INDOLE DERIVATIVES.

132.* SYNTHESIS OF 1-METHYL-5-NITRO-2-ETHYNYLINDOLE AND ITS MONO-AND DIAMINOMETHYL DERIVATIVES

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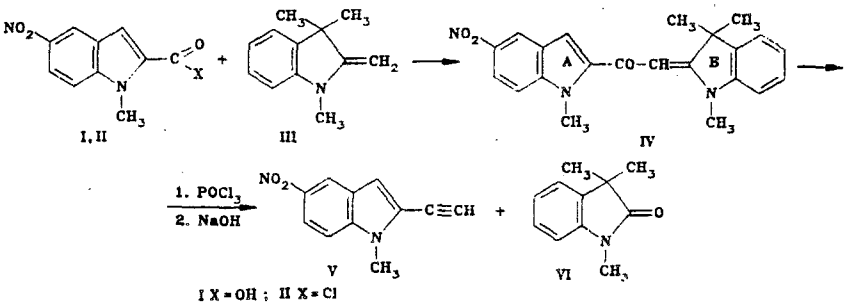
It was shown that it is possible to introduce an ethynyl group into an indole ring by the acetylenic cleavage of an acyl derivative of a base. 1-Methyl-5-nitro-2-ethynylindole was obtained from 1-methyl-5-nitro-2-indolcarboxylic acid, and a series of mono- and diaminomethyl derivatives was prepared by the Mannich reaction.

Acetylene derivatives of indole are a promising class of compounds in which to seek new biologically active compounds. A number of successful studies in this area have been carried out. Methods of introducing the ethynyl group into positions 2 [2, 3], 3 [3-5], and 5 [6] of the indole ring have been reported. However, all of these methods are limited, because the starting compounds are either unstable, or difficult to obtain, and consequently the development of new means of synthesizing acetylene derivatives of indole is an important task.

In the present work, attempts were first made to synthesize ethynyl derivatives of indole by the acetylene fragmentation of acyl derivatives of a Fischer base; this method is reported to give good results in the aromatic [7] and heteroaromatic series [8].

1-Methyl-5-nitro-2-indolcarboxylic acid (I) was chosen as the starting compound. Heating its chloroanhydride II with the Fischer base III gave a heterocyclic enaminoketone IV, which on heating with phosphorus oxychloride, followed by alkaline hydrolysis was converted to 1-methyl-5-nitro-2-ethynylindole (V) and 1,3,3-trimethyl-2-oxyindole (VI).



I X = OH ; II X = Cl

Compounds V and VI were separated by column chromatography. The yield of ethynylindole V was 80%, based on the aminoketone IV, or 55% based on the starting acid I. Its structure was confirmed by elemental analysis and spectral data, the results of which are given in the experimental part.

An attempt was made to obtain 1,2,3-trimethyl-5-ethynylindole by the same method; however, it was not successful because the corresponding enaminoketone could not be isolated.

The ethynylindole V in pyridine in the presence of cuprous chloride readily gave the dimer VII.

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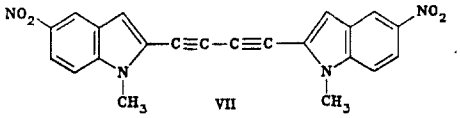
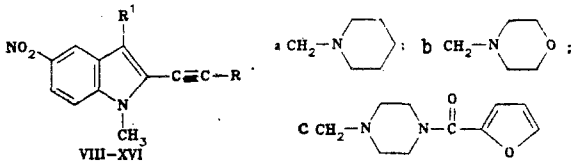


VII

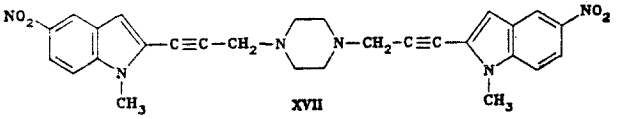
From the ethynylindole V, using the Mannich reaction, a series of mono- and diaminomethyl derivatives VIII-XVI was prepared. Piperidine, morpholine, N-2-furolypiperazine and piperazine were used as amines.



VIII-XVI

VIII R=a, R^1=H; IX R=b, R^1=H; X R=c, R^1=H; XI R=R^1=a; XII R=a, R^1=b, XIII R=b, R^1=a; XIV R=R^1=b, XV R=a, R^1=c; XVI R=R^1=c

Substitution of the hydrogen atom of the ethynyl group was carried out with formaldehyde and an amine in the presence of cuprous chloride [6, 9]. Secondary aminomethylation – substitution of the hydrogen atom in position 2 of the indole ring – was performed in acetic acid [10]. When piperidine was used as the amine, the bisindole compound XVII was obtained.



XVII

Data for the synthesized aminomethyl derivatives of 1-methyl-5-nitro-2-ethynylindole VIII-XVII are given in Table 1.

Biological tests on ethynylindole V and its aminomethyl derivatives VIII-XVII showed that compound VIII possesses moderate antifungal activity, the diaminomethyl derivative XI exhibits moderate antiarrhythmic action, and compound XIV is arrhythmogenic.

EXPERIMENTAL

IR spectrum of compound V in mineral oil was taken on a UR-10. PMR spectra were recorded on a WP-200 SY Bruker (200 MHz) high resolution spectrometer with a superconducting magnet, internal standard TMS. Molecular weights were measured on an MX-1303 mass spectrometer with direct introduction of the compound into the ion source.

1,3,3-Trimethyl-2-(1-methyl-5-nitro-2-indolylacetylidene)indoline (IV). A mixture of 5.1 g (0.023 mole) of indolecarboxylic acid I [11], 8.3 g (0.07 mole) of thionyl chloride, and 1 ml of dimethylformamide in 50 ml of dry benzene was refluxed for 6 h. The excess thionyl chloride was removed on the rotary evaporator. To remove final traces of thionyl chloride, 50 ml of petroleum ether was added to the residue and evaporated. The acid chloride II was dissolved in 250 ml of chloroform and added to a mixture of 4.01 g (0.023 mole) of the Fischer base III and 2.95 g (0.028 mole) of sodium carbonate in 100 ml of chloroform. The mixture was heated to 50°C and maintained at this temperature for 1 h, then left overnight at room temperature. The reaction mixture was filtered, the solution evaporated on the rotary evaporator, and the resulting solid washed with dilute hydrochloric acid, water and isopropyl alcohol. Yield 6.9 g (69%) of compound IV as bright-yellow crystals with mp 258-260°C (from acetic acid). PMR spectrum: 1.84 (6H, s, gem-CH_3); 3.32 [3H, s, N–CH_3 (B)]; 4.11 [3H, s, N–CH_3 (A)]; 5.59 (1H, s, =CH–); 7.17 [1H, s, 3-H (A)]; 6.79-8.57 ppm (7H, m, arom.). Found, %: C 70.0; H 5.9; N 11.0; M 376. $C_{22}H_{22}N_3O_3$. Calculated, %: C 70.2; H 5.9; N 11.2; M 376.

1-Methyl-5-nitro-2-ethynylindole (V). A mixture of 1.7 g (0.0045 mole) of the enaminoketone IV and 6.88 g (0.045 mole) of phosphorus oxychloride in 85 ml of dioxane was refluxed for 7 h at 85°C, then poured with stirring and cooling into 300 ml of 10% aqueous NaOH, and extracted with chloroform. After drying over sodium sulfate and evaporation of the solvent, the residue was passed through a column (100 mm × 30 mm) filled with 80 g of silica gel (100/250 μm), and eluted with CCl_4. Yield 0.72 g (80%) of compound V as yellow-green needles. mp 169-171°C (from ethanol). R_f 0.83 (Silufol UV-254, chloroform). IR spectrum:

TABLE 1. Data for Compounds VIII-XVII

Compound	T_{mp}* °C	Found				Empirical formula	Calculated				PMR spectra. δ, ppm			Yield, %
		C, %	H, %	N, %	M		C, %	H, %	N, %	M	N—CH_3	≡C—CH_2	3-H or —CH_2—N<	
VIII	132...133	68,6	6,5	13,9	297	$C_{17}H_{19}N_3O_2$	68,7	6,4	14,1	297	3,85	3,61	6,88	66
IX	117...118	64,4	5,6	14,4	299	$C_{16}H_{17}N_3O_3$	64,2	5,7	14,7	299	3,86	3,65	6,90	87
X	141...143	64,3	5,0	14,2	392	$C_{21}H_{20}N_4O_4$	64,3	5,1	14,3	392	3,84	3,71	6,90	75
XI	143...144	70,0	7,6	14,5	394	$C_{23}H_{30}N_4O_2$	70,1	7,6	14,2	394	3,83	3,66	3,77	78
XII	142...143	66,6	7,2	13,9	396	$C_{22}H_{28}N_4O_3$	66,7	7,1	14,1	396	3,83	3,66	3,80	83
XIII	125...127	66,6	7,2	14,1	396	$C_{22}H_{28}N_4O_3$	66,7	7,1	14,1	396	3,83	3,68	3,77	45
XIV	150...151	63,3	6,4	13,9	398	$C_{21}H_{26}N_4O_4$	63,3	6,5	14,1	398	3,84	3,79	3,70	68
XV	169...171	66,0	6,1	14,5	489	$C_{27}H_{31}N_5O_4$	66,3	6,3	14,3	489	3,85	3,65	3,85	19
XVI	164...166	63,7	5,7	14,6	584	$C_{31}H_{32}N_6O_6$	63,7	5,5	14,4	584	3,82	3,74	3,82	88
XVII	207 (decomp.)	65,6	5,0	16,4	510	$C_{28}H_{26}N_6O_4$	65,9	5,1	16,5	510	3,84	3,68	6,87	29

*For compounds VIII-XVI – after recrystallization from ethyl alcohol.

2120 (C≡C), 3270 cm^{-1} (≡CH). PMR spectrum: 3.56 (1H, s, ≡CH); 3.87 (3H, s, N–CH_3); 6.79 (1H, s, 3-H); 7.30-8.55 ppm (3H, m, arom.). Found, %: C 65.9; H 4.1; N 13.8; M^+ 200. $C_{11}H_8N_2O_2$. Calculated, %: C 66.0; H 4.0; N 14.0; M 200. Compound VI remained on the silica gel column.

1,4-Bis(1-methyl-5-nitro-2-indolyl)-1,3-butadiyne (VII). To 1 g (0.005 mole) of compound V in 50 ml of pyridine was added 0.1 g of cuprous chloride, and air bubbled through the reaction mixture for 1 h at room temperature. The reaction mixture was poured into water, the precipitated material filtered off, and washed with an aqueous ammonia solution, water, and ether. Yield 0.7 g (35%) of compound VII of light-green crystals (from DMFA). mp 349-350°C (decomp.). PMR spectrum [$(CD_3)_2SO$]: 3.93 (6H, s, N–CH_3); 7.36 (2H, s, 3-H); 7.67-8.58 ppm (6H, m, arom.). Found, %: C 66.4; H 3.6; N 13.9; M^+ 398. $C_{22}H_{14}N_4O_4$. Calculated, %: 66.3; H 3.5; N 14.1; M 398.

1-(1-Methyl-5-nitro-2-indolyl)-3-(N-piperidino)propyne (VIII). To a stirred mixture of 1 g (0.005 mole) of ethynylindole V and 0.02 g of cuprous chloride in 20 ml of dioxane was added 0.44 g of 40% aqueous formaldehyde and 0.48 g (0.0057 mole) of piperidine. The mixture was heated for 30 min at 95°C, cooled, filtered, and chloroform added to the filtrate. The chloroform solution was washed with aqueous ammonia and with water, and dried over Na_2SO_4. The solvent was evaporated to give 1 g of compound VIII.

1-(1-Methyl-5-nitro-2-indolyl)-3-(N-morpholino)propyne (IX) and 1-(1-methyl-5-nitro-2-indolyl)-3-[N-(N^1-2-furoyl)piperazinolpropyne (X). These are prepared in the same way as compound VIII using morpholine and N-2-furoylpiperazine respectively as secondary amines.

1-[1-Methyl-5-nitro-3-(N-piperidine)methyl-2-indolyl]-3-(N-piperidino)propyne (XI). To 0.26 g (0.003 mole) of piperidine with stirring and water-cooling was added 2 ml of glacial acetic acid and 0.25 g of 40% aqueous formaldehyde. After 30 min, a solution of 0.3 g (0.001 mole) of compound VIII in 3 ml of glacial acetic acid was added and the mixture heated at 85°C for 5 h. The reaction mixture was then poured into cold water and made alkaline by the addition of 10% NaOH solution. The precipitated material was filtered off, washed with water, and dried to give 0.31 g of compound XI.

1-[1-Methyl-5-nitro-3-(N-morpholino)methyl-2-indolyl]-3-(N-piperidino)propyne (XII). This was prepared in the same way as compound XI from the aminoacetylene VIII and morpholine.

1-[1-Methyl-5-nitro-3-(N-piperidino)methyl-2-indolyl]-3-(N-morpholino)propyne (XIII). This was prepared in the same way as compound XI from compound IX and piperidine.

1-[1-Methyl-5-nitro-3-(N-morpholino)methyl-2-indolyl]-3-(N-morpholino)propyne (XIV). This was obtained in the same way as compound XI from compound IX and morpholine.

1-{1-Methyl-5-nitro-3-[N-(N^1-2-furoyl)piperazino]methyl-2-indolyl}-3-(N-piperidino)-propyne (XV). This was prepared by the same method as compound XI from the aminoacetylene VIII and N-2-furoylpiperazine.

1-{1-Methyl-5-nitro-3-[N-(N^1-2-furoyl)piperazino]methyl-2-indolyl}-3-N-(N^1-2-furoyl)-piperazinopropyne (XVI). This was prepared from compound X and N-2-furoylpiperazine by the same method as compound XI.

N,N^1-Di[1-(1-methyl-5-nitro-2-indolyl)-3-propynyl]piperazine (XVII). This was prepared the same way as compound VIII, from 0.2 g (0.001 mole) of ethynylindole V and 0.097 g (0.0005 mole) of piperazine hexahydrate.

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INDOLE DERIVATIVES.

133.* SYNTHESIS OF 5-(2-PYRIDYL)INDOLE

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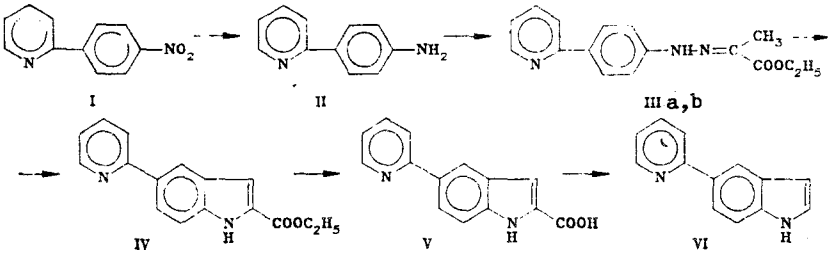
Starting from 2-(4-nitrophenyl)pyridine, the product of the Gomberg arylation of pyridine, 5-(2-pyridyl)indole was prepared by the Japp–Klingman reaction. ^{13}C NMR indicated an inductively transmitted interaction between the pyridine and indole rings.

Continuing our investigations in the field of multinuclear heterocyclic systems containing an indole ring, we have synthesized 5-(2-pyridyl)indole, an open analog of the pyrrolo[f-, g-, and h-]quinolines, which we reported earlier [2-5]. The presence in the molecule of 5-(2-pyridyl)indole of both the π-excessive pyrrole and the π-deficient pyridine rings makes it interesting both from the point of view of reactivity, and also because of the possibility of creating new physiologically active substances.

5-(2-Pyridyl)indole was prepared from 2-(p-nitrophenyl)pyridine by the following scheme:



The starting 2-(p-nitrophenyl)pyridine (I) was synthesized by the arylation of pyridine with p-nitrophenyldiazonium chloride using the conditions for the Gomberg–Bachmann–Hey reaction [6-8]. Reduction of 2-(p-nitrophenyl)pyridine with iron filings in ammonium chloride solution gave 2-(p-aminophenyl)pyridine (II) in good yield. The reaction of II with methylacetoacetic ester, (Japp–Klingmann reaction), gave the p-(2-pyridyl)phenylhydrazone of ethyl pyruvate (III). The hydrazone was separated into the syn-IIIa and anti-IIIb forms by column chromatography on silica gel and the quantitative ratio of the two isomers in the mix-

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