5-Isonitrosorhodanines

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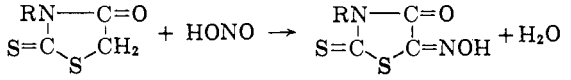
3-Substituted rhodanines were converted to their 5-isonitroso derivatives by reaction with isopropyl nitrite and hydrochloric acid. The 3-benzyl-5-isonitrosorhodanines, which contain a chlorine substituent in the *para* position of the benzyl group, show a considerable increase in fungistatic activity over the corresponding 3-chlorinated benzylrhodanine while the accompanying loss in bacteriostatic activity is relatively slight. Such enhancement is not produced by the presence of 5-ethoxymethylene or 5-dimethylaminomethylene substituents in 3-(*p*-chlorobenzyl)rhodanine.

In an earlier communication,[1] the activity of various 3-phenylrhodanines in inhibiting the growth of *Aspergillus niger* and of 3-benzylrhodanines in inhibiting the growth of *Bacillus subtilis* and, more significantly, *Escherichia coli* was reported. In general, the 3-phenylrhodanines, even those which are effective in suppressing the growth of *A. niger*, show little bacteriostatic activity and the effective bacteriostatic 3-benzylrhodanines little fungistatic activity.

Some knowledge of the effect of further modification of the structure of the 3-substituted rhodanines on the fungistatic and bacteriostatic activity of the molecule seemed desirable. Reactions which involve the methylene group in the 5-position of the rhodanine lead to products which retain the thiazolidinone nucleus and its 3-substituent. Nitrosation is such a reaction and with rhodanine or a 3-substituted rhodanine forms the 5-isonitroso derivative.

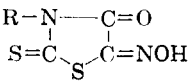


The isonitroso derivatives of rhodanine and of 3-phenylrhodanine were prepared by Gränacher,[2] who used amyl nitrite and hydrochloric acid as the source of the nitrous acid. We have repeated his work and extended it to other 3-substituted rhodanines. In our work we have found that it is advantageous to substitute isopropyl nitrite for amyl nitrite. Table I gives the yields, melting points and analytical data

(1) F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum, and P. Wilder, Jr., *J. Am. Chem. Soc.*, **78**, 384 (1956). See also F. C. Brown, *Chem. Rev.*, **61**, 463 (1961), especially pages 508–510.

(2) C. Gränacher, H. Reis, and E. Pool, *Helv. Chim. Acta*, **5**, 382 (1922).

TABLE I



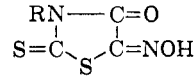
5-ISONITROSORHODANINES

R	M.p., °C.	Yield, %[a]	Formula	Analyses, %: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
H	157–158[b]	39[c]	$C_3H_2N_2O_2S_2$	22.22	22.28	1.24	1.3	17.28	17.55
CH_3	180–180.5	50	$C_4H_4N_2O_2S_2$	27.26	27.53	2.29	2.06	15.90	15.73
CH_2=$CHCH_2$	140–141.5	84	$C_6H_6N_2O_2S_2$	35.63	35.90	2.99	2.99	13.85	14.08
C_6H_5	224–225[d]	42	$C_9H_6N_2O_2S_2$	45.36	45.46	2.54	2.42	11.76	11.91
p-ClC_6H_4	211–212	50[e]	$C_9H_5ClN_2O_2S_2$	39.63	40.32	1.88	2.00	10.27	10.74
$C_6H_5CH_2$	188.5–190	76	$C_{10}H_8N_2O_2S_2$	47.59	77.84	3.19	3.32	11.10	11.04
o-$ClC_6H_4CH_2$	198–200 dec.	89	$C_{10}H_7ClN_2O_2S_2$	41.88	41.95	2.46	2.26		
p-$ClC_6H_4CH_2$	182–184	95	$C_{10}H_7ClN_2O_2S_2$	41.88	41.71	2.46	2.40	9.77	9.98
2,4-Dichlorobenzyl	199–201	46[e]	$C_{10}H_6Cl_2N_2O_2S_2$	37.39	37.54	1.88	1.99		
3,4-Dichlorobenzyl	167–168.5	99[f]	$C_{10}H_6Cl_2N_2O_2S_2$	37.39	38.19	1.88	1.69	8.72	8.54
p-$CH_3C_6H_4CH_2$	211–212	77	$C_{11}H_{10}N_2O_2S_2$	49.60	49.51	3.78	3.85		
p-$CH_3OC_6H_4CH_2$	177–178	40[g]	$C_{11}H_{10}N_2O_3S_2$	46.79	46.93	3.57	3.42	9.92	9.87
p-$FC_6H_4CH_2$	191–192	77	$C_{10}H_7FN_2O_2S_2$	44.42	44.62	2.61	2.41	10.36	10.19
Cyclohexyl[h]	201–202	65	$C_9H_{12}N_2O_2S_2$	44.24	44.17	4.95	4.92		
2-Furyl	164.5–166.5	89[f]	$C_8H_6N_2O_3S_2$	39.66	39.60	2.50	2.73		
2-Thenyl	175–176	86	$C_8H_6N_2O_2S_3$	37.19	37.22	2.34	2.13	10.85	10.75
5-Chloro-2-thenyl	178.5–180.5 dec.	69	$C_8H_5ClN_2O_2S_3$	32.82	32.72	1.72	1.61	9.57	9.55

[a] After one recrystallization unless otherwise noted. [b] Reference 2 reports m.p. 151–153° with sintering at 147°. [c] Recrystallized from dil. HCl. [d] Reference 2 reports m.p. 177–181° dec. A repetition of this experiment yielded a compound which started to melt at 177° and melted completely at 219°. [e] After two recrystallizations. [f] Crude yield. [g] After three recrystallizations. [h] Prepared by Margaret Skorvaga Walker.

TABLE II

FUNGISTATIC AND BACTERIOSTATIC ACTIVITIES OF 3-SUBSTITUTED-5-ISONITROSORHODANINES



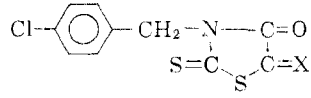
R	*A. niger* % inhibition at varying concn., p.p.m. 250	200	100	50	25	10	Lowest concn., p.p.m. giving complete inhibition—*B. subtilis*	*E. coli*
Hydrogen	7						100	>250
Methyl	3						>250	>250
Allyl	60						>250	>250
Phenyl	20						250	>250
	42							
p-Chlorophenyl	100	100	78	65	60	56	100	200
Benzyl	100	100	100	39	19	12	250	<250
o-Chlorobenzyl	42						100	>250
p-Chlorobenzyl	100	100	100	100	100	38	25	50
2,4-Dichlorobenzyl	100	46	49	65	47	38	25	>250
3,4-Dichlorobenzyl	100	69	81	46	23	19	<10	100
p-Methylbenzyl	45						200	200
p-Methoxybenzyl	47						250	>250
p-Fluorobenzyl	100	50	20				100	100
Cyclohexyl	63						100	>250
2-Furyl	48						>250	>250
2-Thenyl	100	66	33	19	13	3	200	>250
5-Chloro-2-thenyl	66	63	57	68	39	15	50	100

for seventeen 3-substituted-5-isonitrosorhodanines. The 5-ethoxymethylene and 5-dimethylaminomethylene derivatives of 3-(*p*-chlorobenzyl)rhodanine were also prepared.

As our interest is directed primarily toward the synthesis of compounds showing fungistatic activity, we are concerned with the possible enhancement of fungistatic activity of the 3-substituted benzylrhodanines. The data on the activity of the 3-substituted 5-isonitrosorhodanines toward *A. niger* and toward *B. subtilis* and *E. coli* are reported in Table II. Those 5-isonitroso compounds whose benzyl group contains a chlorine atom in the *para* position show a considerable increase in fungistatic power on the introduction of the isonitroso group in the 5-position while accompanying loss in bacteriostatic power is relatively slight. That the unsaturation of the carbon atom in the 5-position is an insufficient explanation of the increased activity is evident from the results in Table III, in which the ethoxymethylene derivative shows approximately the same slight fungistatic

TABLE III

DERIVATIVES OF 3-(*p*-CHLOROBENZYL)RHODANINE



X	*A. niger* % inhibition at 250 ppm.	Lowest concn. giving 100% inhibition, p.p.m. *A. niger*	*B. subtilis*	*E. coli*
Hydrogen (from ref. 1)	52	>250	2.5	10
Isonitroso	100	25	25	50
Ethoxymethylene	71	>250	>250	>250
Dimethylamino-methylene	4	>250	>250	>250

activity as the parent compound, and at the same time loses the bacteriostatic property of 3-(*p*-chlorobenzyl)rhodanine, while the presence of a dimethylaminomethylene substituent destroys both fungistatic and bacteriostatic activity.

Experimental

Rhodanine or its 3-substituted derivative (3.0 g.), 15 ml. of cold absolute ethanol (commercial) saturated with HCl and 30 ml. of absolute ethanol were mixed, and the solution was warmed gently on a steam bath until the rhodanine dissolved. Isopropyl nitrite[3] (15 ml.) was then added dropwise over a period of 15 min. to the warm solution. The solution darkened upon addition of the isopropyl nitrite but cleared upon swirling. It was then poured into ice water and allowed to stand for several min. In some cases, the solvent was partially evaporated under vacuum. The yellow precipitate was filtered and recrystallized from methanol. Data for the isonitroso derivatives of various 3-substituted rhodanines are assembled in Table I. Since our object was to prepare pure samples for microbiological testing, efforts to obtain the maximum yield possible for each compound were not made.

3-(*p*-Chlorobenzyl)-5-ethoxymethylenerhodanine.—The procedure of Knott[4] was used for this compound and the next one. From 12.8 g. of 3-(*p*-chlorobenzyl)-rhodanine, 28 ml. of freshly distilled ethyl orthoformate and 40 ml. of acetic anhydride, 12 g. (77% yield) of product melting at 121–123° was obtained after one recrystallization from isopropyl alcohol. The analytical sample after recrystallization from ligroin melted at 122–123°.

Anal. Calcd. for $C_{13}H_{12}ClNO_2S_2$: C, 49.85; H, 3.86; N, 4.37. Found: C, 50.06; H, 3.91; N, 4.29.

From this compound in ethanol solution and dimethylamine, a 70% yield (after one recrystallization from acetone–ethanol) of 3-(*p*-chlorobenzyl)-5-dimethylaminomethylenerhodanine melting at 217–218° was obtained.

(3) "Organic Syntheses," Collective Volume III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 192.

(4) E. B. Knott, *J. Chem. Soc.*, 1482 (1954).

Anal. Calcd. for $C_{13}H_{13}ClN_2OS_2$: C, 48.78; H, 4.19; N, 8.96. Found: C, 48.84; H, 4.03; N, 8.78.

Fungistatic and bacteriostatic assays were performed by a serial dilution method which has been described previously.[1]

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2-Substituted Cyclopropylamines. I. Derivatives and Analogs of 2-Phenylcyclopropylamine

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A series of analogs and derivatives of 2-phenylcyclopropylamine has been prepared in order to study relationships between chemical structure and monoamine oxidase inhibiting activity.

trans-2-Phenylcyclopropylamine[4,5] is a potent monoamine oxidase (MAO) inhibitor[6] and a clinically useful antidepressant agent. To investigate the effect of structure upon MAO inhibitory activity we have studied numerous analogs, homologs, isomers, and derivatives of this drug. Their preparation is reported in this paper; their biological activity is presented in the following article.

(1) Smith Kline and French Laboratories Postdoctoral Fellow, 1960.
(2) Smith Kline and French Laboratories Postdoctoral Fellow, 1961–1962.
(3) Smith Kline and French Laboratories Postdoctoral Fellow, 1958–1960.
(4) A. Burger and W. L. Yost, *J. Am. Chem. Soc.*, **70**, 2198 (1948).
(5) Tranylcypromine, Parnate®.
(6) R. E. Tedeschi, D. H. Tedeschi, P. L. Ames, L. Cook, P. A. Mattis, and E. J. Fellows, *Proc. Soc. Exptl. Biol. Med.*, **102**, 380 (1959); D. H. Tedeschi, R. E. Tedeschi, and E. J. Fellows, *J. Pharmacol. Exptl. Therap.*, **126**, 223 (1959); H. Green and R. W. Erickson, *ibid.*, **129**, 237 (1960).