SOME TRANSFORMATIONS OF N-AMINOMETHYLISATINS

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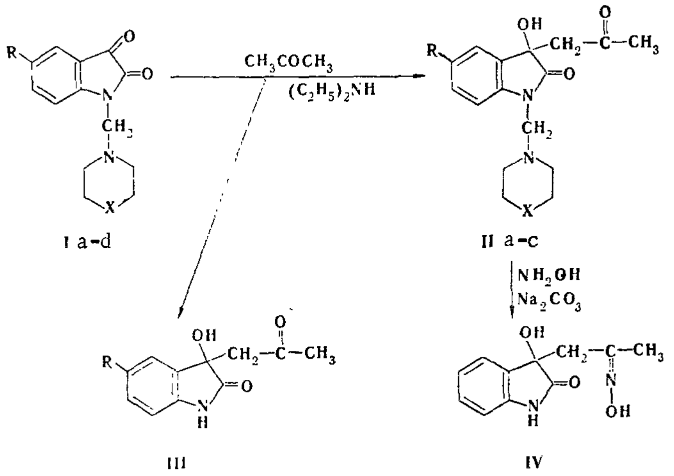
N-Aminomethylisatins readily split out an aminomethyl residue; they condense with acetone to give N-aminomethyl-3-acetonyldioxindoles and with indole to give N-aminomethyl-3-(3-indolyl)dioxindoles, which readily split out an aminomethyl residue.

Isatin undergoes the Mannich reaction to give N-aminomethylisatins (I), which would be interesting to use in the synthesis of new indole derivatives, including 1-aminoalkyltryptamines, via the scheme that has been well developed in the literature.

However, we found that the dioxindole derivatives (II) that are formed in the condensation of bases I with acetone in the presence of diethylamine cannot always be isolated: the bases obtained from 5-bromoisatin very readily split out an aminomethyl residue and are converted to 3-acetonyl-5-bromodioxindole III.

The aminomethyl residue in IIa-c is also readily split out in the presence of basic agents: we isolated the same compound — 3-acetonyldioxindole oxime (IV) — on attempts to convert them to oximes.



I, II a R=H, X=O; b R=H, X=CH$_2$; c R=H, X=NC$_6$H$_5$; I d R=Br, X=CH$_2$

Similar examples are known from the literature. Thus, in the reaction of N-piperidylmethylisatin I with sodium borohydride the aminomethyl residue attached to the nitrogen atom is split out and the compound is rearranged to give 3-piperidyldioxindole [1]. Splitting out of an aminomethyl residue was also observed during an attempt to condense bases I with 5-nitrofurfural hydrazone [2].

The Mannich bases from isatin also readily undergo exchange reactions with other compounds, acting as aminomethyl residue donors: in refluxing alcohols they alkylate acetophenone and 2-naphthol to the corresponding aminomethyl derivatives [3].

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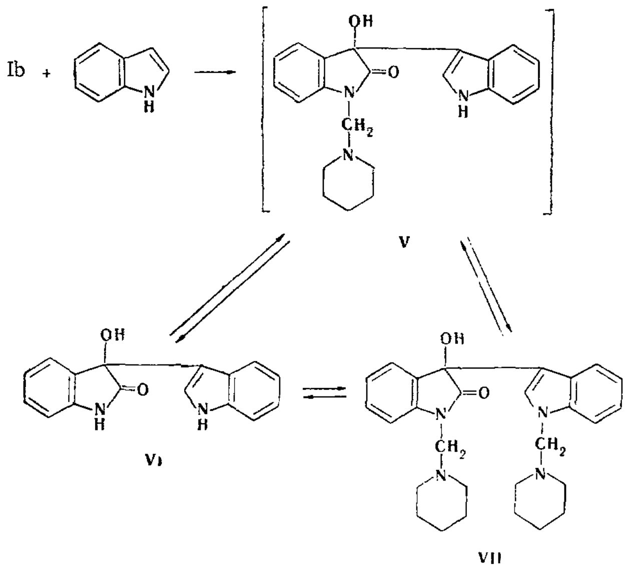
The reaction of N-piperidinylmethylisatin with indole in aqueous alcohol solutions or in alcohol containing a base (piperidine, diethylamine, or NaOH) leads to the formation of two colorless compounds. One of them is identical to the known 3-indolyldioxindole (VI). We assigned the N-piperidylmethyl-3-[1-(1-piperidylmethyl)-3-indolyl]dioxindole structure (VII) to the other on the basis of physicochemical studies and alternative synthesis. According to the results of elementary analysis, it has the empirical formula $C_{28}H_{34}N_4O_2$. Its IR spectrum does not contain the absorption bands characteristic for NH groups, and the intense maximum at 1710 cm^{-1} provides evidence for retention of the amide carbonyl group of isatin. The spectrum also contains intense bands at 1610, 1330, 1300, 1170, and 1110 cm^{-1}.



Compound VII was obtained from a genuine sample of 3-indolyldioxindole (VI) by the Mannich reaction) the use of one equivalent of formaldehyde and one equivalent of piperidine gave VII in 30% yield. The equilibrium can be completely shifted to favor the formation of VII by the additional introduction of excess formaldehyde and piperidine (the source of the aminomethylating agent).

The formation of VI and VII as a result of the reaction of N-aminomethylisatin with indole may be a consequence of an equilibrium interaction between V, VI, and VII. Three spots, two of which correspond to VI (R_f 0.48) and VII (R_f 0.34), are detected by thin-layer chromatography (TLC) of the reaction mixture; the third spot, with R_f 0.56, probably corresponds to the hypothetical V, which we were unable to isolate because of its instability. A mixture in which the same three spots were detected chromatographically is formed when individual VII is heated (or allowed to stand for a long time) in methanol in the presence of diethylamine. Compound VI was isolated from this mixture in 30% yield. Thus, it may be assumed that in the first step of the reaction indole condenses with N-aminomethylisatin I to give intermediate V. In turn, one molecule each of VI and VII is formed as a result of transaminomethylation from two molecules of V; a dynamic equilibrium is established between the concentrations of these three substances.

EXPERIMENTAL

The individuality of all of the compounds obtained in this study was confirmed by chromatography on Silufol UV-254 plates in a $CHCl_3$–CH_3OH system (7:1) with detection in UV light and with iodine vapors. The IR spectra of mineral oil suspensions of the compounds were recorded with a Specord 71 IR spectrometer. The melting points were determined with a Boetius apparatus and were not corrected.

N-Morpholylmethyl-3-acetonyldioxindole (IIa). A red solution of 8.6 g (0.35 mole) of N-morpholylmethylisatin and 0.73 g of diethylamine in 235 ml of acetone was stirred at 20° for 24 h, after which the solvent was removed completely by vacuum distillation, and the residue was triturated with water. The resulting crystals were removed by filtration and dried to give 7.8 g (73.5%) of IIa. Crystallization from benzene–heptane gave 6.5 g of a product with mp 153-154°. Found: C 61.6; H 6.7; N 8.4%. $C_{16}H_{20}N_2O_2 \cdot 1/2H_2O$. Calculated: C 61.3; H 6.7; N 8.8%.

N-Piperidylmethyl-3-acetonyldioxindole (IIb). This compound was prepared as in the preceding experiment from acetone and N-piperidylmethylisatin. The residue remaining after removal of the solvent by distillation was triturated in water—acetone (2:1), and the resulting crystals were removed by filtration and dried to give a product with mp 129-131° [from benzene—heptane (1:5)] in 63% yield. Found: C 67.6; H 7.3; N 9.3%. $C_{17}H_{22}N_2O_3$. Calculated: C 67.6; H 7.3; N 9.3%.

N-(4-Phenylpiperazylmethyl)-3-acetonyldioxindole (IIc). This compound, with mp 141-142° (from benzene), was obtained in 93% yield from acetone and 1-(phenyl-1-piperazylmethyl)-isatin. Found: C 70.3; H 6.5; N 11.1%. $C_{22}H_{25}N_3O_3$. Calculated: C 69.6; H 6.6; N 11.1%.

3-Acetonyl-5-bromodioxindole (III). The introduction of N-piperidylmethyl-5-bromoisatin in the reaction with acetone in the presence of diethylamine as described in the preceding experiments gave 3-acetonyl-5-bromodioxindole, with mp 198-199° in 83% yield. Found: C 46.3; H 3.7; N 5.2%. $C_{11}H_{10}BrNO_3$. Calculated: C 46.4; H 3.5; N 4.9%.

3-(2-Oximinopropyl)dioxindole (IV). An aqueous solution of an equimolar amount of hydroxylamine hydrochloride and sodium carbonate was added to a solution of N-morpholylmethyl-3-acetonyldioxindole in methanol, and the mixture was stirred at 20° for 5 h. It was then allowed to stand overnight at 20°, after which it was vacuum evaporated completely, and the residue was poured into water. The resulting oil was extracted with ether, and the extract was dried. The solvent was removed by crystallization, and the residue was triturated in benzene until crystallization commenced. The crystals were removed by filtration and dried to give a product with mp 177-178° (from benzene—ethyl acetate) in 78% yield. Found: C 60.2; H 5.6; N 12.9%. $C_{11}H_{12}N_2O_3$. Calculated: C 60.0; H 5.5; N 12.7%.

The same compound was obtained by oximation of N-piperidylmethyl- and N-4-phenylpiperazylmethyl-3-acetonyldioxindole.

Reaction of N-Piperidylmethylisatin with Indole. A) A solution of 2.44 g (0.01 mole) of N-piperidylmethylisatin, 1.17 g (0.01 mole) of indole, and 0.73 g (0.01 mole) of diethylamine was stirred at 20° for 2 days, and the resulting precipitate was removed by filtration, crystallized from methanol, and washed twice on the filter with cold methanol to give 1.3 g of VII with mp 188-189°. Found: C 73.4; H 7.4; N 12.1%. $C_{28}H_{34}N_4O_2$. Calculated: C 73.3; H 7.5; N 12.2%.

The filtrate was vacuum evaporated to dryness, and the resinous residue was dissolved in the minimum amount of chloroform. The solution was stirred with a magnetic stirrer for 5-6 h, and the resulting precipitate was separated and washed on the filter with cold chloroform to give 1.6 g (60%) of practically pure VI. Preparative chromatography on silica gel with elution with methanol-chloroform (1:9) was used to obtain an analytical sample with mp 204-205°. Found: C 72.0; H 4.8; N 10.0%. $C_{16}H_{12}N_2O_2$. Calculated: C 72.0; H 4.6; N 10.6%.

The following 5-bromo derivatives were similarly obtained. N-Piperidylmethyl-3-[1-(1-piperidylmethyl)-3-indolyl]-5-bromodioxindole, with mp 178-179° (from ethyl acetate—heptane), was obtained in 27.5% yield. Found: C 63.2; H 6.3; Br 15.3; N 10.0%. $C_{28}H_{33}BrN_4O_2$. Calculated: C 62.6; H 6.2; Br 14.9; N 10.4%; 3-(3-Indolyl)-5-bromodioxindole, with mp 233-234° (from ethyl acetate), was obtained in 46% yield. Found: C 56.0; H 3.5; Br 22.0; N 7.6%. $C_{16}H_{11}BrN_2O_2$. Calculated: C 56.0; H 3.2; Br 23.3; N 8.2%.

B) When chloroform was used as the solvent in this reaction, the yield of VI reached 90%.

C) A 0.24-g (0.01 mole) sample of N-piperidylmethylisatin and 0.117 g (0.01 mole) of indole were stirred in a mixture of 20 ml of alcohol and 10 ml of water for 2 days, and the resulting precipitate was removed by filtration to give 0.2 g (44%) of VII.

N-Piperidylmethyl-3-[1-(1-piperidylmethyl)-3-indolyl]dioxindole (VII). A mixture of 0.264 g of VI, 0.03 g of paraformaldehyde, 0.085 g of piperidine, and 10 ml of methanol was stirred at 20° for 24 h, after which the resulting precipitate was separated to give 0.16 g of VII. A 0.03-g sample of paraformaldehyde and 0.085 g of piperidine were added to the filtrate, and stirring was continued. After 24 h, another 0.15 g of VII was separated. Another 0.015 g of paraformaldehyde and 0.042 g of piperidine were added to the new filtrate. After 2 days, another 0.12 g of VII was isolated. The overall yield was 0.43 g (94%).

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CONVERSION OF 2-ACYL-1-ARYLHYDRAZIDES OF DIARYLGLYCOLIC ACIDS TO 1-ACYLAMINO-3,3-DIARYLOXINDOLES*

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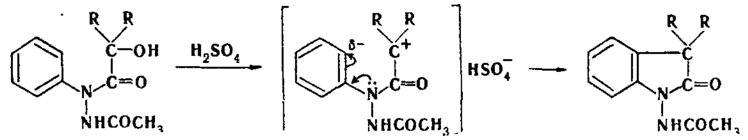
2-Acyl-1-arylhydrazides of diarylglycolic acids are cyclized in the presence of concentrated sulfuric acid to 1-acylamino-3,3-diaryloxindoles through the intermediate formation of a halochromic salt.

1,2-Diacylhydrazines are readily converted to 2,5-disubstituted 1,3,4-oxadiazoles by the action of zinc chloride, phosphorus oxychloride, thionyl chloride, and other condensing agents [2]. Diacylhydrazines are cyclized to 1,3,4-oxadiazole or 1,2,4-triazole derivatives by the action of concentrated sulfuric or polyphosphoric acids [3].

We have established that 2-acetyl- or formyl-1-arylhydrazides of diarylglycolic acids [4] in the presence of concentrated sulfuric acids give a halochromic coloration that vanishes as the mixtures stand; this is associated with the conversion of the initially formed halochromic salt to 1-acylamino-3,3-diaryloxindoles (Table 1).



Compounds I and XVI were reduced with Raney nickel, during which the N—N bond was cleaved in both cases to give 3,3-diphenyloxindole [5]; this proves the structures of the synthesized compounds.

As compared with the IR spectrum of the starting hydrazide, the ν_{OH} and ν_{C-OH} bands vanished in the IR spectrum of III, and this proves splitting out of the OH group during the reaction. The spectrum of III above 3000 cm^{-1} contains one band at 3245 cm^{-1} (at 3400 cm^{-1} in the spectrum of a solution); there are two bands at 1736 and 1680 cm^{-1} (as compared with 1690 and 1680 cm^{-1} in the spectrum of the starting compound) corresponding to two amide carbonyl groups in the region of carbonyl group vibration. The band at 1736 cm^{-1} corresponds to the $\nu_{C=O}$ band from the carbonyl group in the oxindole ring [6], and a band with the same frequency is also observed in the spectrum of 3,3-diphenyloxindole.

As compared with the UV spectra of the starting hydrazides, absorption at 250-260 nm, which, according to the data in [7], can be linked with the indole ring, appeared in the UV spectra of I and VI (Fig. 1).

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*Communication CI from the series "Substituted Hydrazides of Hydroxy Carboxylic Acids." See [1] for communication C.

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