

Studies in Heterocyclic Compounds. III
Reaction of Indoles with Dienophiles

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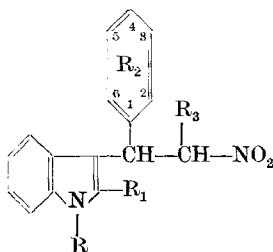
Summary

A number of adducts have been obtained by the condensation of indole, 2-Methylindole, 2-Phenylindole, 5,6-Methylenedioxyindole and 5,6-Methylenedioxy-2-methylindole with different β -nitrostyrene derivatives.

4,5-dimethoxyindole and 5-Methoxy-6-ethoxyindole have been synthesised.

Although a certain amount of work on the condensation of pyrroles with dienophiles has been reported¹⁾, little data was available until recently²⁾ on the reactivity of indole derivatives with different dienophiles.

In this communication are reported the condensations of substituted indoles with β -nitrostyrenes to give adducts of the general structure.



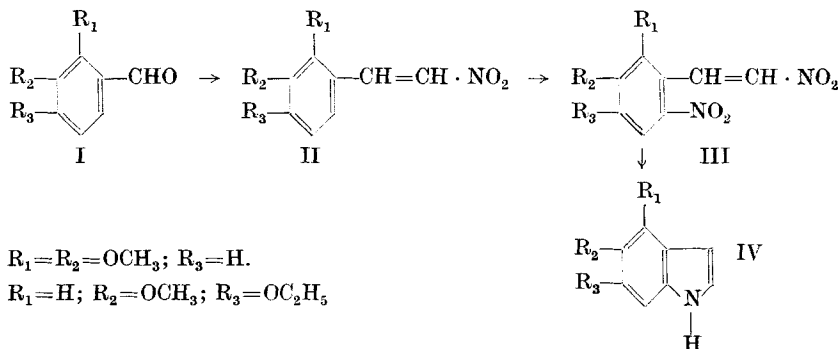
The condensation takes place readily by heating the compounds together at about 100 °C. The β -nitrostyrenes required were prepared from the appropriate aldehydes by refluxing with a mixture of the nitroalkane, ammonium acetate and acetic acid as described in literature³⁾. It was observed that 2-methylindole was the most reactive, while 2-phenylindole and indole itself came next in order of reactivity. The different adducts prepared are listed in table 1.

¹⁾ L. ZECHMEISTER, "Progress in the Chemistry of Natural Products", Vol. III, J. Springer, Vienna, 1939, p. 14.

²⁾ W. E. NOLAND and R. F. LANGE, J. Amer. chem. Soc. **81**, 1203 (1959).

³⁾ J. org. Chem. **18**, 1-3 (1953).

The new indole derivatives namely 4,5-dimethoxyindole and 5-methoxy-6-ethoxyindole have been synthesised according to the steps shown below.



The dimethylether of o-vanillin was refluxed with nitromethane, ammonium acetate and acetic acid to give the known³ β -nitrostyrene (II). The latter was nitrated to give the nitro-derivative (III), which was reduced by iron filings in presence of acetic acid to yield 4,5-di-methoxyindole (IV).

In a similar manner 5-methoxy-6-ethoxyindole was synthesised from 3-methoxy-4-ethoxybenzaldehyde. In both the cases the yields of the indoles were poor.

In two cases, the adducts were reduced by hydrogenation in the presence of RANEY nickel to form the corresponding tryptamine derivatives.

The above indole derivatives have also been condensed with maleic acid, maleic anhydride and methyl vinyl ketone. The structures of the adducts formed will form the subject matter of a future communication.

Experimental

1. General method for the preparation of the adducts

Indole (0.500 mole) and the β -nitrostyrene (0.500 mole) were heated for about 5 hours on a waterbath. The dark liquid mixture usually solidified on keeping. It was treated with alcohol and the solid which separated out was filtered and recrystallised from the same solvent.

2. 2,3-dimethoxy- β -nitrostyrene

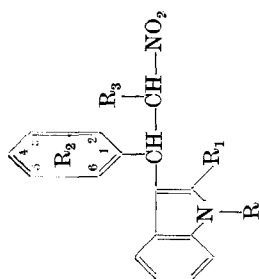
It was prepared by the method of C. B. GAIRAND and G. R. LAPPIN³).

3. 3-Methoxy-4-ethoxy- β -nitrostyrene

A mixture of 5 g of 3-methoxy-4-ethoxybenzaldehyde, 5 ml of nitromethane and 2 g of ammonium acetate in acetic acid solution was refluxed for two hours. The solid which separated on cooling was crystallised from alcohol, m. p. 148°.

Found: N 7.3
 Calc. for $\text{C}_{10}\text{H}_{13}\text{NO}_3$ (193): N 7.25

Table 1



Nos.	R	R ₁	R ₂	R ₃	Molecular Formula	Molecular Weight in g	M. P. °C	C %		H %		N %	
								Calc.	Found	Calc.	Found	Calc.	Found
I	H	H	4-OCH ₃	H	C ₁₇ H ₁₆ N ₂ O ₃	296	149-150°	68.9	68.3	5.4	5.2	—	—
II	H	H	2,3-OCH ₃	H	C ₁₈ H ₁₈ N ₂ O ₄	326	138-139°	66.27	66.2	5.52	5.4	—	—
III	H	H	4-OCH ₃	CH ₃	C ₁₈ H ₁₈ N ₂ O ₃	310	168°	—	—	—	—	9.03	9.0
IV	H	H	3,4-OCH ₃	H	C ₁₈ H ₁₈ N ₂ O ₄	326	149°	—	—	—	—	8.59	9.0
V	H	CH ₃	4-OCH ₃	H	C ₁₈ H ₁₈ N ₂ O ₃	310	119-120°	69.68	69.7	5.8	5.9	—	—
VI	H	CH ₃	2,3-OCH ₃	H	C ₁₉ H ₂₀ N ₂ O ₄	340	174-175°	67.04	66.7	5.88	6.3	—	—
VII	H	CH ₃	3,4-OCH ₃	H	C ₁₉ H ₂₀ N ₂ O ₄	340	164-165°	—	—	—	—	8.82	8.8
VIII	H	CH ₃	4-OH- 3-OCH ₃	CH ₃	C ₁₉ H ₂₀ N ₂ O ₄	340	187°	—	—	—	—	8.82	9.0
IX	H	C ₆ H ₅	4-OCH ₃	H	C ₂₃ H ₂₀ N ₂ O ₃	372	156-157°	74.2	74.3	5.38	5.8	—	—
X	H	C ₆ H ₅	2,3-OCH ₃	H	C ₂₄ H ₂₂ N ₂ O ₄	402	179°	71.64	71.5	5.6	5.6	—	—
XI	H	C ₆ H ₅	3,4-OCH ₃	CH ₃	C ₂₅ H ₂₄ N ₂ O ₄	416	194°	72.11	72.0	5.77	6.1	—	—

4. Nitration of the nitrostyrene⁴)

To a suspension of 5 g of the nitrostyrene in 20 ml of acetic acid was added gradually 15 ml of nitric acid (d. 1.5), so that the temperature of the mixture did not rise above 0°. After the addition of nitric acid was completed, the reaction mixture was kept at 0° for about 3 hours. Dilution with water and crystallisation from alcohol gave the o-nitro-β-nitrostyrene (yield 83–100%).

The m. p. of 2,3-dimethoxy-6-nitro-β-nitrostyrene was 163–164°.

Calc. for C₁₀H₁₀N₂O₆ (254): N 11.3
Found : N 11.03

The m. p. of 3-methoxy-4-ethoxy-6-nitro-β-nitrostyrene was 170–171°.

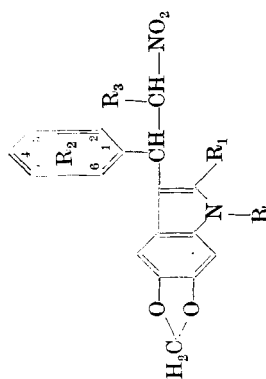
Calc. for C₁₁H₁₂N₂O₆ : N 10.8
Found (268): N 10.45

5. Reduction of the nitro-derivative to indole⁴)

Four gms. of the nitro-derivative of the β-nitrostyrene was dissolved in boiling 80 ml of acetic (80%). To the hot solution 20 g of iron-powder was added in small portions to maintain a steady ebullition and until the reddish-brown colour, which at first developed disappeared. The solution was then decanted into a solution of 100 g of sodium hydrogen sulphite in 500 ml of water in a large separating funnel and the mixture well shaken. The resulting mixture containing much suspended solid was extracted with ether until extract gave a negative EHRICH's reaction. The combined ethereal

⁴) H. BURTON and J. A. DUFFIELD, J. chem. Soc. London 79 (1949).

Table 2



Nos.	R	R ₁	R ₂	R ₃	Molecular Formula	Molecular Weight in g	M. P. °C	C %		H %		N %	
								Calc.	Found	Calc.	Found	Calc.	Found
XII	H	H	2,3-OCH ₃	H	C ₁₉ H ₁₈ O ₆ N ₂	370	170–171°	—	—	—	—	7.57	7.7
XIII	H	CH ₃	2,3-OCH ₃	H	C ₂₀ H ₂₀ O ₆ N ₂	384	140–141°	62.5	62.3	5.2	5.2	—	—

extracts were dried over sodium sulphate and evaporated. The crude indole crystallised from benzene and light petroleum ether (b. p. 40–60°) in colourless clusters of needles, which gave an immediate blue red colouration with cold reagent. The indoles were further purified by sublimation under vacuum.

The 4,5-dimethoxyindole gave m. p. 157°.

Found : C 67.9; H 6.6
Calc. for $C_{10}H_{11}NO_2$ (177): C 67.79; H 6.3

The 5-methoxy-6-ethoxyindole had m. p. 117–118°.

Found : C 68.9; H 6.6
Calc. for $C_{11}H_{13}NO_2$ (191): C 69.11; H 6.8

6. General method for the preparation of tryptamine derivatives

One gram of the adduct was dissolved in alcohol and hydrogenated in the presence of RANEY nickel for 6 hours at 2 atmosphere pressure. The tryptamines thus obtained were crystallised from dilute alcohol.

The tryptamine from II gave m. p. 152°.

Found : N 9.32
Calc. for $C_{18}H_{20}N_2O_2$ (296): N 9.46

The tryptamine from X had m. p. 141°.

Found : N 7.60
Calc. for $C_{24}H_{24}N_2O_2$ (327): N 7.53

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