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SYNTHESIS OF 1,3,4-THIAZOLE DERIVATIVES BY THE REACTION OF THIOBENZHYDRAZIDE WITH SOME ACYLACETYLENES

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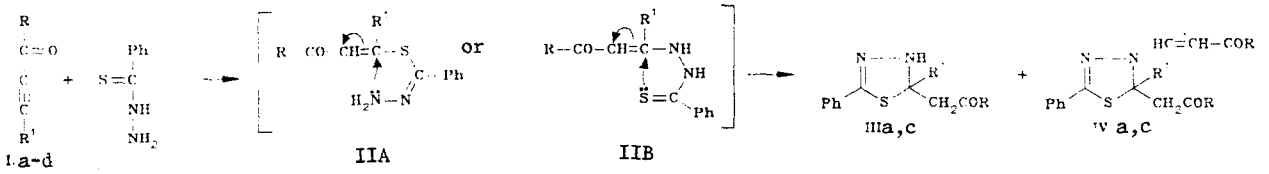
2-Acylmethyl-5-phenyl- and 3-acylvinyl-2-acylmethyl-5-phenyl-1,3,4-thiadiazol-4-ines were obtained by the reaction of terminal α-acetylenic ketones with thiobenzhydrazide. Substituted acetylenic ketones react with thiobenzhydrazide in alcohol to give N,S-bis(acylvinyl)thiobenzhydrazides.

The reaction of aromatic thiohydrazides with dimethyl acetylenedicarboxylate and methyl propylate by heating in anhydrous methanol leads to the formation of substituted 1,3,4-thiadiazoles [1]. 1,3,4-Thiadiazole derivatives have a number of practically valuable properties and can be used as chemical agents for the protection of plants [2, 3], antibacterial agents [4], and antioxidants for oils [5].

We have investigated the reaction of acylacetylenes Ia-d with thiobenzhydrazide.

Terminal α-acetylenic ketones Ia,c in methanol react with thiobenzhydrazide at 20°C and an equimolar reagent ratio to give 3-acylvinyl-2-acylmethyl-5-phenyl-1,3,4-thiadiazol-4-ines IVa,c in 80% yields (based on the ketone) and a small amount (8-11%) of 2-acylmethyl-5-phenyl-1,3,4-thiadiazol-4-ines IIIa, c. A change in the ketone—thiobenzhydrazide ratio (2:1) has virtually no effect on the yields of IVa, c.



a R=Ph, R¹=H; b R=R¹=Ph; c R=α-C₄H₃S, R¹=H; d R=α-C₄H₃S, R¹=Ph

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp, °C	Yield, %	
			A	B
IIIa	$C_{16}H_{14}N_2OS$	105...106*	11	78
IIIc	$C_{14}H_{12}N_2OS_2$	121,5...123	8	56
IVa	$C_{25}H_{20}N_2O_2S$	143...145	79	10
IVc	$C_{21}H_{16}N_2O_2S_3$	175...177	80	20
Vb	$C_{37}H_{28}N_2O_2S$	137...138	74	
Vd	$C_{33}H_{24}N_2O_2S_3$	146...148		70

*According to the data in [7], this compound had mp 121°C.

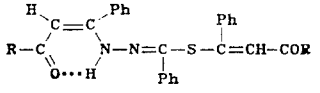
In an aprotic solvent (benzene) with an equimolar reagent ratio at 20°C derivatives IIIa, c (56-78% yields) and small amounts (10-20%) of IVa,c are formed as a result of the reaction. 2,5-Di-phenyl-1,3,4-thiadiazole — the product of the intermolecular condensation of two molecules of the starting thiobenzhydrazide — is primarily formed when the reaction temperature is raised to 60-80°C [6].

Intense absorption bands at 690-705 (C—S), 1660-1675 (C=O), 1580-1610 (C=C, ring C=N), and 3315 cm^{-1} (NH) are observed in the IR spectra of 2-acylmethyl-5-phenyl-1,3,4-thiadiazol-4-ines IIIa, c. Absorption band of a conjugated carbonyl group at 1635-1665 cm^{-1}, of an unconjugated C=O group at 1660-1695 cm^{-1}, of a C—S bond 690-715 cm^{-1}, and of a C—H bond at 960-970 cm^{-1} (CH=CH, trans) and of stretching vibrations of C=C and C=N bonds in the thiadiazoline ring at 1520-1600 cm^{-1} are present in the IR spectra of IVa, c.

The PMR spectrum of IIIa corresponds completely to the data in [7]. The PMR spectrum of 3-benzoylvinyl-2-benzoylmethyl-5-phenyl-1,3,4-thidiazol-4-ine (IVa) contains two doublets of olefin protons at 6.28 and 8.20 ppm (J = 13.1 Hz); this constitutes evidence for a trans orientation of the protons of the vinyl group. The protons of the methylene group give a multiplet at 3.54-4.03 ppm ($^2J_{AB}$ = 18.3, $^3J_{AX}$ = 9.6, $^3J_{BX}$ = 3.8 Hz). The triplet of the methylidyne proton is superimposed on the doublet of the olefinic proton of the COCH= group and shows up at 6.28 ppm. A multiplet of protons of benzene rings is observed at 7.43-7.92 ppm.

The reaction of 1-phenyl-2-acylacetylenes Ib,d with thiobenzhydrazide in methanol at 20°C at a reagent molar ratio of 1:1 and 2:1 led to the formation of exclusively N,S-bis(acylvinyl)thiobenzhydrazides Vb, d. When the reaction was carried out in benzene at 80°C, 2,5-diphenyl-1,3,4-thiadiazole was isolated from the reaction mixture.

Singlets of olefinic protons of aminovinyl fragments at 6.08 and 5.93 ppm are observed in the PMR spectra of Vb, d; the signals of the protons of the thiovinyl group are overlapped by a multiplet of the protons of benzene rings at 7.20-8.12 ppm.



V b,d

V b R = Ph, d R = α-C_4H_3S

The significant shift of the signals of the protons of the NH groups to weak field (14.00 and 14.07 ppm for Vb and Vd, respectively) constitutes evidence that an intramolecular hydrogen bond with a Z configuration is realized in the keto aminovinyl fragment.

The first step in the reaction is evidently nucleophilic attack by the sulfur atom of the thiocarbonyl group or the primary amino group at the electron-deficient β-carbon atom of the acetylenic bond with the formation of intermediate S- or N-monoadducts IIA or IIB. Since the mercapto group is a stronger nucleophile than the amino group [8, 9], one might expect primarily the formation of S-monoadducts IIA. However, the primary amino group in thiobenzhydrazide may have high nucleophilicity comparable to the nucleophilicity of the sulfur atom due to the α effect [10]. As a consequence of this, one cannot exclude the formation of intermediate N-monoadducts IIB. In the case of substituted acetylenic ketones Ib,d (R^1 = Ph) adducts II contain a bulky phenyl substituent attached to a double bond, which creates steric hindrance to intramolecular cyclization. In this case nucleophilic addition of the

intermediate monoadducts II to yet another molecule of substituted acylacetulenes Ib,d with the formation of Vb,d is more easily realized.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were obtained with a UR-20 spectrometer. The PMR spectra of solutions in $CDCl_3$ were obtained with a Tesla BS-487C spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) as the internal standard.

The characteristics of the synthesized compounds are presented in Table 1. The results of elementary analysis of III-V for C, H, N, and S corresponded to the calculated values.

Reaction of Benzoylacetylene (Ia) with Thiobenzhydrazide. A) A solution of 0.65 g (5 mmole) of ketone Ia in 5 ml of MeOH was added slowly with vigorous stirring to a solution of 0.76 g (5 mmole) of thiobenzhydrazide in 15 ml of MeOH, and the mixture was stirred for 2 h at 20°C and allowed to stand overnight. The resulting precipitate was removed by filtration and recrystallized from ethanol–ether (1:1) to give 0.81 g of 3-benzoylvinyl-2-benzoylmethyl-5-phenyl-1,3,4-thiadiazol-4-ine (IVa). The solution after isolation of IVa was evaporated at 20°C in vacuo to half its original volume, and the concentrate was maintained at 0°C for 24 h to give 0.15 g (11%) of 2-benzoylmethyl-5-phenyl-1,3,4-thiadiazol-4-ine (IIIa).

In the case of a Ia-thiobenzhydrazide ratio of 2:1, 1.75 g (85%) of IVa was formed under similar conditions.

B) A mixture of 0.65 g (5 mmole) of Ia and 0.76 g (5 mmole) of thiobenzhydrazide in 20 ml of benzene was stirred for 2 h at 20°C and allowed to stand overnight. The resulting precipitate was removed by filtration, washed with cold ether, and dried in vacuo to give 0.1 g (17%) of 2,5-diphenyl-1,3,4-thiadiazole with mp 140–142°C (mp 141–142°C [6]).

The solvent was evaporated in vacuo at 20°C, and the residue was recrystallized from ether to give 1.1 g (78%) of 2-benzoylmethyl-5-phenyl-1,3,4-thiadiazol-4-ine (IIIa) and 0.14 g (10%) of IVa. When this reaction was carried out in refluxing benzene (80°C), we observed pronounced resinification of the reaction mixture and the formation of IIIa (15% yield) and 2,5-diphenyl-1,3,4-thiadiazole (70% yield).

2-Thenoylmethyl-5-phenyl-1,3,4-thiadiazol-4-ine (IIIc). This compound was obtained as in the case of IIIa by method B from 0.68 g (5 mmole) of thenoylacetylene (Ic) and 0.76 g (5 mmole) of thiobenzhydrazide. The yield was 0.8 g. We also isolated 0.2 g (20%) of IVc from the reaction mixture.

3-Thenoylvinyl-2-thenoylmethyl-5-phenyl-1,3,4-thiadiazol-4-ine (IVc). This compound was obtained as in the case of IVa by method A from 0.68 g (5 mmole) of Ic and 0.76 g (5 mmole) of thiobenzhydrazide. The yield was 0.84 g (80%). PMR spectrum ($CDCl_3$): 6.27 (2H, m, COCH=, SCH), 8.12 (1H, d, J = 13 Hz, N–CH=), 3.48-3.98 (2H, m, CH_2CO), 7.43-7.70 ppm (11H, m, C_4H_3S, C_6H_5).

1,3,6,8,10-Pentaphenyl-7-thia-4,5-diaza-2,5,8-decatriene-1,10-dione (Vb). This compound was obtained as in the case of IVa by method A from 1.03 g (5 mmole) of 2-benzoyl-1-phenylacetylene (Ib) and 0.76 g (5 mmole) of thiobenzhydrazide. The yield was 1.05 g (74%). At a 1b–thiobenzhydrazide ratio of 2:1 the yield of Vb was 1.14 g (81%). IR spectrum: 1640, 1660 (C=O), 1550-1580 (C=C, C=N), 690 cm^{-1} (C–S).

When the reaction was carried out in benzene at 80°C, only 2,5-diphenyl-1,3,4-thiadiazole was isolated. The yield was 0.38 g (63%).

1,10-Di(2-thienyl)-3,6,8-triphenyl-7-thia-4,5-diaza-2,5,8-decatriene-1,10-dione (Vd). This compound was obtained as in the case of IVa from 1.06 g (5 mmole) of 2-thenoyl-1-phenyl-acetylene (Id) and 0.38 g (2.5 mmole) of thiobenzhydrazide. The yield was 1.01 g (70%). IR spectrum: 1625, 1640 (C=O), 1540-1580 (C=C, C=N), 705 cm^{-1} (C–S).

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NEW METHOD FOR THE PREDICTION OF ANTIBACTERIAL PROPERTIES OF SEMISYNTHETIC PENICILLINS.

2.* EVALUATION OF ACTIVITY LEVELS

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In the case of various types of semisynthetic penicillins it is demonstrated that it is possible to use statistical indexes that characterize the probability of the development of structural elements in fixed positions of the side chain to predict the antibacterial properties of semisynthetic penicillins.

Predictive information regarding the optimal location of functional groups, heteroatoms, and cyclic systems in the side chain of the antibiotic was found as a result of an analysis of the structural-biological principles in a series of semisynthetic penicillins by means of the TOPLOG program system. This information can be used to obtain new compounds with improved antibacterial properties [1]. However, its practical application in synthetic planning is complicated by the lack of a method that makes it possible to pass from a fragmentary to an integral structural-statistical evaluation that quantitatively characterizes the activity levels of new compounds.

The fact is that the inclusion in the side chain of penicillin of groupings that intensify its antibacterial action is often inseparably associated with the development of accompanying structural elements with moderate or unfavorable predictive evaluations.

To solve these problems we proposed a computational predictive index (P_{am}) that takes into account the cumulative effect of all of the descriptor centers that form the side chain of the antibiotic. The P_{am} index is calculated as the arithmetic mean of the probabilities P_i of the structural characteristics that enter into the structural formulas of the side chains of compounds that one plans to synthesize:

$$P_{am} = \left(\sum_{i=1}^{N} P_i\right)/N,$$

where N is the number of characteristics. The following reasoning constitutes the basis for this calculation.

When the compounds are divided into activity classes in the TOPLOG system, either 1, which designates the presence of activity (exceeding of a predesignated threshold of minimal suppressing concentration (MSC) with respect to at least one of the activity tests) or 0, which designates the lact of activity (below the predesignated threshold of MSC with respect to all activity tests) is actually assigned to each compound as an activity characteristic;

*See [1] for Communication 1.

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