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THE SYNTHESIS OF SOME NEW DIMETHYLTETRAHYDROQUINOLINES

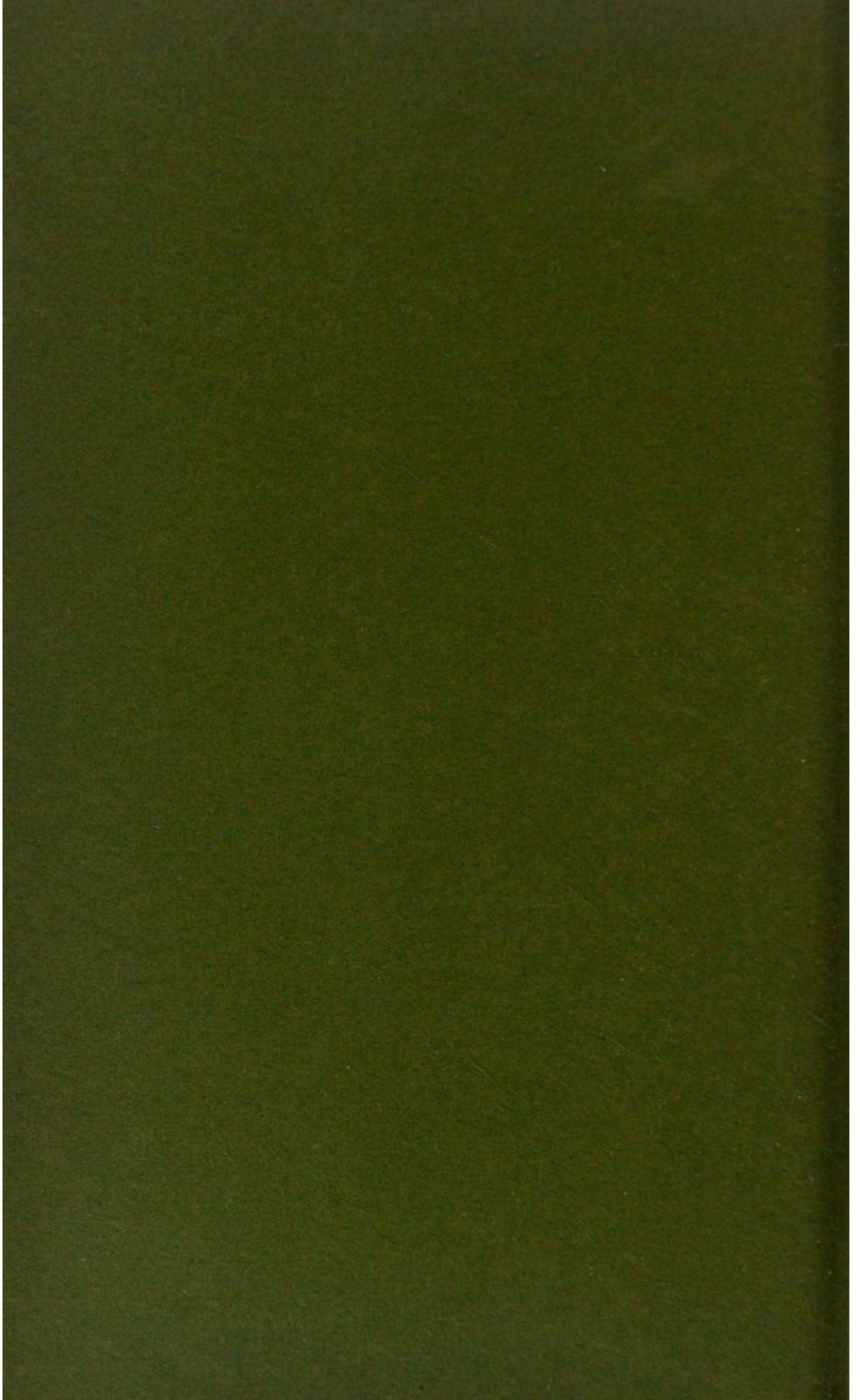
BY
ARTHUR JAMES EWINS, B.Sc.
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From

THE WELLCOME PHYSIOLOGICAL RESEARCH LABORATORIES
BROCKWELL HALL
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XV.—*The Synthesis of Some New Dimethyltetrahydroquinolines.*

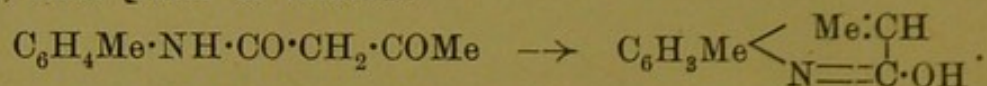
By ARTHUR JAMES EWINS and HAROLD KING.

IN the course of an investigation which is being carried out by one of us in conjunction with Dr. G. Barger, it became necessary for the purpose of comparison to prepare certain hydroxydimethylquinolines and their reduction products. Reference to the literature showed that a number of such substituted hydroxyquinolines had already been prepared, chiefly by Knorr (*Ber.*, 1884, **17**, 542; *Annalen*, 1889, **245**, 358) and Conrad and Limpach (*Ber.*, 1888, **21**, 525).

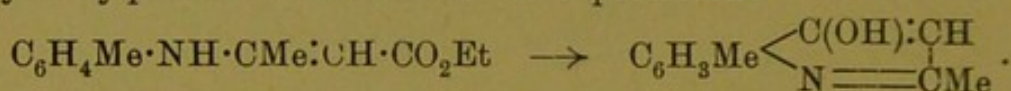
In the first place, we attempted the preparation of 2-hydroxy-4:8-dimethylquinoline by Knorr's method. This consists in heating molecular proportions of *o*-toluidine and ethyl acetoacetate in sealed tubes at 150—160° for several hours, and subsequently treating the crude product with cold concentrated sulphuric acid. On pouring into water, the hydroxyquinoline is precipitated. The method,

however, gave very unsatisfactory results, a poor yield of an obviously very impure product being obtained. We subsequently found that the product described by Knorr as 2-hydroxy-4:8-dimethylquinoline must also have been very impure, since he gives for this compound a melting point of 185° , whereas we find that the pure substance melts at 217° .

The formation of a hydroxyquinoline by the above process depends on the production of the toluidide of acetoacetic acid, which then, under the dehydrating action of concentrated sulphuric acid, loses water as follows:



The intermediate toluidide was not isolated by Knorr. Pawlewski (*Ber.*, 1889, **22**, 2203), however, described a substance obtained from the product, which he considered to be β -tolyliminocrotonic acid (isomeric with the toluidide), in accordance with Knorr's original view (*Ber.*, 1884, **17**, 542) that condensation took place, not as indicated above, but according to the following scheme, whereby 4-hydroxyquinoline derivatives were produced:



Knorr, however, had already corrected his original interpretation of the reaction, and Pawlewski's substance was in all probability, from its melting point and the analytical figures, the *o*-toluidide of acetoacetic acid. The 4-hydroxyquinolines were afterwards synthesised by Conrad and Limpach from the β -toluidinocrotonic esters obtained by the interaction of the substances in the cold (*Ber.*, 1888, **21**, 525).

As we required considerable quantities of these hydroxyquinolines for our purpose, we experimented with the object of obtaining the required toluidides in a state of purity and improved yield. After several attempts we found that by simply boiling together molecular proportions of the necessary toluidine and ethyl acetoacetate for a very short time (one to one and a-half minutes) the product solidified on cooling to a mass of crystals, which, after recrystallisation, were obtained pure in good yield, averaging 55 per cent. of the theoretical.* The toluidides so obtained are readily and almost quantitatively converted into the corresponding hydroxyquinolines (carbostyrils) by heating at 100° for ten to fifteen minutes with concentrated sulphuric acid. On pouring into water, the hydroxyquinolines separate out immediately in an almost pure condition.

The hydroxyquinolines so obtained on reduction with sodium

* The preparation of the anilide of ethyl acetoacetate can be readily carried out in a precisely similar manner.

and alcohol are converted mainly into the corresponding tetrahydroquinolines. There are indications of the formation of intermediate products, possibly hydroxydihydroquinolines, but this has not so far been investigated. On distillation with zinc dust, the hydroxyquinolines are converted into dimethylquinolines (Knorr, *Annalen*, 1889, **245**, 358). The reduction, however, takes place only with some difficulty, a rather high temperature and a current of hydrogen being essential in order to obtain a satisfactory yield of base. The characterisation of these dimethylquinolines as at present recorded is very unsatisfactory and incomplete. We have accordingly redetermined the boiling points of these bases, and place on record some of their more characteristic salts and derivatives.

The new dimethyltetrahydroquinolines described in this communication are readily distinguished from the corresponding dimethylquinolines by the following properties. Whilst the dimethylquinolines give no coloration when dissolved in sulphuric acid (the solution, however, shows a marked blue fluorescence) and treated with a drop of nitric acid, with the tetrahydro-derivatives well-marked colour reactions are obtained. Again, the salts of the tetrahydro-bases generally melt at a considerably lower temperature than those of the dimethylquinolines, the picrates, for example, differing by about 60—70°. The picrates of the tetrahydro-bases are orange or orange-yellow salts, moderately soluble in water, and very readily so in acetone. Those of the dimethylquinolines are pale yellow, and very sparingly soluble in hot water or alcohol. The tetrahydro-bases also yield characteristic benzoyl derivatives of low melting point by the Schotten-Baumann reaction.

EXPERIMENTAL.

Acetoaceto-o-toluidide, $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{NH} \cdot \text{C}_6\text{H}_4\text{Me}$.

A mixture of 30 grams of ethyl acetoacetate and 24 grams of *o*-toluidine was rapidly heated to boiling, and the liquid kept vigorously boiling for one to one and a-half minutes. The cooled product set to a mass of crystals, which were collected and recrystallised from ethyl acetate, when short, rectangular prisms (25 grams) melting at 107—108° were obtained:

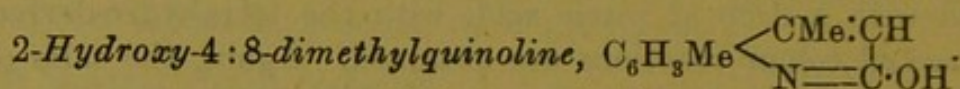
0.1562 gave 0.3943 CO_2 and 0.1008 H_2O . C=68.8; H=7.2.

0.1950 „ 12.5 c.c. N_2 (moist) at 10° and 760 mm. N=7.6.

$\text{C}_{11}\text{H}_{13}\text{O}_2\text{N}$ requires C=69.1; H=6.8; N=7.3 per cent.

We were also able to isolate a certain amount of this toluidide from the reaction product obtained by Knorr's method (heating to 150—160° in sealed tubes), and it is most probable that the

substance isolated by Pawlewski (*Ber.*, 1889, **22**, 2203) from this reaction product, and considered by him to be *o*-tolyliminocrotonic acid (m. p. 111—112°), was, in fact, acetoaceto-*o*-toluidide. Since, however, no details of the method of isolation or of the properties of the substance are given, it is not possible to determine this point except by synthesis of the acid. That the toluidide possesses the constitution assigned to it by the present authors is obvious from the fact that the product is insoluble in sodium carbonate, showing the absence of the carboxyl group, and that the alcoholic solution gives with ferric chloride a purple coloration indicative of the enolic form of the acetoacetic grouping which could hardly be the case if the substituting toluidine were in the position assigned to it by Pawlewski. Its constitution further follows from its ready conversion into 2-hydroxy-4:8-dimethylquinoline by the action of dehydrating agents, whereas the acid described by Pawlewski would be expected to give the isomeric 4-hydroxy-2:8-dimethylquinoline obtained by Conrad and Limpach by another method.

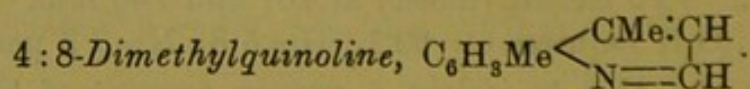


Acetoaceto-*o*-toluidide (19 grams) was dissolved in concentrated sulphuric acid (20 c.c.), and the mixture heated in the boiling-water bath for fifteen minutes. The product was then poured into about ten volumes of water, when a white, crystalline solid separated. After some time this was collected, and recrystallised from dilute acetic acid, when it separated in long, thin plates, melting at 217—218°:

0.1180 gave 0.3310 CO₂ and 0.0628 H₂O. C=76.5; H=5.9.

C₁₁H₁₁ON requires C=76.3; H=6.3 per cent.

This carbostyryl was originally described by Knorr (*Ber.*, 1884, **17**, 542), who obtained it in a very impure form, melting at 185° from the crude product obtained as described. The substance is a weak base, very sparingly soluble in cold water, more readily so in hot. It forms salts with concentrated mineral acids, but these are decomposed by excess of water with liberation of the crystalline base. On distillation with zinc dust it yields 4:8-dimethylquinoline, and on reduction by sodium and alcohol, 4:8-dimethyl-1:2:3:4-tetrahydroquinoline.



This base was originally described by Knorr as a pungent oil boiling at 273—274°/751 mm. It is obtained by distilling

2-hydroxy-4:8-dimethylquinoline over zinc dust in a current of hydrogen. In order to purify the base it was converted into the pure picrate described below. The salt so obtained was treated with a concentrated solution of potassium hydroxide, and distilled in a current of steam. The oily liquid was extracted from the distillate by means of ether, and, after drying and removal of the solvent, distilled. The base was an almost colourless, limpid oil, boiling at 134—135°/12 mm. and 258—259°/758 mm., which on keeping solidified to a crystalline mass melting at 54—55°. (Found, C=83.5; H=7.0. $C_{11}H_{11}N$ requires C=84.0; H=7.0 per cent.)

4:8-Dimethylquinoline picrate was obtained by precipitating the ethereal solution of the base by an ethereal solution of picric acid. The salt was recrystallised from dilute alcohol, and was obtained in lemon-yellow, rhombic prisms, melting at 216—217°:

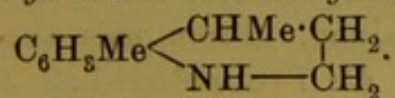
0.1821 gave 0.3506 CO_2 and 0.0582 H_2O . C=52.6; H=3.5.

$C_{11}H_{11}N, C_6H_3O_7N_3$ requires C=52.8; H=3.6 per cent.

The salt is very sparingly soluble in hot water or alcohol, but rather more readily so in acetone.

The *platinichloride* crystallises from dilute alcohol in buff-coloured needles, melting and decomposing at 226—227° (Knorr gives 220°).

4:8-Dimethyl-1:2:3:4-tetrahydroquinoline,



2-Hydroxy-4:8-dimethylquinoline (7.5 grams) was reduced by sodium (15 grams) in concentrated absolute alcoholic solution. The solution was diluted with an equal volume of water, the alcohol distilled off, and the residue distilled in a current of steam. The oily liquid which passed over was extracted with ether, the ethereal solution dried over potassium carbonate, and after evaporating off the ether the residue was fractionally distilled. The distillate was converted into the picrate, which was obtained pure by recrystallising from dilute alcohol. The regenerated base then boiled at 133—134°/16 mm. and at 256—258°/750 mm.:

0.1566 gave 0.4708 CO_2 and 0.1322 H_2O . C=82.0; H=9.4.

$C_{11}H_{15}N$ requires C=82.0; H=9.3 per cent.

4:8-Dimethyl-1:2:3:4-tetrahydroquinoline is a colourless oil, very sparingly soluble in water, and easily volatile with steam. When treated with concentrated sulphuric acid and a drop of nitric acid a deep orange-red colour is produced.

The *picrate*, obtained in the usual manner, forms orange-yellow,

rhombic prisms, melting at 160° . It is sparingly soluble in cold water, but fairly readily so in hot water, alcohol, or acetone:

0.1090 gave 0.2096 CO_2 and 0.0448 H_2O . $\text{C}=52.4$; $\text{H}=4.6$.

$\text{C}_{11}\text{H}_{15}\text{N}, \text{C}_6\text{H}_3\text{O}_7\text{N}_3$ requires $\text{C}=52.3$; $\text{H}=4.6$ per cent.

The *benzoyl* derivative, $\text{C}_{18}\text{H}_{19}\text{ON}$, prepared by the Schotten-Baumann reaction, crystallises from dilute alcohol in prisms melting at $104-105^{\circ}$.

Acetoaceto-m-toluidide, $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{NH}\cdot\text{C}_6\text{H}_4\text{Me}$.

This compound is obtained by a method exactly similar to that employed in the preparation of the ortho-compound. On recrystallisation from benzene and light petroleum it separated in pearly leaflets melting at $57-58^{\circ}$:

0.1570 gave 0.3972 CO_2 and 0.0980 H_2O . $\text{C}=69.0$; $\text{H}=6.93$.

$\text{C}_{11}\text{H}_{13}\text{O}_2\text{N}$ requires $\text{C}=69.1$; $\text{H}=6.8$ per cent.

Its general properties are in all respects similar to those of the isomeric ortho-compound.

Owing to the low melting point of the solid, however, its separation from the crude product was found to be somewhat troublesome. In the preparation of the corresponding 2-hydroxy-4:7-dimethylquinoline, therefore, the crude product was directly treated with concentrated sulphuric acid at 100° for fifteen minutes, and the product poured into water. After crystallisation from dilute acetic acid a good yield (41 per cent.) of the hydroxyquinoline melting at 220° was readily obtained. From this the corresponding 4:7-dimethylquinoline and 4:7-dimethyl-1:2:3:4-tetrahydroquinoline were obtained by zinc dust distillation and reduction by sodium in alcohol respectively.

4:7-Dimethylquinoline, $\text{C}_{11}\text{H}_{11}\text{N}$.

2-Hydroxy-4:7-dimethylquinoline was distilled with zinc dust as described in the case of the corresponding 2-hydroxy-4:8-dimethylquinoline, and the product worked up as before. In this way from 10 grams of hydroxyquinoline were obtained 3.3 grams of a colourless oil. In order to obtain the pure base it was converted into the picrate, and the base regenerated from the pure salt boiled at $140-141^{\circ}/15$ mm.

The *picrate* was prepared in the manner described for the picrate of 4:8-dimethylquinoline, and was crystallised from dilute alcohol. It forms broad, rectangular, golden-yellow prisms, melting at 224° :

0.1736 gave 0.3374 CO_2 and 0.0566 H_2O . $\text{C}=53.0$; $\text{H}=3.6$.

$\text{C}_{11}\text{H}_{11}\text{N}, \text{C}_6\text{H}_3\text{O}_7\text{N}_3$ requires $\text{C}=52.8$; $\text{H}=3.6$ per cent.

This salt is very sparingly soluble in cold water, and only moderately so in hot water or alcohol.

4:7-Dimethyl-1:2:3:4-tetrahydroquinoline.

Ten grams of 2-hydroxy-4:7-dimethylquinoline were dissolved in boiling absolute alcohol, and 12 grams of sodium added to the boiling solution in small quantities at a time. The sodium salt of the hydroxyquinoline separates as a spongy mass, but slowly dissolves as the reduction proceeds. The dimethyltetrahydroquinoline was recovered as previously described. Yield, 5 grams.

The base was converted into the picrate, and recovered from the pure picrate by steam distillation from alkaline solution.

4:7-Dimethyl-1:2:3:4-tetrahydroquinoline is a colourless oil, which dissolves in concentrated sulphuric acid with a faint yellow colour, and on addition of a drop of concentrated nitric acid gives a purple-brown coloration. It boils at 136—138°/13 mm., and 268—270°/769 mm.:

0.1456 gave 0.4364 CO₂ and 0.1260 H₂O. C=81.8; H=9.3.

C₁₁H₁₅N requires C=82.0; H=9.3 per cent.

The *picrate* crystallises from dilute alcohol in long, orange-yellow, serrated needles, melting at 155—156°. Its solubilities resemble those of the 4:8-dimethyltetrahydroquinoline picrate already described:

0.1420 gave 0.2728 CO₂ and 0.0598 H₂O. C=52.4; H=4.7.

C₁₁H₁₅N, C₆H₃O₇N₃ requires C=52.3; H=4.6 per cent.

The *benzoyl* derivative, C₁₈H₁₉ON, prepared by the Schotten-Baumann reaction, crystallises from light petroleum in bundles of leaflets, and melts at 84—85°.

Acetoaceto-p-toluidide, CH₃·CO·CH₂·CO·NH·C₆H₄Me.

This compound was prepared in the same way as the toluidides already described, and was similar to them in general properties. After crystallisation from ethyl acetate it was obtained in well-formed prisms melting at 94—95°:

0.1356 gave 0.3442 CO₂ and 0.0844 H₂O. C=69.2; H=6.9.

C₁₁H₁₃O₂N requires C=69.1; H=6.8 per cent.

The corresponding hydroxyquinoline (2-hydroxy-4:6-dimethylquinoline) was obtained by the action of concentrated sulphuric acid, as described before, and was found to agree in melting point and properties with the compound described by Knorr. It was submitted to distillation with zinc dust and reduction by sodium and alcohol, yielding 4:6-dimethyl- and 4:6-dimethyl-1:2:3:4-tetrahydro-quinolines respectively.

4:6-Dimethylquinoline.

Ten grams of 2-hydroxy-4:6-dimethylquinoline were distilled with zinc dust. The crude 4:6-dimethylquinoline so obtained was dis-

tilled, yielding 3.5 grams, which were converted into the picrate. The pure base was recovered from the purified picrate, and boiled at 140—141°/12 mm. and 255—256°/760 mm.

4:6-Dimethylquinoline picrate crystallises from dilute alcohol in long, rectangular prisms, melting at 236—237° (Knorr gives 230°). (Found, C=52.7; H=3.6. Calc., C=52.8; H=3.6 per cent.)

The solubilities are similar to the dimethylquinoline picrates already described.

4:6-Dimethyl-1:2:3:4-tetrahydroquinoline.

Ten grams of 2-hydroxy-4:6-dimethylquinoline were reduced in concentrated boiling alcoholic solution by 24 grams of sodium. The dimethyltetrahydroquinoline was recovered by steam distillation, and after distillation under diminished pressure yielded 4.3 grams of base.

The pure base was obtained from the purified picrolonate by steam distillation in alkaline solution. It boiled at 135—137°/15 mm. and 254—256°/750 mm.

4:6-Dimethyl-1:2:3:4-tetrahydroquinoline is a colourless oil. It dissolves in concentrated sulphuric acid with a deep purple colour, which slowly passes into blue, and finally becomes deep green:

0.1764 gave 0.5296 CO₂ and 0.1482 H₂O. C=81.9; H=9.4.

C₁₁H₁₅N requires C=82.0; H=9.3 per cent.

The *picrolonate*, prepared in ethereal solution and crystallised from dilute alcohol, crystallises in hard, yellow rhombs, and melts at 204—205°. It is very sparingly soluble in boiling water or alcohol:

0.1494 gave 0.3252 CO₂ and 0.0732 H₂O. C=59.4; H=5.4.

C₁₁H₁₅N, C₁₀H₈O₅N₄ requires C=59.3; H=5.4 per cent.

The *picrate* is obtained as a gummy solid by precipitating the ethereal solution with light petroleum. It can be recrystallised from benzene, and separates in rectangular plates melting at 116—117°:

0.1162 gave 0.2234 CO₂ and 0.0494 H₂O. C=52.4; H=4.7.

C₁₁H₁₅N, C₈H₃O₇N₃ requires C=52.3; H=4.6 per cent.

The *benzoyl* derivative, prepared by the Schotten-Baumann reaction, crystallises from dilute alcohol in pearly leaflets melting at 109—110°:

0.1372 gave 0.4094 CO₂ and 0.0880 H₂O. C=81.4; H=7.1.

C₁₈H₁₉ON requires C=81.5; H=7.2 per cent.

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