Antimalarial 2-Alkoxy-6-chloro-9-dialkylaminoalkylamino-1 : 10-diaza-anthracenes.

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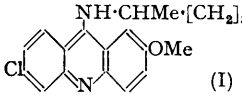
2-Alkoxy-6-chloro-9-dialkylaminoalkylamino-1 : 10-diaza-anthracenes have been synthesised because of their structural relation to mepacrine and pamaquine. One of these, 6-chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxy-1 : 10-diaza-anthracene dihydrochloride ("Azacrin"), is highly active against human malaria due to *P. falciparum* and *P. vivax*.

Condensation of 2-alkoxy-5-aminopyridines with 2 : 4-dichlorobenzoic acid gave 2-(6-alkoxy-3-pyridylamino)-4-chlorobenzoic acids. Cyclisation with phosphoryl chloride yielded 2-alkoxy-6 : 9-dichloro-1 : 10-diaza-anthracenes which reacted with dialkylaminoalkylamines to give the desired compounds.

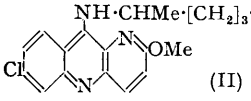
Observations have been made upon the failure of *o*-3-pyridylaminobenzoic acids to cyclise unless the pyridine ring contains an electron-releasing substituent. It has been proved by rational synthesis that ring closure takes place on the 2-position of the pyridine ring.

Analogues (II) of mepacrine (I) derived from 1 : 10-diaza-anthracene were required for examination for antiplasmodial activity because they bear structural resemblance to pamaquine (III; R = R′ = Et) inasmuch as the dialkylaminoalkylamino-side-chain is *peri* to a ring-nitrogen atom. Pamaquine and primaquine (III; R = R′ = H) are the most effective of the known antimalarials against the secondary exoerythrocytic stages of the parasite

responsible for relapse in infections due to *P. vivax* (Report by Council on Pharmacy & Chemistry, *J. Amer. Med. Assoc.*, 1952, **149**, 1558); the possibility was envisaged that compounds of type (II) might combine the schizonticidal activity of mepacrine with the radically curative properties of pamaquine. A further point of interest arises from the hypothesis (Madinaveitia, *Biochem., J.* 1946, **40**, 373) that antimalarials function by virtue of their ability to antagonise riboflavine, an essential factor for the survival of the plasmodium. 1 : 10-Diaza-anthracenes of type (II) are more closely related to riboflavine than is mepacrine and might therefore be expected to be superior flavin antagonists.



(I)



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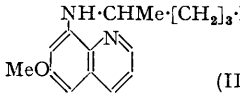


(III)

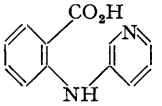
Previous attempts to prepare 9-dialkylaminoalkylamino-diaza-anthracenes from *o*-pyridylaminobenzoic and 3-phenylaminopicolinic acids have been unsuccessful (Kermack and Wetherhead, *J.*, 1942, 726; Petrov, *J.*, 1945, 927; 1949, 1157; Price and Roberts, *J. Org. Chem.*, 1946, **11**, 463; Bachmann and Barker, *ibid.*, 1949, **14**, 97); in the few instances where ring closure was accomplished, trans-annular tautomerism of the central ring was inhibited and the 9-chlorodiaza-anthracene, essential for introduction of the dialkylaminoalkylamino-side-chain, was unobtainable. The present communication records the synthesis of a number of 2-alkoxy-6-chloro-9-dialkylaminoalkylamino-1 : 10-diaza-anthracenes and related compounds.

Condensation of 5-amino-2-methoxypyridine with 2 : 4-dichlorobenzoic acid gave 4-chloro-2-(6-methoxy-3-pyridylamino)benzoic acid. The Ullmann condensation between an *o*-chlorobenzoic acid and an arylamine is normally effected in presence of a considerable excess of potassium carbonate which functions as acid acceptor for the hydrogen chloride eliminated. During the latter part of the work it was observed that better yields were obtained by use of 0·5 mole of potassium carbonate for each mole of the *o*-chlorobenzoic acid, less tar being formed by alkaline decomposition of the pyridylamine. Under these conditions the condensation is essentially a reaction between the potassium *o*-chlorobenzoate and the pyridylamine in the absence of an inorganic acid acceptor: the potassium *o*-pyridylaminobenzoate, as it is formed, acts as acid acceptor by virtue of the fact that *o*-pyridylaminobenzoic acids have considerably higher pK_a values than the *o*-chlorobenzoic acids. At termination, the reaction mixture has pH *ca.* 4; that the reaction takes place at this pH conforms with the suggestion (Goldberg, *J.*, 1953, 4368) that it proceeds *via* a copper chelate complex and only in an environment which allows this to exist, since a number of well-known copper chelate compounds, including copper acetylacetone, are stable in boiling amyl alcohol–acetic acid solution. Cyclodehydration of 4-chloro-2-(6-methoxy-3-pyridylamino)benzoic acid by Magidson and Grigowski's method (*Ber.*, 1933, **66**, 866) yielded 6 : 9-dichloro-2-methoxy-1 : 10-diaza-anthracene which, when heated in phenol with 4-diethylamino-1-methylbutylamine, was converted into 6-chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxy-1 : 10-diaza-anthracene, conveniently isolated as the dihydrochloride. By the above synthetic procedure, using various 2-alkoxy-5-aminopyridines, substituted *o*-chlorobenzoic acids and dialkylaminoalkylamines, a number of 2-alkoxy-9-dialkylaminoalkylamino-1 : 10-diaza-anthracenes bearing substituents in the 6- and the 7-position have been prepared and screened for activity against *P. gallinaceum* and *P. berghei* infections in chicks and mice respectively.

Treatment of *o*-(6-benzyloxy-3-pyridylamino)benzoic acids with phosphoryl chloride effected cyclisation and simultaneous chlorinolysis of the benzyloxy-group with production of 2 : 9-dichloro-1 : 10-diaza-anthracenes. These are of interest because the difference in reactivity of the halogen substituents permits their stepwise replacement with any desired amine; the 2-chloro-atom has the comparatively low mobility associated with that in 2-chloropyridine and the 9-chloro-atom the high reactivity of the halogen in 5-chloroacridine.

The Cyclisation of o-3-*Pyridylaminobenzoic Acids.*—*o*-3-Pyridylaminobenzoic acids (IV) may give rise to the 9-hydroxy- or the 9-chloro-derivative of 1 : 10- (V) or 3 : 10-diaza-anthracene (VI) according to whether cyclisation proceeds upon the 2- or the 4-position of

the pyridine ring. Similar types of cyclodehydration occur with 2-carboxy-3'-nitrodiphenylamines which cyclise principally upon the 2'-position (Goldberg and Kelly, *J.*, 1946, 103; cf. the ring closure of 2-carboxy-3'-nitrodiphenyl ethers upon the 2'-position; Goldberg and Walker, *J.*, 1953, 1348). The striking similarity between the substitution reactions of pyridine and nitrobenzene (Elderfield, " Heterocyclic Compounds," Wiley, New York, 1950, Vol. I, pp. 408 *et seq.*) suggests that *o*-3-pyridylaminobenzoic acids would similarly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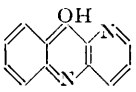
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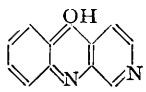
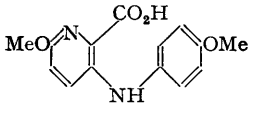

(VI)

cyclise upon the 2-position of the pyridine ring and this is supported by the fact that, in compounds of type (IV), ability to cyclise is suppressed by blockage of the 2- but not of the 4-position: 4-chloro-2-(6-methoxy-4-methyl-3-pyridylamino)benzoic acid is, and 4-chloro-2-(6-methoxy-2-methyl-3-pyridylamino)benzoic acid is not, cyclodehydrated by sulphuric acid or phosphoryl chloride.

Cyclodehydration of *o*-3-pyridylaminobenzoic acids in strong acid comprises the initial protonisation of the carbonyl oxygen followed by the attack of the carbonium ion on the pyridine nucleus. The reaction will proceed if the electron density at the available points for ring closure ($C_{(2)}$ and $C_{(4)}$ of the pyridine ring) is sufficiently high, its direction being governed by the relative electron densities. With regard to the direction it is significant that the total mobile electron densities computed by the method of molecular orbitals (Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87) at the 2-position in pyridine is considerably higher than it is at the 4-position; this must also be the case with 3-aminopyridine which is chlorinated in acid (Schick, Binz, and Schultz, *Ber.*, 1936, **69**, 2593) and sulphonated (Plazek, *Roczn. Chem.*, 1937, **17**, 97), and undergoes the Skraup cyclisation (Klisiecki and Sucharda, *ibid.*, 1927, **7**, 204; Bobranski and Sucharda, *Ber.*, 1927, **60**, 1081), exclusively at the 2-position. The electromeric shift induced by the 6-alkoxy-group cannot assist the electron distribution at either $C_{(2)}$ or $C_{(4)}$ of the pyridine ring; it would therefore be expected that 2-(6-alkoxy-3-pyridylamino)benzoic acid would cyclise upon the 2-position of the pyridine ring. That this is the case has been shown by rational synthesis of a typical compound of the series. 3-Chloro-6-methoxypicolinic acid was condensed with *p*-anisidine; the product (VII) cyclised with phosphoryl chloride to 9-chloro-2 : 7-dimethoxy-1 : 10-diaza-anthracene identical with the product obtained by ring closure of 5-methoxy-2-(6-methoxy-3-pyridylamino)benzoic acid (VIII).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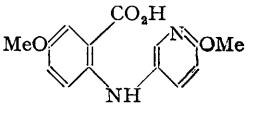
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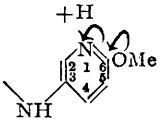
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The failure of unsubstituted *o*-3-pyridylaminobenzoic acids to cyclise requires comment in view of the facility with which *o*-3-nitroanilinobenzoic acids undergo ring closure. Consideration of the electrophilic and nucleophilic substitution reactions of pyridine and nitrobenzene in acid media indicates that the $-I$ effect of the protonised nitrogen of the former is considerably more powerful than that of the nitro-group in the latter, their $-T$ effects being of a comparable order. It is therefore not surprising that the electron density at the 2- and the 4-position in the pyridine ring in an unsubstituted *o*-3-pyridylaminobenzoic acid should be below the threshold value required for cyclisation. The $+T$ effect of an alkoxy-group is greater than the combined $-I$ and $-T$ effects of the pyridine-nitrogen atom as shown by the ease with which 3-alkoxypyridines are nitrated at the 2-position (den Hertzog, *Rec. Trav. chim.*, 1949, **68**, 275). In a 2-(6-methoxy-3-pyridylamino)benzoic acid the electromeric effect of the alkoxy-group cannot *directly* affect the electron density at the 2- and the 4-position of the pyridine ring although the mesomerism of the protonised cyclic

imino-ether (IX) may cause partial bond fixation and suppress the inductive and tautomeric mechanisms by which the nitrogen atom normally creates electron defect at $C_{(2)}$ and $C_{(4)}$. Cyclisation would in consequence proceed at $C_{(2)}$ since ring closure can only take place across a double bond (cf. Lellmann and Schmidt, *Ber.*, 1887, **20**, 3154; Markwald, *Annalen*, 1894, **279**, 1).

Chemotherapeutic Activity.—6-Chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxy-1 : 10-diaza-anthracene dihydrochloride (" Azacrin ") at an oral dosage of 25 mg./kg. per day gives the same effective control of *P. gallinaceum* infections in chicks as 50 mg./kg. per day of mepacrine, or 12·5 mg./kg. of chloroquine; in mice, 5 mg./kg. of " Azacrin " (LD_{50} = 900 mg./kg.) per day has the same suppressive activity as 5 mg./kg. per day of mepacrine (LD_{50} = 850 mg./kg.) or 3·0 mg./kg. of chloroquine (LD_{50} = 400 mg./kg.). Making use of these results Bruce-Chwatt and Archibald (*Brit. Med. J.*, 1953, I, 539) and Ang'awa and Fendall (*J. Trop. Med. Hyg.*, 1954, **57**, 59) have found " Azacrin " to be a very effective schizonticide in human malaria due to *P. falciparum*, having shorter pyrexia- and parasite-clearance times, and allowing fewer relapses, than mepacrine.

Experimental

Substituted 3-aminopyridines

The 2-alkoxy-5-aminopyridines were obtained from 2-chloro-5-nitropyridine (Caldwell and Kornfield, *J. Amer. Chem. Soc.*, 1942, **64**, 1696) and the sodium alkoxide, the nitroalkoxypyridine then being reduced with iron powder (Friedman, Braitberg, Tolstoouhov, and Tizsa, *ibid.*, 1947, **69**, 1204). The overall yield from 2-aminopyridine was in each case *ca.* 40%. 5-Amino-2-methoxypyridine had b. p. 98—102°/3 mm., 5-amino-2-*n*-butoxypyridine b. p. 128—130°/2 mm., 5-amino-2-benzyloxypyridine m. p. 46—48°, and 5-amino-2-phenoxypyridine m. p. 70—72°.

2-*Amino*-4-*methyl*-5-*nitropyridine*.—Nitration of 2-amino-4-methylpyridine (40 g.) by Seide's method (*Ber.*, 1924, **57**, 791) gave non-volatile 2-amino-4-methyl-5-nitropyridine (30 g.), m. p. 220—222°, and the steam-volatile 3-nitro-isomer (11 g.), m. p. 140°.

2-*Hydroxy*-4-*methyl*-5-*nitropyridine*.—To a solution of 2-amino-4-methyl-5-nitropyridine (17·4 g.) in water (300 c.c.) and sulphuric acid (30 c.c.; *d* 1·84), stirred at 10—15°, was added dropwise sodium nitrite (17·5 g.) in water (35 c.c.); the mixture was stirred a further 2 hr. at room temperature, then raised cautiously (frothing) to the b. p. and then chilled in ice water. The precipitate, on crystallisation from water (*ca.* 200 c.c.), gave 2-*hydroxy*-4-*methyl*-5-*nitropyridine* (15 g.) as orange plates, m. p. 186—188° (Found : N, 18·0. $C_6H_6O_3N_2$ requires N, 18·2%).

2-*Chloro*-4-*methyl*-5-*nitropyridine*.—The foregoing compound (19·8 g.) was refluxed for 4 hr. with phosphorus pentachloride (27 g.) and phosphoryl chloride (5 c.c.). Excess of phosphoryl chloride was distilled off at reduced pressure, the residue quenched on ice, and the sticky product drained on porous tile. The air-dried material, mixed with charcoal, was extracted with ligroin (b. p. 40—60°) (Soxhlet). On cooling of the ligroin liquors, 2-*chloro*-4-*methyl*-5-*nitropyridine* (16·4 g.) separated as yellow prisms, m. p. 40—44° (Found : N, 16·6; Cl, 20·8. $C_6H_5O_2N_2Cl$ requires N, 16·2; Cl, 20·6%).

2-*Methoxy*-4-*methyl*-5-*nitropyridine*.—The foregoing compound (15 g.) was added portionwise to a solution of sodium (2·1 g.) in anhydrous methanol (100 c.c.). Next morning the mixture was refluxed for ½ hr., then poured on ice (800 g.), and the 2-*methoxy*-4-*methyl*-5-*nitropyridine* (13·8 g.; m. p. 80—84°) collected and dried at 30°; a sample crystallised from ligroin (b. p. 60—80°) in needles, m. p. 82—84° (Found : N, 17·1. $C_7H_8O_3N_2$ requires N, 16·7%).

5-*Amino*-2-*methoxy*-4-*methylpyridine*.—The foregoing nitro-compound (13·6 g.) was added portionwise during 45 min. to a stirred, refluxing mixture of water (100 c.c.), alcohol (100 c.c.), acetic acid (2 c.c.), and Pacteron iron dust (33 g.). After a further 2 hours' stirring at the b. p., potassium hydrogen carbonate (50 g.) was cautiously added, the mixture stirred at the b. p. for a further 3 hr., and the iron oxide filtered off and washed with boiling alcohol (250 c.c.). The combined filtrates were concentrated almost to dryness at reduced pressure, the residue was extracted with ether (3 × 100 c.c.), and the ethereal solution dried (K_2CO_3). Distillation of the ether left the *product* (10 g.) as a mass of needles, m. p. 94—96°; a sample separated from ligroin (b. p. 60—80°) in needles, m. p. 97° (Found : N, 20·1. $C_7H_{10}ON_2$ requires N, 20·3%).

5-*Amino*-2-*methoxy*-6-*methylpyridine*.—Nitration of 2-amino-6-methylpyridine (50 g.) by Parker and Schine's method (*J. Amer. Chem. Soc.*, 1947, **69**, 63) and crystallisation of the non-volatile product twice from boiling water (130 c.c./g.) yielded 2-amino-6-methyl-5-nitropyridine

(31 g.), m. p. 190°, pure enough for the next stage. (The amount of steam-volatile 3-nitro-isomer obtained was 16 g., having m. p. 156—158°.) The 5-nitro-compound was converted into the amine as described above. The intermediate compounds thus obtained and the yields were: 2-hydroxy-6-methyl-5-nitro- (95%), m. p. 234—236°, 2-chloro-6-methyl-5-nitro- (96%), m. p. 55°, *2-methoxy-6-methyl-5-nitro-* (93%), m. p. 70—72° (Found: N, 17·1. $C_7H_8O_3N_2$ requires N, 16·7%), and *5-amino-2-methoxy-6-methyl-pyridine* (75%), b. p. 97°/1 mm. (Found: N, 19·9. $C_7H_{10}ON_2$ requires N, 20·3%).

o-3-Pyridylaminobenzoic acids

General Procedure.—The *o*-chlorobenzoic acid (0·1 mole) was dissolved in amyl alcohol (100 c.c.) in a 3-necked flask and stirred at *ca.* 100° for ½ hr. with the copper catalyst and anhydrous potassium carbonate (0·05—0·125 mole) in order to obtain the potassium salt in a voluminous state. The aminopyridine (0·1 mole) was added and the mixture stirred at the b. p. for the stated time; water formed was removed by a Dean and Stark apparatus. The mixture was poured into water and basified (if necessary) with potassium carbonate, the amyl alcohol removed in steam, and the residual aqueous liquor filtered from tar. Acidification to pH 6·5 frequently precipitated more tar; after removal of this with charcoal the solution was stirred at *ca.* 80°, and adjusted to pH 4 by addition of hydrochloric acid. The precipitated *o*-pyridylaminobenzoic acid was collected and washed with boiling water to remove unchanged starting material.

4-Chloro-2-(6-methoxy-3-pyridylamino)benzoic Acid.—2 : 4-Dichlorobenzoic acid (19·1 g.), anhydrous potassium carbonate (6·9 g.), copper oxide (0·1 g.), 5-amino-2-methoxypyridine (13 g.), and amyl alcohol (100 c.c.) gave, in 3 hr., the crude product as a bluish white powder (19 g., 68%); the pure *acid* separated from ethanol or ethyl methyl ketone in almost colourless needles, m. p. 208° (Found: equiv., 278; N, 10·1; Cl, 12·7%. $C_{13}H_{11}O_3N_2Cl$ requires equiv., 278·5; N, 10·1; Cl, 12·75%).

2-(6-n-Butoxy-3-pyridylamino)-4-chlorobenzoic Acid.—2 : 4-Dichlorobenzoic acid (19·1 g.), potassium carbonate (17·25 g.), 5-amino-2-*n*-butoxypyridine (20·8 g.), copper oxide (0·5 g.) and cuprous iodide (0·5 g.), in amyl alcohol (300 c.c.) at 132° for 3 hr., gave the required *acid* in buff crystals (11 g.), m. p. 148° (from aqueous methanol) (Found: equiv., 319; N, 9·0; Cl, 11·0%. $C_{16}H_{17}O_3N_2Cl$ requires equiv., 320·5; N, 8·7; Cl, 11·1%).

4-Chloro-2-(6-phenoxy-3-pyridylamino)benzoic Acid.—2 : 4-Dichlorobenzoic acid (14 g.), potassium carbonate (10·5 g.), cupric oxide (0·1 g.), 5-amino-2-phenoxypyridine (9·3 g.), and amyl alcohol (50 c.c.) in 10 hr. gave a light brown tar which solidified under 60% acetic acid; recrystallisation from methanol or toluene gave the pure colourless *acid* (2·3 g.), m. p. 186—188° (Found: equiv., 342; N, 8·3; Cl, 10·4%. $C_{18}H_{13}O_3N_2Cl$ requires equiv., 340·5; N, 8·2; Cl, 10·4%).

4-Chloro-2-(6-benzyloxy-3-pyridylamino)benzoic Acid.—2 : 4-Dichlorobenzoic acid (24 g.), potassium carbonate (20 g.), copper oxide (0·25 g.), amyl alcohol (100 c.c.), and 5-amino-2-benzyloxypyridine (20 g.) were stirred for 3 hr. The glutinous crude product was triturated with cold alcohol (100 c.c.) and the residual solid crystallised from boiling alcohol to give the pure *acid* in colourless needles (5·4 g.), m. p. 188—190° (Found: equiv., 349; N, 8·2; Cl, 10·1%. $C_{19}H_{15}O_3N_2Cl$ requires equiv., 354·5; N, 7·9; Cl, 10·0%).

5-Chloro-2-(6-benzyloxy-3-pyridylamino)benzoic Acid.—2 : 5-Dichlorobenzoic acid (24 g.), potassium carbonate (18 g.), copper oxide (0·25 g.), amyl alcohol (100 c.c.), and 5-amino-2-benzyloxypyridine (20 g.) (3 hr.) gave a glutinous crude product. Trituration with cold methanol (100 c.c.) and crystallisation from dilute acetic acid gave the pure *acid* as grey needles (20 g.), m. p. 222° (Found: equiv., 348; N, 8·0; Cl, 9·9%. $C_{19}H_{15}O_3N_2Cl$ requires equiv., 354·5; N, 7·9; Cl, 10·0%).

5-Methoxy-2-(6-methoxy-3-pyridylamino)benzoic Acid.—Boiling 2-chloro-5-methoxybenzoic acid (28 g.), potassium carbonate (21 g.), amyl alcohol (100 c.c.), cupric oxide (0·25 g.), and 5-amino-2-methoxypyridine (14·8 g.) for 4 hr. gave a pale yellow *acid* (6 g.), m. p. 190—192° (from alcohol) (Found: equiv., 278; N, 10·3%. $C_{14}H_{14}O_4N_2$ requires equiv., 274; N, 10·2%).

2-(6-Benzyloxy-3-pyridylamino)benzoic Acid.—*o*-Chlorobenzoic acid (49 g.), potassium carbonate (45 g.), copper oxide (0·25 g.), cuprous iodide (0·25 g.), amyl alcohol (250 c.c.), and 5-amino-2-benzyloxypyridine (48 g.) (7 hr.) gave a semi-solid *product* which, when washed with cold alcohol and then toluene, and crystallised from alcohol had m. p. 178—180° (45 g.) (Found: equiv., 320; N, 8·8%. $C_{19}H_{16}O_3N_2$ requires equiv., 320; N, 8·75%).

4-Chloro-2-(6-methoxy-4-methyl-3-pyridylamino)benzoic Acid.—2 : 4-Dichlorobenzoic acid (8·8 g.), potassium carbonate (3·25 g.), 5-amino-2-methoxy-4-methylpyridine (6·4 g.), amyl alcohol

(50 c.c.), and traces of copper bronze and cuprous iodide (5 hr.) gave the *acid* (5 g.), as needles (from alcohol), m. p. 250—252° (Found : equiv., 293; N, 9·8; Cl, 12·3%. $C_{14}H_{13}O_3N_2Cl$ requires equiv., 292·5; N, 9·6; Cl, 12·1%).

4-*Chloro*-2-(6-*methoxy*-2-*methyl*-3-*pyridylamino*)*benzoic Acid*.—2 : 4-Dichlorobenzoic acid (25 g.), potassium carbonate (8 g.), 5-amino-2-methoxy-6-methylpyridine (14 g.), amyl alcohol (100 c.c.), copper oxide (0·1 g.), and cuprous iodide (0·1 g.) (5 hr. at 132°) gave an *acid* (17·7 g.) which crystallised from 95% alcohol in yellow prisms, m. p. 228—230° (Found : equiv., 292; N, 9·7; Cl, 12·1%. $C_{14}H_{13}O_3N_2Cl$ requires equiv., 292·5; N, 9·6; Cl, 12·1%).

1 : 10-*Diaza-anthracenes*

6 : 9-*Dichloro*-2-*methoxy*-1 : 10-*diaza-anthracene*.—Anhydrous 4-chloro-2-(6-methoxy-3-pyridylamino)benzoic acid (54 g.) was refluxed with freshly distilled phosphoryl chloride (330 c.c.) for 4 hr. Excess of phosphoryl chloride (*ca.* 250 c.c.) was pumped off (at 70°) and the residual thick liquid poured slowly on crushed ice (1500 g.) and aqueous ammonia (500 c.c.; *d* 0·88). More ice and ammonia were added when necessary to keep the temperature at 0° and the mixture just alkaline. After 6—12 hr. at 0° the friable solid was collected, washed with ice water, and dried (KOH) at 15°/5 mm. The 6 : 9-*dichloro*-2-*methoxy*-1 : 10-*diaza-anthracene* (53 g.) was obtained as a light yellow powder, m. p. 180—184°, pure enough for the next stage; a sample crystallised from acetone in yellow needles, m. p. 186—188° (Found : N, 10·4; Cl, 24·9. $C_{13}H_8ON_2Cl_2$ requires N, 10·0; Cl, 25·4%).

The following compounds were obtained in the same manner from the appropriate 2-3′-pyridylaminobenzoic acid; in all cases the yield of crude material (having m. p. *ca.* 4° below the m. p. of the recrystallised material) was *ca.* 95%. These 9-chloro-1 : 10-diaza-anthracenes are very soluble in chloroform, less soluble in benzene, and still less soluble in ligroin. They are stable in aqueous media provided they are slightly alkaline and may be crystallised from aqueous ammoniacal alcohol; in aqueous media sufficiently acid for the central nitrogen atom to become protonised, the 9-chloro-substituent rapidly undergoes hydrolysis (cf. 5-chloroacridines). The crystallising solvent is given in parentheses.

2-n-*Butoxy*-6 : 9-*dichloro*-1 : 10-*diaza-anthracene*, light yellow needles (acetone), m. p. 126—128° (Found : N, 8·9; Cl, 22·0. $C_{16}H_{14}ON_2Cl_2$ requires N, 8·7; Cl, 22·1%).

6 : 9-*Dichloro*-2-*phenoxy*-1 : 10-*diaza-anthracene*, colourless needles (large volume of ligroin, b. p. 80—100°), m. p. 184° (Found : N, 8·2; Cl, 20·5. $C_{18}H_{10}ON_2Cl_2$ requires N, 8·2; Cl, 20·8%).

9-*Chloro*-2 : 7-*dimethoxy*-1 : 10-*diaza-anthracene* [obtained by cyclisation of 5-methoxy-2-(6-methoxy-3-pyridylamino)benzoic acid], colourless needles (ligroin, b. p. 80—100°), m. p. 220° alone and on admixture with a sample obtained by cyclisation of 6-methoxy-3-*p*-methoxyanilinopicolinic acid (see below) (Found : N, 10·4; Cl, 13·2. $C_{14}H_{11}O_2N_2Cl$ requires N, 10·2; Cl, 12·9%).

6 : 9-*Dichloro*-2-*methoxy*-4-*methyl*-1 : 10-*diaza-anthracene*, pale lemon-yellow needles (ethyl acetate), m. p. 171—173° (Found : N, 9·6; Cl, 24·4. $C_{14}H_{10}ON_2Cl_2$ requires N, 9·55; Cl, 24·2%).

2 : 7 : 9-*Trichloro*-1 : 10-*diaza-anthracene*.—5-Chloro-2-(6-benzyloxy-3-pyridylamino)benzoic acid (12 g.) and phosphoryl chloride (75 c.c.) were refluxed for 4 hr. The crude product, isolated as above, was drained on tile and dried (KOH) at 15°/2 mm. Washing with a little cold ligroin (b. p. 40—60°) gave 2 : 7 : 9-*trichloro*-1 : 10-*diaza-anthracene* as a buff powder (9 g.), m. p. 230—234°; it crystallised from carbon tetrachloride–ligroin (b. p. 80—100°) in pale olive needles, m. p. 238—240° (Found : N, 9·9; Cl, 37·4. $C_{12}H_5N_2Cl_3$ requires N, 9·9; Cl, 37·6%).

2 : 6 : 9-*Trichloro*-1 : 10-*diaza-anthracene* was obtained in the same manner in 80% yield from 4-chloro-2-(6-benzyloxy-3-pyridylamino)benzoic acid as pale yellow needles, m. p. 228—230° (Found : N, 10·2; Cl, 37·9%).

2 : 9-*Dichloro*-1 : 10-*diaza-anthracene*, obtained in 75% yield from 2-(6-benzyloxy-3-pyridylamino)benzoic acid by similar means, crystallised from chloroform–ligroin (b. p. 60—80°) in felted colourless needles, m. p. 200° (Found : N, 11·3; Cl, 28·4. $C_{12}H_6N_2Cl_2$ requires N, 11·2; Cl, 28·5%).

Attempted Cyclisation of 4-*Chloro*-2-(6-*methoxy*-2-*methyl*-3-*pyridylamino*)*benzoic Acid*.—This acid (10 g.) was refluxed for 4 hr. with phosphorus oxychloride (100 c.c.), the excess of oxychloride distilled off at reduced pressure, and the residual oil poured on crushed ice and ammonia. The precipitate was collected, drained, and extracted with chloroform. The extract, on evaporation, gave a dark sticky solid, which was converted in benzene into a grey powder; crystallisation of this from aqueous alcohol containing a little ammonia yielded the *benzamide* (1·5 g.),

m. p. 182—184° (Found: N, 14·9; Cl, 12·4. $C_{14}H_{14}O_2N_3Cl$ requires N, 14·4; Cl, 12·2%). Hydrolysis of this (0·8 g.) with 5N-sodium hydroxide (10 c.c.) in alcohol (10 c.c.) yielded the original acid, m. p. and mixed m. p. 228—230°. No 9-chloro-1 : 10-diaza-anthracene or 1 : 10-diaza-anthrone was isolated.

9-*Amino*-6-*chloro*-2-*methoxy*-1 : 10-*diaza-anthracene*.—A solution of 6 : 9-dichloro-2-methoxy-1 : 10-diaza-anthracene (8·6 g.) in phenol (40 g.; previously dried at 130° for 1 hr.) was heated to 110° for 1 hr., and then ammonium carbonate (20 g.) was added portionwise as rapidly as the frothing would permit (*ca.* 1 hr.). After a further 1½ hr. at 110° the mixture was cooled and poured into, and macerated with, dry ether (400 c.c.). Next morning the crystalline yellow *hydrochloride* (8·6 g.; m. p. 282—284°) was collected, washed with ether, and dried at 50° (Found: N, 14·0; Cl, 23·8. $C_{13}H_{11}ON_3Cl_2$ requires N, 14·2; Cl, 24·0%). The free *amine* was obtained by shaking a suspension of the hydrochloride in an excess of 2N-sodium hydroxide with glass beads for 3 hr.; the insoluble material crystallised from aqueous pyridine in pale yellow needles, m. p. 294—296° (Found: N, 16·4; Cl, 14·9. $C_{13}H_{10}ON_3Cl$ requires N, 16·2; Cl, 13·7%).

9-*Amino*-2-n-*butoxy*-6-*chloro*-1 : 10-*diaza-anthraceme hydrochloride*, obtained in the same manner in 90% yield, crystallised from methanol containing a trace of hydrochloric acid in yellow needles, m. p. 254—256° (decomp.) (Found: N, 12·5; Cl, 21·0. $C_{16}H_{17}ON_3Cl_2$ requires N, 12·4; Cl, 21·0%).

9-*Amino*-6-*chloro*-2-*phenoxy*-1 : 10-*diaza-anthracene hydrochloride* crystallised from ethanol in yellow prisms, m. p. 278—280° (decomp.) (Found: N, 11·7; Cl, 20·2. $C_{18}H_{13}ON_3Cl_2$ requires N, 11·7; Cl, 19·8%).

9-*Amino*-2-*chloro*-1 : 10-*diaza-anthracene hydrochloride* was obtained from 2 : 9-dichloro-1 : 10-diaza-anthracene in like manner. The crude product precipitated by ether was a black powder; this was ground with excess of cold 5N-sodium hydroxide, the insoluble residue dissolved in butanol containing a little ether and the filtered (charcoal) solution extracted with aqueous acetic acid. The solution was basified with sodium hydroxide, and the precipitate dissolved in hot 2N-hydrochloric acid; 9-amino-2-chloro-1 : 10-diaza-anthracene hydrochloride separated in yellow needles (Found: N, 16·1; Cl, 27·4; Cl^-, 13·8. $C_{12}H_8N_3Cl,HCl$ requires N, 15·8; Cl, 26·7; Cl^-, 13·4%). The free base had m. p. 240—244°.

9-*Benzylamino*-6-*chloro*-2-*methoxy*-1 : 10-*diaza-anthracene Hydrochloride*.—6 : 9-Dichloro-2-methoxy-1 : 10-diaza-anthracene (5 g.) and benzylamine (15 g.) were heated to 120° for 4 hr. and poured into acetone (100 c.c.). The precipitated *hydrochloride* (5·6 g., 81%) crystallised from 95% alcohol as a yellow powder, m. p. 274—276° (Found: N, 10·7; Cl, 18·4. $C_{20}H_{17}ON_3Cl_2$ requires N, 10·9; Cl, 18·4%).

2 : 9-*Bis*-p-*chloroanilino*-1 : 10-*diaza-anthracene*.—2 : 7-Dichloro-1 : 10-diaza-anthracene (5 g.) was refluxed with *p*-chloroaniline (25 g.) for 5 min., then cooled and the excess of *p*-chloroaniline distilled off in steam. The residue, after extraction with cold 60% pyridine, was dissolved in boiling 80% dioxan (200 c.c.), and the solution adjusted to pH 10 with sodium hydoxide and diluted with boiling water (500 c.c.); the *product* (3·3 g.) separated as an orange microcrystalline powder, m. p. 268—270° (Found: N, 13·0; Cl, 16·8. $C_{24}H_{16}N_4Cl_2$ requires N, 13·0; Cl, 16·5%).

6-*Chloro*-9-(4-*diethylamino*-1-*methylbutylamino*)-2-*methoxy*-1 : 10-*diaza-anthracene Dihydrochloride* ("Azacrin").—A solution of 6 : 9-dichloro-2-methoxy-1 : 10-diaza-anthracene (8·6 g.) in dried phenol (40 g.) was heated to 110° for 1 hr., 2-amino-5-diethylaminopentane (4·8 g., 1·1 mol.) was added dropwise with stirring during ½ hr., and the mixture kept at 110° for a further 1½ hr. The cooled mixture was poured into anhydrous ether (500 c.c.) containing 7·5N-ethanolic hydrogen chloride (4·2 c.c.); the precipitate of reddish-black tar solidified on being set aside with occasional scratching. The resulting orange solid was filtered off, washed with ether, drained, and dissolved in warm water (40 c.c.), and the filtered solution (charcoal) was diluted with acetone (400 c.c.). In the refrigerator the solution deposited 8·6 g. (58%) of a yellow microcrystalline powder, m. p. 172—174° (decomp.) with sintering at 165°. This was the *dihydrochloride trihydrate* (Found: loss of wt. at 100°; 11·2%. Required for trihydrate: 10·2%). Dehydration at 100°/2 mm. yielded the anhydrous *dihydrochloride* as a yellow powder, m. p. 224—226° (Found: N, 12·0; Cl, 22·2. $C_{22}H_{31}ON_4Cl_3$ requires N, 11·8; Cl, 22·5%). The compound is slightly hygroscopic.

The following compounds were prepared by heating the 9-chloro-compound (0·02 mol.) in phenol (40 g.) with the dialkylaminoalkylamine (0·022 mol.) in the same manner and pouring the mixture into anhydrous ether or acetone; it was necessary, however, to isolate and purify the salts by differing means. The yields are given in parentheses.

6-*Chloro*-2-*methoxy*-9-2′-*morpholinoethylamino*-1 : 10-*diaza-anthracene dihydrochloride*. The crude compound was dissolved in boiling water (200 c.c.), hot 2N-hydrochloric acid (*ca.* 50 c.c.) added until crystallisation commenced, and the solution set aside; the compound separated in yellow needles (81%), m. p. 258—260° (Found: N, 12·6; Cl, 23·9. $C_{19}H_{23}O_2N_4Cl_3$ requires N, 12·6; Cl, 23·9%).

6-*Chloro*-2-*methoxy*-9-2′-*piperidinoethylamino*-1 : 10-*diaza-anthracene dihydrochloride* was obtained in the same manner in yellow needles (68%), m. p. 248—250° (Found: N, 12·9; Cl, 23·8. $C_{20}H_{25}ON_4Cl_3$ requires N, 12·6; Cl, 24·0%).

2-n-*Butoxy*-6-*chloro*-9-2′-*diethylaminoethylamino*-1 : 10-*diaza-anthracene dihydrochloride*. Crystallisation of the crude product from ethanol containing a trace of 2N-hydrochloric acid gave the pure salt in light yellow needles, m. p. 228—230° (decomp.) (Found: N, 11·9; Cl, 22·4. $C_{22}H_{31}ON_4Cl_3$ requires N, 11·8; Cl, 22·5%).

2-n-*Butoxy*-6-*chloro*-9-(4-*diethylamino*-1-*methylbutylamino*)-1 : 10-*diaza-anthracene dihydrochloride*. The crude product was ground with dry acetone to remove dark colouring matter, and the yellow residue dried at 15°/2 mm. and dissolved in anhydrous ethanol (*ca.* 20 c.c.); the filtered (charcoal) solution was diluted with dry acetone, crystallisation being initiated by scratching. The *dihydrochloride* separated in bright yellow needles, m. p. 174—178° (sintering at 165°) (Found: N, 10·4; Cl, 21·4. $C_{25}H_{37}ON_4Cl_3$ requires N, 10·9; Cl, 20·7%). The *bis*-p-*nitrobenzoate* of the base separated from dilute alcohol in small yellow prisms, m. p. 154—156° (Found: N, 10·9. $C_{39}H_{45}O_9N_6Cl$ requires N, 10·8%).

5-*Acetamido*-2-*methoxy*-6-*methylpyridine*.—5-Amino-2-methoxy-6-methylpyridine (20 g.), mixed with acetic anhydride (16 c.c.), gave, exothermally, the *acetamide* (26 g.), m. p. 130—131° (from ligroin, b. p. 60—80°) (Found: N, 15·9. $C_9H_{12}O_2N_2$ requires N, 15·6%).

3-*Acetamido*-6-*methoxypicolinic Acid*.—A solution of the foregoing crude compound (26 g.) in water (4 l.) was stirred on the water-bath with light magnesium oxide (10 g.) and magnesium sulphate (80 g.); finely powdered potassium permanagnate (80 g.) was added portionwise during ¾ hr. and stirring continued for a further ¼ hr. The mixture was filtered hot and the filter-cake washed with boiling water (1 l.); the combined filtrates were evaporated at reduced pressure to a volume of 1 l., and then extracted with ether (3 × 100 c.c.). The extract on evaporation yielded 1·0 g. of unoxidised starting material; the aqueous solution was acidified with 2N-hydrochloric acid, and the 3-*acetamido*-6-*methoxypicolinic acid* (12 g.; m. p. 186—188°) collected. A sample crystallised from alcohol in colourless needles of the same m. p. (Found: equiv., 210; N, 13·4%. $C_9H_{10}O_4N_2$ requires equiv., 210; N, 13·3%).

3-*Chloro*-6-*methoxypicolinic Acid*.—The foregoing acetamido-acid (6·0 g.) was boiled for ½ hr. with 2·5N-sodium hydroxide (48 c.c.). After addition of 10N-hydrochloric acid (50 c.c.), the solution was diazotised at 0° with sodium nitrite (*ca.* 2·5 g.) in water (15 c.c.), then added dropwise to a stirred solution of cuprous chloride (freshly prepared from 7 g. of hydrated cupric chloride, copper powder, and hydrochloric acid and precipitated with water) in 10N-hydrochloric acid (50 c.c.) at 0—5°; the mixture was stirred for 2 hr. at this temperature and then at 30° for a few minutes until no further nitrogen was evolved. The mixture was diluted with water (165 c.c.) to effect solution and extracted with ether (7 × 50 c.c.), which gave 3-*chloro*-6-*methoxypicolinic acid* (5·0 g.; m. p. 98—100°), forming colourless needles, m. p. 103—104°, from water after removal of copper (Found: equiv., 189; N, 7·5; Cl, 19·1%. $C_7H_6O_3NCl$ requires equiv., 187·5; N, 7·5; Cl, 18·9%).

6-*Methoxy*-3-p-*methoxyanilinopicolinic Acid*.—The foregoing acid (3·75 g., 0·02 mole), potassium carbonate (1·4 g., 0·01 mole), *p*-anisidine (2·5 g.; 0·02 mole), and amyl alcohol (20 c.c.) were stirred at the b. p. for 2 hr. with a trace of copper and copper oxide. Treatment in the manner previously described gave the desired *acid* which crystallised from ligroin (b. p. 80—100°) in yellow needles (1·0 g.), m. p. 108—109° (Found: equiv., 278; N, 10·3%. $C_{14}H_{14}O_4N_2$ requires equiv., 274; N, 10·2%).

9-*Chloro*-2 : 7-*dimethoxy*-1 : 10-*diaza-anthracene*.—The anilino-acid (1·6 g.) was refluxed with phosphorus oxychloride (10 c.c.) for 4 hr. and the mixture poured on crushed ice and ammonia. Next morning the precipitate (1·6 g.; m. p. 218°) was collected and dried at 30°; recrystallisation from acetone (250 c.c./g.), with activated alumina as decolorising agent, gave the pure product as a microcrystalline light yellow powder, m. p. 222—223° (Found: N, 10·1; Cl, 12·8. $C_{14}H_{11}O_2N_2Cl$ requires N, 10·2; Cl, 12·9%).

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