Homologous **20c** was prepared by a different procedure. DMAC (7.5 ml) was added to a stirred solution of $Li_3PSO_3 \cdot 6H_2O$[4,29] (3.60 g, 15.0 mmoles) in H_2O (15 ml) followed by crystalline **19c** (5.57 g, 15.0 mmoles). The resultant solution was kept at 25–30° for 2 hr, chilled in an ice–water bath, and DMAC (15 ml) was added dropwise to the rapidly stirred solution. The white gum that separated initially soon solidified. EtOH (300 ml) was added, and after a few minutes of continued stirring, the white solid was collected, washed thoroughly with EtOH, and air dried (see Table III).

S-2-(ω-Octylaminoalkylamino)ethyl Dihydrogen Phosphorothioates (30a and 30c).—DMF (20 ml) was added to a stirred solution of $Li_3PSO_3 \cdot 6H_2O$ (4.80 g, 20.0 mmoles) in H_2O (40 ml). To the resultant solution the appropriate **29** (22.0 mmoles, pulverized to a fine powder) was added in portions during 15–20 min. In each preparation the corresponding **30** commenced separation before all the **29** had been added. Stirring was continued 2–3 hr. **30a** was isolated by the addition of EtOH (100 ml), and the white solid that formed was collected, washed with EtOH, and suction dried on the funnel. **30c** was isolated by adding more DMF (40 ml) to the stirred mixture containing precipitated **30c** as a semisolid. EtOH (100 ml) was also added, and continued stirring led to complete solidification of the precipitate. The solid was collected, washed (EtOH, 30–60° ligroin), and air dried (see Table III).

Acknowledgments.—The authors are indebted to Dr. D. P. Jacobus for antiradiation data, to Dr. Jacobus and Dr. T. R. Sweeney for their interest and encouragement, and to Dr. W. J. Barrett and members of the Analytical and Physical Chemistry Division of Southern Research Institute for microanalytical and spectral determinations.

Synthesis of Potential Antiradiation Agents from 3-Substituted 2-Oxazolidinones Derived from Phenol, Benzenethiol, and Related Compounds[1]

ROBERT D. ELLIOTT AND THOMAS P. JOHNSTON

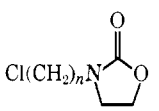
Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

Received August 5, 1968

The HBr cleavage of 3-substituted 2-oxazolidinones was effectively applied in the synthesis of N-substituted and N,S-disubstituted derivatives of 2-aminoethanethiol in which the N substituent is a 2-phenoxy-, (phenylthio)-, (phenylsulfonyl)-, or (2-pyridylthio)ethyl or a correspondingly 3-substituted propyl group. None of these modifications of the amino group led to radioprotective activity approaching that of the parent compounds. Among the thiols, disulfides, thiosulfates, and phosphorothioates prepared, the following were slightly radioprotective in mice: sodium S-2-(2-phenoxyethylamino)ethyl hydrogen phosphorothioate (**4c**), S-2-[2-(phenylthio)-ethylamino]ethyl hydrogen thiosulfate (**4g**), S-2-[3-(phenylthio)propylamino]ethyl hydrogen thiosulfate (**4j**), N,N′-(dithiodiethylene)bis[3-(phenylthio)propylamine] dihydrochloride (**5c**), and lithium S-2-[3-(phenylsulfonyl)propylamino]ethyl hydrogen phosphorothioate (**10c**). N,N′-(Sulfonyldiethylene)bis(S-2-aminoethyl hydrogen thiosulfate) (**7b**), which was prepared by an aziridine ring-opening reaction, showed fair radioprotection.

The general utility of the hydrogen bromide cleavage of 3-substituted 2-oxazolidinones in the synthesis of uniquely substituted N-(2-bromoethyl)amines has been described in a preliminary communication,[2] and its subsequent application in the synthesis of potentially radioprotective derivatives of 2-aminoethanethiol (thiols, thiosulfates, and phosphorothioates), in which the N substituent is some type of aminoalkyl group, has recently been reported.[3] This paper describes the introduction of other types of substituents through the use of nucleophiles other than amines and amine derivatives in the preparation of suitable 2-oxazolidinone intermediates.

The 3-substituted 2-oxazolidinones **2**, which were derived by the alkylation of phenol and benzenethiol with the commerically available 3-(ω-chloroalkyl)-2-oxazolidinones **1**, proved to be suitable starting points



1a, $n = 2$
b, $n = 3$

for the conversions depicted in Scheme I. The hydrogen chloride cleavage of **2c** in refluxing 1-propanol[4] in an initial experiment was eventually superseded by the milder, more convenient and productive hydrogen bromide cleavage in AcOH. The halides **3c** and **3d** afforded the same thiosulfate, **4g**, but, apparently because of the reaction rate difference between **3c** and **3d**, a phosphorothioate could not be derived from **3c**, the required longer reaction time allowing extensive decomposition of the reagent Na_3PSO_3. Attempted purifications of the impure, hygroscopic sodium hydrogen phosphorothioates derived from **3d** and **3e** succeeded only in the case of **4k**, but the reaction of **3d** with the more soluble Li_3PSO_3 proceeded smoothly in aqueous DMF and produced the hydrated crystalline Li salt **4h**.

Three methods for the synthesis of N-substituted S-2-aminoethyl hydrogen thiosulfates in which the N substituent is an ω-(alkylsulfonyl)alkyl or ω-(arylsulfonyl)alkyl group were described recently.[5] Another method, which is shown in Scheme II, has been demonstrated by the preparation of N,N′-(sulfonyldiethylene)bis(S-2-aminoethyl hydrogen thiosulfate) (**7b**) by ring opening of the bisaziridine **6** with $Na_2S_2O_3$ and AcOH.[6] The generality of this method, however, is

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2028.

(2) J. R. Piper, R. D. Elliott, C. R. Stringfellow, Jr., and T. P. Johnston, *Chem. Ind.* (London), 2010 (1966).

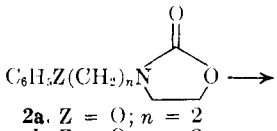
(3) (a) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **33**, 636 (1968); (b) J. R. Piper, C. R. Stringfellow, Jr., R. D. Elliott, and T. P. Johnston, *J. Med. Chem.*, **12**, 236 (1969); (c) J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *ibid.*, **12**, 244 (1969).

(4) H. Arnold and H. Beckel, *Arzneim.-Forsch.*, **14**, 750 (1964).

(5) O. L. Salerni, R. N. Clark, and B. E. Smart, *J. Chem. Soc.*, 645 (1966).

(6) *Cf.* F. C. Schaefer, J. T. Geoghegan, and D. W. Kaiser, *J. Amer. Chem. Soc.*, **77**, 5918 (1955); J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *J. Med. Chem.*, **9**, 911 (1966).

SCHEME I



2a, Z = O; *n* = 2
b, Z = O; *n* = 3
c, Z = S; *n* = 2
d, Z = S; *n* = 3

$C_6H_5Z(CH_2)_nNHCH_2CH_2X \cdot HX$ ⟶

3a, Z = O; *n* = 2; X = Br
b, Z = O; *n* = 3; X = Br
c, Z = S; *n* = 2; X = Cl
d, Z = S; *n* = 2; X = Br
e, Z = S; *n* = 3; X = Br

$C_6H_5Z(CH_2)_nNHCH_2CH_2SY$ ⟶

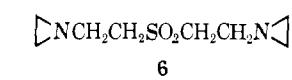
4a, Z = O; *n* = 2; Y = H
b, Z = O; *n* = 2; Y = SO_3H
c, Z = O; *n* = 2; Y = PO_3HNa
d, Z = O; *n* = 3; Y = H
e, Z = O; *n* = 3; Y = PO_3HNa
f, Z = S; *n* = 2; Y = H
g, Z = S; *n* = 2; Y = SO_3H
h, Z = S; *n* = 2; Y = PO_3HLi
i, Z = S; *n* = 3; Y = H
j, Z = S; *n* = 3; Y = SO_3H
k, Z = S; *n* = 3; Y = PO_3HNa

$[C_6H_5Z(CH_2)_nNHCH_2CH_2S—]_2 \cdot 2HCl$

5a, Z = O; *n* = 3
b, Z = S; *n* = 2
c, Z = S; *n* = 3

SCHEME II

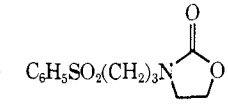
$(CH_2{=}CH)_2SO_2$ ⟶



6

$SO_2(CH_2CH_2NHCH_2CH_2SY)_2$

7a, Y = H
b, Y = SO_3H

$C_6H_5SO_2Na$ ⟶  ⟶

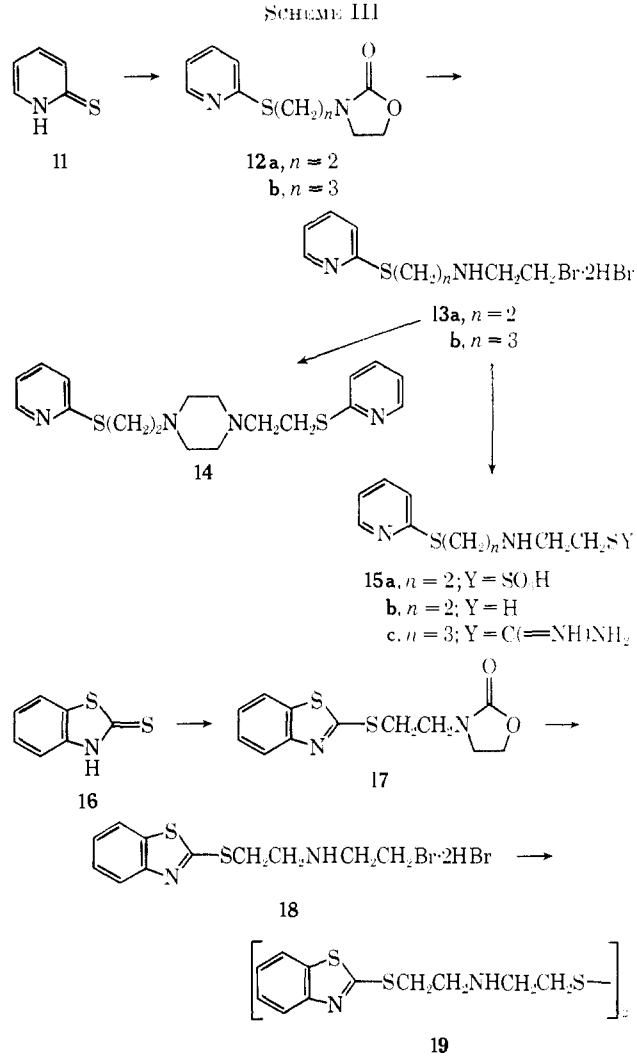
8

$C_6H_5SO_2(CH_2)_3NHCH_2CH_2Br \cdot HBr$ ⟶ $C_6H_5SO_2(CH_2)_3NHCH_2CH_2SY$

9

10a, Y = H
b, Y = SO_3H
c, Y = PO_3HLi

SCHEME III



11

12a, *n* = 2
b, *n* = 3

13a, *n* = 2
b, *n* = 3

14

15a, *n* = 2; Y = SO_3H
b, *n* = 2; Y = H
c, *n* = 3; Y = $C(=NH)NH_2$

16

17

18

19

limited by the availability of appropriately substituted aziridines; for example, the addition of ethylenimine to methyl vinyl sulfone as in the reported addition to vinyl sulfone[7] gave a crude product that polymerized during an attempted distillation at 0.075 mm. A potentially general method is exemplified by the reaction sequence in Scheme II beginning with sodium benzenesulfinate. The thiol **10a** derived from **9** and isolated as the hydrochloride was impure; pure **10a**·HCl was obtained, however, by the acid hydrolysis of the thiosulfate **10b**, which was derived from **9** in high yield in contrast to the low yield of the corresponding phosphorothioate **10c**. The H_2SO_4 liberated in the hydrolysis of **10b** was removed as $BaSO_4$.

The success of the reaction sequence based on the alkylation of benzenethiol with **1a** and **1b** suggested a similar utilization of heterocyclic thiones; sequences beginning with 2(1H)-pyridinethione (**11**) and 2-benzothiazolidinethione (**16**) are shown in Scheme III. The action of NaOH on **13a** apparently produced 1,4-bis[2-(2-pyridylthio)ethyl]piperazine (**14**) instead of the expected aziridine, which would have been a convenient precursor of the thiosulfate **15a** and the thiol **15b** through ring-opening reactions. The thiosulfate **15a** was prepared, however, by the partial *in situ* neutralization of **13a** with $NaHCO_3$ prior to treatment with $Na_2S_2O_3$ in hot aqueous solution and was converted into the thiol **15b** dihydrochloride by hydrolysis with HCl. The corresponding phosphorothioate could not be isolated from the reaction of **13a** with Li_3PSO_3 in aqueous dimethylacetamide because of the high solubility of the product in H_2O and EtOH, which prevented its separation from by-products. A characterizable thiosulfate could not be derived from **13b** with prior partial neutralization with $NaHCO_3$, NaOH, or NaOAc, a surprising result in view of the easy preparation of the lower homolog; the isothiuronium salt **15c** was prepared as an alternative derivative. The attempted conversions of the bromide **18** into the corresponding thiol, thiosulfate, and phosphorothioate by direct displacements were also unsuccessful. The intentional and prolonged air oxidation of the crude product of the reaction of **18** with NaSH in MeOH gave the disulfide **19**, but proper conditions for the conversions of **19** into the thiol by catalytic hydro-

(7) H. Bestian, *Ann. Chem.*, **566**, 210 (1950).

genolysis[8] and into the thiosulfate by bisulfite cleavage[9] were not found.

Most of the end products of the reaction sequences described here have not shown appreciable radioprotective activity in tests carried out at the Walter Reed Army Institute of Research, Washington, D. C., in mice against radiation that was lethal to untreated control mice, *i.e.*, 1000 R (γ rays) or 825 R (X-rays). These results do not compare favorably with the good activity shown by the parent compounds unsubstituted on the amino group. Slight protection (5–24% survival) was observed with **4c**, **4g**, **4j**, **5c**, and **10c**; fair protection (33% survival) was observed with **7b** at a nontoxic dose of 320 mg/kg. The inactivity or slight activity of the phosphorothioates **4c**, **4e**, **4h**, **4k**, and **10c** contrasts sharply the high level of activity observed with the corresponding amino analogs.[3b,c] Antiradiation results for **4b**, **4d**, and **10a** are not yet available.

Experimental Section[10]

3-(2-Phenoxyethyl)-2-oxazolidinone (2a).[2]—A mixture of anhydrous K_2CO_3 (13.8 g, 0.100 mole), phenol (9.41 g, 0.100 mole), and DMF (50 ml) was stirred at 100° for 5 min, cooled to 60°, and treated with **1a** (15.0 g, 0.100 mole). The mixture was stirred at 100° for 2.5 hr, cooled to 25°, and poured into H_2O (200 ml). The organic products were extracted with four 50-ml portions of C_6H_6, and the combined C_6H_6 layers were washed twice with 25-ml portions of H_2O, dried ($MgSO_4$), and evaporated *in vacuo*. The residual oil was redried ($MgSO_4$), filtered, and heated in a Hickman still at 95° (0.005 mm) for 5 hr to remove volatile impurities. The oil remaining in the still was analytically pure **2a**, which eventually solidified; yield 7.05 g (34%), mp ~50°. *Anal.* ($C_{11}H_{13}NO_3$) C, H, N.

3-(3-Phenoxypropyl)-2-oxazolidinone (2b).[2]—The oxazolidinone **2b** was prepared from **1b** and phenol by the same procedure and on the same molar scale as **2a**; the yield of crystalline **2b**, mp 62°, was 55%. *Anal.* ($C_{12}H_{15}NO_3$) C, H, N.

3-[2-(Phenylthio)ethyl]-2-oxazolidinone (2c).[2]—The oxazolidinone **1a** (21.7 g, 0.145 mole) was added dropwise to a stirred mixture of anhydrous K_2CO_3 (20.1 g, 0.145 mole), benzenethiol (16.0 g, 0.145 mole), and DMF (80 ml) at 25°. The exothermic reaction was moderated by cooling in an ice bath. The solution was then heated at 70° for 30 min, cooled to 25°, and poured into H_2O (400 ml). The resulting mixture was extracted twice with 200-ml portions of C_6H_6, and the C_6H_6 solution was washed with four 120-ml portions of H_2O, dried ($MgSO_4$), and evaporated *in vacuo*. The residual oil was redried ($MgSO_4$), filtered, and heated in a Hickman still at 105° (0.005 mm) to remove volatile impurities leaving pure **2c**, yield 29.5 g (91%), $n^{23.5}$D 1.5832. *Anal.* ($C_{11}H_{13}NO_2S$) C, H, N, S.

3-[3-(Phenylthio)propyl]-2-oxazolidinone (2d).[2]—The oxazolidinone **2d** was prepared from **1b** and benzenethiol on the same molar scale and by the same procedure as **2c** except that a 10% excess of **1b** was used; **2d** was obtained as a pale yellow oil, $n^{22.4}$D 1.5714, in 97% yield. *Anal.* ($C_{12}H_{15}NO_2S$) C, H, N, S.

N-(2-Bromoethyl)-3-phenoxypropylamine Hydrobromide (3b)[2] **and the N-(2-Bromoethyl)amine Hydrobromides 3a**, d, e,[2] **13**,[2] **and 18.**—The following procedure typifies the method used for the preparation of the N-(2-bromoethyl)amine hydrobromides of Table I, some of which required recrystallization as indicated. The oxazolidinone **2b** (12.2 g, 55.3 mmoles) was added to a solution of phenol (100 mg) in 30% dry HBr in AcOH solution (50 ml). This mixture was stirred for 16 hr at ~25°, and treated with Et_2O to precipitate **3b**, which was collected under N_2, washed (Et_2O), and dried *in vacuo* (P_2O_5); yield 17.5 g (93%).

TABLE I
N-(2-BROMOETHYL)AMINE HYDROBROMIDES

Compd	Scale, mmoles	Yield, %	Mp, °C	Formula	Analyses
3a[a]	33.5	86	148	$C_{10}H_{14}BrNO \cdot HBr$	C, H, Br, N
3b	55.3	93	142	$C_{11}H_{16}BrNO \cdot HBr$	C, H, Br, N
3d	44.8	91	98–99	$C_{10}H_{14}BrNS \cdot HBr$	C, H, Br, N
3e[a]	34.0	62	95–96	$C_{11}H_{16}BrNS \cdot HBr$	C, H, Br
13a[b]	33.8	93	~170	$C_9H_{13}BrN_2S \cdot 2HBr$	C, H, N
13b	42.0	95	157–160	$C_{10}H_{15}BrN_2S \cdot 2HBr$	C, H, N
18[a]	71.3	91	171–174[c]	$C_{11}H_{13}BrN_2S \cdot 2HBr$	C, H, Br, N

[a] Recrystallized from MeOH–Et_2O. [b] Recrystallized from EtOH. [c] Determined with a Mel-Temp apparatus.

TABLE II
N-SUBSTITUTED S-2-AMINOETHYL HYDROGEN THIOSULFATES

Compd	Scale, mmoles	Yield, %	Mp, °C	Formula	Analyses
4b	6.15	90	204 dec	$C_{10}H_{13}NO_4S_2$	C, H, N, S
4g[a]	3.97	92	178	$C_{10}H_{15}NO_3S_2$	C, H, N, S
4g[b]	11.7	92	179		
4j	14.1	89	138–142[c]	$C_{11}H_{17}NO_3S_3$	C, H, N, S
10b	10.0	89	180, 196[d]	$C_{11}H_{17}NO_3S_3$	C, H, N, S
15a[e]	19.7	80	151	$C_9H_{14}N_2O_3S_3$	C, H, N, S

[a] From **3c**. [b] From **3d**. [c] Determined with a Mel-Temp apparatus. [d] Double melting point. [e] An equivalent amount of $NaHCO_3$ was added to the $Na_2S_2O_3$ solution before heating, and the solution of product was concentrated to 60% of the original volume in order to cause crystallization.

2-Chloro-2′-(phenylthio)diethylamine Hydrochloride (3c).—A solution of **2c** (5.00 g, 22.4 mmoles) in *n*-AmOH (60 ml) was heated under reflux while a slow stream of dry HCl was introduced for 6 hr. Cooled to 25°, the solution deposited crystalline **3c**, which was collected, washed (cold *n*-AmOH), and dried *in vacuo* (P_2O_5); yield 4.41 g (78%), mp 116–118°. *Anal.* ($C_{10}H_{14}ClNS \cdot HCl$) C, H, N.

2-(2-Phenoxyethylamino)ethanethiol (4a) Hydrochloride.—A MeOH solution of NaHS was prepared by saturating at 0° a solution of NaOMe (from Na, 0.425 g, 18.5 mg-atoms) in MeOH (30 ml). While a slow stream of H_2S was passed through the stirred solution, **3a** (3.00 g, 9.23 mmoles) was added in small portions during 15 min at 0°. The solution was stirred at 0° for 30 min and at 25° for 16 hr in a tightly stoppered flask. The MeOH was removed on a rotary evaporator, and the crude thiol was decanted from the solid NaBr. The NaBr was rinsed with EtOH and the washings were added to the crude thiol. The EtOH was removed *in vacuo* and the residual oil distilled in a modified Hickman still. The thiol **4a** (1.39 g, 7.05 mmoles), bp ~70° (0.25 mm), was dissolved in Et_2O (75 ml) and treated with a 4.6 *N* solution of dry HCl in *i*-PrOH (1.69 ml, 7.75 mmoles). The refrigerated solution deposited a white solid, which was recrystallized from MeOH–Et_2O to give **4a**·HCl as white crystals, mp 151°, in 71% yield (1.54 g). *Anal.* ($C_{10}H_{15}NOS \cdot HCl$) C, H, N, S, SH.

S-2-(Phenoxyethylamino)ethyl Hydrogen Thiosulfate (4b) and the Analogous Thiosulfates 4g, 4j, 10b, 15a.—The following procedure is typical of the preparation of the thiosulfates of Table II. A solution of **3a** (2.00 g, 6.15 mmoles) in H_2O (10 ml) at 95° was added to a solution of $Na_2S_2O_3 \cdot 5H_2O$ (1.53 g, 6.15 mmoles) in H_2O (10 ml) at 95°. The resulting solution was held at 95° for 30 min and allowed to cool. The white crystalline **4b** that formed was collected, washed (cold H_2O), and dried *in vacuo* (P_2O_5); yield 1.53 g (90%).

Sodium S-2-(2-Phenoxyethylamino)ethyl Hydrogen Phosphorothioate (4c).—Na_3PSO_3[11] (1.80 g, 10.0 mmoles) was added in small portions to H_2O (10 ml) at 10° with stirring. DMF (5 ml) was added dropwise to the cold stirred solution followed by **3a** (3.25 g, 10 mmoles) in small portions. Stirring was continued at 25° while the lumps were broken up with a glass rod. Crystallization occurred after about 30 min, and stirring was continued for 1 hr. The white crystalline **4c** was collected, triturated with four 10-ml portions of EtOH, and dried *in vacuo* (P_2O_5);

(8) *Cf.* T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **28**, 1305 (1963).

(9) *Cf.* T. P. Johnston and A. Gallagher, *ibid.*, **27**, 2452 (1962).

(10) Unless otherwise noted, melting points were determined with a Kofler Heizbank. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values. Some of the analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(11) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **32**, 1261 (1967).

yield 2.30 g (77%), melting point indefinite. *Anal.* ($C_{10}H_{15}NNaO_4PS$) C, H, N, P, S.

Sodium S-2-(3-Phenoxypropylamino)ethyl Hydrogen Phosphorothioate (4e).—The procedure used in the preparation of **4c** was followed in the reaction of **3b** (3.39 g) with Na_3PSO_3 to give **4e** in 77% yield as a hygroscopic solid, melting point indefinite. *Anal.* ($C_{11}H_{17}NNaO_4PS$) C, H, N, P; S: calcd, 10.24; found, 9.8.

2-[2-(Phenylthio)ethylamino]ethanethiol (4f) Hydrochloride.—The hydrochloride of **4f** was prepared from **3d** *via* the free thiol, bp ~90° (0.5 mm), by the procedure used for **4a**·HCl. The product was isolated as a white crystalline solid, mp 74°, in 71% yield, and was not recrystallized. *Anal.* ($C_{10}H_{15}NS_2$·HCl) C, H, N, S, SH.

Lithium S-2-[2-(Phenylthio)ethylamino]ethyl Hydrogen Phosphorothioate (4h).—**3d** (3.41 g, 10.0 mmoles) was added in small portions to a stirred solution of $Li_3PSO_3 \cdot 6H_2O$[12] (2.40 g, 10.0 mmoles), H_2O (20 ml), and DMF (5 ml). The resulting mixture was stirred for 2 hr, treated with EtOH (25 ml), stirred for an additional 2 hr, treated with more EtOH (75 ml), and refrigerated. The crystalline **4h**·H_2O was collected, washed (cold EtOH), and equilibrated at 58% relative humidity; yield 1.65 g (48%), melting point indefinite. *Anal.* ($C_{10}H_{15}LiNO_3PS_2 \cdot 2.5H_2O$) C, H, N, P; S: calcd, 18.63; found, 19.05.

2-[3-(Phenylthio)propylamino]ethanethiol (4i) hydrochloride was prepared from **3e** *via* the free thiol, bp ~120° (0.05 mm), by the procedure used for **4a**·HCl. The product was isolated as a white crystalline solid, mp 114–115°, in 43% yield. *Anal.* ($C_{11}H_{17}NS_2$·HCl) C, H, N, S, SH.

Sodium S-2-[3-(Phenylthio)propylamino]ethyl Hydrogen Phosphorothioate (4k).—Crude **4k** was prepared from **3e** on the same scale and by the same procedure as described for **4c**. A solution of the product in cold H_2O (17 ml) was charcoaled, filtered, and treated with EtOH until cloudy. Refrigeration caused the crystallization of **4k** as a hydrate, which was collected and dried *in vacuo* (P_2O_5); yield 1.35 g (40%), melting point indefinite. *Anal.* ($C_{11}H_{17}NNaO_3PS_2 \cdot 0.5H_2O$) C, H, N, S; P: calcd, 9.16; found, 9.6.

N,N′-(Dithiodiethylene)bis(3-phenoxypropylamine) Dihydrochloride (5a).—2-(3-Phenoxypropylamino)ethanethiol (**4d**) (2.92 g, 13.8 mmoles), bp ~100° (0.025 mm), was prepared from **3b** in 69% yield by the procedure described for **4a** and stirred with H_2O (10 ml) containing a trace of $FeCl_3$ (~0.5 mg) in the presence of air for 3 days. The reaction mixture (nitroprusside-negative) was extracted with Et_2O (35 ml); the extract was washed with H_2O (10 ml), dried ($MgSO_4$), charcoaled, and filtered. The solvent was removed *in vacuo*, and the residual oil was dissolved in EtOH (20 ml) and 6.4 *N* dry HCl in *n*-PrOH (4.75 ml, 30.4 mmoles) was added. Addition of Et_2O (20 ml) to the mixture and refrigeration gave a white precipitate (**5a**), which was collected, washed (Et_2O), and dried *in vacuo* (P_2O_5); yield 3.22 g (95% from **4d**), mp 247–250°. *Anal.* ($C_{22}H_{32}N_2O_2S_2 \cdot 2HCl$) C, H, N, S.

N,N′-(Dithiodiethylene)bis[2-(phenylthio)ethylamine] Dihydrochloride (5b).—A solution of **4f** (2.27 g, 10.7 mmoles) and NaOH (0.428 g, 10.7 mmoles) in H_2O (60 ml) was stirred while a slow stream of air was blown through. After being stirred for 24 hr with air and for an additional 24 hr with pure O_2, the solution still gave a strong nitroprusside test for SH. The solution was neutralized with 1 *N* HCl (10.7 ml) and extracted (C_6H_6). The extract was dried ($MgSO_4$) and evaporated *in vacuo* to an oil, from which unchanged **4f** (0.684 g, 30%) was recovered by heating at 105° (0.05 mm) in a modified Hickman still. The residual disulfide was dissolved in Et_2O (75 ml) and converted into **5b** by addition of dry HCl in *i*-PrOH. The dihydrochloride was collected, washed (Et_2O), and dried *in vacuo* (P_2O_5); yield (corrected for recovered **4f**) 61% (1.13 g), mp 220° with softening and darkening from ~180°. *Anal.* ($C_{20}H_{28}N_2S_4 \cdot 2HCl$) C, H, N, S.

N,N′-(Dithiodiethylene)bis[3-(phenylthio)propylamine] dihydrochloride (5c), mp ~231° (darkening from 150°, Mel-Temp), was prepared from **4i** in 76% yield by the procedure used for the preparation of **5a**. *Anal.* ($C_{22}H_{32}N_2S_4 \cdot 2HCl$) C, H, N, S.

N,N′-(Sulfonyldiethylene)bis(2-aminoethanethiol) (7a) Dihydrochloride.—A solution of **6**[7] (5.00 g, 24.5 mmoles) in MeOH (5 ml) was added to a solution of H_2S (4.14 g, 122 mmoles) in MeOH (25 ml at −60°). The solution was kept at −30° for 2 hr and at 0° for 16 hr and was then decanted from a small amount of solid that had formed and evaporated *in vacuo*; the residual oil was dissolved in EtOH (5 ml), and Et_2O (50 ml) was added. The addition of 8.55 *N* dry HCl in *i*-PrOH (5.87 ml, 49.0 mmoles) caused the precipitation of white crystalline **7a**·2HCl, which, after refrigeration for several hours, was collected and dried *in vacuo* (P_2O_5): yield 7.32 g (87%), mp 211–212°. *Anal.* ($C_8H_{22}Cl_2O_2S_2 \cdot 2HCl$) C, H, N; SH: calcd, 19.15; found, 18.4.

N,N′-(Sulfonyldiethylene)bis(S-2-aminoethyl Hydrogen Thiosulfate) (7b).—Aziridine **6** (5.00 g, 24.5 mmoles) was added dropwise to a cold (0°), stirred solution of $Na_2S_2O_3 \cdot 5H_2O$ (12.2 g, 49.0 mmoles) in H_2O (20 ml). After the resulting solution had been stirred for 1.3 hr at 0°, AcOH (2.95 g, 49.0 mmoles) was added slowly, and stirring was continued for 30 min. Additional AcOH (2.95 g) was added, and stirring was continued for 3.5 hr. The resulting mixture was refrigerated overnight and the white crystalline **7b** that had precipitated was collected by filtration, washed (H_2O), and dried *in vacuo* (P_2O_5): yield 8.77 g (83%), mp 144° dec. *Anal.* ($C_8H_{20}N_2O_8S_5$) C, H, N.

3-[3-(Phenylsulfonyl)propyl]-2-oxazolidinone (8).[2]—A mixture of **1b** (27.0 g, 16.5 mmoles), sodium benzenesulfinate (24.6 g, 150 mmoles), and DMF (150 ml) was stirred at 85° for 6.5 hr, refrigerated, and filtered. The filter cake was washed with DMF (5 ml), and the filtrate and washings were combined and evaporated to dryness *in vacuo* at 80° (rotary evaporator). The residue was triturated with H_2O (75 ml) and the mixture was refrigerated overnight. The precipitate was collected, washed (H_2O), dried *in vacuo*, and dissolved in boiling EtOH (75 ml). The resulting solution, after charcoal treatment and refrigeration, deposited **8** as white crystals, which were collected, washed (cold EtOH), and dried *in vacuo* (P_2O_5); yield 20.9 g (52%), mp 98°. *Anal.* ($C_{12}H_{15}NO_4S$) C, H, N, S.

N-(2-Bromoethyl)-3-(phenylsulfonyl)propylamine Hydrobromide (9).[2]—A solution of phenol (1.0 g) and **8** (19.0 g, 73.9 mmoles) in 15% dry HBr in AcOH solution (200 ml) was stirred at 25° for 16 hr. The slow addition of Et_2O (200 ml) precipitated pure **9**, which was collected, washed with 1:1 AcOH–Et_2O, and dried *in vacuo* (P_2O_5); yield 27.3 g (95%), mp 156–157°. *Anal.* ($C_{11}H_{16}BrNO_2S \cdot HBr$) C, H, Br, N.

2-[3-(Phenylsulfonyl)propylamino]ethanethiol Hydrochloride (10a). A solution of **10b** (3.29 g, 9.70 mmoles) in 4 *N* HCl (115 ml) was refluxed under N_2 for 45 min; $Ba(OH)_2 \cdot 8H_2O$ (3.06 g, 9.70 mmoles) was added to the stirred solution, and refluxing was continued for 20 min. The resulting mixture was cooled in an ice bath and filtered under N_2. The filtrate was evaporated at 100° (0.2 mm) to a syrup, a solution of which in EtOH (25 ml) was filtered and again evaporated *in vacuo* to a syrup, which crystallized and was further dried *in vacuo* (P_2O_5). Recrystallization from EtOH–Et_2O afforded analytically pure **10a**, mp 137°, in 81% yield (2.32 g). *Anal.* ($C_{11}H_{17}NO_2S_2$·HCl) C, H, N, S; SH: calcd, 11.18; found, 10.70.

Lithium S-2-[3-(Phenylsulfonyl)propylamino]ethyl Hydrogen Phosphorothioate (10c).—**9** (3.87 g, 10.0 mmoles) was added in small portions to a stirred solution of $Li_3PSO_3 \cdot 6H_2O$ (2.40 g, 10.0 mmoles) in H_2O (16 ml) and DMF (4 ml) at 10°. The resulting mixture was stirred for 15 min, diluted with EtOH (10 ml), stirred 30 min, treated with EtOH (75 ml), and refrigerated for 16 hr. The mixture was filtered, and the filtrate was treated with additional EtOH and refrigerated. The crystalline **10c** hydrate was collected, washed with cold EtOH, and equilibrated at 58% relative humidity: yield 1.04 g (26%), melting point indefinite. *Anal.* ($C_{11}H_{17}LiNO_5PS_2 \cdot 2.5H_2O$) C, N, P, S; H: calcd, 5.68; found, 4.75. (The low H value is undoubtedly due to loss of H_2O of hydration during venting of the combustion chamber prior to C and H analysis.)

3-[2-(2-Pyridylthio)ethyl]-2-oxazolidinone (12a). A suspension of 2(1H)-pyridinethione (22.2 g, 0.200 mole) and K_2CO_3 (27.6 g, 0.200 mole) in DMF (100 ml) was stirred at 65° for 15 min and treated with **1a** (29.9 g, 0.200 mole). The resulting mixture was stirred at 65° for 1 hr, poured into H_2O (550 ml), and continuously extracted with C_6H_6 for 16 hr. The extract was concentrated, and the residual oil was further dried at 120° (0.025 mm) leaving pure **12a** as a viscous liquid, yield 44.0 g (98%), $n^{25}D$ 1.5817. *Anal.* ($C_{10}H_{12}N_2O_2S$) C, H, N.

3-[3-(2-Pyridylthio)propyl]-2-oxazolidinone (12b). A mixture of 2(1H)-pyridinethione (11.1 g, 0.100 mole), **1b** (16.1 g, 0.100 mole), anhydrous K_2CO_3 (13.8 g, 0.100 mole), and DMF

(12) J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *J. Med. Chem.*, **9**, 563 (1966).

(50 ml) was stirred for 16 hr. The temperature of the reaction mixture rose spontaneously to a maximum of 65°. The mixture was poured into H_2O (375 ml) and extracted with five 100-ml portions of C_6H_6. The C_6H_6 solution was washed twice with 20-ml portions of H_2O, dried ($MgSO_4$, charcoal), and evaporated to a yellow syrup at 100° (0.2 mm), yield 21.2 g (89%), $n^{25}D$ 1.5749. *Anal.* ($C_{11}H_{14}N_2O_2S$) C, H, N.

1,4-Bis[2-(2-pyridylthio)ethyl]piperazine (14) Tetrahydrochloride.—A mixture of **13a** (4.23 g, 10.0 mmoles) and 50% aqueous NaOH (20 ml) was stirred for 16 hr. The resulting mixture was extracted with C_6H_6 (10 ml), and the C_6H_6 solution was dried ($MgSO_4$). Removal of the solvent at 100° (0.3 mm) left a viscous oil, which did not react with H_2S in cold MeOH and was treated with dry HCl in EtOH to give **14**·4HCl, yield 1.12 g (44%), melting point indefinite. *Anal.* ($C_{18}H_{24}N_4S_2$·4HCl) C, H, N. The mass spectrum of the oil showed a peak at a mass-to-charge ratio of 360 corresponding to that expected for the molecular ion of **14**.

S-[2-(2-Pyridylthio)ethylamino]ethanethiol Dihydrochloride (15b).—The thiol **15b**, mp 129–131° (Mel-Temp), was prepared from **15a** in 95% yield by the procedure used for the preparation of **10a**. Recrystallization was unnecessary. *Anal.* ($C_9H_{14}N_2S_2$·2HCl) C, H, N, S; SH: calcd, 11.51; found, 10.4.

2-{2-[3-(2-Pyridylthio)propylamino]ethyl}-2-thiopseudourea Trihydrobromide (15c).—A solution of **13b** (2.00 g, 4.58 mmoles) and thiourea (349 mg, 4.58 mmoles) in EtOH (20 ml) was refluxed under N_2 for 30 min and evaporated to dryness *in vacuo*. Trituration of the gummy residue with EtOH (4 ml) gave a white crystalline solid, which was collected, washed (EtOH), and dried *in vacuo* (P_2O_5); yield 2.11 g (90%), mp 174–176° (Mel-Temp). *Anal.* ($C_{11}H_{18}N_4S_2$·3HBr) C, H, N, S.

3-[2-(2-Benzothiazolylthio)ethyl]-2-oxazolidinone (17).—A mixture of **16** (16.7 g, 0.100 mole), **1a** (15.0 g, 0.100 mole), and DMF (80 ml) was stirred at 80° for 2.5 hr and poured into H_2O (400 ml). The resultant mixture was refrigerated for 2.5 days, and the crystalline **17** that had precipitated was collected, washed (cold H_2O, 100 ml), and dried *in vacuo* (P_2O_5); yield 26.4 g (94%), mp 86°. *Anal.* ($C_{12}H_{12}N_2O_2S_2$) C, H, N, S.

2,2′-[Dithiodiethylenebis(iminoethylenethio)]dibenzothiazole (19).—A solution of NaOMe prepared from Na (0.432 g, 18.8 mg-atoms) and anhydrous MeOH (30 ml) was saturated with H_2S at 0°. While H_2S was bubbled slowly through the solution, **18** (3.00 g, 6.27 mmoles) was gradually added over 20 min. The solution was stirred at 0° for 1 hr in a stream of H_2S and warmed to 25°. The resulting solution, after standing 16 hr in a stoppered flask, was evaporated to dryness. The gummy residue was stirred with H_2O (30 ml) containing $FeCl_3$ (about 2 mg) and exposed to the air until a negative SH test (nitroprusside) was obtained. The tan precipitate obtained after 2 days of stirring was collected, washed (H_2O), and dried *in vacuo* (P_2O_5); yield 1.54 g (80%), mp 90–95°. *Anal.* ($C_{22}H_{26}N_4S_6$) C, H, N, S.

Acknowledgments.—The authors are indebted to Dr. D. P. Jacobus for antiradiation data, to Dr. J. R. Piper for helpful advice, and to Dr. W. J. Barrett and members of the Analytical and Physical Chemistry Division of Southern Research Institute for microanalytical determinations.

Aryl-Substituted Triazines with Antidepressant Activity

DONALD L. TREPANIER, KENNETH L. SHRIVER, AND JOHN N. EBLE

Chemistry Research and Pharmacology Departments, Human Health Research and Development Centers, The Dow Chemical Company, Zionsville, Indiana

Received August 1, 1968

A series of 1,4,5,6-tetrahydro-*as*-triazines that possessed 3-aryl substituents, including dihydrodibenzocycloheptenyl, benzhydryl, naphthyl, phenethyl, diphenylethyl, and phenylisopropyl, was synthesized and tested for potential antidepressant activity. Structure–activity relationships are discussed.

Practically all of the clinically active nonmonoamine oxidase inhibiting antidepressants are composed of a basic moiety, such as amino, alkylamino, dialkylamino, cycloalkylamino, or pyridyl, attached by an aliphatic side chain to a lipid-soluble, electron-donating benzenoid-containing moiety. Examples of these moieties are dibenzazepine, dibenzocycloheptene, dihydrodibenzocycloheptene, dibenzoxepin, benzothiazepinone, benzhydrol, and naphthalene. In two review articles[1] summarizing structure–activity relationships of antidepressant drugs, Biel discusses the effects on pharmacological and clinical activity produced by alterations in the tricyclic moiety and the amine group in thymoleptic and neuroleptic agents. In changing the tricyclic moiety from phenothiazine to dibenzazepine to dihydrodibenzocycloheptene as in promazine, imipramine, and amitriptyline, the clinical activity spectrum changes from tranquilizing to tranquilizing–antidepressant to antidepressant. Changing the amine group from tertiary to secondary as in imipramine–desimipramine and amitriptyline–nortriptyline also changes the pharmacodynamic and clinical profile. In general the secondary amine congeners appeared to be less of a central depressant. This is analogous to the pressor–depressor change in the series norepinephrine–epinephrine–methepinephrine and also the loss of central stimulant activity N,N-dimethylamephetamine as compared to methamphetamine.

This paper reports the results of a study in our laboratories on structure–activity relationships of some new substituted 1,4,5,6-tetrahydro-*as*-triazines synthesized and tested for antidepressant activity. These new compounds are structurally similar to known antidepressant drugs in that they are composed of the basic 1,4,5,6-tetrahydro-*as*-triazine ring attached either directly or by means of an alkyl chain to a lipid-soluble benzenoid or benzenoid-containing moiety. These moieties include dihydrodibenzocycloheptenyl, benzhydryl, naphthyl, phenethyl, diphenylethyl, and phenylisopropyl. The 1,4,5,6-tetrahydro-*as*-triazine was chosen as the basic moiety because of the variety of amino group types that it afforded. This interested us because of the demonstrated difference in activity profile of secondary and tertiary amine derivatives in CNS active compounds. A variation in the amino groups using the 1,4,5,6-tetrahydro-*as*-triazine heterocycle was accomplished by altering the degree of substitution on the three ring nitrogen atoms. Aziridine (Ia), 2-

(1) (a) J. H. Biel, "Molecular Modification in Drug Design," Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D. C., 1964, pp 115–129; (b) J. H. Biel, "Annual Reports in Medicinal Chemistry, 1965," Academic Press, New York, N. Y., 1966, pp 12–29.