2-AMINO-Δ^2-THIAZOLIN-4-ONES IN ACYLATION REACTIONS

S. M. Ramsh, Yu. G. Basova,
A. I. Ginak, N. A. Smorygo, and
A. A. Rodin

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It is shown that 2-acetyl derivatives are formed in the acetylation of 2-amino-Δ^2-thiazolin-4-one and its 2-phenyl analog with acetic anhydride in acetic acid. 2-Amino-Δ^2-thiazolin-4-one is not acetylated by acetyl chloride in the presence of alkaline agents, while 2-phenylamino-Δ^2-thiazolin-4-one gives a 3-acetyl derivative. In both cases in the acetylation of 2-phenylamino-Δ^2-thiazolin-4-one a 3,4-diacetyl derivative is formed along with a monoacetylation product. The structures of the compounds obtained were confirmed by their IR, PMR, UV, and mass spectra.

Continuing our systematic study of the dual reactivity of ambifunctional 2-substituted 4-thiazolidinones we directed our attention to the acylation of 2-amino-Δ^2-thiazolin-4-one (I). It is known that the reactivity of the nucleophilic reagent with respect to the carbonyl group is determined chiefly by its basicity [1]. Compound I can be regarded as a pseudoacid to which a highly basic anion corresponds (the pK_a value in water is 11.7 [2]). One therefore might have expected that the reaction would proceed quite readily in the presence of a strong base such as the ethoxide ion. In fact, I is not acetylated either in ethanol in the presence of an equimolar amount of sodium ethoxide or in benzene in the presence of triethylamine (in the latter case general base catalysis and nucleophilic catalysis of the acylation reaction are possible) even in the case of prolonged treatment with acetyl chloride and can be isolated from the reaction mixture in ~100% yield. The disparity in the basicity of the anion of I with respect to the proton and with respect to the carbonyl carbon atom is evidently due to the same reasons as the low nucleophilicity of this anion in reactions with alkylating agents [3]. In the absence of a base the acetylation of I also does not occur in benzene, although acylation products could be isolated in the case of chlorides of some other acids under these conditions [4]. In the case of acylation with acetic anhydride in acetic acid, in which the formation of an anion of the nucleophile is excluded and general acid catalysis of the reaction occurs, an acetylated derivative of I is obtained readily but in much lower yield than the yield reported in [5].

We were unable to find original studies in which the structure of acetylated derivative II was proved. In [5], in which the preparation of this compound is described, with reference to [6] it is asserted that the acetyl group is located in the 2 position, although neither the method for the preparation of this compound nor proof of its structure is presented in [6]. Data of this type are also absent in [4], in which the tautomerism of acylated derivatives of I, including II, is discussed. A review [7] gives a citation to a Japanese patent and an abstract [8], in which a description of the preparation of an acetyl derivative of I by the action of acetic anhydride on this compound is presented but the structure of the acetyl derivative obtained is not proved in any way; the melting point presented for the acetyl derivative is 35°C lower than that reported in [5].

Chemical evidence (alkaline or acidic hydrolysis and methylation) does not constitute a reliable argument in favor of the selection of one or another isomeric structure for the acetylated 2-amino-Δ^2-thiazolin-4-one, since it is known that 2- and 3-substituted derivatives of I are capable of undergoing rearrangement to one another, depending on the pH of the medium [9]. The spectral characteristics confirm that II is the 2-acetyl derivative. This is above all indicated by the absence in the IR spectrum of a solid sample of an absorption band of an unconjugated C=N bond, which in the case of 2-imino-3-methylthiazolidin-4-one lies at 1620 cm^{-1}. The band at 1535 cm^{-1} is characteristic for the vibrations of a conjugated C=N bond (1565 cm^{-1} for 2,2-dimethylamino-Δ^2-thiazolin-4-one). The UV spectrum of II in ethanol is sim-

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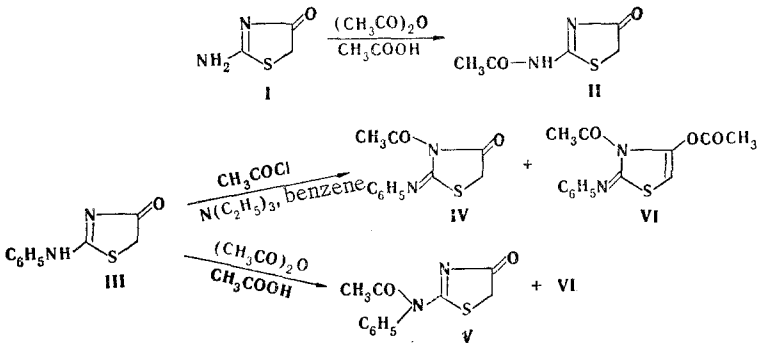
ilar to the UV spectrum of I, but the maxima are shifted bathochromically 15-20 nm. The signal of an NH proton is not detected in the PMR spectrum of II, wheras the PMR spectrum of 2-imino-3-methylthiazolidin-4-one contains a distinct signal of an N_2H proton at 9.29 ppm.

For the phenyl analog of I, viz., 2-phenylamino-Δ^2-thiazolin-4-one (III) one observes p–π conjugation of the unshared electron pair of the nitrogen atom with the phenyl ring [10], which hinders resonance isomerization of this pair with the carbonyl group, owing to which the polarity of the molecule in the neutral state decreases substantially, and the degree of delocalization of the charge in the anion increases, i.e., its "hardness" decreases. In analogy with methylation [3], it should be expected that acylation of III (pK_a in methanol 12.0 [10]) in the presence of an alkaline agent would take place with greater ease than in the case of I.



Previous attempts to obtain monoacetyl derivatives by direct acylation of III with acetyl chloride in benzene and pyridine were unsuccessful [11]. In a review [7] with a reference to [12] it is indicated that the acylation of III gives 3-acetyl derivative IV; however, in the original paper [12] the subject matter is the acylation with thioacetic acid of the so-called "labile" isomer of III, viz., 2-imino-3-phenylthiazolidin-4-one. In [12] Wheeler and Johnson assigned the 2-acetimido-3-phenylthiazolidin-4-one structure to the acetylation product, whereas in a later paper [11] it is asserted that 2-acetylphenylamino-Δ^2-thiazolin-4-one (V) was actually obtained, since the melting point of this compound coincides with the melting point (191-192°C) of the product of condensation of unsymmetrical acetylphenylthiourea with chloracetyl chloride. Compound V was also obtained from the "labile" 2-imino-3-phenylthiazolidin-4-one and acetic anhydride [12]. The diacetyl derivative of III, which is obtained when it is subjected to reaction with acetic anhydride or with excess acetyl chloride in benzene [12], is, as demonstrated in [11], 2-phenylimino-3-acetyl-4-acetoxy-Δ^4-thiazoline (VI).

We were able to obtain two monoacetyl derivatives of III: One monoacetyl derivative was obtained by acylation with acetyl chloride in the presence of triethylamine in benzene (IV), while the other was obtained by acylation with acetic anhydride in acetic acid (V); diacetyl derivative VI is also formed in both cases. The spectral characteristics of the acetyl derivatives obtained prove that IV is 2-phenylimino-3-acetylthiazolidin-4-one and confirm the structures of V and VI proposed in [11]. A signal of protons of a methylene group is present in the PMR spectra of both monoacetyl derivatives IV and V, and this excludes the possible O-acetyl structure with an enolized keto-methylene group for both isomers. Two bands of carbonyl absorption and a band at 1670 cm^{-1}, which we assigned to the stretching vibrations of an unconjugated $C{=}N_{exo}$ bond [10], are present in the IR spectrum of IV. With respect to its form, the UV spectrum of this compound resembles the UV spectrum of 2-phenylimino-3-methylthiazolidin-4-one [10], except that the maxima are shifted bathochromically 13-24 nm, and the short-wave maximum is more intense. Compound IV forms diacetyl derivative VI both with acetyl chloride in the presence of triethylamine in benzene and with acetic anhydride in acetic acid, and this not only concretely indicates a 3-acetyl rather than a 2-acetyl structure but also repudiates the possible lactim O-acetyl structure.

A band at 1485 cm^{-1} of stretching vibrations of a ring C=N bond conjugated with a carbonyl group is present in the IR spectrum of the acetyl derivative that we isolated (V), and its UV spectrum is similar to the UV spectrum of 2-methylphenylamino-Δ^2-thiazolin-4-one [10]. The coincidence of the melting points of V and the compound obtained in [11] from unsymmetrical acetylphenylthiourea leaves no doubt that acetyl derivative V is 2-acetylphenylamino-Δ^2-thiazolin-4-one.

According to the results of thin-layer chromatography (TLC), in the preparation of monoacetyl derivatives IV and V only one of them and diacetyl derivative VI are always present in the reaction mixtures. Whereas the formation of VI in the presence of an alkaline agent is explained by repeated acetylation of the initially formed IV, the fact of the simultaneous formation of V and VI requires the assumption that 3-acetyl derivative IV, which is rapidly converted to VI, is formed simultaneously with V, although the possibility that diacetyl derivative VI is obtained through the intermediately formed O-acetylation product is also not excluded in this case. 2-Acetyl derivative V remains unchanged under the conditions of the conversion of IV to diacetylation product VI and can be isolated from the reaction mixture, in which IV and VI are absent, according to TLC data. The diacetylation products that we obtained from III and IV are identical to the diacetyl derivative obtained by the method in [11] and undoubtedly have the structure of diacetyl derivative VI. The PMR spectrum of VI contains, in addition to two singlets of protons of methyl groups, a signal of a $C_4{=}C_5H$ proton. The IR spectrum is particularly characteristic: Of the two bands of carbonyl absorption at 1770 and 1735 cm^{-1}, the high-frequency band undoubtedly belongs to the O-acetyl carbonyl group and has the same value as in the case of phenyl acetate [13]. The $\nu C_5{-}H$ band at 3120 cm^{-1}, the $\nu C_2{=}N_{exo}$ band at 1680 cm^{-1}, the $\nu C_4{=}C_5$ band at 1535 cm^{-1}, and the $\nu C_4{-}O$ band at 1190 cm^{-1} confirm that VI is the product of 3,4-diacetylation.

The presence in the mass spectra (Table 1) of peaks of $[M - CH_3]^+$ ions (m/z 143 and 219, respectively) is characteristic for 2-acetyl derivatives II and V. The mass spectrum of VI contains a $[CH_3CO_2H]^+$ ion peak with m/z 60, which, of course, is absent in the mass spectra of II, IV, and V.

The formation of 3-acetyl derivative IV in the presence of an alkaline agent is in agreement both with the fact of the existence of III in the imino form in low-polarity solvents [10] and with the completely reasonable assumption of the greater "rigidity" of the ring (amide) nitrogen atom as compared with the exocyclic nitrogen atom in the ambident anion of III owing to the closeness of the amide nitrogen atom to the carbonyl group. The parallel acetylation of III at two nitrogen atoms in acetic acid, which proceeds via a mechanism involving general acid catalysis, confirms the conclusion that an amino-imine tautomeric equilibrium exists for this compound in hydroxy-containing solvents [10]. Compound I, which exists in the amino form in hydroxy-containing solvents [2], gives only 2-acetyl derivative II in acetic acid.

The inability of 2-acetyl derivatives II and V to undergo acylation at the oxygen atom is yet another argument in favor of their structures. Enolization of the ketomethylene fragment (probably at the moment that the reaction takes place; in other words, transfer of the reaction center [14] from the C_5 atom to the oxygen atom) in both alkaline and acidic media is possible only when the substituent (and not the hydrogen atom) attached to the ring nitrogen atom interrupts the conjugation chain between the exocyclic nitrogen atom and the carbonyl group.

EXPERIMENTAL

The PMR spectra were recorded with a Tesla BS-487C spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The IR spectra of mineral oil and perfluorinated oil suspensions of the compounds were recorded with an IKS-29 spectrometer. The UV spectra of ethanol solutions of the compounds were recorded with an SF-16 spectrophotometer. The mass spectra were recorded with an MKh-1303 spectrometer with a system for direct introduction of the samples at an ionizing voltage of 70 V and temperatures of 100 to 160°C. Thin-layer chromatography was carried out on Silufol UV-254 plates [elution with ether and benzene–hexane (2:1)].

2-Acetamido-Δ^2-thiazolin-4-one (II). A 2.9-g (0.025 mole) sample of 2-amino-Δ^2-thiazolin-4-one (I) was refluxed in a mixture of 45 ml of acetic anhydride and 105 ml of acetic acid for 15 min, after which the solvent was removed *in vacuo* to a volume of 10-15 ml, and the resulting precipitate was removed by filtration and crystallized from acetone to give 0.4 g (10.1%) of a product that decomposed at 237-240°C (245-250°C [5]). IR spectrum: 3120 (N–H), 1720 ($C_4{=}O$), 1700 ($C_{Ac}{=}O$), and 1535 cm^{-1} ($C_2{=}N_2$). UV spectrum, λ_{max} (log ε): 235 (4.28) and 279 nm (3.91). PMR spectrum (in DMSO): 3.75 (2H, s, C_5H_2) and 2.12 ppm (3H, s, CH_3). Found: N 17.7; S 20.8%. $C_5H_6N_2O_2S$. Calculated: N 17.7; S 20.3%.

2-Phenylimino-3-acetylthiazolidin-4-one (IV). A 1.9-g (0.024 mole) sample of acetyl chloride and 2.4 g (0.024 mole) of triethylamine dissolved in 20 ml of absolute benzene were added dropwise simultaneously with stirring at 5°C to 3.8 g (0.02 mole) of 2-phenyliminothiazolidin-4-one (III) in 150 ml of absolute benzene, after which the reaction mixture was stirred

TABLE 1. Mass Spectra of Acetyl Derivatives of 2-Amino-Δ^2-thiazolin-4-one and 2-Phenylamino-Δ^2-thiazolin-4-one

Compound	m/z values (relative intensity, %)*
II	158 M+, (1,6), 143 (3,3), 69 (9,9), 47 (23), 46 (37), 45 (31), 44 (3,4), 43 (100), 42 (26), 41 (5,6)
IV	235 (5,0), 234 M+, (21), 194 (11), 193 (24), 192 (100), 191 (6,7), 163 (2,5), 159 (4,6), 150 (3,3), 146 (4,0), 145 (36), 123 (2,9), 122 (2,2), 120 (4,6), 119 (54), 118 (89), 117 (3,4), 104 (3,6), 93 (2,4), 92 (3,6), 91 (14), 78 (11), 77 (43), 76 (3,1), 65 (8,5), 64 (4,5), 63 (3,8), 52 (3,8), 51 (20), 50 (5,8), 47 (2,5), 46 (8,3), 45 (7,3), 44 (2,0), 43 (70), 42 (5,8), 39 (8,6)
V	235 (2,8), 234 M+, (17), 233 (6,0), 219 (25), 193 (2,5), 192 (13), 191 (11), 163 (2,5), 145 (9,3), 123 (4,2), 120 (3,3), 119 (17), 118 (23), 117 (2,0), 104 (2,8), 103 (2,8), 92 (2,7), 91 (10), 78 (2,7), 77 (23), 65 (7,2), 64 (6,2), 57 (5,0), 51 (13), 46 (11), 45 (10), 44 (12), 43 (100), 42 (7,3), 41 (6,3), 40 (2,2), 39 (9,7)
VI	276 M+, (1,6), 233 (2,2), 232 (14), 193 (4,4), 192 (31), 135 (2,2), 119 (21), 118 (8,1), 93 (3,7), 92 (3,1), 91 (4,1), 79 (6,2), 78 (81), 77 (22), 76 (5,6), 64 (2,2), 63 (5,3), 60 (6,2), 57 (19), 56 (6,6), 53 (2,2), 52 (20), 51 (23), 50 (19), 46 (2,8), 45 (17), 44 (24), 43 (100), 42 (12), 41 (19), 40 (2,5), 39 (20)

*The molecular ion and the ions with relative intensities no less than 2% are presented.

at 20°C for 1.5 h, and the precipitated triethylamine hydrochloride was removed by filtration. The benzene was removed from the filtrate by distillation, and the residue was treated with boiling benzene–hexane (1:2), from which 0.18 g (3.3%) of VI with mp 160°C was precipitated by cooling. The undissolved residue was treated with hot benzene, from which 0.19 g (4.0%) of IV with mp 144–145°C [benzene–hexane (1:2)] was precipitated by the addition of hexane. IR spectrum: 1725 ($C_{Ac}=O$), 1705 ($C_4=O$), and 1670 cm^{-1} ($C_2=N_2$'). UV spectrum, λ_{max} (log ε): 241 (4.26) and 280 nm (3.88). PMR spectrum (in $CDCl_3$): 3.75 (2H, s, C_5H_2) and 2.05 ppm (3H, s, CH_3). Found: N 12.0; S 13.7%. $C_{11}H_{10}N_2O_2S$. Calculated: N 12.0; S 14.2%.

2-Acetylphenylamino-Δ^2-thiazolin-4-one (V). A 2.9-g (0.015 mole) sample of III was refluxed in a mixture of 45 ml of acetic anhydride and 105 ml of acetic acid, after which the solvent was removed by distillation, and the residue, which began to crystallize, was treated with 10 ml of boiling absolute benzene. The benzene extract was cooled, and the resulting precipitate was crystallized twice from ethanol to give 0.05 g (1.4%) of a product with mp 188–189°C (mp 191–192°C [11]). IR spectrum: 1730 ($C_{Ac}=O$), 1665 ($C_4=O$), and 1485 cm^{-1} ($C_2=N_3$). UV spectrum, λ_{max} (log ε): 255 nm (4.12). PMR spectrum (in $CDCl_3$): 3.88 (2H, s, C_5H_2), and 2.18 ppm (3H, s, CH_3). Found: N 12.3; S 14.6%. $C_{11}H_{10}N_2O_2S$. Calculated: N 12.0; S 14.2%.

2-Phenylimino-3-acetyl-4-acetoxy-Δ^4-thiazoline (VI). Method A [12]. A 1.0-g (0.005 mole) sample of III was refluxed in 40 ml of acetic anhydride, after which the acetic anhydride was removed by vacuum distillation, and the solid residue was crystallized from benzene–hexane (1:2) to give 0.2 g (14.5%) of a product with mp 159–160°C (mp 161–162°C [12]). IR spectrum: 3120 (C_5-H), 1770 ($C_4-Ac=O$), 1735 ($C_3-Ac=O$), 1680 ($C_2=N_2$'), 1535 ($C_4=C_5$), and 1190 cm^{-1} (C_4-O). UV spectrum, λ_{max} (log ε): 273 nm (3.93). PMR spectrum (in $CDCl_3$): 6.65 (1H, s, C_5-H), 2.10 (3H, s, $CH_3{}^{3}-Ac$), and 1.92 ppm (3H, s, $CH_3{}^{4}-Ac$). Found: N 10.4; S 11.9%. $C_{15}H_{12}N_2O_3S$. Calculated: N 10.2; S 11.6%.

Method B. A 5.8-g (0.03 mole) sample of III was refluxed in a mixture of 90 ml of acetic anhydride and 210 ml of acetic acid for 15 min, after which the solvent was removed *in vacuo*, and the solid residue was crystallized twice from ethanol to give 1.9 g (22.9%) of a product with mp 160°C.

Method C. A 0.12-g (5 mmole) sample of IV was refluxed in a mixture of 1.5 ml of acetic anhydride and 3.5 ml of acetic acid for 15 min, after which the mixture was worked up as described above in method B to give 0.02 g (14.5%) of VI with mp 160°C.

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BROMINATION OF 4-(2-THIENYL)THIAZOLES AND 2-(2-THIENYL)QUINOLINE

V. A. Smirnov, A. V. Zimichev, G. A. Lyzhova, and A. E. Lipkin

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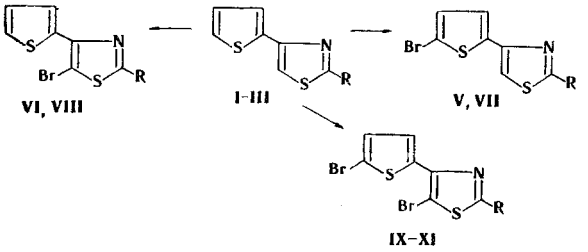
Depending on the substituent, the bromination of 4-(2-thienyl)thiazoles and 2-(2-thienyl)quinoline takes place in the 5 position of the thiophene or thiazole ring. When an amino group is present in the 2 position of the thiazole ring, bromination takes place in the 5 position of the thiazole ring. When excess brominating agent is present, a second bromine atom enters the 5 position of the free ring.

It is known that thiazole and its homologs with an unsubstituted 2 position are brominated with difficulty by both bromine and N-bromosuccinimide (NBS) [1-3]. Depending on the nature of the substituent in the 4 position, in the bromination of 2-amino- and 2-acetamidothiazoles bromine either enters the 5 position of the thiazole ring, or substitution takes place in the substituent [4-6]. At the same time, the bromination of thiophene and its homologs takes place readily and primarily in the α position of the ring [7-10].

In the present research we studied the bromination of 4-(2-thienyl)thiazole (I) and its 2-amino (II) and 2-acetamido (III) derivatives, as well as 2-(2-thienyl)quinoline (IV), with bromine and NBS in glacial acetic acid or acetic anhydride at 20, 40, 60, and 80°C.



We have previously shown [10] that the addition of acetic anhydride to glacial acetic acid in the bromination of thiophene with NBS leads to a 16% increase in the yield of 2-bromothiophene. We observed a similar effect in the bromination of I-IV: The yields of bromo deriva-

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