634. *The Synthesis of Some Dialkylamino-2-quinolones.*

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The synthesis of 3-dialkylamino- and 3-dialkylamino-4-hydroxy-2-quinolones is described.

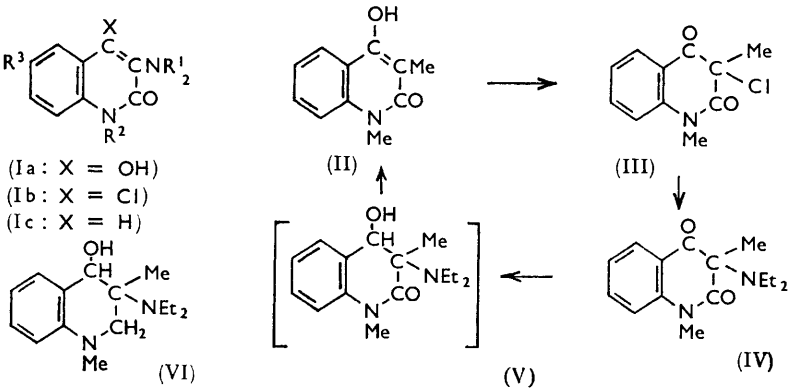
Waldmann [1] showed that *N*-methylaniline reacts with diethyl malonate to give 4-hydroxy-1-methyl-2-quinolone. Using the appropriate monoalkylmalonates, Bowman, Campbell, and Tanner [2] prepared 1,3-dialkyl-4-hydroxy-2-quinolones by a similar route.

This method has been extended to the reaction of *N*-monoalkylanilines with diethyl dialkylaminomalonates, which give 1-alkyl-3-dialkylamino-4-hydroxy-2-quinolones (Ia). The action of phosphorus oxychloride on the 4-hydroxy-compound (Ia) afforded the corresponding 1-alkyl-4-chloro-3-dialkylamino-2-quinolone (Ib), the hydrochloride of which could be hydrogenated to give the 1-alkyl-3-dialkylamino-2-quinolone (Ic). In many cases, the hydrochloride of the chloro-compound (Ib) was difficult to purify but was satisfactory for conversion into (Ic).

A study was made of the effect of reducing conditions on a 3-dialkylamino-2,4-dioxoquinoline derivative in which an alkyl group had been introduced to prevent the formation of a double bond in the 3,4-position. Condensation of *N*-methylaniline with diethyl methylmalonate gave 4-hydroxy-1,3-dimethyl-2-quinolone (II) which was converted into the chloro-derivative (III) with sulphuryl chloride; subsequent reaction with diethylamine furnished 3-diethylamino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxoquinoline (IV), hydrogenation of which, in the presence of palladised charcoal, resulted in an uptake of 1 mole of hydrogen per mole of quinoline and yielded the original 2-quinolone (II), the reaction probably proceeding through the hydroxy-intermediate (V). A similar result was achieved with phosphorus and hydriodic acid reduction.

The action of lithium aluminium hydride on the 3-diethylamino-derivative (IV) gave a

[1] Waldmann, *J. prakt. Chem.*, 1937, **147**, 321.
[2] Bowman, Campbell, and Tanner, *J.*, 1959, 444.



compound which almost certainly had the structure (VI) and which gave a small amount of 1,2,3,4-tetrahydro-1,3-dimethylquinoline on hydrogenation.

Experimental

Diethyl Dialkylaminomalonates.—Diethyl dimethylaminomalonate was prepared by the method of Jones and Wilson.[3] Diethyl diethylaminomalonate, prepared by the same method, had b. p. 130—134°/16 mm. (lit.,[4] 95—100°/4 mm.).

1-*Alkyl*-3-*dialkylamino*-4-*hydroxy*-2-*quinolones* (Ia).—Interaction of equimolecular quantities of the appropriate *N*-alkylaniline and the diethyl dialkylaminomalonate in a manner similar to that used by Bowman *et al.*[2] afforded the *products* (Ia) (Table 1).

Table 1.

1-Alkyl-3-dialkylamino-4-hydroxy-2-quinolones (Ia).

						Found (%)			Required (%)		
R^1	R^2	R^3	M. p.	Form	Formula	C	H	N	C	H	N
Me	Me	H	202—203° *	Prisms	$C_{12}H_{14}N_2O_2$	65·5	6·5	12·6	66·0	6·5	12·8
Me	Me	MeO	210 *	Needles	$C_{13}H_{16}N_2O_3$	63·1	6·6	11·3	62·9	6·5	11·3
Me	Ph	H	227 *	Prisms	$C_{17}H_{16}N_2O_2$	72·2	5·8	9·7	72·8	5·75	10·0
Me	Et	H	184—185 †	Prisms	$C_{13}H_{16}N_2O_2$	67·6	7·0	12·0	67·2	6·9	12·1
Me	Me	Me	221—223 ‡	Needles	$C_{13}H_{16}N_2O_2$	67·8	7·1	11·7	67·2	6·9	12·1
Et	Me	Me	197—198 ‡	Needles	$C_{15}H_{20}N_2O_2$	69·55	7·75	10·5	69·2	7·7	10·8
Me	Et	Me	163—165 ‡	Prisms	$C_{14}H_{18}N_2O_2$	68·0	7·45	11·2	68·3	7·4	11·4
Et	Et	Me	188—190 ‡	Needles	$C_{16}H_{22}N_2O_2$	70·5	7·95	10·2	70·0	8·1	10·2
Me	Pr^n	H	196—198 †	Needles	$C_{14}H_{18}H_2O_2$	68·6	7·7	11·6	68·3	7·4	11·4
Me	$PhCH_2$	H	184—186 †	Prisms	$C_{18}H_{18}N_2O_2$	73·1	5·9	9·6	73·45	6·2	9·5

* From ethyl acetate. † From ethanol. ‡ From acetone.

1-*Alkyl*-4-*chloro*-3-*dialkylamino*-2-*quinolone Hydrochlorides* (Ib).—The appropriate 4-hydroxy-compound (Ia) was refluxed with phosphorus oxychloride (*ca.* 6-fold excess on a molar basis) for 1 hr. The cooled mixture was poured on to crushed ice, basified with 5N-sodium hydroxide, and extracted with ether. Addition of ethereal hydrogen chloride to the dried ether extracts afforded the hydrochloride. In most cases, an oil was obtained which did not crystallise and was used directly to prepare the 1-alkyl-3-dialkylamino-2-quinolone. Hydrochlorides which crystallised were as follows: 4-*chloro*-3-*dimethylamino*-1-*methyl*-2-*quinolone hydrochloride*, pale yellow needles (from ethanol–ether), m. p. 171—172° (Found: C, 50·6; H, 5·7; Cl, 25·25; N, 9·6. $C_{12}H_{14}Cl_2N_2O,\frac{1}{2}H_2O$ requires C, 51·1; H, 5·4; Cl, 25·1; N, 9·9%); 4-*chloro*-3-*dimethylamino*-6-*methoxy*-1-*methyl*-2-*quinolone hydrochloride*, m. p. 171—173° (from ethanol–ether) (Found: C, 50·2; H, 5·9; N, 8·9. $C_{13}H_{16}Cl_2N_2O_2,\frac{1}{2}H_2O$ requires C, 50·0; H, 5·5; N, 9·0%); 4-*chloro*-3-*dimethylamino*-1-*n*-*propyl*-2-*quinolone hydrochloride*, buff prisms, m. p. 160—161° (from acetone) (Found: C, 55·6; H, 5·7; N, 9·7. $C_{14}H_{18}Cl_2N_2O$ requires C, 55·8; H, 6·0; N, 9·3%).

1-*Alkyl*-3-*dialkylamino*-2-*quinolone Hydrochlorides* (Ia).—A mixture of a 5% ethanolic

[3] Jones and Wilson, *J.*, 1949, 547.
[4] Goldhahn, *Acta Chim. Acad. Sci. Hung.*, 1959, **18**, 395.

solution of the 4-chloro-2-quinolone (Ib) hydrochloride and half the volume of a 5% aqueous solution of sodium acetate was hydrogenated in the presence of 10% palladised charcoal. The catalyst was filtered off, and the residue, after evaporation of the filtrate, dissolved in 2N-sodium hydroxide and extracted with ether. The *hydrochlorides* (Table 2), obtained by addition of ethereal hydrogen chloride to the dried ether extracts, normally crystallised as prisms.

TABLE 2.

1-Alkyl-3-dialkylamino-2-quinolone hydrochlorides (Ic).

				Re-cryst.		Found (%)			Required (%)		
R^1	R^2	R^3	M. p.	from *	Formula	C	H	N	C	N	N
Me	Me	H	212—213°	A	$C_{12}H_{15}ClN_2O$	60·3	6·4	11·4	60·4	6·3	11·7
Me	Me	MeO	203—205	B	$C_{13}H_{17}ClN_2O_2,2\frac{1}{2}H_2O$	49·9	7·0	8·9	49·8	7·1	8·9
Me	Et	H	172—173	A	$C_{13}H_{17}ClN_2O,\frac{1}{2}H_2O$	59·9	6·5	10·7	59·7	6·9	10·7
Me	Me	Me	167—168	B	$C_{13}H_{17}ClN_2O,3H_2O$	50·7	7·3	9·1	50·9	7·6	9·1
Et	Me	Me	96—99	C	$C_{15}H_{21}ClN_2O,H_2O$	60·7	8·0	9·2	60·3	7·8	9·4
Me	Et	Me	167—168	A	$C_{14}H_{19}ClN_2O$	63·0	7·1	10·2	63·0	7·2	10·5
Et	Et	Me	73—77	C	$C_{16}H_{23}ClN_2O,\frac{1}{2}H_2O$	63·3	8·4	9·45	63·2	8·0	9·2
Me	Pr^n	H	192—193	A	$C_{14}H_{19}ClN_2O$	63·4	7·1	10·6	63·0	7·2	10·5

* A, Ethanol–ether; B, ethanol; C, acetone.

4-Hydroxy-1,3-dimethyl-2-quinolone (II).—Reaction of *N*-methylaniline (20 g.) with diethyl methylmalonate [5] (39 g.) in the manner described by Bowman *et al.*[2] afforded the *product* (35 g.) as needles, m. p. 217—218° (from methyl ethyl ketone) (Found: C, 69·6; H, 5·8; N, 7·3. $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·9; N, 7·4%).

3-Chloro-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxoquinoline (III).—4-Hydroxy-1,3-dimethyl-2-quinolone (10 g.) and sulphuryl chloride (7·5 ml.) in benzene (50 ml.) were refluxed for 1½ hr. The mixture was filtered hot and the cooled filtrate washed with 10% aqueous sodium carbonate solution (2 × 100 ml.), water, dried (Na_2SO_4), and evaporated *in vacuo*. The *chloro-compound* (8 g.) was obtained as yellow needles from light petroleum (b. p. 60—80°), m. p. 97—98° (Found: C, 58·6; H, 4·5; Cl, 16·5; N, 6·3. $C_{11}H_{10}ClNO_2$ requires C, 59·1; H, 4·5; Cl, 15·85; N, 6·3%).

3-Bromo-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxoquinoline.—Bromine (4 g.) was added dropwise with stirring to 4-hydroxy-1,3-dimethyl-2-quinolone (4 g.) in benzene (45 ml.). The mixture was strongly illuminated throughout the reaction. The solution was set aside overnight, treated with 10% aqueous sodium carbonate solution (3 × 100 ml.), washed with water, dried (Na_2SO_4), and evaporated *in vacuo*, to give the *3-bromo-compound* (4 g.) as pale yellow prisms, m. p. 87—90° (from propan-2-ol) (Found: C, 47·4; H, 3·6; N, 5·2. $C_{11}H_{10}BrNO_2,\frac{1}{2}H_2O$ requires C, 47·7; H, 4·0; N, 5·05%).

3-Diethylamino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxoquinoline (IV).—(a) *Preparation.* 3-Chloro-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxoquinoline (10 g.) and diethylamine (49 ml.) in ethanol (300 ml.) were refluxed for 26 hr. Ethanol was removed by distillation; the residual oil in water (200 ml.) was extracted with ether (2 × 150 ml.) and back into 2N-hydrochloric acid (2 × 150 ml.). The aqueous solution was basified, and extracted with ether, and the ether extracts were washed with water, dried (Na_2SO_4), and evaporated. The *product* (5·5 g.) formed prisms, m. p. 79—80° [from light petroleum (b. p. 60—80°)] (Found: C, 69·5; H, 8·1; N, 10·9. $C_{15}H_{20}N_2O_2$ requires C, 69·2; H, 7·7; N, 10·8%). The product was obtained similarly from the 3-bromo-compound.

(b) *Hydrogenation.* The quinoline (2 g.) in ethanol (50 ml.) was hydrogenated in the presence of 10% palladised charcoal (1 g.). Removal of the catalyst by filtration and evaporation of the filtrate yielded 4-hydroxy-1,3-dimethyl-2-quinolone (1·3 g.) as needles, m. p. and mixed m. p. 214—217°. A similar hydrogenation in the presence of one equivalent of hydrogen chloride (in ethanol) gave the same product.

(c) *Reduction with phosphorus and hydriodic acid.* Red phosphorus (2·5 g.) and hydriodic acid (66 ml.; 55%) were boiled together for 30 min., allowed to cool slightly, and the quinoline compound (3·3 g.) added. The mixture was refluxed for 6 hr., filtered while hot, and the crystals which separated from the filtrate were dried *in vacuo* (KOH). The product (3 g.) was washed with water and ether, and formed needles, m. p. 216—218° (from methyl ethyl ketone); there was no depression of m. p. when mixed with 4-hydroxy-1,3-dimethyl-2-quinolone.

[5] Cox and McElvain, *Org. Synth.*, 1943, Coll. Vol. II, 279.

(d) *Reduction with lithium aluminium hydride.* The quinoline compound (5 g.) in benzene (100 ml.) was added dropwise to a refluxing suspension of lithium aluminium hydride (2·5 g.) in ether (100 ml.). The mixture was refluxed for 5 hr., and, after cooling, wet ether (50 ml.) was added, followed by water (30 ml.) and 5N-sodium hydroxide (10 ml.). The mixture was refluxed for 2 hr., filtered, the residue washed with ether and hot ethyl acetate, and the filtrate washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. Recrystallisation of the residue (4 g.) from light petroleum (b. p. 60—80°) gave small rods (2·1 g.), m. p. 110—111°, which were almost certainly 3-*diethylamino*-1,2,3,4-*tetrahydro*-4-*hydroxy*-1,3-*dimethylquinoline* (VI) (Found: C, 72·9; H, 9·6; N, 11·4. $C_{15}H_{24}N_2O$ requires C, 72·5; H, 9·7; N, 11·3%), $\nu_{max.}$ (Nujol) 3350 $cm.^{-1}$ (OH). A sample of the product was dissolved in anhydrous ether and ethereal hydrogen chloride was added dropwise. The white hygroscopic microcrystalline *monohydrochloride* had m. p. 104—107° (Found: C, 62·4; H, 8·15; Cl, 12·7; N, 9·7. $C_{15}H_{25}ClN_2O$ requires C, 63·25; H, 8·85; Cl, 12·45; N, 9·8%).

Hydrogenation of 3-*Diethylamino*-1,2,3,4-*tetrahydro*-4-*hydroxy*-1,3-*dimethylquinoline.*—The hydroxy-compound (1 g.) in absolute ethanol (50 ml.) containing hydrogen chloride (0·56 g.) was hydrogenated at *ca.* 37° in the presence of 10% palladised charcoal (1 g.). (The uptake of hydrogen corresponded to 2 moles per mole of quinoline.) The catalyst was filtered off and the filtrate evaporated *in vacuo*. The residue was dissolved in 2N-sodium hydroxide and extracted with ether. After extraction of the base into 2N-hydrochloric acid, the aqueous solution was basified and extracted with ether. The ether extracts were washed, dried, and evaporated, to give an oil (0·5 g.). The oil gave a hygroscopic hydrochloride, but afforded prisms of 1,2,3,4-tetrahydro-1,3-dimethylquinoline picrate, m. p. 126—127° (lit.,[6] 131°) (Found: C, 52·4; H, 4·4; N, 14·2. Calc. for $C_{17}H_{18}N_4O_7$: C, 52·3; H, 4·65; N, 14·35%).

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[6] Braun, Seemann, and Schultheiss, *Ber.*, 1922, **55**, 3803.