We wish to thank Mr. José Corrêa Gomes, administrator of the Rio de Janeiro Botanical Garden, for supplying most of the plant material used in this work, and Dr. Leo Marion, National Research Council, Canada, for providing us with an authentic sample of scopoletin from *Gelsemium sempervirens*. We are indebted to the Rockefeller Foundation for a fellowship to one of us (W.B.M.) and to the Conselho Nacional de Pesquisas, Brazil for financial aid. We also extend our thanks to Prof. Carl Djerassi, Chemistry Department, Wayne, State University, for his valuable help and advice.

INSTITUTO DE QUIMICA AGRICOLA
MINISTERIO DA AGRICULTURA
RIO DE JANEIRO, BRAZIL

Synthesis and Investigation of Organic Fluorine Compounds. XXII. The Preparation of Newer 2-Fluoroethylurethan Derivatives

GEORGE A. OLÁH, STEVEN J. KUHN, AND GEORGINA KOVÁCS-BRUCKNER

Received April 30, 1956

Biologically active fluorinated derivatives have been mentioned by Schrader[1] and Knunyants[2] among the derivatives of 2-fluoroethyl chloroformate. In two preceding papers[3,4] we have described a number of 2-fluoroethylurethan derivatives. Simultaneously with our investigations Sawicki, Ray, and Oliverio[5-7] have also published papers about the preparation of new fluorinated urethans.

The inhibiting action of fluoroacetic acid and 2-fluoroethanol, respectively, on the growth of experimentally produced malignant tumors has already been mentioned by us.[8,9] However, due to the rather high toxicity of both compounds, an attempt was made to find less toxic, biologically active derivatives. It appeared possible that the derivatives of 2-fluoroethylurethan would meet these requirements because their pharmacological tests[10] only show the appearance of toxic symptoms after a longer period of latency.

The compounds were too toxic in the chemotherapeutical experiments,[11] so that no significant effect could be observed. However, in some cases there was a slight but definite therapeutic activity toward cancer and we have therefore continued the preparation of further derivatives in the hope of finding less toxic members of the 2-fluoroethyl series. The new derivatives thus prepared are listed in Table I.

Some of the newly prepared derivatives have a toxicity of over 200 mg./kg./rat. The biological and probable insecticidal activity, which was observed by us in previous investigations,[12] will be reported elsewhere.

TABLE I

PREPARATION AND PROPERTIES OF 2-FLUOROETHYLURETHAN DERIVATIVES

R—NR′—$COOC_2H_4F$								
R	R′	B.P., °C.	Mm.	M.P., °C.	Method of preparation	Yield, %	Nitrogen Calcd.	Nitrogen Found
C_2H_5	H	116–117	30		A	90	13.59	13.52
iso-C_3H_7	H	110	30		A	91	9.40	9.28
C_4H_9	H	126–128	10		B	83	8.53	8.39
tert-C_4H_9	H	100	25		A	94	8.60	8.34
CH_2=$CHCH_2$	H	98–100	5		B	77	9.52	9.46
C_6H_{11}	H			63	A	88	7.43	7.27
$>CH_2$	$>CH_2$	91–93	12		B	90	9.78	9.77
o-C_2H_5-C_6H_4	H			81–82	B	79	6.66	6.36
2-CH_3-4-Cl-C_6H_3	H			88–89	B	81	6.06	6.01
2-CH_3-5-Cl-C_6H_3	H			84–85	B	77	6.06	6.00
C_6H_5	C_6H_5			83–84	C	69	5.40	5.33
p-CH_3CO-C_6H_4	H			153–154	A	81	6.25	6.14

(1) G. Schrader, *Die Entwicklung neuer Insektizide auf Grundlage organischer Fluor- und Phosphor-Verbindungen*, 2nd ed., Verlag Chemie, Weinheim, 1952.
(2) I. L. Knunyants, O. V. Kil'disheva, and I. P. Petrov, *J. Gen. Chem., U.S.S.R.*, **19**, 101 (1949) [*Chem. Abstr.*, **43**, 6163 (1949)].
(3) G. Oláh and A. Pavláth, *Acta Chim. Acad. Sci. Hung.*, **4**, 89 (1954) [*Chem. Abstr.*, **49**, 6094 (1955)].
(4) G. Oláh, A Pavláth, and L. Noszkó, *Acta Chim. Acad. Sci. Hung.*, **7**, 443 (1955).
(5) E. Sawicki and F. E. Ray, *J. Org. Chem.*, **18**, 1561 (1953).
(6) V. T. Oliverio and E. Sawicki, *J. Org. Chem.*, **20**, 363 (1955).
(7) V. T. Oliverio and E. Sawicki, *J. Org. Chem.*, **20**, 1733 (1955).
(8) C. Sellei, G. Oláh, S. Eckhart, and L. Kapás, *Magyar Orvosi Hetilap*, **93**, 756 (1952).
(9) C. Sellei, G. Oláh, S. Eckhart, and L. Kapás, *Arch. Geschwulstforschung*, **5**, 263 (1953).
(10) F. Herr, G. Oláh, and A. Pavláth, *Acta Physiol. Acad. Sci. Hung.*, **6**, 105 (1954).
(11) L. Nemeth, G. Oláh, S. Cellei, and B. Kellner, *Arch. Geschwulstforschung*, in press.
(12) G. Oláh and A. Pavláth, *Chem. Tech. (Berlin)*, **7**, 204 (1955).

EXPERIMENTAL

2-Fluoroethanol was prepared in 50% yield from ethylene chlorohydrin and potassium fluoride by ultraviolet irradiation as described by Oláh and Pavláth.[13]

2-Fluoroethyl chloroformate was prepared in 72% yield by the method of Oláh and Pavláth.[4]

General procedures for the preparation of the 2-fluoroethylurethan derivatives. (A). A 0.1-mole portion of the amine was dissolved in 40 ml. of absolute ethyl ether in a three-necked round-bottomed flask fitted with a reflux condenser, a mechanical stirrer, and a dropping-funnel; then 6.32 g. (0.05 mole) of 2-fluoroethyl chloroformate was slowly dropped on to the ice cooled solution. The stirring was continued for an hour after which time the precipitated amine hydrochloride was filtered. The ether was removed by distillation and the remaining oil was fractionated *in vacuo*. If crystalline the product was recrystallized from hexane.

(B). A 0.1-mole portion of the amine was dissolved in a solution of 4.8 g. (0.12 mole) of sodium hydroxide in 25 ml. of water. The resultant solution was cooled in an ice-water bath and efficiently stirred while 12.65 g. (0.1 mole) of 2-fluoroethyl chloroformate was dropped into the mixture. Stirring was continued without further cooling for 2 hr. The 2-fluoroethylurethan formed was extracted with ether, the ether was evaporated, and the residue was fractionated *in vacuo*. In the case of crystalline products the substances were recrystallized from hexane.

(C). A 0.1-mole portion of the amine was dissolved in 25 ml. of benzene and 6.32 g. (0.05 mole) of 2-fluoroethyl chloroformate was added; the reaction then was continued and worked up as under (A).

CHEMICAL CENTRAL RESEARCH INSTITUTE OF
THE HUNGARIAN ACADEMY OF SCIENCES
BUDAPEST, XIV, HUNGARIA-KRT. 114

(13) G. Oláh and A. Pavláth, *Acta Chim. Acad. Sci. Hung.*, **3**, 199 (1953) [*Chem. Abstr.*, **48**, 7533 (1954)].

Synthesis from Thiolacetates. I. Synthesis of Alkanesulfonyl Chlorides[1]

F. G. BORDWELL AND WILLIAM A. HEWETT

Received September 11, 1956

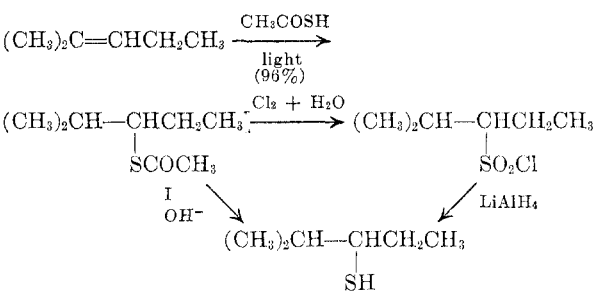
The reaction of thiolacetic acid with olefins has been found to be generally applicable, and to give high yields of thiolacetates.[2] Hydrolysis of these thiolacetates provides an excellent route for the synthesis of thiols.[2] Oxidative chlorination of thiolacetates is utilized herein as a route to the preparation of alkanesulfonyl chlorides from olefins.

Douglass and Johnson included two thiolesters in their general study of the oxidative chlorination of divalent sulfur compounds.[3] They obtained a 71% yield of ethanesulfonyl chloride from ethyl thiolacetate and a mixture of benzyl disulfide, benzyl phenylmethanethiosulfonate, and phenylmethanesulfonyl chloride from benzyl thiolacetate.

In the present study the thiolacetates were prepared in yields of 92–96% from 4-methyl-1-pentene, 2-methyl-2-pentene, and cyclohexene. Oxidative chlorination of these thiolacetates by the method of Douglass and Johnson[3] gave 77%, 62%, and 72% yields of the corresponding sulfonyl chlorides.

The method is, therefore, applicable to the preparation of primary, secondary, and cycloalkanesulfonyl chlorides from the olefins in overall yields of 58–71%. Compounds in which the sulfur atom is attached to a secondary carbon atom appear not to have been subjected to oxidative chlorination of this type before.

The addition of thiolacetic acid to olefins occurs exclusively in an anti-Markownikoff manner,[2b] so the sulfonyl chlorides prepared from them should be of high purity. Their structures should correspond to those of the thiolacetates. However, to make certain that rearrangement does not accompany the oxidative chlorination of thiolacetates to sulfonyl chlorides, the sulfonyl chloride from 1-ethyl-2-methylpropyl thiolacetate (I) was reduced



with lithium aluminum hydride to the thiol. The 2,4-dinitrophenyl sulfide derivative of this thiol was found to be identical with that obtained from the thiol prepared from the original thiolacetate. Since rearrangement is more likely to occur with a secondary thiolacetate having a tertiary hydrogen on an alpha carbon, such as I, than for other types of thiolacetates it seems safe to conclude that rearrangements will not often occur in this reaction.

2-Phenyl-1-propanesulfonyl chloride was prepared by oxidative chlorination of 2-phenylpropyl thiolacetate with the purpose of synthesizing 2-methyl-2,3-dihydrobenzothiophene-1-dioxide from it by ring closure. This is potentially a route to cyclic sulfones of this type from styrenes, but Friedel-Crafts type ring closures were unsuccessful in our hands in this instance.

EXPERIMENTAL[4]

1-Ethyl-2-methylpropyl thiolacetate Thiolacetic acid (Eastman Kodak Co., practical grade) was purified by distillation prior to use. One hundred fifty-two and two-tenths

(1) This investigation was carried out as part of American Petroleum Institute Research Project 48B, given in part at the 126th Meeting of the AMERICAN CHEMICAL SOCIETY, New York, N. Y., September 1954 (p. 6-0 of Abstracts).

(2) (a) The first report of this reaction was B. Holmberg, *Arkiv. Kemi, Mineral Geol.*, **12B**, No. 47, 3 (1938). (b) The literature concerning this reaction, together with numerous further examples, may be found in the Ph.D. dissertation of W. A. Hewett, Northwestern University, August 1955.

(3) I. B. Douglass and T. B. Johnson, *J. Am. Chem. Soc.*, 60, 1486 (1938).

(4) Microanalyses were by Miss Hilda Beck.