INDOLE DERIVATIVES

XXXV. Behavior of Indole-3-aldehyde and Its N-Acetyl Derivative in the Wittig Reaction*

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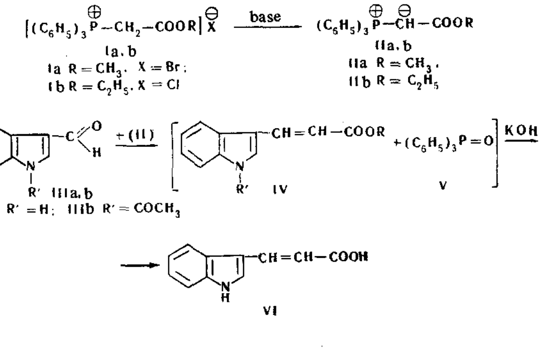
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 2, pp. 250–254, 1969

UDC 547.752.756:541.67:543.422.4.6

The Wittig reaction with indole-3-aldehyde and its N-acetyl derivative has been studied. Data are presented on the influence of various factors on the formation of the unsaturated compound. Some hypotheses are put forward concerning the reactivity of indole-3-aldehydes under the conditions of this reaction. The previously unknown α-(indol-3-yl)-β-phenylethylene has been obtained with a yield of 54%.

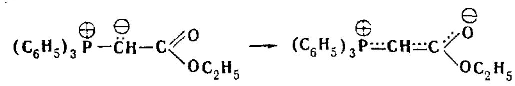
The Wittig reaction has been found to take an anomalous course in only a few cases [1–3]. Since the behavior of carbonyl compounds of the hetrocyclic series in the Wittig reaction has been studied to an extremely small extent [4, 5], it appeared of interest to us to investigate the reaction of aldehydes of the indole series with phosphorus ylides and also to elucidate the influence of the heterocyclic nitrogen atom on the course of the reaction.

For the initial investigations we used alkoxycarbonylmethylenephosphoranes (**IIa, b**), which were obtained either by the action of aqueous alkalis on the corresponding phosphonium salt (**Ia, b**) or by means of sodium methoxide as a proton acceptor without the isolation of the phosphorus ylide from the reaction mixture. In neither case did compound **IIa, b** react with indole-3-aldehyde (**IIIa**) when benzene, diethyl ether, or methanol was used as the solvent. The reaction did take place in dimethylformamide, but it proved to be extremely difficult to isolate the ester of β-(indol-3-yl)acrylic acid (IV) in the pure state, so that β-(indol-3-yl)acrylic acid (VI) was obtained with a yield of only 21%.

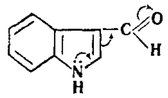


When the reaction was carried out in dimethylformamide, a substance the IR spectrum of which had absorption bands at 3000–3150 cm^{-1} (NH_2 group participating in the formation of a hydrogen bond), 1640 cm^{-1} (C═O group), 735–770 cm^{-1} (C—H bond of a benzene ring), 1180 cm^{-1} (P═O group at a hydrogen bond), and 1435–1450 cm^{-1} (P—C_6H_5). It may be assumed that this compound is the adduct of triphenylphosphine oxide (V) with indole-3-aldehyde (**IIIa**), particularly since such compounds of V with indole are known [6].

Since ethoxycarbonylmethylenephosphorane (**IIb**) belongs to the group of stable phosphoranes and, consequently, is relatively unreactive, the difficulty of its reaction with indole-3-aldehyde (**IIIa**) is completely explicable. The presence of an electron-accepting substituent in compound **II** lowers the electron density on the indole carbon atom, decreasing its nucleophilicity:

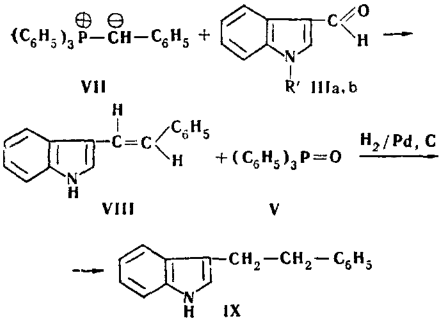


In addition, the carbonyl group in indole-3-aldehyde has a reduced electrophilicity in view of the displacement of the electron pair of the heterocyclic nitrogen atom into position 3:



These two factors exert a negative influence on the probability of the nucleophilic attack of the carbonyl group by an ylide carbon atom. An analogous phenomenon has been observed in the reaction of p-hydroxybenzaldehyde with the phosphorane prepared from γ-bromocrotonic ester, when the unsaturated compound was obtained in very low yield, which is also explained by the positive mesomeric effect of the hydroxy group [7].

In view of this it appeared of interest to study a more reactive phosphorus ylide in the Wittig reaction with indole-3-aldehyde and subsequently, therefore, we used benzylidenephosphorane (VII), which belongs to the series of unstable phosphoranes. Compound VII was obtained from benzyltriphenylphosphonium chloride by the action of sodium methoxide. The reaction of VII with indole-3-aldehydes led to the formation of β-(indol-3-yl)-α-phenylethylene (VIII):



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*For part XXXIV, see [15].

Table 1

Reaction of Indole-3-aldehyde with Benzylidenephosphorane

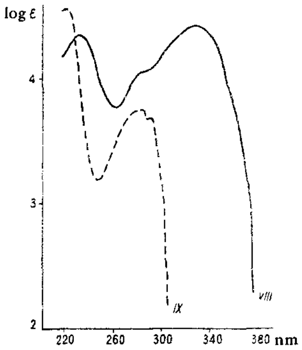
Solvent	Dielectric constant	Reaction time, hr	Temperature, °C	Yield, %	
				VIII	V
Benzene	2.3	43	20—21	26.6	41.3
Diethyl ether	4.5	36+1.5	19—20 55—60	39.5	39.8
Methanol	32—33	40+3.5	18—20 62—65	54.1	70.9

The IR spectrum of compound VIII showed the presence of the characteristic absorption bands for an indole ring at 3400 cm^{-1} (stretching vibrations of the NH group), 1600–1635 cm^{-1} (three low-intensity bands which can be ascribed to the nonplanar deformation vibrations of the C—H bonds in the aromatic ring and to the stretching vibrations of a double bond conjugated with the aromatic system), 700–745 cm^{-1} (absorption characteristic for a monosubstituted and 1,2-disubstituted benzene ring), and 965–970 cm^{-1} (deformation vibrations of a C—H bond at a double bond with the trans configuration of the substituents) [8]. The UV spectrum is shown in the figure.

The NMR spectrum of compound VIII exhibits a complex signal in the range from 7.18 to 8.22 δ which cannot be given an unambiguous assignment, but does not contradict the proposed structure. [As is known from literature data, the values of the chemical shifts (c. s.) of the protons of the indole nucleus are between 6.80 and 8.30 δ, and those of the protons of a double bond present in the α-position with respect to an aromatic nucleus are between 6.55 and 7.50 δ [9]].

In order to obtain more accurate information, compound VIII was catalytically hydrogenated to 3-(β-phenylethyl)indole (IX). In the NMR spectrum of compound IX, the protons of the indole nucleus give a complex signal in the range from 6.90 to 7.55 δ. A broadened peak at δ 2.95 with an intensity of four proton units must apparently be ascribed to two CH_2 groups, one of which is present in the α-position of the benzene nucleus and the other in the α-position of an indole nucleus. They have similar values of the c. s., which corresponds to the structure IX.

A comparison of the c. s. of the α-proton on the double bond in trans-cinnamic acid at (δ 7.83) [10] with the c. s. of the analogous proton in trans-indolylacrylic acid (δ 7.50) [9] permits the conclusion that the replacement of a phenyl group by an indole ring leads to a shift in the signal of this proton to a stronger field (by about 0.3 ppm). Consequently, it may be assumed that if compound VIII were the cis isomer, the c. s. of the proton at the C═C bond in the α-position to the indole nucleus would be less than the c. s. of the corresponding proton in cis-stilbene (δ 6.55) [10, No. 305]. The above ranges of the signals observed on the c. s. scale for compound VIII given above enabled this possibility to be excluded.



IR spectra of compounds VIII and IX.

An additional confirmation of the trans configuration of VIII was the construction of a Stuart-Briegleb model of α-(indol-3-yl)-β-phenylethylene, which showed that the cis structure of the compound is sterically unlikely.

The IR spectrum of 3-(β-phenylethyl)indole (IX) has the following characteristic absorption bands: indole ring at 3420 cm^{-1} (stretching vibration of the NH group), 1625–1600 cm^{-1} (aromatic system of bonds of the indole ring), and 700–755 cm^{-1} (nonplanar deformation vibrations of the C—H bonds of mono- and disubstituted benzene rings); there are no absorption bands in the 965–970-cm^{-1} region. The authors express their deep gratitute to Prof. Yu. N. Sheinker for a discussion of the IR and NMR spectra.

Because of the disturbance of the system of conjugated multiple bonds, the characteristic bathochromic shift observed in the UV spectrum of compound VIII does not take place in that of the hydrogenated compound IX (see figure).

To elucidate the influence of the solvent and the formation of the unsaturated compound, polar solvents

Table 2

Reaction of N-Acetylindole-3-aldehyde with Benzylidenephosphorane

Solvent	Reaction time, hr	Temperature, °C	Yield, %	
			VIII	V
Benzene	45	18—19	29.8	40.6
Diethyl ether	48	18—19	34.0	35.7
Methanol	5+1.5	18—19 50—53	34.5	42.0

(both protonic and aprotic) and nonpolar solvents were used (Table 1).

The reaction was carried out both at room temperature and with heating, a rise in the temperature giving a slight increase in the yield of unsaturated compound and at the same time leading to the resinification of the reaction mixture.

It is an interesting fact that when N-acetylindole-3-aldehyde (IIIb) reacted with benzylidenephosphorane, the acetyl group was split off under the reaction conditions and the olefin VIII was formed just as in the case of IIIa. Consequently, the desired reduction in the positive mesomeric effect of the nitrogen by the replacement of the hydrogen by an electronegative acetyl group cannot be achieved under these conditions.

The yields of VIII is benzene and diethyl ether are approximately the same as in the case of IIIa while in methanol they are 20% lower (see Table 2).

When the reaction was carried out in dimethylformamide, VIII and V were not isolated, although there was the formation of the adduct of triphenylphosphine oxide (V) and indole-3-aldehyde (IIIa), the IR spectrum and analytical data of which were similar to those of the adduct isolated in the reaction of II and III in dimethylformamide. There was no formation of such a compound in other solvents.

EXPERIMENTAL

The IR spectra of the compounds obtained were recorded on a UR-10 instrument in the form of mulls in paraffin oil, the UV spectra on an SF-4 spectrophotometer, and the NMR spectra on a JNM-4H-100 spectrometer at a working frequency of 100 MHz in dimethyl sulfoxide (for VIII) and in CD_3OD (for IX) with tetramethylsilane as internal standard.

The phosphonium salts Ia, b and the phosphoranes IIa, b corresponding to them were obtained by published methods [11, 12].

Reaction of indole-3-aldehyde (IIIa) with methoxycarbonylmethylenetriphenylphosphorane (IIa) in dimethylformamide. a) A solution of 0.78 g (5.4 mM) of IIIa in 12 ml of dimethylformamide was added to a solution of 2.04 g (6 mM) of the phosphorus ylide IIa in 8 ml of freshly distilled dimethylformamide. The mixture was stirred at 18–19° C for 24 hr, and the solvent was distilled off in a vacuum of 20 mm. The oily residue (2.7 g) was saponified with aqueous-alcoholic caustic potash (10% alkali in 80% aqueous methanol) at 18–19° C for 3 hr. The aqueous solution was acidified with dilute sulfuric acid (1 : 4) to pH 5 and was extracted with ether (4 x 20 ml), and the combined extracts were dried with sodium sulfate. After the elimination of the solvent, 125 mg (12.5%) of a substance with mp 189–191° C (decomp.) was obtained. This gave no depression of the melting point with a sample of indolylacrylic acid obtained by the Doebner reaction. Chromatography in a thin layer of silica gel in the carbon tetrachloride—acetic acid (12 : 1) system yielded a single spot with R_f 0.12 in both cases. Paper chromatography (Leningrad and Whatman No. 3 papers) gave R_f 0.09 for both compounds in the CH_3COOH—C_4H_9OH—H_2O (2 : 10 : 0.5) system.

A comparison of the IR spectra of the acids obtained by the Wittig reaction and by the Doebner reaction showed their identity: 3150–3300 cm^{-1} (NH group in the low-frequency region because of the formation of hydrogen bonds); 2500–2800 cm^{-1} (composite frequencies of a dimeric COOH group); 1620–1635 cm^{-1} (vibrations of a carbonyl group); and 745–770 cm^{-1} (aromatic system of bonds of the indole ring).

b) The sodium ethoxide prepared from 0.28 g (12.1 mg-atom) of sodium in 7 ml of absolute ethanol was treated with 9 ml of dimethylformamide. With vigorous stirring, a solution of 5.04 g (12 mM) of the phosphonium salt Ib in 9 ml of dimethylformamide was added to this mixture. Stirring was continued at 18–19° C for 1 hr, and then a solution of 1.02 g (6.7 mM) of IIIa in 4 ml of dimethylformamide was added over 30 min. The mixture was allowed to stand at 18–19° C for 24 hr and was then heated at 60–65° C for 15 hr. The solvent was driven off in a vacuum of 18 mm. The reaction products were extracted from the residue with absolute ether, and the ethereal extracts were evaporated to a volume of 15–20 ml. After some hours, triphenylphosphine oxide deposited, and this was filtered off, mp 144–145° C; after recrystallization from ethyl acetate, mp 153–154° C (according to the literature [12], mp 151.5–152.5° C). Weight was 0.42 g (22%). After the elimination of the solvent and saponification of the residual substance under the conditions described above, 300 mg of indolylacrylic acid VI was obtained; mp 186–188° C, after purification 190–192° C (decomp., from aqueous ethanol); yield 21%.

From the unsaponifiable fraction was isolated 0.38 g of the adduct of triphenylphosphine oxide (V) with indole-3-aldehyde (IIIa); mp 143–144° C (from acetone). Found, %: C 76.82; H 5.67; N 3.49; P 7.20. Calculated for $C_{27}H_{22}NO_2P$, %: C 76.59; H 5.20; N 3.30; P 7.32.

Benzyltriphenylphosphonium chloride was obtained as described by Horner and Mentrup [13], mp 345–347° C (according to the literature [14], 314–315° C [12], and 325–330° C [14]).

Reaction of indole-3-aldehyde (IIIa) with benzylidenephosphorane (VII) in ether. Sodium methoxide was prepared from 0.18 g (7.82 mg-atom) of sodium in dry methanol, and the excess of methanol was distilled off. A 7-ml quantity of dry ether was added, and the suspension of sodium methoxide in ether was stirred for 10 min. Then 3.0 g (7.71 mM) of benzyltriphenylphosphonium chloride was added, whereupon the bright orange coloration characteristic for the phosphorusylide appeared. The resulting suspension was stirred for 20 min, after which 0.54 g (3.75 mM) of IIIa was added. The mixture was kept at 19–20° C for 36 hr and was then boiled for 1 hr 30 min. The precipitate that deposited was filtered off and washed with 25 ml of dry ether. The residue amounted to 1.83 g (thin-layer chromatography in alumina showed the presence of the phosphonium salt and of IIIa). The ethereal filtrate was evaporated to a volume of 5–6 ml and cooled, and 0.25 g of triphenylphosphine oxide (V) separated out. The solvent was distilled off completely, and the substance was treated with n-hexane to give 0.16 g of V, mp 150–152° C. The total yield of V was 39.8%; mp 153–154° C (from a 4 : 1.5 mixture of n-heptane and benzene).

The elimination of the hexane in vacuum left a residue of 0.32 g of α-(indol-3-yl)-β-phenylethylene (VIII), mp 196–197° C (from ethanol). Found, %: C 87.60; H 5,95; N 6.37. Calculated for $C_{16}H_{13}N$, %: C 87.59; H 5.97; N 6.38. UV spectrum: λ_{max} 234, 330 nm log ε 4.34, 4.42).

The reaction with N-acetylindole-3-aldehyde took place similarly under the same conditions.

3-(β-Phenylethyl)indole (IX). The hydrogenation of 0.25 g (1.14 mM) of compound VIII was carried out at room temperature with 0.15 g of Pd/C in 10 ml of absolute methanol. After 4 hr, 29.8 ml of hydrogen had been absorbed (calculated: 27.6 ml). After hydrogenation was complete, the catalyst was filtered off and the solvent was driven off in vacuum to give 0.22 g (87.3%) of IX with mp 122–123° C (from 60% ethanol). Found, %: C 86.75; H 6.82; N 6.30. Calculated for $C_{16}H_{15}N$, %: C 86.80; H 6.80; N 6.31. IR spectrum: λ_{max} 224, 282, 290 nm (log ε 4.55, 3.76, 3.69).

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19 November 1966

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