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2-ALLYLAMINOTHIAZOLIN-4-ONE IN ACYLATION REACTIONS

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2-Acetylallylamino-4-acetoxythiazole is obtained via treatment of 2-allylaminothiazolin-4-one with acetic anhydride for a short period of time. After extended reaction times with a mixture of acetic anhydride and acetic acid a noncondensed bicyclic derivative of thiazolidin-4-one is obtained.

2-Aminothiazolines are polyfunctional compounds which are capable of forming substitution products in acylation reactions at any of four nucleophilic sites in the molecules: at the endo- and exocyclic nitrogen atoms, at the $C_{(4)} = O$ carbonyl group, and at the carbon atom in the 5-position of the ring [1, 2]. Since the literature does not contain any reports concerning the acylation of 2-alkylaminothiazolin-4-ones [3, 4], which are potentially tautomeric compounds, we decided to investigate the acylation reaction of 2-allylaminothiazolin-4-one and the structures of the products formed in this reaction.

Acylation of 2-phenylaminothiazolin-4-one has been shown [1] to give three isomers: 2-acetylphenylaminothiazolin-4-one (acidic catalysis), 2-phenylimino-3-acetylthiazolidin-4-one (basic catalysis), and 2-phenylimino-3-acetyl-4-acetoxythiazoline (both cases).

Using the previously described method [1, 2], we were unable to isolate a single monoacyl derivative (IIa, b) after acylation of 2-allylaminothiazolin-4-one (I), under either basic or general acid-catalyzed reaction conditions. Acylation of thiazolinone I with acetic anhydride for a short reflux period resulted in the isolation of a diacetyl derivative from the reaction mixture, based on its elemental analysis and mass spectrum. In analogy with [1], we had assumed that this compound has the structure 2-allylamino-3-acetyl-4-acetoxythiazoline (IIIb). However, results of physicochemical characterization revealed that the compound was actually 2-acetylallylamino-4-acetoxythiazole (IIIa) (see top of following).

IR and UV spectral data, as well as mass spectroscopy and PMR and ^{13}C-NMR spectroscopy, were used to decide the question of the site of addition of the acetyl groups.

The IR spectrum of compound IIIa contains CH stretching vibrational bands in the 3100 cm^{-1} region, as well as intense carbonyl group stretches at 1780 and 1664 cm^{-1} [5]. Although the assignment of the first of these carbonyl bands to the vibrations of an O-acetyl group does not raise any doubts, it is impossible to assign unequivocally the second band

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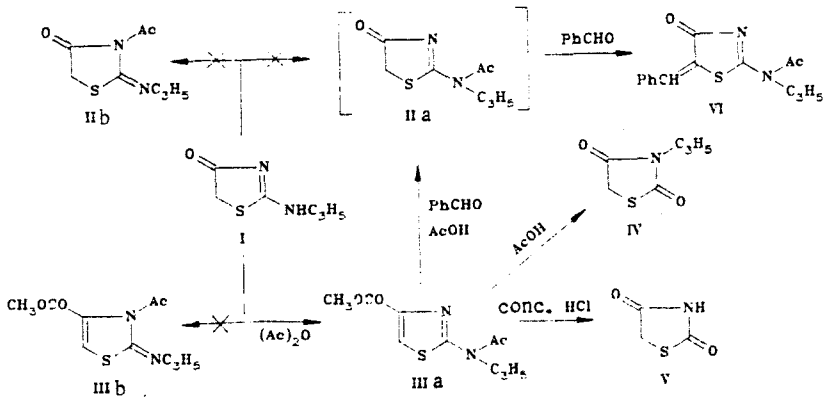


to stretching vibrations of a CO group attached to either a ring or exocyclic nitrogen atom, based on existing data and understanding. The band at 1664 cm^{-1} may be ascribed not only to an amide carbonyl group stretch, but may also reflect vibrations of the exocyclic C=N group in structure IIIb. An intense band observed at 1535 cm^{-1} in the IR spectrum is assigned to thiazoline ring vibrations, but it is not completely characteristic, since analogous bands have been noted previously in the spectra of compounds possessing thiazole [6] and thiazoline [7] structures as well. In addition, the literature contains references to the assignment of an analogous band to the vibrations of an amide carbonyl group [8-10].

The UV spectrum of compound IIIa shows only a single intense absorption band with a maximum at 273 nm ($\log \varepsilon$ 4.02). An analogous band has been noted in the spectrum of 2-acetylaminothiazole [1] and 2-phenylimino-3-acetyl-4-acetoxythiazoline [1].

The mass spectrum of compound IIIa contains a molecular ion peak at M^+ 240 (10).* Further decay proceeds via successive elimination of two ketene molecules: $[M - COCH_2]^+$ 198 (63) and $[M - COCH_2, -COCH_2]^+$ 156 (100), with increasing stability of the resulting fragments. These results are consistent with earlier results [12], in which mass spectroscopic decomposition of acyl derivatives of alkylaminothiazoles and alkylaminothiazolines was studied, and which demonstrated that a discriminatory indication of the presence of the amino form is elimination of a ketene molecule. Further decomposition of compound IIIa involves loss of a methyl group from the allyl fragment 141 (7), α-cleavage and elimination of a vinyl radical 129 (10), and of the entire allyl residue 115 (7). An intense ion peak at 83 (38), which is also present in the spectrum of compound I, can be attributed to a $HN{=}C{=}\overset{+}{N}HC_3H_5$ fragment. The acetyl and allyl fragments formed during mass spectroscopic decay give rise to intense peaks at 43 (73) and 41 (25), respectively.

The PMR spectrum is also consistent with a diacetyl structure: Two methyl group proton signals are observed at 2.26 and 2.34 ppm, along with a singlet for the ring methine proton at 6.62 ppm, and a series of signals for the allyl group at 4.74 ($N{-}CH_2$), 5.12 (H_A), 5.22 (H_B), and 5.96 ppm (H_C). It is, however, also impossible to conclude the sites of addition of the acetyl groups based on these data.

The uncertainty was finally settled using ^{13}C-NMR spectroscopy. This spectrum contains, in addition to the signals for the carbon atoms of the thiazole ring and allyl functional group, signals for the carbon atoms of the methyl groups at 22.7 and 21.3 ppm, as well as for two carbonyl group carbon atoms at 170.9 and 168.4 ppm (Fig. 1a). Using the method of selective proton decoupling, it was shown that for saturation of the methyl group resonance at 2.26 ppm the quartet at 168.4 ppm is transformed to a singlet (Fig. 1b); this is consistent with the assignment of these signals to an O-acetyl group. At the same time, saturation of the 2.34 ppm signal leads to degeneration of the multipler for the carbonyl group carbon atom at 170.9 ppm to a triplet with J = 4.2 Hz (Fig. 1c). This is indicative of the presence of a spin interaction between this nucleus and both methyl and methylene group protons of the allyl group. This latter fact is verified unequivocally by selective decoupling of the methylene group protons. The value of the spin-spin coupling constant (J = 4.2 Hz) is characteristic of the interaction of ^{13}C and ^1H nuclei across three bonds in aliphatic amides [13].

*Here and elsewhere m/e values are denoted (ion peak intensity given in % of maximum).

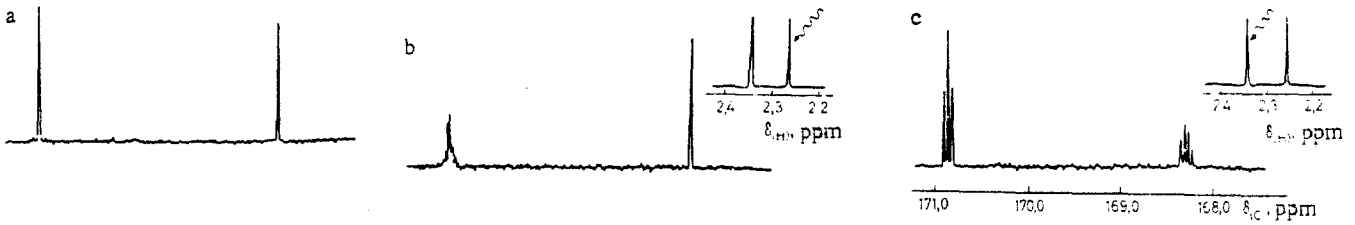


Fig. 1. Carbonyl group region of the ^{13}C-NMR spectrum of 2-acetylamino-4-acetoxythiazole (IIIa): a) complete proton decoupling; b) selective decoupling of the methyl group protons at 2.26 ppm; c) selective decoupling of the methyl group protons at 2.34 ppm.

The data presented herein lead to the conclusion that the signal at 168.4 ppm corresponds to the position of the ester functional group in the 4-position of the ring, and that the signal at 170.9 ppm belongs to an amide group, in which the nitrogen atom is bound to an allyl functional group.

Acidic hydrolysis of compound IIIa, which was carried out in order to prepare the monoacyl derivatives IIa or IIb, gives either the starting material I (1 h reflux in acetic acid) or 3-allylthiazolidin-2,4-dione (IV, 3 h reflux in acetic acid), or thiazolidin-2,4-dione (V, 2 h reflux in concentrated HCl), depending on the reaction time and acid strength; the structures of these materials were elucidated by physicochemical characterization and comparison with authentic samples [14].

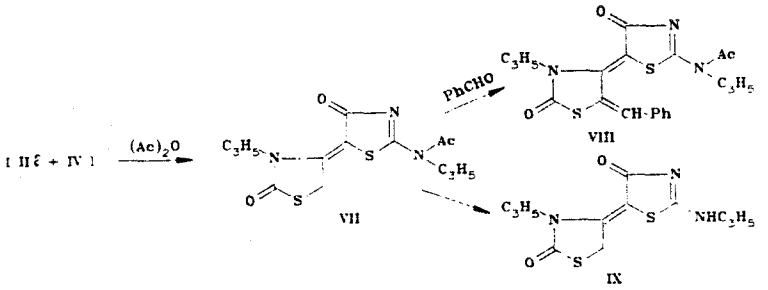
The formation of compounds IV and V is not unexpected. We have previously demonstrated that refluxing compound I in concentrated HCl leads to thiazolidin-2,4-dione [14]. The formation of compound IV may be rationalized in terms of a rearrangement process which is characteristic of 2-alkylaminothiazolidinones [3, 14], as well as by the ease of hydrolysis of the imino group in the 2-position of the thiazolidine ring.

Treatment of thiazole IIIa with benzaldehyde in acetic acid using methylamine as a catalyst resulted in the formation of 2-acetylallylamino-5-benzylidenethiazolin-4-one (VI), whose structure was also solved using physicochemical methods. It is apparent that this aldol condensation reaction involves compound IIa, which is formed during hydrolysis of the acetoxy group in the more stable compound, IIIa.

Extended reflux of thiazolinone I in a mixture of acetic anhydride and acetic acid gave a noncondensed cyclic derivative, 2-acetylallylamino-4-oxo-5-(3-allylthiazolidin-2-on-4-ylidene)thiazoline (VII). The UV spectrum of this compound exhibited, in addition to the absorption band at 273 nm (3.80), the appearance of two new absorption bands, with maxima at 376 (4.19) and 448 nm (2.56), as a consequence of the increased length of the conjugation chain due to the addition of a second thiazolidine ring. The IR spectrum of this compound contains carbonyl group stretches at 1732 ($C_{(2)}$ = O), 1678 (acetyl C=O group), and 1660 ($C_{(4)}$ = O group) cm^{-1}. An intense band in the 1530 cm^{-1} region is assigned to ring C=N bond vibrations. The PMR spectrum ($CDCl_3$) does not contradict this proposed structure. The spectrum contains an acetyl group singlet at 2.33, a singlet due to the thiazolidine ring methylene group at 3.85, and signals due to the allyl fragments at 4.69 (N–CH_2 thiazoline ring) and 4.57 ppm (N–CH_2 thiazolidine ring).

In an analogous manner, compound VII could also be prepared by treatment of compound IIIa with a mixture of acetic anhydride and acetic acid, which leads to an alternative possibility for its formation, namely, via interaction of intermediate compounds IIa and IV.

The site of addition of the two rings is related to the functional properties of the substituents and their effects on the reactive sites. As has been shown previously [15], the reactivity of the methylene group in the 5-position of the ring with respect to aldol



condensation reactions, is considerably enhanced in compounds containing strongly electron withdrawing groups in the 2-position. Furthermore, a high propensity of thiazolidin-2,4-dione derivatives to undergo nucleophilic substitution at the carbonyl group in the 4-position has also been noted before [16]. Apparently, these factors are also facilitated by the formation of a compound in which the thiazolidine rings are bound together at the 5-4'-positions.

The presence of a free methylene group in the 5'-position of the thiazoline ring in compound VII is confirmed by its ability to undergo a Knoevenagel condensation, which occurs upon treatment with benzaldehyde in acetic acid in the presence of methylamine catalyst and which yields the 5-benzylidene derivative VIII. The introduction of the benzylidene group is accompanied by a sharp increase in the intensity of the long-wavelength band in the UV spectrum of compound VIII in the 418-nm region (4.33), and also of the remaining bands with maxima at 250 (4.01), 275 (3.84), and 310 nm (4.03). The IR spectrum contains carbonyl group stretching frequencies at 1722 ($C_{(2)}$ = O), 1687 (acetyl group C=O), 1665 ($C_{(4)}$ = O), as bands at 1615, 1595 (C=C), and 1545 cm^{-1} ($C_{(2)}$=$N_{(3)}$).

The presence of a second ring stabilizes the molecule to a substantial degree, which was demonstrated by acid hydrolysis of compound VII. Boiling for 5 h in conc. HCl yielded 2-allylamino-4-oxo-5-(3-allylthiazolidyn-2-on-4-ylidene)thiazoline (IX). The UV spectrum of this compound is characterized by bands at 242 (3.86), 342 (4.25), and 430 nm (3.08). In the IR spectrum bands are observed at 1730 ($C_{(2)}$ = O), ($C_{(4)}$ = O), 1630, 1565, and 1510 cm^{-1} ($C_{(2)}$ = $N_{(3)}$, NH).

The mass spectra of compounds VI-IX are characterized by the presence of molecular ion peaks M^+ at 286 (13) for compound VI, 337 (47) for VII, 425 (11) for VIII, and 295 (100) for compound IX, which is consistent in all cases with the proposed structures.

It has thus been demonstrated that acylation of 2-allylaminothiazolin-4-one under conditions of acidic catalysis results in nucleophilic attack that converts the carbonyl group and exocyclic nitrogen atom to diacetyl derivatives of a thiazole structure. Extended reflux in a mixture of acetic anhydride and acetic acid results in condensation of the intermediate 3-allylthiazolidin-2,4-dione and 2-acetylallylaminothiazolin-4-one to generate a noncondensed bicyclic derivative.

EXPERIMENTAL

PMR and ^{13}C-NMR spectra were recorded on Varian XL-100 and XL-200 spectrometers versus TMS as internal standard. IR spectra were obtained on a Perkin–Elmer 599 spectrophotometer using Vaseline mulls, while UV spectra were measured on a Perkin–Elmer 575 spectrophotometer for alcohol solutions. Mass spectra, electron impact, were obtained on a Varian MAT-112 spectrometer. The system of direct sample introduction to the ion source was employed. The ionizing electron energy was 70 eV. The temperature of the ionization chamber was 180°C. TLC was carried out on Silufol UV-254 plates with acetone–hexane, 2:1, as the eluent.

2-Acetylallylamino-4-acetoxythiazole (IIIa). A mixture of 1.56 g (10 mmole) 2-allylaminothiazolin-4-one (I) in 15 ml acetic anhydride was refluxed for 30 min. The solution was cooled and poured onto ice water and the resulting oily product was stirred until it solidified. The precipitate was filtered and purified by crystallization from isopropyl alcohol. Yield 1.14 g (58%), mp 83-84°C. Found, %: N 11.6; S 13.4. $C_{10}H_{12}N_2O_3S$. Calculated, %: N 11.7, S 13.3.

Acidic Hydrolysis of Thiazole IIIa. The following are obtained:

2-Allylaminothiazolin-4-one (I). To 1.2 g (5 mmole) thiazole IIa was added 10 ml glacial acetic acid and the mixture was refluxed for 1 h with constant stirring. The solvent was evaporated to dryness and the residue was recrystallized from propanol. Yield 1.15 g (74%), mp 102-103°C [14].

3-Allylthiazolidin-2,4-dione (IV). To 1.2 g (5 mmole) IIIa was added 10 ml glacial CH_3COOH and the mixture was refluxed for 3 h in an oil bath with constant stirring. The solvent was evaporated to dryness and the oily residue was distilled under vacuum. bp 100-101°C (4 hPa), yield 0.83 g (53%) [14].

Thiazolidin-2,4-dione (V). To 1.2 g (5 mmole) of thiazole IIIa was added 10 ml concentrated HCl and the mixture was refluxed for 2 h with constant stirring. The solvent was evaporated to dryness and the residue was crystallized from water. Yield 0.66 g (56%), mp 124-125°C [14].

2-Acetylallylamino-5-benzylidenethiazolin-4-one (VI). A solution of 1.2 g (5 mmole) thiazole IIIa in 10 ml CH_3COOH was treated with 0.5 ml (5 mmole) benzaldehyde and 2 drops of 25% aqueous methylamine. The mixture was heated at 115°C in an oil bath for 30 min while maintaining constant stirring. After being cooled, the precipitate was filtered, washed with ether two times, 30 ml each, and purified by crystallization from acetic acid. Yield 1.2 g (84%), mp 127-128°C. IR spectrum: 1710 (acetyl group C=O), 1680 ($C_{(4)}$=O), 1610, 1590 (C=C), 1480-1500 cm^{-1} $C_{(2)}$=$N_{(3)}$). Found, %: N 10.0, S 11.1. $C_{15}H_{14}N_3O_2S$. Calculated, %: N 10.0, S 11.2.

2-Acetylallylamino-4-oxo-5-(3-allyl-2-oxothiazolidin-4-ylidene)thiazoline (VII). A. A mixture of 1.56 g (10 mmole) thiazoline I and 5 ml acetic anhydride and 10 ml acetic acid was heated in an oil bath at 140°C for 4 h while maintaining constant stirring. After being cooled the reaction mixture was poured onto water, and the residue was filtered and crystallized from isopropyl alcohol. Yield 1.2 g (35%), mp 76-77°C. Found, %: N 12.40, S 19.1. $C_{14}H_{15}N_3O_3S_2$. Calculated, %: N 12.45, S 19.0.

B. To 1.2 g (5 mmole) thiazoline IIa in a mixture of 10 ml acetic anhydride and 2 ml acetic acid was added 0.78 g (5 mmole) 3-allylthiazolidin-2,4-dione and the mixture was refluxed for 3 h with stirring on an oil bath at 140°C. After being cooled, the reaction mixture was diluted with 50 ml water and the precipitate was removed by filtration. Yield 0.9 g (53%), mp 76-77°C.

2-Acetylallylamino-4-oxo-5-(3-allyl-5-benzylidene-2-oxothiazolidin-4-ylidene)thiazoline (VIII). A mixture of 1.68 g (5 mmole) thiazoline VII in 10 ml acetic acid was treated with 0.5 ml (5 mmole) benzaldehyde and 2 drops 25% aqueous methylamine. The mixture was heated for 2 h at 120°C on an oil bath. After cooling the reaction mixture was poured into water and filtered, washed with 2 × 30 ml ether on the funnel. Yield 1.6 g (76%), mp 133-134°C (acetic acid). Found, %: N 10.0, S 15.1. $C_{21}H_{19}N_3O_3S_2$. Calculated, %: N 10.0, S 15.1.

2-Allylamino-4-oxo-5-(3-allyl-2-oxothiazolidin-4-ylidene)thiazoline (IX). To 2.12 g (5 mmole) thiazoline VII was added 10 ml concentrated HCl and the mixture was refluxed with stirring for 5 h; the precipitate was filtered, washed with sodium bicarbonate solution, and washed again with water on the funnel. It was purified by crystallization from acetic acid. Yield 1.0 g (63%), mp 268-269°C (decomp.). Found, %: N 14.2, S 21.7. $C_{12}H_{13}N_3O_2S_2$. Calculated, %: N 14.2, S 21.7.

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