITHIOSALICYLIDES THEIR CONFORMATIONAL BEHAVIOUR IN SOLUTION

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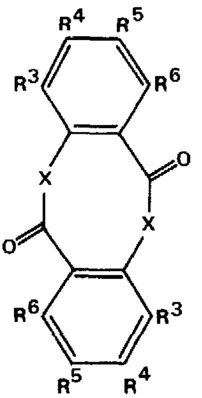
Summary The trithiosalicylide derivatives (11) - (14) have been synthesised and shown to exist in solution as ring inverting (15 ⇌ 15*) enantiomeric helical conformations

Dynamic ^{1}H n.m.r. spectroscopy of suitably-substituted disalicylides (i.e. 1 and 2) and trisalicylides (i.e. 3, 4, and 5) has led[1-3] to a more detailed understanding of the conformational behaviour of these compounds in solution than was possible on the basis of the dipole moment measurements carried out earlier[4] In particular, tri-3,6-dimethylsalicylide (3), tri-o-thymotide (4), and tri-o-carvocrotide (5) were all found[3] to exist as an interconverting binary mixture of chiral non-planar conformational diastereoisomers in which all three ester linkages adopt trans geometries In all cases, the isomer with C_3 symmetry (the propeller conformation[3]) predominates at equilibrium over the asymmetric isomer (the helical conformation[3]) Both di-o-thymotide (1) and di-o-carvocrotide (2) contain[2] two cis-ester linkages associated with chiral enantiomeric boat conformations which undergo ring inversion. Activation parameters for conformational inversions and interconversions have also been deduced[1-3] from line shape analysis of appropriate variable temperature ^{1}H n.m.r. spectra In this communication we describe the synthesis of some suitably-substituted[5] di- (6 - 10) and tri- (11 - 14) thiosalicylides and discuss their conformational behaviour in solution

Thiothymotic acid (3-isopropyl-6-methyl-2-mercaptobenzoic acid) was obtained[6,7] from the methyl ester[8] of thymotic acid in three steps (i) formation (Me$_2$NCSCl, NaH, Me$_2$NCHO) of the O-aryl dimethylthiocarbamate, (ii) pyrolysis (320–340°C for 2 min) to afford the S-aryl dimethylthiocarbamate,



	X	R^3	R^4	R^5	R^6	
	O	Me	H	H	Me	3
1	O	CHMe$_2$	H	H	Me	4
2	O	Me	H	H	CHMe$_2$	5
6	S	Me	H	H	H	11
7	S	H	H	Me	H	12
8	S	H	H	H	Me	13
9	S	Me	H	H	Me	14
10	S	CHMe$_2$	H	H	Me	

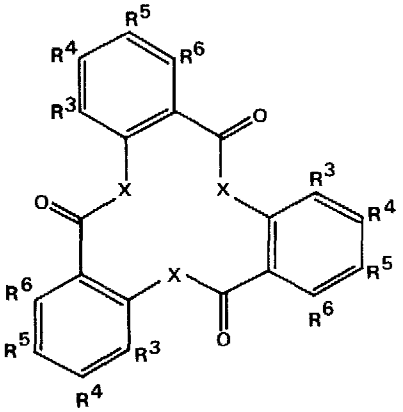


Table. The percentage yields and melting points of products obtained on cyclisation of selected 2-mercaptobenzoic acid derivatives in dry toluene in the presence of phosphoric anhydride

2-Mercaptobenzoic acid derivatives		Dithiosalicylide Yield (%)	Dithiosalicylide M p (°C)		Trithiosalicylide Yield (%)	Trithiosalicylide M.p. (°C)
3-Methyl [a]	(6)	4	245–250	(11)	7	300–302
5-Methyl [b]	(7)	1	155–157	(12)	10	250–255
6-Methyl [c]	(8)	31	155	(13)	8	>300
3, 6-Dimethyl [d]	(9)	31	235	(14)	7	> 300
3-Isopropyl-6-methyl [e]	(10)	12	203	-	-	-

[a] M p 160–165° [b] M p 155–157° (This m p is also reported by F Krollpfeiffer, H. Schultze, E Schlumbohn, and E Sommermeyer, Chem Ber , 1925, 58, 1668) [c] M p 110° (M.p 110–111° is reported by L Amoretti and G Pagani, Farmaco Ed Sci , 1967, 22, 917) [d] M p 110°. [e] Isolated as an oil

and (iii) hydrolysis (H_2O, MeOH, HCl) to give thiothymotic acid The other 2-mercaptobenzoic acid derivatives listed in the Table were prepared from the corresponding 2-aminobenzoic acid derivatives[9] by a sequence of reactions[10] involving (i) diazotisation ($NaNO_2$, HCl) of the amino group, (ii) conversion (Na_2S $2H_2O$, S, NaOH) of the diazonium salt to a disulphide, and (iii) reduction (Zn, HOAc) of the disulphide bridge to afford the desired thiol function Cyclisation (P_4O_{10}, toluene) of the 2-mercaptobenzoic acid derivatives led to the isolation and characterisation[9] of the di- and tri-thiosalicylide derivatives[11] listed in the Table

The ^{1}H n m r spectra of the trithiosalicylide derivatives (11) - (14) all showed temperature dependences (see Figure) for their constitutionally homotopic aryl methyl groups consistent with the compounds adopting asymmetric conformations in which these groups are clearly stereoheterotopic. Thus, the tri-3- and tri-6-methylthiosalicylides (11) and (13) each exhibit three singlets at low

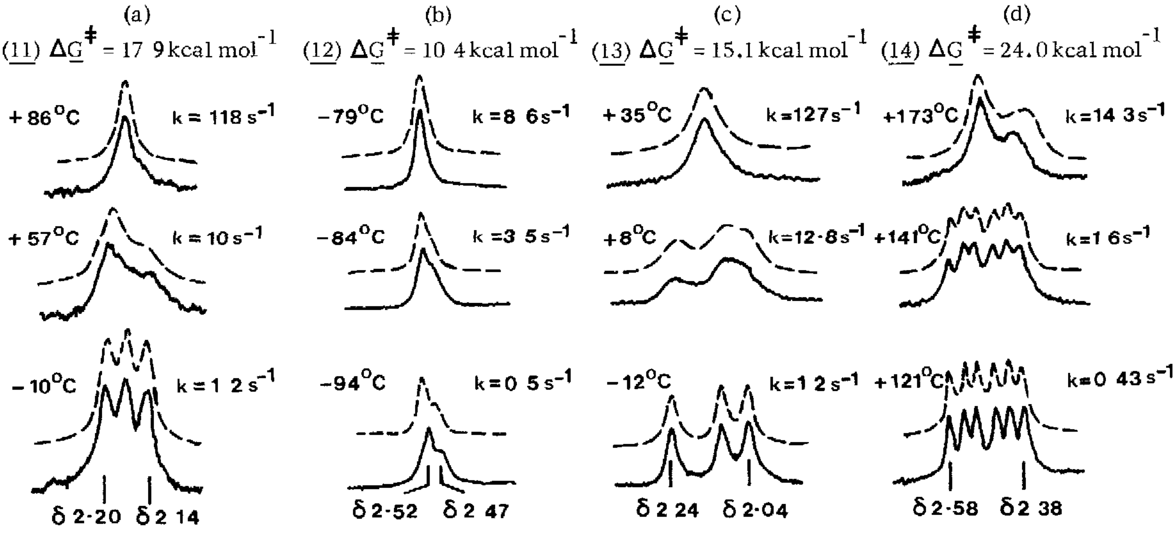
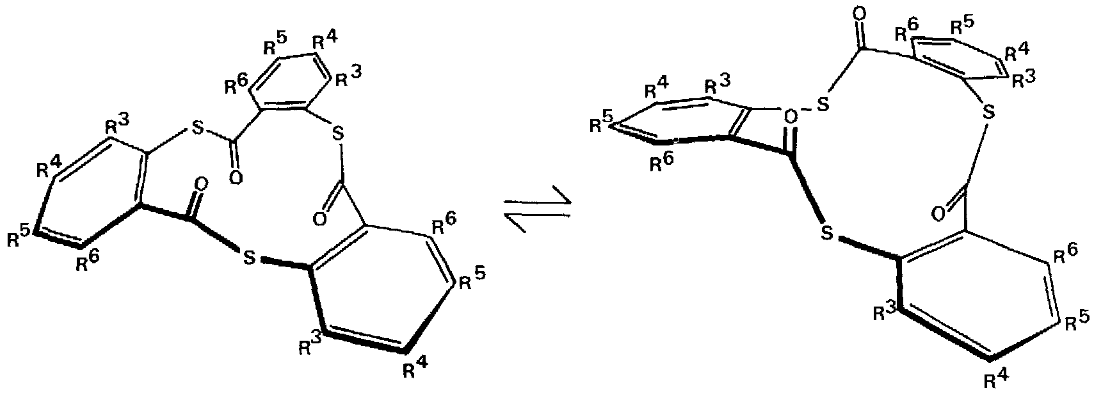

(a) (11) $\Delta G^{\ddagger}$ = 17 9kcal mol^{-1}
(b) (12) $\Delta G^{\ddagger}$ = 10 4kcal mol^{-1}
(c) (13) $\Delta G^{\ddagger}$ = 15.1kcal mol^{-1}
(d) (14) $\Delta G^{\ddagger}$ = 24.0kcal mol^{-1}

Figure 1. Observed (full line) and computed (broken line) spectra of the aryl methyl protons of compounds (11) in C_5D_5N, (12) in $CDCl_3$–CS_2 (1 1), (13) in $C_6H_5NO_2$, and (14) in C_5D_5N.



15 15*

temperatures (−10°C and −12°C, respectively) which coalesce (Figures 1a and c, respectively) into broad singlets as the temperature is raised Tri-5-methylthiosalicylide (12), which may be regarded as a model compound for studying the conformational behaviour of trithiosalicylide,[12] gives two singlets in the ratio of 2 1 at −94°C which undergo coalescence (Figure 1b) to give one singlet at higher temperatures. Finally, the tri-3,6-dimethyl derivative (14) exhibits two sets (arising from the stereoheterotopic sets of constitutionally heterotopic aryl methyl groups) of three singlets at +121°C which coalesce (Figure 1d) into broad singlets as the temperature is raised. There is no experimental evidence for the population of more than *one* conformational type − an asymmetric one! Inspection of both framework and space-filling molecular models demonstrates that the trithiosalicylides (11) - (14) can adopt enantiomeric helical conformations (15) and (15*) in which the three thioester groups all assume *trans* geometries and are oriented such that one sulphur atom occupies the opposite face of the 12-membered ring from the other two sulphur atoms.[13] Moreover, X-ray structural investigations[14] on crystals of (11) and (13)[15] reveal that conformations of the helical type are adopted in the solid state Thus, we have interpreted the dynamic ^{1}H n m r spectroscopic evidence in solution in terms of a ring inversion ($15 \rightleftharpoons 15^*$) process and have deduced (see Figure) free energies of activation for this process by line shape analysis These values are significantly higher (by from 4 to 10 kcal mol^{-1}) than the corresponding activation parameters found[1,3] in the trisalicylide series We ascribe this dramatic difference to the fact that the trithiosalicylides cannot − because of the greater steric demands of sulphur atoms compared with oxygen atoms − undergo "pedalling"[16] of the *trans*-thioester linkages after the manner proposed[3] for the *trans*-ester linkages in the corresponding trisalicylides In contrast, the ring inversion ($15 \rightleftharpoons 15^*$) process must proceed *via* an intermediate where one of the thioester linkages assumes a *cis* geometry with the consequent loss of resonance stabilisation within this thioester unit at the associated transition states giving rise to appreciable destabilisation in addition to that introduced by the inevitable increases in steric strain Strong evidence for the importance of this electronic factor comes from the observation[17] that the barrier to ring inversion between enantiomeric boat conformations of di-*o*-thiothymotide (10) is 24 6 kcal mol^{-1} compared with a value[2] of 17 7 kcal mol^{-1} for di-*o*-thymotide (1) There is little doubt that the *cis*-thioester and *cis*-ester linkages in the enantiomeric boat conformations of these molecules must lose much of their resonance stabilisation by becoming non-planar (see ref. 2) in the transition state conformations associated with their ring inversions. Our results are in harmony with the expectation that the resonance stabilisations of planar *cis*- and *trans*-thioester linkages will be considerably greater than those of structurally-related *cis*- and *trans*-ester linkages.

References and Footnotes

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7. The compositions of all new compounds were confirmed by elemental analyses. Structural assignments were based upon the results of mass spectrometry and ^{1}H n.m.r. spectroscopic evidence.
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9. 2-Amino-3-methyl- and -5-methyl-benzoic acids (W. Findeklee, *Chem. Ber.*, 1905, **38**, 3553), 2-amino-6-methylbenzoic acid (S. Gabriel and A. Thieme, *Chem. Ber.*, 1919, **52**, 1079), 2-amino-3,6-dimethylbenzoic acid (S. Gronowitz and G. Hansen, *Ark. Kem.*, 1967, **27**, 145).
10. *Cf.* C. F. H. Allen and D. D. MacKay, *Org. Syn.*, Coll. Vol. 2, Wiley, New York, 1943, p. 508.
11. Note (*i*) that no tri-*o*-thiothymotide was formed during the cyclisation of thiothymotic acid and (*ii*) that tetra-3-methylthiosalicylide (0.4%) was also obtained from the treatment of 3-methylthiosalicylic acid with phosphoric anhydride.
12. Attempts to study the conformational behaviour of trithiosalicylide by variable temperature ^{1}H-decoupled ^{13}C n.m.r. spectroscopy were thwarted by the low solubility of the compound in a range of solvents particularly at low temperatures.
13. It is significant that the asymmetrical helix conformation is the only ground state conformation for 6*H*, 12*H*, 18*H*-tribenzo[*b*, *f*, *j*][1, 5, 9]trithiacyclododecin as well (W. D. Ollis, J. S. Stephanatou, J. F. Stoddart, and M. Nógrádi, *J. Chem. Soc. Perkin I*, 1978, 1421).
14. E. Gill, A. Quick, and D. J. Williams, *Tet. Letters*, following communication.
15. Tri-6-methylthiosalicylide (13) exhibits (see ref. 14) spontaneous resolution on crystallisation, *cf.* tri-*o*-thymotide (4) (A. C. D. Newman and H. M. Powell, *J. Chem. Soc.*, 1952, 3747).
16. For an explanation of this term, see D. J. Brickwood, W. D. Ollis, J. S. Stephanatou, and J. F. Stoddart, *J. Chem. Soc. Perkin I*, 1978, 1398.
17. This $\Delta G^{\ddagger}$ value was obtained from line shape analysis of the temperature dependent ^{1}H n.m.r. signals for the isopropyl methyl groups in (10). The two overlapping doublets observed in nitrobenzene at δ 1.04 and 1.11 at +176°C coalesced to one doublet as the temperature was raised to +201°C. Note that (6) - (9) lack an n.m.r. probe suitable for the investigation of their conformational behaviour in solution.

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