CHEMOTHERAPY OF MALARIA

II. Synthesis of Some Thiazole Derivatives

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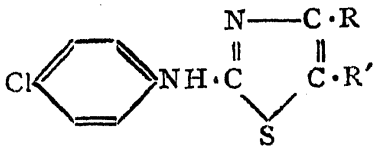
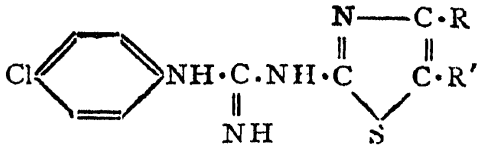
Received April 24, 1951

As indicated in the previous Part,[1] we were interested in tracing the antimalarial activity of compounds of the thiazole group having a simple structure as well as a formal resemblance to the pyrimidine derivatives which led to the development of paludrine in the hands of the British investigators. For this, attempts were made to synthesise compounds of types (I) and (II).



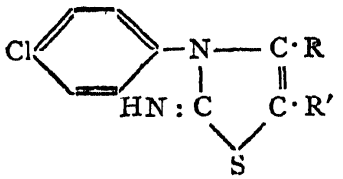
(I)



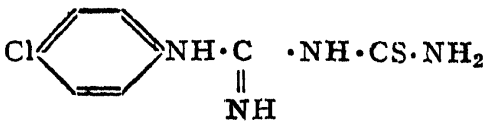
(II)

Compounds of type (I) have been prepared by the standard procedure which consisted in reacting a phenyl (or a naphthyl) thiourea derivative with chloracetal, chloracetone and ethyl α-chloroacetoacetate respectively. The twenty-one thiazole derivatives thus obtained are listed in Table I.

Condensation of the thiourea derivative with the α-halogenoketones can lead to two types of compounds (I) or (II). It has been shown already by Traumann[2] as well as by Hantsch and Weber[3] that only compounds of the type (I) are produced. This has now been confirmed also by the result that the condensation product of *p*-chloroaniline with 2-bromothiazole is identical with the compound obtained by reacting *p*-chlorophenylthiourea with chloracetal.



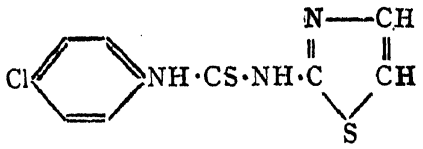
(III)



(IV)

In attempting to evolve a general method of synthesising compounds of formula (II), several methods were tried. The attempts to synthesise the guanidylthioformamide derivative (IV) which could easily be converted into the guanidylthiazoles by reaction with α-chloroketones, ended in failure. Condensation of *p*-chlorophenylcyanamide with thiourea led only to the self-condensation products of the former. Though dicyandiamide has been converted into guanidylthioformamide by the action of hydrogen sulphide,

p-chlorophenylcyanamide could not be converted into the compound (IV) under the standard conditions. The condensation of *p*-chlorophenylcyanamide with 2-aminothiazole did not furnish the guanidylthiazole derivative (II). In view of this, it was not surprising to find that *p*-chlorophenylthiourea and 2-aminothiazole did not react also in the presence of desulphurising agents. However, the guanidylthiazole derivative (II, R = R′ = H) was successfully prepared by desulphurising in the presence of alcoholic ammonia 2-(*p*-chlorophenylthiocarbamido) thiazole (V) itself obtained by the action of *p*-chlorophenylisothiocyanate on 2-aminothiazole. This method appears to be of general applicability and other guanidine derivatives are being prepared.



(V)

The results of testing these compounds for their antimalarial properties will be reported later on.

Experimental

Preparation of thiourea derivatives.—To the amine hydrochloride in alcohol was added potassium thiocyanate (a little over one molecular equivalent) and the mixture refluxed for four hours on the steam-bath. The inorganic salt that separated was filtered off and the filtrate concentrated to dryness. The residue was crystallised from a suitable solvent. The yields of the thiourea derivatives thus obtained were uniformly good. The compounds not reported before are listed in the following table:

Name of Compound	Formula	M. P. °C.	% Nitrogen	
			Found	Required
2-Chlorophenylthiourea	$C_7H_7N_2SCl$	141–3	14·84	15·05
3-Chlorophenylthiourea	$C_7H_7N_2SCl$	137–8	15·42	15·05
2:4-Dichlorophenylthiourea	$C_7H_6N_2SCl_2$	154–6	12·22	12·67
2:5-Dichlorophenylthiourea	$C_7H_6N_2SCl_2$	193–4	12·30	12·67
3:4-Dichlorophenylthiourea	$C_7H_6N_2SCl_2$	198	12·73	12·67

Preparation of thiazole derivatives.—The thiourea derivative taken up in alcohol was treated with the α-halogenoketone or chloracetal (1·1

molecular equivalent) and the mixture refluxed for thirty minutes to four hours, in most cases the reaction being completed in about thirty minutes. The solvent was removed and the residue treated with water and made basic with ammonium hydroxide whereby the thiazole derivative separated. The product was filtered and crystallised from dilute alcohol. The yields of the thiazoles obtained and listed in Table I, are invariably good.

TABLE I

No.	-thiazole	Formula	M. P. °C.	% Nitrogen	
				Found	Required
1	2-*p*-Chloranilino-	$C_9H_8N_2SCl$	167–8	13·66	13·33
2	2-*p*-Chloranilino-4-methyl-	$C_{10}H_9N_2SCl$	146–7	12·42	12·47
3	2-*p*-Chloranilino-4-methyl-5-carbethoxy-	$C_{13}H_{13}N_2O_2SCl$	147–8	9·04	9·44
4	2-*o*-Chloranilino-	$C_9H_8N_2SCl$	92–4	13·66	13·33
5	2-*o*-Chloranilino-4-methyl-	$C_{10}H_9N_2SCl$	70	12·75	12·47
6	2-*o*-Chloranilino-4-methyl-5-carbethoxy-	$C_{13}H_{13}N_2O_2SCl$	99–100	9·57	9·44
7	2-*m*-Chloranilino-	$C_9H_8N_2SCl$	109–11	13·56	13·33
8	2-*m*-Chloranilino-4-methyl-	$C_{10}H_9N_2SCl$	135–6	12·75	12·47
9	2-*m*-Chloranilino-4-methyl-5-carbethoxy-	$C_{13}H_{13}N_2O_2SCl$	145–6	9·26	9·44
10	2-(2′:4′-Dichloranilino)-	$C_9H_6N_2SCl_2$	110–12	10·93	11·43
11	2-(2′:4′-Dichloranilino)-4-methyl-	$C_{10}H_8N_2SCl_2$	132–3	10·88	10·81
12	2-(2′:4′-Dichloranilino)-4-methyl-5-carbethoxy-	$C_{13}H_{12}N_2O_2SCl_2$	139–40	8·29	8·46
13	2-(2′:5′-Dichloranilino)-	$C_9H_6N_2SCl_2$	132–3	11·74	11·43
14	2-(2′:5′-Dichloranilino)-4-methyl-	$C_{10}H_8N_2SCl_2$	183–4	10·95	10·81
15	2-(2′:5′-Dichloranilino)-4-methyl-5-carbethoxy-	$C_{13}H_{12}N_2O_2SCl_2$	112–3	7·95	8·46
16	2-(3′:4′-Dichloranilino)-	$C_9H_6N_2SCl_2$	170	11·33	11·43
17	2-(3′:4′-Dichloranilino)-4-methyl-	$C_{10}H_8N_2SCl_2$	115–6	11·22	10·81
18	2-(3′:4′-Dichloranilino)-4-methyl-5-carbethoxy-	$C_{13}H_{12}N_2O_2SCl_2$	192–3	8·57	8·46
19	2-(4′-Chloro-α-naphthylamino)	$C_{13}H_9N_2SCl$	182–4	10·55	10·76
20	2-(4′-Chloro-α-naphthylamino)-4-methyl-	$C_{14}H_{11}N_2SCl$	158–60	9·8	10·2
21	2-(4′-Chloro-α-naphthylamino)-4-methyl-5-carbethoxy-	$C_{17}H_{15}N_2O_2SCl$	177–8	7·57	8·08

2-p-*Chloroanilinothiazole.*—An intimate mixture of 2-bromothiazole (4 g.) and p-chloraniline (2·5 g.) in phenol medium was maintained for four hours at 150–60° in an oil-bath. The reaction product was cooled and then poured into 5% sodium hydroxide solution. The brown product obtained was filtered and on crystallisation from dilute alcohol it separated in glistening white plates, m.p. 167–8°, which did not show any depression in m.p. on admixture with the thiazole obtained by the reaction of *p*-chlorophenylthiourea with chloracetal.

2-(p-*Chlorophenylthiocarbamido*) *thiazole* (*V*).—*p*-Chlorophenylisothiocyanate (4·2 g.) and 2-aminothiazole (2·5 g.) in benzene (30 c.c.) was refluxed for five hours, the solvent removed and the residue crystallised from dilute alcohol. The thiazole derivative thus obtained (yield 3 g.) had m.p. 185–6° (Found: N, 15·4. $C_{10}H_8N_3S_2Cl$ requires N, 15·58%).

2-(p-*Chlorophenylguanidino*)*thiazole* (*II*, $R = R' = H$).—To the above described thiourea derivative (1·3 g.) in alcoholic ammonia (30 c.c.) was added mercuric oxide (1·1 g.) and the mixture refluxed for five hours. The black precipitate that separated was filtered off, the filtrate concentrated *in vacuo* and the residue crystallised from alcohol to obtain the guanidine derivative (0·8 g.), m.p. 114–5°. (Found: N, 22·49. $C_{10}H_9N_4SCl$ requires N, 22·2%).

Summary

To trace the antimalarial activity in the thiazole compounds, twenty-one thiazole derivatives of general formula I have been synthesised by the standard method of reacting the corresponding thiourea derivatives with chloracetal, chloracetone and ethyl α-chloracetoacetate respectively. The guaridino compound of formula II could not be prepared by the action of *p*-chlorophenylcyanamide on thiourea or by the action of desulphurising agents on a mixture of *p*-chlorophenylthiourea and 2-aminothiazole. *p*-Chlorophenylguanidinothioformamide (IV) could not be prepared by the action of hydrogen sulphide on *p*-chlorophenyldicyandiamide. *p*-Chlorophenylisothiocyanate reacted with 2-aminothiazole to furnish 2-(*p*-chlorophenylthiocarbamido) thiazole (V) which on treatment with mercuric oxide in alcoholic ammonia solution furnished the guanidinothiazole derivative (II).

References

1. Fernandes and Ganapathi .. *Proc. Ind. Acad. Sci.*, 1948, **28 A**, 563.
2. Traumann .. *Annalen*, 1888, **249**, 31.
3. Hantsch and Weber .. *Ber.*, 1887, **20**, 3118, 3131.