TABLE II

ALKYL ω-(2-THIAZOLIN-2-YLTHIO)ALKANOATES (IV)

Compd	Yield, %	Bp, °C (mm)	n^{25}D	ν(C=N),[a] cm⁻¹	Formula	Analyses
IVa	23	122–126 (0.4)	1.5613[25]	1570	$C_6H_9NO_2S_2$	C, H, N, S
IVb	76	122–128 (0.03)	1.5353[24]	1565	$C_9H_{15}NO_2S_2$	C, H, S
IVc	55	137–143 (0.4)	1.5400[24]	1570	$C_9H_{15}NO_2S_2$	C, H, N, S
IVd	29	133–137 (0.2)	1.5350[26]	1565	$C_{10}H_{17}NO_2S_2$	C, H, N, S

[a] Strong absorption.

TABLE III

S-2-AMINOETHYL S′-ω-CARBOXYALKYL DITHIOCARBONATE HYDROCHLORIDES (V)

Compd	Yield, %	Mp, °C	ν, cm⁻¹ C=O[a] CO_2H	ν, cm⁻¹ C=O[a] SCOS	ν, cm⁻¹ SCS[a]	Formula	Analyses
Vb	31	167–169	1710	1640	870	$C_7H_{13}NO_3S_2 \cdot HCl$	C, H, N, S, Cl
Vc[b]	19	142–144	1715	1645	870	$C_8H_{15}NO_3S_2 \cdot HCl$	C, H, N, S, Cl
Vd	18	132–135	1715	1645	860	$C_9H_{17}NO_3S_2 \cdot HCl$	C, H, N, S

[a] Strong absorption; *cf.* ref 2a. [b] Recrystallized from 6 *N* HCl.

alkanoate in DMF (1 ml/g of ester) at such a rate that the reaction temperature did not rise above 50°. The resulting mixture was stirred for 1–4 hr and filtered to remove inorganic salts; DMF was removed from the filtrate under reduced pressure (water aspirator) at 70–75° (hot-water bath). The residual, crude, oily products were sufficiently pure for use as intermediates in the preparation of the corresponding dithiocarbonates, but successive vacuum distillations (short path) were required in order to obtain analytically pure samples as colorless oils (see Table II).

S-2-Aminoethyl S′-ω-Carboxyalkyl Dithiocarbonate Hydrochlorides (V).—Mixtures of IVb–d (~0.1 mole) and 6 *N* HCl (2.5 ml/g of IV) were refluxed for 4 hr. The resulting solutions, while still hot, were clarified by filtration and chilled. The dithiocarbonate hydrochlorides (see Table III) were collected as white crystals, washed (cold EtOH), and dried (P_2O_5) *in vacuo*.

Methyl 2-Thioxo-3-thiazolidinepropionate (VI).—A solution of methyl 3-bromopropionate (42.9 g, 0.257 mole) in DMF (50 ml) was added dropwise to a stirred mixture of III (30.0 g, 0.252 mole), K_2CO_3 (38.5 g, 0.252 mole), and DMF (150 ml), the rate of addition being controlled so that the reaction temperature did not exceed 50°. After the exothermic reaction the mixture was stirred at room temperature for 4 hr and then filtered. *In vacuo* concentration of the filtrate left a residual yellow oil, which was purified by vacuum distillation; the yield of VI as a colorless oil, bp 180–188° (0.07 mm), was 26.1 g (42%). *Anal.* ($C_7H_{11}NO_2S_2$) C, H, S.

2-Thioxo-3-thiazolidinepropionic Acid (VII). A. From VI.—A mixture of VI (26.1 g, 0.127 mole) and 6 *N* HCl (600 ml) was refluxed for 4 hr. The resulting solution, filtered hot and then chilled, deposited VII as white crystals, which were dried (P_2O_5) *in vacuo;* yield 6.73 g (22%), mp 99–101°. *Anal.* ($C_6H_9NO_2S_2$) C, H, N, S.

B. From VIII.—K_2CO_3 (4.86 g, 34.1 mmoles) was added in portions to a stirred solution of VIII (4.00 g, 15.5 mmoles), CS_2 (4.0 ml, 66 mmoles), and DMF (30 ml), the reaction temperature being kept below 35° by intermittent use of an ice–water bath. The mixture was stirred overnight at room temperature, then poured into H_2O (100 ml), and extracted with three 75-ml portions of Et_2O. The Et_2O phase, washed with H_2O and dried ($MgSO_4$), was concentrated under reduced pressure, leaving crude 2-thioxo-3-thiazolidinepropionitrile (IX) as a yellow oil. A solution of the oil in 6 *N* HCl (10 ml) was refluxed for 4 hr, filtered hot, and chilled. The off-white, crystalline VII that precipitated was collected, washed (cold EtOH), and dried (P_2O_5) *in vacuo;* yield 0.42 g (14%), mp 105–107°, mmp 103–106°, with product from A, lit.[5] mp 103.3–104.6°. *Anal.* ($C_6H_9NO_2S_2$) C, H.

3-(2-Bromoethylamino)propionitrile Hydrobromide (VIII).—1-Aziridinepropionitrile[8] (19.2 g, 0.200 mole) was added dropwise to cold (−5 to 0°) 48% HBr (50 ml) with vigorous stirring. The solution was evaporated to dryness under reduced pressure, and the crystalline residue was reprecipitated from MeOH by the addition of Et_2O; yield 49.0 g (95%), mp 96–98°. *Anal.* ($C_5H_9BrN_2 \cdot HBr$) C, H, Br.

S-2-Aminoethyl S′-(Methoxycarbonyl)methyl Dithiocarbonate Hydrochloride (XIa).—A solution of IVa (2.00 g, 10.5 mmoles) in 6 *N* HCl (20 ml) was refluxed for 6 hr and then evaporated to dryness *in vacuo*. A solution of the residue in MeOH (20 ml) was refluxed for 2 hr, treated with Norit, and filtered. The filtrate was concentrated *in vacuo* to a viscous oil, which crystallized. Recrystallization (MeOH–Et_2O) afforded 0.47 g (17%) of XIa: mp 134–137° dec with presoftening; $\bar{\nu}$ (in cm⁻¹) 1730 (s, C=O of CO_2Me), 1640 (s, C=O of SCOS), and 870 (s, SCS). *Anal.* ($C_6H_{11}NO_3S_2 \cdot HCl$) C, H, N, Cl.

S-2-Aminoethyl S′-2-(Ethoxycarbonyl)ethyl Dithiocarbonate Hydrochloride (XIb).—A mixture of crude 3-(2-thiazolin-2-ylthio)propionic acid[5] (mp 62–65°, lit.[5] mp 76.6–77.5°; 10.0 g, 48.7 mmoles) and 6 *N* HCl (100 ml) was refluxed for 6 hr; and the resulting solution was concentrated under reduced pressure to an oil, which crystallized on standing. A solution of the crude solid (S-2-aminoethyl S′-2-carboxyethyl dithiocarbonate hydrochloride) in boiling EtOH (50 ml), cooled and diluted with Et_2O (100 ml), deposited 5.00 g (38%) of XIb as sparkling, white crystals: mp 111–112°; $\bar{\nu}$ (in cm⁻¹) 1725 (s, C=O of CO_2Et), 1645 (s, C=O of SCOS), and 870 (s, SCS). *Anal.* ($C_8H_{15}NO_3S_2 \cdot HCl$) C, H, N, S, Cl.

Acknowledgments.—The authors are indebted to Dr. D. P. Jacobus for antiradiation data and to Dr. W. J. Barrett and members of the Analytical and Physical Chemistry Division of Southern Research Institute for microanalytical and spectral determinations.

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

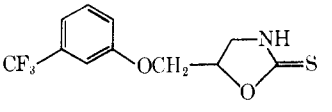
Synthesis and Antifertility Activity of 4- and 5-(ω-Arylalkyl)oxazolidinethiones

DANIEL LEDNICER AND D. EDWARD EMMERT

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

Received May 24, 1968

The substituted oxazolidinethione **1** has been shown previously to be an effective antifertility agent in the rat.[1] The relatively low potency of that compound



1

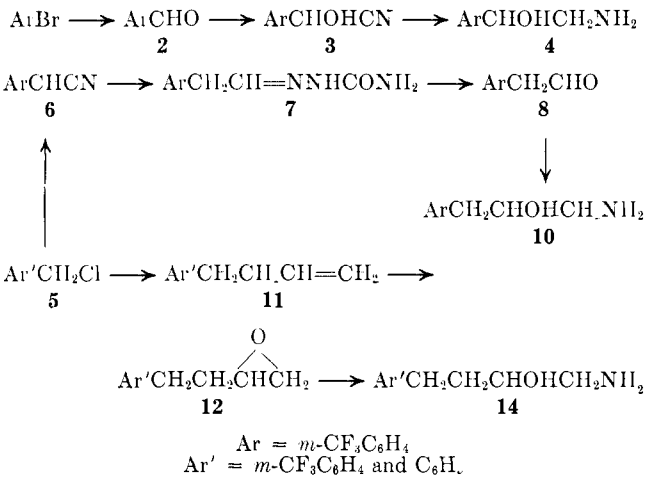
led us to prepare additional analogs. The unexpected finding that the phenolic oxygen could be replaced by a

(1) G. A. Youngdale, G. W. Duncan, D. E. Emmert, and D. Lednicer, *J. Med. Chem.*, **9**, 155 (1966).

methylene group with no loss of activity (see below) permitted an examination of the effect of chain length on antifertility activity. A report in the literature that 4-substituted oxazolidinethiones are less effective antithyroid agents than the 5-substituted isomers[2,3] prompted us to prepare the 4-substituted isomers of the present series in an effort to dissociate the antifertility and antithyroid activities[4] of **1**.

Starting Materials.—The amino alcohols needed for the formation of 5-oxazolidine-2-thiones were prepared as shown in Scheme I.

SCHEME I

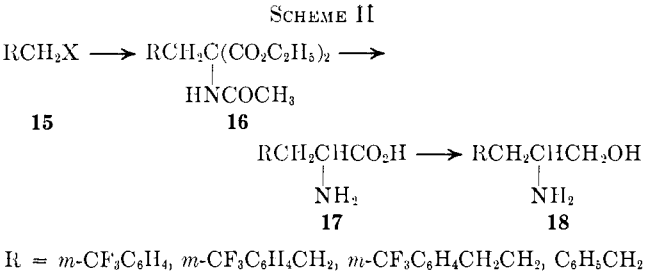


Aldehyde **2** was obtained by reaction of *m*-trifluoromethylphenylmagnesium bromide with N-methylformanilide. Reaction of the benzyl chloride **5** with cyanide gave nitrile **6**. This was reduced with Raney nickel in the presence of semicarbazide; transformation of the semicarbazone (**7**) thus obtained with hot formalin gave the aldehyde **8**. Each of these compounds was converted to its cyanohydrin and this reduced ($LiAlH_4$) to the corresponding amino alcohol. Reaction of the benzyl chloride **5** with allylmagnesium bromide afforded the olefin **11**; this was epoxidized by means of trifluoroperacetic acid and the epoxide was taken on to the amino alcohol **14** by the method of Petrow and Stephenson.[5]

Scheme II illustrates the general method used to obtain the isomeric amino alcohols. Thus, the benzyl chloride **15** was used to alkylate diethyl acetamidomalonate and the product of this reaction was treated with strong acid to afford the corresponding amino acid. This was esterified with methanolic HCl and the ester was reduced ($LiAlH_4$).

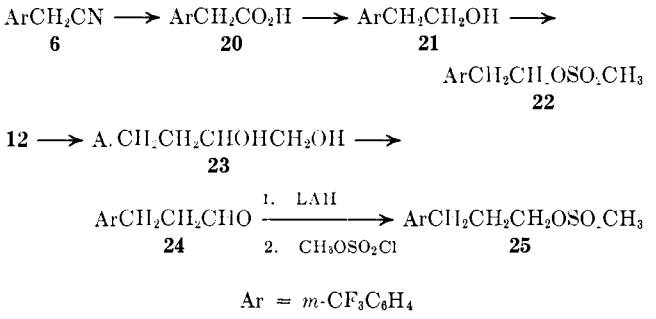
The nitrile **6** was hydrolyzed to the acid **20** (Scheme III); reduction with $LiAlH_4$ gave the alcohol. This was converted to its mesylate and subjected to the same set of reaction conditions as in Scheme II to afford the homologous amino alcohol. The epoxide **12** was opened to the glycol with aqueous acid. Cleavage with $Pb(OAc)_4$ followed by reduction of the aldehyde gave the alcohol; this was then taken on to its mesylate and converted to the amino acid as above.

SCHEME II



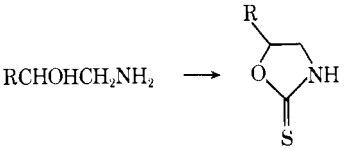
R = *m*-$CF_3C_6H_4$, *m*-$CF_3C_6H_4CH_2$, *m*-$CF_3C_6H_4CH_2CH_2$, $C_6H_5CH_2$

SCHEME III

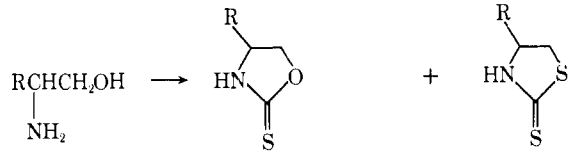


Ar = *m*-$CF_3C_6H_4$

Oxazolidinethiones and Thiazolidinethiones.—Reaction of the amino alcohols **4**, **10**, and **14** with CS_2 and NaOH[6] led in workable yields to the corresponding 5-substituted 2-oxazolidinethiones. The isomeric amino alcohols, however, gave mixtures of the corresponding 4-substituted 2-oxazolidinethiones and 2-thiazolidinethiones which were readily separable by chromatography.



26, R = $C_6H_5CH_2CH_2$
27, R = *m*-$CF_3C_6H_4$
28, R = *m*-$CF_3C_6H_4CH_2$
29, R = *m*-$CF_3C_6H_4CH_2CH_2$



30, R = $C_6H_4CH_2CH_2$
31, R = *m*-$CF_3C_6H_4CH_2$
32, R = *m*-$CF_3C_6H_4(CH_2)_2$
33, R = *m*-$CF_3C_6H_4(CH_2)_3$
34, R = $C_6H_4CH_2CH_2$
35, R = *m*-$CF_3C_6H_4CH_2$
36, R = *m*-$CF_3C_6H_4(CH_2)_2$
37, R = *m*-$CF_3C_6H_4(CH_2)_3$

Screening Results.—The compounds recorded in Table I were screened for antifertility activity in the rat at 50 mg/kg sc.[7] Of these, **27**, **29**, **32**, **35**, and **36** were found to effect 100% inhibition of pregnancy at this dose. These were then administered orally and the dose was titrated; **29** was effective at 7.5 mg/kg and its isomer **32** at 15 mg/kg. It is of interest that **1** is effective at 15 mg/kg in this assay. Preliminary testing suggests that the goitrogenic potency of **32** is of the same order as that of **1**.[8]

(2) M. Viscontini and K. Adank, *Helv. Chim. Acta*, **33**, 2251 (1950).

(3) Subsequent to the completion of this work, the preparation of a series of 4-substituted oxazolidinethiones was reported: H. J. Eichel, R. J. Meyer, and P. F. Buzzi, *J. Med. Chem.*, **10**, 942 (1967).

(4) H. D. Webster, R. L. Johnston, and G. W. Duncan, *Toxicol. Appl. Pharmacol.*, **10**, 322 (1967).

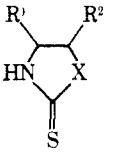
(5) V. Petrow and O. Stephenson, *J. Pharm. Pharmacol.*, **5**, 359 (1953).

(6) H. A. Bruson and J. W. Eastes, *J. Amer. Chem. Soc.*, **59**, 2011 (1937).

(7) G. W. Duncan, J. C. Babcock, S. C. Lyster, and D. Lednicer, *Proc. Soc. Exptl. Biol. Med.*, **109**, 163 (1962).

(8) Private communication from Dr. R. L. Johnston of these laboratories.

TABLE I
2-OXAZOLIDINETHIONES AND 2-THIAZOLIDINETHIONES



R¹	R²	X	No.	Mp, °C	Recrystn solvent	Formula	Analyses[a]
H	$C_6H_5CH_2CH_2$	O	26	87–90	H_2O–MeOH	$C_{11}H_{13}NOS$	C, H
H	*m*-$CF_3C_6H_4$	O	27	120–122.5	Me_2CO–C[b]	$C_{10}H_8F_3NOS$	C, H
H	*m*-$CF_3C_6H_4CH_2$	O	28	87–89	C_6H_6–C	$C_{11}H_{10}F_3NOS$	H; C[c]
H	*m*-$CF_3C_6H_4CH_2CH_2$	O	29	87–89	H_2O–MeOH	$C_{12}H_{12}F_3NOS$	H; C[d]
$C_6H_5CH_2CH_2$	H	O	30	56–58	Et_2O	$C_{11}H_{13}NOS$	C, H, S
m-$CF_3C_6H_4CH_2$	H	O	31	120–123	Me_2CO–C	$C_{11}H_{10}F_3NOS$	H, N, S; C[e]
m-$CF_3C_6H_4CH_2CH_2$	H	O	32	111–113	C_6H_6	$C_{12}H_{12}F_3NOS$	C, H, S
m-$CF_3C_6H_4CH_2CH_2CH_2$	H	O	33	74.5–76.5	CH_2Cl_2–C	$C_{13}H_{14}F_3NOS$	C, H, S
$C_6H_5CH_2CH_2$	H	S	34	111–113	C_6H_6	$C_{11}H_{13}NS_2$	C, H; S[f]
m-$CF_3C_6H_4CH_2$	H	S	35	144.5–146.5	Me_2CO–C	$C_{11}H_{10}F_3NS_2$	H, S; C[g]
m-$CF_3C_6H_4CH_2CH_2$	H	S	36	82–84	C	$C_{12}H_{12}F_3NS_2$	C, H, S
m-$CF_3C_6H_4CH_2CH_2CH_2$	H	S	37	70–72	C	$C_{13}H_{14}F_3NS_2$	C, H, S

[a] For a review of the problems of C analysis of fluorinated compounds see G. Ingram, *Analyst*, **86**, 539 (1961). [b] Cyclohexane. [c] C: calcd, 50.56; found, 49.97, 50.00. [d] C: calcd, 52.35; found, 51.74. [e] C: calcd, 50.56; found, 51.13. [f] S: calcd, 28.71; found, 28.17. [g] C: calcd, 47.63; found, 48.07.

Experimental Section[9]

***m*-Trifluoromethylbenzaldehyde (2).**—To the ice-cooled Grignard reagent prepared from 30 g (0.133 mole) of *m*-trifluoromethylbromobenzene and 3.16 g (0.13 g-atom) of Mg in 300 ml of Et_2O was added 18.0 g (0.133 mole) of *N*-methylformanilide in 20 ml of Et_2O. The mixture was stirred at room temperature for 3 hr and then cooled in ice. Over 20–30 min there was then added 130 ml of 2.5 *N* HCl. Following an additional 30 min stirring, the organic layer was separated and washed (aqueous $NaHCO_3$, H_2O, NaCl). The residue which remained when the solution was taken to dryness was distilled to afford 13.55 g (58.5%) of **2**, bp 55–64° (8.5 mm), lit.[10] bp 80–82° (21 mm).

1-Amino-2-hydroxy-2-(*m*-trifluoromethylphenyl)ethane (4).—To an ice-cooled solution of 2.60 g (0.04 mole) of KCN in 3 ml of H_2O there was added 2.40 g (0.038 mole) of AcOH in 20 ml of THF. Over 15 min a solution of 3.76 g (0.0216 mole) of the acetaldehyde **2** in 20 ml of THF was added to this. Following 30 min stirring at room temperature, the mixture was diluted (Et_2O), washed (H_2O), and dissolved in C_6H_6 and again taken to dryness, to afford crude cyanohydrin, ν_{max} 3450 cm^{-1}, no C=O (neat).

A solution of the cyanohydrin in Et_2O (100 ml) was added to a suspension of 1.30 g (0.034 mole) of $LiAlH_4$ in Et_2O (20 ml) over 15 min. The mixture was stirred under reflux for 3 hr and then cooled in ice. There was then added in turn 4 ml of H_2O and 1.5 ml each of 15% NaOH and H_2O. The precipitated inorganic salts were removed by filtration. The organic filtrate was extracted with five portions of 50 ml each of 2.5 *N* HCl. These extracts were made strongly basic and extracted (Et_2O). This last solution was taken to dryness to afford the crude amino alcohol as a solid. The product was recrystallized from Skellysolve B to give 2.45 g (55.5%) of **4**, mp 67.5–69.5°. *Anal.* ($C_9H_{10}F_3NO$) C, H.

(*m*-Trifluoromethylphenyl)acetonitrile (6).—*m*-Trifluoromethylbenzyl chloride (40.0 g, 0.208 mole) was added to a solution of 40.0 g (0.615 mole) of KCN and 0.40 g of KI in 300 ml of H_2O and 600 ml of MeOH. The mixture was heated under reflux for 45 min and the bulk of MeOH was removed *in vacuo*. Ether was added and the organic layer was washed.[9] The oil which remained when the ethereal layer was taken to dryness was distilled, yield 29.60 g (77%) of **6**, bp 64–69.5° (0.35 mm).

Semicarbazone of (*m*-Trifluoromethylphenyl)acetaldehyde (7).—A mixture of 14.95 g (0.081 mole) of the nitrile **6**, 9.15 g (0.08 mole) of semicarbazide hydrochloride, 6.9 g of NaOAc, and 5 g of Raney nickel in 100 ml each of EtOH and H_2O was shaken under H_2 until the theoretical amount of gas was taken up (12 hr). The mixture was diluted to 1 l. with H_2O and the solid was collected on a filter. The filter cake was pressed dry and extracted well (EtOAc). The organic washes were combined, washed,[9] and taken to dryness. The residual solid was recrystallized (EtOAc–cyclohexane) to give 10.90 g (55%) of **7**, mp 158–159°. *Anal.* ($C_{10}H_{11}F_3N_3O$) C, H, N.

***m*-Trifluoromethylphenyl)acetaldehyde (8).**—A mixture of 10.90 g (0.044 mole) of the semicarbazone **7** and 100 ml of formalin (37%) was heated on the steam bath with gentle swirling for 10 min. The resulting solution was diluted with an equal volume of ice–water and extracted five times with Skllysolve B. These extracts were washed (H_2O, NaCl) and taken to dryness. The residual oil was distilled through an oil-jacketed flask (95–100°) at 2.5 mm to give 5.90 g (50.8%) of **8**: ν_{max} 2720, 1750 cm^{-1} (neat); thiosemicarbazone, mp 145–148°. *Anal.* ($C_{10}H_{10}F_3N_3S$) C, H, N.

1-Amino-2-hydroxy-3-(*m*-trifluoromethylphenyl)propane (10).—Proceeding exactly as in the case of **2**, the aldehyde **8** (3.69 g, 0.051 mole) was converted to the cyanohydrin. Reduction ($LiAlH_4$) afforded the crude amino alcohol. Two recrystallizations from Et_2O–Skellysolve B gave 3.10 g (36%) of **10**, mp 80–83°. *Anal.* ($C_{10}H_{12}F_3NO$) C, H, N.

4-Phenylbut-1-ene (11a).—To a solution of 19 ml (27.3 g, 0.16 mole) of $C_6H_5CH_2Br$ in 200 ml of Et_2O there was added the Grignard reagent prepared in an inverse addition flask from 34.4 ml (48 g, 0.4 mole) of allyl bromide and 58 g of Mg in 250 ml of Et_2O. Following 4 hr of heating under reflux the mixture was cooled in ice and treated with 20 ml of H_2O and 250 ml of saturated NH_4Cl. The organic layer was separated, washed,[9] and taken to dryness. The residue was distilled to give 14.08 g (66.3%) of **11a**, bp 177–179°, lit.[11] 181°.

4-Phenylbutene 1,2-Epoxide (12a).—A mixture of 14.08 g (0.016 mole) of olefin **11a** and 51.2 g of anhydrous Na_2CO_3 in 85 ml of CH_2Cl_2 was treated with peroxytrifluoroacetic acid prepared from 27 ml of trifluoroacetic anhydride and 4.4 ml of 90% H_2O_2. The mixture was stirred under reflux for 1 hr and the solid was removed by filtration. The oil which remained when the filtrate was taken to dryness was distilled to give 12.68 g (55%) of **12a**, bp 113–117° (17 mm). *Anal.* ($C_{10}H_{12}O$) C, H.

N-(2-Hydroxy-4-phenylbutyl)succinimide (13a).—A mixture of 12.68 g (0.058 mole) of the oxide, 8.60 g (0.087 mole) of succinimide, and 4 drops of pyridine in 120 ml of MeOH was heated under reflux for 24 hr. The solvent was removed *in vacuo* and

[9] Melting points are uncorrected and recorded as obtained on a Thomas–Hoover melting point apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The authors are indebted to the Department of Physical and Analytical Chemistry of The Upjohn Company for elemental analyses. Acetone–Skellysolve B mixtures were used for chromatography; only the percentage acetone is specified. Ethereal extracts were washed with H_2O and brine.

[10] R. Filler and H. Novar, *J. Org. Chem.*, **25**, 733 (1960).

[11] D. Bryce-Smyth and E. E. Turner, *J. Chem. Soc.*, 1975 (1950).

the residue was recrystallized twice (EtOAc), yield 12.90 g of **13a** (61.5%), mp 118–121°. *Anal.* ($C_{14}H_{17}NO_3$) C, H.

2-Hydroxy-4-phenylbutylamine Hydrobromide (14a).—A mixture of 12.90 g (0.052 mole) of the imide **13a**, and 144 g of NaOH in 1.4 l. of EtOH was heated under reflux for 17 hr. The bulk of the solvent was removed *in vacuo* and the residue was taken up in Et_2O and H_2O. The organic layer was separated, washed,[9] and taken to dryness. The residual gum was dissolved in a small amount of Et_2O and saturated with HBr. The precipitated solid was recrystallized twice (MeCN) to give 10.74 g (90%) of **14a**, mp 102° (to viscous clear gum). *Anal.* ($C_{10}H_{16}BrNO$) C, H, Br. The salt was converted to 5.65 g of the free base.

4-(*m*-Trifluoromethylphenyl)but-1-ene (11b).—A solution of 24 g (0.2 mole) of allyl bromide in Et_2O (120 ml) was added over 2 hr to a well-stirred mixture of 2.90 g (1.2 moles) of Mg and Et_2O (20 ml) in an inverse addition flask. The Grignard reagent was then added through a glass wool plug to a solution of 19.4 g (0.1 mole) of *m*-trifluoromethylbenzyl chloride in Et_2O (200 ml). Following 2 hr heating under reflux, the mixture was cooled in ice and treated with 10 ml of H_2O and 250 ml of saturated aqueous NH_4Cl. The organic layer was separated, washed,[9] and taken to dryness. The residual oil was distilled to afford 12.78 g (64%) of **11b**, bp 30° (0.6 mm).

Anal. Calcd for $C_{11}H_{11}F_3$: C, 65.99; H, 5.54. Found: C, 65.56; H, 5.32.

4-(*m*-Trifluoromethylphenyl)but-1-ene Epoxide (12b).—Trifluoroacetic anhydride (16.1 ml) was added to an ice-cooled mixture of 17 ml of CH_2Cl_2 and 2.62 ml of 90% H_2O_2 over 10 min. The resulting solution was then added over 30 min to a well-stirred mixture of 12.78 g (0.064 mole) of the olefin **11b** and 30.6 g of Na_2CO_3 in 50 ml CH_2Cl_2. The mixture was heated at reflux for 1 hr and the inorganic salts were removed by filtration. The filter cake was washed well (CH_2Cl_2) and the combined filtrates were taken to dryness. The residual oil was distilled to yield 10.75 g (78%) of **12b**, bp 63–70° (0.5 mm). *Anal.* ($C_{11}H_{11}F_3O$) C, H.

N-[2-Hydroxy-4-(*m*-trifluoromethylphenyl)butyl] succinimide (13b).—Proceeding exactly in the same manner as above 10.75 g (0.05 mole) of the oxide **12b** was heated with 1 equiv of succinimide. The reaction mixture was worked up as above and the product recrystallized from MeOH–H_2O to give 8.4 g (53%) of **13b**, mp 94–99°. *Anal.* ($C_{15}H_{16}F_3NO_3$) C, H.

1-Amino-4-(*m*-trifluoromethylphenyl)-2-butanol (14b).—A mixture of 8.13 g (0.026 mole) of the succinimide (**13b**) and 50 ml of concentrated HCl was heated at reflux for 20 hr. The cooled solution was then washed twice (Et_2O), cooled in ice, and made strongly alkaline. This was then extracted (CH_2Cl_2), and the extract was washed[9] and taken to dryness to afford the amino alcohol as an amorphous gum. HCl was passed through a solution of this product in Et_2O and the solid salt collected on a filter. One "crystallization" of the salt (Me_2CO) gave 4.64 g of the hydrochloride as an amorphous powder. This was dissolved in H_2O and converted to the free base with 45% NaOH. Extraction of the alkaline solution followed by evaporation of the extract gave 3.77 g (67%) of crude amorphous amino alcohol.

***m*-(Trifluoromethylphenyl)acetic Acid (20).**—A solution of 28.84 g (0.156 mole) of the nitrile **6** and 29 g of NaOH in 300 ml of EtOH was heated at reflux overnight. The bulk of the solvent was removed *in vacuo* and the solution was washed (Et_2O). The aqueous layer was acidified, saturated with $(NH_4)_2SO_4$, and extracted (Et_2O). These extracts were washed[9] and taken to dryness. The solid residue was recrystallized from Skellysolve B to afford 26.38 g (83%) of **20**, mp 70–74.5°. The analytical sample from a previous run melted at 73–74.4°. *Anal.* Calcd for $C_9H_7F_3O_2$: C, 52.95; H, 3.46. Found: C, 53.38; H, 4.03.

2-(*m*-Trifluoromethylphenyl)ethyl Methanesulfonate (22).—A solution of 26.38 g (0.13 mole) of the acid **20** in 150 ml of Et_2O was added to 7.4 g (0.2 mole) of $LiAlH_4$ in 70 ml of Et_2O. Following 30 min heating at reflux the mixture was cooled in ice and treated with H_2O (11 ml), 100 ml of saturated aqueous NH_4Cl, and 7.5 ml of 2.5 *N* HCl. The organic layer was separated (centrifuge), washed,[9] and taken to dryness. The residual oil was distilled to yield 22.26 g of **21**, bp 68–70.5° (0.35 mm).

To an ice-cooled solution of 23.86 g of the alcohol in 97 ml of pyridine was added over 15 min 19.0 g (0.17 mole) of $MeSO_2Cl$. Following 1 hr of stirring in the cold, the mixture was diluted with 300 ml of ice–water. The precipitated oil was extracted (Et_2O) and the extract was washed (H_2O, 2.5 *N* HCl, H_2O, NaCl). The organic solution was taken to dryness to give 34.46 g (99%) of an oil. This was used without further purification.

3-(*m*-Trifluoromethylphenyl)propionaldehyde (24).—A mixture of 18.29 g (0.084 mole) of the oxide **12b** and 1.85 g of $HClO_4$ in 90 ml of THF and 180 ml of H_2O was stirred at room temperature for 6 hr. The mixture was then extracted (Et_2O). The organic layer was washed (aqueous $NaHCO_3$) and taken to dryness. The residual solid, mp 56–59°, was used without further purification.

A solution of 15.89 g (0.68 mole) of the glycol in 80 ml of CH_2Cl_2 was added to a stirred suspension of 31 g (0.07 mole) of $Pb(OAc)_4$ in 300 ml of CH_2Cl_2 over 45 min. Following 1 hr of stirring the solid was removed by filtration and washed (CH_2Cl_2). The combined filtrates were taken to dryness and the residual oil distilled to yield 9.92 g (53%) of **24**, bp 74° (0.6 mm), ν_{max} 1750 cm^{-1} (neat); thiosemicarbazone, mp 127–128.5°. *Anal.* ($C_{11}H_{12}F_3N_3S$) C, H, N.

3-(*m*-Trifluoromethylphenyl)propyl Methanesulfonate (25).—A solution of 19.99 g (0.073 mole) of **24** in 200 ml of Et_2O was added to a well-stirred suspension of 3.8 g (0.1 mole) of $LiAlH_4$ in 40 ml of Et_2O over 50 min. Following 1 hr of heating under reflux, the mixture was cooled in ice and treated with H_2O (6 ml) and 15 ml of 2.5 *N* HCl. The organic layer was separated, washed,[9] and taken to dryness. The residual oil (18.58 g) had bp 76–79° (0.3 mm).

$MeSO_2Cl$ (13.8 g, 0.12 mole) was added to a solution of 18.58 g of the alcohol in 70 ml of pyridine. The mixture was stirred in the cold for 1 hr and diluted with H_2O (300 ml). The precipitated oil was extracted (Et_2O) and this solution was washed thoroughly with 2.5 *N* HCl. Following one wash each with H_2O and NaCl the solution was taken to dryness. The mesylate (**25**) was obtained as a viscous oil (25.90 g).

Acetamido Esters (16) (Table II).—In a typical experiment solid diethyl acetamidomalonate (20.65 g, 0.095 mole) and 1 g of KI was added to a solution of 2.2 g (0.096 g-atom) of Na in 80 ml of EtOH. A solution of 0.095 g of the appropriate mesylate or chloride in 55 ml of EtOH was then added and the mixture was heated under reflux for 6.5 hr. The bulk of the solvent was removed *in vacuo* and the residue was treated with H_2O (300 ml). The precipitated gum was extracted with Et_2O. The organic layer was washed[9] and taken to dryness. The residual gum was chromagraphed on Florisil. The product proved difficult to characterize and was used without further purification.

TABLE II

ACETAMIDO ESTERS

$R^3CH_2C(NHCOCH_3)(CO_2C_2H_5)_2$

R^3	% yield	Mp, °C
m-$CF_3C_6H_4$	78	100–102.5
m-$CF_3C_6H_4CH_2$	24	...
m-$CF_3C_6H_4CH_2CH_2$	83	...
$C_6H_4CH_2$	47	111–114

Amino Acids (17) (Table III).—In a typical example a mixture of 19.89 g of the ester and 100 ml of concentrated HCl was refluxed for 8 hr; a crystalline solid separated. The mixture was cooled in the freezer and the product collected on a filter. This was then recrystallized once from HCl.

TABLE III

AMINO ACIDS

$R^3CH_2CH(NH_2)CO_2H \cdot HCl$

R^3	% yield	Mp, °C	Formula	Analyses
m-$CF_3C_6H_4$	78	240–248 dec	$C_{10}H_{11}ClF_3NO_2$	C, H, Cl
m-$CF_3C_6H_4CH_2$	69	237–240 dec	$C_{11}H_{13}ClF_3NO_2$	C, H, Cl
m-$CF_3C_6H_4CH_2CH_2$	76	230 dec	$C_{12}H_{15}ClF_3NO_2$	C, H, Cl
$C_6H_5CH_2$	88	269–272	$C_{10}H_{14}ClNO_2$	H; C[a]

[a] C: calcd, 55.68; found, 56.53.

Amino Alcohols (18) (Table IV).—In a typical experiment a solution of the amino acid hydrochloride (12 g) obtained above in 250 ml of MeOH was saturated with dry HCl. Following 18 hr of standing at room temperature the solution was taken to dryness. The residue was suspended in Et_2O and cautiously made basic with aqueous $NaHCO_3$. The organic layer was separated,

washed,[9] and taken to dryness to give a gum, ν_{max} 3350, 1760 cm^{-1} (neat).

This amino ester in Et_2O (100 ml) was added to 2.0 g of $LiAlH_4$ in Et_2O (20 ml). Following 90 min of heating at reflux the reaction mixture was cooled in ice and treated with 2 ml of H_2O, 2 ml of 15% aqueous NaOH, and H_2O (6 ml). The precipitated solid was collected on a filter and washed (Et_2O). The filtrates were taken to dryness and redissolved in Et_2O. The product was precipitated as its hydrochloride by passing in gaseous HCl.

TABLE IV

AMINO ALCOHOLS

$R^3CH_2CH(NH_2)CH_2OH \cdot HCl$

R^3	% yield	Mp, °C	Formula	Analyses
m-$CF_3C_6H_4$	33	*a*	$C_{10}H_{13}ClF_3NO$	
m-$CF_3C_6H_4CH_2$	75	183–186	$C_{11}H_{15}ClF_3NO$	C, H, Cl
m-$CF_3C_6H_4CH_2CH_2$	66	188–191	$C_{12}H_{17}F_3NO$	C, H, Cl
$C_6H_4CH_2$	22	108–110	$C_{10}H_{16}ClNO$	C, H, Cl

[a] Could not be recrystallized satisfactorily; sintered at 158°.

Oxazolidinethiones and Thiazolidinethiones.—In a typical experiment a mixture of 0.03 mole of the oily amino alcohol, 2.7 ml of CS_2, 2.48 g of KOH, and 6.4 ml of H_2O in 110 ml of EtOH was heated under reflux for 5.5 hr. The solvent was removed *in vacuo*. The residue was suspended in H_2O and made acidic; the precipitated gum was extracted (Et_2O). The organic layer was washed[9] and taken to dryness. The residual gum (8.09 g) was chromatographed over 800 ml of Florisil. Elution with 10% acetone–Skellysolve B gave first 4.99 g of thiazolidinethione followed by 4.18 g of the oxazolidinethione.

Acknowledgment.—The authors wish to express their appreciation to Dr. G. W. Duncan and Mr. S. C. Lyster for making the results of their biological work available for publication.

Synthesis and Pharmacology of *p*-Methoxycinnamic Acid Derivatives

EUN BANG LEE, KUK HYUN SHIN, AND WON SICK WOO

Natural Products Research Institute, Seoul National University, Seoul, Korea

Received July 9, 1968

In previous publications from our laboratory, it has been reported that *p*-methoxycinnamate shows good antipyretic and analgetic activities.[1] It is rapidly absorbed when administered orally to rabbits and oxidized rapidly *in vivo* to *p*-methoxybenzoic acid which is excreted in the urine as conjugates of glycine and glucuronic acid.[2]

These observations have led us to search for improved potential antipyretic and analgetic compounds. This communication describes the synthesis of several new *p*-methoxycinnamic acid derivatives of salicylic acid and aminophenols, and their preliminary pharmacological properties.

p-Methoxycinnamoylsalicylic acid (I), *p*-acetamidophenyl *p*-methoxycinnamate (II), N-(*p*-methoxycinnamoyl)-*p*-aminophenol (III), and N-(*p*-methoxycinnamoyl)-*p*-phenetidine (IV) were easily obtained by reaction of *p*-methoxycinnamoyl chloride with salicylic acid, *p*-acetaminophenol, *p*-aminophenol, and *p*-phenetidine, respectively.

Pharmacology.—In preliminary pharmacological evaluations all compounds were administered, by the route specified in Table I, as a suspension in 2% aqueous starch solution except that sodium *p*-methoxycinnamate was administered as an aqueous solution. The highest dose employed of a compound having low toxicity was 500 mg/kg. LD_{50} values were calculated by the method of Litchfield and Wilcoxon.[3]

Antipyretic and hypothermal activities were measured by the method described by Almirante, *et al.*[4] In the evaluation of antipyretic activity, drugs were given 5 hr after injection of 0.5 ml of 15% yeast in 10% aqueous acacia mucilage/100 g of body weight into both thighs of the rat. Antipyretic and hypothermal activities were expressed as the temperature indices which constituted the total of the differences between each of the six readings obtained at 60-min intervals for 6 hr after administration of drug and the mean value of two temperature readings 60 min and immediately before administration of drug.

The analgetic activity was assessed by a modification of the hot plate method based on that described by Woolfe and MacDonald.[5] The increases in reaction time were averaged for four observations made at 30-min intervals for 2 hr after administration of drug. The degree of analgetic activity was calculated as the mean per cent increase in thermal pain threshold of treated mice over the average variation of pain threshold of controls. The antiinflammatory effect was investigated by means of the rat-foot edema test,[6] employing 10% yeast suspension in saline, 3.5% formaldehyde–saline, 1% croton oil–olive oil, 10% egg white saline, and 3% dextran–saline as phlogistics. Drugs were given orally immediately before injections of 0.1 ml of each of the phlogistics into the plantar surface of the right hind foot. At 60-min intervals for 5 hr after injection, the volume of the foot was measured by Harris and Spencer's method.[7] The difference between the volume of the foot determined immediately after the injection of phlogistics and the mean value of the five determinations was recorded as that of edema. The activity was expressed as the mean per cent inhibition of swelling in treated rats, compared with that of controls.

The pharmacological results are shown in Table I, which also includes results obtained with the standard drugs such as sodium *p*-methoxycinnamate, acetylsalicylic acid, and acetophenetidine for comparison. All of the compounds lowered body temperature in the yeast-fevered rats. Compound III was the most active antipyretic; however, it affected body temperature in normal rats. Compound I exhibited increased activity compared with that of sodium *p*-methoxycinnamate or acetylsalicylic acid, and, interestingly, had a somewhat more prolonged duration of activity (not shown). All of the compounds synthesized, with the exception of

(1) (a) W. S. Woo, *J. Pharm. Soc. Korea*, **7**, 55 (1963); (b) *ibid.*, **9**, 31 (1965).

(2) (a) W. S. Woo, *ibid.*, **8**, 76 (1964); (b) *J. Pharm. Sci.*, **57**, 27 (1968).

(3) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

(4) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba, and M. Murmann, *J. Med. Chem.*, **8**, 305 (1965).

(5) G. Woolfe and A. D. MacDonald, *J. Pharmacol. Exptl. Therap.*, **80**, 300 (1944).

(6) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).

(7) J. M. Harris and P. S. Spencer, *J. Pharm. Pharmacol.*, **14**, 643 (1962).