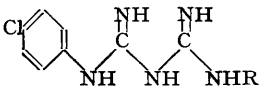
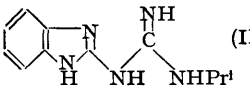
596. *The Reaction of "Paludrine" (Proguanil) with Ethyl Acetoacetate.*

By GEORGE P. FRASER and WILLIAM O. KERMACK.

Proguanil ("Paludrine") (I; R = Pr^i) and ethyl acetoacetate yield 3-*p*-chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-*iso*propylguanidinopyrimidine (V) and 6-acetonyl-2-*p*-chloroanilino-4-*iso*propylamino-*s*-triazine (IV; R = Ac, R′ = Pr^i). The former product has also been synthesised by a route which establishes its structure. Alkaline hydrolysis of the triazine yields 2-*p*-chloroanilino-6-methyl-4-*iso*propylamino-*s*-triazine (IV; R = H, R′ = Pr^i) which is also obtained from proguanil and acetic anhydride.

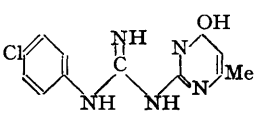
EVIDENCE has been adduced by Hawking and Perry (*Brit. J. Pharmacol.*, 1948, **3**, 320) that "Paludrine" (proguanil B.P.C.) (I; R = Pr^i) does not act directly on the malarial parasite, but that it is first converted, probably in the liver of the host, into an active derivative. When the present work was begun it was known that various possible metabolic products of proguanil such as the benziminazole (II) (King, Acheson, and Spensley, *J.*, 1948, 1366) were without antimalarial activity and there was no definite indication as to what the active product might be. The possibility fell to be considered that proguanil was activated, not by undergoing

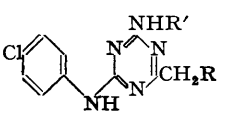
(I) 

 (II)

some process of oxidation or dehydrogenation, but by condensation of the diguanyl side chain with some normal metabolite. Such a metabolite which might readily condense with proguanil, was acetoacetic acid which is an intermediate product of fatty acid metabolism. It was therefore considered desirable to examine the reaction between proguanil and ethyl acetoacetate to ascertain whether any of the products possessed antimalarial activity.

The general idea that some such condensation might be involved in the activation of proguanil was supported by the well-known fact that N^1-*p*-chlorophenyldiguanide (I; R = H) is devoid of antimalarial activity whereas the 5-alkyl derivatives are active. It appeared possible that, in the absence of the 5-alkyl group, condensation with the β-keto-acid might occur in such a way as to involve the 5-nitrogen atom, whereas when this position was substituted by an alkyl group, condensation not involving N^5 might be favoured. Curd and Rose (*J.*, 1946, 362) had already shown that the main product of the reaction between N^1-*p*-

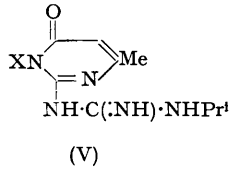
(III) 

 (IV)

chlorophenyldiguanide and ethyl acetoacetate was the pyrimidine (III) involving the atoms N^4 and N^5 in the condensation, accompanied by a small quantity of the triazine (IV; R = Ac, R′ = H) involving N^2 and N^4 or N^5. When proguanil and ethyl acetoacetate were heated

together in equimolecular proportions a crystalline solid was obtained in 10—15% yield. When an excess of ethyl acetoacetate was employed the yield of this compound could be increased to about 30% calculated on proguanil. The rest of the product was a brown viscous oil. The crystalline product, m. p. 299—300° (decomp.), had the formula $C_{15}H_{18}ON_5Cl$ and was evidently formed from one molecule of each of the reactants by the loss of one molecule of water and one of ethanol.

Hydrolysis of this compound with 2·5N-hydrochloric acid yielded a crystalline product $C_{11}H_9O_2N_2Cl$, m. p. *ca.* 342° (decomp.). As this contained two nitrogen atoms it appeared most probably to be a pyrimidine derivative. During the treatment with hydrochloric acid three nitrogen atoms had been lost but the *p*-chlorophenyl group had been retained. Presumably the compound, m. p. 299—300°, contained the pyrimidine nucleus and of the two nitrogen atoms in that nucleus, one must be N^1 as otherwise the *p*-chlorophenyl group could not have been retained on hydrolysis. Thus, of the five nitrogen atoms of proguanil, those involved in the condensation with ethyl acetoacetate must be N^1 and either N^2 or N^3. The formulæ (V, VI, VII, and VIII) are therefore possible for the compound, m. p. 299—300°. Hydrolysis of (V) or (VII) would yield (IX), whilst (VI) or (VIII) would yield (X). It was therefore decided to synthesise (IX) and (X) by unambiguous methods so as to determine the structure of the hydrolytic product.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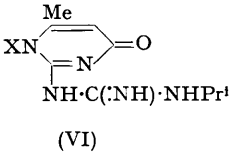
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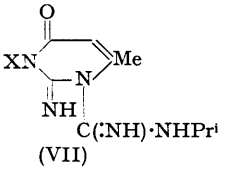
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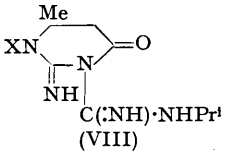
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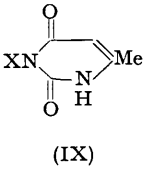
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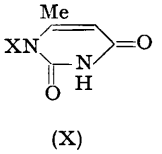
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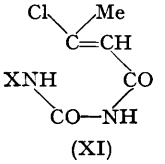
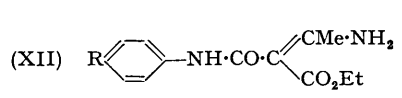

(XI)

(X = *p*-C_6H_4Cl)

1-*p*-Chlorophenyl-6-methyluracil (X) was synthesised by heating β-chlorocrotonyl chloride (Shriner and Keyser, *J. Amer. Chem. Soc.*, 1938, **60**, 286) with *p*-chlorophenylurea to give *N*-β-chlorocrotonyl-N′-*p*-chlorophenylurea (XI). This cyclized in refluxing pyridine to give 1-*p*-chlorophenyl-6-methyluracil, m. p. 143°, which was not identical with the hydrolytic product.

The isomer (IX) was synthesised as follows. Behrend, Meyer, and Buchholz (*Annalen*, 1901, **314**, 209) synthesised 6-methyl-3-phenyluracil from phenyl *iso*cyanate and ethyl β-aminocrotonate, the compound (XII; R = H) being obtained as a by-product. When equimolecular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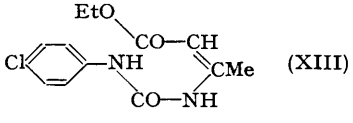
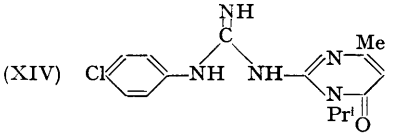

(XIII)

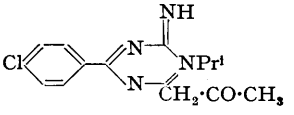
proportions of *p*-chlorophenyl *iso*cyanate and ethyl β-aminocrotonate were heated together in the presence of a trace of triethylamine, ethyl β-*N*′-*p*-chlorophenylureidocrotonate (XIII) was formed, which on further heating cyclized to 3-*p*-chlorophenyl-6-methyluracil (IX), m. p. *ca.* 342° (decomp.). This gave no depression of the melting point of the hydrolytic product obtained above. It seemed likely therefore that the hydrolytic product was 3-*p*-chlorophenyl-6-methyluracil but in view of its high melting point and rather wide decomposition range further evidence was required. This was kindly furnished by Dr. H. C. Carrington, Imperial Chemical Industries Limited, Dyestuffs Division, Blackley, Manchester, who had examined them and reported the ultra-violet spectra of the substances to be identical.

It follows that the condensation product, m. p. 299—300°, must be either (V) or (VII). Of these structures, (V) was considered the more probable both because in proguanil N^2 might be expected to be more reactive than N^3 and also because the formation of (IX) from (V)

appeared to be more probable than that from (VII). One puzzling observation may be mentioned here, however, which emphasised the need for considering both possibilities. The maximum yield of the uracil derivative, m. p. 342°, from the hydrolysis of the condensation product, m. p. 299—300°, never exceeded 30%. It was observed that the filtrate from the hydrolysis after removal of the uracil contained a diazotisable amino-group and finally *p*-chloroaniline was isolated. Colorimetric observations showed that this amine might account for 35% of the original compound. It appeared surprising that fission of the pyrimidine ring should take place with such relative ease. Prolonged boiling of 3-*p*-chlorophenyl-6-methyluracil (IX) with 2·5N-hydrochloric acid showed that, with this pyrimidine derivative, ring fission with liberation of *p*-chloroaniline took place only slowly, 3·3% being liberated in 8 hours. This result excluded the possibility that ring fission occurred after removal of the side chain.

A possibility which had to be considered was that the condensation product, m. p. 299—300°, was a mixture of two isomers, one of which was (V) or (VII) and the other a pyrimidine or triazine derivative carrying a *p*-chloroanilino-group as a side chain, as in (XIV). Numerous

(XIV) 


(XV)

attempts to separate possible isomers by fractional crystallisation or by chromatography completely failed. The only impurity detected was an occasional very small quantity of proguanil. In the circumstances it seemed advisable to synthesise the pyrimidine condensation compound by some independent and unambiguous route. This was done as follows.

Behrend, Meyer, and Buchholz (*loc. cit.*) reported that phenyl *iso*thiocyanate and ethyl β-aminocrotonate gave 6-methyl-3-phenyl-2-thiouracil in very small yield. In our experiments *p*-chlorophenyl *iso*thiocyanate, ethyl β-aminocrotonate, and a trace of triethylamine were heated rapidly to 150° and kept at this temperature for one hour. 3-*p*-Chlorophenyl-6-methyl-2-thiouracil was obtained although in poor yield. This compound was methylated readily with methyl iodide and sodium ethoxide, to give 3-*p*-chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-methylthiopyrimidine, which when heated with *iso*propylguanidine (Crowther, Richardson, and Rose, *J.*, 1948, 1641) lost methanethiol to give 3-*p*-chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-*iso*propylguanidinopyrimidine (V), m. p. 299—300°, giving no depression of the melting point with the original condensation compound.

Confirmation of the structure of the 2-methylthiopyrimidine was obtained when the reaction with *iso*propylguanidine was carried out in aqueous ethanol. A very low yield of the 2-*iso*propylguanidino-compound was obtained and it was found that hydrolysis of the 2-methylthiopyrimidine had taken place, methanethiol having been lost and 3-*p*-chlorophenyl-6-methyluracil, identical with that synthesised above, obtained.

It must be concluded therefore that the condensation compound is undoubtedly (V) and that the guanidino-group facilitates the fission of the ring with the formation of *p*-chloroaniline.

Advantage was taken of the availability of 3-*p*-chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-methylthiopyrimidine to synthesise 3-*p*-chlorophenyl-2-2′-diethylaminoethylamino-3 : 4-dihydro-4-keto-6-methylpyrimidine. This was effected by refluxing the former with diethylaminoethylamine. The product was an oil and was conveniently isolated as its dihydrobromide, m. p. 253°.

The brown viscous oil obtained in the condensation of proguanil and ethyl acetoacetate yielded an amorphous hydrochloride from which alkali liberated a weak base, $C_{15}H_{18}ON_5Cl$, m. p. 121°, in which all five nitrogen atoms of proguanil were retained. When boiled with alkali this yielded a product, $C_{13}H_{16}N_5Cl$, m. p. 173·5—174°, an acetyl group having been lost and the five nitrogen atoms and the *p*-chlorophenyl and *iso*propyl groups retained. These facts strongly suggested these substances to be triazines.

6-Acetonyl-4-amino-2-*p*-chloroanilino-*s*-triazine (IV; R = Ac, R′ = H), obtained by Curd and Rose (*loc. cit.*) in the reaction of *p*-chlorophenyldiguanide and ethyl acetoacetate, was converted by boiling dilute alkali into 4-amino-2-*p*-chloroanilino-6-methyl-*s*-triazine (IV; R = R′ = H). This triazine was also obtained by treatment of *p*-chlorophenyldiguanide with acetic anhydride. We have found that when proguanil was treated with acetic anhydride 2-*p*-chloroanilino-6-methyl-4-*iso*propylamino-*s*-triazine (IV; R = H, R′ = Pr^i) was formed

which gave no depression of melting point with the product, m. p. 173·5—174°, obtained as above by alkaline hydrolysis. This indicated the original compound to be 6-acetonyl-2-*p*-chloroanilino-4-*iso*propylamino-*s*-triazine (IV; R = Ac, R′ = Pr^i). The other possible formulation, where N^2 and N^5 of proguanil are involved in the ring so as to give the imino-derivative (XV), appeared less likely but required consideration. Prolonged acid and alkaline hydrolysis of the substance produced, however, little decomposition and no new compound could be isolated. Cuthbertson and Moffatt (*J.*, 1948, 561) obtained 6-chloro-2-*p*-chloroanilino-4-*iso*propylamino-*s*-triazine by successive replacement of the two chlorine atoms in cyanuric chloride by *p*-chloroaniline and *iso*propylamine, respectively. The chlorine atom in the 6-position could not be replaced by hydrogen, except by methods of reduction which also removed the chlorine atom of the benzene ring to give 2-anilino-4-*iso*propylamino-*s*-triazine. By heating proguanil with ethyl formate they obtained a triazine which on dechlorination yielded 2-anilino-4-*iso*propylamino-*s*-triazine. Here clearly the ethyl formate has reacted with N^2 and N^4 of the diguanide system. It appears safe to conclude from this analogy that ethyl acetoacetate similarly reacts with N^2 and N^4 and that the resulting compound has the structure (IV; R = Ac, R′ = Pr^i).

Antimalarial tests of 3-*p*-chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-*iso*propylguanidinopyrimidine have been kindly carried out in the Biological Laboratories of Imperial Chemical Industries Limited. The compound shows slight antimalarial activity against *P. gallinaceum* infections in chicks. The activity, however, is substantially less than that of proguanil, apparently excluding the possibility that this might be the active compound into which proguanil is converted in the animal body. 6-Acetonyl-2-*p*-chloroanilino-4-*iso*propylamino- and 2-*p*-chloroanilino-6-methyl-4-*iso*propylamino-*s*-triazine have been found to be inactive.

Experimental.

Condensation of Proguanil and Ethyl Acetoacetate.—Proguanil (31·2 g.) and ethyl acetoacetate (150 c.c.) were refluxed for 5 hours. Most of the excess of ethyl acetoacetate was removed by distillation under reduced pressure, leaving a thick yellow paste. This was filtered and the residue washed with ether (2 × 100 c.c.). The filtrate and washings were combined and left overnight and a further precipitate filtered off, washed, and combined with the first. This material was recrystallised from a large volume of ethanol, from which 3-p-*chlorophenyl*-3 : 4-*dihydro*-4-*keto*-6-*methyl*-2-iso*propylguanidinopyrimidine* (V) separated as a microcrystalline powder, m. p. 299—300° (decomp.) (12·2 g., 30·1%) (Found : C, 56·4; H, 5·9; N, 22·4; Cl, 10·9. $C_{15}H_{18}ON_5Cl$ requires C, 56·3; H, 5·7; N, 21·9; Cl, 11·2%).

The mother-liquor yielded, after removal of the ether, a brown viscous oil which slowly hardened to a glass. This was dissolved in acetone (200 c.c.), and concentrated hydrochloric acid (20 c.c.) was added. The hydrochloride which separated overnight was filtered off and recrystallised from water acidified with a few drops of hydrochloric acid. The white amorphous hydrochloride (14·2 g.) melted at 242—245°. This was stirred with acetone (30 c.c.), and sufficient 2·5N-sodium hydroxide added to liberate the base, which dissolved in the acetone to give a clear solution. The base was precipitated by the addition of much water, filtered off, washed with water, and recrystallised from light petroleum (b. p. 40—60°), from which 6-*acetonyl*-2-p-*chloroanilino*-4-iso*propylamino*-s-*triazine* (IV; R = Ac, R′ = Pr^i) separated as fine white crystals (10·2 g.), m. p. 121° (Found : C, 56·8; H 5·4; N, 21·6; Cl, 11·3. $C_{15}H_{18}ON_5Cl$ requires C, 56·3; H, 5·7; N, 21·9; Cl, 11·2%).

Hydrolysis of 3-p-*Chlorophenyl*-3 : 4-*dihydro*-4-*keto*-6-*methyl*-2-iso*propylguanidinopyrimidine* (V).—3-*p*-Chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-*iso*propylguanylpyrimidine (2·0 g.) was boiled with 2·5N-hydrochloric acid (20 c.c.) for 0·5 hour. 3-p-*Chlorophenyl*-6-*methyluracil*, which was precipitated during the hydrolysis, was filtered off and crystallised from ethanol–water as shining plates, m. p. 342° (decomp.) (0·43 g.) (Found : C, 55·6; H, 3·9; N, 12·4; Cl, 15·65. $C_{11}H_9O_2N_2Cl$ requires C, 55·8; H, 3·8; N, 11·95; Cl, 15·0%).

Hydrolysis of 6-*Acetonyl*-2-p-*chloroanilino*-4-iso*propylamino*-s-*triazine* (IV; R = Ac, R′ = Pr^i).—6-Acetonyl-2-*p*-chloroanilino-4-*iso*propylamino-*s*-triazine (5 g.) was refluxed with 2·5N-sodium hydroxide (20 c.c.) and ethanol (20 c.c.) for 1 hour. The alcohol was boiled off. The precipitate of 2-p-*chloroanilino*-6-*methyl*-4-iso*propylamino*-s-*triazine* recrystallised from light petroleum (b. p. 100—120°) as white hemispherical rosettes (on the walls of the flask), m. p. 173·5—174° (Found : C, 56·4; H, 5·8; N, 24·8; Cl, 13·0. $C_{13}H_{16}N_5Cl$ requires C, 56·2; H, 5·8; N, 25·2; Cl, 12·8%).

2-p-*Chloroanilino*-6-*methyl*-4-iso*propylamino*-s-*triazine* (IV; R = H, R′ = Pr^i).—Proguanil (2·0 g.) and acetic anhydride (5·0 c.c.) were heated at 100° for 1 hour. The solution was cooled, diluted with water (30 c.c.), and made alkaline with 2·5N-sodium hydroxide. The precipitate was filtered off, washed with water, and boiled with 10N-sodium hydroxide (2 c.c.) in methanol (30 c.c.) for 3 minutes. The solution was cooled and water (30 c.c.) added. The precipitate of 2-*p*-chloroanilino-6-methyl-4-*iso*propylamino-*s*-triazine was recrystallised from light petroleum (b. p. 100—120°); it had m. p. 173·5—174° (yield, 1·04 g.) (Found : C, 55·9; H, 6·2; N, 25·3; Cl, 12·5%). This triazine gave no depression of the m. p. with the triazine derived as above.

N-*β*-*Chlorocrotonyl*-N′-p-*chlorophenylurea* (XI).—*β*-Chlorocrotonyl chloride (13·9 g.), *p*-chlorophenylurea (17·5 g.), and benzene (50 c.c.) were refluxed in a water-bath for 10 hours. The benzene

was boiled off and the product recrystallised from chlorobenzene. N-*β-Chlorocrotonyl*-N'-p-*chlorophenylurea* was obtained as needles, m. p. 243·5—244·5° (13·6 g.) (Found: C, 48·9; H, 4·1; N, 10·3; Cl, 25·3. $C_{11}H_{10}O_2N_2Cl_2$ requires C, 48·4; H, 3·7; N, 10·3; Cl, 26·0%).

1-p-*Chlorophenyl*-6-*methyluracil* (X).—*N*-Chlorocrotonyl-*N'*-*p*-chlorophenylurea (8·2 g.) was heated under reflux in pyridine (20 c.c.) for 1·5 hours. Most of the pyridine was removed under reduced pressure, leaving a thick dark red syrup. This was dissolved in alcohol (10 c.c.) and treated with charcoal. After several recrystallisations from alcohol, 1-p-*chlorophenyl*-6-*methyluracil* separated as long feathery needles, m. p. 143° (4·2 g.) (Found: C, 56·1; H, 3·9; N, 11·6; Cl, 15·0. $C_{11}H_9O_2N_2Cl$ requires C, 55·8; H, 3·8; N, 11·95; Cl, 15·0%).

Ethyl β-(N'-p-*Chlorophenylureido*)*crotonate* (XIII).—*p*-Chlorophenyl *iso*cyanate (9·2 g.) and ethyl *β*-aminocrotonate (7·8 g.) were melted together in a water-bath at 50°, in the presence of a trace of triethylamine as catalyst. The mixture was left at room temperature for 20 minutes after which the solid product was fractionally crystallised from alcohol, from which *ethyl β*-(N'-p-*chlorophenylureido*)-*crotonate* separated as colourless prisms, m. p. 135° (5·6 g.) (Found: C, 55·4; H, 5·5; N, 10·2; Cl, 12·6. $C_{13}H_{15}O_3N_2Cl$ requires C, 55·3; H, 5·3; N, 9·9; Cl, 12·4%). Evaporation of the mother-liquors and recrystallisation of the solid product from light petroleum (b. p. 80—100°) yielded *ethyl β-amino-α*-p-*chlorophenylcarbamylcrotonate* (XII; R = Cl), crystallising in tufted needles, m. p. 161° (Found: C, 55·75; H, 5·4; N, 10·2. $C_{13}H_{15}O_3N_2Cl$ requires C, 55·3; H, 5·3; N, 9·9%).

3-p-*Chlorophenyl*-6-*methyluracil* (IX).—Ethyl *β*-(*N'*-*p*-chlorophenylureido)crotonate (5·6 g.), when heated in an oil-bath at 150° for 3 hours in the presence of a trace of pyridine or triethylamine gave 3-*p*-chlorophenyl-6-methyluracil (3·5 g., 23·8%), m. p. 342° (decomp.), as shining plates (Found: C, 55·85; H, 4·0; N, 12·1. $C_{11}H_9O_2N_2Cl$ requires C, 55·8; H, 3·8; N, 11·95%). Its m. p. was not depressed by the addition of the hydrolysis product from 3-*p*-chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-*iso*propylguanidinopyrimidine, but charring took place around the m. p.

3-p-*Chlorophenyl*-6-*methyl*-2-*thiouracil*.—*p*-Chlorophenyl *iso*thiocyanate (16·9 g.), ethyl *β*-aminocrotonate (12·9 g.), and a few drops of triethylamine were heated rapidly to 150°. After 1 hour the resulting dark brown oil was cooled and the precipitate of 3-*p*-chlorophenyl-6-methyl-2-thiouracil filtered off. Ether (50 c.c.) was added to the filtrate and it was left overnight in the refrigerator. The resulting precipitate was filtered off, washed with ether (10 c.c.) and combined with the first yield. This product, recrystallised from alcohol–water, gave 3-p-*chlorophenyl*-6-*methyl*-2-*thiouracil* (7·4 g.) as a fine pale yellow powder, m. p. 275—280° (decomp.) (Found: C, 52·3; H, 3·6; N, 11·3; Cl, 14·2. $C_{11}H_9ON_2SCl$ requires C, 52·3; H, 3·6; N, 11·1; Cl, 14·0%).

3-p-*Chlorophenyl*-3 : 4-*dihydro*-4-*keto*-6-*methyl*-2-*methylthiopyrimidine*.—To a solution of sodium ethoxide [from sodium (0·38 g.) in alcohol (30 c.c.)] was added 3-*p*-chlorophenyl-6-methyl-2-thiouracil (4·2 g.) and methyl iodide (3·2 g., 1·25 mols.). The mixture was refluxed for 1 hour during which the methyl derivative started to crystallise. Cooling and filtering the solution, and recrystallising the product from alcohol–water gave 3-p-*chlorophenyl*-3 : 4-*dihydro*-4-*keto*-6-*methyl*-2-*methylthiopyrimidine* (4·3 g., 97·7%) as needles, m. p. 151° (Found: C, 53·9; H, 4·3; N, 10·8; Cl, 13·05. $C_{12}H_{11}ON_2ClS$, requires C, 54·0; H, 4·2; N, 10·5; Cl, 13·3%).

3-*p*-*Chlorophenyl*-3 : 4-*dihydro*-4-*keto*-6-*methyl*-2-iso*propylguanidinopyrimidine* (V).—3-*p*-Chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-methylthiopyrimidine (2·7 g.) and *iso*propylguanidine (1·0 g.) were heated at 120° for 5 hours. The reaction-tube was evacuated during the final hour of heating to remove the last traces of methanethiol. The resulting white solid was broken up and crystallised from a large volume of alcohol from which 3-*p*-chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-*iso*propylguanidinopyrimidine (2·27 g., 71%) separated as fine needles, m. p. 299—300° (decomp.) (Found: C, 56·3; H, 5·8; N, 22·0; Cl, 10·8. $C_{15}H_{18}ON_5Cl$ requires C, 56·3; H, 5·7; N, 21·9; Cl, 11·2%). This substance did not depress the m. p. of the pyrimidine obtained from the reaction of proguanil and ethyl acetoacetate.

3-p-*Chlorophenyl*-2-2'-*diethylaminoethylamino*-3 : 4-*dihydro*-4-*keto*-6-*methylpyrimidine*.—3-*p*-Chlorophenyl-3 : 4-dihydro-4-keto-6-methyl-2-methylthiopyrimidine (1·08 g.) and 2-diethylaminoethylamine (5 c.c.) were refluxed for 7 hours. Most of the excess of diethylaminoethylamine was removed under reduced pressure, leaving a dark brown oil. This was extracted with 2% acetic acid (100 c.c.) which was then neutralised with aqueous ammonia and extracted with ether (3 × 50 c.c.). The ether was evaporated off at room temperature and the product extracted again in the same way. The resulting pale yellow oil was dried and dissolved in ether (10 c.c.), and anhydrous alcoholic hydrobromic acid added until the solution was just acid. Acetone (75 c.c.) was added and the precipitate of 3-p-*chlorophenyl*-2-2'-*diethylaminoethylamino*-3 : 4-*dihydro*-4-*keto*-6-*methylpyrimidine dihydrobromide*, m. p. 253°, was filtered off (0·54 g.) (Found: C, 41·15; H, 5·2; N, 11·4. $C_{17}H_{25}ON_4ClBr_2$ requires C, 41·1; H, 5·1; N, 11·3%).

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