Doubling of Fluorinated Chains

By Albert L. Henne

Received June 17, 1953

When a molecule of $CF_3CF_2CF_2I$ is treated with zinc in acetic anhydride, a very vigorous reaction takes place at once, resulting in a doubling of the chain length with formation of normal C_6F_{14} in excellent yield. For efficient results, operation at a controlled low temperature is essential, easily accomplished by running the reaction in refluxing methylene chloride. The unused iodide is recovered in the methylene chloride fraction, which can be used in the next run after computation of its composition from its index of refraction.

A molecule of $C_3F_3Cl_4Br$[1] is doubled to $C_6F_6Cl_8$ with equal facility. Conversely, CH_3CF_2Cl and $CHCl_2CF_2CF_2Cl$ react in exceedingly poor yield, $CCl_3CF_2CCl_2CCl_3$ undergoes customary dechlorination to $CCl_3CF_2CCl{=}CCl_2$, and propyl or butyl bromide fails to give any detectable octane. These results seem to indicate that the doubling of the chain length might depend on a terminal $-CF_2X$ or $-CFClX$ group, where X is bromine or iodine, at least for a fast, efficient reaction.

Miller's report[2] that highly fluorinated organozinc derivatives were obtainable in dioxane solution, and his private remarks that they were very sensitive to protonic hydrogen, yet did not seem to condense well with carbonyl compounds prompted a search for a solvent which would not cause reduction and side reactions, as do the conventional alcohols, or delay reaction inconveniently, as does ether. All the experimental results were obtained by my collaborators, as named.

Experimental

A. Synthesis of C_6F_{14} (Robert Brown).—C_3F_7I (40 g. or 0.135 mole), granular zinc (9.3 g. or 0.142 mole), acetic anhydride (28 g. or 0.28 mole) and methylene chloride (67 g. or 50 ml.) were mixed in a 300-ml. flask provided with a sealed stirrer and a water cooled reflux condenser trailed by two Dry Ice traps. Stirring at room temperature caused only a slight cloudiness, but with external heating applied to cause refluxing at 40–45°, a white precipitate began to form; in 24 hours the precipitate was so thick that it interfered with stirring, and the reaction was worked up.

While cooling in an ice-bath, water (20 ml.) was added dropwise. It dissolved the precipitate and caused the formation of three layers. There was no gas evolved; the empty Dry Ice trap showed that $CF_3CF{=}CF_2$ had not been formed during the zinc attack, nor $CF_3CF_2CF_2H$ during the hydrolysis. The top layer (81 g.) contained acetic acid, water, acetic anhydride and zinc iodide; the middle layer (54 g.) was methylene chloride with about 4% of unused iodide; the bottom layer (17 g.) was the doubled up molecule, C_6F_{14}, quite pure. As 5.5 g. of zinc was recovered, the aggregate weights show a loss of 6.6 g. of material, attributed to mechanical handling and inexperience. There was no indication of a ketonic material which would have resulted from action of the organometallic on the solvent.

The top and middle layers were returned to the flask and neutralized with sodium carbonate. The organic layer was drained from the aqueous layer, and proved to be a clean mixture of methylene chloride with 4% of unused iodide.

The bottom layer was dried on sodium sulfate and distilled; it came over entirely at 57°, the correct boiling point for C_6F_{14}. The refractive index (1.25) was too low to be read on the available instrument; the density was found to be 1.6707 at 25° (lit. 1.6995 at 20°).

The conversion from the iodide was 74%, and as 3.4% of iodide was recovered, the net yield was 77%. A computation based on the amount of zinc consumed shows that an additional 12% might have been formed and lost.

B. Synthesis of $C_6F_6Cl_8$ (Dorothy Kraus).—$C_3F_3Cl_4Br$ (205 g. or 0.65 mole), obtained by addition of CCl_3Br to $CF_2{=}CFCl$, see ref. 1, granulated zinc (42 g.), a volume of acetic anhydride equal to that of $C_3F_3Cl_4Br$ and another volume of methylene chloride were placed together and stirred under reflux. The reaction started spontaneously and was held under control at 40–45° by external cooling; this shows that much more anhydride and methylene chloride should have been used, as in A. White salt came out progressively and the mixture remained clean and only light yellow, but when the solid accumulated, control of the temperature became inadequate, and the mixture was quenched before deterioration set in appreciably.

The working up recovered 31 g. (0.1 mole) of starting material, and 60 g. of a solid, m.p. 39–39.5°, which contained 24.1% F and 59.6% Cl (analysis by Mary Renoll); the correct values for $C_6F_6Cl_8$ are 24.2% F and 60.4% Cl. As the solid represents 0.13 mole, a 40% conversion was obtained or a 55% yield when the recovered material is taken into count.

C. Synthesis of $CCl_3CF_2CCl{=}CCl_2$ (Mary Renoll).—Crude $CCl_3CF_2C_2Cl_5$ (32 g. or 0.09 mole) was dissolved in chloroform (30 ml.) and dripped into a flask containing mossy zinc (5.85 g. or 0.09 mole) covered with acetic anhydride (75 ml.). The reaction started promptly and raised the temperature to 45–50°, where it was kept by control of the rate of addition and stirring. Addition took an hour, after which the mixture was stirred at 45–50° for another 40 minutes. The mixture remained clean, pale yellow and the salt which came down was not gummy; this is in marked contrast with the amount of resinification, decomposition and difficulty in handling which occur with other solvents.[3] After pouring into ice-water and adding 50 ml. of chloroform, the two layer mixture was kept overnight at 4° for good decantation, and recovery of 2.4 g. of zinc. This indicated that 58% of the zinc had been used. From the bottom layer, distillation separated chloroform, 12 g. of the olefin $C_4F_2Cl_6$ and 12 g. of the original paraffin $C_4F_2Cl_8$. There was no still residue. The conversion to the olefin was 45%, or after deducing recovered material, a 76% yield. There was no doubling up.

This dechlorination is to be contrasted with the difficulties reported by Newby,[3] whose maximum yields were 30% in ethanol and 10–15% in dioxane, with resinification of the balance of his material. The observed properties, b.p. 85–86° at 10 mm., d_4 1.7842 and n_D 1.5052 at 20°, MR 49.69 and AR_F 1.24 agree well with Newby's who found: m.p. −6.0 to −6.8°, b.p. 212° at 745 mm., d_4 1.7803 and n_D 1.5029 at 25°, MR 49.64 and AR_F 0.97. The last figure is miscalculated and should be 1.2, in good agreement.

D. Attempted Synthesis of *n*-Octane (John Gordon).—Butyl bromide (28 g. or 0.2 mole), granular zinc (13.1 g. or 0.2 mole), acetic anhydride (27.6 g. or 0.3 mole) with an equal volume of Skellysolve F (b.p. 35–60°) were stirred at 65° for 4 days. After that period, 12.2 g. of zinc was recovered unused, showing that practically no reaction had occurred. The working up recovered 3 g. of material b.p. 65–100° (a mixture of solvent and bromide), then 15 g. of butyl bromide, and there was less than 1 g. of a black residue. There was no indication of octane, and about 40% of the starting material was lost by decomposition.

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(1) A. L. Henne and D. W. Kraus, This Journal, **73**, 1791 (1951). Also Dorothy W. Kraus, Ph.D. dissertation, The Ohio State University, 1953.

(2) W. T. Miller, Atlantic City Meeting, September, 1952.

(3) Thomas Newby, Master's Thesis, Ohio State University, 1944, also A. L. Henne and Thos. Newby, This Journal, **70**, 130 (1948).

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Ionization Constant of Fluorinated Acids. II

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Received July 6, 1953

The fact that butyric acid is a little more highly ionized than its lower homolog ($K_A \times 10^{-5}$ being 1.51 and 1.34, respectively) is sometimes explained[1]

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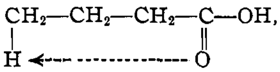
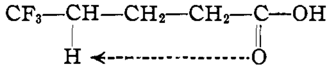
(1) J. F. Dippy, *J. Chem. Soc.*, 1122 (1938).

by ability to form a six-membered ring involving hydrogen bonding, such as  $\underset{\displaystyle H}{\underset{|}{CH_2}}{-}CH_2{-}CH_2{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}OH$, and the same explanation applies to isovaleric acid (1.67) and diethyl acetic acid (1.77). These differences of acidity are quite small, and it occurred to us that the effect would be magnified in the $CF_3(CH_2)_nCO_2H$ series. We have previously reported[2] K_A for $n = 0$, 1 and 2. Assuming that the induction of the CF_3 group on the acid function falls substantially as the square of the distance, K_A for trifluorovaleric acid should not differ appreciably from K_A for unfluorinated valeric acid. Computations by various procedures,[3,4] give a probable value of 1.7, certainly not higher than 2. If, however, ring formation should take place, such as  $CF_3{-}\underset{\displaystyle H}{\underset{|}{CH}}{-}CH_2{-}CH_2{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}OH$, the observed K_A should be appreciably higher than 1.7, since the hydrogen atoms on the carbon adjacent to the CF_3 group are quite acidic.

Trifluorovaleric acid, $CF_3(CH_2)_3CO_2H$, was synthesized, and from its *p*H at half neutralization, its K_A was found to be $3.2 \pm 0.03 \times 10^{-5}$, nearly twice as large as the extrapolated value of 1.7.

Experimental

1. **Preparation of $CF_3(CH_2)_3CH_2Cl$.**—$CCl_3(CH_2)_3CH_2Cl$ (210 g., 1 mole) in $CCl_2{=}CClCCl{=}CCl_2$ (200 ml.) is added by drops to a vigorously stirred slurry of SbF_3 (138 g., 0.77 mole) and SbF_3Cl_2 (220 g., 0.88 mole, total 65 mole % excess of fluorinating agent) in $CCl_2{=}CClCCl{=}CCl_2$ (30 ml.) cooled in an ice-bath. When addition is complete, more SbF_3Cl_2 (80 g., 0.3 mole) is added to promote fluorination of mono- and difluorinated products. Under these conditions of high SbF_3Cl_2 concentration and low temperature, the solvent C_4Cl_6 is left practically intact. After 2 hours the mixture is permitted to warm up and is stirred 4 hours at room temperature then hydrolyzed with HCl in ice and steam distilled. The distillate is washed with aqueous $NaHCO_3$, H_2O saturated NaCl and dried over $MgSO_4$. Distillation gives material (19 g.): b.p. 97–98°, $n^{29}{}_D$ 1.3521, $d^{29}{}_4$ 1.195; $CF_3(CH_2)_3CH_2Cl$ (11 g., 0.07 mole, 7%), b.p. 121°, $n^{27}{}_D$ 1.3691, $d^{27}{}_4$ 1.217, *MR* 29.6, AR_F 0.93; found, 32.40% F, 25.07% Cl; calcd., 35.6% F, 21.9% Cl, indicative of a contaminated sample; and material (27 g.), b.p. 150–152°, $n^{29}{}_D$ 1.4070, $d^{29}{}_4$ 1.264. The solvent and starting material are not readily separated. Similar reactions give identical products in the same relative amounts.

2. **Preparation of $CF_3(CH_2)_3CH_2OH$.**—Redistilled $CF_3(CH_2)_3CH_2Cl$ (43 g., 0.27 mole) in 150 ml. of dry ether is added to Mg (8 g., 0.3 mole) stirred in 150 ml. of dry ether. Reaction starts when several crystals of I_2 are added to the reaction, but not when $CF_3(CH_2)_3CH_2Cl$ (2 g.) is heated with Mg or when C_2H_5I (20 drops) is added to the reaction (although C_2H_5I reacts), and proceeds satisfactorily when heated slightly with formation of an orange precipitate. The suspension is siphoned into an addition funnel and added slowly to dry ether into which oxygen is bubbled while stirring and which is cooled in an acetone–Dry Ice-bath. When addition is complete, oxygen is slowly bubbled into the mixture for another eight hours; precipitation is voluminous. The suspension is hydrolyzed with dilute HCl and two clear layers form. The ether layer and ether extract of the aqueous layer are washed with saturated NaCl, dried over $MgSO_4$ and the ether is distilled. The residue is mixed with mercury to remove free iodine, filtered, and benzene is added and distilled to remove the water. Distillation of the residue gives crude $CF_3(CH_2)_3CH_2OH$ (18 g., 0.13 mole, 48% yield), b.p. 80–85° at 69 mm. which reacts slowly with Na but not with Lucas reagent. No further attempt at purification or identification is made, and the crude alcohol is directly oxidized to the acid.

3. **Preparation of $CF_3(CH_2)_3CO_2H$.**—$CF_3(CH_2)_3CH_2OH$ (18 g., 0.13 mole) is added by drops to a solution of $Na_2Cr_2O_7{\cdot}2H_2O$ (24 g., 0.08 mole) and 95% H_2SO_4 (15 ml., 0.34 mole) in 250 ml. H_2O stirred at 50° for 48 hours. Additional H_2SO_4 (50 ml.) is added to the cold mixture which is then continuously extracted with ether. Benzene is added to the extract and distilled to remove H_2O. Distillation under reduced pressure gives crude $CF_3(CH_2)_3CO_2H$ (11 g., 0.07 mole, 54% yield) b.p. 93–100° at 16 mm., neut. equiv., 163, which contains a small amount of H_2O insoluble material. Neutralization of an aqueous solution with NaOH and extraction with ether (3 times) removes about 0.5 g. of oil in the extract. The aqueous solution is acidified with H_2SO_4 (50 ml.), continuously extracted with ether and the extract is dried over $MgSO_4$; benzene is added and distilled to remove ether and water. Distillation under reduced pressure gives $CF_3(CH_2)_3CO_2H$ (9 g.), b.p. 93.8–95° at 15 mm.; cut b.p. 94.8–95.0° at 15 mm., has $n^{25}{}_D$ 1.3632, $d^{25}{}_4$ 1.293, *MR* 26.83, AR_F 1.10, neut. equiv., 155.3 (calcd. 156), found 36.9% F (calcd. 36.5%), qualitative test for Cl on fusion with Na is negative.

4. **Attempted Preparation** of $CF_3(CH_2)_3CH_2OH$ from $CF_3CH_2CH_2Cl$.—Reaction of $CF_3CH_2CH_2MgCl$ (1 mole) with ethylene oxide is carried out as described for the preparation of *n*-hexyl alcohol.[5] The reaction proceeds normally and the rearrangement occurs smoothly. However, after hydrolysis no material is isolated other than solid decomposition products. Direct oxidation with $Na_2Cr_2O_4$ and H_2SO_4 after hydrolysis also fails to give any product.

5. **Attempted Preparation** of $CF_3(CH_2)_3CO_2C_2H_5$ from $CF_3CH_2CH_2Cl$.—$CF_3CH_2CH_2Cl$ treated with $NaCH(CO_2C_2H_5)_2$ undergoes only dehydrohalogenation to $CF_3CH{=}CH_2$.

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(2) A. L. Henne and C. J. Fox, This Journal, **73**, 2323 (1951).

(3) D. A. MacInnes, *ibid.*, **50**, 2587 (1928).

(4) J. C. Greenstein, *ibid.*, **58**, 1314 (1936).

(5) "Organic Syntheses," Coll. Vol. I, 2d Ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 306.

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11-Oxygenated Steroids. VIII. The Synthesis of 16,17-Oxido-4-pregnen-11α-ol-3,20-one Acetate

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RECEIVED JUNE 12, 1953

In connection with other studies in this Laboratory 16,17-oxido-4-pregnen-11α-ol-3,20-one acetate (VII) was required. The synthesis was accomplished according to the following scheme. Pregnan-3α,11α-diol-20-one diacetate[1] (I) was brominated at the 17-position in acetic acid solution. The bromide II was dehydrobrominated by refluxing with collidine to yield 16-pregnen-3α,11α-diol-20-one diacetate (III). Epoxidation of III by the procedure of Julian[2] afforded the corresponding 16,17-epoxide IV from which the acetate group at 3-, but not at 11-, had been hydrolyzed.[3] The

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(1) E. P. Oliveto, H. L. Herzog and E. B. Hershberg, This Journal, **75**, 1505 (1953).

(2) P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, *ibid.*, **72**, 5145 (1950).

(3) Following the completion of this work, J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *ibid.*, **75**, 1277 (1953), reported that potassium hydroxide could be employed to hydrolyze selectively the 3- and 21-acetate groups in allopregnan-3β,11α,17α,21-tetrol-20-one 3,11,21-triacetate. The same paper described the epoxidation of 16-allopregnen-3β,11α-diol-20-one diacetate with alkaline hydrogen peroxide; in this experiment no attempt was made to isolate 16,17-oxidoallopregnan-3β,11α-diol-20-one 11-acetate, the reaction mixture being subjected to vigorous alkaline hydrolysis prior to isolation of the product in order to remove any acetate groups which survived the initial reaction.