SYNTHESIS OF SOME DERIVATIVES OF INDOLE AND INDOLOINDOLES UNDER CONDITIONS OF INTERPHASE CATALYSIS

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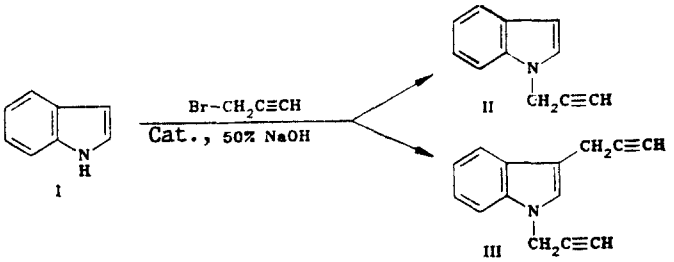
The preparation of N-alkyl and N,N-dialkyl derivatives of indole, 3H,8H-indolo[4,5-e]-, 3H,8H-indolo[5,4-e]-, and 1H,6H-indolo[7,6-d]indole under conditions of interphase catalysis is studied. In the case of indole, it is found possible to form 1,3-dipropargylindole.

We have successfully used alkyl halides under conditions of interphase catalysis to introduce substituents into indole and indoloindole heterocycles [1].

The present paper describes the alkylation of indole in a 50% aqueous solution of NaOH using a stoichiometric amount of propargyl bromide without a solvent at a catalyst:substrate ratio of 1:10 [2].

By means of TLC, 1-propargyl- and 1,3-dipropargylindole were isolated in a total yield of 78%. The major reaction product is 1,3-dipropargylindole (36% yield) prepared and characterized by us for the first time:



In the PMR spectrum (Table 1) of 1-propargylindole (II), the 2-H and 3-H proton signals appear as doublets with J_{23} = 2.93 Hz and the characteristic signal of the proton of the indole ring NH-group is absent, indicating the presence of the propargyl group in position 1. In the spectrum of compound III, no signals of 1-H and 3-H protons are found, while the 2-H proton signal appears as a singlet. In the spectrum, high field signals of two propargyl groups are also found. The signals of the methylene groups (in positions 1 and 3) appear as a doublet of doublets with SSCCs of 2.20 and 2.93 Hz at 4.83 and 3.68 ppm, respectively. Triplet signals of the acetylenic protons of 1,3-dipropargylindole III are observed at 2.38 and 2.14 ppm.

In the IR spectra of compounds II and III, absorption bands from the fundamental vibrations of the C≡C and ≡C–H functional groups are found (see Experimental).

We also adopted the method of interphase catalysis for the dialkylation of previously synthesized isomeric indoloindoles [3, 4]. Studies in this area allow us to say that the reactions in nonpolar solvents with vigorous stirring at a temperature of 60-65°C take place slowly (~12 h). Obviously, this is due to the poor solubility of indoloindoles in nonpolar solvents. Alkylation in 1,2-dichloroethane with a ratio of catalyst (tetrabutylammonium bromide) to substrate of 1:5 at 40-45°C leads to the formation primarily of N,N-dialkylindoloindoles.

3H,8H-Indolo[4,5-e]indole (VII) undergoes N,N-dialkylation more readily than isomeric compounds IV and X because of its better solubility in 1,2-dichloroethane.

The site of the substitution in heterocycles IV, VII, and X was determined by comparing the PMR spectra (Table 1) of these compounds and the initial indoloindoles. As can be seen from the data in the table, the signals of the protons of the NH groups disappear in all cases, along with the characteristic SSCCs with the corresponding protons. This is in accord with the dialkylation of the isomeric indoloindoles at the indole nitrogen atoms. The signals of the aromatic protons of the angular isomers of the N,N-dialkylated compounds form an AB system with a characteristic SSCC (Table 1), showing the symmetry of the molecules. The characteristic signals of the introduced alkyl substituents are also observed in the PMR spectra of the N,N-dialkylated compounds.

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TABLE 1. NMR Spectra of Compounds II, III, V, VI, VIII, IX, XI, and XII*

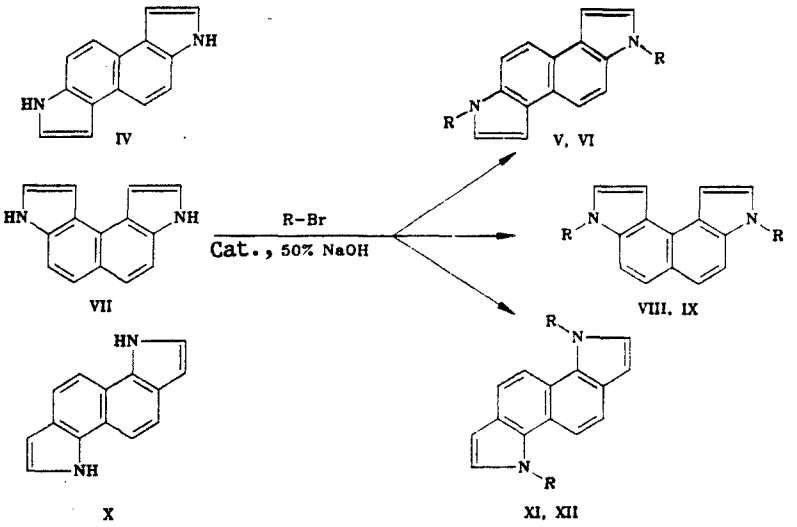
Compound	Chemical shifts δ, ppm											J, Hz
	1-H	2-H	3-H, d	4-H	5-H, d	6-H, d	7-H, d	CH_2	CH_3, d	CH_3, t	C_6H_5	
II	—	7,20 d	6,53	7,64 d	7,25	7,13	7,40	4,86 d	2,38	—	—	$J_{23}=2,93$; $J_{67}=7,3$; $J_{45}=7,31$; $J_{56}=7,31$; $J_{CH_2CH}=2,2$
III	—	7,18 s	—	7,62 d	7,26	7,15	7,37	4,83 d (at $C_{(1)}$) 3,68 d (at $C_{(3)}$)	2,38 (at $C_{(1)}$) 2,14 (at $C_{(3)}$)	—	—	$J_{45}=J_{56}=J_{67}=7,31$; $J_{CH_2CH}=2,20$ (at $C_{(1)}$); $J_{CH_3CH}=2,93$ (at $C_{(3)}$)
V	6,99 d	7,32 d	—	7,64 d	8,00	—	—	4,35 q	—	1,48	—	$J_{12}=29$; $J_{45}=8,8$; $J=6,6$
VI	7,04 d.d	7,38 d	—	7,60 d.d	7,99	—	—	5,55 s	—	—	7,2 ... 7,3	$J_{12}=3,3$; $J_{45}=8,8$; $J_{14}=0,7$
VIII	7,28 d	7,41 d	—	7,53 d	7,69	—	—	4,38 q	—	1,5	—	$J_{12}=2,9$; $J_{45}=8,8$; $J_{CH_2CH_3}=7,3$
IX	7,38 d	7,50 d	—	7,48 d	7,63	—	—	5,58 s	—	—	7,2 ... 7,3	$J_{12}=3,3$; $J_{45}=8,8$
XI	—	7,30 d	6,58	7,76 d	8,15	—	—	4,76 q	—	1,56	—	$J_{23}=2,9$; $J_{CH_2CH_3}=6,6$; $J_{45}=8,7$
XII	—	7,33 d	6,61	7,55 d	7,99	—	—	5,95 s	—	—	7,1 ... 7,3	$J_{23}=2,9$; $J_{45}=8,6$

*PMR spectra of compounds II and III were taken in $CDCl_3$, of compounds V, VI, VIII, IX, XI, and XII, in acetone-d_6.

TABLE 2. Physical Chemical Properties of Compounds II, III, V, VI, VIII, IX, XI, and XII

Compound	Starting materials	Molecular formula	mp, °C	R_f*	IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	Yield, %
II	Indole, propargyl bromide	$C_{11}H_9N$	36 ... 37	0,67	3310 (≡CH); 2115 (C≡C); 750 (CH_2); 520 (CH_3)	222 (4,55); 260 sh. (3,52); 266 sh. (3,70); 280 (3,77); 287 sh. (3,70)	21
III	Indole, propargyl bromide	$C_{14}H_{11}N$	89 ... 90	0,59	3220 (≡CH); 2215 (C≡C)	224 (4,59); 280 (3,85); 295 sh. (3,73)	57
V	3H, 8H-Indolo[5,4-e]-indole, ethyl bromide	$C_{18}H_{18}N_2$	204 ... 205	0,33	750 (CH_2); 520 (CH_3)	212 (4,64); 220 (4,72); 252 (4,81); 312,5 sh. (4,15); 324 (4,36); 334 sh. (4,27); 339 (4,32)	42
VI	3H,8H-Indolo[5,4-e]-indole, benzyl chloride	$C_{28}H_{22}N_2$	117 ... 118	0,35	1585 arom); 750 (CH_2)	204 sh. (4,66); 254 (4,57); 330 (4,18); 338 sh. (4,16)	23
VIII	3H,8H-Indolo[4,5-e]-indole, ethyl bromide	$C_{18}H_{18}N_2$	166 ... 167	0,31	730 (CH_2); 480 (CH_3)	216 sh. (4,91); 237 (4,97); 260 sh. (5,00); 269 (5,06); 278 (5,54); 307 (4,70)	35
IX	3H, 8H-Indolo[4,5-e]-indole, benzyl chloride	$C_{28}H_{22}N_2$	185 ... 186	0,32	1620 ... 1565 (arom), 635 (CH_2)	204 sh. (5,00); 206 (5,02); 208 sh. (4,98); 236 (4,56); 262 sh. (4,71); 268 (5,01); 279 (5,17); 309 (4,31); 330 sh. (3,56)	21
XI	1H,6H-Indolo[7,6-g]-indole, ethyl bromide	$C_{18}H_{18}N_2$	174 ... 175	0,5	700 (CH_2); 470 (CH_3)	216 sh. (3,74); 263 sh. (4,87); 217 (5,25); 290 (4,04); 302 (4,14); 313 sh. (3,77); 324 (3,51); 333 sh. (3,52); 339 (3,71)	35
XII	1H,6H-Indolo[7,6-g]-indole, benzyl chloride	$C_{28}H_{22}N_2$	291 ... 292	0,48	1665 (arom); 720 (CH_2)	208 (3,58); 265 sh. (3,18); 272 (3,41); 292 sh. (3,53); 302 (3,53); 339 (3,42); 356 (3,41)	20

*For compounds II and III, benzene/petroleum ether, 2:1; for the others, benzene/hexane, 1:1.



V, VIII, XI R = C_2H_5; VI, IX, XII R = $CH_2C_6H_5$

The NH group stretching bands are missing in the IR spectra of compounds V, VI, VIII, IX, XI, and XII, and the characteristic bands of the substituted groups are observed in the 750-700, 520, and 470 cm^{-1} regions for ethyl groups and 750-635 and 1665-1565 cm^{-1} for benzyl groups.

The molecular masses of compounds V, VI, VIII, IX, XI, and XII were determined by mass spectrometry and correspond to the calculated values. The nature of the fragments confirm the proposed structures.

EXPERIMENTAL

The course of the reaction and the purity of the compounds were monitored by TLC on Silufol UV-254 and UV-360 plates. IR spectra were taken on a UR-20 instrument in mineral oil, the UV spectra on a Specord spectrophotometer in ethanol, and the PMR spectra on a Varian CFT-20 spectrometer with TMS as an internal standard. The precision of the chemical-shift measurements was ±2 ppm, and of the SSCC ±1 Hz. Molecular masses were determined mass spectrometrically on an MKh-1303 instrument with direct introduction of the sample into the ion source with an energy of ionizing electrons of 50 eV.

The elementary analyses of the synthesized compounds for C, H, and N corresponded to the calculated values.

The characteristics of the synthesized compounds are given in Tables 1 and 2.

1-Propargylindole (II) and 1,3-Dipropargylindole (III). To 15 ml of a 50% solution of NaOH and 1 g (8.5 mmole) of indole is added, with stirring, 0.017 g of trimethylbenzylammonium chloride and 2.38 g (20 mmole) of propargyl bromide. This is stirred at 20°C for 20 min, and the aqueous solution extracted with ether. The ethereal extracts are washed with water and dried with anhydrous Na_2SO_4. The solvent is evaporated off to obtain 0.93 g of an oil. The mixture, 0.07 g, is separated into individual compounds by means of preparative TLC on silica gel (20 × 22 cm plates), 1:4 benzene/hexane eluent, to obtain 15 mg of compound II (pale yellow crystals) and 40 mg of compound III (yellow crystals).

3,8-Diethylindolo[5,4-e]indole (V). To a suspension of 0.1 g (0.48 mmole) of 3H,8H-indolo[5,4-e]indole (IV) and 8 ml of 1,2-dichloroethane is added 10 ml of a 50% solution of NaOH, 0.016 g of $[CH_3(CH_2)_3]_4NBr$, and 0.25 g (2.3 mmole) of ethyl bromide. This is stirred for 1 h at 40-45°C, and the aqueous layer extracted with 1,2-dichloroethane. The organic extract is washed with water until a neutral reaction is obtained, and dried with Na_2SO_4. The solvent is evaporated off under vacuum at 35-40°C. The yield is quantitative. The resultant substance is purified by preparative TLC, 1:2 benzene/hexane eluent. Indole (V), 55 mg, is isolated in the form of colorless crystals.

Compounds VI, VIII, IX, XI, and XII are obtained in a manner analogous to compound V (Table 2).

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ACETALS OF LACTAMS AND ACID AMIDES.

66.* SYNTHESIS AND SPECTRAL STUDIES OF 4(AND 6)-AMINO-5-HYDROXYINDOLE DERIVATIVES

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A method has been developed for the selective N-alkylation of derivatives of 4-amino-5-hydroxy- and 6-amino-5-hydroxyindoles, based on the preliminary closure of the oxazolone ring by reaction with sodium cyanate and alkylation of the resulting oxazolo[4,5-e]- and oxazolo[5,4-f]-indole derivatives in an alkaline medium. The latter, on heating in an alkali, convert into 5-hydroxy-6-methylaminoindoles, while the former give substituted N-methyl-N-indolylurethanes under these conditions. The reaction of amino-hydroxyindoles with DMFA diethylacetal and certain reactions of the resulting amidines were studied.

Compounds having hydroxy and substituted amino groups in the ortho positions of the aromatic ring are known to be promising in the search for antitumorigenic agents, protein synthesis inhibitors, and antiviral compounds [2]. The synthesis of systems of this type are complicated in view of the possible occurrence of processes at two reaction centers (amino and hydroxy groups) and specific methods are required for carrying out selective reactions. We chose 4-amino-5-hydroxy-6-bromo- [3] and 5-hydroxy-6-amino-1,2-dimethyl-3-ethoxycarbonylindoles (I, II) as starting compounds in the present work. Compound II was obtained by the reduction of the corresponding nitro derivative [4].

At the first stage, we studied the possibility of the selective preparation of N-alkyl derivatives in the two series of compounds. The reaction of aminophenols I, II with sodium cyanate in an acid medium proceeds similarly, and as a result oxazoloindoles III, IV, respectively, are obtained. Heating of compound I with urea in acetic acid also leads to the formation of the tricyclic compound III, while when hydrochloric acid is used, the ureido derivative V is obtained. Alkylation of tricyclic compounds III, IV proceeds smoothly, and N-methyl derivatives VI, VII are formed in satisfactory yields.

However, substantial differences were revealed at the stage of hydrolytic splitting of the oxazolone ring in compounds VI and VII, which are probably due to the steric interaction of the substituent at the 4-position (in the series of 4-aminoindole I derivatives) and the ethoxycarbonyl group at the 3-position. Thus, while the alkaline hydrolysis of oxazolo[5,4-f]indole VII proceeds as usual with the formation of 6-methylamino-5-hydroxy derivative VIII, a similar treatment of oxazolo[4,5-e]indole VI leads to urethanes IXa, b, which are very stable with respect to alkalies: we were unable to split off the N-alkoxycarbonyl fragments without the destruction of the molecule. This anomalous stability of compounds (IXa, b) required a reliable confirmation of their structure by means of PMR spectroscopy (Table 1), and especially ^{13}C NMR spectroscopy. The ^{13}C NMR spectra of compounds IXa, b and 5-O-acetyl derivative X under the conditions of a complete uncoupling from protons, contain a double set of signals, whereby the

*For communication 65, see [1].

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