

POTENTIAL ANTICANCER COMPOUNDS. II.¹ SYNTHESIS OF SOME NITROSIMINODIACETIC ACID HYDRAZIDES

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The activity of bis (2-chloroethyl) sulfide and of several N-analogs (nitrogen mustards) against certain types of cancer is well established. However, besides a more or less pronounced toxicity, all of these compounds suffer from several other unfavorable physiological properties. Therefore, the synthesis of compounds

was undertaken which have the structural element $\begin{array}{c} -N-CH_2- \\ | \\ CH_2- \end{array}$ of the nitrogen

mustards but which have instead of the CH_2Cl -unit the groups $-C(O)-NHN=R$ (R =arylidene) or $-C(O)-NHNRR'$ ($R=H$, $R'=C_6H_5$; $R=R'=CH_3$). Since certain N-oxides (Ishidate, 1954) of the nitrogen mustards have been found to possess valuable anticancer properties, the group $N-N=O$ resembling somewhat the $\equiv N \rightarrow O$ unit was incorporated into the compounds. It was hoped that these compounds would retain anticancer activity but exhibit less unfavorable side-effects than nitrogen mustard itself or the other compounds of this class. The $-C(O)-NHN=$ group was chosen to provide the compounds with some hydrophilic solubility. Preliminary tests against three types of experimental tumors in mice, Adenocarcinoma (Ca-755), Sarcoma (Sa-180), and Leukemia (L-1210), however, reveal so far no activity against these tumor systems.

The compounds were prepared by established methods. Diethyl iminodiacetate was nitrosated and the diethyl nitrosiminodiacetate formed was converted into the corresponding hydrazides by being refluxed with an excess of the corresponding hydrazine in the presence of a few drops of glacial acetic acid as a catalyst. The nitrosiminodiacetic acid dihydrazide was converted into the hydrazones by the method of Zimmer and George (1956). The hydrazones were rather insoluble in most of the common solvents. They could best be recrystallized from aqueous N, N-dimethylformamide.

Attempts to prepare the corresponding hydrazides of 3,3'-nitrosiminodipropionic acid met with failure. The corresponding diethyl ester did not react with hydrazine or with 1,1-dimethylhydrazine. The failure of the latter to undergo the expected reaction is in agreement with similar results published recently by Hinman and Fulton (1958). Even after 48 hours refluxing of the mixtures with hydrazine or 1,1-dimethylhydrazine respectively, and diethyl 3,3'-nitrosiminodipropionate none of the corresponding hydrazides could be obtained. Also, the heating of these mixtures for 48 hours in pressure bottles did not yield the desired hydrazides.

EXPERIMENTAL METHODS AND RESULTS

Melting points are uncorrected. Microanalyses are by A. Bernhardt, Microanalytisches Laboratorium im Max-Planck-Institut, Mulheim/Ruhr, Germany.

Materials. Generally, Eastman white label products were employed without further purification.

Nitrosiminodiacetic acid, bis (p-methoxybenzylidene-hydrazide). A solution of 2.5 g of nitrosiminodiacetic acid, dihydrazide in aqueous ethanol was added to a solution of 4 g of anisaldehyde in ethanol. After the mixture had stood for a

¹First paper in this series: H. Zimmer and E. Shaheen, Potential anticancer compounds. I. Synthesis of thiodiuretic acid hydrazides and homologs. J. Organic Chem. **24**, 1140-1144, (1959).

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brief period, the hydrazide precipitated. The crystals were recrystallized from aqueous N,N-dimethylformamide, yield 5 g (89%), mp (unc) 252–253° C.

Anal. Calcd. for $C_{20}H_{22}N_6O_5$: C, 56.33; H, 5.20; N, 19.71.

Found: C, 56.29; H, 5.21; N, 19.65.

Analogously, the following hydrazides were prepared:

Nitrosiminodiacetic acid bis (o-hydroxybenzylidene-hydrazide). From salicylaldehyde, 76% yield, mp (unc) 232–233° C.

Anal. Calcd. for $C_{18}H_{18}N_6O_5$: C, 54.27; H, 4.55; N, 21.10.

Found: C, 54.17; H, 4.44; N, 20.95.

Nitrosiminodiacetic acid, bis (p-chlorobenzylidene-hydrazide). From *p*-chlorobenzaldehyde, 85% yield, mp (unc) 252–253° C.

Anal. Calcd. for $C_{18}H_{16}Cl_2N_6O_3$: C, 49.67; H, 3.71; N, 19.32.

Found: C, 49.40; H, 3.64; N, 19.03.

Nitrosiminodiacetic acid, bis (cinnamylidenehydrazide). From cinnamaldehyde, 82% yield, mp (unc) 231–232° C.

Anal. Calcd. for $C_{22}H_{22}N_6O_3$: C, 63.14; H, 5.26; N, 20.09.

Found: C, 63.37; H, 5.53; N, 20.30.

Nitrosiminodiacetic acid, bis (m-nitrobenzylidenehydrazide). From *m*-nitrobenzaldehyde, 67% yield, mp (unc) 246–247° C.

Anal. Calcd. for $C_{18}H_{16}N_8O_7$: C, 47.37; H, 3.53; N, 24.56.

Found: C, 46.80; H, 3.53; N, 24.50.

Nitrosiminodiacetic acid, bis (2,2-dimethylhydrazide). A mixture of 20 g diethyl nitrosiminodiacetate and 80 ml 1,1-dimethylhydrazine and a few drops glacial acetic acid was refluxed for 8 hours. Excess dimethylhydrazine was distilled off; on cooling the hydrazide crystallized, white crystals (17.5 g 78%). The analytical sample was recrystallized from dioxane or ethyl acetate, mp (unc) 182–183° C.

Anal. Calcd. for $C_8H_{18}N_6O_3$: C, 39.01; H, 7.37.

Found: C, 38.83; H, 7.40.

Nitrosiminodiacetic acid, bis (2-phenylhydracide). Analogously from phenylhydrazine, 75% yield, mp (unc) 234–235° C. The analytical sample was recrystallized from N,N-dimethylformamide—water.

Anal. Calcd. for $C_{16}H_{18}N_6O_3$: C, 56.13; H, 5.30.

Found: C, 56.14; H, 5.26.

Diethyl 3, 3'-nitrosiminodipropionate. This substance was obtained in good yield by nitrosation of diethyl 3, 3'-iminodipropionate, yielding a liquid bp 129–130° at 0.1 to 1.0 mm Hg.

Anal. Calcd. for $C_{10}H_{18}N_2O_5$: C, 48.77; H, 7.37.

Found: C, 48.80; H, 7.49.

This compound did not react with hydrazine or with 1,1-dimethylhydrazine under the mentioned conditions.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the financial help by the National Institutes of Health through Grant CY-2904. The test results were obtained by the Cancer Chemotherapy National Service Center, Bethesda 14, Maryland.

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