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

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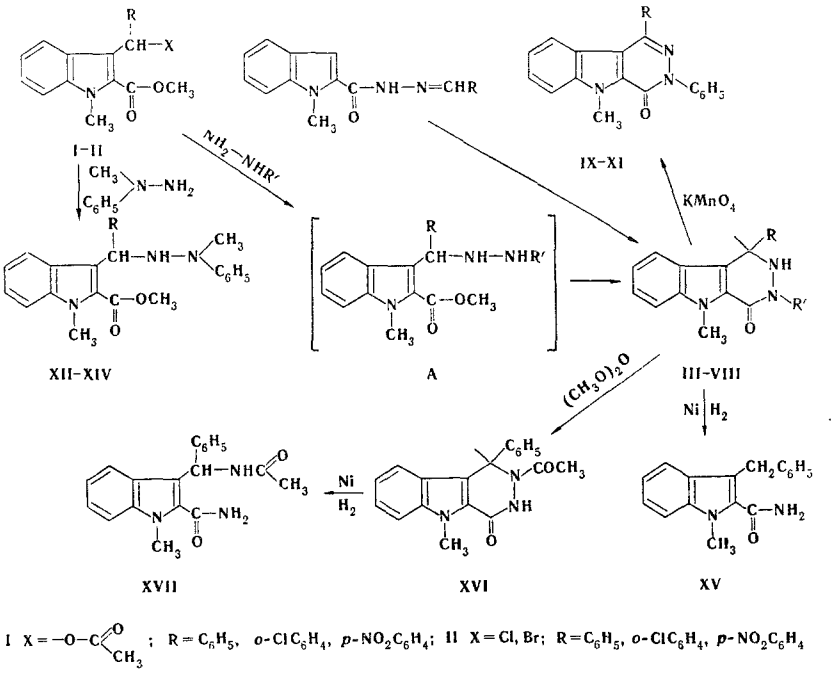
The possibility of the synthesis of substituted 1,2-dihydropyridazino[4,5-b]indoles by the reaction of 1-methyl-2-carbomethoxy-3-(α-halobenzyl)indole or 1-methyl-2-carbomethoxy-3-(α-acetoxybenzyl)indole with hydrazines was demonstrated. The oxidation, reduction, and acylation reactions of the resulting 1,2-dihydropyridazino[4,5-b]indoles were studied.

The preparation of 1,2-dihydropyridazino[4,5-b]indoles by cyclization of 2-indolylmethylhydrazines [1] and 3-indolylmethylhydrazines [2] with aromatic aldehydes is well known. We have previously described the synthesis of 1,2-dihydropyridazino[4,5-b]indol-4-ones by intramolecular cyclization of 2-indolylhydrazones of aromatic aldehydes [3].

In the present communication we report the preparation of 1,2-dihydropyridazino[4,5-b]indol-4-ones (III-VIII) in high yields by reaction of 1-methyl-2-carbomethoxy-3-(α-acetoxybenzyl)indole (I) or 1-methyl-2-carbomethoxy-3-(α-halobenzyl)indole (II) with hydrazines. Compounds III-V (but not VI-VIII) dissolve on heating in strongly alkaline solutions and are recovered by acidification of the solutions; this is evidence in favor of the existence of the O-sodium salt of the lactim structure in alkaline solutions as an anion with the charge on the oxygen.



I X = $-O-C(=O)-CH_3$; R = C_6H_5, o-ClC_6H_4, p-$NO_2C_6H_4$; II X = Cl, Br; R = C_6H_5, o-ClC_6H_4, p-$NO_2C_6H_4$

*See [3] for communication I.

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TABLE 1. 1-R^1-R-3-R^2-5-Methyl-1,2-dihydropyridazino[4,5-b]indol-4-ones (III-VIII)

Compound	R^1	R^2	mp, °C	Empirical formula	Found, %				Calc., %				λ_{max}, nm (lg ε)	Yield, %
					C	H	Cl	N	C	H	Cl	N		
III	C_6H_5	H	235	$C_{17}H_{15}N_3O$	73.7	5.4	—	15.1	73.6	5.4	—	15.2	230 (4,45) 300 (4,19)	83
IV	o-ClC_6H_4	H	224—226	$C_{17}H_{14}ClN_3O$	65.4	4.5	11.4	13.5	65.5	4.5	11.4	13.5	227 (4,45) 302 (4,23)	80
V	p-$NO_2C_6H_4$	H	254—256	$C_{17}H_{14}N_4O_3$	63.4	4.4	—	17.5	63.4	4.3	—	17.4	227 (4,45) 298 (4,25)	78
VI	C_6H_5	C_6H_5	212—214	$C_{23}H_{19}N_3O$	78.2	5.4	—	11.8	78.2	5.4	—	11.9	233 (4,56) 300 (4,25)	76
VII	o-ClC_6H_4	C_6H_5	242—244	$C_{23}H_{18}ClN_3O$	71.2	4.6	9.1	10.8	71.2	4.6	9.2	10.8	230 (4,61) 300 (4,25)	75
VIII	p-$NO_2C_6H_4$	C_6H_5	175—177	$C_{23}H_{18}N_4O_3$	69.2	4.5	—	14.2	69.3	4.5	—	14.1	233 (4,48) 295 (4,28)	76

Compounds III-V exist in the crystalline state in the lactam form, inasmuch as the IR spectra contain the absorption band of a carbonyl group at 1650-1660 cm^{-1}. The ability of VI-VIII to undergo oxidation to give pyridazino [4,5-b]indol-4-ones and their insolubility in alkaline solutions indicates that the phenyl group is attached to $N_{(3)}$. Alkylation of the NH_2 group of the hydrazine to give substituted hydrazine A, which then undergoes acylation and cyclizes, apparently occurs initially during the synthesis. Consequently, if the hydrogen atom in the NH group of the phenylhydrazine is alkylated, only hydrazines XII-XIV, which are not cyclized on heating, are obtained.

The synthesis of a substance with mp 156°, to which the IX structure, obtained by heating 1-methyl-2-carboxy-3-benzoylindole with phenylhydrazine in ethanol [4], was assigned has been reported. However, it was later shown that cyclization does not occur under these conditions and that the corresponding noncyclic hydrazones are obtained [5].

The IX that we synthesized melted at 353° and had physicochemical characteristics peculiar to compounds of this series [5-8].

Identical substances (XV), the elementary composition of which corresponds to the loss of one nitrogen atom, were obtained by catalytic reduction of III, VI, and VII on Raney nickel in dioxane. It has been previously established [9] that reductive dehalogenation occurs under the conditions of this reaction; this explains the identical character of the hydrogenated derivatives of VI and VII. Compound XV has the characteristic (for primary amides) strong band of carbonyl absorption at 1642 cm^{-1} and an amide II band at 1618 cm^{-1}. The bands at 3200 and 3395 cm^{-1} correspond to the stretching vibrations of the NH_2 group. The deamination that is observed during the reduction is hindered if there is a deficit of electron density on the nitrogen atom; this is confirmed by hydrogenation of acylated derivative XVI, in which only N—N bond cleavage occurs.

The formation of amide XV from VII instead of the expected anilide is apparently explained by participation of the adjacent phenyl group and migration of it from the $N_{(3)}$ to $N_{(2)}$

EXPERIMENTAL

The UV spectra of alcohol solutions of the compounds were recorded with an SF-16 spectrophotometer; the IR spectra of mineral oil suspensions were recorded with a UR-20 spectrometer.

1-Phenyl-5-methyl-1,2-dihydropyridazino[4,5-b]indol-4-one (III). A 3.4-g (0.01 mole) sample of I (R = C_6H_5) was heated with 10 ml of hydrazinehydrate in 20 ml of ethylene glycol at 125-130° for 40 min. The cooled mixture was diluted with 10 ml of water, and the resulting precipitate was removed by filtration and crystallized from dioxane to give 2.3 g (83%) of III (see Table 1).

Compound IV was synthesized by a similar method. Compound V was also obtained from II (R = p-$NO_2C_6H_5$), but the reaction mixture was heated at 100° for 3 min until a copious precipitate had formed.

1,3-Diphenyl-5-methyl-1,2-dihydropyridazino[4,5-b]indol-4-one (VI). A 3.4-g (0.01 mole) sample of I (R = C_6H_5) was heated with 16 ml of phenylhydrazine in 25 ml of ethylene glycol at 125-

TABLE 2. 1-R-3-Phenyl-5-methylpyridazino[4,5-]indol-4-ones (IX-XI)

Compound	R	mp, °C	Empirical formula	Found, %				Calc., %				λ_{max}, nm (lg ε)	Yield, %
				C	H	Cl	N	C	H	Cl	N		
IX	C_6H_5	353	$C_{23}H_{17}N_3O$	78,7	4,8	—	11,9	78,6	4,8	—	12,0	240 (4,44) 272 (4,48) 345 (4,12)	90
X	p-$NO_2C_6H_4$	408	$C_{23}H_{16}N_4O$	69,8	4,0	—	14,2	69,7	4,0	—	14,1	272 (4,56) 330 (4,13)	90
XI	o-ClC_6H_4	262—265	$C_{23}H_{16}ClN_3O$	71,6	4,1	9,2	10,9	71,6	4,2	9,2	10,9	245 (4,45) 272 (4,48) 350 (4,12)	90

TABLE 3. N_1-Methyl-N_1-phenyl-N_2-(1-methyl-2-carbomethoxy-3-indolyl-R-phenylmethyl)hydrazines (XII-XIV)

Compound	R	mp, °C	Empirical formula	Found, %				Calc., %				λ_{max}, nm (lg ε)	Yield, %
				C	H	Cl	N	C	H	Cl	N		
XII	C_6H_5	120—122	$C_{25}H_{25}N_3O_2$	75,2	6,3	—	10,5	75,2	6,3	—	10,5	235 (4,49) 298 (4,26)	80
XIII	o-ClC_6H_4	180—182	$C_{25}H_{24}ClN_3O_2$	69,3	5,5	8,2	9,6	69,2	5,5	8,2	9,7	235 (4,46) 298 (4,22)	83
XIV	p-$NO_2C_6H_4$	78—80	$C_{25}H_{24}N_4O_4$	67,3	5,4	—	12,5	67,6	5,4	—	12,6	232 (4,47) 295 (4,35)	82

130° for 40 min. Water (20 ml) was added to the cooled mass, and VI separated as an oil, which crystallized on heating in ethanol. The crystals were removed by filtration and crystallized from ethanol to give 2.8 g (79%) of VI.

Compounds VII and VIII were synthesized by a similar procedure, but IX and XI were obtained from the appropriate 1,2-dihydropyridazino[4,5-b]indol-4-ones by the method described in [3]. Compounds IX and X were oxidized in dioxane with aqueous $KMnO_4$ for 40 min at 80° (XI was heated at 100° for 50 min). The characteristics of the compounds are presented in Table 2.

$N_{(1)}$-Methyl-$N_{(1)}$-phenyl-$N_{(2)}$-(1-methyl-2-carbomethoxy-3-indolylphenylmethyl)hydrazine (XII). A 3.4-g (0.01 mole) sample of I (R = C_6H_5) was heated with 18 ml of methylphenylhydrazine in 25 ml of ethylene glycol at 125-130° for 40 min. The cooled mixture was diluted with 20 ml of water, and XII separated as an oil, which crystallized on heating in ethanol. The crystals were removed by filtration and crystallized from ethanol to give 3.2 g (80%) of XII.

Compounds XIII-XIV were synthesized by a similar method. The characteristics of the compounds are presented in Table 3.

1-Methyl-2-carboxamido-3-benzylindole (XV). This compound, with mp 188° (from benzene), was obtained in 80-83% yield by the method in [3] by catalytic reduction of III, VI, and VII on Raney nickel. UV spectrum, λ_{max}, nm (log ε): 223 (4.50), 292 (4.12). Found: C 77.4; H 6.1; N 10.6%. $C_{17}H_{16}N_2O$. Calculated: C 77.3; H 6.1; N 10.6%.

1-Phenyl-2-acetyl-1,2-dihydropyridazino-5-methyl[4,5-b]indol-4-one (XVI). A 2.77-g (0.01 mole) sample of III was heated with 5.4 g (0.05 mole) of acetic anhydride in 30 ml of benzene for 30 min. The solution was vacuum evaporated, and the residue was triturated in ether. The mixture was filtered, and the solid was crystallized from benzene to give 1.6 g (50%) of XVI with mp 197°. Found: C 71.7; H 5.4; N 13.1%. $C_{19}H_{17}N_3O_2$. Calculated: C 71.5; H 5.3; N 13.2%.

1-Methyl-2-carboxamido-3-(α-acetamidobenzyl)indole (XVII). This compound, with mp 290-292° (dioxane), was obtained in 84% yield by catalytic reduction of XVI on Raney nickel by the method in [3]. UV spectrum, λ_{max}, nm (log ε): 290 (4.13). Found: C 70.8; H 5.9; N 13.0%. $C_{19}H_{19}N_3O_2$. Calculated: C 71.0; H 5.9; N 13.1%.

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