332. *Contributions to the Chemistry of Synthetic Antimalarials. Part IX. Some Pyrimidine Derivatives.*

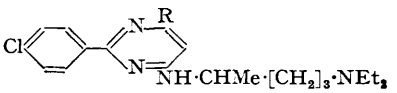
By J. S. MOFFATT.

The syntheses of 4-(4-diethylamino-1-methylbutylamino)-2-*p*-chlorophenylpyrimidine and certain of its chloro-, amino-, and methoxy-derivatives are described. Of these, only the first mentioned has been found to show some activity against *Plasmodium gallinaceum*.

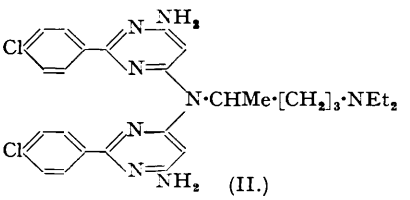
THIS work was initiated in continuation of a project to prepare and examine for antimalarial activity alkylaminoalkylamino-derivatives of simple heterocyclic systems (cf. Part I, Ashley and Grove, *J.*, 1945, 768). The pyrimidine ring was chosen since, at the time this work was begun, it did not appear to have received attention in previous antimalarial investigations although its biological importance was well known. Moreover, the amidine grouping, which may be considered to form part of the pyrimidine ring, is present in certain aromatic diamidines such as 1 : 5-di-*p*-amidinophenoxypentane (Pentamidine) which show some chemotherapeutic

activity in experimental malaria (Fulton, *Ann. Trop. Med. and Parasitol.*, 1940, **34**, 53; Yorke, *Trans. Roy. Soc. Trop. Med. and Hygiene*, 1940, **33**, 463). Considerations which led to the study first of derivatives of 2-*p*-chlorophenylpyrimidine were: (i) 2-arylpyrimidines appeared to be among the more readily accessible of pyrimidine derivatives and therefore one of the objectives of this work became the preparation of (I; R = OMe) which is of the same order of molecular complexity, and contains the same basic side-chain, and chloro- and methoxy-substituents as Mepacrine; (ii) it has been found in these laboratories (Moffatt, unpublished observation) that introducing a *p*-chlorophenyl group into one of the amidine groups of 1 : 3-di-*p*-amidinophenoxypropane (Propamidine) enhances the slight antimalarial activity of the diamidine. During the course of the preliminary work described below, a number of derivatives of 2-alkylaminoalkylamino- and 2-amino-4-alkylaminoalkylamino-pyrimidine were described by Adams and Whitmore (*J. Amer. Chem. Soc.*, 1945, **67**, 735, 1159), and shortly after it was completed, the author learned (Curd and Rose, Scientific Meeting, Chemical Society, February 7th, 1946) of the series of comprehensive researches, which had been initiated by Curd, Rose, *et al.* (see *J.*, 1946, 343 and subsequent papers), on alkylaminoalkylaminopyrimidine derivatives. Accordingly, further work along similar lines was abandoned. It is now apparent that the preparation of the pyrimidine derivatives described in the present work was not undertaken by these authors or their collaborators, and therefore the syntheses are now recorded.

p-Chlorobenzamidine was condensed with ethyl malonate in presence of excess of sodium ethoxide (cf. Dox and Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 361) to give 4 : 6-dihydroxy-2-*p*-chlorophenylpyrimidine which was converted, by Baddiley and Topham's method (*J.*, 1944, 678), into 4 : 6-dichloro-2-*p*-chlorophenylpyrimidine. Use was made of the oft-observed fact (see *e.g.* Buttner, *Ber.*, 1903, **36**, 2227) that the chlorine atoms in 4 : 6-dichloropyrimidines, by choice of conditions, may stepwise be made to react with reagents such as sodium methoxide and amines. Thus, 4 : 6-dichloro-2-*p*-chlorophenylpyrimidine with 4-diethylamino-1-methylbutylamine at 80—90° gave 4-chloro-6-(4-diethylamino-1-methylbutylamino)-2-*p*-chlorophenylpyrimidine (I; R = Cl). A large excess of the aliphatic diamine and a temperature of



(I.)



(II.)

ca. 210° gave 4 : 6-di-(4-diethylamino-1-methylbutylamino)-2-*p*-chlorophenylpyrimidine (I; R = NH·CHMe·[CH_2]$_3$·NEt_2). With ethanolic ammonia at 125—130° and one equivalent of sodium methoxide in boiling methanol the 4 : 6-dichloropyrimidine afforded, respectively, 4-chloro-6-amino- and 4-chloro-6-methoxy-2-*p*-chlorophenylpyrimidine. With 4-diethylamino-1-methylbutylamine at 200°, the former yielded 4-amino-6-(4-diethylamino-1-methylbutylamino)-(I; R = NH_2) and the latter 4-(4-diethylamino-1-methylbutylamino)-6-methoxy-2-*p*-chlorophenylpyrimidine (I; R = OMe). These were accompanied by small quantities of by-products; in the case of the former condensation, the by-product was identified as 4-diethylamino-*NN*-di-(4-amino-2-*p*-chlorophenyl-6-pyrimidyl)-1-methylbutylamine (II). For the preparation of 4-(4-diethylamino-1-methylbutylamino)-2-*p*-chlorophenylpyrimidine (I; R = H), it was considered desirable to start from the appropriate monohydroxy-pyrimidine in order to avoid the ambiguity which might arise from removal of one chlorine atom from the corresponding 6-chloro-derivative of 4-(4-diethylamino-1-methylbutylamino)-2-*p*-chlorophenylpyrimidine (I; R = Cl). This appeared to be accessible by application of the method of Gabriel (*Ber.*, 1904, **37**, 3638), who obtained 4-hydroxy-2-methylpyrimidine by interaction of approximately equimolecular proportions of acetamidine hydrochloride and ethyl sodioformylacetate. However, interaction of similar proportions of the latter and *p*-chlorobenzamidine hydrochloride yielded a substance, $C_{17}H_{14}ON_4Cl_2$, which, on being heated at its m. p., decomposed to give ammonia, *p*-chlorobenzonitrile, and 4-hydroxy-2-*p*-chlorophenylpyrimidine. The hydroxypyrimidine was the principal product of the interaction of equimolecular amounts of *p*-chlorobenzamidine and ethyl sodioformylacetate. It was converted into 4-chloro-2-*p*-chlorophenylpyrimidine which, with 4-diethylamino-1-methylbutylamine at 190°, yielded 4-(4-diethylamino-1-methylbutylamino)-2-*p*-chlorophenylpyrimidine (I; R = H).

Each of the compounds (I; R = H), (I; R = Cl), (I; R = NH_2), (I; R = OMe), and

(I; R = NH·CHMe·[CH_2]$_3$·NEt_2) was examined against *P. gallinaceum* in chicks, but only (I; R = H) showed any activity, and then only of a low order.

Experimental.

4 : 6-*Dihydroxy*-2-p-*chlorophenylpyrimidine*.—A solution of sodium (13·5 g.) in anhydrous ethanol (225 c.c.) was gradually treated with *p*-chlorobenzamidine hydrochloride (Ekeley, Tieszen, and Ronzio, *J. Amer. Chem. Soc.*, 1935, **57**, 381) (33 g.), followed by ethyl malonate (25·5 g.). The mixture was heated under reflux on a water-bath for 5 hours, and then distilled from the water-bath to remove ethanol. The residual solid was treated with water (600 c.c.), and the resulting solution was filtered from a small quantity of insoluble material. Acidification of the filtrate with acetic acid gave the *dihydroxy-pyrimidine* [29·8 g.; m. p. 308—311° (decomp.)], which was sufficiently pure for the next stage. A sample separated from glacial acetic acid in sheaves of thick needles, m. p. 326—327° (decomp.) (Found: N, 12·3; Cl, 15·7. $C_{10}H_7O_2N_2Cl$ requires N, 12·6; Cl, 15·9%).

4 : 6-*Dichloro*-2-p-*chlorophenylpyrimidine*.—A mixture of the dihydroxypyrimidine (25 g.) and phosphoryl chloride (125 c.c.) was cautiously treated with dimethylaniline (28 c.c.). The resulting solution was boiled under reflux for 2·5 hours, cooled, and then poured on crushed ice. The precipitate, on crystallisation from ethanol, formed clusters of colourless needles (24·5 g.) of the 4 : 6-*dichloro-pyrimidine*, m. p. 123° (Found: N, 10·6; Cl, 41·0. $C_{10}H_5N_2Cl_3$ requires N, 10·8; Cl, 41·0%).

4-*Chloro*-6-(4-*diethylamino*-1-*methylbutylamino*)-2-p-*chlorophenylpyrimidine*.—The foregoing chloro-compound (3 g.) was heated under reflux with a mixture of 4-diethylamino-1-methylbutylamine (5 c.c.) and ethanol (15 c.c.) in an oil-bath at 100—105°, for 3 hours. Most of the solvent was then allowed to distil off, and the residue was treated with water and ether. The ethereal layer was washed several times with water, and the solvent then evaporated. The residual *base* distilled at 195—200°/0·05 mm. (bath temp.), as a viscous, yellow oil (4·1 g.) (Found: N, 14·7; Cl, 18·6. $C_{15}H_{26}N_4Cl_2$ requires N, 14·7; Cl, 18·6%). It gave a *monopicrate* which formed orange rhombs (from ethanol), m. p. 158° (Found: C, 49·4; H, 4·8; N, 15·9. $C_{19}H_{26}N_4Cl_2,C_6H_3O_7N_3$ requires C, 49·2; H, 4·8; N, 16·1%).

4 : 6-*Di*-(4-*diethylamino*-1-*methylbutylamino*)-2-p-*chlorophenylpyrimidine*.—4 : 6-Dichloro-2-*p*-chlorophenylpyrimidine (3 g.) was heated with a mixture of 4-diethylamino-1-methylbutylamine (14·6 g.) and anhydrous methanol (12 c.c.) at 200—210° for 5 hours in a sealed tube. The reaction mixture was concentrated on a water-bath, and the residue treated with water and ether. The ethereal solution was washed several times with water and the solvent then evaporated. The residue was fractionally distilled under reduced pressure, and the fraction (5·1 g.) which distilled at 205—220°/0·02 mm. (bath temp.) was collected. This was extracted with 0·5N-hydrochloric acid, and the extract was filtered, extracted twice with ether, and then made alkaline with dilute sodium hydroxide solution. The *base* which separated distilled at 222—230°/0·01 mm. (bath temp.) as a pale yellow oil (4·9 g.), which became very viscous on cooling (Found: C, 67·4; H, 9·2; Cl, 7·9. $C_{28}H_{47}N_6Cl$ requires C, 66·9; H, 9·4; Cl, 7·1%). Its *dipicrate* separated from ethanol in minute, glittering rhombs, m. p. 195—197° (Found: C, 49·0; H, 5·2; N, 17·4. $C_{28}H_{47}N_6Cl,2C_6H_3O_7N_3$ requires C, 49·9; H, 5·4; N, 17·5%).

4-*Chloro*-6-*amino*-2-p-*chlorophenylpyrimidine*.—A mixture of 4 : 6-dichloro-2-*p*-chlorophenylpyrimidine (5 g.) and anhydrous ethanol (30 c.c.) saturated with ammonia was heated at 125—128° for 3 hours in a sealed tube. The reaction mixture was concentrated on a water-bath; the residue was triturated with water, filtered off, and then repeatedly recrystallised from ethanol to give the *amine* as needles (3 g.), m. p. 190° (Found: N, 17·1; Cl, 30·0. $C_{10}H_7N_3Cl_2$ requires N, 17·5; Cl, 29·6%).

4-*Amino*-6-(4-*diethylamino*-1-*methylbutylamino*)-2-p-*chlorophenylpyrimidine*.—The 4-chloro-6-amino-pyrimidine (2·8 g.) was heated with 4-diethylamino-1-methylbutylamine (5 c.c.) and anhydrous methanol (15 c.c.) for 3 hours at 205—210° in a sealed tube. The crude product distilled at 202—212°/0·05 mm. (bath temp.). It was extracted with 0·5N-hydrochloric acid. The insoluble residue, on treatment with ethanol followed by repeated recrystallisation from the same solvent, formed needles (80 mg.) m. p. 157—158°, of 4-*diethylamino*-NN-*di*-(4-*amino*-2-p-*chlorophenyl*-6-*pyrimidyl*)-1-*methylbutylamine* (II) (Found: C, 61·7; H, 5·9; N, 19·6; Cl, 12·6. $C_{29}H_{34}N_8Cl_2$ requires C, 61·6; H, 6·0; N, 19·8; Cl, 12·6%). The aqueous acid extract was made alkaline with dilute sodium hydroxide; the resulting 4-*amino*-6-(4-*diethylamino*-1-*methylbutylamino*)-2-p-*chlorophenylpyrimidine* distilled at 204—212°/0·05 mm. (bath temp.) and formed a viscous, fluorescent oil (2·8 g.), which set to a clear, green glass on cooling (Found: C, 63·0; H, 7·2; N, 19·6; Cl, 10·8. $C_{19}H_{28}N_5Cl$ requires C, 63·1; H, 7·7; N, 19·4; Cl, 9·9%). The *dipicrate*, crystallised from ethanol, had m. p. 155—156° (Found: C, 45·9; H, 4·4; N, 18·8. $C_{19}H_{28}N_5Cl,2C_6H_3O_7N_3$ requires C, 45·4; H, 4·2; N, 18·8%).

4-*Chloro*-6-*methoxy*-2-p-*chlorophenylpyrimidine*.—A suspension of 4 : 6-dichloro-2-*p*-chlorophenyl-pyrimidine (5 g.) in methanol (150 c.c.) was boiled under reflux and treated dropwise, during 15 minutes, with a solution of sodium (0·44 g.) in methanol (10 c.c.). The mixture was boiled under reflux for one hour and then concentrated to a small bulk. The *chloromethoxy*-compound, which crystallised out, was filtered off, washed with water, and recrystallised from methanol to give needles (3·4 g.), m. p. 95—96° [Found: N, 10·9; OMe, 12·5. $C_{10}H_5N_2Cl_2(OMe)$ requires N, 11·0; OMe, 12·2%].

4-(4-*Diethylamino*-1-*methylbutylamino*)-6-*methoxy*-2-p-*chlorophenylpyrimidine*.—The chloromethoxy-compound (3·5 g.) was heated with 4-diethylamino-1-methylbutylamine (6 c.c.) and anhydrous methanol (20 c.c.) at 200—205° for 3 hours in a sealed tube. Isolated in the usual manner and purified by extraction with 0·5N-hydrochloric acid, the *base* distilled at 175—185°/0·05 mm. (bath temp.) as a viscous yellow oil (2 g.) [Found: N, 15·1; OMe, 8·4. $C_{19}H_{26}N_4Cl(OMe)$ requires N, 14·9; OMe, 8·2%]. Its *dipicrate* formed yellow needles (from ethanol), m. p. 146—147° (Found: C, 46·0; H, 4·4; N, 16·9. $C_{20}H_{29}ON_4Cl,2C_6H_3O_7N_3$ requires C, 46·0; H, 4·2; N, 16·8%).

The Reaction of p-*Chlorobenzamidine Hydrochloride with Ethyl Sodioformylacetate*.—A solution of the amidine hydrochloride (3·82 g.) in warm anhydrous ethanol (25 c.c.) was treated with ethyl sodioformyl-acetate (Gabriel, *loc. cit.*) (2·75 g.). The mixture was heated under reflux on a water-bath for 3 hours

and then filtered hot to remove sodium chloride. The solid (2·3 g.) which separated from the filtrate was collected, washed with water, and recrystallised from ethanol to give crystals, m. p. 131—134° (decomp.), of a substance (Found, on material dried in a vacuum desiccator: N, 13·8%) which, on being heated at 100°/12 mm. for 8 hours, lost 11·8% of its weight and gave the solvent-free *substance*, m. p. 199—200° (decomp.) (Found: C, 56·6; H, 4·1; N, 15·3. $C_{17}H_{14}ON_4Cl_2$ requires C, 56·5; H, 3·9; N, 15·5%. $C_{17}H_{14}ON_4Cl_2,C_2H_6O$ requires N, 13·8; loss in weight 11·3%). The latter (135 mg.), on being heated at 190—200° for one hour, gradually decomposed. Ammonia was evolved and white needles (40 mg.) of *p*-chlorobenzonitrile sublimed from the mixture. The non-volatile residue, on crystallisation from ethanol, yielded needles (60 mg.), m. p. 244—245°, of 4-*hydroxy*-2-p-*chlorophenylpyrimidine* (Found: C, 58·0; H, 3·6; N, 13·4. $C_{10}H_7ON_2Cl$ requires C, 58·1; H, 3·4; N, 13·6%).

The Reaction of p-*Chlorobenzamidine with Ethyl Sodioformylacetate.*—A solution of sodium (1·38 g.) in ethanol (60 c.c.) was treated with *p*-chlorobenzamidine hydrochloride (11·5 g.). The mixture was shaken and warmed gently until separation of sodium chloride was complete. It was then treated with ethyl sodioformylacetate (8·28 g.), heated under reflux on a water-bath for 5·5 hours, and then set aside for 12 hours. The residue left on concentration of the mixture on the water-bath was treated with water (80 c.c.), and the solution filtered from a small quantity of gelatinous material. The filtrate, on being kept, deposited orange plates (2·0 g.), which, on recrystallisation from ethanol, yielded large rhombs, m. p. 145—148° (decomp.), of p-*chlorobenzamidine monohydrate* (Found: N, 16·3. $C_7H_7N_2Cl,H_2O$ requires N, 16·2%) which, with ethanolic hydrogen chloride, yielded *p*-chlorobenzamidine hydrochloride. The aqueous filtrate, when acidified with 50% acetic acid, gave a precipitate (6·8 g.), which was separated by fractional crystallisation from ethanol into *p*-chlorobenzamidine monohydrate (1·0 g.) as the more soluble product, and, as the less soluble product, needles (4·4 g.) of 4-hydroxy-2-*p*-chlorophenylpyrimidine.

4-*Chloro*-2-p-*chlorophenylpyrimidine.*—4-Hydroxy-2-*p*-chlorophenylpyrimidine (4·5 g.) was boiled under reflux for 2·5 hours with phosphoryl chloride (22 c.c.) and dimethylaniline (5 c.c.). The *chloro*-compound (3·4 g.) was sublimed at 100°/0·04 mm. and then recrystallised from ethanol to give plates, m. p. 121—122° (Found: N, 12·0; Cl, 31·8. $C_{10}H_6N_2Cl_2$ requires N, 12·5; Cl, 31·5%).

4-(4-*Diethylamino*-1-*methylbutylamino*)-2-p-*chlorophenylpyrimidine.*—The chloro-compound (2·25 g.) was heated with 4-diethylamino-1-methylbutylamine (6·3 g.) and anhydrous methanol (8 c.c.) at 185—190° for 4·5 hours in a sealed tube. The *base* distilled as a colourless oil (3 g.) at 178—184°/0·01 mm. (bath temp.) (Found: C, 65·7; H, 7·6; N, 16·2. $C_{19}H_{27}N_4Cl$ requires C, 65·8; H, 7·8; N, 16·2%). Its *dipicrate* separated from acetone–ether in yellow needles, m. p. 171—173° (Found: C, 46·3; H, 4·2; N, 17·2. $C_{19}H_{27}N_4Cl,2C_6H_3O_7N_3$ requires C, 46·2; H, 4·1; N, 17·4%).

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