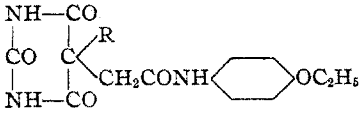
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Alkylacetanilidobarbituric Acids. III. *p*-Ethoxy Derivatives

BY JOHN A. TIMM

The fact that the administration of mixtures or addition products of hypnotic and antipyretic substances produces an analgesic effect is well known.[1] This series of papers reports the preparation of 5-alkylbarbituric acids in which antipyretic and anesthetic groups replace the second hydrogen atom on the 5-carbon atom. Derivatives of acetanilide[2] and *p*-carbethoxyacetanilide[3] have been reported in the previous papers. The series has been extended in this paper to the preparation of 5-alkyl-5-*p*-ethoxyacetanilidobarbituric acids, *i. e.*, derivatives of the antipyretic, phenacetin



These derivatives, together with those reported in the first two papers of this series, are being tested pharmacologically. The results will be published elsewhere.

Experimental Part

Barbituric Acids Containing the *p*-Ethoxyacetanilido Group.—Equimolecular proportions of the appropriate 5-alkylbarbituric acid and *p*-ethoxychloroacetanilide,[4] a one and one-half molecular proportion of sodium acetate and a one-fourth molecular proportion of potassium iodide were dissolved in 70% alcohol by heating on a water-bath in a flask provided with a mechanical stirrer and a reflux condenser. The heating was continued for twenty-four hours. Crystals of the product separated during the course of the reaction. Approximately one-half of the alcohol was distilled off and the mixture cooled in an ice-bath. The products were recrystallized from absolute alcohol. They are white, crystalline solids which melt with decomposition. The usual difficulty was experienced in crystallizing the isopropyl derivative, which comes out of solution at first as a brown oil.

TABLE I

Barbituric acid, 5-*p*-ethoxyacetanilido-	Melting range, °C., with dec.	Yield, %	N Analyses, %		
			Calcd.	Found	
5-Ethyl-	194–205	60	12.6	12.5	12.6
5-Isopropyl-	210–215	20	12.1	12.1	11.8
5-*n*-Butyl-	231–232	40	11.6	11.6	11.7
5-Isobutyl-	217–219	50	11.6	11.6	11.6
5-Isoamyl-	219–220	80	11.2	11.4	11.5
5-Allyl-	215–218	60	12.2	12.0	12.0

The author wishes to express his appreciation to Mr. Paul M. Hauser and to Mr. DeFrance Clarke, Jr., for their help in the analyses and in the preparation of the intermediates of these compounds.

Summary

The following 5-*p*-ethoxyacetanilidobarbituric acids have been prepared: 5-ethyl-, 5-isopropyl-, 5-*n*-butyl-, 5-isobutyl-, 5-isoamyl-, and 5-allyl-.

NEW HAVEN, CONN. RECEIVED JULY 25, 1939

---

[1] See Hepner and Frenkenberg, *Ber.*, **65B**, 123 (1932).

[2] Timm, THIS JOURNAL, **57**, 1943 (1935).

[3] Timm and Howard, *ibid.*, **58**, 1805 (1936).

[4] Bistrzycki and Ulffers, *Ber.*, **31**, 2790 (1898).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE PENNSYLVANIA STATE COLLEGE]

Fluorocarbons. The Reaction of Fluorine with Carbon

BY J. H. SIMONS AND L. P. BLOCK[1]

Carbon tetrafluoride has been obtained from the reaction of fluorine with carbon.[2] Ruff and Keim isolated hexafluoroethane from the reaction products and obtained small amounts of higher boiling material, which they assumed to be mixtures of higher molecular weight fluorocarbons, but in insufficient quantity to separate and isolate the compounds. Several difficulties are encountered in the study of this reaction. Frequent and sometimes violent explosions occur; and as the higher molecular weight compounds are produced in relatively small quantities, large amounts of reaction products are necessary in order to isolate them. Ruff, Bretschneider and Ebert[3] studied these explosions in detail and found a

---

[1] The authors gratefully acknowledge a grant from the American Academy of Arts and Sciences which aided in financing the preparation of these compounds.

[2] Moissan, *Compt. rend.*, **110**, 951 (1890); Lebeau and Damiens, *ibid.*, **191**, 939 (1930); Ruff and Keim, *Z. anorg. allgem. Chem.*, **192**, 249 (1930).

[3] Ruff, Bretschneider and Ebert, *ibid.*, **217**, 1 (1934).

white crystalline compound (CF) which exploded when heated. From the products of these explosions they obtained small quantities of higher boiling material. They suggest the possibility of the reaction proceeding smoothly with proper temperature control. We have attempted to do this without success. There is a short initial period before explosions begin but the amount of products that can be obtained in this time is very small.

Other reactions which might be expected to yield higher molecular weight fluorocarbons so far have produced only hexafluoroethane and tetrafluoroethylene. Fluorine has been caused to react with hydrocarbons[4] either pure or in solution in solvents such as carbon tetrachloride or dichlorodifluoromethane. Fredenhagen and Cadenbach and also Bigelow and Calfee have controlled the explosions frequent in these reactions by the use of a copper gauze catalyst. The reactions of fluorine with compounds of carbon and other halogens also have been studied.[5] The use of other fluorinating agents such as antimony trifluoride on such compounds is also possible but to replace the third halogen atom on a carbon atom is difficult although it may be accomplished in some cases.[6] Hexafluoroethane has been made by the electrolysis of trifluoroacetic acid,[7] and both hexafluoroethane and tetrafluoroethylene have been obtained by the passage of carbon tetrafluoride and dichlorodifluoromethane through an electric arc.[8] Swarts[9] assumed the formation of C_6F_6 and C_6F_{12} from the pressure effect and the proportion of hydrolysis products (CO_2, CO, HF, and CF_4) when hexafluoroethane was passed over a hot platinum wire. These effects could be explained equally well from the recorded leaks in his apparatus and the reaction of hydrogen fluoride with the glass vessel.

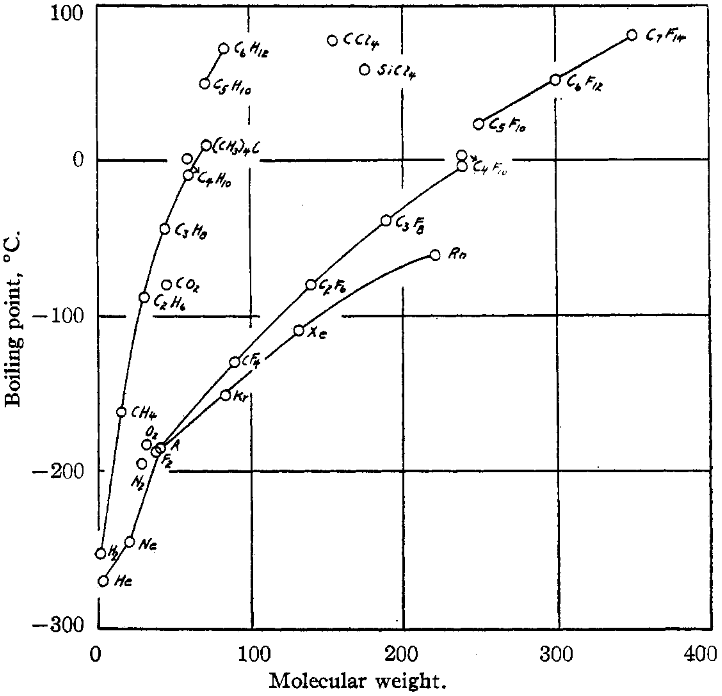


Fig. 1.

Preparation of Fluorocarbon Mixture.—We have been able to overcome the technical difficulties of the reaction of fluorine with carbon and have obtained about 150 cc. of liquid of molecular weight greater than 138. A preliminary report of this work has been published,[10] but we had only a small amount of material then and some of our reported data are in error due to incomplete separation.

A large and constant supply of fluorine was required. Different types of electrolyte cells were tried. The V-shaped cells[11] worked satisfactorily for a short time but the corrosion of the cell wall was excessive in long periods of operation. Cells operating at 70 to 100°[12] with an electrolyte of approximately the composition KF·2HF gave undue corrosion of the positive electrode whether this was nickel or graphite. The most rugged, simple, and generally satisfactory cell for long and constant use was a modification of the cell devised by one of the authors.[13] A description of this cell and the technique of its operation is given in the first volume of "Inorganic Syntheses."[14]

Four cells were employed. Two were kept in operation twenty-four hours a day with the operators working in shifts. The other two were either in reserve or in the process of regeneration, cleaning, or repair.

Several different kinds of carbon were used among which

---

(4) Bancroft and Jones, *Trans. Am. Electrochem. Soc.*, Preprint, 55 (1929); Bigelow, Pearson, Cook and Miller, THIS JOURNAL, **55**, 4614 (1933); Bockemüller, *Ann.*, **506**, 20 (1933); Fredenhagen and Cadenbach, *Ber.*, **67B**, 928 (1934); Bigelow and Calfee, THIS JOURNAL, **59**, 2073 (1937).

(5) Humiston, *J. Phys. Chem.*, **23**, 572 (1919); Bancroft and Whearty, *Proc. Natl. Acad. Sci.*, **17**, 183 (1931); Bigelow and Pearson, THIS JOURNAL, **56**, 2773 (1934).

(6) Henne, *ibid.*, **59**, 1200 (1937); Simons and Lewis, *ibid.*, **60**, 492 (1938).

(7) Swarts, *Bull. sci. acad. roy. Belg.*, **20**, 782 (1934).

(8) Ruff and Bretschneider, *Z. anorg. allgem. Chem.*, **210**, 173 (1933); Thornton, Burg and Schlesinger, THIS JOURNAL, **55**, 3177 (1933).

(9) Swarts, *Bull. soc. chim. Belg.*, **42**, 114 (1933).

(10) Simons and Block, THIS JOURNAL, **59**, 1407 (1937).

(11) Dennis, Veeder and Rochow, *ibid.*, **53**, 3263 (1931); Miller and Bigelow, *ibid.*, **58**, 1583 (1936); Henne, *ibid.*, **60**, 96 (1938).

(12) Lebeau and Damiens, *Compt. rend.*, **181**, 917 (1925); Henne, THIS JOURNAL, **60**, 96 (1938).

(13) Simons, *ibid.*, **46**, 2175 (1924).

(14) Simons, "Inorganic Syntheses," McGraw-Hill Book Co., Inc., New York, **1939**, Vol. I, p. 142.

were Norit and finely divided sugar charcoal. Neither the course of the reaction nor the products obtained appeared to be influenced by the kind of carbon used.

Both an elevated temperature and the addition of a mercury catalyst were employed. The reaction proceeded steadily and without explosions, when the reaction tube was heated to just below a dull red. An amalgamated copper tube was used in some of the earlier work, but it was found that about 1% of a mercury salt such as mercurous or mercuric chloride well mixed with the finely divided carbon was satisfactory. Copper gauze packed in the reaction tube in a manner similar to that found satisfactory for the direct fluorination of hydrocarbons did not prevent explosions. If, however, the gauze was amalgamated or if the carbon was mixed with a mercury catalyst no explosions occurred.

The fluorine, direct from the generator and without the removal of hydrogen fluoride, was passed through the copper tube containing the carbon and catalyst. The gaseous products were bubbled through traps containing sodium hydroxide solution and then collected over water. The gases were purified further by an additional passage through sodium hydroxide solution, then through concentrated sulfuric acid, and finally through phosphorus pentoxide.

The separations were made with the low temperature fractionating column described by one of the authors,[15] and the molecular weights determined in an all glass density balance a design of which has been published recently.[16] The vapor densities were checked by determinations made by the Dumas method. The two methods gave results in close agreement. The perfect gas law was assumed in those determinations. The liquid densities were determined by weighing known volumes in small sealed tubes. The freezing points were determined from warming curves, and the vapor pressures by direct measurement on a mercury manometer, while the material was warming slowly. The bulb, which served as a container, had an internal thermocouple and was surrounded by a heavy copper tube inside a vacuum flask. Three to five hours were required for the warming process. The thermocouples were made from calibrated copper and constantan wire and checked on the apparatus. The precision of the temperature measurements is better than one degree.

Analysis.—The constant boiling fractions of the fluorocarbons were analyzed by the following method. Two to three times the amount of sodium necessary for complete reaction was placed in a nickel boat. This was surrounded with a nickel tube and placed in a quartz tube which was sealed at one end. The open end of the quartz tube was sealed with a vacuum wax to a vacuum system. The air was exhausted and the tube baked out by heating strongly with a burner. An air-free sample of the fluorocarbon (0.5 to 1.0 g.) was weighed in a glass bulb. It was introduced into the vacuum system and condensed into a bulb which connected to the quartz tube. Upon evaporation it produced a pressure in the quartz tube. The quartz tube just below the nickel boat was then heated to a red heat with a gas burner. When the pressure was reduced to nearly zero by the reaction, the heating was stopped. When cold, air was admitted and the quartz tube removed. The excess sodium was removed by reaction with absolute alcohol and the sodium fluoride and carbon washed with alcohol onto a Gooch crucible. It was weighed, the sodium fluoride dissolved by washing with hot water, and it was weighed again. The carbon was burned by ignition and a final weight obtained.

This method was tried with a known sample of carbon tetrafluoride: F, calcd. 86.4%, found 86.1%; C, calcd. 13.6%, found 13.8%. With the higher boiling sample of C_4F_{10} an appreciable amount of sodium carbide apparently was formed. In this case the fluorine was determined by calcium fluoride precipitation. Fluorine also was determined by calcium fluoride precipitation for C_6F_{12}. In all samples the pressure fell to practically zero after reaction, which proved that the compounds did not contain hydrogen atoms in the molecules. The aqueous solution formed by dissolving the salt from the crucible was tested in every case with a silver nitrate solution. Only a trace of precipitate was formed in any sample. This proves that the compounds did not contain halogen other than fluorine, sulfur, etc.

Calcd. for C_3F_8: F, 80.85; C, 19.15. Found: F, 80.5; C, 19.9. Calcd. for C_4F_{10} (low boiling): F, 79.85; C, 20.15. Found: F, 80.5; C, 18.8. Calcd. for C_4F_{10} (high boiling): F, 80.5. Found: F, 78.8. Calcd. for C_5F_{10}: F, 76.0; C, 24.0. Found: F, 76.4; C, 24.2. Calcd. for C_6F_{12}: F, 76.0; C, 24.0. Found: F, 76.1; C, 24.6. Calcd. for C_7F_{14}: F, 76.0; C, 24.0. Found: F, 76.0; C, 23.1.

Results.—The results of our last preparation are given in the table. The first six fractions were obtained as constant boiling cuts. From a boiling temperature at atmospheric pressure of about 25°, there is a continuous rise of the boiling temperature as material is removed during distillation except for two temperatures, 51 and 80°, where constant boiling fractions are obtained. The molecular weights of the constant boiling fractions correspond with the formulas tentatively assigned. Apparently an homologous series of saturated fluorocarbons is formed in the reaction in addition to compounds not belonging to this series. Carbon tetrafluoride and hexafluoroethane are obtained in the largest amounts. Octafluoropropane with its long liquid range can be obtained fairly pure, and two fractions are separated which are apparently the two isomers of decafluorobutane. The determined molecular weight of the lower boiling was less than, and the higher boiling greater than, the theoretical. This is undoubtedly because, with only a small amount of material and a small difference in boiling temperature between the fractions, we crowded both fractions, leaving some lower boiling material in the lower and higher boiling in the upper. The

---

[15] Simons, *Ind. Eng. Chem., Anal. Ed.*, **10**, 29 (1938).

[16] Simons, *ibid.*, **10**, 587 (1938).

TABLE I

PHYSICAL PROPERTIES OF PRODUCTS OBTAINED IN DISTILLATION OF FLUOROCARBONS

Fraction	Volume of liquid Cc.	%	Assumed formula[e]	M. p., °C.	B. p., °C.	Molecular weight, Found	Calcd.	Liquid density g./cc. at 0.2°	8.8°	20.8°	Vapor pressure $\log_{10} P$ mm. $= -A/T + B$ A	B	ΔH of vaporization, calcd. cal. per mole
1	246	54.5	CF_4[a]	−184	−128	88	88	(1.96	at	−184°)			2947
2	57	12.6	C_2F_6[a]	−100.6	− 78.2	138	138	(1.85	at	− 78°)			4005
3	37	8.2	C_3F_8	−183	− 38	188	188	1.45			1070	7.43	4920
4	24	5.3	C_4F_{10}	Glass	− 4.7	230	238	1.53	1.49	1.47	1217	7.43	5600
5	6	1.3	C_4F_{10}	Glass	3.0	241	238				1260	7.44	5800
6	25	5.5	C_5F_{10}[b]	*Ca.* −12	23	254–9	250	1.72	1.69	1.67	1350	7.43	6200
7	20	4.4	C_6F_{12}[b]	Glass	51	300–3	300	1.65	1.63	1.60	1500	7.51	6900
8	6	1.3	C_8F_{14}[b]	Glass	80	350–5	350	1.83	1.82	1.78	1610	7.43	7400
9	25	5.5	Mixture[c]		25 to 95								
10	7	1.5	Mixture[d]		95 to 160								

[a] Physical constants from Ruff, *Angew. Chem.*, **46**, 739 (1933). [b] We believe these compounds to be cyclic in structure, fraction number 6 is probably decafluorocyclopentane, number 7 is probably dodecafluorocyclohexane, and number 8 is probably also a derivative of a cyclic compound. [c] This mixture probably contains a variety of fluorocarbons containing from five to eight carbon atoms, inclusive. [d] This mixture probably contains fluorocarbons having from eight to twelve carbon atoms, inclusive. One-third of this mixture boiled between 95 and 105°, one-third between 105 and 120° and the remainder up to 160°. [e] A system of nomenclature for these compounds is desired. They are distinctly not derivatives of hydrocarbons as their properties show. To name them as such requires long names which will become even more cumbersome as more complex compounds with their isomers and substitution derivatives are made and isolated. The authors wish to suggest the following nomenclature: methfluorane, ethfluorane, ethfluorene, profluorane, bufluorane, cyclopentfluorane, methfluorylcyclohexfluorane, etc.

fraction boiling at 23° we have assumed to be decafluorocyclopentane. It has a much higher freezing point than the other fractions and appears to be mostly one compound. However, neither a sharp freezing point nor an entirely reproducible molecular weight could be obtained, and this latter was uniformly higher than the theoretical. As the saturated dodecafluoropentane isomers would boil at about the same temperature, it is assumed that the compound is contaminated with a small amount of them. If this is correct, then the higher fractions having constant boiling temperatures are probably either CF_3 derivatives of decafluorocyclopentane or dodecafluorocyclohexane and its trifluoromethyl derivative. The material from which no constant boiling fractions could be obtained is assumed to be a mixture of higher boiling fluorocarbons probably with many of the isomers present. This would be analogous to petroleum ether.

The substances are colorless and either odorless or very nearly so. They are very stable chemically. Many of the tubes containing these were sealed off while an appreciable pressure of the vapor existed inside. No trace of etching or carbonization could be observed in the Pyrex glass seal, which must have been at least 700°. The different fractions were tested for unsaturation with bromine in carbon tetrachloride solution, and no decolorization could be observed.

Discussion.—The formation of stable compounds of carbon and fluorine containing more than three carbon atoms per molecule indicates the possibility of the synthesis of a large number of similar compounds provided that methods can be discovered. Such compounds should be of considerable interest both theoretically and as useful substances.

To indicate the relatively low attractive force between the molecules of these compounds, a graph is shown in the figure. The molecular weight is plotted against the boiling point. On the same graph are represented the inert gases, the hydrocarbons, and a few other substances. The fluorocarbon curve does not lie greatly above the inert gas curve, whereas the hydrocarbon curve is very much higher. The fluorocarbons approach the inert gases in properties more closely than any other compounds. This curve also shows that we cannot be greatly in error in the formulas of these compounds. The three and four carbon compounds fall on a smooth curve with the previously known one and two carbon compounds. The three higher boiling compounds are slightly above this curve analogous to the positions of cyclopentane and cyclohexane relative to the hydrocarbon curve. The presence in the molecules of these compounds of one or more hydrogen atoms would both lower the molecular weight and raise the boiling point due to the introduction of an electric moment. This would place the compounds far above the curve.

The authors wish to acknowledge gratefully the assistance in the preparation and separation of these compounds of the following Graduate Students at the Pennsylvania State College: R. L. Bond, J. W. Ford, R. E. McArthur, D. I. Randall, T. K. Sloat, and A. C. Werner.

Summary

A continuous reaction between fluorine and carbon without explosions has been accomplished.

Compounds corresponding in molecular weight to octafluoropropane, two isomers of decafluorobutane, decafluorocyclopentane, a dodecafluorohexane, and a tetradecafluoroheptane have been isolated in addition to carbon tetrafluoride and hexafluoroethane.

The properties of these compounds have been determined. A mixture of fluorocarbons boiling from 25 to 160° has been obtained.

STATE COLLEGE, PENNA. RECEIVED NOVEMBER 2, 1938

[CONTRIBUTION FROM THE PEARSON MEMORIAL LABORATORY OF TUFTS COLLEGE]

The Action of *p*-Tolyl Isothiocyanate on Ethyl Acetonedicarboxylate

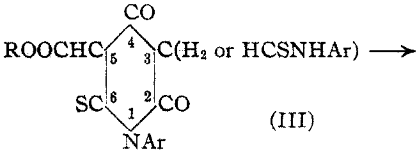
BY DAVID E. WORRALL

In connection with a study of the chemistry of isothiocyanates it seemed desirable to investigate their reactivity toward molecules containing two active methylene groups. Ethyl acetonedicarboxylate (I), a relatively common substance which contains such a system, was selected for this purpose. It quickly became apparent that this ester does not follow the pattern of substances previously studied,[1] but reacts in a highly characteristic manner.

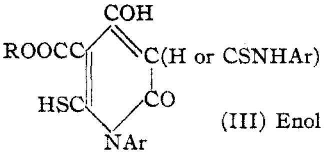
Through the sodium derivative I probably does form the expected thiotoluide, either with one or two equivalents of tolyl isothiocyanate. An additional reaction follows in which the elements of ethyl alcohol are lost. Ring closure suggests itself, particularly as the product contains a nucleus comparatively stable toward acid or alkali which remains intact through certain transformations. Sulfur is labile in the monosulfo derivative; therefore it is concluded that a piperidine ring is formed.

$$\mathrm{ROOCCH_2COCH(COOR)CSNHAr} \longrightarrow \underline{\mathrm{OCCH_2COCH(COOR)CSNAr}}\ \mathrm{(II)} + \mathrm{ROH}$$

The same reaction takes place, using two equivalents of metal and isothiocyanate, although the second methylene group is converted into a thioamide producing III. Sulfur in the side chain is comparatively non-reactive. These pyridones are sufficiently acidic to decompose alkali carbonates forming salts stable toward acetic acid, thus functioning as hydroxypyridines. Because of the presence of tertiary nitrogen, isomerization is restricted to the introduction of two double bonds.



(III)



(III) Enol

II and III obviously form thio ethers with methyl iodide in alkaline solution, for the products contain inactive sulfur, whereas the parent substances readily lose this element. Hence one double linkage is located between positions 5 and 6 in the pyridine ring. Further alkylation is possible since the mono methyl ethers still are capable of forming metal derivatives. It is believed that these changes involve the shifting of hydrogen to position 4 rather than 2 which contains oxygen more completely neutralized. With dimethyl sulfate a third hydrogen, that attached to the amide nitrogen is replaced. Ethyltoluidine and a dimethylpyridine dicarboxylate, result from secondary reactions. The carbethoxy group is easily lost both with II and III.

II forms a stable bromine derivative. The methyl ether does likewise, therefore bromine is

---

[1] Worrall, THIS JOURNAL, 46, 2834 (1924).