Isothiazoles III: 2-Carbamoyl-4-isothiazolin-3-ones

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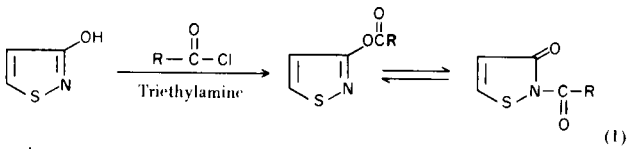
The reaction of several 3-hydroxyisothiazoles with alkyl and aryl isocyanates has given high yields of 2-carbamoyl-4-isothiazolin-3-ones as the only isolable products. Reaction with an isothiocyanate, however, afforded a mixture of the isomeric 2-thiocarbamoyl-4-isothiazolin-3-one and 3-isothiazolyl thiocarbamate.

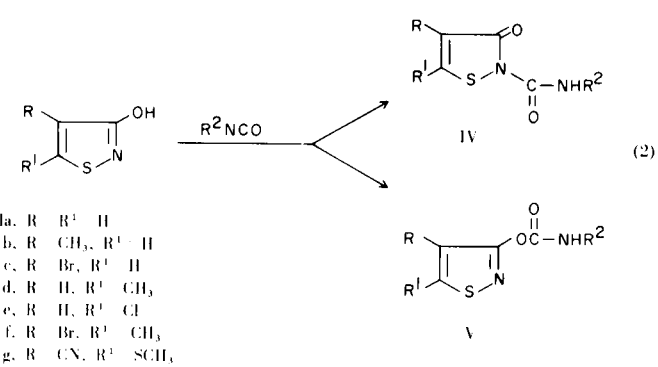
Recent interest (1a-c) in the chemistry of 3-hydroxyisothiazoles prompts us to report our work on their reaction with alkyl and aryl isocyanates as a preparative source of 2-carbamoyl-4-isothiazolin-3-ones.

Chan and Crow (1b) have reported that acylation of Ia, under conditions of kinetic control, gave 3-acyloxyisothiazoles (II) almost exclusively; subsequently O → N acyl migration then provided an equilibrated product distribution of II and III which varied with the nature of the acyl group (eq. 1). In contrast to this experience, we



Ia II III (1)

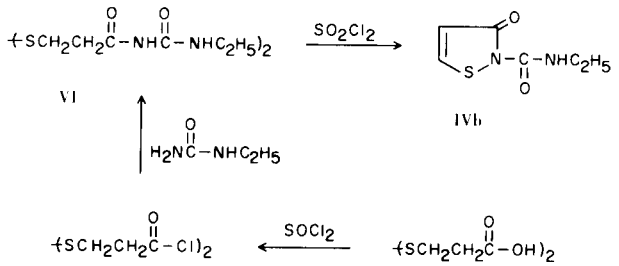
have found that the reaction of 3-hydroxyisothiazoles (Ia-g) with a comprehensive series of isocyanates (eq. 2) gives, in every instance, a high yield of a single adduct. These adducts have been assigned the *N*-carbamoyl structure IV by virtue of strong infrared absorption at both 5.80-5.90 μ (carbamoyl C=O) and 6.0-6.2 μ (ring C=O) and identity with the same compounds independently prepared by the halogenative cyclization of 3,3'-dithiodipropionimides VI (Scheme I -- see first paper in this series (2)).



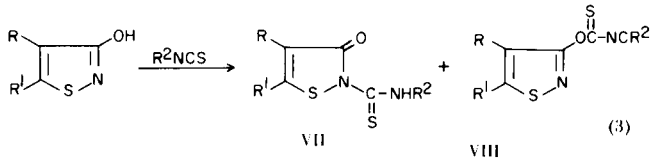
IV V (2)

Ia, R = R¹ = H
b, R = CH₃, R¹ = H
c, R = Br, R¹ = H
d, R = H, R¹ = CH₃
e, R = H, R¹ = Cl
f, R = Br, R¹ = CH₃
g, R = CN, R¹ = SCH₃

SCHEME I



Reaction of Ia and Ic with isothiocyanates (eq. 3) afforded only poor yields of the purified *N*-thiocarbamoyl adducts (VIIa - 24%; VIIb - 17%) as indicated by strong carbonyl absorption at 6.05 μ (ring C=O). Spectral and elemental analysis of the crude product obtained in 85% yield from Id showed it to be a 2:1 mixture of the isomers VIIc and VIIIc. NMR (deuteriochloroform) spectra



VII VIII (3)

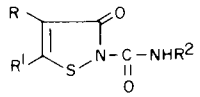
Ia, R = R¹ = H
c, R = Br, R¹ = H
d, R = H, R¹ = CH₃

a, R = R¹ = H, R² = CH₃
b, R = Br, R¹ = H, R² = C₄H₉-*n*
c, R = H, R¹ = CH₃, R² = C₂H₅

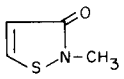
clearly distinguished the 4-proton absorptions of VIIc (δ 5.87, m) and VIIIc (δ 6.08, m), assigned in agreement with the 4-proton relationship displayed by the model compounds IX (2) and X (3) at δ 6.05 (d, $J_{4,5}$ 6.0 Hz) and δ 6.51 (d, $J_{4,5}$ 5.0 Hz) and the N and O acetyl derivatives III and II (R = CH_3) at δ 6.25 and 6.98, respectively (1b).

TABLE I

2-Carbamoyl-4-isothiazolin-3-ones (IV)



Compound	R	R^1	R^2	M.p. °C	% Yield	Formula	Elemental Analysis, % Calcd C	H	N	S	Found C	H	N	S
IVa	H	H	CH_3	138-140	70	$C_5H_6N_2O_2S$	37.98	3.80	17.72	20.25	38.16	4.04	17.45	20.24
b	H	H	C_2H_5	103-105	73	$C_6H_8N_2O_2S$	41.86	4.65	16.28	18.60	41.91	4.71	16.10	18.22
c	H	H	C_3H_7-*n*	84-88	69	$C_7H_{10}N_2O_2S$	45.16	5.39	15.05	17.21	45.06	5.39	14.66	16.90
d	H	H	C_3H_7-*i*	53-56	68	$C_7H_{10}N_2O_2S$	45.16	5.39	15.05	17.21	44.86	5.45	14.89	17.05
e	H	H	C_4H_9-*n*	oil	35	$C_8H_{12}N_2O_2S$	48.00	6.00	14.00	16.00	47.91	6.01	13.92	16.03
f	H	H	C_8H_{17}-*t*	oil	79	$C_{12}H_{20}N_2O_2S$	56.25	7.81	10.94	12.50	56.09	7.58	10.44	12.59
g	H	H	$C_{12}H_{25}$-*n*	60-62	100	$C_{16}H_{28}N_2O_2S$	61.54	8.97	8.97	10.26	61.41	8.84	8.90	10.12
h	H	H	$CH_2CO_2C_2H_5$	80-83	100	$C_8H_{10}N_2O_4S$	41.74	4.35		13.91	42.02	4.64		13.81
i	H	H	C_6H_4Cl-3	120-123	69	$C_{10}H_7ClN_2O_2S$	47.15	2.75	11.00	12.58	47.30	3.06	10.98	12.24
j	H	H	$C_6H_3Cl_2$-3,4	172-174	82	$C_{10}H_6Cl_2N_2O_2S$	41.52	2.08	9.69		41.51	2.10	9.67	
k	H	H	$C_6H_3Cl_2$-2,5	179-180	75	$C_{10}H_6Cl_2N_2O_2S$	41.52	2.08	9.69	11.07	41.41	2.27	9.77	10.89
l	H	H	$C_6H_4OCH_3$-4	134-137	62	$C_{11}H_{10}N_2O_3S$	52.80	4.00	11.20	12.80	52.88	4.19	11.23	12.68
m	H	H	$C_6H_4NO_2$-4	225-230	89	$C_{10}H_7N_3O_4S$	45.28	2.64	15.85	12.08	45.59	2.79	15.75	11.98
n	H	H	$C_6H_4NO_2$-3	195-198	92	$C_{10}H_7N_3O_4S$	45.28	2.64	15.85	12.08	45.07	2.68	15.79	11.89
o	H	H	$SO_2C_6H_4CH_3$-4	105-109	59	$C_{11}H_{10}N_2O_4S_2$	44.30	3.35	9.40		44.26	3.48	9.36	
p	CH_3	H	C_2H_5	54-57	64	$C_7H_{10}N_2O_2S$	45.16	5.38	15.05	17.20	45.07	5.78	15.03	16.81
q	Br	H	CH_3	194-197	97	$C_5H_5BrN_2O_2S$	25.32	2.11	11.81	13.50	25.74	2.21	11.60	13.73
r	H	CH_3	CH_3	138-145	93	$C_6H_8N_2O_2S$	41.86	4.65	16.28	18.60	41.55	4.63	15.60	18.23
s	H	CH_3	C_6H_5	148-151	70	$C_{11}H_{10}N_2O_2S$	56.41	4.28		13.68	56.70	4.46		13.45
t	H	CH_3	C_6H_4Cl-3	142-144	100	$C_{11}H_9ClN_2O_2S$	49.16	3.36	10.43	11.92	49.38	3.36	10.11	12.02
u	H	CH_3	C_6H_4Cl-2	162-164	72	$C_{11}H_9ClN_2O_2S$	49.16	3.36	10.43	11.92	49.45	3.58	10.78	11.72
v	H	CH_3	$C_6H_3Cl_2$-3,4	203-209	91	$C_{11}H_8Cl_2N_2O_2S$	43.56	2.63	9.24	10.56	43.27	2.74	9.25	10.28
w	H	CH_3	$SO_2C_6H_4CH_3$-4	170-173	88	$C_{12}H_{12}N_2O_4S_2$	46.15	3.85	8.97	20.51	46.18	4.03	9.01	20.92
x	H	Cl	C_2H_5	53-55	100	$C_6H_7ClN_2O_2S$	34.87	3.39	13.56	15.50	35.12	3.42	13.47	15.33
y	Br	CH_3	CH_3	190-196	83	$C_6H_7BrN_2O_2S$	28.68	2.79	11.16		28.74	2.98	10.90	
z	Br	CH_3	C_6H_4Cl-3	200-202	81	$C_{11}H_8BrClN_2O_2S$	38.64	2.04	7.65		38.32	2.37	7.86	
aa	Br	CH_3	$C_6H_3Cl_2$-3,4	235-237	90	$C_{11}H_8BrCl_2N_2O_2S$	34.46	2.09	7.31		34.42	1.84	7.20	
bb	Br	CH_3	$SO_2C_6H_4CH_3$-4	199-203	81	$C_{12}H_{11}BrN_2O_4S_2$	36.83	2.82	7.16	16.37	36.68	2.98	6.95	16.66
cc	CN	SCH_3	C_6H_5	183-186	90	$C_{12}H_9N_3O_2S_2$	49.48	3.09	14.43	21.99	49.31	3.16	14.51	21.90
dd	CN	SCH_3	C_6H_4Cl-3	192-194	90	$C_{12}H_8ClN_3O_2S_2$	44.24	2.45	12.89	19.66	44.43	2.57	12.78	19.94
ee	CN	SCH_3	$C_6H_3Cl_2$-3,4	118-120	90	$C_{12}H_7Cl_2N_3O_2S_2$	40.00	1.94	11.67	17.78	39.96	2.10	11.52	18.22
ff	CN	SCH_3	$SO_2C_6H_4CH_3$-4	163-168	68	$C_{13}H_{11}N_3O_4S_3$			11.38	26.02			11.65	26.01
gg	CN	SCH_3	CH_3	213-215	91	$C_7H_7N_3O_2S_2$	36.68	3.06	18.34	27.95	36.79	3.07	18.18	27.87



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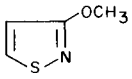

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EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian T-60 Spectrometer. Elemental analyses were performed by the analytical department of the Research Division of Rohm and Haas Company. The 3-hydroxyisothiazoles Ia-g were prepared according to published procedures (2,4a,b).

2-(*N*-Arylcarbamoyl)-4-isothiazolin-3-one (IV). The following procedure illustrates the general method.

The 3-hydroxyisothiazole (Ia-g), 0.10 mole, was placed in 250 ml. of dry benzene, and to this reaction mixture was added at 25° 0.10 mole of an arylisocyanate. The reaction was then stirred at 25° for 18 hours and the precipitate which formed was filtered, washed with benzene and dried. Compound IV obtained in this way was analyzed without further purification.

2-(*N*-Alkylcarbamoyl)-4-isothiazolin-3-one (IV). The following procedures illustrate the general methods.

A.

The 3-hydroxyisothiazole (Ia-g), 0.10 mole, was placed in 250 ml. of dry benzene and was treated at 25° with 0.10 mole of an alkylisocyanate in 25 ml. of benzene. The reaction solution was then stirred at 25° for 18 hours, after which time the solvent was removed under vacuum to give IV as a solid residue generally crystallizable from benzene-hexane.

B.

In the case of long carbon chain (C_8-C_{12}) alkylisocyanates, which were less reactive than the shorter chain homologs, 2 g. (0.02 mole) of triethylamine was added to the reaction, which otherwise was the same as method A.

2-(*N*-Methylthiocarbamoyl)-4-isothiazolin-3-one (VIIa).

A solution of 2.9 g. (28.7 mmoles) of Ia in 50 ml. of benzene was treated at 25° with 2.1 g. (28.7 mmoles) of methylisothiocyanate in 10 ml. of benzene. After heating at 55-60° for 10 hours the reaction solution was evaporated to a residue, which on crystallization from ethanol gave 1.2 g. (24%) of VIIa, m.p. 155-158° dec.; NMR (60 Mc in deuteriochloroform) δ 3.27 (d, CH_3), 6.28 (d, $J_{4,5}$ = 6.0 Hz, 4-H), 8.18 (d, $J_{4,5}$ = 6.0 Hz, 5-H), 11.2 (broad m, N-H).

Anal. Calcd. for $C_5H_6N_2OS_2$: C, 34.48; H, 3.45; N, 16.09. Found: C, 34.62; H, 3.66; N, 15.76.

4-Bromo-2-(*N*-*n*-butylthiocarbamoyl)-4-isothiazolin-3-one (VIIb).

To a mixture of 7.2 g. (0.04 mole) of Ic in 100 ml. of benzene was added 5 drops of triethylamine and 4.60 g. (0.04 mole) of *n*-butylisothiocyanate. The mixture was allowed to stir for three days at 25° and was refluxed then for one hour. The mixture was filtered, and the filtrate evaporated to a gummy solid residue. Crystallization of this material from boiling ligroin (60-90°) gave 2.0 g. (17%) of VIIb, m.p. 88-94°; NMR (60 Mc in deuteriochloroform) δ 8.28 (s, 5-H), 1.00 (m) 1.60 (m) 3.75 (q) (C_4H_9-*n*).

Anal. Calcd. for $C_8H_{11}BrN_2OS_2$: C, 32.54; H, 3.73; N, 9.49; S, 21.69. Found: C, 32.33; H, 3.95; N, 9.38; S, 21.26.

2-(*N*-Ethylthiocarbamoyl)-5-methyl-4-isothiazolin-3-one (VIIc) and 3-(5-Methylisothiazolyl)-*N*-ethylthiocarbamate (VIIIc).

A solution of 1.0 g. (8.7 mmoles) of Id and 0.76 g. (8.7 mmoles) of ethylisothiocyanate in 30 ml. of benzene was refluxed for 24 hours. After this time the reaction solution was evaporated to 1.5 g. (85%) of a solid product, m.p. 87-102°, which by NMR analysis was an isomer mixture of VIIc and VIIIc in an approximate ratio of 2:1; NMR (60 Mc in deuteriochloroform) δ 1.30 (t) 3.63 (m) (C_2H_5), 5.87 (m, 4-H of VIIc), 2.33 (d, 5-CH_3 of VIIc), 6.08 (m, 4-H of VIIIc), 2.45 (d, 5-CH_3 of VIIIc).

Anal. Calcd. for $C_7H_{10}N_2OS_2$: C, 41.58; H, 4.95; N, 13.86; S, 31.68. Found: C, 41.44; H, 4.86; N, 13.79; S, 31.60.

N,N'-Bis-ethylcarbamoyl-3,3'-dithiodipropionamide (VI).

To a mixture of 88 g. (1.0 mole) of ethylurea and 79 g. (1.0 mole) of pyridine in 1400 ml. of ethylene dichloride was added at 25-35°, 123.5 g. (0.50 mole) of 3,3'-dithiodipropionyl dichloride (2) over two hours. After two hours additional stirring the reaction slurry was filtered, and the precipitate was dried. The solid was then washed thoroughly with water and again dried to yield 150 g. (86%) of VI, m.p. 202-206° from dimethylformamide.

Anal. Calcd. for $C_{12}H_{22}N_4O_4S_2$: C, 41.15; H, 6.29; N, 16.00; S, 18.27. Found: C, 41.51; H, 6.20; N, 15.43; S, 18.41.

2-(*N*-Ethylcarbamoyl)-4-isothiazolin-3-one (IVb). Cyclization of amide-disulfide (VI).

To a slurry of 210 g. (0.60 mole) of VI in 2500 ml. of ethylene dichloride at 10-15° was added 243 g. (1.80 moles) of sulfuryl chloride over two hours. After 18 hours of additional stirring at 25°, the solvent was removed under vacuum to leave an oil residue. Toluene extraction at 70° of this residue, and evaporation of the toluene gave an oily solid which upon crystallization from benzene-ligroin (90-120°) gave 142 g. (69%) of IVb, m.p. 103-105°; NMR (60 Mc in deuteriochloroform) δ 7.91 (d, $J_{4,5}$ = 7.0 Hz, 5-H), 6.27 (d, $J_{4,5}$ = 7.0 Hz, 4-H), 1.25 (t) 3.47 (m) (C_2H_5), 8.87 (broad m, N-H); UV max (methanol) 290 mμ (ε 3.95).

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