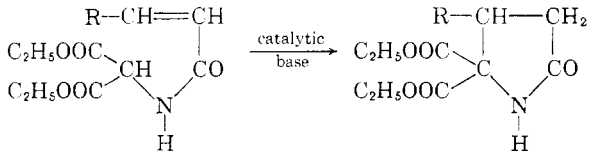

Accordingly a solution was prepared from 0.023 g. of sodium (0.001 g.-atom) in 250 ml. of anhydrous ethanol, and to this was added 2.73 g. of VI (0.009 mole); the container was fitted with a reflux condenser with calcium chloride tube at the upper opening. The solution was refluxed for 12 hr.; it was then neutralized with acetic acid, the first portion of ethanol was removed by distillation, and the final portion was allowed to evaporate at room temperature. The product, weighing 2.0 g., crystallized first from dilute ethanol and then from benzene–petroleum ether (b.p. 30–60°), melted at 107–108°. The expected pyrrolidinone melts 96–98°.[15] The product still gave a positive test for ethylenic bond; molecular weight determination gave values of 220–230.

Anal. Calcd. for $C_{12}H_{15}NO_3$, m.w., 233: C, 66.95; H, 6.44; N, 6.01. Found: C, 66.98, 66.89; H, 6.35, 6.40; N, 5.86, 5.94.

An authentic sample of ethyl cinnamamidoacetate was prepared from cinnamyl chloride and ethyl glycinate, m.p. 109°; the melting point when mixed with product obtained was not depressed.

Such decarbethoxylation probably proceeds by the same mechanism by which diethyl diphenylmalonate and diethyl phenylethylmalonate form ethyl diphenylacetate and ethyl α-phenylbutyrate, respectively, when heated in an alcoholic solution containing an equivalent of sodium ethoxide.[16]

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(15) G. H. Cocolas and W. H. Hartung, *J. Am. Chem. Soc.*, **79**, 5203 (1957).

(16) A. C. Cope and S. M. McElvain, *J. Am. Chem. Soc.*, **54**, 4319 (1932).

1-Alkyl-3-(α,α,α-trifluorotolylsulfonyl)ureas

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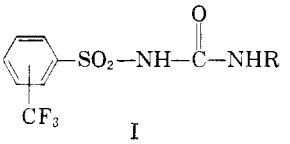
We are reporting the preparation of a group of 1-alkyl-3-(α,α,α-trifluorotolylsulfonyl)ureas(I). These compounds are now being evaluated for hypoglycemic activity.[1]



I

The literature on the procedures which may be employed for the synthesis of compounds like I has been reviewed recently.[2a,b] In our approach, the α,α,α-trifluoro-o- and -m-tolyl derivatives were prepared as shown in Chart I. The synthesis of the *p*-derivative differed only in the procedures used for the preparation of the intermediate (α,α,α - trifluoro - *p* - tolyl)sulfonamide (Chart II A,B)

Chart I

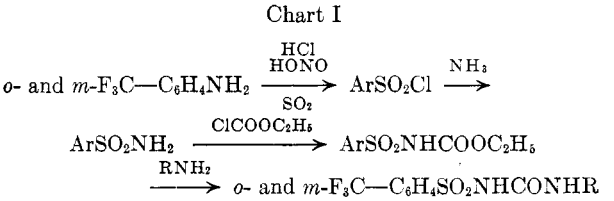
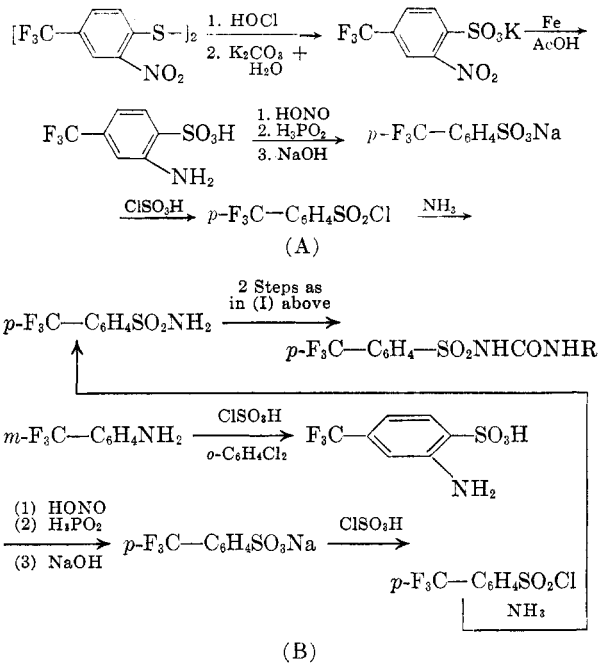


Chart II



Kracker and Herrlein[3a] have reported that one mole each of α,α,α-trifluoro-*m*-toluidine and chlorosulfonic acid in *o*-dichlorobenzene at 180° gave 4 - amino - α,α,α - trifluoro - *o* - toluenesulfonic acid. Similarly, Zitscher and Kehlen[3b] stated that α,α,α-trifluoro-*m*-acetotoluidide and an excess of fuming sulfuric acid in tetrachloroethane at 145° gave 4-acetamido-α,α,α-trifluoro-*o*-toluenesulfonic acid. Neither group of workers provided proof for their structural assignments. We have repeated[4] the procedure described by Kracker and Herrlein and obtained an amino-α,α,α-trifluorotoluenesulfonic acid whose infrared spectrum was identical with that obtained from the 2-amino-α,α,α-

(1) The role of the trifluoromethyl group in medicinal chemistry has been reviewed by H. L. Yale, *J. Med. Pharm. Chem.*, **1**, 121 (1959).

(2a) D. R. Cassady, C. Ainsworth, N. R. Easton, M. Livesey, M. V. Sigal, Jr., and E. Van Heyningen, *J. Org. Chem.*, **23**, 923 (1958); (b) F. J. Marshall and M. V. Sigal, Jr., *J. Org. Chem.*, **23**, 927 (1958).

(3a) H. Kracker and F. Herrlein, U.S. Patent **2,119,882**, June 7, 1938; (b) A. Zitscher and H. Kehlen, U. S. Patent **2,141,893**, Dec. 27, 1938.

(4) This experiment was carried out by Dr. W. B. McDowell of the Chemical Development Section, Squibb Institute for Medical Research.

TABLE I

COMPOUNDS OF THE GENERAL FORMULA $F_3C—C_6H_4—SO_2NHY$

Position of —CF_3	Y	Formula	Yield, %	M.P.	Analyses, % Calcd. C	H	N	Found C	H	N
2	—H	$C_7H_6F_3NO_2S$[a]	80	186–188	37.36	2.69		37.34	3.06	
3	—H	$C_7H_6F_3NO_2S$[b]	65	111–112	37.36	2.69		37.29	2.58	
4	—H	$C_7H_6F_3NO_2S$[c]	68	176–177	37.36	2.69		37.30	2.63	
2	—$CO_2C_2H_5$	$C_{10}H_{10}F_3NO_4S$[b]	87	131–132	40.41	3.39		40.93	3.63	
3	—$CO_2C_2H_5$	$C_{10}H_{10}F_3NO_4S$[d]	69	68–69	40.41	3.39		40.36	3.58	
4	—$CO_2C_2H_5$	$C_{10}H_{10}F_3NO_4S$[d]	81	93–95	40.41	3.39		40.47	3.69	
2	—$CONHC_4H_9$-*n*	$C_{12}H_{15}F_3N_2O_3S$[c]	49	134–135	44.44	4.66	8.64	44.50	4.88	8.95
2	—$CONHC_6H_{11}$	$C_{14}H_{17}F_3N_2O_3S$[c]	52	172–173	47.98	4.89	7.99[e]	47.71	4.84	8.27
3	—$CONHC_4H_9$-*n*	$C_{12}H_{15}F_3N_2O_3S$[c]	63	113–114	44.44	4.66	8.64	44.41	4.79	8.80
3	—$CONHC_6H_{11}$	$C_{14}H_{17}F_3N_2O_3S$[c]	42	132–133	47.98	4.89	7.99[f]	48.76	5.16	7.89
4	—$CONHC_4H_9$-*n*	$C_{12}H_{15}F_3N_2O_3S$[c]	62	127–128	44.44	4.66	8.64	44.42	4.51	8.65
4	—$CONHC_6H_{11}$	$C_{14}H_{17}F_3N_2O_3S$[c]	43	177–178	47.98	4.89	7.99	48.13	5.01	8.08

[a] Recrystallized from 95% ethanol. [b] Recrystallized from benzene. [c] Recrystallized from aqueous ethanol. [d] Recrystallized from benzene-hexane (1:1). [e] Calcd.: S, 9.15; Found: S, 9.01. [f] Calcd.: S, 9.15; Found: S, 9.43.

trifluoro-*p*-toluenesulfonic acid prepared according to Chart II, A. Furthermore, each sulfonic acid, when subjected to the sequence of reactions indicated in Chart II, A and B, gave identical sulfonamide and carbamate derivatives. The structure of the product from the Kracker and Herrlein procedure is, consequently, 2-amino-α,α,α-trifluoro-*p*-toluenesulfonic acid and it may be inferred that the Zitscher and Kehlen product must have been 2-acetamido-α,α,α-trifluoro-*p*-toluenesulfonic acid.

Two observations made during the synthesis of the 1-alkyl-3-(α,α,α-trifluorotolylsulfonyl)ureas are worthy of mention. In this series of sulfonylureas, there was a great tendency to form fairly stable salts with the excess of amine present during the reaction with the carbamate. These could, in some instances, be isolated and were stable to recrystallization. Decomposition was effected by solution in warm aqueous sodium hydroxide followed by acidification with dilute hydrochloric acid. In addition, with cyclohexylamine, a small amount of dicyclohexylurea was isolated as a by-product of the reaction.

EXPERIMENTAL

All melting points and boiling points are uncorrected.

The preparation below is typical of the syntheses in the *o*- and *m*-tolylsulfonylurea series.

Analytical data not given in the text will be found in Table I.

1-Butyl-3-(α,α,α-trifluoro-o-tolylsulfonyl)urea. α,α,α-Trifluoro-o-toluenesulfonyl chloride.[5] α,α,α-Trifluoro-*o*-toluidine,[6] 48.6 g. (0.3 mole), 105 ml. of concd. hydrochloric acid, and 30 ml. of glacial acetic acid at −5 to 0° were treated dropwise, with a solution of 22.8 g. (0.3 mole) of sodium nitrite in 45 ml. of water. The diazotized solution was allowed to warm to 4° and then added to 6 g. of cuprous chloride in 400 ml. of a saturated solution of sulfur dioxide in glacial acetic acid, also at 4°. The vigorous reaction accompanied by considerable frothing caused a rise in temperature to 27°. One-half hour later, the reaction mixture was poured into 1 l. of ice-water and the product extracted with ether. The ether extract was washed until neutral with saturated aqueous sodium bicarbonate solution, then dried, concentrated, and distilled to give 53.5 g. (72% yield) of the *sulfonyl chloride*, b.p. 123–126° (5 mm.).

Anal. Calcd. for $C_7H_4ClF_3O_2S$: C, 34.37; H, 1.65. Found: C, 34.29; H, 1.75.

α,α,α-Trifluoro-o-toluenesulfonamide. To 550 ml. (8.1 moles) of concd. aqueous ammonia was added a solution of 66.1 g. (0.27 mole) of the sulfonyl chloride in 50 ml. of anhydrous ether, dropwise. The mixture was warmed gradually to 70°, kept at 70° for 1 hr., cooled, the solid filtered and recrystallized from aqueous ethanol to give 48.7 g. (80% yield) of the *sulfonamide*, m.p. 184–185°.

Ethyl (α,α,α-trifluoro-o-tolylsulfonyl)carbamate. To 47.7 g. (0.21 mole) of the sulfonamide, 76.3 g. of anhydrous potassium carbonate and 250 ml. of dry acetone was added 30.4 g. (0.28 mole) of ethyl chloroformate. The mixture was stirred and refluxed overnight, cooled, and the solid filtered with suction, dissolved in 500 ml. of water, the aqueous solution filtered, and the filtrate acidified with dilute hydrochloric acid. The solid which separated was filtered and dried to give 54.5 g. (87% yield) of carbamate, m.p. 130–132°. An analytical sample was recrystallized twice from benzene and melted at 131–133°.

1-Butyl-3-(α,α,α-trifluoro-o-tolylsulfonyl)urea. A solution of 23.4 g. (0.08 mole) of the carbamate in 36.5 g. (0.5 mole) of *n*-butylamine was concentrated at 5 mm. and room temperature to remove excess amine and the residue heated by means of an oil bath at an internal temperature of 115–120° at 5 mm. for 3 hr. and then cooled. The residual solid was dissolved in warm 1% aqueous sodium hydroxide solution, the solution acidified with dilute hydrochloric acid, the precipitated solid filtered and recrystallized from aqueous alcohol to give 12.7 g. (49% yield) of product, m.p. 134–135°.

1-Butyl-3-(α,α,α-trifluoro-p-tolylsulfonyl)urea. (Chart II, A) *2-Nitro-α,α,α-trifluoro-p-toluenesulfonyl chloride.*[7] Chlorine gas was passed into a stirred suspension of 408 g. (0.9 mole) of 4,4′-bis(trifluoromethyl)-2,2′-dinitrodiphenyldisulfide[8] in 1800 ml. of 90% acetic acid at such a rate that the temperature was maintained at 50–55°. The oxidation

(5) This procedure described is essentially that of H. Meerwein, G. Dittmar, R. Göllner, K. Hafner, F. Mensch, and O. Steinfort, *Chem. Ber.*, **90**, 841 (1957).

(6) Obtained from Maumee Chemical Co., Toledo 5, Ohio.

(7) This procedure is alluded to by A. H. Knight, Brit. Patent **732,121**, but no experimental details are presented.

(8) A. I. Kiprianov and L. M. Yagupolskii, *Zhur. Obshcheĭ Khim.*, **22**, 2209 (1952); *Chem. Abstr.*, **47**, 4769 (1953).

required about 5 hr. Excess chlorine was swept out with nitrogen, the mixture was filtered, and the filtrate concentrated *in vacuo* on the steam bath. The residual oil was extracted with 500 ml. of toluene, the extract was treated with Darco, filtered, dried, and concentrated to give 434 g. (81% yield) of crude sulfonyl chloride as a dark oil. This was used without further purification.

Potassium 2-nitro-α,α,α-trifluoro-p-toluenesulfonate. A suspension of 5.8 g. (0.02 mole) of 2-nitro-α,α,α-trifluoro-p-toluenesulfonyl chloride, 3 g. (0.02 mole) of anhydrous potassium carbonate, and 24 ml. of water was stirred and refluxed for 1 hr., filtered, and cooled to give 6.1 g. (98% yield) of the potassium salt, as broad yellow plates. An analytical sample was recrystallized from 90% ethanol; when heated in an open flame, the compound decomposed without melting.

Anal. Calcd. for $C_7H_3F_3KNO_5S$: K, 12.64. Found K, 12.39.

2-Amino-α,α,α-trifluoro-p-toluenesulfonic acid. The solution of the potassium salt obtained as in the previous example by the treatment of 428 g. (1.48 moles) of 2-nitro-α,α,α-trifluoro-p-toluenesulfonyl chloride with 225 g. (1.64 moles) of anhydrous potassium carbonate and 1750 ml. of water, was reduced by the procedure of Wertheim.[9] The yield of air-dried amino derivative was 286.4 g. (80%). An analytical sample was obtained from dimethylformamide-ether; this material decomposed in an open flame without melting.

Anal. Calcd. for $C_7H_6F_3NO_3S$: C, 34.85; H, 2.51. Found: C, 34.78; H, 2.62.

Sodium α,α,α-trifluoro-p-toluenesulfonate.[10] To the diazonium compound obtained from 270 g. (1.12 moles) of the amino compound[7] was added dropwise 582 ml. (5.6 moles) of 50% hypophosphorous acid, maintaining the temperature at 0 to 5°; the reaction mixture was kept for 48 hr. at 5°, filtered, and the filtrate concentrated to about one fourth its original volume and cooled. The precipitated solid was filtered and extracted with 3 l. of boiling methanol. The methanol extract was made strongly alkaline with 50% aqueous sodium hydroxide, concentrated, and cooled to give 182.4 g. (65% yield) of the sodium sulfonate.

α,α,α-Trifluoro-p-toluenesulfonyl chloride. To 116.5 g. (1.0 mole) of chlorosulfonic acid was added in small portions a total of 49.6 g. (0.2 mole) of the sodium sulfonate. Subsequently, the mixture was heated for 1 hr. on the steam bath, cooled somewhat, and poured on about 1 kg. of ice. The crystalline sulfonyl chloride which separated was filtered, washed well with water, and used directly in the next step.

α,α,α-Trifluoro-p-toluenesulfonamide. The sulfonyl chloride obtained in the previous step was added rapidly, with stirring, to 600 ml. of cold concd. aqueous ammonia, the mixture was slowly warmed by means of a steam bath to 75–80° and kept at this temperature for 1 hr. The mixture was cooled, the solid filtered and recrystallized from aqueous alcohol to give 30.6 g. (68% yield over-all for the last two steps) of sulfonamide, m.p. 176–177°.

Ethyl α,α,α-trifluoro-p-tolylsulfonylcarbamate. Employing the procedure described above, 30.6 g. (0.14 mole) of the sulfonamide, 49 g. (0.35 mole) of anhydrous potassium carbonate, and 19.6 g. (0.18 mole) of ethyl chloroformate afforded 28.6 g. (71% yield) of the crude ethyl carbamate, m.p. 85–87°. An analytical sample recrystallized from benzene-hexane (1:1), melted at 93–95°.

1-Butyl-3-(α,α,α-trifluoro-p-tolylsulfonyl)urea. From 8.9 g. (0.03 mole) of the ethyl carbamate and 11.5 g. (0.1 mole) of *n*-butylamine, by the procedure above, there was obtained 6.0 g. (62% yield) of product, m.p. 127–128° after recrystallization from aqueous ethanol.

Alternate procedure to ethyl α,α,α-trifluoro-p-tolylsulfonylcarbamate. Chart II, B. α,α,α-Trifluoro-*m*-toluidine and chlorosulfonic acid according to the procedure of Kracker and Herrlein[3a] gave a 95% yield of an amino-α,α,α-trifluorosulfonic acid whose infrared spectrum was identical with that obtained above. This acid, 241 g. (1.0 mole), when diazotized and the diazonium group reductively eliminated, gave 146 g. (59% yield) of sodium *α,α,α-trifluoro-p-toluenesulfonate.*

Anal. Calcd. for $C_7H_4F_3NaO_3S$: S, 12.92. Found: S, 12.97.

The sodium salt, 17.4 g. (0.07 mole) and 46.5 g. (0.39 mole) of chlorosulfonic acid gave the *sulfonyl chloride,* and this without purification was treated with 200 ml. of concd. aqueous ammonia to give 9.8 g. (62% yield in two steps) of *α,α,α-trifluoro-p-toluenesulfonamide,* m.p. 176–177°; a mixture melting point with the product obtained above was 176–177°, and the infrared spectra of both products were identical. The sulfonamide, 9.8 g., gave an 81% yield of ethyl *α,α,α-trifluoro-p-tolylsulfonylcarbamate,* m.p. 93–94°; a mixture melting point with the product obtained above was 93–94°, and the infrared spectra of both products were identical.

Isolation of the cyclohexylamine salt of 1-cyclohexyl-3-(α,α,α-trifluoro-p-tolylsulfonyl)urea and 1,3-dicyclohexylurea from the reaction of cyclohexylamine with α,α,α-trifluoro-p-tolylsulfonylcarbamate. A solution of 20.8 g. (0.07 mole) of ethyl α,α,α-trifluoro-*p*-tolylsulfonylcarbamate and 50 g. (0.5 mole) of cyclohexylamine was treated as above. The pyrolysis product crystallized spontaneously and was recrystallized from aqueous ethanol to give the pure salt, m.p. 177–179°.

Anal. Calcd. for $C_{14}H_{17}F_3N_2O_3S \cdot C_6H_{13}N$: C, 53.44; H, 6.73; N, 9.35. Found: C, 53.25; H, 6.29; N, 9.43.

The salt was dissolved in 300 ml. of warm 0.5*N* aqueous sodium hydroxide and filtered from 0.9 g. of 1,3-dicyclohexylurea, m.p. 226–227°.[11] The warm filtrate was acidified with aqueous hydrochloric acid. The precipitated solid was filtered and recrystallized from 95% ethanol to give 10.5 g. (43% yield) of 1-cyclohexyl-3-(α,α,α-trifluoro-*p*-tolylsulfonyl)urea, m.p. 177–178°.

Acknowledgment. The authors are indebted to Mr. J. F. Alicino and his associates for the microanalyses reported and to Dr. Nettie Coy and Miss Barbara Keeler for the infrared spectra.

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(9) E. Wertheim, *Org. Syntheses,* Coll. Vol. II, 471 (1943).

(10) This compound was screened for ascaricidal activity but no description of its synthesis is reported; *cf. J. Am. Pharm. Assoc.,* **38,** 570 (1949).

(11) A. Skita and H. Rolfes, *Ber.,* **53,** 1242 (1920) have reported the melting point for 1,3-dicyclohexylurea as 229–230°.

Indole-3-alkanamides

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Since the first implication of indole-3-acetic acid in the growth of plants,[1] the series of indole-3-alkanoic acids has received a great deal of attention from both chemists and biologists. Although the acetic acid was first prepared by Ellinger in 1904,[2] it was not until twenty-one years later that its amide was reported[3] and still another twenty-

(1) F. Kögl, A. J. Haagen-Smit, and H. Erxleben, *Z. physiol. Chem.,* **228,** 90(1934).

(2) A. Ellinger, *Ber.,* **37,** 1801 (1904).

(3) R. Majima and T. Hoshino, *Ber.,* **58,** 2046 (1925).