Hypoglycemic Activity in Relation to Chemical Structure of Potential Oral Antidiabetic Substances. III. 2-Benzenesulfonamido-5-alkyl-1,3,4-thiadiazoles and -oxadiazoles[1]

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A number of 5-alkyl-2-arylsulfonamido-1,3,4-thia- and oxadiazoles has been prepared. Several of them exerted a powerful hypoglycemic activity in rats and rabbits following oral administration.

Early investigations of the hypoglycemic activity of 2-(*p*-aminobenzenesulfonamido-5-isopropyl-1,3,4-thiadiazole[2] revealed that hypoglycemic activity was generally exerted by a great number of related sulfanilamidoalkylthiadiazoles. Optimal activity was found in compounds possessing an alkyl group comprising three to five carbon atoms. The finding that 2-benzenesulfonamido-5-isopropyl-1,3,4-thiadiazole was inactive made Bovet and Dubost[2] conclude that the *p*-amino group was a prerequisite for hypoglycemic activity in this series of compounds. During our experiments[3,4] with hypoglycemic sulfonyl urea derivatives of the general type $RSO_2NHCONHR'$ we had obtained evidence that there are very specific structural requirements on the middle ($SO_2NHCONH$) section of the molecule but that the end groups R and R′ may vary within fairly wide limits; the *p*-amino group in carbutamide, *e.g.*, is by no means essential. It therefore occurred to us that similar conditions might hold true for the thiadiazole derivatives. Consequently we started the investigation of a number of such compounds in which the substituent

(1) Part II, *J. Med. Pharm. Chem.*, **5**, 240 (1962).
(2) See Part I, *ibid.*, **5**, 231 (1962), refs. 1–4.
(3) B. Hökfelt and Å. Jönsson, *ibid.*, **5**, 231 (1962).
(4) B. Hökfelt and Å. Jönsson, *ibid.*, **5**, 240 (1962).

in the phenyl nucleus was varied to elucidate the possibility of finding useful therapeutic agents. A few similar studies have been published recently.[5] Because of the close connection between 1,3,4-thiadiazoles and 1,3,4-oxadiazoles (*cf.* Brooks *et al.*[6]) a number of oxadiazole derivatives were also included in the investigation.

Evaluation of the Hypoglycemic Effect.—The compounds, either in form of aqueous solutions of their sodium salts or as suspensions in water containing 0.1% Tween 80 and 1% low viscosity CMC, were tested for oral hypoglycemic effect in rabbits by the method previously described.[3] Some of the more interesting compounds were also tested in the rabbit after subcutaneous administration and also in the rat administered both perorally and subcutaneously. In the latter case white, inbred rats weighing 200 to 300 g. were fasted 12 to 18 hr. prior to drug administration. Blood sugar determinations were performed principally in accordance with what has been described for the rabbit at different intervals for a 24 hr. period. In the Tables the hypoglycemic potency has been graded from + to +++ referring to the lowest blood sugar level registered within 8 hr. following the administration of the substance; ++ corresponds to the hypoglycemic effect exerted by the same dose of 1-*p*-toluenesulfonyl-3-*n*-butylurea. Compounds less potent than this standard but still definitely active have been designated by + and those definitely more active by +++. Parentheses have been used to indicate a less clear cut result. Zero sign has been used to denote either lack of effect on blood sugar level or hyperglycemic response. In those instances where the hypoglycemic effect is presented in diagrams absolute blood sugar values are given.

Results and Discussion

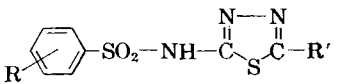
The results of the screening by oral administration in rabbits are given in Tables I–III. The thia- and oxadiazole derivatives presented in Tables I and II are generally active whereas a variety of closely related compounds in Table III are inactive. This justifies the conclusion that as in the sulfonylurea series there are also in these new compounds very specific requirements on the structure of the central part of the molecules, whereas the terminal groups are less specific,

(5) F. L. Chubb and J. Nissenbaum, *Canadian Chem. J.*, **10**, 58 (1958).

(6) J. D. Brooks, P. T. Charlton, P. E. Macey, D. A. Peak, and W. F. Short, *J. Chem. Soc.*, 452 (1950).

TABLE I

HYPOGLYCEMIC ACTIVITY, MELTING POINTS, AND ANALYTICAL DATA OF SOME 2-BENZENESULFONAMIDO-5-ALKYL-1,3,4-THIADIAZOLES

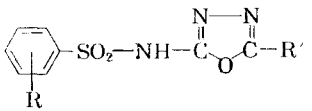


Serial No.	R	R′	M.p., °C.	Composition	Analyses: Calcd., % C	H	N	Found, % C	H	N	Activity[a]
338	*p*-CH_3	C_2H_5	133.5–134.5 (Lit.[19] 132–132.5)								++
339	*p*-CH_3O	C_2H_5	140–141[b]	$C_{11}H_{13}N_3O_3S_2$	44.1	4.38	14.0	44.7	4.52	13.3	++
340	*p*-CH_3O	*n*-C_3H_7	126.5–127.5	$C_{12}H_{15}N_3O_3S_2$	46.0	4.82	13.4	46.0	4.87	13.4	+(+)
341	*p*-F	*n*-C_3H_7	119.5–121	$C_{11}H_{12}FN_3O_2S_2$	43.8	4.01	13.9	44.0	4.10	13.7	++
356	*p*-C_2H_5O	*n*-C_3H_7	124.5–125.5	$C_{13}H_{17}N_3O_3S_2$	47.7	5.23	12.8	47.8	5.56	12.1	0
343	*p*-C_2H_5O	*n*-C_4H_9	113–114	$C_{14}H_{19}N_3O_3S_2$	49.2	5.61	12.3	48.7	5.49	12.0	0(+)
344	*m*-CH_3	*n*-C_4H_9	127.5–129	$C_{13}H_{17}N_3O_2S_2$	50.1	5.50	13.4	50.7	5.66	13.0	+(+)
346	*p*-F	*n*-C_4H_9	96–97	$C_{12}H_{14}FN_3O_2S_2$	45.7	4.47	13.3	45.4	4.59	13.0	++
266	H	iso-C_4H_9	180–181	$C_{12}H_{15}N_3O_2S_2$	48.5	5.08	14.1	48.3	5.35	14.0	+(+)
251	*p*-CH_3	iso-C_4H_9	172–173.5	$C_{13}H_{17}N_3O_2S_2$	50.1	5.50	13.5	50.1	5.70	13.3	++
250	*p*-CH_3CONH	iso-C_4H_9	154–156 (Lit.[9] 149–150)								0
252	*p*-NH_2	iso-C_4H_9	220–222 (Lit.[20] 223.5–225)								++
347	*p*-CH_3O	iso-C_4H_9	147.5–148.5	$C_{13}H_{17}N_3O_3S_2$	47.7	5.23	12.8	47.2	5.33	12.7	++
348	*p*-Cl	*n*-C_5H_{11}	135.5–136.5	$C_{13}H_{16}ClN_3O_2S_2$	45.1	4.66	12.2	45.7	4.42	12.0	+(+)
349	*p*-CH_3O	*n*-C_5H_{11}	133.5–134.5	$C_{14}H_{19}N_3O_3S_2$	49.2	5.61	12.3	49.8	5.79	12.4	+(+)
350	*o*-CH_3O	*n*-C_5H_{11}	185–186	$C_{14}H_{19}N_3O_3S_2$	49.2	5.61	12.3	49.6	5.74	12.1	++
351	*o*-Br	*n*-C_5H_{11}	142–143.5	$C_{13}H_{16}BrN_3O_2S_2$	40.0	4.13	10.8	40.0	4.12	10.6	++(+)
352	*m*-Cl	*n*-C_5H_{11}	100–102	$C_{13}H_{16}ClN_3O_2S_2$	45.1	4.66	12.2	44.8	4.64	11.9	+
353	*p*-CH_3O	*n*-C_7H_{15}	123.5–126	$C_{16}H_{23}N_3O_3S_2$	52.0	6.27	11.4	52.3	6.00	10.9	0
354	*p*-CH_3	*n*-C_7H_{15}	99–101	$C_{16}H_{23}N_3O_2S_2$	54.4	6.56	11.9	54.2	6.50	11.7	0

[a] See text. [b] Melts at 140–141°, resolidifies and remelts at 152–153°.

TABLE II

HYPOGLYCEMIC ACTIVITY, MELTING POINTS, AND ANALYTICAL DATA OF SOME 5-ALKYL-2-BENZENESULFONAMIDO-1,3,4-OXADIAZOLES



Serial No.	R	R′	M.p., °C.	Composition	Analyses — Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Activity (see text)
392	*p*-F	CH_3	140.5–141.5	$C_9H_8FN_3O_3S$	42.0	3.13	16.3	42.4	3.38	16.1	++
393	*p*-CH_3O	CH_3	137.5–139.5	$C_{10}H_{11}N_3O_4S$	44.6	4.11	15.6	44.5	4.04	15.6	+
395	*o*-Br	CH_3	175–177	$C_9H_8BrN_3O_3S$	34.0	2.53	13.2	34.2	2.46	12.9	0
358	H	C_2H_5	98.5–99.5	$C_{10}H_{11}N_3O_3S$	47.4	4.38	16.6	47.3	4.35	16.7	0
359	*p*-CH_3O	C_2H_5	144.5–146	$C_{11}H_{13}N_3O_4S$	46.6	4.63	14.8	46.1	4.32	14.6	0
360	H	*n*-C_3H_7	87.5–88.5	$C_{11}H_{13}N_3O_3S$	49.4	4.90	15.7	49.6	4.97	15.6	++(+)
361	*m*-CH_3	*n*-C_3H_7	96–97	$C_{12}H_{15}N_3O_3S$	51.2	5.37	14.9	50.7	5.38	14.6	+(+)
362	*p*-CH_3O	*n*-C_3H_7	91.5–92.5	$C_{12}H_{15}N_3O_4S$	48.5	5.06	14.1	48.4	5.22	14.0	+++
363	*p*-F	*n*-C_3H_7	115.5–116.5	$C_{11}H_{12}FN_3O_3S$	46.3	4.24	14.7	46.5	4.15	14.6	++
364	*o*-Br	*n*-C_3H_7	149–150	$C_{11}H_{12}BrN_3O_3S$	38.2	3.49	12.1	38.2	3.29	12.0	
380	*p*-CH_3	*n*-C_3H_7	112.5–113.5	$C_{12}H_{15}N_3O_3S$	51.2	5.37	14.9	51.4	5.48	14.7	+++
390	*p*-Cl	*n*-C_3H_7	102–103	$C_{11}H_{12}ClN_3O_3S$	43.8	4.01	13.9	43.3	4.10	13.6	++
391	*p*-I	*n*-C_3H_7	127–128.5	$C_{11}H_{12}IN_3O_3S$	33.6	3.07	10.7	33.8	2.89	10.5	++
394	*o*-I	*n*-C_3H_7	150.5–152	$C_{11}H_{12}IN_3O_3S$	33.6	3.07	10.7	33.5	3.07	10.9	++
383	H	iso-C_3H_7	150–151	$C_{11}H_{13}N_3O_3S$	49.4	4.90	15.7	49.6	5.01	15.5	
384	*p*-CH_3	iso-C_3H_7	189.5–190.5	$C_{12}H_{15}N_3O_3S$	51.2	5.37	14.9	51.8	5.60	14.7	++
385	*p*-CH_3O	iso-C_3H_7	162–163	$C_{12}H_{15}N_3O_4S$	48.5	5.06	14.1	48.7	5.16	13.8	++
389	*p*-CH_3	*n*-C_4H_9	103.5–104.5	$C_{13}H_{17}N_3O_3S$	52.9	5.80	14.2	52.8	6.13	14.4	+++
267	H	iso-C_4H_9	105.5–106.5	$C_{12}H_{15}N_3O_3S$	51.2	5.37	14.9	51.8	5.60	14.7	++
268	*p*-CH_3	iso-C_4H_9	113.5–114.5	$C_{13}H_{17}N_3O_3S$	52.9	5.80	14.2	52.9	5.99	14.1	+++
269	*p*-CH_3CONH	iso-C_4H_9	187–188	$C_{14}H_{18}N_4O_4S$	49.7	5.36	16.6	49.8	5.46	16.3	0
270	*p*-NH_2	iso-C_4H_9	149–150.5	$C_{12}H_{16}N_4O_2S$	48.6	5.44	18.9	48.8	5.56	18.9	0
381	*p*-CH_3O	iso-C_4H_9	95–97.5	$C_{13}H_{17}N_3O_4S$	50.1	5.50	13.5	50.2	5.54	13.4	+++

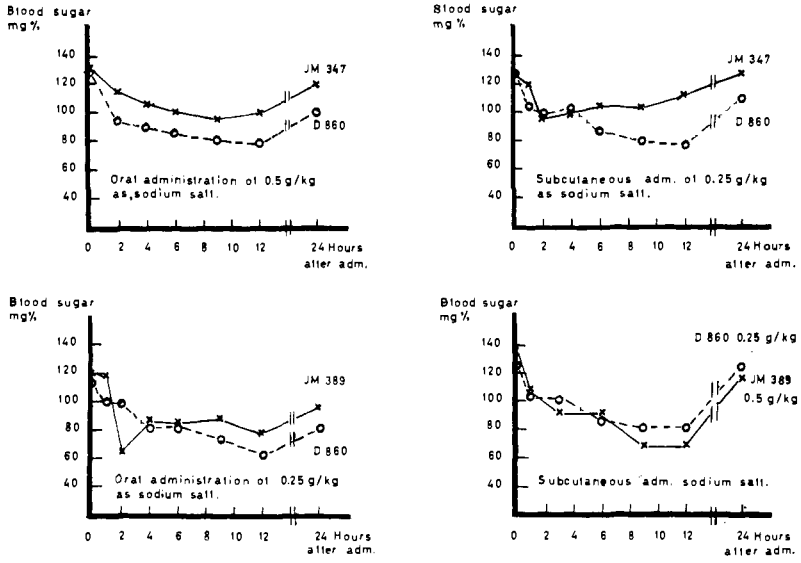


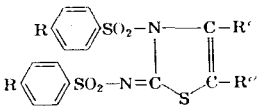
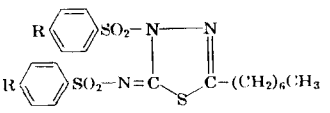
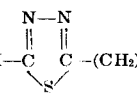
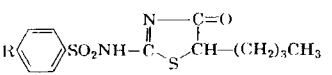
Fig. 1.—Effect of JM 347, JM 389 and D 860 (tolbutamide) on the blood sugar level of rabbit: mean values for 3 to 10 animals.

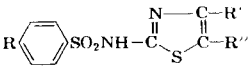
and may vary considerably. In agreement with earlier findings optimal activity was found in compounds carrying three to five carbon atoms in the alkyl side chain. The conclusion of Bovet and Dubost[2] (ref. 2) based on results with 2-benzenesulfonamido-5-isopropyl-thiadiazole that a *p*-amino group should be essential was found to be incorrect. Not only could it be substituted by a wide number of other groups but also the unsubstituted parent phenyl derivatives possessed considerable activity. The influence of substitution in the phenyl nucleus is approximately the same as was found in the sulfonylureas. The only compound tested with an aliphatic side chain, 5-*n*-amyl-2-*n*-hexanesulfonamido-1,3,4-thiadiazole, seems to exert only moderate hypoglycemic activity.

Generally the oxadiazole derivatives produce a greater reduction of the blood sugar concentration in rabbits than the thiadiazoles. The effect is, however, of fairly short duration, suggesting either a rapid excretion or a rapid break-down in the organism. In view of the results from studies with sulfanilamidoöxadiazoles as antibacterial agents reported by Brooks, *et al.*,[6] the latter appears to be the most

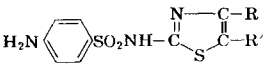
TABLE III

HYPOGLYCEMIC ACTIVITY, MELTING POINTS, AND ANALYTICAL DATA OF MISCELLANEOUS SULFONAMIDO HETEROCYCLIC COMPOUNDS

Serial No.	Structural formula	M.p., °C.	Composition	Analyses- Calcd., % C	H	N	Found, % C	H	N	Activity[a]
										
214	R = CH_3, R′ = CH_3, R″ = —$CH(CH_3)_2$	153–155	$C_{21}H_{24}N_2O_4S_3$	54.3	5.21	6.04	54.5	5.27	5.96	(+)[b]
215	R = H, R′ = CH_3, R″ = —$CH(CH_3)_2$	155.5–157	$C_{19}H_{20}N_2O_4S_3$	52.3	4.62	6.42	52.6	5.01	6.44	0[b]
272	R = CH_3, R′ = H, R″ = —$CH(CH_3)_2$	162–164	$C_{20}H_{22}N_2O_4S_3$	53.3	4.92	6.22	52.8	5.15	6.19	0[b]
										
353	R = CH_3O	140–141	$C_{23}H_{29}N_3O_6S_3$	51.2	5.42	7.79	51.0	5.41	7.92	(+)[b]
354	R = CH_3	128.5–129.5	$C_{23}H_{29}N_3O_4S_3$	54.4	5.76	8.28	54.1	5.78	8.28	0[b]
357	$CH_3(CH_2)_5SO_2NH$—  —$(CH_2)_4CH_3$	87–88.5	$C_{13}H_{25}N_3O_2S_2$	48.9	7.89	13.2	49.0	7.95	12.9	+
										
237	R = CH_3	133–134.5	$C_{14}H_{18}N_2O_3S_2$	51.5	5.56	8.58	51.8	5.83	8.37	0[b]
238	R = H	120–122	$C_{13}H_{16}N_2O_3S_2$	50.0	5.16	8.97	50.2	5.27	8.66	(+)[b]



214B	R = CH_3, R′ = CH_3, R″ = $CH(CH_3)_2$	188.5–190	$C_{14}H_{18}N_2O_2S_2$	54.2	5.84	9.02	54.0	5.69	8.94	
215B	R = H, R′ = CH_3, R″ = $CH(CH_3)_2$	186–188	$C_{13}H_{16}N_2O_2S_2$	52.7	5.44	9.46	52.4	5.26	9.55	
217	R = H, R′ = $CH_2CH(CH_3)_2$, R″ = H	101–102	$C_{13}H_{16}N_2O_2S_2$	52.7	5.44	9.46	52.5	5.21	9.28	0[b]
218	R = CH_3, R′ = $CH_2CH(CH_3)_2$, R″ = H	156–157	$C_{14}H_{18}N_2O_2S_2$	54.2	5.84	9.03	53.9	5.87	8.96	0[b]
271	R = CH_3CONH, R′ = $CH_2CH(CH_3)_2$, R″ = H	212–213	$C_{15}H_{19}N_3O_3S_2$	51.0	5.42	11.9	50.8	5.72	11.5	0[b]
274	R = NH_2, R′ = $CH_2CH(CH_3)_2$, R″ = H	211.5-212.5	$C_{13}H_{17}N_3O_2S_2$	50.1	5.50	13.5	50.3	5.66	13.4	0[b]
272B	R = CH_3, R′ = H, R″ = $CH(CH_3)_2$	153–155	$C_{13}H_{16}N_2O_2S_2$	52.7	5.44	9.46	52.9	5.55	9.30	

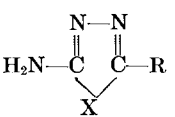


228	R = CH_3, R′ = $CH(CH_3)_2$	155-156	$C_{13}H_{16}N_2O_2S_2$	52.7	5.44	9.46	52.7	5.45	9.31	0[b]
231	R = $CH_2CH(CH_3)_2$, R′ = H	140–141.5	$C_{13}H_{16}N_2O_2S_2$	52.7	5.44	9.46	52.7	5.55	9.24	0[b]

[a] See text. [b] Only tested at 1 g./kg. dose level.

TABLE IV

MELTING POINTS AND ANALYTICAL DATA OF SOME NEW 2-AMINO-5-ALKYL-1,3,4-THIA- AND -OXADIAZOLES



				Analyses					
				Calcd., %			Found, %		
X	R	M.p., °C.	Composition	C	H	N	C	H	N
S	*n*-C_7H_{15}	195–196	$C_9H_{17}N_3S$	54.2	8.60	21.1	53.9	8.45	20.9
O	C_2H_5	180–181	$C_4H_7N_3O$	42.5	6.24	37.2	42.5	6.25	37.0
O	*n*-C_3H_7	154–154.5	$C_5H_9N_3O$	47.2	7.14	33.1	47.8	7.37	33.0
O	iso-C_3H_7	182–183	$C_5H_9N_3O$	47.2	7.14	33.1	47.2	7.21	32.0
O	*n*-C_4H_9	140–140.5	$C_6H_{11}N_3O$	51.1	7.85	29.8	51.9	7.77	30.2
O	iso-C_4H_9	168–169.5	$C_6H_{11}N_3O$	51.1	7.85	29.8	51.3	7.72	29.7

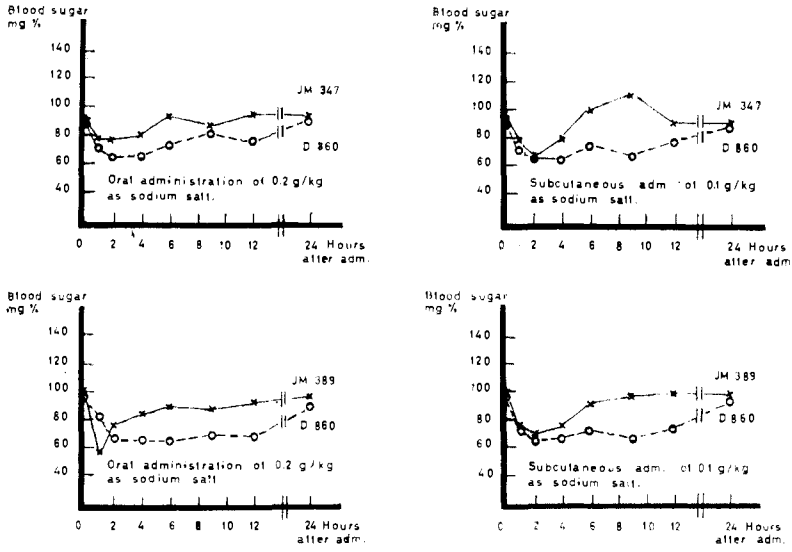


Fig. 2.—Effect of JM 347, JM 389, and D 860 (tolbutamide) on the blood sugar level of rat: mean values for 3 to 10 animals.

probable reason. It is interesting that whereas the decrease in blood sugar concentration obtainable with carbutamide does not exceed about 30%, these new compounds in high doses often seem to induce much greater reductions. It is noteworthy that in some instances the blood sugar response following oxadiazoles when compared to those after an equal dose of 1-*p*-toluenesulfonyl-3-*n*-butylurea was less pronounced in the rat than in the rabbit.[7]

Experimental[8]

5-Alkyl-2-amino-1,3,4-thiadiazoles.—These compounds were prepared from thiosemicarbazide and the appropriate acyl chloride following the general directions given by Wojahn and Wuckel.[9] Most of the substances have been described by these authors and by Ohta and Higashijima.[10] The 5-*n*-heptyl derivative

(7) After the completion of this investigation some similar thiadiazoles have been described by F. L. Chubb and J. Nissenbaum [*Can. J. Chem.*, **37**, 1121 (1959)] and by D. McColl [*Appl. Therapeutics*, **2**, 203 (1960)]. One of them, 2-*p*-methoxybenzenesulfonamido-5-*iso*butyl-1,3,4-thiadiazole (Stabinol®) has been successfully tested clinically by M. F. Healy and J. D. Arneaud, (*Brit. Med. J.*, **1960 II**, 913).

(8) All melting points are corrected.

(9) H. Wojahn and H. Wuckel, *Arch. Pharm.*, **284**, 53 (1951).

appears to be new and its analytical data are included in Table IV.

5-Alkyl-2-amino-1,3,4-oxadiazoles.—These compounds were prepared by acylating thiosemicarbazide with the appropriate acid anhydride and treating the acylthiosemicarbazide thus obtained with lead oxide as described by Stollé and Fehrenbach[11] (*cf.* Brooks *et al.*[6]) for the synthesis of 2-amino-5-methyl-1,3,4-oxadiazole. Melting points and analytical data are given in Table IV.

2-Amino-5-isopropylthiazole was prepared according to Sunagawa *et al.*,[12] and **2-amino-5-*n*-butylthiazolone-4** according to Nicolet and Bate.[13]

2-Amino-4-methyl-5-isopropylthiazole.—3-Bromo-4-methylpentanone-2 (269 g., 1.5 mole), obtained by bromination of methyl isobutyl ketone[14,15] was slowly added to a solution of thiourea (129 g., 1.7 mole) in water (150 ml.). When the vivid reaction subsided the mixture was heated under reflux for a further 2 hr. After cooling the mixture was made strongly alkaline by the addition of 30% sodium hydroxide solution. An oil separated which slowly crystallized. Crystallization from petroleum ether afforded coarse prisms, m.p. 71–73° (lit.[14] m.p. 72–73°), yield 158 g. (67%).

2-Amino-4-isobutylthiazole was obtained similarly in 85% yield from 1-bromo-4-methylpentanone-2. The product formed an oil, b.p. 131° (9 mm.) (lit.[14] b.p. 111–112.5° (1.5 mm.)), which slowly crystallized. Recrystallization from petroleum ether afforded prisms, m.p. 53–54°.

Sulfonamidoheterocycles.—The aminoheterocycles were converted into sulfonamido compounds by treatment with an equivalent amount of the respective sulfonyl chloride in pyridine solution. In general the mixture was cooled in water in order to prevent the temperature from rising above about 30° and the mixture was kept at room temperature for 2 days. In the preparation of the thiadiazole derivatives, however, it was found advantageous to carry out the reaction at 100° for 2 hr. The reaction mixture was poured into excess 2 *N* hydrochloric acid, the product which separated was taken up in ether, chloroform or benzene, washed with water and extracted with *N* sodium hydroxide. Acidification of the alkaline extract afforded the crude sulfonamido compound which was further purified by crystallization. Melting points and analytical data of the compounds are given in Tables I–III. The yields of purified compounds were generally in the order of 50%. The main by-products were alkali-insoluble disulfonyl derivatives. In some experiments these were isolated (Table III, Nos. 214, 215, 272, 353, 354). They were easily converted into the corresponding monosulfonyl derivatives by boiling 10% aqueous-ethanolic sodium hydroxide solution. The formation of such neutral disulfonyl derivatives has been reported.[16,17]

(10) M. Ohta and T. Higashijima, *J. Pharm. Soc. Japan*, **72**, 376 (1952); from *Chem. Abstr.*, **47**, 3856 (1953).

(11) R. Stollé and K. Fehrenbach, *J. prakt. Chem.*, [2] **122**, 289 (1929).

(12) G. Sunagawa, S. Okada, and H. Hamatsu, *J. Pharm. Soc. Japan*, **73**, 879 (1953); from *Chem. Abstr.*, **48**, 8777 (1954).

(13) B. H. Nicolet and L. F. Bate, *J. Am. Chem. Soc.*, **49**, 2064 (1927).

(14) H. M. E. Cardwell and A. E. H. Kilner, *J. Chem. Soc.*, 2430 (1951).

(15) J. R. Catch, D. F. Elliot, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948).

(16) K. A. Jensen and Th. Thorsteinsson, *Dansk Tidsskr. Farm.*, **15**, 41 (1941).

(17) K. A. Jensen and B. Possing, *Dansk Tidsskr. Farm.*, **15**, 191 (1941).

4-Isobutylthiazole-2-thiol.—To a stirred mixture of ammonium dithiocarbamate (200 g., 1.8 mole) and absolute ethanol (500 ml.) there was slowly added 1-bromo-4-methylpentanone-2 (208 g., 1.15 mole) with cooling in tap water. When the vigorous reaction had subsided the mixture was refluxed for a further 2 hr. Most of the solvent was removed under reduced pressure on a water bath. Water (750 ml.) was added and the oil which separated was taken up in ether, washed with water and dried ($CaCl_2$). After evaporation of the ether the remaining oil crystallized on cooling. Crystallization from petroleum ether afforded coarse prisms, m.p. 66–67°; yield 110 g. (55%).

Anal. Calcd. for $C_7H_{11}NS_2$: C, 48.5; H, 6.40; N, 8.08. Found: C, 48.9; H, 6.44; N, 7.92.

5-Isopropyl-4-methylthiazole-2-thiol was obtained similarly in 57% yield from 3-bromo-4-methylpentanone-2 as needles from petroleum ether, m.p. 132.5–133.5°.

Anal. Calcd. for $C_7H_{11}NS_2$: C, 48.5; H, 6.40; N, 8.08. Found: C, 48.8; H, 6.45; N, 8.05.

4-Isobutyl-2-*p*-nitrobenzenesulfonylthiazole was prepared by the general method of Backer and Buisman.[18] 4-Isobutylthiazole-2-thiol (32.2 g., 0.215 mole) was added to a solution of sodium (5.0 g., 0.215 mole) in absolute ethanol (100 ml.) followed by *p*-nitrochlorobenzene (34 g., 0.24 mole). The mixture was refluxed for about 12 hr. and the solvent was removed under reduced pressure on a water bath. The remaining oil could not be induced to crystallize and was dissolved in glacial acetic acid (300 ml.) and slowly treated on the water bath with 30% hydrogen peroxide (100 ml.) during 3 hr. Water (600 ml.) was added and the precipitated oil was forced to crystallize by cooling and scratching. Crystallization from ethanol and from benzene–petroleum ether afforded prisms, m.p. 116–117.5°; yield, 36 g. (51%).

Anal. Calcd. for $C_{13}H_{14}N_2O_4S_2$: C, 47.8; H, 4.32. Found: C, 47.7; H, 4.43.

2-*p*-Nitrobenzenesulfonyl-4-methyl-5-isopropylthiazole was prepared similarly from 5-isopropyl-4-methylthiazole-2-thiol in 77% yield; m.p. 161.5–163.5°.

Anal. Calcd. for $C_{13}H_{14}N_2O_4S_2$: C, 47.8; H, 4.32; N, 8.58. Found: C, 48.2; H, 4.39; N, 8.70.

2-*p*-Aminobenzenesulfonyl-5-isopropyl-4-methylthiazole.—To a mixture of 2-*p*-nitrobenzenesulfonyl-4-methyl-5-isopropylthiazole (10 g., 0.033 mole), 96% ethanol (200 ml.) and concentrated hydrochloric acid (0.5 ml.), iron powder (100 g.) was added. The mixture was refluxed for 10 hr., made alkaline with ammonium hydroxide solution and filtered. The iron sludge was thoroughly washed with ethanol and the combined filtrate and washings concentrated to about 100 ml. Concentrated hydrochloric acid (100 ml.) and water (200 ml.) were added and the solution was treated with decolorizing carbon, filtered and made alkaline with ammonia. On cooling colorless plates were obtained (6.5 g., 67%). Melting point and analytical data are given in Table III.

2-*p*-Aminobenzenesulfonyl-4-isobutylthiazole was obtained similarly in 53% yield from 2-*p*-nitrobenzenesulfonyl-4-isobutylthiazole; see Table III.

(18) H. J. Backer and J. A. K. Buisman, *Rec. trav. chim.*, **64**, 102 (1945).
(19) R. Dahlbom and T. Ekstrand, *Svensk Kem. Tidskr.*, **55**, 122 (1943).
(20) A. R. Frisk, *Acta Med. Scand.*, **142**, Suppl. I (1942).

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Dihydro-1,3-oxazines as Antitumor Agents

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Dihydro-*m*-benzoxazines were prepared by condensation of phenols, β-naphthol and 7-hydroxycoumarins with formaldehyde and primary amines. The products were quaternized or cleaved hydrolytically to aminophenols which could be condensed with aromatic aldehydes to yield 2-substituted dihydro-1,3-oxazines. From hydroquinone, isomeric pairs of bis-dihydroöxazines were obtained and structures assigned on the basis of dipole measurements. The dihydro-*m*-oxazines as a class show inhibition of adenocarcinoma E0771. This activity is retained in the corresponding methiodides and aminophenols as well as non-benzenoid tetrahydro-*m*-oxazines.

Introduction.—The organic chemist's intensive efforts to synthesize compounds which will inhibit unrestricted neoplastic growth have led to effective agents which may be grouped into three categories: (a) alkylating agents, (b) antimetabolites and (c) diverse unrelated compounds which have been discovered either by random antitumor screening or because of a special therapeutic interest in some other

Abbreviations Used in Tables I–X.—Solvents: *a*, (methylene chloride-) methanol; *b*, (methylene chloride-) ethanol; *c*, (methylene chloride-) benzene; *d*, (methylene chloride-) ethyl acetate; *e*, (methylene chloride-) cyclohexane; *f*, (methylene chloride-) heptane; *g*, chloroform; *h*, methanol-ether; *i*, water. Substituent groups: *j*, 3-picolyl; *k*, 4-picolyl; *l*, 3,4-dimethoxyphenethyl; *m*, 2-picolyl; *p*, 4-pyridyl; *q*, 3-pyridyl; *r*, 2-pyridyl. Other: *n*, partial destruction on chromatography; *o*, 0.01 molar in benzene except 0.004 molar for no. 76, 77, 84, 85; *s*, orally active.

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