REACTION OF 1-CHLOROMETHYLISATIN WITH INDOLE

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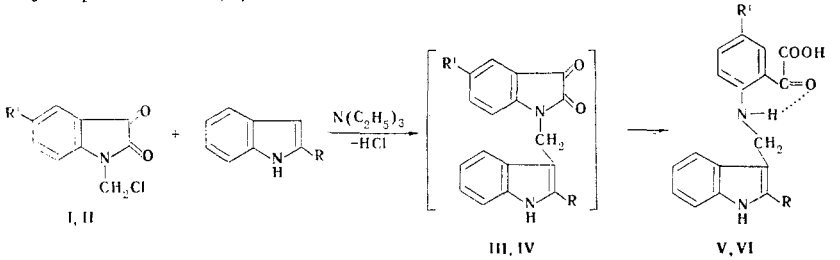
In the condensation of N-chloromethylisatin with indole and 2-methylindole in the presence of triethylamine, instead of the expected N-skatylisatins the products of their subsequent transformations with opening of the five-membered ring of isatin – o-(N-skatylamino)- and o[N-(2-methylskatyl)amino]benzoylcaproic acids – were isolated. In addition to the formation of these α-keto acids, under the indicated conditions one observes dimerization of N-chloromethylisatin and N-chloromethyl-5-methylisatin to give 2-(1-isatinylmethyloxy-3H-indolin-3-one and 2-(5-methyl-1-isatinylmethyloxy)-5-methyl-3H-indolin-3-one, respectively, i.e., dimers containing isatin rings in lactam and lactim forms. The structures of the compounds were confirmed by IR, PMR, and mass-spectral data.

The five-membered ring in isatins under certain conditions is relatively easily cleaved, and this can be used for the synthesis of new interesting compounds, including anthranilic acid derivatives. In particular, one should have anticipated that new gramine analogs can be obtained from substituted isatins [1].

We have shown that when indole or 2-methylindole is treated with 1-chloromethylisatin (I) in chloroform, the reaction proceeds very rapidly with an appreciable heating effect: Crystals in the form of red prisms begin to grow on the bottom of the reaction flask, but after 2-3 min the entire reaction mixture practically instantaneously turns completely black, and a crystalline compound cannot be isolated. However, if the reaction is carried out in the presence of triethylamine (to tie up the evolved hydrogen chloride) colorless crystals of p-(N-skatylamino)benzoylcaproic acid (V) can be isolated.



I, IV, VI R' = H; II R' = CH_3; III, V R = R' = H; IV, VI R = CH_3

A singlet of protons of a methyl group at 2.75, a quartet of a methylene group at 5.14 (J_{gem} = 12 Hz), a multiplet of aromatic protons at 6.6-7.5, and two broad singlets of amino and hydroxyl groups at 8.7 and 11.89 ppm (the third signal of the labile proton evidently falls in the region of the signals of the solvent or the signals of other protons) are observed in the PMR spectrum of V in deuteropyridines. The intense absorption bands at 3400, 3100, 1700, and 1610 cm^{-1} in the IR spectrum confirm the presence of NH, OH, C=O, and C=C groups, respectively. 1-Chloromethylisatin (I) also reacts similarly with 2-methylindole: Instead of the expected 1-(2-methylskatyl)isatin (IV), we were able to isolate o-[N-(2-methylskatyl)amino]benzoylcaproic acid (VI). The PMR and IR spectral data confirm the proposed structure and indicate the presence of an intramolecular hydrogen bond in this compound. Opening of the five-membered ring to give the α-keto acids that we isolated probably occurs in the initially formed N-skatylisatins (III, IV) under the influence of water or methanol in the presence of traces of triethylamine.

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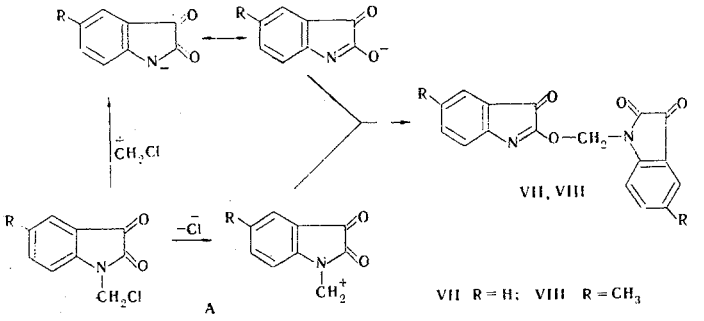
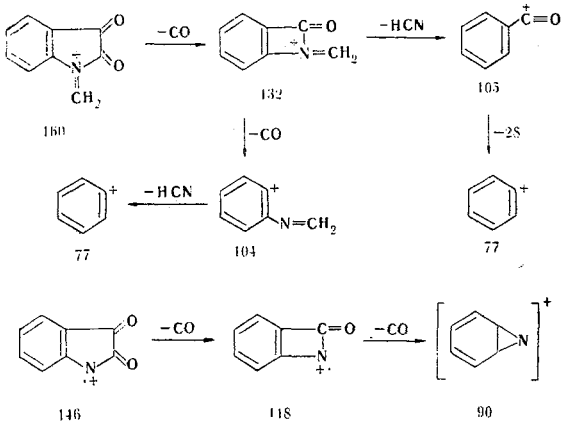
Red-orange compounds (VII, VIII), which are only slightly soluble in methanol, acetone, and chloroform but soluble in dimethyl sulfoxide (DMSO), nitromethane, and glacial acetic acid, are formed along with the α-keto acids (V, VI). Special experiments demonstrated that these substances are formed by treatment of N-chloromethylisatin with triethylamine in refluxing chloroform. Their formation can be represented as follows: In the first step a methyl chloride residue is detached to give the isatin anion, the lactim form of which can subsequently react with cation A.



VII R = H; VIII R = CH_3

The orange-red color of the compound makes it possible to assume that the five-membered ring of isatin is not cleaved under the reaction conditions. From the PMR data we assigned 2-(1-isatinylmethyloxy-3H-indolin-3-one (VII) and 2-(5-methyl-1-isatinylmethyloxy)-5-methyl-3H-indolin-3-one (VIII) structures, respectively, to these two substances.

The mass spectrum of VII contains a molecular ion peak (306* for $C_{17}H_{10}N_2O_4$) and peaks characteristic for isatins at 160 and 146, which undergoes subsequent fragmentation with ejection of CO and HCN.



Structures VII and VIII are confirmed by the presence of intense maxima in the IR spectra in the region of absorption of vinyl ethers (1000-1200 cm^{-1}).

Isatin, 5-methylisatin, and the corresponding N-hydroxymethyl derivatives can be detected by thin-layer chromatography (TLC) when solutions of VII and VIII in an aqueous methanol solution of alkali are acidified (the substances remain unchanged in methanol acidified with HCl). O-Methylisatin is known to behave similarly [2].

We noted that the reaction proceeds in different ways depending on the order of addition of the reagents: The corresponding N-skatylaminobenzoylcaproic acids V and VI and VII and VIII were obtained in the condensation of 1-chloromethylisatin in chloroform with triethylamine and subsequent addition of indole. However, if N-chloromethylisatin is added, with cooling, in portions to a chloroform solution of indole containing triethylamine, a substance with mp 164-166° and VII are isolated. The substance with mp 164-166° is evidently "triindolyl," since it is known that indole polymerizes in the presence of hydrogen chloride [3].

It should be noted that these condensations are best carried out at 0°, for further lowering of the temperature does not change either the composition of the reaction mixture or the yield. However, raising the reaction temperature and increasing the reaction time lead to resinification.

Compounds VII and VIII can be obtained in high yields when triethylamine is replaced by boron trifluoride etherate.

*Here and subsequently, the m/e values are presented.

EXPERIMENTAL

The individuality of all of the compounds obtained in this research was confirmed by chromatography on Silufol UV-254 plates (development in UV light or with iodine vapors). The IR spectra of mineral oil suspensions of the compounds were recorded with a Specord 71IR spectrometer. The UV spectra of methanol solutions of the compounds were recorded with a Specord UV-vis spectrophotometer. The mass spectra were recorded with an MKh-1303 mass spectrometer with a system for direct introduction of the samples into the ionizing source at I = 100 mA and a voltage of 70 eV. The PMR spectra of solutions of the compounds in warm deuteropyridine were obtained with JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The melting points were determined with a Boetius apparatus and were not corrected.

o-(N-Skatylamino)benzoylcarboxylic Acid (V). A solution of 0.66 g (0.006 mole) of indole in 3 ml of dry chloroform was added dropwise to a cooled (to 0°) and stirred solution of 1.2 g (0.006 mole) of isatin I and 0.82 ml of triethylamine in 10 ml of dry chloroform. After 20-30 min, the solvent was removed by distillation at reduced pressure (at no higher than 30°), and the residue was crystallized from methanol to give 0.2 g of orange crystals of VII with mp 316-317° and 0.9 g (50%) of rose-colored crystals of acid V with mp 178-180° and R_f 0.64 [chloroform–methanol (9 : 1)]. Found: C 69.7; H 5.3; N 10.2%. $C_{17}H_{14}N_2O_3$. Calculated: C 69.4; H 4.8; N 9.6%.

o-[N-(2-Methylskatyl)amino]benzoylcarboxylic Acid (VI). A similar procedure gave 1.6 g of acid VI and 0.4 g of VII, with mp 174-175° (from ethyl acetate–petroleum ether), in 52% yield from 2 g of isatin I, 1.2 g of 2-methylindole, and 1.36 ml of triethylamine. IR spectrum: 3400, 3200, 1700, 1620, 1310, 1190 cm^{-1}. Mass spectrum [m/e (relative intensity)]: 322 (34.01) (M^+), 306 (13.52), 277 (11.47), 233 (7.37), 218 (24), 191 (23.35), 146 (100), 130 (55.73), 118 (19.67), 90 (24.55), 77 (34.42). Found: C 70.2; H 5.6; N 9.2%. $C_{18}H_{16}N_2O_3$. Calculated: C 70.1; H 5.2; N 9.1%.

2-(1-Isatinylmethyloxy)-3H-indolin-3-one (VII). A 1.3-ml sample of triethylamine was added to a suspension of 1.95 g (0.01 mole) of isatin II in 20 ml dry chloroform, and the resulting dark-cherry-red solution was refluxed for 20 min, after which it was evaporated to dryness. The residue was washed with water to remove the triethylamine hydrochloride, and the residue was dissolved in methanol. Workup gave 1 g (67%) of VII with mp 316-317° (from acetic acid). IR spectrum: 1725, 1630, 1600, 1330, 1320, 1230 cm^{-1}. PMR spectrum, δ, ppm: 5.8 s (2H, CH_2) and 6.94-7.75 m (5H, C_6H_5). Found: C 66.0; H 3.4; N 8.7%. $C_{17}H_{10}N_2O$. Calculated: C 66.6; H 3.3; N 9.1%.

2-(5-Methyl-1-isatinylmethyloxy)-5-methyl-3H-indolin-3-one (VIII). A) Similarly, 0.45 g (57%) of VIII, with mp 312° (from acetic acid), was obtained from 1 g of isatin II, 0.68 ml of dry triethylamine, and 20 ml of dry chloroform. IR spectrum: 1710, 1650, 1610, 1590, 1320, 1300, 1270, 1240 cm^{-1}. PMR spectrum: δ, ppm: 2.1 s (3H, CH_3); 5.73 s (2H, CH_2); 7.1-7.6 m (5H, C_6H_5). Found: C 68.1; H 4.2; N 9.0%. $C_{19}H_{14}N_2O_4$. Calculated: C 68.2; H 4.2; N 8.4%.

B) A 0.7-g sample of boron trifluoride etherate was added to 1.05 g of isatin II in 25 ml of dry nitromethane, and the mixture was refluxed for 1 h. It was then cooled and worked up to gove 0.7 g (80%) of indolinone VIII.

Condensation of N-Chloromethylisatin with Indole in Chloroform. A 0.6-g sample of isatin was added in portions to a stirred and cooled solution of 0.41 ml of triethylamine and 0.33 g (0.003 mole) of indole in 30 ml of absolute chloroform, and the mixture was allowed to stand at room temperature for 20 min. It was then evaporated to dryness, and the residue was separated with a column filled with silica gel to give the following fractions: 1) 0.14 g of cream-colored crystals of "triindolyl" with mp 164-166° (from benzene). Found: C 81.5; H 5.6; N 11.2%. $C_8H_7N_3$. Calculated: C 82.1; H 6.0; N 11.9%; 2) 0.22 g of crystals of VII, 3) 0.1 g of isatin, and 4) 0.2 g of triethylamine hydrochloride.

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