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SYNTHESIS AND STRUCTURE OF NONCONDENSED BICYCLIC THIAZOLIDINO-4-ONE DERIVATIVES

I. B. Levshin, V. V. Chistyakov, O. A. Anisimova, and Yu. N. Sheinker

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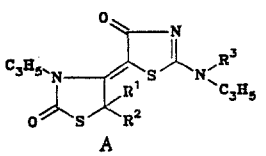
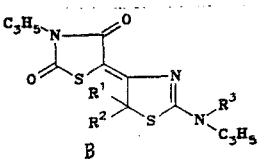
The synthesis of novel noncondensed bicyclic thiazolidin-4-one derivatives has been achieved. The bond between the thiazolidinone rings has been shown, using mass spectrometry, to be located at the 5–4' positions.

It has previously been demonstrated [1] that a noncondensed bicyclic thiazolidin-4-one derivative, namely, 2-acetylallylamino-4-oxo-5-(3-allyl-2-oxothiazolidin-4-ylidene)thiazoline (I), could be synthesized via condensation of an unstable intermediate, 2-acetylallylamino-thiazolin-4-one with 3-allylthiazolidin-2,4-dione in an acetic anhydride–acetic acid medium.

Based on the reactivity of the functional groups in the thiazolidin-4-one molecule, theoretically two isomers should be able to be formed, bonded to one another through either the 5–4' (A) or 4–5' positions (B).



A



B

I $R^1=R^2=H$, $R^3=COCH_3$; II $R^1=R^2=R^3=H$; III $R^1=R^2=CHPh$, $R^3=COCH_3$

In choosing between the alternative structures A and B in our previous paper [1], we relied on experimentally verified data concerning the greater reactivity of the methylene group in 2-acylamino thiazolidin-4-one derivatives with respect to aldol condensation reactions, compared to the reactivity of thiazolidin-2,4-dione derivatives [2]. This was supported also by the negative result obtained in the attempted self-condensation of 3-allylthiazolidin-2,4-dione upon refluxing in acetic anhydride or in a mixture of the latter with acetic acid. It was not possible, however, based on the data reported in [1], to reach an unequivocal conclusion concerning the site of addition of the two rings.

In order to confirm our assumptions concerning the structure of these compounds, and, furthermore, to establish the position of the double bond between the two rings, we have carried out a mass spectroscopic investigation of both the known compounds in this class (I-III [1]) as well as some new derivatives, which were prepared as a result of condensation

S. Ordzhonikidze All-Union Scientific Research Chemical-Pharmaceutical Institute, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1568-1571, November, 1987. Original article submitted March 5, 1986.

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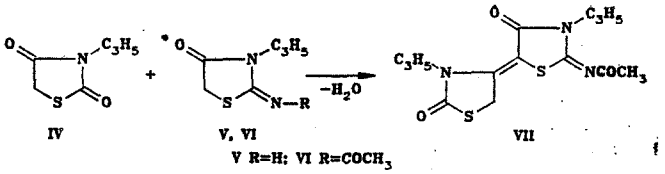
of 3-allylthiazolidin-2,4-dione (IV) with several thiazolidin-4-one derivatives. The condensation reaction in this paper, in contrast to those in [1], was carried out with stable, specially synthesized compounds, namely, 2-imino-3-allylthiazolidin-4-one (V) and 2-acetylimino-3-allylthiazolidin-4-one (VI).

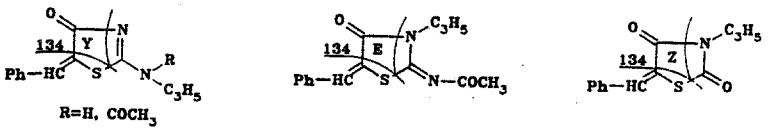
When the reaction between compounds IV and V (R = H) was carried out in acetic anhydride, or in a mixture with acetic acid, for an extended reflux period, the noncondensed bicyclic derivative 2-acetylimino-3,3'-diallyl-4,2'-dioxo-5,4'-dithiazolidinylidene (VII) was obtained, based on elemental analysis and mass spectral data.

The same compound was obtained via reaction of IV with VI (R = $COCH_3$) under the same conditions.



Analysis of the group of molecular ion peaks (M^+) in the mass spectrum of compound VII indicates that two sulfur atoms ($I_{[M+2]^+}$ = 9% of I_{M^+}) are present in the molecule [4].

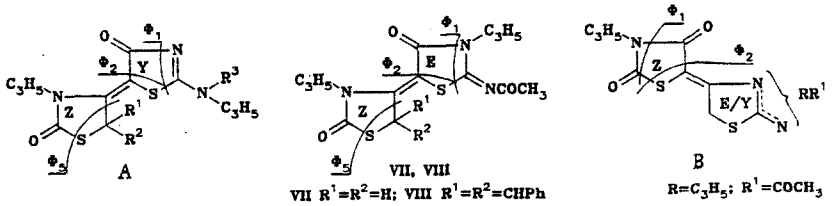
The site of addition of the two rings was deduced based on analysis of the mass spectra of 5-benzylidenethiazolidin-4-ones [1, 5], which revealed that the most characteristic mode of decomposition of these compounds involves the formation of a $[Ph{-}CH{=}C_{(5)}{=}S]^+$ fragment at m/z 134; this is the maximum intensity peak in all cases.



This observation indicated that, in the presence of a substituent in position 5 which is bound to the ring via a double ylidene type bond [regardless of whether it has a thiazolinyl structure (Y) or thiazolidine structure (E, Z)], decomposition of the molecular ion via electron impact occurs via cleavage of the $S{-}C_{(2)}$ and $C_{(4)}{-}C_{(5)}$ bonds and the formation of a $[Ph{-}CH{=}C_{(5)}{=}S]^+$ fragment. In addition, cleavage of the $N{-}C_{(4)}$ bond and elimination of a CO group can also take place.

It is apparent from these considerations that in the bicyclic compounds under investigation herein bond cleavage takes place at the 1–2 and 4–5 positions in the ring in which the double bond is located α to the sulfur atom. Thus, depending on the presence of the double bond in the 5–4' (A) or 4–5' (B) positions, the resulting fragments will differ in their mass numbers.

Based on these discussions, the mass spectroscopic fragmentation of bicyclic thiazolidin-4-one derivatives (I-III, VII, VIII*) can be illustrated in the form of the following two variations A and B:



For example, in the case of variation A (for compounds I, II, and VI), the fragment (Φ_2) would be expected to have an m/z value of 185 $[S{=}C_{(5)}{=}\text{ring Z}]^+$, and in the case of variation B the Φ_2 fragment would be expected to have an m/z value of 226 $[S{=}C_{(5)}{=}\text{ring E or Y}]^+$ (for compounds I and VII) or 184 (for II).

With respect to cleavage of the thiazolidine ring at the $S{-}C_{(2)}$ and $N{-}C_{(4)}$ bonds, for variation A the m/z value of the Φ_1 fragment would be expected to be 213, whereas for variation B the m/z value would be 254.

*Compound VIII was prepared from VII; see Experimental section.

We have also carried out a mass spectroscopic analysis of the newly synthesized compounds using the spectra of the metastable ions, which were obtained via the DADI technique; this revealed that mass spectroscopic decomposition of these compounds occurs via the following pathways: elimination of an acyl substituent from M^+ (for compounds I, III, VII, and VIII), as well as via cleavage of the E or Y ring and the formation of fragments giving rise to maximum intensity peaks at m/z 185 (Φ_2) and m/z 213 (Φ_1) (for compounds I and VII). The absence of spectral fragments corresponding to structure B, with m/z 226 and 254, provides unequivocal evidence for bond formation between the rings at the 5–4' positions.

Further decomposition of Φ_2 ions for compounds I, II, and VII occurs with elimination of a CO molecule from ring Z (Φ_3 ion), or with concomitant cleavage of a 42 amu fragment (apparently an NCO group Φ_4). The acyl and allyl substituents give rise to mass spectral fragment peaks at m/z 43 and 41, respectively.

The bicyclic structure of compound VII is entirely consistent with its UV spectral data; the increase in the conjugation chain length as a consequence of addition of the second thiazolidine ring leads to the appearance of new bands with absorption maxima in the visible region: 378 (4.02) and 445 nm (2.56); these are in addition to the highly intense band with a maximum at 276 nm (log ε 3.75).

The IR spectrum of compound VII contains characteristic carbonyl group stretching bands for the thiazolidinone rings at 1735 ($C_{(2')}$=O) and 1678 ($C_{(4)}$=O), as well as at 1535 cm^{-1} (for the C=O of the acetyl group). The absorption band for the exocyclic C=N bond gives rise to the intense peak at 1640 cm^{-1}.

In order to confirm the presence of a free methylene group in ring Z of compound VII, we carried out the condensation reaction with benzaldehyde in acetic acid in the presence of methylamine. The UV spectrum of the 5-benzylidene derivative VIII, in contrast to the spectrum of the unsubstituted compound VII, exhibited a hypsochromic shift and an increase in the intensity of the absorption band in the visible region of the spectrum, and also contained intense peaks in the ultraviolet region: at 230 (4.08), 273 (4.12), 327 (4.03), and 426 nm (4.34). The largest difference between compounds VII and VIII was observed, however, in the IR spectrum of compound VIII, which exhibited a shift of the carbonyl group stretching frequency from 1735 to 1700 cm^{-1}. Furthermore, the bands which appear in the spectrum of compound VII at 1678, 1640, and 1530 cm^{-1} are replaced by bands at 1600 and 1590 cm^{-1} in the spectrum of VIII, corresponding to C=C stretching vibrations of the benzylidene group.

In the case of bicyclic compounds III and VIII, which contain a benzylidene group in the 5-position of the Z ring, mass spectroscopic decomposition of rings E and Y occurs in an analogous manner to that described previously (see Table 1), while decomposition of the Z ring occurs via a pathway characteristic of 5-benzylidene derivatives, with the formation of a $[Ph–CH=C=S]^+$ fragment (Φ_5) ion giving rise to the most intense peak in the spectrum.

Mass spectroscopic analysis of the compounds synthesized herein has revealed that the structures of the noncondensed bicyclic compounds can be described by structure A, with the bond between the thiazolidinone rings located at the 5–4' positions.

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer 599 spectrophotometer using Vaseline mulls or oils; UV spectra were obtained on a Perkin–Elmer 575 spectrophotometer using alcohol solutions. Electron impact mass spectra as well as metastable ion spectra were measured using DADI technology and defocused on a Varian MAT 112 (FRG) spectrometer. The energy of the ionizing electrons was 70 eV. The ionization chamber temperature was 180°C. Direct introduction of the sample to the ion source was used.

Compounds I-V were prepared according to the method described previously [1, 3].

2-Acetylimino-3-allylthiazolidin-4-one (VI). A solution of 1.56 g (10 mmole) 2-imino-3-allylthiazolidin-4-one in 10 ml acetic anhydride was heated on a water bath at 80°C for 15 min with constant stirring. After being cooled the reaction mixture was poured into water and the precipitate was removed by filtration. It was purified by recrystallization from acetic acid to give 1.36 g (69%). UV spectrum, λ_{max}: 253 nm (log ε, 4.23). IR spectrum: 1728 ($C_{(4)}$=O), 1645 ($C_{(2)}$=N), 1495-1519 cm^{-1} (C=O of the acetyl group).* Found: N 14.16;

*The assignments of the two latter bands in the IR spectrum of compound VI have been refined and differ from those reported earlier [6].

S 16.17%. $C_8H_{10}N_2O_2S$. Calculated: N 14.15; S 16.19%.

2-Acetylimino-3,3'-diallyl-4,2'-dioxo-5,4'-dithiazolidinylidene. A. To a solution of 1.56 g (10 mmole) compound V in 10 ml acetic anhydride was added 1.56 g (10 mmole) 3-allylthiazolidin-2,4-dione (IV), and the reaction mixture was heated for 4 h with constant stirring. After being cooled the reaction mixture was poured into ice water, and the precipitate was filtered, dried, and crystallized from isopropyl alcohol. Yield 1.73 g (54%), mp 150-151°C. Found: N 12.40; S 19.01%. $C_{14}H_{15}N_3O_3S_2$. Calculated: N 12.45; S 19.00%.

B. To a solution of 1.98 g (10 mmole) compound VI in 10 ml acetic anhydride was added 1.56 g (10 mmole) compound IV; the mixture was further worked up according to the above procedure. Yield 2.05 g (61%), mp 150-151°C.

2-Acetylimino-3,3'-diallyl-4,2'-dioxo-5'-benzylidene-5,4'-dithiazolidinylidene (VIII). To a solution of 1.68 (5 mmole) compound VII in 10 ml acetic acid was added 0.5 g (5 mmole) benzaldehyde and 2 drops of 25% aqueous methylamine solution. The mixture was heated in an oil bath at 110-120°C for 2 h with constant stirring. After being cooled the reaction mixture was poured into water and filtered. The product was washed on the filter with ether and dried. Yield 1.6 g (76%), mp 211-212°C (acetic acid). Found: N 10.02; S 14.98%. $C_{21}H_{19}N_3O_3S_2$. Calculated: N 9.89; S 15.06%.

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INTRAMOLECULAR CYCLIZATION OF GUANIDINOALKANETHIOLS IN AQUEOUS SOLUTION

A. A. Mandrugin, V. M. Fedoseev, S. M. Khomutov, A. A. Rodyunin, and Yu. A. Leshchev

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We have demonstrated the basic possibility of cyclizing guanidinoalkanethiols of different structure to thiazolines and thiazines. The rate of reaction depends on the pH of the medium. The concentration of buffer and the addition of heavy water and α-D,L-alanine have virtually no effect on the rate of reaction.

Methods are known for obtaining dihydrothiazines and thiazolines by the reaction of potassium thiocyanate with suitable haloaminoalkanes [1] as well as by cyclization of derivatives of S-2(3)-aminoalkylisothioureas in acid solution [2].

We have studied the behavior of 2-guanidinoethanethiol (I), 3-guanidinopropanethiol (II), 3-guanidinobutanethiol (III), and 2-guanidinobutanethiol (IV) in aqueous solution. When compounds I-IV are heated in water without admission of oxygen, dihydrothiazine or

M. V. Lomonosov Moscow State University, Moscow 119899.

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