Synthesis of Possible Antimalarials. Part III. Synthesis of* 1- *and* 3-iso*Quinolyl- and 2-Quinolyl-2′-quinuclidylmethanol.*

By G. R. Clemo and M. Hoggarth.

[Reprint Order No. 4669.]

The synthesis of 3-*iso*quinolyl-2′-quinuclidylmethanol (VII; R = 3-*iso*quinolyl) (cf. Part II *) has been completed, and 1-*iso*quinolyl- and 2-quinolyl-2′-quinuclidylmethanol have been prepared.

Ethyl *iso*quinoline-3-carboxylate (I; R = 3-*iso*quinolyl), previously obtained in 30% yield by the sulphur dehydrogenation of ethyl 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate (cf. Swan, *J.*, 1950, 1536), has been obtained in good yield by a modified procedure. Esterification of 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylic acid with sulphuric acid as catalyst gives a partially dehydrogenated ester $C_9H_8N{\cdot}CO_2Et$, and this was completely dehydrogenated to ethyl *iso*quinoline-3-carboxylate in 80—90% yield by sulphur in tetralin.

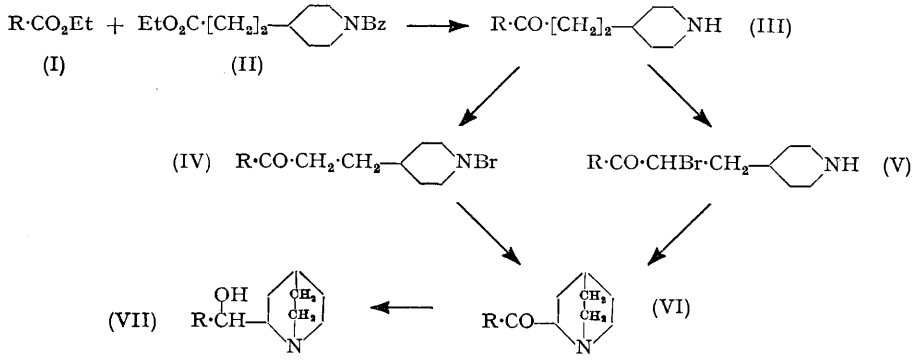
Ethyl quinaldate (I; R = 2-quinolyl) was prepared by the method of Campbell, Helbing, and Kerwin (*J. Amer. Chem. Soc.*, 1946, **68**, 1841), and ethyl *iso*quinoline-1-carboxylate by Padbury and Lindwall's modification of Reissert's method (*ibid.*, 1945, **67**, 1268).

The low yield in the preparation of 2-4′-piperidylethyl 3-*iso*quinolyl ketone (III; R = 3-*iso*quinolyl) has been ascribed to the presence of benzoic acid in the ester (II), but when this ester was prepared by Kleinman and Weinhouse's method (*J. Org. Chem.*, 1945,

* Part II, *J.*, 1951, 1406.

10, 562) and a modified procedure was used in the Claisen reaction the yield was increased from 10 to 30%.

3-*iso*Quinolyl-2′-quinuclidylmethanol (VII; R = 3-*iso*quinolyl) was obtained by catalytic reduction of 3-*iso*quinolyl 2-quinuclidyl ketone (VI; R = 3-*iso*quinolyl) over Adams catalyst in 0·5N-hydrochloric acid at room temperature and pressure. The product was a mixture of approximately equal amounts of two racemates, which were separated by chromatography on activated alumina and characterised as their dipicrates and dipicrolonates.



2-4′-Piperidylethyl 2-quinolyl ketone (III; R = 2-quinolyl) was obtained in good yield by condensation of ethyl quinaldate with (II) under Claisen conditions. Cyclisation was achieved *via* both the *N*-bromo- (IV) and the *C*-bromo-derivative (V; R = 2-quinolyl), and 2-quinolyl 2-quinuclidyl ketone (VI; R = 2-quinolyl) was thus obtained as a colourless crystalline hydrate. It formed a 2 : 4-dinitrophenylhydrazone hydrochloride and a monopicrolonate. Di-derivatives could not be obtained. Reduction to the alcohol and separation of the racemates were carried out as with 3-*iso*quinolyl-2′-quinuclidylmethanol. One of the racemates formed a monohydrochloride and a monopicrolonate, while the other gave a dihydrochloride and a dipicrolonate. [An examination of models offered no explanation of this apparent anomaly. The two compounds were shown to be structurally identical by oxidation of the alcohol group by the method of Woodward *et al.* (*J. Amer. Chem. Soc.*, 1945, **67**, 1428). In each case 2-quinolyl 2-quinuclidyl ketone (VI; R = 2-quinolyl) was obtained.]

Condensation of ethyl *iso*quinoline-1-carboxylate and (II) gave 2-4′-piperidylethyl 1-*iso*quinolyl ketone (III; R = 1-*iso*quinolyl) as a colourless crystalline hydrate. Attempted cyclisation via the *N*-bromo-derivative failed, the ketone being recovered, but it was effected *via* the *C*-bromo-derivative (V) which gave good yields of 1-*iso*quinolyl 2-quinuclidyl ketone (VI; R = 1-*iso*quinolyl) as a colourless highly crystalline solid. On reduction to the alcohol by the usual method, only one racemate was obtained—as a pale yellow uncrystallisable glass, which formed a colourless dihydrochloride.

Experimental

*Ethyl Dihydro*iso*quinoline-3-carboxylate.*—To crude, dry 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylic acid [prepared from phenylalanine (50 g.); cf. Part II] were added absolute alcohol (300 c.c.) and concentrated sulphuric acid (25 c.c.), and the mixture was refluxed for 5 hr. Alcohol was removed by distillation under reduced pressure, and the brown viscous residue was basified with sodium hydroxide solution (20%) and extracted with ether; the ethereal extracts were dried (Na_2SO_4), solvent was removed and the residue distilled, giving a colourless *dihydroester* (44 g.), b. p. 108—110°/0·5 mm., which solidified overnight and then had m. p. 39—40° (Found: C, 70·6; H, 6·4. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4%). The *picrate* (from alcohol) had m. p. 147—148° (Found: C, 50·0; H, 3·6. $C_{12}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 50·0; H, 3·6%). The ester (25 mg.) absorbed 3·09 c.c. of hydrogen over platinum at 18°/760 mm. (1·05 equivs.). The solution was filtered and concentrated, picric acid (12 mg.) in hot ethanol

was added, and the picrate which separated recrystallised from ethanol; it had m. p. 204° not depressed by the picrate of ethyl 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate.

Ethyl iso*Quinoline-3-carboxylate*.—Ethyl dihydro*iso*quinoline-3-carboxylate (10 g.) and sulphur (4·0 g.) in tetralin (30 c.c.) were heated at 160—165° (oil-bath) for 5 hr. The cooled solution was diluted with benzene and extracted with dilute hydrochloric acid (4 × 70 c.c.), the acid extracts were washed with ether and basified (solid sodium carbonate), and the liberated oil was extracted with ether, dried (Na_2SO_4), and distilled, giving ethyl *iso*quinoline-3-carboxylate as a pale yellow oil (8·4 g.), b. p. 144—145°/0·5 mm. The picrate (from alcohol) had m. p. 154—155°, not depressed by the picrate of the material prepared as described by Swan.

2-4′-*Piperidylethyl* 3-iso*Quinolyl Ketone* (III; R = 3-*iso*Quinolyl).—To a well-cooled suspension of potassium ethoxide (8·0 g., 0·095 mol.) in pure dry benzene was added a mixture of ethyl *iso*quinoline-3-carboxylate (16·0 g., 0·08 mol.) and (II) (23·1 g., 0·08 mol.), and the mixture, which immediately became red-brown, was refluxed for 2 hr. The solvent was then removed, and the tarry residue heated in the steam-bath under reduced pressure for a further 2 hr. After cooling, the residue was dissolved in 8N-hydrochloric acid (200 c.c.) and refluxed gently for 10 hr. On cooling, benzoic acid (9·5 g.) was precipitated and filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was basified (30% sodium hydroxide solution) and extracted with ether, the extract dried (Na_2SO_4), and the ether removed. The residue solidified on cooling, and recrystallised from light petroleum (b. p. 40—60°), giving the colourless ketone (6·4 g.), m. p. 93—94°.

3-iso*Quinolyl-2′-quinuclidylmethanol* (VII; R = 3-*iso*Quinolyl).—The keto-base (VI; R = 3-*iso*quinolyl) (0·98 g.) in hydrochloric acid (5%; 40 c.c.) was hydrogenated at room temperature and pressure over Adams catalyst (0·1 g.). The reduction was stopped when one equiv. of hydrogen had been absorbed (about 2 hr.). The filtrate from the catalyst was basified (6% aqueous sodium hydroxide) and exhaustively extracted with ether. After drying of the extract (Na_2SO_4), the ether was removed and the residual pale yellow glass (0·95 g.) was dissolved in chloroform–benzene (1 : 1) and applied to a column of alumina (100 g.; activated at 110° for 2 hr.). The two rather diffuse bands which developed were eluted with chloroform–methanol (10 : 1). The first band yielded a pale yellow *racemate* " *A* " (0·264 g.) which slowly solidified and was recrystallised from light petroleum (b. p. 60—80°) (m. p. 84°, after sintering at 58°) (Found: C, 71·6; H, 7·8. $C_{17}H_{20}ON_2,H_2O$ requires C, 71·3; H, 7·7%). The second band yielded a similar *racemate* " *B* " (0·270 g.) which did not crystallise (Found: C, 76·2; H, 7·7. $C_{17}H_{20}ON_2$ requires C, 76·1; H, 7·5%). " A " gave a *dipicrate*, m. p. 104—105° after sintering at 99° (Found: C, 47·3; H, 4·4. $C_{17}H_{20}ON_2,2C_6H_3O_7N_3,CH_3{\cdot}OH$ requires C, 47·4; H, 4·0%), and " B " a *dipicrate*, m. p. 106—109° after sintering at 99° (Found: C, 47·1; H, 4·3%), their mixed m. p. being 96—99°. The dipicrolonate of " A " had m. p. 224°, and that of " B " had m. p. 215°; the mixed m. p. was 208°.

2-4′-*Piperidylethyl* 2-*Quinolyl Ketone* (III; R = 2-Quinolyl).—Ethyl quinaldate and (II) were condensed as described above, giving a pale yellow *ketone* (71·5%) (Found: C, 76·1; H, 7·6. $C_{17}H_{20}ON_2$ requires C, 76·1; H, 7·5%), which solidified after several days in the refrigerator. Recrystallised from ether, it had m. p. 105—107° (Found: C, 71·3; H, 7·6. $C_{17}H_{20}ON_2,H_2O$ requires C, 71·3; H, 7·7%). The colourless *hydrochloride* (from methanol–ether) had m. p. 229° (Found: C, 67·0; H, 6·9. $C_{17}H_{20}ON_2,HCl$ requires C, 67·0; H, 6·9%). The 2 : 4-*dinitrophenylhydrazone dihydrochloride* (from ethanol) was orange and had m. p. 267—268° (Found: C, 52·7; H, 5·3. $C_{23}H_{24}O_4N_6,2HCl$ requires C, 53·0; H, 5·0%).

2-(1-*Bromo-4-piperidyl*)*ethyl* 2-*Quinolyl Ketone* (IV; R = 2-Quinolyl).—The above ketone (25 g.) was dissolved in hydrochloric acid (108 c.c.; 1 : 10), and ether (650 c.c.) was added. To this mixture, vigorously stirred, was added dropwise a solution of bromine (13·8 g.) in sodium hydroxide (6% solution; 175 g.), and the mixture was stirred for a further 15 min. The aqueous layer was extracted with ether. The combined ethereal layers were dried (Na_2SO_4), and concentrated and on cooling the *bromo*-compound separated as a cream-coloured solid (14·5 g.), m. p. 234—236° (Found: C, 58·6; H, 5·4; Br, 22·9. $C_{17}H_{19}ON_2Br$ requires C, 58·8; H, 5·5; Br, 23·2%).

2-*Quinolyl* 2-*Quinuclidyl Ketone* (VI; R = 2-Quinolyl).—(*a*) A boiling solution of the above *N*-bromo-ketone (8·7 g.) in ethanol (660 c.c.) was added to a cold solution of sodium ethoxide (from 1·57 g. of sodium and 660 c.c. of ethanol), and the mixture was refluxed on a water-bath for ½ hr., cooled, and made slightly acidic (dilute hydrochloric acid). The alcohol was removed under reduced pressure and the residue basified (20% aqueous sodium hydroxide) and extracted with ether. The extract was dried (Na_2SO_4) and on removal of the ether the *keto-base* solidified and was recrystallised from light petroleum (b. p. 40—60°) (yield 5·1 g.; m. p. 125°)

(Found: C, 71·9; H, 7·4. $C_{17}H_{18}ON_2,H_2O$ requires C, 71·8; H, 7·0%). The orange 2 : 4-*dinitrophenylhydrazone hydrochloride*, recrystallised from alcohol, had m. p. 290° (Found: C, 57·3; H, 5·2. $C_{23}H_{22}O_4N_6,HCl$ requires C, 57·2; H, 4·8%). The *monopicrolonate*, recrystallised from a solution of picrolonic acid in ethanol, had m. p. 240—241° (Found: C, 60·8; H, 4·7. $C_{17}H_{18}ON_2,C_{10}H_8O_5N_4$ requires C, 61·1; H, 4·9%).

(*b*) The keto-base (III; R = 2-quinolyl) (2·5 g.) was heated in hydrobromic acid (40%; 12·5 c.c.) at 70°, while a solution of bromine (1·65 g.) in hydrobromic acid (40%; 18·5 c.c.) was added dropwise. The resulting bright yellow solution was evaporated in a vacuum at 50—60° and the bright yellow crystalline residue dissolved in a little water and vigorously stirred with ether in an ice-bath, while sodium carbonate solution (65 c.c.; 5%) was added dropwise during ½ hr., followed by sodium hydroxide (18 c.c.; 5%). The mixture was allowed to come to room temperature with continued stirring, the ethereal layer was separated, and the aqueous layer extracted with ether. The combined extracts were dried (K_2CO_3) and the ether was removed, leaving a pale yellow oil which gradually solidified and, recrystallised from moist ether, had m. p. 125° (1·4 g.).

2-*Quinolyl*-2′-*quinuclidylmethanol* (VII; R = 2-Quinolyl).—This was obtained by catalytic reduction of the above keto-base as described for the 3-*iso*quinolyl isomer. The *product* was a pale yellow uncrystallisable oil (Found: C, 76·2; H, 7·6. $C_{17}H_{20}ON_2$ requires C, 76·1; H, 7·5%). The racemates were separated by chromatography on alumina and were non-crystalline. The hydrochlorides, recrystallised from hydrochloric acid (50%), were colourless. The first, "A," was a *monohydrochloride*, m. p. 229—230° (Found: C, 66·7; H, 7·1. $C_{17}H_{20}ON_2,HCl$ requires C, 67·0; H, 6·9%). The second, "B," was a *dihydrochloride*, m. p. 208—209° (Found: C, 60·2; H, 7·1. $C_{17}H_{20}ON_2,2HCl$ requires C, 59·8; H, 6·5%). The yellow *monopicrolonate* of "A" had m. p. 237—238° (Found: C, 61·0; H, 5·8. $C_{17}H_{20}ON_2,C_{10}H_8O_5N_4$ requires C, 60·9; H, 5·3%), recovered unchanged after recrystallisation from alcohol containing picrolonic acid. The yellow *dipicrolonate* of "B" had m. p. 214—215° (Found: C, 55·4; H, 5·2. $C_{17}H_{20}ON_2,2C_{10}H_8O_5N_4,C_2H_5{\cdot}OH$ requires C, 55·6; H, 5·0%).

To pure, dry potassium butoxide (90 mg.), prepared as described by Woodward *et al.* (*loc. cit.*), was added pure, dry benzophenone (300 mg.) and the alcohol "A" (or "B") (100 mg.) in benzene (5 c.c.). The mixture was refluxed under nitrogen for 18 hr., cooled, and extracted with dilute hydrochloric acid, and the acid extracts were washed with ether, basified, and extracted with ether. The ethereal extracts were dried (Na_2SO_4) and the ether was removed, leaving an oil which crystallised from light petroleum (b. p. 40—60°). In each case, 2-quinolyl 2-quinuclidyl ketone (60 mg.) was obtained, having m. p. and mixed m. p. 105°.

2-4′-*Piperidylethyl* 1-iso*Quinolyl Ketone* (III; R = 1-*iso*Quinolyl).—Ethyl *iso*quinoline-1-carboxylate (17·3 g., 0·086 mol.) and (II) (27·5 g., 0·095 mole) were condensed in the usual way, with dry potassium ethoxide (9·0 g., 0·107 mol.), giving the keto-base as a pale yellow oil, which readily supercooled. By allowing a solution in moist ether to remain for a week in the refrigerator, a small amount of *hydrate*, m. p. 113—114°, was obtained (Found: C, 70·8; H, 7·5. $C_{17}H_{20}ON_2,H_2O$ requires C, 71·3; H, 7·7%). The *dipicrate* crystallised in yellow needles (from alcohol), m. p. 161° (Found: C, 48·6; H, 4·1. $C_{17}H_{20}ON_2,2C_6H_3O_7N_3,C_2H_5{\cdot}OH$ requires C, 48·2; H, 4·15%). The orange *phenylhydrazone dipicrate*, recrystallised from alcohol, had m. p. 199° (Found: C. 51·9; H, 4·3. $C_{23}H_{26}N_4,2C_6H_3O_7N_3$ requires C, 51·7; H, 4·0%).

2-(1-*Bromo*-4-*piperidyl*)*ethyl* 1-*isoQuinolyl Ketone* (IV; R = 1-*iso*Quinolyl).—This N-*bromo-ketone* was prepared by the usual method and obtained as a tan crystalline solid (53%), m. p. 195°, darkening at 185° (Found: C, 58·6; H, 5·9; Br, 23·5. $C_{17}H_{19}ON_2Br$ requires C, 58·8; H, 5·5; Br, 23·1%).

1-iso*Quinolyl* 2-*quinuclidyl ketone* (VI; R = 1-*iso*quinolyl), obtained (73%) *via* the *C*-bromo-derivative by the method described for the 2-quinolyl isomer, was colourless and had m. p. 134° (Found: C, 76·7; H, 6·9. $C_{17}H_{18}ON_2$ requires C, 76·7; H, 6·7%). The yellow *picrolonate* (from alcohol) had m. p. 188—189° (decomp.) (Found: C, 61·1; H, 5·2. $C_{17}H_{18}ON_2,C_{10}H_8O_5N_4$ requires C, 61·2; H, 4·9%). The yellow *picrate* (from alcohol) had m. p. 150° (Found: C, 55·5; H, 4·5. $C_{17}H_{18}ON_2,C_6H_3O_7N_3$ requires C, 55·7; H, 4·2%).

1-iso*Quinolyl*-2′-*quinuclidylmethanol* (VII; R = 1-*iso*Quinolyl).—The above keto-base (0·91 g.) in ethanol (50 c.c.) was shaken with hydrogen at room temperature and pressure over platinum catalyst (0·2 g.) until one equiv. of hydrogen had been absorbed (1 hr.). The catalyst was filtered off and the solution made slightly acidic with dilute hydrochloric acid. The alcohol was removed in a vacuum, the residue basified and extracted with ether, the extract dried (Na_2SO_4), and the ether removed, leaving a pale yellow glass. This was chromatographed in benzene on alumina. A small amount of the keto-base was recovered, no further separation

being observed. The *dihydrochloride*, recrystallised from methanol–ether, was colourless, having m. p. 195° (sinters at 185°) (Found : C, 59·9; H, 6·8. $C_{17}H_{20}ON_2,2HCl$ requires C, 59·8; H, 6·5%). The yellow *picrate* (from alcohol) had m. p. 194—195° (Found : C, 47·8; H, 3·5. $C_{17}H_{20}ON_2,2C_6H_3O_7N_3$ requires C, 47·9; H, 3·6%).

One of us (M. H.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

KING'S COLLEGE, NEWCASTLE-ON-TYNE. [*Received, September 22nd*, 1953.]