CONSTITUTION OF MANASSE'S HYDROXYCAMPHOR.[1]

By M. O. Forster and P. P. Shukla.

At various times the name hydroxycamphor, or *oxycampher* in German, has been applied to numerous compounds having the empirical formula, $C_{10}H_{16}O_2$. Beilstein classifies campholenic acid under that heading, and an early paper by R. Schiff[2] mentions without reference one substance prepared by Wheeler melting at 137°, and another by Schmiedeberg and Meyer with the alternative name camphol. Schiff's own contribution to the series was produced in association with much camphoric acid by the action of nitrous acid on α-aminocamphor, and melted at 154–155°, whilst Kachler and Spitzer[3] oxidised the hydrocarbon, $C_{10}H_{16}$ from camphor dichloride with chromic acid, and obtained a small quantity of a substance melting at 59–61°. Schrötter[4] oxidised bornyl acetate with chromic acid and obtained an acetyl derivative, $C_{12}H_{18}O_3$ hydrolysable to a hydroxycamphor which melted at 248–249°.

No further additions were made to the group until Manasse[5] reduced camphorquinone with zinc dust and acetic acid, and subsequently[6] claimed to recognise two isomeric substances, indistinguishable in appearance and optical activity; the 'α' modification melted at 203–205° with $[\alpha]_D$ 12·8°, whilst the 'β' modification, produced by hydrolysing the solid methyl ether, melted at 212–213° with $[\alpha]_D$ 12·3°.

It is unfortunate that Manasse denominated his materials in this perplexing manner, because it was already known that replacement of hydrogen in the camphor molecule might occur elsewhere than at the α-position; $\alpha\beta$-dibromocamphor, originally called β-dibromocamphor, was first prepared in 1866 by Swarts and reinvestigated many times after 1881, whilst β-bromocamphor was isolated in 1901. Hence, at the time of publishing his experiments, Manasse might well have been aware that a substance called β-hydroxycamphor should correspond in orientation with β-bromocamphor; confusion

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[1] Excepting the opening paragraphs, this paper was published under the title 'Studies in the Camphane Series. Part XL. Constitution of Manasse's Hydroxycamphor,' in the *Journal of the Chemical Society*, 1925, **127**, 1855.

[2] *Ber.*, 1880, **13**, 1404.

[3] *Annalen*, 1880, **200**, 358.

[4] *Montash.*, 1881, **2**, 224.

[5] *Ber.*, 1897, **30**, 659.

[6] *Ber.*, 1902, **35**, 3811.

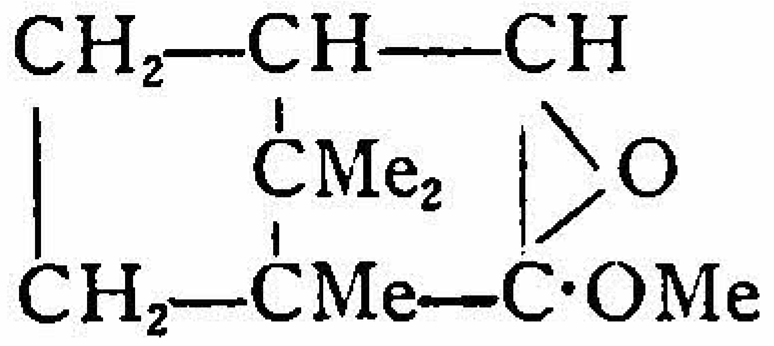
with true β-hydroxycamphor, obtained by Forster and Howard[1] on hydrolysing with oxalic acid the semicarbazone, $C_{11}H_{19}O_2N_3$ produced from β-aminocamphor and semicarbazide, might thus have been avoided.

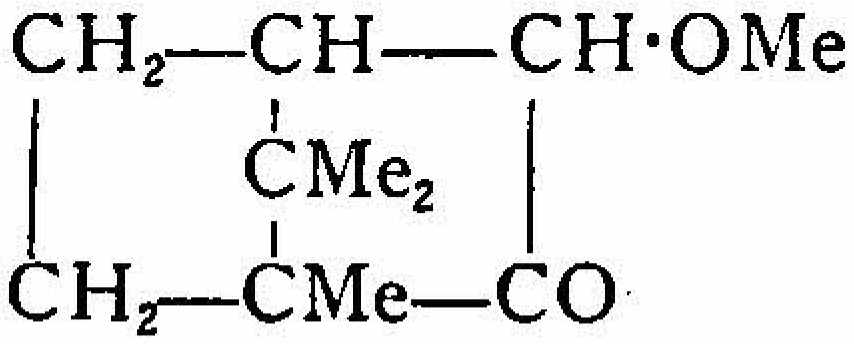
Finally, Bredt and Goeb[2] re-examined Schrötter's acetoxycamphor and found that his hydroxycamphor is oxidisable to a *para*diketocamphane which, being optically active, must have the definite constitution implied by that name. They were further led to regard Schrötter's hydroxycamphor as a mixture of the *exo* and *endo*forms, of which the former, corresponding to borneol, melts at 237·5–238°.

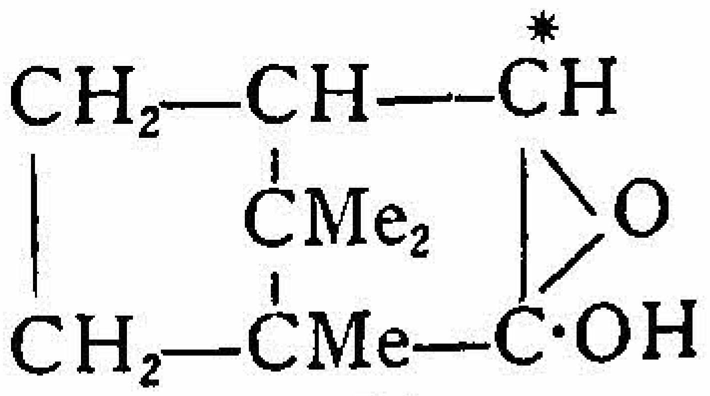
Thus, among all these forms of hydroxycamphor, the only compounds which appear to arise by replacement of an α-hydrogen atom in the camphor molecule are those of Schiff and of Manasse, and our object has been to explain the isomerism of the two modifications which the latter investigator claimed to recognise.

Manasse supported his belief in the existence of two distinct modifications by the production of two oximes, m.p. 86–87° (α) and 83–84° (β), two phenylhydrazones, m.p. 137·5° (α) and 111–113° (β), two semicarbazones, m.p. 182–183° (α) and 202–204° (β) and two benzenesulphonyl derivatives, m.p. 95–96° (α) and 111–113° (β). Excepting the last-named, however, these pairs might have arisen from a single hydroxycamphor, and in view of the slender distinction between the two parents, one of us (M. O. F.) with Dr. A. Zimmerli began in 1911 an inquiry which was interrupted and could not be resumed until eighteen months ago.

Simultaneous light and shadow have now been cast on the subject by Karrer and Takashima,[3] who suggest that the solid methyl ether is the *cyclo*acetal (I) and not the true α-methoxycamphor formulated by Manasse (II):


(I.)


(II.)


(III.) *

Thereupon they propose for Manasse's α-and β-hydroxycamphors the representation (III), ascribing to configuration-change in one of the asterisked carbon atoms the respective divergence in properties.

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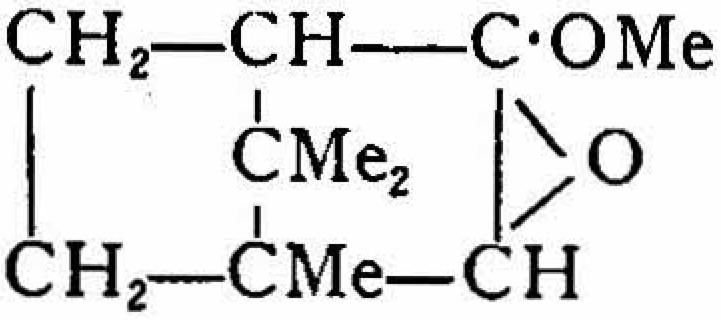
[1] *J. Chem. Soc.*, 1913, **103**, 63.

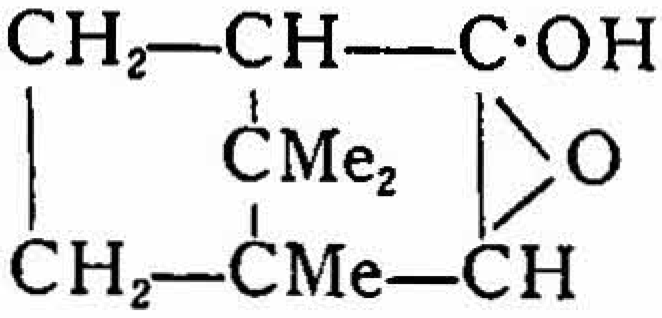
[2] *J. pr. Chem.*, 1920 [ii], **101**, 273.

[3] *Helv. Chim. Acta*, 1925, **8**, 242.

Our experiments amply confirm the above suggestion that the solid methyl ether is a *cyclo*acetal, but we cannot support the complete constitutional formula given by Karrer and Takashima. We prefer the alternative representation (IV) with the consequence that Manasse's 'β'-hydroxycamphor is the individual (V), whilst his 'α'-hydroxycamphor is probably that substance associated with a variable amount of the stereoisomeride in which the hydroxyl group and hydrogen atom both occupy the alternate plane.

(IV.)

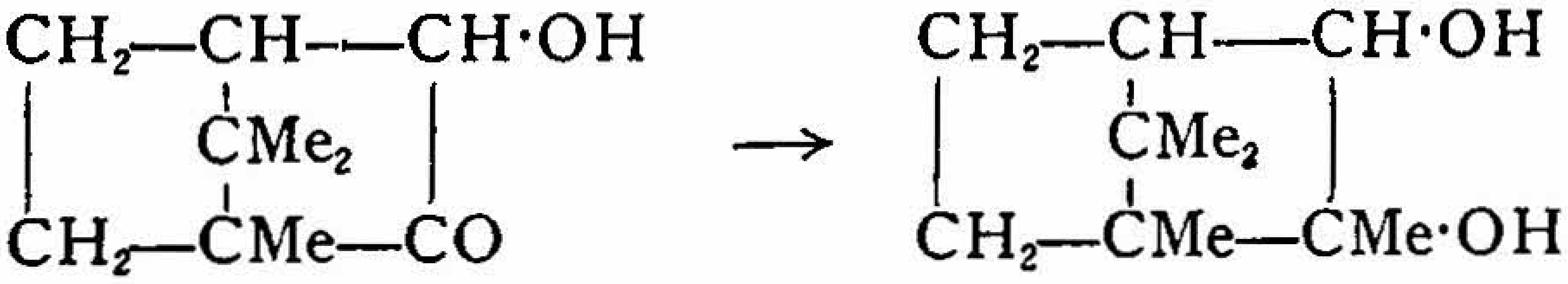




(V.)

With Karrer and Takashima, we agree that the solid methyl ether does not reveal a carbonyl group; we failed to produce an oxime and recovered the substance unchanged by treatment with magnesium methyl iodide. Moreover, on treating separately (1) the crude product of reducing camphorquinone, (2) 'α'-hydroxycamphor, and (3) 'β'-hydroxycamphor with excess of the Grignard agent, the quantitative amount of methane required by one hydroxyl group was liberated in each case, and the original product was recovered unchanged. If Manasse's hydroxycamphor had the conventional constitution (VI), it could scarcely escape at least partial conversion into the secondary-tertiary diol (VII), in view of the readiness with which camphorquinone is transformed into the dimethyldiol by magnesium methyl iodide.[1]

(VI.)



(VII.)

Our reason for questioning the transference of the hydroxyl group from the true α-position (in V) to the adjacent carbon atom (in III), as represented by Karrer and Takashima, is the one familiar to all chemists who have closely studied the members of this family, namely, the greatly superior activity of the α-carbon atom to that of its ketonic neighbour. The comparative behaviour of camphor and of camphorquinone towards aniline, phenylhydrazine, hydroxylamine, semicarbazide, nitromethane, ethyl cyanoacetate, and phenylacetonitrile may be recalled in this connexion: and finding that Manasse's hydroxycamphor is readily formed by reducing a cold ethereal solution of camphorquinone with aluminium amalgam, we

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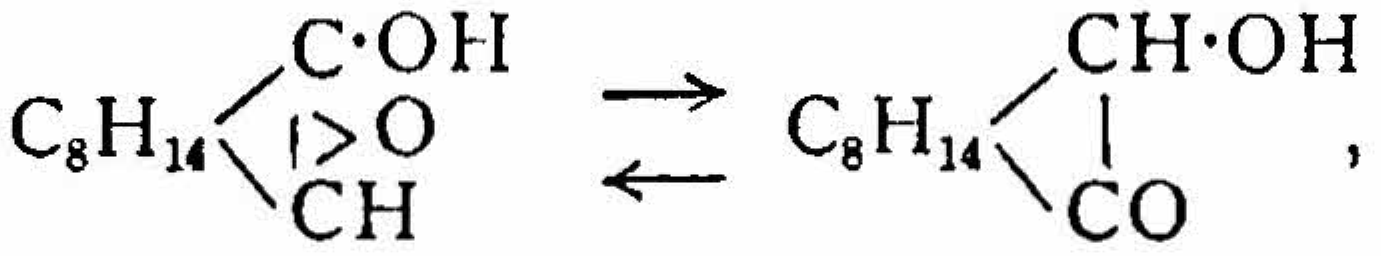
[1] Forster, *J. Chem. Soc.*, 1905, 87, 241.

cannot believe that in this reaction alone the diketone has belied itself.

Aside from the question of orientation, however, the above diagnosis by Karrer and Takashima has, in our judgment, clarified a situation which has been hitherto most obscure, and harmonises with the occurrence of Manasse's oximes, phenylhydrazones and semicarbazones, these doubtless arising from cleavage of the ethylene oxide-ring. The two benzenesulphonyl derivatives, to which we have added two hydrogen phthalic esters, are reasonably attributable to the stereoisomeric forms represented by formula V, because, although tertiary alcohols do not generally incur the formation of hydrogen phthalic esters, even limited occurrence of the equilibrium,



$$C_8H_{14}\left<\begin{matrix}C\cdot OH\\ |>O\\ CH\end{matrix}\right. \rightleftarrows C_8H_{14}\left<\begin{matrix}CH\cdot OH\\ |\\ CO\end{matrix}\right. ,$$

would account for the result observed. Moreover, the irregular course of ester-hydrolysis revealed by the polarimeter indicates the operation of concurrent mutarotation in the hydroxycamphor regenerated.

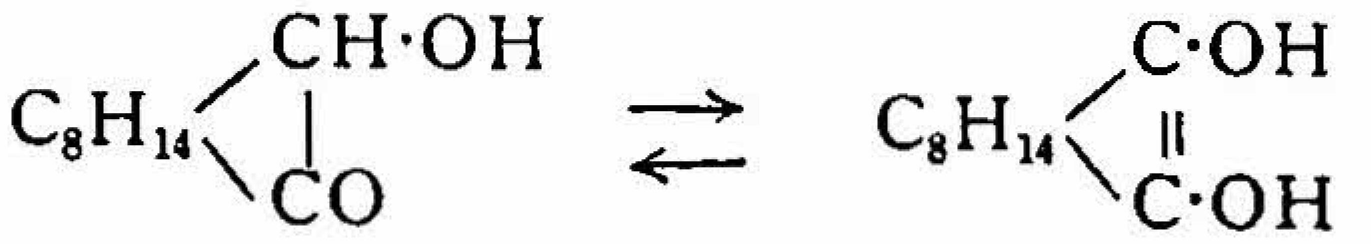
EXPERIMENTAL.

Reduction of Camphorquinone.—(*a*) *Zinc and acetic acid.* Camphorquinone (40 g.) dissolved in hot glacial acetic acid (70 c.c.) was precipitated by hot water (500 c.c.), and zinc dust (40 g.) added in small quantities to the continuously shaken suspension. The clear, pale green liquid was heated to coagulate undissolved zinc, the filtrate from which was saturated with salt and allowed to cool. Hydroxycamphor was filtered; after treating the filtrate with just sufficient sodium hydroxide (20%) to redissolve the zinc hydroxide, more was extracted by ether (three times), in which the filtered portion was then dissolved. Dried with calcium chloride, the ether was distilled and left a very pale yellow, camphoraceous residue (32·5 g.) (yield 80%).

(*b*) *Aluminium amalgam.* Camphorquinone dissolved in undried ether was left in contact with freshly amalgamated aluminium during 12 hours. The colour faded to very pale green, and the decanted liquid with ether-washings having been dried and distilled, deposited a colourless residue (yield 85%).

After crystallisation from petroleum the material prepared by each of the above methods melts at 203–205°; the less readily fusible product described by Manasse has been obtained only by hydrolysing the solid methyl ether. This compound crystallises in colourless plates from a solution of the initial product in methyl alcohol containing hydrogen chloride (6%); it melts at 149—150° (Found: MeO, 15·9. Calc., MeO, 17·0%) and has $[\alpha]_D$ 182·8° (1% in chloroform). The methyl ether is not affected by boiling alcoholic potassium hydroxide (10%), but is rapidly hydrolysed by cold hydrochloric acid, from which sodium carbonate precipitates the less readily fusible form of hydroxycamphor; this melts at 215°, and in all other respects is indistinguishable from the material arising directly on reduction of camphorquinone.

The Hydroxyl Value of Hydroxycamphor.—At one time it seemed possible that the peculiar behaviour of hydroxycamphor might be due to its representing the equilibrium mixture,



$$C_8H_{14}\left\langle\begin{matrix}CH\cdot OH\\ |\\ CO\end{matrix}\right. \rightleftarrows C_8H_{14}\left\langle\begin{matrix}C\cdot OH\\ \|\\ C\cdot OH\end{matrix}\right. ;$$

but this is now precluded by several indications. In the first place, hydroxycamphor in chloroform does not decolorise bromine, and in ether does not develop a coloration with ferric chloride; moreover, the aqueous solution does not give a precipitate with copper acetate, and the methyl ether is equally indifferent to all these agents. When the action of bromine is pressed by heating hydroxycamphor with the halogen in acetic acid which has dissolved sodium acetate, a very slow action occurs; but this leads to camphoric anhydride without any indication of addition or substitution. The same treatment converts the solid methyl ether also into camphoric anhydride, and in both cases a considerable proportion of unchanged hydroxycamphor is recovered, having survived this attack during several hours.

Conclusive evidence against the above possibility, however, was given by the behaviour of hydroxycamphor towards magnesium methyl iodide, from which the quantitative amount of methane for one hydroxyl group was liberated equally by the crude product of reducing camphorquinone and by specimens of hydroxycamphor melting at 203–205° and at 215°, whilst the methyl ether also remains unaltered by the Grignard agent without liberating methane. These experiments were conducted in phenetole, and appeared remarkable in view of the observations by Bredt-Savelsberg and others[1] relating to enolisation of camphor by the Grignard agent,

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[1] *J. pr. Chem.*, 1924, 107, 65.

which may exceed 40% ; but they now receive their explanation in the *cyclo*acetal representation of Karrer and Takashima.[1]

The Camphoryl Hydrogen Phthalates.—A mixture of phthalic anhydride and hydroxycamphor (m. p. 215°) in equal weights, and therefore containing a slight molar excess of the anhydride, was heated at 110–120° during 8 hours and kneaded in a solution of sodium carbonate. On extracting the filtered liquid with ether, about 15% of the hydroxycamphor was recovered unchanged whilst the hydrogen phthalate was precipitated along with phthalic acid by neutralising the solution of sodium salts ; it was separated by dissolution in chloroform, which deposited crystals on evaporation. Recrystallisation from benzene-petroleum gave *camphoryl hydrogen phthalate* in rectangular plates, m. p. 164–165° (Found : C, 68·2 ; H, 6·6. $C_{18}H_{20}O_5$ requires C,68·3 ; H, 6·3%). The $[\alpha]_D$ in aqueous alcohol (1 : 1) was 53·7°.

On repeating this operation with hydroxycamphor melting at 203–205°, or with a specimen recovered unchanged by the methylation process, the proportion of unconverted hydroxycamphor was about the same, and the first crop of crystals melted at 152–156° ; this was ultimately resolved into a mixture of the foregoing substance with an isomeric *camphoryl hydrogen phthalate* crystallising in slender needles, m. p. 147° (Found : C, 68·1 ; H, 6·4%). The $[\alpha]_D$ in aqueous alcohol (1 : 1) was 42·2°.

Thus there appear to be two definite hydrogen phthalates, but it has not been possible to decide whether hydrolysis leads to the respective parents. In fact, on following the hydrolysis polarimetrically, there is an indication of the result being an equilibrium system.

A clear solution prepared by mixing equal volumes of alcohol (97·5%) and aqueous potassium hydroxide (20%) was used. When dissolved in this, the higher-melting hydrogen phthalate passed from the initial $[M]_D$ 102·7° to 61·6° during 200 hours, while the isomeride changed from $[M]_D$ 55·0° to 64·4°. Intermediate stages were various, however, the higher-melting form having sunk to $[M]_D$ 60·3° when the isomeride was at 98·6° (after 50 hours), and rising again to $[M]_D$ 73·0° when the isomeride had fallen to 78·3° (after 145 hours). These changes are probably due to varying rates of hydrolysis overlapping unequal mutarotation of the resulting hydroxycamphor, because, in the same alcoholic alkali, higher-melting hydroxycamphor with initial $[M]_D$ 34·2° reaches a maximum of 82·6° in 26 hours and

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[1] *Loc. cit.*

begins to fall after 48 hours, whilst the lower-melting form has initial $[M]_D$ 50·9°, reaches its maximum of 69·0° at about the same time as the other, and then remains constant. The later observations are only approximate because the liquids, although initially colorless, develop a brown tint which increases in depth with passage of time: moreover, the hydroxycamphor recovered from such solutions melts lower and more indefinitely than the original materials.

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