CXXIII.—*The Intermolecular Condensation of Acetylmethylanthranilic Acid by Means of Phosphorus Pentachloride and the Formation of a Complex* iso*Cyanine Dye.*

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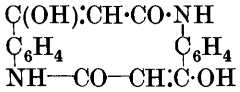
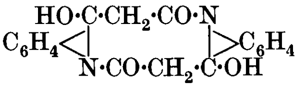
By the action of phosphoryl chloride upon ethyl acetylanthranilate, Anschütz and Schmidt (*Ber.*, 1902, **35**, 3463) obtained an acid, $C_{18}H_{14}O_4N_2$, to which they ascribed the constitution (I) or (II).

(I.)

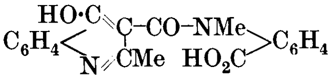


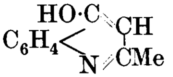


(II.)

The same compound was incidentally isolated by Heller and Grundmann (*Ber.*, 1923, **56**, 200) by treatment of benzenesulphonylanthranilic acid with acetic anhydride, followed by hydrolysis of the sulphonic residue with aqueous sodium hydroxide. These authors showed, however, that the constitution must be represented by (III), because scission of the acid with glacial acetic acid and hydrochloric acid at 100° gave 4-hydroxyquinaldine (IV).

(III.)

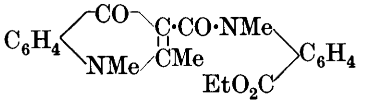


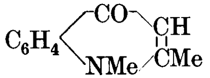


(IV.)

A study has now been made of the complex products obtained by the action of phosphorus pentachloride upon acetylmethylanthranilic acid. When the reactants in equimolecular proportion were heated under reflux in presence of acetyl chloride, hydrogen chloride was evolved and a substance was gradually deposited which, after treatment with alcohol, finally yielded a product, m. p. 245°, of formula $C_{22}H_{22}O_4N_2$. After removal of solvent and phosphorus chlorides from the original filtrate, the residual gum was dissolved in alcohol, and a second substance (m. p. 209°), $C_{22}H_{22}O_3N_2Cl_2$, was isolated. This compound was the sole product of the reaction when $1\frac{1}{2}$ mols. of phosphorus pentachloride were employed, whereas with only $\frac{1}{2}$ mol. of phosphorus chloride the chlorine-free compound alone was produced. That the latter substance has the structure (V), analogous to (III), follows from the isolation of 1 : 2-dimethyl-4-quinolone (VI) and methylanthranilic acid as products of its hydrolysis by means of concentrated hydrochloric acid.

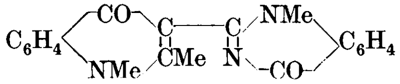
(V.)



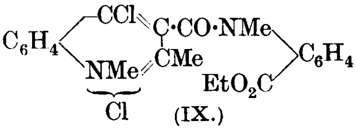


(VI.)

Intermolecular condensation, therefore, must have occurred so as to produce in the first instance the acid chloride (VII; = V with COCl instead of CO_2Et), and this view has been confirmed both by the preparation of the free acid and also by the ready formation of 4 : 4′-*diketo*-1 : 1′ : 2′-*trimethyl*-1′ : 4′-*dihydro*-2(3′)-*quinolylquinazoline* (VIII) on treatment of the original reaction product (VII) with concentrated ammonia.

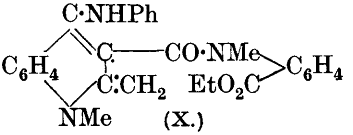


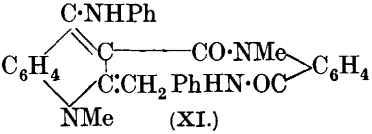
(VIII.)



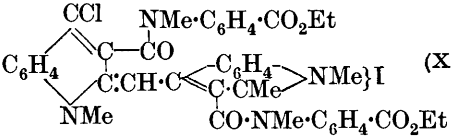
(IX.)

The compound $C_{22}H_{22}O_3N_2Cl_2$, m. p. 209°, proved to be the chloride of a monacid base, the second chlorine atom being non-ionic. When refluxed with alcoholic potash, it was readily converted into the chlorine-free *acid* derived from (VII), a reaction reminiscent of the formation of 4-hydroxypyridine derivatives from the corresponding 4-chloro-compounds (compare Sedgwick and Collie, J., 1895, **67**, 399), and one which indicates formula (IX) as representing its structure. The ready formation of the *anilide* (X) when the ester is heated with aniline in acetic acid solution, and the isolation of 4-hydroxyquinaldine methochloride as a product of hydrolysis are in complete harmony with such a formulation.


(X.)


(XI.)

On the other hand, when the original acid chloride from which (IX) is derived was warmed with an excess of aniline, the *methylene base* (XI) was produced, a reaction paralleled by the production of 4-anilino-1-methyl-2-methylene-1 : 2-dihydroquinoline from 4-chloroquinaldine methiodide (compare O. Fischer, Diepolder, and Wölfel, *J. pr. Chem.*, 1925, **109**, 59).


(XII.)

When 4-*chloro*-3-o-*carbethoxyphenylmethylcarbamyl*-2-*methylquinoline methochloride* (IX) is neutralised with aqueous alkali, the free base is precipitated as a yellow solid. This substance is extraordinarily labile and rapidly passes into a purple, gummy dye, soluble in water to a reddish-purple solution, the colour of which is discharged by strong mineral acids. These reactions, and the fact that the anilino-derivative (X) fails to produce a dye, lead to the conclusion that the dye is a member of the *iso*cyanine group. The dye was isolated and analysed in the form of its *iodide* (XII), its formation being analogous to the preparation of a chloro-*iso*cyanine by O. Fischer, Müller, and Vilsmeier from 4-chloroquinaldine methiodide (*J. pr. Chem.*, 1925, **109**, 69).

The action of phosphorus pentachloride upon 5-bromoacetylmethylanthranilic acid has also been studied. This compound was prepared by converting 5-bromoanthranilic acid into its methyl derivative and acetylating this under the conditions described in the experimental part. Attempts to methylate the corresponding

5-bromoacetylanthranilic acid were unsuccessful. The course of the reaction with phosphorus pentachloride is completely analogous to that already described, resulting in the formation of 6-*bromo*-3-p-*bromo*-o-*carbethoxyphenylmethylcarbamyl*-1 : 2-*dimethyl*-4-*quinolone* and 4-*chloro*-6-*bromo*-3-p-*bromo*-o-*carbethoxyphenylmethylcarbamyl*-2-*methylquinoline methochloride.*

EXPERIMENTAL.

3-o-*Carbethoxyphenylmethylcarbamyl*-1 : 2-*dimethyl*-4-*quinolone* (V).—Dry acetylmethylanthranilic acid (42 g.) was suspended in acetyl chloride (250 c.c.) and mixed with phosphorus pentachloride (25 g.; $\frac{1}{2}$ mol.). A vigorous reaction started immediately and after the evolution of hydrogen chloride had slackened the whole was heated under reflux on the water-bath. The cream-coloured solid obtained was washed repeatedly with small quantities of acetyl chloride and finally with dry ether, and dissolved in alcohol; a vigorous reaction then occurred which was completed by refluxing the mixture for $\frac{1}{2}$ hour. The cold solution was diluted with water and the crystals obtained after 12 hours were repeatedly crystallised from aqueous alcohol, from which the *quinolone* separated in colourless needles containing $1H_2O$. The hydrated compound melts at 124°, resolidifies at 200°, and melts again at 240°. The anhydrous compound, which is obtained by boiling the hydrate with dry benzene and separates as a microcrystalline powder, melts at 245°. It is fairly easily soluble in warm alcohol, but insoluble in ether and benzene (yield, 62%) (Found: C, 70·2, 70·0; H, 5·7, 5·8; N, 7·5, 7·5. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·8; N, 7·4%).

The corresponding *methyl* ester, obtained by decomposing the acid chloride with methyl alcohol, also separates as a hydrate, which partly melts at 115°. The anhydrous compound, obtained by crystallisation of the hydrate from dry acetone–chloroform, forms long, prismatic needles, m. p. 244° (Found: C, 69·0; H, 5·5; N, 7·9. $C_{21}H_{20}O_4N_2$ requires C, 69·2; H, 5·5; N, 7·7%).

3-o-*Carboxyphenylmethylcarbamyl*-1 : 2-*dimethyl*-4-*quinolone*.—The chloride (VII) was warmed with dilute sodium hydroxide solution, and the acid precipitated with hydrochloric acid. Recrystallised from aqueous alcohol, it separated as a hydrate, m. p. 130—131°. The anhydrous acid was obtained, by crystallisation from acetone–chloroform, in colourless prisms, m. p. 247°, soluble in alcohol, insoluble in ether and benzene (Found: C, 68·4, 68·6; H, 5·2, 5·2; N, 8·2. $C_{20}H_{18}O_4N_2$ requires C, 68·6; H, 5·2; N, 8·0%).

The *anilide*, prepared by warming the acid chloride with aniline, crystallised from aqueous alcohol (charcoal) in lustrous plates, m. p. 115° (Found: N, 10·1. $C_{26}H_{23}O_3N_3$ requires N, 9·9%).

4 : 4′-*Diketo*-1 : 1′ : 2′-*trimethyl*-1′ : 4′-*dihydro*-2(3′)-*quinolylquinazoline* (VIII) was prepared by treating the acid chloride with cold concentrated ammonia; after the vigorous reaction had ceased, the mixture was diluted with water. The *quinazoline* crystallised from alcohol in colourless prisms, m. p. 260° (Found: N, 11·8. $C_{20}H_{17}O_2N_3$ requires N, 12·0%). It is readily soluble in warm dilute hydrochloric acid and separates unchanged on cooling.

Acid Hydrolysis of 3-o-*Carbethoxyphenylmethylcarbamyl*-1 : 2-*dimethyl*-4-*quinolone*.—The quinolone (3 g.) was boiled for 6 hours under reflux with concentrated hydrochloric acid (10 c.c.); 1 : 2-dimethyl-4-quinolone hydrochloride separated on cooling. The free base, isolated by means of dilute ammonia, formed colourless needles, m. p. 175—176° (Found: C, 76·1; H, 6·3; N, 8·0. Calc. for $C_{11}H_{11}ON$: C, 76·3; H, 6·4; N, 8·1%).

4-*Chloro*-3-o-*carbethoxyphenylmethylcarbamyl*-2-*methylquinoline Methochloride* (IX).—Dry acetylmethylanthranilic acid (15 g.) was suspended in acetyl chloride (150 c.c.) and treated with phosphorus pentachloride (25 g.; 1½ mols.). When the evolution of hydrogen chloride had almost ceased, the mixture was refluxed on the water-bath until all the solid had dissolved to form a deep red solution. The thick red gum left after removal of the solvent and phosphorus chlorides under reduced pressure was warmed with absolute alcohol, and the resultant red solution mixed with an equal volume of ethyl acetate. The cream-coloured needles which separated on standing were repeatedly crystallised from alcohol (charcoal), and the *methochloride*, finally crystallised by addition of ethyl acetate, was obtained in colourless needles, m. p. 209° (decomp. to a purple mass), readily soluble in alcohol and water, sparingly soluble in ethyl acetate, insoluble in ether and benzene (yield, 50%). The free base was precipitated by aqueous alkali as a yellow solid, which rapidly turned purple and formed a tar. The methochloride may also be prepared by treating 3-*o*-carbethoxyphenylmethylcarbamyl-1 : 2-dimethyl-4-quinolone as described above with phosphorus pentachloride (1 mol.) (yield, 66% of the quinolone employed) (Found: C, 58·6, 58·4; H, 5·4, 5·3; N, 6·4, 6·5; total Cl, 15·8; ionised Cl, 7·9. $C_{22}H_{22}O_3N_2Cl_2,H_2O$ requires C, 58·5; H, 5·3; N, 6·2; total Cl, 15·7; ionised Cl, 7·9%).

Salts. The *methoperchlorate*, precipitated from an aqueous solution of the methochloride by perchloric acid in slight excess, crystallised from alcohol, containing a few drops of perchloric acid, in colourless needles, m. p. 224—225° (decomp. to a purple mass). When heated in a flame, it melted and then decomposed explosively (Found: N, 6·0. $C_{22}H_{22}O_7N_2Cl_2$ requires N, 5·6%).

The *methiodide*, obtained from potassium iodide and the methochloride in aqueous solution, separated from aqueous alcohol in golden-yellow needles, much less soluble in water and alcohol than the corresponding chloride. It became purple-red at 210° and decomposed to a dark red mass at 215° (Found : C, 50·1; H, 4·3. $C_{22}H_{22}O_3N_2ClI$ requires C, 50·4; H, 4·2%).

The *methopicrate* separated from aqueous alcohol, in which it dissolved to a dark red solution, in golden-yellow needles, decomp. 168—169° [Found : N, 13·4.

$$C_{22}H_{22}O_3N_2Cl(O{\cdot}C_6H_2O_6N_3),C_6H_2(NO_2)_3{\cdot}OH$$

requires N, 13·2%].

4-*Chloro*-3-o-*carbomethoxyphenylmethylcarbamyl*-2-*methylquinoline methochloride*, prepared by treating the gummy acid chloride with methyl alcohol and precipitated from the resulting red solution by ethyl acetate, crystallised from ethyl alcohol, on addition of ethyl acetate, in white needles. These began to turn purple at 145° and melted to a purple mass at 189—190° (Found : C, 57·7; H, 5·3; N, 6·8. $C_{21}H_{20}O_3N_2Cl_2,H_2O$ requires C, 57·7; H, 5·0; N, 6·4%). The *methiodide* formed golden-yellow needles, m. p. 214° (decomp.) (Found : N, 5·7. $C_{21}H_{20}O_3N_2ClI$ requires N, 5·5%).

4-*Anilino*-3-o-*carbethoxyphenylmethylcarbamyl*-1-*methyl*-2-*methylene*-1 : 2-*dihydroquinoline* (X).—The red solution obtained by refluxing 4-chloro-3-*o*-carbethoxyphenylmethylcarbamyl-2-methylquinoline methochloride (2 g.) and aniline (2 g.) in glacial acetic acid (5 c.c.) for 1 hour was diluted with water, extracted with ether to remove acetanilide, and rendered alkaline. The precipitated *methylene base*, removed and dried in ether, crystallised from alcohol (charcoal), on slight dilution with water, in orange prisms, m. p. 191—192°; it dissolved readily in mineral acids to give yellow solutions (Found : C, 74·5; H, 6·1; N, 9·3. $C_{28}H_{27}O_3N_3$ requires C, 74·2; H, 6·0; N, 9·3%).

The corresponding 4-*piperidino-methylene base* was obtained in a similar manner by refluxing an alcoholic solution of the ethyl ester with piperidine. It separated from benzene–light petroleum in yellow needles, m. p. 260°, readily soluble in dilute acids and the usual organic solvents with the exception of light petroleum (Found : C, 73·0; H, 6·9; N, 9·8. $C_{27}H_{31}O_3N_3$ requires C, 72·8; H, 7·0; N, 9·4%).

4-*Anilino*-3-o-*anilinophenylmethylcarbamyl*-1-*methyl*-2-*methylene*-1 : 2-*dihydroquinoline* was obtained by refluxing the acid chloride reaction product with aniline; the whole set to a brittle mass, which was extracted with alcohol. The yellow powder precipitated on dilution of the alcoholic solution with dilute hydrochloric acid was repeatedly dissolved in alcohol and precipitated with water. Although readily soluble in alcohol, benzene, and acetone, giving deep red solutions showing a brilliant green fluorescence, this compound could not be obtained in a crystalline form. It melted indefinitely at about 165° with previous softening (Found : N, 11·6. $C_{32}H_{28}O_2N_4$ requires N, 11·2%).

*Acid Hydrolysis of 4-Chloro-3-*o*-carbethoxyphenylmethylcarbamyl-2-methylquinoline Methochloride.*—The ester (5 g.) was gently boiled for 6 hours under reflux with concentrated hydrochloric acid (150 c.c.), and the cooled solution was almost neutralised with alkali and extracted with ether to remove methylanthranilic acid. The aqueous portion was concentrated under reduced pressure; 4-hydroxyquinaldine methochloride, which separated slowly, after several crystallisations from alcohol–ether, was obtained in colourless needles, m. p. 217° (Found : C, 58·2; H, 6·3; N, 6·5. Calc. for $C_{11}H_{12}ONCl,H_2O$: C, 58·2; H, 6·2; N, 6·2%).

*4′-Chloro-*3 : 3′-*di*(o-*carbethoxyphenylmethylcarbamyl*)-1 : 2 : 1′-*trimethyl*isocyanine *Iodide* (XII).—A solution of 4-chloro-3-*o*-carbethoxyphenylmethylcarbamyl-2-methylquinoline methochloride (2 g.) in hot absolute alcohol, when treated with 10 c.c. of dilute ammonia (equivalent to 0·24 c.c. of NH_3 *d* 0·88), became reddish-purple; it was boiled for ½ hour and then treated with a slight excess of concentrated potassium iodide solution. The *iodide* slowly separated from the cold solution in tiny, brownish-olive needles having a bronze reflex. On heating, the salt darkened at 200° and decomposed to a black mass at 203°. It was somewhat sparingly soluble in water and alcohol, giving intense purple solutions the colour of which was discharged on addition of excess of mineral acid. The dye showed two well-defined bands with heads at 574 μμ and 325 μμ (Found : C, 59·5; H, 4·6; N, 6·5. $C_{44}H_{42}O_6N_4ClI$ requires C, 59·7; H, 4·8; N, 6·3%). The *perchlorate* formed a heliotrope powder soluble in alcohol and benzene to purple solutions. The *picrate*, precipitated from an alcoholic solution of the iodide by means of sodium picrate, separated in wine-coloured needles with a metallic reflex, containing two molecules of picric acid; it is practically insoluble in water and sparingly soluble in alcohol (Found : N, 11·4. $C_{56}H_{47}O_{10}N_{10}Cl$ requires N, 11·5%).

5-Bromomethylanthranilic Acid.—Methylanthranilic acid (22·5 g.) was dissolved in chloroform, and bromine (24 g.) slowly run in. The solid obtained, after being washed with cold chloroform, crystallised from dilute alcohol in cream-coloured needles, m. p. 185—186° (yield, 73%). Mixed with 5-*bromomethylanthranilic acid* prepared by Wheeler and Oates's method (*J. Amer. Chem. Soc.*, 1910, **32**, 770), it showed no depression of m. p. (Found : N, 6·4. $C_8H_8O_2NBr$ requires N, 6·1%).

5-Bromomethylacetylanthranilic Acid.—Great difficulty was experienced in acetylating 5-bromomethylanthranilic acid. By the use of acetic anhydride alone, a high-melting compound (above 300°) was obtained which was not further examined. The method finally adopted consisted in refluxing the acid (12 g.) with a mixture of acetic anhydride (70 c.c.), glacial acetic acid (5 c.c.), water (10 c.c.), and a trace of *d*-camphorsulphonic acid. The solution was poured into water, and the solid recrystallised from dilute alcohol. 5-*Bromomethylacetylanthranilic acid* forms colourless prisms, m. p. 204° (yield, 70%) (Found: C, 44·4; H, 3·6. $C_{10}H_{10}O_3NBr$ requires C, 44·1; H, 3·7%).

6-*Bromo*-3-p-*bromo*-o-*carbethoxyphenylmethylcarbamyl*-1 : 2-*dimethyl*-4-*quinolone*.—The above acid (5 g.) was suspended in acetyl chloride (50 c.c.) and treated with phosphorus pentachloride (2 g.; ½ mol.). No reaction occurred in the cold, but on heating on the water-bath under reflux the original solid material dissolved to a yellow solution, from which a yellow solid gradually separated. This was worked up in a precisely similar manner to that detailed in the case of the parent quinolone. The *ester*, crystallised from alcohol and then from acetone, was obtained as a hydrate, m. p. 123°. The anhydrous compound, which forms colourless crystals, m. p. 212°, was obtained by dissolving the hydrated product in boiling benzene and allowing the solution to crystallise after the addition of light petroleum (Found: C, 49·2; H, 3·9; N, 5·6. $C_{22}H_{20}O_4N_2Br_2$ requires C, 49·3; H, 3·7; N, 5·2%).

4-*Chloro*-6-*bromo*-3-p-*bromo*-o-*carbethoxyphenylmethylcarbamyl*-2-*methylquinoline methochloride* was prepared by heating 5-bromomethylacetylanthranilic acid with phosphorus pentachloride (1½ mols.) in acetyl chloride solution as described under the preparation of (IX). The residual gum was decomposed with alcohol, and the *methochloride* precipitated from the resultant deep red solution by addition of ether. The product crystallised from alcohol–ether in colourless needles, m. p. 194°. It exhibited the same properties as the parent compound and readily passed into the *iso*cyanine dye on treatment with alkali (Found: C, 43·3; H, 4·0; N, 5·0. $C_{22}H_{22}O_3N_2Cl_2Br_2,H_2O$ requires C, 43·3; H, 3·6; N, 4·6%).

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