Conformational Behaviour of Medium-sized Rings. Part 11.[1] Dianthranilides and Trianthranilides

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Two approaches to the stepwise syntheses of N,N'-di- and N,N',N''-tri-substituted trianthranilide derivatives (5)—(20) are described. In the shorter synthetic route, the key acyclic intermediate, N-[2-(o-nitrobenzamido)-benzoyl]anthranilic acid (26) is prepared in a stepwise manner from anthranilic acid, isatoic anhydride (23), followed by o-nitrobenzoyl chloride. Alkylations of the amide functions at nitrogen, reductions of the aromatic nitro-groups, and cyclisations of the acyclic amino-acid derivatives provide a direct route to N,N'-dimethyl- (5) and N,N'-dibenzyl- (14) trianthranilides. Further alkylations or acylations of either (5) or (14) afford (i) N,N',N''-trimethyltrianthranilide (7) and its trideuteriomethyl analogue (8), (ii) N,N'-dimethyl-N''-acetyl- (10), -N''-benzoyl- (11), and -N''-benzyl- (12) trianthranilides, (iii) N,N',N''-tribenzyltrianthranilide (15), and (iv) N,N'-dibenzyl-N''-methyltrianthranilide (16). In the longer synthetic route, the key acyclic intermediate, methyl N-methyl-N-[2-(o-nitrobenzamido)benzoyl]anthranilate (42) is prepared in a stepwise manner from anthranilic acid and two molar equivalents of o-nitrobenzoyl chloride. Alkylations of the unsubstituted amide functions at nitrogen, reductions of the aromatic nitro-groups, and cyclisations of the acyclic amino-acid derivatives provide, not only an alternative route to N,N'-dimethyltrianthranilide (5) but also, a general route to the N-methyl-N'-trideuteriomethyl- (6), N-methyl-N'-benzyl- (17), and N-methyl-N'-ethyl- (19) analogues. Further alkylations of these N,N'-disubstituted derivatives afford N-methyl-N',N''-di(trideuteriomethyl)- (9), N-methyl-N'-trideuterio-methyl-N''-benzyl- (13), N-methyl-N'-benzyl-N''-ethyl- (18), and N-methyl-N'-ethyl-N''-benzyl- (20) trianthranilides.

The constitutionally symmetrical N,N',N''-trimethyl- (7) and N,N',N''-tribenzyl- (15) trianthranilides exist in solution as an equilibrium mixture of propeller and helical conformations. In the case of the N,N',N''-trimethyl derivative (7), the predominant diastereoisomer with the helical conformation has been isolated as a pure compound. In the case of the N,N',N''-tribenzyl derivative (15), the propeller and helical conformational diastereoisomers have both been characterised as crystalline compounds. For both these compounds, the free-energy barriers to conformational inversion and interconversion processes in solution have been obtained from (i) direct equilibration experiments and (ii) dynamic [1]H n.m.r. spectroscopy. Constitutionally unsymmetrical N,N'-di- and N,N',N''-tri-substituted trianthranilide derivatives can adopt three helical conformations in addition to a propeller conformation. Assignments have been made to conformations and conformational diastereoisomers of the N,N'-dimethyl- (5), N,N'-dimethyl-N''-benzyl- (12), N,N'-dibenzyl- (14), N,N'-dibenzyl-N''-methyl- (16), N-methyl-N'-benzyl- (17), N-methyl-N'-benzyl-N''-ethyl- (18), N-methyl-N'-ethyl- (19), and N-methyl-N'-ethyl-N''-benzyl- (20) derivatives on the basis of (i) kinetically controlled trideuteriomethylations of N,N'-dimethyl- (5) and N-methyl-N'-trideuteriomethyl- (6) trianthranilides and (ii) a kinetically controlled benzylation of N,N'-dibenzyltrianthranilide (14). These experiments permit unambiguous site assignments to be made in the [1]H n.m.r. spectra to (i) the homotopic N-methyl groups in the propeller conformation and the diastereotopic N-methyl groups in the helical conformation of N,N',N''-trimethyltrianthranilide (7) and (ii) the homotopic N-benzylic-methylene groups in the propeller conformation and the diastereotopic N-benzylic-methylene groups in the helical conformation of N,N',N''-tribenzyltrianthranilide (15). Correlations between site assignments and chemical shifts, for these two [1]H n.m.r. probes, lead to conformational assignments to other N,N'-di- and N,N',N''-tri-substituted derivatives. In most cases, free-energy barriers for conformational inversion and interconversion processes in solution could be obtained by dynamic [1]H n.m.r. spectroscopy. A satisfying complementary experimental approach is illustrated in the case of N,N'-dimethyltrianthranilide (5) where the occurrence of spontaneous resolution on crystallisation allows the barrier to racemisation to be measured by polarimetry.

The temperature dependence of the [1]H n.m.r. spectrum of 5,11,17-tribenzyl-6,6,12,12,18,18-hexadeuterio-5,6,11,12,17,18-hexahydrotribenzo[b,f,j][1,5,9]triazacyclododecine (22) can be interpreted in terms of ring inversion between enantiomeric helical conformations of this cyclic triamine. The barrier to conformational change is considerably lower than those for the N,N',N''-trisubstituted trianthranilide derivatives.

Variable-temperature [1]H n.m.r. spectroscopy on N,N'-dibenzyldianthranilide (4) indicates that its eight-membered ring exists in enantiomeric boat conformations where ring inversion is slow on the [1]H n.m.r. time scale even at +180 °C.

Inclusion compounds are formed on crystallisation between (i) ethanol and N,N'-dimethyl-N''-benzyltrianthranilide (12) as a mixture of its conformational diastereoisomers, (ii) toluene and a helical conformation of N,N'-dibenzyltrianthranilide (14), (iii) ethanol and the helical conformation of N,N',N''-tribenzyltrianthranilide (15), and (iv) ethanol and the helical conformation of 5,11,17-tribenzyl-6,6,12,12,18,18-hexadeuterio-5,6,11,12,17,18-hexahydrotribenzo[b,f,j][1,5,9]triazacyclododecine (22).

In solution, disalicylide[2] and dithiosalicylide[1] derivatives have both been shown to adopt chiral boat conformations with ring inversions occurring at elevated temperatures on the [1]H n.m.r. time scale between the enantiomerically related boat conformations. In the

case of those trisalicylide derivatives so far investigated, dynamic [1]H n.m.r. spectroscopy has shown[2,3] that at room temperature they exist in solution as slowly interconverting diastereoisomeric mixtures of chiral propeller and helical conformations. In solution the enantio-

merically related propeller conformations of the trisalicyl-ides invariably predominate over the enantiomerically related helical conformations. On the other hand, those trithiosalicylide derivatives, which have also been investigated [1] at different temperatures in solution by [1]H n.m.r. spectroscopy, have been found to adopt only helical conformations with ring inversions occurring at elevated temperatures on the n.m.r. time scale between these enantiomerically related helical conformations.

Although dianthranilide (1) and derivatives have been reported [4-8] in the literature, when we began the present investigation there was no information available con-cerning their conformational behaviour in solution. It did not prove difficult to rectify this situation. By


	R¹	R²
(1)	H	H
(4)	CH₂Ph	CH₂Ph
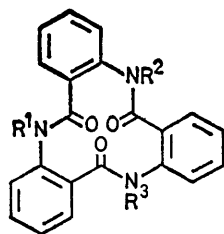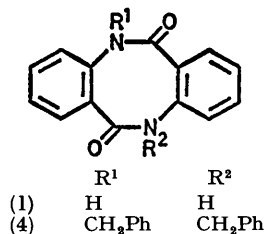
	R¹	R²	R³
(2)	H	H	H
(5)	Me	Me	H
(6)	Me	CD₃	H
(7)	Me	Me	Me
(8)	Me	Me	CD₃
(9)	Me	CD₃	CD₃
(10)	Me	Me	COMe
(11)	Me	Me	COPh
(12)	Me	Me	CH₂Ph
(13)	Me	CD₃	CH₂Ph
(14)	CH₂Ph	CH₂Ph	H
(15)	CH₂Ph	CH₂Ph	CH₂Ph
(16)	CH₂Ph	CH₂Ph	Me
(17)	Me	CH₂Ph	H
(18)	Me	CH₂Ph	Et
(19)	Me	Et	H
(20)	Me	Et	CH₂Ph

contrast, trianthranilide (2) and its derivatives provided a much greater challenge. Trianhydro-derivatives of anthranilic acid were unknown at the outset of our investigations, despite the reported [9] isolation and

characterisation of the acyclic trimer (3) at the turn of the century.

In this paper, we report the syntheses of N,N'-dibenzyl-dianthranilide (4) and some suitably substituted † tri-anthranilide derivatives (5)—(20) and discuss their conformational behaviour in solution. In addition, advantage was taken of the availability of N,N',N''-trimethyl-(7) and N,N',N''-tribenzyl-(15) trianthranilides to prepare the corresponding cyclic triamines (21) and

(3)

|	R	X
(21)	Me	CH₂
(22)	CH₂Ph	CD₂
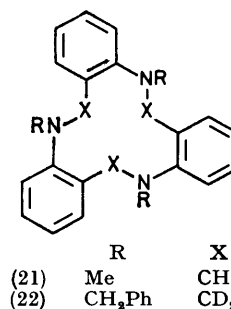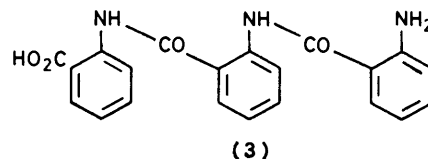
(22) in order to compare their conformational behaviour in solution with those exhibited [10] by their sulphur analogues, 6H,12H,18H-tribenzo[b,f,j][1,5,9]trithia-cyclododecin and its 5,5,11,11,17,17-hexaoxide.

At the outset, dianthraniloylanthranilic acid (25) was identified as a key intermediate in an attempted syn-thesis (see Scheme 1) of trianthranilide (2). Our syn-thetic approach was based upon the known [11,12] reaction of anthranilic acid with isatoic anhydride (23) to give
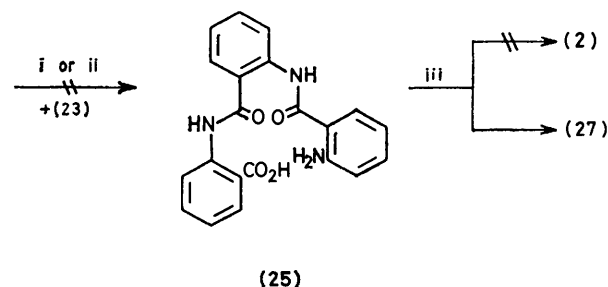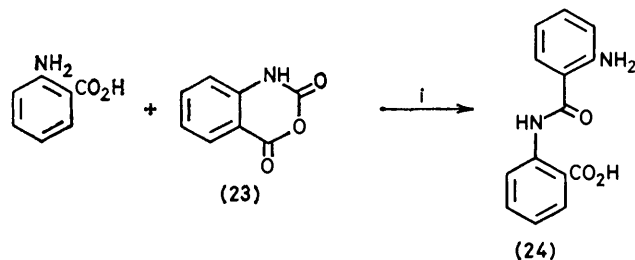

Scheme 1 Reagents: i, NaOH, H₂O; ii, C₅H₅N; iii, C₆H₁₁N=C=N C₆H₁₁, C₅H₅N

anthraniloylanthranilic acid (24). However, attempts to condense (24) with a further molar equivalent of isatoic anhydride (23) proved to be fruitless and hence the less direct route to dianthraniloylanthranilic acid (25) had to be adopted (see Scheme 2). Treatment of

(24)   (26)

(25)
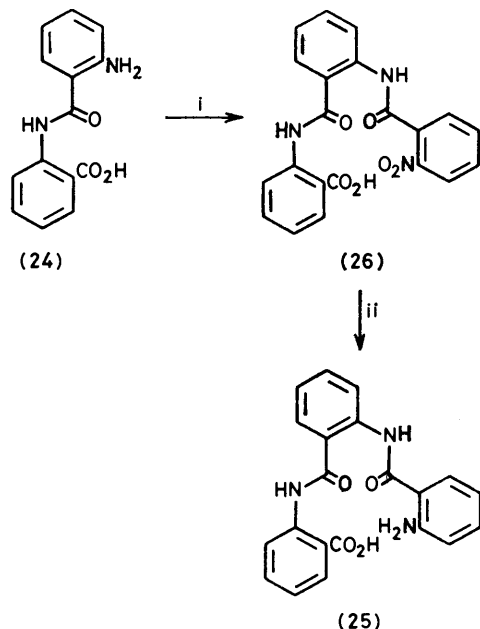
SCHEME 2   *Reagents:* i, *o*-NO$_2$C$_6$H$_4$COCl, LiOH, C$_6$H$_6$, H$_2$O; ii, TiCl$_3$, EtOH, H$_2$O then LiOH
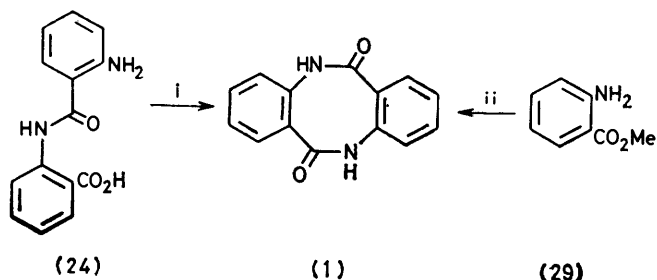
anthraniloylanthranilic acid (24) with *o*-nitrobenzoyl chloride gave [9] the *o*-nitrobenzoyl derivative (26) which underwent reduction of its aromatic nitro-group with titanium(III) chloride [13] to give (25). Alas, attempts to obtain trianthranilide (2) from the cyclisation of dianthraniloylanthranilic acid (25) were unsuccessful. Although intramolecular cyclodehydration of (25) was achieved (see Scheme 3) with *N,N'*-dicyclohexylcarbodi-

(25) X = NH$_2$ (27) R = *o*-COC$_6$H$_4$NH$_2$

(26) X = NO$_2$ (28) R = *o*-COC$_6$H$_4$NO$_2$
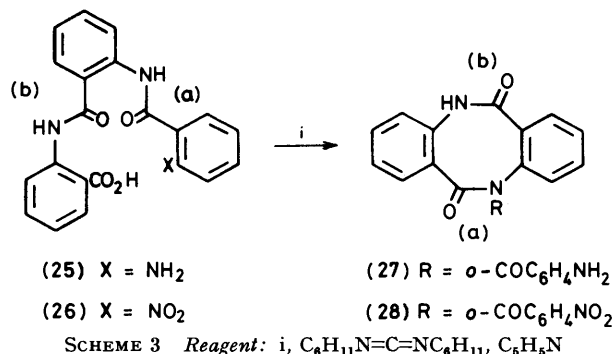
SCHEME 3   *Reagent:* i, C$_6$H$_{11}$N=C=NC$_6$H$_{11}$, C$_5$H$_5$N

imide, the product which was isolated was characterised as the *o*-aminobenzoyl derivative (27) of dianthranilide (1). In similar fashion, the *o*-nitrobenzoyl derivative (28) of (1) could be prepared from *N*-[2-(*o*-nitrobenz-amido)benzoyl]anthranilic acid (26) and then the aromatic nitro-group in (26) was reduced catalytically

to afford *N*-(*o*-aminobenzoyl)dianthranilide (27). All attempts to effect rearrangement of this derivative (27) to trianthranilide (2) failed. The availability of anthraniloylanthranilic acid (24) led to the successful production of dianthranilide (1) by the obvious route shown in Scheme 4. Dianthranilide (1) was also obtained in high yield directly from methyl anthranilate (29). Benzylation of dianthranilide (1) afforded the *N,N'*-dibenzyl derivative (4).


(24)   (1)   (29)

SCHEME 4   *Reagents:* i, C$_6$H$_{11}$N=C=NC$_6$H$_{11}$, C$_5$H$_5$N; ii, NaH, THF

The propensity for dianthraniloylanthranilic acid (25) to give an 8-membered ring bislactam (27) rather than trianthranilide (2) suggests the need to block at least one of the two amide functions identified as (a) and (b) in Scheme 3 towards intramolecular acylation in the subsequent cyclisation step. In the first instance, it was decided to block amide group (a) in (25) as its *N*-methylated derivative, *i.e.* to prepare *N*-[2-(*o*-amino-*N*-methylbenzamido)benzoyl]anthranilic acid (32) as the obvious acyclic precursor to *N*-methyltrianthranilide (34). This was accomplished as shown in Scheme 5 starting from anthraniloylanthranilic acid (24). Chemoselective *N*-methylation (MeI) of the more basic nitrogen function (NH$_2$) in (24) was achieved in aqueous solution with a weak base to give the *N*-methyl derivative (30). *o*-Nitrobenzoylation of (30) yielded *N*-[2-(*o*-nitro-*N*-methylbenzamido)benzoyl]anthranilic acid (31) which, on reduction of its aromatic nitro-grouping with titanium-(III) chloride, gave the desired amino-acid derivative (32) with amide linkage (a) *N*-methylated. Unfortunately, all attempts to obtain *N*-methyltrianthranilide (34) from this derivative (32) failed; under the extreme conditions of refluxing naphthalene only dianthranilide (1) and *N*-methyldianthranilide (33) could be characterised as cyclisation products. The identity of the *N*-methyl derivative (33) was established by comparison with the product of the cyclisation of *N-o*-(methylaminobenzoyl)anthranilic acid (30). The isolation of (33), presumably as a result of the cleavage of amide linkage (b) with concomitant loss of anthranilic acid, from the attempted preparation of *N*-methyltrianthranilide (34) is further evidence for the marked preference for 8-membered ring formation. Finally, in order to ensure closure of a 12-membered ring, it was decided to *N*-methylate both the (a) and (b) amide

(b) NH₂ / (24)   (b) NHMe / (30)   (b) (a) NMe / (31)

(32)   (33)
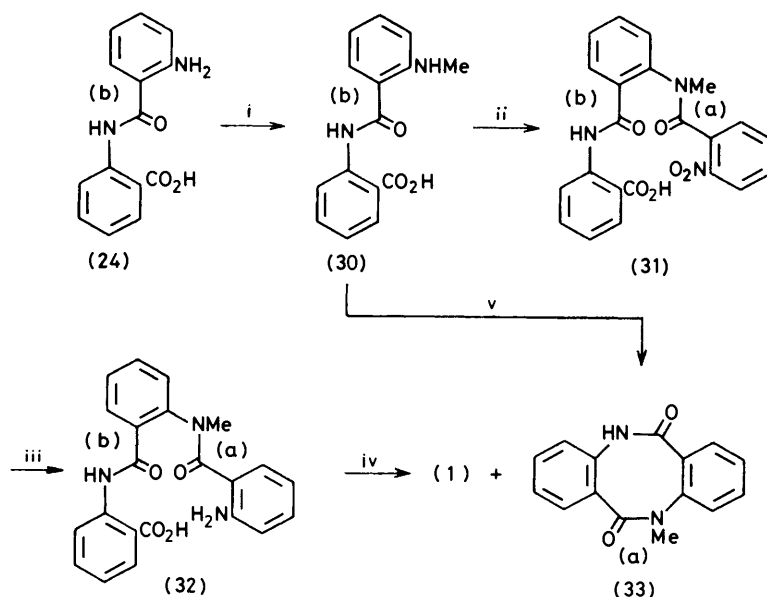
SCHEME 5 *Reagents and conditions:* i, MeI, K_2CO_3, H_2O; ii, o-$NO_2C_6H_4COCl$, LiOH, C_6H_6, H_2O; iii, $TiCl_3$, EtOH, H_2O then LiOH; iv, $C_{10}H_8$, Δ; v, $C_6H_{11}N=C=NC_6H_{11}$, C_5H_5N

linkages (see Scheme 3) in dianthraniloylanthranilic acid (25). N-[2-(o-Amino-N-methylbenzamido)benzoyl]-N-methylanthranilic acid (45) was the obvious acyclic precursor to N,N'-dimethyltrianthranilide (5). This objective was eventually reached by a route outlined in Scheme 6.* N-Methylanthranilic acid (35) was obtained [14] from anthranilic acid on refluxing with methyl iodide in an aqueous solution of potassium carbonate. The amino-acid derivative (37) [4] was obtained from N-methylanthranilic acid (35) in a two-step reaction sequence involving (i) o-nitrobenzoylation of (35) followed by (ii) reduction of the aromatic nitro-grouping

(34)
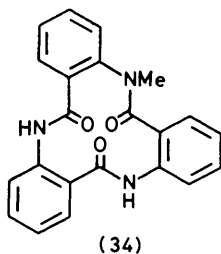
in (36).[4,9,15] It was also found that (37) could be prepared in good yield directly from anthraniloylanthranilic acid (24) when methylation was carried out with dimethyl sulphate in refluxing tetrahydrofuran. Treatment of the amino-acid derivative (37) with methyl iodide and

* An asterisk has been employed throughout this paper in order to distinguish the N-methyl group in amide linkage (b) from that in linkage (a). This is necessary in order to be able to indicate assignments of ¹H n.m.r. signals to constitutionally heterotopic N-methyl groups in the Experimental section. Although the asterisk is used in formulae, as well as in the listing of ¹H n.m.r. data, it has not been introduced into the names of the relevant compounds.

potassium carbonate in refluxing ethyl methyl ketone for a brief period of time (25 min) afforded the ester (39).[15] Refluxing for a prolonged period of time (16 h) resulted in methylation of the amino-group in addition to ester formation to give methyl N-methyl-N-(o-methylaminobenzoyl)anthranilate (40). The amino-acid ester (39) was also obtained in two steps from anthraniloylanthranilic acid (24) involving (i) esterification of (24) with 1-methyl-3-p-tolyltriazene [16] to give (38) [12] followed by (ii) chemoselective methylation of the amide nitrogen with dimethyl sulphate in refluxing tetrahydrofuran. Repeated attempts to prepare methyl N-methyl-N-[2-(o-nitro-N-methylbenzamido)benzoyl]anthranilate (43) by o-nitrobenzoylation of compound (40) failed. Indeed, it proved quite impossible to acylate this compound with numerous reagents under a variety of reaction conditions. Only methylation proved possible albeit very slowly. A low yield (18%) of the dimethylamino-derivative (41) could be isolated after refluxing (40) in ethyl methyl ketone in the presence of methyl iodide and potassium carbonate for 16 h. Thus, compound (43) had to be obtained from the amino-acid ester (39) by first of all carrying out the o-nitrobenzoylation to afford (42), which was then successfully N-methylated with methyl iodide in dimethyl sulphoxide. Subsequently, we found that methyl N-methyl-N-[2-(o-nitro-N-methylbenzamido)-benzoyl]anthranilate (43) could be obtained in excellent yield (80%) directly by methylation (see Scheme 7) of N-[2-(o-nitrobenzamido)benzoyl]anthranilic acid (26). This provides a much shorter route and more general method for the synthesis of numerous N,N'-disubstituted and N,N',N''-trisubstituted trianthranilide derivatives. Titanium(III) chloride reduction of the aromatic nitro-grouping in (43) followed by treatment of the reaction mixture with lithium hydroxide afforded the amino-acid

ester (44) or the amino-acid (45) itself depending upon the reaction conditions employed during the base treatment prior to the isolation of the reaction products. The aromatic amino-group in (44) could be methylated (MeI, K_2CO_3) in refluxing ethyl methyl ketone to give both the methylamino- (46) and dimethylamino- (47) derivatives. Treatment of the amino-acid derivative (45) in dichloromethane with N,N'-dicyclohexylcarbodi-

imide resulted in the isolation of the N-acylurea derivative (48) as a crystalline compound. The result (Figure 1) from an X-ray structural analysis [17] leaves no doubt about the constitutional assignment made to this compound. Carboxylic acid groups are known (cf. ref. 18) to react with carbodi-imides to form O-acylurea intermediates which are generally too reactive to be isolated because they experience a facile intramolecular rearrange-
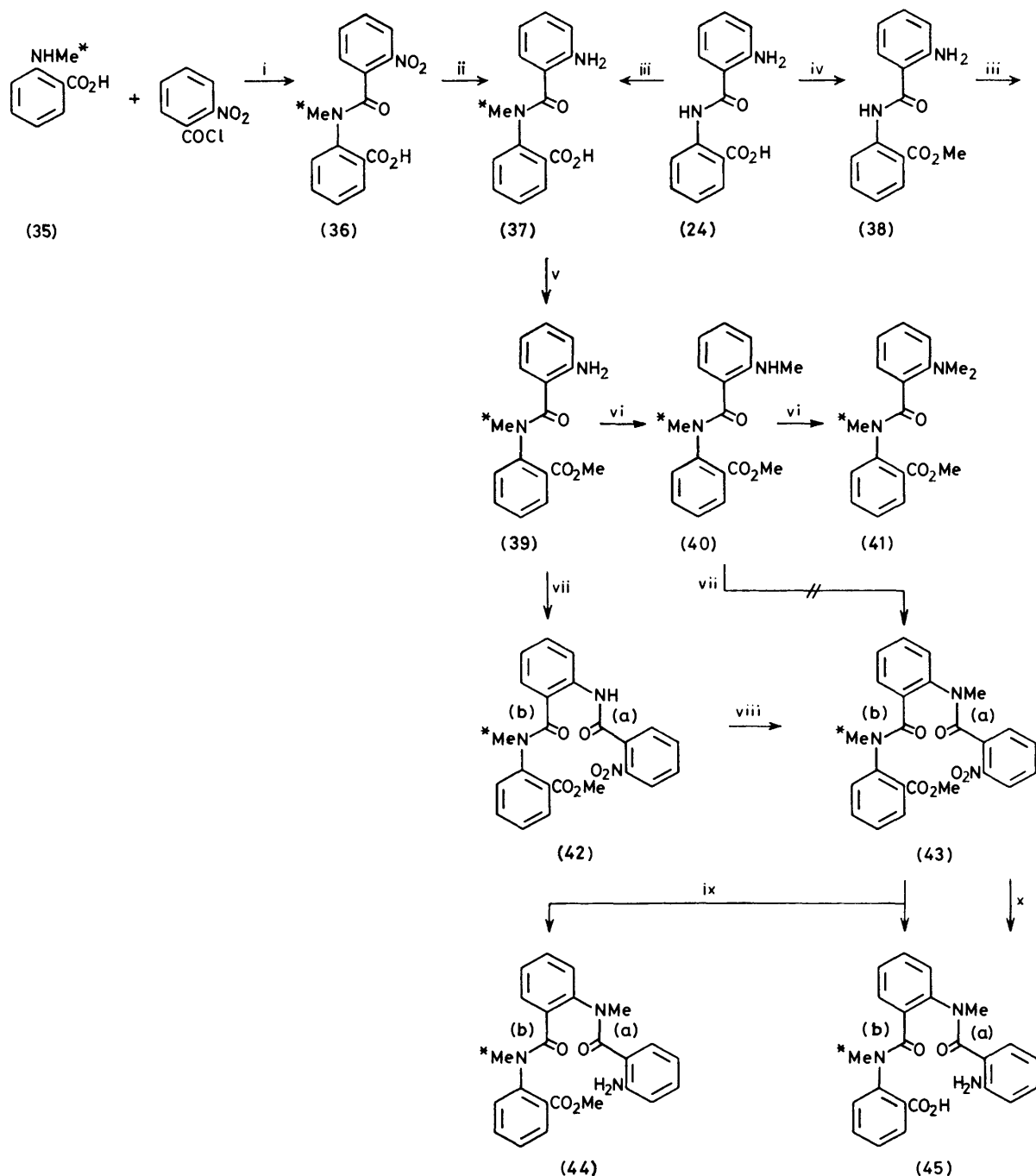
Scheme 6 Reagents and conditions: i, KOH, C_6H_6, H_2O; ii, $TiCl_3$, EtOH, H_2O; iii, Me_2SO_4, THF; iv, p-MeC$_6$H$_4$N=NNHMe, THF; v, MeI, K_2CO_3, MeCOEt, refluxed 25 min; vi, MeI, K_2CO_3, MeCOEt, refluxed 16 h; vii, o-NO$_2$C$_6$H$_4$COCl, LiOH, C_6H_6, H_2O; viii, MeI, NaH, Me$_2$SO; ix, $TiCl_3$, EtOH, H_2O then LiOH at 40 °C; x, $TiCl_3$, EtOH, H_2O then LiOH under reflux for 1 h

(46) X = NHMe
(47) X = NMe₂

(48)
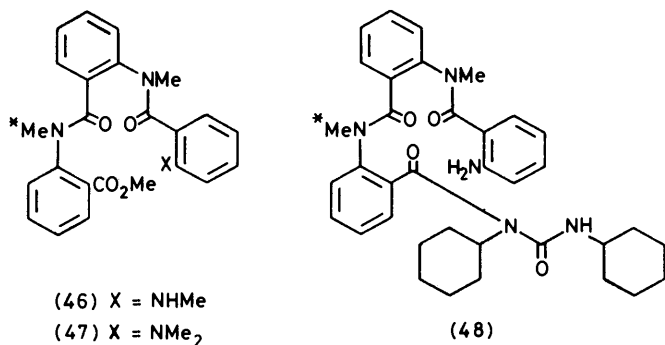
ment to the corresponding N-acylurea intermediates. The N-acylurea derivative (48) undergoes cyclisation to N,N'-dimethyltrianthranilide (5) in refluxing ethanol.
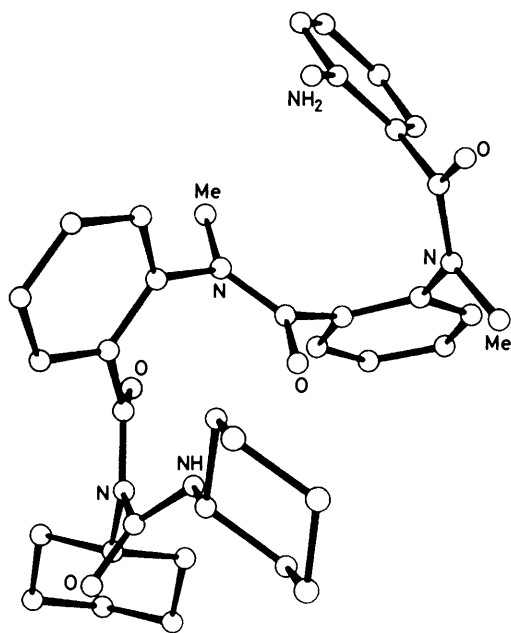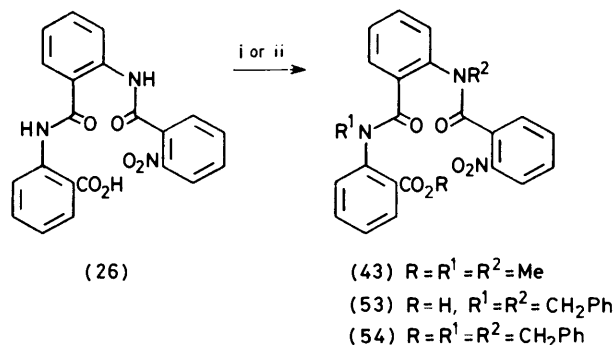

FIGURE 1   The structure of the N-acylurea derivative (48) in the solid state [17]

Figure 2 summarises our mechanistic proposal for the formation of the macrocycle (5) from the amino-acid derivative (45). Treatment of this derivative (45) with thionyl chloride in chloroform also resulted in its cyclis-

(26)

(43) R = R¹ = R² = Me
(53) R = H, R¹ = R² = CH₂Ph
(54) R = R¹ = R² = CH₂Ph

SCHEME 7   Reagents: i, MeI, NaH, Me₂SO; ii, PhCH₂Br, NaH, THF

ation to give N,N'-dimethyltrianthranilide (5) but in very low yield.

It became necessary during the course of our investigations of the conformational behaviour of N,N',N''-trimethyltrianthranilide (7) and other N,N',N''-trisubstituted trianthranilide derivatives to synthesise N-methyl-N'-trideuteriomethyltrianthranilide (6). This synthesis was achieved using the sequence of reactions outlined in Scheme 8. o-Nitrobenzoylation of N-methyl-N-(o-aminobenzoyl)anthranilic acid (37) afforded compound (49).   Conversion of (49) into compound (50) with trideuteriomethyl iodide was followed by titanium-(III) chloride reduction of the aromatic nitro-group under conditions effecting simultaneous de-esterification to produce the amino-acid (51).   Treatment of (51) with N,N'-dicyclohexylcarbodi-imide in dichloromethane gave the intermediate N-acylurea derivative (52) which was refluxed in ethanol to effect cyclisation to N-methyl-N'-trideuteriomethyltrianthranilide (6).

(37)   (49)

(50)   (51)

(52)

(6)
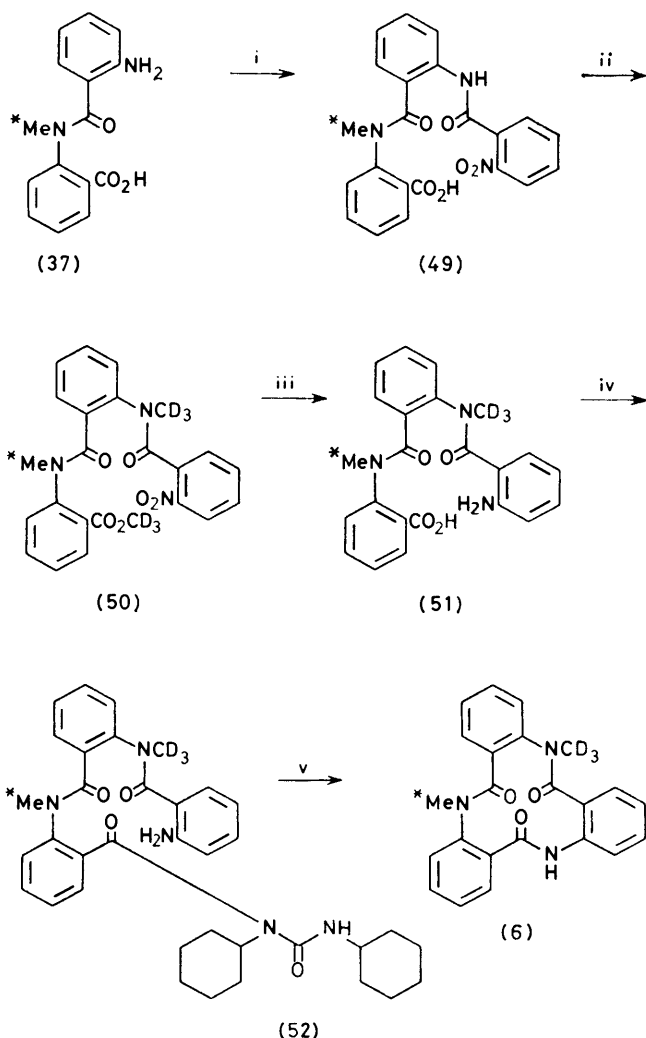
SCHEME 8   Reagents and conditions: i, o-NO₂C₆H₄COCl, LiOH, C₆H₆, H₂O; ii, CD₃I, NaH, Me₂SO; iii, TiCl₃, EtOH, H₂O, then LiOH under reflux; iv, C₆H₁₁N=C=NC₆H₁₁, CH₂Cl₂; v, EtOH, reflux
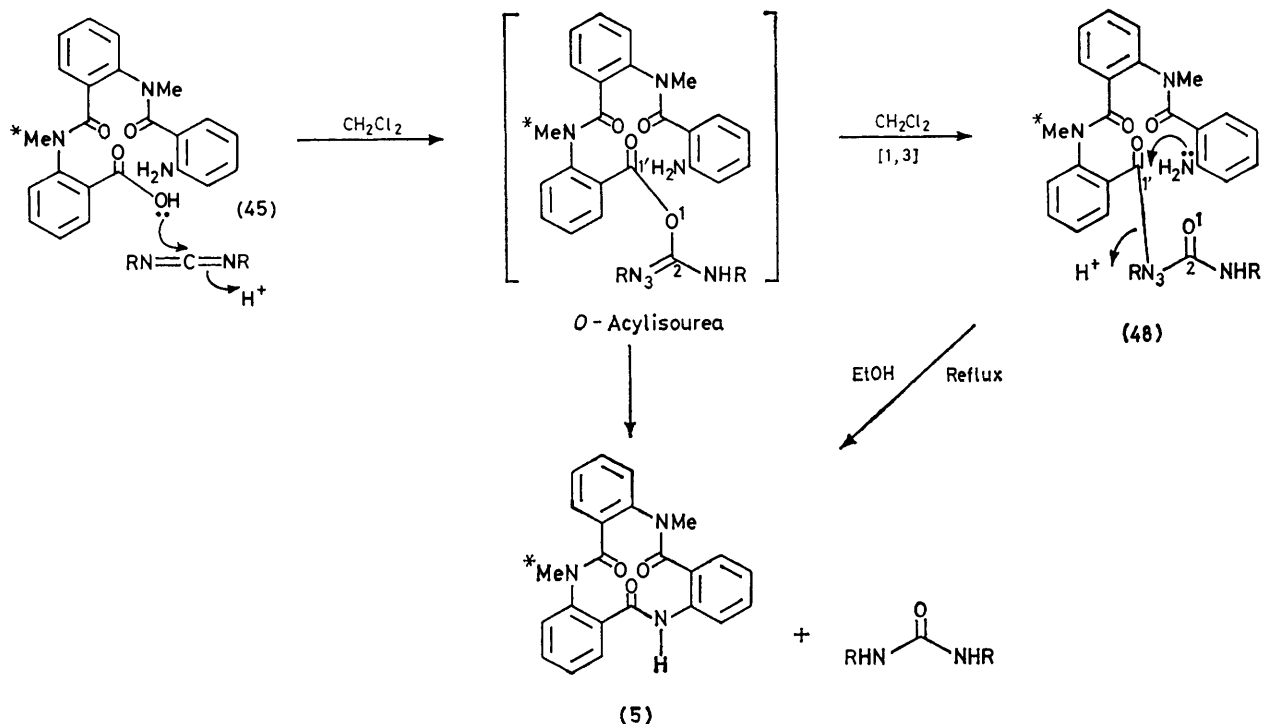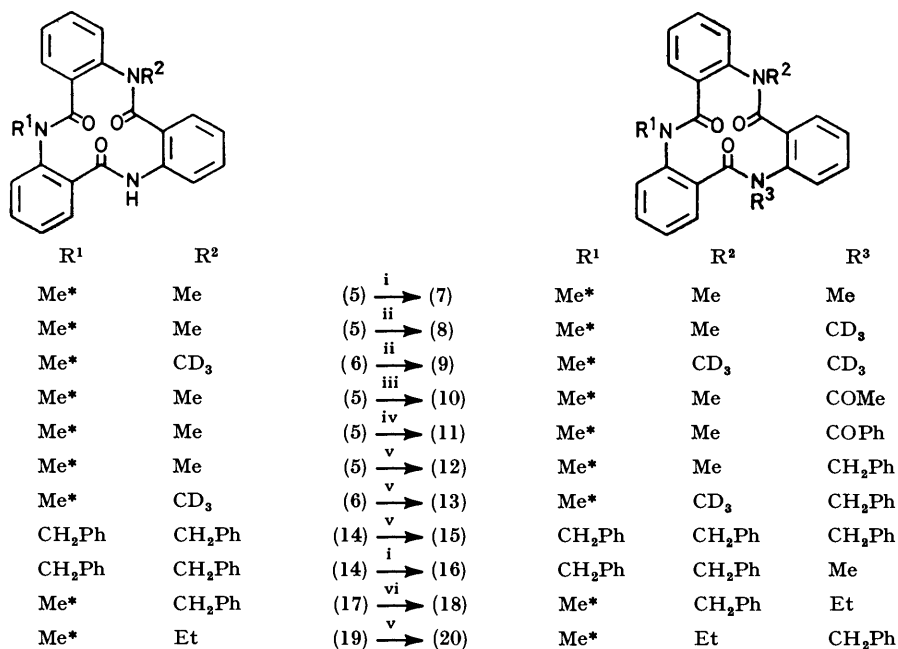
FIGURE 2 The proposed mechanism for the formation of N,N'-dimethyltrianthranilide (5) from the amino-acid derivative (45);
R = cyclohexyl

Methylation (MeI, NaH, Me$_2$SO) of N,N'-dimethyl-trianthranilide (5) gave (see Scheme 9) N,N',N''-tri-methyltrianthranilide (7) in good yield (76%). Much lower yields ($\leqslant 7\%$) of (7) were obtained (see Scheme 10) on (i) base-promoted cyclisation of compound (44) followed by methylation and (ii) base-promoted cyclisation of compound (46). Attempts in independent

experiments to prepare N,N',N''-trimethyltrianthran-ilide (7) from (i) anthranilic acid with N,N'-dicyclohexyl-carbodi-imide followed by methylation of the crude reaction products and (ii) treatment of N-methyl-anthranilic acid (35) with N,N'-dicyclohexylcarbodi-imide both failed. The monotrideuteriomethyl (8) and ditrideuteriomethyl (9) analogues of (7) were prepared

R^1	R^2			R^1	R^2	R^3
Me*	Me	(5) $\xrightarrow{\text{i}}$ (7)		Me*	Me	Me
Me*	Me	(5) $\xrightarrow{\text{ii}}$ (8)		Me*	Me	CD$_3$
Me*	CD$_3$	(6) $\xrightarrow{\text{ii}}$ (9)		Me*	CD$_3$	CD$_3$
Me*	Me	(5) $\xrightarrow{\text{iii}}$ (10)		Me*	Me	COMe
Me*	Me	(5) $\xrightarrow{\text{iv}}$ (11)		Me*	Me	COPh
Me*	Me	(5) $\xrightarrow{\text{v}}$ (12)		Me*	Me	CH$_2$Ph
Me*	CD$_3$	(6) $\xrightarrow{\text{v}}$ (13)		Me*	CD$_3$	CH$_2$Ph
CH$_2$Ph	CH$_2$Ph	(14) $\xrightarrow{\text{v}}$ (15)		CH$_2$Ph	CH$_2$Ph	CH$_2$Ph
CH$_2$Ph	CH$_2$Ph	(14) $\xrightarrow{\text{i}}$ (16)		CH$_2$Ph	CH$_2$Ph	Me
Me*	CH$_2$Ph	(17) $\xrightarrow{\text{vi}}$ (18)		Me*	CH$_2$Ph	Et
Me*	Et	(19) $\xrightarrow{\text{v}}$ (20)		Me*	Et	CH$_2$Ph

SCHEME 9 Reagents: i, MeI, NaH, Me$_2$SO; ii, CD$_3$I, NaH, Me$_2$SO; iii, AcCl, NaH, C$_6$H$_5$CH$_3$; iv, PhCOCl, NaH, THF; v, PhCH$_2$Br, NaH, Me$_2$SO; vi, EtI, NaH, Me$_2$SO

during very short reaction times (15 min) by trideuteriomethylation of N,N'-dimethyltrianthranilide (5) and its monotrideuteriomethyl analogue (6), respectively. The requirement for a short reaction time will become apparent later on in the Experimental as well as in the Results and Discussion sections of this paper.

Acetylation (AcCl, NaH, toluene) and benzoylation (BzCl, NaH, THF) of N,N'-dimethyltrianthranilide (5) gave (see Scheme 9) the N''-acetyl (10) and N''-benzoyl (11) derivatives, respectively.

Benzylation (PhCH₂Br, NaH, THF) of N,N'-dimethyltrianthranilide (5) and its monotrideuteriomethyl analogue (6) afforded (see Scheme 9) N,N'-dimethyl-N''-benzyltrianthranilide (12) and N-methyl-N'-trideuteriomethyl-N''-benzyltrianthranilide (13), respectively. ¹H N.m.r. spectroscopy indicates that both these compounds exist as mixtures of four conformational diastereoisomers. In the case of compound (12) two of these isomers were isolated by preparative t.l.c. and characterised (see the Experimental as well as the Results and Discussion sections). Since the prochiral benzylic methylene groups are extremely useful ¹H n.m.r. probes for following conformational changes in trianthranilides, we were obliged to extend the range of N-benzylated derivatives beyond those represented by compounds (12) and (13) above. This was accomplished by recognising that N-[2-(o-nitrobenzamido)benzoyl]anthranilic acid (26) is an appropriate starting material and subjecting (see Scheme 7) this compound to benzylation to afford a mixture of the acid (53) and the benzyl ester (54) of the N,N'-dibenzylated derivative. N,N'-Dibenzyltrianthranilide (14) was obtained from this mixture by the sequence of reactions outlined in Scheme 11. Titanium-(III) chloride reduction of the aromatic nitro-groups in

(53) R = H, R¹ = R² = CH₂Ph

+

(54) R = R¹ = R² = CH₂Ph

(14)
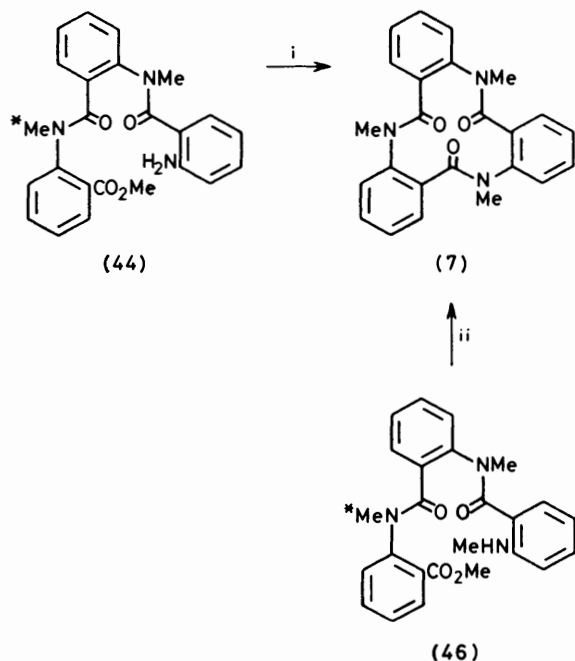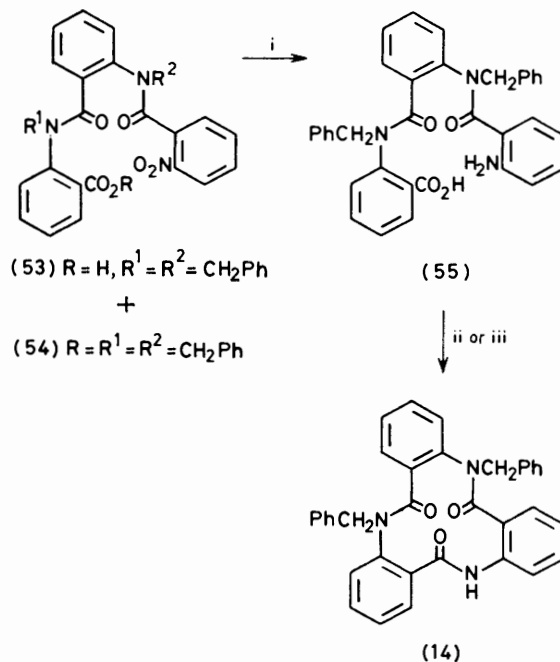
SCHEME 11 *Reagents:* i, TiCl₃, EtOH, H₂O then LiOH under reflux; ii, C₆H₁₁N=C=NC₆H₁₁, CH₂Cl₂; iii, SOCl₂, CHCl₃

this mixture resulted in characterisation of the aminoacid derivative (55) as a pure compound after de-esterification prior to isolation. Treatment of this compound (55) with N,N'-dicyclohexylcarbodi-imide in dichloromethane led to the formation of the macrocycle (14) in good yield (50%). When thionyl chloride in chloroform was used to promote this cyclisation, the yield of N,N'-dibenzyltrianthranilide (14) was extremely low. Benzylation of (14) afforded (see Scheme 9) N,N',N''-tribenzyltrianthranilide (15) as a mixture of two conformational diastereoisomers which could be separated from each other by preparative t.l.c. and characterised as crystalline compounds (see the Experimental as well as the Results and Discussion sections). Methylation of N,N'-dibenzyltrianthranilide (14) afforded (see Scheme 9) N,N'-dibenzyl-N''-methyltrianthranilide (16) in the form of a mixture of four conformational diastereoisomers judging from the ¹H n.m.r. spectroscopic data. Two of the isomers were isolated and characterised after preparative t.l.c. (see the Experimental as well as the Results and Discussion sections).

In order to complete the stereochemical investigation of N,N',N''-trisubstituted trianthranilide derivatives, it was necessary to study an example where the three substituent groups on the amide nitrogen atoms are constitutionally different not just on account of isotopic substitution. This goal was accomplished by the preparation (see Scheme 9) of N-methyl-N'-benzyl-N''-ethyltrianthranilide (18) and N-methyl-N'-ethyl-N''-benzyltrianthranilide (20) from N-methyl-N'-benzyltrianthranilide (17) and N-methyl-N'-ethyltrianthranilide (19) respectively by ethylation of (17) and benzylation of (19). The N,N'-disubstituted trianthranilide derivatives (17) and (19) were both obtained in a sequence


(44)   (7)

(46)

SCHEME 10 *Reagents:* i, MeI, NaH, THF; ii, NaH, THF

of reactions starting from methyl N-methyl-N-[2-(o-nitrobenzamido)benzoyl]anthranilate (42) as shown in Scheme 12. Benzylation of (42) gives compound (56); ethylation of (42) gives compound (60). Titanium(III)

(42)

(56) R² = CH₂Ph
(60) R² = Et

(57) R = Me, R² = CH₂Ph
(58) R = H, R² = CH₂Ph
(61) R = Me, R² = Et
(62) R = H, R² = Et

(17) R² = CH₂Ph
(19) R = Et
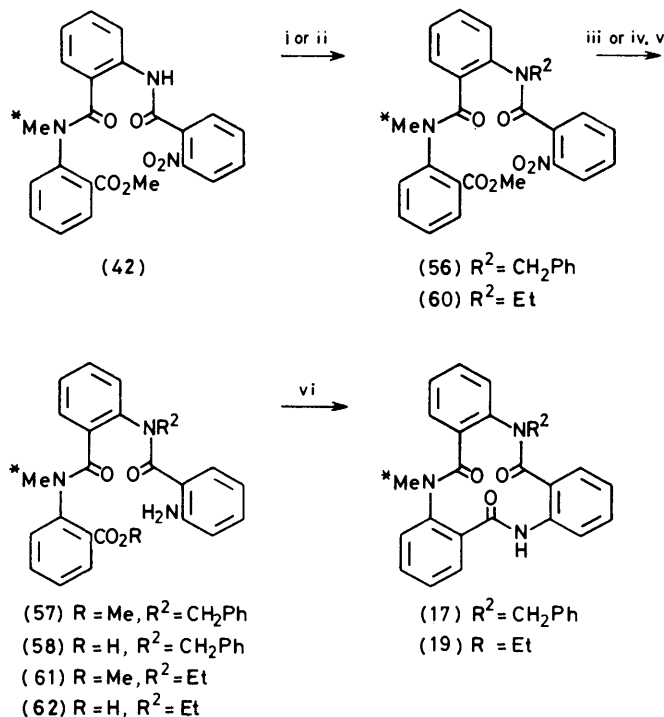
SCHEME 12 *Reagents:* i, PhCH₂Br, NaH, Me₂SO; ii, EtI, NaH, Me₂SO; iii, TiCl₃, EtOH, H₂O then LiOH under reflux; iv, TiCl₃, EtOH, H₂O; v, LiOH, MeOH; vi, C₆H₁₁N=C=NC₆H₁₁, CH₂Cl₂

chloride reduction of compound (56) followed by attempted de-esterification with lithium hydroxide resulted in a mixture of the amino-acid derivative (58) and its methyl ester (57). Since this mixture was prone to polymerisation it was treated directly with N,N'-dicyclohexylcarbodi-imide in dichloromethane to afford N-methyl-N'-benzyltrianthranilide (17). Titanium(III) chloride reduction of compound (60) affords the amino-acid methyl ester (61) which was de-esterified yielding the amino-acid derivative (62). Cyclisation of (62) in dichloromethane in the presence of N,N'-dicyclohexylcarbodi-imide led to the isolation of N-methyl-N'-ethyltrianthranilide (19).

(7) R¹ = R² = R³ = Me
(15) R¹ = R² = R³ = CH₂Ph

(21) R = Me, X = CH₂
(22) R = CH₂Ph, X = CD₂
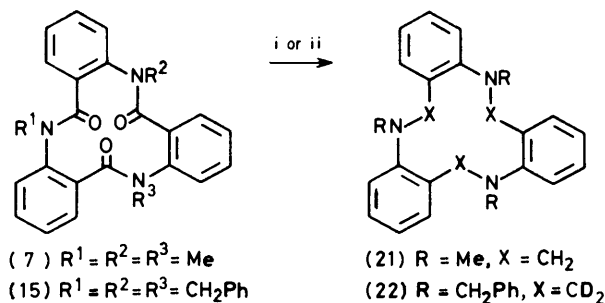
SCHEME 13 *Reagents:* i, LiAlH₄, THF; ii, LiAlD₄, THF

Finally, advantage was taken of the availability of quantities of N,N',N''-trimethyl- (7) and N,N',N''-tribenzyl- (15) trianthranilides to prepare (see Scheme 13) the corresponding cyclic triamines (21) and (22) by reduction of the amide linkages in (7) and (15). In order to simplify the ¹H n.m.r. spectrum in the chemical-shift region of the benzylic methylene protons in (22), the reduction of N,N'N''-tribenzyltrianthranilide (15) was carried out with lithium aluminium deuteride to yield the triamine (22) as its hexadeuterio-derivative.

Parts of this investigation have been the subjects of preliminary communications,[19–21] and have also been summarised briefly in a review article [22] on the conformational behaviour of some medium-sized ring systems. The X-ray crystal structures of N,N'-dimethyl- (5) and N,N'-dibenzyl- (14) trianthranilides have also been communicated [23] in a preliminary form.

EXPERIMENTAL

The general methods have been discussed in Parts 3 [24] and 6.[25]

Methyl Anthranilate (29).—Anthranilic acid (2 g), methyl iodide (1.2 ml), and potassium carbonate (0.5 g) were refluxed in acetone (20 ml) for 1 h and then the reaction mixture was filtered. The colourless oil obtained on evaporation of the filtrate was identified as methyl anthranilate (29) (1.8 g, 82%), τ (CDCl₃) 1.90—3.54 (4 H, m, ArH), 4.30 (2 H, bs, NH₂), and 6.13 (3 H, s, Me).

N-*Methylanthranilic Acid* (35).[14]—Anthranilic acid (137 g) was dissolved in a solution of potassium carbonate (69 g) in water (30 ml). The solution was filtered and methyl iodide (60 ml) was added to the filtrate. The reaction mixture was refluxed for 2 h. On cooling, N-methylanthranilic acid (35) (100 g, 66%), m.p. 187—189 °C (lit.,[14] m.p. 182 °C) separated as a yellow solid which was collected and recrystallised from ethanol (Found: C, 63.8; H, 6.2; N, 9.4%; M (mass spec.), 151. Calc. for C₈H₉NO₂: C, 63.6; H, 6.0; N, 9.3%; M, 151), ν_max. (Nujol), 3 380 (OH) and 1 670 cm⁻¹ (CO); τ [CDCl₃–(CD₃)₂CO], 1.48 (2 H, bs, CO₂H and NHMe*), 1.96—2.53 (4 H, m, ArH), and 7.10 (3 H, s, NHMe*). [The reason for identifying·this methyl group (Me*) here and throughout the Experimental section is given in a footnote in the Introductory section.]

N-(o-*Aminobenzoyl)anthranilic Acid* (*Anthraniloylanthranilic Acid*) (24).[11,12]—Anthranilic acid (1.4 g) was dissolved in a solution of sodium hydroxide (0.6 g) in water (5 ml). Isatoic anhydride (23) (1.6 g) was added and the mixture was heated at 55 °C for *ca.* 15 min until the evolution of carbon dioxide had ceased. After cooling the crude product was precipitated by addition of glacial acetic acid. Recrystallisation from methanol–water (4 : 1) gave pale brown needles of anthraniloylanthranilic acid (24) (1.9 g, 74%), m.p. 203—204 °C (lit.,[11] m.p. 203 °C) [Found: M (mass spec.), 256. Calc. for C₁₄H₁₂N₂O₃: M, 256], ν_max. (Nujol) 3 495 (OH), 3 460 (CONH), 3 385 and 3 350 (NH₂), 1 690 (CO₂H) and 1 600 cm⁻¹ (CONH); τ [(CD₃)₂CO] −2.08 (1 H, bs, CONH), 1.07—3.44 (8 H, m, ArH), and 3.68 (3 H, bs, NH₂ and CO₂H).

Attempts to prepare dianthraniloylanthranilic acid (25) from reaction of anthraniloylanthranilic acid (24) with isatoic anhydride (23) in the presence of (a) aqueous sodium hydroxide and (b) pyridine were unsuccessful. In both cases, only starting material was isolated.

Dibenzo[b,f][1,5]*diazocine*-6,12(5H,11H)-*dione* (*Dianthranilide*) (1).—(a) A solution of anthraniloylanthranilic acid (24) (512 mg) and *N,N'*- dicyclohexylcarbodi-imide (412 mg) in dry pyridine (10 ml) was kept at 0 °C for 30 min and then at room temperature for a further 2 h. The reaction mixture was filtered to remove *N,N'*- dicyclohexylurea and the filtrate was concentrated to give a solid. Recrystallisation from aqueous ethanol gave yellow crystals of dianthranilide (1) (430 mg, 90%), m.p. 333 °C (lit.,[6] m.p. 335—337 °C) [Found: C, 70.7; H, 4.5; N, 11.9%; *M* (mass spec.), 238. Calc. for $C_{14}H_{10}N_2O_2$: C, 70.6; H, 4.2; N, 11.8%; *M* 238], τ (Me₂SO) 1.75—3.58 (all protons, m and bs, ArH, and NH).

(b) A solution of methyl anthranilate (29) (2 g) was stirred for 4 days in dry tetrahydrofuran containing sodium hydride (0.5 g). The crude product was obtained on pouring the reaction mixture into dilute hydrochloric acid. Recrystallisation from aqueous ethanol yielded dianthranilide (1) (1.5 g, 95%).

5,11-*Dibenzyldibenzo*[b,f][1,5]*diazocine*-6,12(5H,12H)-*dione* (N,N'-*Dibenzyldianthranilide*) (4).—Sodium hydride (0.6 g) and benzyl bromide (1.87 g) were added to a solution of dianthranilide (1) (1.3 g) in dry dimethyl sulphoxide (30 ml). The reaction mixture was stirred in an atmosphere of nitrogen at room temperature for 4 h. It was then poured into ice–water and the resulting precipitate was crystallised from methanol to give N,N'-*dibenzyldianthranilide* (4) (1.45 g, 64%), m.p. 158—159 °C [Found: *M* (mass spec.), 418.1682. $C_{28}H_{22}N_2O_2$ requires *M*, 418.1681], τ (CDCl₃) 2.60—3.22 (18 H, m, ArH) and 4.91 and 5.04 (4 H, 2 overlapping AB systems, J_{AB} 16 Hz, 2 × PhC*H*₂).

o-*Nitrobenzoyl Chloride*.—A solution of *o*-nitrobenzoic acid (33.4 g) and redistilled thionyl chloride (18 ml) in dry benzene (120 ml) was refluxed until the evolution of hydrogen chloride and sulphur dioxide had ceased. The solution was then cooled and filtered and the *o*-nitrobenzoyl chloride was subsequently used without further purification in benzene solution. [The solution contains *o*-nitrobenzoyl chloride (37 g) in benzene (120 ml).]

N-[2-(o-*Nitrobenzamido*)*benzoyl*]*anthranilic Acid* (26).[9]—A solution of *N*-(*o*-aminobenzoyl)anthranilic acid (24) (1.3 g) and lithium hydroxide (0.2 g) in water (15 ml) was stirred with the *o*-nitrobenzoyl chloride solution (3 ml) diluted with benzene (12 ml). The solid which precipitated was filtered off and recrystallised from ethanol to give pale yellow crystals of *N*-[2-(*o*-nitrobenzamido)benzoyl]anthranilic acid (26) (1.6 g, 76%), m.p. 223—224 °C (lit.,[9] m.p. 224 °C) [Found: *M* (mass spec.), 405. Calc. for $C_{21}H_{15}N_3O_6$: *M*, 405], τ (Me₂SO) −2.07 and −1.37 (2 H, 2 × bs, 2 × CONH) and 1.25—2.95 (13 H, m and bs, ArH and CO₂H).

5-(o-*Nitrobenzoyldibenzo*[b,f][1,5]*diazocine*-6,12(5H,11H)-*dione* [N-o-(*Nitrobenzoyl*)*dianthranilide*] (28).—Treatment of the acid (26) (405 mg) with *N,N'*-dicyclohexylcarbodi-imide (206 mg) in pyridine gave a crude product which was recrystallised from acetone to yield pale yellow crystals of N-o-(*nitrobenzoyl*)*dianthranilide* (28) (350 mg, 90%), m.p. 210 °C [Found: *M* (mass spec.), 387. $C_{21}H_{13}N_3O_5$ requires *M*, 387].

N-[2-(o-*Aminobenzamido*)*benzoyl*]*anthranilic Acid* (*Dianthraniloylanthranilic Acid*) (25).—A titanium(III) chloride solution (1 ml; 15%) was added dropwise during 10 min to a stirred solution of the nitro-acid (26) (500 mg) in refluxing ethanol (25 ml). After being heated for a further 10 min, this solution was poured into boiling water (150 ml) and heated for a further 30 min. After being cooled, the mixture was made alkaline by addition of aqueous lithium hydroxide

and allowed to stand at 40 °C. The precipitate which formed was filtered off, heated again with water, and re-filtered. The combined filtrates were acidified with glacial acetic acid. The pale yellow solid which precipitated was filtered off, dried, and recrystallised from pentyl acetate to give cream-coloured crystals of dianthraniloylanthranilic acid (25) (430 mg, 93%), m.p. 256 °C (lit.,[9] m.p. 228 °C) [Found: C, 67.2; H, 4.7; N, 11.0%, *M* (mass spec.), 375. Calc. for $C_{21}H_{17}N_3O_4$: C, 67.2; H, 4.6; N, 11.2%; *M*, 375], τ (Me₂SO) −2.05 and −1.45 (2 H, 2 × bs, 2 × CONH) and 1.30—3.58 (15 H, m and bs, ArH, CO₂H, and NH₂).

Attempted cyclisations of dianthraniloylanthranilic acid (25) to give dianthranilide (1) and/or trianthranilide (2) employing either (i) thionyl chloride in dry benzene containing a trace of triethylamine or (ii) refluxing xylene in the presence of molecular sieves were both unsuccessful.

5-(o-*Aminobenzoyl*)*dibenzo*[b,f][1,5]*diazocine*-6,12(5H,-11H)-*dione* [N-o-(*Aminobenzoyl*)*dianthranilide*] (27).—(a) Reaction of dianthraniloylanthranilic acid (25) (375 mg) with *N,N'*-dicyclohexylcarbodi-imide (206 mg) in dry pyridine as described previously for anthraniloylanthranilic acid (24) afforded needles (from chloroform–light petroleum) of N-o-(*aminobenzoyl*)*dianthranilide* (27) (350 mg, 98%), m.p. 191 °C [Found: C, 70.2; H, 4.3; N, 11.5%; *M* (mass spec.), 357. $C_{21}H_{15}N_3O_3$ requires C, 70.6; H, 4.2; N, 11.8%; *M* 357], τ (Me₂SO) −2.45 (1 H, bs, CONH) and 1.22—3.83 (14 H, m and bs, ArH and NH₂).

(b) N-o-(Nitrobenzoyl)dianthranilide (28) (100 mg) was dissolved in ethyl methyl ketone and hydrogenated using a Raney nickel catalyst. When 170 ml of hydrogen had been taken up, the catalyst was filtered off and the solution was concentrated to give a product which was identical by t.l.c. on silica gel (CHCl₃) with that obtained from cyclisation of dianthraniloylanthranilic acid (25).

Attempts to effect rearrangement of *N-o*-(aminobenzoyl)-dianthranilide (27) to trianthranilide (2) by heating (i) under reflux in xylene over a molecular sieve for 24 h, (ii) under reflux in *N,N*-dimethylformamide for 24 h, and (iii) under reflux in naphthalene over a molecular sieve for 12 h, all proved to be unsuccessful. Starting material was isolated in all three cases.

N-(o-*Methylaminobenzoyl*)*anthranilic Acid* (30).—Anthraniloylanthranilic acid (24) (2.6 g) was dissolved in a solution of potassium carbonate (0.7 g) in water (10 ml). Methyl iodide was added and the reaction mixture was heated under reflux for 2 h. On cooling, a solid separated which was filtered off, dried, and crystallised from aqueous ethanol to afford needles of N-(o-*methylaminobenzoyl*)-*anthranilic acid* (30) (2.1 g, 77%), m.p. 221 °C [Found: C, 66.7; H, 5.4; N, 10.7%; *M* (mass spec.), 270. $C_{15}H_{14}N_2O_3$ requires C, 66.7; H, 5.2; N, 10.4%; *M* 270], τ (C₅H₅N) 7.23 (s, NHMe).

5-*Methyldibenzo*[b,f][1,5]*diazocine*-6,12(5H,11H)-*dione* (N-*Methyldianthranilide*) (33).—Reaction of N-(o-methyl-aminobenzoyl)anthranilic acid (30) (270 mg) with *N,N'*-dicyclohexylcarbodi-imide (206 mg) in dry pyridine as described previously for anthraniloylanthranilic acid (24) afforded crystals, after crystallisation from ethanol, of N-*methyldianthranilide* (33) (200 mg, 80%), m.p. 164—165 °C [Found: C, 71.1; H, 4.9; N, 10.6% *M* (mass spec.), 252. $C_{15}H_{12}N_2O_2$ requires C, 71.4; H, 4.8; N, 11.1%; *M*, 252].

N-[2-(o-*Nitro-N-methylbenzamido*)*benzoyl*]*anthranilic Acid* (31).—N-(o-Methylaminobenzoyl)anthranilic acid (30) (270 mg) was dissolved in a solution of lithium hydroxide (42 mg) in water (1 ml) and shaken with the *o*-nitrobenzoyl

chloride solution (1 ml) for 10 min. The yellow solid which separated was collected and crystallised from aqueous ethanol to yield yellow crystals of the *nitro-acid* (31) (160 mg, 38%), m.p. 226 °C [Found: C, 63.3; H, 4.4; N, 9.5%; *M* (mass spec.), 419. $C_{22}H_{17}N_3O_6$ requires C, 63.0; H, 4.1; N, 10.0%; *M*, 419].

N-[2-(o-*Amino-N-methylbenzamido*)*benzoyl*]*anthranilic Acid* (32).—Reduction of the aromatic nitro-group in the nitro-acid (31) (1 g) with titanium(III) chloride (15 ml; 15%) as described previously for the nitro-acid (26) gave pale yellow crystals (from ethanol) of the *amino-acid* (32) (600 mg, 65%), m.p. 200 °C [Found: C, 67.9; H, 5.0; 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].

Attempted cyclisations of this amino-acid (32) to give *N*-methyltrianthranilide (34) employing (i) *N,N'*-dicyclo-hexylcarbodi-imide in dry pyridine and (ii) refluxing xylene in the presence of molecular sieves were both unsuccessful. When the amino-acid (32) was heated under reflux in naphthalene for 12 h, t.l.c. examination and mass spectral analysis of the crude product indicated the presence of dianthranilide (1) and *N*-methyldianthranilide (33).

N-*Methyl*-N-(o-*nitrobenzoyl*)*anthranilic Acid* (36.)[4,15]—*N*-Methylanthranilic acid (35) (50 g) was dissolved in a solution of potassium hydroxide (25 g) in water (400 ml), o-nitrobenzoyl chloride solution (200 ml) diluted with benzene (200 ml) was added, and the mixture was stirred at room temperature for 5 min. *N*-Methyl-*N*-(o-nitro-benzoyl)anthranilic acid (36) (75 g, 75%), m.p. 218—219 °C (lit.,[4] m.p. 216 °C, lit.,[15] m.p. 217—218 °C) was obtained as a pale yellow solid which was recrystallised from ethanol [Found: C, 60.1; H, 4.3; N, 9.3%; *M* (mass spec.), 300. Calc. for $C_{15}H_{12}N_2O_5$: C, 60.0; H, 4.0; N, 9.3%; *M*, 300], $\nu_{max.}$ (Nujol), 2 600 and 2 480 (OH), 1 700 (CO_2H), 1 620 (CO), and 1 530 and 1 350 cm^{-1} (NO_2); τ (C_5D_5N) −0.58 (1 H, s, CO_2H), 1.56—2.95 (8 H, m, ArH), and 6.38 and 6.74 (3 H, 2 × s in the approximate ratio of 77 : 34, NMe*).†

N-*Methyl*-N-(o-*aminobenzoyl*)*anthranilic Acid* (37.)—(a) *N*-Methyl-*N*-(o-nitrobenzoyl)anthranilic acid (36) (25 g) was dissolved in boiling ethanol (2 l) and a solution of titanium(III) chloride (750 ml; 12.5%) was added dropwise. This solution was heated under reflux for 10 min, poured into boiling water (2 l), and heated for a further 30 min. On cooling, the reaction mixture was extracted with chloroform several times. The combined chloroform extracts were washed with water and dried ($MgSO_4$). After filtration, the chloroform solution was concentrated to afford a yellow solid, crystallisation of which from ethanol yielded N-methyl-*N*-(o-aminobenzoyl)anthranilic acid (37) (15.6 g, 69%), m.p. 239—240 °C (lit.,[4] m.p. 239—240 °C) [Found: C, 66.8; H, 5.5; N, 10.4%; *M* (mass spec.), 270.1005. Calc. for $C_{15}H_{14}N_2O_3$: C, 66.7; H, 5.2; N, 10.4%; *M*, 270.1004], $\nu_{max.}$ (Nujol) 3 450 (NH_2), 3 220 (OH), 1 710 (CO_2H), and 1 660 and 1 630 cm^{-1} (CONH); τ [$(CD_3)_2SO$] −2.90 (1 H, s, CO_2H), 1.27—3.41 (10 H, m and bs, ArH and NH_2), and 7.16 (3 H, s, NMe*).

(b) Dimethyl sulphate (0.5 ml) was added to a solution of anthraniloylanthranilic acid (24) (1.28 g) in refluxing tetrahydrofuran (13 ml). The reaction mixture was heated under reflux for a further 2.5 h. The hot solution was then

poured into water with stirring and the yellow solid which separated was collected by filtration. This solid was purified by preparative t.l.c. on silica gel using chloroform–methanol (4 : 1) as eluant to yield *N*-methyl-*N*-(o-amino-benzoyl)anthranilic acid (37) (1 g, 74%), m.p. 239—240 °C.

Methyl N-(o-*Aminobenzoyl*)*anthranilate* (38).[12]—Anthraniloylanthranilic acid (24) (1.66 g) and 1-methyl-3-*p*-tolyltriazene[16] (1 g) in tetrahydrofuran (12.5 ml) were allowed to react at room temperature for 3 h. The solution was concentrated, washed with ether–hexane (1 : 1), and the residue crystallised from ethanol to yield methyl *N*-(o-aminobenzoyl)anthranilate (38) as needles (1.1 g, 63%), m.p. 115—116 °C (lit.,[12] m.p. 109—111 °C) [Found: *M* (mass spec.), 270. Calc. for $C_{15}H_{14}N_2O_3$: *M*, 270], $\nu_{max.}$ (Nujol) 3 470 (NH), 3 360 and 3 330 (NH_2), 1 680 (CO_2Me), and 1 660 cm^{-1} (CONH); τ (CDCl$_3$) −1.74 (1 H, bs, CONH), 1.15—3.37 (8 H, m, ArH), 4.28 (2 H, bs, NH_2), and 6.10 (3 H, s, CO_2Me).

Methyl N-*Methyl*-N-(o-*aminobenzoyl*)*anthranilate* (39).[15]—(a) The acid (37) (23 g) was refluxed in ethyl methyl ketone (460 ml) for 25 min with methyl iodide (11.5 ml) and potassium carbonate (11.5 g). The reaction mixture was filtered, the solvent was evaporated from the filtrate, and the residue was recrystallised from ethanol to give yellow crystals of methyl *N*-methyl-*N*-(o-aminobenzoyl)anthranilate (39) (20.8 g, 86%), m.p. 104—105 °C (lit.,[15] m.p. 88—89 °C [Found: C, 67.6; H, 5.8; N, 9.7%; *M* (mass spec.), 284. Calc. for $C_{16}H_{16}N_2O_3$: C, 67.6; H, 5.7; N, 9.9%; *M*, 284], $\nu_{max.}$ (Nujol), 3 320 (NH_2), 1 680 (CO_2Me), and 1 650 cm^{-1} (CONH); τ (CDCl$_3$) 1.16—3.42 (10 H, m and bs, ArH and NH_2), 6.11 (3 H, s, CO_2Me), and 7.13 (3 H, s, NMe*).

(b) Dimethyl sulphate (2.4 g) was added to a solution of methyl *N*-(o-aminobenzoyl)anthranilate (38) (5.2 g) in boiling tetrahydrofuran (60 ml). The reaction mixture was heated under reflux for 2.5 h, cooled, and aqueous potassium carbonate (5.2 ml, 50%) added with stirring. After the evolution of carbon dioxide had subsided, the reaction mixture was stirred for an additional 30 min. The inorganic salt was filtered off and the solvent was evaporated under reduced pressure to afford a solid residue which was subjected to column chromatography on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant. The purified product was crystallised from ethanol to yield methyl *N*-methyl-*N*-(o-aminobenzoyl)anthranilate (39) (4.3 g, 79%) as pale yellow needles, m.p. 98—99 °C.

Methyl N-*Methyl*-N-(o-*methylaminobenzoyl*)*anthranilate* (40) *and Methyl* N-*Methyl*-N-(o-*dimethylaminobenzoyl*)-*anthranilate* (41).—Methyl *N*-methyl-*N*-(o-aminobenzoyl)-anthranilate (39) (201 mg), potassium carbonate (500 mg), and methyl iodide (1.14 g) in ethyl methyl ketone (20 ml) were heated under reflux for 16 h. Filtration and evaporation of the filtrate gave a pale yellow gum which was purified by preparative t.l.c. on silica gel using benzene as eluant. The crude product was crystallised from hexane to give *methyl* N-*methyl*-N-(o-*methylaminobenzoyl*)*anthranilate* (40) (150 mg, 71%) as colourless crystals, m.p. 68 °C [Found: *M* (mass spec.), 298.1322. $C_{17}H_{18}N_2O_3$ requires *M*, 298.1317], τ (CDCl$_3$) −2.60 (1 H, bs, N*H*Me), 0.92—3.08 (8 H, m, ArH), 6.15 (3 H, s, CO_2Me), and 7.20 (6 H, s, CONMe* and NHC*H*$_3$).

All attempts to prepare methyl *N*-methyl-*N*-[2-(o-nitro-*N*-methylbenzamido)benzoyl]anthranilate (43) by reaction of methyl *N*-methyl-*N*-(o-methylaminobenzoyl)anthranil-ate (40) with o-nitrobenzoyl chloride failed. In general, acylations of this derivative proved to be impossible in our

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† In the case of compounds (36), (42)—(44), (46), (47), (49), (50), (56), (60), (61), and (62) there is evidence, in their ^{1}H n.m.r. spectra, for the presence of slowly equilibrating conformational diastereoisomers in solution resulting from hindered rotation about amide bonds.

hands. However, methylation was accomplished with difficulty. A mixture of (40) (70 mg), potassium carbonate (500 mg), and methyl iodide (4.6 g) in ethyl methyl ketone (20 ml) was heated under reflux for 16 h. Starting material (40) (50 mg) was separated from a colourless oil by preparative t.l.c. on silica gel (CHCl$_3$) and this product was identified as *methyl* N-*methyl*-N-(o-*dimethylaminobenzoyl*)*anthranilate* (41) (13 mg, 18%), τ (CCl$_4$) 2.35—3.71 (8 H, m, ArH), 6.17 (3 H, s, CO$_2$Me), 6.68 (3 H, s, CONMe*), and 7.48 (6 H, s, NMe$_2$).

Methyl N-*Methyl*-N-[2-(o-*nitrobenzamido*)*benzoyl*]-*anthranilate* (42).—The ester (39) (20 g) was suspended in a solution of lithium hydroxide (4 g) in water (200 ml). o-Nitrobenzoyl chloride solution (8 ml) diluted with benzene (192 ml) was added and the reaction mixture was stirred at room temperature for 1 h. The solid which separated was collected and more o-nitrobenzoyl chloride solution (8 ml) was added to the filtrate. Stirring was continued for 2 h during which time the filtrate afforded more solid. Re-crystallisation of the combined solids from ethanol gave *methyl* N-*methyl*-N-[2-(o-*nitrobenzamido*)*benzoyl*]*anthranilate* (42) (30.5 g, 74%), m.p. 183—184 °C [Found: C, 64.0; H, 4.7; N, 9.5%; *M* (mass spec.), 433. C$_{23}$H$_{19}$N$_3$O$_6$ requires C, 63.7; H, 4.4; N, 9.7%; *M*, 433], τ (CDCl$_3$) −1.44 (1 H, bs, CONH), 1.02—2.94 (12 H, m, ArH), 6.10 and 6.13 (3 H, 2 × s, in the approximate ratio of 78 : 22, CO$_2$Me),† and 6.51 and 6.77 (3 H, 2 × s in the approximate ratio of 78 : 22, NMe*).†

Methyl N-*Methyl*-N-[2-(o-*nitro*-N-*methylbenzamido*)-*benzoyl*)*anthranilate* (43).—(a) Methyl iodide (25 ml) was added to a suspension of the ester (42) (23 g) and sodium hydride (5.2 g) in dry dimethyl sulphoxide (70 ml) and the reaction mixture was stirred at room temperature for 2 h. The excess of sodium hydride was destroyed by careful addition of water. Pouring the reaction mixture into water gave a white solid. Recrystallisation from ethanol afforded *methyl* N-*methyl*-N-[2-(o-*nitro*-N-*methylbenzamido*)-*benzoyl*]*anthranilate* (43) (20.6 g, 87%), m.p. 204—206 °C [Found: C, 64.3; H, 5.0; N, 9.5%; *M* (mass spec.), 447.1425. C$_{24}$H$_{21}$N$_3$O$_6$ requires C, 64.4; H, 4.7; N, 9.4%; *M*, 447.1430], ν$_{max.}$ (Nujol) 1 750 (CO$_2$Me), 1 670 and 1 630 (CO), and 1 530 and 1 370 cm^{-1} (NO$_2$); τ (CDCl$_3$) 1.68—3.20 (12 H, m, ArH), 6.01, 6.08, and 6.09 (3 H, 3 × s in the approximate ratio of 40 : 30 : 30, CO$_2$Me),† 6.43, 6.72, and 6.83 (3 H, 3 × s in the approximate ratio of 20 : 40 : 40, NMe*),† and 6.64 (3 H, s, NMe).

(b) N-[2-(o-Nitrobenzamido)benzoyl]anthranilic acid (26) (14 g) was methylated with methyl iodide (15 ml) and sodium hydride (4.5 g) in dry dimethyl sulphoxide (100 ml) by stirring the solution at room temperature for 3 h. Addition of water afforded a precipitate which was recrystallised from methanol to give *methyl* N-*methyl*-N-[2-(o-*nitro* N-*methylbenzamido*)*benzoyl*]*anthranilate* (43) (12.3 g, 80%), m.p. 204—206 °C.

Methyl N-*Methyl*-N-[2-(o-*amino*-N-*methylbenzamido*)-*benzoyl*]*anthranilate* (44) *and* N-[2-(o-*A mino*-N-*methyl*-*benzamido*)*benzoyl*]-N-*methylanthranilic Acid* (45).—A titanium(III) chloride solution (130 ml, 12.5%) was added dropwise to a boiling solution of the ester (43) (10 g) in ethanol (500 ml). The mixture was heated for 10 min and then poured into boiling water (1 l) and heated for a further 30 min. The solution was cooled, made alkaline by addition of aqueous lithium hydroxide, and allowed to stand at 40 °C. The precipitate was collected, heated again with water, and refiltered. The combined filtrates were acidified with glacial

† See footnote at the bottom of preceding page.

acetic acid. *Methyl* N-*methyl*-N-[2-(o-*amino*-N-*methyl*-*benzamido*)*benzoyl*]*anthranilate* (44) (4.8 g, 52%), m.p. 79—80 °C [Found: *M* (mass spec.), 417.1672. C$_{24}$H$_{23}$N$_3$O$_4$ requires *M*, 417.1688], ν$_{max.}$ (Nujol) 3 400 and 3 310 (NH$_2$), 1 730 (CO$_2$Me), and 1 640 and 1 620 cm^{-1} (CO); τ (CDCl$_3$) 1.95—3.44 (12 H, m, ArH), 5.39 (2 H, bs, NH$_2$), 6.01, 6.04, 6.09, and 6.12 (3 H, 4 × s, in the approximate ratio of 16 : 32 : 17 : 35, CO$_2$Me) † and 6.44, 6.57, 6.61, 6.64, 6.72, and 6.83 (6 H, 6 × s in the approximate ratio of 5 : 20 : 30 : 10 : 15 : 20, NMe* and NMe),† separated as an oil and crystallised from light petroleum (b.p. 60—80 °C) to give a white solid. Concentration of the aqueous filtrates by evaporation of the water produced a white solid (3.7 g) which was shown by t.l.c. to be a mixture of methyl N-methyl-N-[2-(o-amino-N-methylbenzamido)benzoyl]-anthranilate (44) and N-[2-(o-amino-N-methylbenzamido)-benzoyl]-N-methylanthranilic acid (45). It was convenient to boil the filtrates for 1 h before acidification with glacial acetic acid to effect complete hydrolysis of the ester (44). In this manner, the only product which was isolated, after acidification and concentration by evaporation of the solvent, was N-[2-(o-*amino*-N-*methylbenzamido*)*benzoyl*]-N-*methyl*-*anthranilic acid* (45) (7.0 g, 78%), m.p. 203—206 °C [Found: *M* (mass spec.), 403.1510. C$_{23}$H$_{21}$N$_3$O$_4$ requires *M*, 403.1532], ν$_{max.}$ (Nujol) 3 500 (OH), 3 400 and 3 280 (NH$_2$), 1 710 (CO$_2$H), and 1 650 and 1 630 cm^{-1} (CO); τ [CDCl$_3$–(CD$_3$)$_2$CO] 1.90—3.50 (15 H, m, ArH, NH$_2$, and CO$_2$H) and 6.50—7.10 (6 H, 3 × s and bs, NMe* and NMe). Attempts to purify this acid (45) either by recrystallisation from ethyl acetate or by chromatography on silica gel led to polymeris-ation.

Methyl N-*Methyl*-N-[2-(o-*methylamino*-N-*methylbenz*-*amido*)*benzoyl*]*anthranilate* (46) *and Methyl* N-*Methyl*-N-[2-(o-*dimethylamino*-N-*methylbenzamido*)*benzoyl*]*anthranilate* (47).—(a) A mixture of the ester (44) and the acid (45) (2.8 g) was refluxed in ethyl methyl ketone (40 ml) with methyl iodide (5 ml) and potassium carbonate (1.0 g) for 20 min. Filtration to remove inorganic material and evaporation of the filtrate afforded an oil (2.1 g) which was fractionated by column chromatography on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) solvent mixture as eluant. The following fractions were characterised after recrystallisation from light petroleum (b.p. 60—80 °C). Fraction 1 was *methyl* N-*methyl*-N-[2-(o-*methylamino*-N-*methylbenzamido*)*benzoyl*]*anthranilate* (46) (19 mg), m.p. 67 °C [Found: *M* (mass spec.), 431.1821. C$_{25}$H$_{25}$N$_3$O$_4$ requires *M*, 431.1845], ν$_{max.}$ (Nujol) 3 380 (NH), 1 740 (CO$_2$Me), and 1 650 cm^{-1} (CO); τ (CDCl$_3$), 1.90—3.50 (m, 12 H, ArH), 6.04 and 6.12 (3 H, 2 × s in the approximate ratio of 35 : 65, CO$_2$Me), 6.61, 6.65, 6.73, and 6.85 (6 H, 3 × s and bs in the approximate ratio of 18 : 33 : 18 : 31, NMe*, NMe, and NHMe),† and 7.11 and 7.34 (3 H, 2 × s in the approximate ratio of 40 : 60, NH*Me*).† Fraction 2 was *methyl* N-*methyl*-N-[2-(o-*dimethylamino*-N-*methylbenz*-*amido*)*benzoyl*]*anthranilate* (47) (15 mg), m.p. 65 °C [Found: *M* (mass spec.), 445.1988. C$_{26}$H$_{27}$N$_3$O$_4$ requires *M*, 445.2001], ν$_{max.}$ (Nujol) 1 740 (CO$_2$Me) and 1 650 cm^{-1} (CO); τ (CDCl$_3$) 1.90—3.30 (m, 12 H, ArH), 6.01 and 6.09 (3 H, 2 × s in the approximate ratio of 32 : 68, CO$_2$Me), 6.62, 6.68, 6.70, and 6.80 (6 H, 4 × s in the approximate ratio of 30 : 20 : 20 : 30, NMe* and NMe),† and 7.08 and 7.10 (6 H, 2 × s in the approximate ratio of 45 : 55, NMe$_2$).† Fraction 3 was methyl N-methyl-N-[2-(o-amino-N-methylbenz-amido)benzoyl]anthranilate (44) (32 mg), m.p. 79—80 °C. Mixtures of fractions 1 and 2 containing compounds (46)

and (47) (590 mg) and mixtures of fractions 2 and 3 containing compounds (47) and (44) (430 mg) were also obtained. The proportion of the products formed during this methylation depends upon the reaction time. A reaction time of 2 h leads to the formation of increased amounts of compounds (46) and (47) and only traces of compound (44).

(b) The acid (45) (7 g) and potassium carbonate (2.3 g) were refluxed in ethyl methyl ketone (95 ml) for 15 min. Filtration to remove inorganic material and evaporation of the filtrate afforded an oil, which was extracted into chloroform. Examination of the chloroform solution by t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant showed the presence of three components corresponding to compounds (44), (46), and (47).

N-[2-(o-*Amino*-N-*methylbenzamido*)*benzoyl*]-N-*methyl-anthraniloyldicyclohexylurea* (48).—A solution of the amino-acid (45) (11.6 g) in dichloromethane (400 ml) was added dropwise with stirring at room temperature to a solution of N,N'-dicyclohexylcarbodi-imide (10.5 g) in dichloromethane (20 ml). The reaction mixture was stirred for 3 h at room temperature. The precipitated N,N'-dicyclohexylurea was collected and the solvent was evaporated to give a solid. Extraction of this solid with methanol yielded the N-*acylurea* derivative (48) (6.0 g, 38%), m.p. 182—184 °C [Found: C, 70.8; H, 6.8; N, 11.3%; M (mass spec.), 609. $C_{36}H_{43}N_5O_4$ requires C, 70.9; H, 7.1; N, 11.5%; M, 609], $\nu_{max.}$ (Nujol) 3 320 (NH) and 1 660 and 1 630 cm^{-1} (CO). An X-ray crystallographic examination (Figure 1) established [17] the constitution (48) of this compound.

5,11-*Dimethyltribenzo*[b,f,j][1,5,9]*triazacyclododecine*-6,12,18(5H,11H,17H)-*trione* (N,N'-*Dimethyltrianthranilide*) (5).—(a) The intermediate N-acylurea derivative (48) (300 mg) was heated under reflux in ethanol for 3 h. Evaporation of the solvent under reduced pressure afforded a solid which was purified by preparative t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (2 : 1) as eluant to give a crystalline product. Recrystallisation from either toluene or ethanol affords well formed crystals of N,N'-*dimethyltrianthranilide* (5) (166 mg, 89%), m.p. 251—254 °C, $[\alpha]_D$ +87° (c, 0.142 in CHCl$_3$) for a selected dextrorotatory crystal [Found: C, 71.9; H, 5.1; N, 10.8%; M (mass spec.), 385.1437. $C_{23}H_{19}N_3O_3$ requires C, 71.7; H, 5.0; N, 10.9%; M, 385.1426], $\nu_{max.}$ (CHCl$_3$) 3 290 (NH) and 1 675 and 1 655 cm^{-1} (CO); τ (CDCl$_3$) 1.31 (1 H, bs, NH), 1.86—2.80 (12 H, m, ArH), 6.73 (3 H, s, NMe), and 6.83 (3 H, s, NMe*). An X-ray crystallographic examination (see Results and Discussion section) confirmed the constitution of this compound and showed that it undergoes spontaneous resolution on crystallisation.[23]

(b) A solution of the amino-acid (45) (800 mg) and thionyl chloride (8 ml) in chloroform (15 ml) was refluxed for 3 h. Evaporation of the solvent and removal of excess of thionyl chloride afforded an oil. Examination of this oil by t.l.c. indicated the presence of a very small yield of N,N'-dimethyltrianthranilide (5).

N-[2-(o-*Nitrobenzamido*)*benzoyl*]-N-*methylanthranilic Acid* (49).—N-Methyl-N-(o-aminobenzoyl)anthranilic acid (37) (5 g) was suspended in a solution of lithium hydroxide (1.0 g) in water (50 ml). o-Nitrobenzoyl chloride solution (2 ml), diluted with benzene (49 ml), was added and the reaction mixture was stirred at room temperature for 1 h. The product which separated was collected, additional o-nitrobenzoyl chloride solution (2 ml) was added to the filtrate, and stirring was continued for a further 2 h. More product was obtained after filtration. Recrystallisation of

the combined crude products from ethanol yielded N-[2-(o-nitrobenzamido)benzoyl]-N-*methylanthranilic acid* (49) as a yellow solid (6.4 g, 82%), m.p. 224—226 °C (Found: C, 63.8; H, 4.6; N, 9.8%. $C_{22}H_{17}N_3O_6$ requires C, 63.0; H, 4.1; N, 10.0%), $\nu_{max.}$ (Nujol) 3 400 (NH$_2$), 3 200 (OH), 1 690 (CO$_2$H), 1 670 and 1 640 (CO), and 1 540 and 1 350 cm^{-1} (NO$_2$); τ (CF$_3$CO$_2$H) 1.30—2.74 (12 H, m, ArH), and 6.61 and 6.65 (3 H, 2 × s in the approximate ratio of 40 : 60, NMe*).†

Trideuteriomethyl-N-*methyl*-N-[2-(o-*nitro*-N-*trideuterio-methylbenzamido*)*benzoyl*]*anthranilate* (50).—Sodium hydride (300 mg) was added to a solution of N-[2-(o-nitrobenzamido)-benzoyl]-N-methylanthranilic acid (49) (1 g) and [$^2H_3$]-methyl iodide (1 ml) in dry dimethyl sulphoxide (20 ml). The reaction mixture was stirred at room temperature for 3 h. Addition of water was followed by extraction with chloroform. The organic layer was dried (MgSO$_4$) and the solvent was evaporated to produce, upon recrystallisation from ethanol, trideuteriomethyl N-*methyl*-N-[2-(o-*nitro*-N-trideuteriomethylbenzamido)benzoyl]anthranilate (50) (1 g, 91%), m.p. 204—205 °C [Found: M (mass spec.), 453.1825. $C_{24}H_{15}D_6N_3O_6$ requires M, 453.1807], $\nu_{max.}$ (Nujol) 1 720 (CO$_2$CD$_3$), 1 690 and 1 640 (CO), and 1 530 and 1 360 cm^{-1} (NO$_2$); τ (CDCl$_3$) 1.68—3.44 (12 H, m, ArH) and 6.44, 6.70, and 6.83 (3 H, 3 × s in the approximate ratio of 20 : 40 : 40, NMe*).†

N-[2-(o-*Amino*-N-*trideuteriomethylbenzamido*)*benzoyl*]-N-*methylanthranilic Acid* (51).—Titanium(III) chloride (12 ml; 12.5%) was added dropwise to a refluxing solution of trideuteriomethyl N-methyl-N-[2-(o-nitro-N-trideuterio-methylbenzamido)benzoyl]anthranilate (50) (900 mg) in ethanol (45 ml). The mixture was heated for 10 min and then poured into boiling water (100 ml) and heated for a further 30 min. The solution was cooled, made alkaline by addition of aqueous lithium hydroxide, and allowed to stand at 40 °C. The precipitate was filtered off, heated again with water, and refiltered. The combined filtrates were refluxed for 1 h before being acidified with glacial acetic acid and concentrated by evaporation of the solvent. During evaporation of the solvent N-[2-(o-amino-N-trideuterio-methylbenzamido)benzoyl]-N-*methylanthranilic acid* (51) separated from the solution as an oil (800 mg, 98%) [Found: M (mass spec.), 406. $C_{23}H_{18}D_3N_3O_4$ requires M, 406]. Although examination of this product by t.l.c. showed that it contained several impurities, it was used without further purification because of its tendency to polymerise during attempted crystallisation.

5-*Methyl*-11-*trideuteriomethyltribenzo*[b,f,j][1,5,9]*triaza-cyclodecine*-6,12,18(5H,11H,17H)-*trione* (N-*Methyl*-N'-*tri-deuteriomethyltrianthranilide*) (6).—A solution of N,N'-dicyclohexylcarbodi-imide (500 mg) in dichloromethane (5 ml) was added dropwise with stirring to a solution of N-[2-(o-amino-N-trideuteriomethylbenzamido)benzoyl]-N-methylanthranilic acid (51) (700 mg) in dichloromethane (25 ml). The stirring was continued for 2 h at room temperature after the addition of N,N'-dicyclohexylcarbodi-imide solution. The precipitated N,N'-dicyclohexylurea was collected and the solvent was evaporated to give an oil. Addition of a small amount of methanol gave crystals of the N-acylurea derivative (52) (272 mg, 57%), m.p. 180—183 °C. When this derivative (52) (150 mg) was refluxed in ethanol (30 ml) for 3 h, and the volume of the solvent was reduced by evaporation, N-*methyl*-N'-*trideuteriomethyl-trianthranilide* (6) crystallised (70 mg, 72%), m.p. 251—254

† See footnote at the bottom of p. 1659.

°C [Found: M (mass spec.), 388.1598. $C_{23}H_{16}D_3N_3O_3$ requires 388.1615], τ (CDCl$_3$) 1.31 (1 H, bs, NH), 1.86—2.80 (12 H, m, ArH), and 6.83 (3 H, s, NMe*) as a white solid.

5,11,17-*Trimethyltribenzo*[b,f,j][1,5,9]*triazacyclododecine*-6,12,18(5H,11H,17H)-*trione* (N,N',N''-*Trimethyltrian-thranilide*) (7).—(a) N,N'-Dimethyltrianthranilide (5) (300 mg), methyl iodide (1 ml), and an excess of sodium hydride (200 mg) were stirred in dry dimethyl sulphoxide (30 ml) at room temperature for 4 h. The excess of sodium hydride was destroyed by careful addition of a few drops of water followed by the reaction mixture being poured into water. A product separated from the reaction mixture as a white solid. This product could be recrystallised from (i) benzene, (ii) toluene, (ii) methanol, and (iv) chloroform–ether–light petroleum (b.p. 60—80 °C) to afford N,N',N''-*trimethyltrianthranilide* (7) (236 mg, 76%), m.p. >320 °C [Found: C, 72.1; H, 5.5; N, 10.2%; M (mass spec.), 399.1587. $C_{24}H_{21}N_3O_3$ requires C, 72.2; H, 5.3; N, 10.5%; M 399.1583], $\nu_{max.}$ (Nujol) 1 670 and 1 640 cm^{-1} (CO); τ (CDCl$_3$) 2.35—2.70 (12 H, m, ArH) and 6.51, 6.67, 6.79, and 6.87 (9 H, 4 × s with relative intensities of 0.055 : 0.315 : 0.315 : 0.315, 3 × NMe), δ (CDCl$_3$; SiMe$_4$ as standard) 172.3, 171.2, and 170.5 (carbonyl carbons), 139.8, 139.6, 139.1, 137.0, 136.8, 135.6, 130.6, 130.4, 130.3, 129.0, 128.8, 128.4, 128.1, 128.0, 127.9, 126.8, 126.6, and 126.3 (aromatic carbons), and 41.3, 40.8, and 40.4 (N-methyl carbons). Methylation was also achieved by using dry tetrahydrofuran as solvent (73%).

Slow crystallisation from (i) benzene or (ii) chloroform–ether–light petroleum provided crystals, which on dissolution in [^{2}H]chloroform at room temperature and recording of the ^{1}H n.m.r. spectrum immediately showed three singlets of equal intensity at τ 6.67, 6.79, and 6.87 for the N-methyl groups. After 4 min a fourth signal at τ 6.51 began to appear and attained a maximum relative intensity after *ca.* 15 min. When this experiment was repeated at −30 °C only the three signals of equal intensity at τ 6.67, 6.79, and 6.87 were observed. The relatively low intensity low-field singlet arises from a propeller conformation and the three equal-intensity singlets arise from a helical conformation of N,N',N''-trimethyltrianthranilide (7) (see Results and Discussion section). The rate of interconversion of the propeller and helical conformations was measured by monitoring the relative intensities of the N-methyl signals at +10 °C as a function of time. The results are discussed in detail later on in the Results and Discussion section.

N,N',N''-Trimethyltrianthranilide (7) can also be purified by vacuum sublimation at 250 °C (3 mmHg).

(b) Methyl N-methyl-N-[2-(o-amino-N-methylbenz-amido)benzoyl]anthranilate (44) (300 mg) was stirred with sodium hydride (36 mg) in dry tetrahydrofuran (20 ml) at room temperature for 24 h. Methyl iodide (1 ml) was then added and the stirring was continued for 48 h. The excess of sodium hydride was destroyed by careful addition of water and the reaction mixture was extracted with chloroform. Examination of the chloroform extract by t.l.c. indicated the presence of a small amount (20 mg, 7%) of N,N',N''-trimethyltrianthranilide (7) which was purified by prepara-tive t.l.c. on silica gel using chloroform–methanol (4 : 1) as eluant.

(c) Methyl-N-methyl-N-[2-(o-methylamino-N-methyl-benzamido)benzoyl]anthranilate (46) (30 mg) was stirred with sodium hydride (20 mg) in dry tetrahydrofuran (10 ml) at room temperature for 24 h. Careful addition of water was followed by extraction with chloroform. Examination

of the chloroform extract by t.l.c. indicated the presence of a small amount of N,N',N''-trimethyltrianthranilide (7).

(d) To a solution of a mixture of methyl N-methyl-N-[2-(o-amino-N-methylbenzamido)benzoyl]anthranilate (44), methyl N-methyl-N-[2-(o-methylamino-N-methylbenz-amido)benzoyl]anthranilate (46), and methyl N-methyl-N-[2-(o-dimethylamino-N-methylbenzamido)benzoyl]-anthranilate (47) (460 mg) in dry tetrahydrofuran (50 ml) sodium hydride (60 mg) was added and the reaction mixture was stirred at room temperature for 24 h. Methyl iodide (2 ml) was then added and the stirring was continued for 24 h. Addition of water was followed by extraction with chloro-form. Preparative t.l.c. on the chloroform extract using chloroform–methanol (4 : 1) as eluant afforded N,N',N''-trimethyltrianthranilide (7) in low yield (25 mg).

(e) A solution of anthranilic acid (0.5 g) and N,N'-dicyclohexylcarbodi-imide (1 g) in dichloromethane (50 ml) was stirred at room temperature for 16 h. After filtration to remove N,N'-dicyclohexylurea and evaporation of the filtrate, a residue was obtained. This residue was stirred in dry dimethyl sulphoxide (50 ml) with methyl iodide (5 ml) and sodium hydride (300 mg) for 4 h. Addition of water was followed by extraction with chloroform. Examination of the chloroform extract by t.l.c. revealed the presence of several compounds but no N,N',N''-trimethyltrianthranilide (7) was identified.

(f) A solution of N-methylanthranilic acid (35) (0.1 g) and N,N'-dicyclohexylcarbodi-imide (0.2 g) in dichloromethane (50 ml) was stirred at room temperature for 24 h. After filtration to remove N,N'-dicyclohexylurea the filtrate was examined by t.l.c. The reaction mixture contained only polymeric material and no N,N',N''-trimethyltrianthranilide (7) was identified.

5,11-*Dimethyl*-17-*trideuteriomethyltribenzo*[b,f,j][1,5,9]-*triazacyclododecine*-6,12,18(5H,11H,17H)-*trione* (N,N'-*Dimethyl*-N''-*trideuteriomethyltrianthranilide*) (8).—A solu-tion of N,N'-dimethyltrianthranilide (5) (50 mg) in dry dimethyl sulphoxide (10 ml) was stirred with [^{2}H$_3$]methyl iodide (1 ml) and sodium hydride (50 mg) at room temper-ature for 1 h. Addition of water was followed by extraction with chloroform. The organic layer was dried (MgSO$_4$) and the solvent was evaporated to afford N,N'-*dimethyl*-N''-*trideuteriomethyltrianthranilide* (8), which was recrystallised from chloroform and ether (37 mg, 73%), m.p. >320 °C [Found: M (mass spec.), 402.1783. $C_{24}H_{18}D_3N_3O_3$ requires M, 402.1771], $\nu_{max.}$ (Nujol) 1 650 and 1 620 cm^{-1} (CO); τ (CDCl$_3$) 2.35—2.70 (m, 12 H, ArH), 6.51, 6.67, 6.79, and 6.87 (6 H, 4 × s, with relative intensities 0.041 : 0.295 : 0.379 : 0.285, 2 × NMe). An ^{1}H n.m.r. spectrum recorded im-mediately after dissolving the trideuteriomethyl derivative (49) in [^{2}H]chloroform showed the presence of four signals at τ 6.51, 6.67, 6.79, and 6.87 for the N-methyl protons. However, the three high-field signals were not of equal intensity but had relative intensities of 61 : 78 : 59. For this reason the reaction was repeated with a shorter reaction time (15 min) in order to minimise the extent of scrambling of the labelled N-methyl group during the reaction. Alas, the relative intensities of the three high-field signals was 58 : 81 : 58 in this case. The rate of scrambling of the labelled N-methyl group was followed directly by measuring the relative intensities of these three signals at +30 °C as a function of time. The results are discussed in detail later on in the Results and Discussion section.

5-*Methyl*-11,17-*di*(*trideuteriomethyl*)*tribenzo*[b,f,j][1,5,9]-*triazacyclododecine*-6,12,18(5H,11H,17H)-*trione* [N-*Methyl*-

N',N''-di(trideuteriomethyl)trianthranilide] (9).—A solution of N-methyl-N'-trideuteriomethyltrianthranilide (6) (40 mg) in dry dimethyl sulphoxide (10 ml) was stirred with sodium hydride (40 mg) and [$^2H_3$]methyl iodide (0.5 ml) at room temperature for 15 min. Addition of water was followed by extraction with chloroform. The organic layer was dried (MgSO$_4$) and the solvent was evaporated to afford N-methyl-N',N''-di(trideuteriomethyl)trianthranilide (9) (27 mg, 68%), m.p. >320 °C [Found: M (mass spec.), 405.1960. C$_{24}$H$_{15}$D$_6$N$_3$O$_3$ requires M, 405.1959], τ (CDCl$_3$) 2.35—2.70 (m, 12 H, ArH), 6.51, 6.67, 6.79, and 6.87 (6 H, 4 × s, with relative intensities 25 : 117 : 204 : 204, NMe). The rate of scrambling of the labelled N-methyl groups was followed directly by measuring the relative intensities of the three high-field signals at +30 °C as a function of time. The results are discussed in detail later on in the Results and Discussion section.

5,6,11,12,17,18-Hexahydro-5,11,17-trimethyltribenzo-[b,f,j][1,5,9]triazacyclododecine (21).—N,N',N''-Trimethyl-trianthranilide (7) (250 mg) was added portionwise to a suspension of lithium aluminium hydride (310 mg) in anhydrous tetrahydrofuran (26 ml) during 20 min. The mixture was stirred and heated under reflux for 4 h. Water (0.1 ml) and aqueous sodium hydroxide (20%, 0.2 ml) were added. After filtration the organic layer was concentrated, the residue was extracted with chloroform, and the chloroform extract was dried (MgSO$_4$). Preparative t.l.c. using light petroleum (b.p. 60—80 °C)–ethyl acetate (3 : 1) as eluant gave 5,6,11,12,17,18-hexahydro-5,11,17-trimethyltribenzo-[b,f,j][1,5,9]triazacyclododecine (21) (85 mg, 38%) as an oil [Found: M (mass spec.), 357. C$_{24}$H$_{27}$N$_3$ requires M, 357], τ (CDCl$_3$) ,2.71—3.50 (12 H, m, ArH), 5.47 (6 H, s, 3 × CH$_2$), and 7.20 (9 H, s, 3 × NMe). This compound is unstable.

5-Acetyl-11,17-dimethyltribenzo[b,j,f][1,5,9]triazacyclo-dodecine-6,12,18(5H,11H,17H)-trione (N,N'-Dimethyl-N''-acetyltrianthranilide) (10).—N,N'-Dimethyltrianthranilide (5) (130 mg) was added to a suspension of sodium hydride (200 mg) in dry toluene (16 ml) at room temperature. The mixture was stirred for 3 h and then acetyl chloride (1 ml) dissolved in dry toluene (2 ml) was added during 0.5 h. Stirring was continued for 78 h. Further amounts of acetyl chloride (1 ml) and sodium hydride (200 mg) were added and the reaction mixture was heated at 80 °C overnight. Filtration and evaporation of the solvent afforded an oil which was purified by preparative t.l.c. on silica gel using ethyl acetate as solvent to give N,N'-dimethyl-N''-acetyl-trianthranilide (10) (70 mg, 49%), m.p. 262—264 °C (decomp.) [Found: C, 70.2; H, 5.2; N, 9.6%; M (mass spec.), 427.1545. C$_{25}$H$_{21}$N$_3$O$_4$ requires C, 70.2; H, 5.0; N, 9.8%; M, 427.1532], ν$_{max.}$ (Nujol) 1 730 (CH$_3$CO), and 1 690, 1 670, and 1 640 cm^{-1} (CO); τ (CDCl$_3$–CS$_2$; 1 : 1) 2.36—2.80 (12 H, m, ArH), 6.85 and 6.90 (6 H, 2 × s, 2 × NMe), and 8.04 (3 H, s, NAc).

5-Benzoyl-11,17-dimethyltribenzo[b,f,j][1,5,9]triazacyclo-dodecine-6,12,18(5H,11H,17H)-trione (N,N'-Dimethyl-N''-benzoyltrianthranilide) (11).—Benzoyl chloride (0.5 ml) was added to a mixture of sodium hydride (200 mg) and N,N'-dimethyltrianthranilide (5) (90 mg) in dry tetrahydrofuran (10 ml) and the reaction mixture was stirred at room temperature for 48 h. Further amounts of benzoyl chloride (0.5 ml) and sodium hydride (200 mg) were added and the reaction mixture was heated at 50 °C overnight. Excess of sodium hydride was destroyed by careful addition of water to the cooled reaction mixture, which was then extracted

with chloroform (3 × 50 ml). The combined chloroform extracts were washed with water, dried (MgSO$_4$), filtered, and evaporated 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$_F$, 0.25) and a product with an R$_F$ of 0.55. This product was purified by preparative t.l.c. on silica gel using the above mentioned solvent system. Crystallisation from toluene gave colourless crystals of N,N'-dimethyl-N''-benzoyltrian-thranilide (11) (47 mg, 38%), m.p. 259—261 °C [Found: C, 72.9; H, 4.5; N, 8.2%; M (mass spec.), 489.1653. C$_{30}$H$_{23}$N$_3$O$_4$ requires C, 73.6; H, 4.7; N, 8.6%; M, 489.1689], ν$_{max.}$ (Nujol) 1 695 and 1 645 cm^{-1} (CO); τ (CDCl$_3$) 2.10—3.08 (17 H, m, ArH) and 6.71 and 6.76 (6 H, 2 × s, 2 × NMe).

5-Benzyl-11,17-dimethyltribenzo[b,f,j][1,5,9]triazacyclo-dodecine-6,12,18(5H,11H,17H)-trione (N,N'-Dimethyl-N''-benzyltrianthranilide) (12).—N,N'-Dimethyltrian-thranilide (5) (400 mg) was dissolved in dry tetra-hydrofuran (50 ml) and an excess of sodium hydride (200 mg) was added followed by benzyl bromide (0.4 ml). The reaction mixture was stirred at room temperature for 24 h. The excess of sodium hydride was destroyed by careful addition of water and the reaction mixture was extracted with chloroform. The chloroform layer was dried (MgSO$_4$) and after evaporation of the solvent an oil remained. This oil solidified on addition of a small amount of light petroleum (b.p. 60—80 °C) and was recrystallised from chloroform–ether–light petroleum (b.p. 60—80 °C) to afford crystals of N,N'-dimethyl-N''-benzyltrianthranilide (12) containing approximately one-third of a mole of ethanol. [Ethanol (2%) is present in chloroform as stabiliser.] The ethanol could be removed under vacuum (3 mmHg) at +80 °C to give N,N'-dimethyl-N''-benzyltrianthranilide (12) (390 mg, 81%) [Found: C, 75.3; H, 5.4; N, 8.9%; M (mass spec.), 475.1896. C$_{30}$H$_{25}$N$_3$O$_3$ requires C, 75.8; H, 5.3; N, 8.8%; M, 475.1886]. ^{1}H N.m.r. spectroscopy revealed that this compound exists as an equilibrium mixture of four con-formational diastereoisomers in CDCl$_3$ solution. See Table 8 in the Results and Discussion section for the ^{1}H n.m.r. data.

T.l.c. on silica gel using ethyl acetate as eluant showed the presence of two components with approximately the same R$_F$ value. These two components, separated by preparative t.l.c. on silica gel at +5 °C and by high pressure liquid chromatography using ethyl acetate as eluant, were shown to be conformational diastereoisomers. The minor and faster-moving component corresponds to a helical con-formation which is defined as Helix 3 (68) in the Results and Discussion section. The major and slower-moving com-ponent corresponds to a second helical conformation which is defined as Helix 1 (66) in the Results and Discussion section. Helix 3 (68) (99 mg, 21%) has m.p. 152—154 °C (>98% diastereoisomeric purity as estimated by ^{1}H n.m.r. spectro-scopy), ν$_{max.}$ (Nujol) 1 660 and 1 630 cm^{-1} (CO); τ (CDCl$_3$) 2.29—3.14 (17 H, m, ArH), 5.02 and 5.33 (2 H, AB system, J$_{AB}$ 15.6 Hz, benzylic CH$_2$), 6.68 (3 H, s, NMe*), and 6.86 (3 H, s, NMe). Helix 1 (66) (159 mg, 32%) has m.p. 153—154 °C (>98% diastereoisomeric purity as estimated by ^{1}H n.m.r. spectroscopy), ν$_{max.}$ (Nujol) 1 660 and 1 630 cm^{-1} (CO); τ (CDCl$_3$) 2.19—3.44 (17 H, m, ArH), 5.26 and 5.42 (2 H, AB system, J$_{AB}$ 14.7 Hz, benzylic CH$_2$), 6.58 (3 H, s, NMe), and 6.82 (3 H, s, NMe*). The other two isomers were not present in sufficient quantities at equilibrium to permit their isolation.

5-Benzyl-11-methyl-17-trideuteriomethyltribenzo[b,f,j]-[1,5,9]triazacyclododecine-6,12,18(5H,11H,17H)-trione

(N-*Methyl*-N'-*trideuteriomethyl*-N''-*benzyltrianthranilide*) (13).—An excess of sodium hydride (50 mg) and benzyl bromide (0.3 ml) were added to a solution of N-methyl-N'-trideuteriomethyltrianthranilide (6) (50 mg) in dry tetrahydrofuran (20 ml). The reaction mixture was stirred overnight at room temperature. Excess of sodium hydride was destroyed by careful addition of water and the reaction mixture was extracted with chloroform. The chloroform residue was dried (MgSO₄) and the solvent evaporated to afford an oily residue. Crystallisation from chloroform–light petroleum (b.p. 60—80 °C) gave N-*methyl*-N'-*trideuteriomethyl*-N''-*benzyltrianthranilide* (13) (47 mg, 76%) [Found: M (mass spec.), 478.2066. $C_{30}H_{22}D_3N_3O_3$ requires M, 478.2085], [1]H n.m.r. data: see Table 8 in the Results and Discussion section.

N-[2-(o-*Nitro*-N-*benzylbenzamido*)*benzoyl*]-N-*benzylanthranilic Acid* (53) *and Benzyl* N-*Benzyl*-N-[2-(o-*nitro*-N-*benzylbenzamido*)*benzoyl*]*anthranilate* (54).—A solution of N-[2-(o-nitrobenzamido)benzoyl]anthranilic acid (26) (15 g) in dry tetrahydrofuran (200 ml) was stirred overnight at room temperature with benzyl bromide (18 ml) and sodium hydride (4.2 g). Excess of sodium hydride was destroyed by careful addition of water followed by extraction of the reaction mixture with chloroform. The chloroform extract was dried (MgSO₄) and the solvent was evaporated to afford an oil, which crystallised on addition of light petroleum (b.p. 60—80 °C) to give a mixture (24 g) of N-[2-(o-*nitro*-N-*benzylbenzamido*)*benzoyl*]-N-*benzylanthranilic acid* (53) and *benzyl* N-*benzyl*-N-[2-(o-*nitro*-N-*benzylbenzamido*)*benzoyl*]-*anthranilate* (54). This mixture was used without further purification in the next step of the reaction sequence.

N-[2-(o-*Amino*-N-*benzylbenzamido*)*benzoyl*]-N-*benzylanthranilic Acid* (55).—A titanium(III) chloride solution (203 ml; 12.5%) was added dropwise to a solution of N-[2-(o-nitro-N-benzylbenzamido)benzoyl]-N-benzylanthranilic acid (53) and benzyl N-benzyl-N-[2-(o-nitro-N-benzylbenzamido)benzoyl]anthranilate (54) (23 g) refluxing in ethanol (750 ml). The solution was heated for 10 min, poured into boiling water (1 l), and heated for a further 30 min. After cooling, the solution was made alkaline by addition of aqueous lithium hydroxide and allowed to stand at 40 °C. The precipitate formed was filtered off, heated again with water, and refiltered. The combined alkaline filtrates were refluxed for 2.5 h and then acidified with glacial acetic acid. Evaporation of the solvent afforded a crystalline product corresponding to N-[2-(o-*amino*-N-*benzylbenzamido*)*benzoyl*]-N-*benzylanthranilic acid* (55) (14 g), m.p. 128—131 °C [Found: M (mass spec.), 555. $C_{35}H_{29}N_3O_4$ requires M, 555], $v_{max.}$ (Nujol) 3 450 (NH₂), 3 350 (OH), 1 720 (CO₂H), and 1 640 cm⁻¹ (CO).

5,11-*Dibenzyltribenzo*[b,f,j][1,5,9]*triazacyclododecine*-6,12,18(5H,11H,17H)-*trione* (N,N'-*Dibenzyltrianthranilide*) (14).—(a) A solution of N,N'-dicyclohexylcarbodi-imide (14 g) in dichloromethane (50 ml) was added to a solution of N-[2-(o-amino-N-benzylbenzamido)benzoyl]-N-benzylanthranilic acid (55) (14 g) in dichloromethane (200 ml) and the reaction mixture was stirred at room temperature overnight. The precipitated N,N'-dicyclohexylurea was filtered off and the solvent was evaporated from the filtrate to yield an oil. This oil was extracted first of all with light petroleum (b.p. 60—80 °C) to remove excess of N,N'-dicyclohexyl-carbodi-imide, then repeatedly with ether, and finally was refluxed with ether for 6 h. The product which remained was characterised as N,N'-*dibenzyltrianthranilide* (14) (6.8 g, 50%), m.p. 177—179 °C [Found: C, 78.5; H, 5.2; N,

7.7%; M (mass spec.), 537. $C_{35}H_{27}N_3O_3$ requires C, 78.2; H, 5.1; N, 7.8%; M, 537], $v_{max.}$ (Nujol) 3 330 (NH) and 1 660 and 1 640 cm⁻¹ (CO); τ (CDCl₃) 1.18 (1 H, bs, NH), 1.84—3.16 (22 H, m, ArH), 5.00 and 5.54 (2 H, AB system, J_{AB} 14.7 Hz, benzylic CH₂), and 5.17 and 5.33 (2 H, AB system, J_{AB} 14.8 Hz, benzylic CH₂). More product was crystallised from the combined ether extracts. N,N'-Dibenzyltrianthranilide (14) can be recrystallised from either ethanol or toluene. An X-ray crystallographic examination (see Results and Discussion section) of the crystals obtained from toluene confirmed the constitution of this compound and showed that it forms an inclusion complex with toluene.[23] Also, this derivative, in contrast with N,N'-dimethyltrianthranilide (5), crystallises as a racemate.

(b) A solution of N-[2-(o-amino-N-benzylbenzamido)-benzoyl]-N-benzylanthranilic acid (55) (100 mg) in chloroform (5 ml) and thionyl chloride (0.5 ml) was refluxed for 24 h. Evaporation of the solvent and an excess of thionyl chloride yielded an oil. Examination of this oil by t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) as eluant indicated the presence of small amounts of N,N'-*dibenzyltrianthranilide* (14).

5,11,17-*Tribenzyltribenzo*[b,f,j][1,5,9]*triazacyclododecine*-6,12,18(5H,11H,17H)-*trione* (N,N',N''-*Tribenzyltrianthranilide*) (15).—Benzylation of N,N'-dibenzyltrianthranilide (14) (240 mg) was carried out in dry tetrahydrofuran (15 ml) with sodium hydride (200 mg) and benzyl bromide (1 ml) by stirring at room temperature for 6 h. The reaction was followed by t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant. During the first 30 min two products were formed, a minor component moving faster than the starting material and a major component moving slower than the starting material, N,N'-dibenzyltrianthranilide (14). After 90 min all the starting material had reacted and the relative proportion of the two components was qualitatively unchanged. However, during the following 3.5 h equilibration occurred until a situation was reached where the proportion of the faster-moving component exceeded that of the slower-moving component. Excess of sodium hydride was destroyed by addition of water and the reaction mixture was extracted with chloroform. The chloroform layer was dried (MgSO₄) and the solvent was evaporated to yield an oil, which crystallised on addition of light petroleum (b.p. 60—80 °C). The two components were separated at +5 °C by preparative t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant. The reaction was repeated at 0 °C and gave the same result. Complete equilibration of both components could be achieved by refluxing the pure component in chloroform for 30 min. The faster-moving component could be obtained from the crude reaction mixture as a pure crystalline compound by slow crystallisation from light petroleum (b.p. 60—80 °C). The slower-moving component contained a molar proportion of ethanol, which was present as a stabiliser (2%) in the chloroform used to extract the compound from the silica gel. The faster-moving component was assigned to the propeller conformation (75) and the slower-moving component to the helical conformation (76) of N,N,N''-*tribenzyltrianthranilide* (15). The diastereoisomer with the propeller conformation (75) (164 mg, 59%) has m.p. 260—263 °C (>98% diastereoisomeric purity as estimated by [1]H n.m.r. spectroscopy) [Found: M (mass spec.), 627.2510. $C_{42}H_{33}N_3O_3$ requires M, 627.2522], τ (CDCl₃) 2.54—3.44 (27 H, m, ArH) and 3.96 and 5.32 (6 H, AB system, J_{AB} 14.4 Hz, 3 × benzylic CH₂).

The diastereoisomer with the helical conformation (76) (54 mg, 19%) has m.p. 134—144 °C followed by resolidification and a final m.p. 260—263 °C (93% diastereoisomeric purity as estimated by ^{1}H n.m.r. spectroscopy) [Found: M (mass spec.), 627. $C_{42}H_{33}N_3O_3$ requires M, 627], τ (CDCl$_3$) 2.12—3.46 (27 H, m, ArH), 4.67 and 5.50 (2 H, AB system, J_{AB} 16.4 Hz, benzylic CH$_2$), 4.93 and 5.34 (2 H, AB system, J_{AB} 13.8 Hz, benzylic CH$_2$), and 5.04 and 5.39 (2 H, AB system, J_{AB} 15.8 Hz, benzylic CH$_2$). The technique of spin tickling was used in order to assign the three AB systems arising from the benzylic methylene protons of the helical conformation (76). The ^{1}H decoupled ^{13}C n.m.r. spectrum of an equilibrated sample of N,N',N''-tribenzyltrianthranilide (15) was also examined (see Results and Discussion section).

5,11,17-*Tribenzyl*-6,6,12,12,18,18-*hexadeuterio*-5,6,11,12,-17,18-*hexahydrotribenzo*[b,f,j][1,5,9]*triazacyclododecine* (22). —N,N',N''-Tribenzyltrianthranilide (15) (200 mg) was added portionwise to a suspension of lithium aluminium deuteride (200 mg) in anydrous tetrahydrofuran (20 ml) during 20 min. The mixture was stirred and heated under reflux for 4 h. Water (0.1 ml) and aqueous sodium hydroxide (20%, 0.2 ml) were added. After filtration, the organic layer was concentrated, the residue was extracted with chloroform, and the chloroform extract was dried (MgSO$_4$). Preparative t.l.c. on silica gel using light petroleum (b.p. 60—80 °C)–ethyl acetate (9 : 1) as eluant afforded 5,11,17-*tribenzyl*-6,6,12,12,18,18-*hexadeuterio*-5,6,11,12,17,18-*hexahydrotribenzo*[b,f,j][1,5,9]*triazacyclododecine* (22) (200 mg, 94%), m.p. 165—166 °C [Found: M (mass spec.), 591. $C_{42}H_{33}N_3D_6$ requires M, 591], τ (CS$_2$) 2.74—3.27 (27 H, m, ArH) and 5.99 (6 H, s, 3 × benzylic CH$_2$).

5,11-*Dibenzyl*-17-*methyltribenzo*[b,f,j][1,5,9]*triazacyclo-decine*-6,12,18(5H,11H,17H)-*trione* (N,N'-*Dibenzyl*-N''-*methyltrianthranilide*) (16).—Methylation of N,N'-dibenzyltrianthranilide (14) (400 mg) was carried out in dimethyl sulphoxide (50 ml) with sodium hydride (400 mg) and methyl iodide (2 ml) by stirring at room temperature for 2 h. The reaction was followed by t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant. After 5 min all the starting material had reacted to give mainly one component which migrated slower on t.l.c. than the starting material, N,N'-dibenzyltrianthranilide (14). A small amount of a second faster-moving component was also formed. During the following 2 h the amount of the faster-moving component increased until it attained equilibrium with the slower-moving component which showed a corresponding decrease in its relative intensity. Excess of sodium hydride was destroyed by addition of water and the reaction mixture was extracted with chloroform. The two components were separated at +5 °C by preparative t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant. The faster-moving component was shown to correspond to the propeller conformation (77), whilst the slower-moving component could be assigned to the helical conformation defined (see Results and Discussion section) as Helix 2 (79) of N,N'-*dibenzyl*-N''-*methyltrianthranilide* (16). Helix 2 (79) contained traces of the other two helical conformation diastereoisomers, Helix 1 (78) and Helix 3 (80). The diastereoisomer with the propeller conformation (77) (53 mg, 13%) has m.p. 120—128 °C (65% diastereoisomeric purity as established by ^{1}H n.m.r. spectroscopy) [Found: M (mass spec.), 551.2206. $C_{36}H_{29}N_3O_3$ requires M, 551.2209], τ (CDCl$_3$), 2.20—3.46 (22 H, m, ArH), 4.01 and 5.36 (2 H, AB system, J_{AB} 14.6

Hz, benzylic CH$_2$), 4.01 and 5.39 (2 H, AB system, J_{AB} 14.0 Hz, benzylic CH$_2$), and 6.40 (3 H, s, NMe). Helix 2 (79) (290 mg, 71%) has m.p. 125—140 °C (82% diastereoisomeric purity as estimated by ^{1}H n.m.r. spectroscopy) [Found: M (mass spec.), 551. $C_{36}H_{29}N_3O_3$ requires M, 551], τ (CDCl$_3$), 2.14—3.47 (22 H, m, ArH), 5.09 and 5.30 (2 H, AB system, J_{AB} 15.9 Hz, benzylic CH$_2$), 5.22 and 5.43 (2 H, AB system, J_{AB} 14.0 Hz, benzylic CH$_2$), and 6.59 (3 H, s, NMe).

^{1}H N.m.r. spectroscopic data for Helix 1 (78) and Helix 3 (80) are given in Table 6 and in the Results and Discussion section.

Methyl N-*Methyl*-N-[2-(o-*nitro*-N-*benzylbenzamido*)-*benzoyl*]*anthranilate* (56).—Benzyl bromide (1 ml) was added to a mixture of sodium hydride (210 mg) and methyl N-methyl-N-[2-(o-nitrobenzamido)benzoyl]anthranilate (42) (800 mg) in dry dimethyl sulphoxide (30 ml) and the reaction mixture was stirred at room temperature for 6 h. Excess of sodium hydride was destroyed by careful addition of water to the cooled reaction mixture which was then extracted with chloroform (3 × 50 ml). The combined chloroform extracts were washed with water, dried (MgSO$_4$), filtered, and concentrated under reduced pressure to yield an oil. Preparative t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant followed by crystallisation from ether–light petroleum (b.p. 60—80 °C) gave *methyl* N-*methyl*-N-[2-o-*nitro*-N-(*benzylbenzamido*)-*benzoyl*]*anthranilate* (56) (680 mg, 70%), as colourless crystals, m.p. 65—67 °C [Found: C, 68.8; H, 5.0; N, 7.5%, M (mass spec.), 523. $C_{30}H_{25}N_3O_6$ requires C, 68.8; H, 4.8; N, 8.0%; M 523], $\nu_{max.}$ (Nujol) 1 725 (CO$_2$Me), 1 655 and 1 600 (CO), and 1 530 and 1 380 cm^{-1} (NO$_2$); τ (CDCl$_3$) 1.70—3.20 (17 H, m, ArH), 4.20—5.86 (2 H, AB system at τ_A 4.34 and τ_B 5.76, J_{AB} 14.8 Hz, and a singlet centred on τ 4.97 in the approximate ratio of 82 : 18, benzylic CH$_2$),† 6.00 and 6.18 (3 H, 2 × s in the approximate ratio of 82 : 18, CO$_2$Me),† and 6.72 and 6.80 (3 H, 2 × s in the approximate ratio of 18 : 82, NMe).†

Methyl N-*Methyl*-N-[2-(o-*amino*-N-*benzylamido*)benzoyl]-*anthranilate* (57) *and* N-[2-(o-*Amino*-N-*methylbenzamido*)-*benzoyl*]-N-*benzylanthranilic Acid* (58).—A titanium(III) chloride solution (10 ml; 12.5%) was added dropwise to a solution of methyl N-methyl-N-[2-(o-nitro-N-benzylbenzamido)benzoyl]anthraniliate (56) (650 mg) in boiling ethanol (26 ml). The reaction mixture was heated for an additional 10 min, poured into boiling water (165 ml), heated for a further 30 min, and then allowed to cool. The solution was made alkaline by addition of aqueous lithium hydroxide and maintained at 40 °C. The precipitate which formed was filtered off, heated again with water, and re-filtered. The combined filtrates were boiled for 3 h in an attempt to effect hydrolysis of the methyl ester (57). After acidification and concentration of the solution to a smaller volume by evaporation of the solvents under reduced pressure, the solid (520 mg) which separated was isolated. Mass spectrometry and t.l.c. on silica gel indicated the presence of a mixture of *methyl* N-*methyl*-N-[2-(o-amino-N-*benzylamido*)benzoyl]anthranilate (57) and N-[2-(o-amino-N-*methylbenzamido*)benzoyl]-N-*benzylanthranilic acid* (58). All attempts to fractionate this mixture by chromatography on silica gel led to polymerisation. Accordingly, this mixture was used without further purification in the next step of the reaction squence.

5-*Methyl*-11-*benzyltribenzo*[b,f,j][1,5,9]*triazacyclododecine*-

† See footnote at the bottom of p. 1659.

6,12,18(5H,11H,17H)-*trione*   (N-*Methyl*-N'-*benzyltrian-thranilide*) (17).—A solution of N-[2-(o-amino-N-methyl-benzamido)benzoyl]-N-benzylanthranilic acid (58) containing some of its methyl ester (57) (500 mg) in dichloromethane (7.5 ml) was added with stirring to a solution of N,N'-dicyclohexylcarbodi-imide (480 mg) in dichloromethane (2 ml) at room temperature. The reaction mixture was stirred overnight at room temperature and the N,N'-dicyclohexyl-urea which formed as a precipitate was collected by filtration. The solvent was evaporated under reduced pressure to afford a yellow solid which was purified by preparative t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant. The product obtained was crystallised from toluene to give N-*methyl*-N'-*benzyltrianthranilide* (17) (210 mg), m.p. 190—193 °C [Found: C, 74.2; H, 5.1; N, 9.0%; M (mass spec.), 461.1731. $C_{29}H_{23}N_3O_3$ requires C, 75.5; H, 5.0; N, 9.1%; M, 461.1739], $v_{max.}$ (Nujol) 3 320 (NH) and 1 675 and 1 650 cm^{-1} (CO); τ (CDCl$_3$) 1.36 (1 H, bs, NH) 1.96—3.20 (17 H, m, ArH), 4.98 and 5.55 (2 H, AB system, J_{AB} 14.7 Hz, benzylic CH$_2$), and 6.76 (3 H, s, NMe).

5-*Methyl*-11-*benzyl*-17-*ethyltribenzo*[b,f,j][1,5,9]*triaza-cyclododecine*-6,12,18(5H,11H,17H)-*trione*   (N-*Methyl*-N'-*benzyl*-N''-*ethyltrianthranilide*) (18).—Ethyl iodide (1 ml) was added to a mixture of sodium hydride (100 mg) and N-methyl-N'-benzyltrianthranilide (17) (70 mg) in dry dimethyl sulphoxide (15 ml) and the reaction mixture was stirred at room temperature for 5 h. Excess of sodium hydride was destroyed by addition of water to the reaction mixture which was then extracted with chloroform (3 × 50 ml). The combined chloroform extracts were washed with water, dried (MgSO$_4$), filtered, and concentrated under reduced pressure to give an oil. Preparative t.l.c. on silica gel using ethyl acetate as eluant followed by crystallisation from toluene gave N-*methyl*-N'-*benzyl*-N''-*ethyltrianthran-ilide* (18) (48 mg, 65%), as colourless crystals, m.p. 254—255 °C [Found: C, 75.5; H, 5.6; N, 8.1%; M (mass spec.), 489.2025. $C_{31}H_{27}N_3O_3$ requires C, 76.0; H, 5.6; N, 8.6%; M, 489.2052], $v_{max.}$ (Nujol) 1 665 and 1 600 cm^{-1} (CO); τ (CDCl$_3$) 2.10—3.45 (17 H, m, ArH), 5.26 and 5.44 (2 H, AB system, J_{AB} 14.0 Hz, benzylic CH$_2$), 6.12—6.50 (2 H, m, NCH$_2$Me), 6.60 (3 H, s, NMe), and 8.94 (3 H, J 6.4 Hz, NCH$_2$CH$_3$).

Methyl N-*Methyl*-N-[2-(o-*nitro*-N-*ethylbenzamido*)*benzoyl*]-*anthranilate* (60).—Ethyl iodide (3 ml) was added to a mixture of sodium hydride (450 mg) and methyl N-methyl-N-[2-(o-nitrobenzamido)benzoyl] anthranilate (42) (3.27 g) in dry dimethyl sulphoxide (35 ml) and the reaction mixture was stirred at room temperature for 4 h. Excess of sodium hydride was destroyed by careful addition of water to the cooled reaction mixture which was then extracted with chloroform (3 × 100 ml). The combined chloroform extracts were washed with water, dried (MgSO$_4$), filtered, and concentrated under reduced pressure to yield an oil which solidified on the addition of a small amount of light petroleum (b.p. 60—80 °C). This product was crystallised from ethanol to yield *methyl* N-*methyl*-N-[2-(o-*nitro*-N-*ethylbenzamido*)*benzoyl*]*anthranilate* (60) (3.44 g, 99%), m.p. 136—137 °C [Found: C, 65.0; H, 4.9; N, 9.0%; M (mass spec.), 461. $C_{25}H_{23}N_3O_6$ requires C, 65.0; H, 4.9; N, 9.1%, M 461], $v_{max.}$ (Nujol) 1 725 (CO$_2$Me), 1 645 and 1 600 (CO), and 1 535 and 1 375 cm^{-1} (NO$_2$); τ (CDCl$_3$) 1.68—3.20 (12 H, m, ArH), 5.22—5.88 (2 H, m, NCH$_2$Me), 6.01, 6.08, and 6.44 (3 H, 3 × s in the approximate ratio of 46 : 35 : 19, CO$_2$Me),† 6.63, 6.71, and 6.84 (3 H, 3 × s in the approximate ratio of 23 : 47 : 30, NMe),† and 8.57 and 8.87 (3 H, 2 × t

in the approximate ratio of 32 : 68, J 6.0 Hz in each case, NCH$_2$CH$_3$).†

Methyl   N-*Methyl*-N-[2-(o-*amino*-N-*ethylbenzamido*)-*benzoyl*]*anthranilate* (61).—A titanium(III) chloride solution (50 ml, 12.5%) was added dropwise to a solution of methyl N-methyl-N-[2-(o-nitro-N-ethylbenzamido)benzoyl]-anthranilate (60) (3 g) in boiling ethanol (175 ml). The reaction mixture was heated under reflux for 10 min, poured into boiling water (350 ml), and heated for a further 30 min. The cooled solution was extracted with chloroform, washed with water, dried (MgSO$_4$), and concentrated under reduced pressure to give a solid. Crystallisation of this crude product from ethanol yielded *methyl* N-*methyl*-N-[2-(o-*amino*-N-*ethylbenzamido*)*benzoyl*]*anthranilate* (61) (2.5 g, 89%), m.p. 150—151 °C [Found: C, 69.6; H, 5.9; N, 9.5%; M (mass spec.), 431. $C_{25}H_{25}N_3O_4$ requires C, 69.6; H, 5.8; N, 9.7%; M, 431], $v_{max.}$ (Nujol) 3 440 and 3 350 (NH$_2$), 1 720 (CO$_2$Me), and 1 630 and 1 610 cm^{-1} (CO); τ (CDCl$_3$), 1.90—3.40 (12 H, m, ArH), 5.00—5.70 (4 H, m, NCH$_2$Me and NH$_2$), 6.03 and 6.12 (3 H, 2 × s in the approximate ratio of 50 : 50, CO$_2$Me),† 6.55 and 6.63 (3 H, 2 × s in the approximate ratio of 52 : 48, NMe),† and 8.86 and 8.94 (3 H, 2 × t in the approximate ratio of 50 : 50, J 6.0 Hz in each case, NCH$_2$-CH$_3$).†

N-[2-(o-*Amino*-N-*methylbenzamido*)*benzoyl*]-N-*ethyl-anthranilic Acid* (62).—Aqueous lithium hydroxide (200 ml; 10%) was added to a solution of methyl N-methyl-N-[2-(o-amino-N-ethylbenzamido)benzoyl]anthranilate (61) (2.15 g) in methanol (20 ml). The reaction mixture was refluxed for 2 h and allowed to cool before it was acidified with concentrated hydrochloric acid. The precipitate which separated out was collected. Crystallisation from methanol-ether yielded N-[2-(o-*amino*-N-*methylbenzamido*)*benzoyl*]-N-*ethylanthranilic acid* (62) (1.95 g, 94%), m.p. 181—184 °C [Found: M (mass spec.), 417.1655. $C_{24}H_{23}N_3O_4$ requires M, 417.1687], $v_{max.}$ (Nujol) 3 420 and 3 330 (NH$_2$), 1 705 (CO$_2$Me), and 1 630 cm^{-1} (CO); τ (CDCl$_3$) 1.85—3.80 (13 H, m, ArH and CO$_2$H), 5.25—5.70 (2 H, m, NCH$_2$Me), 6.10—7.12 (2 H, bs, NH$_2$), 6.54 and 6.60 (3 H, 2 × s in the approximate ratio of 56 : 44, NMe),† and 8.94 and 9.02 (3 H, 2 × t in the approximate ratio of 56 : 44, NCH$_2$CH$_3$).†

5-*Methyl*-11-*ethyltribenzo*[b,f,j][1,5,9]*triazacyclododecine*-6,12,18(5H,11H,17H)-*trione*   (N-*Methyl*-N'-*ethyltrian-thranilide*) (19.)—A solution of N-[2-(o-amino-N-methyl-benzamido)benzoyl]-N-ethylanthranilic acid (62) (1.25 g) in dichloromethane (45 ml) was added dropwise with stirring to a solution of N,N'-dicyclohexylcarbodi-imide (1.2 g) in dichloromethane (3 ml) at room temperature. The reaction mixture was stirred for 5 h at room temperature and N,N'-dicyclohexylurea which formed as a precipitate was collected by filtration. The solvent was evaporated under reduced pressure to afford a yellow solid which was purified by preparative t.l.c. on silica gel using ethyl acetate as eluant. The crude product was crystallised from toluene to give N-*methyl*-N'-*ethyltrianthranilide* (19) (680 mg, 67%), m.p. 225—228 °C [Found: C, 72.0; H, 5.6; N, 10.4%; M (mass spec.), 399. $C_{24}H_{21}N_3O_3$ requires C, 72.2; H, 5.3; N, 10.5%; M, 399], $v_{max.}$ (Nujol) 3 245 (NH) and 1 670 and 1 660 cm^{-1} (CO); τ (CDCl$_3$) 1.23 (1 H, bs, NH), 1.88—2.86 (12 H, m, ArH), 6.10—6.70 (2 H, m, NCH$_2$Me), 6.81 (3 H, s, NMe), and 9.02 (3 H, t, J 6.7 Hz, NCH$_2$CH$_3$).

5-*Methyl*-11-*ethyl*-17-*benzyltribenzo*[b,f,j][1,5,9]*triaza-cyclododecine*-6,12,18(5H,11H,17H)-*trione*   (N-*Methyl*-N'-*ethyl*-N''-*benzyltrianthranilide*) (20).—Benzyl bromide (0.5

† See footnote at the bottom of p. 1659.

ml) was added to a mixture of sodium hydride (100 mg) and N-methyl-N'-ethyltrianthranilide (19) (80 mg) in dry tetrahydrofuran (15 ml) and the reaction mixture was stirred at room temperature overnight. Excess of sodium hydride was destroyed by addition of water to the cooled reaction mixture which was then extracted with chloroform (3 × 50 ml). The combined chloroform extracts were washed with water, dried (MgSO₄), filtered, and concentrated under reduced pressure to yield an oil. Preparative t.l.c. on silica gel using ethyl acetate as eluant afforded an oily product which solidified on the addition of a small amount of light petroleum (b.p. 60—80 °C). Crystallisation of the solid from toluene yielded N-*methyl*-N'-*ethyl*-N''-*benzyltrianthranilide* (20) (73 mg, 63%), m.p. 238—239 °C [Found: C, 75.6; H, 6.1; N, 8.1%; M (mass spec.), 489.2022. $C_{31}H_{27}N_3O_3$ requires C, 76.1; H, 5.6; N, 8.6%; M, 489.2026], $\nu_{max.}$ (Nujol) 1 600 and 1 660 cm⁻¹ (CO); τ (CDCl₃) 2.17—3.52 (17 H, m, ArH), 3.95—6.04 (2 H, 4 AB systems, J_{AB} ca. 15 Hz in all cases, benzylic CH₂), 6.24—6.88 (2 H, m, NCH_2Me), 6.46, 6.64, 6.68, and 6.81 (3 H, 4 × s in the approximate ratio of 12 : 11 : 36 : 41, NMe), 8.70 and 8.98 (3 H, 2 × t in the approximate ratio of 50 : 50, J 6.8 Hz in each case, NCH₂CH_3) (see Table 10 and Figure 35 in the Results and Discussion section).

Determination of Rates of Conformational Changes by Dynamic ^{1}H N.m.r. Spectroscopy.—The methods used have been described in Parts 1,[26] 2,[27] 3,[24] 4,[28] 6,[25] 7,[29] 8,[10] 9,[2] and 10.[1] The computer programs (coded in FORTAN IV) used to generate the theoretical line shapes are now described for the general methods I—IV.

Method I. A program V † for exchange of nuclei between four equally or unequally populated sites A, B, C, and D with no mutual coupling. This program has already been discussed at some length in our publication [3] on the conformational behaviour of tri-3,6-dimethylsalicylide, tri-o-thymotide, and tri-o-carvacrotide as well as in Part 6.[25] In the present investigation it was used to simulate the spectral line shapes associated with the protons in the N-methyl groups of N,N',N''-trimethyltrianthranilide (7), N-methyl-N'-trideuteriomethyl-N''-benzyltrianthranilide (13), and N,N'-dibenzyl-N''-methyltrianthranilide (16).

Calculated spectra are shown in Figure 3 beside selected observed spectra for the N-methyl protons in N,N',N''-trimethyltrianthranilide (7) recorded in nitrobenzene. Values for the site-exchange rate constants (*i.e.* k_{DA}, k_{DB}, k_{DC}) corresponding to an interconversion process between conformational diastereoisomers were obtained over a range of temperatures between +86 and +119 °C. By plotting ln k_{DA} etc. against $1/T$ and extrapolating the best straight line resulting from a least-squares analysis, projected values for these site-exchange rate constants at higher temperature were obtained. These values were used in order to find the site-exchange rate constants (*i.e.* k_{AB}, k_{BA}, k_{AC}, k_{CA}, k_{BC}, k_{CB}) for an inversion process between conformational enantiomers in the temperature range +130 to +199 °C. Predicted values for k_{AB} etc. at lower temperatures were obtained by plotting ln k_{AB} etc. against $1/T$ at these higher temperatures and extrapolating the best straight line resulting from a least-squares analysis to the lower temperature range.

† The program numbers (II, V, and VI) established in Parts 3,[24] 6,[25] and 8 [10] are adhered to in this paper and together with the additional program (VIII) described here, these programs will form the basis of a collection for reference in future Parts of this series.

Calculated spectra are shown in Figure 4 beside observed spectra for the N-methyl protons in N-methyl-N'-trideuteriomethyl-N''-benzyltrianthranilide (13) recorded in nitrobenzene. Inspection of these temperature-dependent spectra reveals that they represent conformational changes
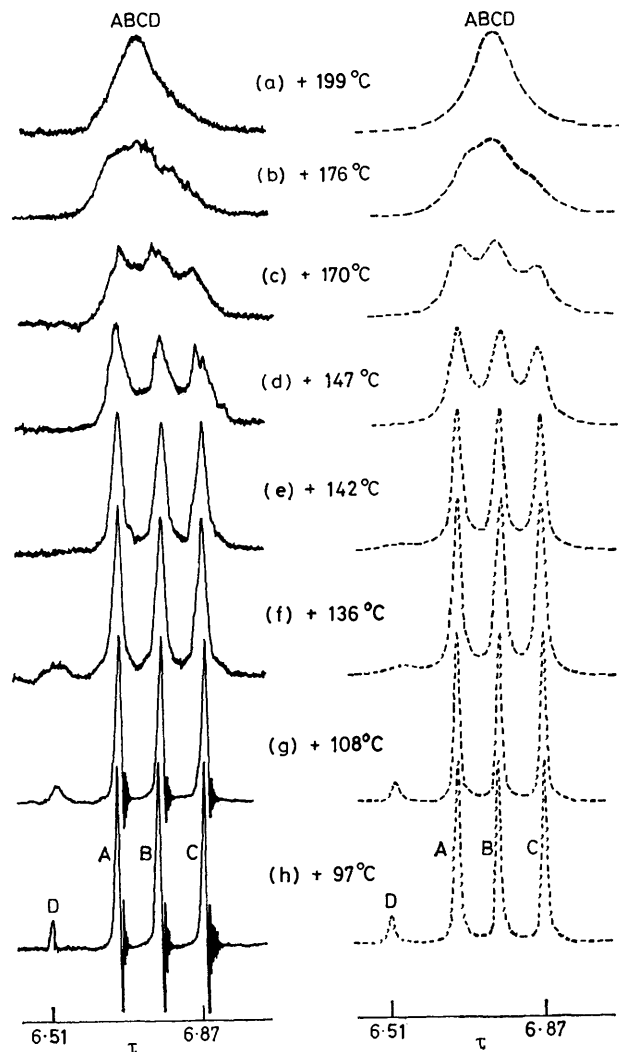

FIGURE 3 Observed (full line) and computed (broken line) spectra of the N-methyl protons of N,N',N''-trimethyltrianthranilide (7) using program V for exchange of protons between four sites A, B, C, and D with relative populations of 0.315, 0.315, 0.315, and 0.055, respectively: (a) at +199 °C, k_{DA} etc. 358 s⁻¹ and k_{AB} etc. 10.7 s⁻¹; (b) at +176 °C, k_{DA} etc. 90.0 s⁻¹ and k_{AB} etc. 5.0 s⁻¹; (c) at +170 °C, k_{DA} etc. 64.0 s⁻¹ and k_{AB} etc. 4.2 s⁻¹; (d) at +147 °C, k_{DA} etc. 13.2 s⁻¹ and k_{AB} etc. 1.3 s⁻¹; (e) at +142 °C, k_{DA} etc. 8.8 s⁻¹ and k_{AB} etc. 1.1 s⁻¹; (f) at +136 °C, k_{DA} etc. 6.1 s⁻¹ and k_{AB} etc. 0.74 s⁻¹; (g) at +108 °C, k_{DA} etc. 0.97 s⁻¹ and k_{AB} etc. 0.17 s⁻¹; (h) at +97 °C, k_{DA} etc. 0.25 s⁻¹ and k_{AB} etc. 0.084 s⁻¹

between four conformational diastereoisomers that are unequally populated since the four sites A, B, C, and D are unequally populated. It was clear at the outset that any attempt to vary *twelve* different site-exchange rate constants simultaneously would not constitute either a sensitive or unambiguous approach to the analysis of the spectral line shapes. With the nature of the conformational problem in
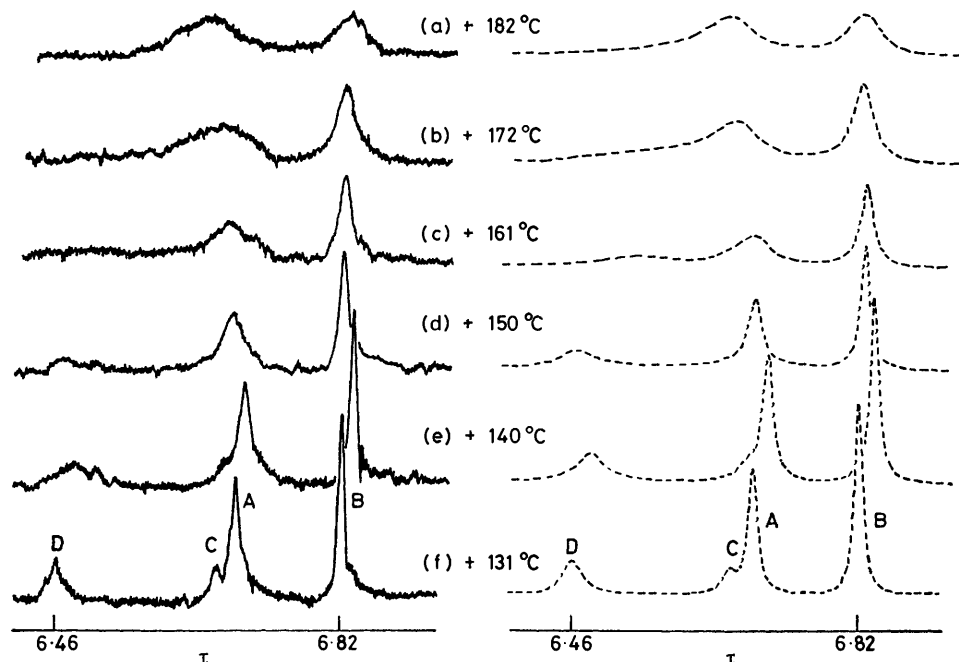
FIGURE 4   Observed (full line) and computed (broken line) spectra of the N-methyl protons of N-methyl-N'-trideuteriomethyl-N''-benzyltrianthranilide (13) using program V for exchange of protons between four unequally populated sites A, B, C, and D (see the Results and Discussion section for the assignment of sites to signals) with relative populations of 0.326, 0.409, 0.073, and 0.192, respectively: (a) at $+182$ °C, k_1' 25.3 s^{-1}, k_2' 2.4 s^{-1}; (b) at $+172$ °C, k_1' 15.2 s^{-1}, k_2' 1.3 s^{-1}; (c) at $+161$ °C, k_1' 8.0 s^{-1}, k_2' 0.57 s^{-1}; (d) at $+150$ °C, k_1' 4.4 s^{-1}, k_2' 0.25 s^{-1}; (e) at $+140$ °C, k_1' 2.4 s^{-1}, k_2' 0.12 s^{-1}; (f) at $+131$ °C, k_1' 1.3 s^{-1}, k_2' 0.057 s^{-1}

mind, it was decided to replace (i) the three site-exchange rate constants k_{DA}, k_{DB}, k_{DC} with an average first-order rate constant, k_1', (ii) the three site-exchange rate constants k_{AD}, k_{BD}, k_{CD} with an average first-order rate constant, k_{-1}', and

(iii) the six site-exchange rate constants k_{AB}, k_{BA}, k_{AC}, k_{CA}, k_{BC}, k_{CB} with an average first-order rate constant, k_2'.   By using the same method as that employed in the case of N,N',N''-trimethyltrianthranilide (7), projected values for k_1' at 161, 172, and 182 °C were obtained by extrapolating the straight line obtained by plotting ln k_1' against $1/T$ to higher temperatures.   In a similar manner, projected values for k_2' at 131, 140, and 150 °C were obtained by extrapolating the straight line obtained by plotting ln k_2' against $1/T$ to lower temperatures.

Calculated spectra are shown in Figure 5 beside observed spectra for the N-methyl protons in N,N'-dibenzyl-N''-methyltrianthranilide (16).   Once again, we were confronted with the problem of four unequally populated sites reflecting the presence of an equilibrating mixture of four unequally populated conformational diastereoisomers.   The same solution as that described above for compound (13) was applied to this problem successfully.   In this case, however, it was possible to match line shapes without having to resort to graphical treatments of the rate constants k_1' and k_2'.

Method II.   A program (II) † for exchange of nuclei between two sites, A and B, with equal populations and a mutual coupling constant.   This program was used to simulate the spectral line shapes of the AB system exhibited
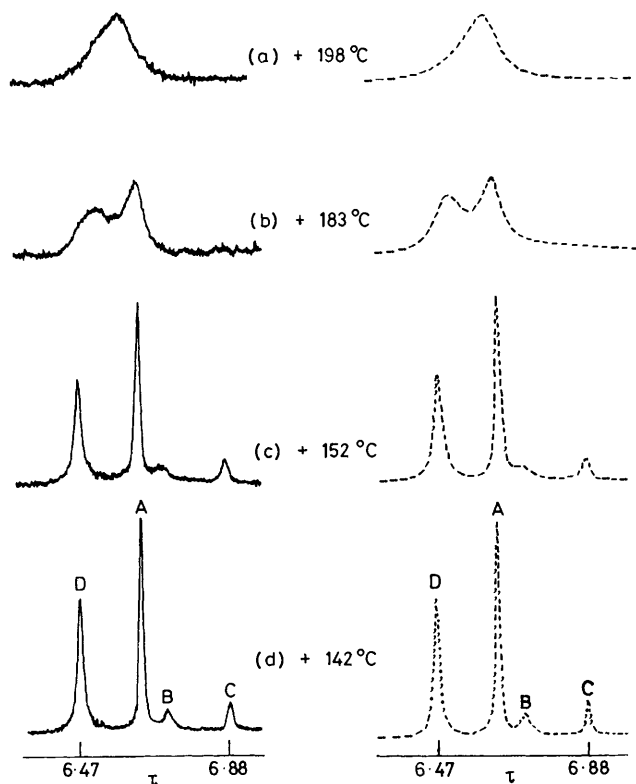
† As footnote on p. 1667.

FIGURE 5   Observed (full line) and computed (broken line) spectra of the N-methyl protons of N,N'-dibenzyl-N''-methyltrianthranilide (16) using program V for exchange of protons between four unequally populated sites A, B, C, and D (see the Results and Discussion section for the assignment of sites to signals) with relative populations of 0.478, 0.087, 0.078, and 0.357, respectively: (a) at $+198$ °C, k_1' 25.0 s^{-1}, k_2' 9.0 s^{-1}; (b) at $+183$ °C, k_1' 7.0 s^{-1}, k_2' 3.8 s^{-1}; (c) at $+152$ °C, k_1' 0.57 s^{-1}, k_2' 0 s^{-1}; (d) at 142 °C, k_1' 0.25 s^{-1}, k_2' 0 s^{-1}
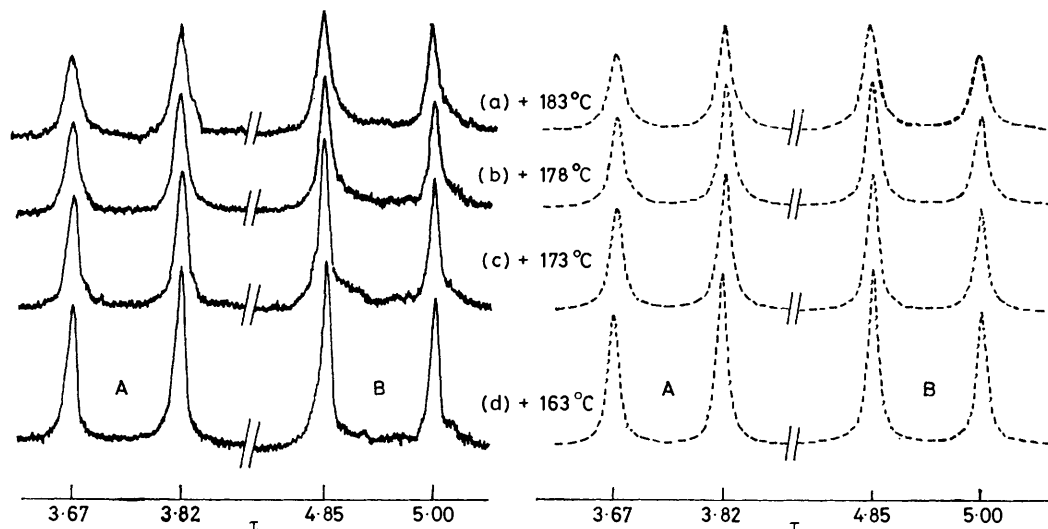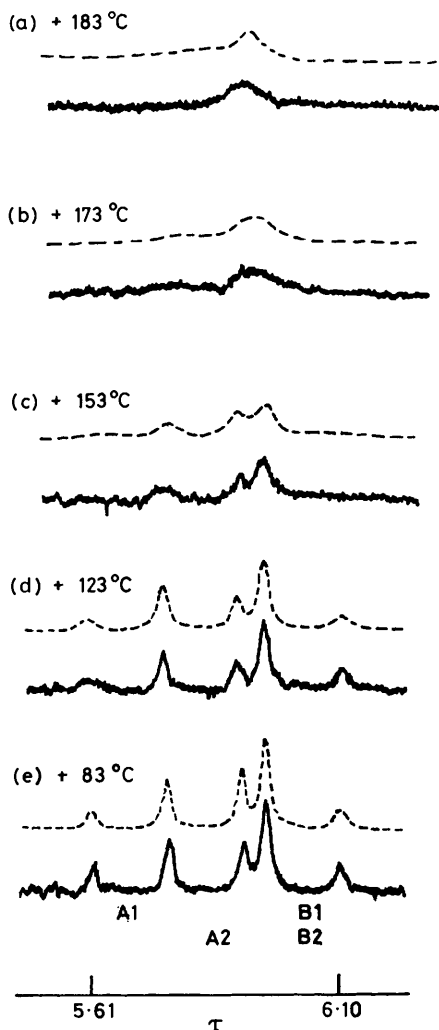
FIGURE 6   Observed (full line) and computed (broken line) spectra of the benzylic-methylene protons of N,N,N''-tribenzyltrianthranilide (15) using program II for exchange of protons between two sites, A and B, with equal populations (*i.e.* p_A 0.50, p_B 0.50) and a mutual coupling constant ($J_{AB} = 15.0$ Hz): (a) At $+183$ °C, k_{AB} 2.87 s^{-1}; (b) at $+178$ °C, k_{AB} 1.99 s^{-1}; (c) at $+173$ °C, k_{AB} 1.66 s^{-1}; (d) at $+163$ °C, k_{AB} 1.15 s^{-1}

by the benzylic-methylene protons in N,N',N''-tribenzyltrianthranilide (15) at high temperatures. Calculated and observed spectra are shown in Figure 6.

Method III.   A program (VIII) † to sum the spectra of two superimposed AB systems, A1B1 and A2B2, with the same relative summed intensities and with exchange between the pairs of sites A1 and B1, and A2 and B2 with the same rate constant, k, but with no exchange between the two AB systems. This program was used to simulate the spectral line shapes of the two AB systems associated with the constitutionally heterotopic benzylic-methylene groups of N,N'-dibenzyltrianthranilide (14) at high temperatures. Calculated and observed spectra are shown in Figure 7.

Method IV.   A program (VI) † for exchange of nuclei between all six sites of three AB systems, A1B1, A2B2, and A3B3. This program is discussed in considerable detail in Part 8.[10] It is based upon a density matrix approach in which four different site exchange schemes (i)—(iv) must be considered. These schemes were all examined (see Figure 8) in an attempt to match a calculated with the observed spectrum at -54 °C for the three AB systems arising from the three pairs of methylene protons in the cyclic triamine (22).

Method V.   For the AB system for the benzylic-methylene protons in N-methyl-N'-benzyltrianthranilide (17) the site-exchange rate constant, k_c, was calculated (see Results and Discussion section) at the coalescence temperature, T_c, by using the approximate relationship (1), which is suitable for

$$k_c = \pi[(\nu_A - \nu_B)^2 + 6J_{AB}^2]^{\frac{1}{2}}/2^{\frac{1}{2}} \qquad (1)$$

† As footnote on p. 1667.

FIGURE 7   Observed (full line) and computed (broken line) spectra of the benzylic-methylene protons of N,N'-dibenzyltrianthranilide (14) using program VIII for exchange of protons between the pairs of sites A1 and B1, and A2 and B2, with the same rate constant, k: (a) At $+183$ °C, k 106 s^{-1}; (b) at $+173$ °C, k 63 s^{-1}; (c) at $+153$ °C, k 16.9 s^{-1}; (d) at $+123$ °C, k 4.3 s^{-1}; (e) at $+83$ °C, k 0.5 s^{-1}
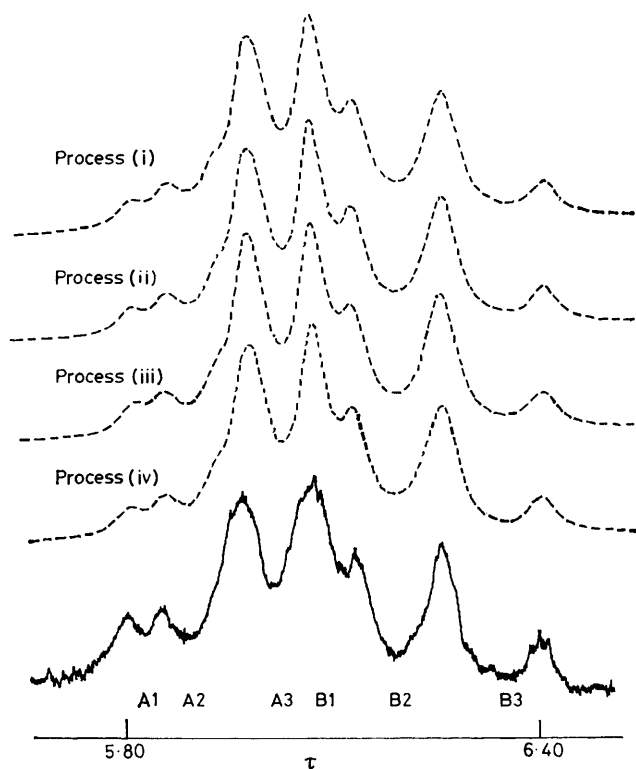
FIGURE 8 Observed (full line) and computed (broken line) spectra of the methylene protons of 5,11,17-tribenzyl-6,6,12,12,-18,18-hexadeuterio-5,6,11,12,17,18-hexahydrotribenzo[b,f,j]-. [1,5,9]triazacyclododecine (22) using program VI for exchange of nuclei between six equally-populated sites A1, B1, A2, B2, A3, and B3 (the input values for all the rate constants, k_{12} etc., were the same so they will be referred to collectively as k) at -54 °C: (a) process (i), k 1.96 s^{-1}; (b) process (ii), k 1.37 s^{-1}; (c) process (iii), k 1.96 s^{-1}; (d) process (iv), k 1.92 s^{-1}

exchange of nuclei between two sites A and B with equal populations and chemical shifts, ν_A and ν_B, respectively, and a mutual coupling constant, J_{AB}.

RESULTS AND DISCUSSION

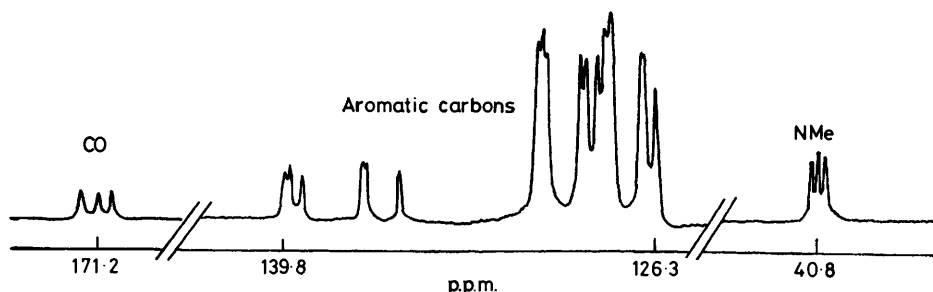The conformational behaviour of the trianthranilide derivatives (5)—(20) is discussed first. Then the treat-

^{1}H-decoupled ^{13}C n.m.r. spectrum (see Figure 9) of N,N',N''-trimethyltrianthranilide (7) was recorded in deuteriochloroform at room temperature, (i) three signals of approximately equal intensities were observed at 40.4, 40.8, and 41.3 p.p.m. for the N-methyl carbon atoms, (ii) eighteen signals between 126.3 and 139.8 p.p.m. were observed for the aromatic carbon atoms, the two groups of three signals of lower intensities at lower field arising from the quaternary centres, and (iii) three signals of approximately equal intensities were observed for the carbonyl carbon atoms, resonating at 170.5, 171.2, and 172.3 p.p.m. These observations demonstrate the presence of (i) three stereoheterotopic N-methyl groups, (ii) three stereoheterotopic aromatic rings, and (iii) three stereoheterotopic carbonyl groups and are consistent with N,N',N''-trimethyltrianthranilide (7) adopting enantiomeric helical † conformations (63a and b) as the major isomers in solution. This conformational assignment is proposed in the knowledge that the helical conformations (63a and b), in which the three amide linkages all assume trans-geometries, have the required asymmetry (they belong to point group, C_1) to account for the spectroscopic results. It is also supported by inspection of space-filling molecular models which suggests that the helical conformations (63a and b) with two N-methyl groups and one carbonyl oxygen atom pointing towards one face and two carbonyl oxygen atoms and one methyl group pointing towards the other face is more stable than the enantiomeric propeller † conformations (64a and b) where the three amide groups also assume trans-geometries but have all three N-methyl groups pointing towards one face leaving all three carbonyl oxygen atoms pointing towards the other face. The nonbonded interactions experienced by three N-methyl groups on the same face of the 12-membered ring probably destabilise the propeller conformations (64a and b). On the other hand, favourable electronic factors might stabilise the helical conformations (63a and b) by virtue of attractive permanent dipole-permanent dipole interactions between appositely oriented trans-amide linkages across the 12-membered ring. Although the propeller conform-

FIGURE 9 The ^{1}H-decoupled ^{13}C n.m.r. spectrum of N,N,N''-trimethyltrianthranilide (7) recorded in deuteriochloroform at room temperature.

ment of the conformational properties of N,N'-dibenzyldianthranilide (4) and the cyclic triamines (21) and (22) follows.
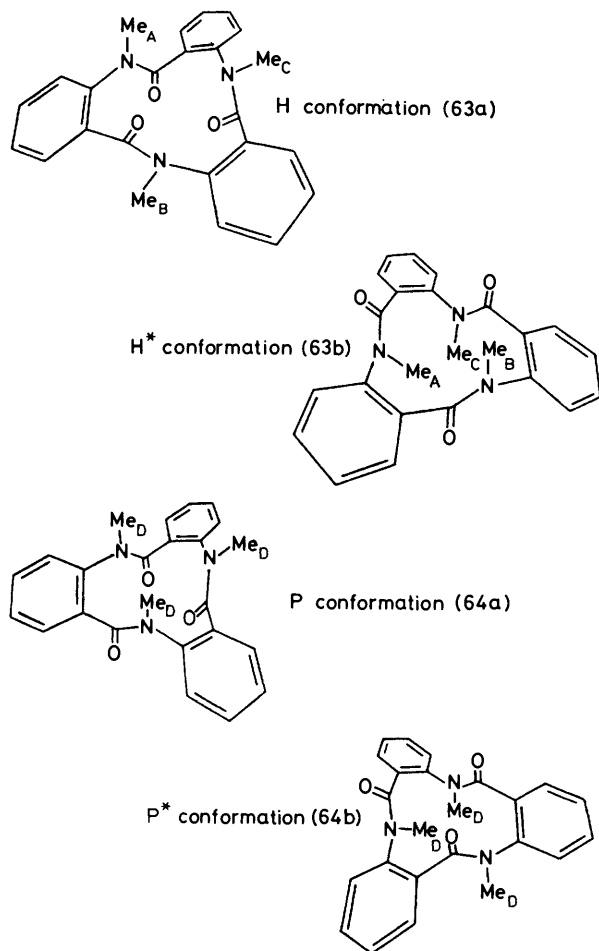
The Conformational Behaviour of N,N'-*Dimethyl-* (5) *and* N,N',N''-*Trimethyl-* (7) *trianthranilides.*—When the

ations (64a and b) have C_3 symmetry and so might be expected to be disfavoured relative to the asymmetrical

† The definition of the conformational descriptors 'helical' and 'propeller' is discussed at some length in Part 9 [2] of this series.

helical conformations (63a and b) on entropic grounds, this does not turn out to be the case in practice (see p. 1675). The choice of helical (63a and b) and propeller (64a and b) conformations for consideration as ground-state

H conformation (63a)

H* conformation (63b)

P conformation (64a)

P* conformation (64b)

conformations for N,N',N''-trimethyltrianthranilide (7) seems a logical one in view of our experience [22] gained from studying the conformational behaviour of tri-salicylides [2,3,30] and trithiosalicylides [1,31] in solution.

Although there were no identifiable signals which could be attributed to the propeller conformations (64a and b) in the [1]H-decoupled [13]C n.m.r. spectrum of N,N',N''-tri-methyltrianthranilide (7) in deuteriochloroform, when the [1]H n.m.r. spectrum of the same sample was recorded (see Figure 10), the appearance of a low intensity singlet at τ 6.51, in addition to the expected three singlets at τ 6.67, 6.79, and 6.87 of equal and much higher intensities, for the N-methyl protons was strongly indicative of a low population (5.5%) of propeller conformations (64a and b). The N-methyl groups (Me$_D$) of the propeller con-formations (64a and b) are homotopic as a result of the C_3 symmetry and so must have the same chemical shift.

† We find it convenient (cf. ref. 1) to refer to pseudorotational processes (i) connecting enantiomers as inversions and those (ii) connecting diastereoisomers as interconversions.

The three N-methyl groups (Me$_A$, Me$_B$, and Me$_C$) of the asymmetrical helical conformations (63a and b) are diastereotopic and so are expected to be anisochronous. The unambiguous assignment of the N-methyl groups labelled Me$_A$, Me$_B$, and Me$_C$ in the helical conformations (63a and b) to the signals appearing (see Figure 10) at τ 6.67, 6.79, and 6.87 respectively was made on the basis of labelling studies (see p. 1680). The absolute nature of these assignments ultimately assume importance in the identification of conformational diastereoisomers of unsymmetrically N,N',N''-trisubstituted derivatives such as N,N'-dimethyl-N''-benzyltrianthranilide (12) and N,N'-dibenzyl-N''-methyltrianthranilide (16).

By analogy with the known conformational properties of trisalicylide derivatives [2,3,22,30] in solution, we were led to consider that trianthranilides such as the N,N',N''-trimethyl derivative (7) should be able to undergo ring inversions † and interconversions † involving enantio-meric and diastereoisomeric conformations of the propeller (P and P*) and helical (H and H*) types according to the scheme:

$$P(64a) \rightleftharpoons H(63a) \rightleftharpoons H*(63b) \rightleftharpoons P*(64b)$$

However, inspection of space-filling molecular models of compound (7) suggests that the reorientation of a trans-amide linkage, which must accompany each conform-ational change in the above scheme, cannot proceed by the pedalling mechanism [25] that probably character-ises [2,3,22] the reorientations of trans-ester linkages in the analogous conformational changes involving trisalicylide derivatives. Ring inversion and interconversion pro-cesses by pedalling of a trans-CONMe linkage would imply that either the carbonyl oxygen atom or the N-methyl group would have to pass through the central portion of the 12-membered ring. This is sterically impossible. Thus, N,N',N''-trimethyltrianthranilide (7) is obliged to undergo ring inversions and intercon-versions via intermediates having cis-amide linkages. In this regard the conformational behaviour of (7) is reminiscent of that of trithiosalicylide derivatives.[1,31] It follows that barriers to conformational changes in N,N',N''-trisubstituted trianthranilides are expected to be high (>20 kcal mol^{-1}). If this is indeed the case, then it should be possible to study the interconversions between helical (63a and b) and propeller (64a and b) conformations in solutions of N,N',N''-trimethyl-trianthranilide (7) by direct methods. First of all, however, the preferred conformation in the solid state was established by dissolving crystals ‡ of (7), obtained on slow recrystallisation from chloroform–ether–light petroleum (b.p. 60—80 °C), in deuteriochloroform at −30 °C and recording the [1]H n.m.r. spectrum of the solution at this temperature. Only three signals of equal intensities were observed at τ 6.67, 6.79, and 6.87 for the N-methyl protons (Figure 10). This behaviour accords with N,N',N''-trimethyltrianthranilide (7) adopt-

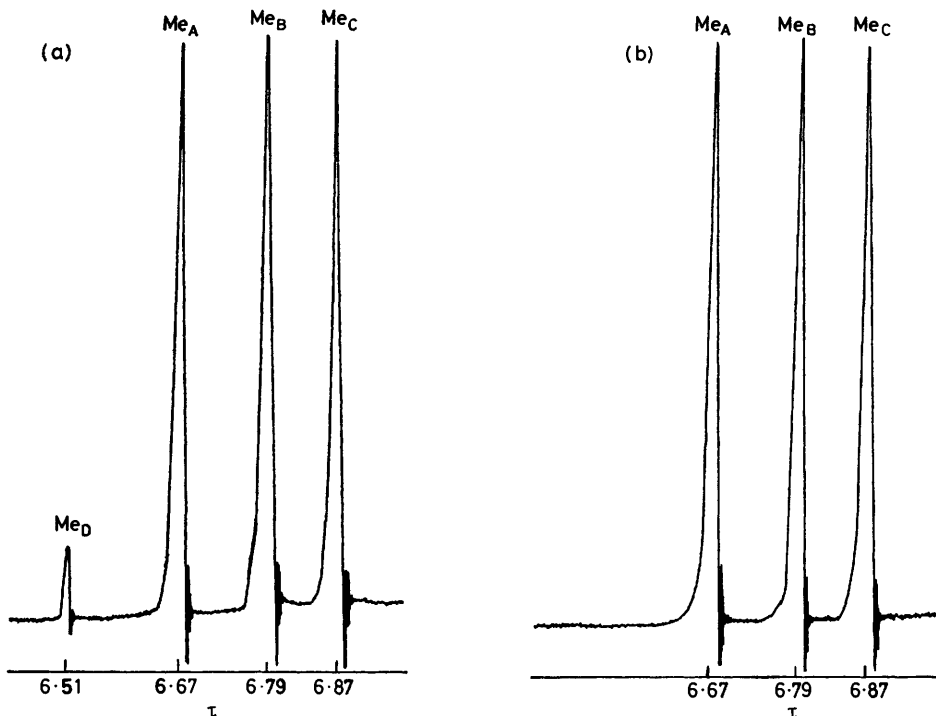‡ Single crystals were not of sufficiently good quality to lend themselves to X-ray structural analysis.

FIGURE 10 The signals for the N-methyl protons of N,N',N''-trimethyltrianthranilide (7) recorded in deuteriochloroform in the ¹H n.m.r. spectrum on (a) an equilibrated sample at room temperature and on (b) a slowly recrystallised sample at -30 °C

ing helical conformations (73a and b) in the crystal. When the same experiment was carried out at ambient temperature, the appearance of the low-field signal at τ 6.51 for the N-methyl protons in the propeller conformations (64a and b) was immediate and the growth in the area under the associated peak was rapid until the equilibrium conformer population of 5.5% was reached within a few minutes. Preliminary experiments revealed that a temperature of $+10$ °C provided ideal conditions under which the rates of the conformational changes could be measured by monitoring the relative areas of the N-methyl signals as a function of time. Table 1 records the changes in the percentage peak areas (Area$_{P/P*}$ and Area$_{H/H*}$) of the N-methyl signals for the propeller (64a and b) and helical (63a and b) conformations with time, t. Values for the forward (k_1) and reverse (k_{-1}) rate constants for the equilibria (2) were calculated using the

$$P \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H \text{ and } P^* \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H^* \quad (2)$$
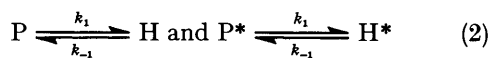
expression (3) which is an adaption [32] of the usual expression [33] for a reversible first-order reaction between

$$\ln[(R - K)/(1 + R)] = -(k_1 + k_{-1})t \ldots \quad (3)$$

diastereoisomers where R is the ratio of the diastereoisomers at time t and K is the equilibrium constant (i.e. $K = R$ at $t = \infty$). Values for R were obtained from the relative peak areas (Area$_{H/H*}$/Area$_{P/P*}$) at different times, t, and are recorded in Table 1. Note that the value calculated for K is 17. Substituting in the expression, $\Delta G° = -RT\ln K$, this value for the equilibrium constant corresponds to a free-energy difference between helical (63a and b) and propeller (64a and b) conformations of 1.6 kcal mol⁻¹ in favour of the helical conformations (63a and b) at $+10$ °C. A value (1.8 × 10⁻⁴ s⁻¹) for the sum ($k_1 + k_{-1}$) of the rate constants for the $P \longrightarrow H$ and $H \longrightarrow P$ interconversion processes was obtained from the slope of the line obtained on plotting $\ln[(R - K)/(1 + R)]$ versus t (see Table 1).

TABLE 1

Experimental and calculated data relating to the equilibration of helical (63a and b) and propeller (64a and b) conformations of N,N',N''-trimethyltrianthranilide (7) at $+10$ °C in deuteriochloroform obtained by ¹H n.m.r. spectroscopy

t/min	Area$_{P/P*}$ [a] (%)	Area$_{H/H*}$ [a] (%)	R [b]	$(R - K)$	$(1 + R)$	$\dfrac{(R - K)}{(1 + R)}$	$\ln\dfrac{(R - K)}{(1 + R)}$
15	0.9	99.1	116	99	117	0.85	-0.18
20	1.3	98.7	73	56	74	0.76	-0.26
25	1.8	98.2	54	37	55	0.67	-0.40
30	2.1	97.9	47	30	48	0.63	-0.48
45	2.3	97.7	42	25	43	0.58	-0.55
60	2.6	97.4	38	21	39	0.54	-0.64
∞	5.5	94.5	17 [c]				

[a] Obtained by integration of ¹H n.m.r. spectra. [b] $R = $ Area$_{H/H*}$/Area$_{P/P*}$. [c] $K = R$ at $t = \infty$.

Values for the forward ($k_1 = 1.7 \times 10^{-4}$ s^{-1}) and reverse ($k_{-1} = 0.1 \times 10^{-4}$ s^{-1}) rate constants were obtained from the relationship, $K = k_1/k_{-1}$. Employing the Eyring equation, $\Delta G^{\ddagger}$ (P $\longrightarrow$ H) and $\Delta G^{\ddagger}$ (H $\longrightarrow$ P) were calculated to be 21.5 ± 0.5 and 23.0 ± 0.5 kcal mol^{-1}, respectively.

The signals for N-methyl groups in the ^{1}H n.m.r.

11. The P $\longrightarrow$ H interconversion processes, which involve site exchanges between the pairs of N-methyl groups designated Me$_D$ and Me$_A$, Me$_D$ and Me$_B$, and Me$_D$ and Me$_C$, account for the coalescence of the low-intensity signal with the three high-intensity signals at $+147$ °C. The broadening and eventual coalescence at higher temperatures of the three high intensity signals to one
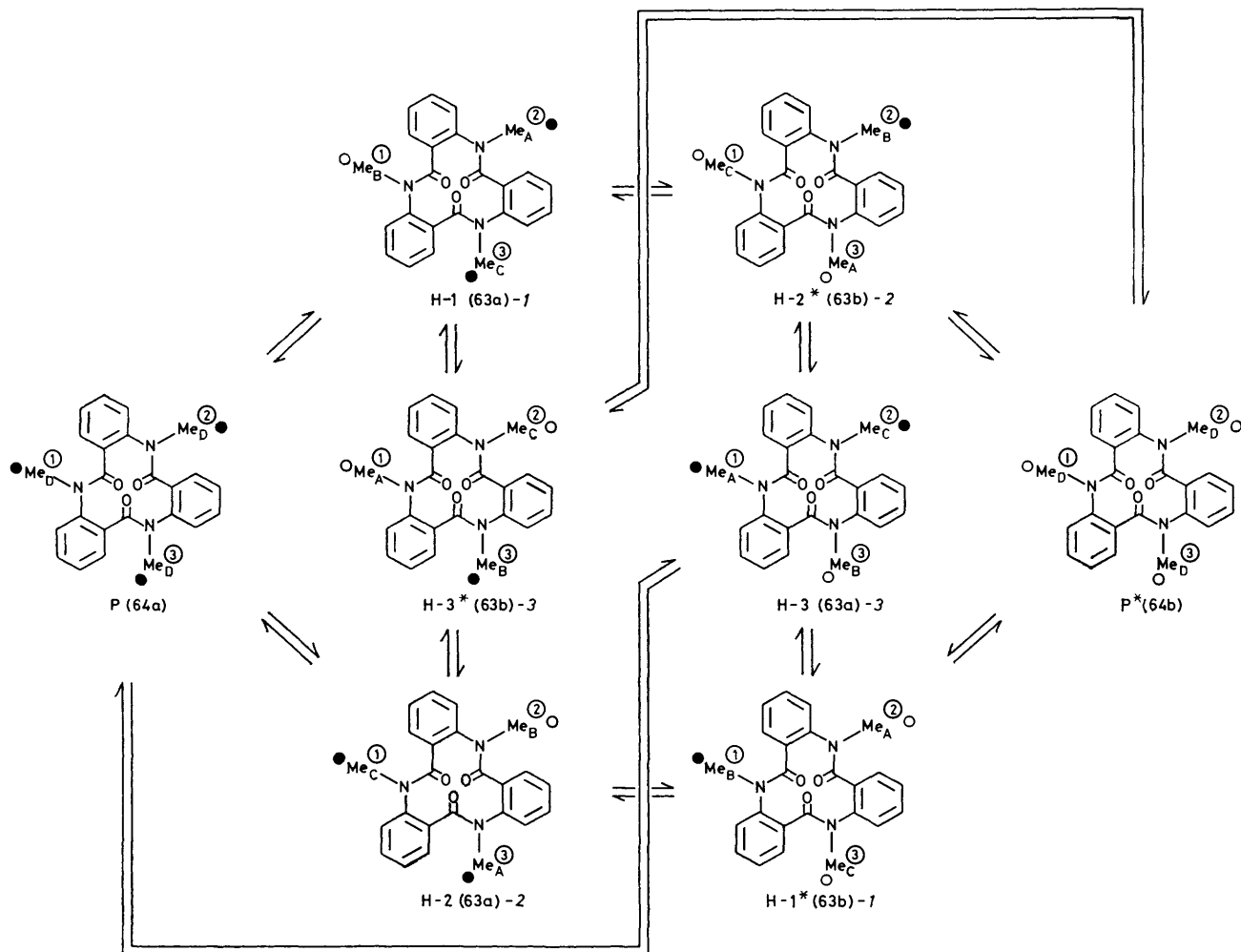

FIGURE 11 Conformational itinerary and site exchange scheme for the N-methyl groups in the H (63a), H* (63b), P (64a), and P* (64b) conformations of N,N',N''-trimethyltrianthranilide (7). ● ≡ An N-methyl group above the mean plane of the ring: ○ ≡ an N-methyl group below the mean plane of the ring. The constitutional identities of the N-methyl groups are indicated by encircled superscripts

spectrum of N,N',N''-trimethyltrianthranilide (7) recorded in nitrobenzene exhibit the temperature dependences shown in Figure 3. As the temperature is raised, the low intensity signal for the propeller conformations (64a and b) at low field broadens until at $+147$ °C it has coalesced with the three high-intensity signals for the helical conformations (63a and b) at higher field. Finally, these three high-intensity signals start to broaden as the temperature is raised further and eventually a broad singlet is observed at $+176$ °C. These observations can be satisfactorily accounted for in terms of the conformational equilibria and associated site exchanges for the N-methyl groups outlined in Figure

broad singlet arises from H $\rightleftharpoons$ H* inversion processes associated with site exchanges between Me$_A$, Me$_B$, and Me$_C$. In the scheme shown in Figure 11, each diagram represents a ground-state conformation on the conformational itinerary. Since it is necessary to follow the site exchanges of individual N-methyl groups, the identity of each N-methyl group is indicated by an encircled superscript. The conformations are represented such that the mean plane of the 12-membered ring lies in the plane of the paper and the N-methyl groups are indicated as being oriented above (●) and below (○) the mean plane. The propeller (P) conformation (64a) has a choice of three possible interconversions to one of the

three degenerate helical (H) conformations [(63a)-*1*, (63a)-*2*, or (63a)-*3*] by reorientation of any one of the three homotopic *trans*-amide linkages with respect to the mean plane of the ring. Subsequent reorientation of either one of the other two *trans*-amide linkages in each

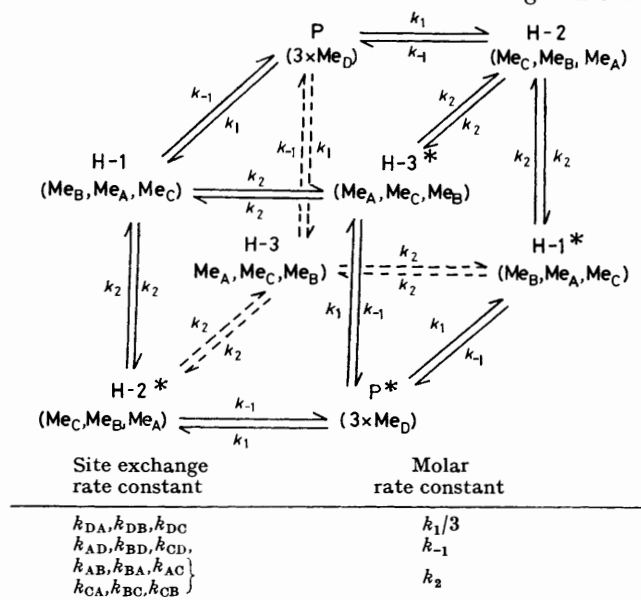| Site exchange rate constant	Molar rate constant
k_{DA}, k_{DB}, k_{DC}	$k_1/3$
$k_{AD}, k_{BD}, k_{CD},$	k_{-1}
$\left.\begin{array}{l}k_{AB}, k_{BA}, k_{AC}\\ k_{CA}, k_{BC}, k_{CB}\end{array}\right\}$	k_2

FIGURE 12 Cubic array diagram showing the site exchanges for N-methyl groups in propeller (P and P*) and degenerate helical (H-1, H-2, H-3, and H-1*, H-2*, H-3*) conformations of N,N',N''-trimethyltrianthranilide (7). The sites indicated in parentheses read from left to right corresponding to the nuclei associated with the N-methyl groups labelled with the encircled superscripts 1, 2, and 3 in Figure 11

case leads to one of the three degenerate enantiomeric helical (H*) conformations [(63b)-*1*, (63b)-*2*, and (63b)-*3*]. Reorientation of the remaining *trans*-amide linkage in each case gives rise to the enantiomeric propeller (P*) conformation (64b). A simplified diagrammatic representation of these conformational changes, together with the associated site exchanges experienced by the

N-methyl groups, are summarised in the cubic array diagram in Figure 12.

Line-shape analyses of the signals for the N-methyl groups at a range of different temperatures from $+86$ to $+199$ °C, including those partial spectra reproduced in Figure 3, gave the rate constant data and derived free energies of activation for the appropriate conformational changes in N,N',N''-trimethyltrianthranilide (7) which are listed in Table 2. The rate constants for the site exchanges (see Figure 12) are defined in terms of concentrations measured as site populations. They are not necessarily the same as the rate constants associated with conformational changes. These rate constants should be defined in terms of concentrations measured on the usual molar basis. Thus, the molar rate constants have to be obtained by correction of the apparent rate constants derived from line-shape analyses. The molar rate constants for the P $\longrightarrow$ H, H $\longrightarrow$ P, and H $\rightleftharpoons$ H* equilibria in Figure 12 have been given the descriptors k_1, k_{-1}, and k_2, respectively. Consider the P $\rightleftharpoons$ H equilibrium first. At equilibrium, the rate constants, k_1 and k_{-1} are related to the concentrations of the propeller (64a and b) and helical (63a and b) conformations by the expression $k_1[P] = k_{-1}[H]$. As each molecule in a propeller conformation (64a or b) has *three* homotopic N-methyl groups, the population of propeller N-methyl groups is proportional to *three* times the molar concentration of the propeller conformation (64a or b). On the other hand, the population of *one* of the helical N-methyl groups is *directly* proportional to the molar concentration of the helical conformation (63a or b). It follows that,

$$k_1 \cdot \frac{\text{pop. of propeller } N\text{-Me signal}}{3} =$$
$$k_{-1} \cdot \text{pop. of helix } N\text{-Me signal}$$

or

$$(k_1/3) \cdot \text{pop. of propeller } N\text{-Me signal} =$$
$$k_{-1} \cdot \text{pop. of helix } N\text{-Me signal}$$

TABLE 2

Rate constants (s⁻¹) and the derived free energies of activation (kcal mol⁻¹) for the conformational changes associated with P $\longrightarrow$ H and H $\longrightarrow$ P interconversions and H $\rightleftharpoons$ H* inversions of N,N',N''-trimethyltrianthranilide (7) in nitrobenzene solution at various temperatures (°C)

T/°C	$k_1/3$ [a]	k_1	$\Delta G^\ddagger$ (P $\longrightarrow$ H) [d]	k_{-1} [b]	$\Delta G^\ddagger$ (H $\longrightarrow$ P) [e]	k_2 [c]	$\Delta G^\ddagger$ (H $\rightleftharpoons$ H*) [f]	ΔG° (H $\longrightarrow$ P) [g]
86	0.12	0.36	21.9	0.021	23.9	0.042 [i]	23.4	2.0
97	0.25	0.75	22.0	0.043	24.1	0.084 [i]	23.6	2.1
108	0.97	2.9	21.7	0.17	23.8	0.17 [i]	23.8	2.2
119	1.1	3.3	22.1	0.18	24.5	0.31 [i]	24.1	2.2
130	3.9 [h]	11.7	21.9	0.67	24.1	0.50	24.4	2.3
136	6.1 [h]	18.3	21.8	1.06	24.1	0.74	24.4	2.3
142	8.8 [h]	26.4	21.8	1.5	24.1	1.1	24.4	2.3
147	13.2 [h]	39.4	21.8	2.3	24.2	1.3	24.6	2.4
153	20.5 [h]	61.5	21.8	3.6	24.2	1.5	24.9	2.4
159	29.9 [h]	89.7	21.7	5.2	24.2	2.4	24.8	2.4
164	43.4 [h]	130	21.4	7.6	24.1	3.2	25.0	2.5
170	64.0 [h]	192	21.6	11.1	24.1	4.2	25.1	2.5
176	90.0 [h]	270	21.6	15.7	24.2	5.0	25.2	2.5
187	181 [h]	543	21.6	31.6	24.2	7.4	25.5	2.6
199	358 [h]	1 074	21.5	62.4	24.2	10.7	25.8	2.7

[a] $k_1/3 = k_{DA}, k_{DB}, k_{DC}$. [b] $k_{-1} = k_{AD}, k_{BD}, k_{CD}$. [c] $k_2 = k_{AB}, k_{BA}, k_{AC}, k_{CA}, k_{BC}, k_{CB}$. [d] Average value for $\Delta G^\ddagger$ (P $\longrightarrow$ H) = 21.7 kcal mol⁻¹. [e] Average value for $\Delta G^\ddagger$ (H $\longrightarrow$ P) = 24.1 kcal mol⁻¹. [f] Average value for $\Delta G^\ddagger$ (H $\rightleftharpoons$ H*) = 24.6 kcal mol⁻¹. [g] Average value for ΔG° (H $\longrightarrow$ P) = 2.4 kcal mol⁻¹. [h] Values obtained by extrapolation of a ln $(k_1/3)$ *versus* $1/T$ plot to higher temperatures. [i] Values obtained by extrapolation of a ln k_2 *versus* $1/T$ plot to lower temperatures.

Thus, $k_1/3 = k_{DA} = k_{DB} = k_{DC}$ and $k_{-1} = k_{AD} = k_{BD} = k_{CD}$ (see Figure 12). In the case of the $H \rightleftharpoons H^*$ equilibrium, the site-exchange rate constants, k_{AB}, k_{BA}, k_{AC}, k_{CA}, k_{BC}, k_{CB} correspond to the molar rate constant, k_2. Values for the site-exchange rate constants were found (for selected examples, see Figure 3) which gave good agreement between experimental and computed spectra. The site populations used throughout the line-shape analysis were 0.055 for Me_D, 0.315 for Me_A, 0.315 for Me_B, and 0.315 for Me_C. Thus the propeller conformation (64a and b) contributes 5.5% at equilibrium. This proportion is invariant with temperature indicating the absence of any appreciable contribution to the free energy difference between the propeller (64a and b) and helical (63a and b) conformations arising from a difference in entropies. An average value of 2.4 kcal mol⁻¹ for $\Delta G°(H \rightarrow P)$ was obtained using the relationship, $\Delta G°(H \rightarrow P) = RT\ln[P]/[H]$ where R is the gas constant and T is the absolute temperature. Values for k_1, k_{-1}, and k_2, are listed in Table 2. The values for $k_1(P \rightarrow H)$ and $k_2(H \rightleftharpoons H^*)$ were deduced from the site-exchange rate constants. The values for $k_{-1}(H \rightarrow P)$ were obtained from k_1 using the expression $k_1[P] = k_{-1}[H]$. From these rate constants, average values of 21.7 ± 0.3, 24.1 ± 0.4, and 24.6 ± 1.2 kcal mol⁻¹ were obtained (see Table 2) for $\Delta G^{\ddagger}$ (P → H), $\Delta G^{\ddagger}$ (H → P), and $\Delta G^{\ddagger}$ (H ⇌ H*) respectively using the Eyring equation. These values imply that the transition states for P ⇌ H interconversions and H ⇌ H* inversion are very similar in their energetic demands. They are also in agreement with the average value of 2.4 kcal mol⁻¹ previously deduced for the free-energy difference between the helical (63a and b) and propeller (64a and b) conformations. It should also be noted that the average values obtained for $\Delta G^{\ddagger}$ (P → H) and $\Delta G^{\ddagger}$ (H → P) by line-shape analysis are in reasonable agreement with those (21.5 ± 0.5 and 23.0 ± 0.5 kcal mol⁻¹, respectively) calculated from the equilibration experiment described previously.

An understanding of the conformational behaviour of N,N'-dimethyltrianthranilide (5) in solution proved
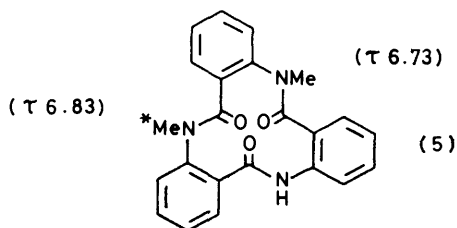
much more difficult to achieve. Two singlets were observed at τ 6.73 and 6.83 for the constitutionally heterotopic N-methyl groups (N-Me and N-Me*) in the ¹H n.m.r. spectrum recorded at room temperature in deuteriochloroform solution. It was possible to make an assignment of these two singlets to the N-Me and N-Me* groups respectively following the observation that only the higher field singlet (τ 6.83) was present in the ¹H

n.m.r. spectrum of N-methyl-N'-trideuteriomethyl-trianthranilide (6). Assuming that N,N'-dimethyl-trianthranilide (5) will adopt only conformations in which the three amide groups have *trans*-geometries then there are *four* possible diastereoisomerically related conformations, (i) a propeller (P) conformation (65a; $R^1 = R^2 =$ Me, $R^3 = $ H) and (ii) three helical conformations which we shall refer to as H-1 (66a; $R^1 = R^2 = $ Me, $R^3 = $ H), H-2 (67a; $R^1 = R^2 = $ Me, $R^3 = $ H), and H-3 (68a; $R^1 = R^2 = $ Me, $R^3 = $ H) according as to whether R^1, R^2, or R^3 in Figure 13 are oriented towards the opposite

P conformation (65a)

H-1 conformation (66a)

H-2 conformation (67a)
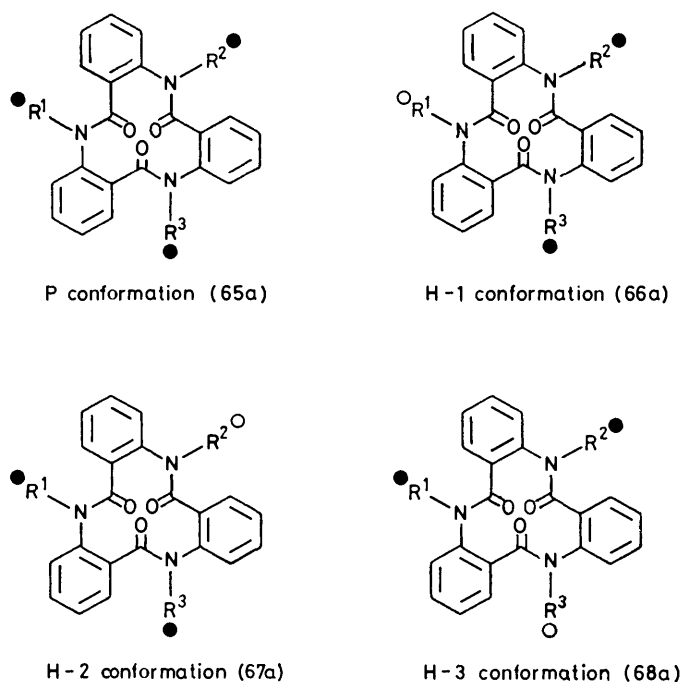
H-3 conformation (68a)

FIGURE 13 The four possible conformational diastereoisomers with *trans*-amide linkages for asymmetrically N,N',N''-trisubstituted trianthranilide derivatives: ● ≡ an R group above the mean plane of the ring and ○ ≡ an R group below the mean plane of the ring

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, four enantiomerically-related conformations (P*, H-1*, H-2*, and H-3*) corresponding to each diastereoisomerically related conformation. A diagrammatic representation of the complete conformational itinerary involving these eight conformations is summarised by the cubic array in Figure 14. The ¹H n.m.r. spectrum of N,N'-dimethyl-trianthranilide (5) in deuteriochloroform–carbon di-sulphide (2 : 1) did not exhibit any temperature dependences other than small chemical shift changes, increased resolution of the NH signal, and a modest amount of line broadening (normally associated with the increase in solvent viscosity) of the other signals on cooling down to −80 °C. Thus, it may be concluded that either (i) any conformational changes which can occur are rapid on the ¹H n.m.r. time scale at −80 °C or (ii) only one of the four possible conformational isomers is populated in solution at low temperatures. Comparison of the chemical shifts
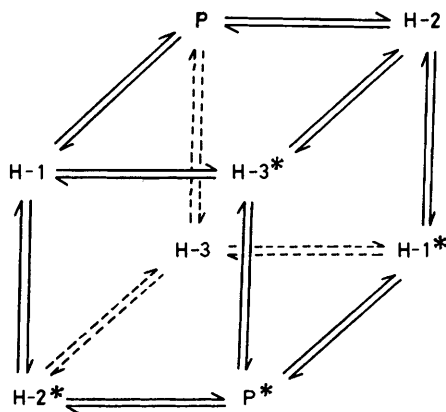
FIGURE 14 Cubic array diagram illustrating the conformational itinerary involving P, P*, H-1, H-1*, H-2, H-2*, H-3, and H-3* conformations of asymmetrically N,N',N''-trisubstituted trianthranilide derivatives

for the N-methyl signals in (5) with those in N,N',N''-trimethyltrianthranilide (7) in deuteriochloroform at ambient temperatures suggests that N,N'-dimethyltrianthranilide (5) prefers to adopt conformations of the helical type shown in Figure 13. Labelling experiments involving N-trideuteriomethylation of N,N'-dimethyl-(5) and N-methyl-N'-trideuteriomethyl- (6) trianthran-

ilide confirmed this belief and demonstrated, moreover, that the helical conformations (see Figure 13 with $R^1 = R^2 = $ Me and $R^3 = $ H) which are appreciably populated in solution are H-1 (66a) and/or H-2 (67a) and their enantiomers H-1* (66b) and/or H-2* (67b). This novel approach to conformational analysis is dependent upon the assumption that trideuteriomethylation of the CONH function in N,N'-dimethyltrianthranilide (5) occurs much faster than does the conformational reorientation of the other two CONMe linkages in (5). T.l.c. analysis indicated that N-trideuteriomethylation of (5) in dimethyl sulphoxide in the presence of sodium hydride and N-trideuteriomethyl iodide is complete in less than 5 min at room temperature. Conformational reorientation of CONMe linkages is associated with a half-life of *ca.* 5 min at room temperature. Since the CONH linkage and its derived anion can probably alter their orientation by means of a pedalling motion, the rate at which this conformational change can occur will be considerably faster than those involving reorientation of the CONMe linkages. We shall assume that the rate of pedalling of a CONH linkage is of the same order as its alkylation rate. Whatever else, N-trideuteriomethylation of N,N'-dimethyltrianthranilide (5) is expected to give information regarding the relative orientations of the CONMe
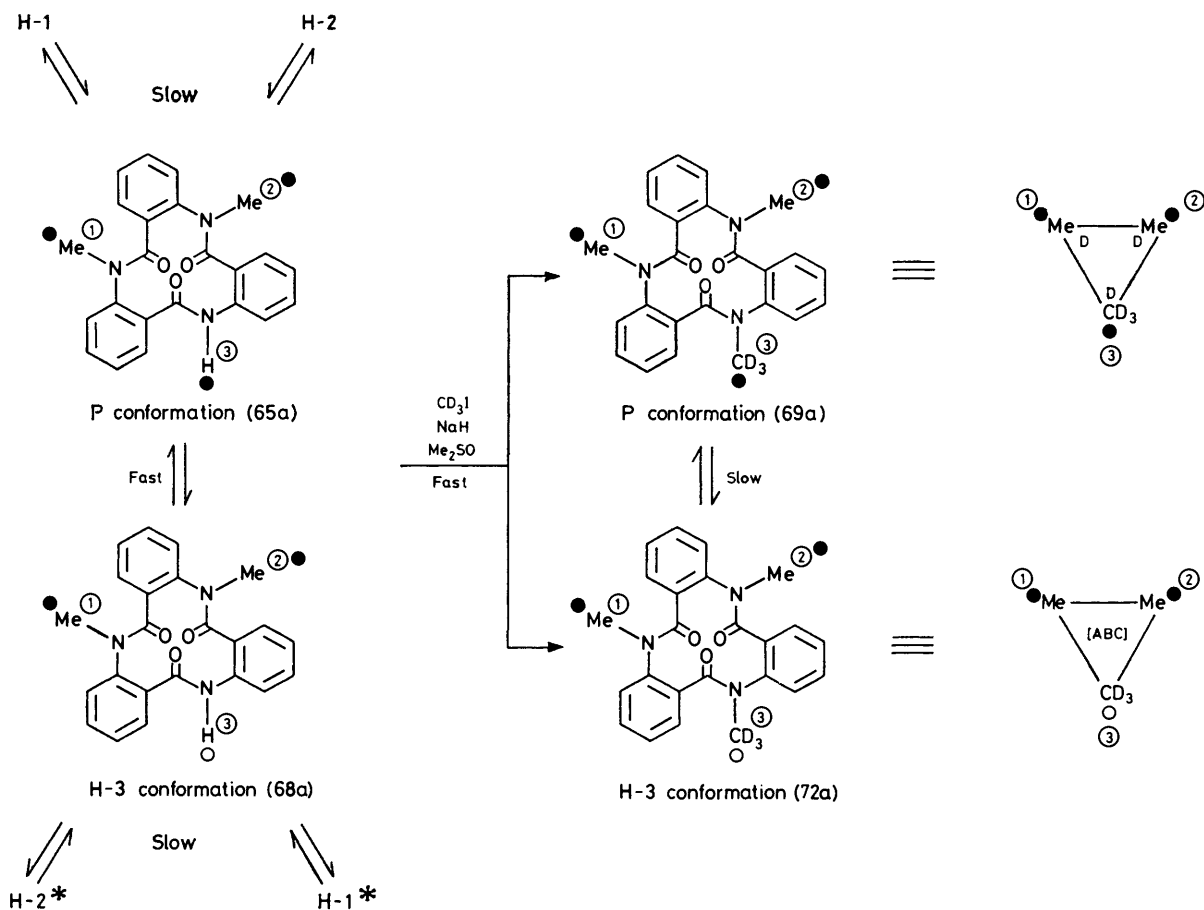

FIGURE 15 N-Trideuteriomethylation of N,N'-dimethyltrianthranilide (5) assuming situation (I) holds. The triangle notation describes the relative orientation (● or ○) of the N-methyl groups with respect to the mean plane of the ring
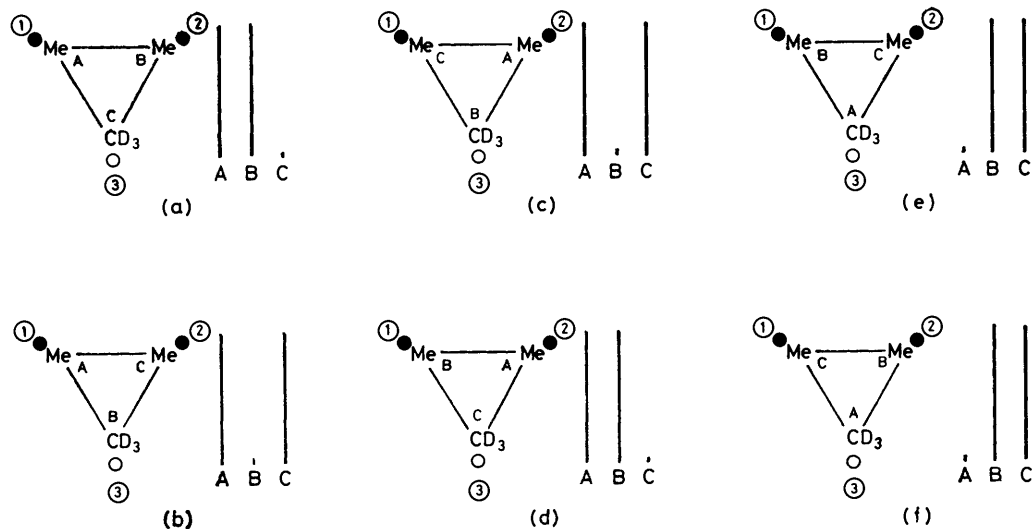
FIGURE 16 The six possible ways [(a)—(f)] of assigning the N-methyl groups in the H-3 conformation (73a) of N,N'-dimethyl-N''-trideuteriomethyltrianthranilide (8) to sites A, B, and C, and the predicted relative intensities of these sites in the ¹H n.m.r. spectrum

linkages. Two situations can be identified: (I) one in which the two N-methyl groups reside on the same side of the 12-membered ring and (II) another in which the two N-methyl groups reside on opposite sides of the 12-membered ring. We shall consider these two situations

in turn. In the case of situation (I), N-trideuterio-methylation of (5) can lead (see Figure 15) to both the propeller (P) conformation (69a) and a helical (H-3) conformation (72a) of N,N'-dimethyl-N''-trideuterio-methyltrianthranilide (8) if the energies of the transition
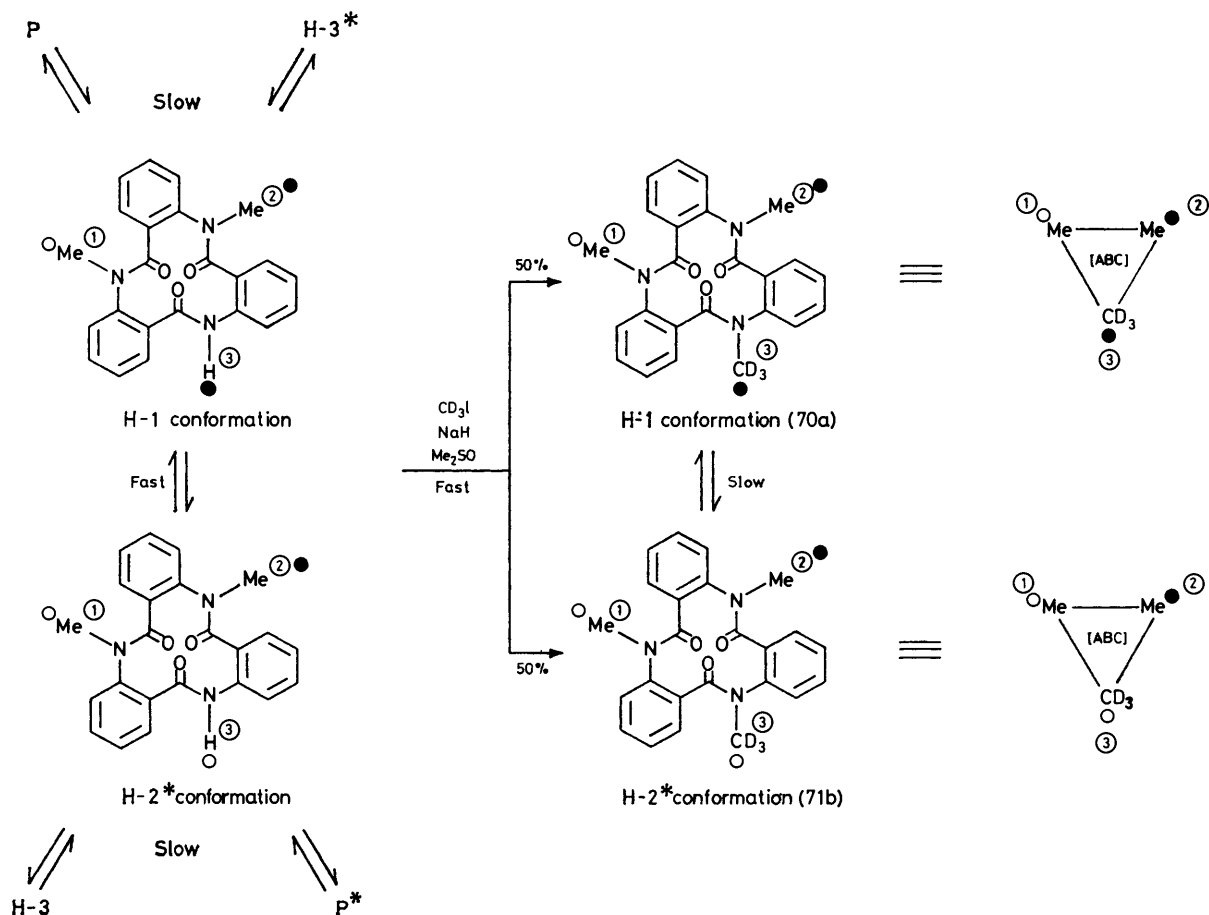

FIGURE 17 N-Trideuteriomethylation of N,N'-dimethyltrianthranilide (5) assuming situation (II) holds

states leading to these conformational diastereoisomers are similar.† The triangular symbolism introduced in Figure 15 provides a diagrammatic representation of the relative orientations of the substituents on nitrogen through the use of the dot (●) and circle (○) notation as well as establishing their constitutional identities with encircled superscripts. Site assignments are recorded inside the triangles. Fortunately, the assignments of the two NMe groups and the NCD_3 group in the P conformation (69a) to site D is a trivial matter. By contrast,

and H-2* (71b), of N,N'-dimethyl-N''-trideuteriomethyltrianthranilide (8) if the energies of the transition states leading to these conformational diastereoisomers are similar.† If we assume as a basis for discussion that the reaction transition states are of equal energy then it follows that equal amounts of the two helical conformations will be formed. Using the triangular symbolism introduced in Figure 15, the assignments of the two NMe groups and the NCD_3 group in the H-1 (70a) and H-2* (71b) conformations to sites A, B, and C can each be
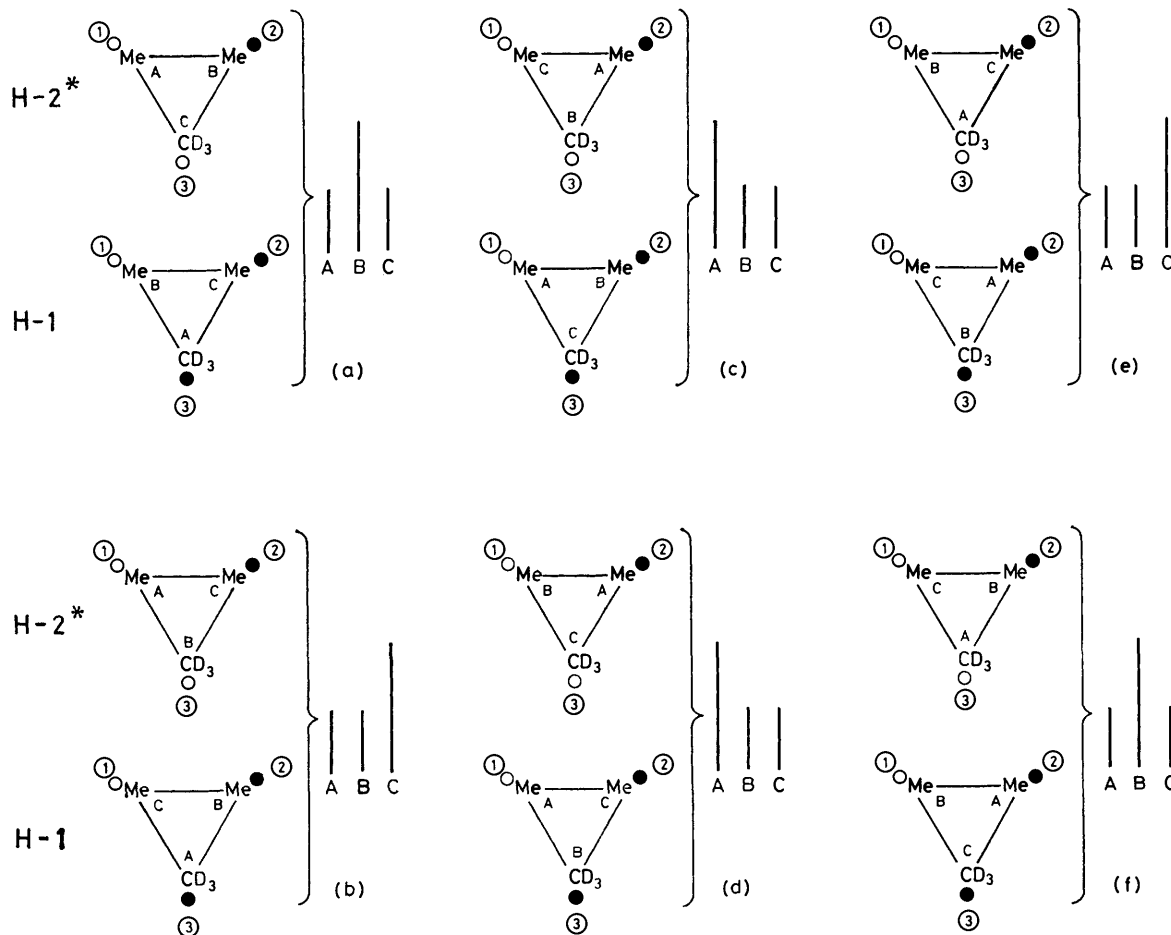

FIGURE 18 The six possible ways [(a)—(f)] of assigning the N-methyl groups in the H-1 (70a) and H-2* (71b) conformations of N,N'-dimethyl-N''-trideuteriomethyltrianthranilide (8) to sites A, B, and C, and the predicted relative intensities of the associated signals in the ^1H n.m.r. spectrum

the assignment of these same groups in the H-3 conformation (72a) to sites A, B, and C can be made in *six* different ways and these are shown in Figure 16. The predicted consequences of these six assignments upon the relative intensities in the ^1H n.m.r. spectrum of the signals associated with these three sites are also illustrated diagrammatically in Figure 16. These predictions are made on the basis of the idealised assumption that there is no conformational scrambling of the NCD_3 group with the two NMe groups during the course of the reaction and/or the isolation of the product. In the case of situation (II), N-trideuteriomethylation of (5) can lead (see Figure 17) to two helical conformations, H-1 (70a)

made in six different ways. These are presented in pairs in Figure 18 and the predicted consequences of the six assignments upon the relative intensities in the ^1H n.m.r. spectrum of the signals associated with these three sites are also illustrated diagrammatically in this Figure. Once again, these predicted relative intensities are made on the basis of the idealised assumption that there is no conformational scrambling of the NCD_3 group with the

† The statement assumes that conformational interconversion of the substrate is occurring more rapidly than reaction of the substrate. If this is the case, the product ratio is determined by the relative heights of the reaction barriers, *i.e.* the Curtin–Hammett principle [34] is operating.
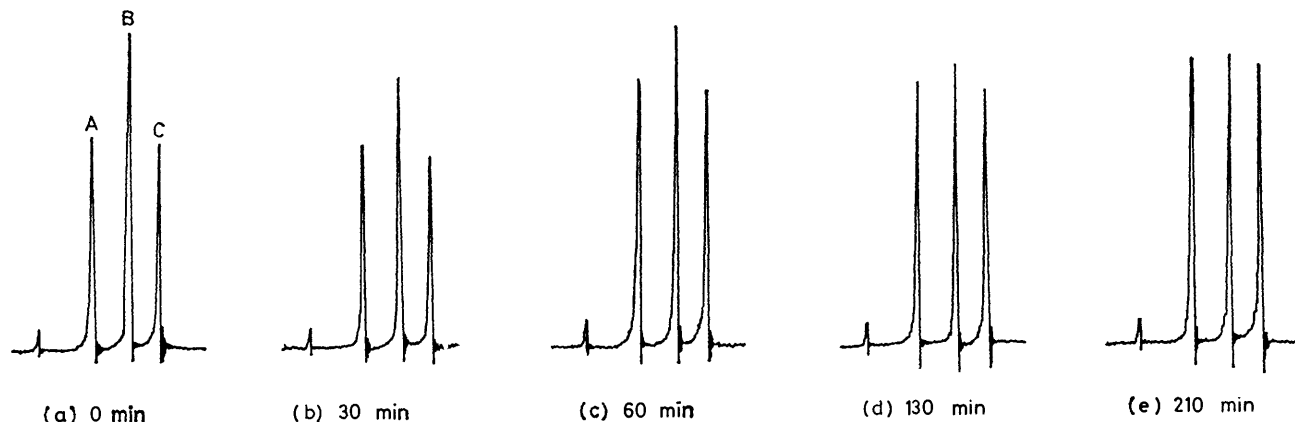
FIGURE 19 The equilibration in deuteriochloroform solution at $+30$ °C of the NCD_3 and NMe groups of N,N'-dimethyl-N''-trideuteriomethyltrianthranilide (8) between sites A, B, and C: (a) At 0 min; (b) at 30 min; (c) at 60 min; (d) at 130 min; (e) at 210 min. The rate of equilibration of the NCD_3 group was calculated to be 2.2×10^{-4} s^{-1} using an expression analogous to that given in equation (3). This rate constant corresponds at $+30$ °C to a $\Delta G^{\ddagger}$ value of 22.7 kcal mol^{-1} which is in good agreement with $\Delta G^{\ddagger}$ values obtained by other methods for conformational changes of N,N',N''-trimethyltrianthranilide (7) in deuteriochloroform solution

two NMe groups during the course of the reaction and/or isolation of the product.

When the ^{1}H n.m.r. spectrum of the derived N,N'-dimethyl-N''-trideuteriomethyltrianthranilide (8) was recorded *immediately* after dissolution in deuteriochloroform at $+30$ °C, three singlets for the N-methyl groups in the helical conformations were observed and they had the relative intensities of 29 : 42 : 29 for Me$_A$: Me$_B$: Me$_C$. The subsequent equilibration of the NCD_3 group between sites A, B, and C was followed (see Figure 19) by ^{1}H n.m.r. spectroscopy. The initially observed pattern of relative intensities for Me$_A$, Me$_B$, and Me$_C$ immediately excludes the P (65a and b) and H-3 (68a and b) conformations of N,N'-dimethyltrianthranilide (5) associated with situation (I) from further consideration. It follows, therefore that (5) populates either the H-1 (66a and b) or H-2 (67a and b) conformations or both these helical conformations in solution. On recrystallisation from p-dioxan, N,N'-dimethyltrianthranilide (5) gave single crystals which were suitable for X-ray crystallographic investigation.[23] The crystal structure (see Figure 20) reveals that this compound adopts either a distorted H-1 (66a) or a distorted H-1* (66b) conform-
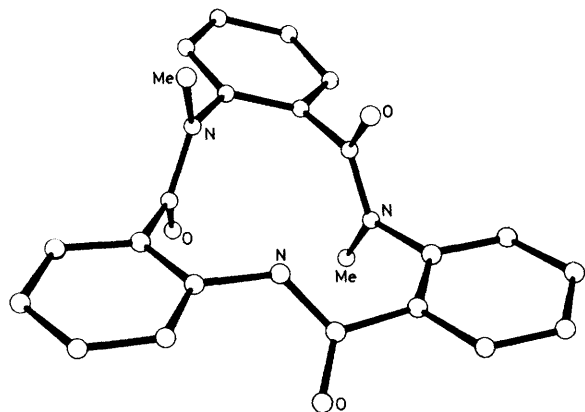

FIGURE 20 The structure of N,N'-dimethyltrianthranilide (5) in the solid state [23]

ation in the solid state. Returning to the conformational behaviour of (5) in solution, it is obvious that only patterns (a) and (f) under situation (II) in Figure 18 are compatible with the observed ^{1}H n.m.r. spectra recorded in Figure 19. The initial relative intensities of 29 : 42 : 29
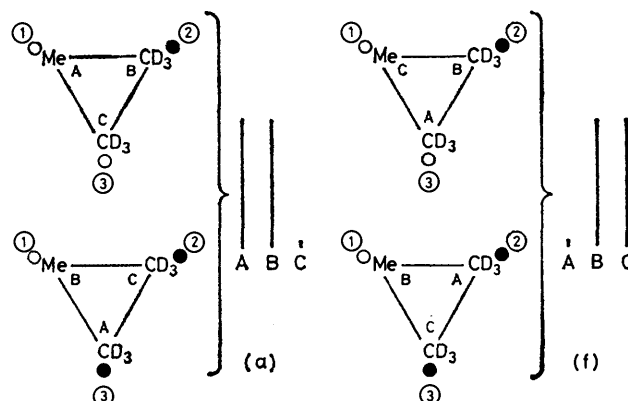

FIGURE 21 The two possible ways [(a) and (f)] of assigning the N-methyl group in the H-1 and H-2* conformations of N-methyl-N',N''-ditrideuteriomethyltrianthranilide (9) to sites A, B, and C and the predicted relative intensities of the associated signals in the ^{1}H n.m.r. spectrum

for Me$_A$: Me$_B$: Me$_C$ indicate (i) that some equilibration of the NCD_3 group within sites A, B, and C occurs either during N-trideuteriomethylation of (5) or during the isolation of (8), and (ii) that the transition-state energy levels leading to the formation of the H-1 (70a and b) and H-2 (71a and b) conformations of (8) are associated with the same barrier heights within experimental error. It is possible to differentiate between the site assignments (a) and (f) in Figure 18 on the basis of an experiment involving N-trideuteriomethylation of N-methyl-N'-trideuteriomethyltrianthranilide (6) to give N-methyl-N',N''-di(trideuteriomethyl)trianthranilide (9). Figure 21 summarises the predicted consequences of these two site assignments upon the relative intensities of sites A, B, and C in the ^{1}H n.m.r. spectrum of (9) obtained on N-trideuteriomethylation of (6) with the established assump-
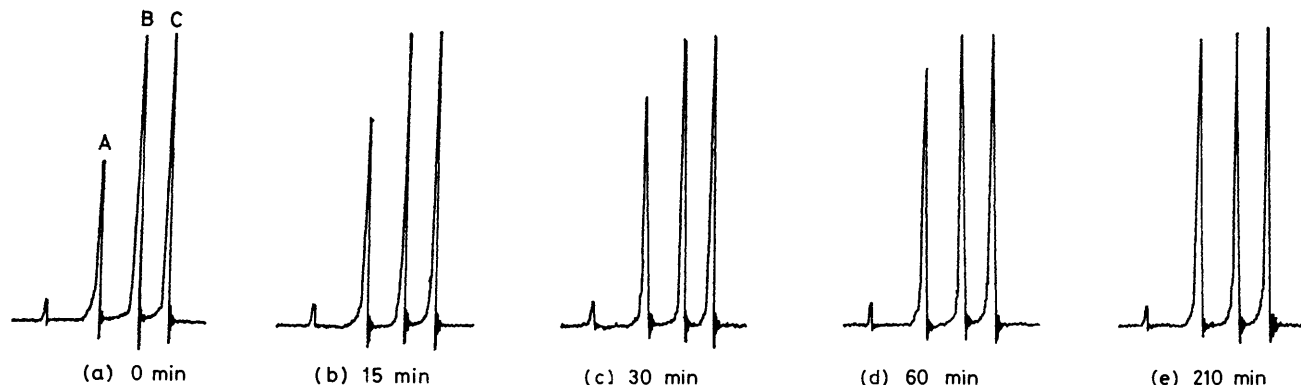
FIGURE 22 The equilibration in deuteriochloroform solution at $+30$ °C of the NCD_3 and NMe groups of N-methyl-N',N''-ditrideuteriomethyltrianthranilide (9) between sites A, B, and C: (a) At 0 min; (b) at 15 mins; (c) at 30 min; (d) at 60 min; (e) at 210 min. The rate of equilibration was calculated to be 2.4×10^{-4} s^{-1} using an expression analogous to that given in equation (3). This rate constant corresponds at $+30$ °C to a $\Delta G^{\ddagger}$ value of 22.6 kcal mol^{-1} which is in good agreement with $\Delta G^{\ddagger}$ values obtained by other methods for conformational changes of N,N',N''-trimethyltrianthranilide (7) in deuteriochloroform solution

tions operating. When the ^{1}H n.m.r. spectrum of N-methyl-N',N''-di(trideuteriomethyl)trianthranilide (9) was recorded *immediately* after dissolution in deuteriochloroform at $+30$ °C, three singlets for the N-methyl groups of the helical conformations were observed and they had the relative intensities of 22 : 39 : 39 for Me$_A$: Me$_B$: Me$_C$. The subsequent equilibration of the two N-trideuteriomethyl groups between sites A, B, and C was followed (see Figure 22) by ^{1}H n.m.r. spectroscopy. The initial relative intensities of 22 : 39 : 39 confirmed (i) that some equilibration of the NCD_3 groups within sites A, B, and C occurs either during N-trideuteriomethylation or during isolation of (9) and (ii) that the transition-state energy levels leading to the formation of the H-1 and H-2 conformations are associated with the same barrier heights within experimental error. The fact that the initially observed pattern (see Figure 22) of relative intensities for Me$_A$, Me$_B$, and Me$_C$ arises from site assignment (f) in Figure 21 permits an unambiguous assignment of sites A, B, and C to be made to the three diastereotopic N-methyl groups in the helical conformations (63a and b) of N,N',N''-trimethyltrianthranilide (7). The influence of stepwise additions of tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium (III) [Eu(fod)$_3$] to a deuteriochloroform solution of

H conformation (63a)
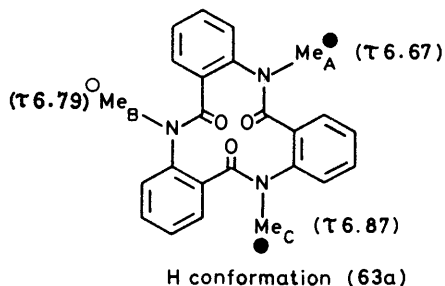
N,N',N''-trimethyltrianthranilide (7) upon the chemical shifts of the N-methyl groups in the ^{1}H n.m.r. spectrum may be interpreted in terms of the above assignment. The singlets for the two N-methyl groups in sites A and C

on the same side of the 12-membered ring in the helical conformations (63a and b) are shifted downfield to a much greater extent (see Figure 23) than is the singlet for the third N-methyl group in site B on the opposite side of the ring. Interestingly, the proportion of the propeller
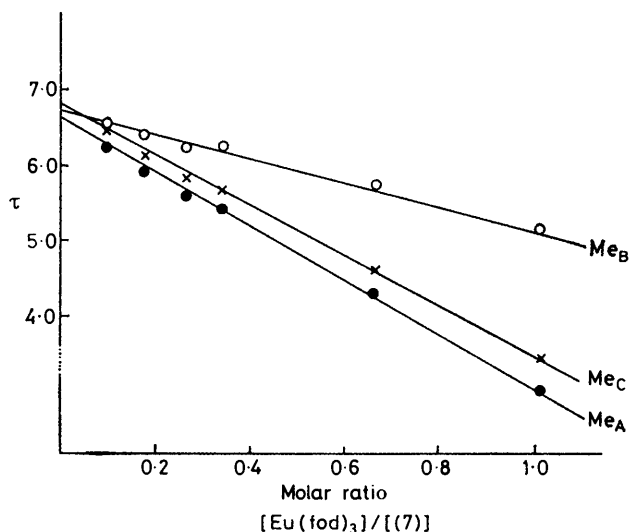

FIGURE 23 The effect of the addition of the chemical-shift reagent, Eu(fod)$_3$, to a deuteriochloroform solution of N,N',N''-trimethyltrianthranilide (7) upon the chemical shifts of the three N-methyl signals arising from Me$_A$, Me$_B$, and Me$_C$ in the helical conformation (63)

(64a and b) to helical (63a and b) conformations is not altered by complex formation between (7) and [Eu(fod)$_3$]. In the case of the helical conformation (63a and b), it would appear that the chemical-shift reagent complexes preferentially with the face carrying two N-methyl and one carbonyl groups rather than with the face carrying one N-methyl and two carbonyl groups.

In addition to defining its solid-state conformation (see Figure 20), the X-ray crystal-structure investigation [23] of N,N'-dimethyltrianthranilide (5) also revealed that this compound crystallises from both ethanol and p-dioxan in a noncentrosymmetric space group ($P2_1$)

which contains molecules of one chirality only, *i.e.* it undergoes spontaneous resolution, *cf.* tri-*o*-thymotide (73) and tri-6-methylthiosalicylide (74).[1,31] This result was

	X	R³	R⁶
(73)	O	CHMe₂	Me
(74)	S	Me	Me
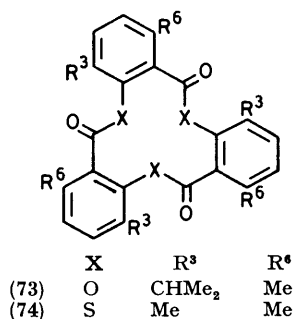
confirmed by polarimetric examination of sufficiently large single crystals of *N*,*N*'-dimethyltrianthranilide (5) obtained on recrystallisation from toluene. Both dextrorotatory and laevorotatory single crystals were identified on recrystallisation. Immediately upon dissolution of a selected single crystal in chloroform, the solution exhibited optical activity which diminished rapidly as a result of racemisation of (5). Indeed, at room temperature, racemisation was complete within *ca.* 10 min. The opportunity was taken to obtain a $\Delta G^{\ddagger}$ value for the conformational inversion process in *N*,*N*'-dimethyltrianthranilide (5) by following the rate of racemisation of a hand-picked crystal in chloroform. This situation is a particularly fortunate one since dynamic n.m.r. spectroscopy could not be used to probe the H $\rightleftharpoons$ H* inversion barrier in (5). The rate of racemisation of *N*,*N*'-dimethyltrianthranilide (5) was determined in chloroform solution at +2 °C on a Perkin-Elmer 141 automatic polarimeter equipped with a Hitachi recorder. The decay in the optical activity of the solution measured at the sodium D-line over a 50-min period was followed. Table 3 records the change in optical rotation, α_t, with time, *t*, for a 0.142% solution. Racemisation is a

TABLE 3

The change in the optical rotation, α_t, at the sodium D-line with time, *t*, and values for α_0/α_t and log (α_0/α_t) for the racemisation of a single crystal of *N*,*N*'-dimethyltrianthranilide (5) in a 0.142% chloroform 'solution examined in a 1 dm cell

t/min	α_t	α_0/α_t	log (α_0/α_t)
0	0.123 ᵃ	1.00	0.000
2	0.118	1.04	0.017
4	0.113	1.09	0.037
6	0.108	1.14	0.057
8	0.104	1.18	0.072
12	0.095	1.295	0.112
16	0.084	1.46	0.164
18	0.079	1.56	0.193
20	0.075	1.64	0.215
24	0.069	1.78	0.250
28	0.062	1.99	0.299
32	0.056	2.20	0.342
36	0.051	2.41	0.382
40	0.047	2.62	0.418
44	0.043	2.86	0.456
50	0.037	3.32	0.521

ᵃ Obtained by extrapolation of the exponential curve obtained on plotting α_t against *t*.

reversible first-order process [35] involving the dextrorotatory and laevorotatory forms in an equilibration where the forward and reverse rate constants are equal. A value for this rate constant, *k*, was obtained by employing the usual expression (4) for a reversible first-order process

$$\log \frac{\alpha_0}{\alpha_t} = \frac{2k}{2.303} \, t \, \ldots \tag{4}$$

between enantiomeric species. A value for α_0, the original rotation, was deduced from extrapolation to *t* = 0 of the exponential curve obtained on plotting α_t against *t*. This value (α_0 = +0.123°) was used to calculate a value of +87° for the specific rotation of the particular dextrorotatory single crystal selected for the kinetic experiment. The rate constant, *k*, was calculated from the slope of a plot (see Figure 24) of log (α_0/α_t)
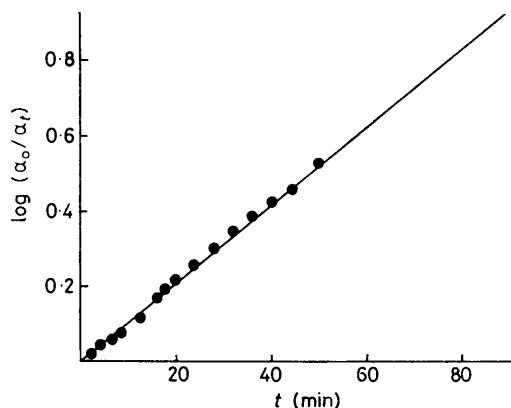

FIGURE 24 A plot of log (α_0/α_t) against time *t* for the racemisation of *N*,*N*'-dimethyltrianthranilide (5) in chloroform solution at +2 °C

against *t* by reference to equation (4). The value of 2.0×10^{-4} s⁻¹ for *k* was used to obtain the half-life time, $t_{\frac{1}{2}}$, of the racemisation from the usual expression (5):

$$t_{\frac{1}{2}} = \frac{2.303}{2k} \log 2 \, \ldots \tag{5}$$

The $\Delta G^{\ddagger}_{rac}$ value was calculated using the Eyring equation. At +2 °C, $t_{\frac{1}{2}}$ was found to be 28.9 min and the $\Delta G^{\ddagger}_{rac}$ value, 20.7 kcal mol⁻¹. This value for the free energy of racemisation is undoubtedly associated with an H $\rightleftharpoons$ H* ring-inversion process and provides evidence that the ring inversion (see Figure 14) between H-1 and H-1* (66a and b) and/or H-2 and H-2* (67a and b) ground-state conformations involving P (65a and b) and H-3 (68a and b) intermediates is a relatively slow conformational change which is associated with the reorientation of two CONMe linkages and one CONH linkage, *i.e.* R¹ = R² = Me and R³ = H in Figures 13 and 14.

The Conformational Behaviour of N,N'-*Dibenzyl-* (14) *and* N,N',N''-*Tribenzyl-* (15) *trianthranilides.*—By analogy with *N*,*N*'-dimethyltrianthranilide (5), the *N*,*N*'-dibenzyl derivative (14) could adopt conceivably as ground-state conformations up to four enantiomeric pairs of diastereoisomerically related conformations,

namely a propeller (P/P*) conformation (65a and b) and three helical conformations, H-1/H-1* (66a and b), H-2/H-2* (67a and b), and H-3/H-3* (68a and b), where $R^1 = R^2 = CH_2Ph$ and $R^3 = H$ in Figure 13. The cubic array presented in Figure 14 summarises all the possible pathways for inversions and interconversions between these eight conformations.

The ^1H n.m.r. spectrum of N,N'-dibenzyltrianthranilide (14) showed (Figure 25) two overlapping AB systems in the range τ 4.88 to 5.66 for the constitutionally heterotopic benzylic methylene groups in deuteriochloroform solution at room temperature. No significant change

the assignment of one AB system (A1B1) directly and the assignment of the other AB system (A2B2) by exclusion. They also demonstrate that the geminal coupling constants are actually negative. A comparison of the chemical shifts (see Table 12) of the AB systems arising from the benzylic methylene protons in N,N'-dimethyl-N''-benzyltrianthranilide (12), N,N'-dibenzyl-N''-methyltrianthranilide (16), and N,N',N''-tribenzyltrianthranilide (15) suggests that N,N'-dibenzyltrianthranilide (14) adopts a helical conformation in solution. Moreover, the fact (i) that (14) affords helical conformations of N,N'-dibenzyl-N''-methyltrianthranilide (16) as
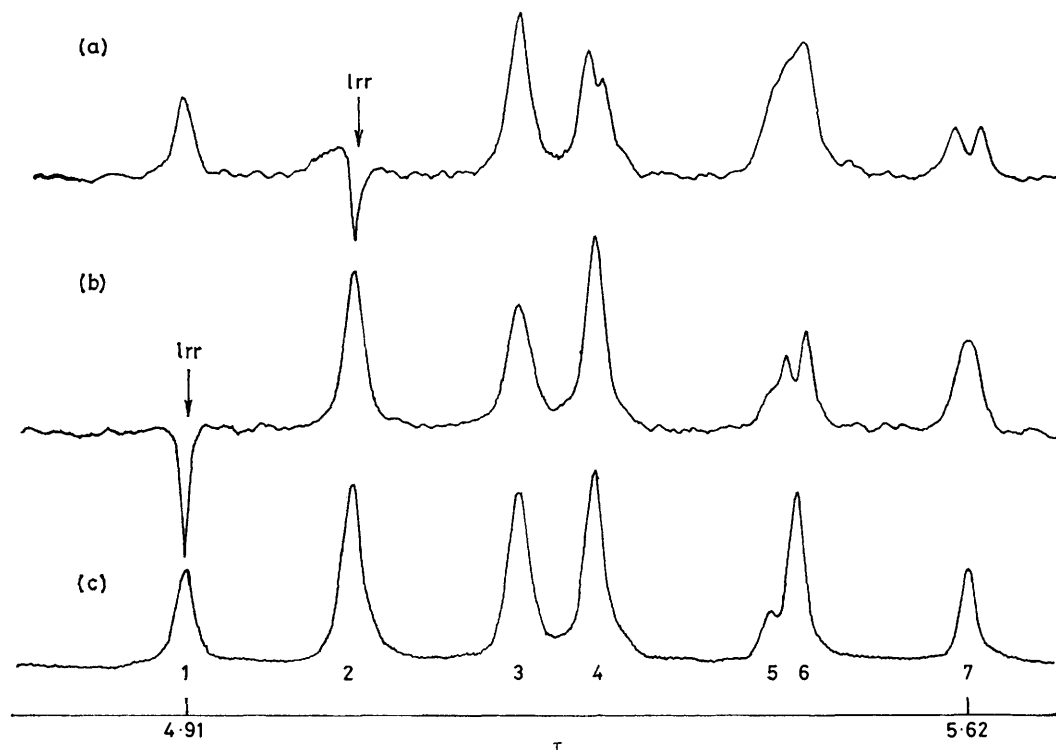

FIGURE 25 The signals in the ^1H n.m.r. spectrum for the benzylic-methylene protons of N,N'-dibenzyltrianthranilide (14) dissolved in deuteriochloroform. (a) and (b) show the results of spin-tickling experiments and (c) the normal spectrum

was observed on cooling a deuteriochloroform–carbon disulphide (2 : 1) solution down to —70 °C. Thus, it may be concluded that either (i) any conformational changes which can occur are rapid on the ^1H n.m.r. time scale at —70 °C, or (ii) only one of the four possible conformational diastereoisomers is populated in solution. On careful inspection of the spectra (Figure 25) obtained in deuteriochloroform solution, two AB systems were identified ($τ_{A1} = 5.00$, $τ_{B1} = 5.54$, $J_{A1B1} = 14.7$ Hz; $τ_{A2} = 5.17$, $τ_{B2} = 5.33$, $J_{A2B2} = 14.8$ Hz) for the benzylic methylene protons on the basis of a conventional spectral analysis paying particular attention to relative peak areas. This assignment of the two AB systems associates A1B1 with peaks 1, 2, 6, and 7 and A2B2 with peaks 2, 3, 4, and 5 in Figure 25 and was confirmed by spin-tickling experiments. Irradiation of peak 1 caused peak 6 to be split into a doublet. Irradiation of peak 2 caused peak 7 to be split into a doublet. These observations confirm

the kinetically controlled products on methylation (see p. 1687 and also (ii) that (14) affords the helical conformation of N,N',N''-tribenzyltrianthranilide (15) as the kinetically-controlled product on benzylation (see 1685) is consistent with the proposal that the N,N'-dibenzyl derivative (14) adopts a helical conformation with the two N-benzyl groups on opposite sides of the mean ring plane. An X-ray crystal structure analysis has shown (see Figure 26) that N,N'-dibenzyltrianthranilide (14) adopts a helical conformation of this type in the solid state. Indeed, in common with N,N'-dimethyltrianthranilide (5), it exists as a distorted H-1 (H-1*) conformation (66a and b in Figure 13). However, in this case the crystals belong to a centrosymmetric space group (P_{2_1}/a) and so a single crystal of N,N'-dibenzyltrianthranilide (14) obtained from toluene solution was found to be optically inactive immediately after dissolution in chloroform. Interestingly, these crystals were found to contain trapped toluene

molecules which could be removed *in vacuo*. This suggests that (14) like tri-*o*-thymotide [36] (73) has the ability to form inclusion complexes in the solid state.
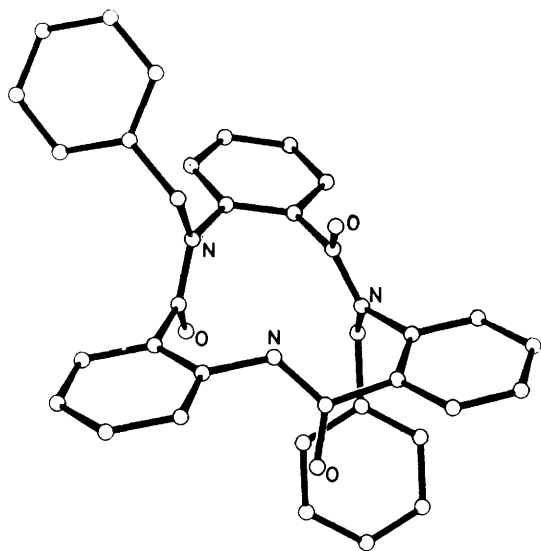

FIGURE 26 The structure of *N*,*N*'-dibenzyltrianthranilide (14) in the solid state [23]

Although the kinetics of the H ⇌ H* inversion process in solutions of *N*,*N*'dibenzyltrianthranilide (14) are not amenable to investigation by polarimetry, the presence of two benzylic methylene groups provide the necessary prochiral probes to permit the study of the kinetics of this inversion process by dynamic ¹H n.m.r. spectroscopy. The temperature dependence of the ¹H n.m.r. spectra of (14) was investigated in hexadeuterio-dimethyl sulphoxide solution. The two AB systems

observed at room temperature coalesce (Figure 7) to give a broad singlet on heating the solution up to +183 °C. This observation is consistent with H ⇌ H* ring inversion becoming rapid on the ¹H n.m.r. time scale at high temperatures. Since the two *N*-benzyl groups in *N*,*N*'-dibenzyltrianthranilide (14) are constitutionally heterotopic, the two AB systems for the benzylic-methylene protons might be expected to coalesce into two singlets at high temperatures. The fact that they tend to coalesce into only one broad singlet can be explained in terms of accidental chemical shift equivalence of the protons in the two benzylic methylene groups. When line-shape analysis was carried out (Figure 7), rate constants were obtained at five different temperatures which yielded an average $\Delta G^{\ddagger}$ value of 22.6 ± 0.3 kcal mol⁻¹ for the H ⇌ H* ring inversion process. Thus, as in the case of the *N*,*N*'-dimethyl derivative (5), *N*,*N*'-dibenzyltrianthranilide (14) undergoes slow ring inversion between H-1 and H-1* (66a and b) or H-2 and H-2* (67a and b) ground-state conformations and involves P (65a and b) and H-3 (68a and b) intermediates in a conformational itinerary (see Figure 14) that involves re-orientation of two CONCH₂Ph linkages and one CONH linkage (see Figure 13 where R¹ = R² = PhCH₂ and R³ = H).

N,*N*',*N*''-Tribenzyltrianthranilide (15) was prepared by benzylation (PhCH₂Br) of *N*,*N*'-dibenzyltrianthran-ilide (14) at room temperature in tetrahydrofuran in the presence of sodium hydride as base. The reaction was followed (see Figure 27) by t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant. During the first 30 min, two products were formed, a major component migrating slower than the starting material and a minor component migrating faster than
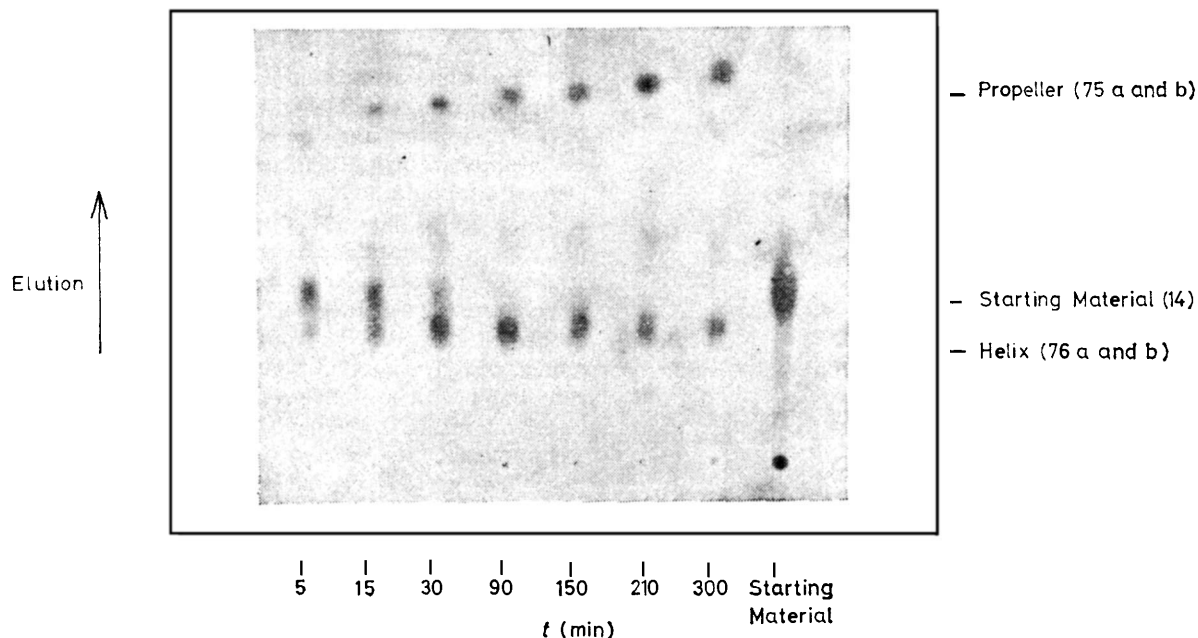

FIGURE 27 A photograph of a thin layer chromatogram showing the progress of the benzylation of *N*,*N*'-dibenzyltrianthranilide (14) with time

the starting material. After 90 min, all the starting material had reacted and the relative proportions of the two components were qualitatively unchanged. However, during the following 3.5 h, equilibration took place until an equilibrium was reached where the proportion of the faster-migrating component exceeded that of the slower migrating component. When the reaction was repeated on a large scale at 0 °C and followed by t.l.c. as described above, the same phenomenon, where the slower-migrating component corresponds to a product formed under kinetic control and the faster-migrating component corresponds to the product formed under thermodynamic control, was clearly evident. The two components were separated as crystalline compounds by preparative t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant and cooled (to 0 °C) chloroform to extract the product from the stationary phase. Complete equilibration of both products to afford the same equilibrium mixture was achieved by refluxing the two pure compounds in separate experiments in chloroform solutions for 30 min. The faster-migrating component on t.l.c. could also be isolated from the crude reaction mixture as a pure crystalline compound by slow crystallisation from light petroleum (b.p. 60—80 °C). It had a melting-point of 260—263 °C whereas the other pure compound melted at 134—144 °C before resolidifying and melting again at 260—263 °C.

The ^{1}H n.m.r. spectra of both crystalline compounds were examined (see Figure 28 for partial spectra) immediately after dissolution in deuteriochloroform at room temperature. The compound with m.p. 260—263 °C

corresponding to the faster migrating component on t.l.c. exhibited *one* AB system ($\tau_A = 3.96$, $\tau_B = 5.32$, $J_{AB} = 14.4$ Hz) for the benzylic-methylene protons. The compound with m.p. 134—144 °C corresponding to
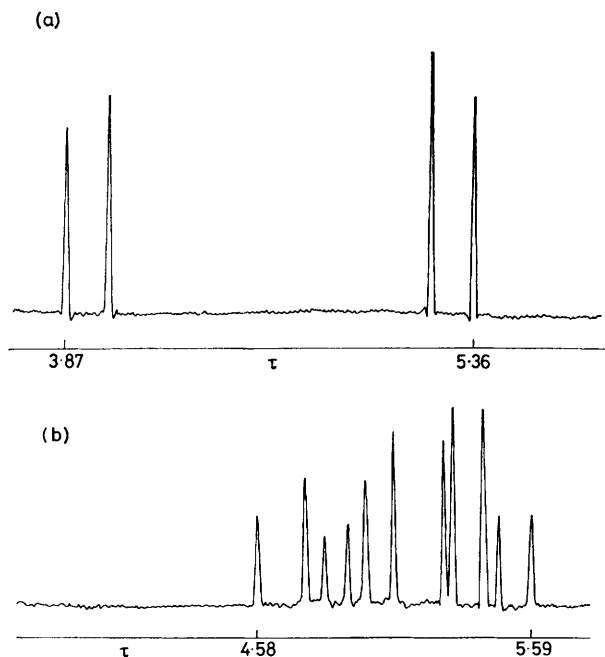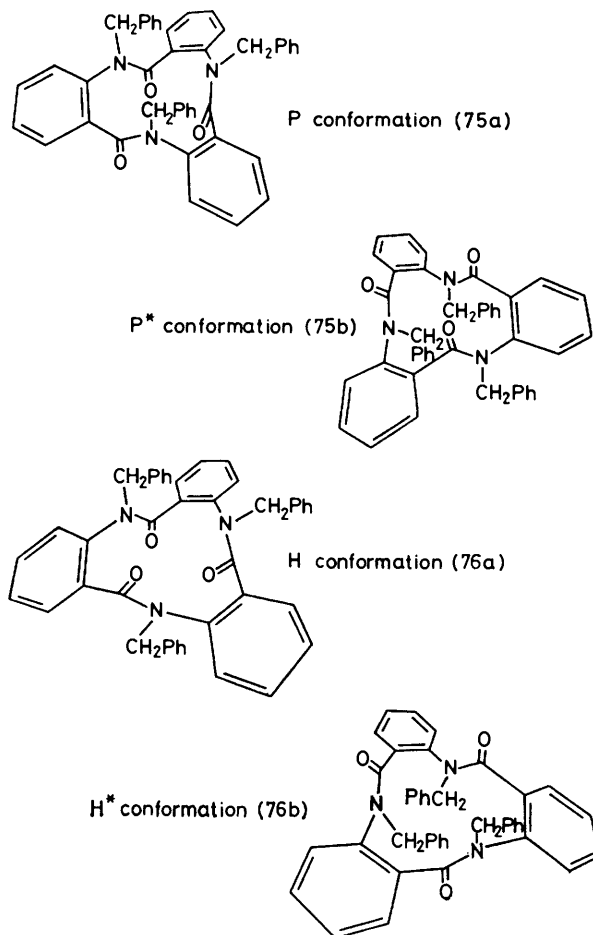

the slower-migrating component on t.l.c. exhibited a complex array of signals which could be associated with *three* overlapping AB systems of equal intensities between τ 4.58 and 5.59 for the benzylic methylene protons. This compound contained a molar equivalent of ethanol which it must have included from the 2% of alcohol present as a stabiliser in the chloroform which was employed in the isolation of the compounds from the silica gel after preparative t.l.c. The benzylic methylene groups of the propeller conformations (75a and b) are homotopic on account of their C_3 symmetries. Thus, the compound with m.p. 260—263 °C corresponding to the faster-migrating component on t.l.c. and giving only one AB system in its ^{1}H n.m.r. spectrum for the benzylic methylene protons, can be assigned to the propeller conformations (75a and b). The benzylic methylene groups in the asymmetrical helical conformations (76a and b) are stereoheterotopic. Thus, the compound with m.p. 134—144 °C corresponding to the slower-migrating component on t.l.c. and giving three AB systems in its ^{1}H n.m.r. spectrum for the benzylic methylene protons, can

FIGURE 28 The partial ^{1}H n.m.r. spectra recorded in deuteriochloroform showing the signals for the benzylic-methylene protons in (a) the propeller (75a and b) and in (b) the helical (76a and b) conformations of N,N',N''-tribenzyltrianthranilide (15)

be assigned to the helical conformations (76a and b). It is evident that the helical conformations (76a and b) of N,N,N''-tribenzyltrianthranilide (15) are formed under kinetic control during benzylation of N,N'-dibenzyl-trianthranilide (14). This implies that (14) exists in a helical conformation with the two N-benzyl groups residing on opposite sides of the mean plane of the 12-membered ring leaving the $-CONH-$ linkage to become

linkages. Thus, it is not surprising that the barriers to conformational changes in N,N',N''-tribenzyltrian-thranilide (15) are high. In fact, they are sufficiently high to permit the isolation of conformational diastereo-isomers as crystalline compounds. In order to obtain quantitative information about these barriers from dynamic ^1H n.m.r. spectroscopy, it appeared to be necessary at the outset to be able to assign the signals
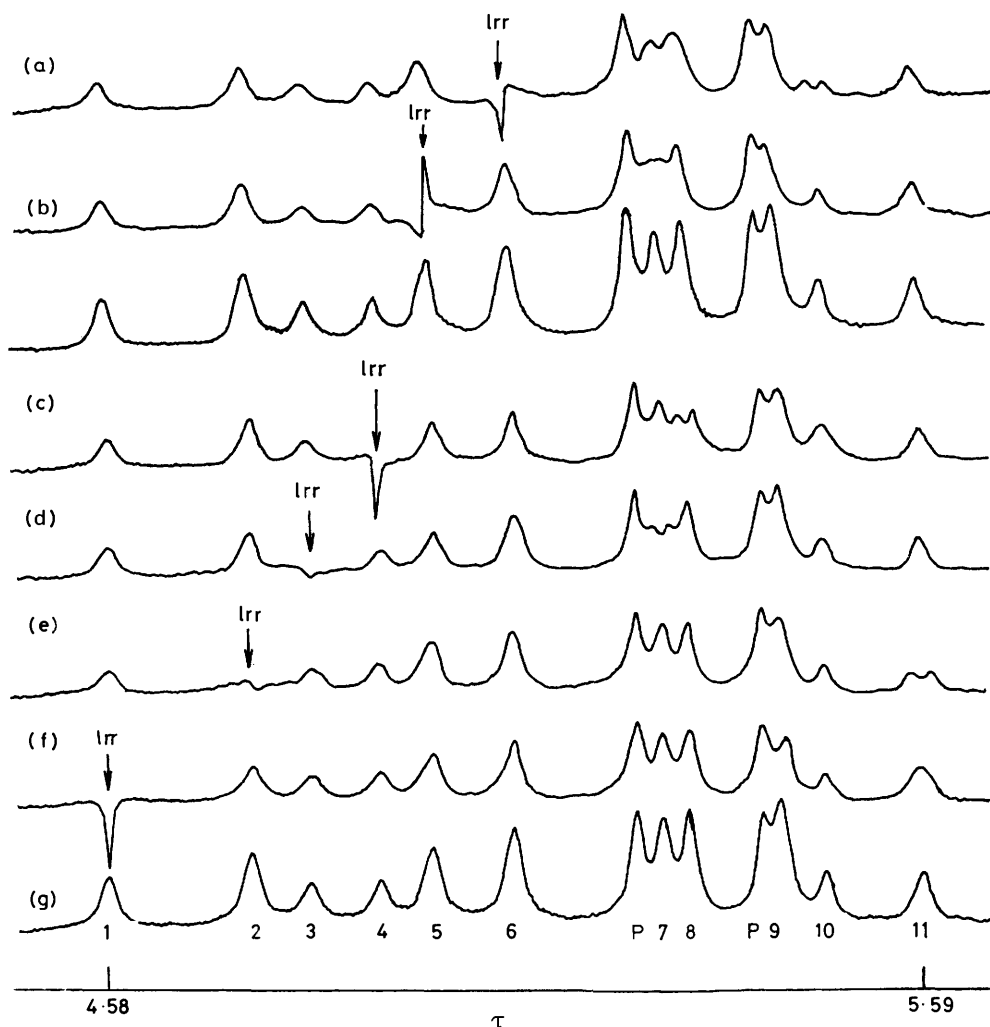

Figure 29　The spin-tickling experiments (a)—(g) on the partial ^1H n.m.r. spectrum of N,N',N''-tribenzyltrianthranilide (15) which allow assignments to be made to the three AB systems associated with the helical conformations (76a and b)

N-benzylated on either side of this plane and still give rise to N,N',N''-tribenzyltrianthranilide (15) in its helical conformations (76a and b). Clearly, the propeller conformations (75a and b) of N,N',N''-tribenzyltrian-thranilide (15) are then obtained under thermodynamic control from the helical conformations (76a and b) by conformational interconversions according to the following scheme:

$$P\ (75a) \rightleftharpoons H\ (76a) \rightleftharpoons H^*\ (76b) \rightleftharpoons P^*\ (75b)$$

Each interconversion and inversion process implied by this scheme involves reorientations of the $CONCH_2Ph$

for the benzylic-methylene protons in the helical conformations (76a and b) to the three anisochronous AB systems in Figure 28. Spin tickling was once again successful in finding a solution to this problem. The results are summarised in Figure 29. The sample which was employed in the spin-tickling experiments was partially equilibrated and so contains some of the propeller conformations (75a and b). The two peaks arising from the B part of the propeller AB system are identified by the descriptor P in Figure 29. The other peaks are identified by numbers 1—11 demonstrating that eleven out of the twelve possible peaks for the three

AB systems of the helical conformations (76a and b) can be identified. The results of irradiation of peaks 1 to 6 in turn showed convincingly (Figure 29) that peaks 1, 2, 9, and 11 are associated with one AB system (A1B1), peaks 3, 5, 7, and 9 with a second AB system (A2B2), and peaks 4, 6, 8, and 10 with a third AB system (A3B3). The chemical shifts and coupling constants for these three AB systems are summarised in Table 4, and identified in

TABLE 4

The chemical shifts and coupling constants for the AB systems associated with the benzylic-methylene protons in the ^{1}H n.m.r. spectrum recorded in deuterio-chloroform at ambient temperature arising from the propeller (75a and b) and helical (76a and b) conform-ations of N,N',N''-tribenzyltrianthranilide (15)

Conformation	AB system	τ_A	τ_B	J_{AB}
			Chemical shifts and coupling constants (Hz)	
P/P* (75a and b)	AB	3.96	5.32	14.4
H/H* (76a and b)	A1B1	4.67	5.50	16.4
	A2B2	4.93	5.34	13.8
	A3B3	5.04	5.39	15.8

Figure 28. The ^{1}H n.m.r. spectrum of an equilibrated sample of N,N',N''-tribenzyltrianthranilide (15) was found to show (see Figure 6) temperature dependence in hexadeuteriodimethyl sulphoxide solution. The three AB systems associated with the helical conformations (76a and b) start to broaden as the temperature is raised. However, their relative intensities with respect to the AB system associated with the propeller conformations (75a and b) also decrease until eventually at +173 °C, they are undetectable. Thus, the equilibrium population is shifted toward the propeller conformations (75a and b) as the temperature is raised. Since the helical conform-ations (76a and b) become undetectable in the temperature range where site exchanges begin to influence line shapes, the opportunity to employ an eight-site exchange pro-gram in which nuclei are exchanged between all possible pairs of sites associated with four AB systems did not avail itself. Consequently, the rate constants associated with conformational interconversions were unobtainable by line-shape analysis and had to be sought by a direct equilibration procedure (see below). The rate constant for H ⇌ H* ring inversion was also unobtainable from line-shape analysis. However, the AB system for the propeller conformations (75a and b) begins to show line broadening above +163 °C and could be subjected to line-shape analysis despite the modest asymmetry which is presumably caused by site exchange processes involv-ing helical conformations (76a and b) as intermediates. An average $\Delta G^{\ddagger}$ value of 26.2 ± 0.1 kcal mol^{-1} was cal-culated for P ⇌ P* inversion from the four rate con-stants obtained (see Figure 6) at +163, +173, +178, and +183 °C.

The ^{1}H-decoupled ^{13}C n.m.r. spectrum of an equili-brated sample of N,N',N''-tribenzyltrianthranilide (15) was also examined over a range of temperatures in both deuteriochloroform and pentadeuterionitrobenzene in the

hope that the detection of low intensity signals and the site-exchange problem could be simplified to one involv-ing four singlets arising from either (i) the carbonyl or (ii) benzylic-methylene carbon atoms. However, the results confirmed the observation from the temperature-depen-dent ^{1}H n.m.r. spectra that the proportion of the helical conformations (76a and b) decreases markedly as the temperature is raised and so the opportunity to perform a four-site exchange spectral analysis was also denied to us. At room temperature the following signals were identi-fied in deuteriochloroform solution. (i) Four signals at 170.1, 169.8, 169.4, and 167.9 p.p.m. for the carbonyl carbon atoms. The three signals of approximately equal intensities at low field were assigned to the helical con-formations (76a and b) and the high-field signal was assigned to the propeller conformations (75a and b). An approximate ratio of 59 : 41 for P : H was deduced from the relative peak areas associated with these signals. (ii) A total of 23 signals between 137.8 and 127.2 p.p.m. for the aromatic carbon atoms. (iii) Three signals at 56.7, 55.8, and 53.8 p.p.m. for the benzylic-methylene carbon atoms. The high-field signal was assigned to the propeller conformations (75a and b) and the two lower-field signals with approximate relative intensities of 2 : 1 were assigned to the helical conformations (76a and b). An approximate ratio of 62 : 38 for P : H was deduced from the relative peak areas associated with these signals. At higher temperatures in pentadeuterionitrobenzene, signals arising from carbon atoms in the helical conform-ations (76a and b) were found to decrease in intensity without any appreciable line broadening until they were virtually undetectable at +175 °C.

It has already been noted that propeller (75a and b) and helical (76a and b) conformations interconvert on refluxing in chloroform solution. Heating a sample of pure H/H* conformational diastereoisomer (76a and b) dissolved in hexadeuteriodimethyl sulphoxide resulted in the appearance in the ^{1}H n.m.r. spectrum of the AB system associated with the P/P* conformational diastereoisomer (75a and b). The rates of intercon-versions of the propeller (75a and b) and helical (76a and b) conformations were measured by monitoring the relative intensities of the AB systems for the benzylic-methylene protons at +63 °C as a function of time. Table 5 records the changes in the percentage peak areas (Area$_{P/P*}$ and Area$_{H/H*}$) of these AB systems with time, t. Values for the forward (k_1) and reverse (k_{-1}) rate constants for the equilibria (6) were calculated using the

$$P \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H \quad \text{and} \quad P^* \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H^* \qquad (6)$$
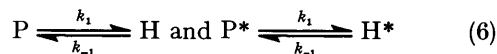
expression (7) [32,33] where R is the ratio of the diastereo-

$$\ln[(R - K)/(1 + R)] = -(k_1 + k_{-1})t \qquad (7)$$

isomers at time t and K is the equilibrium constant. Values of R were obtained from the relative peak areas (Area$_{P/P*}$/Area$_{H/H*}$) at different times, t, and are recorded in Table 5. A value of 0.59 was found for K using the relationship $K = $ [H]/[P] and corresponds to an equili-

TABLE 5

Experimental and calculated data relating to the equilibration of propeller (75a and b) and helical (76a and b) conformations of N,N',N''-tribenzyltrianthranilide (15) at $+63$ °C in hexadeuteriodimethyl sulphoxide obtained by ^1H n.m.r. spectroscopy

t/min	Area$_{P/P*}$ [a] (%)	Area$_{H/H*}$ [a] (%)	R [b]	$(R - K)$	$(1 + R)$	$\dfrac{(R - K)}{(1 + R)}$	$\ln \dfrac{(R - K)}{(1 + R)}$
5	33	67	2.06	1.47	3.06	0.48	−0.32
10	41	59	1.41	0.82	2.41	0.34	−0.47
15	48	52	1.07	0.48	2.07	0.23	−0.64
25	57	43	0.75	0.16	1.75	0.092	−1.04
30	59	41	0.69	0.10	1.69	0.059	−1.23
	63	37	0.59 [c]	–	–	–	–

[a] Obtained by integration of ^1H n.m.r. spectra. [b] $R = \text{Area}_{H/H*}/\text{Area}_{P/P*}$. [c] $K = R$ at $t = \infty$.

brium ratio of 63 : 37 for P : H. A value of $k_1 + k_{-1}$ was calculated from the slope of the line obtained on plotting $\ln[(R + K)/(1 + R)]$ versus t (see Table 5). Values for the forward ($k_1 = 5.0 \times 10^{-4}$ s^{-1}) and reverse ($k_{-1} = 8.5 \times 10^{-4}$ s^{-1}) rate constants were obtained using the relationship $K = k_1/k_{-1}$. Employing the Eyring equation, $\Delta G^{\ddagger}$ (P $\longrightarrow$ H) and $\Delta G^{\ddagger}$ (H $\longrightarrow$ P) were calculated to be 24.8 ± 0.5 and 24.3 ± 0.5 kcal mol^{-1}, respectively. Comparison of these activation parameters with the value of 26.2 ± 0.1 kcal mol^{-1} for $\Delta G^{\ddagger}$ (P $\rightleftharpoons$ P*) obtained from line-shape analysis suggests that the free energy of the transition state associated with H $\rightleftharpoons$ H* inversion is very similar to that associated with P $\rightleftharpoons$ H (P* $\rightleftharpoons$ H*) interconversion.

The Conformational Behaviour of N,N'-Dimethyl-N''-benzyl- (12) and N,N'-Dibenzyl-N''-methyl- (16) trianthranilides.—N,N'-Dibenzyl-N''-methyltrianthranilide (16) was prepared by methylation (MeI) of N,N'-dibenzyltrianthranilide (14) at room temperature in dimethyl sulphoxide in the presence of sodium hydride as base. The reaction was followed by t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant. After 5 min all the starting material had reacted to give mainly one component which migrated slower than the starting material. A small amount of a second and much faster-migrating component was also detected. During the first 2 h, the amount of the faster-migrating component increased until ultimately (>2 h) it reached equilibrium with the slower-migrating component which showed a corresponding decrease in its relative intensity. This pattern of reactivity is reminiscent of that observed (see Figure 27) during the benzylation of (14) discussed in the previous subsection. The two components were separated as crystalline compounds by preparative t.l.c. on silica gel using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) as eluant. The faster-migrating component, which had m.p. 120—128 °C, was shown to be 65% diastereoisomerically pure by ^1H n.m.r. spectroscopy. The slower-migrating component was shown in the same manner to be 82% diastereoisomerically pure and had m.p. 125—140 °C. Their partial ^1H n.m.r. spectra recorded at room temperature in deuteriochloroform are shown in Figure 30. The faster-migrating component exhibited two AB systems ($\tau_{A1} = 4.01$, $\tau_{B1} = 5.36$, $J_{A1B1} = 14.6$ Hz; $\tau_{A2} = 4.01$, $\tau_{B2} = 5.39$, $J_{A2B2} = 14.0$ Hz) for the benzylic methylene protons and one singlet (τ 6.40) for the N-methyl protons. The slower-

migrating component showed a complex range of signals corresponding to several overlapping AB systems situated between τ 4.50 and 5.68 for the benzylic-methylene protons. On careful inspection, it was possible to identify two major AB systems (τ_{A1} 5.09, $\tau_{B1} = 5.30$,
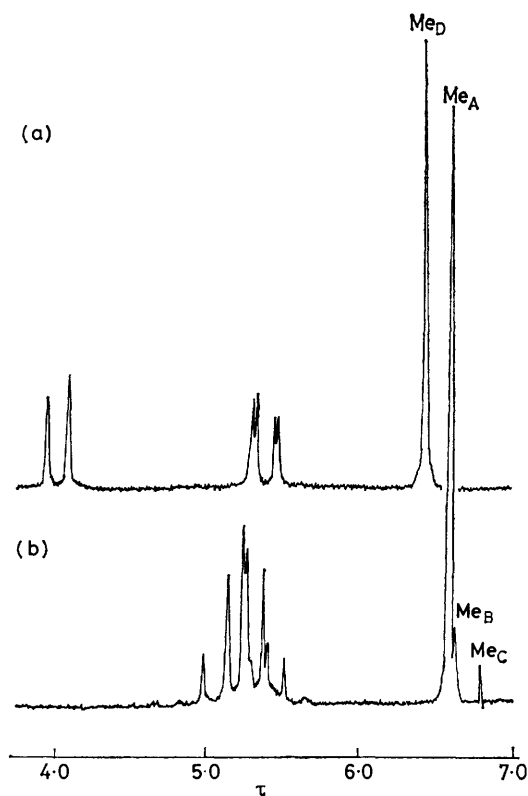

FIGURE 30 The partial ^1H n.m.r. spectra recorded in deuteriochloroform showing the signals for the benzylic-methylene and N-methyl protons in (a) the propeller (77a and b) and in (b) the H-2/H-2* (79a and b) conformations of N,N'-dibenzyl-N''-methyltrianthranilide (16)

$J_{A1B1} = 15.9$ Hz; $\tau_{A2} = 5.22$, $\tau_{B2} = 5.43$, $J_{A2B2} = 14.0$ Hz) and several minor AB systems. A high-intensity singlet was observed at τ 6.59 for the N-methyl groups together with a pair of very low-intensity singlets at τ 6.63 and 6.80. On heating a sample of the slower-migrating component in nitrobenzene solution at $+100$ °C, equilibration took place within a few minutes. This sample gave (see Figure 5) four singlets of unequal intensities at τ 6.47, 6.65, 6.71, and 6.88 for the N-methyl

protons. The relative intensities of these four signals at +111 °C were 36 : 48 : 9 : 7. In common with other constitutionally unsymmetrical trianthranilide derivatives, there are four possible conformational diastereoisomers (see Figure 31) for N,N'-dibenzyl-N''-methyltrianthranilide (16). The assignment of the faster-migrating component on t.l.c. to the propeller conformations (77a and b) was reached (i) by comparison of its chromatographic behaviour with that of the propeller

H-3* (80a and b). If it is assumed that the sites occupied by the single N-methyl groups in these diastereoisomeric helical conformations have the same relative chemical shifts as the sites occupied by the corresponding N-methyl groups in N,N',N''-trimethyltrianthranilide (7), then the major helical conformations are H-2 and H-2* (79a and b). This conformational assignment (see Table 6) is supported (i) by similar chemical-shift correlations for the AB systems of the benzylic-methylene
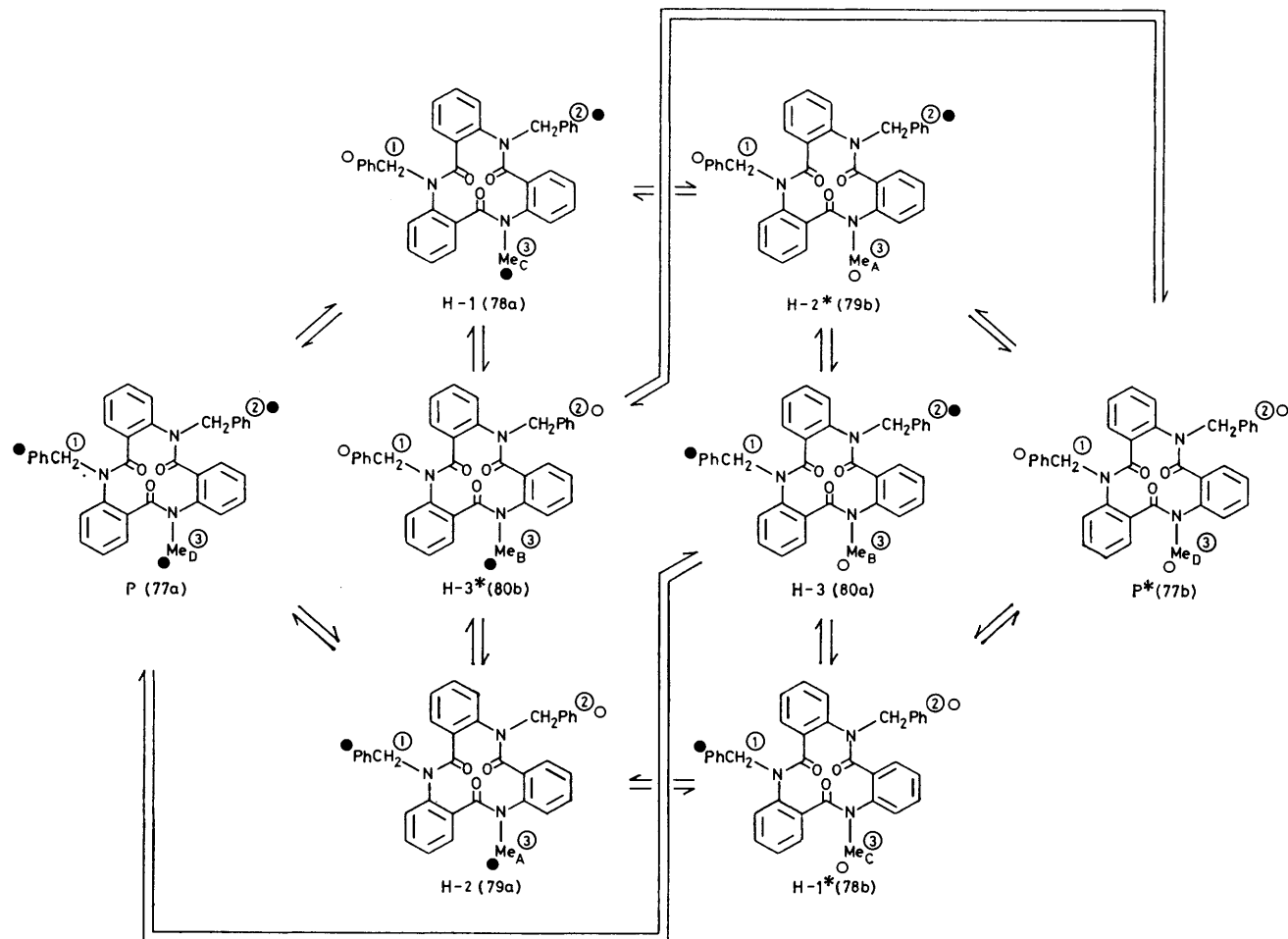

FIGURE 31 Conformational itinerary and site exchange scheme for the N-methyl groups in the propeller (77a and b) and helical (78a and b), (79a and b), and (80a and b) conformations of N,N'-dibenzyl-N''-methyltrianthranilide (16): ● ≡ an N-methyl or N-benzyl group above the mean plane of the ring and ○ ≡ an N-methyl or N-benzyl group below the mean plane of the ring. The constitutional identity of the N-methyl groups are indicated by encircled superscripts

conformations (75a and b) of N,N',N''-tribenzyltrianthranilide (15) and (ii) by comparison of the chemical shift (τ 6.40) of its N-methyl signal with that (τ 6.51) for the N-methyl signal of the propeller conformations (64a and b) in trimethyltrianthranilide (7), and (iii) by comparison (cf. Tables 4 and 6) of the chemical shifts of its benzylic-methylene protons with those for the benzylic-methylene protons of the propeller conformations (75a and b) of N,N',N''-tribenzyltrianthranilide (15). It follows that the slower-migrating component must be comprised of a mixture of the helical conformations H-1/H-1* (78a and b), H-2/H-2* (79a and b), and H-3/

protons in analogous conformations of different trianthranilide derivatives (see p. 1694), and (ii) by the fact that the H-2/H-2* conformations (79a and b) are formed under kinetic control during methylation of N,N'-dibenzyltrianthranilide (14), which probably adopts H-2/H-2* conformations (67a and b in Figure 13 where $R^1 = R^2 = PhCH_2$ and $R^3 = H$) in solution.

The ${}^1H$ n.m.r. spectrum of an equilibrated sample of N,N'-dibenzyl-N''-methyltrianthranilide (16) was found to exhibit (see Figure 5) temperature dependence. The four singlets observed for the N-methyl groups in nitrobenzene solution at room temperature undergo little if

TABLE 6

The chemical shifts for the singlets associated with the N-methyl protons and the chemical shifts and coupling constants for the AB systems associated with the benzylic-methylene protons in ^{1}H n.m.r. spectra recorded in deuteriochloroform at ambient temperature arising from the propeller (77a and b) and helical (78a and b), (79a and b), and (80a and b) conformations of N,N'-dibenzyl-N''-methyltrianthranilide (16)

Conformation	Chemical shifts of N-methyl protons τ	Chemical shifts and coupling constants (Hz) of the benzylic-methylene protons					
		τ_{A1}	τ_{B1}	J_{A1B1}	τ_{A2}	τ_{B2}	J_{A2B2}
P/P* (77a and b)	6.40	4.01	5.36	14.6	4.01	5.39	14.0
H-1/H-1* (78a and b)	6.80	n.d.^{a}	n.d.		n.d.	n.d.	
H-2/H-2* (79a and b)	6.59	5.09	5.30	15.9	5.22	5.43	14.0
H-3/H-3* (80a and b)	6.63	n.d.	n.d.		n.d.	n.d.	

^{a} Not detected.

any change up to +142 °C. On raising the temperature, however, broadening starts to occur especially in relation to the singlets (Me_D and Me_B, respectively) associated with the propeller (77a and b) and H-3/H-3* (80a and b) conformations. At +162 °C, the signal for Me_B coalesces with the neighbouring signal (Me_A) for the N-methyl protons in the H-2/H-2* conformations (79a and b). At +183 °C, the signals for Me_A, and Me_B, and the third signal (Me_C) associated with the H-1/H-1* conformations (78a and b), coalesce to give a broad signal, while the signal for Me_D remains as a broad singlet. Eventually, at +198 °C, only one broad signal is observed. The line-shape changes are, therefore, a consequence of both H $\rightleftharpoons$ H* inversion and P $\rightleftharpoons$ H (P* $\rightleftharpoons$ H*) interconversion processes becoming rapid on the ^{1}H n.m.r. time scale. Matching (see Figure 5) of experimental and calculated spectra was carried out with the aid of a computer program suitable for exchange of nuclei between four unequally populated sites. However, the analysis was only sufficiently sensitive to provide *average* rate constants, k_1', k_{-1}', and k_2' for the P $\rightarrow$ H, H $\rightarrow$ P, and H $\rightleftharpoons$ H* conformational changes (see the Experimental section for a more detailed discussion of this point). The rate constants obtained (see Figure 5) over a temperature range from +142 to +198 °C are listed in Table 7 together with the derived free energies of activation. The average $\Delta G^{\ddagger}$ values were found to be

25.4 ± 0.4 and 25.6 ± 0.5 kcal mol^{-1} respectively for the P $\rightarrow$ H and H $\rightarrow$ P interconversion processes and 25.9 ± 0.1 kcal mol^{-1} for the H $\rightleftharpoons$ H* inversion process.

N,N'-Dimethyl-N''-benzyltrianthranilide (12) was also found to exist as an equilibrating mixture of four enantiomeric pairs of diastereoisomeric conformations of the propeller (65a and b) and helical (66a and b, 67a and b, and 68a and b) types (see Figure 13 where $R^1 = R^2 =$ Me and $R^3 = PhCH_2$). The ^{1}H n.m.r. spectrum of an equilibrated sample recorded in deuteriochloroform solution at ambient temperature exhibited seven singlets (τ 6.46, 6.58, 6.65, 6.68, 6.75, 6.82, and 6.86) for the two constitutionally heterotopic N-methyl groups. However, the same sample revealed (see Figure 32) eight singlets in nitrobenzene solution. In particular, the low-field singlet observed in deuteriochloroform solution at τ 6.46 was resolved into two equally intense singlets. This observation establishes that the low-field singlet is associated with the accidental chemical-shift equivalence of two heterotopic N-methyl groups when deuteriochloroform is the solvent. The six remaining singlets are composed (see Figure 32) of three pairs of singlets, the partners of which exhibit equal intensities. This feature is also discernible in the ^{1}H n.m.r. spectrum recorded in deuteriochloroform where the three pairs of singlets resonate at τ 6.58 and 6.82, τ 6.68 and 6.86, and τ 6.65 and 6.75, respectively. The signals for the benzylic-methylene protons appear as a complex pattern of overlapping AB systems resonating between τ 3.96 and 5.86 in deuteriochloroform solution. Two crystalline conformational diastereoisomers were separated by a combination of separation techniques involving (i) preparative t.l.c. at 5 °C followed by (ii) high-pressure liquid chromatography, both carried out on silica gel using ethyl acetate as eluant. The ^{1}H n.m.r. spectra of these two isomers were examined in deuteriochloroform solution, since they both exhibited very similar melting points, namely 152—154 °C and 153—154 °C. Both isomers were found to be >98% diastereoisomerically pure. Conformational assignments (with reference to Figure 13 where $R^1 = R^2 =$ Me and $R^3 = PhCH_2$) were made (see p. 1691) to both these isomers, and to the other two minor isomers which were not isolated, by correlating (see p. 1694) the chemical shifts of (i) the N-methyl protons, and (ii) the benzylic-methylene protons with those found for other trianthranilide derivatives substituted with

TABLE 7

Rate constants (s^{-1}) and the derived free energies of activation (kcal mol^{-1}) for the conformational changes associated with P $\rightarrow$ H and H $\rightarrow$ P interconversions and H $\rightleftharpoons$ H* inversions of N,N'-dibenzyl-N''-methyltrianthranilide (16) in nitrobenzene at various temperatures (°C)

T/°C	k_1' ^{a}	$\Delta G^{\ddagger}$ (P $\rightarrow$ H) ^{d}	k_{-1}' ^{b}	$\Delta G^{\ddagger}$ (H $\rightarrow$ P) ^{e}	k_2' ^{c}	$\Delta G^{\ddagger}$ (H $\rightleftharpoons$ H*) ^{f}
142	0.25	25.7	0.18	26.0		
152	0.57	25.7	0.41	25.9		
183	7.0	25.3	6.2	25.4	3.8	25.8
198	25.0	25.0	22.2	25.1	9.0	25.9

^{a} $k_1' = k_{DA}, k_{DB}, k_{DC}$. ^{b} $k'_{-1} = k_{AD}, k_{BD}, k_{CD}$. ^{c} $k_2' = k_{AB}, k_{BA}, k_{AC}, k_{CA}, k_{BC}, k_{CB}$. ^{d} Average value for $\Delta G^{\ddagger}$ (P $\rightarrow$ H) = 25.4 ± 0.4 kcal mol^{-1}. ^{e} Average value for $\Delta G^{\ddagger}$ (H $\rightarrow$ P) = 25.6 ± 0.5 kcal mol^{-1}. ^{f} Average value for $\Delta G^{\ddagger}$ (H $\rightleftharpoons$ H*) = 25.9 ± 0.1 kcal mol^{-1}.

methyl and/or benzyl groups at the amide nitrogen atoms. The major and slower-migrating component on t.l.c. which can be assigned to the helical conformations H-1 and H-1* (66a and b) showed two singlets of equal intensities at τ 6.58 and 6.82 for the N-methyl protons and an AB system ($\tau_A = 5.26$, $\tau_B = 5.42$, $J_{AB} = 14.7$
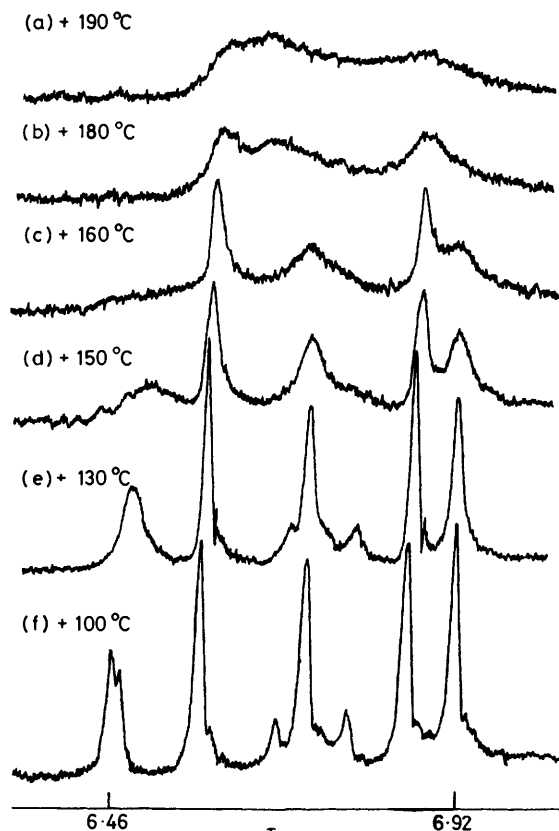

FIGURE 32 The temperature dependence of the signals for the N-methyl protons of N,N'-dimethyl-N''-benzyltrianthranilide (12) in the ^{1}H n.m.r. spectrum recorded in nitrobenzene: (a) at +190 °C; (b) at +180 °C; (c) at +160 °C; (d) at +150 °C; (e) at +130 °C; (f) at +100 °C

Hz) for the benzylic-methylene protons. The minor and faster-migrating component on t.l.c. which was assigned to the helical conformations H-3 and H-3* (68a and b) showed two singlets of equal intensities at τ 6.68 and 6.86 and an AB system ($\tau_A = 5.02$, $\tau_B = 5.33$, J_{AB} 15.6 Hz) for the benzylic-methylene protons. Both isomers undergo equilibration when set aside in deuteriochloroform solution for 3 days at room temperature to give a mixture of four conformational diastereoisomers exhibiting the same complex ^{1}H n.m.r. spectrum which was observed before the isolation of the two crystalline isomers. Heating of the crystals of H-1/H-1* (66a and b) in nitrobenzene solution at +80 °C resulted in complete equilibration within 10 min. The signals for the two minor isomers, which could be detected in the deuteriochloroform solution of an equilibrated sample of N,N'-dimethyl-N''-benzyltrianthranilide (12) were assigned to the H-2 and H-2* conformations (67a and b) and propeller conformations (65a and b). The H-2/

H-2* conformations (67a and b) exhibited two N-methyl singlets at τ 6.65 and 6.75 but only the B portion ($\tau = 5.76$, $J_{AB} = 15.0$ Hz) of the AB system for the benzylic methylene protons could be assigned with certainty since the A portion was masked by two other prominent AB systems. The propeller conformations (65a and b) gave one singlet at τ 6.46 and only the A portion (τ 4.06, $J_{AB} = 15.0$ Hz) of the AB system for the benzylic-methylene protons could be assigned with certainty since the B portion was masked by the two other prominent AB systems. Both these isomers exist in such small quantities in the equilibrium mixture that their separation was not practicable. The conformational assignments and the chemical shifts of the N-methyl and benzylic-methylene protons of the four isomers are summarised in Table 8. The major isomer which adopts the H-2/

TABLE 8

The chemical shifts for the singlets associated with the N-methyl protons and the chemical shifts and coupling constants for the AB systems associated with the benzylic-methylene protons in ^{1}H n.m.r. spectra recorded in deuteriochloroform at ambient temperature arising from the propeller (65a and b) [a] and helical (66a and b), (67a and b), and (68a and b) [a] conformations of N,N'-dimethyl-N''-benzyltrianthranilide (12)

Conformation	Chemical shifts of N-methyl protons		Chemical shifts and coupling constants (Hz) of the benzylic-methylene protons		
	τ_{Me*}	τ_{Me}	τ_A	τ_B	J_{AB}
P/P* (65a and b) [a]	6.46	6.46	4.06	n.d.[c]	15.0
H-1/H-1* (66a and b) [a]	6.82 [b]	6.58 [b]	5.26	5.42	14.7
H-2/H-2* (67a and b) [a]	6.65 [b]	6.75 [b]	n.d.	5.76	15.0
H-3/H-3* (68a and b) [a]	6.68 [b]	6.86 [b]	5.02	5.33	15.6

[a] $R^1 = R^2 = $ Me and $R^3 = $ PhCH$_2$ in Figure 13. [b] Assignments were made to the constitutionally heterotopic N-methyl groups by comparison of the ^{1}H n.m.r. spectra for (12) and (13). [c] Not detected.

H-2* conformations (67a and b) crystallises out from an equilibrium mixture by slow crystallisation from chloroform–ether–light petroleum (b.p. 60—80 °C). Rapid crystallisation from the same solvent mixture affords an inclusion compound containing the propeller (65a and b), H-1/H-1* (66a and b), H-2/H-2* (67a and b), and H-3/H-3* (68a and b) conformations in the ratio of 19 : 41 : 7 : 33 and one-third of a molar equivalent of ethanol [N.B. ethanol was present (2%) in the chloroform as a stabiliser!].

The ^{1}H n.m.r. spectrum of an equilibrated mixture of N,N'-dimethyl-N''-benzyltrianthranilide (12) in nitrobenzene solution was found to be temperature dependent. From inspection of Figure 32, it is obvious that the eight singlets observed for the N-methyl protons at room temperature undergo little if any change up to +100 °C. On raising the temperature further, however, broadening starts to occur especially in relation to the two low-field singlets associated with the propeller conformations (65a and b). At +160 °C, these signals coalesce with the neighbouring low-field singlet. By +180 °C, the whole
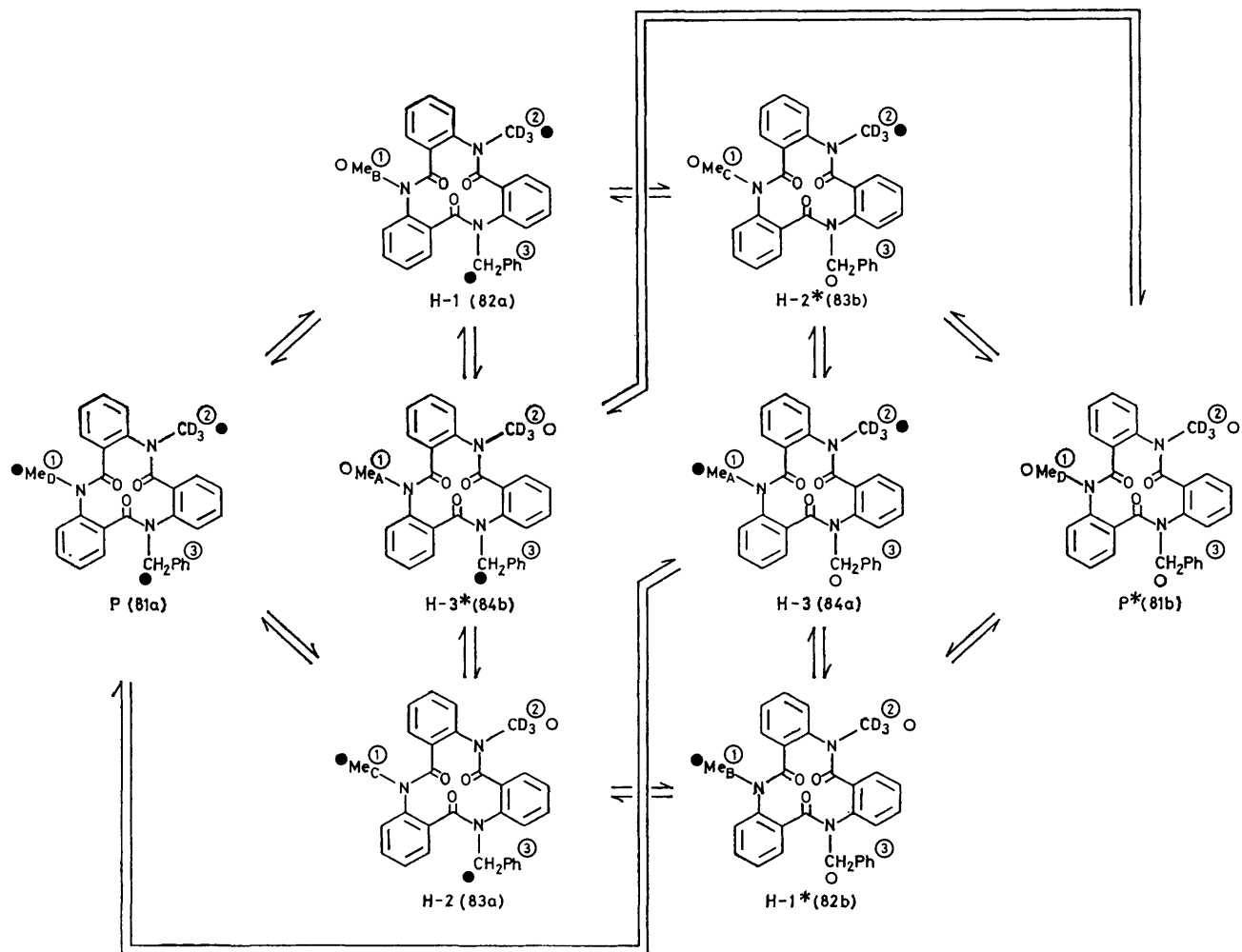
FIGURE 33 Conformational itinerary and site-exchange sceheme for the N-methyl groups in the propeller (81a and b) and helical (82a and b), (83a and b), and (84a and b) conformations of N-methyl-N'-trideuteriomethyl-N''-benzyltrianthranilide (13): ● ≡ an N-methyl or N-benzyl group above the mean plane of the ring and ○ ≡ an N-methyl or N-benzyl group below the mean plane of the ring. The constitutional identity of the N-methyl groups are indicated by encircled superscripts

spectrum has become broad. Since the two low-field singlets originate from the propeller conformations (65a and b), the changes in the spectral line shapes observed around $+160$ °C are associated primarily with P ⇌ H interconversion processes while the changes observed at higher temperatures are associated primarily with H⇌H* inversion processes. In contemplating line-shape analyses of the temperature-dependent spectra shown in Figure 32, we were confronted by at least two problems. (i) The assignments of the four pairs of singlets with equal intensities to the constitutionally heterotopic N-methyl groups, Me* and Me, could not be made with absolute certainty. (ii) Although simulation of the spectra involving two independent site-exchange processes between four sites in each case was feasible, unambiguous matches between experimental and theoretical spectra would most likely be difficult to achieve in the presence of so many signals with very similar chemical shifts. Both these problems were surmounted by synthesing N-methyl-N'-trideuteriomethyl-N''-benzyltrianthranilide (13). The

^{1}H n.m.r. spectrum of this derivative (13) in deuteriochloroform at ambient temperature revealed the presence of the four diastereoisomeric conformations [(81), (82), (83), and (84) in Figure 33] and allowed the singlets resonating at τ 6.46, 6.65, 6.68, and 6.82 to be assigned to the N-methyl groups denoted by Me* in (13) and to be

(τ 6.46 , 6.65 , 6.68 , 6.82)

(13)
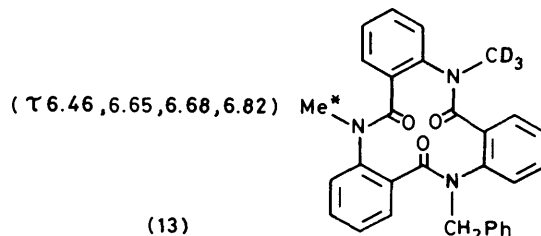
associated (see Table 8) with conformations of the type P/P*, H-2/H-2*, H-3/H-3*, and H-1/H-1*, respectively. An analogous pattern of overlapping AB systems to that obtained for N,N'-dimethyl-N''-benzyltrianthranilide
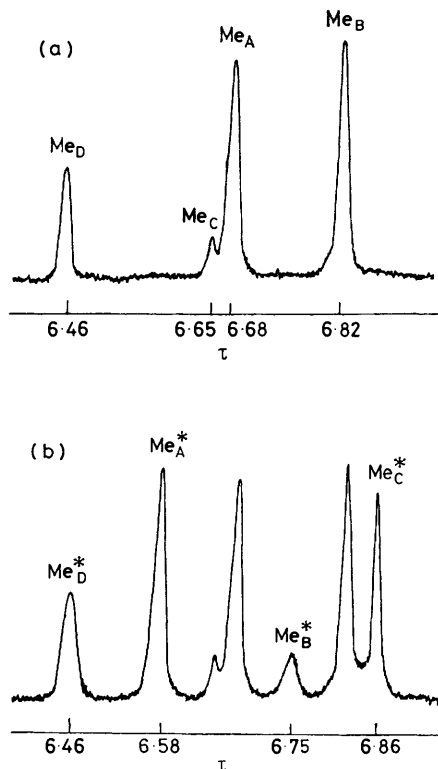
FIGURE 34 The partial ^{1}H n.m.r. spectra recorded in deuterio-chloroform showing the N-methyl proton signals for (a) N-methyl-N'-trideuteriomethyl-N''-benzyltrianthranilide (13) and (b) N,N'-dimethyl-N''-benzyltrianthranilide (12)

(12) was observed for the benzylic-methylene protons of the trideuteriomethyl derivative (13). Figure 34 represents a comparison between the four singlets observed

(τ 6.46, τ 6.58, τ 6.75, τ 6.86)

(12)
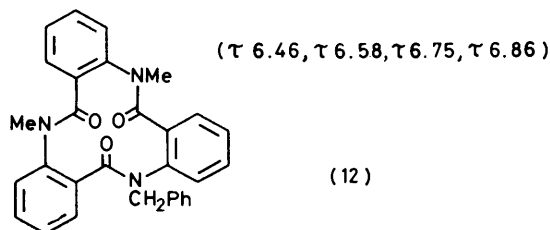
for the N-methyl protons denoted by Me* in (13) with the eight singlets for the constitutionally heterotopic N-methyl groups in (12). It follows that signals reson-

ating at τ 6.46, 6.58, 6.75, and 6.86 arise from the N-methyl protons denoted by Me and may be associated with conformations of the type P/P*, H-1/H-1*, H-2/H-2*, and H-3/H-3*, respectively. The ^{1}H n.m.r. spectrum of N-methyl-N'-trideuteriomethyl-N''-benzyltrianthranilide (13) in nitrobenzene solution exhibited line broadening at temperatures above 131 °C. Line-shape analysis was carried out (see Experimental section) with the computer program suitable for generating line shapes arising from exchange between four unequally populated sites. As in the case of N,N'-dibenzyl-N''-methyltrianthranilide (16), only the average rate constants, k_1', k_{-1}', and k_2' for the P $\longrightarrow$ H, H $\longrightarrow$ P, and H $\rightleftharpoons$ H* conformational changes in the itinerary detailed in Figure 33 could be obtained. These are listed in Table 9 along with the derived free energies of activation. The average $\Delta G^{\ddagger}$ values were found to be 23.9 $\pm$ 0.2 and 25.1 $\pm$ 0.3 kcal mol^{-1} respectively for the P $\longrightarrow$ H and H $\longrightarrow$ P interconversion processes and 26.2 $\pm$ 0.2 kcal mol^{-1} for the H $\rightleftharpoons$ H* inversion process.

The Conformational Behaviour of N,N'-*Dimethyl*-N''-*acetyl*- (10) *and* N,N'-*Dimethyl*-N''-*benzoyl*- (11) *trianthranilides.*—The ^{1}H n.m.r. spectrum of N,N'-dimethyl-N''-acetyltrianthranilide (10) recorded in deuterio-chloroform–carbon disulphide (1 : 1) at ambient temperature shows two singlets of equal intensities at τ 6.85 and 6.90 for the two constitutionally heterotopic N-methyl groups and one singlet of the same intensity for the N-acetyl protons. No noticeable change occurred in the spectrum when the sample was cooled down to -80 °C. Likewise, the ^{1}H n.m.r. spectrum of N,N'-dimethyl-N''-benzoyltrianthranilide (11) in deuteriochloroform solution showed singlets for the N-methyl protons resonating with equal intensities at τ 6.71 and 6.76. On cooling the solution down to -45 °C, no significant change occurred in the spectrum. The one conclusion that can be drawn from these observations is that neither compound comprises an equilibrium mixture of propeller and helical conformations in solution. They adopt (see Figure 13 where R^1 = R^2 = Me and R^3 = COMe or COPh) either exclusively the propeller conformations (65a and b) or exclusively one of the three helical conformations (66a and b), (67a and b), or (68a and b). Comparison of the chemical shifts noted above for the N-methyl groups in (10) and (11) with those observed at

TABLE 9

Rate constants (s^{-1}) and the derived free energies of activation (kcal mol^{-1}) for the conformational changes associated with P $\longrightarrow$ H and H $\longrightarrow$ P interconversions and H $\rightleftharpoons$ H* inversions of N-methyl-N'-trideuteriomethyl-N''-benzyltrianthranilide (13) in nitrobenzene solution at various temperatures (°C)

T/°C	k_1' [a]	$\Delta G^{\ddagger}$ (P $\longrightarrow$ H) [d]	k_{-1}' [b]	$\Delta G^{\ddagger}$ (H $\longrightarrow$ P) [e]	k_2' [c]	$\Delta G^{\ddagger}$ (H $\rightleftharpoons$ H*) [f]
131	1.3	23.7	0.30	24.9	0.057 [h]	26.2
140	2.4	23.7	0.57	24.9	0.12 [h]	26.2
150	4.4	23.8	1.04	25.0	0.25 [h]	26.2
161	8.0 [g]	23.8	1.9	25.2	0.57	26.2
172	15.2 [g]	24.0	3.6	25.3	1.3	26.2
182	25.3 [g]	24.1	5.6	25.4	2.4	26.2

[a] $k_1' = k_{DA}, k_{DB}, k_{DC}$. [b] $k_{-1}' = k_{AD}, k_{BD}, k_{CD}$. [c] $k_2' = k_{AB}, k_{BA}, k_{AC}, k_{CA}, k_{BC}, k_{CB}$. [d] Average value for $\Delta G^{\ddagger}$ (P $\longrightarrow$ H) = 23.9 $\pm$ 0.2 kcal mol^{-1}. [e] Average value for $\Delta G^{\ddagger}$ (H $\longrightarrow$ P) = 25.1 $\pm$ 0.3 kcal mol^{-1}. [f] Average value for $\Delta G^{\ddagger}$ (H $\rightleftharpoons$ H*) = 26.2 $\pm$ 0.2 kcal mol^{-1}. [g] Values obtained by extrapolation of a ln k_1' *versus* $1/T$ plot to higher temperatures. [h] Values obtained by extrapolation of a ln k_2' *versus* $1/T$ plot to lower temperatures.

τ 6.67, 6.79, and 6.87 for the three N-methyl groups in N,N',N''-trimethyl-trianthranilide (7) suggests that both compounds exist in solution as *one* of the three possible diastereoisomeric helical conformational isomers.

The Conformational Behaviour of N-*Methyl*-N'-*benzyl*- (17) *and* N-*Methyl*-N'-*ethyl*- (19) *trianthranilides.*— The ^{1}H n.m.r. spectra of these two N,N'-disubstituted trianthranilide derivatives recorded at ambient temperature in deuteriochloroform indicate that they exist as only *one* conformational diastereoisomer in solution. In common with the N,N'-dimethyl- (5) and N,N'-dibenzyl- (14) derivatives, it is a helical isomer, *i.e.* either (66a and

observed for the benzylic-methylene protons in hexa-deuteriodimethyl sulphoxide at $+40$ °C coalesces to a broad singlet at $+160$ °C. The rate constant at this temperature was calculated to be 91 s^{-1}, which corresponds to a free energy of activation of 21.8 kcal mol^{-1} for the H $\rightleftharpoons$ H* inversion process.

The Conformational Behaviour of N-*Methyl*-N'-*benzyl*-N''-*ethyl*- (18) *and* N-*Methyl*-N'-*ethyl*-N''-*benzyl*- (20) *trianthranilides.*—The ^{1}H n.m.r. spectrum of N-methyl-N'-benzyl-N''-ethyltrianthranilide (18) in deuteriochloroform at ambient temperature shows an AB system ($\tau_A = 5.28$, $\tau_B = 5.44$, $J_{AB} = 14.0$ Hz) for the
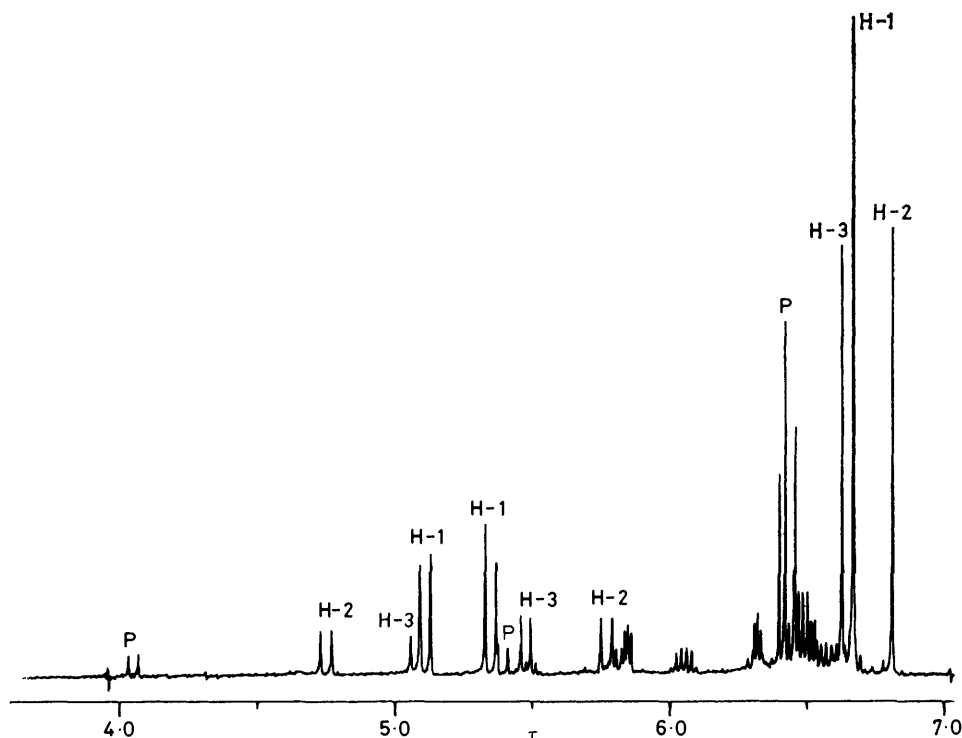

FIGURE 35   The partial ^{1}H n.m.r. spectrum recorded in deuteriochloroform at 400 MHz showing the benzylic methylene and N-methyl proton signals for N-methyl-N'-ethyl-N''-benzyltrianthranilide (20)

b) or (67a and b) in Figure 13 where (i) $R^1 =$ Me, $R^2 =$ CH$_2$Ph, and $R^3 =$ H, and (ii) $R^1 =$ Me, $R^2 =$ Et, and $R^3 =$ H, of either the H-1/H-1* or H-2/H-2* type which is adopted preferentially by both N-methyl-N'-benzyl- (17) and N-methyl-N'-ethyl- (19) trianthranilides in solution. This conclusion is based upon good correlations † (see p. 1694) between the chemical shifts of the N-methyl and benzylic-methylene protons in other N,N'-di- and N,N',N''-tri-substituted trianthranilides. The anisochronous nature of the signals for the methylene protons associated with the N-benzyl group in (17) and the N-ethyl group in (19) indicates that ring inversion is slow at room temperatures on the ^{1}H n.m.r. time scale. In the case of N-methyl-N'-benzyltrianthranilide (17), the AB system ($\tau_A = 5.16$, $\tau_B = 5.54$, $J_{AB} = 15$ Hz)

† In fact, a slightly better correlation exists for the conformational assignment H-2/H-2* than for the conformational assignment H-1/H-1*.

benzylic-methylene protons, a multiplet between τ 6.12 and τ 6.83 for the methylene protons of the N-ethyl group, a singlet at τ 6.60 for the N-methyl protons, and a triplet ($\tau = 8.96$, $J = 6.4$ Hz) for the methyl protons of the N-ethyl group. No change was observed in the spectra after the solution had stood at room temperature for two days. Moreover, the AB system for the benzylic-methylene protons, which was observable in hexa-deuteriodimethyl sulphoxide could still be identified up to $+190$ °C with only slight line broadening occurring in the temperature range $+180$ to $+190$ °C. It follows that the ring-inversion process for this N,N',N''-tri-substituted trianthranilide derivative (18) is associated with a free energy of activation of >27 kcal mol^{-1}. On the basis of chemical-shift correlations (see p. 1694) involving signals for the N-methyl and benzylic-methylene protons between N-methyl-N'-benzyl-N''-ethyltrianthranilide (18) and other N,N'-di- and N,N',N''-tri-

TABLE 10

The chemical shifts for the singlets associated with the N-methyl protons and the chemical shifts and coupling constants for the AB systems associated with the benzylic-methylene protons in ^{1}H n.m.r. spectra recorded in deuteriochloroform at ambient temperature arising from the propeller (65a and b) ^{a} and helical (66a and b), (67a and b), and (68a and b) ^{a} conformations of N-methyl-N'-ethyl-N''-benzyltrianthranilide (20)

Conformation	Chemical shifts of N-methyl protons τ	Chemical shifts and coupling constants (Hz) of the benzylic-methylene protons		
		τ_A	τ_B	J_{AB}
P/P* (65a and b) ^{a}	6.43	4.04	5.39	14.0
H-1/H-1* (66a and b) ^{a}	6.67	5.10	5.35	15.0
H-2/H-2* (67a and b) ^{a}	6.82	4.74	5.75	15.0
H-3/H-3* (68a and b) ^{a}	6.64	5.06	5.47	14.0

^{a} R^1 = Me, R^2 = Et, and R^3 = PhCH$_2$ in Figure 13.

substituted trianthranilide derivatives, compound (18) is believed to adopt H-3/H-3* conformations (68a and b in Figure 13 where R^1 = Me, R^2 = CH$_2$Ph, and R^3 = Et) in solution. By way of contrast, the constitutional isomer (20) of (18) exists (see Table 10) as all four conformational diastereoisomers, P/P*, H-1/H-1*, H-2/H-2*, and H-3/H-3* [(65a and b) in Figure 13 where R^1 = Me, R^2 = Et, and R^3 = PhCH$_2$] in the ratio of 8 : 52 : 21 : 19 respectively in deuteriochloroform solution at ambient temperature. The partial ^{1}H n.m.r. spectrum recorded at 400 MHz under these conditions is reproduced in Figure 35. Once again, the conformational assignments proposed in Table 10 are based (see p. 1695) upon correlations of chemical shifts for N-methyl and benzylic-methylene protons within the complete series of trian-

thranilide derivatives discussed in this paper. Of the four triplets with J = 6.4 Hz observed at τ 8.67, 8.79, 8.91, and 8.96, those resonating at τ 8.79 and 8.96 can be assigned with certainty on the basis of their relative intensities to the P/P* and H-1/H-1* conformations. The assignments of the other two triplets of intermediate and similar intensities at τ 8.67 and 8.91 are not possible from such a limited data base. In common with its constitutional isomer, N-methyl-N'-ethyl-N''-benzyltrianthranilide (20) undergoes slow conformational changes in hexadeuteriodimethyl sulphoxide with barrier heights in excess of 27 kcal mol^{-1} estimated from the temperature-dependent spectra.

A Summary of the Conformational Behaviour of N,N'-Di- and N,N',N''-Tri-substituted Trianthranilides.— Tables 11 and 12 present a complete and self-consistent analysis of the chemical-shift data for (i) the N-methyl protons in compounds (5), (7), (12), and (14)—(20). They relate τ values to site assignments and hence to conformational types. The sites A—D have been assigned unambiguously on the basis of deuteriation studies to N-methyl groups in the propeller (64a and b) and helical (63a and b) conformations of N,N',N''-trimethyltrianthranilide (7). These assignments have been used (i) to designate the sites A, B, C, and D to N-methyl groups in propeller and diastereoisomeric helical conformations of compounds (7), (12), and (16)—(20), and (ii) to designate the sites E, F, G, and I to benzylic-methylene groups in propeller and diastereoisomeric helical conformations of compounds (12), (14)—(18), and (20). The small variations in chemical shifts associated with each site are presented in Table 13 and the situation is illustrated diagrammatically in

TABLE 11

A correlation chart between conformational assignments to N,N'-di- and N,N',N''-tri-substituted trianthranilide derivatives and the ^{1}H n.m.r. sites associated with the signals for their N-methyl protons based upon the known site assignments to the N-methyl groups in N,N',N''-trimethyltrianthranilide (7)

No.	Compound ^{a,b}			Conformation ^{a}	Chemical shifts (τ) for N-Me groups ^{c}		
	R^1	R^2	R^3		R^1	R^2	R^3
(7)	Me$_B$	Me$_A$	Me$_C$	H/H*	6.79(B)	6.67(A)	6.87(C)
(12)	Me$_B$	Me$_A$	CH$_2$Ph	H-1/H-1*	6.82(B)	6.58(A)	
(16)	CH$_2$Ph	CH$_2$Ph	Me$_C$	H-1/H-1*			6.80(C)
(20)	Me$_B$	Et	CH$_2$Ph	H-1/H-1*	6.67(B)		
(5)	Me$_C$	Me$_B$	H	H-2/H-2*	6.83(C)	6.73(B)	
(12)	Me$_C$	Me$_B$	CH$_2$Ph	H-2/H-2*	6.65(C) ^{d}	6.75(B)	
(16)	CH$_2$Ph	CH$_2$Ph	Me$_A$	H-2/H-2*			6.59(A)
(17)	Me$_C$	CH$_2$Ph	H	H-2/H-2*	6.76(C)		
(19)	Me$_C$	Et	H	H-2/H-2*	6.81(C)		
(20)	Me$_C$	Et	CH$_2$Ph	H-2/H-2*	6.82(C)		
(12)	Me$_A$	Me$_C$	CH$_2$Ph	H-3/H-3*	6.68(A)	6.86(C)	
(16)	CH$_2$Ph	CH$_2$Ph	Me$_B$	H-3/H-3*			6.63(B)
(18)	Me$_A$	CH$_2$Ph	Et	H-3/H-3*	6.60(A)		
(20)	Me$_A$	Et	CH$_2$Ph	H-3/H-3*	6.64(A)		
(7)	Me$_D$	Me$_D$	Me$_D$	P/P*	6.51(D)	6.51(D)	6.51(D)
(12)	Me$_D$	Me$_D$	CH$_2$Ph	P/P*	6.46(D)	6.46(D)	
(16)	CH$_2$Ph	CH$_2$Ph	Me$_D$	P/P*			6.40(D)
(20)	Me$_D$	Et	CH$_2$Ph	P/P*	6.43(D)		

^{a} For conformational assignments to compounds, refer to Figure 13. ^{b} Site assignments to N-methyl groups are shown by means of a subscript. ^{c} The site associated with each signal is shown in parentheses after each τ value. ^{d} The chemical shift of Me$_C$ appears at lower field than expected. Examination of molecular models of the H-2 and H-2* conformations of (12) reveals that the N-methyl group at position (1) could experience deshielding by the phenyl ring of the N-benzyl group at position (3) on the same side of the 12-membered ring.
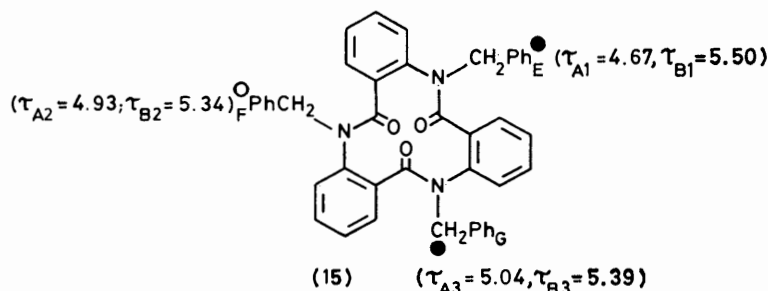
TABLE 12

A correlation chart between conformational assignments to N,N'-di- and N,N',N''-tri-substituted trianthranilide deriv-atives and the ^{1}H n.m.r. sites associated with the AB systems for their N-benzylic-methylene protons deduced from the known site assignments to the N-methyl groups in N,N',N''-trimethyltrianthranilide (7)

| | Compound [a,b] | | | | Chemical shifts (τ_A and τ_B) for N-benzylic-methylene protons [c] | | | | | |
| | | | | | R¹ | | R² | | R³ | |
No.	R¹	R²	R³	Conformation [a]	τ_A	τ_B	τ_A	τ_B	τ_A	τ_B
(15)	CH_2Ph_F	CH_2Ph_E	CH_2Ph_G	H/H*	4.93(F)	5.34(F)	4.67(E)	5.50(E)	5.04(G)	5.39(G)
(12)	Me	Me	CH_2Ph_G	H-1/H-1*					5.26(G)	5.42(G)
(20)	Me	Et	CH_2Ph_G	H-1/H-1*					5.10(G)	5.35(G)
(12)	Me	Me	CH_2Ph_E	H-2/H-2*						5.76(E)
(14)	CH_2Ph_G	CH_2Ph_F	H	H-2/H-2*	5.17(G)	5.33(G)	5.00(F)	5.54(F)		
(16)	CH_2Ph_G	CH_2Ph_F	Me	H-2/H-2*	5.22(G)	5.43(G)	5.09(F)	5.30(F)		
(17)	Me	CH_2Ph_F	H	H-2/H-2*			4.98(F)	5.55(F)		
(20)	Me	Et	CH_2Ph_E	H-2/H-2*					4.74(E)	5.76(E)
(12)	Me	Me	CH_2Ph_F	H-3/H-3*					5.02(F)	5.33(F)
(18)	Me	CH_2Ph_G	Et	H-3/H-3*			5.28(G)	5.44(G)		
(20)	Me	Et	CH_2Ph_F	H-3/H-3*					5.06(F)	5.47(F)
(12)	Me	Me	CH_2Ph_I	P/P*					4.06(I)	
(15)	CH_2Ph_I	CH_2Ph_I	CH_2Ph_I	P/P*	3.96(I)	5.32(I)	3.96(I)	5.32(I)	3.96(1)	5.32(I)
(16)	CH_2Ph_I	CH_2Ph_I	Me	P/P*	4.01(I)	5.36(I)	4.01(I)	5.36(I)		
(20)	Me	Et	CH_2Ph_I	P/P*					4.04(I)	5.39(I)

[a] For conformational assignments, refer to Figure 13.   [b] Site assignments to N-benzylic-methylene groups are shown by means of a subscript.   [c] The site associated with each signal is shown in parentheses after each τ value.

Figure 36.   The correlation is considered to be sufficiently good between different compounds in different conform-ations to allow an absolute site assignment to be made to the stereoheterotopic benzylic-methylene groups in N,N',N''-tribenzyltrianthranilide (15).   This assignment of sites E, F, and G to the helical conformations (76a and b) of N,N',N''-tribenzyltrianthranilide (15) could be checked by deuteration studies similar to those described for N,N',N''-trimethyltrianthranilide (7).

The relative ground state stabilities of propeller and helical conformations of trianthranilide derivatives are rather finely balanced in solution.   In N,N',N''-tri-methyltrianthranilide (7), the helical conformation is preferred (94.5 : 5.5), whereas in N,N',N''-tribenzyl-trianthranilide (15), the propeller conformation is preferred (63 : 37).   Table 14 summarises the picture which emerges for the asymmetrically substituted deriv-atives.   Five compounds adopt only one of the three

(15)

(τ_{A1} =4.67, τ_{B1}=5.50)
(τ_{A2} = 4.93; τ_{B2} = 5.34)
(τ_{A3} = 5.04, τ_{B3}=5.39)

TABLE 13

A list [a] of τ values (i) for N-methyl groups associated with sites A—D and (ii) for N-benzylic-methylene groups associated with sites E, F, G, and I

Conformational type	H	H	H	P	H	H	H	H	H	H	P	P
Chemical shifts	$\tau(A)$	$\tau(B)$	$\tau(C)$	$\tau(D)$	$\tau_A(E)$	$\tau_B(E)$	$\tau_A(F)$	$\tau_B(F)$	$\tau_A(G)$	$\tau_B(G)$	$\tau_A(I)$	$\tau_B(I)$
of compounds	6.58	6.63	6.65	6.40	4.67	5.50	4.93	5.30	5.04	5.33	3.96	5.32
listed from	6.59	6.67	6.76	6.43	4.74	5.76	4.98	5.33	5.10	5.35	3.96	5.32
low to high field	6.60	6.73	6.80	6.46		5.76	5.00	5.34	5.17	5.39	3.96	5.32
	6.64	6.75	6.81	6.46			5.02	5.47	5.22	5.42	4.01	5.36
	6.67	6.79	6.82	6.51			5.06	5.54	5.26	5.43	4.01	5.39
	6.68	6.82	6.83	6.51			5.09	5.55	5.28	5.44	4.04	5.39
			6.86	6.51							4.06	
			6.87									
Mean τ value	6.63	6.73	6.80	6.47	4.71	5.67	5.01	5.42	5.18	5.39	4.00	5.35
Maximum deviations from the mean τ value	−0.05 ↓ +0.05	−0.10 ↓ +0.09	−0.15 ↓ +0.07	−0.07 ↓ +0.04	−0.04 ↓ +0.03	−0.17 ↓ +0.09	−0.08 ↓ +0.08	−0.12 ↓ +0.13	−0.14 ↓ +0.10	−0.06 ↓ +0.05	−0.04 ↓ +0.06	−0.03 ↓ +0.04

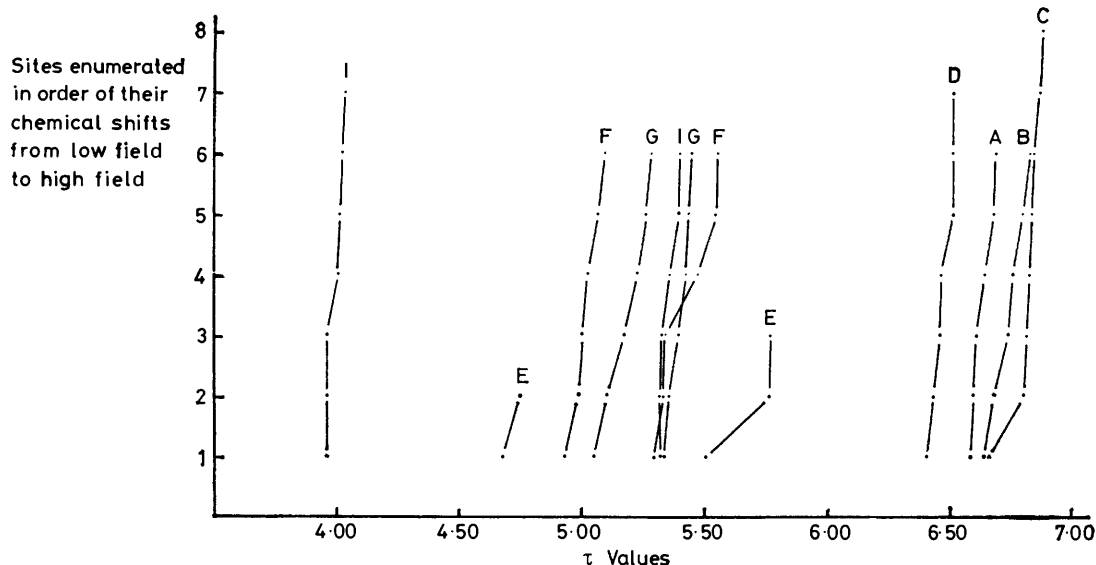[a] This list has been compiled from the correlation charts in Tables 11 and 12.

FIGURE 36   A diagrammatic representation of the correlation between conformational and site assignments (see Tables 12 and 13) in N,N'-di- and N,N',N''-tri-substituted tri-anthanilides

helical conformations whereas three compounds exist as an equilibrium mixture of the four conformational diastereoisomers.   This situation is to be contrasted with those previously observed (i) for trisalicylide derivatives [2,3,30] where the propeller conformation is generally the more stable, and (ii) for trithiosalicylide derivatives [1,31] where only helical conformations have been characterised.

Table 15 lists the activation parameters for conformational interconversions and inversions in the various N,N'di- and N,N',N''-tri-substituted trianthranilides. We propose that, although a pedalling mechanism [25] is possible during the reorientation of trans-CONH-linkages, substituted trans-CONR-linkages must undergo re-orientation via cis-intermediates (cf. trithiosalicylides [1,31]). This mechanism avoids the necessity of having either the carbonyl oxygen atom or a bulky R substituent pass through the middle of the twelve-membered ring. Inspection of space-filling molecular models demonstrates that both these situations are denied to N,N',N''-tri-substituted trianthranilide derivatives on steric grounds.

The Conformational Behaviour of 5,11,17-Trimethyl-

(21) and 5,11,17-Tribenzyl-6,6,12,12,18,18-hexadeuterio-(22) 5,6,11,12,17,18-hexahydrotribenzo[b,f,j][1,5,9]tri-azacyclododecine.—It was decided to take advantage of the ready availability, from hydride and deuteride reductions, of N,N',N''-trimethyl- (7) and N,N',N''-tribenzyl- (15) trianthranilides respectively, of the two cyclic triamines (21) and (22) to investigate their conformational behaviour in solution. The ¹H n.m.r. spectrum of the N,N',N''-trimethyl cyclic triamine (21) in deuteriochloroform–carbon disulphide (2 : 1) exhibited singlets at τ 5.47 and 7.20 for the methylene and N-methyl protons, respectively. When the temperature was lowered to −90 °C only very slight broadening of these signals occurred.   Thus, any conformational changes in solution appear to be proceeding rapidly on the ¹H n.m.r. time scale even at −90 °C.   In principle, it might have been possible to obtain spectral data capable of interpretation at temperatures considerably lower than −90 °C.   In practice, such experiments were not performed because of (i) difficulties in finding a solvent system which would not freeze between −100 °C and −150 °C and in

TABLE 14

The ground-state populations (%) in deuteriochloroform solutions at room temperature for N,N'-di- and N,N',N''-tri-substituted trianthranilides

	Compound			Conformations				
No.	R¹	R²	R³	P/P*	H-1/H-1*		H-2/H-2*	H-3/H-3*
(5)	Me	Me	H	0		100 ᵃ		0
(12)	Me	Me	CH₂Ph	19	41		7	33
(14)	CH₂Ph	CH₂Ph	H	0		100 ᵃ		0
(16)	CH₂Ph	CH₂Ph	Me	36	7		48	9
(17)	Me	CH₂Ph	H	0		100 ᵃ		0
(18)	Me	CH₂Ph	Et	0	0		0	100
(19)	Me	Et	H	0		100 ᵃ		0
(20)	Me	Et	CH₂Ph	8	52		21	19

ᵃ Although the chemical shift data suggest that the N,N'-disubstituted derivatives (5), (14), (17), and (19) prefer to adopt H-2/H-2* conformations, the fact that distorted H-1 and/or H-1* conformations, stabilized by intramolecular hydrogen bonding involving the unsubstituted amide linkages, are observed for N,N'-dimethyl- (5) and N,N'-dibenzyl- (14) trianthranilides in the solid state prompts us to be cautious about assignments of ground-state conformation or conformations to (5), (14), (17), and (19) in deuteriochloroform solution.

which the compound would remain soluble and (ii) the inherent instability of the N,N',N''-trimethyl cyclic triamine (21) itself. Consequently, it was decided to investigate the conformational behaviour of the corresponding hexadeuteriated N,N',N''-tribenzyl derivative (22) in solution. The ^{1}H n.m.r. spectrum of this compound in deuteriochloroform–carbon disulphide (1 : 1) solution showed a singlet at τ 5.99 for the benzylic-methylene protons at ambient temperature, which became very broad at −37 °C (see Figure 37). By −54 °C, a well resolved set of signals could be discerned which can be assigned tentatively at least to three AB systems as shown in Figure 8. Attempts to assign the individual AB systems (i) by conventional decoupling techniques and (ii) by spin-tickling experiments in the FT mode were unsuccessful on account of the relatively small chemical-shift differences between the overlapping AB systems. The coalescence of the three AB systems into a singlet at higher temperatures can be associated with a process involving ring inversion between asymmetric enantiomeric helical conformations. There are four site-exchange processes (see Experimental section) corresponding to the four ways in which three AB systems can be assigned to the six benzylic-methylene sites in a helical conformation. The fact that it was not possible to obtain a good match with any of the four processes (see Figure 8) suggests that some propeller conformations might be present in the equilibrium mixture. Nonetheless, an approximate value of 12.4 kcal mol^{-1} for the free energy of activation associated with a conformational change in this compound was calculated from estimates of the rate constant. This value is in accord with expectation (for tribenzocyclododecatriene,[25] $\Delta G^{\ddagger}$ (H $\rightleftharpoons$ H*) ≃10.0 kcal mol^{-1}, for 6,12,18-trihydrotribenzo[b,f,j]-[1,5,9]trithiacyclododecine,[10] $\Delta G^{\ddagger}$ (H $\rightleftharpoons$ H*) = 9.3 ± 0.2 kcal mol^{-1}, and 6,12,18-trihydrotribenzo[b,f,j]-
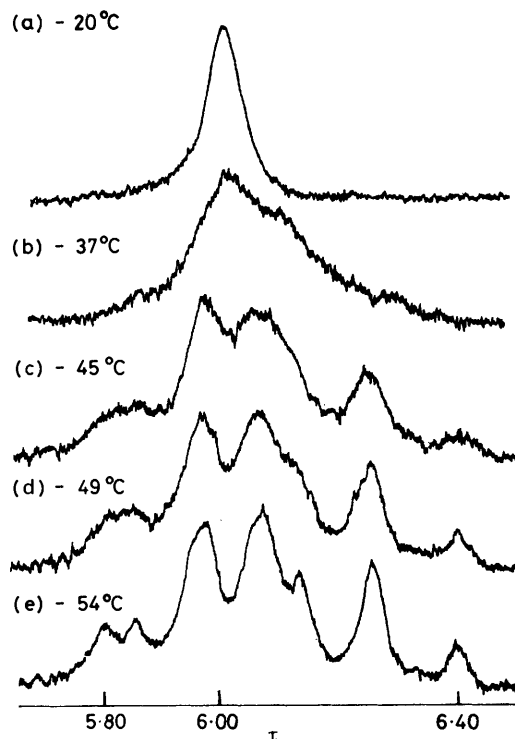

FIGURE 37 The temperature dependence of the signals for the methylene protons in the ^{1}H n.m.r. spectrum of the N,N',N''-tribenzyl cyclic triamine (22) recorded in deuteriochloroform–carbon disulphide: (a) at −20 °C; (b) at −37 °C; (c) at −45 °C; (d) at −49 °C; (e) at −54 °C

[1,5,9]trithiacyclododecine 5,5,11,11,17,17-hexaoxide,[10] $\Delta G^{\ddagger}$ (H $\rightleftharpoons$ H*) = 11.3 ± 0.4 kcal mol^{-1}.

An interesting additional property of the N,N',N''-tribenzyl cyclic triamine (22) is its propensity to form an inclusion compound with ethanol. The ethanol can be

TABLE 15

The free energies of activation ($\Delta G^{\ddagger}$/kcal mol^{-1}) for conformational changes in N,N'-di- and N,N',N''-tri-substituted trianthranilides

No.	Compound R^1	R^2	R^3	Solvent	Process	$\Delta G^{\ddagger}$
(5)	Me	Me	H	CHCl$_3$	H $\rightleftharpoons$ H*	20.7 (+2 °C) ^{a}
(7)	Me	Me	Me	PhNO$_2$	P $\longrightarrow$ H	21.7 ± 0.3 ^{b}
					H $\longrightarrow$ P	24.1 ± 0.4 ^{b}
					H $\rightleftharpoons$ H*	24.6 ± 1.2 ^{b}
				CDCl$_3$	P $\longrightarrow$ H	21.5 ± 0.5 (+10 °C) ^{c}
					H $\longrightarrow$ P	23.0 ± 0.5 (+ 10 °C) ^{c}
(12)	Me	Me	CH$_2$Ph	PhNO$_2$	P $\longrightarrow$ H	23.9 ± 0.2 ^{b}
					H $\longrightarrow$ P	25.1 ± 0.3 ^{b}
					H $\rightleftharpoons$ H*	26.2 ± 0.2 ^{b}
(14)	CH$_2$Ph	CH$_2$Ph	H	CD$_3$SOCD$_3$	H $\rightleftharpoons$ H*	22.6 ± 0.2 ^{b}
(15)	CH$_2$Ph	CH$_2$Ph	CH$_2$Ph	CD$_3$SOCD$_3$	P $\longrightarrow$ H	24.8 ± 0.5 (+63 °C) ^{c}
					H $\longrightarrow$ P	24.3 ± 0.5 (+63 °C) ^{c}
					P $\rightleftharpoons$ P*	26.2 ± 0.1 ^{b}
(16)	CH$_2$Ph	CH$_2$Ph	Me	PhNO$_2$	P $\longrightarrow$ H	25.4 ± 0.4 ^{b}
					H $\longrightarrow$ P	25.6 ± 0.5 ^{b}
					H $\rightleftharpoons$ H*	25.9 ± 0.1 ^{b}
(17)	Me	CH$_2$Ph	H	CD$_3$SOCD$_3$	H $\rightleftharpoons$ H*	21.6 (+160 °C) ^{d}
(18)	Me	CH$_2$Ph	Et	CD$_3$SOCD$_3$	P $\longrightarrow$ H, H $\longrightarrow$ P	>27
(20)	Me	Et	CH$_2$Ph	CD$_3$SOCD$_3$	P $\longrightarrow$ H, H $\longrightarrow$ P	>27

^{a} Determined by polarimetry. ^{b} Determined by line-shape analysis. ^{c} Determined by equilibration. ^{d} Calculated at the coalescence temperature.

removed under reduced pressure (<1.0 mmHg) at $+70$ °C in 5 h.

The Conformational Behaviour of N,N'-*Dibenzyldianthranilide* (4).—The benzylic methylene protons of N,N'-dibenzyldianthranilide (4), which resonated as an AB system ($\tau_A = 4.77$, $\tau_B = 5.35$, $J_{AB} = 15.0$ Hz) in the ^{1}H n.m.r. spectrum recorded in hexadeuteriodimethyl sulphoxide at $+22$ °C remained unaltered apart from small chemical-shift changes on heating the solution up to $+180$ °C. It follows that (4) undoubtedly exists in enantiomeric boat conformations (*cf.* di-*o*-thymotide,[2] di-*o*-carvacrotide,[2] and di-*o*-thiothymotide[1]) with a barrier to their ring inversion in excess of 27 kcal mol⁻¹. In view of the observations [21] (i) that the barrier to ring inversion between enantiomeric boat conformations in the cyclic lactam (85) is 21.4 kcal mol⁻¹ in nitrobenzene, and (ii) that the constitutionally isomeric bislactam (86) also exhibits independence of line shapes in its ^{1}H n.m.r. spectrum upon heating a hexadeuteriodimethyl sulphoxide solution up to $+180$ °C, this result is not surprising. It merely stresses the fact that the resonance

(85)   (86)
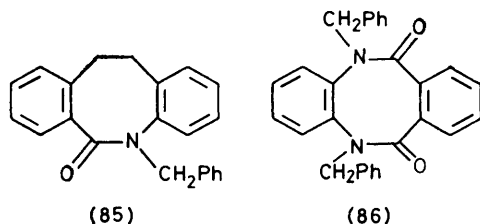
demands of *cis*-amide linkages are appreciable and are considerably greater than those of *cis*-ester or *cis*-thioester linkages.

Note added in proof. There is a satisfying correlation between the conformational behaviour of the 12-membered trianthranilides reported in this paper and the conformational behaviour of 13-membered lactams (87)—(89) which have been discussed recently by J. M. Brown, P. A. Chaloner, and D. R. M. Martens [*J. Chem. Res.* (*S*), 1981, 380].
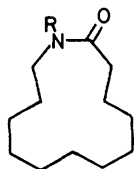
(87) R = H
(88) R = Me
(89) R = PhCH₂

Three compounds have been examined including the parent lactam (87), its N-methyl derivative (88), and its N-benzyl derivative (89). Their conformational behaviour has been interpreted in terms of the existence in solution of two conformational isomers: the chiral *trans*-lactams with planar *trans*-amide groupings and the *cis*-lactams with planar *cis*-amide groupings. Three processes are considered

for inversion between the two enantiomeric conformations of the chiral *trans*-lactams: (i) pedalling of the planar *trans*-amide grouping so that the R-substituent of the NR group passes *inside* through the 13-membered ring, (ii) pedalling of the planar *trans*-amide grouping so that the oxygen atom of the carbonyl group passes *inside* through the 13-membered ring, and (iii) bond rotation within the amide group so that the following route for inversion is permitted:

trans-lactam ⇌ *cis*-lactam ⇌ *trans*-lactam*

The parent lactam (87) is presumed to adopt only one conformation with a *trans*-amide grouping. This compound (87) shows no detectable evidence of temperature dependence of its n.m.r. spectrum down to -60 °C. It is therefore assumed that inversion of the chiral *trans*-lactam (87) is fast and occurs by process (i).

The *cis*- and *trans*-lactam conformations are both populated in the N-methyl derivative (88) and the consequences of inversion between enantiomeric *trans*-lactam conformations is detectable in its temperature-dependent n.m.r. spectrum. It is proposed that this inversion occurs by process (ii) and that the amide rotation required for process (iii) is not involved.

The *cis*- and *trans*-lactam conformations are both populated in the N-benzyl derivative (89) and it is proposed that process (ii) and process (iii) are both involved in the inversion of the chiral *trans*-lactam (89). From the results quoted, the following free energies of activation can be calculated using the Eyring equation. Process (ii) ($\Delta G_{\ddagger}^{\ddagger} = 15.3$ kcal mol⁻¹) which involves *inside* passage of the carbonyl oxygen through the 13-membered ring is less demanding than process (iii) ($\Delta G_{\ddagger}^{\ddagger} = 17.3$ kcal mol⁻¹) in which amide-rotation (*trans*-amide ⇌ *cis*-amide) is involved. The relative rates of process (ii) and process (iii) for the N-benzyl derivative (89) contrasts with our results on the inversion of trianthranilide derivatives. Our proposal for trianthranilide inversion necessarily requires amide-rotation with the involvement of conformations with *cis*-amide linkages as transition states. This is an acceptable consequence of the relatively greater rigidity and relatively smaller size of the 12-membered ring of trianthranilides as compared with the 13-membered ring of the lactams (87)—(89). Processes which are believed to involve *trans*-amide ⇌ *cis*-amide equilibration in trianthranilides all have free energies of activation (see Table 15, page 1697) which are greater than 20.7 kcal mol⁻¹. Since this value exceeds that required for amide-rotation process (iii) ($\Delta G_{\ddagger}^{\ddagger} = 17.3$ kcal mol⁻¹) exhibited by the *trans*-lactam (89), the results recently reported by Brown, Chaloner, and Martens provide a very satisfying model for our proposal for the conformational behaviour of trianthranilides.

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