by ability to form a six-membered ring involving hydrogen bonding, such as $CH_2—CH_2—CH_2—C—OH$ (H ⟵ O), 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 $CF_3—CH—CH_2—CH_2—C—OH$ (H ⟵ O), 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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(4) J. C. Greenstein, *ibid.*, **58**, 1314 (1936).

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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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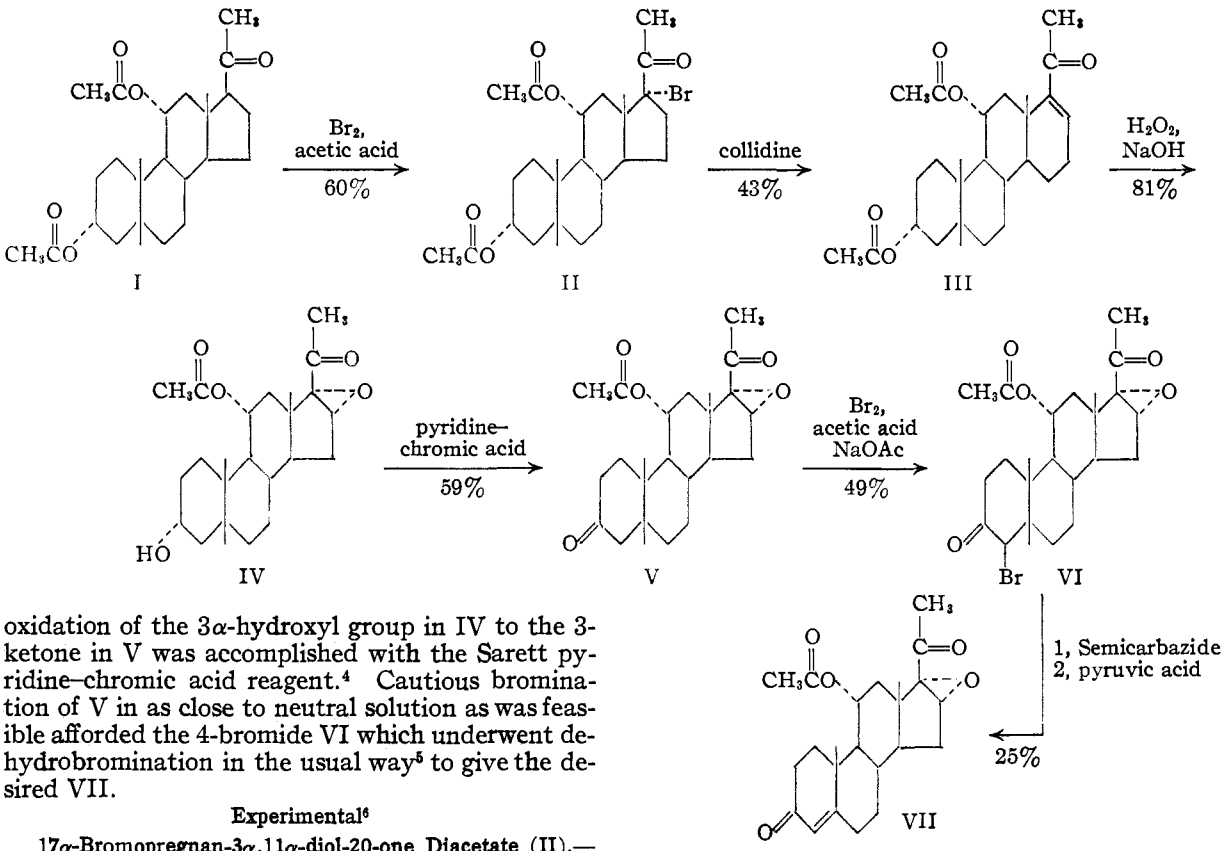
RECEIVED JUNE 12, 1953

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

(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.



oxidation of the 3α-hydroxyl group in IV to the 3-ketone in V was accomplished with the Sarett pyridine–chromic acid reagent.[4] Cautious bromination of V in as close to neutral solution as was feasible afforded the 4-bromide VI which underwent dehydrobromination in the usual way[5] to give the desired VII.

Experimental[6]

17α-Bromopregnan-3α,11α-diol-20-one Diacetate (II).—To a solution of 20 g. of I in 500 ml. of glacial acetic acid and 14 drops of 0.28 *N* hydrogen bromide in glacial acetic acid was added dropwise with stirring at room temperature 2.6 ml. of bromine in 100 ml. of glacial acetic acid. The addition required two hours, and the mixture was then stirred an additional 15 minutes. Five volumes of water was then added and the resulting precipitate was collected by filtration. The filtrate was extracted with methylene chloride, and the extracts were washed free of acid and dried over magnesium sulfate. The residue from the concentration of the methylene chloride solution was combined with the precipitate previously isolated, and recrystallized from hexane. There was obtained 14.4 g. (60%) of II, m.p. 182–186° dec., which on further recrystallization melted at 185–187° dec., $[\alpha]^{25}D$ −48.1° (1% in chloroform).

Anal. Calcd. for $C_{25}H_{37}O_5Br$: Br, 16.06. Found: Br, 16.33.

16-Pregnen-3α,11α-diol-20-one Diacetate (III).—A mixture of 3.28 g. of II in 50 ml. of collidine was refluxed for 45 minutes. The reaction was then cooled, diluted with ether and filtered to remove the precipitated collidine hydrobromide. The filtrate was washed free of collidine with dilute sulfuric acid and then washed to neutrality with sodium carbonate and water. After the ethereal solution had been dried over magnesium sulfate it was concentrated to a small volume, hexane was added, and the resulting precipitate was removed by filtration. There was obtained 1.26 g. (43%) of III, m.p. 192–194.5°. Recrystallization from methylene chloride–hexane raised the m.p. to 198–200°, $[\alpha]^{25}D$ +25.8° (1% in chloroform), ϵ_{236} 9,200 (ethanol).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.39; H, 9.04.

16,17-Oxidopregnan-3α,11α-diol-20-one 11-Acetate (IV).—To a solution of 1.15 g. of III in 76 ml. of methanol at 15° was added 2.28 ml. of 4 *N* aqueous sodium hydroxide and 4.45 ml. of 30% hydrogen peroxide. The reaction mixture was stored at 5° for 40 hours. Initially a heavy precipitate of starting material formed which was almost completely in solution at the end of the reaction period. The reaction mixture was filtered and the filtrate was diluted with 325 ml. of water. The resulting solution was extracted with methylene chloride, and the extracts were washed well with water and dried. Concentration of the dried solution followed by addition of hexane gave a heavy, gelatinous precipitate which was filterable. The solid gave up the solvent upon drying at 60°, leaving 0.88 g. (81%) of IV, m.p. 191–193°. Recrystallization from methylene chloride–hexane raised the m.p. to 193–195°, $[\alpha]^{25}D$ +18.8° (1% in chloroform).

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 71.03; H, 8.97.

16,17-Oxidopregnan-11α-ol-3,20-dione Acetate (V).—A solution of 3.0 g. of IV in 30 ml. of pyridine was added slowly to a slurry of 1.5 g. of chromic acid in 15 ml. of pyridine and the resulting mixture was stirred overnight at room temperature. (Caution! In preparing the reagent the chromic acid must be added to the pyridine under controlled conditions.[4]) To the reaction was then added 4.5 g. of sodium sulfite in 45 ml. of water and stirring was continued for two hours. The reaction mixture was poured into 600 ml. of water and the resulting solution was extracted with methylene chloride. The extracts were washed neutral with dilute sulfuric acid, aqueous sodium carbonate and water, and dried over magnesium sulfate. Concentration of the dried solution followed by the addition of hexane resulted in the crystallization of 1.8 g. (59%) of V, m.p. 222–224°, $[\alpha]^{25}D$ +25.3° (1% in chloroform).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.39; H, 8.52.

4-Bromo-16,17-oxidopregnan-11α-ol-3,20-dione Acetate (VI).—To a solution of 1.0 g. of V in 100 ml. of glacial acetic acid was added 1.0 ml. of 0.28 *N* hydrogen bromide in glacial acetic acid. Then there was added, dropwise with good agitation, a solution containing 412.5 mg. of bromine, 210 mg. of sodium acetate and 25 ml. of glacial acetic acid at such a rate that each drop had the opportunity to react

(4) G. I. Poos, G. E. Arth, R. E. Beyles and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(5) B. A. Koechlin, T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **184**, 393 (1950); E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948); V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951).

(6) Analyses and optical data were obtained by the Microanalytical and Physical Chemical Departments of these laboratories.

before another was added (time of addition, five hours). The reaction mixture was then poured into five volumes of water and the resulting precipitate was collected. Recrystallization from methylene chloride–hexane afforded 0.69 g. (49%) of VI, m.p. 186–188° dec. (with recrystallization at 115–120°), $[\alpha]^{25}D$ +44° (1% in chloroform).

Anal. Calcd. for $C_{23}H_{31}O_5Br$: Br, 17.09. Found: Br, 17.04.

16,17-Oxido-4-pregnen-11α-ol-3,20-dione Acetate (VII).—To a solution of 0.5 g. of VI in 50 ml. of glacial acetic acid was added, under an atmosphere of carbon dioxide, a solution containing 272 mg. of semicarbazide hydrochloride, 195 mg. of anhydrous sodium acetate, 10 ml. of water and 10 ml. of glacial acetic acid. The mixture was agitated for ten minutes and there was then added 20 ml. of 1 *N* sodium acetate in glacial acetic acid. Agitation was continued for ten minutes longer, 2 ml. of pyruvic acid was added, and the mixture was refluxed for ten minutes. The cooled solution was diluted with water and extracted with methylene chloride. The extracts were washed free of acid with water, dried over magnesium sulfate and concentrated to a small volume. Hexane was then added to the point of opalescence and the solution was chromatographed on 20 g. of Florisil prepared with hexane. Elution with hexane and mixtures of hexane and ether stripped nothing from the column. From elution with ether there resulted five 50 ml. fractions containing a total of 0.103 g. (25%) of VII, m.p. 212–214°. Recrystallization from methylene chloride–hexane raised the m.p. to 217–218°, $[\alpha]^{25}D$ +112.9° (1% in chloroform).

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.55; H, 8.00.

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The Preparation of 2-C^{14}-Adenine

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RECEIVED JUNE 25, 1953

As a preliminary to a study of the metabolism of the purines, with especial reference to the 2-position of the ring, the synthesis of adenine labeled in the 2-position with C^{14} was undertaken. The method described by Shaw,[1] in which 4-amino-5-imidazolecarboxamidine is formylated and the product cyclized to give adenine, appeared to be suitable since by using C^{14}-formic acid for the formylation 2-labeled adenine would be obtained. An advantage of this method is that the isotope would be introduced at a late step in the synthesis, thereby minimizing losses of radioactive material. The undesirable feature of the method, however, as far as economy of radioactive material is concerned, is that the formylation is carried out with a large excess of 98% formic acid in the presence of acetic anhydride. This would necessitate the use of an inordinately large amount of C^{14}-formate in order to obtain adenine with appreciable radioactivity.

In order to avoid the use of such a large excess of formic acid, experiments were carried out to study the feasibility of formylating the carboxamidine with an aqueous solution of formic acid, since such conditions have been used to formylate other amines.[2,3] The formylation reaction was found to proceed in 6 *M* formic acid, and by using this modification it was possible to obtain 2-C^{14}-adenine in yields of 60–65%, based on the carboxamidine used. The unreacted C^{14}-formate can be recovered almost quantitatively and used for further preparations of labeled adenine.

Method.—A solution of 0.200 g. of 4-amino-5-imidazolecarboxamidine dihydrochloride[1] in 2.0 ml. of 20% formic acid was placed in a reaction tube made from the outer member of a 24/40 standard taper joint. To this solution was added 0.170 g. of potassium formate, making the solution 6.3 *M* with respect to formate. The solution was then boiled gently under reflux for 4 hours. The formamido derivative was not isolated but was cyclized to adenine by diluting the solution to 8 ml. with water, adding sufficient potassium bicarbonate to neutralize the formic acid and to make the solution 0.5 *M* in bicarbonate, and then boiling under reflux for 1 hour. An amount of hydrochloric acid slightly less than that required to neutralize the solution was added, and the solution was concentrated under reduced pressure to a volume of 2–3 ml. On placing the solution in the refrigerator for several hours crude adenine precipitated. This material was collected by centrifugation, washed 3 times with ice-cold water and dried *in vacuo*. The supernatant and wash liquids were saved for the recovery of unreacted formate. The crude material was sublimed at 220° and a pressure of 1 mm. to give 0.083 g. of pure adenine, a yield of 61% based on the carboxamidine. Yields of 40–42% were obtained when the formylation was carried out with 4.0 *M* formic acid.

Anal. Calcd. for $C_5H_5N_5$: C, 44.44. Found: C, 44.27.

The compound formed a picrate which melted with decomposition at 286–287°.[1] Admixture with picrate prepared from authentic adenine did not depress the m.p. The ultraviolet absorption spectrum and R_f values obtained by paper chromatography[4] were identical with those of authentic adenine.

2-C^{14}-Adenine was prepared by using C^{14}-potassium formate in the above procedure. In a typical experiment, adenine having a specific activity of 1.055×10^6 c.p.m. per m*M* was synthesized and the formate recovered from the reaction mixture had a specific activity of 1.025×10^6 c.p.m. per m*M*.

The unreacted C^{14}-formate in the supernatant fluid and washings after separation of the crude adenine was recovered almost quantitatively by steam distillation.[5] For further use in preparing radioactive adenine, the steam distillate was titrated with standard potassium hydroxide solution and concentrated to small volume under reduced pressure. The concentrate was then transferred to the reaction tube and evaporated to dryness. The appropriate amount of 4-amino-5-imidazolecarboxamidine dihydrochloride was added, followed by hydrochloric acid equivalent to the formate present less the amount of hydrochloric acid present as the dihydrochloride salt. The procedure outlined above was then followed for the remainder of the synthesis.

Acknowledgment.—This work was supported by grants from the National Research Council of Canada.

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The Tetrachlorophthalic Anhydride Derivatives of Some Alkylbenzenes

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RECEIVED JULY 31, 1953

In a previous note[2] the authors reported the phthalic anhydride derivatives of several substituted alkylbenzenes. In general these derivatives distinguish satisfactorily among the alkylbenzene hydrocarbons. However, it is not possible by

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