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THE CONSTITUENTS OF AN ESSENTIAL OIL OF RUE

BY

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AND

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(From the Transactions of the Chemical Society, 1902.)

METHYL β-METHYLHEXYL KETONE

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THE WELLCOME CHEMICAL RESEARCH LABORATORIES.

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CLVIII.—*The Constituents of an Essential Oil of Rue.*

By Frederick B. Power and Frederic H. Lees.

The incentive to this investigation arose from the requirement of preparing some methyl nonyl ketone, the most convenient source of which is the essential oil of rue. A portion of the oil was therefore obtained from an English firm of distillers, and although there was no reason to doubt its purity, it was found to possess some decidedly abnormal characters. As it bore the designation *Ol. Rutae Ang.*, we inferred that not only had the oil been distilled in Britain, but possibly native-grown herb had been used, inasmuch as the ordinary commercial oil appears to be always distilled from fresh material. This afforded a possible explanation of its deviation from the accepted standards of the ordinary oil, and, under these circumstances, it seemed to merit a more complete investigation. Soon after beginning the work, we observed a brief preliminary notice by Soden and Henle (*Pharm. Zeit.*, 1901, 277) of an Algerian oil of rue, which was subsequently further examined by them (*ibid.*, 1901, 1026). As the oil supplied to us, on further examination, was found to resemble, in some of its physical and chemical characters, that described by Soden and Henle, we sought information as to its origin. It was thus ascertained that it had not been distilled from native-grown herb, and as it appears that the rue has never been cultivated in this country for the purpose of distillation, it is highly probable that the article supplied to us was an Algerian oil.

Thoms (*Ber. deut. pharm. Ges.*, 1901, 10, 3) has shown that, besides the chief constituent and the only one which had hitherto been positively identified, namely, methyl nonyl ketone, ordinary oil of rue contains about 5 per cent. of methyl *n*-heptyl ketone, together with some free fatty acids and a very small amount of a phenol-like substance, from which crystals separated which melted at 155—156°, but were not further characterised.

Soden and Henle (*loc. cit*), in their investigation of the Algerian oil, found that while, like the ordinary European oil, it contains about 90 per cent. of ketones, there is about twice as much methyl heptyl ketone as methyl nonyl ketone. They have also indicated that, "besides these ketones, the Algerian oil contains a not inconsiderable amount of esters which boil chiefly at 200—210°, and appear to consist, for the most part, of the acetic esters of the secondary alcohols corresponding to the two ketones, or of similar aliphatic alcohols, but that they were not yet able to determine the true nature of these esters on account of insufficient material."

In view of the fact that our investigation of what was assumed to be an English oil had progressed to a considerable extent before the probability of its Algerian origin became apparent, and that we have not only identified the alcohols but also several minor constituents, it seemed desirable that the results of the investigation should be recorded.

Experimental.

The oil was light yellow in colour; it had a density d 15·5°/16° = = 0·8405, and a_D −3°48′ in a 100 mm. tube. It was completely soluble in 2 parts of 70 per cent. alcohol. The total amount of oil employed was 1800 grams.

Treatment with 20 per cent. Sulphuric Acid.—As Schimmel & Co. (*Semi-annual Report*, Oct., 1901, 46) have obtained from ordinary oil of rue a small quantity of a basic oil, possessing a blue fluorescence, which they regarded as methyl methylanthranilate, it seemed desirable to ascertain whether our oil contained a similar substance. It was therefore extracted with 20 per cent. sulphuric acid, and this liquid made alkaline with sodium carbonate and shaken out with ether. From the ethereal liquid about 0·5 gram of a light brown syrup was obtained, which had an odour suggestive of quinoline or its homologues; it was alkaline to litmus, and caused white fumes in contact with hydrochloric acid. On standing for some time, a few crystals were formed, but were too small in amount to admit of separation. The substance, when dissolved in hydrochloric acid, gave with auric chloride a brownish precipitate, which almost immediately

became resinous. It was evident that the basic substance in this oil was not methyl methylanthranilate.

Treatment with Sodium Carbonate.—In order to separate any uncombined fatty acids, the oil was subsequently extracted with a 5 per cent. solution of sodium carbonate. The alkaline liquid was concentrated, acidified with sulphuric acid, and distilled with steam. The distillate, which contained oily drops, was shaken out with ether, and from the ethereal liquid a small amount of a light brown oil was obtained. This, on distillation, gave two fractions: (1) below 200°, and (2) 220—270°. These were converted into silver salts of which one salt (*a*) was prepared from fraction (1), and two salts (*b*) and (*c*), from fraction (2). They were respectively well washed, dried, and analysed:

(*a*) 0·0601 gave 0·0262 Ag. Ag = 43·5 per cent.
(*b*) 0·1004 ,, 0·0390 Ag. Ag = 38·8 ,,
(*c*) 0 0948 ,, 0·0400 Ag. Ag = 42·2 ,,

It was evident from these results that the free fatty acids contained in the oil consist of a mixture, the constituents of which were too small in amount to admit of identification.

Identification of Methyl Salicylate.

Treatment with Potassium Hydroxide.—After the treatment with sodium carbonate, the oil was extracted with a 5 per cent. solution of potassium hydroxide. The alkaline liquid was acidified with sulphuric acid and extracted with ether. The ethereal liquid afforded a small amount of a dark brown oil, which had the characteristic odour of methyl salicylate, and on standing a short time formed a crystalline paste. This was spread on a porous tile, when the oily mother liquor was removed and a small quantity of white crystals obtained, which, after recrystallisation from hot water, melted at 155—156°, gave a deep violet colour with ferric chloride, and were identified as salicylic acid.* On analysis:

0·1304 gave 0·2899 CO_2 and 0·0528 H_2O. C = 60·6; H = 4·5.
$C_7H_6O_3$ requires C = 60·9; H = 4·4 per cent.

From the porous tile, by extraction with warm ether, a small amount of an oily liquid was obtained which distilled between 190° and 250°. This, on hydrolysis, yielded a further amount of salicylic acid.

As the original oil had been previously extracted with sodium carbonate, the salicylic acid could not have existed in it as such, but must

* The substance obtained by Thoms (*loc. cit.*), which melted at 155—156°, would also appear to have been salicylic acid.

have been present as an ester which had become partially hydrolysed in the process of isolation. It was evident that this ester was methyl salicylate.

Ketonic Constituents of the Oil.

Treatment with Sodium Bisulphite.—The whole of the oil, after the treatment just described, was diluted with ether and then repeatedly shaken with a saturated solution of sodium bisulphite. The crystalline compound was well washed with ether, drained, and pressed. The combined ethereal filtrate and washings were first shaken with a solution of sodium carbonate to remove sulphurous acid, then with water, finally dried with calcium chloride, and the ether removed. The residual oil, thus deprived of the larger portion of its ketonic constituents, was set aside for subsequent examination.

The bisulphite compound was suspended in ether and decomposed with a 10 per cent. solution of sodium hydroxide. The ethereal solution was washed with water, dried with calcium chloride, and the ether removed. The residual oil was then fractionally distilled. After prolonged fractionation, it was resolved chiefly into two large fractions, one distilling at 190—200° and the other at 225—235°.

Identification of Methyl n-*Heptyl Ketone.*

Fraction 190—200°.—On redistilling this fraction, the greater part boiled at 194—197°; it was most constant at 194·5—195·5° under 763 mm. pressure and this portion had a density d 14°/16° = 0·8296. On analysis:

0·0934 gave 0·2617 CO_2 and 0·1080 H_2O. C = 76·4; H = 12·8.
$C_9H_{18}O$ requires C = 76·1; H = 12·7 per cent.

The semicarbazone melted at 119—120°. On analysis:

0·1272 gave 0·2790 CO_2 and 0·1214 H_2O. C = 59·8; H = 10·6.
$C_{10}H_{21}ON_3$ requires C = 60·3; H = 10·6 per cent.

Identification of Methyl n-*Nonyl Ketone.*

Fraction 225—235°.—On redistilling this fraction, it boiled for the most part at 229—233° under 759 mm. pressure.

The semicarbazone melted at 122°. On analysis:

0·1376 gave 0·3195 CO_2 and 0·1358 H_2O. C = 63·3; H = 11·0.
$C_{12}H_{25}ON_3$ requires C = 63·4; H = 11·0 per cent.

The boiling point of methyl nonyl ketone is generally stated to be 224°; Thoms (*loc. cit.*) likewise records it as 223—224° under 774 mm.

pressure, whereas Soden and Henle (*loc. cit.*) have indicated it to be 230—231° under 740 mm. pressure. We have confirmed this observation by regenerating the ketone from the repeatedly crystallised semicarbazone; it then distilled completely at 231·5—232·5° under 761 mm. pressure, and had a density d 20·5°/16° = 0·8263. On analysis:

0·0845 gave 0·2398 CO_2 and 0·0994 H_2O. C = 77·4; H = 13·1.
$C_{11}H_{22}O$ requires C = 77·6; H = 12·9 per cent.

Non-ketonic Constituents of the Oil.

The portion of the original oil which did not combine with sodium bisulphite was subjected to fractional distillation. Under the ordinary pressure, a portion distilled over below 207°; this on further distillation afforded the following fractions: 120—145°, 145—165°, 165—170°, 170—180°, and 180—185°. The portion distilling above 185° was finally mixed with that which boiled above 207° in the first instance.

Fractions 120—145°, 145—165°, and 165—170°.—These fractions were examined as follows:

Fraction 120—145°.—This had a density d 16°/16° = 0·8416 and was optically inactive. On analysis:

0·0932 gave 0·2516 CO_2 and 0·0987 H_2O. C = 73·6; H = 11·8.

Fraction 145—165°.—This had a density d 16°/16° = 0·852 and a_D −2°45′ in a 25 mm. tube. On analysis:

0·098 gave 0·282 CO_2 and 0·106 H_2O. C = 78·5; H = 12·0.

These two fractions had a combined weight of not more than 5 grams. They possessed an odour of terpene and also one recalling that of ethyl valerate.

Identification of a Valeric Ester.

The above two fractions were mixed and boiled for some hours with a dilute aqueous solution of potassium hydroxide. There still floated on the surface of the liquid a considerable proportion of the oil, which was taken up with ether and examined in connection with the fraction boiling at 165—170°. The alkaline liquid was acidified, and again extracted with ether, which dissolved a small amount of a fatty acid from which a silver salt was prepared. This by recrystallisation from hot water was separated into three fractions, which were analysed:

(1) 0·0638 gave 0·0324 Ag. Ag = 50·8.
(2) 0·0558 „ 0·0287 Ag. Ag = 51·4.
$C_5H_9O_2Ag$ requires Ag = 51·7 per cent.

It was thus evident that the oil contained an exceedingly small amount of a valeric ester, which was probably ethyl valerate.

Identification of Pinene.

The oil separated by the hydrolysis of the two preceding fractions, 120—145° and 145—165°, was mixed with the small fraction 165—170°. The total liquid, which amounted to 3 grams, evidently contained a terpene, and from it a small amount of a nitrosochloride was prepared. The latter was converted into the nitrolepiperidide which, after recrystallisation from methyl alcohol, melted at 119—120°.

Identification of Limonene and Cineol.

Fractions 170—180° and 180—185°.—These two fractions weighed respectively 11 and 5 grams, and had the following characters:

Fraction 170—180°.—This had a density d 15·5°/16° = 0·8606 and α_D −20°16′ in a 50 mm. tube. On analysis:

(1) 0·1306 gave 0·3987 CO_2 and 0·1405 H_2O. C = 83·3; H = 12·0.
(2) 0·1238 „ 0·3780 CO_2 „ 0·1340 H_2O. C = 83·3; H = 12·0.

Fraction 180—185°.—This had a density d 15·5°/16° = 0·8588 and α_D −10°30′ in a 25 mm. tube.

Both these fractions were insoluble in 70 per cent. alcohol, and were otherwise practically identical. Their general characters indicated that they contained a considerable proportion of a terpene, but they also had an odour suggesting the presence of cineol.

The presence of limonene in the two preceding fractions was determined by means of the tetrabromide, which melted at 103°; the high lævorotation of the fractions made it evident that it was *l*-limonene.*

The fraction 170—180° was specially tested for phellandrene, but with a negative result.

The identification of cineol in these two fractions was effected by means of its compound, $C_{10}H_{18}O{\cdot}C_4I_4NH$, with tetraiodopyrrole (Hirschsohn, *Pharm. Zeit. Russ.*, 1893, 32, 49, 67), and also by the additive product with hydrogen bromide. The former melted with decomposition at 114—115°, and the latter at 55—56°. On warming the hydrobromide with dilute alkali, it developed the unmistakable odour of cineol.

Portion of Oil boiling above 185°.—This was hydrolysed with alcoholic potassium hydroxide. The alcohol was then removed, water added,

* It is stated in "Die aetherischen Oele," by Gildemeister and Hoffmann, p. 596, that "the terpene found in oil of rue by different investigators is in all cases to be referred to an adulteration with oil of turpentine," and Thoms (*loc. cit.*) also states that it contains no terpene. No constituent of the genuine oil has, however, hitherto been isolated which would account for its optical activity, and the possibility of the presence of a small amount of terpene would therefore not seem to be excluded.

and the separated oil taken up with ether. The ethereal solution was washed, dried quickly with calcium chloride, and the ether removed. The alkaline liquid was acidified, distilled with steam, and the distillate neutralised with sodium carbonate, concentrated, acidified, and extracted with ether. From the ethereal solution an appreciable quantity of a light yellow, pungent liquid was obtained. This distilled almost completely below 120°, leaving a very small amount of an acid of higher boiling point in the flask.

Identification of Acetic Acid.

The portion of acid which distilled below 120° was converted into its barium salt, and from a portion of this a silver salt was prepared. On analysis:

0·2208 gave 0·1426 Ag. Ag = 64·6.

$C_2H_3O_2Ag$ requires Ag = 64·7 per cent.

The higher boiling portion of volatile acid was dissolved in a little dilute aqueous ammonia, decolorised by animal charcoal, and converted into a silver salt, which was for the most part insoluble in hot water. On analysis:

0·0704 gave 0·0304 Ag. Ag = 43·2 per cent.

The small amount of this acid did not permit of its identification.

The Alcohols.

The oil obtained by the above hydrolysis, when tested with semicarbazide, was found still to contain a considerable amount of ketone, notwithstanding the previous exhaustive treatment with bisulphite. A preliminary distillation showed that the greater part passed over between 190° and 250°; that boiling above 250°, which will be subsequently referred to, possessed a beautiful indigo-blue colour. The oil was therefore fractionally distilled until that passing over below 250° was quite free from any blue colour. In order to separate from this oil the last portion of ketones, recourse was had to the following method.

20·7 Grams of sodium were dissolved in 250 c.c. of absolute alcohol, and 100 grams of semicarbazide hydrochloride, made into a paste with alcohol, were introduced. An alcoholic solution of semicarbazide was thus obtained, sufficient in amount to combine with the 128 grams of oil employed, had the latter consisted entirely of methyl heptyl ketone. This mixture was boiled for half an hour, and then, while still hot, filtered from the sodium chloride. On concentrating the filtrate, a considerable amount of the crystalline semicarbazones separated, which

was removed by means of a pump, and washed well with cold alcohol. On the addition of water to the filtrate, there separated the substances which had not combined with the semicarbazide, together with a small amount of the semicarbazones. These were taken up with ether, which was subsequently removed, and the oily residue rapidly distilled in steam. The non-ketonic substances quickly came over, and it was only after these had distilled that the semicarbazones began slowly to decompose. The oil was extracted with ether, dried with potassium carbonate, and, after the removal of the ether, fractionally distilled. The principal fractions were collected at 190—200° and 220—235°, and of these the latter was much smaller than the former. Smaller fractions were also collected at 200—205°, 205—210°, and 210—220°.

*Identification of Methyl-*n*-heptylcarbinol.*

Fraction 190—200°, on redistillation, yielded a fraction boiling constantly at 195—196°. On analysis:

(1) 0·0931 gave 0·2605 CO_2 and 0·1130 H_2O. C = 76·3; H = 13·5.
(2) 0·1048 „ 0·2931 CO_2 „ 0·1285 H_2O. C = 76·3; H = 13·6.

Fraction 200—205°.—This was also analysed:

0·1007 gave 0·2780 CO_2 and 0·1258 H_2O. C = 75·3; H = 13·9.
$C_9H_{20}O$ requires C = 75·0; H = 13·9 per cent.

As the principal fraction was evidently not quite pure, the separation of any trace of terpene it might still contain was effected by converting the alcohol into its acetic ester. For this purpose, the two fractions were mixed and boiled with an equal weight of acetic anhydride and a little anhydrous sodium acetate. A product was thus obtained which distilled chiefly at 212—217°, and most constantly at 213—215°. This was analysed:

0·1210 gave 0·3174 CO_2 and 0·1300 H_2O. C = 71·5; H = 11·9.
$C_{11}H_{22}O_2$ requires C = 71·0; H = 11·8 per cent.

*Methyl-*n*-heptylcarbinyl acetate*, $CH_3{\cdot}CH(O{\cdot}C_2H_3O){\cdot}C_7H_{15}$, was a colourless oil of pleasant odour, and had a density d 20·5°/16° = 0·8605 and a_D −3°3′ in a 50 mm. tube.

Hydrolysis afforded methyl-*n*-heptyl carbinol, which boiled at 198—200° under 765 mm. pressure, and had a density d 19°/16° = 0·8273 and a_D −3°44′ in a 50 mm. tube. On analysis:

0·1222 gave 0·3348 CO_2 and 0·1529 H_2O. C = 74·7; H = 13·9.
$C_9H_{20}O$ requires C = 75·0; H = 13·9 per cent.

On oxidation with chromic acid, this optically active alcohol afforded

methyl *n*-heptyl ketone, which had the characteristic odour, distilled at 195—199°, and yielded a semicarbazone melting at 118—119°. The proof was thus afforded that this alcohol is methyl-*n*-heptylcarbinol.

*Identification of Methyl-*n*-nonylcarbinol.*

The fraction boiling at 220—235° was relatively very small in amount. It was acetylated, as in the case of the alcohol of lower boiling point. The product, on fractionation, distilled principally between 240° and 248°, and was most constant at 245°. Hydrolysis afforded the alcohol, which boiled at 230—235°, and was most constant at 231—233°; it had a_D −1°18′ in a 25 mm. tube. This fraction was analysed :

0·0991 gave 0·2793 CO_2 and 0·1220 H_2O. C = 76·9 ; H = 13·7.
$C_{11}H_{24}O$ requires C = 76·7 ; H = 14·0 per cent.

This optically active alcohol afforded, on oxidation with chromic acid, a ketone, which formed an oxime melting at 46—47°. It was thus identified as methyl-*n*-nonylcarbinol.

A Blue Oil.

It has already been noted that from that portion of the oil used for the identification of the alcohols a fraction was separated, boiling above 250°, which possessed a deep blue colour. It was relatively small in amount, and had a rank, weed-like odour. On redistillation, it passed over between 250° and 320°, but was at no point constant. The liquid was dichroic, the colour, in reflected light, being a deep indigo-blue, and in transmitted light, red. It was sparingly soluble in 70 per cent. alcohol. When dissolved in glacial acetic acid, it gave a reddish-brown colour on the addition of a drop of hydrochloric acid. The presence of a blue oil in an oil of rue has not hitherto been observed. The small amount, and the complex character of this liquid, rendered it impossible to determine its composition.

Summary.

From the preceding details it will be seen that this essential oil of rue, which was apparently of Algerian origin, contained the following substances :

1. Methyl-*n*-heptylketone.
2. Methyl-*n*-nonylketone.
3. Methyl-*n*-heptylcarbinol.
4. Methyl-*n*-nonylcarbinol.
5. A blue oil of high and inconstant boiling point.

6. Acetic acid, in combination with the alcohols.
7. A basic substance, having the odour of quinoline.
8. A mixture of free fatty acids.
9. Methyl salicylate.
10. Ester of valeric acid, apparently ethyl valerate.
11. Pinene.
12. *l*-Limonene.
13. Cineol.

The relative proportion of the above constituents is approximately as follows:

The two ketones represented 80 per cent. of the oil, and were present in about equal amounts.

The two alcohols represented about 10 per cent., and were present partly in the uncombined state and partly as acetic esters. The methyl-*n*-heptylcarbinol preponderated.

The two terpenes, together with cineol, represented about 1 per cent. of the oil. There was very little pinene, and the amounts of limonene and cineol were about equal.

The amount of blue oil was about 0·5 per cent., and finally there was separated from the non-ketonic portion of the oil a small amount of undistillable, viscous substance, which was probably a decomposition product.

The fact that the substances associated with the ketones and alcohols are present in such small amount, and that the limonene is the more rarely occurring *l*-form, enables us to conclude that all these substances are natural constituents of the oil.

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CLIX.—*Methyl β-Methylhexyl Ketone.*

By FREDERIC HERBERT LEES.

IN the course of an investigation of the ketones contained in an essential oil of rue (this vol., p. 1585), *methyl β-methylhexyl ketone*, $CH_3 \cdot CO \cdot CH_2 \cdot CH(CH_3) \cdot [CH_2]_3 \cdot CH_3$, was prepared and characterised. It was obtained by the hydrolysis of *ethyl* sec.*-hexylacetoacetate*, $CH_3 \cdot CO \cdot CH(C_6H_{13}) \cdot CO_2Et$, which was prepared by the condensation of *sec.*-hexyl iodide (from mannitol) with ethyl acetoacetate.

Ethyl sec.*-hexylacetoacetate.*—Sodium (5·8 grams) was dissolved in absolute alcohol (60 c.c.), and to the solution were successively added, ethyl acetoacetate (32·5 grams), and *sec.*-hexyl iodide (53 grams). The

resulting clear liquid was then heated in a soda-water bottle at 100° for 14 hours, when the product became neutral. The greater part of the alcohol was removed by distillation, water was then added, and the precipitated oil taken up with ether. The ethereal solution was washed with water, dried with calcium chloride, and the ether removed. The residue was then fractionally distilled under diminished pressure, when a quantity of the pure substance, amounting to 30 per cent. of that theoretically obtainable, distilled as a nearly colourless oil at 130—132° under 17 mm. pressure. Under the ordinary pressure, it boiled at 243—245°. Its alcoholic solution gave a brown coloration with ferric chloride. On analysis:

0·131 gave 0·3198 CO_2 and 0·1185 H_2O. C = 66·6; H = 10·1.
$C_{12}H_{22}O_3$ requires C = 67·3; H = 10·3 per cent.

Methyl β-Methylhexyl Ketone.—Ethyl *sec.*-hexylacetoacetate (16 grams) was boiled with a solution of potassium hydroxide (10 grams) in water (20 c.c.) for nine hours. The oil was then dissolved in ether, the ethereal solution washed with water, dried with calcium chloride, and the ether removed. The residual oil was then fractionated, when the ketone was obtained, to the extent of 80 per cent. of the theoretical, as a colourless, pleasantly odorous liquid, which boiled at 184° under 769 mm. pressure. A density determination gave *d* 15°/16° = 0·8319. On analysis:

0·127 gave 0·3538 CO_2 and 0·1447 H_2O. C = 76·0; H = 12·7.
$C_9H_{18}O$ requires C = 76·1; H = 12·7 per cent.

The *semicarbazone*, recrystallised from petroleum, formed rosettes of fine needles and melted at 75°. On analysis:

0·1804 gave 0·4 CO_2 and 0·1728 H_2O. C = 60·5; H = 10·6.
$C_{10}H_{21}ON_3$ requires C = 60·3; H = 10·6 per cent.

The *oxime*, at the ordinary temperature, is a colourless oil. On analysis:

0·1482 gave 0·3728 CO_2 and 0·1606 H_2O. C = 68·6; H = 12·0.
$C_9H_{19}ON$ requires C = 68·8; H = 12·1 per cent.

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