shows an effect for nicotinamide similar to that observed for *p*-aminobenzoic acid. Absorption is significantly lower than for corresponding amounts of nicotinic acid. The nicotinamide, like *p*-aminobenzoic acid and unlike nicotinic acid, is almost completely washed from the cells. The remaining amount (less than 0.5 γ/cc.) is presumably fixed and utilized.

Incubation of red blood cells with saline containing varying quantities of non-radioactive nicotinic acid plus a constant amount of radioactive nicotinic acid produces the effects seen in Figs. 2 and 3 and in Table I. The dilution of the isotope changes the uptake of the radioactive nicotinic acid as would be expected if the red cells have a saturation point for nicotinic acid. From Table I, this saturation point is reached at about 10 γ/cc. of packed red cells. (This value has been obtained on the blood of two normal men.) This figure is in agreement with that which is calculated from the values given in the *in vivo* experiments of Hoagland, Ward and Shank,[1] if one assumes that daily ingestion of 20 mg. of nicotinic acid/kg. will produce saturation of the erythrocytes.

TABLE I

UPTAKE OF RADIOACTIVITY BY RED BLOOD CELLS AS A FUNCTION OF MOLE FRACTION[a] OF RADIOACTIVE NICOTINIC ACID

Mole % of radioactive nicotinic acid added	Radioactivity in c./sec./0.05 cc. 20 minutes Supernate	20 minutes Cells	24 hours Supernate	24 hours Cells	24 hours Washed cells[b]
1	17.4	8.0	15.0	12.8	1.2
2	16.0	8.8	14.6	12.2	1.4
10	20.3	8.1	13.2	11.3	2.2
50	19.6	7.1	5.2	13.1	10.1
75	21.0	7.1	2.5	15.9	11.0
100	20.0	9.0	1.6	22.6	19.0

[a] In each experiment, 0.005 mg. of radioactive nicotinic acid was added to 1 cc. of whole blood and the non-radioactive nicotinic acid was varied. [b] One-half cc. of cells washed three times with six times the volume of normal saline.

An experiment similar to the one described above was performed substituting mouse blood for human blood. It was found that in this case both nicotinic acid and nicotinamide are utilized and fixed in the erythrocytes to the same extent. The saturation obtained for a series of six mice was 4 γ/cc. of packed red cells. From this it can be seen that there is a species difference in the utilization of nicotinic acid and nicotinamide. This is significant in evaluating the *in vivo* experiments on mice described elsewhere by the authors.[5]

Conclusions

1. Nicotinic acid *in vitro* is quantitatively taken up by the red blood cells and is fixed in the cells in a non-diffusible form, presumably as coenzyme.
2. Nicotinamide and *p*-aminobenzoic acid, like nicotinic acid, are freely diffusible through the cell membrane, but differ from nicotinic acid in that all but a relatively small amount (less than 0.5 γ/cc. of blood) can be removed from the cells with repeated washings—thus confirming a marked difference of utilization of nicotinic acid and its amide in the human erythrocyte.
3. Isotope dilution techniques indicate that for two normal men approximately 10 γ of nicotinic acid are utilized by 1 cc. of packed erythrocytes.
4. Mouse erythrocytes *in vitro* utilize nicotinic acid and nicotinamide to a similar degree.

(5) Lloyd Roth, Edgar Leifer, John Hogness and Wright Langham, *J. Biol. Chem.*, to be published.

LOS ALAMOS, N. M. RECEIVED APRIL 28, 1948

[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

A Grignard Reagent from 3-Chloro-1,1,1-trifluoropropane

BY E. T. McBEE AND ANTHONY TRUCHAN

Grignard reagents containing fluorine offer possibilities for the preparation of many interesting fluoro compounds. Numerous attempts have been made to prepare Grignard reagents from polyfluoroalkyl chlorides, bromides and iodides but with little success in the past. Henne[1,2] treated several fluorine-containing aliphatic halides with magnesium in ether solution and in each instance either reaction failed to occur or an olefin resulted through the loss of the halogens on adjacent carbon atoms. Thus far, there is no evidence that a Grignard *alpha* to a fluorinated group has been prepared except in one instance,[3] for which the art as yet discloses no corroboration.

It has now been found that $CF_3CH_2CH_2Cl$ reacts in an ether solution with magnesium to form the Grignard reagent, $CF_3CH_2CH_2MgCl$. The success of the reaction is dependent upon anhydrous condition. The $CF_3CH_2CH_2Cl$ may be dried satisfactorily over Drierite or by distillation from phosphorus pentoxide. Analytical grade diethyl ether was used successfully. A crystal of iodine or methyl iodide was employed in the usual way to initiate the reaction. The Grignard re-

(1) A. L. Henne, THIS JOURNAL, **60**, 2275 (1938).
(2) A. L. Henne and A. M. Whaley, *ibid.*, **64**, 1157 (1942).
(3) T. J. Brice, W. H. Pearlson and J. H. Simons, *ibid.*, **68**, 968 (1946).

agent, $CF_3CH_2CH_2MgCl$, was converted to $CF_3CH_2CH_3$ by hydrolysis, to $CF_3CH_2CH_2OH$ by oxygen and hydrolysis, and to $CF_3CH_2CH_2CO_2H$ by carbon dioxide and hydrolysis. The alcohol was found to be identical to the one prepared by Scherer[4] following another procedure. The γ,γ,γ-trifluorobutyric acid is a new compound.

The $CF_3CH_2CH_2Cl$, used in the preparation of the Grignard reagent, was prepared by the vapor-phase chlorination of $CF_3CH_2CH_3$ following an improved synthesis which gives a preponderance of monochlorides.

Experimental

Chlorination of 1,1,1-Trifluoropropane.—Chlorinations were carried out at 110° in a 2-liter round-bottom flask surrounded by three 200-watt incandescent lamps. The lamps served a dual purpose of furnishing light for the photochemical reaction and heat to maintain the temperature. Chlorine and trifluoropropane were introduced at predetermined rates through calibrated flow meters. The products were led from the reaction flask to the bottom of a countercurrent water scrubber to remove hydrogen chloride. Gases leaving the scrubber were dried and collected in a receiver cooled by Dry Ice. The organic material was separated by rectification.

In a typical experiment, 1,1,1-trifluoropropane and chlorine were introduced into the reactor at a rate of 45 l./hr. and 11.5 l./hr., respectively. After 14.7 moles of trifluoropropane had been introduced, the system was purged with air and the product was rectified to strip out unreacted trifluoropropane for recycling. This procedure was continued until 10.4 moles had reacted. Upon rectification of the final product, there was obtained 2.2 moles of $CF_3CHClCH_3$, 5.8 moles of $CF_3CH_2CH_2Cl$, and 1.7 moles of $CF_3CH_2CHCl_2$ or a yield of chlorinated product of 93%. This is a different ratio of products than obtained by Henne using a different technique,[2] although the preferential path of chlorination is still substitution of hydrogen beta to the trifluoromethyl group.

Synthesis of 3,3,3-Trifluoropropanol.—A 1-liter, 3-necked flask was equipped with a mercury-sealed stirrer, a dropping funnel and a reflux condenser the top of which contained a calcium chloride tube. Magnesium turnings (0.8 mole) was placed in the flask and the system was flushed with dry nitrogen. A solution of 3-chloro-1,1,1-trifluoropropane (0.8 mole) in dry ethyl ether (300 ml.) was added from the dropping funnel. The reaction was slow in starting and had to be catalyzed with a crystal of iodine. Once started, the reaction was very vigorous. Dry oxygen was introduced into the flask until no more was absorbed. Then 200 ml. of 25% sulfuric acid was added. The water phase was continuously extracted with ether for five hours. The ether extract was dried over Drierite and then rectified to give 36 g. of 3,3,3-trifluoropropanol, b. p. 100°, d^{28}_4 1.2937, $n^{28}D$ 1.3200.

Anal. Calcd. for $C_3H_5F_3O$: F, 50.0. Found: F, 50.0.

Synthesis of γ,γ,γ-Trifluorobutyric Acid.—The Grignard reagent was prepared as before starting with 0.4 mole of $CF_3CH_2CH_2Cl$ and small lumps of solid carbon dioxide were dropped into the ether solution. The resulting mixture was then treated with 100 ml. of dilute sulfuric acid. The layers were separated and the aqueous layer was extracted several times with fresh portions of ether. The combined ether layers were dried over anhydrous calcium chloride and the ether was then boiled away. The residue was transferred to a 50-ml. side arm distilling flask fitted with an air condenser. The fraction boiling in the range 162–176° was collected as $CF_3CH_2CH_2CO_2H$ (24 g., 0.17 mole). The $CF_3CH_2CH_2CO_2H$ was dissolved in (30–60°) petroleum ether, decolorized with Norite and recrystallized twice to give a white solid (m. p. 33.2°, b. p. 166.6°) having an odor similar to that of butyric acid. Neutral equivalent calcd. for $C_4H_5F_3O_2$: 142.1. Found: 141.4.

Acknowledgment.—The authors express their thanks to the Mallinckrodt Chemical Works, St. Louis, Missouri, for financial assistance of this work.

Summary

A Grignard reagent containing fluorine was obtained by treating $CF_3CH_2CH_2Cl$ in diethyl ether with magnesium turnings to give $CF_3CH_2CH_2MgCl$. The latter was converted to $CF_3CH_2CH_3$, $CF_3CH_2CH_2OH$ and $CF_3CH_2CH_2CO_2H$ by reactions common to Grignard reagents.

LAFAYETTE, INDIANA RECEIVED MAY 3, 1948

(4) Scherer, Off. Pub. Bd. Report PB743, 1941.

[CONTRIBUTION NO. 11 FROM THE THERMODYNAMICS LABORATORY, PETROLEUM EXPERIMENT STATION, BUREAU OF MINES]

The Heat Capacities, Heats of Transition, Heats of Fusion and Entropies of Cyclopentene and Cyclohexene

BY HUGH M. HUFFMAN, MARGARET EATON AND GEORGE D. OLIVER

As a part of the program of the Bureau of Mines to obtain thermodynamic data on petroleum hydrocarbons and related substances, low-temperature thermal investigations have been made on the two unsaturated alicyclics, cyclopentene and cyclohexene. Parks and Huffman[1] investigated cyclohexene over the temperature range of 90° K. to about room temperature. In general, their results agree with those of this research within their estimated error of 1%.

Materials.—These hydrocarbons were A.P.I.–N.B.S. "best" samples purified by A. P. I. Project 6 at the National Bureau of Standards.[2] An estimate of the mole per cent. impurity

(1) Parks and Huffman, THIS JOURNAL, **52**, 4381 (1930).

(2) These samples of API–NBS hydrocarbons have been made available by the American Petroleum Institute and the National Bureau of Standards through the A. P. I. Research Project 44 on the "Collection, analysis, and calculation of data on the properties of hydrocarbons." These samples were purified at the National Bureau of Standards by the API Research Project 6 in the "Analysis, purification, and properties of hydrocarbons," under the supervision of Frederick D. Rossini, from materials supplied by the following laboratories: Cyclopentene, by the Atlantic Refining Company, Philadelphia, Pa., and the American Petroleum Institute Research Project 45 at The Ohio State University, under the supervision of C. E. Boord. Cyclohexene, by the American Petroleum Institute Research Project 6 at the National Bureau of Standards.