CCCLI.—*Studies in the Camphane Series. Part XLI. The Unstable Modification of* iso*Nitrosocamphor.*

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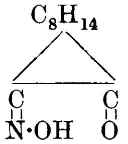
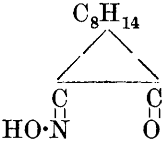
ALTHOUGH the existence of a low-melting, unstable *iso*nitroso-derivative in the product of the action of sodium and amyl nitrite on camphor has long been established (J., 1903, **83**, 534), the substance has remained obscure because the method of obtaining it is inconvenient. This consists in hydrolysing under strictly defined conditions the yellow *m*-nitrobenzoyl derivative produced in association with a colourless isomeride when *m*-nitrobenzoyl chloride acts on the Claisen mixture of *iso*nitrosocamphors (J., 1904, **85**, 904).

The principal reason for failing to improve on this process probably lies in the facility with which the unstable modification (m. p. 114°) changes into the less fusible isomeride (m. p. 152°). Transformation begins at the melting point and occurs also in cold aqueous alkali hydroxide, especially when the solution is exposed to light. It was later found that in ethereal solution diazomethane (J., 1908, **93**, 247), ferric chloride (J., 1913, **103**, 666) and probably magnesium methyl iodide (J., 1905, **87**, 236) effect the same change.

The configuration of these two monoximes of camphorquinone, as diagnosed by methods applied to (*a*) the stable form and (*b*) the Claisen mixture of stable and unstable forms, appears to be as follows :



syn-Modification (m. p. 152°).



anti-Modification (m. p. 114°).

The determining factor in this diagnosis is the readiness with which anhydride formation takes place in a compound obtained from the less fusible modification and magnesium methyl iodide, suggest-

$$C_8H_{14}<\begin{matrix}C{:}NOH\\ CMe\cdot OH\end{matrix} \longrightarrow C_8H_{14}<\begin{matrix}C{:}N-\\ CMe\end{matrix}>O$$

ing propinquity of the two hydroxyl groups (*loc. cit.*). The desirability of completing the inquiry by reviewing the behaviour of (*c*) the unstable form of *iso*nitrosocamphor led to the present investigation, which has incidentally revealed a simple method of producing that substance.

Several years ago an attempt was made by one of us to separate the components of the Claisen mixture by steam distillation. Following an observation that the low-melting, unstable hydrazone of camphorquinone (J., 1910, **97**, 2166) and the low-melting, unstable phenylhydrazone (J., 1911, **99**, 484) are volatile in steam and may thus be separated from their isomerides, the same relationship between the monoximes (*iso*nitrosocamphors) might have been expected. Unfortunately, however, although a small proportion of the low-melting oxime is removed from the freshly-prepared Claisen mixture by steam, the passage of its vapour is outpaced by the transformation of its hot aqueous solution into that of the stable isomeride. For the purpose of separating the low-melting oxime, therefore, this method is valueless, and an attempt to remove the more volatile substance by sublimation in a liquid air–charcoal vacuum was unsuccessful.

We have now found that the simplest of all possible methods, namely, fractional precipitation by acetic acid from the original solution of sodium derivatives, effects an excellent separation and incidentally confirms the conclusion (J., 1903, **83**, 526) that the Claisen mixture comprises equal parts of the two isomerides. This precipitation demands exactness, but had Claisen and Manasse used acetic acid instead of carbon dioxide for their attempted fractional precipitation, they might themselves have effected the separation, as they evidently suspected the existence of a low-melting, unstable compound in their product (*Annalen*, 1893, **274**, 71).

It has thus become possible to examine the action of magnesium methyl iodide on the unstable *iso*nitrosocamphor as an individual, and the result shows that the α-oxime alone is formed. From the earlier paper (J., 1905, **87**, 232) it appeared that only the γ-oxime arose from stable *iso*nitrosocamphor, whilst the Claisen mixture gave the α- and γ-oximes associated with a third substance called the β-oxime. The α-oxime does not yield the anhydride when a solution in aqueous potassium hydroxide is boiled, and is thus distinguished from the β- and γ-oximes; and it is this distinction which appears to establish the above-mentioned configuration for the two forms of *iso*nitrosocamphor.

Hence the connexion between the α- and γ-oximes appears to be that of the *iso*nitroso-derivatives from which they spring, but the relationships of the β-oxime are less exact, as this is not produced from either form of *iso*nitrosocamphor alone, but only when they are associated in the Claisen mixture. The properties of this mixture in organic media suggest a loose union between the *syn*- and *anti*-modifications which is not disturbed by solvents, but is resolved by dissolution in alkali hydroxide; and we now believe that the so-called β-oxime is not an individual, but a mixture of the α- and γ-oximes inheriting the characteristic property of the Claisen mixture. This appears a more probable explanation of the experiments than the alternative, which would rest on an inverted configuration of the methyl and hydroxy-groups attached by the Grignard agent.

It also seems justifiable to conclude that formation of the α-oxime alone from low-melting *iso*nitrosocamphor, formerly conjectured but now definitely proved, confirms the *anti*-configuration for the latter substance, and supports the deductions regarding the eight oximino-derivatives from camphorquinone already made (Forster, J., 1913, **103**, 662). In view of recent work by Meisenheimer and his collaborators tending to subvert hitherto accepted generalisations on the geometrical isomerism of oximes, it is proper to point out that the above-mentioned conclusions depend on ring formation even more than upon preferential *cis*-interaction, and that the evidence from both sources is in harmony.

EXPERIMENTAL.

The Claisen Mixture.—Sodium wire (8·5 g.) was immersed in absolute ether (250 c.c.) in a flask (1·5 l.) fitted with a condenser and a drying-tube and surrounded by melting ice. Camphor (54 g.) was added in small quantities and when completely dissolved was followed in dim light by redistilled amyl nitrite (45 g.), also in small amounts. After the first few additions, the liquid became yellow and a tendency to froth was checked by agitation, and control of temperature; subsequently added quota could be safely increased, and when all had been entered the reddish-brown product was left in ice during 1—2 hours, a small quantity of solid appearing. In semi-darkness, ice and water were added until a reddish-brown aqueous layer had separated from the pale yellow ethereal stratum, it being recalled that the sodium derivative of the unstable isomeride, when dissolved in water and exposed to light, is transformed into the stable modification. After removal of the aqueous layer, the ethereal portion was twice washed with water, which, when added to the alkaline fluid, increased its volume to 150 c.c. This in turn was extracted twice with small quantities of ether to remove borneol and unchanged camphor, being finally freed from ether by a current of air.

Separation of the Isomerides.—Dilute acetic acid (20%) was added in small quantities to the constantly shaken alkaline fluid at 0° until 72 c.c. had been used; the faintly yellow, crystalline precipitate was then filtered off, washed with ice-water and very dilute acetic acid, and again with ice-water. Dried in air, this product weighed 7·5 g. (m. p. 110—112°) and was the unstable *iso*nitrosocamphor. The filtrate with washings, now paler but still alkaline, acidified with acetic acid, yielded a colourless, crystalline precipitate (11·6 g.), m. p. 125—130°, the filtrate from which gave up 1·3 g. of stable *iso*nitrosocamphor (m. p. 149—152°) to ether. The fraction weighing 11·6 g. (m. p. 125—130°) was redissolved in 5% aqueous sodium hydroxide, and careful precipitation with 20% acetic acid gave 1·5 g. of the unstable derivative; a smaller quantity of this was obtained by completing the precipitation, passing steam through the product, and extracting the distillate with ether. Thus the separation gave 9—10 g. of unstable *iso*nitrosocamphor and 10—11 g. of the stable isomeride, while 22 g. of borneol and unchanged camphor were recovered from the original ethereal solution. It has been previously stated by one of us that the isomerides cannot be separated by fractional crystallisation from organic solvents; this was the experience of Claisen and Manasse, and our own confirms it. The intermediate fraction (m. p. 125—130°) from another experiment was extracted with hot petroleum (b. p. 60—80°), in which the low-melting form is freely soluble; but the undissolved portion remained a mixture (m. p. 125—128°) and the filtrate deposited a mixture (m. p. 122—125°).

Action of Magnesium Methyl Iodide.—The action of Grignard's agent on (*a*) the stable form and (*b*) the Claisen mixture having been previously observed, it remained to direct this on (*c*) the unstable form, for which purpose the fraction (m. p. 110—112°) obtained above was recrystallised from petroleum. Magnesium

(2 g. of clean turnings) immersed in dry, ice-cold ether (100 c.c.) was dissolved by portion-wise addition of methyl iodide (25 g.), unstable *iso*nitrosocamphor being then added in very small quantities to the constantly shaken liquid. Vigorous action accompanied by hissing and effervescence took place, the added solid becoming red and then dissolving whilst the ether became green. When about one-half the oxime had been added, the green colour suddenly changed to pale yellow and a viscous, dark-grey, heavy syrup appeared, increasing with further additions. Action became noticeably feebler, and the red solid produced on entering the concluding portions remained suspended above the syrup, but dissolved in the course of 24 hours. Ice and aqueous acetic acid were then added until the liquid was clear, and the ethereal portion was shaken with sodium carbonate (10%) and extracted four times (10 c.c. each) with sodium hydroxide (5%) to remove unchanged *iso*nitrosocamphor. The ethereal solution was then shaken twice (25 c.c. each time) with aqueous potassium hydroxide (25%), washed with water, dried, and allowed to evaporate in darkness. The crystalline residue, which had a slight camphoraceous odour, was powdered, mixed with a small quantity of low-boiling petroleum, and drained on earthenware. Recrystallisation of the product (3·2 g.) from aqueous alcohol gave colourless, glistening plates (m. p. 181°, instead of 178°) having $[\alpha]_D$ 86·6° (instead of 84·2°) in chloroform, falling to 69·7° (constant) during 24 hours in strong light. A solution in aqueous potassium hydroxide (10%) remained clear on boiling, and a solution in dilute sulphuric acid (10%) became turbid on boiling, from separation of the anhydride.

The compound is thus identified as the α-oxime (J., 1905, **87**, 237), and is the sole product of acting upon the unstable *iso*nitrosocamphor with magnesium methyl iodide, because the β- and γ-oximes were not present in the aqueous potassium hydroxide (25%) from which they were precipitated on the former occasion (*loc. cit.*). On allowing the chloroform solution of the α-oxime to evaporate after the diminished optical activity had become constant, the γ-oxime was obtained; it crystallised from petroleum in characteristic, sparingly soluble needles and also from boiling water. Solutions of the γ-oxime in aqueous potassium hydroxide (10%) and in dilute sulphuric acid (10%) became turbid when boiled, owing to anhydride formation.

An intimate mixture of the α- and γ-oximes melted mid-way between the melting points of the components, and a solution of this mixture in hot petroleum (b. p. 60—80°) deposited the snow-white, opaque nodules (m. p. 183·5—184·5°, instead of 183°) previously mistaken for an individual substance and called the β-oxime.

This material is very delusive. Its appearance is quite distinct from that of the α- and γ-oximes, and it changes completely into the γ-oxime when heated on the water-bath, although the α-oxime alone remains unchanged by this treatment. Moreover, the rotation of the α-oxime in chloroform falls to a point mid-way between the original angle and that given by the γ-oxime, remaining constant approximately at the value formerly ascribed to the β-oxime. Nevertheless, we believe the last-named substance to be a mixture.

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