ISOMERISM OF ISATIN-α- AROYLHYDRAZONES

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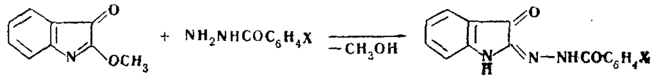
UDC 547.756 : 541.634

The reaction of isatin O-methyl ether with hydrazides of aromatic acids gives the cis and trans forms of α-aroylhydrazones.

In carrying out the reaction of isatin O-methyl ether with the hydrazides of benzoic and substituted benzoic acids (I-III) in order to obtain isatin-α-aroylhydrazones (IV-VI), in each case we isolated two isomers (IVa-VIa and IVb-VIb) with different colors, solubilities in aqueous alkalis and organic solvents, and some different chemical properties (see Table 1).



I - III IV - VI

I,IV X=H; II,V X=o-Br; III,VI X=p-Cl

Compounds IV-VI can exist as several tautomeric forms and two stereoisomers. This sort of isomerism in the isatin series has been studied only in a few cases: isatin α-anil was isolated in two tautomeric forms [1], and isatin-β-guanylhydrazone and N-methyl-β-semicarbazone were obtained in cis and trans forms [2,3]. Contradictory melting point data are presented in the literature for a number of hydrazones of isatin (the β-thiosemicarbazone, for example [4]), which is apparently associated with their existence in different forms.

In this connection, the elucidation of the structure of the compounds that we have obtained seems of general interest.

TABLE 1. Isatin-α- and Isatin-β- aroylhydrazones

Compound	Color	Mp (crystallization solvent)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
IVa	Yellow	263—266*	$C_{15}H_{11}N_3O_2$	67,8 67,7	3,8 4,0	15,5 15,5	67,9	4,2	15,8	30
IVб	Red	266—267 (benzene)	$C_{15}H_{11}N_3O_2$	68,0 68,2	3,9 4,0	15,8 15,8	67,9	4,2	15,8	32
Va	Yellow	258—262*	$C_{15}H_{10}BrN_3O_2$	—	—	12,4 12,2	—	—	12,2	32
Vб	Red	264 (ethanol)	$C_{15}H_{10}BrN_3O_2$	—	—	12,4 12,3	—	—	12,2	2
VIa	Yellow	266—270*	$C_{15}H_{10}ClN_3O_2$	—	—	13,8 13,8	—	—	14,1	6
VIб	Red	272—273 (ethanol)	$C_{15}H_{10}ClN_3O_2$	—	—	13,9 13,8	—	—	14,1	34
VIII	Yellow	239—240 (ethanol)	$C_{15}H_{10}BrN_3O_2$	—	—	12,2 12,1	—	—	12,2	81
IX	Red	303—304 (ethanol)	$C_{15}H_{10}ClN_3O_2$	—	—	13,9 13,9	—	—	14,1	85

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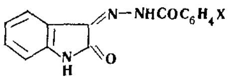
* The compound turns red above 100 deg C.

Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1050-1052, August, 1971. Original article submitted December 21, 1970.

To prove the structures of IV-VI, we recorded their IR and UV spectra (for IVa and IVb), determined the conditions of interconversion of forms a and b, and studied some of their chemical properties. In addition, the corresponding isatin-β-aroylhydrazones (VII-IX) were prepared to compare the absorption spectra.

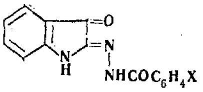

VII-IX

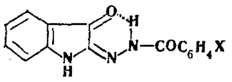
VII X=H; VIII X=o-Br; IX X=p-Cl

The UV spectra of IVa and IVb do not differ from one another (λ_{max} 265, 320, 445 nm), which makes it possible to assume that they have similar chemical structures.

The major differences in the IR spectra of the two forms are observed in the characteristic absorption frequencies of the carbonyl group of the isatin ring. Substances IVa-VIa have an intense band of the absorption of the C=O group at 1728-1730 cm^{-1}, which is close to the absorption of the C=O groups of isatin (1738 cm^{-1}). However, IVb-VIb have an absorption maximum of the C=O group at 1700 cm^{-1}, which corresponds to the C=O absorption in VII-IX. The same shift in the absorption maximum of the C=O group of the isatin ring was observed in a number of isatin-β-hydrazones [5-7] and was due to its participation in the formation of an intramolecular hydrogen bond.

On the basis of this, it can be assumed that IVa-VIa are the trans forms of hydrazones in which the β-carbonyl group of isatin is not tied up in an intramolecular hydrogen bond, while IVb-VIb are the cis forms of the hydrazones with a strong intramolecular hydrogen bond.


IVa-VIa


IVb-VIb

Yellow compounds IVa-VIa are readily converted by heating or by the action of sunlight to red compounds IVb-VIb. The deepening of the color and the greater stability of IVb-VIb can be explained by the presence of an intramolecular hydrogen bond.

Compounds of the *a* form dissolve readily in organic solvents and in aqueous alkalis, while compounds of the b form are soluble with difficulty in most organic solvents and insoluble in aqueous alkalis. Similar observations with respect to the solubility of a number of hydrazones are presented in [8] and are explained by the formation of an intramolecular hydrogen bond.

The difficulty of the formation of dihydrazones in the reaction of IVb-VIb with a second molecule of aroylhydrazine (we could not obtain an isatin dihydrazone from IVb and benzoylhydrazine under the conditions of the formation of VII) can apparently be explained by the participation of the β-carbonyl group of IVb-VIb in the formation of a hydrogen bond. An instance in which the imino group was not acylated because of its participation in the formation of a hydrogen bond is presented in [9].

Compounds IVb-VIb are converted to IVa-VIa under the influence of concentrated hydrochloric acid.

EXPERIMENTAL

Isatin-α-aroylhydrazones (IV-VI). A saturated alcohol solution of 0.01 mole of aroylhydrazine was added to a solution of 0.01 mole of isatin O-methyl ether [10] in 100 ml of anhydrous benzene, and the mixture was stirred and allowed to stand at room temperature. After 5-7 min, a yellow precipitate (IV and V; the precipitate began to redden after 0.5 h) or a reddish precipitate (VI) began to form. After 0.5 h, the precipitate was filtered, washed with a small amount of alcohol, and vacuum dried at room temperature. The reaction product was dissolved in 150 ml of 0.5 N sodium hydroxide and filtered. The filtrate was acidified with 0.5 N hydrochloric acid. The yellow precipitate of IVa-VIa was filtered, washed with water until it gave a neutral reaction, washed with a small amount of alcohol, and vacuum dried at room temperature to constant weight. The red precipitate formed in the preparation of VI contained primarily the alkali-insoluble form. It was washed on the filter with water until it gave a neutral reaction, dried, and combined with VIb (see below), since the substances were identical. Compounds IVa-VIa are yellow, crystalline substances that are readily soluble in alcohol, benzene, acetic acid, and dioxane, very readily soluble in aqueous sodium hydroxide, and insoluble in water and petroleum ether.

The mother liquor was allowed to stand for 12 h at room temperature. The resulting red precipitate of IVb-VIb was filtered, dried, and recrystallized from large amounts of solvents. The red, crystalline substances were slightly soluble in benzene, alcohol, acetic acid, and dioxane, and insoluble in aqueous sodium hydroxide, water, and petroleum ether.

Isomerization of trans-Isatin-α-aroylhydrazones (IVa-VIa) to cis-Isatin-α-aroylhydrazones (IVb-VIb). A) A 0.4 g sample of IVa-VIa was dissolved in 250 ml of boiling benzene, and the solution was refluxed for 20 min on a water bath. The mixture was cooled and allowed to stand for 6 h. The precipitate was filtered, washed with benzene, and dried to give 0.38-0.39 g (95-97%) of products that were identical to IVb-VIb, respectively. Evaporation of the filtrates gave additional amounts of these compounds. The same conversion of IVa-VIa occurs when they are heated in alcohol, acetic acid, dioxane, and other solvents.

B) A 0.1 g sample of IVa-VIa was dissolved in 50 ml of alcohol, and the solutions were allowed to stand in sunlight at room temperature. Compounds IVa-VIa were converted quantitatively to IVb-VIb, respectively, after 3.5 h. The same transformation occurs in diffuse daylight after 12 h.

Isomerization of cis-Isatin-α-aroylhydrazones (IVb-VIb) to trans-Isatin-α-aroylhydrazones (IVa-VIa). A 0.3 g sample of IVb-VIb was dissolved with stirring in 30 ml of concentrated hydrochloric acid, and the solution was allowed to stand for 30 min at room temperature. It was then diluted with a fourfold quantity of water, and the resulting yellow precipitate was filtered, washed with water until it was neutral, and reprecipitated from aqueous sodium hydroxide by the addition of hydrochloric acid. The precipitate was washed and dried as described for the preparation of IVa-VIa to give 0.1-0.12 g (33-40%) of products that were identical to IVa-VIa.

Isatin-β-aroylhydrazones (VII-IX). A saturated alcohol solution of 0.01 mole of acid hydrazide was added to a saturated hot solution of 0.01 mole of isatin in alcohol or dioxane, and the mixture was refluxed on a water bath for 1 h. The precipitate was filtered, washed with hot water, and dried to give 81-85% of products that were soluble in alcohol, dioxane, and acetic acid, slightly soluble in benzene and aqueous alkalis, and insoluble in water and petroleum ether.

Isatin-β-benzoylhydrazone (VII) was obtained by a known method [11].

The IR spectra of potassium bromide pellets of the compounds were recorded with a UR-20 spectrophotometer. The UV spectra of alcohol solutions were measured with an SF-4A spectrophotometer.

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