Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52, H, 7.53; N, 9.52. Found: C, 77.37 H, 7.62 N, 9.36.

The *oxime*, prepared by refluxing the ketone with hydroxylamine hydrochloride and pyridine in ethanol, was recrystallized from methanol, in which it is barely soluble. M.p. 316–319° dec.

Anal. Calcd. for $C_{19}H_{23}N_3O$: N, 13.6. Found: N, 13.9.

Yohimbane. 16-Ketoyohimbane (0.46 g.), 0.2 g of sodium hydroxide, and 3.0 ml. of 85% hydrazine hydrate were refluxed for 70 min. in 8.0 ml. of diethylene glycol. The condenser was removed, and water and hydrazine allowed to distill until the temperature reached 197°. The solution was refluxed at this temperature for 4 hr., diluted with water, and extracted with chloroform. The extracts were washed with water, dried over magnesium sulfate, and evaporated. Sublimation of the residue at 150° and 0.01 mm. gave 0.33 g (75%) of light yellow crystals. Recrystallization from ethanol yielded colorless needles, m.p. 204–206° alone, or mixed with an authentic sample of yohimbane.[6]

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Ozonization of Methylene Chloride and Chloroform[1]

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In studying the preparation of 3-ketobisnor-4-cholen-22-al by the selective ozonolysis of 4,22-stigmastadien-3-one[2] and 4,22-ergostadien-3-one[3] at −78° important new observations were made concerning the behavior of the solvents, methylene chloride and chloroform, towards ozone. This information should be useful to others who are planning to use ozonolysis as a preparative reaction for aldehydes.

As solvents for the above reaction acetic acid, formic acid, methanol, carbon tetrachloride, and ethyl acetate[4] were eliminated for various reasons and the choice was between methylene chloride and chloroform. Furthermore, since selective ozonolysis of the side-chain double bond was desired, it was important to know how much of the ozone was reacting with the solvent.

These solvents were studied by a method somewhat different from that employed by Greenwood,[5] and designed to show how much ozone dissolved in the solvent as well as the amount which reacted with it. The solvents were ozonized at a constant, known rate. The dissolved ozone which imparted an intense blue color was then swept out by a stream of nitrogen and the amount of ozone which had reacted with the solvent was determined by difference. These results are recorded graphically in Fig. 1.

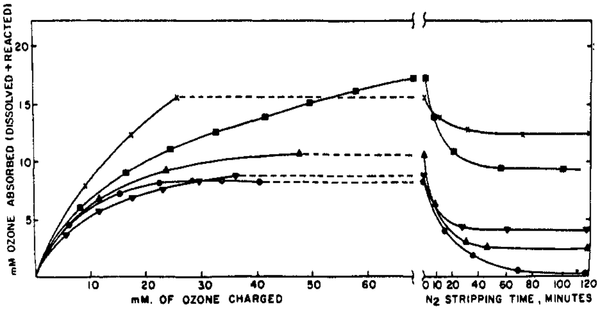

FIG. 1. OZONE ABSORBED BY SOLVENTS AND THE AMOUNT RECOVERABLE BY NITROGEN SPARGING. (⊙–Methylene chloride; △–methylene chloride + pyridine, ⊡–methylene chloride + diphenyl sulfoxide; x–methylene chloride + pyridine 1-oxide, ▽–chloroform.)

The curve obtained from the treatment of stabilized chloroform at −60° with ozone shows that this solvent underwent some attack by ozone. This attack was probably on the ethanol, which was present as the stabilizer, and could account for the acidity observed earlier in these laboratories[6] when chloroform was used as a solvent for ozonolysis of various steroidal olefins and enol acetates.

Ozone attack on methylene chloride at −78° was negligible, a saturated solution about 0.033*M* in ozone being formed from which all of the ozone could be recovered.

The inclusion of an organic base in the ozonolysis solvent for its acid-binding ability has been described[2,6,7] to be beneficial, resulting in higher yields.[8] Solutions of methylene chloride containing about 1% of the Lewis bases pyridine, diphenyl sulfoxide, and pyridine oxide were investigated in a similar manner. All of them consumed some ozone, the amount increasing in the order mentioned. Further investigation showed that the bases were not destroyed but probably only formed salt-like compounds (I) or complexes (II) with the ozone

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(1) Included in part in a paper presented before the First International Ozone Conference, Chicago, Ill., Nov. 28–30, 1956.

(2) F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **72**, 2617 (1950).

(3) D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, J. E. Stafford, R. L. Pederson, and A. C. Ott, *J. Am. Chem. Soc.*, **77**, 1212 (1955).

(4) In ethyl acetate the yield of aldehyde was greatly lowered and large amounts of the corresponding acid were formed.

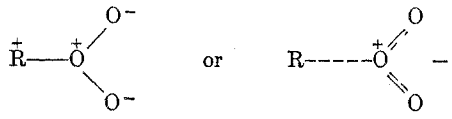
(5) F. L. Greenwood, *J. Org. Chem.*, **10**, 414 (1945).

(6) (a) F. W. Heyl, A. P. Centolella, and M. E. Herr, *J. Am. Chem. Soc.*, **69**, 1957 (1947); (b) F. W. Heyl and M. E. Herr, U.S. Patent **2,554,986** and U.S. Patent **2,601,287**; (c) F. W. Heyl and A. P. Centolella, U.S. Patent **2,623,052**.

(7) (a) W. Logemann and H. Dannenbaum, U.S. Patent **2,344,992**; (b) W. L. Ruigh, U.S. Patent **2,413,000**.

(8) The yield of 3-ketobisnor-4-chloenaldehyde from the ozonolysis of 4,22-ergostadien-3-one was 70% in chloroform. [A. F. Daglish, J. Green, and V. D. Poole, *J. Chem. Soc.*, 2627 (1954).] compared with 94.5%[3] in methylene chloride-pyridine.

which were dissociated on warming to room temperature.



I II

R = C_5H_5N-, $(C_6H_5)_2SO$- or C_5H_5NO-

An unstable white crystalline material was isolated from the pyridine oxide solution which was believed to be one of the above-mentioned products.

These results show that methylene chloride has an advantage over stabilized chloroform as an ozonolysis solvent. The latter solvent undergoes irreversible attack by the ozone. Methylene chloride alone is stable to ozone, but in the mixed solvents which were studied some ozone consumption was observed. The salt-like complex which is postulated for the products will be discussed in a later paper.

EXPERIMENTAL

Ozone. The ozone for this work was generated from oxygen in an apparatus built in our department of physics and quite similar to that described by Henne and Perilstein.[9] The 25-kilovolt ozonizer, operated at 93–95 v. input and oxygen flow rate of 0.3 l. per min. at 12 cm. gauge pressure, generated 0.376 millimole of ozone per min. (2.7 mole % ozone in oxygen).

Ozone assays. The ozone-rich oxygen stream was assayed by means of a concentration meter.[10] The gas stream was passed through a 1-mm. thick cell and the % transmission at 253.7 mμ was read from the dial. A calibration curve at the desired pressure, temperature, and flow enabled a rapid conversion to millimoles of ozone per min. being charged. The % transmission was maintained at a constant value by manipulation of the input voltage.

Several iodometric methods[11] were also investigated for assaying the concentration of ozone in the stream. The reaction of ozone with potassium iodide is quantitative only in neutral solution but as the reaction progresses hydroxyl ions are accumulated which cause erroneously low results. The reaction of ozone with acidified potassium iodide, on the other hand, gave results which were too high. The chosen method involved passing the stream into 75 ml. of 5% solution of potassium iodide for 2 min. adding 1 to 2 ml. of 3*N* hydrochloric acid, and then titrating with 0.1000*N* sodium thiosulfate in the usual manner. The amount of acid added was shown to be unimportant as long as the solution was acidic. At this low ozone concentration the formation of some hydroxyl ions[11] was apparently not critical, *i.e.*, use of aluminum chloride[12] in the potassium iodide solution to remove hydroxyl ions as they were formed afforded the same titration results.

Noninterference of phosgene.[13] A solution of 21.35 g. of phosgene in 250 ml. of methylene chloride was prepared. The solution was sparged at −78° with nitrogen for 1 hr. and the effluent gases were bubbled through a 5% aqueous solution of potassium iodide. No iodine could be detected in the solution.

Absence of chlorine.[13] The effluent gases from the ozonization of methylene chloride at −78° were passed into a 10% solution of sodium carbonate in water for 55 min. A portion of the solution was acidified with nitric acid and showed a negative halide-ion test with silver nitrate.

Ozonization of methylene chloride. A 250 ml. solution of methylene chloride (Du Pont) was ozonized in a tubular reactor equipped with a magnetic stirrer and cooled in a Dry Ice-acetone bath. (The new volume at this temperature was about 220 ml.) The ozone was admitted to the reactor at the bottom through a sparger consisting of a bulb with ten small holes in it. The effluent gas was passed by means of a similar distributor through 500 ml. of 5% solution of potassium iodide. The latter was changed and titrated often enough so that the iodine concentration did not become more than about 16 mmole per liter. The amount of ozone absorbed (dissolved plus reacted) by the solution was determined by difference. The solution began to turn blue immediately and was observed to become saturated at about 0.033 molar in ozone. (This concentration was dependent, of course, on the concentration of ozone in the gas admitted to the reactor.) When a total of 40.23 mmole. of ozone had been charged, as determined from the concentration meter readings, the ozonization was interrupted and the deep blue solution was swept with nitrogen at about the same flow rate to free the dissolved ozone until no more could be detected in the effluent. In this way 99% of it was recovered. The results are indicated in Fig. 1. Potentiometric titration of the reaction mixture showed it contained 0.62 m. equiv. of acid.

Ozonization of chloroform. The ozonization was repated on 250 ml. of chloroform (containing 0.75% ethanol as preservative) at −60° using 35.70 mmole of ozone. A lower solubility of ozone in this solvent than in methylene chloride was indicated by a slower rising curve. All of the ozone could not be recovered by sparging, 4.19 mmole. or 11.7% of it was lost. Apparently the solvent had been attacked by the ozone.

Ozonization of methylene chloride-pyridine. A solution[14] of 250 ml. of methylene chloride and 2.37 ml. of pyridine (29.4 mmole) (0.94 vol. %) was ozonized in a similar manner with 47.58 mmole. of ozone. These results are also shown in Fig. 1. The dissolved ozone was not all recoverable. There was 2.5 mmole. or 5.2% of it lost presumably by reaction with the solvent. Ultraviolet analysis on both cold and warmed samples of the reaction mixture showed 2.37 g. and 2.41 g. of pyridine,[15] respectively. Iodimetric titration showed 0.25 mmole of oxidant and potentiometric titration showed 2.7 m. equiv. of acid present. The solution gave a positive test for chloride ions with silver nitrate.

Ozonization of methylene chloride-diphenyl sulfoxide. The determination was repeated on a solution of 7.0 g. (34.6 mmole.) of diphenyl sulfoxide (B and A plasticizer No. 239, m.p. 62–72°) in 250 ml. of methylene chloride using 67.75 mmole. of ozone. The results are summarized in Fig. 1. There was 91.5 mmole. or 13.5% of the ozone lost. When the outgassing was completed, an aliquot of the solution was evaporated to dryness. There was obtained 6.5 g. (32.2 mmole.) (93% recovery) of white needles of diphenyl sulfoxide of slightly improved purity, m.p. 60–62°. There was no sulfone[16] detectable in the product by infrared analysis.

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(9) A. L. Henne and W. L. Perilstein, *J. Am. Chem. Soc.*, **65**, 2183 (1943).

(10) C. D. Alway and G. Slomp, *Advances in Chemistry Series*, in press.

(11) See Clark E. Thorp, *Bibliography of Ozone Technology*, Vol. 1, Armour Research Foundation, Chicago, Ill., 1954.

(12) C. E. Throp, *Ind. Eng. Chem., Anal. Ed.*, **12**, 209 (1940).

(13) Greenwood[6] found that at higher temperatures phosgene and halogen were liberated by the treatment of chlorinated solvents with ozone.

(14) This solution should be freshly prepared just before use. On storing, white crystals of methylenebispyridinium chloride monohydrate [E. Schmidt, *Arch. Pharm.* **251**, 186 (1913)] are deposited.

(15) F. L. J. Sixma, [*Rec. trav. chim.*, **71**, 1124 (1952)] has already shown that the ozonolysis of pyridine is extremely slow at −78°C.

(16) A. Maggiolo and E. Allan Blair, Abstracts, First International Ozone Conference, Chicago, Ill., Nov. 28–30, 1956, p. 20, have shown that the oxidation of sulfoxides to sulfones with ozone is slow even at room temperature.

Ozonization of methylene chloride-pyridine 1-oxide. A solution of 250 ml. of methylene chloride and 2.87 g. (30.2 mmole.) of pyridine-1-oxide (Reilly Tar) was ozonized at −78°. The ozone was absorbed very rapidly but the blue color of dissolved ozone was only very faint. After outgassing, there was 12.45 mmole. of ozone (or 48.6% of the amount charged) missing and the solution contained a white crystalline material which was presumed to be a pyridine oxide-ozone complex. The solution was difficult to sample, but approximately 4 mmole. of oxidant was found by iodimetric titration and 2.8 g. of pyridine oxide[17] was still present, by ultraviolet analysis.

Some of the white crystalline material was collected on a sintered glass funnel. It melted and then decomposed rapidly at room temperature yielding a brown residue. In one instance air was allowed to suck through the material on the funnel and it decomposed violently. The cold crystalline material liberated iodine from potassium iodide rapidly and when dissolved in methanol showed only a strong absorption in the ultraviolet spectrum corresponding with that of pyridine oxide.[17]

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(17) M. Colonna and A. Risaliti, *Boll. sci. fac. chim. ind., Bologna,* **10,** 157 (1952). H. Hirayama and T. Kubota, *J. Pharm. Soc. Japan,* **72,** 1025 (1952).