The Preparation and Properties of 1 : 2 : 3 : 4-*Tetrahydro*-1-*methyl*-4-*oxoquinoline*.

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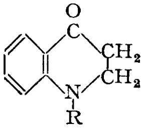
The critical conditions under which the above compound can be prepared by the cyclisation of *N*-2-cyanoethyl-*N*-methylaniline have been determined, and the compound has been characterised by the isolation of several crystalline derivatives. Under other conditions of attempted cyclisation, the cyanoethyl compound furnished *N'*-methyl-*N'*-phenyl-β-methylanilinopropionamidine hydrochloride. The ketone could not be obtained by the cyclisation of β-methylanilinopropionic acid, which however furnished 1 : 4-dihydro-1-methyl-4-oxoquinoline in small yield.

It is noteworthy that whereas the preparation of 1 : 2 : 3 : 4-tetrahydro-4-oxoquinoline (I; R = H) by cyclisation of β-toluene-*p*-sulphonanilidopropionic acid,

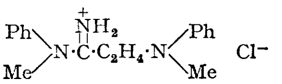
$$Ph{\cdot}N(SO_2{\cdot}C_7H_7){\cdot}C_2H_4{\cdot}CO_2H,$$

followed by hydrolysis, has been described by Clemo and Perkin (*J.*, 1924, **125**, 1608), and that of the 1-phenyl analogue (I; R = Ph) by cyclisation of β-diphenylaminopropionic acid, $Ph_2N{\cdot}C_2H_4{\cdot}CO_2H$, by R. C. Cookson and Mann (*J.*, 1949, 67), very little information has hitherto been available concerning the synthesis of analogous simple 1-alkyl derivatives, although Braunholtz and Mann (*J.*, 1952, 3046; 1953, 1817) have prepared various nuclear-substituted derivatives of the 1-2'-cyanoethyl derivative (I; R = $C_2H_4{\cdot}CN$) by cyclisation of the corresponding bis-2-cyanoethylanilines. It has been claimed however (F.P. 806,715/1936) that when *N*-2-cyanoethyl-*N*-methylaniline, $Ph{\cdot}NMe{\cdot}C_2H_4{\cdot}CN$, is heated with a mixture of aluminium chloride, potassium chloride, and sodium chloride at 130—140°, and the product subsequently hydrolysed, 1 : 2 : 3 : 4-tetrahydro-1-methyl-4-oxoquinoline (I; R = Me) is obtained "in good yield," having b. p. 185—190°/6 mm. and giving a semicarbazone, m. p. 190—191°. Bayer (*Angewand. Chem.*, 1949, **61**, 229) states in a footnote that Reppe has achieved the same cyclisation, but no details are given.

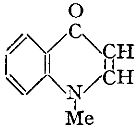
Since this methyl derivative was required as a starting point for further syntheses, we have investigated in some detail its preparation by cyclisation of *N*-2-cyanoethyl-*N*-methylaniline and of β-methylanilinopropionic acid, $Ph{\cdot}NMe{\cdot}C_2H_4{\cdot}CO_2H$. The cyanoethyl compound readily dissociates to methylaniline and vinyl cyanide (or its polymers) when heated with acids, and, possibly because of this restriction, we have found the only practicable conditions of synthesis to be those based on the above specification. Even so, the temperature range is critical, and maximum yields are obtained by short exposure of



(I)



(II)



(III)

the nitrile to the molten metallic chlorides. This is shown in the Table, which records a series of comparable experiments, the yield of ketone in the crude product after hydrolysis being estimated by isolation of the almost insoluble 2 : 4-dinitrophenylhydrazone.

Temp. (oil-bath)	120°	120°	130—5°	130—5°	130—5°	130—5°	145°	155—9°
Time (min.)	1	1	0·5	2	10	1	0·5	0·5
Yield (%) of ketone ...	25	44 *	22	22	22	33 *	9	9

* A trace of Cu_2Cl_2 was added as a catalyst.

These results indicate that 120° is probably the optimum temperature of reaction, and that the maximum yield of the ketone is rapidly attained: considerably longer heating diminishes the yield, however, for other experiments conducted at 130—135° with 45 min.' heating gave only an insignificant yield of ketone. The strongly catalytic effect of cuprous chloride is probably due to its partially suppressing the dissociation of uncyclised nitrile, for this almost certainly is the mechanism by which the chloride so markedly catalyses the initial cyanoethylation of aromatic amines (cf. Braunholtz and Mann, *J.*, 1953, 1817).

When this preparation was carried out on a larger scale, the cold melt being hydrolysed and the liberated ketone extracted with benzene, fractional distillation gave a product which never contained more than 70% of ketone, and the pure ketone could not be isolated by further fractionation. It is highly improbable therefore that the fraction cited in the specification was the pure ketone. Treatment with Girard P reagent gave however the pure ketone as a bright yellow mobile liquid, b. p. 130°/0·01 mm., in 25% yield: it has been characterised as its phenylhydrazone, 2 : 4-dinitrophenylhydrazone, semicarbazone, hydrochloride, picrate, and methiodide. Its ultra-violet spectrum, determined in ethanolic solution, is closely similar to that of the unsubstituted ketone (I; R = H):

(I; R = Me)	$\lambda_{max.}$	383—385	262	239	$\lambda_{min.}$	288	252
	$\varepsilon_{max.}$	4370	7700	22,700	$\varepsilon_{min.}$	55	6230
(I; R = H)	$\lambda_{max.}$	377	259	235	$\lambda_{min.}$	286	251
	$\varepsilon_{max.}$	4000	6800	20,400	$\varepsilon_{min.}$	48	5900

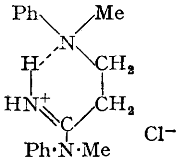
In FIAT Report No. 1298 (1949) the conversion of suitable nitriles into cyclic ketones is performed by heating the nitrile in chlorobenzene containing aluminium chloride and a very small quantity of concentrated hydrochloric acid: this method has subsequently been successfully employed for the preparation of 1 : 6-dioxojulolidine (Mann and Smith, *J.*, 1951, 1898; Braunholtz and Mann, *loc. cit.*) and of 1 : 2 : 2*a* : 3 : 4 : 5 : 8 : 9 : 10 : 10*a*-decahydro-5 : 8-dioxo-2*a* : 10*a*-diazapyrene (Almond and Mann, *J.*, 1951, 1906).

When *N*-2-cyanoethyl-*N*-methylaniline was similarly treated, and the product hydrolysed and distilled in steam, the aqueous residue contained approximately equimolecular quantities of methylaniline and of unchanged nitrile, and only a trace of the required ketone. Considerable dissociation of the nitrile under the influence of the hydrochloric acid had therefore occurred. Further evidence for this dissociation is provided by the fact that the aqueous residue from the distillation also deposited the highly crystalline *N'*-methyl-*N'*-phenyl-β-methylanilinopropionamidine hydrochloride (II). Oxley, Partridge, and Short (*J.*, 1947, 1110) have shown that amidines can be prepared in almost quantitative yield by the addition of secondary amines to nitriles in the presence of aluminium chloride, and our product clearly arises similarly by the addition of the liberated methylaniline to undissociated nitrile. We have confirmed this by an unambiguous preparation of (II) in which an equimolecular mixture of methylaniline, the nitrile, and aluminium chloride was heated at 150° for 1 hr.

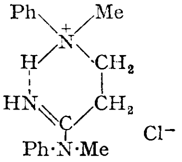
The amidine hydrochloride has considerable stability: it is unaffected by sodium acetate and shows no tendency to form a stable higher hydrochloride. It is possible that in this compound the normal stability of an amidine salt is reinforced by formation of a six-membered hydrogen-bonded ring structure, which could exist as a hybrid of the three canonical forms (II*a*, *b*, and *c*). Clearly the formation of a dihydrochloride would destroy the stability acquired by this hybridisation.

N-2-Cyanoethyl-*N*-methylaniline readily underwent alkaline hydrolysis to β-methylanilinopropionic acid, a viscous oil which gave a crystalline hydrochloride and methiodide.

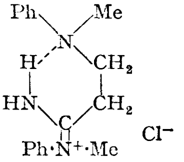
Many attempts to cyclise this acid to the 1-methylquinoline derivative (I; R = Me) were made by using a variety of reagents and conditions, but only traces of the ketone were obtained. A noteworthy by-product was isolated, however, when a solution of the acid in dry xylene containing phosphoric anhydride was boiled under reflux for 4 hr.: after removal of a minute amount of the required ketone, the residue was hydrolysed by alkali, giving methylaniline and 1 : 4-dihydro-1-methyl-4-oxoquinoline (III), m. p. 151—152°, identical with the alkaloid echinopsine obtained by Greshoff (*Rec. Trav. chim.*, 1900, **19**, 360) from the seeds of *Echinops ritro* and identified later by Späth and Kolbe (*Monatsh.*, 1922, **43**, 469). The occurrence of methylaniline was not unexpected in view of the ready dissociation of the earlier nitrile under acid conditions, an instability which Elderfield, Gensler, Bembry, Kremer, Brody, Hageman, and Head (*J. Amer. Chem. Soc.*, 1946, **68**, 1259) have shown to be shared by various β-(*N*-alkyl-*N*-arylamino)propionic acid derivatives. The formation of the quinolone (III) however involves dehydrogenation, but there is at present no decisive evidence as to whether this dehydrogenation occurs before or after the cyclisation.



(II*a*)



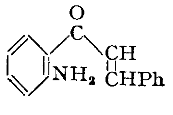
(II*b*)



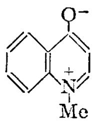
(II*c*)

The use of phosphoric anhydride in benzene, toluene, or tetralin for the cyclisation to the ketone (I; R = Me) also proved valueless, whereas " polyphosphoric acid " caused dissociation of the acid. The use of phosphorus pentachloride followed by aluminium chloride or stannic chloride, or of thionyl chloride followed by aluminium chloride, also proved valueless, partly because the acid chloride was rapidly precipitated as its insoluble hydrochloride, in which the positive pole on the nitrogen atom would furthermore inactivate the hydrogen atoms in the neighbouring *ortho*-positions. Phosphorus oxychloride (Clemo and Perkin, *loc. cit.*; Johnson, Woroch, and Buell, *J. Amer. Chem. Soc.*, 1949, **71**, 1901), sulphuric acid, hydrogen fluoride (Fieser and Hershberg, *ibid.*, 1939, **61**, 1272), and acetic acid, with or without zinc chloride, all failed as cyclising agents, and attempts to use the acid in place of the nitrile for the required synthesis were therefore abandoned.

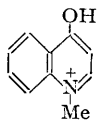
It may be added that the colourless 1 : 4-dihydro-1-methyl-4-oxoquinoline, if it had solely the formal structure (III), might be expected to be pale yellow : compare *o*-aminobenzylideneacetophenone (IV), which has an analogous structure and has this colour (Mannich and Dannehl, *Ber.*, 1938, **71**, 1899). Moreover the quinolone (III) shows no ketonic properties and is unaffected by methyl iodide in boiling methanol. These properties strongly indicate that the ionic " aromatic " form (III*a*) makes the major contribution to the resonance structure. If so, the salt which the base forms with acids must contain the cation (V), and " echinopsine hydrochloride " must be identical with the methochloride of 4-hydroxyquinoline. The structure (V) for the cation is confirmed by the fact that 1 : 4-dihydro-1 : 2-dimethyl-4-oxoquinoline and methyl iodide at 100° ultimately give 4-methoxyquinaldine methiodide (Knorr, *Ber.*, 1897, **30**, 922). The stability of the echinopsine structure is illustrated by its formation when 4-methoxyquinoline is heated at 300—310° (Meyer, *Monatsh.*, 1906, **27**, 257) and when 4-hydroxyquinoline is treated with methyl sulphate and alkali (Simpson and Wright, *J.*, 1948, 1707).



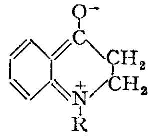
(IV)



(III*a*)



(V)



(I*a*)

The bright yellow colour of the tetrahydro-ketone (I; R = Me) similarly is probably due to a considerable contribution by the form (I*a*), in which the charge separation entails the *o*-quinonoid structure.

EXPERIMENTAL

N-2-*Cyanoethyl*-N-*methylaniline*.—A mixture of pure methylaniline (321 g.) and acetic acid (15 c.c., 0·08 mol.) was heated in a 3-necked flask, carrying a condenser, thermometer, and dropping-funnel, until the temperature reached 130°; vinyl cyanide (318 g., 2 mols.) was then added during 2 hr., during which the temperature fell to 108°. The mixture was then boiled for 8 hr., and on fractionation gave the nitrile as a pale yellow, slightly hygroscopic oil, b. p. 116—117°/0·05 mm. (Found: C, 74·5; H, 7·9; N, 17·6. Calc. for $C_{10}H_{12}N_2$: C, 75·0; H, 7·6; N, 17·5%) (312 g., 65%). The addition of hydrogen chloride to an ethereal solution of the nitrile yielded colourless crystals of the *hydrochloride*, m. p. 112—114° (Found: C, 61·3; H, 6·65; N, 14·2. $C_{10}H_{12}N_2$,HCl requires C, 61·0; H, 6·7; N, 14·2%). This salt is stable indefinitely in dry air but becomes purple on exposure to the atmosphere: it is immediately hydrolysed by water with liberation of the nitrile. The methiodide has been recorded by Braunholtz and Mann (*loc. cit.*).

When an ethanolic hydrogen chloride solution of the nitrile was heated, dissociation to methylaniline and vinyl cyanide rapidly occurred.

1 : 2 : 3 : 4-*Tetrahydro*-1-*methyl*-4-*oxoquinoline* (I; R = Me).—An intimate mixture of aluminium chloride (50 g.), sodium chloride (11 g.), and potassium chloride (11 g.) was heated with stirring at 120° until it gave a uniform and fairly mobile syrup, to which the nitrile (10 g.) was added dropwise during 1 min., and the complete mixture then heated for another minute. The molten mixture was poured directly into an excess of well-stirred ice-water, which was then basified with sodium hydroxide solution and gently heated for 30 min. The cold mixture was extracted with benzene, and the extract, which had a bluish-purple fluorescence, was evaporated gently under reduced pressure.

In earlier experiments, the ketonic residue thus obtained was carefully fractionated at 0·15 mm. during 3 hr., and gave the fractions (*a*) b. p. 108—120° (2·5 g.), (*b*) b. p. 125—135° (0·83 g.), and a dark red viscous residue. There was no real break between (*a*) and (*b*). By the usual method, fraction (*a*) was found to contain *ca.* 68% and (*b*) *ca.* 56% of ketone: the total yield was 2·2 g. (22%). These fractions, although sufficiently pure for the preparation of certain derivatives, could not be significantly purified by further distillation.

The ketonic residue from the benzene extract was therefore dissolved in ethanol (50 c.c.) to which was added acetic acid (5 c.c.) and the Girard P reagent (6 g.). The mixture was boiled under reflux for 2 hr., allowed to cool, and then added to ice-water (500 c.c.) containing sodium hydroxide (3 g.). Unchanged material was removed by extraction with ether (500 c.c.), and the clear orange-brown aqueous solution added to concentrated hydrochloric acid (35 c.c.); after 2 hr., the liberated ketone was extracted with ether (750 c.c.). Evaporation of the ether gave a yellowish-brown liquid, which on distillation gave only the pure 1 : 2 : 3 : 4-*tetrahydro*-1-*methyl*-4-*oxoquinoline* (I; R = Me), a bright yellow mobile liquid (2·5 g., 25%), b. p. 130°/0·01 mm., n_D^{20} 1·6191 (Found: C, 74·3; H, 6·95; N, 8·95. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·9; N, 8·7%). A solution of the ketone in ethanol is yellow with a green fluorescence and in acetone pale yellow with a blue fluorescence.

When the ketone was dissolved in ethanolic hydrogen chloride, the colourless crystalline *hydrochloride*, m. p. 131—132°, rapidly separated (Found: C, 60·6; H, 6·5; N, 7·3. $C_{10}H_{11}ON$,HCl requires C, 60·7; H, 6·1; N, 7·1%). It acquires a pale yellow colour on exposure to the air, and gives a yellowish-orange solution in water, presumably due to hydrolysis. The ketone gave a *picrate*, scarlet crystals (from aqueous ethanol), m. p. 100° (Found: C, 49·5; H, 3·8; N, 14·7. $C_{10}H_{11}ON,C_6H_3O_7N_3$ requires C, 49·25; H, 3·6; N, 14·4%). When a solution of the ketone in methyl iodide was boiled, very little combination occurred: the addition of nitromethane followed by 3 hr.' boiling under reflux gave the *methiodide*, colourless needles, m. p. 166° (effervescence; from ethanol) (Found: C, 43·6; H, 4·9; N, 4·8. $C_{11}H_{14}ONI$ requires C, 43·6; H, 4·7; N, 4·6%).

The ketone gave: a *phenylhydrazone*, pale yellow crystals, m. p. 98° (effervescence) from aqueous ethanol (Found: C, 76·8; H, 6·9; N, 16·9. $C_{16}H_{17}N_3$ requires C, 76·5; H, 6·8; N, 16·7%); a 2 : 4-*dinitrophenylhydrazone*, fine purple plates, insoluble in most cold solvents, m. p. 235° (decomp.) after recrystallisation from xylene and then dioxan (Found: C, 56·6; H, 4·2; N, 20·5. $C_{16}H_{15}O_4N_5$ requires C, 56·3; H, 4·4; N, 20·5%); and a *semicarbazone*, cream-coloured crystals, m. p. 184—185°, from aqueous ethanol (Found : C, 60·7; H, 6·4; N, 25·8. $C_{11}H_{14}ON_4$ requires C, 60·55; H, 6·45; N, 25·65%).

Action of Aluminium Chloride and Hydrochloric Acid on the Nitrile.—The following experiment is typical of the many attempts to employ this reagent. The nitrile (40 g.) was added to a stirred mixture of chlorobenzene (100 c.c.), powdered aluminium chloride (83 g., 2·5 mols.), and concentrated hydrochloric acid (1 c.c.), which was then heated at 140° for 8 hr. with continuous stirring. The mixture became deep red and, if the stirring was stopped, separated into an almost colourless upper and a red lower layer. The mixture was poured on ice, and then steam-distilled to remove chlorobenzene and to hydrolyse any ketimine. Two methods of working up the product were adopted.

(*a*) The residual mixture was repeatedly extracted with chloroform, and the united extracts were dried and distilled. After removal of the solvent, the residual red oil was distilled quickly at 1 mm. (leaving a red residue) and redistilled at 0·5 mm., giving the fractions : (i) b. p. 100—120° (12 g.), mainly methylaniline; (ii) b. p. 125—135° (13 g.), mainly unchanged nitrile with a trace of ketone; and (iii) b. p. 150—155° (2 g.), a viscous yellow liquid. Further fractionation of (iii) still gave a mixture, containing *ca.* 25% of the ketone (I; R = Me), assessed as the 2 : 4-dinitrophenylhydrazone.

(*b*) The product when set aside overnight deposited the crude amidine hydrochloride (II) as red crystals. It was advantageous however to extract the residual mixture with chloroform as above and, after removal of the chloroform, to dissolve the residual red oil in ethanol, from which the *amidine hydrochloride* slowly crystallised, and when recrystallised from methanol or ethanol formed pale yellow needles, m. p. 210·5° (Found: C, 67·7; H, 7·35; N, 13·55. $C_{17}H_{22}N_3Cl$ requires C, 67·3; H, 7·3; N, 13·8%). The addition of potassium iodide to a hot aqueous solution of this salt deposited the *hydriodide*, cream-coloured needles, m. p. 199—200° (from ethanol) (Found : C, 52·2; H, 5·8; N, 10·4. $C_{17}H_{22}N_3I$ requires C, 51·7; H, 5·6; N, 10·6%). The hydrochloride, when added to an excess of 20% aqueous sodium hydroxide and then shaken with a solution of toluene-*p*-sulphonyl chloride in acetone, yielded the *toluene*-p-*sulphonyl* derivative, yellowish crystals, m. p. 147—149° (from ethanol) (Found : C, 67·8; H, 6·6; N, 9·8. $C_{24}H_{27}O_2N_3S$ requires C, 68·3; H, 6·45; N, 10·0%).

When the above experiment was conducted in *o*-dichlorobenzene instead of chlorobenzene, a lower yield of the crude ketone (I; R = Me) was obtained.

Direct Preparation of the Amidine Hydrochloride (II).—A mixture of the nitrile (16 g.), methylaniline (10·7 g., 1 mol.), and aluminium chloride (13·3 g., 1 mol.) was heated with stirring for 1 hr. at 140—160°, and then poured on ice, and the hydrochloride was collected; after recrystallisation from ethanol, it had m. p. 210° (mixed and unmixed with above product) (82% yield). The same result was obtained when the above mixture was diluted with chlorobenzene (60 c.c.) and then boiled under reflux for 1 hr., and the solvent removed by steam-distillation.

β-*Methylanilinopropionic Acid.*—A mixture of the nitrile (240 g.) and a solution of potassium hydroxide (92 g., 1·1 mols.) in water (1000 c.c.) was boiled vigorously under reflux to disperse the nitrile as a fine emulsion. After 2·5 hr., the clear solution was cooled, extracted with ether to remove a greenish impurity, and then made just acid with hydrochloric acid, the required acid being precipitated as an oil. The mixture was then repeatedly extracted with ether, and the united extracts were dried and filtered, and the solvent was removed. The viscous residual acid (204 g., 76%) could not be crystallised : for identification, a sample was dissolved in ethanolic hydrogen chloride, from which the *hydrochloride* separated as a gum which slowly solidified, and was obtained as colourless needles, m. p. 139—141°, from *n*-propanol (Found : C, 56·2; H, 6·85; N, 6·8. $C_{10}H_{13}O_2N,HCl$ requires C, 55·7; H, 6·5; N, 6·5%). Another sample was dissolved in an excess of methyl iodide, which was boiled for a few minutes and allowed to evaporate; the residual *methiodide*, when washed with ether, formed pale yellow crystals, m. p. 150° (decomp.) (Found: C, 41·1; H, 5·0; N, 4·4. $C_{11}H_{16}O_2NI$ requires C, 41·1; H, 5·0; N, 4·4%).

Action of Phosphoric Anhydride in Xylene.—A solution of the above acid (60 g.) in dry xylene (400 c.c.) was added to an intimate mixture of phosphoric anhydride (60 g., 1·3 mols.) and kieselguhr (" Hyflo-Supercel ") (30 g.), and the mixture vigorously agitated to maintain a fine suspension of the solid components. It was then boiled under reflux; a deep yellow colour speedily developed, and after 4 hr.' boiling the anhydride had separated as red lumps, and stirring became difficult. The hot xylene was then decanted through a filter and evaporated, leaving a residue (*ca.* 0·5 g.) of the crude ketone (I; R = Me) identified as its 2 : 4-dinitrophenylhydrazone.

The material remaining in the reaction flask was washed with ether to remove xylene, and then water (500 c.c.) was cautiously added, followed by powdered sodium carbonate (125 g.). The mixture was then made strongly alkaline with sodium hydroxide and repeatedly extracted with chloroform. The united dried extracts on evaporation gave a red oil, which when distilled at 1 mm. gave the fractions: (i) b. p. 110—130° (10 g.), methylaniline; (ii) b. p. 130—180° (5 g.), mainly methylaniline with a trace of ketonic impurity; (iii) b. p. 185—195° (4 g.), reddish liquid forming an orange solid; (iv) b. p. 195—220° (9 g.), a deep red liquid which became semi-solid. Fractions (iii) and (iv) gave no ketonic reactions. Fraction (iv) on attempted recrystallisation gave no definite products. Fraction (iii), after repeated crystallisation from benzene, gave colourless crystals, m. p. 151—152°, of 1 : 4-dihydro-1-methyl-4-oxoquinoline (1·1 g.) (III) (Found: C, 75·6; H, 5·7; N, 9·1. Calc. for $C_{10}H_9ON$: C, 75·4; H, 5·7; N, 8·8%). This gave a yellow picrate, m. p. 229—230° in an evacuated tube (from ethanol) (Found: C, 49·9; H, 3·3; N, 14·6. Calc. for $C_{10}H_9ON,C_6H_3O_7N_3$: C, 49·5; H, 3·1; N, 14·4%), and a chloroplatinate, m. p. 211—212° (decomp.). Späth and Kolbe (*loc. cit.*) record 150—152°, 227—229°, and 211—212° as the m. p.s of the base and these two salts respectively. It also gave a *toluene*-p-*sulphonate*, colourless hygroscopic plates, m. p. 220—221°, from ethanol (Found: C, 62·2; H, 5·17; N, 4·1. $C_{10}H_9ON,C_7H_8O_3S$ requires C, 61·6; H, 5·2; N, 4·2%), and a perchlorate, colourless crystals, m. p. 160—163°, from water.

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