CONDENSATION OF INDOLE WITH ISATIN

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UDC 547.751:756

Isatin undergoes condensation with indole in the presence of diethylamine to give 3-(3-indolyl)dioxindole.

It has been reported [1] that the reaction of indole with isatin in the presence of diethylamine in alcohol at 45°C gives 3-(3-indolyl)dioxindole (I). We have made a more detailed study of this reaction and have shown that a colorless compound with a higher melting point (by about 100°) is formed under the same conditions, i.e., when a mixture of the starting substances is heated in the presence of diethylamine in alcohol for several hours at 60°. However, when the product is heated slowly, it softens at 105-115° with a change in the form of the crystals and finally melts at 215-217°, which is 100° higher than reported in [1]. We explain the actually observed double melting points by the instability and exceptionally high sensitivity of the compound to heating and to the action of bases. The product is homogeneous during chromatography on plates with a thin layer of absorbent. Its IR spectrum contains intense absorption bands at 3400, 3190, 1710, and 1615 cm^{-1}. The absorption maxima in the UV spectra appear at 218, 261, and 290 nm. It might have been assumed that the base (for example, diethylamine) attacks the hydroxyl group with opening of the five-membered ring of I to give amide II (according to the chromatographic data, the substance undergoes appreciable change at 20° on standing in pyridine solution for a few hours). Its PMR spectrum [obtained from a solution in dimethyl sulfoxide (DMSO)] contains the following signals: a singlet at 5.97 ppm (2-H), a multiplet at 6.63 ppm (aromatic ring C—H), a singlet at 7.78 ppm (N—CHO), a singlet at 9.68 ppm (indole NH), and a multiplet at 10.28 ppm (NH—CO). As indicated above, the product is unstable upon heating and undergoes changes at high temperatures (for example, upon melting). Under the influence of electron impact it is possibly converted to a tautomeric form (III), for which the following characteristic peaks are actually present in the mass spectrum: 264 (M^+) (22%), 248 ($M - NH_2$) (100%), 246 ($M - H_2O$) (18%), 247 ($M - OH$) (47%), 235 ($M - CHO$) (8%), 219 ($248 - CHO$) (95%), and 117 (indole) (45%).* The principal characteristic of the spectrum is detachment of the amino group (100%) and the formyl residue (95%). At the same time, the ($M - CO$) peak that is so characteristic for oxindoles and isatines is absent in the spectrum.

When I is refluxed with an alcohol solution of alkali, it gives a mixture of indole and a new substance with the overall composition $C_{24}H_{17}N_3O$. The IR spectrum of the latter contains absorption bands at 3510, 3400, 1710, and 1625 cm^{-1}. Maxima at 219, 255, 283, 291, and 292 nm are observed in the UV spectrum. The mass spectrum contains a molecular ion peak at 363 and fragment ion peaks at 335 ($M - CO$), 334 ($335 - H$), 218 (335 − indole), 201 ($218 - NH_3$), and 117 (indole).

The presence of free indole in the reaction medium makes it possible to suppose that under the influence of alkali, I, on the one hand, is cleaved to indole and an isatin transformation product and, on the other hand, is dehydrated to a hypothetical indolenine derivative (IV), which adds a molecule of indole present in the reaction mixture to give V.

At the same time, when we refluxed I in alcohol with indole in the absence of a base, we did not observe the formation of indole derivative V from I. Compound V is soluble in

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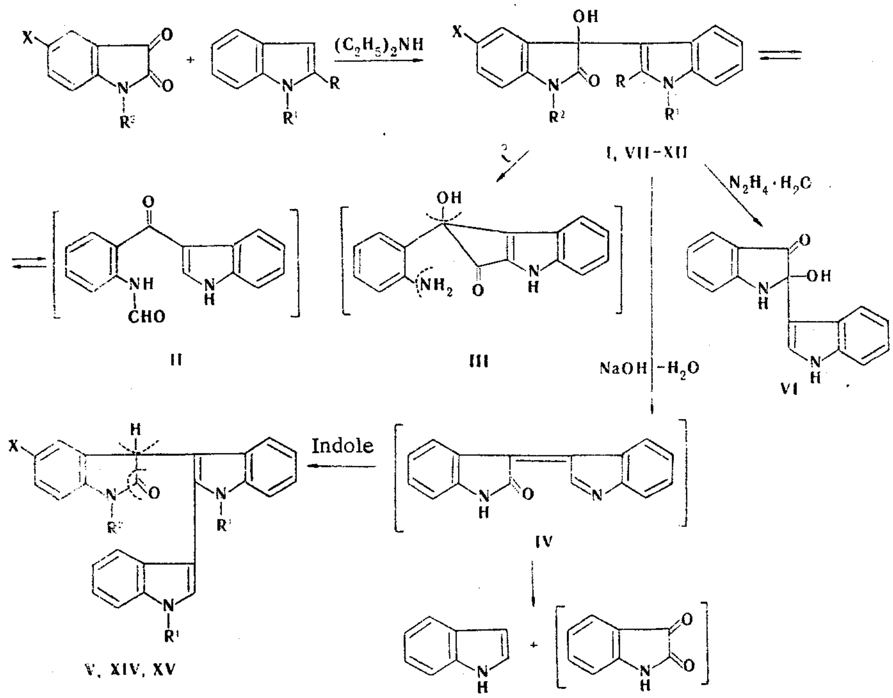
*Here and subsequently, the m/e values are presented along with the intensities in percent of the maximum ion (in parentheses).

Institute of Chemistry, Academy of Sciences of the Moldavian SSR, Kishinev. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 204-208, February, 1976. Original article submitted January 14, 1975.



I—VI $R=R^1=R^2=X=H$; VII $R=R^1=X=H$, $R^2=CH_3$; VIII $R=R^1=R^2=H$, $X=Br$; IX $R^1=R^2=X=H$, $R=CH_3$; X $R=R^2=H$, $R^1=CH_3$, $X=Br$; XI $R=R^1=CH_3$, $R^2=X=H$; XII $R=R^1=CH_3$, $R^2=H$, $X=Br$; XIV $R^1=R^2=H$, $X=Br$; XV $R^1=X=H$; $R^2=CH_3$

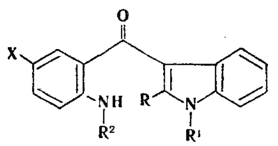
alcohol (this is characteristic for 3-monosubstituted oxindoles in which the unsubstituted hydrogen atom attached to the C_3 atom is distinguished by high lability) and in order to isolate it completely, the reaction mixture should be poured into water, and the aqueous mixture should be acidified. The rearrangement to 2-hydroxyindoxyls characteristic for 3-substituted dioxindoles and the possible formation of VI should be excluded in this case, inasmuch as the frequency of the carbonyl group in the IR spectrum of substances of the VI type is shifted, as compared with dioxindoles, to the lower wavelength region and appears at about 1680 cm^{-1}.

Compound V is also formed on attempts to oxidize dioxindole I with hydrogen peroxide in alkali at 95° after 5-10 min, i.e., oxidation does not occur under these conditions, and the peroxide "does not work."

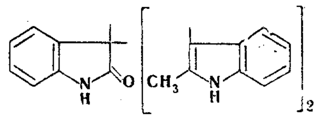
Hydrazine hydrate in refluxing methanol isomerizes I to a substance for which we propose the 2-(3-indolyl)-2-hydroxy-3-indolinone structure (VI). The band of the carbonyl group in its IR spectrum was shifted to 1670 cm^{-1} (it appears at 1710 cm^{-1} in the spectrum of starting I), and the mass spectrum contains primarily peaks of the same ions as in the case of I, but their intensities differ appreciably. In addition, peaks of ions due to detachment of a hydroxyl group and a water molecule show up distinctly. The peak at 219 ($M - NH_2 - CHO$) becomes the most intense peak (100%). The intensities are as follows for the other peaks: 264 (M^+) (35%), 246 ($M - H_2O$) (30%), 247 ($M - OH$) (25%), 248 ($M - NH_2$) (30%), and 235 ($M - CHO$) (12%).

In addition to indole and isatin, we also used 2-methyl- and 1,2-dimethylindole and 1-methyl- and 5-bromoisatin in the indicated reaction: The physical characteristics of the compounds obtained (VII-XII) are presented in Table 1. (In individual cases, they retain solvent molecules upon crystallization.)

However, despite this variation of the substituents, we were unable in a single case to achieve oxidation of the dioxindoles (I, VII, XII) with hydrogen peroxide in alkali to the



XIII



XVI

TABLE 1. Physical Characteristics of (3-Indolyl)dioxindoles

Compound	mp, °C	Empirical formula	Found, %				Calc., %				R_f	IR spectrum, ν_{max}, cm⁻¹	UV spectrum, λ_{max}, nm (log ε)	Yield, %
			C	H	Br	N	C	H	Br	N				
VII	170—171	$C_{17}H_{14}N_2O_2$	73,4	5,1	—	10,2	73,4	5,1	—	10,1	0,67	1625, 1700, 3260	219(4,76), 266(4,06), 280(3,96), 290(3,88)	87
VIII	238—241	$C_{16}H_{11}BrN_2O_2$	56,7	3,3	21,9	8,2	56,0	3,2	23,2	8,2	0,63	1620, 1700, 3160, 3240, 3440	219(3,36), 266(2,83) 290(2,51)	73
IX	189—190	$C_{17}H_{14}N_2O_2 \cdot 0{,}5H_2O$	70,9	5,4	—	9,6	71,1	5,2	—	9,7	0,45	1620, 1710, 3150, 3390	213(3,38), 220(3,37) 290(2,60)	89,4
X	139—140	$C_{17}H_{13}N_2BrO_2 \cdot CH_3OH$	56,0	4,6	19,8	7,5	55,5	4,4	20,5	7,2	0,68	1620, 1710, 3220, 3440, 3480	214(3,33), 266(2,81) 290(2,53)	87
XI	166—167,5	$C_{18}H_{16}N_2O_2$	74,4	5,9	—	9,4	74,0	5,5	—	9,5	0,31*	1620, 1700, 3150, 3500	214(2,85), 223(2,84) infl. 258(2,23), 294(2,18)	34
XII	210—211	$C_{18}H_{15}N_2BrO_2 \cdot 0{,}5H_2O$	56,8	4,4	19,3	6,7	56,8	4,2	21,0	7,3	0,29	1615, 1710, 3300	215(3,63), 220(3,63) infl. 268(3,06), 294(2,93)	53

*Determined in a benzene—ether system (1:1).

desired indole analogs (XIII) of o-aminobenzophenone — in all cases we observed the formation of trimers of the V type along with indole or its corresponding homolog. In particular, in addition to V, we isolated XIV and XV.

Treatment of 3-(2-methyl-3-indolyl)dioxindole (IX) with alkali in alcohol gives a substance for which we propose the 3,3-di(2-methyl-3-indolyl)oxindole structure (XVI) (see the Experimental section).

EXPERIMENTAL

The individuality of each of the compounds obtained in this research was confirmed by chromatography on Silufol UV-254 plates in a chloroform—methanol system (9:1). The plates were developed in UV light or with iodine vapors. The IR spectra of methanol solutions of the compounds were recorded with a Specord 71IR spectrometer. The mass spectra were recorded with an MKh-1303 spectrometer with a system for direct introduction of the substance into the ion source at I = 100 mA and an ionizing voltage of 70 eV. The PMR spectra were recorded with an RS-60 spectrometer with hexamethyldisiloxane or tetramethylsilane as the internal standard. The melting points were determined with a Boetius apparatus and are not corrected.

3-(3-Indolyl)dioxindole (I). A mixture of 2.34 g (0.02 mole) of indole, 2.94 g (0.02 mole) of isatin, and 0.9 ml (0.01 mole) of diethylamine in 70 ml of methanol was stirred for several hours at 60° until the solid material had dissolved completely. Water (40-50 ml) was added until the mixture became turbid, and it was then placed in a refrigerator for crystallization. The precipitated rose-colored crystals were removed by filtration after a few minutes and crystallized from methanol to give 4.7 g (89%) of a substance with mp 215-217° and R_f 0.58. Found, %: C 72.3; H 4.6; N 10.3. $C_{16}H_{12}N_2O_2$. Calculated, %: C 72.7; H 4.6; N 10.6.

The following compounds were obtained under similar conditions: 3-(3-indolyl)-1-methyldioxindole (VII), 3-(3-indolyl)-5-bromodioxindole (VIII), 3-(2-methyl-3-indolyl)dioxindole (IX), 3-(2-methyl-3-indolyl)-5-bromodioxindole (X), 3-(1,2-dimethyl-3-indolyl)dioxindole (XI), and 3-(1,2-dimethyl-3-indolyl)-5-bromodioxindole (XII) (see Table 1).

3-(3-Oxindolyl)-2-(3-indolyl)indole (V). A) A 3.2-g (0.012 mole) sample of I was added at 95° to a vigorously stirred 10% aqueous solution of NaOH (24 ml), after which the resulting suspension was cooled to 80°, and 12 ml of 10% hydrogen peroxide solution was added. The mixture was again heated to 90°, and after 10 min the reaction began to proceed vigorously, judging from the instantaneous change of the color of the mixture from bright yellow to pale yellow. The mixture was then diluted with 36 ml of water, cooled, and acidified with dilute hydrochloric acid. The resulting precipitate, consisting of mixture of V and a small amount of indole, was removed by filtration. Crystallization from ethyl acetate—ethanol gave 0.8 g (18.2%) of V with mp 312-314° and R_f 0.51. Found, %: C 80.0; H 4.7; N 11.3. $C_{24}H_{17}\cdot N_3O$. Calculated, %: C 79.3; H 4.7; N 11.5.

B) A 1.5-g (0.006 mole) sample of I was dissolved by heating in a small amount of ethanol, after which 0.36 g of NaOH in 5 ml of water was added. The mixture was then refluxed for 4 h, cooled, and poured into a sixfold volume of water. The resulting yellowish precipitate was removed by filtration, and the mother liquor was acidified with hydrochloric acid to give an additional amount of product. Crystallization of the product gave 0.8 g (40%) of V.

3,3-Di(2-methyl-3-indolyl)oxindole (XVI). As in method B in the preceding experiment, 0.84 g (0.003 mole) of 3-(2-methyl-3-indolyl)dioxindole (IX) gave 0.5 g (50%) of XVI with mp 290-291° (from alcohol). Found, %: C 79.7; H 5.2; N 10.7. $C_{26}H_{21}N_3O$. Calculated, %: C 79.8; H 5.4; N 10.7. IR spectrum: 3425, 3340, 3300, 1710, and 1620 cm^{-1}

2-(3-Indolyl)-3-(5-bromo-3-oxindolyl)indole (XIV). Oxidation of VIII with hydrogen peroxide in alkali under conditions similar to those in method A gave XIV, with mp 306-307° and R_f 0.69, in 25% yield. Found, %: C 64.5; H 3.7; Br 18.7; N 9.5. $C_{24}H_{16}BrN_3O$. Calculated, %: C 65.1; H 3.6; Br 18.1; N 9.5. IR spectrum: 3330, 1700, and 1610 cm^{-1}. UV spectrum, λ_{max} (log ε): 219 (4.87), 259 (4.26), 289 (4.16) inflection, and 292 (4.09) nm (in methanol). Mass spectrum: M^+ 442.

2-(3-Indolyl)-3-(1-methyl-3-oxindolyl)indole (XV). This compound, with mp 301-302° and R_f 0.71, was obtained in 42% yield under conditions similar to those in method A by oxidation of VII with hydrogen peroxide in alkali. Found, %: C 79.4; H 5.1; N 10.5. $C_{25}H_{19}N_3O_4$. Calculated, %: C 79.5; H 5.1; N 11.1. IR spectrum: 1615, 1670, and 3370 cm^{-1}. UV spectrum, λ_{max} (log ε): 219 (4.81), 258 (4.09), 283 (4.08), and 292 nm (4.01).

2-(3-Indolyl)-2-hydroxy-3-indolinone (VI). An 0.12-g (0.005 mole) sample of hydrazine hydrate was added to a solution of 1.32 g (0.005 mole) of 3-(3-indolyl)dioxindole in 10 ml of methanol, and the mixture was refluxed for 15 min. It was then cooled to room temperature and acidified with glacial acetic acid. The precipitated 2-(3-indolyl)-2-hydroxy-3-indolinone was removed by filtration, washed with water, and crystallized from methanol to give 0.85 g of VI with mp 215-217° and R_f 0.5. Found, %: C 68.8; H 5.5; N 9.4. $C_{16}H_{12}N_2O_2 \cdot CH_3OH$. Calculated, %: C 68.8; H 5.4; N 9.5.

LITERATURE CITED

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INDOLIZINES.

II.* SYNTHESIS AND PROPERTIES OF 2-METHYL(ARYL)-ETHOXYCARBONYLINDOLIZINES

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UDC 547.759.4.07

2-Substituted indolizine-6-carboxylic acids and their derivatives were synthesized. Their electrophilic substitution reactions are described.

We have previously described 2-alkyl(aryl)indolizine-7-carboxylic acids and their derivatives [1]. In a continuation of our research on the synthesis of indolizine derivatives with functional groups in various positions of the pyridine portion of the molecule, we synthe-

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*See [1] for communication I.

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