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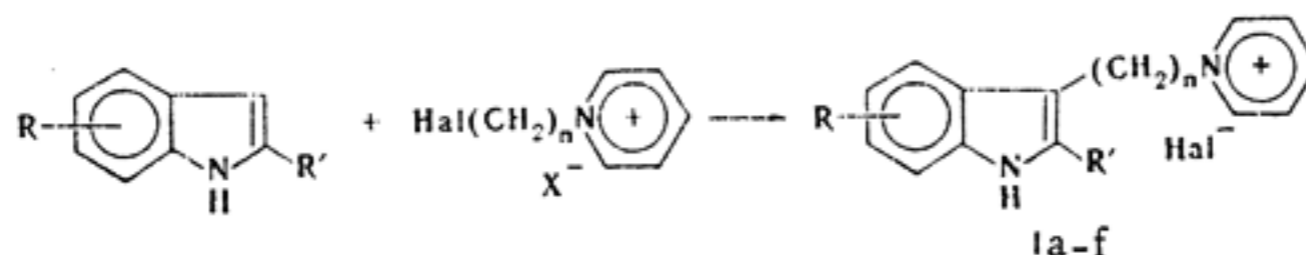
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A method for the alkylation of 3-unsubstituted indoles by means of 1-(ω -haloalkyl)pyridinium salts via the Friedel-Crafts reaction with the aid of complex catalysts, viz., complexes of zinc, tin, and titanium chlorides with pyridine, was developed. On the basis of a study of the electronic spectra of the resulting 1-(3-indolyl-alkyl)pyridinium salts it was shown that they are molecular self-complexes. The stabilities of the molecular self-complexes were investigated as a function of the length of the alkyl chain and the character of the substituents in the indole ring.

An independent research area, viz., the study of intramolecular charge-transfer complexes (CTC) (molecular self-complexes), in which interaction of a donor and acceptor contained in a single molecule and separated by an alkyl chain that does not conduct conjugation, has recently evolved in studies of CTC (for example, see [1]).

For the synthesis of molecular self-complexes of the indole series we have developed a method for the direct alkylation of 3-unsubstituted indoles with alkyl halides that contain an acceptor pyridinium ring at the end of the chain.



One example of the preparation of 1-(3-indolylalkyl)pyridinium salts (I) via the Zincke reaction [2], which is based on the use of difficult-to-obtain tryptamines and requires that they be present in a twofold excess as compared with the Zincke salt, is known in the literature.

A complex catalyst for the alkylation of indoles via the Friedel-Crafts reaction, viz., dipyridinezinc chloride [3], which is a weak Lewis acid and does not resinify acidophobic indoles, was recently discovered. We used this catalyst for the alkylation of indoles with 1-(ω -haloalkyl)pyridinium salts and obtained salts I in 50-75% yields. The alkylation process proved to be the primary process, although one might have expected that the strongly nucleophilic indole and substituted indoles would undergo hetarylation by the pyridinium cations (for example, see [4, 5]).

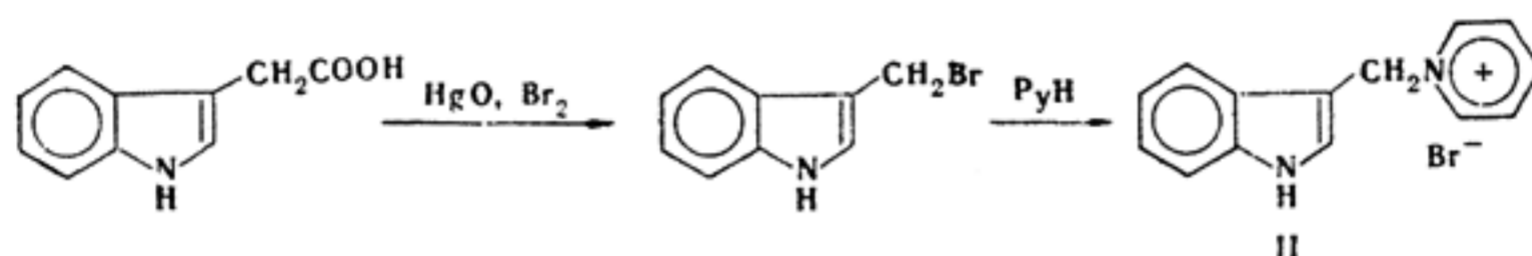
In addition to dipyridinezinc chloride, we also used complexes to Ti(IV) and Sn(IV) chlorides as the alkylation catalysts. A previous attempt [6] to use these catalysts was unsuccessful. This is evidently due to the fact that the catalysts were prepared directly

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in the reaction mixture, and the complexity of the precise proportioning of TiCl_4 and SnCl_4 and the ease of their hydrolysis inevitable led to the presence of strongly acidic impurities (HCl , MeCl_4), which resinify the starting indoles. To avoid these complications, we isolated the TiCl_4 and SnCl_4 complexes with pyridine (Py_2TiCl_4 and Py_4SnCl_4) in pure form. Our experiments showed that both catalysts can be successfully used for the Friedel-Crafts reaction in the indole series. Despite the fact that the use of the tin complex did not give a significant increase in the yields of salts I as compared with the zinc complex (salt Ia was obtained in 72 and 65% yields, respectively), the virtually complete absence of resinification is an obvious advantage in its use. However, the use of Py_2TiCl_4 made it possible to raise the yield of salt Ia to 92%.

The method for the direct alkylation of 3-unsubstituted indoles with 1-(ω -haloalkyl)-pyridinium salts that we developed makes it possible to obtain compounds with substituents with both strongly expressed donor and acceptor character in the indole ring and with different lengths of the alkyl chain ($n = 2$ and 3), and this makes these models convenient subjects for the study of the effect of the structure on the stabilities of the molecular self-complexes. To study the effect of the length of the alkyl chain on the stabilities of the complexes we also needed a model with one methylene link between the indole and pyridinium parts of the molecule. We synthesized it (II) by successive transformation via the Borodin-Hunsdiecker reaction [8] of 3-indolylacetic acid [7] to 3-bromomethylindole, by means of which (without isolation) pyridine was quaternized.



For the synthesis of 3-unsubstituted 2-methylindoles we used (for the first time) Fischer indolization, which was previously used only to obtain 2,3-dialkylindoles [9] (by heating the hydrochloride of the corresponding phenylhydrazine with the carbonyl compound in acetic acid).

On the basis of the data from the electronic spectra, we proved that 1-(3-indolylalkyl)-pyridinium salts (I) exist primarily in that conformation in which the indole (donor) and pyridinium (acceptor) parts are oriented one above the other and interact through space. In fact (Table 1), in addition to the absorption bands of the indole (250-280 nm) and pyridinium (252 nm) parts of the molecule, long-wave maxima of charge-transfer bands (350-600 nm) are also characteristic for the spectra of such structures. Since conjugation between the donor and acceptor parts of the molecules is disrupted by the polymethylene chain, this character of the electronic spectrum can be due only to an interaction of the type peculiar to charge-transfer complexes (CTC). The effect of the length of the alkyl chain and the character of the substituents on the stability of the self-complex can be followed distinctly. Thus an increase in the length of the alkyl chain from one methylene link (II) to three (Ib) leads to a regular long-wave shift of the charge-transfer band (from 390 to 550 nm) due to an increase in the conformational freedom of the molecule, which facilitates the optimal orientation of the donor and acceptor parts. The introduction of donor groupings in the benzene ring of the indole part of the molecule also increases the stabilities of the complexes. Thus in the case of identical lengths of the alkyl chain in the order $\text{H} \rightarrow \text{CH}_3 \rightarrow \text{OCH}_3$ for Ia, Id, and Ie the maxima of the charge-transfer bands are 500, 560, and 584 nm, respectively. When an acceptor nitro group is present in the 5 position of the indole molecule (If), the complex evidently is not formed at all, since new absorption bands as compared with the bands that are characteristic for the donor and acceptor separately cannot be observed in the electronic spectrum.

The selected models also make it possible to follow the influence of steric effects on the stability of the self-complex. It is known that the most effective donor bond in the indole molecule is the C_2-C_3 bond, and it is precisely this bond that is responsible for participation of the indole molecule in complexing [10]. The introduction of a bulky methyl group in position 2 of the indole part of the molecule therefore hinders the formation of a complex to a certain extent. Thus the absorption band in the electronic spectrum of 1-(2-methyl-3-indolylolethyl)pyridinium bromide (Ic) lies at 470 nm, whereas it is shifted substantially to the long-wave region (560 nm) in the case of 1-(7-methyl-3-indolylolethyl)-pyridinium bromide (Id).

TABLE 1. Position and Intensity of the Charge-Transfer Bands in Self-Complexes II and Ia-e

Compound	n	R	R'	λ_{max} , nm	lg ϵ
II	1	H	H	390	1,70
Ia	2	H	H	500	2,65
Ib	3	H	H	550	2,90
Ic	2	H	CH ₃	470	3,06
Id	2	7-CH ₃	H	560	3,01
Ie	2	5-OCH ₃	H	584	3,17

However, such peculiarities in the electronic spectra may also arise in the case of interaction of the donor and acceptor parts of different molecules. The intramolecular character of the complexes obtained therefore requires separate proof. The dependence of the position and intensity of the charge-transfer bands on the concentration serves as a confirmation of the formation of precisely molecular self-complexes in our case. In view of the fact that the charge-transfer band is not shifted upon dilution and its intensity is proportional to the concentration, the conclusion that the CTC is an intramolecular complex is completely logical.

All of the lines in the PMR spectra of salts I are markedly broadened; this may be due to the presence of paramagnetic particles in solutions of these salts. The presence of such particles is evidently associated with the partial formation of ion-radical salts in solution. This assumption is confirmed by the observation of an EPR signal.

EXPERIMENTAL

The UV spectra of solutions of the compounds in methanol were recorded with Unicam SP-800 and Specord spectrophotometers. Monitoring of the course of the reactions was accomplished by thin-layer chromatography (TLC) on Silufol UV-254 and in a fixed layer of Ferack polyamide on glass plates (8 by 4 cm). The 1-(3-indolylalkyl)pyridinium salts (I) were isolated with columns filled with the polyamide (250-500 μ).

5-Methoxyindole was obtained by the method in [11], while 7-methylindole was obtained by the method in [12].

2-Methylindole. A 3.5-ml (0.06 mole) sample of acetone was added to a solution of 7 g (0.05 mole) of phenylhydrazine hydrochloride in 20 ml of glacial acetic acid, and the mixture was heated until a vigorous reaction commenced (at $\sim 90^\circ\text{C}$). At the end of the reaction, the mixture was refluxed for another 3 h, after which it was poured over 50 g of ice. The resulting precipitate was removed by filtration, washed with 100 ml of cold water, dried in vacuo, and chromatographed with a column filled with silica gel (100/200 μ) (elution with benzene) to give 2.5 g (38%) of 2-methylindole with mp $58-59^\circ\text{C}$ (mp $58-59^\circ\text{C}$ [13]).

2-Methyl-5-nitroindole. A mixture of 17.7 g (0.115 mole) of p-nitrophenylhydrazine, 100 ml of glacial acetic acid, 25 ml of acetic anhydride, 8 ml of concentrated HCl, and 7 ml (0.12 mole) of acetone was refluxed for 18-20 h, after which it was cooled and poured over 150 g of ice. After 30 min, the precipitated crystals were removed by filtration and chromatographed on silica gel (100/200 μ) in a benzene-methanol system (20:1) to give 12.3 g (74%) of 2-methyl-5-nitroindole with mp $175-177^\circ\text{C}$ (mp $176-176.5^\circ\text{C}$ [14]).

Dipyridinezinc Chloride. A 13-g (0.1 mole) sample of anhydrous zinc and 24 g (0.3 mole) of dry distilled pyridine were refluxed in nitromethane until the zinc chloride dissolved completely. The nitromethane and excess pyridine were then removed by vacuum distillation to give 28.8 g (100%) of dipyridinezinc chloride with mp 80°C (dec.).

Dipyridinetitanium Tetrachloride. An 8-ml (0.1 mole) sample of dry pyridine was added with cooling and stirring to a solution of 4.4 ml (0.04 mole) of TiCl_4 in 30 ml of acetone (the reaction was exothermic), and the resulting precipitate was removed by filtration, washed with acetone, and dried in vacuo at no higher than 100°C to give 13.9 g (100%) of a very hygroscopic complex with mp 137°C (dec.).

Tetrapyridinetin Tetrachloride. As in the preceding experiment, the reaction of 1.4 ml (0.012 mole) of SnCl_4 and 4.35 ml (0.055 mole) of dry pyridine gave 6.92 g (100%) of a white finely crystalline complex with a sublimation temperature of 250°C (dec.); the product hydrolyzed in air.

2-Bromoethylpyridinium Bromide. A solution of 8 ml (0.1 mole) of dry pyridine and 19 g (0.1 mole) of distilled ethyl bromide in 50 ml of acetone was refluxed for 15 h, after which it was cooled, and the precipitated crystals were removed by filtration to give 26 g (96%) of hygroscopic 2-bromoethylpyridinium bromide with mp 111°C .

1-(3-Chloropropyl)pyridinium Bromide. This compound, with mp 120°C , was similarly obtained in 97% yield.

1-(3-Indolylmethyl)pyridinium Bromide (II). A 10-g (0.02 mole) sample of red mercuric oxide was added with vigorous stirring to a solution of 3.2 g (0.03 mole) of 3-indolylacetic acid in 9.5 ml of acetone and 10 ml of carbon tetrachloride, and the reaction temperature was raised to 55°C and maintained at this level for 10 min, after which a solution of 1.5 ml (0.035 mole) of bromine in 2 ml of carbon tetrachloride was added slowly dropwise. The reaction mixture was filtered, 200 ml of ether was added to the filtrate, and the ether layer was removed from the precipitate by filtration and washed successively with water, 7% aqueous NaHSO_3 solution, and water. The ether extract was dried with CaCl_2 and evaporated, 2.1 ml (0.03 mole) of dry pyridine in 50 ml of absolute alcohol was added to the residue, and the mixture was refluxed for 5 h. The alcohol and excess pyridine were removed by distillation to give 1.5 g (20%) of salt II with mp 150°C (from alcohol, dec.). UV spectrum, λ_{max} (log ϵ): 265 (3.79), 300 sh (2.90), and 390 nm (1.70). Molecular weight (by cryoscopy) 297. $\text{C}_{14}\text{H}_{13}\text{BrN}_2$. Calculated: molecular weight 288.

1-(3-Indolyethyl)pyridinium Bromide (Ia). A) A mixture of 1.07 g (9 mmole) of indole, 2.4 g (9 mmole) of 1-(2-bromoethyl)pyridinium bromide, 2.65 g (9 mmole) of dipyridinezinc chloride, and 40 ml of dry nitromethane was refluxed with stirring until the starting indole vanished (according to chromatographic monitoring), i.e., ~ 12 h. The nitromethane was removed by vacuum distillation, the nonsaltlike impurities were removed by washing with ether, and the residual oil was chromatographed with a column filled with polyamide in a methanol-chloroform system (3:1) to give 1.8 g (65%) of salt Ia with mp $235\text{--}238^\circ\text{C}$ (from methanol). UV spectrum, λ_{max} (log ϵ): 274 (4.28), 293 (3.90), and 505 nm (2.64). Found: C 59.6; H 5.1%. $\text{C}_{15}\text{H}_{15}\text{BrN}_2$. Calculated: C 59.4; H 4.9%.

B) As in the preceding experiment, 2 g (72%) of salt Ia was obtained when tetrapyridinetin chloride was used as the catalyst.

C) A total of 2.52 g (92%) of salt Ia was obtained by a similar procedure when dipyridinetitanium chloride was used as the catalyst.

1-(5-Methoxy-3-indolyethyl)pyridinium Bromide (Ie). A solution of 1 g (6 mmole) of 5-methoxyindole and 2 g (6 mmole) of 1-(2-bromoethyl)pyridinium bromide in 20 ml of absolute nitromethane was heated to the boiling point, and a solution of 1.6 g (6 mmole) of dipyridinezinc chloride in 20 ml of absolute nitromethane was added dropwise in the course of 1 h. The mixture was then refluxed for another 30 h, after which the nitromethane was removed by vacuum distillation, and the residue was washed with ether to remove the unchanged indole. The residual oil was chromatographed with a column filled with polyamide in a methanol-chloroform system (5:1) to give 1.3 g (65%) of salt Ie with mp $219\text{--}220^\circ\text{C}$ (from water). UV spectrum, λ_{max} (log ϵ): 234 (4.01), 281 (3.85), 314 (3.64), and 585 nm (3.17). Found: C 58.0; H 4.6%; M (by cryoscopy) 331. $\text{C}_{16}\text{H}_{17}\text{BrN}_2\text{O}$. Calculated: C 58.8; H 5.1%; M 333.

1-(7-Methyl-3-indolyethyl)pyridinium Bromide (Id). This compound, with mp $240\text{--}243^\circ\text{C}$, was similarly obtained in 60% yield. UV spectrum, λ_{max} (log ϵ): 232 (4.47), 280 (4.08), 332 (3.31), and 558 nm (3.01). Found: C 61.0; H 5.0%. $\text{C}_{16}\text{H}_{17}\text{BrN}_2$. Calculated: C 60.6; H 5.0%.

1-(2-Methyl-5-nitro-3-indolylpropyl)pyridinium Chloride (If). Similarly, the reaction of 0.1 mole of 2-methyl-5-nitroindole and 0.12 mole of 1-(3-chloropropyl)pyridinium bromide for 2 h gave 6 g (70%) of salt If with mp 270°C (dec.). UV spectrum, λ_{max} (log ϵ): 227 (4.00), 260 (4.08), and 405 nm (4.46). Found: C 61.0; H 7.0%. $\text{C}_{17}\text{H}_{18}\text{ClN}_2\text{O}_2$. Calculated: C 61.0; H 6.6%.

1-(2-Methyl-3-indolyylethyl)pyridinium Bromide (Ic). A warm solution of 1.36 g (0.01 mole) of zinc chloride and 0.8 ml (0.01 mole) of dry distilled pyridine in nitromethane was added dropwise in the course of 10-15 min to a refluxing solution of 1.3 g (0.01 mole) of 2-methylindole and 2.67 g (0.01 mole) of 1-(2-bromoethyl)pyridinium bromide in 25 ml of nitromethane, and the mixture was refluxed for another 2.5-3 h (until the spot of the starting indole vanished on the chromatogram). The reaction mixture was worked up as described above using a methanol-chloroform system (2:1) as the eluent to give 2.8 g (79%) of salt Ic with mp 254-255°C. UV spectrum, λ_{\max} (log ϵ): 226 (4.34), 276 (4.04), and 470 nm (3.06). Found: C 60.6; H 4.7%. $C_{16}H_{17}BrN_2$. Calculated: C 60.6; H 5.0%.

1-(3-Indolylpropyl)pyridinium Chloride (Ib). A 7.9-g (0.1 mole) sample of dry pyridine and 6.5 g (0.05 mole) of anhydrous zinc chloride were added to a solution of 5.8 g (0.05 mole) of indole in dry distilled nitromethane, and the mixture was heated with stirring for 1 h. A 10.1-g (0.15 mole) sample of 1-(3-chloropropyl)pyridinium bromide was then added rapidly, and the mixture was refluxed with stirring for 48 h. The nitromethane and unchanged pyridine were removed by distillation, and the residual oil was refluxed with ether until the unchanged indole had been removed completely (according to chromatographic monitoring). Alcohol (100 ml) was added to the residue, and the mixture was refluxed for 1 h. The dipyridinezinc chloride was removed by filtration, and the filtrate was evaporated to give 0.9 g (7%) of salt Ib with mp 250-255°C (from water). UV spectrum, λ_{\max} (log ϵ): 275 (4.34), 290 (3.79), and 550 nm (2.91). Found: C 60.9; H 5.6%. $C_{16}H_{16}ClN_2$. Calculated: C 60.9; H 5.6%.

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