

INDOLE DERIVATIVES

XXXIII. Synthesis and Some Reactions of β -(3-Indolyl)acrolein*

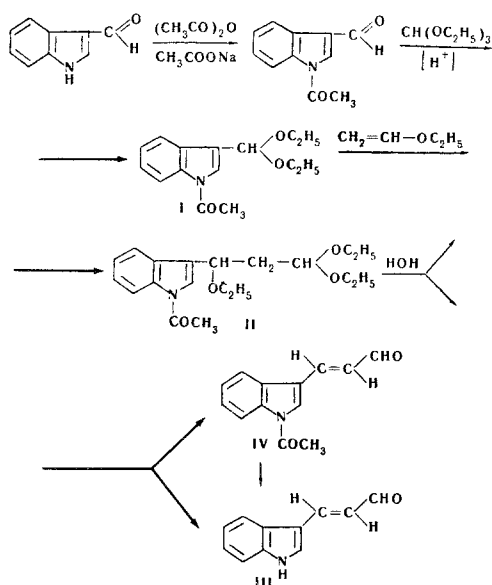
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A method is described for the preparation of β -(3-indolyl)acrolein. Oximation of this followed by dehydration gives β -(3-indolyl)acrylonitrile. Reduction gives γ -(3-indolyl)allyl alcohol.

Unsaturated aldehydes of the indole series have not been obtained hitherto. It was the aim of the present investigation to obtain β -(3-indolyl)acrolein, and this has been successfully accomplished by the following route:



We prepared indole-3-aldehyde by the Vil'smeier reaction [2]. Attempts to obtain the acetal were unsuccessful, no acetalization of the aldehyde by triethyl orthoformate taking place in presence of a variety of acidic catalysts.

The behavior of indole-3-aldehyde is in accordance with literature data on the low electrophilicity of the carbonyl group resulting from the transmission of the effect of the unshared pair on the indole nitrogen through the aromatic bond system to the carbonyl group. In order to increase the reactivity of the aldehyde group, we introduced an acetyl group into the 1-position of the indole-3-aldehyde. Reaction of the 1-acetylindole-3-aldehyde with triethyl orthoformate in the presence of toluene-*p*-sulphonic acid afforded the acetal I in good yield. The 1-acetylindole-3-aldehyde diethyl acetal was then allowed to react with ethylvinyl ether, the best catalyst for this reaction being zinc chloride. The progress of the reaction was followed by thin-layer chromatography on alumina (using ethyl acetate-light petroleum (1:1) and iodine as

developer). Reaction product II was isolated from the reaction mixture by column chromatography, and hydrolyzed without further purification with a mixture of glacial acetic acid, sodium acetate, and water. This gave β -(3-indolyl)acrolein (III) admixed with β -(1-acetyl-3-indolyl)acrolein IV. In order to complete deacetylation, the mixture was treated with aqueous alkali.

β -(3-Indolyl)acrolein is a yellow crystalline solid. It was characterized as the oxime, thiosemicarbazone, and isonicotinoylhydrazone. The last two compounds were prepared for pharmacological evaluation.

By the dehydration of the oxime of β -(3-indolyl)acrolein, the nitrile was obtained, which on hydrolysis, afforded β -(3-indolyl)acrylic acid identical with that obtained by the Knoevenagel reaction [3].

Reduction of β -(3-indolyl)acrolein with sodium borohydride proceeded fairly smoothly to give γ -(3-indolyl)allyl alcohol, an unstable compound which discolors on keeping, and under the influence of acid conditions or on heating is converted to high-melting compounds, the structure of which was not investigated.

The structures of the compounds we have obtained have been confirmed by IR and UV spectroscopy. The IR spectrum of β -(3-indolyl)acrolein (vaseline oil suspension) shows the following absorption bands: a fairly narrow band at 3300 cm^{-1} (N-H), 1655 cm^{-1} (C=O), and 1615 cm^{-1} (C=C bond conjugated with the carbonyl group). In comparison with the spectrum of indole-3-aldehyde, in which the N-H bond appears as a multiplet in the $3120\text{--}2900\text{ cm}^{-1}$ region [4], the N-H band in β -(3-indolyl)acrolein is shifted toward the higher-frequency end of the spectrum.

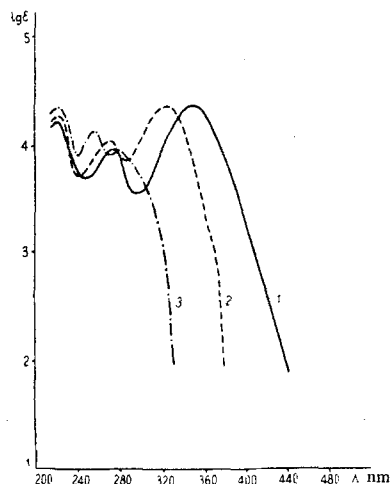
The IR spectrum of β -(3-indolyl)acrylonitrile shows a very narrow peak at 2230 cm^{-1} (C \equiv N), and the band at 1615 cm^{-1} (C=C bond conjugated with (C \equiv N)) persists. The band due to N-H is shifted somewhat towards the higher frequency region (3330 cm^{-1}), apparently as a result of a slight weakening in hydrogen bonding.

In the spectrum of γ -(3-indolyl)allyl alcohol, the band due to the C=C bond appears at 1655 cm^{-1} as a result of the absence of conjugation with the carbonyl group. The band due to N-H is still further shifted toward the high-frequency region (3400 cm^{-1}) as a result of the almost complete disappearance of hydrogen bonding of the indole nitrogen.

The UV spectrum of β -(3-indolyl)acrolein in alcoholic solution (see figure) shows the following bands: λ_{max} 221 nm ($\log \epsilon$ 4.28), 275 nm ($\log \epsilon$ 4.01), and 352 nm ($\log \epsilon$ 4.43). In comparison with the UV spectrum of indole-3-aldehyde [5], a bathochromic shift is ob-

*For part XXXII, see [1].

served with an increase in intensity of the absorption bands caused by the increase in length of the conjugated chain.



UV spectra in alcoholic solution. 1) β -(3-Indolyl)acrolein; 2) β -(3-indolyl)acrylonitrile; 3) γ -(3-indolyl)allyl alcohol.

The UV spectrum of β -(3-indolyl)acrylonitrile shows a small shift of the bands toward shorter wavelengths: λ_{\max} 222 nm ($\log \epsilon$ 4.30), 272 nm ($\log \epsilon$ 4.06), and 325 nm ($\log \epsilon$ 4.38).

The spectrum of γ -(3-indolyl)allyl alcohol shows an absorption maximum at 224 nm ($\log \epsilon$ 4.35), together with two much weaker bands at 260 nm ($\log \epsilon$ 4.17) and 282 nm ($\log \epsilon$ 3.95).

The spatial configurations of β -(3-indolyl)acrolein and γ -(3-indolyl)allyl alcohol were determined by NMR spectroscopy. The values of the chemical shifts of the protons in the side chains and their spin-spin interactions are given in the table. The spin-spin interaction values of the protons through the double bonds ($I_{1,2}$) in the compounds under examination is not less than 15 Hz, which corresponds to the trans-configuration of the interacting protons [6, 7].

EXPERIMENTAL

The experiments were carried out with the participation of Z. A. Zhestkova.

IR spectra were taken in vaseline oil suspension on a UR-10 instrument, and UV spectra in alcoholic solution on an SF-4 spectrophotometer, NMR spectra were recorded on a JEOL type 4H-100 spectrometer with a working frequency of 100 Mhz.

1-Acetylindole-3-aldehyde diethyl acetal. (I). 1-Acetylindole-3-aldehyde (30 g; 0.16 mole) and 0.2 g of toluene-*p*-sulphonic acid were placed in 150 ml of dry benzene, and triethyl orthoformate

(27.6 g; 0.18 mole) added dropwise with vigorous stirring. Stirring was continued at room temperature until solution was complete (about 2 hr). Then, 4 g of calcined potassium carbonate was added and stirring continued until the solution was clarified when the potassium carbonate was filtered off. Removal of the benzene followed by vacuum distillation gave 33.3 g (80%) of product, bp 161° C (1 mm). Found, %: C, 69.11, 69.09; H 7.67, 7.54; N 5.16, 5.22. Calculated for $C_{15}H_{19}NO_3$, %: C 68.96; H 7.28; N 5.36.

α, α, γ -Triethoxy- γ -(1-acetyl-3-indolyl)propane. To a solution of 30 g (0.115 mole) of 1-acetylindole-3-aldehyde diethyl acetal in 90 ml of dry benzene was added 2 ml of a 25% solution of anhydrous $ZnCl_2$ in ethyl acetate, followed dropwise by a solution of 8.7 g (0.12 mole, of freshly-distilled ethyl-vinyl ether in 10 ml of dry benzene at 40–45° C. Stirring was continued at 40–50° C for 1 hr, and the benzene removed in a low vacuum. The condensation product was isolated by chromatography on an alumina column (30 cm \times 30 mm), using ether–light petroleum (1 : 1). Removal of the solvent gave 37.0 g (98.5%) of an oil which solidified in a number of runs. The compound was purified for analysis by distillation, bp 193–194° C (1 mm). Found, %: C, 68.03, 68.27; H 8.30, 8.42; N 4.18, 4.34. Calculated for $C_{19}H_{27}NO_4$, %: C 68.44; H 8.13; N 4.20.

β -(3-Indolyl)acrolein. α, α, γ -Triethoxy- γ -(1-acetyl-3-indolyl)propane (30 g; 0.93 mole) was added to a mixture of 100 ml of glacial acetic acid, 20 g of anhydrous sodium acetate, and 10 ml of water. The mixture was heated in a current of nitrogen for 3 hr at 95–100° C, then cooled, 400 ml of glacial acetic acid added, and kept overnight in the refrigerator. The precipitate was filtered off and suspended in sufficient 2% solution of alkali to give an alkaline reaction. Recrystallization from dilute methanol afforded 13 g (83%) of β -(3-indolyl)acrolein, mp 155–156° C. Found, %: C 76.89, 76.86; H 5.28, 5.36; N 8.05, 8.03. Calculated for $C_{11}H_9NO$, %: C 77.17; H 5.26; N 8.18. **Oxime:** mp 165–166° C (from dilute methanol). Found, %: C 70.71; H 5.24; N 14.88. Calculated for $C_{11}H_{10}N_2O$, %: C 70.95; H 5.36; N 15.05.

Thiosemicarbazone: mp 227–228° C (from 30% methanol). Found, %: C 58.97, 58.98; H 5.07, 4.89; N 22.95, 23.02; S 12.93, 13.21. Calculated for $C_{12}H_{12}N_4S$, %: C 58.99; H 4.95; N 22.97; S 13.12.

β -(3-Indolyl)acrylonitrile. To a solution of 1 g (5.8 mM) of β -(3-indolyl)acrolein and 0.8 g of hydroxylamine hydrochloride in 6 ml of pyridine was added, portionwise, 3 ml of acetic anhydride. The mixture was heated on the water bath for 2 hr, cooled, poured into water and kept overnight in the refrigerator. The precipitate was filtered off and recrystallized from dilute methanol to give 0.54 g of β -(3-indolyl)acrylonitrile, mp 147–148° C. Found, %: C 78.89, 78.94; H 5.30, 5.32; N 16.31, 16.31. Calculated for $C_{11}H_8N_2$, %: C 78.56; H 4.78; N 16.66.

Hydrolysis of β -(3-indolyl)acrylonitrile. Potassium hydroxide (0.5 g) was dissolved in 12 ml of 30% alcohol, and 0.4 g (2.4 mM) of the nitrile added. The mixture was heated on a boiling water bath for 25 hr, cooled, and filtered. The filtrate was acidified with HCl (1 : 1) to pH 4. The precipitate was filtered off and recrystallized from dilute alcohol to yield 0.12 g of β -(3-indolyl)acrylic acid, mp 189–193° C. On admixture with material prepared by a different route [2], it had mp 190–193° C.

Reduction of β -(3-indolyl)acrolein. To a solution of 1 g (5.58 mM) of the aldehyde in 20 ml of methanol was added in small portions sodium borohydride (0.5 g), and the mixture stirred for 1 hr. The reaction mixture was diluted with 20 ml of water, saturated with sodium carbonate, and extracted with ether. The ether extracts were dried

Chemical Shifts of the Side-Chain Groups (Determined Approximately with the Help of Double Resonance) and Spin-Spin Interaction Constants

Compound (Ind = 3-indolyl)	δ_1	δ_2	δ_3	$I_{1,2}$	$I_{2,3}$	$I_{1,3}$	Solvent
Ind $\overset{(1)}{C}H=\overset{(2)}{C}H-\overset{(3)}{C}HO$	7.77	6.73	9.61	16.0	7.8	0	Acetone
Ind $\overset{(1)}{C}H=\overset{(2)}{C}H-\overset{(3)}{C}H_2OH$	6.77	6.30	4.24	16.2	6.2	1.1	CD ₃ OD

over potassium carbonate, the solvent removed and the residue recrystallized from benzene to give 0.5 g of γ -(3-indolyl)allyl alcohol, mp 89–90° C. Found, %: C 76.57, 76.73; H 6.37, 6.60; N 7.75, 7.83. Calculated for $C_{11}H_{11}NO$, %: C 76.28; H 6.40; N 8.09.

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