was no softening, *i. e.*, a good m. p. and the loss was negligible. Three more recrystallizations did not alter this m. p. in the least. A few crystals of the 95.5% yield, on dissolving in ethanol at 20° and adding of water to incipient crystallization, cooling to 0°, recrystallized and were found to melt at 169–170.5° also. *Anal.* Calcd. for $C_{14}H_{24}N_2O_3$: C, 62.63; H, 9.01; N, 10.44. Found: C, 62.50; H, 9.08; N, 10.44, 10.34.

2 - Keto - 4 - phenyl - 5 - carbethoxy - 6 - methylhexahydropyrimidine.—The acid chloride reacted with ethanol to yield a crude ester of m. p. 176–177.5°. One recrystallization raised the m. p. to 178–179.5° and two more did not alter it. *Anal.* Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.07; H, 6.92. Found: C, 63.75; H, 7.03. This ester, on saponification, etc., yielded the original acid of m. p. 255.5–257°.

2 - Keto - 4 - (2 - phenylethyl) - 5 - carbethoxy - 6 - methylhexahydropyrimidine.—The crude ester obtained by reaction of the acid chloride with ethanol melted at 145–146°. One recrystallization raised the m. p. to 145.5–147° and two more did not alter it. *Anal.* Calcd. for $C_{16}H_{22}N_2O_3$; C, 66.16; H, 7.64. Found: C, 65.65; H, 7.77.

Summary

In this preliminary study on the hydrogenation of cyclic ureides under elevated temperatures and pressures, it has been found that 2-keto-1,2,3,4-tetrahydropyrimidines were reduced to isomeric 2-ketohexahydropyrimidines over copper–barium–chromium oxide catalyst at 200°. Hydrogenations of these pyrimidines over nickel catalysts at temperatures up to 175° have been extended.

All the 2-keto-4-R-5-carbethoxy-6-methylhexahydropyrimidines were saponified to the 5-carboxypyrimidines in good yields. These 5-carboxypyrimidines, after reaction with thionyl chloride and subsequent treatment with ethanol, yielded ethyl esters, which differed widely in melting point, but were isomeric with the corresponding esters obtained by hydrogenation.

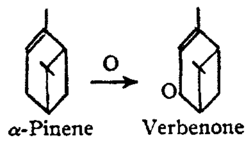
NEW HAVEN, CONN. RECEIVED JANUARY 29, 1934

Effect of Selenious Acid on Terpenes. The Synthesis of Carvotanacetone and Δ-3-Menthenone-5

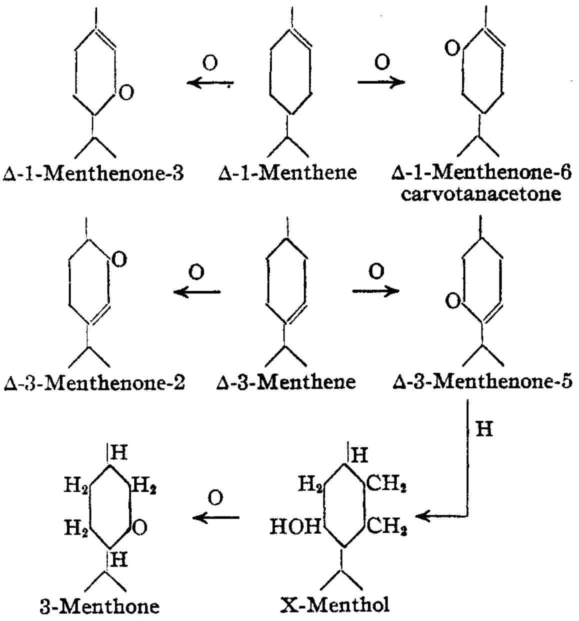
BY ERICH BORGWARDT AND ERWIN SCHWENK

In a previous publication[1] it was shown that it is possible to oxidize α-pinene to verbenone using selenious oxide as an oxidizing agent.

A further investigation has shown the possibility of using this oxidizing agent in the oxidation of other unsaturated compounds. As a new, and from the standpoint of synthetic chemistry, most interesting fact, it has been found that as the main reaction, compounds containing one double bond in a six-membered ring are oxidized in such a manner that only one of the methylene groups adjacent to the double bond is attacked. In the above cited case of α-pinene[2] it is clear that no other compound than verbenone could be isolated.



In the cases of both Δ-1-menthene and Δ-3-menthene, recently studied, two possibilities are open



In each case, however, but one ketone could be found. The product derived from the Δ-1-menthene was identified as carvotanacetone,[3] which through this reaction becomes readily available. The oxidation of the Δ-3-menthene gave a

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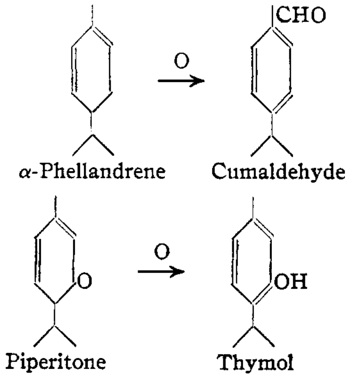
(1) Schwenk and Borgwardt, *Ber.*, **65**, 1501 (1932).

(2) O. Wallach, "Terpene und Campher," Veit und Co., 1914.

(3) Semmler, *Ber.*, **27**, 895 (1899).

new ketone, which by hydrogenation of the double bond and reduction of the carbonyl group yielded a menthol which on subsequent oxidation of the secondary alcohol group was transformed into a menthone and identified as 3-menthone by means of its thiosemicarbazone with m. p. 139–142°. Preparation from Δ-3-menthone gave m. p. 140°. The oxidation product of the Δ-3-menthene must therefore have the constitution of a Δ-3-menthenone-5.

An entirely different course is taken by the reactions in the case of phellandrene[2] and piperitone,[4] the phellandrene yielding cumaldehyde[5] and the piperitone yielding thymol[6]



It must be noted that in these cases the selenious acid has acted not only as an oxidant but also as a dehydrogenating agent.

It would seem that interesting results would develop from a thorough study of the by-products of the above reaction, as part of the original material reacted to form compounds other than the above mentioned.

Besides compounds containing selenium[7] there has been found as by-products of the oxidation of both the menthenes a considerable amount of substances containing oxygen and apparently isomeric with the isolated ketones, which were the chief products of the reaction. As these isomeric compounds are changed by simple heating with dilute sulfuric acid into saturated cyclic ketones, it is concluded that the unknown products are oxides formed by the addition of oxygen to the double bond. There is some doubt, however, about the constitution of these compounds, as it is known that the double bond in the menthenes readily can be rearranged under the influence of acids and other catalysts. No definite conclusion has been reached as to the constitution of these substances, the oxygen possibly adding only to the rearranged molecules.

Experimental Part

Δ-1-Menthene and Selenious Acid.—To 1 kilogram of Δ-1-menthene in 1 liter of alcohol (denatured with toluene) at 80°, a solution of 800 g. of selenious acid in 3.5 liters of alcohol was added dropwise with stirring over a period of nine hours. The whole was refluxed for nine hours and the black metallic selenium (370 g.) then filtered off by suction. Two thirds of the alcohol was removed by distillation; 720 g. of a light yellow oil was obtained by steam distillation of the remainder of the filtrate. This oil was stirred with a solution of 800 g. of sodium sulfite in 2 liters of water at 60–70°, the mixture being kept neutral with acetic acid; 432 g. remained insoluble, the other 288 g. having formed a soluble sodium sulfite compound. The sulfite solution was stirred with approximately 200 cc. of benzene, the benzene layer removed, the solution made strongly alkaline with sodium hydroxide and steam distilled; 231 g. of an oil, with caraway-like odor, boiling at 95° (7–8 mm.) was obtained. It formed a semicarbazone m. p. 177–178°,[2] and otherwise exhibited all the properties of carvotanacetone. The portion insoluble in sulfite was fractionated: Fraction 1, b. p. 56–70° (9 mm.) much unchanged menthene; Fraction 2, b. p. 83–90° (9 mm.) treated with sulfite and gave oil of b. p. 63–65° (0.25 mm.).

Anal. Calcd. for $C_{10}H_{18}O$: C, 78.0; H, 11.7. Found: C, 77.8; H, 11.7.

It formed no semicarbazone and no acyl derivatives. Therefore oxygen was present neither as a hydroxyl nor carbonyl group. Analysis supports the presumption that we are dealing with previously unknown 1,2-oxidomenthene; this supposition is confirmed by the changes this substance undergoes on boiling with dilute sulfuric acid. An oil was obtained which yielded a semicarbazone of m. p. 140–142°. It therefore seems likely that we are dealing with an oxide which after rearrangement forms a saturated ketone. Fraction (3) b. p. 87–100° (2.5 mm.) was not investigated.

Δ-3-Menthene and Selenious Acid.—Solutions of 810 g. of Δ-3-menthene in 900 cc. of alcohol and 640 g. of selenious acid in 2750 cc. of alcohol were stirred together and heated at 80° for twenty-four hours; precipitated selenium, 315 g.; quantity of oil obtained from steam distillation, 682 g. The oil was treated with 450 g. of sodium sulfite in 1500 cc. of water and produced an insoluble portion of 572 g. Besides some unchanged menthene, two fractions obtained: Fraction (1) b. p. 74–83° (7 mm.) was not investigated. Fraction (2) b. p. 89–93° (10 mm.): this furnished a semicarbazone m. p. 172°, which after decomposition with oxalic acid gave an oil of b. p. 107–108° (12.5 mm.); this oil gave a semicarbazone of m. p. 176–177°. After reduction with sodium and alcohol and subsequent oxidation by means of chromic acid, this gave an oil which had a marked menthone-like odor, the thiosemicarbazone of which had m. p. 139–142°. Since the thiosemicarbazone of the inactive Δ-3-menthone which was prepared melted at 140°, it is likely that the unsaturated ketone obtained from Δ-3-menthene was Δ-3-menthenone-5.

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(4) Reed and co-workers, *J. Chem. Soc.*, **125**, 1291 (1924).

(5) Perkin, *ibid.*, **69**, 1199 (1896).

(6) Meldrum, *Chem. News*, **111**, 229 (1915).

(7) Stamm and Gossrau, *Ber.*, **66**, 1558 (1933).

That portion of the oil (79 g.) which was soluble in sulfite had a caraway-like odor, b. p. 92–96° (9 mm.) and formed a semicarbazone with well defined m. p. 148–161°.

α-Phellandrene and Selenious Acid.—Two hundred grams of phellandrene in 400 cc. of alcohol, was treated as above with 160 g. selenious acid in 800 cc. alcohol; solution heated for 24 hours; precipitated selenium, 53 g.; quantity of oil from steam distillation, 135 g.; non-volatile with steam, 96 g.

On fractionating first, distillate was obtained boiling up to 80° (11 mm.), $n_D^{16°}$ 1.492: had a cymene-like odor; the main fraction consisted of a colorless oil b. p. 80–98° (8 mm.), which on further fractionation boiled at 68–70° (0.8 mm.). It formed a semicarbazone of m. p. 207–211° and proved to be the semicarbazone of cumaldehyde.[8] The m. p. of the mixture of this substance and a standard preparation showed no depression.

Piperitone and Selenious Acid.—Fifty grams of piperitone dissolved in 10 cc. of alcohol was treated with 40 g. of selenious acid in 200 cc. of alcohol. Heated twenty-four hours, precipitated selenium filtered off; quantity of oil from steam distillation, 39 g., b. p. 79–82° (0.8 mm.), was nearly completely soluble in sodium hydroxide, could be precipitated from the latter with acids, and then had a b. p. 110–113° (11 mm.) after which it solidified to a crystalline cake m. p. 47–49°. The m. p. of this substance mixed with thymol showed no depression.

Summary

Δ-1-Menthene oxidized with selenious acid gave carvotanacetone; Δ-3-menthene gave a ketone which by means of derivatives could be shown to be Δ-3-menthene-5-one. As by-products oxides of the menthenes were obtained. α-Phellandrene and piperitone were not only oxidized, but also dehydrogenated by the same oxidant to aromatic compounds, and yielded, respectively, cumaldehyde and thymol.

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[8] St. Warunis and Lekos, *Ber.*, **43**, 654 (1910).

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, TEACHERS COLLEGE, COLUMBIA UNIVERSITY]

Larger Yields of Crystalline Antineuritic Vitamin

BY ROBERT R. WILLIAMS, ROBERT E. WATERMAN AND JOHN C. KERESZTESY

The isolation of the antineuritic vitamin has been reported by several groups of workers.[1] Crystalline hydrochlorides of very similar characteristics having the property of curing or preventing polyneuritis in rats, pigeons or rice birds in doses of the order of 1 to 10 micrograms have been obtained from rice polish, bakers' yeast and brewers' yeast by a number of independent groups of workers using a variety of procedures. The chemical study of this hydrochloride is obviously justified even though one may entertain doubts that it represents the fully isolated vitamin. It is the object of this paper to record the results of our recent efforts to obtain the substance in quantity for purposes of further investigation.

The progress of isolation has been gaged at every step by injection tests on polyneuritic rats according to the method of M. I. Smith.[2] The experience of this Laboratory with this method is recorded elsewhere.[3] We have attempted by such tests to trace and progressively eliminate the losses which we believe occur in the course of all fractionation schemes and thus have evolved the following procedure of isolating the crystals. It produces several fold larger yields than heretofore reported.

Preparation of Activated Fullers' Earth

Our raw material, rice polish, has been assayed by boiling 25 g. of the polish three times with 100 cc. of 70% methyl alcohol acidulated to *P*H 4.5 and filtering. The combined extracts are evaporated *in vacuo* to 25 cc. volume. This solution is filtered, neutralized and injected. Repeated tests by this method on several lots of polish have shown that the extract of 0.25 g. of polish represents the minimum curative dose for rats. The activity of rice polish may therefore be taken as about 4000 doses per kilo.

On the large scale 150 to 200 kilos of polish are mixed with 4000 liters of water in a wooden tank equipped with a stirrer. The suspension is brought to *P*H 4.5 by addition of sulfuric acid; 10 liters of toluene are added to prevent bacterial action, the mixture is stirred for five to six hours and allowed to settle for forty-eight hours. About 3000 to 3500 liters of clear liquid is pumped off and the remaining mass of wet polish is stirred up again with the addition of water to replace the extract withdrawn. After another stirring and a settling period the second extract is drawn off as before. In the meantime, the first extract has been stirred for an hour with 4 kilos of fullers' earth for each 100 kilos of polish taken. The fullers' earth is allowed to subside and the clear extract

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[1] B. C. P. Jansen and W. F. Donath, *Mededeel. Dienst Volksgezondheid Nederland. Indië*, pt. 1, 186 (1926); A. Windaus, *Nachrichten v. der Gesell. der Wissenschaften zu Göttingen*, 209 (1932); S. Ohdake, *Proc. Imp. Acad. Tokyo*, **7**, 102 (1931); A. Seidell and M. I. Smith, THIS JOURNAL, **55**, 3380 (1933); W. K. Kinnersley, J. R. O'Brien and R. A. Peters, *Biochem. J.*, **27**, 232 (1933).

[2] M. I. Smith, *U. S. Pub. Health Repts.*, **45**, 116 (1930).

[3] R. E. Waterman and M. Ammerman, to be published shortly.