Synthesis and Properties of 5-Aroylamino-2*H*-1,2,4-thiadiazol-3-ones

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5-Aroylamino-2*H*-1,2,4-thiadiazol-3-ones **3** were obtained from the corresponding 1-aroyl-2-thiobiurets **2** by oxidative cyclization with bromine. 5-Aroylamino-2*H*-1,2,4-thiadiazol-3-ones **3** can exist in two tautomeric forms - a lactam form and a lactim form. On the basis of the ^{13}C nmr spectra and additional experimental information, it has been established that the stable form, in which these compounds exist, is the lactam form.

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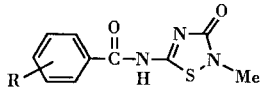
Introduction.

We have recently reported [1] on the synthesis of a series of 5-aroylamino-2-methyl-2*H*-1,2,4-thiadiazol-3-ones **1** within the framework of our systematic studies of biologically active pyrimidines, purines, and their analogs including 1,2,4- and 1,2,3-thiadiazole derivatives [1,2]. 3-Alkoxy(or hydroxy)-5-arylamino-1,2,4-thiadiazoles were first reported by Kurzer [3]. 5-Amino-2*H*-1,2,4-thiadiazol-3-one [4] can be considered an analog of cytosine on the basis of the well-known analogy between a -CH=CH- group in benzenoid hydrocarbons and bivalent sulfur, -S-, in their sulfur-containing heterocyclic analogs [5].



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Similarly as cytosine, 2*H*-1,2,4-thiadiazol-3-one can exist in two tautomeric forms: the lactam (oxo) form and the lactim (enol) form. The tautomeric equilibria of 2*H*-1,2,4-thiadiazol-3-ones have been indirectly shown to exist by acylation [6] and methylation [7] reactions which yielded mixtures of *O*-substituted and *N*-substituted products. A study of the uv absorption spectra of these compounds concluded that the stable tautomers of 3-hydroxy-5-phenyl-1,2,4-thiadiazole and 5-anilino-3-hydroxy-1,2,4-thiadiazole are their lactam forms in a neutral solution [8]. On the other hand, the stable tautomers of 5-aryl-3-hydroxy-1,2,4-thiadiazoles were reported as lactim forms on the basis of the results of studies of their ir and ^{13}C nmr spectra [9]. However, the interpretation of the ^{13}C nmr spectra is an indirect one and is based on a comparison with chemical shifts of 5-aryl-3-hydroxy-1,2,4-oxadiazoles. Thus, the results reported in the literature on the tautomerism of these compounds are ambiguous.

^{13}C nmr spectroscopy has been directly used to study the lactam-lactim tautomerism of heterocyclic compounds [10-13]. In these studies, the chemical shifts have to be directly compared with those of either the lactam or lactim species because the substituent effect on the ^{13}C chemical shifts cannot be predicted in a simple fashion. Usually they are shown as weighted average shifts between the lactam and the lactim species.

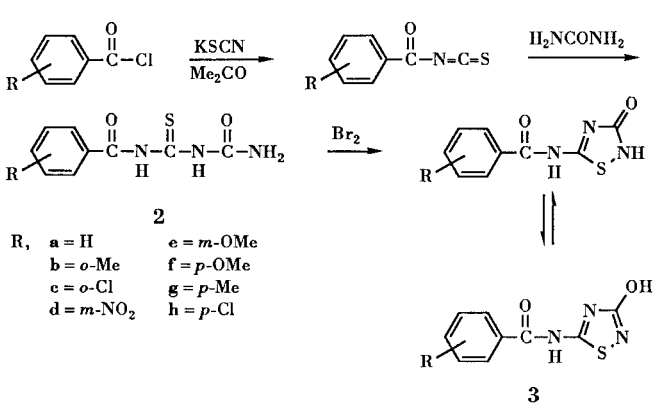
To determine the structures of stable tautomers of 2*H*-1,2,4-thiadiazol-3-ones, we were interested in the synthesis of 5-aroylamino-2*H*-1,2,4-thiadiazol-3-ones **3**. Our contribution describes the details of structural studies on these compounds **3** and a general method of their synthesis from 1-aroyl-2-thiobiurets **2**. The stable tautomers of **3** can be ascertained on the basis of a direct comparison of the ^{13}C nmr spectra of **3** and the unequivocal lactam series - the 5-aroylamino-2-methyl-2*H*-1,2,4-thiadiazol-3-ones **1** which we have already described [1].

Investigations of the relative stability of tautomers in biologically active compounds are important within the framework of structure-biological activity relationship studies.

Results and Discussion.

The synthesis of 5-aroylamino-2*H*-1,2,4-thiadiazol-3-ones **3** followed a pattern similar to that which we had described for the synthesis of 5-aroylamino-2-methyl-2*H*-1,2,4-thiadiazol-3-ones **1** [1] (Scheme 1).

Scheme 1



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R, **a** = H, **b** = *o*-Me, **c** = *o*-Cl, **d** = *m*-NO_2, **e** = *m*-OMe, **f** = *p*-OMe, **g** = *p*-Me, **h** = *p*-Cl

3

Table I

Synthesized 1-Aroyl-2-thiobiurets **2** and their IR and NMR Spectral Data

Compound No.	R	Mp (°)	Yield (%)	IR spectrum (cm^{-1}, potassium bromide) ^1H NMR spectrum (ppm, DMSO-d_6)
2a	H	172-174 [a]	30.7	3300, 3150 (NH), 3020 (CH), 1700, 1670 (C=O) 13.5 (1H, b, NH), 11.2 (1H, b, NH), 7.5-8.0 (7H, m, Ph + NH_2)
2b	*o*-Me	174-176	53.0	3370, 3190 (NH), 3050, 2900 (CH), 1700, 1670 (C=O) 12.9 (1H, b, NH), 11.5 (1H, b, NH), 7.1-7.8 (6H, m, Ph + NH_2), 2.4 (3H, s, Me)
2c	*o*-Cl	180-183	41.3	3100, 3260 (NH), 3000 (CH), 1720, 1680 (C=O) 13.0 (1H, b, NH), 11.5 (1H, b, NH), 7.3-8.3 (6H, m, Ph + NH_2)
2d	*m*-NO_2	191-192	62.0	3400, 3280 (NH), 3060 (CH), 1700, 1680 (C=O) 11.5 (1H, b, NH), 13.5 (1H, b, NH), 7.5-9.0 (6H, m, Ph + NH_2)
2e	*m*-OMe	141-143	47.9	3400, 3250 (NH), 3060, 2950 (CH), 1700 (C=O) 13.5 (1H, b, NH), 11.5 (1H, b, NH), 7.2-7.9 (6H, m, Ph + NH_2), 3.9 (3H, s, OMe)
2f	*p*-OMe	198-200	42.3	3260 (NH), 3020, 2940 (CH), 1720, 1660 (C=O) 13.5 (1H, b, NH), 11.5 (1H, b, NH), 7.3-8.3 (6H, dd, Ph + NH_2), 3.9 (3H, s, OMe)
2g	*p*-Me	186-189	30.0	3300, 3180 (NH), 3070, 2940 (CH), 1700, 1650 (C=O) 13.5 (1H, b, NH), 11.5 (1H, b, NH), 7.0-8.3 (6H, dd, Ph + NH_2), 2.4 (3H, s, Me)
2h	*p*-Cl	204-207	43.9	3300, 3180 (NH), 3000 (CH), 1710, 1660 (C=O) 13.5 (1H, b, NH), 11.5 (1H, b, NH), 7.0-8.6 (6H, dd, Ph + NH_2),

[a] Lit [14] gives 175°.

Table II

Synthesized 5-Aroylamino-2*H*-1,2,4-thiadiazol-3-ones **3**

Compound No.	R	Mp (°)	Yield (%)	Molecular formula (mol wt)	Analysis Calcd.(Found) C %	H %	N %
3a	H	260-262	75.6	$C_9H_7N_3O_2S$ (221.24)	48.86 (48.82)	3.19 (3.06)	18.99 (18.79)
3b	*o*-Me	271-273	75.0	$C_{10}H_9N_3O_2S$ (235.27)	51.05 (51.14)	3.86 (3.84)	17.86 (17.75)
3c	*o*-Cl	266-268	80.0	$C_9H_6ClN_3O_2S$ (255.68)	42.28 (42.19)	2.37 (2.25)	16.43 (16.28)
3d	*m*-NO_2	253-255	60.6	$C_9H_6N_4O_4S$ (266.24)	40.60 (40.63)	2.27 (2.23)	21.04 (20.37)
3e	*m*-OMe	254-256	68.1	$C_{10}H_9N_3O_3S$ (251.27)	47.80 (47.71)	3.61 (3.52)	16.72 (16.68)
3f	*p*-OMe	281-283	75.7	$C_{10}H_9N_3O_3S$ (251.27)	47.80 (47.65)	3.61 (3.45)	16.72 (16.68)
3g	*p*-Me	267-269	82.0	$C_{10}H_9N_3O_2S$ (235.27)	51.05 (50.60)	3.86 (3.80)	17.86 (17.88)
3h	*p*-Cl	292-294	80.5	$C_9H_6ClN_3O_2S$ (255.68)	42.28 (42.07)	2.37 (2.21)	16.43 (16.36)

The yields and the melting points of the intermediate 1-aroyl-2-thiobiurets **2** are summarized in Table I. The ir and ^1H nmr spectra of these compounds can be found in Table I as well. The spectra are in an excellent agreement with the proposed structures and were used for the positive identification of the synthesized **2**.

The oxidative cyclization of 1-aroyl-2-thiobiurets was attempted with an alkaline hydrogen peroxide solution which was previously used for cyclization of 1-aroyl-5-methyl-2-thiobiurets [1]. However, it was not possible to obtain the cyclized products in this way. Thus, molecular bromine, a milder oxidizing agent than hydrogen perox-

Scheme 2

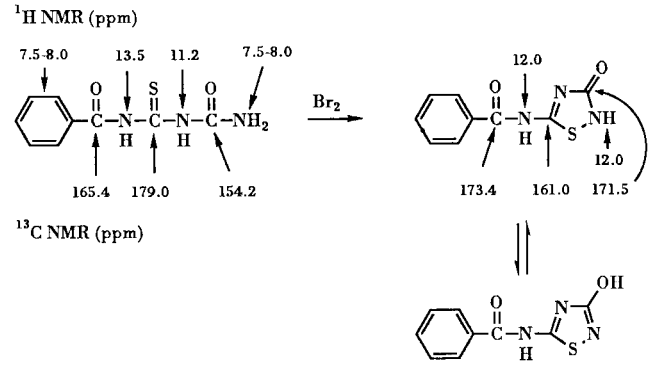


Table III

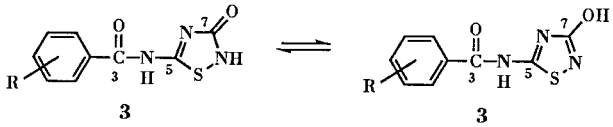
The IR, ^1H NMR and ^{13}C NMR Spectral Data for 5-Aroylamino-2*H*-1,2,4-thiadiazol-3-ones **3**

Compound No.	R	IR spectrum (cm^{-1}, potassium bromide); ^1H NMR spectrum (ppm, DMSO-d_6) [a] ^{13}C NMR spectrum (ppm, DMSO-d_6 [a]
3a	H	3300 (NH), 2640-3200 (CH), 1710, 1650 (C=O); (2) 7.5-8.3 (5H, m, Ph), (4 + 6) 12.0 (2H, b, NH) (2) 128.6-133.1, (3) 173.4, (5) 161.0, (7) 171.5
3b	*o*-Me	3400 (NH), 2600-3000 (CH), 1700, 1630 (C=O); (1) 2.5 (3H, s, Me), (2) 7.2-7.8 (4H, m, Ph), (4 + 6) 12.0 (2H, b, NH) (1) 20.0, (2) 125.7-137.5, (3) 173.0, (5) 163.5, (7) 171.7
3c	*o*-Cl	3400 (NH), 2620-3000 (CH), 1660, 1700 (C=O); (2) 7.4-7.9 (4H, m, Ph), (6) 12.1 (1H, b, NH) (2) 127.2-132.8, (3) 173.3, (5) 163.8, (7) 169.0
3d	*m*-NO_2	3400 (NH), 2620-3060 (CH), 1710, 1650 (C=O); (2) 7.8-8.9 (4H, m, Ph), (6) 11.8 (1H, b, NH) (2) 123.2-147.9, (3) 173.9, (5) 157.9, (7) 171.9
3e	*m*-OMe	3400 (NH), 2640-3060 (CH), 1700, 1640 (C=O); (1) 3.8 (3H, s, OMe), (2) 7.2-7.8 (4H, dd, Ph), (4 + 6) 12.0 (2H, b, NH) (1) 55.4, (2) 113.2-159.4, (3) 173.5, (5) 161.5, (7) 170.9
3f	*p*-OMe	3400 (NH), 2620-3020 (CH), 1710 (C=O); (1) 3.9 (3H, s, OMe), (2) 7.0-8.1 (4H, dd, Ph), (6) 11.7 (1H, b, NH) (1) 55.5, (2) 114.0-163.2, (3) 178.3, (5) 163.2, (7) 173.0
3g	*p*-Me	3400 (NH), 2620-3020 (CH), 1720, 1660 (C=O); (1) 2.3 (3H, s, Me), (2) 7.3-8.0 (4H, dd, Ph), (4 + 6) 11.9 (2H, b, NH) (1) 21.2, (2) 128.6-143.6, (3) 173.3, (5) 161.4, (7) 171.1
3h	*p*-Cl	3400 (NH), 2930-3000 (CH), 1700, 1650 (C=O); (2) 7.5-8.3 (4H, dd, Ph), (4 + 6) 12.0 (2H, b, NH) (2) 128.8-138.0, (3) 173.5, (5) 159.7, (7) 171.6

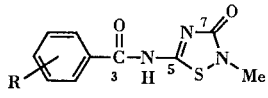
[a] Numbers preceding the chemical shift values in the ^1H and ^{13}C nmr spectra indicate the type of H and C, respectively, as shown in the formula below.

Table IV

Comparison of the ^{13}C NMR Chemical Shifts for 5-Aroylamino-2*H*-1,2,4-thiadiazol-3-ones **3** and 5-Aroylamino-2-methyl-2*H*-1,2,4-thiadiazol-3-ones **1** [1]



3 **3**



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Compound	R	^{13}C NMR chemical shifts (ppm, DMSO-d_6) C(7)		C(5)		C(3)	
		3	**1**	**3**	**1**	**3**	**1**
a	H	173.4	174.0	161.0	156.0	171.5	169.5
b	*o*-Me	173.0	175.2	163.5	157.7	171.7	168.4
c	*o*-Cl	173.3	172.9	163.8	157.5	169.0	168.6
d	*m*-NO_2	173.9	174.0	157.9	154.9	171.9	171.0
e	*m*-OMe	173.5	174.1	161.5	159.3	170.9	169.4
f	*p*-OMe	178.3	179.7	163.2	163.2	173.0	169.0
g	*p*-Me	173.3	176.0	161.4	161.4	171.1	169.2
h	*p*-Cl	173.5	175.7	159.4	165.4	171.6	173.7

ide, was employed. 1-Aroyl-2-thiobiurets **2** were suspended in ethanol and treated with bromine in a chloroform solution at 30-35°. They were easily cyclized to 5-aroylamino-2*H*-1,2,4-thiadiazol-3-ones **3** which are colorless solids.

The yields of **3** vary between 61 and 82% depending on the substituent. The melting points, yields, and elemental analyses of 5-aroylamino-2*H*-1,2,4-thiadiazol-3-ones **3** are summarized in Table II, and their ir, ^1H nmr, and ^{13}C nmr spectra are presented in Table III.

The structures of products **3** were confirmed on the basis of their ir and ^1H and ^{13}C nmr data, in addition to the elemental analyses. The structural elucidation was carried out in the same fashion as previously described [1] (Scheme 2).

The formation of the 2*H*-1,2,4-thiadiazol-3-one ring is supported by the disappearance of two NH groups and the change of the proton chemical shifts of the product as compared with the corresponding 1-aroyl-2-thiobiurets. The ^{13}C nmr spectrum of the benzoyl product **3a**, compared with that of 1-benzoyl-2-thiobiuret (**2a**), shows one upfield shift [from 179.0 ppm (C=S) to 161.0 ppm (N=C-S)], and a downfield shift [change from 154.2 ppm (HNC=O(NH_2)) to 171.5 ppm (C=N-C=O(NH))]. The amidic carbon of the benzoyl amide group shows the

Table V

The IR and NMR Spectral Data for 3-Hydroxy-5-phenyl-1,2,4-thiadiazole (4) and 3-Hydroxy-5-phenyl-1,2,4-oxadiazole (5) [9]

Compound No.	IR (cm^{-1}, potassium bromide)	^1H nmr (ppm, DMSO-d_6) ^{13}C nmr (ppm, DMSO-d_6)
4	1645 (azole ring)	11.5-13.8 (OH) 171.7 (C(3)), 186.9 (C(5))
5	1615 (azole ring)	12.2-13.5 (OH) 173.0 (C(3)), 174.4 (C(5))

smallest change of the chemical shift, from 165.4 ppm to 173.4 ppm, as expected.

To determine the structures of the stable tautomers of 5-aroylamino-2*H*-1,2,4-thiadiazol-3-ones **3**, their ^{13}C nmr spectra were compared with those of 5-aroylamino-2-methyl-2*H*-1,2,4-thiadiazol-3-ones which exist in the lactam (oxo) form (see Table IV). It can be seen (Table IV) that the ^{13}C chemical shifts of C(3) in **1** and **3** are almost the same if the methyl group effect is taken into consideration [15,16]. Thus, one can conclude that 5-aroylamino-2*H*-1,2,4-thiadiazol-3-ones **3** exist in their lactam (oxo) form rather than the lactim (enol) form in a dimethyl sulfoxide solution.

Tsuge [9] reported the following spectral data for 3-hydroxy-5-phenyl-1,2,4-thiadiazole (**4**) (Table V). According to him, the ^{13}C nmr spectrum of compound **4** corresponds to a lactim form, by comparison with 3-hydroxy-5-phenyl-1,2,4-oxadiazole (**5**). However, the chemical shift of C(3) is almost the same as that of 5-aroyl-2-methyl-2*H*-1,2,4-thiadiazol-3-ones **1**. In the ^1H nmr spectrum of **4**, the 11.5-13.8 ppm chemical shift can be interpreted as that of a lactam NH. The 1645 cm^{-1} absorption in the ir spectrum is that of a carbonyl group [6] whereas the 1,2,4-thiadiazole ring absorbs at 1530-1560 cm^{-1} [6]. Therefore, the stable tautomers of 3-hydroxy-1,2,4-thiadiazoles are their lactam forms rather than the lactim forms.

EXPERIMENTAL

All melting points were determined on an electrically heated Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir spectra were taken on a Jasco A-1 spectrophotometer. The ^1H nmr and ^{13}C nmr spectra were measured on a 80 MHz Bruker AC-80 spectrometer. The elemental analyses were carried out on a Perkin-Elmer apparatus, model 240, at the Korea Research Institute of Chemical Technology, Dae Jeon, Korea. Most of the commercially available starting materials were purchased from Aldrich Chemical Company, Milwaukee, WI.

1-(*p*-Toluyl)-2-thiobiuret (**2g**).

The synthesis of 1-(*p*-toluyl)-2-thiobiuret (**2g**) followed the modified procedure described for 1-benzoyl-2-thiobiuret [1,14]. The product was obtained in a 30% yield and was recrystallized from ethanol, mp 186-189°; ir (potassium bromide): ν 3300 (NH), 3180 (NH), 3070, 2940 (CH), 1700, 1650 (C=O); ^1H nmr (DMSO-d_6): δ 13.5 (1H, b, NH) (b = broad), 11.5 (1H, b, NH), 7.0-8.3 (5H, dd, Ph + NH), 2.4 ppm (3H, s, Me); ^{13}C nmr (DMSO-d_6): δ 21.0 (Me), 127.9-143.7 (Ph), 154.5 (O=CNH_2), 179.2 (C=S), 165.2 ppm (PhC=O).

All other 2-thiobiurets **2** were prepared in the same fashion (Table I).

5-(*p*-Toluylamino)-2*H*-1,2,4-thiadiazol-3-one (**3g**).

1-(*p*-Toluyl)-2-thiobiuret (**2g**, 1.0 g, 4.2 x 10^{-3} mole) was suspended in ethanol (10 ml) at 30-35°. A 1*M* solution of bromine in chloroform (4.2 ml, 4.2 x 10^{-3} mole) was added dropwise in the course of 10 minutes. The reaction mixture was then stirred for an additional 10 minutes, and it was filtered to collect the product. The product was washed with ether to remove excess bromine and the colorless solid (0.81 g, 82%) was crystallized from ethanol-dimethylformamide (5:1, vol) to obtain the analytical sample (0.57 g, 58%), mp 267-269°; ir (potassium bromide): ν 3400 (NH), 2620-3020 (CH), 1720, 1660 cm^{-1} (C=O); ^1H nmr (DMSO-d_6): δ 12.5 (1H, b, NH), 11.5 (1H, b, NH), 7.3-8.0 (4H, dd, Ph), 2.3 ppm (3H, s, Me); ^{13}C nmr (DMSO-d_6): δ 21.2 (Me), 128.6-143.6 (Ph), 161.4 (C=N), 171.1 (PhC=O), 173.3 ppm (NC=O).

Elemental analyses are in Table II.

All other substituted 2*H*-1,2,4-thiadiazol-3-ones **3** were obtained by the same procedure (Table II).

Acknowledgements.

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