Synthesis of Some Acridines and 9-Acridones for Spectral Studies

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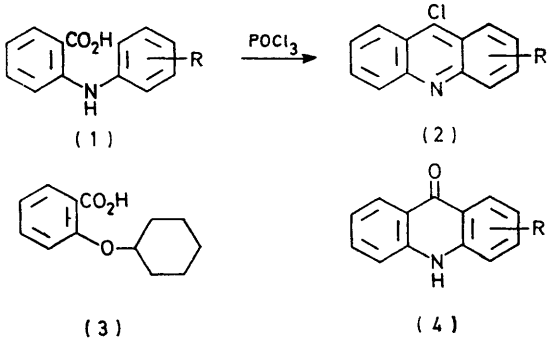
A series of alkyl-substituted 9-chloroacridines and 9-acridones have been synthesised from *N*-arylanthranilic acids; the n.m.r. spectra of the chloroacridines and the i.r. and u.v. spectra of the 9-acridones have been investigated. 2-Cyclohexyloxybenzoic acid was formed from 2-chlorobenzoic acid and the cyclohexanol used as solvent in some Ullmann reactions. Petrow's mechanism for the conversion of 2-anilinomethylenecyclohexanones into tetrahydroacridines has been confirmed. A steric effect is displayed in the homolytic α-bromination of 2- and 4-alkyl-9-chloroacridines.

THIS paper describes the preparation of a series of alkylacridines, alkyl-9-chloroacridines, and the corresponding 9-acridones. The n.m.r. spectra of the acridines have been recorded, and the u.v. and i.r. spectra of the 9-acridones are discussed. The mass spectra of the acridines will be reported elsewhere.

The 9-chloroacridines were obtained by cyclising appropriate *N*-arylanthranilic acids, obtained from 2-chlorobenzoic acid and the aniline in the presence of copper. Although this last type of reaction, the Ullmann reaction, has been much studied, it is impossible to predict reliably the best conditions for a new example. Cyclohexanol proved to be a good solvent for anilines not possessing a 2-substituent larger than a methyl group. With a larger 2-substituent, yields of the resulting anthranilic acid fell and isolation proved difficult or impossible. In the preparation of compound (1; R = 2-Me,5-Pr^i) and attempted preparation of (1; R = 2-Pr^i), 2-cyclohexyloxybenzoic acid (3) was isolated. This must be formed by copper-catalysed nucleophilic attack of the solvent on the 2-chlorobenzoic acid, and suggests that the commonly used high-boiling alcohols are not the best solvents for Ullmann reactions. Nucleophilic attack of this type by alcohols in the presence of



(1) (2)

(3) (4)

carbonate, which is too weak a base to form significant concentrations of the alkoxides, has not been noted before, although alkoxide,[1] phenoxide,[2] and hydroxide ions [3] in the presence of copper and acetate ions [4] can displace the chlorine atom of a 2-chlorobenzoic acid. A

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[2] P. A. Sartoretto and F. J. Sowra, *J. Amer. Chem. Soc.*, 1937, **59**, 603.
[3] H. Goldstein and W. Rodel, *Helv. Chim. Acta*, 1926, **9**, 765.
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three fold improvement in yield of compound (1; R = 2-Me,5-Pr^i) was obtained by using the non-nucleophilic hexamethylphosphoramide as solvent for the reaction with 5-isopropyl-2-methylaniline.

Many of the *N*-arylanthranilic acids could not be isolated from the tarry products of the Ullmann reactions, which were therefore treated directly with phosphoric trichloride, and the resulting 9-chloroacridines were isolated by chromatography (Table 1).

The n.m.r. spectra of the seventeen 9-chloroacridines prepared are recorded in SUP 21252 (see Experimental section) and have been discussed.[5]

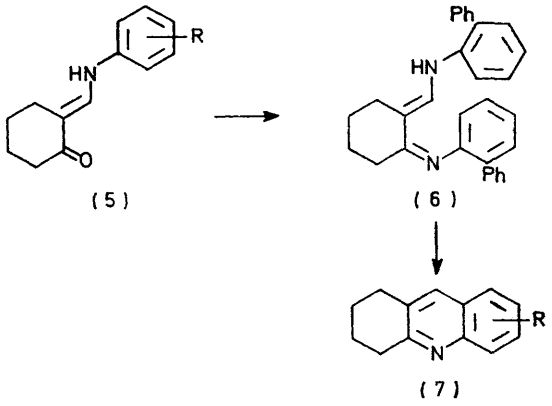
Treatment of 9-chloro-2-ethylacridine with 1 or 2 mol. equiv. of *N*-bromosuccinimide (NBS) gave the α-mono- and αα-di-bromoethyl derivatives, respectively. Similarly, 9-chloro-2-methylacridine with 1 mol. equiv. of NBS gave the 2-bromomethyl derivative. 4-Ethyl- and 4-n-propyl-9-chloroacridine could only be α-monobrominated, and the 4-isopropyl analogue did not react with NBS, probably for steric reasons. 2-Ethylacridine on irradiation in the presence of NBS gave the unstable 2-α-bromoethyl derivative. 9-Chloro-2-(αα-dibromoethyl)acridine was converted into 2-(α-bromovinyl)-9-acridone in good yield in boiling aqueous dioxan.

Aqueous acid hydrolysed the 9-chloroacridines to the corresponding 9-acridones (Table 1).

The N–H and carbonyl (1640—1650 cm^{-1}) absorptions of our 2-alkylacridones are very similar to that of 9-acridone, and the carbonyl frequency is insensitive to hydrogen bonding: it is unchanged in 10-methylacridone (1640 cm^{-1}). The N–H regions, but not the carbonyl absorptions (1630—1640), are very different for the 1- and 4-alkyl derivatives: the absorption moves to higher frequencies.[6] The effect is greatest for 1-isopropyl-4-methyl-9-acridone and is due to the substituents interfering sterically with intermolecular hydrogen bonding. This last acridone shows carbonyl absorption at 1640 and an additional peak at 1690 cm^{-1}, showing that two environments are enjoyed by the carbonyl group in the crystal lattice. Its low m.p. (75°) contrasts with that (*ca.* 360°) of 9-acridone itself, which is highly hydrogen bonded.[7] Resolidification occurs at *ca.* 100°, and remelting at 208—209°. The N–H and carbonyl regions of the i.r. spectrum of the higher m.p. material were similar to those of the 1- and 4-alkyl-9-acridones, showing that a rearrangement in the crystal structure had taken place to give an environment similar to that in these compounds for the NH and carbonyl groups. Material which had melted at 209° did not solidify until near room temperature, when the m.p. 75° form was obtained.

Corresponding differences exist between the u.v. spectra of 2-alkyl- and 1- or 4-alkyl-9-acridones.[8]

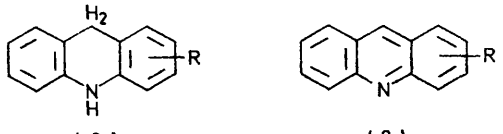
Failure to condense 2-aminobiphenyl with 2-chlorobenzoic acid in the Ullmann reaction [9] led us to synthesise 4-phenylacridine *via* the cyclohexanone (5; R = 2-Ph), which was cyclised in lactic acid to the tetrahydroacridine. The mechanism of this reaction [10] has been the subject of recent discussion; [11,12] it gives tetrahydroacridines, but not tetrahydrophenanthridines, along with *N*-aryl-lactamides,[13] as we have confirmed for our



(5) (6) (7)

examples. In one attempted cyclisation of compound (5; R = 2-Ph) with lactic acid under mild conditions some *N*-[2-(biphenyl-2-ylaminomethylene)cyclohexylidene]biphenyl-2-ylamine (6) was isolated [14] along with starting material, and was identified by comparison with authentic material synthesised from 2-chlorocyclohex-1-enecarbaldehyde and 2-aminobiphenyl by the method of Gagan and Lloyd.[15] Many attempts to prepare compound (6) from (5; R = 2-Ph) with 2-aminobiphenyl either gave back the starting materials or afforded the tetrahydroacridine. The bisanil (6) gave the acridine (7; R = 2-Ph) on warming with acetic acid, conditions under which the monoanil (5; R = 2-Ph) was unchanged, and its formation by disproportionation of the monoanil is the easiest way of accounting for tetrahydroacridine formation.

Attempts to aromatise the tetrahydroacridines (7; R = 7-Et or 5-Ph) by treatment with chloranil, dichlorodicyanoquinone (DDQ), or palladium–charcoal failed,



(8) (9)

but selenium at 300° caused partial dehydrogenation to the 9,10-dihydroacridines (8; R = 2-Et or 4-Ph), which yielded the acridines (9; R = 2-Et or 4-Ph) with chromic

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[6] Ref. 5, p. 668.
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[9] I. A. Selby, personal communication.
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acid. This is in contrast to the observation [16] that palladium–charcoal produced the acridine directly from (7; R = 5-Ph).

EXPERIMENTAL

N.m.r. spectra were recorded at 100 MHz on a Perkin-Elmer R14 or (where specifically noted) at 60 MHz on a Perkin-Elmer R10 instrument. U.v. spectra cited are of solutions in methanol (M) or methanol acidified with one drop of perchloric acid (MA) and were recorded on a Perkin-Elmer Ultracord 137 spectrophotometer. I.r. spectra are of Nujol mulls (solids) or liquid films (liquids) measured on a Perkin-Elmer 257 IR instrument.

Alumina for chromatography was Spence grade H deactivated with water (5% v/v) or aqueous 10% acetic acid (5% v/v) to give basic or neutral deactivated alumina, respectively. Except where otherwise stated, petroleum was the fraction of b.p. 60—80°.

For t.l.c. Eastman K301 R Chromagram sheet was used and all plates were examined under u.v. light (λ 254 nm).

All analyses for new compounds were within accepted limits for C, H, N, and halogen and are available, with details of n.m.r. and u.v. spectra as Supplementary Publication No. SUP 21252 (7 pp).†

N-Arylanthranilic Acids from 2-Chlorobenzoic Acid.—Finely powdered anhydrous (dried at red heat) potassium carbonate (3 mol. equiv.) was added with stirring to 2-chlorobenzoic acid (1 mol. equiv.) in cyclohexanol (7·5 ml g^{-1}) and all water was removed azeotropically (bath at 180°). Redistilled amine (1·02 mol. equiv.) and copper catalyst (0·01 g per g of 2-chlorobenzoic acid) were added, and refluxing and stirring were continued for 4 h, another similar quantity of catalyst being added after 2 h. After steam distillation and treatment of the residue with charcoal, the anthranilic acid was precipitated at pH 5. Yields and m.p.s for the 2′-, 3′-, 4′-methyl- and 2′- and 4′-ethyl derivatives agreed with the literature ranges, and the new compounds are listed in Table 1.

9-Chloroacridines.—The anthranilic acids were refluxed with phosphoric trichloride (5 mol. equiv.) for 1 h; the excess of reagent was removed *in vacuo*, and the residue in chloroform was poured on to stirred ice–aqueous 15% ammonia. The chloroform layer was washed, dried ($MgSO_4$), and concentrated, and the resultant oil was chromatographed over neutral deactivated alumina. Gradient elution with light petroleum–benzene (0—100%) gave the 9-chloroacridines in high purity; the new compounds are listed in Table 1. The mixed 1- and 3-methyl-9-chloroacridines from *N*-(3-methylphenyl)anthranilic acid were separated *via* the corresponding 9-acridones.

9-Acridones.—The 9-chloroacridines were heated with aqueous N-hydrochloric acid for 3 h at 100°; the mixtures were cooled and the precipitates recrystallised from ethanol. New compounds (all as needles) are listed in Table 1.

Alkylanilines.—The appropriate alkylnitrobenzenes were hydrogenated in ethanol at room temperature and 4 atm over 5% palladium–charcoal for 8 h. The catalyst was filtered off and washed and the solution evaporated to yield an oil which was used in the Ullmann synthesis without further purification. The nitro-compounds were prepared by standard methods.[17]

2-Cyclohexyloxybenzoic Acid (3).—In the synthesis of compound (1; R = 2-Me,5-Pr^i) on acidification to pH 6 there was a precipitate of *2-cyclohexyloxybenzoic acid* (3) (42%), obtained as white tablets (from ethanol), m.p. 83—85°. The anthranilic acid was precipitated at pH 5.

α-Bromoalkyl-9-chloroacridines.—The alkyl-9-chloroacridine dissolved in carbon tetrachloride was refluxed with the stoicheiometric quantity of *N*-bromosuccinimide (purified by the method of Fieser [18]) and benzoyl peroxide (5% w/w) under a sodium hydroxide guard tube for 4 h. After cooling, the solution was filtered and evaporated and the resultant solid recrystallised from petroleum to give the α-bromoalkyl-9-chloroacridine. New compounds are listed in Table 2.

TABLE 1

Starting aniline	*N*-Arylanthranilic acid Yield (%); [a] m.p. (°C)	9-Chloroacridine Yield (%); m.p. (°C)	9-Acridone Yield (%); m.p. (°C)
2-Pr^n	Not isolable	9; [b] 60—61	
2-Pr^i	Not isolable [c]	5·5; [b] 108—109	65; 252—253
4-Bu^n	33; 146—149 [d]	70; 49—50	64; 230·5—232
2-Bu^s	Not isolable	10; [b] 68—70	64; 243—246
4-(1-Methylbutyl)	23; 170—179	78; liquid [e]	57; 192—193
2-Me,5-Pr^i	5; [f] 123—127	23; [b,g] 68—71	59; 75 [h]

[a] Based on the aniline. [b] On the two stages from the aniline. [c] In one case trituration of the tar with petroleum gave 2-cyclohexyloxybenzoic acid (9%), off-white needles (from toluene), m.p. 83—85°. [d] Lit., 154·5—155·5° (G. Picciola, R. Gaggi, and W. Caliari, *Farmaco, Ed. Sci.*, 1968, **23**, 502). [e] Chromatographed twice before analysis. [f] After filtration of reaction solution at pH 8, 2-cyclohexyloxybenzoic acid (42%) precipitated at pH 6, and at lower pH the anthranilic acid was obtained. [g] Hexamethylphosphoramide under N_2 was used instead of cyclohexanol in the first stage, and the product cyclised directly. [h] Resolidifies and remelts at 208—209°.

TABLE 2

α-Bromoalkyl-9-chloroacridines from bromination of the 9-chloroacridines with NBS

Product (2) R	NBS (mol. equiv.)	Yield (%)	M.p. (°C) [a]
2-$MeCBr_2$	2	64	128—130
4-MeCHBr	2	64	130—135 [b]
4-EtCHBr	2	53	113—117
2-MeCHBr	1	50	95—99
2-$BrCH_2$	1	39	130—135
2-Pr^nCBr_2	2	21	98—103

[a] Usually with decomp. [b] Sublimes at 103°.

Under the above conditions after a reflux time of 6 h, 9-chloro-4-isopropylacridine was unchanged.

† For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

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[18] L. F. and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 80.

2-(α-*Bromovinyl*)-9-*acridone*.— 9-Chloro-2-(αα-dibromoethyl)acridone (0·4 g) dissolved in dioxan (20 ml) and water (20 ml) was heated under reflux for 30 min; the mixture was then cooled and filtered and the precipitate recrystallised from ethanol to give the *vinylacridone* (4; R = 2-$CBr{:}CH_2$) (0·105 g, 35%) as rhombs (from ethanol), m.p. 255—260°, $\nu_{max.}$ (dil. soln. in $CHCl_3$) 3250w, 1635s, 1595m, 1570m, and 1120m cm^{-1}.

2-α-*Bromoethylacridine*.—2-Ethylacridine (0·5 g) dissolved in carbon tetrachloride was refluxed with NBS (0·86 g) and dibenzoyl peroxide (0·01 g) for 4 h with irradiation from a 100 W medium-pressure u.v. lamp for the first hour. After cooling, the solution was filtered and evaporated to give a yellow pasty solid (0·97 g). N.m.r. examination showed it to be a mixture (3 : 1) of mono- and di-brominated derivatives. 2-α-*Bromoethylacridine* (0·058 g, 8·5%) was obtained as yellow needles (from acetonitrile), m.p. 110—113°, rapidly darkening on exposure to air.

2-(4-*Ethylanilinomethylene*)*cyclohexanone* (5; R = 4-Et).—4-Ethylaniline (12·1 g) dissolved in ethanol was added with stirring to 2-formylcyclohexanone [19] (12·5 g) in ethanol (40 ml). After ½ h the mixture was cooled and filtered to give 2-(4-*ethylanilinomethylene*)*cyclohexanone* (5; R = 4-Et) (18·7 g, 82%), pale yellow needles (from ethanol), m.p. 127—130°.

7-*Ethyl*-1,2,3,4-*tetrahydroacridine*.— 2-(4-Ethylanilinomethylene)cyclohexanone (11·5 g) was heated with lactic acid (48 g) and the product was worked up by the method of Tilak *et al.*[12] The resultant oil was chromatographed on neutral deactivated alumina. Benzene (10—100%)–petroleum eluted 7-*ethyl*-1,2,3,4-*tetrahydroacridine* (4·5 g, 43%), a yellow oil n_D^{22} 1·6008. Chloroform eluted 4-*ethyl*-N-*lactylaniline* (2·5 g, 26%), white needles (from benzene–petroleum), m.p. 79—81°.

2-*Ethylacridine* (9; R = 2-Et).—(i) Treatment of 7-ethyltetrahydroacridine with chloranil, DDQ, or palladium–charcoal in refluxing ethylene glycol yielded only highly coloured tars.

(ii) 7-Ethyltetrahydroacridine (1·0 g) was heated with selenium powder (0·9 g) at 300° for 3 h. The mixture was extracted with boiling ethanol and the extract filtered hot and evaporated. The resultant oil was chromatographed on neutral deactivated alumina. Petroleum–benzene (3 : 1) eluted a solid with a characteristic 9,10-dihydroacridine u.v. spectrum. Oxidation of the solid with chromic acid yielded 2-ethylacridine, yellow needles (from aqueous ethanol), m.p. 73—75° (lit.,[20] 78—79·5°).

2-(2-*Phenylanilinomethylene*)*cyclohexanone* (5; R = 2-Ph).—2-Aminobiphenyl (16·9 g) and 2-formylcyclohexanone (12·5 g) were heated together for 3 h on a boiling water bath. The resulting red syrup crystallised on scratching to give (5; R = 2-Ph) (24·0 g, 85%), golden rhombs (from ethanol), m.p. 97—101° (lit.,[20] 93—98°).

1,2,3,4-*Tetrahydro*-5-*phenylacridine* (7; R = 5-Ph).—(i) The anil (5; R = 2-Ph) (11·5 g) was heated under reflux for 15 h in lactic acid (48 g) containing water (1 ml); the product was worked up by the method of Tilak *et al.*[12] and chromatographed over neutral deactivated alumina. Petroleum eluted N-[2-(*biphenyl*-2-*ylaminomethylene*)*cyclohexylidene*]*biphenyl*-2-*ylamine* (6) (0·108 g, 1%), yellow needles (from petroleum), m.p. 138—140°, *m/e* 428 (M^+). Further elution gave compound (5; R = 2-Ph).

(ii) The anil (5; R = 2-Ph) (2·0 g) was heated under reflux with lactic acid (7·0 ml) for 20 h. After the standard work-up chromatography (elution with petroleum) yielded compound (7; R = 5-Ph) (0·5 g, 25%), yellow rhombs (from petroleum), m.p. 78—81° (lit.,[16] 85—86°). Benzene then eluted 2-*lactylaminobiphenyl* (0·84 g, 47%), white needles (from petroleum–benzene), m.p. 104—105°.

9,10-*Dihydro*-4-*phenylacridine* (8; R = 4-Ph).—The tetrahydroacridine (7; R = 5-Ph) (0·3 g) and selenium powder (0·3 g) were heated together at 300° for 6 h. After extraction into hot ethanol, filtration and evaporation gave an oil which was chromatographed on neutral deactivated alumina. Petroleum (b.p. 40—60°) eluted 9,10-*dihydro*-4-*phenylacridine* (37%), prisms (from ethanol) m.p. 121—123°.

4-*Phenylacridine* (9; R = 4-Ph). The dihydroacridine (8; R = 4-Ph) (0·09 g) was suspended in hot dilute sulphuric acid and oxidised with dilute aqueous potassium dichromate.[21] 4-Phenylacridine (0·05 g, 57%) was obtained as pale yellow needles (from ethanol), m.p. 118—122° (lit.,[17] 122—122·5°).

N-[2-(*Biphenyl*-2-*ylaminomethylene*)*cyclohexylidene*]*biphenyl*-2-*ylamine* (6).—2-Aminobiphenyl (0·75 g) in benzene (1 ml) and ethanol (1 ml) at 0° was added slowly to a stirred solution of 2-chlorocyclohex-1-ene-1-carbaldehyde [15] (0·32 g) in benzene (1 ml) and ethanol (1 ml) at 0°. After 3 days at 0° the solution was evaporated; the residue was dissolved in ethanol and the solution slowly deposited yellow crystals (0·15 g). After treatment of these with dilute aqueous ammonia (15 ml) extraction by toluene gave the free base (6), yellow rhombs (from petroleum), m.p. 141—142°, identical (spectra) with the material described above. 2-Aminobiphenyl with hot 2-formylcyclohexanone alone or with ethanol gave only the monoanil (5), and this did not react with 2-aminobiphenyl in boiling benzene in a Dean-Stark separator, or in glacial acetic acid (1 mol. equiv.) at 100° (18 h).

The bisanil (6) (4 mg) in glacial acetic acid (1 ml) was heated on a steam-bath for 1 h. The product was worked up by the method of Tilak *et al.*[12] A sample of compound (5; R = 2-Ph) was treated identically. The resulting syrups were examined by t.l.c. (Eastman Chromagram Sheet; 4 : 1 toluene–ethyl acetate) in conjunction with compounds (6) (R_F 0·88, dark spot), (5; R = 2-Ph) (R_F 0·68, dark spot), (7; R = 5-Ph) (R_F 0·83, blue fluorescence), and 2-aminobiphenyl (R_F 0·76, dark spot). Compound (6) produced only (7; R = 5-Ph) and 2-aminobiphenyl; compound (5; R = 2-Ph) was unchanged after the treatment.

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