243. *A General Method for the Preparation of 1-Substituted Glyoxalines from Acetalylthiocarbimide and Primary Amines.*

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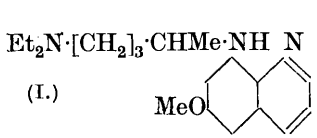
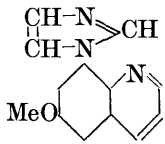
Knowledge that the antimalarial drug plasmoquin is 8-diethylamino*iso*pentylamino-6-methoxyquinoline (I) has stimulated the preparation of other derivatives of 8-amino-6-methoxyquinoline in various quarters. The present authors desired to prepare 8-(glyoxalinyl-1′)-6-methoxyquinoline (II) in order to have it tested for antimalarial properties, and as a preliminary investigation attempted the preparation of 8-(glyoxalinyl-1′)quinoline (III), which is derived from more readily accessible starting material.



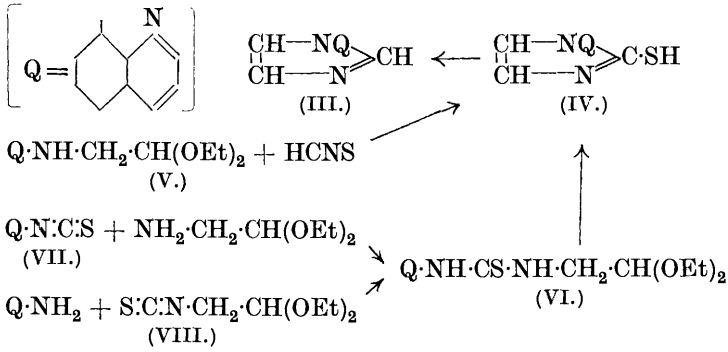
(I.)



(II.)

The possible methods for the synthesis of this compound, all leading through the corresponding 2-thiol compound (IV), were the condensation of the unknown quinolyl-8-aminoacetal (V) with thiocyanic acid, or the hydrolysis of the thiocarbamide (VI) derived from 8-aminoquinoline and aminoacetal. This substance might be prepared theoretically either by the action of (*a*) the unknown

8-thiocarbimidoquinoline (VII) upon aminoacetal or (*b*) the unknown *acetalylthiocarbimide* (VIII) upon 8-aminoquinoline.



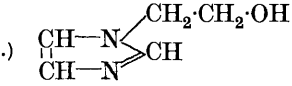
In spite of a considerable number of experiments, we were unable to prepare either quinolyl-8-aminoacetal (V) or quinolyl-8-thiocarbimide (VII). We therefore reinvestigated the preparation of acetalylthiocarbimide (VIII), which had been attempted previously without success by Marckwald (*Ber.*, 1892, **25**, 2354), and were able to determine conditions under which this compound could be produced in fair yield. This substance reacts with primary amines generally, including 8-aminoquinoline, to yield thiocarbamides, not always isolable as crystalline substances, which on hydrolysis yield 2-thiolglyoxalines. Thus, condensation of acetalylthiocarbimide with 8-aminoquinoline and 8-amino-6-methoxyquinoline gave non-crystalline thiocarbamides, which on hydrolysis with acid gave rise to 8-(2′-*thiolglyoxalinyl*-1′)*quinoline* (IV) and 8-(2′-*thiolglyoxalinyl*-1′)-6-*methoxyquinoline* respectively. These gave 8-(*glyoxalinyl*-1′)*quinoline* (III), and 8-(*glyoxalinyl*-1′)-6-*methoxyquinoline* (II) on oxidation; similarly, 2-aminoquinoline was converted into 2-(*glyoxalinyl*-1′)*quinoline* by way of 2-*quinolylacetalylthiocarbamide* and 2-(2′-*thiolglyoxalinyl*-1′)*quinoline*.

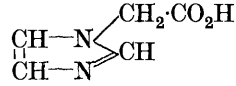
Condensation of acetalylthiocarbimide with aniline gave phenylacetalylthiocarbamide, which had been prepared previously by the condensation of phenylthiocarbimide with aminoacetal (Wohl and Marckwald, *Ber.*, 1889, **22**, 568).

In the aliphatic series, several similar syntheses have been effected. The condensation product of acetalylthiocarbimide with methylamine did not crystallise but gave on hydrolysis 2-thiol-1-methylglyoxaline, which had been made previously from the condensation product of methylthiocarbimide with aminoacetal (Wohl and Marckwald, *Ber.*, 1889, **22**, 1353).

Moreover, the condensation of acetalylthiocarbimide with β-aminoethyl alcohol and ethyl glycine, followed by hydrolysis of the

resulting thiocarbamides, gave rise to 2-*thiol*-1-β-*hydroxyethylglyoxaline* and 2-*thiolglyoxaline*-1-*acetic acid*, which on oxidation gave 1-β-*hydroxyethylglyoxaline* (IX) and *glyoxaline*-1-*acetic acid* (X) respectively.

(IX.) 

 (X.)

It is thus apparent that acetalylthiocarbimide is a reagent generally suitable for the conversion of aliphatic, aromatic, or heterocyclic primary amines into 1-substituted glyoxalines.

By the courtesy of the Chemotherapy Committee of the Medical Research Council, 8-(glyoxalinyl-1')quinoline, 8-(glyoxalinyl-1')-6-methoxyquinoline, and 2-(glyoxalinyl-1')quinoline were tested for antimalarial activity under the direction of Professor Keilin, F.R.S., at the Molteno Institute, Cambridge, and were found to be inactive.

EXPERIMENTAL.

Acetalylthiocarbimide.—A mixture of aqueous sodium hydroxide (45 c.c. of 5*N*), carbon disulphide (20 g.), and a solution of aminoacetal (27 g.) in water (100 c.c.) was warmed gently and shaken until the carbon disulphide had dissolved. The solution was treated at 0° with an ice-cold solution of basic lead acetate (30 g.) in water (100 c.c.), a reddish-yellow precipitate forming; an ice-cold concentrated aqueous solution of normal lead acetate (60 g.) was then added, gradually and with shaking. The mixture was kept cold for 30 minutes, and then gradually warmed on the steam-bath, with continual shaking. The coloured precipitate blackened. Acetalylthiocarbimide was removed by steam distillation, isolated and dried (anhydrous potassium carbonate) in ether, and distilled under diminished pressure. Yield, 21·5 g. (60%).

Acetalylthiocarbimide is a colourless oil with a pungent characteristic odour; *d* 1·041, b. p. (some decomp.) 220—225°/ordinary pressure and (unchanged) 133°/40 mm. It is insoluble in water, and miscible with all ordinary organic solvents. It is not decomposed by hot water and only very slowly by hot dilute mineral acids or dilute caustic alkalis. It is decomposed immediately by heating with mineral acid solutions of lead or mercury salts, or mixtures of lead hydroxide and caustic soda, with deposition of metallic sulphide (Found: C, 47·7; H, 7·7; N, 7·8; S, 18·3. $C_7H_{13}O_2NS$ requires C, 48·0; H, 7·5; N, 8·0; S, 18·3%).

Phenylacetalylthiocarbamide.—Acetalylthiocarbimide (0·85 g.) and aniline (0·45 g.) were heated on the steam-bath for an hour. The product crystallised on cooling, and after recrystallisation from dilute

alcohol, melted at 96—97° (corr.). Wohl and Marckwald (*loc. cit.*) give m. p. 96°.

2-*Quinolylacetalylthiocarbamide*.—A mixture of acetalylthiocarbimide (2·8 g.) and 2-aminoquinoline (2·3 g.) was heated on the steam-bath for several hours. The product crystallised while still hot. The *thiocarbamide* separated from alcohol in needles, m. p. 139—140° (corr.). Yield, 2·3 g. (45%) (Found : S, 10·1. $C_{16}H_{21}O_2N_3S$ requires S, 10·0%).

2-(2′-*Thiolglyoxalinyl*-1′)*quinoline*.—The crude thiocarbamide obtained by heating a mixture of acetalylthiocarbimide (7·6 g.) and 2-aminoquinoline (6·1 g.) was washed with a little ether. The product (10·7 g., m. p. 125—135°), heated on the steam-bath for several hours with 5*N*-sulphuric acid (50 c.c.), dissolved completely. The *thiol* compound, which separated from the hot solution (yield, 6·0 g.; 62%, calculated on the amount of 2-aminoquinoline used), crystallised from alcohol, in which it was not very easily soluble, in needles, m. p. 263—264° (corr.; decomp.), insoluble in water or ether (Found : C, 63·1; H, 4·6; N, 18·1; S, 14·35. $C_{12}H_9N_3S$ requires C, 63·4; H, 4·0; N, 18·5; S, 14·1%).

2-(*Glyoxalinyl*-1′)*quinoline*.—The crude thiol compound (7·8 g.) was added in small portions to hot 5*N*-nitric acid (60 c.c.), and the filtered solution made alkaline and extracted with chloroform. The extract, dried and evaporated, left crude 2-(glyoxalinyl-1′)-quinoline (6·1 g.= 91%; m. p. 115—120°), which crystallised from alcohol–ether in prismatic needles, m. p. 120—121° (corr.), soluble in water, alcohol, or chloroform, but sparingly so in ether. The *monohydrochloride* crystallised from alcohol–acetone in prismatic needles, m. p. 217—218° (corr.). It is very soluble in water, slightly hygroscopic, and is acid to litmus (Found : C, 62·3; H, 4·4; Cl, 15·2. $C_{12}H_9N_3$,HCl requires C, 62·2; H, 4·4; Cl, 15·3%). The picrate separated from glacial acetic acid in needles, m. p. 205—206° (corr.).

8-(2-*Thiolglyoxalinyl*-1′)*quinoline*.—A mixture of acetalylthiocarbimide (6·9 g.) and 8-aminoquinoline (5·8 g.) was heated on the steam-bath for an hour. The product, a thick syrup which did not crystallise, was heated for 1½ hours on the steam-bath with 5*N*-sulphuric acid. Water was added to dissolve the orange-coloured crystals (probably the sulphate of the thiolglyoxaline) which separated, and the *thiolglyoxaline* was then precipitated by adding ammonia. Yield, 7·2 g. (79%). It crystallised from much glacial acetic acid in prisms, m. p. 304° (corr.; decomp.) (Found : S, 13·8. $C_{12}H_9N_3S$ requires S, 14·1%). It is insoluble in water or ether, but slightly soluble in alcohol. The *hydrochloride* crystallised from concentrated hydrochloric acid in orange needles, which were

decolorised on treatment with water (Found: S, 12·1. $C_{12}H_9N_3S$,HCl requires S, 12·1%).

8-(*Glyoxalinyl*-1′)*quinoline*.—Oxidation of the crude thiol compound was carried out in the manner described for the 2-quinoline isomeride. The yield was theoretical. 8-(Glyoxalinyl-1′)quinoline crystallised from alcohol–ether in large, highly refractive prisms, m. p. 124—125° (corr.), slightly soluble in cold water and readily in hot water. The *monohydrochloride* separated from alcohol–acetone in needles, m. p. 247—248° (corr.). The salt is very readily soluble in water and is acid to litmus (Found: C, 62·0; H, 4·4; N, 18·2; Cl, 15·3. $C_{12}H_9N_3$,HCl requires C, 62·2; H, 4·4; N, 18·1; Cl, 15·3%). The picrate crystallised from glacial acetic acid in felted needles, m. p. 197—198° (corr.).

8-(*Thiolglyoxalinyl*-1′)-6-*methoxyquinoline* was prepared from 8-amino-6-methoxyquinoline (10 g.) and acetalylthiocarbimide (12 g.) in the manner described for the preparation of 8-(2′-thiolglyoxalinyl-1′)quinoline. It separated from much glacial acetic acid in microscopic prisms, m. p. 297° (corr.; decomp.) (Found: S, 11·8. $C_{13}H_{11}ON_3S$ requires S, 12·4%).

8-(*Glyoxalinyl*-1′)-6-*methoxyquinoline*.—Oxidation of the above crude thiol compound with 2·5*N*-nitric acid (240 c.c.) gave 8-(glyoxalinyl-1′)-6-methoxyquinoline in 77% yield, calculated on the 8-amino-6-methoxyquinoline. The base separated from alcohol–ether in long prisms, m. p. 139—140° (corr.), sparingly soluble in ether or cold water but readily soluble in hot water. The *monohydrochloride* crystallised from alcohol–acetone in prismatic needles, m. p. 243—244° (corr.). This salt is very readily soluble in water, slightly hygroscopic, and acid to litmus (Found: C, 59·3; H, 5·0; N, 15·6; Cl, 13·2. $C_{13}H_{11}ON_3$,HCl requires C, 59·6; H, 4·6; N, 16·1; Cl, 13·6%). The picrate crystallised from glacial acetic acid in needles, m. p. 219—220° (corr.).

2-*Thiol*-1-*methylglyoxaline*.—Acetalylthiocarbimide (14·5 g.) was added to methylamine (3·6 g.) in alcohol (10 c.c.), the temperature being kept below 25°. On removal of the solvent a syrup remained which did not become crystalline. It was doubtless acetalylmethylcarbamide, which Wohl and Marckwald (*loc. cit.*) prepared from methylthiocarbimide and aminoacetal, and described as non-crystalline, for on hydrolysis with sulphuric acid as described by these authors, it gave 2-thiol-1-methylglyoxaline in 57% yield. This substance had m. p. 143—144° (corr.) (Wohl and Marckwald give 141—142°) (Found: N, 24·6; S, 28·4. Calc.: N, 24·6; S, 28·1%).

2-*Thiol*-1-β-*hydroxyethylglyoxaline*.—Acetalylthiocarbimide (14·2 g.) was mixed with β-aminoethyl alcohol (4·9 g.). A vigorous exother-

mic reaction took place. The mixture was heated on the steam-bath for 30 minutes. The crude thiocarbamide, which did not crystallise, was heated on the steam-bath for 2—3 hours with 5*N*-sulphuric acid (60 c.c.). After removal of sulphate ions quantitatively with barium hydroxide, the filtrate was evaporated to dryness under diminished pressure. On crystallising the residue from alcohol, the *thiol* compound [6·25 g.; 54%; m. p. 151—152° (corr.)] was obtained in prisms, soluble in water, but insoluble in ether (Found : C, 41·2; H, 5·8; S, 22·4. $C_5H_8ON_2S$ requires C, 41·6; H, 5·6; S, 22·2%).

1-β-*Hydroxyethylglyoxaline* was obtained in 29% yield (calculated on the aminoethyl alcohol used) by oxidising the above thiol compound with dilute nitric acid, but can be prepared more conveniently without isolating this substance. The reaction product of acetalylthiocarbimide (22 g.) and aminoethyl alcohol (8·0 g.) was hydrolysed with 5*N*-sulphuric acid (100 c.c.). The solution was added slowly to a boiling 12% aqueous solution of nitric acid (220 c.c.), and boiling continued until evolution of brown fumes had ceased. The solution was neutralised with caustic soda, and treated with the theoretical amount of picric acid. The picrate which separated on cooling was filtered off and shaken with dilute sulphuric acid and ether. The solution of sulphate thus obtained was freed from sulphate ions by means of baryta and concentrated under diminished pressure. The resulting crude *hydroxyethylglyoxaline* was distilled, and collected at 202—206°/20 mm. Yield, 5·0 g. (34%). It had m. p. 36—40°, was miscible with water or alcohol, and soluble in ether (Found : C, 53·4; H, 6·8; N, 25·1. $C_5H_8ON_2$ requires C, 53·5; H, 7·1; N, 25·0%). The picrate crystallised from alcohol in needles, m. p. 142—143° (corr.).

2-*Thiolglyoxaline*-1-*acetic Acid*.—Acetalylthiocarbimide (8·7 g.) was mixed with ethyl glycine (5·0 g.). There was a vigorous exothermic reaction, the temperature rising to 120°. The resulting syrup was hydrolysed by boiling with 5*N*-sulphuric acid (45 c.c.). After removal of sulphate ions by barium hydroxide, and concentration of the filtrate, the residue was crystallised from alcohol, from which the *thiol* compound separated in thin prisms [Yield, 2·45 g.; 32%; m. p. 205—206° (corr.)]. It is readily soluble in water, but insoluble in ether (Found : C, 37·6; H, 4·0; S, 20·0. $C_5H_6O_2N_2S$ requires C, 38·0; H, 3·8; S, 20·2%).

Glyoxaline-1-*acetic acid* is most conveniently prepared without isolating the thiol compound. The condensation product from acetalylthiocarbimide (21 g.) and ethylglycine (11·8 g.) was hydrolysed with 5*N*-sulphuric acid (100 c.c.). The solution was added carefully to hot 2·5*N*-nitric acid (200 c.c.). When oxidation was complete,

sulphate ions were removed with baryta and the filtrate was evaporated to a small bulk under diminished pressure. The residue was treated with alcohol to remove excess nitric acid, and vacuum evaporation continued until a dry residue, consisting of the crude *glyoxalineacetic acid*, was left. Yield, 10·3 g. (70%). After crystallising from water, it formed thin prisms, m. p. 268—269° (corr.; decomp., sintering at 264°), readily soluble in water, sparingly so in alcohol, and insoluble in ether (Found : C, 47·9; H, 5·0; N, 21·7. $C_5H_6O_2N_2$ requires C, 47·6; H, 4·8; N, 22·2%).

Ethyl glyoxaline-1-*acetate picrate* was prepared by passing dry hydrogen chloride into a mixture of the above acid and ethyl alcohol, removing the excess of hydrogen chloride and alcohol under diminished pressure in the cold, and adding aqueous picric acid. On crystallisation from alcohol, the ester picrate separated in leaflets, m. p. 124—125° (corr.) (Found : C, 40·8; H, 3·6. $C_7H_{10}O_2N_2,C_6H_3O_7N_3$ requires C, 40·7; H, 3·4%).

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NOTTINGHAM. [*Received, May 4th*, 1932.]