Conformational Behaviour of Medium-sized Rings. Part 12.[1] Tri-3-methyltrianthranilide

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The stepwise synthesis of the *N,N'*-di- and *N,N',N''*-tri-substituted tri-3-methyltrianthranilides (13)—(19) are described. The amino-acid derivatives (34), (38), and (45), which are the key acyclic precursors in the synthesis of the tri-3-methyltrianthranilides, were all prepared from 2-amino-*m*-toluic acid (22) and 2-nitro-*m*-toluoyl chloride as starting materials.

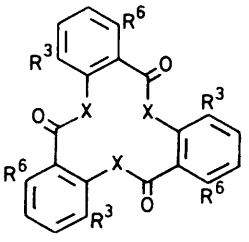
Tri-3-methyltrianthranilide derivatives with three equivalent *N,N',N''*-substituents can exist in either propeller or helical conformations. The *N,N',N''*-trimethyl derivative (14) adopts enantiomeric helical conformations in solution and the barrier to ring inversion is 26.8 kcal mol^{-1}. The *N,N',N''*-tribenzyl derivative (19) populates both propeller and helical conformations in solution: these two conformational diastereoisomers have been separated by chromatography and isolated as crystalline compounds.

Tri-3-methyltrianthranilide derivatives with two or three non-equivalent *N,N',N''*-substituents can, in principle, exist in either propeller or three different helical conformations. One of these three helical conformations is specifically populated in deuteriochloroform solution by compounds (13) and (15)—(17). The *N,N'*-dibenzyl derivative (18) populates the propeller and one helical conformation in solution: two conformational diastereoisomers have been isolated, one as an oil and the other as a crystalline compound.

The *N,N'*-dimethyl-*N''*-benzyl derivative (15) undergoes spontaneous resolution when it crystallises as a 1 : 1 adduct from toluene. The *N*-methyl-*N'*-benzyl derivative (16) also forms a 1 : 1 inclusion compound on crystallisation from toluene. Although this derivative exists as only one conformational diastereoisomer of the helical type in deuteriochloroform solution, two different diastereoisomeric conformations undergo equilibration in hexadeuteriodimethyl sulphoxide with a barrier to interconversion of 16.1 kcal mol^{-1}.

PREVIOUSLY, we have demonstrated that the free energies of activation for ring inversion and interconversion processes † in solution for the trisalicylides [2] (1)—(5) and trithiosalicylides [3] (6)—(9) are raised dramatically by the introduction of alkyl substituents into the *ortho*-positions of the aromatic rings. Subsequently, the conformational behaviour of a wide range of *N,N'*-di- and *N,N',N''*-tri-substituted trianthranilide derivatives [1,4] (10) in solution was studied by us in considerable detail. However, there was little or no incentive during our initial investigations reported [1] in the preceding paper to incorporate alkyl substituents into the *ortho*-positions of the aromatic rings for two reasons: (i) the substituents associated with the nitrogen atoms of the *trans*-amide linkages provided the necessary n.m.r. probes with which to investigate the conformational behaviour of the trianthranilide derivatives in solution, and (ii) the barriers to ring inversions and interconversions involving enantiomeric pairs of diastereoisomeric propeller and helical conformations were generally in excess of 20 kcal mol^{-1}. In some instances it even proved possible to isolate conformational diastereoisomers and characterise them as crystalline compounds. Nonetheless, it eventually became imperative for us to examine the effect upon the conformational behaviour of trianthranilide derivatives of introducing alkyl substituents into either position-3 or position-6 of the aromatic rings. While we could anticipate a further raising of the barriers to ring inversions and interconversions in these tri-methylaryl derivatives relative to those observed [1] in the parent trianthranilides, we could not predict how the positions of the conformational equilibria in solution would be influenced or what the consequences would be for inclusion compound formation and/or spontaneous resolution on crystallisation.

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



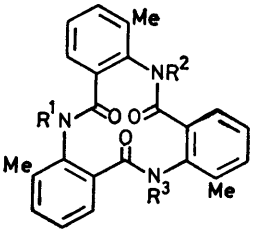
	X	R^3	R^6
(1)	O	H	H
(2)	O	Me	H
(3)	O	Me	Me
(4)	O	Me	$CHMe_2$
(5)	O	$CHMe_2$	Me
(6)	S	H	H
(7)	S	Me	H
(8)	S	H	Me
(9)	S	Me	Me
(10)	NR	H	H
(11)	NR	Me	H
(12)	NR	H	Me

In the event, we have only been able to synthesise the tri-3-methyltrianthranilide derivatives (11) by the stepwise approach that proved so successful in the preparation of the parent compounds. To date, all our preliminary attempts to prepare tri-6-methyltrianthranilide derivatives (12) have failed. This paper gives (i) an account of the synthesis of the tri-3-methyltrianthrani-

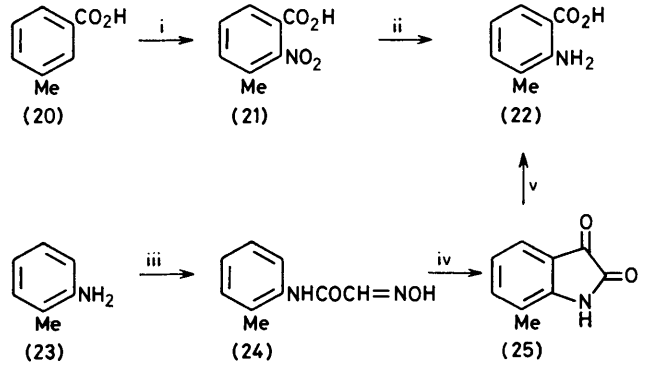
lide derivatives * (13)—(19), (ii) discusses their conformational behaviour in solution, and (iii) reflects briefly upon their solid-state properties. A communication reporting our preliminary investigations on the *N,N'*-dimethyl- (13), *N,N',N''*-trimethyl- (14), and *N,N'*-dimethyl-*N''*-benzyl- (15) derivatives has already appeared.[5]

The starting materials, namely 2-nitro-*m*-toluic acid (21) and 2-amino-*m*-toluic acid (22) for the stepwise syntheses of the tri-3-methyltrianthranilide derivatives (13)—(19) were obtained from *m*-toluic acid and *o*-toluidine (23) by routes (see Scheme 1) already reported in the literature.[6-9] A solution of 2-nitro-*m*-toluoyl chloride [10] in benzene was prepared ($SOCl_2$) from the acid (21) just prior to its use in the various acylations described below. *N,N'*-Dimethyltri-3-methyltrianthranilide (13) was obtained from 2-amino-*m*-toluic acid (22) and 2-nitrotoluoyl chloride as a result of the following stepwise procedures: (i) reaction (KOH, H_2O, C_6H_6) of (22) with 2-nitro-*m*-toluoyl chloride afforded the amide (26), albeit in admixture with (21) and (22), (ii) methylation (MeI, NaH, Me_2SO) of this mixture of products yielded the methyl ester (27), and (iii) reduction ($TiCl_3$, EtOH) of the aromatic nitro-grouping in (27) gave the methyl ester (28) which was (iv) saponified (LiOH, MeOH, H_2O) to give the amino-acid (29); (v) reaction (LiOH, H_2O, C_6H_6) of the amino-acid (29) with 2-nitro-*m*-toluoyl chloride gave the bisamide (30) contaminated with (22) and (29) whereas the methyl ester (28) treated in the same manner afforded the pure bisamide (31) after fractional crystallisation; (vi) methylation (MeI, NaH, Me_2SO) of both the impure bisamide (30) and the pure bisamide (31) yielded the methyl ester (32), which was (vii) subjected to reduction ($TiCl_3$, EtOH) of its aromatic nitro-grouping in order to afford the methyl ester (33); (viii) de-esterification (NaOH, MeOH, H_2O) of (33) gave the key acyclic amino-acid derivative (34) which (ix) underwent cyclisation ($SOCl_2$, $CHCl_3$) to provide the desired *N,N'*-dimethyltri-3-methyltrianthranilide (13) as the minor (19% yield) product and the quinazolinedione (35) as the major (41% yield) product. Cyclisation of the acyclic amino-acid derivative (34) with *N,N'*-dicyclohexylcarbodiimide in CH_2Cl_2 proceeded to give (13) in extremely low yield (<1%). This result is in marked contrast to the success [1] of the intramolecular condensation in affording *N,N'*-dimethyltrianthranilide from its acyclic amino-acid precursor. Methylation (MeI, NaH, Me_2SO) of (13) yielded *N,N',N''*-trimethyltri-3-methyltrianthranilide (14). Benzylation ($PhCH_2Br$, NaH, THF) of (13) yielded *N,N'*-dimethyl-*N''*-benzyltri-3-methyltrianthranilide (15).

N-Methyl-*N'*-benzyltri-3-methyltrianthranilide (16) was prepared by the following four-step reaction sequence

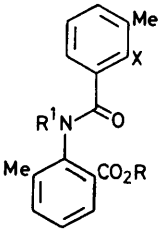


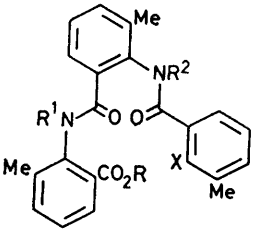
	R^1	R^2	R^3
(13)	Me	Me	H
(14)	Me	Me	Me
(15)	Me	Me	CH_2Ph
(16)	Me	CH_2Ph	H
(17)	Me	CH_2Ph	CH_2Ph
(18)	CH_2Ph	CH_2Ph	H
(19)	CH_2Ph	CH_2Ph	CH_2Ph



SCHEME 1 *Reagents*: i, HNO_3; ii, $H_2NNH_2{\cdot}H_2O$, Raney Ni, EtOH; iii, Cl_3CCHO, H_2O, HCl, Na_2SO_4 then $HONH_2{\cdot}HCl$; iv, H_2SO_4; v, H_2O_2, NaOH

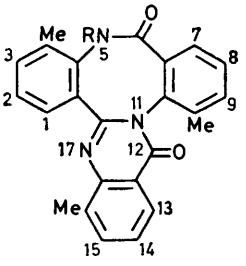
* In naming the substituents on the nitrogen atoms of the amide linkages in these compounds, it is necessary for ease of constitutional comparison and the presentation of complex stereochemical arguments for the *N,N'*, and *N''* substituents respectively to be named in the order R^1, R^2, and R^3 defined by the general formula. This precedence has been adopted and followed throughout this Paper (*cf.* ref. 1) rather than the usual rule based upon the substituents assuming a preference determined by the first letters of the names of substituents having to appear in alphabetical order.





	R	R^1	R^2	X	
(26)	H	H	—	NO_2	
(27)	Me	Me	—	NO_2	
(28)	Me	Me	—	NH_2	
(29)	H	Me	—	NH_2	
	H	Me	H	NO_2	(30)
	Me	Me	H	NO_2	(31)
	Me	Me	Me	NO_2	(32)
	Me	Me	Me	NH_2	(33)
	H	Me	Me	NH_2	(34)
	Me	Me	CH_2Ph	NO_2	(36)
	Me	Me	CH_2Ph	NH_2	(37)
	H	Me	CH_2Ph	NH_2	(38)
(40)	H	CH_2Ph	—	NO_2	
(41)	H	CH_2Ph	—	NH_2	
	H	CH_2Ph	H	NO_2	(42)
	CH_2Ph	CH_2Ph	CH_2Ph	NO_2	(43)
	CH_2Ph	CH_2Ph	CH_2Ph	NH_2	(44)
	H	CH_2Ph	CH_2Ph	NH_2	(45)

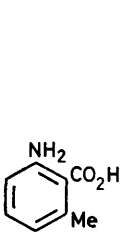
from the bisamide (31). (i) Benzylation ($PhCH_2Br$, NaH, THF) of (31) gave the *N*-methyl-*N'*-benzyl derivative (36) which was (ii) reduced ($TiCl_3$, EtOH) to (37); (iii) de-esterification (NaOH, MeOH, H_2O) of the methyl ester (37) afforded the acyclic amino-acid derivative (38) which (iv) underwent cyclisation ($SOCl_2$, $CHCl_3$) to provide the desired *N*-methyl-*N'*-benzyltri-3-methyltrianthranilide (16) as the minor (13% yield) product and the quinazolinedione (39) as the major (24% yield) product. Benzylation ($PhCH_2Br$, NaH, THF) of (16) yielded *N*-methyl-*N'*,*N''*-dibenzyltri-3-methyltrianthranilide (17).



(35) R = Me
(39) R = CH_2Ph

N,*N'*-Dibenzyltri-3-methyltrianthranilide (18) was synthesised from the amide (26) by a reaction sequence involving the following seven steps. (i) Benzylation ($PhCH_2Br$, NaH, Me_2SO) of the amide (26), which contained 2-nitro-*m*-toluic acid (21) and 2-amino-*m*-toluic acid (22) as impurities, yielded the *N*-benzyl derivative (40), and (ii) reduction ($TiCl_3$, EtOH) of the aromatic nitro-grouping in (40) gave (41) which was (iii) condensed (LiOH, H_2O, C_6H_6) with 2-nitro-*m*-toluoyl chloride to afford the bisamide (42); (iv) benzylation ($PhCH_2Br$, NaH, THF) of (42) yielded the benzyl ester (43) which was (v) subjected to reduction ($TiCl_3$, EtOH) of its aromatic nitro-grouping in order to afford the benzyl ester (44); (vi) de-esterification (NaOH, MeOH, H_2O) of (44) gave the acyclic amino-acid derivative (45) which (vii) underwent cyclisation ($SOCl_2$, $CHCl_3$) to afford an extremely low yield (*ca.* 1%) of the desired *N*,*N'*-dibenzyltri-3-methyltrianthranilide (18) as a mixture of conformational diastereoisomers which could be separated by h.p.l.c. (see Experimental and Results and Discussion sections). The yield of (18) was not improved beyond 1% by employing *N*,*N'*-dicyclohexylcarbodi-imide in CH_2Cl_2 to promote the intramolecular condensation of (45). Benzylation ($PhCH_2Br$, NaH, THF) of (18) yielded *N*,*N'*,*N''*-tribenzyltri-3-methyltrianthranilide (19) as a mixture of conformational diastereoisomers which could be separated by h.p.l.c. (see Experimental and Results and Discussion sections).

The synthesis of tri-6-methyltrianthranilide derivatives (12) was attempted using the same approach as that which had been successful in the preparation of the tri-3-methyl analogues (11). When 2-amino-*o*-toluic acid [11] (46) was treated (KOH, H_2O, C_6H_6) with 2-nitro-*o*-toluoyl chloride, it was only possible to recover starting materials. No evidence for the presence of the amide (47) was obtained. Presumably, attack by the nucleophilic amino-group at the carbonyl carbon atom of the acid chloride is hindered by the 2-nitro- and 6-methyl-substituents. Other approaches to the synthesis of the amide (47) have not been investigated.



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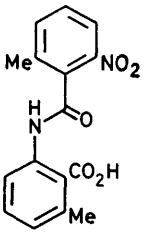


(47)

EXPERIMENTAL

The general methods have been discussed in Parts 3 [12] and 6.[13]

2-Nitro-m-*toluic Acid* [6] (21).—This compound, m.p. 223—224 °C (lit.,[6] m.p. 213—220 °C), was prepared [6] from *m*-toluic acid.

2-Nitro-m-*toluoyl Chloride*.[10]—A solution of 2-nitro-*m*-toluic acid (21) (12 g) and redistilled thionyl chloride (6 ml) in dry benzene (60 ml) was refluxed until the evolution of hydrogen chloride and sulphur dioxide had ceased. The solution was then cooled, filtered, and the 2-nitro-*m*-toluoyl chloride subsequently used without further purification in benzene solution. [The solution contains 14.4 g of 2-nitro-*m*-toluoyl chloride in benzene (60 ml).]

2'-Methyl(*hydroxyimino*)*acetanilide* [7] (24).—This compound, m.p. 118—120 °C (lit.[7] m.p. 121 °C), was prepared [7] from *o*-toluidine.

7-Methylisatin [8] (25).—This compound, m.p. 262—264 °C (lit.,[8] m.p. 263—264 °C), was prepared [8] from 2'-methyl(hydroxyimino)acetanilide (24).

2-Amino-m-*toluic Acid* [9] (22).—(a) Hydrazine hydrate (2 ml) was added to 2-nitro-*m*-toluic acid (21) (2 g) dissolved in ethanol (20 ml), the reaction mixture was heated to 40 °C, and a small amount of Raney nickel was added. More catalyst was added after 1 and 2 h and the solution was refluxed overnight. The hot solution was filtered to remove the catalyst and the ethanol was evaporated off to give a residue. Crystallisation of this crude product from aqueous methanol afforded 2-amino-*m*-toluic acid (22) (1.4 g, 84%), m.p. 173—175 °C (lit.,[9] m.p. 176 °C).

(b) A 10% solution of hydrogen peroxide was added dropwise to a stirred suspension of 7-methylisatin (25) (11.1 g) in an aqueous solution (100 ml) of 10% aqueous sodium hydroxide maintained at 85—90 °C until an acidified test sample did not give a red coloration indicative of the presence of 7-methylisatin (25). The solution was then treated with charcoal, filtered, and acidified with 3N-hydrochloric acid to pH 3.6—3.7, whereupon the crude product precipitated as a white solid. Recrystallisation from methanol–water afforded 2-amino-*m*-toluic acid (22) (6 g, 58%).

3-Methyl-N-(*3-methyl-2-nitrobenzoyl*)*anthranilic Acid* (26).—2-Amino-*m*-toluic acid (22) (5 g) was dissolved in a solution of potassium hydroxide (3 g) in water (36 ml). A

solution of 2-nitro-*m*-toluoyl chloride (30 ml) diluted with benzene (20 ml) was added and the reaction mixture was stirred for 5 min. A solid which precipitated and was isolated at this stage was found to correspond to the starting material. This solid was redissolved in a solution of potassium hydroxide (2 g) in water (24 ml) and was added once again to the reaction mixture. Stirring was continued for a further 15 min. The precipitated material was filtered off, additional acid chloride was added to the filtrate, and the reaction mixture was stirred for a further 1 h. More product was obtained in this manner. Examination of the combined crude products by t.l.c. and i.r. spectroscopy showed that they comprised a mixture (7.5 g) of 2-nitro-*m*-toluic acid (21), 2-amino-*m*-toluic acid (22), and 3-*methyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthranilic acid* (26). This mixture was used in the next step of the reaction sequence without further purification.

Methyl 3-*Methyl*-N-*methyl*-N-(3-*methyl*-2-*nitrobenzoyl*)-*anthranilate* (27).—The mixture (23 g) of (21), (22), and (26) was stirred with methyl iodide (50 ml) and sodium hydride (4 g) in dry dimethyl sulphoxide (200 ml) at room temperature for 4 h. Excess of sodium hydride was destroyed by addition of water to the reaction mixture. The solid which separated out was filtered off and washed, firstly with ether, and then with light petroleum (b.p. 60—80 °C). This procedure afforded a crude product which crystallised from methanol to give *methyl* 3-*methyl*-N-*methyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthranilate* (27) (13.8 g), m.p. 137—138 °C [Found: C, 62.9; H, 5.5; N, 8.1%; *M* (mass spec.), 342. $C_{18}H_{18}N_2O_5$ requires C, 63.2; H, 5.3; N, 8.2%; *M*, 342], $\nu_{max.}$ (Nujol) 1 720 (CO_2Me), 1 640 (CO), and 1 530 and 1 360 cm^{-1} (NO_2); τ($CDCl_3$) 2.06—2.81 (6 H, m, ArH), 6.12 (3 H, s, CO_2Me), 6.80 (3 H, s, NMe), and 7.55 and 7.60 (6 H, 2 × s, 2 × Ar*Me*).

Methyl 3-*Methyl*-N-*methyl*-N-(3-*methyl*-2-*aminobenzoyl*)-*anthranilate* (28).—A titanium(III) chloride solution (160 ml; 12.5%) was added dropwise to a boiling solution of the methyl ester (27) (9.75 g) in ethanol (375 ml). The solution was heated for 10 min, poured into boiling water (900 ml), heated for a further 30 min, and allowed to cool. The aqueous reaction mixture was extracted with chloroform (3 × 150 ml) and the combined organic layers were washed with water (2 × 100 ml) and dried (Na_2SO_4). After filtration, the solvent was evaporated off under reduced pressure to afford *methyl* 3-*methyl*-N-*methyl*-N-(3-*methyl*-2-*aminobenzoyl*)*anthranilate* (28) (8.3 g, 93%) as an oil which crystallised from glacial acetic acid, m.p. 84—86 °C [Found: *M* (mass spec), 312. $C_{18}H_{20}N_2O_3$ requires *M*, 312], $\nu_{max.}$ (Nujol) 3 450 and 3 350 (NH_2), 1 720 (CO_2Me), and 1 630 cm^{-1} (CO); τ($CDCl_3$) 2.06—4.02 (6 H, m, ArH), 5.39 (2 H, bs, NH_2), 6.14 and 6.18 (3 H, 2 × s in the approximate ratio of 50 : 50, CO_2Me), 6.68 and 6.80 (3 H, 2 × s in the approximate ratio of 50 : 50, NMe), and 7.66, 7.84, and 7.96 (6 H, 3 × s in the approximate ratio of 50 : 20 : 30, 2 × ArMe).†

3-*Methyl*-N-*methyl*-N-(3-*methyl*-2-*aminobenzoyl*)*anthranilic Acid* (29).—The methyl ester (28) (8.2 g) was dissolved in methanol (30 ml) and lithium hydroxide solution (100 ml, 10%) was added. The aqueous reaction mixture was refluxed for 3 h, filtered whilst hot, and acidified with glacial acetic acid. On concentrating the solution by evaporation under reduced pressure a white solid precipitated. This solid was collected and dried to afford 3-*methyl*-N-*methyl*-N-(3-*methyl*-2-*aminobenzoyl*)*anthranilic acid* (29) (6.3 g, 80%) [Found: *M* (mass spec.), 298. $C_{17}H_{18}N_2O_3$ requires *M*, 298], $\nu_{max.}$ (Nujol) 3 450 and 3 350 (NH_2), 1 700 (CO_2H), and 1 620 cm^{-1} (CO).

3-*Methyl*-N-*methyl*-N-[3-*methyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthraniloyl*]*anthranilic Acid* (30).—The amino-acid (29) (6.0 g) was suspended in a solution of lithium hydroxide (1 g) in water (50 ml). A solution of 2-nitro-*m*-toluoyl chloride (30 ml) diluted with benzene (15 ml) was added dropwise to the stirred reaction mixture during 1 h. The product was collected by filtration and additional acid chloride (2 ml) was added to the filtrate. More solid material was obtained after the mixture has been stirred overnight. The combined solids were found to comprise a mixture (12.2 g) of 2-nitro-*m*-toluic acid (22), the starting material (29), and 3-methyl-*N*-methyl-*N*-[3-methyl-*N*-(3-methyl-2-nitrobenzoyl)anthraniloyl]anthranilic acid (30). This mixture was used in a subsequent step of the reaction sequence without further purification.

Methyl 3-*Methyl*-N-*methyl*-N-[3-*methyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthraniloyl*]*anthranilate* (31).—The methyl ester (28) (8.3 g) was dissolved in benzene (20 ml) and added to a solution of lithium hydroxide (1.4 g) in water (65 ml). A solution of 2-nitro-*m*-toluoyl chloride in benzene (40 ml), diluted with benzene (20 ml), was added dropwise with stirring to the aqueous suspension during 1 h. A solid precipitated out. It was collected by filtration and more acid chloride solution (5 ml) was added to the filtrate. The precipitate which formed on stirring overnight was collected and the products were combined. T.l.c. and i.r. spectroscopy indicated that the solids were comprised of a mixture of 2-nitro-*m*-toluic acid (22) and the desired product. Fractional crystallisation from chloroform afforded *methyl* 3-*methyl*-N-*methyl*-N-[3-*methyl*-N-(3-*methyl*-2-*nitrobenzoyl*)-*anthraniloyl*]*anthranilate* (31) (6.1 g, 61%), m.p. 251—252 °C [Found: C, 65.5; H, 5.5; N, 8.8%; *M* (mass spec.), 475. $C_{26}H_{25}N_3O_6$ requires C, 65.7; H, 5.3; N, 8.8%; *M*, 475], $\nu_{max.}$ (Nujol) 3 200 (NH), 1 725 (CO_2Me), 1 665 and 1 625 (CO), and 1 520 cm^{-1} (NO_2); τ($CDCl_3$) 0.34 and 0.92 (1 H, 2 × bs in the approximate ratio of 64 : 36, NH); 2.06—3.37 (9 H, m, ArH), 6.30 and 6.34 (3 H, 2 × s in the approximate ratio of 64 : 36, CO_2Me), 6.62, 6.70, and 6.88 (3 H, 3 × s in the approximate ratio of 23 : 43 : 34, NMe), and 7.65, 7.70, 7.78, and 7.92 (9 H, 4 × s in the approximate ratio of 24 : 12 : 49 : 15, 3 × Ar*Me*).†

Methyl 3-*Methyl*-N-*methyl*-[3-*methyl*-N-*methyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthraniloyl*]*anthranilate* (32).—(a) The methyl ester (31) (3 g) was stirred with methyl iodide (3 ml) and sodium hydroxide (0.5 g) in dry dimethyl sulphoxide (25 ml) at room temperature overnight. Excess of sodium hydride was destroyed by the careful addition of water. The precipitate formed was collected by filtration, dried, and crystallised from methanol to afford *methyl* 3-*methyl*-N-*methyl*-N-[3-*methyl*-N-*methyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthraniloyl*]*anthranilate* (32) (2.0 g, 65%), m.p. 221—222 °C [Found: C, 65.5; H, 5.7; N, 8.4%; *M* (mass spec.), 489. $C_{27}H_{27}N_3O_6$ requires C, 66.2; H, 5.6; N, 8.6%, *M*, 489], $\nu_{max.}$ (Nujol) 1 710 (CO_2Me), 1 640 (CO), and 1 530 and 1 350 cm^{-1} (NO_2); τ($CDCl_3$) 2.12—2.82 (9 H, m, ArH), 6.12 (3 H, s, CO_2Me), 6.79 and 6.82 (6 H, 2 × s, 2 × NMe), 7.56 (6 H, s, 2 × ArCH_3), and 7.95 (3 H, s, ArCH_3).

† In the case of compounds (28), (31), (36), and (42) there is evidence in their ^1H n.m.r. spectra for the presence of slowly equilibrating conformational diastereoisomers in solution resulting from hindered rotation about amide bonds.

(b) The mixture (6 g) of (22), (29), and (30) was dissolved in dry dimethyl sulphoxide (50 ml). Sodium hydride (1 g) and methyl iodide (6 ml) were added and the reaction mixture was stirred at room temperature overnight. Addition of water produced a solid which was shown by t.l.c. to contain several products. However, column chromatography on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant gave the previously characterised title compound (32) (5.5 g) which, after crystallisation from methanol, had m.p. 221—222 °C.

Methyl 3-*Methyl*-N-*methyl*-N-[3-*methyl*-N-*methyl*-N-(3-*methyl*-2-*aminobenzoyl*)*anthraniloyl*]*anthranilate* (33).—A titanium(III) chloride solution (35 ml; 12.5%) was added dropwise with stirring to a boiling solution of the methyl ester (32) (2 g) in ethanol (100 ml). The solution was heated for 10 min, poured into boiling water (150 ml), and heated again for a further 30 min. After cooling, the aqueous reaction mixture was extracted with chloroform (3 × 100 ml). The combined organic layers were washed with water (2 × 100 ml), dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure to afford an oil. Crystallisation from aqueous methanol afforded *methyl* 3-*methyl*-N-*methyl*-N-[3-*methyl*-N-*methyl*-N-(3-*methyl*-2-*aminobenzoyl*)*anthraniloyl*]*anthranilate* (33) (1.8 g, 94%), m.p. 176—177 °C [Found: C, 70.0; H, 6.6; N, 9.4%; *M* (mass spec.), 459. $C_{27}H_{29}N_3O_4$ requires C, 70.6; H, 6.4; N, 9.2%; *M*, 459], $\nu_{max.}$ (Nujol) 3 440 and 3 350 (NH_2), 1 720 (CO_2Me), and 1 640 cm^{-1} (CO); τ($CDCl_3$) 2.11—3.50 (9 H, m, ArH), 5.49 (2 H, bs, NH_2), 6.11 (3 H, s, CO_2Me), 6.73 and 6.80 (6 H, 2 × s, 2 × NMe), 7.69 (3 H, s, Ar*Me*), and 7.85 (6 H, s, 2 × Ar*Me*).

3-*Methyl*-N-*methyl*-N-[3-*methyl*-N-*methyl*-N-(3-*methyl*-2-*aminobenzoyl*)*anthraniloyl*]*anthranilic Acid* (34).—The methyl ester (33) (1 g) was dissolved in methanol (20 ml) and 10% aqueous sodium hydroxide solution (40 ml) was added. The reaction mixture was refluxed for 2 h, filtered, and the filtrate was acidified with glacial acetic acid. The solution was concentrated by evaporation of the solvent under reduced pressure and 3-*methyl*-N-*methyl*-N-[3-*methyl*-N-*methyl*-N-(3-*methyl*-2-*aminobenzoyl*)*anthraniloyl*]*anthranilic acid* (34) was precipitated as a crystalline solid (0.85 g, 88%), m.p. 195—197 °C [Found: *M* (mass spec.), 445.1979. $C_{26}H_{27}N_3O_4$ requires *M*, 445.2001], $\nu_{max.}$ (Nujol) 3 450 (NH_2), 3 350 (OH), 1 710 (CO_2H), and 1 640 cm^{-1} (CO); τ($CDCl_3$) 2.12—3.10 (9 H, m, ArH), 4.18 (3 H, bs, NH_2 and CO_2H), 6.70 and 6.82 (6 H, 2 × s, 2 × NMe), 7.66 (3 H, s, Ar*Me*), and 7.84 (6 H, s, 2 × Ar*Me*).

3,5,10,16-*Tetramethyldibenzo*[3,4:7,8][1,5]*diazocino*[2,1-b]*quinazoline*-6,12(5H)-*dione* (35) *and* 4,5,10,11,16-*Pentamethyltribenzo*[b,f,j][1,5,9]*triazacyclododecine*-6,12,18(5H,11H,17H)-*trione* (N,N′-*Dimethyltri*-3-*methyltrianthranilide*) (13).—(a) Thionyl chloride (0.22 ml) was added dropwise with stirring to a solution of the amino-acid (34) (1.0 g) in chloroform (5 ml) and the reaction mixture was refluxed for 8 h. Removal of the chloroform and excess of thionyl chloride under reduced pressure afforded an oil which was purified by preparative t.l.c. using ethyl acetate–light petroleum (b.p. 60—80 °C) (2 : 1) as eluant to give two products. The major and faster-moving component was recrystallised from methanol to give 3,5,10,16-*tetramethyldibenzo*[3,4:7,8][1,5]*diazocino*[2,1-b]*quinazoline*-6,12(5H)-*dione* (35) (350 mg, 41%), m.p. 245—253 °C [Found: C, 75.0; H, 6.1; N, 10.4%; *M* (mass spec.), 395.1625. $C_{25}H_{21}N_3O_2$ requires C, 75.9; H, 5.4; N, 10.6%; *M*, 395.1634], $\nu_{max.}$ (Nujol) 1 690 and 1 660 cm^{-1} (CO); τ($CDCl_3$) 1.74—2.90 (9 H, m, ArH), 6.84 (3 H, s, NMe), and 7.36, 7.82, and 8.04 (9 H, 3 × s, 3 × Ar*Me*). The minor and slower-moving component, after recrystallisation from methanol or toluene, afforded N,N′-*dimethyltri*-3-*methyltrianthranilide* (13) (190 mg, 19%), m.p. >300 °C [Found: *M* (mass spec.), 427.1898. $C_{26}H_{25}N_3O_3$ requires *M*, 427.1896], τ($CDCl_3$) 1.94 (1 H, s, NH), 2.41—2.80 (9 H, m, ArH), 6.86 and 6.95 (6 H, 2 × s, 2 × NMe), 7.59 (3 H, s, Ar*Me*), and 7.63 (6 H, s, 2 × Ar*Me*); δ($CDCl_3$; $SiMe_4$ as standard) 171.4, 169.8, and 166.5 (carbonyl carbons), 138.7, 137.2, 136.3, 136.0, 135.4, 135.2, 132.8, 132.4, 131.5, 131.0, 128.7, 128.3, 128.1, 127.6, 124.0, and 123.3 (aromatic carbons), 40.1 and 39.3 (*N*-methyl carbons) and 18.1, 17.4, and 17.2 (aryl methyl carbons).

(b) A solution of the amino-acid (34) (0.5 g) in dichloromethane (75 ml) was added dropwise with stirring at room temperature to a solution of *N*,*N*′-dicyclohexylcarbodiimide (0.5 g) in dichloromethane (5 ml). The reaction mixture was stirred for 48 h and then the solvent was evaporated off to afford an oil. This oil was extracted with light petroleum (b.p. 60—80 °C) to remove excess of *N*,*N*′-dicyclohexylcarbodi-imide and the remainder of the solid was subjected to column chromatography on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) as eluant to give a very low yield (<1%) of *N*,*N*′-dimethyltri-3-methyltrianthranilide (13).

4,5,10,11,16,17-*Hexamethyltribenzo*[b,f,j][1,5,9]*triazacyclododecine*-6,12,18(5H,11H,17H)-*trione* (N,N′,N″-*Trimethyltri*-3-*methyltrianthranilide*) (14).—*N*,*N*′-Dimethyltri-3-methyltrianthranilide 13) (50 mg), sodium hydride (60 mg), and methyl iodide (1 ml) were stirred in dry dimethyl sulphoxide (10 ml) for 3 h at room temperature. Addition of water destroyed excess of sodium hydride and afforded the crude product as a white solid. Crystallisation from methanol, toluene, or ether–light petroleum (b.p. 60—80 °C) gave N,N′,N″-*trimethyltri*-3-*methyltrianthranilide* (14) (39 mg, 62%), m.p. >300 °C [Found: *M* (mass spec.), 441.2037. $C_{27}H_{27}N_3O_3$ requires *M*, 441.2052], τ($CDCl_3$) 2.56—2.80 (9 H, m, ArH), 6.78, 6.86, and 6.88 (9 H, 3 × s, 3 × NMe), 7.62 (6 H, s, 2 × Ar*Me*), and 7.65 (3 H, s, Ar*Me*); δ($CDCl_3$; $SiMe_4$ as standard) 169.6 and 169.0 (carbonyl carbons), 137.5, 137.3, 137.2, 136.9, 136.7, 136.1, 132.1, 131.7, 131.4, 128.6, 128.4, 128.2, 125.3, 124.4, and 123.7 (aromatic carbons), 40.0, 39.6, and 39.1 (*N*-methyl carbons), and 18.0, 17.3, and 17.0 (aryl methyl carbons).

5-*Benzyl*-4,10,11,16,17-*pentamethyltribenzo*[b,f,j][1,5,9]*triazacyclododecine*-6,12,18(5H,11H,17H)-*trione* (N,N′-*Dimethyl*-N″-*benzyltri*-3-*methyltrianthranilide*) (15).—*N*,*N*′-Dimethyltri-3-methyltrianthranilide (13) (57 mg), sodium hydride (60 mg), and benzyl bromide (0.5 ml) were stirred in dry tetrahydrofuran (10 ml) at room temperature for 6 h. Excess of sodium hydride was destroyed by addition of water and the aqueous mixture was extracted with chloroform (3 × 50 ml). The combined organic layers were washed with water (100 ml), dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure to afford an oil which crystallised from light petroleum (b.p. 60—80 °C). Recrystallisation from toluene afforded N,N′-*dimethyl*-N″-*benzyltri*-3-*methyltrianthranilide* (15) (44 mg, 64%), m.p. 252—254 °C [Found: *M* (mass spec.), 517.2362. $C_{33}H_{31}N_3O_3$ requires *M*, 517.2365] as a 1 : 1 inclusion compound with toluene as indicated by the ^1H n.m.r. spectral data: τ($CDCl_3$) 2.52—3.22 (19 H, m, ArH), 5.20 (2 H, bs, PhCH_2), 6.70 and 6.96 (6 H, 2 × s, 2 × NMe), 7.58 (6 H, s,

2 × Ar*Me*), 7.69 (3 H, s, Ph*Me*), and 8.55 (3 H, s, Ar*Me*). The toluene can be completely removed from the crystals *in vacuo* (<1.0 mmHg) at +60 °C within 3 h. Crystals subjected to this treatment were examined by ^{1}H n.m.r. spectroscopy: τ(C_6D_6–$CDCl_3$, 2 : 1) 2.56—3.30 (14 H, m, ArH), 5.16 and 5.24 (2 H, AB system, J_{AB} 13.5 Hz, PhCH_2), 6.98 and 7.05 (6 H, 2 × s, 2 × NMe), and 7.76, 7.85, and 8.52 (9 H, 3 × s, 3 × Ar*Me*).

An *X*-ray crystallographic examination (see Figure 5 in the Results and Discussion section) showed that, as its 1 : 1 inclusion compound with toluene, this derivative (15) adopts a helical conformation (H-2/H-2*) in the solid state and also undergoes spontaneous resolution on crystallisation.[5]

Methyl 3-*Methyl*-N-*methyl*-N-[3-*methyl*-N-*benzyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthraniloyl*]*anthranilate* (36).—Methyl 3-methyl-*N*-methyl-*N*-[3-methyl-*N*-(3-methyl-2-nitrobenzoyl)anthraniloyl]anthranilate (31) (3 g) was stirred in dry tetrahydrofuran (100 ml) with benzyl bromide (10 ml) and sodium hydride (3 g) for 36 h at room temperature. Excess of sodium hydride was destroyed by addition of water. Tetrahydrofuran was removed by evaporation under reduced pressure and the aqueous residue was extracted with chloroform (3 × 50 ml). The combined organic layers were washed with water (50 ml), dried (Na_2SO_4), and filtered. The solvent in the filtrate was evaporated off under reduced pressure to afford an oil. Excess of benzyl bromide was removed under high vacuum to give a yellow oil. T.l.c. indicated the presence of several products. Column chromatography on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 2 as eluant) afforded a white solid which was crystallised from ethanol to yield *methyl* 3-*methyl*-N-*methyl*-N-[3-*methyl*-N-*benzyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthraniloyl*]*anthranilate* (36) (1.8 g, 50%), m.p. 216—218 °C [Found: *M* (mass spec.), 565.2210. $C_{33}H_{31}N_3O_6$ requires *M*, 565.2213], $\nu_{max.}$ (Nujol) 1 720 (CO_2Me), 1 640 (CO), and 1 530 cm^{-1} (NO_2); τ($CDCl_3$) 2.02—3.94 (14 H, m, ArH), 4.54 and 5.10 (2 H, 2 × s of approximately equal intensities, benzylic CH_2), 6.10 (3 H, s, CO_2Me), 6.64 and 6.96 (3 H, 2 × s of approximately equal intensities, NMe), and 7.55, 7.60, 7.80, 7.96, 8.40, and 8.67 (9 H, 6 × s of approximately equal intensities, 3 × Ar*Me*).†

3-*Methyl*-N-*methyl*-N-[3-*methyl*-N-*benzyl*-N-(3-*methyl*-2-*aminobenzoyl*)*anthraniloyl*]*anthranilic Acid* (38).—The methyl ester (36) (1.5 g) was heated in ethanol (65 ml) and titanium(III) chloride solution (25 ml; 12.5%) was added dropwise with stirring during 30 min. The reaction mixture was refluxed for a further 10 min before being poured into boiling water (100 ml). The aqueous suspension was allowed to cool and then it was extracted with chloroform (3 × 50 ml). The combined organic layers were washed with water (50 ml), dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure to afford methyl 3-methyl-*N*-methyl-*N*-[3-methyl-*N*-benzyl-*N*-(3-methyl-2-aminobenzoyl)anthraniloyl]anthranilate (37) (1.4 g) [Found: *M* (mass spec.), 535. $C_{33}H_{33}N_3O_4$ requires *M*, 535] as a solid residue. This residue was dissolved in methanol (10 ml) and the solution was refluxed in the presence of sodium hydroxide solution (40 ml; 10%) for 2 h. The reaction mixture was filtered and the filtrate was acidified with dilute hydrochloric acid. The aqueous solution was extracted with chloroform (3 × 100 ml) and the combined organic layers were washed with water (100 ml), dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure to afford a white solid. Crystallisation of this solid from aqueous methanol yielded 3-*methyl*-N-*methyl*-N-[3-*methyl*-N-*benzyl*-N-(3-*methyl*-2-*aminobenzoyl*)*anthraniloyl*]*anthranilic acid* (38) (1.1 g, 80%), m.p. 178—180 °C [Found: *M* (mass spec.), 521.2306. $C_{32}H_{31}N_3O_4$ requires *M*, 521.2315], $\nu_{max.}$ (Nujol) 3 460 and 3 350 (NH_2), 1 710 (CO_2H), and 1 630 cm^{-1} (CO).

5-*Benzyl*-3,10,16-*trimethyldibenzo*[3,4:7,8][1,5]*diazocino*-[2,1-*b*]*quinazoline*-6,12(5H)-*dione* (39) and 5-*Benzyl*-4,10,16,-17-*tetramethyltribenzo*[b,f,j][1,5,9]*triazacyclododecine*-6,12,-18(5H,11H,17H)-*trione* (N-*Methyl*-N′-*benzyltri*-3-*methyltri*-*anthranilide*) (16).—The amino-acid (38) (1.0 g) was dissolved in dry redistilled chloroform (5 ml). Thionyl chloride (0.5 ml) was added dropwise to the solution with stirring and the reaction mixture was heated under reflux for 24 h. Evaporation of the solvent together with the excess of thionyl chloride under reduced pressure produced a residue. T.l.c. indicated the presence of two products with R_F values of 0.53 and 0.16 in ethyl acetate–light petroleum (b.p. 60—80 °C) (2 : 1). Preparative t.l.c. on silica gel using this solvent system as eluant afforded two fractions. Fraction 1 (R_F 0.53) was crystallised from ethanol to yield 5-*benzyl*-3,10,16-*trimethyldibenzo*[3,4:7,8]-[1,5]*diazocino*[2,1-b]*quinazoline*-6,12(5H)-*dione* (39) (240 mg, 24%), m.p. 275—278 °C [Found: *M* (mass spec.), 471.1935. $C_{31}H_{25}N_3O_2$ requires *M*, 471.1947], $\nu_{max.}$ (Nujol) 1 680 and 1 660 cm^{-1} (CO); τ($CDCl_3$) 1.78—3.51 (14 H, m, ArH), 4.13 and 6.24 (2 H, AB system, J_{AB} 14 Hz, benzylic CH_2), 7.60, 7.72, and 8.13 (9 H, 3 × s, 2 × Ar*Me*). On crystallisation from toluene, Fraction 2 (R_F 0.16) yielded N-*methyl*-N′-*benzyltri*-3-*methyltrianthranilide* (16) (127 mg, 13%), m.p. 131—133 °C [Found: *M* (mass spec.), 503.2201. $C_{32}H_{29}N_3O_3$ requires *M*, 503.2209] as a 1 : 1 inclusion compound with toluene as indicated by the ^{1}H n.m.r. spectral data: τ($CDCl_3$) 2.09 (1 H, bs, NH), 2.30—3.18 (19 H, m, ArH), 5.16 and 5.34 (2 H, AB system, J_{AB} 14 Hz, benzylic CH_2), 6.94 (3 H, s, NMe), 7.56 and 7.59 (6 H, 2 × s, 2 × Ar*Me*), 7.68 (3 H, s, Ph*Me*), and 8.50 (3 H, s, Ar*Me*). The toluene can be completely removed from the crystals *in vacuo* (<1.0 mmHg) at +60 °C within 3 h. Crystals subjected to this treatment were examined by ^{1}H n.m.r. spectroscopy in $CDCl_3$. In addition to a change in the signal pattern observed in the aromatic region (τ 2.30—3.18), the singlet at τ 7.68 was absent in the spectrum.

5,11-*Dibenzyl*-4,10,16,17-*tetramethyltribenzo*[b,f,j][1,5,9]-*triazacyclododecine*-6,12,18(5H,11H,17H)-*trione* (N-*Methyl*-N′,N″-*dibenzyltri*-3-*methyltrianthranilide*) (17).—*N*-Methyl-*N*′-benzyltri-3-methyltrianthranilide (16) (47 mg) was stirred with benzyl bromide (0.6 ml) and sodium hydride (80 mg) in dry tetrahydrofuran (10 ml) at room temperature for 6 h. Excess of sodium hydride was destroyed by addition of water and the tetrahydrofuran was removed by evaporation under reduced pressure. The aqueous suspension was extracted with chloroform (3 × 25 ml) and the combined organic layers were washed with water (2 × 25 ml), dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure to afford an oil from which benzyl bromide was removed by evaporation under high vacuum. T.l.c. of the solid residue on silica gel in ethyl acetate–light petroleum (b.p. 60—80 °C) (2 : 1) as eluant indicated the presence of starting material (R_F 0.16) and a product (R_F 0.53). Preparative t.l.c. on silica gel using the same solvent system as eluant afforded, after crystallisation from toluene, N-*methyl*-N′,N″-*dibenzyltri*-3-*methyl*-

† See footnote on p. 1704.

trianthranilide (17) (41 mg, 74%), m.p. 294—296 °C [Found: *M* (mass spec.), 593.2964. $C_{39}H_{29}N_3O_3$ requires *M*, 593.2678], $\nu_{max.}$ (Nujol) 1 740 and 1 660 cm^{-1} (CO); τ($CDCl_3$) 2.44—3.28 (19 H, m, ArH), 5.19 (2 H, s, benzylic CH_2), 5.28 and 5.34 (2 H, AB system, J_{AB} 14 Hz, benzylic CH_2), 6.74 (3 H, s, NMe), 7.56, 8.34, and 8.52 (9 H, 3 × s, 3 × Ar*Me*).

3-*Methyl*-N-*benzyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthranilic Acid* (40).—A mixture (16 g) of 2-nitro-*m*-toluic acid (21), 2-amino-*m*-toluic acid (22), and 3-methyl-*N*-(3-methyl-2-nitrobenzoyl)anthranilic acid (26) was stirred with benzyl bromide (20 ml) and sodium hydride (3 g) in dry dimethyl sulphoxide (200 ml) under an atmosphere of nitrogen at room temperature overnight. Excess of sodium hydride was destroyed by addition of water. The aqueous mixture was extracted with chloroform (3 × 150 ml) and the combined organic layers were washed with water (5 × 150 ml). The chloroform solution was dried (Na_2SO_4), filtered to remove the inorganic material, and the filtrate evaporated under reduced pressure to afford an oil. Evaporation under high vacuum removed excess of benzyl bromide. The crude product was subjected to column chromatography on alumina with chloroform as eluant. The solid which was isolated was crystallised from methanol to yield 3-*methyl*-N-*benzyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthranilic acid* (40) (5.6 g), m.p. 132—133 °C [Found: C, 68.1; H, 5.2; N, 6.8%; *M* (mass spec.), 404. $C_{23}H_{20}N_2O_5$ requires C 68.3; H, 5.0; N, 6.9%; *M*, 404], $\nu_{max.}$ (Nujol) 1 690 (CO_2H), 1 670 (CO), and 1 520 and 1 345 (NO_2) cm^{-1}; τ($CDCl_3$) 2.04—2.94 (12 H, m, ArH and CO_2H), 4.70 (2 H, s, benzylic CH_2) and 7.66 and 7.70 (6 H, 2 × s, 2 × Ar*Me*).

3-*Methyl*-N-*benzyl*-N-(3-*methyl*-2-*aminobenzoyl*)*anthranilic Acid* (41).—Titanium(III) chloride solution (60 ml; 12.5%) was added dropwise with stirring to a refluxing solution of 3-methyl-*N*-benzyl-*N*-(3-methyl-2-nitrobenzoyl)anthranilic acid (40) (3.8 g) in ethanol (125 ml). The reaction mixture was heated for 10 min, poured into boiling water (300 ml), and heated for a further 30 min. On cooling, the aqueous suspension was extracted with chloroform (3 × 150 ml). The combined organic layers were washed with water (2 × 100 ml), dried (Na_2SO_4), filtered to remove the inorganic material, and the filtrate concentrated under reduced pressure to afford an oil. Crystallisation from methanol gave 3-*methyl*-N-*benzyl*-N-(3-*methyl*-2-*aminobenzoyl*)*anthranilic* acid (41) (2.3 g, 66%), m.p. 118—120 °C [Found: C, 73.9; H, 6.2; N, 7.6%; *M* (mass spec.), 374. $C_{23}H_{22}N_2O_3$ requires C, 73.8; H, 5.9; N, 7.5%, *M*, 374], $\nu_{max.}$ (Nujol) 3 460 and 3 320 (NH_2), 1 680 (CO_2H) and 1 660 cm^{-1} (CO); τ($CDCl_3$) 2.08—3.46 (12 H, m, ArH and CO_2H), 4.26 (2 H, bs, NH_2), 4.73 (2 H, s, benzylic CH_2), and 7.68 and 7.84 (6 H, 2 × s, 2 × Ar*Me*).

3-*Methyl*-N-*benzyl*-N-[3-*methyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthraniloyl*]*anthranilic Acid* (42).—The amino-acid derivative (41) (2.3 g) was suspended in a solution of lithium hydroxide in water (20 ml). A benzene solution (20 ml) of 2-nitro-*m*-toluoyl chloride, diluted with benzene (10 ml), was added to the aqueous suspension and the reaction mixture was stirred for 3 h. The solid which separated was collected by filtration and additional acid chloride (5 ml) was added to the filtrate which was stirred overnight. More solid was obtained and was combined with that previously isolated. Fractional crystallisation of this crude product from methanol afforded 3-*methyl*-N-*benzyl*-N-[3-*methyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthraniloyl*]-*anthranilic acid* (42) (2.84 g, 86%), m.p. 294—295 °C [Found: C, 69.0; H, 5.1; N, 7.95%; *M* (mass spec.), 537. $C_{31}H_{27}N_3O_6$ requires C, 69.3; H, 5.1; N, 7.8%; *M*, 537], $\nu_{max.}$ (Nujol) 3 240 (NH), 1 690 (CO_2H), 1 670 (CO), and 1 530 cm^{-1} (NO_2); τ[$CDCl_3$–$(CD_3)_2CO$] 0.16 and 0.50 (1 H, 2 × bs of approximately equal intensities, NH), 2.09—2.92 (14 H, m, ArH), 4.77 (2 H, s, benzylic CH_2), and 7.65, 7.69, and 7.73 (9 H, 3 × s, 3 × Ar*Me*).†

Benzyl 3-*Methyl*-N-*benzyl*-N-[3-*methyl*-N-*benzyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthraniloyl*]*anthranilate* (43).—3-Methyl-*N*-benzyl-*N*-[3-methyl-*N*-(3-methyl-2-nitrobenzoyl)anthraniloyl]anthranilic acid (42) (2.8 g) was stirred with benzyl bromide (3 ml) and sodium hydride (1 g) in dry tetrahydrofuran (25 ml) at room temperature for 24 h. Excess of sodium hydride was destroyed by addition of water and the aqueous mixture was extracted with chloroform (3 × 100 ml). The combined organic layers were washed with water (2 × 100 ml), dried (Na_2SO_4), and filtered. The inorganic material was removed by filtration and the filtrate was concentrated under reduced pressure to afford an oil. Excess of benzyl bromide was removed by evaporation under high vacuum. Column chromatography of the crude product on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 2) as eluant afforded a solid which was crystallised from ethanol to yield *benzyl* 3-*methyl*-N-*benzyl*-N-[3-*methyl*-N-*benzyl*-N-(3-*methyl*-2-*nitrobenzoyl*)*anthraniloyl*]*anthranilate* (43) (1.5 g, 46%), m.p. 193—194 °C [Found: *M* − 91 (mass spec.) 626.2282. $C_{38}H_{32}N_3O_6$ requires *M* − 91, 626.2291], $\nu_{max.}$ (Nujol) 1 710 (CO_2CH_2Ph), 1 630 (CO), and 1 530 cm^{-1} (NO_2).

3-*Methyl*-N-*benzyl*-N-[3-*methyl*-N-*benzyl*-N-(3-*methyl*-2-*aminobenzoyl*)*anthraniloyl*]*anthranilic Acid* (45).—The benzyl ester (43) (1.25 g) was dissolved in ethanol (50 ml) and the solution was heated under reflux. Titanium(III) chloride solution (20 ml; 12.5%) was added dropwise to the refluxing solution during 30 min. The reaction mixture was then heated for a further 10 min before being poured into boiling water (75 ml). The aqueous solution was allowed to cool and was then extracted with chloroform (3 × 50 ml). The combined organic layers were washed with water (50 ml) and dried (Na_2SO_4). The inorganic material was removed by filtration and the filtrate was concentrated under reduced pressure to afford an oil. Mass spectrometry (Found: *M*, 687. $C_{45}H_{41}N_3O_4$ requires *M*, 687) indicated the presence of the benzyl ester (44). The crude oil was dissolved in methanol (10 ml) and the solution was refluxed for 3 h in the presence of sodium hydroxide solution (40 ml, 10%). The aqueous reaction mixture was filtered whilst still hot and then allowed to cool. On acidification with dilute hydrochloric acid, 3-*methyl*-N-*benzyl*-N-[3-*methyl*-N-*benzyl*-N-(3-*methyl*-2-*aminobenzoyl*)*anthraniloyl*]*anthranilic acid* (45) precipitated as a solid (1.0 g, 96%), m.p. 143—145 °C [Found: *M* (mass spec.), 597.2627. $C_{38}H_{35}N_3O_4$ requires *M*, 597.2628], $\nu_{max.}$ (Nujol) 3 460 and 3 360 (NH_2), 1 715 (CO_2H), and 1 630 cm^{-1} (CO).

5,11-*Dibenzyl*-4,10,16-*trimethyltribenzo*[b,f,j][1,5,9]*triazacyclododecine*-6,12,18(5H,11H,17H)-*trione* (N,N′-*Dibenzyltri*-3-*methyltrianthranilide*) (18).—(a) The amino-acid derivative (45) (860 mg) was dissolved in dry chloroform (5 ml) and redistilled thionyl chloride (1 ml) was added dropwise with stirring. The reaction mixture was heated under reflux for 24 h. Evaporation of the solvent and excess of thionyl chloride under reduced pressure afforded an oil.

† See footnote on p. 1704.

Column chromatography on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant afforded a product which was separated into two fractions by h.p.l.c. on ' Spherisorb 5 '. The two fractions were found to correspond to conformational diastereoisomers of N,N'-*dibenzyltri*-3-*methyltrianthranilide* (18). Fraction 1 crystallised from chloroform to afford one of the helical conformational isomers (H-1/H-1*, H-2/H-2*, or H-3/H-3*) (4 mg, 0.5%), m.p. >300 °C [Found: *M* (mass spec.), 579.2511. $C_{38}H_{33}N_3O_3$ requires 579.2522], τ($CDCl_3$) 2.10 (1 H, bs, NH), 2.36—3.30 (19 H, m, ArH), 5.10, 5.15, 5.40, and 5.64 (4 H, 2AB systems, J_{AB} 14 Hz, benzylic CH_2), and 7.58, 8.20, and 8.46 (9 H, 3 × s, 3 × Ar*Me*). Fraction 2, which failed to crystallise from chloroform or toluene, was assigned to the diastereoisomer with the propeller conformation (P/P*) (3 mg, 0.4%) [Found: *M* (mass spec.), 579.2511. $C_{38}H_{33}N_3O_3$ requires *M*, 579.2522], τ($CDCl_3$) 2.65—3.15 (19 H, m, ArH), 3.25 (1 H, bs, NH), 4.37 and 5.82 (4 H, AB system, J_{AB} 14 Hz, benzylic CH_2), and 7.79, 7.86, and 8.45 (9 H, 3 × s, 3 × Ar*Me*).

(b) The amino-acid derivative (44) (100 mg) was dissolved in dichloromethane (1 ml) and a solution of *N,N'*-dicyclohexylcarbodi-imide (70 mg) in dichloromethane was added. The reaction mixture was stirred for 48 h before the solvent was evaporated off under reduced pressure to afford an oil. Preparative t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant gave *N,N'*-dibenzyltri-3-methyltrianthranilide (18) (1 mg, 1%) as a mixture of conformational diastereoisomers which could be separated by h.p.l.c. on ' Spherisorb 5 '.

5,11,17-*Tribenzyl*-4,10,16-*trimethyltribenzo*[b,f,j][1,5,9]-*triazacyclododecine*-6,12,18-(5H,11H,17H)-*trione* (N,N',N''-*Tribenzyltri*-3-*methyltrianthranilide* (19).—*N,N'*-Dibenzyltri-3-methyltrianthranilide (18) (10 mg) was stirred with benzyl bromide (0.2 ml) and sodium hydride (60 mg) in dry tetrahydrofuran (10 ml) for 24 h. Excess of sodium hydride was destroyed by addition of water and 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 inorganic material was removed by filtration and the filtrate was concentrated under reduced pressure to afford an oil. Excess of benzyl bromide was removed by evaporation under high vacuum and the residue was then subjected to preparative t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant. Further purification by h.p.l.c. on ' Spherisorb 5 ' afforded two fractions which were identified as the two conformational diastereoisomers of N,N',N''-*tribenzyltri*-3-*methyltrianthranilide* (19). Fraction 1 crystallised from toluene to give the helical conformational isomer (H/H*) (3 mg, 26%), m.p. 260—263 °C [Found: *M* (mass spec.), 669.3012. $C_{45}H_{39}N_3O_3$ requires *M*, 669.2991], τ($CDCl_3$) 2.20—3.40 (24 H, m, ArH), 4.65 and 5.03, and 4.87 and 5.55 (4 H, 2AB systems, J_{AB} 14 Hz, benzylic CH_2), 5.32 (2 H, s, benzylic CH_2), and 8.26, 8.50, and 8.52 (9 H, 3 × s, 3 × Ar*Me*). Fraction 2 crystallised from toluene to give the propeller conformational isomer (P/P*) (1 mg, 9%), m.p. 305—307 °C [Found: *M* (mass spec.), 669.3012. $C_{45}H_{39}N_3O_3$ requires *M*, 669.2991], τ($CDCl_3$) 1.80—3.50 (24 H, m, ArH), 4.15 and 6.23 (6 H, AB system, J_{AB} 14.2 Hz, benzylic CH_2), and 8.74 (9 H, s, 3 × Ar*Me*).

2-*Nitro*-o-*toluoyl Chloride*.—A solution containing 14.4 g of 2-nitro-*o*-toluoyl chloride in benzene (60 ml) was prepared using the same procedure as has been described for the preparation of 2-nitro-*m*-toluoyl chloride.

2-*Amino*-o-*toluic Acid* [11] (46).—Catalytic reduction of 2-nitro-*o*-toluic acid (2 g) with hydrazine in the presence of Raney nickel in ethanol gave 2-amino-*o*-toluic acid (46) (1.1 g, 66%), m.p. 125—127 °C (lit.,[11] m.p. 128 °C).

Attempted Preparation of 6-*Methyl*-N-(6-*methyl*-2-*nitrobenzoyl*)*anthranilic Acid* (47).—2-Amino-*o*-toluic acid (46) (2.5 g) was dissolved in a solution of potassium hydroxide (1.5 g) in water (18 ml). A solution (15 ml) of 2-nitro-*o*-toluoyl chloride diluted with benzene (10 ml) was added and the procedure described earlier for the preparation of 3-methyl-*N*-(3-methyl-2-nitrobenzoyl)anthranilic acid (26) was followed. Only 2-amino-*o*-toluic acid (46) was detected in the precipitated products.

Determination of Rates of Conformational Changes by Dynamic ^{1}H *N.m.r. Spectroscopy*.—The methods used are fully described in Parts 6 [13] and 7.[14] The computer programs (coded in FORTRAN IV) used to generate the theoretical line shapes are now described for the general methods I and II.

Method I. *N,N',N''*-Trimethyltri-3-methyltrianthranilide (14) exhibits two singlet signals with a ratio of inten-

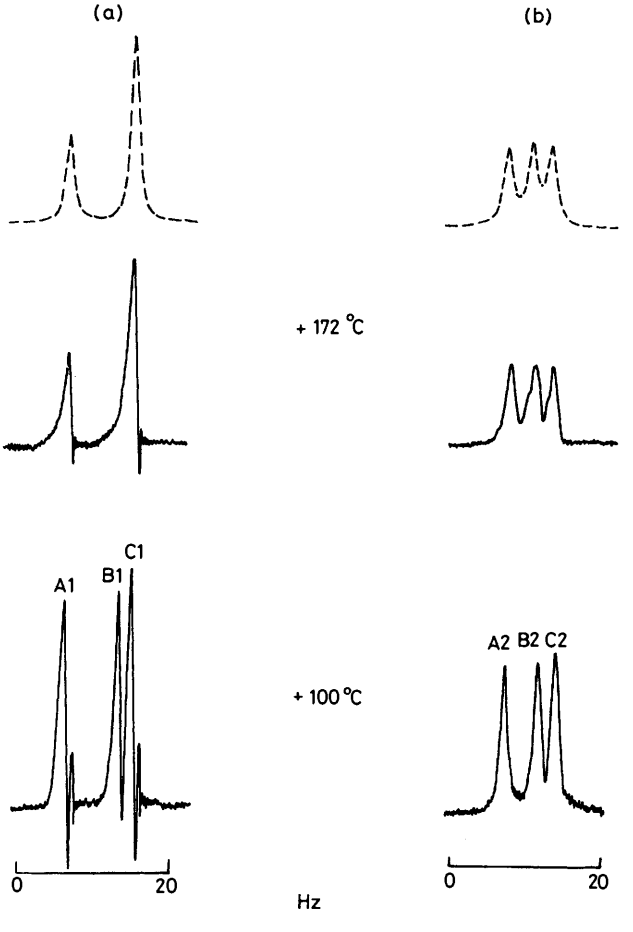


FIGURE 1 Observed (full line) and computed (broken line) spectra of the *N*-methyl and aryl-methyl protons of *N,N',N''*-trimethyltri-3-methyltrianthranilide (14) using program (IV) for exchange of nuclei between three equally populated sites in each case: (a) *N*-methyl proton signals at +172 °C, *k* 0.51 s^{-1}; (b) aryl-methyl proton signals at +172 °C, *k* 0.77 s^{-1}

sities of 1 : 2 at room temperature in nitrobenzene for the constitutionally homotopic *N*-methyl groups. By allowing superimposition of sites B1 and C1, a program (IV) † for exchange of nuclei between three equally populated sites A1, B1, and C1 with no mutual coupling was employed to simulate the broadening of the spectral line shapes at +172 °C. The same program was used to simulate the line broadening also evident at +172 °C in the three singlet signals (A2, B2, and C2) of equal intensities observed for the constitutionally homotopic aryl methyl groups in compound (14) at room temperature. The calculated and observed spectra for both these ^{1}H n.m.r. probes are shown in Figure 1.

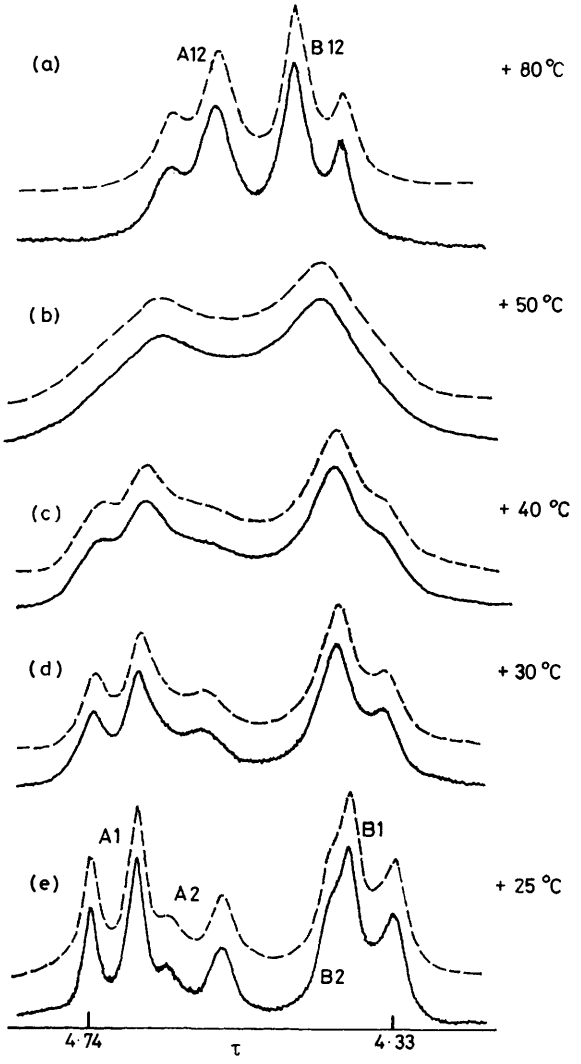


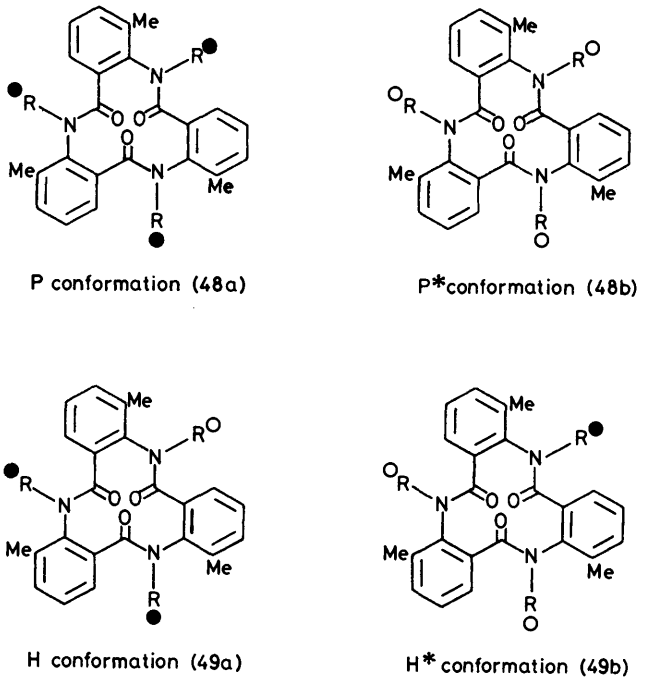
FIGURE 2 Observed (full line) and computed (broken line) spectra of the benzylic methylene protons in *N*-methyl-*N'*-benzyltri-3-methyltrianthranilide (16) using program (III) for exchange of nuclei between sites A1 and A2 and B1 and B2 of two AB systems of relative intensities 70 : 30 assuming k_1 and k_2 equal 0 s^{-1}: (a) at +80 °C, k_{12} 512 s^{-1}; (b) at +50 °C, k_{12} 64 s^{-1}; (c) at +40 °C, k_{12} 32 s^{-1}; (d) at +30 °C, k_{12} 16 s^{-1}; (e) at +25 °C, k_{12} 8 s^{-1}

† The program numbers (*viz.* III and IV) established in Parts 3 [12] and 6 [13] will be adhered to in this paper; these programs will form the basis of a collection for reference in future Parts of this Series.

Method II. A program (III) † for exchange of nuclei between pairs of sites A1 and B1, A2 and B2, A1 and A2, and B1 and B2 in two AB systems. This program was used to simulate the ^{1}H n.m.r. spectral line shapes associated with the benzylic methylene protons of *N*-methyl-*N'*-benzyltri-3-methyltrianthranilide (16) between +25 and +80 °C. The exchange rates k_1 and k_2, between sites A1 and B2, and A2 and B2 respectively were assumed to be slow compared with the exchange rates k_{12} and k_{21} between sites A1 and A2, and B1 and B2. The calculated and observed spectra are shown in Figure 2.

RESULTS AND DISCUSSION

The ground-state conformations of the tri-3-methyltrianthranilide derivatives (11) are expected to be characterised by three *trans*-amide linkages in exactly

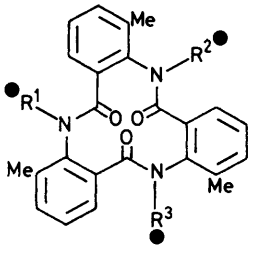


(14) R = Me
(19) R = CH_2Ph

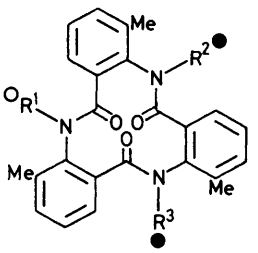
FIGURE 3 The two possible conformational diastereoisomers with *trans*-amide linkages for symmetrically *N,N',N''*-trisubstituted tri-3-methyltrianthranilide derivatives: ● ≡ an R group above the mean plane of the ring and ○ ≡ an R group below the mean plane of the ring

the same way [1] as the ground-state conformations of the parent trianthranilide derivatives (10). Thus, with the constitutionally symmetrical ($R^1 = R^2 = R^3 = R$) *N,N',N''*-trimethyl- (14) and *N,N',N''*-tribenzyl- (19) derivatives, propeller (P and P*; 48a and b) and helical (H and H*, 49a and b) conformations have to be considered (see Figure 3) as enantiomeric pairs of diastereoisomerically related conformations. In the case of the constitutionally unsymmetrical ($R^1 \neq R^2 = R^3$, $R^1 = R^2 \neq R^3$, or $R^1 \neq R^2 \neq R^3$) derivatives exemplified by *N,N'*-dimethyl- (13), *N,N'*-dimethyl-*N''*-benzyl- (15),

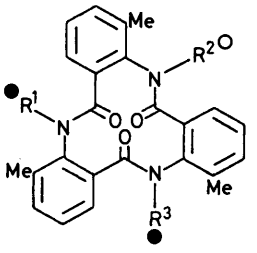
N-methyl-*N'*-benzyl- (16), *N*-methyl-*N',N''*-dibenzyl- (17), and *N,N'*-dibenzyl- (18) tri-3-methyltrianthranilides, it is possible to differentiate (see Figure 4)



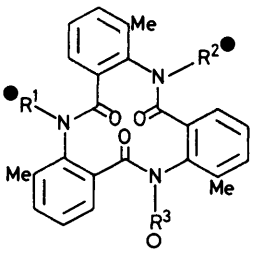
P conformation (50a)



H-1 conformation (51a)



H-2 conformation (52a)



H-3 conformation (53a)

	R^1	R^2	R^3
(13)	Me	Me	H
(15)	Me	Me	CH_2Ph
(16)	Me	CH_2Ph	H
(17)	Me	CH_2Ph	CH_2Ph
(18)	CH_2Ph	CH_2Ph	H

FIGURE 4 The four possible conformational diastereoisomers with *trans*-amide linkages for unsymmetrically *N,N'*-disubstituted and *N,N',N''*-trisubstituted tri-3-methyltrianthranilide derivatives: ● ≡ an R group above the mean plane of the ring and ○ ≡ an R group below the mean plane of the ring

between three diastereoisomeric helical conformations (51a), (52a), and (53a) as well as a propeller (P) conformation (50a). The helical conformations will be designated (*cf.* ref. 1) as H-1, H-2, and H-3 according as to whether R^1, R^2, or R^3 are oriented towards the opposite face of the 12-membered ring from R^2 and R^3, R^1 and R^3, and R^1 and R^2 respectively. There are, of course, also four enantiomerically related (P*, H-1*, H-2*, and H-3*) conformations (50b), (51b), (52b), and (53b) to be considered.

N.m.r. spectroscopy reveals that the *N,N',N''*-trimethyl derivative (14) adopts (R = Me in Figure 3) only helical conformations (H and H*) which undergo H ⇌ H* ring inversion in solution. On the other hand, two crystalline conformational diastereoisomers of *N,N',N''*-tribenzyltri-3-methyltrianthranilide (19) corresponding to propeller (P and P*) and helical (H and H*) conformations (R = CH_2Ph in Figure 3) were isolated by chromatography. Conformational assignments were made by recognising averaged C_3 symmetry in the propeller conformations and asymmetry in the helical conformations and relating these symmetry elements to the number of signals observed for constitutionally homotopic probes in the ^1H n.m.r. spectra. Chemical-shift data for appropriate (i) benzylic methylene, (ii) *N*-methyl, and (iii) aryl-methyl protons are listed in the Table for the assigned conformations of compounds (14) and (19). This Table also contains similar data and conformational assignments for compounds (13) and (15)—(18). The key compound which allows conformations to be assigned to these constitutionally unsymmetrical derivatives is *N,N'*-dimethyl-*N''*-benzyltri-3-methyltrianthranilide (15). An *X*-ray crystal structure (see Figure 5) established that this compound adopts either the H-2 or H-2* conformation [(52a or b; R^1 = R^2 = Me and R^3 = CH_2Ph) in Figure 4] in the solid state, *i.e.* it undergoes spontaneous resolution on crystallisation restricting its involvement with only one of the four possible diastereoisomerically related conformations

TABLE

Chemical-shift data for appropriate (i) benzylic-methylene, (ii) *N*-methyl, and (iii) aryl-methyl protons in assigned conformations of compounds (13)—(19)

	Compound				Chemical shifts (τ) [a]		
No.	R^1	R^2	R^3	Conformation	N-CH_2Ph Protons [b]	N-*Me* Protons	Aryl-*Me* Protons
(13)	Me	Me	H	H-1/H-1*	—	6.86; 6.95	7.59; 7.63; 7.63
(14)	Me	Me	Me	H/H*	—	6.78; 6.86; 6.88	7.62; 7.62; 7.65
(15)	Me	Me	CH_2Ph	H-2/H-2*	5.20 and 5.20 [c]	6.70; 6.96	7.58; 7.69; 8.55
(16)	Me	CH_2Ph	H	H-1/H-1*	5.16 and 5.34	6.94	7.56; 7.68; 8.50
(17)	Me	CH_2Ph	CH_2Ph	H-2/H-2*	5.19 and 5.19; [c] 5.28 and 5.34	6.74	7.56; 8.34; 8.52
(18)	CH_2Ph	CH_2Ph	H	P/P*	4.37 and 5.82; 4.37 and 5.82 [d]	—	7.79; 7.86; 8.45
				H-1/H-1*	5.10 and 5.15; 5.40 and 5.64	—	7.58; 8.20; 8.46
(19)	CH_2Ph	CH_2Ph	CH_2Ph	P/P*	4.15 and 6.23; 4.15 and 6.23; 4.15 and 6.23 [e]	—	8.74; 8.74; 8.74
				H/H*	4.65 and 5.03 4.87 and 5.55 5.32 and 5.32 [c]	—	8.26; 8.50; 8.52

[a] In $CDCl_3$. [b] AB systems. [c] Singlet observed. [d] Two superimposed AB systems. [e] Three superimposed AB systems.

shown in Figure 4. Furthermore, ^{1}H n.m.r. spectroscopy reveals that this is also the conformation the molecule adopts in solution. The chemical-shift data listed in the Table for compound (15) can be correlated in a most convincing manner (see Figure 6) with similar data for compounds (13) and (16)—(18). Conformational assignments can be made (see the Table and Figure 6) to all these derivatives on the basis of the excellent correlation between chemical shifts exhibited by protons in three

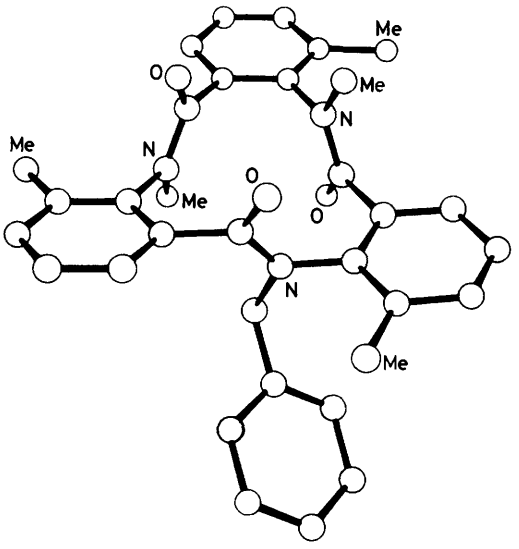


FIGURE 5 The structure of *N,N'*-dimethyl-*N''*-benzyltri-3-methyltrianthranilide (15) in the solid state [5]

constitutionally different ^{1}H n.m.r. probes. While *N*-methyl-*N',N''*-dibenzyltri-3-methyltrianthranilide (17) adopts H-2/H-2* conformations [(52a and b; R^1 = Me and $R^2 = R^3 = CH_2Ph$) in Figure 4], the *N,N'*-dimethyl- (13), *N*-methyl-*N'*-benzyl- (16), and *N,N'*-dibenzyl- (18) derivatives all adopt H-1/H-1* conformations [(51a and b; $R^1 = R^2$ = Me and R^3 = H; R^1 = Me, $R^2 = CH_2Ph$, and R^3 = H; and $R^1 = R^2 = CH_2Ph$ and R^3 = H), respectively in Figure 4]. Confidence in the diagnostic nature of the chemical-shift correlations leading to these conformational assignments emanates principally from a dramatic shielding of *ca.* 0.7—0.9 p.p.m. experienced by aryl-methyl protons when they are in the vicinity of an *N*-benzyl group. The *X*-ray crystal structure (Figure 5) of compound (15) demonstrates that it is possible for an aryl-methyl group to find itself in the shielding zone of the phenyl group of a neighbouring *N*-benzyl group. In addition to existing as a crystalline compound in H-1/H-1* conformations [(51a and b; $R^1 = R^2 = CH_2Ph$ and R^3 = H) in Figure 4], the *N,N'*-dibenzyl derivative (18) has also been characterised as a non-crystalline diastereoisomer which has been assigned (see the Table) to propeller (P/P*) conformations [(50a and b; $R^1 = R^2 = CH_2Ph$ and R^3 = H) in Figure 4] on the basis of the diagnostic low-field resonance (τ 4.37) for the A protons associated with the isochronous AB systems for its benzylic-methylene protons. In the parent trianthranilide derivatives (10), propeller conformations were found [1] to be characterised by very low field doublets for the A portions of the AB systems arising from their benzylic-methylene protons.

The Conformational Behaviour of N,N',N''-*Trimethyl-* (14) *and* N,N',N''-*Tribenzyl-* (19) *tri-3-methyltrianthranilides.*—When the ^{1}H-decoupled ^{13}C n.m.r. spectrum of *N,N',N''*-trimethyltri-3-methyltrianthranilide (14) was recorded in deuteriochloroform at room temperature (i) three singlets of approximately equal intensities were observed at 17.0, 17.3, and 18.0 p.p.m. for the aryl-methyl carbon atoms, (ii) three singlets of approximately equal intensities were observed at 39.1, 39.6, and 40.0 p.p.m. for the *N*-methyl carbon atoms, (iii) fifteen signals between 123.7 and 137.5 p.p.m. were observed for the aromatic carbon atoms, and (iv) two signals in the ratio of approximately 2 : 1 were observed for the carbonyl carbon atoms at 169.0 and 169.6 p.p.m., respectively. These spectral data, together with the ^{1}H n.m.r. spectral data (Table), are consistent with the *N,N',N''*-trimethyl derivative (14) adopting enantiomeric helical (H/H*) conformations [(49a and b; R = Me) in Figure 3] in solution. In nitrobenzene solution, the ^{1}H n.m.r. spectrum exhibited (see Figure 1) temperature dependence. At +100 °C, three singlets were observed for the *N*-methyl groups and another three singlets for the aryl-methyl groups. Although the three aryl-methyl singlets were still observable at +172 °C, considerable line broadening had occurred. Also, at this temperature, in addition to line broadening, two of the three *N*-methyl singlets had become accidentally coincident. The changes in the spectral line shapes at +172 °C may be interpreted in terms of an H $\rightleftharpoons$ H* inversion process. Line-shape analyses (see Figure 1) of the signals for the *N*-methyl groups and the signals for the aryl-methyl groups afforded rate constants of 0.51 and 0.77 s^{-1}, respectively at +172 °C. A free energy of activation of 26.8 kcal mol^{-1} was obtained from the average value of 0.64 s^{-1}. Hence, introduction of methyl substituents into positions-3 of the aromatic rings of *N,N',N''*-trimethyltrianthranilide (10; R = Me) increases (*cf.* ref. 1) the barrier to H $\rightleftharpoons$ H* inversion by 2.2 kcal mol^{-1} and destabilises the propeller (P/P*) conformations [(48a and b; R = Me) in Figure 3] relative to the helical (H/H*) conformations [(49a and b; R = Me) in Figure 3].

In the case of *N,N',N''*-tribenzyltri-3-methyltrianthranilide (19), propeller (P/P*) and helical (H/H*) conformational diastereoisomers [(48a and b; R = CH_2Ph) and (49a and b; R = CH_2Ph) respectively in Figure 3] were isolated as crystalline compounds. However, the very small amounts (1 and 3 mg respectively) of these compounds available for spectroscopic study precluded their investigation by dynamic ^{1}H n.m.r. spectroscopy. Nonetheless, it may be concluded that the barriers to conformational changes in the *N,N',N''*-tribenzyl derivative (19) are in excess of 27 kcal mol^{-1}.

The Conformational Behaviour of N,N'-*Dimethyl*-N''-*benzyl-* (15) *and* N-*Methyl*-N',N''-*dibenzyl-* (17) *tri-3-*

methyl-trianthranilides.—These two constitutionally unsymmetrical *N,N',N''*-trisubstituted derivatives, *i.e.* (15) and (17), adopt (see the Table and Figure 6) H-2/H-2* conformations in solution. However their ^{1}H n.m.r. spectra in hexadeuteriodimethyl sulphoxide solutions were found to be independent of temperature even when the solutions were heated up to +180 °C, indicating that the barriers † to conformational changes must exceed 27 kcal mol^{-1}.

The *X*-ray crystal structure (Figure 3) of the *N,N'*-dimethyl-*N''*-benzyl derivative (15) reveals that, when it crystallises from toluene in an H-2 or H-2* conformation [(52a or b; $R^1 = R^2 = Me$ and $R^3 = CH_2Ph$) in Figure 4], it undergoes spontaneous resolution and forms a 1 : 1 adduct with the toluene in which the guest solvent molecules are trapped in chiral channels of the host lattice. To our knowledge, this is only the second example following tri-*o*-thymotide [15] (5) to share these two fascinating and potentially useful properties. Two structural differences between (5) and (15) are highly significant and important: (i) tri-*o*-thymotide (5) crystallises [15] in chiral *propeller* conformations whereas the tri-3-methyltrianthranilide derivative (15) crystal-

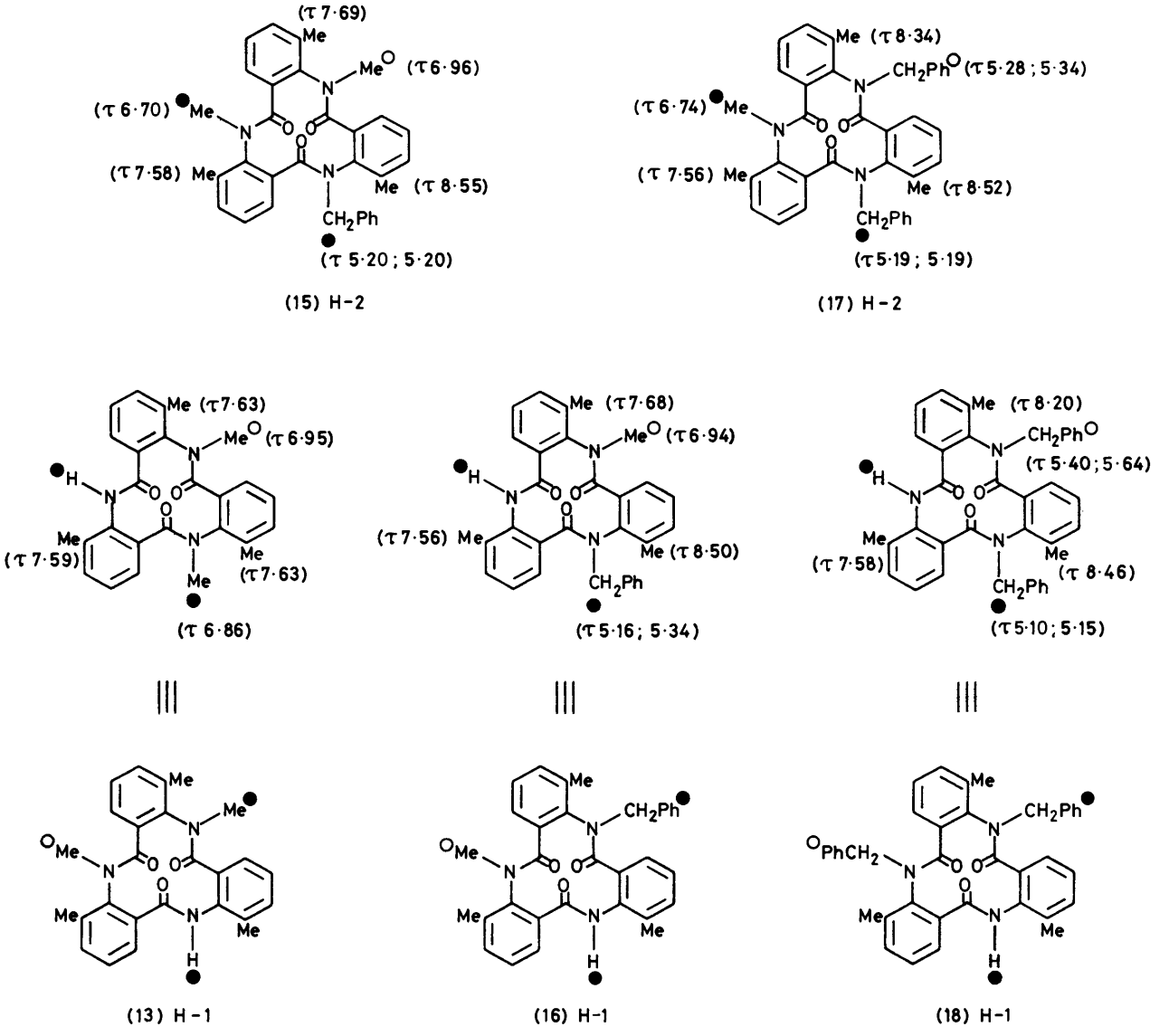


FIGURE 6 Correlations between conformational assignments to compounds (13) and (15)—(18) and the chemical shifts of (i) benzylic-methylene, (ii) *N*-methyl, and (iii) aryl-methyl proton in deuteriochloroform. Note that the H-1 conformations for compounds (13), (16), and (18) have been drawn in such a way as to emphasise their relationship with the H-2 conformations for compounds (15) and (17). ● ≡ an R group above the mean plane of the ring. ○ ≡ an R group below the mean plane of the ring

† The free energy of activation for the H-2 ⇌ H-2* inversion of compound (15) could, of course, be determined by polarimetry in the manner described in Part 11 [1] for *N,N'*-dimethyltrianthranilide (10; in which two of the R substituents are methyl groups and the other one is a hydrogen atom).

lises [5] in chiral *helical* conformations, and (ii) the potential to modify the constitution of a trianthranilide derivative by changing the nature of the substituents on the nitrogen atoms during stepwise synthesis is much greater than is feasible with tri-*o*-thymotide. This is an obvious advantage of *N,N'*-dimethyl-*N''*-benzyltri-3-methyltrianthranilide (15) over tri-*o*-thymotide (5) when the necessity to introduce functionality into the host as a prelude to the investigation of reactions in the solid state on entrapped guest substrates is considered.

The Conformational Behaviour of N,N'-*Dimethyl-* (13), N-*Methyl*-N'-*benzyl-* (16), *and* N,N'-*Dibenzyl-* (18) *tri-3-methyltrianthranilides.*—These three constitutionally unsymmetrical *N,N'*-disubstituted derivatives, *i.e.* (13), (16), and (18), all adopt (see the Table and Figure 6) H-1/H-1* conformations in solution. There is no suitable n.m.r. probe in the *N,N'*-dimethyl derivative (13) to permit investigation of the conformational behaviour of this compound in solution. Furthermore, in experiments which would have relied upon the benzylic-methylene protons as suitable prochiral probes, the small amounts (3 and 4 mg, respectively) of the P/P* [(50a and b; $R^1 = R^2 =$ Me and $R^3 = H$) in Figure 4] and H-1/H-1* [(51a and b; $R^1 = R^2 =$ Me and $R^3 = H$) in Figure 4] conformational isomers of the *N,N'*-dibenzyl derivative (18) precluded their investigation by dynamic ^{1}H n.m.r. spectroscopy. However, the ^{1}H n.m.r. spectrum of *N*-methyl-*N'*-benzyltri-3-methyltrianthranilide (16) recorded in hexadeuteriodimethyl sulphoxide solution at +25 °C indicates (see Figure 2) that two conformational diastereoisomers are present in this solution. Since the spectrum observed in deuteriochloroform solution is consistent with the adoption of only one of the three helical conformational diastereoisomers, namely that having H-1/H-1* conformations [(51a and b; $R^1 =$ Me, $R^2 = CH_2Ph$, and $R^3 = H$) in Figure 4], in this solution, there is clearly an important solvent effect influencing the position of the conformational equilibrium. It is possible that the H-1/H-1* conformations [(51a and b; $R^1 =$ Me, $R^2 = CH_2Ph$, and $R^3 = H$) in Figure 4] are stabilised by a transannular hydrogen bond involving the hydrogen atom in the CONH linkage and either (i) a carbonyl oxygen atom or (ii) an amide nitrogen atom in one or other of the two CONMe linkages. Examples of intramolecular hydrogen bonding interactions have been observed [1,16] in the *X*-ray crystal structures of *N,N'*-dimethyl- (10; in which two of the R substituents are methyl groups and the other one is a hydrogen atom) and *N,N'*-dibenzyl (10; in which two of the R substituents are benzyl groups and the other one is a hydrogen atom) trianthranilides, respectively. While stabilisation of conformations by transannular hydrogen bonds of this nature could be significant in deuteriochloroform solution, intermolecular hydrogen bonding to the solvent is expected to compete favourably with intramolecular hydrogen bonds in hexadeuteriodimethyl sulphoxide. The temperature dependence (see Figure 2) of the ^{1}H n.m.r. spectrum of the *N*-methyl-*N'*-benzyl derivative (16) may be explained in terms of the H-1 ⇌ H-2* (H-1* ⇌ H-2) interconversion process shown in Figure 7. The hydrogen atom of the CONH linkage is assumed to be hydrogen bonded to the oxygen atom of the sulphoxide group in a solvent molecule. At +25 °C, two AB systems with relative intensities of 70 : 30 are observed for the benzylic methylene protons in the ^{1}H n.m.r. spectrum. Above room temperature, these two

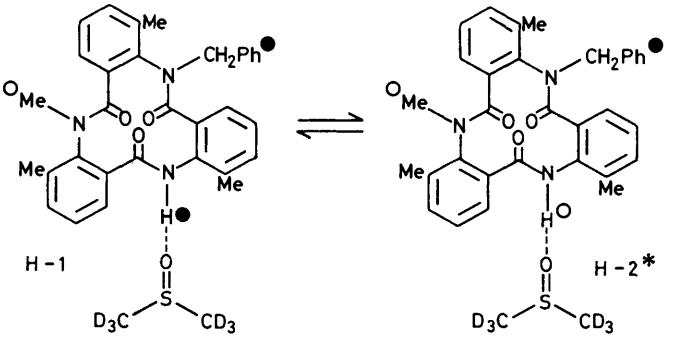


FIGURE 7 The H-1 ⇌ H-2* conformational equilibrium for compound (16) in hexadeuteriodimethyl sulphoxide

AB systems coalesce to give one AB system. Line-shape analysis (see Figure 2) of the signals at five different temperatures provided a series of rate constants from which a range of $\Delta G^{\ddagger}$ values could be calculated. The average value for the free energy of activation for H-1 ⇌ H-2* (H-1* ⇌ H-2) interconversion was found to be 16.1 kcal mol^{-1}. This value can be equated with the barrier to ring interconversion for the *major* conformational isomer being transformed into the *minor* conformational isomer. We cannot be certain of the assignment of these isomers to the H-1/H-1* [(51a and b; $R^1 =$ Me, $R^2 = CH_2Ph$, and $R^3 = H$) in Figure 4] and H-2/H-2* [(52a and b; $R^1 =$ Me, $R^2 = CH_2Ph$, and $R^3 = H$) in Figure 4] conformations. Clearly, the presence of aryl-methyl groups at positions-3 of the aromatic rings raises the energy barrier to reorientation of a CONH linkage by several kcal mol^{-1} relative to the barriers for this conformational change in the parent *N,N'*-disubstituted trianthranilide derivatives.[1] The H-1 ⇌ H-2* (H-1* ⇌ H-2) interconversion process for compound (16) could either involve a reorientation of the CONH linkage (i) by pedalling of the *trans*-amide linkage or (ii) by a mechanism that requires the *trans*-amide linkage to assume a *cis*-geometry in a conformational intermediate. It is not possible at this stage to distinguish between these two different itineraries.

N-Methyl-*N'*-benzyltri-3-methyltrianthranilide (16) crystallises from toluene in the H-1/H-1* conformation [(51a and b; $R^1 =$ Me, $R^2 = CH_2Ph$, and $R^3 = H$) in Figure 4] as a 1 : 1 adduct with the solvent. The toluene can be removed *in vacuo* at +60 °C inside 6 h indicating that it may be entrapped in channels in the crystals in much the same way as toluene is included [5] in crystalline *N,N'*-dimethyl-*N''*-benzyltri-3-methyltrianthranilide (15). It is not known, however, if the *N*-methyl-*N'*-

benzyl derivative (**16**) undergoes spontaneous resolution on crystallisation.

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