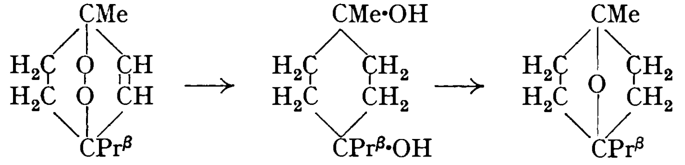
160. *Chenopodium Oil. Part III. Ascaridole.*

By HUMPHREY PAGET.

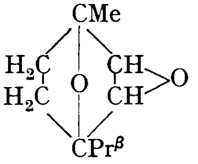
Ascaridole, the active principle of chenopodium oil, is an unsaturated terpene peroxide. It is decomposed explosively by heat or by treatment with concentrated mineral acids. Difficulty has been experienced in estimating its amount in chenopodium oil, and the only chemical methods described, by reduction with acid solutions of titanous chloride or of potassium iodide, involve the use of empirical factors. This may be due either to ascaridole being in reality a mixture or to the complexity of its reaction with these reducing agents. Ascaridole has now been

obtained crystalline by cooling to about −20°, but purification in this way has given no evidence that it is a mixture. Reduction by titanous chloride leads to a complex mixture of products. Rupture of the peroxide bridge with evolution of propane and formation of *p*-cresol takes place to the extent of 33%; isomerisation and condensation also occur. *Dihydroascaridole,* a saturated peroxide formed by hydrogenation of ascaridole with one mol. of hydrogen, is reduced by titanous chloride with production, in 90% yield, of propane and 1-*methyl*cyclo*hexan*-1-*ol* 3 : 4-*oxide*. The latter substance is oxidised by chromic acid to the lactone of β-hydroxy-β-methyladipic acid.

ASCARIDOLE, the anthelmintic constituent of chenopodium oil, was given the formula of an unsaturated 1 : 4-peroxide (I) by Wallach (*Annalen*, 1912, **392**, 59) from consideration of the products of hydrogenation in presence of palladium. He showed that it absorbed two mols. of hydrogen, yielding *cis*-1 : 4-terpin (II), which on dehydration by oxalic acid solution gave Δ^1-*p*-menthen-4-ol and 1 : 4-cineole (III).



(I.) (II.) (III.)



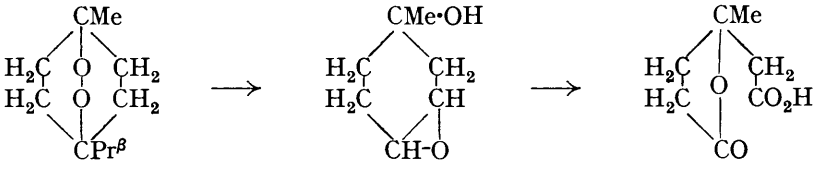
(IV.)

Although ascaridole absorbs the calculated quantity of hydrogen for conversion into 1 : 4-terpin, it does not react in a quantitative manner with reducing agents such as titanous chloride (Paget, *Analyst*, 1926, **51**, 170) or potassium iodide in hydrochloric and acetic acids (Cocking and Hymas, *Analyst*, 1930, **55**, 180), and methods of estimation based on the use of these reagents require the application of an empirical factor. On the basis of the addition of four atoms of hydrogen, 34·7% of the calculated amount of reducing agent is utilised in the case of titanous chloride, and 63·3% in the case of the second reagent by the process described in the British Pharmacopœia (1932). These facts suggest either that ascaridole is a mixture of two substances which cannot be separated by distillation or that attack by these somewhat strongly acid reagents on the peroxide bridge involves a number of reactions leading to a complex mixture of products.

Ascaridole is not easily purified by distillation, since it is isomerised by heat to a more stable dioxide (IV), the boiling point of which lies near that of ascaridole itself. By cooling in solid carbon dioxide it has now been obtained crystalline; it separates from a number of solvents, such as alcohol, light petroleum, *iso*propyl ether or the terpene fraction of chenopodium oil, but repeated crystallisation in this way has not resulted in a separation.

The principal products of reduction of ascaridole by an acid solution of titanous chloride, which have been identified, are propane and *p*-cresol, each in about 33% yield. The evolution of a combustible gas has already been observed by Nelson (*J. Amer. Chem. Soc.*, 1911, **33**, 1407) during reduction by ferrous sulphate, and by Wallach (*loc. cit.*) during isomerisation to the dioxide by heat. No intermediate products of reduction have been identified and if they were formed they would undoubtedly be rapidly decomposed under the conditions of the reaction, since all the products of catalytic hydrogenation are highly unstable in presence of mineral acids. A considerable amount of an uncrystallisable syrup is obtained, which contains chlorine and cannot be distilled without decomposition. This has yielded very small amounts of crystalline acylated products, an unsaturated *glycol*, $C_{10}H_{18}O_2$, m. p. 84°, and a *substance*, $C_{10}H_{19}O_3Cl$, m. p. 191°, which has the composition of a chlorotrihydroxymenthane. The identification of ascaridole-α-glycol as its *mono*- and *di-nitrobenzoates* indicates that some isomerisation to the dioxide has taken place.

By partial hydrogenation of ascaridole with one mol. of hydrogen, using a palladised charcoal catalyst, Richter and Presting (*Ber.*, 1931, **64**, 878) obtained Δ^2-*p*-menthene-1 : 4-diol, in which the peroxide structure alone is reduced and which does not react with titanous chloride. This is not, however, the sole product, and an oil has been isolated which is no doubt *dihydroascaridole* (V), formed by preferential hydrogenation of the ethylenic linkage, leaving the peroxide bridge intact. When partial hydrogenation is carried out in presence of platinum oxide instead of palladium, dihydroascaridole appears to be the only product. It contains no hydroxyl group, but, like the menthenediol, on further hydrogenation yields *cis*-1 : 4-terpin. On reduction by titanous chloride it gives rise to propane in about 90% yield and a corresponding amount of a substance, $C_7H_{12}O_2$, containing one hydroxyl group and forming a *mono*-p-*nitrobenzoate*. The second oxygen atom is neither hydroxylic nor ketonic, and is probably similar to the oxidic group in the isomeric form of ascaridole. The substance is stable in presence of potassium permanganate in neutral solution, but is readily oxidised by Beckmann's chromic acid mixture to the lactone of β-hydroxy-β-methyladipic acid (VII). It is therefore considered to be 1-*methyl*cyclo*hexan*-1-*ol* 3 : 4-*oxide* (VI).



(V.) (VI.) (VII.)

EXPERIMENTAL.

In the following experiments Zerewitinoff determinations of replaceable hydrogen can indicate only the hydrogen in hydroxyl groups and are shown as " OH%." The quantity of titanous chloride used or of iodine liberated is shown in c.c. of N-solution required by 1 g. of the substance, the calculated value for ascaridole being based on the addition of 4 atoms of hydrogen. Thus, by the titanous chloride method of estimation (Paget, *loc. cit.*) 1 g. of ascaridole is equivalent to 8·25 c.c. of N-solution, and by the B.P. method to 15·05 c.c. (calc., 23·8 c.c.).

Although chenopodium oil decomposes explosively on heating, it can be fractionally distilled at reduced pressure. Ascaridole thus obtained had b. p. 112—115°/20 mm., $d_{18^\circ}^{18^\circ}$ 1·0074, $[\alpha]_D$ $-2·3°$. Estimated by titanous chloride, it contained 100% ascaridole (Found : 1 g. = 8·25 c.c. of N-solution). It was dissolved in 2 vols. of light petroleum (b. p. 40—60°) and cooled in solid carbon dioxide with gentle stirring until, at about $-20°$, a good crop of crystalline matter separated. The supernatant solution was removed by suction, and the solid recrystallised twice more in the same way. The final crop (43%), freed from solvent by distillation, had m. p. 2°, b. p. 113—114°/20 mm., $d_{18^\circ}^{18^\circ}$ 1·0114, $[\alpha]_D$ $-0·03°$ [Found : by titanous chloride, 1 g. = 8·95 c.c. of N-solution; by B.P. method, 1 g. = 16·0 c.c. of N-solution; iodine absorption value (Wijs), 144·5. Calc. for ascaridole : 1 g. = 23·8 c.c. of N-solution; iodine absorption value, 151·2%]. It contained no replaceable hydrogen. These figures were not appreciably altered by crystallisation six more times from light petroleum or from 95% alcohol.

Reduction by Titanous Chloride.—Ascaridole (5 g.) in alcohol (5 c.c.) was added to a cold solution of 50 c.c. of titanous chloride (commercial 15% solution in 15% hydrochloric acid), diluted with 50 c.c. of water, and gently shaken while carbon dioxide was passed slowly through the flask. A gaseous product, which was collected over potassium hydroxide solution, amounted to 230 c.c. at N.T.P. It was wholly liquefied by cooling in solid carbon dioxide, and had b. p. $-37·5°$/754 mm. [Found : *M* (by density), 44·1. Calc. for propane : *M*, 44·0]. It reacted slowly with bromine in sunlight, without diminution of volume and with production of hydrogen bromide. The acid liquor was shaken with ether, and the extract washed successively with 1% solutions of sodium carbonate and sodium hydroxide. From the sodium carbonate washing was obtained by ether a small crystalline extract, which separated from benzene in colourless prisms, m. p. 191° [Found : C, 54·0; H, 8·55; Cl, 15·85; OH, 22·1. $C_{10}H_{16}Cl(OH)_3$ requires C, 53·9; H, 8·55; Cl, 15·95; OH, 22·9%]. It has not been possible, on the quantity available, to determine the constitution of this substance, but it has the composition of a *chlorotrihydroxymenthane*. A *mono*-p-*nitrobenzoate* was obtained from it, crystallising from chloroform in nearly colourless needles, m. p. 124° (Found : N, 3·7; Cl, 9·65. $C_{17}H_{22}O_6NCl$ requires N, 3·8; Cl, 9·55%). It was not reduced by catalytic hydrogenation, and it could not be prepared by addition of hypochlorous acid to Δ^2-*p*-menthene-1 : 4-diol. It does not therefore afford indication of the formation of this substance as an intermediate reduction product, which, as shown below, is a product of partial hydrogenation of ascaridole. The sodium hydroxide washings on acidification furnished *p*-cresol, which after distillation melted at 35° (Found: C, 78·0; H, 7·25. Calc.: C, 77·8; H, 7·4%). It was identified as the *p*-nitrobenzoate, m. p. 102° (Found: N, 5·55. Calc.: N, 5·45%), and α-naphthylurethane, m. p. 144° (Found: N, 5·1. Calc.: N, 5·1%). The yield of *p*-cresol was about 33%.

The oil remaining after washing with alkali still contained some chlorine and distilled only with decomposition. It was shaken with water, extracted once with light petroleum, and then exhaustively with ether. From the latter extract a small amount of an unsaturated *glycol* separated, crystallising in colourless needles, m. p. 84°, from chloroform–light petroleum [Found: C, 70·6; H, 10·6; OH, 17·3. $C_{10}H_{16}(OH)_2$ requires C, 70·6; H, 10·6; OH, 20·0%]. Admixture of Δ^2-*p*-methene-1 : 4-diol (m. p. 82°) depressed the m. p. to 67—70°. In presence of Adams's platinum oxide catalyst, it slowly absorbed 1 mol. of hydrogen (Found: 1 g. = 126 c.c. Required, 132 c.c.). The saturated *glycol* crystallised from benzene in white needles, m. p. 114°, depressed by admixture of *cis*-1 : 4-terpin (m. p. 117°), of terpin hydrate (m. p. 116°), or of *trans*-1 : 4-terpin (m. p. 137°).

The oily product from light petroleum and from ether was dissolved in dry pyridine and gently warmed with twice its weight (about 2 mols.) of *p*-nitrobenzoyl chloride, yielding an ester which, after crystallisation from ethyl acetate, melted at 174°, alone or mixed with *ascaridole α-glycol di-*p*-nitrobenzoate* (Found: C, 59·65; H, 5·0; N, 5·8. $C_{24}H_{24}O_9N_2$ requires C, 59·5; H, 5·0; N, 5·8%). *Ascaridole-α-glycol mono-*p*-nitrobenzoate*, prepared from ascaridole α-glycol and 1 mol. of *p*-nitrobenzoyl chloride in a similar way, formed colourless needles, m. p. 150°, from chloroform (Found: C, 61·0; H, 6·25; N, 4·3. $C_{17}H_{21}O_6N$ requires C, 60·9; H, 6·3; N, 4·2%). No further crystalline products were obtained from the syrupy residue.

Hydrogenation of Ascaridole.—Ascaridole (0·5 g.) in 10 c.c. of 95% alcohol was hydrogenated as described by Wallach (*loc. cit.*) (Found: 1 g. = 234 c.c. Calc. for $2H_2$, 266·6 c.c.), yielding *cis*-1 : 4-terpin, which was characterised by the preparation with *p*-nitrobenzoyl chloride in pyridine solution of a *mono-*p*-nitrobenzoate*, which formed pale yellow prisms, m. p. 117°, from methyl alcohol (Found: C, 63·7; H, 7·45; N, 4·65. $C_{17}H_{23}O_5N$ requires C, 63·55; H, 7·15; N, 4·35%), and a *di-*p*-nitrobenzoate*, which crystallised in pale yellow needles, m. p. 172°, from methyl alcohol–benzene (Found: C, 61·45; H, 5·7; N, 6·2. $C_{24}H_{26}O_8N_2$ requires C, 61·3; H, 5·5; N, 5·95%).

Ascaridole (20 g.) in 95% alcohol (20 c.c.) was hydrogenated in presence of 0·1 g. of Adams's platinum oxide catalyst, until the point was reached at which the rate of absorption slackened, corresponding with the addition of 1 mol. (Found: 1 g. = 134·0 c.c.). The product after filtration and removal of the solvent crystallised from 2 vols. of light petroleum cooled in ice–salt. *Dihydroascaridole* was thus obtained, m. p. 19·5°, b. p. 112—115°/18 mm., $[\alpha]_D$ ±0° (Found: C, 71·0; H, 10·8. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·6%). It contained no replaceable hydrogen and did not absorb iodine by the Wijs process, but was readily reduced by titanous chloride (Found: 1 g. = 10·6 c.c. of N-solution. Required, 11·8 c.c.). On further hydrogenation dihydroascaridole yielded *cis*-1 : 4-terpin quantitatively.

When ascaridole was partly hydrogenated in presence of palladised charcoal instead of platinum oxide (Richter and Presting, *loc. cit.*), and the product digested with light petroleum, a part (47%) was insoluble. Crystallised from light petroleum–chloroform, it had m. p. 82°, $[\alpha]_D$ ±0° [Found: C, 70·6; H, 10·85; OH, 20·65; iodine absorption value (Wijs), 132·0. Calc. for $C_{10}H_{16}(OH)_2$: C, 70·6; H, 10·6; OH, 20·0%; iodine absorption value, 149·3%], and is no doubt Δ^2-*p*-methene-1 : 4-diol. It was not reduced by titanous chloride. The *di-*p*-nitrobenzoate* crystallised from methyl alcohol in pale yellow needles, m. p. 130° (Found: C, 61·4; H, 5·4; N, 6·2. $C_{24}H_{24}O_8N_2$ requires C, 61·55; H, 5·1; N, 6·0%). The fraction of the reduction product which was soluble in light petroleum, after concentration and cooling in a freezing mixture, yielded dihydroascaridole (23%).

Reduction of Dihydroascaridole by Titanous Chloride.—Dihydroascaridole (5 g.) was treated with a solution of titanous chloride in an atmosphere of carbon dioxide as already described above. A gaseous product was evolved (601 c.c.), which was identified as propane [*M* (by density), 43·1. Yield, 91%]. The liquors were thoroughly extracted by ether, yielding an oil (3·5 g.), which distilled without decomposition, was readily soluble in water, and crystallised from *iso*propyl ether in colourless rods, m. p. 45°, b. p. 110°/5 mm. [Found: C, 65·7; H, 9·4; OH, 12·8. $C_7H_{11}O(OH)$ requires C, 65·6; H, 9·4; OH, 13·3%]. No semicarbazone could be obtained, but it gave a *mono-*p*-nitrobenzoate*, crystallising from *iso*propyl ether–ethyl acetate in yellow leaflets, m. p. 157° (Found: C, 60·7; H, 5·5; N, 5·05. $C_{14}H_{15}O_5N$ requires C, 60·6; H, 5·4; N, 5·05%). This substance is considered to be 1-*methyl*cyclo*hexan*-1-*ol* 3 : 4-*oxide* (VI)

It was not attacked by potassium permanganate in acetone solution, but was (2·0 g.) rapidly oxidised by Beckmann's chromic acid mixture (50 c.c.), yielding a lactone acid (2·3 g.), readily soluble in water. In cold aqueous solution 0·1858 g. was neutralised by 11·7 c.c. of N/10-baryta (M = 158·8. Calc. for $C_6H_9O_2{\cdot}CO_2H$, 158) and, on heating with an excess of baryta, by 23·5 c.c. The barium salt was readily soluble in water (Found: Ba, 44·6. Calc. for $C_7H_{10}O_5Ba$: Ba, 44·1%). The acid crystallised after some days in a vacuous desiccator in hygroscopic prisms, m. p. 49—52°, and this was not altered by admixture with a specimen of β-hydroxy-β-methyladipic acid lactone, prepared by the method of Duden and Freydag (*Ber.*, 1903, **36**, 953), which crystallised in the same way in a vacuous desiccator and melted at 50—52°.

The author thanks Messrs. D. Warren and R. G. Bardrick for assistance with experimental work and Messrs. A. Bennett and H. C. Clarke for micro-analyses.

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[*Received, April* 14*th*, 1938.