Synthesis of Several Mesoionic 1,3,4-Thiadiazoles

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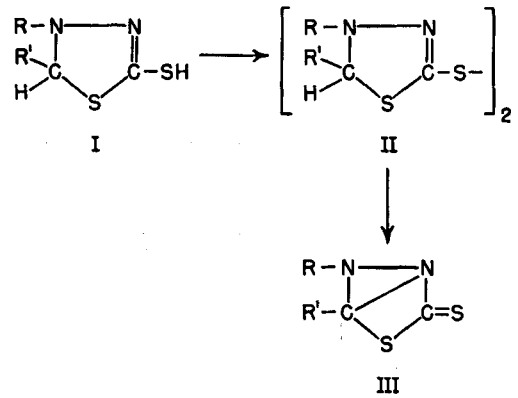
Several mesoionic 1,3,4-thiadiazoles, more properly termed anhydro-4-phenyl-5-substituted-2-thio-1-thia-3,4-diazolinium thiols, have been synthesized. Physical constants for the compounds have been determined and recorded. Preliminary screening against selected microorganisms indicated some useful inhibitory activity *in vitro*. The compounds were determined to have low intraperitoneal acute toxicity in the mouse.

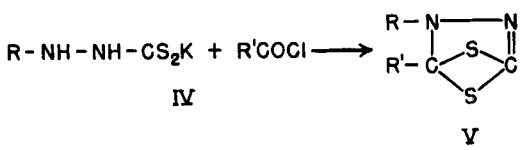
For the past several years, the authors have been engaged in a program of investigation of the mesoionic compounds. Initial interest was aroused by the unique chemical constitution of one of these compounds, the sydnones. The similarity of these compounds to existing medicinally active heterocycles, as well as the unique chemistry, led to the synthesis and study of the pharmacological activity of a number of sydnones. Efforts revealed interesting biological activity and structural dependence (1–3).

As an extension of the philosophy that unique chemical constitution may portend unusual biological properties, other mesoionic structures reported in the literature were reviewed. That each of these monocyclic mesoionic rings is isoelectronic with the pharmacologically potent sydnones, led to the concept that a bioisosterism may exist among monocyclic mesoionic ring systems, thus forming the justification for studying the potential pharmacological activity of these compounds.

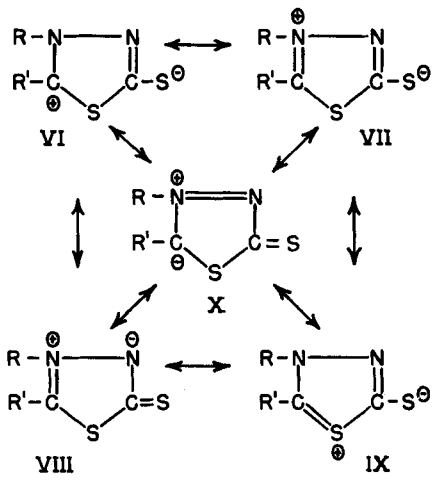
In 1895, Busch (4) noted that a thiadiazolinethiol (I) oxidized to its disulfide (II), underwent a disproportionation to give the original thiadiazolinethiol plus a new compound, which Busch concluded was III. (Scheme I.) Compound III was synthesized later by reaction of the potassium salt of an aryldithiocarbazinic acid (IV) with a carboxylic acid chloride (5). Busch subsequently revised his structural assignment to V and named these compounds endothiodihydrothiodiazoles (6). In 1938, Schoenberg (7), utilizing advances in chemical theory, claimed that such compounds described by Busch would be represented best by a hybrid structure involving charged forms. (Scheme II.) The endo structure (V) was held to be untenable on the basis of inability to conform to Bredt's rule, and the initial structure (III) was rejected on the basis of strain considerations. It was concluded that the compounds were resonance hybrids and should be represented by charged structures of which VI–X is only a partial list. (Scheme III.)



Scheme I



Scheme II



Scheme III

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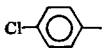
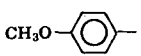
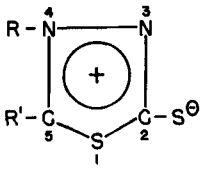
TABLE I.—CONSTANTS FOR 4-PHENYL-5-R MESOIONIC 1,3,4-THIADIAZOLES

R	Yield, %	M.p., °C.	I. R. Max., −thioketo	U. V. Max.	U. V. Max.	Anal. Calcd. C	H	N	S	Found C	H	N	S
CH_3—	82	219–221[a]	7.40	261 (ϵ = 12,000)	353 (ϵ = 3000)	51.89	3.87	13.45	30.79	51.86	3.73	13.60	30.00
CH_3—CH_2—	5	191–192	7.45	261 (ϵ = 11,500)	356 (ϵ = 3100)	54.02	4.53	12.60	28.84	53.84	4.60	12.43	28.96
$(CH_3)_2$—CH—	7	133–136	7.40	261 (ϵ = 11,000)	358 (ϵ = 3400)	55.90	5.12	11.85	27.13	55.98	5.21	11.79	27.26
CH_3—CH_2—CH_2—	52	162–163	7.45	261 (ϵ = 11,800)	358 (ϵ = 3400)	...	...	...	...	55.82	5.22	11.67	27.21
$(CH_3)_3$—C—	13	233–235	7.40	267 (ϵ = 10,000)	357 (ϵ = 3700)	57.56	5.64	11.19	25.61	57.48	5.73	10.94	25.75
CH_3—$(CH_2)_3$—	22	115–116	7.45	261 (ϵ = 11,600)	358 (ϵ = 3400)	...	...	...	...	57.73	5.48	11.49	25.55
CH_3—$(CH_2)_4$—	44	109–111	7.45	261 (ϵ = 11,700)	358 (ϵ = 3400)	59.05	6.10	10.59	24.25	58.96	6.14	10.44	24.01
	17	228–229[b]	7.50	275 (ϵ = 18,900)	...	62.19	3.73	10.36	23.72	62.40	3.48	10.04	23.22
	16	231–232[c]	7.55	278 (ϵ = 20,400)	...	55.16	2.98	9.19	21.04	54.98	2.88	9.03	21.05
	32	228–229	7.50	233 (ϵ = 14,600)	279 (ϵ = 14,200)	59.97	4.03	9.33	21.35	59.60	4.02	9.22	20.50
	19	221–224	7.55	260 (ϵ = 16,700)	...	55.16	2.98	9.19	21.04	55.10	2.92	9.36	20.85

[a] Lit. m.p. 216° (4). [b] Lit. m.p. 223–224° (4). [c] Lit. m.p. 233–234° (4).

Baker and Ollis (8) included these compounds in a broad classification termed "mesoionic." They defined this term as a five or six-membered heterocyclic compound which cannot be represented satisfactorily by any one covalent or polar structure. They possess a sextet of π electrons in association with all of the ring atoms; hence, they are aromatic. Finally, the ring bears a fractionally positive charge balanced by a corresponding negative charge on an exocyclic atom or group. The term mesoionic developed from the need to describe certain aromatic compounds whose chemical properties seem not to be in accord with the structural representations advanced at the time of their discovery. Under this terminology, a new notation was introduced to summarize the polar canonical forms which represent the compound. For the compounds first synthesized by Busch and later studied by Schoenberg, the presently accepted structural



XI

notation is XI, with the ring atoms numbered from the sulfur.

The nomenclature, essentially that used for the betaines, was recommended by Katritzky (9) for the mesoionic compounds. Compound XI, in which both R groups are phenyl, becomes anhydro - 4,5 - diphenyl - 2 - thio - 1 - thia - 3,4-diazolinium thiol. Baker and co-workers (10) called this compound ψ-4,5-diphenyl-2,4-dihydro-2-thio-1-thia-3,4-diazole. For expediency, these compounds will be referred to as mesoionic 1,3,4-thiadiazoles.

DISCUSSION

In this first study, a series of 4-phenyl-5-alkyl mesoionic 1,3,4-thiadiazoles were synthesized and studied. (See Table I.) The starting material, potassium phenyldithiocarbazinate (XII), was prepared in good yield—up to 88%, if water was scrupulously excluded. The reactions involved in its preparation are

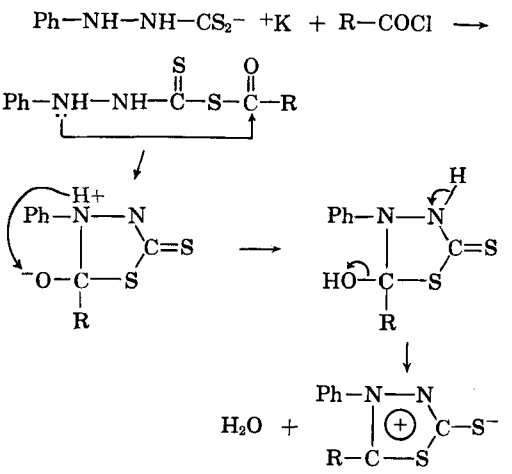
$$2\ \mathrm{Ph{-}NH{-}NH_2} + \mathrm{CS_2} \xrightarrow{\mathrm{EtOH}}$$

$$\mathrm{Ph{-}NH{-}NH{-}CS_2^-\ {}^+H_3N{-}NH{-}Ph} \xrightarrow[\mathrm{KOH}]{\mathrm{EtOH}}$$

$$\mathrm{Ph{-}NH{-}NH{-}CS_2^-\ {}^+K} + \mathrm{Ph{-}NH{-}NH_2} + \mathrm{H_2O}$$

XII

The mechanism of the reaction leading to the mesoionic 1,3,4-thiadiazole ring is unknown. It is not likely that acylation occurs on the α nitrogen since first, this would be a less basic point of attack than the dithiocarboxylic acid group, and second, ring closure would have to proceed through an isothiocyanate, thus eliminating one of the two necessary sulfur atoms. A more likely mechanism would be the formation of a mixed anhydride, analogous to that mechanism proven for the sydnones. Thus, for the formation of the mesoionic 1,3,4-thiadiazoles, a possible route of formation would be



In addition to being isoelectronic, hence possibly bioisosteric with the sydnones, the mesoionic 1,3,4-thiadiazoles presented a structural similarity to a

TABLE II.—SENSITIVITY OF MICROORGANISMS TO MESOIONIC 1,3,4-THIADIAZOLES

Compd. R	*S. aureus*	*D. pneumoniae*	*E. coli*
CH_3-	4	3	1
CH_3-CH_2-	4	3	0
$(CH_3)_2CH-$	4	3	1
$CH_3-CH_2-CH_2-$	4	3	0
$(CH_3)_2CH-C(CH_3)_2-$	1	1	0
$CH_3-(CH_2)_8-$	1	1	1
$CH_3-(CH_2)_4-$	0	0	0
C_6H_5-	1	1	1
$Cl-C_6H_4-$	1	1	0
$CH_3O-C_6H_4-$	1	1	0
ClC_6H_4-	0	0	0
Control	0	0	0
Ref. std., penicillin G	4	4	...

number of compounds known to possess bacteriostatic and bactericidal properties. Included in this group would be the nonmesoionic 1,3,4-thiadiazoles and the 1,3,5-thiadiazines. Therefore, a preliminary test was made against several microorganisms (Table II). It is interesting that in this series of compounds, appreciable activity resided in compounds not bulky in the 5 position. Any chain length above 3 or bulk greater than isopropyl caused a marked fall in activity. This lack of bulk and the planar cationic surface presented by the ring may be responsible for the antibacterial action. This is true of a large number of unrelated antibacterial agents. The presence of a bulky substituent may prevent a close approach of the cationic ring to the acceptor surface, thereby lowering or obliterating its activity.

Preliminary pharmacological studies in mice indicated a low order of acute intraperitoneal toxicity with doses up to 500 mg./Kg. for all of the compounds. Studies are being extended on these compounds and their biological activity.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary melting point apparatus. Microchemical analyses were performed by Weiler and Strauss, Oxford, England, and Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were determined on a Perkin-Elmer model 137. Ultraviolet spectra were determined on a Cary model 15. Melting points are uncorrected.

Potassium Phenyldithiocarbazinate.—Phenylhydrazine (32 Gm., 0.29 mole) was dissolved in 350 ml. of absolute ethanol; carbon disulfide (24 Gm., 0.31 mole) was added with stirring. A precipitate of the phenylhydrazinium salt of phenyldithiocarbazinic acid formed rapidly, accompanied by a slight evolution of heat. The mixture was allowed to cool, and potassium hydroxide (17 Gm., 0.31 mole) in 120 ml. of absolute ethanol was added. The initial precipitate dissolved, producing an orange solution, which soon deposited a voluminous precipitate of potassium phenyldithiocarbazinate. After 10 min., 100 ml. of anhydrous ether was added, and the mixture was stirred. The suspended material became blue-gray; but on refrigeration at −5° for 30 min., it became white or pale yellow. The solid was removed by filtration and washed with 300 ml. of anhydrous ether, giving an 88% yield, m.p. 144–146° dec. The amorphous material could not be purified further because of its lability to atmospheric decomposition. The material was used immediately or stored under nitrogen at −5° for short periods.

4-Phenyl-5-alkyl Mesoionic 1,3,4-Thiadiazoles.—Potassium phenyldithiocarbazinate (22.3 Gm., 0.1 mole) was suspended in 500 ml. of toluene. The stirred suspension was warmed to 60° and the proper acyl chloride (0.1 mole) added. In the case of the 5-methyl compound, the potassium salt was suspended in anhydrous ether and the temperature raised to 40°. In all cases, the addition of the acyl chloride was adjusted to a rate which maintained a yellow color in the reaction mixture. The temperature was maintained to within 5° of the stated temperature. After the addition, the reaction was allowed to cool. The mesoionic compound was filtered off, washed with water, and recrystallized from ethanol. For physical constants, see Table I.

4-Phenyl-5-aryl Mesoionic 1,3,4-Thiadiazoles.—The procedure used for the aryl derivatives was basically the same as for the 5-alkyl compounds, except for the use of water to dissolve the potassium phenyldithiocarbazinate. The appropriate acyl chloride was added to this solution at a rate of 2 to 4 drops per minute at room temperature with vigorous stirring. A solid formed during the addition, which was washed with 5% sodium bicarbonate solution, then absolute ethanol. The compounds were recrystallized from hot chloroform–ethanol. For physical constants, see Table I.

Microbiological Screening.—The test organisms selected were two Gram-positive cocci, *Staphylococcus aureus* and *Diplococcus pneumoniae*, and a Gram-negative bacillus, *Escherichia coli*. The organisms were cultured in a Difco nutrient broth and incubated at 37° for 48 hr. prior to use. A standard brain heart infusion agar was used as the medium for sensitivity tests. Absorbent paper disks were saturated with the mesoionic compound, sterilized, then incubated with the agar test medium for 24 hr. at 37°. The sensitivity is measured as a zone of inhibition of growth around the test disk. Penicillin G potassium was used as the reference standard, giving a zone of inhibition defined as 4, a blank disk was used as a control, giving a zone of inhibition defined as 0. The results are summarized in Table II.

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