SYNTHESIS AND PROPERTIES OF 1,2-DIHYDROPYRIDAZINO[4,5-b]INDOLE

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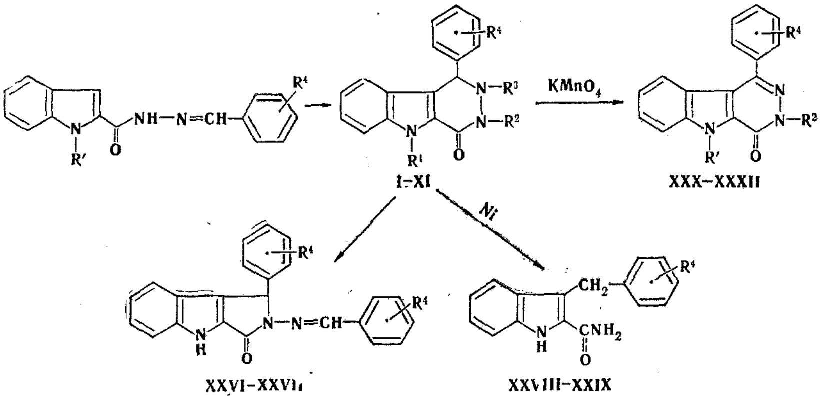
The intramolecular cyclization of 2-indoylhydrazones of aromatic aldehydes leads to 1-aryl-1,2-dihydropyridazino[4,5-b]indol-4-ones. The chemical properties of the compounds obtained were studied.

The synthesis of a heterocyclic system containing condensed indole and pyridazine rings – the aza analog of carbolines – has been accomplished by a number of investigators by closing of 3-formyl- or 3-aroylindole-2-carboxylic acid and its derivatives with hydrazine hydrate and substituted hydrazines [1-4]. In the present research we have synthesized the dihydro derivatives of this system via a new path by means of the reaction



The azomethine group here acts as an intramolecular electrophilic agent as in the Pictet–Spengler reaction for the formation of tetrahydroisoquinolines. The reaction of indole with azomethines to give di(3-indolyl)phenylmethanes is described in [5, 6]. The absence of the deactivating effect of the carboxyl group on the adjacent position facilitates electrophilic substitution reactions at the $C_{(3)}$ position. Cyclization products I-XI, in contrast to the starting hydrazones, do not undergo acid and alkaline hydrolysis. The UV spectra of cyclization product III and starting anisaldehyde 2-indoylhydrazone, which are characteristic for the investigated compounds, are presented in Fig. 1. The cyclic hydrazides (I-XI) of indole-2-carboxylic acid have the same spectra as indole-2-carboxylic acid hydrazide (λ_{max} 298 nm, log ε 4.20).

The PMR spectra of I-XI in dimethyl sulfoxide (DMSO) contain a 5-H proton at 11.8 ppm (absent in the spectra of $N_{(5)}$-methylated compounds) and an amide proton at 8.75 ppm. Spin–spin coupling leading to splitting into two doublets (J_{AX} = 8 Hz) appears between 1-H (6.0 ppm) and 2-H (5.3 ppm).

The stretching vibrations of the carbonyl group of I-XI lie at 1643-1650 cm^{-1}, while the frequency increases to 1660 cm^{-1} in $N_{(5)}$-methylated derivatives II, IV, and VI because of the absence of an intramolecular hydrogen bond. The stretching vibrations of the NH groups are expressed by two – and sometimes three – peaks at 3170-3280 cm^{-1}, while a peak at 3260 cm^{-1} is characteristic for the hydrochlorides.

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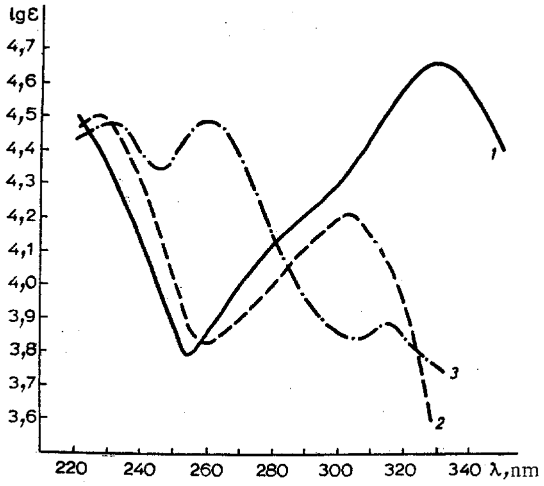

Fig. 1. UV spectra: 1) anisaldehyde 2-indoylhydrazone; 2) III; 3) XXXI.

Acylation of I-XI with the anhydrides of acetic and benzoic acids and benzoyl chloride leads to the formation of mono- and diacyl derivatives XII-XX. The first acyl residue is added to the secondary amino group in the 2 position. A new band at 1685 cm^{-1} appears in the IR spectrum. The second acyl residue is included under more severe conditions at the imino group of the pyrrole ring; this is confirmed by the bathochromic shift of the absorption maximum in the UV spectrum from 300 to 315 nm and by the appearance of a new band in the IR spectrum at 1725 cm^{-1}. Alkylation of I-XI with alkyl halides and arenesulfonic acid esters was unsuccessful, and only ethylene chlorohydrin and epichlorohydrin in alkaline media underwent reaction to give the corresponding hydroxy- (XXI-XXIV) and dihydroxyalkylated (XXV) derivatives in 40-55% yield.

A characteristic peculiarity of 1-aryl-1,2-dihydropyridazino[4,5-b]indol-4-ones was their ability to undergo oxidation in alcohol solutions in air to 1-arylpyridazino[4,5-b]indol-4-ones, which we previously erroneously took for isomerization of the cyclization products [7]. For preparative purposes, the oxidation was carried out with $KMnO_4$ in dioxane. The PMR spectra of the oxidation products (XXXI, for example) contain only a multiplet of aromatic protons and two singlets at 3.8 (OCH_3) and 3.95 ($N-CH_3$) ppm. Their IR spectra are close to those of the 1-unsubstituted pyridazino[4,5-b]indol-4-ones described in [1]. The IR spectrum of the 3,5-dimethyl derivative (XXXII) does not contain bands of N–H stretching vibrations.

The reaction of X-XI with aldehydes gave the previously described [8] 1-aryl-2-alkylideneamino-1,2-dihydropyrrolo[3,4-b]indol-3-ones (XXVI, XXVII). Reduction of I and III with Raney nickel in dioxane leads to the loss of one nitrogen atom, and the UV spectra of products XXVIII and XXIX are similar to the spectrum of indole-2-carboxamide. The presence in the PMR spectrum of a multiplet at 7.4 ppm and a singlet at 4.4 ppm of two proton units makes it possible to consider the reduced product to be 3-benzyl-2-carboxamidoindole (XXVIII, XXIX).

EXPERIMENTAL

1-Phenyl-1,2-dihydropyridazino[4,5-b]indol-4-one (I). A 2.63-g (0.01 mole) sample of benzaldehyde 2-indoylhydrazone was dissolved in 15 ml of amyl alcohol at 125°, and a stream of hydrogen chloride was passed through the solution. After 3 min, the hydrochloride of I precipitated. It was washed with aqueous pyridine until it gave a negative reaction for chloride ions and was then worked up to give 2.12 g (80%) of I.* Compounds II-XI were similarly obtained. PMR spectrum of IV in CF_3COOH, δ, ppm: 7.2 (aromatic protons), 6.36 (1-H), 4.03 ($N-CH_3$), 3.82 (OCH_3).

1-Phenyl-2-acetyl-1,2-dihydropyridazino[4,5-b]indol-4-one (XII). A mixture of 2.63 g (0.01 mole) of I and 5.4 g (0.05 mole) of acetic anhydride was refluxed in benzene for 30 min. Compound XII precipitated after all of the solid had dissolved. Compounds XIII-XVI were similarly obtained.

1-(p-Methoxyphenyl)-2-benzoyl-1,2-dihydropyridazino[4,5-b]indol-4-one (XVII). A solution of 1.54 g (0.011 mole) of benzoyl chloride in 5 ml of toluene was added to a cooled (to 10°) mixture of 2.93 g (0.01 mole) of III in 30 ml of toluene and 0.9 ml of pyridine, and the mixture was heated at 90° for 45 min. It was then cooled, and the precipitated crystals were removed by filtration to give 2.14 g of XVII. Compound XVIII was similarly obtained.

1-Phenyl-2,5-diacetyl-1,2-dihydropyridazino[4,5-b]indol-4-one (XIX). A 2.63-g (0.01 mole) sample of I was heated at 110° in 15 ml of acetic anhydride for 2 h, after which the acetic anhydride was removed by vacuum distillation to give a viscous mass, which was triturated in ether. The product was purified by crystallization from ethanol to give 1.6 g of XIX. The same method was used to obtain XX.

1-Phenyl-2-(2-hydroxyethyl)-1,2-dihydropyridazino[4,5-b]indol-4-one (XXI). A 55.3-g (0.4 mole) sample of K_2CO_3 was added at 140° to a solution of 2.63 g (0.01 mole) of I in 64.4 g (0.8 mole) of ethylene

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*Here and elsewhere, the characteristics of the compounds synthesized are listed in Table 1.

TABLE 1. 1-Aryl-1,2-dihydropyridazino[4,5-b]indol-4-ones (I-IX)

Compound	R^1	R^2	R^3	R^4	mp, °C*	Empirical formula	Found, %				Calc., %				Yield, %
							C	H	N	halogen	C	H	N	halogen	
I	H	H	H	H	250	$C_{16}H_{13}N_3O$	72,8	5,0	16,0		73,0	4,9	16,0		80
II	CH_3	H	H	H	235	$C_{17}H_{15}N_3O$	73,5	5,4	15,1		73,6	5,4	15,2		75
III	H	H	H	p-OCH_3	218	$C_{17}H_{15}N_3O_2$	69,5	5,2	14,2		69,6	5,1	14,3		90
IV	CH_3	H	H	p-OCH_3	208	$C_{18}H_{17}N_3O_2$	70,2	5,5	13,8		70,4	5,5	13,7		80
V	H	CH_3	H	p-OCH_3	216	$C_{18}H_{17}N_3O_2$	70,3	5,5	13,6		70,4	5,5	13,7		75
VI	CH_3	CH_3	H	p-OCH_3	208	$C_{19}H_{19}N_3O_2$	71,1	5,9	13,0		71,0	5,9	13,1		80
VII	H	H	H	p-Cl	238	$C_{16}H_{12}ClN_3O$	64,4	4,0	14,1	12,0	64,5	4,0	14,1	11,9	85
VIII	H	H	H	o-Cl	290	$C_{16}H_{12}ClN_3O$	64,3	4,0	14,1	12,0	64,5	4,0	14,1	11,9	75
IX	H	H	H	p-Br	264—265	$C_{16}H_{12}BrN_3O$	56,4	3,5	12,2	23,3	56,2	3,5	12,3	23,4	90
X	H	H	H	p-OH, m-OCH_3	265	$C_{17}H_{15}N_3O_3$	65,9	4,8	13,5		66,0	4,8	13,6		90
XI	H	H	H	p-CH_3	242	$C_{17}H_{15}N_3O$	73,6	5,3	15,0		73,6	5,4	15,2		90
XII	H	H	$COCH_3$	H	272	$C_{18}H_{15}N_3O_2$	71,0	5,0	13,6		70,8	4,9	13,8		52
XIII	CH_3	H	$COCH_3$	H	197	$C_{19}H_{17}N_3O_2$	71,7	5,4	13,1		71,5	5,3	13,2		50
XIV	H	H	$COCH_3$	p-OCH_3	248	$C_{19}H_{17}N_3O_3$	68,2	5,1	12,5		68,1	5,1	12,5		55
XV	CH_3	H	$COCH_3$	p-OCH_3	213—215	$C_{20}H_{19}N_3O_3$	68,7	5,4	12,1		68,8	5,4	12,0		50
XVI	H	H	$COCH_3$	p-Cl	281—283	$C_{18}H_{14}ClN_3O_2$	63,7	4,2	12,3	10,3	63,6	4,1	12,4	10,5	60
XVII	H	H	COC_6H_5	p-OCH_3	263—265	$C_{24}H_{19}N_3O_3$	72,4	4,8	10,7		72,5	4,8	10,6		55
XVIII	H	H	COC_6H_5	o-Cl	283—284	$C_{23}H_{16}ClN_3O_2$	68,7	4,0	10,5	8,9	68,7	4,0	10,5	8,8	56
XIX	$COCH_3$	H	$COCH_3$	H	190—192	$C_{20}H_{17}N_3O_3$	69,3	4,9	12,1		69,2	4,9	12,1		46
XX	$COCH_3$	H	$COCH_3$	p-OCH_3	214—216	$C_{21}H_{19}N_3O_4$	66,7	5,0	11,0		66,8	5,0	11,1		46
XXI	H	H	CH_2CH_2OH	H	143—145	$C_{18}H_{17}N_3O_2$	70,3	5,6	13,6		70,4	5,5	13,7		55
XXII	CH_3	H	CH_2CH_2OH	H	94—96	$C_{19}H_{19}N_3O_2$	70,9	5,9	13,0		71,0	5,9	13,1		53
XXIII	H	H	CH_2CH_2OH	p-OCH_3	119—121	$C_{19}H_{19}N_3O_3$	67,6	5,6	12,5		67,7	5,6	12,5		50
XXIV	H	H	CH_2CH_2OH	o-Cl	131—134	$C_{18}H_{16}ClN_3O_2$	63,1	4,7	12,3	10,4	63,3	4,7	12,3	10,4	55
XXV	H	H	$CH_2\underset{OH}{CH}\underset{OH}{CH_2}$	H	141—143	$C_{19}H_{19}N_3O_3$	67,5	5,6	12,5		67,7	5,6	12,5		40

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* Compounds I, IX, XI, XII, XIV, XVI, XIX, and XX were crystallized from alcohol, while II-IV, VI, X, and XVII were crystallized from dioxane, V-VII and XVIII were crystallized from methanol, XIII and XV were crystallized from benzene, XXI was crystallized from water—isopropyl alcohol (3 : 1), and XXV was crystallized from water—alcohol (1 : 1).

chlorohydrin, and the mixture was held at 140° for 4 h. It was then poured into ice water, and the resulting crystals were removed by filtration. The product was purified by crystallization from isopropyl alcohol–water (1:3) to give 1.7 g of XXI.

Compounds XXII–XXIV were similarly obtained.

1-Phenyl-2-(2,3-dihydroxypropyl)-1,2-dihydropyridazino[4,5-b]indole-4-one (XXV). A mixture of 2.63 g (0.01 mole) of I, 140 ml of ethanol, 30 ml of water, 11 ml (0.14 mole) of epichlorohydrin, and 9.66 g (0.07 mole) of K_2CO_3 was stirred on a boiling-water bath for 4 h, after which the alcohol was removed by vacuum distillation, and the residue was crystallized from alcohol–water (1:1) to give 1.35 g of XXV.

1-Phenyl-2-benzylideneamino-1,2-dihydropyrrolo[3,4-b]indol-3-one (XXVI). A mixture of 3 g (0.01 mole) of the hydrochloride of I and 1.06 g (0.01 mole) of benzaldehyde in 15 ml of amyl alcohol was refluxed until a precipitate formed. The mixture was worked up to give 1.54 g (54%) of XXVI with mp 290°. Found: C 78.6; H 4.9; N 11.9%. $C_{23}H_{17}N_3O$. Calculated: C 78.6; H 4.8; N 12.0%.

1-(p-Methoxyphenyl)-2-(p-methoxybenzylideneamino)-1,2-dihydropyrrolo[3,4-b]indol-3-one (XXVII). This compound, with mp 271-272° (from dioxane), was obtained by the method used to prepare XXVI. Found: C 72.9; H 5.0; N 10.1%; mol. wt. (by the Rast method) 400. $C_{25}H_{21}N_3O_3$. Calculated: C 73.0; H 5.1; N 10.2%; mol. wt. 411.

3-Benzylindole-2-carboxamide (XXVIII). A mixture of 2.63 g (0.01 mole) of I and 52 g of Raney nickel in 520 ml of dioxane and 100 ml of water was refluxed at 75° for 3 h in a stream of nitrogen, after which it was filtered, and the filtrate was vacuum-evaporated to dryness. The residue was crystallized from benzene to give 2.15 g (86%) of a product with mp 193-195°. UV spectrum: λ_{max} 295 nm (log ε 4.26). Found: C 76.7; H 5.6; N 11.1%. $C_{16}H_{14}N_2O$. Calculated: C 76.8; H 5.6; N 11.2%.

A similar method was used to obtain XXIX ($R = p\text{-}OCH_3$) with mp 150-152°. UV spectrum: λ_{max} 225, 295 nm (log ε 4.49, 4.23). Found: C 73.0; H 5.7; N 9.9%. $C_{17}H_{16}N_2O_2$. Calculated: C 72.9; H 5.7; N 10.0%.

1-Phenylpyridazino[4,5-b]indol-4-one (XXX). A solution of 1.58 g (0.03 g-equivalent) of $KMnO_4$ in 10 ml of water was added to a solution of 2.63 g (0.01 mole) of I in 100 ml of dioxane at 80°, and the mixture was held at this temperature for 40 min and filtered to remove the MnO_2. Addition of 20 ml of water to the filtrate precipitated XXX, which was crystallized from dioxane to give 2.38 g (91%) of a product with mp 348-350°. UV spectrum: λ_{max} 230, 253, 314 nm (log ε 4.58, 4.45, 3.93). Found: C 73.4; H 4.2; N 16.0%. $C_{16}H_{11}N_3O$. Calculated: C 73.6; H 4.2; N 16.1%.

A similar method was used to obtain XXXI ($R^1 = R^2 = H$, $R^4 = p\text{-}OCH_3$) with mp 320°. UV spectrum: λ_{max} 230, 260, 315 nm (log ε 4.48, 4.49, 3.89). Found: C 70.3; H 4.6; N 14.3%. $C_{17}H_{13}N_3O_2$. Calculated: C 70.1; H 4.5; N 14.4%.

The same method was used to obtain XXXII ($R^1 = R^2 = CH_3$, $R^4 = p\text{-}OCH_3$) with mp 285-287°. UV spectrum: λ_{max} 235, 263, 325 nm (log ε 4.50, 4.49, 3.92). Found: C 71.7; H 5.4; N 13.3%. $C_{19}H_{17}N_3O_2$. Calculated: C 71.5; H 5.3; N 13.2%.

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