[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

THE SYNTHESIS OF 1-ETHYL-, 2-ETHYL-, 3-ETHYL- AND 4-ETHYL-ACRIDINE[1]

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Received September 14, 1953

In a recent communication from this Laboratory (1) dealing with new departures in acridine chemistry, attention was drawn to the fact that the elucidation of the structural features of certain key compounds described therein had to await the availability of several new acridine derivatives arrived at by unambiguous paths. These derivatives are now in hand, and it is the purpose of this report to describe their preparation and properties. Succeeding papers will demonstrate their utility in clarifying the structural problems referred to.

Initial experiments directed towards the synthesis of 1-ethylacridine (XVI) were patterned after those employed in preparing the homologous 1-methylacridine (2), thereby designating 2-bromo-6-ethylbenzoic acid a key intermediate. Two unsuccessful approaches to this substance were tested: nitration of *o*-acetaminoethylbenzene (I) to the 3-nitro derivative (II) was followed by transformation to the nitrile (III) *via* standard procedures. Several attempts to hydrolyze the latter to the corresponding carboxylic acid yielded either the amide (IV) or unchanged nitrile. In the belief that the related bromonitrile (VI) might be more amenable to hydrolysis, the latter was prepared from III using the modified Sandmeyer reaction described by Bachmann (3). Here, again, all attempts at hydrolysis resulted in the amide (VII), or starting material. Since related hydrolyses succeeded in the methyl series (2, 4), it is conceivable that the steric effect of the ethyl group operates adversely here.

Another approach to 1-ethylacridine involved the readily available *m*-ethylaniline (VIII). 3′-Ethyldiphenylamine-2-carboxylic acid (IX), prepared from *m*-ethylaniline and *o*-chlorobenzoic acid, was cyclized ($POCl_3$) to a mixture of the isomeric 1- and 3-ethyl-9-chloroacridines according to Albert's procedure (5), but the resulting syrup could not be resolved into the corresponding acridones as had been done in the methyl series. In view of this, the syrup was shaken in hydrogen in the presence of Raney nickel and the halogen-free material (mixture of 1- and 3-ethyldihydroacridines?) was oxidized with potassium dichromate (6). Treatment of the product with alcoholic perchloric acid afforded a mixture of perchlorates from which 3-ethylacridine perchlorate was isolated in 30% yield by fractional crystallization. In addition a more soluble perchlorate was isolated which gave rise to a base whose rather high melting point and analysis suggested a bimolecular compound[2] (probably related to biacridyl)—a result occasionally encountered in the reductive dehalogenation of 9-chloroacridines (6).

[1] Studies In The Acridine Series VII.

[2] No attempt was made to establish this as being derived from either 1- or 3-ethylacridine.

1-Ethylacridine (XVI) was ultimately prepared as outlined in the scheme XI → XVI. While this approach is now known to be straightforward, it should perhaps be pointed out that, whereas the 9-chlorine atom in XV was readily removed by Albert's process (6) (Raney nickel and hydrogen), the bromine atom at C-4 largely resisted this treatment. In order to arrive at a completely halogen-free derivative, it was necessary to hydrogenate in two stages using nickel in the first instance, and palladium on strontium carbonate in the second.

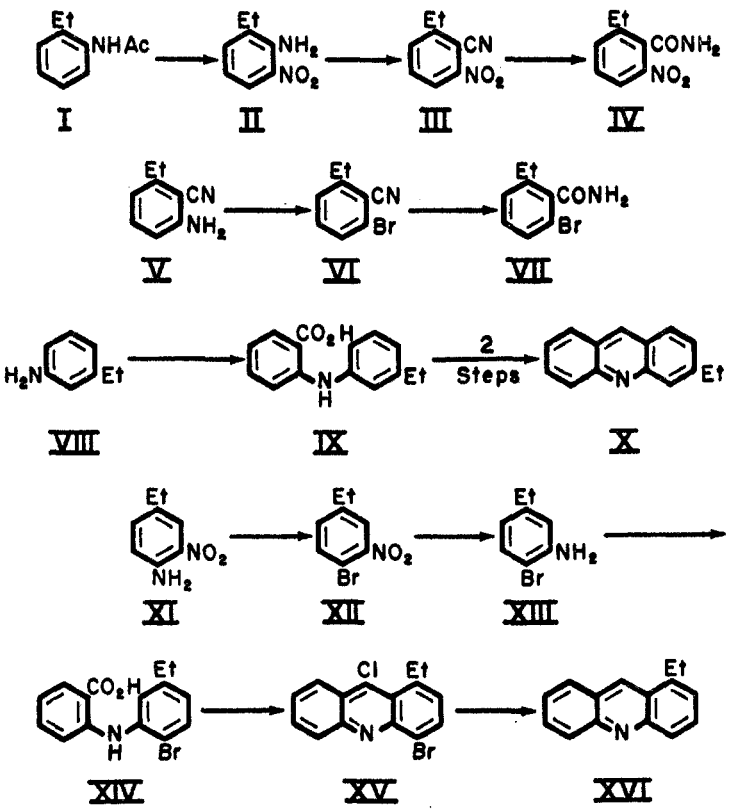

CHART I

The synthesis of 2-ethylacridine (XIX) was achieved according to the reaction path XVII → XIX, and proceeded smoothly.

It will be recalled that in the attempt to prepare 1-ethylacridine from the mixed, isomeric 1- and 3-ethyl-9-chloroacridines resulting from IX, there was isolated instead 3-ethylacridine (X) in the form of its perchlorate, along with another substance. Since, however, the purpose of this investigation was to devise unambiguous routes to the respective isomers, this approach to 3-ethylacridine was not considered sufficiently reliable. It was, therefore, necessary to work out a reaction scheme which would lead to 3-ethylacridine exclusively, and this is represented by formulas XX → XXIV.

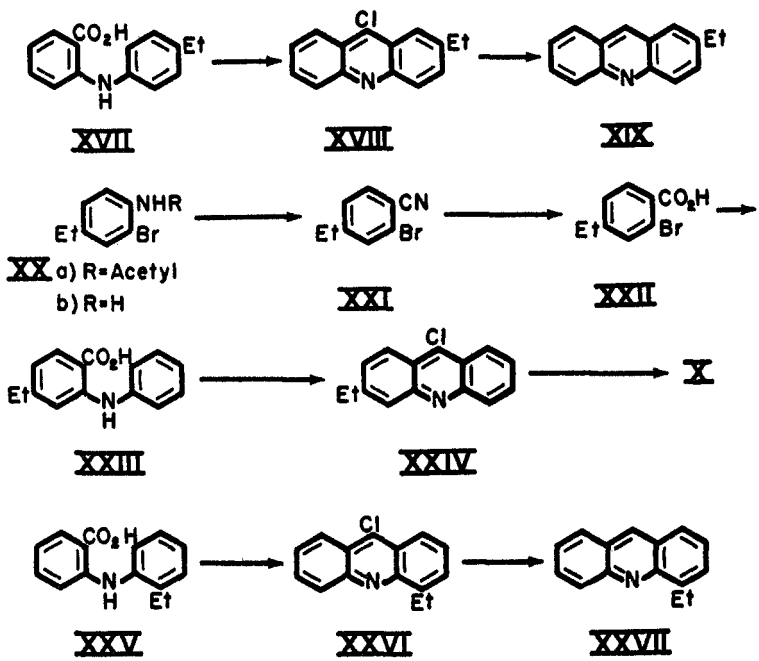

CHART II

The preparation of 4-ethylacridine from *o*-aminoethylbenzene and *o*-chlorobenzoic acid was carried out as outlined in formulas XXV → XXVII.

EXPERIMENTAL[3]

2-Ethyl-6-nitrobenzonitrile (III). The nitration of *o*-acetaminoethylbenzene (I)[4] was carried out essentially as outlined by Kondo (8) except that it was found advantageous to use larger volumes of solvents to insure a homogeneous system at the temperature of the reaction (3°). Thus nitration of 55 g. of I in a mixture of 90 ml. of acetic anhydride and 110 ml. of glacial acetic acid with a mixture of 19.3 ml. of fuming nitric acid (*sp. gr.* 1.49) and 28 ml. of glacial acetic acid with subsequent hydrolysis of the reaction product gave 30.5 g. (55%) of 2-amino-3-nitroethylbenzene (II), b.p. 151–153°/6 mm., m.p. 30–31° (lit. yield—44%). The latter substance (20 g.), in a large, ice-cooled glass mortar, was first rubbed with 25 ml. (2.5 equivs.) of conc'd HCl then diluted with 180 ml. of cold water and the precipitated base was finely pulverized.[5] The stirred, ice-cooled suspension was diazotized with a solution of 8.6 g. (1.03 equivs.) of sodium nitrite in 35 ml. of water, added during 1.25 hrs. After an additional hour's stirring (at 0°), the solution was filtered (4 g. of amine recovered) and added during 20 mins. to a cooled and stirred solution of cuprous

[3] Melting points are uncorrected. Analyses are by the Institutes' Microanalytical Laboratory under the supervision of Dr. William C. Alford.

[4] *o*-Aminoethylbenzene, prepared in 95% yield, by reduction of *o*-nitroethylbenzene (7) at 170° using copper chromite and a hydrogen pressure of 160 atms., was acetylated with a mixture of acetic anhydride and glacial acetic acid; m.p. 114–115°.

[5] If the base is not finely divided much of it escapes diazotization.

cyanide.[6] The nitrile (III) separated in crystalline form and was collected after 30 mins., washed with water, and dried; 15.3 g. (73%). A sample was sublimed at 95–100°/0.4 mm.; m.p. 94–95°.

Anal. Calc'd for $C_9H_8N_2O_2$: C, 61.4; H, 4.6; N, 15.9.
Found: C, 61.3; H, 4.7; N, 15.8.

2-Ethyl-6-nitrobenzamide (IV). A suspension of 5.1 g. of III in 75 ml. of 50% (w/w) H_2SO_4 was refluxed at 140–145° (oil-bath) for 20 hrs., and at 155° for 10 hrs. more. Dilution of the cooled, yellow solution with ice-water (300 ml.) afforded a crystalline precipitate which was collected, washed with water, and dried; 4.6 g. Sublimation of a specimen at 160°/0.4 mm. gave colorless needles, m.p. 167–168.5°.

Anal. Calc'd for $C_9H_{10}N_2O_3$: C, 55.7; H, 5.2.
Found: C, 55.9; H, 5.5.

2-Ethyl-6-aminobenzonitrile (V). To a stirred solution of 105 g. of stannous chloride in a mixture of 90 ml. of conc'd. HCl and 1.5 ml. of water, 22.9 g. of III (finely powdered) was added during 1.75 hrs., the temperature of the solution being maintained at 25–30°. After stirring at 25° for an additional 3 hrs., 270 ml. of conc'd HCl was added and the system was refrigerated for 15 hrs. The colorless salt was collected (sintered glass funnel), washed with conc'd HCl, sucked as dry as possible, and decomposed (cold 2 *N* NaOH and ether) yielding 11.6 g. (60%) of the pale-yellow, crystalline amino compound. The analytical sample was sublimed at 100°/0.3 mm., colorless crystals, m.p. 102–104°.

Anal. Calc'd for $C_9H_{10}N_2$: C, 73.9; H, 6.9.
Found: C, 74.1; H, 7.1.

2-Ethyl-6-bromobenzonitrile (VI). The diazotization of 7 g. of V (as a stirred suspension in a mixture of 8.4 ml. of conc'd H_2SO_4 and 100 ml. of water) was effected during 10 mins. (at 5°) with a solution of 3.45 g. (1.04 equivs.) of sodium nitrite in 12 ml. of water. After 30 mins. the cold, filtered solution was treated, dropwise, with a solution of 52 g. of mercuric bromide and 52 g. of potassium bromide in 230 ml. of water (3). Following an hour's stirring, the yellow double-salt was collected, washed with water, air-dried, (27.4 g.), and decomposed portionwise: 9.1 g. of the latter was intimately mixed with 18 g. of powdered potassium bromide and cautiously was heated in a 500-ml. flask over a free flame until the initial vigorous reaction subsided. On cooling, the brown cake was pulverized and leached several times with benzene. The combined benzene extracts from three such runs were filtered and concentrated (*in vacuo*) yielding 9 g. of a dark oil. Evaporative distillation of this oil at 100°/0.3 mm. gave a pale-yellow oil admixed with a little crystalline material. Because of the latter's apparent insolubility in ligroin (28–38°), it could be removed by filtration affording 6.6 g. (65%) of the bromonitrile. A sample was evaporatively distilled a second time—colorless oil, n_D^{20} 1.5698.

Anal. Calc'd for C_9H_8BrN: C, 51.5; H, 3.8.
Found: C, 51.7; H, 4.0.

The crystalline fraction, m.p. 180–200°, was not further examined.

2-Ethyl-6-bromobenzamide (VII). A stirred suspension of 0.5 g. of VI in 8 ml. of 70% (w/w) H_2SO_4 was heated at 155–160° (reflux) for 5 hrs. The gum which separated on pouring the reaction mixture into a slurry of ice and water was taken up in ether. From the latter there resulted 0.22 g. of crystalline material which, after sublimation at 110°/0.4 mm., appeared as slender, colorless prisms, m.p. 135–136°.

Anal. Calc'd for $C_9H_{10}BrNO$: C, 47.4; H, 4.4.
Found: C, 47.2; H, 4.3.

The same amide resulted in somewhat lower yield (0.17 g.) on heating the bromonitrile (0.5 g.) with 0.5 g. of KOH in 10 ml. of Cellosolve[7] for 20 hrs. at 150°.

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[6] Prepared as outlined in *Org. Syntheses*, Coll. Vol. I, 514 (1944) using 45 g. of $CuSO_4 \cdot 5H_2O$ and 11.7 g. of NaCl in 170 ml. of H_2O; 9.6 g. of $NaHSO_3$ and 6.4 g. of NaOH in 80 ml. of H_2O; 31 g. of NaCN in 65 ml. of H_2O.

[7] 2-Ethoxyethanol.

3-Ethylaniline (VIII). Reduction of 61.5 g. of *m*-nitroacetophenone (9) according to Rupe's method (10) using iron filings and dilute acetic acid yielded 41 g. (82%) of *m*-aminoacetophenone, m.p. 98–99.5°. Wolf-Kishner reduction (11) of the latter employing 42 g. of KOH, 30 ml. of 95% hydrazine hydrate, and 3 ml. of water in 300 ml. of triethylene glycol gave, after 1 hour's refluxing and 3 hours at 175° and the usual processing, an oil which was fractionally distilled; yield 31.3 g. (79%), colorless oil, b.p. 91.5–92.5°/9.5 mm. The *acid oxalate*, prepared in ether solution, crystallized in plates, from methanol-ether, m.p. 152–153° dec. The analytical sample was dried for 2 hrs. at 100° (*vacuo*).

Anal. Calc'd for $C_{10}H_{13}NO_4$: C, 56.9; H, 6.2.

Found: C, 56.6; H, 6.4.

3'-Ethyldiphenylamine-2-carboxylic acid (IX). A suspension of 46 g. of potassium *o*-chlorobenzoate and 32.5 g. of anhydrous K_2CO_3 in 250 ml. of redistilled *iso*amyl alcohol (b.p. 130–132°) was heated in an open 1-l. flask (oil-bath) until the vapor temperature rose to 129°. After cooling to *ca.* 80°, 31 g. of *m*-ethylaniline, 2 drops of water, 0.5 g. of copper-bronze powder, and 100 mg. each of cupric oxide and cupric acetate were added and the system was heated under reflux (bath temperature 165°) for 5 hrs. The solvent and unreacted amine were removed by steam-distillation and the hot aqueous residue was digested with Norit and filtered. Acidification with conc'd HCl precipitated a dark grey solid which was digested twice with 750-ml. portions of boiling water, collected, and dried. Recrystallization from ligroin (60–70°) (Norit) gave 28.8 g. (50%) of pale-yellow prisms. A sample was sublimed at 145°/0.3 mm., m.p. 117–118.5°.

Anal. Calc'd for $C_{15}H_{15}NO_2$: C, 74.6; H, 6.3.

Found: C, 74.7; H, 6.2.

Mixed 1- and 3-ethyl-9-chloroacridines. A mixture of 7.1 g. of IX and 20 ml. of $POCl_3$ was refluxed (oil-bath, 100–105°) for 30 mins. and the excess reagent was removed (*in vacuo*). The residual syrup was thinned with 35 ml. of $CHCl_3$, poured into a stirred slurry of ice and NH_4OH (225 ml. of conc'd. NH_4OH diluted with 500 ml. of water) and the product was taken up in ether, washed with water, dried, and concentrated (*in vacuo*); yield, 6.6 g. of a thick syrup. Attempts to selectively hydrolyze this material to the corresponding ethylacridones, as had been done in the methyl series (2), were unpromising.

Mixed 1- and 3-ethyl-9,10-dihydroacridines (?). A mixture of 6 g. of the above syrup in 25 ml. of benzene with 1.8 g. (1 equiv.) of KOH in 150 ml. of ethanol was shaken in hydrogen with *ca.* 8 g. of Raney nickel (6); hydrogen uptake (0.8 mole) ceased after 3 hrs. Concentration (*in vacuo*) of the filtered solution gave 5 g. of a viscous, halogen-free syrup.

Mixed 1- and 3-ethylacridines (?). A hot, stirred suspension of the latter syrup in a mixture of 66 ml. of 2 *N* H_2SO_4 and 450 ml. of water (steam-bath) was oxidized with 2.6 g. of potassium dichromate in 45 ml. of hot water as described by Albert (6), and the product was precipitated as the dichromate salt by the further addition of 6.5 g. of potassium dichromate in 60 ml. of water. After refrigeration the salt was collected and decomposed (NH_4OH, ether) giving 4 g. of an amber syrup which was taken up in 10 ml. of methanol and treated with a slight excess of 1 *N* alcoholic $HClO_4$. The tacky precipitate which resulted on diluting with 500 ml. of ether was rubbed with fresh ether and the yellow solid was collected and dried; 4 g. Trituration of the latter with 4 ml. of cold methanol left a bright-yellow solid which was collected, rinsed with a few ml. of cold methanol, and dried; 1.2 g. Recrystallization from methanol-ether gave yellow needles, m.p. 183–185°, alone or admixed with 3-ethylacridine perchlorate (*q.v.* below). Regeneration of the free base from a sample of the perchlorate and sublimation of the product, afforded pale-yellow prisms, m.p. 86–88°, not depressed when mixed with pure 3-ethylacridine. A mixture of these prisms with pure 1-ethylacridine melted at 64–66°.

The perchlorate mother liquor was diluted with 500 ml. of ether and the gummy precipitate was rubbed with fresh ether. Recrystallization of the resulting solid from acetone-ether (Norit) gave 1 g. of yellow crystals, m.p. 294–297° dec. Regeneration of the free base from this material yielded 0.63 g. of a yellow solid which crystallized from acetone in light-yellow, micro-prisms, m.p. 204–207°. (Apparently a biacridyl derivative).

Anal. Calc'd for $C_{30}H_{24}N_2$: C, 87.3; H, 5.87; N, 6.79.
Found: C, 87.2; H, 6.02; N, 6.71.

3-Nitro-4-aminoethylbenzene (XI). Employing the procedure described by Kondo (8), the nitration of 62 g. of *p*-acetaminoethylbenzene[8] and subsequent hydrolysis and steam-distillation of the crude product yielded 36.3 g. (60%) of XI. Since no analytical data were reported for this compound, the following are recorded for a sample sublimed at 100°/0.3 mm., orange prisms, m.p. 47–48.5°.

Anal. Calc'd for $C_8H_{10}N_2O_2$: C, 57.8; H, 6.07.
Found: C, 57.9; H, 5.89.

The *acetyl* derivative, sublimed at 110°/0.3 mm., yellow prisms, m.p. 45–46.5°.

Anal. Calc'd for $C_{10}H_{12}N_2O_3$: C, 57.7; H, 5.81.
Found: C, 57.6; H, 5.85.

3-Nitro-4-bromoethylbenzene (XII). The Sandmeyer replacement by bromine of the amino group in XI was effected as described for the analogous treatment of 3-nitro-4-aminoanisole (12). Starting with 28.5 g. of XI, there resulted 25.2 g. (67%) of redistilled XII, b.p. 85–87°/0.2 mm.

Anal. Calc'd for $C_8H_8BrNO_2$: C, 41.8; H, 3.51.
Found: C, 42.5; H, 3.67.

3-Amino-4-bromoethylbenzene (XIII). To a stirred solution of stannous bromide[9] (at 15°), 24.7 g. of XII was added at one time and the system was warmed gently (steam-bath). As the internal temperature approached 85°, a spontaneous reaction set in (heat source quickly removed) accompanied by a rapid temperature rise to 100° and a color change from orange to yellow. After heating for 20 mins. longer, the reaction mixture was cooled in ice and the complex salt was collected on a sintered glass funnel. The cold filtrate was basified with cold, 40% NaOH and extracted with ether. Decomposition of the complex salt was effected with dilute NaOH and the base was taken up in ether. The dark oil obtained from the combined ether extracts was cooled in ice and treated with a small excess of 35% HBr and the hydrobromide was collected and dried. Recrystallization from acetone-ether gave 14.3 g. of nearly colorless needles, m.p. 225–227° dec., from which XIII was recovered as a light-pink oil—10.9 g. (50%).

The *acetyl* derivative, after sublimation at 100°/0.3 mm., colorless needles, m.p. 111.5–112°.

Anal. Calc'd for $C_{10}H_{12}BrNO$: C, 49.6; H, 5.00.
Found: C, 49.8; H, 4.9.

2'-Bromo-5'-ethyldiphenylamine-2-carboxylic acid (XIV). The product resulting from the condensation of 5.4 g. of potassium *o*-bromobenzoate, 4.6 g. of XIII, and 100 mg. of copper-bronze powder in 25 ml. of isoamyl alcohol—4 hrs. at 170°—[*cf.* preparation IX; 2 equivs. of sodium hydroxide added prior to steam-distillation step], was triturated with a little ligroin (30–60°) and digested for 5 mins. with 300 ml. of boiling water. Recrystallization from ether-ligroin (28–38°, Norit) afforded yellow prisms, 2.7 g. (37%). After sublimation at 130°/0.3 mm., m.p. 147–149°.

Anal. Calc'd for $C_{15}H_{14}BrNO_2$: C, 56.3; H, 4.41.
Found: C, 55.9; H, 4.32.

1-Ethyl-4-bromo-9-chloroacridine (XV). From 1.92 g. of XIV and 6 ml. of $POCl_3$—1.5 hrs. at 110°—[*cf.* preparation of mixed 1- and 3-ethyl-9-chloroacridines], and subsequent recrystallization of the product from ligroin (30–60°), there was obtained 1.3 g. (70%) of lemon-yellow needles, m.p. 121–122°. The substance is not stable and darkens within a few hours, probably with loss of halogen, as is evidenced by the analytical data.

Anal. Calc'd for $C_{15}H_{11}BrClN$: C, 56.2; H, 3.5.
Found: C, 56.7; H, 4.1.

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[8] *p*-Aminoethylbenzene was obtained in 90% yield from *p*-nitroethylbenzene under the conditions given in footnote 4. Acetyl deriv., m.p. 96–97.5°.

[9] Freshly prepared from 25.6 g. of mossy tin and 150 ml. of 47% HBr as described in *Org. Syntheses*, Coll. Vol. II, 132 (1943).

1-Ethylacridine (XVI). Because of the necessity of removing both the 9-chlorine and 4-bromine atoms from XV, Albert's method (6) of dehalogenation was modified as follows: a mixture of 1.2 g. of XV in 15 ml. of benzene and 0.49 g. (2 equivs.) of KOH in 60 ml. of ethanol was shaken in hydrogen in the presence of *ca.* 3 g. of Raney nickel. With the uptake of a little more than 2 moles of hydrogen in 15 mins., the absorption rate slowed markedly. The reaction mixture was filtered and the catalyst was washed with several small portions of boiling ethanol which were combined with the main filtrate. Dehalogenation was resumed in the presence of 1.2 g. of palladium-strontium carbonate (10% Pd) catalyst, the third mole of hydrogen being absorbed in *ca.* 4 hrs. After filtration and concentration (*in vacuo*), the remaining oil (0.7 g.) was suspended in a hot mixture of 8 ml. of 2 *N* H_2SO_4 and 30 ml. of water, oxidized with 0.33 g. potassium dichromate in 4 ml. of water, and the product was converted to the dichromate salt with 0.82 g. potassium dichromate in 8 ml. of water (6). Regeneration of the free base (NH_4OH, ether) gave 0.5 g. of an oil which crystallized spontaneously. Recrystallization from ligroin (28–38°) afforded 0.3 g. of pale-yellow prisms, which were obtained virtually colorless on sublimation at 110°/0.3 mm., m.p. 89–90°.

Anal. Calc'd for $C_{15}H_{13}N$: C, 86.9; H, 6.32.
Found: C, 86.9; H, 6.37.

The *perchlorate*, yellow prisms (ethanol-ether), m.p. 201–203°.

4'-Ethyldiphenylamine-2-carboxylic acid (XVII). The condensation of 17.2 g. of potassium *o*-chlorobenzoate, 12.5 g. (2 equivs.) of anhydrous potassium carbonate, 12.3 g. (1.1 equivs.) of *p*-aminoethylbenzene[8] and 0.5 g. of copper-bronze powder in 100 ml. of isoamyl alcohol (3 hrs. at 160°) was carried out and worked up as usual. The air-dried acid was recrystallized from benzene; 11.5 g. (53%) of pale-yellow plates. A sample was sublimed at 155°/0.5 mm., m.p. 174–175°.

Anal. Calc'd for $C_{15}H_{15}NO_2$: C, 74.6; H, 6.27.
Found: C, 74.4; H, 6.03.

2-Ethyl-9-chloroacridine (XVIII). Cyclization of XVII (11.5 g.) was effected by heating with 31 ml. of $POCl_3$ for 1.25 hrs. (at 110–115°) and the reaction mixture was worked up as usual. Recrystallization from ligroin (30–60°) gave 8.6 g. (74%) of yellow needles which, after sublimation at 110°/0.3 mm., melted at 87–88.5°.

Anal. Calc'd for $C_{15}H_{12}ClN$: C, 74.5; H, 5.0.
Found: C, 74.4; H, 5.0.

2-Ethylacridine (XIX). To a solution of 1 g. of XVIII in 4 ml. of benzene, 0.275 g. (1 equiv.) of KOH in 25 ml. of ethanol was added and the mixture was shaken in hydrogen with 2 g. of Raney nickel; hydrogen uptake (2 moles) was complete in 15 mins. After removal of the catalyst and concentration (*in vacuo*), the residue was oxidized as usual in a mixture of 11.5 ml. of 2 *N* H_2SO_4 and 75 ml. of H_2O with 0.43 g. potassium dichromate in 10 ml. of H_2O. The dichromate salt of the product was precipitated by the addition of 1.1 g. of potassium dichromate in 15 ml. of H_2O, and the base was regenerated (NH_4OH, ether). Sublimation of crude XIX gave 0.5 g. of colorless prisms, m.p. 77–78.5°.

Anal. Calc'd for $C_{15}H_{13}N$: C, 86.9; H, 6.32.
Found: C, 87.2; H, 6.37.

The *perchlorate* crystallized in yellow needles (ethanol-ether), m.p. 155–157°.

3-Bromo-4-acetamino-ethylbenzene (XXa). From 75 g. (0.62 mole) of *p*-aminoethylbenzene, 250 ml. of glacial acetic acid, 45 ml. of acetic anhydride, and 100 g. (0.625 mole) of bromine there resulted, according to the parallel reaction with *p*-toluidine (13), 122 g. of crude product. A sample sublimed at 115°/0.4 mm. melted at 95–96°.

Anal. Calc'd for $C_{10}H_{12}BrNO$: C, 49.6; H, 5.0.
Found: C, 49.9; H, 5.1.

Hydrolysis of the above and simultaneous formation of 3-bromo-4-aminoethylbenzene (XXb) hydrochloride was effected by refluxing XXa (120 g.) in a mixture of 155 ml. of conc'd HCl and 175 ml. of absol. ethanol for 3 hrs. The salt was collected from the cooled reaction mixture, washed with a little cold ethanol, and dried in a vacuum desiccator—89.4 g. (61%).

2-Bromo-4-ethylbenzonitrile (XXI). A suspension of XXb hydrochloride (89 g.) in 100

ml. of dilute HCl (38 ml. of conc'd HCl diluted to 100 ml.) was diazotized at 0° with 27 g. of sodium nitrite in 80 ml. of water (during 10 mins.), and the filtered diazonium solution was added to the cooled and stirred cuprous cyanide solution[10] and the product was worked up as usual. The yield of redistilled XXI was 42 g. (53%), b.p. 92.5–95°/0.75 mm. A specimen was evaporatively distilled at 90°/0.4 mm., m.p. 42–44°.

Anal. Calc'd for C_9H_8BrN: C, 51.5; H, 3.84.
Found: C, 51.3; H, 3.82.

2-Bromo-4-ethylbenzoic acid (XXII). Compound XXI (30 g.) was added to 80 ml. of hot (150°) 75% H_2SO_4 (14), and after heating for 4 hrs., the reaction mixture was cooled and poured over ice. The mushy precipitate was taken up in *N* sodium bicarbonate and the solution was washed with alcohol-free ether. Dissolved ether was removed by heating the aqueous solution on the steam-bath and the desired acid was liberated with 2 *N* H_2SO_4 (cooling). The air-dried material was sublimed at 140°/0.4 mm.; 15.6 g.[11] of colorless prisms, m.p. 87–88.5°, was obtained.

Anal. Calc'd for $C_9H_9BrO_2$: C, 47.2; H, 3.96.
Found: C, 47.2; H, 3.91.

5-Ethyldiphenylamine-2-carboxylic acid (XXIII). The synthesis of this acid from 8.8 g. of potassium 2-bromo-4-ethylbenzoate, 4.9 g. of anhydrous potassium carbonate, 4 g. (1.2 equivs.) of redistilled aniline, and 200 mg. of copper-bronze powder in 50 ml. of isoamyl alcohol (2.5 hrs. reflux) was carried out as usual. Recrystallization of the crude acid from benzene gave 4 g. (50%) of yellow needles which, after sublimation at 155°/0.4 mm., melted at 154–155°.

Anal. Calc'd for $C_{15}H_{15}NO_2$: C, 74.7; H, 6.27.
Found: C, 74.9; H, 6.23.

3-Ethyl-9-chloroacridine (XXIV). Refluxing 4.8 g. of XXIII with 13 ml. of $POCl_3$ for 1.25 hrs. (125°) and working up in the usual way yielded 4.8 g. of a yellow oil which crystallized. From ligroin (28–38°) the substance separated as yellow prisms, m.p. 51–52.5°, which decomposed slowly on keeping.

Anal. Calc'd for $C_{15}H_{12}ClN$: C, 74.5; H, 5.00.
Found: C, 74.2; H, 4.96.

3-Ethylacridine (X). Dehalogenation of XXIV (4 g.) in 20 ml. of benzene, in the presence of 1.1 g. of KOH (1 equiv.), 100 ml. of ethanol, 6 g. of Raney nickel, and hydrogen gave 3.2 g. of the intermediate dihydro-derivative which was oxidized with potassium dichromate (*cf.* preparation of XIX). The yield of 3-ethylacridine was 1.4 g. Sublimation at 110°/0.4 mm. gave colorless prisms, m.p. 90–91.5°.

Anal. Calc'd for $C_{15}H_{13}N$: C, 86.9; H, 6.32.
Found: C, 87.0; H, 6.33.

The *perchlorate* separated as yellow prisms from ethanol-ether, m.p. 184–185°.

2'-Ethyldiphenylamine-2-carboxylic acid (XXV). From 17.7 g. of potassium *o*-chlorobenzoate, 12.5 g. (2 equivs.) of anhydrous potassium carbonate, 12.5 g. (1.1 equiv.) of *o*-aminoethylbenzene, 100 ml. of isoamyl alcohol, and 0.5 g. of copper-bronze powder (2.75 hrs. reflux at 160°), there was obtained, after recrystallization from benzene, 10.7 g. (49% of pale-yellow plates. A sample, sublimed at 155°/0.4 mm., melted at 169–170.5°; lit. (15) m.p. 168°.

Anal. Calc'd for $C_{15}H_{15}NO_2$: C, 74.7; H, 6.27.
Found: C, 74.8; H, 6.28.

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[10] *Cf.* footnote 6; prepared from 119 g. of $CuSO_4 \cdot 5H_2O$ and 31 g. of NaCl in 400 ml. of H_2O; 26 g. of $NaHSO_3$ and 17.2 g. of NaOH in 200 ml. of H_2O; 65 g. of NaCN in 100 ml. of H_2O.

[11] It was subsequently found that alkaline hydrolysis gave superior yields: thus, heating 3 g. of XXI with a mixture of 15 ml. of 3 *N* KOH and 20 ml. of Methyl Cellosolve (2-methoxyethanol) for 20 hrs. gave, after sublimation of the product, 2.6 g. of acid identical with XXII.

4-Ethyl-9-chloroacridine (XXVI). Cyclization of XXV (6.8 g.) with 18 ml. of $POCl_3$ (1 hr. at 115°) ultimately gave 6.2 g. of product which was sublimed at 105°/0.4 mm., pale-yellow prisms, m.p. 68–69.5°.

Anal. Calc'd for $C_{15}H_{12}ClN$: C, 74.5; H, 5.00.
Found: C, 74.5; H, 5.20.

4-Ethylacridine (XXVII). A mixture of XXVI (5.7 g.) in 30 ml. of benzene, 1.56 g. (1 equiv.) of KOH, 140 ml. of ethanol, and 6 g. of Raney nickel was shaken in hydrogen and the product was oxidized with potassium dichromate (*cf.* preparation of XIX) to give 4-ethylacridine initially as an oil. Since the latter showed little tendency to crystallize, it was converted to the *perchlorate* (alcoholic $HClO_4$) and the salt was recrystallized from methanol; 4.5 g., bright-yellow, irregular-shaped prisms, m.p. 216–217°. From the latter, 4-ethylacridine was obtained as a pale yellow oil (2.6 g.) which crystallized when chilled in Dry Ice-acetone. Evaporative distillation at 100°/0.4 mm. gave an oil which crystallized in massive, colorless prisms, m.p. 37–38.5°.

Anal. Calc'd for $C_{15}H_{13}N$: C, 86.9; H, 6.32.
Found: C, 87.0; H, 6.43.

SUMMARY

1-Ethyl-, 2-ethyl-, 3-ethyl- and 4-ethyl-acridine have been synthesized by unequivocal routes.

BETHESDA 14, MD.

REFERENCES

(1) SARGENT AND SMALL, *J. Org. Chem.*, **13**, 447 (1948).
(2) GLEU AND NITZSCHE, *J. prakt. Chem.*, **153**, 200 (1939).
(3) BACHMANN AND BOATNER, *J. Am. Chem. Soc.*, **58**, 2194 (1936).
(4) CLAUS, *Ann.*, **265**, 371 (1891); **269**, 212 (1892); **274**, 298 (1893); BERGER AND OLIVIER, *Rec. trav. chim.*, **46**, 600 (1927); **48**, 568 (1929); SUDBOROUGH, *J. Chem. Soc.*, **67**, 601 (1895).
(5) ALBERT, *The Acridines*, Arnold and Company, London, 1951, p. 40.
(6) ALBERT AND WILLIS, *J. Soc. Chem. Ind. (London)*, **65**, 26 (1946).
(7) SARGENT AND MILLER, in press.
(8) KONDO AND UYEO, *Ber.*, **70**, 1094 (1937).
(9) *Org. Syntheses*, Coll. Vol. II, p. 434 (1943).
(10) RUPE, BRAUN, AND VON ZEMBRUSKI, *Ber.*, **34**, 3522 (1902).
(11) HUANG-MINLON, *J. Am. Chem. Soc.*, **68**, 2487 (1946).
(12) SAMANT, *Ber.*, **75**, 1008 (1942).
(13) *Org. Syntheses*, Coll. Vol. I, p. 111 (1944).
(14) *Cf. Org. Syntheses*, Coll. Vol. II, p. 588 (1943).
(15) ALBERT AND GLEDHILL, *J. Soc. Chem. Ind. (London)*, **64**, 169 (1945).