[Chem. Pharm. Bull. 26(1) 314—317 (1978)]

UDC 547.496.3.04 : 547.381.04

Reaction of Biguanides and Related Compounds. XIV.[1] Cyclization of Amidinothioureas with Some Carbonyl Compounds

Mitsuru Furukawa, Tadashi Okawara, Yoshihide Noguchi, and Ryuichi Miyazaki

Faculty of Pharmaceutical Sciences, Kumamoto University[2]

(Received June 18, 1977)

The reaction of amidinothioureas (II) with aldehydes or acetone and with methyl chloroacetate were found to form 6-amino-4-mercapto-2-substituted 1,2-dihydro-1,3,5-triazines (III) and 2-guanidylidene-4-thiazolidones (V), respectively.

Keywords——1,3,5-triazines; amidinothioureas; 2,4-thiazolidinedione; 4-thiazolidones; methyl chloroacetate; benzaldehyde; biguanides; thioureas; cyclization

A number of previous workers have shown that the addition of biguanides to aldehydes, ketones and carboxylic esters is followed by the immediate cyclization of the intermediate to the corresponding amino-*s*-triazines.[3] In continuation of our works on the cyclization of biguanides (I) and its homologues, we investigated the reaction of amidinothioureas (II), in which the similar structural moiety to (I) is involved, with some carbonyl compounds.

I II

Chart 1

Reaction of Amidinothioureas with Aldehydes and Ketones

When equimolar quantities of II and benzaldehyde were heated in ethanol for three hours, a product was obtained in a comparatively good yield. By analogy with the reaction of I with ketones, the isomeric cyclization products, III and IV, due to the orientation of the cyclization, are possible to form in this case. The infrared (IR) spectra of the products exhibited the characteristic absorptions assignable to the amino and imino groups near 3440, 3240, and 3100 cm^{-1} and that due to the carbon-nitrogen double bond near 1620 cm^{-1}.

The elemental analysis of the products agreed with the possible compounds (III and IV). The similar cyclization of II with isobutylaldehyde and with acetone also proceeded under the similar conditions to give the corresponding similar products, whose IR absorption patterns were analogous to that of the reaction product with benzaldehyde.

Among the assigned structures (III and IV) for the product, the support for III was provided by the following considerations. It is known that the reaction of arylbiguanides with ketones gives 1-aryl-4,6-diamino-1,2-dihydro-1,3,5-triazines under the acid-catalyzed conditions and affords 4-amino-6-arylamino-1,2-dihydro-1,3,5-triazines under the base-catalyzed conditions.[4] The former is irreversibly converted into the latter by the treatment with alkali or fusion. The conversion is believed to proceed through cleavage followed by recyclization,[4] as shown in the following scheme.

1) Part XIII: M. Furukawa, T. Yoshida, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **23**, 580 (1974).
2) Location: *5-1 Oe-hon-machi, Kumamoto 862, Japan.*
3) *a*) E.J. Modest, "Heterocyclic Compounds," Vol. 7, ed. by R.C. Elderfield, ed. Wiley, New York and London, 1961, p. 627, 663; *b*) E.M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives," Interscience, New York, 1959, p. 239, 242, 258, 283.
4) E.J. Modest, *J. Org. Chem.*, **21**, 1 (1956); *b*) E.J. Modest and P. Levin, *J. Org. Chem.*, **21**, 14 (1956).

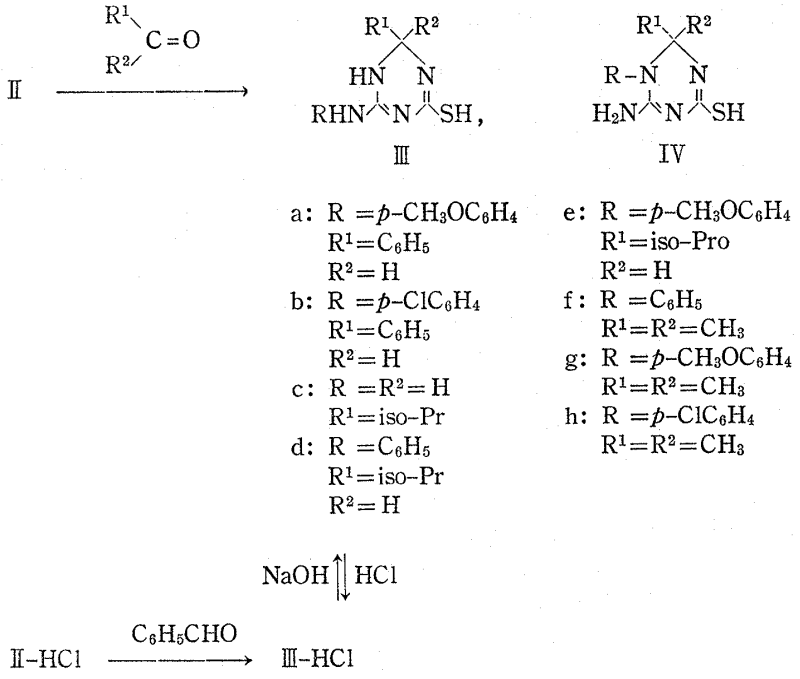


Chart 2

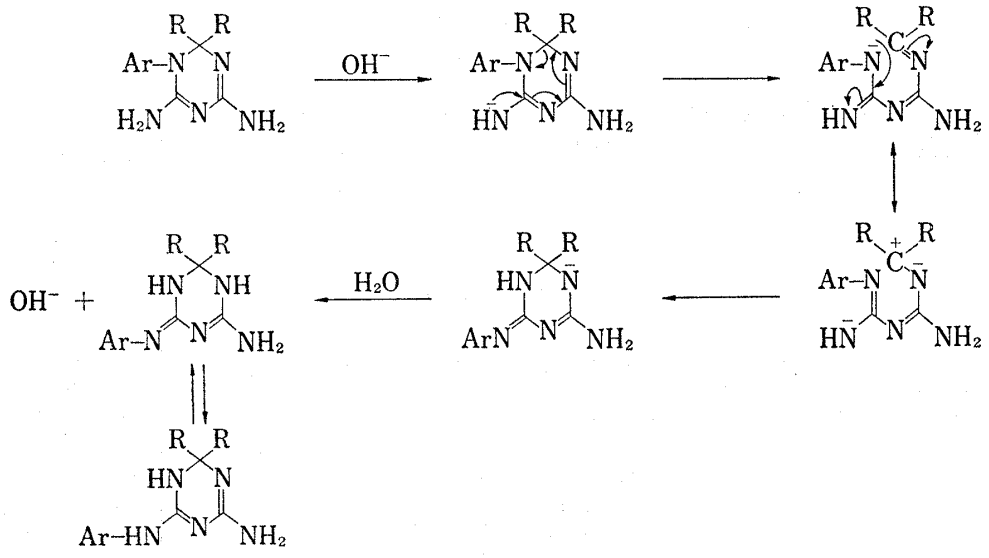


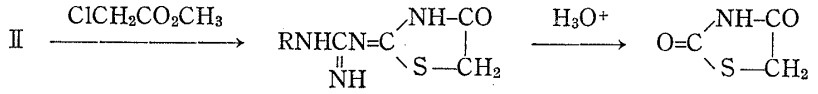
Chart 3

In our cases, the product was readily converted with hydrochloric acid into the hydrochloride, which was also prepared by heating the hydrochloride of II with benzaldehyde. The hydrochloride again underwent the facile conversion with alkali to the free base, which was identical with the above product. If the hydrochloride is the type of IV compound, the irreversible conversion into III might occur, because of the structural similarity to 1-aryl-4,6-diamino-1,2-dihydro-1,3,5-triazines described above. Another sufficient support for III was given by the result that the mass spectrum of the reaction product of II ($R=C_6H_5$) with isobutyraldehyde indicated the fragment ion peak, *m/e* 93, corresponding to aniline. This suggests that the anilino moiety should be involved as the substituent. By these results, it is reasonable to conclude that III would be more appropriate structure for the product.

Reaction of Amidinothioureas with Methyl Chloroacetate

It is reported that the biguanides reacted with ethyl chloroacetate to yield 2,4-diamino-6-chloromethyl-1,3,5-triazines.[5] On the other hand, thioureas react with chloroacetic acid to give thiazolidones,[6] which are formed by cyclization between the nitrogen and thiocarbonyl sulfur atoms in the thioureas. As II involves the structural fragments similar to both of biguanides and thioureas, the behaviors toward methyl chloroacetate are of much interest.

The reaction easily proceeded by treating II (R=*p*-$CH_3OC_6H_4$) with an equimolecular quantity of methyl chloroacetate in methanol at room temperature for two days. The mass spectrum of the product indicated the molecular ion to that of the condensation product of molecular equivalent of II (R=*p*-$CH_3OC_6H_4$) and methyl chloroacetate with loss of methanol and hydrochloric acid. The IR spectrum exhibited the characteristic absorption assignable to amine or imino group at 3200 and 3080 cm^{-1} and that due to the carbonyl group at 1670 cm^{-1}. By consideration of these spectral data and analytical data, a variety of five and seven membered ring structures are possible for the product. In order to elucidate the structure, the product was hydrolyzed with 18% hydrochloric acid under the reflux condition for 24 hours. In the result, 2,4-thiazolidinedione (VI) was obtained, which was confirmed by the comparison of the IR spectrum[7] with that of the authentic sample.



V a: R=H
b: R=*p*-$CH_3OC_6H_4$

VI

Chart 4

On the basis of these results, the product is undoubtedly presumed to be 2-(*p*-methoxyphenyl)guanidylidene-4-thiazolidone (Vb). The reaction of amidinothiourea (II, R=H) with methyl chloroacetate also proceeded similarly by heating in methanol for 3 hours to afford Va.

Experimental

All the melting points are uncorrected. IR spectra were measured on a JASCO IRA-1 Grating Infrared Spectrometer. Mass spectra were determined at 75 eV on a JEOL JMS-01SG Mass Spectrometer.

6-Amino-4-mercapto-2-phenyl-1,2-dihydro-1,3,5-triazines (IIIa, b)——A suspension of amidinothiourea[8] (0.01 mol) in anhyd. EtOH (40 ml) containing benzaldehyde (0.01 mol) was heated for 3 hr under reflux. Precipitates deposited on cooling were collected by filtration and recrystallized from EtOH.

6-Amino-2-isopropyl-4-mercapto-1,2-dihydro-1,3,5-triazines (IIIc—e)——A suspension of amidinothiourea[8] (0.005 mol) in anhyd. EtOH (40 ml) containing isobutyraldehyde (0.005 mol) was refluxed for 8 hr and then concentrated. After cooling, the precipitates deposited were collected by filtration and recrystallized from EtOH.

6-Amino-2,2-dimethyl-4-mercapto-1,2-dihydro-1,3,5-triazines (IIIf—h)——A suspension of amidinothiourea[8] (0.005 mol) in acetone (40 ml) containing piperidine (0.5 ml) was heated for 3 hr under reflux. The precipitates deposited on cooling were collected by filtration and recrystallized from dimethylformamide.

The compounds (IIIa—h) obtained are listed in Table I.

6-Amino-4-mercapto-2-phenyl-1,2-dihydro-1,3,5-triazine Hydrochloride (III-HCl)——A mixture of amidinothiourea hydrochloride[8] (0.005 mol) and benzaldehyde (0.005 mol) was heated for several minutes. The mixture was clearly fused and then immediately solidified. The solid was recrystallized from EtOH.

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6) *a*) F.B. Dains, R. Irvin, and C.G. Harrel, *J. Am. Chem. Soc.*, **43**, 613 (1921); *b*) F.A. Eberly and F.B. Dains, *J. Am. Chem. Soc.*, **58**, 2554 (1963).
7) C.J. Pouchart, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Company, 1970, p. 358.
8) C.P. Joshua and V.P. Rajan, *Chem. and Ind.*, 1974, 301.

Table I. 6-Amino-4-mercapto-2-substituted 1,2-dihydro-1,3,5-triazines (IIIa—h)

	mp (°C)	Yield (%)	Formura	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1}
IIIa	178—179	78	$C_{16}H_{16}N_4OS$	61.52 (61.44)	5.16 (5.39)	17.74 (17.95)	3440, 3260, 3100 (NH). 1620 (C=N).
IIIb	195—196	59	$C_{15}H_{13}ClN_4S$	56.87 (57.03)	4.14 (4.10)	17.69 (17.40)	3420, 3240, 3140 (NH). 1610 (C=N).
IIIc	174—175	39	$C_6H_{12}N_4S$	41.84 (42.01)	7.02 (7.12)	32.53 (32.28)	3300, 3260, 3190, 3080 (NH). 1630 (C=N).
IIId	179—180	80	$C_{12}H_{16}N_4S$	58.03 (57.93)	6.49 (6.33)	22.56 (22.41)	3440, 3240, 3040 (NH). 1630 (C=N).
IIIe	193—194	82	$C_{13}H_{18}N_4OS$	56.09 (56.29)	6.52 (6.72)	20.13 (20.05)	3420, 3230, 3040 (NH). 1620 (C=N).
IIIf	196—197	78	$C_{11}H_{14}N_4S$	56.38 (56.37)	6.02 (6.26)	23.91 (23.58)	3400, 3100 (NH). 1620 (C=N).
IIIg	192—193	82	$C_{12}H_{16}N_4OS$	54.52 (54.86)	6.10 (6.14)	21.20 (21.55)	3440, 3120 (NH). 1620 (C=N).
IIIh	200—201	64	$C_{11}H_{13}ClN_4S$	49.16 (49.40)	4.88 (4.99)	20.85 (20.81)	3440, 3120 (NH). 1610 (C=N).

IIIa-HCl: Yield 71%. mp 172—173°. *Anal.* Calcd. for $C_{16}H_{16}N_4OS$–HCl: C, 52.38; H, 5.22; N, 15.27. Found: C, 52.81; H, 5.49; N, 15.25. This hydrochloride was easily converted into the free base IIIa by treatment with NaOH, and IIIa was again converted into the hydrochloride (IIIa–HCl) with HCl. 6-Anilino-4-mercapto-2-phenyl-1,2-dihydro-1,3,5-triazine hydrochloride: Yield 80%. mp 194—195°. *Anal.* Calcd. for $C_{15}H_{14}N_4S$–HCl: C, 56.51; H, 4.74; N, 17.50. Found: C, 56.01; H, 5.13; N, 17.50. 6-Amino-4-mercapto-2-phenyl-1,2-dihydro-1,3,5-triazine hydrochloride: Yield 76%. mp 213—214°. *Anal.* Calcd. for $C_9H_{10}N_4S$–HCl: C, 44.74; H, 4.55; N, 23.00. Found: C, 45.14; H, 4.58; N, 22.89.

2-Guanidylidene-4-thiazolidone (Va)——A suspension of amidinothiourea (0.60 g, 0.005 mol) in anhyd. EtOH (40 ml) containing methyl chloroacetate (0.54 g, 0.005 mol) was heated for 3 hr under reflux. The precipitates deposited on cooling were collected by filtration and recrystallized from H_2O to give Va (0.32 g, 40%) melting at 250—251°. *Anal.* Calcd. for $C_4H_6N_4OS$: C, 30.71; H, 3.82; N, 35.42. Found: C, 31.03; H, 3.99; N, 35.22. IR ν_{max}^{KBr} cm^{-1}: 3360, 3280 (NH). 3050 (=NH). 1670 (C=O).

2-(*p*-Methoxyphenylguanidylidene)-4-thiazolidone (Vb)——A suspension of *p*-methoxyphenylamidinothiourea (1.12 g, 0.005 mol) in anhyd. MeOH (50 ml) containing methyl chloroacetate (0.54 g, 0.005 mol) was stirred for 1 hr at room temperature and then allowed to stand for 2 days. After the solvent was removed by distillation under reduced pressure, the residue was recrystallized from MeOH to give Vb (1.02 g 77%) melting at 200—201°. *Anal.* Calcd. for $C_{11}H_{12}N_4O_2S$: C, 49.99; H, 4.56; N, 21.20. Found: C, 50.06; H, 4.29; N, 20.94. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 3080 (=NH), 1670 (C=O), 1600 (C=N).

2,4-Thiazolidinedione (VI)——A solution of 2-(*p*-methoxyphenyl)guanidylidene-4-thiazolidone in 18% HCl solution was refluxed for 24 hr and then evaporated. The precipitates deposited were collected by filtration and recrystallized from MeOH to give VI, which was confirmed by comparison of the IR spectrum with that of authentic sample.[7]

Acknowledgement The authors are indebted to Mrs. K. Shiraki for the microanalytical data and to Mr. K. Takeda for the measurement of mass spectra.