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. Cristol, *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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Received October 8, 1963

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) F. 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).

TABLE I

BENZENESULFONYLUREAS R-C6H4-SO2NHCONHR'

R	R'	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Blood glucose, % change from controls after 2 hr.	4 hr.	6 hr.
CH_3CO	$(CH_2)_2C_6H_5$[a,e,j]	160	$C_{17}H_{18}N_2O_4S$	58.95	5.24	59.13	5.33	−8	0	0
C_2H_5CO	$CH_2C_6H_5$[a,e,i]	198–201	$C_{17}H_{18}N_2O_4S$	58.95	5.24	58.95	5.58	0	0	0
C_2H_5CO	$(CH_2)_2C_6H_5$[a,d,j]	137–138	$C_{18}H_{20}N_2O_4S$	59.98	5.60	60.10	5.85	+7	+9	+18
C_2H_5CO	n-C_6H_{13}[a,e,b,h]	131–134	$C_{16}H_{24}N_2O_4S$	56.45	7.11	56.55	7.13	+17	+23	+14
C_2H_5CO	cyclo-C_5H_{11}[b,e]	153–156	$C_{15}H_{20}N_2O_4S$	55.54	6.27	55.55	6.37	−24	−28	−28
C_2H_5CO	cyclo-$C_6H_{11}CH_2$[c,e]	178–179	$C_{17}H_{24}N_2O_4S$	57.94	6.87	58.18	6.90	−17	−17	−17
C_2H_5CO	cyclo-C_7H_{13}[a,e,g]	163–165	$C_{17}H_{24}N_2O_4S$	57.94	6.87	58.08	6.96	−4	−4	−4
C_4H_9CO	n-C_4H_9[a,e]	145	$C_{16}H_{24}N_2O_4S$	56.45	7.11	56.58	6.95	0	0	
C_4H_9CO	cyclo-C_6H_{11}[a,e]	187	$C_{18}H_{26}N_2O_4S$	59.62	7.23	59.47	7.23	0	0	
$Cl(CH_2)_3$	n-C_4H_9[a,d]	90	$C_{14}H_{21}ClN_2O_3S$	50.50	6.34	50.78	6.21	+12	+17	
$CH_3O(CH_2)_3$	n-C_4H_9[a,e]	80–82	$C_{15}H_{24}N_2O_4S$	54.83	7.38	54.94	7.25	+6	+13	
$CH_3O(CH_2)_3$	cyclo-C_6H_{11}[a,e]	136–138	$C_{17}H_{26}N_2O_4S$	57.59	7.39	57.54	7.34	−21	−22	−11
CN	n-C_4H_9[a,d,k]	181	$C_{12}H_{15}N_3O_3S$	51.20	5.38	50.91	5.36	+9	+13	
CN	cyclo-C_6H_{11}[a,e,k]	168–169	$C_{14}H_{17}N_3O_3S$	54.71	5.60	54.83	5.72	−23	−11	−12
C_2H_5CO	cyclo-C_6H_{11}[f]	183–185						−20	−33	−36
Tolbutamide								−29	−40	−40

[a] Prepared by method I. [b] Prepared by method II from ethyl-N-(4-propionylbenzenesulfonyl)carbamate (m.p. 103°) and cyclopentylamine. [c] Prepared by method II from ethyl-N-(4-propionylbenzenesulfonyl)carbamate and cyclohexylmethylamine. [d] Crystallized from 70% alcohol. [e] Crystallized from benzene. [f] For the preparation of this compound see footnotes 1 and 2. [g] Cycloheptyl isocyanate, b.p. 88–94° (20 mm.), was obtained from cycloheptylurea according to S. Rossi, A. Riva, and B. Piantamida, *Chim. Ind.* (Milan), **42**, 1243 (1960). [h] n-Hexyl isocyanate, b.p. 74–76° (20 mm.). [i] Benzyl isocyanate, b.p. 102° (20 mm.). [j] Phenethyl isocyanate, b.p. 50° (1 mm.). [h-j] Obtained according to C. F. H. Allen and A. Bell, "Organic Syntheses," Coll. Vol. III, New York, N. Y., 1955, p. 846. [k] p-Cyanobenzenesulfonamide was prepared according to E. Miller, J. M. Sprague, L. W. Kissinger, and L. F. McBurney, *J. Am. Chem. Soc.*, **62**, 2099 (1940).

p-Valerylbenzenesulfonamide was prepared from p-aminovalerophenone as described for p-butyrylbenzenesulfonamide. After crystallizing twice from water, white platelets, m.p. 110–112°, were obtained.

Anal. Calcd. for $C_{11}H_{15}NO_3S$: C, 54.73; H, 6.27. Found: C, 54.73; H, 6.39.

p-(Chloropropyl)benzenesulfonamide.—p-(Chloropropyl)benzenesulfonyl chloride, prepared from γ-chloropropylbenzene and chlorosulfonic acid, was converted to the sulfonamide with alcoholic ammonia. After three crystallizations from benzene a pure product, m.p. 77° was obtained.

Anal. Calcd. for $C_9H_{12}ClNO_2S$: C, 46.25; H, 5.18. Found: C, 46.30; H, 5.34.

p-(α-Methoxypropyl)benzenesulfonamide was prepared from γ-phenylpropyl methyl ether[9] as described for p-(γ-chloropropyl)-benzenesulfonamide and was crystallized from benzene, giving colorless crystals, m.p. 94°.

Anal. Calcd. for $C_{10}H_{15}NO_3S$: C, 52.36; H, 6.60; N, 6.11. Found: C, 52.59; H, 5.95; N, 6.15.

N-Arylsulfonyl-N'-alkylureas were prepared either from the arylsulfonamide and an alkyl isocyanate in the presence of potassium carbonate (method I) or from the carbamates and amines (method II) according to published procedures.[1-3]

Acknowledgment.—The author is indebted to Dr. M. Grotto and Dr. R. Horn for their interest and for the permission to publish this note.

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Insect Chemosterilants. I. N-Acylaziridines

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Received January 6, 1964

In recent years interest has grown in the chemistry of aziridines because of the antitumor or carcinostatic activity shown by many of these compounds. More recently it has been found that many of these compounds have the ability to cause sexual sterility in insects.[1] We wish to report the synthesis of a series of N-acylaziridines which were prepared to examine the effect of N-substitution on chemosterilant activity. It is remarkable that the synthesis of these compounds has not previously been reported,[2] since several references describing their antitumor or other properties may be found.[3,4]

The general method of preparation of the N-acylaziridines listed in Tables I and II consisted of reacting equivalent weights of the acid chloride with the appropriate aziridine using a sodium hydroxide solution to neutralize the hydrochloric acid formed in the reaction. Methylene chloride was found to be a convenient solvent and the temperature was held between −10 and 0° during the addition of the acid chloride. While this did not appear to be critical in the majority of reactions, it was found that a change of 15° in either direction led to greatly decreased yields of oxalyl- or malonylbisaziridine. The method used by Bestian[5] for the preparation of some ethyleneamides in which a halide was allowed to react with ethylenimine in the presence of triethylamine was also found applicable to the preparation of a number of our compounds, but in general led to lower yields and a less pure product.

The purification of the solid products by recrystallization presented no difficulty except when an alcohol was used; in such instances it was necessary to limit the heating to avoid reaction with the solvent. Distil-

(1) A. B. Bořkovec, *Science*, **137**, 1034 (1962).

(2) The synthesis of succinylbisaziridine (compound XIX, Table II) and glutarylbisaziridine has been reported by K. C. Tsou, K. Hoegerle, and H. C. F. Su, *J. Med. Chem.*, **6**, 435 (1963).

(3) J. A. Hendry, R. F. Homer, F. L. Rose, and A. L. Walpole, *Brit. J. Pharmacol.*, **6**, 357 (1951).

(4) T. H. Goodridge, W. T. Huntress, and R. T. Bratzel, *Cancer Chemotherapy Rept.*, **26**, 407 (1963).

(5) H. Bestian, *Ann. Chem.*, **566**, 210 (1950).