597. *Reactions of 2,2-Dialkyl-1,2-dihydroquinolines. Part II.*[1] *Bromo-derivatives of 1,2-Dihydro-2,2,4-trimethylquinoline.*

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Five successive bromination products have been obtained from 1-acetyl-1,2-dihydro-2,2,4-trimethylquinoline and, in lower yield, from 1,2-dihydro-2,2,4-trimethylquinoline hydrobromide. These have been shown to be 4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline hydrobromide; 6-bromo-4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline hydrobromide; 3,6-dibromo-4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline hydrobromide; 3,6,8-tribromo-4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline and 3,6,8-tribromo-4-dibromomethyl-1,2-dihydro-2,2-dimethylquinoline. These structures have been confirmed by measurement of nuclear magnetic resonance spectra. The di- and tri-bromo-compounds are fungistatic at low concentrations.

The polychlorination of 1-acetyl-1,2-dihydro-2,2,4-trimethylquinoline takes a different course.

In a search [1] for biologically-active derivatives of the readily-accessible 1,2-dihydro-2,2,4-trimethylquinoline, the introduction of halogen into the molecule was an obvious step. Johnson and Ridd [2] have studied the bromination of 1-cyano-1,2-dihydro-2-hydroxyquinoline in aqueous media. Under these conditions, the first stage involves addition of bromine to the 3-4-double bond. In acidic media, the tetrahydroquinoline so formed undergoes elimination to give 3-bromoquinoline. In the present work on the bromination of the *N*-acetyl derivative and hydrobromide of 1,2-dihydro-2,2,4-trimethylquinoline in chloroform, no product of addition of bromine to the 3,4-double bond could be isolated and

[1] Part I, Brown, *J.*, 1964, 3012.
[2] Johnson and Ridd, *J.*, 1962, 291.

introduction of bromine at the 3-position did not occur, in the main reaction sequence at least, until the tribromination stage.

In the original experiments the *N*-acetyl compound was treated with one molecular proportion of bromine at room temperature * in chloroform containing about 1% of ethanol as a stabiliser. Removal of the solvent at low temperature gave a solid which could be freed from a green resinous by-product by washing it with acetone. (*Caution:* Most bromination products of 2,2,4-trialkyl-1,2-dihydroquinolines are extremely irritant to the skin. Use of acetone in isolation procedure leads to the formation of lachrymatory bromoacetone). Recrystallisation of the solid was difficult but crystals, giving analytical data for $C_{12}H_{15}Br_2N$, were obtained from ethanol. (Prolonged boiling in this solvent produced a violet resin.) This formula indicates replacement of the acetyl group by hydrogen with addition of two atoms of bromine. When the compound was shaken with cold water, an immediate liberation of strong acid occurred, but a large part of the substance could be recovered unchanged from its solution in cold aqueous ethanol after storage overnight. Hence the compound appeared to be the hydrobromide of a weakly basic monobromo-substitution product of 1,2-dihydro-2,2,4-trimethylquinoline, rather than the isomeric 3,4-dibromo-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline. The ethanol in the chloroform was apparently participating in the deacetylation, for the product was obtained in high yield (79% of material of 95% purity). Partial deacetylation occurred in alcohol-free chloroform, and, as the mixed product was inconvenient to handle, the stabilised solvent was used in all subsequent work. The same bromo-compound was later obtained in lower yield from 1,2-dihydro-2,2,4-trimethylquinoline hydrobromide in chloroform solution and also from the free base, although in the last case, more resin was formed.

Attempts to isolate a crystalline free base from the monobromination product were unsuccessful. Basification of a freshly prepared, alcoholic solution with aqueous alkali gave an oil, which rapidly resinified, especially on gentle warming. In distinction to 1,2-dihydro-2,2,4-trimethylquinoline,[1] treatment of a boiling aqueous alcoholic solution of the monobromination product with dicyandiamide did not generate isobutene. This indicated that the monobromination product had not been produced by entry of bromine into the aromatic ring, since this type of substitution does not interfere with the dicyandiamide reaction. The infrared spectrum confirmed the absence of substituents in the aromatic ring and was consistent with the presence of a quaternary nitrogen atom as in a hydrobromide.

Repetition of the bromination with two molecular proportions of bromine gave, after evaporation of the solvent, a resin which began to crystallise after some weeks. After removal of adherent resin with acetone, the crude solid was recrystallised from ethanol. Needles, giving analytical data for dibromo-1,2-dihydro-2,2,4-trimethylquinoline hydrobromide, were obtained. The yield of the crude solid was 64% and a comparison of its infrared spectrum with that of the pure compound indicated that it contained about 85% of the latter. The infrared spectrum indicated that bromine had now been introduced into the aromatic ring, probably at the 6-position. An attempt to isolate the free base gave oily material which resinified in a similar way to the base from the monobromo-compound.

Bromination with large amounts of bromine was now studied. Four molecular proportions were rapidly absorbed at 0—10° and, on evaporation of the solvent, ready crystallisation of a yellow product occurred. Recrystallisation of this gave a pure compound which analysed as tetrabromo-1,2-dihydro-2,2,4-trimethylquinoline and was the free base and not the hydrobromide salt, in spite of the hydrogen bromide dissolved in the non-aqueous mixture. The yield of crude compound on the basis of this formula was 87%, and of pure compound 68%. The infrared spectrum confirmed the presence of a free

* Cooling to 0—10° gives a purer product. See Experimental section.

NH group and indicated that a second substituent had entered the benzene ring, probably *meta* to the substituent present in the dibromination product.

Bromination of 1-acetyl-1,2-dihydro-2,2,4-trimethylquinoline with six molecular proportions of bromine gave a mixture containing a large excess of bromine. The main product was the tetrabromo-compound, but a second compound containing an extra bromine substituent was obtained in about 20% yield. Increasing the reaction time and amount of bromine did not raise this yield, but the compound was eventually obtained in 86% yield by treating a chloroform solution of the tetrabromo-compound with a very large excess of bromine.

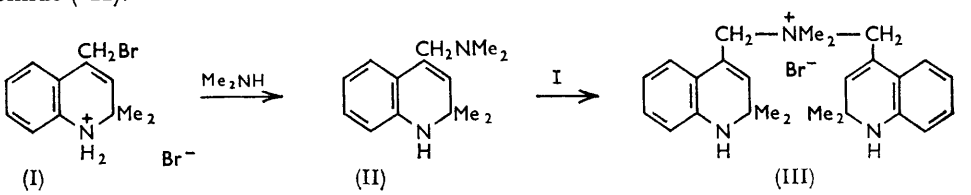
Finally, a tribromo-1,2-dihydro-2,2,4-trimethylquinoline hydrobromide was isolated from the bromination with three molecular proportions of bromine. Admixed tetrabromo-compound was removed with hot acetone, giving a crude product in 63% yield, from which the pure tribromo-hydrobromide was obtained by recrystallisation. The infrared spectra of the crude and pure materials indicated that the former contained about 60% of the latter. Gradual addition of alkali to an alcoholic solution of pure hydrobromide gave the corresponding free base in almost quantitative yield. Rapid addition of alkali gave a low yield of base, together with much resin, and the free base also resinified when boiled for several hours in toluene. Infrared spectra of the tribromo-base and hydrobromide indicated that no additional substitution of the benzene ring took place on passing from dibromo- to tribromo-compound. In later experiments, the di-, tri-, and tetrabromo-compounds were prepared by bromination of 1,2-dihydro-2,2,4-trimethylquinoline hydrobromide, but the yields obtained were somewhat lower than those from the *N*-acetyl derivative.

Initial chemical work on the structure of this series of compounds was concentrated on the tetrabromo-compound since it was stable and readily accessible. Oxidative degradation was contemplated and the preparation of the *N*-acetyl compound was attempted. The material was unchanged after prolonged boiling with acetic anhydride. This suggested that there was considerable steric hindrance around the NH group, a deduction supported by the failure to isolate a hydrobromide. Aqueous suspensions of the tetrabromo-compound developed acidity slowly. This suggested that the tetrabromo-compound contained labile bromine, and the presence of one such atom was demonstrated by the rapid formation at 50° of a crystalline tribromo-dimethylamino-1,2-dihydro-2,2,4-trimethylquinoline on treatment of an ethanolic solution with aqueous dimethylamine, and by the formation of a tribromo-ethoxy-derivative on boiling an 85% ethanolic solution with sodium hydroxide. (Reactions with other nucleophiles will be described later.) The most likely place for the labile bromine seemed to be an exocyclic methyl group, probably the 4-methyl-group, since this would be an example of allylic bromination and since bromination of only one of the *gem*-dimethyl groups seemed unlikely.

On conducting the dimethylamine reaction with crude tetrabromo-compound, the separation of a small amount of a high-melting yellow compound was observed towards the end. This proved to be pure pentabromo-compound, which had evidently been present as contaminant. Further study showed that the pentabromo-compound was surprisingly resistant to dimethylamine. The best explanation seemed to be that pentabromination involved the attachment of a second bromine atom to the carbon atom carrying the labile bromine and that the resultant dibromomethyl group was resistant to the attack of the dimethylamine. (There is surprisingly little recorded about the reactions of *gem*-dihalides with nucleophiles.) If this were the case, aldehyde formation might be expected in alkaline hydrolysis of the pentabromo-compound. In fact, under the same conditions as those in which the tetrabromo-compound yielded a tribromodihydromonoethoxyquinoline, the pentabromo-compound yielded a compound which readily gave a 2,4-dinitrophenylhydrazone. The microanalytical results, however, showed clearly that only two bromine atoms per molecule were present; for, besides the two removed by hydrolysis, a third had been removed reductively and replaced by hydrogen. (This is attributed to the reducing

action of the sodium hydroxide–ethanol system.[3] An attempt to conduct the reaction in methanol gave only resin.) It seemed clear that this reductive removal of a bromine substituent was taking place under the influence of the generated aldehyde group (or, less probably, under the influence of the dibromomethyl group), since there was no sign of its removal, under the same conditions, from the tetrabromo-compound, in which the substituent must also be present. To confirm this, the tetrabromo-compound was treated with hexamine in hot acetic acid (Sommelet reaction). The resin gave a crystalline 2,4-dinitrophenylhydrazine in about 10% yield. This, on analysis, appeared to be a derivative of tribromoformyl-1,2-dihydro-2,2,4-trimethylquinoline; it was not identical with the 2,4-dinitrophenylhydrazone of the hydrolysis product of the pentabromo-compound. The resinous Sommelet product was now boiled with sodium hydroxide in 85% ethanol under the conditions used to hydrolyse the pentabromo-compound. The product was also resinous, but again yielded a crystalline 2,4-dinitrophenylhydrazone in about 10% yield. This derivative contained only two atoms of bromine and was identical with the 2,4-dinitrophenylhydrazone of the hydrolysis product of the pentabromo-compound.

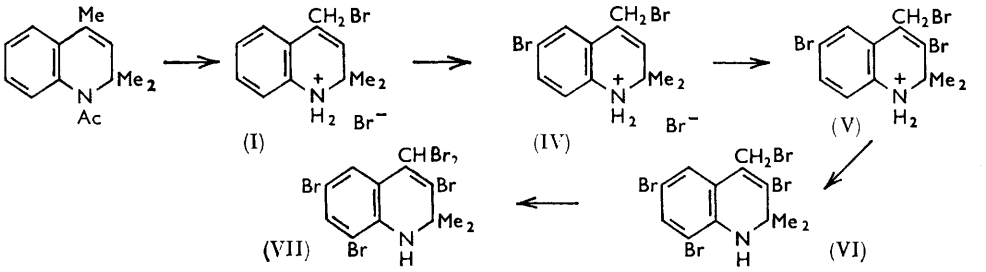
The most likely place for a bromine atom, capable of being influenced by a 4-formyl group, is the 3-position. The structure of the tetrabromo-compound could therefore be written as 3,*x*,*y*-tribromo-4-bromomethyl-1,2-dihydro-2,2,4-trimethylquinoline, and the pentabromo-compound as the 4-dibromomethyl analogue. Attention was now directed towards the lower bromination products. Since the monobromo-compound was a powerful skin irritant, it was suspected that the 4-bromomethyl group was already present. Studies of the action of nucleophiles were here complicated by the tendency of the free base to resinify, but treatment with dimethylamine gave, as well as the main product which was a basic resin, a crystalline substance, $C_{26}H_{34}BrN_3$ (1·1 g. from 10 g. of monobromo-hydrobromide). Its formation is explained if the monobromo-compound is formulated as the hydrobromide of 4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline (I) which is partially converted into the diamine (II) with dimethylamine. The latter then reacts with unchanged (I) to give bis-(1,2-dihydro-2,2-dimethyl-4-quinolylmethyl)dimethylammonium bromide (III).



The infrared spectrum of the dibromo-compound indicated that the second bromine atom entered the 6-position of (I). This was confirmed chemically. Treatment of the dibromo-compound with zinc in acetic acid very rapidly removed the labile bromine atom, restoring the original 4-methyl group. There was a strong tendency to remove the second bromine atom also; but, by modification of the conditions, it was eventually possible to obtain a crystalline monobromo-1,2-dihydro-2,2,4-trimethylquinoline. An attempt to prepare this compound from *p*-bromoaniline and acetone failed, complete resinification apparently occurring. (Resinification is also observed with *m*-bromoaniline and *p*-chloroaniline, but with the latter a low yield of crystalline dihydroquinoline can be isolated.) With dicyandiamide in an acidic medium, the product of zinc-reduction gave a monobromo-2-guanidino-4-methylquinazoline, which was identical with the product from 5-bromo-2-aminoacetophenone hydrochloride [4] and dicyandiamide,[5] thus showing that the dibromo-dihydroquinoline is 6-bromo-4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline hydrobromide (IV).

[3] Hargreaves and Owen, *J.*, 1947, 750; Campbell and McCall, *J.*, 1951, 2413.
[4] Gibson and Levin, *J.*, 1931, 2394.
[5] Cf. Theiling and McKee, *J. Amer. Chem. Soc.*, 1953, **75**, 2252.

By elimination, the third and fourth bromine atoms enter at the 3-position and at a second position in the benzene ring, not necessarily in that order. The infrared spectra of the tribromo- and tetrabromo-compounds indicate that this is, in fact, the correct order and that the 8-position is the one occupied by the fourth bromine atom. Bromine in the



8-position accords with the apparent impossibility of preparing a hydrobromide from the tetrabromo-compound. (It does not seem possible to attribute this to the decreased basicity of the amino-group because of polybromo-substitution. Even 2,4,6-tribromoaniline forms a hydrobromide, hence steric factors must be invoked.) It has not yet been determined whether the resinification of the monobromo- and dibromo-bases formally resembles the polymerisation of styrenes, or whether it involves an attack on the amino-group of one molecule by the bromomethyl-group of a second. (Fully aromatic halogenomethylpyridines are also unstable.[6]) In either case, introduction of a 3-bromo-group might be expected to interfere, thus explaining the successful isolation of the tribromo-base.

The positions of substitution of the bromine atoms in the tribromo-base and the tetrabromo- and pentabromo-derivatives were confirmed from the nuclear magnetic resonance spectra (n.m.r.) of these compounds.

Tribromo-compound. The spectrum confirms the structure 3,6-dibromo-4-bromomethyl-1,2-hydro-2,2-dimethylquinoline (V). The bands at τ 8·58 (CMe), 6·41 (NH-broad), and 5·58 (CH_2Br) show the intensity ratio 6 : 1 : 2. The aromatic region shows the typical pattern of a 1,2,4-substituted benzene. The doublet (J = 8·3 c./sec.) at 3·57 can be assigned to the 8-proton which is specifically shielded by the adjacent nitrogen atom.[7] This is *o*-coupled to the 7-proton absorbing at τ 2·80. This band is a double doublet (J = 8·3; 2·0 c./sec.) one component of which is under the chloroform line. The remaining doublet (τ 2·60; J = 2·0 c./sec.) arises from the 5-proton which is slightly deshielded by the double bond.[7]

Tetrabromo-compound. The spectrum confirms the structure 3,6,8-tribromo-4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline (VI). The bands at τ 8·53 (Me_2), 5·9 (NH; broad), and 5·58 (CH_2Br) show the expected intensity ratio of 6 : 1 : 2. The aromatic region consists of a double doublet (τ 2·63, 2·52; J = 2·0 c./sec.) arising from a pair of *m*-protons. From the low τ-values, neither of these can be adjacent to nitrogen.

Pentabromo-compound. The spectrum confirms the structure, 3,6,8-tribromo-4-dibromomethyl-1,2-dihydro-2,2-dimethylquinoline (VII). The signal arising from $CHBr_2$ is at τ 2·70 and is just resolved from the chloroform line. The aromatic region is a double doublet (τ 2·47, 1·77; J = 2·0 c./sec.) arising from *m*-interacting protons. There is a pronounced shift to lower fields of, presumably, the 5-proton due to the altered nature of the 4-substituent.

The hydrobromides of the monobromo- and dibromo-compounds were unsuitable for examination by this technique, because of their poor solubility. However, bromination

[6] Mathes, Schüly, *Z. angew. Chem.*, 1963, **75**, 235.
[7] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1959.

of 1-acetyl-1,2-dihydro-2,2,4-trimethylquinoline with *N*-bromosuccinimide gave a monobromo-compound with the *N*-acetyl group intact. This compound readily reacted with nucleophiles in aprotic solvents to give crystalline derivatives in high yields. In the presence of moisture, deacetylation rapidly occurred during these reactions with nucleophiles. Thus, on reaction with dimethylamine in aqueous ethanol, under the conditions used with 4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline hydrobromide, a basic resin was again the main product and the same quaternary salt as that previously prepared from the hydrobromide was isolated in slightly improved yield (2·2 g. from 11·6 g. of bromo-compound). The product of *N*-bromosuccinimide bromination is therefore also the 4-bromomethyl compound and this was confirmed by its conversion into 4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline hydrobromide (I) in good yield, by keeping its solution in moist chloroform containing dissolved hydrogen bromide. The compound is then 1-acetyl-4-bromomethyl-1,2-dihydro-2,2-dimethyl quinoline, this structure being in good agreement with its n.m.r. spectrum. Thus the bands at τ 8·44 (CMe_2), 7·83 (Ac), 5·69 (CH_2Br), and 4·08 (:CH) show the expected intensity ratio of 6 : 3 : 2 : 1. The CH_2Br protons show the expected small coupling with the olefinic proton absorbing at τ 4·08

Hence only the dibromo-compound lacks confirmation of its assigned structure by n.m.r. data, and here the chemical evidence seems fully adequate. The positions of the substituents found for these bromo-derivatives seem in accord with current views on the substitution of quinolines and their derivatives.[8]

6-Bromo-4-bromomethyl-1,2-dihydro-2,2,4-trimethyl-1,2-dihydroquinoline hydrobromide, incorporated into agar at 0·01% concentration, completely inhibits growth of the common spoilage fungi, *Penicillium expansum* and *Aspergillus niger*, while the figures for the 3,6-dibromo-4-bromomethyl analogue for these fungi are 0·001 and 0·0005%, respectively.

Chlorination of 1-acetyl-1,2-dihydro-2,2,4-trimethylquinoline has also been studied. With either chlorine or sulphuryl chloride, the same monochloro-compound was obtained. This is presumably 4-chloromethyl-1,2-dihydro-2,2-dimethylquinoline hydrochloride. Further chlorination was difficult to control, but, with sulphuryl chloride, a crude dichloro-compound was obtained and, with large excess of this reagent, poor yields of two crystalline compounds, a hexachloro-1,2-dihydro-2,2,4-trimethylquinoline dichloride and a hexachloro-1,2-dihydro-2,2,4-trimethylquinoline tetrachloride, have been obtained. The hexachloro-dichloride was not converted to the hexachloro-tetrachloride on treatment with excess of sulphuryl chloride. Clearly, the hexachloro-tetrachloride no longer retains a fully aromatic benzene ring and this is possibly true of the hexachloro-dichloride also.

Experimental

Note. The chloroform used in these experiments contained about 1% of ethanol.

Nuclear magnetic resonance spectra were obtained with a Varian A 60 spectrometer and solutions (50 mg./ml.) in deuterochloroform.

4-Bromomethyl-1,2-dihydro-2,2-dimethylquinoline Hydrobromide.—(*a*) *From 1-acetyl-1,2-dihydro-2,2,4-trimethylquinoline.* The *N*-acetyl compound (20·6 g.) in chloroform (100 ml.) was stirred at 0—10° while bromine (5·4 ml.) in chloroform (200 ml.) was added during 4 hr. Next day, the bulk of the solvent was removed at reduced pressure, with gentle warming (maximum 40°). Ethanol (*ca.* 50 ml.) was added and the greenish *bromo-compound* (26·3 g.), m. p. 182—185° (decomp.), filtered off. Recrystallisation from ethanol gave the pure compound in glistening prisms m. p. 189—191° (decomp.). The recovery was very low but i.r. spectral studies indicated that the original material was 95% pure (Found: C, 43·8; H, 4·8; N, 4·0; Br, 47·5. $C_{12}H_{15}Br_2N$ requires C, 43·3; H, 4·5; N, 4·2; Br, 48·0%). In runs at 20—25°, the products were occasionally contaminated with a compound, which i.r. spectra suggested might be a fully aromatic quinoline derivative. Attempts to increase the proportion of this product failed.

(*b*) *From 1,2-dihydro-2,2,4-trimethylquinoline hydrobromide.* A solution of the hydrobromide

[8] de la Mare, Paper presented at the symposium on heterocyclic nitrogen compounds, Hatfield Technical College, 1962; de la Mare, Kiamud-din, and Ridd, *J.*, 1960, 564.

(25·4 g.) in chloroform (200 ml.) was stirred at 10° while bromine (5·2 ml.) in chloroform (100 ml.) was added during 5 hr. Two days later, the pale yellow solution was evaporated under reduced pressure. The resinous residue was dissolved in acetone (100 ml.). Two crops of crystals were obtained. The first (10·9 g.), m. p. 181° (decomp.), was over 90% pure (i.r. spectrum) but the second (11·25 g.), m. p. 181° (decomp.), contained less than 50% of the 4-bromomethyl compound.

(*c*) *From* 1,2-*dihydro*-2,2,4-*trimethyldihydroquinoline*. The dihydroquinoline base (34·6 g.) in chloroform (180 ml.) was treated with bromine (10·8 ml.) in chloroform (400 ml.), as in the above experiments. Removal of solvent gave a violet resin which did not crystallise until treated with acetone. A first crop (6 g.), m. p. 183° (decomp.), gave the bromomethyl compound on recrystallisation (Found: C, 43·9; H, 4·8; Br, 47·0. Calc. for $C_{12}H_{15}Br_2N$: C, 43·3; H, 4·5; Br, 48·0%). From the acetone liquors, discoloured impure material (19·1 g.), m. p. 175° (decomp.), was recovered.

6-*Bromo*-4-*bromomethyl*-1,2-*dihydro*-2,2-*dimethylquinoline Hydrobromide*.—(*a*) *From* 1-*acetyl*-1,2-*dihydro*-2,2,4-*trimethylquinoline*. The *N*-acetyl compound (21·5 g.) was treated as in the preparation of the monobromo-compound but with twice the proportion of bromine. The residue after removal of the solvent crystallised after a few days. After addition of acetone (20 ml.), the crude *dibromo-hydrobromide* was filtered off. The first crop (21·5 g.), m. p. 185° (decomp.), contained over 90% of the pure material. The second crop (5·0 g.), m. p. 183° (decomp.), contained about 70%. The pure compound was obtained in poor yield by recrystallisation from ethanol. It formed needles, m. p. 190—194° (decomp. with previous darkening) (Found: C, 35·3; H, 3·5; N, 3·1; Br, 57·3. $C_{12}H_{14}Br_3N$ requires C, 35·0; H, 3·4; N, 3·4; Br, 58·2%).

(*b*) *From* 1,2-*dihydro*-2,2,4-*trimethylquinoline hydrobromide*. The hydrobromide (25·4 g.) yielded two crops after bromination: (1) 12·55 g., m. p. 187° (decomp.), and (2) 9·1 g., m. p. 186° (decomp.), which were estimated to contain about 70 and 40% of the dibromo-hydrobromide.

3,6-*Dibromo*-4-*bromoethyl*-1,2-*dihydro*-2,2-*dimethylquinoline Hydrobromide*.—(*a*) *From* 1-*acetyl*-1,2-*dihydro*-2,2,4-*trimethylquinoline*. After bromination in the usual way with 3 mols. of bromine, acetone treatment of the residue from the *N*-acetyl compound (21·5 g.) and bromine (15·4 g.) gave the crude *tribromo-hydrobromide* (35·4 g.). The solid was treated with boiling acetone (120 ml.)—the extracts contained tetrabromo-compound—and the residue (31·2 g.), m. p. 184° (decomp.), was *ca.* 60% pure. A purified specimen was obtained in very low yield, by recrystallisation from ethanol, as off-white prisms, m. p. 180—182° (decomp.) (Found: C, 29·9; H, 2·9; N, 2·7; Br, 64·4. $C_{12}H_{13}Br_4N$ requires C, 29·3; H, 2·6; N, 2·9; Br, 65·2%).

On brominating with 3·2 mols. of bromine, the tribromo-hydrobromide, obtained in 27% yield after removal of tetrabromo-compound in hot acetone, was especially suitable for the preparation of the free base. This material (10 g.) was dissolved in ethanol (40 ml.) and stirred while aqueous sodium hydroxide (8%; 10 ml.) was slowly added. The crystalline *free base* (4·7 g.), m. p. 96—97°, separated. A second crop (3·5 g.), m. p. 95—97° (softens at 85°) separated from the mother-liquors. A sample recrystallised from ethanol gave yellow plates, m. p. 98—99° (Found: C, 35·0; H, 3·1; N, 3·2. $C_{12}H_{12}Br_3N$ requires C, 35·1; H, 2·9; N, 3·4%).

(*b*) *From* 1,2-*dihydro*-2,2,4-*trimethylquinoline hydrobromide*. From the hydrobromide (25·4 g.), crude tribromo-hydrobromide (25·7 g.), m. p. 180° (decomp.), purity *ca.* 75% was prepared in the usual way. This material (10 g.) gave crystalline free base (3·85 g.), m. p. 95—96°.

3,6,8-*Tribromo*-4-*bromomethyl*-1,2-*dihydro*-2,2-*dimethylquinoline*.—(*a*) *From* 1-*acetyl*-1,2-*dihydro*-2,2,4-*trimethylquinoline*. Bromination of the *N*-acetyl compound (21·5 g.) with bromine (20·8 ml.) gave a solution which soon deposited yellow crystals on concentration. The residue after removal of solvent was boiled for a few minutes with ethanol (50 ml.). After cooling, the crude *tetrabromo-compound* (42·6 g.), m. p. 153—154°, was filtered off. Crystallisation from ethyl methyl ketone gave large yellow prisms (32·3 g.), m. p. 161—162° (Found: C, 30·1; H, 2·6; N, 2·7; Br, 64·7. $C_{12}H_{11}Br_4N$ requires C, 29·4; H, 2·2; N, 2·9; Br, 65·2%).

(*b*) *From* 1,2-*dihydro*-2,2,4-*trimethylquinoline hydrobromide*. The hydrobromide (25·4 g.) gave crude tetrabromo-compound; recrystallisation gave the pure compound (26·8 g.), m. p. 162—164°.

3,6,8-*Tribromo*-4-*dibromomethyl*-1,2-*dihydro*-2,2-*dimethylquinoline*.—(*a*) *From* 1-*acetyl*-1,2-*dihydro*-2,2,4-*trimethylquinoline*. The *N*-acetyl compound (20·6 g.) in chloroform (100 ml.) was treated with bromine (32·4 ml.) in chloroform (200 ml.) in the usual way. The bulk of the chloroform was distilled off before any solid separated. A first crop (27·1 g.), m. p. 144—146°, proved to be largely the tetrabromo-compound. A second crop (11 g.) was recrystallised from ethanol, forming shining yellow plates, m. p. 170°. This proved to be the *pentabromo-compound* mixed with about 20% of tetrabromo-compound (Found: C, 26·1; H, 2·05; N, 2·6; Br, 69·6. $C_{12}H_{10}Br_5N$ requires C, 25·4; H, 1·8; N, 2·5; Br, 70·4%). It was later found that recrystallisation in the presence of dimethylamine gave the pure pentabromo-compound, m. p. 186—188° (Found: C, 25·2; H, 1·9%).

(*b*) *From* 3,6,8-*tribromo*-4-*bromomethyl*-1,2-*dihydro*-2,2-*dimethylquinoline*. The tetrabromo-compound (4·9 g.) in chloroform (100 ml.) was treated with bromine (5 ml.). Two days later, the solvent and excess of bromine were removed under reduced pressure. The residue was triturated with ethanol and blue-green crystals (4·9 g.), m. p. 179—181°, filtered off. Recrystallisation from ethanol gave yellow needles (3·3 g.), m. p. 182—183°. Infrared spectra confirmed the identity of the compound with that prepared from the *N*-acetyl compound.

3,6,8-*Tribromo*-4-*dimethylaminomethyl*-1,2-*dihydro*-2,2-*dimethylquinoline*.—The tetrabromo-compound (5 g.) was dissolved in boiling ethanol (325 ml.). The solution was quickly cooled to 44° and aqueous dimethylamine (36%, 3 ml.) was added. Next day, the bulk of the ethanol was removed and the *dimethylamino-compound* (4 g.), m. p. 81—82°, filtered off. Crystallisation from ethanol gave pale yellow needles, m. p. 82—83° (Found: C, 37·2; H, 3·7; N, 6·0; Br, 52·8. $C_{14}H_{17}Br_3N_2$ requires C, 37·1; H, 3·7; N, 6·2; Br, 53·0%).

3,6,8-*Tribromo*-4-*ethoxymethyl*-1,2-*dihydro*-2,2-*dimethylquinoline*.—The tetrabromo-compound (0·35 g.), partly dissolved in hot ethanol (15 ml.), was treated with sodium hydroxide (1 g.) in water (0·9 ml.). The solution was boiled for 1 hr., then diluted with water (10 ml.) and allowed to cool. The white crystalline *product* (0·25 g.) was crystallised from ethanol, forming prisms, m. p. 78—79·5° (Found: C, 37·3; H, 3·7; N, 3·1; Br, 52·4%; *M* (Rast), 427. $C_{14}H_{16}Br_3NO$ requires C, 37·0; H, 3·5; N, 3·1; Br, 52·9%; *M*, 454).

6,8-*Dibromo*-4-*formyl*-1,2-*dihydro*-2,2-*dimethylquinoline*.—The pentabromo-compound (1 g.) in ethanol (20 ml.) was boiled with sodium hydroxide (1 g.) in water (2 ml.) for 2 hr. Most of the ethanol was then distilled off, water (100 ml.) was added, and the *formyl compound*, m. p. 230—232°, was filtered off. When recrystallised from ethanol it formed needles, m. p. 244—245° (Found: C, 41·95; H, 2·9; N, 4·4; Br, 46·4. $C_{12}H_{11}Br_2NO$ requires C, 41·7; H, 3·2; N, 4·1; Br, 46·4%). The compound gave a 2,4-*dinitrophenylhydrazone* as orange-red prisms, m. p. 250° (decomp.) (from glacial acetic acid) (Found: C, 41·5; H, 2·7. $C_{18}H_{15}Br_2N_5O_4$ requires C, 41·1; H, 2·9%).

3,6,8-*Tribromo*-4-*formyl*-1,2-*dihydro*-2,2-*dimethylquinoline* 2,4-*Dinitrophenylhydrazone*.—The tetrabromo-compound (1 g.) and hexamine (2 g.) were boiled for 10 min. in acetic acid (20 ml.). Solid by-products (0·5 g.) were filtered off. Resin separated on addition of water to the filtrate. This material gave a yellow *hydrazone* (0·08 g.) when boiled with an alcoholic solution of 2,4-dinitrophenylhydrazine. It formed glistening orange spangles, m. p. 215°, from acetic acid (Found: C, 36·2; H, 2·4; N, 11·2; Br, 39·2. $C_{18}H_{14}Br_3N_5O_4$ requires C, 35·8; H, 2·3; N, 11·6; Br, 39·7%).

Repetition of the experiment, solution of the resinous product in boiling ethanol (4 ml.), addition of sodium hydroxide (0·4 g.) in water (0·6 ml.), and boiling for 2 hr. gave a resin from which an orange-red 2,4-dinitrophenylhydrazone (0·08 g.), m. p. 250° (decomp.), was obtained. This was identical (i.r. spectra) with the hydrazone from 6,8-dibromo-4-formyl-1,2-dihydro-2,2-dimethylquinoline.

1-*Acetyl*-4-*bromo*-1,2-*dihydro*-2,2-*dimethylquinoline*.—A solution of 1-acetyl-1,2-dihydro-2,2,4-trimethylquinoline (163 g.) in carbon tetrachloride (2700 m.) containing *N*-bromosuccinimide (138 g.) and benzoyl peroxide (10 g.) was boiled and stirred for 30 min. After cooling, succinimide (74·2 g.) was filtered off and the solution concentrated. The *bromo-compound* (158·5 g.) m. p. 104—106°, formed needles, m. p. 107—109°, from ethanol (Found: C, 56·8; H, 5·5; N, 5·0; Br, 27·1. $C_{14}H_{16}BrNO$ requires C, 57·2; H, 5·4; N, 4·8; Br, 27·2%).

***Bis*-(1,2-*dihydro*-2,2-*dimethyl*-4-*quinolylmethyl*)*dimethylammonium Bromide*.**—(*a*) *From* 4-*bromomethyl*-1,2-*dihydro*-2,2-*dimethylquinoline hydrobromide*. The hydrobromide (10 g.) was dissolved in boiling ethanol (100 ml.) and cooled quckly. Aqueous dimethylamine (36%, 15 ml.) was added. Next day, the solvent was removed in a current of air. The resinous

product contained particles of solid. Ethanol (30 ml.) was added to dissolve the resin, and the undissolved *quaternary salt* (1·1 g.), m. p. 215—217° (decomp.), was filtered off and crystallised from ethanol (Found: C, 66·3; H, 7·5; N, 8·8; Br, 17·3. $C_{26}H_{34}BrN_3$ requires C, 66·7; H, 7·3; N, 9·0; Br, 17·1%).

(*b*) *From* 1-*Acetyl*-4-*bromomethyl*-1,2-*dihydro*-2,2-*dimethylquinoline*. The *N*-acetyl compound (11·6 g.) in ethanol (100 ml.) was treated with aqueous dimethylamine (36%, 20 ml.). After 3 hr., the solution was boiled for 1 hr., cooled, treated with 48% hydrobromic acid (40 ml.), and boiled for 15 min. The cooled solution was basified and the mixture shaken with ether. The solid (2·2 g.), m. p. 215—216° (decomp.), in both ethereal and aqueous layers, was identical (i.r. spectra) with the quaternary salt prepared in (*a*).

Conversion of 1-*Acetyl*-4-*bromomethyl*-1,2-*dihydro*-2,2-*dimethylquinoline into* 4-*Bromomethyl*-1,2-*dihydro*-2,2-*dimethylquinoline Hydrobromide*.—A solution of *N*-acetyl compound (2 g.) in moist chloroform (20 ml.) was saturated with hydrogen bromide. Next day, the chloroform was evaporated and ethanol (5 ml.) added to the residue. The 4-bromomethyl hydrobromide, m. p. 178—180° (decomp.), was identified by its infrared spectrum.

6-*Bromo*-1,2-*dihydro*-2,2,4-*trimethylquinoline*.—6-Bromo-4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline hydrobromide (5 g.) in acetic acid (100 ml.) and water (2·5 ml.) at 100° was treated with zinc dust (5 g.), added in portions during 2 min. Three min. later, inorganic solids were filtered off and the filtrate diluted with water. A brown oil (2·35 g.) was isolated in ether. On being kept, this partially solidified and off-white crystals (1·28 g.) were filtered off and washed with petroleum. Recrystallisation from petroleum gave the pure 6-*bromo*-2,2,4-*trimethyl compound*, m. p. 86—89° (Found: C, 56·5, 57·6; H, 5·8, 5·5; N, 5·6; Br, 30·8. $C_{12}H_{14}BrN$ requires C, 57·1; H, 5·6; N, 5·6; Br, 31·7%).

6-*Bromo*-2-*guanidino*-4-*methylquinazoline Hydrochloride*.—(*a*) *From* 6-*bromo*-1,2-*dihydro*-2,2,4-*trimethylquinoline*. The 6-bromo-compound (0·12 g.), dicyandiamide (0·06 g.) and concentrated hydrochloric acid (0·06 ml.) were boiled in ethanol (0·5 ml.) for 2 hr. Isobutene was evolved. After 30 min. fresh ethanol (0·5 ml.) was added. The mixture was basified and the yellow quinazoline base (0·064 g.), m. p. 263—264° (decomp.), filtered off and washed with ethanol. This product was suspended in ethanol (1 ml.), and concentrated hydrochloric acid (0·05 ml.) was added. A clear solution was obtained momentarily, then the *guanidinoquinazoline hydrochloride* (0·044 g.), m. p. 293—295° (softens 270°), separated (Found: C, 38·1; H, 3·7; N, 23·7. $C_{10}H_{11}BrClN_5$ requires C, 37·9; H, 3·7; N, 23·7%).

(*b*) *From* 2-*amino*-5-*bromoacetophenone hydrochloride*. The hydrochloride (2·1 g.), m. p. 185° (decomp.), was boiled for 3 hr. with dicyandiamide (1 g.), concentrated hydrochloric acid (0·2 ml.), water (8 ml.), and ethanol (4 ml.). The pH was adjusted to 6—7 and unchanged amino-ketone filtered off. On basifying the filtrate, a pale yellow solid (1·0 g.) separated, m. p. 267—270° (decomp.). This quinazoline base was converted into the hydrochloride which was shown by i.r. spectroscopy to be the compound prepared in (*a*) (Found: C, 38·4; H, 3·5; N, 24·4. Calc. for $C_{10}H_{11}BrClN_5$: C, 37·9; H, 3·7; N, 23·7%).

4-*Chloromethyl*-1,2-*dihydro*-2,2-*dimethylquinoline Hydrochloride*.—(*a*) *Use of chlorine*. Chlorine was passed into 1-acetyl-1,2-dihydro-2,2,4-trimethylquinoline (43 g.) in carbon tetrachloride (200 ml.) until 14·3 g. had been absorbed. A few crystals of the *chloromethyl compound* separated from the reaction mixture. After addition of ethanol (3 ml.) to the filtrate, more of the product (5·4 g.), m. p. 177—178° (decomp.), separated (Found: C, 59·0; H, 6·4; N, 6·0; Cl, 28·7. $C_{12}H_{15}Cl_2N$ requires C, 59·0; H, 6·1; N, 5·7; Cl, 29·1%).

(*b*) *Use of sulphuryl chloride*. Sulphuryl chloride (6·7 g.) in carbon tetrachloride (20 ml.) was added during 30 min. to a stirred solution of 1-acetyl-1,2-dihydro-2,2,4-trimethylquinoline (10·7 g.) in carbon tetrachloride (80 ml.). The temperature was kept below 25°. After 2 hr., ethanol (2 ml.) was added. Next day, the greyish solid (8·6 g.), m. p. 182—184° (decomp.), was filtered off. The i.r. spectrum was substantially identical with that of the chlorine product.

Dichlorination of 1-*acetyl*-1,2-*dihydro*-2,2,4-*trimethylquinoline*.—Repetition of the above chlorination with twice the proportion of sulphuryl chloride gave the crude *dichloro-compound*, presumably 6-chloro-4-chloromethyl-1,2-dihydro-2,2-dimethylquinoline hydrochloride (15·5 g.), m. p. 175—178° (decomp.), from the *N*-acetyl compound (21·5 g.). Crystallisation gave poorly-defined greenish crystals, m. p. 180° (decomp.), which, analysis indicated, contained about 10—20% of the monochloro-compound (Found: C, 52·9; H, 5·2; N, 4·9; Cl, 37·2. $C_{12}H_{14}Cl_3N$ requires C, 51·7; H, 5·0; N, 5·0; Cl, 38·2%).

Polychlorination of 1-*Acetyl*-1,2-*dihydro*-2,2,4-*trimethylquinoline*.—The *N*-acetyl compound

(10·7 g.) was chlorinated as above with sulphuryl chloride (24 ml.). Next day, the solvent was evaporated. The dark gum contained solid (2·2 g.), m. p. 165—166°, which was isolated by addition of ethanol. The *compound* formed pale yellow needles (m. p. 168—169°) from ethanol (Found: C, 32·0; H, 2·0; N, 3·1; Cl, 62·8. $C_{12}H_9Cl_8N$ requires C, 31·9; H, 2·0; N, 3·1; Cl, 62·8%). The i.r. spectrum indicated the absence of NH and of quaternary ammonium ion. Repetition of the chlorination with a larger amount of sulphuryl chloride (32 ml.) gave the same compound as a first crop (5·6 g.). A second crop (3·7 g.) was shown by its infrared spectrum to be a second *compound*. (The substitution pattern was different. NH groups and ammonium ions were absent.) Crystallisation from acetone gave large prisms (1 g.), m. p. 180—183° (Found: C, 27·6; H, 1·8; N, 2·7; Cl, 67·9. $C_{12}H_9Cl_{10}N$ requires C, 27·6; H, 1·7; N, 2·7; Cl, 68·0%).

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