Synthesis of Some 9-Aminoacridines with Bulky Substituents

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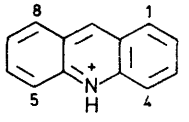
2-s-Butyl-, 2-t-butyl-, and 2,7-di-t-butyl-9-aminoacridine, and other acridines, have been synthesised from the corresponding 2-carboxydiphenylamines (diphenylamine-2-carboxylic acids). Their ^{1}H n.m.r. spectra have shown that earlier assignments made for 9-aminoacridine must be revised. The n.m.r. spectra for intermediates in the syntheses show a steric effect for the t-butyl group and indicate the presence of geometric and rotational isomers of the sterically hindered benzimidates, which were rearranged to give the carboxydiphenylamine derivatives. The t-butyl group was eliminated in all attempts to prepare 9-t-butylaminoacridine. Acridine, 9-aminoacridine, and a number of other derivatives could not be alkylated at position 10 by a variety of large alkylating agents because preferential elimination took place.

AMINOACRIDINES have an immense range of biological activity,[1] much of which may be due to their ability to react with nucleic acids. Two types of interaction with DNA have been characterised experimentally.[2] In one, for which the binding energy is *ca.* 25—42 kJ mol^{-1}, the acridine molecule is thought to slip into the double helix between successive base pairs, and *ca.* 0.2 mol acridine is bound per mol of DNA phosphate. In the other, for which the binding energy is much less (< *ca.* 10 kJ mol^{-1}), the acridine is considered to be attached to the outside of the helix (*ca.* 1 mol per mol of DNA phosphate).

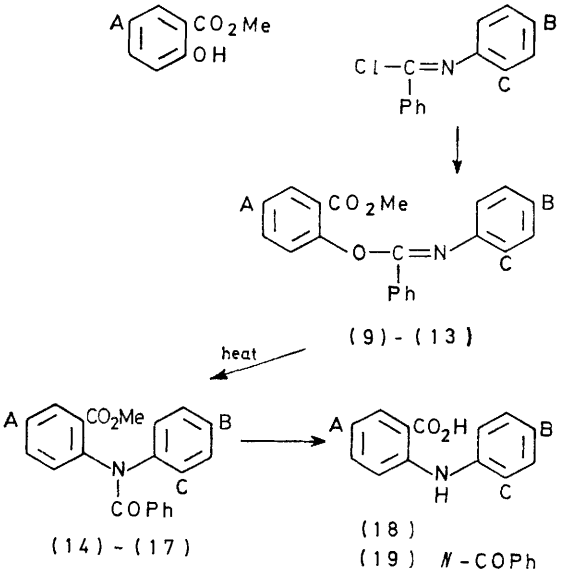
To study the steric requirements for binding within and without the helix, a number of 9-aminoacridines (1)—(8) with bulky substituents have been synthesised. The binding experiments are in progress and will be reported elsewhere.

The 9-aminoacridines (1), (2), and (8) were obtained from the appropriate 2-carboxydiphenylamines (diphenylamine-2-carboxylic acids by successive treatment with phosphoryl chloride and ammonium carbonate, the carboxylic acids being prepared by Ullmann [3] reactions. 6-Amino-2-s-butylacridinium chloride (3) was synthesised from 2-carboxy-5-nitro-4'-s-butyldiphenylamine by successive treatment with phosphoryl chloride, hydrochloric acid, sodium amalgam, and iron(III) chloride.



(1) 9-NH_2-2-Bu^s
(2) 9-NH_2-2-Bu^t
(3) 6-NH_2-2-Bu^s
(4) 9-NH_2-2,7-Bu^t_2
(5) (+)-9-Bu^sNH
(6) (−)-9-Bu^sNH
(7) 9-NH_2-4-Et
(8) 9-NH_2-2-Bu^s-6-NO_2 (base)

As the 2-carboxydiphenylamines required for the synthesis of the 4-t-butyl- and 2,5- and 2,7-di-t-butyl-9-aminoacridine could not be obtained by the Ullmann reaction, the Jamieson–Turner synthesis,[4] involving the Chapman rearrangement, was examined (Scheme). Although the benzimidate (10) did not rearrange and the benzoyldiphenylamine (15) resisted hydrolysis, the synthesis of 9-amino-2,7-di-t-butylacridine (4) was achieved.



Compound	A	B	C
(9), (14), (18)	Bu^t	Bu^t	H
(10)	Bu^t	H	Bu^t
(11), (15), (19)	H	H	Bu^t
(12), (16)	H	H	Me
(13), (17)	H	Bu^t	H

SCHEME

All attempts to prepare 9-t-butylaminoacridine failed, the butyl group being eliminated: cyclisation of 2-t-butylcarbamoyldiphenylamine with phosphoryl chloride or phosphorus pentachloride, and the reactions of 9-chloro- and 9-phenoxy-acridine and their 2,7-di-t-butyl derivatives with t-butylamine, gave only the 9-aminoacridines.

As the s-butylacridines (1) and (3) could not be resolved into their optical isomers by chromatography

[1] 'The Acridines,' ed. R. M. Acheson, 2nd edn., Wiley, New York, 1973.
[2] A. R. P. Peacocke, in ref. 1, p. 723.
[3] J. M. F. Gagan, in ref. 1, p. 161.
[4] M. M. Jamison and E. E. Turner, *J. Chem. Soc.*, 1937, 1954; J. M. F. Gagan, in ref. 1, p. 171.

on Woelm acetylcellulose,[5] or by crystallisation of the salts of (+)-camphor-10-sulphonic acid or 3-bromo-(+)-camphor-8-sulphonic acid, (+)- and (−)-9-s-butylaminoacridinium chlorides (5) and (6) were synthesised from 9-phenoxyacridine by treatment with (+)- and (−)-s-butylamine in phenol.[6] These amines were separated from the racemic mixture by multiple crystallisation of the hydrogen tartrates,[7] monitored by formation of *N*-s-butylbenzamide.[8] (+)-s-Butylamine was obtained optically pure, but (−)-s-butylamine was only obtained in 71.5% optical purity by this procedure.

Attempts to prepare (9,10)acridinophanes (a 9,10-bridge would shield one side of the aromatic system from interaction with nucleic acids) were unsuccessful. The 3% yield of 9-(11-methoxyundecyl)acridan from acridine and 11-methoxyundecylmagnesium bromide could not be increased. 11-Bromoundecylamine with 2-chlorocarbonyldiphenylamine surprisingly gave the diacylamine, whatever the conditions, so cyclisation of the monoamide to the 9-aminoacridine and intramolecular quaternisation could not be attempted. Attempts were made to quaternise acridine, methyl acridine-9-carboxylate, methyl 3-(acridin-9-yl)propionate, and 9-aminoacridine with n-propyl iodide, methyl chloroacetate, chloroacetonitrile, chloroacetic acid, methyl 3-iodopropionate, methyl 6-iodo- and 6-bromo-hexanoate, methyl 11-iodo-, 11-bromo-, and 11-tosyl-undecanoate, and 1-iodo-11-methoxyundecane without solvent and in dimethylformamide, xylene, nitrobenzene, and butanol, in the expectation that this could be followed eventually by cyclisation and lead to an acridinophane. However no quaternary salts were obtained except from acridine and n-propyl iodide in xylene, in general agreement with the less extensive results of Zanker *et al.*[9] Acridinium chloride was obtained from acridine in nitrobenzene with methyl chloroacetate, chloroacetic acid, and chloroacetonitrile, and acridinium iodide was obtained both from acridine and all the iodo-compounds in butanol and from methyl 3-iodopropionate in all the solvents. 9-Aminoacridinium iodide was obtained from 9-aminoacridine in xylene with n-propyl iodide, and methyl 6-iodohexanoate and 11-bromoundecanoate, in agreement with the observation of Ioffe and Selezneva [10] that 9-aminoacridine could not be quaternised with groups larger than the ethyl group. There is clearly a strong tendency towards Hoffmann elimination, rather than alkylation in the acridine series, and this can be associated with the steric hindrance caused to 10-substituents by the 4- and 5-hydrogen atoms.

The n.m.r. spectra of the acridines and their synthetic precursors are presented in Table 1 (and the Supplementary Publication). The n.m.r. spectrum for acridine at 60 MHz has previously been simulated [11] to ±0.1 Hz, and almost as good agreement has now been obtained by using the same parameters and a LAOCOON III calculation for the 100 MHz spectrum. The assignment of the particular resonances to the 1-, 2-, 3-, and 4-protons respectively could have been made in the reverse order, but are correct for they agree with the definite assignments which are possible for 2,7,9-trideuterioacridine.[12] Unambiguous proton assignments can also be made for 9-amino- and 9-chloro-2,7-di-t-butylacridine, and comparing the resonance positions of the protons in the former compound with those reported for the computer simulated spectrum of 9-aminoacridine,[11] shows that the four-spin system for this last compound was previously assigned the wrong way round. The lowest field aromatic protons for both 9-amino-2,7-di-t-butylacridine (4) and its hydrochloride are at positions 1 and 8, and the downfield shifts for protons on cation formation are in the order H-3 > H-1 > H-4 > H-2, the last hardly changing position. This can be correlated with the impossibility of placing the formal positive charge of the cation at position 2. The 1- and 8-protons of methyl acridine-9-carboxylate are not significantly deshielded by the ester group, which must therefore be forced out of the ring plane by the nearby atoms; however these protons are significantly deshielded by a 9-chlorine atom or a 9-cyano-group, and in dimethyl acridin-9-ylmalonate.

The n.m.r. spectra of the 2-carboxydiphenylamines (Table 1 and Supplementary Publication) could be assigned on the assumption that the lowest field proton (τ *ca.* 2) was *ortho* to the carboxy-group, and that the amino-group exerts its usual shielding effect on *ortho*- and *para*-hydrogen atoms. The unambiguous assignments which can be made for 2-carboxy-4,4′-di-t-butyldiphenylamine are consistent with these interpretations.

Restricted rotation about the N–C bond for various amides, which may be considered due to contributions from charged resonance structures [*e.g.* (24)] and not to nitrogen inversion, accounts for the variable temperature n.m.r. phenomena shown by several amides, the coalescence temperatures for *NN*-dimethylbenzamide [13] and 2-benzoylisoindoline [14] being 11 and 56 °C respectively. The variable temperature phenomena shown by the diphenylamides (15) and (16) are too complex (Table 2) to be accounted for solely on a similar hypothesis. The single ring-methyl resonance for the amide (16) splits into two, then three, and then four peaks on lowering the temperature, although the ester-methyl signal remains as a singlet, while for (15) the t-butyl and the ester-methyl resonances split into two peaks at *ca.* 55 and 30 °C, respectively. Two types

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[6] D. J. Dupré and F. A. Robinson, *J. Chem. Soc.*, 1945, 549.
[7] A. Fleury-Larsonneau, *Bull. Soc. chim. France*, 1939, **6**, 1576.
[8] P. Bruck, I. N. Denton, and A. H. Lamberton, *J. Chem. Soc.*, 1956, 921.
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[11] J. P. Kokko and J. H. Goldstein, *Spectrochim. Acta*, 1963, **19**, 1119.
[12] R. G. Bolton, D.Phil. Thesis, Oxford, 1970.
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[14] K. Farig and J. T. Gerig, *J. Amer. Chem. Soc.*, 1969, **91**, 3045.

TABLE 1

N.m.r. spectra (100 MHz; τ values; J in Hz; Me_4Si internal reference)

Acridines [in $(CD_3)_2SO$]	Proton resonances
Unsubstituted	1,8-H_2, 1.98; 2,7-H_2, 2.60; 2,6-H_2, 2.21; 4,5-H_2, 1.75; 9-H, 0.90
9-Cl [a]	1,8-H_2, 1.77m; 2,7-H_2, 2.53m; 3,5-H_2, 2.31m; 4,5-H_2, 1.88m
2,7-Bu^t_2-9-Cl [a]	1,8-H_2, 1.67d; 3,6-H_2, 2.08q; 4,5-H_2, 1.80d; $J_{1,3}$ 1.5; $J_{3,4}$ 9.0; Bu^t_2, 8.50s
9-CN [a]	1,8-H_2, 1.75m; 2,7-H_2, 2.26m; 3,6-H_2, 2.13m; 4,5-H_2, 1.68m
9-$CH(CO_2Et)_2$	1,8-H_2, 1.58m; 2,7-H_2, 2.22m; 3,6-H_2, 1.98m; 4,5-H_2, 1.68m; $CH(CO_2Et)_2$, 3.31s; $(CH_2{\cdot}CH_3)_2$, 5.71q; $(CH_2{\cdot}CH_3)$, 7.91t
9-CO_2Me [a]	1,8-H_2, 2.02m; 2,7-H_2, 2.44m; 3,6-H_2, 2.22m; 4,5-H_2, 1.76m; Me, 5.81s
9-Me	1,8-H_2, 1.92m; 2,7-H_2, 2.53m; 3,6-H_2, 2.30m; 4,5-H_2, 1.83m; Me, 7.45s
Acridinium chlorides [in $(CD_3)_2SO$]	
9-NH_2	1,8-H_2, 1.14; 2,7-H_2, 2.4m; 3,4,5,6-H_4, 1.9m
9-NH_2 [b]	1,8-H_2, 2.14m; 2,7-H_2, 2.66m; 3,6-H_2, 2.35m; 4,5-H_2, 1.56m
9-NH_2-2,7-Bu^t_2	1,8-H_2, 1.35m; 3,6-H_2, 1.85m; 4,5-H_2, 2.05m; 10-H, 0.09br, s; $J_{3,4}$ 9
9-NH_2-2,7-Bu^t_2 [d]	1,8-H_2, 1.83;[c] 3,6-H_2, 2.38;[c] 4,5-H_2, 2.38;[c] Bu^t_2, 8.60s
2-Carboxydiphenylamines [in $(CD_3)_2SO$]	
4′-Bu^t	3-H, 2.50q; 4-H, 3.21m; 5-H, 2.60m; 6-H, 2.80;[d] $J_{3,4}$ 8; $J_{3,5}$ 1.5; $J_{4,5}$ 7; $J_{4,6}$ 1.5; $J_{5,6}$ 8; 2′,6′-H_2, 2.80;[d] 3′,5′-H_2, 2.56d; $J_{2',3'}$ 8; Bu^t, 8.63s
4,4′-Bu^t_2	3-H, 2.10d; 5-H, 2.58q; 6-H, 2.86d; $J_{3,5}$ 2; $J_{5,6}$ 8; 2′,6′-H_2, 2.90d; 3′,5′-H_2, 2.66d; $J_{2',3'}$ 8.5; Bu^t_2, 8.73s
Benzene derivatives [in $CDCl_3$]	
1-NH_2-2-Bu^t [e]	3-H, 2.90q; 4-H, 3.47m; 5-H, 3.08m; 6-H, 3.33q; $J_{3,4}$ 7.5; $J_{3,5}$ 1.5; $J_{4,6}$ 8; NH_2, 5.3br, s;[f] Bu^t, 8.65s
1-NH_2-4-Bu^t [g]	2,6-H_2, 3.40d; 3,5-H_2, 2.83d; $J_{2,3}$ 8.5; Bu^t, 8.70s; NH_2, 6.58br, s
2,4-$(NO_2)_2$-1-Bu^t [g]	3-H, 1.75d; 5-H, 1.66q; 6-H, 2.16d; $J_{3,5}$ 2.5; $J_{5,6}$ 8.5; Bu^t, 8.61s
1-NO_2-4-Bu^t [g]	2,6-H_2, 2.45d; 3,5-H_2, 1.85d; $J_{2,3}$ 8.5; Bu^t, 8.60s
1-NO_2-2-Bu^t	ArH_4, 2.35—2.75m; Bu^t, 8.60s

[a] In $CDCl_3$. [b] Free base; lit. value.[11] [c] Apparent singlet, but showed signs of splitting. [d] Resonances overlap. [e] In $(CD_3)_2SO$. [f] Disappears in D_2O. [g] At 60 MHz.

TABLE 2

N.m.r. spectra of some N-benzoyl-2-methoxycarbonyldiphenylamines (in $CDCl_3$ at 100 MHz; Me_4Si as internal reference; τ values)

Compd.	Proton resonances
(14)	ArH_{12}, 2.0—3.0m; Bu^t_2, 8.68, 8.73 (1 : 1); OMe, 6.18s
(15) [a]	Bu^t, 8.35,[b] 8.71 [b] (2 : 3); OMe, 6.27,[c] 6.35 [c] (2 : 3)
(16)	ArH_{13}, 1.8—3.2m; Me, 7.60br,[d] 7.80 [d] (1 : 1); OMe, 6.19s
(17)	ArH_{13}, 2.0—3.0m; Bu^t, 8.74s; OMe, 6.20s
(19) [e]	ArH_{13}, 2.0—3.2m; Bu^t, 8.48, 8.81 (4 : 3)

[a] In pyridine, aromatic region obscured. [b] Unchanged from +50 to −75 °C and at 60—80 °C single resonance at 8.55 observed. [c] Unchanged from +25 to −75 °C; single resonance at 6.28 between +35 and +70 °C. [d] Singlet at 7.65 above 35 °C in o-dichlorobenzene; in $CDCl_3$ splits to resonances at 7.41, 7.61, and 7.77 from −12 to −48 °C, and to 7.45, 7.65, 7.75, and 7.85 at −67 to −75 °C. [e] In $(CD_3)_2SO$. The shifts of the double peaks are followed, in parentheses, by their relative intensities expressed as ratios.

of geometric isomerism are therefore being detected, and these arise from restricted rotation about the amide C–N bond and about the aryl–N bonds; in structure (24) the R and ester groups can be '*cis*' or '*trans*,' and examples of this type of isomerism are known.[15] It is not possible to be certain which type of isomerism is responsible for the first peak splitting observed on cooling the hot solutions, but it is likely that this is due to restriction of rotation of the N-aryl substituents, as these are the closest groups [particularly in the case of the t-butyl compound (15)]. As diphenylamines are relatively non-basic, the contribution of the lone pair of the nitrogen atom to charged resonance structures such as (24) would be less than in the case of *NN*-dialkylamides, which could result in lower coalescence temperatures.

The n.m.r. spectra of the benzimidates (9)—(13) and (20)—(23) in deuteriochloroform (Table 3) showed normal features, but in trifluoroacetic acid (Table 4),

TABLE 3

N.m.r. spectra of benzimidates (in $CDCl_3$; τ values; Me_4Si internal reference; 100 MHz)

Compd.	Proton resonances
(9)	ArH_{12}, 2.0—3.5m; Bu^t_2, 8.68s, 8.79s; OMe, 6.12s
(10)	ArH_{12}, 1.9—3.8m; Bu^t_2, 8.68s, 8.79s; OMe, 6.14s
(11) [a]	Bu^t, 8.65s; OMe, 6.20s
(12)	ArH_{13}, 1.8—3.6m; Me, 7.89s; OMe, 6.10s
(13)	ArH_{13}, 1.9—3.5m; Bu^t, 8.75s; OMe, 6.10s
(20)	ArH_{14}, 2.2—3.5m; Bu^t, 8.62s
(21)	ArH_{13}, 1.9—3.4m; Bu^t, 8.65s; OMe, 6.10s
(22)	ArH_{14}, 2.2—3.5m; Bu^t, 8.64s
(23)	ArH_{13}, 2.4—3.5m; $CH_2{\cdot}CH_3$, 5.51q; $CH_2{\cdot}CH_3$. 8.59t; Bu^t, 8.72s

[a] In pyridine, aromatic region obscured.

TABLE 4

N.m.r. spectra of benzimidates (in $CF_3{\cdot}CO_2H$; τ values; Me_4Si internal reference; 60 MHz) *

Compd.	Proton resonances
(9)	Bu^t_2, 8.57, 8.59, 8.63, 8.65 (1 : 5 : 5 : 1); OMe, 5.84, 5.96 (5 : 1)
(10)	Bu^t_2, 8.39, 8.42, 8.65 (1 : 2 : 1); OMe, 5.83, 5.90 (1 : 1)
(11)	Bu^t, 8.33, 8.45 (1 : 1); OMe, 5.96, 6.02 (1 : 1)
(12)	Ring Me, 7.42, 7.62 (1 : 1); OMe, 5.85, 5.97 (1 : 1)
(13)	Bu^t, 8.60, 8.67 (2 : 1); OMe, 5.87, 5.98 (1 : 2)
(20)	Bu^t, 8.38, 8.55 (3 : 2)
(21)	Bu^t, 8.55, 8.65 (1 : 1); OMe, 5.85, 5.97 (1 : 1)
(22)	Bu^t, 8.60s
(23)	Bu^t, 8.59s; $CH_2{\cdot}CH_3$, 5.20q; $CH_2{\cdot}CH_3$, 8.41t, J 7 Hz

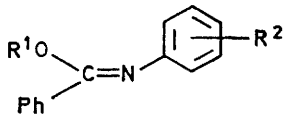
* The shifts of the multiple peaks are followed, in parentheses, by their relative intensities expressed as ratios.

where N-protonation is expected, all except (22) and (23) showed two or more resonances each for both ring alkyl and ester methyl groups. The phenomenon can be associated with the presence of *ortho*-substituents on the aryl groups. The spectra of compounds (10) and (11) did not alter over 5 days, and the compounds were recovered unchanged. Protonation of the benzimidates at the nitrogen atom could give two geometrically isomeric cations (25), and models show that *ortho*-substituents on either aryl group could cause restricted

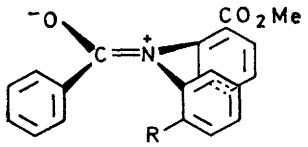
[15] R. M. Acheson and I. A. Selby, *J.C.S. Perkin I*, 1974, 423.

rotation. A combination of these two types of geometrical isomerism, as for the benzoyldiphenylamines (24), could be the cause of the multiple resonances.

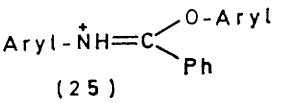
The n.m.r. spectra of relatively few t-butylbenzenes (Table 1 and Supplementary Publication) have been recorded; the steric effect of the large alkyl group on adjacent substituents is of interest. The usual deshielding effect of the nitro-group on the *ortho*-protons



	R^1	R^2
(20)	Ph	2-Bu^t
(21)	4-Bu^t-2-CO_2Me·C_6H_4	H
(22)	Ph	4-Bu^t
(23)	Et	4-Bu^t



(24)



(25)

(τ 1.85) of 1-nitro-4-t-butylbenzene is much reduced in the 2-t-butyl isomer (ArH_4 2.35—2.75m) where the nitro-group cannot be coplanar with the ring; there is little difference between the chemical shifts of the *ortho*-protons of the corresponding amines. As the resonance position (τ 1.75) for the 2-proton of 2,4-dinitro-1-t-butylbenzene shows less deshielding than that of the 5-proton (1.66), it appears that the non-planar 2-nitro-group exerts a small shielding effect in this situation. The shifts caused to the *ortho*-protons by introducing a t- or s-butyl group varied by up to 0.2 p.p.m.

EXPERIMENTAL

The u.v. spectra of the aminoacridines in sodium phosphate buffer at pH 6.9 were recorded with a Cary 14 spectrophotometer; the other instruments and procedures have been described.[15] Light petroleum had b.p. 60—80°. The n.m.r. spectra for the substituted alkanes and acridines, 2-carboxydiphenylamines, and butylbenzenes not detailed here and the u.v. spectra and analytical data for new compounds are available as Supplementary Publication No. SUP 21647 (10 pp., 1 microfiche).* The compound numbers (26)—(47) are used to refer to data in the Supplementary Publication; they do not refer to illustrated structures.

* For details of Supplementary Publications, see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

[16] P. W. B. Harrison, J. Kenyon, and J. R. Shepherd, *J. Chem. Soc.*, 1926, 658.

[17] H. C. Duffin, E. D. Hughes, and C. Ingold, *J. Chem. Soc.*, 1959, 2734.

[18] D. Craig, *J. Amer. Chem. Soc.*, 1935, **57**, 195.

Preparation of 9-Amino-2-s-butyl- and -2-t-butyl-acridinium Chlorides.—*1-Amino-4-s-butylbenzene.* 1-Nitro-4-s-butylbenzene (25 g), obtained in 65% yield [b.p. 141—144° at 100 mmHg (lit., 142—144° at 12 mmHg)] as described,[16] was shaken with palladium–charcoal (1 g) in methanol (300 ml) under hydrogen (5 atm) until absorption ceased. After filtration, distillation gave 1-amino-4-s-butylbenzene (20.2 g), b.p. 116—118° at 13 mmHg [lit.[16] (different procedure), 118° at 15 mmHg].

1-Amino-4-t-butylbenzene was prepared similarly from the nitro-compound;[17] b.p. 113° at 50 mmHg, n_D^{20} 1.5389 (lit.,[18] b.p. 228—230° at 762 mmHg, n_D^{20} 1.5380).

2-Carboxy-4′-s-butyldiphenylamine (26). Potassium carbonate (25 g) was added slowly, with vigorous stirring, to 2-chlorobenzoic acid (10 g) in refluxing cyclohexanol (60 ml). Water and cyclohexanol were distilled off until the reflux temperature reached 162 °C. Activated copper catalyst[19,20] (1 g) and 1-amino-4-s-butylbenzene (10 g) were then added, and the mixture was refluxed for 2 h. Cyclohexanol (20 ml) was distilled off and then refluxing was continued for 3 h. Solvent was then removed by steam distillation and the aqueous residue was boiled for 10 min with charcoal (Norite) (3 g) and filtered hot. The filtrate was acidified to pH 4 at the boil with concentrated hydrochloric acid. The black precipitate yielded the *acid* (26) (35%) as pale yellow needles (from toluene; washed with light petroleum), m.p. 179—181°.

9-Chloro-2-s-butylacridine was prepared from this diphenylamine in the usual way,[21] except that the chloroform-soluble materials in toluene were chromatographed on deactivated alumina, and was obtained initially as a brown oil.

9-Amino-2-s-butylacridinium chloride (1), obtained from the 9-chloroacridine in the usual way,[21] was treated with concentrated hydrochloric acid–methanol (1 : 1) to give *9-amino-2-s-butylacridinium chloride* (60%) as yellow microneedles (from water), m.p. 289—291°. Treatment with sodium hydroxide yielded *9-amino-2-s-butylacridine* as yellow rhombs, m.p. 209—210°.

2-Carboxy-4′-t-butyldiphenylamine was produced (48%), by the method used for the 4′-s-butyl acid, as pale yellow plates (from ethanol; washed with light petroleum), m.p. 205—206° (lit.,[12] 205—206°).

9-Chloro-2-t-butylacridine (27). 2-Carboxy-4′-t-butyldiphenylamine (6 g), by the method used for 9-chloro-2-s-butylacridine, yielded *9-chloro-2-t-butylacridine* (3.5 g, 58%) as yellow needles (from light petroleum), m.p. 67—70°.

9-Amino-2-t-butylacridinium chloride (2). 9-Chloro-2-t-butylacridine (3 g), by the method used for 9-amino-2-butylacridinium chloride, yielded 9-amino-2-t-butylacridinium chloride (2.9 g, 89%) as brilliant yellow needles (from water), m.p. 300—310° (decomp.). Dissolution of this compound in water and treatment with sodium hydroxide (2M) yielded 9-amino-2-t-butylacridine as yellow needles, m.p. 114—115°.

Preparation of 9-Amino-6-nitro-2-s-butylacridine and 6-Amino-2-s-butylacridinium Chloride.—*2-Carboxy-5-nitro-4′-s-butyldiphenylamine* (28). 2-Chloro-4-nitrobenzoic acid, by the procedure used for 2-carboxy-4′-s-butyldiphenylamine

[19] R. Q. Brewster and T. Groening, *Org. Synth.*, Coll. Vol. 2, 1946, p. 445.

[20] R. C. Fuson and E. A. Cleveland, *Org. Synth.*, Coll. Vol. 3, 1955, p. 339.

[21] A. Albert and B. Ritchie, in *Org. Synth.*, Coll. Vol. 3, 1955, p. 53.

except that isopentyl alcohol was used and the reflux temperature was 128 °C, yielded 2-*carboxy*-5-*nitro*-4'-*s*-*butyldiphenylamine* (58%) as orange microcrystals (from toluene), m.p. 184—185°.

9-*Chloro*-6-*nitro*-2-*s*-*butylacridine* (29). 2-Carboxy-5-nitro-4'-s-butyldiphenylamine (1 g), by the method used for 9-chloro-2-s-butylacridine, yielded 9-*chloro*-6-*nitro*-2-*s*-*butylacridine* (0.55 g, 55%) as pale yellow needles (from light petroleum), m.p. 149—150°.

9-*Amino*-6-*nitro*-2-*s*-*butylacridine* (8) 9-Chloro-6-nitro-2-s-butylacridine (0.4 g), by the method used for 9-amino-2-s-butylacridinium chloride, yielded 9-amino-6-nitro-2-s-butylacridinium chloride which, on dissolution in water and pouring into sodium hydroxide (2N), gave 9-*amino*-6-*nitro*-2-*s*-*butylacridine* (0.18 g) (45%) as a dark red amorphous solid (purified by alkaline precipitation from a solution of the hydrochloride), m.p. 154—156°.

6-*Nitro*-2-*s*-*butyl*-9-*acridone* (30). 2-Carboxy-5-nitro-4'-s-butyldiphenylamine (11 g) yielded, by the literature method [22] for 4-nitro-9-acridone, 6-*nitro*-2-*s*-*butyl*-9-*acridone* (7 g, 63%) as yellow needles (from toluene–ethanol, 4 : 1), m.p. 334—335° (blackened at 320°).

6-*Amino*-2-*s*-*butylacridan*. 6-Nitro-2-s-butyl-9-acridone (6 g) was reduced, by the literature method for 4-aminoacridan,[23] with sodium amalgam (4%),[24] to give 6-amino-2-s-butylacridan (4.5 g, 93%), which was too quickly oxidised by air to give good analytical data.

6-*Amino*-2-*s*-*butylacridinium chloride* (3). 6-Amino-2-s-butylacridan (4 g) was oxidised by iron(III) chloride, by the literature method for the conversion of acridans into acridines,[25] to give crude 6-amino-2-s-butylacridine, which was briefly boiled with hydrochloric acid (2M); the solution was filtered and kept overnight at 0 °C to give 6-*amino*-2-*s*-*butylacridinium chloride* (72%) as deep red microcrystals (from 2M-hydrochloric acid), m.p. 169—170°.

2-*Hydroxy*-5-*t*-*butylbenzoic Acid* (31).—*p*-t-Butylphenol (50 g) under the optimum conditions for carboxylation of *p*-cresol,[26] yielded 2-*hydroxy*-5-*t*-*butylbenzoic acid* (49.9 g, 73%) as needles (from benzene), m.p. 159°. Acetylation, by the procedure described for acetylsalicyclic acid,[27] yielded 2-*acetoxy*-5-*t*-*butylbenzoic acid* (32) (52%) as plates (from acetic acid) (30%), m.p. 120—130°; esterification with methanol and sulphuric acid gave *methyl* 2-*hydroxy*-5-*t*-*butylbenzoate* (33) as plates (from methanol), m.p. 51.5—52.5°.

1-*Benzamido*-4-*t*-*butylbenzene* was prepared (65%), by the literature method for benzanilide,[28] as plates (from ethanol), m.p. 143—144° (lit.,[18] 134°).

N-(4-*t*-*Butylphenyl*)*benzimidoyl Chloride*.—1-Benzamido-4-t-butylbenzene (20 g) was refluxed for 2 h with thionyl chloride (80 ml); the excess was removed *in vacuo* and the resulting oil kept *in vacuo* at 70 °C for 0.5 h. The residual crude benzimidoyl chloride was immediately used in the preparation of the benzimidates. This procedure was used for all the benzimidoyl chlorides employed in the synthesis of the benzimidates (Table 5) by the literature procedure.[4] Rearrangement as described gave (Table 6) the corresponding *N*-benzoyl-2-methoxycarbonyldiphenylamines.

[22] A. Albert and W. Gledhill, *J. Soc. Chem. Ind.*, 1945, **64**, 169.
[23] G. R. Clemo, W. H. Perkin, and R. Robinson, *J. Chem. Soc.*, 1924, **125**, 1751.
[24] L. F. Fieser and M. Fieser, ' Reagents for Organic Syntheses,' Wiley, New York, 1967, p. 1180.
[25] A. Albert and J. B. Willis, *J. Soc. Chem. Ind.*, 1946, **65**, 26.
[26] D. Cameron, H. Jeskey, and O. Baine, *J. Org. Chem.*, 1950, **15**, 233.

2-*Carboxy*-4,4'-*di*-*t*-*butyldiphenylamine* (18). *N*-Benzoyl-2-methoxycarbonyl-4,4'-di-t-butyldiphenylamine, by the general literature method,[4] yielded 2-*carboxy*-4,4'-*di*-*t*-*butyldiphenylamine* (91%) as pale yellow needles (from toluene), m.p. 218—219°.

9-*Chloro*-2,7-*di*-*t*-*butylacridine* (34).—2-Carboxy-4,4'-di-t-butyldiphenylamine, by the method for 9-chloro-2-s-butylacridine, yielded 9-*chloro*-2,7-*di*-*t*-*butylacridine* (61%) as yellow needles (from light petroleum), m.p. 124—125°.

TABLE 5

Synthesis of benzimidates

Compd.	Yield (%)	M.p. (°C)	Appearance [a]
(9)	51	114—115	Needles
(10) [b]	74	109—110	Needles
(11)	91	131—132	Rhombs [c]
(12)	91	79—81	Needles
(13)	88	115—117	Plates
(20)	16	49—50	Needles
(21)	80	105—106	Needles
(22)	59	84—85	Needles
(23)	96	64.5—65	Needles

[a] From ethanol. [b] Attempted rearrangements of (10) failed. [c] From benzene–light petroleum.

TABLE 6

Rearrangement of benzimidates

Product	Yield (%)	M.p. (°C)	Appearance [a]
(14)	89	145	Rhombs
(15)	75	146—147	Needles
(16)	85	139—140	Needles
(17)	87	109—110	Needles

[a] From ethanol.

9-*Amino*-2,7-*di*-*t*-*butylacridinium Chloride* (4).—9-Chloro-2,7-di-t-butylacridine, by the method for 9-amino-2-s-butylacridinium chloride, yielded 9-*amino*-2,7-*di*-*t*-*butylacridinium chloride* (87%) as brilliant orange needles (from ethanol), m.p. 314—316°. Dissolution of this compound in water and treatment with sodium hydroxide (2M) yielded 9-*amino*-2,7-*di*-*t*-*butylacridine*, m.p. 190—192°.

Attempted Preparation of 9-*Amino*-2,5-*di*-*t*-*butylacridinium Chloride*.—2,4-Dinitro-1-t-butylbenzene was prepared in 90% yield as reported;[29] reduction as for *m*-dinitroaniline [30] yielded first 2-*nitro*-4-*t*-*butylanilinium chloride* (35) (78%) as needles (from 2M-hydrochloric acid), m.p. 165—166°, and then, after treatment with concentrated aqueous ammonia, 1-amino-3-nitro-4-t-butylbenzene as yellow plates (from ethanol–water), m.p. 55° (lit.,[31] 55°).

1-Amino-2-t-butylbenzene was prepared (almost quantitatively) by the procedure for 1-amino-4-s-butylbenzene except that Raney nickel and 1-t-butyl-2-nitrobenzene [31] were used, and obtained (70%) as an oil, b.p. 105—106° at 20 mmHg (lit.,[29] 102° at 10 mmHg), which afforded white needles (from ethanol), m.p. 199—200°.

N-*Benzoyl*-2-*carboxy*-2'-*t*-*butyldiphenylamine* (19).—*N*-Benzoyl-2-methoxycarbonyl-2'-t-butyldiphenylamine, on hydrolysis, yielded N-*benzoyl*-2-*carboxy*-2'-*t*-*butyldiphenylamine* (87%) as pale yellow plates (from ethanol), m.p.

[27] A. I. Vogel, 'A Textbook of Practical Organic Chemistry,' Longmans, London, 1956, p. 996.
[28] Ref. 27, p. 582.
[29] J. B. Shoesmith and A. Mackie, *J. Chem. Soc.*, 1928, 2334.
[30] Ref. 27, p. 574.
[31] J. F. Bunnett and M. M. Rauhut, *J. Org. Chem.*, 1956, **21**, 934.

233—235°; all attempts to remove the benzoyl group failed.

2-Bromo-4-nitro-1-t-butylbenzene, obtained in 66% yield,[29] did not undergo the von Richter rearrangement.[31]

Attempts to prepare 9-t-Butylaminoacridinium Chloride and 9-t-Butylamino-2,7-di-t-butylacridinium Chloride.—t-Butylamine (10 ml) was slowly stirred into 2-chloroformyldiphenylamine [32] (10 g) in dry benzene (100 ml). The benzene was removed *in vacuo* and the residue stirred with sodium hydroxide (2M); filtration gave 2-(*t-butylcarbamoyl*)-*diphenylamine* (37) (10.1 g, 78%) as needles (from ethanol), m.p. 121—122°.

9-*Phenoxy*-2,7-*di-t-butylacridine* (38).—By the procedure for 9-chloroacridine, the 2,7-di-t-butyl derivative yielded 9-*phenoxy*-2,7-*di-t-butylacridine* (75%) as yellow needles (from light petroleum–benzene), m.p. 168—170°.

Preparation of Optically Active Acridines.—9-*Amino*-2-*s-butylacridinium* (+)-*camphor*-10-*sulphonate* (39) was obtained when the base (4 g, 1 mol) in the minimum of acetone was added to (+)-camphor-10-sulphonic acid (3.3 g, 1 mol) in the minimum of acetone. After 0.5 h, filtration yielded bright yellow rhombs (from ethanol–water), m.p. 112—113°.

The appropriate acridines similarly gave 6-*amino*-2-*s-butylacridinium* (+)-*camphor*-10-*sulphonate* (40) as deep red plates (from ethanol–water), m.p. 125—126°, 9-*amino*-2-*s-butylacridinium* 3-*bromo*-(+)-*camphor*-8-*sulphonate* (41) as bright yellow needles (from ethanol–water), m.p. 106—107°, and 6-*amino*-2-*s-butylacridinium* 3-*bromo*-(+)-*camphor*-8-*sulphonate* (42) as deep red needles (from ethanol–water), m.p. 132—133°.

Repeated slow crystallisations of all these salts from ethanol–water, acetone, dimethylformamide, nitromethane, and propan-2-ol–water gave, after regeneration of the free base with alkali, material with no detectable optical rotation at the sodium D-line.

(+)- *and* (−)-*s-Butylammonium Chlorides.*—s-Butylamine yielded, by the published procedure,[7,8] optically pure (+)-s-butylammonium chloride as needles, m.p. 151—152° (lit.,[8] 152—153°), and (−)-s-butylammonium chloride of 71.5% optical purity and m.p. 150—151° (lit.,[8] 152—153°).

(+)- *and* (−)-9-*s-Butylaminoacridinium Chlorides* [(5) *and* (6)].—9-Phenoxyacridine and (+)- and (−)-s-butylammonium chlorides yielded, by the general literature procedure,[6] (+)- and (−)-9-*s-butylaminoacridinium chlorides* (69 and 60%, respectively) as yellow needles (precipitation with ether from hot methanol), m.p. (both compounds) 279—282° (decomp.), $[\alpha]_D^{27}$ for the (+)-compound +413° and for the (−)-compound −295°.

1-*Iodo*-11-*methoxyundecane.*—This was prepared in 85% yield [m.p. 26—27° (lit., 27°)] by the reported general method [26] from the tosylate from 11-methoxyundecanol,[33] and was refluxed for 3 h with sodium iodide (58 g) in the minimum of acetone. Solvent was removed *in vacuo*, the solid residue was stirred with ether (200 ml), the solid was filtered off, and the filtrate was distilled to give 1-iodo-11-methoxyundecane (24 g), b.p. 118—120° at 0.15 mmHg (lit.,[33] 114—116° at 0.15 mmHg).

9-(11-*Methoxyundecyl*)*acridan* (43).—The Grignard reagent from 1-iodo-11-methoxyundecane (4 g), magnesium turnings (0.3 g), and dry ether (10 ml) was poured on to acridine (1.2 g). The mixture was refluxed for 2 days, then stirred well into sulphuric acid (10%; 50 ml) and ice (50 g), and extracted with chloroform (3 × 25 ml). The extracts were dried (Na_2SO_4) and evaporated; the residue on trituration with benzene (2 ml) gave 9-(11-*methoxyundecyl*)*acridan* (0.08 g) as dark green rhombs (from ethanol), m.p. 145—146°. The filtrate, when chromatographed on deactivated alumina with benzene as eluant, yielded as the first band 1-*methoxyundecane* (44) (3 g) as needles (from light petroleum at −70 °C), m.p. 25—26°.

NN-*Bis*-(2-*anilinobenzoyl*)-11-*bromoundecylamine* (45).—11-Bromoundecylammonium bromide [34] (3.2 g) was shaken with benzene (10 ml) and sodium hydroxide (20 ml; 2M). 2-Chloroformyldiphenylamine (2.3 g) in dry benzene (10 ml) was added to the benzene extract immediately after separation. The gelatinous orange-red mixture was refluxed for 40 min, cooled, and filtered to yield 11-bromoundecylammonium chloride (1.2 g) as needles (from benzene), m.p. 134—135° (lit.,[35] 135°). The filtrate was evaporated to about 3 ml and chromatographed on deactivated alumina (benzene as eluant) to yield, as first band, a yellow oil that crystallised on addition of a little ethanol to give the *imide* (45) (0.78 g, 12%) as plates (from ethanol), m.p. 114—115°.

Methyl 11-*Iodoundecanoate* (46).—Methyl 11-bromoundecanoate (24 g), sodium iodide (70 g), and ethyl methyl ketone (250 ml) were refluxed for 16 h; the mixture was cooled, filtered, and distilled to give *methyl* 11-*iodoundecanoate* (27.5 g) as an oil, n_D^{20} 1.4895, b.p. 131—132° at 0.1 mmHg.

Methyl 11-*Tosylundecanoate* (47).—Methyl 11-hydroxyundecanoate [36] (30 g), by the general method for tosylates,[26] but at 0 °C for 1 week, yielded *methyl* 11-*tosylundecanoate* (29 g, 60%) as rhombs (from light petroleum at −70 °C), m.p. 28—29°.

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