CCLXIX.—*Piperitone. Part IX. Some Oxidation Reactions of Piperitone.*

By JOHN READ, ANDREW JAMES WATTERS, GEORGE JAMES ROBERTSON, and REGINALD SLATER HUGHESDON.

THE disruptive oxidation of piperitone, leading to α-*iso*propylglutaric acid and various intermediate products, has been studied in some detail (compare J., 1924, **125**, 129); but only scanty information is available concerning milder oxidative processes which leave the ring intact. Among the most noteworthy observations of the latter type, Smith and Penfold (*J. Proc. Roy. Soc. N.S. Wales*, 1920, **54**, 40) described the oxidation of the ketone to thymol, by means of ferric chloride in glacial acetic acid, and Roberts (J., 1915, **107**, 1467) was able to establish the production from it of diosphenol as a minor product of oxidation with neutral permanganate. Further, in 1923, a preliminary note was published by one of us (*Sydney University Science J.*, **7**, 25) pointing out that thymol is produced in appreciable quantities during the catalytic hydrogenation of piperitone by methods which were described at that time (J., 1923, **123**, 2916). A brief description is given below of a few experiments selected as typical of a prolonged series of investigations which we have since carried out in this field.

In reviewing the main results of this work, it may be stated that thymol appears to be produced invariably during the catalytic hydrogenation of piperitone in presence of palladium, platinum, or nickel, the yield depending upon the conditions of the particular experiment. The results of most interest were obtained with the first of these catalysts. When the hydrogenation was accomplished at or near the ordinary temperature in the presence of colloidal palladium, according to Skita's method (*ibid.*, p. 2920), the first fraction of the product (b. p. 90—95°/16 mm.) consisted essentially of *iso*menthone. A second fraction (b. p. 95—116°/16 mm.), containing thymol, formed from about 10 to 65% of the product in different experiments; by extraction with alkali, this fraction furnished some 20—40% of its weight of crystalline thymol. Thus, under the conditions in question, piperitone gave yields of thymol of some 3—25%, the remaining material being chiefly *iso*menthone. In agreement with these observations, although the volume of hydrogen absorbed was always less than one molecular proportion, no unchanged piperitone could be detected in the product. As a test for menthol, the combined second fractions from several experiments were treated with chromic acid, but the density rose slightly in consequence, instead of declining.

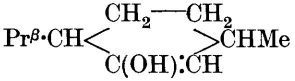
The formation of thymol from piperitone by Skita's process is conditioned partly by undetermined factors, but dehydrogenation appears to be favoured *inter alia* by the presence of impurities in the piperitone and also by rise of temperature. Thus, a specimen of the ketone which had not been distilled after extraction by the sulphite process absorbed only 54% of the calculated volume of hydrogen when hydrogenated under an excess pressure of 0·5 atm. at 40°, about 23% being in this instance converted into thymol. Under similar conditions at 20—25°, the yield of thymol declined to 15%. Moreover, *l*-piperitone, obtained by directly distilling the oil of *Eucalyptus dives*, without the intervention of sodium sulphite, absorbed practically the calculated volume of hydrogen at 35°, and the product contained only about 2% of thymol. A specimen of *d*-piperitone, isolated from the oil of *Andropogon Jwarancusa* in a similar way, gave still less thymol when hydrogenated at 18°. Of the other catalysts examined, palladised asbestos produced little effect on a mixture of vaporised piperitone and hydrogen at 350°; whereas a marked dehydrogenation to thymol was brought about under similar conditions by platinised asbestos. At 180°, the action of nickel in presence of hydrogen was mainly additive, only about 1% of thymol being formed after 5 hours' circulation; at about 360°, however, yields of thymol up to about 20% were obtained. According to a recent publication by Treibs and Schmidt (*Ber.*, 1927, **60**, 2335), a single distillation of piperitone over a nickel catalyst at 280° yielded a product containing 45% of thymol and 32% of menthone, and similar results attended the use of the same catalyst at 200° and of a copper catalyst at 280°. These yields of thymol are appreciably higher than any we have observed; but most experiments of the kind under consideration are complicated by deterioration of the catalyst.

It is thus clear that the hydrogenation of piperitone is a reversible process, and that an optimum temperature exists for any specific set of conditions; above this temperature dehydrogenation is accelerated, in conformity with the general principle of Sabatier and Senderens. As regards the mechanism of the process, Treibs and Schmidt (*loc. cit.*) state that piperitone may be dehydrogenated more easily than menthone, and that partial conversion to thymol occurs when it is merely heated to boiling (233°) in the presence of the catalyst. Under the conditions prevailing in our experiments, however, we consider the hydrogenation of piperitone to be an essential preliminary to its dehydrogenation. No trace of thymol could be detected in a specimen of piperitone which had been stirred continuously for 6 hours with Skita's solution, in a current of nitrogen; hence, colloidal palladium appears to be incapable of dehydrogenating piperitone in the absence of hydrogen. Similarly, a nickel catalyst described below was able to effect a partial dehydrogenation at a high temperature in the presence of hydrogen, but not in an atmosphere of nitrogen.

Even if direct dehydrogenation of piperitone may be excluded under certain conditions, the position is complicated by the undoubted existence of mobile keto-enol equilibria, so that the main possibilities may be summarised in the following form (compare Read and Robertson, J., 1926, 2210) :

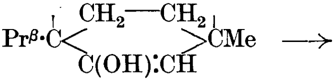
$$\begin{tikzcd}
\text{Piperitone (keto-)} \arrow[r, "(+2H)"] \arrow[d, shift right] \arrow[dr] & \text{\textit{iso}Menthone (keto-)} \arrow[d, shift right] \arrow[dr, "(-4H)"] & \\
\text{Piperitone (enol-)} \arrow[r] \arrow[u, shift right] & \text{Menthone (enol-)} \arrow[r] \arrow[u, shift right] \arrow[d, shift right] & \text{Thymol} \\
& \text{Menthone (keto-)} \arrow[u, shift right] \arrow[ur] &
\end{tikzcd}$$

Of the various tautomeric forms of menthone, Δ^2-enol-menthone (I) appears to offer particular promise as a precursor of thymol, since the hydrogen atoms at positions (1) and (4) are each subjected to the conjoined activation of an ethylene linking and an alkyl group; passage to the unstable form (II), conditioned by the loss of these two hydrogen atoms, may perhaps be regarded as a preliminary to the complete stabilisation of the molecule by a further loss of two hydrogen atoms from positions (5) and (6), with a consequent passage to thymol (III). It is evident from a consideration of activating influences that enol-piperitone (IV) presents a molecular equilibrium of a higher order of stability than that of Δ^2-enol-menthone (I).



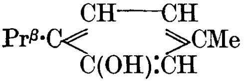
$\mathrm{Pr^{\beta}\cdot CH}\langle{}^{\mathrm{CH_2-CH_2}}_{\mathrm{C(OH):CH}}\rangle\mathrm{CHMe} \longrightarrow$

(I.)



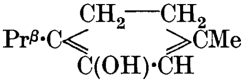
$\mathrm{Pr^{\beta}\cdot C}\langle{}^{\mathrm{CH_2-CH_2}}_{\mathrm{C(OH):CH}}\rangle\mathrm{CMe} \longrightarrow$

(II.)



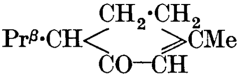
$\mathrm{Pr^{\beta}\cdot C}\langle\!\langle{}^{\mathrm{CH-CH}}_{\mathrm{C(OH):CH}}\rangle\!\rangle\mathrm{CMe}$

(III.)



$\mathrm{Pr^{\beta}\cdot C}\langle\!\langle{}^{\mathrm{CH_2-CH_2}}_{\mathrm{C(OH)\cdot CH}}\rangle\!\rangle\mathrm{CMe}$

(IV.)



$\mathrm{Pr^{\beta}\cdot CH}\langle{}^{\mathrm{CH_2\cdot CH_2}}_{\mathrm{CO-CH}}\rangle\!\rangle\mathrm{CMe}$

(V.)

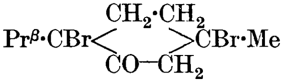
It is interesting to note that the hydrogenation of either enol-piperitone (IV) or keto-piperitone (V), proceeding in strict accordance with Thiele's theory, would lead directly to Δ^2-enol-menthone (I). This product may be pictured as remaining enolic for a longer or shorter period, depending upon conditions, and possibly only those molecules which undergo dehydrogenation before tautomerisation are capable of giving rise to thymol, the remainder appearing as stable ketonic menthone or *iso*menthone. According to this view, which is reserved for further experimental inquiry, enolising influences operating during the course of the hydrogenation should favour the formation of thymol.

In certain respects piperitone is remarkably stable towards oxidising influences; thus, it was practically unaffected when vaporised and passed over a nickel oxide catalyst at 360° in admixture with air. Further, it is stable towards alkaline potassium ferricyanide and other mild oxidants.

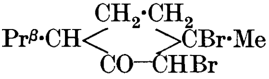
Piperitone appears not to form stable additive compounds with the halogens (compare Wallach, *Annalen*, 1918, **414**, 271; Read and Smith, J., 1921, **119**, 779). Although a molecular proportion of bromine is absorbed slowly by the ketone in various organic solvents, spontaneous evolution of hydrogen bromide accompanies the process. The decomposition is accelerated by heat, and the resulting thymol is formed in company with relatively large quantities of bromomenthenone and tarry material. With the aim of controlling the conversion of the dibromide into thymol, numerous experiments have been carried out in which the product obtained by brominating the ketone in the presence of various liquids (ether, toluene, methyl and ethyl alcohols, water) was decomposed by heating it alone or with certain organic and inorganic bases (quinoline, piperidine, aniline, ammonia, sodium methoxide, potassium hydroxide, potassium carbonate, soda–lime, calcium carbonate). The highest yield of crystalline thymol recorded in these experiments, of which a few are outlined below, was 35%; this was achieved when the decomposition was allowed to proceed under the influence of heat, without the interposition of a base.

A reason for the poor yields of thymol furnished by such processes may perhaps be sought along the following lines. 1 : 4-Dibromomenthone (VI), obtained by brominating menthone, yields thymol (III) readily when heated with quinoline (*Ber.*, 1896, **29**, 418), presumably owing to the proximity of the bromine atoms to the two methylene groups (5) and (6). In the case of piperitone dibromide (VII), however, no such smooth mechanism is apparent, since the elimination of the second molecule of hydrogen bromide from the intermediate bromomenthenone (VIII) demands a rearrangement of the molecule. The low yields of thymol from piperitone dibromide, and the presence of bromomenthenone in the product, may apparently be ascribed in part to this circumstance.

(VI.)



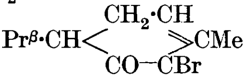
$$\mathrm{Pr^{\beta}\cdot CBr}<\begin{matrix}\mathrm{CH_2\cdot CH_2}\\ \mathrm{CO{-}CH_2}\end{matrix}>\mathrm{CBr\cdot Me}$$



$$\mathrm{Pr^{\beta}\cdot CH}<\begin{matrix}\mathrm{CH_2\cdot CH_2}\\ \mathrm{CO{-}CHBr}\end{matrix}>\mathrm{CBr\cdot Me}$$

(VII.)

(VIII.)



$$\mathrm{Pr^{\beta}\cdot CH}<\begin{matrix}\mathrm{CH_2\cdot CH}\\ \mathrm{CO{-}CBr}\end{matrix}\gg\mathrm{CMe}$$

Chlorine, when passed into ice-cold piperitone, was absorbed with the formation of a product which liberated hydrogen chloride spontaneously. Chlorinated piperitone was found to behave very similarly to the brominated ketone, but the yields of thymol were somewhat lower. The highest yield, amounting to 25%, was obtained by chlorinating piperitone without a solvent and distilling the product directly. The results were not modified essentially by conducting the chlorination in the presence of solid calcium carbonate or potassium carbonate. Iodine also reacted slowly with piperitone in alcoholic solution, and the product furnished a 10% yield of thymol when distilled.

When emulsified with ice-cold bromine water, piperitone reacted to form a mixture of dibromide and bromohydrin, 42% of the bromine functioning in the latter reaction. It was not possible to isolate a bromohydrin in this way, but crystalline dl-*piperitone chlorohydrin* (m. p. 101—102°) was readily produced by Detœuf's method (*Bull. Soc. chim.*, 1922, **31**, 102, 169, 176). The behaviour of this derivative towards oxidising and reducing agents was interesting: it was unaffected by chromic anhydride in glacial acetic acid, and was reconverted to piperitone by sodium amalgam or zinc dust. Although this new derivative might be expected to provide an easy route to diosphenol and other difficultly accessible compounds, the elimination reactions so far examined have led to mixed products. In this last respect a similarity is apparent between the chlorohydrin and the dihalogenides of piperitone, although the two types differ widely in general stability. Sodium methoxide, in reaction with the chlorohydrin, gave a methoxyl derivative in association with other chlorine-free products; and moist silver oxide furnished in small yield a compound which appeared to be an isomeride of diosphenol, this being possibly 2-hydroxy-Δ^6-menthen-3-one.

EXPERIMENTAL.

Catalytic Dehydrogenation.—In the first of the experiments described below, the piperitone was extracted from the essential oil of *E. dives* with sodium sulphite, without being subsequently distilled; in the remaining instances it was purified further, either by distillation under diminished pressure or by steam distillation. Electrolytic hydrogen was used throughout.

1. Piperitone (35 g.) when hydrogenated under an excess pressure of 0·25 atm. in the presence of colloidal palladium at 25° (J., 1923, **123**, 2921), yielded a product of which 60% distilled at 90—95°/16 mm. and consisted mainly of *iso*menthone. A second fraction, forming 27% of the crude product, distilled at 95—116°/16 mm. and smelt strongly of thymol. It underwent a contraction of 40% when extracted with dilute aqueous sodium hydroxide, and the oil obtained upon acidifying the extract crystallised when nucleated with pure

thymol, the yield of which in this instance was about 10% of the original piperitone.

2. Vaporised piperitone mixed with hydrogen was passed at 350° over a palladium catalyst prepared by heating 5% palladised asbestos in a current of hydrogen for a short time at 200° (Zelinski, *Ber.*, 1911, **44**, 3121; 1927, **60**, 1096). After one passage over the catalyst, the bulk of the product consisted of unchanged piperitone, but a small fraction with $n_D^{15^\circ}$ 1·4970 contained about 25% of thymol.

3. A platinum catalyst was prepared by heating 5% platinised asbestos in a current of hydrogen at 350° for 2·5 hours. Piperitone (10 c.c.) was vaporised and passed slowly over the catalyst in a current of hydrogen at 350°. The product obtained after a single passage had $n_D^{15^\circ}$ 1·4958, and contained about 22% of thymol. No marked effect was apparent on reducing the pressure to about 17 mm. during the process.

4. The apparatus designed for the last two experiments was used also in further work with nickel catalysts. It consisted of a U-tube of fused silica (length 26·5 cm., diameter 1·8 cm.), provided with a side-tube on each limb. The catalyst occupied the bottom region of the tube, and was covered on both sides with purified pumice grains or asbestos wool in which the bulbs of two controlling thermometers were immersed. The U-tube was mounted in an electrically heated oven, and a special device allowed the mixture of hydrogen, piperitone, and reaction products to be circulated repeatedly in the gaseous phase over the heated catalyst (*J. Soc. Chem. Ind.*, 1929, **48**, 263T).

The nickel catalyst was prepared in two ways. (i) Small pieces of purified pumice were soaked in an aqueous solution of pure nickel nitrate (25 g. in 25 c.c. of water), excess of sodium hydroxide was added, and the mixture was boiled for a minute. The impregnated pumice was then washed free from alkali and dried in a porcelain dish on the water-bath. (ii) The pumice (22 g.), after having been stirred into molten nickel nitrate (25 g.) in a nickel basin, was calcined at a dull-red heat.

Piperitone was practically unaffected when passed once, in admixture with nitrogen, at 290° or 350° over catalyst (i) which had been reduced in hydrogen at 360° for 2·5 hours. In a similar experiment, in which hydrogen was substituted for nitrogen at 355°, the product had $n_D^{13^\circ}$ 1·4915 after one passage over the catalyst and contained about 10% of thymol. A practically identical result attended the similar application of catalyst (ii), reduced at 360°. The yield of thymol was not increased appreciably by circulating the piperitone through the apparatus continuously for 5 hours. Slightly higher yields of thymol, ranging from 12% to

16%, were obtained by using preparations of catalyst (ii) which had been reduced at 290—300°, instead of at 360°. In an experiment mentioned by Hughesdon, Smith, and Read (J., 1923, **123**, 2924), continuous circulation for 5 hours at 180° of a mixture of liquid piperitone (145 g.) and hydrogen over catalyst (ii), reduced at 340—350°, resulted in the formation of less than 1% of thymol. It may be added that in all experiments of the above types conducted at high temperatures with piperitone which had been isolated from the oil of *E. dives* by fractional distillation only, the product displayed a deep indigo-blue colour (compare Treibs and Schmidt, *loc. cit.*).

Direct Oxidation.—1. Upon passing a slow stream of oxygen through *dl*-piperitone (25 c.c., $n_D^{18°}$ 1·4859), maintained at 200—210°, the value of $n_D^{18°}$ rose to 1·4912 and 1·4992 after 3·5 and 9 hours, respectively. A minute quantity of thymol was extracted from the product by means of aqueous alkali, and the change in refractive index appeared to be due mainly to slight polymerisation.

2. When piperitone vapour mixed with air was passed once over nickel oxide prepared according to method (ii) above, the ketone remained substantially unaltered at temperatures up to 360°. Upon passing a mixture of vaporised piperitone and oxygen once over 5% platinised asbestos at 340°, nearly 10% of the ketone was oxidised to thymol.

Bromination.—1. A cooled solution of piperitone in dry ether was gradually treated with bromine (1 mol.) in the same solvent. The heavy oil which remained after removal of the ether in a current of dry air at the ordinary temperature evolved hydrogen bromide slowly, and eventually yielded a viscid black liquid with an odour of thymol. The decomposition was hastened by heating the product on the water-bath, and a preparation which was treated in this way and then distilled in a vacuum gave a 30% yield of thymol. The yield was depressed by adding piperidine or aniline (2 mols.) before heating the brominated product, and no definite anilide or piperidide could be isolated. The yield of thymol was not improved by brominating piperitone in toluene and heating the product with aqueous potassium hydroxide. In such instances, the organic or inorganic base removed only a part of the bromine, and hydrogen bromide was liberated during the subsequent vacuum distillation. The thymol was accompanied by a heavy oil, insoluble in alkali. This contained bromine and behaved as a bromomenthenone. A considerable proportion of the piperitone was converted into a black tarry material, which remained in the distilling flask.

2. Bromination of piperitone (20 g.) in cold methyl alcohol, followed by heating with sodium methoxide (2 mols.) in the same

solvent, yielded a product (13·2 g.) which passed over slowly when steam-distilled. The first fraction (11 g.) was a clear yellow oil, which contained no bromine and behaved as an unsaturated substance; it possibly consisted partly of 2-methoxy-Δ^6-menthen-3-one (Found: C, 71·1; H, 8·9. Calc. for $C_{11}H_{18}O_2$: C, 72·5; H, 9·8%).

3. When piperitone (11 g.), emulsified with ice-water (250 c.c.), was shaken continuously during the gradual addition to it of bromine (11·6 g.) dissolved in an aqueous solution (150 c.c.) of potassium bromide (10 g.), decolorisation occurred slowly. Titration disclosed that 58·2% of the bromine had reacted to form dibromide, leaving 41·8% to function in producing bromohydrin and hydrogen bromide (compare J., 1928, 1487). A small quantity (2·6 g.) of crystalline thymol was obtained by heating the oily product under reflux with dilute aqueous potassium hydroxide.

In other experiments the formation of bromohydrin was reduced to a minimum by adding a 25% solution of bromine in aqueous potassium bromide to a non-emulsified mixture of equal weights of piperitone and cold water. Treatment of the product with aqueous potassium hydroxide, followed by distillation, afforded a 30% yield of thymol. The yield rose to 35% when the product was distilled directly, without the intervention of the alkali.

4. Bromine (1 mol.) was slowly absorbed when shaken with an aqueous solution of the bisulphite compound of piperitone. Hydrogen bromide was liberated upon evaporating the solution to small bulk on the water-bath, and when extracted with alkali the product gave a 35% yield of thymol.

Action of Hypochlorous Acid.—The addition of hypochlorous acid to piperitone was conveniently effected by the method of Detœuf (*loc. cit.*), a solution of piperitone in acetone containing glacial acetic acid being shaken for several hours with a slight excess of an aqueous solution of monochlorocarbamide. Most of the acetone was removed by distillation under diminished pressure, and the remaining liquid was extracted with ether. The resulting yellow oil crystallised partly when cooled in ice. After six recrystallisations from light petroleum, fine needles of dl-*piperitone chlorohydrin*, m. p. 101—102°, were obtained (Found: C, 58·6; H, 8·7; Cl, 17·1. $C_{10}H_{17}O_2Cl$ requires C, 58·7; H, 8·3; Cl, 17·3%). The substance has a faint mint-like odour, and is readily soluble in organic solvents. A yield of 9·1 g. was obtained from 20 g. of *dl*-piperitone, a lachrymatory oil being formed as a by-product. Piperitone with a high lævorotation gave only a minute quantity of a crystalline derivative, associated with much oil; a specimen of the ketone having $\alpha_D^{16^\circ}$ $-$ 24·3° gave an intermediate yield of crystalline chlorohydrin, having $[\alpha]_D$ + 5·2° (in acetone, c = 1·0). The liquid product appeared also to consist of chlorohydrin, but it decomposed when submitted to distillation under diminished pressure.

The chlorohydrin failed to give a crystalline derivative when treated with benzoyl chloride or *p*-nitrobenzoyl chloride in pyridine. It was unaffected when heated on the water-bath with a solution of chromic anhydride in glacial acetic acid. No definite product was obtained by heating it with aqueous or alcoholic potassium hydroxide or with quinoline. When reduced in 55% aqueous alcohol with sodium amalgam, it yielded piperitone. A certain amount of piperitone was also formed by reducing the chlorohydrin with zinc dust in the presence of methyl alcohol. Treatment with sodium methoxide in methyl alcohol removed the chlorine and yielded a colourless oil ($n_D^{25°}$ 1·4748), consisting of an impure methoxyl derivative (Found : OMe, 9·3. $C_{10}H_{15}O{\cdot}OMe$ requires 17·1%). When heated on the water-bath with an excess of moist silver oxide, the chlorohydrin gave a yellow oil which still contained chlorine. Repeated fractional distillation of the oil under diminished pressure furnished a first fraction which was free from chlorine and had $n_D^{17°}$ 1·4640. This *substance* (Found : C, 71·8; H, 9·9. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·5%) decolorised bromine in carbon tetrachloride, and was insoluble in dilute aqueous potassium hydroxide, but further characterisation could not be undertaken with the small amount of material available.

We express our indebtedness to the Carnegie Trust for a Scholarship and a Fellowship which enabled one of us (A. J. W.) to take part in this investigation, which is being continued.

UNITED COLLEGE OF ST. SALVATOR AND ST. LEONARD,
UNIVERSITY OF ST. ANDREWS,
AND UNIVERSITY OF SYDNEY.

[*Received*, *July* 31*st*, 1929.]