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CCXXV.—Piperitone. Part IV. The Interaction of dl-Piperitone and Semicarbazide, and the Isolation of Pure dl-Piperitone.

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In our original note on the interaction of *dl*-piperitone and semicarbazide (T., 1921, **119**, 784), the effect was described of mixing the ketone in cold aqueous alcoholic solution with an excess of the hydrochloride of the base. The material which separated after a few hours, when once recrystallised from boiling alcohol, melted at 219-220°, and seemed to be similar to the semicarbazone of the synthetic Δ^1 -*p*-menthen-3-one described by Wallach (*Annalen*, 1908, **362**, 272). From the data then at our disposal, the two products appeared, however, to be distinct, owing to apparent differences in solubility, melting point (Wallach, *loc. cit.*), and ease of formation (compare Roberts, T., 1915, **107**, 1466). The lack of reference in these two papers to a benzylidene derivative, which in the case of piperitone is capable of such ready production, seemed to support this conclusion. Unfortunately, also, these sources afforded no reference to hydroxylamine derivatives of the ketones concerned. The question of the identity of piperitone was accordingly reserved for discussion in a later communication, after the accumulation of further data (*loc. cit.*, p. 783).

Subsequently, we were able to obtain access to Schimmel's Semi-Annual Report for October, 1910 (compare Roberts, loc. cit.), giving a description (p. 97) of a Δ^1 -*p*-menthen-3-one from Japanese peppermint oil, which yielded not only a semicarbazone melting at 224-226°, but also an oxime melting at 107-109° and a hydroxylaminooxime melting at 164-165°. The strong case thus established for the acceptance of the chemical identity of piperitone with the ketonic constituent of Schimmel's Japanese peppermint oil and Roberts's oil of Cymbopogon sennaarensis, and with Wallach's synthetic ketone, was strengthened in a striking manner by Simonsen's contemporaneous investigation of the dextrorotatory ketone from the oil of the Himalayan grass, Andropogon Jwarancusa (T., 1921, 119, 1644). In a more recent communication (this vol., p. 589) this conclusion was confirmed by the establishment of the crystallographic identity of dl-piperitone- α -oxime, prepared from the lævorotatory ketone of Eucalyptus dives, with a corresponding product derived by Simonsen from the dextrorotatory ketone of A. Jwarancusa. The additional observation, recorded below, that dl-piperitone from E. dives yields two semicarbazones, melting after careful purification at 226-227° and 174-176°, respectively, provides a further indication of the chemical identity of the ketones from the various sources which have been mentioned.

Judging from the small, but distinct dextrorotations shown by the preparations, extracted with sodium sulphite solution, from the oils of Japanese peppermint and *C. sennaarensis*, piperitone occurs in these oils, as in that of *A. Jwarancusa*, in the dextrorotatory form. Thus, the ketone isolated by Simonsen from the last-named source by fractional distillation under diminished pressure had $[\alpha]_{1}^{36} + 36.76^{\circ}$, but after treatment with sodium sulphite and alkali the value for the purified ketone had declined, owing to partial racemisation, to $[\alpha]_{1}^{36} + 7.92^{\circ}$. Specimens prepared from the oil of *E. dives* by fractional distillation under diminished pressure often exhibit values in the vicinity of $[\alpha]_{1}^{36} - 50^{\circ}$. It is thus noteworthy that piperitone appears to occur in the dextrogyrate modification in the natural sources known in the Northern

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hemisphere,* whilst in the Southern hemisphere it is the lævogyrate modification which is produced (compare this vol., p. 584).

A consideration of the constitution of piperitone in relation to its general chemical behaviour is reserved for a later communication. In the present paper, we are able for the first time to record certain physical constants for pure *dl*-piperitone. The value 46.70, determined for the molecular refractivity, is the highest yet recorded for this substance; the calculated value for a ketone, C₁₀H₁₆O, with one ethylenic linking is 45.82, the exaltation being therefore 0.88. The physical evidence thus corresponds with conjugation of the two unsaturated groupings, but it is noteworthy that the calculated value of the molecular refractivity for the enolic form of the substance is 46.76. The density of pure *dl*-piperitone is appreciably lower than the values hitherto recorded, the discrepancy amounting to as much as 0.4 per cent. in the case of Wallach's synthetic product. The boiling point of the pure substance. when distilled under atmospheric pressure, is also somewhat lower than the temperatures observed in the investigations to which reference has been made (compare Roberts, loc. cit.).

It may be pointed out that no formal proof has yet been adduced of the constitutional identity of the optically active and inactive ketones. Most of the derivatives yet described have been optically inactive, and the possibility of racemisation being accompanied by isomerisation is forming the subject of inquiry. The physical and chemical properties of the optically active ketone are also under investigation.

Although pure benzylidene-dl-piperitone is readily prepared from the crude ketone, isolated from the essential oil of E. dives by fractional distillation under atmospheric pressure, yet it proved impracticable to obtain a pure semicarbazone directly from material of this kind. In our original communication (*loc. cit.*, p. 781) we ascribed the slight but persistent lævorotation shown by specimens of the racemised ketone, isolated from E. dives, to contamination with small quantities of a lævorotatory impurity. This foreign substance, the identity of which we hope to investigate, appears to form a semicarbazone which is difficult to separate from the semicarbazones of dl-piperitone : in an experiment described below, for example, the crude ketone had $[\alpha]_{10}^{\infty} - 0.50^{\circ}$, whilst the regenerated specimens from the purified α - and β -semicarbazones had the respective values $[\alpha]_{10}^{\infty} - 0.13^{\circ}$ and $[\alpha]_{10}^{\infty} - 1.37^{\circ}$. In order to obtain pure dl-piperitone, it is therefore necessary to

^{*} The sense of the optical rotation of the Δ^1 -menthen-3-one reported by Schimmel and Co. to occur in camphor oil is not evident (compare Gildemeister and Hoffman, "Die ätherischen Öle," Leipzig, 1913, II. 482).

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submit the crude ketone to a preliminary purification by the sulphite method before converting it to semicarbazone.

Further investigations on the preparation of *dl*-piperitonesemicarbazones disclosed several points of interest. The reaction between the ketone and semicarbazide hydrochloride takes place fairly readily at the ordinary temperature in aqueous alcoholic solution, and the separation from the acid liquid consists of almost pure α -semicarbazone; the β -compound appears to be more strongly basic than the a-compound, since it is not precipitated when the filtrate is diluted with water. On the other hand, by heating an aqueous alcoholic solution of *dl*-piperitone, semicarbazide hydrochloride, and sodium acetate for several hours, the yield of the α -compound is nearly doubled, the formation of the isomeric substance being almost completely suppressed.

The readiness with which *dl*-piperitone yields a hydroxylaminooxime rendered it of interest to attempt the preparation of a semicarbazido-semicarbazone, particularly in view of the conclusions of Rupe and later investigators concerning the constitutional peculiarities which appear to favour the formation of such derivatives (compare von Auwers, Ber., 1921, 54, [B], 987; Heilbron and Buck, T., 1921, 119, 1515). Although no evidence was forthcoming of the occurrence of such a derivative in this instance, vet in aqueous alkaline mixtures, favouring enolisation of the ketone, very slow reaction ensued, leading to the production of a stable and well-defined additive compound of *dl*-piperitone and semicarbazide. From the behaviour of this substance it appears that the addition is associated with the ketonic group, and not with the ethylenic linking. The new substance, besides being the most distinctive semicarbazide derivative of *dl*-piperitone, is of exceptional interest as establishing a definite intermediate additive stage in the formation of these semicarbazones :

 $C_9H_{16}:C:O \rightarrow C_9H_{16}:C(OH)\cdot NH\cdot NH\cdot CO\cdot NH_2 \rightarrow$

 C_9H_{16} :C:N·NH·CO·NH₂ + H₂O.

An investigation of the behaviour, under similar conditions, of other ketones and related substances is in progress, and we reserve this field of work.

EXPERIMENTAL.

Methods of Preparing the α - and β -Semicarbazones of dl-Piperitone.— 1. dl-Piperitone (35 grams; 1 mol.) was added to an excess of semicarbazide hydrochloride (30 grams; 1.2 mols.) dissolved in water (120 c.c.), and the homogeneous liquid which resulted upon adding methylated spirit was kept at the ordinary temperature for about two days. The ensuing crystalline deposit, which had formed

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to a considerable extent after the lapse of a few hours, when collected, washed with warm alcohol, and dried (16 grams), melted at 226-227°. By diluting the filtrate with water and treating the precipitate in a similar manner, a further small quantity (1.4 grams) of the same substance was obtained. The total yield (17.4 grams) of the α -semicarbazone was 36 per cent. of the calculated amount.

The addition of a slight excess of ammonia to the aqueous alcoholic filtrate produced a copious precipitate (13.8 grams) of the β -semicarbazone, and evaporation of the filtered liquid gave a little more (2.5 grams) of the same substance. The total yield of the crude β -semicarbazone (16.3 grams) was 34 per cent. of the calculated amount, and after one recrystallisation from alcohol it melted at 174—176°. It possessed a distinct yellow tinge, which was not lessened by repeated crystallisation from alcohol (Found : N = 20.3. C₁₁H₁₉ON₃ requires N = 20.1 per cent.).

In a similar experiment, the original solution was raised to the boiling point for a short time, after adding the methylated spirit, but the only apparent result was an acceleration of the reaction.

2. Crystallised sodium acetate (41.5 grams) was dissolved in water (50 c.c.) containing an equivalent amount of semicarbazide hydrochloride (30 grams) in solution; *dl*-piperitone (35 grams) was added, and the mixture diluted with warm methylated spirit until the attainment of a clear solution. After two days, the crystalline deposit (18.6 grams) was collected and washed with warm alcohol; it melted at 210° and consisted of a mixture of the α - and β -semicarbazones, from which almost pure α -semicarbazone, melting at 225—226°, was obtained after two recrystallisations from acetic acid.

The aqueous alcoholic filtrate from the crude product gave a precipitate when diluted with water; this consisted of a mixture of the α - and β -semicarbazones, in which the latter compound predominated. The pure β -compound, melting at 174—176°, was obtained after patient recrystallisations from alcohol.

Very similar results were achieved by using acetic acid in place of alcohol in the original reaction mixture.

3. dl-Piperitone (65 grams; 1 mol.) was added to a solution in water (66 c.c.) of semicarbazide hydrochloride (54 grams; 1·1 mols.) and sodium acetate (75 grams). Sufficient hot methylated spirit was added to clear the solution, which was then boiled gently under reflux on the water-bath. Separation of semicarbazone began after about two hours, and at the end of six hours the product was transferred to a hot filter, the solid being washed successively with hot methylated spirit, hot water, and hot alcohol. The dry

substance (40 grams) melted at 226-227° and consisted of pure α -semicarbazone (Found: N = 20.2 per cent.). The filtrate and washings, on evaporation, yielded further amounts of crystalline material, which after purification with hot alcohol proved to be mainly a-semicarbazone (15 grams), melting at 226-227°. From the mother-liquors was isolated a small quantity (2.4 grams) of the β -semicarbazone melting at 174-176°. The total amount of α semicarbazone isolated (55 grams) was 62 per cent. of the theoretical. The yield was not increased by neutralising the filtrate with ammonia.

Properties of the a- and β -Semicarbazones of dl-Piperitone.-dl-Piperitone-a-semicarbazone crystallises in minute, glistening leaflets, which, in bulk, possess a soapy feel. The substance is quite devoid of colour, and melts to a clear, colourless liquid at 226-227°. When heated somewhat above its melting point, it loses ammonia, but does not yield piperitone, the residue consisting of a dark, resinous mass. It is characterised by sparing solubility in most of the ordinary solvents, but it may be crystallised from hot acetic acid or nitrobenzene, a certain amount of decomposition occurring in the latter solvent at temperatures near the boiling point.

The α -semicarbazone is practically insoluble in cold dilute hydrochloric acid, but it dissolves in the cold concentrated acid, yielding a colourless solution, from which it is reprecipitated on the addition of ammonia or sodium hydroxide solution. It undergoes comparatively slow hydrolysis in hot, strongly acid solutions. Solutions in hot acetic acid show no marked reaction with bromine. The substance forms a clear, colourless solution when suspended in chloroform and submitted to the action of dry hydrogen chloride.

dl-Piperitone- β -semicarbazone, when prepared as stated above, forms minute needles, melting at 174-176° to a clear, faintly yellow liquid, which, on cooling, solidifies to a transparent resin. When heated above the melting point, it decomposes slightly, with evolution of ammonia and formation of a pale yellow resin. It is readily soluble in alcohol, chloroform, and other organic solvents, and it dissolves very sparingly in hot water. The crystals exhibit a faint, but distinct yellow tinge, whilst solutions in dilute hydrochloric acid are deep yellow; neutralisation with alkali reprecipitates the original faintly tinged solid. Solutions in chloroform also become deep yellow on treatment with dry hydrogen chloride. The β -semicarbazone is readily hydrolysed by hot dilute hydrochloric acid, yielding piperitone. Bromine does not appear to affect it in hot acetic acid solution.

When prepared from semicarbazido-dl-piperitone, in the manner described below, the β-semicarbazone was quite colourless, and it melted at $174-176^{\circ}$ to a colourless liquid which formed a transparent resin on cooling. Neither preparation appeared to be affected when maintained at 150° for fifteen minutes, and a mixture of the two melted unchanged at $174-176^{\circ}$: the yellow colour thus seems to be due to the presence of traces of an impurity. The yellow specimen was hydrolysed with distinctly greater rapidity than the other, when boiled with dilute hydrochloric acid.

Semicarbazido-dl-piperitone, C_9H_{16} :C(OH)·NH·NH·CO·NH₂.—A mixture of a solution of semicarbazide hydrochloride (5 grams) in water (25 c.c.) with *dl*-piperitone (6·2 grams) was rendered slightly alkaline by the addition of 10 per cent. sodium hydroxide solution and shaken in a stoppered flask at intervals. After keeping overnight, a further quantity of semicarbazide hydrochloride (5 grams) in water (25 c.c.) was added, and the mixture again made alkaline. No sign of reaction was evident for several days, but after keeping for a week, with frequent shaking, a considerable amount of solid material had separated in small, opaque granules, and after the lapse of about three weeks the reaction appeared to be complete.

The product was collected and freed from inorganic impurities and unchanged piperitone by washing with water and ether. The substance was first recrystallised from hot alcohol, in which it was moderately soluble, and finally from hot water, in which it dissolved rather sparingly. It was moderately soluble in chloroform and almost insoluble in ether or benzene. The yield of purified product amounted to about 75 per cent. of the weight of the ketone taken, best results being achieved by the use of small quantities of the reactants (Found : C = 58.2; H = 9.0; N =19.3. $C_{11}H_{21}O_2N_3$ requires C = 58.1; H = 9.3; N = 18.5 per cent.).

Semicarbazido-dl-piperitone crystallises in colourless, glistening leaflets, which attain a much larger size than the crystals of the semicarbazones of *dl*-piperitone. The substance melts at $186-187^{\circ}$; slightly above this temperature it decomposes with vigorous evolution of ammonia, and at higher temperatures piperitone is regenerated. It dissolves readily in cold dilute hydrochloric acid, and on the addition of ammonia separates slowly from the solution in glistening leaflets. The solution in concentrated hydrochloric acid, when slightly warmed, becomes cloudy, owing to the liberation of piperitone. The ketone is also slowly evolved from the boiling aqueous solution of the derivative.

A suspension of semicarbazido-dl-piperitone in chloroform, unlike similar suspensions or solutions of the α - and β -semicarbazones, readily yielded a colourless precipitate when saturated with dry hydrogen chloride. This substance, which was apparently *semi*- carbazido-dl-piperitone hydrochloride, melted and decomposed at 165-167°; it was stable in air, and dissolved readily in water and rather sparingly in dilute hydrochloric acid (Found : HCl = 14.4. $C_{11}H_{21}O_{2}N_{3}$, HCl requires HCl = 13.8 per cent.). The original base (m. p. $186-187^{\circ}$) was precipitated from the aqueous solution when neutralised with ammonia. The same derivative was produced, in a well-defined crystalline form, by moistening semicarbazido-dlpiperitone with concentrated hydrochloric acid; on keeping such a mixture, the crystals soon disappeared, and the resulting solution, when diluted with water after the lapse of an hour, yielded piperitone.

When a solution of semicarbazido-dl-piperitone in the least possible quantity of dilute hydrochloric acid was kept for fortyeight hours and then neutralised with ammonia, it yielded a colourless precipitate, consisting of a mixture of the α - and β semicarbazones of dl-piperitone. The β -derivative, prepared in this manner, was devoid of colour, as noted above (Found : N =20.1 per cent.). A similar result was attained by mixing aqueous solutions of semicarbazido-dl-piperitone and semicarbazide hydrochloride and keeping for the same period, with or without the addition of sodium acetate; no indication was obtained of the formation of a semicarbazido-semicarbazone.

An aqueous solution of semicarbazido-dl-piperitone, when heated on the water-bath for two hours with a slight excess of hydroxylamine hydrochloride and sodium acetate, failed to yield an oxime, most of the substance being recovered unchanged.

Solutions of the derivative in warm acetic acid readily underwent oxidation with bromine, yielding carbon dioxide, ammonium bromide, thymol, and other products.

The derivative obtained from *l*-piperitone under the prescribed conditions was identical with the semicarbazido-dl-piperitone just described; its saturated alcoholic solution exhibited no measurable optical activity in a 2-dcm. tube when examined in sodium light at the ordinary temperature.

The Preparation of Pure dl-Piperitone.-In the initial attempt to prepare pure dl-piperitone, quantities of the α - and β -semicarbazones were prepared by method (1), as described above, from a specimen of the ketone isolated from the crude oil of E. dives by fractional distillation under atmospheric pressure and having $\left[\alpha\right]_{D}^{20} - 0.50^{\circ}$. The ketone was regenerated from each of the semicarbazones by means of steam distillation in the presence of 20 per cent. oxalic acid solution; the two specimens were then separated from the aqueous distillates, dried over calcium chloride, and filtered, but not redistilled. Since both specimens were still distinctly optically

active, they could not be regarded as pure dl-piperitone, but certain physical constants were nevertheless determined. The specimen regenerated from the α -semicarbazone had $[\alpha]_{D}^{20} - 0.13^{\circ}$, d_{4}^{20} (vac.) 0.9335, and n_{D}^{20} 1.4848; whilst that from the β -semicarbazone had $[\alpha]_{D}^{20} - 1.37^{\circ}$, and n_{D}^{20} 1.4848. Both specimens boiled at 115—116°/ 20 mm.

Pure *dl*-piperitone was eventually prepared by extracting the crude oil of *E. dives* with sodium bisulphite and converting the ketone from the recrystallised bisulphite compound into the α -semicarbazone, according to method (3) described above. After the preliminary purification over the bisulphite compound, the ketone * boiled at $152^{\circ}/75$ mm. and had $[\alpha]_{10}^{\infty} - 3.67^{\circ}$. The derived α -semicarbazone (40 grams, m. p. $226-227^{\circ}$) was boiled under reflux with a 20 per cent. aqueous solution of oxalic acid for thirty minutes, after which the mixture was steam distilled. The separated piperitone, when dried over calcium chloride and filtered (27.9 grams), amounted to about 96 per cent. of the calculated yield. It exhibited no measurable optical activity in a 2-dcm. tube, when examined in sodium light at 20° ; the density prior to redistillation, d_{40}^{30} (vac.) 0.9336, was almost identical with that of the foregoing preparation.

Physical Properties of Pure dl-Piperitone.—When distilled under diminished pressure, from an oil-bath maintained at $145-150^{\circ}$, the purified ketone passed over completely at $113^{\circ}/18$ mm., the first few drops of the distillate, which contained traces of water, being collected separately.

Determinations of density (reduced to vacuum) were made as follows : d_4^{30} 0.9331, d_4^{35} 0.9294, d_4^{30} 0.9257.

The further value, d_{30}^{30} 0.9296, stands in satisfactory agreement with the corresponding value, d_{30}^{30} 0.9307, found by Simonsen (*loc. cit.*, p. 650) for a specimen of the ketone from *A. Jwarancusa* which had been purified by solution in sodium sulphite solution.

The refractive index was determined, at the same three temperatures, in the Abbé instrument: $n_{\rm D}^{20}$ 1.4845, $n_{\rm D}^{25}$ 1.4825, $n_{\rm D}^{30}$ 1.4805. The value of R_L , calculated from the data determined at 20°, is thus 46.70.

When a specimen of pure dl-piperitone was distilled under atmospheric pressure (768.6 mm.), about 25 per cent. passed over at 232—233° (corr.), and by the time 50 per cent. had distilled the temperature had reached 235°. The distillate was colourless, but

^{*} A similar specimen, having $[a]_D^{20} - 1.44^\circ$, boiled at $164^\circ/106$ mm. The results of investigation on the extraction of the ketone will be published in due course, but it may be mentioned that the optical activity of specimens purified in this manner is to be attributed to incomplete racemisation.

the odour indicated slight decomposition. The residue had a distinct yellow colour.

Pure dl-piperitone is quite colourless, and it does not exhibit the marked tendency of the somewhat impure specimens to become yellow when kept.

The bisnitroso-derivative of dl-piperitone, obtained in small yield by applying the method of Baeyer and Henrich (Ber., 1895, **28**, 654) and keeping the mixture at a low temperature for a day or two, corresponded closely with the description given by Roberts (loc. cit.) for the derivative obtained in the same way from the ketonic constituent of the oil of C. sennaarensis. It formed colourless crystals which melted at 97–98° and decomposed when kept for several months.

dl-Piperitone failed to yield an additive product with hydrogen sulphide, when treated in the manner described by Wallach for carvone (*Annalen*, 1899, **305**, 224).

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