An Arrhenius plot for k_{ep} is illustrated in Fig. 8. By applying the method of least squares to the plots, the energy of activation for epimerization to epihetacillin was 21.2 kcal/mole.

In plots of log k_1 *versus* pH at 35° in water, slight positive deviation from the first-order dependence on the hydroxide ion was observed at alkaline pH < 10 (not presented in Fig. 7). This result may have been due to the considerable contribution of the hydrolysis rate, k_2, to the k_1 value estimated from the optical rotatory dispersion method. This result would occur because of the pH-dependent degradation behavior of hetacillin in which the epimerization process is a major pathway in a highly basic solution, whereas hydrolysis to ampicillin becomes increasingly significant in medium basic and neutral solutions (2, 3, 6).

No significant β-lactam cleavage reaction probably would take place in hetacillin itself, since the disappearance of hetacillin was virtually accompanied, even in highly basic solutions, with two competing reactions, the formation of epihetacillin (k_1 reaction) and the conversion to ampicillin (k_2 reaction), as verified by quantitative NMR studies (Figs. 3–5). The extreme stability of the β-lactam in the hetacillin molecule was also revealed in epihetacillin degradation. The k_4 reaction concerned with the disappearance of epihetacillin is controlled by hydrolysis of the β-lactam ring and conversion to epiampicillin. The pH dependency of k_4 at 35° (Table III) indicates that the hydroxide-ion-catalyzed hydrolysis of the β-lactam moiety of epihetacillin is predominant above pH 11.5, and conversion to epiampicillin seems to be significant below this pH.

The second-order rate constant for the β-lactam hydrolysis of epihetacillin was calculated to be 65.8 M^{-1} hr^{-1} at 35°, one-twentieth of the value for the hydrolysis of ampicillin β-lactam (19). The remarkable stability of both β-lactam rings of hetacillin and its epimer may be attributed to the steric hindrance of *gem*-dimethyl groups of the imidazolidine rings toward the attack by a hydroxide ion.

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[x] To whom inquiries should be directed.

Reactions of Benzenesulfonohydrazides and Benzenesulfonamides with Hydrogen Chloride or Hydrogen Bromide in Acetic Acid

D. K. YUNG [*x], T. P. FORREST [‡], A. R. MANZER [*], and M. L. GILROY [*]

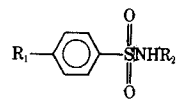
Abstract □ Benzenesulfonohydrazides capable of yielding a sulfinic acid intermediate by virtue of a basic nitrogen atom in the second position of the hydrazide moiety produced thiosulfonates when treated with 1 *N* hydrogen chloride in acetic acid and produced disulfides when treated with 1 *N* hydrogen bromide in the same solvent. In two cases, a crystalline mixture of *p*-nitrophenyl *p*-nitrobenzenethiosulfonate and bis(*p*-nitrophenyl) disulfide was isolated from the hydrogen chloride reactions. No reaction product was obtained from either the hydrogen chloride or hydrogen bromide reaction with benzenesulfonohydrazides that were unable to form a sulfinic acid intermediate. Reduction of benzenesulfonamides to disulfides appeared to be possible only with hydrogen bromide in acetic acid. No thiosulfonate was isolated from the treatments of benzenesulfonamides with 1 *N* hydrogen chloride in acetic acid. *p*-Nitrophenyl *p*-nitrobenzenethiosulfonate and *p*-bromophenyl *p*-bromobenzenethiosulfonate exhibited some antimicrobial activities against Gram-positive bacteria. The latter compound also showed analgesic properties in the phenylquinone test.

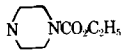
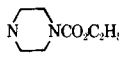
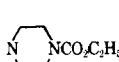
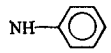
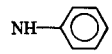
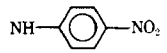
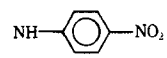
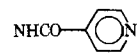
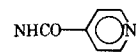
Keyphrases □ Benzenesulfonohydrazides and benzenesulfonamides—reaction with hydrogen chloride or bromide in acetic acid, pharmacological activity of thiosulfonates formed □ Thiosulfonates—formed by reaction of benzenesulfonohydrazides and benzenesulfonamides with hydrogen chloride in acetic acid, pharmacological activity screened □ Antimicrobial activity—screened in thiosulfonates formed by reaction of benzenesulfonohydrazides and benzenesulfonamides with hydrogen chloride in acetic acid

While preparing some potential antimicrobial unsymmetrical piperazine compounds, it was necessary to synthesize 1-(*p*-acetamidobenzenesulfonamido)piperazine from 1-(*p*-acetamidobenzenesulfonamido)-4-ethoxycarbonylpiperazine (Ia, Table I). Removal of ethoxycarbonyl groups of piperazine derivatives is usually accomplished by either acidic or alkaline hydrolysis (1, 2).

A nonhydrolytic method utilizing dry hydrogen bromide

Table I—Benzenesulfonohydrazides



Compound	R_1	R_2	Yield, %	Melting Point	Formula	Analysis, % Calc.	Found
Ia	$NHCOCH_3$		54	173.5–174.5° dec.	$C_{15}H_{22}N_4O_5S$	C 48.63 H 5.99 N 15.12 S 8.66	48.62 6.10 15.18 8.42
Ib	Br		61	148–150°	$C_{13}H_{18}BrN_3O_4S$	C 39.80 H 4.62 Br 20.37 N 10.71 S 8.18	39.69 4.58 20.76 10.39 7.96
Ic	NO_2		67	154–155°	$C_{13}H_{18}N_4O_6S$	C 43.56 H 5.07 N 15.64 S 8.95	43.73 5.00 15.79 8.90
IIa	Br		46	143.5–144.5°	$C_{11}H_{15}BrN_2O_2S$	C 41.38 H 4.74 Br 25.03	41.25 4.77 25.12
IIb	NO_2		74	155–157° dec.	$C_{11}H_{15}N_3O_4S$	C 46.30 H 5.30 N 14.73 S 11.24	46.65 5.32 14.88 11.50
IIIa	Br		43	161–162°	$C_{10}H_{13}BrN_2O_3S$	C 37.39 H 4.08 Br 24.88	37.40 4.17 25.11
IIIb	NO_2		85	182–184°[a]	$C_{10}H_{13}N_3O_5S$	—	—
IVa	Br		74	139–140°	$C_{12}H_{11}BrN_2O_2S$	C 44.05 H 3.39 Br 24.42	43.80 3.37 24.62
IVb	NO_2		91	147–148.5° dec.[b]	$C_{12}H_{11}N_3O_4S$	—	—
Va	Br		81	175.5–176°	$C_{12}H_{10}BrN_3O_4S$	C 38.72 H 2.71 Br 21.47 S 8.62	38.88 2.90 21.75 8.58
Vb	NO_2		50	170.5–171°[c]	$C_{12}H_{10}N_4O_6S$	—	—
VIa	Br		64	198–198.5°	$C_{12}H_{10}BrN_3O_3S \cdot H_2O$	C 38.51 H 3.23 Br 21.36	38.61 3.29 21.47
VIb	NO_2		93	211–212°	$C_{10}H_{10}N_4O_5S$	C 44.72 H 3.13 N 17.39	45.03 3.25 17.21

[a] Lit. (19) mp 180.5–181°. [b] Lit. (20) mp 150°. [c] Lit. (20) mp 172–173°.

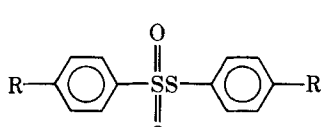
in acetic acid for 1-alkyl-4-ethoxycarbonylpiperazines and 1-ethylsulfonyl-4-ethoxycarbonylpiperazine was reported (3). Similarly, other studies (4, 5) used dry hydrogen bromide or dry hydrogen chloride in acetic acid to remove benzoxycarbonyl groups from the nitrogen atoms in peptides. This paper describes the products isolated from the reactions of Ia and other structurally related compounds with dry hydrogen chloride in acetic acid and with dry hydrogen bromide in acetic acid.

RESULTS AND DISCUSSION

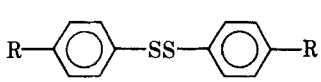
In the original attempt to remove the ethoxycarbonyl group of Ia, two problems were envisioned. First, the generally useful hydrolytic methods were considered unsuitable because of another vulnerable acetamido substituent in the molecule. Second, treatment of Ia with dry hydrogen bromide in acetic acid could result in the cleavage of the sulfonamide linkage, giving bis(*p*-acetamidophenyl) disulfide (XIIa) (6, 7) instead of the desired product.

However, in view of reported success with 1-ethylsulfonyl-4-ethoxycarbonylpiperazine (3), Ia was treated with 1 *N* hydrogen bromide in acetic acid. The desired product was not obtained; only XIIa in a 48% yield was isolated. Since it was reported that cleavage of sulfonamide with hydrogen bromide in acetic acid was a reduction process (8), it was decided to replace the dry hydrogen bromide with hydrogen chloride, a less active reducing agent. The reaction of Ia with 1 *N* hydrogen chloride in acetic acid produced a product characterized by IR, NMR, and elemental analysis to be the thiosulfonate XIa in about an 80% yield. No other products could be isolated from the reaction mixture.

In view of these results, two other piperazine compounds (Ib and Ic) were examined. In each instance, the corresponding thiosulfonates (XIb and XIc) were obtained in good yield on reaction with hydrogen chloride in acetic acid. However, treatment of Ib and Ic with 1 *N* hydrogen bromide in acetic acid resulted in the formation of disulfides (XIIb and XIIc).



XIa: R = $NHCOCH_3$
XIb: R = Br
XIc: R = NO_2



XIIa: R = $NHCOCH_3$
XIIb: R = Br
XIIc: R = NO_2

Table II—Major Reaction Products of Benzenesulfonohydrazides (I–VI) and Benzenesulfonamides (VII–X) with 1 *N* Hydrogen Chloride and/or 1 *N* Hydrogen Bromide in Acetic Acid

Compound	Reaction Product with 1 *N* Hydrogen Chloride in Acetic Acid	Yield, %	Recovery of Starting Compound %	Reaction Product with 1 *N* Hydrogen Bromide in Acetic Acid	Yield, %	Recovery of Starting Compound, %
I*a*	*p*-Acetamidophenyl *p*-acetamidobenzenethiosulfonate	82	—	Bis(*p*-acetamidophenyl) disulfide monohydrate	48	—
I*b*	*p*-Bromophenyl *p*-bromobenzenethiosulfonate	77	—	Bis(*p*-bromophenyl) disulfide	60	—
I*c*	*p*-Nitrophenyl *p*-nitrobenzenethiosulfonate	72	—	Bis(*p*-nitrophenyl) disulfide	84	—
II*a*	*p*-Bromophenyl *p*-bromobenzenethiosulfonate	50	—	—	—	—
II*b*	Mixture of *p*-nitrophenyl *p*-nitrobenzenethiosulfonate and bis(*p*-nitrophenyl) disulfide	—	—	Bis(*p*-nitrophenyl) disulfide	62	—
III*a*	*p*-Bromophenyl *p*-bromobenzenethiosulfonate	68	—	Bis(*p*-bromophenyl) disulfide	56	—
III*b*	*p*-Nitrophenyl *p*-nitrobenzenethiosulfonate	94	—	Bis(*p*-nitrophenyl) disulfide	42	—
IV*a*	*p*-Bromophenyl *p*-bromobenzenethiosulfonate	70	—	—	—	—
IV*b*	Mixture of *p*-nitrophenyl *p*-nitrobenzenethiosulfonate and bis(*p*-nitrophenyl) disulfide	—	—	Bis(*p*-nitrophenyl) disulfide	90	—
V*a*	None isolated	—	33	—	—	—
V*b*	None isolated	—	45	—	—	—
VI*a*	None isolated	—	88	None isolated	—	95
VI*b*	None isolated	—	84	None isolated	—	99
VII*a*	None isolated	—	76	Bis(*p*-nitrophenyl) disulfide	91[a]	35
VIII*a*	None isolated	—	65	—	—	—
VIII*b*	None isolated	—	70	Bis(*p*-nitrophenyl) disulfide	99[a]	33
IX*a*	None isolated	—	85	Bis(*p*-nitrophenyl) disulfide	98[a]	30
X*a*	None isolated	—	70	—		
X*b*	None isolated	—	73	—		

[a] Yield is calculated on the basis of unrecovered starting compound.

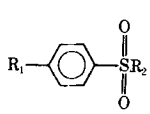
To determine the scope of the reaction involving 1 *N* hydrogen chloride in acetic acid, 10 other benzenesulfonohydrazides without the piperazine ring (Table I) were investigated. As indicated in Table II, thiosulfonates were obtained from II*a*, III*a*, III*b*, and IV*a*. The hydrazides II*b* and IV*b*, however, produced the disulfide (XII*c*) in addition to the thiosulfonate (XI*c*). The two products were isolated as a crystalline solid (mp 157–158°), which consisted of an equimolar mixture of the two, as indicated by the proton NMR spectrum. Recrystallizations from common organic solvents failed to separate the two compounds; however, they could be separated by TLC (silica gel) using carbon tetrachloride–benzene (4:1) as the eluant. The melting point and IR spectrum of the mixture were identical to those of the authentic mixture (1:1) of XI*c* and XII*c*.

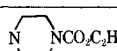
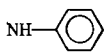
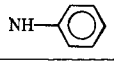
The other four benzenesulfonohydrazides (V*a*, V*b*, VI*a*, and VI*b*) do not have a basic nitrogen in the second position and did not yield any isolatable products in the reaction with hydrogen chloride in acetic acid. A significant amount of unreacted starting compound was recovered in each instance when the acid was removed *in vacuo*. Thus, the formation of thiosulfonates in the reactions with hydrogen chloride in acetic acid apparently depends on the availability of a basic nitrogen atom in the second position of the benzenesulfonohydrazides. Such a postulation is supported by the fact that none of the benzenesulfonamides (Table III) produced any thiosulfonates under similar conditions.

Thiosulfonates and sulfonic acids are known to result from disproportionation of sulfinic acids. In the acid-catalyzed hydrolysis of toluenesulfonohydrazides, sulfinic acids were formed as intermediates (9). Kice and coworkers (10, 11) proposed that the mechanism for the disproportionation of sulfinic acids involved an initial equilibrium between benzenesulfinic acid (XIII) and a sulfinyl sulfone intermediate (XIV), followed by the rearrangement of XIV to a sulfenyl sulfonate (XV). Reaction of XV with an additional molecule of XIII led to thiosulfonate and sulfonic acid as final products. Sulfonohydrazides are also reported to undergo a pyrolytic disproportionation, presumably *via* sulfinic acids, to yield a mixture of disulfide and thiosulfonate (12).

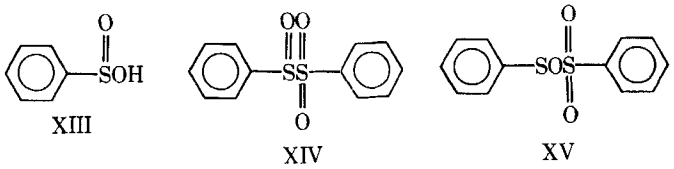
In the present study, all those benzenesulfonohydrazides that yielded thiosulfonates when treated with hydrogen chloride in acetic acid are capable of forming a sulfinic acid by electron shift from the basic nitrogen atom in the second position to the SO_2 group (Scheme I). Thus, the formation of thiosulfonates from these hydrazides probably proceeds *via* a sulfinic acid intermediate. When the same benzenesulfonohydrazides were allowed to react with 1 *N* hydrogen bromide in acetic acid, only the

Table III—Benzenesulfonamides



Compound	R_1	R_2	Yield, %	Melting Point	Formula	Analysis, % Calc.	Analysis, % Found
VII*a*	NO_2		70	157–159°	$C_{13}H_{17}N_3O_6S$	C 45.47 H 4.99 N 12.24 S 9.34	45.27 5.14 12.17 9.15
VIII*a*	Br		52	90–91°[a]	$C_{11}H_{14}BrNO_2S$	—	—
VIII*b*	NO_2		74	170.5–171°	$C_{11}H_{14}N_2O_4S$	C 48.87 H 5.22 N 10.37	48.84 5.38 10.33
IX*a*	NO_2		89	172.5–173°	$C_{10}H_{12}N_2O_5S$	C 44.11 H 4.44 N 10.29	44.05 4.44 10.09
X*a*	Br		64	117.5–118.5°[b]	$C_{12}H_{10}BrNO_2S$	—	—
X*b*	NO_2		68	168–170.5°[c]	$C_{12}H_{10}N_2O_4S$	—	—

[a] Lit. (21) mp 91–91.5°. [b] Lit. (22) mp 116–117°. [c] Lit. (23) mp 168–169°.



XIII XIV XV

disulfides were formed. This finding is in contrast to reported results for the reactions of toluenesulfonohydrazides and aqueous hydrobromic acid, in which the thiosulfonates were the major products (9). A plausible explanation for the exclusive disulfide formation could be that the bromide ions attack the sulfinyl sulfur in XIV to give sulfinyl bromide (XVI) and XIII before the sulfenyl sulfonate (XV) is formed. In dioxane–water (60:40), the bromide ion was about five times more active a nucleophile than chloride ion toward the sulfinyl sulfur atom in XIV (13). Reduction of XVI by hydrogen bromide would yield the sulfenyl bromide (XVII), which has been suggested to be an intermediate for disulfide formation in the cleavage of sulfonamide with aqueous hydrogen bromide (7).

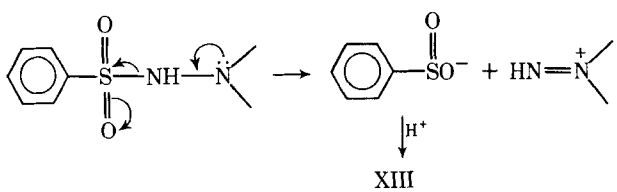
The fact that the sulfonamides (VII*a*, VIII*b*, and IX*a*) are not capable of producing the sulfinic acid intermediate and are still reduced to the disulfides suggests that the benzenesulfonohydrazides might react in a similar manner with hydrogen bromide to form the disulfides. However, the almost quantitative recovery of VI*a* and VI*b* from the reactions with hydrogen bromide in acetic acid does not support this suggestion.

Although thiosulfonates are not novel compounds, information on their biological properties is lacking. For this reason, a general screening of the pharmacological activities was performed on XI*b* and XI*c*. Preliminary results indicated that none of the compounds showed any significant antidepressant, cardiovascular, anti-inflammatory, antidiabetic, antihistaminic, or antiallergic activities. However, both compounds did exhibit some antimicrobial activities against Gram-positive bacteria such as *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 8030), *Streptococcus pyogenes* (ATCC 6538), *Streptococcus faecalis* (a clinical isolate), and *Diplococcus pneumoniae* (ATCC 6303) but not against Gram-negative bacteria. In addition, XI*b* showed some analgesic activity in the phenylquinone test[1].

EXPERIMENTAL[2]

The benzenesulfonohydrazides and benzenesulfonamides were prepared from the amine and the corresponding benzenesulfonyl chloride in pyridine and were purified by recrystallization from ethanol or aqueous ethanol. With the exception of 1-amino-4-ethoxycarbonylpiperazine, all amines and benzenesulfonyl chlorides were obtained commercially. 1-Amino-4-ethoxycarbonylpiperazine was prepared by a previously reported method (14). The physical data of the benzenesulfonohydrazides and benzenesulfonamides are listed in Tables I and III, respectively.

p-Acetamidophenyl p-Acetamidobenzenethiosulfonate (XI*a*)—In a flask fitted with a gas-absorption trap were placed 0.8 g (0.0022 mole) of I*a* and 70 ml of 1 *N* hydrogen chloride in acetic acid, prepared by adding acetic acid to 10–15% hydrogen chloride in acetic acid. The mixture was warmed in a steam bath for 25 min and at 60° for 3 hr. The solution was allowed to stand at room temperature overnight and then filtered. About 0.2 g of crystalline XI*a* was collected and washed with ether. The filtrate was concentrated *in vacuo* to give a residue which, upon mixing with a small amount of ethanol, yielded an additional 0.12 g of XI*a*. Removal of the ethanol gave an unmanageable tar-like material. The total yield of XI*a* was 82%, mp 227–228°, after recrystallization from aqueous ethanol.

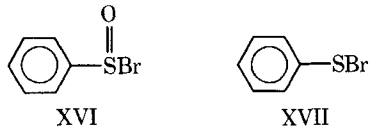


XIII

Scheme I

[1] The preliminary biological data were supplied by the Bio-Research Laboratories Ltd., Montreal, Quebec, Canada.

[2] Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J. IR spectra were recorded on a Perkin-Elmer model 237B spectrophotometer in potassium bromide. A Varian model T-60 spectrometer was used to record the NMR spectra, with deuterochloroform as the solvent and tetramethylsilane as the internal reference.



XVI XVII

Anal.—Calc. for $C_{16}H_{16}N_2O_3S$: C, 52.73; H, 4.43; N, 7.69; S, 17.60. Found: C, 52.36; H, 4.77; N, 7.72; S, 17.98.

p-Bromophenyl *p*-bromobenzenethiosulfonate (XI*b*), mp 157–158° [lit. (15) mp 160–161°], and *p*-nitrophenyl *p*-nitrobenzenethiosulfonate (XI*c*), mp 181–181.5° [lit. (16) mp 180–181°], were similarly prepared. The yields of these thiosulfonates are listed in Table II.

Bis(*p*-acetamidophenyl) Disulfide (XII*a*)—The procedure described for XI*a* was followed to synthesize this compound from the reaction of I*a* with 1 *N* hydrogen bromide in acetic acid, prepared by adding acetic acid to 30–32% hydrogen bromide in acetic acid. Compound XII*a* was recrystallized from aqueous ethanol, mp 217.5–219°. The yield was 48%.

Anal.—Calc. for $C_{16}H_{16}N_2O_2S_2 \cdot H_2O$: C, 54.83; H, 5.18; N, 8.00; S, 18.30. Found: C, 54.79; H, 5.14; N, 8.13; S, 18.54.

Bis(*p*-bromophenyl) disulfide (XII*b*), mp 92–93° [lit. (17) mp 95–96°], and bis(*p*-nitrophenyl) disulfide (XII*c*), mp 181–182.5° [lit. (18) mp 182°], were similarly prepared. The yields of these disulfides are shown in Table II.

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