Conformational Behaviour of Medium-sized Rings. Part 14.[1] Tetra-anthranilides

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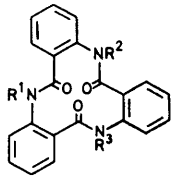
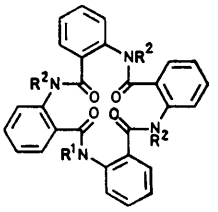
The stepwise synthesis of *N,N',N''*-trimethyltetra-anthranilide (13) is reported and the temperature dependence of the ^{1}H n.m.r. spectrum of *N*-benzyl-*N',N'',N'''*-trimethyltetra-anthranilide (15) is interpreted in terms of equilibration between three diastereoisomeric conformations in solution. Although there is ^{1}H n.m.r. spectral evidence for the presence in solution at room temperature of at least six conformational diastereoisomers of (13), *N,N',N'',N'''*-tetramethyltetra-anthranilide (14) appears to adopt a single conformation of high symmetry in solution.

Two families of chiral non-planar conformations, in which all three amide linkages adopt *trans*-geometries, have been identified [2] for the 12-membered rings of the *N,N'*-disubstituted trianthranilide derivatives (1)—(4) and *N,N',N''*-trisubstituted trianthranilide derivatives (5)—(12). In solution, these compounds exist as equilibrating mixtures of conformational enantiomers and/or diastereoisomers of the propeller and helical types. The ring inversion and interconversion processes which occur respectively between enantiomeric and diastereoisomeric conformational isomers in solution are believed [2] to involve the intermediacy of highly strained conformations in which one of the three amide bonds adopts a *cis*-geometry. Examination of molecular models of tetra-anthranilide derivatives revealed that both *cis*- and *trans*-amide linkages can be accommodated within their 16-membered rings in numerous strain-free conformational isomers. Thus, it became necessary to synthesise *N,N',N''*-trimethyl- (13), *N,N',N'',N'''*-tetramethyl- (14), and *N*-benzyl-*N',N'',N'''*-trimethyl- (15) tetra-anthranilides and examine their conformational behaviour in solution, recognising at the outset that the complexity of the situation might demand information on the conformation adopted by at least one of these derivatives in the solid state.

Methyl *N*-methylbenzamido-*N*-methyl-*N*-[2-(*o*-nitro-*N*-methylbenzamido)benzoyl]anthranilate (23) was identified as a key intermediate in the synthesis of *N,N',N''*-trimethyltetra-anthranilide (13). The acyclic *N,N',N''*-trimethyl derivative (23) was prepared by two different routes, (i) one starting from methyl *N*-methyl-*N*-[2-(*o*-nitro-*N*-methylbenzamido)benzoyl]anthranilate [2] (19) and (ii) the other starting from *N*-[2-(*o*-nitrobenzamido)benzoyl]anthranilic acid [2,3] (16). With reference to route (i), the reduction of the aromatic nitro-grouping in the methyl ester (19) has already been reported [2] to proceed smoothly to give compound (20). Subsequent *o*-nitrobenzoylation of (20) afforded (22) which yielded the acyclic *N,N',N''*-trimethyl derivative (23) on methylation. The first step in route (ii) was the esterification of (16) with 1-methyl-3-*p*-tolyltriazene [4] to give the methyl ester (17). Titanium(III) chloride reduction [5] of the aromatic nitro-grouping in (17) provided methyl *N*-[2-(*o*-aminobenzamido)benzoyl]anthranilate (18) which was subjected to *o*-nitrobenzoylation to afford the methyl ester (21). Methylation of (21) yielded the acyclic *N,N',N''*-trimethyl derivative (23). Conversion of this derivative (23) into the acyclic amino-acid precursor (25) of *N,N',N''*-trimethyltetra-anthranilide



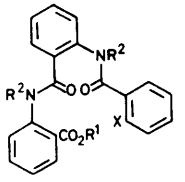
	R^1	R^2	R^3
(1)	Me	Me	H
(2)	Me	Et	H
(3)	Me	CH_2Ph	H
(4)	CH_2Ph	CH_2Ph	H
(5)	Me	Me	Me
(6)	Me	Me	COMe
(7)	Me	Me	COPh
(8)	Me	Me	CH_2Ph
(9)	Me	Et	CH_2Ph
(10)	Me	CH_2Ph	Et
(11)	CH_2Ph	CH_2Ph	Me
(12)	CH_2Ph	CH_2Ph	CH_2Ph



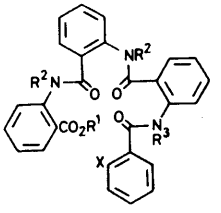
	R^1	R^2
(13)	H	Me
(14)	Me	Me
(15)	CH_2Ph	Me

(13) was achieved by reduction of the aromatic nitro-grouping with titanium(III) chloride to give the amino-acid ester (24), followed by de-esterification. Cyclisation of (25) was achieved by treatment with *N,N'*-dicyclohexylcarbodi-imide in dichloromethane. However, *N,N',N''*-trimethyltetra-anthranilide (13) was obtained in very low yield (*ca.* 2%) and the major product of the reaction was the *N*-acylurea (26). In the synthesis of *N,N'*-dimethyltrianthranilide (1), the corresponding *N*-acylurea could be cyclised to (1) by heating it in ethanolic sclution under reflux. Unfortunately, the conversion of (26) into (13) did not take

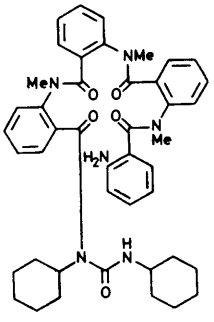
place under these or any other reaction conditions which were examined. When (25) was refluxed with thionyl chloride in chloroform the major product was *N,N'*-dimethyltrianthranilide (1); *N,N',N''*-trimethyltetra-anthranilide (13) was isolated in less than 1% yield. From this limited experience, it would appear that



	R^1	R^2	X
(16)	H	H	NO_2
(17)	Me	H	NO_2
(18)	Me	H	NH_2
(19)	Me	Me	NO_2
(20)	Me	Me	NH_2



	R^1	R^2	R^3	X
(21)	Me	H	H	NO_2
(22)	Me	Me	H	NO_2
(23)	Me	Me	Me	NO_2
(24)	Me	Me	Me	NH_2
(25)	H	Me	Me	NH_2



(26)

cyclisations to produce tetra-anthranilides proceed only with difficulty. Hence, 16-membered ring formation occurs less readily than does 12-membered ring formation to give trianthranilides. Previously, it had been noted,[2] in appropriate circumstances, that 8-membered ring formation to give dianthranilides is preferred exclusively over 12-membered ring formation to give trianthranilides.

The relatively small amounts of *N,N',N''*-trimethyltetra-anthranilide (13) we had at our disposal severely curtailed our investigations of the conformational behaviour of *N,N',N'',N'''*-tetra-substituted tetra-anthranilide derivatives in solution. These were limited to a consideration of (i) the *N,N',N'',N'''*-tetramethyl derivative (14), obtained on methylation of (13), and (ii) the *N*-benzyl-*N',N'',N'''*-trimethyl derivative (15), obtained on benzylation of (13). The results discussed in this paper have already been presented in a preliminary form as a short communication.[6]

EXPERIMENTAL

The general methods have been discussed in Parts 3 [7] and 6.[8]

Methyl N-*Methylbenzamido*-N-*methyl*-N-[2-(o-*nitrobenzamido*)*benzoyl*]*anthranilate* (22).—Methyl *N*-methyl-*N*-[2-(*o*-amino-*N*-methylbenzamido)benzoyl]anthranilate [2] (20) (12 g) was suspended in a solution of lithium hydroxide (2.5 g) in water (120 ml). A solution [2] of *o*-nitrobenzoyl chloride (10 ml) diluted with anhydrous benzene (120 ml) was added dropwise and the reaction mixture was stirred for 3 h. After separation the aqueous layer was extracted with chloroform (3 × 200 ml). The combined organic layers were washed with water (200 ml) and dried (Na_2SO_4). Evaporation of the solvents under reduced pressure gave an oil which crystallised from ether yielding *methyl* N-*methylbenzamido*-N-*methyl*-N-[2-(o-*nitrobenzamido*)*benzoyl*]-*anthranilate* (22) (13.5 g, 83%), m.p. 194—196 °C [Found: C, 64.7; H, 4.8; N, 9.0%; *M* (mass spec.), 566.1796. $C_{31}H_{26}N_4O_7$ requires C, 65.7; H, 5.6; N, 9.9%; *M*, 566.1802], τ($CDCl_3$) 1.72—3.02 (17 H, m, NH and ArH), 6.00 and 6.08 (3 H, 2 × s, in the approximate ratio of 38 : 62, CO_2Me), and 6.43, 6.64, 6.72, and 6.83 (6 H, 4 × s, in the approximate ratio of 12 : 37 : 23 : 28, 2 × NMe).

Methyl N-[2-(o-*Nitrobenzamido*)*benzoyl*]*anthranilate* (17):—*N*-[2-(*o*-Nitrobenzamido)benzoyl]anthranilic acid [2,3] (16) (9.12 g) and 1-methyl-3-*p*-tolyltriazene [4] (3.8 g) were allowed to react overnight at room temperature in tetrahydrofuran (100 ml). The solution was then concentrated to afford a residue which was washed with ether–hexane (1 : 1) and crystallised from ethanol to yield *methyl* N-[2-(o-*nitrobenzamido*)*benzoyl*]*anthranilate* (17) (6.5 g, 69%), m.p. 155 °C [Found: *M* (mass spec.), 419.1132. $C_{22}H_{17}N_3O_6$ requires *M*, 419.1117], τ($CDCl_3$) −2.15 and −1.88 (2 H, 2 × bs, 2 × NH), 1.19—2.89 (12 H, m, ArH), and 6.04 (3 H, s, CO_2Me).

Methyl N-[2-(o-*Aminobenzamido*)*benzoyl*]*anthranilate* (18).—Methyl *N*-[2-(*o*-nitrobenzamido)benzoyl]anthranilate (17) (5 g) was heated in ethanol (600 ml) and titanium(III) chloride solution (90 ml) was added dropwise during 30 min. The reaction mixture was refluxed for a further 10 min before being poured into boiling water (900 ml). On cooling, it was extracted with chloroform (3 × 300 ml), and the combined organic layers were washed with water (200 ml) and dried (Na_2SO_4). The solvents were evaporated off under reduced pressure to afford a yellow solid which was recrystallised from methanol to give *methyl* N-[2-(o-*aminobenzamido*)*benzoyl*]*anthranilate* (18) (3.9 g, 87%), m.p. 155—156 °C [Found: C, 67.9; H, 5.1; N, 10.9%; *M* (mass spec.), 389. $C_{22}H_{19}N_3O_4$ requires C, 67.9; H, 4.9; N, 10.8%; *M* 389], τ($CDCl_3$) −2.04 and −1.93 (2 H, 2 × bs, 2 × NH), 1.16—3.32 (12 H, m, ArH), 4.4 (2 H, bs, NH_2), and 6.05 (3 H, s, CO_2Me).

Methyl N-*Benzamido*-N-[2-(o-*nitrobenzamido*)*benzoyl*]-*anthranilate* (21).—Methyl *N*-[2-(*o*-aminobenzamido)benzoyl]anthranilate (18) (4.6 g) was suspended in a solution of lithium hydroxide (900 mg) in water (45 ml). A solution [2] of *o*-nitrobenzoyl chloride (14 ml) diluted with anhydrous benzene (90 ml) was added dropwise and the

reaction mixture was stirred at room temperature for 2 h. The solid which separated was collected by filtration. Recrystallisation from ethanol afforded *methyl* N-*benzamido*-N-[2-(o-*nitrobenzamido*)*benzoyl*]*anthranilate* (21) (5.2 g, 82%), m.p. 226—228 °C [Found: C, 64.5; H, 4.1; N, 10.4%; *M* (mass spec.), 538. $C_{29}H_{22}N_4O_7$ requires C, 64.7; H, 4.1; N, 10.4%; *M* (mass spec.), 538. $C_{29}H_{22}N_4O_7$ requires C, 64.7; H, 4.1; N, 10.4%; *M*, 538], τ(CF_3CO_2H) 1.58—2.62 (16 H, m, ArH) and 5.92 (3 H, s, CO_2Me).

Methyl N-*Methylbenzamido*-N-*methyl*-N-[2-(*o-nitro*-N-*methylbenzamido*)*benzoyl*]*anthranilate* (23).—(a) Methyl *N*-methylbenzamido-*N*-methyl-*N*-[2-(*o*-nitrobenzamido)-benzoyl]anthranilate (22) (6 g) was stirred in dry dimethyl sulphoxide (50 ml) with methyl iodide (6.5 ml) and sodium hydride (1.8 g) at room temperature for 4 h. Excess of sodium hydride was destroyed by careful addition of water. The aqueous mixture was extracted with chloroform (3 × 100 ml) and the combined organic layers were washed with water (5 × 100 ml) and dried (Na_2SO_4). The solvents were evaporated off under reduced pressure to afford an oil. T.l.c. on silica gel in ethyl acetate–light petroleum (b.p. 60—80 °C) (2 : 1) indicated the presence of starting material (R_F 0.55) and a product with R_F 0.25 which was purified by column chromatography on silica gel using the solvent system mentioned above. Crystallisation of the crude product from ether gave *methyl* N-*methylbenzamido*-N-*methyl*-N-[2-(o-*nitro*-N-*methylbenzamido*)*benzoyl*]*anthranilate* (23) (3.5 g, 57%), m.p. 190—191 °C [Found: C, 66.2; H, 4.7; N, 9.6%; *M* (mass spec.), 580. $C_{32}H_{28}N_4O_7$ requires C, 66.2; H, 4.9; N, 9.7%; *M*, 580], τ($CDCl_3$) 2.31—3.68 (16 H, m, ArH), 6.60, 6.65, and 6.68 (3 H, 3 × s, in the approximate ratio of 30 : 11 : 59, CO_2Me), and 7.01, 7.07, 7.11, 7.18, 7.22, 7.24, 7.30, 7.35, and 7.36 (9 H, 9 × s, in the approximate ratio of 9 : 5 : 4 : 8 : 12 : 22 : 8 : 6 : 26, 3 × NMe).

(b) Methyl iodide (1 ml) was added to a mixture of sodium hydride (300 mg) and methyl *N*-benzamido-*N*-[2-(*o*-nitrobenzamido)benzoyl]anthranilate (21) (1 g) in dry dimethyl sulphoxide (20 ml) and the reaction mixture was stirred at room temperature overnight. The crude product was isolated by a procedure similar to that described in method (a). Crystallisation of this product from ether afforded the methyl ester (23) (400 mg, 37%) which was spectroscopically identical with the fully characterised sample isolated by method (a).

Methyl N-*Methylbenzamido*-N-[2-(o-*amino*-N-*methylbenzamido*)*benzoyl*]*anthranilate* (24).—Titanium(III) chloride solution (35 ml; 12.5%) was added dropwise to a boiling solution of the methyl ester (23) (3 g) in ethanol (175 ml). The reaction mixture was heated for 10 min, poured into boiling water (350 ml), and heated for a further 30 min. On cooling, the aqueous mixture was extracted with chloroform (3 × 200 ml). The combined organic layers were washed with water (200 ml), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield an oily residue. This oil was subjected to column chromatography on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (2 : 1) as eluant. The product obtained was crystallised from ether to yield *methyl* N-*methylbenzamido*-N-[2-(o-*amino*-N-*methylbenzamido*)*benzoyl*]*anthranilate* (24) (2.6 g, 91%), m.p. 205—206 °C [Found: C, 69.6; H, 5.2; N, 10.0%; *M* (mass spec.), 550. $C_{32}H_{30}N_4O_5$ requires C, 69.8; H, 5.5; N, 10.2%; *M*, 550], τ($CDCl_3$) 1.86—3.40 (16 H, m, ArH), 5.40 (2 H, bs, NH_2), 6.02, 6.05, and 6.10 (3 H, 3 × s, in the approximate ratio of 28 : 8 : 64, CO_2Me), and 6.51, 6.54, 6.66, and 6.72 (9 H, 4 × s, in the approximate ratio of 18 : 37 : 5 : 40, 3 × NMe).

N-[2-(o-*Amino*-N-*methylbenzamido*)*benzoyl*]-N-*methylbenzamidoanthranilic Acid* (25).—The *N*,*N*′,*N*″-trimethyl derivative (24) (2 g) of methyl trianthraniloylanthranilate was dissolved in methanol (40 ml) and aqueous lithium hydroxide solution (80 ml, 10%) was added. The reaction mixture was refluxed for 1 h, filtered, and the filtrate acidified with dilute hydrochloric acid. The aqueous solution was extracted with chloroform (3 × 100 ml). The combined chloroform layers were washed with water (150 ml), dried ($MgSO_4$), and filtered. The filtrate was concentrated under reduced pressure whereupon N-[2-(o-*amino*-N-*methylbenzamido*)*benzoyl*]-N-*methylbenzamido-anthranilic acid* (25) was precipitated as a crystalline solid (1.6 g, 87%), m.p. 173—177 °C [Found: *M* (mass spec.), 536.2093. $C_{31}H_{28}N_4O_5$ requires *M*, 536.2059], τ($CDCl_3$) 2.04—3.44 (16 H, m, ArH), 3.62 (3 H, s, CO_2H and NH protons), and 6.62, 6.66, 6.75, and 6.82 (9 H, 4 × s, in the approximate ratio of 22 : 35 : 6 : 37, 3 × NMe).

N,N′,N″-*Trimethyltetra-anthranilide* (13).—(a) The amino-acid derivative (25) (1.6 g) was dissolved in dichloromethane (10 ml) and a solution of *N*,*N*′-dicyclohexylcarbodi-imide (900 mg) in dichloromethane (10 ml) was added with stirring at room temperature. The reaction mixture was stirred for 68 h at room temperature and *N*,*N*′-dicyclohexylurea (220 mg) which formed as a precipitate was collected by filtration. The solvent was evaporated off under reduced pressure to give a solid residue. T.l.c. on silica gel using ethyl acetate as eluant indicated the presence of two products with R_F values of 0.75 and 0.40. Preparative t.l.c. on silica gel using ethyl acetate as eluant afforded two fractions. Fraction 1 (R_F 0.75) was crystallised from ethanol to yield N-[2-(o-*amino*-N-*methylbenzamido*)*benzoyl*]-N-*methylbenzamidoanthraniloyldicyclohexylurea* (26) (700 mg, 32%), m.p. 224—225 °C [Found: *M* − 125 (mass spec.), 617.3006. $C_{44}H_{50}N_6O_5 - C_6H_{11}N{=}C{=}O$ requires *M* − 125, 617.3002], τ($CDCl_3$) 1.92 (1 H, bs, NH), 2.46—3.77 (16 H, m, ArH), 5.30 (2 H, bs, NH_2), 5.72 (2 H, m, CH), 6.58 and 6.74 (9 H, 2 × s of approximately equal intensities, 3 × NMe), and 7.85—9.20 (20 H, m, CH_2). Fraction 2 (R_F 0.40) was crystallised from ethyl acetate–light petroleum (b.p. 60—80 °C) yielding N,N′,N″-*trimethyltetra-anthranilide* (13) (35 mg, 2.3%), m.p. 295 °C [Found: C, 71.8; H, 5.1; N, 10.9%; *M* (mass spec.), 518.1953. $C_{31}H_{26}N_4O_4$ requires C, 71.8; H, 5.1; N, 10.8%; *M*, 518.1954], τ($CDCl_3$) −0.13, 0.03, 0.62, 0.92, 0.94, and 0.99 (1 H, 6 × s in the approximate ratio of 37 : 14 : 9 : 16 : 16 : 8, NH), 1.60—3.45 (16 H, m, ArH), and 6.14, 6.23, 6.43, 6.47, 6.50, 6.55, 6.56, 6.58, 6.65, 6.69, 6.70, 6.71, 6.79, 6.87, 6.88, 7.38, and 7.44 (9 H, 17 × s, signals of different intensities and variable line shapes, 3 × NMe).

Recrystallisation of (13) from methanol–*p*-dioxan during four months yielded crystals which were suitable for *X*-ray crystallographic analysis [6] (Figure 2).

The *N*-acylurea (26) (300 mg) was refluxed in ethanol (150 ml) for 24 h. The solvent was evaporated off under reduced pressure to afford a solid. T.l.c. on silica gel in ethyl acetate–light petroleum (b.p. 60—80 °C) (2 : 1) indicated the presence of starting material only. When the attempted cyclisation was repeated with a few drops of concentrated hydrochloric acid added to the ethanolic solution of (25), a compound other than *N*,*N*′,*N*″-trimethyltetra-anthranilide (13) was formed slowly. This new compound was not characterised.

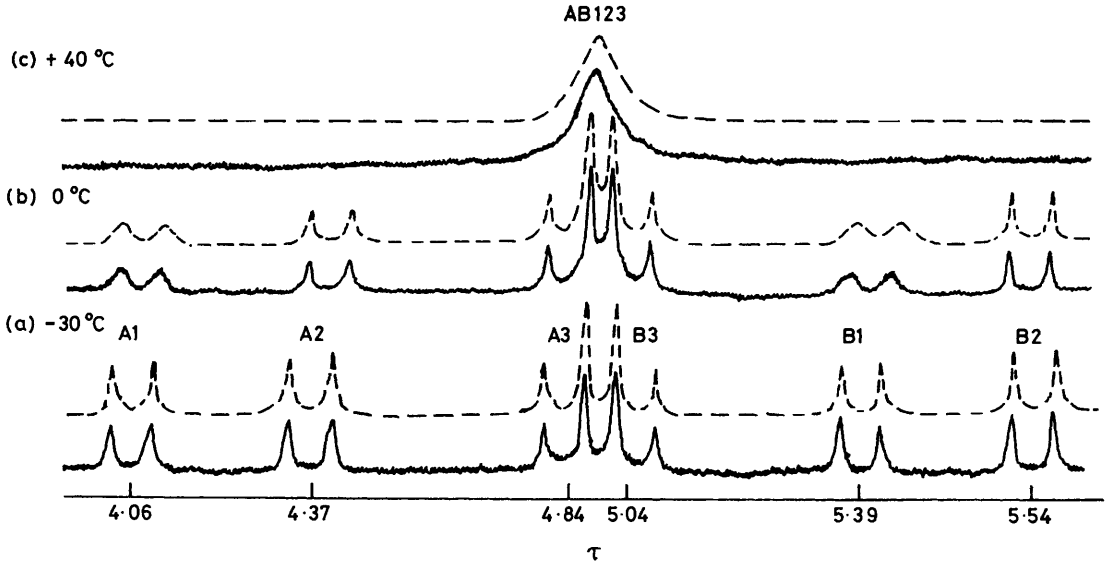


FIGURE 1 Observed (full line) and computed (broken line) spectra of the benzylic-methylene protons of *N*-benzyl-*N'*,*N''*,*N'''*-trimethyltetra-anthranilide (15) using program VI for exchange of nuclei between three pairs of unequally populated sites, A1B1, A2B2, and A3B3 (the input parameters of all the rate constants were the same so they will be referred to collectively as *k*): (a) at −30 °C, *k* 3.5 s^{-1}; (b) at 0 °C, *k* 6.2 s^{-1}; (c) at +40 °C, *k* 2 400 s^{-1}

(b) The amino-acid derivative (25) (1.34 g) was dissolved in dry chloroform (7 ml) and redistilled thionyl chloride (0.3 ml) was added. The reaction mixture was refluxed for 8 h. Evaporation of the solvent and excess of thionyl chloride under reduced pressure afforded an oil. T.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (2 : 1) as eluant indicated the presence of two products with R_F values of 0.40 and 0.35. Column chromatography on silica gel using the solvent system mentioned above as eluant afforded two fractions. Fraction 1 (R_F 0.40) was crystallised from methanol to yield N,N',N''-*trimethyltetra-anthranilide* (13) (5 mg, 0.4%), which was spectroscopically identical with that of an authentic sample obtained by method (a). Fraction 2 (R_F 0.35) was crystallised from methanol to yield *N,N'*-dimethyltrianthranilide (1) (200 mg), m.p. 245—248 °C (lit.,[2] m.p. 251—254 °C). This compound had spectroscopic properties indistinguishable from those of an authentic sample.[2]

N,N',N'',N'''-*Tetramethyltetra-anthranilide* (14).—*N,N',N''*-Trimethyltetra-anthranilide (13) (14 mg) was stirred with methyl iodide (0.5 ml) and sodium hydride (60 mg) in dimethyl sulphoxide (10 ml) at room temperature for 3 h. Excess of sodium hydride was destroyed by careful addition of water to the reaction mixture. The aqueous solution was extracted with chloroform (3 × 50 ml). The combined organic layers were washed with water (5 × 50 ml) and dried (Na_2SO_4). The solvents were evaporated off under reduced pressure to give a solid residue. When this residue was subjected to preparative t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (2 : 1) as eluant, it yielded a colourless solid. Slow crystallisation from methanol afforded pure crystals of N,N',N'',N'''-*tetramethyltetra-anthranilide* (14) (10 mg, 70%), m.p. >300 °C [Found: *M* (mass spec.), 532.2095. $C_{32}H_{28}N_4O_4$ requires *M*, 532.2110], τ(CD_2Cl_2) 2.33—2.65 (16 H, m, ArH) and 6.74 (12 H, s, 4 × NMe).

N-*Benzyl*-N',N'',N'''-*trimethyltetra-anthranilide* (15).—*N,N',N''*-Trimethyltetra-anthranilide (13) (15 mg) was stirred with benzyl bromide (0.4 ml) and sodium hydride (60 mg) in dry tetrahydrofuran (10 ml) at room temperature for 16 h. Excess of sodium hydride was destroyed by careful addition of water and most of the tetrahydrofuran was removed by evaporation under reduced pressure. The aqueous solution was extracted with chloroform (3 × 25 ml) and the combined organic extracts were washed with water (2 × 25 ml) and dried (Na_2SO_4). The solvents and excess of benzyl bromide were evaporated off under reduced pressure to afford an oil. T.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (2 : 1) as eluant indicated the presence of starting material (R_F 0.40) and a product (R_F 0.65). N-*Benzyl*-N',N'',N'''-*trimethyltetra-anthranilide* (15) (R_F 0.65) was purified by preparative t.l.c. using the same solvent system. Crystallisation of the crude product from toluene gave colourless crystals (10 mg, 57%), m.p. >300 °C [Found: *M* (mass spec.), 608.2396. $C_{38}H_{32}N_4O_4$ requires *M*, 608.2423], τ($CDCl_3$) 2.15—3.15 (21 H, m, ArH), 4.93 (2 H, bs, benzylic CH_2), and 6.50, 6.57, 6.61, and 6.66 (9 H, 4 × s, signals of different intensities and variable line shapes, 3 × NMe).

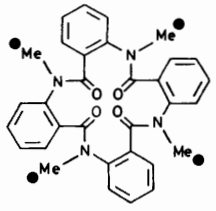
Determination of Rates of Conformational Changes by Dynamic ^{1}H *N.m.r. Spectroscopy*.—A program VI [9] (coded in FORTRAN IV) for exchange of nuclei between all six sites of three AB systems, A1B1, A2B2, and A3B3, was used to simulate the spectral line shapes associated with the benzylic-methylene protons in *N*-benzyl-*N'*,*N''*,*N'''*-trimethyltetra-anthranilide (15). Calculated spectra employing site-exchange scheme (ii) [9] are shown in Figure 1 beside selected observed spectra. Although the relative intensities of A1B1, A2B2, and A3B3 were 0.27, 0.23, and 0.50 respectively at −30 °C, it was only possible to match observed and calculated spectra using one averaged rate constant, *k*, particularly in the low and high temperature limits.

RESULTS AND DISCUSSION

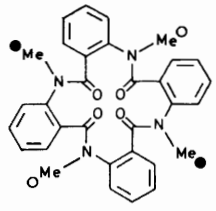
The ^{1}H n.m.r. spectrum of *N,N',N'',N'''*-tetramethyltetra-anthranilide (14) in dideuteriodichloromethane

exhibited a singlet at τ 6.74 for the *N*-methyl protons. Although this signal broadened slightly on cooling the solution down to −100 °C, it showed no signs of temperature-dependent behaviour which could be ascribed to slow conformational changes occurring in solution. It follows that either (i) ring inversion and interconversion process are still occurring rapidly on the ^{1}H n.m.r. time scale even at −100 °C or (ii) a ground-state conformation with homotopic or enantiotopic *N*-methyl groups has been adopted. In this regard, three conformations† with all-*trans* amide linkages have to be considered: one (27) has averaged C_4 symmetry, another (28) has averaged S_4 symmetry, and yet another (29) has averaged S_2 symmetry. The conformation with all-*cis* amide linkages having averaged C_4 symmetry can be discounted because of the nonbonded interactions it experiences between *ortho* hydrogen atoms on neighbouring aromatic rings.

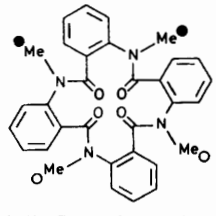
In order to achieve a better understanding of the conformational behaviour of tetra-anthranilides in solution, it was decided to investigate the temperature dependence of the ^{1}H n.m.r. spectrum of the *N*-benzyl-*N'*,*N''*,*N'''*-trimethyl derivative (15). The benzyl group provides the prochiral methylene protons necessary to probe ring-inversion processes. However, the temperature dependent ^{1}H n.m.r. spectra of (15) in deuteriochloroform revealed the presence of three conformational diastereoisomers in equilibrium with each other.



(27) C_4 conformation



(28) S_4 conformation



(29) S_2 conformation

† These conformations are represented in (27)—(29) such that the mean plane of the 16-membered ring lies in the plane of the paper and the *N*-methyl groups are oriented above (●) or below (○) this mean plane.

The broad singlet observed for the benzylic-methylene protons at +40 °C eventually separated (see Figure 1) into three AB systems (τ_{A1} 4.06, τ_{B1} 5.39, J_{A1B1} = 15.0 Hz; τ_{A2} 4.37, τ_{B2} 5.54, J_{A2B2} = 15.5 Hz; τ_{A3} 4.84, τ_{B3} 5.04, J_{A3B3} = 15.1 Hz) with relative intensities of 0.27, 0.23, and 0.50 for A1B1, A2B2, and A3B3 respectively at −30 °C. Line-shape analysis of the partial spectra (Figure 1) for the benzylic-methylene protons led to an average free energy of activation of 13.6 kcal

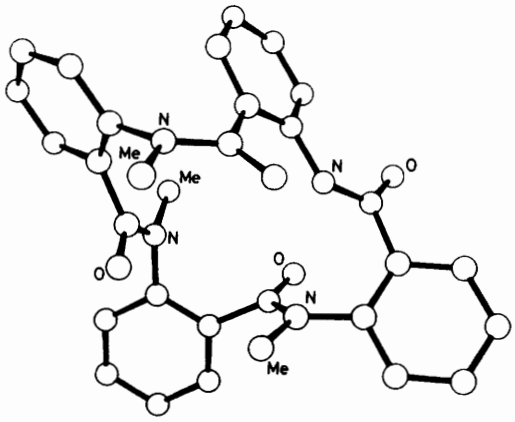


FIGURE 2 The structure of *N*,*N'*,*N''*-trimethyltetra-anthranilide (13) in the solid state [6]

mol^{-1} for the conformational changes occurring in *N*-benzyl-*N'N''*,*N'''*-trimethyltetra-anthranilide (15) in deuteriochloroform solution. This energy barrier is very much lower (>10 kcal mol^{-1}) than those found previously [2] for *N*,*N'*,*N''*-trisubstituted trianthranilide derivatives and suggests that the conformational changes could involve pedalling [8,10] of *trans*-amide linkages. Although it is not possible on present evidence to assign conformations to the three diastereoisomers of (15), the all-*trans* conformations with averaged C_4 (27), S_4 (28), and S_2 (29) symmetry are possible candidates.

The ^{1}H n.m.r. spectrum of *N*,*N'*,*N''*-trimethyltetra-anthranilide (13) in deuteriochloroform at ambient temperature reveals the presence of no less than six amide (CONH) signals at low field and seventeen *N*-methyl (CONMe) signals at high field. Hence, at least six diastereoisomeric conformations of (13) are populated in solution at room temperature and the energy barriers to their interconversions are obviously significantly higher than that found for the *N*-benzyl derivative (15). This suggests that transannular hydrogen bonds are providing a stabilising influence to the ground state conformations of (1) and/or *cis*-amide linkages are featuring as structural units in some of the conformational diastereoisomers. Fortunately, *N*,*N'*,*N''*-trimethyltetra-anthranilide (13) gave crystals, after being allowed to stand in methanol–*p*-dioxan for 4 months,[6] which were amenable to *X*-ray crystallography. The crystal structure analysis revealed [6] (see Figure 2) that, in the solid state, (13) adopts a conformation which is apparently stabilised by a strong intramolecular

$>C=O \cdots H-N<$ hydrogen bond (2.71 Å) and contains one *cis*-amide linkage in addition to three *trans*-amide linkages.

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