

LXXIV.—*Studies in the Camphane Series. Part XXXIV. Configuration of the Eight Oximino-derivatives of Camphorquinone.*

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BENZIL is the model case of a symmetrical  $\alpha$ -diketone in which the configuration of each oximino-derivative has been established. This is due to Beckmann and Köster (*Annalen*, 1893, **274**, 1) who, by following the course of a Beckmann transformation applied to the two monoximes and three dioximes, drew conclusions regarding the spacial disposition of the hydroxyl groups relative to the other parts of the molecule.

The discovery of isonitrosoepicamphor in two modifications, constituting the third and fourth monoximes of camphorquinone (T., 1912, **101**, 1340), thereby completing the series of eight oximino-derivatives from that diketone, invited an attempt to establish the configuration of these materials on the lines of the Hantzsch-Werner hypothesis, because they present the only recorded case in which all the possible derivatives of an unsymmetrical  $\alpha$ -diketone have been isolated.

Owing to the stability of the camphor nucleus, the method of Beckmann and Köster can be applied in only modified form to

the monoximes, and in the case of the dioximes it has been necessary to rely on arguments which, although perhaps appearing less conclusive at first, certainly have the advantage of depending on less drastic transformations. Briefly stated, this part of the investigation has resolved itself into an inquiry as to the identity of the dioximes arising by the action of hydroxylamine on each monoxime, and then, by a process of elimination based on preliminary knowledge of the configuration of the monoximes themselves, deciding the disposition of the hydroxyl groups in the four dioximes. For this purpose it has appeared desirable to repeat much of the earlier work on the dioximes (T., 1903, **83**, 514), and by improving the methods of separating these, to determine with greater certainty their relationship to the monoximes.

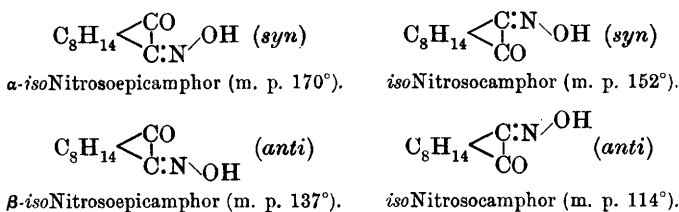
Beyond giving the following table, in which details regarding more highly purified materials are slightly amended, it is not necessary to recapitulate the information which has been published from time to time concerning the eight oximino-derivatives of camphorquinone, the history of these compounds having been summarised recently:

	M. p.	[ $\alpha$ ] <sub>D</sub> .	
		Chloroform.	2 per cent. NaOH.
<i>iso</i> Nitrosocamphor (unstable).....	114°	172·9°	275·3°
„ (stable) .....	152	197·0	288·0
<i>iso</i> Nitrosoepicamphor (unstable) ...	137	- 179·4	- 278·5
„ (stable) .....	170	- 200·1	- 422·0
Camphorquinone $\alpha$ -dioxime .....	201	- 51·7	- 103·8
„ $\beta$ -dioxime .....	248	—	- 24·5
„ $\gamma$ -dioxime .....	136	16·4	14·3
„ $\delta$ -dioxime .....	194	52·8	87·0

It must be recalled, however, that the configuration of the two modifications of *isonitrosocamphor* has been established (T., 1905, **87**, 232), and the recognition of the stable and unstable forms as *syn*- and *anti*-modifications respectively is the starting point of the present inquiry.

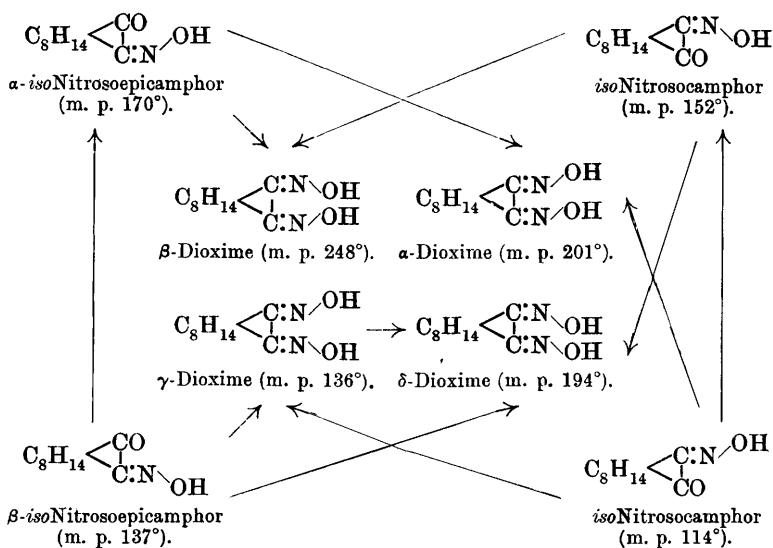
On comparing these isomerides with the third and fourth monoximes of camphorquinone, a similar relationship for the latter suggests itself. The unstable, more readily fusible, more freely soluble, and less optically active *isonitrosoepicamphor* corresponds exactly with the *anti*-monoxime represented by the unstable form of *isonitrosocamphor*, and most probably has, therefore, the *anti*-configuration. This diagnosis is strengthened by the effect of magnesium methyl iodide examined by Dr. Spinner, who has found that the behaviour of unstable *isonitrosoepicamphor* is strictly analogous to that of unstable *isonitrosocamphor*, there being produced a hydroxy-oxime which does not yield the anhydride with

hot alkali, whilst the stable *isonitrosoepicamphor* gives a mixture of the hydroxy-oxime with the anhydride. Moreover, whilst the unstable *isonitrosoepicamphor* may be extracted unchanged from hydrochloric acid (1:2) after boiling the latter during one minute, the stable modification is largely transformed into  $\beta$ -camphornitrilic acid. It is reasonable, therefore, to represent the four monoximes of camphorquinone in the manner following:



Passing now to the dioximes, it is at once noticeable that the  $\gamma$ -modification possesses in marked degree the characteristics associated with the *anti*-monoximes; it dissolves much more freely in organic media, melts at a far lower temperature, and has lower specific rotatory power than the three isomerides, into one of which ( $\delta$ ) it passes when heated. Being the only dioxime convertible into another, resembling in this respect the *anti*-monoximes, and displaying the attributes indicated above, it is natural to conclude that the *anti*-configuration prevails in the  $\gamma$ -dioxime, and as the greatest contrast is presented by the  $\beta$ -dioxime, it seems reasonable to regard the latter as the *syn*-modification. The two *amphi*-configurations are thus left for the  $\alpha$ - and  $\delta$ -dioximes, and in considering how these may be apportioned, cognisance must be taken of the fact that the *anti*-modification of *isonitrosoepicamphor* is more stable than the corresponding derivative of *isonitrosocamphor*, whence it follows that, since the change in configuration on passing from the  $\gamma$ -dioxime to the  $\delta$ -isomeride is restricted to a single oximino-group, that group is the one present in *isonitrosocamphor*.

The foregoing hypothesis has been submitted to a practical test by ascertaining, in the case of each dioxime, which monoximes are involved in its production. The results of this test, which are embodied in the following diagram, support the hypothesis in every particular; in fact, no one among the numerous observations which have been made in connexion with these compounds will be found in conflict with the suggestions here made as to their configuration.



Furthermore, it is worth remarking that a qualitative relationship in respect of specific rotatory power among the dioximes may be calculated in the following manner:

$$\begin{aligned}
 \alpha\text{-Dioxime} &= \frac{1}{2}[\text{isoNitrosocamphor (anti)} + \text{isonitrosoepicamphor (syn)}] \\
 &= \frac{1}{2}(275.3 - 422.0^\circ) = -73.3^\circ. \\
 \beta\text{-Dioxime} &= \frac{1}{2}[\text{isoNitrosocamphor (syn)} + \text{isonitrosoepicamphor (syn)}] \\
 &= \frac{1}{2}(288.0 - 422.0^\circ) = -67.0^\circ. \\
 \gamma\text{-Dioxime} &= \frac{1}{2}[\text{isoNitrosocamphor (anti)} + \text{isonitrosoepicamphor (anti)}] \\
 &= \frac{1}{2}(275.3 - 278.5^\circ) = -1.6^\circ. \\
 \delta\text{-Dioxime} &= \frac{1}{2}[\text{isoNitrosocamphor (syn)} + \text{isonitrosoepicamphor (anti)}] \\
 &= \frac{1}{2}(288.0 - 278.5^\circ) = 4.7^\circ.
 \end{aligned}$$

This is in qualitative agreement with the facts so far as (1) the  $\alpha$ - and  $\beta$ -dioximes are both levorotatory, (2) the  $\alpha$ -dioxime has a higher rotatory power than the  $\beta$ -modification, (3) the  $\gamma$ -dioxime has the lowest rotatory power of all, and (4) the  $\delta$ -dioxime is dextro-rotatory. The above calculation is based on the values in alkali because the  $\beta$ -dioxime is so very sparingly soluble in organic media.

Without going into unnecessary details it may be stated that alternative relationships between the eight oximino-derivatives of camphorquinone have been considered, but these have been found, at some cardinal point or other, to be in direct conflict with experimental observation.

## EXPERIMENTAL.

*Separation of isoNitrosocamphor (m. p. 152°) from the Claisen Mixture.*

One hundred grams of the mixture were dissolved in 300 c.c. of ether and treated with the ferric chloride dissolved from 90 grams by 500 c.c. of ether; an intense, brownish-red coloration was immediately developed, and after an interval of twelve hours the solvent was allowed to evaporate in a current of air. On filtering the treacly residue there remained a crystalline paste, which was drained on porous earthenware, suspended in water, washed on the filter, and dissolved in 5 per cent. sodium hydroxide; a small quantity of ferric hydrate having been filtered, dilute sulphuric acid precipitated the *isonitroso*-derivative in crystals instead of an oil. Recrystallisation from dilute methyl alcohol gave 50 grams of the stable modification quite free from the isomeride. The original mother liquor was a viscous, dark brown oil, yielding a crystalline product when shaken with water; it was hoped that this might consist of the unstable modification, but proceeding as above, an additional 30 grams of the stable isomeride was obtained. This portion was far from pure, but was suitable for the preparation of aminocamphor.

The action of ferric chloride in this process is somewhat obscure, as the amount of iron in the crystalline residue deposited from the ether is insufficient for a ferric derivative analogous to the metallic compounds obtained by Francesconi and Piazza (*Atti R. Accad. Lincei*, 1903, [v], 12, ii, 128) from the Claisen mixture and silver nitrate or mercurous nitrate. Nevertheless, it has the effect which solvents fail to accomplish.

*Action of Hydroxylamine on the Claisen Mixture.*

The facility with which the unstable modification of *isonitroso*-camphor is transformed into the isomeride made it desirable to study the action of hydroxylamine in cold solutions, so that the maximum of dioxime from the former might be isolated.

Fifty grams of the Claisen mixture dissolved in 250 c.c. of alcohol and treated with a solution containing 40 grams of hydroxylamine hydrochloride and 80 grams of crystallised sodium acetate in 260 c.c. of water formed a clear liquid, from which, after twelve weeks, 40 grams of pale brown crystals had separated. On extracting this material four times with 250 c.c. of boiling acetone, 5 grams of snow-white powder consisting of almost pure  $\beta$ -dioxime remained. Each of the two first extracts deposited

5 grams of pure  $\alpha$ -dioxime, the third yielding 2 grams of  $\alpha$ -dioxime mixed with a very small proportion of  $\beta$ -dioxime, 0.2 gram of the latter being the only deposit from the fourth. On evaporating the acetone mother liquors, the residue weighed 19 grams, almost completely soluble in 400 c.c. of boiling acetone, which deposited 4.3 grams of  $\alpha$ -dioxime on cooling, whilst the filtrate yielded 14 grams of brown residue when evaporated. On extracting this with cold benzene, 12.5 grams of colourless material remained, dissolving in 250 c.c. of boiling ethyl acetate, from which 4.4 grams of  $\alpha$ -dioxime separated; reducing the mother liquor to one-half its original bulk gave 2.2 grams of  $\alpha$ -dioxime mixed with a small proportion of  $\delta$ -dioxime, still further concentration yielding 5 grams of the latter substance. Meanwhile, the mother liquor from the original 40 grams was freed from alcohol on the water-bath, when the yellow, sticky mass, which separated was found to leave, on extraction with cold benzene, 7 grams of colourless dioxime, consisting principally of the  $\delta$ -modification. Under the conditions stated, therefore, 50 grams of the Claisen mixture furnished approximately 23 grams of  $\alpha$ -dioxime, 5 grams of  $\beta$ -dioxime, and 12 grams of  $\delta$ -dioxime.

Proceeding as above with the stable modification of *isonitrosocamphor*, and subjecting the product to systematic fractionation, the only dioximes isolated were the  $\beta$ - and  $\delta$ -isomerides, whence it follows that the  $\alpha$ -dioxime, which formed the major product from the Claisen mixture, must arise from the unstable *isonitrosocamphor* present in that material.

The action of hydroxylamine in alkaline solution was then studied, 100 grams of hydroxylamine hydrochloride dissolved in water being added to an alkaline solution containing 100 grams of the Claisen mixture and 90 grams of sodium hydroxide, the total volume of water being 1000 c.c. After three weeks the liquid was extracted with ether, and fractionally acidified with dilute sulphuric acid, which precipitated a red, tarry material first, followed by a honey-like gum; as soon as the aqueous liquid failed to develop colour with ferrous sulphate, it was decanted from the precipitate, yielding 24 grams of snow-white  $\gamma$ -dioxime with more acid. The gummy precipitate left 6 grams of  $\gamma$ -dioxime when extracted with cold benzene to remove unaltered *isonitrosocamphor*, whilst the tarry material gave 6 grams of  $\delta$ -dioxime as a result of the same treatment. It having been shown already that under these conditions the stable *isonitrosocamphor* does not yield the  $\gamma$ -dioxime, it follows that this substance arises from the unstable modification.

The  $\gamma$ -dioxime was recrystallised from methyl alcohol diluted

with a small proportion of water, separating in snow-white needles melting at  $136^{\circ}$ . One per cent. solutions in chloroform, alcohol, and 2 per cent. aqueous sodium hydroxide gave  $[\alpha]_D$   $16.4^{\circ}$ ,  $22.7^{\circ}$ , and  $14.3^{\circ}$  respectively.

The  $\delta$ -dioxime has been obtained in condition somewhat purer than that previously described by dissolving 25 grams of the  $\gamma$ -dioxime in 50 c.c. of cold absolute alcohol and heating the solution under reflux during eight hours, when 13 grams of the  $\delta$ -dioxime crystallised on cooling, whilst the mother liquor furnished 8 grams on concentration. Recrystallisation from methyl alcohol diluted with a small proportion of water yielded a specimen melting at  $194^{\circ}$ , giving  $[\alpha]_D$   $52.8^{\circ}$ ,  $80.0^{\circ}$ , and  $87.0^{\circ}$  in chloroform, alcohol, and 2 per cent. sodium hydroxide respectively.

*Action of Hydroxylamine on the isoNitroso-derivatives of Epicamphor.*

It has been shown (T., 1912, 101, 1353) that with hydroxylamine acetate,  $\alpha$ -isonitrosoepicamphor (m. p.  $170^{\circ}$ ) yields the  $\alpha$ - and  $\beta$ -dioximes, whilst the  $\delta$ -dioxime is the sole product from the  $\beta$ -modification (m. p.  $137^{\circ}$ ).

$\alpha$ -isoNitrosoepicamphor (3 grams) dissolved in sodium hydroxide (3 grams) was treated with hydroxylamine hydrochloride (3 grams), the bright yellow solution being diluted to 30 c.c. Within a few minutes the colour had perceptibly faded, and during three days, massive, transparent crystals separated, becoming opaque when rubbed with water; this was the sodium derivative of the  $\beta$ -dioxime, yielding nearly 2 grams of that material. The filtrate on acidification gave 0.75 gram of  $\beta$ -dioxime mixed with a small proportion of the  $\alpha$ -modification.

When  $\beta$ -isonitrosoepicamphor was treated in the same way, the colour faded rapidly, but crystals did not separate. Fractional precipitation with dilute sulphuric acid gave (1) 1.5 gram of  $\gamma$ -dioxime mixed with  $\delta$ -dioxime in the proportion of 2:1, and (2) 1.5 grams of almost pure  $\gamma$ -dioxime; thus the principal product is the  $\gamma$ -dioxime, with about 15 per cent. of the  $\delta$ -modification.

*Action of Magnesium Methyl Iodide on isoNitrosoepicamphor.*

An ethereal solution of  $\beta$ -isonitrosoepicamphor (3 grams) was added slowly to the well-cooled Grignard agent from 1.2 gram of magnesium and 7.5 grams of methyl iodide, the product after twelve hours being decomposed with ice and acetic acid. The ethereal liquid having been extracted four times with 10 c.c. of 5 per cent. sodium hydroxide solution to remove unchanged iso-

nitrosoepicamphor, a crystalline residue was left on evaporation; after being recrystallised three times from dilute alcohol, the colourless needles melted at  $96^{\circ}$ :

0.1365 gave 0.3227  $\text{CO}_2$  and 0.1191  $\text{H}_2\text{O}$ .  $\text{C}=64.48$ ;  $\text{H}=9.76$ .

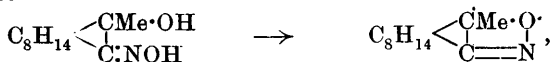
0.1631 „ 10.0 c.c.  $\text{N}_2$  at  $22^{\circ}$  and 758 mm.  $\text{N}=6.96$ .

0.2836 lost 0.0128 at  $100^{\circ}$ .  $\text{H}_2\text{O}=4.51$ .

$\text{C}_{11}\text{H}_{19}\text{O}_2\text{N}$  requires  $\text{C}=66.95$ ;  $\text{H}=9.71$ ;  $\text{N}=7.11$  per cent.

$\text{C}_{11}\text{H}_{19}\text{O}_2\text{N}, \frac{1}{2}\text{H}_2\text{O}$  requires  $\text{C}=64.02$ ;  $\text{H}=9.78$ ;  $\text{N}=6.80$ ;  
 $\text{H}_2\text{O}=4.37$  per cent.

The substance is readily soluble in organic media, including hot petroleum, but is insoluble in water. It is amphoteric, and whilst the alkaline solution remains clear when boiled, the acid solution rapidly becomes turbid when heated, doubtless owing to the transformation:



just as in the case of the  $\beta$ - and  $\gamma$ -modifications of the corresponding derivative from isonitrosocamphor (T., 1905, 87, 232).

When  $\alpha$ -isonitrosoepicamphor was treated in the same way the ethereal liquid yielded with sodium carbonate  $\beta$ -camphornitrilic acid, which was not produced from the isomeride; after unchanged material had been removed with sodium hydroxide the solvent deposited a viscous oil, which did not crystallise during many weeks in the desiccator. Analysis indicated a mixture of the expected oxime with its anhydride, and this fact, in conjunction with the production of  $\beta$ -camphornitrilic acid, may be taken as suggesting the *syn*-configuration for  $\alpha$ -isonitrosoepicamphor.

I desire to express my indebtedness to Dr. H. Spinner for his valuable assistance in connexion with the two modifications of isonitrosoepicamphor.

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