Potential Antidiabetics, 11. Preparation of 4-Arylazo-3,5-disubstituted-(2*H*)-1,2,6-thiadiazine 1,1-Dioxides

H. G. Garg* and Chandra Prakash

Department of Chemistry, University of Roorkee, Roorkee, India.
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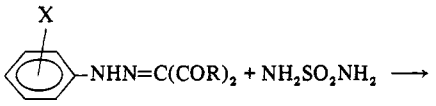
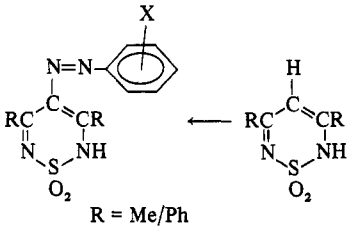
The synthesis and evaluation of pyrazoles which are potent inhibitors of the release of free acids from tissue, causing a hypoglycemic effect,[1,2] have been previously reported from this laboratory.[3] Urea derivatives comprising the structural elements, $>NSO_2NHC=C<$, on the other hand, reduce blood sugar by releasing insulin from pancreatic β cells.[4,5] Hence, the present study was initiated to prepare arylazo derivatives of 1,2,6-thiadiazine 1,1-dioxide (I) containing this sequence. They were synthesized by the reaction of sulfamide with 2,3,4-pentanetrione-3-arylhydrazones[6] in EtOH containing dry HCl at 60° (Table I). Similarly, 4-arylazo-3,5-diphenyl-(2*H*)-1,2,6-thiadiazine 1,1-dioxide (Table I) were prepd by the addition of sulfamide to 1,3-diphenyl-1,2,3-propanetrione 2-arylhydrazones[7] under the same experimental conditions.



II



R = Me/Ph

I III

In the other route, 3,5-dimethyl-(2*H*)-1,2,6-thiadiazine 1,1-dioxide (III) prepd by reported method,[8] was coupled with several diazotized anilines. The product so obtd after refluxing in glacial AcOH gave **1**. The ir spectra of **1** were in accord with these structures and had stretching vibrations in the regions 3130-3141 (NH), 2970-2994 (CH), 1599-1621 (N=N), 1615-1639 (=N), 1320-1333 (SO_2) cm^{-1}, respectively.

Biological Results. 4-(2,3-Dimethylphenylazo)- and 4-(3,5-dichlorophenylazo)-3,5-dimethyl-(2*H*)-1,2,6-thiadiazine 1,1-dioxides were found to possess considerable blood sugar lowering effect (>20%, dose 1.5 mmoles/kg) in mice with the aid of a Technicon auto-analyzer using the modified method of Hoffman.[9] No appreciable activity (<10%) has been displayed by the remaining compounds.

Experimental Section

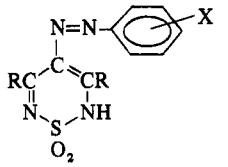
Melting points were taken with a Kofler hot-stage type apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, and results for elements were within ±0.4% of the theor values. 2,3,4-Pentanetrione, 3-arylhydrazones[6] 1,3-diphenyl-1,2,3-propanetrione, and 2-arylhydrazones[7] were prepd according to lit. procedures.

4-Phenylazo-3,5-dimethyl-(2*H*)-1,2,6-thiadiazine 1,1-Dioxide. Method A. A mixt of 0.48 g (0.005 mole) of sulfamide and 1.02 g (0.005 mole) of 2,3,4-pentanetrione 3-phenylhydrazone in 10 ml of EtOH (99%) was treated with HCl gas for 4 min, and heated for 3 hr at 60° and then under reflux for 20 min. It was evapd to dryness *in vacuo*. The residue was triturated with several portions of Et_2O and filtered after each treatment. The Et_2O-insol residue was stirred with several portions of H_2O, filtered after each washing. The product (58%) gave light orange plates, mp 163° (EtOH). *Anal.* ($C_{11}H_{12}N_4O_2S$) C, H, N, S.

Method B. 3,5-Dimethyl-(2*H*)-1,2,6-thiadiazine 1,1-dioxide was prepd from sulfamide and 0.005 mole of 2,4-pentanedione by method A and coupled with PhN_2Cl in the presence of AcONa at 0°. After diazotization, the soln was kept at room temp for 6 hr and then concd on a steam bath. On cooling, an orange-colored residue was obtd. This was triturated with Et_2O several times and filtered. It was heated under reflux for 1 hr with 30 ml of glac AcOH and poured over crushed ice. Shining orange cyrstals of 4-phenylazo-3,5-dimethyl-(2*H*)-1,2,6-thiadiazine 1,1-dioxide were obtd, mp 163°. Mmp with the compd obtd by method A, was undepressed, and their spectra were indistinguishable. Other

*To whom correspondance should be addressed at Harvard University Medical School, Laboratory for Carbohydrate Research, Massachusetts General Hospital, Boston, Mass. 02114.

Table I. 4-Arylazo-3,5-dimethyl/diphenyl-(2*H*)-1,2,6-thiadiazine 1,1-Dioxides



No.	X	R	Yield, %	Mp, °C	Color[a]	Formula[b]
1	3-Cl	Me	58	95	OPl	$C_{11}H_{11}ClN_4O_2S$
2	4-Cl	Me	55	123	PYl	$C_{11}H_{11}ClN_4O_2S$
3	2-Br	Me	55	143	YN	$C_{11}H_{11}BrN_4O_2S$
4	4-Br	Me	60	137	YN	$C_{11}H_{11}BrN_4O_2S$
5	2-Me	Me	65	112	DYPl	$C_{12}H_{14}N_4O_2S$
6	3-Me	Me	60	81	DyPl	$C_{12}H_{14}N_4O_2S$
7	4-Me	Me	63	99	BN	$C_{12}H_{14}N_4O_2S$
8	2-NO_2	Me	68	189	DYPl	$C_{11}H_{11}N_5O_4S$
9	3-NO_2	Me	65	136	PYPl	$C_{11}H_{11}N_5O_4S$
10	2-MeO	Me	60	139	YN	$C_{12}H_{14}N_4O_3S$
11	3-MeO	Me	63	132	BPl	$C_{12}H_{14}N_4O_3S$
12	2-EtO	Me	67	129	PYPl	$C_{13}H_{16}N_4O_3S$
13	4-SO_2NH_2	Me	70	226	YN	$C_{11}H_{13}N_5O_4S_2$
14	2,5-Cl_2	Me	60	112	YPl	$C_{11}H_{10}Cl_2N_4O_2S$
15	3,5-Cl_2	Me	63	231	YOPl	$C_{11}H_{10}Cl_2N_4O_2S$
16	2,5-Br_2	Me	60	148	YPl	$C_{11}H_{10}Br_2N_4O_2S$
17	2,3-Me_2	Me	55	109	YPl	$C_{13}H_{16}N_4O_2S$
18	2,4-$(MeO)_2$	Me	63	158	YPl	$C_{13}H_{16}N_4O_4S$
19	2-Cl-6-Me	Me	60	97	YON	$C_{12}H_{13}ClN_4O_2S$
20	4-Cl-2,5-$(MeO)_2$	Me	65	216	YOPl	$C_{13}H_{15}ClN_4O_4S$
21	5-Cl-2,5-$(MeO)_2$	Me	65	179	LBN	$C_{13}H_{15}ClN_4O_4S$
22	3-Cl	Ph	60	159	ON	$C_{21}H_{15}ClN_4O_2S$
23	4-Cl	Ph	63	285	GPl	$C_{21}H_{15}ClN_4O_2S$
24	2-Me	Ph	58	146	YN	$C_{22}H_{18}N_4O_2S$
25	4-Me	Ph	60	267	PYN	$C_{22}H_{18}N_4O_2S$
26	2-NO_2	Ph	65	180	YPl	$C_{21}H_{15}N_5O_4S$
27	3-NO_2	Ph	65	165	PYPl	$C_{21}H_{15}N_5O_4S$
28	4-NO_2	Ph	63	164	YPl	$C_{21}H_{15}N_5O_4S$
29	3-MeO	Ph	60	270	YPl	$C_{22}H_{18}N_4O_3S$
30	4-EtO	Ph	65	184	LBPl	$C_{23}H_{20}N_4O_3S$
31	2,4-Me_2	Ph	63	153	OYN	$C_{23}H_{20}N_4O_2S$
32	2,5-Me_2	Ph	60	261	LOPl	$C_{23}H_{20}N_4O_2S$
33	2,6-Me_2	Ph	63	168	OPl	$C_{23}H_{20}N_4O_2S$
34	3,4-Me_2	Ph	65	270	BPl	$C_{23}H_{20}N_4O_2S$
35	2,5-$(MeO)_2$	Ph	65	266	LOPl	$C_{23}H_{20}N_4O_4S$
36	2,5-$(EtO)_2$	Ph	68	152	BPl	$C_{25}H_{24}N_4O_4S$
37	2,3-Cl_2	Ph	60	263	YPl	$C_{21}H_{14}Cl_2N_4O_2S$
38	2,4-Cl_2	Ph	60	273	LYPl	$C_{21}H_{14}Cl_2N_4O_2S$
39	2-Cl-6-Me	Ph	53	269	PYPl	$C_{22}H_{17}ClN_4O_2S$
40	4-Cl-2,5-$(MeO)_2$	Ph	55	171	DYN	$C_{23}H_{19}ClN_4O_4S$
41	5-Cl-2,4-$(MeO)_2$	Ph	58	239	DYN	$C_{23}H_{19}ClN_4O_4S$

[a] B, brown; D, dark; L, light; N, needles; O, orange; P, pale; Pl, plates; Y, yellow. [b] All compds were analyzed for N and S; compds: **1-4, 13-15, 19-23,** and **37-41** were analyzed for halogens.

4-arylazo-3,5-dimethyl-(2*H*)-1,2,6-thiadiazine 1,1-dioxides prepd in a similar way are listed in Table I.

4-Phenylazo-3,5-diphenyl-(2*H*)-1,2,6-thiadiazine 1,1-Dioxide. Sulfamide (0.48 g) when reacted with 1.64 g of 1,3-diphenyl-1,2,3-propanetrione-2-phenylhydrazone as in method A, gave pale yellow plates (55%), mp 268° (EtOH). *Anal.* ($C_{21}H_{16}N_4O_2S$) C, H, N, S. Properties of the other 4-arylazo-3,5-diphenyl-(2*H*)-1,2,6-thiadiazine 1,1-dioxides prepd are given in Table I.

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Potential Antitumor Agent Dicyclohexylammonium 2-{4-[*N*,*N*-Bis(2-chloroethyl)amino]phenoxy}-2-methylpropionate

Harold Z. Sommer* and George E. Wicks, Jr.

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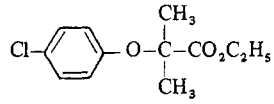
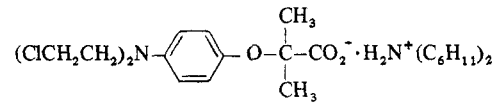
The antihyperlipidemic agent ethyl 2-(*p*-chlorophenoxy)-2-methylpropionate (1) (clofibrate)[1] has been applied as a drug to reduce serum lipids. After absorption from the gastrointestinal tract clofibrate undergoes rapid hydrolysis by serum enzymes to the free acid which is strongly bound to plasma proteins. Animal studies indicate that clofibrate remains almost exclusively in the blood. Distribution of the free acid is limited to the plasma and extracellular fluids. After administration of effective doses, no trace was found in muscle, fat, heart, spleen, cerebrospinal fluid, or bile. With larger doses transient amounts were detected in the liver.[1-4]



I

In man, absorption from the gastrointestinal tract is uniform. Serum levels are linearly proportional to dosage, from 3 to 24 hr after administration of effective doses. Furthermore, clofibrate is cleared from the plasma in an average half-life time of 12 hr.

It was surmised that a cytotoxic compound, selective to malignant cells, of similar pharmacological properties as described above, could serve as a potential chemotherapeutic agent against neoplastic diseases of blood. Thus, the N mustard II was synthesized which differs from I, mainly, in that Cl on the Ph ring is replaced by a bis(chloroethyl)amino group. The preparation of an amine salt of the free acid rather than the ester was decided upon in order to favor slow absorption from the gastrointestinal tract. These modifications in structure, it was anticipated, would not significantly alter the ability of the molecule to bind to plasma proteins. Hence, a distribution limited predominantly to blood and extracellular fluids might be expected.



Dicyclohexylammonium 2-{4-[*N*,*N*-bis(2-chloroethyl)-amino]phenoxy}-2-methylpropionate (II) was prepared in a 6-step procedure as outlined in Scheme I.

Scheme I

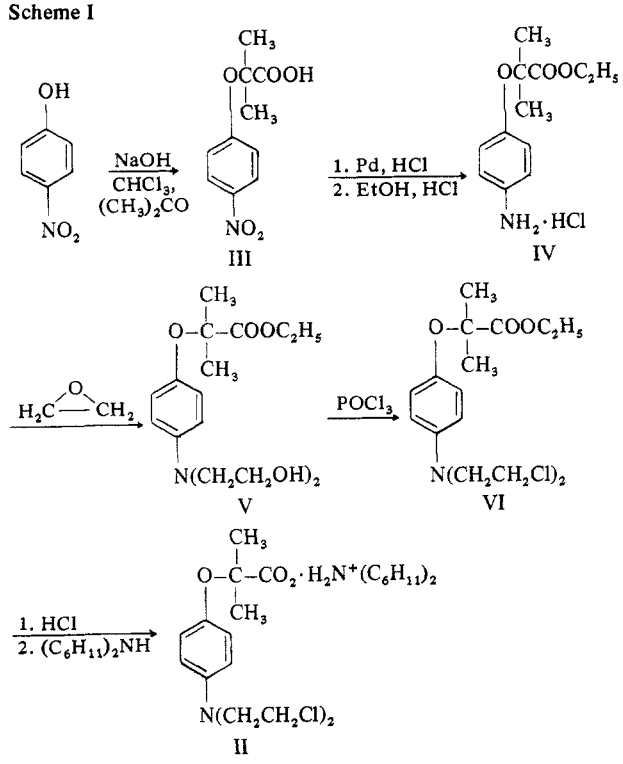


Table I. Antitumor Activity of Dicyclohexylammonium 2-{4-[*N*,*N*-Bis(2-chloroethyl)amino[phenoxy}-2-methylpropionate against Lymphoid Leukemia L-1210 in Mice

Dose,[a] mg/kg	Survivors	Animal wt diff[b] (*T* − *C*), g	Survival days Test	Survival days Control	*T*/*C*,[c] %
400	0/6	−0.4	0	9.4	
300	0/6	−0.4	0	9.6	
150	4/6	−4.3	7.5	9.6	
75	6/6	−3	13.7	9.6	142
50	6/6	−1.8	12.2	9.6	127
33	6/6	−1	10.8	9.6	112
22	6/6	−1.1	10.5	9.6	109
75[d]	6/6	−3.6	8.7	9.3	93
50[d]	6/6	−4.5	8.8	9.3	94
33[d]	6/6	−3.8	9.0	9.3	96
22[d]	6/6	−3.7	13.7	9.3	147

[a] Ip route. [b] Average wt change of test group minus control group. [c] Ratio of survival time of test to control animals. [d] Dose was repeated for 9 consecutive days.

The activity against L-1210 lymphoid leukemia is presented in Table I.

Experimental Section

2-(4-Nitrophenoxy)-2-methylpropionic Acid (III).[5] $CHCl_3$ (100 g, 0.83 mole) was gradually added to a mixt of *p*-nitrophenol