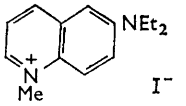
818. *The Quaternary Salts of 6-Dialkylaminoquinolines*

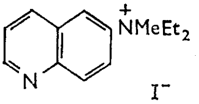
By W. O. Sykes

By the identification of their ferricyanide oxidation products, the directly-prepared methiodides of 6-diethylaminoquinoline and 1,2,3,4-tetrahydro-4-methyl-4,7-phenanthroline are both shown conclusively to be quinolinium-type salts. The respective isomeric quinolinylammonium salts are prepared by a method of general application, *i.e.*, by means of a Skraup reaction performed on the appropriate aromatic acetamido-compound carrying a quaternary ammonium group as nuclear substituent. The diquaternary iodide of 6-diethylaminoquinoline is conveniently prepared from the quinolinylammonium salt.

From the time of the earliest studies[1] of the direct quaternisation of 6-dialkylamino-quinolines, it has been assumed that the principal products are quinolinium salts such as compound (I) and not quinolinylammonium salts such as compound (II).



(I)



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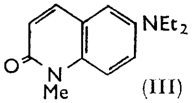

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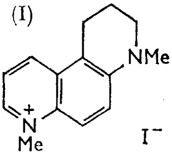

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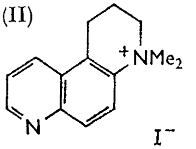

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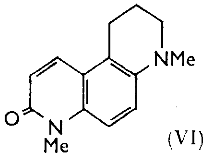

(VI)

However, the direct chemical evidence in support of the quinolinium structure for such products has hitherto consisted only of the finding that they are converted into dyes[2] when they are subjected to the usual conditions for the preparation of cyanines, together with positive identification of the quaternised product[3] in the single closely-related case of 6-aminoquinoline methiodide. Karrer, Pletscher, and Manz,[4] on the other hand, represent as (V) the structure of the methiodide of the analogous base 1,2,3,4-tetrahydro-4-methyl-4,7-phenanthroline, and this formulation would account for the failure of dithionite to reduce the salt.[4]

We have now obtained conclusive evidence that the products of direct quaternisation, with iodomethane, of 6-diethylaminoquinoline and of 1,2,3,4-tetrahydro-4-methyl-4,7-phenanthroline are the quinolinium-type salts (I) and (IV), respectively.

The red methiodide prepared directly from 6-diethylaminoquinoline was oxidised by alkaline ferricyanide to yield 6-diethylamino-1,2-dihydro-1-methyl-2-oxoquinoline (III), which also was the product obtained by diethylating the known[5] 6-amino-compound; the methiodide is therefore the salt (I). In its formation only a minute proportion of another quaternised product, the dimethiodide, was detected.

Barbier[2] concluded that the relatively colourless contaminants found in some quaternised products, particularly those derived from 6-dialkylaminoquinaldines, were quinolinyl-ammonium salts. We have synthesised such a salt by applying the Skraup reaction to *N*-(4-acetamidophenyl)-*NN*-diethylmethylammonium iodide. The product was isolated as the dipicrate from which the faintly coloured methiodide (II) was obtained. This salt

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[1] W. La Coste, *Ber.*, 1883, **16**, 669.
[2] H. Barbier, *Bull. Soc. chim. France*, 1920, [4], **27**, 427.
[3] H. Decker and A. Kaufmann, *J. prakt. Chem.*, 1911, [2], **84**, 425.
[4] P. Karrer, A. Pletscher, and W. Manz, *Helv. Chim. Acta*, 1947, **30**, 1146; 1948, **31**, 1431.
[5] H. Decker and H. Engler, *Ber.*, 1903, **36**, 1169.

was converted into a mixture of red salts by heating it strongly in ethanolic solution as prescribed by Barbier [2] for the isomerisation of his atypical quaternised products. The isolated product was not the salt (I); presumably, it was a 6-dialkylamino-1-ethylquinolinum iodide. Paper chromatography revealed the presence in the mother-liquor of a mixture of red salts among which the salt (I) figured prominently. In this connection, it is interesting to note that apparently no considerable degree of isomerisation took place in the conditions of the Skraup reaction described above, and this accords with the finding [6] for certain 5-substituted 4-methyl-4,7-phenanthrolinium salts which also have to be prepared by means of a Skraup reaction.

Whilst the diquaternary salt, a compound not previously described, was readily formed by reaction of iodomethane with *NN*-diethyl-*N*-methyl-6-quinolinylammonium iodide (II), only a trace of the salt was produced by similar treatment of 6-diethylamino-1-methylquinolinium iodide (I), as would be expected from the excellent preparative characteristics of the latter. The monoquaternary (quinolinium) salt persisted as a large proportion of the product even when a methyl toluene-*p*-sulphonate solution of the base was boiled for two minutes.

In view of the clear-cut response of 6-diethylaminoquinoline to direct quaternisation, the report [3] that an impure product is obtained by reacting 6-aminoquinoline with iodomethane is remarkable. We, also, have found this contamination, even when mild conditions are used for the reaction, and we have detected the presence of 6-aminoquinoline (presumed hydriodide) in the impure product.

The red methiodide prepared [4] from 1,2,3,4-tetrahydro-4-methyl-4,7-phenanthroline was oxidised with alkaline ferricyanide, and the product was found to be identical with the 1,2,3,4,7,8-hexahydro-4,7-dimethyl-8-oxo-4,7-phenanthroline (VI) obtained by catalytic hydrogenation of the known [7] 3,4-dihydro-4,7-dimethyl-3-oxo-4,7-phenanthrolinium iodide; therefore, this directly prepared methiodide is compound (IV).

We have found that the Skraup reaction applied to 6-acetamido-1,2,3,4-tetrahydro-1-methylquinoline (prepared by catalytic reduction of 6-acetamido-1-methylquinolinium iodide) produces 1,2,3,4-tetrahydro-4-methyl-4,7-phenanthroline, which has previously been prepared [4] by catalytic reduction of 4-methyl-4,7-phenanthrolinium iodide. It is possible that this Skraup reaction may have produced, along with the phenanthroline derivative isolated, some of the isomeric diaza-anthracene, for the corresponding " angular " and " linear " annulated compounds were identified [8] as products of a Skraup reaction performed on 6-amino-1,2,3,4-tetrahydronaphthalene. It is noteworthy, however, that Lindner [9] also isolated only the phenanthroline derivative from the products of a Doebner–von Miller reaction applied to 6-amino-1,2,3,4-tetrahydro-1-methylquinoline. When 6-acetamido-1,2,3,4-tetrahydro-1-methylquinoline was replaced in the Skraup reaction by its methiodide, a new quaternary salt was produced, and it was isolated as its perchlorate in good yield. Its pale yellow iodide was converted into the deep red salt (IV) by heating it in ethanolic solution; the Skraup reaction product is, therefore, confirmed to be a salt of which the corresponding iodide is compound (V).

EXPERIMENTAL

6-*Diethylamino*-1-*methylquinolinium Iodide* (I).—When 6-diethylaminoquinoline was heated in acetone solution with an excess of iodomethane for 15 min. at 100°, or 1 hr. at 37°, an excellent yield of almost pure *methiodide* was obtained. It crystallised from butanol–ethyl acetate as orange-red prisms, m. p. 162° (Found: I, 37·5. $C_{14}H_{19}IN_2$ requires I, 37·1%). On no occasion was the product of m. p. 148° described by Barbier [2] isolated.

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[6] W. O. Sykes, *J.*, 1953, 3543.
[7] B. Douglas, R. G. Jacomb, and W. O. Kermack, *J.*, 1947, 1659.
[8] J. von Braun and H. Grüber, *Ber.*, 1922, **55**, 1710.
[9] J. Lindner, *Monatsh.*, 1921, **42**, 421.

The very small residues obtained by evaporating to dryness the acetone mother-liquors contained, as revealed by paper chromatography, the 1-methylquinolinium salt together with a trace of the diquaternary salt.

6-*Diethylamino*-1,2-*dihydro*-1-*methyl*-2-*oxoquinoline* (III).—(*a*) The iodide (I) (5 g.) was oxidised in cold aqueous solution with potassium ferricyanide solution (10%; 120 ml.) added in alternate portions with sodium hydroxide solution (10%; 30 ml.). A dried chloroform extract of the reaction mixture left, on evaporation, a residue of *oxo-compound* (2·8 g.) which crystallised from light petroleum as yellow prisms, m. p. 77—78° (Found: C, 73·2; H, 7·9. $C_{14}H_{14}N_2O$ requires C, 73·0; H, 7·9%).

The *methiodide*, prepared by heating the oxo-compound with an excess of iodomethane in acetone, crystallised from ethanol–ethyl acetate as pale yellow prisms, m. p. about 175° (decomp.) (Found: I, 34·9. $C_{15}H_{21}IN_2O$ requires I, 34·1%).

(*b*) 6-Amino-1,2-dihydro-1-methyl-2-oxoquinoline (4 g.) was heated in a sealed tube with iodoethane (8·5 g.), sodium hydroxide (2 g.), and water (2 ml.) for 6 hr. at 120°. A dried benzene extract of the diluted reaction mixture was distilled to yield a solidifying fraction (1 g.), m. p. about 75°, which after recrystallisation from light petroleum had m. p. 77—78°, not depressed by admixture with the above oxo-compound (III).

NN-*Diethyl*-N-*methyl*-6-*quinolinylammonium Iodide* (II).—*N*-(4-Acetamidophenyl)-*NN*-diethylmethylammonium iodide (10 g.) was refluxed in a mixture with sulphuric acid (*d* 1·84; 20 ml.) water (16 ml.), glycerol (8 ml.), and arsenic acid (*d* 2·0; 8 ml.) until, after 2—4 hr., a test sample did not give a positive reaction to the diazo-test (coupling with α-naphthol, not phenol). Iodine liberated on mixing the reactants did not interfere with the Skraup reaction but was best removed at the outset, by distillation. The cooled and diluted reaction mixture, adjusted to near neutrality with ammonia solution (*d* 0·88), was treated with charcoal, filtered, and fractionally precipitated with saturated aqueous picric acid solution (total vol. 1—1½ l.). The first-formed dark, oily deposit was rejected and the subsequent solidifying precipitate of crude *dipicrate* was collected (8—13 g.). It crystallised from water as yellow needles, m. p. 166° (Found: C, 46·7; H, 3·8. $C_{26}H_{24}N_8O_{14}$ requires C, 46·4; H, 3·6%).

The dipicrate was neutralised in hot aqueous solution with sodium hydroxide solution (indicator phenolphthalein), and the *monopicrate*, which was precipitated as a solidifying oil on cooling the mixture, was crystallised from water as yellow platelets, m. p. 131—133° (Found: C, 54·4; H, 4·9. $C_{20}H_{21}N_5O_7$ requires C, 54·2; H, 4·8%).

The monopicrate in aqueous ethanolic solution (*ca.* 50% v/v) was passed through a column of ion-exchange resin in the iodide form (2 g. Amberlite 400 CG per g. picrate) to yield a solution of the *iodide* (II). This salt crystallised from butanol–ethyl acetate as very pale yellow prismatic platelets, m. p. about 155° depending on the rate of heating (Found: I, 37·3%).

6-(NN-*Diethylmethylammonio*)-1-*methylquinolinium Di-iodide*.—The substituted ammonium iodide (II) (1 g.) was heated for 30 min. at 100° with iodomethane (1 ml.) and methanol (2 ml.). The *diquaternary salt* (0·9 g.), which separated during the reaction and further on cooling the mixture, crystallised from ethanol–methanol as yellow prisms, m. p. 186—187° (Found: I, 52·9. $C_{15}H_{22}I_2N_2$ requires I, 52·4%). The orange discoloration which developed in the reaction mixture was due to formation of a quinolinium-type quaternary salt in a side-reaction.

6-*Acetamido*-1,2,3,4-*tetrahydro*-1-*methylquinoline*.—6-Acetamido-1-methylquinolinium iodide (10 g.) was suspended in aqueous ethanol (50% v/v; 150 ml.) and saturated (over several hr.) with hydrogen at near atmospheric pressure in the presence of Adams platinum oxide catalyst (1 g.). The solution, concentrated by distillation and basified, yielded the *tetrahydro-compound* (6 g.) as a solidifying oil which crystallised from light petroleum–ethyl acetate mixture as colourless needles, m. p. 99° (Found: C, 70·4; H, 7·8. $C_{12}H_{16}N_2O$ requires C, 70·6; H, 7·9%).

When this compound was heated in acetone solution with iodomethane for 15 min. at 100°, it was converted into 6-*acetamido*-1,2,3,4-*tetrahydro*-1,1-*dimethylquinolinium iodide* which crystallised from water as colourless prisms, m. p. (decomp.) 234° with previous darkening and softening (Found: I, 37·0. $C_{13}H_{19}ION_2$ requires I, 36·7%).

1,2,3,4-*Tetrahydro*-4-*methyl*-4,7-*phenanthroline*.—A mixture of 6-acetamido-1,2,3,4-tetrahydro-1-methylquinoline (5 g.), sulphuric acid (*d* 1·84; 10 ml.), water (8 ml.), glycerol (4 ml.), and nitrobenzenesulphonic acid (4 g.) was refluxed for 5—6 hr. and the cooled and diluted reaction was basified with ammonia. Combined benzene extracts of the precipitated tar and supernatant liquid were extracted with dilute hydochloric acid from which the base was then reprecipitated as a solidying oil. Boiling light petroleum (b. p. 60—80°) extracted from the dried solid (2 g.) the crude tetrahydro-compound (0·8 g., m. p. about 98°), which was recrystallised from light petroleum as yellow platelets, m. p. 101—102°, not depressed by admixture with a specimen of the same m. p. prepared[4] by catalytic reduction of 4-methyl-4,7-phenanthrolinium iodide. Karrer, Pletscher, and Manz[4] state that the compound is colourless from ethanol, m. p. 98—99°. When the base was heated in acetone solution with an excess of iodomethane for 10 min. at 100°, an excellent yield of almost pure 1,2,3,4-*tetrahydro*-4,7-*dimethyl*-4,7-*phenanthrolinium iodide* (IV) was obtained. It was crystallised as red platelets from absolute ethanol, m. p. 217—218° (Found: I, 37·7. $C_{14}H_{17}IN_2$ requires I, 37·3%). Karrer, Pletscher, and Manz[4] give no m. p.

1,2,3,4-*Tetrahydro*-4,4-*dimethyl*-4,7-*phenanthrolinium Iodide* (V).—6-Acetamido-1,2,3,4-tetrahydro-1,1-dimethylquinolinium iodide (5 g.) was subjected to a Skraup reaction with reagents in the proportions stated for preparation of the salt (II). When a concentrated solution of ammonium perchlorate was added to the neutralised (ammonia solution), charcoal-treated, and filtered reaction mixture, the *perchlorate salt* precipitated as a solidifying oil which crystallised from ethanol–methanol as colourless platelets, m. p. 178—179° with previous darkening and softening (Found: Cl, 11·4. $C_{14}H_{17}ClO_4N_2$ requires Cl, 11·3%).

The corresponding *iodide* (V), prepared from the perchlorate by passing it in aqueous ethanol through a column of ion-exchange resin in the iodide form, crystallised from absolute ethanol as colourless platelets, m. p. about 175° depending on the rate of heating (Found: I, 37·1%).

When the iodide (0·1 g.) was heated in ethanol solution (0·5 ml.) at about 170°, the solution quickly turned red. When the solution was cooled after 1 hr., the isomeric iodide (IV) (0·07 g.) separated in a crude state, m. p. 211—212° after recrystallisation from ethanol, mixed m. p. 212—213°.

1,2,3,4,7,8-*Hexahydro*-4,7-*dimethyl*-8-*oxo*-4,7-*phenanthroline* (VI).—3,4-Dihydro-4,7-dimethyl-3-oxo-4,7-phenanthrolinium iodide (5 g.) was saturated with hydrogen in aqueous ethanolic solution (50% v/v; 200 ml.) in the presence of Adams platinum oxide catalyst (0·5 g.). The ethanol was largely removed from the acidified (dilute hydrochloric acid) solution which was then basified with sodium hydroxide solution to yield a precipitate of crude *oxo-compound* (3 g.); it crystallised from aqueous ethanol in yellow platelets, m. p. 143—145° and then, after partial resolidification, 156—158° (Found: C, 73·3; H, 7·0. $C_{14}H_{16}N_2O$ requires C, 73·7; H, 7·1%).

The compound obtained by oxidising the methiodide (IV) with alkaline ferricyanide (proportions as for the oxidation of 6-diethylamino-1-methylquinolinium iodide) had the same melting characteristics as the above oxo-compound, unchanged by admixture with it.

Paper Chromatography of Quaternary Salts.—The chromatography was carried out on Whatman No. 1 paper, used as supplied. Suitable developing solvent mixtures are stated in proportions by volume.

(a) *Quaternisation products from* 6-*aminoquinoline.* The precipitate formed after a mixture of 6-aminoquinoline (2 g.) dissolved in slightly warmed acetone (10 ml.) and iodomethane (2 ml.) had been set aside for 1 hr. was washed with ether. Samples of the crude product, melting over a wide range about 150°, and of material obtained by successive recrystallisations from water, were subjected to ascending chromatography for about 2 hr. (10 cm. movement) with butan-1-ol : water : glacial acetic acid (100 : 25 : 8). Spots on the dried chromatogram were detected by spraying with an acidified mixture of starch and sodium nitrite solutions (iodide blue, $R_F = 0{\cdot}2$), and then α-naphthol in sodium hydroxide solution (6-aminoquinoline, scarlet, $R_F = 0{\cdot}55$; 6-amino-1-methylquinolinium salt, purple-brown, $R_F = 0{\cdot}35$). The proportion of 6-aminoquinoline fell away as the m. p. improved. Decker and Kaufmann[3] give m. p. 199° and we found m. p. 196—197° for the methiodide after it had been prepared in a purer state *via* the 6-acetamido-compound.

(b) *Mono- and di-quaternary iodides of* 6-*diethylaminoquinoline, in various mixtures.* The upper layer from butan-1-ol : acetone : water (225 : 25 : 250) was used for ascending chromatography over 16 hr. (about 40 cm. movement). Spots on the dried chromatogram were detected by their orange colour in the case of 1-alkylquinolinium salts, and all by a modified Dragendorff reagent in two sprays, first 0·5% potassium iodide and then, after drying, bismuth oxynitrate dissolved in perchloric acid and diluted to 1% with water. Orange spots on a dark grey background were shown by: (I), $R_F = 0{\cdot}6$; (II), $R_F = 0{\cdot}45$; diquaternary salt, $R_F = 0{\cdot}01$ (streaks) The iodide, detected by spraying a separate chromatogram with mixed solutions of starch, hydrogen peroxide, and dilute acid, formed variable streaks of R_F 0·1—0·5. As the iodide is thus shown to be dissociated from the applied quaternary salts and replaced by some other unknown anion presumably associated with the paper, there is a potential weakness in this chromatographic technique. However, separations of the quaternary ions with the above approximate R_F values were found to be reproducible in numerous trials.

My thanks are offered to Mr. J. A. Davidson for assistance in the preparative work.

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[*Received, February 9th,* 1965.]