SYNTHESIS OF INDOLE ANALOGS OF TOLAN

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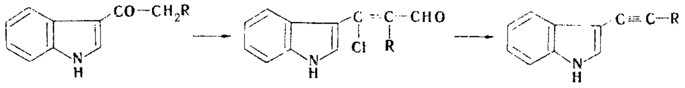
A method for the preparation of indole analogs of tolan, viz., indolylphenylacetylene and diindolylacetylene, from indolyl benzyl ketone and indolyl skatyl ketone, respectively, by reaction with a Vilsmeier–Haack reagent was developed. The synthesis of indolyl skatyl ketone and 3-(3-indolyl)-3-chloro-2-phenyl-2-propen-1-al was realized.

Tolan (diphenylacetylene) is widely used as a reagent for diverse syntheses and is also used as a scintillator [1].

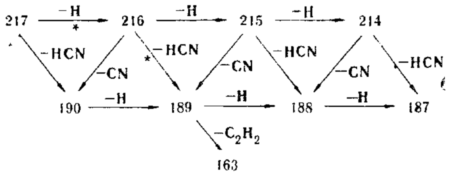
We have accomplished the synthesis of indole analogs of tolan, i.e., 3-indolyphenylacetylene (I) and di(3-indolyl)acetylene (II) from 3-indolyl benzyl ketone (III) and 3-indolyl skatyl ketone (IV), respectively. The latter ketone was obtained via the Oddo reaction from indolylmagnesium bromide and 3-indolylacetyl chloride. Ketone III reacts readily with the Vilsmeier–Haack reagent obtained from phosphorus pentachloride and dimethylformamide (DMF) to give 3-(3-indolyl)-3-chloro-2-phenyl-2-propen-1-al (V). Treatment of the latter with a concentrated solution of alkali in the presence of a quaternary ammonium salt leads to acetylene I. We were able to obtain acetylene II in low yield from ketone IV under similar conditions.



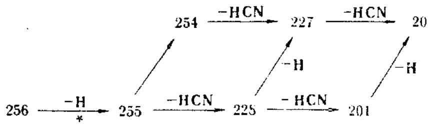
III, IV V I, II

I, III, V $R = C_6H_5$; II, IV R = 3-indolyl

The maximum peak in the mass spectrum of acetylene I is the molecular-ion peak (m/e 217, M^+):



The maximum peak in the mass spectrum of acetylene II is also the molecular-ion peak (m/e 256, M^+):



A comparison of the mass spectra of acetylenes I and II with the mass spectrum of tolan [2] shows that the fragmentation in all cases proceeds at the indole and phenyl parts of the molecules without involving the acetylene grouping.

The IR spectrum of acetylene I contains an intense absorption band at 2240 cm^{-1} that is due to the presence of an asymmetrically disubstituted triple bond in the molecule. In the case of acetylene II the absorption band of the triple bond, as expected, is not displayed as a consequence of prohibition by the symmetry.

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* The decomposition pathways that are confirmed by the peaks of metastable ions are denoted by asterisks in the schemes.

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EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of solutions of the compounds in ethanol were recorded with a Specord spectrophotometer. The PMR spectra were recorded with a CFT-20 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 mass spectrometer with direct introduction of the samples into the ion source at an ionizing-electron energy of 50 eV.

3-(3-Indolyl)-3-chloro-2-phenyl-2-propen-1-al (V). A 10.95-g (53 mmole) sample of phosphorus pentachloride was added in 0.3- to 0.5-g portions with stirring to 50 ml of DMF while maintaining the temperature of the reaction mixture at 20-25°C by means of external cooling with water. The resulting yellow solution began to thicken after 1-2 g. The suspension was stirred at 20°C for 5-6 h, after which 11.27 g (48 mmole) of ketone III was added in 0.1- to 0.2-g portions in the course of 20 min while maintaining the temperature of the reaction mixture at ~20°C by means of external cooling with water. At the end of the exothermic reaction, the mixture was maintained at 20°C for 12-13 h, after which 100 ml of ice water was added, and the mixture was stirred vigorously for 5-6 h. The precipitate was removed by filtration, washed with water (two 50-ml portions), dried, and recrystallized from benzene to give 7.07 g (53%) of aldehyde V with mp 123-124°C (dec., from heptane). IR spectrum: 3470 (indole NH), 1670 (C=O), and 1590 cm^{-1} (C=C). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 208 (32.6), 217 (34.3), 277 (12.7), 377Hm (10.6). PMR spectrum (in CD_3COCD_3): s 9.74 (CH=O); s 7.33 (C_6H_5); m, 7.08-7.88 ppm (arom.) Found: C 72.4; H 4.3; N 5.0%. $C_{17}H_{12}ClNO$. Calculated: C 72.5; H 4.3; N 5.0%.

3-Indolylphenylacetylene (I). A 75-ml sample of a 40% aqueous solution of sodium hydroxide containing 0.1 g of trimethylbenzylammonium chloride was added to a solution of 2.82 g (10 mmole) of aldehyde V in 500 ml of benzene, and the mixture was stirred vigorously for 40 min. The organic layer was separated, and the aqueous layer was diluted with 150 ml of water and extracted with benzene (three 50-ml portions). The extract was washed with water until the wash waters were neutral, dried with $MgSO_4$, and evaporated in vacuo. The residue was chromatographed with a 2- by 45-cm column filled with 150-200 μ of silica gel (elution with benzene) to give 0.453 g (35%) of acetylene I with mp 164-165°C (dec., from benzene). IR spectrum: 3480 (indole NH) and 2240 cm^{-1} (C≡C). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 205 (26.0), 225 (31.9), 241 (18.8), 253 (11.4), 281 (13.7), 308 (20.2), 322 HM (17.9). PMR spectrum (in CD_3COCD_3): s, 7.08 (C_6H_5); m, 7.0-8.0 ppm (arom). Found: C 88.4; H 5.2; N 6.4%. $C_{16}H_{11}N$. Calculated: C 88.4; H 5.1; N 6.4%.

3-Indolyl Skatyl Ketone (IV). A solution of 7.25 g (62 mmole) of indole in 50 ml of absolute ether was added to a Grignard reagent prepared from 1.51 g (62 mmole) of magnesium and 6.76 ml of ethyl bromide in 100 ml of absolute ether. At the end of the exothermic reaction, the mixture was maintained at 25-30°C for 1 h, after which it was cooled to −10°C and treated with a solution of 4.8 g (24 mmole) of 3-indolylacetyl chloride in 50 ml of absolute ether at such a rate that the temperature of the reaction mixture did not rise above 5°C. The mixture was then heated slowly to room temperature and allowed to stand at this temperature for 12-14 h. It was then decomposed with a saturated solution of ammonium chloride and treated with 100 ml of benzene, and the precipitate was removed by filtration, washed with benzene (three 30-ml portions), dried, and recrystallized from chloroform to give 2.41 g of keton IV. The organic part of the filtrate was separated, and the aqueous part was extracted with benzene (three 50-ml portions). The combined extracts were dried with $MgSO_4$ and evaporated, and the residue was chromatographed with a 2- by 40-cm column filled with 150-200 μ of silica gel (initial elution with hexane, followed by benzene and chloroform) to give another 0.61 g of ketone IV. The overall yield of product with mp 220-222°C (dec., from chloroform) was 3.02 g (44%). IR spectrum: 3400 and 3250 (indole ring NH); 1620 and 1640 cm^{-1} (C=O). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 208 (49.3), 220 (59.1), 244 (18.6), 263 (17.0), 285 (19.2), 292 HM (19.7). PMR spectrum (in CD_3COCD_3): s, 3.95 (CH_2); m, 6.57-8.10 ppm (arom). Mass spectrum (m/e): 274 (M^+), 144 (174 - skatyl), 130 (274 - indoyl). 129 (130 - H), 117 (274 - indoylmethyl), 116 (144 - CH_2, 130 - CO), 89 (116 - HCN). Found: C 78.7; H 5.1; N 10.0%. $C_{18}H_{14}N_2O$. Calculated: C 78.7; H 5.1; N 10.0%.

Di(3-indolyl)acetylene (II). A solution of 4.2 g (15 mmole) of ketone IV in 20 ml of DMF was added at no higher than 20°C to a Vilsmeier–Haack reagent obtained, as described above, from 3.52 g (17 mmole) of phosphorus pentachloride and 30 ml of DMF, and the mixture was allowed to stand at 20°C for 12-14 h. It was then diluted with 200 ml of benzene, 200 ml of a saturated solution of potassium acetate in water was added rapidly, and the mixture was stirred vigorously for 5-6 h. The organic layer was separated, and the aqueous layer was extracted with benzene (three 50-ml portions). The extract was washed with water (three 50-ml portions), dried with $MgSO_4$, and evaporated in vacuo. The residue was chromatographed with a 2- by 40-cm column filled with 150-200 of silica gel (elution with benzene) to give 0.3 g (8%) of acetylene II with mp 268-

270 :C (dec., from benzene). IR spectrum: 3400 cm^{-1} (indole ring NH). UV spectrum, λ_{max} ($\varepsilon \cdot 10^{-3}$): 208 (35.4), 227 (38.4), 256 (16.9), 279 (17.3), 303 (11.6), 327 HM (9.2). Found: C 84.1; H 4.5; N 11.0%. $C_{18}H_{12}N_2$. Calculated: C 84.4; H 4.7; N 10.9%.

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ANHYDRO BASES OF 3-PYRIDYLINDOLES

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The reactions of quaternary salts of 3-pyridyl- and benzopyridylindoles with alkali proceed via two pathways, viz., deprotonation, the products of which are anhydro bases, and dealkylation of the pyridine ring, as a consequence of which the corresponding nonquaternized bases are formed. The reactions are interpreted from a quantum-chemical point of view.

It is known [1, 2] that quaternary pyridinium salts in alkaline media add a hydroxide ion to give covalent hydration products that exist in equilibrium with the open prototropic form. In a number of cases the latter may undergo ring closure to give a new cyclic system as, for example, in the recyclization of quaternary salts of α-picoline to aniline [3], nicotyrine to indole [4], and 2-(3-pyridyl)indole to carbazole [5]. It is usually assumed that these rearrangements proceed through the formation of the corresponding anhydro bases [3], and this is also responsible for the recent increased interest in the study of this interesting class of organic compounds.

Pyridylindoles are of interest because the presence of an indole NH group in the molecule makes deprotonation to give anhydro bases through the action of alkali on their quaternary salts more likely. Thus, for example, it has been shown [6] that a stable anhydro base, viz., 1-methyl-4-(3-indolenylidene)-1,4-dihydropyridine, is formed under these conditions, and its electronic structure, UV spectra, and basicity constant have been studied. In the present research we investigated the UV spectra and the prototropic transformations of the quaternary salts of benzopyridylindoles in relationship to their structures.

Colored anhydro bases are formed in the reaction of quaternary salts of substituted 2-phenyl-3-(4-pyridyl)indoles (I) with an alcohol solution of alkali. Anhydro bases were obtained under similar conditions from the isomeric 2-phenyl-3-(2-pyridyl)indole methiodide and from the quaternary salts of 3-(2-quinolyl)-, 3-(1-isoquinolyl)-, 3-(benzo[f]-quinolyl)-, and 3-(9-acridinyl)indoles (III–VI). The color of the anhydro bases of benzopyridylindoles is deeper than that of the anhydro bases of pyridylindoles and deepens in the series presented from red to violet, apparently because of an increase in the conjugation chain.

In addition to attack by the nucleophile on the NH group of the indole fragment, which leads to anhydro bases (VII–X), one also observes competitive N-dealkylation, which increases in the order I, III, and VI. In the latter example dealkylation becomes the principal process, whereas anhydro base X is formed in low yield under comparable conditions.

To explain this fact we performed a quantum-chemical calculation of the cations of III, IV, and VI by the Pariser–Parr–Pople (PPP) method with the parametrization proposed in [7]; it was assumed that these compounds are nonplanar, and the dihedral angle (θ) was calculated from the van der Waals radii of the sterically hindered groups and was found to be 68° for the cis conformers of the cations of III and IV and 71° for the

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