CHEMOTHERAPY OF MALARIA

V. Synthesis of 4-(Thiazolylamino)-Quinolines and 4-Phenoxyquinolines

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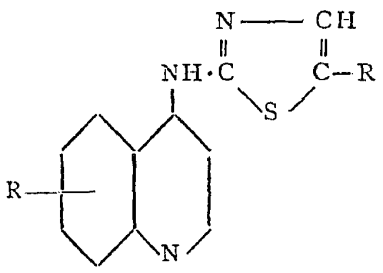
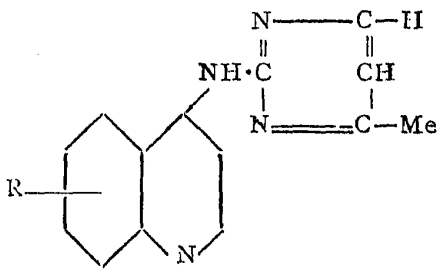
As an extension of the work reported in the previous parts, this paper records the synthesis of some derivatives of 4-amino-quinolines wherein the amino group bears a thiazole and pyrimidine ring as a substituent. It should be noted that in such compounds of formula (I) and (II), the significant groups —NH—C(S)=N— and —NH—C(N)=N— are present.



(I)



(II)

Compounds of type (I) can be synthesised by condensing 4-thiocarbamido-quinolines with halogenoketones according to the standard procedure of preparing thiazoles, but as was indicated in Part III, the starting thiocarbamido derivatives could not be prepared. Since we have also found that the amino group in the 4-aminoquinolines is very inert, the only method of preparing the compounds of formula (I) consisted in the condensation of 4-chloro-quinolines with the 2-aminothiazoles. Such a condensation could not be effected by boiling the constituents in alcohol but the reaction proceeded when conducted in phenol medium. Thus the amino group in thiazoles resemble the aliphatic amino rather than the aromatic amino groups.

The general procedure adopted to condense 4-chloroquinolines with 2-aminothiazoles in phenol medium was to heat the mixture at 150-60° for three to six hours and then pour the cooled mixture into dilute alkali solution. The yields of the condensation products were about 40 to 50% in the case of the quinolines while with the quinaldines, the yields were less and the

products were also difficult to purify. Thus, 4:7-dichloroquinoline was reacted in turn with 2-aminothiazole, 2-amino-5-ethylthiazole and 2-amino-5-isopropylthiazole to furnish respectively 4-(thiazolyl-2′-amino)-7-chloroquinoline (I, R = 7 — Cl; R′ = H), 4-(5′-ethylthiazolyl-2′-amino)-7-chloroquinoline (I, R = 7—Cl; R′ = C_2H_5) and 4-(5′-isopropylthiazolyl-2′-amino-7-chloroquinoline (I, R = 7—Cl; R′ = $CHMe_2$). Similarly, 4-chloro-8-methoxyquinaldine, 4-chloro-6-methoxyquinaldine and 4:6-dichloroquinaldine were each reacted in turn with 2-amino-thiazole, 2-amino-5-ethylthiazole and 2-amino-5-isopropylthiazole to obtain the corresponding thiazolylaminoquinoline derivatives of formula (I) in most cases. The condensation of 4-chloro-6-methoxy quinaldine and of 4:6-dichloroquinaldine with 2-aminothiazole in phenol medium furnished only the 4-phenoxy quinaldine derivatives instead of the thiazolylamino compounds of formula (I). On the other hand, 2-aminothiazole condensed alright with 4:7-dichloroquinoline and 4-chloro-8-methoxyquinoline furnishing the thiazolylaminoquinolines. This indicates that the reactivity of the chlorine atom in position 4 of the quinoline ring is significantly altered by the nature and position of the substituents in the quinoline ring.

Attempts to condense 2-chlorolepidine with the aminothiazoles were not successful. Refluxing the constituents in alcoholic medium did not lead to condensation while in phenol medium, only the 2-phenoxy compound was produced. This type of reduced reactivity of the chlorine atom in position 2 is not unexpected.

The condensation of 4:7-dichloroquinoline with 2-aminopyrimidine, 2-amino-4-methylpyrimidine and 2-amino-4:6-dimethylpyrimidine were tried. Refluxing the constituents in alcoholic solution led to no condensation. When they were heated in phenol medium, only a small quantity of the desired condensation product (II) was obtained when using 2-amino-4-methylpyrimidine. When the other two pyrimidines were used, no condensation product could be isolated. In these cases, 4-phenoxy-7-chloroquinoline was the other product isolated. When 2-amino-4-methyl-6-chloropyrimidine was tried, the products isolated were 4-phenoxy-7-chloropyrimidine and 2-amino-4-methyl-6-phenoxypyrimidine. When they were refluxed in amylalcohol, the quinoline was converted into 4-hydroxy-7-chloroquinoline but no condensation took place.

The above observations led us to doubt the validity of theory that the role of the phenol in the condensation is to provide first the phenoxy compound which subsequently reacts with the amines to furnish the aminoquinolines.[1] Walker,[2] on the other hand, refuses to give any importance

to the role of phenol. To study this we have prepared a number of phenoxy compounds and have studied their properties. 4-Phenoxy-7-chloroquinoline on treatment with ammonia remains unaffected; even if the phenoxy compound is suspended in phenol and ammonia passed through the hot mixture, no amino compound could be prepared. The phenoxy compound is stable to alkali and acids even on boiling. So, clearly the phenoxy compound cannot be the intermediate in the formation of the amino compounds and the role of phenol is not to furnish the phenoxy compound. We have also found that 4-phenoxy-7-chloroquinoline does not react with novaldiamine, guanidine carbonate, guanidine acetate, 2-aminopyrimidine and 2-aminothiazole. Phenol cannot be replaced by glycerol either. The role of phenol appears to be to facilitate the nucleophilic attack at the carbon atom 4 in the quinoline nucleus by the negative ion, similar to the mechanism postulated by Cutler and Surrey[3] who found that the action of acetic acid on 4:7-dichloroquinoline furnished 4-hydroxy-7-chloroquinoline.

Experimental

4-(*Thiazolyl-2'-amino*)-7-*chloroquinoline*.—An intimate mixture of 4:7-dichloroquinoline (10 g.), 2-aminothiazole (5 g.) and phenol (50 g.) was heated at 160-70° C. for 4 hours. The reaction mixture on cooling was treated with dil. sodium hydroxide (8%, 500 c.c.) and the dark red syrupy substance which was thrown out was separated, washed with little water and taken up in dil. hydrochloric acid (1:2). The acidic solution was treated with charcoal, filtered and the filtrate cooled and basified with sodium hydroxide solution (10%) whereupon the desired condensation product was obtained as a granular yellow solid. The product crystallised in needles and had m.p. 231–33° (Found: N, 16·19. $C_{12}H_8N_3SCl$ requires N, 16·06%). Picrate, m.p. 218–20°.

4-(5'-Ethylthiazolyl-2'-amino)-7-chloroquinoline.—This compound was prepared as described above from a mixture of 4:7-dichloroquinoline (5 g.), 2-amino-5-ethylthiazole (3·4 g.) and phenol (25 g.) at 145–50°. The compound crystallised from ethanol in flakes and had m.p. 236–7° (Found: N, 14·57. $C_{14}H_{12}N_3SCl$ requires N, 14·51%). Picrate, m.p. 238–40°.

4-(5'-Iso*propylthiazolyl-2'-amino*)-7-*chloroquinoline*.—This was prepared from 4:7-dichloroquinoline (5 g.), 2-amino-5-isopropylthiazole (3·6 g.) and phenol (25 g.) by heating the mixture at 145–50°. This compound, crystallised first from alcohol and then from acetone, separated in flakes and had m.p. 233–34° (Found: N, 13·61. $C_{15}H_{14}N_3SCl$ requires N, 13·82%). Hydrochloride, m.p. 283–5°; picrate, m.p. 249–50°.

4-(*Thiazolyl-2'-amino*)-8-*methoxyquinaldine*.—This was prepared by heating a mixture of 4-chloro-8-methoxyquinaldine (5 g.), 2-aminothiazole (2·35 g.) and phenol (25 g.) at 150–60° for 7 hours. The compound on crystallisation from a mixture of benzene and ligroin was obtained in flakes and had m.p. 207–9° (Found: N, 15·23. $C_{14}H_{13}ON_3S$ requires N, 15·50%).

4-(5'-*Ethylthiazolyl-2'-amino*)-8-*methoxyquinaldine*.—Prepared as described above, crystallised from ethanol, had m.p. 184–89° (Found: N, 14·19, $C_{16}H_{17}ON_3S$ requires N, 14·04%).

4-(5'-Iso*propylthiazolyl-2'-amino*)-8-*methoxyquinaldine*.—Prepared from a mixture of 4-chloro-8-methoxyquinaldine (5 g.), 2-amino-5-isopropylthiazole (3·1 g.) and phenol (25 g.). On crystallisation from benzene ligronin mixture, it had m.p. 202–4° (Found: N, 13·49. $C_{17}H_{19}ON_3S$ requires N, 13·41%).

4-(5'-*Ethylthiazolyl-2'-amino*)-6-*methoxyquinaldine*.—This compound prepared from a mixture of 4-chloro-6-methoxyquinaldine (5 g.), 2-amino-5-ethylthiazole (3·1 g.) and phenol (25 g.), on crystallisation from ethanol separated in pale yellow plates had m.p. 176–7° (Found: N, 13·88. $C_{16}H_{17}ON_3S$ requires N, 14·05%).

4-(5'-Iso*propylthiazolyl-2'-amino*)-6-*methoxyquinaldine*.—Prepared as above by using 2-amino-5-isopropylthiazole in the place of 2-aminothiazole in the above reaction. On crystallisation from alcohol, it separated in needles and had m.p. 226–8° (Found: N, 13·30. $C_{17}H_{19}ON_3S$ requires N, 13·4%).

4-(5'-*Ethylthiazolyl-2'-amino*)-6-*chloroquinaldine*.—Prepared from 4:6-dichloroquinaldine (5 g.) and 2-amino-5-ethylthiazole (3·05 g.) by heating them with phenol (25 g.). On crystallisation from benzene-ligroin, it had m.p. 169–70° (Found: N, 13·85. $C_{15}H_{14}N_3SCl$ requires N, 13·83%).

4-(5'-Iso*propylthiazolyl-2'-amino*)-6-*chloroquinaldine*.—Prepared from 4:6-dichloroquinaldine (5 g.), 2-amino-5-isopropylthiazole (3·4 g.) and phenol (25 g.). On crystallisation, it had m.p. 161–6° (Found: N, 13·18. $C_{16}H_{16}N_3SCl$ requires N, 13·23%).

4-(4'-*Methylpyrimidyl-2'-amino*)-7-*chloroquinoline*.—This compound was prepared by heating a mixture of 2-amino-4-methylpyrimidine (2·2 g.) 4:7-dichloroquinoline (3 g.) and phenol (20 g.) at 150° for 4 hours. The product crystallised from acetone in fine greenish yellow needles, m.p. 155° (Found: N, 20·45. $C_{14}H_{11}N_4Cl$ requires N, 20·70%).

Attempted condensation of 2-amino-4-methyl-6-chloropyrimidine with 4:7-dichloroquinoline.—The two compounds did not condense when they were refluxed in alcohol or pyridine or Dowtherm. When refluxed in amyl

alcohol, the compound obtained was identified to be 4-hydroxy-7-chloroquinoline, m.p. 272–3° (Found: N, 7·89. C_9H_6ONCl requires N, 7·77%). When the reactants were heated in phenol, 4-phenoxy-7-chloroquinoline hydrochloride, m.p. 203–5° and 2-amino-4-methyl-6-phenoxypyrimidine, m.p. 195–6° (Found: N, 20·20; 20·06. $C_{11}H_{11}ON_3$, $\frac{1}{2}$ H_2O requires N, 20·00) causing no depression with a sample prepared independently, were obtained.

4-*Phenoxy*-6-*chloroquinaldine*.—This was prepared from 4:6-dichloroquinaldine and phenol by heating them together. On crystallisation from acetone, it had m.p. 159–60° (Found: N, 5·27. $C_{16}H_{12}ONCl$ requires N, 5·19%).

4-*Amino*-7-*chloroquinoline*.—(i) A mixture of 4-phenoxy-7-chloroquinoline (1 g.) and ammonium acetate (5 g.) was heated at 170–75° for 3 hours. The reaction mixture was poured into water and rendered alkaline with aq. sodium hydroxide when a solid product separated. It was filtered and crystallised from hot benzene; m.p. 148–50° (yield, 0·45 g.).[4]

(ii) 4-Methoxy-7-chloroquinoline (1 g.) was mixed with ammonium acetate (5 g.) heated at 130–5° for 3 hours and the product worked up as usual. 4-Amino-7-chloroquinoline was obtained in a yield of 70%.

Summary

Ten thiazolylaminoquinolines of formula (I) have been prepared by heating the 4-chloroquinolines with 2-aminothiazoles in phenol medium, at about 150–60°. In some cases, instead of the compounds of formula (I), only the 4-phenoxyquinolines could be isolated. The 2-chlorolepidines do not undergo this condensation at all. 4:7-Dichloroquinoline condensed with 2-amino-4-methylpyrimidine to yield the compound (II); but 2-aminopyrimidine and 2-amino-4-methyl-6-chloropyrimidine did not react with the chloroquinoline. Evidence has been presented to show that in the condensation of the chloroquinolines with amines in phenol medium, the phenoxyquinoline is not the intermediate as was supposed by some authors. A different mechanism seems to operate.

References

1. Backberg and Marais .. *J. Chem. Soc.*, 1942, 381.
2. Walker, J. .. *Ibid.*, 1947, 1552.
3. Cutler and Surrey .. *J. Amer. Chem. Soc.*, 1950, **72**, 3394.
4. Simpson and Wright .. *J. Chem. Soc.*, 1948, 1707.