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SYNTHESIS AND CONFORMATIONAL BEHAVIOUR OF TRI-3-METHYLTRIANTHRANILIDES. A NEW EXAMPLE OF SPONTANEOUS RESOLUTION AND INCLUSION COMPOUND FORMATION ON CRYSTALLISATION

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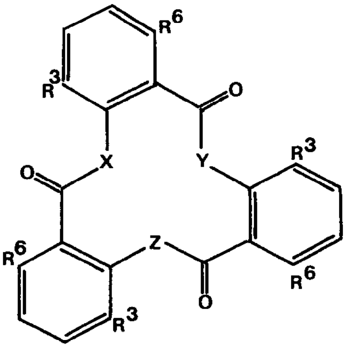
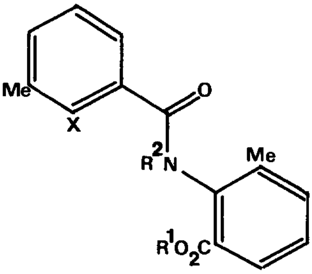
Summary. The tri-3-methyltrianthranilide derivatives (7)–(9) have been synthesised. Dynamic ^{1}H n.m.r. spectroscopy indicates that the N,N',N''-trimethyl derivative (8) exists in solution as slowly ring inverting (16 $\rightleftharpoons$ 16*) enantiomeric helical conformations. X-Ray crystallography shows that the N,N'-dimethyl-N''-benzyl derivative (9) undergoes spontaneous resolution when it crystallises as a 1:1 adduct from toluene. The host molecules adopt a helical conformation (Figure 1) within a lattice structure that contains chiral channels (Figure 2) occupied by guest solvent molecules.

Recently, interest[2,3] has been revived in the uniqueness of tri-o-thymotide (1) to combine spontaneous resolution[4] on crystallisation with an ability to provide a host lattice in the formation of inclusion compounds[5] with a wide range of guest molecules. Tri-6-methylthiosalicylide[6] (2) and N,N'-dimethyltrianthranilide[7] (3) undergo spontaneous resolution[8-10] on crystallisation without showing any tendency to form inclusion compounds, while N,N'-dimethyl-N''-benzyl-[10] (4), N,N'-dibenzyl-[9-11] (5), and N,N',N''-tribenzyl-[10,11] (6) trianthranilides form inclusion compounds[12] without undergoing spontaneous resolution. In this communication, we report on (i) the synthesis of the tri-3-methyltrianthranilide derivatives (7)–(9), (ii) their conformational behaviour in solution, (iii) the ability of N,N'-dimethyl-N''-benzyltri-3-methyltrianthranilide (9) to undergo spontaneous resolution on crystallisation from toluene, and (iv) its ability to form an inclusion compound of the channel type with the solvent.

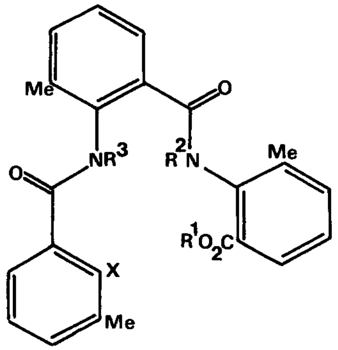
Compound (7) was obtained[13] from 2-amino-m-toluic acid[14] and 2-nitro-m-toluoyl chloride[15] in seven steps:[16] (i) these two compounds afforded the amide (10), (ii) methylation of (10) yielded the methyl ester (11), (iii) reduction of the aromatic nitro group in (11) followed by saponification of its ester function



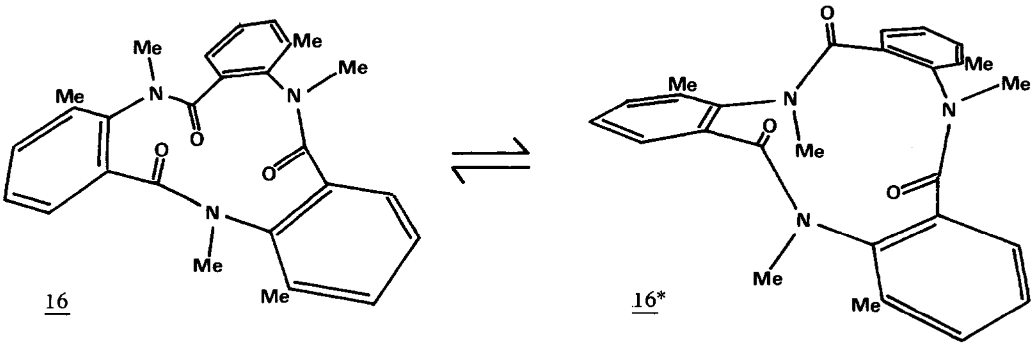
	X	Y	Z	R^3	R^6
1	O	O	O	$CHMe_2$	Me
2	S	S	S	H	Me
3	NMe	NMe	NH	H	H
4	NMe	NMe	NCH_2Ph	H	H
5	NCH_2Ph	NCH_2Ph	NH	H	H
6	NCH_2Ph	NCH_2Ph	NCH_2Ph	H	H
7	NMe	NMe	NH	Me	H
8	NMe	NMe	NMe	Me	H
9	NMe	NMe	NCH_2Ph	Me	H



	R^1	R^2	R^3	X	
10	H	H	-	NO_2	
11	Me	Me	-	NO_2	
12	H	Me	-	NH_2	
	H	Me	H	NO_2	13
	Me	Me	Me	NO_2	14
	H	Me	Me	NH_2	15



gave the amino acid (12), (iv) the acid chloride and (12) afforded the amide (13), (v) methylation of (13) yielded the N, N'-dimethyl derivative (14), (vi) reduction of the aromatic nitro group in (14) followed by saponification of its ester function gave the key acyclic amino acid intermediate (15) which (vii) underwent cyclisation ($SOCl_2$, $CHCl_3$) to provide N, N'-dimethyltri-3-methyltrianthranilide (7), m.p. $>300^o$ in 19% yield. Methylation (MeI, NaH, Me_2SO) of (7) gave the N, N', N''-trimethyl derivative (8), m.p. $> 300^o$, ^{1}H n.m.r. data: τ($CDCl_3$) 2.52–2.86 (9H, m, aromatic protons), 6.78, 6.86, and 6.88 (9H, 3 x s, 3 x NMe), and 7.62 and 7.65 (6H and 3H, 2 x s, 3 x ArMe). These spectra data are consistent with (8) adopting in solution enantiomeric helical conformations (16, 16*) in which both the N-methyl groups and the aryl-methyl groups are stereoheterotopic. The ^{1}H n.m.r. spectrum of (8) in nitrobenzene solution shows temperature dependence above $+100^oC$. Although neither the three singlets for the N-methyl groups nor the three singlets for the aryl methyl groups coalesced to the expected two singlets by $+172^oC$, the broadening of the spectral line shapes at this temperature was sufficient to permit line shape analysis[17] of each set of signals yielding values of 0.51 s^{-1} and 0.77 s^{-1}, respectively, for the site-exchange rate constants. A free energy of activation of 26.8 kcal mol^{-1} for the ring inversion process (16 $\rightleftharpoons$ 16*) was calculated from the average value of 0.64 s^{-1} for these rate constants. A barrier to enantiomerisation of this order of magnitude is a necessary, but not a sufficient, condition for spontaneous resolution to be observed. Fortunately, benzylation ($PhCH_2Br$, NaH, Me_2SO) of (7) gave a N, N'-dimethyl-N''-benzyl derivative (9), which furnished single crystals (m.p. 252–254°) containing molecules of one, and only one,



16

16*

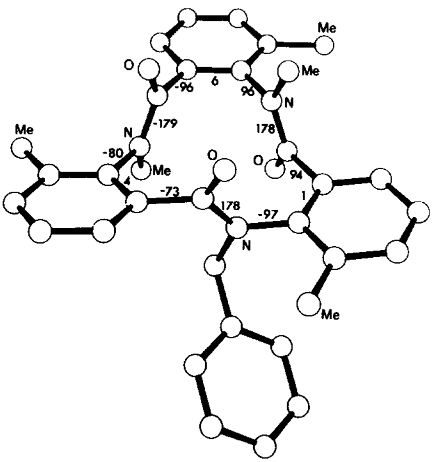


Figure 1. The solid state conformation of the N, N'-dimethyl-N''-benzyl derivative (9).

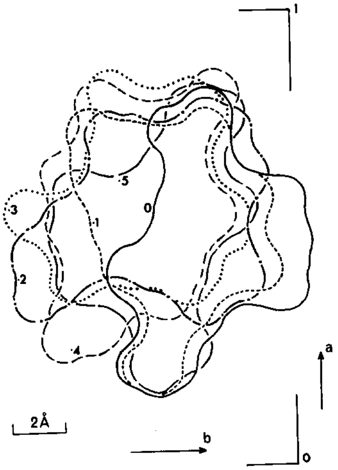


Figure 2. A contour map representing the bounds of the channels formed in crystals of (9). The contours are spaced at equal intervals of 0.1 (ca. 1.1 Å) of a unit cell translation in the c direction. Only half of the depth of the channel is illustrated, the remainder being generated by the crystallographic two-fold screw axis.

chirality from toluene. In addition an X-ray crystal structure analysis of these crystals has shown (see Figure 1) that (9) forms a 1:1 inclusion compound with toluene in which the host molecules adopt a helical conformation in accordance with the ^{1}H n.m.r. data: τ ($CDCl_3$) 2.46–3.25 (19H, m, aromatic protons), 5.20 (2H, bs, $PhCH_2$),[18] 6.70 and 6.96 (6H, 2 x s, 2 x NMe), 7.58 and 8.55 (6H and 3H, 2 x s, 3 x ArMe), and 7.69 (3H, s, PhMe). The formation of transannular hydrogen bonds as observed[8] in the structures of N, N'-dimethyl- (3) and N, N'-dibenzyl- (5) trianthranilides is precluded by the fact that all three nitrogen atoms in (9) carry substituents. As a consequence, molecules of (9) adopt a more 'ideally helical' geometry, i.e. the planes of the trans-amide linkages are more nearly orthogonal to their adjacent aromatic rings than they are in (3) and (5). By plotting the van der Waals radii of all the host atoms in the unit cell, there are found to be large continuous channels (see Figure 2) in the crystal running parallel to the cell translation, c. These channels[19] have an average minimum dimension of ca. 5.5 Å and an average maximum dimension of ca. 9.0 Å. Thus, we have observed amongst trianthranilide derivatives for the first time, the formation of a chiral channel structure analogous to that formed by tri-o-thymotide. Clearly, N, N'-dimethyl-N''-benzyltri-3-methyltrianthranilide (9) has the potential to effect chiral recognition of guest species in the solid state.

Crystallographic Data: Crystals of (9) [$C_{33}H_{31}O_3N_3$, C_7H_8] are orthorhombic, a = 17.358 (1), b = 17.262 (1), c = 10.993 (1) Å, U = 3294 Å^3; space group $P2_12_12_1$, Z = 4, D_c = 1.23 g cm^{-3}. Of the 3580 independent reflections ($\theta \leq 71^\circ$) measured on a diffractometer using Cu–K_α radiation, 331 were classified as unobserved. The structure was solved by direct methods and refined to give an R value of 0.049.

References and Footnotes

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12. Compound (4) as a crystalline conglomerate of four conformational diastereoisomers retains[10] one-third of a molar proportion of ethanol on recrystallisation from chloroform – ether – light petroleum (b.p. 60 – 80°C) of the residue obtained after concentration of an ethanol-stabilised chloroform solution. Compound (5) crystallises from toluene as a racemate in which the host molecules adopt[9] enantiomeric helical conformations forming a 1 : 1 inclusion compound with the solvent. Isolation of the helical conformational isomer of compound (6) by preparative t.l.c. followed by its extraction from silica gel with ethanol-stabilised chloroform affords[10,11] a crystalline residue which contains a molar proportion of ethanol.
13. The compositions of all new compounds were confirmed by elemental analyses. Structural assignments were based upon the results of mass spectrometry and ^1H n.m.r. spectroscopic evidence.
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16. Reagents for steps (i) and (iv): o-$NO_2MeC_6H_3COCl$, KOH, C_6H_6, H_2O; reagents for steps (ii) and (v): MeI, NaH, Me_2SO; reagents for steps (iii) and (vi): $TiCl_3$, EtOH, H_2O followed by addition of LiOH.
17. A computer program suitable for exchange of nuclei between three equally populated sites with no mutual coupling was employed (see D. J. Brickwood, W. D. Ollis, J. S. Stephanatou, and J. F. Stoddart, *J.Chem.Soc. Perkin I*, 1978, 1398).
18. In CD_3SOCD_3, this broad singlet appears in the ^1H n.m.r. spectrum as an AB system (τ_A 5.33, τ_B 5.43, J_{AB} = 14.4 Hz) which does not coalesce to a singlet on heating up to +180°C. Consequently, the barrier to ring inversion in this compound must exceed 27 kcal mol^{-1}.
19. Significant portions of the channels are bounded by the aryl methyl groups and the aromatic ring of the benzyl group.

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