## 269. *Attempts to find New Antimalarials. Part XIII. Synthesis of ω-Substituted Derivatives of 8-Methylquinoline.*

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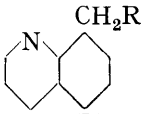
Antimalarials of the plasmoquin type contain a basic side chain attached in the 8-position of the quinoline nucleus through a nitrogen atom. It seemed desirable to prepare compounds in which the nitrogen atom of the basic side chain was separated from the nucleus by one carbon atom. In order to explore methods for the synthesis of compounds of this type, *o*- and *p*-nitrobenzyl chlorides were condensed with piperidine to yield respectively *o*- and *p*-nitrobenzylpiperidine (cf. Lellmann and Pekrum, *Annalen*, 1890, **259**, 46), from which by reduction (cf. West, J., 1925, **127**, 494) *o*- and *p*-aminobenzylpiperidines were obtained. Application of the Skraup synthesis to these compounds afforded a small yield of the desired 8- and 6-ω-piperidinomethylquinolines (I and II; R = $NC_5H_{10}$). Both are oils but were conveniently purified as *monopicrates*.

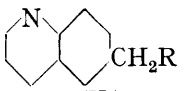
The second method of synthesis consisted in allowing 8-bromomethylquinoline, prepared by a modification of the method of Müller and Lang (Diss., Freiburg, 1897; cf. also

Howitz and Nother, *Ber.*, 1906, **39**, 2709), to react with the appropriate secondary base; *e.g.*, from piperidine, 8-piperidinomethylquinoline was obtained as an oil which formed a picrate, m. p. 183°, giving no depression with the picrate of the base isolated from the Skraup reaction.

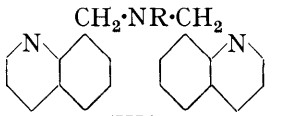
Similarly from diethylamine, an oily base (I; R = $NEt_2$) was obtained as *hydrobromide* $C_{14}H_{18}N_2,2HBr$. Attempts to isolate this compound from the tarry product of the Skraup reaction performed on *o*-aminobenzyldiethylamine (cf. Noelting and Kregezy, *Bull. Soc. chim.*, 1916, **19**, 339) were unsuccessful. Aniline gave an anologous *base* (I; R = NHPh). With monoethylamine, the only product isolated was di(quinolyl-8-methyl)ethylamine (III; R = Et) as *hydrobromide* $C_{22}H_{21}N_3,3HBr$; *p*-aminoacetanilide similarly gave a *base* (III; R = $C_6H_4$·NHAc).



(I.)



(II.)



(III.)

## Experimental.

8-*Piperidinomethylquinoline*.—(i) *From* o-*aminobenzylpiperidine*. Boric acid (4 g.) dissolved in glycerol (25 g.) was mixed with *o*-aminobenzylpiperidine (12 g.), *o*-nitrobenzylpiperidine (9 g.), and ferrous sulphate (2·3 g., cryst.). Concentrated sulphuric acid (12 c.c.) was then added, and the contents heated to boiling and allowed to simmer for 20 hrs. The dark-coloured solution was steam-distilled, basified, and again steam-distilled. It was then extracted with ether several times, the extract washed with water, dried (potassium carbonate), and the ether removed. The oily residue did not crystallise, but yielded a somewhat tarry yellow *picrate* which, after numerous recrystallisations from alcohol, formed yellow needles, m. p. 179° (Found: C, 55·2; H, 4·7; N, 15·6. $C_{21}H_{21}O_7N_5$ requires C, 55·4; H, 4·6; N, 15·4%).

(ii) *From* 8-*bromomethylquinoline*. 8-Bromomethylquinoline (1 g.) was added to a solution of piperidine (1 g.) in benzene (6 c.c.), and the whole refluxed for 1 hr. The resulting solution, from which needles of piperidine hydrobromide had separated, was extracted with dilute hydrochloric acid, and the extract basified. The oil separating was extracted with ether, the extract washed with water, dried, and the ether removed. The light brown oil was dissolved in alcohol and converted into a picrate. Recrystallised from alcohol, it formed yellow needles, m. p. 183° (Found: C, 55·0; H, 4·6%). This picrate was rather lighter in colour than that obtained as in (i), but a mixture of the two gave no depression of m. p. The oily base is readily soluble in the usual organic solvents.

6-*Piperidinomethylquinoline*.—This was prepared from *p*-aminobenzylpiperidine (12 g.) and *p*-nitrobenzylpiperidine (9 g.) by the method (i) above, and the oily base converted into the *picrate*, which crystallised from alcohol as small prisms, m. p. 195—196° (decomp.) (Found: C, 55·0; H, 4·7; N, 15·2. $C_{21}H_{21}O_7N_5$ requires C, 55·4; H, 4·6; N, 15·4%).

8-*Diethylaminomethylquinoline*.—8-Bromomethylquinoline (2 g.) and diethylamine (1 g.) were refluxed in benzene solution (10 c.c.) in presence of potassium carbonate (2 g.) for 2 hrs. The oily base was isolated as in the analogous experiment with piperidine, and converted by means of alcoholic hydrogen bromide into the *hydrobromide*, which separated from alcohol as long, colourless, rectangular plates, m. p. 238—239° (Found: Br, 42·7. $C_{14}H_{18}N_2,2HBr$ requires Br, 42·6%).

*Di*(*quinolyl*-8-*methyl*)*ethylamine*.—8-Bromomethylquinoline (2 g.), ethylamine (1·2 c.c. of 33% aqueous soln.), and alcohol (10 c.c.) were heated under reflux for 2 hrs., diluted with water, made strongly alkaline with sodium hydroxide, and the mixture extracted with ether. The extract was washed with water, dried, and the ether evaporated. The oily base obtained did not crystallise but was converted as before into a *hydrobromide*, which crystallised from alcohol as colourless plates, m. p. 202° (Found: Br, 42·0. $C_{22}H_{21}N_3,3HBr$ requires Br, 42·1%). This was only moderately soluble in water, in contrast to the preceding hydrobromide.

8-*Anilinomethylquinoline*.—8-Bromomethylquinoline (2 g.) was added gradually to aniline (2 g.). The mixture immediately deposited reddish-orange crystals which had formed a solid cake by the time the addition was complete. After 1 hr.'s heating on the steam-bath, the cake was dissolved in a little water, made alkaline with sodium carbonate, and steam-distilled. The dark brown oily residue, which solidified on standing overnight, crystallised from the minimum

of hot alcohol as light brown plates, m. p. 71—73° (Found: N, 11·7. $C_{16}H_{14}N_2$ requires N, 12·0%). This *base* is readily soluble in acetone, benzene, alcohol, chloroform, and ether, but only slightly soluble in dilute mineral acids. It forms a white crystalline hydrobromide.

N-*Di*(*quinolyl*-8-*methyl*)-p-*aminoacetanilide*.—8-Bromomethylquinoline (2·2 g.) was added to a concentrated solution of *p*-aminoacetanilide (1·5 g.) in alcohol, and the whole refluxed for 1½ hrs. After cooling, the light yellow crystalline hydrobromide was filtered off, dissolved in hot dilute hydrochloric acid, and basified; a rose-coloured precipitate was obtained, which, when recrystallised from alcohol, yielded ruby-coloured plates, m. p. 236—237° (Found: N, 13·0. $C_{28}H_{24}ON_4$ requires N, 13·0%). The *base* is sparingly soluble in dilute mineral acids, acetone, alcohol, and chloroform, but insoluble in benzene and ether.

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