999. *Potential Antimalarial Derivatives of Triaza-anthracene.*

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An analogue of mepacrine containing the 1 : 3 : 10-triaza-anthracene nucleus has been synthesised but has no antimalarial activity.

The quinoline derivatives pamaquine and primaquin, in which the (dialkyl)aminoalkylamino-side-chain is *peri* to a ring-nitrogen atom are the only known antimalarials [1] which are effective against the secondary exo-erythrocytic stages of the parasite reponsible for relapse in human *P. vivax* infections. The possibility was entertained that 1 : 3 : 10-triaza-anthracenes of type (I; R = OMe, R′ = H or OMe), because of the *peri* situation of the side-chain to a ring-nitrogen atom, might combine the schizonticidal activity of the acridine derivative, mepacrine, with the radically curative properties of pamaquine. Recently, a derivative (" Azacrin ") of 1 : 10-diaza-anthracene [2] has been shown to be a very effective schizonticide in human malaria due to *P. falciparium* [3,4] *and P. vivax*; [5] it has a shorter pyrexia- and parasite-clearance time, and allows fewer relapses, than mepacrine or chloroquin. Up to the present, however, the possibility of determining whether " Azacrin " has radically curative properties against *P. vivax* disease has not presented itself.

A further point of interest arises from Madinaveitia's hypothesis that antimalarials function by virtue of their ability to antagonise riboflavin, an essential factor for the survival of the parasite. 1 : 3 : 10-Triaza-anthracenes are more closely related to riboflavin than is mepacrine and might therefore be expected to be superior flavin antagonists.

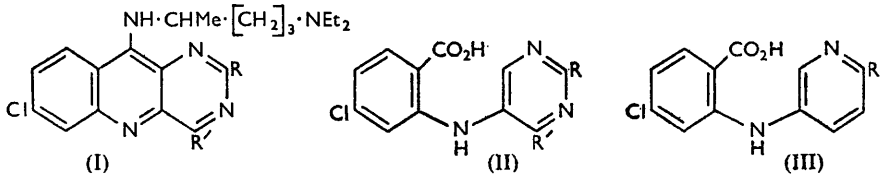
A derivative of 2 : 4 : 10-triaza-anthracene [7] has been found to be inactive; this is not surprising since the situation of the dialkylaminoalkylamino-group in the 3- and not in the 9-position of the ring, gives the compound no formal resemblance to mepacrine.

Three approaches have been made to the desired compounds. 5-Bromo-2-methylpyrimidine-4-carboxylic acid was condensed with aniline to give 5-anilino-2-methylpyrimidine-4-carboxylic acid; and 2 : 4-dichlorobenzoic acid was condensed with 5-amino-2-methoxypyrimidine to give 4-chloro-2-(2-methoxy-5-pyrimidylamino)benzoic acid (II;

[1] Report by Council on Pharmacy and Chemistry, *J. Amer. Med. Assoc.*, 1952, **149**, 1558.
[2] Besly and Goldberg, *J.*, 1954, 2448.
[3] Bruce-Chwatt and Archibald, *Brit. Med. J.*, 1953, **7**, 539.
[4] Ang'awa and Fendall, *J. Trop. Med. Hyg.*, 1954, **57**, 59.
[5] Pasquel, *Rev. Inst. Salubridad y Enfermedades Trop.*, 1955, **15**, 51.
[6] Madinaveitia, *Biochem. J.*, 1946, **40**, 373.
[7] King and King, *J.*, 1947, 726.

R = OMe, R′ = H). Although both acids were obtained in acceptable yield neither would undergo the Magidson–Grigorovski cyclisation with phosphorus oxychloride to give the *meso*-chlorotriaza-anthracene necessary for the introduction of the side-chain.

The presence of $-I$, $-M$ groups in the non-carboxylated ring of 2-carboxy-diphenylamine or diphenyl ether increases the energy of activation [8] of the cyclisation process. In acids of this type in which the non-carboxylated ring is replaced by a pyridine ring



(III; R = H) the $-I$ effect of the protonised ring-nitrogen atom (in the acid cyclising agent) prevents [2] cyclisation unless there is present a $+M$ group (alkoxyl) in the position R. Although the $+E$ effect of this alkoxy-group cannot *directly* increase the electron-density at the position of cyclisation it appears that the mesomerism of the protonised cyclic imidate grouping in such compounds can cause partial bond-localisation and suppress the inductive and tautomeric mechanisms by which the nitrogen atom normally creates electron defect at neighbouring carbon atoms. In this connexion it is noteworthy that, while pyridine is much more resistant to electrophilic attack than nitrobenzene,[9] the ease [10] of electrophilic substitutions becomes comparable with that of benzene when the pyridine nucleus contains a $+M$ substituent in the 2- or 4-position. In pyrimidines, the ability to undergo electrophilic attack at position 5, completely suppressed in pyrimidine itself, reappears [11] when the nucleus contains a $+M$ group in *both* the 2- and the 4-position.

It therefore seemed that the difficulties might be surmounted by the use of an amino-pyrimidine containing *two* $+M$ groups which might be expected to neutralise the $-I$ effects of the two pyrimidine ring-nitrogen atoms. Accordingly 2 : 4-dichlorobenzoic acid was condensed with 5-amino-2 : 4-dimethoxypyrimidine, 5-amino-2 : 4-diphenoxy-pyrimidine, and 5-aminouracil, to give the acids (II; R = R′ = OMe, OPh, and OH respectively). Treatment of acid (II; R = R′ = OMe) with phosphorus oxychloride effected cyclisation in good yield but unfortunately with loss of one (presumably the 4-) methoxy-group.

The same was observed with the acid (II; R = R′ = OPh), one phenoxy-group being lost. With the acid (II; R = R′ = OH) 2 : 4 : 6 : 9-tetrachloro-1 : 3 : 10-triaza-anthracene was obtained but could not be isolated in the pure state; when, however, the crude material was heated with phenol and 4-diethylamino-1-methyl-*n*-butylamine, 6-chloro-9-(4-diethylamino-1-methylbutylamino)-4(or 2)-hydroxy-2(or 4)-phenoxy-1 : 3 : 10-triaza-anthracene (I; R = OPh, R′ = OH) was obtained in the form of the phosphate. It is evident that, in addition to the replacement of the *meso*-substituent by a phenoxy-group, followed by normal reaction of the phenoxy-group with the dialkylaminoalkylamine, one of the chloro-groups in the pyrimidine nucleus has also been replaced and the other hydrolysed during isolation of the product.

Antimalarial Activity.—Daily oral dosage of 100 mg./kg. of compound (I; R = OPh, R′ = OH) for 3 consecutive days gave no significant protection to 50 g. chicks infected intravenously on day 0 with 20×10^6 *P. gallinaceum* merozoites. All the infected birds had a 40—50% blood parasitæmia on day 5, death ensuing on day 6—8. Chicks similarly infected and given 25 mg./kg. of mepacrine daily for 3 days were only 0—5% parasitised

[8] Goldberg, in preparation.
[9] Elderfield, "Heterocyclic Compounds," Wiley, New York, 1950, Vol. I, pp. 408 *et seq.*
[10] Maier-Bode, "Das Pyridin und seine Derivate," Knapp, Halle, Saale, 1934.
[11] Lythgoe, *Quart. Rev.*, 1949, **3**, 181.

on day 5 and survived until day 14—18. It is believed that the lack of antiplasmodial activity in this compound is due to the presence of the 4-hydroxyl group which by virtue of the hydroxypyrimidine–dihydropyrimidone tautomerism at the 3 : 4-position removes aromatic character from the compound.

Experimental

5-Aminouracil.—The following method was easier than that using ferrous sulphate.[12] Sodium dithionite (200 g.) was added in one lot to a stirred suspension of 5-nitrouracil (42 g.) in water (670 c.c.) and ammonia (*d* 0·88; 27 c.c.). The mixture developed heat and the salt slowly dissolved; more ammonia was added from time to time to maintain pH 8·5. When the reaction was finished, as shown by constancy of pH, the mixture was set aside. The precipitate was collected and dissolved in cold water (400 c.c.) and 2N-hydrochloric acid (150 c.c.), the solution filtered (charcoal) and basified with ammonia, and the precipitate of 5-aminouracil (31 g., 91%) collected and dried at 40°.

2 : 4-*Dimethoxy-5-nitropyrimidine.*—2 : 4-Dichloro-5-nitropyrimidine [13] (17·7 g.) was added portionwise to a stirred solution of sodium (4·3 g.) in methanol (80 c.c.) at 0—5°. The mixture was kept at room temperature overnight, then refluxed for 4 hr., and poured on ice-water (500 c.c.). The *ether* (15·6 g., 92%; m. p. 90°) was collected, washed with water, and dried at 35°; this was pure enough for further use. A sample crystallised from methanol in pale orange needles, m. p. 94—96° (Found: N, 23·4. $C_6H_7O_4N_3$ requires N, 22·7%).

2 : 4-*Dimethoxy-5-aminopyrimidine.*—(*a*) The foregoing nitro-compound (1·85 g.) was hydrogenated in methanol (50 c.c.) at 30°/760 mm. over 10% palladium–charcoal; absorption was rapid and ceased at the theoretical uptake. Evaporation of the filtered mixture gave the required *amine* (1·4 g., 91%) as a pink solid, m. p. 86—88°; this separated from ligroin (b. p. 60—80°) in colourless needles of the same m. p. (Found: N, 27·4. $C_6H_9O_2N_3$ requires N, 27·1%).

(*b*) 2 : 4-Dimethoxy-5-nitropyrimidine (35 g.) was added portionwise during ½ hr. to a stirred, refluxing mixture of alcohol (160 c.c.), water (160 c.c.), acetic acid (4 c.c.), and Pacteron iron powder (from Staveley Iron Co.) (60 g.). After a further 2 hours' refluxing the mixture was adjusted to pH 8·0 with saturated aqueous sodium carbonate, then, after addition of potassium hydrogen carbonate (20 g.), refluxed with stirring for a further 2 hr. and filtered, and the solid residue washed into the filtrate with boiling alcohol (400 c.c.). The filtrate was evaporated to small volume at reduced pressure and the residue subjected to continuous ether-extraction for 7 hr. Distillation of the ether left the base as a mauve crystalline mass (27 g., 92%), m. p. 86°.

5-*Nitro*-2 : 4-*diphenoxypyrimidine.*—A mixture of phenol (47 g.) and xylene (500 c.c.) was stirred and part (40 c.c.) of the xylene distilled off to remove moisture. The mixture was cooled, sodium (11·5 g.) added in one lot, stirring continued on the water-bath until the metal had dissolved (1 hr.), and the mixture chilled. 2 : 4-Dichloropyrimidine (40 g.) was added portionwise during 20 min. and the mixture stirred at 5° for a further hour. After being kept at room temperature overnight the mixture was heated on the water-bath for 4 hr., cooled, and poured into excess of water. The xylene layer was separated and washed with water, and the xylene distilled off at reduced pressure. Crystallisation of the residue from ligroin (b. p. 60—80°; 500 c.c.) gave the *product* (52 g., 83%) as brown prisms, m. p. 104—106°; a sample crystallised from benzene–ligroin in colourless prisms, m. p. 108—110° (Found: N, 13·5. $C_{16}H_{11}O_4N_3$ requires N, 13·6%).

5-*Amino*-2 : 4-*diphenoxypyrimidine.*—The foregoing nitro-compound (31 g.) was reduced in the same manner as the dimethoxy-compound, with alcohol (100 c.c.), water (100 c.c.), acetic acid (4 c.c.). and iron powder (40 g.). The filtrate from the iron oxide cake and the alcohol washings (500 c.c.) were combined, diluted with ice-water (3 l.), and refrigerated overnight. The 5-*amino*-2 : 4-*diphenoxypyrimidine* (23 g., 82%; m. p. 126—128°) was collected and dried at 80°; a sample separated from benzene–ligroin (b. p. 60—80°) as a powder, m. p. 130—132° (Found: N, 14·9. $C_{16}H_{13}O_2N_3$ requires N, 15·0%).

4-*Chloro*-2-(2 : 4-*dimethoxy-5-pyrimidyl*)*benzoic Acid.*—2 : 4-Dichlorobenzoic acid (28·4 g.,

[12] Johnson and Matsuo, *J. Amer. Chem. Soc.*, 1919, **41**, 784.
[13] Whitaker, *J.*, 1951, 1568.

0·148 mol.), anhydrous potassium carbonate (10·3 g., 0·074 mol.), 5-amino-2 : 4-dimethoxypyrimidine (23 g., 0·148 mol.), pentyl alcohol (150 c.c.), and a trace of cupric oxide were stirred at the b. p. for 3 hr., water being removed in a Dean and Stark trap. Water (250 c.c.) and potassium carbonate (11 g.) were added, the alcohol removed in steam, and the filtered solution (charcoal) acidified to bromocresol-green with 10% acetic acid. The glutinous precipitate was collected and dissolved in water (150 c.c.) and the minimum amount of sodium hydrogen carbonate, and the hot solution poured into a solution of sodium chloride (100 g.) in hot water (250 c.c.). The sodium salt separated as a red oil which slowly solidified. This was collected, dissolved in boiling water (100 c.c.), and filtered (charcoal) and the hot solution was acidified with 10% acetic acid to give the *product* as a mauve powder (24 g., 52%), m. p. 186—190°. Crystallisation from *n*-butyl acetate (200 c.c.) gave a purer acid (14 g.), m. p. 202—204°, together with a further 7 g. of lower m. p. from the mother-liquor. The analytical sample separated from the same solvent in colourless flakes, m. p. 208—210° (Found: *M*, 306; N, 14·2; Cl, 11·8%. $C_{13}H_{12}O_4N_3Cl$ requires *M*, 309·5; N, 13·6; Cl, 11·5%).

4-*Chloro*-2-(2 : 4-*dihydroxy*-5-*pyrimidyl*)*benzoic Acid*.—2 : 4-Dichlorobenzoic acid (38·2 g., 0·2 mol.) was added to a solution of potassium carbonate (13·8 g., 0·1 mol.) in water (400 c.c.), and the resulting solution adjusted to pH 7·0. 5-Aminouracil (25·4 g., 0·2 mol.), copper bronze (0·5 g.), and cupric oxide (0·25 g.) were added, and the mixture was stirred at the b. p. for 6 hr. and filtered hot. The solid was stirred with *ca.* 0·01N-hydrochloric acid (200 c.c.) to remove adhering 5-aminouracil, filtered, washed with water, and then suspended in hot water (350 c.c.), and sufficient sodium hydrogen carbonate was added to effect dissolution. Sodium chloride (80 g.) was added to the stirred solution whence the crystalline sodium salt was soon precipitated. Next morning the precipitate was collected and dissolved in boiling water (750 c.c.), and the solution acidified with acetic acid (30 c.c.) and digested on the water-bath to effect coagulation of the precipitated acid. The *acid* was obtained as a cream powder (16·6 g., 30%), m. p. 350—352° (decomp.) [Found: *M* (by electrometric titration), 283; N, 15·1; Cl, 12·4%. $C_{11}H_8O_4N_3Cl$ requires *M*, 281·5; N, 14·9; Cl, 12·6%).

4-*Chloro*-2-(2 : 4-*diphenoxy*-5-*pyrimidylamino*)*benzoic Acid*.—2 : 4-Dichlorobenzoic acid (9·6 g., 0·05 mol.), potassium carbonate (3·5 g., 0·025 mol.), 5-amino-2 : 4-diphenoxypyrimidine (14 g., 0·05 mol.), pentyl alcohol (100 c.c.), and a trace of copper oxide were stirred at the reflux for 5 hr. After removal of the alcohol, potassium carbonate (4 g.) was added and the solution filtered (charcoal) and acidified with 20% acetic acid. The resinous precipitate was collected and triturated with hot toluene (15 c.c.) until it crystallised. After being kept overnight the crystals were drained and recrystallised from methanol (100 c.c.), to give the pure *acid* as colourless needles (5·0 g., 23%), m. p. 196—198° (Found: *M*, 433; N, 9·9; Cl, 8·1%. $C_{23}H_{16}O_4N_3Cl$ requires *M*, 433·5; N, 9·7; Cl, 8·2%).

6-*Chloro*-2 : 4-*dihydroxy*-1 : 3 : 10-*triaza*-*anthr*-9-*one*.—4-Chloro-2-(2 : 4-dihydroxy-5-pyrimidylamino)benzoic acid (5·6 g.) was heated on the water-bath with 90% sulphuric acid (60 c.c.) for 1¼ hr., then poured on crushed ice (200 g.). After digestion on the water-bath for 2 hr. the precipitate was collected, washed with water, and dried. The yellow powder (4·0 g., 76%) thus obtained contained sulphur, presumably as a sulphonic acid; it was desulphonated by 90% orthophosphoric acid (130 g.) at 160° for 3 hr., the whole being poured into water. The insoluble precipitate of *triaza-anthrone* (3·4 g.) was washed with water and obtained as a yellow powder, free from sulphur, m. p. >400° (Found: N, 16·1; Cl, 13·6. $C_{11}H_6O_3N_3Cl$ requires N, 15·9; Cl, 13·4%).

6-*Chloro*-9-(4-*diethylamino*-1-*methylbutylamino*)-4(or 2)-*hydroxy*-2(or 4)-*phenoxy*-1 : 3 : 10-*triaza*-*anthracene Phosphate*.—4-Chloro-2-(2 : 4-dihydroxy-5-pyrimidylamino)benzoic acid (2·8 g.) was refluxed with phosphoryl chloride (28 c.c.) for 24 hr. Excess of phosphoryl chloride was distilled off at reduced pressure, the residue dissolved in phenol (25 g.), and the solution heated for 2 hr. at 110°. 5-Diethylamino-1-methylbutylamine (1·6 c.c.) was added, and the mixture heated for a further 1½ hr. at 110°, and poured into acetone (200 c.c.) containing 10N-hydrochloric acid (2 c.c.). The small precipitate was removed, the filtrate diluted with excess of dry ether, and the glutinous precipitate separated and triturated with a little water until it solidified. The buff-yellow product (1·4 g., 24%) had m. p. >320°; crystallisation from dioxan gave the pure *phosphate* as a bright yellow powder (1·0 g.), m. p. >320° (Found: N, 12·1; Cl, 6·25; P, 5·1. $C_{26}H_{30}O_2N_5Cl,H_3PO_4$ requires N, 12·1; Cl, 6·15; P, 5·35%).

5-*Anilino*-4-*carboxy*-2-*methylpyrimidine*.—5-Bromo-4-carboxy-2-methylpyrimidine (10·9 g.) and potassium carbonate (11 g.) were stirred with aniline (30 c.c.), pentyl alcohol (70 c.c.), and

a trace of copper–copper iodide catalyst at 132—140° for 5 hr. After removal of the alcohol in steam, the residual solution was filtered to remove tar, and the filtrate acidified to pH 4 with sulphuric acid. Crystallisation of the precipitate (4·0 g.; m. p. 212°) from aqueous-alcoholic dioxan gave the acidic *product* (3·2 g.) as yellow needles, m. p. 218° [Found: *M* (by titration), 231; *N*, 18·2%. $C_{12}H_{11}O_2N_3$ requires *M*, 229; N, 18·4%].

Treatment of this acid with phosphoryl chloride did not give a *meso*-chlorotriaza-anthracene; a dark insoluble material, difficult to purify, was obtained which was presumably the crude triazanthrone.

4-*Chloro*-2-(2-*methoxy*-5-*pyrimidylamino*)*benzoic Acid* (III; R = OMe, R′ = H).—2 : 4-Dichlorobenzoic acid (5·75 g.), potassium carbonate (4·2 g.), 5-amino-2-methoxypyrimidine (3·0 g.), and a trace of copper–copper oxide catalyst were refluxed with pentyl alcohol (25 c.c.) for 3 hr. The alcohol was removed in steam, and the residual solution filtered (charcoal) and adjusted to pH 4·0 with hydrochloric acid. The precipitate was extracted with boiling alcohol (125 c.c.), the filtered solution refrigerated, and the precipitate (1·0 g.; m. p. 230°) collected. Crystallisation from ethyl acetate gave the *product* as colourless leaves, m. p. 236° (Found: *M*, 277; N, 15·2; Cl, 12·7%. $C_{12}H_{10}O_3N_3Cl$ requires *M*, 279·5; N, 15·0; Cl, 12·7%).

Attempts to cyclise this acid failed. For example, the acid (2 g.) with boiling phosphoryl chloride (30 c.c.) for 3 hr. gave an amorphous brown solid, insoluble in acetone, benzene, or ligroin, and this could not be purified.

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