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Abstract

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SYN-ANTI ISOMERISM OF 3-ARYLHYDRAZONES OF 6-METHYLPIPERIDINEDIONE-2,3

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In the synthesis of biologically active derivatives of tryptamine, alkylated in the side chain (1), we established that 3-arylhydrazones of 6-methylpiperidinedione-2,3 exist in the form of two isomers sharply differing in physical properties. The present article gives proof of the structure of these substances as syn–anti isomers by means of infrared spectroscopy. The arylhydrazones were obtained by the Japp–Klingemann reaction from the corresponding diazo compounds and 6-methyl-3-carboxypiperidone-2:

$$\mathrm{ArN_2Cl}+\text{6-methyl-3-carboxypiperidone-2} \longrightarrow \text{3-arylhydrazone of 6-methylpiperidinedione-2,3}$$

$$\mathrm{Ar} = \mathrm{C_6H_5},\ p\text{-}\mathrm{FC_6H_4},\ p\text{-}\mathrm{ClC_6H_4},\ p\text{-}\mathrm{BrC_6H_4},\ p\text{-}\mathrm{JC_6H_4},\ \beta\text{-naphthyl}$$

In each case it proved possible to isolate the yellow-colored, benzene-soluble α-isomer and the β-isomer, formed in larger amount and insoluble in benzene. The yields and properties of the compounds obtained were published by us earlier (2). It is known that hydrazones of α-dicarbonyl compounds can exist as syn- or anti-isomers, the syn form differing sharply in physical properties from the anti form owing to the formation of chelate structures with a hydrogen bond (3,4).

Until now, conclusions about the configuration of compounds of this kind have been drawn on the basis of consideration of such properties as solubility, color, and the form of the absorption curves in ultraviolet light.

In our case the α-isomers could be assigned the structure of chelate compounds with an intramolecular hydrogen bond (syn form I), and the β-isomers the structure of the anti form (II):

(I) (II) (III)

The possibility of structural isomerism due to formation of azo derivatives of type III could be excluded, since the ultraviolet spectra of all the hydrazones obtained are very similar; moreover, for each pair of isomers the absorption maximum of the α-form is shifted toward longer wavelengths. Azo derivatives of type III should have had a different character of absorption curve (^{5}). See Table 1. The IR spectra of the solid substances in vaseline oil show—

Table 1

Absorption maxima of arylhydrazones in the UV region
(SF-4 spectrophotometer. Solvent—alcohol)

3-Hydrazones of 6-methylpiperidinedione-2,3	Syn isomer* $\lambda_{\max}$ (mμ)/lg $\varepsilon_{\max}$	Syn isomer* $\lambda_{\max}$ (mμ)/lg $\varepsilon_{\max}$	Syn isomer* $\lambda_{\max}$ (mμ)/lg $\varepsilon_{\max}$	Anti isomer* $\lambda_{\max}$ (mμ)/lg $\varepsilon_{\max}$	Anti isomer* $\lambda_{\max}$ (mμ)/lg $\varepsilon_{\max}$	Anti isomer* $\lambda_{\max}$ (mμ)/lg $\varepsilon_{\max}$
Phenylhydrazone	2424.06	2983.82	3464.32	2324.10	2954.02	3294.36
p-Fluorophenylhydrazone	2403.90	3063.92	3444.22		2994.15	3274.28
p-Chlorophenylhydrazone	2484.00	3093.97	3454.28	2433.98	3024.19	3304.31
p-Bromophenylhydrazone	2474.03	3084.02	3494.38	2404.03	3034.28	3314.42
p-Iodophenylhydrazone	2504.04		3504.36	2463.96		3344.34
β-Naphthylhydrazone	2494.11	2923.99	3684.36	2764.06	2884.14	3344.36

* Above the line is $\lambda_{\max}$, below the line is $\varepsilon_{\max}$.

show a difference in the characteristic absorption frequencies of the NH group for each pair of isomers. For the anti isomers, two absorption bands of the NH group are observed: one in the region 3170–3240 cm^{-1} and a second—less intense—in the region 3000–3090 cm^{-1}. The syn isomers have only one NH absorption band, shifted, in comparison with the principal band of the anti isomers, by 60-75 cm^{-1} toward lower wave numbers (see Table 2 and Fig. 1).

Table 2

IR spectra of 3-arylhydrazones of 6-methylpiperidinedione-2,3
(solid substance in Vaseline oil. Recorded on an IKS-14 instrument)

Aryl	Isomer	Characteristic vibration frequencies, cm^{-1}>CO	Characteristic vibration frequencies, cm^{-1}>NH
C_6H_5	syn	1645	3125
C_6H_5	anti	1647	3191 3094
p-FC_6H_4	syn	1653	3104
p-FC_6H_4	anti	1645	3175 3000
p-ClC_6H_4	syn	1648	3104
p-ClC_6H_4	anti	1645	3165 2994
p-BrC_6H_4	syn	1645	3103
p-BrC_6H_4	anti	1642	3182 3018
p-JC_6H_4*	syn	1652	3150
p-JC_6H_4*	anti	1654	3240 3090
β-$C_{10}H_7$	syn	1645	3135
β-$C_{10}H_7$	anti	1647	3204 3036

* All spectra of the *p*-iodophenylhydrazones were recorded on a UR-10 instrument.

Thus, only the anti isomers exhibit the NH-group absorption characteristic of lactams ([6]). In chloroform solution the syn and anti isomers have absorption bands at 3420 cm^{-1}, i.e., a phenomenon characteristic of lactams is observed. Apparently, the absorption of the NH group of the arylhydrazone residue is overlapped by the absorption bands of the lactam ring.

The characteristic absorption frequencies of the carbonyl group for each pair of syn–anti isomers remain practically constant and are close to the absorption frequency of the carbonyl group of 2-piperidone (1651 cm^{-1}) ([7,8]). This can be explained by the fact that in the anti isomer the carbonyl group is bound by intermolecular hydrogen bonds (association of lactams). Indeed, in a solution of ethyl cellosolve the absorption of the carbonyl group of the syn isomer does not change (for Ar = *n*-JC_6H_4 in the solid phase ν =

[IR spectra diagram]

Fig. 1. IR spectra of 3-phenylhydrazone of 6-methylpiperidinedione-2,3.
a —syn isomer, *b* —anti isomer

= 1652 cm^{-1}, in solution $\nu = 1648$ cm^{-1}), whereas for the anti isomer it changes (in the solid phase $\nu = 1654$ cm^{-1}, in solution $\nu = 1663$ cm^{-1}. Ar = *n*-JC_6H_4). 2-Piperidone in chloroform has a characteristic absorption frequency of the carbonyl group of 1667 cm^{-1} ([6]).

When an attempt is made to carry out alkylation of the anti isomer (sodium alcoholate in alcohol or sodium hydride in toluene, benzyl chloride or dimethyl sulfate), isomerization of the anti isomer into the syn isomer is observed; in some cases the conversion can be effected to 60%. As a possible explanation of the isomerization mechanism, the formation of the following structure (IV) may be envisaged:

C_6H_5—N=N—[[chemical structure (IV): sodium enolate form of the hydrazone, with CH_3, NH, ONa substitu

(IV)

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