The conventional methods for removal of carbobenzoxy and ethyl ester groups gave poor results. Thus, the hydrogen bromide–acetic acid procedure[4,18] led to several products which were detected by paper electrophoresis. Saponification followed by catalytic hydrogenation also gave mixtures. Because this pentapeptide was known[2] to be resistant to concentrated hydrochloric acid at 37° the procedure described above was used and was found to give a pure product.

L-Seryl-L-histidyl-L-leucyl-L-valyl-L-glutamic Acid Diethyl Ester. A.—A 40-mg. sample of carbobenzoxy-L-seryl-L-histidyl-L-leucyl-L-valyl-L-glutamic acid diethyl ester was dissolved in 3 ml. of ethanol and hydrogenated with palladium–carbon catalyst for 4 hr. The catalyst was removed and the solution concentrated. Addition of water gave 20 mg. of a gelatinous precipitate. Paper electrophoresis in 0.1 *M*, *p*H 5.0 pyridine acetate indicated a single ninhydrin-positive spot (mobility relative to histidine 0.74). However, the Pauly test showed in addition a small amount of starting material (mobility relative to histidine 0.32).

B.—A small sample of the carbobenzoxy pentapeptide ester was treated with an excess of *N* hydrogen bromide in acetic acid at 25° for 90 min.[19] This produced only one detectable compound with the same relative mobility (0.74) as preparation A. These two preparations were used without further purification for microbiological assay and the specific activities, which were nearly identical, were calculated on the basis of the quantitative Pauly reaction.

D-Seryl-L-histidyl-L-leucyl-L-valyl-L-glutamic Acid.—A 41-mg. sample of carbobenzoxy-D-seryl-L-histidine hydrazide was converted to the azide and condensed with L-leucyl-L-valyl-L-glutamic acid diethyl ester as described for the L-serine-containing isomer. The yield was 40 mg. of a gelatinous product. This was hydrolyzed in 1 ml. of concentrated hydrochloric acid at 37° for 130 min. and worked up as described previously for the L-isomer. Almost all of the Pauly-positive and ninhydrin-positive material migrated in paper electrophoresis exactly like the "all L" pentapeptide (mobility relative to histidine 0.18 in 1 *M*, *p*H 5.0 pyridine acetate). However, small amounts of the mono- and diethyl esters also were detected. This material was used without further purification for strepogenin assay.

(18) G. W. Anderson, J. Blodinger and A. D. Welcher, THIS JOURNAL, **74**, 5309 (1952).

(19) R. A. Boissonnas and G. Preitner, *Helv. Chim. Acta*, **36**, 875 (1953).

NEW YORK, N. Y.

[CONTRIBUTION FROM THE MEDICINAL CHEMICAL SECTION, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

1,3,4-Thiadiazole- and Thiadiazolinesulfonamides as Carbonic Anhydrase Inhibitors. Synthesis and Structural Studies

BY RICHARD W. YOUNG, KATHRYN H. WOOD, JOYCE A. EICHLER, JAMES R. VAUGHAN, JR., AND GEORGE W. ANDERSON

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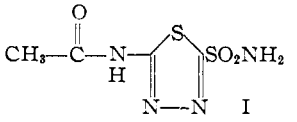
The preparation of 2-(N-methylacetamido)-1,3,4-thiadiazole-5-sulfonamide (II) and of 5-acetylimino-4-methyl-Δ^2-1,3,4-thiadiazoline-2-sulfonamide (XIII) is reported. These compounds, and analogs of II, are potent inhibitors of carbonic anhydrase. The structures of II and related derivatives of 2-acetamido-1,3,4-thiadiazole-5-thiol are established.

The success of 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide (I)[1,2] as a therapeutically effective inhibitor of the enzyme carbonic anhydrase has



encouraged further syntheses of structural variants so that the effects of these changes on *in vitro* inhibitory activity and on some pharmacological properties might be studied. Of particular interest were the monobasic acid analogs of the weak dibasic acid I. These differ from I in that the dissociable hydrogen atom on the carboxamide is replaced by an alkyl or aryl group.[3]

The simplest compound of this type, 2-(N-methylacetamido)-1,3,4-thiadiazole-5-sulfonamide (II), was synthesized by first acetylating 2-methylamino-1,3,4-thiadiazole-5-thiol (III)[4] to give 2-(N-methylacetamido)-1,3,4-thiadiazole-5-thiol (IV). Oxidative chlorination[2] of this compound to the sulfonyl chloride followed by amidation with anhydrous liquid ammonia gave the sulfonamide II. Several analogous compounds were prepared by this procedure and are reported in Table I.

The chemical and physical properties of II are especially interesting when compared to I. The acidity and spectra are quite similar, although II is only a monobasic acid. The behavior in alkaline solution, however, is quite different. Compound I is stable at *p*H 11–13 at room temperature for at least 8 hours, but II is deacylated under these conditions to 2-methylamino-1,3,4-thiadiazole-5-sulfonamide (XV).[5] This instability appears to be general; 2-(N-phenylacetamido)-1,3,4-thiadiazole-5-sulfonamide (XXVII) is also rapidly deacylated in dilute alkali.[6]

The resistance of I to alkaline degradation is probably associated with anion formation at the carboxamide, which would inhibit attack at the carbonyl group by hydroxide ion. This mode of stabilization is not available for II or its congeners. However, the validity of this rationalization depends on the assumption that I and II represent the true structures of these compounds. The subsequent investigation was undertaken to confirm these assignments.

Structural Studies.—The preparation of III by alkaline cyclization of 4-methylthiosemicarbazide with carbon disulfide (*cf.* Fig. 1) has not been reported, although Guha[7] prepared the related 2-

(1) Diamox ® Acetazolamide.

(2) R. O. Roblin, Jr., and J. W. Clapp, THIS JOURNAL, **72**, 4890 (1950).

(3) In a previous paper [J. R. Vaughan, Jr., J. A. Eichler and G. W. Anderson, *J. Org. Chem.*, **21**, 700 (1956)] variations on the acyl group of I were reported.

(4) M. Busch and H. Lotz, *J. prakt. Chem.*, [2] **90**, 257 (1914).

(5) Pseudo first-order rate constants for this decomposition were estimated by following the disappearance of the 267 mμ peak in buffers at room temperature: at *p*H 9.2, *k ca.* 2×10^{-5} sec.$^{-1}$; at *p*H 11.0, *k ca.* 2×10^{-3} sec.$^{-1}$.

(6) At *p*H 9.2, *k ca.* 2×10^{-5} sec.$^{-1}$; at *p*H 11.0, *k ca.* 8×10^{-4} sec.$^{-1}$.

(7) P. C. Guha, THIS JOURNAL, **44**, 1510 (1922).

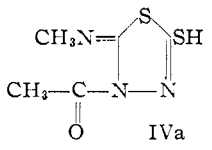
TABLE I

1,3,4-THIADIAZOLE- AND THIADIAZOLINESULFONAMIDES

	Compound	Activity[a] (*in vitro*)	pK_a[b]	Ultraviolet absorption maxima, mμ (log ε) 95% EtOH	0.1 *N* HCl	0.1 *N* NaOH	Infrared >C=O amide[e] cm.$^{-1}$
1,3,4-Thiadiazole-5-sulfonamide							
I	2-Acetylamino[d]	1.0	7.47; 9.04	264 (4.01)	265 (c)	240 (3.56) 292 (4.11)	1675
	2-Amino-[d]	0.24	7.68	278 (3.89)	274 (3.79)	270 (3.87)	...
II	2-(N-Methylacetamido)-	1.4	7.40	267 (4.01)	269 (c)	267 (4.03)	1674
XV	2-Methylamino-	0.35	7.80	286 (3.97)	286 (3.80)	280 (3.94)	...
XXVII	2-(N-Phenylacetamido)-	1.0	7.32	265 (4.03)	267 (c)	265 (4.04)	1670
XXVIII	2-Anilino-	2.1	7.70; 11.11	...	245 (c) 309 (c)	302 (c) *p*H 9 276 (3.82) 342 (4.00)	...
XXIV	2-(N-Ethylacetamido)-	0.9	...	...	...	...	1674
XXV	2-(N-Butylacetamido)-	1.9	...	...	...	...	1673
XXVI	2-(N-Methylpropionamido	1.2	...	...	...	...	1675
4-Methyl-Δ^2-1,3,4-thiadiazoline-2-sulfonamide							
XIII	5-Acetylimino-	1.5	7.30	254 (3.66) 290 (4.09)	255 (c) 290 (c)	247 (3.61) 288 (4.12)	1605
XIVa	5-Imino-	0.1	...	294 (3.68) 225sh (3.73)	261 (3.83)	286 (3.76) 223 (3.83)	...

[a] The *in vitro* carbonic anhydrase inhibitory activity was measured by the method of T. H. Maren, V. I. Ash and E. M. Bailey, *Bull. Johns Hopkins Hosp.*, **95**, 244 (1954), and represents the ratio of the weight of I to the weight of compound required to produce 50% inhibition. [b] The values were determined by the "Spectrotitrimeter" method of F. T. King and R. C. Hirt, *Applied Spectroscopy*, **7**, 164 (1953). [c] Sample had not completely dissolved. [d] W. H. Miller, A. M. Dessert and R. O. Roblin, Jr., THIS JOURNAL, **72**, 4893 (1950), and ref. 2. [e] The spectra were taken in Nujol mull.

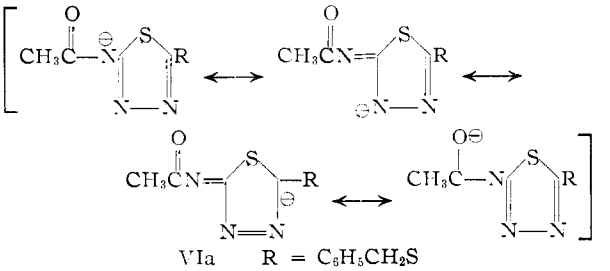
anilino and amino compounds by this procedure. By showing that these compounds possessed a single mercapto group, he differentiated them from the isomeric dimercapto triazoles; this conclusion for III is confirmed by the present work. Acetylation with acetic anhydride using concentrated sulfuric acid as catalyst afforded, after brief hydrolysis, the monoacetyl mercaptan IV.[8] The base solubility and subsequent conversions of IV to the sulfide V and sulfonyl chloride demonstrate the presence of a free or potential mercapto function. Consideration of the expression IVa (and the analogous structures for V and II) is required.



IVa

In order to confirm the position of the acetyl group, it appeared desirable to synthesize these compounds by introducing a methyl group into a suitable molecule in which the position of the acetyl group was known, and which could be converted readily to a sulfonamide.[9] No known compound possessed these features[10]; therefore, 2-acetylamino-5-benzylmercapto-1,3,4-thiadiazole (VI) was synthesized for this purpose. The benzyl sulfide may be converted to the sulfonyl chloride by oxidative chlorination.[11] VI was prepared by benzylation of 2-acetylamino-1,3,4-thiadiazole-5-thiol (IX),[2] or alternatively by benzylation of 2-amino-1,3,4-thiadiazole-5-thiol (VII)[12] to give 2-amino-5-benzylmercapto-1,3,4-thiadiazole (VIII),[4] followed by acetylation. The latter route is preferred, since it avoids using the difficultly soluble mercaptan IX. Oxidative chlorination of both IX[2] and VI produced the same sulfonyl chloride which was converted to I by amidation. Benzylation of 2-ethylamino-1,3,4-thiadiazole-5-thiol (XI)[12] (prepared from ethyl isothiocyanate; *cf.* Fig. 1) gave 2-ethylamino-5-benzylmercapto-1,3,4-thiadiazole (X). Lithium aluminum hydride reduction of VI also produced X, thus establishing the position of the acetyl group in the key intermediate.

For methylation VI was dissolved in methanolic sodium methoxide, forming the resonating ion VIa which on treatment with methyl bromide produced 5-acetylimino-4-methyl-2-benzylmercapto-Δ^2-1,3,4-thiadiazoline (XII), an isomer of V. However,



VIa R = $C_6H_5CH_2S$

alkylation of VI with methyl iodide in *t*-butyl alcohol containing potassium *t*-butoxide produced V as the major product, identical in m.p. and in-

(8) A diacetyl compound was reported as the product of acetylation of III, although the conditions were not described (Ref. 4).

(9) Chemical degradation of II or its derivatives is unattractive, in view of the lability of the acetyl group. Attempted reduction of V with lithium aluminum hydride resulted in deacetylation.

(10) The structure of acetylated aminothiadiazoles has not received attention since G. Young and W. Eyre [*J. Chem. Soc.*, **79**, 54 (1901)] established the structure of 2-acetylamino-5-phenyl-1,3,4-thiadiazole. Although most authors have assumed that amino-acetylation is preferred, there are still occasional references to ring acetylation [*cf.* E. Seebeck, *Helv. Chim. Acta*, **30**, 149 (1947)].

(11) T. Zincke and O. Kruger, *Ber.*, **45**, 3468 (1912); R. H. Baker R. M. Dodson and B. Riegel, THIS JOURNAL, **68**, 2636 (1946).

(12) M. Freund and H. Imgart, *Ber.*, **28**, 948 (1895).

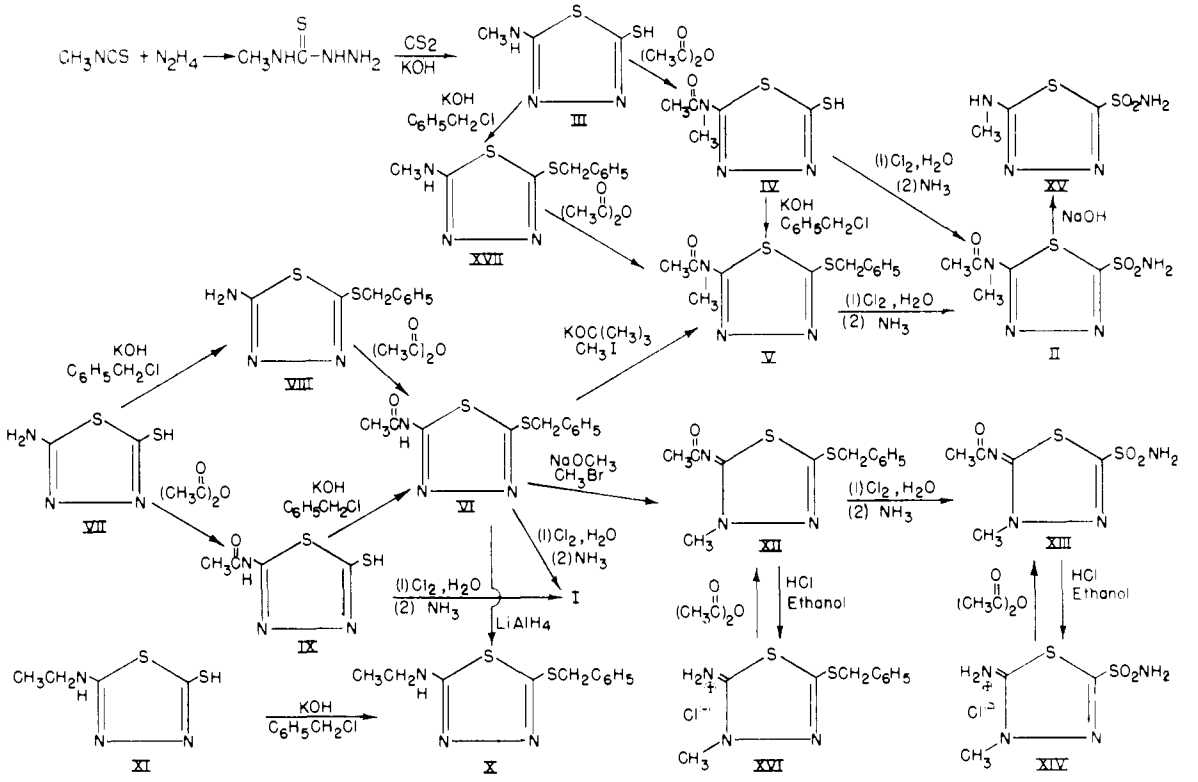
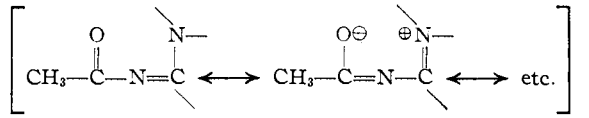


FIGURE I

frared spectrum with the preparations from III. This coincidence, therefore, establishes the structure II.[13] The structures of the alkyl and aryl derivatives in Table I are based on the similarity of their infrared spectra to that of II.

The isomeric methylated benzyl sulfide (XII) was oxidatively chlorinated to a sulfonyl chloride and amidated to give 5-acetylimino-4-methyl-Δ^2-1,3,4-thiadiazoline-2-sulfonamide (XIII), isomeric with II. Both XII and XIII exhibit unusually low amide absorption at 1605 cm.$^{-1}$ in the infrared, in contrast with II, which absorbs at 1674 cm.$^{-1}$. Hot ethanolic hydrochloric acid effected deacetylation of XII to 5-imino-4-methyl-2-benzylmercapto-Δ^2-1,3,4-thiadiazoline hydrochloride (XVI), and of XIII to 5-imino-4-methyl-Δ^2-1,3,4-thiadiazoline-2-sulfonamide hydrochloride (XIV). Acetylation of the imino hydrochlorides regenerated the original substances. These facts, coupled with the negative C-methyl and positive N-methyl determinations on XIV, support the proposed structures for XII and XIII.

In contrast to II, XIII is stable at *p*H 9–11 but is hydrolyzed slowly at *p*H 13.[14] The alkali stability and low carbonyl frequency in the infrared are doubtless due to the participation of the carbonyl group in the conjugated system[15]



The corresponding thiadiazole and thiadiazoline bases also differ markedly. The aminothiadiazole does not form a stable hydrochloride, and the ultraviolet absorption is independent of *p*H. The thiadiazoline forms a stable hydrochloride XIV and the ultraviolet absorption maximum shifts to shorter wave lengths in acid. Further investigations with aminothiadiazolines will be reported in a subsequent paper.

Biological Activity.—As is evident from Table I, there is little correlation between acidity and *in vitro* inhibitory activity, even in this closely related series. *In vivo*, both II[16] and XIII[17] show better penetration than I into the brain and eye of dogs. XIII shows a high order of activity in inhibiting experimental electroshock in the mouse[18] and reduces the intraocular pressure in rabbits.[19]

Acknowledgments.—The analyses were performed by the Staff of the Microanalytical Group under the direction of Dr. J. A. Kuck, and the infrared spectra were determined by Dr. R. C. Gore and his staff. We are especially indebted to Dr. R. A. Hirt and Mr. R. G. Schmitt for the ultraviolet spectra, pK_a determinations, and for the hydrolysis measurements. We are grateful to

(13) The production of two isomeric methylated benzyl sulfides confirms the assignment of the acyl group to the 2-amino position of VI by internal consistency. A ring acylated isomer could give rise to only *one* alkylated product. This is essentially the classical proof of Young and Eyre (*cf.* Ref. 10).

(14) At *p*H 13.0, *k ca.* 4×10^{-5} sec.$^{-1}$.

(15) A similar explanation has been used to rationalize the reduced carbonyl reactivity and lowered carbonyl stretching frequency in the case of β-amino-α,β-unsaturated ketones [N. H. Cromwell, *et al.*, THIS JOURNAL, **71**, 3337 (1949)].

(16) G. M. Sisson and T. H. Maren, unpublished results.

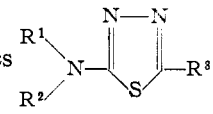
(17) G. M. Sisson and T. H. Maren, *Federation Proc.*, **15**, 484 (1956).

(18) W. D. Gray, T. H. Maren, G. M. Sisson and F. Smith, *ibid.*, **15**, 430 (1956).

(19) Prof. B. Becker, University of St. Louis Medical School; private communication.

TABLE II

1,3,4-THIADIAZOLES



	R¹	R²	R³	M.p., °C.	Yield, %	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	III	CH_3	H	SH	190–194[a]	77	...	...	...	...	...	...	...
2	XI	C_2H_5	H	SH	142–144[b]	88	...	...	...	...	...	...	...
3	XVIII	*n*-C_4H_9	H	SH	139–140	30	$C_6H_{11}N_3S_2$	38.1	5.86	22.2	38.0	5.87	22.0
4	XIX	C_6H_5[c]	H	SH	218–221	20		...	...	...	...	...	...
5	IV	CH_3	$CH_3C=O$	SH	232–235	91	$C_5H_7N_3OS_2$	31.7	3.73	22.2	32.2	3.93	21.8
6	XXII	CH_3	C_2H_5CO	SH	245–250	57	$C_6H_9N_3OS_2$	35.4	4.46	20.7	35.4	4.30	20.8
7	XX	C_2H_5	$CH_3C=O$	SH	243–246	88	$C_6H_9N_3OS_2$	35.4	4.46	20.7	35.3	4.53	20.9
8	XXI	*n*-C_4H_9	$CH_3C=O$	SH	181.5–182.5	87	$C_8H_{13}N_3OS_2$	41.5	5.66	18.2	41.5	5.70	18.0
9	XXIII	C_6H_5	$CH_3C=O$	SH	242–249[d]	89	$C_{10}H_9N_3OS_2$	47.8	3.61	16.7	48.1	3.86	16.7
10	II	CH_3	$CH_3C=O$	SO_2NH_2	216–217	67	$C_5H_8N_4O_3S_2$	25.4	3.41	23.7	25.3	3.45	23.8
11	XXVI	CH_3	C_2H_5CO	SO_2NH_2	204–205	34	$C_6H_{10}N_4O_3S_2$	28.8	4.03	22.4	28.8	4.11	22.7
12	XXIV	C_2H_5	$CH_3C=O$	SO_2NH_2	231–232	78	$C_6H_{10}N_4O_3S_2$	28.8	4.03	22.4	28.4	4.11	22.6
13	XXV	*n*-C_4H_9	$CH_3C=O$	SO_2NH_2	169–170[e]	10	$C_8H_{14}N_4O_3S_2$	34.5	5.07	20.1	34.5	5.46	19.9
14	XXVII	C_6H_5	$CH_3C=O$	SO_2NH_2	236–237	57	$C_{10}H_{10}N_4O_3S_2$	40.3	3.38	18.8	40.3	3.58	18.7
15	XV	CH_3	H	SO_2NH_2	228–230	84	$C_3H_6N_4O_2S_2$	18.6	3.12	28.9	18.8	3.28	28.8
16	XXVIII	C_6H_5	H	SO_2NH_2	232–234	61	$C_8H_8N_4O_2S_2$	37.5	3.15	21.9	37.2	3.37	22.0

[a] Reference 4 gives m.p. 187°. [b] Reference 12 gives m.p. 140°. [c] Reference 12 gives m.p. 219°. [d] Reference 7 gives m.p. 244°. [e] In this preparation, the sulfonyl chloride was obtained as an oil which was extracted into ether. The dried ethereal solution was added to liquid ammonia.

Drs. Thomas H. Maren and George M. Sisson and the staff of the Pharmacological Research Department for the biological data.

Experimental[20]

The general methods for the preparation of the compounds in Table II will be exemplified by the procedures employed for the 2-N-methyl analogs.

2-Methylamino-1,3,4-thiadiazole-5-thiol (III) and Compounds 1–4, Table II.—The addition of 83.9 g. (1.49 moles) of 85% potassium hydroxide in 50 cc. of water to a slurry of 132 g. (1.27 moles) of 4-methylthiosemicarbazide[21] in 1700 cc. of absolute alcohol produced a clear solution. Carbon disulfide (100 cc.) was added with stirring and the solution was heated. After a few minutes a solid precipitated which redissolved in the first 4 hours of the 23-hour reflux period. The mixture was concentrated to dryness *in vacuo*, and the yellow residue which was produced was dissolved in 400 cc. of water. The solution was filtered (Darco G-60) and acidified to *p*H 2 with concentrated hydrochloric acid; 168 g. (89%), m.p. 188–194°, was obtained. Recrystallization from 1100 cc. of ethanol yielded 144 g. (77%) of III.

2-(N-Methylacetamido)-1,3,4-thiadiazole-5-thiol (IV) and Compounds 6–9, Table II.—A mixture of 30 g. (0.20 mole) of II and 105 cc. (1.1 moles) of acetic anhydride containing 0.5 cc. of concentrated sulfuric acid was heated on the steam-bath to effect solution. The solution was heated for 2 hours before being diluted cautiously with 261 cc. of water. The resultant mixture was boiled for 10 minutes and then allowed to cool slowly. For purification, the 37 g. (94%), m.p. 225–232°, was dissolved in 250 cc. of water containing 25 cc. of concentrated ammonium hydroxide and was treated with Darco (G-60). After removal of the charcoal, the solution was acidified with concentrated hydrochloric acid to give 35.2 g. (91%) of IV.

2-(N-Methylacetamido)-1,3,4-thiadiazole-5-sulfonamide (II) and Compounds 11–14, Table II.—A suspension of 18.6 g. (0.098 mole) of IV in 300 cc. of 33% acetic acid was cooled to 10°. Chlorine gas was introduced in a fine stream for 1 hour, keeping the temperature at 10–15°, during which time the character of the precipitate changed. The solid was filtered off, washed with cold water and recrystallized from a mixture of 75 cc. of ethylene dichloride and 75 cc. of petroleum ether (b.p. 30–60°). The sulfonyl chloride was obtained as colorless plates, 17.0 g. (78%), m.p. 117–119° dec. Under an atmosphere of dry nitrogen 16.0 g. of the sulfonyl chloride was added in portions to 50 cc. of freshly condensed liquid ammonia. The excess ammonia was removed *in vacuo* and the colorless solid residue was redissolved in 125 cc. of cold water. The solid obtained by acidification of this solution was recrystallized from 500 cc. of hot water; 9.8 g. (67%) of II was obtained.

In the preparation of sulfonamides, care should be taken to avoid the presence of moisture throughout the amidation.

2-Methylamino-1,3,4-thiadiazole-5-sulfonamide (XV) and Compound 16, Table II.—A solution of 0.24 g. (0.0001 mole) of II in 2.5 cc. of 1 *N* sodium hydroxide was allowed to remain overnight at room temperature. Acidification of the solution with 2.5 cc. of 1 *N* hydrochloric acid gave 0.16 g. (84%) of XV. The compounds may be recrystallized from ethanol.

2-Amino-5-benzylmercapto-1,3,4-thiadiazole (VIII).—Addition of 301 g. (5.36 moles) of 85% potassium hydroxide to a slurry of 608 g. (4.56 moles) of 2-amino-1,3,4-thiadiazole-5-thiol[12,22] (VII) in 456 cc. of water produced a brown solution. This solution was clarified with Darco (G-60) and diluted with 1300 cc. of ethanol. Benzyl chloride (575 g., 4.56 moles) was added rapidly with stirring. The thick reaction mixture which formed almost immediately was stirred and cooled for 30 minutes and then diluted with 2 l. of cold water. The solid was removed by filtration and washed with water and ether. VIII was obtained in 96% yield (973 g.), m.p. 159–161°, lit.[4] m.p. 157–158°.

2-Acetylamino-5-benzylmercapto-1,3,4-thiadiazole (VI). (a) **Acetylation of VIII.**—A slurry of 893 g. (4.0 moles) of VIII in 449 g. (4.4 moles) of acetic anhydride and 1500 cc. of acetic acid was heated over a free flame until solution occurred (5–10 minutes). The solution was cooled gradually and, at the first appearance of crystals, 2 l. of water was added. The suspension was cooled to 0° and 1028 g. (97%), m.p. 167–172°, of VI was removed by filtration.

(b) **Benzylation of IX.**—A suspension of 1.77 g. of IX[12,22] in 50 cc. of ethanol containing 0.23 g. of dissolved sodium was almost completely dissolved by the addition of 20 cc. of water. Benzyl chloride (2 g.) was added, and the mixture was agitated vigorously for 10 minutes before being allowed to stand at room temperature overnight. Dilution of the suspension with water gave a solid which was filtered off

(20) All melting points are corrected and were taken on a Fisher–Johns block.

(21) G. Pulvermacher, *Ber.*, **27**, 622 (1894).

(22) Supplied by the Fine Chemicals Division, American Cyanamid Co.

and recrystallized from 75 cc. of ethanol; 1.65 g. (62%) of VI was obtained, m.p. 164–166°.

Anal. Calcd. for $C_{11}H_{10}N_3OS_2$: C, 50.0; H, 3.81; N, 15.9. Found: C, 50.2; H, 3.62; N, 15.8.

The infrared spectra of VI prepared by these two procedures were identical.

2-Acetylamino-1,3,4-thiadiazole-5-sulfonamide (I).—A suspension of 0.50 g. of VI in 40 cc. of 50% acetic acid was chlorinated for 0.5 hour at 5°. The solid was filtered off after this time and added to 20 cc. of liquid ammonia. After evaporation of the ammonia and dilution of the dry residue with water, the aqueous solution was filtered. Acidification with hydrochloric acid gave 270 mg. (70%) of I, m.p. 260–261° dec. Mixed m.p. with an authentic sample of I[2] was not depressed, and the infrared spectra were identical.

2-Ethylamino-5-benzylmercapto-1,3,4-thiadiazole (X).—A solution of 4.0 g. of lithium aluminum hydride was prepared by stirring the gray solid with 250 cc. of absolute ether for 1 hour in a flask equipped with a Hershberg stirrer and a condenser fitted with a calcium sulfate drying tube. A slurry of 2.67 g. of VI in 100 cc. of anhydrous ether was added portionwise. A vigorous evolution of gas followed each addition. The mixture was held at reflux for 3 hours before the excess lithium aluminum hydride was decomposed by the addition of 50 cc. of ethyl acetate. Further decomposition was effected by the addition of 10 cc. of water. Addition of 75 cc. of 4 *N* sodium hydroxide did not cause separation of two clear layers, but the ethereal layer could be decanted from the lower flocculent precipitate. Evaporation of the ether afforded a white crystalline solid which, when recrystallized from alcohol, gave 1.58 g. (41%), m.p. 120–121°, of X.

Anal. Calcd. for $C_{11}H_{13}N_3S_2$: C, 52.6; H, 5.21; N, 16.7. Found: C, 52.6; H, 5.37; N, 16.6.

An authentic sample of X was prepared as follows: A solution of 2.5 g. of 2-ethylamino-1,3,4-thiadiazole-5-thiol (XI) was prepared by dissolving the solid in 10 cc. of water containing 1.02 g. of potassium hydroxide and diluting with 10 cc. of ethanol. Benzyl chloride (1.95 g.) in 20 cc. of ethanol was added, and the mixture was allowed to remain at room temperature overnight. The solution was concentrated to a small volume and the resulting precipitate was filtered off. The crude solid (4.2 g. (100%), m.p. 118–120°) was crystallized from 70 cc. of absolute alcohol to give X, 2.3 g. (60%), m.p. 121.5–122°.

The infrared spectra of X prepared by *benzylation of XI* and by *reduction of VI* were identical.

2-Methylamino-5-benzylmercapto-1,3,4-thiadiazole (XVII).—In a solution of 3.3 g. of potassium hydroxide (0.05 mole of 85%) in 25 cc. of water there was dissolved 7.3 g. (0.05 mole) of III. Benzyl chloride (6.3 g., 0.05 mole) was added, along with sufficient alcohol to create a homogeneous solution. This reaction mixture was allowed to remain at room temperature for 2 days, during which time solid was deposited. The crude solid, m.p. 85–87°, was filtered off and recrystallized from 50 cc. of 50% alcohol to give 7.0 g. (59%), m.p. 88.5–90°, of XVII.

Anal. Calcd. for $C_{10}H_{11}N_3S_2$: C, 50.6; H, 4.67; N, 17.7. Found: C, 50.3; H, 4.62; N, 17.5.

2-(N-Methylacetamido)-5-benzylmercapto-1,3,4-thiadiazole (V). (a) **Benzylation of IV.**—A solution of 1.89 g. (0.01 mole) of IV in 25 cc. of alcohol and 2 cc. of water containing 0.56 g. of potassium hydroxide was allowed to stand overnight at room temperature with 1.26 g. of benzyl chloride. After being concentrated in an air stream, the resultant oil was diluted with water; after a short time the oil solidified. The solid was filtered off, air-dried and crystallized from 10 cc. of methanol giving V, 1.18 g. (42%), m.p. 94–96°.

Anal. Calcd. for $C_{12}H_{13}N_3OS_2$: C, 51.6; H, 4.67; N, 15.1. Found: C, 51.7; H, 4.91; N, 15.2.

(b) **Acetylation of XVII.**—A solution of 580 mg. of XVII in 5 cc. of glacial acetic acid containing 0.5 cc. of acetic anhydride was warmed on the steam-bath for 1 hour. The solution was poured into cold water and the resulting precipitate was filtered off and air-dried yielding 700 mg. (100%), m.p. 94–96°, of V. This material was identical in m.p. and infrared with the substance prepared by benzylation of IV.

(c) **Methylation of VI.**—A solution of potassium *t*-butoxide in *t*-butyl alcohol was prepared by dissolving 4.0 g. of potassium metal in 150 cc. of *t*-butyl alcohol, previously dried over anhydrous calcium sulfate (Drierite). VI (26.7 g., 0.1 mole) was added to the hot solution but did not dissolve, although it appeared to change character. A solution of 15 g. (0.1 mole) of methyl iodide in 50 cc. of *t*-butyl alcohol was added, reflux being maintained for 5 hours. The suspension became pink and the solid gradually thinned out. The suspension was filtered hot and the filtrate was diluted with about 600 cc. of ice. The gummy mass was adjusted to about *p*H 7 (*p*H paper) by the addition of a few drops of concentrated hydrochloric acid, and after a short time solidification occurred. The solid was removed by filtration and dried in air. V (24.7 g. (87%), m.p. 73–83°) was obtained and was recrystallized from 150 cc. of methanol. The 15.7 g. (55%), m.p. 91–95°, so obtained was recrystallized twice from methanol to give pure V, m.p. 93–94° (8.9 g., 31%). The infrared spectrum was identical with the spectra of V prepared from IV or XVII.

Oxidative Chlorination of V.—A suspension of 2.79 g. (0.01 mole) of V in 28 cc. of 33% acetic acid was chlorinated for 1.25 hours, while the mixture was stirred and cooled to 5°. The sulfonyl chloride was filtered off, washed with water, dried in a desiccator for 1 hour and added portionwise to about 30 cc. of liquid ammonia in a nitrogen atmosphere. After the evaporation of the excess ammonia, the solid residue was triturated with 20 cc. of water and removed by filtration. The filtrate was acidified giving 0.51 g. of II, m.p. 209–212°. The insoluble portion, 0.88 g., m.p. 206–213°, and the product from the filtrate were crystallized separately from water giving 0.63 g., m.p. 214–217.5°, and 0.40 g., m.p. 215–217°, respectively. The combined yield was 1.03 g. (44%). Both samples were identical in m.p. and infrared spectra with II prepared from IV.

5-Acetylimino-4-methyl-2-benzylmercapto-Δ^2-1,3,4-thiadiazoline (XII).—A solution of 26.5 g. (0.1 mole) of VI in 200 cc. of methanol containing 2.5 g. of dissolved sodium was boiled for 3 hours in a flask fitted with a Dry Ice condenser while a stream of methyl bromide was introduced. The solution was held at room temperature overnight and then concentrated to a small volume. Dilution with water gave 16.2 g. (58%), m.p. 60–80°, of a sticky solid which was slurried with 4 *N* sodium hydroxide to remove unreacted VI. This treatment improved the quality (m.p. 75–80°, 12.1 g. (43%)) and subsequent recrystallization from 40 cc. of methanol gave 7.6 g. (27%) of XII, m.p. 84–85°.

Anal. Calcd. for $C_{12}H_{13}N_3OS_2$: C, 51.6; H, 4.69; N, 15.0. Found: C, 51.7; H, 4.67; N, 15.1.

In subsequent experiments it was found to be more convenient to alkylate in aqueous potassium hydroxide using dimethyl sulfate.

Compound VI (106.1 g., 0.4 mole) was dissolved in 200 cc. of water containing 26.2 g. (0.467 mole) of 85% potassium hydroxide by stirring at 30° for 5–10 minutes. The solution was diluted with 200 cc. of 95% ethanol, and after a few minutes of additional stirring, 52 g. (0.42 mole) of dimethyl sulfate was added rapidly in one portion. The solution became yellow and after 1–2 minutes an oil separated. The mixture was heated at reflux for 5 minutes and then cooled to 15° before being diluted with 200 cc. of cold 4 *N* sodium hydroxide. After solidification had begun, 200–300 cc. of water was added. The slurry was stirred and cooled for 1 hour before filtering. The product was washed with 1–1.5 liters of water and dried to constant weight in air, giving 80.0 g. (71%) of XII, m.p. 66–74°. This material, though malodorous, is suitable for oxidative chlorination, but purification may be effected by crystallization from methanol.

5-Imino-4-methyl-2-benzylmercapto-Δ^2-1,3,4-thiadiazoline Hydrochloride (XVI).—A solution of 500 mg. of XII in 10 cc. of ethanol containing 1 cc. of concentrated hydrochloric acid was heated on the steam-bath for 10 minutes until most of the ethanol had evaporated. On cooling, beautiful plates of XVI crystallized, m.p. 207–209° dec., in quantitative yield. Recrystallization from 10 cc. of ethanol and 1 cc. of concentrated hydrochloric acid produced the analytical sample, m.p. 210–212° dec.

Anal. Calcd. for $C_{10}H_{12}ClN_3S_2$: C, 43.9; H, 4.42; N, 15.4. Found: C, 43.7; H, 4.54; N, 15.1.

A solution of 100 mg. of XVI was heated for 1 hour on the steam-bath with 2 cc. of glacial acetic acid containing

0.2 cc. of acetic anhydride. Dilution of the solution with water produced XII in 90% yield, m.p. 80–82°. The infrared spectrum was identical and the mixed m.p. was not depressed when this sample was compared with authentic XII.

5-Acetylimino-4-methyl-Δ²-1,3,4-thiadiazoline-2-sulfonyl Chloride.—A solution of 11.2 g. (0.042 mole) of XII, m.p. 82–84°, in 40 cc. of glacial acetic acid containing 4 cc. of water was cooled to 15°. Chlorine gas was introduced rapidly for 10 minutes during which time the temperature was maintained at 25°. The completion of the reaction was noted by a rapid fall in temperature. The solution was poured onto 200 cc. of ice-water and the resulting sulfonyl chloride was removed by filtration. The precipitate was washed with water and pressed dry (to remove the benzyl chloride) before it was triturated with a minimum quantity of cold ether. The sulfonyl chloride was obtained in 76% yield (8.1 g.), m.p. 103–106°.[23] An analytical sample, m.p. 106–107°, was prepared by recrystallizing the crude material from heptane or ether.

Anal. Calcd. for $C_5H_6ClN_3O_3S_2$: C, 23.5; H, 2.37; N, 16.4. Found: C, 23.4; H, 2.52; N, 16.4.

In numerous other experiments, using poorer quality XII (m.p. *ca.* 60–80°), good quality sulfonyl chloride was obtained in yields of 50–80%. The yields were better on a larger scale because less was lost on trituration with ether.

5-Acetylimino-4-methyl-Δ²-1,3,4-thiadiazoline-2-sulfonamide (XIII).—To 500 cc. of liquid ammonia contained in a 3-necked r.b. flask fitted with a Hershberg stirrer there was added portionwise 69 g. (0.27 mole) of sulfonyl chloride. After the addition was complete the ammonia was evaporated by warming the flask with a stream of water. The last traces of ammonia were removed *in vacuo* and the solid residue was redissolved in 750 cc. of water by stirring for about 10 minutes. The solution was clarified with 15 g. of Darco (G-60), and after filtration was cooled and acidified to *p*H 4 with concentrated hydrochloric acid. XIII was filtered off and dried in a steam-oven; 59 g. (90%), m.p. 213–214° dec., was obtained.

Anal. Calcd. for $C_5H_8N_4O_3S_2$: C, 25.4; H, 3.41; N, 23.7. Found: C, 25.4; H, 3.42; N, 23.6.

Compound XIII may be recrystallized from water (30 cc./g.) or precipitated by acidification of the solution obtained by dissolving the sulfonamide in 1 *N* sodium hydroxide.

5-Imino-4-methyl-Δ²-1,3,4-thiadiazoline-2-sulfonamide Hydrochloride (XIV).—A solution of 0.50 g. (0.002 mole) of XIII in 10 cc. of ethanol and 1 cc. of concentrated hydrochloric acid was refluxed for 1 hour during which time a solid slowly deposited. Upon cooling the solution, the solid was filtered off and air-dried giving 0.40 g. (82%) of XIV.

Anal. Calcd. for $C_3H_7ClN_4O_2S_2$: C, 15.6; H, 3.06; N, 24.3; N-CH_3, 6.5. Found: C, 15.4; H, 3.51; N, 23.7; N-CH_3, 7.1. The Kuhn–Roth C-CH_3 was negative.

The free base XIVa, m.p. 135–141° dec., was obtained in 77% yield by dissolving the hydrochloride in 1 mole of 1 *N* sodium hydroxide. The product precipitated when the solution was cooled. A small sample was recrystallized from ethanol for analysis, m.p. 140–141.5° dec.

Anal. Calcd. for $C_3H_6N_4O_2S_2$: C, 18.6; H, 3.12; N, 28.8. Found: C, 18.6; H, 3.20; N, 28.8.

Compound XIV, 2.3 g. (0.01 mole), was heated for 2 hours on the steam-bath with 1.12 g. (0.011 mole) of acetic anhydride in 4 cc. of acetic acid. When the solution was diluted with water and cooled, 1.63 g. (69%), m.p. 212.5–213.5°, of XIII was obtained.

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(23) In two cases, a vigorous decomposition occurred when the crude, damp sulfonyl chloride was kept overnight in a desiccator. The recrystallized sample is stable.

[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Decomposition of 5-Substituted-3-nitroso-2-oxazolidones

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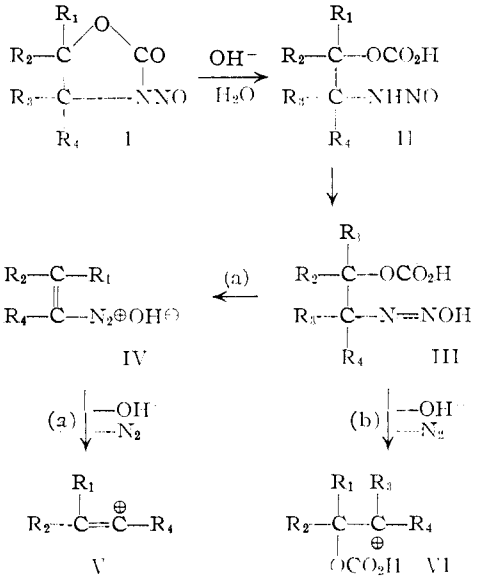
The significance of the fact that alkaline treatment of 3-nitrosopiro[fluorene-9',5-oxazolidin]-2-one (VII) yields mainly 9-(methoxymethylene)-fluorene (VIII) is discussed.

In previous papers the alkaline decompositions of 5,5-disubstituted-3-nitroso-2-oxazolidones[2] and of 4,4-disubstituted-3-nitroso-2-oxazolidones[3] were described. A mechanism, shown below, was proposed[2] and the products obtained in both studies were consistent with those to be expected.

Disregarding the timing of proton additions or removals, the first step was considered to be ring opening to a nitrosoamine II followed by tautomerism to an hydroxyazo intermediate III. This intermediate could go to an unsaturated diazonium hydroxide intermediate IV by base-catalyzed elimination of carbonic acid, followed by loss of nitrogen to yield the unsaturated carbonium ion V and thence to products. Path (a) is only possible if R_3 (at least) is hydrogen. Alternatively, III could lose nitrogen first to yield the saturated carbonium ion VI which then yields products. Path (b) is mandatory if neither R_3 nor R_4 is hydrogen and is always a possibility. In our work[3] with 4,4-disubstituted oxazolidones (I, R_3, $R_4 \neq H$) all of the products obtained could be accounted for by the mechanism proceeding *via* path (b). Since it



(1) Taken from the Ph.D. thesis of A. E. W., Ohio State, March, 1956. Union Carbide and Carbon Fellow, 1955–56.

(2) M. S. Newman and A. Kutner, THIS JOURNAL, **73**, 4199 (1951).

(3) M. S. Newman and W. M. Edwards, *ibid.*, **76**, 1840 (1954).