SYNTHESIS OF 2,4-DISUBSTITUTED 2,3-DIHYDRO-1H-1,5-BENZODIAZEPINES OF THE 1,3-INDANEDIONE SERIES

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2,4-Disubstituted 2,3-dihydro-1H-1,5-benzodiazepines were synthesized by reacting o-phenylenediamine with α,β -unsaturated ketones of the indane-dione series.

The 2,4-diary1-2,3-dihydro-1H-1,5-benzodiazepines are known as very reactive compounds [1-3] and many of them have found practical applications, including as active tranquilizers, blood pressure depressants, analgesics, and sedatives [4]. The problems of stereochemistry, tautomerism, chromaticity of such structures are also of interest [4].

In the present work, we synthesized 2,4-disubstituted 2,3-dihydro-1H-1,5-benzodiazepines (I-VI) by reaction of o-phenylenediamine with α,β -unsaturated ketones of the 1,3indanedione series.

The starting ketones were obtained by a known method [5] consisting of the condensation of 2-acetyl-1,3-indanedione with substituted benzaldehydes.



I Ar = m-NO₂C₆H₄; II Ar = p-NO₂C₆H₄; III Ar = o-OHC₆H₄; IV Ar = p-ClC₆H₄; V Ar = C₆H₅; VI Ar = p-CH₃C₆H₄

In the reaction of the unsaturated ketones with o-phenylenediamine only the cyclization products were isolated - the disubstituted benzodiazepines I-V, in a yield of ~60%, and no products of β -amination at the double bond of the starting ketone were detected.

An attempt to react an α,β -unsaturated ketone containing a p-dimethylaminophenyl substitutent by this reaction (even with longer heating of the reaction mixture) was unsuccessful, while benzodiazepine VI with a p-methoxy group in the phenyl radical was obtained in 10% yield only. This is probably due to the much lower electrophilicity of the double bond in the starting ketones.

There are bands in the IR spectra of compounds I-VI (Table 1) which are characteristic for the vibrations of the NH groups while bands corresponding to the NH_2 group vibrations are absent [1]. The presence of a diazepine ring in compounds I-VI is also confirmed by the presence of absorption maxima in the UV spectra in the ~390 nm region, due to the NH- C_6H_4 -N=C-Ind chromophore group [1]. The bathochromic shift and increase in the intensity of this band, compared with the corresponding values for 2,4-diaryl-2,3-dihydro-1H-1,5benzodiazepines [2], may be due to an increase in the conjugation chain length, when the indanedione fragment is introduced into the molecule.

In the PMR spectra of dihydrobenzodiazepines I, III, V, and VI, there is, besides the aromatic protons multiplet, a broadened singlet of the NH group, while the protons of the $CH-CH_2$ fragment appear in the form of three quartets with an SSCC characteristic for dihydrobenzodiazepines with aromatic substituents in the 2- and 4-positions [6] (Table 2). The weak field shift of the signal of one of the methylene protons (H_M) preferentially occupying

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TABLE 1. Characteristics of 2-Ary1-4-(indane-1,3-dion-2-y1)-2,3-dihydro-1H-1,5-benzodiazepines

Com- pound	Empirical formula	mp,°C	v, cm ⁻¹				λ_{\max} , nm	Yield
			C=C	C=N	R−H	C=O	(ε · 10 ⁴)	%
I III IV V VI	$\begin{array}{c} C_{24}H_{17}N_8O_4\\ C_{21}H_{17}N_3O_4\\ C_{24}H_{18}N_2O_7\\ C_{24}H_{15}N_2O_7\\ C_{22}H_{17}CIN_2O_2\\ C_{24}H_{15}N_2O_2\\ C_{25}H_{20}N_2O_3 \end{array}$	$\begin{array}{c} 193 \dots 197 \\ 225 \dots 226 \\ 275 \dots 277 \\ 217 \dots 218 \\ 244 \dots 246 \\ 243 \dots 244 \end{array}$	1610 1605 1620 1610 1615 1620	1635 1655 1645 1645 1648 1650	3395 3348 3340 3350 3380 3380	1698 1695 1600 1680 1680 1680	384 (5.97) 384 (1,15) 384 (3,82) 382 (3,92) 390 (2,42) 386 (5,46)	62 61 61 53 69 10

TABLE 2. PMR Spectra of Compounds I, IV, V, VI*

Com-	δ, ppm						δ		
pound	HA	H _M	H _X	NH	ОН	AX	МХ	AM	, H _M -H _A
I IV V VI**	3,62 3,21 3,14 3,10	3,87 4,00 4,28 4,27	5,32 5,06 5,12 5,10	4,11 4,05 4,05 4,02	12,10 12,03 12,15 12,16	7,9 9,0 9,8 9,9	3,8 3,3 3,2 3,3	13.3 13,5 13,3 13,4	$0,25 \\ 0,79 \\ 1,14 \\ 1,17$

*The PMR spectra of compounds II and III are not given because of their low solubility.

**The signals of the aromatic protons of compounds I, IV-VI, occur in the 6.80...7.90 ppm region, while for compound VI the signal of the CH₃O group protons is at 3.81 ppm.

an equatorial position, is probably due to the anisotropic screening effect of the C=O group of indanedione. The second C=O group is enolized considerably and participates in the formation of an intramolecular hydrogen bond with the nitrogen atom of the azomethine fragment of the seven-membered ring. This is indicated by the strong shift to the weak field of the methine proton signal in the 2-position of indanedione.

The change in the electronic character of the aromatic substituent has an opposite effect on the CS of the methylene protons (H_A and H_M) of the heterocyclic ring (the δ_{H_A} increases with increase in the electronegativity of the substituent, while δ_{H_M} decreases), whereby the change in the CS of proton A, preferentially occupying the axial position, is considerably greater. The latter property is probably due to a change in the anisotropic screening of this proton by a carbonyl group of the indianedione ring or by the aromatic ring, and indicates a certain change in the conformation of the entire molecule on transition to another substituent. A regular decrease [7, p. 73] is also observed in the vicinal constant J_{AX} with increase in the electronegativity of the aromatic substituent of the heterocyclic ring.

EXPERIMENTAL

The UV spectra were recorded in ethanol on a Cary-219 spectrophotometer at a concentration of $5\cdot10^{-5}$ mole/liter. The IR spectra were run in mineral oil on a UR-20 spectrophotometer, and the PMR spectra were measured in CDCl₃ on Bruker WH-360 and Bruker AM-360 spectrometers (using TMS as internal standard). The course of the reactions was monitored by TLC on Silufol-254 plates, using an ethyl acetate-hexane, 1:2, mixture as eluent, R_f 0.4. The data of the elemental analysis for C and H of compounds I-VI correspond to the calculated values.

<u>2,3-Dihydro-2-aryl-4-(indane-1,3-dion-2-yl)-1H-1,5-benzodiazepines (I-VI)</u>. A mixture of 10 mmoles of the corresponding unsaturated ketone, 15 mmoles of o-phenylenediamine, and 0.5 ml of triethylamine in 50 ml ethanol is boiled for 10 h. The precipitate that separates after cooling, is filtered, and recrystallized from ethanol (compound II - from acetone).

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CONFIGURATION OF 2-(2-THIENYL)-5-ARYLOXAZOLES IN THEIR GROUND

AND EXCITED STATES

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The electronic absorption and emission spectra of a series of 2-(2-thienyl)-5-aryloxazoles in solutions, vapors, and matrices (ethanol-ether, 77 K) have been studied, and the fluorescence quantum yields have been determined. The basicity constants in aqueous solutions in the ground state have been measured spectrophotometrically. The set of spectroscopic data indicate that the configuration of the 2-(2-thienyl)-5-aryloxazoles in the ground state is nearly planar and is practically independent of the temperature and the state of aggregation. Conversely, in the excited state the configuration of these molecules is generally nonplanar and depends on external factors.

We previously [1, 2] studied the influence of the temperature and phase transitions on the conjugation between the rings and the configuration of the ground (S_0) and excited (S_1) states of 2-(4-pyridyl)-5-aryloxazoles with the aid of electronic spectroscopy and mass spectrometry. It was shown that the configuration of such molecules is significantly dependent on the state of aggregation and the temperature. An analysis of the position and form of the bands in the electronic spectra of 2-(4-pyridyl)-5-aryloxazoles showed [2] that the conformations of these molecules in the S_0 and S_1 states are different in solutions and in the crystalline state; the excited state is planar, and the ground state is nonplanar, the degree of nonplanarity being dependent on the nature of the substituent in the aromatic ring. In the vapor phase the configurations of these compounds in the S_0 and S_1 are identical, and they are both essentially nonplanar.

In [3] we proposed an approach to the determination of the configuration of molecules with structures of the diphenyl type in the ground and excited states on the basis of the electronic absorption and emission spectra.

The purpose of the present investigation was to examine the configuration of 2-(2-thienyl)-5-aryloxazoles I-VI in the framework of this approach (see scheme on following page).

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