absorption[9] at 1340 cm^{-1} to 39. *Anal.* ($C_7H_{13}NOS$) C, H, N. The oily mixt eventually crystd with apparently complete conversion to 39, mp ~28–31°.

2-(Tetrahydrothiopyran-4-ylamino)ethanol (40). A soln of 39 (34.5 g, 0.217 mole) in MeOH (150 ml) at 0° was treated with $NaBH_4$ (8.20 g, 0.217 mole) and worked up as in the prepn of 26 (R = Me). Evapn of the Et_2O ext up to 100° (H_2O aspirator) left a residue of cryst 40; yield 32.1 g (92%), mp 53–54°. *Anal.* ($C_7H_{15}NOS$) C, H, N.

1-Thionia-4-azabicyclo[3.2.2]nonane Bromide Hydrobromide (42). A soln of 40 (26.5 g, 161 mmoles) and 48% HBr (1 l.) was distd slowly over a period of 18 hr until 925 ml of distillate was collected. The residue was refrigd, and the cryst 42 was collected, washed with EtOH, and dried *in vacuo* (P_2O_5); wt 14.2 g, mp 254° dec. The above-described distn was repeated on the concd filtrate dissolved in 48% HBr (500 ml) to give addl 42 (11.0 g), mp 254° dec; total yield 51%. *Anal.* ($C_7H_{14}BrNS \cdot HBr$) C, H, N, S.

Br^- Determination. Analysis of 42 and *N*-(2-Bromoethyl)amine Hydrobromides. A soln of $AgNO_3$ (340 mg, 2.00 mmoles) in 2 *N* HNO_3 (5 ml) was added to a soln of 42 (305 mg, 1.00 mmoles) in 2 *N* HNO_3 (10 ml). The mixt was swirled for 1 min. The AgBr was collected by filtration in the dark, washed with 2 *N* HNO_3 and then EtOH, and dried *in vacuo* (P_2O_5); yield 379 mg (2.02 Br^- per mole).

The utility of this detn for distinguishing ionic from covalent Br was demonstrated by reactions of 6g (n = 2, X = S) with 2 $AgNO_3$ to give 1.01 AgBr, 27 (R = Me) with 2 $AgNO_3$ to give 1.08 AgBr, and *N,N'*-bis(2-bromoethyl)ethylenediamine dihydrobromide[8a] with $AgNO_3$ to give 2.03 AgBr.

***S*-2-(Tetrahydro-2*H*-thiopyran-4-ylamino)ethyl Sodium Hydrogen Phosphorothioate (44).** A stirred suspension of Na_3PSO_3 (2.36 g, 13.1 mmoles) in H_2O (26 ml) at 10° was treated in small portions with 41 (4.00 g, 13.1 mmoles), stirred 30 min, treated dropwise with *N,N*-dimethylacetamide (DMAC) (13 ml) at 10°, stirred at 25° for 2 hr, and filtered. Dropwise addn of DMAC (39 ml) to the filtrate at 0° gave a cryst product, which was washed successively with cold DMAC–H_2O (2:1), DMAC, and Et_2O, and dried *in vacuo* (P_2O_5); yield 3.33 g (91%), mp indef. *Anal.* ($C_7H_{15}NNaO_3PS_2$) C, H, N, P, S.

Acknowledgments. The authors are indebted to Dr. D. P. Jacobus, Dr. T. R. Sweeney, and Miss Marie M. Grenan for antiradiation data and to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute for spectral data.

References

(1) R. Adams and J. B. Segur, *J. Amer. Chem. Soc.*, 45, 785 (1923).
(2) A. F. McKay and R. O. Braun, *J. Org. Chem.*, 16, 1829 (1951).
(3) A. Boncherie, G. Carraz, and J. Bonnin, *Bull. Soc. Chim. Fr.*, 231 (1958).
(4) J. R. Piper, R. D. Elliott, C. R. Stringfellow, Jr., and T. P. Johnston, *Chem. Ind. (London)*, 2010 (1966).
(5) L. Wei and E. A. Steck, *Can. J. Chem.*, 42, 2623 (1964).
(6) J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *J. Med. Chem.*, 14, 1212 (1971).
(7) N. Bortnick, L. S. Luskin, M. D. Hurwitz, W. E. Craig, J. L. Exner, and J. Mirza, *J. Amer. Chem. Soc.*, 70, 4045 (1948).
(8) (a) J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *J. Med. Chem.*, 9, 911 (1966); (b) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, 33, 636 (1968).
(9) R. M. Srivastova, K. Weissman, and L. B. Clapp, *J. Heterocycl. Chem.*, 4, 114 (1967).
(10) F. Cortese, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 91.
(11) D. L. Klayman, M. M. Grenan, and D. P. Jacobus, *J. Med. Chem.*, 12, 510 (1969).
(12) R. D. Westland, J. L. Holmes, M. L. Mouk, D. D. Marsh, R. A. Cooley, Jr., and J. R. Dice, *ibid.*, 11, 1190 (1968).
(13) J. L. Pinkus, G. Pinkus, and T. Cohen, *J. Org. Chem.*, 27, 4356 (1962).
(14) T. P. Johnston, G. S. McCaleb, P. S. Opliger, W. R. Laster, and J. A. Montgomery, *J. Med. Chem.*, 14, 600 (1971).
(15) C. Barkenbus and J. A. Wuellner, *J. Amer. Chem. Soc.*, 77, 3866 (1955).
(16) V. A. Zakoreskii and N. V. Dudykina, *J. Gen. Chem. USSR*, 32, 3856 (1962).
(17) H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, 92, 1629 (1959).

Optically Active Dithiothreitol. Toxicity and Radiation-Protective Activity

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The optical isomers of dithiothreitol (DTT) (Cleland's reagent) and their oxidized forms were prepared from L_g-(+)- and D_g-(−)-tartaric acid by an improved procedure, and their toxicity and radiation-protective activity were investigated in mice. The LD_{50} (mg/kg) of D_g-DTT is 255 compared to 179 and 169 for L_g-DTT and *rac*-DTT, respectively. The radiation-protective activity of D_g-DTT (60, 120, 150, and 200 mg/kg) was determined in mice exposed to X-radiation (600, 625, 700, and 750 R). Administration of 200 mg/kg of D_g-DTT ip increased survival at the end of 30 days by 50% in mice exposed to 650 R. Comparable studies on L_g-DTT show that this enantiomer affords no protection. The oxidized forms of D_g- and L_g-DTT were less toxic (LD_{50} = 435 and 410 mg/kg, respectively) and exhibited no protective activity (200 and 300 mg/kg against 625, 650, and 750 R). This work indicates that attention should be given to molecular asymmetry in designing more potent, selective, and less toxic radiation-protective agents, and in investigating their mechanisms of action.

Research on the development of radiation-protective compounds and the elucidation of their mechanisms of action has been reviewed recently.[1-3] Little work has been reported in which the importance of molecular asymmetry in a protective agent was evaluated. In one study, Doherty and Shapira[4] reported that D_s-2-aminobutylisothiourea dihydrobromide is twice as protective against X-radiation in the mouse as the L_s enantiomer. Foye[2] points out that more information on the comparative activity of the enantiomers of optically active radiation-protective agents would allow one to assess the importance of stereochemistry in radiation protection.

Falconi, *et al.*,[5-7] have reported that *rac*-dithiothreitol

†Work supported by grants from the National Institutes of Health, the Scully Foundation, and Smith, Kline, and French Laboratories.

‡National Science Foundation Graduate Trainee (Summer, 1969), and Predoctoral Fellow (1969–1971), National Institutes of Health Graduate Fellowship GM43317, National Institute of General Medical Sciences.

§Biological testing was supported by a contract from the Medical Research and Development Command, U. S. Army.

(*rac*-DTT) affords protection in mice against X-radiation. *rac*-DTT seemed most interesting not for its radiation-protective activity *per se*, which is moderate, but more because it was reported[7] to be effective in reducing mortality when given to mice as much as 24 hr *after* their exposure to X-radiation, and because its oxidized form, *rac-trans*-4,5-dihydroxy-1,2-dithiane, was also found to possess similar protective and "recovery-enhancing" activity. These properties, of potential interest from a mechanistic point of view, prompted us to consider the possibility of using optically active dithiothreitol as a system with which to explore further the effect of stereochemistry in radiation protection. Having synthesized[8] (-)-1,4-dithio-L_g-threitol (L_g-DTT) from L_g-tartaric acid (natural tartaric acid of known absolute configuration[9]), we proceeded to prepare its enantiomer, D_g-DTT (dextrorotatory), from D_g-tartaric acid by a similar procedure and to determine the radiation-protective activity of each of these two optical isomers, studying their oxidized (dithiane) analogs as well. In addition, we sought to determine the toxicities of optically active and *rac*-dithiothreitol (available commercially as Cleland's Reagent). The latter enjoys popularity as a versatile and effective reagent for the reduction of disulfide bonds and the protection of thiol groups.# We report here the results of our studies.

Experimental Section

Chemistry. The synthesis of (-)-1,4-dithio-L_g-threitol has been published.[8] The series of compds leading to and including (+)-1,4-dithio-D_g-threitol is derived from D_g-(-)-tartaric acid (unnatural enantiomer). The intermediates in this series were prepared by procedures identical, with one exception (*vide infra*), with those of Carmack and Kelley.[8] All members of this series exhibit chemical and spectral properties identical with those of the members of the series leading to and including (-)-1,4-dithio-L_g-threitol.[8] In all cases, the optical rotatory properties of the former series of compds are identical in magnitude but opposite in sign to those of the latter series. An improved procedure for the prepn of the initial deriv of tartaric acid is presented here. The comparison between the data presented below on the enantiomers of this derivative is typical of the comparison observed between enantiomeric intermediates throughout the series. Optical rotations were measured with a Rudolph polarimeter, Model 80, in a 2-dm cell.

Dimethyl 2,3-*O*-Isopropylidene-L_g-tartrate. A mixt of 50 g (0.344 mole) of L_g-tartaric acid (Matheson), 62 ml of dry MeOH, 0.3 g of TsOH, and 80 g (0.770 mole) of 2,2-dimethoxypropane (Eastman) was warmed gently with stirring on a steam bath to 30° until it became homogeneous. The soln was stirred at room temp for 24 hr. Volatile components were removed *in vacuo*. To the resulting oil was added 100 ml of dry PhH and 60 g (0.577 mole) of 2,2-dimethoxypropane. The soln was refluxed while the PhH–MeOH azeotrope was slowly removed at the head of a vacuum-jacketed, helix-packed distn column. In a typical run, 86.5 g of azeotrope (bp 58.0–58.5°) was collected over a 12-hr period. When the vapor temp dropped below 40°,[8] heating was stopped, 1.0 g of anhyd K_2CO_3 was added to neutralize the catalyst, volatile components were removed, and the crude product was distd, yielding 65.4 g (90%) of a light yellow liquid, bp 90–98° (0.01 mm), d^{26}_4 1.1909, $[\alpha]^{28}D$ −50.1° (neat liquid).

Dimethyl 2,3-*O*-Isopropylidene-D_g-tartrate. The above procedure using 50 g (0.344 mole) of D_g-tartaric acid (unnatural) (Aldrich) yielded 64.1 g (88%) of the desired product, bp 90–98° (0.01 mm), $[\alpha]^{28}D$ +50.2° (neat liquid).

Toxicology. Acute Toxicity. Adult male, Carworth Farms (CF_1) mice (8 weeks old) were used for these experiments. The initial body weight ranged from 20 to 26 g. The mice were housed in an air-conditioned room (23.9–26.7°) and were fed Rockland mouse pellets and H_2O *ad libitum*. The controls and treated mice for each experiment were selected from a single shipment so that their age and physical condn would be comparable. The compds used in these studies were dissolved in H_2O immediately before use.

#For a bibliography of uses, with references through 1970, *cf.* ref 10.

Table I. Acute Toxicities in Mice

Compound	No. of mice	LD_{50} ± SE, mg/kg
rac-DTT	70	169.0 ± 2.7
L_g-DTT	36	179.0 ± 4.2
D_g-DTT	54	254.9 ± 8.5
Oxidized L_g-DTT	24	410.0 ± 20.2
Oxidized D_g-DTT	20	435.0 ± 19.4

Table II. Radiation-Protective Activity of D_g-DTT in Mice

Dose of D_g-DTT, mg/kg	Time of D_g-DTT admin before X-ray, min	Dose of X-ray, R	Mortality	% mortality
		500	4/10	40
		600	5/10	50
		625	9/10	90
		650	10/10	100
		700	10/10	100
		750	10/10	100
60	10	625	9/10	90
120	10	625	9/10	90
150	10	625	6/10	60
150	10	650	7/10	70
200	10	625	4/10	40
200	10	600	2/10	20
200	10	650	5/10	50
200	10	700	6/10	60
200	10	750	6/10	60

The concn of chemical agent in soln was adjusted so that mice always received vols equiv to 1% of their body wt ip.

Various doses of the compds listed in Table I were administered ip to groups of 4–5 mice. The LD_{50} values were obtd by a log-probit analysis of the resulting mortality data using an IBM 7094 computer. *rac*-DTT was obtd commercially (Nutritional Biochemicals).

Radiation Protection. X-Radiation was administered using a General Electric Maximar III unit operated at 250 KVP and 15 mA. Added filtration consisted of 0.25 mm of Cu and 1.0 mm of Al. The focal skin distance was 56 cm, and the dose rate was 66.6 R/min. The dose rate was checked before each series of exposures using a 250-R Victoreen ionization chamber that has been compared with a Bureau of Standards calibrated cobalt-60 source. Mice were housed 10 to a cage after radiation exposure. Radiation-protective activity was based on a 30-day survival period.

Results and Discussion

Chemistry. The trans-ketalization of tartaric acid ester was improved by using benzene to remove, by azeotropic distillation, the MeOH formed in the reaction. The use of cyclohexane[8] to remove MeOH is less satisfactory because cyclohexane is immiscible with the reactants. This improved procedure has been applied to the syntheses** of diethyl 2,3-*O*-ethylidene-L_g-tartrate and diethyl 2,3-*O*-benzylidene-L_g-tartrate, starting in both cases with diethyl L_g-tartrate[8] and using acetal and PhCHO, respectively.

Acute Toxicity. The results of acute toxicity studies are given in Table I. The oxidized forms of the optical isomers of dithiothreitol (4,5-dihydroxy-1,2-dithianes) exhibit the least toxicity of the 5 compounds. It is of interest that there is a significant difference between the toxicities of L_g-DTT and D_g-DTT, respectively. The toxicity of the commercially available *rac*-DTT most nearly resembles that of its more toxic enantiomeric component, L_g-DTT. When toxic doses of either L_g-DTT or D_g-DTT were administered, the resulting symptoms were the same. These consisted of hyperexcitability progressing to convulsions when lethal doses were administered. Symptoms appeared within 10 min after administration of toxic doses of the compounds,

**M. Carmack and S. D. Harrison, Jr., unpublished work, Indiana University, Bloomington, Ind., 1970.

Table III. Radiation-Protective Activity of L_g-DTT in Mice

Dose of L_g-DTT, mg/kg	Time of L_g-DTT admin before X-ray, min	Dose of X-ray, R	Mortality	% mortality
120	10	625	9/10	90
150	10	625	9/10	90
150	10	650	10/10	100
150	10	700	10/10	100
150	10	750	10/10	100

and death occurred within 1 hr after lethal doses.

Radiation Protection. Tables II, III, and IV summarize the radiation-protective activity of D_g-DTT, L_g-DTT, and the dihydroxydithianes, respectively. Data on control mice are included in Table II. It is known, however, from previous determinations[11] under the same conditions in a large number of mice, that the LD_{50} is 542 ± 18 R.

D_g-DTT (Table II) was found to protect mice against an otherwise lethal dose of X-radiation. Maximal protection was achieved by administration of doses of 200 mg/kg. Significant protection could be obtained with a dose of 150 mg/kg against 625- or 650-R X-radiation seems to indicate the administration of 200 mg/kg. The data in Table III indicate that L_g-DTT provides no protection against any of the dose levels of radiation administered when compared with controls (Table II). Comparison of the radiation-protective activity of L_g-DTT and D_g-DTT at a dose of 150 mg/kg against 625 or 650 R X-radiation seems to indicate that the protective activity observed[7] for *rac*-DTT is due primarily to the D_g enantiomer.

Proof that the radiation-protective activity of *rac*-DTT is accounted for by the action of only 1 of the enantiomers present might be obtained directly. Falconi, *et al.*,[7] studied *rac*-DTT at a dose of 120 mg/kg. Half that dose should provide the protection attributable to one enantiomer. By administration of D_g-DTT in a dose of 60 mg/kg with exposure to 625 R (Table II), we hoped to compare our results with those of Falconi and coworkers. This low dose, however, falls outside the dose range of protective activity (using mortality as the endpoint) of D_g-DTT. Yet we have shown that by using pure D_g-DTT, one removes the toxicity attributable to L_g-DTT and can thus administer higher doses of D_g-DTT than of *rac*-DTT. This capability results in protective activity twice that obtained[7] with *rac*-DTT against 625-R X-radiation. Further, against 750 R one can still achieve protection with D_g-DTT equal to the best obtained with *rac*-DTT against 625 R.

Falconi, *et al.*,[7] reported the oxidized form of *rac*-DTT to be more protective against 625 R of X-radiation than *rac*-DTT itself when the former was given in larger doses. We investigated the radiation-protective activity of both oxidized L_g-DTT and oxidized D_g-DTT against 625–750 R of X-radiation. The results are presented in Table IV. We observed no protection by either oxidized enantiomer. Our irradiation conditions were admittedly harsh in order to probe the limits of the protection obtainable from the oxidized forms of DTT and to eliminate the inconclusive results frequently obtained in radiation protection experiments at lower radiation doses with small numbers of animals.

As already mentioned, the most interesting data presented by Falconi and coworkers concern the ability of both oxidized and reduced *rac*-DTT to enhance the recovery†† of irradiated mice when the compounds are administered *after* irradiation.[7] This recovery-enhancing ability of a compound is uncommon, and, as noted,†† is not within the scope of the accepted definition of a chemical radiation protector. A limited number of data on the effects of D_g-DTT and both enantiomeric dithianes administered *after* radiation are shown in Table V. It is clear that at radiation levels of 700 R or greater no significant recovery-enhancement effects were observed. It would be interesting and desirable to investigate the possible recovery-enhancing effects of these and related compounds in more extended experiments.

To indicate the relative effectiveness of D_g-DTT as a radiation-protective agent, its activity was compared with that of mercaptoethylamine (MEA). An attempt was also made to ascertain whether MEA and D_g-DTT have additive protective effects. The results of these measurements are presented in Table VI. Comparison of the protective activity of MEA with the results for D_g-DTT (Table II) show that D_g-DTT is approximately equivalent in activity to MEA on a molar equivalent basis, or two-thirds as active on a weight basis. When attempts were made to combine MEA and D_g-DTT, it was found that the toxicity is additive. It was necessary to reduce the dose of MEA to 150 mg/kg plus 85 mg/kg of D_g-DTT. The protective activity of this combination is greater than when MEA is given alone at 150 mg/kg, confirming the ability of D_g-DTT to protect mice against lethal levels of X-radiation.

The importance of molecular asymmetry at the chemical foundation of many biological effects is well known.[13] Our results provide further[4] evidence for the importance of stereochemistry as a variable affecting chemical radiation

Table IV. Radiation-Protective Activity of Oxidized Forms of DTT in Mice

Compound	Dose of compound, mg/kg	Time of admin before X-ray, min	Dose of X-ray, R	Mortality	% mortality
Oxidized D_g-DTT	200	15	750	10/10	100
	300	15	625	10/10	100
	300	15	650	10/10	100
Oxidized L_g-DTT	150	15	750	10/10	100
	200	15	750	10/10	100
	300	15	625	9/10	90
	300	15	650	10/10	100

††Chemical protection is usually taken to mean a reduction in the detrimental effects of radiation by a compound administered *prior to* exposure.[2,12] The term "restoration" has been used[12] to refer to the alleviation of radiation lesions by compounds given *after* radiation exposure. With respect to mortality as an endpoint, Falconi, *et al.*,[7] used the term "recovery" to describe an increase in survival rate of mice exposed to a lethal level of radiation. To be consistent with the terminology used by Falconi, *et al.*, we shall use the term "recovery-enhancing" to describe that property of a compound whereby, when the compound is administered subsequent to radiation exposure, survival rate is increased.

Table V. Effects of D_g-DTT and Enantiomeric Dithianes Administered *after* Irradiation

Compound	Dose of compound, mg/kg	Time of admin after X-ray, min	Dose of X-ray, R	Mortality	% mortality
D_g-DTT	200	10	600	8/10	80
	200	10	625	7/10	70
	200	10	700	10/10	100
	200	10	750	10/10	100
Oxidized L_g-DTT	300	10	625	8/10	80
Oxidized D_g-DTT	300	10	625	8/10	80

Table VI. Radiation-Protective Activity of MEA Alone and in Combination with D_g-DTT in Mice

Dose of MEA, mg/kg	Dose of D_g-DTT, mg/kg	Time of admin before X-ray, min	Dose of X-ray, R	Mortality	% mortality
200	0	10	650	2/10	20
200	0	10	750	4/10	40
150	0	10	750	7/10	70
150	85	10	750	5/10	50

protection. The mechanism of action of dithiothreitol as a radiation-protective agent has not been delineated. On considering the various mechanisms of action that have been proposed for radiation-protective thiols[2] and in attempting to rationalize the difference in the protective activity of L_g-DTT and D_g-DTT, one can at this point reach no final conclusion as to why one enantiomer exhibits a protective capability while the other does not.

It is possible that L_g-DTT has restricted access to the primary loci of action at which D_g-DTT affords its radiation protection. A restriction could be imposed upon the L_g-DTT molecule in one of several ways. Pharmacological inactivation of L_g-DTT could occur in the form of stereoselective nonspecific binding to plasma proteins or to cell-membrane or intracellular constituents. L_g-DTT would thus be unavailable to afford protection while D_g-DTT, of opposite configuration and failing to meet a stereochemical requirement for binding, would remain active. In their study of protection by optically active 2-aminobutylisothiourea dihydrobromide, Doherty and Shapira,[4] using labeled enantiomers to determine intracellular distribution, found significant differences in binding in the cellular fractions between the enantiomers.

An appropriate restriction on L_g-DTT would arise in the ability of D_g-DTT (failure of L_g-DTT) to meet a stereochemical requirement for transfer across a critical barrier in allowing the molecule to reach a locus of action for affording protection. One should not exclude the possible sequestration of L_g-DTT by processes, other than binding, that are stereoselective. Involvement of L_g-DTT in a mammalian metabolic pathway with the exclusion of its enantiomer would be an example. We note that the least protective enantiomer of dithiothreitol, L_g-DTT, has the same absolute configuration as L_g-threitol, the mammalian metabolism of which has been discussed.[14] The natural configuration of L_g-DTT would be expected to influence its pharmacological behavior *in vivo*. The pharmacodynamics of racemic and optically active dithiothreitol have not, however, been investigated. Definition of the precise role played by stereochemistry in influencing the radiation-protective activity of optically active dithiothreitol must await further studies of this multifaceted problem. Our aim here is to call attention to the use that might be made of molecular asymmetry in designing more potent, selective, and less toxic radiation-protective agents and in investigating their mechanisms of action.

References

(1) E. R. Atkinson, *Annu. Rep. Med. Chem.*, 1969, 346 (1970).
(2) W. O. Foye, *J. Pharm. Sci.*, 58, 283 (1969).
(3) C. J. Carr, J. E. Huff, K. D. Fisher, and T. E. Huber, *Arch. Environ. Health*, 21, 88 (1970).
(4) D. G. Doherty and R. Shapira, *J. Org. Chem.*, 28, 1339 (1963).
(5) C. Falconi, P. Scotto, and P. DeFranciscis, *Boll. Soc. Ital. Biol. Sper.*, 44, 326 (1968).
(6) C. Falconi, *ibid.*, 44, 1998 (1968).
(7) C. Falconi, P. Scotto, and P. DeFranciscis, *Experientia*, 26, 172 (1970).
(8) M. Carmack and C. J. Kelley, *J. Org. Chem.*, 33, 2171 (1968).
(9) J. N. Baxter, *J. Chem. Educ.*, 41, 619 (1964).
(10) "Cleland's Reagent, A Current Bibliography," Calbiochem, Los Angeles, Calif.
(11) V. Plzak and J. Doull, "A Further Survey of Compounds for Radiation Protection," SAM-TR-69-1, USAF School of Aerospace Medicine, Brooks Air Force Base, Texas, Feb 1969.
(12) A. Pihl and L. Eldjarn, *Pharmacol. Rev.*, 10, 437 (1958).
(13) R. Bentley, "Molecular Asymmetry in Biology," Vols. I and II, Academic Press, New York, N. Y., 1969 and 1970.
(14) O. Touster and D. R. D. Shaw, *Physiol. Rev.*, 42, 181 (1962).