INDOLE DERIVATIVES

XXXVI. The Reactions of 3-β-Nitrovinyl Indoles with Nucleophilic Reagents*

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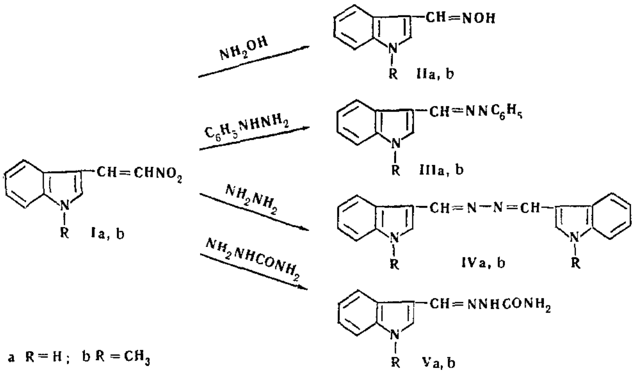
The behavior of some 3-nitrovinyl indoles in their reactions with nitrogen-containing nucleophilic reagents is examined. It is shown that hydroxylamine, phenylhydrazine, hydrazine, and semicarbazide react with 3-β-nitrovinyl indole to give the corresponding oxime, phenylhydrazone, azine, and semicarbazone of indole-3-aldehyde, possibly by decomposition of intermediates formed by the addition of the nucleophilic reagents to the nitrovinyl indole. 3-β-Nitropropenyl indole and N-methyl-3-β-nitrovinyl indole react similarly. Only the addition products of phenylhydrazine with N-acetyl-3-nitrovinyl indole and N-acetyl-3-β-nitropropenyl indole are stable. The reaction conditions and constants of the compounds prepared are given, and explanations are offered for the results obtained.

3-β-Nitrovinyl indoles are hetero analogs of β-nitrostyrene, for which addition reactions at the activated β-nitrovinyl bond have been extensively investigated.

It might be expected that the nitrovinyl group in nitrounsaturated indoles would be sufficiently reactive to undergo the chemical reactions characteristic of β-nitro olefins, in particular those with alcohols, amines, and other nucleophilic reagents [1].

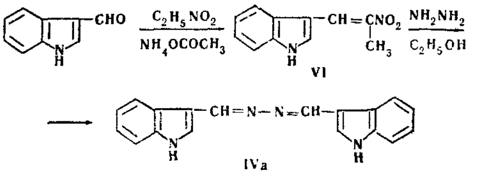
In the case of 3-β-nitrovinyl indole (Ia), however, instead of the expected addition products with hydroxylamine, phenylhydrazine, hydrazine, and semicarbazide, we obtained the corresponding derivatives of indole-3-aldehyde (IIa–Va),



despite the fact that the reaction proceeds under the mild conditions usual for nucleophilic addition to β-nitro-olefins, namely, in alcoholic solution at room temperature (in the case of hydrazine and phenyl-hydrazine), or at a temperature not exceeding 70–80° C (in the case of hydroxylamine and semicarbazide) (see table).

Similar results were obtained with N-methyl-3-β-nitrovinyl indole (Ib).

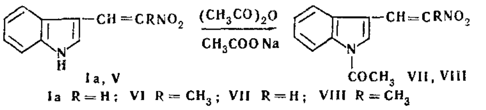
It is interesting that the reaction, under the same conditions, of 3-β-nitropropenyl indole (VI) with hydrazine also gives indole-3-aldehyde azine (IVa).

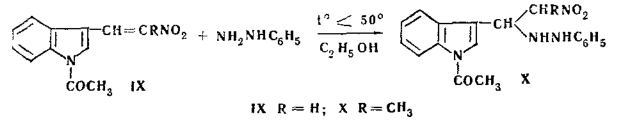


The structures of the compounds obtained were established by comparison of their melting points with those of authentic samples, and by the identity of their IR spectra. It is suggested that the formation of the corresponding indole-3-aldehyde derivatives by reaction of 3-β-nitrounsaturated indoles with nitrogen-containing nucleophiles may be explained by their formation as decomposition products from intermediate addition compounds (there are indications in the literature of the possibility of similar decompositions with the addition products from β-nitrostyrene [2, 3]).

Most 3-substituted indoles show characteristic instability [4], usually connected with the presence of an electron pair on the nitrogen of the indole ring, conjugated with the double bond in the 3-position [5]. For example, examination of the IR and UV spectra shows that nitrovinyl indoles exist in the internal nitrone salt form [12]. The introduction of a powerful electronegative group in the 1-position might be expected to reduce the possibility of a similar electron shift, leading to more stable products. In practice, by 'fixing' the free electron pair on the nitrogen atom by N-acetylation of β-nitrovinyl indoles we obtained comparatively stable addition products of phenylhydrazine with N-acetyl-3-β-nitrovinyl indole (VII) and N-acetyl-3-β-nitropropenyl indole (VIII).

Compound VIII was obtained in 70% yield by acetylation of 3-β-nitropropenyl indole. This is the first example of the direct acetylation of a nitro-unsaturated indole (the condensation of N-acetyl-indole-3-aldehyde is typically very slow). N-Acetyl-3-β-nitrovinyl indole (VII) was obtained similarly in higher yields (79%) than previously [6].





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*For part XXXV, see [14].

Reactions of Nitrovinyl Indoles with Nitrogen-Containing Nucleophiles*

Nucleophile	Nitro-vinyl indole	Reaction product	Reaction					Analyses					
			temperature, °C	time, hr	mp, °C	yield, %	molecular formula	found, %			calculated, %		
								C	H	N	C	H	N
Semicarbazide	I	Va	75–80	1	225–226	70	$C_{11}H_{10}N_4O$	59.43	5.14	27.60	59.46	4.95	27.72
	VII	Va	75–80	1	226	65	$C_{11}H_{10}N_4O$	—	—	—	—	—	—
	Ib	Vb	75–80	1	209–210	78	$C_{11}H_{12}N_4O$	61.08	5.98	26.13	61.11	5.55	25.92
Hydroxylamine	Ia	IIa	80	3	204–205[a]	61	$C_9H_8N_2O$	—	—	17.38	—	—	17.50
	Ib	IIb	Bp	5.5	154–155	35	$C_{10}H_{10}N_2O$	—	—	15.82	—	—	16.09
Phenylhydrazine	Ia	IIIa	Room	12	203–204[a, b]	60	$C_{15}H_{13}N_3$	76.69	5.76	17.96	76.59	5.52	17.87
	Ib	IIIb	Room	12	169–170	90	$C_{16}H_{15}N_3$	—	—	16.84	—	—	16.83
Hydrazine hydrate[c]	Ia	IVa	Room	1	322	43	$C_{18}H_{14}N_4$	75.29	4.87	19.41	75.52	4.89	19.58
	VII	IVa	Room	1	322	70	$C_{18}H_{14}N_4$	—	—	—	—	—	—
	VI	IVa	Room	0.5	322	80	$C_{18}H_{14}N_4$	—	—	—	—	—	—
	Ib	IVb	Room	2	232–233	51	$C_{20}H_{18}N_4$	—	—	17.72	—	—	17.83

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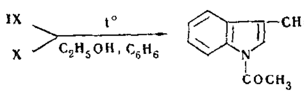
*Solvent, alcohol. Molar proportions of nitrounsaturated compound to nucleophile, 1 : 2. [a]Ref [13]. [b]The reaction was carried out in benzene. [c]25% aqueous solution of hydrazine hydrate.

Comparison of the UV spectra of Ia with VII, and of VI with VIII shows that the introduction of the N-acetyl group into the molecule of the nitrovinyl indoles substantially diminishes the system of conjugated double bonds, and also the characteristic UV spectra. Thus, the absorption maximum at 400 nm characteristic for N-unsubstituted nitrovinyl indoles (Ia and VI) is considerably displaced in the spectra of VII and VIII, to 254 nm in the case of VII, and to 255 nm in the case of VIII. This rearrangement of the double bond structure following the introduction of an acetyl group may help to increase the stability of the addition products IX and X.

The addition compounds IX and X are formed readily by carrying out the reaction in alcoholic medium for a few hours at room temperature (IX), or at a temperature not exceeding 50° C for 20-30 min (X). As would be expected [2], these compounds are thermally unstable, being converted readily into N-acetylindole-3-aldehyde phenylhydrazone (XI) by boiling for 1–2 hr in alcohol or benzene. Compound XI, therefore, may occur



XI

as a contaminant in the addition products IX and X when the reaction is carried out at high temperatures, and also when these compounds are recrystallized from concentrated solutions in high-boiling solvents. The structures of IX and X were proved by their UV, IR, and NMR spectra. Thus, the NMR spectra show the presence of an N-acetyl group in the molecules of IX and X, the protons of the methyl group linked to the carbonyl giving a clear peak at 2.57 and 2.62 ppm for IX and X, respectively. The protons of the α- and β-carbon atoms of the side chain give several signals at 4.85 to 5.15 ppm and 4.75 to 5.20 ppm for IX and X, respectively. The aromatic protons of the indole and benzene rings give rise to a group of peaks from 6.50 to 8.50 ppm. Finally, the protons of the α-methyl group in the side chain of X give a doublet at 1.37–1.40 ppm. It should be mentioned that reaction of N-acetyl-3-β-nitrovinyl indole with semicarbazide and hydrazine gives the corresponding indole-3-aldehyde derivatives (IVa and Va), that is, the reaction may proceed via a preliminary de-acetylation stage. Despite attempts to carry out the reaction under various conditions, we did not succeed in reacting 3-β-nitrovinyl indole with aniline. Heating for many hours with an excess of aniline, followed by removal of the excess aniline in steam, resulted in the isolation of indole-3-aldehyde. In the case of N-acetyl-3-β-nitrovinyl indole, in addition to indole-3-aldehyde, acetanilide was formed.

EXPERIMENTAL

The IR spectra of the addition products were recorded in vaseline oil suspension on a UR-10 instrument, and the UV spectra in alcohol on an SF-4 instrument. The NMR spectra were obtained on a JEOL type 4H-100 spectrometer with a working frequency of 100 MHz.

3-β-Nitrovinyl indole (Ia). 15 g of indole-3-aldehyde [7], 1.6 g of ammonium acetate, and 30 ml of nitromethane were boiled with stirring for 15 min. After cooling, 20 ml of ethanol and 8 ml of water were added, the mixture was cooled to 5° C, and the precipitate filtered off, washed with dil alcohol, and dried in air to give 11.5 g (60%), mp 171–172° C (mp 167–168° C [8]; 171–172° C [9]).

N-Methyl-β-nitrovinyl indole (Ib). A mixture of 15 g of N-methylindole-3-aldehyde [10], 1.2 g of ammonium acetate, and 60 ml of nitromethane were stirred at 90° C for 20–25 min, the crystalline mixture diluted with 60 ml of methanol, cooled to 5° C, and the precipitate filtered off, yielding 12.5 g (69%) of golden-yellow needles, mp 164–165° C (after two recrystallizations from aqueous methanol). Found, %: C 65.44; H 4.98; N 13.58. Calculated for $C_{11}H_{10}N_2O_2$, %: C 65.35; H 4.95; N 13.86.

3-β-Nitropropenyl indole (VI). A mixture of 7.5 g of indole-3-aldehyde, 0.9 g of ammonium acetate, and 15 ml of nitroethane were boiled with stirring for 10 min, the mixture diluted with 35 ml of hot ethanol, 1 ml of water added, and the mixture allowed to crystallize. There was obtained 8.1 g (77.9%) of product, mp 195–196° C (from ethanol) (mp 195–196° C [9]). Found, %: C 65.32; H 5.03; N 13.76. Calculated for $C_{11}H_{10}N_2O_3$, %: C 65.35; H 4.95; N 13.86.

N-Acetyl indole-3-aldehyde was prepared by a modification of the method given in [11]. Indole-3-aldehyde (30 g), 45 g of fused sodium acetate, and 105 ml of acetic anhydride were stirred at 120° C for 2.5 hr. The hot mixture was poured into 900 ml of ice water and stirred for 2–3 hr. The colorless, amorphous precipitate was filtered off and washed with cold water followed by dilute methanol, giving 38.3 g (98%), mp 162–164° C (from ethyl acetate) (mp 161–164° C [10]).

N-Acetyl-3-β-nitrovinyl indole (VII). A) 1.5 g of N-acetyl indole-3-aldehyde, 1.5 g of dry ammonium acetate, and 40 ml of nitromethane were heated with stirring on a boiling water bath for 30 min, kept overnight, diluted with 10 ml of 50% methanol, and cooled to 5° C, giving 9.1 g (49.4%), mp 197–198° C (from ethanol) (mp 189–192° C [10]; 187–188° C [6]).

B) A mixture of 1.8 g of I, 2.7 g of fused sodium acetate, and 10 ml of acetic anhydride were stirred at 120° C for 40 min. Ice-water (150 ml) was then added with vigorous stirring, which was continued for a further 30 min. The yellow, amorphous precipitate was filtered off, washed with water, and recrystallized from a mixture of acetone and methanol to give 1.85 g (79%) of bright yellow needles, mp 197–198° C (from acetone).

N-Acetyl-3-β-nitropropenyl indole (VIII). 5 g of VI, 7.5 g of fused sodium acetate, and 25 ml of acetic anhydride were stirred at 120° C for 30 min, poured with vigorous stirring into 0.5 *l* of ice water, and stirred for 1 hr. The precipitate was filtered off, washed with water, and recrystallized from a 4:1 mixture of methanol and acetone to yield 4.5 g (70%), mp 117–118° C (recrystallized twice from acetone). Found, %: C 64.23; H 4.95; N 11.71. Calculated for $C_{13}H_{12}N_2O_3$, %: C 63.93; H 4.95; N 11.48.

3-(α-Phenylhydrazino-β-nitroethyl)-N-acetyl indole (IX). A mixture of 3.5 g of VII, 5 ml of phenylhydrazine, and 30 ml of anhydrous ethanol (or benzene) were stirred at room temperature for several hours, and kept overnight. The precipitate was filtered off, and washed with ethanol, giving 4.5 g (85.3%), mp 147–148° C (from aqueous acetone). Found, %: C 63.95; H 5.77; N 16.57. Calculated for $C_{18}H_{18}N_4O_3$, %: C 63.96; H 5.33; N 16.56. IR spectrum, cm^{-1}: 3315 (NH); 1700 (C=O); 1600 (C=C aromatic); 1554 ($C-NO_2$). UV spectrum, λ_{max}, nm: 239, 290, 358–360: lg ε: 4.38, 3.87, 3.63.

3-(α-Phenylhydrazino-β-nitropropyl)-N-acetyl indole (X). A mixture of 1.0 g of VIII, 1.5 ml of phenylhydrazine, and 15 ml of ethanol was stirred at a temperature not exceeding 50° C for 30 min, then kept overnight. The precipitate was filtered off, and washed with ethanol and ether to yield 0.9 g (66%), mp 177–178° C (after two recrystallizations from aqueous acetone). Found, %: C 65.05; H 6.06; N 15.91. Calculated for $C_{19}H_{20}N_4O_3$. IR spectrum, cm^{-1}: 3339 (NH); 1700 (C=O); 1600 (C=C aromatic); 1554 ($C-NO_2$). UV spectrum, λ_{max}, nm: 239, 290, 342–346; lg ε: 4.42, 3.99, 3.7.

Thermal degradation of IX and X in boiling ethanol. After boiling in alcoholic solution for 2–3 hr, IX and X afforded N-acetylindole-3-aldehyde phenylhydrazone (XI). A mixed melting point with an authentic sample gave no depression.

N-Acetylindole-3-aldehyde phenylhydrazone (XI). A mixture of 0.5 g of N-acetylindole-3-aldehyde and 0.4 g of phenylhydrazine in 10 ml of ethanol was boiled for 5 min. The crystals were filtered off and washed with ethanol to give 0.5 g, mp 183–184° C (from ethanol). Found, %: N 14.90. Calculated for $C_{17}H_{15}N_3O$, %: N 14.80.

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