EFFECT OF A TOSYL PROTECTIVE GROUP ON THE DIRECTION OF THE ACYLATION OF 2-AMINOINDOLE

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The introduction of a tosyl grouping in the 2-aminoindole molecule substantially changes the direction of the acylation reaction. Not only substitution at the $C_{(3)}$ atom but also transacylation at the amino group with the elimination of the tosyl group are observed in the acylation of 2-tosylamidoindole in the presence of phosphoric acid.

It is known that the acetylation of a 2-aminoindole salt by means of acetic anhydride gives a product of acetylation at both nitrogen atoms, which, in the case of mild hydrolysis, splits out an acetyl group bonded to the ring nitrogen atom [1, 2]. Subsequent acetylation of the resulting 2-acetamidoindole takes place primarily in the 3 position of the indole ring. The reaction of 2-aminoindole with acetyl chloride in pyridine leads primarily to 1-acetyl-2-aminoindole [3]. Thus the acetylation of unsubstituted 2-aminoindole, depending on the reaction conditions, may take place at any of the three nucleophilic centers of the molecule. It has been recently shown that mono- and diacetyl derivatives with respect to the exocyclic nitrogen atom are formed by the action of acetic anhydride in triethylamine on a 2-amino-1,3-dialkylindole salt [4].

We have previously established [5] that the introduction of a tosyl grouping at the exocyclic nitrogen atom of 2-aminoindole leads, upon the whole, to a decrease in the reactivity of the molecule, although in some cases, such as in the reactions with 1,3-diketones, the same compounds as those that are formed with unsubstituted 2-aminoindole, i.e., α-carbolines, can be obtained. Of course, pyrimido[1,2-a]indoles, which are also obtained from 2-aminoindole and 1,3-diketones under other conditions [6], cannot be obtained from 2-arenesulfonamidoindoles.

In this connection, it seemed of interest to ascertain the effect of a tosyl protective group on the direction of the acylation of 2-aminoindole.

Virtually no reaction is observed between 2-tosylamidoindole (I) and acetic anhydride, even upon prolonged refluxing. If it is subjected to the action of acetic anhydride in pyridine, the resulting 1-acetyliapyridinium salt is not acylated but the I molecule is hetarylated by attack on the 3 position to give II [7]. We obtained the same result when we replaced acetic anhydride by acetyl chloride [8].

The N,N'-diacetyl derivative of 2-tosylamidoindole (III) is formed when sodium acetate is introduced as the base. The IR spectrum of the compound obtained does not contain absorption bands at 3100-3400 cm^{-1}, which makes it possible to exclude from consideration structures with an NH group and to assume a structure that contains acetyl groups attached to both nitrogen atoms. Singlets of three methyl groups at, respectively, 2.00, 2.36, and 2.65 ppm, a singlet of a 3-H proton (6.35 ppm), and a multiplet of eight aromatic protons at 7.06-8.13 ppm are observed in the PMR spectrum ($CDCl_3$) of III. Signals of NH protons are absent. A positive reaction with Erlich's reagent confirms a free 3 position in the indole ring. The presence in the mass spectrum of III of fragment ions* at 328, 286, 221, 173, and 131 and a molecular-ion peak at 370 also confirms the proposed structure.

*Here and subsequently, the m/z values are given for the ion peaks, and the intensities in percent of the maximum ion peaks are given in parentheses.

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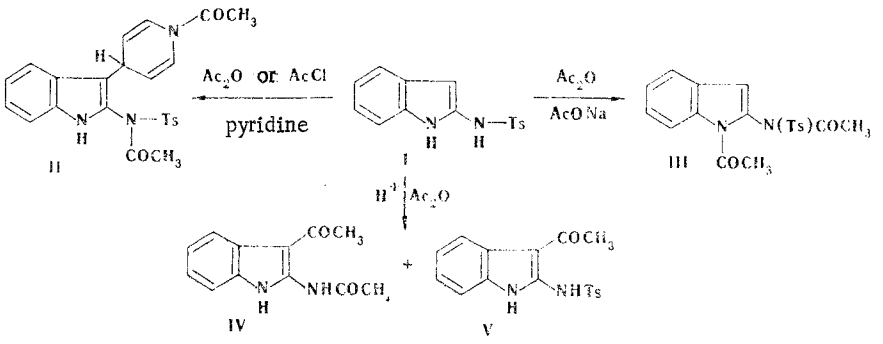
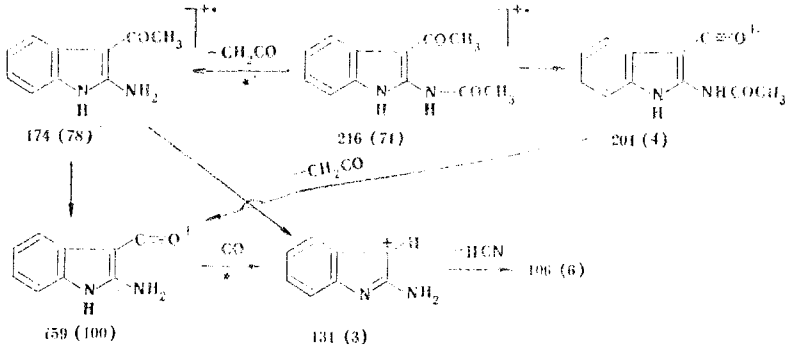
Refluxing of 2-tosylamidoindole I with acetic anhydride in the presence of phosphoric acid led to the primary formation of diacetyl derivative IV with simultaneous elimination of the tosyl group. 3-Acetyl-2-tosylamidoindole (V) was also isolated from the same reaction mixture in low yield.



In action to an intense molecular-ion peak and the peak of an $[M-15]^+$ ion, an ion corresponding to the elimination of ketene from the molecular ion was observed in the mass spectrum of IV; this is characteristic for acetyl derivatives of indole, in which the acetyl group is bonded to the nitrogen atom [9]. At the same time, the subsequent fragmentation of this ion radical (174) to give ions at 159 and 131 is characteristic for 3-acetylindoles [9]. The presence of metastable peaks makes it possible to represent the fragmentation scheme in the following way:



In the PMR spectrum (in $CDCl_3$) of IV the signals of the protons of the methyl groups were observed at 2.23 and 2.57 ppm, and signals of the protons of the NH groups were observed at 10.8 and 11.47 ppm. The signal of the 3-H proton was absent in the spectrum. According to the spectral data, the monoacetyl derivative isolated in this reaction has the V structure. The IR spectrum of this compound contained broad bands of a carbonyl group (1690-1720 cm^{-1}) and NH groups (3220 and 3410 cm^{-1}). The PMR spectrum (in $CDCl_3$) of V does not contain the signal of a proton in the 3 position but does contain broad signals at 9.2 and 11.31 ppm, which are characteristic for NH groups.

It must be noted that the acetylation of 2-tosylaminoindole in phosphoric acid is not reduced to the primary formation of a 2-aminoindole salt, since the hydrolytic cleavage of 2-tosylamidoindole requires more prolonged heating and proceeds, as demonstrated by our experiments, with cleavage of the C–N bond, i.e., it leads to an oxindole (with the loss of an amino group) [8].

Thus the introduction of a tosyl grouping in the 2-aminoindole molecule substantially changes the direction of the acylation reaction. Whereas the ring nitrogen atom is preferentially acylated in 2-aminoindole itself, the $C_{(3)}$ atom of the pyrrole ring of the exocyclic nitrogen atom or the exocyclic nitrogen atom proves to be more reactive in the case of 2-tosylamidoindole, i.e., the sulfonamido group is more reactive.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions in $CDCl_3$ were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the external standard. The UV spectra of solutions of the compounds in chloroform ($c = 10^{-2}$-10^{-3} mole/liter) were recorded with a Cary-15 spec-

trophotometer. The mass spectra were obtained with an MKh-1303 spectrometer with a modified system for recording with an H-105 circuit oscillator with introduction of the substances into the ionization region at an ionizing-electron energy of 50 eV. The course of the reactions and the purity of the compounds obtained were monitored by means of TLC (Silufol-254).

1-Acetyl-1,4-dihydro-4-[2-(N-acetyltosylamido)-3-indolyl]pyridine (II). A 3-ml (42 mmole) sample of acetyl chloride was added to a solution of 0.5 g (1.6 mmole) of 2-tosylamidoindole in 4 ml (49 mmole) of pyridine, and the mixture was allowed to stand for 24 h. It was then mixed with 5 ml of methanol containing 2.5 ml of 2 N hydrochloric acid. The resulting precipitate was separated, washed with methanol, and air dried to give 0.54 g (68%) of 1-acetyl-1,4-dihydro-4-[2-(N-acetyltosylamido)-3-indolyl]pyridine with mp 152-153°C (dec., from ethyl acetate); according to the data in [7], this compound had mp 150-160°C (dec.).

1-Acetyl-2-(N-acetyltosylamido)indole (III). A 1-g sample of calcined sodium acetate was added to a mixture of 0.5 g (1.6 mmole) of 2-tosylamidoindole and 5 ml (52 mmole) of freshly distilled acetic anhydride, and the mixture was stirred at 70°C for 3 h. It was then cooled and poured into 100 ml of water, and the aqueous mixture was neutralized with a 0.2 N solution of hydrochloric acid until a precipitate formed. The precipitate was separated and air dried to give 0.49 g (78%) of 1-acetyl-2-(N-acetyltosylamido)indole in the form of white needles with mp 174-176°C (from alcohol). Found: C 61.4; H 5.3; N 7.7%. $C_{19}H_{19}N_2O_4S$. Calculated: C 61.7; H 5.2; N 7.6%. IR spectrum: broad band at 1680-1720 cm^{-1} (CO). PMR spectrum: 2.0 (3H, s, $COCH_3$), 2.36 (3H, s, CH_3), 2.66 (3H, s, $COCH_3$), 6.33 (1H, s, 3-H), and 7.0-8.1 ppm (8H, m, aromatic protons). Mass spectrum*: 77 (41), 104 (14), 131 (100), 173 (12), 221 (9), 286 (24), 328 (28), and 370 (2).

3-Acetyl-2-acetamidoindole (IV) and 3-Acetyl-2-tosylamidoindole (V). A 0.5-ml sample of 85% phosphoric acid was added to 2 g (6.4 mmole) of 2-tosylamidoindole in 10 ml (0.1 mmole) of acetic anhydride, and the mixture was heated at 80-100°C for 1 h, after which it was cooled and poured with stirring into 300 ml of water, and the aqueous mixture was allowed to stand overnight. The resulting precipitate was separated and washed with 50% aqueous alcohol to give 1.1 g of a mixture of reaction products. Separation of these products was carried out on Silpearl silica gel plates [benzene—ethyl acetate (3:1)] to give 0.6 g (41%) of 3-acetyl-2-acetamidoindole IV with mp 221-222°C (from alcohol) (mp 221°C [3]). We also isolated 0.32 g (1.4%) of 3-acetyl-2-tosylamidoindole with mp 206-208°C (dec., from alcohol). Found: C 62.1; H 5.1%. $C_{17}H_{17}N_2O_3S$. Calculated: C 62.2; H 5.2%. UV spectrum, λ_{max} (log ε): 247 (4.30), 275 (4.20), and 322 nm (3.98). IR spectrum: 1690-1720 (CO) and 3220 and 3410 cm^{-1} (NH). PMR spectrum: 1.73 (3H, s, CH_3), 2.0 (3H, s $COCH_3$), 6.5-7.5 (8H, m, aromatic protons), 9.2 (1H, s, NH), and 11.3 ppm (1H, s, NH). Mass spectrum: 328 (33), 313 (3), 286 (9), 222 (4), 221 (5), 219 (3), 218 (4), 206 (3), 205 (4), 199 (3), 183 (5), 173 (100), 158 (6), 155 (5), 150 (3), 131 (18), 130 (3), 91 (21).

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*Here and subsequently, the peaks of ions with intensities greater than 3% of the maximum peak are presented.