1-ACETYLINDOXYL IN REACTIONS WITH HYDRAZINE AND THIOSEMICARBAZIDE

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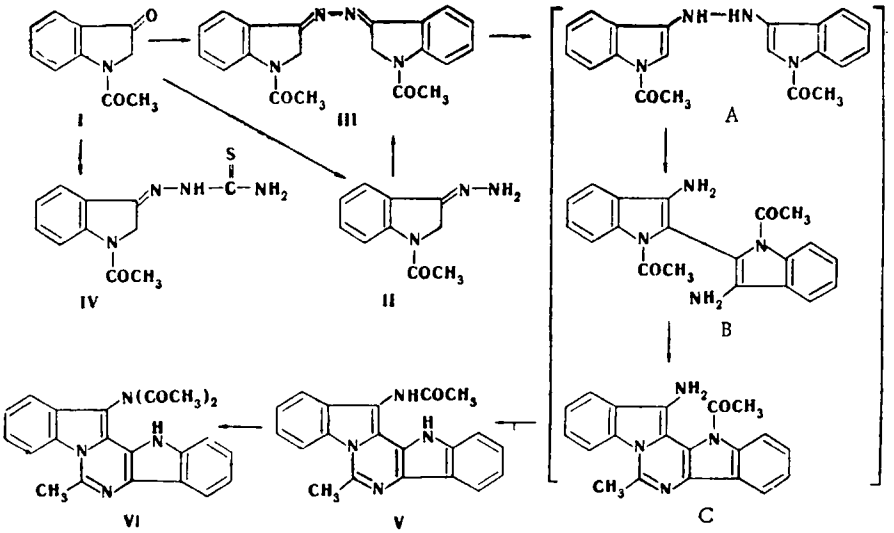
The use of 1-acetylindoxyl (I) in the Wittig reaction [1], Reformatsky reaction [2], and Claisen condensation [3, 4] has revealed new synthetic routes to various indole derivatives. Further study of the reactions of 1-acetylindoxyl seems to merit attention.

In the work described here we have established that indoxyl (I) forms 1-acetylindoxyl hydrazone (II) when refluxed with hydrazine hydrate in alcohol, 1-acetylindoxyl azine (III) with anhydrous hydrazine in acetic acid at room temperature, and 1-acetylindoxylthiosemicarbazones (IV) with thiosemicarbazide. 1-Acetylindoxyl hydrazone (II) can be prepared in comparatively high yield only by reaction of 1-acetylindoxyl (I) with a large excess of hydrazine in the presence of triethylamine. We adjusted the quantities of hydrazine hydrate and triethylamine experimentally, taking account of the reported synthesis of benzophenone hydrazone [5]. We verified the structures of compounds (II) and (IV) from their PMR spectra, which have the protons of the methylene groups at 4.55 and 4.86 ppm. The protons of the methylene group of indoxyl (I) appear at 4.45 ppm under the same conditions, demonstrating the presence of the hydrazone structure in compounds (II) and (IV). We verified the structure of azine (III) from its IR spectrum, which lacks the NH bands. Both hydrazone (II) and azine (III) are converted to 7-methyl-13-acetylaminopyrimido[3,4-a:5,6-b']diindole (V) by heating for a short time in acetic acid.



We may view the process of formation of compound (V) as analogous to that of indolo[1,2-c]quinazolines from 3-arylazoindoles [6, 7]. Then azine (III) will first isomerize to the hydrazo derivative A, which then undergoes an o-benzidine type rearrangement to compound B. The rearrangement product is converted to compound C by cyclocondensation involving the acetyl and amino groups. The acetyl group then migrates from position 1 to the 13-amino group to form 7-methyl-13-acetylaminopyrimido[3,4-a:5,6-b']diindole (V). The IR spectrum of compound (V) contains one intense absorption band at 3280 cm^{-1}, which is typical of the NH but not of the NH_2 group. The presence in its PMR spectrum of two broad singlet signals at 9.73 and 11.34 ppm due to uncoupled nitrogen protons demonstrates the absence of the NH_2 group.

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When heated in acetic acid, hydrazone (II) probably disproportionates to azine (III), which is then converted via hydrazo derivative A to pyrimido[3,4-a:5,6-b']diindole (V). Compound (V) is also formed by reaction of hydrazine with a twofold excess of 1-acetylindoxyl (I) in refluxing in acetic acid.

Unlike hydrazone (II) and azine (III), thiosemicarbazone (IV) is unaffected by heating in acetic acid.

Acylation of compound (V) with acetic anhydride in the presence of sodium acetate forms 13-diacetylaminopyrimido[3,4-a:5,6-b']diindole (VI). Its PMR spectrum has a singlet of the acetyl protons at 2.37 ppm whose intensity corresponds to two acetyl groups. The chemical shifts of the protons of the two acetyl groups of compound (VI) are identical in dimethyl sulfoxide-d_6 and in pyridine-d_5. This points to the equivalence of these acetyl groups, which is possible only when they are both attached to the same nitrogen atom, and specifically the nitrogen atom of the 13 substituent.

EXPERIMENTAL

Spectra were recorded on: IR: UR-10 and UR-20 spectrophotometers in Vaseline oil; UV: a Specord; PMR: JNM-4H-100 with hexamethyldisiloxane (HMDS) as internal standard, Varian CFT-20 and Varian XL-100A-12 with tetramethylsilane (TMS) as internal standard. Mass spectra were derived with an MX-1303 mass spectrometer with direct sample insertion into the ion source at ionizing energy 30 eV.

1-Acetylindoxyl Hydrazone (II). To a suspension of 1-acetylindoxyl (3.5 g, 0.02 mole) in alcohol (40 ml) were added hydrazine hydrate (7 ml, 0.14 mole) and triethylamine (0.85 ml, 0.006 mole). The reaction mixture was refluxed for 30 min and then cooled. The precipitate was filtered off and washed with alcohol. The yield was 2.15 g (52%), mp 154-156°C (from methanol). IR spectrum: 1640 (C=O), 3160, 3300, 3380 cm^{-1} (NH_2). PMR spectrum (acetone-d_6–DMSO-d_6, 1:1): 2.17 (s, $COCH_3$), 4.55 (s, CH_2), 6.52-7.50 ppm (m, aromatic protons). Found: C 63.3; H 5.9; N 22.4%. $C_{10}H_{11}N_3O$. Calculated: C 63.5; H 5.0; N 22.2%.

1-Acetylindoxyl Azine (III). To a gently warmed solution of 1-acetylindoxyl (0.86 g, 4.8 mmole) in acetic acid (6 ml) was added anhydrous hydrazine (0.08 g, 2.5 mmole). The reaction mixture was kept at room temperature for 10-12 h. The precipitate was then filtered off and washed with alcohol and with ether to give the azine (0.5 g, 60%), decomposition point above 250°C. IR spectrum: 1610 (C=N), 1670 cm^{-1} (C=O). Found: C 69.2; H 5.4; N 16.3%; M^+ 346. $C_{20}H_{18}N_4O_2$. Calculated: C 69.4; H 5.2; N 16.2%; M 346.

1-Acetylindoxyl Thiosemicarbazone (IV). A mixture of 1-acetylindoxyl (0.18 g, 0.001 mole), thiosemicarbazide (0.1 g, 0.0011 mole), and acetic acid (1 ml) was refluxed for 5-7 min. The precipitate was filtered off and washed with acetic acid, alcohol, and ether. The yield was 0.22 g (88%), mp 260-262°C (from acetic acid). IR spectrum: 1610, 1660 (C=N and C=O), 3200, 3300, 3450 cm^{-1} (NH, NH_2). PMR spectrum (acetone-d_6–DMSO-d_6, 1:1): 2.23 (s, $COCH_3$), 4.86 (s, CH_2), 6.62-8.37 ppm (m, aromatic protons). Found: C 52.7; H 4.7; N 22.6; S 12.1%; M^+ 248. $C_{11}H_{12}N_4OS$. Calculated: C 53.2; H 4.9; N 22.6; S 12.9%; M 248.

7-Methyl-13-acetylaminopyrimido[3,4-a:5,6-b']diindole (V). A) A mixture of 1-acetylindoxyl (1.72 g, 0.02 mole) and anhydrous hydrazine (0.16 g, 0.01 mole) in acetic acid (16 ml) was refluxed for 40 min. The precipitate was filtered off and washed with acetic acid, alcohol, and ether. The yield was 1.5 g (91%), decomposition point above 350°C (from acetic acid). IR spectrum: 1630 (C=O), 3280 cm^{-1} (N–H). PMR spectrum (in DMSO-d_6): 2.31 (s, $COCH_3$), 3.21 (s, CH_3), 7.15-8.35 (m, aromatic protons), 9.73, 11.34 ppm (s, 2NH). Found: C 72.8; H 5.0; N 17.0%; M^+ 328. $C_{20}H_{16}N_4O$. Calculated: C 73.2; H 4.9; N 17.1%; M 328.

B) A solution of hydrazone (II) (3 g, 0.016 mole) in acetic acid (30 ml) was heated to 100°C. The precipitate that formed on cooling to room temperature was filtered off and washed with acetic acid and methanol to give compound (V) (1.92 g, 74%).

C) A suspension of azine (III) (0.35 g, 0.001 mole) in acetic acid (5 ml) was refluxed for 30 min. The precipitate was filtered off and washed with alcohol and ether. The yield of compound (V) was 0.3 g (91%). A mixture of samples of compound (V) prepared by methods (b) and (c) with a sample prepared by method (a) showed no depression of the melting point. Their IR spectra were identical.

7-Methyl-13-diacetylaminopyrimido[3,4-a:5,6-b']diindole (VI). A suspension of compound (V) (0.2 g, 0.6 mmole), sodium acetate (0.2 g, 2.4 mmole), acetic acid (10 ml), and acetic

anhydride (20 ml) was refluxed for 1 h and then evaporated under vacuum to half volume. The precipitate that formed on cooling was filtered off and washed with water, alcohol, and ether to give compound (VI) (0.2 g, 76%), mp above 330°C (decomposition; from alcohol). IR spectrum: 1660, 1710 (C=O), 3390 cm^{-1} (NH). UV spectrum, λ_{max}: 210, 235, 247, 258, 279, 289, 302, 313, 339, 358, 379, 389 nm (log ε 4.41, 4.33, 4.45, 4.38, 4.36, 4.31, 4.21, 4.30, 4.42, 4.25, 4.15, and 3.97). PMR spectrum (in DMSO-d_6): 2.37 (s, $2COCH_3$), 3.28 (s, CH_3), 7.15-8.35 (m, aromatic protons), 11.75 ppm (s, NH). Found: C 71.0; H 4.8; N 15.1%; M^+ 370. $C_{22}H_{18}N_4O_2$. Calculated: C 71.3; H 4.9; N 15.1%; M 370.

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SUBSTITUTED AZAINDOLES.

58.* COMPARATIVE KINETICS OF THE NITRATION OF ISOMERIC 4-, 5-, 6-, AND 7-AZAINDOLES

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The distinctive features of the interaction of π-electron-deficient pyridine and π-electron-excessive pyrrole rings in the condensed systems of isomeric pyrrolopyridines (azaindoles) have been discussed on several occasions [2, 3]. Hückel and PPP calculations of the indices of the electronic structure of isomeric azaindoles [4, 5] have revealed that the π-electron density distribution, ionization potential, and electron affinity vary only slightly on going from one isomer to another: the electron affinity increases slightly in the order 5-, 6-, 7-, and 4-azaindole and the ionization potential in the order 5-, 7-, 6-, and 4-azaindole.

Purely qualitative comparisons of the reactivity of the isomeric azaindoles in electrophilic substitution reactions have also failed to clarify the marked differences among these compounds [6]. Study of the kinetics of acid-catalyzed hydrogen exchange at position 3 of the isomeric 4-, 5-, and 7-azaindoles has revealed that 4-azaindole is more reactive than the 5-aza isomer, in which the electron-accepting effect of the pyridine nitrogen atom, which is para to the pyrrole nitrogen atom, is more effective [7].

In the work described here we have sought a more quantitative comparison of the reactivity by using a more complete series of the isomeric azaindoles, which included 6-azaindole in addition to 4-, 5-, and 7-azaindoles. Moreover to ascertain the generality of the correlations found earlier [7] we used another electrophilic substitution reaction, nitration, which under first-order reaction conditions takes place exclusively at position 3 and proceeds reasonably here to completion [6].

*For Communication 57 see [1].

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