concentrated to a crystalline residue. Recrystallization from ether-hexane gave 18 mg. of 4-androstene-3,17-dione, m.p. 157–165°, with an infrared spectrum identical with that of an authentic sample.

4-Pregnene-17α,20α,21-triol-3,11-dione (XII) *from cortisone.* From the action of *R. longissima* (OFV No. 2) on 2 g. of cortisone (final concentration of steroid in medium 0.5 g./l.; added in 40 ml. of ethanol; transformation in 5 days) there was obtained, after crystallization from acetone-hexane, 0.65 g. of XII, m.p. 229–231° dec. Several recrystallizations from the same solvent mixture raised the m.p. to 240–242° (dec.), $[\alpha]_D^{25}$ + 158° (dioxane), λ_{max}^{Nujol} 2.89, 2.96, and 3.03 μ (OH), 5.87 μ (11-carbonyl), 6.02 and 6.19 μ (Δ^4-3-one).

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.97; H, 7.83. Found: C, 69.69; H, 8.01.

4-Pregnene-17α,20α,21-triol-3,11-dione 20,21-diacetate. Acetylation in the usual way afforded a 20,21-diacetate m.p. 273–275° (dec.) after recrystallization from acetone, $[\alpha]_D^{25}$ + 107°, $\lambda_{max}^{methanol}$ 238 mμ (ϵ = 15,500), λ_{max}^{Nujol} 2.91 μ (OH), 5.76 and 5.80 μ (acetate carbonyls), 5.85 μ (11-carbonyl), 5.94 and 6.16 μ (Δ^4-3-one), 8.00 and 8.11 μ (C—O—C of acetate).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.09; H, 7.87.

1,4-Pregnadiene-17α,20α,21-triol-3,11-dione (XIII) *from 1-dehydrocortisone.* From the action of *R. longissima* (OFV No. 2) on 1.875 g. of VII (final concentration of steroid in medium 0.25 g./l. added in 40 ml. of methanol; transformation in 6 days) there was isolated after recrystallization from acetone-hexane 0.41 g. of XIII, m.p. 233–235° dec. Additional recrystallization raised the m.p. to 238–240° dec. with a phase change at 225° (polymorphic samples of XIII which melted at 225–228° have also been obtained), $[\alpha]_D^{25}$ + 117° (dioxane), $\lambda_{max}^{methanol}$ 239 mμ (ϵ = 15,400), λ_{max}^{Nujol} 2.95 μ (OH), 5.85 μ (11-carbonyl), 6.01, 6.19, and 6.23 μ ($\Delta^{1,4}$-diene-3-one).

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 70.06; H, 7.71.

1,4-Pregnadiene-17α,20α,21-triol-3,11-dione 20,21-diacetate. Preparation of the 20,21-diacetate in the usual way gave a compound, m.p. 250–251° dec. (samples have also been obtained m.p. 267–270° dec.) $[\alpha]_D^{25}$ + 75° (dioxane), $\lambda_{max}^{methanol}$ 239 mμ (ϵ = 15,100), λ_{max}^{Nujol} 2.92 μ (OH), 5.74 and 5.81 μ (split acetate carbonyls), 5.86 μ (11-carbonyl), 5.97, 6.11, and 6.21 μ ($\Delta^{1,4}$-diene-3-one) and 8.05 μ (C—O—C of acetate).

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.67; H, 7.13.

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The Pyrolysis of Perfluoroethyl Ether[1]

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Received October 14, 1958

In this work perfluoroethyl ether, $C_2F_5OC_2F_5$, was pyrolyzed by passing it slowly over a bed of sodium fluoride pellets in a nickel reactor heated to 800°. The isolable and identified products were C_2F_6, COF_2, C_3F_8, $CF_3CF{=}CF_2$, $(CF_3)_2C{=}CF_2$ and carbon. In the main this ether shows a pyrolytic stability comparable to most fluorocarbons. Except for the COF_2 evolved the ether yields products similar to many of the fluorocarbons pyrolyzed by the hot filament technique.[3] At least one report[4] shows that under pyrolytic conditions in a static system at pressures less than an atmosphere $CF_2{=}CF_2$ corrodes nickel less than it does stainless steel at temperatures between 600–700°.

In general past work tends to show that nature of the pyrolysis reaction of a simple molecule such as $CF_2{=}CF_2$ depends at least upon the variables of temperature, pressure, the contact time, and the geometry and composition of the reaction vessel.[4–7] A correlation of the results is further complicated by whether the pyrolysis is performed by a static or flow method.

EXPERIMENTAL

The perfluoroethyl ether was prepared by the electrochemical (Simons) process[8] in a nominally 50-ampere cell not unlike that described by Hoffmann, Simmons, *et al.*[9] Seven hundred and four g. of ether (11 moles) produced 690 g. of product condensable at −80° of which 450 g. (1.77 moles) was the fluorocarbon ether, b.p. 2.5°, mol. wt. 254.

The pyrolysis equipment was simple. The ether was allowed to escape from a cylinder through a needle valve, its flow being observed with a flow meter. It was then passed through a 1/2-in. i.d. nickel tube, packed with 1/8-in. sodium fluoride pellets, which was heated in a Hoskins furnace. Products were collected in cold traps. A pressure of about 1 atm. in the system was controlled by a valve before the traps and was observed on a manometer. Air was never in contact with the system. Temperatures were measured with a thermocouple placed in a well welded to the top the reactor.

Several small trial pyrolyses established that at contact times as high as 3.5 min. there was no reaction at 650°, 3% conversion to products at 700° and 30–50% conversion to products at 800°. It was also established that the number of equivalents of COF_2 formed was always equal to the number of equivalents of fluorocarbon ether used.

Finally, in order to effect a more complete study of the reaction 102 g. (0.402 mole) of $C_2F_5OC_2F_5$ were pyrolyzed at a flow rate of 0.03 g./min., equivalent to a theoretical contact time of not less than 6.3 min. The reaction products were collected in a liquid air-cooled trap, transferred to the pot of a low temperature microcolumn and allowed to reflux from the head cooled with a mixture of Dry Ice and acetone. A liquid air-cooled trap was attached to the head outlet in which the uncondensed gases that escaped overhead were collected. The column equilibrated at a head

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[1] This work was supported by the Chemistry Branch, Office of Naval Research. Reproduction of all or any part of this paper is permitted for purposes of the United States Government.

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temperature of −56°. Fifty-two g. of material were carried overhead. It was passed through conc. NaOH solution to remove the COF_2 which was formed, amounting to 18.0 g., while the residual C_2F_6 amounted to 34.0 g. Aliquots of the basic solution was acidified with conc. H_2SO_4 and the evolved gas dried. The amounts of CO_2 (mol. wt. 44) evolved agreed within 1% with the amount of COF_2 trapped out. It had been shown previously that the base-soluble gas was COF_2 rather than CF_3COF. Pure COF_2 from an independent source was found to form an insoluble derivative, bis(*p*-chlorophenyl)carbonate (m.p. 144–146°) when reacted with sodium *p*-chlorophenolate in dry isopropyl ether. The COF_2 in a gas mixture prepared by pyrolysis of the fluorocarbon ether formed the same derivative under the same conditions. Furthermore, the sodium fluoride formed on hydrolysis gave a fluorine analysis in good (within 2%) agreement for the amount of COF_2 involved. The residual 34 g. of C_2F_6 were identified by mol. wt. (137–138) and a comparison infrared spectrum. No vestigial unsaturation was detected.

The following fractions were found in the fractionation:

(1) Boiling range −56° to −40°, 58 g. This was scrubbed through NaOH solution to remove any trace of COF_2. An infrared spectrum from the top of this material showed about equal amounts of C_2F_6 and C_3F_8 to be present and nothing else. The mol. wt. range of the fraction varied between 157 and 167.

(2) Boiling range −39° to −35°, mol. wt. 183 to 176, 6.0 g. An infrared spectrum showed a mixture of C_2F_6 and C_3F_8 with a preponderance of the former. There was $C{=}C$ evidence at 5.55 microns. Several parts of this fraction were checked by gas chromatography and averaged about 90% C_3F_8 by wt. The whole fraction was reacted with excess bromine in a sealed ampoule, after which the mol. wt. of the bromine-free volatile portion was exactly 188 and the infrared spectrum was that of C_3F_8. The bromine-free less volatile portion amounted to 1.6 g. and boiled at 71° but the n_D^{25} was somewhat higher than that of pure $CF_3CFBrCF_2Br$.

(3) Boiling range −35° to −25°, mol. wt. 165 to 155, 3.0 g. Its infrared showed a much stronger $C{=}C$ assignment at 5.55 microns than Fraction 2 did at the same experimental pressure. When this portion was similarly treated with bromine, a recovery of $CF_3CFBrCF_2Br$ amounting to 3.0 g. was obtained.

(4) At this point the head temperature rose abruptly to −3.0° and no attempt was made to fractionate further. This residue amounted to 34.3 g. It showed weak infrared evidence for $C{=}C$ at 5.70 microns which is the correct value for $(CF_3)_2C{=}CF_2$.[10] The mol. wt. range of the material was 246–254. Chromatographically it showed several very minor impurities and one large impurity which was in the order of 5% by wt., besides the main peak of the ether, which were not present in the starting material. As the amount of suspected iso C_4F_8 was not present in sufficient quantity to remove successfully by chemical means, the 5% impurity was recovered in a large scale chromatographic separation unit[11] described in detail elsewhere. In the main it consisted of 2 meters of 1-in. tubing packed with the ethyl ester of Kel-F and 8114 supported on Celite. The material under pressure was charged into the column in 2-cc. quantities and developed with nitrogen. The separated fractions were collected in separate traps as they eluted from the column. Over 1.5 g. of the portion corresponding to the impurity under consideration was recovered. It had a mol. wt. of 196 and its infrared spectrum was that reported for iso C_4F_8.[10]

When the reaction vessel was emptied of its contents, the sodium fluoride pellets in the reaction zone were black. The discoloration was suspected of being free carbon and was observed to permeate the pellets completely. The number of pellets so affected indicated that a 9-in. length of the tube was effectively involved as the reaction zone. The blackened pellets were returned to the tube and treated with oxygen at 500° to 700°. One and three quarters g. of carbon dioxide equivalent to 0.48 g. carbon were recovered. The decarbonized pellets now appeared opalescent and had shrunk somewhat but were essentially white and free of carbon.

The product material balance of the pyrolysis of 102 g. of $C_2F_5OC_2F_5$ is given in the following table. Only 69.3 g. were converted to products.

Substance	Wt., G.	Mole	Carbon, Moles
COF_2	18.0	0.273	0.273
C_2F_6	36.6	0.265	0.530
C_3F_8	9.5	0.050	0.15
C_3F_6	2.7	0.018	0.054
iso C_4F_8	1.7	0.0085	0.026
C	0.45	0.037	0.037
	68.9		1.07
Ether	69.3	0.273	1.09

The conversion of ether to products was in the order of 68%.

Discussion of the results. While evidence regarding a detailed reaction mechanism cannot be in any way conclusive as kinetic data are lacking, a few comments based on product data and other evidence may be appropriate.

Unpublished work from this laboratory has shown that COF_2 is always a product of the ultimate pyrolysis of oxygen-containing perfluoro materials. In at least one other case an ether linkage was involved. The failure to detect any evidence of $CF_3OC_2F_5$ in this pyrolysis of $C_2F_5OC_2F_5$ suggests that the first bond cleavage occurs at a C—O bond. Similarly the lack of any $n{-}C_4F_{10}$ suggests that no significant amount of C_2F_5 and OC_2F_5 radicals was formed but rather that the first step in the reaction may be regarded as a concerted disproportionation of the ether to form C_3F_8 and COF_2, involving a shift in a CF_3 group. As COF_2 is formed in quantitative amounts, the other observed products must form as a consequence of further decomposition of the C_3F_8. It would not be amiss to assume that C_3F_8 would crack to C_2F_6 and CF_2 radicals as suggested by Steunenberg and Cady[3b] at a lower temperature in a hot tube than by the heated filament technique they used. They observed the products C_2F_6, C_3F_6, iso C_4F_8, C and $(-CF_2-)_n$ polymer, which deposited on the cool walls of the reaction vessel, as a consequence of the pyrolysis of C_3F_8 with a wire temperature as low as 1050°. Lewis and Naylor[5] have shown that Teflon polymers would not exist at 800° in a hot tube. If the CF_2 radicals formed from the pyrolysis of C_3F_8 combine to form $CF_2{=}CF_2$, the work of Atkinson and Atkinson[4] shows the steps whereby C_3F_6 and iso C_4F_8 are formed. They also show that iso C_4F_8 can be cracked to C_2F_6 and other products and that for contact times of 6 min. the amounts of C_2F_4 and perfluorocyclobutane involved are vanishingly small. If it can be stipulated that over sodium

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fluoride iso C_4F_8 cracks to C_2F_6, CF_2 and C, the amount of carbon and C_2F_6 formed in the pyrolysis of $C_2F_5OC_2F_5$ can be readily explained and is compatible with the stoichiometry of the following set of reactions:

$$C_2F_5OC_2F_5 \longrightarrow COF_2 + C_3F_8 \qquad (1)$$

$$C_3F_8 \longrightarrow C_2F_6 + CF_2\cdot \qquad (2)$$

$$2CF_2 \rightleftarrows C_2F_4 \qquad (3)$$

$$C_2F_4 + CF_2 \longrightarrow C_3F_6 \qquad (4)$$

$$C_3F_6 + CF_2 \longrightarrow \text{iso } C_4F_8 \qquad (5)$$

$$\text{iso } C_4F_8 \longrightarrow C_2F_6 + CF_2\cdot + C \qquad (6)$$

Equation 2 is suggested by the work of Steunenberg and Cady, Equations 4 and 5 are proposed by Atkinson and Atkinson, and Equation 6 is suggested by their work.

Acknowledgments. The authors wish to thank Dr. G. H. Cady of the University of Washington for his helpful comments in a communication.

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6-Methoxy-8-(5-propylaminopentylamino)-quinoline Phosphate

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Received October 15, 1958

The marked toxicity of 8-aminoquinoline derivatives is clinically hazardous, and their use as gametocides in the treatment of malaria must be accompanied by laboratory studies. This is true for for the newer drugs (*cf.* refs. 2–5) as well as pamaquin,[2,3,6,7] all of which should be administered with attention to possible blood dyscrasia. Our work has led to the synthesis of 6-methoxy-8-(5-propylaminopentylamino)quinoline phosphate, an 8-aminoquinoline drug, which has a high chemotherapeutic index, and produces an unusually low incidence of blood dyscrasia. This isomer of pentaquine (the related isopropylamino type[2–4,8,9]) had a definitely superior profile of activity[10] over both pentaquine[3,4] and primaquine.[5] The synthesis of the new antimalarial agent was achieved by conversion of dihydropyran to 5-propylaminopentyl chloride hydrochloride and the reaction of the latter with 8-amino-6-methoxyquinoline, all described below.

EXPERIMENTAL[11]

5-Propylaminopentanol hydrochloride (*cf.* ref. 8). Dihydropyran (112 g., 1.33 mole) was added to a mixture of 28 ml. of conc. hydrochloric acid and 333 ml. of water at 5°. The entire mixture was stirred for 0.5 hr. without cooling, then was chilled to 10° and 22 g. (0.372 mole) of propylamine added to give *p*H 8. To this was added more of the amine (79.0 g., 1.33 mole) at 5°, and the resulting mixture reduced at 25° under 2525 p.s.i. of hydrogen pressure, using 1 g. of Adams' catalyst. Reduction ceased after 4 hr., when 83% of the theoretical maximum had been absorbed. The filtered liquors were basified to *p*H 9 and concentrated until the still-head temperature was 95°. Two layers had formed. The aqueous phase was extracted with hexane and the united organic layers were dried by refluxing under a Dean-Stark water separator. 5-Propylaminopentanol hydrochloride was precipitated by the addition of dry hydrogen chloride to the hexane solution of the base. The crude, pinkish salt (121 g., 50% yield) was crystallized from propanol-2 and ether with use of charcoal, m.p. 97–98°.

Anal. Calcd. for $C_8H_{19}No\cdot HCl$: N, 7.71; Cl^-, 19.51. Found: N, 7.78; Cl^-, 19.48.

5-Propylaminopentyl chloride hydrochloride. The above hydrochloride (80.4 g., 0.445 mole) was suspended in hexane (450 ml.) and kept at 0° to +5° during the addition of thionyl chloride (58.5 g., 0.49 mole) in 2 hr. The reaction mixture was then heated at 50° for 1 hr., and refluxed for 6 hr. Excess of thionyl chloride was removed by distillation, and the greyish hydrochloride (87 g.) collected. It crystallized from acetone and absolute ether as needles, m.p. 201–202°. The yield was 70.5 g. (79%).

Anal. Calcd. for $C_8H_{18}Cln\cdot HCl$: N, 7.00; Cl^-, 17.72. Found: N, 6.97; Cl^-, 17.60.

6-Methoxy-8-(5-propylaminopentylamino)quinoline phosphate. A mixture of 40.0 g. (0.2 mole) of 5-propylaminopentyl chloride hydrochloride and 69.6 g. (0.4 mole) of commercial 8-amino-6-methoxyquinoline in 50 ml. of water was stirred at 80° for 20 hr., and at 100° for 4 hr. It was diluted with 200 ml. of water and adjusted carefully to *p*H 4.5 with aqueous sodium hydroxide, and then aqueous sodium acetate added to *p*H 5.1. The excess 8-amino-6-methoxyquinoline was removed by extraction with benzene (200 ml. each, 4 times) at 65°. When chilled, the aqueous layer gave a brownish solid; this was taken up in 200 ml. of water at 50° and basified. The crude base was extracted well with ether, washed well with saturated brine, dried, and the solvent removed. 6-Methoxy-8-(5-propylaminopentylamino)quinoline (38.2 g., 63.5% yield) was obtained as a brownish oil.

The base (14.8 g.) was dissolved in ether (150 ml.) and treated with ethanolic phosphoric acid (5.52 g. of 85% acid

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