154. *Mechanism of the Molecular Rearrangement produced by the Action of Alkali on Chloral-quinaldine* [2-(3 : 3 : 3-*Trichloro*-2-*hydroxypropyl*)-*quinoline*].

By B. R. Brown, D. Ll. Hammick, and Sir Robert Robinson.

It is shown that the re-arrangement named in the title is equivalent to an $\alpha\gamma$-change of a substituted 1-*o*-aminobenzylidenepropanone to a substituted 3-*o*-aminobenzylidenepropanone. This statement is only intended as a description of the basic change in the carbon skeleton and it does not represent the authors' view of the actual mechanism of the process.

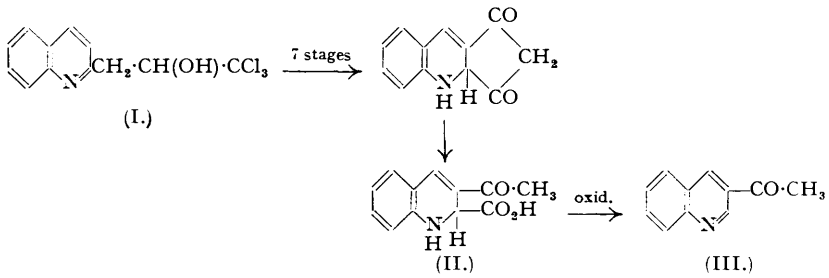
2 : 3-Dimethylquinoline was condensed with chloral and the adduct treated with aqueous-alcoholic sodium hydroxide.

The main product was the normal methylquinolylacrylic acid but oxidation of the coloured material in the mother-liquor afforded 3-quinolyl ethyl ketone in small yield.

An orange salt, $C_{12}H_{10}O_2NNa,3H_2O$, was obtained by Einhorn (*Ber.*, 1886, **19**, 904; Einhorn and Sherman, *Annalen*, 1895, **287**, 38) as a by-product of the hydrolysis of chloral-quinaldine [2-(3 : 3 : 3-trichloro-2-hydroxypropyl)quinoline] (I) by means of aqueous alcoholic sodium hydroxide. It was oxidised *via* a carbonyl compound to an acid which was much later proved by Borsche and Manteuffel (*Annalen*, 1936, **526**, 22) to be quinoline-3-carboxylic acid.

A molecular rearrangement at some stage was thus revealed but the German workers did not follow up the implications. Woodward and Kornfeld (*J. Amer. Chem. Soc.*, 1948, **70**, 2508) showed that the carbonyl compound obtained by oxidation of the orange sodium salt is 3-quinolyl methyl ketone (III) and made it very probable that the Einhorn salt is a dihydroquinoline

derivative (cf. II). Their view (*A*) of the mechanism of the process is schematically illustrated below.

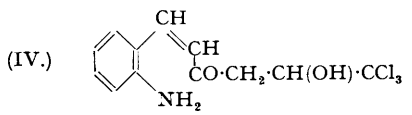


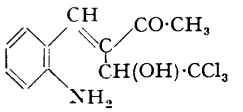
An alternative hypothesis (*B*) was considered by Woodward and Kornfeld but was rejected for good reasons. This involved the disruption of (I) into *o*-aminobenzylideneacetone and chloral, or their equivalents, and recombination of these elements of the structure in a new position.

In the particular case of chloral-quinaldine this allows of an intermediate stage identical with a possibility in our own hypothesis (*C*, below), but this is derived in a different manner and would not give the same results, for example in an investigation with labelled atoms.

Our interest in this subject arose from the fact that we found Woodward and Kornfeld's theoretical explanations unconvincing, especially that advanced to justify the assumption of the formation of the *cyclo*pentane ring of a postulated intermediate by attack on the β-position of the quinoline nucleus. This seemed to overlook the much greater probability of the formation of a pyrrolidine ring, if cyclisation were to occur at all.

The view (*C*) of the rearrangement which appeared most acceptable to us can best be explained didactically by noting that chloral-quinaldine by imaginary hydrolytic fissions would yield the unsaturated ketone (IV) which is the 1-*o*-aminobenzylidene derivative of $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH(OH){\cdot}CCl_3$. We suggest that the *o*-aminobenzylidene group is transferred from the 1- to the 3-position in the pentanone chain. This gives (V) which is dehydrated and hydrolysed to give (II).

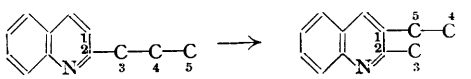




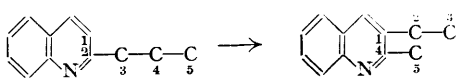
(V.)

It would be of interest to study the rearrangement by means of labelled carbon atoms and the following scheme shows what results are to be expected on the basis of the three hypotheses (*A*), (*B*), and (*C*).

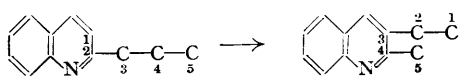
(*A*) Woodward and Kornfeld (favoured) :



(*B*) Woodward and Kornfeld (rejected) :



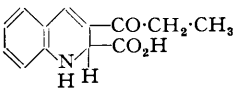
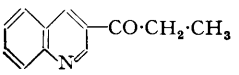
(*C*) Present authors :



It will be noticed that (*A*) could readily be distinguished from (*B*) and (*C*) by the isotope method but that a distinction between (*B*) and (*C*) would require a quinaldine labelled at the methyl group or at the carbon atom in the 3-position of the quinoline nucleus, but not at both points simultaneously in the same way. The slight preparative difficulty so indicated can best be overcome by a quinaldine synthesis from quinoline.

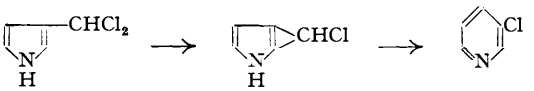
In the meantime the hypothesis (*C*) is seen to be in harmony with the results obtained by Woodward and Kornfeld with related substances in the quinoline and pyridine series.

According to hypotheses (*A*) and (*B*), 2 : 3-dimethylquinoline-chloral could not undergo the rearrangement but if (*C*) is correct we could obtain (VI) and by oxidation 3-quinolyl ethyl ketone (VII). Actually the colour change indicates that the reaction proceeds as expected, but

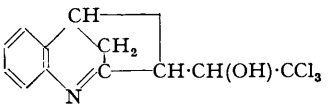
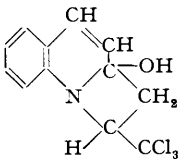
(VI.)   (VII.)

the yield is certainly low and we were unable to isolate the salt of (VI). On oxidation, a small amount of (VII) was isolated and identified as the 2 : 4-*dinitrophenylhydrazone*. The ketone (VII) was synthesised by an unambiguous method described in the Experimental section. We are fully convinced that this result establishes the correctness of hypothesis (*C*) but in view of the small yield we hope to obtain confirmation by the isotope method applied to the original case.

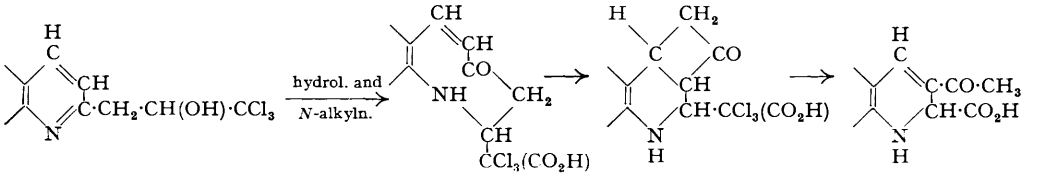
On the assumption that (*C*) is essentially correct, the stages of the process call for consideration. We do not favour a theory of fission and recombination of the parts; it seems almost certain that the molecule undergoes a change somewhat similar to that which may be postulated for the ring-enlargement of pyrrole to 3-chloropyridine :



In the quinaldine-chloral case, two four-ring intermediates are plausible (VIII and IX) :

(VIII.)   (IX.)

These represent two parts of the completed rearrangement, and the third is hydrolysis of the imine linkage. These three elements occur in undetermined succession but, since the benzylidene group should be more active after hydrolysis of the imine, a probable sequence is that shown below.



The formation of a four-ring and other precisions of this scheme are not necessary to our theory which can be interpreted with the aid of several different detailed mechanisms.

Experimental.

Ethyl 3-*Propionylquinaldate*.—A mixture of *o*-aminobenzaldehyde (3·9 g.), ethyl propionylpyruvate (5·6 g.) (Diels, Sielisch, and Müller, *Ber.*, 1906, **39**, 1333), alcohol (50 ml.), and potassium hydroxide (0·05 g.) was boiled under reflux for 10 hours. Colourless, slender needles (3·2 g.) separated from the cooled reaction mixture. A further 1·2 g. were obtained by dilution of the mother-liquor with water. *Ethyl* 3-*propionylquinaldinate* separated from alcohol as colourless needles, m. p. 107—108° (Found : C, 70·2; H, 5·8. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·8%).

3-*Propionylquinaldic Acid*.—The above ester (1·1 g.) was heated on the steam-bath with water (50 ml.) and potassium hydroxide (2·0 g.). After ½ hour the hot solution was filtered and acidified with dilute sulphuric acid. Slender, colourless needles (0·9 g.) separated on cooling. Recrystallisation from water yielded 3-*propionylquinaldic acid* as colourless needles, m. p. 153° (decomp.) (Found: C, 67·9; H, 4·8. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8%). The acid forms a very sparingly soluble, pale green copper salt.

3-*Quinolyl Ethyl Ketone* (VII).—3-Propionylquinaldic acid (2·3 g.) was refluxed with moist anisole (20 ml.) until decarboxylation was complete (3 hours). The mixture was extracted with 10% hydrochloric acid and benzene, and the acid layer was basified, giving a colourless oil which quickly solidified. The dry solid (1·8 g.) was crystallised from light petroleum (b. p. 60—80°) and then from aqueous methanol, from which it separated as silky, colourless needles, m. p. 79—80° (Found : C, 77·6; H, 5·9. $C_{12}H_{11}ON$ requires C, 77·8; H, 5·9%). The 2 : 4-*dinitrophenylhydrazone* crystallised from pyridine–alcohol as deep orange-red needles, m. p. 248—249° (Found : C, 59·6; H, 4·0; N, 19·5. $C_{18}H_{15}O_4N_5$ requires C, 59·2; H, 4·1; N, 19·2%).

3-*Methyl*-2-(3 : 3 : 3-*trichloro*-2-*hydroxypropyl*)*quinoline*.—A mixture of 2 : 3-dimethylquinoline (6·0 g.), chloral (6·0 g.), and pyridine (6·0 ml.) was heated on the steam-bath for 2 hours. The solid obtained by addition to water was washed free from pyridine and recrystallised several times from 75% aqueous alcohol, to yield the *adduct* (9·0 g.) as colourless needles which, dried at 80° in a vacuum, had m. p. 134—135° (Found : N, 4·7. $C_{13}H_{12}ONCl_3$ requires N, 4·6%).

Action of Alkali on 3-*Methyl*-2-(3 : 3 : 3-*trichloro*-2-*hydroxypropyl*)*quinoline*.—A suspension of the quinoline derivative (15·5 g.) in a hot mixture of alcohol (60 ml.) and water (50 ml.) was treated rapidly with aqueous sodium hydroxide (10 g. in 35 ml. of water). The resulting clear orange-yellow solution was evaporated to dryness, and the solid sodium salts were dissolved in a little water and treated with a slight excess of acetic acid to liberate a mixture of crude brown acids. Treatment of this mixture with concentrated hydrochloric acid (15 ml.) and filtration gave a pale brown residue (11·5 g.) and a deep brownish-red filtrate. Crystallisation of the solid from alcohol yielded the *β-(3-methyl-2-quinolyl)-acrylic acid hydrochloride* as slightly yellow, opaque laminæ, m. p. 220° (decomp.) (Found : N, 5·1. $C_{13}H_{11}O_2N,HCl,C_2H_6O$ requires N, 5·0%). Partial neutralisation with aqueous sodium carbonate and crystallisation from aqueous alcohol yielded *β-(3-methyl-2-quinolyl)acrylic acid* as colourless needles, m. p. 173—178° (decomp.) (Found : C, 72·8; H, 5·2. $C_{13}H_{11}O_2N$ requires C, 73·3; H, 5·2%).

The deep brownish-red filtrate was nearly neutralised with sodium carbonate, and the dark brown solid separated, washed with water, and dried (0·4 g.). This mixture of acids was dissolved in dilute acetic acid, and air was bubbled through the solution for 11 days, during which the colour faded appreciably. The solution was made alkaline with aqueous sodium hydroxide, and the basic products were taken up in ether. Evaporation of the ether left a small amount of oil, which was dissolved in alcohol and treated with alcoholic 2 : 4-dinitrophenylhydrazine sulphate. The orange-red solid (0·1 g.) which separated was twice crystallised from alcohol–pyridine, from which it separated as deep orange-red micro-needles, m. p. 247—248° (Found : C, 59·8; H, 4·1; N, 18·5. Calc. for $C_{18}H_{15}O_4N_5$: C, 59·2; H, 4·1; N, 19·2%). The m. p. was not depressed on admixture with a specimen of the 2 : 4-dinitrophenyl hydrazone of 3-quinolyl ethyl ketone, prepared as described above. A comparison of the behaviour of the two specimens with solvents and in habit of crystallisation confirmed their identity.

The 2 : 4-*dinitrophenylhydrazone* of 3-quinolyl methyl ketone separated from nitrobenzene as minute red prisms, m.p. 261—262° (Found : C, 58·1; H, 3·7. $C_{17}H_{13}O_4N_5$ requires C, 58·2; H, 3·7%). Mixed with the above dinitrophenylhydrazone from 2 : 3-dimethylquinoline, the m. p. was depressed to 242—246°.

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