rated to dryness *in vacuo*. The residue was recrystallized from water-alcohol-ether to give 4.55 g. (27%) of pure 4(5)-amino-5(4)-imidazolecarboxamide hydrochloride: m.p., 254° (lit.,[7a] 255–256°); $\lambda_{max}^{pH\ 7}$ 277 mμ (ε12,300).

4(5)-Amino-5(4)-imidazolecarboxamide hydrochloride. Method B (catalytic reduction). To 3 g. of 30% palladium-on-charcoal catalyst[10] wetted with 6 ml. of water and 10 ml. of methyl cellosolve in a 500-ml. pressure bottle was added phenylazomalonamamidine hydrochloride (30.0 g.) suspended in 270 ml. of 98% formic acid.[11] Reduction in a Parr shaker required 3–4 hr. The catalyst was removed by filtration and the formic acid by evaporation *in vacuo*. The resulting white solid was triturated with absolute ethanol (50 ml.) to remove the by-product formanilide and traces of hypoxanthine. The residue, practically pure 4(5)-formylamino-5(4)-imidazolecarboxamide, was suspended in 1*N* hydrochloric acid (150 ml.), and the mixture was refluxed for 15 min.

This solution was evaporated to dryness *in vacuo* and the residual white solid dried *in vacuo* over phosphorus pentoxide: yield, 14.4 g. (71%); m.p., 256°; $\lambda_{max}^{pH\ 13}$ 277 mμ (ε 12,500). Three other runs gave an average yield of 70%.

An aqueous solution of 4(5)-amino-5(4)-imidazolecarboxamide hydrochloride (500 mg.) was converted to the free base by treatment with Dowex 1(carbonate form); yield, 218 mg. (56%); m.p. 170–171° (lit.[12] 169.8–171.4°).

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(10) Baker and Co., Inc.

(11) When 98% formic acid was added to the dry catalyst, a violent reaction ensued. It was necessary with some batches of phenylazomalonamamidine to pretreat the solution with a portion of catalyst which was then replaced with fresh catalyst before reduction. In all cases this pretreatment increased the rate of reduction.

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Preparation of Hydroperoxide by the Autoxidation of 4-Vinylcyclohexene

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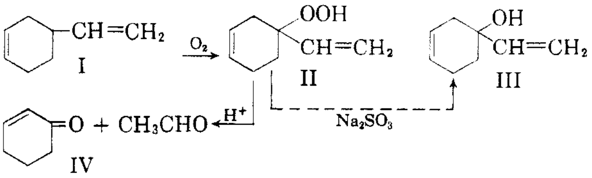
Received September 2, 1958

In 1911, Lebedew and Skawronskaja[1] prepared 4-vinylcyclohexene (I) by dimerizing butadiene and observed that it readily took up air. This observation is in agreement with our present knowledge concerning the autoxidation of olefins which indicates that the ease with which olefins react with molecular oxygen, forming hydroperoxide initially, depends upon the presence of reactive allylic hydrogen.[2] 4-Vinylcyclohexene has three positions alpha to a double bond where oxidation may be expected. The rate of its uncatalyzed oxidation and the isolation of hydroperoxide and alcohol fractions from the oxidation product is reported in this paper.

The identification of II in the hydroperoxide isolated indicates the high reactivity of ring hydrogen activated by a vinyl group. Structure II was demonstrated by acid decomposition of the hydroperoxide to 2-cyclohexenone (IV) and acetaldehyde. If the hydroperoxy function were located elsewhere on the ring, fission of the vinyl group would not be anticipated. The formation of 2-cyclohexenone is expected since it has been reported[3] that the rearrangement of 3-cyclohexenone, the first predicted product, to the conjugated ketone occurs readily under acid conditions. No evidence for the existence of other hydroperoxides was obtained.



Oxidations conducted at 90° give rise to the alcohol III which distills before the hydroperoxide and has an infrared spectra indistinguishable from it. The relative yields of alcohol and hydroperoxide obtained at different reaction times and temperatures indicate that the alcohol arises by thermal decomposition of the hydroperoxide. The same alcohol, as demonstrated by its spectra, may be prepared by reduction of the hydroperoxide with sodium sulfite, a reagent which is known to selectively reduce the hydroperoxide group to the hydroxyl group.[4] Hydrogenation of III required two moles of hydrogen but the products formed were not identified. The lack of any distinguishing differences between the spectra of II and III confirms the statement of Philpotts and Thain,[5] who studied the spectra of a series of alcohols and their corresponding hydroperoxides, that at higher molecular weights it is difficult to distinguish between an alcohol and its hydroperoxide.

The rate at which 4-vinylcyclohexene reacts with oxygen was determined at 70° and 90°. The oxidation begins immediately and the rate increases until it becomes constant and maximum at 20% reacted. The maximum rate is 1.6 times faster than that of cyclohexene under the same conditions. The rapidity of this oxidation can best be seen by comparing it to the frequently studied oxidation of cumene which has a comparable rate only when catalyzed by cobalt naphthenate. The formation of hydroperoxide was followed, as is commonly done, by iodometric analysis of the reaction solution. Only an approximate picture of the relationship between hydroperoxide formation and oxygen consumption was obtained in this way

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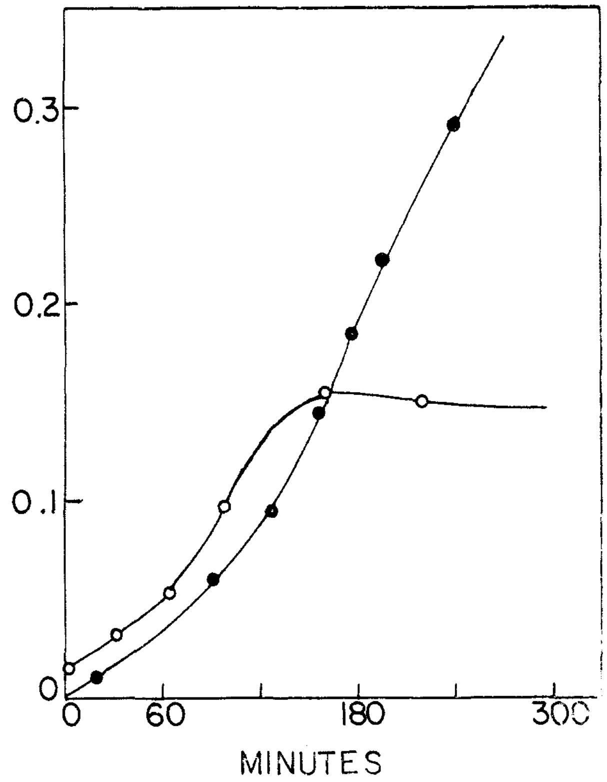

Fig. 1. Oxidation of 4-vinylcyclohexene at 90°. Closed circles, moles of oxygen reacted per mole of olefin charged; open circles, fraction of reaction mixture titrating as vinylcyclohexene hydroperoxide

(Fig. 1) since evaluation of the analytical procedure indicated it to be unreliable, probably giving low results. It is certain, however, that most of the oxygen consumed appears as hydroperoxide in the early stages of the reaction. The attainment of a steady state concentration of hydroperoxide corresponds with the attainment of a constant oxidation rate.

EXPERIMENTAL

Oxidation of 4-vinylcyclohexene. The apparatus consisted of a reaction flask fitted with a condenser, gas inlet, and an aniline point thermometer covering the appropriate temperature range. The flask was heated with a Glas-Col mantle and the temperature controlled to ±0.2° with a Thermocap relay. Stirring at over 1000 r.p.m. was provided by a Teflon covered magnetic stirring bar. Oxygen was fed into the system through a precision wet type pressure governor, a wet test meter, and a tower filled with Drierite. The exit gas passed from the outlet condenser through a Dry Ice trap, a drying tower, a carbon dioxide absorption bulb filled with Ascarite, another drying tower, a wet test meter, and an exit capillary.

A carefully cleaned 100-ml. flask was filled with 43.28 g. (0.4 mole) of redistilled Phillips "99 mole %" 4-vinylcyclohexene, n_D^{20} 1.4630. The olefin was quickly heated to 70°, rapid stirring initiated, and the oxygen admitted. Adjustment of the pressure governor and exit capillary gave an exit gas of from 8 to 9 ml./min. The oxygen absorbed was determined at frequent intervals from the difference in the inlet and exit wet test meter readings. The reaction becomes exothermic, and provisions must be made to cool the outside of the flask with air to allow the Thermocap to operate. The production of heat was not investigated but since it appeared to be somewhat greater than anticipated from work with other olefins, there is some possibility that polymerization or hydroperoxide decomposition is involved.

A plot of the oxygen consumed against time indicates that the rate gradually increases and becomes constant at approximately 600 min. at 70° and from 160 to 180 min. at 90°. The maximum rates for these temperatures in moles of oxygen absorbed/mole initial olefin, sec. are 1.4×10^{-5} and 3.4×10^{-5}, respectively.

Oxidation of cyclohexene and cumene. In the same manner, 32.85 g. (0.4 mole) of redistilled cyclohexene, n_D^{20} 1.4451, was oxidized at 70°. A constant rate of 8.7×10^{-6} was attained in approximately 450 min. The oxidation of pure cumene, n_D^{20} 1.4910, was attempted at 90° but no reaction was observed in 435 min. Negligible reaction occurred with cumene containing 2% cumene hydroperoxide as initiator in 420 min. but in the presence of 1% by weight of Nuodex cobalt naphthenate, cumene showed a maximum rate of 3.7×10^{-5} after an induction period of 120 min.

Rate of formation of hydroperoxide. The formation of hydroperoxide was followed by duplicating rate runs and removing samples for analysis at intervals. At 90°, a constant concentration of hydroperoxide was reached in 160 min. The peroxide values obtained depended on the method of analysis, the highest steady state concentration being 22% by method C and 15% by method A (see last section—values reported in this paper were obtained by A, unless otherwise indicated). The separation of a light yellow oil on the walls of the flask became perceptible at approximately the time in which the maximum hydroperoxide concentration was reached but these phenomena are not associated since the concentrations of hydroperoxide in the oil and the solution were nearly the same.

Isolation of products. (a) The reaction product from the oxidation of 108.2 g. (1.0 mole) of 4-vinylcyclohexene for 245 min. at 90° was poured off from 22.6 g. of insoluble oil and simply distilled under reduced pressure. After removal of the 4-vinylcyclohexene, 8.2 g. of distillate (46% hydroperoxide) was collected between 55 and 78° below 1 mm. Redistillation through a 1 ft. semimicro Vigreux gave 2.5 g. of alcohol at 46°/1 mm., titrating for 3.5% hydroperoxide, and 2 g. of hydroperoxide, titrating for 60% hydroperoxide, at 50–55°/0.5 mm.

(b) The oxidation product obtained by oxidizing 1189 g. (11 moles) of 4-vinylcyclohexene for 190 min. at 90° was removed from an insoluble oil coating the reaction flask, and the unreacted 4-vinylcyclohexene distilled off at 30 mm. through a 2 ft. unpacked column. After adding 0.5 g. of 2,6-di-*tert*-butyl-*p*-cresol, 255 g. of residue was transferred to a 500 ml. flask and the following fractions collected at 0.5 mm.: (1) 25–41°, 10.8 g., 2.3% hydroperoxide; (2) 41–52°, 8.9 g., 6.6% hydroperoxide; (3) 53–67°, 31 g., 23% hydroperoxide; (4) 67°, 26 g., 46% hydroperoxide (76.8% by method C); (5) 67–70°, 14.3 g., 51.9% hydroperoxide. The distillation was discontinued at this point because of decomposition evidenced by a slight rise in pressure, in spite of continuous pumping, and a sharp rise in pot temperature. The pot residue analyzed for 38% hydroperoxide. All the distillates had identical infrared spectra.

(c) Oxidation of 216.4 g. (2.0 moles) of 4-vinylcyclohexene at 90° for 22.4 hr. gave an increase in weight of 40.6 g. and resulted in the formation of approximately equal volumes of immiscible layers. Distillation gave 4 g. of water, 84.3 g. of 4-vinylcyclohexene, 38.5 g. of alcohol (6% hydroperoxide), 114.6 g. of red pot oil containing 3.9×10^{-4} mole active oxygen/g., and 14.3 g. of gray residue. A brown powder could be obtained from the red oil by taking it up in ethanol and reprecipitating with ether. The powder dissolved on warming with alkali and could be reprecipitated with acid. It could not be purified by recrystallization and became gummy on further treatment.

(d) At 50°, 432.7 g. (4.0 moles) of 4-vinylcyclohexene was oxidized for 48 hr. with an off gas of 18 ml./hr. to give an oxidate analyzing for 9.4% hydroperoxide. Distillation gave a forerun of 383 g. of 4-vinylcyclohexene, 23 g. of hydroperoxide (68.5%) at 64–66°/0.5 mm., 20.3 g. of pot residue and 3 g. of trap residue. The hydroperoxide was fractionated in a 1-ft. semimicro Vigreux column to give 9 ml. of distillate boiling at a constant 55°/0.5 mm. with n_D^{25} 1.4951 and D_4^{20} 1.0164 and analyzing for 81% hydroperoxide. M_D is 40.9 (calculated M_D 39.2).

Reduction with sodium sulfite. To 50 ml. of a stirred 25% solution of sodium sulfite, cooled in an ice bath, was added dropwise 14.1 g. (0.1 mole) of hydroperoxide of 76.8% purity (method C). After 1 hr. the reaction was allowed to reach room temperature and stirred for 1.5 hr. more. The product was extracted with ether and dried over Drierite. After removing the ether, 10 g. of distillate was collected at 46–49°/0.5 mm. It analyzed for 5.25% hydroperoxide (method C). Its infrared spectra were superimposable on that of the starting hydroperoxide, both spectra being obtained with a Baird IR model 4-55 using a 0.03-mm. cell. Both spectra showed a band at 5.8μ indicating an estimated carbonyl impurity of less than 5%.

Acid decomposition. A solution of 14.1 g. (0.1 mole) of hydroperoxide (76.8%—method C) in 80 ml. of glacial acetic acid containing 0.16 ml. of 70% perchloric acid was allowed to stand overnight at room temperature. A slurry of 26 g. of sodium bicarbonate in 150 ml. of water was added dropwise, and the gas evolved passed through a saturated solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid. The precipitate formed was identified as acetaldehyde 2,4-dinitrophenylhydrazone by a mixed melting point determination. The decomposition mixture was extracted with ether and the ether washed with sodium bicarbonate and water and dried. Distillation through a Vigreux column gave 5.1 g. of ketone at 64–70°/4 mm., n_D^{20} 1.4818 and a pot residue of 5.0 g. of black tar.

The infrared spectra of the distillate showed the expected bands at 6.0μ and 6.1μ as well as a band at 5.8μ probably due to the unconjugated 3-cyclohexenone. Absorption due to hydroxyl, vinyl unsaturation, or aldehyde carbonyl (C—H stretching) was absent. The ultraviolet spectra showed the reported[3] max. 225 mμ for 2-cyclohexenone. The semicarbazone melted at 161–162° (reported m.p. 161°, 163°) after one recrystallization from water. The 2,4-dinitrophenylhydrazone after several recrystallizations from alcohol, yielded cerise crystals melting at 180–181° (rapid heating). An authentic sample of 2-cyclohexenone, prepared by oxidizing cyclohexene,[6] yielded an orange derivative melting at the reported[3] 160–161°. Its melting point was not depressed by admixture with the decomposition product derivative. Both 2,4-dinitrophenylhydrazones showed maxima in the ultraviolet at 377 mμ (ϵ = 21,000), 285 mμ and 250 mμ and a minimum at 310 mμ.

Fractionation of the ketone, from a similar experiment, through a spinning band column gave a fraction at 41°/1 mm. n_D^{25} 1.4950, which had a carbonyl equivalent weight of 99 (calculated for cyclohexenone 96) by hydroxylamine titration.[7]

Hydrogenation. Fifteen g. of alcohol, containing 6.34 m. eq. of hydroperoxide impurity, was hydrogenated at 60 lb. pressure using 170 ml. of ethanol as solvent and 0.5 g. of rhodium on alumina as catalyst. The absorption of hydrogen ceased after 0.13 mole was consumed. With 0.2 g. of platinum oxide, a total of 0.256 mole of hydrogen was used. Addition of fresh catalyst did not result in any further reduction. Compensating for the reduction of the hydroperoxide impurity, the hydrogen consumed was 0.242 mole; calculated for vinylcyclohexenol 0.240 mole.

Fractionation of the reduction product gave the following fractions after removal of the solvent: (1) 2.3 g. 100–107.5°/50 mm., n_D^{25} 1.4522; (2) 4.4 g., 107.5–111.5°/50 mm., n_D^{25} 1.4500; (3) 3.8 g., 111.5–119.5°/50 mm., n_D^{25} 1.4600.

Analysis of hydroperoxide. Approximately 0.5 g. samples of oxidate were analyzed by refluxing in isopropyl alcohol containing 1 ml. of saturated potassium iodide and titrating the iodine released with sodium thiosulfate (A). The arsenious oxide procedure gave equivalent results.[7] Other iodometric methods were checked using approximately 0.1 g. samples of distilled hydroperoxide. The variations in conditions and the percentage vinylcyclohexene hydroperoxide found for the identical liquid are: (A) 49.1%; (B) 0.5 g. powdered potassium iodide in 100 ml. isopropyl alcohol, 10 ml. acetic acid, 10 ml. acetic anhydride, reflux 30 min., 46.1%; (C) 0.5 g. powdered potassium iodide in 25 ml. acetic acid, 60° for 30 min., 76.8%; (D) as in C, dark for 120 min., 64%; (E) as in C with 1 ml. saturated potassium iodide, 51.9%. Elemental analysis of this sample assuming the remaining component to be vinylcyclohexenol gives agreement with method C. Calcd. for 76.82% $C_3H_{12}O_2$ and 23.18% $C_3H_{12}O$: C, 70.20; H, 8.93. Found: C, 70.09; H, 8.87.

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Potential Purine Antagonists. XVIII. Preparation of Some 6-Alkylthiopurines and 4-Alkylthiopyrazolo[3,4-*d*]pyrimidines[1]

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Received September 2, 1958

Since 6-methylthiopurine has been shown to inhibit R C carcinoma in mice,[2] a number of additional 6-alkylthiopurines have been synthesized in our Laboratory. Since antitumor activity has recently been found with various derivatives of pyrazolo[3,4-*d*]pyrimidine,[3] it seemed of interest to prepare analogous isomeric 4-alkylthiopyrazolo-[3,4-*d*]pyrimidines to see if these derivatives would possess antitumor activity.

Skinner, Shive, *et al.*[4,5] have previously reported the preparation of several 6-alkylthiopurines by alkylation of 6-purinethiol with the appropriate alkyl halide.

Recent preparation of 1-methyl-4-methylthiopyrazolo[3,4-*d*]pyrimidine[6] from 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine[6] and methanethiol in a

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(1) Supported in part by research grant CY-4008 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

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