Journal of Medicinal and Pharmaceutical Chemistry

VOL. 4, No. 1 (1961)

Synthesis and Hypoglycemic Activity of Trifluoromethylated Sulphonylureas

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Introduction

The replacement of chlorine, methyl, or other groups by a trifluoromethyl group has sometimes resulted in an improvement of the biological activity or in a desirable modification of the pharmacological profile of certain drugs. The effect of the introduction of a trifluoromethyl group into the structures of biologically active prototype molecules has been reviewed recently.[1]

As part of a programme aimed at developing useful oral hypoglycemic agents, the synthesis of a series of sulphonylureas containing the trifluoromethyl group was undertaken. A few compounds of this type have been described recently by Yale and Sowinski[2] although their pharmacology was not discussed.

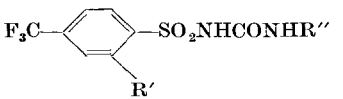
Chemistry

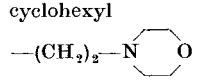
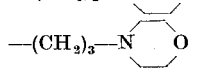
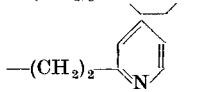
All the compounds described in this report were derived from one key intermediate, namely 2-nitro-4-trifluoromethylbenzenesulphonamide (I), which has been reported recently.[4] The desired trifluoromethylated sulphonylureas were obtained from this intermediate by three different methods which are designated in Table I as A, B and C.*

Method A consisted of condensing the trifluoromethylbenzenesulphonamide (I or II) with appropriate alkylisocyanates. This procedure gave high yields of the expected trifluoromethylbenzenesulphonylureas (III, IV). When the isocyanate was not

* The chemical literature contains many procedures for the preparation of sulphonylureas and these have been reviewed recently.[4,5]

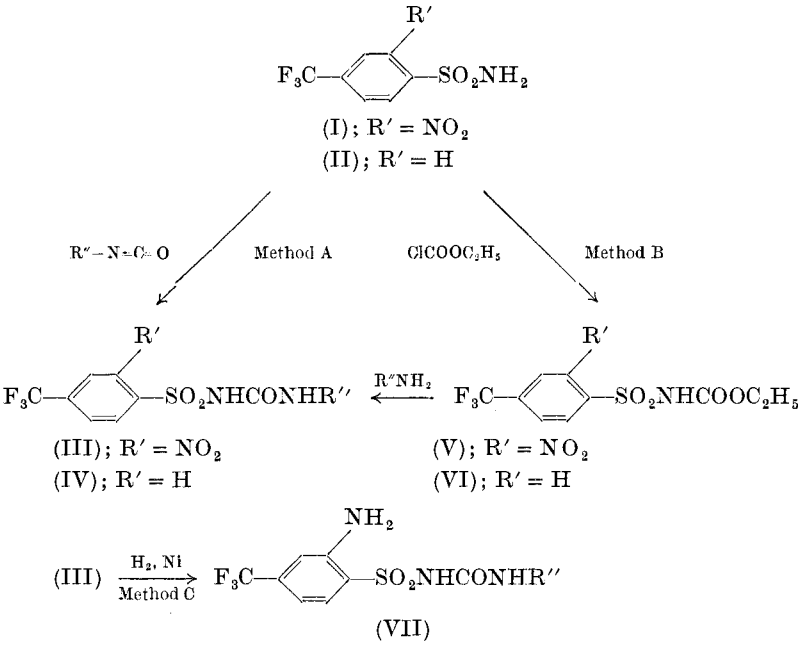
Table I. 1-Alkyl-3-(4-trifluoromethylarylsulphonyl)-ureas



No.	R′	R″	m.p., °C[a]	Method	Yield,[f] %	Formula	Analysis, % Calcd. C	Calcd. H	Found C	Found H
1	H	*n*-C_3H_7	149–150[b]	A	93	$C_{11}H_{13}F_3N_2O_3S$	42·58	4·18	42·90	4·03
2	H	*n*-C_4H_9	133–135[c]	A	61	$C_{12}H_{15}F_3N_2O_3S$[g]	44·44	4·62	44·58	4·71
3	H	cyclohexyl	181–182[c]	B	17	$C_{14}H_{17}F_3N_2O_3S$[g]	48·00	4·90	47·94	4·81
4	2-NO_2	*n*-C_3H_7	191–192[c]	A	83	$C_{11}H_{12}F_3N_3O_5S$	37·18	3·38	37·22	3·58
5	2-NO_2	*n*-C_4H_9	180–181[d]	A	74	$C_{12}H_{14}F_3N_3O_5S$	39·02	3·79	39·40	3·62
6	2-NH_2	*n*-C_3H_7	142–143[d]	C	88	$C_{11}H_{14}F_3N_3O_3S$	40·61	4·30	40·65	4·37
7	2-NH_2	*n*-C_4H_9	155–165 (dec.)[d]	C	80	$C_{12}H_{16}F_3N_3O_3S.HCl$	38·34	4·52	38·52	4·66
8	2-NO_2	cyclohexyl	173–175[c]	B	10	$C_{14}H_{16}F_3N_3O_5S$	42·58	4·08	42·76	4·12
9	H		196–197[e]	B	23	$C_{14}H_{18}F_3N_3O_4S$	44·24	4·76	44·18	4·58
10	H		197–199[c]	B	48	$C_{15}H_{20}F_3N_3O_4S$	45·69	5·07	45·72	5·11
11	H		166–167[c]	B	65	$C_{15}H_{14}F_3N_3O_3S$	48·38	3·78	48·58	3·99

[a] Melting points are uncorrected. [b] Recrystallized from benzene. [c] Recrystallized from 2-propanol–water. [d] Recrystallized from 2-propanol. [e] Recrystallized from dioxane–water. [f] No attempt was made to find the conditions for optimum yield. [g] Previously reported by Yale and Sowinski.[2]

readily available method B was employed. In this method, the trifluoromethylbenzenesulphonamides (I, II) were first converted into their corresponding *N*-carbethoxy derivatives (V, VI) by treatment with ethyl chlorocarbonate in the presence of potassium carbonate. The trifluoromethylbenzenesulphonylcarbamates thus obtained gave rise to the sulphonylureas of type III and IV upon cleavage with amines. The sulphonylureas (III) obtained by



methods A and B, which contained an *ortho*-nitro substituent, were hydrogenated to the corresponding amines (VII) in the presence of Raney nickel (Method C).

Method A was found to be the most general for preparation of this class of compounds. Method B was quite satisfactory in most cases but it gave very low yields when applied to the benzenesulphonylcarbamates of type V which contained a nitro group in the *ortho* position. In those cases the major competing reaction was a smooth nucleophilic displacement of the sulphonamide group to yield aniline derivatives.[6]

Experimental*

Preparation of Intermediates

4-Trifluoromethylbenzenesulphonamide (*II*). Although this compound has been described by Yale and Sowinski in a recent Note,[2] we have independently carried out a slightly different preparation. To a cold solution of concentrated sulphuric acid (180 ml) in 95 per cent ethanol (1·2 l.) was added 2-amino-4-trifluoromethylbenzenesulphonamide (161·4 g, 0·67 mole).[3] After cooling to −5°, sodium nitrite (185·4 g, 2·69 mole) was added followed by the slow addition of 840 ml of water while keeping the temperature of the stirred reaction mixture at −5°. The reaction mixture was allowed to warm up slowly to room temperature and then refluxed during 1 h. The cooled resulting solution was basified to pH 10–12 with a 50 per cent sodium hydroxide solution. The inorganic material was filtered and washed twice with 250-ml portions of 95 per cent ethanol. The combined filtrate and washings were acidified with concentrated hydrochloric acid and then basified again with a slight excess of sodium carbonate. After vacuum removal of the solvent, the solid residue was dried overnight *in vacuo* at 105°.

After adding phosphorus oxychloride (282 g) to the dry residue, the mixture was refluxed during 20 h in an oil-bath maintained at 170–175°. The cooled mixture was poured into 2 l. of crushed ice and extracted with four 500-ml portions of carbon tetrachloride. The combined extracts were briefly dried (Na_2SO_4 anhyd.) and evaporated to dryness *in vacuo*. To the residue was added 180 g of ammonium carbonate; the mixture was heated during 2 h on a steam-bath with frequent shaking, then dissolved in 1·5 l. of boiling water, filtered off from insoluble materials, and the filtrate was allowed to cool slowly to room temperature. The crystalline material thus obtained was recrystallized (charcoal) from a methanol–water mixture; yield 110 g (72·8 per cent), m.p. 182–184°.

Anal. Calcd. for $C_7H_6F_3NO_2S$: C, 37·36; H, 2·69. Found: C, 37·32; H, 2·71.

Ethyl N-(*2-nitro-4-trifluoromethylbenzenesulphonyl*)-*carbamate*

* Melting points are uncorrected. No attempt was made to find the conditions for optimum yields. Microanalyses were performed by Mr. R. M. Downing.

(*V*). Ethyl chlorocarbonate (163 g, 1·5 mole) was added dropwise, during 3 h, to a stirred mixture of 2-nitro-4-trifluoromethylbenzenesulphonamide[3] (270·5 g, 1 mole) and anhydrous potassium carbonate (358·8 g, 2·6 moles) in dry acetone (1·2 l.). When the addition had been completed, the reaction mixture was stirred and refluxed during 16 h. After cooling at 0–5°, the insoluble material was filtered off, washed several times with acetone, and the combined filtrates were evaporated to dryness at reduced pressure. The residue was dissolved in 3 l. of water, filtered from insoluble materials and acidified slowly, with cooling, with concentrated hydrochloric acid. The white crystalline solid which separated was collected by filtration and recrystallized from a methanol–water mixture yielding 283 g (82·7 per cent) of pure crystalline material, m.p. 116–118°.

Anal. Calcd. for $C_{10}H_9F_3N_2O_6S$: C, 35·20; H, 2·65. Found: C, 35·35; H, 2·87.

Ethyl N-(*4-trifluoromethylbenzenesulphonyl*)-*carbamate* (*VI*). The procedure described above for V was employed using 45 g (0·2 mole) of 4-trifluoromethylbenzenesulphonamide (II), 71·7 g (0·52 mole) of anhydrous potassium carbonate and 32·6 g (0·3 mole) of ethyl chlorocarbonate. After recrystallization of the reaction product from a benzene–cyclohexane mixture this procedure afforded 51·4 g (86·5 per cent) of pure crystalline material, m.p. 94–95°.

Anal. Calcd. for $C_{10}H_{10}F_3NO_4S$: C, 40·40; H, 3·40. Found: C, 40·68; H, 3·61.

Method A

N-(n-*Propyl*)-N′-(*2-nitro-4-trifluoromethylbenzenesulphonyl*)-*urea* (III; R″ = *n*-C_3H_7). The following example illustrates a typical procedure. A solution of *n*-propyl isocyanate (68 g, 0·8 mole) in dimethylformamide (100 ml) was added, during 45 min, to a stirred solution of 2-nitro-4-trifluoromethylbenzenesulphonamide[3] (135 g, 0·5 mole) in triethylamine (350 ml). When the addition had been completed, the reaction mixture was allowed to stand for 3 h at room temperature. The resulting clear solution was slowly added, with stirring, to 4 l. of a 20 per cent aqueous acetic acid solution. The crystalline material which separated was collected by filtration, washed several times with cold water, and then

dissolved in 1·5 l. of a 5 per cent aqueous sodium carbonate solution. After filtration, to remove a small amount of insoluble material, the clear filtrate was added dropwise to 5 l. of a vigorously stirred 20 per cent acetic acid solution. The almost pure crystalline compound which separated was recrystallized once from 2-propanol–water. This procedure afforded 148 g (83 per cent) of light yellow crystals, m.p. 191–192°. See Table I for the analysis.

Method B

N-(*3-Morpholinopropyl*)-N′-(*4-trifluoromethylbenzenesulphonyl*)-*urea* (IV; R″ = morpholinopropyl). The following preparation is typical of a general procedure. A mixture of ethyl (4-trifluoromethylbenzenesulphonyl)-carbamate (VI) (14·9 g, 0·05 mole), *N*-(3-aminopropyl)-morpholine (21·6 g, 0·15 mole) and benzene (50 ml) was refluxed on the steam-bath, with occasional shaking, until a clear solution was obtained. After vacuum removal of the solvent, the residue was heated in an oil-bath at 120–125° and 0·5 mm during 4 h. The cooled residue was crystallized from 2-propanol–water yielding 9·6 g (48 per cent) of crystalline solid, m.p. 197–199°. Analyses are reported in Table I.

Method C

N-(n-*Propyl*)-N′-(*2-amino-trifluoromethylbenzenesulphonyl*)-*urea* (VII; R″ = n-C_3H_7). The preparation of this compound is described as a specific example to illustrate the general method. A solution of *N*-(*n*-propyl)-*N*′-(2-nitro-4-trifluorobenzenesulphonyl)-urea (53·2 g, 0·15 mole) (III, R″ = n-C_3H_7) in methanol (250 ml) was hydrogenated, in the presence of Raney nickel, at an initial pressure of 50 lb/in^2. When the absorption of hydrogen had ceased, the catalyst was filtered off, and the filtrate was concentrated to dryness at reduced pressure. The crystalline residue was dissolved in boiling 2-propanol; the resulting solution was treated with charcoal and filtered. The hot filtrate was diluted to the cloud point with water and allowed to cool slowly to room temperature. The white crystalline material which separated was collected by filtration and dried. There was thus obtained 30 g (88 per cent) of pure crystals, m.p. 142–143°. See Table I for analysis.

Hypoglycemic Activity

The hypoglycemic activity of the eleven compounds described in Table I was compared with that exhibited by tolbutamide in unanaesthetized adult mongrel dogs. Graded doses of the material being tested were administered orally in capsule form to pairs of fasted animals. Blood samples were routinely obtained prior to drug administration and 1, 3, 5, and 24 h after administration. In some cases, additional samples were obtained at 48, 72, and

Table II. Oral hypoglycemic activity in dogs

Compound no.	Dose, mg/kg	No. dogs	Mean serum glucose conc. (mg per cent)							
			0	1	3	5	24	48	72	96 h
1	25	2	86	77	69	77	76	79		
	50	4	86	78	72	68	86	91		
	100	2	86	76	57	56	57	70		
2	50	2	89	86	70	75	82			
	100	5	84	80	61	64	58	67	70	84
3	50	2	89	82	57	58	58	64	58	
	100	2	86	63	64	70	78			
4	25	2	82	71	72	65	79			
	100	2	89	71	67	65	82			
5	100	2	80	68	78	75				
	250	2	86	73	63	70				
6	25	2	92	89	85	86	91			
	50	2	95	93	79	77	82			
	100	2	88	76	70	79	87			
7	200	2	95	Toxic, both animals died						
8	25	2	91	88	74	70	77	84	84	
	50	2	86	77	72	77	84			
	100	2	90	84	70	63	91			
9	25	2	82	81	81	79	78	80		
	100	2	90	81	71	70	79			
10	100	2	89	81	70	77	83			
11	50	2	89	84	84	86	88			
	100	2	82	73	67	81	83			
Tolbutamide	25	3	88	74	63	58	78	89		
	50	3	92	78	53	55	63		93	

Mean control serum glucose concentration of 30 pairs of dogs = $88 \pm 3{\cdot}9$ mg per cent (S.D.).

96 h in order to complete duration-of-action studies. Serum glucose determinations were carried out on these samples by the Folin–Malmros micro method.[7] The results of these experiments are presented in Table II. The control serum glucose concentrations obtained on thirty pairs of dogs was found to be $88 \pm 3 \cdot 9$ mg per cent. Serum glucose concentrations below 76 mg per cent may then be considered indicative of hypoglycemic effect induced by the test compounds (99 per cent confidence limit).

It is evident that compounds 1, 2, and 3 where R′ = hydrogen and R″ = *n*-propyl, *n*-butyl or cyclohexyl, respectively, were the most potent hypoglycemic compounds of the series. Compounds 2 and 3 lowered serum glucose concentrations markedly and rapidly but exhibited prolonged duration of action (up to 72 h). There appeared to be little difference between these compounds with regard to their hypoglycemic potential.

Substitution of a nitro group in the 2-position on the phenyl ring reduced the activity of all three compounds to about the same extent (compounds 4, 5, and 8). Although activity was still apparent, recovery then occurred within 24 h. Substitution of an amino group in the 2-position of the phenyl ring of the *n*-propyl and *n*-butyl derivatives (compounds 6 and 7) resulted in even greater diminution of hypoglycemic activity than did substitution by a nitro group. Replacement of the alkyl substituent (R″) on the urea nitrogen by *N*-ethylmorpholine (compound 9) resulted in a compound having very weak hypoglycemic activity. When R′ = NH_2 and R″ = *n*-butyl (compound 7), oral administration of 200 mg/kg resulted in the death of both animals before blood samples could be obtained for glucose determinations. When R″ = 2-ethylpyridine (compound 11), the compound was weakly hypoglycemic but possessed a very short duration of action (less than 5 h) when given at a dose of 100 mg/kg.

In this series, therefore, maximum hypoglycemic activity was associated with those compounds devoid of ring substituents where R″ is a simple alkyl moiety.

When compared with tolbutamide, these compounds appear to be somewhat less potent. The *n*-butyl derivative (compound 2), where R′ = H, was somewhat less active than tolbutamide but possessed a longer duration of activity at a dose of 100 mg/kg, producing hypoglycemia equivalent in degree to that produced

by 25 mg/kg of tolbutamide. The substitution of a trifluoromethyl group in the *para*-position for the methyl group of tolbutamide apparently decreased activity somewhat.

Summary. A series of eleven trifluoromethylbenzenesulphonylureas are described. These were prepared by direct condensation of alkyl isocyanates with appropriate trifluoromethylbenzenesulphonamides. When the isocyanates were not readily available, the trifluoromethylbenzenesulphonamides were converted into their *N*-carbamates and these, upon cleavage with primary amines, gave rise to the desired benzenesulphonylureas. The benzenesulphonylureas containing a nitro group in the phenyl ring were converted into the corresponding aminobenzenesulphonylureas by catalytic hydrogenation.

All the compounds described in this report possessed hypoglycemic activity to different degrees. The most active compounds of Table I were those where R′ = H and R″ = *n*-propyl, *n*-butyl and cyclohexyl. The activity of these compounds was decreased when a nitro group was introduced in the phenyl ring and further decreased when this group was reduced to the corresponding amino group.

(Received 13 January, 1961)

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