95% ethanol to yield 0.6 g. of the hydrochloride of Xb, m.p. 273–274° dec.

Anal. Calcd. for $C_{19}H_{19}ON_4Cl$: C, 64.31; H, 5.40; N, 15.79. Found: C, 64.61; H, 5.44; N, 15.93.

Infrared spectrum of the hydrochloride of Xb (Nujol mull): 2.91m, 3.02m, 3.40i, 3.47i, 5.87i, 5.97i, 6.29m, 6.39i, 6.71m, 6.90i, 6.99sm, 7.18m, 7.30w, 7.36m, 7.59m, 7.90w, 8.06w, 8.44m, 8.61w, 8.91bw, 9.34w, 9.76w, 10.05w, 10.31w, 10.49w, 12.03w, 12.65bw, 12.99m, 13.90m, 14.09m, 14.40bm.

2-Amino-6-cyclohexyl-4-phenyl-3,4-dihydro-5*H*-pyrrolo[3,4-*d*]-pyrimidin-7(6*H*)-one (Xc).—A solution of guanidine in absolute ethanol was prepared from 2.0 g. (0.02 mole) of guanidine hydrochloride, 0.46 g. (0.02 g.-atom) of sodium and a total of 50 ml. of absolute ethanol, by the same procedure used in the preparation of Xb, described previously. Reaction of the guanidine solution with 2.7 g. (0.01 mole) of compound VIIIc in 200 ml. of ethanol was carried out at the reflux temperature, but otherwise the procedure was as described above. When the reaction mixture was then concentrated nearly to dryness under reduced pressure over a steam cone, a yellow gum separated and was washed with 200 ml. of water. The resulting cream-colored solid was collected by filtration and dried in a desiccator. The yield was 3.0 g. (95%); m.p. 244–247° dec. The compound was obtained as a white microcrystalline solid, m.p. 247–249° dec., after it had been washed with dimethylformamide, then with acetone. After recrystallization from a small volume of methanol the m.p. was 254–256° dec.

Anal. Calcd. for $C_{18}H_{22}ON_4$: C, 69.65; H, 7.14; N, 18.05. Found: C, 69.14; H, 6.85; N, 18.16.

Infrared spectrum (Nujol mull): 2.86m, 2.95i, 3.06m, 3.38i, 3.45i, 6.02i, 6.07i, 6.24i, 6.34i, 6.61i, 6.71sm, 6.82sm, 6.92i, 7.04m, 7.19i, 7.28sm, 7.46bm, 7.80i, 7.90m, 8.13m, 8.26w, 8.45m, 8.54m, 8.73bm, 9.18m, 9.73w, 10.16w. 11.19w, 11.36w, 11.98w, 12.28w, 12.52w, 12.72m, 12.89w, 13.32m, 14.20i.

The substance yielded a hydrochloride in the form of white crystals, m.p. 298–299° dec. when recrystallized from 10% hydrochloric acid containing some ethanol.

Anal. Calcd. for $C_{18}H_{23}ON_4Cl$: C, 62.33; H, 6.68; N, 16.15. Found: C, 62.65; H, 6.75; N, 15.84, 15.70.

Infrared spectrum (Nujol mull): 3.03bm, 3.19m, 3.38i, 3.45i, 5.83m, 6.00i, 6.19m, 6.34i, 6.71w, 6.89i, 7.09m, 7.13sm, 7.30w, 7.46w, 7.88m, 8.00w, 8.01m, 8.33m, 8.39sw, 8.50w, 8.75bw, 9.03bw, 10.14w, 11.20w, 12.13bw, 12.54w, 12.89bm, 14.23bm, 14.35m.

It was advantageous to obtain the purified free base Xc from the purified hydrochloride rather than by the direct methanol recrystallization. The hydrochloride was dissolved in boiling water and the free base was precipitated by addition of a few drops of concentrated ammonium hydroxide, then collected and washed on the filter with water and acetone to give material melting at 254–256° dec.

Investigations in Heterocycles. XII. The Synthesis of Pyrazolo[1,5-*c*]quinazolines[1]

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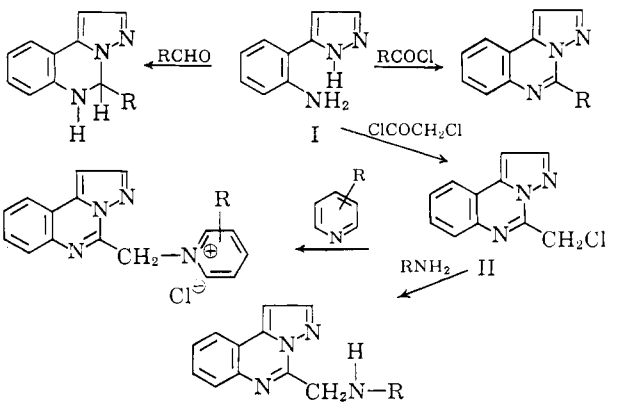
The facile rearrangement of 4-hydroxyquinoline and its derivatives in the presence of excess hydrazine hydrate gives rise to 5(*o*-aminophenyl)pyrazoles. These compounds in turn serve as intermediates in the synthesis of some new heterocycles, pyrazolo[1,5-*c*]quinazolines. The chemical and spectral properties of these substances are discussed.

In a recent review[2] we discussed the application of the intramolecular Mannich reaction and the organic acid ring closure condensations in the synthesis of several new heterocyclic systems; *e.g.*, dihydrobenzothiadiazine 1,1-dioxide, tetrahydro-1,3-benzodiazepines, and indolo[2,3-*a*]quinolizines. The principle therein expounded, *i.e.*, insertion of a one carbon fragment between two hetero atoms to form a ring, has now been extended to include the preparation of other heterocycles. Thus, the synthesis and the chemical and physical properties of pyrazolo[1,5-*c*]quinazolines will be the subject of this report.

The preparation of this new heterocycle has been facilitated by the ready availability of 5(*o*-aminophenyl)-pyrazole (I). This substance was reported recently by Alberti[3] to be obtainable *via* a one-step synthesis. Compound I is similar from a reactivity standpoint to *o*-aminobenzamide. This was indeed manifested by its condensation with aldehydes or acid chlorides, and acid anhydrides. Some of these reactions leading to the synthesis of various pyrazolo[1,5-*c*]quinazolines are outlined in Scheme I and the compounds prepared in this series are listed in Table I.

Condensation of I with excess formic acid under reflux gave a 78% yield of the parent heterocycle (compound 1, Table I). However, when I was allowed to react with excess acetic anhydride under reflux, the sole

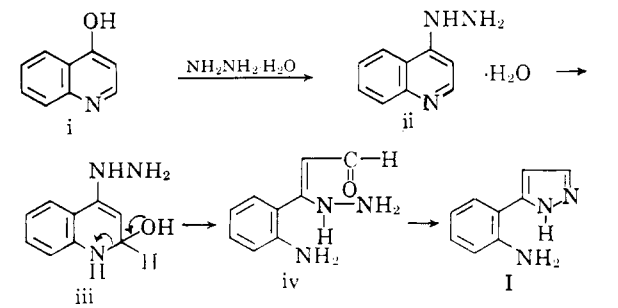


SCHEME I

(1) This subject was discussed in part by G. deStevens in a Symposium lecture on The Chemistry of Nitrogen Heterocycles sponsored by the Medicinal Chemistry Division, 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962.

(2) G. deStevens, *Record Chem. Progr.*, **23**, No. 2, 195 (1962).

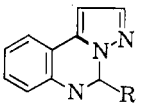
(3) G. Alberti, *Gazz. chim. ital.*, **87**, 772 (1957). Although this author did not express a mechanistic rationale for this transformation, it seems more than likely that a pseudo base is generated leading to an α,β-unsaturated



aldehyde which undergoes intramolecular dehydrative condensation with the hydrazino portion of the molecule to form I.

TABLE I

PYRAZOLO[1,5-c]QUINAZOLINES[a]

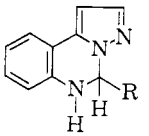


	R	M.p., °C.	Yield, %	Empirical formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	—H	83–84	78	$C_{10}H_7N_3$[a]	70.95	4.17	24.82	71.00	4.20	24.96
2	—CH_3	91	70	$C_{11}H_9N_3$[b]	72.10	4.95	22.93	71.74	5.24	22.23
3	—C_2H_5	65	51	$C_{12}H_{11}N_3$[a]	73.07	5.62	21.30	72.75	5.73	20.87
4	—CH_2Cl	142	65	$C_{11}H_8ClN_3$[c]	60.70	3.71	19.31	60.47	3.88	19.09
5	—CHCl | CH_3	154	40	$C_{12}H_{10}ClN_3$[c]	62.20	4.35	18.13	62.17	4.38	17.86
6	—C_6H_{11}[d]	64.5–65	32	$C_{16}H_{17}N_3$[e]	76.43	6.82	16.71	75.92	6.89	16.45
7	—CH_2—C_5H_9[f]	B.p. 148 0.3 mm.	41	$C_{16}H_{17}N_3$	76.43	6.82	16.71	76.48	6.79	16.37
8	—CH_2—N(H)—CH_3	235	45	$C_{12}H_{12}N_4 \cdot HCl$[c]	57.95	5.27	22.53	57.93	5.39	22.35
9	—CH_2—N(H)—CH_2—C$_6$H$_4$—F	230	22	$C_{18}H_{15}FN_4 \cdot HCl$[c]	63.07	4.71	16.35	62.68	4.94	15.95
10	—C_5H_5	125–127	72	$C_{16}H_{11}N_3$[c]	78.32	4.52	17.14	78.01	4.71	16.97
11	3,4,5(OCH_3)$_3$—C_6H_2—	124–125	30	$C_{19}H_{17}N_3O_3$[c]	68.05	5.11		68.37	5.24	
12	—CH_2—N$^{\oplus}$(C$_6$H$_4$)—$Cl^{\ominus}$	270–272	44	$C_{16}H_{13}ClN_4$[g]	64.74	4.42	18.88	64.65	4.53	18.66
13	—CH_2—N$^{\oplus}$(C$_6$H$_4$)—$Cl^{\ominus}$, H_3C	231	54	$C_{17}H_{15}ClN_4$[g]	65.69	4.86	18.03	65.47	5.02	17.71

Solvents used in recrystallization: [a] Ethyl alcohol–water. [b] Ether–petroleum ether (low boiling). [c] Ethyl alcohol. [d] Cyclohexyl group. [e] Acetone–hexane. [f] Cyclopentyl group. [g] Ethyl alcohol–ether.

TABLE II

1,2-DIHYDROPYRAZOLO[1,5-c]QUINAZOLINES



	R	M.p., °C.	Yield, %	Empirical formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
14	—H	150	15	$C_{10}H_9N_3$[c]	70.45	5.25		70.12	5.16	
15	—C_6H_5	105–106	64	$C_{16}H_{13}N_3$[b]	77.78	5.30	16.98	77.68	5.44	16.68
16	4-Cl—C_6H_4	137–138	61	$C_{16}H_{12}ClN_3$[d]	68.20	4.29	14.91	67.95	4.58	14.61
17	4-F—C_6H_4	196–197	59	$C_{16}H_{12}FN_3$[a]	72.44	4.56	15.84	72.56	3.94	15.55
18	3,4-(Cl_2)$_2$—C_6H_3—	99–100	60	$C_{16}H_{11}Cl_2N_3$[a]	60.78	3.51	13.23	60.41	3.69	12.85
19	3,4,5-(OCH_3)$_3$—C_6H_2	122–124	35	$C_{19}H_{19}N_3O_3$[a]	67.64	5.67	12.46	67.49	5.85	12.67

Solvents used in recrystallizations: [a] Ethyl alcohol–water. [b] Ether–petroleum ether (low boiling). [c] Ethyl alcohol. [d] Cyclohexyl group.

product obtained was 1-acetyl-5-(*o*-acetomidophenyl)-pyrazole (III). Elemental analytical data in addition to infrared absorption studies provided strong support for this structural assignment. A strong band at 1685 cm.$^{-1}$ corresponds to the acetamido grouping whereas an intense sharp absorption band at 1750 cm.$^{-1}$ is typical of the acetyl pyrazole grouping.[4] It was observed subsequently that an equivalent amount of acid chloride usually served as an effective condensing agent giving rise to good yields of 2-substituted pyrazolo-[1,5-*c*]quinazolines.

On the other hand, interaction of I with formaldehyde in the presence of acid or base catalyst, or even under neutral conditions, gave a poor yield of 1,2-dihydropyrazolo[1,5-*c*]quinazoline whereas condensation with other aliphatic aldehydes did not afford the desired tricyclic compounds. When I was allowed to react with aromatic aldehydes, fairly good yields of products were obtained. However, the dihydropyrazolo[1,5-*c*]quinazoline structure for these compounds could not be readily assumed from the mode of preparation. The Schiff base derivative could also be formed under these conditions. Several factors favor the closed ring system (compounds 15 through 19, Table II). First of all no reaction with sodium borohydride was observed with any of these compounds, starting material being recovered almost quantitatively. The Schiff base surely would have been reduced to the benzylamine derivative under these conditions.[5] In addition, the spectral data lend support to the cyclic structures. The 2-aryl sub-

(4) W. Ried and F. J. Königstein, *Ann. Chem.*, **625**, 54 (1959).

(5) This type of reaction proved very useful in establishing unequivocally the structure of 1,2,4,5-tetrahydro-1,3-benzodiazepines. See ref. 2 and others therein.

TABLE III

ULTRAVIOLET ABSORPTION DATA ON PYRAZOLO[1,5-*c*]QUINAZOLINES AND 1,2-DIHYDROPYRAZOLO[1,5-*c*]QUINAZOLINES[a]

Compound	λ_{max} in ethyl alcohol, mμ	ε
1	255	36,090
	316	3,680
	328	...
2	237	27,480
	253	31,580
	315	4,670
	328	4,230
3	237	30,390
	253	34,260
	314	4,910
	327	4,380
4	254	33,030
	278	5,200
	326	3,280
5	255	34,960
	280	4,740
	323	3,390
6	237	33,110
	253	35,900
	314	5,710
	327	5,290
7	237	29,250
	254	31,950
	315	4,730
	329	4,270
8	236	28,100
	254	34,830
	316	19,140
	326	3,070
9	237	28,330
	254	33,830
	316	4,040
	329	3,300
10	255	39,760
	298	8,180
11	256	33,290
	308	14,270
12	238	28,120
	252	35,400
	317	3,370
13	238	26,830
	254	35,320
	317	3,390
14	230	28,100
	318	2,787
15	227	25,920
	328	4,480
16	227	31,880
	328	4,550
17	227	25,520
	329	4,640
18	227	31,070
	329	4,670
19	230	34,200
	329	4,500

[a] A Beckman recording spectrophotometer, Model DlC, was used.

stituted compounds give two maxima in the ultraviolet (see Table III), one from 228 to 230 mμ and the other at 328 mμ. These maxima are at wave lengths comparable to those of the parent dihydropyrazolo[1,5-*c*]-quinazoline (compound 15). As a rule, Schiff bases absorb at 255 to 260 mμ and at 310 to 320 mμ.[6] Also, the n.m.r. of these compounds offer confirmatory evidence for the cyclic structure. The azomethine proton of benzalaniline absorbs at 8.35 δ[7] whereas the methine proton of the 2-aryl substituted dihydropyrazolo[1,5-*c*] quinazoline is found at 6.37 δ.[8]

Compound I was allowed to react with a wide variety of aliphatic and aromatic acid chlorides. However, chloroacetyl chloride proved to be the most versatile agent. (See Scheme I and Table I.) Condensation of chloroacetyl chloride with I dissolved in dioxane containing sodium hydroxide gave a 65% yield of 2-chloromethylpyrazolo[1,5-*c*]quinazoline (II). The halogen group in this compound is very reactive and thus II served as a useful intermediate in other transformations. For instance, when II was allowed to react with primary and secondary amines, compounds with basic moieties at the methylene group of position 2 were formed. The condensation of II with pyridine and picoline gave rise to the corresponding quaternary salts.

Experimental[9]

Pyrazolo[1,5-*c*]quinazoline.—5(*o*-Aminophenyl)pyrazole[3,10] (1.6 g.; 0.01 mole) was dissolved in 10 ml. of formic acid and the resulting solution was refluxed for 2 hr. The excess formic acid was then removed *in vacuo* and the resulting white powder was collected on a Büchner funnel and was washed well with water. One recrystallization of this powder from ethyl alcohol–water (1:2) yielded analytically pure needles.

Pyrazolo[1,5-*c*]quinazoline Hydrochloride.—Two hundred milligrams of pyrazolo[1,5-*c*]quinazoline dissolved in 5 ml. of ethyl alcohol was treated with 3 ml. of ethyl alcohol saturated with hydrogen chloride. After stirring for a few minutes a white precipitate was obtained which was recrystallized from ethyl alcohol to afford white crystals, m.p. 184–185°.

Anal. Calcd. for $C_{10}H_8N_3Cl$: C, 58.41; H, 3.92; N, 20.44. Found: C, 58.02; H, 4.05; N, 19.82.

The dissolution of the above salt in water resulted in the precipitation of the free base from solution on standing at room temperature.

5-Methylpyrazolo[1,5-*c*]quinazoline.—5(*o*-Aminophenyl)-3-methylpyrazole[3] (3.4 g.; 0.02 mole) was allowed to react under reflux with 20 ml. of formic acid for 2 hr. The reaction mixture was worked up in the same manner as described above. Recrystallization of the crude product from ethyl alcohol–water (1:2) gave a 75% yield of pure substance, m.p. 93–94°.

Anal. Calcd. for $C_{11}H_9N_3$: C, 72.07; H, 4.95; N, 22.93. Found: C, 71.85; H, 4.98; N, 22.56.

1-Acetyl-5-(*o*-acetamidophenyl)pyrazole (III).—2-(*o*-Aminophenyl)pyrazole (I) (1.6 g.; 0.01 mole) was dissolved in 15 ml. of acetic anhydride and the resulting solution was heated at reflux temperature for 2 hr. The acetic anhydride was removed at the water pump and the remaining crystalline residue was recrystallized twice from ethyl alcohol to give 0.5 g. of white needles, m.p. 153–155°.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.22. Found: C, 64.22; H, 5.41; N, 17.12.

Infrared spectra: 1750 cm.$^{-1}$ (CH_3CO of pyrazole); 1685 cm.$^{-1}$ (N-acetamidophenyl), as a mull in Nujol.

General Procedure for the Preparation of 2-Substituted Pyrazolo[1,5-*c*]quinazolines (Compounds 2, 3, 4, 5, 6, 7, 10 and 11 in Table I). 2-Chloromethylpyrazolo[1,5-*c*]quinazoline (II).—5(*o*-Aminophenyl)pyrazole (I) (9.6 g.; 0.06 mole) was dissolved in 100 ml. of dioxane containing 2.4 g. of sodium hydroxide and 2 ml. of water. To this solution there was added 6.8 ml. of chloroacetyl chloride and the whole was heated on the steam bath for 3 hr. After standing overnight at room temperature the mixture was added with stirring to 1 l. of water whereupon a precipitate was formed. This light tan solid material was collected on a filter, washed well with water, and then dried *in vacuo*. The yield

(6) F. W. Holly and A. C. Cope, *J. Am. Chem. Soc.*, **82**, 3977 (1960).

(7) J. F. King and T. Durst, *Can. J. Chem.*, **40**, 883 (1962).

(8) The spectra of these compounds were run in deuteriochloroform using an A60 Varian n.m.r. spectrometer. The internal standard was tetramethylsilane.

(9) The melting points reported herein and in Tables I and II are uncorrected.

(10) E. Koenig and J. Freund, *Chem. Ber.*, **80**, 143 (1947).

of crude compound, m.p. 135–140°, was 8.8 g. One recrystallization from ethyl alcohol gave analytically pure substance.

Condensation of II with Primary Amines. 2-(N-Methylaminomethyl)pyrazolo[1,5-*c*]quinazoline.—One hundred milliliters of ethyl alcohol containing methylamine (0.17 g. per ml.) was added dropwise over a period of 15 min. to 2.0 g. of II dissolved in 100 ml. of ethyl alcohol. After stirring the reaction mixture at room temperature for 20 hr. the solution was concentrated to a viscous residue at the water pump. The residue was taken up in a minimum amount of ethyl alcohol and the solution was treated with 5 ml. of ethyl alcohol saturated with hydrogen chloride gas. Addition of this solution to 1 l. of dry ether resulted in the formation of a white precipitate which was collected and recrystallized from ethyl alcohol–ether. The desired compound was isolated as the monohydrochloride salt.

Preparation of 1-(Pyrazolo[1,5-*c*]quinazolin-2-ylomethyl)pyridinium Chloride. Method A.—A mixture of 1.6 g. (0.01 mole) I, 1.13 g. (0.01) mole of chloroacetyl chloride and 10 ml. of pyridine was heated on the steam bath for 3 hr. On chilling the solution, a white crystalline mass was obtained which was collected on a filter and then recrystallized from ethyl alcohol–ether.

Method B.—A mixture of 2.17 g. (0.01 mole) of 2-chloromethylpyrazolo[1,5-*c*]quinazoline and 10 ml. of pyridine was heated in a sealed tube at 100° for 4 hr. The crystalline mass that was formed was collected on a Büchner funnel and recrystallized from ethyl alcohol–ether. Compound 13 in Table I was prepared in similar manner.

1,2-Dihydropyrazolo[1,5-*c*]quinazoline.—5(*o*-Aminophenyl)-pyrazole (1.6 g.; 0.01 mole) and a molar equivalent of 37% formalin were added to 25 ml. of ethyl alcohol containing one pellet of sodium hydroxide. The solution was heated at reflux on the steam bath for 15 min. After filtering off some amorphous material, the filtrate was neutralized and evaporated to viscous residue *in vacuo*. This residue was extracted with a small amount of hot alcohol. On standing at room temperature, a crystalline substance was obtained which was recrystallized from ethyl alcohol to give an analytically pure product.

General Method for the Preparation of 2-Aryl Substituted 1,2-Dihydropyrazolo[1,5-*c*]quinazolines.—One-tenth molar equivalents of I and of an aromatic aldehyde were dissolved in 50 ml. of ethyl alcohol and the resulting solution was refluxed on the steam bath for 3 hr. After removal of the solvent *in vacuo* the remaining semisolid residue was triturated well with water. The precipitate was collected and recrystallized from a suitable solvent for analysis.

Acknowledgment.—The authors extend their gratitude to Dr. E. Schlittler for his interest in this project. We also wish to thank Mr. L. Dorfman and the members of his microanalytical and spectral sections for their coöperation.

Synthesis of D- and L-2-Aminobutylisothiourea Dihydrobromide Isomers and Their Conversion to Guanidothiols, Disulfides, and Thiazolines

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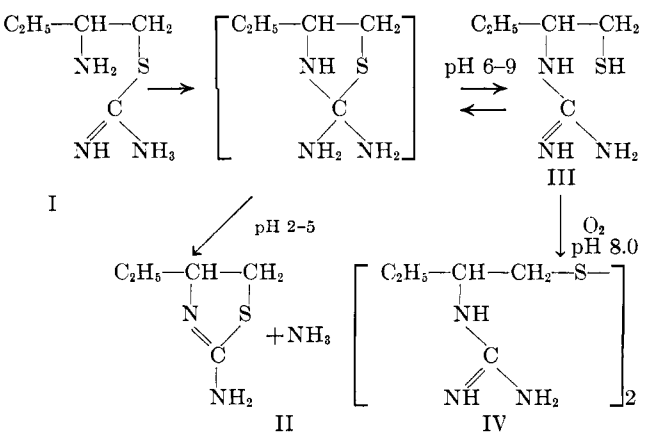
Optically active D- and L-2-aminobutyl bromide was prepared from the enzymatically resolved 2-aminobutyric acids, establishing their configuration. Condensation with thiourea yielded the D- and L-2-aminobutylisothioureas, which readily underwent a pH-dependent intramolecular rearrangement to give the D- and L-2-guanidobutane thiols or D- and L-4-ethyl-2-aminothiazolines. Oxidation of the thiols yielded the optically active 2-guanidobutyl disulfides.

Among the many aminoalkylisothioureas that are capable of protecting mice against a single lethal dose of X radiation, one compound, DL-S, 2-aminobutylisothiourea·HBr (2-ABT), seemed of particular interest. Treatment with this compound at a dose level of 4–5 μmoles per mouse (as compared with 16 μmoles per mouse for a parent compound, S,2-aminoethylisothiourea·di·HBr, AET[3]) prior to 900 r. whole-body X-irradiation enables 95–100% of the mice to survive more than 30 days. Ion exchange analysis[4] confirms that 2-ABT(I) participates in the same intramolecular rearrangements as the parent compound, AET, forming 2-amino-4-ethylthiazoline, II, at a pH of 2.5–5.0, and 2-guanidobutane thiol, III, at a pH of 6.0–9.0. Oxidation of the thiol with air or oxygen at an alkaline pH yields the corresponding 2-guanidobutyldisulfide, IV.



I II III IV

In view of these findings, especially the increased activity on a molar dose level, it seemed desirable to prepare the optically active isomers of 2-ABT and the corresponding thiazolines and examine them for protective activity in mice. If a difference in protective activity exists between the optical isomers, then these compounds, isotopically labeled, might provide some insight to the sensitive cellular and biochemical processes affected by radiation. Indeed, when prepared by the methods described herein, the D-2-ABT is twice as active as the L isomer in protecting mice against 900 r. X-radiation. Intracellular distribution studies using S^{35}- and C^{14}-labeled compounds[5] reveal significant differences in binding in the cellular fractions between the two compounds. In addition, the 2-ABT isomers were found to have interesting pharmacological proper-

(1) Department of Biochemistry, Emory University, Atlanta, Ga.

(2) Operated by Union Carbide Corporation for the U. S. Atomic Energy Commission.

(3) R. Shapira, D. G. Doherty, and W. T. Burnett, Jr., *Radiation Res.*, **7**, 22 (1957).

(4) J. X. Khym, D. G. Doherty, and R. Shapira, *J. Am. Chem. Soc.*, **80**, 3342 (1958).

(5) R. H. Bradford, R. Shapira, and D. G. Doherty, *Intern. J. Radiation Biol.*, **3**, 595 (1961).