MOBILITY OF HYDROGEN ATOMS OF THE METHYLENE GROUP OF CERTAIN ACYLPSEUDOTHIOHYDANTOINS

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Derivatives of thiazolidone-4 are used in the treatment of tuberculosis, malaria, and fungal infections [1]. Also, because of their high chelating power, they suppress the metabolism of bacterial cells, for which purpose the presence of traces of metals is necessary. This property of forming precipitates with metallic ions is made use of in the qualitative and quantitative analysis of microquantities of gold, silver, and other metals.

Our work was done on 2-iminothiazolidone-4, a pseudothiohydantoin [2]. It seemed worthwhile to study the condensation reaction with aromatic aldehydes in position 5 in relation to the introduction of acetyl and benzoyl substitution groups into the imino group, because the nucleophile properties of the carbon atom at position 5 are associated with the electron-acceptor properies of the substitution group at the second carbon atom.

Pseudothiohydantoin was acetylated by acetic anhydride in acetic acid [3]. Acetylpseudothiohydantoin was condensed with equimolecular amounts of aldehydes by heating for two hours with butanol and a few drops of acetic acid added as catalyst. In this way we prepared derivatives II to V containing at position 5 residues of benzaldehyde, p-dimethyl-,p-diethyl-,or p-di-(2-chorethyl)-aminobenzaldehyde at a yield of about 70% (see Table 1). The reaction took twice as long without the catalyst. Other catalysts (acetic acid and sodium acetate, zinc chloride, piperidine) gave a lower yield, or else there was no reaction. Thus, compounds III, IV, V were produced in glacial acetic acid with sodium acetate in yields of 28.6%, 33.7%, and 45%, respectively.

The absence of an acetyl group from pseudothiohydantoin strongly influenced condensation with aldehydes. Condensation of pseudothiohydantoin with benzaldehyde in acetic acid in the presence of sodium acetate by the method described in [4] gave a 38% yield, and we have shown that under the same conditions the corresponding acetylpseudothiohydantoin gives a yield of 67%. In the reaction of nonacetylated pseudothiohydantoin with p-dimethylaminobenzaldehyde we obtained only 3.5% of the product.

Compounds II-V where chromatographed on a nonreinforced 0.8 mm layer of aluminum oxide of second degree of activity in the system ethanol-formamide-dioxane (5:5:1); to develop the chromatograms we used a PRK-4 UV lamp. Compounds II-V were soluble in acetic acid, alcohols, dioxane, acetone, formamide, dichlorethane, dilute mineral acids and alkalis, and were insoluble in water, ether, and hexane. Alcoholic solutions of V gave an insoluble dark-yellow precipitate when mixed with silver nitrate, and a pale blue precipitate with copper sulfate. With concentrated sulfuric, nitric, and hydrochloric acids a crimson color appeared which disappeared on addition of acid, but reappeared after gradual neutralization with weak alkali. After further addition of alkali the color changed to yellow.

Pseudothiohydantoin was benzoylated with benzoyl chloride in dry pyridine. Condensation of equimolecular quantities of benzoylpseudohydantoin and aromatic aldehydes

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	., %	<i>ა</i>	3 13,30	3 12,16	3 11,08	3 10,02	7 8,30	3 10,39	9 9,10	9 9,10	5 9,12	5 7,16	4 10,74	
2-Acylimino-5-arylidenethiazolidone-4 R-CH=CH=CH=CH=CH=CH=CH=CH=CH=CH=CH=CH=CH=C	Calc	z	11,23	11,38	14,73	13,23	10,87	30'6	11,85	11,85	11,96	9,36	9,4	
	Empirical formula		C ₁₀ H ₈ N ₈ OS .HCI	C ₁₂ H ₁₀ N ₂ O ₂ S	C ₁₄ H ₁₆ N ₃ O ₂ S	$C_{1.6}H_{1.9}N_{3}O_{2}S$	C16H17C12N3O2S	$C_{17}H_{12}N_{2}O_{2}S$	C ₁₇ H ₁₁ N ₃ O ₄ S	C ₁₇ H ₁₁ N ₃ O ₄ S	C ₁₉ H ₁₇ N ₃ O ₂ S	C21H19C12N3O2S	C ₁₅ H ₁₀ N ₂ O ₃ S	
	Found, %	s	12,92	11,74	11,01	9,84	8,16	10,48	9,33	9,41	9,00	7,40	11,06	
		z	11,38	11,46	14,60	13,14	10,41	9,28	12,04	12,11	12,31	9,25	9,42	
	Rft		J	0,38]	0,35	0,31	0,19	0,35	0,21	0,29	0,38	0,31	
	Color of crystals		Yellow	Yellow	Dark red	Red	Orange yellow	Brown	Yellow	Reddish violet	Orange	Pale brown	Reddish brown	
	Melting point (in deg)*		284	277	301	285	2534°	238-241	25861	2568	2402	2525	2002	
	Yield,		29	74	62	63	70	58	60	02	65	75	65	
	(×		н	CH ₃ CO	CH ₃ CO	CH ₃ CO	CH ₃ CO	C ₆ H ₅ CO	C ₆ H ₅ CO	C ₆ H ₅ CO	C ₆ H ₅ CO	C ₆ H ₅ CO	C ₆ H ₅ CO	
	Ж		C ₆ H ₅	C ₆ H ₅	$p = (CH_3)_2 NC_6 H_4$	$p = (C_2H_6)_2 NC_6H_4$	$p = (CICH_2CH_2)_2NC_6H_4$	C ₆ H ₅	$p = NO_2C_6H_4$	$m = NO_2C_6H_4$	$p = (CH_3)_2 NC_6 H_4$	$p = (CICH_2CH_2)_2NC_6H_4$	d.	
TABLE 1.	Com-	punod	1	II	111	IV	Λ	ΛI	ΝI	VIII	IX	X	IX	

*Compounds I, II, and V-VIII were recrystallized from acetic acid, compound III from dioxane or butanol, compound IV from ethanol, compounds IX and X from amyl alcohol, and compound XI from toluol. †For compounds II-V we used the system: ethanol-formamide-dioxane (5:5:1); for compounds VI-XI we used formamide-ethanol (1:10). ‡ Same as melting point of the nonacetylated product [3].

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was effected by heating them in butanol together with catalytic amounts of piperidine and acetic acid. For a concentration of 0.01 moles of the original substances we took not more than 8 ml of butanol; increase in the amount of the latter makes it more difficult to separate the product and gives a lower yield. When acetic acid alone was used as catalyst the same yield was obtained but only when the mixture was heated for twice as long. During the course of the reaction the initial reagents were dissolved, and subsequently separated out as colored crystals. Benzaldehyde separated only after it had been cooled, the other reagents did so during the course of the reaction. The products obtained (VI-XI) were soluble in dioxane, acetic acid, benzene and its homologs, ethanol, amyl alcohol, dimethyl formamide, and alkalis; they were only slightly soluble in butanol and acetone, insoluble in water, acids, and carbon tetrachloride. The melting point of the purified substances was between 200 and 258°. The yield depended on the heating time: With 5-min heating it was 40-50%, and with 1-h heating it rose to 75%. Further heating caused but little further increase in yield. Alcoholic solutions of compounds VI-XI formed a colored amorphous or finely crystalline precipitate with copper sulfate, cobalt chloride, and silver nitrate, because of the acidic properties of the cyclic nitrogen. In UV light the silver salts fluoresced with a color ranging from vellowish-brown to reddish-brown while the initial reagents gave a pale-vellow, dark-green, or brown fluorescence. Chromatograms were run in the system formamideethanol (1:10), and values of R_f are given in Table 1.

IR spectra of V in vaseline recorded on a UR-20 spectrometer showed lines at 3150, 3030, 3020, 1690, 1660, 1640, 1618, 1583, 1525 cm⁻¹, and others; compound X gave lines at 3150, 3040, 1682, 1646, 1618, 1570, 1555, 1520 cm⁻¹, and others. We observed a marked increased in the intensity of the absorption bands of X in the carbonyl region; and the presence of additional bands in the region 1555 cm⁻¹ made it possible to distinguish with certainty the frequency of absorption of benzoyl associated with the exocyclic linkage -C=N. The color of the solutions obtained obeyed the law of Lambert-Beer. Thus, we found a linear relationship between the optical density and concentration for V and X (about $2.5 \cdot 10^{-6}$ moles/liter in dioxane).

A microbiological study of the products was carried out in the department of tuberculosis (E. S. Korobkov) of our institute; tests were made on the tubercle bacillus "Akademiya" cultured in thick Levinstein-Jensen medium at 37° for 21 days. In a dilution of 1:100,000 all of the substances suppressed growth.

The first tests of anticarcinogenic activity were made by A. A. Nikulin and V. V. Dunaev at the Department of Pharmacology. It was found that cytostatic activity was high (index of suppression was 33). The experiments were carried out on female rats weighing 100-150 g (tumors RS-1). The dose was 400 mg/kg by mouth daily from the second to the 11th day. Tumors were weighed on the 31st day. The index of suppression was defined as the ratio of a control tumor to the weight of the tumor in the treated animals.

EXPERIMENTAL METHOD

<u>Acetylpseudothiohydantoin</u>. For 15 min 11.6 g of pseudothiohydantoin were heated in 12 ml of acetic anhydride and 10 ml of acetic acid. The mixture was then cooled to room temperature. An abundant yellowish precipitate settled out. Yield 14.7 g (93%) paleyellow crystals decomposing at 245-250° (from glacial acetic acid). Percentages found: N 11.49. Formula $C_5H_6N_2O_2S$. Percentage of nitrogen calculated: 11.38. The substance was soluble in alcohols, dioxane, formamide, and acetic acid.

5-Benzylidenepseudothiohydantoin Hydrochloride (I). A mixture of 0.95 g of monochloracetic acid, 1.5 g of thiourea and 2 ml of benzaldehyde in 10 ml of galcial acetic acid was heated for 30 min in the presence of 1 g anhydrous sodium acetate. When heated, the mixture turned orange. After 50 ml of 20% sodium chloride solution had been added to the mixture a yellow precipitate was formed which was recrystallized from glacial acetic acid in the presence of a few drops of concentrated hydrochloric acid. Yield 1.22 g. The substance was soluble in alcohols, dioxane, and in dilute acids and alkalis. In dilute nitric acid it gave a positive reaction for chloride ion. 2-Acetylimino-5-benzylidenethiazolidone-4 (II). A mixture of 0.32 g acetylpseudothiohydantoin and 0.4 ml of benzaldehyde was boiled in 10 ml butanol in the presence of five drops of glacial acetic acid for 1 h. The solution turned yellow, and yellow crystals separated out. Yield 0.35 g.

Compounds III-V were obtained in a similar way by heating the reagents under the same conditions.

Benzoylpseudothiohydantoin. To a continuously shaken and cooled suspension of 5.8 g of pseudothiohydantoin in 20 ml of anhydrous pyridine, 5.75 ml of benzoyl chloride was added drop by drop. The mixture was heated for 2 h under a reflux condenser. It turned yellow and changed into a clear orange solution, which after being cooled to room temperature was poured out onto finely crushed ice. After 12 h the dark-brown crystals which had separated out were filtered, and dried at 30° in a vacuum. Yield 9.9 g (90%), mp 182-184° (recrystallized from ethanol). Percentage of nitrogen found: 12.60. Formula $C_{10}H_8N_2O_2S$. Percentage nitrogen, calculated: 12.73. The compound was soluble in alcohols, benzene and its homologs, acetic acid, dioxane, formamide, dimethyl formamide, water, alkalis; it was slightly soluble in ether and acetone, and insoluble in carbon tetrachloride and in acid solutions. In UV light it gave a pale-yellow fluorescence, while the silver salt fluoresced yellow-green. It is precipitated by copper sulfate from alcoholic and weakly alkaline solutions.

2-Benzoylimino-5-benzylidenepseudothiohydantoin (VI). A mixture of 1.1 g benzoylpseudothiohydantoin and 0.5 ml of benzaldehyde together with two drops of an equimolecular mixture of piperidine and glacial acetic acid as catalyst was heated for 1 h in 3 ml butanol at 117°. The benzoylpseudothiohydantoin dissolved and the liquid turned dark orange. After it had been cooled a pale-brown precipitate was formed; it was filtered off, washed with ether, and dried in a vacuum. Yield 0.9 g.

Compounds VII-XI were obtained in the same way.

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