

443. The Instability of Some Aminobenzyl Quaternary Salts.

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Of the *m*- and *p*-aminobenzyl quaternary salts of quinoline, isoquinoline, pyridine, and dimethylaniline, only the *m*-compounds are stable; the *p*-compounds decompose readily with liberation of the tertiary base and are stable only in the presence of mineral acid or as their acetyl derivatives. A mechanism for this abnormal instability is suggested, and its implications are discussed.

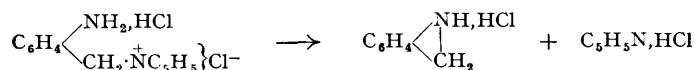
DURING a search for new trypanocidal drugs the aminobenzyl quaternary salts of a number of *N*-heterocyclic compounds were examined. Although failing to disclose any substance of biological interest, the work provided examples of abnormal instability in such salts.

The aminobenzylquinolinium salts were investigated in most detail. *p*-Nitrobenzylquinolinium chloride was prepared by von Walther and Weinhagen (*J. pr. Chem.*, 1917, **96**, 50), and in the experimental section is described an improved method of carrying out this type of condensation. Reduction of the nitro-group by means of Raney nickel in methanol, iron powder and water, or ferrous hydroxide gave quinoline in good yield as the only recognisable product. Removal of a benzyl residue by reduction is well known, and Snyder and Speck (*J. Amer. Chem. Soc.*, 1939, **61**, 668, 2895) have shown that in quaternary salts containing benzyl, that radical is removed by certain inorganic sulphur compounds. In the present example, however, it was considered unlikely that such a mild reducing agent as ferrous hydroxide would cause reductive debenzylation and, moreover, no trace of *p*-toluidine was detectable in the products of reduction by any of the above reagents.

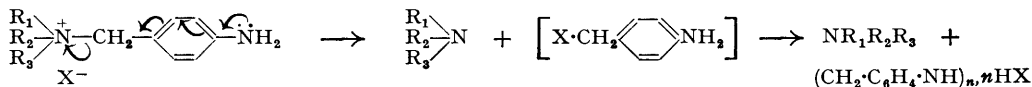
The situation was clarified when *p*-nitrobenzylquinolinium chloride was reduced at room temperature in dilute hydrochloric acid solution with hydrogen and palladised charcoal. Six atoms of hydrogen were smoothly absorbed and examination of the colourless filtrate established the following facts: (a) evaporation in a vacuum at low temperature left *p*-aminobenzylquinolinium chloride hydrochloride as a light-coloured, hygroscopic powder, fairly stable if stored in a dry state (e.g., only slight decomposition after 3 weeks); (b) diazotisation and coupling under acid conditions with β -naphthylamine gave the expected red azo-compound; (c) on addition of sodium acetate the solution became orange and rapidly deposited orange-yellow needles of *p*-aminobenzylquinolinium chloride as a dihydrate, which could be dried rapidly in a vacuum and analysed, but very quickly began to smell of quinoline and after 3 weeks had undergone extensive decomposition; an aqueous solution of the crystals decomposed rapidly on being heated, giving a good yield of quinoline together with a brown amorphous substance; (d) addition of sodium acetate, followed by acetic anhydride, gave colourless *p*-acetamidobenzylquinolinium chloride, stable to boiling water.

o-Aminobenzylquinolinium chloride was similarly unstable but the *m*-isomer was found to be quite stable in hot aqueous solution. To investigate the generality of these observations, the *m*- and *p*-aminobenzyl quaternary salts of 6-amino- and 6-carbethoxyamino-quinoline, isoquinoline, pyridine, and dimethylaniline were prepared, in each case by reduction of the corresponding nitro-compound. Palladised charcoal and hydrogen smoothly and exclusively reduced the nitro-group, except for the two derivatives of dimethylaniline where this reagent, as well as Raney nickel and hydrogen, brought about further reduction at the quaternary centre with formation of the corresponding toluidines. The use of ferrous hydroxide, however, obviated this difficulty. In every example, the distinction between the *m*- and the *p*-isomer was clear-cut; the former was stable in hot aqueous solution, but the latter was rapidly broken down with liberation of the corresponding tertiary base and was stable only in the presence of excess of mineral acid or in the form of its acetyl derivative.

The instability of *p*-aminobenzylpyridinium chloride appears to have been recognised by the chemists of Meister, Lucius and Brüning (cf. D.R.-P. 123,613, 128,726) and also by Lellmann and Pekrun (*Annalen*, 1890, **259**, 40). The latter prepared all three isomeric aminobenzylpyridinium chloride hydrochlorides, but only for the *p*-isomer did they record their attempt to obtain the free amino-compound, noting the ease with which it broke down into pyridine and an amorphous substance. They were more interested in the decomposition which all the isomeric hydrochlorides underwent at temperatures above 200° and which they formulated thus:



Volatilisation of pyridine hydrochloride left a residue identified as the hydrochloride of the isomeric, amorphous (and probably polymeric) benzyleneimides. Formation of such a polymeric imide probably accounts for the amorphous substances which accompany the tertiary bases in the above decompositions of *o*- and *p*-aminobenzyl quaternary salts. The breakdown has been represented (preliminary communication; *Nature*, 1949, **163**, 485) in the manner shown below for a *p*-aminobenzyl salt, the strain in the benzyl-N bond due to the presence of



the adjacent positive charge being magnified to the point of rupture by the powerful electromeric effect of a *free* amino-group in the *p*-position. The greater stability of the *m*-isomers as well as that of the salts and acetyl derivatives of the *p*-isomers is then understandable. Apart from the German work on the pyridinium salts, however, the present observations, and the interpretation offered for them, appear to be new. Reilly and Drumm (*J.*, 1935, 871; see also Pressmann *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 250) have prepared trimethyl-*p*-aminobenzylammonium chloride hydrochloride, and all three isomeric 3-(aminobenzyl)-4-methylthiazolium chloride hydrochlorides have been described by Clark (*ibid.*, 1944, **66**, 652) and Livermore and Sealock (*J. Biol. Chem.*, 1947, **167**, 699), but in no instance was the free amino-quaternary salt examined.

The question arises whether groups other than amino- could cause similar instability in benzyl quaternary salts. It would appear that only those groups able to show a powerful electromeric effect (OH, OAlkyl) need be considered. Alkoxy has a less pronounced effect than acetoamido (cf. influence on nitration in benzene derivatives, Ingold and Ingold, *J.*, 1926, 1310), and the literature reveals many instances of apparently stable *p*-alkoxybenzyl quaternary salts (quaternary salt formation is often reversed at higher temperatures but in the present discussion, "stability" is used in a restricted sense, applying to the temperature range 20—100°, particularly in aqueous solution). With hydroxybenzyl quaternary salts, examples are few and the position is not clear. Zemplén and Kunz (*Ber.*, 1922, **55**, 979) and Stedman (*J.*, 1927, 1902) have described trimethyl-*o*-hydroxybenzylammonium salts. On the other hand, Stedman and Stedman (*J.*, 1929, 609) studied the quaternisation of the three isomeric dimethylhydroxy- α -methylbenzylamines with methyl iodide and only in the case of the *m*-compound could they isolate a quaternary salt. The methiodides of the *o*- and *p*-compounds were unstable and, in the former case, elimination of the basic group was shown by the isolation of tetramethylammonium iodide. Of course, the presence of the α -methyl substituent would enhance the tendency to instability by the suggested mechanism.

If the above mechanism for these degradations is correct, the phenyl ring of the benzyl group acts solely as an electrical conductor of effects arising primarily in the substituent and suggests that instability might be found in quaternary salts carrying either amino- or hydroxy-methyl groups. On both these points information is available. Whereas 2-aminoethyl quaternary salts have been prepared by acid hydrolysis of 2-phthalimidoethyl salts (*e.g.*, Gabriel, *Ber.*, 1920, **53**, 1985; Seshadri, *J.*, 1929, 2952), even excess of acid does not stabilise aminomethyl salts, for Kipping and Mann (*J.*, 1927, 528) found that phthalimidomethylpyridinium bromide, with hot dilute hydrochloric acid, gave phthalic acid, ammonia, formaldehyde, and pyridine. Many analogues of choline chloride (2-hydroxyethyl quaternary salts) have been described, but Stewart and Kung (*J. Amer. Chem. Soc.*, 1933, **55**, 4813) have shown that hydroxytetramethylammonium chloride (formocholine chloride) and hydroxymethyltriethylammonium chloride are decomposed very rapidly in solution in water, liberating the tertiary base and formaldehyde. Kröhnke's observation (*Ber.*, 1933, **66**, 1386) that ω -bromophenacylpyridinium bromide is decomposed by hot water giving, *via* the corresponding hydroxy-compound, phenylglyoxal and pyridine is possibly another example of the same type of instability.

Steric Factors in the Formation of Nitrobenzyl Quaternary Salts.—Von Walther and Weinlagen (*loc. cit.*) observed that *p*-nitrobenzyl chloride condensed with pyridine, α -picoline, and quinoline but not with collidine or quinaldine. During the present work it has been found that reaction does not occur with 2- or 8-methyl- or 8-chloro-quinoline; it occurs with 8-methoxyquinoline, though more sluggishly than with quinoline, which itself reacts much less rapidly than pyridine or isoquinoline.

EXPERIMENTAL.

p-Nitrobenzylquinolinium Salts.—Von Walther and Weinhagen (*loc. cit.*) condensed quinoline with nitrobenzyl chlorides by heating the reactants together on the water-bath; after separation from a red pigment the products were characterised as dichromates. The yields are considerably improved and the formation of red pigment avoided if the condensation is carried out in boiling aqueous suspension. This method of preparing quaternary salts has proved very satisfactory throughout this work.

Quinoline (24 ml.), *p*-nitrobenzyl chloride (34.3 g.), water (200 ml.), and alcohol (50 ml.) were heated under reflux with stirring for 8 hours. After steam-distillation, the aqueous liquid was decanted from a little tar, decolorised with charcoal, and evaporated to dryness in a vacuum. Digestion of the residue with ethyl acetate and filtration gave *p*-nitrobenzylquinolinium chloride (80%), m. p. ca. 190°. Crystallisation from alcohol-ethyl acetate gave rosettes of colourless needles, m. p. 203–205° (Found : C, 63.5; H, 3.8; N, 9.35; Cl, 11.8. $C_{16}H_{13}O_2N_2Cl$ requires C, 63.9; H, 4.3; N, 9.3; Cl, 11.8%). The iodide formed stout yellow prisms from methyl alcohol, m. p. 186° (Found : C, 49.1; H, 3.6; N, 7.0; I, 32.6. $C_{16}H_{13}O_2N_2I$ requires C, 49.0; H, 3.3; N, 7.1; I, 32.4%).

p-Aminobenzylquinolinium Salts and Derivatives.—When the above nitro-compound (1 mole), in aqueous solution containing hydrochloric acid (2 moles), was shaken with hydrogen and palladised charcoal, 6 atoms of hydrogen were rapidly absorbed. The colourless filtrate was divided and used for the following experiments.

(a) Evaporation at low temperature in a vacuum and digestion of the residue with acetone left *p*-aminobenzylquinolinium chloride hydrochloride as a buff-coloured hygroscopic powder which softened at >80° and decomposed at 170–175°. Before analysis it was dried at 40° in a vacuum (Found : N, 9.1; Cl, 22.5. $C_{16}H_{16}N_2Cl_2$ requires N, 9.1; Cl, 23.1%).

(b) Diazotisation and coupling with β -naphthylamine in excess of hydrochloric acid gave an insoluble red azo-compound, deep red rosettes of prisms from alcohol; m. p. 154° (Found : N, 13.1; Cl, 8.0. $C_{26}H_{21}N_4Cl$ requires N, 13.2; Cl, 8.35%).

(c) On addition of sodium acetate the liquid became orange and then deposited orange-yellow needles of *p*-aminobenzylquinolinium chloride, which were washed with ice-water and rapidly dried in a high vacuum for immediate analysis (m. p. 87–88°) (Found : N, 8.9, 9.3; Cl, 11.4, 11.7. $C_{16}H_{15}N_2Cl_2 \cdot 2H_2O$ requires N, 9.15; Cl, 11.6%). Warm solvents caused rapid decomposition. When the filtrate from the reduction was treated with sodium acetate and steam-distilled, quinoline was removed (picrate; 85% yield), leaving a brown amorphous powder, m. p. 179–184°, insoluble in boiling alcohol. Analysis suggested that this was the acetate of polymeric benzyleneimide [Found : N, 8.3, 8.45; Cl, nil. $(C_7H_7N)_n \cdot nC_2H_4O_2$ requires N, 8.5%]; digestion with dilute sodium hydroxide left a similar amorphous powder, m. p. 180–190° [Found : N, 13.5, 13.7. $(C_7H_7N)_n$ requires N, 13.3%], presumably the free imide.

(d) Addition of sodium acetate was followed by the addition of acetic anhydride at <20° with stirring. A clear solution was formed, which then deposited colourless crystals (probably hydrated; m. p. 151–153°); crystallisation from alcohol gave *p*-acetamidobenzylquinolinium chloride as colourless woolly needles, m. p. 225° (Found : N, 8.9, 8.8; Cl, 11.1, 11.0. $C_{18}H_{17}ON_2Cl$ requires N, 8.95; Cl, 11.35%)*. The iodide formed bright yellow prisms from alcohol; m. p. 207–208° (Found : C, 53.5; H, 4.65; N, 7.0; I, 31.3. $C_{18}H_{17}ON_2I$ requires C, 53.5; H, 4.2; N, 6.9; I, 31.4%).

o-Nitrobenzylquinolinium Iodide.—Quinoline and *o*-nitrobenzyl chloride (free from the *p*-isomer, having been synthesised from *o*-nitrotoluene) were condensed together, and the product was converted into the iodide, long golden-yellow needles, m. p. 203–204°, from methyl alcohol (Found : N, 7.0; I, 32.4. $C_{16}H_{13}O_2N_2I$ requires N, 7.1; I, 32.4%). This was converted into the chloride by means of silver chloride, and reduced in dilute hydrochloric acid with palladised charcoal and hydrogen; the filtrate, on treatment with sodium acetate followed by steam-distillation, gave a copious yield of quinoline (identified as picrate).

m-Nitrobenzylquinolinium chloride, prepared by the general method (66% yield), formed colourless prisms from alcohol-ethyl acetate; m. p. 196–197° (Found : N, 9.4; Cl, 11.6. $C_{16}H_{13}O_2N_2Cl$ requires N, 9.3; Cl, 11.8%)*.

m-Aminobenzylquinolinium Chloride.—The above nitro-compound was reduced in dilute hydrochloric acid with palladised charcoal and hydrogen, and the filtrate evaporated to dryness in a vacuum. Crystallisation of the residue from 90% alcohol gave the hydrochloride in pale brown prisms, m. p. 231–233° (decomp.) (Found : C, 63.3; H, 5.8; N, 9.3; Cl, 22.8. $C_{16}H_{16}N_2Cl$ requires C, 62.6; H, 5.2; N, 9.1; Cl, 23.1%). The aqueous solution became yellow on addition of sodium acetate and could then be boiled without decomposition; addition of potassium iodide precipitated *m*-aminobenzylquinolinium iodide, dichromate-coloured prisms from methyl alcohol; m. p. 181–182° (Found : C, 53.6; H, 4.7; N, 7.6; I, 35.1. $C_{16}H_{15}N_2I$ requires C, 53.05; H, 4.15; N, 7.75; I, 35.1%).

6-Amino-*p*-nitrobenzylquinolinium Chloride.—6-Acetamidoquinoline (35.35 g.), *p*-nitrobenzyl chloride (32.6 g.), water (200 ml.), and alcohol (50 ml.) were stirred under reflux for 10 hours. The liquid was steam-distilled, treated with charcoal, heated for 2 hours on the steam-bath with half its volume of concentrated hydrochloric acid, and then evaporated to dryness. The residue was taken up in a little hot water, and the solution strongly cooled until the separated oil had become largely crystalline. The product was filtered off and digested with acetone, which left the required chloride as an orange crystalline powder, m. p. 182–183° (60% yield). This crystallised from 90% alcohol in orange leaflets of the same m. p. (Found : C, 60.6; H, 4.6; N, 13.2; Cl, 11.1. $C_{16}H_{14}O_2N_3Cl$ requires C, 60.8; H, 4.4; N, 13.3; Cl, 11.25%). The iodide formed orange prisms from 60% acetic acid; m. p. 221–222° (Found : N, 10.5; I, 31.4. $C_{16}H_{14}O_2N_3I$ requires N, 10.3; I, 31.2%).

The corresponding *p*-aminobenzyl salt, formed by reduction, was unstable.

6-Amino-*m*-nitrobenzylquinolinium chloride, prepared in the same manner as the *p*-isomer (50% yield), had m. p. 219° after crystallisation from 95% alcohol (Found : N, 13.4; Cl, 10.65%).

* Compounds marked thus did not give reproducible values for C and H.

6-Amino-*m*-aminobenzylquinolinium chloride separated after catalytic reduction of the above nitro-compound and addition of sodium acetate; it crystallised from hot water in long orange needles, m. p. indefinite $>125^\circ$ (Found: N, 14.55; Cl, 12.5. $C_{16}H_{18}N_3Cl$ requires N, 14.7; Cl, 12.4%).

6-Carbethoxyaminoquinoline.—6-Aminoquinoline (28.8 g.), alcohol (100 ml.), and diethylaniline (35 ml.) were heated on a steam-bath, and ethyl chloroformate (20 ml.) was added gradually; after a further $\frac{1}{2}$ hour's boiling, the mixture was poured into water, and the product (40 g.) collected and dried. It separated from methyl alcohol as colourless tablets, m. p. 168—168.5° (Found: N, 13.3. $C_{12}H_{12}O_2N_2$ requires N, 13.0%).

6-Carbethoxyamino-*p*-nitrobenzylquinolinium Chloride.—6-Carbethoxyaminoquinoline (20 g.), *p*-nitrobenzyl chloride (15.9 g.), water (100 ml.), and alcohol (25 ml.) were heated under reflux for 9 hours. The liquid was steam-distilled, treated with charcoal, concentrated to small bulk, and cooled, whereupon the chloride separated (60% yield). It crystallised from alcohol in golden-yellow prisms, m. p. 225—226° (decomp.) (Found: N, 11.0; Cl, 9.3. $C_{19}H_{18}O_4N_3Cl$ requires N, 10.8; Cl, 9.2%). Hydrolysis at 150° with 70% sulphuric acid gave 6-amino-*p*-nitrobenzylquinolinium sulphate, converted into the iodide, m. p. 222°, identical with the substance already described. Catalytic reduction yielded 6-carbethoxyamino-*p*-aminobenzylquinolinium chloride, which was unstable; the derived acetyl derivative was stable but a number of salts examined were gelatinous.

6-Carbethoxyamino-*m*-nitrobenzylquinolinium chloride, prepared in the same manner as the *p*-isomer, crystallised from alcohol in small, pale yellow rosettes, m. p. 220—221° (decomp.) (Found: C, 59.3; H, 4.6; N, 10.9; Cl, 9.1. $C_{19}H_{18}O_4N_3Cl$ requires C, 58.8; H, 4.7; N, 10.8; Cl, 9.2%).

6-Carbethoxyamino-*m*-aminobenzylquinolinium Chloride.—The above nitro-compound was reduced catalytically in dilute hydrochloric acid, and the filtrate evaporated to dryness to yield the hydrochloride, colourless crystals from methyl alcohol-ethyl acetate; m. p. 190—191° (decomp.) (Found: N, 10.8; Cl, 17.9. $C_{19}H_{21}O_2N_3Cl_2$ requires N, 10.65; Cl, 18.0%)*. The aqueous solution remained unchanged on addition of sodium acetate and boiling.

p-Nitrobenzylisoquinolinium chloride, prepared in the general manner in quantitative yield, formed long thin prisms from alcohol-ethyl acetate; m. p. 222° (Found: N, 9.3; Cl, 11.8. $C_{16}H_{15}O_2N_2Cl$ requires N, 9.3; Cl, 11.8%)*.

p-Aminobenzylisoquinolinium chloride was obtained as yellow crystals (m. p. 94—95°) by reduction of the above nitro-compound. It decomposed rapidly in warm water, liberating isoquinoline, and could not be recrystallised. The acetamido-compound was stable, giving an iodide, m. p. 203°, colourless prisms from methyl alcohol (Found: C, 53.5; H, 4.0; N, 6.8; I, 31.5. $C_{18}H_{17}ON_2I$ requires C, 53.5; H, 4.2; N, 6.9; I, 31.4%).

m-Nitrobenzylisoquinolinium chloride formed fine colourless needles from alcohol; m. p. 224—225° (yield 92%) (Found: N, 9.45; Cl, 11.9%)*.

m-Aminobenzylisoquinolinium chloride was stable in hot aqueous solution; the hydrochloride formed small rosettes of buff-coloured needles from methyl alcohol-ethyl acetate, m. p. 238° (Found: N, 8.9; Cl, 23.0. $C_{16}H_{16}N_2Cl_2$ requires N, 9.1; Cl, 23.1%).

p-Nitrobenzylpyridinium chloride obtained in 80% yield, formed colourless prisms from alcohol-ethyl acetate; m. p. 207° (Found: N, 11.3; Cl, 14.4. Calc. for $C_{12}H_{11}O_2N_2Cl$: N, 11.2; Cl, 14.2%). Grainger (*Chem. News*, 1923, **126**, 182) gave m. p. 208°; Jacobs and Heidelberger (*J. Biol. Chem.*, 1915, **20**, 667) gave m. p. 204—207°; Lellmann and Pekrun (*loc. cit.*) described a much lower-melting form which is probably a hydrate.

p-Aminobenzylpyridinium chloride, by catalytic reduction of the above nitro-compound in dilute hydrochloric acid, formed a hydrochloride, m. p. 195—196°, colourless plates from methyl alcohol-ethyl acetate (Found: N, 10.8; Cl, 27.4. Calc. for $C_{12}H_{14}N_2Cl_2$: N, 10.9; Cl, 27.6%). Lellmann and Pekrun (*loc. cit.*) gave m. p. 183—185°. The aqueous solution was unchanged on addition of sodium acetate, but, on boiling, decomposition gave pyridine and a brown amorphous material; mere boiling of an aqueous solution of the hydrochloride brought about some decomposition, as shown by cooling and addition of sodium acetate.

m-Nitrobenzylpyridinium chloride, obtained in nearly quantitative yield, formed long needles from alcohol-ethyl acetate, m. p. 194° (Found: N, 10.8; Cl, 14.15%). Lellmann and Pekrun (*loc. cit.*) described a hydrate, m. p. 100°, and Kröhnke (*Ber.*, 1938, **71**, 2583) a solvate, m. p. 191°.

m-Aminobenzylpyridinium chloride was stable in boiling aqueous solution. The hydrochloride formed long, colourless needles from methyl alcohol-ethyl acetate; m. p. 222—223° (Found: N, 10.8; Cl, 27.6%). Lellmann and Pekrun (*loc. cit.*) gave m. p. ca. 220°.

Phenyldimethyl-*p*-nitrobenzylammonium chloride, from the components in boiling aqueous suspension, formed stout prisms from alcohol-ethyl acetate; m. p. 111—112° (Found: N, 9.45; Cl, 12.0. Calc. for $C_{15}H_{17}O_2N_2Cl$: N, 9.6; Cl, 12.1%) (Wedekind, *Annalen*, 1899, **307**, 287, gave m. p. 118—120°). On reduction in dilute hydrochloric acid with palladised charcoal, 8 atoms of hydrogen were absorbed; addition of sodium acetate and acetic anhydride followed by steam-distillation separated the product into dimethylaniline (picrate, m. p. 162°) and acet-*p*-toluidide (mixed m. p.). Reduction with warm neutral ferrous hydroxide gave a copious yield of dimethylaniline (picrate, m. p. 162°) as the only identifiable product.

Phenyldimethyl-*m*-nitrobenzylammonium chloride, colourless prisms from alcohol-ethyl acetate, had m. p. 151—152° (Found: N, 9.6; Cl, 12.4%). Peacock (*J. Soc. Dyers Col.*, 1926, **42**, 53) gave m. p. 144°.

Catalytic reduction and working up as described for the *p*-isomer gave dimethylaniline (picrate, m. p. 162°) and aceto-*m*-toluidide (mixed m. p.).

Phenyldimethyl-*m*-aminobenzylammonium chloride, formed when the above nitro-compound was reduced with warm neutral ferrous hydroxide, was stable in boiling aqueous solution. It was characterised as the dipicrate, long orange-yellow prisms from acetic acid; m. p. 159—160° (Found: C, 47.55; H, 3.1; N, 17.0. $C_{27}H_{22}O_{14}N_8$ requires C, 47.5; H, 3.2; N, 16.4%).

8-Methoxy-*m*-nitrobenzylquinolinium chloride, from its components in boiling aqueous suspension

(24 hours, 53%), formed pale yellow prisms from alcohol-ethyl acetate; m. p. 157—158° (Found: N, 8.5; Cl, 11.2. $C_{17}H_{15}O_3N_2Cl$ requires N, 8.5; Cl, 10.8%).

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