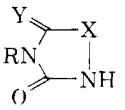
TABLE III



R	M.p., °C.	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	% Nitrogen Calcd.	% Nitrogen Found
A. 1-Amino-5,5-dimethylhydantoin Derivatives (Y = $(CH_3)_2$, X = O)								
$C_6H_5CH{=}N-$	190–192[a]	$C_{12}H_{13}N_3O_2$						
$C_6H_5CH_2NH-$	132–133	$C_{12}H_{15}N_3O_2$	61.78	61.55	6.48	6.55	18.02	17.91
B. 4-Aminourazole Derivatives (Y = O, X = NH)								
$C_6H_5CH{=}N-$	255–257[b]	$C_9H_8N_4O_2$						
$C_6H_5CH_2NH-$	249–251	$C_9H_{10}N_4O_2$	52.42	52.33	4.89	4.83	27.17	27.08

[a] Lit.[12] m.p. 191–192. [b] Lit.[46] m.p. 253–254.

Experimental[7]

The 1-aminomorpholine used was a commercial sample obtained from Food Machinery Corp. Published procedures were used to prepare 3-aminooxazolidinone,[8] 1-amino-2-morpholinone,[9] and 4-aminourazole.[10] The 3-benzylideneamino-2-oxazolidinone and 3-phenethylidineamino-2-oxazolidinone were also prepared by the method of Gever, *et al.*,[4] starting from the hydrazino alcohol. The 1-benzylidineamino-5,5-dimethylhydantoin was also prepared by the method of Bailey and Read.[11] Condensation of *p*-chlorobenzyl chloride with 3-amino-2-oxazolidinone in alcoholic solution resulted in a 10% yield of 3-(*p*-chlorobenzylamino)-2-oxazolidinone.

1-Benzylidineamino-5,5-dimethylhydantoin (Electrolytic Preparation.)—Utilizing the set-up described in "Organic Syntheses,"[12] a mixture of 57 g. (0.33 mole) of 1-nitro-5,5-dimethylhydantoin and 1500 ml. of 20% H_2SO_4 was subjected to a current of 15 ± 1 amp. at *ca.* 6 v./8 hr. The temperature was maintained at 5–10° by stirring in an ice–salt bath. At the end of the 8-hr. period, approximately 800 ml. of electrolyte was removed under vacuum, and the residue was filtered and neutralized (to pH 7) with solid sodium hydroxide in an ice bath. A solution of 53 g. (0.5 mole) of benzaldehyde in 500 ml. of 95% ethanol was added, and the mixture was heated to boiling and put aside to cool. After standing overnight in a refrigerator, filtration yielded off-white crystals. Recrystallization from 50% aqueous ethanol resulted in colorless crystals (26.4 g., 56%), m.p. 190–192°.

(7) All melting points are corrected.
(8) British Patent 735,169 (1955).
(9) J. Shavel, Jr., F. Leonard, F. H. McMillan, and J. A. King, *J. Am. Pharm. Assoc.*, **42**, 402 (1953).
(10) A. M. Munro and F. J. Wilson, *J. Chem. Soc.*, 1257 (1928).
(11) J. R. Bailey and W. T. Read, *J. Am. Chem. Soc.*, **37**, 1884 (1915).
(12) H. Gilman and A. H. Blatt, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 485.

The Synthesis of 2-Amino-3-trifluoromethylbutyric Acid[1]

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The synthesis of amino acids containing a terminal trifluoromethyl group as possible amino acid antagonists has been reported.[3] Of several amino acids prepared, only 2-amino-5,5,5-trifluorovaleric acid greatly inhibited the growth of *Escherichia coli*. This encouraged the synthesis of the corresponding isomeric acid, 2-amino-3-trifluoromethylbutyric acid, *viz.*, 4,4,4-trifluorovaline.

Walborsky, *et al.*,[3] have shown previously that the ammonolysis of ethyl 2-bromo-4,4,4-trifluorobutyrate gave 3-amino-4,4,4-trifluorobutyramide instead of the expected 2-amino isomer. The mechanism for this transformation was postulated[3b] as an initial loss of hydrogen bromide to give ethyl 4,4,4-trifluorocrotonate followed by the addition of ammonia into the β-position. This was confirmed from the fact that addition

$$CF_3CH_2CHBrCOOC_2H_5 \xrightarrow{-HBr} CF_3CH{=}CHCOOC_2H_5 \xrightarrow{NH_3} CF_3CH(NH_2)CH_2CONH_2$$

of gaseous ammonia to ethyl 4,4,4-trifluorocrotonate and ammonolysis of ethyl 3-bromo-4,4,4-trifluorobutyrate with concentrated ammonium hydroxide gave the same 3-amino compound. The desired compound, 2-amino-4,4,4-trifluorobutyramide, was finally obtained byutilizing the less basic and more nucleophilic azide ion to decrease the tendency for elimination and favor the direct displacement of the bromine atom.[3c]

Since it was anticipated that ammonolysis of ethyl 2-bromo-3-trifluoromethylbutyrate would yield the 3-amino compound by a similar mechanism, displacement of the bromine atom with azide ion was chosen as the best possible path to the desired α-amino acid.[4]

$$CF_3CH(CH_3)CH_2COOH \xrightarrow[(2)\ C_2H_5OH]{(1)\ PCl_3\text{–}Br_2} CF_3CH(CH_3)CHBrCOOC_2H_5 \xrightarrow{NaN_3} CF_3CH(CH_3)CH(N_3)COOC_2H_5 \xrightarrow[(2)\ H_3O^+]{(1)\ Pd\text{–}H_2} CF_3(CH)CH_3CH(NH_2)COOH$$

Refluxing 3-trifluoromethylbutyric acid with bromine and phosphorus trichloride for several hours, followed by dilution with anhydrous ethyl alcohol, afforded a 32% yield of the α-bromo ester. Treatment of the bromo ester with a large excess of sodium azide gave the α-azido ester which was subsequently hydrogenated with palladium and finally hydrolyzed with concentrated hydrochloric acid. This final step afforded a 56.5% yield of practically pure amino acid.

(1) This investigation was supported by the National Cancer Institute of the National Institutes of Health, Public Health Service.
(2) (a) Taken from a portion of the thesis submitted by D. F. Loncrini in partial fulfillment of the requirements for the Ph.D. degree in Chemistry, Florida State University, 1956; (b) General Electric Co., Insulating Materials Department, Schenectady, N. Y.
(3) (a) H. M. Walborsky and M. Schwarz, *J. Am. Chem. Soc.*, **75**, 3241 (1953); (b) H. M. Walborsky, M. Blum, and D. F. Loncrini, *ibid.*, **77**, 3637 (1955); (c) H. M. Walborsky and M. Baum, *J. Org. Chem.*, **21**, 538 (1956).
(4) It was recently demonstrated [I. L. Knunyants and Yu. A. Cheburkov, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (English Transl.)*, **6**, 977 (1961); *Chem. Abstr.*, **55**, 27046 (1961)] that nucleophilic reagents add at the 3-position of 3-trifluoromethylcrotonic acid as we had anticipated.

The amino acid was tested for its ability to inhibit the growth of *E. coli*, ATCC 9723, and *S. cerevisiae*, strain 139, according to the method of Dittmer, *et al.*[5] It was inactive on both the yeast strain and on the *E. coli* up to 100γ/7 ml. of medium.

Experimental[6]

3-Trifluoromethylbutyric Acid.—4-Trifluoromethylcrotonic acid (100 g., 0.65 mole) was hydrogenated with 3.0 g. of 5% palladium-on-charcoal at an initial pressure of 4.22 kg./cm.^{2} After the theoretical absorption of hydrogen was completed (0.75 hr.), the catalyst was removed by filtration, the solution was washed with chloroform, and the combined filtrate was distilled to yield 90.5 g. (89%) of product, b.p. 90–91° (25 mm.), n^{24}D 1.3580.

Anal. Calcd. for $C_5H_9F_3O_2$: C, 38.47; H, 4.52. Found: 38.64; H, 4.64.

Ethyl 2-Bromo-3-trifluoromethylbutyrate.—A mixture of 50 g. (0.32 mole) of 3-trifluoromethylbutyric acid, 41 g. (0.3 mole) of phosphorus trichloride, and 80 g. (0.5 mole) of bromine was heated for 20 hr. at 125°. The excess bromine and phosphorus trichloride were removed *in vacuo* and 47 g. (1.0 mole) of absolute ethanol was added dropwise with stirring. The mixture was distilled through a Wheeler column to yield 23.5 g. (40%) of ethyl 3-trifluoromethylbutyrate, b.p. 136–137, n^{24}D 1.3631, d^{20}_4 1.148; and 27.1 g. (32%) of α-bromoester, b.p. 180°, $n^{22.5}$D 1.4071, d^{20}_4 1.468, MRD 44.11 (calcd. 43.83).

Anal. Calcd. for $C_7H_9BrF_3O_2$: C, 31.95; H, 3.83. Found: C, 31.97; H, 4.12.

Ethyl 2-Azido-3-trifluoromethylbutyrate.—The bromo ester (27 g., 0.1 mole), 100 g. (1.5 moles) of sodium azide, 50 ml. of ethyl alcohol, and enough water to dissolve the sodium azide were refluxed for 127 hr. The reaction mixture was steam distilled, heavily salted, and extracted with ether. The extract was dried over sodium sulfate and stripped *in vacuo*. Distillation yielded 5 g. (22%) of product, b.p. 69–70° (11 mm.), $n^{22.5}$D 1.4000; d^{20}_4 1.230; MRD 44.33 (calcd. 44.65).

4,4,4-Trifluorovaline.—The azido ester (5 g. 0.22 mole) in 10 ml. of ethanol was hydrogenated for 22 hr. at 4.43 kg./cm.^{2} with 5% palladium-on-charcoal. The catalyst was filtered and washed with ether. Dry hydrogen chloride gas was bubbled into the solution and the solvent was evaporated *in vacuo*. The resulting paste was refluxed for 23 hr. with 30 ml. of concentrated HCl. The mixture was evaporated to dryness *in vacuo*, and absolute ethanol was added and again evaporated to dryness *in vacuo*. The resulting solid was dissolved in absolute ethanol, neutralized with pyridine, and refrigerated. There was obtained 2.1 g. (56.5%) of practically pure amino acid. Recrystallization from water–alcohol gave white plates, m.p. 239° dec., R_f (80% butanol and 20% acetic acid) 0.61; R_f (65% pyridine and 25% water) 0.94. The product gave a positive ninhydrin test.

Anal. Calcd. for $C_5H_8F_3NO_2$: C, 35.09; H, 4.74; N, 8.18. Found: C, 35.20; H, 4.87; N, 8.05.

Acknowledgment.—We wish to express our sincere appreciation to Dr. Karl Dittmer and his staff for the microbiological assay.

(5) K. Dittmer, H. L. Goering, I. Goodman, and S. J. Crisrol, *J. Am. Chem. Soc.*, **70**, 2499 (1948).

(6) Melting points were taken on a Nalge–Axelrod melting point apparatus and are corrected. Boiling points are uncorrected. Analyses were performed by Mr. E. Thommen, Basel, Switzerland.

para-Substituted Benzenesulfonylureas

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Recently, papers and patents have been published in which *p*-acylphenylsulfonylurea[1–3] with hypoglycemic activity has been described. In this note we wish to describe new compounds in this series as well as sulfonylureas derived from *p*-(γ-chloropropyl)-, *p*-(γ-methoxypropyl)-, and *p*-cyanobenzenesulfonamide. The last three mentioned have been synthesized because of their analogy to the active ureas derived from *p*-chloro- and *p*-methoxybenzenesulfonamide.

The sulfonylureas were prepared either by reaction between an arylsulfonamide and an alkyl isocyanate in the presence of potassium carbonate (method I) or by the pyrolysis of an amine salt of an arylsulfonylcarbamate (method II). Method I worked smoothly and gave high yields with all sulfonamides used, whereas method II failed in some cases to produce the expected results. N-(*p*-Cyanobenzenesulfonyl)-N′-butylurea was obtained from the appropriate carbamate, whereas the N′-cyclohexyl compound could not be prepared in this way.

The preparation of *p*-acetyl and *p*-propionylbenzenesulfonamide according to Meerwein, *et al.*,[4] starting from the *p*-aminoacylphenones has been described.[1–3] We used this method to prepare *p*-butyryl- and *p*-valerylbenzenesulfonamide. *p*-(γ-Chloropropyl)benzenesulfonamide and *p*-(γ-methoxypropyl)benzenesulfonamide were prepared by the chlorosulfonation of the appropriately substituted benzene derivative followed by treatment of the resulting sulfonyl chloride with ammonia.

The evaluation of the hypoglycemic activity was carried out with male rats weighing 150–160 g. The animals were fasted 20 hr. prior to testing and then were treated orally with 100 mg./kg. of the test compounds. Blood glucose levels were determined enzymatically, using four rats per group, tolbutamide and N-(*p*-propionylbenzenesulfonyl)-N′-cyclohexylurea serving as standards. The results obtained with *p*-acylbenzenesulfonylureas show that only compounds with an acetyl or propionyl residue possess hypoglycemic activity, while valeryl-substituted compounds are inactive. In the series of *p*-propionylbenzenesulfonylureas the highest activity was observed when N′ was substituted by cyclohexyl. Replacing the latter by cyclopentyl, hexahydrobenzyl, or by cycloheptyl resulted in gradually diminished activity. The benzyl compound was inactive and the phenethyl- and the hexylureas of this group were hyperglycemics.

Experimental[5,7]

***p*-Butyrylbenzenesulfonamide.**—*p*-Aminobutyrophenone[8] (11 g.) was converted to the sulfonyl chloride by the method of Meerwein.[4] The sulfonyl chloride was then dissolved in dioxane and was added to 6 *N* NH_4OH, the mixture was warmed to 60°, and the solvent and ammonia were removed *in vacuo*, yielding 10 g. of crude sulfonamide, m.p. 108–110°. It was crystallized twice from water, giving slightly cream-colored crystals, m.p. 111°.

Anal. Calcd. for $C_{10}H_{13}NO_3S$: C, 52.85; H, 5.77. Found: C, 52.88; H, 5.81.

(1) Eli Lilly and Co., Israeli Patent 15,227 (March, 1962).

(2) Farbwerke Höchst A. G. French Patent 1,300,893 and 1,393M (July, 1962).

(3) E. J. Marshall, M. V. Sigal, Jr., H. R. Sullivan, C. Cesnik, and M. A. Root, *J. Med. Chem.*, **6**, 60 (1963).

(4) H. Meerwein, C. Dittmar, R. Göllner, K. Hafner, F. Mensch, and O. Steinfort, *Chem. Ber.*, **90**, 841 (1957).

(5) Melting points were determined on a Fisher-Johns block and are corrected; boiling points are uncorrected.

(6) Elemental analyses were obtained from Mr. A. Bernhardt, Mühlheim (Ruhr).

(7) The author is grateful to Mrs. S. Weiss for her technical assistance.

(8) F. Kunkell, *Chem. Ber.*, **33**, 2641 (1900).