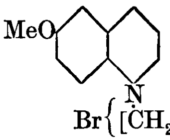
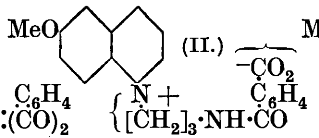
CCCXCVIII.—*Attempts to find New Anti-malarials. Part II. Aminoalkylquinolinium Salts and Some Related Substances.*

By TIRUVENTAKA RAJENDRA SESHADRI.

GABRIEL (*Ber.*, 1920, **53**, 1985) obtained quaternary salts by the interaction of β-bromoethylphthalimide with pyridine and trimethylamine, and the present communication describes the preparation of similar derivatives of quinoline, 6-methoxyquinoline, and *iso*quinoline; moreover, γ-bromopropylphthalimide has been employed in addition to the lower homologue. The types of substance obtained in the course of the work are illustrated by following the case of γ-phthalimidopropyl-6-methoxyquinolinium bromide (I). This, by the action of silver oxide and water, yields a *betaine* (II) which is hydrolysed by boiling concentrated hydrochloric acid, giving the *quaternary chloride hydrochloride* (III). At 150° in a sealed tube, demethylation occurs under the influence of concentrated hydrochloric acid.


(I.)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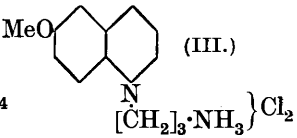
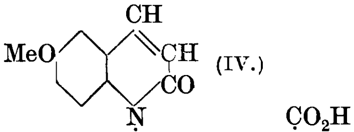
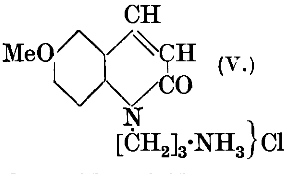

(III.)

Oxidation of the carbinol-amines, corresponding to type (III), did not proceed smoothly, but the phthalimido-salts were easily transformed by ferricyanide in alkaline solution into quinolones of the type (IV) (compare Decker, *J. pr. Chem.*, 1892, **45**, 161).


(IV.)

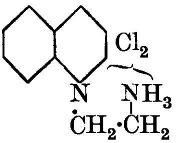

(V.)

The latter were readily hydrolysed by acids, yielding (V) and analogous salts, but the corresponding phthalimides obtained by heating the phthalamic acids were resistant to hydrolysis.

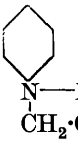
It will serve to avoid repetitions in the experimental section to note that the quaternary bromides and chlorides were very hygroscopic; they all tended to retain solvent of crystallisation at 100°. For analysis, the specimens were dried at 110° in a good vacuum, unless otherwise stated.

When sodium hydroxide was added to an aqueous solution of β-aminoethylquinolinium bromide hydrobromide (as VI), an oily base was precipitated and soon crystallised. This discoloured in contact with air; it was freely soluble in ether, benzene, or chloroform and is, therefore, not an ammonium hydroxide. The original salts were recoverable by the action of the appropriate acids. Gabriel (*loc. cit.*) regarded a corresponding pyridine derivative as (VII), but the formula (VIII) is now suggested as being more in accordance with modern conceptions.

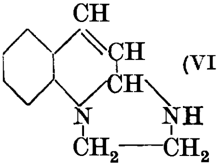
VI.)



(VII.)



(VIII.)



EXPERIMENTAL.

β-*Phthalimidoethylquinolinium Bromide* (IX, as I).—β-Bromoethylphthalimide was conveniently made in the same way as γ-bromopropylphthalimide (Ing and Manske, J., 1926, 2349), and had m. p. 83° after crystallisation from alcohol (compare Gabriel, *Ber.*, 1889, **22**, 1137). Combination with quinoline occupied 6 hours at 100°, and the product, a coloured crystalline solid, was washed successively with ether and a restricted volume of hot alcohol. After repeated crystallisations from hot water (charcoal), the *bromide* was obtained in stout, colourless prisms, m. p. 264—265° (yield, 70%) (Found: Br, 20·8. $C_{19}H_{15}O_2N_2Br$ requires Br, 20·9%). The picrate crystallised from water in yellow plates, m. p. 216—218°.

β-*Aminoethylquinolinium Bromide Hydrobromide.*—The above bromide was boiled with aqueous hydrobromic acid (saturated at 0°, mixed with an equal volume of water) for 5 hours; the yield was quantitative. Phthalic acid was separated after cooling, and the solution evaporated to dryness. The *hydrobromide* crystallised from aqueous alcohol in colourless cubes, melting at 275—277° to a red liquid (Found: Br, 47·8. $C_{11}H_{14}N_2Br_2$ requires Br, 47·9%).

The corresponding *chloride hydrochloride* (VI), prepared in the same way as its 6-methoxy-derivative (below), crystallised from aqueous alcohol in colourless, rectangular prisms, m. p. 270—271° (Found: Cl, 28·9. $C_{11}H_{14}N_2Cl_2$ requires Cl, 28·9%). The picrate forms yellow cubes, m. p. 238—239°.

1-β-o-*Carboxybenzamidoethyl-2-quinolone* (X, as IV) *and* 1-β-*Phthalimidoethyl-2-quinolone* (XI).—Oxidation of (IX) by means of alkaline potassium ferricyanide in the manner described below in other cases gave a mixture of these substances, and (X) could not be obtained pure on account of the ease with which it yields (XI) by dehydration. The mixture was, therefore, heated, and the dehydration to (XI) was rapid at 100°. The *product* was very sparingly soluble in alcohol and crystallised from acetic acid in colourless tetrahedra, m. p. 272—273° (Found : N, 8·7. $C_{19}H_{14}O_3N_2$ requires N, 8·8%).

1-β-*Aminoethyl*-2-*quinolone Hydrochloride*.—This salt was obtained by boiling the mixture of (X) and (XI) with dilute hydrochloric acid. The alkylphthalimide remained undissolved and the yield was small, owing to the rapid formation of this substance. In a sealed tube at 150°, the hydrolysis was, however, complete. The *salt* crystallised from ethyl alcohol in colourless, rectangular plates, m. p. 245—246° (Found : Cl, 15·6. $C_{11}H_{13}ON_2Cl$ requires Cl, 15·8%). The picrate, yellow needles from water, has m. p. 225° (decomp.).

γ-*Phthalimidopropylquinolinium Bromide* (XII).—As in other reactions, γ-bromopropylphthalimide condensed with quinoline more smoothly than β-bromoethylphthalimide under similar conditions. The additive *product*, readily soluble in water, crystallised from alcohol in colourless, stout prisms, m. p. 259—260° (Found : Br, 20·3. $C_{20}H_{17}O_2N_2Br$ requires Br, 20·1%).

Hydrolysis with boiling aqueous hydrobromic acid furnished γ-*aminopropylquinolinium bromide hydrobromide* in good yield. This salt crystallised from aqueous alcohol in colourless rhombohedra, melting at 271—273° to a red liquid (Found : Br, 45·8. $C_{12}H_{16}N_2Br_2$ requires Br, 45·9%). The corresponding *chloride hydrochloride* crystallised from aqueous alcohol in rectangular rods, m. p. 267—268° (Found : Cl, 27·3. $C_{12}H_{16}N_2Cl_2$ requires Cl, 27·4%).

The substance (XII) was oxidised in the usual manner (see below), and the acid precipitated from the alkaline solution was twice crystallised from alcohol in colourless, rhombic prisms, m. p. 153—154° (decomp.) (Found : C, 68·2; H, 5·3. $C_{20}H_{18}O_4N_2$ requires C, 68·6; H, 5·1%). This 1-γ-o-*carboxybenzamidopropyl*-2-*quinolone* is stable at 100°, but is dehydrated at its m. p. to the related phthalimide derivative. The latter crystallises from alcohol in colourless cubes, m. p. 149—150°.

On hydrolysis by means of 15% hydrochloric acid, the substituted phthalamic acid or phthalimide yields 1-γ-*aminopropyl*-2-*quinolone hydrochloride*, colourless needles, m. p. 217—218° (Found : Cl, 14·8. $C_{12}H_{15}ON_2Cl$ requires Cl, 14·9%), from alcohol.

β-*Phthalimidoethyl*-6-*methoxyquinolinium Bromide* (XIII; as I).—When equimolecular quantities of 6-methoxyquinoline and β-bromoethylphthalimide were heated together at 100°, crystals appeared after 15 minutes, and after 6 hours the mass had solidified completely.

The powdered product was extracted with a little hot alcohol, and the undissolved *salt* (yield, 60%) crystallised from boiling water in colourless, rectangular plates, m. p. 248—250° (decomp.). The crystals retain $1H_2O$ at 100°, but are completely dehydrated by heating at 110° under diminished pressure (Found, in anhydrous material: N, 6·7; Br, 19·1. $C_{20}H_{17}O_3N_2Br$ requires N, 6·8; Br, 19·4%). The picrate crystallised from hot water in golden-yellow plates, m. p. 199—200°.

β-*Aminoethyl*-6-*methoxyquinolinium Chloride Hydrochlortde* (XIV; as III) (R. 12).—A dilute aqueous solution of (XIII) was shaken with freshly precipitated alkali-free silver oxide until precipitation of silver bromide was completed. The filtered solution was rendered slightly acid with hydrochloric acid, and concentrated on the steam-bath. The concentration of hydrochloric acid was then raised to about 15% and the liquid refluxed for 5 hours [the volume was adjusted to 5—10 c.c. per g. of (XIII)]; after cooling, the phthalic acid that separated was removed, and the filtrate evaporated to dryness. The *salt* was obtained by washing this residue with alcohol in an almost pure condition and in practically quantitative yield; it crystallised from alcohol containing a few drops of water in flat, colourless needles, m. p. 264—265° (decomp.) (Found: C, 52·5; H, 6·1; Cl, 25·7. $C_{12}H_{16}ON_2Cl_2$ requires C, 52·4; H, 5·9; Cl, 25·8%). On the addition of sodium hydroxide to an aqueous solution, a red oil, changing to a pasty solid, was precipitated. The picrate crystallised from water in yellow plates, m. p. 203—205°, with slight previous sintering.

β-*Aminoethyl*-6-*hydroxyquinolinium Chloride Hydrochloride* (R. 9). —Demethylation of (XIV) was effected by heating with five times its weight of concentrated hydrochloric acid at 150—160° in a sealed tube for 4—5 hours. The solution was evaporated to dryness, and the colourless, crystalline residue (yield, quantitative) crystallised from alcohol containing a few drops of concentrated hydrochloric acid in colourless, rectangular rods, m. p. 267—269° (Found: C, 51·0; H, 5·3. $C_{11}H_{14}ON_2Cl_2$ requires C, 50·6; H, 5·4%). An aqueous solution of this salt became dark red on the addition of ferric chloride. The picrate crystallised from water in yellow plates, m. p. 248—249° (decomp.) with slight previous softening.

1-β-o-*Carboxybenzamidoethyl*-6-*methoxy*-2-*quinolone* (XV, as IV).—A cold, dilute, aqueous solution of (XIII) (8·0 g.) was gradually added with shaking to one of potassium ferricyanide (12·0 g.) containing sodium hydroxide (4·0 g.); after 1 hour, the oxidation was completed by 15 minutes' heating on the steam-bath. The liquid was then cooled in an ice-bath and carefully acidified with hydrochloric acid until incipient separation of ferrocyanic acid occurred. The rather sticky precipitate was isolated and crystallised from alcohol in colourless, rectangular rods, m. p. 144—145° (decomp.)

(yield, 5·0 g.) (Found: C, 65·1; H, 4·8. $C_{20}H_{18}O_5N_2$ requires C, 65·6; H, 4·9%). When this *substance* was heated to 140—150°, it lost its power of dissolution in aqueous sodium carbonate, being changed by loss of water into 1-β-*phthalimidoethyl*-6-*methoxy*-2-*quinolone*. This substance, devoid of acidic or basic properties, crystallised from ethyl alcohol in colourless, rhombic plates, m. p. 188—189° (Found: C, 69·2; H, 4·4. $C_{20}H_{16}O_4N_2$ requires C, 69·0; H, 4·6%). This imide is quite stable towards boiling concentrated hydrochloric acid, although the phthalamic acid can be hydrolysed as shown below.

1-β-*Aminoethyl*-6-*methoxy*-2-*quinolone Hydrochloride* (XVI) (R. 10).—The acid (XV) (4·0 g.) was boiled with 15% hydrochloric acid (100 c.c.) for 15 minutes, whereupon crystals separated from the clear solution. After ½ hour on the steam-bath, the liquid was cooled and filtered. The solid (1·0 g.) was found to consist of the above-described phthalimide derivative, m. p. 188—189°, and the solution was evaporated to dryness, and the residue washed with alcohol in order to remove phthalic acid; it crystallised from alcohol containing a few drops of water as a voluminous mass of feathery needles, m. p. 266—267° (yield, 1·5 g.) (Found: C, 57·0; H, 5·6; Cl, 13·8; MeO, 11·6. $C_{12}H_{15}O_2N_2Cl$ requires C, 56·6; H, 5·9; Cl, 13·9; 1MeO, 12·2%). This *salt* is sparingly soluble in alcohol and readily soluble in water. The picrate formed deep yellow needles, m. p. 237°.

1-β-*Aminoethyl*-6-*hydroxy*-2-*quinolone Hydrochloride* (R. 13).—Compound (XVI) was demethylated in exactly the same way as (XIV), and the product crystallised from ethyl alcohol containing hydrochloric acid as a mass of colourless, flat needles, m. p. 281—282° (decomp.) (Found: C, 54·9; H, 5·4; Cl, 14·7. $C_{11}H_{13}O_2N_2Cl$ requires C, 54·9; H, 5·4; Cl, 14·7%). An aqueous solution gave a deep blue coloration with ferric chloride, and a red coloration with nitric acid. The picrate crystallised from aqueous alcohol in golden-yellow, truncated pyramids, m. p. 254—256°.

γ-*Phthalimidopropyl*-6-*methoxyquinolinium Bromide* (I).—This salt separated in 70% yield from the hot alcoholic solution of the glassy mass obtained by heating equimolecular proportions of γ-bromopropylphthalimide and 6-methoxyquinoline at 100° for 6 hours. The colourless, rhombic prisms melted at 125—127° with vigorous decomposition; the resulting oil crystallised again on scratching with a glass rod, and the m. p. was then 198—200°. The anhydrous salt was extremely hygroscopic, becoming pasty in the air and then crisp again when the requisite amount of water was absorbed. The salt is readily soluble in water, but can be crystallised from concentrated solutions in prisms, m. p. 125—127°. This *hydrate* retains $\frac{1}{2}H_2O$ at

100°, but loses all its water at 110° in a vacuum (Found, after drying: N, 6·7; Br, 18·7. $C_{21}H_{19}O_3N_2Br$ requires N, 6·6; Br, 18·7%). Both the hydrated and the anhydrous specimen dissolved readily in chloroform. The picrate was obtained in deep yellow rhombohedra, m. p. 208—210°.

*Anhydro-γ-*o*-carboxybenzamidopropyl-*6*-methoxyquinolinium Hydroxide* (II).—A hot aqueous solution of (I) was shaken with an excess of silver oxide and filtered; a bulky mass of colourless needles separated on cooling, the yield being almost quantitative. This *betaine* was sparingly soluble in cold water or alcohol, and crystallised from these solvents in needles which sintered at 140° and turned pink and underwent vigorous decomposition at 198—199° (Found, in an air-dried specimen: C, 60·0; H, 6·4. $C_{21}H_{20}O_4N_2,3H_2O$ requires C, 60·3; H, 6·2%). The substance was readily soluble in cold, dilute hydrochloric acid, but insoluble in cold, aqueous sodium hydroxide; on heating, the solution became crimson.

*γ-Aminopropyl-*6*-methoxyquinolinium Chloride Hydrochloride* (III) (R. 6).—The betaine (II) was dissolved in five times its weight of 15% hydrochloric acid, and the solution refluxed for 5 hours. After cooling and separation of phthalic acid, the solution was evaporated to dryness; the residue crystallised from aqueous alcohol in colourless needles, m. p. 259—261° (decomp.) (Found: C, 54·4; H, 5·9; Cl, 24·4. $C_{13}H_{18}ON_2Cl_2$ requires C, 54·0; H, 6·2; Cl, 24·5%). On demethylation (as with XIV), *γ-aminopropyl-*6*-hydroxyquinolinium chloride hydrochloride* (R. 8) was obtained. This salt crystallised from alcohol containing hydrochloric acid in colourless, rectangular rods, m. p. 274—276° (Found: Cl, 25·6. $C_{12}H_{16}ON_2Cl_2$ requires Cl, 25·8%); its aqueous solution gave a brownish-red coloration with ferric chloride and a deep yellow coloration with sodium hydroxide.

1-*γ-*o*-Carboxybenzamidopropyl-*6*-methoxy-*2*-quinolone* (IV).—The preparation of this *acid* from (I) was like that of (XV) from (XIII) (above) and the yield was very good. The substance crystallised from alcohol in colourless, rectangular prisms, m. p. 164—165° (decomp.) (Found: C, 66·6; H, 5·1. $C_{21}H_{20}O_5N_2$ requires C, 66·3; H, 5·3%). Although stable at 100°, (IV) is changed at its m. p. into 1-*γ-phthalimidopropyl-*6*-methoxy-*2*-quinolone*, colourless, rectangular plates from alcohol, m. p. 149—150° (Found: C, 69·2; H, 4·8. $C_{21}H_{18}O_4N_2$ requires C, 69·6; H, 5·0%). On boiling with 15% hydrochloric acid for ½ hour, (IV) gave this substituted phthalimide in 20% yield, and the solution contained 1-*γ-aminopropyl-*6*-methoxy-*2*-quinolone hydrochloride* (V) (R. 7), which crystallised from aqueous alcohol in colourless needles, m. p. 239—240° (Found: C, 57·7; H, 6·3. $C_{13}H_{17}O_2N_2Cl$ requires C, 58·1; H, 6·3%). Demethylation of (IV), or the related phthalimide, or (V) in the usual manner yielded 1-γ-*aminopropyl*-6-*hydroxy*-2-*quinolone hydrochloride* (R. 11), which separated from ethyl alcohol containing hydrochloric acid in colourless, compact, rhombohedral plates, m. p. 277—279° (Found : C, 57·0; H, 6·2; Cl, 14·0. $C_{12}H_{15}O_2N_2Cl$ requires C, 56·6; H, 5·9; Cl, 13·9%). The reactions of this compound resembled very closely those of the analogous substance in the aminoethyl series.

β-*Phthalimidoethyl*iso*quinolinium Bromide* (XVII).—The product obtained by heating equal quantities of *iso*quinoline and β-bromoethylphthalimide at 100° was practically pure after being washed with ether and subsequently with a small volume of hot alcohol. The yield was quantitative, calculated on the bromoethylphthalimide. The *bromide* is sparingly soluble in alcohol, and crystallised from water in colourless rhombohedra, m. p. 291—292° (Found : Br, 20·7. $C_{19}H_{15}O_2N_2Br$ requires Br, 20·9%). By treatment with boiling hydrobromic acid exactly as in the case of the quinoline derivative, the *hydrobromide* of β-*aminoethyl*iso*quinolinium bromide* was readily obtained in a pure condition. This salt crystallised from dilute ethyl alcohol in colourless prisms, m. p. 286—288° (Found : Br, 48·0. $C_{11}H_{14}N_2Br_2$ requires Br, 47·9%).

β-*Aminoethyl*iso*quinolinium Chloride Hydrochloride* (XVIII).—When an aqueous solution of (XVII) was shaken with an excess of freshly precipitated silver oxide and the filtered solution evaporated on the steam-bath, the betaine remained as a dark syrup which crystallised on stirring. After repeated crystallisation from ethyl alcohol (charcoal), it was obtained in colourless, square tablets, m. p. 186—189° (decomp.). Hydrolysis with dilute hydrochloric acid yielded (XVIII), which, however, could be obtained in better yield in the same way as the quinoline derivative without isolating the intermediate betaine. The *hydrochloride* crystallised from aqueous alcohol in colourless, rhombic prisms, m. p. 273—275° (Found : Cl, 28·8. $C_{11}H_{14}N_2Cl_2$ requires Cl, 28·9%).

2-β-o-*Carboxybenzamidoethyl*iso*quinolone* (XIX).—Oxidation of (XVII) by the method already described in other cases gave a good yield of the acid (XIX), which crystallised from ethyl alcohol in colourless, thin needles, m. p. 167—168° (decomp.). The product of decomposition, namely, 2-β-*phthalimidoethyl*iso*quinolone*, crystallised from ethyl alcohol in colourless needles, m. p. 185—186° (Found : N, 8·6. $C_{19}H_{14}O_3N_2$ requires N, 8·8%).

2-β-*Aminoethyl*iso*quinolone hydrochloride* was derived by methods analogous to those already described. It crystallised from ethyl alcohol in colourless laminæ, m. p. 237—239° (Found : Cl, 15·5. $C_{11}H_{13}ON_2Cl$ requires Cl, 15·8%).

γ-*Phthalimidopropyl*iso*quinolinium bromide* (XX), obtained from γ-propylphthalimide and *iso*quinoline, was easily soluble in ethyl alcohol and in water, and crystallised in colourless rhombohedra, m. p. 243—245° (Found: Br, 20·3. $C_{20}H_{17}O_2N_2Br$ requires Br, 20·1%). From it were obtained by the usual methods the *hydrobromide* of *γ-aminopropyl*iso*quinolinium bromide* as colourless prisms from aqueous ethyl alcohol, m. p. 228—229° (Found: Br, 45·8. $C_{12}H_{16}N_2Br_2$ requires Br, 45·9%), and the *hydrochloride* of *γ-aminopropyl*iso*quinolinium chloride* as colourless cubes (very hygroscopic) from ethyl alcohol, m. p. 236—237° with marked sintering at about 135° (Found: Cl, 27·4. $C_{12}H_{16}N_2Cl_2$ requires Cl, 27·4%).

The oxidation of (XX) with alkaline ferricyanide gave a semisolid product which could not be crystallised. When it was boiled for ½ hour with hydrochloric acid (15%) and cooled, a colourless, crystalline precipitate was the major product. This was 2-*γ-phthalimidopropyl*iso*quinolone*, insoluble in aqueous sodium carbonate, and easily crystallisable from ethyl alcohol in colourless, flat needles, m. p. 157—158° (Found: N, 8·4. $C_{20}H_{16}O_3N_2$ requires N, 8·4%). When hydrolysed with concentrated hydrochloric acid in a sealed tube at 140—150°, it gave rise to 2-*γ-aminopropyl*iso*quinolone hydrochloride*, which crystallised from ethyl alcohol in colourless, thin needles, m. p. 189—191° (Found: Cl, 14·8. $C_{12}H_{15}ON_2Cl$ requires Cl, 14·9%).

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