23. *Contributions to the Chemistry of Synthetic Antimalarials. Part V. Attempted Synthesis of 6-Methoxy-8-quinolyl-α-dialkylaminomethyl-carbinols.*

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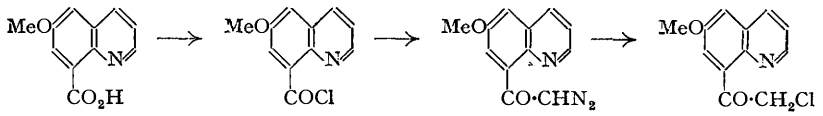
6-*Methoxy*-8-*quinolyl chloromethyl ketone* has been synthesised and converted into 6-methoxy-8-quinolyl diethylaminomethyl and dibutylaminomethyl ketone. The reduction product of the former ketone has been characterised as the *styphnate*.

The appearance of the publication entitled " α-Dialkylaminomethyl-8-quinoline methanols " by Campbell, Kerwin, LaForge, and Campbell (*J. Amer. Chem. Soc.*, **1946**, **68**, **1844**) prompts us to place on record our results obtained in an attempted synthesis of 6-methoxy-8-quinolyl-α-dialkylaminomethylcarbinols.

Much of our unsuccessful experimental work accords with the experience of the American workers, though we have successfully carried out (albeit in poor yield) the following synthesis of 6-methoxy-8-quinolyl chloromethyl ketone.



8-Cyano-6-methoxyquinoline (Rubtzow, *J. Gen. Chem. Russia*, **1939**, **9**, **1493**) was readily hydrolysed to the corresponding carboxylic acid (Rubtzow, *loc. cit.*) by boiling 60% sulphuric acid. This acid, as noted by Campbell *et al.*, was very difficult to esterify, and Rubtzow's method (heating with ethyl sulphate in alkaline solution) could not be repeated. In agreement

with the American workers, however, it was found that, of several methods tried, treatment of the acid chloride with ethyl alcohol gave the best results.

Condensation of ethyl 6-methoxyquinoline-8-carboxylate with ethyl acetate gave ethyl 6-methoxy-8-quinolylacetate which was characterised as the *picrate* and *sulphate*. Bromination of this keto-ester in chloroform or 24% hydrobromic acid led to polybrominated products as found by the American workers.

6-Methoxy-8-quinolyl methyl ketone gave, on treatment with bromine, one of two products depending on the solvent used. In chloroform a nuclear brominated product was obtained, since oxidation yielded an acidic material containing 27·8% of bromine, probably a bromoquinoline-8-carboxylic acid, though this was not investigated further. Bromination in sulphuric acid apparently led to the same polybromo-product as was obtained from the keto-ester.

Campbell *et al.* reported unsuccessful attempts to prepare 6-methoxy-8-quinolyl halogenomethyl ketones by reaction of 6-methoxyquinoline-8-carboxyl chloride with diazomethane and hydrogen chloride or bromide. In our hands 6-methoxyquinoline-8-carboxyl chloride was converted into the diazoketone which with hydrogen chloride yielded *6-methoxy-8-quinolyl chloromethyl ketone*. We found that reaction of the acid chloride in ethereal solution with a large excess of diazomethane below 0° gave the solid diazo-ketone which was stable at 0°, but decomposed rapidly at room temperature with evolution of gas and formation of an oil. The diazo-ketone was more stable in ethereal solution. If the reaction were carried out in ether above 5°, a different product was isolated, possibly 6-methoxy-8-quinolylmethyl hydroxymethyl ketone (cf. Meerwein and Hinz, *Annalen*, 1931, **484**, 1). Attempts to prepare the corresponding bromomethyl ketone led to formation of tars.

6-Methoxy-8-quinolyl chloromethyl ketone reacted normally with diethylamine and dibutylamine to give the corresponding dialkylamino-ketones. The diethyl derivative was reduced catalytically in alcoholic solution in presence of platinum oxide, reduction being terminated when 1 mol. of hydrogen had been absorbed. The dark red oil so obtained could not be distilled without decomposition, but was characterised as the *styphnate*. In view of the unpromising biological results and the difficulties of synthesis, this line of research was not followed further.

Experimental.

Ethyl 6-Methoxy-8-quinolylacetate.—A stirred mixture of sodamide (0·5 g.), ethyl 6-methoxyquinoline-8-carboxylate (2·3 g.), and ethyl acetate (0·9 g.) in benzene (6 c.c.) was heated to 90° for 3 hours. After cooling and addition of ether, the semi-solid mass was filtered off and the residue decomposed in presence of ether with 2N-acetic acid. 6-Methoxyquinoline-8-carboxylic acid (0·6 g.) was removed by filtration, and the ethereal filtrate after drying over potassium carbonate yielded a yellow oil (2·4 g.) which gave a *picrate* crystallising from alcohol in rhombs or hair-like crystals (2·55 g.), m. p. 122° (Found: N, 11·0. $C_{15}H_{15}O_4N,C_6H_3O_7N_3$ requires N, 11·1%). The *sulphate*, prepared by dissolving the keto-ester in methyl alcohol–sulphuric acid at − 70°, crystallised from alcohol in colourless crystals, m. p. 140° (decomp.) after darkening at 134° (Found: C, 48·0; H, 4·2; N, 4·0. $C_{15}H_{15}O_4N,H_2SO_4$ requires C, 48·5; H, 4·2; N, 3·8%).

Bromination of 6-Methoxy-8-quinolyl Methyl Ketone.—(*a*) A solution of the ketone (1·2 g.) in chloroform (20 c.c.) was treated gradually with bromine (0·3 g.) in chloroform (8 c.c.). The mixture was then heated to 50° for 1 hour, cooled, and filtered. The residue (1 g.) crystallised from alcohol in yellow needles, m. p. 98° followed by solidification and m. p. 150° (Found: Br, 52·0. $C_{12}H_{10}O_2NBr,2HBr$ requires Br, 54·0%).

Evaporation of the chloroform filtrate from the bromination gave a residue (0·9 g.), m. p. 166° after crystallisation from alcohol. The same *substance* was also obtained by treating the product, m. p. 98°, with 2N-sodium hydroxide (Found: Br, 28·6. $C_{12}H_{10}O_2NBr$ requires Br, 29·1%).

Oxidation of the above substance, m. p. 166° (0·4 g.), with potassium permanganate (0·5 g.) and 2N-sodium hydroxide (20 c.c.) at 100° for 6 hours yielded an acidic *substance* which crystallised from aqueous acetone in colourless plates, m. p. 220° (Found: Br, 27·8. $C_{11}H_8O_3NBr$ requires Br, 28·4%).

(*b*) A solution of the ketone (0·8 g.) in sulphuric acid (*d* 1·84; 2·5 c.c.) was treated gradually with bromine (0·65 g.). After 30 minutes, evolution of hydrogen bromide had almost ceased, and addition of ether (20 c.c.) precipitated an oil which was washed with ether. This oil crystallised when treated with a little ice, and the solid (1·15 g.) was dissolved in water and the solution basified. The resulting oil was extracted with light petroleum (b. p. 80—100°) and yielded a colourless crystalline solid (0·6 g.), m. p. 91° (Found: Br, 41·8. $C_{12}H_9O_2NBr_2$ requires Br, 41·0%).

6-Methoxy-8-quinolyl Chloromethyl Ketone.—Crude 6-methoxyquinoline-8-carboxyl chloride hydrochloride (prepared from 20 g. of acid) was added slowly during 1 hour to a stirred solution of diazomethane [from nitrosomethylurea (40 g.)] in anhydrous ether (500 c.c.) at − 5°. After 0·5 hour the mixture was filtered, and the residue washed well with ether. The combined ethereal solution was added slowly to stirred hydrochloric acid (*d* 1·16; 45 c.c.) at − 10°, the ether was decanted, the aqueous solution cooled at − 20° for 0·5 hour, filtered, and the yellow crystalline residue recrystallised from hydrochloric acid. Yield, 7·6 g. The filtrates were combined and evaporated over sulphuric acid in a vacuum desiccator. The residual tarry product, after draining on porcelain, was crystallised from hydrochloric acid. Yield,

1·4 g. The combined products were recrystallised from 5% alcoholic hydrochloric acid to give the *hydrochloride* in yellow needles, m. p. 151—152° (Found: N, 4·7; Cl, 27·9. $C_{12}H_{10}O_2NCl,HCl$ requires N, 5·1; Cl, 26·1%). The free 6-*methoxy*-8-*quinolyl chloromethyl ketone*, obtained by addition of cold 2N-sodium hydroxide to an aqueous solution of the hydrochloride, crystallised from light petroleum (b. p. 80—100°) in slightly pink felted needles, m. p. 120° when heated rapidly; slow heating caused decomposition without melting at 116° (Found: Cl, 14·5. $C_{12}H_{10}O_2NCl$ requires Cl, 15·1%).

When the above reaction was carried out at 5—10° the product was a dark oil which slowly crystallised as the hydrochloride from alcoholic hydrogen chloride. The free base crystallised from alcohol (some decomp.) in large yellow rhombs, m. p. 80°. The *hydrochloride* crystallised from alcohol in yellow needles which fell to a powder when dried in a vacuum, and which sintered at 168°, began to decompose at 175° (with evolution of gas), and melted at 180—200° (Found: N, 5·3. $C_{13}H_{13}O_3N,HCl$ requires N, 5·3%).

6-*Methoxy*-8-*quinolyl Diethylaminomethyl Ketone*.—The above chloromethyl ketone hydrochloride (11 g.), diethylamine (16·5 g.), and anhydrous benzene (100 c.c.) were heated under nitrogen at 40° for 3 hours. After removal of diethylamine hydrochloride the benzene was evaporated at 30° under reduced pressure. The residue was thoroughly extracted with boiling light petroleum (b. p. 40—60°). Removal of the solvent under reduced pressure gave a deep red oil (5·3 g.), b. p. 150—160°/0·1 mm. (some decomp.). The *dipicrate* crystallised from acetone in yellow prisms, m. p. 142° (Found: C, 45·8; H, 3·6; N, 15·35. $C_{16}H_{20}O_2N_2,2C_6H_3O_7N_3$ requires C, 46·0; H, 3·6; N, 15·3%).

6-*Methoxy*-8-*quinolyl Di*-n-*Butylaminomethyl Ketone*.—A mixture of the chloromethyl ketone hydrochloride (1 g.), di-*n*-butylamine (1·4 g.), and benzene (10 c.c.) at 25° for 16 hours gave 0·9 g. of a deep red oil, b. p. 186—190°/0·5 mm. (some decomp.). The *dipicrate* crystallised from acetone in yellow prisms, m. p. 141° (decomp.) (Found: N, 14·2. $C_{20}H_{28}O_3N_2,2C_6H_3O_7N_3$ requires N, 14·2%).

Reduction of 6-*Methoxy*-8-*quinolyl Diethylaminomethyl Ketone*.—The ketone (2·75 g.) in 0·5 methanolic N-hydrochloric acid (20 c.c.) was hydrogenated at 25° under atmospheric pressure in presence of Adams's catalyst (0·2 g.); 330 c.c. (theory, 290 c.c.) of hydrogen were absorbed in 0·5 hour. After filtration, the solution was evaporated to 5 c.c., diluted with water (10 c.c.), basified with 2N-ammonia, and filtered. The residue was washed and the filtrate extracted with ether. The combined extract, after being dried (K_2CO_3), yielded a red oil (2·2 g.). Extraction of this with boiling light petroleum (b. p. 40—60°) gave a red oil (1·75 g.). The *styphnate* crystallised from acetone in red needles, m. p. 164° (Found: C, 51·0, 51·2; H, 5·4, 5·6; N, 13·55. $C_{16}H_{22}O_2N_2,C_6H_3O_8N_3$ requires C, 51·0; H, 4·85; N, 13·5%).

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