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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Reaction of α-Chloro-β-oxobutanal with Indole Derivatives

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Abstract—The reactions of 2-methylindole and 2-methylindol-3-yldiphenylphosphine with α-chloro-β-oxobutanal was studied.

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Indole and its derivatives are structural fragments of various alkaloids [1].

Proceeding with studies on synthesis of indolyl-substituted carbonyl compounds [2–4], we examined the reactions of 2-methylindole and 3-methylindol-2-yldiphenylphosphine with α-chloro-β-oxobutanal and cyclization of the resulting unsaturated ketones.

α-Chloro-β-oxobutanal was prepared by the procedure described in [5]. The reaction of 2-methylindole with α-chloro-β-oxobutanal was performed in acetonitrile or ethanol (with addition of catalytic amounts of pyridine) at the boiling point of the solvent. Acetonitrile is preferable as solvent because of high yield of product 1 (85%). The structure, composition, and purity of the compound synthesized were proved by spectral data and elemental analysis:

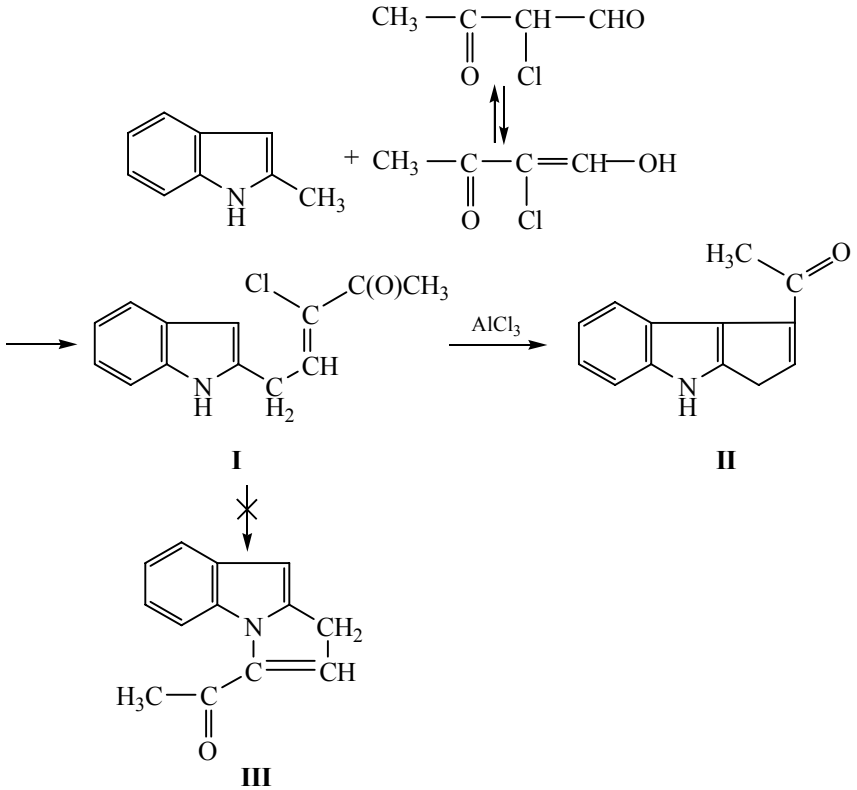


Table 1. Physicochemical and spectral characteristics of the compounds synthesized

Comp. no.	Yield, %	T_m, °C	Found, % / Calculated, %			Formula	^{1}H NMR spectrum, δ, ppm (acetone-d_6)	IR spectrum, ν, cm^{-1}
			N	P	Cl			
I	85	180–181	5.86 / 6.00	–	15.68 / 15.20	$C_{13}H_{12}NOCl$	2.6 s (3H, CH_3CO); 3.9 d (2H, CH_2); 7.00 d (2H, C_5H+C_6H); 7.6 d (2H, C_4H+C_7H); 8.00 t (1H, CH=); 8.8 br.s (1H, NH)	1580–1620 (C=C); 1720 (C=O); 3240 (NH amide)
II	77	234–236	7.59 / 7.11	–	–	$C_{13}H_{11}NO$	2.5 s (3H, CH_3O); 3.6 d (2H, CH_2); 6.9 d (2H, C_5H+C_6H); 7.55 d (2H, C_4H+C_7H); 7.78 t (1H, CH=); 8.6 br.s (1H, NH)	1620 (C=C); 1715 (C=O); 3260 (NH amide)
IV	68	Oil	3.29 / 3.35	7.64 / 7.43	8.33 / 8.50	$C_{25}H_{21}NOPCl$	2.4 s (3H, CH_3); 3.8 d (2H, CH_2); 6.8 d (2H, C_5H+C_6H); 7.3 d (2H, C_4H+C_7H); 7.5–7.75 m (1H, Ph); 7.9 t (1H, CH=); 9.00 br.s (1H, NH)	1715 (C=O); 1580–1600 (C=O); 3280 (NH amide)
V	59	149–150	3.86 / 3.67	8.22 / 8.14	–	$C_{25}H_{20}NOP$	2.45 s (3H, CH_3); 3.8 d (2H, CH_2); 6.85 d (2H, C_5H+C_6H); 7.3 d (2H, C_4H+C_7H); 7.5–7.8 m (1H, Ph); 8.2 d (1H, CH=)	1690 (C=C); 1580–1620 (C=C indol)

The IR spectrum of product **I** contains absorption bands confirming its structure: $\nu_{C=Carom}$ (1580–1620 cm^{-1}), $\nu_{C=O}$ (1720 cm^{-1}), ν_{NH} (3240 cm^{-1}), ν_{C-Cl} (660–690 cm^{-1}).

The ^{1}H NMR spectrum also confirms the structure of **I**. The CH_2 protons give a doublet at 3.9 ppm; the NH proton, a broadened singlet at 8.8 ppm; and the methine proton, a triplet at 8.00 ppm.

Despite activation of the halogen atom at the α-carbon atom by the carbonyl group, in most cases it is replaced difficultly. However, in product **I** in the Z configuration the Cl atom is sterically close to the C^3H proton of the indole ring. Therefore, an intramolecular attack of the C^3 position of the indole ring by the α-C atom of the aldehyde can be expected, as it is observed for compounds with labile halogen. At the same time, the hydrogen atom bonded to the N atom is also labile, and therefore the attack of the C^2 atom by the nitrogen atom cannot be ruled out.

To determine the possible pathway of cyclization of **I**, it was heat-treated in dioxane in the presence of catalytic amounts of a Lewis acid ($AlCl_3$). We found that, under the action of $AlCl_3$, compound **I** underwent cyclization into **II** at the C^3 position and not at the N atom. In the process, the starting compound **I** gradually dissolves, and the reaction is complete in 5–6 h with a high yield of heterocycle **II**.

The resulting heterocyclic compound is a high-melting crystalline substance stable in storage.

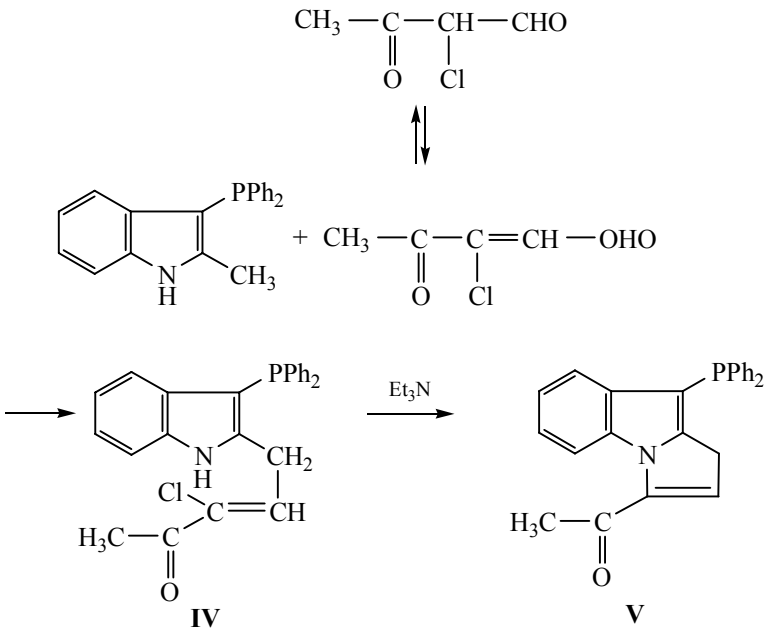
The IR spectrum of the cyclization product contains a band at 3260 cm^{-1}, confirming that the NH proton is not involved in cyclization, i.e., that the reaction occurs at the C^3 atom (Table 1).

In the ^{1}H spectrum of heterocycle **II**, the CH=C proton gives a triplet at 7.78 ppm, in contrast to linear product **I** giving the corresponding the signal at 8.00 ppm. The CH_2 signal is observed at 3.95 ppm, which confirms the formation of compound **II** in the reaction.

The formation of heterocycle **II** was also confirmed by mass spectrometry: The molecular ion with *m*/*z* 197 corresponds to the empirical formula $C_{13}H_{11}NO$.

Then, with the aim to perform cyclization at the indole nitrogen atom, we studied the reaction of 2-methylindol-3-yldiphenylphosphine with α-chloro-β-oxobutanal. The reaction was performed in refluxing dioxane with addition of catalytic amounts of piperidine. The final cyclization product **V** is formed in a two-step process. The first step is formation of stable product **IV**, which was isolated pure. The reaction was accompanied by darkening of the reaction

mixture. The brown mother liquor was passed through silica gel L100/400, and phosphorylated product **IV** was isolated from the resulting yellow solution as viscous oil. Its attempted crystallization failed:



The product was identified as compound **IV** on the basis of spectroscopic data. The ^{1}H NMR spectrum of **IV** contains the following signals, ppm: 2.4 s (CH_3CO), 3.8 d (CH_2), 6.8 and 7.3 d.d (C_5H + C_6H; C_4H + C_7H), 7.5–7.75 m (2Ph), 7.9 d (CH=), 9.00 br.s (NH).

The ^{31}P NMR spectrum is characterized by a signal at –5.8 ppm. In the IR spectrum, there are absorption bands at 3238 (ν_{NH} assoc.), 1580–1600 ($\nu_{C=C}$ of indole), and 1715 cm^{-1} ($\nu_{C=O}$).

With the aim of subsequent heterocyclization, the isolated oil was dissolved in absolute ethanol, an equimolar amount of triethylamine was added to bind HCl, and the reaction mixture was kept first for 1 h at room temperature and then for 2 h at 60°C.

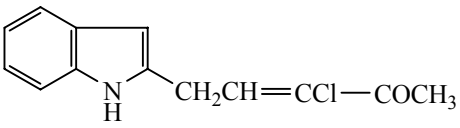
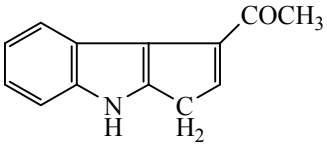
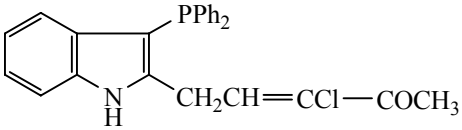
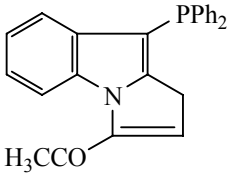
The reaction progress was monitored by IR and ^{31}P NMR spectroscopy. The ^{31}P NMR signal is shifted by 1 ppm (from –5.8 to –6.8 ppm). In the IR spectrum, the absorption band of the associated NH group at 3280 cm^{-1} disappears. In the ^{1}H NMR spectrum, the methine proton signal shifts from 7.9 to 8.2 ppm. These data also show that the reaction occurs along the heterocyclization pathway.

The synthesized compounds **I**, **II**, **IV**, and **V** were tested as antimicrobial additives to DS-11 lubricating oil according to GOSTs (State Standards) 9.052–75 and 9.085–75 (Table 2). The data we obtained show that all the compounds exhibit pronounced antimicrobial effect at a low concentration (0.5–1.0%), are well soluble in DS-11 oil, and do not stimulate corrosion. With respect to performance, indolyl-substituted compounds **I**, **II**, **IV**, and **V** surpass the commercial antimicrobial additive, sodium pentachlorophenolate, used as reference. At 0.5% concentrations of the compounds we prepared, the suppression zone width was 0.9–1.3 cm for bacteria and 1.2–1.5 cm for fungi, whereas with sodium pentachlorophenolate at the same concentration the suppression zone width for bacteria and fungi was 0.7 cm. Similar pattern was observed at 1% concentration.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded with a Bruker DPX-300 spectrometer operating at 300 MHz (solvent $CDCl_3$). The IR spectra were measured on a Specord-75-IR spectrometer. The mass spectra were taken with a Finnigan MAT Incos 50 device with ionization by electron impact (70 eV). Elemental analysis was performed with a Hewlett–Packard 185 B CHN analyzer.

Table 2. Antimicrobial activity of compounds in DS-11 oil

Compound	Concentration, %	Diameter the microorganism growth suppression zone, mm	
		mixture of bacteria meat–peptone agar)	mixture of fungi (must–agar medium)
 **I**	0.5 1.0	0.9 2.0	1.2 2.5
 **II**	0.5 1.0	0.8 1.9	1.0 2.2
 **IV**	0.5 1.0	1.2 2.6	1.3 2.8
 **V**	0.5 1.0	1.3 2.8	1.5 2.9
Sodium pentachlorophenolate (reference)	0.5 1.0	0.7 1.3	0.7 1.4

3-Chloro-5-(indol-2-yl)pent-3-en-2-one (I). A mixture of 2.62 g (0.02 mol) of 2-methylindole and 2.41 g (0.02 mol) of α-chloro-β-oxobutanal with addition of 1.0 g of pyridine was refluxed in 60 ml of acetonitrile for 8 h. After removing the solvent from the filtrate at reduced pressure, a dark brown oil was obtained. It was dissolved in 20 ml of a 1 : 1 ether–hexane mixture, and the solution was left overnight in a refrigerator. The crystals of **1** were filtered off and vacuum-dried. Yield 3.97 g (85%).

1-Acetylcyclopent-1-eno[4,5-*b*]indole (II). 4.67 g (0.02 mol) of **I** was dissolved in 30 ml of dioxane, a catalytic amount of $AlCl_3$ was added, and the mixture was refluxed for 6 h. Then the solvent was removed at reduced pressure, and 15 ml of an ether–MeCN mixture (2 : 1) was added to the residue. The precipitated crystals were filtered off and dried. Yield 3.03 g (77%).

3-Chloro-5-(3-diphenylphosphinoindol-2-yl)pent-3-en-2-one (IV). A mixture of 6.3 g (0.02 mol) of 3-methylindol-2-yldiphenylphosphine and 2.41 g (0.02 mol) of α-chloro-β-oxobutanal with addition of 0.3 g of piperidine was refluxed in dioxane for 4 h. The resulting brown mother liquor was passed two times through silica gel. By evaporation of the resulting yellow solution, we obtained phosphorylated product **IV** in the form of viscous oil. Yield 5.68 g (68%).

1-Acetylcyclopent-1-eno[5,4-*a*]-3-diphenylphosphinoindole (V). A solution of 4.18 g (0.01 mol) of

4 in 100 ml of absolute ethanol and 1.01 g (0.01 mol) of Et_3N, cooled to 0°C, was stirred for 2 h. Then the mixture was kept for 1 h at room temperature and for 2 h at 50–60°C. The triethylamine hydrochloride precipitate was filtered off, the solvent was removed, and the product was purified by reprecipitation from ethanol solution into anhydrous hexane. Yield 2.25 g (59%).

CONCLUSIONS

(1) The reactions of 2-methylindole and (2-methylindol-3-yl)diphenylphosphine with α-chloro-β-oxobutanal were carried out.

(2) Cyclization of the reaction products at both the C^3 atom and indole nitrogen atom was performed.

(3) The compounds synthesized exhibit high antimicrobial activity.

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