Notes

S-[(N,N'-Diarylamidino)methyl] Diethyldithiocarbamates and Related Amides as Potential Radioprotectants

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A series of symmetrically and unsymmetrically N,N'-diaryl-substituted amidinomethyl diethyldithiocarbamates and corresponding amides have been synthesized and tested for potential radioprotective activity. Antiradiation data for 10 amidines are presented. Half of the amidines showed low toxicity and radioprotective activity, based on both protective index (PI) and 30-day survival (>35%) after lethal irradiation (800-rad X-rays). All (N-arylcarbamoyl)methyl diethyldithiocarbamates investigated were nonprotective.

Recently, as a result of our search for radiation-protective agents we reported the synthesis of a series N- and S-substituted derivatives of α-mercaptoacetamidine.[1-8] It had been shown by many authors that when the thiol group in the basic compound ($HSCH_2C(=NH)NH_2$) was replaced by an isothiouronium,[9] a thiosulfate,[10-13] or a phosphorothioate[14] group, the protective activity against lethal irradiations equalled that of the parent, but some members were much less toxic.

On the other hand, it is well-known that the immunomodulator sodium diethyldithiocarbamate (DDC), which has been used in many patients, appears to have a good protective activity against total body irradiation.[15-17]

In this paper we report the synthesis of corresponding S-(diethyldithiocarbamates) of N,N'-diaryl-α-mercaptoacetamidines. The preliminary antiradiation test data are presented for these compounds.

Chemistry. The starting material for the synthesis was α-chloroacetyl chloride (1). Most of the precursors, α-chloroacetanilides 2, were prepared by a method previously reported by Bauer and Welsh[9] (Scheme I). Briefly, α-chloroacetyl chloride (1) was reacted with aromatic amines according to the Schotten-Bauman technique to generate 2. These amides were treated with PCl_5 and then with the corresponding aromatic amines to yield N,N'-diaryl chloroacetamidines 3. When these amidines were treated with sodium diethyldithiocarbamate, highly crystalline amidinium diethyldithiocarbamates 4 were obtained. The reactions between α-chloroacetanilides 2 and sodium diethyldithiocarbamate generate the corresponding anilidomethyl dithiocarbamates 5, which were synthesized for purposes of comparison.

Scheme I

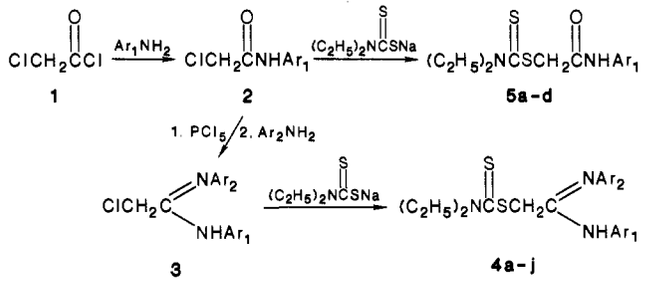

Table I. Radioprotective Activity[a] of S-[(N,N'-Diarylamidino)methyl] Diethyldithiocarbamates 4

no.	ca. LD_{50}, mg kg^{-1}	drug dose,[b] mg kg^{-1}	30-day survival, %	ca. PI[c]	MST,[d] days
4a	840	150	5	0	8.1
4b	720	125	10	6.3	9.6
4c	780	150	10	5.7	10.8
4d	800	150	35	7.2	9.1
4e	970	210	0	0	6.1
4f	970	250	40	5.4	9.8
4g	850	210	25	5.1	10.5
4h	1370	340	60	6.4	14.3
4i	1270	280	60	7.3	13.5
4j	1240	360	70	5.9	13.5
controls (120 mice)			5		6.5

[a] Antiradiation test in mice against a lethal dose of X-rays (800 rads). [b] Lowest dose that gives the highest survival rate. [c] The protective index (PI) approximated for the lowest effective dose to provide a common basis for comparison of test compounds: PI = [1 + (% survival/100)] × LD_{50} (mg kg^{-1})/dose (mg kg^{-1}); ref 14. [d] Mean survival time for mice that died over a 30-day period.

It was found that the α-chloroacetanilides 2 and chloroacetamidines 3 were satisfactory for use in the next step without purification.

Antiradiation Evaluation. In tests conducted in mice by a previously described procedure,[4] lower toxicity of diethyldithiocarbamate analogues of α-mercaptoacetamidines was obtained in comparison to the parent thiols, Bunte salts, and phosphorothioates[9,14] (Table I).

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Table II. *S*-[(*N*,*N*′-Diarylamidino)methyl] Diethyldithiocarbamates **4** [$Ar_1NH(Ar_2N)CCH_2SC(S)N(C_2H_5)_2$]

no.	Ar_1	Ar_2	recrystn solvent	mp, °C dec	yield, %	formula	anal.
4a	C_6H_5	C_6H_5	cyclohexane	116–117	70	$C_{19}H_{23}N_3S_2$	C, H, N, S
4b	C_6H_5	*p*-$CH_3C_6H_4$	*n*-heptane	83–86	36	$C_{20}H_{25}N_3S_2$	C, H, N, S
4c	C_6H_5	*p*-$CH_3OC_6H_4$	1-butanol	119–120	48	$C_{20}H_{25}N_3OS_2$	C, H, N, S
4d	C_6H_5	*p*-$C_2H_5OC_6H_4$	methanol	79–81	52	$C_{21}H_{27}N_3OS_2$	N, S
4e	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	benzene	150–152	65	$C_{21}H_{27}N_3S_2$	C, H, N, S[a]
4f	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	1-butanol	96–97	58	$C_{21}H_{27}N_3OS_2$	C, H, N, S
4g	*p*-$CH_3C_6H_4$	*p*-$C_2H_5OC_6H_4$	1-butanol	94–95	40	$C_{22}H_{29}N_3OS_2$	N, S
4h	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	1-butanol	117–119	52	$C_{21}H_{27}N_3O_2S_2$	C, H, N, S
4i	*p*-$CH_3OC_6H_4$	*p*-$C_2H_5OC_6H_4$	*n*-heptane	98–99	45	$C_{22}H_{29}N_3O_2S_2$	C, H, N, S
4j	*p*-$C_2H_5OC_6H_4$	*p*-$C_2H_5OC_6H_4$	cyclohexane	108–109	60	$C_{23}H_{31}N_3O_2S_2$	C, H, N, S[b]

[a] S: calcd, 16.62; found, 17.24. [b] S: calcd, 14.38; found, 13.90.

Table III. *S*-[(*N*-Arylcarbamoyl)methyl] Diethyldithiocarbamates **5** [$ArNHC(O)CH_2SC(S)N(C_2H_5)_2$]

no.	Ar	recrystn solvent	mp, °C dec	yield, %	formula	anal.
5a	C_6H_5	cyclohexane	94–96	68	$C_{13}H_{18}N_2OS_2$	C, H, N, S
5b	*p*-$CH_3C_6H_4$	cyclohexane	95–96	65	$C_{14}H_{20}N_2OS_2$	C, H, N, S
5c	*p*-$CH_3OC_6H_4$	cyclohexane	92–93	72	$C_{14}H_{20}N_2O_2S_2$	N, S
5d	*p*-$C_2H_5OC_6H_4$	benzene/petroleum ether (2:1)	89–92	79	$C_{15}H_{22}N_2O_2S_2$	C, H, N, S[a]

[a] S: calcd, 19.63; found, 19.20.

Five of the ten *N*,*N*′-disubstituted amidinomethyl diethyldithiocarbamates **4a–j** showed radioprotective activity. Symmetrically substituted *p*-methoxyphenyl and *p*-ethoxyphenyl amidines **4h** and **4j**, respectively, as well as its unsymmetrical analogue **4i** afforded good radioprotection, i.e., >40% 30-day survival. Fair protection (35–40% survival) was observed with compounds **4d** and **4f** and slight protection (10–25% survival) with **4b**, **4c**, and **4g** was observed. The other two members of the **4** series and all members of the **5** series were nonprotective.

The antiradiation effectiveness of diethyldithiocarbamate derivatives of α-mercaptoacetamidines included in this study is noteworthy because (1) the diethyldithiocarbamate group confers decreased toxicity, (2) minimum effective doses were well below toxic levels, and (3) several compounds were good radioprotectors, on the basis of both 30-day survival and protective index (PI).

Further evaluation of these compounds is indicated.

Experimental Section

Biological Methods. White mice, strain "H" of both sexes, approximately 6 weeks old and weighing 23–25 g, were randomly assigned to treatment groups (20 mice per group). Toxicity estimations were based on a 5-day observation period following intraperitoneal injections. The LD_{50} values were calculated by the Litchfield–Wilcoxon method.

The drugs were given as homogenized suspensions containing 0.3% methylcellulose (3000 cP) and 0.4% Tween-80. Half-milliliter volumes were injected.

The mice were irradiated with 800-rad (206.4 mC kg^{-1}) X-rays with a Müller RT-250 unit with radiation factors of 220 kV, 15–16 mA, 0.35 mm Cu, F = 50 cm, dose rate in air 96 rads min^{-1} (4.13×10^{-6} A kg^{-1}).

Six mice were exposed per run in a perforated tissue-equivalent plastic cage, which rotated continuously during exposure; three mice were used for protection study and an equal number for control.

The mice were housed jointly 10 to a cage and given food and water ad libitum.

Mortality was tabulated for a 30-day period. Under our conditions, 800 rads of X-rays, 95% of the 120 control animals died between the 9th and 26th days following exposure.

Chemistry. Melting points were determined with a Koffler Heizbank. IR spectra were determined in Nujol for all amidines with a Perkin-Elmer Model 521 spectrophotometer. Microanalyses for C, H, S were performed by Dr. G. Angelov, Bulgarian Academedy of Science, Sofia, and those for nitrogen by us using the Kjeldahl method. Products were dried in vacuo (oil pump) at room temperature over P_2O_5.

Chloroacetyl chloride and sodium diethyldithiocarbamate were commercially obtained. The chloroacetanilides **2** and chloroacetamidines **3** were prepared by a published general procedure.[9] It was not imperative to obtain pure amides for the amidine synthesis.

***S*-[(*N*,*N*′-Diarylamidino)methyl] Diethyldithiocarbamates 4a–j.** Ten amidines were prepared with variation of the N and N′ substituents. An example is the synthesis of *S*-[(*N*,*N*′-diphenylamidino)methyl] diethyldithiocarbamate (**4a**).

N,*N*′-Diphenylchloroacetamidine[9] (4.89 g, 20 mmol) was dissolved in 50 mL of absolute ethanol. Powdered sodium diethyldithiocarbamate (3.12 g, 20 mmol) was added to the stirred solution during a 10-min period. The mixture was stirred at room temperature for 30 min and kept in a refrigerator overnight. The product was filtered in vacuo, washed with cold water, and recrystallized twice from cyclohexane in 70% yield; mp 116–117 °C dec; IR 1700 (ν(C=N)), 3330 (ν(NH)), 1355, 1220, 980, 635 cm^{-1}. Anal. ($C_{19}H_{23}N_3S_2$) C, H, N, S.

The amidines prepared by the same procedure are summarized in Table II.

***S*-[(*N*-Arylcarbamoyl)methyl] Diethyldithiocarbamates 5a–d.** An example is the synthesis of *S*-[(*N*-phenylcarbamoyl)-methyl] diethyldithiocarbamate (**5a**).

Powdered sodium diethyldithiocarbamate (3.12 g, 20 mmol) was added during 10 min to a stirred solution of α-chloroacetanilide[9] (3.32 g, 20 mmol) in absolute ethanol (30 mL). The mixture was stirred at room temperature for 30 min and was diluted with H_2O. Cooling caused separation of a solid, which was filtered off and washed with cold water. The dried yellowish product was recrystallized twice from cyclohexane in 68% yield; mp 94–95 °C dec. Anal. ($C_{13}H_{18}N_2OS_2$) C, H, N, S.

The amides prepared by the same procedure are listed in Table III.

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Registry No. **1**, 79-04-9; **2a**, 587-65-5; **2e**, 16634-82-5; **2h**, 22303-36-2; **2j**, 2153-08-4; **3a**, 40403-43-8; **3b**, 105858-96-6; **3c**, 105858-97-7; **3d**, 105858-98-8; **3e**, 105858-99-9; **3f**, 105859-00-5; **3g**, 105859-01-6; **3h**, 93018-08-7; **3i**, 105859-02-7; **3j**, 40403-45-0; **4a**, 105858-86-4; **4b**, 105858-87-5; **4c**, 105858-88-6; **4d**, 105858-89-7; **4e**, 105858-90-0; **4f**, 105858-91-1; **4g**, 105858-92-2; **4h**, 105858-93-3; **4i**, 105858-94-4; **4j**, 105858-95-5; **5a**, 51661-15-5; **5b**, 105859-03-8; **5c**, 105859-04-9; **5d**, 105859-05-0; $C_6H_5NH_2$, 62-53-3; *p*-$CH_3C_6H_4NH_2$, 106-49-0; *p*-$MeOC_6H_4NH_2$, 104-94-9; *p*-$EtOC_6H_4NH_2$, 156-43-4; $(Et)_2NCS_2H{\cdot}Na$, 148-18-5.